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SUBSPECIALTY ABSTRACTS

AIRWAY MANAGEMENT

AIRWAY MANAGEMENT 1

Offsite Airway Management: A National Survey of Anesthesiology Residency Programs Prior To and During COVID-19

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INTRODUCTION: Offsite airway management has become more challenging in recent years, due in part to increasing obesity in our population[1] and the association between obesity and COVID-19[2]. Factors known to increase difficulty of offsite intubations include: multiple glottic visualization attempts, poor glottic view, and the offsite location itself[3]. Based upon our anecdotal experience, appropriate airway management equipment is not available in many patient care areas. However, availability of equipment and personnel to help manage the unexpected difficult airway has been shown to dramatically reduce the incidence of airway-related complications[4]. The purpose of this research is to assess the use of airway equipment, personal protective equipment (PPE), and provider availability for offsite (other than anesthetizing locations) airway management in practices similar to our own. The hypothesis of this study taps into the dearth of nationwide standardization for offsite airway management in anesthesiology training programs. In addition, the COVID-19 pandemic has presented several further challenges, for which only rudimentary recommendations exist at this point[5]. Our objective was to determine if a de facto standard exists among the aforementioned programs with regard to equipment used to manage airways, presence of anesthesia providers, and PPE availability offsite. Our motivation for performing this study comes from both literature review and our anecdotal evidence that availability of proper airway equipment and anesthesia personnel is associated with better offsite airway outcomes. Ultimately, the availability of PPE for our fellow anesthesia providers is key to ensure continued safe offsite airway management over the future course of the COVID-19 pandemic.

METHODS: This study seeks to determine if a national standard exists among anesthesiology residency programs (ARP) for equipment, personnel and PPE availability in management of offsite airways before and during COVID-19. To answer these questions, a qualitative and quantitative (mixed method) survey was created *(Image 1)*. The 161 active ARP's were queried using the program coordinators known points of contact. Three weeks were given for responses from contacted programs at which time the same email was sent to all programs asking those programs that did not respond to please do so. Three additional weeks were given for programs to respond, after which results obtained were tabulated in whole. The PI and co-investigators made themselves available to answer any questions via email. Due to the fact that no individual patients were enrolled, no individual patient data was collected (nor medical records reviewed), consents were not needed and no identifiers were collected. The results obtained are expressed as percentages of responding programs.

RESULTS: 52 responses were received from the 161 ARPs (32%) currently in the US *(Image 2)*. The response rate for this survey is consistent with our previous physician survey experience as well as published literature[5]. Among various results, the use of carry bags (71%) and offsite anesthesia airway carts (42%) were present for offsite airway management, and 75% of respondents had a dedicated offsite airway cart that they brought with them. In addition, video laryngoscopy was used 92% of the time during the COVID-19 pandemic. Also, an assortment of PPE was routinely available during COVID-19. 88% of respondents had a COVID-19 protocol in place and it was followed 90% of the time. Finally, attending involvement in offsite intubations was far greater during COVID-19 (79%) as opposed to an earlier survey (39%) conducted in 2018[7].

CONCLUSION: We observed that availability of an adequate assortment of PPE was available at the time this survey was conducted. In addition, airway management equipment was more readily available during than prior to the COVID-19 pandemic. In 88% of programs, a COVID-19 protocol exists and was followed 90% of the time. Also, attending presence for offsite intubations has increased during COVID-19. Finally, video laryngoscopy is being utilized during COVID-19 to a far greater extent than before. In conclusion, adequate PPE and offsite airway equipment, use of a hospital-specific COVID-19 protocol, as well as the use of video laryngoscopy and direct attending involvement are trends that set the stage for development of a nationwide standard for offsite airway management during the era of COVID-19.

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COVID-19 Offsite Airway Survey

Prior to the COVID-19 Pandemic:

1. Was any of the following difficult airway equipment already at the location and immediately available offsite? (chose all that apply)
    a. Basic Airway Equipment (ETT'S, Oral Airways, Laryngoscopes, McGill Forceps, Etc...)
    b. Video Laryngoscope (i.e. - McGrath, Glidescope, etc...)
    c. Supraglottic Airways (LMA, King, Etc...)
    d. Rigid Stylet for ETT's
    e. Bougee and exchange catheters
    f. Manual Jet Ventilator/Manual Jet Ventilator
    g. Alternative ETT's (Armored, Parker)
    h. Fiberoptic Bronchoscope
    i. ETT's with diameter < 7mm
    j. Cricothyrotomy Kit
2. Is there a dedicated offsite airway intubation cart at your institution?
    a. Yes
    b. No

During the COVID-19 Pandemic:

3. Was any of the following airway equipment already at the location and immediately available offsite? (chose all that apply)
    a. Basic Airway Equipment (ETT'S, Oral Airways, Laryngoscopes, McGill Forceps, Etc...)
    b. Video Laryngoscope (i.e. - McGrath, Glidescope, etc...)
    c. Supraglottic Airways (LMA, King, Etc...)
    d. Rigid Stylet for ETT's
    e. Bougee and exchange catheters
    f. Manual Jet Ventilator Manual Jet Ventilator
    g. Alternative ETT's (Armored, Parker)
    h. Fiberoptic Bronchoscope
    i. ETT's with diameter < 7mm
    j. Cricothyrotomy Kit
    k. None
4. If no equipment is available offsite, which of the following modalities is used to obtain these devices? (check all that apply)
    a. Offsite Airway Intubation Cart
    b. Dedicated Carry Bags
    c. Colleagues / Anesthesia Technicians
    d. Other

For COVID-19 positive or presumed positive patients:

5. Was any of the following airway equipment used for intubation? (chose all that apply)
    a. Basic Airway Equipment (ETT'S, Oral Airways, Laryngoscopes, MaGill Forceps, Etc...)
    b. Video Laryngoscope (i.e. - McGrath, Glidescope, etc...)
    c. Supraglottic Airways (LMA, King, Etc...)
    d. Rigid Stylet for ETT's
    e. Bougee and exchange catheters
    f. Manual Jet VentilatorManual Jet Ventilator
    g. Alternative ETT's (Armored, Parker)
    h. Fiberoptic Bronchoscope
    i. ETT's with diameter < 7mm
    j. Cricothyrotomy Kit
    k. Dedicated Offsite Airway Cart
6. Is the following Personal Protective Equipment available for intubations (chose all that apply):
    a. Gloves
    b. Fluid-resistant gowns
    c. Fluid-resistant shoe covers
    d. Hair covers (i.e. surgeon cap, bouffant cap)
    e. Surgical masks
    f. Eye protection
    g. Face shields
    h. N95 masks
    i. Powered Air-purifying respirators (PAPRs)
    j. Respirators (P100)
7. Who was the primary intubator? (chose all that apply)
    a. Attending Anesthesiologist
    b. Housestaff (residents, fellows)
    c. CRNA
    d. Other Provider or Service As Primary Intubator
8. Does A Protocol Exist For All COVID-19 Intubations for the Anesthesia Department, Including Offsite and Anesthetizing Locations?
    a. Yes
    b. No
9. If So, Was Protocol Routinely Followed?
    a. Yes
    b. No
10. During the COVID-19 Pandemic, Were All Intubations Treated As COVID Positive?
    a. Yes
    b. no

	% OF TOTAL RESPONSES
Prior to the COVID-19 Pandemic:	
Was any of the following difficult airway equipment already at the location and immediately available offsite? (choose all that apply)	
Basic Airway Equipment	92%
Video Laryngoscope	80%
Supraglottic Airways	82%
Rigid Stylet for ETT's	59%
Bougee/exchange catheters	59%
Manual Jet Ventilator	12%
Alternative ETT's	6%
Fiberoptic Bronchoscope	27%
ETT's with diameter < 7mm	57%
Cricothyrotomy Kit	31%
Is there a dedicated offsite airway intubation cart in your institution?	
Yes	75%
No	25%
During the COVID-19 pandemic:	
Was any of the following airway equipment already at the location and immediately available offsite? (chose all that apply)	

Basic Airway Equipment	93%
Video Laryngoscope	78%
Supraglottic Airways	67%
Rigid Stylet for ETT's	58%
Bougee/exchange catheters	51%
Manual Jet Ventilator	9%
Alternative ETT's	9%
Fiberoptic Bronchoscope	27%
ETT's with diameter < 7mm	51%
Cricothyrotomy Kit	8%

If no equipment is available offsite, which of the following modalities were used to obtain these devices? (check all that apply)

Offsite Airway Intubation Cart	42%
Dedicated Carry Bags	71%
Colleagues / Anesthesia Technicians	63%

For COVID-19 positive or presumed positive patients:

Was any of the following airway equipment used for intubation? (chose all that apply)

Basic Airway Equipment	72%
Video Laryngoscope	93%
Supraglottic Airways	23%
Rigid Stylet for ETT's	47%
Bougee/exchange catheters	21%
Manual Jet Ventilator	2%
Alternative ETT's	4%

Fiberoptic Bronchoscope	14%
ETT's with diameter < 7mm	19%
Cricothyrotomy Kit	7%
Dedicated offsite airway cart	14%

Is the following Personal Protective Equipment available for intubations (chose all that apply):

Gloves	95%
Fluid-resistant gowns	86%
Fluid-resistant shoe covers	72%
Hair covers	88%
Surgical masks	88%
Eye protection	93%
Face shields	81%
N95 masks	95%
Powered Air-purifying respirators (PAPRs)	51%
Respirators (P100)	16%

Who was the primary intubator? (chose all that apply)

Attending anesthesiologist	79%
Housestaff	58%
CRNA	33%
Other Provider or Service	5%

Does A Protocol Exist For All COVID-19 Intubations for the Anesthesia Department, Including Offsite and Anesthetizing Locations?	
Yes	88%
No	12%
If So, Was Protocol Routinely Followed?	
Yes	90%
No	10%
During the COVID-19 Pandemic, Were All *(offsite)* Intubations Treated As COVID Positive?	
Yes	69%
No	31%

AIRWAY MANAGEMENT 2

Difficult Airway Management in the ICU: Evaluating Performance of the Difficult Airway Response Team (DART) in the ICU – Six Years in Review

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INTRODUCTION: The University of Rochester Medical Center (URMC) Difficult Airway Response Team (DART) was created in September 2015 to reduce adverse outcomes during difficult airway management outside of the operating room. The DART is comprised of a multidisciplinary group of providers from five clinical departments, including Anesthesiology, ENT Surgery, Trauma Surgery, Critical Care Medicine, and Emergency Medicine[1]. The purpose of this study was to identify common presenting airway pathologies for DART activations and the advanced airway techniques used to address them[2].

METHODS: A single-institution retrospective chart review was performed for years 2015 to 2021 of all patients that required airway management by DART in the ICUs. Airway pathologies for DART activations and advanced airway techniques were analyzed to elucidate trends in difficult airway events in the ICUs. There was a total of 149 hospital-wide DART activations, with 43 (28.9%) activations occurring in the ICU setting. Analysis of cases demonstrated three large presenting airway pathologies: head and neck cancers, known difficult airway, and tracheostomy emergencies. Head and neck cancers represented 27.9% (n=12) activations. Known difficult airways represented 18.6% (n=8) activations. Tracheostomy emergencies represented 14% (n=6) activations. Advanced airway techniques used for these three presenting airway pathologies were analyzed in a case series.

RESULTS: Head and neck cancer case series analysis revealed that advanced airway techniques used were video laryngoscopy technique 50.0% (n=6), awake nasal fiberoptic intubation 25% (n=3), bedside tracheostomy by ENT 16.6% (n=2), and awake oral fiberoptic intubation 8.3% (n=1). Known difficult airway case series analysis showed that advanced airway techniques used included video laryngoscopy technique 62.5% (n=5), endotracheal tube (ETT) exchange with video laryngoscopy and bougie 12.5% (n=1), bedside tracheostomy 12.5% (n=1), and observation 12.5% (n=1). Analysis of advanced airway techniques used during tracheostomy emergencies showed as follows: tracheostomy device exchange in the ICU 33.3% (n=2), tracheostomy exchange in the OR 16.7% (n=1), intubation by video laryngoscopy technique 16.7% (n=1), fiberoptic tracheostomy exchange 16.7% (n=1), and ventilation through a bleeding tracheostomy during CPR without difficulty 16.7% (n=1). Analysis of all presenting airway pathologies and advanced airway techniques used in the ICU can be found in Tables 1 and 2 respectively.

CONCLUSION: The URMC DART Program established a multidisciplinary team capable of delivering high quality and safe patient-centered care for difficult airway management. DART has added significant value to the medical center and improved the safety of difficult airway management at out-of-OR locations such as the ICU. There were no airway related deaths, sentinel events or malpractice claims for difficult airway cases since the implementation of DART. Anesthesiologists secured the airway using primarily video laryngoscopy technique, ENT surgeons performed surgical airways for front-of-neck-airway access and tracheostomy device exchanges, and ICU providers participated in endotracheal tube (ETT) exchange using video laryngoscopy with airway exchange catheter (AEC). Head and neck cancers, known difficult airway cases, and tracheostomy emergencies represented a significant number of DART activations in the ICU. Case series analyses suggest that different airway pathologies were addressed with unique advanced airway techniques, which may have a role in equipment preparation and provider education. This also warrants future studies to investigate ways to predict and address difficult airways in patients with high-risk airway pathologies. Lastly, educational components of DART Program, Multidisciplinary Difficult Airway Course, and Emergency Medicine Difficult Airway Course, were implemented for senior residents and fellows from five DART departments with 100% participation.

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Presenting Airway Pathology	Cases	Percentage
Head & Neck Cancer	12	27.9%
Known Difficult Airway	8	18.6%
Tracheostomy Emergency	6	14.0%
Bleeding Airway	3	7.0%
Unexpected DA, Failed DL, VL, FOI	2	4.7%
Angioedema	2	4.7%
Migration of Nasotracheal Tube	1	2.3%
Esophageal Cancer	1	2.3%
Cervical Spine Injury	1	2.3%
Airway Edema	1	2.3%
Bilateral Vocal Cord Paralysis	1	2.3%
Retropharyngeal Abscess	1	2.3%
Vomiting and Aspiration	1	2.3%
Kyphosis & Chronic Neck Flexion	1	2.3%
Facial Trauma	1	2.3%
ETT Malfunction	1	2.3%

Table 1. Presenting airway pathologies in the ICU

Advanced Airway Technique Used	Cases	Percentage
Video Laryngoscopy Technique	21	48.8%
Awake Nasal Fiberoptic Intubation	5	11.6%
Bedside Tracheostomy	3	7.0%
Awake Oral Fiberoptic Intubation	2	4.7%
Tracheostomy Device Exchange	2	4.7%
Direct Laryngoscopy after Unsuccessful Video Laryngoscopy	2	4.7%
Observation	2	4.7%
Asleep Oral Fiberoptic Intubation	1	2.3%
Fiberoptic Intubation via Supraglottic Airway Device	1	2.3%
Tracheostomy Device Exchange in OR	1	2.3%
Fiberoptic Tracheostomy Device Exchange	1	2.3%
ETT Exchange with Video Laryngoscopy and Bougie	1	2.3%
ETT Exchange with Video Laryngoscopy and AEC	1	2.3%

Table 2. Advanced airway techniques used

AIRWAY MANAGEMENT 3

Emergency Airway Management in a Tertiary Trauma Centre: A 1-year Prospective Longitudinal Study

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INTRODUCTION: Emergency orotracheal intubation is a life-saving procedure commonly performed in the Intensive Care Unit (ICU) and Emergency Department (ED) as a part of resuscitation of critically ill or injured patients. Orotracheal intubation is typically accomplished easily and without incident, however, when complications do occur they can be devastating including permanent neurologic disability and death.

METHODS: We performed a single centre, prospective, observational study, including all adult patients (>17 years old) that were intubated by Emergency Medicine or Critical Care Medicine teams. We collected data on all consecutive emergent orotracheal intubations over a seven-month period at a tertiary care trauma centre. The primary outcome was the first pass success rate with emergency intubations. Secondary outcomes were to identify factors associated with successful first pass intubation and factors associated with adverse events peri-intubation. Descriptive statistics are reported as mean and standard deviation or frequency and percent. Univariate logistic regression models were used to explore the unadjusted relationships between each predictor and the odds of a failed intubation attempt, hypoxemia, and hypotension. Results are presented as odds ratios and their 95% confidence intervals and p-values.

RESULTS: In a 7-month period, there were 416 emergency intubations and a first pass success rate of 73.08%. First pass success rates varied widely between locations; ward intubations were the lowest with 57.5%, followed by 66.1% in the ICU's and 84.3% in the Emergency Department. Equipment used also varied significantly by location; direct laryngoscopy was used most frequently on the ward at 89.4% and least in the Emergency Department at 34.9%. Physiologically difficult airways, those associated with time pressure based on pre-existing patient characteristics, were associated with first pass success of 64.4%.

CONCLUSION: First pass success rates vary widely between locations within the hospital and are less than published numbers from similar institutions. We are re-vamping ICU protocols to improve first pass success rate.

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AIRWAY MANAGEMENT 4

Influence of I-gel® introduction on intraoperative respiratory disturbances: A retrospective cohort study

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INTRODUCTION: The laryngeal mask airway (LMA®)-Unique™ and i-Gel® are safe and effective supraglottic device (SGD) alternatives to tracheal intubation in a variety of surgeries[1]. The i-Gel® is a second-generation device with superior design attributes and is associated with greater ease of insertion, greater accuracy in positioning over the glottic opening, a faster time to placement, reduced gastric insufflation, and a lower incidence of postoperative nausea and vomiting in prospective randomized studies[2,3]. Despite the reported benefits of the i-Gel®[4] from multiple RCTs, systematic analyses of real-world safety with their introduction into practice are largely lacking. We hypothesized that the introduction of i-Gel® to a large university anesthesia practice would be associated with a decreased risk of intraoperative adverse respiratory events.

METHODS: This is a retrospective cohort study that analyzed adult surgical patients who required general anesthesia with SGD between January 2006 to June 2020 with available information for exposure and outcome at Beth Israel Deaconess Medical Center, Boston, Massachusetts. Patients with an American Society of Anesthesiologists (ASA) physical status classification >IV and patients who were intubated for procedural requirements were excluded. Our primary exposure was a binary variable that classified patients according to use of (LMA®)-UniqueTM or i-Gel®. The primary outcome of intraoperative respiratory disturbances (IRDs) was defined as a composite of occurrence of prolonged intraoperative desaturation (defined as a cohering episode of more than two minutes of hemoglobin oxygen saturation <90%), hypocapnia (<25mmHg EtCO2), or hypercapnia (> 50mmHg EtCO2), high driving pressures (>30 cmH2O), low tidal volumes (median tidal volume over surgery duration <4 ml/kg), multiple attempts of insertion or SGD failure, defined as the requirement to abandon the device and proceed to endotracheal intubation (emergency intubation). We conducted multivariable logistic regression analysis adjusted for a priori defined factors including patient demographics, comorbidities, and intraoperative factors to evaluate the association of the LMA®-Unique™ versus the i-Gel® with the occurrence of IRDs. In an exploratory attempt, we tested the effect modification of Score for Prediction of Postoperative Respiratory Complications (SPORC)[5] on the association between SGD type and IRDs.

RESULTS: A total of 37,339 cases were included in the final study cohort as noted in Figure 1. Patient demographics and characteristics by the occurrence of IRDs and by the type of SGD are provided in Table 1 and Table 2, respectively. The i-Gel® was used in 6,387 cases (17.1%), while the LMA®-Unique™ was used in 30,952 cases (82.9%), and a total of 11,012 (29.5%) patients suffered from IRDs. 9,698 (31.3%) IRDs occurred with the use of the LMA®-Unique™ as compared to 1,314 (20.6%) with the i-gel®. Our primary analysis revealed that the use of the i-Gel® during general anesthesia was associated with a decreased risk of IRDs (adjusted odds ratio 0.46; 95% Confidence Interval [CI] 0.43 to 0.50, p<0.001) when compared to the LMA®-Unique™, corresponding to a decrease in adjusted risk difference by 12% (95% CI -13.2 to -10.9, p<0.001). The association between the type of SGD used and IRDs was significantly modified by the risk of respiratory complications score (SPORC), (p-for-interaction<0.001). In patients with low SPORC (<7), i-Gel® was associated with reduced risk of IRDs (aOR 0.44, 95%CI 0.1 to 0.49, p<0.001), corresponding to a decrease in adjusted risk difference by 12.5% (95%CI -13.6 to -11.4, p<0.001), while in patients with high SPORC (≥7), the modifying effect was not significant (p=0.5). Table 3 represents the estimated risks of IRDs among these four groups of patients in our cohort.

CONCLUSION: The i-Gel® was associated with a reduced risk of IRDs when compared to the LMA®-Unique™ during use for general anesthesia in adult patients. This outcome difference was more pronounced in patients with a low preoperative risk of developing respiratory complications, suggesting a possible mediating role of dynamic events such as intraoperative laryngospasm.

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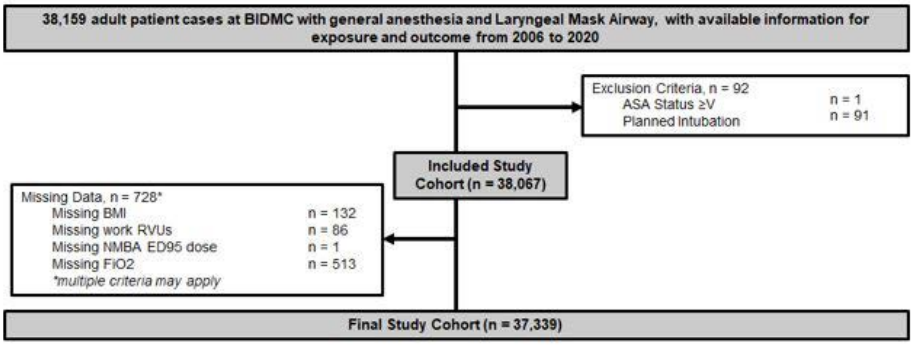

Figure 1. Study flow diagram.

ASA: American Society of Anesthesiologists; BIDMC: Beth Israel Deaconess Medical Center; BMI: Body Mass Index; ED95: median effective dose required to achieve a 95% reduction in maximal twitch response from baseline; FiO2: Fraction of inspired oxygen; NMBA: neuromuscular blocking agents; work RVUs: work Relative Value / Units.

Table 1. Patient demographics and characteristics by the occurrence of intraoperative respiratory disturbances (IRDs).

Characteristics	No IRDs	IRDs	Standardized difference
	N = 26,327	N = 11,012	
Age, years	52.4 ± 16.4	51.2 ± 16.9	0.073
Sex			0.042
Male	11,935 (45.3%)	5,220 (47.4%)	
Female	14,392 (54.7%)	5,792 (52.6%)	
Body mass index, kg/m^2	27.1 ± 5.4	27.2 ± 5.8	-0.031
ASA physical status classification			-0.063
I	5,597 (21.3%)	2,687 (24.4%)	
II	14,748 (56.0%)	5,098 (46.3%)	
III	5,642 (21.4%)	2,954 (26.8%)	
IV	340 (1.3%)	273 (2.5%)	
Duration of surgery, minutes	73.0 (55.0 - 104.0)	72.0 (53.0 - 100.0)	0.059
Work relative value units	7.0 (4.6 - 9.6)	5.4 (4.0 - 8.0)	0.213

Mean arterial pressure below 55mmHg, minutes	0.0 (0.0 - 1.0)	0.0 (0.0 - 2.0)	-0.031
Total vasopressor dose, mg norepinephrine equivalents	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	-0.030
Packed red blood cells, units			
0	26,291 (99.9%)	11,000 (99.9%)	0.007
1	26 (0.1%)	8 (0.1%)	
2	8 (0.0%)	4 (0.0%)	
>2	2 (0.0%)	0 (0.0%)	
Crystalloid and colloid infusions, ml	700.0 (500.0 - 900.0)	700.0 (500.0 - 1000.0)	-0.040
Short-acting opioids, mg oral morphine equivalents	18.8 (6.3 - 25.0)	25.0 (12.5 - 37.5)	-0.236
Long-acting opioids, mg oral morphine equivalents	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.088
Number of patients that received NMBA	242	863	-0.343

NMBA ED_{95} dose[a], mg in patients that received NMBA	1.35 (0.9 - 1.9)	1.5 (0.9 - 2.2)	-0.081
MAC of volatile agents and nitrous oxide	1.0 (0.8 - 1.1)	0.9 (0.6 - 1.1)	0.311
Number of patients that received neostigmine	94	448	-0.254
Neostigmine, mg/kg in patients that received neostigmine	3 (2.0 - 4.0)	3 (2.5 - 4.0)	-0.305
Charlson Comorbidity Index	0.0 (0.0 - 2.0)	0.0 (0.0 - 2.0)	-0.124
SPORC ≥7	413 (1.6%)	383 (3.5%)	-0.122
Smoking	2,077 (7.9%)	938 (8.5%)	-0.023
COPD	827 (3.1%)	749 (6.8%)	-0.169
CHF	800 (3.0%)	440 (4.0%)	-0.052
FiO_2	59.8 ± 17.4	63.1 ± 22.2	-0.168

Data are expressed as frequency (prevalence in %), mean ± standard deviation, or median (interquartile range [25th-75th percentile]).

IRDs: intraoperative respiratory disturbances; ASA: American Society of Anaesthesiologists; COPD: chronic obstructive pulmonary disease; CHF: Chronic heart failure; NMBA: neuromuscular blocking agents; FiO_2: fraction of inspired oxygen; MAC: minimum alveolar concentration; SPORC: Score for Prediction of Postoperative Respiratory Complications.

a: ED95 dose of neuromuscular blocking agents (NMBA): median effective dose required to achieve a 95% reduction in maximal twitch response from baseline.

Table 2. Patient demographics and characteristics by the use of LMA®-Unique™ versus i-Gel®.

Characteristics	LMA®-Unique™	i-Gel®
	N=30,952	N=6,387
Age, years	51.4 ± 16.5	55.2 ± 16.7
Sex		
Male	14,258 (46.1%)	2,897 (45.4%)
Female	16,694 (53.9%)	3,490 (54.6%)
Body mass index, kg/m^2	27.0 ± 5.4	27.7 ± 6.0
ASA physical status classification		
I	7,382 (23.8%)	902 (14.1%)
II	16,640 (53.8%)	3,206 (50.2%)
III	6,457 (20.9%)	2,139 (33.5%)
IV	473 (1.5%)	140 (2.2%)
Duration of surgery, minutes	72.0 (54.0 - 102.0)	76.0 (56.0 - 106.0)
Work relative value units	6.7 (4.3 - 8.8)	6.4 (4.5 - 9.2)
Mean arterial pressure below 55mmHg, minutes	0.0 (0.0 - 2.0)	0.0 (0.0 - 0.0

Total vasopressor dose, mg norepinephrine equivalents	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)
Packed red blood cells, units		
0	30,915 (99.9%)	6,376 (99.8%)
1	26 (0.1%)	8 (0.1%)
2	10 (0.0%)	2 (0.0%)
>2	1 (0.0%)	1 (0.0%)
Crystalloid and colloid infusions, ml	700.0 (500.0 - 1000.0)	600.0 (500.0 - 800.0)
Short acting opioids, mg oral morphine equivalents	18.8 (6.3 - 25.0)	25.0 (0.0 - 25.0)
Long acting opioids, mg oral morphine equivalents	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)
NMBA ED95[a] dose, mg	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)
MAC of volatile agents and nitrous oxide	1.0 (0.8 - 1.1)	0.9 (0.7 - 1.1)
Neostigmine, mg	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)
Respiratory rate	14.0 (11.0 - 17.0)	12.0 (10.0 - 15.8)
Charlson Comorbidity Index	0.0 (0.0 - 2.0)	0.0 (0.0 - 2.0)
SPORC ≥7	596 (1.9%)	200 (3.1%)

Smoking	2,006 (6.5%)	1,009 (15.8%)
COPD	1,148 (3.7%)	428 (6.7%)
CHF	900 (2.9%)	340 (5.3%)
FiO_2	59.5 ± 19.0	66.9 ± 18.0
Hypoxemia for more than two consecutive minutes	494 (1.6%)	117 (1.8%)
Tidal volume, ml/kg ideal body weight	5,905 (19.1%)	836 (13.1%)
Driving pressure >30 cmH_2O	69 (0.2%)	6 (0.1%)
$EtCO_2$ <25 mmHg or >50 mmHg	4,399 (14.2%)	646 (10.1%)
More than one intubation attempt	633 (2.0%)	37 (0.6%)
Emergency intubation	622 (2.0%)	107 (1.7%)

Data are expressed as frequency (prevalence in %), mean ± standard deviation, or median (interquartile range [25th-75th percentile]).

ASA: American Society of Anaesthesiologists; COPD: chronic obstructive pulmonary disease; CHF: Chronic heart failure; NMBA: neuromuscular blocking agents; $EtCO_2$: end-tidal carbon dioxide; *FiO_2: fraction of inspired oxygen; MAC: minimum alveolar concentration; SPORC: Score for Prediction of Postoperative Respiratory Complications.*

a: ED95 dose of neuromuscular blocking agents (NMBA): median effective dose required to achieve a 95% reduction in maximal twitch response from baseline.

Table 3. Estimated risk of IRDs in %.

	I-gel®	LMA®-Unique™	p-value
SPORC <7	0.19 (0.18-0.20)	0.31 (0.31-0.32)	<0.001
SPORC ≥7	0.33 (0.26-0.41)	0.31 (0.26-0.35)	<0.001

Table 3. Adjusted, estimated risk of intraoperative respiratory disturbances (IRDs) for patients with a low versus high risk of postoperative respiratory complications (as defined by a Score for Prediction of Postoperative Respiratory Complications [SPORC] ≥7) with the use of I-gel® versus LMA®-Unique™.

AIRWAY MANAGEMENT 5

Introducing a New Dimension for Assessing Central Airway Pathology in Mucopolysaccharidosis type-IVA: 3D Reconstruction, 3D Printing and Virtual Endoscopy – Advanced Airway Analytics

Johnny Kenth[1], Iain Bruce[2], Robert Walker[3], Collin Butler[4], Richard Hewitt[4], Reema Nandi[4]

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INTRODUCTION: Three-dimensional reconstruction (3D-recon), 3D printing and virtual endoscopy (VE) — collectively defined as Advanced Airway Analytics (AAA), have expanded rapidly in the past decade with a broad uptake in healthcare and beyond. There is currently a paucity of investigatory and validation studies within the anaesthetic literature for AAA. The Mucopolysaccharidosis (MPS) are a group of rare, lysosomal-storage-disease that feature profound, central airway pathology. MPS-IVA is characterised by tracheal tortuosity, 'buckling' and narrowing that leads to progressive, multi-level airway obstruction and respiratory failure. Current modalities for imaging the large airways including plain x-ray films, computerised-tomography (CT) and magnetic-resonance-imaging (MRI). The modalities of imaging remain suboptimal for assessing complex airway pathology as they fail to accurately delineate the true character of the aberrations in anatomy and consequently plan for cognisant airway management during anaesthesia.

METHODS: Objective–To ascertain how 3D-tracheal reconstruction, 3D prints and VE compare to traditional 2D CT images and fibreoptic airway endoscopy respectively. Methods: Segmentation of CT neck and thorax images were undertaken from five children with MPS type-IVA. This yielded 3D-reconstructions of the airway (saved as stereolithography-STL files) and dynamic VE (MPEG-4 video). 3D-recons were then 3D-printed to create life-size models. The VE were then compared to actual airway endoscopy undertaken during general anaesthesia. AAA was validated qualitatively by a panel of experts in MPS airway, and quantitatively by assessing limits of agreement between measurements of radial tracheal calibre from CT and 3D modelling; assessing Bland-Altman plots and assessing mean difference and 95% limits of agreement.

RESULTS: 3D-reconstructions offered superior imaging to traditional 2D CT imaging (Figures 1&2). Additionally, VE was found to be comparable to traditional endoscopy and allowed for the demarcation of airway pathology beyond the point of critical airway narrowing, thus providing visualisation of distal structures when traditional rigid or flexible endoscopy would not be possible, or considered safe. Moreover, airway narrowing could be assessed from multiple perspectives, including dynamic airway assessment. There was no significant difference between measurements of tracheal dimensions when assessed by Bland-Altman analysis (bias: 0.03; 95% Limits of Agreement: -0.105-0.173) (Figure 3).

CONCLUSION: Three-dimensional reconstruction (3D-recon) including 3D-printing and VE are an innovative, non-invasive, malleable and easily accessible technology that our own practice has found to be both safe, reliable and reproducible. VE offers a safe, non-invasive alternative to traditional endoscopy under general anaesthesia, in an otherwise very high-risk patient cohort.

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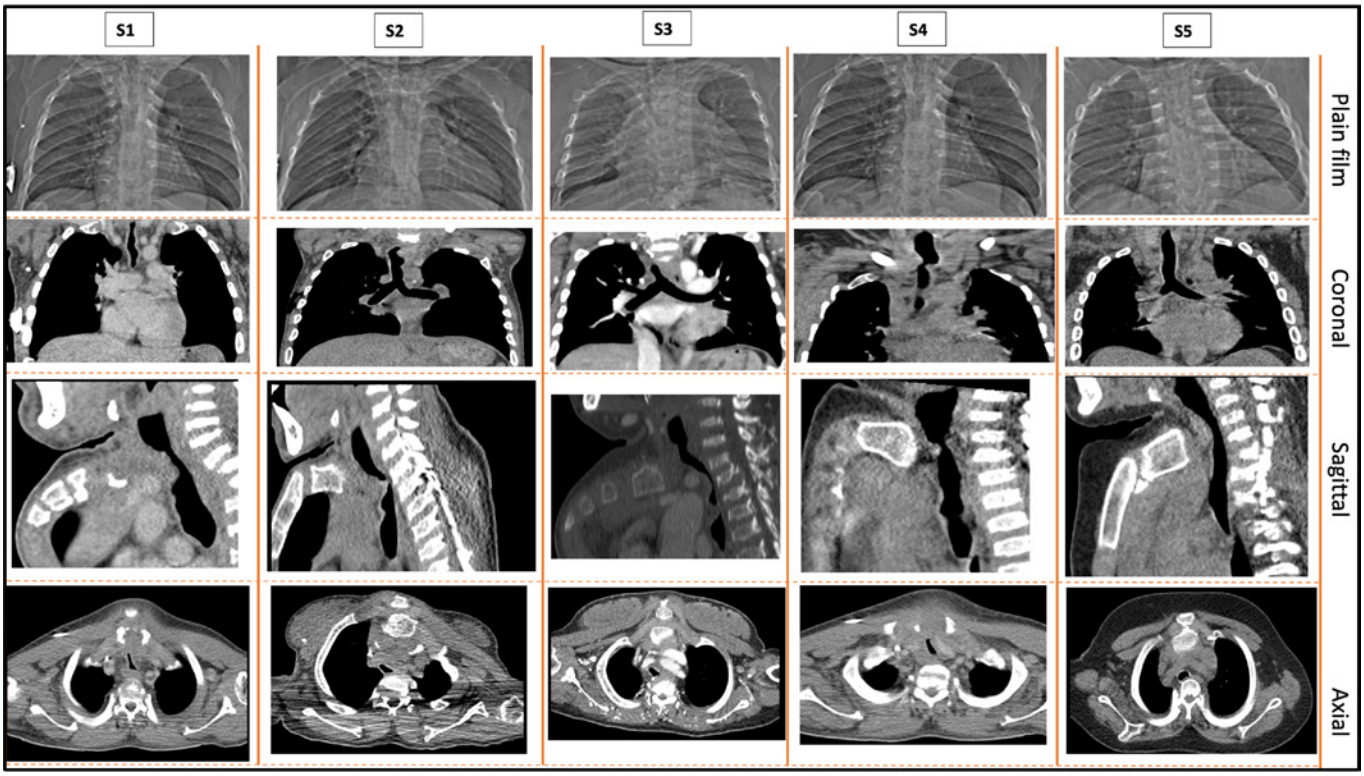

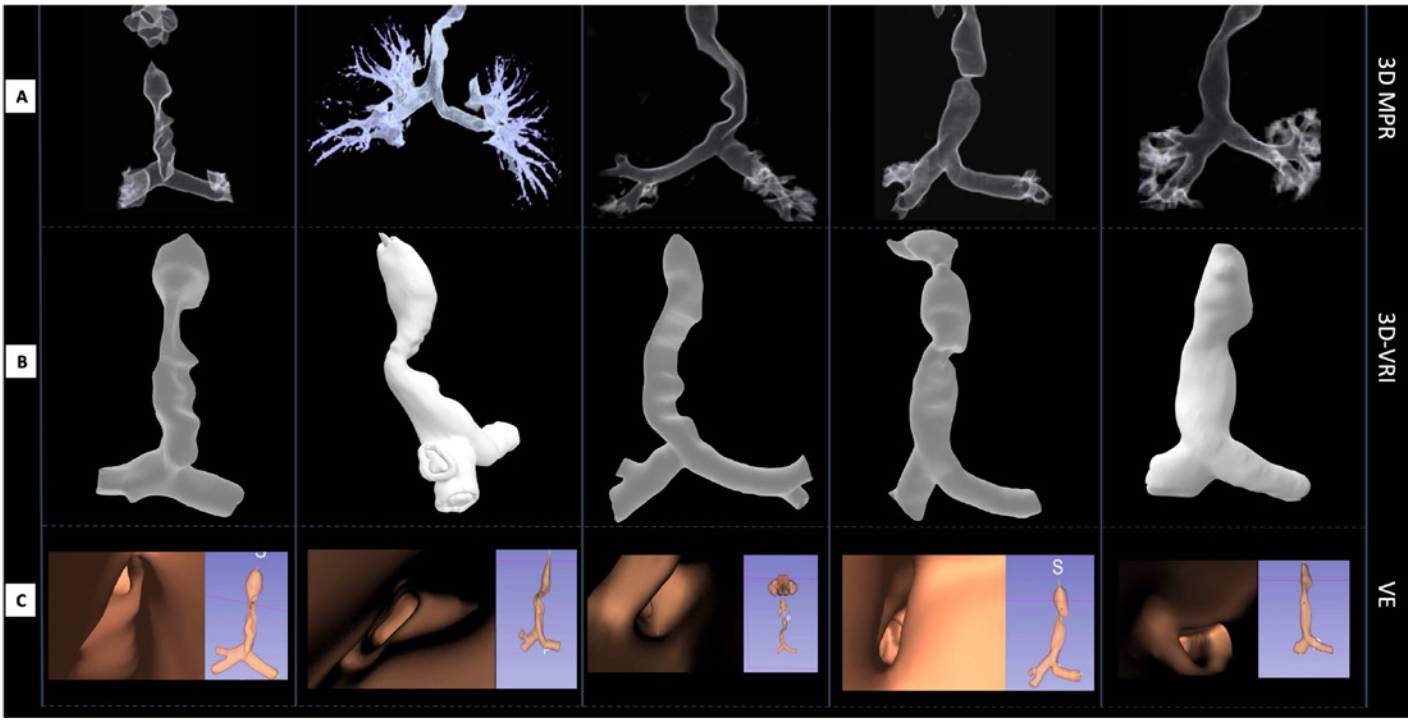

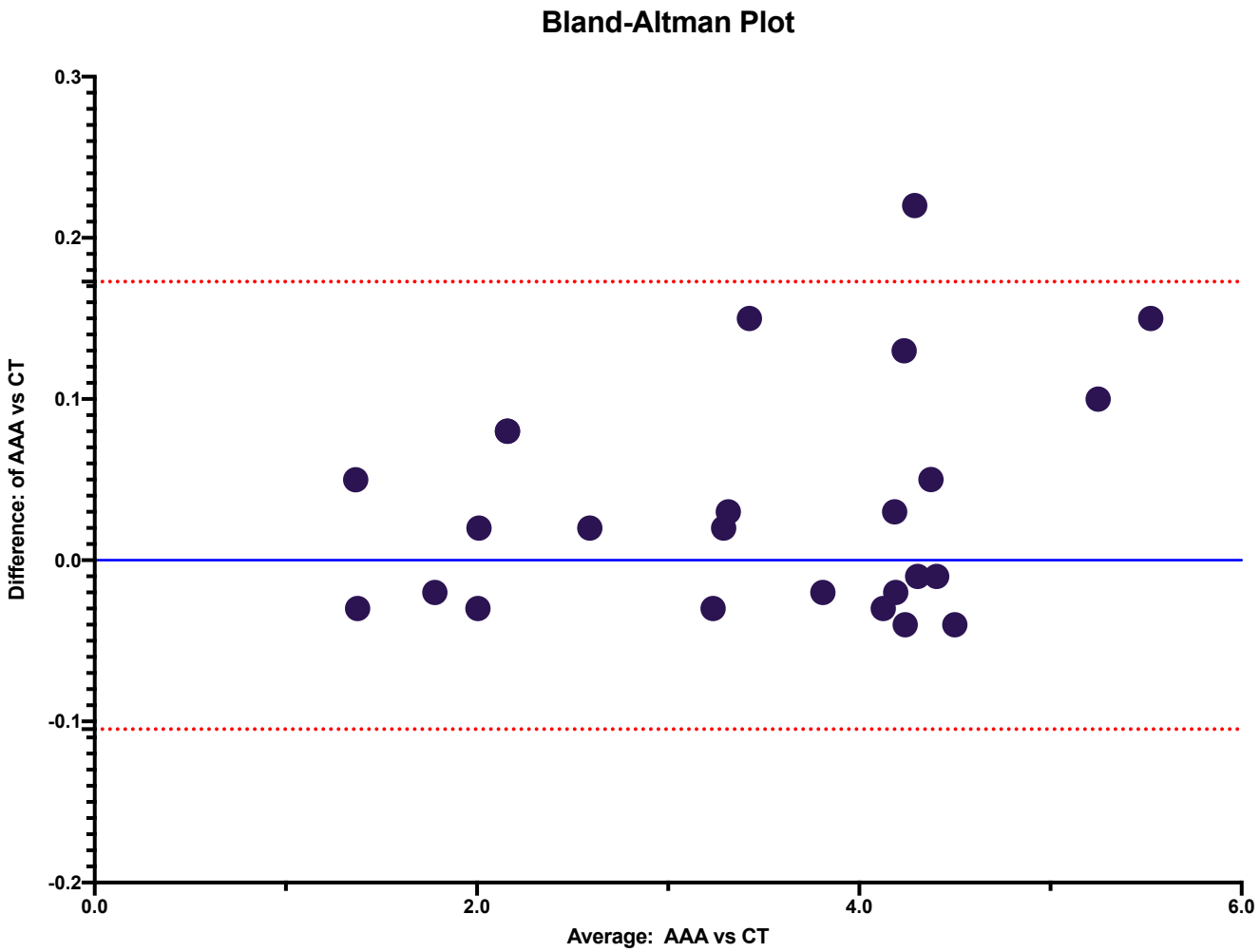

AIRWAY MANAGEMENT 6

Increasing Faculty Competency in Pediatric Fiberoptic Intubation: A Quality Improvement Project

Raj Subramanyam[1], Ayodele Oke[2], Benjamin Bruins[3], Annery Garcia-Marcinkiewicz[4]

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INTRODUCTION: Personnel performing pediatric fiberoptic intubation (FOI) is on the decline due to availability of videolaryngoscopes and the spread of pediatric anesthesia to many non operating room locations where sedation or natural airway is provided. This poses a challenge and potential threat to patient safety when an emergency situation arises or in case of a difficult airway. Continued maintenance of fiberoptic skills is imperative to be proficient. Our hospital cares for complex airway cases in syndromic and non syndromic children. Most faculty take overnight call and serve as a resource for emergency airway support. Previous projects have focused on anesthesia residency training.1 We targeted pediatric anesthesia faculty in this quality improvement (QI) project. The SMART aim was to increase the percentage of faculty completing 5 FOI from 50% to 90% by June 2022 in children.

METHODS: The project was QI and did not require IRB approval. The Key Driver Diagram is shown in Figure 1. The setting is a large tertiary pediatric center with 60 board certified pediatric anesthesiologists. With approximately 45,000 anesthetics per year, there was ample opportunity for FOI. The FOI was done either for emergency or elective airway securement for procedures requiring anesthesia. Data was tracked in REDCap. The primary outcome was a process measure of percentage of faculty completing the FOI. Analysis was done using the Institute for Healthcare Improvement (IHI) run chart template 2.

RESULTS: Baseline data showed only 50% faculty completed ≥ 5 FOI over a year. All faculty participated in this QI project. There were 3 PDSA cycles tested. PDSA#1 involved incorporation of airway proficiency as a quality incentive metric. PDSA#2 was a hands on workshop provided by a core team of 7 faculty from the airway group. This group conducts airway related simulation, education and research. PDSA#3 included a series of airway educational videos created by the airway team on tips and tribulations of airway management. Figure 2 shows that the primary measure, percentage of faculty completing FOI increased over time with a special cause variation as indicated by 8 points above the median.

CONCLUSION: FOI completion amongst pediatric anesthesia faculty was improved using a QI approach using PDSA methodology. We expect to see a second special cause variation with the median above the goal. The spread and sustain plan will be introduced. Hospitals requiring a similar improvement in their practice can benefit from this QI project.

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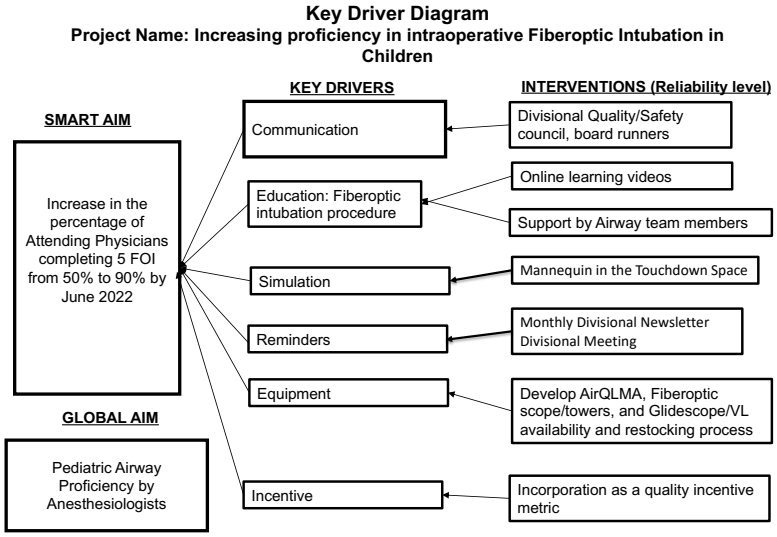
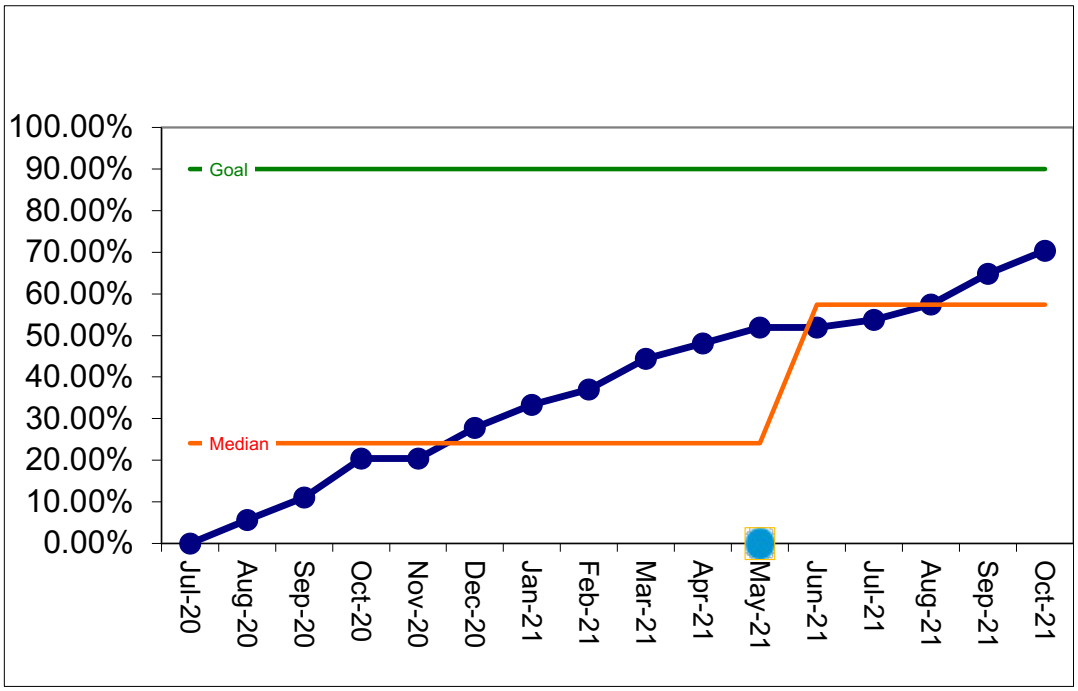
Figure 1: Key Driver Diagram



Key Driver Diagram showing the primary process measure, global aim, key drivers and interventions. The interventions will affect the key drivers and in turn the primary SMART aim as shown by the direction of the arrows.

Figure 2: Run Chart



Legend: This is a Run Chart with months on the x-axis and the percentage of pediatric anesthesia faculty who have completed more than 5 fiberoptic intubations on the y-axis. The blue line indicates the data plotted over time. The red line is the median. The deflection of the red line in May 2021 indicates a special cause variation noted by 8 points above the median. The green line indicates the goal line.

AIRWAY MANAGEMENT 7

Endotracheal Intubation in Mucopolysaccharidosis type IVA: A Single Institutional Experience

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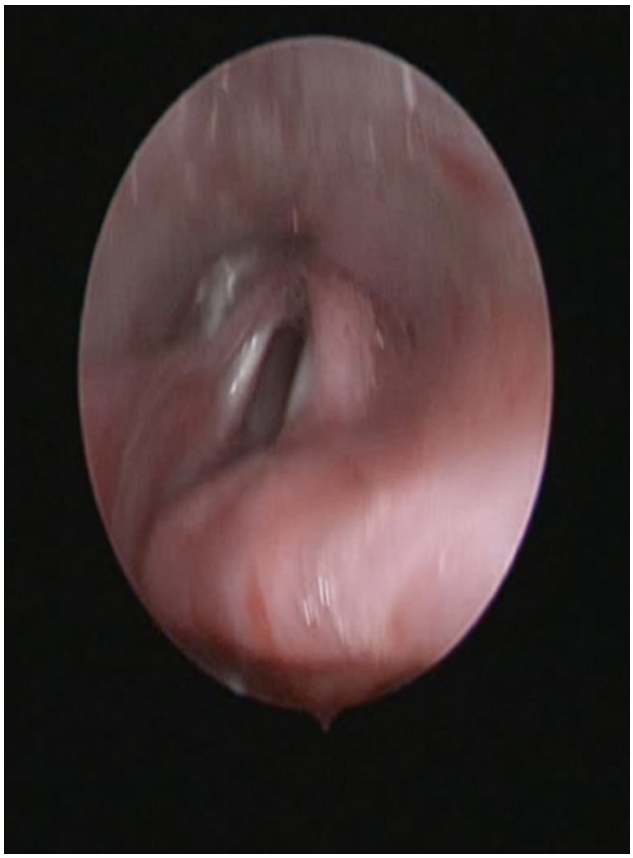
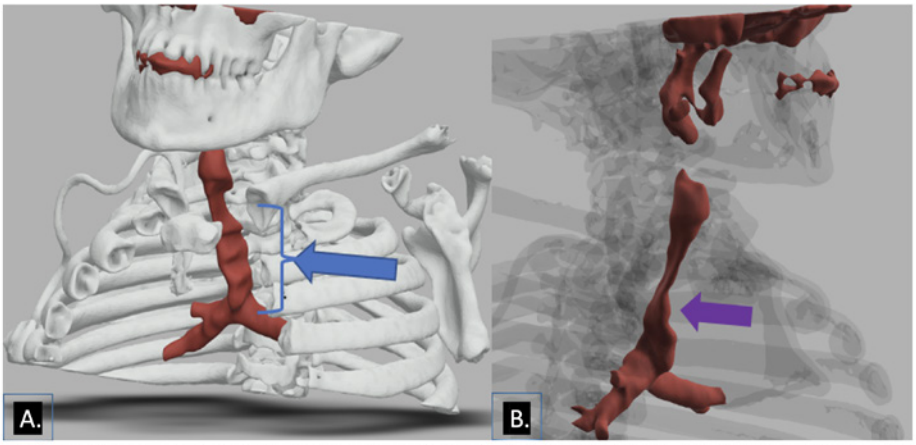
INTRODUCTION: Mucopolysaccharidosis type IVA (MPS IVA; Morquio Syndrome [OMIM #253000]) is a rare, autosomal recessive lysosomal storage disorder (LSD) that is caused by a deficiency of the enzyme N-acetyl-galactosamine-6-sulfatase - GALNS[1,2]. Whilst there is heterogeneity in the context of severity and phenotype, patients with MPS IVA rarely survive past their second decade of life[1-3]. The majority of children with MPS IVA cease growing before the age of eight years, are wheelchair-bound by their teenage years and often require multiple anaesthetics for surgical interventions throughout their lifetime[1,3-5]. Airway obstruction and respiratory failure remain the leading cause of death in this cohort[1,3,5]. Intubation and extubation can be particularly challenging in patients with MPS IVA due to limited mouth opening, short neck length and a reduced range of motion, large tongue, micrognathia, subglottic narrowing, and atlanto-axial instability (due to odontoid hypoplasia and ligamentous laxity). Airway obstruction is often multilevel, with upper airway obstruction caused by adenotonsillar hypertrophy secondary to glycosaminoglycan (GAGs) infiltration (Figure. 1). Commonly, there is also significant tracheal narrowing, deviation and buckling that is pathognomonic for the condition (Figure. 2). Recently, global, consensus based multidisciplinary guidance by Akyol et al (2019) recommend the use of videolaryngoscopy (VL) to aid intubation in all patients with MPS IVA. However, there remains a paucity of reporting of endotracheal intubation grade and technique (including adjuncts) in patients with MPS IVA undergoing anaesthesia.

METHODS: A retrospective chart review was undertaken from 2009-2019, at a single institution (highly specialised tertiary referral centre for paediatric inherited metabolic diseases) to ascertain the frequency of surgery, difficulty in endotracheal intubation, as well as the techniques and modality for airway management during anaesthesia.

RESULTS: 16 patients with MPS IVA were identified from our institutional central database, that had undergone anaesthesia. The median age was 13.5 (range: 6-17) years. The mean number of anaesthetics per individual was 6 (range: 4-9). 13/16 patients were either currently or had previous administration of enzyme replacement therapy with elosulfase alfa (Vimizim®). There was an absence of genotype-phenotype correlation, There was ubiquitous presence of both restrictive and obstructive airway disease in all patients, with 11/16 patients having symptoms of obstructed sleep apnoea, 9/16 patients having undergone adenotonsillectomy, 7/16 having macroglossia on clinical examination and 14/16 having evidence of tracheal narrowing on radiological imaging. We ascertained that Cormack-Lehane airway grading varied amongst individuals, with four individuals being grade 1, eight being grade 2 and four being grade 3. VL was the preferred modality for endotracheal intubation in most individuals (12/16), with three cases of failure to secure the airway with conventional, direct laryngoscopy was then successful with VL. Interestingly, in two individuals that had grade 1 and 2b view during direct laryngoscopy, the anaesthesiologist were unable to secure the airway due to severe subglottic stenosis and the patient was ventilated via a laryngeal mask airway as a rescue measure.

CONCLUSION: Patients with MPS IVA may frequently present for surgery and present a number of challenges to anaesthesiologists in the context of airway management. Even when airway grading appears reasonable at direct laryngoscopy, the presence of subglottic stenosis can preclude successful endotracheal intubation. We thus recommend that patients with MPS IVA should undergo pre-anaesthesia airway imaging and indirect, flexible fibre-optic airway assessment, to allow for dynamic airway assessment, planning and risk stratification. Moreover, anaesthesia for MPS IVA should be undertaken at specialised centres by experienced anaesthesiologists.





Legend: 3D rendered tracheal reconstructions in a patient with severe, end-stage MPS IVA. Note the multi level airway tortuosity, obstruction with narrowing and buckling causing a 'ribbon like' appearance of the trachea (blue arrow)that is a classical hallmark feature of the disease. The narrowest segment (purple arrow) is 2mm and at the level of the tracheal inlet.

Table 1. Baseline Demographics

Patient	Presentation	Age at Diagnosis	Consan-guinity	Sex	Genetics	Age ERT started	OSA	Adeno-tonsillectomy	BIPAP	Tracheal Stenosis	Macro glossia
ERT treated subjects											
A	Difficulty walking	37	No	F	Heterozygous p.(Gly155Arg)	43	No	No	No	Yes	No
B	Gibbus	27	No	M	Homozygous p.(A291T)	112	Yes	Yes (72 , 147)	Yes	Yes	Yes
C	Gibbus	22	N/A	M	Not recognised gene	39	Yes	(41)	No	No	Yes
D	Difficulty walking	18	No	M	Homogenous p.(w141x)	78	Yes	No	Yes	Yes	No
E	Difficulty walking, scoliosis	30	N/A	F	N/A	67	No	No	No	Yes	Yes
F	Chest deformity	43	No	F	Heterozygous p.(arg251Ter)	69	Yes	Yes (121)	No	Yes	No
G	N/A	132	No	M	Homozygous p.(A291T)	78	Yes	Yes (70, 142)	Yes	Yes	No
H	N/A	35	N/A	F	c.423-11_425del14/ c.860C>T	38	Yes	Yes (32, 51, 89)	No	Yes	No
I	Family history, chest deformity	31	No	M	Hetero/I113F, Y240C	183	Yes	Yes (36)	No	Yes	Yes
J	Difficulty walking	131	Yes	F	Homozygous p. (His166Arg)	175	Yes	No	No	Yes	No
K	Gibbus	14	No	M	Heterogenous p. (I113F) and p. (R386H)	43	Yes	Yes (35)	No	No	Yes
L	Difficulty walking	73	No	F	Heterozygous p.(tyr254cys) and p. (Gln311Pro)	108	No	No	No	Yes	No
M	Gibbus, stiff joints	33	Yes	F	Homozygous p.(A291T)	129	No	Yes (121)	No	Yes	Yes
Non ERT treated subjects											
N	Difficulty walking	29	No	M	Homogenous p.(Ser264Asn)	N/A	Yes	No	Yes	Yes	No
O	Growth, skeletal dysplasia	96	N/A	F	Homogenous p. (Gly116Val)	N/A	Yes	Yes (134)	Yes	Yes	Yes
P	Difficulty walking	161	N/A	F	Heterozygous p.901G>T (Gly301Cys)	N/A	No	No	No	Yes	No

Table 1. above illustrates the baseline demographics of the 16 subjects, including age (months) at diagnosis, consanguinity, what the presenting symptom was, the genetic mutation identified, the date when ERT therapy commenced (if applicable). We also record whether the child was diagnosed with obstructive sleep apnoea (OSA), if they had undergone an adenotonsillectomy (age at surgery in months) and the whether the child had been instituted on non-invasive, bilevel ventilation (BIPAP). * All ages are reported in months.

Table 2. Airway Grading

Patient	Airway Grade Cormack-Lehane	Intubation Technique
A	Grade 2	Glidescope - ET
B	Grade 1	Conventional, Difficult ET (tortuous trachea) -> LMA
C	Grade 2	Glidescope - ET
D	Grade 2b	Glidescope - ET (tortuous trachea) -> LMA
E	Grade 1	Glidescope - ET
F	Grade 3	Conventional, , Boogie - ET
G	Grade 2	Glidescope - ET (tortuous trachea)
H	Grade 1	Glidescope - ET
I	Grade 2	Glidescope - ET
J	Grade 1	Conventional, ET
K	Grade 2	Glidescope - ET
L	Grade 3	Conventional, , Boogie - ET
M	Grade 2	Glidescope - ET
N	Grade 3	Glidescope - ET
O	Grade 2b	Glidescope + bougie - ET (tortuous trachea)
P	N/A	Glidescope + bougie - ET (tortuous trachea)

AIRWAY MANAGEMENT 8

Factors associated with emergency airway management and difficult intubation in hospitalized patients outside of the operating room at a cancer treatment center

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INTRODUCTION: There is limited data published on why emergency non-operating room difficult tracheal intubations are reported with higher incidences (6-23%) than in the operating room (OR) setting (0.43-5.8%).[1-5] More than two intubation attempts, Cormack-Lehane (C-L) grade III or IV laryngoscopic view,[6] and non-OR location has been associated with increased airway complications.[1] Some potential reasons for increased difficulty encountered during emergency intubations outside of the OR that have been proposed include the need to act quickly, patient unfamiliarity, unstable condition, lack of optimal/familiar equipment, suboptimal positioning, and airway contamination.[1-5] The objective of this study was to determine factors associated with emergency airway management and difficult intubation for hospitalized patients outside the OR at a cancer treatment center.

METHODS: After institutional review board approval and waiver of informed consent was obtained, non-OR emergency tracheal intubation procedure notes were reviewed from May 6, 2016 to May 6, 2019 prior to COVID-19 pandemic intubation protocol changes (routine use of videolaryngoscopy, personal protective equipment, etc.) at a cancer treatment center. A difficult intubation (DI) was catalogued when C-L grade III or IV laryngoscopic view and/or greater than 2 attempts at intubation was documented. A difficult airway (DA) was cataloged when DI, advanced airway device (AAD) use, and/or need for surgical airway was documented. Cases with missing data, endotracheal tube exchanges, patients under 18 years old, and non-anesthesiologist staff were excluded. Fisher's exact test was used to evaluate categorical variables. Wilcoxon's rank sum test was used to compare continuous variables. Univariate and multivariable logistic regression model was used to examine associations. P-value <0.05 was considered significant.

RESULTS: There were 796 cases reviewed with difficult intubation and difficult airway incidence of 9.7% [95% CI, 0.078-0.119] and 30.4% [95% CI, 0.273-0.337], respectively. Difficult intubation was associated with ongoing CPR (p=0.0059), resident involvement (p=0.0484), head/neck radiation (p<0.0001), head/neck cancer (p<0.0001), and head/neck surgery (p=0.0013) with univariate analysis. Multivariate analysis revealed that difficult intubation was associated with CPR only (OR 3.366; 95% CI, 1.395-8.127, p=0.0069). No association was found between difficult intubation and age, sex, BMI, induction drug use, or 30-day mortality. Difficult airway encounter with advanced airway device use was found to be associated with patient history of head/neck radiation (p<0.0001), larger BMI (p=0.0064), and increased 30-day mortality (p=0.0038) with univariate analysis. Multivariate analysis demonstrated that difficult airway management was associated with patient history of head/neck radiation only (OR 3.855; 95% CI, 1.059-14.039, p=0.0407). Overall 30-day mortality was 67.2% [95% CI, 0.6387-0.7038]. See Tables 1-3.

CONCLUSION: The high incidence of a difficult airway encounters suggest need for readily available access to advanced airway equipment when attending emergency intubations outside of the operating room setting. Ongoing CPR was associated with difficult intubation and patient history of head/neck radiation was associated with difficult airway management and use of advanced airway equipment. For hospitalized cancer patients requiring emergency intubation, overall 30-day mortality was high.

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Table 1. Incidence of difficult and failed intubation techniques

Intubation method	No. cases	%	95% CI	No. of cases with DI	% cases with DI	P value	Odds Ratio (OR) for DI	95% Confidence Interval (CI)	P value	No. of failed	% failed	95% CI
Total number of non-operating room intubations	796											
No. cases with difficult laryngoscopy/intubation (DI)	77	9.7	0.0781-0.1192									
No. cases with DI and/or AAD used (DA)	242	30.4	0.2731-0.3369									
Miller laryngoscope	346	43.5	0.4006-0.4693	36	10.4	0.5405				29	8.4	0.0590-0.1178
Macintosh laryngoscope	277	34.8	0.3157-0.3817	33	11.9	0.1183				22	8.0	0.0530-0.1173
C-MAC videolaryngoscope	169	21.2	0.1853-0.2421	23	13.6	<0.0001	5.332	2.829-10.049	<0.0001	7	4.1	0.0202-0.0830
Airtraq	31	3.9	0.0276-0.0547	9	29.0	0.0051	31.479	12.714-77.938	<0.0001	3	9.7	0.0335-0.2490
Fiberoptic intubation	26	3.3	0.0224-0.0474	8	30.8	0.0002	6.210	1.912-20.166	0.0024	2	7.7	0.0214-0.2414
Laryngeal mask airway (LMA)	7	0.9	0.0043-0.0180	5	71.4	0.0001	5.542	0.674-45.584	0.1112	1	14.3	0.0257-0.5131
Gum-elastic bougie	11	1.4	0.0077-0.0246	9	81.8	<0.0001	13.41	2.483-72.434	0.0026			
Tracheostomy	1	0.1	0.0002-0.0071	1	100							

Table 2. Continous variables	Univariate analysis of DI cases						Univariate analysis of DA cases						Multivariate analysis of DA cases		
	No. of cases	Mean	Standard D	Median	Range	P value	No. of cases	Mean	Standard Deviation	Median	Range	P value	OR for DA cases	95% CI	P value
Age (years)		59.13	14.91	62	18-87										
Cases without DI	719	59.07	15.03	62	18-87	0.9018	554	59.37	15.01	62	18-87	0.435			
Cases with DI	77	59.64	13.82	63	21-87		242	58.57	14.68	62	20-87				
BMI		28.61	7.63	27.49	12.30-59.07										
Cases without DI	719	28.58	7.62	27.45	12.3-59.07	0.5630	554	27.98	6.95	27.11	12.30-56.55	0.0064	1.022	0.990-1.055	0.1855
Cases with DI	77	28.92	7.76	28.86	16.01-48.8		242	30.06	8.85	28.87	14.63-59.07				

Table 3. Categorical variables				Univariate analysis of DI cases			Multivariate analysis of DI cases			Univariate analysis of DA cases			Multivariate analysis of DA cases		
	No. of cases	%	95% CI	No. of cases wit	% cases w	P value	OR for DI cases	95% CI	P value	No. of cas	% cases w	P value	OR for DA cases	95% CI	P value
Male Sex	441	55.4	0.5193-0.5882	40	9.1	0.5212				142	32.2	0.2191			
Female Sex	355	44.6		37	10.1					100	28.2				
History of chemotherapy	660	82.9	0.8014-0.8537	64	9.7	0.9604				203	30.8	0.6309			
No chemotherapy	136	17.1		13	9.6					39	28.7				
History of radiation therapy (XRT)	254	31.9	0.2876-0.3523	38	15.0	0.0006	1.329	0.689-2.565	0.3962	149	27.5	0.0091	1.372	0.796-2.363	0.2549
No XRT	542	68.1		39	7.2					93	36.6				
History of head/neck (H/N) XRT	54	6.8	0.0524-0.0875	18	33.3	<0.0001	2.342	0.654-8.386	0.1910	39	72.2	<0.0001	3.855	1.059-14.039	0.0407
No XRT to H/N	742	93.2		59	8.0					203	27.4				
History of H/N cancer	242	30.4	0.2731-0.3369	13	28.9	<0.0001	1.056	0.269-4.4148	0.9383	33	73.3	<0.0001	1.205	0.265-5.486	0.8096
No H/N cancer	554	69.6		64	8.5					209	27.8				
History of H/N surgery	30	3.8	0.0265-0.0533	8	26.7	0.0013	0.516	0.121-2.204	0.3720	25	83.3	<0.0001	2.903	0.604-13.951	0.1833
No H/N surgery	766	96.2		69	9.0					217	28.3				
With induction drugs	223	28.0	0.2501-0.3123	49	8.6	0.0861	0.776	0.406-1.485	0.4442	172	30	0.7054			
Without induction drugs	573	72.0		28	12.6					70	31.4				
Resident physician involvement	15	1.9	0.0115-0.0309	4	26.7	0.0484	3.653	0.754-17.701	0.1077	5	33.3	0.7819			
Faculty anesthesiologist only	781	98.1		73	9.3					237	30.3				
Active CPR	68	8.5	0.0679-0.1069	13	19.1	0.0059	3.366	1.395-8.127	0.0069	19	27.9	0.6446			
Without CPR	728	91.5		64	8.8					223	30.6				
Survival less than 30 days	535	67.2	0.6387-0.7038	49	9.2	0.4820				145	27.1	0.0038	1.220	0.737-2.020	0.4385
Survival 30 days or beyond	261	32.8		28	10.7					97	37.2				

AIRWAY MANAGEMENT 9

Out-of-Operating Room Emergency Intubation Practice Patterns

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INTRODUCTION: The purpose of this research is to evaluate anesthesiologists' approach to emergency out-of-operating room (OR) intubations given various clinical scenarios. Outside of the OR, the critical nature of airway control escalates complications and concerns for patient safety. Emergency airway control prompts providers to cautiously approach intubations and optimize their initial attempts. To better understand emergency intubation strategies, we surveyed anesthesia providers to examine how their approach to emergency intubations outside of the OR alters across clinical scenarios.

METHODS: An online survey was distributed via REDCap to anesthesiologists at the University of Chicago Medical Center. Demographics collected include years of anesthesia experience, comfortability of emergency airway management, and the number of out-of-OR intubations performed. We asked respondents to consider out-of-OR emergency intubations in four clinical scenarios regarding a combination of (1) the patient's airway exam (favorable or unfavorable) and (2) the patient's hemodynamic condition (stable or unstable) (Figure 1). For each scenario, respondents were asked questions regarding typical initial intubation strategy (direct laryngoscopy, video laryngoscopy, fiberoptic bronchoscopy), how often or percentage of time they induce general anesthesia, and how often they used neuromuscular blocking agents (NMBAs). Survey data was analyzed descriptively to determine the current out-of-OR emergency intubation practice patterns.

RESULTS: Respondents (n=65) ranged in clinical experiences from less than five years (43%, 28) to more than 16 years of practice (23%, 15), and many were fellowship-trained (48%, 31). Majority of the participants were either comfortable (28%, 18) or very comfortable (40%, 26) with emergency airway management outside the OR and had performed more than 15 emergency intubations in the past five years (82%, 53). Direct laryngoscopy was the primary intubation strategy in scenarios 1 (69%, 45) and 2 (62%, 40). Video laryngoscopy was the primary strategy in scenarios 3 (63%, 41) and 4 (58%, 38). Nearly half of providers almost never or rarely use general anesthesia in scenarios 2 and 3 (48%, 31), and majority of providers in scenario 4 (86%, 56) almost never or rarely use general anesthesia. The frequency of NMBAs use decreases as the clinical scenarios increase in complexity. Majority of respondents often or always use NMBAs in scenario 1 (66%, 43), while the majority of respondents in scenario 3 (54%, 35) and scenario 4 (68%, 44) almost never or rarely use NMBAs in emergency intubations settings.

CONCLUSION: As clinical scenarios increase in airway and hemodynamic complexity for emergency intubations out-of-OR, the need for more dynamic airway visualization increases while the use of general anesthesia and neuromuscular blocking agents decreases. The described practice patterns may affect patient outcomes and quality improvement strategies regarding emergency intubations outside the OR.

Table 1. Demographic characteristics of the respondents.

Variable	Number	Percentage
Years of Anesthesia experience (including residency)		
0-5	28	43
6-10	15	23
11-15	7	11
16-20	3	4.6
>20	12	18
Fellowship Training		
Yes	31	48
No	34	52
Comfortability with out-of-OR emergency airway management		
Not at all	3	4.6
Somewhat comfortable	18	28
Comfortable	18	28
Very comfortable	26	40
Number of emergency intubations performed (within 5 years)		
1-5	1	1.5
6-10	5	7.7
10-15	6	9.2
>15	53	82

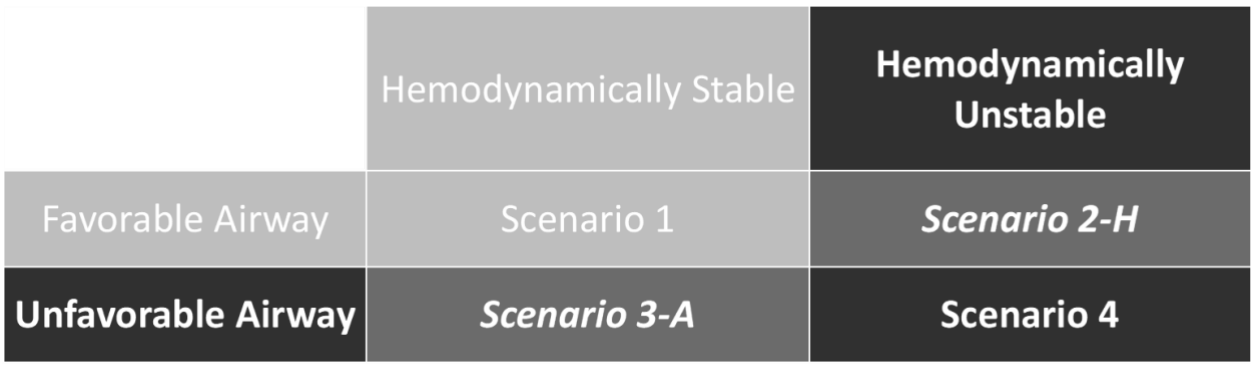

Figure 1. Clinical Scenarios. Scenarios 1 and 4 ask respondents to consider a clinical situation where both the airway exam and hemodynamics are favorable or not, respectively. Scenario 2 is denoted with an "H" for only hemodynamic instability. Scenario 3 is denoted with an "A" for only an unfavorable airway exam.

Table 2. Intubation Strategy.

	Scenario 1	Scenario 2-H	Scenario 3-A	Scenario 4
Direct Laryngoscopy	45 (69%)	40 (62%)	3 (4.6%)	4 (6.2%)
Video Laryngoscopy	20 (31%)	24 (37%)	41 (63%)	38 (58%)
Fiberoptic Bronchoscopy	-	1 (1.5%)	20 (31%)	22 (34%)
Other	-	-	1 (1.5%)	1 (1.5%)

Table 3. Frequency of General Anesthetic Use.

	Scenario 1	Scenario 2-H	Scenario 3-A	Scenario 4
Almost Never (<1%)	3 (4.6%)	12 (18%)	11 (17%)	33 (51%)
Rarely (1-10%)	2 (3.1%)	19 (29%)	20 (31%)	23 (35%)
Sometimes (11-50%)	19 (29%)	24 (37%)	24 (37%)	8 (12%)
Often (51-90%)	27 (42%)	6 (9.2%)	9 (14%)	-
Almost Always (91-100%)	14 (22%)	4 (6.2%)	1 (1.5%)	1 (1.5%)

Table 4. Frequency of Neuromuscular Blockade Use.

	Scenario 1	Scenario 2-H	Scenario 3-A	Scenario 4
Almost Never (<1%)	3 (4.6%)	11 (17%)	17 (26%)	26 (40%)
Rarely (1-10%)	1 (1.5%)	10 (15%)	18 (28%)	18 (28%)
Sometimes (11-50%)	18 (28%)	24 (37%)	20 (31%)	17 (26%)
Often (51-90%)	25 (38%)	14 (22%)	7 (11%)	1 (1.5%)
Almost Always (91-100%)	18 (28%)	6 (9.2%)	3 (4.6%)	3 (4.6%)

SUBSPECIALTY ABSTRACTS

AMBULATORY ANESTHESIA

AMBULATORY ANESTHESIA 1

Postoperative Discharge and Pulmonary Outcomes in Ambulatory Surgery Patients Undergoing Laparoscopic Cholecystectomy with Sugammadex Neuromuscular Blockade Reversal

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INTRODUCTION: The use of neuromuscular blockade (NMB) for laparoscopic surgery is common practice, including in the ambulatory setting. In 2015, the drug Sugammadex provided a new tool to dependably reverse NMB compared to traditional reversal drugs. Studies have shown that by more reliably reversing NMB, certain patients are at a decreased risk of postoperative complications.[1,2,3] However, other studies have questioned the benefit of widespread sugammadex usage.[4] In the ambulatory setting, lower rates of pulmonary complications would lead to more reliable discharge post operatively. Given this advancement, we hypothesize that Sugammadex administration in patients undergoing an ambulatory laparoscopic procedure will be discharged to home at higher rates compared to patients who receive conventional acetylcholinesterase inhibitors.

METHODS: Using a retrospective cohort study with data from the Premier Healthcare database from 2016 to 2018, our group investigated if Sugammadex usage in patients undergoing laparoscopic cholecystectomy in an ambulatory setting had an effect on discharge rates and respiratory complications. Inclusion criteria required patients who underwent elective laparoscopic cholecystectomy to be at least 18 years old, receive a NMB and a single reversal agent (Figure 1). The exposure of interest was NMB reversal choice (Sugammadex versus Neostigmine), and the primary outcome was discharge to home. A propensity score model was built using logistic regression adjusting for patient and hospital characteristics. After matching, univariable logistic regression models for binary outcomes were used to determine the association between reversal agents.

RESULTS: Post-match (8,916 cases) patient characteristics included an average patient age of 49 years, 74% female, 77% white, 7% black, 52% managed care insurance. Patient comorbidities included 31% of patients having hypertension. 18% obesity, 12% chronic lung disease, and 13% diabetes. In the matched sample (Table 1), no significant difference was observed in the incidence of discharge to home between the Sugammadex (99.6 %) and Neostigmine (99.4%) groups (OR 1.318, 95%CI 0.725 TO 2.396). Additionally, no differences were observed in the incidence of respiratory complications (OR 0.837, 95% CI 0.577 TO 1.213). These findings were stable across the sub cohorts of patients with an age greater than 65, obesity, or chronic lung disease.

CONCLUSION: In this study, no statistically significant benefit was observed in patients who received Sugammadex NMB reversal compared to neostigmine in terms of discharge to home, postoperative pulmonary complications, noninvasive ventilation, or invasive mechanical ventilation. Given the ambulatory nature of this surgical cohort and likely smaller comorbidity burden compared to previous mixed surgical cohort studies where benefit was observed, our results suggest that the use of Sugammadex may not provide a benefit in outpatient laparoscopic cholecystectomy.

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Figures:

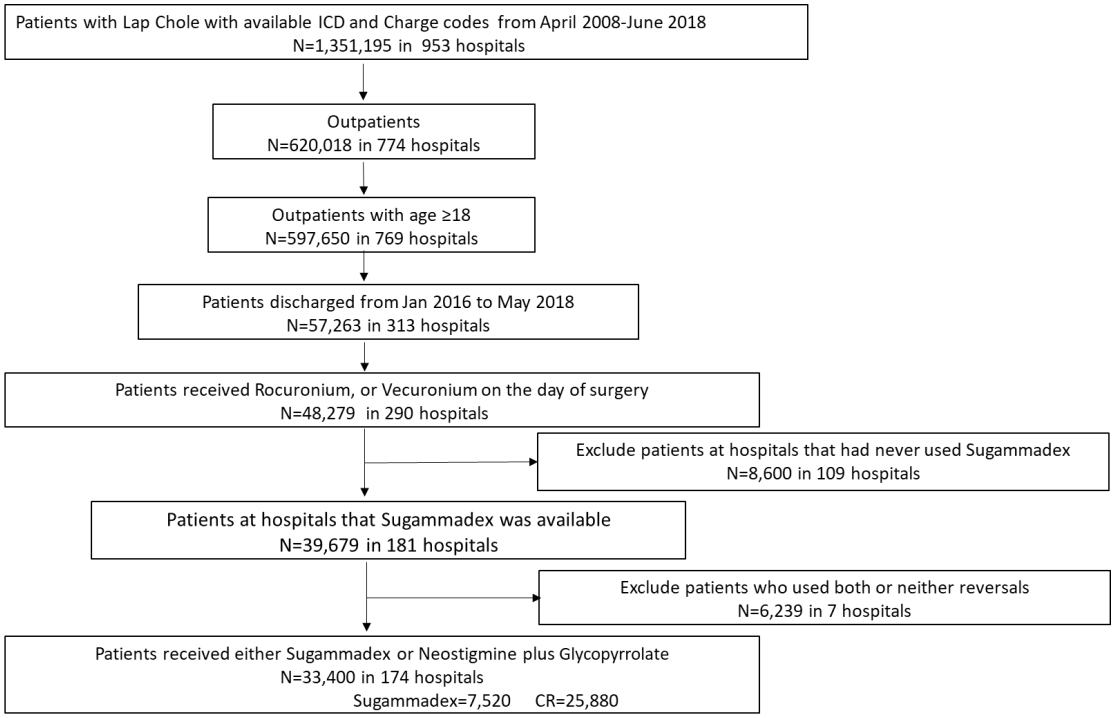

Figure 1

Retrospective Sugammadex Exposure Outcomes				
Outcome	**Odds Ratio**	**95% Wald CI**		**P**
Discharge to home	1.318	0.725	2.396	0.366
Postoperative Pulmonary Complication	0.734	0.492	1.096	0.131
Invasive Mechanical Ventilation	0.333	0.035	3.204	0.341
Noninvasive Ventilation	1.429	0.544	3.758	0.469
Complication (any of PPC, IMV, NIV)	0.837	0.577	1.213	0.347

Table 1

AMBULATORY ANESTHESIA 2

Comparison of ketamine-dexmedetomidine combination with fentanyl-dexmedetomidine as procedural sedoanalgesia for CT-guided painful interventional radiology procedures: A randomized controlled study

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INTRODUCTION: The quest for an ideal sedoanalgesic-combination exhibiting the triad of efficacy, safety and patient comfort has led to administration of several permutations and combinations of drugs (midazolam, fentanyl, remifentanil, dexmedetomidine, propofol, ketamine, pethidine, pentazocine).[1,2] The ideal sedoanalgesic for CT-guided core-biopsy of spine and radiofrequency/microwave ablation (RFA/MWA) of hepatic/pulmonary lesions, which are exquisitely painful procedures commonly performed in oncology setups, has so far been elusive. Dexmedetomidine, a highly selective α2-agonist, is gaining popularity as a sedative-analgesic for conscious procedural sedation. However, short bursts of excruciating pain during CT-guided core-biopsy and RFA/MWA mandate profound analgesia where dexmedetomidine infusion alone fails to suffice. Sub-dissociative/analgesic doses of ketamine (≤ 0.5mg/kg) produce profound analgesia comparable to morphine.[3,4] Ketamine and dexmedetomidine comprise a symbiotic pair of drugs complementing each-other and nullifying mutual side-effects.[5] In the absence of any guidelines, we compared a ketamine-dexmedetomidine combination (Group-K) with fentanyl-dexmedetomidine combination (Group-F).

METHODS: This prospective, interventional, single-centric, parallel-armed, randomized controlled study enrolled 60 patients undergoing CT-guided core biopsy/radiofrequency/microwave ablation in a remote location, allocated to Group-K and Group-F. Primary outcome measure was the pain score, heart rate and mean arterial pressure recorded at specific intraoperative time points. Secondary outcome measures were postoperative NRS score, adverse events and interventionalist -satisfaction. Independent/paired-sample t-tests were utilized and data expressed as dotted box-whisker plots, forest plots and trendlines, using Medcalc statistical software (version 15; MedCalc Software Ltd; Ostend, Belgium); p-value <0.05 being statistically significant.

RESULTS: All ASA physical state I-II patients of either sex, aged 18-75 years, weighing 40-85 kg, undergoing CT-guided core-biopsy/radiofrequency/microwave ablation in remote location (CT-scan suite) were included in the study. Patients with raised intracranial pressure, opioid dependence and bradycardia (Heart Rate< 60/min) were excluded. There was a significant difference in intraprocedural pain-scores between both groups (p-values 0.0001, 0.0011, 0.0092 and 0.0201 at 0-10mins, 10-20mins, 20-30mins and 30-40mins respectively). More patients in Group-F required rescue-analgesic with reduced interventionist-satisfaction score versus Group-K. In Group-K, mean arterial pressure and heart rate (95.1mmHg;79.6/min) increased after initial ketamine bolus, but were maintained/decreased at intervention-initiation (93.2mmHg;79.4/min) and at 10mins and 30mins thereafter. In Group-F, MAP and HR decreased after initial fentanyl bolus (83.5mHg;71.9/min), peaked at intervention-initiation (90.1mmHg;77/min), progressively decreasing at every time-point thereafter. VAS-scores (resting; on coughing) were lower in Group-K.

CONCLUSION: A ketamine-dexmedetomidine combination technique demonstrated a superior sedoanalgesic effect and may emerge as the ideal procedural sedoanalgesic for patients undergoing CT-guided core-biopsy and radiofrequency/microwave ablation. Further, it had less intra-procedural bradypnea/bradycardia and rescue-drug requirement, reduced post-procedural complications and enhanced interventionist-satisfaction. Ketamine and dexmedetomidine comprise a symbiotic pair of drugs complementing each-other and nullifying mutual side-effects. While, dexmedetomidine may prevent the tachycardia, hypertension, hypersalivation, and emergence phenomena that characterize ketamine, ketamine may prevent the bradycardia, hypotension, xerostomia and respiratory depression reported with dexmedetomidine administration. An additional benefit rendered by ketamine is to hasten the onset of sedation, thereby eliminating the slow onset-time when dexmedetomidine is the sole agent. Opioid-free analgesia is becoming coveted as it circumvents the nausea, sedation, constipation, addiction, immunosuppression and cancer progression concerns attributable to opioid use and a ketamine-dexmedetomidine combination is a step in this direction.

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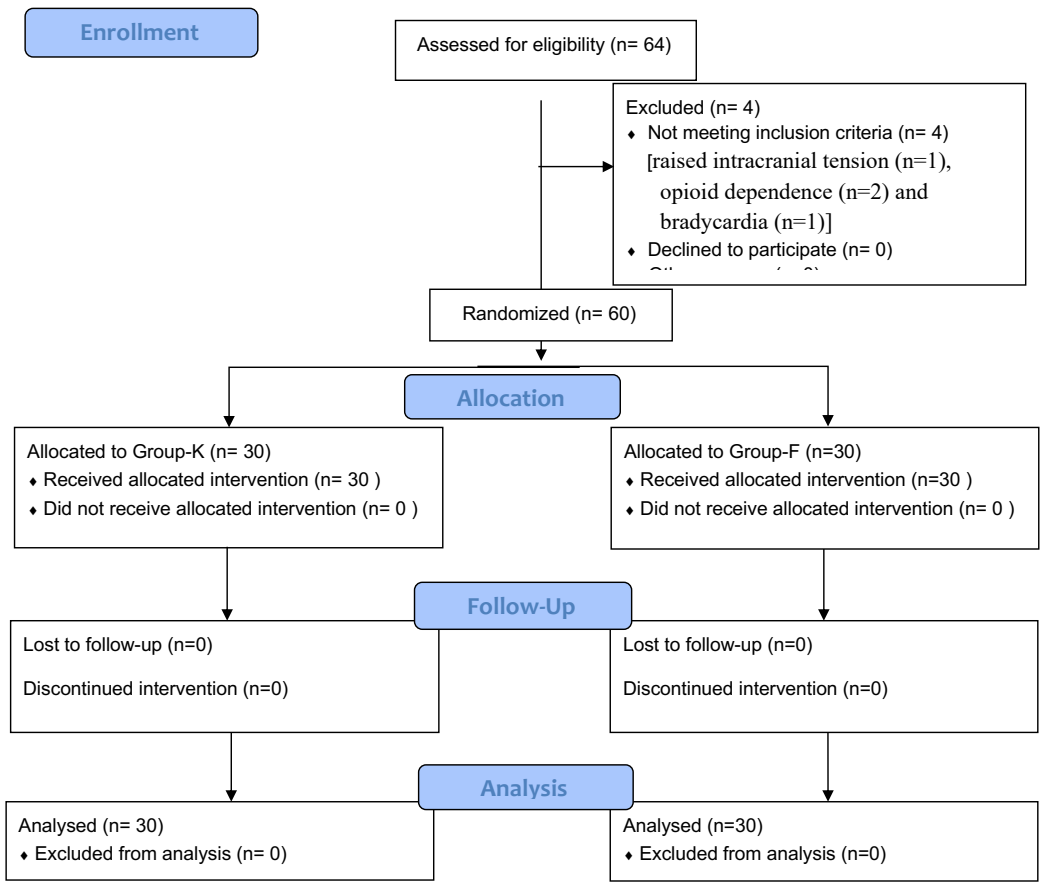
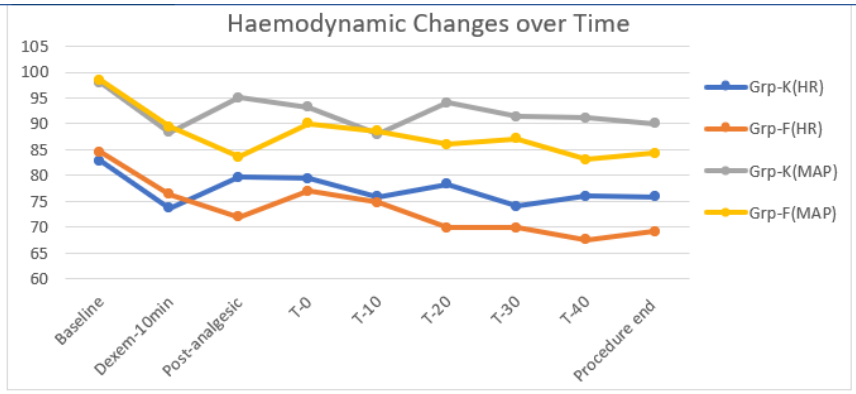
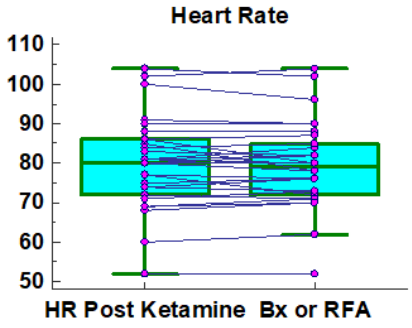
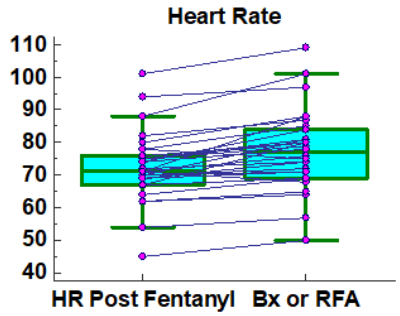
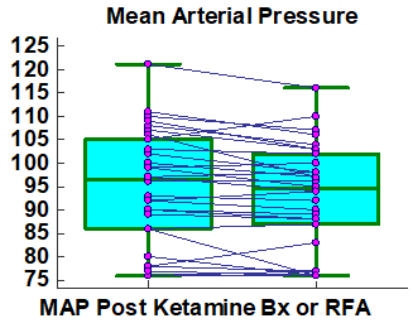
Figure-1: CONSORT Flow diagram











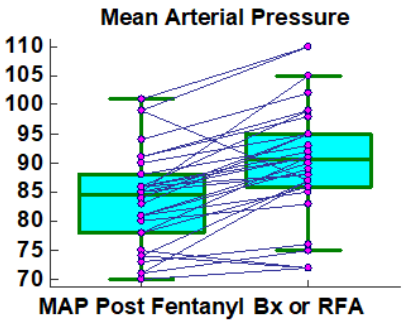


Table-1: Demographic parameters and drug consumption

	N	Mean	95% CI	SD	Min	Max	P
Age (Years; Group-K)	30	51.6	46.85 to 56.35	12.72	18	71	0.79
Age (Years; Group-F)	30	52.5	47.37 to 57.70	13.83	18	72	
Sex (Male:Female; Group-K)	30		15:15				0.60
Sex (Male:Female; Group-F)	30		18:12				
Weight (Group-K)	30	65.6	61.49 to 69.78	11.1	40	85	0.96
Weight (Group-F)	30	65.8	61.76 to 69.74	10.68	42	85	
Duration (Group-K)	30	46.5	41.49 to 51.58	13.52	29	82	0.12
Duration (Group-F)	30	51.0	48.01 to 54.06	8.11	39	72	
Total Dexmed (Group-K)	30	87.4	81.69 to 93.11	15.29	54	113	0.80
Total Dexmed (Group-F)	30	86.3	79.86 to 92.81	17.35	46	124	
Total Ketamine (Group-K)	30	51.3	45.1 to 57.6	16.81	25.0	80.0	
Total Fentanyl (Group-F)	30	59.0	54.1 to 63.9	13.09	35.0	80.0	

Table-2: Comparison of Pain score, Richmond agitation sedation score (RASS) and Visual Analog Score (VAS); CST=Chi squared test; FET=Fisher Exact Test

Time point	n	Pain Score (Mean ±SD)	Min	P-value	RASS	<1	0	>1	p-value
Baseline (Grp-K)	30	0.33 ± 0.92	0-3	0.88 (t-test)	(Grp-K)	1 (3.3%)	26 (86.7%)	3 (10%)	0.56 (Chi-sq. test)
Baseline (Grp-F)	30	0.3 ± 0.84	0-3		(Grp-F)	6 (20%)	24 (80%)	0	
0-10(Grp-K)	30	0.37± 0.72	0-3	0.00	VAS-r	0	1-3	4-7	P
0-10(Grp-F)	30	1.73± 1.05	0-4		(Grp-K)	30	0	0	0.10
10-20(Grp-K)	30	0.27±0.74	0-3	0.00	(Grp-F)	20	10	0	(CST)
10-20(Grp-F)	30	1.17±1.23	0-4		VAS-c	0	1-3	4-7	P
20-30(Grp-K)	29	0.14±0.44	0-2	0.01	(Grp-K)	0	0	0	0.00
20-30(Grp-F)	30	0.63±0.89	0-4		(Grp-F)	11	18	1	(CST)
30-40(Grp-K)	22	0.18±0.40	0-1	0.02	Surg. Sat. (Grp-K)		Yes/No: 30/0		0.00
30-40(Grp-F)	30	0.70±0.95	0-4		Surg. Sat. (Grp-F)		Yes/No: 18/12		(FET)

Table-3: Trends in heart rate, mean arterial pressure and respiratory rate over time

Timepoint	n	HR Mean±SD	HR 95%CI	p-value	MAP Mean ±SD	MAP 95%CI	p-value	RR Mean±SD	RR 95%CI	p-value
Grp-K (baseline)	30	82.80 ±15.97	76.84 to 88.76	0.64	98.03 ±10.80	94-102.07	0.87	19.13 ±2.21	18.31 to 19.96	0.22
Grp-F (baseline)	30	84.53 ±12.44	79.89 to 89.18		98.5 ±11.61	94.17-102.84		19.83 ±2.14	19.04 to 20.63	
Grp-K (dexem10m)	30	73.67 ±14.73	68.17 to 79.17	0.43	88.27 ±9.87	84.58-91.95	0.65	16.23± 2.08	15.46 to 17.01	0.27
Grp-F (dexem10m)	30	76.40 ±11.60	72.07 to 80.73		89.4 ±9.38	85.9-92.9		16.83± 2.19	16.04 to 17.62	
Grp-K (Post Ket)	30	79.63 ±11.47	75.35 to 83.92	0.01	95.1 ±12.01	90.62-99.59	0.00	18.07± 2.95	16.97 to 19.17	0.00
Grp-F (Post Fent)	30	71.93 ±11.13	67.78 to 76.09		83.53 ±8.42	80.39-86.68		14.5± 2.15	13.7 to 15.30	
Grp-K (Bx-0)	30	79.37 ±10.89	75.30 to 83.43	0.44	93.17 ±11.16	89-97.33	0.27	17.93±2.7	16.92 to 18.94	0.01
Grp-F (Bx-0)	30	77.00 ±12.72	72.25 to 81.75		90.1 ±10.18	86.3-93.90		16.03±3.0	14.93 to 17.14	
Grp-K (Bx-10)	30	75.83 ±10.06	72.08 to 79.59	0.71	87.93 ±9.85	84.25-91.61	0.82	17.0±2.36	16.09 to 17.85	0.02
Grp-F (Bx-10)	30	74.73 ±12.94	69.9 to 79.56		88.6 ±12.34	83.99-93.21		15.43±2.46	14.52 to 16.35	
Grp-K (Bx-20)	29	78.28 ±11.48	73.91 to 82.64	0.01	94.04 ±11.8	89.55-98.52	0.01	18.35±3.0	17.22 to 19.47	0.00
Grp-F (Bx-20)	30	69.87 ±13.41	64.86-74.87		86 ±11.97	81.53-90.47		14.27±2.2	13.46 to 15.08	
Grp-K (Bx-30)	22	74 ±10.06	69.54-78.46	0.27	91.41 ±10.6	86.71-96.11	0.24	18.14±2.2	17.13 to 19.15	0.00
Grp-F (Bx-30)	30	69.8 ±15.18	64.13-75.47		87.07 ±14.51	81.65-92.49		14.27±2.5	13.35 to 15.18	
Grp-K (Bx-40)	12	76.0 ±9.79	69.78-82.22	0.05	91.15 ±9.13	85.88-96.46	0.047	19.92±1.6	18.92 to 20.91	0.00
Grp-F (Bx-40)	26	67.5 ±13.06	62.22-72.78		83.04 ±13.17	77.72-88.36		13.31±2.3	12.37 to 14.25	
Grp-K (End)	30	75.83 ±9.44	72.31-79.36	0.02	90 ±10.30	86.15-93.85	0.037	17.73±2.15	16.93 to 18.54	0.00
Grp-F (End)	30	69.10 ±12.34	64.49-73.71		84.3 ±10.34	80.44-88.16		13.97±1.85	13.28 to 14.66	

AMBULATORY ANESTHESIA 3

Sugammadex Use in the Outpatient Surgical Setting: A Retrospective Cohort Study

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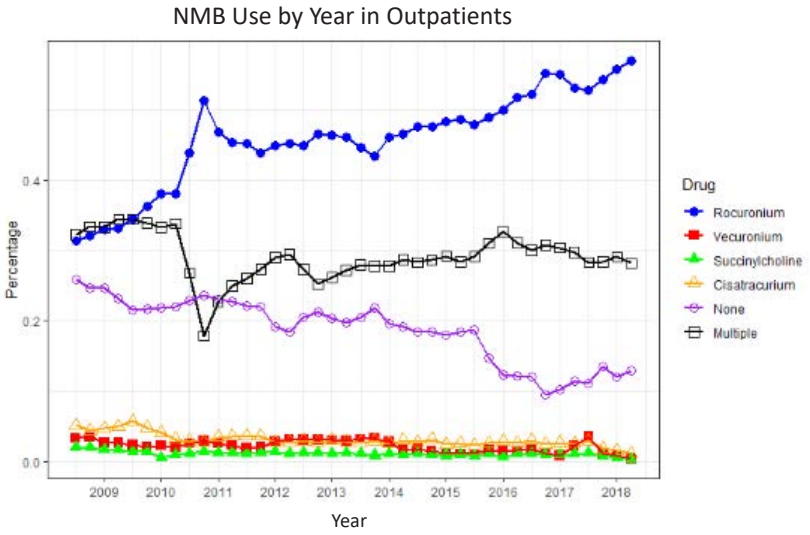
INTRODUCTION: Outpatient surgery in the United States is experiencing rapid growth including an increase in minimally invasive procedures requiring neuromuscular blockade. Previous studies have largely focused on Sugammadex utilization in mixed surgical cohorts largely within inpatient settings. This study sought to characterize patient and institutional factors associated with Sugammadex use and describe temporal trends of Sugammadex uptake in elective outpatient laparoscopic cholecystectomy.

METHODS: In this retrospective cohort study, the Premier Health database was used to identify adult patients undergoing ambulatory laparoscopic cholecystectomy receiving non-depolarizing neuromuscular blockade between 2009 and 2018. Patients were stratified by type of neuromuscular blockade reversal agent with the primary outcome being exposure to Sugammadex. Longitudinal trends in both neuromuscular blockade and reversal were examined. A mixed effects model was used to examine patient and institutional factors associated with Sugammadex receipt. To examine patterns of Sugammadex adoption by institution, a restricted cohort of hospitals performing a consistent number of laparoscopic cholecystectomies was examined from 2016-2018. Hospitals were evaluated for predominant use of Sugammadex and speed of uptake.

RESULTS: A total of 51,035 patients met inclusion criteria. Time trends in neuromuscular blockade and reversal are presented in Figure 1. In the mixed effect model, a large proportion of the variance in Sugammadex utilization was associated with hospital characteristics (ICC: 0.65). Non white patients and hospitals with fewer beds were associated with decreased Sugammadex use, while comorbidities such as pulmonary circulation disorders, obesity, complicated diabetes, renal failure, liver disease, and administration of bronchodilators or antihypertensives on the day of surgery were positively associated with Sugammadex use (Table 1). A group of 28 hospitals was studied closely to describe trends of Sugammadex use following FDA approval. Ten hospitals were defined as 'switching' to Sugammadex with over 50% use (Figure 2). Eighteen hospitals displayed minimal use of Sugammadex.

CONCLUSION: Our data demonstrates an increase in the use of Sugammadex in an outpatient surgical cohort following FDA approval in 2015 with a corresponding decrease in the use of neostigmine. Overall utilization of Sugammadex was lower (30%) in our exclusively outpatient cohort as compared to other studies in mixed cohorts. While multiple patient characteristics were associated with Sugammadex administration, an ICC of 0.65 indicates that individual hospital was the primary determinant of Sugammadex use and significant variation in Sugammadex adoption existed between institutions. Age and PRODIGY score are strong predictors of postoperative pulmonary complications which did not predict use of Sugammadex. This demonstrates that at a population level, Sugammadex was not being used where it is expected to be most beneficial.

Figure 1



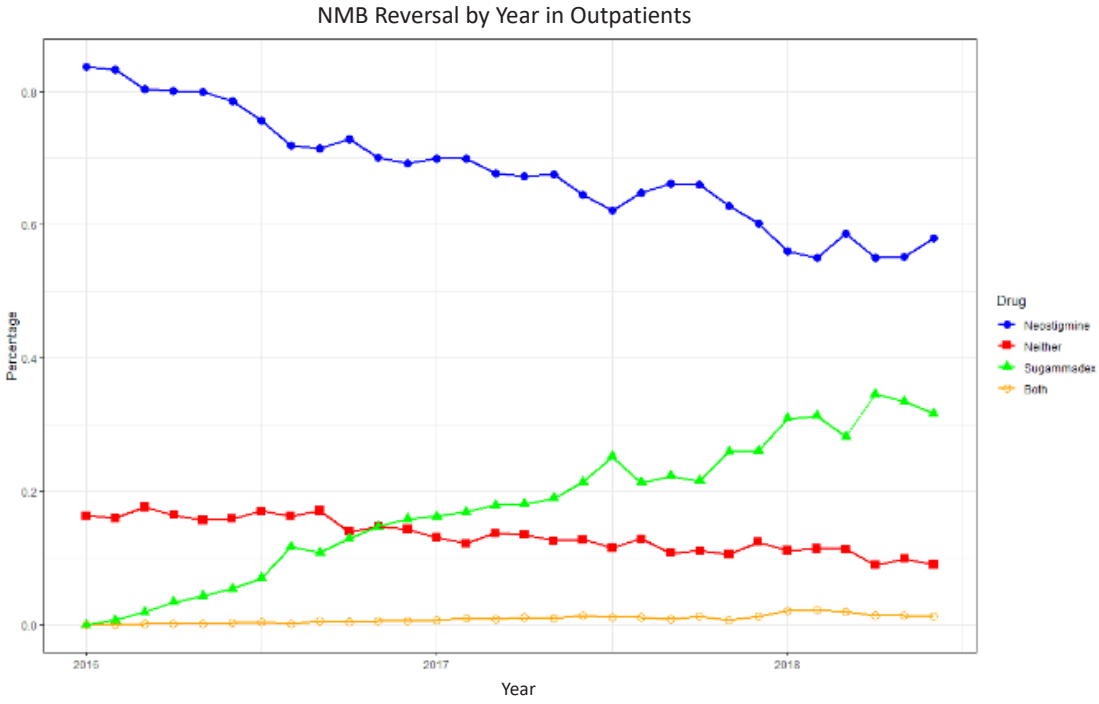


Figure 2

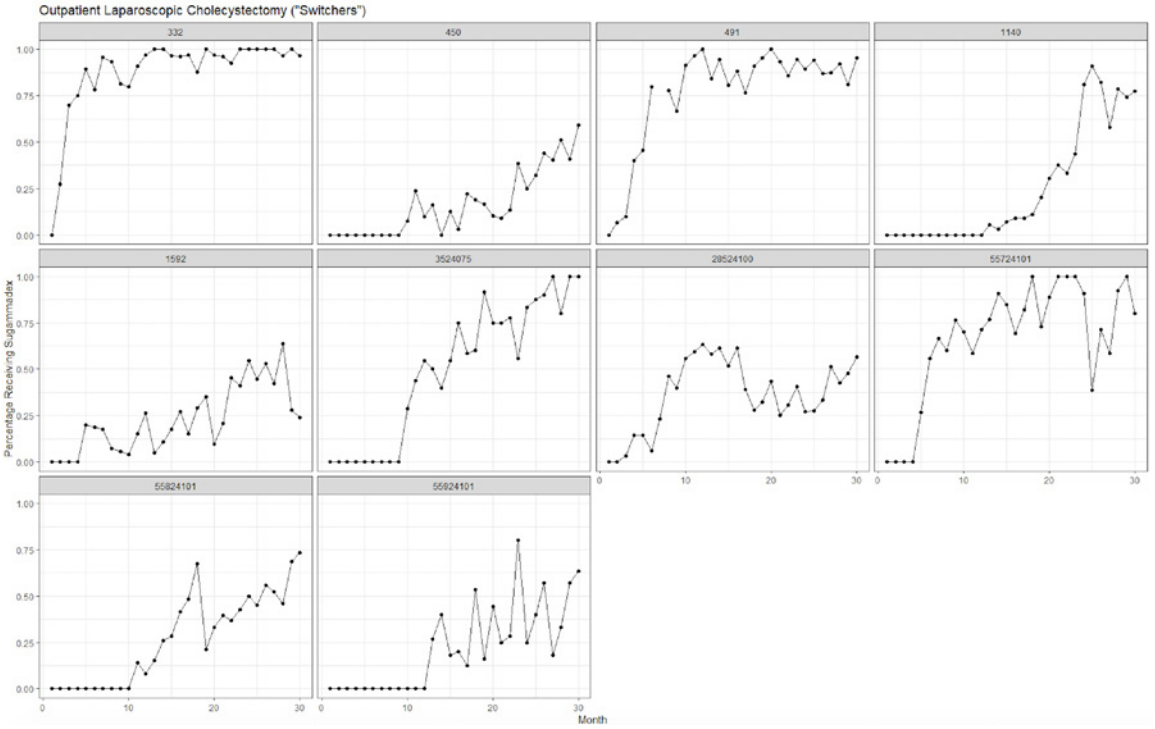


Table 1

Variable	OR (95% CI)	p-value
Age (per year)	1.01 (1.00, 1.01)	<0.001
Gender (Female vs. Male)	0.99 (0.92, 1.06)	0.684
Race		0.007
Black vs. White	1.12 (0.98, 1.29)	0.090
Other vs. White	0.85 (0.76, 0.95)	0.005
Unknown vs. White	0.86 (0.65, 1.13)	0.278
Ethnicity		0.262
Hispanic vs. Non-Hispanic	1.09 (0.98, 1.22)	0.124
Unknown vs. Non-Hispanic	1.06 (0.90, 1.26)	0.490
Payor Category		0.440
Medicaid vs. Managed Care	0.93 (0.84, 1.02)	0.123
Medicare vs Managed Care	1.01 (0.92, 1.12)	0.793
Other vs Managed Care	0.99 (0.89, 1.11)	0.904
Non-Home Admission Source*	0.98 (0.85, 1.13)	0.793
Rural vs. Urban	0.80 (0.30, 2.17)	0.666
Teaching vs. Nonteaching	1.29 (0.55, 3.04)	0.555
Bed Count		0.079
0-99 vs. 500+	0.21 (0.06, 0.82)	0.025
100-199 vs. 500+	0.41 (0.11, 1.47)	0.169
200-299 vs. 500+	0.41 (0.12, 1.38)	0.147
300-399 vs. 500+	0.19 (0.05, 0.71)	0.014
400-499 vs. 500+	0.19 (0.05, 0.69)	0.012
Provider Region		0.979
Midwest vs South	1.06 (0.38, 2.95)	0.907
Northeast vs South	0.77 (0.20, 3.03)	0.706
West vs South	1.01 (0.45, 2.30)	0.976
Insulin Used	1.08 (0.85, 1.37)	0.526
Bronchodilators Used	1.13 (1.06, 1.21)	0.001
Antihypertensives Used	1.21 (1.04, 1.41)	0.014
Comorbidities		
CHF	0.93 (0.70, 1.25)	0.629
Valvular Disease	0.86 (0.63, 1.16)	0.318
Pulmonary Circulation Disorder	11.50 (2.18, 60.79)	0.007
Peripheral Vascular Disease	0.88 (0.60, 1.29)	0.512
Paralysis	0.75 (0.36, 1.58)	0.443
Other Neurological Disorders	1.08 (0.85, 1.37)	0.536
Chronic Lung Disease	1.02 (0.92, 1.12)	0.750
Diabetes (uncomplicated)	0.93 (0.83, 1.03)	0.170
Diabetes (complicated)	1.40 (1.10, 1.79)	0.007
Hypothyroidism	0.99 (0.88, 1.11)	0.798
Renal Failure	0.74 (0.58, 0.95)	0.020
Liver Disease	1.15 (1.00, 1.31)	0.043
Peptic Ulcer	0.62 (0.30, 1.30)	0.200
AIDS/HIV	1.08 (0.31, 3.72)	0.896
Lymphoma	2.33 (0.74, 7.32)	0.142
Metastatic Cancer	1.06 (0.47, 2.39)	0.879
Solid Tumor without Metastasis	0.77 (0.46, 1.29)	0.324
Rheumatoid Arthritis	1.05 (0.81, 1.37)	0.703
Coagulopathy	1.30 (0.72, 2.34)	0.374
Obesity	1.14 (1.04, 1.24)	0.003
Weight Loss	0.44 (0.23, 0.88)	0.020
Fluid/Electrolyte Disorders	1.20 (0.55, 2.62)	0.649
Blood Loss Anemia	1.15 (0.22, 6.06)	0.857
Deficiency Anemia	0.92 (0.77, 1.10)	0.338
Alcohol Abuse	0.65 (0.38, 1.11)	0.112
Drug Abuse	1.06 (0.59, 1.90)	0.850
Psychoses	1.16 (0.87, 1.56)	0.314
Depression	1.10 (0.98, 1.24)	0.096
Hypertension	1.07 (0.99, 1.16)	0.099

AMBULATORY ANESTHESIA 4

Institutional Complications of Arteriovenous Fistulas in Hemodialysis Patients: A Retrospective Review

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INTRODUCTION: Arteriovenous fistulas (AVF) are a type of permanent vascular access available for hemodialysis. Although AVFs are preferred due to decreased long term vascular events, hemodialysis patients still present with complications including mechanical, infectious, and vascular.[1] Anesthetic options for the creation of AVFs include regional anesthesia (RA), general anesthesia (GA) and monitored anesthesia care (MAC). However, studies analyzing the relationship between anesthesia modality and AVF complications are limited. Therefore, the purpose of the study is to quantify the number of complications present in our institution compared to nationwide rates and determine whether complication rates differ depending on anesthesia modality.

METHODS: Charts of 107 hemodialysis patients at our institution were reviewed between 2017-2021. Patients were divided into complications and no complications groups. In addition to baseline demographics, outcome variables studied were complications (mechanical, infectious, and vascular) and anesthesia used during AVF creation (GA, RA, or MAC). Complication rates at our institution were compared to complication rates nationwide.[2] Statistical analysis was performed using two population proportion tests and χ^2 test when appropriate. A p-value < 0.05 was considered significant.

RESULTS: Subjects included in the study were patients who had an AVF created between 2017-2021. Of the 107 patients studied, 100 patients (93.5%) met inclusion criteria whereas 7 patients (6.5%) did not. Exclusion criteria included patients who were <18 years old and patients who had an AVF created before 2017. 53 patients (53%) had at least one complication following AVF creation while 47 patients (47%) had no complications. Patient demographics were similar between patients with and without complications except for race [Blacks (p < 0.001), Hispanics (p = 0.031), Other (p = 0.071)] and BMI (p = 0.034). There was a significant difference in overall complication rate at our institution compared to national complication rates (47% vs. 10.7%, p < 0.001), respectively. Specifically, thrombosis rates were significantly higher in our institution compared to national rates (42.55% vs. 21.37%, p < 0.001). There was no significant difference in infection (6.38% vs. 5.1%, p = 0.697) and ischemic steal syndrome (0% vs. 3.15%, p = 0.215) rates compared to national rates. There was no significant difference in anesthesia given during AVF creation and complication rates.

CONCLUSION: Our results demonstrate a significant difference in complication rates among our patients compared to the national rate, specifically thrombosis rates. Complications with the greatest incidence included malfunctioning AVF, thrombosis and stenosis. Anesthesia modality during AVF creation did not differ between the two groups studied. Institutional measures should be placed in order to reduce complication rates in hemodialysis patients with AVFs.

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2. Complications of the Arteriovenous Fistula: A Systematic Review. 2017;28(6)

Table 1. Baseline demographics of patients who had an AVF created between 2017 and 2021.

Characteristic	No Complications (n=53)	Complications (n=47)	*p*-value
Age (years)	59.38±14.34	57.83±13.98	0.59
Race			
Black/African American	34 (64.2)	45 (95.7)	< 0.001*
Caucasian	7 (13.2)	2 (4.3)	0.119
Hispanic	5 (9.4)	0 (0)	0.031*
Other	6 (11.3)	0 (0)	0.017*
Undisclosed	1 (1.9)	0 (0)	0.342
Gender			0.359
Females	20 (37.7)	22 (46.8)	
Males	33 (62.3)	25 (53.2)	
BMI (kg/m^2)	28.57± 0.76	25.98± 0.95	0.034*
Comorbidities[†]			
Coronary Artery Disease	15 (28.3)	9 (19.1)	0.285
Congestive Heart Failure	13 (24.5)	13 (27.7)	0.719
Diabetes Mellitus	37 (69.8)	25 (53.2)	0.087
Hypertension	53 (100)	46 (97.9)	0.285
Peripheral Vascular Disease	1 (1.9)	3 (6.4)	0.250
Hyperlipidemia	25 (47.2)	24 (51.1)	0.697
Obesity	18 (34.0)	12 (25.5)	0.358

Data are expressed as mean ± SD or n (%)
[†]Some patients had multiple comorbidities; therefore, total percentages may exceed 100.

Table 2. Institutional Complications

Type of Complication	Number of Events
Thrombosis	20 (21.3)
Malfunctioning AVF	34 (36.2)
Failure of Maturation	5 (5.3)
Infection	3 (3.2)
Aneurysm/Pseudo-aneurysm	7 (7.4)
Stenosis	16 (17.0)
Swelling	3 (3.2)
Bleeding	1 (1.1)
Hematoma	2 (2.1)
Vein Transposition	3 (3.2)
Total	94

Table 3. Comparison of National and Institutional Complication Rates

Complication Type (%)	National	Institutional	*p*-value
Infection	5.10	6.38	0.697
Ischemic Steal Syndrome	3.15	0.00	0.215
Thrombosis	21.37	42.55	< 0.001
Overall Complication Rate (%)	10.70	47.00	< 0.001

Table 4. Anesthesia Modality Given During AVF Creation

Anesthesia Modality	No Complications (n=53)	Complications (n=47)	*p*-value
General Anesthesia	8 (15.1)	12 (25.5)	0.098
Monitored Anesthesia Care (MAC)	25 (47.2)	26 (55.3)	
MAC + Regional Anesthesia	20 (37.7)	9 (19.1)	

Data is expressed as n (%)

AMBULATORY ANESTHESIA 5

Comparison of Electronic versus Phone-based Assessment of Quality of Recovery after Ambulatory Anesthesia

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INTRODUCTION: As surgical and anesthetic techniques have improved, serious morbidity and mortality have become rare events, particularly in ambulatory surgery. Therefore, patient-centered outcomes, such as quality of recovery after anesthesia, are considered increasingly important in clinical studies (1). The 40-item Quality of Recovery Score (QoR-40) is a validated questionnaire that assesses multiple domains of recovery including physical comfort, emotional state, physical independence, psychological support, and pain (2). The QoR-40 has been used in more than 60 perioperative studies (3). Previous studies in the ambulatory patient population have administered the QoR-40 instrument via mail or phone interview. However, limited information is available on the success of follow-up based on the modality of survey administration. We designed a study to compare a) completion of the QOR-40 survey and b) mean QOR-40 scores with survey administration via email versus phone interview after discharge from ambulatory surgery.

METHODS: This was a prospective observational study conducted at Yale New Haven Hospital. Patients were randomly assigned to complete the QoR-40 either via electronic survey or via phone interview on postoperative days 1, 2, and 7. In the phone interview group, the QoR-40 instrument was administered by a study investigator via telephone call with responses recorded into the study database. For the electronic group, the surveys were sent via email, with responses directly transmitted by the patient into the study database. The primary endpoint was the proportion of completion of the QoR-40 for each modality (electronic versus phone interview) on post-operative day 1. Secondary endpoints included survey completion on post-operative days 2 and 7, and mean QoR-40 scores.

RESULTS: A total of 122 patients were approached for participation, and 107 were enrolled. 7 patients were excluded after unanticipated hospital admission and 1 withdrew from the study. A total of 99 patients were randomized upon discharge from same-day surgery. Demographic data including relevant details of their anesthetic care were recorded for each patient and were comparable between groups (Table 1). Overall completion of the QoR-40 was 79/99 (80%) on postoperative day 1, 76/99 (77%) on day 2, and 71/99 (72%) on day 7 (Table 2). Completion of QoR-40 on day 1 was 76% for the electronic survey and 84% for the phone interview. Mean scores were overall similar for both electronic and phone-administered surveys (Table 3).

CONCLUSION: In this prospective study of quality of recovery after ambulatory surgery, we found that there was overall similar proportions of responders and of retention on subsequent administrations postoperatively when the QoR-40 survey was provided electronically or via phone. Moreover, the mean scores were the same between the two groups suggesting lack of systematic bias when answering via either modality.

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Variable	Number of Participants (n=99)	Email-based participants (n=49)	Phone Interview-Based Participants (n=50)
Gender	Female: 84	Female: 41	Female: 43
	Male: 14	Male: 7	Male: 7
	Other: 1	Other: 1	Other: 0
Ethnicity	Hispanic: 11	Hispanic: 2	Hispanic: 9
	Non-Hispanic: 84	Non-Hispanic: 45	Non-Hispanic: 39
	Unknown: 4	Unknown: 2	Unknown: 2
Race	Asian: 6	Asian: 2	Asian: 4
	Black/African American: 22	Black/African American: 11	Black/African American: 11
	White: 67	White: 35	White: 32
	Other: 4	Other: 1	Other: 3
Surgical Specialty	GYN: 58	GYN: 31	GYN: 27
	ENT: 24	ENT: 7	ENT: 17
	General: 5	General: 5	General: 0
	Plastics: 6	Plastics: 2	Plastics: 4
	Ophthalmology: 2	Ophthalmology: 1	Ophthalmology: 1
	Other: 4	Other: 3	Other: 1
Airway	ETT: 43	ETT: 23	ETT: 20
	LMA: 56	LMA: 26	LMA: 30
Anesthesia Maintenance	TIVA: 16	TIVA: 5	TIVA: 11
	Inhalational: 19	Inhalational: 10	Inhalational: 9
	Inhalational/Propofol: 64	Inhalational/Propofol: 34	Inhalational/Propofol: 30
Intra-operative Opiates Administered	Fentanyl: 95/99	Fentanyl: 47/49	Fentanyl: 48/50
	Hydromorphone: 18/99	Hydromorphone: 11/49	Hydromorphone: 7/50
	Remifentanil: 25/99	Remifentanil: 8/49	Remifentanil: 17/50
Pre/Intraoperative Antiemetics Administered	Ondansetron: 98/99	Ondansetron: 49/49	Ondansetron: 49/50
	Dexamethasone: 82/99	Dexamethasone: 40/49	Dexamethasone: 42/50
	Scopolamine: 3/99	Scopolamine: 0/49	Scopolamine: 3/50
	Metoclopramide: 6/99	Metoclopramide: 4/49	Metoclopramide: 2/50
	Olanzapine: 2/99	Olanzapine: 0/49	Olanzapine: 2/50
	Droperidol: 5/99	Droperidol: 2/49	Droperidol: 3/50
Neuromuscular Blockade Reversal	Sugammadex: 42	Sugammadex: 19	Sugammadex: 23
	Neostigmine: 3	Neostigmine: 1	Neostigmine: 2
	None:54	None: 29	None: 25
Average Surgical Duration (mins)	60	62	58
PACU Medications (percent administered)	Fentanyl: 41/99	Fentanyl: 24/49	Fentanyl: 17/50
	Hydromorphone: 5/99	Hydromorphone: 1/49	Hydromorphone: 4/50
	Oxycodone: 24/99	Oxycodone: 11/49	Oxycodone: 13/50
	Ondansetron: 9/99	Ondansetron: 5/49	Ondansetron: 4/50
	Dimenhydrinate: 4/99	Dimenhydrinate: 0/49	Dimenhydrinate: 4/50

Table 1: Demographics of study participants

Post-Operative Day	Response Percentage of All Participants	Response Percentage of Email-Based Administration	Response Percentage of Phone Interview-Based Administration
POD #1	80%	76%	84%
POD #2	77%	76%	78%
POD #7	72%	71%	72%

Table 2: Response proportions of study participants

Post-Operative Day	Mean QoR-40 Score (All Participants)	Mean QoR-40 Score (Email-Based Participants)	Mean QoR-40 Score (Phone Interview-Based Participants)
POD #1	176.2 (STDEV 18.1)	176.0 (STDEV 18.0)	176.4 (STDEV 18.6)
POD #2	179.7 (STDEV 19.6)	181.0 (STDEV 17.6)	178.8 (STDEV 21.3)
POD #7	188.2 (STDEV 13.0)	189.9 (STDEV 11.5)	186.5 (STDEV 14.2)

Table 3: Average QoR-40 scores of study participants

AMBULATORY ANESTHESIA 6

Most Common Diseases Diagnosed by the Preoperative Clinic and Their Associations with Postoperative Complications: A Review Of 13506 Patients

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INTRODUCTION: As part of the perioperative surgical home, a preoperative evaluation (POE) clinic provides a comprehensive history and physical exam, diagnosing and coordinating treatments for new medical conditions for patients scheduled for surgeries. Studies showed that the POE clinic is associated with reduced surgery cancelation, shorter length of stay, and lower in-hospital mortality.[1,2] This study aims to identify the most common new diagnoses made by the POE clinic and their associations with postoperative complications. It also aims to access the patient demographics needing additional optimization and having the new diagnoses as the patient population most in need to receive POE prior to surgery.

METHODS: A retrospective chart review was conducted on patients evaluated by the POE clinic at our institution from January 1, 2017 to December 31, 2018. Patients less than 18 years old were excluded. Data collection included: Patient demographics, new diagnosis, revised cardiac risk index (RCRI) score, surgery type, procedure risks, additional preoperative testing, specialty consultation, and 30 days postoperative complications (hospital re-admission, blood transfusion, reoperation due to postop bleeding, surgical sites infection, unintended intensive care unit stay, myocardial infarction, stroke, and death). Categorical variables were summarized as frequency (percentage) and continuous variables were reported as median (range) and mean (SD). Wilcoxon rank sum test was used to compare the continuous variables between two groups of patients and Chi-squared test was used to compare the categorical variables. Multivariable logistic regression model was used to evaluate the association between new diagnosis and postop complication with baseline characteristics adjusted. All tests were two-sided with p value <0.05 considered statistically significant. The analysis was done using R3.6.2.

RESULTS: A total of 13,056 patients were included in the study. If the patient received multiple POE visits, only the first visit was included in the study. Demographics comparing patients with and without new diagnosis are shown in Table 1. Of the 13,506 patients, 1,374 (10.5%) had pre-existing medical conditions requiring optimization (Table 2). The most common new diagnoses were anemia 9.7%, followed by thrombocytopenia 3.7%, chronic kidney disease 3.3%, hypo/hyperkalemia 2.7%, hypo/hypernatremia 2.2%, new onset of arrhythmia 1.8%, and diabetes mellitus 1.0%. A total of 580 patients had postoperative complications. Among all the new diagnoses, anemia (complication rate: 8.0% with vs 4.1% without, $P < 0.001$), new onset of arrhythmia (complication rate: 8.7% with vs 4.4% without, $P = 0.002$), and thrombocytopenia (complication rate: 6.4% with vs 4.4% without, $P = 0.035$) are associated with postop complications. The multivariable model analysis on predicting postoperative complication found anemia (OR=1.90, 95%CI: 1.49- 2.39, p<0.001) and new onset of arrhythmia (OR=2.09, 95%CI: 1.25-3.29, p=0.003) significantly associated with postoperative complication after adjusting for demographic and baseline characteristics (Table 3). The other predicting factors of postoperative complications included: procedure risk and high RCRI scores.

CONCLUSION: Our results demonstrated the importance of in-person evaluation by the POE clinic. For low acuity patients with minimal to no documented pre-exiting co-morbidities, >20% had new diagnosis and >10% required optimization by the POE clinic. For high acuity patients already diagnosed with multiple diseases, >35% still had new diagnoses by the POE clinic. Anemia, new onset of arrhythmia, and thrombocytopenia are associated with postop complications. As this study identified the top 3 diagnoses associated with postoperative complications, the POE clinic plan to design new preoperative optimization processes for these specific diseases to improve surgical outcomes.

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Table 1. Patient demographic and clinical data by if patients received new diagnosis

	Yes (N=3285)	No (N=9771)	Total (N=13056)	P value
Age				**<0.001**
N	3285	9771	13056	
Median (Range)	67.0 (14.0, 97.0)	61.0 (13.0, 98.0)	63.0 (13.0, 98.0)	
Mean (SD)	64.2 (14.4)	58.8 (15.4)	60.2 (15.4)	
Sex				**<0.001**
Male	1678 (51.1%)	4182 (42.8%)	5860 (44.9%)	
Female	1607 (48.9%)	5589 (57.2%)	7196 (55.1%)	
Race				**<0.001**
White/Caucasian	2637 (80.3%)	8175 (83.7%)	10812 (82.8%)	
Black/African American	308 (9.4%)	622 (6.4%)	930 (7.1%)	
Asian/pacific islander	66 (2.0%)	217 (2.2%)	283 (2.2%)	
Hispanic	88 (2.7%)	327 (3.3%)	415 (3.2%)	
American Indian/Alaskan native	5 (0.2%)	23 (0.2%)	28 (0.2%)	
Other	181 (5.5%)	407 (4.2%)	588 (4.5%)	
Procedure risk estimate:				**<0.001**
Low	1351 (41.1%)	5162 (52.8%)	6513 (49.9%)	
Intermediate	1786 (54.4%)	4338 (44.4%)	6124 (46.9%)	
High	148 (4.5%)	271 (2.8%)	419 (3.2%)	
RCRI				**<0.001**
0	2255 (68.6%)	8154 (83.5%)	10409 (79.7%)	
1	747 (22.7%)	1266 (13.0%)	2012 (15.4%)	
2	224 (6.8%)	272 (2.9%)	497 (3.8%)	
>=3	59 (1.8%)	79 (0.8%)	138 (1.1%)	
Acuity level by pre-existing co-morbidities:				**<0.001**
High (Multiple co-morbidities)	1304 (39.7%)	2255 (23.1%)	3559 (27.3%)	
Low (Minimal co-morbidities)	1981 (60.3%)	7516 (76.9%)	9497 (72.7%)	

For categorical variables, row % is provided, indicating the % of patients with or without new diagnosis in the subgroup with specific baseline characteristics

Table 2. Patient demographic and clinical data by if patients required optimization for pre-exiting disease

	Yes (N=1374)	No (N=11672)	Total (N=13046)	P value
Age				0.74
N	1374	11672	13046	
Median (Range)	62.0 (17.0, 97.0)	63.0 (13.0, 98.0)	63.0 (13.0, 98.0)	
Mean (SD)	60.5 (14.8)	60.1 (15.4)	60.2 (15.4)	
Gender				**0.031**
Male	654 (47.6%)	5199 (44.5%)	5860 (44.9%)	
Female	720 (52.4%)	6473 (55.5%)	7196 (55.1%)	
Race				**0.001**
White/Caucasian	1122 (81.7%)	9690 (82.9%)	10812 (82.8%)	
Black/African American	130 (9.5%)	800 (6.8%)	930 (7.1%)	
Asian/pacific islander	34 (2.5%)	249 (2.1%)	283 (2.2%)	
Hispanic	27 (2.0%)	388 (3.3%)	415 (3.2%)	
American Indian/Alaskan native	4 (0.3%)	24 (0.2%)	28 (0.2%)	
Other	57 (4.1%)	531 (4.5%)	588 (4.5%)	
Procedure risk estimate:				**<0.001**
Low	567 (41.3%)	5946 (50.9%)	6513 (49.9%)	
Intermediate	736 (53.6%)	5388 (46.1%)	6124 (46.9%)	
High	71 (5.2%)	348 (3.0%)	419 (3.2%)	
RCRI				**<0.001**
0	1043 (75.9%)	9361 (80.2%)	10409 (79.7%)	
1	236 (17.2%)	1772 (15.2%)	2012 (15.4%)	
2	74 (5.4%)	422 (3.6%)	497 (3.8%)	
>=3	21 (1.5%)	117 (1.0%)	138 (1.1%)	
Acuity level by pre-existing co-morbidities:				**<0.001**
High (Multiple co-morbidities)	274 (19.9%)	3285 (28.1%)	3559 (27.3%)	
Low (Minimal co-morbidities)	1100 (80.1%)	8397 (71.9%)	9497 (72.7%)	

For categorical variables, row % is provided, indicating the % of patients with or without optimization in the subgroup with specific baseline characteristics

Table 3. Multivariable model predicting postop complication(s)

Term	OR (95%CI)	P value
Age (per 1 year increase)	1 (0.99 , 1)	0.414
Female vs male	1.07 (0.9 , 1.28)	0.445
Procedure risk: intermediate vs low	2.79 (2.29 , 3.4)	<0.001
Procedure risk: high vs low	5.82 (3.95 , 8.51)	<0.001
RCRI 1 vs 0	1.03 (0.78 , 1.36)	0.812
RCRI 2 vs 0	1.11 (0.7 , 1.73)	0.638
RCRI >=3 vs 0	2.96 (1.6 , 5.19)	<0.001
Acuity level by pre-existing co-morbidities: low vs high	1.34 (1.07 , 1.71)	0.014
Days between surgery and POE (per 1-day increase)	1 (0.99 , 1.02)	0.740
New diagnosis: anemia	1.9 (1.49 , 2.39)	<0.001
New diagnosis: new onset other arrhythmia	2.09 (1.25 , 3.29)	0.003
New diagnosis: thrombocytopenia	1.25 (0.83 , 1.81)	0.270

SUBSPECIALTY ABSTRACTS

ANESTHETIC PHARMACOLOGY

ANESTHETIC PHARMACOLOGY 1

Local anesthetics induce an anti-tumoral immune response in vitro and in tumor established in mice

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INTRODUCTION: Retrospective studies observed a surprising expended overall survival and significant less relapse after local anesthetics (LAs) injection during oncological surgery.[1,2,3,4] We hypothesized that LAs may exert cytotoxic effects on tumor cells and trigger molecular signaling, which promote anticancer immune response.

METHODS: Bupivacaine, chloroprocaine, levobupivacaine, lidocaine, ropivacaine and prilocaine were studied in vitro in human osteosarcoma wild-type cells or in cells stably expressing fusion proteins to investigate cell stress and cell death (U2OSwt, U2OS GFP-LC3, U2OS GFP-ATF4, U2OS GFP-ATF6 and U2OS venus-XBP1-RFP-FYVE). Results were validated in vivo in immunocompetent C57Bl/6 mice transplanted with subcutaneous murine fibrosarcoma (MCA205wt or MCA205 K3 knock-out designed with CRISPR-Cas9 technology or MCA205 Atg5 knock-down obtained with sh-RNA technology) and colon adenocarcinoma (MC38wt). Tumor growth, survival and immune response were investigated after treatment with lidocaine and ropivacaine alone or combined with immunotherapy (anti-PD-1). Data normality was tested by the Kolmogorov-Smirnov test. In vitro, statistical analyses were performed with a Student t-test to compare parametric data to a control. In vivo, statistical analyses were performed with a Wilcoxon-Mann-Whitney test for tumor growth and with a log-rank test for survival analysis. Algorithm was engineered with a deep learning approach. Data analysis was performed using R software. For all test, significance was assessed for $p<0.05$. Ethical Committee approvement: CEEA IRCIV/IGR n¬∞26, French Ministry of Research, ref: 16946/2018100309413893v2, ref: 27492/2020100809149728v2.

RESULTS: LAs triggered premortem stress such as autophagy (Fig 1) and endoplasmic reticulum stress (Fig 2), which were both dependent on EIF2A kinase 3 and its downstream pathway phospho-eIF2alpha. LAs also mimicked mitochondrial uncouplers triggering mitochondrial toxicity and then cell death. In vivo, lidocaine and ropivacaine significantly decreased tumor growth and improved overall survival in different models of solid cancer (MCA205wt, MC38wt) established in immunocompetent mice (C57Bl/6). Associated with immune checkpoint blockade, these anticancer effects were significantly potentiated. Interestingly, LAs failed to induce antitumor responses in immunodeficient mice (nu/nu) or in tumors unable to trigger endoplasmic reticulum stress (MCA205 K3 knock-out) or autophagy (MCA205 Atg5 knock-down). Moreover, after rechallenge, cured mice did not develop tumors, proof of immunological memory development. Taken together, this data suggest that LAs-induced cellular stress triggers immune response that participate to the anticancer effect. Based on these findings, we designed an algorithm that allows to confront the biological effects of LAs with their physicochemical properties and to predict potential anticancer response of all clinically-employed anesthetic agents. Thus, intravenous agents such as propofol and ketamine seem to possess anticancer properties whereas opioids and volatile agents promote major procarcinogenic effects.

CONCLUSION: LAs enhance direct cytotoxicity in vitro and in vivo, which is preceded by premortem stress and mitochondrial dysfunction. LAs used as stand-alone agents trigger anticancer immune responses in vivo that can be enhanced by additional combination with standard anticancer immunotherapy. These observations led us to design an algorithm predicting effects of the different anesthetic agents. We suggest that the use of such 'immune-LAs' during oncological surgery may help clinicians to improve cancer care and clinical outcome.

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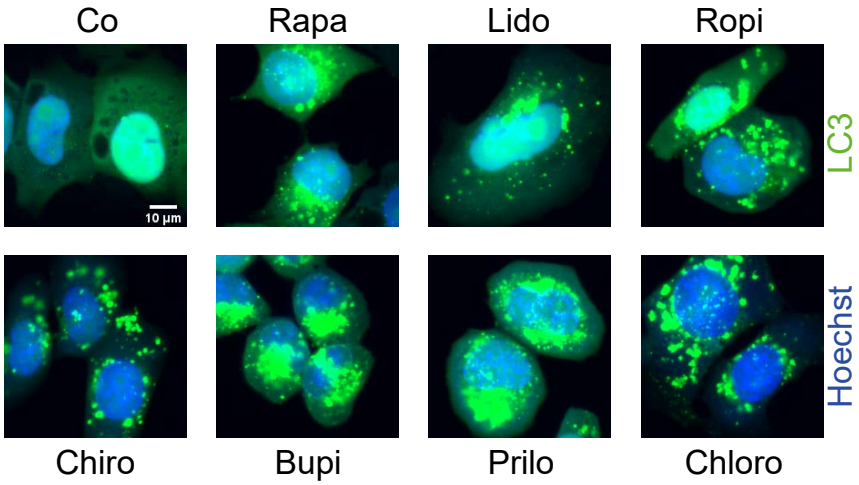

Figure 1. Local anesthetics induce autophagic flux
(Co: untreated, negative control ; Rapa: rapamycin, positive control;
Lido: lidocaine;Ropi: ropivacaine;Chiro: chirocaine;Bupi: bupivacaine;
Prilo: prilocaine; Chloro:chloroprocaine)

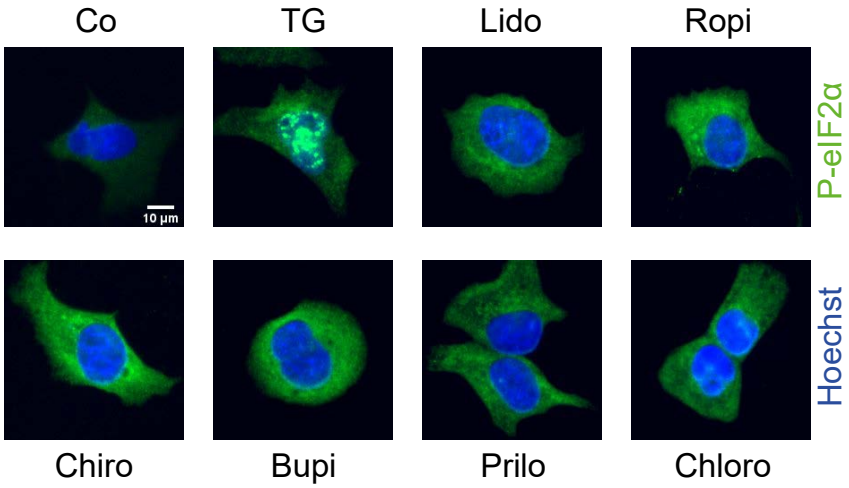

Figure 2. Local anesthetics induce endoplasmic reticulum stress
(Co: untreated, negative control ; TG: thapsigargin, positive control;Lido:lidocaine
Ropi: ropivacaine;Chiro: chirocaine;Bupi: bupivacaine;Prilo:prilocaine;Chloro:chloroprocaine)

ANESTHETIC PHARMACOLOGY 2

Substituted Cysteine Modification-Protection Suggests Novel Anesthetic pTFD-di-iPr-BnOH Does Not Bind in α+/ γ− Pocket

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INTRODUCTION: Potent intravenous anesthetics act in part through pentameric γ-aminobutyric acid type A receptors (GABAARs), the major inhibitory ligand-gated ion channels in the central nervous system. Typical synaptic GABAARs contain two alpha, two beta, and one gamma subunit surrounding a central pore, arranged β-α-β-α-γ. This creates four distinct subunit interface types: α+/β−, α+/γ−, β−/ γ+, and two β+/α− (Fig 1). Etomidate binds in the two outer transmembrane β+/α− interfaces, R–mTFD- MPAB binds to homologous α+/β− and γ+/β− sites, and propofol binds to all four of these interfaces. Until recently, no anesthetics were thought to bind in the outer transmembrane α+/γ− interface, leading to its designation as an "orphan site"[1,2]. However, exploratory hydrophobic mutagenesis and subunit-level photolabeling-protection studies suggest that pTFD-di-iPr-BnOH binds in outer transmembrane α+/β− and α+/γ− interfaces[3]. The current study aimed to further map pTFD-di-iPr-BnOH binding using the Substituted Cysteine Modification-Protection (SCAMP) method, which correlates better than hydrophobic mutant function studies with anesthetic photolabeling results[2].

METHODS: Xenopus laevis were used with IACUC. Harvested Xenopus oocytes were injected with messenger RNA mixtures encoding α1, β3, and γ2L subunits at 1α:1β:5γ ratios. SCAMP experiments were conducted in oocytes expressing four different cysteine mutants: α1S270Cβ3γ2L, α1β3L231Cγ2L, α1β3γ2LL246C, and α1β3γ2LI242C. Exposure to the sulfhydryl modifier, p-chloromercuribenzenesulfonic acid (pCMBS), was performed at room temperature in the presence of maximal-activating GABA (3 mM). pCMBS modification was detected using two-electrode voltage-clamp electrophysiology from changes in low:high GABA current response ratios (EC3 vs. 3 mM). Duplicate low:high ratios were measured before and after pCMBS + 3 mM GABA exposure, with intervening 5 min buffer washes. Modification ratios were calculated as average post-modification normalized to average pre-modification low:high ratios within oocytes. Control pCMBS exposures were chosen to produce 50% of the maximal modification ratio for each mutant receptor. In protection experiments, oocytes were pre-exposed to anesthetic for 30s before exposure to pCMBS + GABA + anesthetic. Modification ratio comparisons between control and protection used unpaired two-tailed Student's t-tests with n=3-5 oocytes per condition. Protection was inferred from significant concentration-dependent inhibition of modification.

RESULTS: Modification conditions selected for the four mutants resulted in control modification ratios ranging from 3.7 to 9.2 (Fig 2). Notably, pTFD-di-iPr-BnOH weakly protected β3L231C and γ2LL246C but displayed no concentration-dependent protection at these sites (Fig 3). No protection was observed at γ2LI242C. Etomidate protected none of the four engineered cysteines (none are in the β+/α− interfaces), but enhanced modification in three (α1S270C, γ2LL246C and γ2LI242C). R-mTFD-MPAB protected α1S270C and β3L231C, consistent with previous results (2). MPAB protection at β3L231C was concentration-dependent and more profound than pTFD-di-iPr-BnOH at this site (Fig 3).

CONCLUSION: Our preliminary SCAMP results for etomidate and R-mTFD-MPAB are fully consistent with previous photolabeling, mutational analysis, SCAMP studies, and for etomidate, cryo-EM. Our results for pTFD-di-iPr-BnOH are not fully consistent with the hypothesis that this drug binds in the outer transmembrane α+/γ− "orphan" anesthetic site (3). No protection was observed at α1S270C. Weak protection at γ2LL246C was observed with 30 μM pTFD-di-iPr-BnOH, but not at 100 μM and no protection was observed one helical turn away at γ2LI242C. Additionally, 10 to 100 μM pTFD-di-iPr-BnOH similarly protected β3L231C. This lack of concentration-dependent protection and its weakness relative to R-mTFD-MPAB suggests an allosteric effect or possibly binding near only one of the two β3 subunits. Thus, our results remain compatible with subunit photolabeling protection results suggesting that MPAB and pTFD-di-iPr-BnOH bind to one common site. However, current results only partially cover α+, γ–, and β− subunit faces. A more complete survey of potential anesthetic contact residues is underway. Funded by NIH R01GM089745 and R35GM141951.

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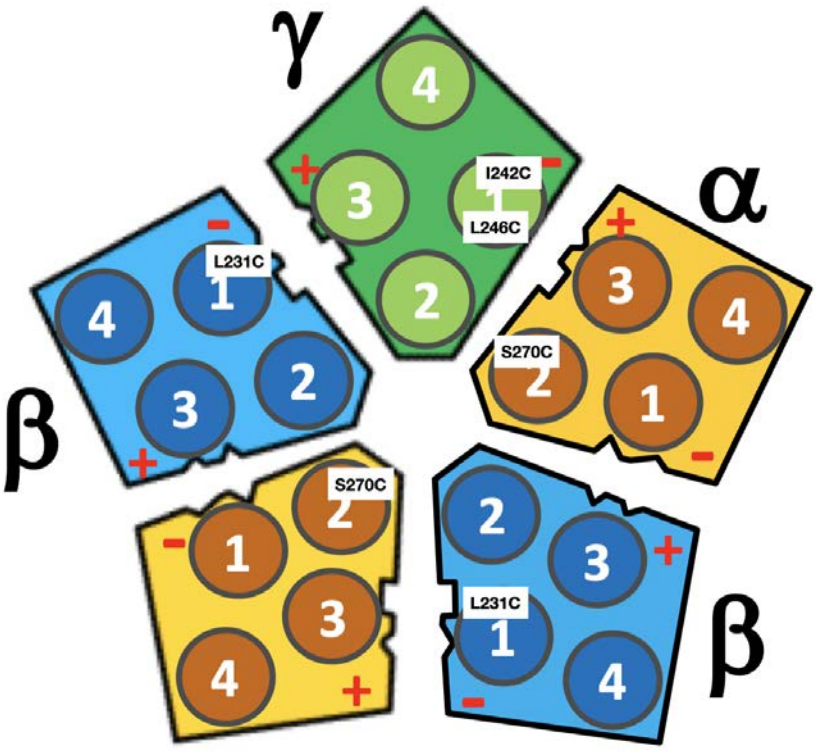

Figure 1. Schematic of GABA$_A$ receptor consisting of two alpha, two beta, and one gamma subunit with four distinct subunit interfaces: α+/ β−, α+/ γ−, β−/ γ+, and two β+/ α− sites. β_3L231C, α_1S270C, γ_{2L}L246C, and γ_{2L}I242C mutations are labeled on appropriate M1, M2, and M3 domains.

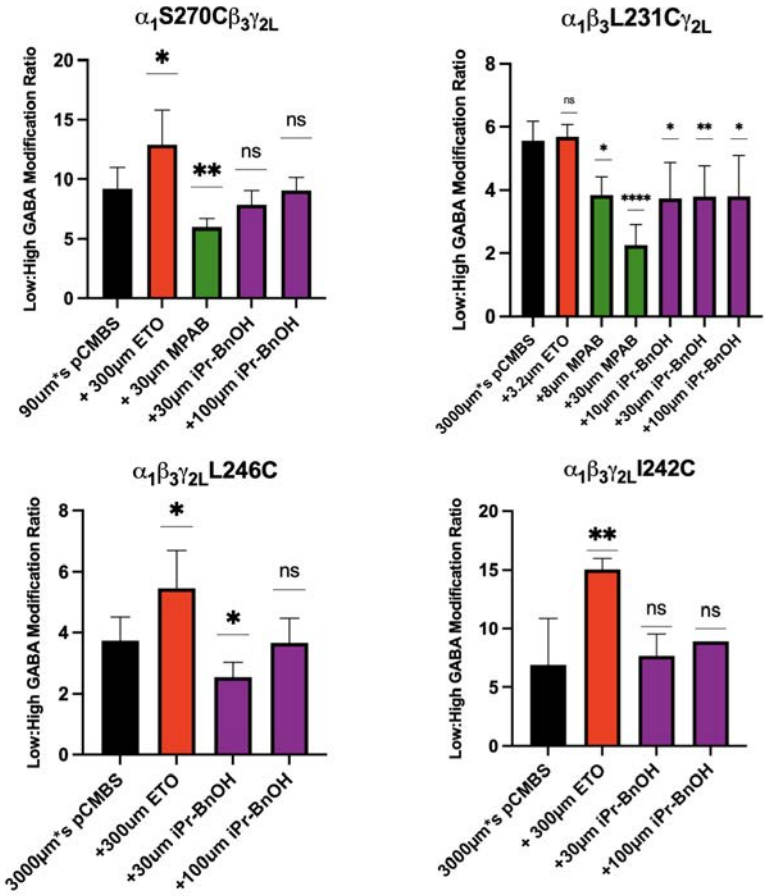

Figure 2. Substituted cysteine modification and anesthetic protection in α_1S270C$\beta_3\gamma_{2L}$, $\alpha_1\beta_3$L231Cγ_{2L}, $\alpha_1\beta_3\gamma_{2L}$L246C, and $\alpha_1\beta_3\gamma_{2L}$I242C mutants. The bar graph summarizes the pCMBS modification ratio in the presence of GABA alone and in the presence of ETO (red), R-mTFD-MPAB (green), or pTFD-di-iPr-BnOH (purple). P-values were calculated using student's t-test, with $p < 0.05$ as a significance threshold (****=p<0.0001, ***=p<0.001, **=p<0.01, *=p<0.05).

pCMBS Protection

Mutant	pTFD-di-iPr-BnOH	Etomidate	MPAB
α_1S270C$\beta_3\gamma_{2L}$	No	No	Yes
$\alpha_1\beta_3$L231Cγ_{2L}	Yes	No	Yes
$\alpha_1\beta_3\gamma_{2L}$L246C	No*	No	No
$\alpha_1\beta_3\gamma_{2L}$I242C	No	No	No

Figure 3. Summary of anesthetic protection at four cysteine residues. *Note: $\alpha_1\beta_3\gamma_{2L}$L246C showed weak anesthetic protection with pTFD-di-iPr-BnOH at 30µm but this effect was not dose-dependent and no protection was shown at 100µm.

ANESTHETIC PHARMACOLOGY 3

Desired Remimazolam Infusion Rate Can Be Determined Based on Patient's Age and Estimated Remimazolam Effective Site Concentration

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INTRODUCTION: Ultra-short acting benzodiazepine, Remimazolam (RZL), is very useful anesthetic. Its recommended maintenance dose is 1.0 mg/kg/h and reduced to 0.6 mg/kg/h in senile patients. But that age to reduce infusion is not clear. We estimated RZL effective site concentration and determine RZL infusion rate to achieve adequate anesthetic depth in a patient.

METHODS: After obtaining IRB approval and patients' informed consent, 353 patients undergoing scheduled orthopedic surgery were enrolled in this study. RZL induction dose was 0.3 mg/kg and maintenance doses were 1 mg/kg/h in patients under 60 years old, randomly 1 or 0.6 mg/kg/h in patients between 60 and 75 years old and 0.6 mg/kg/h in patients over 75 years old. General anesthesia was maintained with RZL and 0.1 μg/kg/min of remifentanil and peripheral nerve blocks. We collected raw frontal EEG by means of a Root® monitor and a SedLine® sensor (Masimo, Irvine, CA, USA). Patient state index (PSI) was recorded every 2 seconds during RZL infusion. RZL effective site concentration at the end of RZL infusion (Ce) was calculated with Runge - Kutta method.[1] Parameters were based on published data.[2, 3] A multiple linear regression was calculated to predict PSI at the end of RZL infusion based on age, gender and Ce.

RESULTS: Results are shown in tables and graph. A significant regression equation was found $F(3, 349) = 4.42$, $p = 0.005$ with an R^2 of 0.028. Predicted PSI is equal to (-0.1382×age) + (2.4059×gender) + (-0.006×Ce) + 50.3402 where gender is coded as 0 = male, 1 = female. Variance expansion factors of age, gender, and Ce are 1.382, 1.067 and 1.350 in turn.

CONCLUSION: PSI between 25 and 50 means adequate anesthesia. With our equation, Ce = 162.7972×PSI + 22.5046×age - 391.6689×gender – 8195.2545, patient's age, gender and desired PSI give necessary Ce at that moment. With Runge - Kutta method, RZL infusion rate gives Ce. These mean that it is not necessary to care about 1.0 or 0.6 mg/kg/h infusion rate. Age, gender, height, total body weight and wanted PSI give desired Ce which RZL infusion rate should reach. Remimazolam infusion rate to achieve desired anesthesia depth is the infusion rate which gives desired PSI and which reach desired Ce calculated with Ce = 162.7972×PSI + 22.5046×age - 391.6689×gender - 8195.2545 (male = 0, female = 1).

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Table 1. Demographic data (mean ± S.D. [range])

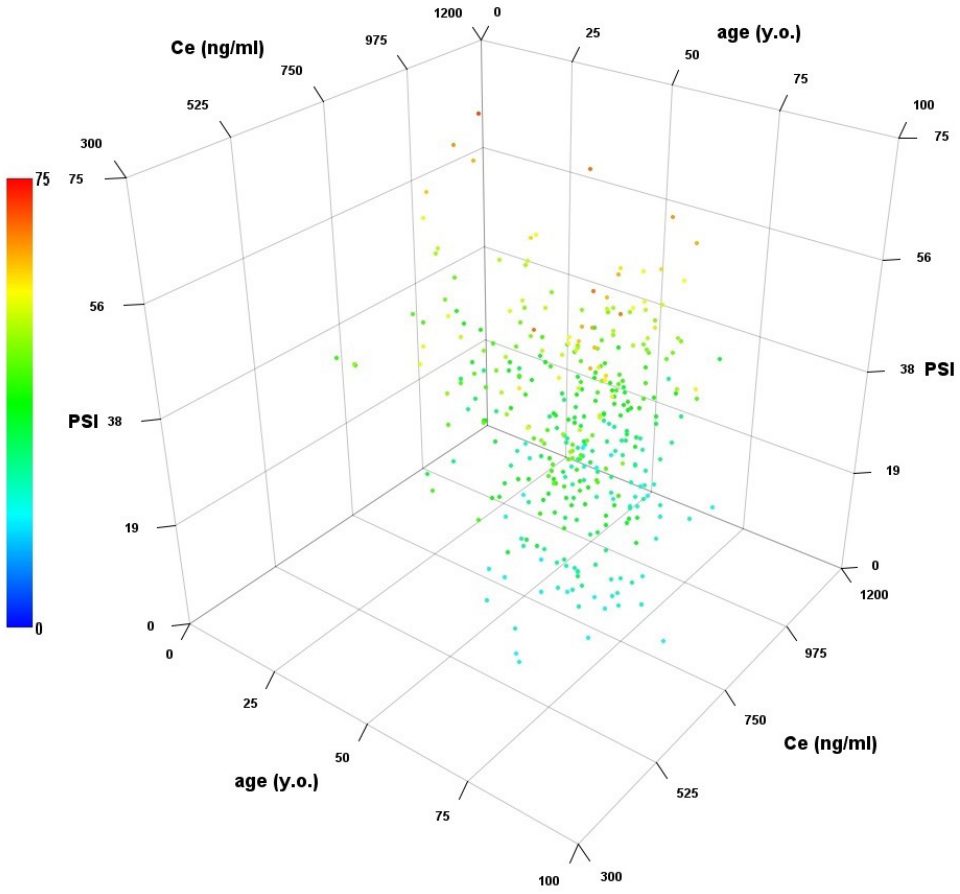
group	M/F	age (y.o.)	Height (cm)	TBW (kg)	BMI (kg/m²)
All cases	144 / 209	64.8 ± 17.3 [11 – 98]	16.0 ± 10.1 [135 – 189]	61.9 ± 14.0 [28 – 128]	24.0 ± 4.2 [13.9 – 38.2]
1.0U60	64 / 57	46.9 ± 15.1 [11 – 86]	165.0 ± 10.0 [135 – 184]	68.2 ± 15.8 [32 – 128]	24.9 ± 4.7 [16.0 – 38.2]
1.0O60	42 / 66	68.4 ± 4.1 [60 – 74]	158.7 ± 8.7 [142 – 180]	60.6 ± 11.3 [37.9 – 90]	24.0 ± 3.4 [16.0 – 34.2]
0.6U75	7 / 16	68.4 ± 4.1 [60 – 74]	158.6 ± 11.3 [146 – 189]	59.4 ± 14.9 [42.2 – 103]	23.4 ± 4.2 [17.2 – 37.4]
0.6O75	31 / 70	68.4 ± 4.1 [60 – 74]	155.9 ± 9.2 [138 – 180]	56.1 ± 11.2 [28 – 88]	23.1 ± 4.1 [13.9 – 37.6]

1.0U60: patients under 60 y.o. and RZL infusion at 1.0 mg/kg/h, 1.0O60: patients over 60 and under 75 y.o. and RZL infusion at 1.0 mg/kg/h, 0.6U75: patients over 60 and under 75 y.o. and RZL infusion at 0.6 mg/kg/h, 0.6O75: patients over 75 y.o. and RZL infusion at 0.6 mg/kg/h

Table 2. Results (mean ± S.D. [range])

group	Duration of Anesthesia (minute)	Duration of Surgery (minute)	Duration of Remimazolam (minute)	Ce at the end of Remimazolam Infusion (ng/ml)	PSI at the end of Remimazolam Infusion
All cases	114 ± 52 [38 – 362]	69 ± 46 [5 – 312]	88 ± 50 [9 – 323]	716 ± 168 [339 – 1165]	38.4 ± 11.4 [18 – 70]
1.0U60	108 ± 46 [39 – 260]	64 ± 40 [10 – 197]	83 ± 45 [23 – 234]	811 ± 128 [442 – 1165]	38.0 ± 11.2 [19 – 70]
1.0O60	112 ± 54 [38 – 283]	70 ± 48 [5 – 227]	87 ± 51 [16 – 245]	819 ± 95 [564 – 1125]	38.3 ± 11.0 [18 – 64]
0.6U75	100 ± 31 [60 – 159]	55 ± 29 [23 – 121]	76 ± 28 [41 – 138]	522 ± 55 [356 – 617]	36.1 ± 9.7 [20 – 54]
0.6O75	126 ± 57 [39 – 362]	79 ± 52 [12 – 312]	98 ± 55 [9 – 323]	537 ± 76 [339 – 826]	38.8 ± 12.5 [19 – 67]

1.0U60: patients under 60 y.o. and RZL infusion at 1.0 mg/kg/h, 1.0O60: patients over 60 and under 75 y.o. and RZL infusion at 1.0 mg/kg/h, 0.6U75: patients over 60 and under 75 y.o. and RZL infusion at 0.6 mg/kg/h, 0.6O75: patients over 75 y.o. and RZL infusion at 0.6 mg/kg/h



ANESTHETIC PHARMACOLOGY 4

A propofol binding site on ryanodine receptor 1

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INTRODUCTION: Malignant hyperthermia (MH), as part of a spectrum of muscle pathologies, arises from the combination of triggering anesthetics and a mutant ryanodine receptor 1 (RyR1), a calcium channel embedded in skeletal muscle sarcoplasmic reticulum[1]. The channel becomes biased open, resulting in a large calcium ion flux. Clearing the excess calcium from the cytoplasm generates a large metabolic load, which leads to the pathophysiologic sequelae of MH. Supportive care includes discontinuing triggering anesthetics in favor of non-triggering anesthetics such as propofol, which would then have an opportunity to bind to RyR1. Whether propofol binding occurs and its potential consequences are not yet understood. We have identified a propofol binding site on RyR1 using photoaffinity labeling and characterized it using molecular dynamics simulations.

METHODS: Photoaffinity labeling was conducted using m-azipropofol (AziPm)[2], a photolabel analog of propofol. The RyR1 protein was incubated with AziPm and irradiated to form a reactive carbene version of AziPm which bonds covalently to RyR1 in the AziPm binding site. The adducted protein was then subjected to proteolysis and mass spectrometry. Identifying the peptides whose sizes grew by the size of the adduct allowed identification of adducted residues. In order to ascertain whether the identified site could be shared with propofol, a protection assay was conducted to determine whether co-incubation with propofol would competitively inhibit photoadduction by AziPm. Molecular dynamics (MD) simulations were conducted of the wild-type RyR1 transmembrane domain with a single propofol molecule placed in the photoaffinity-identified putative binding site on the tetrameric RyR1. This site is distinct from previous L4827 sites as it is among alpha helices with relatively little solvent exposure. Double-decoupling free energy perturbation (FEP) MD with a flat-well volume restraint[3] was used to calculate the standard binding free energy of each ligand.

RESULTS: Photoaffinity labeling revealed an AziPm binding site at L4827 in RyR1. A protection assay was consistent with this also being a propofol binding site. This site is located in the transmembrane domain of RyR1. Since these experimental methods cannot quantify the affinity or configuration of these ligands in the site, we therefore conducted equilibrium MD simulations that suggested that propofol was stable in the site. FEP MD simulations with both closed and open state RyR1 predicted binding affinities of propofol that corresponded to dissociation constants KD = 0.5–3 μM. Examination of the bound propofol configuration shows that its hydroxyl group is oriented toward Y4851 with a distance roughly 9".

CONCLUSION: Our data shows that propofol binds RyR1 at a clinically relevant concentration in the L4827 site on RyR1. Our previous work identified a propofol binding site near to this site with fewer interacting protein residues, also consistent with photoaffinity labeling of L4827, but with a lower affinity. As propofol is a nontriggering anesthetic, this is a novel example of the ability of a commonly-used non-triggering anesthetic to bind to RyR1. Future work would include reproducing these studies in RyR1 containing an MH-causative mutation.

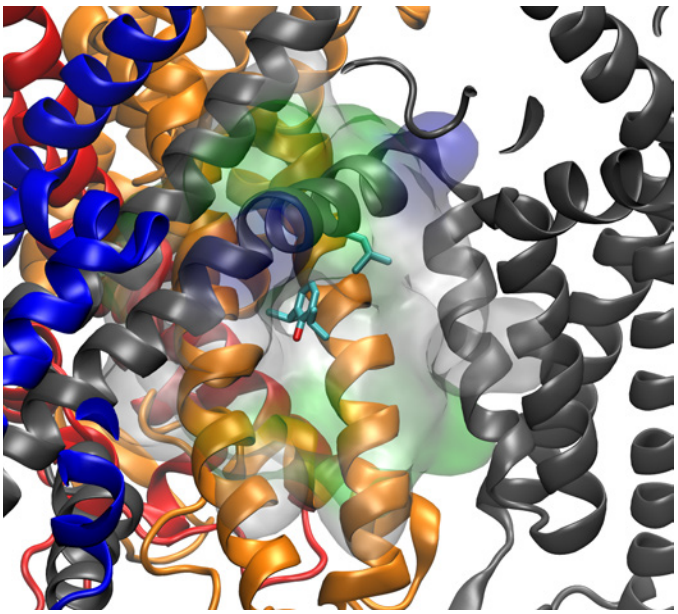

Fig. 1

ANESTHETIC PHARMACOLOGY 5

EEG Profile for a Selective GABAA-Slow Agonist, Compared to Propofol, in Rats

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INTRODUCTION: Anesthetic agents like propofol increase power in slow delta frequencies (0.1 to 3 Hz), with a general decrease in EEG frequencies above 30 Hz. Propofol is non-selective for GABAA response subtypes, it enhances all three GABAA-subtypes (slow, fast, and tonic). A new anesthetic, BB, selectively targets GABAA-slow synapses to depress brain responsiveness. We hypothesized that a selective GABAA-slow agonist, BB, would produce a different EEG signature compared to the broad spectrum GABAA agonist (propofol), and tested this using rat EEG recordings.

METHODS: Male rats were used following IACUC approval from the US Army Medical Research Institute of Chemical Defense and the University of Michigan. Rats were anesthetized using isoflurane (3-5% induction, 1-3% maintenance; with oxygen @ 0.5-1.0 L/min. Stainless steel screws were used to capture cortical EEG activity.

RESULTS: Propofol administration generated increased power in slow delta frequencies (0.1 to 4 Hz) and a general decrease in EEG power above 30 Hz at loss of consciousness (LOC). By contrast, BB administration increased theta activity markedly (3-5 Hz and 8-10 Hz), and slightly increased delta power, but did not depress high frequency responses above 30 Hz. Neither agent produced burst suppression activity at LOC. Both anesthetics produced a characteristic flattening of time-delayed embeddings, similar to volatile and dissociative anesthetics at LOC. Propofol's EEG effects were in agreement with those seen in previous studies across individuals and species. At LOC a generalized slowing in EEG was seen with increased power in frequencies below 4 Hz. BB produced a markedly different EEG pattern, with a selective increase observed in the theta frequency range.

CONCLUSION: Conclusion: Increased theta frequencies are interesting because GABAA slow synapses have previously been suggested to underlie theta frequency oscillations, while fast synapses control high, gamma frequency oscillations (30-60 Hz). Tonic GABAA responses produce a generalized depression of neuronal activity across all frequencies. BB and propofol share the ability to flatten EEG time-delayed embeddings at LOC. Flattened embeddings are also observed in humans and thought to reflect a decrease in EEG information content at LOC. It appears that propofol's effects on fast and/or tonic responses contribute to its respiratory and cardiovascular unwanted side effects, since these were not produced by BB. Figure 1. Power spectral density plots comparing the effects produced by propofol (A & B) and BB (C & D). BB produced a selective increase in theta frequencies produced by prolonging GABA-slow synaptic inhibition following loss of consciousness (LOC-blue vs red-preLOC).

ANESTHETIC PHARMACOLOGY 6

An Analysis the Potency of a Series of Halogenated Hydrocarbon Anesthetics

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INTRODUCTION: My studies of chemically similar halogenated ether anesthetics[1] and the noble gas anesthetics xenon, krypton and argon[2] quantitatively demonstrated strong correlations between the surface area of the respective differing halogen or noble gas and the potency of the anesthetic. This was attributed to London forces due to the formation of instantaneous dipoles. The present study was undertaken to see if a similar relationship would apply to a series of halogenated hydrocarbon anesthetics.

METHODS: MAC values for mice for halogenated two carbon anesthetics with the general formula CF3CHBrX where X=F, Cl or Br were obtained from Larsen et.[3] and the radii of the differing halogens were obtained from Vogt[4]. The spherical surface area was then computed for each differing halogen. Linear regression analysis was employed to obtain the correlation coefficient between the surface areas and the MAC values for the anesthetics.

RESULTS: The correlation between MAC values and the surface areas of the differing halogens was -0.980. The negative value is due to the lower MAC values for larger halogens.

CONCLUSION: The correlation of the boiling points of many halogenated organic compounds and the surface areas of the respective halogens has been attributed to London forces due to the formation of instantaneous dipoles[5]. Also, it has been shown that boiling point is correlated with volatile anesthetic potency[6]. To investigate how this line of reasoning may apply to the potency of certain volatile anesthetics, my recent study[1] evaluated halogenated ether anesthetics including desflurane and isoflurane. Each anesthetic had exactly the same chemical structure except for a different halogen at a single location. The study demonstrated a strong correlation between the surface area of the differing halogen and the potency of the respective anesthetic. The potency was, as suggested by Pauling[7], attributed to London forces due to the formation of instantaneous dipoles. The conclusion was that the anesthetics interact with the site(s) of action by London forces. Another study of mine investigated argon, krypton and xenon[2]. It also found a strong correlation between the surface area of the respective noble gas and its potency as an anesthetic. The present study was designed to see if a similar line of reasoning would apply to a series of identical halogenated hydrocarbon anesthetics differing only in a halogen at the same location. In common with my previous studies, this investigation demonstrated a strong correlation between the surface area of the atoms of each differing halogen and the halogenated hydrocarbon anesthetic's potency. The results strongly suggest that in common with certain ether anesthetics and noble gas anesthetics, these halogenated hydrocarbon anesthetics also interact with the site(s) of anesthesia action by London forces.

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ANESTHETIC PHARMACOLOGY 7

Caffeine accelerates emergence from general anesthesia maintained by propofol infusion in rats

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INTRODUCTION: Currently there are no pharmacological agents in routine clinical use that can accelerate emergence from anesthesia. As patients recover from anesthesia at varying rates depending on numerous factors including genetics, age and comorbid burden[1] the availability of such a drug would have significant clinical utility. Our group has previously shown that an intravenous bolus of caffeine administered near the end of a general anesthetic with isoflurane can significantly accelerate emergence in both rats[2] and healthy human volunteers[3], an effect likely due caffeine's ability to elevate intracellular cAMP concentration and antagonize adenosine receptors[4]. Additionally we have shown that a bolus of caffeine can significantly accelerate emergence from a single induction bolus of propofol in rats in a dose dependent manner[2]. However, initial experiments attempting to employ a terminal caffeine bolus to accelerate emergence from 90 mins of anesthesia maintained with propofol infusion in human volunteers demonstrated limited efficacy. Returning to the animal model, we hypothesize that a strategy of continuous co-infusion of caffeine during general anesthesia maintained with propofol infusion will be able to accelerate emergence at the termination of the anesthetic.

METHODS: These studies on rats were approved by The University of Chicago Institutional Animal Care and Use Committees (IACUCs). Adult Sprague Dawley rats (Charles River, Wilmington, MA), weighing 300–450 gm were used in this cross-over study. Rats were initially rendered unconscious by placement in a closed chamber where they were exposed to 2% isoflurane for 10 min. At this point, an intravenous cannula was placed in their tail vein and connected to a dual port adapter. As the rats began to emerge from isoflurane, a 5 mg/kg bolus induction dose of propofol was administered and a propofol infusion of varying doses (200 µg/kg/min thru 1000 µg/kg/min) was initiated through one of the infusion ports. Meanwhile, the second infusion port was connected to either a saline infusion or an infusion of caffeine at varying doses (25 mg/kg thru 100 mg/kg total caffeine dose). After 60 minutes, all infusions were stopped, and emergence time was measured as time to righting. Heart rate, oxygen saturation and respiratory rate were monitored at 10 minute intervals throughout the anesthetic. At 30 minutes, anesthetic depth was monitored by assessing motor response to tail clamp applied for 30 seconds. At all dosing conditions tested, each rate received the saline infusion and the caffeine infusion with an interval time in between of at least one week.

RESULTS: A propofol infusion dose of 600 µg/kg/min was needed to achieve a 90% insensitivity to tail clamping. At this dose, a caffeine co-infusion of 800 µg/kg/min decreased time to emergence by 49% (16.38 min control vs 8.28 min caffeine, $p = 0.0008$ [$n = 8$]), while a single bolus dose of caffeine at the end of the anesthetic session did not significantly alter emergence time. At propofol infusion doses above 800 µg/kg/min, caffeine co-infusion up to the maximum tested dose was unable to significantly accelerate emergence. Vital signs did not vary significantly between control and caffeine infused rats.

CONCLUSION: In rats maintained under general anesthesia with a continuous propofol infusion, a co-infusion strategy of caffeine administration is able to significantly accelerate emergence at the termination of the anesthetic. These results extend the utility of caffeine as a potential reversal agent for intravenous anesthetics. Our group has recently reported EEG evidence that caffeine is able to reverse unconsciousness under light isoflurane anesthesia in rats5. Similar studies are ongoing to examine the effects of caffeine administration on the EEG spectra of rats maintained under propofol anesthesia. The ability to reverse unconsciousness engendered by propofol infusion would suggest applications to accelerating recovery in procedural contexts where propofol infusions are commonly used, such as the endoscopy suite.

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ANESTHETIC PHARMACOLOGY 8

A novel peptide targets radixin to reduce activity of α5GABA$_A$ receptors in mice

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INTRODUCTION: Dysregulation of α5GABA$_A$ receptors (α5GABA$_A$Rs) contributes to a variety of neurocognitive disorders, including Alzheimer's disease, stroke, and possibly memory loss after general anesthesia.[1-4] α5GABA$_A$Rs are located primarily in the extrasynaptic regions of neurons, where they generate a tonic inhibitory conductance that impairs cognition.[1,2] As an example, exposure to a general anesthetic drug triggers a persistent increase in α5GABA$_A$R activity that causes memory deficits.[2] Various negative allosteric modulators have been developed to reduce α5GABA$_A$R activity; however, to date, none have proven to be effective in clinical trials.[5,6] Thus, new treatment strategies are needed.

Radixin is a cytosolic anchoring protein that tethers α5GABA$_A$Rs to extrasynaptic regions of neurons by binding the receptors to the actin cytoskeleton; phosphorylation of radixin is thought to be a prerequisite for α5GABA$_A$R binding.[7] We hypothesized that we could reduce α5GABA$_A$R activity by disrupting the interaction between radixin and these receptors. To disrupt this interaction, we designed a peptide that mimics the α5GABA$_A$R binding site on radixin (US patent 10,981,954; Figure 1). The goals of this study were to determine 1) whether radixin phosphorylation increases endogenous binding of radixin to α5GABA$_A$Rs, 2) whether the peptide disrupts radixin–α5GABA$_A$R binding after phosphorylation, and 3) whether the peptide prevents an increase in a tonic current in hippocampal neurons triggered by exposure to an anesthetic drug.

METHODS: Studies were approved by the local animal ethics committee. Hippocampal slices were prepared from mice aged 8–9 weeks. Slices were preincubated with okadaic acid (1 μM), a phosphatase inhibitor that induces phosphorylation. Radixin–α5GABA$_A$R binding was assessed using co-immunoprecipitation and western blots. In other studies, co-cultures of hippocampal neurons and cortical astrocytes prepared from embryonic mice[2,4] were treated with etomidate (1 μM) or vehicle, with or without TAT-peptide (0.1 μM) or TAT-scrambled peptide (0.1 μM) for 1 h. Etomidate was washed away after 1 h, and the tonic current generated by GABA (0.5 μM) was recorded 24 h later. The GABA$_A$ receptor antagonist bicuculline (20 μM) was used to measure the amplitude of the tonic current.

RESULTS: Okadaic acid increased radixin-α5GABA$_A$R binding, whereas the rho-kinase inhibitor Y-27632 reduced this binding (Figure 2). The peptide markedly reduced radixin-α5GABA$_A$R binding. The tonic current generated by α5GABA$_A$Rs was increased by etomidate, and its amplitude was reduced by the peptide, but not the scrambled peptide (Figure 3).

CONCLUSION: Our results provide the first evidence of a novel strategy to reduce α5GABA$_A$R activity by disrupting the binding of these receptors to radixin. This promising strategy may be helpful in developing treatments for disorders associated with over-activity of α5GABA$_A$Rs.

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ANESTHETIC PHARMACOLOGY 9

Meta-analysis: a study of adverse effects and turnover rates of sugammadex versus neostigmine for neuromuscular blockade reversal

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INTRODUCTION: For many years, neostigmine, an acetylcholinesterase inhibitor, was the drug of choice for reversing neuromuscular blockades in the operating room. However, there are disadvantages to using neostigmine including autonomic dysfunction like bradycardia and post-operative nausea & vomiting (PONV), and the necessity to administer the drug at the correct time due to its lag time in effect. Recent studies have been performed on sugammadex, a new reversal agent, which does not have a 'lag time effect.' Although it is considered safer, some studies cite harmful effects. Given its rapid rise in usage, a more comprehensive characterization of the clinical and practical aspects of sugammadex compared to the standard of neostigmine is needed.

METHODS: In accordance with the PRISMA guidelines, a systematic review of PubMed and Scopus databases was performed in search of publications that compared the efficacy and safety of sugammadex versus neostigmine. All publications that included either endpoints were included irrespective of date of publication, country of origin, language, age range of patients, type of surgical procedure, or ASA grade. Data were analyzed using Microsoft Excel.

RESULTS: 57 articles totaling n = 66157 patients met inclusion criteria for this meta-analysis. Compared to neostigmine, sugammadex showed a significant reduction in extubation time (mean difference [MD] = -2.77 min, 95% CI (-3.95, -1.59)), Recovery to TOF >0.9 time (MD =-11.27 min, 95% CI (-12.7, -9.89)), OR discharge time (MD = -3.74 min, 95% CI (-4.77, -2.71)), and PACU discharge time (MD = -8.51 min, 95% CI (-14.9, -2.07)). Sugammadex shows a significant reduction in pneumonia (RR = 0.593, 95% CI (0.361, 0.671)) and bradycardia (RR = 0. 535, 95% CI (0.424, 0.675)), and a significant increase in PONV (RR = 1.21, 95% CI (1.05, 1.39)). No significant difference was found for atelectasis (RR = 0.964, 95% CI (0.853, 1.09)).

CONCLUSION: This study supports that administration of sugammadex as a reversal agent for neuromuscular blockade facilitates faster extubation time, OR turnover time, and PACU discharge time. Sugammadex is associated with lower risk of bradycardia and pneumonia, but higher risk of PONV. In an ongoing study, we are investigating the shorter times of sugammadex in the context of a cost-benefit analysis. These results serve as a strong basis for future work on neuromuscular blockage reversal agents, with large implications in improving the quality of patient care, bolstering the efficiency of the surgery and anesthesiology services, as well as improving healthcare costs of surgery and anesthesia.

SUBSPECIALTY ABSTRACTS

BLOOD MANAGEMENT

BLOOD MANAGEMENT 1

Clinical Audit for introduction of Pre-filled Suxamethonium and Ephedrine syringes in Tallaght University Hospital

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INTRODUCTION: Routine daily safety procedures in all theatre locations requires anaesthetists to have emergency intravenous medications immediately available for instances of severe reductions in blood pressure. However, the medications required for these emergencies are currently only available in glass ampoules which require a sterile drawing up procedure into disposable syringes for each case before they can be administered to the patient. The process of preparation area disinfection, opening syringes, drawing up needles, opening sterile ampoules, drawing up medications and labelling of syringes can last several minutes to perform. This constitutes an issue in anaesthetic emergencies that require immediate actions as well as in microbial contamination[1], drug administration errors[2,3] and workplace efficiency[4]. Pre-filled syringes (PFS) are now available and medications such as suxamethonium and ephedrine are supplied in individually wrapped pre-labelled and pre-filled syringes designed for immediate patient administration without the need for the prolonged drawing up process[4]. We aimed to audit the cost-effectiveness of using PFS instead of glass ampoules and evaluate the benefit of these when considering waste disposal, environmental impact, infection risk and physician error.

METHODS: An audit on all of the theatre events from January 2019 to January 2020 in Tallaght University Hospital was performed. We analysed data the amounts of suxamethonium and ephedrine drawn up, administered or disposed of without administration (waste) for all patients operated on for one calendar year. Accurate information was obtainable as all medication dispensed by pharmacy to theatre was provided by pharmacy and all administration of these drugs was recorded electronically in the anaesthesia information system GE Centricity.

RESULTS: During the study period suxamethonium and ephedrine were made available for use in 8,519 patient theatre episodes. Taking current prices paid by the hospital for suxamethonium and ephedrine and comparing this to the indicative costs of pre-filled syringes, inclusion of PFS reflect an overall cost saving for the hospital of €7,831.00 per year. These calculations do not take into account peripheral costs such as needle stick injuries, waste, preparation of drugs, risk of microbial contamination, preparation errors and other financial burdens which are likely to be significantly reduced by the use of pre-filled syringes. Savings rise to €31,048.48 when considering these benefits of reduced medication error costs, reduced waste, reduced risk of microbial infection and patient safety.

CONCLUSION: There are great potential advantages to the use of PFS in theatre management of blood pressure as they have the potential to improve system safety and work efficiency from an economic, environmental, infection control, patient and staff safety viewpoint. Understanding this change at a hospital level from an organisational perspective, however, is key to implementing this and building safer systems in the future.

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BLOOD MANAGEMENT 2

Intraoperative blood transfusion in elderly patients on antithrombotic therapy: A secondary analysis of the prospective, observational POSE study

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INTRODUCTION: Many elderly patients are receiving antithrombotics which may increase intraoperative blood loss. We aimed to assess whether chronic antithrombotic therapy was associated with intraoperative transfusion of Packed Red Blood Cells in patients >80 years of age undergoing elective surgery.

METHODS: A secondary analysis of a prospective observational European multicenter study including 9497 surgical patients >80 years of age in 177 centers was performed. We included patients who underwent elective surgery with available data on chronic antithrombotic therapy. The primary outcome was intraoperative transfusion of Packed Red Blood Cells and results were analyzed using multiple logistic regression.

RESULTS: A total of 7174 patients were included of which 4073 (56.8%) were on antithrombotic therapy. Among patients on antithrombotic therapy 191 (4.7%) received intraoperative blood transfusion compared with 98 (3.2%) of patients not on chronic antithrombotic therapy (crude OR 1.51, 95% CI 1.18 to 1.94). When adjusted for age, sex, Body Mass Index, American Society of Anesthesiologist classification, baseline haemoglobin concentration, disseminated cancer, and type and majority of surgery, the OR was 0.98; 0.73 to 1.32.

CONCLUSION: When adjusted for predetermined risk factors chronic antithrombotic therapy was not found to be associated with intraoperative blood transfusion in elderly patients undergoing elective surgery.

Table 1. Patient Characteristics

Characteristic	Antithrombotic Therapy N=4073[1]	No Antithrombotic Therapy N=3101[1]	P-value
Age			
	83.00 [81.00; 86.00]	83.00 [81.00; 85.00]	<0.001
Sex			
Male	2285 (56 %)	1341 (43 %)	<0.001
Body Mass Index	N=4029*	N=3080*	0.002
Underweight (<18.5 kg/m^2)	0 (0 %)	0 (0 %)	
Normal Weight (18.5-24.9 kg/m^2)	1603 (40 %)	1336 (43 %)	
Obesity (≥25.0 kg/m^2)	2426 (60 %)	1744 (57 %)	
Baseline Haematocrit, %	N=2846*	N=2023*	
	38.00 [34.00; 41.10]	38.90 [35.00; 42.00]	<0.001
Baseline Haemoglobin Concentration, g/dL	N=3123*	N=2264*	
	12.60 [11.20; 13.80]	12.80 [11.60; 14.00]	<0.001
Baseline Creatinine Concentration, mg/dL	N=3045*	N=2145*	
	1.00 [0.82; 1.31]	0.90 [0.75; 1.11]	<0.001
Baseline Albumin Concentration, g/dL	N=840*	N=602*	
	3.70 [3.20; 4.20]	3.80 [3.34; 4.20]	0.03
ASA	N=4069*		<0.001
I-II	1110 (27%)	1927 (62%)	
III-V	2959 (73%)	1174 (38%)	
Currently Smoking	N=3100*	N=4072*	
	225 (5.5 %)	169 (5.5 %)	0.89

Diabetes			
	1003 (25 %)	465 (15 %)	<0.001
Severe COPD			
	360 (8.8 %)	190 (6.1 %)	<0.001
Hypertension Requiring Medication			
	3383 (83 %)	1985 (64 %)	<0.001
Congestive Heart Failure			
	841 (21 %)	162 (5.2 %)	<0.001
Disseminated Cancer	N=4071*	N=3100*	
	210 (5.2 %)	172 (5.5 %)	0.47
Type of Surgery			<0.001
Minor	969 (24 %)	726 (23 %)	
Intermediate	1517 (37 %)	1339 (43 %)	
Major	1587 (39 %)	1036 (33 %)	
Surgical Category			<0.001
Orthopaedic	643 (16 %)	593 (19 %)	
Gynaecologic	122 (3.0 %)	162 (5.2 %)	
Vascular	355 (8.7 %)	78 (2.5 %)	
Abdominal	991 (24 %)	891 (29 %)	
Cardiothoracic	565 (14 %)	120 (3.9 %)	
Neurosurgical	71 (1.7 %)	62 (2.0 %)	
Other	1326 (33 %)	1195 (39 %)	
Intraoperative Transfusion of Packed Red Blood Cells	N=4071*		
	191 (4.7 %)	98 (3.2 %)	0.001
Intraoperative Transfusion of Plasma and/or Platelets	N= 4072*		

	70 (1.7 %)	34 (1.1 %)	0.03
Hospital Length of Stay (days)			
	3.00 [1.00; 7.00]	2.00 [0.00; 5.00]	<0.001
Complications in and out of Hospital within 30 days	N=4071*		
	208 (5.1 %)	99 (3.2 %)	<0.001
All Cause 30-Day Mortality	N=3960*	N=3060*	
	104 (2.6 %)	42 (1.4 %)	<0.001

[1]Median [25%;75%]; n/N (%)
*Number of patients with available data

Variable	OR[1]	95% CI[1]	p-value
Antithrombotic Therapy			
No	—	—	
Yes	0.98	0.73, 1.32	1.0

[1]OR = Odds Ratio, CI = Confidence Interval

Table 3. Odds Ratio of the association of intraoperative blood transfusion and antithrombotic therapy, adjusted for sex, age, Body Mass Index, ASA class, baseline haemoglobin concentration, disseminated cancer and type and majority of surgery.

Variable	OR[1]	95% CI[1]	p-value
Antithrombotic Therapy			
No (reference)	-	-	
Yes	0.98	0.73, 1.32	1.0
Age (increment = 1 year)	0.93	0.90, 0.97	0.001
Sex			
Female (reference)	-	-	
Male	0.78	0.59, 1.03	0.09
Body Mass Index			
Underweight*	-	-	
Normal Weight (reference)	-	-	
Obesity	1.01	0.78, 1.32	1.0
ASA Classification			
I-II (reference)	-	-	
III-V	1.33	0.96, 1.88	0.09
Baseline haemoglobin concentration (increment = 0.1)	0.62	0.57, 0.67	<0.001
Disseminated Cancer			
No (reference)	-	-	
Yes	1.09	0.64, 1.80	0.7
Type of Surgery			
Minor (reference)	-	-	
Intermediate	12.50	2.57, 225	0.01
Major	102	22.60, 1802	<0.001
Surgical Category			
Orthopaedic (reference)	-	-	
Gynaecologic	1.14	0.56, 2.17	0.7
Vascular	1.00	0.57, 1.69	1.0
Abdominal	0.72	0.50, 1.04	0.08
Cardiothoracic	1.76	1.20, 2.58	0.004
Neurosurgical	0.73	0.21, 1.87	0.6
Other	0.20	0.06, 0.50	0.002

[1]OR = Odds Ratio, CI = Confidence Interval
*No underweight patients in the study

Table 4. Regression table of the association of intraoperative blood transfusion and antithrombotic therapy and age, sex, Body Mass Index, ASA class, baseline haemoglobin, disseminated cancer and majority and type of surgery with OR, CI and p-values.

BLOOD MANAGEMENT 3

Low platelet-to-red cell but not low plasma-to-red cell ratios predict early mortality in massively transfused, non-trauma surgical cases

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[1]Anesthesiology and Pathology & Laboratory Medicine, University of Wisconsin-Madison, Madison, WI, [2]Harborview Injury Prevention and Research Center, Seattle, WA, [3]Pathology & Laboratory Medicine, University of Wisconsin-Madison, Madison, WI

INTRODUCTION: The optimal resuscitation strategy in massive bleeding is unknown. Research in trauma supports transfusing red blood cells (RBCs) plasma, and platelets in balanced '1:1:1' ratios to mimic whole blood.[1] Other surgical specialties have adopted the 1:1:1 strategy,[2] but evidence for this practice is lacking,[3] and ideal ratios may be different in other surgical situations.[4] We hypothesized that low (<1:1) ratios of platelet:RBC and plasma:RBC transfusion would be associated with increased 1-day mortality among patients who had a massive transfusion during a non-trauma surgery.

METHODS: We performed a retrospective cohort study of all inpatients in our record who were massively transfused during surgery. Inclusion criteria were age >18 years and transfusion of at least 10 units of RBCs in any two-calendar day period. Participants were excluded if the massive transfusion was associated with trauma, if not associated with a surgical case, or inclusion at a prior transfusion. Baseline admission, demographic, biometric, and laboratory data were abstracted for all participants. A transfusion ratio of 1:1 was defined as 1 unit of apheresis platelets or 5 units of plasma for every 5 units of RBCs. Results were summarized with conventional measures. Bivariate results were compared with parametric and nonparametric tests. Mortality models were constructed using multivariate logistic regression. Based on prior data, we included APACHE II score and total RBC dose in all models.[5,6]

RESULTS: 323,340 unique records from 2008 through 2020 were screened: 28,155 had an RBC transfusion, and 364 met all inclusion criteria. Baseline characteristics are summarized in Table 1. Platelet:RBC ratio was higher among participants alive at 1 day, but not plasma:RBC ratio, and participants alive at 1 day received more platelets and less RBCs (Table 2). In a multivariable logistic regression model, death within 1 day of massive transfusion was associated with platelet:RBC ratio <1:1, higher APACHE II score, and higher RBC dose (Table 3). Platelet:RBC ratio <1:1 was also a predictor of 72-hour mortality, but not in-hospital, 30-day, or 365-day mortality. Plasma:RBC ratio was not associated with mortality in any model. Parameterizing transfusion ratios as actual values or dichotomizing at a permissive ratio of 0.67:1 did not alter the results of any model.

CONCLUSION: A platelet:RBC ratio < 1:1 during massive transfusion was associated with higher 1-day mortality during non-trauma surgical cases, but a plasma:RBCs ratio <1:1 was not. These findings are distinct from results in trauma patients, where low ratios of both platelets and plasma during massive transfusion appears to increase mortality. Differences in the mechanisms of traumatic and surgical injury may account for this distinction. Direct application of trauma resuscitation techniques to other massive surgical bleeding scenarios may not be appropriate.

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Anesth Analg. 124:216-232. 2017

JAMA Surg. 152:574-580. 2017

JAMA Surg. 148:127-136. 2013

Transfusion. 56:558-63. 2016

Anesthesiology. 124:387-395. 2016

TABLE 1: Participant characteristics at baseline among all non-trauma surgical cases who received perioperative massive transfusion (n = 364)

	N (%) or mean ±SD
Male sex	253 (69)
Age (years)	59 ± 14
APACHE II Score	8 ± 5
Surgery type*	
Abdominal Transplant	99 (27)
Cardiac	64 (17)
General†	114 (32)
Neurosurgery	8 (2)
Thoracic	15 (4)
Vascular	64 (18)
Dead at 1 day	28 (8)

*****No obstetric cases are performed at the study institution
†Includes 3 urology, 3 gynecology, and 2 otolaryngology cases

TABLE 2: Baseline characteristics and transfusion doses among non-trauma surgical cases receiving perioperative massive transfusion who did or did not die within 1 day of massive transfusion (n = 364).

	Alive at 1 day *Median (IQR) or mean ±SD*	Dead at 1 day *Median (IQR) or mean ±SD*	p
Male sex *(n[%]))*	20 (71)	230 (68)	0.744**
Age (years)	58±14	57±16	0.299‡
APACHE II Score	7 (6)	10 (13)	0.007†
Total RBC (units)	14 (8)	24 (23)	< 0.001†
Total platelet (units)	5 (5)	4 (4)	0.004†
Total plasma (units)	8 (10)	17 (23)	0.355†
Platelet:RBC ratio*	1.7±1.1	0.6±0.1	< 0.001‡
Plasma:RBC ratio*	0.6±0.4	0.6±0.4	0.803‡

* A transfusion ratio of 1:1 was defined as 1 unit of apheresis platelets or 5 units of plasma for every 5 units of RBCs.
**Pearson chi-square
†Wilxocon
‡Student's T

TABLE 3: Multivariable logistic regression model of 1-day mortality among non-trauma surgical cases receiving perioperative massive transfusion (n = 364).

Covariate	Adjusted Odds Ratio of death at 1 day† *aOR (95% confidence interval)*	P‡
Platelet:RBC < 1:1*	10.2 (3.8 – 27.8)	< 0.001
Total RBCs (per unit)	1.1 (1.0 – 1.1)	< 0.001
Baseline APACHE II (per unit)	1.2 (1.1 – 1.3)	< 0.001

* A transfusion ratio of 1:1 was defined as 1 unit of apheresis platelets or 5 units of plasma for every 5 units of RBCs.
† Covariates not significant in the final model included sex, surgical case type, and age.
‡ Wald

BLOOD MANAGEMENT 4

Low cryoprecipitate-to-red cell ratios predict early mortality in massively transfused, non-trauma surgical cases

Aaron S Hess[1], Joseph Connor[2], Thomas Raife[2]

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INTRODUCTION: Fibrinogen is an essential component of hemostasis, and transfused cryoprecipitate is the first-line therapy for acquired hypofibrinogenemia in bleeding. Randomized trials and large observational studies in trauma suggest that lower platelet:RBC and plasma:RBC ratios results in excess hemorrhagic death,[1] but the benefit of high cryoprecipitate:RBC ratios is not established.[2] Many surgical specialties have adopted high fibrinogen targets in massive transfusion on weak evidence of benefit[3,4] or in spite of weak evidence of harm.[5] We hypothesized that low (<1:1) ratios of cryoprecipitate:RBC transfusion would be associated with increased 1-day mortality among patients who had a massive transfusion during a non-trauma surgery.

METHODS: We performed a retrospective cohort study of all inpatients in our record who were massively transfused during non-trauma surgery. Inclusion criteria were age >18 years and transfusion of at least 10 units of RBCs in any two-calendar day period. Participants were excluded if the massive transfusion was associated with trauma, if not associated with a surgical case, or inclusion at a prior transfusion. Baseline admission, demographic, biometric, and laboratory data were abstracted for all participants. A transfusion ratio of 1:1 was defined as one 5-unit pool of cryoprecipitate for every 5 units of RBCs. Results were summarized with conventional measures. Bivariate results were compared with parametric and nonparametric tests. Mortality models were constructed using multivariate logistic regression. Based on prior data, we included APACHE II score and total RBC dose in all models.[6,7]

RESULTS: 323,340 unique records from 2008 through 2020 were screened: 28,155 had an RBC transfusion, and 364 met all criteria for inclusion. Baseline characteristics are summarized in Table 1. Cryoprecipitate:RBC ratio was higher among participants alive at 1 day, and participants alive received equivalent absolute cryoprecipitate doses and less RBCs (Table 2). In a multivariable logistic regression model, death within 1 day of massive transfusion was associated with lower cryoprecipitate:RBC ratio, higher APACHE II score, and higher RBC dose (Table 3). A model using total cryoprecipitate dose instead of cryoprecipitate: RBC ratio was similarly predictive of 1-day mortality. Lower cryoprecipitate:RBC ratios or total cryoprecipitate dose did not predict mortality beyond 1 day.

CONCLUSION: Low cryoprecipitate:RBC ratios during massive transfusion were associated with higher 1-day mortality during non-trauma surgical cases. Similar to studies of transfusion ratios with other products, cryoprecipitate:RBC ratios were only associated with acute mortality. Our results may be confounded by severity of illness and indication for transfusion. These data support secular trends in resuscitation practice that suggest greater fibrinogen replacement in massive bleeding, but optimal dosing remains uncertain.

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4. JAMA Surg. 152:574-580. 2017
5. Transplantation. 105:1771-1777. 2021
6. Transfusion. 56:558-63. 2016
7. Anesthesiology. 124:387-395. 2016

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*No obstetric cases are performed at the study institution
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TABLE 2: Baseline characteristics and transfusion doses among non-trauma surgical cases receiving perioperative massive transfusion who did or did not die within 1 day of massive transfusion (n = 364).

	Alive at 1 day *Median (IQR) or mean ±SD*	Dead at 1 day *Median (IQR) or mean ±SD*	p
Male sex *(n[%]))*	20 (71)	230 (68)	0.744**
Age (years)	58±14	57±16	0.299†
APACHE II Score	7 (6)	10 (13)	0.007‡
Total RBC (units)	14 (8)	24 (23)	< 0.001‡
Total cryoprecipitate (units)	2 (5)	4 (6)	0.396
Cryoprecipitate:RBC ratio*	1.0±1.0	0.5±0.5	< 0.001†

* A transfusion ratio of 1:1 was defined as 1 pool of 5 units of cryoprecipitate for every 5 units of RBCs.
**Pearson chi-square
†Student's T
‡Wilcoxon

TABLE 3: Multivariable logistic regression model of 1-day mortality among non-trauma surgical cases receiving perioperative massive transfusion (n = 364).

Covariate	Adjusted Odds Ratio of death at 1 day† *aOR (95% confidence interval)*	P‡
Cryoprecipitate:RBC ratio	0.4 (0.2 – 0.9)	0.012
Total RBCs (per unit)	1.1 (1.0 – 1.1)	< 0.001
Baseline APACHE II (per unit)	1.2 (1.1 – 1.3)	< 0.001

* A transfusion ratio of 1:1 was defined as 1 pool of 5 units of cryoprecipitate for every 5 units of RBCs.
† Covariates not significant in the final model included sex, surgical case type, and age.
‡ Wald

BLOOD MANAGEMENT 5

Survey Of Patient Blood Management Knowledge Among Anesthesiologists

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INTRODUCTION: Patient Blood Management (PBM) is an evidence-based, multidisciplinary approach to minimize blood loss and ensure hemostasis that improves outcomes and decreases cost.[1] Anesthesiologists order about half of hospital blood,[2] so they should have strong PBM knowledge. This study aims to assess PBM knowledge among US anesthesiology trainees and attendings.

METHODS: Senior investigators designed a survey with 20 PBM content questions, and demographic questions. Content questions were checked by a PBM expert for clarity, accuracy, and one best answer. The assessment was distributed by e-mail to 15 U.S. anesthesiology residency programs and administered online. Using snowball recruitment, the Program Director recruited trainees at all levels, and attending anesthesiologists, via email. Completion of the survey was voluntary, and responses anonymous. The survey was also emailed to anesthesiology experts in PBM. The primary goals of the survey were to assess: 1) PBM knowledge of CA-3 residents (the survey was administered within 8 weeks of graduation); and 2) analyze differences in knowledge between training levels. A tertiary goal was to evaluate PBM knowledge among attending anesthesiologists. Experts were identified by leaders of PBM organizations. These experts were recruited to assess construct validity. Descriptive statistics and frequencies are reported. Analyses included tests for normality and parametric and non-parametric means comparison, with $p < 0.05$ considered significant.

RESULTS: Five outliers (scores ≤ 20) were removed from the sample. Further work will consider if these comprise a specific subset of testees. The final dataset included 415 respondents. The distribution of cumulative scores both satisfied and violated assumptions of normality. Kolmogorov-Smirnov and Shapiro Wilk tests for normality indicated significance, $p < .001$. Visual inspection of data showed a typical histogram with no outliers, box plot with limited skewness, and linear Q-Q plot. Therefore, researchers pursued parametric and nonparametric tests to determine potential differences in means; similar results were derived from ANOVA with Tukey post-hoc comparisons and Kruskal-Wallis H-tests. Results for nonparametric (Kruskal-Wallis) are reported in this abstract. SPSS 28.0 was used for basic descriptives and non-parametric tests. The PBM exam will be further analyzed for construct validity to determine a potential cut score. For this abstract, training levels were compared to Experts. Mean (SD) scores increased with level of training, while Attendings' scores were lower than CA-4s and CA-3s (Fig. 1 and Table 1). Mean (SD) scores of CA-3s, 68 (11.76), and Attendings, 66.67 (14.28), were significantly lower than Experts, 79.07 (12.09), $p = 0.006$ and $p < 0.001$ respectively (Table 1). Mean (SD) of CA-4s, 72.50 (7.07) were not significantly different than Experts, $p = 0.383$ (Tables 1 and 2). Mean (SD) of CA-2s, 65.48 (12.34), were not significantly different than CA-3s, 68 (11.76), $p = 0.418$, but were significantly different than experts, $p < 0.001$ (Table 1 and 2). Differences in CA-3 mean scores between programs approximated significance, but the subsample of CA-3 residents constituted a limited n. Since CA-2 and CA-3 mean scores were not significantly different, we combined CA-2 and CA-3 residents within programs, and compared this subsample between programs and to Experts. The CA-2 and CA-3 group reached significance (Tables 3 and 4). Specifically, 10/15 programs' CA2-CA3s did not differ from Experts, while 5/15 (33.3%) programs' CA2-CA3s reached statistically-significant levels.

CONCLUSION: If construct validity and test reliability evidence can be confirmed, the data suggest 33.3% of programs stand to improve PBM education. Future validity and reliability considerations will include controlling for potential bias for specific sample demographics (ethnicity, gender, cognitive profile, languages spoken, country of birth), underlying latent constructs related to PBM, possible influences on test administration, and interpretations of final score.

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Figure 1. Box Plots of Mean Cumulative Score by Training Year

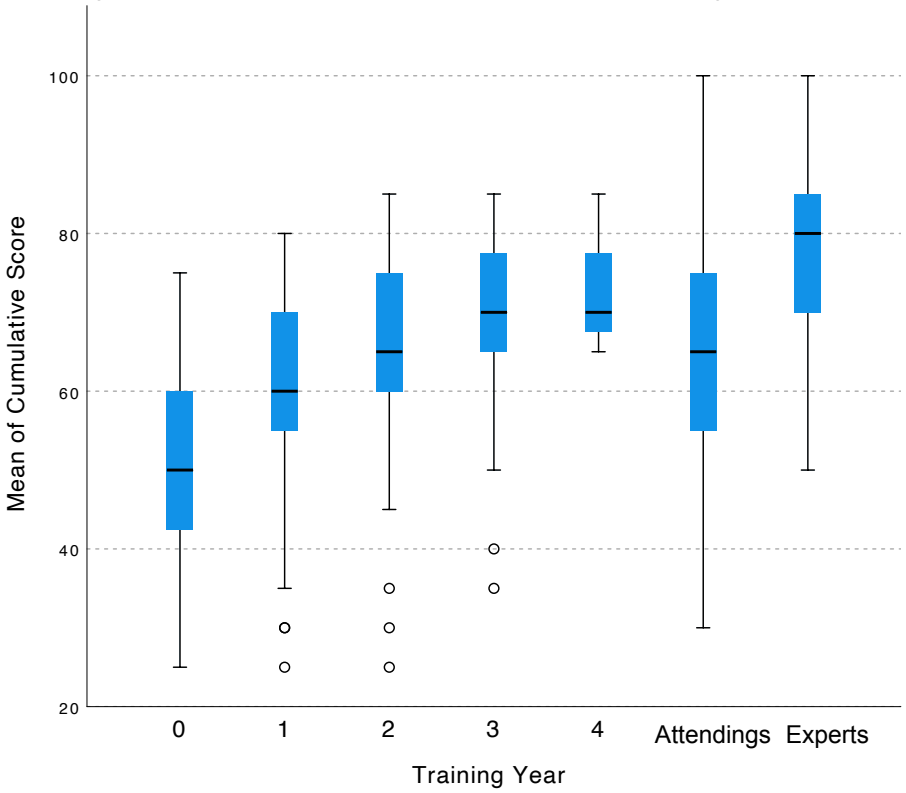

Table 1. Means of Cumulative Scores by Anesthesiology Training Year/Status

Training Year/Status	*n*	Mean	Standard Deviation	Range
CA-0	68	51.52	12.99	25-75
CA-1	45	60.11	14.00	25-80
CA-2	52	65.48	12.34	25-85
CA-3	40	68.00	11.76	35-85
CA-4	8	72.50	7.07	65-85
Attendings	171	66.67	14.28	25-100
Experts	27	79.07	12.09	50-100

n is lower within sub-populations (compared to total sample of 415) because four testees were removed because they did not indicate year of training.

Table 2. Kruskal-Wallis Pair-Wise Comparison of Means of Cumulative Score by Anesthesiology Training Year/Status

Sample 1	Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
CA-0	CA-1	-68.051	22.696	-2.998	0.003
CA-0	CA-2	-114.281	21.757	-5.253	<.001
CA-0	CA-3	-134.405	23.534	-5.711	<.001
CA-0	CA-4	-174.305	44.145	-3.948	<.001
CA-0	Attendings	-115.512	16.932	-6.822	<.001
CA-0	Experts	-215.766	26.866	-8.031	<.001
CA-1	CA-2	-46.230	24.046	-1.923	0.055
CA-1	CA-3	-66.354	25.665	-2.585	0.010
CA-1	CA-4	-106.254	45.317	-2.345	0.019
CA-1	Attendings	-47.461	19.788	-2.399	0.016
CA-1	Experts	-147.715	28.751	-5.138	<.001
CA-2	Attendings	-1.231	18.704	-0.066	0.948
CA-2	CA-3	-20.124	24.839	-0.810	0.418
CA-2	CA-4	-60.024	44.854	-1.338	0.181
CA-2	Experts	-101.485	28.016	-3.622	<.001
Attendings	CA-3	18.893	20.744	0.911	0.362
Attendings	CA-4	58.793	42.723	1.376	0.169
Attendings	Experts	-100.253	24.458	-4.099	<.001
CA-3	CA-4	-39.900	45.742	-0.872	0.383
CA-3	Experts	-81.361	29.417	-2.766	0.006
CA-4	Experts	-41.461	47.542	-0.872	0.383

Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed. *Significant at p <.05

Table 3. Means of Cumulative Scores of CA-2 and CA-3 Residents by Program compared to Experts

Program	*n*	Mean	Standard Deviation	Range
Program 1	0	-	-	-
Program 2	1	-	-	-
Program 3	11	59.09	19.73	25-80
Program 4	5	69.00	13.87	55-85
Program 5	3	75.00	10.00	65-85
Program 6	15	65.33	11.72	35-85
Program 7	1	-	-	-
Program 8	1	-	-	-
Program 9	10	71.00	7.75	60-85
Program 10	8	65.00	7.56	55-75
Program 11	6	72.50	7.58	65-85
Program 12	18	66.39	9.04	45-80
Program 13	8	71.88	7.04	60-80
Program 14	1	-	-	-
Program 15	3	58.33	24.66	30-75
Experts	27	79.07	12.09	50-100

Means not reported for samples of $n = 1$.

Table 4. Kruskal-Wallis Pair-Wise Comparison of Means of Cumulative Score of CA-2 and CA-3 Samples by Program and Expert Status

Sample 1	Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.
Program 2 CA-2/CA-3	Experts	-70.741	34.799	-2.033	0.042
Program 10 CA-2/CA-3	Experts	-42.241	13.756	-3.071	0.002
Program 3 CA-2/CA-3	Experts	-41.377	12.223	-3.385	0.001
Program 6 CA-2/CA-3	Experts	-37.807	11.005	-3.436	0.001
Program 12 CA-2/CA-3	Experts	-36.352	10.398	-3.496	0.000

Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same.

Asymptotic significances (2-sided tests) are displayed. *Significant at $p < .05$

SUBSPECIALTY ABSTRACTS

CARDIOVASCULAR ANESTHESIOLOGY

CARDIOVASCULAR ANESTHESIOLOGY 1

Identification of mineralocorticoid and glucocorticoid receptors as potential targets to regulate parasympathetic, sympathetic and sensory neurons within rat intracardiac ganglia

Lukas Dehé[1], Mohammed Shaqura[1], Shaaban Mousa[1], Michael Schäfer[1], Sascha Treskatsch[2]

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INTRODUCTION: Recent interest has focused on the steroid-mediated regulation of heart performance; however, specific allocation of glucocorticoid (GR)- and mineralocorticoid receptors (MR) to the parasympathetic, sympathetic and sensory innervations of the heart is scarce. Therefore, the present study aimed to characterize such specific target sites for aldosterone and/or cortisol in intracardiac ganglia which act as a complex network for the integration of the heart's neuronal in- and output.

METHODS: Following IRB approval, tissue samples from Wistar rat heart atria were subjected to real-time polymerase chain reaction (RT-PCR), Western blot, and double immunofluorescence confocal analysis of GR, MR, aldosterone and its processing enzyme CYP11B2 for co-localization with the neuronal markers vesicular acetylcholine transporter (VAChT), tyrosine hydroxylase (TH), calcitonin gene-related peptide (CGRP) and substance P (SP).

RESULTS: Our results demonstrated MR and GR specific mRNA and receptor protein in rat heart atria. Double immunofluorescence confocal microscopy revealed that aldosterone and its processing enzyme CYP11B2 predominantly localized in MR-IR peripheral neurons of cardiac ganglia. Moreover, MR and GR immunoreactivity were colocalized with VAChT in large diameter parasympathetic principal neurons, with TH-immunoreactive small intensely fluorescent (SIF) cells and on nearby TH-IR varicose terminals. In addition, MR and GR immunoreactivity were scarcely identified on CGRP- and SP-IR sensory neurons throughout intracardiac ganglia and atrial myocardium.

CONCLUSION: Our findings show that MR and GR are expressed as mRNA and translated into specific receptor proteins in cardiac parasympathetic, sympathetic and sensory neurons as potential binding sites for corticosteroids. Thus, they may well play a role within the complex network for the integration of the heart's neuronal in- and output.

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Cardiac GR and MR: From Development to Pathology. Trends Endocrinol Metab 2016; 27:35-43

CARDIOVASCULAR ANESTHESIOLOGY 2

Bilateral Lung Transplantation after Severe COVID-19 Infection. Single Institutional Experience

Christine Acho[1], Nicola D'Attellis[1], Reinaldo Rampolla[2], Pedro Catarino[3], Dominick Megna[3], Dominic Emerson[3], Eliza Granflor[3], Alice Chan[3], Tariq Nassem[2]

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INTRODUCTION: The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the development of coronavirus disease 2019 (COVID-19) in humans, continues to pose significant challenges to our health care system. As of November 2021, over 47 million patients in the United States have been infected with SARS-CoV-2 resulting in more than 760,000 deaths.[1] Survivors may develop such severe lung damage, that despite all other treatments the only therapeutic option for recovery is lung transplantation.[2] So far over 130 lung transplants have been performed in the United States due to COVID-19.[3] Here we share our institutional experience with double lung transplantation due to pulmonary fibrosis from long standing COVID-19 associated acute respiratory distress syndrome (ARDS).

METHODS: All patients who underwent lung transplantation due to COVID-19, from January to October 2021 were identified. The data was retrospectively collected and analyzed. A multivariable analysis, including time from infection, need for venous-venous extracorporeal membrane oxygenation (VV-ECMO) support prior to transplantation, ICU and hospital length of stay, discharge to home and mortality data, was performed.

RESULTS: So far 8 patients have undergone lung transplantation at our institution due to COVID-19. All 8 patients were transferred from other centers due to failure to fully recover in the setting of pulmonary fibrosis. The median recipient age was 38 years (range 34-56 years). Two patients were female. Median time from diagnosis with SARS-CoV-2 infection to transplantation was 106 days (range 78-168 days). Seven out of 8 patients required the support of VV-ECMO prior to transplantation and remained on support until the time of surgery. Median time from VV-ECMO cannulation to transplantation was 105 days (range 40-145 days). One patient was not placed on VV-ECMO, and instead required supplemental oxygenation through a high flow nasal cannula for 73 days prior to surgery. The most common complication prior to transplantation included sepsis, right ventricular dysfunction, and severe deconditioning. Intraoperatively, all 8 patients were placed on venous-arterial-ECMO (VA-ECMO). Seven of these patients were able to be decannulated from VA-ECMO at the conclusion of surgery. All patients required inhaled nitric oxide intraoperatively. Mean number of RBC transfused were 11 units per case (range 6-18 units). Post-operatively, the two patients who had not required a tracheostomy during their hospital course were extubated on postoperative day (POD) 1 and 2 and weaned to room air by POD 3 and 5, respectively. Of the remaining six patients, fours patients were weaned off mechanical ventilatory by POD 1, 14, 19, and 21. These patients were then weaned to room air over the course of 2-7 days. Two patients died within 3 weeks of transplantation. One patient died on POD 13 secondary to hyperammonia syndrome. The other patient could not be weaned from VA-ECMO and died on POD 19 secondary to cardiogenic shock. No patient required renal replacement therapy (RRT) prior to transplantation. Only the two patients who died required RRT after transplantation. Our patient who developed hyperammonia syndrome was placed on RRT for solute clearance, but otherwise had normal renal function. All 6 survivors were successfully discharged. Their median length of hospital stay after transplantation was 34.5 days (range 13-47 days). Four patients were discharged home. The remaining two patients were discharged to a rehabilitation facility and are now home.

CONCLUSION: Lung transplantation in COVID-19 patients with chronic hypoxemic lung disease, is emerging as the only sustainable option towards survival. This is especially true for younger patients not showing any significant recovery after prolonged support on VV-ECMO. Our patients were referred from other institutions due to lack of therapeutic options and arrived at various stages in their disease process. All patients except one were dependent on VV-ECMO. Despite these limitations, our experience shows lung transplantation in a well selected cohort is a safe and, in many cases, the only survivable option. This is a positive finding given the long-term manifestation of severe COVID-19 includes irreversible lung damage. Centers with experience in lung transplantation in COVID-19 population should continue to share their experience, as these reports will help guide our decision making.

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CARDIOVASCULAR ANESTHESIOLOGY 3

Association of pre-procedural ultra-short-term heart rate variability with one-year mortality after transcatheter aortic valve replacement: A nested, case-control, pilot study

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INTRODUCTION: Transcatheter aortic valve replacement (TAVR) is a minimally invasive, interventional approach to managing severe aortic stenosis (AS) in patients with significant co-morbidities.[1] Despite improvements in design and technique, morbidity and mortality associated with TAVR remains high.[2] Targeted pre-procedural risk-stratification may identify patients with greater likelihood of long-term survival after TAVR. Heart rate variability (HRV) is linked to clinical outcomes in various cardiovascular diseases, but it has remained largely underexplored in patients with AS.[3-5] Therefore, our goal was to investigate whether pre-procedural ultra-short-term (UST)-HRV is associated with 1-year survival after TAVR.

METHODS: In the parent study, we prospectively enrolled 100 TAVR patients between 07/2012 and 09/2015. Pre-procedural UST-HRV was assessed in all patients using a 10 second strip of electrocardiographic recording to derive the root mean square of successive differences (RMSSD) and standard deviation of NN interval (SDNN) using the RR intervals for time domain metrics (Figure 1). For the current analysis, we performed a retrospective, nested case control study using a 2:1 matching based on age, Society of Thoracic Surgeons adult cardiac surgery risk score, New York Heart Association functional classification, and pre-procedural left ventricular ejection fraction. We then constructed Kaplan-Meier curves to graphically represent the intensive care unit (ICU) length of stay (LOS) for 1-year survivors vs non-survivors. Then, to investigate whether pre-procedural UST-HRV is associated with 1-year survival, we performed a logistic regression analysis controlling for Kansas City Cardiomyopathy Questionnaire 12 score.

RESULTS: In the parent cohort, 1-year mortality was 17%. To minimize confounding, we first excluded 3 patients who died within 24 hours of their TAVR procedure. Then, to facilitate a 2:1 matching for the case control analysis, our analytic cohort included 42 patients (28 survivors and 14 non-survivors). Crude median pre-procedural UST-HRV using RMSSD and SDNN were lower in 1-year survivors vs non-survivors (Table 1). Kaplan-Meier curves demonstrated lower ICU LOS (log-rank test, p=0.03) in 1-year survivors vs non-survivors (Figure 2). Logistic regression analysis demonstrated a trend in the association of pre-procedure RMSSD with 1-year mortality (OR 1.02; 95%CI 1.00-1.05, p=0.09) and a 5% higher risk of 1-year mortality with each unit increment in UST-HRV using SDNN (OR 1.05; 95% CI 1.01-1.09, p=0.02).

CONCLUSION: The results of our pilot study suggest that low pre-procedural UST-HRV is associated with greater likelihood of survival at 1-year post-TAVR. We hypothesize that low baseline HRV may identify patients with the most physiologically severe AS who may benefit the most from TAVR. Further studies are needed to investigate whether patient selection based on pre-procedural HRV can improve outcomes after TAVR.

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Table 1. Characteristics of study cohort (n=42)

	1-year survivors (n = 28)	**1-year non-survivors (n = 14)**	**P - value**
Age (years)	80 (IQR 70-85)	79 (IQR 73-83)	0.78
Sex (%)			0.83
Female	46	50	
Male	54	50	
BMI (kg/m^2)	27 (IQR 24-20)	27 (IQR 26-32)	0.47
CCI	4 (IQR 3-5)	4 (IQR 3-5)	0.89
STS Risk score	8 (IQR 7-10)	8 (IQR 6-11)	0.58
AVA (cm^2)	0.72 (IQR 0.70-0.73)	0.72 (IQR 0.70-0.73)	0.93
AMG (mm Hg)	38 (IQR 30-50)	41 (IQR 24-50)	0.77
LVEF (%)	55 (IQR 52-65)	55 (IQR 39-60)	0.32
NYHA Classification	3 (IQR 3-3)	3 (IQR 3-3)	0.91
KCCQ12	50 (IQR 31-65)	34 (IQR 19-61)	0.19
RMSSD	10 (IQR 8-23)	23 (IQR 17-33)	**0.04**
SDNN	10 (IQR 7-16)	17 (IQR 11-40)	**0.03**
ICU LOS (hours)*	52 (IQR 30-79)	103 (IQR 45-191)	**0.03**

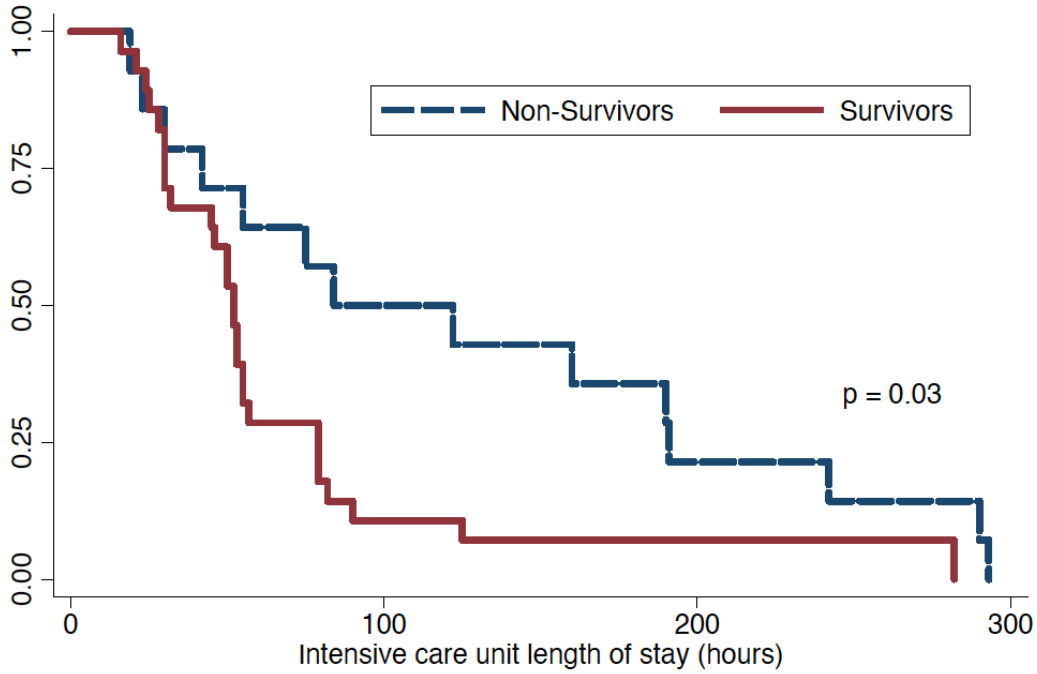
BMI = body mass index; CCI = Charlson Comorbidity Index; STS = Society of Thoracic Surgeons; AVA = aortic valve area; AMG = aortic valve mean gradient; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; KCCQ12 = Kansas City Cardiomyopathy Questionnaire 12 ; RMSSD = root mean square of successive differences; SDNN = standard deviation of NN intervals; ICU = intensive care unit; LOS = length of stay. Aggregate data are presented as either median (interquartile range) or proportions, and compared using Mann Whitney U tests or log rank tests (*) and chi-square tests, respectively. Statistically significant p-values are shown in bold.

Figure 1. Formula for root mean square of successive differences (RMSSD) and standard deviation of NN interval (SDNN)

$$\text{RMSSD} = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(RR_{i+1} - RR_i)^2}$$

$$\text{SDNN} = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(RR_i - \overline{RR})^2} \qquad (\overline{RR} = \text{mean of RR intervals})$$

Figure 2. Kaplan-Meier curve demonstrating intensive care unit length of stay between 1-year survivors and non-survivors post transcatheter aortic valve replacement (n=42). Time between groups was compared using log-rank test.



CARDIOVASCULAR ANESTHESIOLOGY 4

Preoperative Diagnostic Accuracy of Heart Failure Among Patients Undergoing Major Noncardiac Surgery

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INTRODUCTION: Reliable diagnosis of heart failure (HF) during a preoperative evaluation remains essential to safe perioperative care, but is challenged by varied presentation and disease course.[1] Among patients with HF detected by simplistic electronic health record (EHR)-based algorithms, a failure to document HF preoperatively is associated with increased length of stay and mortality.[2] Currently, data are lacking as to the accuracy of HF diagnoses during preoperative evaluations. The aims of this study were to (i) characterize the diagnostic agreement of HF diagnoses adjudicated by a panel of HF experts; (ii) compare the quality of HF diagnoses documented preoperatively to those established via expert adjudication; and (iii) explore characteristics of patients with both positive and negative mis-diagnoses related to HF.

METHODS: We performed an observational cohort study among adult patients >40 years old undergoing major noncardiac surgical procedures at an academic quaternary care center between 2015-2019. A preoperative clinical diagnosis of HF was defined as a diagnosis code or documentation of HF in the preoperative history and physical. Among patients meeting inclusion criteria, statistically balanced random subsets of patients with and without a clinical diagnosis of HF were selected for expert review. The subset of patients without a preoperative clinical diagnosis of HF was further stratified into (i) patients suspicious for having HF, defined as lacking a preoperative clinical diagnosis but then developing HF documentation within 365 days postoperatively, and (ii) all other remaining non-suspicious patients. To maximize the value of HF expert adjudications, patients suspicious for preoperative HF were over-sampled; post-stratification weights were retained in order to determine performance characteristics of preoperative clinical diagnoses of HF across the entire study cohort. Within stratified subsamples of cases with and without preoperative clinical diagnoses of HF, health records were intensively reviewed by an expert panel to develop an adjudicated HF reference standard. We calculated HF reference standard diagnostic agreement among experts, and analyzed performance of HF clinical diagnoses compared to the adjudicated HF reference standard. We compared characteristics of patients with mis-diagnoses related to HF using standardized differences.

RESULTS: Within a cohort of 40,555 major noncardiac surgeries, 511 patients were reviewed by the expert panel, including 247 patients with a clinical diagnosis of HF, and 264 patients without a clinical diagnosis (composed of 72 suspicious patients and 192 non-suspicious patients), Figure 1. Overall agreement and interrater reliability (kappa) among HF experts were 90% and 0.79, respectively (Table 1). Of the 40,555 surgeries, 4,013 (9.9%) had a preoperative clinical diagnosis of HF (Table 2). Based upon expert adjudication and adjusted for subsample stratification weights, HF was clinically diagnosed with an estimated accuracy of 94.4% (95% CI 92.4-96.4%), sensitivity 67.7% (63.7-71.8%), specificity 98.0% (96.8-99.2%), positive predictive value 82.6% (79.3-85.9%) and negative predictive value 95.7% (93.9-97.4%). Compared to the 9.9% prevalence of clinically-diagnosed HF, the true prevalence of HF estimated by the expert panel was 12.1% (95% CI 9.2-14.9). Among patients with an adjudicated diagnosis of HF, those without a clinical diagnosis of HF (false negatives) had fewer comorbidities and were classified as lower ASA physical status compared to patients with a clinical diagnosis of HF (true positives), Table 3. Conversely, among patients without an adjudicated diagnosis of HF, those with a clinical diagnosis of HF (false positives) were more commonly older, had more cardiovascular comorbidities, and were classified as higher ASA status compared to patients without a clinical diagnosis of HF (true negatives).

CONCLUSION: Despite high inter-rater agreement among adjudicated diagnoses of HF via expert panel review, considerable limitations exist to the preoperative clinical diagnosis of HF. Given the substantial health risks untreated HF poses on postoperative outcomes and long-term health trajectories, our findings (i) represent a call to action for improved preoperative diagnosis of HF, and (ii) offer caution to the interpretation of epidemiologic studies and preoperative risk models using simple EHR-based definitions not adjudicated by expert clinician review.

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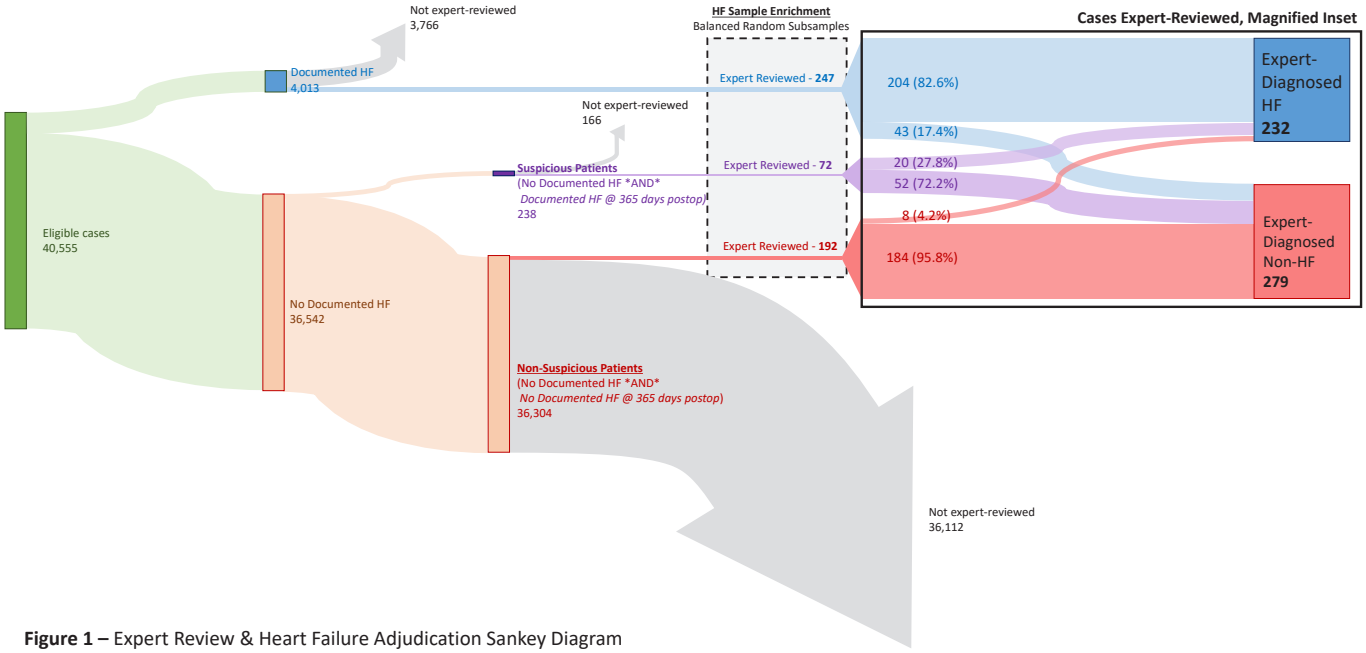

Figure 1 – Expert Review & Heart Failure Adjudication Sankey Diagram

Table 1 - Inter-rater agreement of adjudicated heart failure diagnoses, among two experts selected from heart failure expert panel (*disagreements resolved by third expert*).

	Expert X		
Expert Y		**No Heart Failure**	**Heart Failure**
	No Heart Failure	252 (49.3%)	--
	Heart Failure	53 (10.4%)	206 (40.3%)

Table 2. Study Cohort Baseline Characteristics

		Entire cohort (n=40,555)				HF Preoperative Clinical Diagnosis Present (n=4,013)				HF Preoperative Clinical Diagnosis Absent (n=36,542)				
Variable	Level	N	%	Mean	Std Dev	N	%	Mean	Std Dev	N	%	Mean	Std Dev	Standardized Differences
Age		40555		61	12	4013		67	12	36542		61	11	0.56
Anesthesia Duration (minutes)		40555		234	128	4013		241	128	36542		233	128	0.06
Height (cm)		40476		170	11	4004		171	11	36472		170	11	0.06
Weight (kg)		40521		87	23	4005		90	25	36516		87	22	0.14
Preoperative Creatinine, mg/dL		34762		1.1	1.0	3771		1.5	1.6	30991		1.0	0.9	0.37
Preoperative Glucose, mg/dL		35550		108	35	3850		118	42	31700		107	34	0.28
Preoperative Hematocrit, %		34490		40.0	5.3	3753		37.5	6.3	30737		40.3	5.1	-0.49
Preoperative Platelet Count, K/uL		34077		245	81	3700		226	87	30377		247	80	-0.25
Sex	(missing)	2	0.0							2	0.01			0.18
	Male	20667	51.0			2360	58.8			18307	50.1			
	Female	19886	49.0			1653	41.2			18233	49.9			
ASA Physical Status	(missing)	25				4				21				
	1	765	1.9			3	0.1			762	2.09			1.10
	2	15417	38.0			215	5.4			15202	41.63			
	3	22639	55.9			2996	74.7			19643	53.79			
	4	1709	4.2			795	19.8			914	2.5			
Emergent	(missing)	25				4				21				
	No	37950	93.6			3554	88.7			34396	94.18			0.20
	Yes	2580	6.4			455	11.4			2125	5.82			
Primary Procedural Service	Dentistry	334	0.8			21	0.5			313	0.86			0.51
	General	7253	17.9			608	15.2			6645	18.18			
	Neurosurgery	4124	10.2			313	7.8			3811	10.43			
	Obstetrics / Gynecology	1707	4.2			100	2.5			1607	4.4			
	Ophthalmology	1568	3.9			135	3.4			1433	3.92			
	Oral / Maxillofacial	1484	3.7			122	3.0			1362	3.73			
	Orthopedics	4570	11.3			499	12.4			4071	11.14			
	Other/Unknown	297	0.7			155	3.9			142	0.39			
	Otolaryngology	5666	14.0			429	10.7			5237	14.33			
	Plastics	1596	3.9			63	1.6			1533	4.2			
	Thoracic	2409	5.9			254	6.3			2155	5.9			
	Transplant	1067	2.6			223	5.6			844	2.31			
	Trauma	1953	4.8			283	7.1			1670	4.57			
	Urology	4905	12.1			377	9.4			4528	12.39			
	Vascular	1622	4.0			431	10.7			1191	3.26			
Anemia	Yes	2373	5.9			588	14.7			1785	4.88			
	No	38182	94.2			3425	85.4			34757	95.12			0.33
Cardiac Arrhythmias	Yes	7565	18.7			1960	48.8			5605	15.34			
	No	32990	81.4			2053	51.2			30937	84.66			0.77
Chronic Pulmonary Disease	Yes	7868	19.4			1304	32.5			6564	17.96			
	No	32687	80.6			2709	67.5			29978	82.04			0.34
Diabetes	Yes	7980	19.7			1524	38.0			6456	17.67			
	No	32575	80.3			2489	62.0			30086	82.33			0.47
Hypertension	Yes	22225	54.8			3380	84.2			18845	51.57			
	No	18330	45.2			633	15.8			17697	48.43			0.75
Liver Disease	Yes	2594	6.4			422	10.5			2172	5.94			
	No	37961	93.6			3591	89.5			34370	94.06			0.17
Peripheral Vascular Disorders	Yes	3194	7.9			1100	27.4			2094	5.73			
	No	37361	92.1			2913	72.6			34448	94.27			0.61
Pulmonary Circulation Disorders	Yes	1476	3.6			636	15.9			840	2.3			
	No	39079	96.4			3377	84.2			35702	97.7			0.49
Renal Failure	Yes	5054	12.5			1517	37.8			3537	9.68			
	No	35501	87.5			2496	62.2			33005	90.32			0.70
Valvular Disease	Yes	1721	4.2			728	18.1			993	2.72			
	No	38834	95.8			3285	81.9			35549	97.28			0.52
Coronary Artery Disease	Yes	4414	10.9			1613	40.2			2801	7.67			
	No	36006	88.8			2372	59.1			33634	92.04			0.83
	(missing)	135	0.3			28	0.7			107	0.29			
Cerebrovascular Disease	Yes	1374	3.4			319	8.0			1055	2.9			
	No	39046	96.6			3666	92.0			35380	97.1			0.23
	(missing)	135				28				107				
Tobacco Smoking Classification	Former Smoker	98	48.0			1	3.6			81	34.3			0.24
	History of Smoking, Status Unknown	2	1.0			9	32.1			2	0.9			
	Missing	68	33.3			12	42.9			100	42.4			
	Non-Smoker	16	7.8			2	7.1			24	10.2			
	Smoker	20	9.8			4	14.3			26	11.0			

CARDIOVASCULAR ANESTHESIOLOGY 5

Effects Of Levosimendan On Right Ventricular Hydraulic Afterload During Acute Global Hypoxia In Anesthetized Rabbits

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INTRODUCTION: In situations of global hypoxia (Hx) (i.e., high altitude ascent), hypoxic pulmonary vasoconstriction (HPV) is generalized and results in elevated pulmonary arterial pressure (PAP), which, if exaggerated, may cause acute right-heart failure[1]. Pulmonary vasoreactivity to Hx occurs predominantly in distal resistance pulmonary arteries (RPA). It varies significantly between species and is relevant to ventilation-perfusion (V/Q) matching. Levosimendan (LSM) produced different relaxation effects depending on proximal (conduit) to RPA, with higher relaxation potency in isolated RPA rings, reduced during Hx[2]. We analyzed the stationary and pulsatile components of pulmonary hemodynamics response to normobaric acute global Hx and the effects of LSM by the PA pressure waveform analysis (PWA, time-domain) in anesthetized rabbits.

METHODS: 14 females New Zealand rabbits (2.9 ± 0.1 Kg) were anesthetized and mechanically ventilated. A left thoracotomy was performed. Central venous (CVP) left atrial (LAP), and femoral arterial pressures (AoP) (fluid column catheter), and pulmonary arterial pressure (PAP) (Millar), and flow (PF) (Transonic) were monitored (Figure 1, LabChart, 1KHz). We assessed pulmonary vascular resistance (PVR); pulmonary arterial capacitance (PAC); input (Zo) and characteristic impedance (Zc, Li method); time (Ti); and magnitude (Ew) of the reflected wave; and augmentation index (AI) (Figure 2) (1,3). The animals were randomized to a control Hx group (n=6) (FiO2 0.1, for 5 min), and LSM Hx group (n=7) (Hx after 60 min LSM 0.2 µg/kg/min i.v., Hx-LSM).

RESULTS: HPV stimulus (PsO2, Marshall equation) obtained during Hx was 24 ± 7 mmHg (4). HPV determined a significant increase in the dynamic afterload of the RV, both in stationary and pulsatile components, without a significant change of the AoP (Table 1). The high absolute values of Zc and Zo obtained could be associated with the reduced diameter of major vessels and fewer parallel vessels at any level of the vascular tree due to the small size of the rabbit. LSM infusion led to a decrease in mPAP, Zo, and the inflection pressure (Pi) ($P < 0.05$) with an increase of PF and stroke volume (SV). However, Hx-LSM showed a similar hemodynamic response (relative change) without preventing the increase in PAP and RV hydraulic load secondary to the Hx (Table 2).

CONCLUSION: Pressure waveform analysis allowed the time-domain quantification of the dynamic RV afterload. HPV was associated with an increase in all the dynamic afterload parameters. Low-dose infusion of LSM did not prevent the increase in RV hydraulic load secondary to HPV.

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Figure 1: Representative tracings during Hypoxia

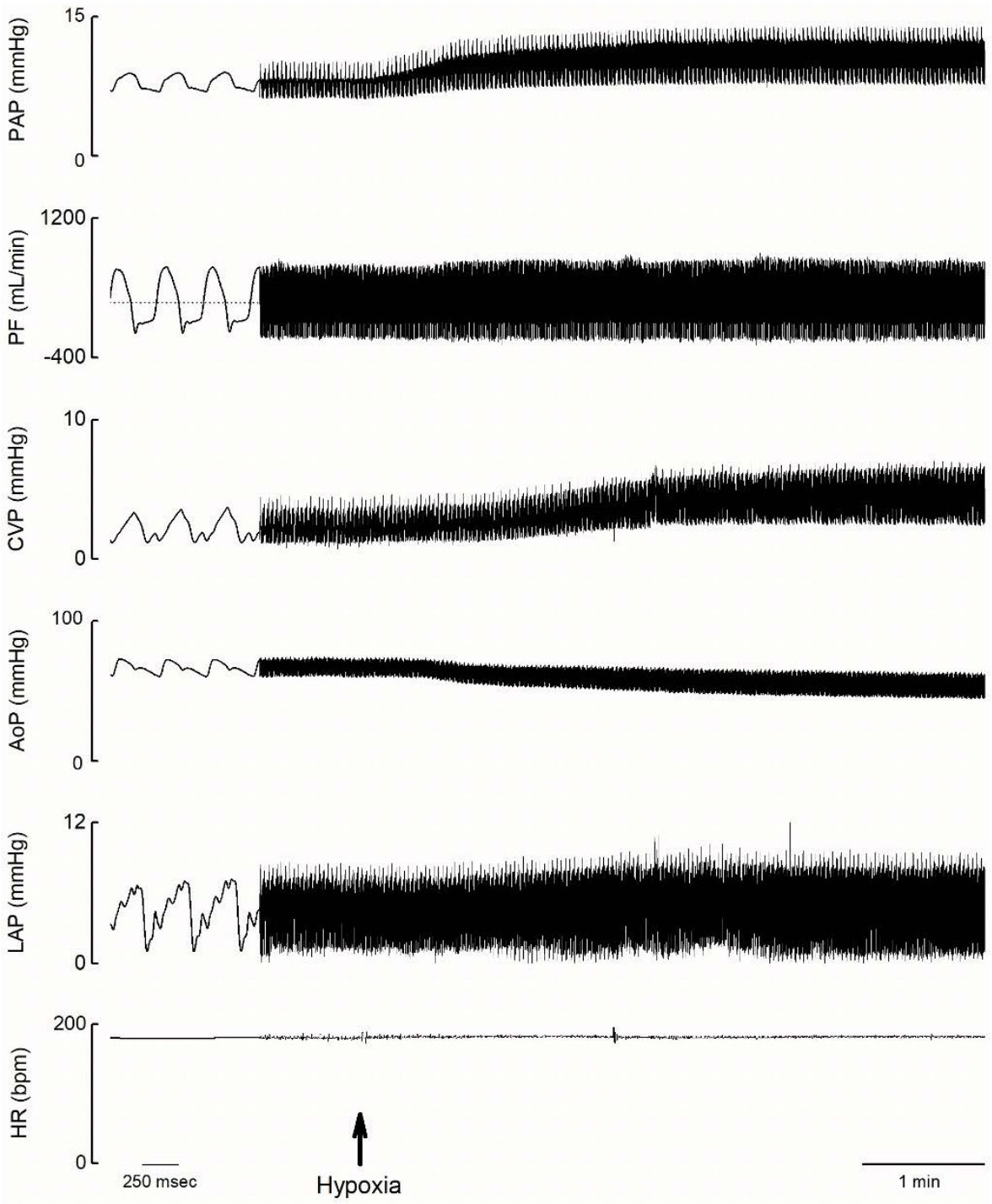

Figure 2: Representative tracings of the pulmonary arterial pressure (PAP), its second derivative ($dPAP^2/dt^2$) and pulmonary flow (PF) showing the pulse wave analysis and assessment of characteristic impedance (Zc).

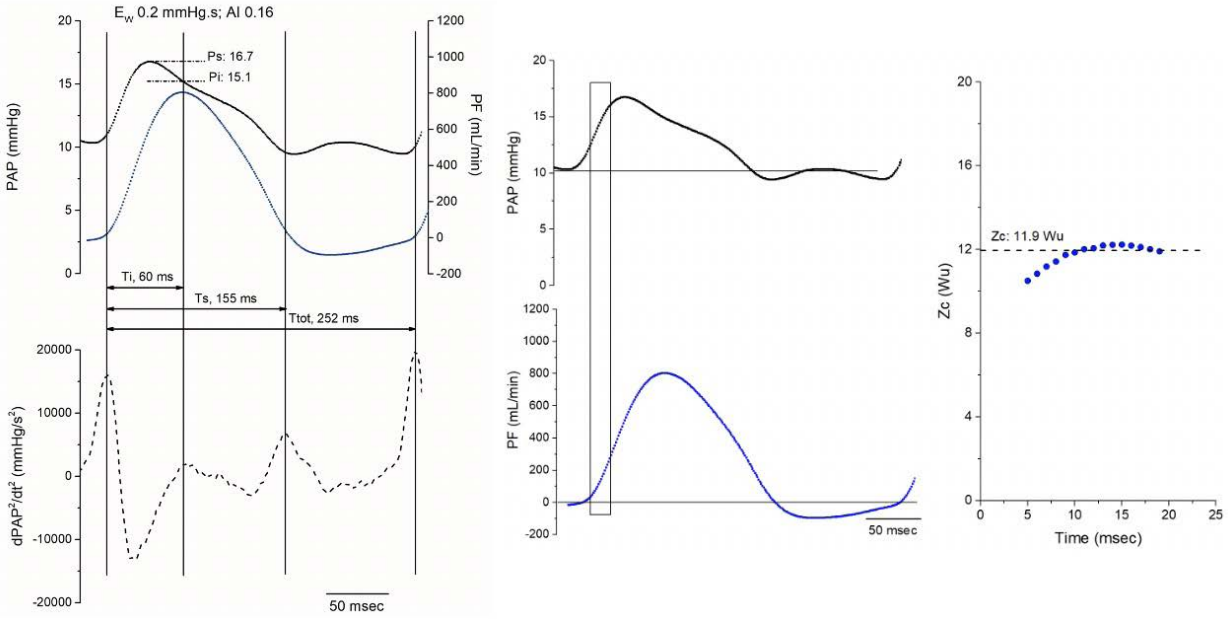

Table 1: Absolute grouped values of the two experimental situations

	Hypoxia group (n=7)		LSM-Hx group (n=7)		
	Basal	Hx	Basal	LSM	LSM-Hx
mAoP, mmHg	56±19	53±12	52±10	59±18	41±14*°
mPAP, mmHg	6.3±1.5	7.8±1.8*	7.8±2.9	6.8±3*	9.2±2.8°
pPAP, mmHg	8.3±1.5	10±1.7*	7.6±1.5	7.7±1.3	10.8±2.2*°
LAP, mmHg	2.0±1.1	2.1±1.5	2.3±2	1.4±0.4	1.2±0.9
RAP, mmHg	3.1±1.6	4.2±1.9*	2.2±1	2.6±1.2	4.4±1.3*°
PF, mL/min	220±62	191±76	190±40	240±90	170±80°
HR, bpm	194±20	181±27	180±28	175±16	173±27
SV, mL	1.1±0.3	1.0±0.3	1.1±0.3	1.4±0.4	0.95±0.3°
PVR, Wu	20±8	33±15*	29±14	25±13	56±35*°
Zo, Wu	30±6.5	47±15*	40±9	31±16*	64±35*°
PAC, mL/mmHg	0.14±0.05	0.1±0.04*	0.15±0.06	0.17±0.03	0.09±0.03*°
Pi, mmHg	11±1.9	13±1.8*	11.5±2.9	10.3±2.8*	13.3±3°
Ti, ms	60±11	50±11	70±20	60±10	50±10*°
Ti/Ttot	0.20±0.04	0.17±0.05*	0.21±0.04	0.17±0.05*	0.14±0.02*°
Zc, Wu	11±4	15±6*	6.7±2.1	7.6±2.6	9.4±3.4*
Ew, mmHg.s	0.10±0.07	0.19±0.1*	0.26±0.13	0.34±0.26	0.6±0.3*°
AI	0.07±0.05	0.10±0.08	0.19±0.09	0.21±0.12	0.28±0.12°

Mean ± SD. P <0.05 *vs. Basal; °vs. LSM

Table 2: Relative grouped values (%) of the two experimental situations

	ΔHx	ΔLSM-Hx
mPAP	23±9	25±15
pPAP	23±9	47±14
PF	-14±7	-6±2
HR	-6±5	-3±3
PVR	72±21	100±40
Zo	52±18	50±23
PAC	-22±8	-30±14
Ti/Ttot	-14±4	-32±8
Zc	33±7	44±21
Ew	158±63	171±90
AI	76±41	63±40

Mean ± SE. Δ: [(Hx-Basal)/Basal]*100

CARDIOVASCULAR ANESTHESIOLOGY 6

Diastolic retrograde flow and wall shear stress in the proximal descending aorta

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INTRODUCTION: Retrograde flow from descending aorta with atherosclerosis could cause embolic stroke. We investigated the retrograde flow and Wall Shear Stress (WSS) in 4 cohorts using Vector Flow Mapping (VFM) software.

METHODS: Ten healthy volunteers (group A), 10 heart failure patients (group B), 5 patients with HeartMate,© (group C), and 3 patients with HeartMate2 (group D) were enrolled. Echocardiographic color Doppler images scanned from suprasternal notch were stored and analyzed using VFM software in all subjects. Retrograde flow and WSS values on both great curvature and lesser curvature of 5 cm distal from left subclavian artery were analyzed.

RESULTS: Retrograde flow was recognized in all group A subjects, 7 subjects in group B, 3 subjects in group C, 1 subject in group D. WSS values on great curvature were 0.061 [0.037-0.24], 0.074 [0.034-0.14], 0.079 [0.073-0.13], 0.052 [0.037-0.09] Pa/m in group A, B, C, D respectively (no significant difference). WSS values on lesser curvature were 0.63 [0.28-0.92], 0.32 [0.14-0.45], 0.18 [0.17-0.39], 0.28 [0.17-0.41] Pa/m in group A, B, C, D respectively (no significant difference). WSS values on lesser curvature were significantly higher than on great curvature in group A and B ($p<0.0001$).

CONCLUSION: Atherosclerosis at lesser curvature of distal arch may be likely to peel away than at great curvature.

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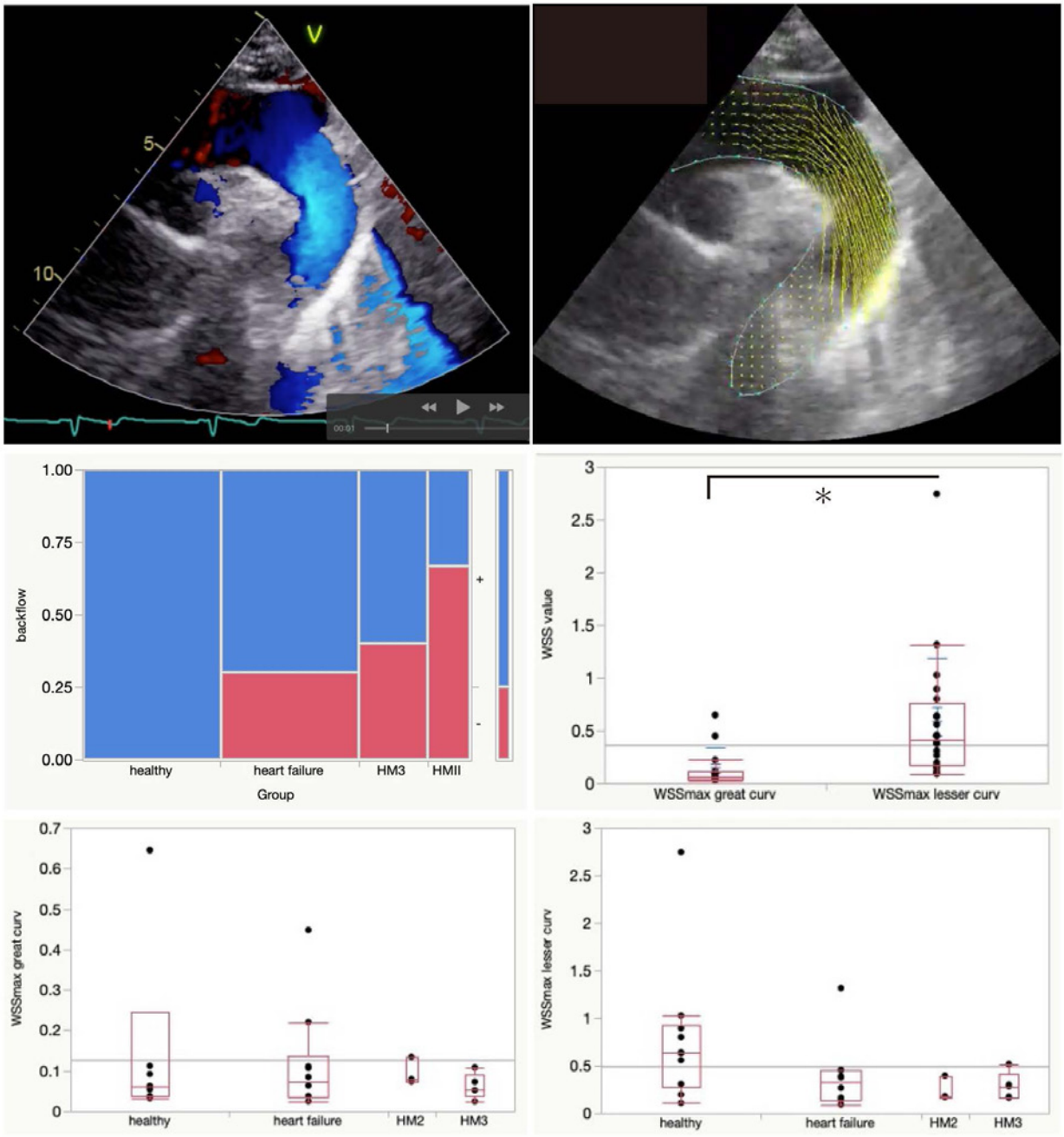

Fig. 1

CARDIOVASCULAR ANESTHESIOLOGY 7

The effect of high frequency jet ventilation on recovery and safety in patients undergoing pulmonary vein isolation: A hospital registry study

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INTRODUCTION: The use of high frequency jet ventilation (HFJV) during pulmonary vein isolation (PVI) for atrial fibrillation has been associated with a reduced rate of disease recurrence[1 - 3]. This technique enhances ablation catheter stability and tissue-contact through the use of ultra-low, high frequency tidal volumes with minimum thoracic volume changes; HFJV for PVI has therefore gained increasing popularity[1]. However, HFJV may predispose patients to hemodynamic instability, acid base disturbances, as well as respiratory complications, especially during lengthy procedures[3 - 5]. Limited evidence exists on the peri-procedural safety of HFJV for PVI compared to standard mechanical ventilation. We investigated the association between the use of HFJV and post-procedural recovery as well as peri-procedural respiratory and hemodynamic safety parameters.

METHODS: This hospital registry study included patients that underwent PVI for recurrent atrial fibrillation between January 2013 and July 2020 at Beth Israel Deaconess Medical Center (Boston, Massachusetts, USA). The primary exposure was the use of HFJV versus standard mechanical ventilation and the primary outcome was postoperative recovery, measured as length of stay in the post-anesthesia care unit (PACU). The key-secondary outcome was intra-procedural hypoxemia, defined as the occurrence of any peripheral hemoglobin oxygen saturation (SpO2) <90%. Further secondary outcomes were prolonged hypoxemia (SpO2 <90% for a coherent episode longer than 2 minutes), the occurrence of post-procedural hypoxemia (SpO2 <90% within 10 minutes after extubation), intra-procedural abnormalities in carbon dioxide partial pressure (defined as any PaCO2 lesser than 35 mmHg or greater than 45 mmHg, measured via central venous or arterial blood gas analysis) and intraoperative hypotension, defined as a minimum of 5 minutes of mean arterial pressure measurements below 55 mmHg. Multivariable negative binomial and logistic regression analyses, adjusted for a priori defined factors including patient demographics, comorbidities, dynamic respiratory system compliance, intraoperative factors and the year of the procedure were applied. Adjusted odds ratios with 95% confidence intervals [CI] are reported. Alpha was set to 0.05.

RESULTS: Of 1822 patients included in the primary cohort, 1,157 (63%) were treated with HFJV (Figure 1). Female patients represented 30% (n=545) of the total cases. The median age in the cohort was 62 (interquartile range 56-69) years (Table 1). There was an increasing proportion of patients receiving HFJV over time (Figure 2). In adjusted analyses, patients receiving HFJV had a longer stay in the PACU than patients receiving conventional ventilation (adjusted absolute difference [adjAD] 36.4 minutes [95% CI, 4.7-68.1]; p=0.02; incidence rate ratio [IRR] 1.11). There was no association between HFJV versus conventional ventilation and the occurrence of intra- or post-procedural hypoxemia (Table 2). Patients receiving HFJV further had a higher risk of developing intra-procedural abnormalities in PaCO2, which consisted of hypercarbia in 474 (43.1%) and hypocarbia in 454 (41.2%) of cases. A high proportion (96.9%) of all patients required vasopressors, which was not associated with the use of HFJV versus conventional ventilation.

CONCLUSION: HFJV compared to conventional mechanical ventilation for PVI is associated with an increased risk of intra-procedural abnormal carbon dioxide homeostasis and a prolonged stay in the post-anesthesia care unit. Protocols for HFJV during PVI should aim to implement strategies to maintain normocarbia.

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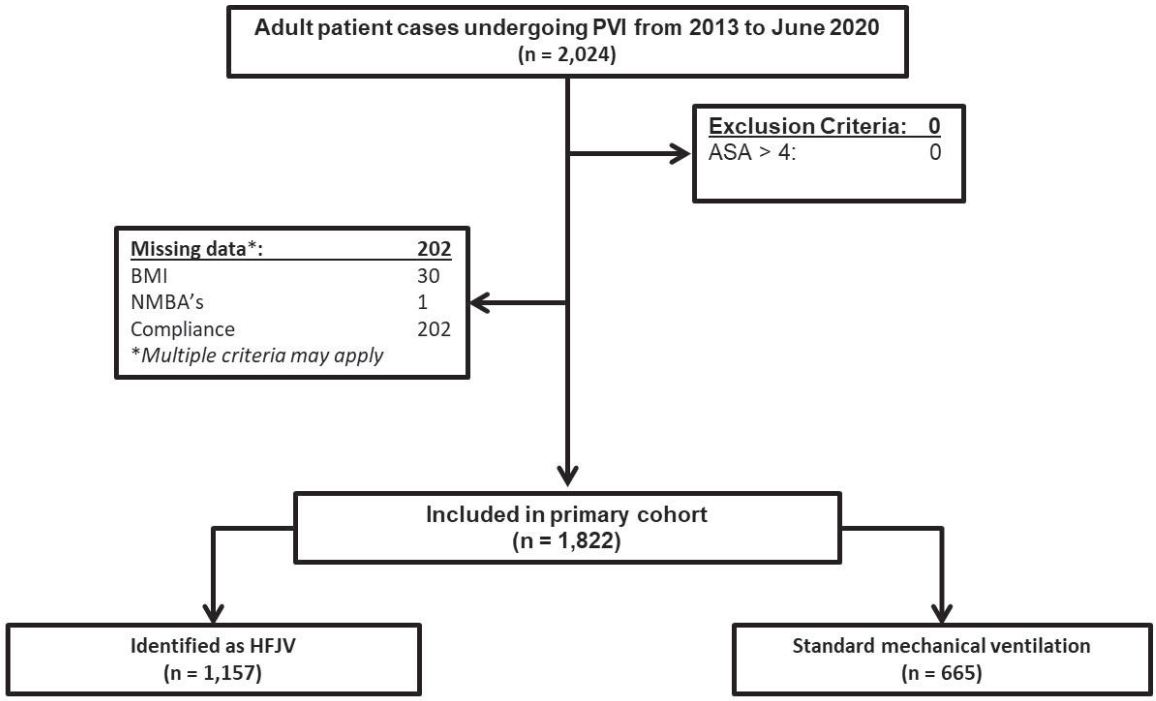

Figure 1. Study flow diagram
ASA: American Society of Anesthesiology physical status classification ; BMI: Body mass index; HFJV: High frequency jet ventilation; NMBA: Neuromuscular blocking agents; PVI: Pulmonary vein isolation.

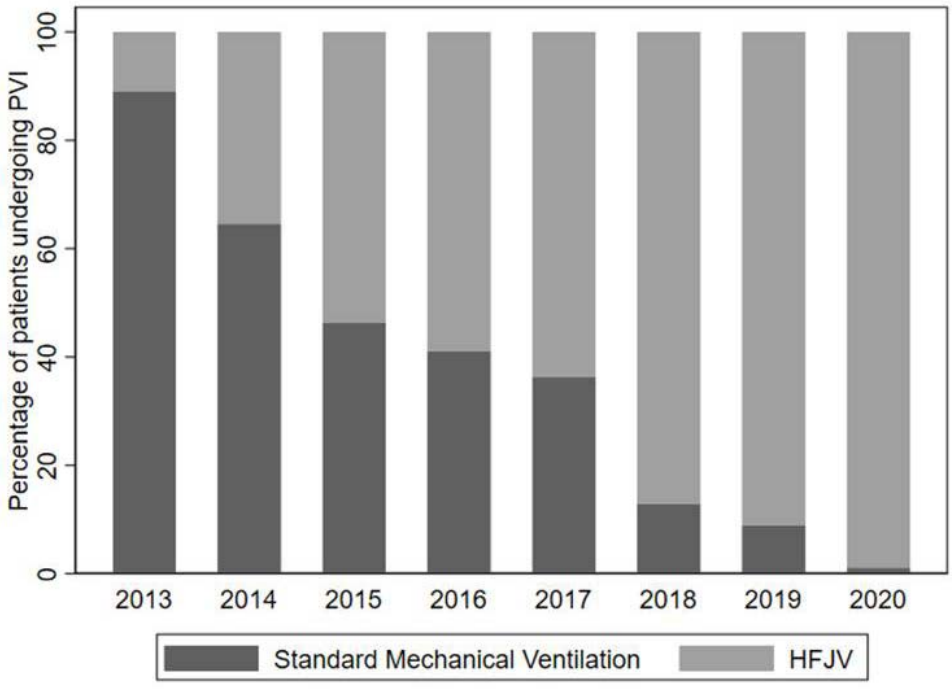

Figure 2. Percentage of patients undergoing PVI under standard mechanical ventilation versus under HFJV from 2013 to June 2020.
HFJV: high frequency jet ventilation; PVI: pulmonary vein isolation

Table 1. Patient characteristics and distribution of variables.

		Standard Ventilation n = 665	HFJV n = 1,157	Standardized Difference
Demographics				
Age, years		63 (56-69)	63 (56-69)	0.02
BMI, kg/m^2		30.9 ± 7.1	29.6 ± 5.7	0.199
Gender	Male	201 (30.2%)	344 (29.7%)	
	Female	464 (69.8%)	813 (70.3%)	
Comorbidities				
ASA physical status > II		440 (66.2%)	717 (62.0%)	0.087
Anemia		42 (6.3%)	56 (4.8%)	0.064
Smoking		40 (6.0%)	102 (8.8%)	-0.107
COPD		49 (7.4%)	64 (5.5%)	0.075
Chronic heart failure		134 (20.2%)	201 (17.4%)	0.071
Chronic renal failure		33 (5.0%)	53 (4.6%)	0.019
Cerebrovascular disease		21 (3.2%)	40 (3.5%)	-0.017
Diabetes mellitus		75 (11.3%)	78 (6.7%)	0.158
Intraoperative factors				
Duration of surgery, min		294.4 ± 101.2	313.1 ± 83.2	-0.202
Non-depolarizing NMBA, ED95		2.6 ± 1.8	2.7 ± 2.0	-0.075
Total opioid dose, mg OME		37.5 (25.0-62.5)	450 (205-752.5)	-1.323
Crystalloid and colloid infusion, ml		1300 (900-2200)	1500 (1000-2350)	-0.116
Normalized dynamic compliance, ml/kg/cmH_2O		0.5 ± 0.2	0.5 ± 0.2	-0.117
Number of BGAs		1.0 (1.0-2.0)	4.0 (3.0-5.0)	-1.306

Data are presented as mean ± SD or median (IQR) for continuous measures, and n (%) for categorical measures.

ASA: American Society of Anesthesiology; BMI: Body mass index; BGA: Blood gas analyses; COPD: Chronic obstructive pulmonary disease; ED95: Median effective dose requires to achieve a 95% reduction in maximal twitch response from baseline; HFJV: High frequency jet ventilation; NMBA: Neuromuscular blocking agents; OME: Oral morphine equivalent.

Table 2. Key secondary outcomes in patients treated with PVI under HFJV versus standard mechanical ventilation.

	Standard Ventilation n (%)	HFJV n (%)	aOR (CI 95%)	aRD (CI 95%)	p-value
Altered BGA	30 (56.6%)	840 (80.1%)	3.97 (2.00-7.85)	26.8% (0.12-0.42)	< 0.001
Any Intraprocedural hypoxemia	95 (14.29%)	139 (12.0%)	0.96 (0.64-1.44)	-0.4% (-0.05-0.04)	0.84
Intraprocedural hypoxemia over 2 minutes	13 (1.95%)	18 (1.5%)	0.74 (0.26-2.1)	-0.5 (-0.02-0.01)	0.57
Postextubation desaturation	21 (4.04%)	19 (3.5%)	0.85 (0.35-2.06)	-0.6% (-0.04-0.03)	0.72
Intraoperative hypotension	82 (12.3%)	158 (13.6%)	1.49 (0.98-2.26)	4% (0-0.08)	0.07
Use of vasopressors	640 (96.2%)	1,126 (97.3%)	1.41 (0.60-3.33)	1% (-0.16-0.04)	0.42

aOR: Adjusted odds ratio; aRD: Adjusted risk difference; BGA: Blood gas analyses; CI: Confidence intervals; HFJV: High frequency jet ventilation.

CARDIOVASCULAR ANESTHESIOLOGY 8

Intraoperative Oxygen Concentration and Pulmonary Complications after Cardiac Surgery – A Secondary Analysis of a Randomized Controlled Trial

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INTRODUCTION: Cardiac surgery with cardiopulmonary bypass carries significant risk for postoperative pulmonary complications (PPCs), which can increase postoperative length of stay, cost, morbidity, and mortality[1-5]. While oxygen-related free radical production is implicated in pulmonary adverse events[1-3], the effect of hyperoxia on the development of PPCs after cardiac surgery is not yet understood. This study investigates the effect of intraoperative oxygen concentration on PPCs after coronary artery bypass grafting (CABG) to determine if there is an association between conservative oxygen therapy and fewer PPCs.

METHODS: This study is a secondary analysis of a parallel arm randomized controlled trial of 100 patients that evaluated the relationship between intraoperative oxygen concentration and neurocognitive outcomes after CABG[6,7]. Patients were prospectively randomized to either receive normoxia (35% FiO2, experimental group) or hyperoxia (100% FiO2, control group) intraoperatively. While on bypass, the experimental group maintained a PaO2 of 100-150mmHg while the control continued on 100% FiO2. Other anesthetic management occurred at the discretion of the clinical team. Patients who required single-lung ventilation, off-pump CABG, mechanical circulatory support, were in cardiogenic shock, or for whom there were physician or nursing concerns were excluded. Development of PPCs was abstracted from the medical record (Table 1)[2,3]. The primary endpoint was the development of any PPC. Secondary outcomes were individual PPCs, postoperative vasoplegia, time to extubation, number of ventilator free days, reintubation, and readmission. Demographic data, comorbidity data, and outcomes in the two groups were assessed with a chi-squared test, Wilcoxon Rank Sum or t-test, based on the variable type and distribution.

RESULTS: 51 patients were randomized to normoxia, and 49 patients were randomized to hyperoxia. Smoking status differed between groups, however other demographic measures and medical comorbidities were similar (Table 2). The composite incidence of PPC in the normoxia group was 22% (11/51), compared to 35% (17/49) in the hyperoxia group (p = 0.14)(Table 3). While the development of most PPCs was not statistically different between groups, the difference in development of respiratory failure was statistically significant between groups, with a greater incidence of respiratory failure in the hyperoxia group (Table 4). The hyperoxia group also required higher mean norepinephrine equivalents upon arrival to the intensive care unit than the normoxia group (Table 3). The number of ventilator free days, time to extubation, incidence of reintubation, and readmission did not differ between groups.

CONCLUSION: In our study, the normoxia group trended toward having fewer PPCs when compared to the hyperoxia group, driven by the increased development of respiratory failure in the hyperoxia group. These data suggest that conservative and usual liberal oxygen delivery may differ in the acute postoperative setting but do not differ in the risk of long-term respiratory complications in patients undergoing CABG. Given that our results are limited by sample size, further work is necessary to understand the relationship between intraoperative oxygen delivery and the development of PPCs, particularly respiratory failure.

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Table 1. Definition of postoperative pulmonary complications.[3]	
Pulmonary Complication	**Definition***
Respiratory infection	Received antibiotics for a suspected respiratory infection and met at least one of the following criteria: new or changed sputum, new or changed lung opacities, fever, leukocyte count >12,000
Respiratory failure	Postoperative P_aO_2 < 60mmHg, or S_pO_2 < 90% and requiring oxygen therapy, or P_aO_2/F_iO_2 ratio < 100, or Oxygenation index > 25
Bronchospasm	"Newly detected expiratory wheezing treated with bronchodilators"
Aspiration pneumonitis	"Acute lung injury after the inhalation of regurgitated gastric contents"
*Developed within the first 7 postoperative days or entire length of stay, if shorter than 7 days	

Table 2. Characteristics of normoxia and hyperoxia groups.			
	Hyperoxia *N = 49*	**Normoxia** *N = 51*	**P-Value**
Age, *years*	71 (67, 75)	70 (68, 75)	0.88
Male Sex	43 (87.76)	41 (80.39)	0.32
Body Mass Index, *kilograms/meter*^{2}	29.3 (26.6, 31.8)	29.0 (24.4, 32.0)	0.91
Charlson Comorbidity Index	4 (3, 5)	4 (3, 5)	0.41
Respiratory Infection in the Month Prior to Surgery	2 (4.08)	2 (3.92)	0.97
Smoking Status			0.01
Current Every Day Smoker	11 (22.45)	2 (3.92)	
Current Some Day Smoker	0 (0)	1 (1.96)	
Former Smoker	28 (57.14)	30 (58.82)	
Never Smoker	10 (20.41)	18 (35.29)	
Preoperative Oxygen Saturation	98 (96, 99)	97 (96, 99)	0.84
Preoperative Serum Hemoglobin	13.5 (12.2, 14.3)	12.9 (11.5, 14.1)	0.37
Preoperative Serum Albumin	4.05 ± 0.38	3.91 ± 0.55	0.15
Baseline Telephonic-Montreal Cognitive Assessment Score	17 (15, 19)	17 (16, 19)	0.96
Values are presented as mean ± standard deviation, median (quartile 1, quartile 3), or n (%) depending on type and distribution.			

Table 3. Postoperative complications in the study cohort.

	Hyperoxia *N = 49*	**Normoxia** *N = 51*	**P-Value**
Any Postoperative Pulmonary Complication	17 (34.69)	11 (21.57)	0.14
Respiratory Infection	2 (4.08)	1 (1.96)	0.61
Respiratory Failure[a]	15 (30.61)	5 (9.80)	0.01
Bronchospasm	9 (18.37)	6 (11.76)	0.36
Aspiration Pneumonitis	1 (2.04)	1 (1.96)	0.98
Hours of Initial Intubation, *hours*[b]	4.8 (3.7, 8.7)	5.5 (3.7, 8.7)	0.68
Ventilator Free Days to Day 30	29 (28, 29)	29 (29, 29)	0.65
Reintubation	2 (4.08)	1 (1.96)	0.61
Norepinephrine Equivalents[c]			
Arrival to the ICU	0.05 (0.03, 0.07)	0.03 (0.00, 0.05)	0.02
POD 1	0 (0, 0.04)	0 (0, 0.05)	0.79
POD 2	0 (0, 0)	0 (0, 0)	0.47
POD 3	0 (0, 0)	0 (0, 0)	0.60
Mean Arterial Pressure / Norepinephrine Equivalents			
Arrival to the ICU	1310.0 (900.0, 2020.0)	1770.0 (866.7, 2533.3)	0.23
Readmission			
Within 30 Days	5 (10.20)	6 (11.76)	0.80
Within One Year	10 (20.41)	9 (17.65)	0.73
Reason For Readmission			0.92
Postsurgical Complication	4 (40.00)	2 (22.22)	
Postoperative Pulmonary Complication	1 (10.00)	2 (22.22)	
Other Cardiac Reason	2 (20.00)	2 (22.22)	
Other Medical Reason	3 (30.00)	3 (33.33)	

Values are presented as mean ± standard deviation, median (quartile 1, quartile 3), or n (%) depending on type and distribution.

[a]Defined using P_aO_2/F_iO_2 < 100 in addition to the items listed in table 1.

[b]Time interval between arrival to intensive care unit and extubation

[c]Norepinephrine equivalents were calculated as the sum of norepinephrine, (dopamine/100), (phenylephrine/10), epinephrine, and (vasopressin*2.5).

Table 4. Sensitivity analysis for respiratory failure defined by different P_aO_2/F_iO_2.

	Hyperoxia *N = 49*	**Normoxia** *N = 51*	**P-Value**
P_aO_2/F_iO_2 < 300	45 (91.84)	37 (72.55)	0.01
P_aO_2/F_iO_2 < 200	30 (61.22)	14 (27.45)	0.001
P_aO_2/F_iO_2 < 100	7 (14.29)	2 (3.92)	0.09
Complications Using the Cutoff P_aO_2/F_iO_2 < 300 in the Definition of Respiratory Failure*			
Respiratory Failure*	45 (91.84)	37 (72.55)	0.01
Any Postoperative Pulmonary Complication	45 (91.84)	37 (72.55)	0.01
Complications Using the Cutoff P_aO_2/F_iO_2 < 200 in the Definition of Respiratory Failure*			
Respiratory Failure	30 (61.22)	17 (33.33)	0.01
Any Postoperative Pulmonary Complication	31 (63.27)	19 (37.25)	0.01
Complications Using the Cutoff P_aO_2/F_iO_2 < 100 in the Definition of Respiratory Failure*			
Respiratory Failure	15 (30.61)	5 (9.80)	0.01
Any Postoperative Pulmonary Complication	17 (34.69)	11 (21.57)	0.14

Values are presented as n (%).
**Respiratory failure and any postoperative pulmonary complication were defined using the P_aO_2/F_iO_2 ratio specified in addition to the other items listed in Table 1.*

CARDIOVASCULAR ANESTHESIOLOGY 9

Enhanced Recovery After Cardiac Surgery Reduces Duration of Ventilation and Likelihood of Re-Intubation Following Urgent and Emergency Isolated Coronary Artery Bypass Surgery

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INTRODUCTION: The effects of an enhanced recovery after cardiac surgery protocol (ERACS) on urgent and emergency cardiac surgery are not known. Coronary artery bypass (CABG) is commonly performed under urgent and emergency priority. We sought to determine if ERACS had effects on outcomes following urgent and emergency CABG.

METHODS: We conducted a 5-year, retrospective study for consecutive adults undergoing urgent/emergency CABG at an urban teaching hospital. Patient demographics, clinical data, and postoperative outcome data were collected from the Society of Thoracic Surgery (STS) Adult Cardiac Surgery Database and hospital medical records. Analyses were performed for two periods: 1) prior to implementation of ERACS (2016-2017); and 2) following implementation of ERACS (2018-2020). Statistical comparisons used chi-square tests for categorical variables, t-tests for continuous variables, and a Mann Whitney U test when continuous variables did not meet assumptions for normal distribution. Using 80% power and alpha = .05, 190 patients in each cohort were required to detect statistical significance based on a reported reduction in readmission rate associated with enhanced recovery implementation [1,2]. Statistical analyses were performed with SPSS 21.0 (SPSS, Chicago, Illinois).

RESULTS: The pre-ERACS and post-ERACS cohorts were similar regarding demographic data, cardiovascular risk factors, comorbidities, beta blocker utilization, cardiac catheterization data, and STS risk score (Table 1). The post-ERACS cohort had a statistically higher mean left ventricular ejection fraction, was less likely to have dyslipidemia, and was more likely to have prior percutaneous coronary intervention, prior carotid artery surgery/stent, aortic stenosis, mitral stenosis, liver disease, and intra-aortic balloon pump (Table 1). The pre-ERACS subgroup had a longer mean aortic cross clamp duration, longer mean bypass duration, and higher likelihood of bilateral internal mammary harvest (Table 1). Regarding ERACS outcomes, there was a trend toward increased likelihood of early extubation in the post-ERACS cohort (Table 2), and the post-ERACS cohort had a shorter median duration of ventilation, lower likelihood of re-intubation, and lower morphine milliequivalent utilization without adverse effect on discharge to home, 30-day re-admission, or 30-day mortality (Table 2, Figures 1-3).

CONCLUSION: These data provide a novel report that ERACS decreased morphine milliequivalent utilization, decreased ventilation duration, and decreased likelihood of re-intubation following urgent/emergency CABG. A limitation of our retrospective study design is that we could not determine which ERACS protocol elements conferred benefits following urgent/emergency CABG. Future prospective studies should evaluate the effect of ERACS on outcomes following cardiac surgery procedures performed under urgent and emergency priority.

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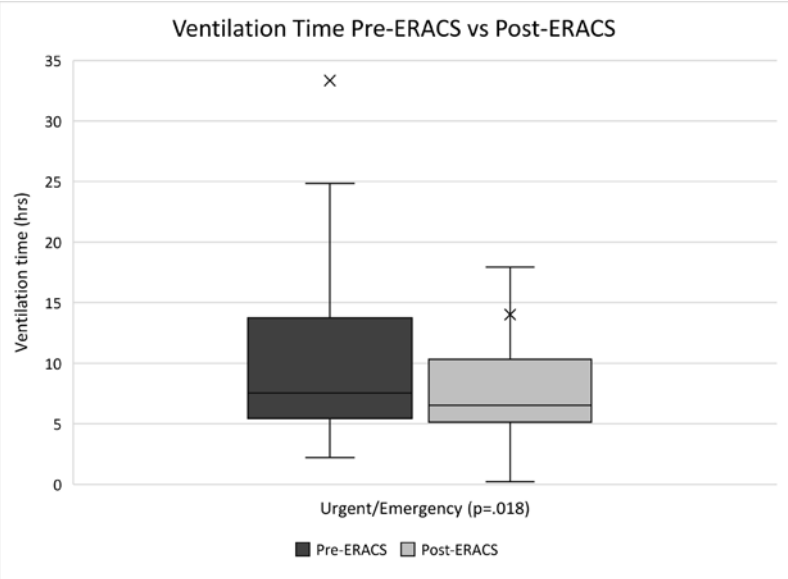

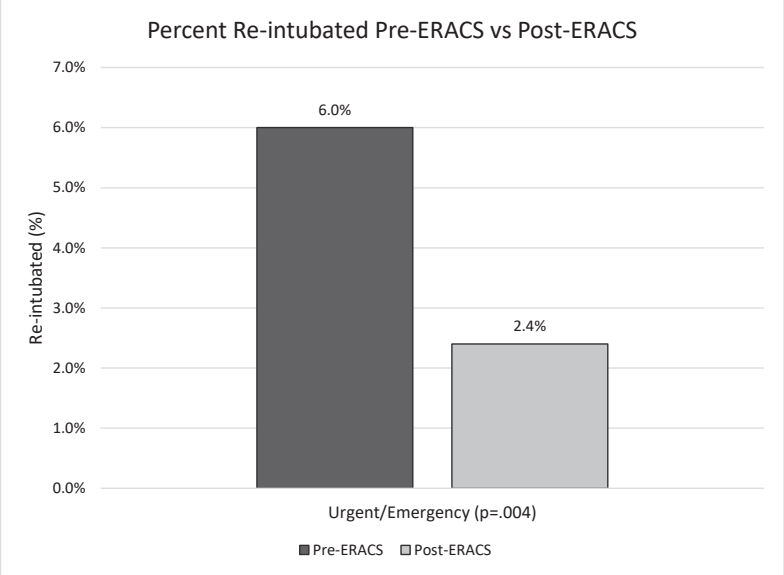

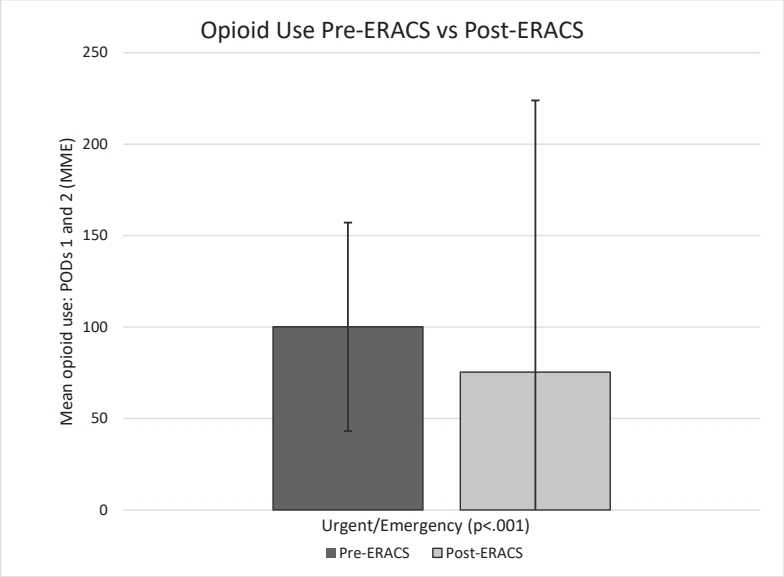

Table 1. Demographics and clinical data.

Parameter	Urgent/Emergent, Pre-ERACS (n = 348)	Urgent/Emergent, Post-ERACS (n = 664)	P Value
Demographic data			
Age, years, mean ± SD	67.1 ± 9.7	60.4 ± 10.1	.493
Male, n (%)	279 (19.8)	510 (76.8)	.232
Body mass index, kg/m^2, mean ± SD	30.2 ± 6.2	29.8 ± 6.5	.326
Cardiovascular risk factors			
Diabetes, n (%)	161 (46.3)	334 (50.3)	.355
Hypertension, n (%)	300 (86.2)	591 (89.0)	.221
Dyslipidemia, n (%)	319 (91.7)	544 (81.9)	<.001
Family history of coronary disease, n (%)	62 (17.8)	107 (16.1)	.535
Smoking			.062
Never, n (%)	117 (33.6)	244 (36.8)	
Former, n (%)	148 (42.5)	287 (43.2)	
Current, n (%)	80 (23.0)	133 (20.0)	
Unknown, n (%)	3 (0.9)	0 (0.0)	
Prior cardiac interventions			
Prior percutaneous coronary intervention, n (%)	66 (19.0)	187 (28.2)	.001
Prior coronary artery bypass, n (%)	5 (1.4)	11 (1.7)	.790
Prior valve surgery, n (%)	1 (0.3)	7 (1.1)	.276
Prior carotid artery surgery/stent, n (%)	77 (22.1)	217 (32.7)	<.001
Comorbidities			
Prior transient ischemic attack, n (%)	15 (4.3)	25 (3.8)	.735
Prior stroke, n (%)	20 (5.8)	61 (9.2)	.067
Chronic obstructive lung disease, n (%)	82 (23.6)	160 (24.1)	.850
Atrial fibrillation			.341
None, n (%)	318 (91.4)	604 (91.0)	
Paroxysmal, n (%)	21 (6.0)	50 (7.5)	
Persistent, n (%)	9 (2.6)	10 (1.5)	
Dialysis, n (%)	20 (5.8)	61 (9.2)	.407
Peripheral vascular disease, n (%)	43 (12.4)	93 (14.0)	.465
Liver disease, n (%)	4 (1.2)	31 (4.7)	.004
Cancer diagnosis within 5 years, n (%)	25 (7.2)	49 (7.4)	.910
History of mediastinal radiation, n (%)	6 (1.7)	13 (2.0)	.999
Immunosuppression therapy, n (%)	12 (3.5)	32 (4.8)	.336
Medication use			
Preoperative beta blockers, n (%)	326 (93.7)	618 (93.1)	.563
Postoperative beta blockers, n (%)	328 (94.3)	637 (95.9)	.227

Table 2. Clinical outcomes.

Parameter	Urgent/Emergent, Pre-ERACS (n = 348)	Urgent/Emergent, Post-ERACS (n = 664)	P Value
Primary ERACS Outcomes			
Extubation < 6 hours, n (%)	132 (37.9)	291 (43.8)	.081
Ventilation, hours, median (IQR)	7.5 (5.4–13.7)	6.5 (5.1–10.3)	.018
Prolonged ventilation, n (%)	30 (8.6)	44 (6.6)	.247
Re-intubated, n (%)	21 (6.0)	16 (2.4)	.004
ICU length of stay, hours, median (IQR)	43.8 (23.6–76.0)	45.2 (23.1–77.8)	.554
ICU readmitted, n (%)	42 (12.1)	92 (13.9)	.426
Postoperative length of stay, days, median (IQR)	5 (4–8)	5 (4–7)	.116
Secondary ERACS Outcomes			
Total MME, PODs 1 and 2, mean ± SD	100.1 ± 61.1	75.4 ± 65.8	<.001
Additional Outcomes			
Stroke, n (%)	5 (1.4)	12 (1.8)	.663
Renal failure, n (%)	9 (2.6)	13 (2.0)	.515
Deep sternal wound infection, n (%)	6 (1.7)	22 (3.3)	.143
Re-exploration for bleeding, n (%)	9 (2.6)	12 (1.8)	.409
Postoperative atrial fibrillation, n (%)	110 (31.6)	188 (28.3)	.275
Discharge home, n (%)	261 (77.2)	478 (72.9)	.305
30-day readmission, n (%)	42 (12.1)	92 (13.9)	.127
30-day mortality, n (%)	8 (2.3)	9 (1.4)	.267

Abbreviations: ERACS, enhanced recovery after cardiac surgery protocol; IQR, interquartile range; ICU, intensive care unit; MME, morphine milligram equivalent; POD, postoperative day; SD, standard deviation.

CARDIOVASCULAR ANESTHESIOLOGY 10

Neural biomarkers do not predict postoperative delirium in cardiac surgery patients with cardiopulmonary bypass

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INTRODUCTION: Over 300,000 patients undergo cardiac surgery with cardiopulmonary bypass (CPB) annually in the United States.[1] Delirium is commonly observed following CPB[2-4] and is associated with longer hospital stays, higher healthcare costs,[5,6] long-term cognitive impairment,[7,8] and increased mortality.[9,10] Phenotypical delirium following CPB may be due to oxidative reperfusion injury[11] and neuroinflammation.[12] Prior studies have demonstrated elevated neuronal biomarker levels, possibly reflecting these injury patterns, following CPB.[13] If these biomarkers are elevated in patients who develop postoperative delirium, then we would better understand the mechanism. Based on these findings, we hypothesized that elevated levels of neuronal biomarkers following CPB will be associated with delirium. To explore this association, we measured four biomarkers of neuronal injury at two distinct time points and conducted postoperative delirium assessments in adults undergoing cardiac surgery with CPB.

METHODS: We conducted a nested case-control study of 46 participants originally enrolled in a single-center randomized controlled trial investigating the effects of hyperoxia versus normoxia on delirium and neurocognitive outcomes among cardiac surgery patients.[14] Blood samples were collected pre- and post-CPB; the serum concentrations of four biomarkers were measured using a custom R&D Human Premixed Multi-Analyte Panel. Two biomarkers (S100B and gamma enolase, ENO2, also known as neuron-specific enolase, NSE) were selected based on their validity in predicting neurocognitive outcomes supported by previous studies.[15,16] Two novel biomarkers that have not yet been studied in the context of post-operative delirium (ubiquitin carboxyl-terminal hydrolase isozyme L1, UCHL1 and chitinase-3-like protein 1, CH3L1) were also selected. Delirium was assessed using the Confusion Assessment Method (CAM-S). Pre-operative and post-operative biomarker levels were compared using paired student t-test. A series of stratified analyses was used to compare pre-operative and post-operative biomarker levels according to delirium/non-delirium status, hyperoxia/normoxia treatment, sex, CPB duration, and BMI. Finally, multiple regression analysis was used to model the relationship between delirium/non-delirium status and biomarker levels, hyperoxia/normoxia treatment, duration of CPB, or the interaction between these predictors.

RESULTS: Twelve patients (26%) were delirium cases. Of the four biomarkers, UCHL1 was undetectable in the blood samples, and ENO2 and CHI3L1 were not elevated relative to baseline (Figure 1). Postoperative S100B levels were increased from baseline (8.04 to 10.14 pg/mL, $P<0.001$). Stratified analyses show that this effect was present regardless of delirium/non-delirium status ($P<0.001$), intraoperative oxygen treatment ($P<0.001$), BMI ($P<0.001$), or sex ($P=0.001$). Multiple regression analysis showed that neither postoperative change in S100B levels, duration of CPB, hyperoxia treatment, nor the interactions between these variables contributed significantly to the occurrence of delirium in this cohort.

CONCLUSION: In our study of four biomarkers of neuronal injury, only S100B was elevated from baseline following CPB. Elevated levels of S100B following cardiopulmonary bypass were not associated with post-operative delirium. Given the large burden of neurological injury following cardiac surgery, future studies are needed to examine the mechanism responsible for neurologic injury post anesthesia and cardiac surgery.

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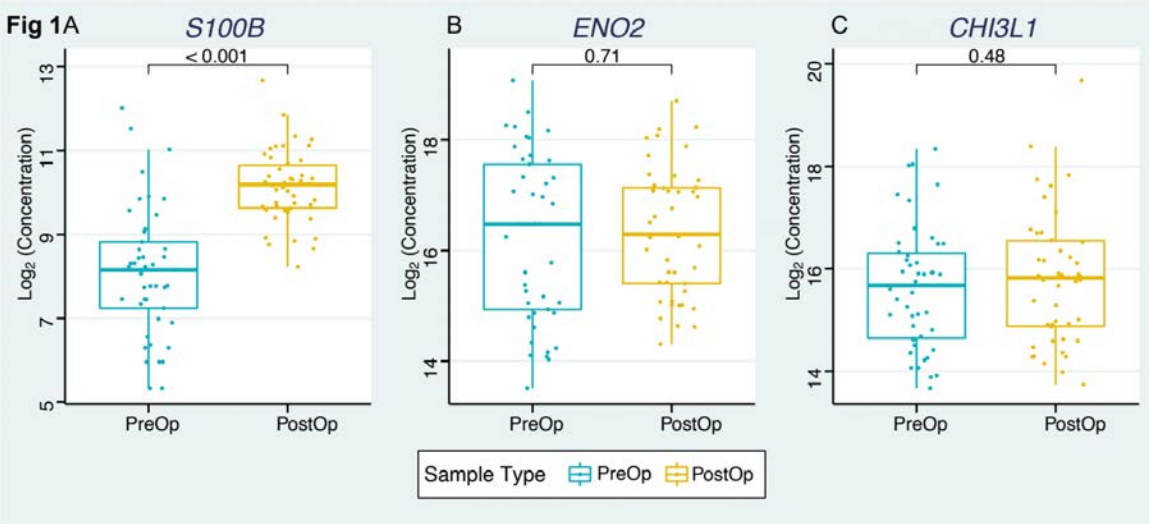

CARDIOVASCULAR ANESTHESIOLOGY 11

Cardiac function decline after general anesthesia and cardiac catheterization in pediatric cardiac transplant recipients

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INTRODUCTION: Pediatric cardiac transplant recipients undergo routine cardiac catheterizations for graft surveillance commonly facilitated with general anesthesia[1]. Some patients show echocardiographic declines in ventricular function from the pre-catheterization (pre-cath) to post-catheterization (post-cath) times without clear etiology. Anesthetic agents are known myocardial depressants[2]. As primary outcome, we aimed to find the rate of significant acute cardiac function decline - defined as a pre-cath echocardiographic left ventricular shortening fraction (LVSF) >28% (normal) to post-cath LVSF <28% (abnormal) in pediatric cardiac transplant recipients undergoing cardiac catheterizations with endomyocardial biopsy (CC/EMBx) under general anesthesia. Secondary outcomes were the associations of anesthesia and patient factors.

METHODS: Following IRB approval, retrospective chart review and analysis of 167 patients with transplanted hearts undergoing CC/EMBx under general anesthesia between 2017 and 2020 was performed. Collected data includes demographic information, intraprocedural cardiac catheterization findings, anesthetic data, pre-catheterization (awake) and post-catheterization (under anesthesia) echocardiographic data. Descriptive statistics and univariate analysis were conducted.

RESULTS: 142 of 167 subjects had complete data for analysis. 17% (24/142) had significant acute cardiac function decline, LVSF% [median (IQR)], from pre-cath 32% (30-35) to post-cath 23% (22-26). The remainder 83% (118/142), went from pre-cath 36% (33-39) to post-cath 33% (31-37). Factors associated with the significant acute cardiac function decline were: older age (p=0.015), elevated right ventricular end diastolic pressure (RVEDP >12 mmHg, p=0.017), and angiotensin converting enzyme inhibitor (ACEI) use (p=0.049); no association were found with the other factors analyzed: propofol use, beta blockers, calcium channel blockers, total minimum alveolar concentration (MAC)-hours, biopsy grade >1R, contrast use, or less than 1 year since transplant.

CONCLUSION: In this study population, 1 of 6 patients showed echocardiographic evidence of significant acute left ventricular decline after CC/EMBx under general anesthesia. Associated factors were older patients, ACEI use, and elevated RVEDP. No anesthetic factors, including propofol and total MAC-hours were associated with this outcome.

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CARDIOVASCULAR ANESTHESIOLOGY 12

Impact of Induced Total Spinal Anesthesia on Fast-track Strategy in Pediatric Cardiac Surgery: Retrospective Study

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INTRODUCTION: The benefits of fast-tracking have been outlined in pediatric cardiac surgery[1]. Thus, a neuraxial block, such as caudal, epidural, or spinal anesthesia, has been combined with general anesthesia (GA) in pediatric cardiac surgery patients to facilitate fast recovery by blunting the surgical stress response and minimizing the negative effects of opioid-induced respiratory suppression[2-4]. Total spinal anesthesia (TSA) is a type of spinal anesthesia where total spinal block is intentionally induced with a high dose of intrathecal bupivacaine. With the concomitant use of intrathecal morphine, TSA combined with GA provides adequate perioperative analgesia with minimal opioid use in cardiac surgery[5]. Nevertheless, few studies have investigated the impact of TSA on the fast-track extubation in pediatric cardiac surgery.

METHODS: Patients aged 1-day to 18-years who had open cardiac surgeries at our institution from November 1, 2010 to December 31, 2017 were included. Patients who were not a candidate for fast-track extubation were excluded. The cases were divided into two groups: cases with TSA in combination with GA (TSA group) and cases with GA without any additional neuraxial blocks (GA group). In the TSA group, intrathecal medications were injected at a lumbar level between L3 and L5 under GA. The intrathecal medications consisted of 0.75% hyperbaric bupivacaine (0.2 mL/kg for the first 10 kg weight, then additional 0.1 mL/kg, limited up to 8 mL) with preservative-free morphine (7 mcg/kg, limited up to 500 mcg/kg). Immediately after the intrathecal injection, the patient was placed in the supine position at 30 to 45 degrees Trendelenburg to facilitate the cephalad spread of spinal anesthesia. Mydriasis confirmed the completion of total spinal block. GA was maintained with sevoflurane or isoflurane (0.5-1.0 minimal alveolar concentration (MAC)). Few doses or no dose of opioid, except for remifentanil, was used intravenously during the intraoperative period in the TSA group. In GA group, no neuraxial block was provided, and GA was maintained with sevoflurane or isoflurane (0.5-1.0 MAC) with low-to-moderate doses of intravenous opioids intraoperatively. Typical opioids used were fentanyl, hydromorphone and/or morphine. An excessive dosage of opioids was avoided in order to facilitate fast-track strategy. The comparison was made between the two groups (TSA group vs GA group). The primary outcome was extubation in the operating room. Secondary outcomes include time to extubation, length of stay (LOS) in the ICU, and LOS in the hospital.

RESULTS: This is a preliminary analysis of an ongoing data collection. A total of 520 cases were analyzed (196 cases in the TSA group and 324 cases in the GA group). The rate of extubation in the operating room was significantly higher in the TSA group (n=128/196) vs GA group (n=109/324). A multinomial logistic regression for the probability of extubating in the operating room was performed with the group allocation (TSA and GA) as the main factor and age, sex, BMI, use of CPB, ASA status and surgical duration as covariates. The logistic regression model was statistically significant, $\chi 2(7) = 71.02$, $p < .0001$. Odds of extubation in the operating room was 3.39 (95% CI 2.11, 5.43, $p<0.001$) times more likely with the use of TSA. Other factors affecting the model to a lesser degree was surgical duration (Odd ratio 1.006, 95% CI 1.003, 1.009, $p<0.001$). A log rank test to determine the differences in time to extubation after surgery were statistically significantly different, $\chi 2(1) = 8.006$, $p = .005$ but such differences in extubation times were not deemed to be clinically significant. Patients were likely to have a shorter ICU and hospital LOS with the use of TSA (see Table 1).

CONCLUSION: The preliminary results of this retrospective study suggests that the TSA technique may facilitate faster recovery in pediatric cardiac surgery patients. A high dose of intrathecal bupivacaine provides complete sensory block; thus, few intravenous opioids are required intraoperatively. At the same time, intrathecal morphine can provide adequate pain control immediately after surgery. A combination of these intrathecal medications significantly reduces perioperative opioid requirement while providing adequate analgesia, and this could contribute to a fast-track extubation. Further randomized controlled trial is warranted to clarify this outcome.

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Table 1. Characteristics of patients and surgeries, and secondary outcome measures (ICU-LOS, Hospital-LOS)

	TSA (n=196)	GA (n=324)	p-value
Age, year	1.83 (4.90)	1.62 (3.38)	<0.05
Gender, male: female	195:129	111:85	0.42
BMI, kg/m²	16.2 (3.1)	16.0 (3.3)	0.58
CPB, Yes/No	156/40	234/90	0.06
Surgical time, min	348(258)	147 (92)	0.17
ICU-LOS, hour	122 (123)	193 (357)	<0.001
Hospital-LOS, day	5.4 (7.1)	10.25 (24.31)	<0.001

Values are expressed as median (interquartile range). TSA, total spinal anesthesia; GA, general anesthesia; BMI, body mass index; CPB, cardiopulmonary bypass; ICU-LOS, length of stay in the intensive care unit; Hospital-LOS, length of stay in the hospital.

CARDIOVASCULAR ANESTHESIOLOGY 13

Interdependent Regulation of Vascular Endothelial Adenosinergic Signaling by Estrogen and Hypoxia: Implications for Microvascular Injury and Diastolic Heart Failure

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INTRODUCTION: Estrogen has multiple beneficial roles in the vasculature and protects premenopausal women from cardiovascular disease[1]. These salutary effects on the vasculature appear especially pronounced under experimental hypoxic conditions, which may be linked to increased generation of extracellular adenosine by CD39 and CD73[2]. The impacts of estrogen on the expression of these ectonucleotidases and modulation of adenosinergic pathways are largely unknown. We have therefore dissected out elements of the estrogen-hypoxia-adenosinergic pathways in vitro to define those mechanisms necessary for vascular protection in vivo.

METHODS: Human umbilical venous endothelial cells (HUVECs) were exposed to hypoxia (1% oxygen for 24 hours) or Cobalt Chloride (100uM for 24 hours). HUVECs were then treated with estradiol (E2) and/or YC-1 compound (HIF-1α inhibitor). Expression levels of CD39, CD73, adenosine transporters (ENT1), HIF-1α and VEGFA and interactions were measured using western blotting, qRT-PCR, immunofluorescence studies and immunoprecipitation.

RESULTS: Immunofluorescent expression of CD39 and HIF-1α was markedly increased under hypoxia following on E2 exposure. VEGFA expression increased likewise under hypoxia and/or E2 exposure, as measured by qRT-PCR. Increases in CD39, HIF-1α and VEGFA expression levels under hypoxic conditions and/or E2 exposure were attenuated by inhibition of HIF-1α. In contrast, ENT1 expression was down-regulated by E2 exposure and impacted by inhibition of HIF-1α. No differences were noted in expression of adenosine receptors (ADORA 2A or 2B). However, phosphorylation of ERK, a downstream adenosine signaling target, increased with E2 exposure, and was boosted by inhibition of HIF-1α. Estrogen receptor alpha (ERα) increased in hypoxic HUVECs, but no significant changes were observed with estrogen receptor beta (ERβ). ERα protein expression decreased with stimulation of aryl-hydrocarbon receptor (AhR), a transcription factor known to boost CD39 transcription, while AhR expression decreased following E2 exposure. No protein-protein interaction was observed between HIF-1α and ERα or between CD39 and either ERα or AhR. ERα interacted with AhR under hypoxic conditions, which increased in the presence of the proteosome inhibitor, MG-132.

CONCLUSION: We show that E2 treatment and/or hypoxia increase CD39 expression and decrease the expression of ENT1. These hormonal changes induced by E2 and/or hypoxia substantially increase extracellular adenosine availability and provide vascular protection. Altered regulation of ERα by AhR in hypoxia, likely through ubiquitination, infers additional regulatory mechanisms for E2 in mediating adenosinergic signaling. Further characterization of these regulatory pathways may provide effective, well tolerated therapeutic options to ameliorate post-menopausal cardiovascular disease, as noted in the Yentl syndrome.

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CARDIOVASCULAR ANESTHESIOLOGY 14

Contraindications to neuraxial anesthesia in patients undergoing lower limb revascularization surgeries: A retrospective chart-review

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INTRODUCTION: Patients requiring lower limb revascularization surgeries experience high rates of morbidity, mortality and resource utilization. As the incidence of peripheral arterial disease continues to increase, strategies to improve outcomes are needed. Recent population-level data demonstrate a strong association between neuraxial (compared to general) anesthesia and lower rates of postoperative morbidity (OR 0.73, 95%CI 0.63-0.85), mortality (OR 0.68, 95%CI 0.57-0.83) and length of stay.[1] However, rates of neuraxial anesthesia use in lower limb revascularization surgery are decreasing.[1] We aimed to identify the proportion of lower limb revascularization patients with absolute and relative contraindications to neuraxial anesthesia, and to describe the reasons for these contraindications and related processes in anesthesia type selection.

METHODS: We conducted a retrospective cross-sectional study at a regional vascular care center of excellence. We identified all lower limb revascularization cases from May 2019 to May 2021, excluding endovascular cases. Electronic chart review identified demographic, admission and procedure-level variables and confirmed anesthesia, presence of any absolute (patient refusal, infection at injection site, active coagulation deficit (intrinsic or extrinsic due to medications), severe hypotension, intracranial mass) or relative (anticipated long duration of surgery, lack of (or anticipated) patient cooperation). Reasons underlying contraindications were identified, along with stated patient preferences for anesthesia type. Baseline characteristics between those with and without absolute contraindications were quantified using standardized differences. Proportions were calculated, along with 95% confidence intervals using Wilson's method.

RESULTS: We identified 340 cases (50% elective). Mean age was 68 (SD 11); 68% were male. Isolated general anesthesia was used in 219 (64.4%), isolated neuraxial (spinal, epidural or combined) in 106 (31.2%) and neuraxial plus general in 15 (4.4%). Discussion for primary anesthesia options was documented in 319/340 cases (93.8%); 73 patients had a preference for anesthesia type (21.4%, 52 general and 21 neuraxial). Seventy eight (22.9%, 95%CI 18.8-27.7) patients had an absolute contraindication to neuraxial anesthesia, primarily due to extrinsic coagulation deficit (70/78, 89.4%). Twenty one patients (6.2%, 95%CI 4.1-9.3) had a relative contraindication, primarily a long expected duration of surgery (16/21, 76.2%).

CONCLUSION: Most lower limb revascularization patients do not have absolute contraindications to neuraxial anesthesia. As anesthesiologists already engage patients to support evidence-informed and preference-sensitive choice of primary anesthesia technique, incorporation of recent data supporting neuraxial anesthesia use could support increased uptake. Multicenter randomized trial data is required to inform this decision point with high certainty evidence. Our findings support aspects of feasibility of such a trial.

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CARDIOVASCULAR ANESTHESIOLOGY 15

Perioperative fluid dynamic assessment for a patient with aortic and pulmonary regurgitation 20 years after the Ross-Konno procedure

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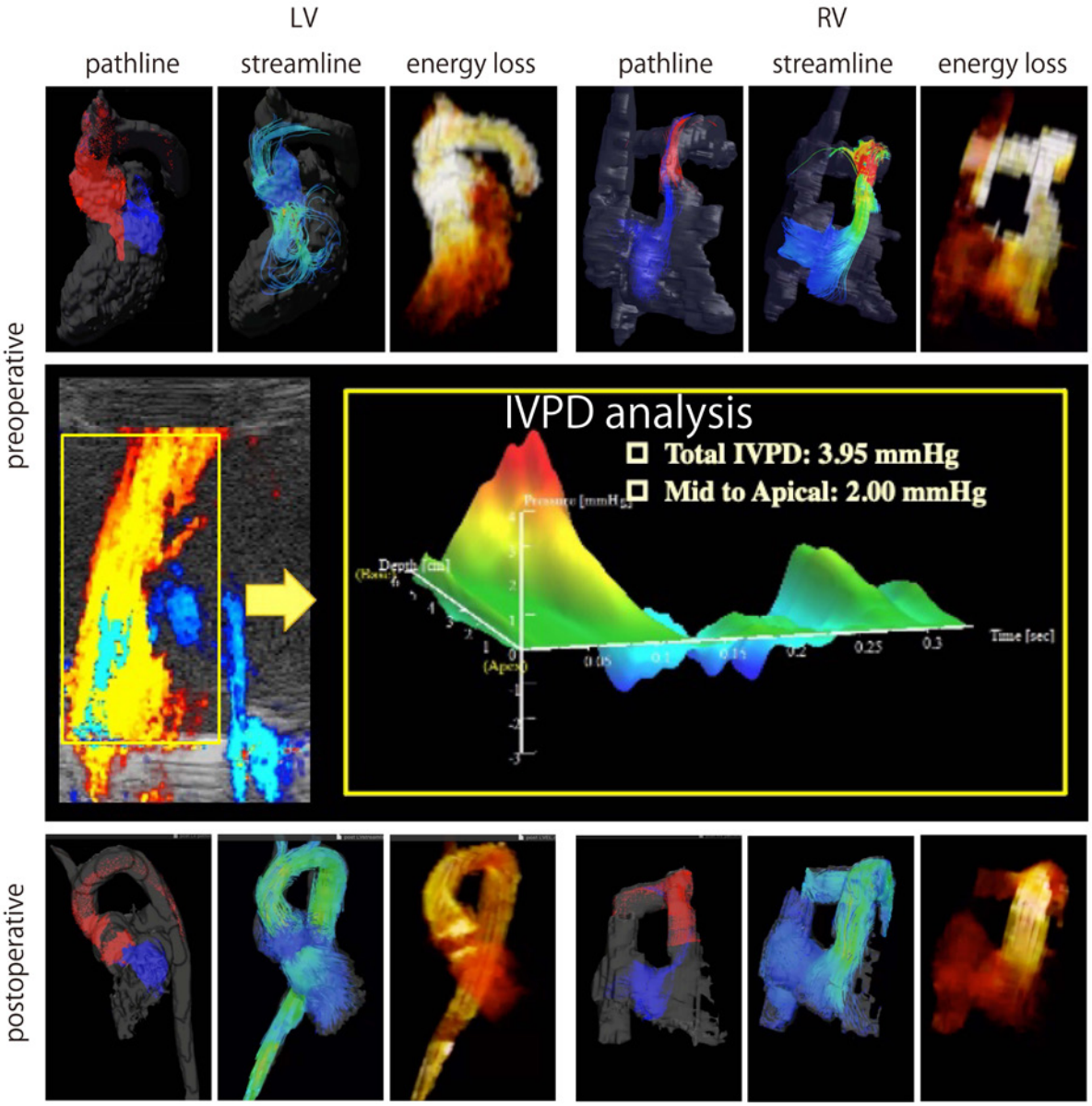
INTRODUCTION: Thirty-one years old man who had undergone Ross-Konno procedure for congenital aortic stenosis 20 years ago. Although severe aortic regurgitation, moderate to severe mitral regurgitation, moderate pulmonary stenosis, moderate pulmonary regurgitation, and mild to moderate tricuspid regurgitation were observed, he had almost no symptom.

METHODS: Preoperative analysis of 4D flow MRI showed very large left and right ventricular volume (LVEDV 361.85 ml, LVESV 211.63 ml, RVEDV 143. 53ml, EVESV 77.96 ml) and energy loss (systemic circulation 13.78 mW, pulmonary circulation 8.37 mW). Intraventricular pressure difference was also analyzed for assessing left ventricular diastolic function (Analyzing color M-mode image using Matlab with in-house programming code). The result was that total IVPD was 3.95 mmHg and apical IVPD was 2.00mmHg, which meant left ventricular diastolic function was within normal range. Therefore, aortic valve replacement, mitral valve repair, aortic root reinforcement, and right ventricular outflow tract reconstruction were scheduled and performed.

RESULTS: After the surgery, Ventricular volumes and energy loss were reduced drastically (LVEDV 170.0 ml, LVESV 87.1 ml, RVEDV 102.01 ml, RVEDV 42.3 ml, systemic circulation 3.4 mW, pulmonary circulation 3.4 mW).

CONCLUSION: Perioperative fluid dynamic assessment encouraged us to perform the second surgery and led the patient to good clinical course.



CARDIOVASCULAR ANESTHESIOLOGY 16

Recovery of left ventricular diastolic function after cardiopulmonary bypass

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INTRODUCTION: Intraventricular pressure difference (IVPD) is a driving force of the left ventricular (LV) suction during early diastole[1]. It correlates well with the Tau index which is the gold standard measurement of the diastolic function[2]. IVPD is divided into two parts (basal IVPD and apical IVPD) at 2 cm below the mitral annulus and defined the sum of the two as total IVPD. The basal IVPD reflects the left atrial pressure and the apical IVPD reflects the LV suction. We measured IVPD during cardiac surgery and assessed the recovery of the left ventricular diastolic function after the cardiopulmonary bypass (CPB). Case:We measured the IVPD in a 78-year-old man who was diagnosed with chronic atrial fibrillation. He developed severe mitral regurgitation. Minimally invasive mitral valve repair, tricuspid valve repair, Maze procedure, and left atrial appendage closure were performed.

METHODS: We stored the color M-mode Doppler images of the mitral inflow before CPB (T1). One minute (T2), 15 minutes (T3) and 30 minutes (T4) after weaning from CPB we stored the images again. Then we estimated the IVPD using an in-house MATLAB programing code (MathWorks, MA, USA).

RESULTS: A continuous infusion of milrinone 0.5 mcg/kg/min and noradrenaline of 0.05 mcg/kg/min was administrated after the aortic cross-clamp release. Total IVPD at T1, T2, T3, and T4 were 2.088, 0.272, 3.988, 2.129 mmHg, respectively. Apical IVPD at T1, T2, T3, and T4 were 0.207,0.0457, 0.154, 0.341 mmHg, respectively.

CONCLUSION: Both total and apical IVPD were low immediately after weaning from CPB. It took more than 15 minutes to recover from the impaired diastolic function. Our results suggest that we should be careful to identify the appropriate volume load after CPB.

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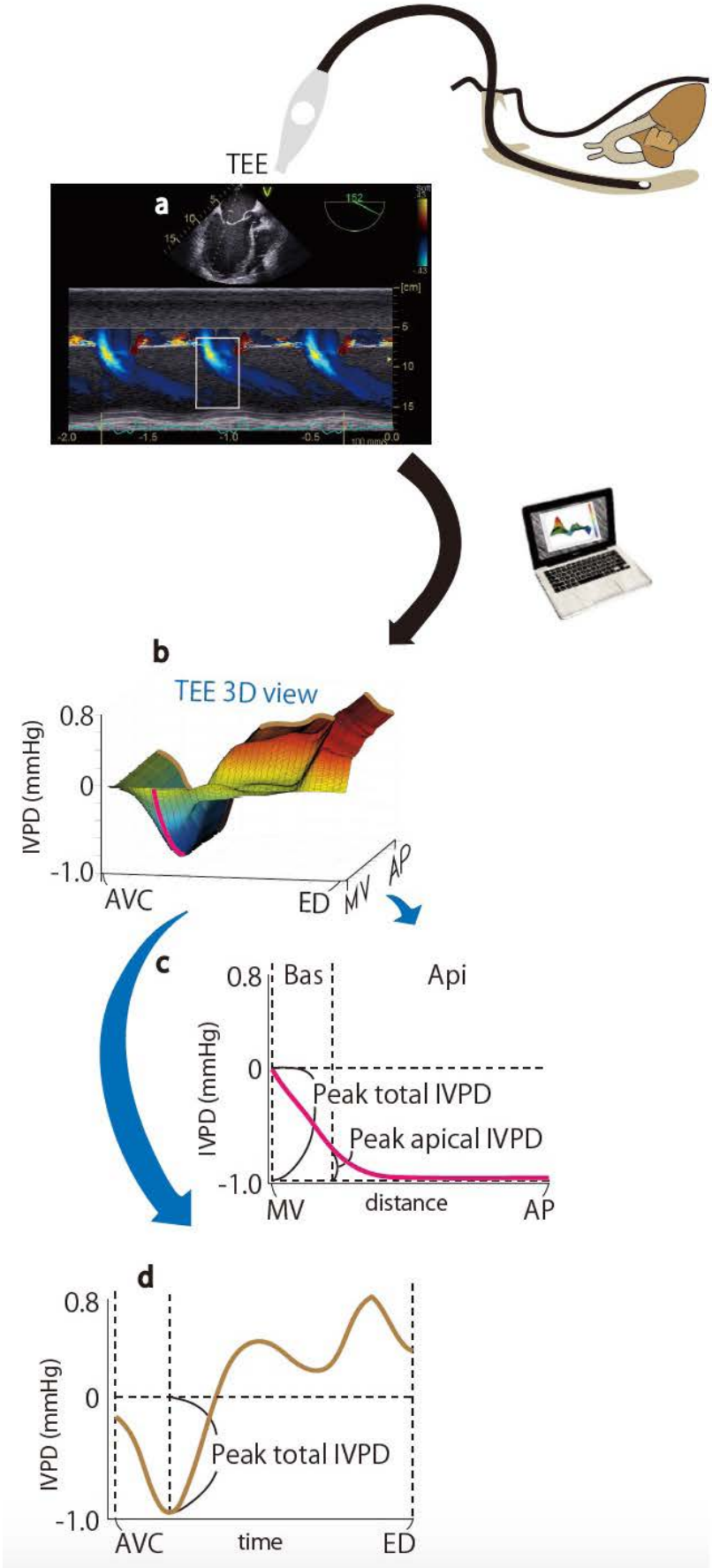

Fig. 1

CARDIOVASCULAR ANESTHESIOLOGY 17

Protection of Cardiomyocytes against Simulated Ischemia/Reperfusion Injury by Di-Block Membrane Stabilizers Depends on Optimal Chemical Composition

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INTRODUCTION: The tri-block copolymer-based cell membrane stabilizer (CCMS) Poloxamer (P)188, consisting of 30 central hydrophobic PPO units flanked by 75 hydrophilic PEO units (PEO_{75}-PPO_{30}-PEO_{75}) on each side, has been shown to dose-dependently protect mouse cardiomyocytes (CMs) against simulated ischemia/reperfusion (IR) injury as evidenced by decreased release of lactate dehydrogenase (LDH) and increased viability[1]. Chemical modifications to di-block CCMS and addition of a strongly hydrophobic with *tert*-butyl terminal resulted in stronger cellular protection against hypotonic shock in muscle myoblasts than P188 as evidenced by LDH release[2]. Thus, we hypothesized that the chemical composition of di-block CCMS can be optimized to provide profound cardioprotection against prolonged hypoxia/reoxygenation (HR) when given as postconditioning agents at the clinically relevant time of reoxygenation.

METHODS: In the present study, we used mouse CMs undergoing simulated IR injury by 24 hrs hypoxia (0.01% O_2) followed by 2 hrs reoxygenation to examine the cardioprotective effect of three newly synthesized and custom-made di-block CCMS (PEO_{113}-$PPO_{10}t$, PEO_{226}-$PPO_{18}t$ and PEO_{113}-$PPO_{20}t$)(3); corresponding durations were used for control normoxia (CN, 21% O_2). Upon reoxygenation, CMs were treated by four different concentrations (0–300 μM) of one of the three newly synthesized di-blocks, all with *tert*-butyl terminals, but different PEO/PPO lengths / ratios. Endpoints were cell proliferation and LDH release as marker of cell viability and membrane leakage, respectively. Data in the Figure are represented as mean ± standard error of the mean. Statistics: ANOVA and SNK post-hoc testing, $\alpha = 0.05$, * vs CN, horizontal bars indicate differences among different concentrations in the HR groups.

RESULTS: We found that the three new di-block CCMS significantly prevented HR-induced cell death as well as LDH leakage in the order: PEO_{113}-$PPO_{20}t$ > PEO_{226}-$PPO_{18}t$ > PEO_{113}-$PPO_{10}t$.

CONCLUSION: Our data demonstrate that chemical modifications of CCMS can optimize their cardioprotective properties against simulated IR compared to P188.

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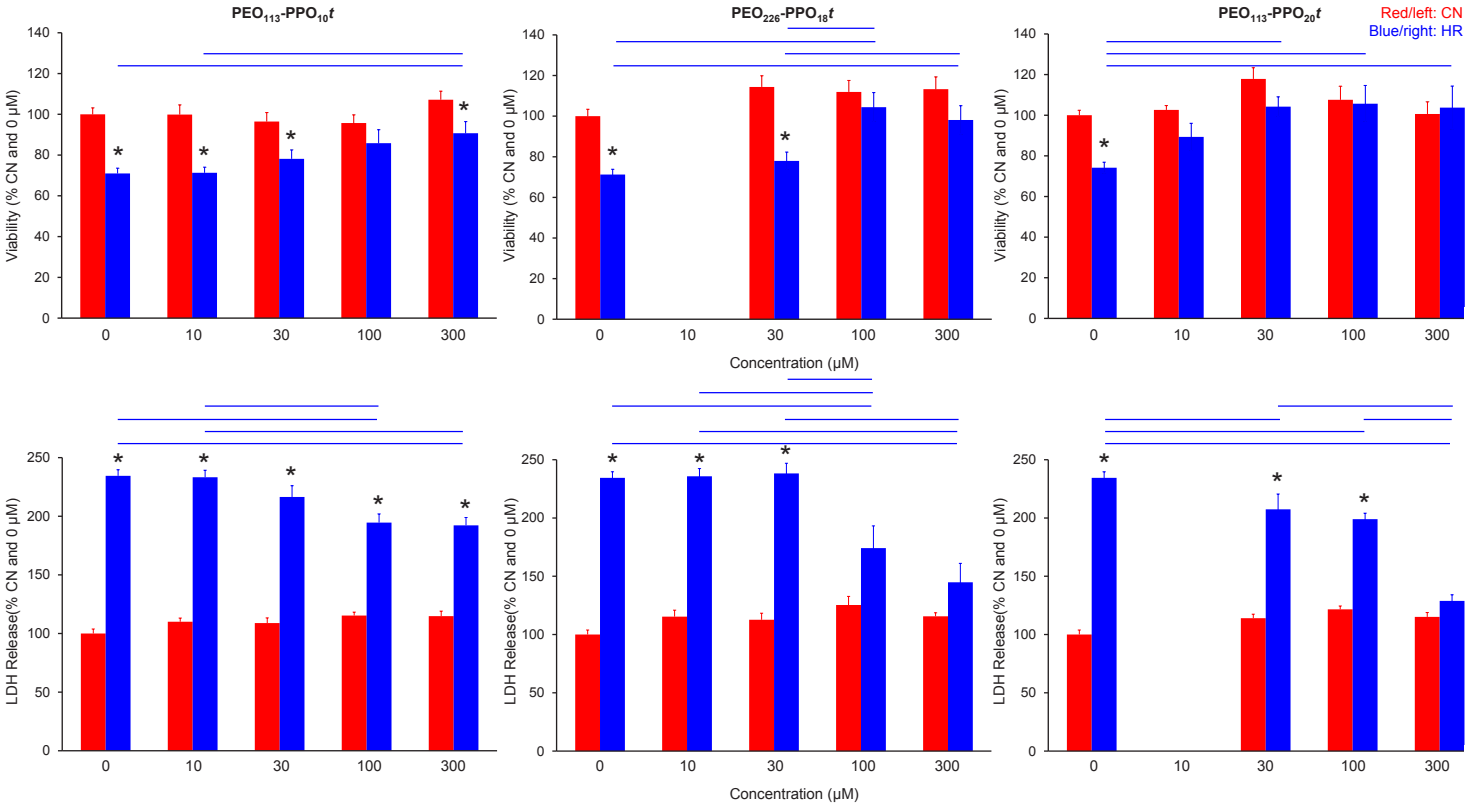

Figure: Cell viability (upper three panels) and release of lactate dehydrogenase (LDH, lower three panels) in mouse cardiomyocytes following 24 hrs hypoxia and 2 hrs reoxygenation (HR, blue/right bars) vs control/normoxia (CN, red/left bars) for different concentrations of three differnt di-block cell membrane stabilizers (PEO_{113}-$PPO_{10}t$, PEO_{226}-$PPO_{18}t$ and PEO_{113}-$PPO_{20}t$) administered upon reperfusion as % of CN and 0 µM. All data are mean +/- standard error of the mean. Statistics: Two-way-ANOVA and Student-Newman-Keul with $P<0.05$ * vs CN and horizontal bars for comparisons among different concentration in the HR groups.

CARDIOVASCULAR ANESTHESIOLOGY 18

Sulfide Quinone Oxidoreductase: A Novel Regulator of the Mitochondrial Permeability Transition Pore

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INTRODUCTION: The mitochondrial permeability transition pore (mPTP) is a voltage-gated, non-selective channel present on the inner mitochondrial membrane[1, 2]. The mPTP plays a fundamental role in the pathophysiology of a variety of dis ease processes, from diabetes to ischemia-reperfusion injury[2,3]. Regulation of mPTP opening is also essential for normal cellular development and homeostasis[4].While the precise proteinaceous identity of the mPTP remains unknown, certain key characteristics of the pore have been detailed. For instance, it is well accepted that the mPTP is voltage-dependent, such that depolarization of the inner mitochondrial membrane (IMM) leads to pore opening. There is a major gap in our knowledge, however, because it is unknown how mPTP voltage-gating is regulated. Prior work demonstrated that the redox status of vicinal thiol groups tunes the putative voltage sensor of the mPTP such that oxidation opens the pore at relatively higher $\Delta\Psi$s and thiol group reduction results in closed mPTP probability. In previous work, we identified a pathologically open mPTP within the forebrain of Fragile X syndrome (FXS) mice due to coenzyme Q (CoQ) deficiency and a relatively closed mPTP within the cardiomyocytes of FXS mice due to CoQ excess. In addition, CoQ replete FXS cardiomyocyte mitochondria appear to have altered voltage gating of their mPTP. Thus, it is clear that CoQ regulates the mPTP and may also contribute to its voltage gating. Interestingly, sulfide quinone oxidoreductase (SQOR), a mitochondrial enzyme that catalyzes the first step of catabolism of hydrogen sulfide (H2S), is a ubiquitously expressed IMM-associated protein, harbors redox-sensitive vicinal thiol groups, and binds CoQ as a requisite electron acceptor. These characteristics render SQOR an attractive candidate to be the voltage gate of the mPTP. We show that inhibition of SQOR in cardiomyocyte mitochondria with antimycin A altered the voltage sensing of the mPTP such that the probability of pore opening was significantly increased at relatively high $\Delta\Psi$s (when it should be closed).

METHODS: The care of mice was in accordance with NIH and CUMC IACUC guidelines. We evaluated cardiac mitochondria harvested from male Fmr1 KO mice (FXS) along with FVB controls on P10 and 8wks. Oxygen consumption and mitochondrial membrane potential were measured simultaneously using polarography and a Tetraphenylphosphonium ion selective electrode. Complex II-dependent proton leak respiration was assessed using succinate, rotenone and oligomycin. In separate experiments, CsA was added at three membrane potential levels (low, intermediate and high) as the proton motive force declined in order to determine open or closed mPTP probability. Significance was assessed via chi-squared test with set $p < 0.05$. We determined the expression of the SQOR in cardiac mitochondria using Western blot. Finally, we evaluated the effect of the SQOR inhibitor, antimycin A, on voltage gating as described above except complex IV-dependent proton leak respiration was measured using N,N,N,N-tetramethyl-p-phenylenediamine /ascorbate, rotenone, malonate and oligomycin. Calcium loading capacity was determined using a calcium selective electrode.

RESULTS: Mitochondria from both Fmr1 KOs and FVB controls demonstrated CsA sensitivity at low membrane potentials, suggesting open mPTP probability at or near 100%. Conversely, both groups showed CsA insensitivity at high membrane potential mitochondria, indicating closed mPTP probability. At median membrane potentials, we found open mPTP probability to be 89% in FVB controls samples compared to 45% in Fmr1 KOs, $p < 0.05$. Fmr1 KO cardiac mitochondria had a 20% increase in SQOR expression. Inhibition of SQOR with antimycin A led to opening of the mPTP at higher membrane potential where it would normally be closed.

CONCLUSION: We identified differences in voltage gating of the mPTP between Fmr1 KO and FVB controls and demonstrate differences in expression of the SQOR protein. We show that inhibition of SQOR disrupts normal voltage gating of the mPTP. This work identifies SQOR as novel regulator of mPTP voltage gating of the mPTP.

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CARDIOVASCULAR ANESTHESIOLOGY 19

Factors Influencing RBC Transfusion Requirement In Adult Cardiac Surgical Patients Treated With Prothrombin Complex Concentrate (PCC) – Single Center Retrospective Cohort Study

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INTRODUCTION: Cardiothoracic surgery involving cardiopulmonary bypass (CPB) is associated with acquired coagulopathy, perioperative bleeding and transfusion of autologous red blood cells (RBCs).[1,2,3] While perioperative coagulopathy in cardiac surgeries has been managed with autologous non-RBC products, recent studies have reported the efficacy and safety of prothrombin complex concentrate (PCC) and fibrinogen concentrate (Fibryga).[4,5] Despite adequate PCC and/or fibrinogen concentrate administration, we have noted variability in the transfusion of autologous red blood cells. Herein, we describe demographic and clinical risk factors for RBC transfusion despite adequate PCC and/or fibrinogen concentrate administration.

METHODS: On March 4, 2020, the Division of Cardiothoracic Anesthesia in collaboration with the Department of Cardiac Surgery recommended the use of PCC and Fibryga as first line therapy for non-surgical coagulopathy based on viscoelastic and static testing and visual inspection of the surgical field in all consecutive cardiac surgical patients older than 18 years having coronary artery bypass grafting (CABG), valve surgery, aortic surgery, heart or lung transplantation, left ventricular assist device (LVAD) placement, or some combination of these procedures. We recommended administering PCC 500 units up to 2000 units and Fibryga 1 gram up to 4 grams in divided doses until the TEG R value and alpha angle, respectively returned toward normal or bleeding in the surgical field stopped. We collected patient demographic information, clinical variables and outcomes from the electronic medical record. Data are described as means (± SD) and percentages.

RESULTS: From March 2020 to April 2021, we collected 404 patients. Thirteen patients were excluded, as they had cardiac surgeries without CPB. Of these, 231 (59%) received no non-RBC blood product or concentrates, 63 (16.1%) received a combination of non-RBC blood product, PCC and/or fibrinogen concentrate, and 97 (24.8%) patients received PCC and/or fibrinogen concentrate. In these 97 patients, the mean age was 61.36 ±14.81 and 28.7% were women, 41.2% had CABG and/or valve surgery; 29.2% had complex surgery, 15.15% had heart or lung transplantation surgery, and 14.5% had LVADs placed. The median number of RBCs transfused was one unit and interquartile range was 2 units. Patients who received higher than the median units of RBC despite PCC and/or Fibryga therapy, were more likely to have liver disease, have received anticoagulants 48 hours prior to surgery, undergoing a re-sternotomy, have a higher preoperative INR and lower perioperative hemoglobin (Hb) (See Table 1-5).

CONCLUSION: In this single academic center experience, we identified several clinical variables including preexisting liver disease, redo surgeries, anticoagulation within 48 hours of surgery, and high preoperative INR, lower perioperative hemoglobin associated with increased RBC transfusions during the perioperative period. Additional analysis will be done to identify independent and actionable risk factors for decreasing the risk of perioperative RBC transfusion in patients receiving PCC and/or Fibryga therapy.

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TABLE 1: DEMOGRAPHICS

	H (N=27)	L(N=70)	P value	Missing %
Age (Median, IQR)	67(20)	65(17.5)	0.44	0
Sex-Female, N (%)	6(22.22%)	19(27.14)	0.61	0
Weight (Mean±SD)	84.35±30.61	88.65 ±24.95	0.52	4.1
Height (Mean±SD)	170.68±14.17	172.88±9.80	0.47	4.1
Co-Morbidities				
Hypertension	N=20 76.92%	N=54 80.60%	0.69	4.1
Diabetes Mellitus	N=6 23.08%	N=15 22.39%	0.9	4.1
Chronic kidney disease-Dialysis	N=2 7.69%	N=4 5.97%	0.7	4.1
Chronic liver diseases	N=7 26.92%	N=4 5.92%	0.02	4.1
Cerebrovascular diseases	N=6 23.08	N=11 16.42%	0.43	4.1
Anticoagulants with in 48 hours	N=14 53.85%	N=21 31.34%	0.04	4.1

TABLE 2: SURGICAL CHARACTERISTICS BETWEEN GROUPS

	H (N=27)	L(N=70)	P value	Missing %
Re do surgery First Second	 N=6 23.08% N=5 19.23%	 N=12 17.91%	0.0007	4.1
Emergency, N (%)	8 (29.63%)	22 (31.43%)	0.86	0
CPB time, Mins, (Median, IQR)	140(129)	149.5(86.5)	0.9	0
Cross clamp, Mins, (Median, IQR)	126(133.5) N=17	109(63.5) N=58	0.34	22.6

TABLE 3: FACTOR, FIBRINOGEN AND PLATELETS DOSING BETWEEN GROUPS

	H (N=27)	L(N=70)	P value
PCC dose, (Median, IQR)	1087(1548)	1088(977.5)	0.91
Fibryga dose, mg, (Median, IQR)	1050(650) N=14	1050(1000) N=28	0.86
Total RBC, ml (Median, IQR)	900(600) N=27	300(0) N=14	0.0001
Total Platelets, ml ((Median, IQR)	488.5(233) N=24	474(267.25) N=44	0.48
24 hours Chest output, ml, (Median, IQR)	465(540) N=27	394(372.5) N=70	0.81
Cell Saver, ml (Median, IQR)	600(375)	559.5(391)	0.41

TABLE 4: PERIOPERATIVE STATIC AND VISCOELASTIC TEST RESULTS BETWEEN GROUPS

	H (N=27)	L(N=70)	P value	Missing %
Preop INR (Median, IQR)	1.24(0.48) N=24	11.13(0.19) N=52	0.0041	21.6
Preop Platelets (Median, IQR)	176(107.5) N=25	185(86.5) N=56	0.24	16.4
Preop Hb (Median, IQR)	9.1(2) N=26	13.05(3.05) N=68	0.0001	3
Lowest Intraoperative Hb (Median, IQR)	6.9(1) N=27	9.25(2.72) N=70	0.0001	0
PP INR, (Median, IQR)	1.68(0.395) N=25	1.73(0.43) N=67	0.6	5.1
PP Platelets, (Median, IQR)	121(74) N=25	127(63.75) N=66	0.34	6.1
PP Fibrinogen, (Median, IQR)	202(92) N=25	207.5(109.25) N=58	0.99	14.4
BL-R BL-K BL-Alpha angle BL-MA (Median, IQR)	5.95(3.67) 1.35(0.55) 71.4(9) 69.9(12.05) N=20	4.95(2.5) 1.37(0.7) 69.55(9.77) 68.65(8.65) N=60	0.09 0.09 0.09 0.38	17.5
PP-R PP-K PP-Alpha angle PP-MA (Median, IQR)	5.3(2.4) 1.8(1.1) 66.1(7.3) 59.6(11.7) N=27	5.35(3.47) 1.7(0.9) 66.9(12.1) 62.65(11.5) N=70	0.88 0.51 0.16 0.26	0
ICU INR, (Median, IQR)	1.48(0.34)	1.45(0.2)	0.26	1
ICU Platelets (Median, IQR)	151(64)	177.5(73.5)	0.028	0
ICU Hb (Median, IQR)	9.9(1.7) N=27	10.85(2.47) N=70	0.091	0
ICU Fibrinogen (Median, IQR)	239(147.25)	177(55.5)	0.30	68

TABLE 5: POSTOPERATIVE OUTCOMES BETWEEN GROUPS

	H (N=27)	L(N=70)	P value	Missing %
Postoperative ventilation, hours, (Median, IQR)	80.4(260.45)	21.7(44.5)	0.01	4.1
ICU Readmission	N=6 26.09%	N=7 10.61%	0.08	8.2
Stroke	N=0	N=2 2.86%	0.25	0
Acute kidney injury	N=6 22.22%	N=13 18.57%	0.68	0
Re exploration within 48 hours	N=5 18.52%	N=5 7.14%	0.11	0
Thromboembolic events within 30 days	N=4 14.81%	N=10 14.29%	0.94	0
Postoperative reintubation	N=6 23.08	N=7 10.45%	0.12	4.1
Mortality with in 30 days	N=3 11.11%	N=6 8.57%	0.14	0

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Antithrombin III Levels After Prothrombin Complex Concentrate (PCC) Compared To Fresh Frozen Plasma (FFP) For Post Cardiopulmonary Bypass Bleeding

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INTRODUCTION: Patients undergoing cardiopulmonary bypass (CPB) are responsible for nearly 50% of all blood product usage in the United States. Reversal and correction of coagulopathy after CBP continues to be an area of ongoing refinement and research, with significant inter-institutional differences with the optimal correction methods unknown; particularly avoiding prothrombic adverse outcomes. Coagulopathic bleeding can be addressed with Prothrombin Complex Concentrate (PCC/ Beriplex) or transfusable plasma (FFP). We tested the hypothesis that the measure of antithrombin III(AT3), after reversal of heparin anticoagulation, would be higher in the FFP group as compared to the PCC group.

METHODS: This was a prospective, open label, randomized controlled clinical trial with a total of 100 patients at risk of coagulopathic bleeding enrolled and allocated to FFP (10-15 mL/kg rounded up to the nearest unit)/PCC (15 units/kg KCentra) via parallel assignment if excessive microvascular bleeding in the surgical field was present 10 minutes after return of ACT to within 10% of baseline along with a PT >16.6 sec/ INR >1.6 sec.

RESULTS: AT3 levels were available for all timepoints, with no baseline differences noted between to the two groups, as illustrated in Figure 1. AT3 levels were significantly higher in the FFP compared to the PCC group at point PTX, higher in the FFP group when accounting for the PP timepoint (PTX-PP), and higher at POD1 (p=0.0024, 0.000005, 0.0039 respectively), as illustrated in Figure 2. These differences did not persist to the POD1, POD3, or POD5 measurements.

CONCLUSION: The FFP group demonstrated higher AT3 levels as compared to the PCC group, which did not persist beyond the POD1 timepoint. However, the clinical relevance needs to be determined by comparing bleeding and transfusion requirements for these two groups, which is beyond the scope of this abstract. This is reassuring from the standpoint of mechanistic risk of postoperative thromboembolic complications, again to be determined by analysis of the clinical endpoints of this prospective randomized study.

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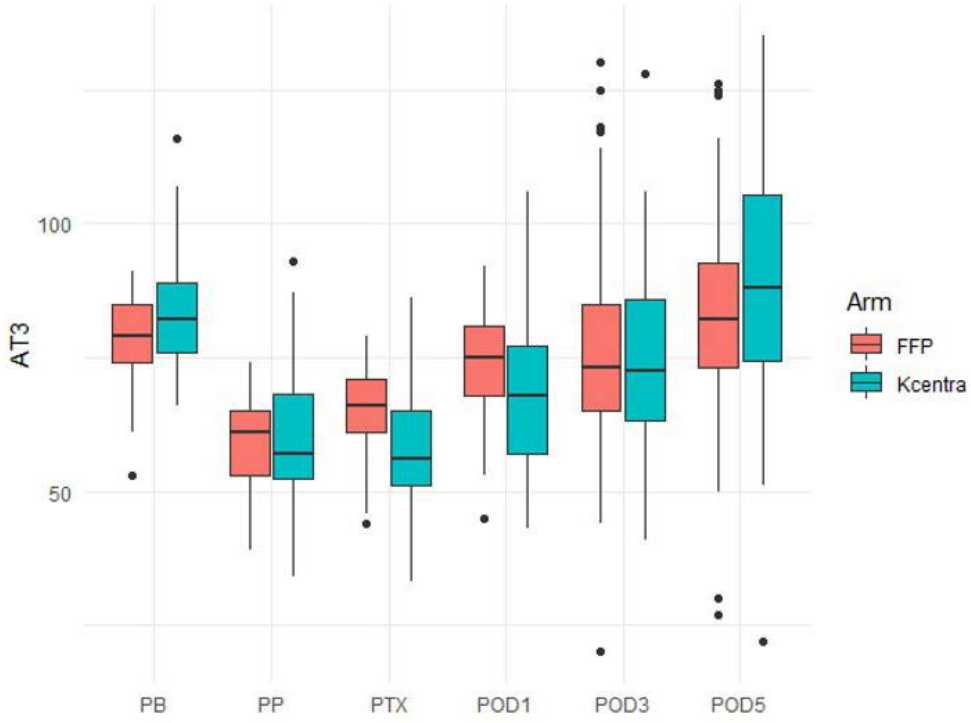

Figure 1. Antithrombin III (AT3) levels at selected timepoints between the FFP and PCC arms.

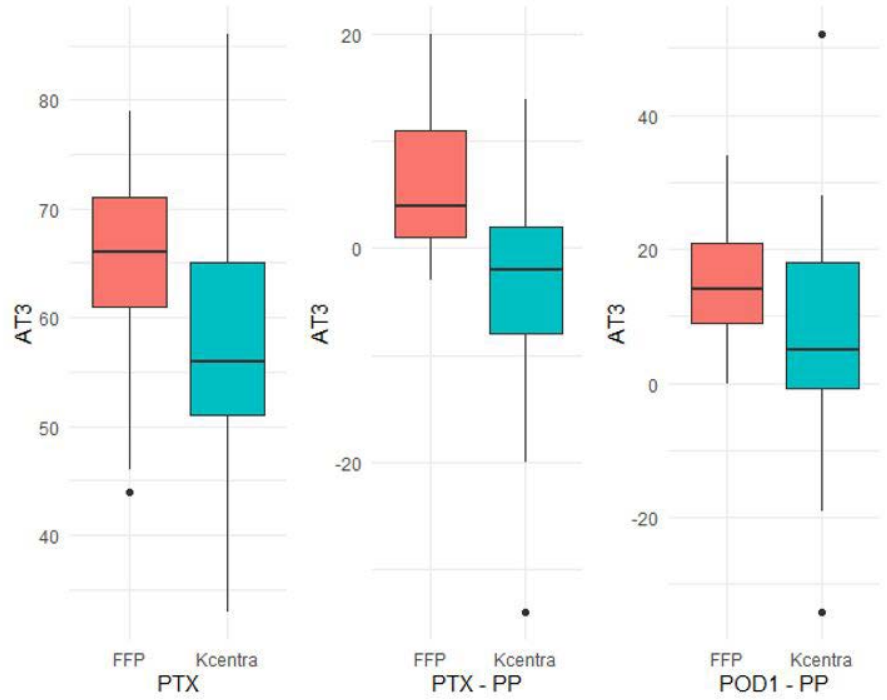

Figure 2. AT3 levels were significantly higher in the FFP group as compared to the PCC group at timepoints post transfusion (PTX), post transfusion to post-protamine (PTX-PP), and between post op day 1 to post protamine (POD1-PP).

CARDIOVASCULAR ANESTHESIOLOGY 21

Anesthetic Management for Ventricular Tachycardia Ablation: A National Anesthesia Clinical Outcomes Registry Analysis

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INTRODUCTION: Ventricular tachycardia (VT) is an arrhythmia defined as a heart rate ≥100 beats per minute originating in the cardiac ventricles[1]. Sudden cardiac death accounts for up to 20% of annual United States (US) mortality and is frequently attributed to VT[2,3]. Management of VT includes pharmacotherapy, automatic implantable cardiac defibrillator (AICD) placement, and/or percutaneous ablation. Ventricular tachycardia ablation (VTa) is primarily recommended for patients who have failed antiarrhythmic therapy, and alternatively used as escalation therapy following a pharmacotherapy trial[4,5]. VTa is commonly performed during AICD placement to minimize the number of antitachycardia pacing and synchronized cardioversion events[6,7].

Monitored anesthesia care (MAC) has historically been preferred by electrophysiologists to minimize anesthetic impact on cardiac conduction, allowing for more accurate mapping and ablation[8]. Despite this, use of general anesthesia (GA) has increased in recent years for prolonged procedures and for patients with unstable rhythms, diminished cardiopulmonary reserve, and anticipated difficult airways[9].To better delineate contemporary patterns of practice, we evaluated trends in anesthetic management during VTa procedures, deriving data from the American Society of Anesthesiologists (ASA) Anesthesia Quality Institute's National Anesthesia Clinical Outcomes Registry (NACOR). We hypothesized that utilization of MAC during VTa has decreased in recent years while usage of GA has increased.

METHODS: A retrospective analysis was conducted using the NACOR dataset, a US clinical data registry that contains electronic reports on procedures involving anesthesia services. Data were evaluated pertaining to all adult patients ≥ 18 years old who underwent elective VTa between 2013 and 2018, using the Current Procedural Terminology code 93654. The primary variable of interest was type of anesthesia administered. Differences across anesthesia type were compared using Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables. Prevalence of anesthesia type over time was determined using a Cochran-Armitage test. Using covariates selected a priori, multivariate models were used to identify patient and hospital characteristics associated with anesthetic type and association between anesthesia type and case duration. To most accurately account for data structure, a three-level hierarchical model was used, nesting patients within practices within each year to best generate variance estimates. Case duration was log-transformed given its skewed nature before multivariate linear regression. Two-sided tests with an alpha of 0.05 were considered significant. STROBE guidelines were followed; statistics were performed using SAS, Version 9.4 (SAS, Cary, NC).

RESULTS: From 2013-2018, the NACOR database included 11,886 VTa procedures from 214 practices in the US. After applying inclusion and exclusion criteria, the dataset included 9,849 ablations from 194 practices. Of these patients, 6,348 (64.5%) received GA. The use of MAC decreased over time ($p<0.0001$) (Table 1). Patients who underwent MAC were more likely to be 19-49 years old (24.2% vs 18.4%), female (41.4% vs 30.0%), have ASA physical status 1-3 (80.2% vs 66.9%), receive treatment in the Northeast (20.6% vs 14.3); $p<0.0001$, and receive care at centers with higher VTa ablation volume (annual median: 70 vs 59); all $p<0.0012$ (Table 2). In multivariate analysis, male patients had 38% lower odds of receiving MAC than females (AOR: 0.62, 95% CI 0.55-0.70). An ASA score >3 was associated with a 61% decrease in odds of receiving MAC compared to an ASA score of ≤3 (AOR 0.39, 95% CI 0.34-0.45). Patients treated in hospitals located in the South or West had substantially lower odds of receiving MAC than patients receiving care in the Northeast (AOR: 0.33, 95% CI 0.22-0.52 and AOR: 0.46, 95% CI 0.22-0.52, respectively). Institution case volume did not demonstrate statistical significance in multivariate analysis. The model was well-calibrated with a c-statistic of 0.863 (Table 3). Patients undergoing MAC compared to GA had shorter median cases durations (211 vs 225 minutes; $p<0.0001$). After log transformation, MAC had 13% shorter median case durations than those receiving GA (Table 4).

CONCLUSION: Use of MAC for VTa has decreased over time with GA being the primary anesthetic type. Anesthetic management, however, varies with patient and hospital characteristics, including geographic location.

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Table 1. Prevalence of Anesthesia Type per Year

Type	2013	2014	2015	2016	2017	2018	p-value
General anesthesia n=6348 (64.5%)	483 (52.79)	812 (60.69)	1268 (63.27)	1573 (65.27)	908 (69.37)	1304 (69.62)	
Monitored anesthesia care n=3501 (35.5%)	432 (47.21)	526 (39.31)	736 (36.73)	837 (34.73)	401 (30.63)	569 (30.38)	<0.0001

Table 2. Descriptive Table of Patient and Hospital Characteristics by Anesthesia Type

Variable	Level	Overall (N=9849)		GA (N=6348)		MAC (N=3501)		p-value
Demographics								
Age	80+	678	6.88	471	7.42	207	5.91	<0.0001
	65-79	3858	39.17	2626	41.37	1232	35.19	
	50-64	3265	33.15	2059	32.44	1206	34.45	
	19-49	2015	20.46	1167	18.38	848	24.22	
	18	33	0.34	25	0.39	8	0.23	
Sex	Male	6315	66.08	4368	70.03	1947	58.64	<0.0001
	Female	3242	33.92	1869	29.97	1373	41.36	
ASA score	5	19	0.20	12	0.20	7	0.21	<0.0001
	4	2636	28.08	1968	32.87	668	19.64	
	3	4648	49.51	2778	46.40	1870	54.98	
	2	1176	12.53	528	8.82	648	19.05	
	1	909	9.68	701	11.71	208	6.12	
US Census Region	West	1294	14.22	943	15.97	351	10.98	<0.0001
	South	4042	44.41	2987	50.58	1055	33.00	
	Midwest	2263	24.86	1130	19.14	1133	35.44	
	Northeast	1503	16.51	845	14.31	658	20.58	
US Census rural/urban area	Urban	5160	52.39	3440	54.19	1720	49.13	<0.0001
	Rural	1181	11.99	788	12.41	393	11.23	
	Unknown	3508	35.62	2120	33.40	1388	39.65	

		Median (IQR)		Median (IQR)		Median (IQR)	p-value	
Age		63 (52-72)		64 (54-72)		61 (50-70)	<0.0001	
Annual number of ventricular tachycardia ablation cases performed		64 (24-133)		59 (20.5-133)		70 (29-119)	0.0012	

Abbreviations: GA, general anesthesia; MAC, monitored anesthesia care; ASA, American Society of Anesthesiologists; IQR, interquartile range.

Table 3. Multivariate Adjusted Odds Ratios for Monitored Anesthesia Care in Ventricular Tachycardia Ablation Procedures

	Level Effect	Adjusted OR (95% CI)	p-value
Age (per 5 years)		0.98 (0.96, 1)	0.0655
Male vs Female		0.62 (0.55, 0.7)	<0.0001
ASA score	4 or 5	0.39 (0.34, 0.45)	<0.0001
	1,2, or 3	Ref	
US Census Region	Midwest	0.72 (0.46, 1.13)	0.1474
	South	0.33 (0.22, 0.52)	<0.0001
	West	0.46 (0.32, 0.64)	<0.0001
	Northeast	Ref	
Total number of VT ablation cases performed at center from 2013-2018 (per 50 cases)		1.01 (0.97, 1.05)	0.6950

Abbreviations: OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists.

Table 4. Case Duration by Anesthesia Type

Anesthesia type	Median (IQR)	p-value	Model estimate	p-value
Monitored anesthesia care	211 (157-275)	<0.0001	0.87 (0.85-0.89)	<0.0001
General anesthesia	225 (172-298)		Ref.	

CARDIOVASCULAR ANESTHESIOLOGY 22

Continuous Propofol Infusion in patients with Brugada Syndrome. Preliminary results of a feasibility study

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INTRODUCTION: Previous studies failed to provide any evidence that could confirm the alleged arrhythmogenicity of propofol in patients with Brugada syndrome. A single-bolus of propofol during induction of anaesthesia did not provoke malignant arrhythmias or clinically significant ST- QRS- or other electrocardiographic alterations. The hypothesis that increased propofol plasma concentrations are more likely to induce arrhythmias or similar electrocardiographic changes as during the provocation challenge with ajmaline, would be tested by providing total intravenous anaesthesia through target-controlled infusion.

METHODS: The study was designed as a prospective, monocentric, non-randomised observational study. All patients underwent a routine, extensive preoperative evaluation before the scheduled surgery, as standard of care prescribes. Eligible patients were identified conform to inclusion and exclusion criteria and were approached for study participation and informed consent. For the current study, total intravenous anaesthesia was provided by an open-target-controlled infusion system incorporated in TCI-pumps, embedded with the pharmacokinetic-pharmacodynamic modelling of the effect-site concentration of Schnider (for propofol) and Minto (for remifentanil). Those models comprise algorithms depending on anthropomorphic characteristics (age, weight, gender, lean body mass and height) and ensure adequate anaesthetic depth. Co-administration of remifentanil-TCI was chosen in this design -as currently often performed-, to ensure a more vigilant approach by reducing propofol requirements up to 50%. The anaesthetic depth was continuously adjusted and fine-tuned during the procedure, based on the continuous intraoperative electroencephalographic (EEG) monitoring achieved by NeuroSENSE, the hemodynamic parameters and the (anticipated) surgical phases. The EEG monitoring was maintained until the emergence of the patient, and transport to the PACU. The NeuroSENSE device, rendered online raw and processed electroencephalographic activity (WAVCNS). A WAVCNS-value of 60-40 was targeted to help the attending anaesthesiologist adjust anaesthetic depth concordantly. Electrocardiographic data analysis occurred post-operatively by a cardiologist, who was not present during the anaesthetic procedure or data acquisition. Clearly this study is hampered by a clear rare disease, with low-prevalence, inclusion bottleneck. Therefore, only seven patients have been included up to date. PROCEDURE: Standard of care monitoring was implemented. Additionally, a modified 12-lead electrocardiogram (12-lead ECG with additional focus on the higher third intercostal space (IC3)) and a NeuroSENSE electroencephalographic (EEG) device were applied. The application of the EasyPrepTM Sensor Kit (EK-901) occurred while the patient was still awake. Adhesive defibrillator pads were connected to an external defibrillator device as a precautionary measure. The first ECG was registered, while the patient was awake, prior to administration of any medication. This was defined as the Baseline-ECG at T0. Consecutive ECG's were registered at intervals of at least ten minutes throughout the first hour of the surgical procedure. The second hour, the interval was increased to thirty minutes. ECG analysis occurred for all registrations. We present the preliminary measurements of the ST- and J-points. Due to low number of patients, no statistics were applied. We present te results in a summarizing table.

RESULTS: Seven consecutive patients were included, scheduled for elective surgery. All of them received target controlled infusion of propofol, based on the effect-site concentration protocol of Schnider, during 60 to 120 minutes. In all seven patients, no changes could be noted at the ST-segment and the J-point, throughout the anaesthetic procedure. No clinical adverse events were noted during or after surgery. An additional ECG prior to discharge for the post-anaesthetic care unit confirmed the absence of ST-changes.

CONCLUSION: Based on prior findings and the preliminary results of unchanged ST-segments, and clinically uneventful anaesthetic procedures in patients with Brugada Syndrome, the authors believe that further collection and exploration of electrocardiographic findings is reasonable. A larger group of patients is required to enhance our knowledge on ECG changes during propofol infusion in patients with Brugada Syndrome.

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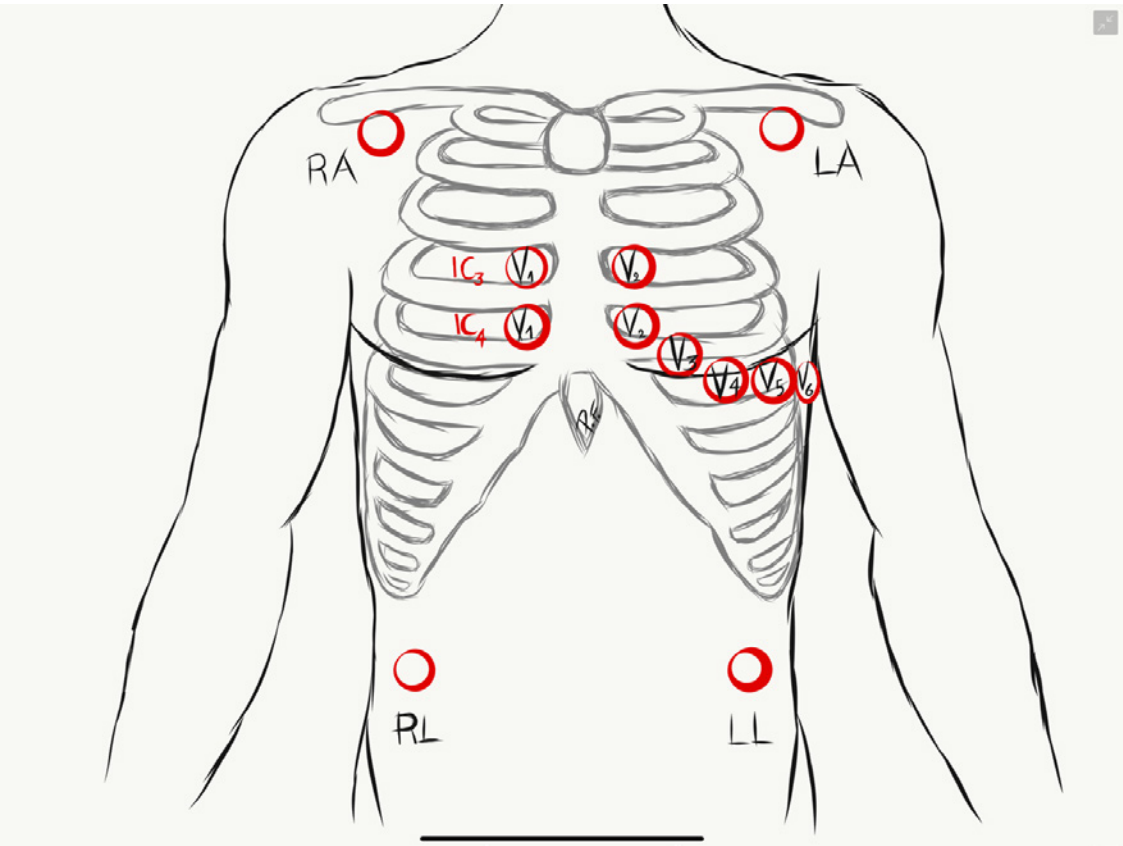

Fig. 1

CARDIOVASCULAR ANESTHESIOLOGY 23

[TIMP-2]*[IGFBP7] as a marker of renal injury after multibranched thoracoabdominal endovascular aortic repair

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INTRODUCTION: Postoperative acute kidney injury (AKI) is a common and morbid complication after vascular surgery that may cause significant long-term decline in renal function. Up to 28% of patients sustain AKI after branched thoracoabdominal or paravisceral endovascular aortic repair (TEVAR). TIMP-2 and IGFBP7 are G1 cell cycle arrest proteins that have been utilized as urinary biomarkers for detection of renal stress as early as 6-12 h after surgery, prior to elevation in serum creatinine. Although urinary TIMP-2 and IGFBP7 have demonstrated modest success in early prediction of AKI after cardiac surgery, their utility after aortic surgery is less clear. We are analyzing urinary [TIMP-2]*[IGFBP7] in an existing cohort of patients who underwent branched-graft TEVAR. We hypothesize that urinary [TIMP-2]*[IGFBP7] will improve prediction of early postoperative AKI when combined with clinical predictors.

METHODS: The study was approved by the local institutional review board and registered with ClinicalTrials.gov (NCT00483249). After informed consent, urine was collected from patients undergoing multibranched TEVAR at three time points: start of surgery, end of surgery, and postoperative day (POD) 1. Clinical data were recorded as part of an ongoing registry. For the pilot biomarker study, 8 patients (5 without AKI and 3 with AKI stage 1 or greater by Kidney Disease Improving Global Outcomes criteria) were selected for blinded measurement of [TIMP-2]*[IGFBP7] using a cartridge-based, commercially available immunoassay. Additionally, clinical variables associated with postoperative AKI stage 1 or greater were identified by univariate analysis. Upon receipt and processing of all three urine samples from all patients, we will conduct logistic regression and receiver operating characteristic analysis to determine if [TIMP-2]*[IGFBP7] improves prediction of postoperative AKI.

RESULTS: Patients who underwent completion of multibranched TEVAR with baseline, POD 0, and POD 1 urine samples available for analysis were included in this retrospective cohort study. Individuals with preoperative end-stage renal disease (estimated glomerular filtration rate (eGFR) <15 mL/min and/or dialysis-dependent) or preoperative AKI requiring renal replacement therapy were excluded. Among 139 patients with complete data, 31.7% (44/139) of patients developed AKI stage 1 or greater within the first 3 days following surgery. Prevalence of major comorbidities in the cohort were as follows: chronic kidney disease (38.1%, 53/139), hypertension (95.7%, 133/139), hyperlipidemia (77.7%, 108/139), diabetes mellitus (16.5%, 23/139), prior cerebrovascular accident (18.0%, 25/159). Mean preoperative creatinine was 1.35 mg/dL (eGFR of 62.5 mL/min). Among the 8 patients in the pilot study, mean urinary [TIMP-2]*[IGFBP7] levels at baseline, POD 0, and POD 1 were 0.28, 0.19, and 0.30 $(ng/mL)^2/1000$, respectively. No statistically significant differences in [TIMP-2]*[IGFBP7] between time points were detected (p=0.206, Friedman test). Using the published cutoff of [TIMP-2]*[IGFBP7] > 0.3 $(ng/mL)^2/1000$ in any measured time point, 5 subjects were identified as being at risk for AKI, yielding a sensitivity of 0.67 and specificity of 0.40.

CONCLUSION: Urinary [TIMP-2]*[IGFBP7] levels have been measured in a pilot sample of individuals within a cohort of patients who underwent multibranched TEVAR. Blinded [TIMP-2]*[IGFBP7] measurements of the remaining cohort are ongoing.

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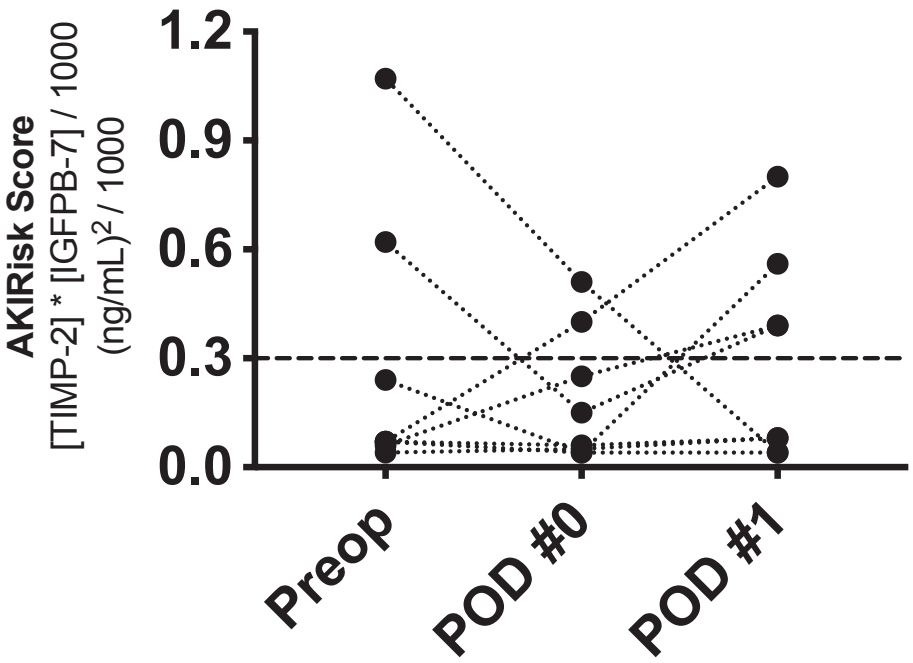

Fig. 1

CARDIOVASCULAR ANESTHESIOLOGY 24

Quantitative effect of positive end expiratory pressure on central venous pressure in closed and open thorax

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INTRODUCTION: Central venous pressure (CVP) is most commonly used monitoring tool to assess the volume status of patients during the perioperative period and intensive care units. The role of positive end expiratory pressure (PEEP) in keeping the lung recruited is not only employed for lung pathologies and left heart failure but also for ventilating normal lungs during intraoperative period as a part of protective ventilation strategy in aiming to prevent collapsing of alveoli. Mechanical ventilation and PEEP are known to influence the measurement of CVP through complex heart-lung interactions. Therefore, the exact volume status of the patient based on central venous pressure may be difficult to determine in patient with positive end expiratory pressure.This magnitude of change in CVP is expected to differ in patients with cardiac disease. Therefore, this study aimed to understand the physiological basis of rise in CVP after PEEP. To unravel the physiological mechanism, we compared the magnitude of change in CVP after PEEP application in closed and open thorax in patients with cardiac disease undergoing cardiac surgeries. Open thorax being referred to post median sternotomy incision over chest and opening of thorax during intraoperative period.

METHODS: This prospective, quasi-experimental study was conducted in tertiary care centre in patients undergoing cardiac surgery. The study began after central trial registration, and ethical approval by the Institute Ethics Committee and the study followed Helsinki guidelines. After induction of anaesthesia and endotracheal intubation, hemodynamic parameters were obtained at baseline (PEEP at 0 cm of H20) and after application of two level of PEEP (5 cm and 10 cm). Three consecutive reading of hemodynamic parameters were obtained at 1, 2 and 3 minutes after application of PEEP in closed chest. Similar levels of PEEP were applied in open thorax after application of sternotomy retractor. The change in CVP after PEEP application was analysed in the closed and open thorax. Additionally, patients were stratified a priori and change in CVP was analysed in lower CVP group (<10 mm Hg) and higher CVP group (≥10 mm Hg), no TR group and TR group and low PCWP group (<15 mm Hg) and high PCWP group (≥15 mm Hg) in closed and open thorax. Sample size was estimated a priori based as per a previous study by N Kim et al. Power calculation for a 2 cm of H2O difference in CVP level, with an alpha level of 0.05 and power of 90%, yielded a sample size of 48 patients. Considering a drop out-rate of 25%, total sample size was calculated to be 62. Normality of distribution of variables was assessed using Shapiro-Wilk test. Paired t test, Independent t test, Repeated measure ANOVA were used. P-value <0.05 was considered statistically significant.

RESULTS: *Inclusion Criteria:* Adult patients between age of 18-60 years, ASA grade I-III, Scheduled for elective cardiac surgery. *Exclusion criteria:* Patient's refusal, Arrhythmia and hemodynamic instability.
62 patients were enrolled for PEEP intervention and all patients were eligible for final analysis. The mean age of participants was 46.2 ± 12.7yrs and mean body mass index (BMI) was 22.7 ± 3.2 kg/m2. Valvular heart disease and coronary artery disease were the most common cardiac disease. The mean difference (MD) in CVP at 5 cm H2O and 10 cm H2O of PEEP was 0.98±0.6 (95% confidence interval (CI), 0.83-1.13; p=0.001) and 2.33±1.13 (95% CI, 2.04-2.62, P=0.001) in closed thorax while the mean difference in open thorax at 5 cm H2O and 10 cm H2O 0.42±0.7 (95% CI, 0.6-0.89, P=0.001) and 1.02±0.77 (95%CI, 0.82-1.22, P=0.001), respectively. The increase in CVP was higher among patients who had a lower CVP group (2.64 ± 0.9 mm Hg vs 1.45± 1.17 mm Hg; p=0.001), without TR (2.64 ± 0.97 mm Hg vs 2.14 ± 1.2 mm Hg, p=0.09) and lower PCWP group (2.4 ± 0.9 mm Hg vs 2.3 ± 1.4 mm Hg, p=0.67) at 10 cm H2O PEEP in closed thorax. In the open thorax, magnitude of change in CVP was lower in all three groups.

CONCLUSION: Among cardiac patients, the loss in intrathoracic pressure does not abolish the effect of PEEP on rise in CVP completely. A 5 and 10 cm H20 of PEEP produced 0.98 and 2.33mm Hg rise in CVP respectively. There is overestimation of CVP values with application of PEEP in mechanically ventilated patients. Higher PEEP up to 10 cm H2O can be applied in cardiac patient if required as part of protective ventilation strategy without any compromise on hemodynamic during intraoperative period.

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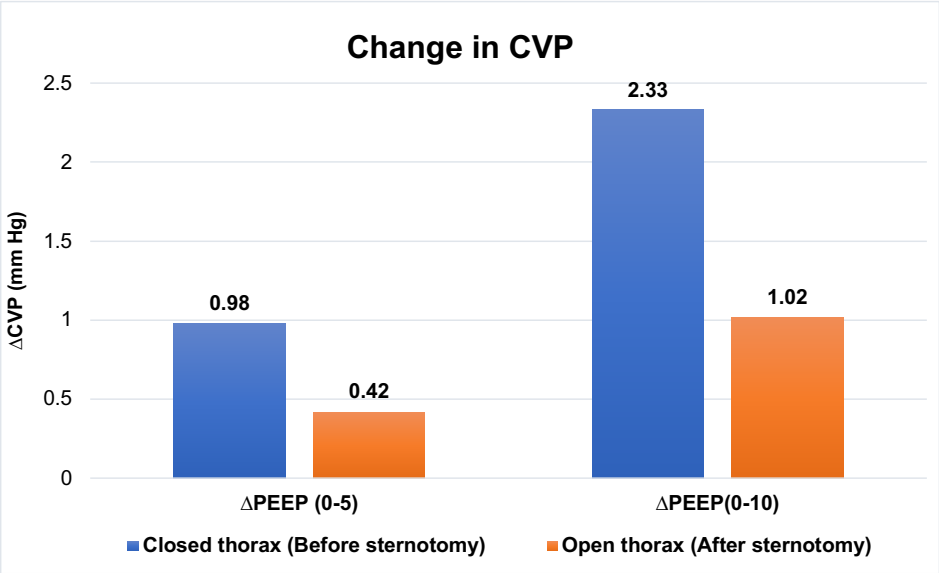
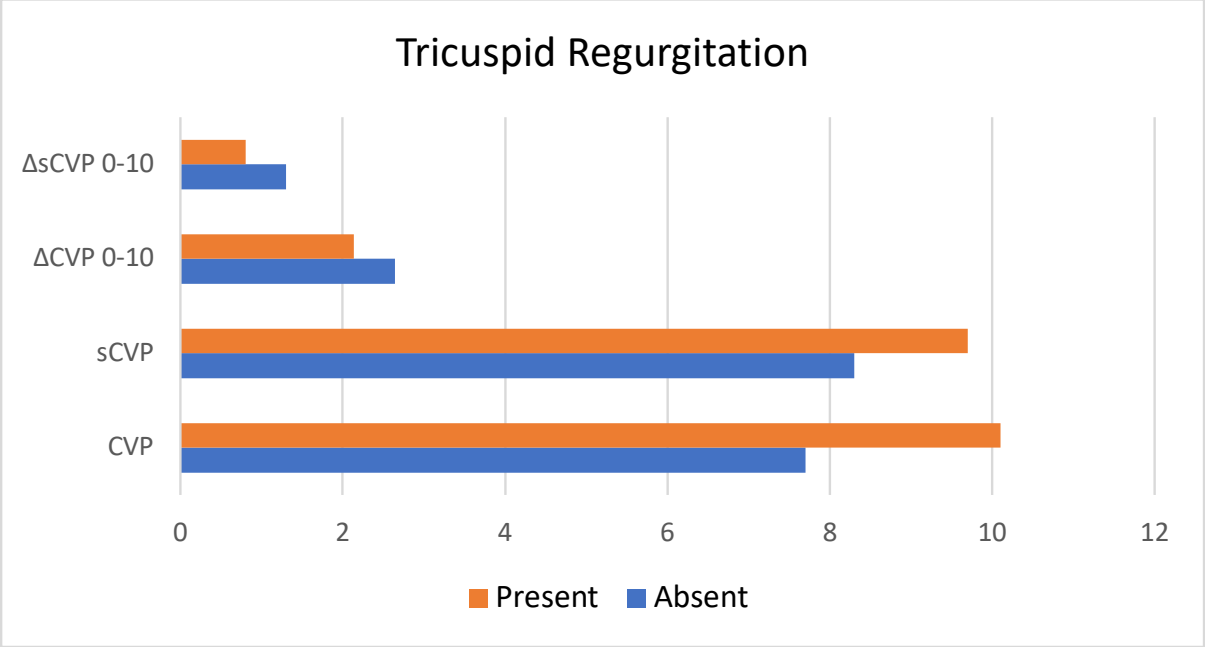
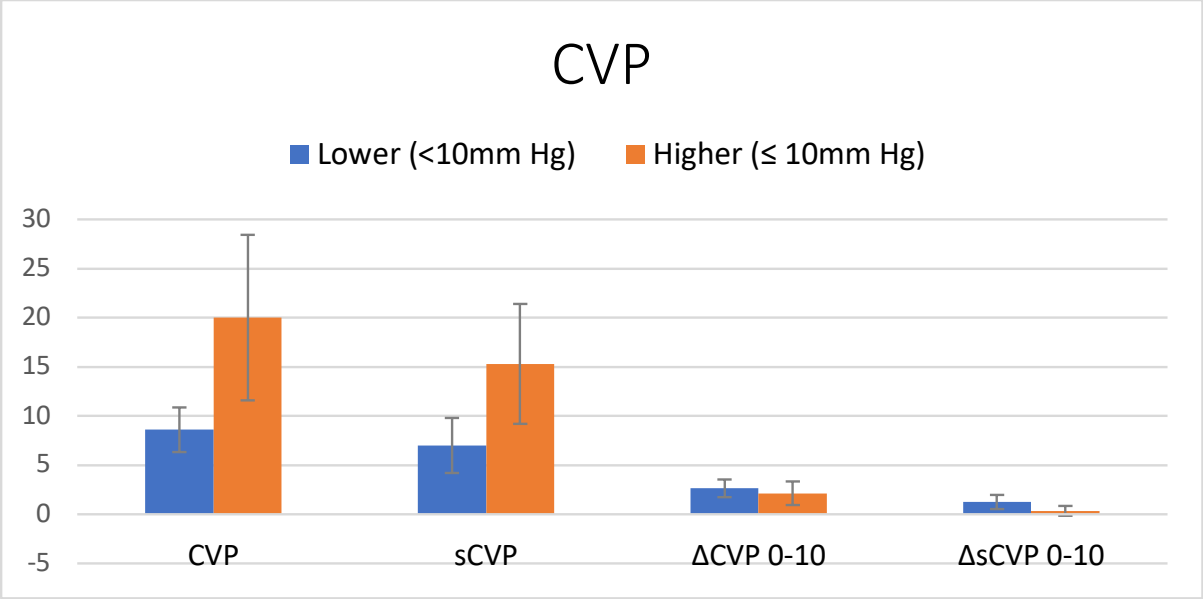
Figure 1 : Relation of Change in central venous pressure (CVP) with application of positive end expiratory pressure (PEEP) from baseline 0 cm H_2O (ZEEP) in closed and open thorax

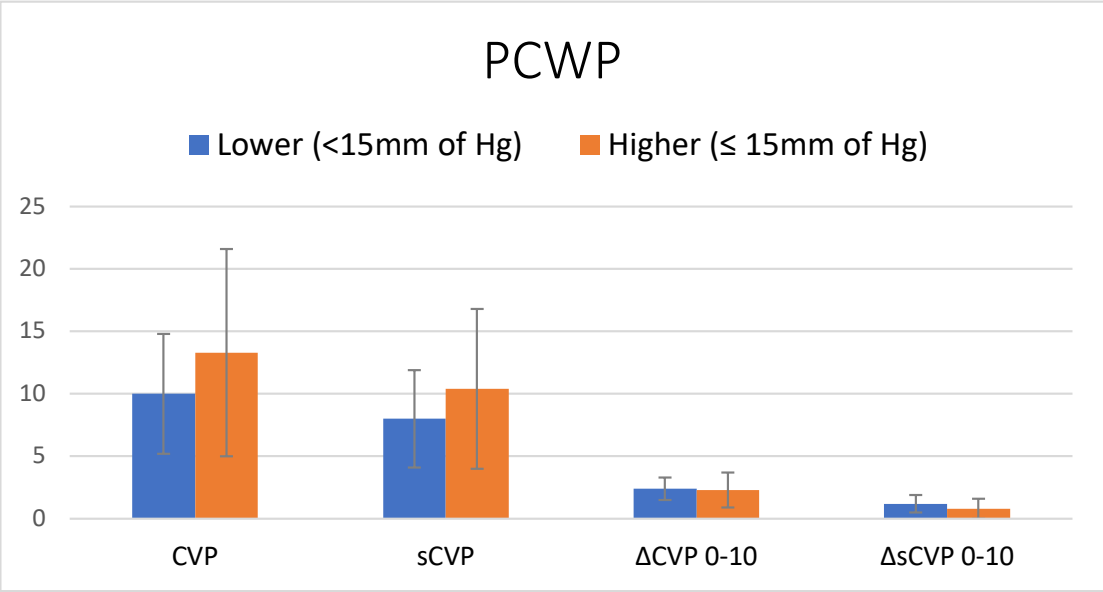


(ΔCVP is the change in central venous pressure measured in mm of Hg and ΔPEEP (0-5) and ΔPEEP (0-10) is the application of PEEP from baseline 0 cm H_2O to 5cm H_2O and 10 cm H_2O)

Effect of PEEP on various subset groups







Temporal sequence of changes in mean arterial pressure, heart rate with application of PEEP at different time points

Variables/Time points		Baseline (ZEEP)	1 min	MD	P-value	2 min	MD	P-value	3 min	MD	P-value
Closed Thorax (5 cm H_20 PEEP)	HR	76.3±21.02	75±21.33	1.3	0.06	75.5±21.63	0.75	0.9	75.08±21.6	1.2	0.06
	MAP	75.40±10.97	73.92±12.53	1.48	0.54	74.47± 12.33	0.93	1	74.53±12.28	0.87	1
Closed Thorax (10 cm H_20 PEEP)	HR	74.76±21.27	75.87±21.04	-1.1	1	76.1±20.97	-1.33	0.91	75.63±21.07	-0.87	1
	MAP	73.24±12.58	75.19±14.11	-1.95	0.43	73.9±13.78	-0.66	1	72.56±13.05	-0.67	1
Open Thorax (5 cm H_20 PEEP)	HR	80.39±20.86	80.45±20.45	-0.065	1	80.79±20.79	-0.403	1	80.44±20.93	-0.048	1
	MAP	81.52±11.69	80.48±12.33	1.03	0.88	80.11±12.34	1.40	0.36	79.19±12.58	2.32	0.055
Open Thorax (10 cm H_20 PEEP)	HR	81.44±21.04	80.45±20.28	0.98	1	80.08±20.34	1.35	0.53	80.26±20.65	1.17	0.81
	MAP	79.11±11.97	76.92±11.63	2.19	0.22	75.29±11.94	3.82	0.01	74.4±12.62	4.71	**0.01**

CARDIOVASCULAR ANESTHESIOLOGY 25

Role Of Magnesium Alone Or In Combination With Diltiazem and / Or Amiodarone In Prevention Of Post-Coronary Artery Bypass Grafting Atrial Fibrillation

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INTRODUCTION: Atrial fibrillation (AF) is a frequently encountered complication following CABG with an incidence of 20-40%. The occurrence of AF increases the morbidity by causing hemodynamic deterioration, increasing incidence of thromboembolism, postoperative stroke and prolonging the hospital length of stay. Many different strategies have been studied with limited success for the prevention of post-CABG AF.

METHODS: This was a prospective observational uncontrolled trial performed on 150 patients more than 18 years of age undergoing off-pump CABG. Group M (patients without arterial grafts) received intraoperative magnesium infusion at 30mg/kg over 1 hour, Group MD (patients receiving arterial grafts) received magnesium infusion with diltiazem infusion at 0.05 µg/kg/h throughout the intraoperative period; Group AMD (patients receiving arterial grafts under the care of a particular surgeon who routinely uses amiodarone preoperatively) received preoperative oral amiodarone along with magnesium and diltiazem infusion as in other groups. All patients were electively ventilated post operatively. The study endpoint was occurrence of AF or end of postoperative day 4 whichever was earlier. AF was defined as any AF lasting for more than 10 min or requiring treatment by way of cardioversion or medicines. The incidence of postoperative AF was compared using ANOVA/ Kruskal Wallis test between the three groups. Our secondary objectives were duration of mechanical ventilation; ICU and hospital length of stay; and neurological morbidity (transient ischemic attack or cerebrovascular accident)

RESULTS: Out of 150 patients (21 patients in group M; 78 patients in group MD; 51 patients in group AMD);19 patients developed AF [4(19.05%) in group M; 9(11.54%) in group MD and 6 (11.76%) in group AMD (P> 0.5)]. The other postoperative parameters like duration of mechanical ventilation (21 ± 2.93 hrs, 19.09 ± 3.92 hrs, 20.69 ± 2.66 hrs) , duration of ICU stay (6 ± 2.35 days, 7.99 ± 2.77 days, 7.55 ± 4.54) days) and duration of hospital stay (13.33 ± 3.12 days, 13.18 ± 4.37 days, 17.06 ± 19.04 days) in groups M, MD, and AMD respectively were similar in the three groups (P >0.05). Only 1 patient developed neurological event (transient ischemic attack), although he did not develop AF. No adverse effects related to any of the drugs were observed.

CONCLUSION: AF following CABG is well studied; however, therapy is still unproven, contradictory and being debated. A significant incidence of AF (12.67%) was observed in our cohort of patients undergoing OPCABG. However, use of amiodarone and/or diltiazem in addition to magnesium did not result in additional benefit in lowering the incidence of of prevention of AF.

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CARDIOVASCULAR ANESTHESIOLOGY 26

ABO Blood Group and Bleeding in VA-ECMO Patients

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INTRODUCTION: ABO blood group has been shown to be a major determinant of plasma von Willebrand factor (vWF) levels. Multiple studies have shown that O blood group is associated with lowest vWF levels and confers an increased risk of hemorrhagic events, while AB blood group has the highest levels and is associated with thromboembolic events. While the relationship between blood type and bleeding has been studied previously in several cardiac surgical populations, little data exist regarding the influence of blood type on transfusions and survival during extracorporeal membrane oxygenation (ECMO). Recent studies show that almost all patients treated with ECMO develop an acquired von Willebrand syndrome (aVWS) that is reversible soon after explantation, making this cohort an ideal population through which to investigate blood type and bleeding susceptibility. Therefore, we tested the hypothesis that O blood type would have the highest and AB blood type would have the lowest transfusion requirements, with an inverse relationship to survival.

METHODS: Retrospective analysis of 307 VA-ECMO patients at a major tertiary referral hospital from 2009 to 2018. For blood types O, A, B, and AB, a univariate analysis was performed using the Kruskal-Wallis test for continuous variables and Fisher's exact test or Chi-square test for categorical variables. A multiple linear regression was performed and blood product usage (packed red blood cells [PRBC], fresh frozen plasma [FFP], platelets, and cryoprecipitate [cryo]) was log-transformed to normality; adjusted estimates with 95% confidence intervals were exponentiated for ease of interpretation. Kaplan-Meier curves were constructed for the four blood groups to illustrate mortality pattern at 30 days and 1 year after treatment with ECMO.

RESULTS: The distribution of blood groups included 124 group O (40%), 122 group A (40%), 44 group B (14%), and 17 group AB (6%) patients. Baseline characteristics between the four comparison groups were similar, including age, BMI, SOFA score, SAVE score, and medical comorbidities such as hypertension, coronary artery disease, diabetes, kidney disease, and liver dysfunction (Table 1). Regarding usage of PRBC, FFP, and platelets, there was a non-statistically significant difference in transfusions, with group O having the least and group AB having the most requirements. However, there was a statistically significant difference in cryo usage when comparing to group O as the reference group: group A (coefficient 1.77, 95% CI 1.05 - 2.97, $p < 0.05$), group B (coefficient 2.05, 95% CI 1.16 - 3.63, $p < 0.05$), and group AB (coefficient 3.43, 95% CI 1.71 - 6.90, $p < 0.001$). Furthermore, a 20% increase in length of days on ECMO was associated with a 2-12% increase in blood product usage (Tables 2 and 3). Based on the Kaplan-Meier curves, the cumulative 30-day mortality rate for groups O and A was 60%, group B was 50%, and group AB was 40% (Figure 1); the cumulative 1-year mortality rate for groups O and A was 65%, group B was 57%, and group AB was 41% (Figure 2).

CONCLUSION: Despite the differential levels of vWF and reported bleeding and thrombosis rates for ABO blood groups, in this analysis there was no significant difference in transfusions of PRBC, FFP, or platelets among the four blood groups. However, for patients who required any cryo transfusion, group O had the lowest and group AB had the highest usage. Longer length of ECMO run is also independently associated with increased blood product requirements. Interestingly, group AB appeared to have improved early and late survival after ECMO support; whether this finding is related to bleeding susceptibility remains elusive and requires further investigation.

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Table 1. Baseline characteristics of the four comparison blood groups

	Blood Type O	Blood Type A	Blood Type B	Blood Type AB	p
n	124	122	44	17	
Age (median [IQR])	56.50 [46.75, 65.25]	58.00 [48.00, 66.00]	58.00 [46.00, 60.25]	51.00 [47.00, 63.00]	0.644
BMI (median [IQR])	27.25 [23.93, 32.00]	29.00 [24.87, 32.62]	28.75 [22.65, 32.75]	29.00 [26.43, 32.23]	0.599
SOFA score (mean (SD))	9.86 (2.47)	9.39 (2.52)	9.16 (2.35)	10.06 (2.11)	0.238
SAVE score (median [IQR])	-7.00 [-11.00, -3.00]	-6.00 [-10.00, -3.00]	-6.00 [-9.00, -3.00]	-5.00 [-7.00, -3.00]	0.897
Hypertension (%)	70 (57.4)	63 (51.6)	21 (47.7)	11 (64.7)	0.51
Diabetes (%)	29 (24.0)	37 (30.3)	6 (13.6)	2 (11.8)	0.087
Chronic kidney disease (%)	24 (19.7)	19 (15.6)	8 (18.2)	4 (23.5)	0.785
Liver dysfunction (%)	11 (9.0)	6 (4.9)	3 (6.8)	1 (5.9)	0.653
Coronary artery disease (%)	49 (40.2)	52 (42.6)	18 (40.9)	6 (35.3)	0.941
Acute kidney injury (%)	37 (30.3)	50 (41.0)	16 (36.4)	6 (35.3)	0.388

A p-value < 0.05 was considered statistically significant.
Abbreviations: IQR, *interquartile range;* SOFA, *sequential organ failure assessment;* SAVE, *survival after veno-arterial ECMO*

Table 2. Log-transformed multiple linear regression model for transfusion of PRBC, FFP, and platelets

	PRBC Estimate (95% CI)	FFP Estimate (95% CI)	Platelets Estimate (95% CI)
(Intercept)	5.96 *** [2.53, 14.06]	3.47 * [1.08, 11.11]	2.58 * [1.11, 5.98]
Blood Type A	1.18 [0.94, 1.48]	1.24 [0.91, 1.69]	1.09 [0.87, 1.36]
Blood Type B	1.10 [0.80, 1.49]	1.21 [0.80, 1.84]	1.12 [0.83, 1.51]
Blood Type AB	1.22 [0.75, 1.98]	1.36 [0.70, 2.62]	1.17 [0.73, 1.89]
Log (length of days on ECMO)	1.86 *** [1.62, 2.14]	1.19 [0.98, 1.44]	1.84 *** [1.61, 2.11]
Platelet count (pre-ECMO)	1.00 * [1.00, 1.00]	1.00 *** [1.00, 1.00]	1.00 *** [1.00, 1.00]
Hemoglobin (pre-ECMO)	1.00 [0.98, 1.02]	0.99 [0.96, 1.01]	1.01 [0.99, 1.03]
Age	1.01 * [1.00, 1.02]	1.01 [1.00, 1.02]	1.01 [1.00, 1.01]
BMI	0.98 [0.97, 1.00]	0.99 [0.97, 1.01]	0.98 * [0.97, 1.00]
SAVE score	1.00 [0.98, 1.03]	1.01 [0.98, 1.04]	1.00 [0.97, 1.02]
SOFA score	0.98 [0.94, 1.03]	1.02 [0.96, 1.09]	1.02 [0.97, 1.07]
N	291	291	291
AIC	762.22	939.88	750.01
BIC	806.30	983.96	794.09
Pseudo R2	0.28	0.11	0.38

All continuous predictors are mean-centered and scaled by 1 standard deviation. The coefficients were exponentiated for ease of interpretation. Blood group comparisons were performed with O blood type as the reference group. Statistically significant at *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

The differences in blood product utilization do not appear to be statistically significant. An increase in the length of days on ECMO is associated with an increased use of blood products.

Abbreviations: PRBC, *packed red blood cells*; FFP, *fresh frozen plasma;* SAVE, *survival after veno-arterial ECMO*; SOFA, *sequential organ failure assessment*

Table 3. Two-layer Hurdle model for transfusion of cryoprecipitate

	Cryoprecipitate (binomial) OR (95% CI)	Cryoprecipitate (truncated Gaussian) Estimate (95% CI)
(Intercept)	0.22 [0.02, 1.98]	5.81 * [1.40, 24.21]
Blood Type A	1.28 [0.72, 2.29]	1.77 * [1.05, 2.97]
Blood Type B	1.41 [0.66, 3.05]	2.05 * [1.16, 3.63]
Blood Type AB	1.71 [0.53, 5.50]	3.43 *** [1.71, 6.90]
Log (length of days on ECMO)	1.10 [0.77, 1.56]	0.74 * [0.58, 0.93]
Platelet count (pre-ECMO)	1.00 [0.99, 1.00]	1.00 [1.00, 1.00]
Hemoglobin (pre-ECMO)	1.02 [0.97, 1.06]	1.00 [0.98, 1.03]
Age	1.02 * [1.00, 1.04]	1.00 [0.99, 1.01]
BMI	0.99 [0.95, 1.03]	0.95 ** [0.92, 0.98]
SAVE score	1.04 [0.98, 1.10]	0.94 ** [0.90, 0.97]
SOFA score	1.01 [0.89, 1.14]	1.03 [0.95, 1.11]
N	291	91
AIC	371.72	465.43
BIC	412.13	495.56
Pseudo R2	0.06	0.21

Since the data regarding cryoprecipitate contained excess structural and sampling zeros, the Hurdle model was used whereby a first-layer logistic regression was developed to model the binary variable representing cryoprecipitate use as zero or non-zero (results shown in middle column), and subsequently, conditional upon a non-zero use of cryoprecipitate, a second-layer truncated Gaussian distribution was fit to the remaining non-zero values (results shown in right column). With blood group O as the reference group, blood groups A, B, and AB were independent predictors of increased cryoprecipitate use *when it was required at all*.

Statistically significant at *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

Abbreviations: SAVE, *survival after veno-arterial ECMO*; SOFA, *sequential organ failure assessment*

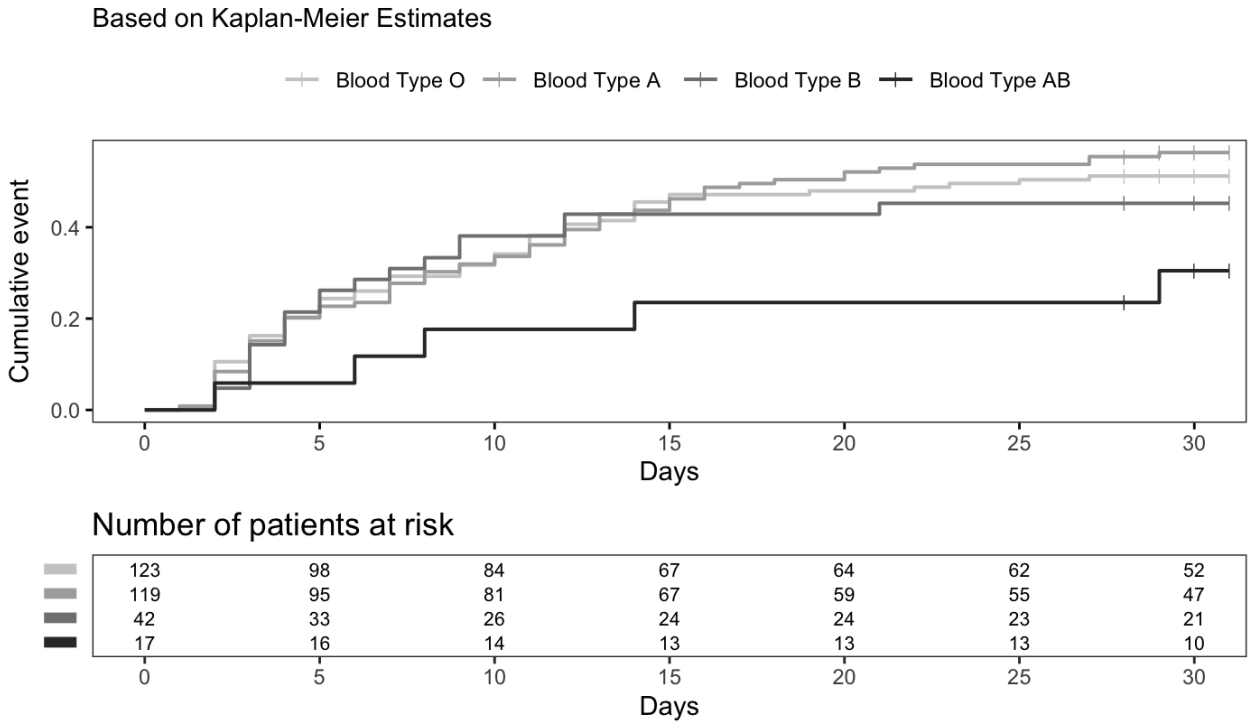

Figure 1. Kaplan-Meier curve for the cumulative risk of death at 30 days from ECMO treatment.
The cumulative 30-day mortality rate for groups O and A was 60%, group B was 50%, and group AB was 40%.

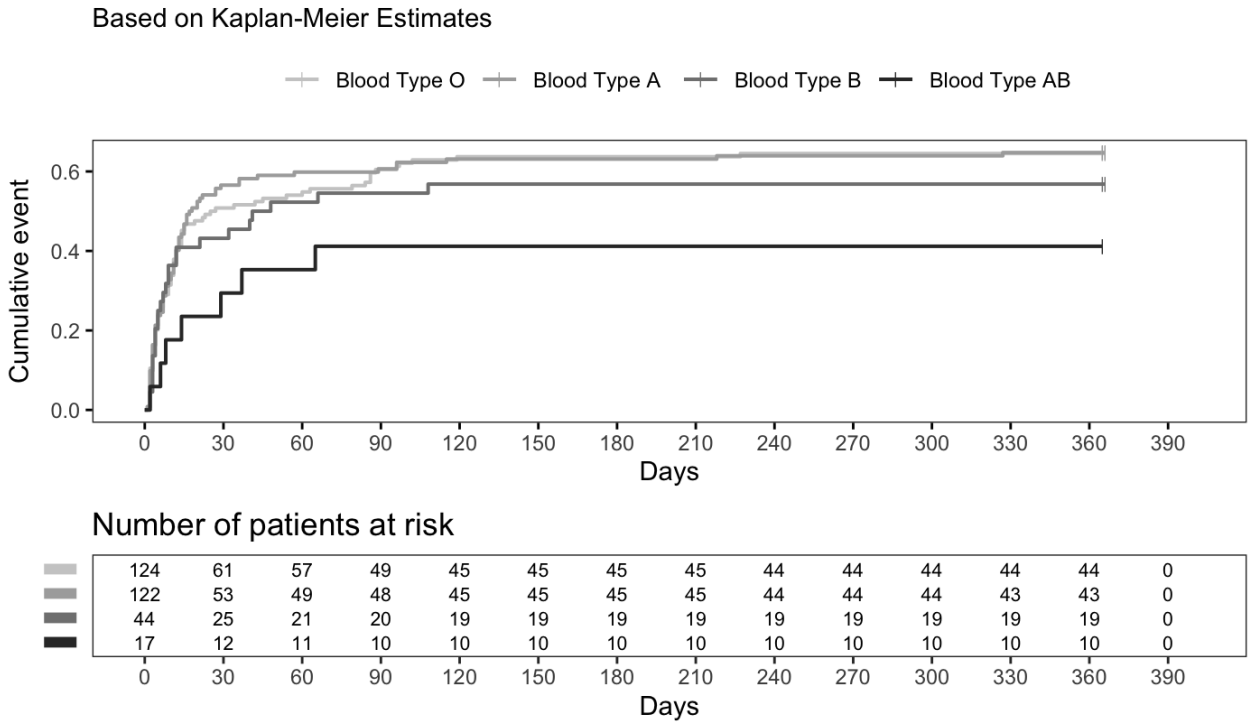

Figure 2. Kaplan-Meier curve for the cumulative risk of death at 1 year from ECMO treatment.
The cumulative 1-year mortality rate for groups O and A was 65%, group B was 57%, and group AB was 41%.

CARDIOVASCULAR ANESTHESIOLOGY 27

ERAS protocols for cardiac surgery: A pilot study to assess an entry point for reducing post-operative atrial fibrillation

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INTRODUCTION: The incidence of postoperative atrial fibrillation (POAF) is 35% for all cardiac surgeries[1]. POAF occurs in 20-30% of all coronary artery bypass graft (CABG) surgeries and 40% of all isolated single valve surgeries[2]. Since POAF is associated with increased mortality, length of stay (LOS) in the hospital, risk of cerebral vascular accidents (CVA), and bleeding[3,4], it is crucial to develop strategies to help reduce this risk. With enhanced recovery after surgery (ERAS) and fast-track protocols for cardiac surgery gaining popularity worldwide[5], it's extremely important to include specific strategies to reduce the risk for POAF. In 2020, our institution had adopted an updated ERAS protocol to include strategies to help reduce the risk of POAF in patients who undergo cardiac surgery. Some of these strategies include early extubation and postoperative amiodarone and steroid administration. The purpose of this early pilot study is to assess if our institutional fast track ERAS protocol decreases the risk of POAF in patients undergoing CABG surgery.

METHODS: After IRB approval, we retrospectively collected data from patients who underwent a CABG in 2019 before our protocol change and in 2021 after our protocol change. A total of 60 patients were analyzed. Our inclusion criteria were patients who underwent an isolated CABG surgery at our institution. Excluded patients were those with a prior history of atrial fibrillation, patients requiring valve surgery in addition to CABG, and patients requiring mechanical circulatory support such as extracorporeal membrane oxygenation, left ventricular assist devices, or intra-aortic balloon pump. Prior to our institution's modernized protocol, there was no formal practice for POAF reduction in patients undergoing cardiac surgery. All patients were being extubated in the intensive care unit (ICU) and the only POAF prevention strategy was perioperative beta blocker administration, which would oftentimes not be administered until postoperative day 2-3 due to the patient's inability to tolerate it.

Our ERAS protocol was implemented throughout 2020, which includes a number of strategies to enhance recovery after cardiac surgery (Table 1). Our protocol includes multimodal pain management strategies, intraoperative extubation, expedited mobilization, postoperative steroid administration, and early postoperative amiodarone prophylaxis. We looked at demographic characteristics of the patients and for our primary outcome, we examined rates of POAF. In addition, we examined hospital LOS as a secondary outcome. The student's t-test and chi-squared tests were used for comparisons when appropriate. Demographic reporting and statistical analysis were done using SPSS (IBM, Chicago, IL).

RESULTS: Of the 29 patients who underwent CABG prior to the protocol change, 65.5% were male and had an average age of 69.7±12.7y. Of the 31 patients who underwent CABG after the protocol change, 82.8% were male and had an average of 61.3±8.4y. The rate of POAF was higher in the pre-protocol change group at 31.0% compared to the post-protocol change group at 6.5% with an odds ratio of 6.53 (95% CI [1.27, 33.49] $p<0.05$) The average hospital LOS in the pre-protocol group was longer at 4.9 ±3.0d than the post-protocol group at 2.2 ±0.5d ($p<0.05$). There were no mortalities in either group.

CONCLUSION: POAF is a common complication from cardiac surgery and has been associated with many adverse outcomes including increased mortality, bleeding, CVA, and hospital LOS. Our institution has adopted an ERAS protocol for patients undergoing cardiac surgery with a specific goal to include reduction of POAF. The results from our study support that extubation in the operating room, oral amiodarone prophylaxis, and steroid administration can help decrease the incidence of POAF. Since this is a pilot study, further studies on a larger cohort are needed to further investigate the impact our protocols have on POAF.

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Strategy	Description
Intraoperative extubation	- Decision made based off of discussion between anesthesiology and surgical teams about patient co-morbidities and surgical considerations
Usage of multimodal analgesics	- Preoperative acetaminophen and gabapentin - Intraoperative dexmedotomadine and IV acetaminophen - Postoperative acetaminophen, lidocaine patches, gabapentin
Expedited mobilization	- Physical therapy evaluation and out of bed to chair within 2.5h of ICU arrival; ambulate within 3h - Early chest tube removal <36h - Subcutaneous heparin within 8-10h of ICU admission
Steroid administration	- POD 0: IV methylprednisolone taper: (qDay: 60mg-40mg-20mg)
Early PO intake	- Advancing diet as soon as 1h after ICU admission - Subcutaneous Methylnaltrexone for constipation
Postoperative amiodarone intake	- Amiodarone 400q8 PO on POD 0-1 - Beta blocker therapy as blood pressure and heart rate tolerates

Table 1: Table of institutional ERAS protocol changes in 2020 (POD=Postoperative day)

CARDIOVASCULAR ANESTHESIOLOGY 28

Hypothermic circulatory arrest (HCA) does not impact cerebral autoregulation

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INTRODUCTION: Hypothermic circulatory arrest (HCA) is associated with post-cardiac surgical neurologic impairment including, cognitive decline. Impaired cerebral pressure-flow autoregulation may contribute to neurologic injury through cerebral hypo-or hyper-perfusion. This study compares the cerebral autoregulation curves between patients who underwent aortic surgery with (HCA) and anterograde cerebral perfusion (ACP) and those who did not. The methodology for this single-center, retrospective observational study is novel in its use of a high-resolution data collection and device integration platform. We hypothesized that HCA alters cerebral autoregulation (CA) after separation from cardiopulmonary bypass. Specifically, we hypothesized that the lower limit of autoregulation (LLA), optimal arterial blood pressure (ABPopt), differs after HCA compared to pre-procedural baseline CA and with patients who underwent off-pump cardiac surgery.

METHODS: Under IRB approval (IRB# 300005436), we analyzed high-resolution real-time waveform data that included systemic ABP and cerebral near-infrared spectroscopy (NIRS) via the Sickbay™ platform and a custom software package. Patients who underwent off-pump coronary artery bypass graft (OPCABG) surgery and those who underwent thoracic aortic arch repairs with HCA were included. LLA, ABPopt, and percent time below LLA were compared before and after HCA with ACP within the aortic repair group using a Welch's t-test. The same parameters were compared between the aortic group after separation from CPB and the OPCABG groups using the same statistical test.

RESULTS: ABP and NIRS data were available for 38 patients undergoing arch repair with circulatory arrest and 28 undergoing OPCABG. Mean LLA before circulatory arrest for those undergoing arch repair was 65 ± 11 mmHg (standard deviation). After circulatory arrest, the mean LLA was 63 ± 6 mmHg. Likewise, the mean ABPopt before circulatory arrest was 77 ± 13 mmHg and 79 ± 8 mmHg after. None of these differences were statistically significant ($p>0.05$). There were no significant differences in those values post-arrest compared to patients who did not undergo arrest.

CONCLUSION: Cerebral autoregulation, as determined with noninvasive technology, was not impaired by hypothermic circulatory arrest. This result may consequently inform and refute underlying assumptions of the brain's vascular response to and recovery from HCA. Indeed, ACP might preserve autoregulation. Additionally, and importantly, we note that the average optimal mean arterial blood pressures obtained in this study are higher than the widely accepted population-based minimally recommended pressure of 65 mmHg.

CARDIOVASCULAR ANESTHESIOLOGY 29

Intravenous Waveform Analysis Correlates with Volume Status in Prone Positioning and Sternotomy in a Rat Model

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INTRODUCTION: Dynamic markers such as pulse pressure variation (PPV) are pivotal tools in volume management in the perioperative period. However, PPV validity does not extend to a large portion of operative cases including those with prone positioning and open chest.[1, 2] Intravenous waveform analysis (IVA) is a novel marker of volume status that is thought to assess the relationship of pressure and volume in the right heart and venous system. It does this by isolating the amplitude of the frequency corresponding to heart rate, termed F1, within the venous waveform. As IVA does not assess changes in preload based on intrathoracic pressure variation it may not be subject to the same physiologic limitations. We hypothesized that IVA-derived F1 would fall in hemorrhage and rise in resuscitation corresponding to circulating volume status in subjects with either sternotomy or in prone positioning.

METHODS: 12 male Sprague Dawley rats were anesthetized with isoflurane, intubated and mechanically ventilated. Estimated blood volume (EBV) was calculated by weight. Subjects were cannulated in the left femoral vein for blood withdrawal, left femoral artery for transduction of mean arterial pressure (MAP) and calculation of PPV, and the right femoral vein for venous waveform recording. Fast Fourier transform was performed on the venous waveform in MATLAB and amplitude of F1 measured. Heart rate (HR) was determined by electrocardiogram. 6 subjects were randomly assigned to each group, sternotomy, or prone positioning. Sternotomy was performed with mayo scissors, and ribs separated with an Alm retractor. Prone positioning was performed onto soft packing foam. Heparinization was then performed. Experimental protocol entailed withdraw of 5% of the EBV over 1 min repeated 4 minutes later, totaling 10% blood loss, and then return of 5% of the EBV over 1 min, repeated 4 minutes later to achieve euvolemia. Subjects were then over-resuscitated with crystalloid in 2 boluses with volumes equivalent to 5% of EBV. Repeated measures ANOVA with pairwise comparison was performed, and Sidak-adjusted p value significance was set at <0.05.

RESULTS: In prone subjects F1 fell significantly in hemorrhage from baseline to 95% EBV, $p=0.01$, and did rise significantly in resuscitation from 95% EBV to 110% EBV, $p=0.02$ and from 100% EBV to 110% EBV $p=0.04$. MAP fell significantly in hemorrhage to 90% EBV, $p=0.001$ and rose in resuscitation to euvolemia, $p=0.01$. In subjects with sternotomy, F1 did not fall in hemorrhage, but once again rose during resuscitation from 95% EBV to 110% EBV, $p=0.03$. MAP fell in hemorrhage to 90% EBV, $p=0.001$, and rose in resuscitation to euvolemia, $p=0.01$. PPV did not change significantly at any timepoint in either group.

CONCLUSION: IVA outperformed PPV in both experimental settings. This proof-of-concept study demonstrates IVA sensitivity to hemorrhage and resuscitation under physiologic conditions where dynamic markers fail. Further evaluation into the widespread utility of IVA is warranted.

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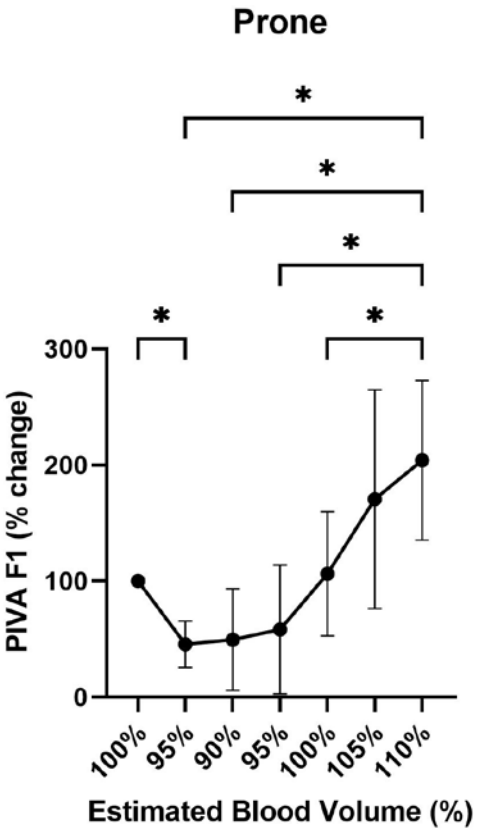

Fig. 1

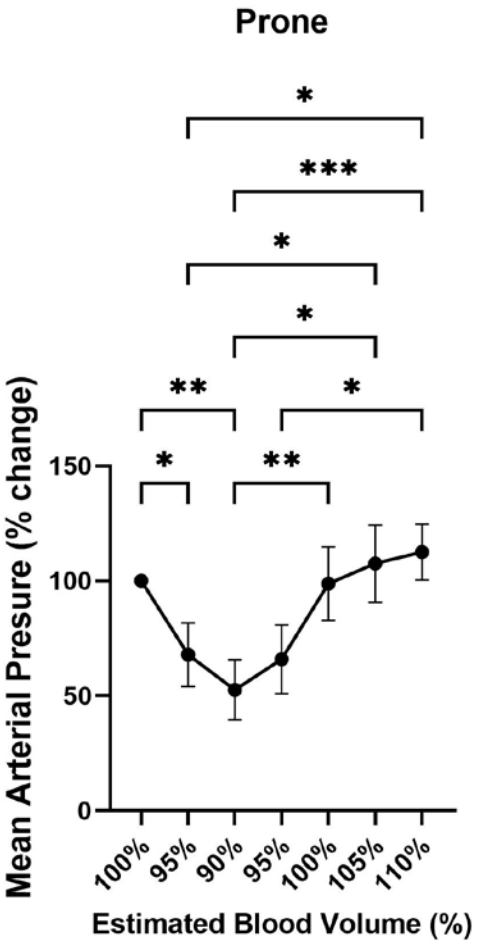

Fig. 2

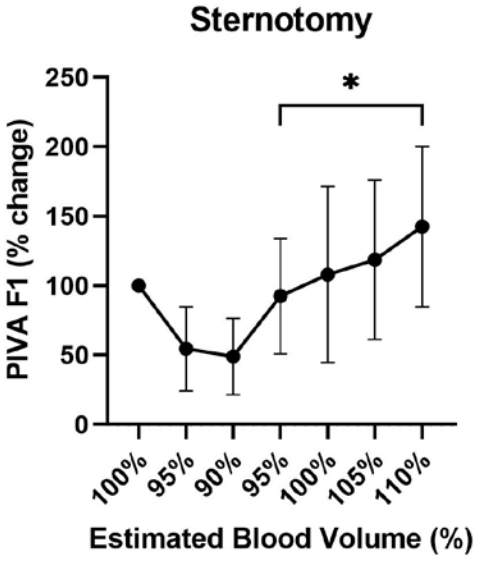

Fig. 3

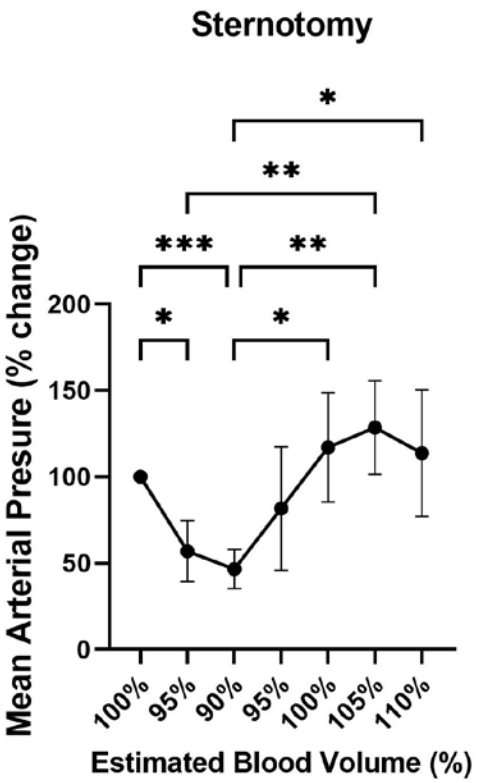

Fig. 4

SUBSPECIALTY ABSTRACTS

CRITICAL CARE

CRITICAL CARE 1

Point of care gastric ultrasound in ICU patients before and after initiation of post-pyloric enteral feeds

Wendy Guo[1], Meghan Brennan[1], Cameron Smith[1], Nikolaus Gravenstein[1]

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INTRODUCTION: Aspiration of gastric contents is a major risk of general anesthesia and associated with significant morbidity and mortality[1]. Preoperative fasting recommendations developed by the American Society of Anesthesiologists may not apply in the critically ill patient population[2]. Currently, no consistent preoperative fasting guidelines exist for patients receiving post pyloric enteral feeds[3,4]. Our study aims to evaluate the use point of care gastric ultrasound (POGUS) to repetitively examine gastric content before and after initiation of post-pyloric enteral feeds in ICU patients in order to assess gastric contents in this patient population and potentially clarify how fasting guidelines should be applied to this patient population.

METHODS: This is a single center prospective observational cohort study of adult patients admitted to surgical ICUs receiving post-pyloric enteral feeds. POGUS was performed prior to initiation of enteral feeds and after feeds had been ongoing at goal rate for at least 6 hours. Ultrasound images were obtained in both the supine and right lateral decubitus positions to identify the gastric antrum and qualitatively characterize its content.

RESULTS: 21 patients have been enrolled in the study with completed ultrasounds in 16 patients before initiation and 9 after achieving goal rate of enteral tube feeds. Before enteral feeds were started, 11 patients were classified as full stomach (5 with moderate to large volume clears, 2 with solids) and 4 patients were considered empty stomach. After enteral feeds were started, 5 patients were classified as full stomach (4 with small to large volume clears, 1 with solids) and 4 were considered empty stomach.

CONCLUSION: Traditional fasting recommendations may not apply in the critically ill patient population even before the initiation of post-pyloric enteral feeds. Gastric emptying also appears to be quite variable after achieving goal rate on enteral tube feeds. Given the significant morbidity and mortality associated with gastric aspiration, especially in the critically ill, further research is needed to clarify optimal fasting guidelines for ICU patients.

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CRITICAL CARE 2

Identifying pro-inflammatory miRNA motifs using an exhaustive computer search algorithm in murine sepsis and trauma

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INTRODUCTION: Organ dysfunction occurs following traumatic injury or septic shock and is due, in part, to body's inappropriate immune responses[1]. The DAMPs such as cellular nucleic acids have been implicated in the immune response in sepsis and trauma[2]. We have reported that many plasma miRNAs are upregulated upon sepsis and ischemia, and some are pro-inflammatory via TLR7[3-4], a RNA sensor. However, while uridine and guanosine are essential for the miRNA-mediated innate immune response[5], neither the specific nucleotide sequence preference nor motifs essential for their activity is known[6].

METHODS: All animal experiments were approved by the IACUC. Anesthetized C57BL/6J mice were subjected to Trauma (bowel ischemia, tibia fracture, and muscle crush), CLP (Cecum ligation and puncture), or Sham (Laparotomy). Blood was collected at 6h and 24h after surgery and plasma RNA isolated using Trizol and profiled by small RNAseq. Cytokines were assayed by ELISA. Brute force search was performed for miRNA motifs of length 4-7 within the two miRNA lists (18 pro-inflammatory vs. 15 non-inflammatory miRNAs). Sequences with at least 10 matches within the pro-inflammatory miRNA list and 0 matches in the non-inflammatory list were selected as potential motifs of interest.

RESULTS: RNAseq identified 1044 and 1206 mature miRNAs in trauma and septic mouse plasma, respectively, among which 65 and 99 miRNAs were upregulated. A list of the upregulated miRNAs (**Fig. 1A**, *training* set, n=33) were tested for their abilities to induce IL-6/CXCL-2 production *in vitro*. Among them, 18 miRNAs induced IL-6/CXCL-2, while 15 did not.

Initial receiver operating characteristic analysis of the nucleotide sequence demonstrated that uridine content predicted inflammatory properties (**Fig. 1B**). Brute force search identified ten uridine-containing sequences that were associated the pro-inflammatory miRNAs (**Fig. 1C**). Two of sequences (UU...U and U..UU) occurred in 55.6% and 61.1% of cases, respectively; thereby correctly classifying 15 out of 18 inflammatory miRNAs (**Fig. 1D**) and an overall predictive accuracy of 90.9% (sensitivity: 83.3%, specificity: 100%) in discriminating pro- from non-inflammatory miRNAs. To experimentally test the necessity of UU…U motif, we made a series of single mutations in miR-146a-5p (**Fig. 2A**) and discovered that the mutations outside of the motif, i.e. $U_1$1→A or U_8→A, had no impact on IL-6 production (**Fig. 2B**). However, mutations within the motif: U_{12}→A or U_{13}→A completely, and U_{17}→A partially, abrogated IL-6 production. Finally, to validate the predictive value of the two motifs, an independent *testing* set of 20 miRNAs (**Fig. 3A**) were tested (**Fig. 3B**). These data demonstrate that the two motifs achieved an overall prediction accuracy of 75% (sensitivity: 69%, specificity: 86%).

CONCLUSION: This study demonstrates that many plasma miRNAs following traumatic injury and sepsis possess strong pro-inflammatory properties. Two nucleotide motifs are identified that are highly associated pro-inflammatory miRNAs.

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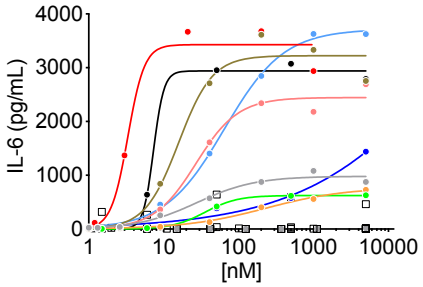
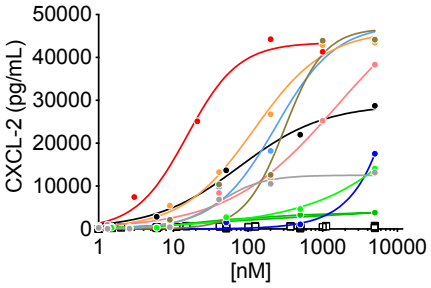
A

	5'-3' sequence	Uridine	Cytokine
let-7b-5p	UGAGGUAGUAGGUUGUGUGGUU	9	+
let-7j	UGAGGUAUUAGUUUGUGCUGUUAU	12	+
miR-122-5p	UGGAGUGUGACAAUGGUGUUUG	8	+
miR-133a-3p	UUUGGUCCCCUUCAACCAGCUG	7	+
miR-142a-3p	UGUAGUGUUUCCUACUUUAUGGA	11	+
miR-145a-3p	AUUCCUGGAAAUACUGUUCUUG	9	+
miR-145a-5p	GUCCAGUUUUCCCAGGAAUCCCU	7	+
miR-146a-5p	UGAGAACUGAAUUCCAUGGGUU	7	+
miR-181d-5p	AACAUUCAUUGUUGUCGGUGGGU	9	+
miR-186-5p	CAAAGAAUUCUCCUUUUGGGCU	8	+
miR-208a-3p	AUAAGACGAGCAAAAAGCUUGU	4	+
miR-215-3p	UCUGUCAUUCUGUAGGCCAAU	8	+
miR-25-3p	CAUUGCACUUGUCUCGGUCUGA	8	+
miR-26b-5p	UUCAAGUAAUUCAGGAUAGGU	7	+
miR-34a-5p	UGGCAGUGUCUUAGCUGGUUGU	9	+
miR-382-5p	GAAGUUGUUCGUGGUGGAUUCG	8	+
miR-7a-5p	UGGAAGACUAGUGAUUUUGUUGU	10	+
miR-802-5p	UCAGUAACAAAGAUUCAUCCUU	7	+
miR-126a-3p	UCGUACCGUGAGUAAUAAUGCG	6	–
miR-144-3p	UACAGUAUAGAUGAUGUACU	7	–
miR-144-5p	GGAUAUCAUCAUAUACUGUAAGU	8	–
miR-150-5p	UCUCCCAACCCUUGUACCAGUG	6	–
miR-192-5p	CUGACCUAUGAAUUGACAGCC	5	–
miR-193b-3p	AACUGGCCCACAAAGUCCCGCU	3	–
miR-1947-5p	AGGACGAGCUAGCUGAGUGCUG	4	–
miR-1a-3p	UGGAAUGUAAAGAAGUAUGUAU	7	–
miR-210-3p	CUGUGCGUGUGACAGCGGCUGA	5	–
miR-22-3p	AAGCUGCCAGUUGAAGAACUGU	5	–
miR-26a-5p	UUCAAGUAAUCCAGGAUAGGCU	6	–
miR-345-3p	CCUGAACUAGGGGUCUGGAGAC	4	–
miR-374b-5p	AUAUAAUACAACCUGCUAAGUG	6	–
miR-451a	AAACCGUUACCAUUACUGAGUU	7	–
miR-499-5p	UUAAGACUUGCAGUGAUGUUU	9	–





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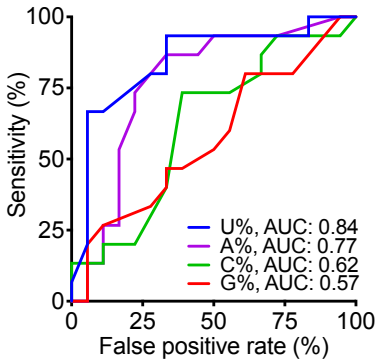

C

Sequence	Permutation Importance Score
UUU.	6.09
UUU..	4.75
UUU...	4.51
UUU....	5.12
UU...U	13.74
UU...U.	13.02
U..UU.	15.31
U..UU..	9.07
U.UU..	12.8
UU.G	4.55

D

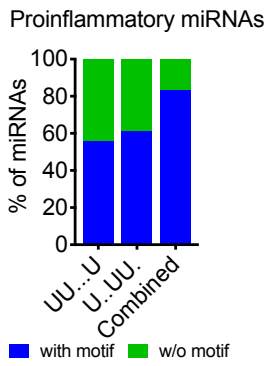

Figure 1. Identification and characterization of pro-inflammatory miRNA motif. A. Two groups of miRNAs that are pro- or non-inflammatory (cytokine production) and used as the *training* set; **B.** AUC analysis of the nucleotide sequences of miRNAs; **C.** Ten uridine-rich nucleotide motif in miRNAs identified by a computer search algorithm; **D.** Presence of the two motifs in the 18 pro-inflammatory miRNAs.

A

ss-miR-146a-5p	5'-3' sequence	Motif (UU...U)
WT	$U_1G_2A_3G_4A_5A_6C_7U_8G_9A_{10}A_{11}$**$U_{12}U_{13}C_{14}C_{15}A_{16}U_{17}$**$G_{18}G_{19}G_{20}U_{21}U_{22}$	+
mut U_1 →A	$A_1G_2A_3G_4A_5A_6C_7U_8G_9A_{10}A_{11}$**$U_{12}U_{13}C_{14}C_{15}A_{16}U_{17}$**$G_{18}G_{19}G_{20}U_{21}U_{22}$	+
mut U_8 →A	$U_1G_2A_3G_4A_5A_6C_7A_8G_9A_{10}A_{11}$**$U_{12}U_{13}C_{14}C_{15}A_{16}U_{17}$**$G_{18}G_{19}G_{20}U_{21}U_{22}$	+
mut U_{12} →A	$U_1G_2A_3G_4A_5A_6C_7U_8G_9A_{10}A_{11}$**$A_{12}U_{13}C_{14}C_{15}A_{16}U_{17}$**$G_{18}G_{19}G_{20}U_{21}U_{22}$	–
mut U_{13} →A	$U_1G_2A_3G_4A_5A_6C_7U_8G_9A_{10}A_{11}$**$U_{12}A_{13}C_{14}C_{15}A_{16}U_{17}$**$G_{18}G_{19}G_{20}U_{21}U_{22}$	–
mut U_{17} →A	$U_1G_2A_3G_4A_5A_6C_7U_8G_9A_{10}A_{11}$**$U_{12}U_{13}C_{14}C_{15}A_{16}A_{17}$**$G_{18}G_{19}G_{20}U_{21}U_{22}$	+
mut U →A	$A_1G_2A_3G_4A_5A_6C_7A_8G_9A_{10}A_{11}$**$A_{12}A_{13}C_{14}C_{15}A_{16}A_{17}$**$G_{18}G_{19}G_{20}A_{21}A_{22}$	–

B

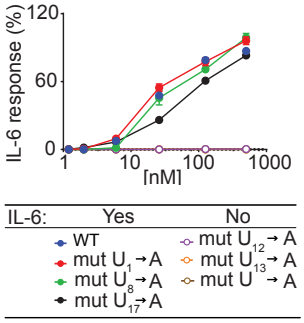

Figure 2. Importance of UU…U motif in miR-146a-5p-induced IL-6 production in macrophages. A. Nucleotide sequences of single-stranded miR-146a-5p and its various U→A mutants. The $U_{12}U_{13}…U_{17}$ motif sequence is highlighted in shade. U→A mutants are in red. **B.** Dose-response of IL-6 production in bone marrow-derived macrophages treated with miR-146a-5p or its various U→A mutants (50 nM), n=3.

A

				CXCL-2 production		
	5'-3' sequence	**UU…U**	**U..UU.**	**Prediction**	**Test**	**UU**
miR-10a	UACCCUGUAGAUCCGAAU**UUGU**G	–	–	–	+	+
miR-28a	CACUAGA**UUGU**GAGCUGCUGGA	–	–	–	+	+
miR-148a	UCAGUGCACUACAGAACU**UUGU**	–	–	–	+	+
miR-652	AAUGGCGCCACUAGGG**UUGU**G	–	–	–	+	+
miR-16b	UAGCAGCACGUAAAUAUUGGCG	–	–	–	–	+
miR-141	UAACACUGUCUGGUAAAGAUGG	–	–	–	–	–
miR-143	GGUGCAGUGCUGCAUCUCUGG	–	–	–	–	–
miR-194	UGUAACAGCAACUCCAUGUGGA	–	–	–	–	–
miR-200a	UAACACUGUCUGGUAACGAUGU	–	–	–	–	–
miR-206	UGGAAUGUAAGGAAGUGUGUGG	–	–	–	–	–
miR-10b	CAGA**UUCGAU**UCUAGGGGAAUA	+	–	+	+	+
miR-26b	CCUGUUCUCCA**UUACUU**GGCUC	+	–	+	+	+
miR-98	UGAGGUAGUAAG**UUGUAU**UGUU	+	–	+	+	+
miR-221	AGCUACA**UUGUCU**GCUGGGUUUC	+	–	+	+	+
miR-377	AUCACACAAAGGCAAC**UUUUGU**	+	–	+	+	+
miR-15b	UAGCAGCACAUCA**UGGUU**UACA	–	+	+	+	+
miR-20a	UAAAG**UGCUU**AUAGUGCAGGUAG	–	+	+	+	+
miR-147	GUGUGCGGAAA**UGCUU**CUGCUA	–	+	+	+	+
miR-215	AUGACCUA**UGAUU**UGACAGAC	–	+	+	–	+
miR-223	CGUG**UAUUU**GACAAGCUGAGUUG	–	+	+	+	+
				Specificity	85.7%	71.4%
				Sensitivity	69%	100%

B

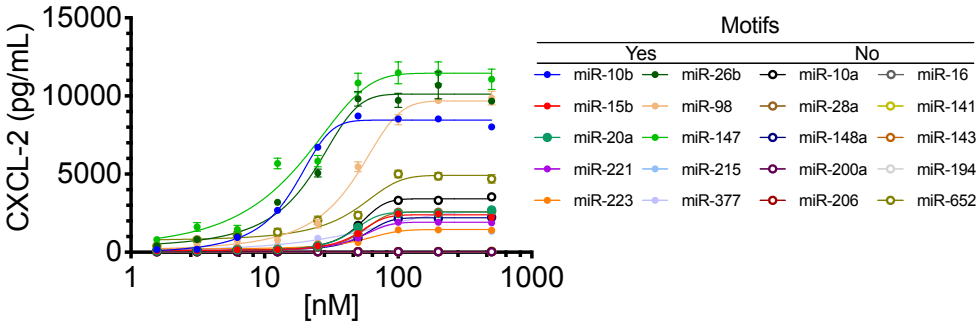

Figure 3. Validation of UU…U and U..UU motif in their association with pro-inflammatory properties of various miRNAs. A. A list of miRNAs with or without the two motifs and their predictive accuracy of CXCL-2 production. **B.** Dose-dependency of cytokine production in cells treated with various doses of miRNA mimics.

CRITICAL CARE 3

Nucleic acid sensing mediates brain inflammation in murine sepsis

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INTRODUCTION: Sepsis is a critical condition with life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis-associated encephalopathy (SAE) occurs in sepsis survivors and is reportedly caused by the blood-brain barrier (BBB) breakdown, brain inflammation, and neurological dysfunction. Extracellular (ex) miR-146a-5p is increased significantly in the plasma of septic mice and humans, and is capable of inducing potent pro-inflammatory cytokines and complement activation via TLR7 signaling, a single-stranded RNA sensor. In the current study, we delineated the impact of ex-miRNAs and TLR7 in SAE.

METHODS: All animal experiments were approved by the IACUC. WT (C57BL/6J) and TLR7-/- mice were employed. Polymicrobial sepsis was created by cecal ligation and puncture. A battery of behavioral tests was conducted. Blood-brain barrier (BBB) breakdown was measured by leakage of the blood sodium fluorescein (376 Da) to the brain. Microglial cells were isolated from neonatal mice and cytokines were tested using ELISA and qRT-PCR. Brain immune cell infiltration was evaluated by flow cytometry. Statistical analysis was performed using GraphPad Prism 9 software. The null hypothesis was rejected for $p < 0.05$ with two tails.

RESULTS: Sepsis significantly increased plasma RNA concentrations and miR-146a-5p for up to 7 days (Fig. A). To test whether miR-146a-5p causes neuroinflammation, we treated microglia cultures or intact brain via intracerebroventricular (ICV) injection with miR-146a-5p mimics. miR-146a-5p, but not its U→A mutant, led to a marked increase in cytokine production in WT microglia cultures (Fig.B). Deficiency of TLR7 (TLR7-/-), but not TLR3 (TLR3-/-, a double-stranded RNA sensor), abolished miR-146a-5p's effect (Fig. B). Additionally, ICV injection of miR-146a-5p mimics upregulated cortical cytokine IL-6, TNFα and chemokine CXCL2 gene expression at 24 h. Flow cytometry analysis within the same time frame revealed a robust increase in the numbers of myeloid cells including monocytes and neutrophils. Importantly, sepsis induced brain inflammation for up to 14 days and neurological dysfunction. Lack of TLR7 attenuated miR-146a-5p-triggered innate immune response manifested as reduced cytokine production (Fig. C) and limited immune cell infiltration (Fig. D). Ablation of TLR7 in TLR7-/- mice preserved BBB integrity at 24 h (Fig. E), reduced microglial expansion and leukocyte infiltration up to 14 days (Fig. F), and attenuated GSK3β signaling in the brain, but did not improve neurobehavioral recovery following sepsis (data not shown).

CONCLUSION: We established a clinically relevant mouse model of SAE and identified the importance of ex-miRNAs-TLR7 signaling in brain inflammation in murine sepsis.

CRITICAL CARE 4

Innate Immune TLR7 Signaling Mediates Platelet Activation in Murine Bacterial Sepsis

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INTRODUCTION: Sepsis is defined as a dysregulated host response to infection resulting in systemic inflammation and hemostatic activation.[1] Thrombocytopenia is a common complication in sepsis and is associated with poor prognosis and higher mortality.[2] Activated platelets express CD62p which facilitates platelet leukocyte aggregate (PLA) formation and will undergo rapid sequestration from the blood contributing to sepsis induced thrombocytopenia. Innate immune signaling via Toll-like receptors (TLRs) plays a pivotal role in inflammation-mediated coagulopathy during sepsis.(3) We have previously reported that the degree of thrombocytopenia in bacterial sepsis was partly attributable to TLR7, a single-stranded RNA sensor. In the current study, we tested the hypothesis that TLR7 stimulation is sufficient to induce platelet activation and mediates PLA formation during bacterial sepsis.

METHODS: Animal experiments were approved by the IACUC. Whole blood was collected from 12-18-week-old, wild-type (WT) C57BL/6J mice and age/sex matched TLR7-deficient mice (TLR7-/-) and then treated with the TLR7 agonist loxoribine (1 mM). Murine sepsis was created by cecal ligation and puncture (CLP). Blood was collected at 4h and 24h after CLP or sham (laparotomy). Platelet activation and PLA formation was determined by flow cytometry based on double positive expression of CD41+/CD62p+ and CD45+/CD62p+ cells, respectively. Data are presented as mean ± SD. Statistical significance was determined by one-way ANOVA or unpaired t test; a $p < 0.05$ was considered statistically significant.

RESULTS: WT blood treated with loxoribine had a significant increase in CD41+/CD62p+ cells compared to control samples (43.8±2.4% vs. 34.8±2.9% control, $p = 0.04$), and TLR7-/- blood treated with loxoribine (vs 30.7±10.8%, $p = 0.003$) (Fig. 1A). Loxoribine induced a similar increase in PLA formation (CD45+/CD62p+ cells) in WT blood when compared to that of WT controls (39.5±2.4% vs. 32.9±3.4% control, $p = 0.01$) or loxoribine-treated TLR7-/- blood (30.9±4.4%, $p = 0.001$) (Fig. 1B). Four and 24 h after CLP, TLR7-/- septic mice had significantly lower number of PLA formation when compared with WT septic mice although no significant difference in CD41+/CD62+ platelets between WT and TLR7-/- mice.

CONCLUSION: Our data suggest that TLR7 stimulation is sufficient to activate blood platelets and that TLR7 signaling may mediate PLA formation during murine sepsis.

REFERENCE(S):

1. Jama. 2016;315:801-10
2. J Clin Med. 2019;8:728
3. Nat Rev Immunol. 2017;17(7):407-20

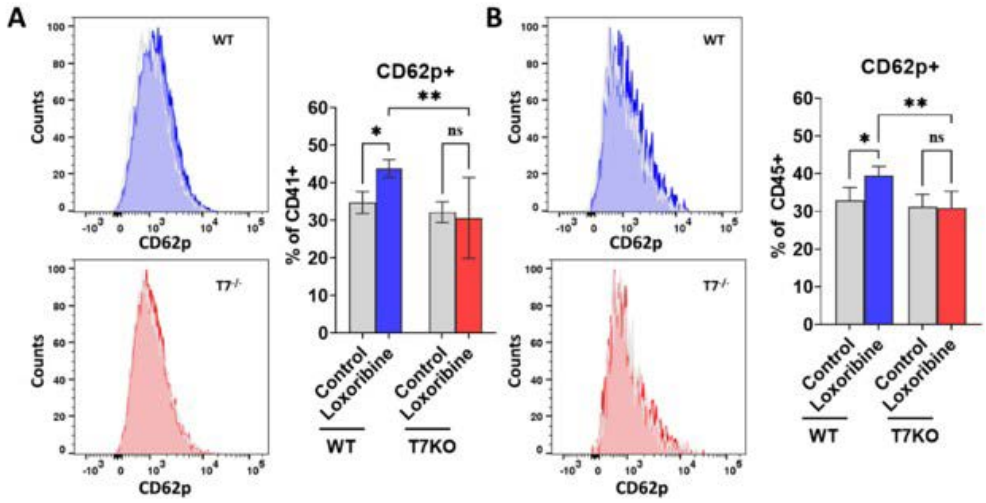

Figure 1: Loxoribine activates platelets via TLR7. Wild type and TLR7$^{-/-}$ mouse blood were treated with or without 1 mM of loxoribine, a known TLR7 agonist. Blood cells were stained with anti-CD41, -CD45, and -CD62P mAbs and analyzed by flow cytometry. **(A)** Histograms show average percent of CD62+ platelets (CD41+); **(B)** average percent of CD62+ leukocytes (CD45+) with representative flow histograms; bars represent the mean ± SD of 2 replicate experiments run with triplicate samples; *p<0.05, **p<0.01.

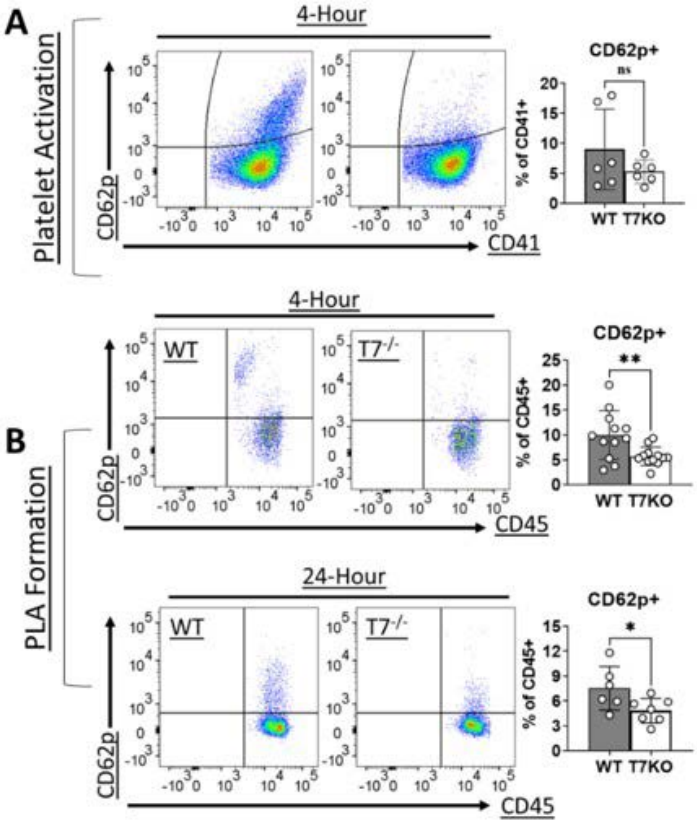

Figure 2: TLR7$^{-/-}$ CLP mice demonstrated reduced circulating platelet-leukocyte aggregates compared to WT CLP mice. Wild-type and TLR7$^{-/-}$ mice underwent CLP surgery. 4h and 24h later whole blood was collected, and platelet activation (CD6241/CD62+) and PLA (CD45+/CD62+) formation quantified. Whole blood from WT and TLR7$^{-/-}$ CLP mice were stained with anti-CD41, -CD45, and -CD62P mAbs and analyzed by flow cytometry. **(A)** Histograms show average percent of CD62+ platelets (CD41+) at 4h and **(B)** average percent of CD62+ leukocytes (CD45+) at 4h and 24h, each with representative flow dot plots; *p<0.05, **p<0.01.

CRITICAL CARE 5

Toll-like receptor 7 drives lung inflammation by sensing miR-146a and causes acute respiratory distress syndrome in murine sepsis

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INTRODUCTION: Sepsis is the leading cause of acute respiratory syndrome (ARDS). Septic patients with ARDS have high morbidity and mortality. Our recent findings suggest that circulating miR-146a-5p, released during sepsis, functions as a danger molecule and induces a robust innate immune response via Toll-like receptor 7 (TLR7), a single stranded RNA sensor. Furthermore, mice lack of TLR7 have attenuated systemic inflammation, organ injury, and lower mortality in sepsis. However, whether miR-146a-5p,ÜíTLR7 signaling has any impact to lung injury in sepsis remains unclear. In this study, we tested the hypothesis that TLR7 in immune cells activated by miR-146a-5p causes endothelial barrier disruption and lung inflammation (Fig. 1).

METHODS: Polymicrobial sepsis was created by cecal ligation and puncture (CLP). Albumin in the bronchoalveolar lavage (BAL) was tested by ELISA. Cytokines were detected by ELISA and qRT-PCR. Conditioned media were collected from macrophages (MœÜ) treated with lipofectamine (lipo) or miR-146a-5p (50 nM) for 24h. Endothelial barrier function was assessed by transendothelial electric resistance and XPerT assay. All animal experiments were approved by IACUC. The null hypothesis was rejected for $p < 0.05$ with two tails.

RESULTS: Sepsis significantly augmented miR-146a-5p level in the BAL at 24 h (Fig. 2A). Intratracheal administration of miR-146a-5p (20 μg) in miR-146a KO mice induced pulmonary inflammation as evidenced by a marked increase in BAL IL-6 (Fig. 2B) and robust neutrophil infiltration in the lung. Absence of TLR7 almost completely blocked the injurious effect of exogenous miR-146a-5p, indicating that miR-146a-5p induced lung injury is exclusively TLR7-dependent. Most importantly, in a CLP sepsis model, TLR7KO mice had preserved alveolar-capillary barrier function (Fig. 2C) and attenuated proinflammatory cytokines when compared with WT mice (Fig. 2D). To decipher the molecular mechanism responsible for miR-146a-5p→TLR7-mediated barrier disruption and activation, we treated endothelial cells (ECs) with miR-146a mimics. Because ECs do not express TLR7, direct treatment of miR-146a-5p, a TLR7 activator, exhibited no impact on permeability. In contrast, the EC permeability increased dramatically when ECs were incubated with conditioned media from miR-146a-treated WT Mϕ or WT septic sera. Absence of TLR7 either in Mϕ or septic mice preserved the barrier function (Fig. 2 E, F). To identify the downstream effectors, cytokine array was performed and revealed over 70 increased cytokines between WT and TLR7KO septic sera. Pathway enrichment analysis implies TNFα singling pathway to be the most promising effector for endothelial barrier dysfunction (Fig. 2G). Indeed, sera from WT-CLP mice lost the ability to induce barrier leaky in the ECs when incubated with anti-TNFα Ab (Fig. 2H).

CONCLUSION: We demonstrate a pivotal role of miR-146a-5p and TLR7 sensing in mediating lung injury induced by polymicrobial sepsis.

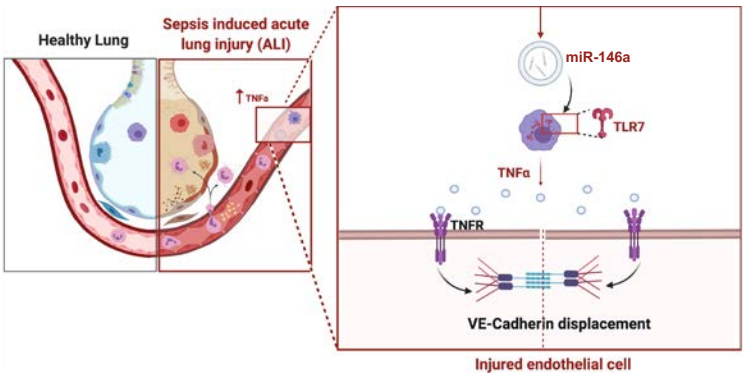

Figure 1. Schematic hypothesis that TLR7 in immune cells activated by miR-146a-5p causes endothelial barrier disruption and lung inflammation in part via TNFα. . Increased lung injury secondary to sepsis was characterized by pulmonary inflammation and alveolar-capillary barrier dysfunction. Increased miRNA in circulation by sepsis activates the immune cells by recognizing TLR7 signaling to release multiple proinflammatory cytokines, including TNFα, which leads to pulmonary barrier damage through disrupting VE-cadherin junctions on endothelial cells.

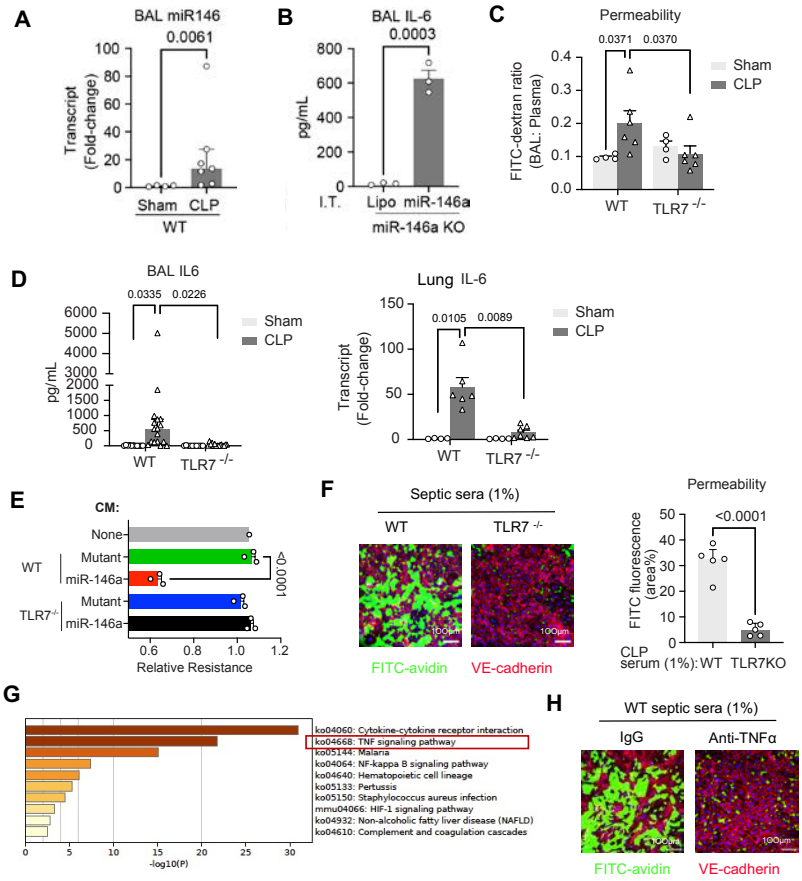

Figure 2. Absence of TLR7 attenuated lung injury elicited by exogenous miR-146a and polymicrolial sepsis. ***A.*** BAL miR-146a tested at 24h after sham and CLP procedure. n=4-7. ***B.*** BAL IL-6 in miR-146a KO mice at 24 h following the intratracheal injection of miR-146a-5p (20μg). n=3. ***C-D.*** WT and TLR7$^{-/-}$ mice are subjected to sham or CLP, permeability (***C***) and IL-6 (***D***) were evaluated at 24 h. n=4-17. ***E.*** miR-146a increases endothelial permeability via macrophage TLR7. ECs were incubated with conditioned media (CM) collected from miR-146a- or mutant- treated WT and TLR7KO macrophage. Resistance was measured at 8 h. ***F.*** Endothelial permeability visualized and quantified by area percentage of FITC-avidin at 24h following treatment of 1% septic sera from WT and TLR7$^{-/-}$ mice. n=5. ***G.*** Pathway enrichment analysis. ***H.*** WT septic sera were preincubated with IgG or anti-TNFα (10ng/mL) prior to the treatment with EC. Permeability was visualized with FITC-avidin.

CRITICAL CARE 6

Proteomic analysis of murine heart mitochondria during sepsis

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INTRODUCTION: Sepsis-induced cardiomyopathy (SIC) is a major contributing factor for morbidity and mortality in sepsis. Accumulative evidence has suggested that cardiac mitochondrial oxidative phosphorylation is attenuated in sepsis, but the underlying molecular mechanisms remain incompletely understood.

METHODS: Adult male mice of 9 to 12 weeks old were subjected to sham or cecal ligation and puncture procedure. Echocardiography in vivo and Langendorff perfused hearts were used to assess cardiac function 24 h after the procedures (Figure 1). Unbiased proteomics analysis was performed to profile mitochondrial proteins in the hearts of both sham and SIC mice.

RESULTS: Of the 665 mitochondrial proteins identified in the proteomics assay, 35 were altered in septic mice (Table 1). The mitochondrial remodeling involved various energy metabolism pathways including subunits of the electron transport chain, fatty acid catabolism, and carbohydrate oxidative metabolism (Figure 2). Some of the notable proteins involved in the electron transport chain include NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 8 (NDUFB8), a subunit of complex I, cytochrome C oxidase subunit 5B (COX5B) and cytochrome C oxidase copper chaperone 17 (COX17), two subunits of complex IV, and NADPH-cytochrome P450 reductase (P450R), an enzyme that is required for electron transfer from NADPH to cytochrome P450. Interesting fatty acid catabolism proteins included methylmalonyl-CoA epimerase (MCE) involved in odd chain-length fatty acid catabolism, phytanol-CoA 2-hydroxylase (PHYH), important for alpha-oxidation of 3-methyl branched fatty acids, and carbonyl reductase [NADPH] 2 (CBR2), involved in carbonyl metabolism from aldehydes and ketones derived from lipid peroxidation. There were also two proteins involved in pyruvate metabolism, pyruvate kinase (PK), and pyruvate dehydrogenase kinase 4 (PDK4), a kinase that plays a key role in the regulation of pyruvate and fatty acid metabolism through reversible inactivation of pyruvate dehydrogenase (PDH) via phosphorylation of the subunits PDHA1 and PDHA2, and is the major isoform in the heart. Consistent with the notable increase in PDK4 expression via proteomics, we also identified a significant increase of pyruvate dehydrogenase (PDH) kinase 4 (PDK4) and inhibition of PDH activity in septic hearts (Figure 3).

CONCLUSION: These data demonstrate a broad mitochondrial protein remodeling, PDH inactivation, and provide a molecular framework for further exploration.

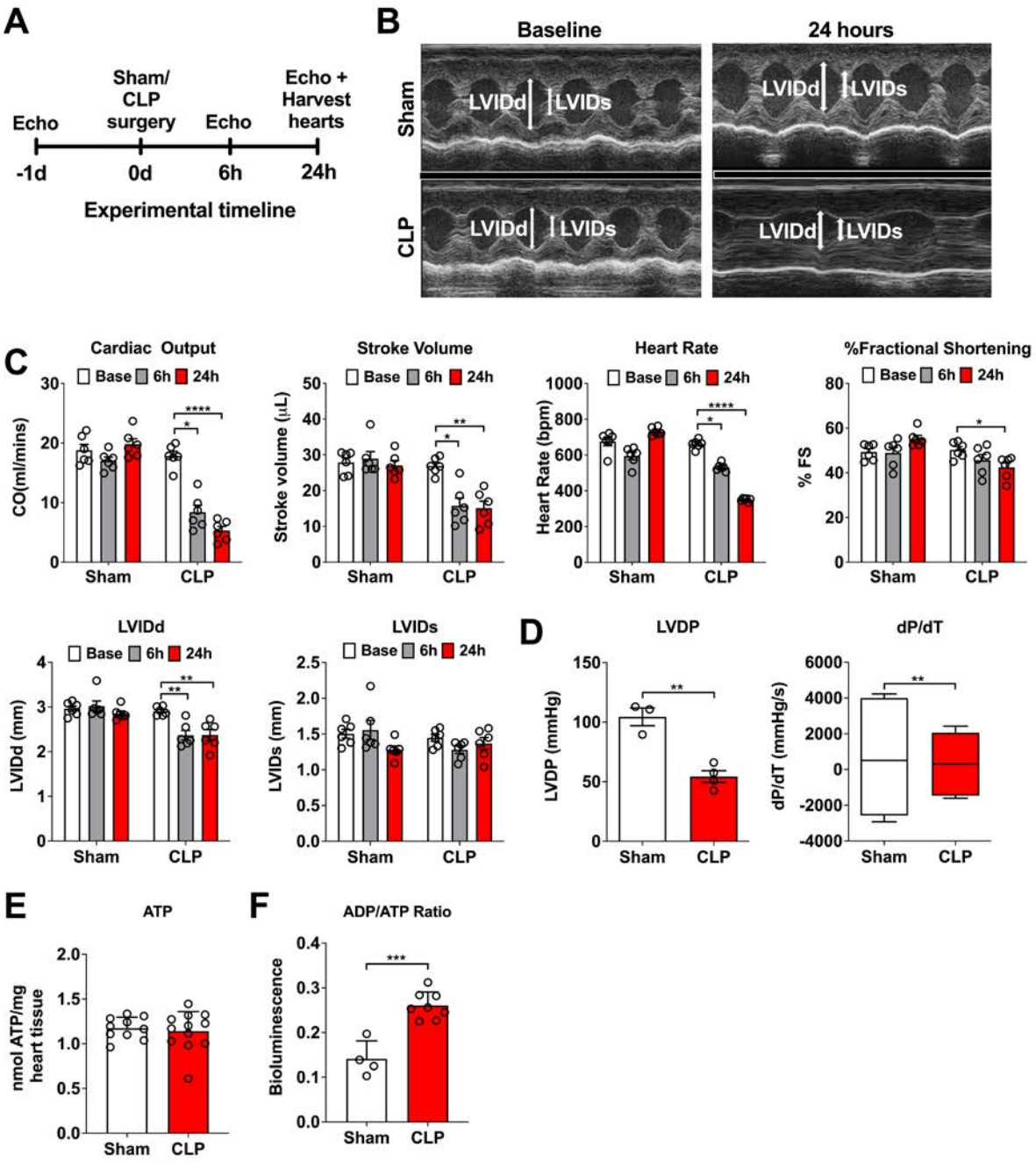

Fig. 1

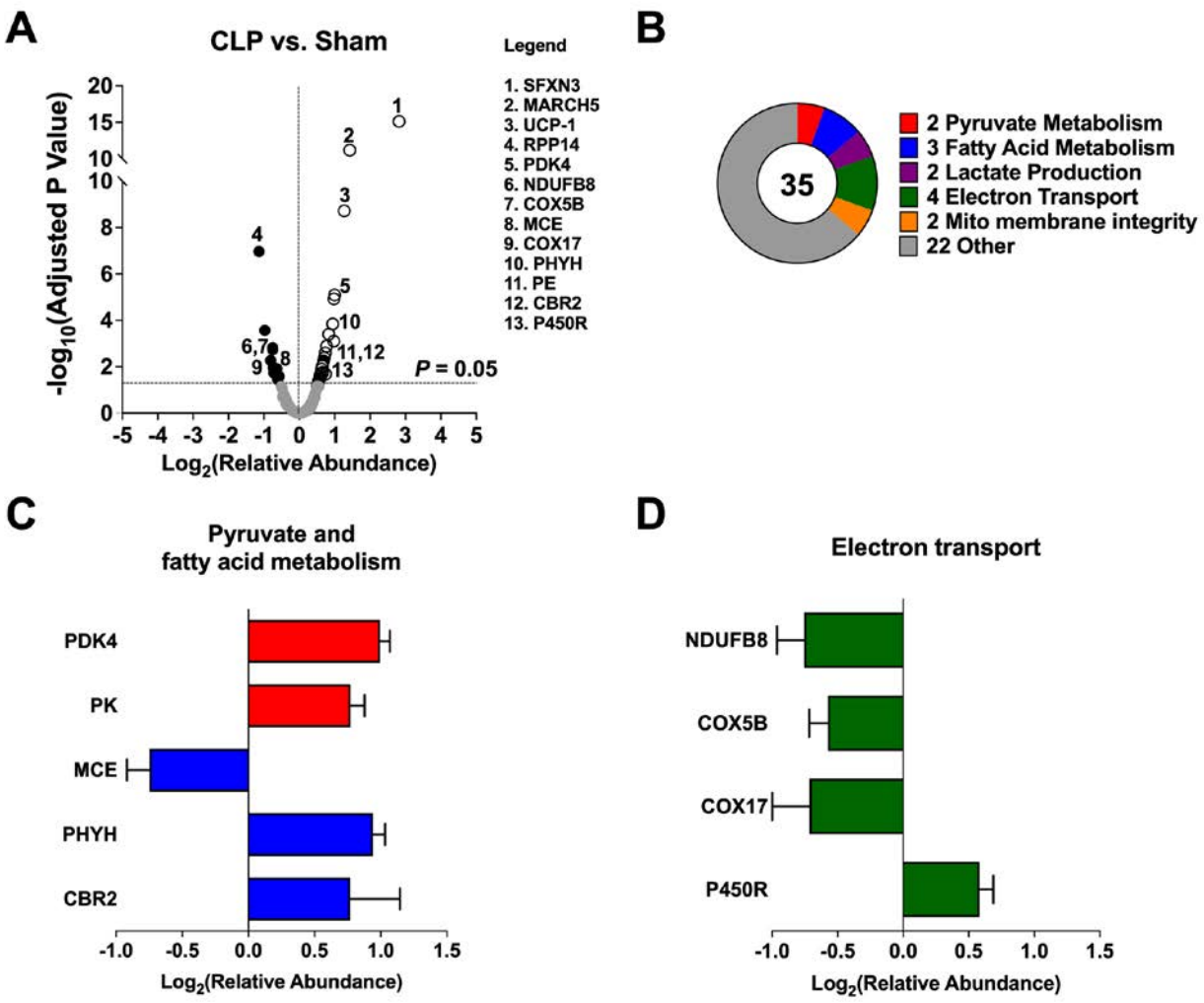

Fig. 2

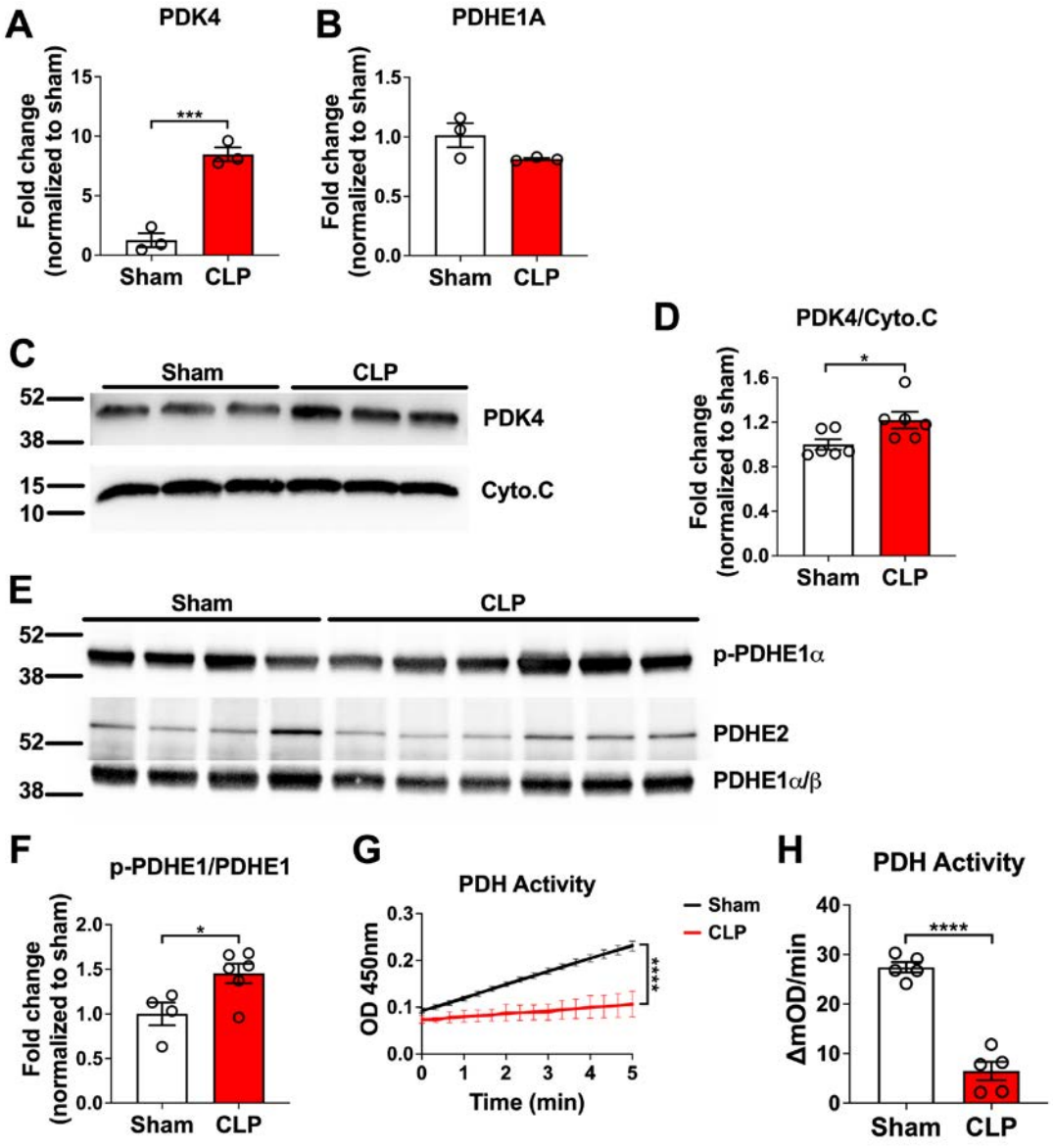

Fig. 3

Table 1. Proteomics analysis of cardiac mitochondrial proteins: 35 differentially expressed proteins between sham and CLP mice.

#		*Accession*	*Gene Name*	*Abundance Ratio (CLP/sham)*
	Pyruvate Metabolism			
1	Pyruvate kinase	P52480	PKM	1.706
2	Pyruvate dehydrogenase (acetyl-transferring)] kinase isozyme 4	O70571	PDK4	1.993
	Fatty Acid Metabolism			
3	Methylmalonyl-CoA epimerase	Q9D1I5	MCEE	0.595
4	Carbonyl reductase [NADPH] 2	P08074	CBR2	1.704
5	Phytanoyl-CoA dioxygenase, peroxisomal	O35386	PHYH	1.921
	Lactate Production			
6	L-lactate dehydrogenase B chain	P16125	LDHB	1.481
7	L-lactate dehydrogenase	A0A1B0GSX0	LDHA	1.668
	Electron Transport			
8	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 8, mitochondrial	Q9D6J5	NDUFB8	0.592
9	Cytochrome c oxidase subunit 5B	Q9D881	GM11273	0.671
10	Cytochrome c oxidase copper chaperone	P56394	COX17	0.609
11	NADPH--cytochrome P450 reductase	P37040	P450R	1.497
	Mito Membrane Integrity			
12	MICOS complex subunit MIC10	Q7TNS2	MINOS1	0.508
13	E3 ubiquitin-protein ligase MARCH5	Q3KNM2	MARCH5	2.685
	Other			
14	Glyceraldehyde-3-phosphate dehydrogenase	A0A0A0MQF6	GAPDH	1.660
15	Cathepsin D	P18242	CTSD	1.607
16	Mitochondrial brown fat uncoupling protein 1	P12242	UCP-1	2.410
17	Phosphate carrier protein	Q8VEM8	SLC25A3	1.575
18	Cathepsin B	P10605	CTSB	1.777
19	Sideroflexin-3	Q91V61	SFXN3	7.061
20	Keratin, type II cytoskeletal 5	Q922U2	KRT5	2.413
21	B-cell receptor-associated protein 31	Q61335	BCAP31	1.631
22	39S ribosomal protein L15	Q9CPR5	MRPL15	1.571
23	Transforming protein RhoA	Q9QUI0	RHOA	1.964
24	Transport and Golgi organization 2 homolog	P54797	TANGO2	1.514
25	Fructose-bisphosphate aldolase	A6ZI44	ALDOA	1.549
26	Tripeptidyl-peptidase 1	O89023	TPP1	1.457
27	Mitochondrial thiamine pyrophosphate carrier	Q9DAM5	SLC25A19	0.645
28	Solute carrier family 35 member F6	Q8VE96	SLC35F6	1.577
29	Ribonuclease P 14 subunit (Human)	J3QMX0	RPP14	0.453
30	Coiled-coil domain-containing protein 58	Q8R3Q6	CCDC58	1.907
31	Haloacid dehalogenase-like hydrolase domain-containing protein 3	Q9CYW4	HDHD3	0.602
32	tRNA methyltransferase 10 homolog C	Q3UFY8	TRMT10C	1.503
33	Deaminated glutathione amidase	Q8VDK1	NIT1	0.571
34	LETM1 domain-containing protein 1	Q924L1	LETMD1	0.656
35	Aurora kinase A-interacting protein	Q9DCJ7	AURKAIP1	1.610

CRITICAL CARE 7

Genome-Wide Association Study of Renal Dysfunction After Cardiac Surgery

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INTRODUCTION: Up to 30% of patients undergoing cardiac surgery develop acute kidney injury (AKI), which portends >4-fold increase in postoperative mortality.[1] Slight increases in serum creatinine (0.3-0.5 mg/dL) also independently predict increased postoperative 30-day mortality following cardiac surgery.[2] Pre-existing diseases and more invasive surgeries are associated with higher risk of AKI, but these parameters alone do not fully predict which patients will develop AKI. We hypothesize that genetic variation among otherwise equal-risk patients may predict which patients develop perioperative AKI.

METHODS: TWe performed whole-exome sequencing of 190 adult patients undergoing cardiac surgery. IRB approval and informed consent were obtained for all study participants. Patients with pre-existing chronic kidney disease or pre-existing reduced ejection fraction (EF=30%) were excluded from the study. Serum creatinine (SCr) levels were obtained for each patient prior to surgery and on each day of hospitalization following surgery. A genome-wide association study (GWAS) was performed with whole-exome sequence data as a genotype and using percent change between preoperative SCr and peak-48-hour postoperative SCr as a quantitative phenotype (n=190). Analyses were performed using linear association in PLINK v1.9 software (Purcell, Boston, MA) with a minimum allele frequency (MAF) of 0.01, minimum allele count (MAC) of 3, population stratification testing with principal components analysis (PCA), and a Hardy Weinberg Equilibrium (HWE) threshold of 0.001.

RESULTS: Sixteen single-nucleotide polymorphisms (SNPs) met the threshold for significance ($p<5$ e-8). Among these, the top 3 SNPs were located in chr13:94482865 within the GPC6 gene ($p=2.3$ e-9), in chr2:238451126 within the MLPH gene ($p=2.3$ e-9) and chr13:33629446 within the Klotho gene ($p=9.96$ e-9).

CONCLUSION: Several of the genes associated with postoperative kidney dysfunction in this study have intriguing roles in renal pathophysiology and may present novel targets for preoperative screening and perioperative treatment. GPC6, the most significant candidate gene in this study, has previously been associated with blood pressure regulation and arterial stiffness.[3] The GPC6 protein may therefore be involved in mediating the ischemia-reperfusion mechanism of AKI. Klotho, the third most significant candidate gene in the study, encodes a hormonal peptide that may mediate the systemic inflammatory mechanism of postoperative kidney injury and has previously been identified as a potential biomarker and therapy for AKI.[4] In conclusion, our study has identified candidate genes that may be involved in both the ischemia-reperfusion mechanism and the systemic inflammatory mechanism of AKI following cardiac surgery.

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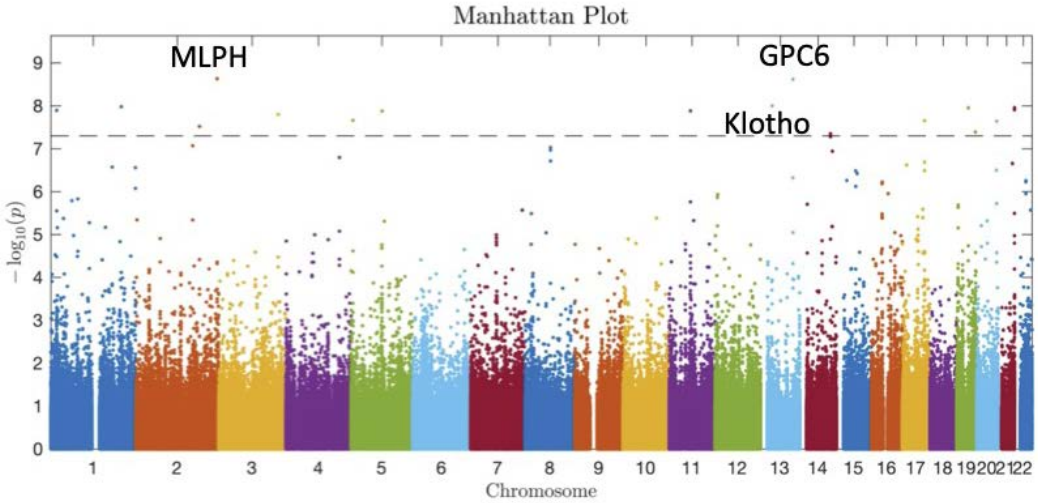

Figure 1: Manhattan Plot depicting -log(P value) as the y-axis and position in genome of each SNP as the x-axis. The threshold for statistical significance ($p < 5x10^{-8}$) is depicted with a dashed line. 16 SNPs rise above the threshold of statistical significance in this study

CRITICAL CARE 8

Plasma extracellular microRNA profiling and their potential role in innate immunity and sepsis

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INTRODUCTION: Sepsis is a critical condition induced by a dysregulated host immune response to infection. The pattern recognition receptors such as Toll-like receptors (TLRs) are an essential part of the innate immunity and recognize pathogen-associated molecular patterns (PAMPs), e.g., endotoxin and viral nucleic acids. While these PAMPs are well known for their roles in triggering host immune response, the contribution of endogenous danger-associated molecules, such as host RNAs and DNAs, in body's innate immune response and in sepsis pathogenesis remains poorly understood. In this study, using small RNA sequencing, we profiled plasma extracellular (ex) miRNAs in mice and humans. We identified miR-146a-5p as one of the most abundant plasma miRNAs in both septic mice and humans. We discovered the underlying molecular mechanism by which miR-146a-5p activates TLR7 and modulate cellular IRAK-1 expression, a kinase critical for innate immune signaling. Finally, we tested the contributory role of miR-146a-5p in the pathogenesis of murine sepsis and its association with clinical manifestations of septic patients.

METHODS: All human and animal studies were approved by the IRB and IACUC, respectively. C57BL/6J mice were subjected to CLP (cecum ligation and puncture), or sham (laparotomy). Plasma RNAs were isolated using Trizol and profiled by small RNAseq. Cytokines were assayed by ELISA. Innate immune cells were analyzed by flow cytometry. Transthoracic echocardiography was performed in non-anesthetized mice to assess cardiac function.

RESULTS: Using small RNA sequencing, we identify that miRNAs are the most abundant RNA species in the plasma and differentially expressed in murine and human sepsis, such as miR-146a-5p. Exogenous miR-146a-5p, but not its double-stranded duplex precursor, induces a strong immunostimulatory response through a newly identified UU-containing nucleotide motif and TLR7 activation, and an immunotolerance by rapid IRAK-1 protein degradation via TLR7→MyD88 signaling and proteasome activation, whereas its duplex precursor acts by targeting 3' UTR of Irak-1 gene via Ago2 binding. miR-146a knockout in mice offers protection against sepsis with attenuated IL-6 storm and organ injury, improved cardiac function, and better survival. In septic patients, the plasma miR-146a-5p concentrations are closely associated with the two sepsis outcome predictors, blood lactate and coagulopathy.

CONCLUSION: This study demonstrates that 1) miRNAs are the predominant RNA biotype in the plasma and markedly altered in sepsis, 2) ex miR-146a-5p stimulates innate immune response via a UU-motif and TLR7 activation, 3) ex miR-146a-5p downregulates IRAK-1 protein through TLR7 and proteasome activation, and 4) Plasma miR-146a-5p is associated with sepsis predictors and plays a role in sepsis. Thus, our study establishes the important role of extracellular miR-146a-5p in innate immune regulation and sepsis pathogenesis.

CRITICAL CARE 9

Role of megalin and sex in AKI-CKD transition due to cardiorenal syndrome type1

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INTRODUCTION: Cardiorenal syndrome type 1 (CRS-1) is acute kidney injury (AKI) due to rapid worsening of cardiac function, and is a common perioperative complication. The megalin-mediated endocytic system is an important component of renal function which may influence AKI and which likely influences development of chronic kidney disease (CKD). Since CKD may be a long-term perioperative outcome, we tested whether megalin deletion affects the severity of CRS-1 and consequential CKD.

METHODS: Male and female proximal tubule-specific inducible megalin deletion mice (iMegKO, LRP2 fl/fl NDRG1-CreERT2) and cre-negative littermate controls received tamoxifen (150 mg/kg) for 5 days, 16 days before cardiac arrest and cardiopulmonary resuscitation (CA/CPR). Urine was collected for 24h after CA/CPR and again 49 days after CA/CPR. Renal function was assessed as glomerular filtration rate (GFR; uL/min/100g body weight) at 24h and 49 days after CA/CPR. Briefly, fluorescein isothiocyanate (FITC)-sinistrin was injected retro-orbitally, then elimination of FITC-sinistrin fluorescence was subcutaneously monitored by using a fluorescence detector (MediBeacon). GFR was calculated from the half-time (t1/2). Significance was assessed by one-way ANOVA with Tukey test, or log-rank test.

RESULTS: All animals had abnormally reduced GFR and oliguria 24h after CA/CPR. Resuscitation time and epinephrine dose were not different between groups. 49-day survival was not different among groups (p=0.66, n=12-14/group). Change in body weight was not different at 24h and 49 days after CA/CPR between groups. Body weight-corrected urine weight (urine weight (g)/body weight (g)x100 (%)) at 24 hours after CA/CPR was not different between iMegKO and cre- littermate control (p=0.17, n=10-14/group; KO male:11.7%, Cont male:10.0%, KO female:11.8%, Con female:6.9%). At 49 days after CA/CPR, urine weight was higher in iMegKO mice than in littermate control in female, but there was no difference in male (p=0.02, n=10/group; KO male: 8.0%, Cont male: 8.7%, KO female: 15.2%, Con female: 6.6%). 24h after CA/CPR, GFR was similar in iMegKO mice and controls (p=0.36, n=5-8/group; KO male: 275.1 uL/min/100gBW, Cont male: 192.0 uL/min/100gBW, KO female: 398.1 uL/min/100gBW, Con female: 446.9 uL/min/100gBW). 49 days after CA/CPR, however, GFR in iMegKO males was preserved compared with control male or iMegKO female (p=0.0001, n=10-11/group; KO male: 1043 uL/min/100gBW, Cont male :827.7 uL/min/100gBW, KO female: 869.1 uL/min/100gBW, Con female: 943.2 uL/min/100gBW).

CONCLUSION: Megalin deletion does not alter susceptibility to or resuscitation from cardiac arrest, survival, or CA/CPR-induced AKI (CRS-1) as indicated by GFR. Megalin deletion ameliorates long-term loss of GFR due to CRS-1 in males, but not in females. This tantalizing sex difference suggests sexually dimorphic mechanisms of AKI-CKD transition, and for the first time implicates this important.

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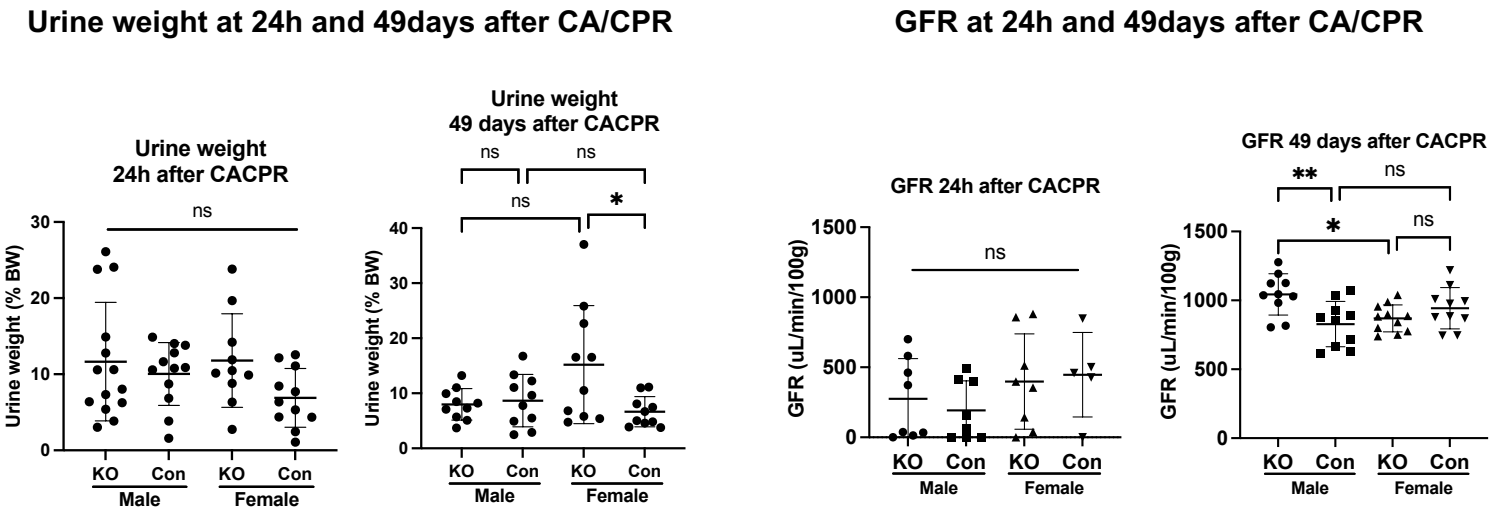

Fig.1

CRITICAL CARE 10

Development and Internal Validation of a Novel Machine Learning-Based Prediction Tool for Postoperative Respiratory Failure

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INTRODUCTION: Postoperative respiratory failure (PRF) is an important surgical complication and quality metric[1-3]. Its incidence after non-cardiac surgery is 0.8-4.2% and this has not changed in two decades[1, 2, 4-7]. One possible reason is a lack of high performing predictive tools. The best supported and AHRQ-recommended preoperative tool, Score for Prediction of Postoperative Respiratory Complications (SPORC1), exhibited somewhat limited accuracy in external validation (area under the receiver operating curve, AUROC, 0.69)[4, 8]. There have been calls for new tools to be developed via machine learning (ML) to better process important pathophysiologic mechanisms[9]. The aim of our study was precisely this.

METHODS: This was a single-center retrospective cohort study of 57,237 adults who had same-day or inpatient non-cardiac, non-labor procedures from 1/2018-6/2021. Exclusions: ASA 6, re-operation within 7 days, or ≥24-hours of invasive ventilation, DNI code status, or tracheostomy preoperatively. The primary composite outcome was a modification of a consensus definition[10] and included: within 7-days postoperative Early Mortality, Prolonged Intubation for ≥24-hours after surgery, or REspiratory Support (EMPIRES) including reintubation, BiPAP, or HFNC. Available predictors included 90 demographic, comorbidity, physiologic, and procedural variables. The total cohort was randomly split into training (70%, 40,066) and validation (30%, 17,171) cohorts. We used the Random Forest (RF) algorithm to predict outcome in the training cohort based on an ensemble of 1000 decision trees. To assess performance of the derived forest in our validation cohort, we estimated the AUROC along with sensitivity, specificity, and PPV corresponding to the optimal threshold for risk based on the Youden index and compared them to SPORC1.

RESULTS: The incidence of EMPIRES in the total cohort was 2,227 (3.9%). In the validation cohort, the derived RF algorithm exhibited an AUROC of 0.90 (95% CI 0.89-0.92) compared to 0.79 (95% CI 0.77-0.80) for SPORC1 ($P<0.0001$ for difference). Sensitivity, specificity, and PPV using optimal cut-points to classify high vs. low risk patients were as follows: 82%, 86%, and 19% for the EMPIRES score compared to 82%, 56%, and 7% for SPORC1. The top 5 most important variables for the RF model were as follows: surgical service; scheduled surgical time; preoperative oxygen support; preoperative hospital length of stay; and ASA score. Model accuracy and performance were equivalent with both normal value imputation and Multiple Imputation by Chained Equations approaches.

CONCLUSION: Compared with an existing PRF prediction score recommended by AHRQ, our novel, ML-based PRF prediction score EMPIRES had superior accuracy and performance for detecting within 7-day post-operative Early Mortality, Prolonged Intubation for ≥24-hours post-operatively, or REspiratory Support including reintubation. While not externally validated, this accuracy and performance are superior to internal validation results reported for all other PRF scores [9]. More importantly, this score utilizes readily available EHR data, thus increasing feasibility for automated preoperative prediction and clinical decision support. Next steps include external and prospective validation of this prediction instrument.

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CRITICAL CARE 11

Motion Analysis Tracks Improvements in Navy SEAL Combat Medics Performing Point-of-Care Ultrasound

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INTRODUCTION: Point of care ultrasound (POCUS) is commonly employed for imaging of the heart, lungs and abdomen in the clinical setting. Transthoracic echocardiography (TTE) is a critical component of POCUS that has been recently employed in austere environments by Navy SEAL combat medics for triage and diagnosis[1]. Despite its utility in both the clinical and combat settings, training for TTE remains largely unstandardized with regard to feedback to learners and indicators of proficiency[2,3]. Our group sought to employ motion analysis as a tool to measure progression in the performance of TTE by two groups of combat medics. We hypothesized that participants would exhibit significant improvements in a comprehensive series of motion metrics. We also hypothesized that motion metrics would exhibit an inverse relationship with expert ratings recorded by attending anesthesiologists.

METHODS: Two groups of combat medics (5 and 10 individuals, respectively) underwent 5-day training courses in which they were taught TTE by a team of attending anesthesiologists. Participants used the same ultrasound probe, which was equipped with an electromagnetic sensor to record their motions. They each performed 2 rapid ultrasound for shock and hypotension (RUSH) exams for the latter 4 days of the course, totaling 8 trials per person. Three attending anesthesiologists graded the exams using a global rating scale (GRS). A generalized estimating equation (GEE) was used to analyze the trend of motion metrics exhibited by the ultrasound probe across all trials. These metrics included total distance travelled (path length), movements performed (translational motions), rotation performed (rotational sum) and time. Pearson correlation coefficients were assessed to determine the degree of correlation amongst motion metrics and expert ratings.

RESULTS: Both groups exhibited negative trends in path length, translational motions, rotational sum, and time ($p < 0.001$) (Table 1). Expert ratings also significantly improved in all aspects ($p < 0.001$). Pearson correlation coefficients revealed weak to strong, inverse correlations amongst motion metrics and expert ratings (Table 2).

CONCLUSION: Motion metrics and expert ratings revealed significant improvements in Navy SEAL combat medics performing TTE. Motion metrics decreased as expert ratings improved, and exhibited weak-to-strong, inverse correlations. Objective analysis of performance may benefit trainees without access to formal training and feedback from experienced sonographers.

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Table 1: Trends of Motion Metrics Across Trials for Overall RUSH Exam

Metric	GEE Coefficient (95% CI)	p-value
Path Length (cm)	-269.49 (-327.06 to -211.92)	p < 0.001
Translational Motions	-326.30 (-437.59 to -215.00)	p < 0.001
Rotational Sum (degrees)	-3177.89 (-3859.85 to -2495.93)	p < 0.001
Time (s)	-34.53 (-40.97 to -28.09)	p < 0.001

RUSH: Rapid Ultrasound in Shock and Hypotension; GEE: Generalized estimating equations; CI: Confidence interval

Table 2: Correlation Coefficients between Motion Metrics and GRS Items

Cohort	Metric	Image finding	Image fine-tuning	Speed	Final Image Accuracy	Global Assessment
All	Path Length (cm)	-0.47 (p < 0.001)	-0.36 (p = 0.001)	-0.52 (p < 0.001)	-0.42 (p < 0.001)	-0.46 (p < 0.001)
	Translational Motions	-0.56 (p < 0.001)	-0.60 (p < 0.001)	-0.52 (p < 0.001)	-0.53 (p < 0.001)	-0.56 (p < 0.001)
	Rotational Sum (degrees)	-0.51 (p < 0.001)	-0.45 (p < 0.001)	-0.53 (p < 0.001)	-0.45 (p < 0.001)	-0.49 (p < 0.001)
	Time (s)	-0.64 (p < 0.001)	-0.60 (p < 0.001)	-0.67 (p < 0.001)	-0.58 (p < 0.001)	-0.65 (p < 0.001)

GRS: Global Rating Scale

Fig. 2

CRITICAL CARE 12

Protease activity profiling as a fast tool for ARDS risk assessment and monitoring

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INTRODUCTION: The acute respiratory distress syndrome (ARDS) is one of the most serious pulmonary complications of critically ill patients and results in catastrophic lung failure with high mortality rates[1]. Although advances in supportive care and lung-protective mechanical ventilation have improved outcomes[2], no targeted therapies and molecular tools for early recognition at the bedside currently exist. Neutrophil influx is a hallmark of ARDS and is associated with the release of tissue-destructive immune effectors[2], such as matrix metalloproteases (MMPs) and membrane-anchored metalloprotease disintegrins (ADAMs). In ARDS progression, proteases are readily activated upon pulmonary insults and their catalytic activities reflect cellular responses to lung damage[3]. Thus, we hypothesize that tracking of ARDS-associated proteases using fluorescent reporter peptides in lung fluids could be a sensitive and quick method to allow stratification of ARDS patients. Ultimately, we unravel the contribution of neutrophil ADAM8 to ARDS pathology in preclinical mouse models and provide evidence that ADAM8 inhibition might allow fine-tuning of neutrophil responses for therapeutic gain.

METHODS: Proteolytic signatures in lung fluids of ARDS patients were measured using fluorescent reporter assays. Short polypeptides with amino acid sequences based on natural protease cleavage sites and flanked by FRET-paired fluorophores were used to track real-time proteolytic activities as changes of fluorescence over time[4]. The function of ADAM8 in ARDS pathology was investigated by pharmacological and genetic ADAM8 inhibition in mice. Intravital microscopy of inflamed mouse lungs[5] was performed to observe immune cell responses in vivo. Mice with pulmonary Pseudomonas aeruginosa infection were evaluated for morbidity, lung injury and bacterial load to validate ADAM8 inhibition as a therapeutic strategy.

RESULTS: In two ARDS cohorts, we analyzed lung fluid proteolytic signatures and found that the detection of proteolytic activities was rapid (obvious quantitative differences within 20-30 min), sensitive and simpler than e.g. ELISA. We identified that ADAM8 activity was positively correlated with disease severity. By intravital imaging of the lung, we observed that ADAM8 inhibition in mice resulted in impaired neutrophil transmigration. In mouse pneumonia models, both genetic deletion and pharmacologic inhibition of ADAM8 attenuated neutrophil infiltration and lung injury while improving bacterial containment. The alterations of neutrophil function were not attributable to impaired proteolytic function but resulted from reduced intracellular signaling that suppressed neutrophil motility. The favorable effect of blocking ADAM8 without compromising bacterial control validates ADAM8 as a therapeutic target for ARDS.

CONCLUSION: We conclude that advancing the tracking of protease activities to point-of-care tests could be a powerful tool for quick risk profile assessment and guidance for therapeutic interventions. Our study provides evidence that ADAM8 drives neutrophil recruitment in ARDS and constitutes a specific target for ARDS therapeutic development.

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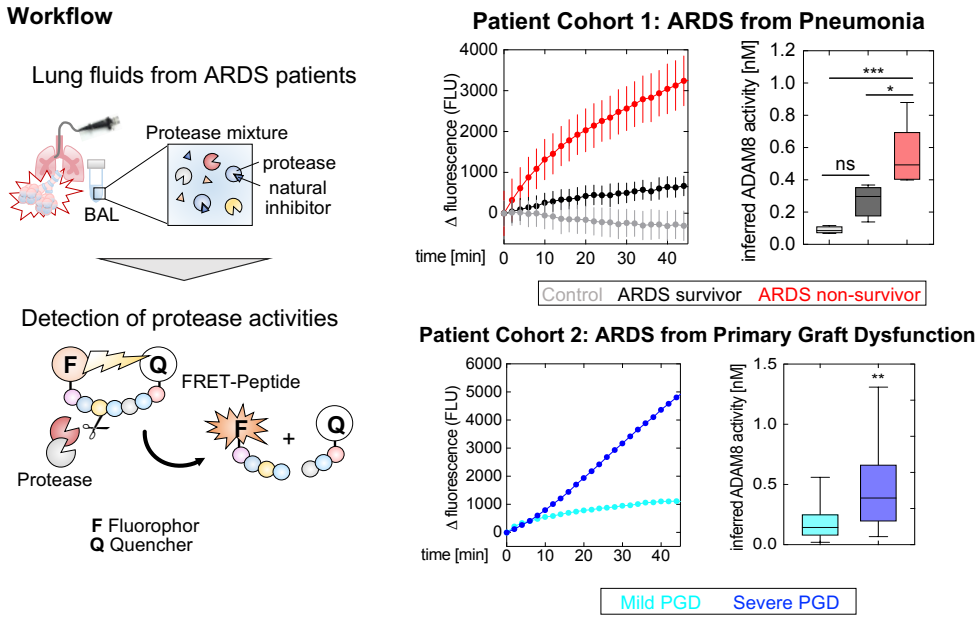

Fig. 1: Protease activities can be detected in lung fluids from ARDS patients and correlate with disease severity. We analyzed lung fluid proteolytic signatures using fluorescent reporter peptides in 2 patient cohorts, representative time-lapse fluorimetries of healthy control BAL (grey) and BAL from patients with ARDS from pneumonia (black; ARDS survivor, red; ARDS non-survivor) are shown in the upper panel. The lower panel shows time-lapse fluorimetries of BAL of patients with mild (cyan) or severe primary graft dysfunction (PGD) after lung transplantation (blue).

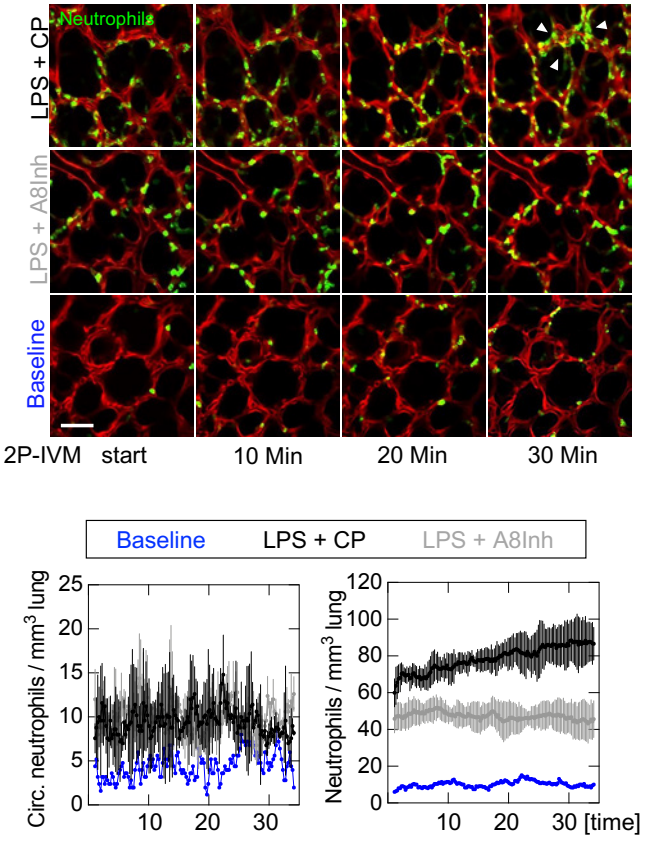

Fig. 2. Pharmacological inhibition of *Adam8* impairs neutrophil motility *in vivo*. MRP8-Cre x mTmG mice were given an ADAM8 inhibitor or control compound (CP) and 2-photon lung intravital imaging (2P-IVM) was performed for 30 minutes at 3 hours after the LPS challenge. Representative images of neutrophil influx (MRP8+, green) during inflammation and at baseline are shown, scale bar, 50µm (upper panel). Numbers of circulating neutrophils and neutrophils migrating through the lung over time are plotted (lower panel).

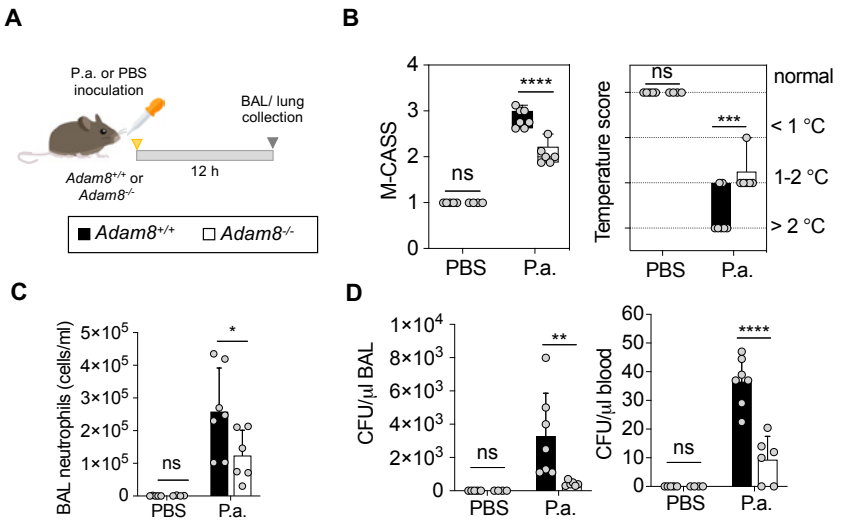

Fig. 3: Genetic deletion of *Adam8* protects mice against severe Pseudomonas aeruginosa infection. **(A)** *Adam8*-deficient mice (*Adam8*$^{-/-}$, white bars) or littermate controls (*Adam8*$^{+/+}$, black bars) were intranasally instilled with Pseudomonas aeruginosa (P.a., strain PA103) or vehicle control (PBS), and sacrificed 12h after infection. **(B)** Morbidity was scored using the Mouse Clinical Score for Sepsis (M-CASS) and temperature scoring was assessed as a surrogate parameter for survival, indicating less severe manifestation of pneumonia in *Adam8*-deficient mice. **(C)** Neutrophil numbers in the BAL were reduced in *Adam8*$^{-/-}$ mice. **(D)** Despite attenuated leukocyte recruitment in *Adam8*$^{-/-}$ mice, less systemic spreading and improved clearance of extracellular P.a. was observed, as reflected by reduced colony forming units (CFU) in the BAL and blood.

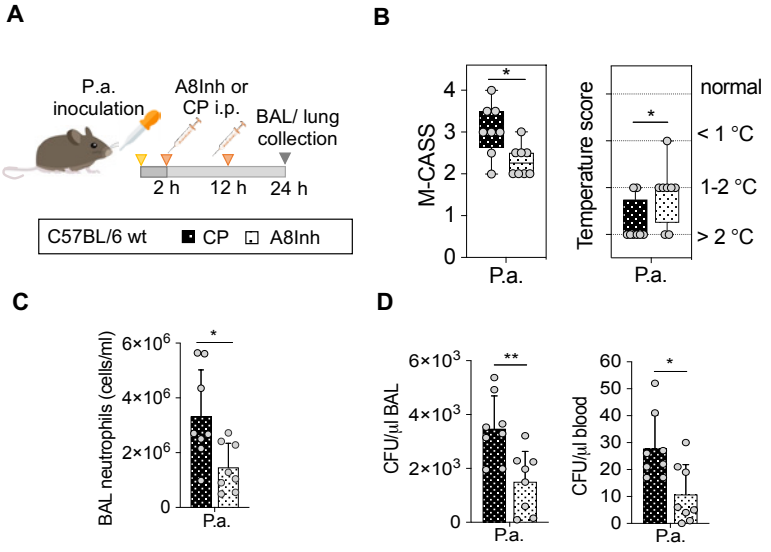

Fig. 4: Pharmacological ADAM8 inhibition during pulmonary Pseudomonas aeruginosa infection reduces disease severity. **(A)** WT mice with pulmonary P.a. infection were treated with an A8Inh at 2h and 12h after inoculation with euthanasia at 24h (*A8Inh*, dotted white bars; CP, dotted black bars). (B) The inhibition of ADAM8 reduced the severity of pneumonia and **(C)** BAL neutrophils were reduced, while **(D)** bacterial clearance was improved, as demonstrated by reduced cfu counts in the BAL and blood.

CRITICAL CARE 13

Baseline metabolic dysregulation and response heterogeneity to pulmonary vasoreactivity in right heart failure after cardiac surgery: Secondary analysis of the INSPIRE-FLO clinical trial

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INTRODUCTION: To protect against right heart failure (RHF) as a major driver of shock after cardiac surgery, inhaled pulmonary vasodilators are initiated to lower pulmonary vascular resistance (PVR) to improve right ventricular performance. However, there is marked heterogeneity in the pulmonary vasoreactive response to these inhaled agents. Given the central role of metabolism in cardiac efficiency and failure, and prior work identifying impaired mitochondrial fatty acid √ü-oxidation in heart failure, we hypothesized that baseline plasma metabolites would be associated with response to inhaled pulmonary vasodilators after cardiac surgery.

METHODS: We leveraged a biospecimen repository associated with the INSPIRE-FLO randomized controlled trial that compared two inhaled pulmonary vasodilators in major cardiac surgery (NCT03081052). We selected 63 patients with precapillary pulmonary hypertension before surgery (baseline), diagnosed by mean pulmonary arterial pressure > 20 mm Hg and PVR ≥ 3 Wood units.[1] Targeted profiling of > 200 metabolites (MxP® Quant 500 kit, Biocrates) was performed in baseline plasma. Principal components analysis (PCA) was used for dimensionality reduction of metabolites; generalized linear models were used to determine the nominal association of baseline factors with clinical endpoints, including percent change in PVR over the one day after surgery, response phenotype (classified as responders vs. nonresponders to the allocated inhaled agent, based on PVR < 3 Wood units vs. PVR remained ≥ 3 Wood units at one day after surgery) and RHF development. In left ventricular assist device recipients alone, factors were assessed for association with the European registry RHF risk score.[2]

RESULTS: Of 63 patients, 28 were classified as responders and 35 as nonresponders. PCA identified twenty-one factors with metabolites clustering in relevant biologic pathways (Table 1). Of these, two factors, weighted heavily with glycerophospholipids (GPs) and amino acids (glu, asp, ala, gln), were nominally associated with both percent change in PVR and response phenotype. While none of the factors were linked to RHF development for the full cohort, three factors, heavily weighted with GPs, were nominally associated with the RHF risk score in left ventricular assist device recipients.

CONCLUSION: In this nested cohort of pulmonary hypertensive patients from a clinical trial in cardiac surgery, we found that GPs and select amino acids in baseline plasma were associated with vasoreactive response to inhaled pulmonary vasodilators. Glycerophospholipids alone were also associated with RHF risk scores in left ventricular assist device recipients. Although GPs are essential to mitochondrial membrane integrity and have been prominently featured in plasma profiles of heart failure,[3] the key amino acids in our study may be indicative of underlying dysregulated hepatic metabolism[4] and critical illness that may predispose to RHF. Thus, targeted profiling in paired right ventricular myocardium and plasma is needed to better characterize metabolic dysregulation in pulmonary hypertensive patients that develop RHF after cardiac surgery.

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Table 1. Summary of principal components factors by metabolite class and clinical endpoints.

	[a]Metabolite Class								[b]Clinical Endpoints			
Factor	AC	AA	Ceramides	Dihydroceramides	FA	Glycerophospholipids	Glycosylceramides	Sphingolipids	% Δ PVR	Phenotype	RHF	[c]EuroMACS
1	5	1	20	0	0	8	26	13	NS	NS	NS	NS
2	30	0	7	1	0	13	0	0	NS	NS	NS	NS
3	5	2	0	0	0	68	1	3	0.08	NS	NS	NS
4	0	0	12	0	0	8	0	3	NS	NS	NS	NS
5	0	17	0	0	0	0	0	0	NS	NS	NS	NS
6	0	0	0	0	0	4	0	2	NS	NS	NS	0.02
7	12	0	0	0	0	0	0	0	NS	NS	NS	NS
8	0	1	0	0	0	8	0	0	NS	NS	NS	NS
9	0	0	0	0	0	4	0	0	0.03	<0.05[d]	NS	NS
10	0	0	0	0	5	0	0	0	NS	NS	NS	NS
11	0	2	0	0	0	0	0	0	NS	NS	NS	NS
12	0	4	0	0	0	0	0	0	0.03	0.01	NS	NS
13	1	1	0	0	0	0	0	0	NS	NS	NS	NS
14	0	0	0	0	1	2	0	0	NS	NS	NS	0.01
15	0	0	0	0	0	0	0	0	NS	NS	NS	
16	0	0	1	0	0	0	0	0	NS	NS	NS	NS
17	2	0	0	0	0	0	0	0	NS	NS	NS	NS
18	0	0	0	0	0	1	0	0	NS	NS	NS	0.02
19	1	0	0	0	0	0	0	0	NS	NS	NS	NS
20	0	0	0	0	0	0	0	0	NS	NS	NS	NS
21	0	0	0	0	0	5	0	0	NS	NS	NS	NS

[a]The weight of each metabolite class per factor is indicated by the number of metabolites present. The glycerophospholipid class, which combined phosphotidylcholines and lysophostidylcholines, was the predominant metabolite class that was associated with both (i) vasoactive response, measured as percent change in PVR and response phenotype for the full cohort, and (ii) EuroMACS RHF risk score for LVAD recipients only.
[b]Clinical endpoints associated with each principal components analysis-derived metabolite factor are indicated by nominal p-values that are unadjusted for covariates or multiple comparisons.
[c]EuroMACS RHF risk score preoperatively predicts RHF development after LVAD with a C-statistic of 0.70 (95% CI: 0.67 to 0.73).[2]
[d]Nominal (unadjusted) p-value is 0.047.

AC, Acylcarnitines; AA, Amino acids; EuroMACS, *Euro*pean registry for patients with *Me*chanically-*A*ssisted *C*irculatory *S*upport; FA, Fatty acids; % Δ PVR, Percent change in PVR from before to after inhaled pulmonary vasodilator therapy; RHF, Right heart failure.

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CRITICAL CARE 14

Association of ICU-Opioid Exposure with Chronic Pain after Critical Illness

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INTRODUCTION: Chronic pain after critical illness is common and interferes with quality of life in survivors, but data are limited on its modifiable risk factors. Exposure to high-dose opioids has been associated with worse pain scores and opioid requirements in the perioperative setting, yet its association with the development of chronic pain after critical illness is incompletely understood. We sought to determine the association between opioid exposure during ICU admission and chronic pain at 6 months following ICU discharge.

METHODS: In this nested cohort within the MENDS2 randomized controlled trial of sedation with dexmedetomidine versus propofol in adult mechanically ventilated ICU patients admitted for sepsis, we collected demographic data and details of the in-hospital course including opioid use. In survivors, we used the Brief Pain Inventory (BPI) to assess rates of chronic pain 6 months after hospital discharge. We used logistic regression to evaluate the independent association of ICU opioid exposure (in fentanyl equivalents) with chronic pain (pain lasting for 3 months or longer), adjusting for potential confounders including age, sex, pre-admission opioid use or diagnosis of chronic pain, Sequential Organ Failure Assessment (SOFA) score, and ICU length of stay.

RESULTS: After accounting for ICU and post-hospital deaths, and some loss to follow up, we obtained BPI outcomes in 152 survivors. Median age (interquartile range) was 58 (48-66), with 54% male, median SOFA score of 9.5 (7-11.2), 59% medical admissions and a median ICU length of stay of 7 days (4-11). Median dose of fentanyl in the ICU was 6,000mcg (2,000-13,000). Of the 152 patients, 88 (58%) reported having pain at 6 months, with 51 (58%) noting it was chronic in nature. Of those with chronic pain, 20 (39%) stated their pain started after their ICU admission, with 13 (65%) specifically relating their pain to their ICU admission. The average pain score of those with chronic pain was 6 (4.5-7). In the regression analysis, we were unable to detect an association between cumulative dose of fentanyl in the ICU and chronic pain (odds ratio [OR 95% confidence interval], 0.78 [0.52-1.18]; $p = 0.25$). A history of chronic pain (OR 2.9 [1.27-6.69]; $p = 0.01$) was associated with increased risk of chronic pain at 6 months, while older age was significantly associated with decreased odds of chronic pain (OR 0.73 [0.61 - 0.87]; $p < 0.001$).

CONCLUSION: Chronic pain after critical illness is common, with a significant portion of patients developing chronic pain directly related to their ICU admission. We were unable to demonstrate an association between opioid exposure in the ICU and increased risk of chronic pain at 6 months, although younger age and a prior history of pain or opioid prescription was associated with increased chronic pain. Further studies with adequate sample size are needed to determine modifiable risk factors to mitigate chronic pain after critical illness.

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CRITICAL CARE 15

Arterial Blood Pressure Waveform Based Cardiac Output Analysis Correlates with Continuous Pulmonary Artery Thermodilution In Post Cardiac Surgery ICU Patients Including Those With Arrhythmia

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INTRODUCTION: Cardiac output estimation is a critical component of monitoring critically ill patients after cardiac surgery. We sought to access the agreement between a traditional continuous pulmonary artery catheter guided thermodilution method and cardiac output estimation using a novel method that performs an analyses of multiple beats of the arterial blood pressure waveform.

METHODS: After institutional review board approval, we prospectively enrolled adult cardiac surgical patients recovering post-operatively in the cardiovascular surgical intensive care unit of our tertiary care university hospital. Eligible patients had a functioning pulmonary artery catheter (PAC) and a radial artery line. Continuous thermodilution cardiac output measurements (CO-CTD) obtained via the PAC were recorded once every minute. The arterial blood pressure waveform was fed, via a reusable cable connected to the bedside patient monitor, into a device that implements the novel BP waveform analysis method. The device analyzes multiple beats of an arterial line BP waveform over longer time intervals (20 s) and provides continuous CO estimates (CO-LTI). Both CO-CTD and CO-LTI were averaged over 1 hour, in order to compare hemodynamically stable periods and to reduce the influence of delayed responses to hemodynamic changes. Blood pressure waveform segments were visually inspected by two anesthesiologists blinded to cardiac output measurements, to determine persistent arrhythmia or extrasystoles. These data segments constituted the arrhythmia subgroup.Correlation between paired values of CO-CTD and CO-LTI was computed within subjects, taking repeated observations into account and removing the between subject variability. Agreement between CO-CTD and CO-LTI was assessed via Bland-Altman analysis, accounting for multiple observations within patients. Similar analyses were performed on data segments containing arrhythmia or extrasystoles (arrhythmia subgroup).

RESULTS: Hundred patients were enrolled, of which 11 were excluded due to unavailability of simultaneous CO-CTD and CO-LTI readings. Ten patients were further excluded due to underdamped arterial BP waveforms evident via square wave tests, dP/dt max and waveform inspection4. After exclusions, 927 hours of data from 79 patients was analyzed. Mean CO-CTD was 5.29 ± 1.14 L/min and mean CO-LTI was 5.36 ± 1.33 L/min. Paired observations showed a moderate correlation (r= 0.64, Fig. 1). Bland-Altman analysis showed a mean difference of 0.04 ± 1.04 L/min (bias ± precision), with 95% limits of agreement from -2.00 to 2.08 L/min (Fig. 2), and a percentage error of 38.2% (Fig. 2). In the arrhythmia subgroup, consisting of data from 26 patients, mean value of CO-CTD across all subjects was 4.95 ± 0.80 L/min. Mean CO-LTI was 5.04 ± 1.07 L/min. Correlation between CO-CTD and CO-LTI was moderate (r = 0.64, Fig. 3). Bias ± precision per Bland-Altman analysis was 0.14 ± 0.90 L/min. Limits of agreement were -1.63 to 1.91 L/min (Fig. 4). The percentage error was 35.4%.

CONCLUSION: Cardiac output measurements using a novel multi-beat analysis of radial artery pressure waveform are reasonably correlated with the traditional more-invasive pulmonary artery thermodilution guided cardiac output measurements. Our results agree with a previous validation of the LTI method in 31 post-cardiac surgery patients in the ICU, where a percentage error of 40.7% was reported. Importantly, results were similar in the arrhythmia subgroup, indicating that the agreement of CO-LTI to CO-CTD is not affected by arrhythmia. Intensivists and anesthesiologists have the option of using a relatively non-invasive, easy to use method of cardiac output estimation in post cardiac surgery patients where arrhythmia is common.

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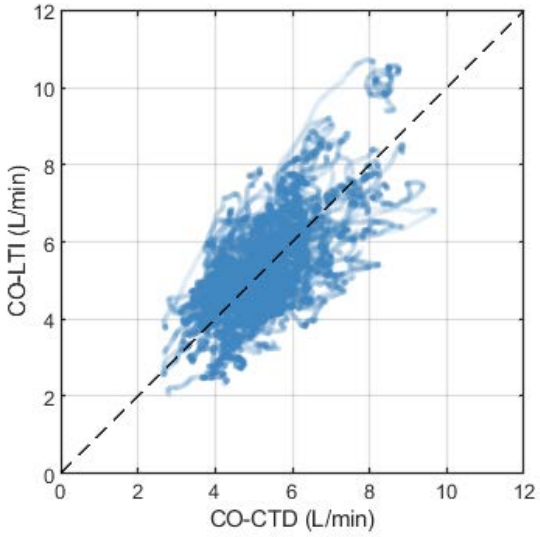

Fig. 1

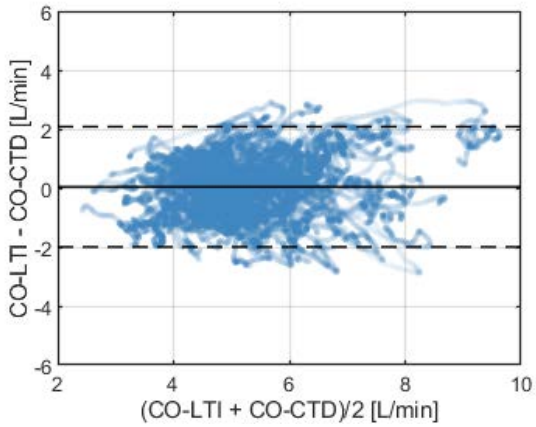

Fig. 2

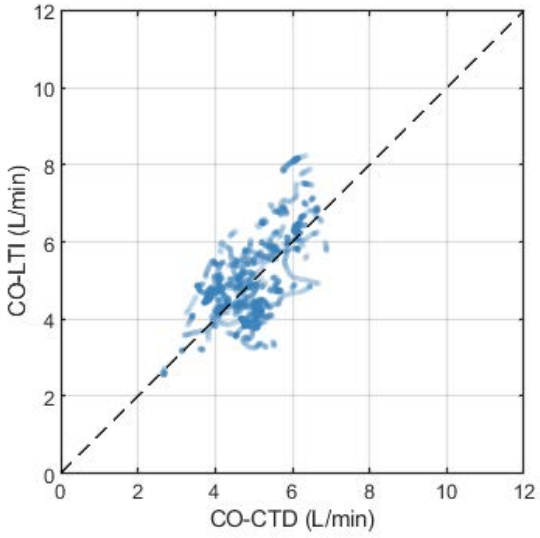

Fig. 3

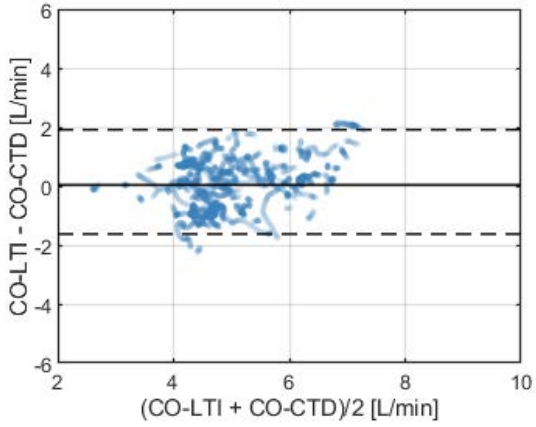

Fig. 4

CRITICAL CARE 16

Comparing Outcomes in Patients Undergoing Elective Vs. Non Elective Cardiac Surgery with Subsequent Multiple Organ Dysfunction Syndrome (MODS)

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INTRODUCTION: High risk cardiac surgeries (CS) have long been known to be associated with increased morbidity and mortality. Often, this will be due to multiple organ dysfunction syndrome (MODS). Defined as a development of potentially reversible physiologic derangement involving multiple organs, MODS can quickly progress to organ failure subsequently requiring multiorgan support (MOS)[1]. We utilized the largest health care discharge database to compare outcomes and overall trends in patients who underwent CS and subsequently developed organ failure with and without organ support stratified by elective vs. non elective surgical status[2].

METHODS: We conducted a retrospective analysis of patients undergoing cardiac surgery from 2008 to 2018 using the Premier, Inc. database. We utilized ICD-9 and 10 codes to determine patients who had undergone high-risk CS, and developed MODS (defined as cardiac, renal and respiratory failure) (Table 1). Procedure charge codes identifying need for vasopressor or mechanical circulatory support, invasive ventilation, and hemodialysis were utilized to identify patients requiring multi organ support. Our primary outcomes compared the mortality rate and average length of stay in patients having elective vs. non elective surgery in patients with organ failure with and without support. Chi-square analysis was utilized for categorical variables, while 2 tailed unpaired t-test was used for continuous variables.

RESULTS: Out of 265,292 patients undergoing high risk cardiac surgery from 2008 to 2018, 31,557 patients had three organ failure. Patients undergoing elective CS and developing organ failure were admitted for an average of 4 less days compared to their non-elective counterparts (median LOS 13.0 days vs. 17.0 days, $P<0.0001$). Furthermore, they also had a lower all-cause mortality rate (18.7% vs. 22.7%, $p<0.0001$). For patients who required three organ support, there was an overall decreased length of stay (median LOS 10.0 days vs. 17.0 days, $p<0.0001$), as well as a decreased mortality rate (16.4% vs. 20.0%, $p<0.0001$) in patients who underwent elective surgery (Table 2). MOS increased in both elective and non-elective cohorts (Figure 1). Of patients requiring MOS, mortality diverged, decreasing in the elective surgical population but increasing in non-elective (Figure 2). Elective and non-elective surgical patients had an overall increasing comorbidity burden annually from 2008 to 2018 (Figure 3).

CONCLUSION: Aggressive interventions following CS have been increasing over time. While patients needing MOS who underwent elective CS had improved mortality, suggesting that aggressive interventions led to improved outcomes, patients who underwent non-elective CS had worse mortality. It is possible that more aggressive interventions are being performed post-operatively without the clinical benefit. This demonstrates an opportunity for early goals of care conversations and the questionable benefit of life-sustaining interventions in certain populations following high-risk CS.

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MODS in Cardiac Surgery Tables and Figures

Table 1: ICD-9 and 10 Codes for Diagnosis of Cardiac, Pulmonary and Renal Failure

Cardiac/shock	Pulmonary	Renal
ICD9—785.5, 785.50, 785.51, 785.52, 785.59, 427.5, 998.00, 669.1, 276.2, 995.92, 998.01, 998.02, 998.09 **ICD10** –R57.0, R57.1, R57.2, R57.8, R57.9, R65.21, T81.10, T81.11, T81.12, T81.19, T79.4, A48.3, I46.2, I46.8, I46.9, E87.2	**ICD9** –96.7, 96.70, 96.71, 96.72, 518.5, 518.51, 518.52, 518.53, 518.81, 518.82, 518.84, 518.0, 518.7, 799.1 **ICD10** – R09.2, J96.0, J96.00, J96.01, J96.02, J96.2, J96.20, J96.21, J96.22, J96.9, J96.90, J96.91, J96.92, J80, J95.2, J95.1, J95.82, J95.821, J95.822, Z99.1, J98.19, R06.03, J95.3, 5A1935Z, 5A1945Z, 5A1955Z	**ICD9** –584, 584.5, 584.6, 584.7, 584.8, 584.9, 39.95, 586 **ICD10**—N17.2, N17.8, N17.9, N17.0, N17.1, Z99.2, N19, 5A1D70Z, 5A1D80Z, 5A1D90Z,

Table 2: Length of Stay and Mortality Rate in Organ Failure and Organ Support Population

Organ Failure					Organ Support				
	Elective (N=10001)	Nonelective (N=21556)	Total (N=31557)	p value		Elective (N=5645)	Nonelective (N=10266)	Total (N=15911)	p value
LOS (Median days)	13.0	17.0	16.0	<0.0001[1]	**LOS (Median days)**	10.0	17.0	15.0	<0.0001[1]
Death	1771 (17.7%)	4477 (20.8%)	6248 (19.8%)	<0.0001[2]	**Death**	925 (16.4%)	2053 (20.0%)	2978 (18.7%)	<0.0001[2]

[1]Kruskal Wallis [2]Chi-Square

Figure 1: Proportion of patients who received multi organ support by year.

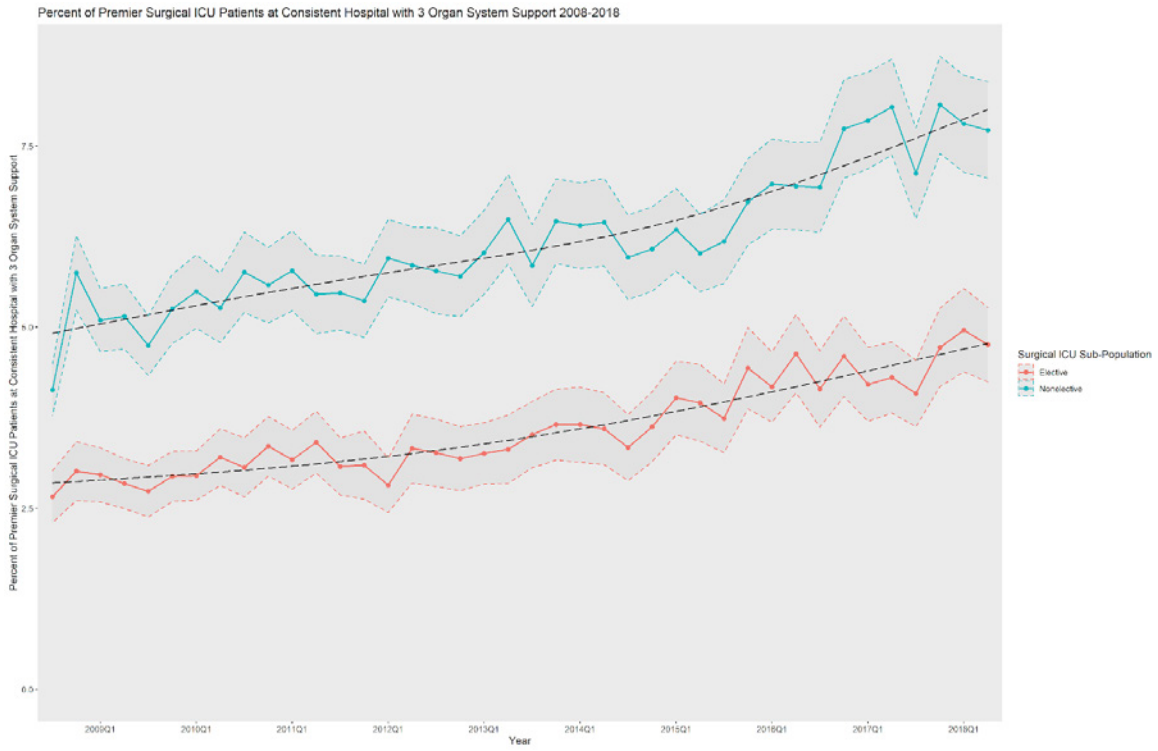


Figure 2: Proportion of patients who received MOS and died or were discharged to hospice.

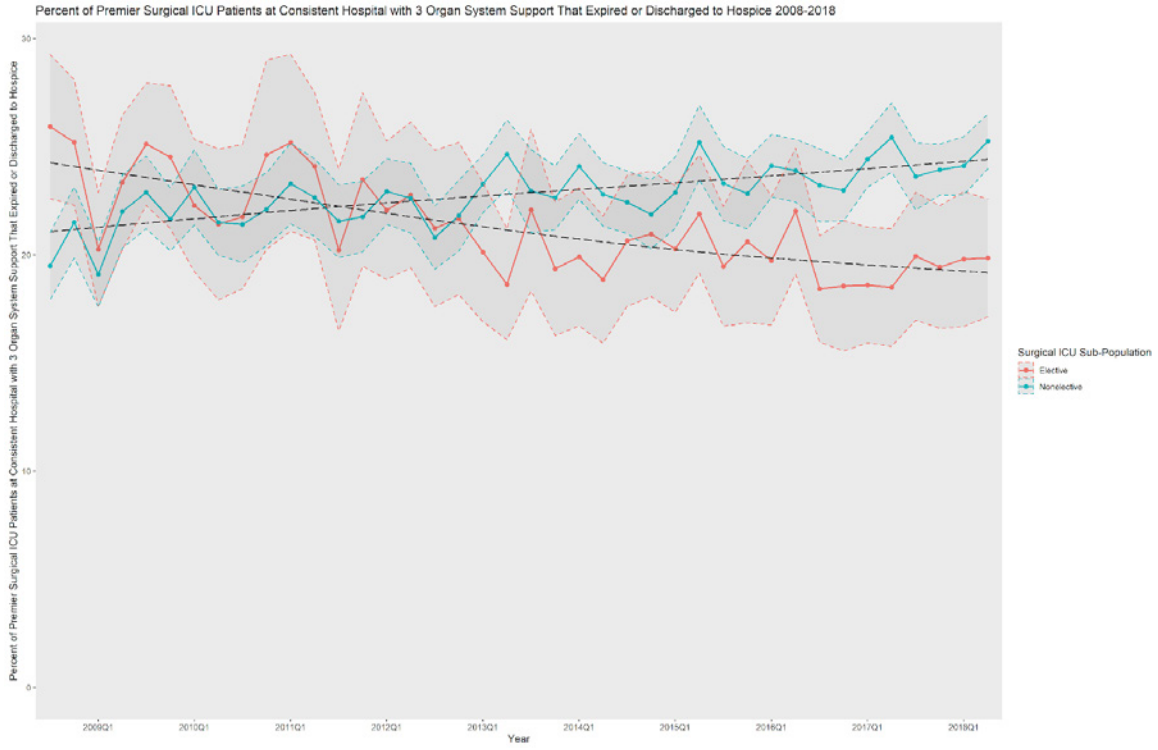
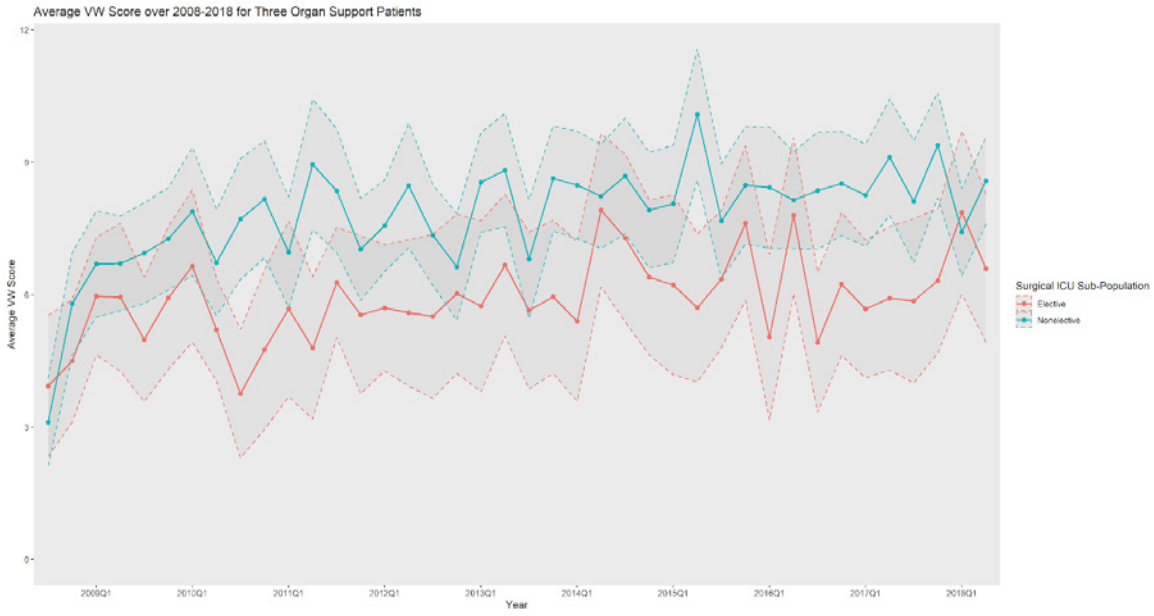


Figure 3: Average vW comorbidity index score for patients who received MOS by year



CRITICAL CARE 17

Initial Pulse Oximetry Readings in Patients Suspicious for SARS-CoV-2 (COVID-19): A Predictor for Hospital Death?

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INTRODUCTION: Early recognition of patient deterioration has been identified as the primary successful determinant of medical intervention.[1, 2] However, recognition of patient deterioration requires measurements with timely decisions based upon these values[3-6] as tissue hypoxia can lead to death under stress-load conditions.[7] We examined the initial vital signs assessments in the Emergency Department (ED) in patients suspicious for COVID-19 and who were subsequently admitted to the ICUs at Ochsner Health.

METHODS: Following IRB approval, initial vital signs in all patients 18 years and older with a diagnosis of COVID-19 were reviewed during ED admission leading to transfer to the COVID ICU. These values underwent multivariable and recursive partitioning analyses. Probability values for all frequentist tests were set at <.005 for statistical significance to minimize the risk for false discovery rates.[8]

RESULTS: In this preliminary study of 121 patients, the overall hospital mortality rate was 22.3 95%CI 15.8-30.5%. The initial vital signs assessments in the ED were entered into a nominal logistic fit model for hospital mortality. The results of that model are shown in Table 1. Temperature, heart rate, respiratory rate, systolic and diastolic blood pressures were not statistically associated with hospital mortality (Table 1). In contrast, pulse oximetry (SpO2) was statistically associated with hospital mortality ($\chi 2=8.1$, P=0.0045). The misclassification rate was 24%. The relationship of hospital mortality to initial SpO2 readings are shown in Figure 1. A progressive increase in hospital mortality was observed with decreasing SpO2 values (Fig. 1). Cut-points for initial SpO2 values based upon hospital mortality were calculated using recursive partitioning and the results of that analysis are shown in Figure 2. A cut-point of 88% identified two groups at different risk for hospital mortality (Fig. 2).

CONCLUSION: These preliminary results in patients suspicious for COVID-19 suggest that SpO2 values during initial ED assessment require earlier attention by healthcare personnel.

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Figure 1

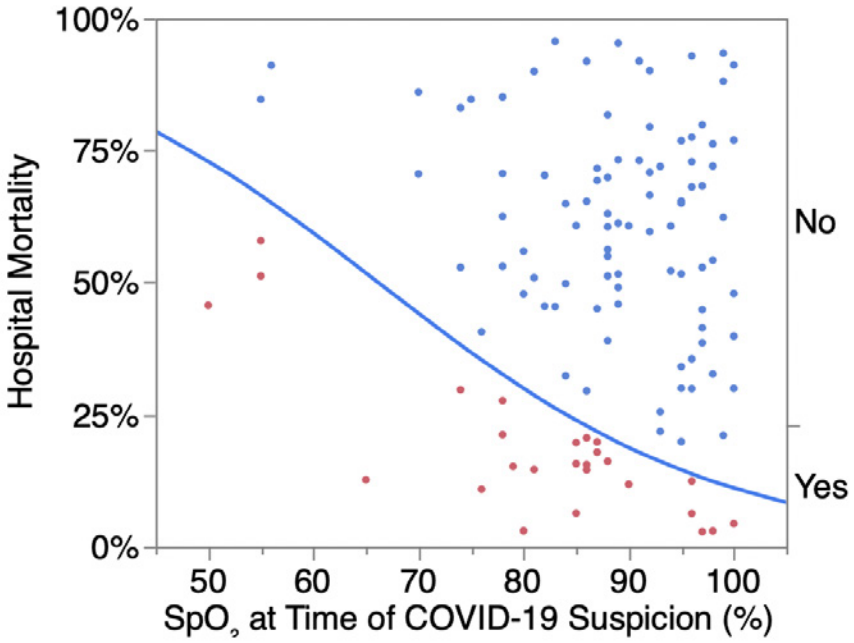
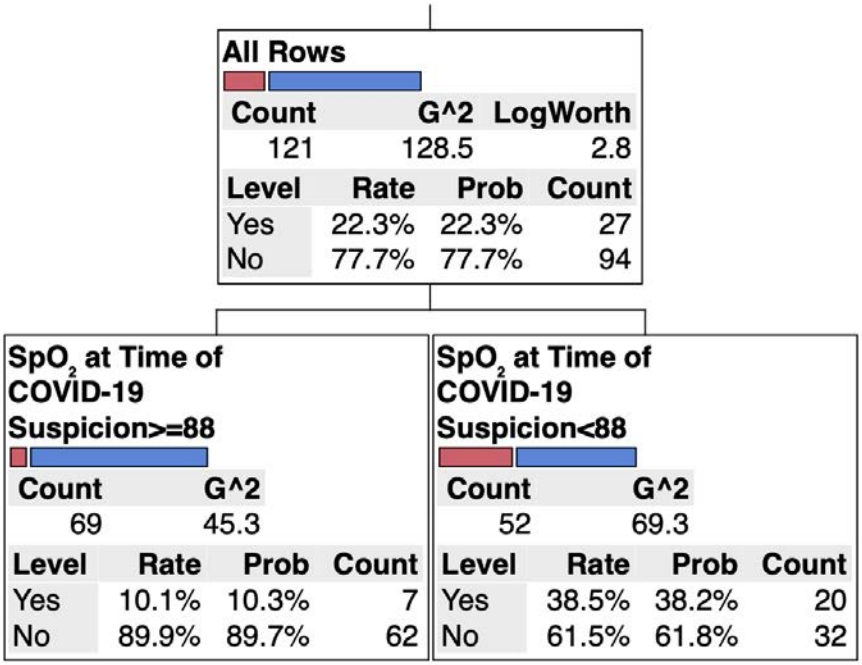


Figure 2



Recursive Partitioning of S_pO_2 readings during initial Emergency Department assessment in patients suspicious for COVID-19. Upper box: the overall incidence of hospital mortality was 22.3% in this patient population. When S_pO_2 was greater than 88%, the incidence of hospital mortality decreased to 10.1% (lower, left box). When S_pO_2 was <88%, the incidence of hospital mortality increased to 38.5% (lower, right box).

Table 1: Nominal Logistic Model of Initial Vital Signs in the ED for ICU admission for COVID-19

Parameter Estimates at Time of COVID-19 Suspicion

Terms	Estimate	Std Error	ChiSquare	Prob>ChiSq
Intercept	6.43	4.69	1.9	0.1701
Temperature	-0.03	0.10	0.1	0.7506
Heart Rate	0.02	0.01	1.5	0.2179
Respiratory Rate	-0.08	0.05	2.2	0.1382
Systolic Blood Pressure	-0.01	0.01	0.3	0.6042
Diastolic Blood Pressure	0.01	0.02	0.1	0.7762
SpO_2	-0.07	0.02	8.1	0.0045

ED: Emergency Department; Std Error: Standard error of the estimates; Prob>ChiSq: Probability that the ChiSquare statistic is due to chance. Values <.005 are statistically significant.[8]

CRITICAL CARE 18

Utilizing the Echocardiographic Assessment using Subcostal view only (EASy) exam in hypotensive peri-operative patients: A single-site retrospective review

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INTRODUCTION: POCUS has been useful in diagnosing and treating cases of hemodynamic instability[1-2]. Its use in peri-operative settings has been documented in a limited number of studies[3-6]. Of note, the subcostal approach to echocardiograms as a single view has the potential to become the superior view due to its ease of access, efficiency, and ability to visualize the IVC consistently[7]. This study seeks to demonstrate how the echocardiographic assessment using subcostal view only (EASy) approach was effective in directing clinical decision making for hypotensive patients using standardized criteria to categorize patient's echocardiograms within etiologic clusters and common cardiac phenotypes.

METHODS: 2075 POCUS exams were collected at Albany Medical Center, an urban level 1 trauma center, between August 2017 and June 2021 and were reviewed for the study. Training of residents to perform the EASy exam consisted of a 4-day ultrasound course with opportunity to gain proficiency in the PACU. We included all patients with hypotension as reason for anesthesia consult who had a completed EASy exam with saved images that were available for review. Patients were then divided into three cohorts: those with an EASy exam completed pre-operatively, intra-operatively, or post-operatively in the post-anesthesia care unit (PACU).

RESULTS: 78 patients were included across the 3 study cohorts. 70 (86.5%) EASy exams were of good/adequate quality upon review, and 91% of exams were completed in less than 5 minutes with an average duration of 2.54 minutes per EASy exam. The other 8 patients' exams were of poor quality or unable to obtain view, thus were corroborated with a FATE exam between apical and parasternal views. At least 50% or more of the exams were completed successfully by anesthesia residents, the rest being completed by attendings. Mortality rates were highest in the pre-op and intra-op patient cohorts and lowest in the PACU cohort (20%, 18.75%, and 1.92%, respectively). All patients who received EASy exams with good/adequate quality (N = 70) or a FATE exam (N = 8) when EASy was poor quality or unable to be obtained benefited from having an exam done as it provided diagnostic information at minimum. The majority of patients also benefited from having an EASy exam +/- FATE due to its ability to aid in clinical interventions: 80%, 81.2%, and 69.2% in the pre-op, intra-op, and PACU cohorts, respectively. Most common interventions included IV volume boluses, administration of pressors and inotropes, and other interventions (procedures, surgery, diuresis).

CONCLUSION: The EASy exam is a novel approach to evaluating hemodynamic status in patients, especially so in a variety of peri-operative settings: pre-operatively, intra-operatively, and immediately post-operatively in the PACU. Training of residents to perform the EASy exam has been demonstrated as both feasible and desirable given the high success rate, alluding to the need for further implementation of this method of POCUS. Mortality rates trending higher in the pre- and intra-operative cohorts could indicate that these patients were sicker and in greater need of acute care (i.e. transfer directly from OR to ICU) than their peers in the PACU. In future studies, we hope to further demonstrate the EASy exam's efficacy in other settings and patient populations.

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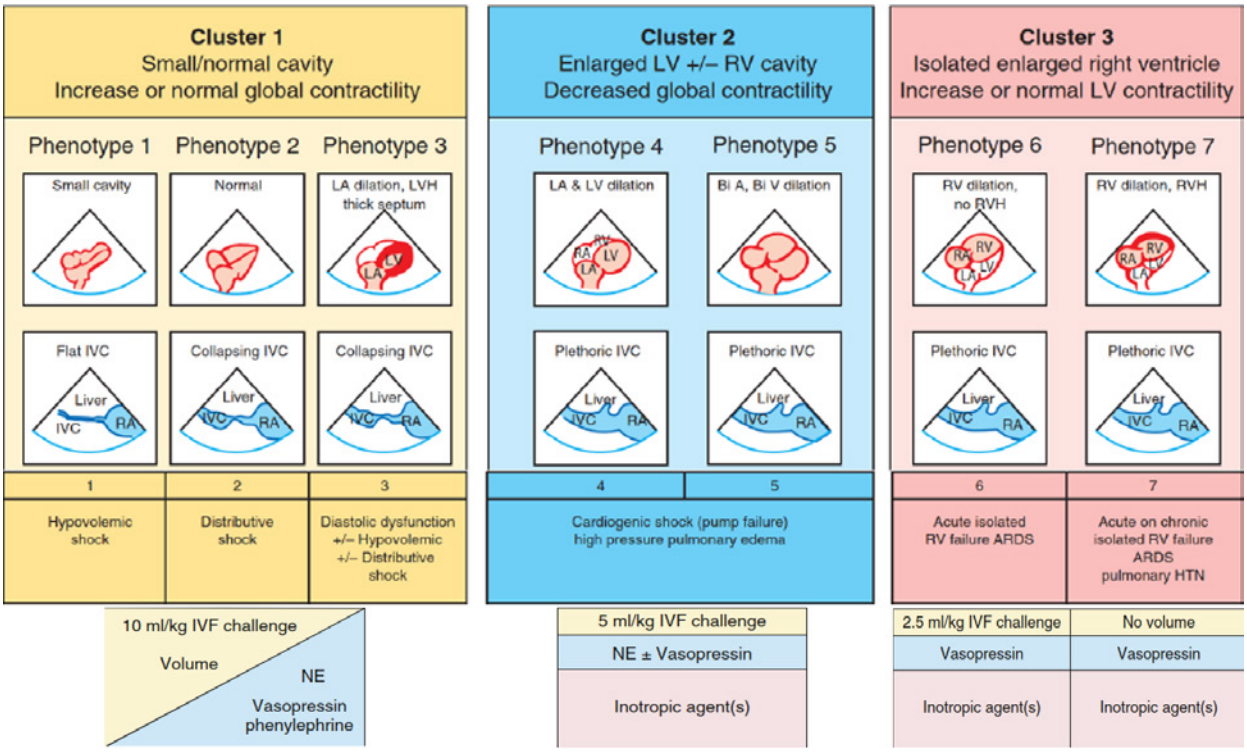

Fig. 1

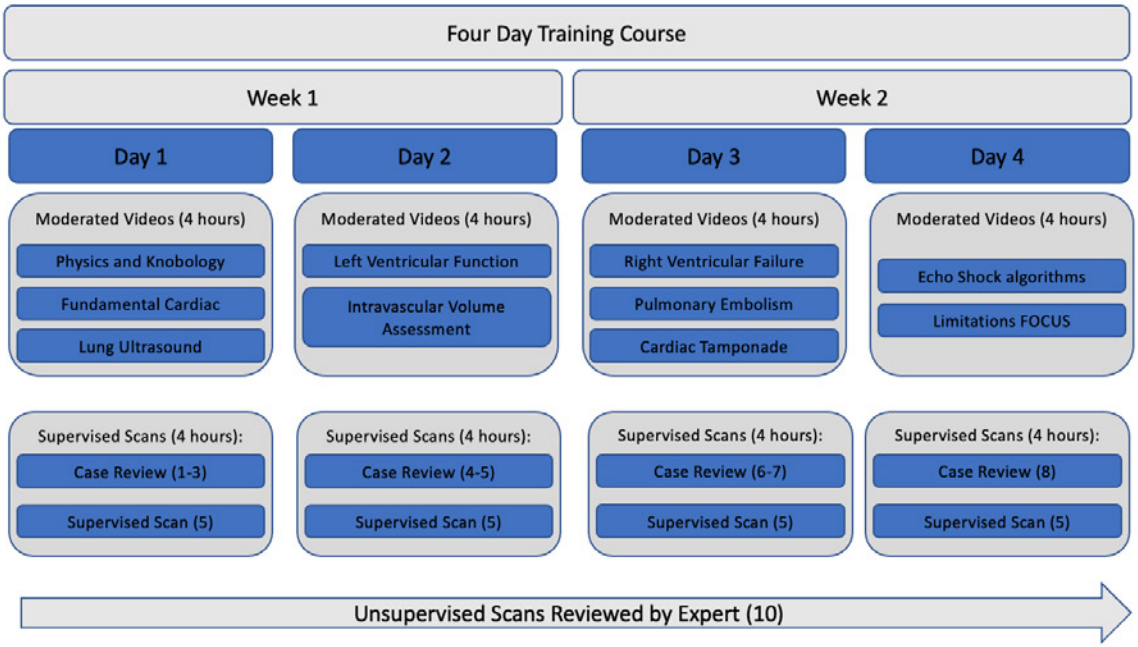

Fig. 2

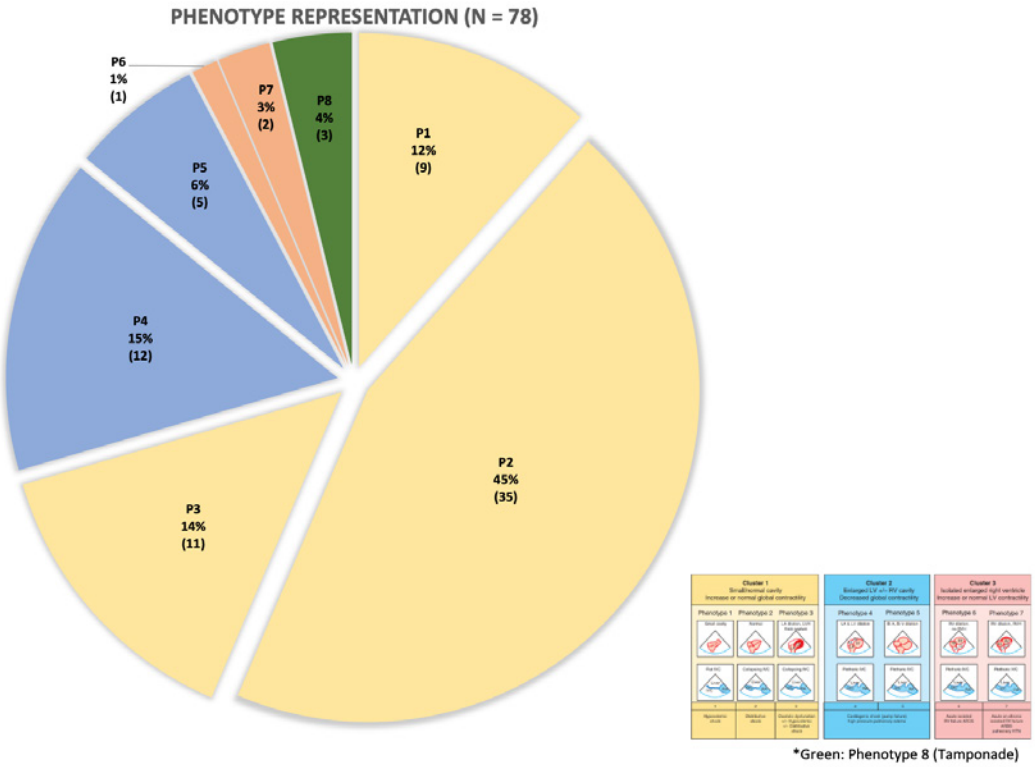

Fig. 3

Intervention Type	Pre-op			Intra-op			PACU		
Total pts (N = 78)	*Cluster 1 (N = 3)*	*Cluster 2 (N = 4)*	*Cluster 4 (N = 3)*	*Cluster 1 (N = 11)*	*Cluster 2 (N = 4)*	*Cluster 3 (N = 1)*	*Cluster 1 (N = 41)*	*Cluster 2 (N = 9)*	*Cluster 3 (N = 2)*
No additional interventions	1	1	0	0	1	0	6	5	1
IV Bolus	1	1	0	1	0	0	24	19	1
Stop IV Fluids	0	0	0	1	0	0	0	0	0
Blood Transfusion	0	2	1	3	0	0	5	5	0
Pressors (Norepinephrine, phenylephrine, vasopressin)	2	1	0	10	4	1	23	19	0
Inotropes (Dopamine, Epinephrine, milrinone)	0	0	0	0	0	0	2	2	0
Stop/reduce Pressors	0	1	1	1	0	0	6	5	0
Stop/reduce inotropes	0	1	0	0	0	0	2	2	0
Other Interventions (procedure, diuresis, surgery, albumin)	1	3	3	5	0	0	13	11	0

Fig. 4

Cohort (N)	% Male (N)	Avg BMI	Average Days in Hospital	Average Days in ICU (N)	Average Days Ventilated (N)	Mortality % (N)	Average Time of EASY Exam (min)	% Exams w/ good or adequate quality (N)	% Exams completed by resident (N)
Pre-op (10)	50.0 (5)	27.71	16.8	8.6 (8)	2.3 (5)	20.0 (2)	2.6	100 (10)	50.0 (5)
OR (16)	62.5 (10)	28.46	20.13	10.81 (13)	4.13 (9)	18.75 (3)	2.14	93.75 (15)	50.0 (8)
PACU (52)	44.23 (23)	27.95	9.83	2.76 (25)	0.45 (6)	1.92 (1)	2.88	86.5 (45)	86.5 (45)

Fig. 5

CRITICAL CARE 19

Studying Unconscious bias in End-of-Life care

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INTRODUCTION: Nearly one in five adults will die in the intensive care unit with substantial scholarship dedicated to maximizing dignity for both patients and their families and evaluating disparities in care. Prior investigators have identified greater intensity of care at the end-of-life in the ICU among patients who are non-white, although whether this stems from differences in physician communication, differences in hospital use, or cultural differences in end of life preferences has yet to be fully elucidated. In the context of the severe COVID-19 pandemic, we conducted a single-center study of care at the end of life in our ICUs (including both medical ICUs and surgical ICUs) by race and ethnicity.

METHODS: A retrospective data review was conducted on EHR data collected from all ICU admissions between June 2019 and December 2020 in a tertiary care center in Boston, MA. The primary outcome was death and secondary outcomes included 'code status,' broken down into the designations: Do Not resuscitate (DNR), DNR/Do not Intubate (DNI) and Comfort measures only (CMO) before death occurred in the ICU. Race and ethnicity categories were determined by patient self-identification of these categories and are described in Table 1. We categorized different 'code statuses' at death by race and ethnicity, and the percentage of patients who died with markers of aggressive care (e.g., ongoing feeding, vasopressors, dialysis, restraints) or markers of conflict (ethics consult).

RESULTS: A total of 13,212 ICU patients were included in the analysis. 1302 patients died (9.9%) and the rest were discharged alive (Fig 1). 4581 (34.7%) were discharged home, and 435 (3.3%) discharged to hospice (home plus medical facility). 9.6% were DNAR +/- DNI, and 8.6% were CMO. 53.5% were males, 6.8% were Hispanic/ Latino, 13.8% were Black and 3.6% were Asian. 10,273 had an HCP available (77.7%). The mean age was 63.3 (± 17.2) (Table 1). 716 patients (5.4%) were COVID positive in the ICU. Of those who died 74.5% were non-Hispanic/ Latino, 13.2% were Black and 57.1% were White. Of Black patients, 9.4% died whilst 8.5% of White patients died. These differences were statistically significant ($p<0.0001$) (Table 2a). The average age of Black patients who died was 69 years (sd 15.2) versus 71.4 years (sd 14.5) among White patients (Table 2 b). At the time of death, White patients were most likely to be DNAR/DNI or CMO (84.1%) as compared with Black patients (77.9%) or Hispanic/Latino patients (67.7%). Black patients were more likely to be DNAR/OK to Intubate (15.1%) as compared with White patients (9%) (Table 3). At the time of demise 53% were intubated, 53.7% were being infused vasopressors, 22.8% had feeding orders, 17% were on dialysis, 31.4% had restraint orders, 87% had a Palliative care consult, 4.8% had an Ethics consult, the mean time between DNR decision and demise in hours was 151 (± 229.8). The median LOS in the ICU was 2.2 (IQR 1,5) and hospital LOS was 6 (IQR 3,12) (Table 4). the mean time between DNR decision and demise in hours was 131.2 (± 137.4). The mean time between DNR decision and demise in hours was 139.9 (± 162.3) hours amongst Black patients and 126.9 (±125.9) hours amongst White patients (Table 5). When comparing this difference prior to and during the COVID pandemic surge (March 2020) younger patients were admitted to the ICU post pandemic (62.9 years (sd 17.1) vs 64 years (sd 17.4) ($p=0.0003$). Table 6 shows a better ICU outcome in this larger cohort. However, compared to pre-pandemic, more Black and Hispanic patients were admitted to the ICU after March 2020. This was opposite to the effect seen with White patients where there was a decrease in ICU admissions ($p=0.023$).

CONCLUSION: Our data has identified several statistically significant disparities within dying patients by race and ethnicity. These include a difference in overall mortality rate, likelihood of being transitioned to 'Comfort Measures Only' status and time between DNR decision and demise. The pandemic also had a disproportionately worse effect on Black and Hispanic patients. This data opens opportunities to move from disparities to equity.

Table 1. Descriptive

Variable	Encounters (n=13212)
DNAR/DNI, No. (%)	917 (6.9)
DNAR/OkInt, No. (%)	352 (2.7)
CMO, No. (%)	1136 (8.6)
Full Code, No. (%)	10807 (81.8)
Gender, No. (%)	
Male	7071 (53.5%)
Ethnicity, No. (%)	
Non Hispanic/Latino	10958 (82.9)
Unobtainable	1357 (10.3)
Hispanic/Latino	897 (6.8)
Race, No. (%)	
American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander	76 (0.6)
Asian	472 (3.6)
Black	1826 (13.8)
Other	648 (4.9)
Unknown	1487 (11.3)
White	8703 (65.9)
Age, Mean (SD)	63.3 (17.2)
Discharged Home, No. (%)	4581 (34.7)
Discharged to Hospice, No. (%)	
Hospice-Home	153 (1.2)
Hospice-Medical Facility	282 (2.1)
Patients died, No. (%)	1302 (9.9)
Covid Status, No. (%)	
COVID +	716 (5.4)
Prior COVID +	38 (0.3)
Not COVID +	12458 (94.3)
LOS	
Median (IQR)	6 (3, 12)
Mean (SD)	10.1 (14.2)

[min, max]	[1, 384]
ICU LOS	
Median (IQR)	2.2 (1, 5)
Mean (SD)	4.6 (7.5)
[min, max]	[0, 170.3]

Table 2a. Mortality by Race and Ethnicity

	Patients who died (n=1302)	**Patients discharged alive (n=11910)**	**P-value**
Ethnicity, No. (%)			<0.0001
Non Hispanic/Latino	970 (74.5) – (8.9)	9988 (83.9) – (91.2)	
Unobtainable	267 (20.5) – (19.7)	1090 (9.2) – (80.3)	
Hispanic/Latino	65 (5.0) – (7.3)	832 (7.0) – (92.8)	
Race, No. (%)			<0.0001
American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander	10 (0.8) – (13.2)	66 (0.6) – (86.8)	
Asian	42 (3.2) – (8.9)	430 (3.6) – (91.1)	
Black	172 (13.2) – (9.4)	1654 (13.9) – (90.6)	
Other	45 (3.5) – (6.9)	603 (5.1) – (93.1)	
Unknown	290 (22.3) – (19.5)	1197 (10.1) – (80.5)	
White	743 (57.1) – (8.5)	7960 (66.8) – (91.5)	

Table 2 b. Average age by race among patients who died

Age in years	**American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander (n=10)**	**Asian (n=42)**	**Black (n=172)**	**White (n=743)**	**Other (n=45)**	**Unknown (290)**

Mean (SD)	75.7 (13.5)	70.6 (17)	69 (15.2)	71.4 (14.5)	68.8 (15.3)	64.3 (17.8)

Table 3. Code status by race/ethnicity among patients who died (n=1302).

	DNAR/DNI (n=134)	**DNAR/OkInt (n=143)**	**Full Code (n=112)**	**CMO (n=913)**
Ethnicity, No. (%)				
Non Hispanic/Latino	105 (78.4) – (10.8)	99 (69.2) – (10.2)	71 (63.4) – (7.3)	695 (76.1) – (71.7)
	26 (19.4) – (9.7)		32 (28.6) – (12)	177 (19.4) – (66.3)
Unobtainable	3 (2.2) – (4.6)	32 (22.4) – (12)	9 (8) – (13.9)	41 (4.5) – (63.1)
		12 (8.4) – (18.5)		
Hispanic/Latino				
Race, No. (%)				
American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander	2 (1.5) – (20)	0 (0.0)	2 (1.8) – (20)	6 (0.7) – (60)
Asian	7 (5.2) – (16.7)	4 (2.8) – (9.5)	5 (4.5) – (11.9)	26 (2.9) – (61.9)
Black	20 (14.9) –(11.6)	26 (18.2) – (15.1)	12 (10.7) – (7)	114 (12.5) –(66.3)
Other	3 (2.2) – (6.7)	7 (4.9) – (15.6)	8 (7.1) – (17.8)	27 (3) – (60)
Unknown	26 (19.4) – (9)	39 (27.3) – (13.5)	34 (30.4) – (11.7)	191 (20.9) – (65.9)
White	76 (56.7) –(10.2)	67 (46.9) – (9)	51 (45.5) – (6.9)	549 (60.1) – (73.9)

Table 4. Markers of Aggressive care or conflict at death

Variable	**N=Died (1302)**
Intubation at demise	693 (53)
Vasopressors at demise	700 (53.7)
Feeding orders at demise	297 (22.8)
Dialysis at demise	221 (17)
Restraint orders at demise	409 (31.4)
Palliative care consult	1134 (8.7)
Ethics consult	63 (4.8)

Table 5. Time between DNR decision and demise by race (only among patients who died and who were not full code (n=1214)

Time between dnr decision and demise (in hours)	**American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander (n=6)**	**Asian (n=44)**	**Black (n=149)**	**White (n=869)**	**Other (n=33)**	**Unknown (113)**	**Total Group (n=1214) (p=0.237)**
Mean (SD)	314.7 (333.9)	178.8 (179.4)	139.9 (162.3)	126.9 (125.9)	98 (84.2)	134.8 (155.5)	131.2 (137.4)
Median (IQR)	198.9 (23.5, 724.8)	116.1 (60, 262.4)	93.7 (43.6, 162.2)	91.8 (45.5, 167.8)	66.4 (32.7, 146.2)	73.5 (43.1, 168.7)	91.7 (45.3, 168.3)
[min, max]	[17.5, 724.8]	[18.3, 836.6]	[0.9, 1053.8]	[0.7, 1080.8]	[6, 354.3]	[2.4, 873.2]	[0.7, 1080.8]

Table 6. Pre and post pandemic surge (row%) – (col%)

Variable	**Pre-COVID (n=4840)**	**Post-COVID (after March surge 2020) (n=8372)**	**p-value**
Code status, No. (%)			<0.0001
DNAR/DNI	395 (43.1) – (8.2)	522 (56.9) – (6.2)	
DNAR/OkInt	129 (36.7) – (2.7)	223 (63.4) – (2.7)	
CMO	487 (42.9) – (10.1)	649 (57.1) – (7.8)	
Full Code	3829 (35.4) – (79.1)	6978 (64.6) – (83.4)	
Gender, No. (%)	2596 (36.7) – (53.6)	4475 (63.3) – (53.5)	0.838
Male			
Ethnicity, No. (%)			0.131
Non-Hispanic/Latino	4017 (36.7) – (83)	6941 (63.3) – (82.9)	
Unobtainable	518 (38.2) – (10.7)	839 (61.8) – (10)	
Hispanic/Latino	305 (34) – (6.3)	592 (66) – (7.1)	
Race, No. (%)			0.023
	35 (46.1) – (0.7)	41 (54) – (0.5)	

American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander			
Asian	178 (37.7) – (3.7)	294 (62.3) – (3.5)	
Black	616 (33.7) – (12.7)	1210 (66.3) – (14.5)	
Other	224 (34.6) – (4.6)	424 (65.4) – (5.1)	
Unknown	569 (38.3) – (11.8)	918 (61.7) – (11)	
White	3218 (37) – (66.5)	5485 (63) – (65.5)	
Age, Mean (SD)	64 (17.4)	62.9 (17.1)	0.0003
Discharged Home, No. (%)	1506 (32.9) – (31.1)	3075 (67.1) – (36.7)	<0.0001
Discharged to Hospice, No. (%)	191 (43.9) – (4)	244 (56.1) – (2.9)	0.0014
Patients died, No. (%)	537 (41.2) – (11.1)	765 (58.8) – (9.1)	0.0003
LOS			<0.0001
Median (IQR)	7 (3, 13)	5 (2, 11)	
ICU LOS			<0.0001
Median (IQR)	2 (1, 4.2)	2.4 (1, 5.7)	

CRITICAL CARE 20

Opportunities in Tele-Critical Care: Analysis of Transfer Center Outcomes of a Large Academic Center

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INTRODUCTION: Involvement of critical care specialists has been shown to improve patient outcomes[1], yet many community-based hospitals lack access to intensivists[2]. Tele-Critical Care (TCC) has evolved to provide specialized critical care services to remote sites[2,3] with evidence supporting that it may improve ICU patient safety, cost-effectiveness, and health care quality[4,5,6]. The purpose of this study is to quantify transfer requests at a large academic hospital and proportion of transfers accepted. We hope to better understand which critically ill patients can and cannot be cared for in the community and how TCC could help larger hospitals better partner with regional hospitals to improve diverse outcomes.

METHODS: In partnership with hospital leadership and an academic tertiary care hospital transfer center, de-identified data from 4/13/2021 to 5/13/2021 regarding consecutive requests to transfer a critically ill patient from community hospitals to the tertiary care center were obtained. Transfer request rationale and ultimate transfer success were analyzed.

RESULTS: In the one- month period, 907 requests were submitted. As TCC services would not impact requests due to a clinical service line not available at the community hospital (i.e., neurosurgical services, interventional cardiology, etc), data were analyzed concerning requests for 'higher level of care' and 'patient/family request'. This yielded 295 transfer requests from 102 different hospitals. 99 (34%) of requests ultimately resulted in actual patient transfer from the community hospital to the academic tertiary care hospital. 110 requests (37%) were declined by the tertiary care hospital, 62 (21%) requests were withdrawn by the community hospital, and 24 (8%) of requests resulted in the patient being transferred away from the community hospital but not to the tertiary care hospital (Figure 1). 45 hospitals had 1 request during the study period, 15 hospitals had 2 requests, 9 hospitals had 3 requests, 10 hospitals had 4 requests, 7 hospitals had 5 requests, 6 hospitals had 6 requests, 3 hospitals had 7 requests, 3 hospitals had 9 requests, 3 hospitals had 9 requests, and 1 hospital had 10 requests (Figure 2). The results of the requests from Top 10 referring hospitals are shown in Figure 3. Reasons for transfer decline varied (Figure 4), with the primary reason for decline being 'no bed availability' (24% of all transfer requests)..

CONCLUSION: Our data suggest that a large academic center may receive numerous requests to transfer a critically ill patient but that less than half actually result in a successful transfer. There also may be a small subset of hospitals that frequently request a transfer and thus, may be more likely to utilize and benefit from TCC services. Further investigation into rationales for transfer request and whether or not community hospitals would utilize a TCC service are needed.

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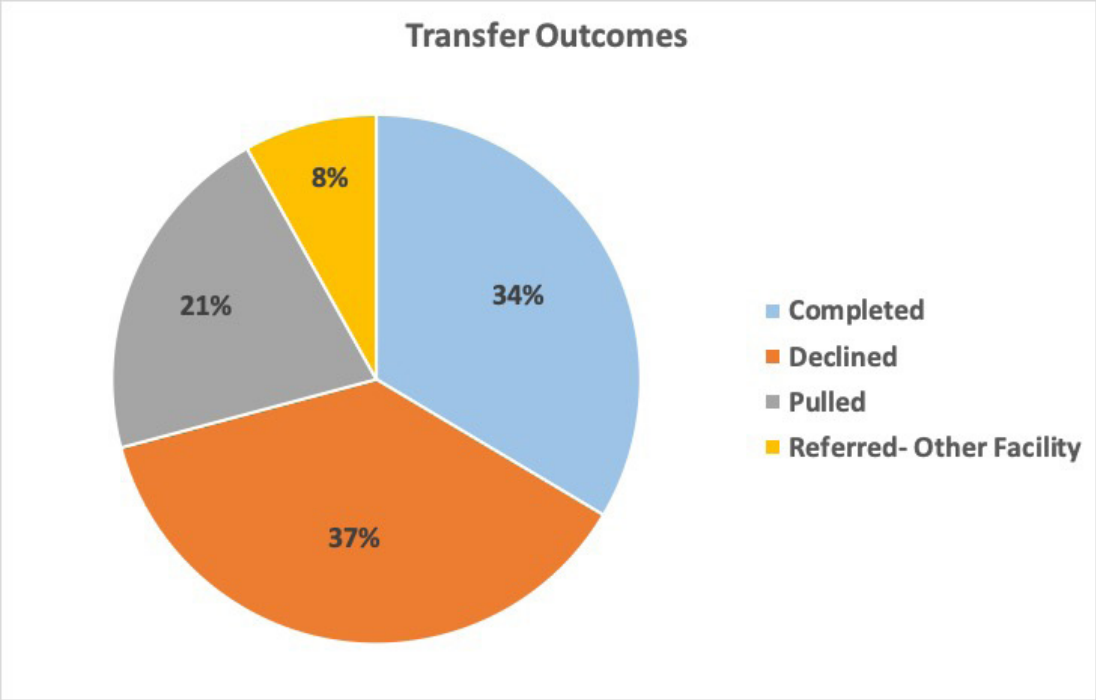

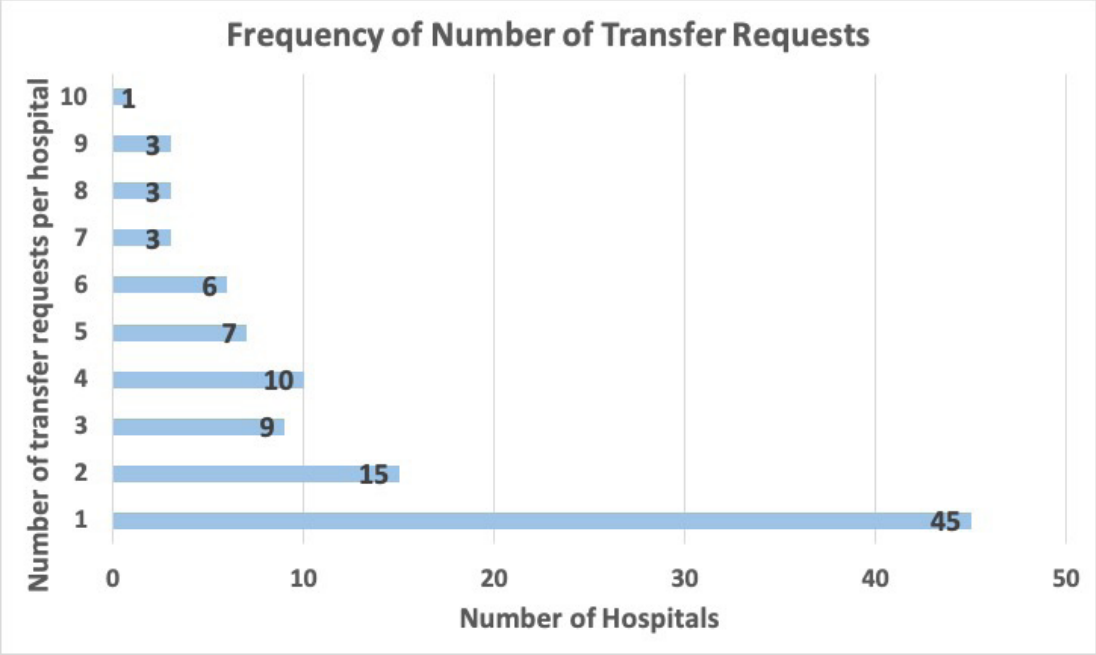

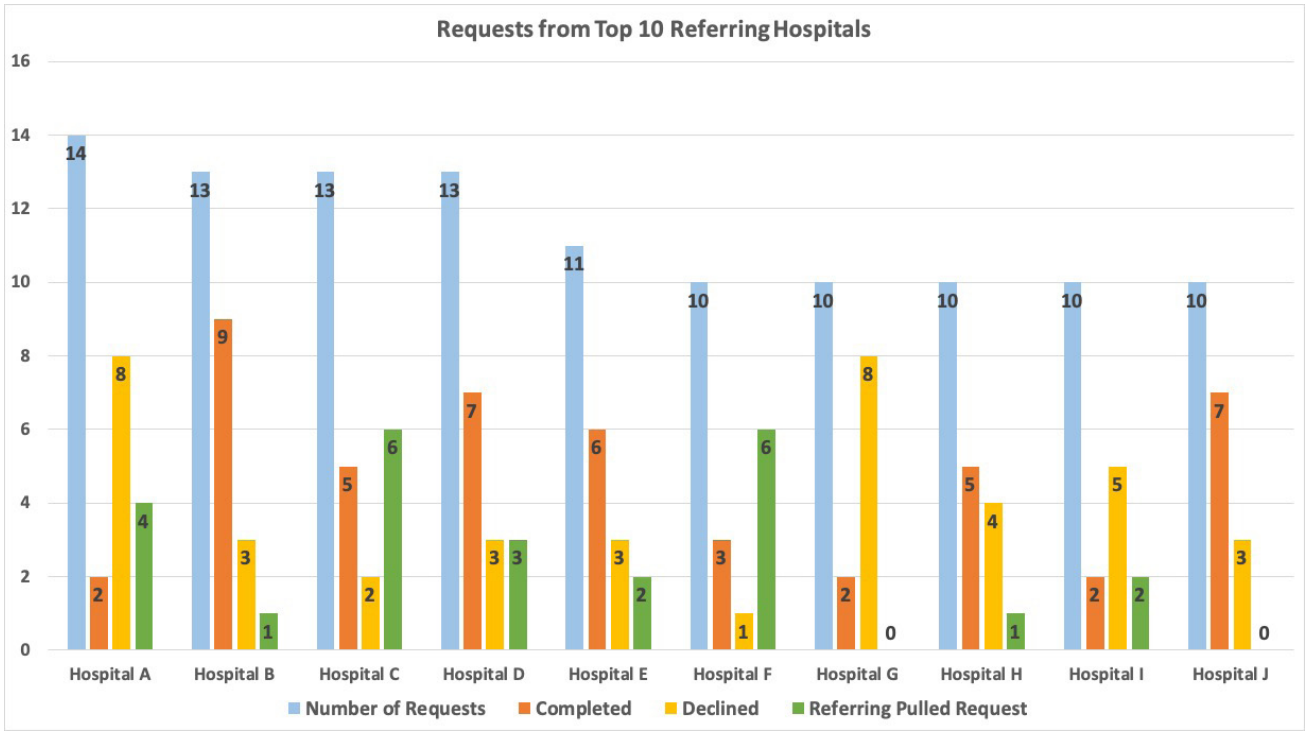

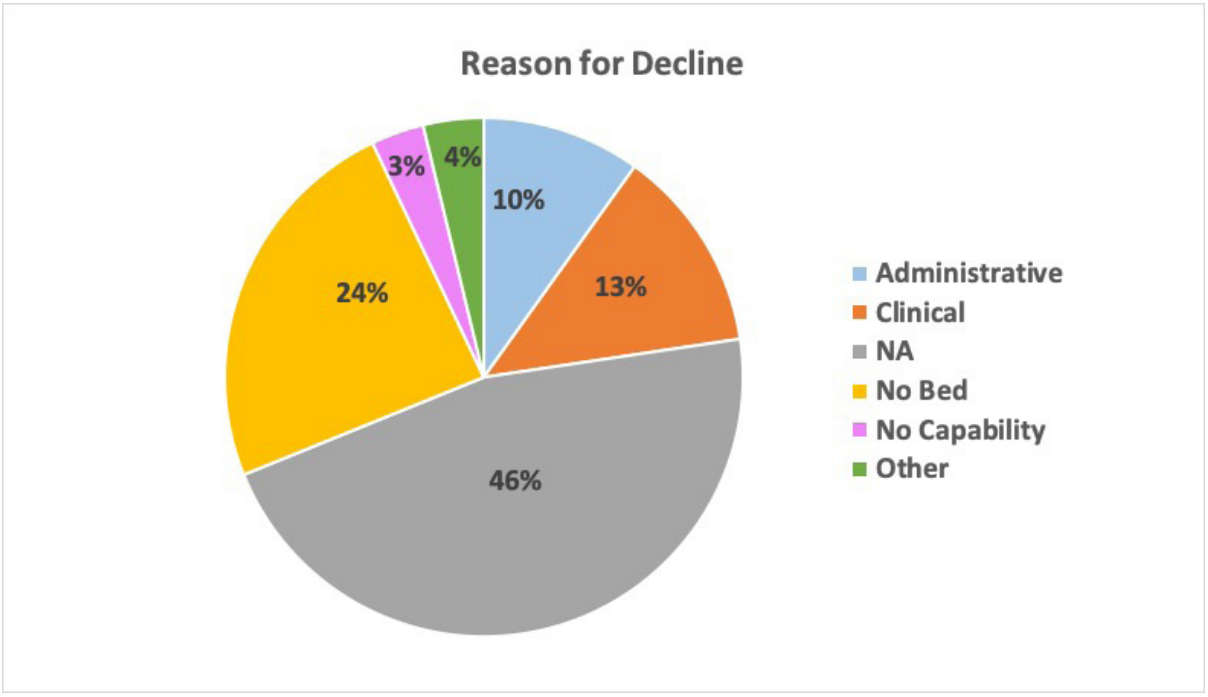

CRITICAL CARE 21

Inter-Rater Reliability for the Pragmatic Evaluation of Point of Care Lung Ultrasound for the Triage of COVID-19 Patients Using a Simple Scoring Matrix

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INTRODUCTION: The COVID-19 pandemic has affected over 244 million patients worldwide with nearly 5 million deaths (coronavirus.jhu.edu/map.html) accessed October 27, 2021). The triage of COVID-19 patients is challenging due to limited predictive value of chest x-rays (CXR) and laboratory findings and efforts to limit exposure to infected patients. Point of Care Lung ultrasound (LUS) can be performed at the patient's bedside and is more sensitive than CXR for the detection of pneumothorax, pneumonia, and pleural effusion. Ideally, structured LUS studies typically require the sonographic evaluation of multiple specific locations from both lungs. However, real-life bedside assessments are often incomplete and imperfect. The lack of accepted scoring principles to evaluate already-obtained LUS images for COVID-19 patients is hampering its widespread use and assessments of impact on patient outcomes. This pragmatic study aimed to evaluate the inter-rater reliability (IRR) of previously obtained LUS images collected for the triage of COVID-19 patients using a pre-defined simple scoring matrix. LUS images were obtained with the Butterfly iQ+ ultrasound probe, a portable, fast, low-cost handheld ultrasound probe.mine global P50 changes in adult cardiac surgery patients.

METHODS: The retrospective study scored LUS images acquired at three medical institutions. We scored any LUS images performed from adults presenting to the Emergency Department for assessment of acute respiratory symptoms possibly related to COVID-19 infection. LUS images were acquired by bedside physicians or advanced practice providers without a specific image acquisition protocol. The study was approved by the Institutional Research Boards before the de-identified assessment of any LUS image. The six image reviewers were attending physicians trained in emergency medicine, anesthesiology, and/or critical care medicine. We modified the proposed model by Soldati et al.[1] using a scoring system of 0-3 (Table 1) based on the presence of the following LUS findings: normal lung, isolated B-lines, diffuse B-lines, thickened/indented pleura, subpleural condensation, interrupted pleura, air bronchogram. All de-identified LUS images available for each patient were scored by at least three reviewers blinded to patients' clinical presentation and outcomes. Patients with an overall worst score of 0 or 1 were classified as 'Low risk' and patients with a worst score of 2 or 3 were classified as 'High risk'. Initial assessments of our simplified scoring rubric showed high inter-rater agreement (≥75%) among scores.

RESULTS: Lung ultrasound images from 68 patient were analyzed. The number of available images (video clips) and the number and location of studied intercostal spaces per patient varied, as expected for this pragmatic study. Out of the 68 cases analyzed, 44(64.7 %) of them had uniform agreement among the 3 reviewers on patient risk classification as low (n=13) or high risk (n=31). Another 22 (32.4 %) cases had at least 66.7% agreement on risk classification. The most frequent pathological finding was isolated B-lines, and air bronchogram the least frequently observed finding. The interclass correlation coefficient (ICC) for the overall risk classification was 0.778 (95%CI 0.667-0.856) ($p<0.001$). The presence of subpleural condensation or thickening was the individual finding with the lowest inter-rater reliability.

CONCLUSION: Our lung ultrasound scoring matrix showed an overall good inter-rater reliability for the risk assessment of previously obtained LUS images during the triage of patients with acute respiratory symptoms possibly related to COVID-19 infection. Developing scoring rubrics that are simultaneously simple to implement and consistent among different providers will strengthen the use of LUS for the triage of patients with acute respiratory symptoms.

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Table 1.

Worst score based on observed individual LUS findings			
Score 0	**Score 1**	**Score 2**	**Score 3**
Intact Pleura	Thickened/indented pleura	Interrupted Pleura	Grossly abnormal pleura
A-lines only	Isolated B-lines ("sun rays")	Diffuse B-lines ("waterfall")	Subpleural consolidation
			Air bronchogram

CRITICAL CARE 22

Impaired human resistance arteriole vascular reactivity is associated with the development of acute kidney injury and delirium in cardiac surgery

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INTRODUCTION: Acute kidney injury (AKI) and delirium affect up to 30% of patients undergoing cardiac surgery and are associated with increased risk of death, duration of mechanical ventilation, and longer hospitalization.[1,2] AKI and delirium may be induced by impaired perfusion, ischemia-reperfusion, oxidative damage, and inflammation, and each of these mechanisms is regulated by the vascular endothelium. The endothelium controls perfusion via its capacity to regulate smooth muscle tone. We tested the hypothesis that impaired vascular reactivity is associated with AKI and delirium in patients undergoing cardiac surgery.

METHODS: We measured vascular reactivity in resistance arterioles from mediastinal fat collected from participants in a clinical trial of hyperoxia versus normoxia during cardiac surgery.[3] Arterioles were mounted on a wire myograph. After inducing vasoconstriction with norepinephrine, we measured endothelium-dependent and -independent vasodilation with escalating doses of acetylcholine and sodium nitroprusside, respectively. We diagnosed AKI using Kidney Disease Improving Global Outcomes creatinine criteria and delirium using the Confusion Assessment Method for the ICU assessed twice daily. We compared responses in patients who did and who did not develop AKI using repeated measures ANOVA and nonlinear mixed effects regression and repeated this in participants who did and who did not develop delirium. Responses were compared with an omnibus test of the effective concentration eliciting a half-maximal response (EC50), rate of the response, and the maximal theoretical response (Emax).

RESULTS: Thirty-five trial participants comprised the study sample. The median (25th, 75th percentile) age was 67 years (59, 73), 15 (42.9%) participants were diabetic, and the median left ventricle ejection fraction was 55% (55,60). Eight participants (22.9%) developed AKI and 7 (20%) developed delirium. Endothelium-dependent vascular reactivity (acetylcholine response) was similar between subjects who did and who did not develop AKI (P=0.36) and between those who did and did not develop delirium (P=0.70). Endothelium-independent vascular reactivity (sodium nitroprusside response) was impaired in participants who developed AKI, evidenced by a 1.7-fold increase in the EC50 and an 11.1% lower Emax compared to participants who did not develop AKI (P<0.001; Fig.1). Similarly, endothelium-independent vascular reactivity was impaired in those who developed delirium, evidenced by a 10-fold increase in EC50 and a 11.9% decreased Emax compared to those who did not develop delirium (P=0.008; Fig. 2).

CONCLUSION: Vascular reactivity was impaired in cardiac surgery patients who subsequently developed AKI and in those who developed delirium. Specifically, endothelium-independent vascular reactivity, but not endothelium-dependent vascular reactivity, was impaired in those with these organ injuries. Impairment of the endothelium-independent response could be explained by impaired activation of soluble guanylyl cyclase in participants who developed organ injury since nitric oxide from sodium nitroprusside directly activates soluble guanylyl cyclase. The similar endothelium-dependent response in patients with and without organ injury may be explained by acetylcholine activation of other vasodilator pathways in addition to activation of endothelial nitric oxide synthase. Future investigations will determine if therapies that augment endothelium-independent vascular reactivity, such as soluble guanylyl cyclase stimulators, decrease perioperative AKI and delirium.

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Fig. 1. Vascular reactivity in patients with acute kidney injury (AKI) vs. those who did not develop AKI

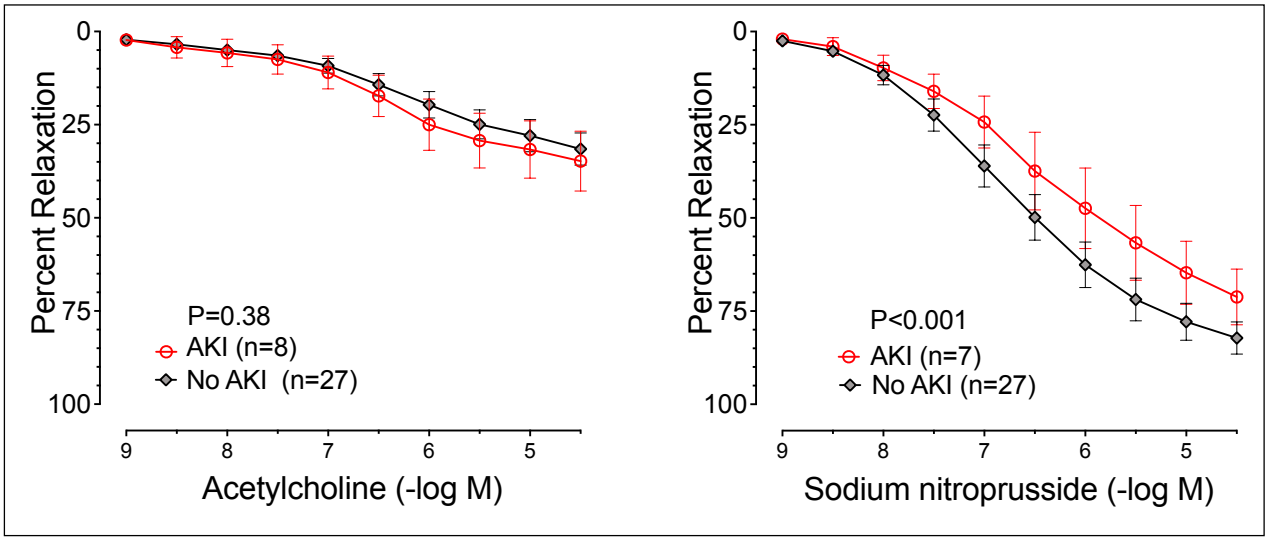
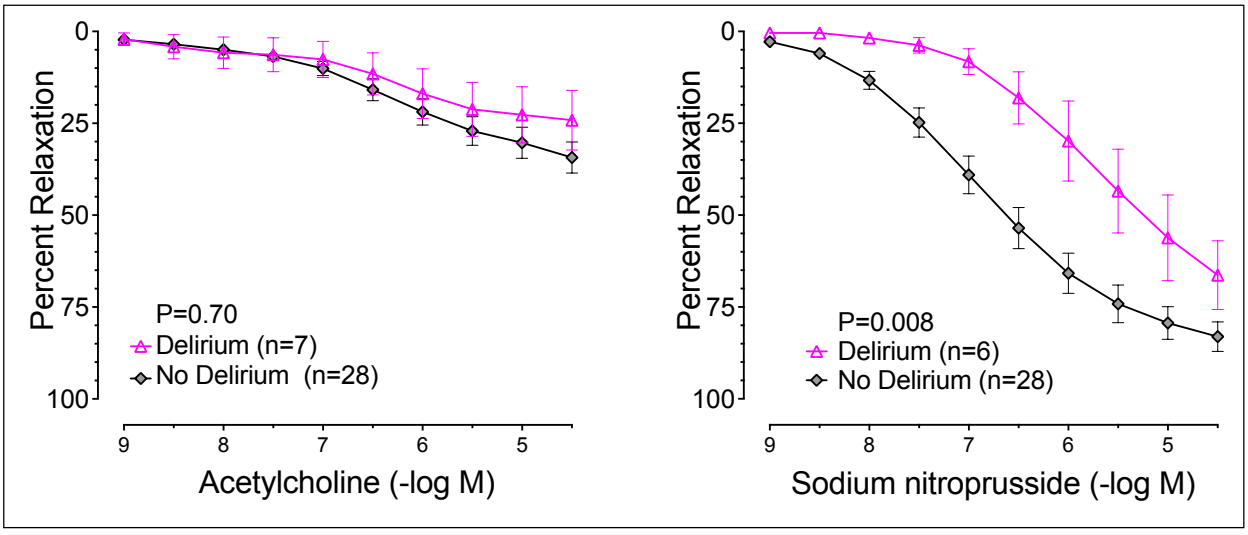


Fig. 2. Vascular reactivity in participants who developed delirium vs. those who did not develop delirium



CRITICAL CARE 23

Long Term Application of Veno-Venous Extracorporeal Membrane Oxygenation for COVID-19Respiratory Failure at a Single Institution

Genevieve Manahan[1], Nicola D'Attellis[2], Reinaldo Rampolla[3], Pedro Catarino[4], Dominick Megna[4], Dominic Emerson[4], Eliza Granflor[4], Alice Chan[5], Tariq Nassem[3]

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INTRODUCTION: Since the World Health Organization declared the outbreak of SARS-CoV-2 a global pandemic on March 11, 2020, we have seen a substantial increase in patients requiring hospital admission, intensive care, and mechanical ventilatory support for management of acute respiratory failure. For patients suffering with COVID-19 ARDS, that are unresponsive to conventional therapies, VV-ECMO (VVE) remains an option of last resort. According to ELSO COVID-19 Registry, over ten thousand patients have been supported with VVE for management of COVID-19 ARDS so far, including 482 patients in North America who remain on ECMO support as of November 2021. This observational study aims to report our experience with VVE in management of COVID-19.

METHODS: All patients diagnosed with SARS-CoV-2 (based on PCR assay) between March 2020 and October 2021, at a single tertiary institution in the US that went on to require VV-ECMO support were identified. Any patient requiring VA-ECMO support (prior to lung transplantation) was excluded. The data was retrospectively collected and analyzed. Outcomes studied included patient characteristics, time to cannulation from onset of infection, length of time on VVE support, recovery of pulmonary function, common complications, and mortality.

RESULTS: Total 49 patients at our institution received VVE support during the studied period. Median age was 43 years, and 70% patients were male. 6 patients developed COVID-19 during peripartum period (ranging from 25 to 36 weeks gestation). All were placed on VVE either immediately after birth of the baby or few days after delivery. 54% patients had BMI > 30 and 14% with BMI > 40. 18% and 12% patients had prior history of diabetes and HTN respectively. Overall mortality rate was 51%. 8 patients (16%) went on to receive double lung transplantation. Median time to cannulation from onset of infection was 7.5 days. Median time on VVE support was 44.8 days. Most common complications included bleeding (37%), AKI (29% patients required CRRT) and ischemic issues (26%) 11 patients were either discharged directly home on room air or have returned home after short LTAC stay. These include 6 patients post-lung transplantation.

CONCLUSION: COVID-19 ARDS has led to prolonged use of VVE support in patients who are unresponsive to conventional treatment such us mechanical ventilation, prone positioning, and paralysis. Our data indicates, a higher in-hospital mortality (51%) than that reported by ELSO registry (40%). We attribute this to a large percentage of patients that are transferred from outside hospital after prolonged treatment course without avail. Many of these patients were cannulated either on arrival or just before transfer to our center. Our patients were supported on VVE for longer period (44.8 vs 24 days), both due to improved ICU care and because for many VVE is being utilized as a bridge to lung transplantation. Bleeding, renal failure and ischemic injuries including vascular insult are the most common complications observed in our cohort. Overall VVE continues to remain a vital and perhaps the only option for patients suffering from severe COVID-19 ARDS. However prolonged treatment course and mortality remains high. As the pandemic continues to inflict disease, lung transplantation is the only long-term survivable option for many patients being supported on VVE.

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CRITICAL CARE 24

Validity of SOFA Score in Patients with Severe Respiratory Distress Secondary to COVID 19 Pneumonia

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INTRODUCTION: SOFA scoring has been validated to predict mortality in patients admitted to ICU[1]. Since COVID-19 pandemic, there is conflicting evidence regarding the accuracy of SOFA score to predict mortality in patients with severe respiratory distress secondary to COVID-19 pneumonia and the concern of that population not being represented in the original SOFA studies[2,3]. The purpose of our study is to evaluate correlation between SOFA score and mortality prediction in patients suffering from COVID-19 pneumonia complicated by severe respiratory distress who needed or not mechanical ventilation. It also aimed at further analysis to determine the best cutoff for discrimination for mortality risk and to compare with previous studies in general ICU population.

METHODS: We performed a retrospective chart review of the patients admitted to Henry Ford Hospital from March to December 2020 whose principal diagnosis were COVID 19 pneumonia complicated by severe respiratory distress. We defined respiratory distress as oxygen saturation below 93% and/or respiratory rate above 30 breaths per minutes for 2 hours. We compared their initial SOFA scores (at time of diagnosis of severe respiratory distress) to mortality outcomes using a grouped analysis. Patients were split into 7 levels of SOFA score (0-1, 2-3, 4-5, 6-7, 8-9, 10-11 and >11) and comparison of mortality in between groups was performed using Chi-square test followed by a Linear trend Analysis. We used ROC curve for analysis of the performance of SOFA score as mortality predictor and to find the optimal discrimination score. All statistical tests were 2-tailed and a P value >0.05 was considered significant.

RESULTS: There was a total of 320 patients, out of these 111 underwent intubation and mechanical ventilation. Overall mortality was 22%, and mortality for patients who needed mechanical ventilation was 50% (Table 1).

Grouped SOFA score analysis showed steep correlation with mortality rate, with ranges from 0% mortality for SOFA 0-1 to 100% mortality rate for SOFA scores above 11 (Figure 1). ROC curve for analysis of performance of SOFA as mortality predictor showed an area under the curve = 0.883, which is comparable to the range of performance previously seen in non-COVID-19 population. The optimal point for discrimination (best balance between false positive fraction and true positive fraction) was for SOFA =5. In the population studied, mortality for SOFA score equal or less than 5 was 8.3% (18/217) versus 51.4% (52/101) for SOFA score above 5 (Figure 2).

CONCLUSION: SOFA score in COVID-19 patients complicated by severe respiratory distress showed strong correlation with mortality rate and could be used as mortality predictor for this population as well. However, the best point of discrimination found was lower (SOFA = 5) than previously seen for non-COVID-19 population, when that point was in the range of 7-8. It is valid to use SOFA scores to predict mortality in COVID-19 patients, but patients seemed to have an increased mortality rate with a lower SOFA score than the general ICU population.

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SOFA Score	Intubated COVID-19 N	Intubated patients mortality N (%)	Total COVID-19 patients N	Total COVID Mortality N (%)	Expected mortality by SOFA in non-COVID-19 patients %
Number total	111	56 (50%)	320	70 (22%)	
0-1	1	0 (0%)	79	0 (0%)	0
2-3	7	1 (14.3%)	71	4 (5.6%)	6.4%
4-5	26	9 (35%)	67	14 (20.9%)	20.2%
6-7	33	12 (36%)	51	18 (35.3%)	21.5%
8-9	22	13 (59%)	26	13 (50%)	33.3%
10-11	14	11 (79%)	17	14 (82.3%)	50%
12-14	6	6 (100%)	6	6 (100)	95.2%
>14	1	1 (100)	1	1 (100%)	95.2%

Table 1. SOFA score and associated mortality in COVID-19 patients with severe respiratory distress.

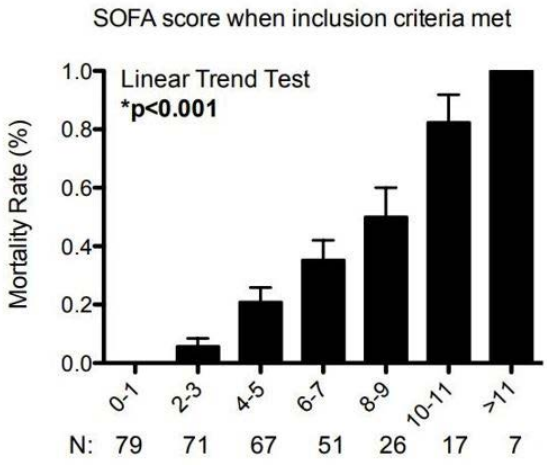

Figure 1. Grouped mortality rate for 7 different levels of SOFA score. Groups differ in between them (Chi-square test, *p<001) and there is linear association between SOFA score level and mortality (Linear Trend Test, *p<0.001).

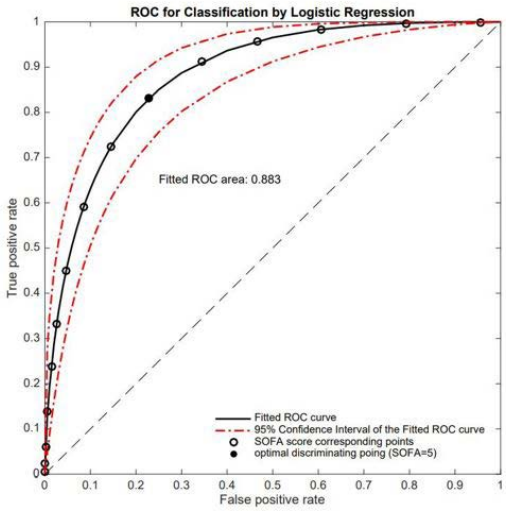

Figure 2. **ROC curve for classification by Logistic Regression. Each classifier level corresponded to a discrete SOFA score level (from 0 to equal or greater than 14). Optimal discrimanation point was calculated as the corresponding classifier point closer to the left upper corner of the graph (coordinates (0,1)).**

CRITICAL CARE 25

A Survey of Contemporary Practice of Critical Care Anesthesiologists in the United States

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INTRODUCTION: An aging and progressively sicker population, the recent pandemic, and concerns around workforce shortages[1-3] has increased discussion around the practice of intensivists. While prior work in the field has looked at the impact of intensivist staffing patterns[4-6], compensation[5-7] and burnout[8-12], there remains little information regarding the practice of critical care anesthesiologists. This survey was conducted to define the current makeup of the contemporary anesthesia critical care workforce and common themes of practice.

METHODS: Following institutional review board approval, a survey was sent to members of the Society of Critical Care Anesthesiologists (SOCCA) using the membership email listserv in May and June of 2021. Members who identified as board-certified critical care anesthesiologists practicing in the United States voluntarily completed an online survey after providing consent. The survey was housed in REDCap and consisted of multiple-choice questions. Biodemographics, intensivist workload, types of intensive care units (ICUs) covered, overnight coverage patterns and compensation were assessed. Analyses were largely descriptive in nature; however, all inferences were evaluated using two-sided tests, with p-values < 0.05 considered statistically significant.

RESULTS: Of the 490 participants invited, 157 (response rate 32.0%) completed surveys were analyzed. The majority of respondents were male (68.8%), under 50 years of age (82.2%) and reported practice across a variety of geographical locations. In addition to their clinical practice in the ICUs, primarily the cardiovascular ICU, and operating room, critical care anesthesiologists reported educational and administrative responsibilities alongside their clinical practice. Respondents that worked in the CVICU were more likely to work in a coverage model with inhouse 24/7 intensivist coverage. Female respondents reported salaries that were $36,739 less than males, however after adjusting for age and practice type these differences were less pronounced (-$27,478, 95% CI: -$57,232.61 to $2,273.03; p = 0.07) when compared to their male counterparts. In both a univariate and multivariable model type of practice and age were associated with compensation, and gender may play a role.

CONCLUSION: This survey provides valuable data around the current anesthesia critical care workforce and the patterns that define its practice. Considerable variability was noted in terms of hours worked per week, shifts worked per month and weeks in an ICU per year. An association between salaries and factors such as practice type and age was observed, however gender may also play a role based on this data. While the survey does not reflect the practice of all critical care anesthesiologists, it opens avenues for further granular investigation, including identifying factors that impact choice of subspecialty and mitigate burnout.

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Table 1. Characteristics of Coverage

	Entire Cohort *N = 157*	Fellowship Graduation Year			
		1986-2004 *N = 21*	2005-2009 *N = 30*	2010-2014 *N = 36*	2015-2020 *N = 70*
ICU Coverage					
Board Certified Intensivists Only	129 (82.2)	18 (85.7)	24 (80.0)	30 (83.3)	57 (81.4)
Intensivists and Non-Intensive Physicians	15 (9.6)	1 (4.8)	3 (10.0)	4 (11.1)	7 (10.0)
24/7 In-House Intensivist Coverage	82 (52.2)	11 (52.4)	19 (63.3)	18 (50.0)	34 (48.6)
Intensivists In-House Daytime & Home Night Call	76 (48.4)	11 (52.4)	10 (33.3)	17 (47.2)	38 (54.3)
Providers Under Their Supervision					
Interns	92 (58.6)	15 (71.4)	16 (53.3)	20 (55.6)	41 (58.6)
Residents	133 (84.7)	20 (95.2)	28 (93.3)	29 (80.6)	56 (80.0)
Fellows	121 (77.1)	17 (81.0)	23 (76.7)	28 (77.8)	53 (75.7)
Nurse Practitioners	125 (79.6)	18 (85.7)	24 (80.0)	29 (80.6)	54 (77.1)
Physician Assistants	105 (66.9)	12 (57.1)	20 (66.7)	24 (66.7)	49 (70.0)
None (Work Independently)	3 (1.9)	---	1 (3.3)	---	2 (2.9)
Daytime Coverage					
Primary Physician of Record	93 (59.2)	11 (52.4)	23 (76.7)	18 (50.0)	41 (58.6)
Consultant Seeing All Unit Patients	86 (54.8)	15 (71.4)	9 (30.0)	21 (58.3)	41 (58.6)
Consultant Seeing Mechanically Ventilated Patients	4 (2.5)	---	1 (3.3)	1 (2.8)	2 (2.9)
Consultant Giving Recommendations on Specific Patients	7 (4.5)	1 (4.8)	1 (3.3)	2 (5.6)	3 (4.3)
Worked Hours / Week When Covering the ICU					
< 40	3 (1.9)	1 (4.8)	1 (3.3)	1 (2.8)	---
40	2 (1.3)	1 (4.8)	---	---	1 (1.4)
41-50	7 (4.5)	2 (9.5)	1 (3.3)	2 (5.6)	2 (2.9)
50-60	25 (15.9)	2 (9.5)	7 (23.3)	5 (13.9)	11 (15.7)
60-70	33 (21.0)	3 (14.3)	3 (10.0)	8 (22.2)	19 (27.1)
70-80	40 (25.5)	6 (28.6)	10 (33.3)	7 (19.4)	17 (24.3)
80-90	34 (21.7)	1 (4.8)	6 (20.0)	11 (30.6)	16 (22.9)
> 90	12 (7.6)	5 (23.8)	2 (6.7)	2 (5.6)	3 (4.3)
Missing	1 (0.6)	---	---	---	1 (1.4)
Consecutive Days/Nights Working in ICU					
1-3	12 (7.6)	2 (9.5)	5 (16.7)	3 (8.3)	2 (2.9)
4-7	114 (72.6)	11 (52.4)	22 (73.3)	28 (77.8)	53 (75.7)
7-14	28 (17.8)	6 (28.6)	3 (10.0)	5 (13.9)	14 (20.0)
14+	2 (1.3)	1 (4.8)	---	---	1 (1.4)
Missing	1 (0.6)	1 (4.8)	---	---	---
Weeks Per Year Coving ICU					
0-5	3 (1.9)	1 (4.8)	---	1 (2.8)	1 (1.4)
5-10	29 (18.5)	5 (23.8)	6 (20.0)	4 (11.1)	14 (20.0)
10-15	71 (45.2)	9 (42.9)	14 (46.7)	18 (50.0)	30 (42.9)
15-20	26 (16.6)	---	5 (16.7)	7 (19.4)	14 (20.0)
20-25	12 (7.6)	4 (19.0)	1 (3.3)	2 (5.6)	5 (7.1)
25-30	9 (5.7)	1 (4.8)	3 (10.0)	1 (2.8)	4 (5.7)
30+	5 (3.2)	1 (4.8)	---	2 (5.6)	2 (2.9)
Missing	2 (1.3)	---	1 (3.3)	1 (2.8)	---
ICU Shifts Covered / Month					
< 5	22 (14.0)	6 (28.6)	5 (16.7)	3 (8.3)	8 (11.4)
5-7	47 (29.9)	4 (19.0)	5 (16.7)	13 (36.1)	25 (35.7)
8-10	40 (25.5)	3 (14.3)	9 (30.0)	11 (30.6)	17 (24.3)

10-12	21 (13.4)	1 (4.8)	6 (20.0)	4 (11.1)	10 (14.3)
13-15	21 (13.4)	5 (23.8)	4 (13.3)	5 (13.9)	7 (10.0)
Other	4 (2.5)	1 (4.8)	1 (3.3)	---	2 (2.9)
Missing	2 (1.3)	1 (4.8)	---	---	1 (1.4)
Most Common Night Coverage Model					
Shift with 24/7 In-House Coverage	85 (54.1)	8 (38.1)	18 (60.0)	18 (50.0)	41 (58.6)
Home Call with Pager After Day Shift	63 (40.1)	10 (47.6)	11 (36.7)	15 (41.7)	27 (38.6)
Handover Fully to Tele-ICU	4 (2.5)	2 (9.5)	---	2 (5.6)	---
No Intensivist Coverage	2 (1.3)	---	---	1 (2.8)	1 (1.4)
Other	3 (1.9)	1 (4.8)	1 (3.3)	---	1 (1.4)
In House Coverage for Faculty on Home Call					
In-Unit Housestaff	38 (24.2)	9 (42.9)	5 (16.7)	9 (25.0)	15 (21.4)
Advance Practice Providers	23 (14.6)	1 (4.8)	6 (20.0)	6 (16.7)	10 (14.3)
Hospitalists	1 (0.6)	---	---	---	1 (1.4)
Tele-ICU Coverage	1 (0.6)	---	---	---	1 (1.4)
Missing					
Responsibilities When Covering ICU	94 (59.9)	11 (52.4)	19 (63.3)	21 (58.3)	43 (61.4)
No Other Formal Responsibilities	135 (86.0)	20 (95.2)	26 (86.7)	29 (80.6)	60 (85.7)
Remote Anesthetizing Locations	8 (5.1)	---	2 (6.7)	3 (8.3)	3 (4.3)
Main Operating Room Anesthesia Provision	1 (0.6)	---	---	---	1 (1.4)
Other	11 (7.0)	---	3 (10.0)	4 (11.1)	4 (5.7)
ICU Coverage Model					
Day Time In-Person Coverage	153 (97.5)	20 (95.2)	30 (100.0)	34 (94.4)	69 (98.6)
Nighttime Coverage In-House	88 (56.1)	9 (42.9)	22 (73.3)	17 (47.2)	40 (57.1)
Nighttime Pager Call	67 (42.7)	10 (47.6)	12 (40.0)	14 (38.9)	31 (44.3)
Tele-ICU	13 (8.3)	5 (23.8)	3 (10.0)	2 (5.6)	3 (4.3)
Other	2 (1.3)	1 (4.8)	1 (3.3)	---	---
N/A	1 (0.6)	---	---	1 (2.8)	---
Beds Covered					
Day Shift	14 (12, 18)	15 (12, 18)	15 (10, 21)	12 (10, 16)	12 (10, 16)
Night Shift	26 (20, 40)	32 (16, 45)	24 (18, 26)	27 (20, 40)	27 (20, 40)
Nighttime Pager Call	19 (12, 24)	22 (17, 24.5)	19 (15, 24)	20 (12, 26)	20 (12, 26)
Tele-ICU	100 (80, 140)	85 (80, 100)	80 (80, 100)	150 (140, 185)	150 (140, 185)
Allied Specialties Involved in Rounds					
Pharmacists	152 (96.8)	20 (95.2)	30 (100.0)	35 (97.2)	67 (95.7)
Social Workers	48 (30.6)	6 (28.6)	9 (30.0)	11 (30.6)	22 (31.4)
Occupational Therapists	29 (18.5)	5 (23.8)	6 (20.0)	4 (11.1)	14 (20.0)
Physical Therapists	36 (22.9)	5 (23.8)	9 (30.0)	7 (19.4)	15 (21.4)
Respiratory Therapists	105 (66.9)	17 (81.0)	22 (73.3)	23 (63.9)	43 (61.4)
Billing Personnel / Coders	6 (3.8)	1 (4.8)	2 (6.7)	1 (2.8)	2 (2.9)
Other	12 (7.6)	2 (9.5)	3 (10.0)	3 (8.3)	4 (5.7)
None of the Above	2 (1.3)	---	---	1 (2.8)	1 (1.4)

Values are presented as n (%) or median (quartile 1, quartile 3) depending on variable type.

Table 2. Characteristics of Organizational Practice

	Entire Cohort *N = 157*	Fellowship Graduation Year			
		1986-2004 *N = 21*	2005-2009 *N = 30*	2010-2014 *N = 36*	2015-2020 *N = 70*
Primary Practice Composition					
Academic	129 (82.2)	18 (85.7)	24 (80.0)	28 (77.8)	59 (84.3)
Private	8 (5.1)	1 (4.8)	2 (6.7)	2 (5.6)	3 (4.3)
Hybrid	18 (11.5)	1 (4.8)	4 (13.3)	5 (13.9)	8 (11.4)
Tele-ICU	1 (0.6)	1 (4.8)	---	---	---
Other	1 (0.6)	---	---	1 (2.8)	---
Practice Type					
Tertiary / Quaternary Medical Center	129 (82.2)	18 (85.7)	24 (80.0)	28 (77.8)	59 (84.3)
Affiliated ICU Community Practice	7 (4.5)	---	---	1 (2.8)	6 (8.6)
Unit Type					
Open	18 (11.5)	3 (14.3)	1 (3.3)	3 (8.3)	11 (15.7)
Semi-Open	30 (19.1)	1 (4.8)	8 (26.7)	8 (22.2)	13 (18.6)
Semi-Closed	67 (42.7)	12 (57.1)	12 (40.0)	16 (44.4)	27 (38.6)
Closed	41 (26.1)	5 (23.8)	9 (30.0)	9 (25.0)	18 (25.7)
Missing	1 (0.6)	---	---	---	1 (1.4)
Unit Director Department					
Anesthesia	125 (79.6)	17 (81.0)	24 (80.0)	29 (80.6)	55 (78.6)
Surgery	80 (51.0)	13 (61.9)	14 (46.7)	20 (55.6)	33 (47.1)
Medicine	26 (16.6)	5 (23.8)	4 (13.3)	7 (19.4)	10 (14.3)
Neurology	20 (12.7)	4 (19.0)	4 (13.3)	6 (16.7)	6 (8.6)
Independent Critical Care	11 (7.0)	2 (9.5)	4 (13.3)	1 (2.8)	4 (5.7)
Other	2 (1.3)	1 (4.8)	---	---	1 (1.4)
Parent Department for ICU Services					
Anesthesia	137 (87.3)	17 (81.0)	23 (76.7)	32 (88.9)	65 (92.9)
Surgery	4 (2.5)	- -	2 (6.7)	- -	2 (2.9)
Medicine	11 (7.0)	2 (9.5)	3 (10.0)	4 (11.1)	2 (2.9)
Other	4 (2.5)	2 (9.5)	2 (6.7)	---	---
Missing	1 (0.6)	---	---	---	1 (1.4)
ICU Provision Performed by Intensivists					
0-24%	19 (12.1)	2 (9.5)	3 (10.0)	8 (22.2)	6 (8.6)
25-49%	15 (9.6)	2 (9.5)	5 (16.7)	4 (11.1)	4 (5.7)
50-74%	58 (36.9)	11 (52.4)	9 (30.0)	13 (36.1)	25 (35.7)
75-100%	64 (40.8)	6 (28.6)	13 (43.3)	11 (30.6)	34 (48.6)
Missing	1 (0.6)	---	---	---	1 (1.4)
Anesthesia Critical Care Provision Within Critical Care					
0-24%	47 (29.9)	3 (14.3)	9 (30.0)	15 (41.7)	20 (28.6)
25-49%	60 (38.2)	7 (33.3)	11 (36.7)	12 (33.3)	30 (42.9)
50-74%	45 (28.7)	9 (42.9)	9 (30.0)	9 (25.0)	18 (25.7)
75-100%	3 (1.9)	1 (4.8)	1 (3.3)	---	1 (1.4)
Missing	2 (1.3)	1 (4.8)	---	---	1 (1.4)
Average CPT 99291 / 9929 Charges Per Day					
< 10	45 (28.7)	4 (19.0)	8 (26.7)	9 (25.0)	24 (34.3)
11-15	71 (45.2)	10 (47.6)	15 (50.0)	17 (47.2)	29 (41.4)

16-20	13 (8.3)	2 (9.5)	2 (6.7)	3 (8.3)	6 (8.6)
21-25	3 (1.9)	---	---	---	3 (4.3)
> 25	2 (1.3)	---	1 (3.3)	---	1 (1.4)
Unsure	23 (14.6)	5 (23.8)	4 (13.3)	7 (19.4)	7 (10.0)
Pay Structure					
Solely per Shift Payment	4 (2.5)	1 (4.8)	---	---	3 (4.3)
Pay Per Shift	2160 (1830, 2480)	2160 (2160, 2160)	---	2160 (1500, 2800)	2160 (1500, 2800)
Solely Salaried with No Incentives for Calls	30 (19.1)	3 (14.3)	12 (40.0)	5 (13.9)	10 (14.3)
Salary with Bonus Structure	34 (21.7)	5 (23.8)	4 (13.3)	12 (33.3)	13 (18.6)
Salary with Additional Pay Per Call	39 (24.8)	5 (23.8)	6 (20.0)	7 (19.4)	21 (30.0)
Salary with Pay Per Call and Bonus Structure	55 (35.0)	8 (38.1)	9 (30.0)	12 (33.3)	26 (37.1)
Hourly Rate Reimbursement for Critical Care					
< $200	50 (31.8)	6 (28.6)	10 (33.3)	15 (41.7)	19 (27.1)
$200-215	16 (10.2)	3 (14.3)	2 (6.7)	3 (8.3)	8 (11.4)
$216-230	6 (3.8)	2 (9.5)	2 (6.7)	---	2 (2.9)
$230-250	6 (3.8)	---	2 (6.7)	3 (8.3)	1 (1.4)
> $250	3 (1.9)	---	2 (6.7)	---	1 (1.4)
Unsure	75 (47.8)	9 (42.9)	12 (40.0)	15 (41.7)	39 (55.7)
Missing	1 (0.6)	1 (4.8)	---	---	---
Stipend to Provide Critical Care					
Yes	27 (17.2)	4 (19.0)	5 (16.7)	8 (22.2)	10 (14.3)
No	112 (71.3)	16 (76.2)	24 (80.0)	21 (58.3)	51 (72.9)
Unsure	17 (10.8)	1 (4.8)	---	7 (19.4)	9 (12.9)
Missing	1 (0.6)	---	1 (3.3)	---	---
Non-Clinical Compensation Following ICU Shifts					
No	56 (35.7)	8 (38.1)	11 (36.7)	12 (33.3)	25 (35.7)
Yes	101 (64.3)	13 (61.9)	19 (63.3)	24 (66.7)	45 (64.3)
Non-Clinical Compensation Days for Every 7 Worked					
1	31 (31.00)	5 (38.46)	5 (26.32)	6 (26.09)	15 (33.33)
2-3	40 (40.00)	6 (46.15)	8 (42.11)	8 (34.78)	18 (40.00)
4-6	17 (17.00)	---	4 (21.05)	4 (17.39)	9 (20.00)
7+	12 (12.00)	2 (15.38)	2 (10.53)	5 (21.74)	3 (6.67)

Values are presented as n (%) or median (quartile 1, quartile 3) depending on variable type.

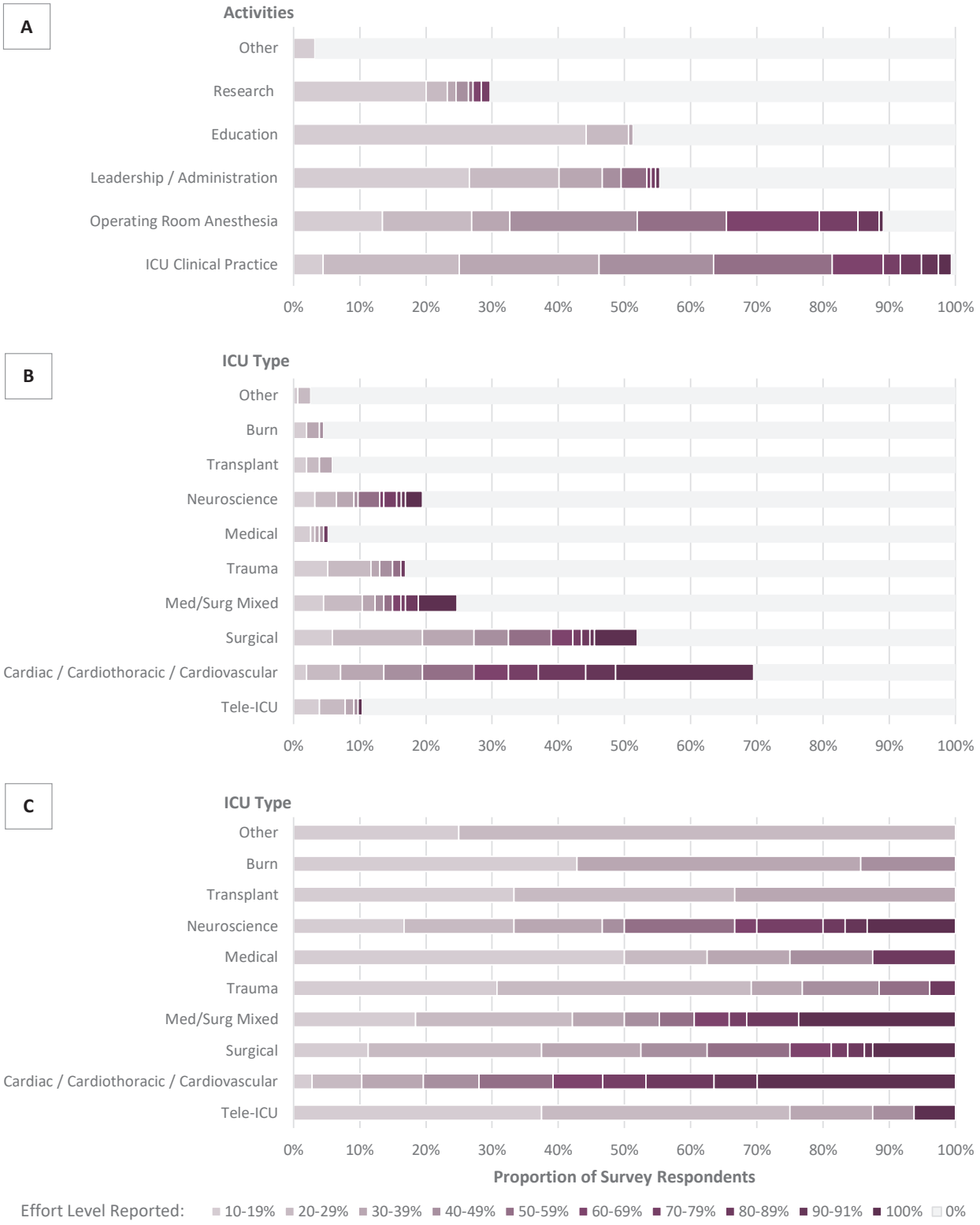

Figure 1. Analysis of Effort Levels
A breakdown of respondents work activities are described in Panel A. In Panel B, ICU units that respondents indicate working in are described, along with the effort levels reported. Respondents primarily reported working in a cardiovascular unit. Further, in Panel C, the breakdown of ICU type is reported *among those who report working in that unit*. Participants who did not report working in a unit are excluded from Panel C.

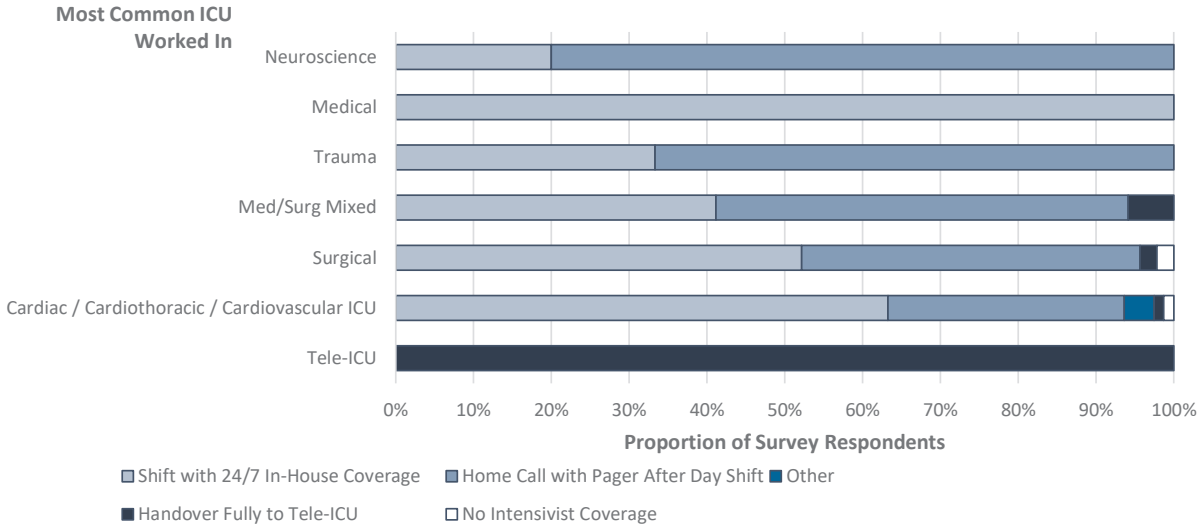

Figure 2. Most Common Night Coverage Model

Data is presented on the most common night time coverage model for each of the ICUs. Respondents were categorized based off the ICU they reported working in most commonly. A significantly different coverage model was reported across units (p = 0.0003).

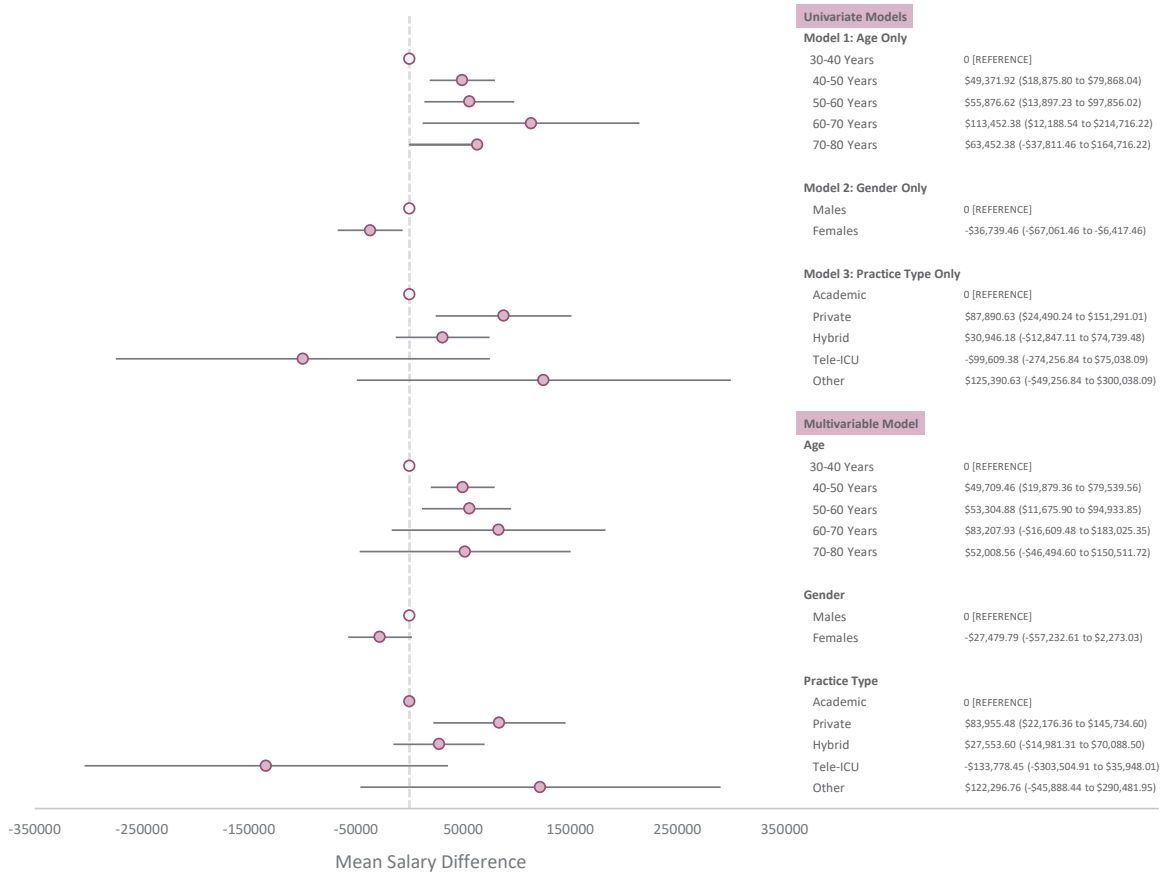

Figure 3. Salary Effect Estimates
The mean difference in salaries (purple dots) and the associated 95% confidence intervals (error bars) are presented in three unadjusted models. Further, estimates are presented from a multivariable model include age, sex and practice type. In order to generate salary levels from the reported categories, the mean values were used for analysis. White points represent the referent category.

CRITICAL CARE 26

Prolonged unconsciousness is common in severe COVID-19 and is associated with hypoxemia

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INTRODUCTION: For survivors of severe coronavirus disease 2019 (COVID-19), the re-emergence of consciousness is often prolonged[1], leading to clinical and ethical uncertainty surrounding neurologic prognosis and goals of care[2]. Early in the pandemic, we and others observed a high incidence of prolonged disorders of consciousness in patients with ARDS from severe COVID-19[3-5], often in those with prior hypoxemia[2,5-7]. However, the natural history of prolonged unconsciousness in severe COVID-19 remains unknown. Here, in a retrospective study of 795 intubated patients with severe COVID-19 at three medical centers during the initial surge (March–July 2020), and 427 patients during the second surge (October 2020–April 2021), we determined the time to recovery of command following and its association with hypoxemia.

METHODS: Patients were included if admitted to one of three academic hospitals with a clinical presentation of severe COVID-19[3], endotracheal intubation for at least seven days, and impairment of consciousness, defined by a Glasgow Coma Scale (GCS) motor score less than six[8]. We estimated the time from intubation to recovery of command following (defined as a GCS motor score of six) using Kaplan-Meier cumulative incidence curves. Our primary outcome was recovery of consciousness, specifically the last recovery of command following during hospitalization. Our primary exposure was hypoxemia, defined as a partial pressure of oxygen (PaO_2) value below two set thresholds (55 mmHg and 70 mm Hg) based on ARDSNet protocols[9]. For the initial surge (n = 795), we estimated the hazard of hypoxemia on time to recovery of command following using univariate Cox proportional-hazards regression models, with multivariate adjustment for demographics (age, sex, race/ethnicity), level of sedation (cumulative sedative dose, days of sedation), and severity of illness (lowest P:F ratio on day of intubation, days of continuous neuromuscular blockade, use of continuous renal replacement therapy). We further computed Kaplan-Meier cumulative incidence curves for 1) the subset of patients in the first surge with no evidence of structural neurologic injury on head imaging (n = 199) and 2) intubated patients in the second surge (n = 427).

RESULTS: In the initial surge, 571 of the 795 included patients recovered command following. The median time to recovery of command following was 30 days (95%-confidence interval [CI]: 27-32). Median time to recovery of command following increased by 16 days for patients with at least one episode of an arterial partial pressure of oxygen (PaO_2) value ≤ 55 mmHg ($p<0.001$), and 25% recovered ≥ 10 days after cessation of mechanical ventilation (Figure 1). The time to recovery of consciousness was associated with hypoxemia (PaO_2 ≤ 55 mmHg hazard ratio (HR): 0. 56, 95%-CI: 0.46 – 0.68; PaO_2 ≤ 70 HR: 0.88, 95%-CI: 0.85 – 0.91), and each additional day of hypoxemia decreased the likelihood of recovery, after accounting for cofactors including level of sedation and severity of illness (Figure 2). Our findings were confirmed in the subset of patients without any imaging evidence of neurologic injury (n = 199; Figure 3), and in a non-overlapping second surge cohort (n = 427; Figure 4).

CONCLUSION: The results of this multi-center, retrospective cohort study demonstrate that in severe COVID-19 recovery of command following 30 days after intubation is common if supportive care is provided. Prolonged unconsciousness is associated with hypoxemic events in a dose-dependent manner. Hypoxemia remains associated with time to recovery of command following in severe COVID-19 after adjustment for demographics, sedation exposures, and disease severity. This prolonged time to recovery, particularly exhibited in patients with hypoxemia, was observed in three large medical centers, and confirmed in patients without evidence of neurologic injury as well as an out-of-sample cohort from the second surge. Prolonged time to recovery of command following, as observed in our study, should be considered in goals of care discussions between clinicians and surrogate decision makers. Further, our results underscore the need to investigate the underlying mechanisms of prolonged recovery of consciousness following severe COVID-19 and motivate studies to identify laboratory, imaging, and electrophysiological predictors of recovery.

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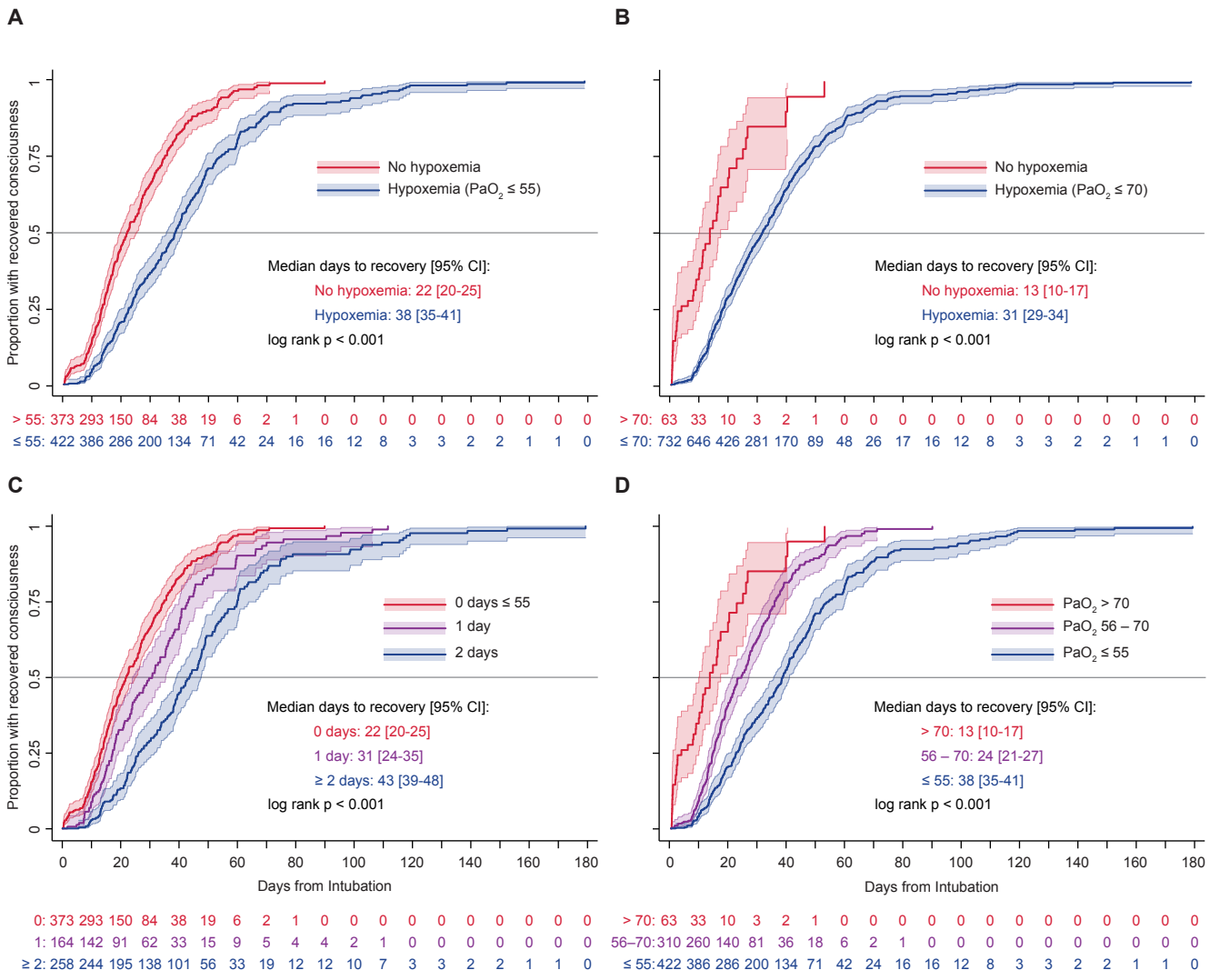
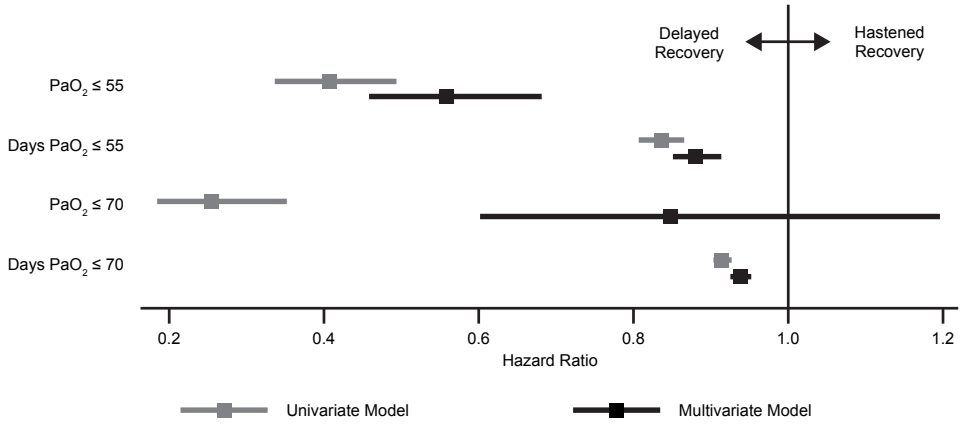
Figure 1. Kaplan-Meier cumulative incidence curves for recovery of consciousness in patients with and without hypoxemia for initial surge (n = 795; March – July 2020).



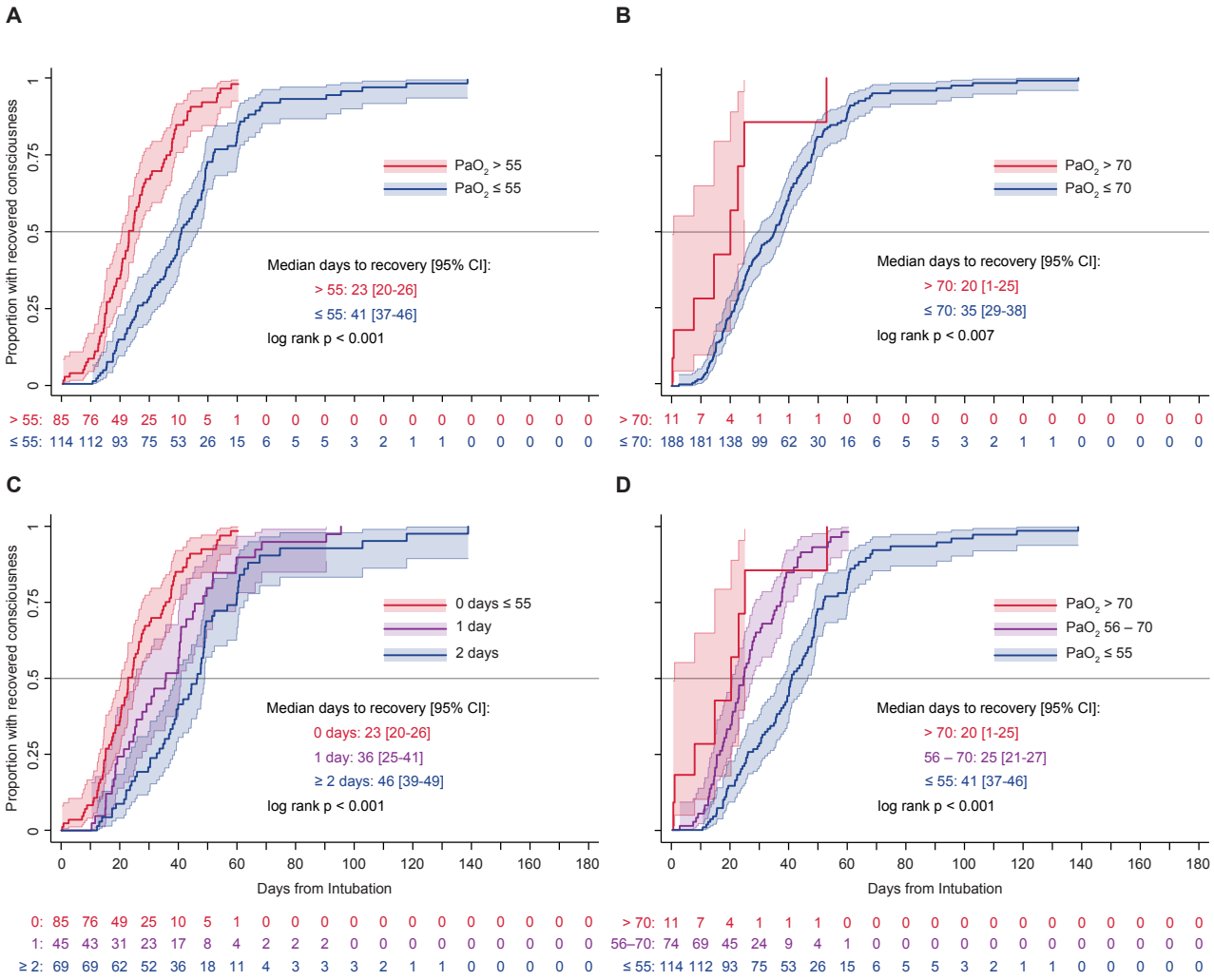
Kaplan-Meier (K-M) curves for recovery of command following in patients grouped by: A) minimum PaO_2 ≤ 55 mmHg versus > 55 mmHg; B) minimum PaO_2 ≤ 70 mmHg versus > 70 mmHg; C) number of days of PaO_2 ≤ 55 mmHg; D) minimum PaO_2 per patient.

Figure 2. Pooled univariate and multivariable hazard ratios of primary hypoxemia exposure from Cox proportional hazard regressions clustered by site, initial surge (March – July 2020).



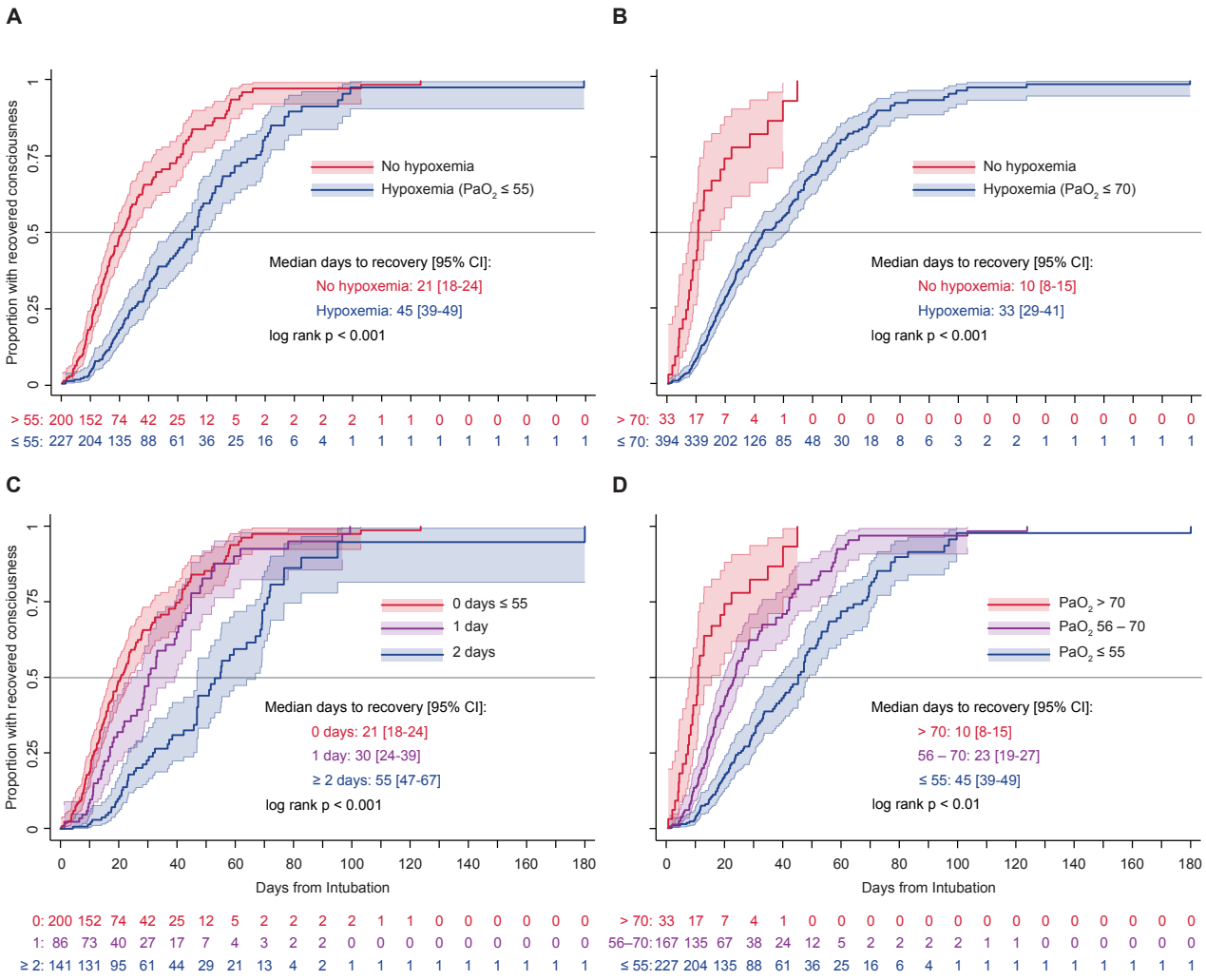
Each point estimate represents an independent regression model; 95% confidence intervals are associated with corresponding bars. Multivariable regressions included the exposure listed as well as covariates for demographics (age, sex, race/ethnicity), level of sedation (cumulative analgesic and sedative dose, duration of continuous analgesic and sedative), and severity of illness (ARDS severity, neuromuscular blockade, CRRT).

Figure 3. Kaplan-Meier cumulative incidence curves for recovery of consciousness in patients in initial surge (March – July 2020) with head imaging and without evidence of neurologic injury (n = 199).



Kaplan-Meier (K-M) curves for recovery of command following in patients grouped by: A) minimum PaO_2 ≤ 55 mmHg versus > 55 mmHg; B) minimum PaO_2 ≤ 70 mmHg versus > 70 mmHg; C) number of days of PaO_2 ≤ 55 mmHg; D) minimum PaO_2 per patient.

Figure 4. Kaplan-Meier cumulative incidence curves for recovery of consciousness in patients with and without hypoxemia for second surge (n = 427; October 2020 – April 2021).



Kaplan-Meier (K-M) curves for recovery of command following in patients grouped by: A) minimum PaO_2 ≤ 55 mmHg versus > 55 mmHg; B) minimum PaO_2 ≤ 70 mmHg versus > 70 mmHg; C) number of days of PaO_2 ≤ 55 mmHg; D) minimum PaO_2 per patient.

CRITICAL CARE 27

Disparities in Survival after Severe COVID-19-related Critical Illness: A Nationwide Study in 466 ICUs in the US

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INTRODUCTION: There is conflicting information on racial and ethnic disparities in survival after hospitalization for COVID-19-related illness in the United States. Our objective was examine the association between race and ethnicity, and death/discharge-to-hospice (primary outcome) amongst adults diagnosed with severe COVID-19 (those receiving mechanical ventilation within two days of hospitalization) between April 1st and December 31st, 2020, (study population).

METHODS: In this cohort study, de-identified data from COVID+ patients was extracted from the Premier Healthcare Database (PHD), one of the nation's largest hospital discharge databases in the US. Inclusion criteria were patients 18 years of age or older with an International Classification of Disease, 10th revision, Clinical Modification [ICD-10-CM] diagnosis code of U0.7, admitted to the ICU between April 1st and June 30th, 2020. Subjects from hospitals were excluded if reported to be unknown/other race/ethnicity. Patients with incomplete information for race or zip code and those who were readmitted to or transferred to another hospital within 30 days of initial admission were also excluded to prevent misattributing hospital-level outcomes among patients admitted to multiple hospitals. The final sample included all critically ill Hispanic, non-Hispanic Black, and non-Hispanic White patients with a diagnosis of COVID-19. Mortality or hospice designation throughout the hospital visit was identified and patients were grouped in nine mutually exclusive categories based on race and ethnicity codes in standard claims forms submitted by PHD member hospitals, however we only reported data on the three largest groups: Hispanic, non-Hispanic Black, and non-Hispanic White patients. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The primary outcome measure was the composite of either inpatient mortality or discharge to hospice. This composite measures a more complete representation of the outcome of interest over mortality alone because it reflects a more accurate depiction of end-of-life care, given known racial disparities in hospice use both in rate and quality (Johnson). A series of nested logistic regression models were created to study the sequential effects of patient-level factors associated with outcomes of interest. In addition to our unadjusted data (model A), subsets created to examine age and sex (model B) as well as comorbidities (model C). All statistical tests were 2-sided, with statistical significance set at $P < 0.05$. All analyses were conducted using SAS version 9.4 (SAS Institute).

RESULTS: In the PHD, 14,370 patients were admitted to 466 hospitals and included in the final analysis. The cohort included 8696 (60.5%) men with a median [IQR] age of 65 [54, 74] years. Non-Hispanic White patients were more likely to be older, married, and admitted from skilled nursing facility or other intensive care-containing facilities. Overall, 1441 (47.6%) Hispanic patients, 1403 (46.8%) non-Hispanic Black, and 2843 (48.4%) non-Hispanic White patients experienced in-hospital mortality while 71 (2.3%), 98 (3.3%), and 289 (4.9%) patients were discharged to hospice, respectively; mortality or discharged-to-hospice rate of 50.0% for Hispanic patients, 50.1% for non-Hispanic Black, and 53.3% for non-Hispanic White patients. Without adjustment, all groups had similar odds of mortality or discharge to hospice (odds ratio [OR], 1.06; 95% CI, 0.99-1.12; $P < 0.05$). Compared with the unadjusted model, adjustments for age and sex increased estimates of the mortality-equivalent disparity given older age and male sex are known to increase risk but less frequently represented in both the Hispanic and non-Hispanic Black patients in the sample. Sequential adjustment for age, sex, and comorbidities only showed a persistent difference between Hispanic and non-Hispanic White patients.

CONCLUSION: In this sample of severe COVID-19 patients across 466 ICUs in the US, race was not but ethnicity was associated with survival in analyses adjusted for age, sex, and baseline chronic illness. Overall, ICUs appear to have provided equitable care across racial groups.

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Table 1. Characteristics of Patients and Hospitals for the three largest Racial/ Ethnic Groups (differences versus NHW, p<0.001)

Baseline Patient Characteristics	**Non-Hispanic White, N (%)**	**Non-Hispanic Black, N (%)**	**Hispanic, N (%)**
Number (Proportion of Total Population) *	5871 (40.8%)	2995 (20.8%)	3027 (21.1%)
Age			
Median in Years [IQR]	69 [59, 77]	64 [54, 72]	60 [48, 71]
Number (Proportions) between 65 - 80 years old	2553 (43.5%)	1116 (37.3%)	850 (28.1%)
Number (Proportions) > 80 years old	1110 (18.9%)	311 (10.4%)	311 (10.3%)
Male	3513 (59.8%)	1595 (53.3%)	1971 (65.1%)
Married	2583 (44.0%)	889 (29.7%)	1064 (35.2%)
Transferred from Different Facility	1231 (21.0%)	494 (16.5%)	481 (15.9%)
Transfer from SNF or Int Care Fac	459 (7.8%)	142 (4.7%)	35 (1.2%)
Insurance			
Managed Care	796 (13.6%)	412 (13.8%)	469 (15.5%)
Medicaid	510 (8.7%)	510 (17.0%)	721 (23.8%)
Medicare	3848 (65.5%)	1655 (55.3%)	1122 (37.1%)
Other	717 (12.2%)	418 (14.0%)	715 (23.6%)
Median vanWalraven Score (IQR)	7 [2, 12]	8 [3, 13]	5 [1, 11]

Comorbidities grouped per the Elixhauser algorithm			
Congestive heart failure	1606(27.4%)	840(28.0%)	481(15.9%)
Hypertension	4309(73.4%)	2481(82.8%)	1939(64.1%)
Other neurological disorders	999(17.0%)	474(15.8%)	311(10.3%)
Chronic pulmonary disease	1933(32.9%)	790(26.4%)	477(15.8%)
Diabetes w/o chronic complications	650(11.1%)	365(12.2%)	375(12.4%)
Diabetes w/ chronic complications	1929(32.9%)	1272(42.5%)	1151(38.0%)
Hypothyroidism	1107(18.9%)	290(9.7%)	295(9.7%)
Renal failure	1242(21.2%)	998(33.3%)	586(19.4%)
Coagulopathy	755(12.9%)	388(13.0%)	408(13.5%)
Obesity	1991(33.9%)	1148(38.3%)	1077(35.6%)
Weight loss	510(8.7%)	245(8.2%)	263(8.7%)
Deficiency Anemias	1560(26.6%)	1099(36.7%)	841(27.8%)
Depression	892(15.2%)	222(7.4%)	182(6.0%)
Hospital Characteristics			
Teaching	3125 (53.2%)	1771 (59.1%)	1724 (57.0%)
Urban	5016 (85.4%)	2620 (87.5%)	2707 (89.4%)
Hospital Size over 500 beds	2115 (36.0%)	1249 (41.7%)	1279 (42.3%)

Table 2. Patient Outcomes for the three largest Racial/ Ethnic Groups (differences versus NHW, p<0.001)

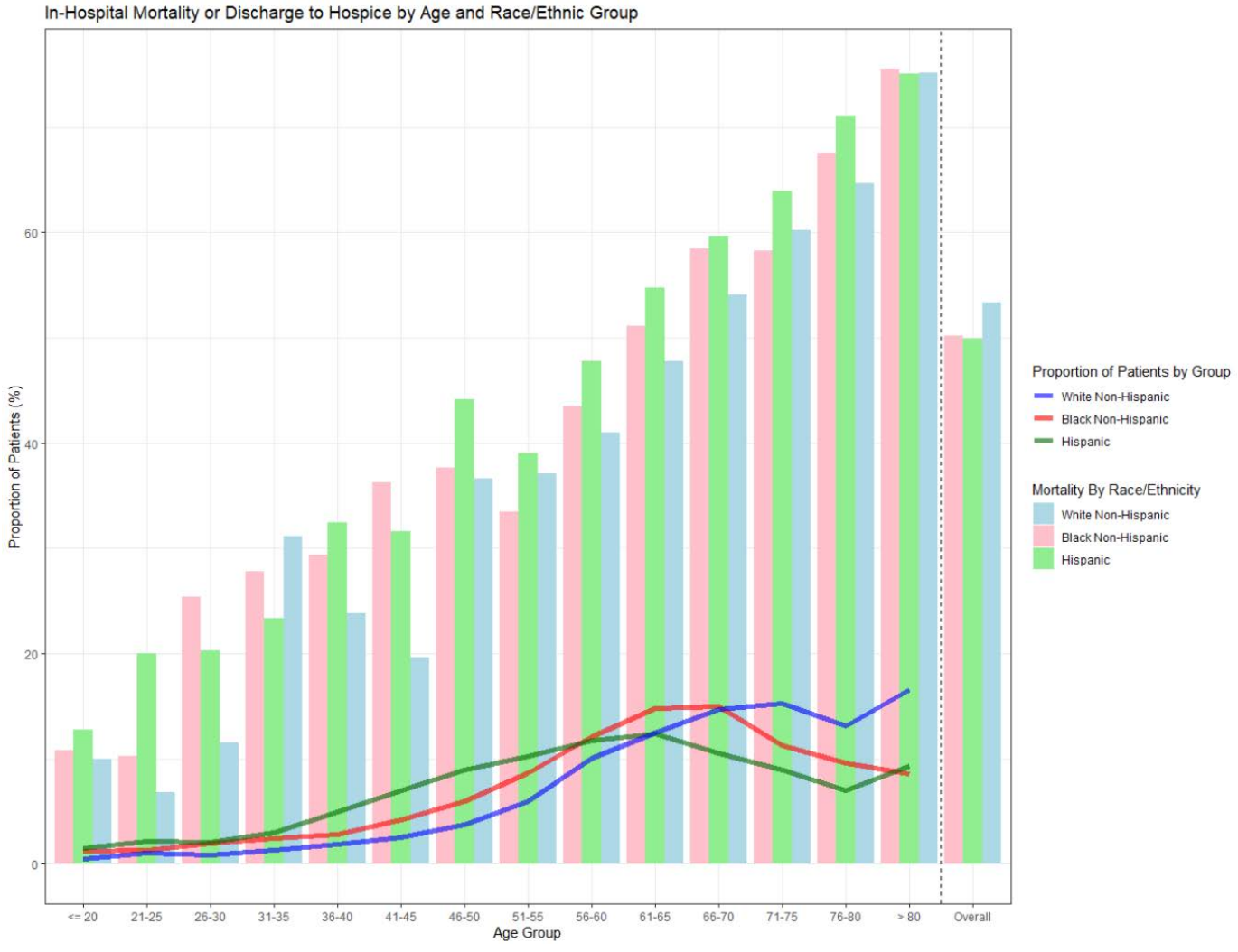
Patient Outcomes	Non-Hispanic White, N (%)	Non-Hispanic Black , N (%)	Hispanic, N (%)
Number (Proportion of Total Population) *	5871 (40.8%)	2995 (20.8%)	3027 (21.1%)
Discharge Status			
Expired in Hospital	2843 (48.4%)	1403 (46.8%)	1441 (47.6%)
Hospice	289 (4.9%)	98 (3.3%)	71 (2.3%)
Expired in Hospital or Hospice	3132 (53.3%)	1501 (50.1%)	1512 (50.0%)
Median Length of Stay (IQR)	10 [5, 18]	12 [6, 21]	14 [7, 24]
ICU Length of Stay Days *Among those admitted			
Median (IQR)	7 [3, 14]	8 [4, 16]	11 [5, 20]
Median IMV Days (IQR)	6 [2, 12]	7 [3, 14]	9 [4, 17]
Vasopressors	3132 (53.3%)	1700 (56.8%)	1793 (59.2%)
Vasopressors on or before Hospital Day 2	2086 (35.5%)	1094 (36.5%)	1051 (34.7%)
Vasopressor Duration Days *Among those with vasopressors			
Median (IQR)	2 [1, 4]	2 [1, 5]	3 [1, 5]
CPR	478 (8.1%)	367 (12.3%)	344 (11.4%)

*Patients within the Hispanic group represent all patients with a Hispanic ethnicity designation (whether the race of Black, White, or undefined). Supplemental table with more expansion that represents all different races within the Hispanic ethnicity designation.

Table 3. Unadjusted and Adjusted Odds Ratios for COVID-19 Inpatient Mortality or Discharge to Hospice Among Non-Hispanic Black and Hispanic Patients Compared with Non-Hispanic White Patients

	Odds Ratios (95% CI) in reference to non-Hispanic White Patients	
Model	**Non-Hispanic Black**	**Hispanic**
A. Unadjusted Odds of Death/Hospice	0.88 (0.81-0.96)	0.87 (0.80-0.95)
B. Adjusted Odds of Death/Hospice for Age and Sex	1.12 (1.02-1.23)	1.26 (1.14-1.38)
C. Same as B plus Comorbidities	1.01 (0.91-1.11)	1.15 (1.04-1.27)
D. Same as C plus adm from SNF & outside hospital	1.14 (1.04-1.26)	1.28 (1.17-1.41)

Figure 1: In-Hospital Mortality or Discharge to Hospice by Age and Race/Ethnicity Stratified by 5-year Increments



CRITICAL CARE 28

Long term renal outcome of patients requiring de novo renal replacement therapy after cardiac surgery

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[1]Columbia University Vagelos College of Physicians and Surgeons, New York, NY, [2]Columbia University Medical Center, New York, NY

INTRODUCTION: Outcomes after cardiac surgery are generally good but occasionally patients may acquire organ failure and specifically acute kidney injury (AKI) due to hemodynamic instability, hypoperfusion and high vasopressor requirements. While the incidence of AKI is up to 30% after cardiac surgery, only a few patients will require (continuous) renal replacement therapy (CRRT) if they had no end-stage renal disease (ESRD) requiring dialysis prior to surgery. 24% of medically critical ill patients with AKI who require CRRT and survive critical illness will chronically need dialysis[1]. We do not know however if this statistic holds true for patients who require de novo CRRT after cardiac surgery.

METHODS: We retrospectively studied all patients who underwent cardiac surgery at an academic medical center in 2011. We identified patients who required CRRT postoperatively and assessed if they had pre-existing ESRD or if this was their first episode of RRT. Chronic dialysis dependence was defined as patients who continued to require RRT 90 days and one year after surgery. Dialysis-free survival was plotted using Kaplan-Meier curve.

RESULTS: All 1551 patients who underwent cardiac surgery at an academic medical center in 2011 were included in this study. As previously reported[2] 449 patients developed AKI defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria. 20 patients (1.28%) required CRRT perioperatively. 15 of these (75%) had pre-existing chronic kidney disease. Two of the 20 patients required CRRT before surgery, four immediately after surgery and 12 within 1 to 15 days after surgery. Six patients required CRRT for less than a week, four less than two weeks and three less than 90 days. Of the remaining seven patients, four patients required RRT for less than a year (three of these died 18 +/- 1 days after surgery) and three required long-term RRT. The figure depicts the liberation from RRT during the first year.

CONCLUSION: Seven of 20 patients who required CRRT after cardiac surgery continued to require RRT after 90 days. One of them was liberated from RRT and the remaining either died or continued to require RRT after one year. This data will help us provide necessary information to families who frequently must make the difficult decision if starting CRRT will help provide good long-term outcomes despite severe multi-organ failure and critical illness.

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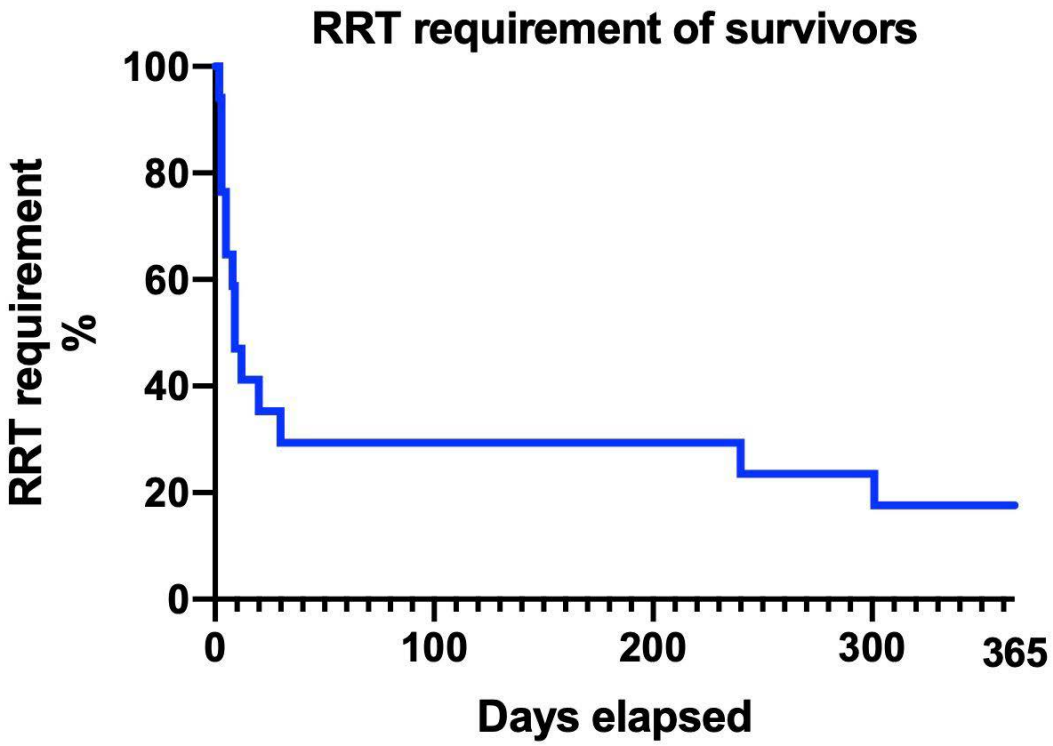

Fig. 1

CRITICAL CARE 29

Antibiotic Use in a Russian Neurosurgical ICU Decreased After Implementing Antibiotic Stewardship Program

Ksenia Ershova[1], Ivan Savin[2], Dustin R Long[1], Gleb Danilov[2], Michael Shifrin[2], Olga Ershova[2]

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INTRODUCTION: Antibiotic stewardship (AS) interventions are effective in decreasing antibiotic use [1]. However, reports on AS implementation and its impact on antibiotic use in Russia are limited. The objective of this study was to assess the use of antibiotics in a Russian neurosurgical ICU over ten years following implementation of an AS program.

METHODS: This prospective cohort study was conducted from 2011 to 2020 and included patients of all ages who stayed >48h in the neurosurgical ICU. An AS program in combination with infection prevention and control program was implemented in 2010. Main AS elements included staff education, active surveillance for antibiotic resistance, and improved antibiotic supply. We calculated daily usage, length of therapy (LOT), and antibiotic use by class and analyzed changes in these metrics over time using yearly, monthly, and daily aggregates. LOT and use by class were evaluated separately in patients with and without ICU infections, including urinary, respiratory, bloodstream, surgical site, and CNS infections. P-values were obtained from a linear regression.

RESULTS: A total of 4258 ICU admissions were included, with one or more ICU infections occurring in 2068 (48.6%) admissions. The mean daily prevalence of ICU infections declined over the study period from 57.5% in 2011 to 55.1% in 2020 (p=0.027).

On average, at any given day in 2011, 96.3±4.7% of patients in the ICU received antibiotics. This number decreased significantly to 87.6±13% in 2020, p-value <0.0001, Figure 1.

In ten years, the median LOT decreased by 54% (13 days [Q1,Q3: 5, 22] in 2011 vs. 6 days [Q1,Q3: 2, 16.75] in 2020) in patients with infections, and in patients without infections it dropped to 0 (2 days [Q1,Q3: 0, 6] in 2011 vs. 0 days [Q1,Q3: 0, 2] in 2020), Figure 2. When adjusted for length of ICU stay, median LOT decreased only for patients without infections (82 days [Q1,Q3: 75, 89] per 100 patient-days in 2011 vs. 55 days [Q1,Q3: 46, 61] per 100 patient-days in 2020, p-value <0.0001). In patients with infections it remained unchanged at a median of 99 days [Q1,Q3: 98, 100] per 100 patient-days, Figure 3.

The most commonly administered antibiotics were carbapenems (18.8%), vancomycin (13.5%), and polymyxins (12.0%). Over the ten-year study period, utilization of more restricted/higher generation antibiotic classes increased (Figures 4-5, red), while utilization of narrower classes with less concern for resistance including lower-generation agents decreased (Figures 4-5, green). Among patients with ICU infection, this shift was driven by increased utilization of carbapenems, polymyxins, tetracyclines (primarily tigecycline), and linezolid (Figure 4). Among patients without infection, increased use of penicillin/inhibitor combinations, carbapenems and fluoroquinolones was observed (Figure 5).

CONCLUSION: The implementation of an AS program in a Russian neurosurgical ICU was associated with a significant reduction in inappropriate prophylactic use of antibiotics among patients without a diagnosis of infection. However, in both patient groups (with and without infection), antibiotic utilization shifted towards higher-generation antibiotic classes with more concern for resistance despite AS measures.

REFERENCE(S):

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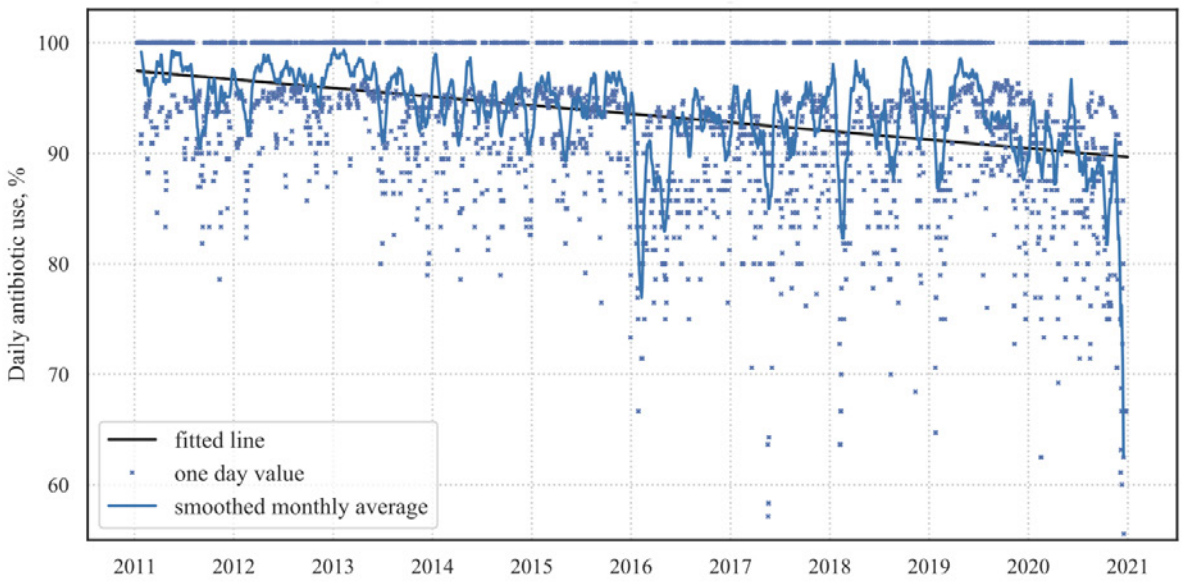

Figure 1. Daily antibiotic use in neurosurgical ICU patients in 2011-2020; % of patients receiving antibiotics at particular day out of all patients in the ICU at that same day.

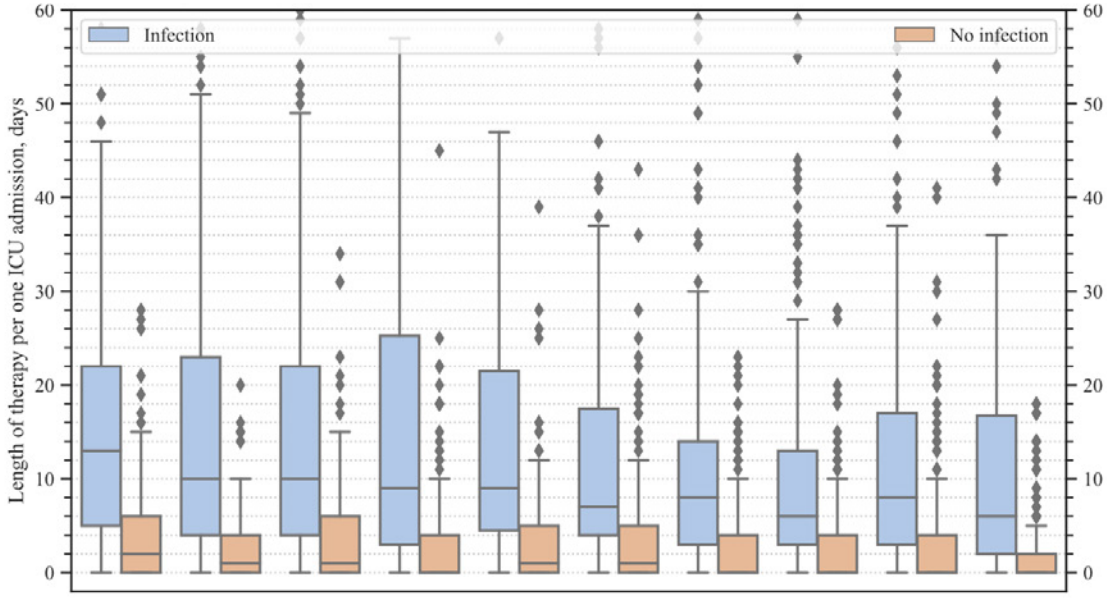

Figure 2. Length of therapy per one ICU admission in neurosurgical ICU patients with an without ICU infections in 2011-20220

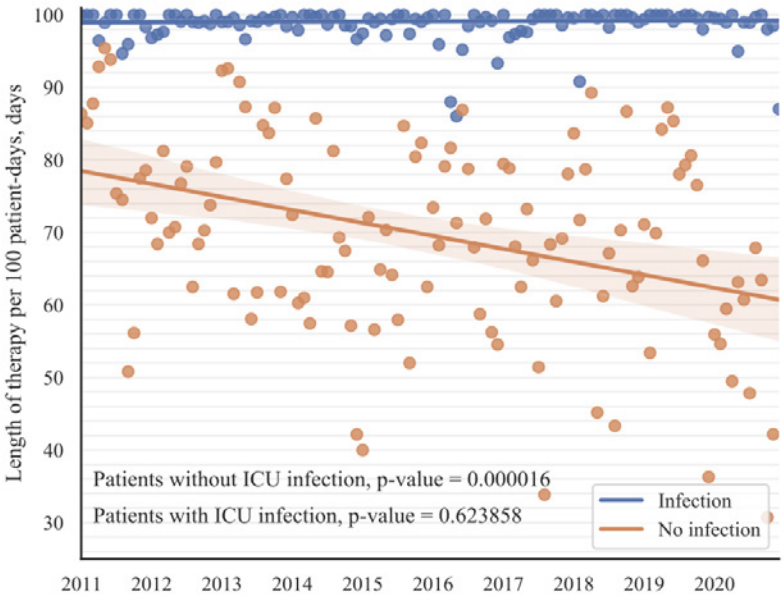

Figure 3. Length of antibiotic therapy per 100 patient-days in neurosurgical ICU patients with and without ICU infections in 2011-2020. P-values obtained from linear regression.

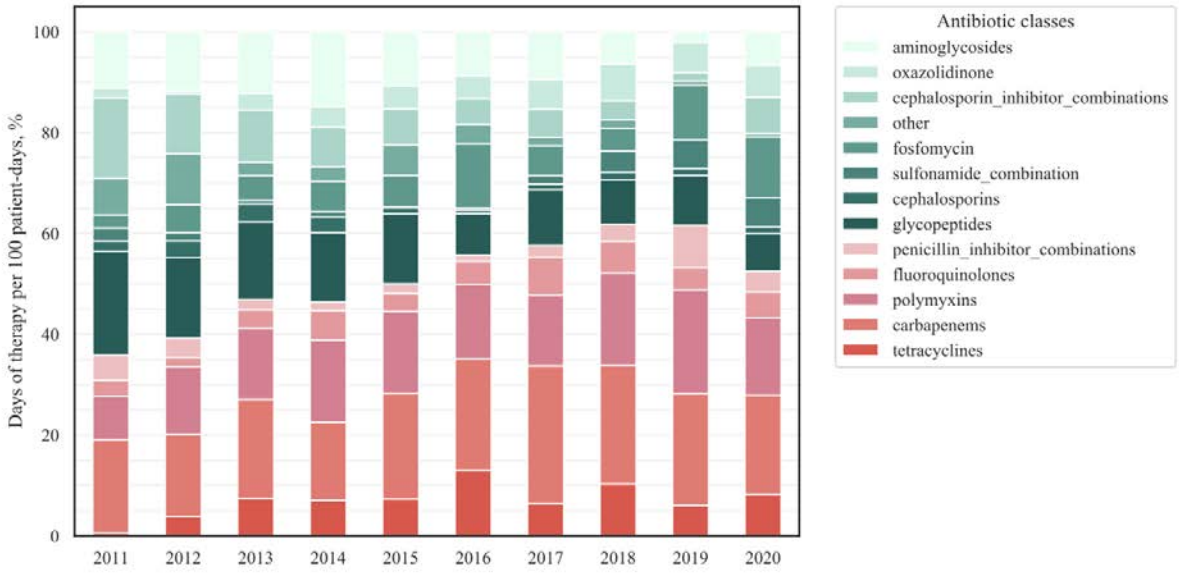

Figure 4. The use of antibiotics by class in neurosurgical ICU patients with ICU infection in 2011-2020. Red color highlights more restricted/higher generation antibiotic classes and green color highlights narrower classes with less concern for antibiotic resistance.

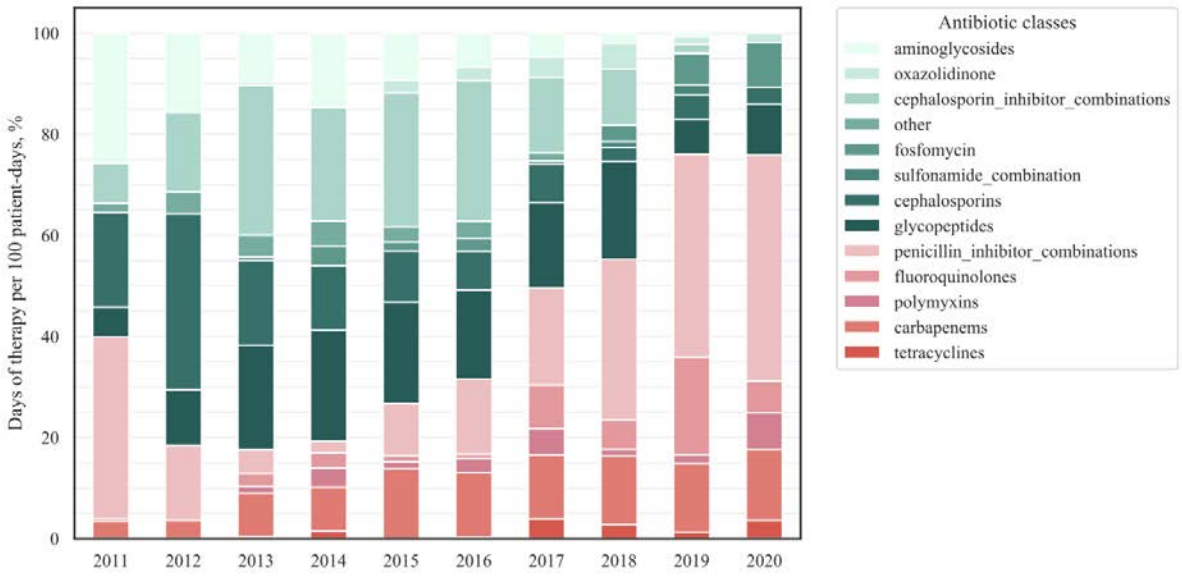

Figure 5. The use of antibiotics by class in neurosurgical ICU patients without ICU infection in 2011-2020. Red color highlights more restricted/higher generation antibiotic classes and green color highlights narrower classes with less concern for antibiotic resistance.

CRITICAL CARE 30

Assessment of Bedside Physiologic Parameters as a Predictive Tool for Unplanned Surgical Intensive Care Unit Admission

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INTRODUCTION: The Modified Early Warning Score (MEWS) had been proposed to warn healthcare providers of adverse events, but subsequent studies were unable to show the benefits of this scoring system[5]. The possibility exists that the components for MEWS were not properly vetted for inclusion into this early warning system[6]. We evaluated all measured bedside vital signs including those used in MEWS during bedside evaluation for unplanned escalation of care as predictors for hospital mortality.

METHODS: Following IRB approval, 495 consecutive unplanned admissions into a surgical intensive care unit over one year were entered into this study. Patient characteristics and vital signs measured during bedside evaluation for unplanned escalation of care were extracted from electronic medical records. A logistic regression model was developed to analyze the interactions of these bedside measurements with future hospital mortality. Diagnostic accuracies of the logistic models were analyzed with misclassification rates calculated with 95% confidence intervals (CI)[6]. Lack-of Fit-test (Goodness-of Fit-test) was utilized to determine whether the multivariate analysis model contained enough information (degrees of freedom) for prediction of future hospital mortality or whether more factors and/or complex terms were needed[6]. P values for associated frequentist tests were set at <0.005 for statistical significance to minimize false discovery rates[6].

RESULTS: In this series of 495 consecutive patients, the incidence of hospital mortality following unplanned escalation of care was 32.9% CI 28.9-37.2%. The associations of individual vital sign measurements to the incidence of hospital mortality are shown in Figure 1. When vital sign measurements are grouped by prognosis (Fig. 2), no discernable difference is observed. A logistic regression model was developed to assess the interactions of these vital sign measurements to hospital mortality obtained with the results of that model shown in Table 1. The association of vital signs under these conditions to hospital mortality was not statistically significant (Table 1A; P=0.0306). In contrast, the Lack-of-Fit Chi-Squared statistic (Table 1B) was significant suggesting the model needs more factors and/or complex terms. A misclassification rate of 29.5% CI 25.8%-34.4% (Table 1A) was observed with this association.

CONCLUSION: Vital signs obtained at the time of bedside assessment for unplanned escalation of care provided no statistical predictive risk for future hospital mortality. The high misclassification rates indicate these measurements under these conditions do not provide the discriminatory support needed to identify patients at risk for hospital mortality. The results in the Lack-of Fit-test suggest more factors and/or complex terms are needed in this predictive model.

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Figure 1

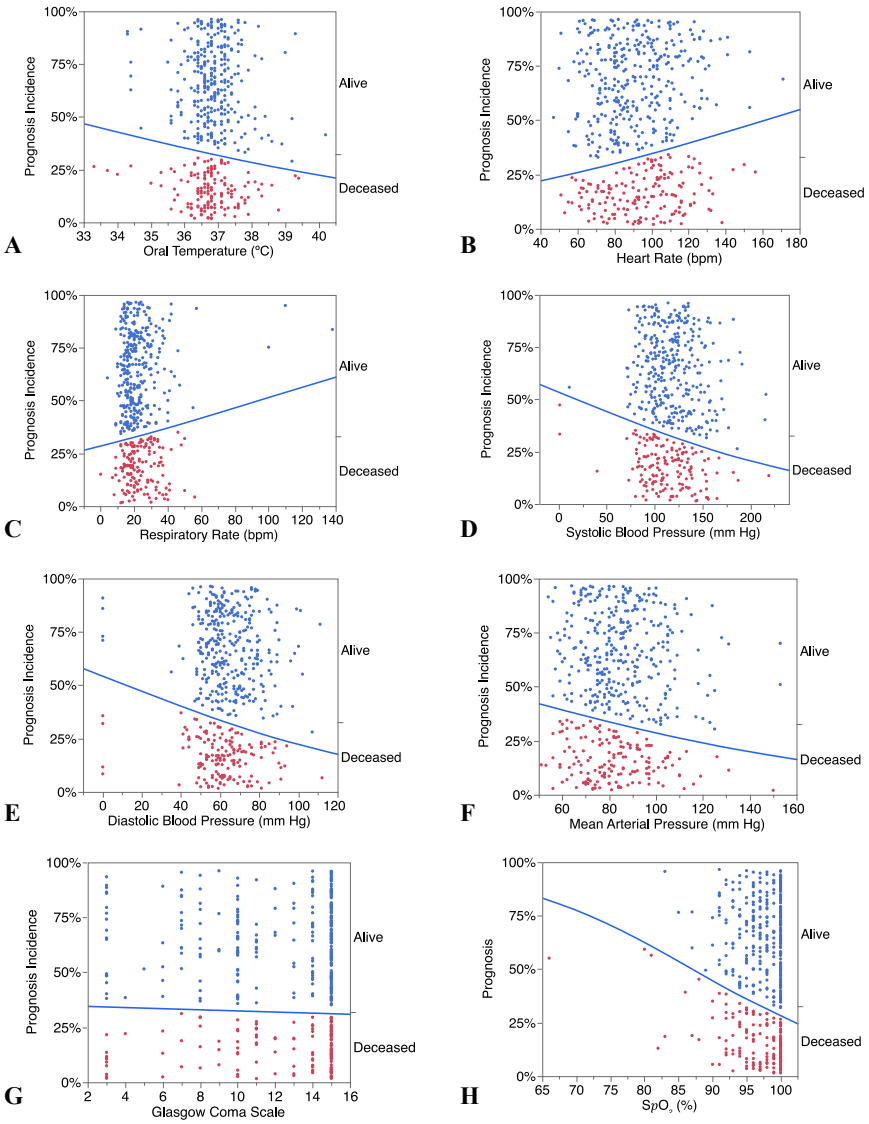

Figure 1 Logistic fit graphs of hospital mortality to vital sign measurements obtained in 495 surgical patients undergoing bedside evaluation for unplanned escalation of care. The blue lines indicate the incidence of mortality. Red dots identify decreased patients. Blue dots identify alive patients. **A**: Oral Temperature, ChiSquare=1.5, P=0.2212, Misclassification Rate=0.32; **B**: Heart Rate, ChiSquare=4.9, P=0.0268, Misclassification Rate=0.33; **C**: Respiratory Rate, ChiSquare=1.4, P=0.2365, Misclassification Rate=0.34; **D**: Systolic Blood Pressure, ChiSquare=4.1, P=0.0425, Misclassification Rate=0.32; **E**: Diastolic Blood Pressure, ChiSquare=4.7, P=0.0304, Misclassification Rate 0.33; **F**: Mean Arterial Pressure, ChiSquare=3.7, P=0.0557, Misclassification Rate=0.33; **G**: Glasgow Coma Score; ChiSquare=0.18, P=0.6696, Misclassification Rate=0.32; **H**: SpO_2, ChiSquare=7.6, P=0.0057, Misclassification Rate=0.32. P values <.005 are statistically significant.[13]

Figure 2

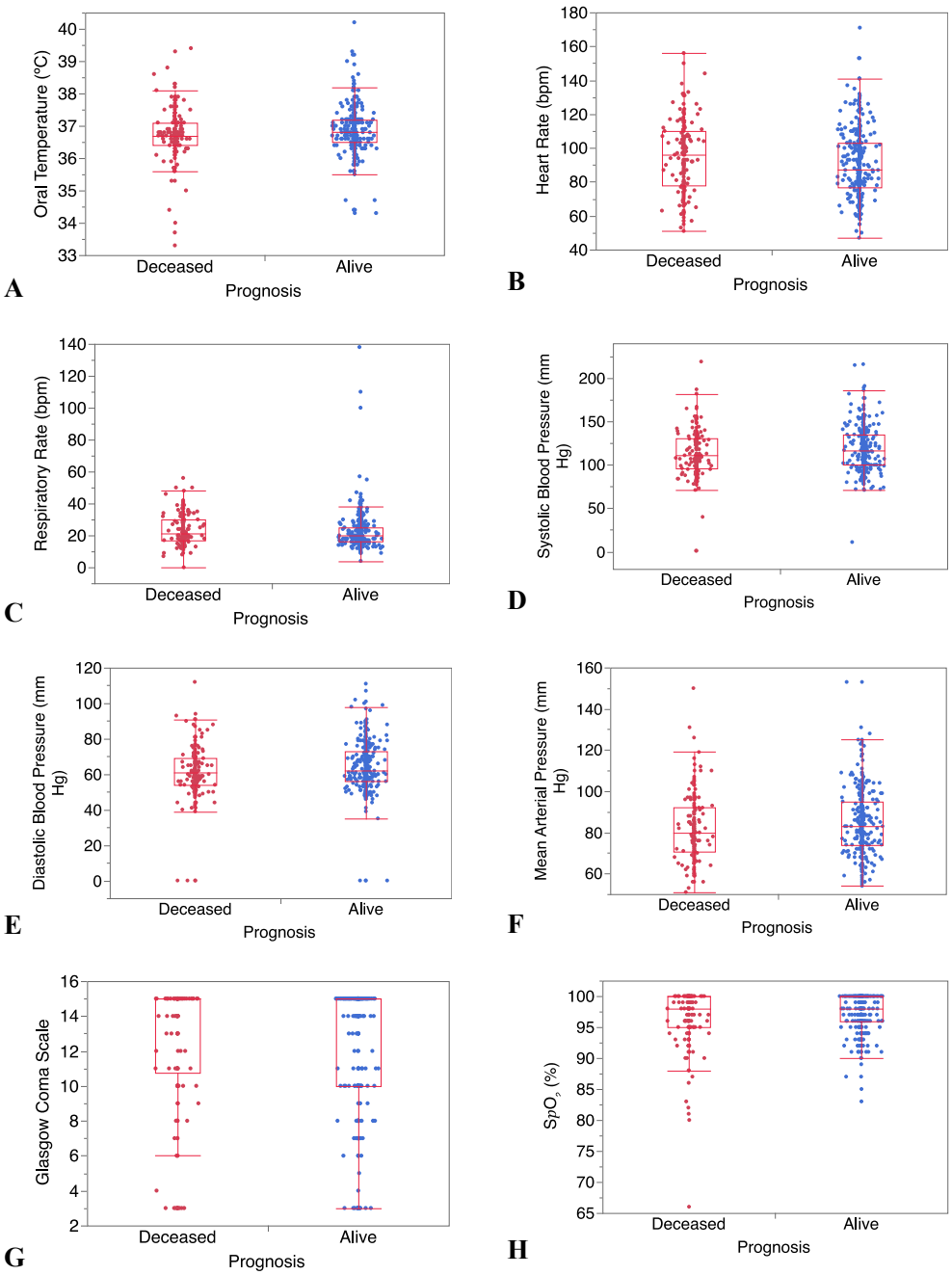

Figure 2 Boxplots of vital signs grouped by prognosis in 495 surgical patients undergoing bedside evaluation for unplanned escalation of care. **A**: Oral Temperature, ChiSquare=1.9, P=0.1662; **B**: Heart Rate, ChiSquare=5.8, P=0.0165; **C**: Respiratory Rate, ChiSquare=5.4, P=0.0201; **D**: Systolic Blood Pressure, ChiSquare=3.6, P=0.0566; **E**: Diastolic Blood Pressure, ChiSquare=4.3, P=0.0381; **F**: Mean Arterial Pressure, ChiSquare=4.1, P=0.0427; **G**: Glasgow Coma Score; ChiSquare=0.22, P=0.6421; **H**: SpO_2, ChiSquare=4.0, P=0.0467. P values <.005 are statistically significant.[13]

Table 1: Nominal Logistic Regression Model for Hospital Mortality by Vital Signs Measurements during Unplanned Escalation of Care in 495 Surgical Patients

A

Terms	Estimate	95%CI	Std Error	ChiSquare	Prob>ChiSq
Intercept	-11.5	-22.6 to -0.86	5.5	4.7	0.0369
Oral Temperature	-0.16	-0.12 to 0.44	0.14	1.2	0.2703
Heart Rate	0.007	-0.08 to 0.003	0.005	1.9	0.1645
Respiratory Rate	0.005	-0.22 to 0.14	0.009	0.3	0.5914
Systolic Blood Pressure	-0.003	-0.011 to 0.018	0.008	0.2	0.6511
Diastolic Blood Pressure	-0.02	-0.009 to 0.056	0.016	1.7	0.1880
Mean Arterial Pressure	0.005	-0.044 to 0.030	0.019	0.1	0.7694
Glasgow Coma Scale	-0.0002	-0.058 to 0.057	0.029	0.0	0.9957
SpO_2	-0.06	-0.007 to 0.11	0.028	4.9	0.0277

SpO_2: Pulse oximetry; 95%CI: 95% Confidence interval; ChiSquare: Chi-Square statistic; Prob>ChiSq: Probability that the Chi-Square statistic is due to chance; Whole model ChiSquare statistic of 17.0 with 8 degrees of freedom and an associated P-value of 0.0306; Misclassification rate: 29.5% CI 25.8%-34.4%. P values <.005 are statistically significant.[13]

B

Lack-of-Fit (Goodness-of-Fit) test

Source	DF	-LogLikelihood	ChiSquare
Lack Of Fit	435	275.5	551.1
Saturated	443	0.0	**Prob>ChiSq**
Fitted	8	275.5	0.0001

DF = degrees of freedom; -LogLikelihood; computed by taking twice the difference in negative log-likelihoods between the Fitted model and the Saturated model; ChiSquare: formed by twice the difference in the log-likelihoods due to the hypothesis. Probability > ChiSq: the probability that the P-value is greater than the ChiSquare statistic.

CRITICAL CARE 31

The Association of Discharge Medication Burden on Long-Term Outcomes Among Intensive Care Unit Survivors

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INTRODUCTION: Intensive care unit (ICU) survivors are at increased risk for inappropriate continuation of centrally acting medications. The Drug Burden Index (DBI) is a validated measure of exposure to these medications, with higher DBI associated with worsened cognitive impairment and mortality in non-hospitalized older adults. These associations have not yet been investigated among ICU survivors who also frequently exhibit cognitive impairment and subsequent mortality. We sought to investigate the independent association of centrally active medication burden at hospital discharge, measured by the DBI, on long-term cognitive function and 90-day mortality among ICU survivors.

METHODS: We performed a cohort study of medical and surgical ICU survivors admitted with respiratory failure and/or septic shock previously enrolled in prospective investigations. Pre-admission and discharge medication lists were extracted retrospectively from electronic health records. DBI was calculated as the sum of each sedative and anticholinergic drug burden values. A score of 0 represents no exposure, <1 represents low exposure, and >1 represents high exposure. Cognitive impairment was assessed 3 to 6 months following hospital discharge using validated batteries and defined as ≥2 standard deviations (SDs) in 1 cognitive test or ≥1.5 SDs in any 2 cognitive tests. Only patients with at least one follow-up cognitive test completed were included in cognitive impairment analysis. 90-day mortality was obtained by chart review and/or surrogate contact. Multivariable proportional odds logistic regression was used to investigate the independent association of discharge DBI on cognitive impairment, adjusting for pre-specified covariates. Cox proportional hazards regression was used to investigate 90-day mortality, adjusting for the same pre-specified covariates.

RESULTS: A total of 676 patients, including 478 with follow-up cognitive assessment, were included in our cohort with a median age 57.6 (47.8-66.6) years, median ICU stay of 4.9 (2.6-10.1) days, and median discharge DBI of 3.1 (2.0-4.3) (Table 1). Overall prevalence of long-term cognitive impairment was 56.1%, and 90-day mortality was 13.6%. We did not find a statistically significant overall association between hospital discharge DBI and long-term cognitive impairment (p=0.19). We found, however, an approximate 20% increased probability of cognitive impairment when hospital discharge DBI increased from 0 to 4 as shown in Figure 1a. We found no statistically significant association between discharge DBI and 90-day mortality (p=0.56), as shown in Figure 1b.

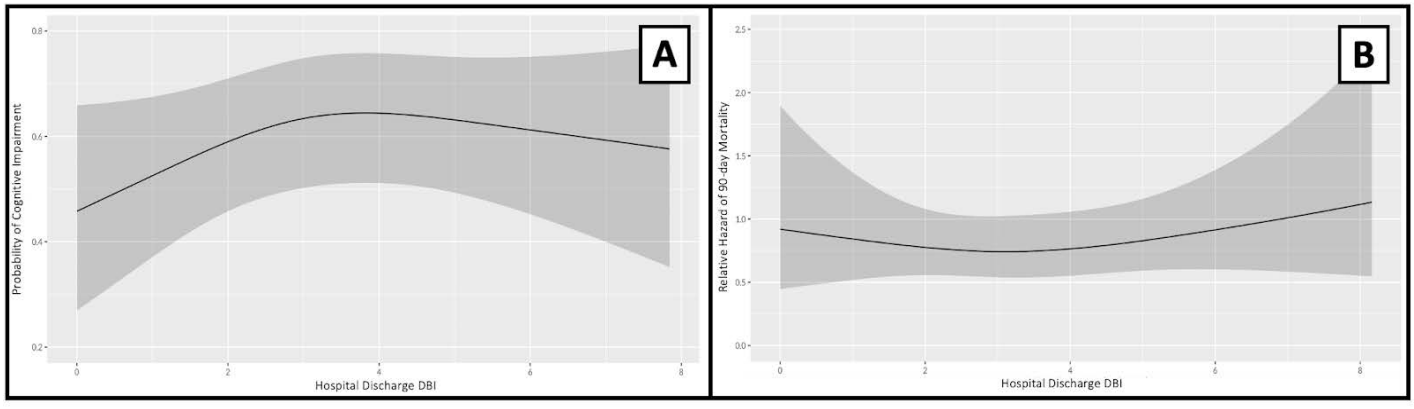
CONCLUSION: We found a high burden of centrally active medications prescribed at discharge in ICU survivors. This burden, as measured by DBI, was not significantly associated with long-term cognitive impairment or 90-day mortality among ICU survivors. There was a potential relationship between discharge DBI and cognitive impairment up to DBI score of 4. Investigation into the differential impact of drug burden on cognitive impairment may identify patients with modifiable medication regimens who could benefit from medication optimization.

Table 1: Baseline Patient Characteristics

Baseline Characteristic	Study Cohort (n=676)
Age (years)	57.6 [47.8-66.6]
Sex (males)	362 (53.6%)
Race (white)	598 (88.5%)
Education (high school or less)	396 (58.6%)
Body Mass Index (BMI)	29.7 [24.8-36.8]
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)	3.0 [3.0-3.2]
Charlson Comorbidity Index	2 [1-4]
Sepsis (yes)	183 (27.1%)
Acute Brain Dysfunction Duration (days)	3 [1-7]
Total Mechanical Ventilation (days)	2.2 [0.9-6.1]
Total ICU stay (days)	4.9 [2.6-10.1]
Hospital Discharge DBI	3.1 [2.0-4.3]

Variables are presented as median [interquartile range] or count (%), as appropriate.

Figure 1: Analysis of Hospital Discharge DBI on Probability of Cognitive Impairment and Hazard of 90-Day Mortality



CRITICAL CARE 32

Non-home Discharge after intensive care unit admission for Coronavirus Disease 2019: Results from VIRUS SCCM

Shahla Siddiqui[1], Lauren Kelly[2], Valerie Banner-Goodspeed[3], Maximilian S Schaefer[4]

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INTRODUCTION: Non-home discharge after ICU stay directly impacts independent living for patients and has financial implications. Our study aimed to describe loss of independent living, defined as non-home discharge to a nursing home or long-term care facility, hospice, or in-hospital death in patients with COVID-19 admitted to the intensive care unit (ICU) in a multicentre, international registry. Our hypothesis was that there is a high (>50%) risk of non-home discharge in acutely ill patients with COVID 19 requiring Intensive Care Unit admission that varied over the course of the pandemic. This was based on the fact that COVID 19 is a debilitating disease and has occurred in several waves.

METHODS: This was an international, retrospective multicentre study including patients with laboratory-confirmed severe acute respiratory syndrome coronavirus-2 infection admitted to the ICU between February 15, 2020, and June 30, 2021. Our study included patient entries from 306 hospitals in 28 countries included in the Society of Critical Care Medicine's Discovery Viral Infection and Respiratory Illness University Study (VIRUS) coronavirus disease 2019 registry. Previously independent adults diagnosed with SARS-COV-2 who were admitted to the ICU with documented discharge status were included. The primary outcome was non-home discharge, defined as discharge to a skilled nursing home, long-time care facility, hospice, or death in-hospital. Secondary outcomes included the change in non-home discharge over the course of the pandemic in patients admitted in the region of the Americas. In an exploratory analysis, we assessed the association between deep sedation (RASS <-3) and non-home discharge in a multivariable logistic regression model adjusted for patient demographics, comorbidities and severity of disease. All analyses were made using SAS version 9.4 with alpha set to 0.05.

RESULTS: 10,820 out of 12,799 patients with COVID-19 who received ICU care were included (Figure 1). Overall, 5,790 (53.5%) patients experienced non-home discharge, including 3,719 (64.2%) patients who died (Figure 2). Out of the 7,101 survivors, 2,071 (29.2%) were not discharged home. Of the 5,030 patients who were discharged home, 1720 (34.2%) required assistance with daily living activities. In the subgroup of patients admitted in the region of the Americas, there was a higher risk of non-home discharge in the quarter October - December 2020 (odds ratio 1.4 [95% CI 1.08 - 1.83] p<0.012) compared to the first quarter of the pandemic, January-March 2020. Patients experiencing non-home discharge were more likely to receive deep sedation during their ICU stay (RASS score<-3); however, deep sedation was not associated with non-home discharge in adjusted analyses (adjusted odds ratio, aOR 0.91, 95% CI 0.59-1.4, p=0.659) . I Four factors predicted non-home discharge after ICU stay for COVID-19: patient age > 65 years [aOR 2.95 (95% CI 2.12-4.11) p<0.001)], requirement of mechanical ventilation [aOR 6.9 (95% CI 3.97-11.98), p<0.001)], a higher maximum SOFA score (median 8) [aOR 1.24 (95% CI 1.17-1.31) p<0.001)], and a lower P/f ratio (median 170) [aOR 0.98 (95% CI 0.96-0.99) per mmHg increase, p<0.001)].

CONCLUSION: ICU admission for COVID-19 is associated with a high risk of non-home discharge, with more than half of patients not being discharged home. Less than half of patients who survive return to unassisted living at home. Physicians should consider discussing a high probability of non-home discharge with patients and families upon ICU admission for COVID-19.

Table 1. Descriptive statistics comparing patients who were discharged home and not discharged home.

Variable	Discharged Home (n=5030)	Not discharged home (n=5790)	P-Value
Age, Mean (SD) Median (IQR)	54.8 (16) 56 (44, 66)	66.8 (14) 68 (59, 77)	*<0.0001*
Age Group, No. (%)			*<0.0001*
<65	3560 (60.7)	2302 (39.3)	
>=65	1470 (29.7)	3488 (70.4)	
Region, No. (%)			*<0.0001*
European Region (EUR)	375 (38.8)	591 (61.2)	
Region of the Americas (AMR)	3553 (42.3)	4841 (57.7)	
Other	1102 (75.5)	358 (24.5)	
Quarter of Admission, No. (No.%)			*<0.0001*
Jan-March 2020	186 (44.9)	228 (55.1)	
Apr-June 2020	676 (45.4)	813 (54.6)	
Jul-Sept 2020	991 (57.3)	740 (42.8)	
Oct-Dec 2020	689 (48.3)	738 (51.7)	
Jan-March 2021	149 (42.3)	203 (57.7)	
Apr-June 2021	55 (45.1)	67 (54.9)	
Hospital Admission Source, No. (%)			*<0.0001*
Home	1308 (42.8)	1748 (57.2)	
Hospital ED	2921 (52.2)	2673 (47.8)	
Outside ED	160 (42.8)	214 (57.2)	
Transfer from other Facility	449 (33.4)	896 (66.6)	
Other	192 (42.6)	259 (57.4)	
Sex, No. (%)			0.098
Male	3084 (45.9)	3635 (54.1)	
Female	1946 (47.5)	2151 (52.5)	
Intersex	0 (0)	2 (100)	
Transgender	0 (0)	1 (100)	
Ethnicity, No. (%)			*0.0076*
Unknown	397 (51)	381 (49)	
Hispanic	1004 (46.9)	1139 (53.2)	
Non-Hispanic	3093 (46.4)	3571 (53.6)	
Not Applicable	525 (43.2)	691 (56.8)	
Race, No (%)			*<0.0001*
African American	893 (42.1)	1230 (57.9)	
Asian	1208 (70.4)	507 (29.6)	
White	2254 (40.5)	3310 (59.5)	
Mixed	148 (43.5)	192 (56.5)	
Other	473 (50.2)	470 (49.8)	
Unknown	50 (41)	72 (59)	
Smoking status, No. (%)			*<0.0001*
Current	164 (43.9)	210 (56.2)	
Former	651 (34.3)	1230 (65.7)	
Non-Smoker	4225 (49.3)	4350 (50.7)	
Alcohol Use Disorder, No. (%)			0.528
Yes	156 (44.8)	192 (55.2)	

No	4874 (46.5)	5598 (53.5)	
Substance Use Disorder, No. (%)			0.264
Yes	134 (43.4)	175 (56.6)	
No	4896 (46.6)	5615 (53.4)	
Mechanical Ventilation, No. (%)			*<0.0001*
Yes	1310 (23.9)	4176 (76.1)	
No	3720 (69.7)	1614 (30.3)	
Non-Invasive Ventilation, No. (%)			*<0.0001*
Yes	765 (38.3)	1233 (61.7)	
No	4265 (48.4)	4557 (51.7)	
HFNC, No. (%)			*<0.0001*
Yes	1458 (43.1)	1927 (56.9)	
No	3572 (48)	3863 (52)	
Proning, No. (%)			*<0.0001*
Yes	836 (36.4)	1459 (63.6)	
No	4194 (49.2)	4331 (50.8)	
ECMO, No. (%)			*<0.0001*
Yes	56 (22)	199 (78)	
No	4974 (47.1)	5591 (52.9)	
Deep Sedation during ICU stay, No. (%)			*<0.0001*
Yes (RASS < -3)	174 (25.9)	498 (74.1)	
No (RASS >= -3)	490 (49.1)	508 (50.9)	
Number of sedatives during ICU stay, Median (IQR)	0 (0, 0)	0 (0, 1)	*<0.0001*
Max Number of sedatives or narcotics per day during ICU stay, No. (%)			*<0.0001*
0	3046 (53.4)	2654 (46.6)	
1	129 (30.9)	288 (69.1)	
2	165 (25.3)	487 (74.7)	
3	175 (27.5)	461 (72.5)	
4	83 (30)	194 (70)	
>=5	25 (31.3)	55 (68.8)	
Patient ever received an NMBA, No. (%)			*<0.0001*
Yes	302 (25.6)	879 (74.4)	
No	503 (39)	786 (61)	
Number of days where NMBA were received for each patient, Median (IQR)	0 (0, 1)	1 (0, 2)	*<0.0001*
Mechanical Ventilation Time, Median (IQR)	8 (4, 14)	10.4 (5, 20)	*<0.0001*
Maximum SOFA Scores, Median (IQR)	4 (2, 6)	8 (5, 11)	*<0.0001*
Maximum p/f ratio, Median (IQR)	211.1 (140, 293.3)	170.2 (111.4, 250)	*<0.0001*

*All percentages are represented as row percentages.

Figure 1. Cohort

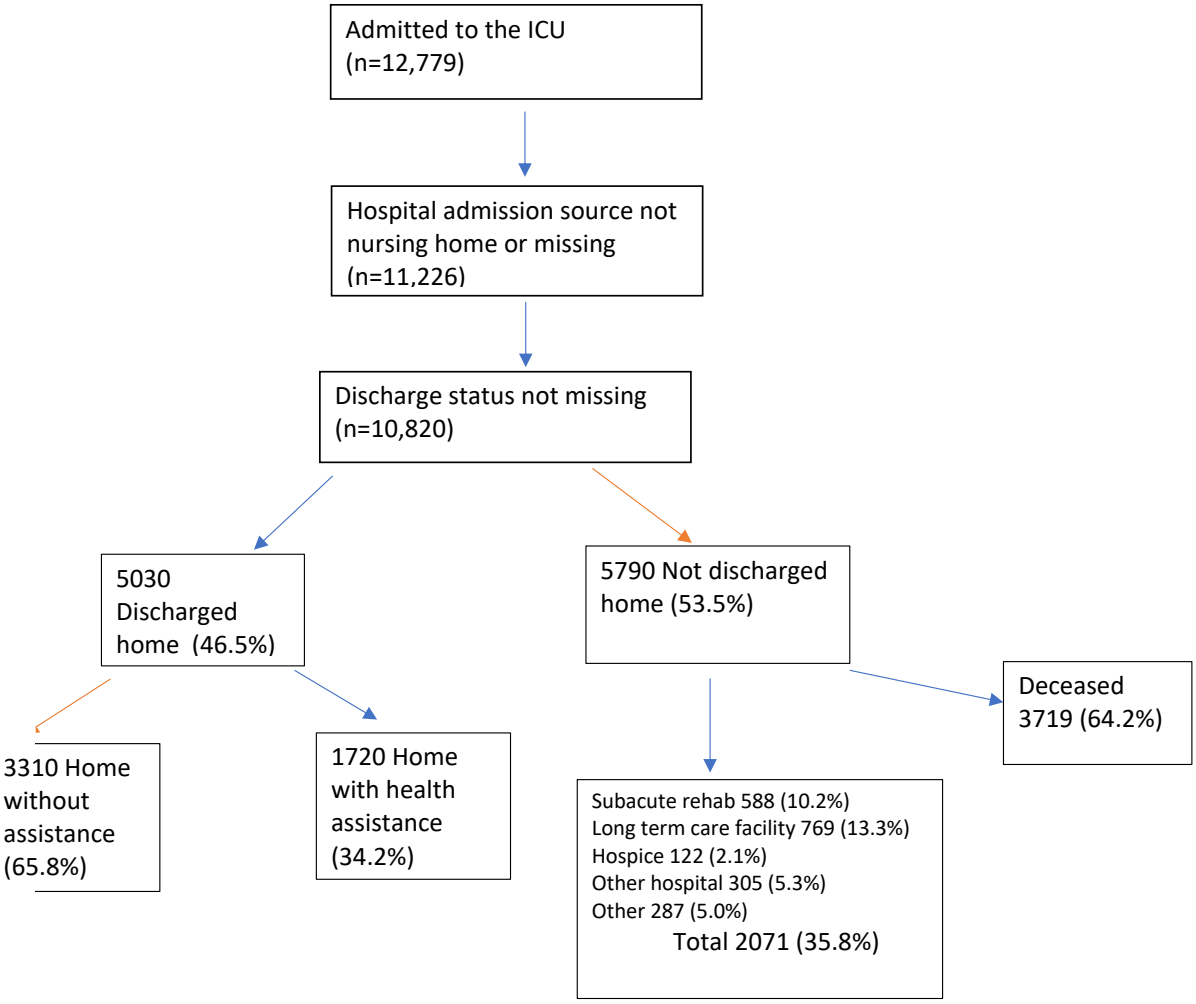
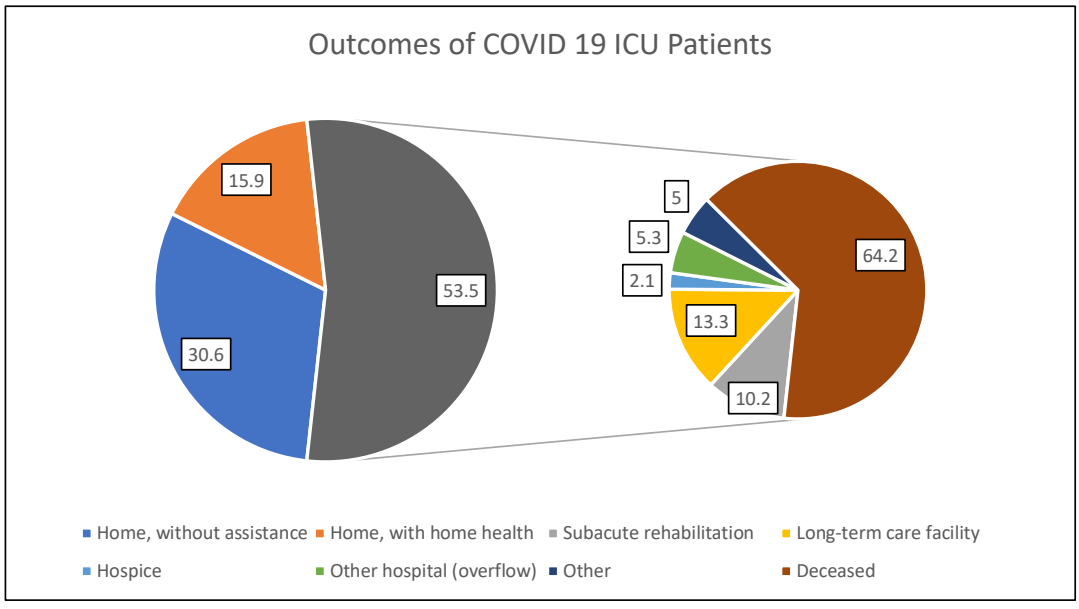


Figure 2. Outcomes of COVID 19 ICU patients



CRITICAL CARE 33

Outcomes in Mechanically Ventilated COVID-19 Patients Sedated with Benzodiazepines or Barbiturates during Pandemic Induced Drug Shortages: a Retrospective Single-Center Cohort Study

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INTRODUCTION: During the COVID-19 pandemic, intensivists used benzodiazepines and barbiturates to sedate mechanically ventilated COVID-19 patients due to drug shortages and abandoned usual practice[1]. We performed a retrospective analysis of outcomes associated benzodiazepine or barbiturate use. We hypothesized that patients sedated with benzodiazepines or barbiturates suffered worse outcomes than those who were not. The primary outcome studied was 30-day mortality and the secondary outcome was whether the patient received a tracheostomy. Institutional Review Board approval was waived.

METHODS: We used a deidentified dataset between 10/17/2019 and 12/10/2020. Inclusion criteria contained adult patients who tested positive for COVID-19 and were supported by invasive mechanical ventilation. The association between binary outcomes (30-day mortality and tracheostomy status) and continuous covariates were evaluated using Wilcoxon's rank-sum test, and Chi-squared test was used for categorical covariates. Multivariable logistic regressions were adopted to quantify the association between treatment groups and outcomes while controlling for the statistically or clinically relevant comorbidities and duration of sedative therapy. Right-skewed variables were log-transformed in logistic regressions. All p-values are two-sided, and analyses were conducted using R.

RESULTS: After applying our inclusion criteria, the final dataset included 950 patients. Of these patients, 483 (51%) died and 294 (31%) received a tracheostomy. 703 (74%) patients were administered benzodiazepines, 92 (9.7%) were administered barbiturates, and 155 (16%) were given neither. After controlling for confounders and adjusting for days of drug exposure, administration of benzodiazepines in COVID-19 patients demonstrated a statistically significant association with the primary outcome, 30-day mortality, with an adjusted OR of 37.1 (95% CI 13.3-106.46). Similarly, administration of barbiturates was associated with an increased 30-day mortality, with an adjusted OR of 36.5 (95% CI 12.6 - 108.5). After controlling for confounders and adjusting for days of drug exposure, administration of benzodiazepines in COVID-19 patients demonstrated a statistically significant negative association with the secondary outcome, tracheostomy, with an adjusted OR of 0.003 (95% CI 0.001-0.013). Similarly, administration of barbiturates for sedation in COVID-19 patients demonstrated a statistically significant negative association with tracheostomy, with an adjusted OR of 0.013 (95% CI 0.003-0.045).

CONCLUSION: In our single-center retrospective analysis, after adjusting for confounding variables and duration of sedative exposure, we found that critically ill mechanically ventilated COVID-19 patients sedated with benzodiazepines or barbiturates were associated with an increased 30-day mortality and decreased rate of tracheostomy. This suggests that if possible, these agents should be avoided.

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CRITICAL CARE 34

Racial and Ethnic Differences in the Prevalence of Advanced Directives Among Geriatric Patients with Traumatic Brain Injury

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INTRODUCTION: With improvements in health care, the older adult population continues to constitute a large portion of the population now accounting for approximately 30% of the US population[1,2]. As the aging population continues to grow so does the number of older adult traumas with trauma now ranking as the seventh leading cause of geriatric mortality.[1] For patients aged 65-74, rate of hospitalization for traumatic brain injury (TBI) was 87.9 per 100,000 and for those >75 years of age, 104.6 per 100,000.2 Over the past decade, there has been an emphasis on the role of advanced directives (AD) to preserve patient wishes and avoid undesired care by health professionals.[3] Despite this focus on advanced directives, the prevalence of ADs in the older adult population with TBI only ranges from 6-18%.[4] In addition, the Institue of Medicine (IOM) Unequal Treatment report concluded that racial disparities are rampant in health care and are associated with worse outcomes in minorities.[5] While recent studies have investigated the prevalence of ADs in this population, no studies have examined the association between race/ethnicity with the utilization of ADs. We hypothesize that the prevalence of advanced directives in older adult severe TBI will be low, and patients of minority race/ethnicity will have a lower prevalence of ADs, compared to White patients.

METHODS: We conducted a retrospective cohort study using the National Trauma Databank (NTDB), which houses the largest collection of trauma data in the United States. We examined data from participating hospitals in the NTDB 2007-2016. We included geriatric patients (age > 65 years) with severe TBI, defined as admission Glasgow Coma Scale score (GCS) < 8. We excluded patients who were not admitted to the hospital or died within 24 hours of hospital admission. Our exposure of interest was race/ethnicity and outcome was the presence of an advanced directive on admission, defined as a documented Do Not Resuscitate (DNR) order. Multivariable logistic regression models, adjusting for demographic and clinical covariates, were used to examine the association between race/ethnicity and the presence of an advanced directive.

RESULTS: Table 1 describes the demographic and clinical characteristics of the cohort. As we focused on severe TBI, no patient had a Glasgow coma scale >8 with a median GCS of 3 and mean of 3.4. Our patient population included 81% White patients, 6.3% Black patients, 8.5% Hispanic patients, 3.3 % Asian patients, and 3.0% other races. XX% of patients had an advanced directive at hospital admission. The most common mechanism of injury was via fall, with 59% of patients without advanced directives and 67.3% patients with an advance directive presenting after fall. The mean(SD) injury severity score was 22.7(10.6) in the no advanced directive group and 22.4(9.5) in the advanced directive group. Compared to White patients, Black patients (OR 0.48, 95% CI 0.35-0.64), Hispanic patients (OR 0.54, 95% CI 0.40-0.70), and Asian patients (OR 0.63, 95% CI 0.44-0.90) had a decreased odds of having an advanced directive at hospital admission (Table 2).

CONCLUSION: This analysis shows that disparities do exist with regard to ADs in older adults with TBI. Non-White older adult TBI patients have a lower prevalence of ADs compared to white patients of the same category. Prior research has illustrated that in general, minorities have higher rates of mortality due to chronic disease compared to non-minorities. In addition, minorities have been shown to have lower quality end of life and more intensive treatment than non-minorities. A multitude of factors contributes to the observed racial disparities including differences in quality of health care, ability to access health centers, difference in economic status, and implicit bias of care providers. [6,7] Further studies should examine whether these differences in advanced directives have effects on patient outcomes such as healthcare utilization, mortality, and quality of death.

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Table 1: Patient population

Category	No Advanced Directive	With Advanced Directive
Total Number	28,782	1,878
Gender	F: 11,153 (38.8%) M: 17,621 (61.2%)	F: 860 (46%) M: 1019 (54%)
Age (years)	Mean: 75.6, SD 7.16	Mean: 79.2, SD: 6.82
Glasgow Coma Scale	Mean: 4.24, SD 1.79	Mean: 4.64, SD: 1.90
Injury Severity Score	Mean: 22.72, SD: 10.59	Mean: 22.41, SD 9.46
Injury Mechanism (%)*	1: 20.79, 2. 59.05, 3: 1.66, 4:3.17, 5: 1.98, 6: 13.36	1: 20.11, 2: 59.55, 3: 1.64, 4: 3.05, 5: 1.90, 6: 13.75

*Key: 1=Motor vehicle trauma, 2=Fall, 3=Firearm, 4=cyclist,pedestrian accident, 5: struck by, against, 6=other

Table 2: Likelihood of having an advanced directive vs white patient's

Race	Odds Ratio	P > l z l	95% CI
White	Ref		
Black	0.48	<0.001	0.35-0.64
Hispanic	0.54	<0.001	0.40-0.74
Asian	0.63	0.01	0.44-0.90
Other	0.49	<0.001	0.33-0.74

CRITICAL CARE 35

Association of Advanced Directives and Clinical Outcomes among Older Adult Patients with Severe Traumatic Brain Injury

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INTRODUCTION: Traumatic brain injury (TBI) is among the leading causes of death and disability worldwide, with older adult TBI patients experiencing significantly higher morbidity and mortality compared to younger patients.[1] In a retrospective study, patients >65 years with severe TBI (GCS 5-8) had a 70-93% mortality and those with critical TBI (GCS 3-4) had a 92-94% mortality.[2] Furthermore, the Eastern Association for the Surgery of Trauma (EAST) recommends consideration of limiting further aggressive interventions in geriatric TBI patients with GCS <8 who have minimal improvement after 72 hours.[3] Given the high morbidity and mortality of elderly TBI patients, advanced directives (AD) are of particular importance in this population in order to align clinical care with the patient's wishes. While elderly trauma patients with AD have higher in-hospital mortality compared to those without, there is a lack of literature on the impact of ADs on clinical outcomes in the elderly TBI patient population.[4] We hypothesize that among older adults with severe TBI, the presence of an AD will result in decreased life sustaining treatments, decreased healthcare utilization, and increased discharge to hospice, compared to patients without an AD.

METHODS: A retrospective cohort study was conducted using the National Trauma Databank (NTDB) from participating hospitals in the United States from 2007-2016. The primary exposure measured was the presence of AD at hospital admission, defined as a documented Do Not Resuscitate (DNR) order. Inclusion criteria: older adults age ≥65 years with severe TBI (defined as the presence of traumatic head injury and GCS ≤8 and head AIS score ≥4). Exclusion criteria: patients with mild and moderate TBI and patients who died within 24 hours of admission. The primary outcome measured was in-hospital mortality, and secondary outcomes included: life-sustaining treatments (mechanical ventilation and intracranial pressure (ICP) monitoring) during hospitalization; healthcare utilization (hospital length of stay and duration of mechanical ventilation); and discharge to hospice. We used descriptive statistics to examine demographic, clinical, facility, and outcome characteristics, stratified by presence/absence of AD on admission. Multivariable, mixed effects linear and logistic regression models (adjusting for demographic and clinical characteristics) were performed to examine the association of AD with primary and secondary outcomes.

RESULTS: 30,660 patients met inclusion criteria in this retrospective cohort study, of which 6.1% (1,878 patients) had advanced directives at hospital admission (Table 1). The mean GCS score and AIS score on admission was similar between the AD and no AD groups. Overall, patients with AD at hospital admission had significantly higher in-hospital mortality compared to those without AD (Table 2). Data also revealed that patients with AD were more likely to be discharged to hospice, have a shorter mean hospital length of stay, and a decreased length of mechanical ventilation; however, there was no statistically significant difference in the utilization of ICP monitoring in patients with AD compared to those without (Table 2).

CONCLUSION: Older adults with TBI have notably lower utilization of advanced directives. This data revealed an association between having ADs and increased in-hospital mortality, decreased hospital length of stay, decreased length of mechanical ventilation, and increased odds of discharge to hospice. Additionally, there was no difference in the use of ICP monitoring, which suggests that despite the presence of AD, these patients still received equivalent acute care. Additional research is needed to better understand factors associated with AD prevalence in older adult TBI patients.

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Table 1: Patient Cohort

	No AD	AD
Total patients	28,782 (93.9%)	1,878 (6.1%)
Mean Age (years)	75.6 (SD 7.16)	79.2 (SD 6.82)
Sex Male	17,621 (61.2%)	1,018 (54.2%)
Female	11,153 (38.8%)	860 (45.8%)
Mean Glasgow Coma Scale Score	4.24 (SD 1.79)	4.64 (SD 1.90)
Mean Injury Severity Score	22.72 (SD 10.59)	22.41 (SD 9.46)

Table 2: Association of Advanced Directives with Treatments and Outcomes

Hospital LOS (mean difference, days)	-2.07	P<0.005	95% CI -3.07 to -1.08
Ventilator Duration (mean difference, days)	-1.09	P<0.005	95% CI -1.52 to -0.67
ICP Monitoring (OR)	0.94	P=0.465	95% CI 0.78-1.12
Discharge to Hospice (OR)	2.08	P<0.005	95% CI 1.75-2.46
In-Hospital Mortality (OR)	2.16	P<0.005	95% CI 1.94-2.42

CRITICAL CARE 36

Pre-menopausal age in females is associated with protection from development of post-operative acute kidney injury, but not mortality following AKI

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INTRODUCTION: Acute kidney injury (AKI) is one of the most common forms of perioperative organ injury. Preclinical and clinical studies examining the influence of sex on AKI have yielded conflicting results. The objective of our study was to determine the association of sex and age on the development of postoperative AKI; and mortality following AKI. We hypothesized that pre-menopausal-aged females would display lower incidence of postoperative AKI, and mortality following AKI, than males of similar age; and the protection would be lost in post-menopausal-aged females.

METHODS: This was a retrospective observational study of the Multi-center Perioperative Outcomes Group database (MPOG). We reviewed surgical patients at 46 institutions between 2013-2019. Our primary exposure was between age younger or older than 50 years and sex. Our primary outcome was development of AKI by KDIGO criteria. A mixed effects multivariable logistic regression was used to determine the association of sex hormone status with postoperative AKI and mortality. Secondary analyses consisted of investigating the association of ascending age deciles over 40 years and postoperative AKI.

RESULTS: After excluding patients with CKD5 and cardiac, transplant, urologic and obstetric procedures, among 390,382 patients undergoing index surgeries, 25809 (6.6%) developed postoperative AKI. In the adjusted model, the lowest risk of AKI was in women under 50 (OR 1.0), with higher risk in men under 50 (OR 1.90 [1.79, 2.01]; p<.0001), women over 50 (OR 1.51 [1.43, 1.59]; p<.0001), and men over 50 (OR 2.06 [1.96, 2.17]; p<.0001). In the secondary analysis, risk of AKI gradually increased in women as they aged, whereas men had very little change in risk based on age (Fig. 1). Of the 24,716 patients who developed postoperative AKI with known hospital mortality data, there was no clear pattern in mortality data, and mortality was broadly similar between men and women at each age group (Fig. 2).

CONCLUSION: Younger age in females is associated with a significantly lower risk of postoperative AKI; and the protective effect is gradually lost with ageing. A similar effect was not found for mortality after AKI. These results suggest that female sex hormones might protect against postoperative AKI.

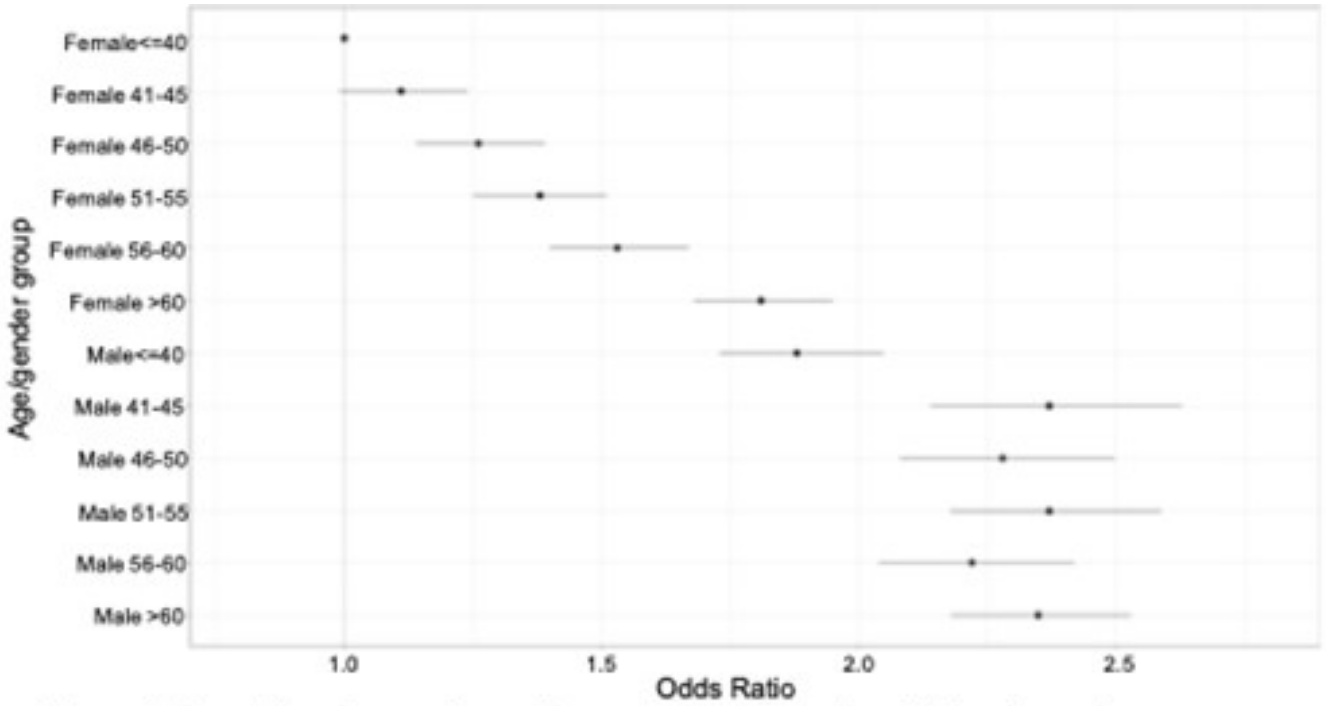

Figure 1: Association of sex and ascending age with post-operative AKI development.

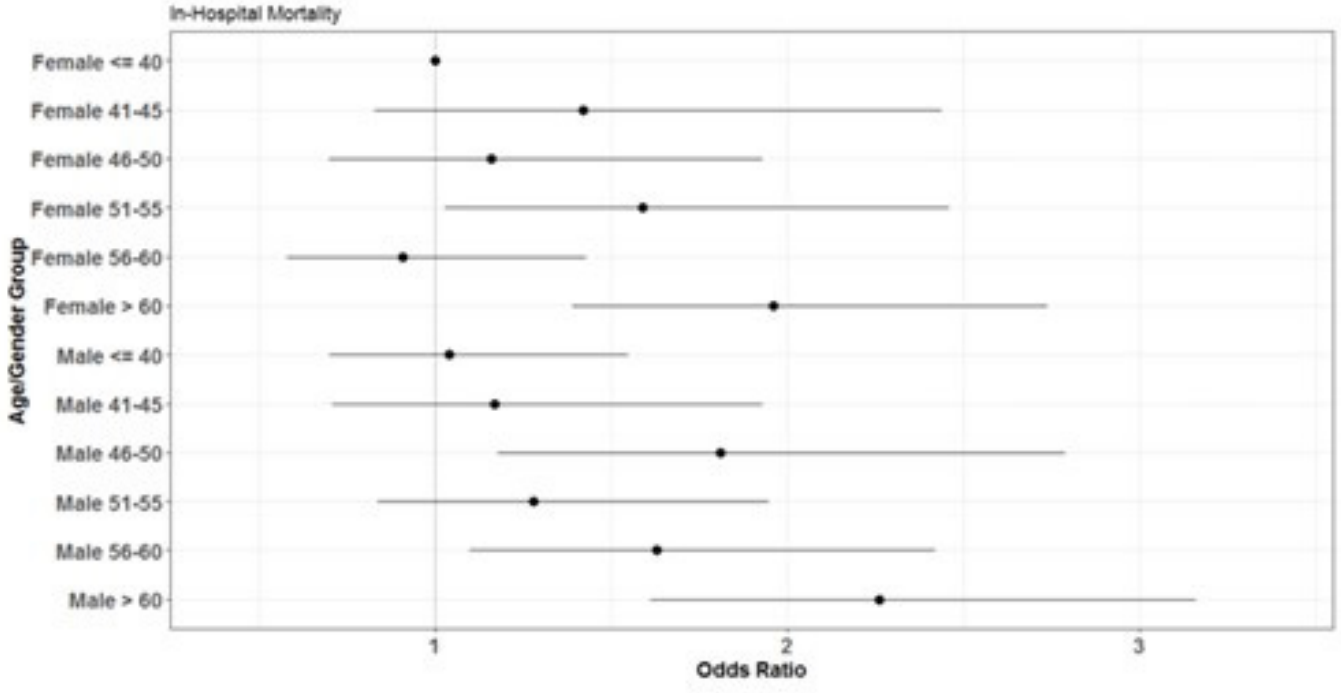

Figure 2: Odds ratio of in hospital mortality data among men and women of differing age groups

CRITICAL CARE 37

A Meta-analysis Comparing Colloid versus Crystalloid for Goal Directed Fluid Therapy in Major Abdominal Surgery

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INTRODUCTION: The main goal of fluid therapy during surgeries is to restore and maintain tissue fluid and electrolyte balance and central euvolemia, while avoiding excessive salt and water. This will facilitate tissue oxygen delivery without causing harm. Goal-directed fluid therapy (GDFT) is considered the gold standard of fluid therapy during surgeries. However, conflicting results were seen among the different studies on which fluid (colloid versus crystalloid) is better to be used in goal-directed fluid therapy (GDFT). This study is a Meta-analysis of previous literature, this will give updated summaries regarding this topic. In a clinical setting, identifying the advantages and disadvantages between the two will help clinicians weigh the benefits over the risks between the two choices. Furthermore, comparing the available literature will help in identifying special situations where colloids will be better used versus crystalloids, and vice versa. Presence of optimal IV fluid therapy improves perioperative outcomes. More so, in terms of developing evidence-based practice, the results of this study can be used as a reference for future researchers, as this Meta-analysis includes the most up-to-date literature associated with fluid of choice in GDFT.

METHODS: A Meta-analysis was conducted which included randomized controlled studies that compared colloid versus crystalloid during intraoperative major abdominal surgery for goal directed fluid therapy. A search was performed in The Cochrane Library, MEDLINE, Pubmed, Clinicaltrial.gov, SCOPUS, Herdin, and Google scholar without language and publication date restrictions. The search strategy consisted of a combination of the following terms: 'colloids versus crystalloids'; 'abdominal surgery', and 'goal directed therapy'. Meta-analysis using pooled risk ratio to compare incidence of adverse events between colloid and crystalloid groups was done.

RESULTS: Six randomized controlled trials with good methodologic quality were included in this Meta-analysis. Only two of the studies reported better patient outcomes associated with use of colloids as perioperative fluid of choice for goal directed fluid therapy. The rest of the studies reported no significant differences between colloid and crystalloid fluid therapies in terms of post-operative complications or adverse events. Pooled risk ratio also showed no significant difference in all adverse events assessed between the two groups (all p-values > 0.05).

CONCLUSION: Colloids in goal-directed fluid therapy protocol have no significant difference with crystalloid-based protocol in patients undergoing major abdominal surgeries with regards to the incidence of postoperative cardiac, respiratory, renal, gastrointestinal, infection, and coagulation complications.

REFERENCE(S):

Perioperative Fluid Therapy for Major Surgery [published correction appears in Anesthesiology. 132(2):405]. Anesthesiology. 2019;130(5):825-832. 2020

Perioperative Goal-Directed Fluid Therapy Is an Essential Element of an Enhanced Recovery Protocol? Anesth Analg. 122(5):1261-3. 2016

Figure 1. Flowchart of study selection

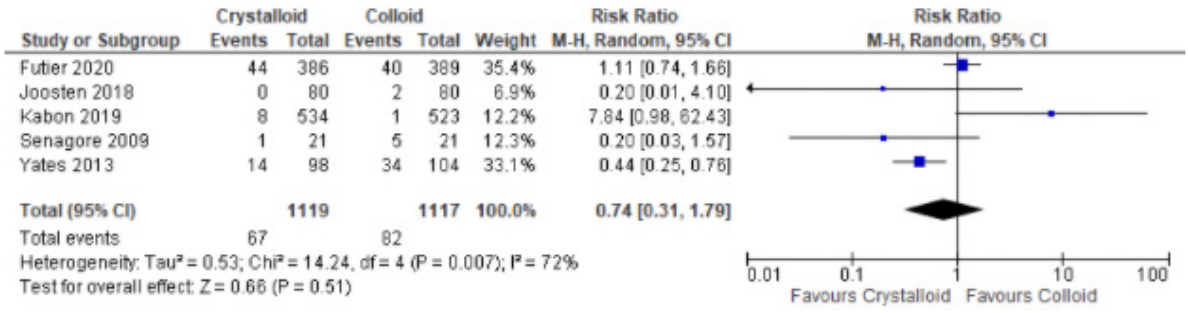

Figure 2. Cardiac related adverse outcomes

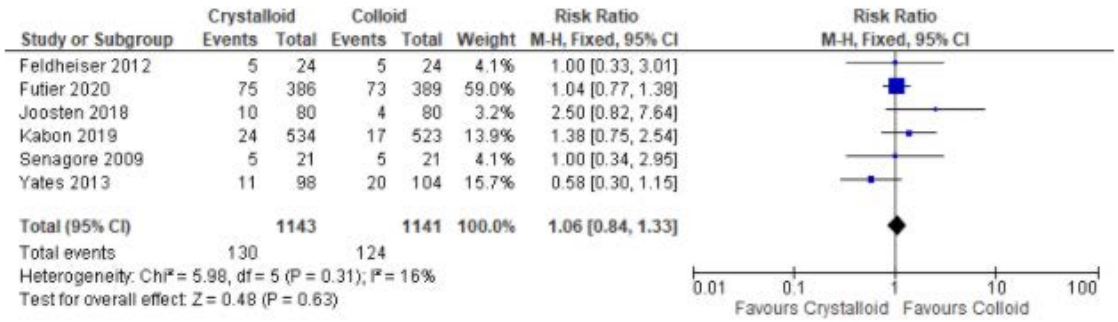

Figure 3. Respiratory related adverse outcomes

No significant difference in risk for renal related adverse outcomes was found between the two groups (RR=0.81, 95% CI=0.63-1.03, p-value=0.09).

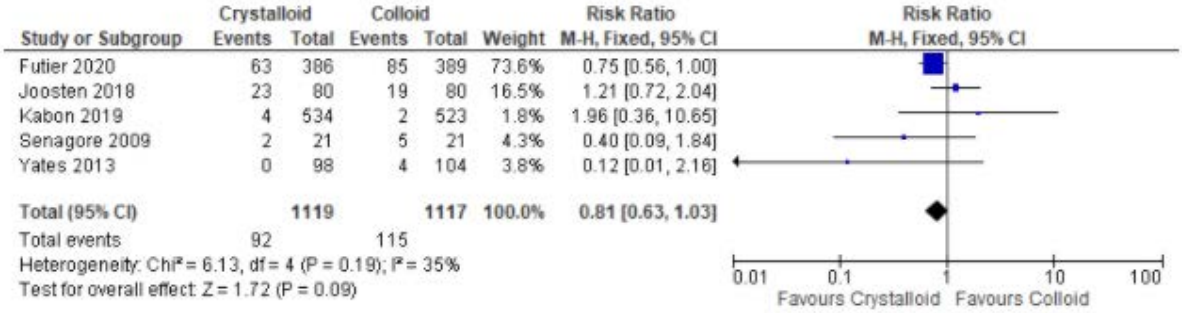

Figure 4. Renal related adverse outcomes

No significant difference in risk for gastrointestinal related adverse outcomes was found between the two groups (RR=0.97, 95% CI=0.52-1.81, p-value=0.92).

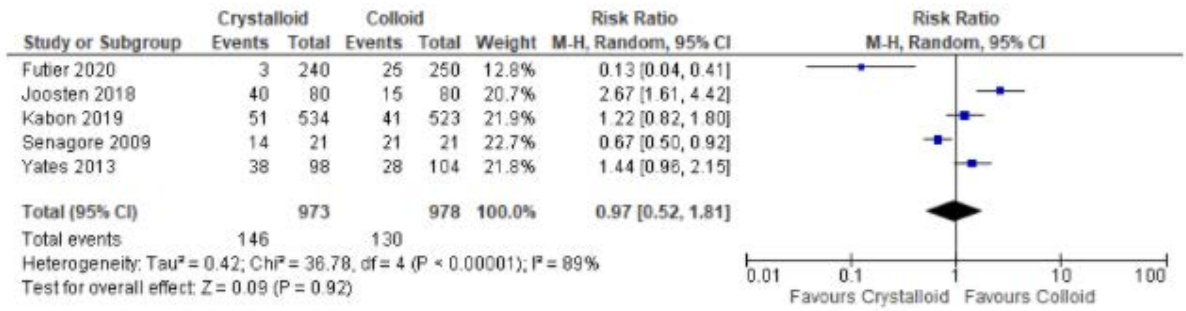

Figure 5. Gastrointestinal adverse outcomes

No significant difference in risk for infection related adverse outcomes was found between the two groups (RR=1.00, 95% CI=0.80-1.25, p-value=0.99).

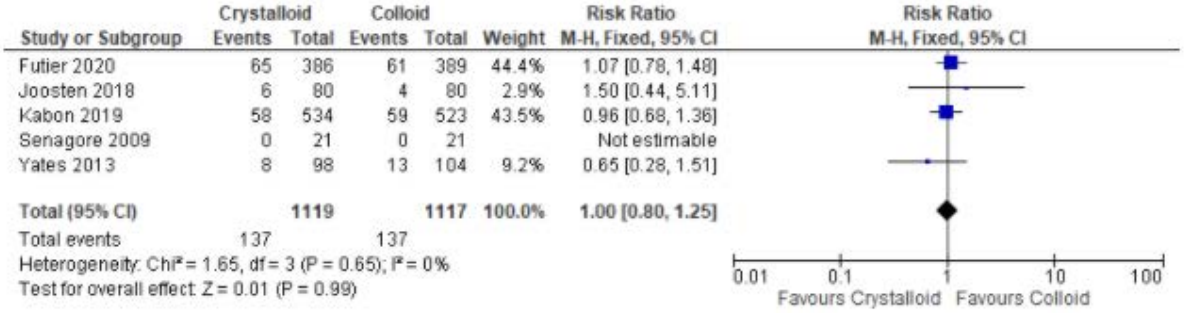

Figure 6. Infection related adverse outcomes

No significant difference in risk for coagulation related adverse outcomes was found between the two groups (RR=0.81, 95% CI=0.47-1.39, p-value=0.45).

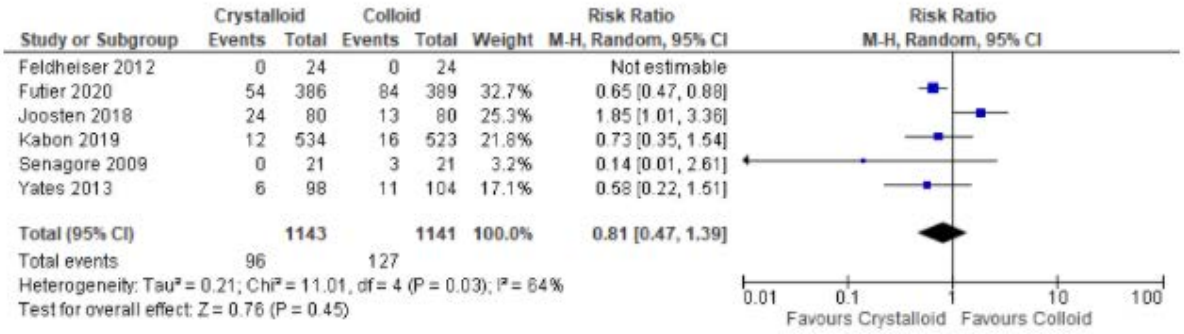

Figure 7. Coagulation related adverse outcomes

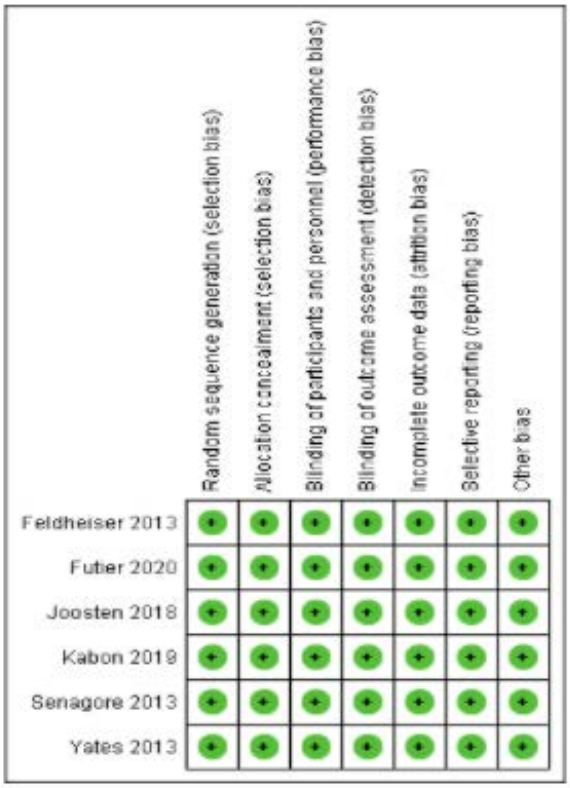

Figure 8. Risk of bias summary of included studies (Cochrane Risk of Bias Assessment Tool).

Table 1. Risk of bias table of included studies (Jadad Quality Assessment Scale).

Author, Year	Randomization	Concealment	Blinding	Withdrawal	Overall
Senagore, 2009	Appropriate	Appropriate	Appropriate	Described (minimal)	Good
Feldheiser, 2012	Appropriate	Appropriate	Appropriate	Described (minimal)	Good
Yates, 2013	Appropriate	Appropriate	Appropriate	Described (minimal)	Good
Joosten, 2018	Appropriate	Appropriate	Appropriate	Described (minimal)	Good
Kabon, 2019	Appropriate	Appropriate	Appropriate	Described (minimal)	Good
Futier, 2020	Appropriate	Appropriate	Appropriate	Described (minimal)	Good

CRITICAL CARE 38

Neuromuscular morbidity on a long-term follow-up of COVID-19 ICU survivors

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INTRODUCTION: Survivors of acute respiratory distress syndrome (ARDS) commonly experience persistent functional disability after discharge from the hospital. There is currently limited data on neuromuscular sequelae of COVID-19 critical illness. The goal of this study was to analyze the prevalence and types of neuromuscular morbidity on a long-term follow-up of COVID-19 ICU survivors.

METHODS: We retrospectively analyzed a cohort of 35 adult patients (age ≥ 18 years) who were admitted to an ICU at Massachusetts General Hospital in Boston, MA between April 2, 2020, and May 4, 2020. These were consecutive admissions with PCR-confirmed COVID-19 pneumonia during the defined enrollment period of 33 days. All patients received invasive mechanical ventilation. The final date of study follow-up for all patients was October 15th, 2021. Electronic medical records from the index hospital admission, rehabilitation facilities, relevant outpatient visits (e.g., MGH Coronavirus Recovery Clinic, pulmonary medicine, neurology, psychiatry, physical therapy, home health services), and tests (CT, MRI, electromyography) were reviewed by two investigators (D.H and K.B), and queried for specific terms, including 'stroke', 'tracheostomy', 'decannulation', 'neuropathy', 'polyneuropathy', 'myopathy', 'weakness', 'deconditioning', 'disability', 'paresis', 'paresthesia', 'numbness', 'wheelchair', 'walker', 'cane', 'brace', 'gait', 'balance', 'physical therapy'. Active medication prescriptions on the day of follow-up were reviewed and the use of analgesics recorded. This detailed review allowed us to determine the rates and types of persistent neuromuscular morbidity following hospital discharge. Summary statistics were prepared using Microsoft Excel (Microsoft Corporation, Redmond, WA). This study was approved by the Partners Healthcare System Institutional Review Board as Protocol# 2020P001048. The Institutional Review Board waived the need for informed consent.

RESULTS: Twenty-seven patients (77%) with median age of 56 years (IQR 52-67) were alive at the time of study follow-up. The date of follow-up was between 449 and 533 days (median 522, IQR 516-527) since hospital discharge. The hospital stay of this cohort was characterized by prolonged mechanical ventilation (median of 22.1 days, IQR 17-27.9) and high rates of tracheostomy (66.7%). The initial discharge destination for majority of patients (81.5%) was another healthcare facility. However, at the time of follow-up, most patients (92.6%) resided at home and all were decannulated (Table 1). We found high rates of neuromuscular morbidity in this cohort. Motor deficit in bilateral or unilateral extremities was documented in 12 (44.4%) patients, sensory neuropathy was documented in 6 (22.2%) patients, and post-COVID deconditioning (generalized weakness) in 18 (66.7%) patients between hospital discharge and follow-up. Five (18.5%) patients underwent formal electrodiagnostic testing (EMG) for the work-up of severe motor deficit. Over 365 days prior to follow-up, 10 (37%) patients required an assistive device (wheelchair, walker, or cane) or orthotics (brace) to facilitate mobility because of significant problems with the gait due to foot drop, leg weakness, or balance. In 8 (29.6%) patients, the need for assistive device started with critical illness, while 2 patients already used an assistive device before the critical illness. We found that the rates of neuromuscular morbidity gradually declined over time, suggesting propensity to improvement or recovery. Utilization of formal physical therapy services also declined over time. During the last 90 days preceding the follow-up, the ongoing motor deficit was documented in 3 (11.1%) patients, sensory neuropathy in 1 (3.7%) patient, and generalized weakness in 1 (3.7%) patient. At the time of follow-up, the most prescribed analgesics were gabapentinoids (29.6%), followed by NSAIDS (11.1%) and opioids (7.4%). (Table 2).

CONCLUSION: We found high rates of neuromuscular morbidity in survivors of COVID-19 critical illness. Neuromuscular morbidity was severe in at least one third of the patients who required various assistive devices to facilitate mobility after hospital discharge. Future studies are required to investigate potential links between the observed neuromuscular sequelae and factors such as prolonged immobilization, deep sedation, use of neuromuscular blockade, and immune-inflammatory parameters, in order to improve the management and outcomes of patients with ARDS.

Patient characteristics	Value
Baseline characteristics	
Patients enrolled (April 2 - May 4, 2020), n	35
In-hospital mortality, n (%)	8 (22.9%)
Patients alive at the follow-up (October 15, 2021), n	27
Gender	
Men, n (%)	18 (66.7%)
Women, n (%)	9 (33.3%)
Age at the time of follow-up, years, median (IQR)	56 (52-67)
Hospital course (survivors)	
Duration of hospital stay, days, median (IQR)	35 (29-47)
Duration of mechanical ventilation, days, median (IQR)	22.1 (17-27.9)
Stroke, n (%)	2 (7.4%)
Received tracheostomy, n (%)	18 (66.7%)
Tracheostomy duration, days, median (IQR)	18 (13.8-33.8)
Days since decannulation, median (IQR)	522 (503.3-526.8)
Discharge characteristics	
Days since hospital discharge, median (IQR)	522 (516-527)
Initial discharge destination	
Home, n (%)	5 (18.5%)
Facility, n (%)	22 (81.5%)
Current residence	
Home, n (%)	25 (92.6%)
Facility, n (%)	2 (7.4%)

Table 1

Neuromuscular morbidity	Value
Electrodiagnostic testing for weakness workup, n (%)	5 (18.5%)
Physical therapy	
Receiving PT during 90 days prior to follow-up, n (%)	2 (7.4%)
Receiving PT during 365 days prior to follow-up, n (%)	12 (44.4%)
Receiving PT at any point since hospital discharge	22 (81.5%)
Documentation of ongoing motor deficit	
90 days prior to follow-up, n (%)	3 (11.1%)
Upper extremity, n	0
Lower extremity, n	3
Bilateral	1
Unilateral	2
365 days prior to follow-up, n (%)	9 (33.3%)
Upper extremity, n	3
Lower extremity, n	8
Bilateral	4
Unilateral	5
Since hospital discharge, n (%)	12 (44.4%)
Upper extremity, n	4
Lower extremity, n	9
Bilateral	6
Unilateral	6
Documentation of ongoing sensory neuropathy	
90 days prior to follow-up, n (%)	1 (3.7%)
Upper extremity, n	0
Lower extremity, n	1
365 days prior to follow-up, n (%)	4 (14.8%)
Upper extremity, n	0
Lower extremity, n	4
Since hospital discharge, n (%)	6 (22.2%)
Upper extremity, n	2
Lower extremity, n	5
Documentation of ongoing post-COVID deconditioning	
During last 90 days, n (%)	1 (3.7%)
During last 365 days, n (%)	9 (33.3%)
Since hospital discharge, n (%)	18 (66.7%)
Utilization of assistive devices and orthotics during last 365 days, n (%)	
Brace, n (%)	1 (3.7%)
Cane, n (%)	2 (7.4%)
Walker, n (%)	4 (14.8%)
Wheelchair, n (%)	3 (11.1%)
Prescription of analgesic drugs at follow-up	
Gabapentinoids, n (%)	8 (29.6%)
NSAIDS, n (%)	3 (11.1%)
Opioids, n (%)	2 (7.4%)

Table 2

CRITICAL CARE 39

Safety and Efficacy of Awake Fiberoptic Intubation in Critically Ill Patients: A Retrospective Case Series

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INTRODUCTION: Intubation in critically ill patients is a high-risk procedure, with recent studies demonstrating that over 40% lead to hemodynamic instability, almost 10% lead to severe hypoxemia, and that propofol is significantly associated with cardiovascular instability[1]. Video laryngoscopy does not shorten time to intubation nor improve first-pass success rates compared to direct laryngoscopy in critically ill patients, irrespective of operator experience[2]. Awake fiberoptic intubation (AFOI) is a well-established tool for airway management in patients with known or suspected difficult airways and can reduce hemodynamic changes during induction[3-5]. We sought to demonstrate the safety and efficacy of AFOI in critically ill patients irrespective of the presence of a difficult airway.

METHODS: We performed a retrospective case series of patients who underwent AFOI attempts in the ICU of a large academic tertiary care hospital between April 2018 and September 2021. We obtained demographic and clinical variables at time of induction and recorded hemodynamic data throughout the peri-intubation period. Primary outcome was development of hemodynamic instability (either systolic pressure <65 at least once or <90 for 30 minutes during the peri-intubation period, new or increased need of vasopressors, or fluid bolus >15 mL/kg). Secondary variables were cardiac arrest during intubation, severe hypoxemia (oxygen saturation <80%), arrhythmia, aspiration, post-intubation ABG, in-hospital mortality, and 30-day mortality. A total of 21 ICU patients underwent AFOI. Indications for intubation and peri-intubation characteristics are shown in Table 1.

RESULTS: All patients were successfully intubated using AFOI. 2 patients had hemodynamic instability during intubation and 1 patient had cardiac arrest. 2 patients had transient oxygen desaturations and 1 patient had severe hypoxemia in the setting of cardiac arrest. 0 patients aspirated. 2 patients had arrhythmias that were present prior to intubation. 15 patients died during hospitalization and 13 patients died within 30 days of intubation. Average post-intubation arterial pH was 7.35, average PaO2 was 135 (average FiO2 0.78), and average PCO2 was 48. Average change in heart rate from beginning to end of intubation was +4.5 bpm, change in blood pressure was -0.5mmHg, and change in oxygen saturation was +0.7 percent (Table 2, Figure 1, Figure 2).

CONCLUSION: In this retrospective series of 21 critically ill patients requiring intubation, we demonstrated that AFOI is a safe method of intubation that preserves hemodynamic stability and oxygenation. Notably, the period of hemodynamic instability, hypoxia, and cardiac arrest in one patient all occurred over 30 minutes after the intubation, suggesting other factors led to the outcome such as positive pressure ventilation and cardiogenic shock. Future studies will prospectively examine safety of AFOI in the ICU.

REFERENCE(S):

1. JAMA. 2021;325(12):1164-1172
2. Crit Care. 2019;23(1):221
3. Anesthesia and Analgesia, v. 128, p. 971-980
4. Anesthesiology, v. 125, p. 105-114
5. Anaesthesia, v. 72, p. 694-703

Table 1: Peri-intubation Characteristics

Characteristic	
Indications	*Difficult airway (3)*
	Aspiration risk (2)
	Hypoxemic hypercapnic respiratory failure (6)
	Neck/mediastinal mass (2)
	Unstable cervical spine (2)
	Massive hemoptysis (1)
	Pulmonary hypertension (2)
	Cardiogenic shock/valvular disease (3)
Average age	57
Average Charlson Comorbidity Index (CCI)	6
Males (%)	10 (48%)
Females (%)	11 (52%)
Vasoactive infusions prior to intubation (%)	6 (29%)
Respiratory support	*HFNC (9)*
	BiPAP (8)
	HFNC and BiPAP (1)
	NC (3)
Patients on 100% FiO2 (%)	13 (62%)
Difficult mask ventilation (%)	5 (24%)
Sedation methods	*fentanyl (5)*
	dexmedetomidine (6)
	ketamine (1)
	hydromorphone (1)
	combination (3)
	none (5)

Table 2: Intubation Outcomes

Outcome	
Hemodynamic instability (%)	2 (9.5%)
Cardiac arrest (%)	1 (4.7%)
Severe hypoxemia (%)	3 (14.3%)
Aspiration (%)	0 (0%)
Arrhythmia (%)	2 (9.5%)
In-hospital mortality	15 (71.4%)
30-day mortality	13 (61.9%)
Performer of intubation	*Attending (8)*
	Fellow (10)
	Resident (3)
Average arterial pH	7.35
Average PaO2 (mmHg)	135
Average FiO2	0.78
Average PCO2 (mmHg)	48
Average PaO2:FiO2	173
Average change in MAP (mmHg)	-0.5
Average change in HR (bpm)	+4.5
Average change in SaO2 (%)	0.7

Figure 1: Heart Rate During AFOI

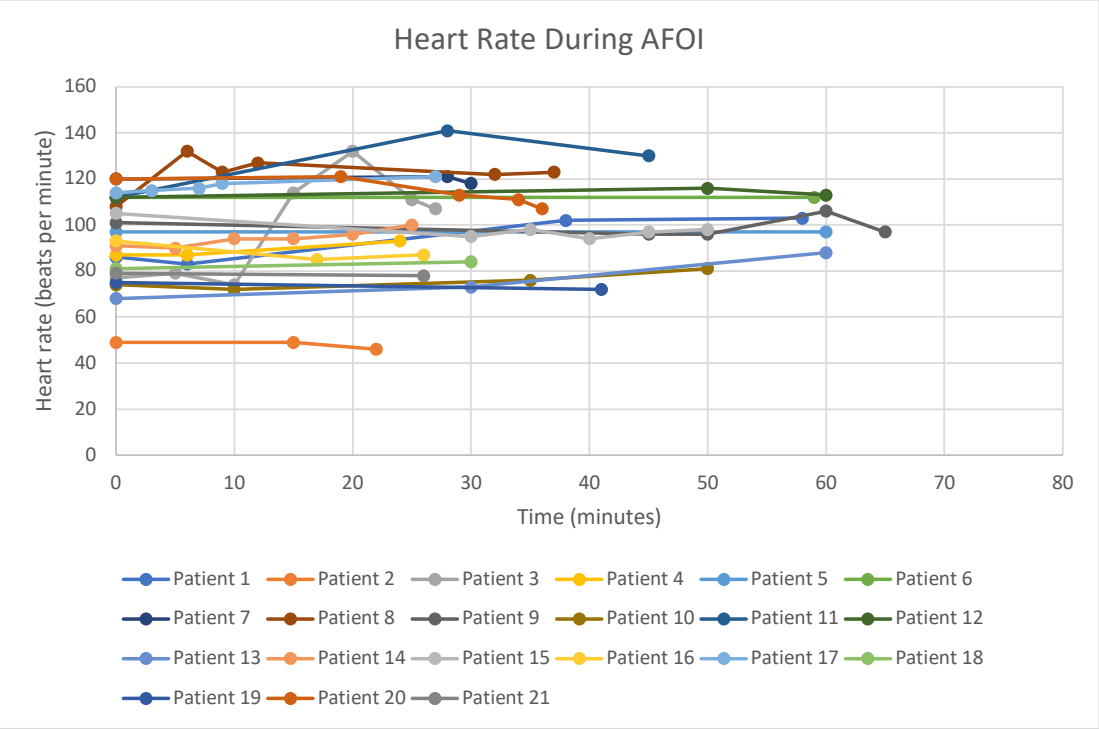


Figure 2: Mean Arterial Pressure (MAP) During AFOI

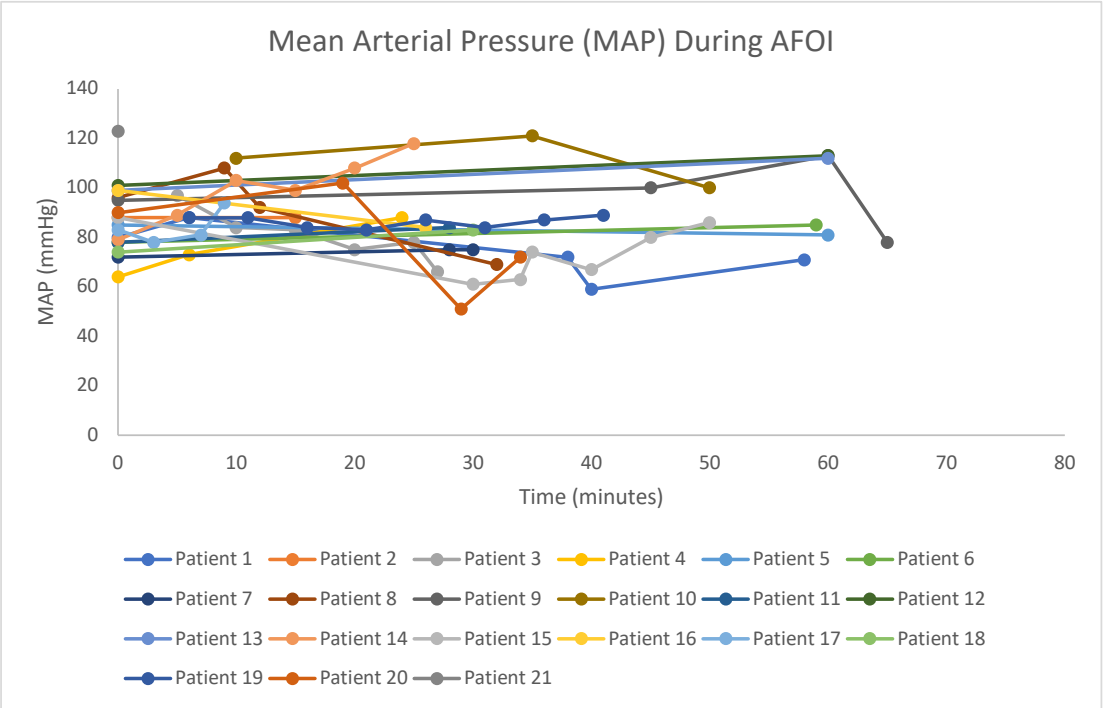
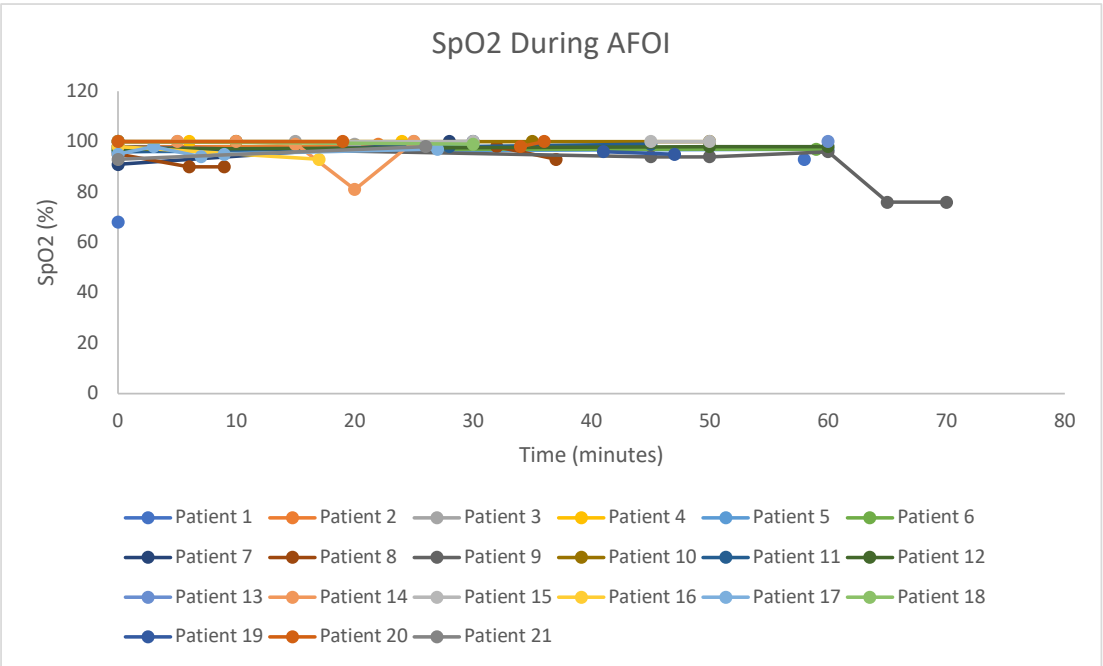


Figure 3: Oxygen Saturation (SpO2) During AFOI



CRITICAL CARE 40

Specialized Pro-Resolving Mediators After LVAD, Cardiac, and Spine surgery

Catherine Ha[1], Erin Hittesdorf[2], Krishna Rao Maddipati[3], Robert Whittington[4], Gebhard Wagener[5]

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INTRODUCTION: Inappropriate resolution of acute inflammation has been recognized as a maladaptive response that may lead to chronic disease.[1-3] Specialized pro-resolving mediators (SPMs) were recently identified as active mediators of inflammation resolution.[2,4-6] During the acute inflammatory phase, fatty acid metabolites prostaglandin (PG) and leukotrienes (LT) are produced to mediate the inflammatory response. At the height of neutrophil infiltration, lipid metabolism shifts to form SPMs rather than PGs and LTs to halt neutrophil recruitment and activate macrophages.[7] SPMs have been studied extensively in pre-clinical models. However, little data exist regarding SPMs in clinical models of acute inflammation. Cardiac surgeries, particularly the insertion of ventricular assist devices, incite a profound inflammatory reaction with outcomes depending on the relationship between rapid resolution of inflammation and the severity of surgery.

METHODS: After IRB approval and written, informed consent, adult (≥18 years old) patients undergoing left ventricular assistance device (LVAD) implantation, cardiac, or spinal (as controls) surgery were recruited between May 2018 and August 2019. Plasma samples were collected in patients undergoing LVAD implantation preoperatively, daily for the initial 10 postoperative days, as well as at 30 and 90 days. In the cardiac and spinal patients, plasma samples were collected preoperatively and daily during their postoperative ICU course. The Lipidomics Core of Wayne State University analyzed for SPMs, prostaglandin metabolites, and metabolites of arachidonic acid pathways via liquid chromatography-mass spectrometry. Quantified cytokine assays (GM-CSF, IFNα2, IFNγ, IL-2, IL-6, IL-8, IL-10) were obtained by Eve Technologies. T-tests were used to determine significance in levels of cytokines and SPMs between LVAD and non-LVAD patients. Spearman's rank correlation coefficients were used to correlate peak cytokine and SPM levels among LVAD, cardiac, and spinal patients within the first 10 days postoperatively.

RESULTS: 10 LVAD, 10 cardiac, and 4 spine surgery patients were enrolled. The SPMs, their associated mediators, and cytokines were analyzed with varying levels of success. A select group of SPMs and cytokines were further analyzed based on availability of data. Levels of RvD1 were the only SPMs reaching significance between LVAD and non-LVAD patients during each matched day of the post-operative period (Figure 1). Significant correlations were found between IL-6 and 11-HETE, 12-HEPE, 12-HETE, 13-HDoHE, 14-HDoHE, 15-HETE, 4-HDoHE, 5-HEPE, 5-HETE. Significant correlations were also found between IL-8 and 11-HETE, 13-HDoHE, 15-HETE, 18-HEPE, 4-HDoHE, 5-HEPE, 5-HETE. However, correlations overall were poor (Figure 2).

CONCLUSION: SPMs were detectable before and after LVAD implantation, cardiac, and spine surgeries. Strong correlations were not found between severity of surgery and levels of SPMs in the initial postoperative period. While significant differences were detected in RvD1 (which is thought to downregulate neutrophil activation in the acute inflammatory phase) between LVAD and non-LVAD patients, the overall lack of identifiable trends points towards the possibility that the conversion from acute to chronic SPMs occurs at a later stage following surgery.[8] Assessment of SPMs for longer periods postoperatively may potentially capture this conversion.

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Figure 1. Select SPMs and cytokines before and after VAD, cardiac and spine surgeries.

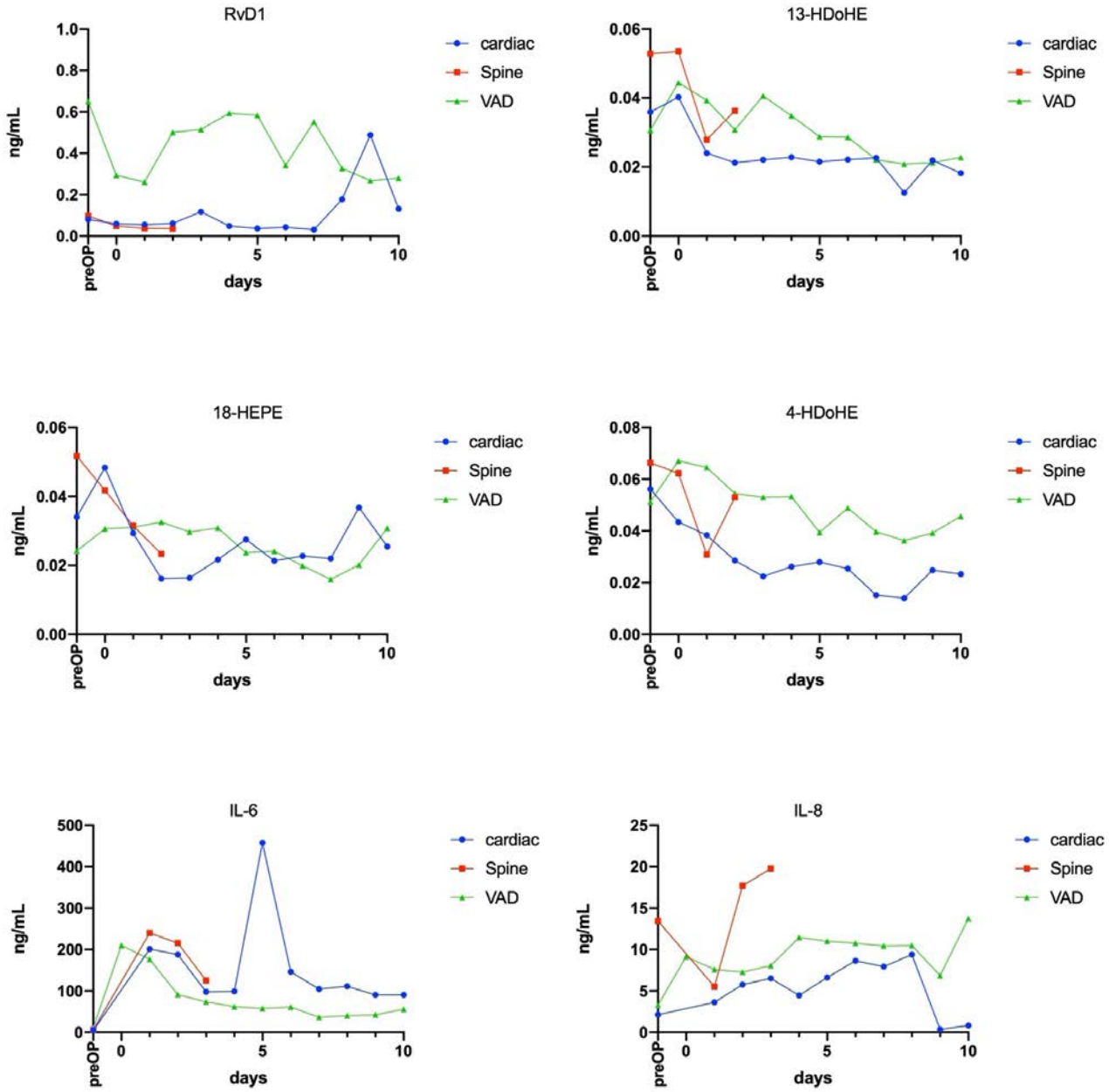

Figure 2. Spearman's rank correlation coefficients between select cytokines and SPMs.

Spearman	Peak IL-2	Peak IL-6	Peak IL-8
11-HETE	-0.043	0.43	0.522
12-HEPE	0.044	0.417	0.371
12-HETE	0.005	0.393	0.314
13-HDoHE	-0.059	0.434	0.648
14-HDoHE	0.035	0.417	0.354
15-HETE	-0.061	0.401	0.434
18-HEPE	0.006	0.381	0.568
4-HDoHE	-0.053	0.415	0.666
5-HEPE	-0.016	0.411	0.529
5-HETE	0.011	0.431	0.529
RvD1	-0.036	0.256	0.357

CRITICAL CARE 41

Mechanical power and compliance as predictors of mortality in patients with COVID-19 related ARDS requiring extracorporeal membrane oxygenation

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INTRODUCTION: Mechanical power (MP) describes the energy transmitted to the respiratory system during mechanical ventilation (MV). MP referenced to respiratory system compliance (MP/compliance) has been shown to predict mortality better than MP alone in acute respiratory distress syndrome (ARDS). In patients receiving veno-venous extracorporeal membrane oxygenation (VV ECMO) for ARDS, MP during the first 3 days of ECMO was independently associated with mortality with MP/compliance being more predictive than MP alone[1]. ARDS caused by COVID-19 (COVID ARDS) behaves differently from other causes of ARDS in that respiratory system compliance is initially relatively good despite very poor oxygenation before potentially progressing to a low compliance disease[2]. We assessed the association between MP and mortality in patients with COVID ARDS requiring VV ECMO. We hypothesized that higher MP and MP/compliance is associated with mortality in patients with COVID ARDS requiring VV ECMO.

METHODS: Following IRB approval, we performed a retrospective cohort study of patients with COVID ARDS requiring VV ECMO within a quaternary referral health system. Between 3/21/2020 and 10/15/21, 95 patients with COVID-19 were cannulated for ECMO. Patients were excluded if their primary reason for ECMO was not COVID ARDS, they required veno-arterial ECMO, had incomplete MV data to calculate MP and MP/compliance. Only primary ECMO runs were included for data analysis. Data collected included demographics, length of MV support before ECMO, duration of ECMO support, MV settings and compliance before ECMO initiation (T1) and at 24 (T2) and 72 hours (T3) after ECMO initiation, and survival to hospital discharge. MP was calculated using the simplified equations described previously (Fig. 1)[3,4]. Student's t test was used to compare continuous variables between groups. Chi-square test was used for categorical variables.

RESULTS: A total of 58 patients met inclusion criteria. Demographics are shown in Table 1. Thirty-one patients survived to discharge (53.4%) with 21 non-survivors (39.6%). MP at T1 differed between survivors (25.6 J/min) and non-survivors (32.56 J/min, p= 0.03, 95% CI 0.55-13.35) (Table 2). MP and MP/compliance were not associated with mortality at all other time points.

CONCLUSION: Unlike previous studies in non-COVID ARDS, we found that only MP at ECMO initiation was associated with mortality. This may be due to the unique pathophysiology underpinning COVID-19. Additionally, while referencing to compliance was used as a measure of functional lung size, other measures may more accurately estimate functional lung size and be better predictors for lung recovery. Limitations of this study include its retrospective nature and single health system data, limiting generalizability. Additionally, MV variables such as compliance are not measured at standard intervals and several patients were excluded due to incomplete MV data. Many patients were transferred as part of our mobile ECMO program and MV parameters before ECMO initiation at the initial hospital were not available. The simplified MP calculations do not account for spontaneous patient respiratory efforts which can significantly increase the stress on the respiratory system. Future directions involve use of additional variables such as severity of illness scores and underlying comorbidities to identify risk factors associated with hospital mortality.

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$$\text{PC MP} = 0.098 \times \text{RR} \times \text{Vt} \times [\text{PEEP} + \Delta P_{insp}]$$

$$\text{VC MP} = 0.098 \times \text{RR} \times \text{Vt} \times [\text{Peak Inspiratory Pressure} - ½ (\text{Plateau pressure} - \text{PEEP})]$$

Figure 1. Simplified equations for mechanical power calculation with pressure-controlled (PC) and volume-controlled (VC) mechanical ventilation. For PC MP, 0.098 is a conversion factor from cmH_2O/min to J/min, RR is respiratory rate, Vt is tidal volume in liters, PEEP is cmH_2O of end expiratory pressure, ΔP_{insp} is pressure above PEEP during PC ventilation. For VC MP, the same conversion factor of 0.098 is used to convert to J/min, RR is respiratory rate, Vt is tidal volume in liters, and peak inspiratory pressure, plateau pressure and PEEP are expressed in cmH_2O.

Table 1. Demographics for overall cohort, survivors to discharge and non-survivors.

	Overall mean (SD)	Survivors	Non-Survivors	P-value
Overall cohort		31 (53.4%)	21 (39.6%)	
Age	47.4 (11.6)	47.55 (11.65)	47.17 (12.11)	p= 0.90
Gender -Male	50 (86.2%)	25 (80.6%)	21 (91.3%)	p= 0.27
Female	8 (13.8%)	6 (19.3%)	2 (8.7%)	
BMI	33.1 (5.8)	33.91 (6.08)	32.32 (5.44)	p= 0.32

Table 2. Comparison of MP and MP referenced to compliance in survivors versus non-survivors

	Survivors	Non-survivors	p-value
MP at T1 (J/min)	25.6	32.45	**0.03**
MP/compliance at T1 (J/min/ml/cmH_2O)	1.14	1.42	0.21
MP at T2	15.81	16.62	0.70
MP/compliance at T2	0.67	0.81	0.25
MP at T3	16.62	13.29	0.16
MP/compliance at T3	0.81	0.74	0.60

CRITICAL CARE 42

The Complexity of Oxidative Stress After In Vitro Ischemia-Reperfusion Injury and Hypothermia: Not All Readouts Are The Same

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INTRODUCTION: Therapeutic Hypothermia (TH) is the gold standard treatment for neuroprotection in post-cardiac arrest patients. However, the TTM2 trial has raised controversy on its clinical application.[1] Additionally, TH's mechanisms are poorly understood and are still under investigation.[2] Oxygen & Glucose Deprivation followed by Reperfusion (OGD-R) is a well-established model for in vitro mechanistic studies on Ischemia and Reperfusion Injury (IRI).[3] Despite its limitations in translation to in vivo models of IRI, in vitro OGD-R represents a unique opportunity to characterize the individual biological response that different cell types experience after OGD-R and TH. Herein, we studied the effects on cell viability (CV), global reactive oxygen species (ROS) production, and lipid peroxidation using single cultures of neurons (NE) and astrocytes (AS) after OGD-R and TH protocols.

METHODS: Neurons (HT-22) and Astrocytes (C8-D1A) were subjected to 6h OGD followed by 20h of Reperfusion (OGD-R). OGD is based on the combination of chemical ischemia (standard culture media depleted of glucose and other energy sources) and severe hypoxia (~ O2 1.5%) for 6h, while 20h of reperfusion consists of the addition of standard culture media and conditions (21% O2, 5% CO2, 37°C). TH group was set at 31.5°C during 20h reperfusion. CV was determined by ATP measurement with the CellTiter-Glo 2.0® assay (ProMega). Global ROS were assessed by the CellROX® assay (Thermo Fisher), while Lipid Peroxidation (LPO) was characterized by the Image-iT® Lipid Peroxidation Kit (Thermo Fisher).

RESULTS: OGD-R decreased CV in NE (Fig. 1A, P value = 0.0001) and AS (Fig. 1B, P value = 0.0001). TH during reperfusion resulted in greater CV when compared with normothermia (NT) group, in both NE (Fig. 1A, P value = 0.0001) and AS (Fig. 1B, P value = 0.0001). In NE, OGD-R resulted in increased ROS production when compared with control, while TH after OGD-R downregulated ROS to control levels (Fig. 2A, P value = 0.0001). In AS, OGD-R resulted in increased ROS production when compared with control, while TH after OGD-R downregulated ROS to below control (Fig. 2B, P value = 0.01 and P value = 0.0001, respectively). In NE, OGD-R decreased LPO, while TH after OGD-R increased LPO when compared with NT group (Fig. 3A, P value = 0.05, P value = 0.08). In AS, OGD-R had no significant effect on LPO production, while, TH after OGD-R increased LPO versus NT (Fig. 3B, P value < 0.05).

CONCLUSION: The increased ATP production correlates with greater cell viability in NE and AS after TH, when compared with NT (Fig. 1A and Fig. 1B, respectively). TH was very effective in downregulating global ROS in NE and AS (Fig. 2A and Fig. 2B, respectively). Unexpectedly, in NE, OGD-R showed lower LPO levels versus control, while TH was associated with a higher LPO trend (Fig. 3A, P value = 0.08). In AS, TH was associated with higher LPO production versus OGD-R, NT group (Fig 3B, P value = 0.05). LPO is the product of ROS reacting with unsaturated fatty acids, which affects normal biological processes dependent on lipid function. These results suggest that oxidative stress characterization is complex and individual readouts like LPO may not be the best marker for simple ROS detection during OGD-R and TH settings. Further studies are required to properly characterize specific ROS behavior after OGD-R and TH.

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Fig.1A

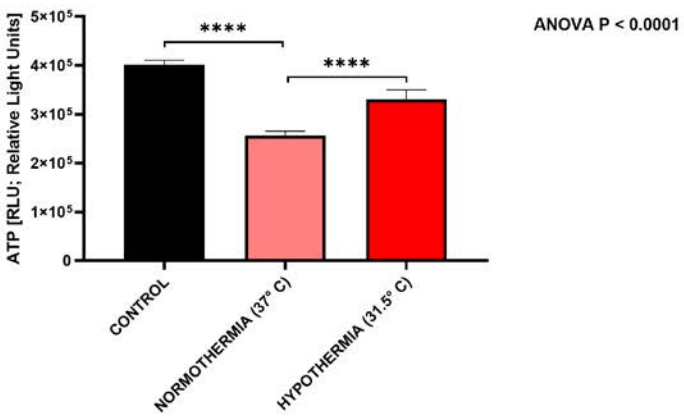


Fig.1B

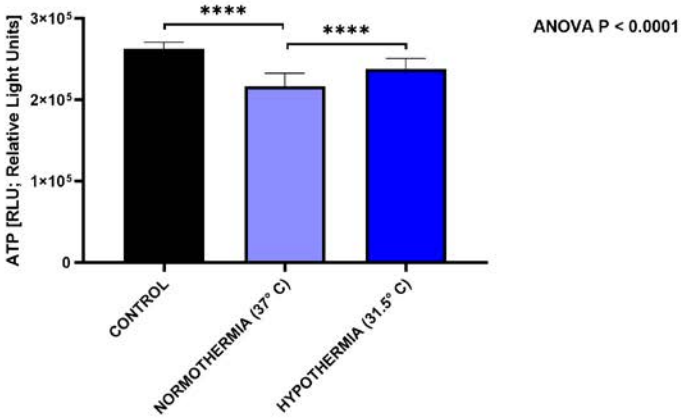


Fig. 2A

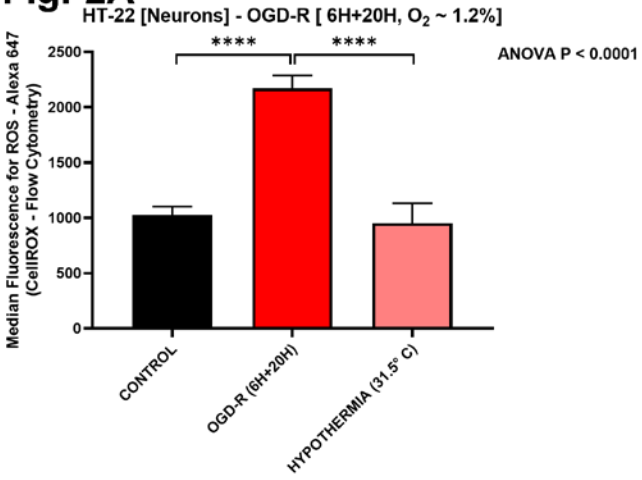


Fig. 2B

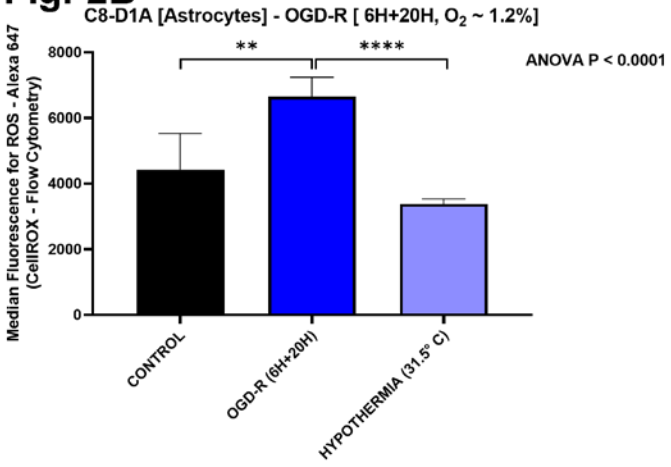


Fig. 3A

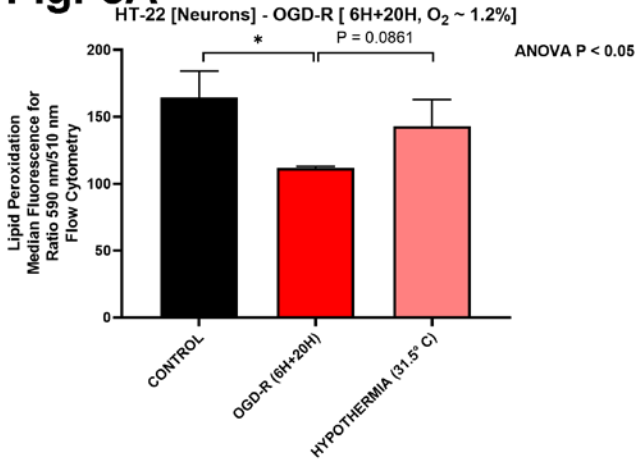
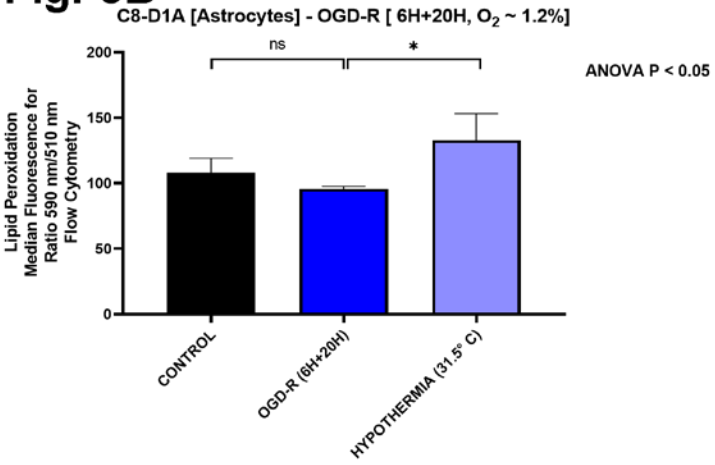


Fig. 3B



CRITICAL CARE 43

Multi-Organ Support after Coronary Artery Bypass Graft Surgery Between 2008 and 2018 Among Adults Over 65 Years Old in the United States: A Retrospective Multicenter Cohort Study

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INTRODUCTION: With over 180,000 surgeries annually[1], Coronary Artery Bypass Grafting (CABG) is the most common cardiac surgery and is associated with significant morbidity and mortality[2]. Postoperative organ injury is common and many patients require postoperative organ support[3-4]. Examining the trends of multi-organ failure (MOF) and support (MOS) in post-CABG patients is critical in understanding how aggressive life-sustaining treatments (LSTs) are utilized and whether they correlate with improved outcomes. In this study, we developed novel definitions of MOF and MOS using both claims and charge codes. We report trends from a large national dataset in the use of MOS in older ICU patients who underwent CABG and had cardiac, pulmonary, and renal failure. We then measured outcomes including mortality and ICU length of stay (LOS) in those patients requiring MOS based on their surgical status (elective vs. non-elective).

METHODS: Organ failure was defined based on previously published ICD 9/10 codes[5] which were modified to reflect a postsurgical population. Since explicit interventions exist for cardiac dysfunction and shock (i.e. vasopressors and mechanical support devices), pulmonary failure (mechanical ventilation) and renal failure (hemodialysis), we limited our definition of MOF to these categories. MOS was defined as the receipt of vasopressors or mechanical circulatory support, invasive ventilation, and hemodialysis using hospital charge codes and Standard Claims Procedure Codes. We conducted a retrospective cohort study analyzing data from the Premier Healthcare Database (Premier Inc., Charlotte, NC, USA) among patients >65 years at time of CABG leading to inpatient admission with an ICU stay >24 hours from 2008-2018. We grouped patients as undergoing either elective or non-elective CABG. Thus, our final cohort represented patients in the ICU who underwent CABG and developed MOF. Primary outcomes were (1) presence of MOS, (2) in-hospital mortality or discharge to hospice and (3) hospital length of stay (LOS) in survivors. We also examined trends in rates of pre-existing comorbidities over this timeframe. All estimates were risk-adjusted using multivariable regression models to account for comorbidities present on admission.

RESULTS: Over the study timeframe, 144,478 patients underwent CABG with 11,077 developing MOF. Of these, 7,212 required multi-organ support. MOS increased in both elective and non-elective subgroups over the study period (Figure 1). Of those requiring MOS, in-hospital mortality/discharge to hospice and hospital LOS decreased after elective surgery but not after non-elective CABG (Figure 2). Pre-existing comorbidities were stable over this timeframe (Figure 3).

CONCLUSION: Receipt of MOS increased over time despite similar rates of pre-existing comorbidities. Among patients receiving MOS, survival increased and LOS decreased after elective but not after non-elective CABG. Given that increased utilization of LSTs in the non-elective CABG population has not correlated with improved outcomes, further study is warranted to ascertain whether these patients are becoming incrementally over-treated over time.

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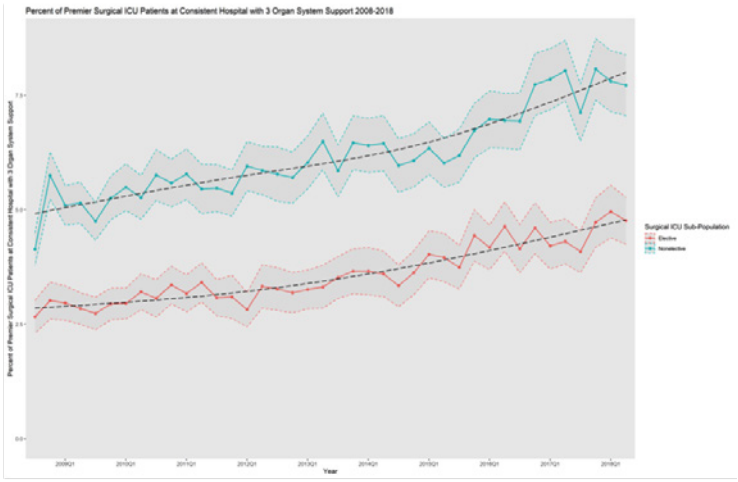

Figure 1: Predicted rates of multi-organ support in CABG patients with multi-organ failure, 2008-2018

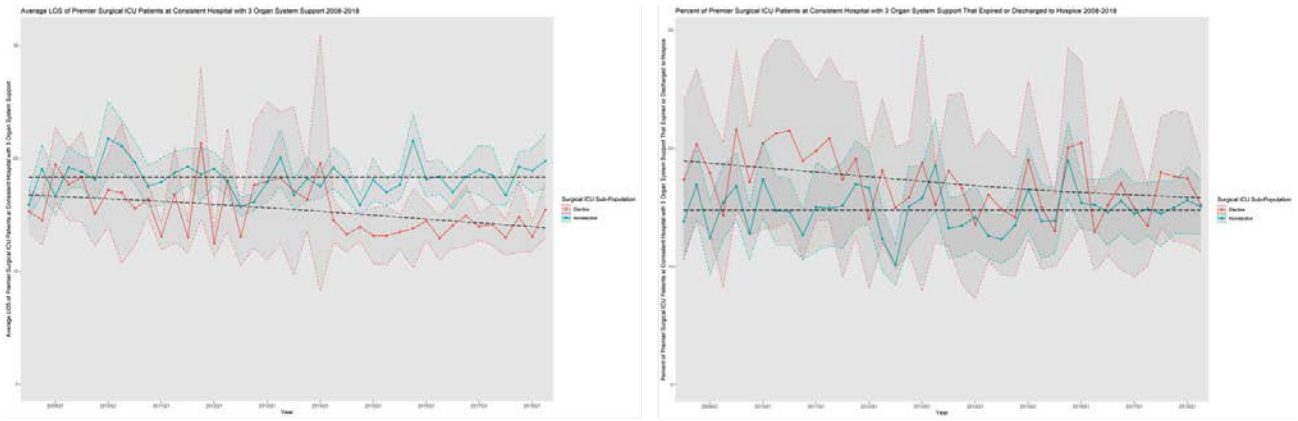

Figure 2: Predicted LOS (Left) and mortality (Right) among CABG patients with multi-organ failure requiring multi-organ support, 2008-2018

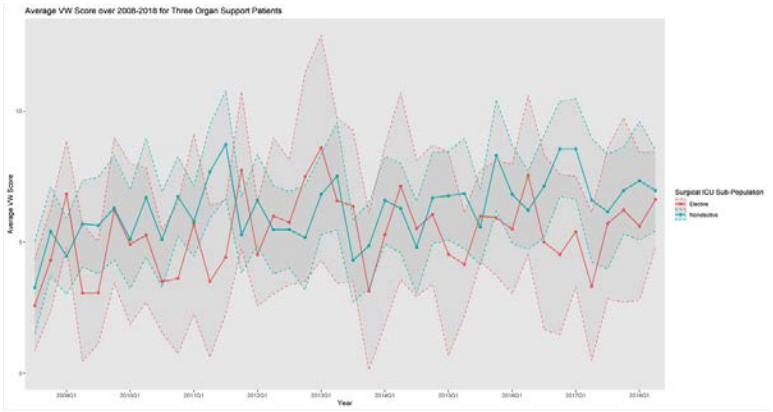

Figure 3: VanWalraven comorbidity score in CABG patients, 2008-2018

CRITICAL CARE 44

Surgical futility: exploring early neonatal postoperative mortality

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INTRODUCTION: Determining whether surgery is unlikely to produce the desired outcome of rescuing a patient from mortality is a complicated, ethically challenging endeavor. Among adult medical patients, the concept of medical futility, defined as a situation when medical care is ineffective at producing the desired physiologic effect on or benefit for the patient, is well described in the bioethics literature.[1] Surgical futility is a relatively less examined and intensely debated subject[2] Although pediatric postoperative mortality is highest among neonates,[4] to date the subject of neonatal surgical futility has not been examined. The purpose of this study was to examine factors associated with early (within 48 hr) postoperative mortality among neonates classified as American Society of Anesthesiologists (ASA) physical status 4 who underwent a surgical procedure.

METHODS: Following IRB approval, we assembled a retrospective cohort of neonates who underwent an inpatient surgical procedure from the National Surgical Quality Improvement Program (2012 - 2019). Extreme risk was defined as ASA physical status 4 and surgical futility was defined as death within 48 hr of the index surgery in these high-risk patients. We estimated the incidence and examined factors associated with surgical futility.

RESULTS: Among a cohort of 42,016 neonates, 10,813 (25.7%) were classifiable as extreme pre-surgical risk. Of these 10,813 extreme pre-surgical risk neonates, 12.4% (n=1048) died within 30 days of surgery. Almost half of the mortality cases occurred within 48 hours of index surgery (47.7%, n=500). In the multivariable model, factors associated with surgical futility include emergency surgery, preoperative sepsis, prematurity, preoperative inotropic requirement. Of note, each kg increment in weight at the time of surgery was associated with a 13% reduction in the risk of surgical futility. Other predictor variables are detailed in Table 1. We derived and validated a scoring system that demonstrated an excellent discriminant ability to predict neonatal surgical futility (cross-validated AUC=0.911; 95%CI: 0.895, 0.922- Fig.1).

CONCLUSION: Although discussing surgical futility can be a difficult and emotive endeavor, we found, using a set of simple clinical and operative variables, that it is possible to predict with excellent discrimination neonates who died within 48hr of surgery. Our data may be used for preoperative risk profiling and counseling of parents and caregivers.

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Characteristics	β coefficient	Odds ratio (95% confidence interval)	P-value	Score
Weight at the time of surgery, per kg increment	-0.14	0.87 (0.77—0.98)	0.02	-1
ASA class 5 vs. 4	1.30	3.66 (2.82—4.73)	<0.01	13
Ventilation support	0.97	2.63 (1.80—3.84)	<0.01	10
Inotropic support	1.17	3.22 (2.54—4.09)	<0.01	12
Transfusion prior to surgery	0.37	1.45 (1.14—1.84)	<0.01	4
Emergency case status	1.22	3.39 (2.57—4.46)	<0.01	12
Gastro-intestinal disorder	0.49	1.64 (1.24—2.16)	<0.01	5
Preoperative sepsis	0.72	2.05 (1.62—2.59)	<0.01	7
Prematurity	0.47	1.61 (1.15—2.24)	0.01	5

Figure 1. Multivariable logistic regression for the prediction of surgical futility and derivation of a prognostic index by incorporating demographic characteristics and pre-operative co-morbidities, NSQIP-P 2012-2019.
The cross-validated C-statistic was 0.911 (**Bias corrected 95% CI: 0.895-0.922**).
The derived prognostic index ranged from 0 to 66.
Abbreviations: ASA, American Society of Anesthesiology; NSQIP-P, National Surgical Quality Improvement Program-Pediatric; CI, confidence

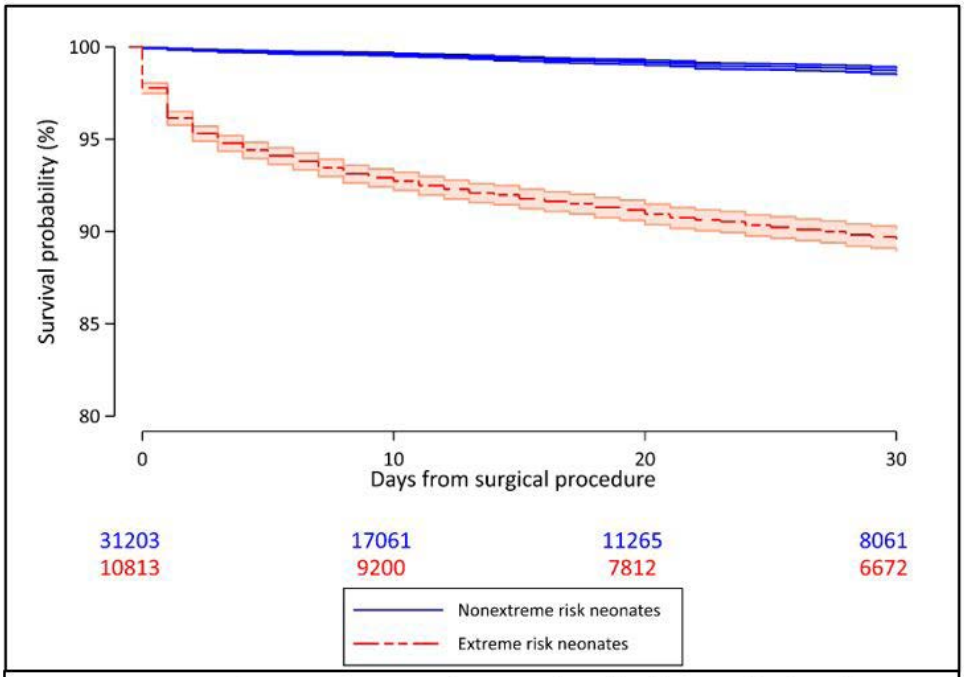

Figure 2. Time to mortality among extreme risk neonates (ASA classification≥ 4), who underwent inpatient surgery in hospitals participating in the National Surgical Quality Improvement Program (2012-2019).

CRITICAL CARE 45

Association of Diastolic Shock Index and Pulse Pressure Index with mortality in septic shock patients

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INTRODUCTION: Septic shock comprises of profound circulatory, cellular, and metabolic abnormalities, leading to mortality in 30% to 50% of the patients[1]. To improve the outcomes of septic shock patients, optimization of hemodynamic parameters is needed. One of these parameters is diastolic shock index, the quotient between heart rate and diastolic blood pressure, which reflects the severity of circulatory dysfunction[2]. Another parameter is pulse pressure index, the quotient between pulse pressure and systolic blood pressure, which is an analog of Ohm's Law and thus is an accurate indicator of vascular compliance[3]. In this study, we evaluated the association of mortality with diastolic shock index and pulse pressure index at the start of vasopressor use in ICU patients admitted for septic shock.

METHODS: The deidentified data was acquired from PhysioNet, which was sourced from electronic health record[4]. It is a retrospective study with 370 million records for 70,000 ICU patients admitted to Beth Israel Deaconess Hospital between 2008 and 2019. The data was filtered based on ICD-10 code of 'R6521' or severe sepsis with septic shock, yielding 2,548 patients. Further, for each patient, the exact time of vasopressor start was determined, which allowed us to ascertain the hemodynamic parameters at that time. These parameters included heart rate, systolic, diastolic, and mean arterial blood pressures. From these, the pulse pressure, diastolic shock index and pulse pressure index were calculated for each patient at the time of vasopressor use. The outcome variable was mortality. The descriptive analysis and independent sample T-tests was performed in SPSS[5]. Artificial intelligence modeling was employed to design a decision tree to examine mortality outcomes based on all the hemodynamic parameters.

RESULTS: The mortality rate of patients admitted with septic shock to ICU was 30.1%. The mortality rate was slightly lower at 28% in SICU, while in MICU, it was 32.1%. As for the hemodynamic parameters, the average diastolic shock index and pulse pressure index in survivors were 1.62 and 0.43, respectively. The average diastolic shock index and pulse pressure index in patients who died were 1.86 and 0.44, respectively. The t-test between the diastolic shock index (DSI) in the two subgroups was statistically significant with a mean difference of 0.24 and p-value of less than 0.001. The decision tree at the first node exhibits the survival rate of 73% if DSI is less than 1.77. For the patients where DSI is greater than 2.60 and pulse pressure is greater than 0.57, the mortality rate is 65%.

CONCLUSION: With the mortality rate of septic shock patients in ICU up to 50%, hemodynamic prognostic factors are vital in ascertaining higher risk patients. The parameter, diastolic shock index, measured at the time of vasopressor start was statistically significantly associated with mortality in septic shock patients in ICU and can be used as a clinical decision-making tool for assessing mortality risk.

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CRITICAL CARE 46

Use of Restraints in COVID-19 Positive ICU Patients across the United States

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INTRODUCTION: Physical restraints have been used in healthcare since the 1700s and are often used in the ICU to ensure patient and staff safety when patients are agitated or incapable of controlling their movements. Despite this, physical restraint use in the ICU is a topic of ethical debate. Restraint use is associated with adverse outcomes including longer hospitalizations, increased rates of in-hospital mortality, nosocomial infections, new continence and pressure ulcers, falls, decreased mobility and discharge to nursing homes[1, 2]. ICUs across the country have experienced an unprecedented challenge due to the COVID-19 pandemic, making this an ideal time to further examine ICU practices. We describe the use of restraints among critically ill COVID-19 positive patients.

METHODS: This study is approved by the Duke University Health System IRB. We used the Premier Healthcare database to identify the study population defined as individuals hospitalized with a diagnosis of COVID-19 and admitted to ICUs (identified based on Room and Board Charges), and mechanically ventilated (based on Charges) with a discharge date between April 1, and December 31, 2020. The sample was limited to adults. Among these patients, the use of restraints was identified by searching for billing for 'restraints.' We excluded hospitals where <5 patients had charges for restraints as this suggested low sensitivity of measurement in these hospitals (ie. a large number of false negatives).

RESULTS: We identified 121 hospitals where 421,695 patients were discharged during the study period. Of these, 12,487 patients carried a diagnosis of COVID-19, and 5.9% had charges for restraints (n=747). The use of restraints doubled among mechanically ventilated patients with COVID-19 from April to August (4.4% to 8.9%) while it decreased in patients without COVID-19 (4.5% to 3.6%) (Table 1). The most common comorbidity among COVID-19 restrained patients was renal dysfunction (87%), followed by hypertension (78%) and diabetes with chronic complications (43%). Less common comorbidities included depression (11%), alcohol abuse (2%) and drug abuse (2%).

CONCLUSION: The use of restraints among mechanically ventilated patients with COVID-19 increased concordant with the pandemic and may reflect ICU strain.

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Table 1: Restraint Use by month in mechanically ventilated patients

	COVID-	COVID+
	N (%)	N (%)
Jan-19	21538 (4.5)	
Feb-19	19171 (4.2)	
Mar-19	21151 (4.0)	
Apr-19	20541 (3.9)	
May-19	20990 (4.1)	
Jun-19	19400 (4.0)	
Jul-19	20741 (4.0)	
Aug-19	20638 (3.9)	
Sep-19	19587 (4.0)	
Oct-19	19446 (4.1)	
Nov-19	18052 (4.1)	
Dec-19	18803 (4.1)	
Jan-20	19103 (3.9)	
Feb-20	17697 (4.3)	
Mar-20	17439 (4.3)	
Apr-20	12444 (4.5)	1728 (4.4)
May-20	14500 (4.2)	1380 (5.8)
Jun-20	15989 (3.8)	1001 (6.8)
Jul-20	15085 (3.5)	1465 (7.0)
Aug-20	14585 (3.6)	1534 (8.9)
Sep-20	14625 (3.3)	1210 (7.6)
Oct-20	14116 (3.4)	1164 (5.3)
Nov-20	9429 (4.2)	1617 (4.0)
Dec-20	4138 (5.3)	1388 (4.6)

CRITICAL CARE 47

Methylene Blue for Vasodilatory Shock in the Intensive Care Unit: A Retrospective, Observational Study

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INTRODUCTION: Refractory vasodilatory shock, or vasoplegia, is a state of uncontrolled vasodilation chiefly mediated by dysregulation of nitric oxide (NO) and soluble guanylate cyclase (sGC) and likely also associated with underlying inflammation and endothelial dysregulation.[1,2] Most sources define vasoplegia as requiring vasopressor doses ranging from above 0.2 µg/kg/min to 0.5 µg/kg/min of norepinephrine equivalents or more, with a cardiac index (CI) of at least 2.2 L/min/m2 and difficulty maintaining a mean arterial pressure (MAP) above 65 mmHg.[2,3,4] Rescue therapy for vasoplegia refractory to catecholamines includes methylene blue (MB) which inhibits endothelial nitric oxide synthase (eNOS), inducible nitric oxide synthase (iNOS), soluble guanylate cyclase, and cytokines such as tumor necrosis factor-α (TNF-α).[1,5,6] MB restores vascular tone and is considered more targeted to the dysregulation of the microcirculation in the setting of NO upregulation.[7]

We report our institutional experience with the use of intravenous MB for refractory shock in patients admitted to the intensive care unit. In accordance with the current literature, we hypothesized in the critically ill population that (1) at least 40% of patients would respond positively to MB administration and (2) that those who responded to MB would have a survival benefit.[8]

METHODS: This study was a retrospective review of prospectively collected data at the Massachusetts General Hospital that included all adult patients admitted to intensive care units that were treated with MB for the indication of refractory vasodilatory shock. The dosing, timing and decision to administer MB was not protocolized and was at the discretion of the care team. Responders to MB were identified as those with a ≥ 10% increase in MAP within the first 1-2 hours after MB administration. Of the patients receiving MB, responders were compared to non-responders with respect to timing of MB administration and post-MB administration MAP and vasopressor requirements. Patients who did not have a reported MAP at 2 hours post-MB were excluded. The primary outcome was mortality in responders versus non-responders. A subgroup analysis in patients undergoing CRRT was also performed.

Statistics:
Statistical calculations were performed in Microsoft Excel® (Redmond, WA, USA). Where appropriate, the comparison of averages and standard deviations of demographics, MB dosing, MAP, and reductions in vasopressor dosing were performed via Chi squared, Fisher's exact test, or two-tailed t-test with a p-value <0.05 being considered as statistically significant. After using the F-test to assess for differences in variance, a two tailed T-test was used to compare SOFA scores among responders versus non-responders.

RESULTS: There were a total of 236 patients who received MB included in the analysis and 223 included in the responder analysis. Of these, 88 (37.3%) had a ≥ 10% increase in MAP post-MB administration that was not associated with a significant change in norepinephrine requirements (p=0.41). There was a trend in improved survival to hospital discharge in the MB responder group compared to the non-responder group, but this result was not statistically significant (21.6% vs 14.8%, p=0.19). There was a statistically significant difference in volume resuscitation within 24 hours after MB administration between responders and non-responders to MB (p=0.01). Responders were less likely to have CKD than those who were non-responders (21.6% vs 35.6%, p=0.03). In 69 patients undergoing CRRT, there were 32 responders who were more likely to survive (n=12, 36.4%) than those who were not, 37, (n=4, 10.8%) (p = 0.0111).

CONCLUSION: In patients with refractory shock receiving MB, identifying patients as responders and non-responders within two hours of administration based on a MAP increase >10% shows a non-statistically significant trend toward improved outcomes in responders. Responders received larger amounts of fluid resuscitation than those who were not which may reflect differences in resuscitation technique or superior cardiac function. Patients supported with CRRT who were identified as responders had decreased ICU mortality compared to non-responders. The CRRT finding may be related to impaired clearance of MB, thereby potentiating its effect. Further research is necessary to identify patients who may receive the most benefit from MB therapy.

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Table 1: Responders versus non-responders

Table 1: Responders vs. non-responders			
	Responders, n=88 (39.5%)	**Non-Responders, n=135 (60.5%)**	**p-value**
Male gender (%)	60 (68.2%)	95 (70.4%)	0.73
Age (years)	63 +/- 13.4	62 +/- 15.5	0.55
Weight (kg)	96.2 +/- 24.3	90.4 +/- 25.1	0.09
Bolus only	44 (50%)	85 (63.0%)	0.056
Bolus and drip	39 (44.3%)	45 (33.3%)	0.098
Average bolus dose (mg/kg)	1.68 +/- 0.49	1.71 +/- 0.43	0.62
Average drip dose (mg/kg/hr)	0.48 +/- 0.21	0.45 +/- 0.21	0.54
Average drip duration (hours)	11.8 +/- 9.5	16.7 +/- 13.4	0.06
Average norepinephrine at 1 hours after MB (mcg/min)	55 +/- 39.1	54 +/- 42	0.86
Average norepinephrine at 2 hours after MB (mcg/min)	49 +/- 30.5	53 +/- 44.1	0.41
Received multiple boluses	14 (15.9%)	24 (17.8%)	0.72
SOFA Score	13 (14.8%)	13 (9.6%)	0.31
Survival of Hospital	19 (21.6%)	23 (17.0%)	0.19
CRRT	57 (64.8%)	91 (67.4%)	0.68
IVF administered (mL) in first 24 hours	3645 +/- 3221	2548 +/- 3143	**0.01**

CRITICAL CARE 48

Soluble Siglec-9 as a Biomarker for COVID-19 Disease Severity

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INTRODUCTION: Coronavirus disease of 2019 (COVID-19), caused by the SARS-CoV-2 virus, is associated with considerable morbidity and mortality, with approximately 15% of hospitalized patients developing acute respiratory distress syndrome (ARDS) and mortality approaching 50%[1]. The mechanism behind the variable disease severity is poorly understood. One possible explanation posits that variable host immune response effects disease course and severity, with a dysregulated immune response in aberrant cytokine secretion and potentiating lung damage[2]. Neutrophil activation is a critical early step in the pathogenesis of ARDS. Siglec-9, an immune receptor found on the surface of neutrophils, binds sialic acid containing glycans and suppresses the immune response. Soluble Siglec-9 (sSiglec-9), the extracellular region of membrane bound Siglec-9, shows pro-inflammatory activity, likely via competitive inhibition of Siglec-9, and has been found in higher levels in patients with COPD related lung injury[3]. The purpose of this study was to determine how well sSiglec-9 levels correlate with disease progression and severity in COVID-19 ARDS.

METHODS: IRB approval from the University of Chicago and consent was obtained from all study participants. We prospectively enrolled patients from our COVID intensive care unit who met the Berlin Criteria definition for ARDS. Subjects younger than 18 years or those who were pregnant, diagnosed with congestive heart failure, admitted with myocardial infarction, or presented with hemorrhagic or ischemic stroke were excluded. We collected blood samples within 24 hours of ARDS diagnosis. These samples were centrifuged at 15,000 RPM at 4¬∞C for 8 minutes, after which the plasma was aliquoted and stored in -80¬∞C freezer until ready for analysis. A single operator blinded to clinical information performed sSiglec-9 assays using the Dynex DS2 fully automated ELISA system.

RESULTS: A total of 58 patients were included in the study. Median age for the cohort was 63 (interquartile range 56-73). Soluble Siglec-9 levels showed a negative correlation with P:F ratio (p= 0.03) and a positive correlation with SOFA score (p= 0.01). Higher median [interquartile range] sSiglec 9 levels were seen in those patients who required mechanical ventilation (573.52 [332.23, 1472.98] vs 263.16 [204.04, 578.01], p=0.003) and those who died (554.49 [402.66, 1662.47] vs 316.19 [236.52, 824.11], p=0.038) during the hospitalization.

CONCLUSION: Serum levels of sSiglec-9 are higher in COVID patients who require mechanical ventilation or who died and show a negative correlation with P:F ratio and a positive correlation with SOFA score. Further study comparing sSiglec-9 level in controls and with a larger sample size is needed.

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Table 1. Demographics and Baseline Characteristics

	COVID ARDS *N = 59*
Age, *years*	63 (56, 73)
Male Sex	30 (51.72)
Height	66 (64, 70)
Weight	180 (151, 231)
BMI	28.12 (23.72, 37.14)
Systolic Blood Pressure	121 (106, 128)
Diastolic Blood Pressure	68 (60, 77)
Heart Rate	95 (81, 107)
Temperature	98.5 (97.7, 99.3)
Respiratory Rate	28 (23, 31)
Oxygen Saturation	93.0 (90.0, 95.0)
sSiglec 9	475.66 (274.25, 962.05)
SOFA Score	6.0 (2.0, 10.5)
P/F	81 (63, 117)
Mechanically Ventilated	38 (65.52)
Died	30 (51.72)

Data is presented as n (%) or median (quartile 1, quartile 3)

CRITICAL CARE 49

Albumin in Cardiac Surgical Patients and Outcomes: A Retrospective Database Review

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INTRODUCTION: This was a retrospective database review analyzing the use of albumin in cardiac surgical patients. Albumin as a volume expander is much more costly than crystalloid therapy. Some studies demonstrate albumin and crystalloid as equivalent while other studies cite that albumin use is associated with kidney injury, sepsis, and bleeding in cardiac surgical patients. Due to high costs and controversial evidence for albumin administration, we sought to determine if adverse outcomes were associated with a higher dose of albumin.

METHODS: Following institutional review board approval, all data was collected from the electronic medical record. The finalized database included 1,491 isolated CAB, CAB+valve, and isolated valve(s) patients in the CTICU. We developed a novel albumin:crystalloid (mg/mL) ratio (A:C) as the intervention based on natural cut-offs for A:C dose as a continuous variable. High A:C was determined to be > 2.7. The primary outcome was acute kidney injury based on Kidney Disease: Improving Global Outcomes (KDIGO) score. Secondary outcomes included sepsis, reoperation for bleeding and 30-day mortality. In order to avoid confounding by preexisting cardiac dysfunction, we stratified patients into three groups based on ejection fraction (EF) (<30%, 31-50% and >50%). EF groups were compared using ANOVA and chi-square test for continuous and discrete variables, respectively. Due to small number of observations and skewness, high vs low A:C ratio groups were compared using non-parametric Wilcoxon rank sum test for continuous and Fisher's Exact test for discrete variables.

RESULTS: Exclusion criteria included patients that died within the first 24 hours of surgery, patients with end-stage renal disease preoperatively, and those who came to the ICU on ECMO. Preoperative baseline characteristics were similar among the cohorts stratified by EF, except diabetes was more common in patients with EF < 30%. (Table 1) Patients who received higher doses of albumin based on A:C ratio > 2.7, had no difference in incidence of renal dysfunction (Table 2, Figure 1). There was also no difference in 30-day mortality or sepsis. Furthermore, higher albumin doses do not appear to increase risk of bleeding as there were no differences in blood product administration or need for reoperation for bleeding. These findings hold true despite patients in the low EF group possibly being more critically ill as demonstrated by increased length of stay, increased ventilation time and more diabetes.

CONCLUSION: Based on these results, albumin appears to be safe in cardiac surgical patients without increased risk of renal failure or other previously associated adverse outcomes such as bleeding and sepsis. These results hold true in each of the three ejection fraction groups. Patients with lower ejection fraction appeared to be more critically ill, however did not have increased renal failure associated with A:C ratio. Furthermore, this study presents a novel strategy to study albumin use in CTICU with the A:C ratio. The A:C ratio is a feasible and straight-forward calculation to assess the effects of the quantity of albumin administration in relation to crystalloid. Due to the retrospective nature of this study, these results are hypothesis generating and should be validated in future randomized controlled trials.

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Table 1. Baseline characteristics of patients stratified by ejection fraction (EF).

Characteristic	**EF < 30%** (n = 108)	**EF 31-50%** (n = 320)	**EF >50%** (n = 1063)	**p value**
Albumin:Crystalloid ratio (mg/mL)*100	2 (2)	3 (2)	3 (3)	0.047
Female	26 (24.1%)	65 (20.3%)	287 (27.0%)	0.052
Age	64.04 (10.09)	63.7 (11.56)	64.3 (10.81)	0.691
Race				0.102
White	85 (79.4%)	256 (82.1%)	893 (85.1%)	
Black	13 (12.2%)	32 (10.3%)	69 (6.6%)	
Other	9 (8.4%)	24 (7.7%)	87 (8.3%)	
Diabetes	57 (52.3%)	138 (43.1%)	377 (35.5%)	0.0003
BMI	29.53 (5.74)	29.53 (5.76)	29.78 (5.84)	0.760
CPB time (minutes)	102.4 (32.53)	103.5 (36.47)	102.7 (35.67)	0.932
Procedure				<0.0001
Isolated CABG	85 (78.7%)	233 (73.3%)	616 (58.1%)	
Isolated valve	9 (8.3%)	62 (19.5%)	315 (29.7%)	
CABG + valve	14 (13.0%)	23 (7.2%)	130 (12.3%)	
Intra-procedure total blood products	2.17 (2.47)	1.96 (1.48)	1.93 (2.04)	0.834
Postoperative total blood products	3.94 (8.10)	3.09 (3.13)	2.67 (3.47)	0.223
Ventilation hours	23.70 (55.67)	12.91 (23.14)	10.17 (8.10)	<0.0001
Surgery to discharge length of stay (days)	8.71 (5.91)	7.29 (4.91)	6.60 (3.73)	<0.0001

All values given as mean (standard deviation) for continuous variables and n (%) for discrete variables. Albumin:Crystalloid ratio = (mg albumin : mL crystalloid)*100, BMI = body mass index, CPB = cardiopulmonary bypass, INR = international normalized ratio, CABG = coronary artery bypass graft

Table 2. Outcomes associated with high albumin:crystalloid (mg albumin : mL crystalloid)*100 ratio defined as greater than 2.7.

	EF<30% (n=28)	p value	EF 31-50% (n=109)	p value	EF > 50% (n=372)	p value
AKI	16 (57.14%)	0.054	25 (22.9%)	0.117	98 (26.3%)	0.169
Reoperation for bleeding	3 (25.9%)	.0750	6 (5.5%)	0.145	8 (2.15%)	0.080
Sepsis	1 (3.6%)	0.433	1 (0.92%)	0.700	4 (1.08%)	0.372
30-day mortality	1 (3.6%)	0.594	3 (2.8%)	0.825	3 (0.8%)	0.915

EF = ejection fraction, AKI = acute kidney injury

CRITICAL CARE 50

ECMO for Severe COVID-19 ARDS: Our 2020 Experience from the THEME Registry

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INTRODUCTION: Extracorporeal membrane oxygenation (ECMO) has been utilized in cases of severe COVID-19 acute respiratory distress syndrome (ARDS). Outcomes reported in the ELSO registry have been poor with mortality around 50%(1). We present our experience within the TandemHeart Experiences and Methods (THEME) Registry utilizing veno-venous (V-V) ECMO in COVID-19 ARDS.

METHODS: THEME is a multi-center, prospective, observational registry. All patients enrolled in the THEME registry in 2020 utilizing V-V ECMO for COVID-19 ARDS were evaluated for 180-days after device insertion.

RESULTS: Twenty-six COVID-19 patients were enrolled in 2020 at Princeton Baptist Medical Center, a 505 bed (45 ICU bed) non-transplant community hospital. Adjunctive therapies were utilized prior to ECMO cannulation, including prone positioning and invasive mechanical ventilation. Lung protective ventilatory strategies were utilized throughout hospitalizations and patients were managed by a multidisciplinary, physician-led comprehensive critical care practice. Bedside management was performed with ICU (non ECMO specialist) staff nurses with perfusionist support available as needed. Presence of comorbidities, such as obesity, were higher than national levels noted within the ELSO registry. Survival at 180-days was 69%. The mean duration of ECMO support was 22 days.

CONCLUSION: Our V-V ECMO demonstrated favorable outcomes in COVID-19 ARDS relative to the ELSO registry. These outcomes were obtained at a community hospital, with an intensivist program, in absence of 24/7 perfusion services. Additionally, ECMO specialist RNs were not utilized. A robust educational program was instituted to avoid the need for ECMO specialists. Future studies intend to investigate potential mortality advantages versus the comparative registry outcomes.

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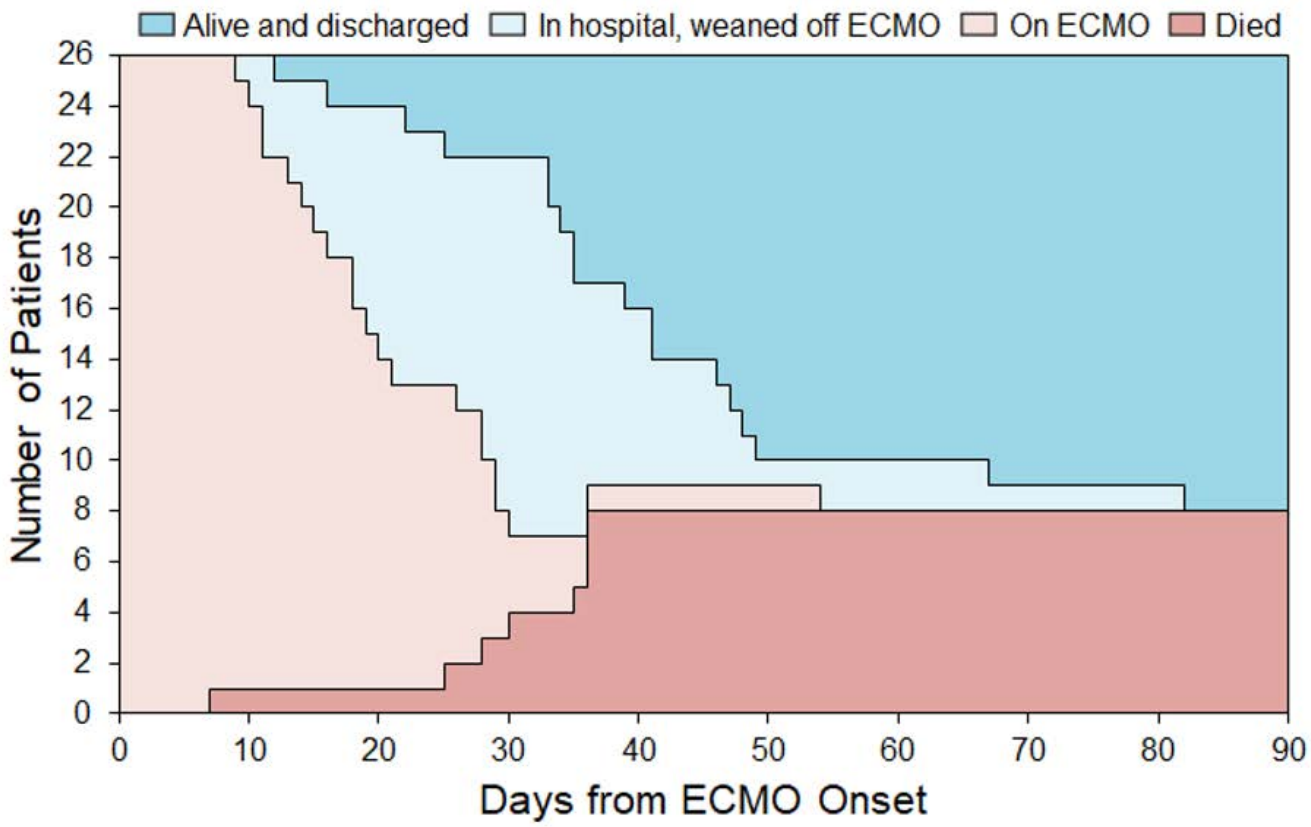

Fig. 1

CRITICAL CARE 51

The Effect of the COVID-19 Pandemic on Proning Practices in the Intensive Care Unit

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INTRODUCTION: Prior to the COVID-19 pandemic, prone positioning (PP) of patients with respiratory failure in the intensive care unit was seldom practiced due to many different factors, including staff familiarity and institutional practice. We sought to determine how the COVID-19 pandemic affected the outlook, practice, and adaptation of PP as well as to identify limiting factors for adoption among ICU registered nurses (RN), respiratory therapists (RT), advanced practice providers (APP) and physicians (MD). Further, we sought to evaluate if there were any differences among providers with the practice of PP.

METHODS: An online survey was constructed using Research Electronic Data Capture (REDCAP), which was emailed to ICU staff. Among those contacted, 146 total respondents replied to the survey, which consisted of questions regarding comfort, explaining physiology, time taken to perform PP and safety of PP. A student's t-test was used to evaluate the difference between all providers while a 2-way ANOVA (time x role) was used to evaluate the effect of provider role between the beginning and later time point in the pandemic.

RESULTS: ICU staff reported that they were more comfortable ($P<0.001$), could better explain why PP was important ($P<0.001$), could prone a patient more quickly ($P<0.001$) and more safely ($P<0.001$) at the later time point vs. at the beginning of the pandemic. There was no effect of provider role (RN/RT/APP/MD) on any variable measured at either time point, while all individual provider roles showed a similar increase in comfort, explanation, time and safety at both time points within the pandemic. Limiting factors for wider adoption of PP included availability of and familiarity with Rotoprone Therapy beds, staff education, and lack of simulation experience.

CONCLUSION: Our results indicate that the COVID-19 pandemic had a substantive and demonstrable effect on the practice of PP across a wide variety of ICU staff roles and could have implications for the use of PP in other respiratory conditions in the future.

CRITICAL CARE 52

Influence of timing and patient co-morbidity on outcomes in venovenous extracorporeal membrane oxygenation in Covid-19: A retrospective analysis

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INTRODUCTION: Venovenous extracorporeal membrane oxygenation (ECMO) remains a novel therapy in covid-19 infection. Though frequently used, optimal patient selection and timing remain uncertain.

METHODS: A single center retrospective chart review study including 52 patients started on venovenous ECMO from March 2020 to September 2021 with a diagnosis of covid-19 infection. Timing of symptom onset, hospital admission, intubation, and cannulation for ECMO were recorded along with various co-morbidities (hypertension, diabetes, chronic kidney disease, immunocompromised status, chronic lung disease or cancer) and age. Variable means were assessed against survival to hospital discharge.

RESULTS: Survivors were cannulated sooner than non-survivors after symptom onset (13.16 days vs 18.16), hospital admission (7.64 days vs 11.41) and intubation (4.8 days vs 7.08). Though these differences were not statistically significant, time to cannulation from hospital admission and time to cannulation from symptom onset trended more significant than time to cannulation from intubation (p 0.056 and p 0.07 vs p 0.216). Diabetics appeared to be at greater, but not statistically significant, risk of death than non-diabetics (60% vs 41% p = 0.28) but hypertension did not appear to convey risk (46% vs 44% mortality without hypertension). Too few patients had the other assessed co-morbidities to comment, though zero out of four patients with pre-existing chronic kidney disease survived. Average age was lower in survivors than non-survivors (47 vs 54) this was not statistically significant (p = 0.056).

CONCLUSION: Although optimal timing of ECMO cannulation remains unclear, earlier cannulation in the Covid-19 disease course appears to be associated with better survival. Time from admission or symptom onset to cannulation appear to trend more significant than time from intubation. This is likely because timing of intubation is often contentious in Covid-19 patients and does not correlate well with duration of illness. Hypertension and diabetes do not appear to reduce survival although there were no other co-morbidities noted in significant numbers. Younger age was associated with survival though no clear cut-off points were ascertainable. Significantly more research is needed to clarify optimal patient selection and timing of venovenous ECMO in Covid-19.

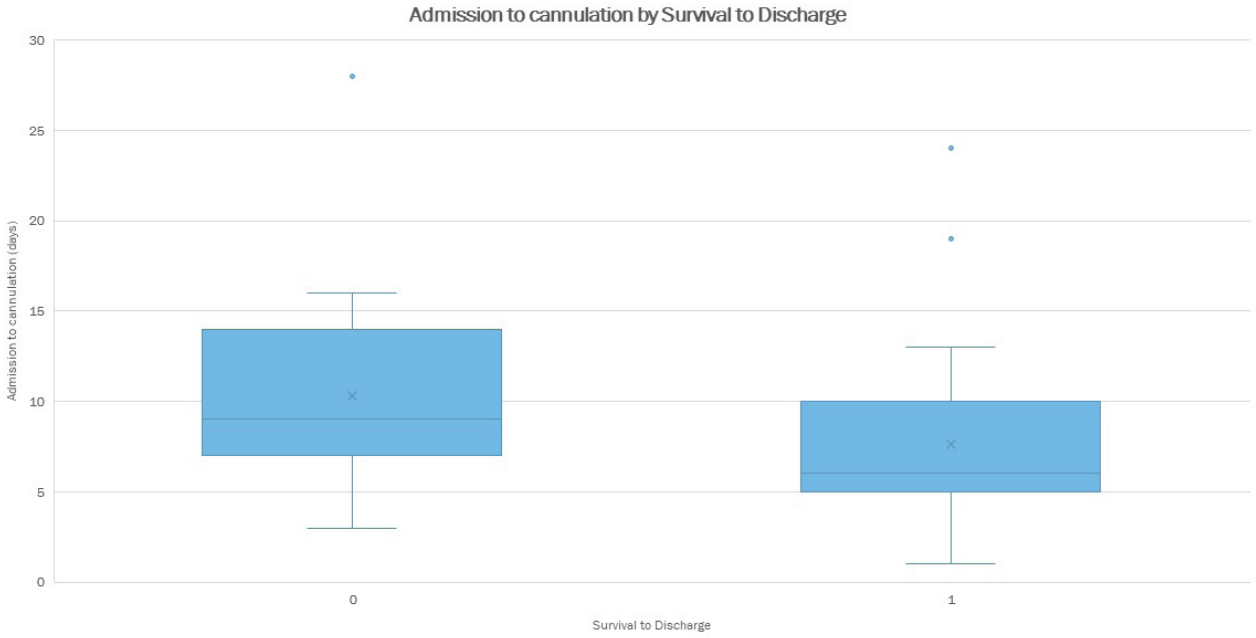
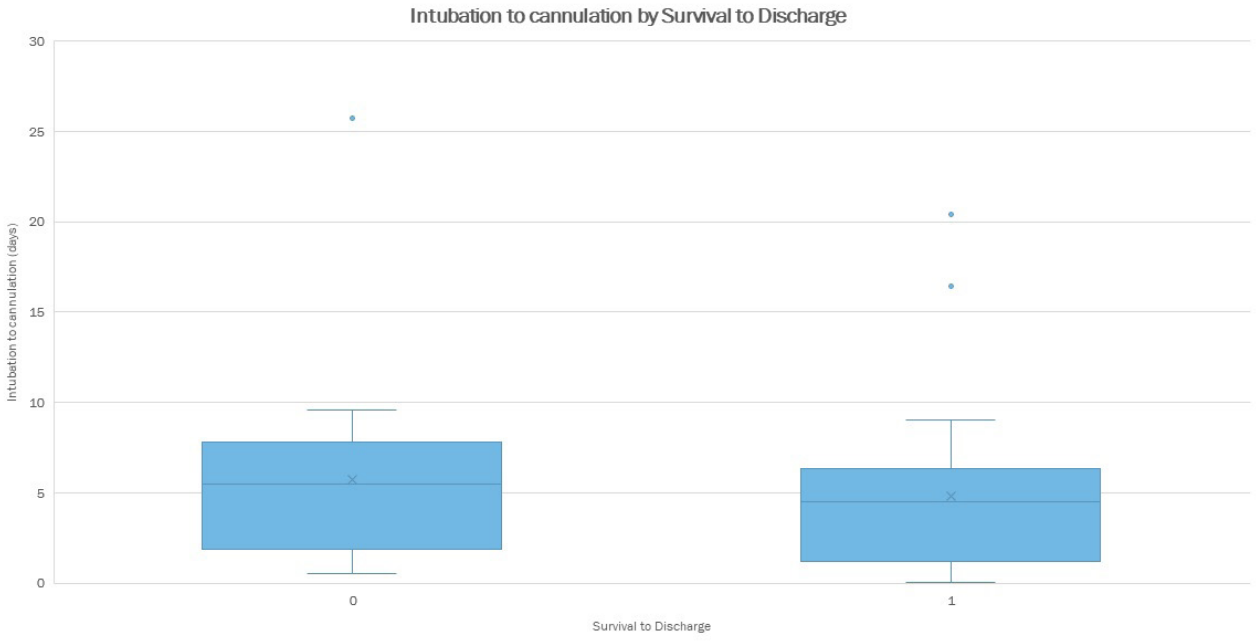


Fig. 1



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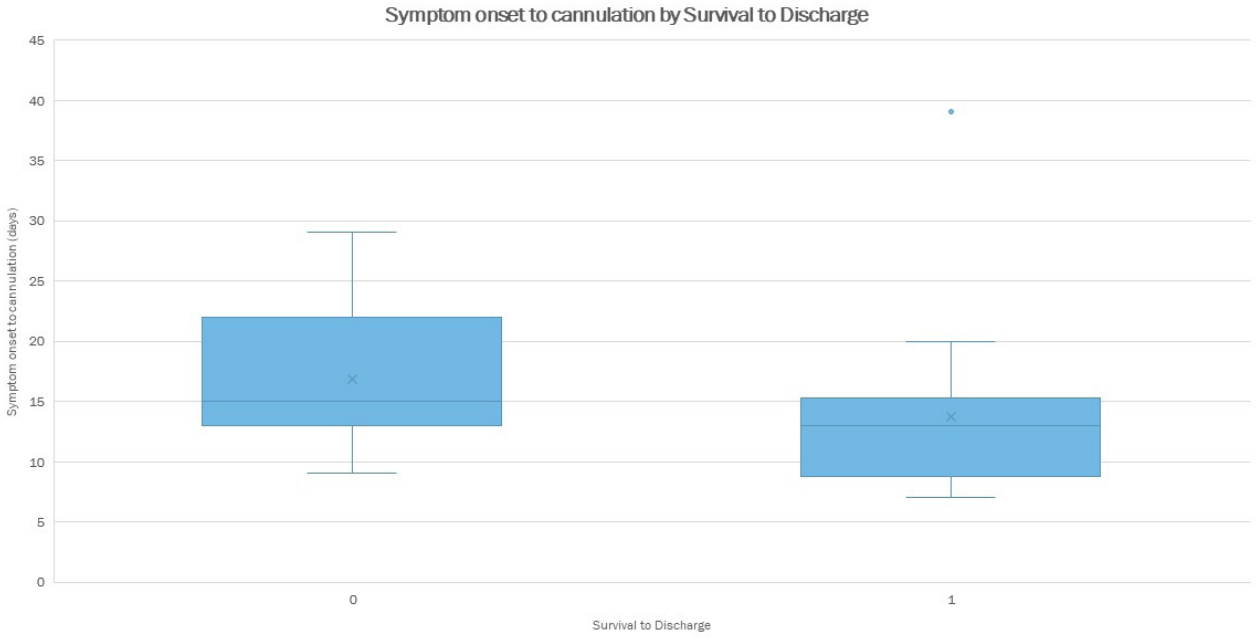

Fig. 3

CRITICAL CARE 53

Burnout and PTSD Among ICU Registered Nurses During the COVID-19 Pandemic

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INTRODUCTION: Burnout among healthcare workers (HCWs) may lead to reduced quality of patient care[1,2]. The COVID-19 pandemic has particularly affected registered nurses (RNs) who have had to quickly adjust to the uncertainty of COVID-19, care for an overwhelming number of critically ill patients, and adapt to rapidly evolving treatment guidelines with limited resources[3,4]. RNs have witnessed numerous deaths while physically isolating from social support[5]. Frontline workers are experiencing critical levels of stress and burnout which may have serious implications[6]. Our study aims to assess the psychological burden of the COVID-19 pandemic on frontline workers by measuring levels of post-traumatic stress, compassion satisfaction (CS), and compassion fatigue (CF) among RNs working at a large metropolitan hospital during the first wave of the pandemic.

METHODS: 130 RNs at a large academic center were surveyed using the Impact of Events Scale - Revised (IES-R) and Professional Quality of Life 5 (Pro-QOL-5). IES-R was used to assess subjective levels of PTSD symptoms after providing direct patient care during the pandemic[7]. Pro-QOL-5 was used to assess CS and CF (subcategorized as burnout and secondary traumatic stress (STS)) related to one's work during the pandemic[8]. Participants were categorized into mild, moderate, and severe PTSD symptoms and low, moderate, and high CS and CF based on pre-determined score cutoffs[7,8]. Results were analyzed as a group and when stratified by gender, years of experience, and work in an ICU. Standard descriptive statistics were used to determine if there is a relationship between the psychological burden of the COVID-19 pandemic on RNs and gender, years of experience, and work in an ICU.

RESULTS: RNs reported an average IES-R score clinically significant for symptoms of PTSD. Average IES-R scores were elevated regardless of gender, but males reported higher scores than their female colleagues. When stratified by years worked, all groups demonstrated IES-R scores consistent with PTSD symptoms but RNs with less than 1 year of experience reported the highest average. ICU RNs reported higher IES-R scores than non-ICU RNs. RNs reported decreased CS and moderate levels of burnout, regardless of stratification. The average of all STS scores was not elevated; however, RNs working in an ICU reported scores consistent with mild STS.

CONCLUSION: The current pandemic has increased the workload of frontline workers. RNs have made sacrifices that have negatively impacted their mental health, manifesting as symptoms of PTSD, CF, and burnout. RNs also report decreased CS. ICU RNs, male RNs, and RNs with fewer years of experience may be at higher risk for developing mental health sequelae from their work during the COVID-19 pandemic. For the safety of RNs and patients, personal and institutional support should be implemented to better understand, prevent, and combat the psychological repercussions of COVID-19 on frontline workers.

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CRITICAL CARE 54

ICU video review as a novel tool to support the Educational, Performance Improvement, and Clinical Care Goals of a Surgical Intensive Care

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INTRODUCTION: Video review has been used for performance improvement in settings such as the emergency department and operating room (1), and to our knowledge, the University of Pennsylvania is the first to utilize it in the intensive care unit (ICU). No study has evaluated the value and psychological safety of video review in the ICU, though this work has been done in other settings (2). The primary objective of this study is to assess the perceived value of ICU video review as an educational tool for improving clinical judgment and performance. The secondary aims are to evaluate whether participants deemed the session to be psychologically safe and to identify barriers to attending the sessions.

METHODS: The study is a descriptive cross-sectional survey. The 9 question survey was distributed to 120 providers and trainees working in the surgical ICU after a monthly video review session for an eight month period from July 2020 to February 2021. Participants were identified through a master ICU scheduling list. Due to COVID 19, all video review sessions were virtual. Using a Likert scale or a selection of descriptive responses, the 9 survey questions were intended to identify whether participants perceived the sessions to be educationally valuable, how video review may have changed clinical practice, whether sessions were psychologically safe, and perceived barriers to participation in the ICU video review sessions. Descriptive statistics including frequencies and percentages were calculated for each survey question. Separate one proportion z-tests were used to determine if for every question, the proportion of Likert scale responses were statistically significantly different from each other. Level of significance was set at alpha = 0.05 prior to conducting any analysis.

RESULTS: Of 120 invited to complete the survey 48 responded (40%), and 33 (27%) attended an ICU video review session. Barriers to attendance were not being aware of the session 13/48 (27%) and clinical duties 14/48 (25%), Of respondents who attended a video review session, 15/33 (45%) found it very educational or extremely educational, 14/33 (42%) found it somewhat educational and 2/33 (6%) found very little or no education benefit. Using Z test for proportions - Z value -0.68, $p = 0.49$, there was not a statistically significant perceived educational benefit for respondents as a group. When grouped by provider type (MDs vs APP/RN), there was a difference at statistical significance of perceived educational benefit for APPs at $p = .10$. 22/48 (46%) respondents endorsed that video review sessions were educational because they learned about effective communication during a critical event. 17/48 (35%) respondents learned competent leadership during a critical event. 13/48 (27%) found educational benefit in witnessing a critical event that they had no previous exposure to. 13/48 (27%) learned new management strategies for a critical event with which they had experience. 7/48 (14%) found benefit in evaluating their own performance in a reviewed event in which they had participated. 23/48 (47%; $Z = 1.5$, $p = 0.05$) respondents agreed that video review provided them with information that will change the way they practice. 28/48 (42%, Z value 1.26, $p = 0.21$) respondents felt that previous participation in video review sessions improved their performance during a subsequently encountered critical event. 27/36 (75%, Z value 3.68, $p < 0.001$) of the respondents who attended the video review sessions perceived the sessions to be psychologically safe. However, in subgroup analysis, there was a nonsignificant ($p=0.06$) trend towards trainees feeling video review was psychologically unsafe.

CONCLUSION: Video review was not perceived to be educationally valuable for providers in aggregate, though there was a signal that subset of APPs did find video review of educational value. However, participants did agree that video review provided them with information that changed their practice. Attendees of video review perceived the sessions to be psychologically safe, though it is possible that trainees feel differently than other attendees. This study was limited by sample size and an altered learning environment due to the COVID pandemic. Additional study is warranted to determine how to best incorporate this novel tool into an ICU setting in a way that enhances the educational, performance and clinical care goals of the surgical intensive care unit in a psychologically safe manner.

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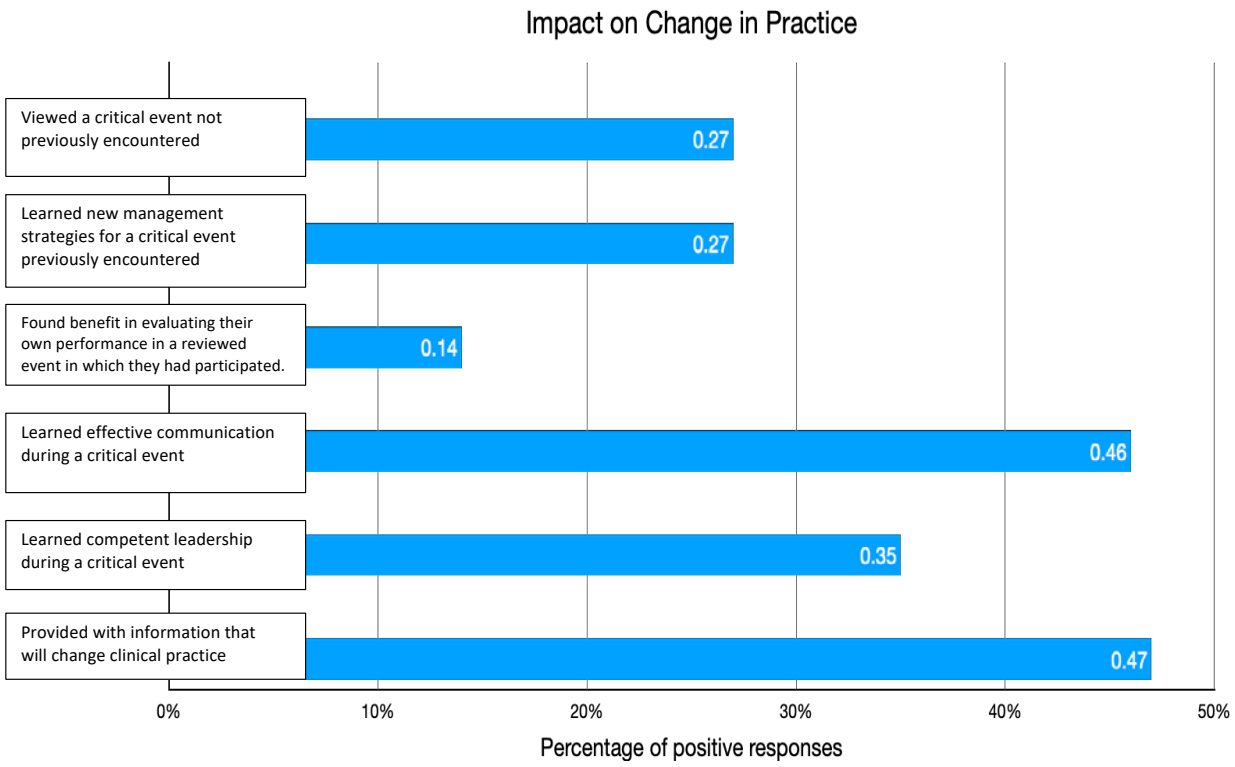

Fig. 1

CRITICAL CARE 55

Systematic Review of Major Bleeding for patients with Covid-19 on ECMO

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INTRODUCTION: Since the beginning of the Covid-19 pandemic extracorporeal membrane oxygenation (ECMO) has gained widespread use for severe refractory ARDS.[1] Bleeding is the one of the most common complications of ECMO, with the incidence of major bleeding ranging from ~20-50% depending on numerous factors, including anticoagulation strategy.[2] Despite its risk in ECMO, the incidence of major bleeding in patients with COVID-19 has not been examined systematically to determine whether or not this specific population possesses an increased bleeding risk while on ECMO.

METHODS: We conducted a systematic review using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Search terms were designed by the authors with assistance from a medical librarian for the detection of major bleeding in patients with Covid-19 on ECMO. The search was run on three different databases. Inclusion criteria were the following: age of equal or greater of 18 years, confirmed Covid-19 infection requiring ECMO, documentation of major bleeding. Exclusion criteria were the following: non-English language articles and case reports studies that included five or fewer patients. Two reviewers screened 116 non-duplicate article abstracts with 15 articles assessed via full-text review for eligibility. A third reviewer served as a tiebreaker.. Both retrospective and prospective studies were included. Full-text articles were excluded due to the studies either examining the wrong patient outcomes or populations. A PRISMA flow diagram detailing the selection of relevant studies is shown in Figure 1.

RESULTS: Our systematic search resulted in six publications describing major bleeding events in COVID-19 patients treated with ECMO. Upon reviewing the publications and references we discovered an additional four publications that were included in the review. All publications were retrospective observational trials that describe 48 patients with major bleeding episodes out of a total of 118 patients receiving ECMO. One of the publications did not provide the total number of ECMO patients, only the amount of major bleeding. Seven of the studies reported on patients treated before the end of July, 2020. One study reported on patients treated up to September, 2020. Types of bleeding included intracranial, oropharyngeal and one reported episode of psoas hematoma. 31 of the 48 reported bleeding events were intracerebral. No study observed a correlation between bleeding and supratherapeutic anticoagulation. No other patient or treatment variables were noted to be clearly linked to bleeding episodes.

CONCLUSION: The coagulopathy associated with COVID-19 and the need for systemic anticoagulation required for VV-ECMO places patients at risk for major bleeding events. We found a major bleeding rate of approximately 41% and an incidence of intracranial hemorrhage of approximately 26%. Lebreton et al. reported major bleeding events in 43% of the ECMO patients, and almost 25% of these patients had evidence of intracranial hemorrhage.[3] Ultimately, various cohorts report a significant percentage of patients experiencing ICH while on VV-ECMO for ARDS, ranging from 6-13%.[4-5] Prior systematic reviews have demonstrated the incidence of ICH on ECMO prior to the COVID-19 pandemic to be between ~2-20%.[6] Our systematic review demonstrates a marked increase in incidence of ICH in the ECMO COVID-19 population. The duration of ECMO support for Covid ARDS is longer and that might contribute to increased cumulative bleeding risk. Clinical judgement should be used with regards to anticoagulation management in these patients. This systematic review suffers from a significant lack of available robust analyses of larger populations. The available studies have no uniform definition of major bleeding, large variances in anticoagulation practices, and demonstrated no standardized protocols in place to report complications to a central database. This is no doubt in part due to the novelty of COVID-19 and the use of ECMO as a therapy for Covid ARDS. Further, this systematic review assesses patients from the initial waves of the pandemic. However, there is evidence that mortality in Covid ECMO populations has increased with following waves of the pandemic. To improve best practices and isolate populations at an increased risk of morbidity or mortality, it will become critical for institutions to create databases through which meaningful conclusions can be derived.

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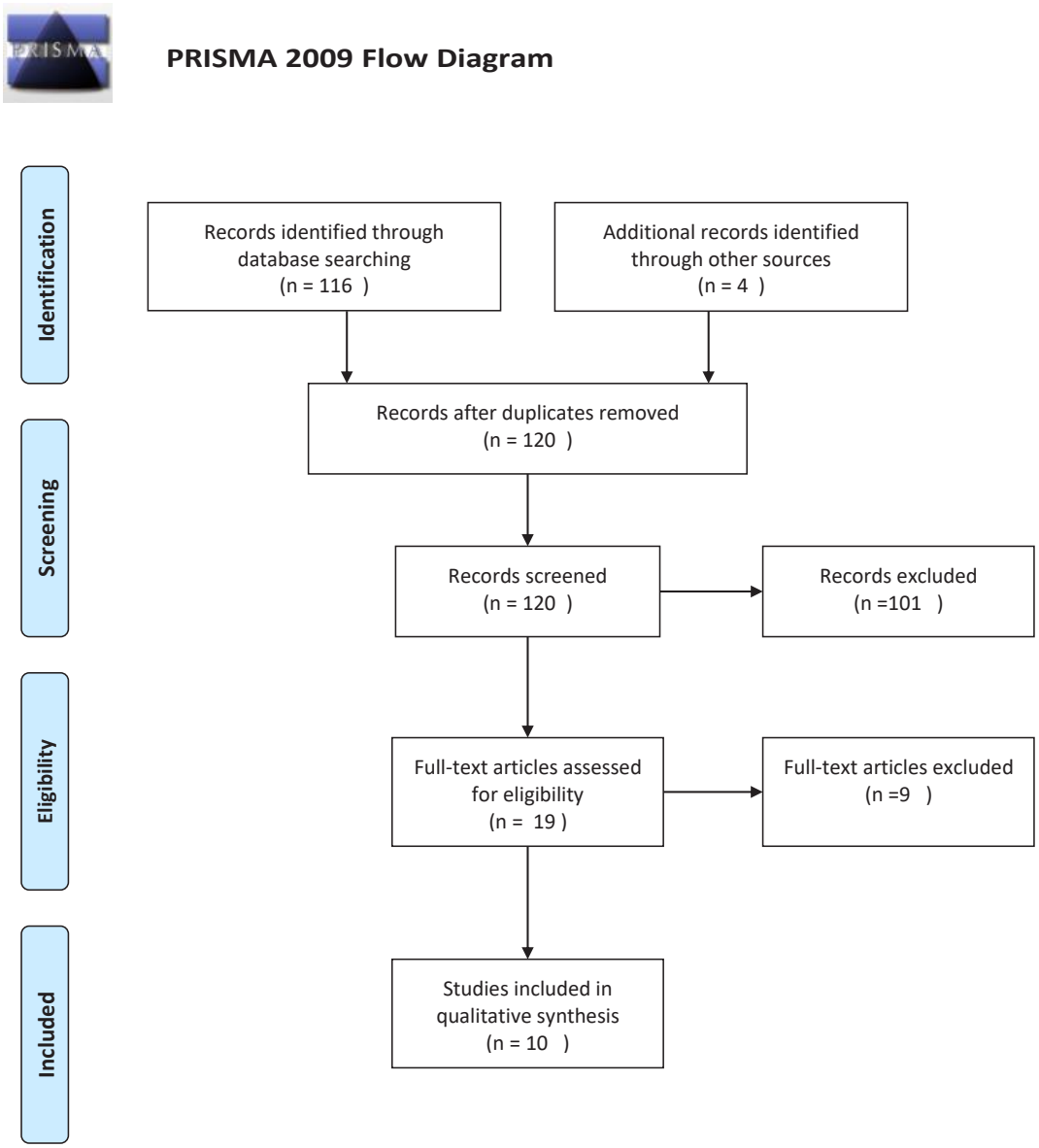
Lead Author	Study Description	Total Number of Covid ECMO Patients	Number of patients on VV ECMO with major bleeding	Type of bleed	Anticoagulation management	Coagulation at time of bleed	Age	Other associated findings	Summary findings
Notz et al [1]	Review of neurologic findings in 38 Covid ARDS patients admitted to ICU	15	Two patients had ICH.	ICH	Not specified	Not specified	Not specified	Not specified	Risk factors for bleeding unclear.
Parzy et al[2]	Review of thrombo-embolic events in 13 Covid patients on VV ECMO	13	Three (3)	Epistaxis (1) ICH (1) Gynecologic (1)	Unfractionated heparin with Anti Xa goal 0.3-0.6	Anti Xa 0.41 Anti Xa 0.39 Anti Xa 0.72	Not specified	Not specified	Precarious balance between clotting and bleeding risk. Risk factors for bleeding unclear

[1] Notz et al. Severe neurological complications in critically ill COVID-19 patients. Journal of Neurology (2021) 268:1576-1579.
[2] Parzy et al. Venous Thromboembolism Events Following Venovenous Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Syndrome Coronavirus 2 Based on CT Scans. Crit Care Med. 2020 Jun 30:10.1097/CCM0000000000004504

Fig. 1



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For more information, visit www.prisma-statement.org.

Fig. 2

CRITICAL CARE 56

Cardiovascular Phenotypes of 196 Perioperative Hypotensive Patients using the Echocardiographic Assessment using Subxiphoid onlY (EASY) Exam

Benjamin Hoenig[1], Michelle Burmistrova[1], David King[1], Rhagav Narravula[1], Ariana Adamski[2], Cheshta Prasad[1], Ashar Ata[2], Khrystyna Korostil[1], Tejas Kollu[1], Priya Uppal[1], Aliaksei Pustavoitau[3], Nibras Bughrara[2]

[1]Albany Medical Center, Albany, NY, [2]Albany Medical College, Albany, NY, [3]Johns Hopkins University, Baltimore, MD

INTRODUCTION: Focused Critical Care Echocardiography (FCCE) can aid in diagnosing undifferentiated shock.[1-4] Organization of cardiovascular presentation on ultrasound into clusters allows for rapid selection of hemodynamic support.[1-2] We implemented a standardized curriculum to use the Echocardiographic Assessment using Subxiphoid OnlY (EASY) exam to initially evaluate patients in shock in lieu of a more comprehensive FCCE exam. The EASY exam is based on pattern recognition of 7 proposed phenotypes grouped into 3 clusters based on similar management using a single subcostal four chamber view of the heart and IVC.1 Cluster 1 is normal to hyperdynamic ventricular function, cluster 2 is LV systolic dysfunction, and cluster 3 is isolated RV dysfunction. The goal of this study is to determine the prevalence of these phenotypes in patients with hypotension and to determine their outcome.

METHODS: We reviewed EASY exams performed by trained anesthesia residents on perioperative patients in the POCU, PACU, ICU, and OR from August 2017 to June 2021. 196 patients who received a consult due to diagnosis of arterial hypotension (MAP < 65) are included here for analysis.

RESULTS: In our cohort, 55% were male and mean age was 64. Prevalence for clusters 1-3 respectively, was 61%, 26%, and 12%. 2 patients had pericardial tamponade. For clusters 1-3, respectively: mean ICU LOS was 13.2 days, 13.8 days, and 9.5 days. ICU mortality was 19.3%, 20%, and 47.8%. The most common 2 interventions in each cluster 1-3 respectively, were: IV fluid boluses given 43 times to 119 patients and phenylephrine (49 (41.2%) patients); norepinephrine (26 (52%) patients) and phenylephrine (15 (30%) patients); norepinephrine (17 (74%) patients) and vasopressin (11 (47.8%) patients); Across all clusters, 69 patients had a diagnosis of sepsis. Across all clusters, the EASY exam duration was 4.7 minutes and interpretable images were obtained in 166 (84.6%) patients. Imaging changed patient management in 113 (57.6%) cases.

CONCLUSION: The EASY exam is a novel approach to evaluating hemodynamic status using a subcostal only view of the heart. Trained physicians obtained interpretable images and assigned a phenotype which guided patient management in most of our cohort. The EASY exam and 7 proposed phenotypes show potential for streamlining care for patients with complex pathology and warrants further investigation and multidisciplinary validation.

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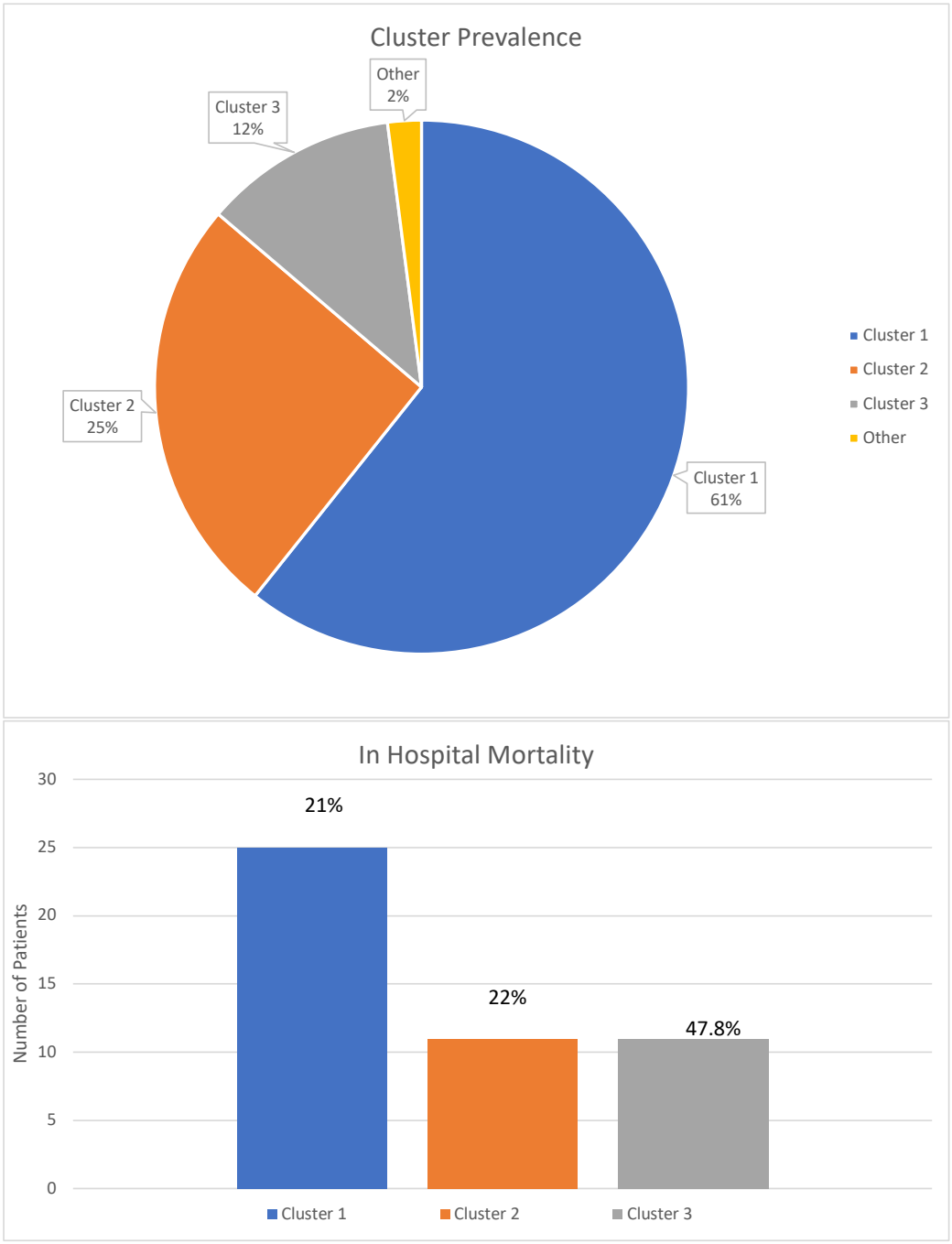

Fig. 1

CRITICAL CARE 57

Early Enteral Nutrition Improves Outcomes in Critically Ill Mechanically Ventilated Patients

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INTRODUCTION: Critically ill mechanically ventilated (MV) patients have variable metabolic needs which often increase and persist over time. Given this variability, the limits to resting energy expenditure estimation and the understanding that both under- and overfeeding can lead to adverse outcomes, there is disagreement on the optimal timing to start enteral nutrition (EN). Recent data suggests targeted early EN delivery may reduce mortality and improve outcomes. Therefore, we examined if early EN would result in improved clinical outcomes and reduced costs in critically ill patients on MV.

METHODS: Data from a nationwide administrative-financial database (Premier Inc., Charlotte, NC) between 2018 and 2020 was utilized to identify medical and surgical adult patients who started MV within 2 days after admission. Patients who died within 7 days after admission were excluded. Patients who received early EN (defined by charge codes for EN products or tube feeding within 3 days after intubation) were compared to patients who started EN after 3 days of intubation (late EN). Outcomes of interest included hospital mortality, hospital and intensive care unit (ICU) length of stay (LOS), MV days, and total cost. We performed inverse-probability-of-treatment weighting (IPTW) to control for confounding on observable characteristics. We modeled the outcomes using a multivariable logistic regression model for hospital mortality, linear regression model for cost, and Cox proportional hazard model with censored observation for MV days, hospital and ICU LOS.

RESULTS: In the overall study population, 27,887 adult patients with early MV were identified, of which, 16,772 (60.1%) received early EN. The mean age was comparable between the groups (60.1 ± 16.5 vs. 60.4 ± 16.1 years for early and late EN groups, respectively). Regression analyses after IPTW showed that the early EN group had lower hospital mortality (OR 0.77, 95% CI, 0.71 to 0.82), shorter MV days (HR 1.23, 95% CI, 1.11 to 1.37), shorter hospital LOS (HR 1.43, 95% CI, 1.33 to 1.54) and ICU LOS (HR 1.36, 95% CI, 1.27 to 1.46), and lower cost (-$21,226, 95% CI, -$23,605 to $-18,848) compared to the late EN group.

CONCLUSION: In real world practice, early EN within 2 days of MV initiation demonstrated improved clinical and economic outcomes. These data suggest that using early EN is associated with decreased mortality, hospital and ICU LOS, time on MV, and lower cost when compared to delayed initiation of EN; thus, highlighting the importance of early EN to optimize the outcomes of critically ill patients on MV.

Table. Univariable and multivariable results comparing early EN with late EN among patients with early mechanical ventilation

	Univariable analyses			Multivariable analyses	
	Late EN	Early EN	SMD	Yes (Reference = Late EN)	*P* value
				OR (95% CI)	
Hospital mortality, n (%)	3230 (19.2)	2584 (15.4)	-0.10	0.77 (0.71, 0.82)	<0.001
				HR (95% CI)	
LOS, days, mean (SD)	23.7 ± 33.5	18.3 ± 17.8	-0.30	1.43 (1.33, 1.54)	<0.001
ICU LOS, days, mean (SD)	13.5 ± 16.0	10.7 ± 10.3	-0.27	1.36 (1.27, 1.46)	<0.001
MV days, mean (SD)	11.8 ± 24.9	9.6 ± 10.2	-0.21	1.23 (1.11, 1.37)	<0.001
				Estimate (95% CI)	
Total cost, mean ± SD	$88216 ± 134984	$67644 ± 72873	-0.28	-21227 (-23605, -18848)	<0.001

Covariates included in the models were age group, male, race, payor category, VW score, elective admission, admission category, admission type (medical vs surgical), early vasopressor, early hemodialysis, bed size, teaching status, and location (rural or urban).
HR >1 means the hazard of discharge alive is shorter in early EN compared to late EN.
Abbreviations: EN, enteral nutrition; LOS, length of stay; ICU, intensive care unit; SD, standard deviation; SMD, standardized mean difference; OR, odds ratio; HR, hazard ratio

CRITICAL CARE 58

Accuracy of Right Lateral US-Window for Measurement of IVC Diameter for Discriminating between CVP Categories in Spontaneously Breathing Patients – an Observational Cohort Study Design

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INTRODUCTION: Both excessive[1] and inadequate[2] fluid administration to critically ill patients have been linked to worsened clinical outcomes. Ultrasonography of the inferior vena cava (IVC) is a commonly used bedside test to assess intravascular volume status. Past analyses have found that lower maximal IVC diameters, conventionally viewed from the subcostal window in the sagittal plane[3], are predictive of low CVPs with high sensitivity.[4] Unfortunately, many post-operative patients have anatomical changes (e.g. subxiphoid chest tubes, residual postoperative pneumoperitoneum) that limit standard IVC measurement. An alternative right lateral transhepatic ultrasonographic window has been described[5], and is useful in patients for whom the IVC cannot be measured via the subcostal window.[6] However, previous investigations have found that measurements from the right-lateral window do not correlate with those from the subcostal window.[7] The right lateral transhepatic window may allow measurement of the IVC that would be otherwise unattainable in certain post-operative cardiac surgery patients. No investigations to date have correlated IVC dimensions via this approach with invasive hemodynamic measurement of CVP. This study investigates the use of the right lateral ultrasonographic window to accurately discriminate between low, medium, and high CVP categories among spontaneously breathing patients.

METHODS: This is a prospective, observational cohort study of patients in the Cardiac Surgery ICU at a single academic medical center. All enrolled patients are not intubated and have an in-situ CVC which is actively transducing the CVP. Using bedside real-time three-dimensional echocardiography with live xPlane ultrasound imaging, maximum antero-posterior IVC diameter [D-IVC(AP)], antero-posterior IVC collapsibility [C-IVC(AP)], medio-lateral IVC diameter [D-IVC(ML)], and medio-lateral IVC collapsibility [C-IVC(ML)] are measured from right lateral, transhepatic ultrasonographic window. Following these measurements, patients are then stratified into 3 groups on enrollment based on their transduced CVP: (1) Low (CVP<5mmHg), (2) Medium (CVP between 5-10mmHg), and (3) High (CVP>10 mmHg). The sensitivity, specificity, positive predictive value, and negative predictive value (with 95% confidence intervals) of right lateral D-IVC(AP), C-IVC(AP), D-IVC(ML), and C-IVC(ML) for discriminating between low, medium, and high CVP - as contemporaneously transduced by central venous catheter - will be calculated. Agreement between the anteroposterior and mediolateral measurements in estimating CVP will be assessed using kappa correlation. The threshold values of right lateral D-IVC(ML) and C-IVC(ML) that provide the highest accuracy for discriminating between CVP categories will also be estimated using receiver operating characteristic (ROC) curve analysis. Our power analysis indicates that enrollment of at least 46 patients will allow for an estimate of the sensitivity with a 95% confidence interval half-width of +/- 0.15.

RESULTS: This abstract presents for discussion our study design and validation strategy for a novel approach to stratify patient's volume status using transhepatic US exams. The preliminary data is pending. We are expected to have the full preliminary data prepared and analyzed at time of presentation.

CONCLUSION: Test characteristics of sensitivity, specificity, positive predictive value, and negative predictive value for right lateral ultrasonographic IVC measurement of maximal diameter and collapsibility for discrimination between low, medium, and high CVPs will be reported. The threshold values of right lateral D-IVC(ML) and C-IVC(ML) providing the highest accuracy for discriminating between CVP categories will also be reported. *Please note that the first two listed authors (Dr. Oliveira and Dr. Cole) share first authorship of this abstract.

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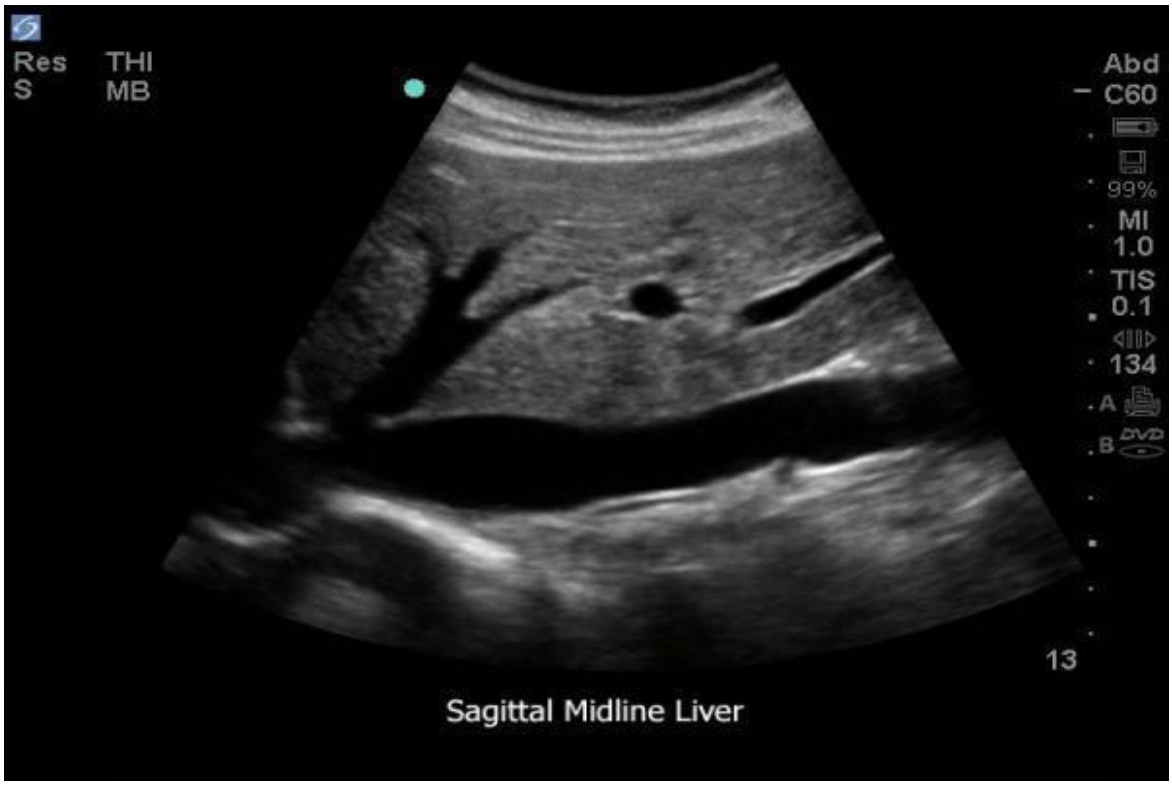

Fig. 1

CRITICAL CARE 59

Do Race and Gender Affect the Outcomes of Rapid Response Team's Evaluation in Critically Ill Patients?

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INTRODUCTION: Racial disparities have been demonstrated in in-hospital cardiac arrest outcomes.[1-2] Rapid Response Teams (RRTs) are commonly utilized by hospitals to address a deterioration in a patient's condition prior to progression to cardiac or respiratory arrest. However, little is known regarding possible outcome disparities for cases requiring the use of RRT resources. This study aimed to identify if disparities related to race or gender existed in outcomes for cases where our hospital's RRT alert was activated.

METHODS: A retrospective chart review of 344 patients that needed RRT called for an escalation of care was done between January 2021 and March 2021 was done. 310 patients with complete data of their race, gender, interpreter status, and outcomes of RRT were included. 34 patients with missing information about race, gender, language interpreter status and outcomes of RRT. In addition, patients whose primary reason for RRT was cardiopulmonary arrest were excluded. All patients were grouped based on their declaration of race or gender or need for interpreter upon admission to the hospital. 4 racial groups including Asian, Black, Other and White and binary gender were included. The percentage of upgrades to intensive care units (cardiac, cardiothoracic, medical, neurosurgical, or surgical) were calculated for each race and gender. The rates of mortality for all patients were calculated for each race and gender. Mortality was defined as death within 10 days of RRT.

RESULTS: Of all patients who had RRT, there was a difference in the percentage of mortality based on race ($p = 0.006$). With patients who needed an interpreter, there was a significant difference for RRT escalation based on race (0.006) and gender ($p = 0.002$). The percentage of upgrades to the intensive care units was different for each race ($p = 0.014$) in patients that needed an interpreter.

CONCLUSION: Our initial analyses suggest that there are differences in outcomes of RRT including upgrades to ICU and mortality in patients of different races and gender. Further analyses are needed to understand the causes of these differences and aim to eliminate them.

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CRITICAL CARE 60

Soluble Siglec-9 as a Biomarker for Acute Lung Injury

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INTRODUCTION: Acute respiratory distress syndrome (ARDS), a potentially fatal form of respiratory failure, accounts for 10% of ICU admissions and 30% of ICU mortality[1]. It is often under-recognized and undertreated, as it is a diagnosis of exclusion and lacks a definitive diagnostic test, as few biomarkers correlate with acute lung injury development. Neutrophil activation is a critical early step in the pathogenesis of ARDS. Siglec-9, an immune receptor found on the surface of neutrophils, binds sialic acid containing glycans and suppresses the immune response. Soluble Siglec-9 (sSiglec-9), the extracellular region of membrane bound Siglec-9, shows pro-inflammatory activity, likely via competitive inhibition of Siglec-9, and has been found in higher levels in patients with COPD related lung injury[2]. It can therefore function as a potential biomarker for acute lung injury (ALI) and progression to ARDS. The purpose of this study was to determine how well sSiglec-9 levels correlate with disease progression and severity in ARDS. To that end, we analyzed plasma sSiglec-9 levels in samples from participants in the Lung Injury Prevention Study with Aspirin (LIPS-A) Trial, a randomized controlled trial of aspirin to prevent ARDS in patients at high risk[3].

METHODS: We obtained plasma samples from LIPS-A study participants and retrospectively analyzed them to determine sSiglec-9 levels. A single operator blinded to clinical information performed sSiglec-9 assays using the Dynex DS2 fully automated ELISA system. The LIPS-A study secondary outcomes included development of ALI or death within 7 days, in hospital mortality, in hospital mortality to 60 days, and ventilator requirement at any time during the hospitalization.

RESULTS: A total of 255 patients were included in the study, with 31 patients having ALI. A higher proportion of patients without ALI were white (165/224 (73.66%) vs 15/31 (48.39%), p=0.004) and had never smoked or were former smokers. The two groups did not otherwise differ in demographics or ARDS risk factors.

Median (interquartile range) sSiglec-9 levels were higher in the ALI group (0.47 (0.15, 1.25) vs 0.21 (0.10, 0.45), p=0.005). Soluble Siglec-9 levels were significantly associated with in hospital mortality (p=0.0004), in hospital mortality to 60 days (p=0.0004), ALI or death within 7 days (p=0.002), and ventilator requirement at any time during disease course (p<0.0001).

CONCLUSION: Serum levels of sSiglec-9 are higher in patients who develop lung injury and are associated with mortality and ventilator requirement.

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Table 1. Demographics and Baseline Characteristics

	No ALI *N = 224*	**ALI** *N = 31*	**P-Value**
Age, *years*	56 (46, 68)	57 (47, 66)	0.83
Male Sex	122 (54.46)	16 (51.61)	0.77
White Race	165 (73.66)	15 (48.39)	0.004
Hispanic or Latino Ethnicity	19 (8.48)	7 (22.58)	0.07
Body Mass Index	27.98 (23.12, 34.09)	25.26 (21.27, 32.05)	0.25
Diabetes	40 (17.86)	7 (22.58)	0.53
History of Alcohol Abuse	38 (16.96)	5 (16.13)	0.91
Tobacco Use			0.02
Never	71 (31.70)	15 (48.39)	
Current	44 (19.64)	10 (32.26)	
Former	77 (34.38)	4 (12.90)	
Unknown	32 (14.29)	2 (6.45)	
ARDS Risk Factor			
Non-cardiogenic Shock	56 (25.00)	3 (9.68)	0.06
Suspected or Witnessed Aspiration	32 (14.29)	5 (16.13)	0.79
Sepsis	178 (79.46)	23 (74.19)	0.50
Pneumonia	138 (61.61)	21 (67.74)	0.51
Lung Contusion	7 (3.13)	3 (9.68)	0.11
Multiple Fractures	6 (2.68)	0 (0)	1.00
Smoke Inhalation	2 (0.89)	0 (0)	1.00
High Risk or Emergent Surgery	7 (5.00)	1 (4.55)	1.00
Ventilated on Day of Randomization	25 (11.16)	18 (58.06)	<0.0001
Ventilated Prior to First Dose of Study Drug	25 (11.36)	18 (60.00)	<0.0001
Lung Injury Prediction Score	5.5 (5.0, 7.0)	6.5 (5.0, 8.5)	0.02
sSiglec-9	0.21 (0.10, 0.45)	0.47 (0.15, 1.25)	0.005
Outcomes			
In Hospital Mortality	11 (4.91)	5 (16.13)	0.03
In Hospital Mortality to 60 Days	9 (4.02)	5 (16.13)	0.02
Vented at Any Time	32 (14.29)	29 (93.55)	<0.0001

Data is presented as n (%) or median (quartile 1, quartile 3);

Table 2. Secondary Outcomes and sSiglec 9

	Log sSiglec 9	
	Odds Ratio *(95% Confidence Interval)*	P-Value
Outcome		
Development of ALI	1.34 (1.09, 1.64)	0.005
In Hospital Mortality	1.64 (1.25, 2.16)	0.0004
In Hospital Mortality to 60 Days	1.68 (1.26, 2.25)	0.0004
ALI or Death Within 7 Days	1.36 (1.12, 1.65)	0.002
Vented at Any Time	1.52 (1.28, 1.82)	<0.0001

Data is presented with the odds ratio for every one *pg/ml point increase in the natural log of Siglec 9. Each outcome is evaluated in a separate model.*

CRITICAL CARE 61

The association of red cell distribution width with new onset atrial fibrillation in surgical intensive care unit patients

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INTRODUCTION: New onset atrial fibrillation (NOAF) is common in the intensive care unit (ICU).[1] Systemic inflammation is thought to play a major role in its pathogenesis.[2] Red cell distribution width (RDW), a recognized biomarker for acute inflammation,[3,4] has been shown to be associated with NOAF in patients with sepsis.[5] However, the relationship between RDW and NOAF has not been well explored in more general ICU populations. Therefore, our goal was to investigate whether admission RDW is associated with NOAF in surgical ICU patients.

METHODS: We performed a retrospective analysis of data from a registry of patients admitted at a single teaching hospital between 01/01/2015 and 06/20/2016. Only post-surgical patients, with RDW assessed within 2 hours of ICU admission, were included in the analyses. NOAF was defined as persistent atrial fibrillation requiring intervention within 72 hours of ICU admission. A locally weighted scatterplot smoothing (LOWESS) curve was generated to graphically represent the relationship between admission RDW and risk of NOAF. Multivariable logistic regression analyses were performed to investigate the association between RDW and NOAF, controlling for age, body mass index, type of surgical patient (general, thoracic, vascular, neurosurgical, and emergency), as well as Acute Physiology and Chronic Health Evaluation II score.

RESULTS: 500 patients comprised the analytic cohort and the incidence of NOAF was 7% (n=36) (Table 1). LOWESS curve analysis demonstrated a rapidly decreasing risk of NOAF between RDW of 11% and 15%, after which, the risk of NOAF decreased more gradually until plateauing around RDW values of 25% (Figure 1). Multivariable regression analysis demonstrated that each unit increment in RDW was associated with approximately 30% reduction in risk of NOAF (OR 0.69; 95%CI 0.52-0.92, p=0.008). When the regression analysis was repeated with RDW as a dichotomized variable, patients with RDW <15% were almost 70% less likely to develop NOAF (OR 0.29; 95%CI 0.11-0.77, p=0.01) compared to patients with RDW >15%. In both models, thoracic surgery patients were at least 3 times more likely to develop NOAF compared to general surgery patients (OR 3.08; 95%CI 1.15-8.24, p=0.03).

CONCLUSION: Our results suggest an inverse relationship between admission RDW and NOAF in surgical ICU patients. We hypothesize that dramatic elevations in RDW immediately after surgery represent an appropriate inflammatory response to physiological stress, which generally subsides within 24-48 hours. We further hypothesize that 'normal' RDW upon ICU admission may represent altered immune responses, where the pro-inflammatory phase may not only peak in a delayed fashion, but also may persist for longer durations, thereby increasing the risk of NOAF. Further studies are needed to validate our findings, build upon our hypotheses, and to determine whether admission RDW may improve risk stratification in surgical ICU patients.

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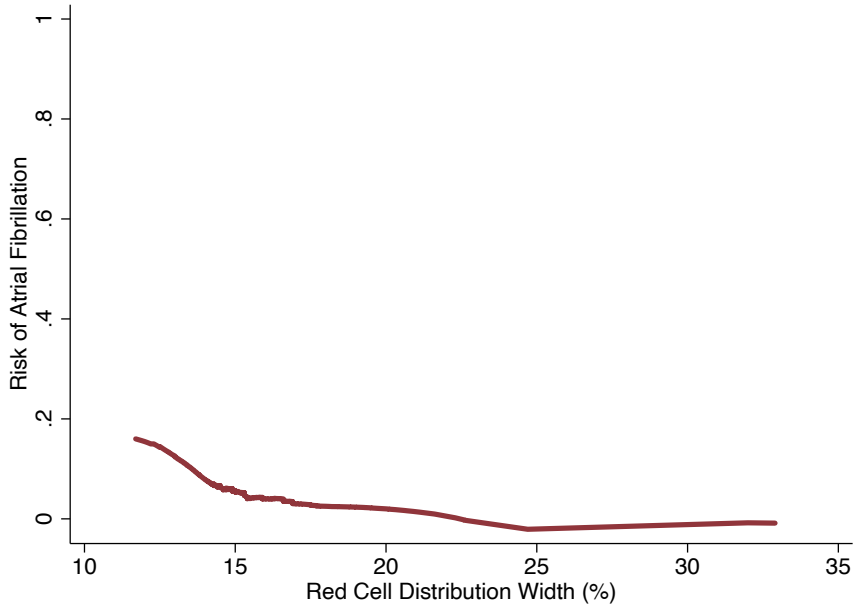

Fig. 1

Table 1. Characteristics of the study cohort (n=500)

	No NOAF (n = 464)	**NOAF (n = 36)**	**P-value**
Age (years)	66 ± 16	65 ± 16	0.72
Sex (%)			0.89
Female	43	42	
Male	57	58	
Race (%)			0.62
Non-white	10	8	
White	90	92	
BMI (kg/m^2)	28 ± 7	31 ± 8	**0.03**
RDW (%)	15 ± 3	14 ± 2	**0.007**
APACHE II	15 ± 8	26 ± 9	**<0.001**
CCI	4 ± 3	4 ± 3	**-**
Type of patient (%)			**<0.001**
General	34	19	
Thoracic	19	39	
Vascular	16	28	
Neurosurgical	7	3	
Emergency	24	11	

Data are shown as mean ± standard deviation or proportions and compared using t-tests and chi-square tests, respectively. Statistically significant p-values are shown in bold. (-) denotes no statistical difference. NOAF = New Onset Atrial Fibrillation; BMI = body mass index; 25OHD = 25-hydroxyvitamin D; APACHE II = Acute Physiology and Chronic Health Evaluation. CCI = Charlson Comorbidity Index.

CRITICAL CARE 62

VV ECMO for COVID-19 ARDS: Better never than late?

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INTRODUCTION: Coronavirus disease 2019 (COVID-19) continues to be associated with high mortality rates of 50-90% in patients requiring endotracheal intubation[1]. In eligible patients with severe COVID-19 respiratory failure, a 3-fold improvement in survival has been noted with VV-ECMO (veno-venous extracorporeal membrane oxygenation) compared to maximum ventilation alone[2]. Studies have noted that late ECMO therapy (beyond the seventh day of mechanical ventilation (MV)) seems futile[3]. It is unclear if similar poor outcomes are observed with prolonged duration of other high-level oxygen support such as high-flow nasal cannula (HFNC) or non-invasive positive pressure ventilation (NIPPV). Given the paucity of existing data, we studied our institutional experience with the use of VV-ECMO for COVID-19 and the impact of various patient and timeline factors on its outcomes.

METHODS: A retrospective review of prospectively collected data was conducted in patients with severe COVID-19 acute respiratory distress syndrome (ARDS) admitted to the ICU that received VV ECMO support from May 2020 to September 2021. Patient charts were reviewed for demographic data, comorbidities, clinical course and timelines, and outcomes. Data from our center inputted into the ECMOCARD study database (Critical Care Consortium, Australia) was reviewed for this study with permission from the Critical Care Consortium.

RESULTS: Out of 13 patients (age 43.5 ± 8.8 years, BMI 33.5 ± 10.9 5 kg/m2, APACHE II score 10.1 ± 5.5 and RESP score 3.7 ± 1.3) placed on VV-ECMO for COVID-19 at our institution, 8 patients (61.5%) were decannulated successfully while 5 patients (38.5%) died. Comparative analysis between the two groups highlighted that while both survivors and non-survivors had similar mean duration of MV prior to ECMO (2.6 days and 3.0 days, p = 0.6), there was a significant difference observed in their total duration of illness - survivors had a significantly shorter mean duration from symptom onset to ECMO cannulation (9.5 days vs. 15 days, p = 0.01; Figure 1). Survivors were also noticed to have a shorter duration of receiving some form of high-level oxygen supplementation (HFNC, NIPPV or MV) compared to the non-survivor group (4.8 days vs. 8.2 days, p = 0.03; Figure 2).

CONCLUSION: While our ability to draw conclusions is limited by the small number of patients, our results suggest that the timing of cannulation from the patient-reported onset of COVID-19 symptoms, i.e., the duration of clinical illness, and the duration spent on high-level oxygen supplementation via high-flow nasal cannula, non-invasive or invasive mechanical ventilation prior to ECMO cannulation may influence the patient's outcome on VV-ECMO.

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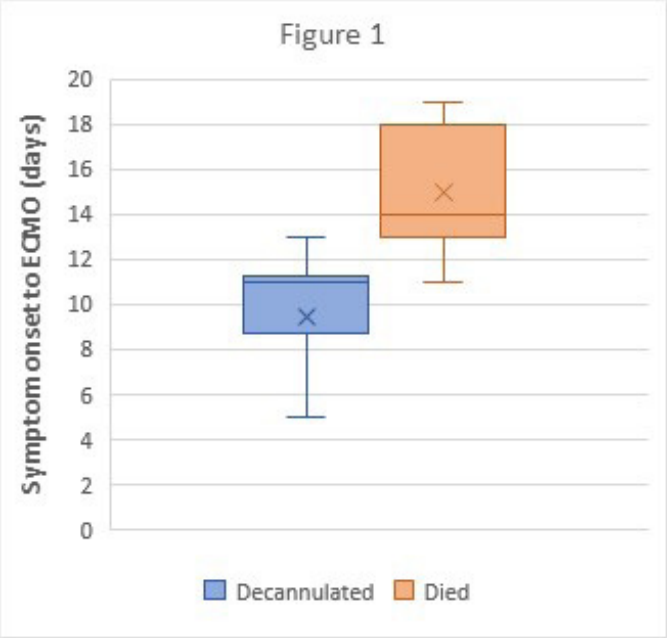

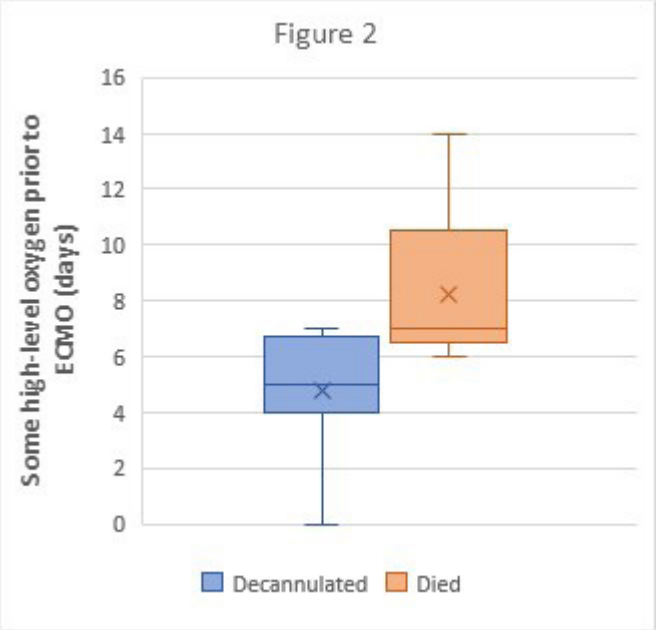

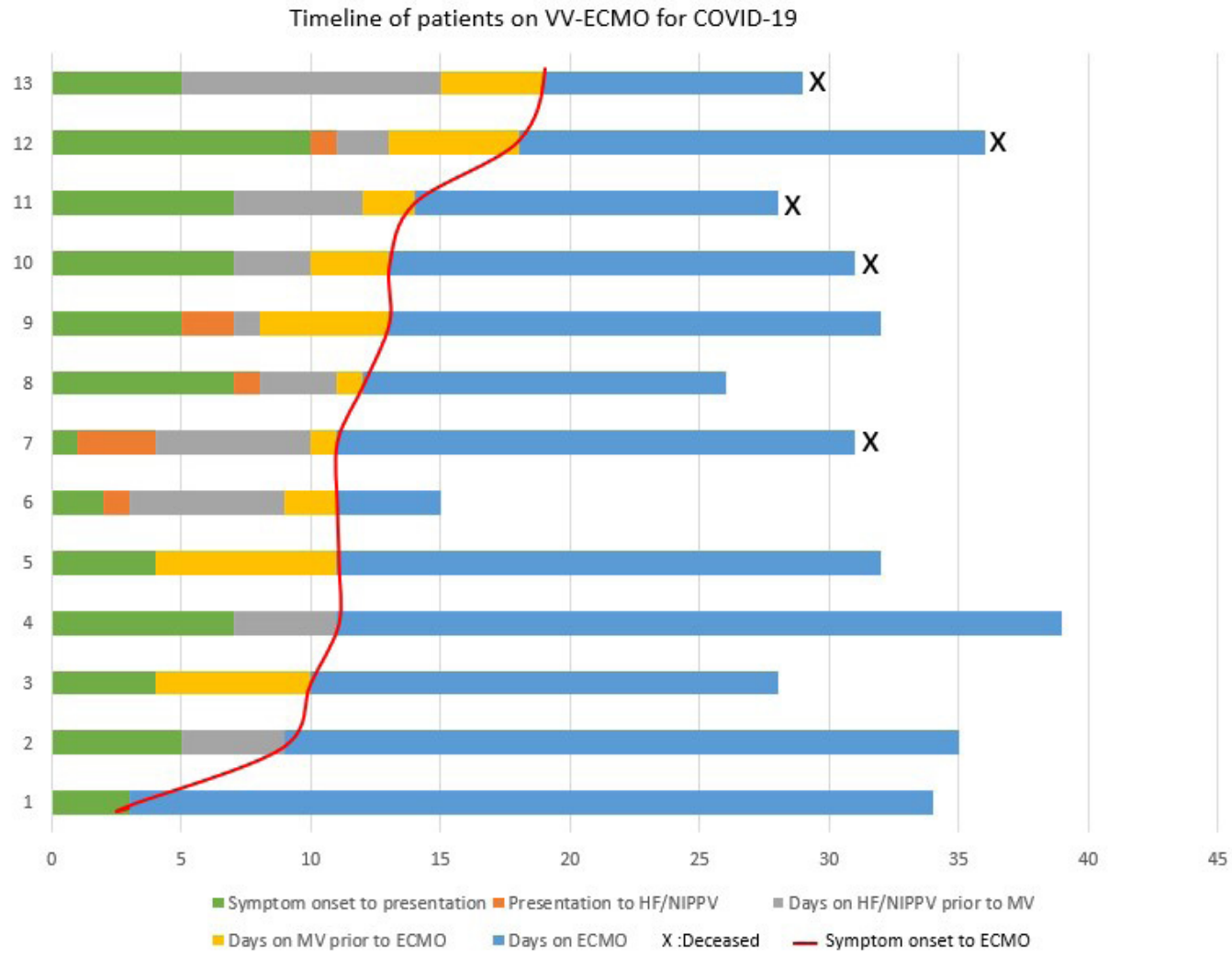

CRITICAL CARE 63

Improving Family Communication in the Intensive Care Unit: A Quality Improvement Initiative

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INTRODUCTION: The importance of active engagement of family members in the care of patients in the intensive care unit has been well established, and has been shown to have long-term benefits for both patients and their families[1,2]. Family members of critically ill patients often report dissatisfaction with the perceived lack of communication about their loved one, inconsistencies in information being provided, and feelings of being overwhelmed with technical information[3]. The more restrictive visitor policies put in place as a result of the COVID-19 pandemic have brought to light many of the challenges ICU providers face in effectively communicating with family members of critically ill patients. Because communication more frequently occurs between one family member and one provider via phone or video conference, it has become more difficult to have an open exchange of information and allow families the opportunity to be actively involved in patient care and decision making[4,5]. Additionally, due to a lack of standardized workflow for documenting family updates in the context of the dynamic nature of the ICU team, it has become more difficult for providers to know who was spoken with, what information was discussed, and if there were and issues requiring follow up. Recognizing this, our quality improvement initiative aims to (1) implement a standardized method for documenting daily discussions with family within the workflow of ICU providers, and (2) gather information regarding information being discussed and the frequency at which topics, such as goals of care and code status, are being addressed.

METHODS: We chose to implement a standardized 'dot phrase' tool that could be incorporated into the daily progress note in the electronic medical record (Epic) to document the most recent family update. In order to introduce and reinforce use of the tool, we sent weekly reminders via email to attendings, residents, and advanced practice providers with instructions on how to use the tool, and encouraged inclusion of the most recent family update as part of presentation on daily bedside rounds. Baseline data regarding frequency of documentation of family updates was collected for the month of September 2021, and the initiative formally launched October 2021. During the initial phase, we chose to focus on patients for whom the ICU was the primary provider team in our medical-surgical ICUs, with a goal of increasing frequency of documented daily updates to 70% of this patient group. Data collected included whether an update had occurred on a given day, who was updated, modality, and topics addressed.

RESULTS: In the first month after implementation, documentation of family updates improved from 1.1% (3/266) to 68% (163/239). Our preliminary analysis suggests that updates are provided more consistently early in the week (Monday through Wednesday), with frequency declining later in the week, and lowest on weekend days (Saturday and Sunday). Data collection is ongoing with respect to topics discussed and frequency at which goals of care and code status are readdressed.

CONCLUSION: Our goal in implementation of the family update tool is to provide a framework to improve the care of critically ill patients by better supporting family members and improving communication between members of the ICU team. Our success thus far indicates that by standardizing workflow and ease of documentation, we can improve consistency in not only frequency, but quality of information provided to families of critically ill patients. Future directions include further analysis of the types of information being discussed, expansion of the tool to eventually include all patients in all ICUs, and modification of both teaching and the tool to encourage readdressing specific topics at more regular intervals. We also hope to use this tool as part of ongoing institutional efforts to quantitatively and qualitatively assess compliance with the SCCM ICU liberation bundle.

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CRITICAL CARE 64

Assessing race and ethnicity in clinical outcomes of patients with COVID-19 admitted to the ICU at a single academic center

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INTRODUCTION: Previous studies investigating the relationship between race and ethnicity and clinical outcomes in coronavirus disease 2019 (COVID-19) patients have resulted in conflicting findings [1-5]. Despite the advantage of analyzing data from large patient cohorts, risk adjustment for important covariates related to geography and practice patterns may not have been possible when using aggregate data from large registries. Furthermore, the majority of studies only compared White, Hispanic/Latino, and Black patients, and did not consider other racial groups (e.g., Asian patients). Therefore, our goal was to investigate whether race/ethnicity is associated with length of stay (LOS), discharge destination, and in-hospital mortality in COVID-19 patients admitted to the intensive care units (ICUs) of a single, teaching hospital that serves a racially and ethnically diverse patient population.

METHODS: We performed a retrospective analysis of data from COVID-19 patients admitted to the ICUs at Tufts Medical Center between 03/01/2020 and 08/31/2020. Only patients with confirmed SARS-CoV-2 infection by positive result on polymerase chain reaction testing of a nasopharyngeal sample were included in the analysis. Self-reported race/ethnicity was categorized as White, Black, Hispanic/Latino, or Asian. To investigate the association of race/ethnicity with ICU LOS we performed a Cox regression analysis controlling for sex, body mass index (BMI), medical insurance status (private vs public vs uninsured), Acute Physiologic and Chronic Health Evaluation (APACHE) II score, and admission high-sensitivity C-reactive protein (hs-CRP) level. To investigate the association of race with discharge destination (non-home vs home) and mortality, we performed logistic regression analyses, adjusting for sex, BMI, insurance status, APACHE II score, and ICU LOS.

RESULTS: A total of 567 patients who met inclusion criteria were initially identified. 200 White, 100 Black, 100 Hispanic/Latino, and 100 Asian patients were randomly selected from each racial/ethnic group to comprise the final analytic cohort (n=500). Mean APACHE II score and median admission hs-CRP level were 17+8 and 79 (IQR 22-157) mg/dL, respectively. 40% of patients did not return to their homes at hospital discharge and overall, in-hospital mortality in the cohort was 12%. Cox regression analysis demonstrated that there was no difference between White, Black, and Asian patients regarding ICU LOS. However, compared to White patients, Hispanic/Latino patients were more likely to have a prolonged ICU LOS (HR 1.37; 95%CI 1.04-1.80, p=0.03). Additionally, BMI (HR 0.96; 95%CI 0.80-0.99, p=0.02) and admission hs-CRP (HR 0.99; 95%CI 0.98-0.99, p<0.001) were inversely related to the risk of prolonged ICU LOS. Logistic regression analysis demonstrated that there was no relationship between race/ethnicity and discharge destination. However, APACHE II score (OR 1.04; 95%CI 1.03-1.06, p<0.001) and medical insurance status (OR 1.94; 95%CI 1.29-2.94, p=0.002) were independently associated with the risk of non-home discharge. Logistic regression analysis also demonstrated that there was no difference in mortality risk between White, Black, and Hispanic/Latino patients. However, Asian patients had almost 60% lower likelihood of mortality compared to White patients (OR 0.42; 95%CI 0.16-0.90, p=0.03). Male sex (OR 2.34; 95%CI 1.25-4.35, p=0.007), APACHE II score (OR 1.06; 95%CI 1.04-1.08, p<0.001), and insurance status (OR 3.13; 95%CI 1.67-5.78, p<0.001) were independently associated with in-hospital mortality.

CONCLUSION: Our results suggest that race may have a modest influence on important clinical outcomes in COVID-19 patients admitted to the ICU. Moreover, we confirm previous findings that factors such as severity of illness and medical insurance status, which likely reflect underlying socioeconomic differences between patients, may have a greater influence on clinical outcomes in severely ill COVID-19 patients [6-7]. Further studies are needed to determine whether addressing socioeconomic inequities such as access to routine medical care, food insecurity, and health literacy, biological reasons can explain these observed differences and to determine whether these risk factors can be modified to improve outcomes in critically ill COVID-19 patients.

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CRITICAL CARE 65

Deep sedation during mechanical ventilation is associated with increased mortality in critically ill patients: A retrospective multicenter cohort study

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INTRODUCTION: Mechanical ventilation is an essential, life-saving therapy for patients with critical illness and respiratory failure. Studies have estimated that more than 300,000 patients receive mechanical ventilation in the United States each year[1]- 85% of whom receive sedatives[1-2]. Despite recommnedations on avoiding deep sedation, only half the patients are lightly sedated in the first 48 h after intensive care unit admission[3]. In this study, we hypothesized that a prolonged duration deep sedation during mechanical ventilation is associated with higher risks of 30-day mortality in critically ill patients.

METHODS: 11,354 adult, mechanically ventilated intensive care unit (ICU) patients across nine medical and surgical ICUs between 2008 and 2019 at Beth Israel Deaconess Medical Center (BIDMC, Boston, MA) were considered for inclusion in this study (Figure 1). The primary exposure variable was the duration of deep sedation defined as a proportion during mechanical ventilation, calculated by dividing the days of deep sedation by the total duration of mechanical ventilation (4). The level of consciousness was routinely recorded at least every 4 hours using the Richmond Agitation Sedation Scale (RASS). A day of deep sedation was defined as a mean RASS of ,àí3 to ,àí5 (4). The proportion of deep sedation was dichotomized into a low and high proportion using the median in the study population (45.5%). The primary endpoint was 30-day mortality and in a secondary analysis, we assessed the association on hospital length of stay. To assess the primary association between the proportion of deep sedation and 30-day mortality, multivariable logistic regression analysis adjusted for a priori defined patient demographics comorbidities, disease severity, ICU-related factors based on available literature and clinical plausibility were applied. Length of hospital stay before admission to the ICU, number of sedation days, ICU length of stay, number of intubation days, use of extracorporeal circulation, and admission type where also added to the confounding model. Negative binomial regression adjusted for the aforementioned confounding factors was used to assess the association between the proportion of deep sedation and hospital length of stay. To further examine the effects of sedation depth on 30-day mortality and hospital length of stay, we performed time-to-event analyses stratified by the proportion of deep sedation.

RESULTS: On average, patients were deeply sedated for one-third of their mechanical ventilation period (28.3 ± 32.0%). The average number of daily RASS assessments was 4.6 ± 1.8 (mean ± SD) per patient. 33.3% (n=1686) and 15.1% (n=821) of patients with a high versus low proportion of deep sedation during the mechanical ventilation period died within 30-days after ICU admission. In adjusted analysis, the risk of 30-mortality was 3.1 times higher in patients who received a high proportion of deep sedation compared to patients who received a low proportion of deep sedation during mechanical ventilation (adjusted odds ratio [ORadj] 3.1; 95%CI 2.8–3.5; p<0.001). Patients who received a high proportion of deep sedation during their mechanical ventilation period were more likely to stay longer in hospital compared to those who received a low proportion of deep sedation (adjusted absolute difference 1.15 days; 95%CI 0.78 to 1.52; p<0.001). In a time-to-event analysis, we demonstrated an increased probability of 30-day mortality and increased hospital stay with increased depth of sedation (Figure 2).

CONCLUSION: Deep sedation during mechanical is associated with increased risk of 30-day mortality and a prolonged hospital length of stay, even when controlled for number of days with sedation. Our data emphasize the importance of a strong focus on light sedation in the ICU. Clinicians should titrate the effects of sedatives appropriately and assess the sedation level frequently to ensure that deeper sedation is avoided in mechanically ventilated patients.

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Table 1. Basic characteristics of the study population

Characteristic	Low-Percentage of Deep sedation (n=5445)	High-Percentage of Deep sedation (n=5056)
Age, years mean (SD)	63.46(16.0)	62.64 (16.1)
Sex, female (%)	2472 (45.4%)	2016 (39.9%)
Body mass index (BMI), kg/m^2	29.09 (8.09)	29.09 (7.29)
APPACHE Score(Median, IQR)	21(17,25)	24(19,28)
CCI(Median, IQR)	1(0,4)	1(0,4)
Ward		
Medical	2149(39.5%)	1897(37.5%)
Surgical	308(5.7%)	443(8.8%)
Trauma	1032(19.0%)	499(9.9%)
Neuro ICU	427(7.8%)	536(10.6%)
CVICU	843(15.5%)	970(19.2%)
CCU	686(12.6%)	711(14.1%)
Source of admission		
Operating Room (%)	1229(22.5 %)	1369(27.1%)
Emergency Department	2159(39.6%)	1860(36.8%)
Floor (%)	610(11.2%)	456(9.0%)
Other Hospital/Facilities	1447(26.5%)	1371(27.1%)
Past Medical History		
Myocardial Infarction	1050(19.3%)	1281(25.3%)
Congestive heart failure	1976(36.3%)	1696(33.5%)
Hypertension	3045(55.9%)	2682(53.0%)
Atrial fibrillation	1225 (22.5%)	1117(22.1%)
COPD	2135 (39.2%)	1506(29.8%)
Diabetes Mellitus	1846(33.9%)	1588(31.4%)
Liver Disease	339(6.2%)	382(7.6%)
Renal Disease	959(17.6%)	834(16.5%)
Cancer	854 (15.7%)	644(12.7%)
Drug Abuse	376(6.9%)	388(7.7%)
Smoking	1442(26.5%)	1420(28.1%)
Alcohol Abuse	729 (13.4%)	760(15%)
Stroke	397(7.3%)	586(11.6%)
Anxiety	388(7.1%)	243(4.8%)
Depression	1225(22.5%)	930(18.4%)
Preadmission Medications		
Benzodiazepines	121(2.2%)	77(1.5%)
Antipsychotics	154(2.8%)	94(1.9%)
Opioids	310(5.7%)	223(4.4%)
Steroids	109(2.0%)	64(1.3%)
Extracorporeal Circulation	310(5.7%)	689(13.6%)

Figures:

Figure 1. Study flow diagram

ASA, American Society of Anesthesiologists

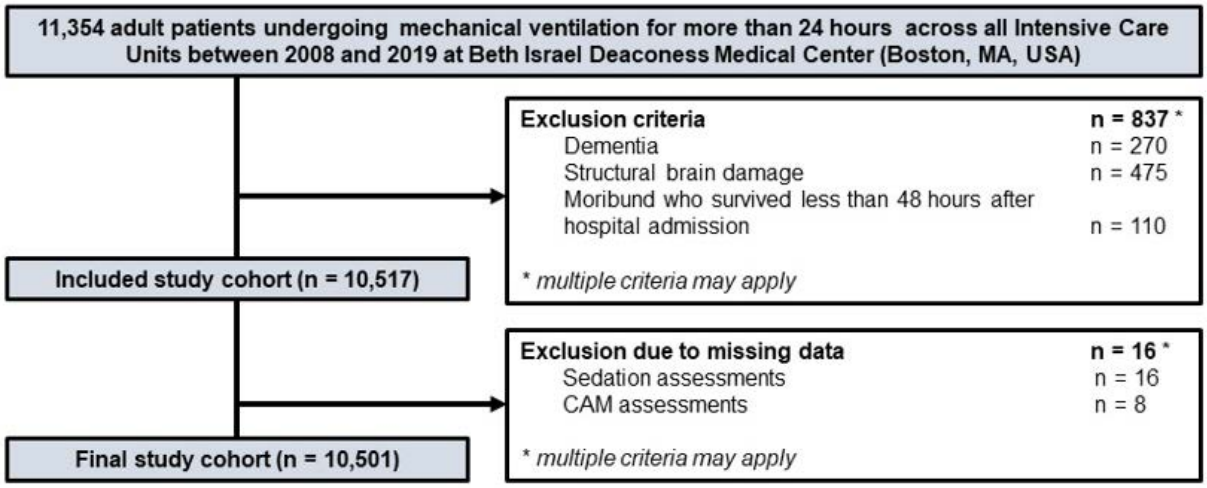
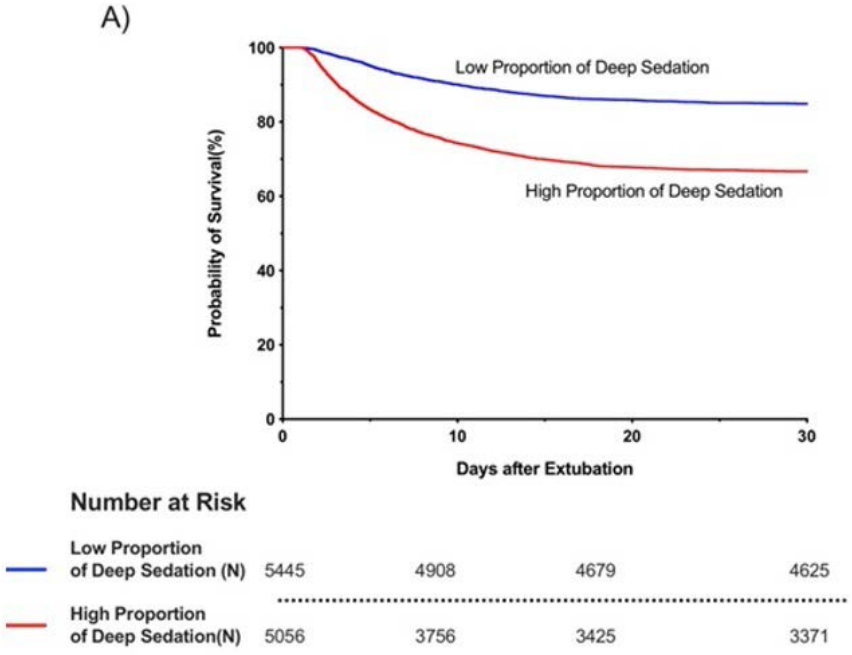


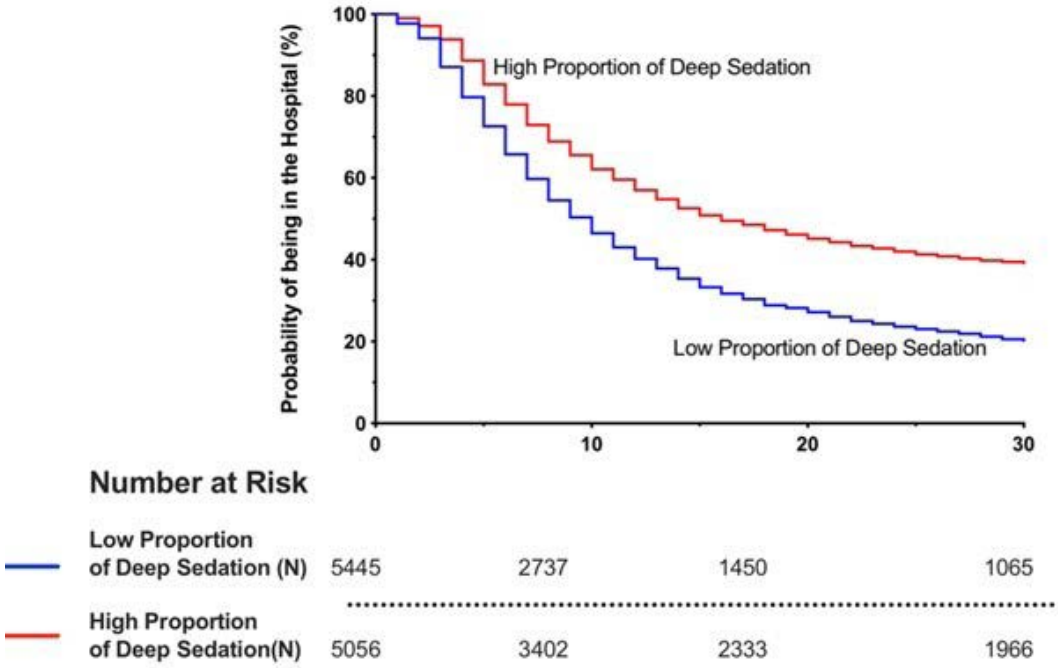
Figure2.Kaplan-Meier analysis for 30-day mortality and hospital length of stay.

In a time-to-event analysis, we demonstrate an A) increased probability of 30-day mortality and B) increased probability of a longer hospital stay with increased depth of sedation.

Kaplan-Meier curves for the probability of A) survival and B) staying in hospital are shown for patients who received a high versus low proportion of deep sedation during their mechanical ventilation period.



B)



CRITICAL CARE 66

Association of ICU-Opioid Exposure with Chronic Pain after Critical Illness

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INTRODUCTION: Chronic pain after critical illness is common and interferes with quality of life in survivors, but data are limited on its modifiable risk factors.[1] Exposure to high-dose opioids has been associated with worse pain scores and opioid requirements in the perioperative setting, yet its association with the development of chronic pain after critical illness is incompletely understood.[2,3] We sought to determine the association between opioid exposure during ICU admission and chronic pain at 6 months following ICU discharge.

METHODS: In this nested cohort within the MENDS2(4) randomized controlled trial of sedation with dexmedetomidine versus propofol in adult mechanically ventilated ICU patients admitted for sepsis, we collected demographic data and details of the in-hospital course including opioid use. In survivors, we used the Brief Pain Inventory (BPI) to assess rates of chronic pain 6 months after hospital discharge. We used logistic regression to evaluate the independent association of ICU opioid exposure (in fentanyl equivalents) with chronic pain (pain lasting for 3 months or longer), adjusting for potential confounders including age, sex, pre-admission opioid use or diagnosis of chronic pain, Sequential Organ Failure Assessment (SOFA) score, and ICU length of stay.

RESULTS: After accounting for ICU and post-hospital deaths, and some loss to follow up, we obtained BPI outcomes in 152 survivors. Median age (interquartile range) was 58 (48-66), with 54% male, median SOFA score of 9.5 (7-11.2), 59% medical admissions and a median ICU length of stay of 7 days (4-11). Median dose of fentanyl in the ICU was 6,000mcg (2,000-13,000). Of the 152 patients, 88 (58%) reported having pain at 6 months, with 51 (58%) noting it was chronic in nature. Of those with chronic pain, 20 (39%) stated their pain started after their ICU admission, with 13 (65%) specifically relating their pain to their ICU admission. The average pain score of those with chronic pain was 6 (4.5-7). In the regression analysis, we were unable to detect an association between cumulative dose of fentanyl in the ICU and chronic pain (odds ratio OR [95% confidence interval], 0.78 [0.52-1.18]; $p = 0.25$). A history of chronic pain (OR 2.9 [1.27-6.69]; $p = 0.01$) was associated with increased risk of chronic pain at 6 months, while older age was significantly associated with decreased odds of chronic pain (OR 0.73 [0.61 - 0.87]; $p < 0.001$).

CONCLUSION: Chronic pain after critical illness is common, with a significant portion of patients developing chronic pain directly related to their ICU admission. We were unable to demonstrate an association between opioid exposure in the ICU and increased risk of chronic pain at 6 months, although younger age and a prior history of pain or opioid prescription was associated with increased chronic pain. Further studies with adequate sample size are needed to determine modifiable risk factors to mitigate chronic pain after critical illness.

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CRITICAL CARE 67

Alternative to arterial blood gas sampling to assess oxygenation status in mechanically ventilated patients with severe coronavirus disease 2019: An exploratory analysis

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INTRODUCTION: The gold standard for assessing oxygenation status in patients with respiratory distress is the use of the partial pressure of oxygen in arterial blood (PaO2) to fractional inspired concentration of oxygen (FiO2) ratio (commonly abbreviated as P:F ratio)[1]. It requires the use of arterial blood sampling and processing, which requires dedicated expertise, time, and costs. Additionally, it is not possible to continuously assess real-time changes in P:F ratios for potentially dynamic and severe lung diseases, such as coronavirus disease 2019 (COVID-19) pneumonia[2]. The oxygen saturation by pulse oximetry (SpO2) to FiO2 ratio (commonly abbreviated as S:F ratio) has been suggested as an alternative to allow non-invasive and continuous monitoring of oxygenation status; however, data supporting its use remains inconclusive[2-5]. Therefore, the purpose of our exploratory study was to build a new model based on the S:F ratio to reliably predict P:F ratios in patients with severe COVID-19 pneumonia.

METHODS: After Institutional Review Board approval, we performed a retrospective analysis of data from two major teaching hospitals in Boston, MA. We accessed data from the electronic medical records of patients who had been admitted to the intensive care unit from 03/01/2020 to 08/31/2020. We only included patients with confirmed SARS-CoV-2 infection by positive result on polymerase chain reaction testing of a nasopharyngeal sample and those who were mechanically ventilated for severe hypoxemia related to COVID-19. Variables abstracted included concurrent measures of: 1) SpO2; 2) PaO2; and 3) ventilator settings, including FiO2, tidal volume (VT), positive end expiratory pressure (PEEP), mean airway pressure, as well as compliance. P:F and S:F ratios were calculated for all concurrent samples. A locally weighted scatterplot smoothing curve (LOWESS) was first used to graphically depict the relationship between S:F and P:F ratios. Based on the observed relationship, a regression model to predict P:F ratio was developed using the concurrent S:F ratio and ventilator settings.

RESULTS: The analytic cohort included 400 randomly selected time point (200 patients from each institution) where all parameters of interest were measured in each patient. LOWESS curve analysis demonstrated that the relationship between S:F and P:F ratios was not linear (Figure 1). A Gaussian regression analysis with bootstrapping (50 replications) was performed by adding potential predictor variables in forward and backward stepwise fashion. The strongest model fit was achieved with the following equation: P:F ratio = (0.5 * S:F ratio) - (0.2 * VT) - (7 * PEEP); (R-squared = 0.95).

CONCLUSION: In this initial exploratory study, our data suggests that the S:F ratio, VT, and PEEP settings in mechanically ventilated COVID-19 patients can be combined to reasonably predict concurrent P:F ratios. This newly-developed model may be helpful to continuously assess oxygenation status in critically ill COVID-19 patients. Further studies are needed to validate our findings and to assess the model performance in a prospective manner. Figure 1. Locally weighted scatterplot smoothing (LOWESS) curve to graphically represent the relationship between the oxygen saturation by pulse oximetry to fractional inspired concentration of oxygen (S:F) ratio and the partial pressure of oxygen in arterial blood to fractional inspired concentration of oxygen (P:F) ratio. LOWESS is a nonparametric regression technique which is based on minimal assumptions about the nature of the relationship between variables. We observe a non-linear relationship between S:F and P:F ratios (n=200).

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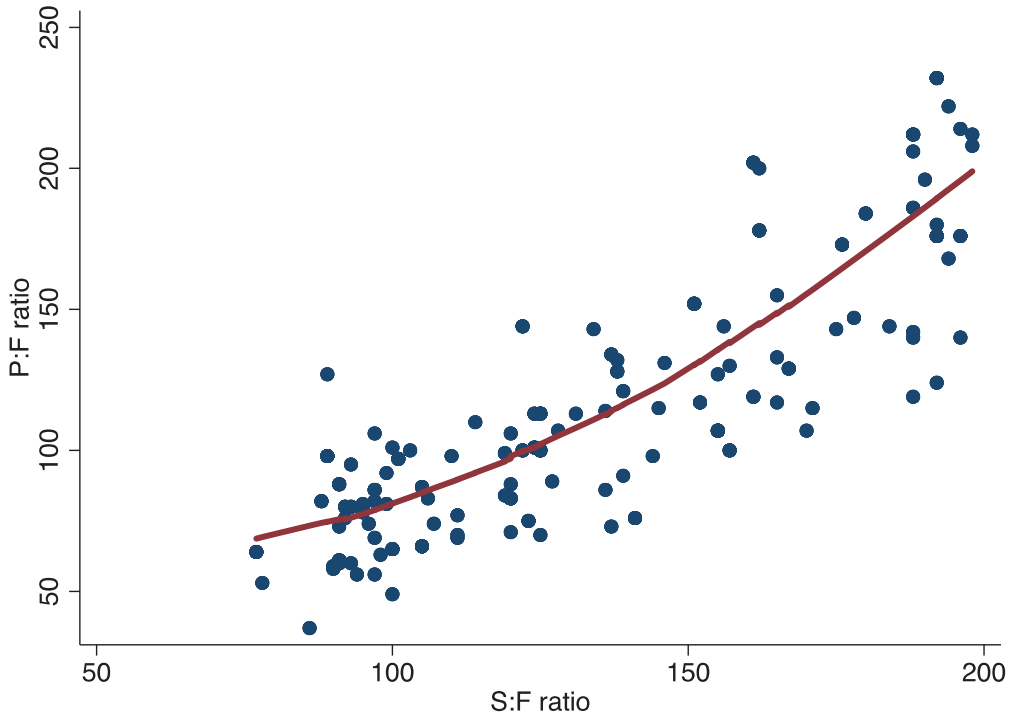

Fig. 1

CRITICAL CARE 68

Traditional visceral proteins versus novel nutrition risk scoring tools for assessing outcomes in critically ill patients

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INTRODUCTION: Historically, visceral proteins have been used to describe nutrition risk in critically ill patients[1]. Although evidence demonstrates that using these biomarkers in such a manner is inaccurate, the practice remains pervasive among clinicians[2]. The 2016 American Society of Parenteral and Enteral Nutrition-Society of Critical Care Medicine consensus guidelines recommend the use of either the Nutrition Risk Screening 2002 (NRS2002) or Nutrition Risk in Critically Ill (NUTRIC) to assess nutrition risk in the intensive care unit (ICU) setting[3]. We have previously shown that the NRS2002 is not suitable for assessing nutrition risk in the ICU[4]. However, evidence suggests that novel scoring tools, such as the modified NUTRIC (mNUTRIC) and the Patient-and Nutrition-Derived Outcome Risk Assessment (PANDORA) may be more useful in determining nutrition risk in critically ill patients[5]. Data comparing visceral proteins to these novel screening tools in terms of their association with clinical outcomes is sparse. Therefore, the goal of our study was to compare the association of admission albumin and pre-albumin levels as well as mNUTRIC and PANDORA scores with clinical outcomes in medical and surgical ICU patients.

METHODS: We conducted a retrospective, cohort study of patients admitted to three ICUs in a large teaching hospital in Boston, MA. To investigate the association of albumin, pre-albumin, mNUTRIC, and PANDORA with 30-day ventilator free days (VFD), ICU length of stay (LOS), and hospital LOS, we performed Poisson regressions. To investigate the association of albumin, pre-albumin, mNUTRIC, and PANDORA with in-hospital as well as 90-day mortality, we performed logistic regressions. In all models, we controlled for age, sex, race, body mass index, creatinine, type of patient (medical vs. surgical), and other relevant covariates. In addition, we constructed receiver operating characteristic (ROC) curves to compare areas under the curve (AUC) to assess the utility of admission albumin, pre-albumin, mNUTRIC, and PANDORA to predict in-hospital as well as 90-day mortality.

RESULTS: The analytic cohort was comprised of 673 adults (Table 1). Mean albumin and pre-albumin were 3.2±0.7 g/dL and 12.9±3.2 mg/dL, respectively. Mean APACHE II, mNUTRIC, and PANDORA were 19±9, 5±2, and 24±9, respectively. Overall in-hospital and 90-day mortality was 22% and 30%, respectively. Albumin levels were associated with ICU and hospital LOS, while pre-albumin levels were associated with hospital LOS and in-hospital mortality (Table 2). On the other hand, mNUTRIC and PANDORA were associated with all assessed clinical outcomes (Table 2). ROC (Figure 1) analysis demonstrated that albumin and pre-albumin significantly underperformed for predicting in-hospital mortality when compared to mNUTRIC and PANDORA (AUC 0.41; 95%CI 0.33-0.49 and AUC 0.41;95%CI 0.33-0.48 vs. AUC 0.71;95%CI 0.64-0.78 and AUC 0.70;95%CI 0.62-0.76, respectively: $p<0.001$). Similarly, ROC analysis (Figure 1) demonstrated that albumin and pre-albumin significantly underperformed for predicting 90-day mortality when compared to mNUTRIC and PANDORA (AUC 0.45;95%CI 0.37-0.52, AUC 0.43;95%CI 0.36-0.50, and AUC 0.71;95%CI 0.65-0.77 vs. AUC 0.70; 95%CI 0.63-0.76, respectively: $p<0.001$).

CONCLUSION: Our data suggest that novel screening tools are likely to be more useful in identifying patients at high nutrition risk when compared to traditional biomarkers. Prospective studies are needed to determine whether nutritional support based on mNUTRIC or PANDORA can improve clinical outcomes in critically ill patients.

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Table 1. Characteristics of adult patients (n=673) to investigate the association of visceral proteins versus nutrition risk screening tools with outcomes stratified by survivors versus non-survivors to 90 days after intensive care unit admission.

	90-day survivors (n= 474)	**90-day non-survivors** (n=199)	**P-value**
Age (years)	58 ± 17	68 ± 14	**<0.001**
Sex (%)			0.39
Female	33	40	
Male	67	60	
Race (%)			**0.005**
Non-white	19	6	
White	81	94	
BMI (kg/m^2)	27 ± 6	28 ± 7	0.08
Type of patient (%)			**<0.001**
Medical	36	57	
Surgical	64	43	
Creatinine (mg/dL)	1.4 ± 2.4	1.8 ± 1.6	**0.01**
hsCRP (mg/L)	137 ± 115	139 ± 112	0.83
Albumin (g/dL)	3.3 ± 0.8	3.1 ± 0.9	**0.01**
Pre-albumin (mg/dL)	13.6 ± 3.7	12.7 ± 3.4	**0.002**
Protein deficit (g)	394 ± 381	476 ± 416	**0.02**
Caloric deficit (kcal)	7,405 ± 5,928	8,824 ± 6,616	**0.01**
APACHE II	18 ± 8	23 ± 9	**<0.001**
mNUTRIC	4 ± 2	6 ± 2	**<0.001**
PANDORA	23 ± 9	28 ± 8	**<0.001**
VFD (days)	22 (14-26)	0 (0-17)	**<0.001**
ICU LOS (days)	11 (7-21)	12 (7-19)	0.96
Hospital LOS (days)	23 (14-35)	23 (12-40)	0.44
In-hospital mortality (%)			**<0.001**
Yes	1	72	
No	99	28	

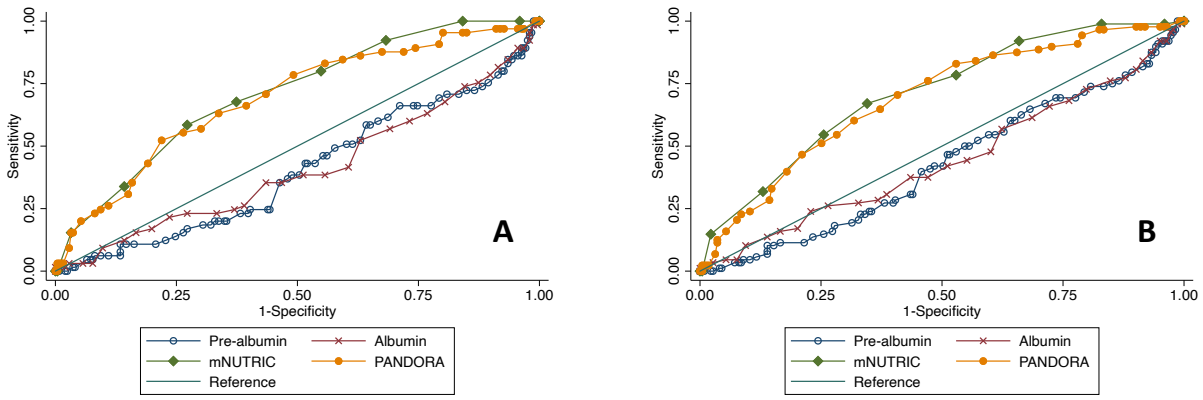
BMI = body mass index; hsCRP = high sensitivity C-reactive protein; APACHE = Acute Physiology and Chronic Health Evaluation; mNUTRIC = modified Nutrition Risk in Critically Ill; PANDORA = Patient-and Nutrition-Derived Outcome Risk Assessment; VFD = 30-day ventilator free days; ICU = intensive care unit; LOS = length of stay. Data are presented as mean ± standard deviation, median (interquartile range), or proportions, and compared using t-tests, long-rank tests, and chi-square tests, respectively. Significant p-values are shown in bold.

Table 2. Regression models to investigate the association of visceral proteins and nutrition risk screening tools with clinical outcomes.

	Albumin	Pre-albumin	mNUTRIC	PANDORA
VFD	IRR 1.01 95%CI 0.97-1.04 (APACHE II, hsCRP, P:F)	IRR 1.00 95%CI 1.00-1.01 (APACHE II, hsCRP, P:F)	**IRR 0.95** **95%CI 0.94-0.96** (P:F)	**IRR 0.98** **95%CI 0.98-0.99** (P:F)
ICU LOS	**IRR 0.96** **95% CI 0.92-0.99** (APACHE II, hsCRP, VFD)	IRR 1.00 95%CI 0.99-1.00 (APACHE II, hsCRP, VFD)	**IRR 1.02** **95%CI 1.01-1.03** (VFD)	**IRR 1.03** **95%CI 1.03-1.04** (VFD)
Hospital LOS	**IRR 0.94** **95%CI 0.92-0.06** (APACHE II, hsCRP, ILOS)	**IRR 0.99** **95%CI 0.98-0.99** (APACHE II, hsCRP, ILOS)	**IRR 1.04** **95%CI 1.03-1.04** (ILOS)	**IRR 1.01** **95%CI 1.01-1.02** (ILOS)
In-hospital mortality	OR 0.70 95%CI 0.48-1.02 (APACHE II, hsCRP, HLOS)	**OR 0.91** **95%CI 0.83-0.99** (APACHE II, hsCRP, HLOS)	**OR 1.41** **95%CI 1.27-1.56** (HLOS)	**OR 1.07** **95%CI 1.03-1.12** (HLOS)
90-day mortality	OR 0.89 95%CI 0.64-1.26 (APACHE II, hsCRP, HLOS)	OR 0.94 95%CI 0.87-1.02 (APACHE II, hsCRP, HLOS)	**OR 1.33** **95%CI 1.21-1.47** (HLOS)	**OR 1.07** **95%CI 1.03-1.11** (HLOS)

PANDORA = Patient-and Nutrition-Derived Outcome Risk Assessment; mNUTRIC = modified Nutrition Risk in Critically Ill; APACHE = Acute Physiology and Chronic Health Evaluation; hsCRP = high sensitivity C-reactive protein; P:F = partial pressure of oxygen: fractional inspired oxygen; VFD = 30-day ventilator-free days; ICU = intensive care unit; LOS = length of stay; ILOS = ICU LOS; HLOS = hospital LOS; IRR = incidence rate ratio; OR = odds ratio; CI = confidence interval. In all regression models, age, sex, race, body mass index, creatinine, and type of patient (medical versus surgical) were entered as covariates. Additional covariates for each respective model are shown within parentheses. Further adjusting these models for ICU-related caloric or protein deficit did not materially change the observed results. Statistically significant risk ratios are shown in bold.

Figure 1: Receiver operating characteristic curves for predicting in-hospital (A) and 90-day (B) mortality in medical and surgical intensive care unit patients (n=673). Albumin and pre-albumin significantly underperformed in predicting in-hospital as well as 90-day mortality compared to modified Nutrition Risk in Critically Ill (mNUTRIC) and Patient-and Nutrition-Derived Outcome Risk Assessment (PANDORA).



CRITICAL CARE 69

Skin Failure: Is the bulk of the problem pressure versus perfusion?

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INTRODUCTION: Skin breakdown in the critically ill has important implications for patient prognostication, recovery, morbidity, mortality, healthcare costs, and family perception of care. The differential diagnosis for skin failure is broad, but pressure is a prevalent etiology and major problem in the USA with more than 2.5 million pressure injury cases per year contributing to over 60,000 deaths and costing approximately $10 billion[1]. Historically, predictors of pressure injuries focused on sensory perception, moisture, mobility, nutrition, and shear, which unfortunately have significant heterogeneity and subjectivity[2] and poor specificity and positive predictive value[3]. This is likely because other factors have larger contributions to tissue survival, such as perfusion and oxygen delivery[4, 5]. The objective of this study is to test the hypothesis that perfusion is a major contributor for some skin breakdown that is classified as a hospital acquired pressure injury (HAPI). Factors related to perfusion / low flow states, such as extracorporeal membrane oxygenation (ECMO), temporary mechanical circulatory support (Temp MCS), infusions of vasopressors/inotropes, and durable MCS (LVAD) were analyzed to determine if these predicted skin injuries more strongly than immobility due to prolonged mechanical ventilation or operating room (OR) time.

METHODS: This study is a secondary analysis of a de-identified, prospectively collected dataset representing 533 patients admitted to a cardiovascular intensive care unit (CVICU). Comparisons were made for demographics, comorbidities that were present on admission (POA), length of stay (LOS), conditions diagnosed in the ICU (DI-ICU), as well as, the high acuity criteria to be tested, including mechanical ventilation greater than 72 hrs (Vent > 72 hrs), cumulative OR time greater than 6 hrs (OR > 6 hrs), ECMO, Temp MCS, two or more vasopressor/inotrope infusions (Inotropes 2+), and LVAD. Statistical analysis was performed using T-tests; Wilcoxon rank-sum tests; Chi-square tests; and Exact tests; as appropriate.

RESULTS: In the study population of 533 critically ill patients followed over approximately 2,574 critical care days there was a total of 17 new or worsened HAPIs while in the ICU, which represents 6.6 HAPIs per 1000 critical care days. After controlling for patient demographics (Table 1), comorbidities POA (Table 2), and critical care diagnoses and LOS (Table 3), there was a significant risk of patients developing a skin injury for each of the criteria tested ($p<0.05$). Number-needed-to-harm (NNTH) analysis demonstrated 95% confidence intervals that did not include infinity, except for durable LVAD support (Table 4).

CONCLUSION: These data are consistent with the hypothesis that skin failure is a pathophysiological process that occurs concurrently with multisystem organ failure due to circulatory malfunction. ECMO, temporary MCS, and inotropes are risk factors for skin failure in our study and these perfusion-related variables had a larger effect size on skin breakdown than variables associated with immobility. The exception to that pattern was the incidence of skin failure in patients with a durable LVAD, which was highly variable. This is likely because the trajectory of patients with a durable LVAD is bimodal such that some have no complications and thus are protected from skin injury, while others are plagued by coagulopathy, fluid shifts, right ventricle failure, and prolonged ICU length of stay that contribute to prolonged low flow states with decreased perfusion of all organs, including the skin. The common underlying pathophysiological problem is skin perfusion pressure (SPP), which is equal to Mean Arterial Pressure (MAP) minus Tissue Pressure (TP). SPP must exceed the requisite for the restoration of microcirculatory or capillary flow that would promote wound healing or avoid skin failure[6]. In a study of patients that underwent amputation, SPP >30 mmHg predicted complete healing in 90% of cases, while SPP <30 mmHg predicted the failure of healing in 75% of cases[7]. Cardiogenic shock states are, of course, disproportionately present in CVICUs and that patient population may be at risk of skin injury that is refractory to Pressure Injury Prevention bundle interventions. Further studies are warranted to investigate and treat the pathophysiological conditions that contribute to skin failure in critically ill patients.

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Table 1. Demographic variables. Patients with or without a HAPI admitted to the CVICU

	New or worsened HAPI while in ICU?			
Variables	**Total N=533 (col %)**	**No N=516 (row %)**	**Yes N=17 (row %)**	**P Value**
Age				*0.339 T*
Mean ± SD	62.4 ± 14.3	62.5 ± 14.3	59.1 ± 13.1	
Median (min - max)	63.0 (19.0 - 93.0)	63.0 (19.0 - 93.0)	62.0 (19.0 - 75.0)	
Gender				*0.677 C*
Female	194 (36.4)	187 (96.4)	7 (3.6)	
Male	339 (63.6)	329 (97.1)	10 (2.9)	
BMI (first after admission)				*0.458 T*
Mean ± SD	30.4 ± 7.4	30.4 ± 7.4	31.7 ± 8.8	
Median (min - max)	29.1 (15.4 - 68.2)	29.1 (15.4 - 68.2)	30.0 (16.4 - 50.5)	
Missing	2	2	0	
Primary Service				*0.568 C+*
Cardiology	82 (31.2)	81 (98.8)	1 (1.2)	
CCA	35 (13.3)	33 (94.3)	2 (5.7)	
CTS	103 (39.2)	99 (96.1)	4 (3.9)	
MICU	30 (11.4)	30 (100.0)	0 (0.0)	
NICU	1 (0.4)	1 (100.0)	0 (0.0)	
Other	4 (1.5)	4 (100.0)	0 (0.0)	
SICU	4 (1.5)	4 (100.0)	0 (0.0)	
TICU	4 (1.5)	4 (100.0)	0 (0.0)	

+Exact test; TT-test; WWilcoxon rank-sum test; CChi-square test

Table 2. Comorbidities POA. Patients with or without a HAPI admitted to the CVICU				
	New or worsened HAPI while in ICU?			
Variables	Total N=533 (col %)	No N=516 (row %)	Yes N=17 (row %)	P Value
Number of POA Conditions				*0.890* [W]
0	335 (63.0)	324 (96.7)	11 (3.3)	
1	160 (30.1)	155 (96.9)	5 (3.1)	
2	34 (6.4)	34 (100.0)	0 (0.0)	
3+	3 (0.6)	2 (66.7)	1 (33.3)	
Pressure injury				*0.627* [C+]
No	494 (92.7)	479 (97.0)	15 (3.0)	
Yes	39 (7.3)	37 (94.9)	2 (5.1)	
Diabetes				*0.501* [C]
No	368 (69.0)	355 (96.5)	13 (3.5)	
Yes	165 (31.0)	161 (97.6)	4 (2.4)	
Vascular disease (PAD)				*0.620* [C+]
No	497 (93.2)	482 (97.0)	15 (3.0)	
Yes	36 (6.8)	34 (94.4)	2 (5.6)	
Renal failure on HD/PD				*1.000* [C+]
No	507 (95.1)	491 (96.8)	16 (3.2)	
Yes	26 (4.9)	25 (96.2)	1 (3.8)	
Liver failure				*0.230* [C+]
No	525 (98.5)	509 (97.0)	16 (3.0)	
Yes	8 (1.5)	7 (87.5)	1 (12.5)	
Spinal cord injury				*1.000* [C+]
No	528 (99.2)	511 (96.8)	17 (3.2)	
Yes	4 (0.8)	4 (100.0)	0 (0.0)	
Pressure injury: sacrum/buttocks				*0.169* [C+]
No	419 (93.7)	409 (97.6)	10 (2.4)	
Yes	28 (6.3)	26 (92.9)	2 (7.1)	
Pressure injury: heel				*1.000* [C+]
No	442 (98.9)	430 (97.3)	12 (2.7)	
Yes	5 (1.1)	5 (100.0)	0 (0.0)	
Pressure injury: head				*NA*
No	447 (100.0)	435 (97.3)	12 (2.7)	
Pressure injury: other				*1.000* [C+]
No	261 (99.2)	254 (97.3)	7 (2.7)	
Yes	2 (0.8)	2 (100.0)	0 (0.0)	
[+]Exact test; [T]T-test; [W]Wilcoxon rank-sum test; [C]Chi-square test				

Table 3. Critical Care Conditions. Patients with or without a HAPI while in the CVICU				
	New or worsened HAPI while in ICU?			
Variables	Total N=533 (col %)	No N=516 (row %)	Yes N=17 (row %)	P Value
Hospital LOS (in Days)				*<.001 T*
Mean ± SD	10 ± 12	9 ± 11	40 ± 27	
Median (min - max)	5 (1 - 87)	5 (1 - 83)	33 (8 - 87)	
Missing	186	178	8	
CVICU LOS (in days)				*<.001 T*
Mean ± SD	5 ± 9	4 ± 7	30 ± 22	
Median (min - max)	2 (1 - 82)	2 (1 - 82)	23 (5 - 82)	
Missing	1	1	0	
Disposition from ICU				*0.249 C+*
0	1 (0.4)	1 (100.0)	0 (0.0)	
Death	17 (6.4)	16 (94.1)	1 (5.9)	
floor	218 (82.6)	212 (97.2)	6 (2.8)	
home	15 (5.7)	15 (100.0)	0 (0.0)	
Hospice	3 (1.1)	3 (100.0)	0 (0.0)	
LTACH	3 (1.1)	2 (66.7)	1 (33.3)	
other hospital	1 (0.4)	1 (100.0)	0 (0.0)	
other ICU	6 (2.3)	6 (100.0)	0 (0.0)	
Disposition of Hospital D/C				*0.003 C+*
0	116 (25.2)	113 (97.4)	3 (2.6)	
Death	35 (7.6)	31 (88.6)	4 (11.4)	
home	251 (54.4)	250 (99.6)	1 (0.4)	
Hospice	8 (1.7)	8 (100.0)	0 (0.0)	
Inpatient rhab	10 (2.2)	9 (90.0)	1 (10.0)	
LTACH	15 (3.3)	12 (80.0)	3 (20.0)	
Other Hospital	2 (0.4)	2 (100.0)	0 (0.0)	
Number conditions DI-ICU				*<.001 W*
0	466 (87.6)	463 (99.4)	3 (0.6)	
1	44 (8.3)	41 (93.2)	3 (6.8)	
2+	22 (4.1)			
Conditions DI-ICU: sepsis				*<.001 C+*
No	500 (94.0)	495 (99.0)	5 (1.0)	
Yes	32 (6.0)	20 (62.5)	12 (37.5)	
Conditions DI-ICU: renal failure (HD/CRRT)				*<.001 C+*
No	486 (91.2)	480 (98.8)	6 (1.2)	
Yes	47 (8.8)	36 (76.6)	11 (23.4)	
Conditions DI-ICU: liver failure				*<.001 C+*
No	522 (97.9)	509 (97.5)	13 (2.5)	
Yes	11 (2.1)	7 (63.6)	4 (36.4)	
Conditions DI-ICU: spinal cord injury				*NA*
No	533 (100.0)	516 (96.8)	17 (3.2)	
Pt dependent for mobility				*0.053 C+*
No	94 (35.7)	94 (100.0)	0 (0.0)	
Yes	169 (64.3)	162 (95.9)	7 (4.1)	
Times repositioned while dependent				*<.001 T*
Mean ± SD	44 ± 89	32 ± 55	254 ± 239	
Median (min - max)	12 (0 - 971)	11 (0 - 398)	189 (14 - 971)	
Missing	218	217	1	
Average hours between turns*				*0.529 T*
Mean ± SD	2.6 ± 1.7	2.6 ± 1.7	2.4 ± 0.9	
Median (min - max)	2.3 (0.5 - 26.0)	2.3 (0.5 - 26.0)	2.1 (1.8 - 5.6)	
Missing	231	230	1	
Hours mechanical ventilation				*<.001 T*
Mean ± SD	67 ± 120	55 ± 104	290 ± 184	
Median (min - max)	19 (1 - 770)	16 (1 - 770)	270 (101 - 638)	
Missing	392	382	10	
Hours of 2+ pressors/inotropes				*<.001 T*
Mean ± SD	47 ± 50	35 ± 32	133 ± 72	
Median (min - max)	28 (0 - 247)	24 (0 - 156)	112 (24 - 247)	
Missing	478	468	10	
Hours on ECMO				*0.199 T*
Mean ± SD	270 ± 198	215 ± 153	353 ± 243	
Median (min - max)	240 (48 - 792)	177 (48 - 452)	298 (112 - 792)	
Missing	518	507	11	
Hours temp MCS				*0.236 T*
Mean ± SD	100 ± 112	90 ± 116	163 ± 65	
Median (min - max)	44 (0 - 420)	36 (0 - 420)	152 (106 - 240)	

Missing	505	492	13	
Hours dependent for mobility				*<.001* [T]
Mean ± SD	85.3 ± 143.9	71.7 ± 122.2	416.6 ± 231.2	
Median (min - max)	24.0 (3.0 - 874.0)	24.0 (3.0 - 815.5)	391.0 (112.0-874.0)	
Missing	356	346	10	
Hours off overlay (mobility/test)				*0.700* [T]
Mean ± SD	8.9 ± 24.0	8.8 ± 24.2	12.4 ± 15.0	
Median (min - max)	4.0 (0.0 - 271.0)	4.0 (0.0 - 271.0)	7.0 (2.5 - 45.5)	
Missing	293	283	10	
First Braden Score on Transfer				*<.001* [T]
Mean ± SD	18.0 ± 3.2	18.1 ± 3.1	12.0 ± 2.6	
Median (min - max)	19.0 (0.0 - 23.0)	19.0 (0.0 - 23.0)	11.0 (10.0 - 15.0)	
Missing	318	304	14	
Hours with Braden mobility sub-score < 3				*<.001* [T]
Mean ± SD	118.0 ± 229.5	82.3 ± 125.7	636.8 ± 578.4	
Median (min - max)	45.5 (1.0 - 1860)	38.0 (1.0 - 859.0)	482.0 (72.0 - 1860)	
Missing	393	385	8	
HAPI after transfer				*1.000* [C+]
No	220 (98.2)	217 (98.6)	3 (1.4)	
Yes	4 (1.8)	4 (100.0)	0 (0.0)	
Number of High Acuity Criteria				*<.001* [W]
0	235 (44.2)	235 (100.0)	0 (0.0)	
1	115 (21.6)	114 (99.1)	1 (0.9)	
2	94 (17.7)	91 (96.8)	3 (3.2)	
3	50 (9.4)	47 (94.0)	3 (6.0)	
4	24 (4.5)	19 (79.2)	5 (20.8)	
5+	14 (2.6)	9 (64.3)	5 (35.7)	
High Acuity Criteria present: Mechanical ventilation				*<.001* [C]
No	256 (48.0)	256 (100.0)	0 (0.0)	
Yes	277 (52.0)	260 (93.9)	17 (6.1)	
High Acuity Criteria present: 2 or more pressors/inotropes				*<.001* [C+]
No	433 (81.2)	428 (98.8)	5 (1.2)	
Yes	100 (18.8)	88 (88.0)	12 (12.0)	
High Acuity Criteria present: Total OR time > 6 hours				*<.001* [C+]
No	397 (74.5)	393 (99.0)	4 (1.0)	
Yes	136 (25.5)	123 (90.4)	13 (9.6)	
High Acuity Criteria present: ECMO				*<.001* [C+]
No	501 (94.2)	494 (98.6)	7 (1.4)	
Yes	31 (5.8)	21 (67.7)	10 (32.3)	
High Acuity Criteria present: LVAD				*0.040* [C+]
No	508 (95.3)	494 (97.2)	14 (2.8)	
Yes	25 (4.7)	22 (88.0)	3 (12.0)	
High Acuity Criteria present: Temp LVAD or RVAD support				*<.001* [C+]
No	482 (90.4)	472 (97.9)	10 (2.1)	
Yes	51 (9.6)	44 (86.3)	7 (13.7)	
High Acuity Criteria Present: open abdomen				*<.001* [C+]
No	264 (97.8)	257 (97.3)	7 (2.7)	
Yes	6 (2.2)	3 (50.0)	3 (50.0)	
High Acuity Criteria Present: open chest				*<.001* [C+]
No	257 (95.2)	251 (97.7)	6 (2.3)	
Yes	13 (4.8)	9 (69.2)	4 (30.8)	

*(hours dependent / repositioning documented); +Exact test;
[T]T-test; [W]Wilcoxon rank-sum test; [C]Chi-square test

Number-needed-to-harm for High Acuity Criteria		
Comparison Variable	**Number needed to harm**	**NNH 95% Confidence Interval**
Vent > 72 hrs	16.3	(11 , 30)
OR > 6 hrs	11.7	(7 , 28)
ECMO	3.2	(2 , 7)
Temp MCS	8.6	(5 , 47)
Inotropes 2+	9.2	(6 , 23)
Durable LVAD	10.8	NNH 5 to Inf to NNTB 28

Table 4. Number needed to harm (NNTH) for exposure to individual high acuity criteria to contribute to skin injury. Criteria that may have a greater contribution of immobility are mechanical ventilation greater than 72 hrs (Vent > 72 hrs) and cumulative operating room time greater than 6 hrs (OR > 6 hrs), whereas, ECMO, temporary mechanical circulatory support (Temp MCS), two or more vasopressor/inotrope infusions, and durable MCS (LVAD) may have a greater contribution of perfusion.

SUBSPECIALTY ABSTRACTS

ECONOMICS, EDUCATION AND POLICY

ECONOMICS, EDUCATION AND POLICY 1

The Individual Impact of Participation in a Diversity Curriculum Among Perioperative Residents

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INTRODUCTION: In recent years, equity and inclusion training in academic medicine broadly focused on providing foundational diversity knowledge. While faculty and emerging trainees confirm the ability to define diversity, equity, and inclusion (DEI) concepts, they also report difficulty in applying these insights throughout clinical, educational, and academic settings. For institutions to effectively engage anti-racist pedagogy, they must create space to discuss and address structural and interpersonal harm that occur in healthcare and academic medicine. Utilizing the framework of the Kirkpatrick Evaluation Model, this graduate medical education training series focuses on transferring DEI knowledge (level 2) into applied behaviors (level 3). The DEI curriculum centers around three core concepts including unconscious bias, microaggressions, and allyship. The series' objective is to curate facilitated spaces that will support faculty and residents in their ability to effectively engage in difficult dialogues and take action to support the lives of people who have long been marginalized within healthcare and society.

METHODS: Using Kern's six steps, this study is a pretest-posttest design of a 4-series workshop utilizing activities to enhance competence and performance around unconscious bias, allyship, and microaggression. We administered a pre-workshop survey 6-8 weeks prior to the workshop series during an introduction session for first-year anesthesia residents that preceded this curriculum. The survey was also emailed out to all surgery and anesthesia residents at UCSF to capture a wider audience including those who were not able to attend the introduction session. This needs assessment captured what the residents felt were lacking in their education regarding DEI training and also their prior experiences with DEI training. Eighty-three percent (79/95) of participants stated that they have not previously received formal DEI training. Participants identified that actionable changes, tools, interactive activities to uncover biases, and small group discussions were important. The diversity curriculum included 2-hrs workshops on unconscious bias, allyship, and microaggression that encompassed pair-share, interactive exercises, role play in small breakout groups as well as evidence-based didactics on a virtual platform to 22 first-year clinical anesthesia residents and 15 senior general surgery residents (PGY-4 and PGY-5). The residents were selected based on available protected educational time with the least scheduling conflicts across the anesthesia and general surgery residency programs. Using Kirkpatrick's framework based on level 1 satisfaction and level 2 competency, the results were then measured using paired t-test analyses. The University of California San Francisco Institution Review Board deemed this study exempt from review (5/14/20).

RESULTS: After participation in the Unconscious Bias workshop, 100% of Anesthesiology CA-1 survey responses and 63% of Surgery PGY-4 and PGY-5 survey responses were completed. On a 5-point Likert Scale, participants rated their agreement with "I believe this unconscious bias workshop is relevant to my workplace" a mean of 4.70 (SD+/-0.54), "I would recommend this unconscious bias workshop to my peers" a mean of 4.67 (SD+/-0.55), and "this unconscious bias workshop has given me insight on biases I didn't know I had" a mean of 4.15 (SD+/-0.86). A total of 15 Anesthesia CA-1 participants who completed both the pre-workshop survey and post-workshop survey were matched to analyze their data using a paired T-Test. Fifteen paired participants increased their agreement with the statement "I know how to define the term unconscious bias" from a pre-workshop mean of 4.1 (SD+/-0.59) to a mean of 4.8 (SD+/-0.41, $P<0.001$). They also self-reported increased agreement with the statement "I have unconscious biases" from a pre-workshop mean of 4.3 (SD±0.70) to a post-workshop mean of 4.8 (SD+/-0.41, $P=0.006$). "My unconscious biases affect my clinical practice and/or interactions with others" mean agreement increased from 2.9 (SD+/-1.51) to 3.8 (SD+/-1.01, $P=0.021$).

CONCLUSION: The Unconscious Bias workshop filled an important need for DEI education for perioperative residents. With high response rates, the survey results demonstrated the residents' great satisfaction as well as increased awareness of their own implicit biases. This workshop also promoted active reflection on how these biases impact their interactions and clinical practice.

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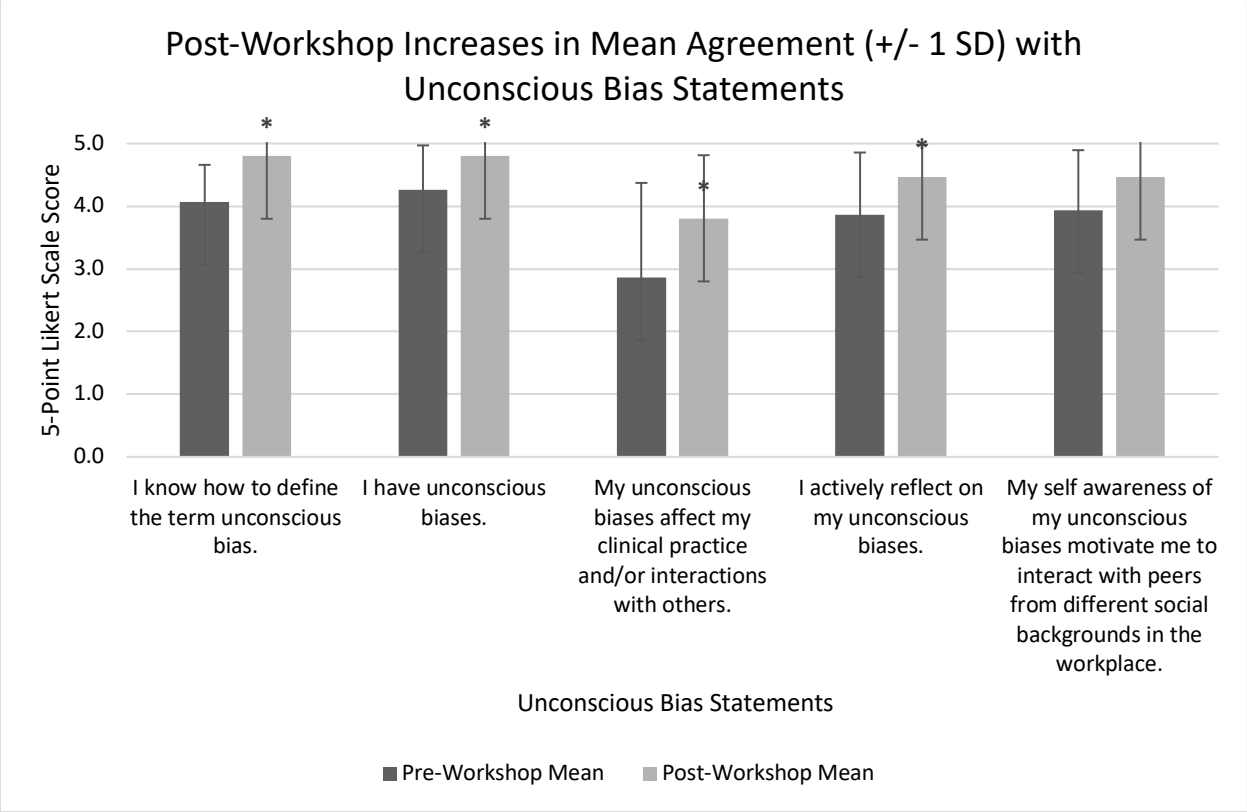

Figure 1. Paired T-Test Analysis Reveals Post-Workshop Increases in Mean Agreement with Unconscious Bias Statements. The * denotes $p<0.05$ for comparison between pre-workshop and post-workshop responses. The error bars represent the range of one standard deviation of the mean agreement. The statements were rated on a 5-point scale (1=*Strongly Disagree*, 5=*Strongly agree*).

Statement	Strongly disagree	Somewhat disagree	Neutral	Somewhat agree	Strongly agree
This unconscious bias workshop is important to my training	0%	0%	4%	26%	70%
I believe this unconscious bias workshop is relevant to my workplace	0%	0%	4%	22%	74%
I would recommend this unconscious bias workshop to my peers.	0%	0%	4%	26%	70%
This unconscious bias workshop has given me insight on biases I didn't know I had	0%	4%	19%	37%	41%

Table 2. Post-Workshop Student Evaluations of Workshop (N = 27).

ECONOMICS, EDUCATION AND POLICY 2

Predicting Academic Success in Anesthesiology Residents - Will USMLE Step1 scores be missed?

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INTRODUCTION: USMLE Step 1 scores were utilized by 95.2% of the programs in the 2021 NRMP Program Director Survey with a mean importance score of 3.8/5[4]. This, however, will likely be changing as USMLE Step1 transitions to a pass/fail scoring system, thus eliminating a score that was previously ranked as high as 4.4/5 in 2018[3]. Studies in the past have suggested a high correlation between USMLE Step scores and in-service ITE exams and ABA exams[1,2]. However, with introduction of the ABA Basic exam, it is unclear if learning behavior has changed due to the in-training placement of this high-stakes exam. Based on these prior studies, we hypothesize that USMLE STEP1 and STEP2 scores and/or Anesthesia Knowledge Test (AKT) scores (pre-residency, post first anesthesia clinical month, or change between pre/post scores) will predict the ability to improve anesthesia related medical knowledge as measured by a change in In-Training Examination (ITE) Scores.

METHODS: Following IRB approval, a retrospective data analysis was performed on a de-identified data set from all anesthesiology residents at the University of Kentucky from 2013 to 2021. Data consisted of USMLE Step 1 and Step 2 scores, AKT exam scores (raw score) taken pre-residency and after first month of clinical anesthesiology rotation, and ITE exam scores taken every January during their four-year residency. The change between pre- and post- AKT exam scores and between yearly ITE exam scores was calculated. Linear correlations between all factors were calculated using Pearson's Correlation coefficient.

RESULTS: Scores from a total of 136 residents were evaluated. All included residents obtained primary board certification. USMLE scores of the included residents were balanced distributed around national mean values during the study period (Figure 1). The raw test score data are shown in Table 1. USMLE Step1 scores had a statistically significant but weak positive correlation with ITE year 1-4 scores ($r=.329$, $p<.001$; $r=.291$, $p=.001$; $r= 3.26$, $p = .001$; $r=2.76$, $p=.007$) with no statistically significant correlation to ITE growth. USMLE Step2 scores showed similar results with a statistically significant and weak positive correlation to ITE year1-4 scores ($r =.317$, $p<.01$; $r=.370$, $p<.01$, $r=.443$, $p<.01$, $r=.309$, $p=.02$) and no correlation to ITE growth. AKT pre-test scores were most strongly correlated with ITE-1 scores ($r=.409$, $p <.001$) with strength of correlation decreasing through training. AKT post-anesthesia rotation scores showed statistically significant, weak positive correlation to ITE year 1-4 ($r=.476$, $p<.01$; $r=.467$, $p<.01$; $r=.438$; $p<.01$; $r=.392$, $p<.01$), with a statistically insignificant negative correlation to ITE growth. AKT growth showed no correlation to either ITE scores or ITE growth. It is important to note that none of the factors were associated with an r-value >0.5 suggesting they were moderate correlations.

CONCLUSION: Using a holistic recruitment and selection approach, recruiting residents with a broad range of academic performance, we made following observations: 1) Neither USMLE Step1 nor Step2 scores are predictive of trainees' ability to improve anesthesia related knowledge as measured by change in ITE scores over the course of training. 2) Neither AKT pre-residency score, AKT post-residency score, nor change in AKT pre/post scores are predictive of trainees' ability to improve anesthesia related knowledge. 3) Further research is needed to identify factors within an objective holistic selection approach to predict trainees' academic performance during anesthesia residency.

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Figure 1 USMLE 1 and 2 (CK) scores

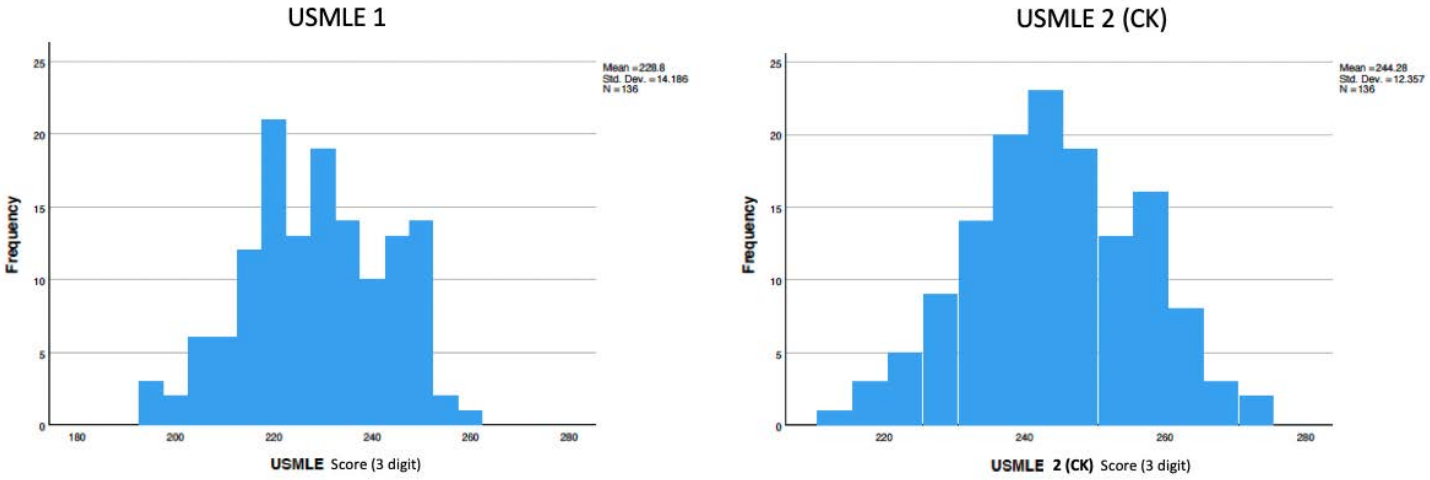

Table 1

Test	n	Test score (mean ± SD)
AKT pre [percentile]	134	43.97 ± 19.87
AKT post [percentile]	131	54.41 ± 21.33
AKT Δ pre-post [percentile]	131	10.52 ± 19.65
USMLE 1	136	228.80 ± 14.19
USMLE 2 (CK)	136	244.28 ± 12.36
ITE PGY1	126	26.63 ± 4.94
ITE CA1	123	34.72 ± 5.86
ITE CA2	107	39.50 ± 5.24
ITE CA3	94	40.20 ± 5.11
ITE Δ PGY1-CA1	123	10.36 ± 8.18
ITE Δ PGY1-CA2	107	15.20 ± 7.37
ITE Δ PGY1-CA3	94	16.23 ± 7.79

ECONOMICS, EDUCATION AND POLICY 3

Mentor-Mentee Program for Faculty Development at a Large Academic Department: The First-Year Survey

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INTRODUCTION: Mentorship is crucial for the development of academic faculty members. Effective mentorship to junior faculty members has resulted in faster academic promotion[1], increased confidence and academic retention[2], and improved academic performance[3]. Many industries have implemented a company-led structured mentor-mentee (MM) program with success[4]. Such a structured mentorship program, however, has rarely been adopted in academic institutions. In a large academic department, we launched a department-led Mentor-Mentee Program for academic anesthesiology faculty members. The first-year survey on both mentors and mentees was conducted.

METHODS: Given the department chair's endorsement, the Vice-Chair of Faculty Development designed the MM Program in 2019. First, a MM program website (https://www.academicprofessionaldevelopment.org/) was created featuring 1) the goal and objective; 2) the basics of mentorship and its difference from coaching, sponsorship, or connecting; 3) a recommended method of MM meetings, and 4) the handbooks for mentor and mentee. Grand Rounds on the mentorship and faculty promotion process were provided to all faculty members in 2019, and they were uploaded on the web. Second, the e-mail invitation to the MM program was sent to junior faculty members (Assistant Professors and newly hired Clinical Assistant Professors), which prompted them to choose up to three faculty mentors. Upon acceptance by the mentor, we initiated the formal MM relationship. The MM program was officially launched in February 2020. In April 2021, the first-year mentor and mentee anonymous survey was administered using Microsoft software. Fifteen external mentors were not included in the department survey.

RESULTS: The department has 211 anesthesiology physicians (76 academic faculty and 135 clinical faculty). Fifty-three mentees (39 Assistant Professors and 14 newly hired Clinical Assistant Professors) were invited as mentees, and 52 (98.1%) participated in the MM Program. Thirty-eight mentors [19 (50.0%) Associate/full Professors, 11 (28.9%) Assistant Professors, 8 (21.1%) Clinical Assistant/Associate Professors] were selected, and all agreed to serve as the mentor. Each mentor had a median of two (range 1-11) mentees. Forty-two (80.8%) mentees and 35 (92.1%) mentors completed the survey. 93% of mentees and 91% of mentors were satisfied with the current number of mentors/mentees. 83% of mentor-mentee pairs met at least bi-monthly. Overall satisfaction of the MM program was 76% (mentees) and 71.4% (mentors), while 21.4% (mentees) and 25.7% (mentors) were neutral. Perceived dissatisfaction for mentees was 1) lack of time or 2) misalignment of the mentor-mentee interest/stage/location/expertise. Perceived dissatisfiers for mentors were lack of mentee's proactiveness, time, and effectiveness. 91% of mentees and 100% of mentors felt mentorship was effective.

CONCLUSION: A department-led structured mentor-mentee program was initiated in a large academic department for junior faculty members. The first-year survey showed the majority of both mentees and mentors perceived the program as effective.

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ECONOMICS, EDUCATION AND POLICY 4

Assessing Diversity among Full-Time Anesthesiology Faculty in United States Medical Schools, 1970-2019

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INTRODUCTION: Studies have shown improved outcomes in racially concordant physician-patient interactions and a greater success rate for pipeline and mentorship programs with racially or ethnically concordant mentors. Over the last 10 years or more, there has been an increased focus on promoting diversity in the healthcare workforce[1,2]. Despite such attention in the workforce diversity, the anesthesiology faculty at United States (U.S.) Medical Schools have been homogenous in areas of race, ethnicity and sex. Here we evaluated the diversity trends in anesthesiology faculty relative to the US census data.

METHODS: This was a repeat cross-sectional study, based on the secondary analysis of data from the Association of American Medical Colleges (AAMC) Faculty Roster and United States Census data for the years between 1970 and 2019. We calculated the descriptive statistics of US allopathic medical school anesthesiology department faculty by sex, race, ethnicity and faculty rank.

RESULTS: The overall number of U.S. medical school anesthesiology faculty increased from 850 in 1970 to 9168 in 2019. This increase appears to have primarily been due to a steady annual increase seen in the number of White and Asian faculty, as the absolute number of Black and Hispanic faculty has changed at a slower rate (Figure 1). Also, compared to White and Asian faculty, Black and Hispanic faculty of both sexes are disproportionately represented in the lower academic ranks (Figure 2). Finally, the proportion of underrepresented in medicine (URM) anesthesiologists does not reflect their representation in the US population (Figure 3).

CONCLUSION: The growth of faculty in U.S. anesthesiology departments over the last 50 years has led to greater representation of diverse groups, however, more work needs to be done to improve racial, ethnic, and sex diversity trends in U.S. anesthesiology departments to reflect the U.S. population. Addressing URM faculty's lagging representation in higher academic ranks requires attention to be paid to mentorship, recruitment, retention, and promotion. Additionally, collaboration with an existing, or creation of, a committee on Diversity, Equity, and Inclusion is invaluable.

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Fig. 1. Proportion (%) of Faculty by Race and Sex Between 1970 and 2019.

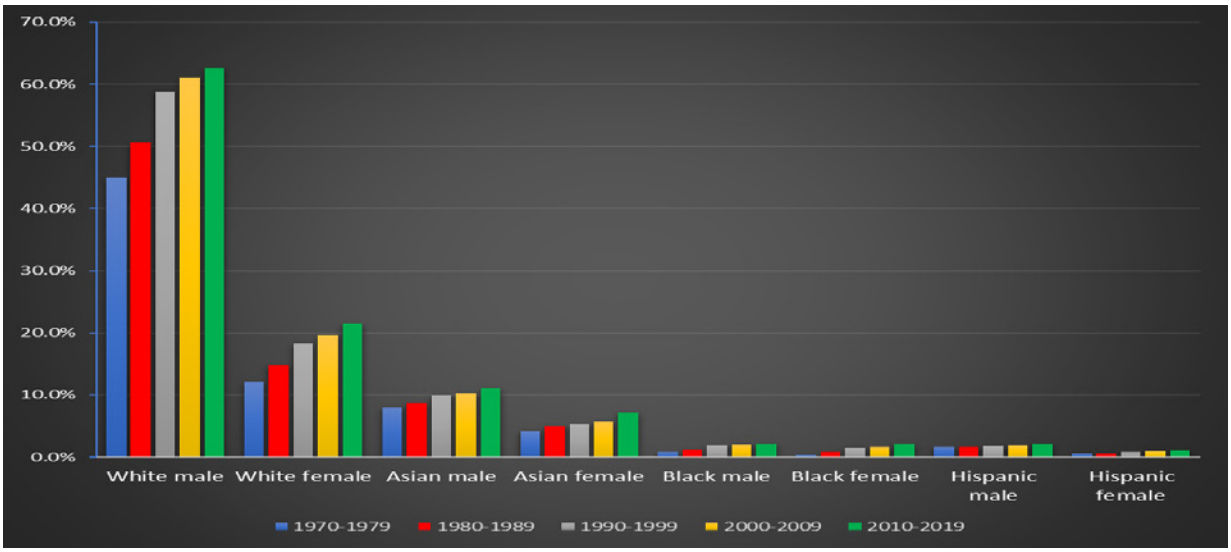


Fig. 2. Proportion (%) of Faculty by Race, Sex and Rank Between 1970 and 2019.

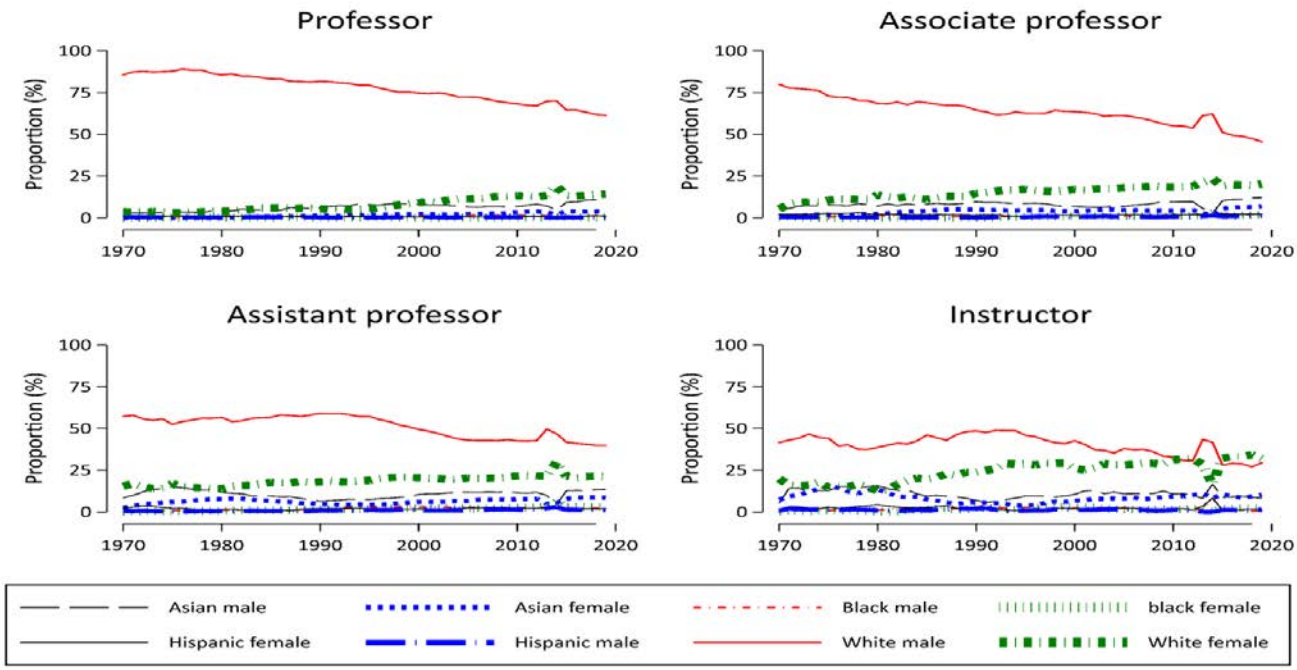
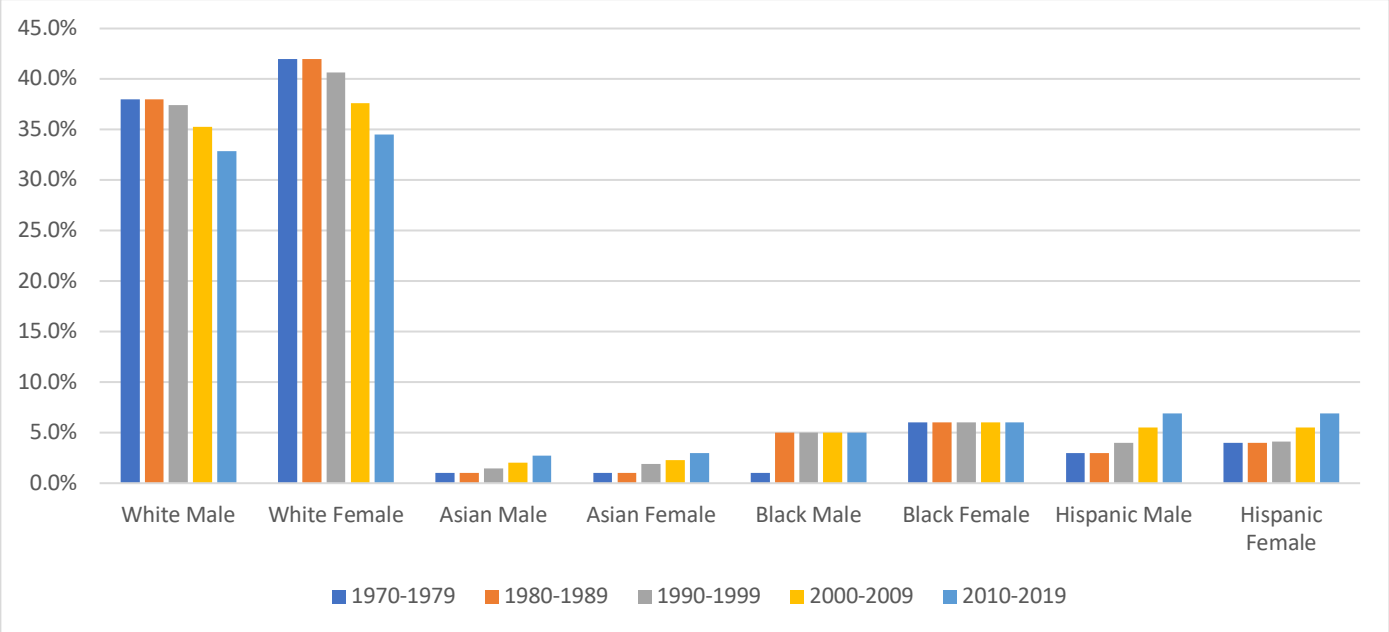


Fig. 3. Proportion (%) of United States Population by Race and Sex Between 1970 to 2019 (US Census Data).



ECONOMICS, EDUCATION AND POLICY 5

Understanding barriers to reducing financial and environmental waste in the OR - A Survey of Anesthesia Providers

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INTRODUCTION: The United States has the most expensive healthcare system amongst high-income countries and spends 16.8% of its gross domestic product on healthcare[1]. In the operating room (OR), high-cost medications and single-use plastics affect the economic and ecological sustainability of health systems[2-4]. Anesthesia care providers can play a critical role in reducing costs by selecting lower cost medications and supplies that also meet standards of care. However, there is limited data describing anesthesia providers' cost awareness of commonly used OR medications and supplies[5-8]. Our study aimed to understand anesthesia care providers' cost awareness and their preferences for choosing high-cost medications and single-use OR supplies over less-expensive and lower carbon-footprint alternatives.

METHODS: At a tertiary academic medical center, an anonymous, electronic survey was distributed to anesthesia attendings, CRNAs, residents, and anesthesia technologists. Participants were asked to estimate costs of 12 commonly used medications and single-use supplies from a list of options, and they were asked to provide reasons for selecting higher-cost supplies. The cost estimations were analyzed using descriptive statistics, while the free-text provider preferences for medications/single-use supplies were analyzed by semantic analysis to identify common influencers.

RESULTS: Out of 341 survey invites, we received completed surveys from 129 respondents (37.8%). The 'correct price estimation' on selected medications and single-use supplies ranged from 16% to 64%, with a mean of 31.1% (Table 1). Accuracy of price estimation failed to correlate with years of clinical experiences (R2 =0.021). Common influencers for selecting specific high-cost medications and single-use supplies over less expensive alternatives included concerns for medication efficacy, drug side effects, drug-drug interactions, patient comorbidities, and department culture.

CONCLUSION: We identified multiple factors, including concerns for patient safety, which may influence healthcare spending and increased waste in the OR. However, anesthesia care providers lack knowledge on the costs of OR medications and supplies. Effort should be made to incorporate cost awareness into resident and faculty education.

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Table 1: **Anesthesia care provider survey results**

N = 129	Actual Cost	% Correct (N = 129)	Most Estimate Cost	Most Estimate % (N = 129)
Most Estimate Low				
6-Port Nanoclave	$10.00 - $14.99	24%	$0.00 - $4.99	39%
P-Lyte (1L)	$5.00 - $9.99	29%	$0.00 - $4.99	34%
Sugammadex (200 mg)	$90.00 - $119.99	30%	$60.00 - $89.99	32%
Remifentanil (2mg)	$120.00 - $150.00	21%	$60.00 - $89.99	22%
Most Estimate High				
A-line Transducer Holder	$15.00 - $19.99	16%	$20.00 - $25.00	57%
Albumin 5% (500 ml)	$90.00 - $119.99	20%	$120.00 - $150.00	29%
Aprepitant 40mg PO	$30.00 - $59.99	23%	$120.00 - $150.00	26%
Most Estimate Correct				
T-piece connector	$20.00 - $25.00	64%		
LR (1L)	$0.00 - $4.99	55%		
Hotline Set	$20.00 - $25.00	49% *		
Primary IV Tubing	$5.00 - $9.99	36%		
Propofol (200 mg)	$5.00 - $9.99	30%		

Cost estimation of commonly used OR medications and single-use supplies are categorized into Estimate Low (cost underestimated), Estimate High (cost overestimated), or Estimate Correct (correct cost identified) group. Actual cost listed in range captures the cost of each item. *N=128.

ECONOMICS, EDUCATION AND POLICY 6

Identifying residents with medical knowledge gaps pre-residency: Do we need test scores?

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INTRODUCTION: The majority of anesthesiology programs are using USMLE Step 1 scores during the applicant selection process to identify qualified applicants[1]. Since USMLE 1 will be transitioned to pass/fail in Spring 2022, there are considerable concerns from residency programs about this change[2]. Amongst the concerns, the reduction in test information may decrease awareness of knowledge gaps by medical students and prospective educators, while still holding residency programs responsible for board certification pass success.[3] Significant knowledge gaps may not be obvious in Step 2 or until later in the anesthesiology residency, creating a significant disadvantage for the learners. To prepare our program for the impending change, we investigated the use of a pre-residency medical knowledge test to indicate potential knowledge gaps allowing learners to address them as early as possible. We hypothesized that a post-match, pre-residency knowledge test, consisting of USMLE STEP1 questions will correlate with USMLE test scores taken during medical school and predict anesthesia knowledge learning success as quantified by Anesthesia Knowledge Test (AKT) scores.

METHODS: Following IRB approval, we created a medical knowledge test, containing 100 multiple choice questions compiled from several USMLE Step 1 test preparation books. Three anesthesiologists identified anesthesiology relevant questions from the total content and created the test using the Delphi method. Following 2021 match, the incoming PGY-1 residents were invited to take the test ('UK Step1') before starting residency in July 2021. Test participation and results were processed independently from residency recruitment by the education specialist (AD). Data processing was handled by the education specialist until de-identification. All residents complete the 'AKTpre' at the beginning of the residency during orientation before July 1st, and on the last day of their first anesthesia month ('AKTpost', July 30th 2021). Data are shown as mean +/- SD. Linear correlations between all factors were calculated using Pearson's Correlation coefficient (IBM SPSS Statistics, version 27).

RESULTS: Eleven residents participated in this study out of a total of 15 matched PGY-1 residents. The USMLE Step 1 score mean was 232 +/- 11, USMLE Step 2 score mean was 244.8 +/- 14.9 (Figure 1). The average increase from Step 1 to Step 2 was 12.82 +/- 15.52, with 2 students experiencing a drop in USMLE scores from Step 1 to Step 2. Using AKT scores as anesthesia related knowledge indicators, AKTpre scores showed a strong correlation with Step 2 scores but not with Step 1 (Table 1). There was also a strong correlation between USMLE score increase (Delta USMLE = USMLE 2- USMLE 1) with AKTpre and AKTpost scores. Neither standardized knowledge test (USMLE step 1 or 2, AKTpre and AKTpost) correlated with the UK Step 1 performance. The correlations between AKTpre and USMLE Step 2 ($r=0.844$, $p<0.01$) but not with USMLE Step 1 ($r=0.032$) are shown in Figure 2.

CONCLUSION: Our data indicate that the USMLE Step 2 performance correlates well with anesthesia knowledge tests, administered early on in the anesthesiology residency (first PGY1 month). Post medical school/pre-residency screening for USMLE Step 1 knowledge gaps does not correlate with standardized knowledge test performance during medical school or AKT. Our findings support several conclusions: 1) without a USMLE Step 1 score, the USMLE Step 2 score will be sufficient to assess anesthesia relevant medical knowledge status; 2) medical knowledge assessment at the beginning of anesthesiology residency is adequate to identify potential knowledge gaps; and 3) Screening for USMLE Step 1 knowledge appears unnecessary. Further directions are to use AKT pre /post for screening and offer additional educational tools/mentorship if indicated.

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Figure 1 USMLE 1 and 2 (CK) scores

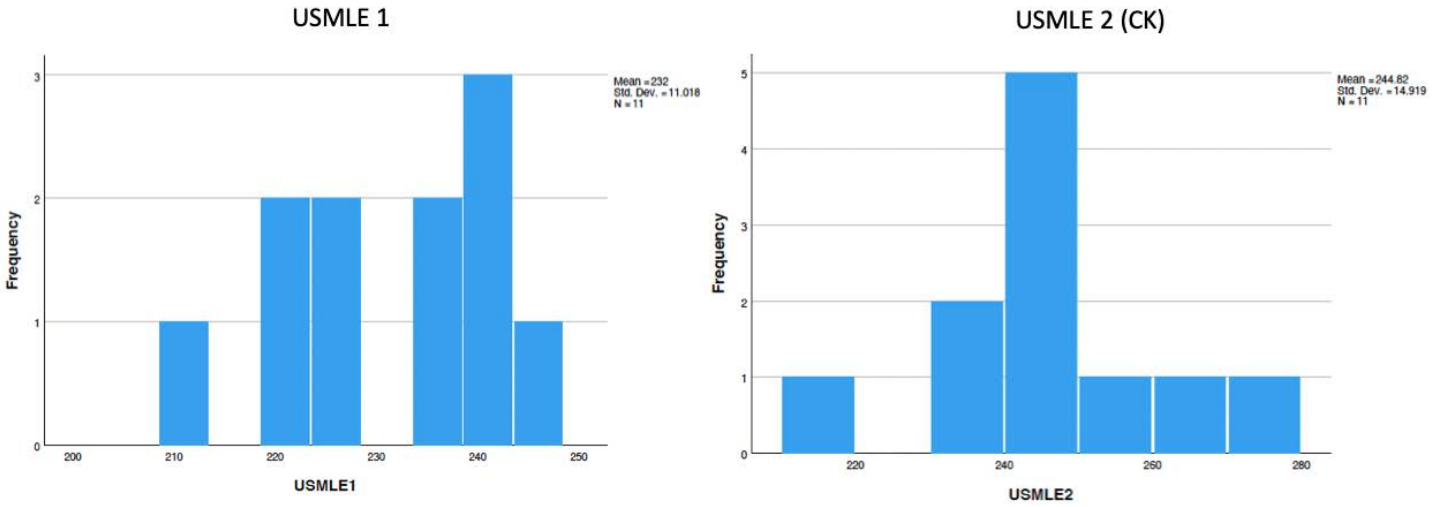
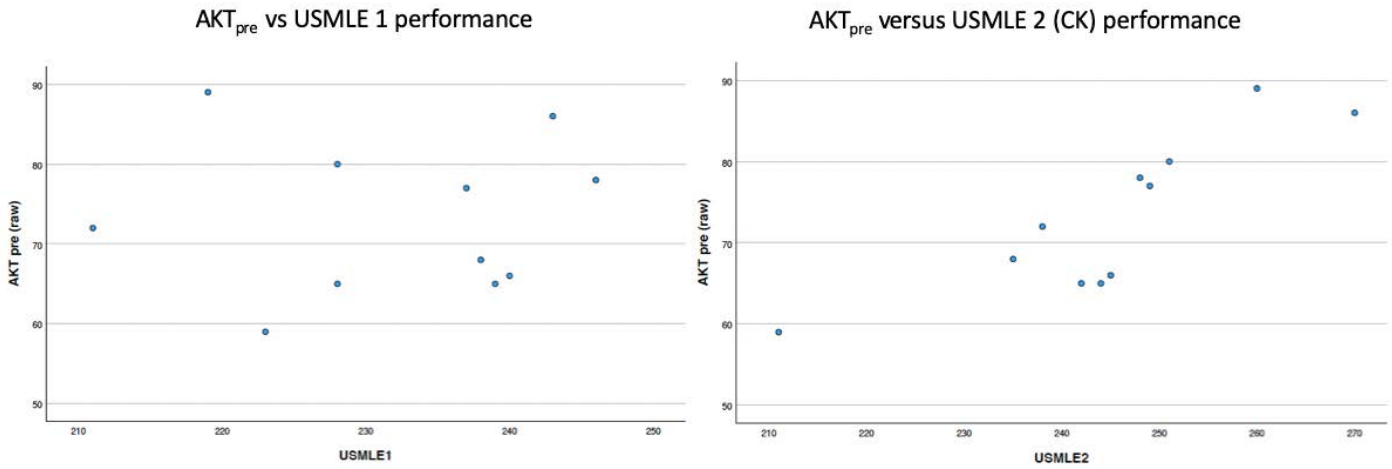


Figure 2
Correlation AKT pre versus USMLE



AKT$_{pre}$ versus USMLE 1: Pearson coefficient r=0.032 (n=11)

AKT$_{pre}$ versus USMLE 2: Pearson coefficient r=0.844 (n=11); p=0.001*

Table 1
Pearson Correlations (n=11)

		UK step 1	USMLE step 1	USMLE step 2	AKT pre	AKT post
USMLE step 1	Pearson correlation	- 0.025				
	P-value (2-tailed)	0.943				
USMLE step 2	Pearson correlation	0.052	0.314			
	P-value (2-tailed)	0.880	0.347			
AKT pre	Pearson correlation	0.191	0.032	0.844		
	P-value (2-tailed)	0.573	0.925	0.001*		
AKT post	Pearson correlation	0.108	- 0.313	0.647	0.684	
	P-value (2-tailed)	0.751	0.349	0.022*	0.020*	
Δ USMLE	Pearson correlation	0.067	- 0.408	0.739	0.788	0.873
	P-value (2-tailed)	0.844	0.213	0.009*	0.004*	0.001*

* P<0.05

ECONOMICS, EDUCATION AND POLICY 7

Effectiveness of Opioid Disposal Kits and Education Methods: A Systematic Review of Randomized Controlled Trials

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INTRODUCTION: More than 70,000 individuals died from opioid overdose in 2017, with over 17,000 deaths attributed to prescription opioid overdose.[1] Notably, of the 9.7 million individuals who misused opioids in 2019, more than 50% received opioids from a friend or family member.[2] Leftover prescription opioids create a reservoir of unused pills that are vulnerable to misuse and diversion. This study aims to determine the effectiveness of two interventions, patient education through verbal or written instruction and opioid-inactivating disposal kits, on opioid disposal rates among patients with leftover prescription medication.

METHODS: A systematic review was performed using PubMed, Scopus, and Cochrane databases for studies describing prescription opioids and opioid disposal methods. Search terms included 'opioids' and 'disposal', 'take back', 'disposal kit', 'opioid diversion', or 'buyback'. Using the systematic review tool Covidence, 476 unique studies were identified. Inclusion criteria included randomized controlled trials (RCTs) involving human subjects in the United States from January 1999 to August 2021. Primary or secondary outcomes included measurement of opioid disposal rate as a result. Two independent reviewers screened study abstracts and titles, reviewed full text, extracted relevant data, and assessed the quality of the studies.

RESULTS: Nine RCTs fulfilled inclusion criteria and collectively included 1,814 patients (Figure 1). In total, 591 patients comprised the control group, 851 received educational intervention, and 372 received an opioid disposal kit. There were no statistically significant age or gender differences for the three groups (Table 1). There was a high risk of bias in blinding of participants and personnel across all studies (Figure 2, 3). Eight trials followed patients up to 6 weeks postoperatively, while one trial followed medical or surgical patients who received short-term (≤7 days) opioid prescriptions (Table 1). One study was not included in the analysis of disposal rate due to reporting of intended disposal and actual disposal rate as a single outcome. The average opioid disposal rate was similar in the control group (30.50%) and the education group (30.85%). Provision of an opioid disposal kit was associated with the highest rate of disposal (51.88%), with a 21.38% increase in disposal participation compared to the control group (Table 2).

CONCLUSION: Our findings suggest that providing an opioid disposal kit increases patient participation in disposing of unused opioids prescribed for short-term use. Patient education minimally influenced patient behavior, suggesting that verbal or written patient instruction does not increase participation in opioid disposal. Rather, widespread distribution of opioid disposal kits could serve as an effective, actionable measure to improve the safe disposal of unused prescription opioids and therefore decrease opioid misuse and diversion in the community.

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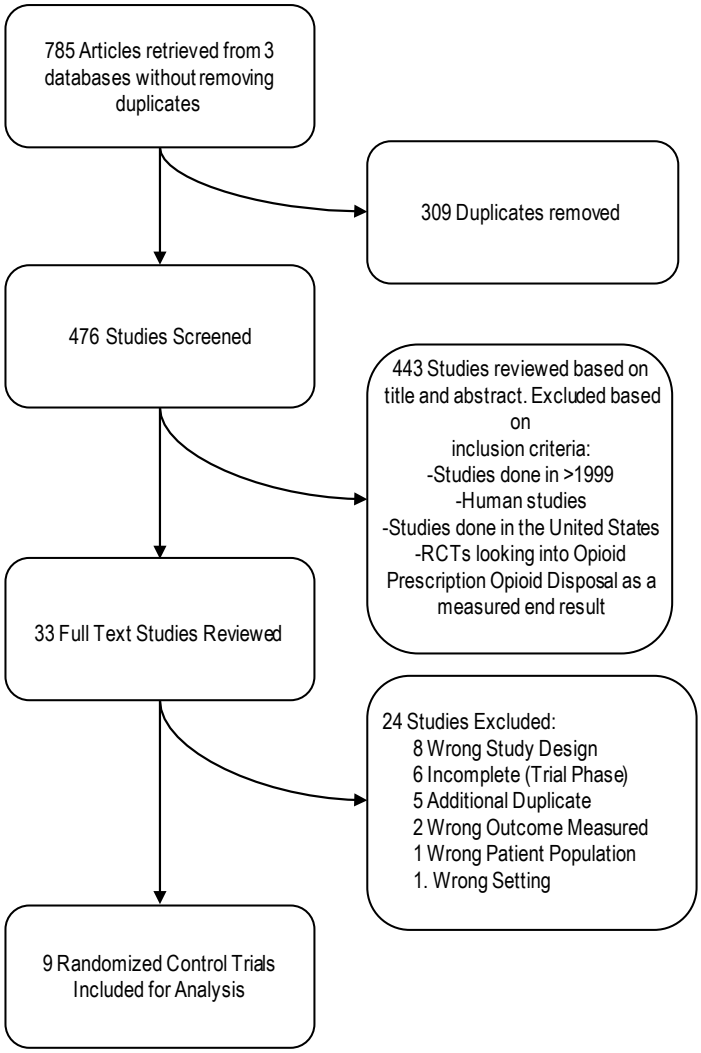

Figure 1. PRISMA flow chart of literature selection process

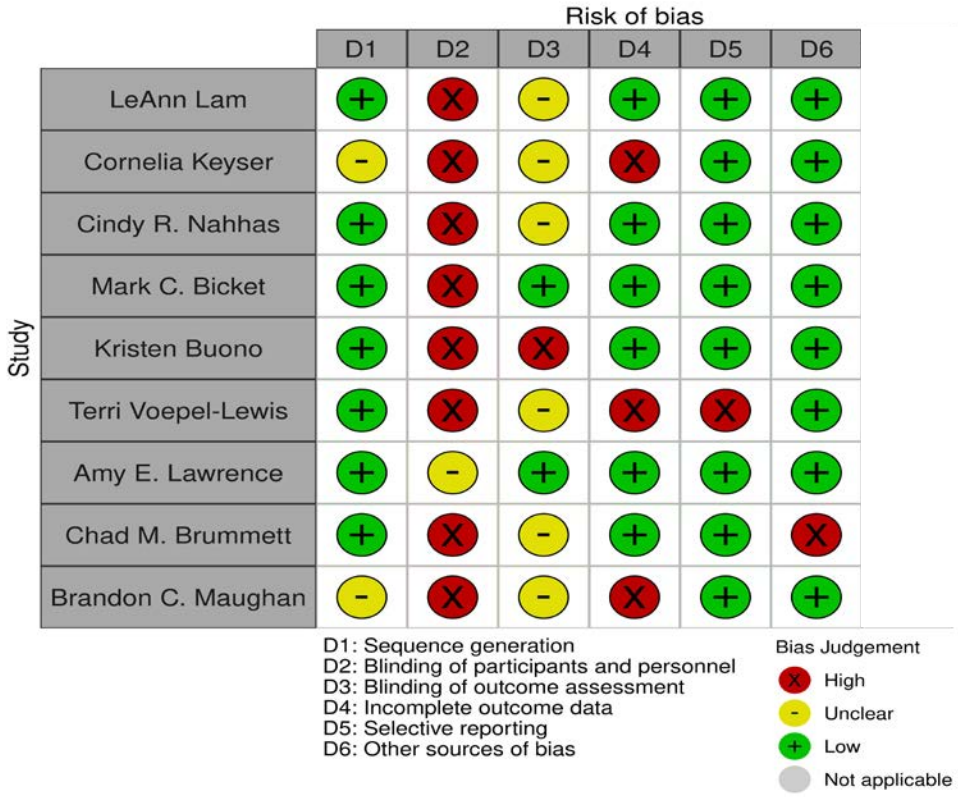

Figure 2. Risk of Bias Summary

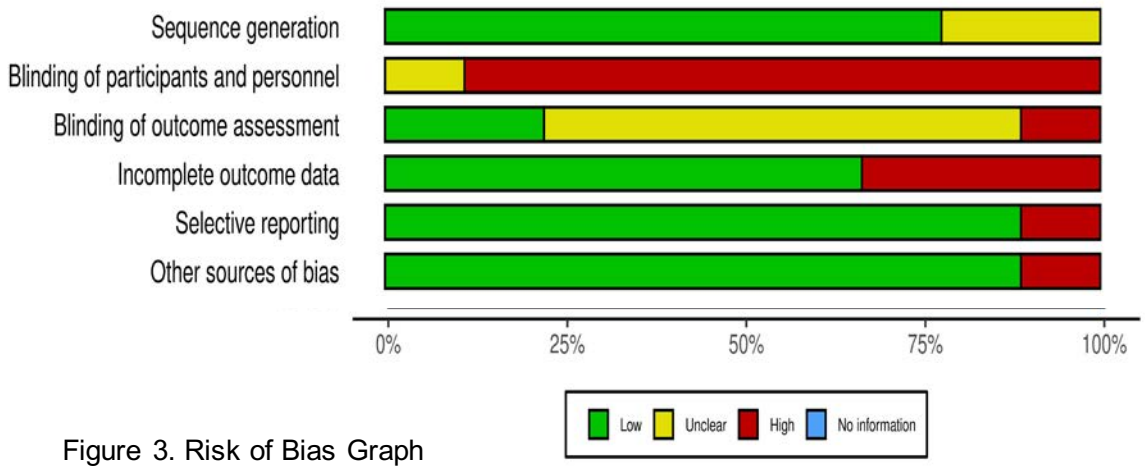

Figure 3. Risk of Bias Graph

Table 1. Description of randomized controlled trials included in systematic review

First Author	Year	Intervention Arms	Surgical Specialty	Total # of Patients (Analyzed*)	% Sex	Age	Method of Obtaining Data	Follow up time
LeAnn Lam	2021	Education	Cesarean Sections	162	100 % Female	No statistically significant difference between groups	Email, text message or phone call	2 weeks
Cornelia Keyser	2020	Disposal Kit	Outpatient Foot and Ankle Surgery	47	No statistically significant difference between groups	Not provided	Survey	6 weeks
Cindy R. Nahhas	2020	Education: 1.Pamphlet 2.Pamphlet & Text Message	Total hip arthroplasty Total knee arthroplasty Unicompartmental knee arthroplasty	489	No statistically significant difference between groups	No statistically significant difference between groups	Survey	6 weeks
Mark C. Bicket	2021	1.Education 2. Education & Disposal Kit	Nonsurgical (Any patient with short term opioid prescription)	227	No statistically significant difference between groups	No statistically significant difference between groups	Phone survey	6 weeks
Kristen Buono	2021	Education (Counseling)	Pelvic Reconstruction Surgery	101	100 % Female	No statistically significant difference between groups	Survey	2 weeks
Terri Voepel-Lewis	2020	1.Education 2.Disposal Kit 3.Education and Disposal Kit	Various	368	No statistically significant difference between groups	No statistically significant difference between groups	Survey	7-14 days
Amy E. Lawrence	2019	Disposal Kit	ENT or Urology	154	No statistically significant difference between groups	No statistically significant difference between groups	Survey	2 & 4 weeks
Chad M. Brummett	2019	1.Education (Pamphlet) 2.Disposal Kit	Outpatient Surgical Procedures	208	No statistically significant difference between groups	No statistically significant difference between groups	Phone or email	4-6 weeks
Brandon C. Maughan	2016	Education	Dental	58	No statistically significant difference between groups	No statistically significant difference between groups	Text message	Postop days 1-7, 14, 21

*We eliminated patients who did not have left over opioids

Table 2. Average disposal rate in control, educational, and disposal kit intervention arms of included randomized controlled trials.

Study	Total Analyzed	Control				Educational Intervention				Disposal Kit Intervention				
		Patients Analyzed	Disposed	Proper Disposal	Improper Disposal	Patients Analyzed	Disposed	Proper Disposal	Improper Disposal	Patients Analyzed	Disposed	Proper Disposal		Improper Disposal
												Total	Disposal kit	
Brummett et al., 2019	208	63	28.57%	88.89%	11.11%	75	33.33%	96.00%	4.00%	70	57.14%	95.00%	87.50%	5.00%
Bicket et al., 2021	227	63	38.10%	41.67%	58.33%	91	25.27%	47.83%	52.17%	73	28.77%	66.67%	N/a	33.33%
Voepel-Lewis et al., 2020	368	122	18.85%	N/a	N/a	120	30.83%	N/a	N/a	126	34.13%	N/a	N/a	N/a
Lawrence et al., 2019	154	77	70.13%	92.59%	7.41%					77	87.01%	98.51%	89.55%	1.49%
Keyser et al., 2020	47	21	38.10%	100%	0%					26	84.62%	100%	100%	0%
Nahhas et al., 2020*	306	89	17.98%	50.00%	50.00%	217	21.20%	91.30%	8.70%					
Nahhas et al., 2020**	183					183	31.15%	84.21%	15.79%					
Buono et al., 2021	101	46	32.61%	93.33%	6.67%	55	63.64%	91.43%	8.57%					
Maughan et al., 2016	58	27	Intended + Disposed n=8			31	Intended + Disposed n=16							
Lam et al., 2021	162	83	16.87%	100%	0%	79	37.97%	100%	0%					
Total	**1814**	**591**	**30.50%**	**80.54%**	**21.48%**	**851**	**30.85%**	**86.57%**	**13.43%**	**372**	**51.88%**	**93.33%**	**90.70%**	**6.67%**
% Change from Control							**0.36%**	**6.04%**	**-8.06%**		**21.39%**	**62.84%**		**-14.81%**
% Change from Education											**21.03%**	**6.76%**		**-6.76%**

* = Pamphlet intervention, ** = Pamphlet + Text interventions; N/a = Data not reported

ECONOMICS, EDUCATION AND POLICY 8

Performance Frontiers in Operating Room Management: A Multi-Institutional Comparative Analysis

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INTRODUCTION: As complex adaptive systems, the operational outcomes in the perioperative services are path-dependent based on a myriad of interactions between surgeons, anesthesiologists, and nurses[1]. As a method of visualizing and analyzing basic operating room (OR) management metrics, performance frontiers have previously been used to model the operational implications of changing release times, benchmark different anesthesia environments, and assess the impact of Acute Care Surgery tactical allocations[2,3]. In this study, we apply a two-objective framework to operating room management data from three academic centers and show how tactical decisions shape operating room efficiency.

METHODS: The following monthly aggregated OR management metrics were extracted from two institutions (Institution A, Institution B) using WiseOR® (Palo Alto, CA) and one institution (Institution C) using the Anesthesia Dashboard platform:

1. After Hours minutes: Operative time utilized by a service after hours (17:30 to 7:30 Monday to Friday at Institution A; 17:00 to 7:00 at Institution B, 15:00 to 07:00 at Institution C).
2. Opportunity Unused minutes: Available operative time within respective service block allocations where services can perform additional cases but did not.
3. Non-Opportunity Unused minutes: Available operative time within respective service block allocations in which additional cases cannot be performed based on median case times.

Under-utilized time and over-utilized time were then calculated as follows:

1. Under-utilized time = (Opportunity Unused minutes) + (Non-Opportunity Unused minutes)
2. Over-utilized time = After Hours minutes

Performance frontiers representing the operational efficiency of each institution were built in GraphPad Prism 9 (San Diego, CA). Monthly aggregates of over-utilized time and under-utilized time as defined above were plotted against each other. Performance frontiers were estimated and represented by the line Y=C/X, where Y is represented by the under-utilized time, X is represented by the over-utilized time, and the constant C is represented by the minimum values for each respective value in the equation C = XY. All data and calculations were maintained in Microsoft Excel (Redmond, WA).

RESULTS: The performance frontier representing the Institution A data lies closer to the origin than the performance frontiers representing the Institution B and Institution C data. The optimal Pareto front for the Institution A data reflects the relative proximity of individual monthly data points to the origin.

CONCLUSION: The performance frontier for Institution A is more efficient than the performance frontiers for Institution B and Institution C. The overall efficiency for Institution A can be attributed to the smaller patient volumes, lower number of operating rooms, and qualitatively different patient populations. The inherent difference in operational efficiencies implies that there might be a limit to scale for organizations with large perioperative services. Future studies should elucidate these limits. Clinical directors must be privy to the implications underlying performance frontiers to make changes regarding the efficiency of their respective services.

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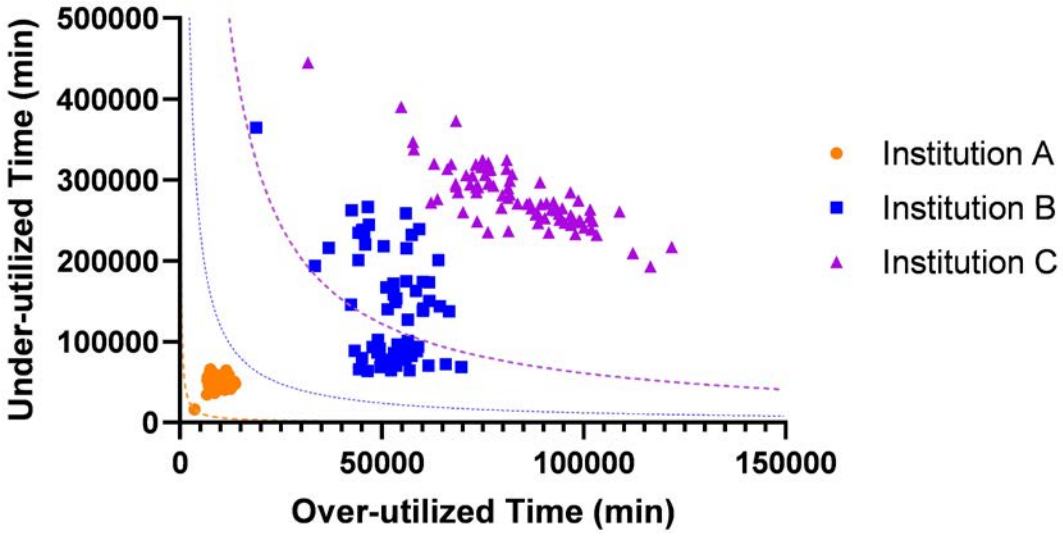

Fig. 1

ECONOMICS, EDUCATION AND POLICY 9

Interrupted Time Series Analysis to Assess the Environmental Impact of Removing Desflurane from Routine Use at an Academic Medical Center

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INTRODUCTION: Inhalational anesthetic agents are potent greenhouse gases[1]; in particular Desflurane and Nitrous Oxide. Given that approximately 5% of an acute hospital's carbon footprint is due to inhalational anesthesia[2], efforts to reduce these emissions have increased. In February 2020 our hospital removed Desflurane from routine usage, following a locally published study which failed to show evidence for its clinical benefit[3]. We therefore anticipated a significant reduction in our equivalent carbon dioxide emissions, which we assessed using an interrupted time series analysis based on monthly purchases of inhalational agents at our academic medical center.

METHODS: After an IRB determination that the project did not constitute human subject research, we collected hospital purchase data for Isoflurane, Sevoflurane, Desflurane and Nitrous Oxide between January 2017 and August 2021. Using the Practice Greenhealth toolkit[4] we converted each months' purchases, and the total of all agents, into metric ton equivalents of carbon dioxide (MTCO2e). An interrupted time series analysis (from February 2020) was performed to assess whether the removal of Desflurane led to a reduction in our hospital's monthly emissions.

RESULTS: Following our intervention, the use and purchase of Desflurane ceased almost immediately, however, a significant reduction in our total monthly emissions was not seen (Table 1). We noted that prior to its removal, our use of Desflurane, and total emissions, were already falling (Figure 1). Interestingly, after our intervention we observed rising emissions which were almost entirely due to our increased use of Nitrous Oxide, although neither of these trends reached statistical significance. Additional variations observed during the study period included a statistically significant reduction in purchasing of Isoflurane and Sevoflurane in the post-intervention period. This may be due to the reduction in workload caused by the COVID-19 pandemic, but regardless, this finding is environmentally insignificant.

CONCLUSION: The removal of Desflurane from routine usage within our hospital did not lead to a reduction in emissions of MTCO2e over the study period. Our department's use of volatile anesthesia still resulted in emissions equivalent to a 155,000 mile car journey each month[5]. The overwhelming majority was due to increased Nitrous Oxide use in the post-intervention period, possibly the result of a balancing measure if providers were consciously using it instead of Desflurane. While there may be some clinical benefits for Nitrous Oxide[6], if we wish to continue to reduce our emissions, we need to consider further interventions to minimize its use and focus on the promotion of further measures known to reduce MTCO2e, such as low flow anesthesia, clinical decision aids, and increased regional and total intravenous anesthesia, whose environmental impact is lower than inhalational agents[7].

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Figure 1

Monthly emissions in MTCO2e during the study period for each agent and in total, with regression lines for both before and after the intervention

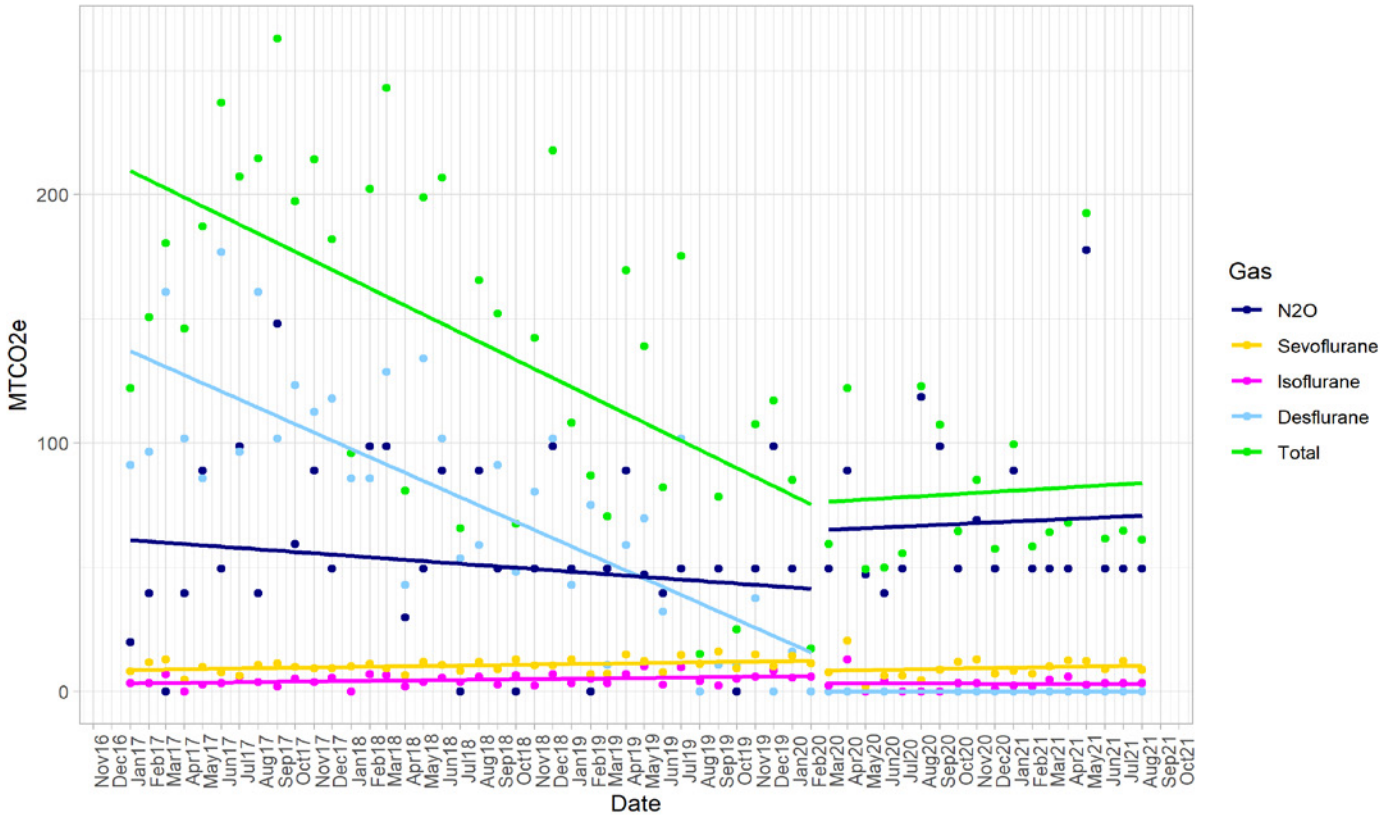

Table 1

Coefficients for the interrupted time series analysis with associated p values for each agent (except desflurane) and their associated emissions.

	Change In Intercept at Intervention (95% CI)	p Value	Change In Gradient After Intervention (95% CI)	P Value
Monthly Total	0.50 (-56.84 to 57.85)	0.99	4.07 (-0.61 to 8.75)	0.09
N2O	23.34 (-19.96 to 66.64)	0.28	0.86 (-2.67 to 4.40)	0.63
Sevoflurane	-4.08 (-7.64 to -0.52)	0.03	0.02 (-0.27 to 0.31)	0.89
Isoflurane	-2.96 (-5.88 to -0.04)	0.05	-0.09 (-0.33 to 0.15)	0.44

ECONOMICS, EDUCATION AND POLICY 10

Anesthesiologist Ethnicity and Sex Influence Patient Perceptions of Physician Competence

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INTRODUCTION: Explicit and implicit biases affect patient perceptions of their physician and influence the physician-patient relationship. We previously demonstrated that factors such as a physicians age, sex and body language influence patient perception of anesthesiologist.[1,2] However, the effect of ethnicity on patient perceptions has not been studied previously. In this follow-up study, we hypothesized that patients display preferences for physicians based on sex and ethnicity and that white male anesthesiologists would be preferred over black female anesthesiologists.

METHODS: 300 consecutive adult, English-speaking patients were recruited in the Preanesthesia Evaluation and Testing Center. Patients were randomized (150 per group) to view a set of 4 pictures with paired audio recordings in random order. Each picture displayed for 90 seconds each featured either a white male, black male, white female, or black female anesthesiologist with a paired audio recording of an actor reciting the same script describing general anesthesia. Patients ranked each anesthesiologist on confidence, intelligence, and likelihood of choosing the anesthesiologist to care for their family member. Patients also chose the one anesthesiologist who seemed most like a leader.

RESULTS: 300 patients viewed the picture with associated audio recording and completed the study questionnaire. Black anesthesiologists had greater odds of being ranked more intelligent (odds ratio, 1.81; 95% CI, 1.39 to 2.36; $P < 0.0001$), more confident (odds ratio, 1.44; 95% CI, 1.10 to 1.68; $P = 0.008$), were more likely to be chosen to care for a family member (odds ratio, 1.85; 95% CI, 1.14 to 2.43; $P < 0.0001$) and had greater odds of being considered a leader (odds ratio, 1.39; 95% CI, 1.08 to 1.20; $P < 0.0001$) when compared with white anesthesiologists. Female anesthesiologists had greater odds of being ranked more intelligent (odds ratio, 1.34; 95% CI, 1.07 to 1.68; $P = 0.01$) and more likely to be chosen to care for one's family member (odds ratio, 1.55; 95% CI, 1.25 to 1.92; $P < 0.001$) compared with male anesthesiologists. These findings were consistent even after adjusting for the respondents' age, sex and ethnicity.

CONCLUSION: Patients display preferences for certain anesthesiologists. Patients preferred black anesthesiologists on the measures of confidence, intelligence, likelihood of choosing the anesthesiologist to care for a family member and leadership. Patients also preferred female anesthesiologists on the measures of intelligence and choice for family care. Understanding how these preferences influence physician-patient relationships may lead to improved cultural competency and better patient outcomes.

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ECONOMICS, EDUCATION AND POLICY 11

The Impact of Introducing Release Times for Operating Rooms on Surgery Waiting Times

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INTRODUCTION: Allocating limited operating room (OR) capacity is an important problem in perioperative service management. Typically, OR time is assigned in blocks to surgeons or surgical services and most perioperative services use release time policies to ensure an equitable distribution in the block allocations that are not utilized. Prior studies have not analyzed how the introduction of such policies affects surgery waiting times, an important indicator of patient access. This study aims to fill this gap using data from the University of Vermont Medical Center (UVMMC).

METHODS: The dataset comprised a census of all 17,004 records for all surgeries performed at UVMMC from May 1, 2018, to August 31, 2019. No release time was in place prior to May 1, 2019, whereas thereafter, UVMMC adopted a 7-day release policy for all specialties (adopters) except acute care surgery, orthopedic trauma, and cardiothoracic surgery and orthopedic hand surgeries (non-adopters). We evaluated the impact of the new release policy on the waiting time for surgery, i.e., the number of days from which a surgery was scheduled to the date that it was performed. The intervention group comprised surgeries performed in August 2019 and scheduled from May 1, 2019. The control group used in our base-case analysis comprised surgeries that were performed in August 2018 and scheduled from May 1, 2018. As a robustness check, we investigated an expanded control group comprising surgeries that were performed between April 30, 2018, to August 31, 2018, and scheduled at most four months prior to the surgery date. We performed subgroup analyses to investigate how changes in mean waiting time differed between adopters vs non-adopters and elective vs non-elective surgeries. Two-tailed t-tests were used to assess mean differences.

RESULTS: The results of the main analysis showed that the introduction of the release time policy was associated with a significantly shorter waiting time at the 0.1 level (intervention = 21.6 days vs control = 27.5 days, $p = 0.061$). Corroborating results were found in the robustness check (21.6 vs 22.9 days vs, $p = 0.098$). Subgroup analyses suggested that the benefits of the 7-day release time policy were only enjoyed by specialties adopting this policy, which saw a significant decrease in waiting time at the 0.1 level between the intervention and control groups (24.4 vs 26.7 days, $p = 0.063$). No evidence of decreased waiting time was found among non-adopters (6.5 vs 7.8 days, $p = 0.364$). The new policy change benefited elective surgeries, which saw a significant reduction in waiting times at the 0.1 level (24.4 vs 26.6 days, $p = 0.073$). No evidence of a change in waiting times was found for non-elective surgeries (0.2 vs 0.3 days, $p = 0.424$).

CONCLUSION: Our results suggest that the introduction of a 7-day release policy can reduce waiting times for surgeries, especially for elective surgeries. Future work can validate the methodology and results at different institutions.

ECONOMICS, EDUCATION AND POLICY 12

Gender-Based Discrimination experienced by surgeons and anesthesiologists: a survey study on its prevalence, forms, perpetrators, and impact in the perioperative setting

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INTRODUCTION: Gender-based discrimination (GBD) has been well described in a variety of professions[1-4] and also in academic medicine.[5-8] Recent studies have detailed the experiences of surgical trainees[9,10] and faculty members[11,12] with GBD in the workplace; however, few explore GBD among attending surgeons and anesthesiologists. The sources of GBD for attending physicians is little studied but could be useful to inform interventions to address GBD. There is evidence suggesting a small number of individuals are responsible for a large portion of workplace misconduct through repeated offenses.[13,14] In our study, we hypothesized that surgeons and anesthesiologists would report a high level of GBD, that women would report a higher level of GBD, including sexual harassment, than would their male colleagues, and that we would observe the presence of repeat offenders.

METHODS: After exempt designation from our institution's review board, we invited all attending surgeons and anesthesiologists at a large academic medical center via departmental email listserv to complete a 15-minute survey on 'experience in OR environment'. REDCap was used to distribute the survey and collect and manage confidential data. The survey consisted of 30 initial items. Participants who indicated any experience with GBD at work received eleven additional items assessing the frequency, source, and impact of their experience, and whether they used available reporting mechanisms. De-identified responses from completed surveys were analyzed. Categorical responses were presented as frequencies and proportions and differences in responses between male and female participants were assessed with a chi-square or Fisher exact test, as appropriate. Ordinal responses were assessed with a Mantel-Haenszel chi-square test or exact test, as appropriate, to compare responses between men and women. Response rates in each category are visually presented with bar graphs. Continuous responses, such as values entered from a scroll bar are presented as median, inter-quartile range (IQR), after confirming with the Shapiro-Wilk test that the data did not follow a normal distribution. Differences in responses between women and men were assessed with a Wilcoxon Rank-Sum test. Statistical significance was defined as a twosided p-value < 0.05. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS: 125 of the 213 faculty members invited to participate completed all items of the survey, representing a 58.7% completion rate. 33.6% (42) of participants were women and 66.4% (83) were men. Refer to Table 1 for participant demographics. Overall, 72.8% of faculty reported experiencing GBD during their practice as an attending physician. More women (97.6%) experienced GBD compared to men (60.2%, $p<0.001$). Women experienced more GBD more frequently than men in all except one form studied (all $p<0.001$, Figure 1). Forty percent of all faculty (71.4% of women and 24.1% of men) reported experiencing sexual harassment at some point in their career as an attending, and 31% of women and 9.6% of men reporting sexual harassment at least once per year or more. Women experienced GBD most commonly from surgeons (78.4%) and patients (73%), whereas men experienced GBD most commonly from patients (45.5%) and nurses (36.4%, Figure 2). Forty-two percent of respondents indicated that at least one of the offenders was responsible for two or more of their experienced incidents of GBD. Significantly more women (66%) reported experience with repeat offenders than did men (18%, $p<0.001$.) Women reported their experiences with GBD had more severe impacts on their job satisfaction, personal risk of burn-out, personal well-being, self-doubt, and personal safety (all $p<0.006$) than did men (Figure 3).

CONCLUSION: This study uniquely demonstrates high levels of GBD experienced by both women and men attending surgeons and anesthesiologists working in the peri-operative setting. The primary source of the GBD for women was surgeons whereas for men it was patients. The majority of women reported the GBD they experienced was from repeat offenders, and this was in contrast to the men's experience. Women were significantly more likely to experience GBD and to experience the negative psychosocial effects. Since GBD

experiences impact physician job satisfaction, personal risk of burn-out, personal well-being, as well as quality of patient care, our study underscores the urgent need for intervention.

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Table 1. Demographic characteristics on survey respondents

Characteristic	N = 125
Gender, No. (%)	
Female	42 (33.6)
Male	83 (66.4)
Ethnicity, No. (%)	
Hispanic or Latino	6 (4.8)
Not Hispanic or Latino	115 (92.0)
Prefer not to answer	4 (3.2)
Race, No. (%)	
White	77 (62.6)
Black or African American	1 (0.8)
Asian	30 (24.4)
Multi-Racial	3 (2.4)
Other	4 (3.3)
Prefer not to answer	8 (6.5)
Leadership role in your department, No. (%)	
Yes	65 (52.4)
No	59 (47.6)
Specialty, No. (%)	
Surgeon	69 (55.7)
Anesthesiologist	54 (43.5)
Other	1 (0.8)
Years in clinical practice, mean (SD)	14.2 (11.0)
Age, mean (SD)	47.8 (10.2)

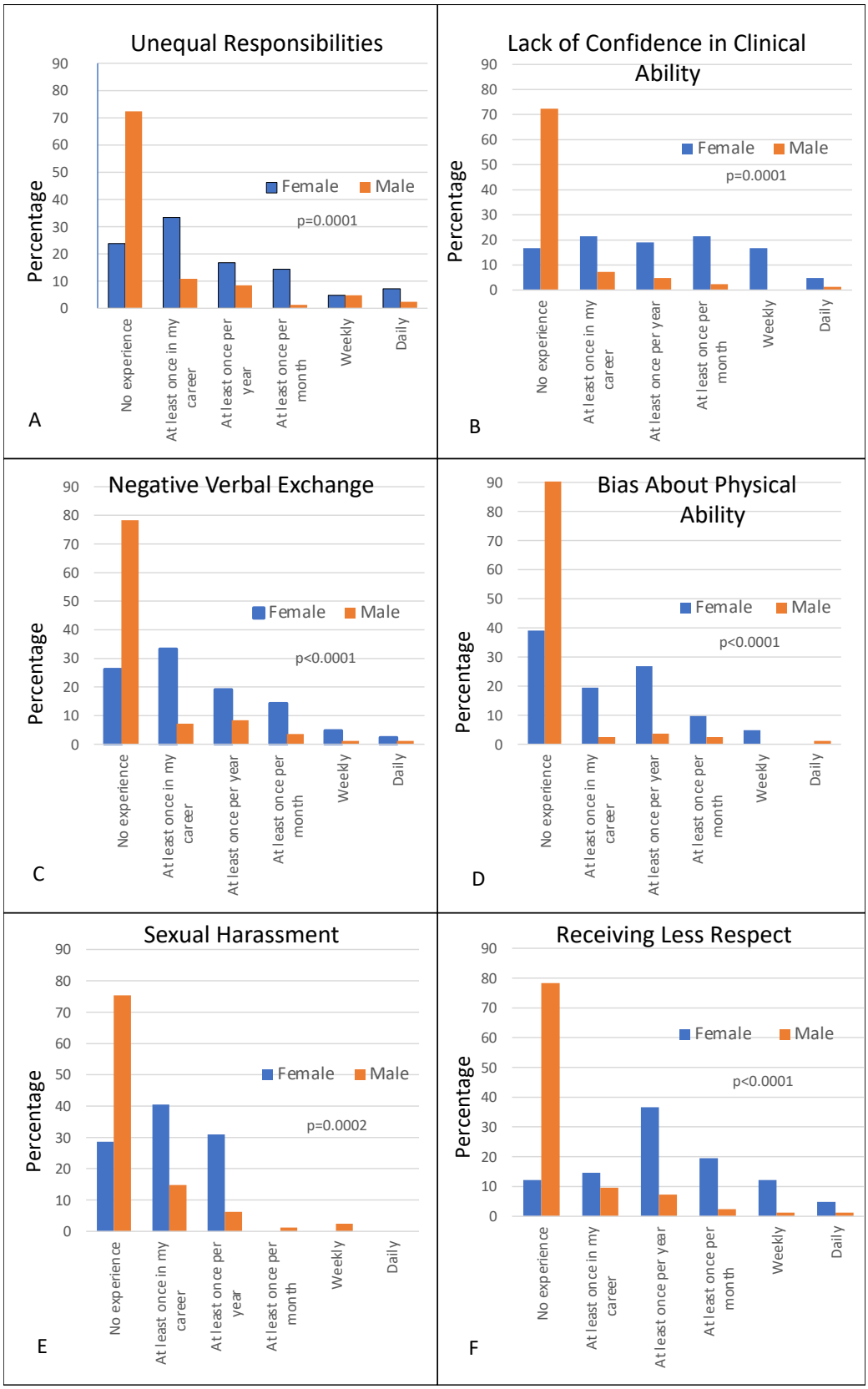

Figure 1. Forms of gender-based discrimination experienced by participants, as reported by men versus women. A. Received unequal (in quantity or significance) administrative or clinical responsibilities from your superiors. B. Perceived lack of confidence in ability to care for patients. C. Negative or inappropriate verbal exchange specific to gender. D. Gender bias about your physical ability to perform clinical work. E. Sexual harassment. F. Receiving less recognition or respect from other health care providers than colleagues of a different gender.

ECONOMICS, EDUCATION AND POLICY 13

The Impact of Language Barriers on Length of Hospitalization, Discharge Disposition, and Readmission Rates Following Craniotomy for Brain Tumor

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INTRODUCTION: Racial and socioeconomic disparities in health outcomes after craniotomy have been well documented.[1,2] However, while language barriers are known to be associated racial identities and socioeconomic markers, the independent effect of language barriers experienced by patients with limited English proficiency (LEP) on perioperative healthcare and outcomes after craniotomy is unclear. In this study we examined the association of LEP with surgical admission length of stay (LOS), discharge disposition, hospitalization cost, and rate of 30-day hospital readmission after craniotomy from brain tumor.

METHODS: This cohort study used electronic health data of patients age ≥18 years who underwent craniotomies for brain tumors from 2015-2019 at an urban academic medical center. Institutional review board approval was obtained with waiver of consent. Primary outcomes included LOS, total hospitalization cost, discharge disposition, and rate of 30-day hospital readmission. The primary predictor was LEP, defined as non-English language preference and need for interpreter services. Covariates were chosen a priori and included age, race/ethnicity, gender, body mass index (BMI), insurance provider, American Society of Anesthesiologists (ASA) status, surgical case length, and intraoperative estimated blood loss (EBL). Statistical comparisons between LEP versus English proficient (EP) groups were performed using χ^2, Fisher's exact, Wilcoxon rank-sum, and t tests as appropriate. Multivariable models were used to examine the association between LEP and primary outcome variables adjusting for covariates of interest. The distribution of length of stay and total hospitalization cost both exhibited overdispersion caused by right skew, which was accommodated using negative binomial regression.

RESULTS: Of the 2232 patients included in this study, 146 (6.5%) had LEP. Characteristics of patients are displayed in Table 1. Among other differences, LEP patients were more likely to have noncommercial insurance and a slightly higher EBL. In univariate analysis, LEP arthroplasty patients had longer LOS, higher costs of hospitalization, and were more likely to be discharged to a skilled care facility versus home. There was no difference in 30-day readmission rates by language status (Table 2). In negative binomial regression models, LEP was associated with both longer LOS (p=0.006) and higher hospitalization costs (p=0.002), adjusted for age, gender, race/ethnicity, BMI, primary insurance, ASA rating, case length, EBL, postoperative recovery location, and discharge disposition. Binomial logistic regressions were used to understand the relationship of language status with discharge disposition and 30-day readmission rates. LEP was associated with discharge to skilled care (OR 1.88, 95% CI 1.21, 2.91), but not with 30-day readmission (OR 0.85, 95% CI 0.45, 1.59) (Table 2).

CONCLUSION: LEP is an independent risk factor for extended LOS, higher cost of hospitalization, and discharge to skilled care after craniotomy for brain tumor. If further research confirms communication barriers as a mediator of delays or complications in perioperative care for craniotomy patients with LEP, the cost differences shown should incentivize investment in interventions that improve communication and care quality for LEP patients. These findings highlight an opportunity to reduce the gap of outcome disparities in brain tumor patients.

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Table 1: Characteristics of patients undergoing craniotomy for brain tumor, by English Proficiency

	Total sample (N = 2232)	**English Proficient (EP) (N = 2086)**	**Limited English Proficiency (LEP) (N = 146)**	
	% (N)	% (N)	% (N)	*P* value
Age, mean (SD), years	53.0 (15.3)	52.8 (15.2)	55.1 (15.3)	0.087[a]
Gender				0.20[b]
Male	50.3% (1,123)	50.7% (1,057)	45.2% (66)	
Female	49.7% (1,109)	49.3% (1,029)	54.8% (80)	
Race/Ethnicity				<0.001[b]
White	70.0% (1,563)	74.2% (1,547)	11.0% (16)	
Asian/Pacific Islander	10.6% (236)	8.6% (179)	39.0% (57)	
Hispanic	11.5% (256)	9.3% (194)	42.5% (62)	
Black	2.4% (54)	2.6% (54)	0.0% (0)	
Other/Unknown	5.5% (123)	5.4% (112)	7.5% (11)	
Language Spoken				<0.001[b]
English	93.2% (2,079)	99.7% (2,079)	0.0% (0)	
Spanish	3.1% (70)	0.1% (2)	46.6% (68)	
Chinese	2.2% (49)	0.0% (0)	33.6% (49)	
Other Non-English	1.5% (33)	0.2% (4)	19.9% (29)	
Primary Insurance Type				<0.001[b]
Private	54.8% (1,223)	56.9% (1,187)	24.7% (36)	
Public	19.1% (427)	17.4% (364)	43.2% (63)	
Medicare	26.1% (582)	25.6% (535)	32.2% (47)	
ASA Status				0.11[c]
ASA 1	5.5% (122)	5.6% (117)	3.4% (5)	
ASA 2	53.3% (1,189)	53.8% (1,122)	45.9% (67)	
ASA 3	39.6% (883)	39.0% (813)	47.9% (70)	
ASA 4	1.6% (36)	1.5% (32)	2.7% (4)	
BMI, mean (SD), min	27.3 (5.9)	27.3 (5.9)	27.1 (5.2)	0.075[a]
Case Length, mean (SD), min	239.5 (105.4)	239.3 (103.8)	242.6 (125.4)	0.72[a]
Postoperative Recovery Location				0.78[b]
ICU	84.4% (1,883)	84.4% (1,761)	83.6% (122)	
PACU	15.6% (349)	15.6% (325)	16.4% (24)	
Estimated Blood Loss, mean (SD), mL	162.4 (184.1)	159.1 (180.5)	209.1 (225.3)	0.002[a]

[a]Two sample t test. [b]Pearson's chi-squared. [c]Fisher's exact. [d]Wilcoxon rank-sum. Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; ICU, intensive care unit; PACU, post-anesthesia care unit; SD, standard deviation.

Table 2: Unadjusted and adjusted effect of limited English proficiency on postoperative outcomes for patients undergoing lower extremity total joint arthroplasty

Outcome Variables		**Univariate Analysis[a]**			**Adjusted multivariable models[d]**	
	Total sample (N = 2232)	**English Proficient (EP) (N = 2086)**	**Limited English Proficiency (LEP) (N = 146)**	**P value**	**Adjusted Coefficient (95% CI)**	**P value**
Length of Stay, days	3.0 (2.0-6.0)	3.0 (2.0-5.0)	5.0 (3.0-8.0)	<0.001[d]	0.15 (0.04, 0.26)	0.006
Total costs, $	23575 (19158-30538)	23422 (19109-30015)	27049 (21118-35689)	<0.001[d]	0.10 (0.03, 0.16)	0.002
					Adjusted OR (95% CI)	**P value**
Discharge to Skilled Facility	22.0% (490)	20.9% (436)	37.0% (54)	<0.001[b]	1.88 (1.21, 2.91)	0.005
30-day Readmission	8.8% (196)	8.7% (181)	10.3% (15)	0.51[b]	0.85 (0.45, 1.59)	0.605

[a]Univariate data are presented as median (IQR) for continuous or percent (n) for categorical measures. [b]Wilcoxon rank-sum. [c]Pearson's chi-squared. [d]Negative binomial regression models accommodated right skew exhibited by variables length of stay and total cost; the resulting coefficient gives the expected difference in the logs of the response variable for LEP versus EP. Logistic regression analyses determined odds ratios for dichotomous outcome variables. Coefficients and odds ratios were adjusted for race/ethnicity, age, gender, primary insurance, ASA status (proxy for medical comorbidities), body mass index, case length, estimated blood loss, and postoperative recovery location. Length of stay and cost coefficients additionally adjusted for disposition location. Reference group: English proficient patients. Abbreviations: OR, odds ratio; CI, confidence interval.

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A comprehensive analysis of direct hospital costs associated with the use of sugammadex versus neostigmine: A multicenter cohort study

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INTRODUCTION: Residual neuromuscular blockade (NMB) after surgery increases the risk of postoperative respiratory complications and may lead to higher costs of care during a patient's hospital stay[1-2]. Sugammadex can eliminate residual NMB and may mitigate associated complications and healthcare utilization, but the drug is more expensive than generic alternatives, and variably used[3-4]. In this study, we hypothesized that the use of sugammadex compared to neostigmine for reversal of NMB is associated with decreased direct hospital costs.

METHODS: Adult patients who underwent surgery under general anesthesia and received NMB agents and reversal with neostigmine or sugammadex at two tertiary academic healthcare networks in Massachusetts and New York between January 2016 and June 2021 were included in this retrospective cohort study. The primary exposure was the administration of either neostigmine or sugammadex and the primary outcome was direct hospital costs, defined as costs arising from patient-care related activities of specific departments (e.g., surgery, anesthesia, etc.), such as staffing, or supply costs attributed to the patient's hospital stay during which the index surgery was performed. To maintain confidentiality, we used proportionally modified direct hospital costs (multiplied by a fixed factor) for analysis; these were then log-transformed, and a multivariable generalized linear model adjusted for a priori defined patient demographics, comorbidities, intraoperative factors, year of surgery, and the healthcare network, was applied. Effect modification was assessed for the most prominent cost-driving factors based on clinical significance in the primary model. Model estimates with 95% confidence intervals (95% CI) are provided and a P-value of <0.05 was considered as statistically significant.

RESULTS: Among 79,474 patients included in this study (Figure 1), 59,643 (75.0%) received neostigmine and 19,831 (25.0%) received sugammadex for reversal of NMB. Sugammadex use varied by the healthcare network. In addition, surgical cases involving sugammadex administration were generally more complex, and the patients were older and had more comorbidities (Table 1). The proportion of sugammadex use versus neostigmine increased during the first years of the study period until arriving at a steady-state status in 2019 (Figure 2). The median (IQR) proportionally modified direct hospital costs were 21,449 Units (13,133-37,744) in patients who received neostigmine and 22,085 Units (12,549-43,245) in patients who received sugammadex. The primary model indicated good model calibration (Figure 3). In the full study cohort and after adjustment for a priori defined confounding factors, the use of sugammadex versus neostigmine was associated with a small but statistically significant decrease in proportionally modified direct hospital costs by 1.3% (adjusted model estimate: 0.987; 95% CI 0.978-0.995; P=0.002; Table 2A). This effect was modified by the healthcare network, admission type, surgical duration, preoperative hospital length of stay, preoperative stay in the Intensive Care Unit (ICU), and by a high American Society of Anesthesiologists (ASA) physical status classification. The use of sugammadex versus neostigmine was associated with decreased direct hospital costs in one healthcare network, in patients undergoing ambulatory surgery or shorter procedures, and in patients who had a lower ASA physical status classification, spent preoperatively less time in the hospital and no time in the ICU. By contrast, sugammadex was associated with higher direct hospital costs in more complex, hospitalized patients with longer preoperative stays (Table 2B). Additional adjustment of the primary model for these interactions confirmed the primary findings of decreased costs with sugammadex (Table 2A).

CONCLUSION: The effect of reversal agent (neostigmine versus sugammadex) on direct costs of perioperative care is small compared to other predictors such as hospital practice, comorbidities, procedural severity, and admission status, which modified the primary association tested. Our study suggests lower direct hospital costs associated with sugammadex versus neostigmine use in an ambulatory setting and among procedures of shorter

duration, whereas sugammadex was associated with higher costs among more complex hospitalized patients. The restriction of sugammadex, which may have had an impact on costs, could not be examined in this study.

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Figure 1. Study flow diagram.

MA, Massachusetts; NY, New York; ASA, American Society of Anesthesiologists; SPORC, Score for Prediction of Postoperative Respiratory Complications; NMBA ED95 dose, median effective dose of neuromuscular blocking agents required to achieve a 95% reduction in maximal twitch response from baseline.

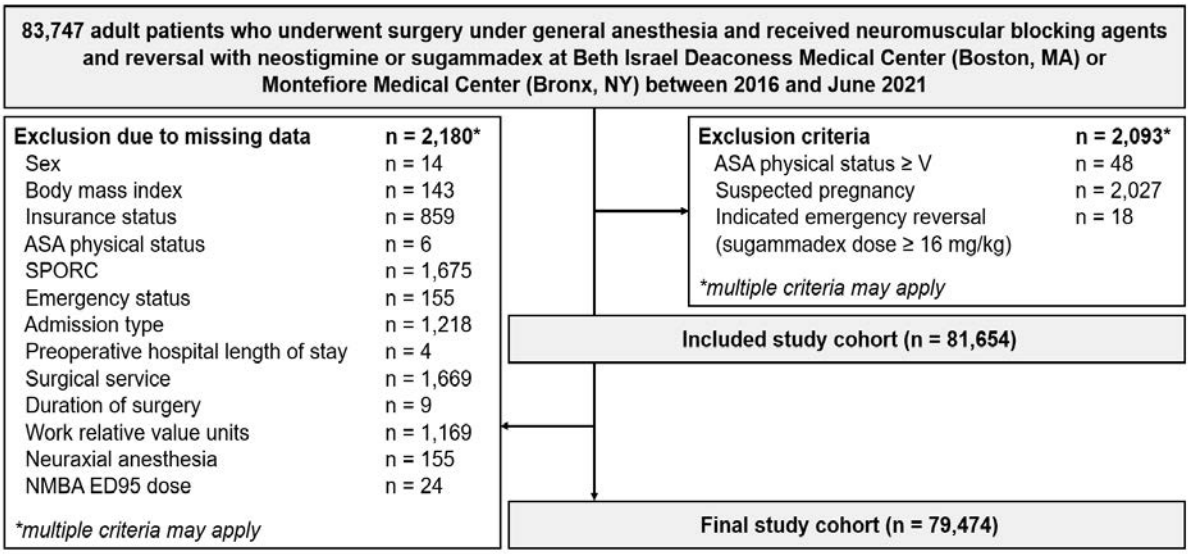

Figure 2. Change in reversal agent use in study cohort over years.

The use of sugammadex (light grey line) and neostigmine (dark grey line) is shown over the years included in this study cohort. The use of sugammadex versus neostigmine significantly increased after 2016 and has arrived at a steady-state status since 2019.

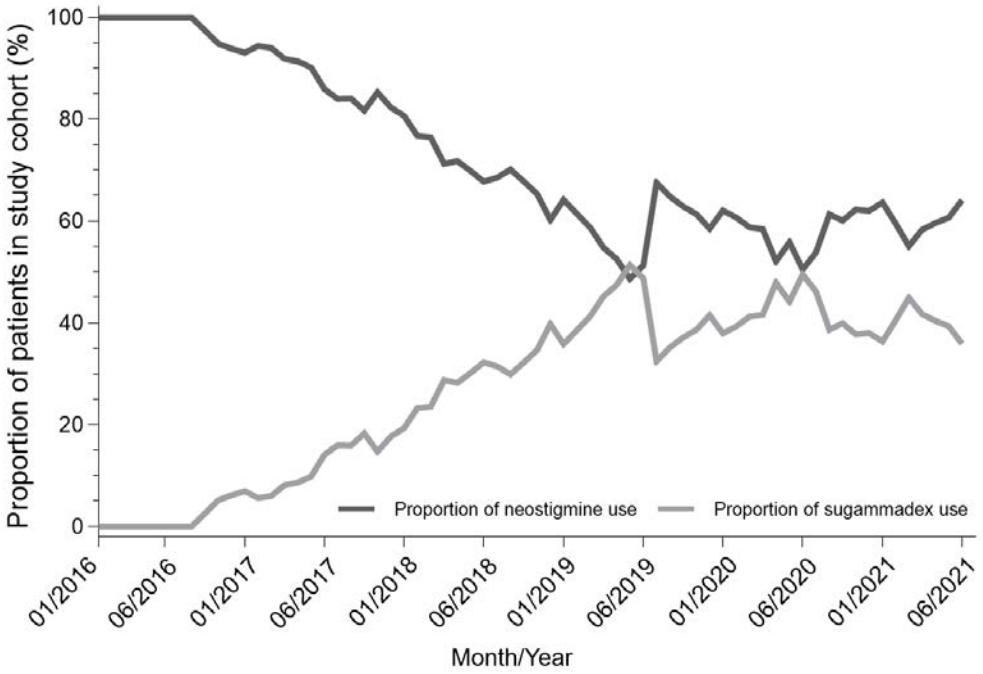

Figure 3. Calibration plot of the primary model.

Calibration plot of the primary generalized linear model showing the log-transformed primary outcome (log(proportionally modified direct hospital costs)) on the y-axis as a function of the predicted log-transformed proportionally modified direct hospital costs (predicted log((proportionally modified direct hospital costs)) on the x-axis. Each individual blue dot displays one observation in the study cohort. An optimal calibration is indicated by a linear increase at same values for x and y.

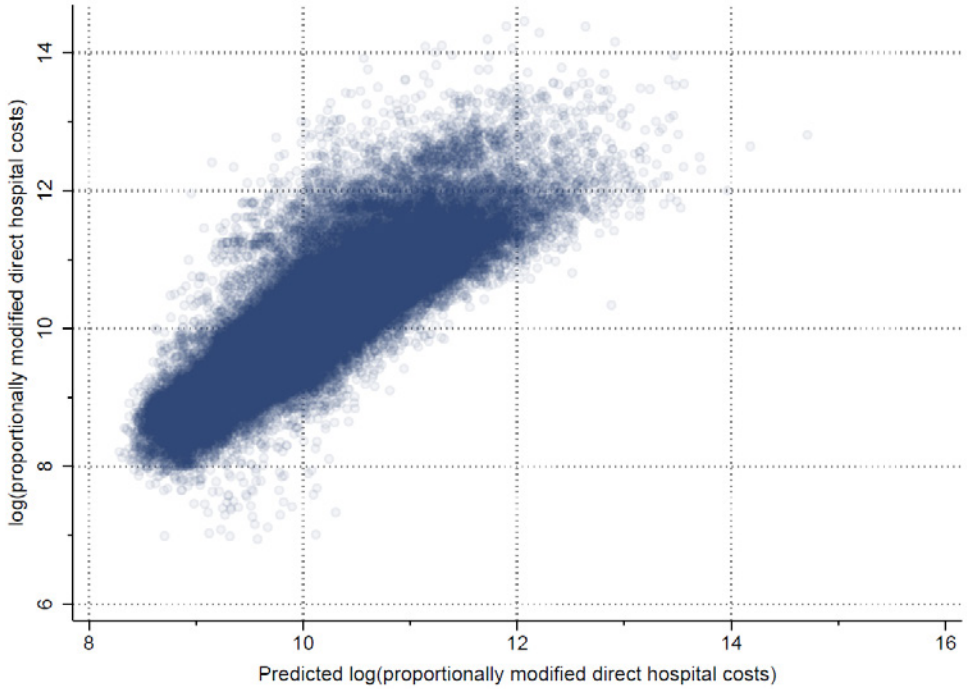

Table 1. Cohort characteristics.

ASA, American Society of Anesthesiologists; SPORC, Score for Prediction of Postoperative Respiratory Complications; NMBA ED95 dose, median effective dose of neuromuscular blocking agents required to achieve a 95% reduction in maximal twitch response from baseline.

Characteristic	Neostigmine (n = 59,643)	Sugammadex (n = 19,831)	Standardized difference
Primary exposure			
Neostigmine dose, mg	3.00 (3.00–4.00)	–	–
Sugammadex dose, mg	–	200.00 (200.00–300.00)	–
Demographics			
Age, years	52.66 ± 16.96	56.15 ± 16.91	-0.205
Sex, female	22,060 (37.0%)	8,360 (42.2%)	-0.106
Body mass index, kg/m^2	30.18 ± 7.60	30.15 ± 7.99	0.027
ASA physical classification III or IV	26,061 (43.7%)	10,904 (55.0%)	-0.227
Federal insurance	30,620 (51.3%)	10,353 (52.2%)	-0.017
Healthcare network			-0.320
Healthcare network 1	21,586 (36.2%)	10,282 (51.8%)	
Healthcare network 2	38,057 (63.8%)	9,549 (48.2%)	
Preoperative factors			
Opioid prescriptions within 90 days	13,015 (21.8%)	3,668 (18.5%)	0.083
Preoperative hospital length of stay			-0.001
0 days	48,324 (81.0%)	16,242 (81.9%)	
1 to 3 days	8,024 (13.5%)	2,404 (12.1%)	
4 to 7 days	2,266 (3.8%)	741 (3.7%)	
>7 days	1,029 (1.7%)	444 (2.2%)	
Emergency surgery	4,178 (7.0%)	14,31 (7.2%)	-0.008
Preoperative ICU stay	1,093 (1.8%)	488 (2.5%)	-0.043
Admission type			0.024
Ambulatory surgery	20,827 (34.9%)	7,222 (36.4%)	
Same-day admission	11,319 (19.0%)	3,589 (18.1%)	
Inpatient surgery	27,497 (46.1%)	9,020 (45.5%)	
Surgical service			-0.111
Cardiac surgery	2,448 (4.1%)	532 (2.7%)	
Colorectal surgery	1,034 (1.7%)	591 (3.0%)	
Ear, nose, and throat	3,326 (5.6%)	1,229 (6.2%)	
Gastroenterology	553 (0.9%)	411 (2.1%)	
General surgery	18,824 (31.6%)	4,922 (24.8%)	
Gynecology	8,496 (14.2%)	2,209 (11.1%)	
Neurosurgery	2,574 (4.3%)	1,532 (7.7%)	
Orthopedic surgery	5,998 (10.1%)	1,928 (9.7%)	
Other	740 (1.2%)	506 (2.6%)	
Plastic surgery	5,049 (8.5%)	1,397 (7.0%)	
Surgical oncology	561 (0.9%)	246 (1.2%)	
Thoracic surgery	1,460 (2.4%)	1,219 (6.1%)	
Transplant surgery	1,241 (2.1%)	637 (3.2%)	
Trauma surgery	1,233 (2.1%)	454 (2.3%)	
Urology	3,648 (6.1%)	1,281 (6.5%)	
Vascular surgery	2,458 (4.1%)	737 (3.7%)	
Comorbidities			
Charlson Comorbidity Index	0 (0–1)	1 (0–2)	-0.144
Cancer diagnosis during index stay	9,715 (16.3%)	3,752 (18.9%)	-0.069
Diabetes mellitus	9,588 (16.1%)	3,370 (17.0%)	-0.025
Severe diabetes mellitus	4,454 (7.5%)	1,810 (9.1%)	-0.060
Heart failure	3,624 (6.1%)	1,724 (8.7%)	-0.100
Coronary artery disease	6,334 (10.6%)	2,430 (12.3%)	-0.051
Atrial fibrillation	2,876 (4.8%)	1,427 (7.2%)	-0.100
Peripheral vascular disease	4,740 (7.9%)	1,811 (9.1%)	-0.042
Renal disease	5,123 (8.6%)	2,172 (11.0%)	-0.080
History of drug abuse	1,862 (3.1%)	681 (3.4%)	-0.018
History of smoking	7,721 (12.9%)	3,081 (15.5%)	-0.074
Chronic pulmonary disease	8,999 (15.1%)	3,304 (16.7%)	-0.043
SPORC Score ≥ 7	2,896 (4.9%)	1,426 (7.2%)	-0.098
Intraoperative factors			
Duration of surgery, min	156 (111–229)	142 (96–221)	0.076
Work relative value units	14.91 (10.05, 20.38)	14.04 (8.28, 20.38)	0.055
Neuraxial anesthesia	57 (0.1%)	6 (0.0%)	0.026
NMBA ED95 dose, mg	2.16 (1.55–3.10)	2.53 (1.83–3.67)	-0.291
NMBA type			0.046
Rocuronium only	59,437 (99.7%)	19,809 (99.9%)	
Vecuronium only	85 (0.1%)	8 (0.0%)	
Both	121 (0.2%)	14 (0.1%)	
Packed red blood cell units			-0.017
0	58,665 (98.4%)	19,452 (98.1%)	
1	473 (0.8%)	196 (1.0%)	
>1	505 (0.8%)	183 (0.9%)	

Data are expressed as frequency (prevalence in %), mean ± standard deviation, or median (interquartile range [25th-75th percentile], values separated by dash).

Table 2. Results.

2A. Effects of sugammadex versus neostigmine on direct hospital costs

Outcome	Neostigmine (n=59,643)	Sugammadex (n=19,831)	Adjusted Analysis [a]		P-value
			Model estimate (95% CI)	Change with sugammadex in % (95% CI)	
Primary analysis					
Proportionally modified direct hospital costs (n=79,474)	21,449 Units (13,133–37,744)	22,085 Units (12,549–43,245)	0.987 (0.978–0.995)	–1.3% (–2.3 to –0.5%)	0.002
Primary analysis with additional adjustment for all interactions [b]					
Proportionally modified direct hospital costs (n=79,474)	—	—	0.950 (0.934–0.968)	–5.0% (–6.6 to –3.2%)	<0.001

Proportionally modified direct costs data are expressed as median (interquartile range [25th-75th percentile], values separated by dash). Statistical analyses were performed using a multivariable generalized linear model of the gaussian family with identity link. For analyses, the primary outcome was log-transformed and used as dependent variable in the regression model. Model estimates are reported for regression analyses as results of the exponential transformation of model coefficients. 95% confidence intervals (CI) are provided and a P-value <0.05 was considered as statistically significant.

[a] Analyses were adjusted for a priori defined confounders, including patient demographics (age, sex, body mass index, insurance status), comorbidities (American Society of Anesthesiologists physical status classification, smoking status, drug abuse, renal disease, SPORC [Score for prediction of postoperative respiratory complications], cancer diagnosis during index stay, Charlson Comorbidity Index, diabetes mellitus, arterial hypertension, heart failure, chronic pulmonary disease, liver disease, cancer, tumor with metastasis, coronary artery disease, peripheral vascular disease), preoperative factors (healthcare network, emergency status, admission type, preoperative hospital stay, opioid prescriptions prior to surgery, preoperative stay in the Intensive Care Unit), and intraoperative factors (surgical service, duration of surgery, work relative value units, use of neuraxial anesthesia, neuromuscular blocking agent dose, packed red blood cell units) as well as the year of surgery and the proportion of surgical volume.

[b] Additional adjustment of the primary regression model for all interaction terms as provided in Table 2B.

2B. Effect modification analyses

	Neostigmine (n=59,643)	Sugammadex (n=19,831)	Adjusted Analysis [a]		P-value	P-for-Interaction
			Model estimate (95% CI)	Change with sugammadex in % (95% CI)		
Effect modification by healthcare network						
Healthcare network 1 (n=31,868)	17,189 Units (9,528–32,513)	17,949 Units (9,557–31,820)	0.913 (0.902–0.924)	–8.7% (–9.8 to –7.6%)	<0.001	<0.001
Healthcare network 2 (n=47,606)	23,619 Units (15,589–40,304)	28,488 Units (16,815–62,164)	1.059 (1.048–1.071)	5.9% (4.8 to 7.1%)	0.001	
Effect modification by ambulatory versus non-ambulatory surgery						
Ambulatory surgery (n=28,049)	11,948 Units (8,124–18,147)	11,370 Units (7,667–18,135)	0.935 (0.923–0.947)	–6.5% (–7.7 to –5.3%)	<0.001	<0.001
Non-ambulatory surgery (n=51,425)	28,903 Units (18,975–49,989)	32,044 Units (19,853–62,780)	1.018 (1.007–1.028)	1.8% (0.7 to 2.8%)	0.001	
Effect modification by surgical duration [b]						
Short surgical duration (n=48,666)	16,407 Units (10,505–24,208)	16,712 Units (9,930–27,818)	0.949 (0.939–0.959)	–5.1% (–6.1 to –4.1%)	<0.001	<0.001
Long surgical duration (n=30,808)	34,640 Units (22,904–56,213)	38,338 Units (23,800–71,034)	1.018 (1.004–1.032)	1.8% (0.4 to 3.2%)	0.012	
Effect modification by preoperative hospital length of stay [c]						
Short preoperative hospital stay (n=74,994)	20,415 Units (12,691–34,073)	20,857 Units (12,055–37,957)	0.982 (0.973–0.990)	–1.8% (–2.7 to –1.0%)	<0.001	<0.001
Long preoperative hospital stay (n=4,480)	68,873 (46,472–110,986)	90,361 (54,358–151,356)	1.090 (1.057–1.124)	9.0% (5.7 to 12.4%)	<0.001	
Effect modification by preoperative Intensive Care Unit (ICU) stay						
Preoperative ICU stay (n=1,581)	64,370 Units (45,994–107,492)	77,814 Units (46,273–153,527)	1.058 (1.007–1.111)	5.8% (0.7 to 11.1%)	0.025	0.005
No preoperative ICU stay (n=77,893)	21,134 Units (13,007–36,487)	21,614 Units (12,373–41,171)	0.985 (0.977–0.993)	–1.5% (–2.3 to –0.7%)	<0.001	
Effect modification by American Society of Anesthesiologists (ASA) physical status classification						
ASA physical status I or II (n=42,509)	17,800 Units (11,109–27,839)	16,833 Units (10,281–27,977)	0.976 (0.965–0.987)	–2.4% (–3.5 to –1.3%)	<0.001	0.006
ASA physical status III or IV (n=36,965)	29,358 Units (17,406–55,168)	29,423 Units (16,563–62,917)	0.996 (0.986–1.007)	–0.4% (–1.4 to 0.7%)	0.516	

Proportionally modified direct costs data are expressed as median (interquartile range [25th-75th percentile], values separated by dash). Statistical analyses were performed using a multivariable generalized linear model of the gaussian family with identity link adjusted for all covariates as indicated in the footnote of Figure 2A. For analyses, the primary outcome was log-transformed and used as dependent variable in the regression model. Model estimates are reported for regression analyses as results of the exponential transformation of model coefficients. 95% confidence intervals (CI) are provided and a P-value <0.05 was considered as statistically significant.

[a] For effect modification analyses, interaction terms were added to the primary regression model. Contingent on significant effect modification (P<0.05), linear combinations of the main effect and exposure-risk interaction were used to estimate the association between the potential effect modifier and proportionally modified direct hospital costs compared between patients who received neostigmine versus sugammadex.

[b] Long duration of surgery defined as surgeries with a duration of >3 hours.

[c] Long preoperative hospital length of stay defined as a hospital length of stay prior to surgery of >3 days.

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Disparities in Multimodal Analgesia among Thoracic Surgery Patients

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INTRODUCTION: Despite efforts within the United States to expand access to healthcare through policies such as the Affordable Care Act, widespread disparities in access and quality of care persist. In particular, postoperative pain is often undertreated in racial and ethnic minorities compared to their white counterparts[1,2]. Comprehensive postoperative/post-traumatic acute pain management has demonstrated the potential to decrease opioid side effects, improve pain scores, and reduce the morbidity and mortality from suboptimal analgesia (i.e. post-operative cognitive dysfunction, pneumonia, deep vein thrombosis)[3,4,5]. This study's aim is to explore the association of race, ethnicity, and payer in patients undergoing thoracic surgery with utilization of multimodal analgesia on day of surgery.

METHODS: This retrospective cohort study utilized the Premier database to collect data on thoracic surgery patients from 2008-2018. These patients underwent open thoracotomy, video assisted thoracoscopic surgery (VATS), or robot assisted thoracoscopic surgery (RATS). Patients were stratified by race, ethnicity, and payer while analyzing age, surgery type, gender, hospital characteristics, region, comorbidities, and analgesics. Race and ethnicity categories included non-Hispanic White (NHW), non-Hispanic Black (NHB), and Hispanic with each of these further broken down by payer including Managed Care and Medicaid. The mean, standard deviation, and the standardized absolute mean difference (SAMD) in relation to NHW Managed Care compared to NHB Medicaid patients was calculated. Statistically significant differences in demographics and outcomes were determined by an absolute SAMD > 0.1.

RESULTS: The analysis included 71,019 patients who underwent open thoracotomy, VATS, and RATS. Of those, 46,357 (65.3%) patients were NHW, 4,467 (6.3%) were NHB, and 3,060 (4.3%) were Hispanic. The team specifically reported disparities between managed care NHW patients (13,825; 19.5%) and Medicaid NHB (569; 0.8%) that highlight differences in race and payer. NHW Managed care patients received more thoracic epidurals (12% vs 8.8%, SAMD 0.105) and received care in Western regions (14.9% vs 4.6%, SAMD 0.355). NHB Medicaid patients received more opioids (19.1 vs 17.1 MME, SAMD 0.102), more gabapentin (12.5% vs 7.8%, SAMD 0.155), were younger (52.9 vs 57.7 y.o., SAMD 0.468), received care in teaching hospitals (66.3% vs 54.8%, SAMD 0.237), and received more care in Mid Western regions (29% vs 21.3%, SAMD 0.179). No differences were found among use of acetaminophen, non steroidal anti-inflammatories, ketamine, liposomal bupivacaine, and the use of at least one or two non-opioid analgesics.

CONCLUSION: Medicaid NHB patients tended to receive care in larger, teaching hospitals compared to managed care NHW patients. Managed care NHW patients received more thoracic epidurals which may have reflected those hospitals' ability to manage catheters after surgery on the wards. Medicaid NHB patients received non-opioid multimodal analgesia as frequently as managed care NHW, but more often with agents like gabapentin which new evidence has shown can increase risk of PPCs. Hospitals may be more likely to favor analgesic plans based on payer mix which may create disparities due to the proportion of NHW, NHB, and Hispanic patients within those payer groups, but more research needs to be completed.

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Table 1: This table displays the mean, standard deviation, and percent of population for the characteristics of the population noted. These are separated into NHW managed care and NHB Medicaid. Significant SAMD values are noted for age, teaching hospital, large hospitals, midwest region, and west region.

	White Managed (n=13825, 29.8 %)		**Black Medicaid (n=569, 12.7 %)**		
	Mean/Count	SD/PCT	Mean/Count	SD/PCT	SAMD
AGE	57.7	9.8	52.9	10.5	0.4677
Surgery Type					
VATS	6158	44.5%	260	45.7%	0.0231
RATS	2565	18.6%	101	17.8%	0.0208
Thoracotomy	5102	36.9%	208	36.6%	0.0072
Gender					
Female	7394	53.5%	329	57.8%	0.0874
Male	6431	46.5%	240	42.2%	0.0874
Unknown	0	0.0%	0	0.0%	.
Hospital Characteristics					
Teaching Status					
Yes	7573	54.8%	377	66.3%	0.2365
No	6252	45.2%	192	33.7%	0.2365
Setting					
Rural	1023	7.4%	45	7.9%	0.0191
Urban	12802	92.6%	524	92.1%	0.0191
Bed Count					
0-99	105	0.8%	2	0.4%	0.0549
100-199	669	4.8%	26	4.6%	0.0127
200-299	1556	11.3%	57	10.0%	0.0401
300-399	2274	16.4%	72	12.7%	0.1078
400-499	2550	18.4%	86	15.1%	0.0892
500+	6671	48.3%	326	57.3%	0.1818
Region					
Midwest	2941	21.3%	165	29.0%	0.1788
Northeast	2183	15.8%	90	15.8%	0.0007
South	6638	48.0%	288	50.6%	0.0520
West	2063	14.9%	26	4.6%	0.3545
Van Walraven Score	3.00	5.31	3.47	6.13	0.0825

Table 2: This table displays the mean, standard deviation, and percent of population for the analgesic types noted. These are separated into NHW managed care and NHB Medicaid. Significant SAMD values are noted for opioid dose, thoracic epidural, and gabapentin. Also significant is that there was no statistical difference in number of non-opioid analgesics given.

	White Managed (n=13825,29.8 %)		**Black Medicaid (n=569,12.7 %)**		
Analgesics	Mean/Count	SD/PCT	Mean/Count	SD/PCT	SAMD
Opioid Dose	17.13	18.85	19.10	19.88	0.1018
Cost Intensive Non Opioid Analgesia					
Acetaminophen_IV	4037	29.2%	159	27.9%	0.0278
Bupivacaine (EXPERIA)	1719	12.4%	79	13.9%	0.0429
Thoracic Epidural	1658	12.0%	50	8.8%	0.1052
Low Cost Non Opioid Analgesia					
NSAIDS_IV(parenteral)	5299	38.3%	200	35.1%	0.066
NSAIDS_Oral	171	1.2%	4	0.7%	0.0545
COX-2	323	2.3%	17	3.0%	0.0405
Gabapentin	1079	7.8%	71	12.5%	0.1553
Ketamine	878	6.4%	31	5.4%	0.0383
Acetaminophen_Oral	1936	14.0%	70	12.3%	0.0504
Patient Controlled Analgesia opioid	2337	16.9%	105	18.5%	0.0406
At least one non opioid analgesic	10387	75.1%	410	72.1%	0.0698
At least two non opioid analgesics	4953	35.8%	198	34.8%	0.0215

ECONOMICS, EDUCATION AND POLICY 16

Trainee readiness for unsupervised endotracheal intubation

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INTRODUCTION: Trainees learning laryngoscopy require multiple attempts at endotracheal intubation (ETI) in 25-35% of patients, increasing the risk of complications.[1-2] Because of the safety issues, education programs closely monitor trainees until they judge that the trainee can safely sustain a high success rate.[3] Several researchers suggest that the number of patient ETI an individual has performed (ETI #) will predict success, but the ETI # predicting 80-90% success varies among reports from 50 to over 200 ETI,4 too broad a range for a decision involving patient safety. We hypothesize that a multivariable model accounting for clinical experience (ETI #) plus ETI skill measured in simulation would allow a more precise prediction of success. The goal of this project was to investigate whether performance metrics from a manikin ETI test would improve predictions of success.

METHODS: Subjects were 40 consenting trainees attending an airway skills event who had 0 - 450 ETI #. At the skills event, trainee ETI performance was tested on a manikin for dental force, laryngoscopy duration, esophageal intubation, and laryngeal view. Clinical performance was observed in 351 patients intubated in the operating room during a period overlapping the manikin test. Potential ETI difficulty was estimated as the number of difficult airway features in the preoperative exam. Multivariable logistic regression (R 3.6.1) analyzed patient first-pass ETI success vs. ETI #, manikin performance, and difficult airway score. The trainee performing the ETI was coded as a random effect variable. Predictors with $P < .05$ were identified by stepwise backward elimination.

RESULTS: Trainee demographics are shown in Table 1. ETI # generally rose with months of anesthesia training. Manikin laryngoscopy duration, dental force, and first-pass success varied with ETI # (Table 2). Trainees had successful first-pass ETI in 265 patients (75%). Individual rates ranged from 50 to 100% with one outlier at 8%. Individual success rates varied directly with ETI # (Figure 1A) and months of anesthesia training (Figure 1B), but some trainees with ETI # over 200 had success rates below 80%. All 8 trainees with 21 months of anesthesia training had success rates above 90%. Multivariable logistic regression revealed four predictors of patient first-pass success. ETI # and manikin laryngeal view were positive predictors, while manikin laryngeal view and patient difficult airway score were negative predictors (Table 3). This 4-factor model had a significantly greater area under the receiver operator characteristic curve than did a 1-factor model with only ETI # (Table 3), suggesting superior discrimination between successful and failed ETI attempts. The success rates predicted by the 4-factor model closely matched the rates observed in trainee groups separated by outcome (Fig 2). The 4-factor model provided a superior fit to the data than did the model with only ETI #, as indicated by the log likelihood ratio test (Chi squared 29.8, 3 degrees of freedom, $P < .0001$).

CONCLUSION: Training programs allow experienced trainees greater autonomy at ETI compared to novices because experience is thought to correlate with success.[3] An ETI # over 100 procedures was associated with first-pass success rates over 90% in most cases in our study, but some trainees with ETI # of 200 or more had success rates of 60-80%, comparable to beginning trainees and too low to justify performing the procedure without supervision. Thus, trainees differ in their speed at acquiring ETI skills, similar to the variability humans exhibit when learning other motor skills.[5] We found that a multivariable model incorporating metrics related to skill was better than ETI # alone at predicting which trainees will perform ETI with a high rate of first-pass success. Additional studies are needed to improve and validate models for predicting trainee ETI outcomes and to test whether these predictions can be used to improve patient safety.

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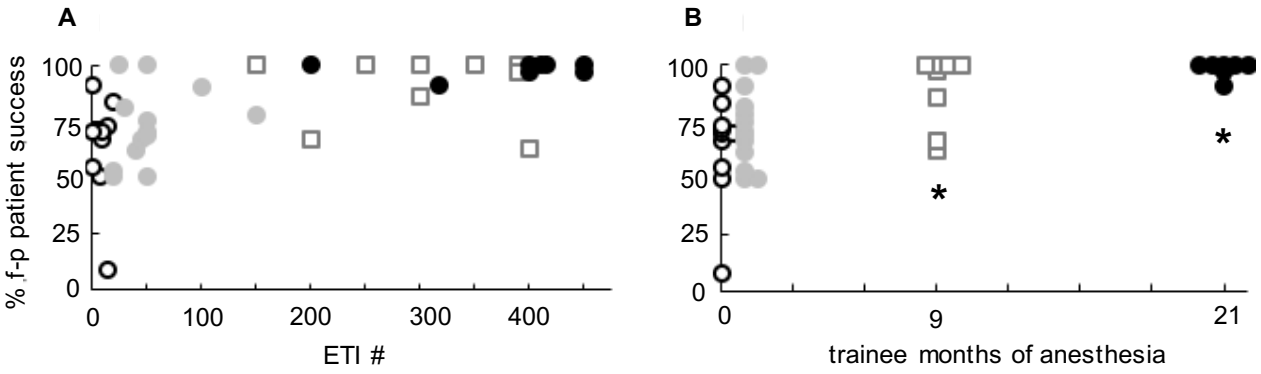

Fig 1A. First-pass ETI success rate was directly related to trainee ETI #, but some individuals with ETI # ≥ 150 had success rates below 80%, similar to novice success. **1B.** First-pass success rates increased with months of anesthesia training. The rate was > 90% for every anesthesia resident with 21 months of training.. *P < .05 vs 0 and 1 month groups. Trainees with 0, 1, 9, and 21 months of anesthesia are signified by open circles, gray circles, open squares, and black squares, respectively.

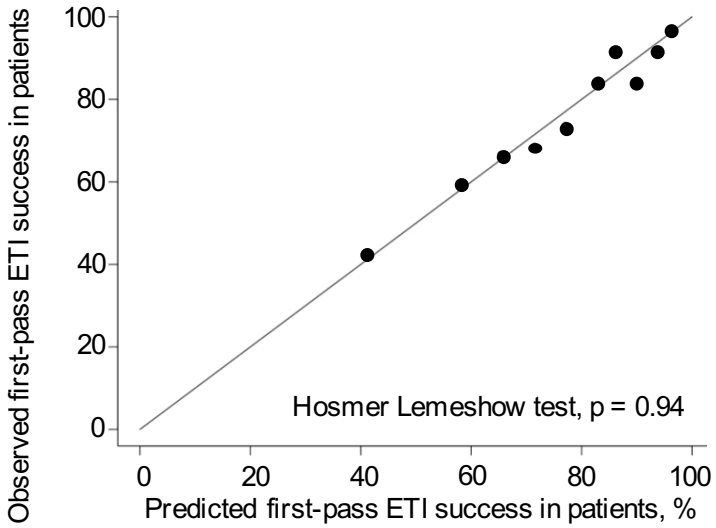

Fig 2. The plot of observed first-pass success vs. values predicted by the 4- covariate logistic regression model. Points tracked the line of identity, suggesting a good fit of data to model.

Table 1. Trainee Demographics and Experience with Patient Intubation

	MS4 0 months of anesthesia	Residents 0 months of anesthesia	Residents 9 months of anesthesia	Residents 21 months of anesthesia
Gender:				
Female	4	5	5	4
Male	4	10	4	4
Race:				
White	6	8	4	6
Black	0	3	3	0
Asian	2	4	2	2
Ethnicity:				
Hispanic	2	0	0	2
Non-Hispanic	6	15	9	6
# of Patient ETI:				
mean ± SD	7 ± 6*	47 ± 36*	294 ± 98*	387 ± 69*
interquartile gap	0 - 11	23 – 50	200 – 400	380 - 420

MS4—4th year medical student
months of anesthesia--length of training before entry into this study
The 0 months group included 2 emergency medicine residents and 13 beginning CA1 residents
# of Patient ETI—number of endotracheal intubations in patients before entry in this study
*P < .05 vs all other groups

Table 2. Mannequin Laryngoscopy Metrics Compared Among Trainee Groups with Differing Amounts of Experience at Patient ETI

Experience ETI # range	Laryngoscopy Duration, sec[a] mean ± SD	Mannequin Dental Force, N[b] mean ± SD	N (%) of Trainees with Mannequin First-Pass Success[c]		N (%) of Trainees Grouped by # of Esophageal Intubations[d]				N (%) of Trainees Classified by Median Laryngeal View[e]			
			Yes	No	0	1	2	3	1	2	3	4
0 – 20 ETI n = 12	43 ± 20*	18± 11	4 (33)	8 (67)	8 (67)	2 (17)	2 (16)	0 (0)	6 (50)	5 (42)	1 (8)	0 (0)
25 – 50 ETI n = 9	48 ± 22*	15 ± 11	5 (56)	4 (44)	5 (56)	3 (33)	1 (11)	0 (0)	6 (67)	3 (33)	0 (0)	0 (0)
100 – 318 ETI n = 9	29 ± 17	25 ± 14	8 (89)	1 (11)	8 (89)	1 (11)	0 (0)	0 (0)	6 (67)	3 (37)	0 (0)	0 (0)
350 – 450 ETI n = 10	23 ± 7*	23 ± 15	10 (100)	0 (0)	10 (100)	0 (0)	0 (0)	0 (0)	2 (20)	8 (80)	0 (0)	0 (0)

"sec" indicates seconds; "N" indicates Newtons for peak force on mannequin teeth
Since trainees attempted laryngoscopy 3 times on each mannequin, they could intubate the esophagus 0 to 3 times.
Median mannequin laryngeal view was determined from a trainee's 3 laryngoscopies.
a P = .006 for ANOVA; 350-450 ETI group significantly different from 0-20 ETI and 25-50 ETI groups, P < .05
b P = .376, non-significant
c Chi-squared 13.7, P = .003, 3 DF
d Chi-squared 8.1, P = .231, 6 DF, 0-20 and 25-50 vs 100-318 and 350-450, Chi-squared 6.39, P = .041, 2 DF
e Chi-squared 8.2, P = .224, 6 DF, 0-20 and 25-50 vs 100-318 and 350-450, Chi-squared 2.18, P = .336, 2 DF

Table 3A. Multivariable logistic regression model of trainee first-pass success at ETI in patients using 4-predictors

Covariates	Coefficient	Standard Error	Odds Ratio	95% CI	p-value
Trainee Experience					
Patient ETI #	0.006	0.001	1.006	1.003 - 1.008	<0.0001
Mannequin Test Metrics					
Laryngoscopy Duration	-0.015	0.008	0.985	0.970 – 0.999	0.0449
Laryngeal View	-0.94	0.23	0.392	0.244 - 0.629	0.0001
Patient Factor					
Difficult Airway Score	-0.87	0.24	0.418	0.259 – 0.675	0.0004
Receiver Operator Characteristic Curve					
Area under the Curve (AUC) and 95% CI	0.754 (0.706 – 0.799)				

Table 3B. Multivariable logistic regression model of trainee first-pass success at ETI in patients with ETI # as the sole predictor

Covariates	Coefficient	Standard Error	Odds Ratio	95% CI	p-value
Trainee Experience					
Patient ETI #	0.006	0.001	1.006	1.003- 1.008	<0.0001
Receiver Operator Characteristic Curve					
AUC and 95% CI	0.675 (0.624 – 0.724)				
P < 0.01 vs. AUC for the 4-covariate model shown in Table 3A					

ECONOMICS, EDUCATION AND POLICY 17

Canada's Rural Anesthesia Workforce: Trends 1996-2018

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INTRODUCTION: Canadians living in rural and remote regions of Canada, many of whom are Indigenous, require access to safe surgical, obstetrical, and anesthesia care. For decades, family practice anesthetists, who bring other generalist skills to rural communities, have responded to an overall shortage of anesthesiologists particularly in the central, western, and northern regions of the country.[1] These physicians have typically completed one year of training after their certification in family medicine, leading to a Certificate of Added Competency issued by the College of Family Physicians of Canada.[2] Ensuring alignment between the anesthesia workforce and the needs of patients in rural and remote communities, requires a data-driven and consensus based national strategy.[1] The goal of this study was to support the development of such a strategy by characterizing the rural anesthesia workforce in Canada.

METHODS: This population-based study used health administrative data from the Canadian Institute for Health Information (CIHI) National Physician Database. According to the CIHI database nomenclature, we identified all physicians in Canada (excluding Quebec) with 'Anesthesia' specialty and those who provided 'Other Anesthesia' and at least five 'Nerve Block' services between 1996 and 2018. We excluded residents and physicians who provided limited episodic care. The sample was limited to physicians practicing in rural areas, defined by CIHI according to the alignment of the physician's primary practice location postal code with census-based Statistical Area Classifications . Physician characteristics, payment, utilization, and scope of practice variables were included in the dataset. The local research ethics board approved the study.

RESULTS: Most rural anesthesia providers were family physicians. The size of the workforce varied from year to year (the number of physicians providing anesthesia services ranged from a low of 113 in 2006 to 2007 to a high of 194 in 2017) but is generally increasing. In 1996, women constituted 9% of the anesthesia workforce; this proportion increased to 18% in 2018. The workforce average age increased over the study period; the average age was 44.4 in 1996 and 49.2 in 2018. Approximately one third of the rural anesthesia workforce trained outside of Canada. Changes in scope of practice metrics suggested that physicians in the rural anesthesia workforce provided anesthesia services in their practices more intensively over time. In 2018, rural anesthetists provided nearly 40,000 nerve blocks and received nearly $2 million in payments for anesthesia services.

CONCLUSION: This study characterizes the rural anesthesia workforce and demonstrates that family practice anesthetists provide a significant number of essential anesthesia services to rural populations. Together with additional characterizations of the overall anesthesia workforce, this study will support the development of a strategy to ensure equitable access to anesthesia services for Canadians living in rural and remote regions.

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ECONOMICS, EDUCATION AND POLICY 18

Health Care Burden Associated with Pediatric Prolonged Opioid Use After Surgery

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INTRODUCTION: Prolonged opioid use after surgery (POUS), filling >1 opioid prescription 90-180 days after surgery, increases healthcare costs and utilization in adult populations; however, its economic burden in pediatric patients is unknown. We sought to determine whether POUS is associated with increased healthcare cost and utilization in adolescent surgical patients.

METHODS: Retrospective cohort study Setting: Insurance claims data from Optum's Clinformatics Data Mart Database from January 1, 2003 and June 30, 2019 Participants: Opioid-naive patients 12-21 years of age in the US who received outpatient prescription opioids Exposure: Prolonged opioid use after surgery Main Outcomes and Measures: Total healthcare costs (prescription drug and inpatient, emergency, and outpatient/other medical costs) and healthcare visits (inpatient, emergency, and outpatient/other) in the 730 day period following the surgical encounter. Multivariable regression analyses accounting for cohort asymmetry in the available surgical and demographic factors were used to determine adjusted healthcare cost and visit differences in dollars and days, respectively.

RESULTS: A total of 126,338 unique patients undergoing 132,107 procedures were included in the analysis, with 4,867 patients meeting criteria for POUS for an incidence of 3.9%. Adjusted mean total healthcare costs in the 730 days after surgery were 52% higher in patients with POUS than in non-POUS patients ($13,443 versus $8,824), with adjusted costs higher for inpatient ($2,163 versus $1,222), emergency ($1,142 versus $602), and outpatient/other ($7,967 versus $5,265) medical visits. Adjusted mean prescription drug costs in the 730 days after surgery were also higher in patients with POUS ($2,083 versus $1,517). Patients with POUS had more adjusted mean days of inpatient (0.54 versus 0.32), emergency (2.04 versus 1.08), and outpatient/other (22.35 versus 16.43) healthcare visits in the 730 days after surgery ($p<0.0001$ for all comparisons).

CONCLUSION: In adolescents, POUS was associated with increased total healthcare costs and utilization in the 730 days following their surgical encounter. Given the increased healthcare burden associated with POUS in adolescents, further investigation of preventative measures for high-risk individuals and additional study of the relationship between opioid prescription and outcomes may be warranted.

ECONOMICS, EDUCATION AND POLICY 19

Professional Barriers to Minority Advancement in Anesthesia

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INTRODUCTION: Underrepresented minorities and women continue to be disproportionately less likely to be in leadership positions relative to their percentages in the total population in the United States.[1] Though social movements in 2020 during the height of the COVID19 pandemic bought new light to the pervasiveness of sexism and racism within the country, it remains unclear if current events led to significant change within the sphere of medicine. The specialty of anesthesiology is not exempt from underrepresentation within leadership among minorities.[2,3] In 2017, a study on diversity within American Society of Anesthesiology (ASA) leadership showed that only 6 percent of respondents identified as an underrepresented minority (URM), disproportionate from comprising 8.6% of the anesthesia workforce and 32% of the general population.4 Women remained a minority in medicine as well, comprising 51% of the population but 38% of the medical physician workforce.[4] While more well-represented within leadership positions in the ASA compared to URMs, studies continue to show that very few women ascend the hierarchy of academic medicine, a situation that continues to exacerbate during the COVID-19 pandemic given the paucity of childcare options.[5] The 2020 census suggests that the United States is poised to become a 'majority-minority' country in the coming decades.[6] However, as social movements over the past few years have shown, this population shift is not reflected in the demographics of professional societies. What systemic changes are possible to make leadership opportunities accessible to Americans of all appearances? The Harvard Business Review has written extensively in recent years about the importance of mentorship for leadership, particularly among minorities in the corporate world.[7] We therefore hypothesized that in an increase in mentoring could decrease professional barriers to minority advancement within anesthesiology.

METHODS: The study was approved by the Tufts Medical Center IRB and registered in the National Institutes of Health (NIH) Clinical Trials registry, NCT04694339. A 12-question survey was developed and circulated among private practice groups and academic anesthesiology departments across the country. Prior to the survey being sent out, an abbreviated survey was sent to the residents at Tufts Medical Center for pilot testing and a sampling of types of response. Funding was provided by the ASA Mentoring Grant, which covered a period of one year with set project updates at periodic intervals. Because of the nature of the grant, survey collection time was limited to a period of six months. Sample Size: Given the timeframe for data collection, an attainable goal for number of survey responses was set a priori. It was estimated that 200 responses from a combination of practicing anesthesiologists and trainee anesthesiologists would be representative of 0.5% of the physician anesthesia workforce. Because contact information was not available for all anesthesiologists, we attempted to contact at least 2000 physicians for a desired response rate of 10%. Survey responses were not incentivized and reminders to complete the survey were not sent. Statistical analysis: For our demographic data, we set to compare our survey respondent population with a November 2015 study published in Anesthesiology on trends in the anesthesiology workforce.[8] Standard deviations between our survey demographic and the baseline demographic information on the anesthesiology workforce were calculated. More than one standard deviation between our survey population and the baseline was considered indicative of nonrespondent bias.[9]

RESULTS: We sent out 2787 surveys with 226 responses, for a response rate of 8.1%. Greater than 95% of survey respondents said they had mentor in their careers. 22.8% of responses had a mentor who they categorized as integral to their career choice and success. 81% of survey respondents did not perceive any barriers to choosing anesthesiology as a specialty. 67.5% of respondents felt they had accomplished any preset goals at the current stage of their careers.

CONCLUSION: Minorities in anesthesiology on average did not feel any barriers to professional advancement and overall most felt they had received some sort of mentoring during their career.

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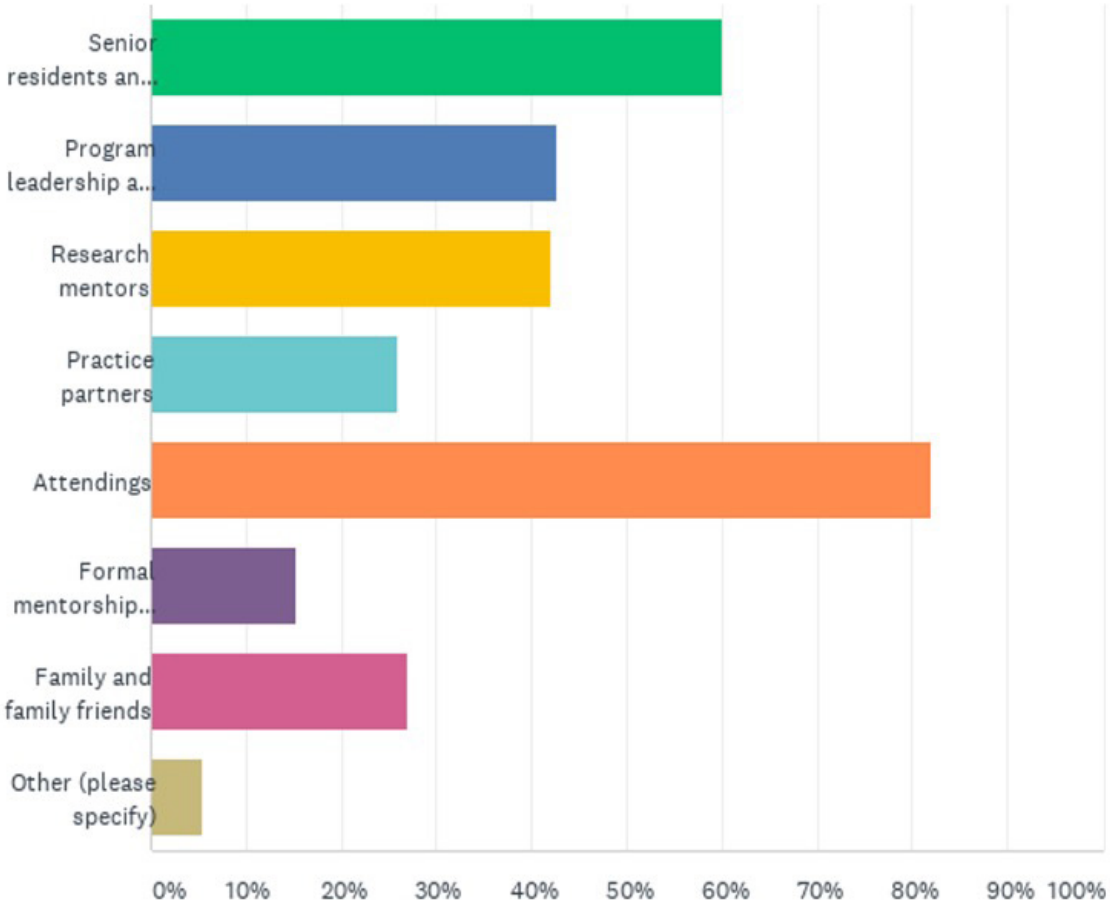

Career Stage of Respondents

Medical Student
Resident/Fellow
Practicing Physician
Retired

Demographics of Respondents

	Respondents	2013	S.D.
Male	50.45%	76.00%	0.18
Female	45.09%	24.00%	0.15
LGBTQ+	7.59%		
Black	9.82%	2.80%	0.05
Caucasian	41.96%	79.53%	0.27
Multiracial	9.38%		
Asian	16.07%	11.61%	0.03
LatinX	7.14%	3.24%	0.03
Other	6.70%	3.94%	0.02

ECONOMICS, EDUCATION AND POLICY 20

The Impact of Social Media on Applicant Perceptions of Anesthesiology Residency Programs during the COVID-19 Pandemic

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INTRODUCTION: Visiting medical student rotations have traditionally been effective opportunities for medical students to gain a better understanding of the residency program, meet current residents and faculty and to showcase their abilities and interest in a program. Although anesthesiology residency programs have increased their social media presence in recent years to help attract applicants, many programs have been slow to adopt social media. The COVID-19 pandemic disrupted the residency application process in 2020-2021 as it greatly reduced elective surgical procedures, restricted visiting medical student rotations, as well as forced the transition to virtual interviews. There is limited data regarding the effectiveness and impact of social media on anesthesia residency applicants' evaluation of potential programs, particularly in the context of the COVID-19 pandemic. We hypothesized that given the COVID-19 restrictions, social media presence of anesthesiology residency programs would play a greater role in how applicants evaluated residency programs.

METHODS: The study was approved by the Mayo Clinic IRB. Email addresses of all anesthesia residency applicants who applied to the authors' program were collected from ERAS and sent a link to the survey along with statements regarding the confidentiality, anonymity, and optional nature of the survey. There was no incentive to complete the survey. Applicants were sent an email reminder to complete the survey one month after the original email. The 20-item survey was hosted on Qualtrics and collected no identifying information. It included questions regarding sub-internship rotation completion, social media resource use, social media impact, and general demographics. Microsoft Excel was used to perform descriptive statistics.

RESULTS: The survey was sent out to 1,091 individuals who applied to the Mayo Clinic - Arizona anesthesiology residency program and 640 unique responses were recorded for a response rate of 58.6%. Many respondents reported an inability to complete 2 or more planned sub-internships due to COVID-19 restrictions (55.9%), with 25% of applicants reporting inability to do any visiting medical student rotations (Figure 1). The majority of applicants reported using residency program-based social media. Official websites (91.5%), Doximity (47.6%), Instagram (38.5%), and Twitter (19.4%) were reported as the most used resource by applicants. A large proportion of applicants agreed that social media was an effective means to inform applicants (67.3%) and that it positively impacted their perception of the program (57.5%). Applicants reported that social media helped convey a program's culture and transparency, with posts of social events rated as most impactful. A third of applicants agreed that social media presence will continue to impact future application cycles (Table 2).

CONCLUSION: As a result of COVID-19 restrictions in 2020-2021, many anesthesiology applicants were unable to complete planned visiting medical student rotations. Social media played a significant role in applicants' perception of programs. It was an effective means to inform applicants and generally positively impacted applicants' perception of programs. Aside from the traditional official website, applicants utilized social media platforms, like Instagram, to gather insight into a program's culture and transparency, with social event posts being the most successful at engaging applicant's interest. Thus, anesthesia residency programs should consider investing time and resources towards building a social media presence as it is an important factor towards recruitment of potential anesthesia residency applicants.

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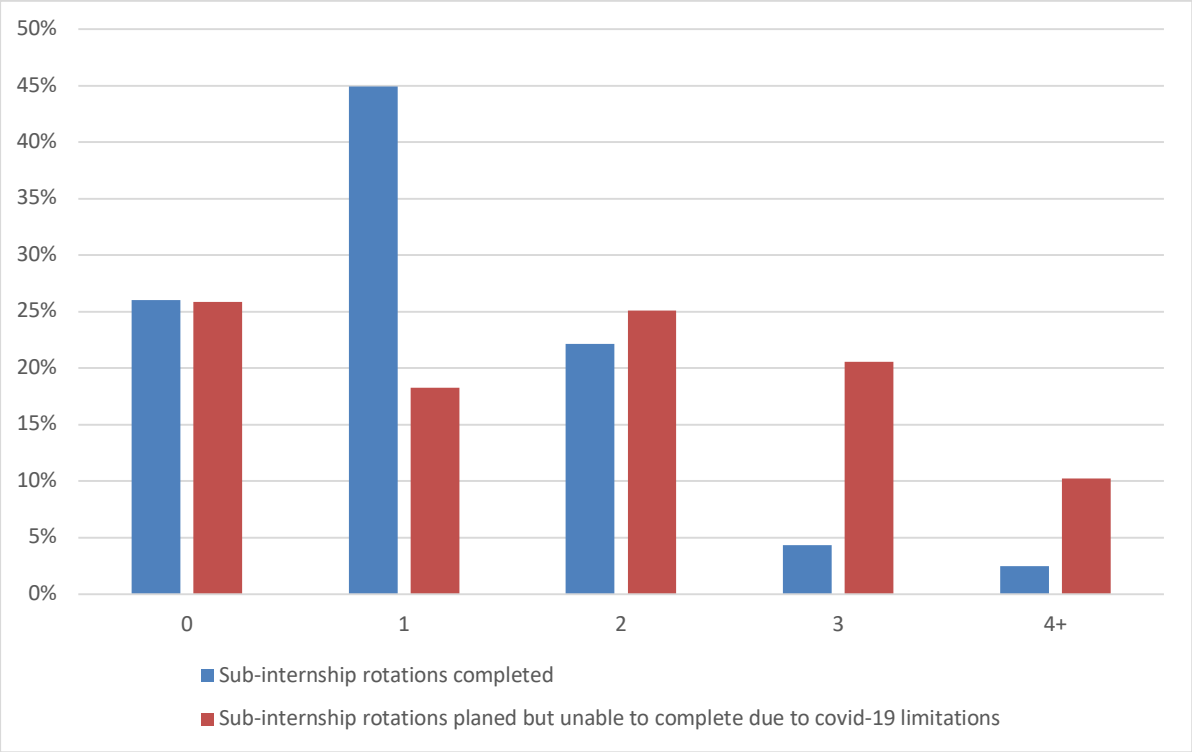
Table 1: Demographics	**n (%)**
Gender	
Female	197 (34.3%)
Male	372 (64.8%)
Gender Variant	1 (0.2%)
Age	
Less than 25	24 (4.2%)
25 -30	439 (76.5%)
31-35	78 (13.6%)
36-40	23 (4.0%)
Greater than 40	8 (1.4%)
Race/Ethnicity	
Black	32 (5.6%)
Native American	2 (0.3%)
White	288 (50.3%)
Asian	136 (23.7%)
Native Hawaiian/Pacific Islander	4 (0.7%)
Hispanic	46 (8.0%)
Multiracial	31 (5.4%)
Unknown	3 (0.5)

Table 2: Impact of Social Media					
	Strongly Agree	**Somewhat Agree**	**Neither Agree nor Disagree**	**Somewhat Disagree**	**Strongly Disagree**
Pages Available and Accessible	108 (18.9%)	259 (45.3%)	135 (23.6%)	54 (9.4%)	16 (2.8%)
Effective Way to Inform Applicants	152 (26.6%)	233 (40.7%)	117 (20.5%)	53 (9.3%)	17 (3.0%)
Impact on Perception of Program	123 (21.7%)	197 (34.7%)	159 (28.0%)	44 (7.7%)	45 (7.9%)
Positive Impact on Opinion of Program	121 (21.2%)	207 (36.3%)	203 (35.6%)	20 (3.5%)	20 (3.5%)
Improved Programs Professional Image	119 (20.8%)	176 (30.8%)	224 (39.2%)	38 (6.7%)	14 (2.5%)
Improved Perception of Programs Prestige	63 (11%)	135 (23.6%)	274 (47.9)	62 (10.8%)	38 (6.6%)
Helps Exhibit Programs Culture and Camaraderie	228 (39.9%)	194 (34.0%)	123 (21.5%)	15 (2.6%)	11 (1.9%)
Improved Programs Transparency	149 (26.0%)	216 (37.8%)	158 (27.6%)	30 (5.2%)	19 (3.3%)
Due to COVID-19, social medial will have significant impact on perception of programs.	170 (29.8%)	207 (36.3%)	125 (21.9%)	52 (9.1%)	17 (3.0%)
Social media will have less of an impact on applicant during future interview cycles not limited by COVID-19.	42 (7.3%)	149 (26.0%)	188 (32.9%)	164 (28.7%)	29 (5.1%)

Figure 1: 2020 – 2021 Sub-Internship Rotations



ECONOMICS, EDUCATION AND POLICY 21

Anesthesiologists with Advanced Degrees in Education: A Qualitative Study of a Changing Paradigm

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INTRODUCTION: Anesthesiology education has undergone profound changes over the past century, from a clinical apprenticeship model to novel, comprehensive curricula based on andragogic learning theories. Combined with institutional and regulatory requirements, these new curricula have propagated the professionalization of the clinician-educator role. A significant number of clinician-educator anesthesiologists have pursued formal health professions education (HPE) training, yet there is no published guidance describing the benefits or costs.

METHODS: Investigators performed a qualitative study of anesthesiologists with HPE degrees working at academic medical centers. Interviews were analyzed via an iterative process. They were coded for recurring themes using a grounded theory approach, and representative quotations were compiled.

RESULTS: Seven anesthesiologists were interviewed, representing diverse geographic regions, subspecialties, and medical institutions. Analyses of interview transcripts resulted in six core themes: outcomes, extrinsic motivators, intrinsic motivators, investment, experience, and recommendations. Interviewees noted advantages of HPE training for those wishing to pursue leadership and scholarship in medical education but noted opportunity cost in relation to preexisting commitments and family time. Interviewees also highlighted considerations regarding optimal timing of HPE training.

CONCLUSION: There are numerous professional and personal benefits to pursuing HPE degrees for faculty interested in education leadership and scholarship. Making an informed decision to pursue HPE training can be challenging when considering the competing pressures of clinical work and personal obligations. The experiences of the interviewed anesthesiologists offer direction to future anesthesiologists and chairs in their decision-making process of whether, and when, to pursue HPE training.

Table 1

Code	Definition	Representative statements
Outcomes	Intended and unintended impacts of the degree on one's career; including how they have utilized the degree and practical day to day application of skills/knowledge	• "It's definitely a factor to get you noticed by people like chairs when they have educational leadership roles to fill." • "I think it has been a good opportunity for me to… further push those key projects…[and] get a better understanding of where the problems are in care delivery within my department." • "I think it influenced much of what I did even beyond education. When I look back, what really happened in the years just after, it just gave me that desire to know my own self, to just go for it. And that was really great to develop more confidence in your own abilities outside of what you do." • "I mean, like the job offers I'm getting, it's insane."
Extrinsic Motivators	Reasons for an individual seeking a degree based on attaining a known, external reward	• "Pretty much… [the chair] told me I had to do it to become faculty." • "I would say that [for] the department and my division, definitely, it was an expectation that I would pursue the degree." • "… my career goals were to kind of move up [to] med ed administration and to publish in medical education." • "My mentor… was a very key proponent in me getting my masters because… to continue to move up that that would be a skill set and a degree that would look good from an experience standpoint."
Intrinsic Motivators	Reasons for an individual seeking a degree for its own sake without an external reward; including emotions, values, goals	• "I was just frustrated with myself. And I felt like I just needed a formalized process and I needed everything at once and I was tired of trying to find it on my own." • "I felt like I needed to know the language and I needed to know the theory behind why things are done the way they're done in medical education. And so that prompted me to get my masters." • "I really wanted advanced training and knowledge in education in general, which I thought would be helpful, just to understand more what's going on" • "I started to really become interested in studying educational processes, and team dynamics even, and the ways we think and how it influences the way we act and just everything like that."
Investment	Positive and negative aspects of obtaining an HPE degree; including personal or financial sacrifices, opportunity costs, time commitment	• "The biggest stressor was that I had to negotiate with my family because of time." • "I didn't jump into the program my first year as an attending even though I was advised to, because I felt like I really needed to lay my ground as a clinician. … We work a lot of days in a row. And that makes doing an online curriculum while you're a full-time employee very difficult…" • "When I enrolled in the program, I had the added pressure to really get through it as fast as possible… because there was this tension with my family, basically." • "First of all, it's a time commitment. …If you just stay in your clinical practice, right, and you try to do things within the division or department, it's already very busy."
Experience	Overall perspectives about the degree program, including opinions about the process of obtaining the degree (i.e. satisfaction with the content covered, mode/format of delivery, and suggestions for improvement)	• "I would have liked more statistics work. But otherwise, I was pretty happy with a lot of the courses." • "It reviews a lot of the scientific methodology that we all appreciate even in other aspects of research. There's an emphasis on leadership, which I really appreciated. I especially appreciated that understanding of ourselves. There was an emphasis on understanding your MBTI scores and what that meant, which really gets into where you understand your strengths, and what works well." • "But what I wish the program did was potentially focus less on individualized projects and potentially allow more collaboration and group projects for your Capstone… It would be really interesting to use the program more to develop interprofessional projects than having everybody do one individual project." • "I think what I really would have loved is if there was somebody in there who could help you either write a case report, you know, or help you with the research part as you're doing it, or help you write a grant."
Recommendations	Advice that the participant would offer to someone interested in pursuing an HPE degree regarding timing, factors to consider, aspects of a program to look for or avoid	• "If you think, look, I love to teach… you don't need a master's degree to be a teacher of residents, right, anybody in an academic center is going to teach residents. But if you think you want to be involved in residency leadership or medical school leadership, if you see yourself as being a program director one day or you know, dean for curriculum of a medical school, that kind of thing, then I think it is a good step because as I said before, I think it will get you noticed when those kinds of opportunities come up." • "I think right out of training, you don't necessarily know which person you are. What I usually advise is to do some workshops, figure out if you just want to become a really good teacher. I think you don't need a master's to do that." • "I think if you want to study teaching and you want to have a foundation in adult learning theory and you want to be able to become an administrator or become a researcher in med[ical] ed[ucation] that I would advise the [HPE degree]." • "If you're going to use this degree, you're pretty much marrying yourself to academics. But then I would also say that I think that there's a lot of opportunities for innovation, and a lot of interesting ways to use the master of education. And I would also say that I would sort of make sure that I had an academic or administrative niche that, you know, you can really start applying the coursework early on. So that you know, like, you can sort of build your academic portfolio while you're working on the degree."

ECONOMICS, EDUCATION AND POLICY 22

Incidence and predictors of a same-day case cancellation

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INTRODUCTION: The cancellation of an operation on the scheduled day of surgery reduces operating room efficiency and may have physical and emotional consequences for patients and their families[1-2]. The incidence of same-day cancellation varies by hospital setting, culture, and socioeconomic status[3-5]. Predictors of case cancellation include patient-, institutional-, and procedural factors[6-7]. The goal of this study was to identify predictors of same-day case cancellation that can then be used for quality improvement projects focused on the reduction of case cancellations.

METHODS: We used data obtained from the institution's electronic medical record system, EPIC (Epic Systems Corporation, Verona, WI, USA), including the Enterprise Data Warehouse and Caboodle. Data from scheduled elective procedures between January 2016 and June 2021 at four campuses (Moses, Einstein, Wakefield, and Hutchinson) of the Montefiore Health System (NY, USA) were included in this retrospective cohort study. We excluded procedures scheduled during the COVID-19 surge (March to June 2020), since case volume was down by more than 40%, and same-day cancellations during the COVID-19 surge may happened for a variety of reasons. The primary outcome, same-day case cancellation, was defined as the cancellation of a scheduled surgical procedure within 24 hours of the scheduled date and time. Our candidate predictors were defined a priori based on literature review and expert clinical judgment and included patient-related factors such as sex, age, ethnicity, race, language, religion, body mass index, comorbidities, previous opioid or benzodiazepine prescriptions, estimated household income, insurance coverage, distance to the hospital, history of no-show visits, number of previous surgeries, and whether the patient had a primary care physician. Surgical candidate predictors were surgical service, type of admission, and estimated surgical duration. Lastly, appointment-related candidate predictors included the day of the week, holiday status, time between scheduling event until surgery, and whether the scheduled procedure was financially cleared on the morning of surgery. A multivariable logistic regression model was used to predict same-day case cancellation. All candidate predictors were included as independent variables in the model. Stepwise backwards elimination was performed with a cut-off p-value of ≤ 0.05 for retaining predictors in the model. Bootstrapping with 1,000 samples was performed to eliminate predictors not contributing to the model's fit. Additionally, we conducted a penalized maximum likelihood estimation to address possible overfitting of the model. The model's accuracy was evaluated using the Brier score. Model calibration was assessed based on a calibration plot. The Youden's index was used to determine the optimal cut-off to differentiate between patient at high versus low risk of same-day case cancellation. As a sensitivity analysis, we performed internal validation using 30-fold cross-validation. By shuffling, splitting, and resampling the data, this cross-validation process was used to estimate how the model is expected to perform in general when used to generate predictions on data that was not used during the development of the model.

RESULTS: Of 246,612 scheduled procedures, 21,243 (8.6%) were cancelled on the same day as the intended procedure (Figure 1). Candidate predictor variables taken into account for score creation are provided in Table 1. The final score contained 26 predictors (Figure 2). A cut-off value of 16.5 score points predicted a 10.4% same-day case cancellation rate. Using this cut-off definition, the same-day case cancellation score had good model discrimination with a sensitivity of 0.67 and specificity of 0.77. The model was well calibrated with the observed same-day cancellation rate with an area under the receiver operating characteristic curve (AUC) of 0.80 (95% CI 0.79-0.80) and a Brier Score of 0.06 (reliability <0.001) (Figure 3). The performance of the model for the score in predicting same-day case cancellation was confirmed by 30-fold cross validation (AUC of 0.80, 95% CI 0.79-0.80).

CONCLUSION: We developed and validated a prediction instrument for same-day case cancellation that can be applied preoperatively in a broad patient population. The score will be used during preoperative assessment to create and implement an intervention dedicated to decreasing same-day cancellations.

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Figure 1. Study flow diagram

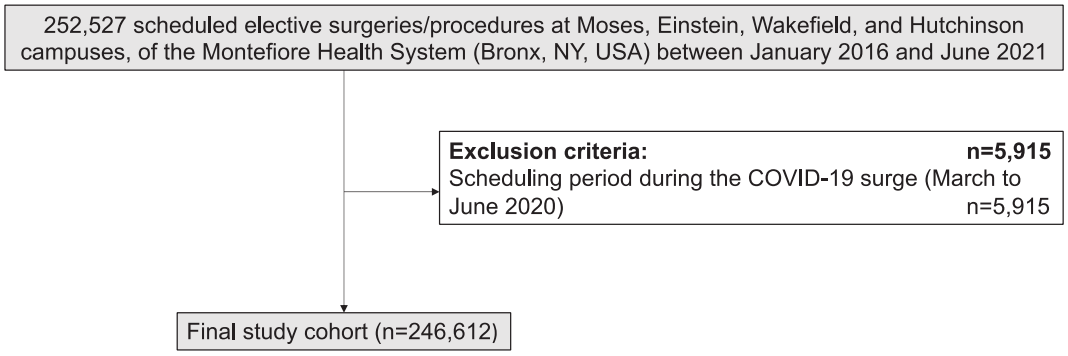


Figure 2. The same-day case cancellation score: Summary Figure.

This figure summarizes the predictors included in the same-day case cancellation score with corresponding score point values. The probability of same-day case cancellation rate was predicted by same-day case cancellation score.

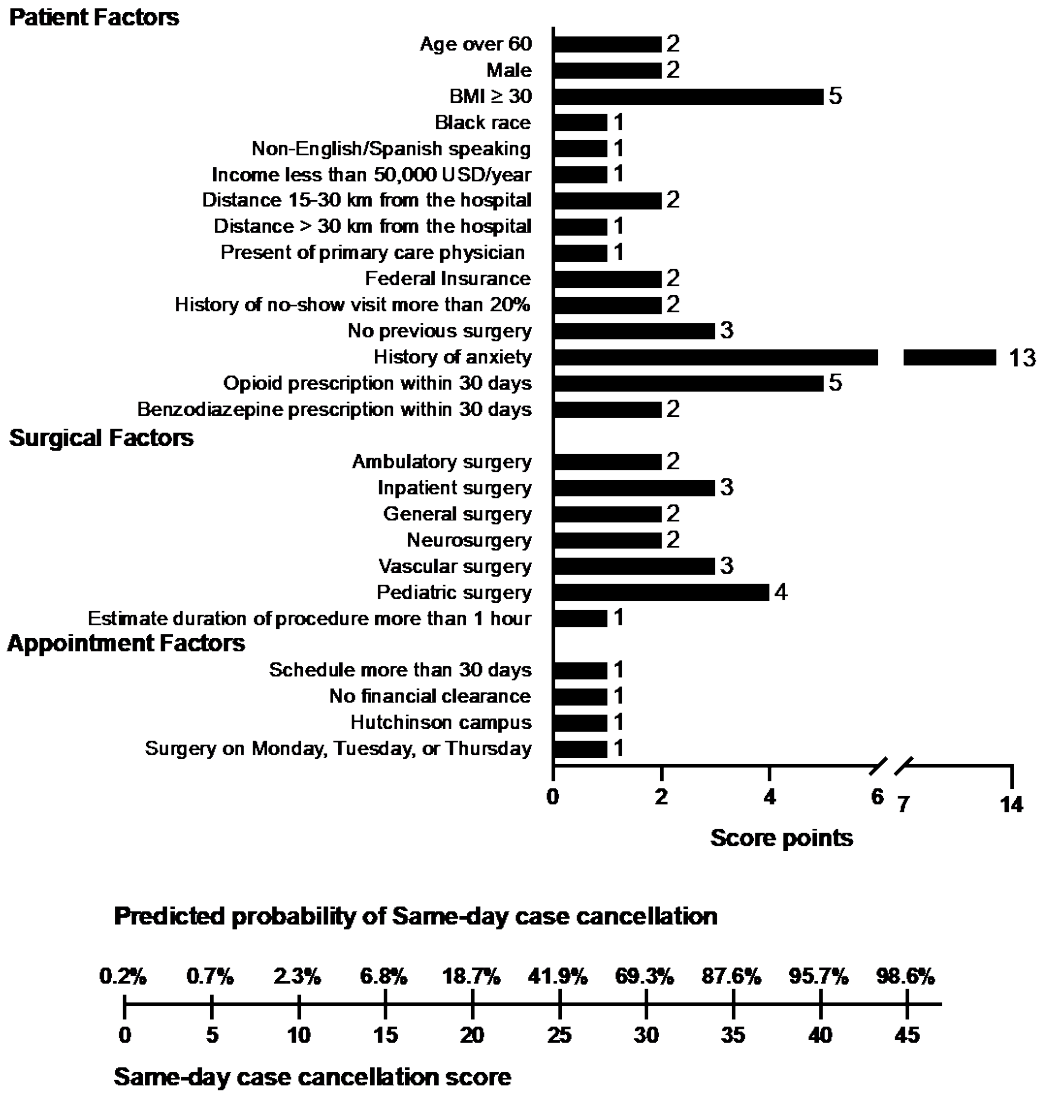


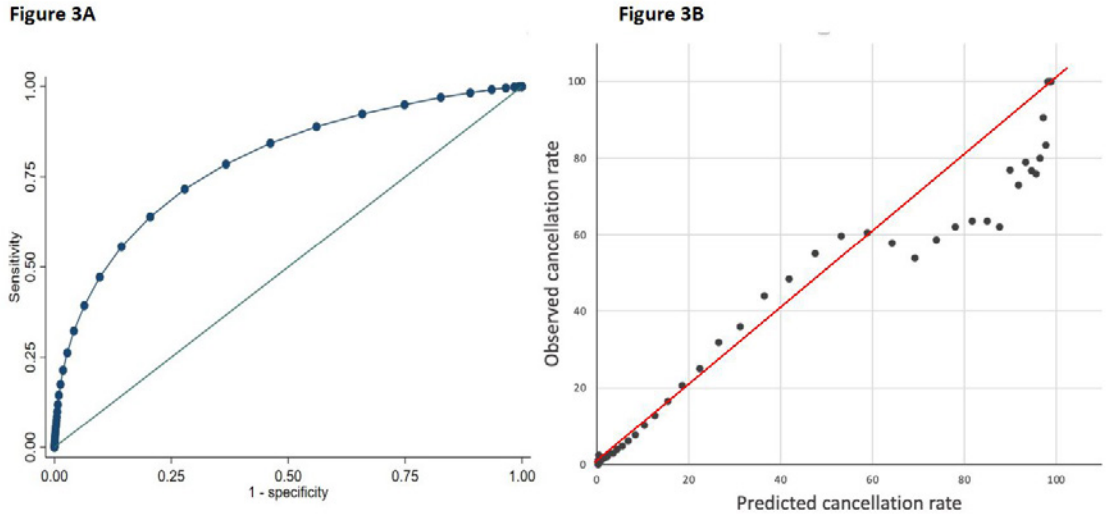
Figure 3. Model performance

Figure 3A Model discrimination

The same-day case cancellation prediction score yielded an AUC of 0.80 (95% CI 0.79-0.80). The sensitivity (y-axis) is shown as a function of 1-specificity (x-axis).

Figure 3B. Calibration plot of the Same-day case cancellation score.

The observed cancellation rate (y-axis) is shown as a function of the predicted cancellation rate (x-axis) with the same respective score. An optimal calibration indicated as the red reference line.



Tables:

Table 1. Cohort characteristics

Characteristic	Non-cancelled cases (n = 225,369)	Cancelled cases (n = 21,243)
Demographics		
Age, years	51.0 ± 21.5	53.0 ± 21.5
Sex, male	96,786 (42.9%)	10,565 (49.7%)
Body mass index, kg/m^2		
< 18.5	15,802 (7%)	542 (2.6%)
18.5 – 24.9	50,976 (22.6%)	2,364 (11.1%)
25.0 – 29.9	63,267 (28.1%)	2,687 (12.6%)
≥ 30	95,324 (42.3%)	15,650 (73.3%)
Hispanic ethnicity	82,939 (46.5%)	1,610 (45.2%)
Race		
Black	65,937 (29.3%)	6,983 (32.9%)
White	31,622 (14.0%)	2,648 (12.5%)
Asian	4,958 (2.2%)	434 (2.0%)
Other	122,852 (54.5%)	11,178 (52.6)
Language		
English	16,6583 (73.9%)	15,805 (74.4%)
Spanish	41,283 (18.3%)	3,701 (17.4%)
Others	17,503 (7.7%)	1,737 (8.1%)
Christian religion	107,340 (47.6%)	10,243 (48.2%)
Socioeconomic factors		
Estimated household income, USD	47,525 (33,498 – 58,480)	41,580 (33,498 – 58,393)
Distance to the hospital, km	4.38 (2.8 – 7.01)	4.33 (2.78 – 6.91)
Documented primary care physician	192,793 (85.5%)	18,183 (85.6%)
Federal Insurance	149,922 (66.5%)	15,717 (74.0%)
History of no-show visits, %	8.7 (3.4 – 15.7)	11.3 (5.6 – 19.9)
Previous surgery/procedure, number	0 (0 – 1)	0 (0 – 0)
Hospital visit within 90 days, number	4 (2 – 7)	4 (2 – 8)
No financial clearance	130,885 (58.1%)	14,626 (68.9%)
Comorbidities		
Cancer	27,927 (12.4%)	2,691 (12.7%)
Anxiety	1,472 (0.7%)	2,096 (9.9%)
Opioid use within 30 days	16,532 (7.3%)	6,103 (28.7%)
Benzodiazepine use within 30 days	3,052 (1.4%)	1,064 (5.0%)
Surgical factors		
Surgical services		

Cardiothoracic	7,268 (3.2%)	845 (4.0%)
Gastroenterology	56,363 (25.0%)	3,684 (17.3%)
General	69,892 (31.0%)	7,419 (34.9%)
Gynecology	12,985 (5.8%)	942 (4.5%)
Neurosurgery	4,638 (2.1%)	674 (3.2%)
Orthopedic	36,238 (16.1%)	2,717 (12.8%)
Vascular	12,188 (5.4%)	2,873 (13.5%)
Pediatric	3,179 (1.4%)	367 (1.7%)
Other	22,618 (10.0%)	1,722 (8.1%)
Estimated surgical duration, minutes	90 (60 – 160)	100 (65 – 160)
Admission Type		
Ambulatory surgery	141,349 (62.9%)	11,172 (52.6%)
Same-day admission	29,432 (13.1%)	1,300 (6.1%)
Inpatient surgery	51,531 (22.9%)	8,273 (38.9%)
Hospital campus		
Moses	93,405 (41.4%)	9,286 (43.7%)
Einstein	39,757 (17.6%)	3,448 (16.2%)
Wakefield	32,705 (14.5%)	3,045 (14.3%)
Hutchinson	59,502 (26.4%)	5,464 (25.7%)
Scheduled day		
Monday	41,452 (18.4%)	4,122 (19.4%)
Tuesday	48,080 (21.3%)	4,883 (23.0%)
Wednesday	45,155 (20%)	3,884 (18.3%)
Thursday	46,777 (20.8%)	4,164 (19.6%)
Friday	39,182 (17.4%)	3,654 (17.2%)
Non-official day	7,663 (3.4%)	826 (3.9%)

Data are expressed as frequency (prevalence in %), mean ± standard deviation, or median (interquartile range (25th-75th percentile).

ECONOMICS, EDUCATION AND POLICY 23

Clinical Anesthesia Research Virtual Program for Undergraduates: 3D printing larynx for teaching anatomy and difficult airway management

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INTRODUCTION: Clinical exposure and experience in the medical setting are essential for undergraduate students considering a career in healthcare. The COVID-19 pandemic reduced opportunities for both medical and undergraduate students to obtain in-person clinical research and shadowing experiences[1]. Due to the importance placed on clinical experience and research by medical school admissions, a search for alternatives to clinical exposure/research was required. Since web-based teaching has been used by many educational institutions, we developed an innovative approach that utilized remote clinical research in tandem with a 3D printed device[2]. A clinical anesthesia research virtual program (CARVP) was developed for undergraduate students at Dartmouth College using a 3D printed larynx to teach anatomy and difficult airway management remotely.

METHODS: The CARVP was structured in six separate phases (see Figure 1). An undergraduate premedical student applied and was awarded the James O. Freedman Presidential Scholars Program Grant. The grant encouraged the student to pursue research with either a Dartmouth College faculty member or Dartmouth-Hitchcock Medical Center (DHMC) physician. The student contacted the Office of Undergraduate Advising & Research (UGAR), utilized a database to discover ongoing Science, Technology, Engineering, and Math (STEM) research projects, and conducted virtual web-based interviews with several faculty members across departments. The student decided to pursue the CARVP developed in the Dartmouth IDEA Lab and joined a team of anesthesiologists, medical students, and a program developer. After virtual anatomy training and an anesthesia literature review, the student developed an original project composed of a 3D printed larynx for difficult airway management.

RESULTS: The student organized web-based video interactions with the lab team to supplement laryngeal anatomy education and airway management literature review, which led to the development of a 3D printed larynx and its application in a simulation laboratory (see Figure 2). The student used an open-source larynx file published by The International Airway Collaboration and a FormLabs Inc. printer to print a 3D larynx, realistic in size, texture, and structure (see Figure 3)[3]. FormLabs Inc. Elastic 80A resin was used for the larynx model, as its hardness offered the most realistic approximation of human cartilage. Coban tape was used to simulate the cricothyroid membrane and skin covering as well as to securely attach the trachea to table-top surfaces. The lab team utilized the 3D larynx in a socially distant, in-person simulation experience to practice cricothyroidotomy and to further the student's understanding of anatomy and difficult airway management.

CONCLUSION: We established a clinical anesthesia research virtual program for an undergraduate premedical student to learn anatomy and difficult airway management by using a 3D printed larynx and a socially distanced simulation experience. Though the COVID-19 pandemic has eliminated many in-person clinical research opportunities, the coupling of a 3D printed anatomical device and web-based collaborations offered a unique alternative and solution. Our experience was limited to one institution and a single undergraduate student. We plan to expand the program, offering more students the opportunity to utilize 3D printed devices for difficult airway management simulations.

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Figure 1. Virtual Clinical Research Journey for Undergraduate Student. The six phases of the virtual clinical anesthesia research program.

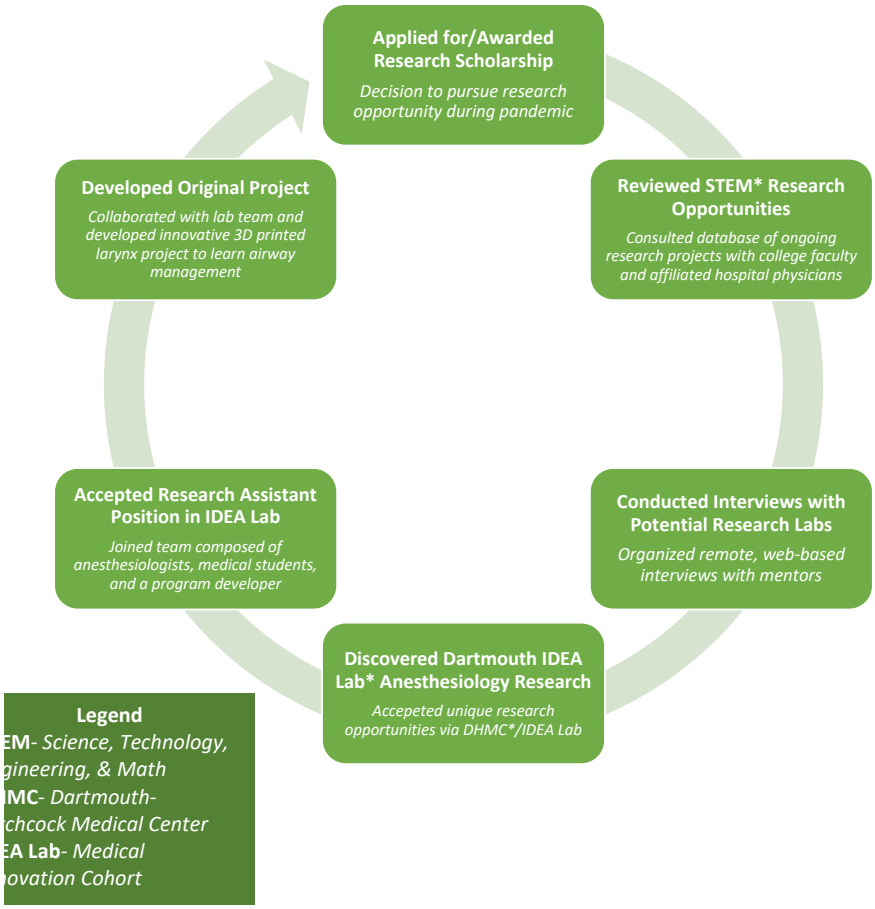


Figure 2. Virtual Clinical Research Experience. The four phases of original project development.

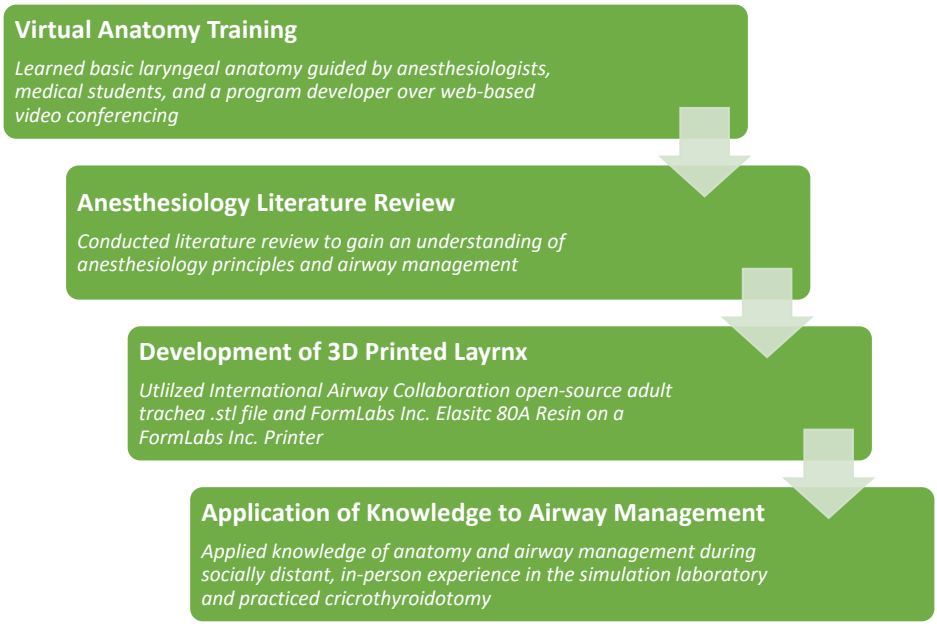
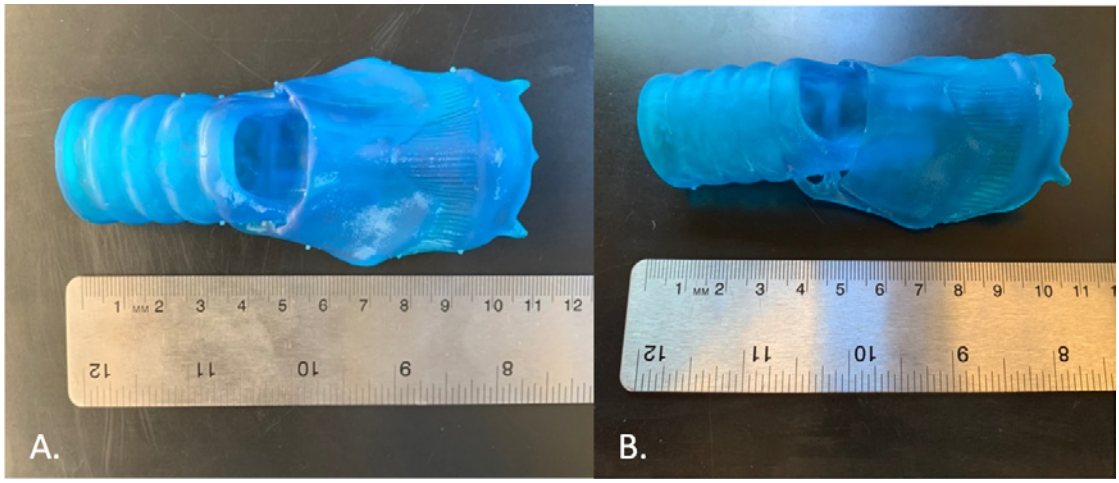


Figure 3. 3D Printed Larynx in FormLabs Inc. resin. Top view (a) and side view (b) of adult human larynx simulation device printed using International Airway Collaboration open source .stl file. Approximate dimensions are 11cm x 3cm. Coban tape not pictured.



ECONOMICS, EDUCATION AND POLICY 24

Wiretap laws and the perioperative physician – the current state of affairs

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INTRODUCTION: Smartphones provide for the ability to easily make audio and video recordings. This has enabled both patients and clinicians to capture high-quality physician-patient interactions. Patients may choose to record physician encounters for benign reasons, such as allowing for future playback for improved understanding, but some patients may record these interactions to be used as the basis for a legal claim. Wiretapping statutes vary from state to state and govern whether an audio recording is being done legally. Given how readily available and concealable recording devices are, it is vital for medical professionals to understand the legality and implications of these recordings in the jurisdictions where they practice.

METHODS: Each state's legislative information, the District of Columbia, and Federal information was accessed via their respective websites following a Google search using the keywords 'federal wiretapping law', 'state wiretapping law', 'exceptions to federal wiretapping law', 'exceptions to state wiretapping law', 'punishment federal wiretapping law', and 'punishment state wiretapping law.' We searched for the relevant wiretapping law data within the legislature and cross-referenced with law.cornell.edu, justia.com, recordinglaw.com, detectiveservices.com, codes.findlaw.com, rcfp.org, casetext.com and markshermanlaw.com. We then compiled a table with each state's relevant wiretap statutes with the corresponding state legislative websites and compiled a separate table of the potential civil and criminal punishments that could be exacted for wiretap statute violations.

RESULTS: Table 1 summarizes the Federal Wiretap Law followed by each state's wiretap law, as well as the District of Columbia (DC). The relevant statutes are listed along with relevant notes and explanations. The state consent laws are identified as being either one-party or all-party. The majority of states are classified as one-party consent state laws (40/52, 76.92%). Federal and DC laws are one-party consent. Nine states (9/52, 17.30%) are classified as requiring all-party consent for wiretap laws. These states are CA, FL, IL, MA, MD, MT, NH, PA and WA. We classified three states (3/52, 5.76%) as 'Mixed'. CT wiretap statute differs between its criminal versus civil classification - criminally it is a two-party law, civilly it is an all-party consent state law. The state of Nevada is classified as being one-party, but the Nevada Supreme court has ruled in Lane v. Allstate Ins. Co., 114 Nev. 1176 (1998) that all parties must consent to the recording of wired (i.e., telephone) communications. Oregon classifies phone conversations as requiring one-party consent, while in-person conversations require all-party consent. Table 2 shows the criminal (penal) and civil punishments that would be exacted if violating the wiretap statue, as broken down by state, and the relevant statutes. The majority of penal punishments are a fine (ranging from $500-$25,000), imprisonment (ranging from 6 months to 20 years, average 4.43 years) or both. The majority of civil punishments are a fine (ranging from $100-$25,000) and usually, in addition to a fine, there could be punitive damages, attorney's fees and litigation costs.

CONCLUSION: Many healthcare professionals and other citizens are unaware of the wiretap laws and the implications they may have when practicing clinically. Most physicians are aware of HIPAA laws protecting patients from being photographed or having videos taken of them, but many patients may not be aware that there are state and federal implications to recording others. Many patients may feel that if the intention behind doing the recording is good (e.g., for personal use), the recording is rendered harmless. However, it is imperative to be aware of the implications of these laws - regardless of the intention behind doing the recording. To our knowledge there are no existing studies summarizing existing wiretap statutes and the implications for healthcare professionals. We have not identified a centralized database for physicians to access these resources, and there is profound heterogeneity and nuances to the law as they vary state-by-state. It should be noted that there are limitations to our study. This study was completed in 2021 and laws do change.

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Extract of larger table

State	One or All-party consent state law	Relevant Law	Notes/comments	Exceptions to the consent
Federal	One-Party	18 U.S. Code §§§ 2510-22 Electronic Communications Privacy Act of 1986 Communications Assistance to Law Enforcement Act Antiterrorism and Effective Death Penalty Act of 1996 USA PATRIOT Act USA PATRIOT Additional Reauthorization Amendments Act of 2006 FISA (Foreign Intelligence Surveillance Act) Amendments Act of 2008 FISA Sunsets Extension Act PATRIOT Sunsets Extension Act of 2011	The ECPA updated the Federal Wiretap Act of 1968, which addressed interception of conversations using "hard" telephone lines, but did not apply to interception of computer and other digital and electronic communications.	18 U.S.C. § 2518
AK	One-Party	AK Stat § 42.20.310, § 42.20.330 Palmer v. State, 604 P.2d 1106 (1979)	The Alaska Supreme Court has held that the eavesdropping statute was intended to address only third-party interception of communications and thus does not apply to a party to a conversation.	AK Stat § 42.20.320
AL	One-Party	AL Code § 13A-11-30, § 13A-11-31	Alabama law requires the consent of at least one party to legally record an in-person or telephone conversation	AL Code § 13A-11-30 (a)

Table 1

Extract of larger table

		Punishment	
	Relevant law	Penal	Civil
Federal	18 U.S.C. §§ 2510, 2511	Illegally recording an in-person, telephone or electronic conversation is punishable by a fine, imprisonment for not more than five years, or both.	Anyone whose telephone, electronic or oral conversation has been recorded or disclosed in violation of federal law can bring a civil suit for injunctive relief and/or to recover actual damages plus profits made by the violator, $100 a day for each day of violation, or $10,000, whichever is greater.
AK	Alaska Stat. Ann. §§ 42.20.330 ; 12.55.135 Alaska Stat. Ann. § 12.55.035	Violation of the eavesdropping statute — including by disclosing illegally obtained information — is a misdemeanor with a penalty of up to a year in jail. Additionally, those convicted of the statute face a fine of up to $25,000.	The statute does not authorize civil lawsuits against violators.
AL	Ala. Code §§ 13A-5-7; 13A-5-12 Ala. Code § 13A-11-33	Unlawfully recording a conversation is a misdemeanor carrying a maximum penalty of one year in jail and a $6,000 fine. Criminal surveillance and disclosing information obtained through these methods are misdemeanors carrying a maximum jail sentence of six months and a fine of $3,000. Installing an eavesdropping device on private property is considered a felony offense carrying a prison sentence between one and 10 years and a potential fine up to $15,000.	The statute does not authorize civil lawsuits against violators.
AR	Ark. Code Ann.§§ 5-4-401, 5-4-201	Intercepting or recording in-person, telephone or electronic communications in violation of the law is a misdemeanor punishable by up to a year in jail. In addition, the court may impose fines of up to $2,500. Violation of the state's video voyeurism law is a felony punishable by up to six years in prison. The court may also impose fines of up to $10,000.	The statute does not authorize civil lawsuits against violators.

Table 2

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Racial and Ethnic Disparities among Thoracic Surgery Patients

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INTRODUCTION: Despite efforts in the United States to expand healthcare access through policy, widespread disparities persist across thoracic surgery services. In particular, in-hospital mortality is often higher among racial and ethnic minorities compared to their white counterparts[1,2]. Although enhanced recovery after surgery (ERAS) protocols have resulted in less postoperative complications in thoracic surgery patients overall[3,4,5], minority and underinsured patients are less likely to receive such interventions[2]. We examined the differences in postoperative outcomes after thoracic surgery based on race, ethnicity, and insurance status.

METHODS: Adult patients undergoing elective video-assisted thorascopic surgery (VATS), robotic-assisted thoracic surgery (RATS), or thoracotomy between 2008 and 2018 were identified within a large, nationwide database (PREMIER, inc.). We excluded patients who had no documented analgesia and those who had extremes of opioid utilization. Exposure was defined as Non-Hispanic White Managed care (NHWMa) and Non-Hispanic Black Medicaid (NHBMe) patients while primary outcomes included mortality as well as discharge to home and postoperative pulmonary complications, defined individually as acute respiratory failure, pulmonary edema, pneumonia, noninvasive ventilation (NIV), prolonged intubation, and reintubation using ICD-10 codes. Secondary outcomes included length of stay (LOS) (>75% of overall cohort). Patient demographics and characteristics including hospital size, location, medical comorbidities, ancillary drug usage, and outcomes were described using means, percentages and standard deviations. Standardized absolute mean difference (SAMD) was utilized to compare differences in demographics and outcomes.

RESULTS: (n=30,382, 42.8%), RATS (n=13,629, 19.2%) and thoracotomy (n=27,008, 38.0%). While no difference in Mortality was apparent, the NHBMe cohort was noted to have a lower probability of discharge to home (SAMD=0.33). NHBMe had significant (SAMD>0.1) increased medical comorbidities including congestive heart failure (5.3% vs 2.0%, SAMD=0.17), hypertension (62.4% vs 46.9%, SAMD=0.29), renal failure (6.0% vs 2.9%, SAMD=0.15), and complicated uncontrolled diabetes (6.2% vs 2.6%, SAMD=0.17). Post-operative mortality was reported to be 1.2% in NHBMe and 0.6% in NHWMa (SAMD=0.06). NHBMe had prolonged LOS (mean 5.9 days) compared to NHWMa (mean 5.1 days) (SAMD=0.17), and higher rates of pulmonary complications (28.6% vs 20.3%, SAMD=0.13).

CONCLUSION: Utilizing a combination of race, ethnicity, and payer, we found that there are differences in postoperative pulmonary complications and discharge to home in NHWBMe compared to NHWMa. Of note, the larger difference in discharge home may reflect various underlying disparities (in education, transportation, housing, employment, and access to care). Whether anesthesiologists can contribute to reductions in downstream disparities by decreasing upstream inequities in treatments, like perioperative analgesia, remains to be seen.

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Table 1

	Total (N=71019)	NHWMa (N=56357, 65.3%)	NHBMe (N=4467, 6.3%)	SAMD
Age (Mean, SD)	65.68 (11.32)	57.67 (9.79)	52.91 (10.53)	0.47
Surgery Type (N, %)				
VATS	30382 (42.8)	6158 (44.5)	260 (45.7)	0.02
RATS	13629 (19.2)	2565 (18.6)	101 (17.8)	0.02
Thoracotomy	27008 (38.0)	5102 (36.9)	208 (36.6)	0.01
Gender (N, %)				
Female	37592 (52.9)	7394 (53.5)	329 (57.8)	0.09
Male	33416 (47.1)	6431 (46.5)	240 (42.2)	0.09
Hospital Characteristics (N, %)				
Teaching Status				
Yes	40792 (57.4)	7573 (54.8)	377 (66.3)	0.24
Setting				
Rural	5694 (8.0)	1023 (7.4)	45 (7.9)	0.02
Bed Count				
0-99	592 (0.8)	1023 (7.4)	45 (7.9)	0.05
100-199	3534 (5.0)	669 (4.8)	26 (4.6)	0.01
200-299	8069 (11.4)	1556 (11.3)	57 (10.0)	0.04
300-399	12122 (17.1)	2274 (16.4)	72 (12.7)	0.11
400-499	11754 (16.6)	2550 (18.4)	86 (15.1)	0.09
500+	34948 (49.2)	6671 (48.3)	326 (57.3)	0.18
Region (N, %)				
Midwest	13733 (19.3)	2941 (21.3)	165 (29.0)	0.18
Northeast	13221 (18.6)	2183 (15.8)	80 (15.8)	0
South	33129 (46.6)	6638 (48.0)	288 (50.6)	0.05
West	10936 (15.4)	2063 (14.9)	26 (4.6)	0.35
Surgery Count at each hospital (N, SD)	447.4 (341.9)	448.5 (326.1)	445.5 (348.7)	0.01
Van Walraven Score (N, SD)	3.82 (5.66)	3.00 (5.31)	3.47 (6.13)	0.08
Ancillary Drugs (N, %)				
Antihypertensive	2961 (4.2)	466 (3.4)	36 (6.3)	0.14
Insulin	4126 (5.8)	766 (5.5)	21 (3.7)	0.09
Bronchodilator	19104 (26.9)	4218 (30.5)	147 (25.8)	0.1
Outcomes (N, %)				
Death	837 (1.2)	88 (0.6)	7 (1.2)	0.06
Discharge to home	48634 (68.5)	11214 (81.1)	381 (67.0)	0.33
Discharge to hospice	106 (0.1)	8 (0.1)	0 (0)	0.03
ICU Admission	35761 (50.4)	6533 (47.3)	245 (43.1)	0.08
Non-Invasive ventilation	6855 (9.7)	1071 (7.7)	61 (10.7)	0.1
Mechanical Ventilation	5212 (7.3)	842 (6.1)	36 (6.3)	0.01
Pulmonary Complications	12719 (17.9)	1871 (13.5)	107 (18.8)	0.14
Acute Respiratory Failure	7384 (10.4)	1060 (7.7)	58 (10.2)	0.09
Pulmonary Edema	3763 (5.3)	422 (3.1)	30 (5.3)	0.11
Pneumonia	4413 (6.2)	706 (5.1)	38 (6.7)	0.07
Reintubation	3136 (4.4)	425 (3.1)	28 (4.9)	0.09
Duration of Mechanical Ventilation (Days, SD)	0.33 (1.62)	0.23 (1.30)	0.44 (2.10)	0.12
Length of Stay (Days, SD)	5.80 (5.29)	5.06 (4.59)	5.91 (5.15)	0.17

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Pilot Implementation of Entrustable Professional Activities in Seven United States Anesthesiology Residency Training Programs

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INTRODUCTION: Entrustable Professional Activities (EPAs) represent a practical and informative framework to assess trainee competency and provide just-in-time feedback. EPAs can also be mapped to ACGME milestones to document trainee progress.[1-7] A set of EPAs for US anesthesiology programs was recently developed and published[8] but has yet to be formally implemented or tested.

METHODS: A three-month trial of EPA implementation via a mobile app (APP) was completed at seven anesthesiology residency training programs. Trainee and faculty satisfaction with EPA usage was assessed via a survey prior to and immediately following the trial. The number of individual EPA assessments during the trial was compared to the quantity of competency assessments in the three-month period immediately prior to the trail using the pre-existing assessment system at each program. EPA results were also tabulated and reported as average scores stratified by post-graduate year in training.

RESULTS: Trainee survey results showed improvements in metrics of timeliness, quality, specificity and amount of feedback after EPA app implementation but not in the perceived frequency of receiving feedback, or the perception of faculty dominating the feedback conversation (Figure 1). Based on faculty survey results, supervising physicians found EPAs and the APP easy to use, preferred the use of EPAs over other assessments, used the EPA APP more frequently than pre-existing assessments, and found EPAs to be a useful tool to assess competency (Table 1). Use of the EPA APP resulted in a larger quantity of feedback submissions as compared to previous feedback formats (Figure 2), and scores in all EPAs had a positive correlation with level of training (Figure 3).

CONCLUSION: A multi-center trial of anesthesiology EPA implementation showed largely positive effects of EPAs on the quality and quantity of feedback from faculty and were found to be user friendly, intuitive and in some ways preferred over other existing forms of competency assessment. EPAs have the potential to improve the assessment of trainee competency in anesthesiology programs, improve feedback discussions, and document individual trainee progression along the ACGME milestone continuum. While this study was limited to seven programs, they were of varying geography and program size. Future directions include studying the validity of the EPAs and how they fit into a larger program of competency assessment to address all anesthesiology milestones.

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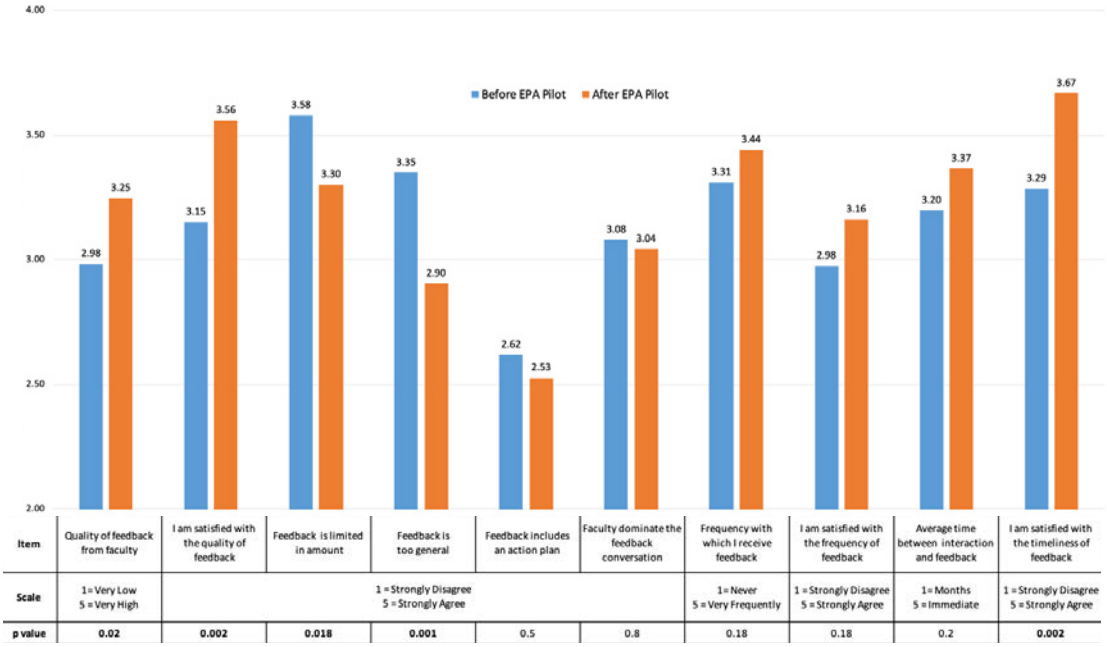
Figure 1. Trainee survey results comparing average response to each item before (n=126) and after (n=93) pilot.



Item	Quality of feedback from faculty	I am satisfied with the quality of feedback	Feedback is limited in amount	Feedback is too general	Feedback includes an action plan	Faculty dominate the feedback conversation	Frequency with which I receive feedback	I am satisfied with the frequency of feedback	Average time between interaction and feedback	I am satisfied with the timeliness of feedback
Scale	1 = Very Low 5 = Very High	1 = Strongly Disagree 5 = Strongly Agree					1 = Never 5 = Very Frequently	1 = Strongly Disagree 5 = Strongly Agree	1 = Months 5 = Immediate	1 = Strongly Disagree 5 = Strongly Agree
p value	**0.02**	**0.002**	**0.018**	**0.001**	0.5	0.8	0.18	0.18	0.2	**0.002**

Figure 2. Number of assessment submissions by month comparing EPAs to pre-existing assessment system (average assessments submitted per trainee per month).

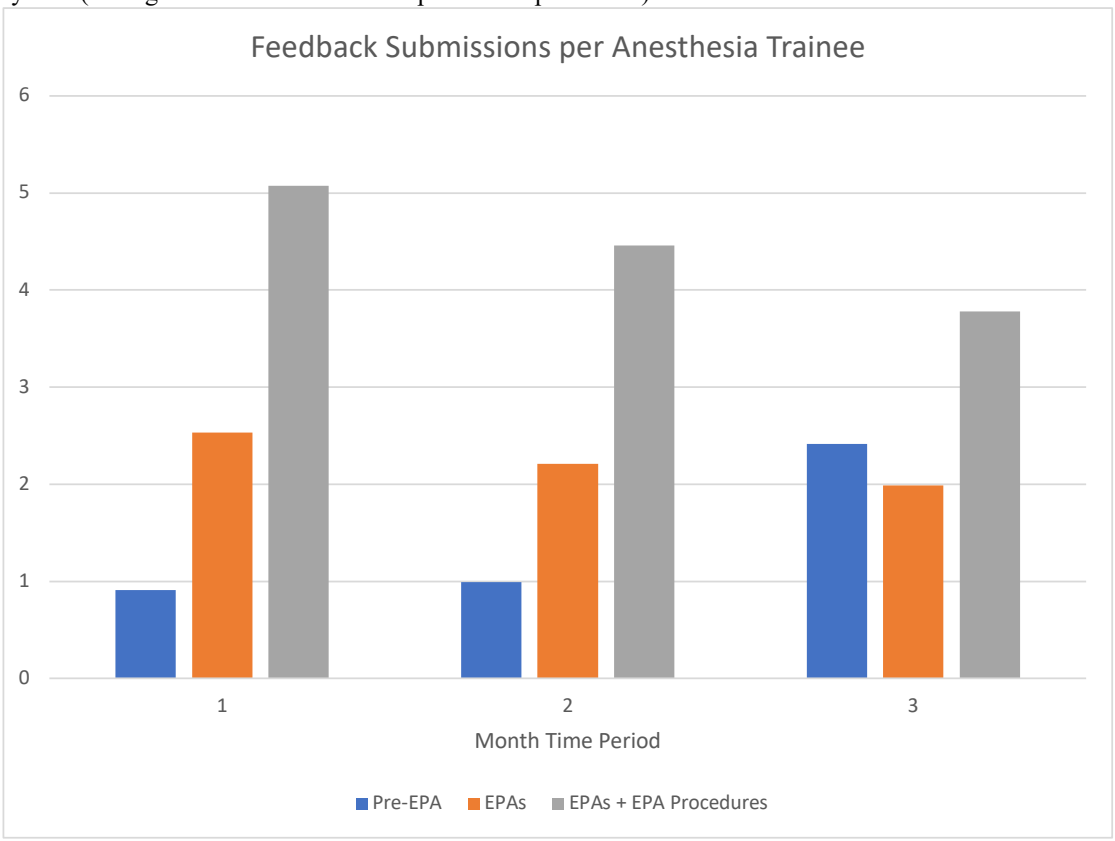


Figure 3. Average scores for each EPA by PGY-year.

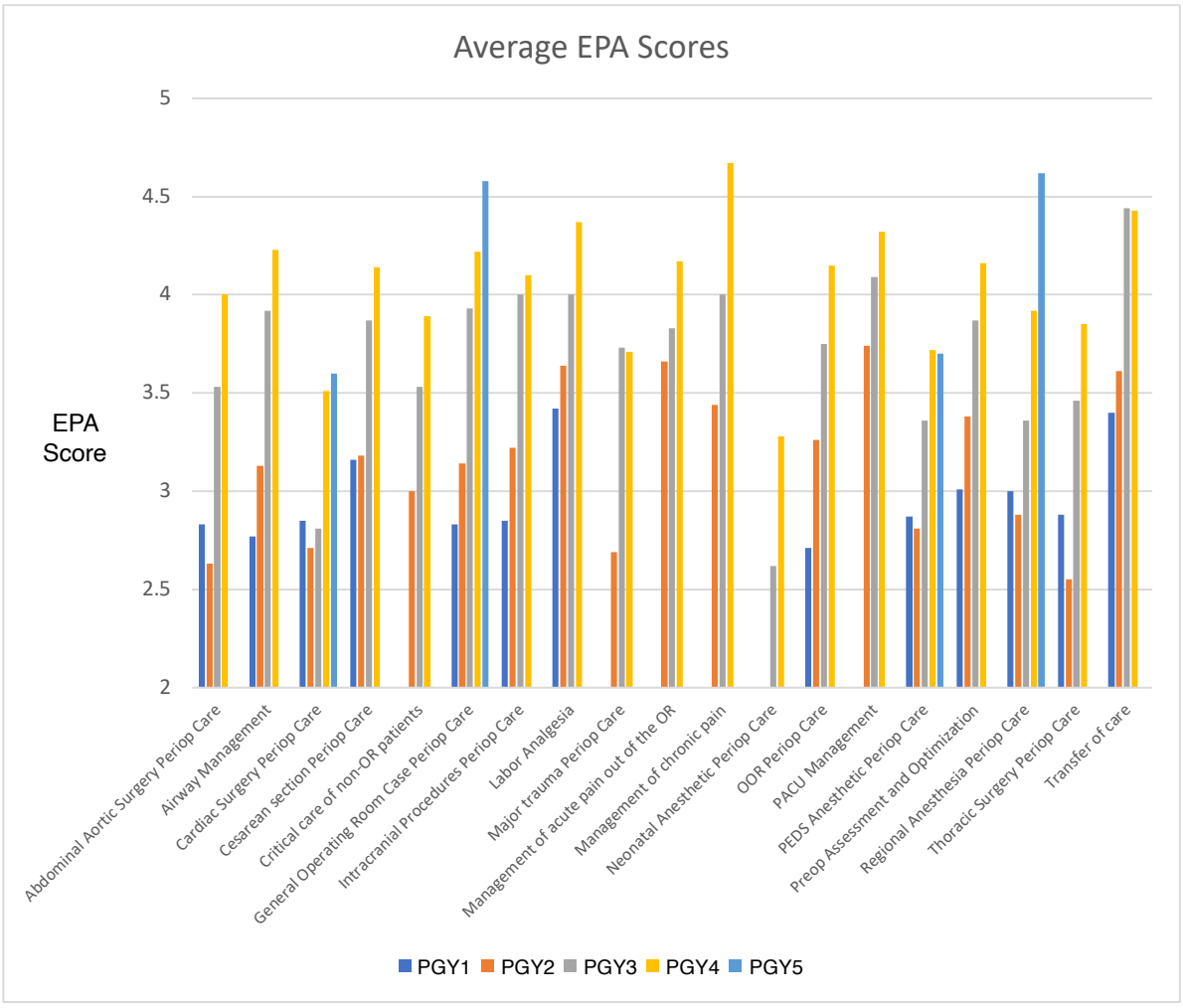


Table 1. Faculty survey results immediately following EPA pilot (n=131).

Item # and Stem	Scale	Average	SD
1. I would like to use this APP frequently	1 = Strongly Disagree 5 = Strongly Agree	3.39	1.19
2. I thought the APP was easy to use	1 = Strongly Disagree 5 = Strongly Agree	3.79	1.04
3. I found the APP to be too complex	1 = Strongly Disagree 5 = Strongly Agree	2.24	0.86
4. I think that I would need the support of a technical person to be able to use this APP	1 = Strongly Disagree 5 = Strongly Agree	1.79	0.94
5. I would imagine that most people would learn to use this APP very quickly	1 = Strongly Disagree 5 = Strongly Agree	4.02	0.73
6. I found the APP very awkward to use	1 = Strongly Disagree 5 = Strongly Agree	2.46	1.08
7. I felt very confident using the APP	1 = Strongly Disagree 5 = Strongly Agree	3.81	0.90
8. I needed to spend a lot of time with the APP before I could use it effectively	1 = Strongly Disagree 5 = Strongly Agree	2.10	0.96
9. Overall, I would rate the user friendliness of this APP as	1= Awful 5 = Excellent	3.69	0.93
10. I would use this APP frequently to submit resident assessments	1 = Strongly Disagree 5 = Strongly Agree	3.50	1.22
11. Assessment data collected from the APP would be useful to evaluate resident competency	1 = Strongly Disagree 5 = Strongly Agree	3.50	1.06
12. I prefer the style of evaluation in the APP compared to the other assessments I am supposed to complete	1 = Strongly Disagree 5 = Strongly Agree	3.38	1.19
13. I filled out the APP evaluations alongside the trainee	1 = Never 5 = All of the time	2.11	1.23
14. I shared my evaluation scores I entered in the APP with the trainee	1 = Never 5 = All of the time	2.50	1.40
15. I discussed with trainee why I assigned the evaluation score	1 = Never 5 = All of the time	2.45	1.39

Average=Average survey response; APP=mobile EPA app; SD=standard deviation

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Assessing Anesthesiology Needs in Simulation Based Medical Education

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INTRODUCTION: New Accreditation Council for Graduate Medical Education (ACGME) milestones emphasize competency-based training with objective performance measures.[1,2] Simulation-based medical education (SBME) is linked to superior clinical performance and skill acquisition.[3] This study's primary aim was to determine how training programs currently use SBME.

METHODS: An anonymous 10-question survey was created in REDcap to assess where and how SBME occurs, which SBME resources are available, frequency of and barriers to SBME's use, and perceived utility of a departmental education lab dedicated to SBME.[4] The survey can be seen in Supplemental File 1. Publicly available contact information was obtained for 148 out of 161 US anesthesiology residency program directors listed on the Fellowship and Residency Electronic Interactive Database (FREIDA).[5] General survey reminders were sent twice (once weekly) following initial distribution on December 7, 2020, followed by targeted emails to nine respondents over approximately 3 weeks (April 22,2021 to May 7, 2021). The targeted respondents were selected due to being considered likely to respond to direct survey requests, and / or had recently assumed positions from preceding directors.

RESULTS: The survey response rate was 30.4% (n=45 out of 148) and included respondents from all US Census regions; full survey results are displayed in Table 1. SBME typically occurred at shared on-campus labs (64.4%), with residents typically participating in SBME one to four times per year (64.4%). Frequently practiced skills included airway management, trauma scenarios, non-technical skills, and ultrasound techniques (all ≥ 77.8%; details displayed in Chart 1). Mannequins, dedicated task trainers, and ultrasound / echocardiography simulators were generally available resources (100%, 84.4%, and 77.8% respectively; details in Chart 2). Frequently cited logistical barriers (details in Chart 3) included COVID-19 precautions (75.6%), scheduling (57.8%), and lack of trainers (48.9%). Most respondents believed a dedicated departmental education lab would be useful or very useful (77.8%).

CONCLUSION: Our findings aligned with other similar surveys: particularly of non-technical skills being frequently practiced via SBME[6] and scheduling difficulties being a prominent SBME barrier.[6,7] A 2018 national survey of ACGME accredited pediatric anesthesiology fellowship programs also notably reported 87% of respondents believed standardized simulation curricula should be developed for voluntary use. When considered alongside our survey's revelation that most anesthesia residency programs consider dedicated education labs as useful or very useful resources, it appears there is a national interest in increased opportunities for / implementation of SBME. As our specialty moves towards competency based-training, it is increasingly important to provide learners with opportunities to improve skills with greater frequency and flexibility.

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Table 1. Survey Results

Question[a]	Responses
1) Geographic area	- Northeast US (ex: Massachusetts, New York, Pennsylvania, etc.) - 15 (33.3%) - South US (ex: Texas, North/South Carolina, Florida, etc.) - 13 (31.1%) - Mid-West US (ex: Michigan, Wisconsin, Illinois, etc.) - 9 (20.0%) - West US (ex: California, Oregon, Colorado, Hawaii, etc.) - 7 (15.6%)
2) Frequency of scheduled simulation education for residents	- 1 to 4 times per year (I.e. quarterly / annually) - 28 (62.2%) - Approximately once a month - 10 (22.2%) - 2 to 4 times per month (I.e., weekly / every other week) - 3 (6.7%) - Other[d] - 4 (8.9%)
3) Estimated participation rate of residents & scheduled simulations	- 80 – 100% - 36 (80%) - 60 – 79% - 8 (17.8%) - 40 – 59% - 0 (0%) - 20 – 39% - 1 (2.2%) - 0 – 19% - 0 (0%)
4) Locations of simulation-based training (Check all that apply)[c]	- On-campus central simulation lab shared with other departments - 38 (84.4%) - Off-campus simulation lab which is not directly affiliated with your organization - 9 (20.0%) - Dedicated space designed exclusively for anesthesia department - 16 (35.6%) - Anesthesia departments break rooms / lounges - 8 (17.8%) - Conference rooms / auditoriums (shared spaces) - 11 (24.4%) - Other[e] – 13 (28.9%)

Chart 1. Skills and Activities at Primary Simulation Spaces.

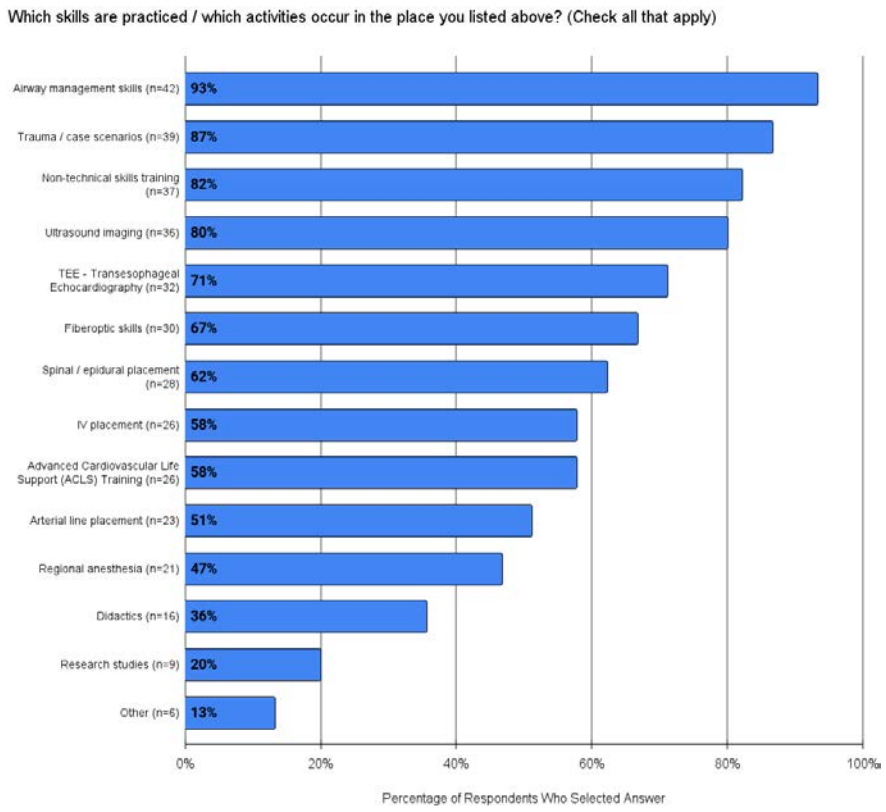


Chart 2. Resources at Primary Simulation Spaces.

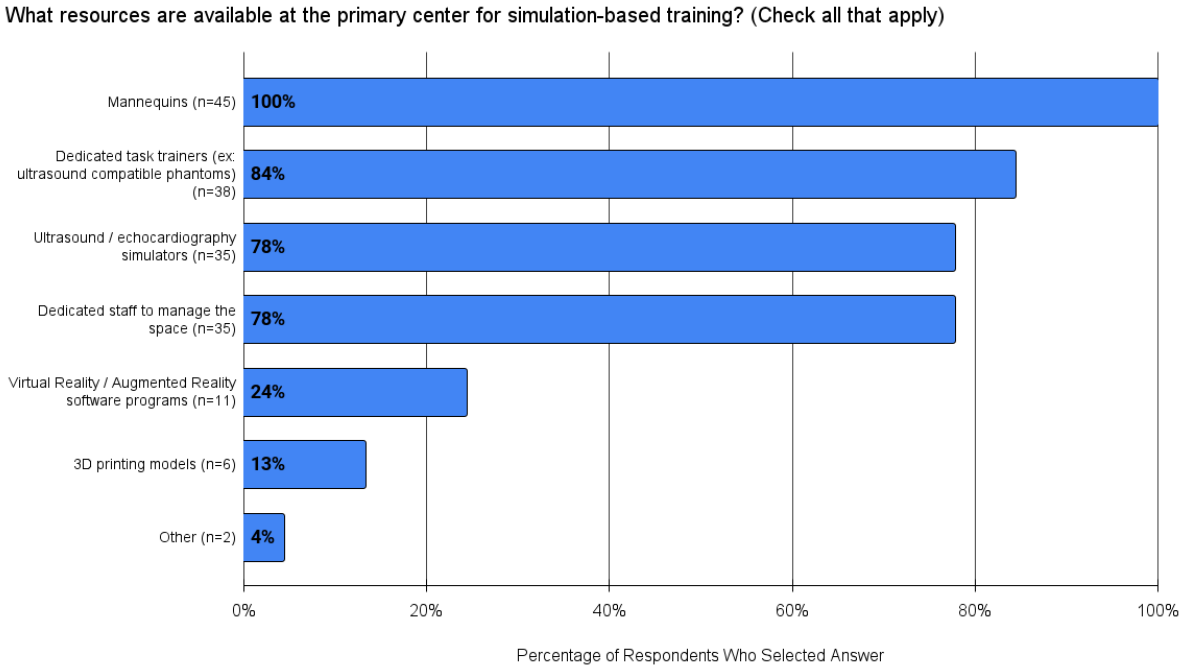
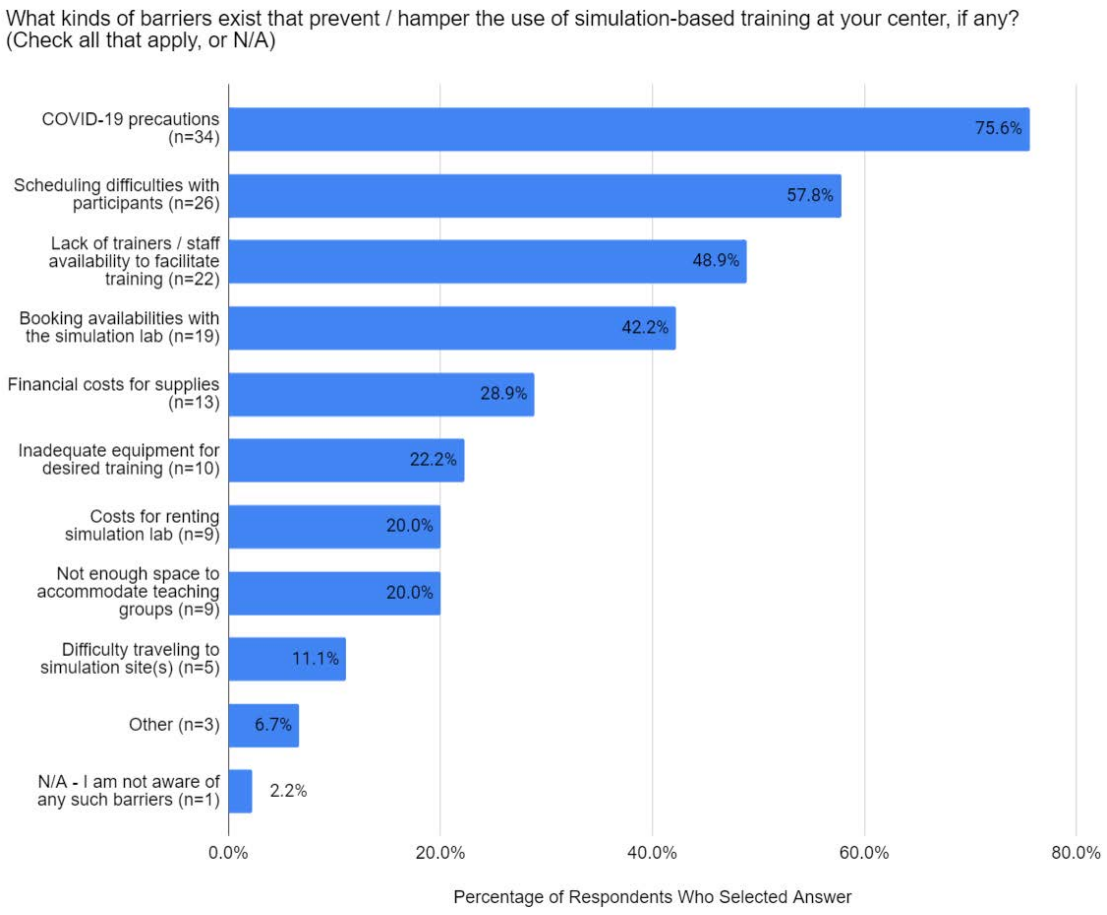


Chart 3. Barriers to Simulation.



Confidential

Simulation and Skills Training Needs Assessment

[redacted] is performing a needs assessment on how anesthesia residency programs use simulation-based medical education (SBME). We wish to determine how frequently SBME occurs, where SBME occurs, what types of training are occurring at those places, what barriers may exist that prevent / complicate conducting SBME. and gauge interests in the concepts of a SBME-compatible space designed specifically for use by an anesthesia department.

Participating in this survey is optional and voluntary, and may not benefit you directly. Responses are anonymous, and you may skip any questions you do not wish to answer. Thank you for your time!

1) Which of the following best describes the geographic area your program is located?	◯ Northeast US (ex: Massachusetts, New York, Pennsylvania, etc.) ◯ Mid-West US (ex: Michigan, Wisconsin, Illinois, etc.) ◯ South US (ex: Texas, North/South Carolina, Florida, etc.) ◯ West US (ex: California, Oregon, Colorado, Hawaii, etc.) ◯ Other
Please note the geographic area your program is located:	_____
2) Which of the following best describes how frequently any given resident participates in simulation based training as part of your program, on average?	◯ Never ◯ Only for orientation / initial training as first-year residents, but never afterwards ◯ 1 to 4 times per year (i.e. quarterly / annually) ◯ Approximately once a month ◯ 2 to 4 times per month (i.e. weekly / every other week) ◯ Other
Please describe how frequently any given resident participates in simulation based training as part of your program, on average:	_____
3) What is the rough estimate of resident participation rates in scheduled simulation training events? (overall)	◯ 80 - 100% participation ◯ 60 - 79% participation ◯ 40 - 59% participation ◯ 20 - 39% participation ◯ 0 - 19% participation ◯ Other
Please note the rough estimate of resident participation rates in scheduled simulation training events (overall):	_____
4) In which locations does simulation-based training take place at your program? (Check all that apply)	☐ On-campus central simulation lab shared with other departments ☐ Off-campus simulation lab which is not directly affiliated with your organization ☐ Dedicated space designed exclusively for anesthesia department ☐ Anesthesia department's break rooms / lounges ☐ Conference rooms / auditoriums (shared spaces) ☐ Other
Please specify the other locations in which simulation-based training takes place at your program:	_____

ECONOMICS, EDUCATION AND POLICY 28

Cognitive Burden and Impact of Anesthesia Trainee Status on Heart Rate Variability

Jacquelin Peck[1], Michael Wishon[2], Harrison Wittels[2]

[1]Mount Sinai Medical Center, Miami Beach, FL, [2]TigerTech Solutions, Miami, FL

INTRODUCTION: Heart rate variability (HRV) has been linked to memory, attention, and cognition.[1] Reduced HRV caused by physical or mental fatigue and has been linked to poor cognitive performance and decreased emotional flexibility.1 HRV has also been extensively studied among elite athletes to optimize performance.[2,3] During medical training, anesthesia trainees face long hours, potentially emotionally distressing clinical situations, and the expectation to master a large body of new information. However, the impact of clinical duty hours on HRV has not yet been evaluated. Aims: The aim of this study is to compare changes in HRV among medical trainees to changes in HRV among licensed anesthesia providers over the course of a clinical shift to determine whether HRV is affected by learning. Secondary aims include evaluating the potential impact that trainee characteristics such as age, sex, BMI, nightly sleep patterns, and self-reported alcohol and caffeine consumption may have on HRV changes.

METHODS: This is an IRB approved, prospective observational study comparing baseline to end-of-shift HRV among anesthesia trainees. Twenty-six trainees (SRNAs or Residents) were randomly selected based upon availability and were compared to thirty-five licensed anesthesia providers in educator roles (CRNAs or Attending Physicians) who were assigned to the same case as the trainee. Each participant underwent a 5-minute biophysical recording consisting of electrocardiogram, plethysmography, temperature, and pulse oximetry before starting clinical duties for the day and again in the afternoon following a 30-minute break. Recordings were performed while stationary and in a seated position. A 9-degree-of-freedom inertial measurement unit was worn throughout the day to control for physical exertion as a potential confounder.

RESULTS: Participant characteristics are presented in Table 1. Compared to licensed providers, trainees were younger, but had similar BMIs, durations of sleep, and rates caffeine and alcohol consumption. Results of HRV analysis are presented in Table 2. Despite higher baseline HRV, trainees experienced a much more significant decline in HRV from morning to afternoon recordings across all domains. Analysis of age, sex, BMI, nightly sleep patterns, and self-reported alcohol and caffeine consumption is currently ongoing.

CONCLUSION: Though younger age is typically associated with improved preservation of HRV, trainees in this study showed significantly greater reductions in HRV across all domains. Reduction in HRV among trainees may reflect the cognitive burden of learning and the emotional stress of trying to perform clinical duties well while under observation. This physiologic decline supports the current use of duty hour protection to allow for adequate recovery. Increased HRV in the morning may also support the use of morning lectures over afternoon lectures to maximize learning and retention. Future studies directly assessing cognitive and behavioral performance among anesthesia trainees in the context of reduced HRV are currently ongoing.

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Table 1. Provider Characteristics

	Male (%)	Age Med (IQR)	BMI Med (IQR)	Caffeine (%)	Alcohol (%)	Sleep Med (IQR)
OVERALL	45	33.5 (38.5-28.5)	24.05 (26.75-21.35)	48.72	53.11	6 (6.9 – 5.1)
Trainee	43.33	29 (32-27)	24.05 (26.95-20.95)	45.98	49.21	6.1 (7.0 - 5.3)
Licensed Provider	36.36	37 (40-32.3)	24.3 (28.65-21.75)	50.82	49.61	5.9 (6.8 - 5.0)

Table 2. Heart Rate Variability Analysis

Type	Category	Median	IQR	Median	IQR	Percent Difference	p-values
pNN50 (%)	Licensed Provider	12.5	(8.5-18.5)	7.5	(4.5-11)	40	0.00076
	Trainee	22	(14-38)	8	(6-14)	63.63636364	0.001192
SDNN (ms)	Licensed Provider	131.5	(114.5-156.5)	101.5	(82.5-142)	22.81368821	0.002674
	Trainee	178	(123-206)	127	(95-141)	28.65168539	0.008538
rMSSD (ms)	Licensed Provider	31.5	(22-49)	27.5	(22-42)	12.6984127	0.052091
	Trainee	49	(24-71)	29.5	(21-36.5)	39.79591837	0.049584
LF/HF	Licensed Provider	1.62	(0.89-1.96)	2.15	(1.34-2.82)	-32.71604938	1.47E-07
	Trainee	1.07	(0.98-1.26)	2.13	(1.58-3.06)	-99.06542056	4.1E-08

ECONOMICS, EDUCATION AND POLICY 29

Multimodal, coached telehealth prehabilitation has high compliance and improves exercise and cognitive capacity prior to surgery: a pilot study

Benjamin Choisy[1], Julien Hedou[1], Franck Verdonk[1], Dyani Gaudilliere[1], Amy S Tsai[2], Kreeti Shankar[1], Masaki Sato[1], Jakob Einhaus[1], Edward A Ganio[3], Adam Bonham[1], Beatta Warrington[1], Somayeh Ahmad[1], Martha Tingle[1], kazuo Ando[3], Serena Bruckman[1], Martin S Angst[3], Cindy Kin[1], Brice Gaudilliere[4]

[1]Stanford University, Stanford, United States of America, [2]UC Davis School of Medicine, Sacramento, CA, [3]Stanford University School of Medicine, Stanford, CA, [4]Stanford University School of Medicine, Stanford, California

INTRODUCTION: Over 30 million surgeries are performed annually in the US, with up to 30% or patients experiencing recovery delays, prolonged pain, opioid consumption and functional impairment, contributing $8 billion annually to US health care costs. Novel interventions that improve pain resolution, minimize opioid exposure, and accelerate functional recovery are urgently needed. Multi-modal pre-operative optimization programs (prehab) integrating exercise with nutrition counseling and stress reduction have been shown to decrease postoperative complications, hasten recovery of functional capacity, decrease length of hospital stay, and decrease healthcare costs[1-5]. Preoperative cognitive training can decrease the incidence of postoperative cognitive decline[6] and postoperative delirium[7]. However, prehab programs are underutilized and compliance remains an issue, as lack of personalized guidance, motivation, and convenient transportation remain as barriers to consistent patient participation. Our approach tested a patient-centered, multimodal, coached prehabilitation program combining telehealth physical exercise training with nutritional counseling, cognitive training, and guided meditation designed to optimize each patient's ability to cope with the physical and mental stress of surgery and to recover faster, with fewer complications.

METHODS: Adult patients (N = 12) scheduled for major elective surgery under general anesthesia were recruited[8]. Baseline cognitive and exercise capacity was assessed using the quick mild cognitive impairment (qMCI) test, the six-minute walk test (6MWT), timed up and go (TUG), five times sit to stand test (5XSTST), and timed wall squat. All patients underwent coached prehabilitation (32.6±15.2 days, 10.67±3.38 sessions) via telehealth. Patients were also prescribed a home regimen of daily exercises, cognitive training with the Lumosity application, Mediterranean Diet nutrition instructions, and guided meditation recordings. Patients repeated the cognitive and fitness tests after the program, and compliance measures were recorded.

RESULTS: High overall patient compliance with nutrition (88%) and physical exercises (72%) was observed, while compliance on the guided meditation (55%) and cognitive exercises (33%) was moderate. We observed significant improvement between baseline and post-prehab scores on the qMCI ($p = 0.001$, 1-tailed, paired t tests), 6MWT ($p = 0.01$), and TUG ($p = 0.03$), as well as a trend towards longer wall squat time ($p = 0.05$). In addition, program length correlated iwth qMCI improvement ($r = 0.69$, $p = .03$), exercise compliance and correlated with 5TSTS improvement ($r = 0.87$, $p = .03$), qMCI improvement, and TUG improvement ($r = 0.90$, $p = .02$).

CONCLUSION: A multimodal, coached telehealth prehab program had high patient compliance for nutrition and physical exercise programs, resulting inimproved exercise and cognitive capacity prior to surgery. Comparative studies between coached telehealth prehab and standard prehab programs will be important to determine whether a high-compliance prehab program can positively alter clinical and biological (including immunological) risk factors for adverse post-operative outcomes.

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ECONOMICS, EDUCATION AND POLICY 30

Difficult Airway Simulation Training for undergraduate and medical students: Using 3D printed larynx for front of neck access (FONA)

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INTRODUCTION: Medical students on anesthesiology rotations may assist and/or perform intubations and learn about difficult airway management. However, most intubations are usually in patients with normal features. Certain programs offer medical students clinical experience with difficult airway management but may not typically practice advanced airway placement such as cricothyrotomies[1]. Surgical airway's require unique training and equipment that medical students may not receive before starting residency[2]. We present the development of a curriculum that was designed with the purpose of teaching difficult airway management to undergraduate clinical research assistants and cricothyrotomies to medical students using a 3D printed larynx for simulation training.

METHODS: Our project was divided into four separate phases (see Figure 1). The FONA device was created using the larynx file published by The International Airway Collaboration by an undergraduate from Dartmouth College. The FONA device was worn by a human participant in order to enhance the realism in the training exercise (see Figure 2)[3]. The medical student reviewed the pertinent anatomy for the undergraduate student and the difficult airway algorithm. Under the supervision of an attending anesthesiologist, the undergraduate and medical student practiced cricothyrotomies in the simulation lab at Dartmouth-Hitchcock Medical Center.

RESULTS: We utilized the 3D printed larynx for our FONA device, which created a realistic training environment for the performance of cricothyrotomies (see Figure 3). The training materials and curriculum developed enabled the training simulation used to train undergraduates as clinical research assistants in advanced airway management. The difficult airway algorithm was reviewed and the hands on training provided a very applicable training for the undergraduate and medical student, all which included the opportunity to learn anatomy, discuss clinical decision making, and practice hands-on experience via cricothyrotomies.

CONCLUSION: We developed a curriculum for students to learn the difficult airway algorithm and practice advanced airway management. We found the 3D-printed airway was a low-cost, high-fidelity means to introduce medical students to the FONA in the difficult airway algorithm. This gave students a more realistic and hands-on experience with cricothyrotomy skills. Our next step is to develop the curriculum by printing alternative models in different sizes and types in order to diversify the training experience by including abnormal anatomy.

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Figure 1. The phases of the advanced airway training for medical student and undergraduates.

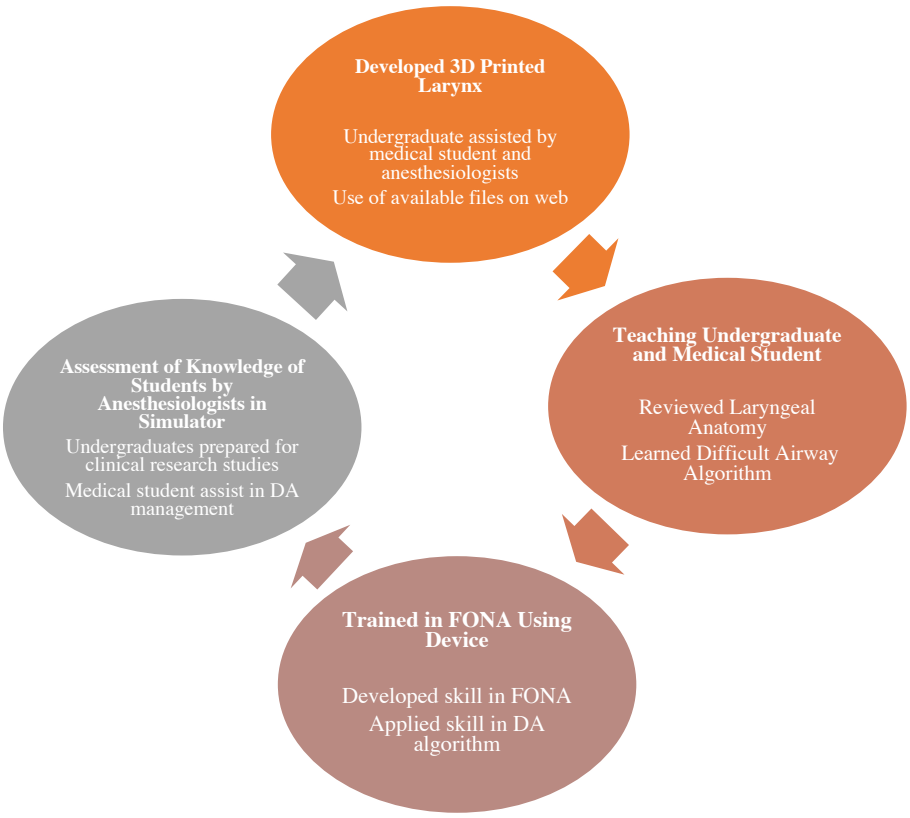


Figure 2. 3D Printed Larynx.

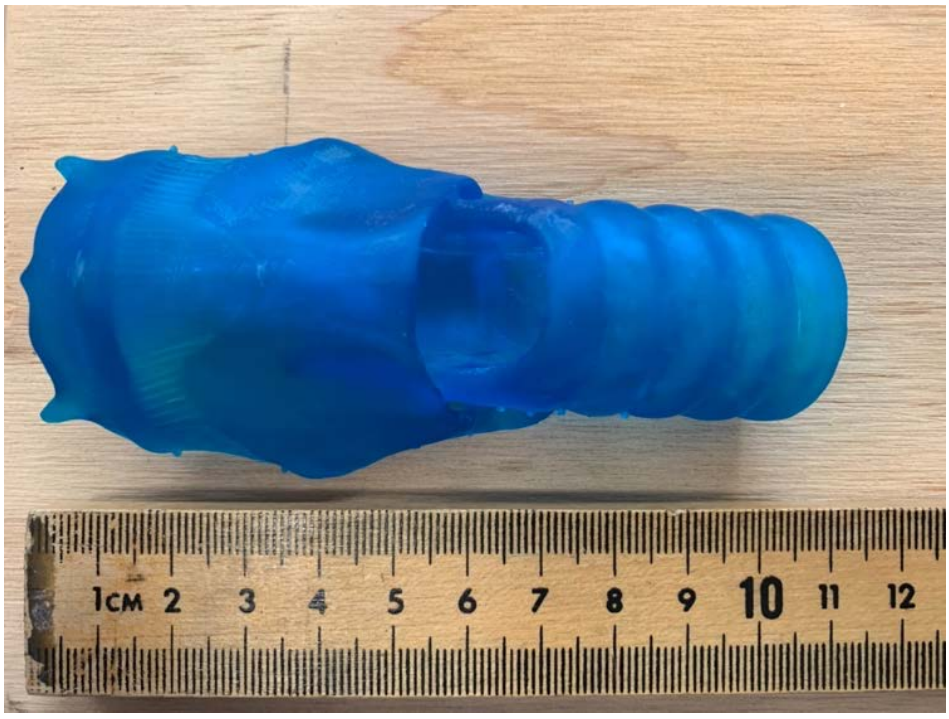
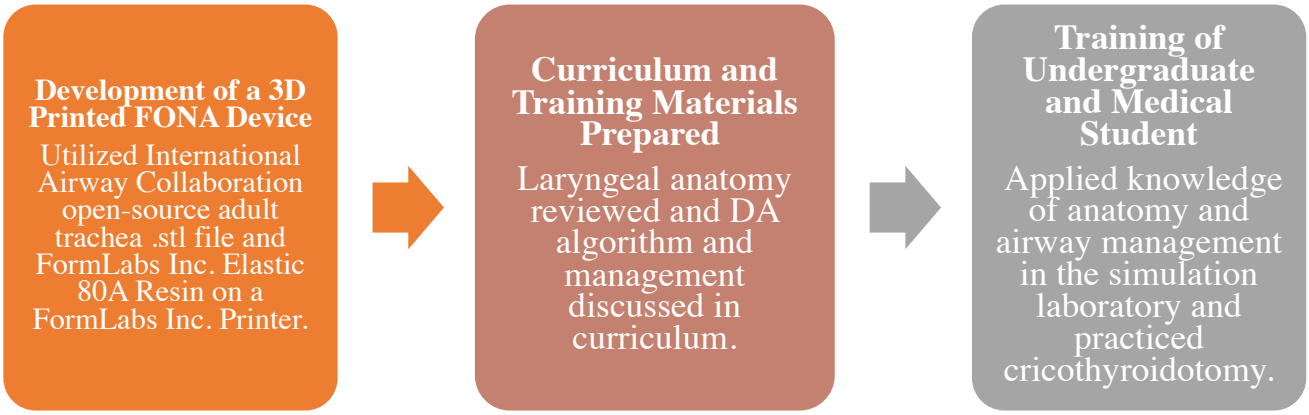


Figure 3. Curriculum for FONA device.



ECONOMICS, EDUCATION AND POLICY 31

A novel quality improvement initiative to increase anesthesia providers' use of quantitative neuromuscular monitoring

Karen McCarthy[1], Leslie C Fowler[1], Robert Freundlich[1], Amy Robertson[2], Matthew D McEvoy[1], Miklos Kertai[3], Pooja Santapuram[1]

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INTRODUCTION: There is strong evidence that using quantitative train of four (TOF) monitoring reduces complications associated with residual neuromuscular blockade (RNMB). Over the past several years, as there has been an increased use of sugammadex at our institution, there has also been a reciprocal decrease in the rate of TOF monitoring. Since the occurrence of RNMB can be as high as 10% after sugammadex administration we sought to increase the use of TOF monitoring in clinical practice. To accomplish this, we designed and tested a novel framework that included the Multicenter Perioperative Outcomes Group (MPOG) Anesthesiology Performance Improvement and Reporting Exchange (ASPIRE) quality improvement initiative program, a web-app based spaced education learning module (LM) and a series of REDCap surveys to help identify facilitators and barriers to department-wide implementation of best practice.

METHODS: The first intervention included monthly personalized provider-level feedback via email based upon institutional performance data uploaded to the MPOG database. Information was sent to each provider that showed the ASPIRE metric, their personal performance, and that of their peers. The second intervention utilized a targeted spaced education LM which included providers being sent multiple-choice questions (MCQs) via SMS text or email. One MCQ was sent to providers Monday through Friday for 4 weeks (May 10 - June 4, 2021). A Booster module of five MCQs selected from the original LM was sent August 30 to September 3, 2021. The primary outcome was a change in the rate of TOF monitoring by anesthesia providers before and after intervention. Facilitators and barriers to implementation of the intervention and to TOF monitoring were also collected. This was done via REDCap survey administered pre- and post-intervention.

RESULTS: There were 384 providers enrolled in the LM (Faculty = 139, Resident = 52, Fellow =14, CRNA = 179). The use of the ASPIRE QI program framework and QT LM was associated with an increase in TOF performance rate by 18.1% at our institution after the first intervention in May 2021 and by an additional 5% after the booster in September 2021. Overall, the TOF performance rate increased by 29% from January 2021 to November 2021.

CONCLUSION: The study demonstrated that the use of a targeted spaced education intervention combined with personalized feedback from the ASPIRE QI program framework was associated with an increase in the utilization of TOF monitoring at our institution. We were also able to identify key barriers to implementation, which remained the same before and after the intervention. This data will drive the focus of future organizational education efforts at our institution.

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ECONOMICS, EDUCATION AND POLICY 32

Burnout in Anesthesiologists Underrepresented in Medicine

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[1]Memorial Sloan Kettering Cancer Center, New York, NY, [2]Boston Children's Hospital and Harvard Medical School, Boston, MA, [3]Children's Hospital Boston, Boston, MA

INTRODUCTION: Burnout is characterized by emotional exhaustion, depersonalization, and low sense of personal accomplishment,[1] and is associated with poorer quality of care and patient safety.[2,3] Anesthesiologists are at high risk for burnout with an alarming 59.2% of US anesthesiologists reporting emotional exhaustion and/or depersonalization.[4,5] In this study we evaluated the risk factors for burnout among anesthesiologists who identify as underrepresented based on race (UiM) and/or consider English as a second language (ESL).

METHODS: Data for this subgroup analysis was collected from a national survey of US attending anesthesiologists conducted between March 6, 2020, and March 30, 2020. Burnout was assessed using the Maslach Burnout Inventory Human Services Survey.[1] We considered high scores in emotional exhaustions and/or depersonalization to indicate high risk for burnout. Burnout syndrome was defined by the presence of the three dimensions of burnout. Additional questions were added to the survey, focusing on personal and occupational risk factors for burnout. For each subgroup univariate comparisons by high risk for burnout were performed. Multivariate logistic regression analysis was performed to investigate the association between identifying as UiM and/or ESL and burnout.

RESULTS: When compared to all respondents (3,898), those who identify as UiM (398), ESL (236) and both UiM and ESL (70) had similar rates of burnout syndrome (13.8% vs 13.1% vs 13.6% vs 14.3%) and high risk for burnout (52.9% vs 56.8% vs 52.5% vs 55.7%). When compared to their non-UiM counterparts, UiM anesthesiologists at high risk for burnout reported significantly lower rates of having someone available to safely talk about concerns at work (26.0% vs 17.7%). Among those considered high risk for burnout, adjusted odds of lack of support in work-life were significantly higher in those who identify as UiM (OR, 19.7; 95% CI, 9.74-39.7), ESL (OR, 7.56; 95% CI, 3.26-17.5) and both UiM and ESL (OR, 10.4; 95% CI, 2.21-49.4) when compared to all respondents (OR, 6.7; 95% CI, 5.3-8.5).

CONCLUSION: Anesthesiologists who identify as racial/ethnic minorities report burnout at comparable rates to their non-minority counterparts. Lack of support in the workplace is the independent risk factor most strongly associated with high risk for burnout among UiM and ESL anesthesiologists. The association of lack of support in work-life and high risk for burnout is significantly greater among UiM anesthesiologist when compared to all respondents. Our study suggests that burnout rate alone, as it is currently measured and reported, does not tell the entire story of burnout among UiM physicians. Our study also suggests that the true identity of burnout among UiM physicians rests in the details of the workplace environment that UiM physicians face.

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Figure 1: Dimensions associated with Burnout

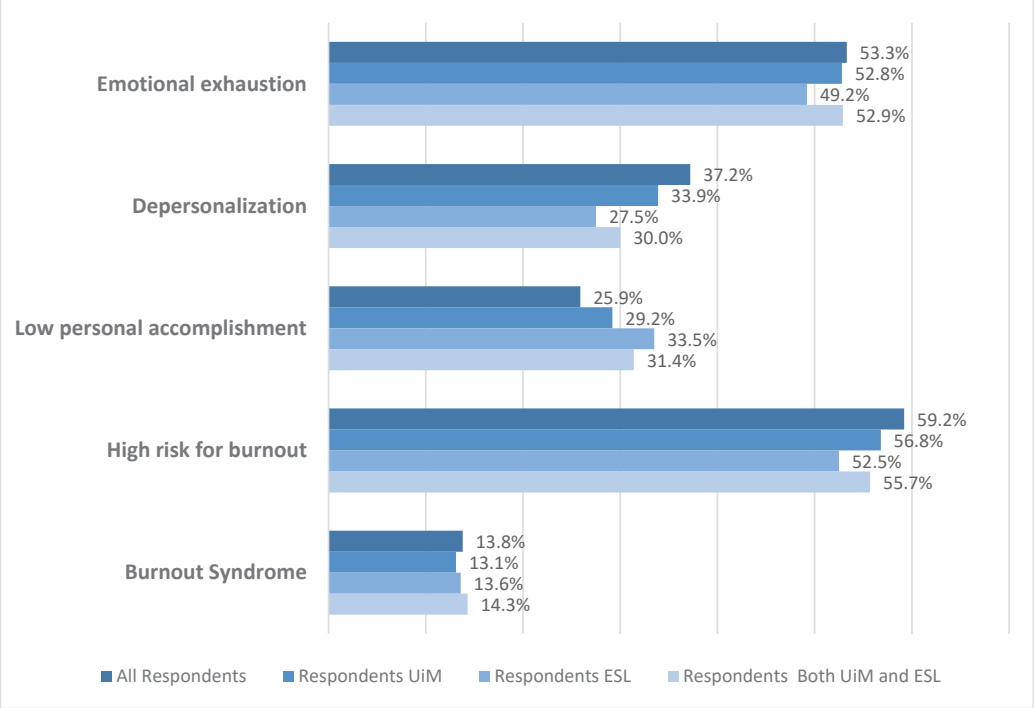
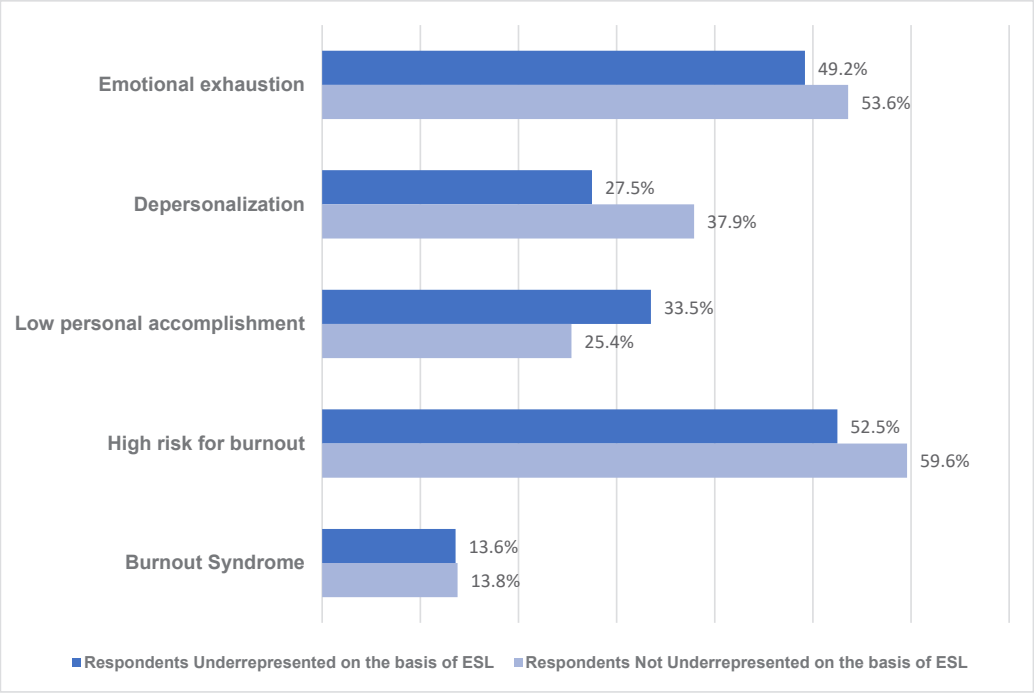
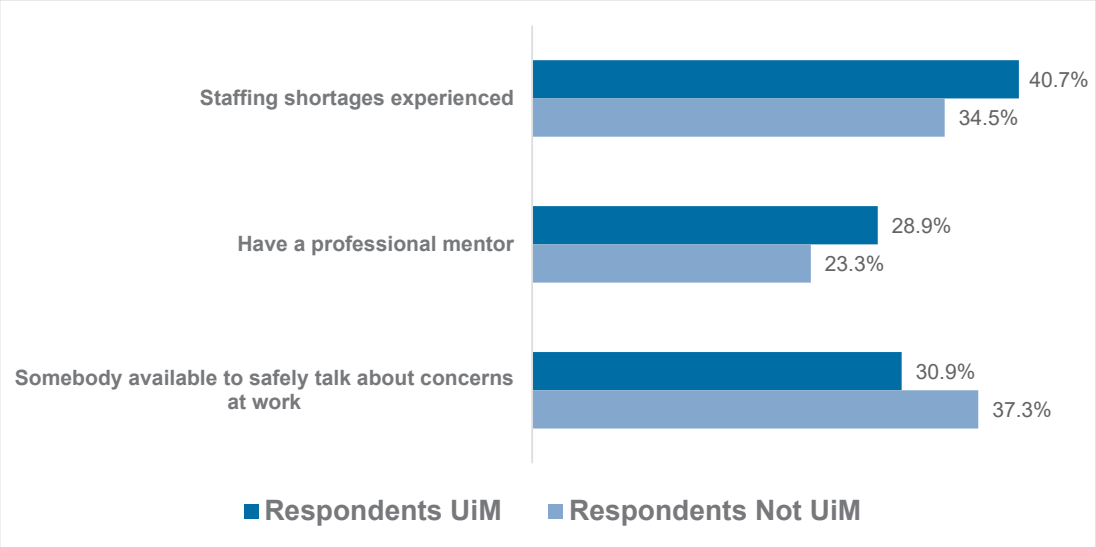


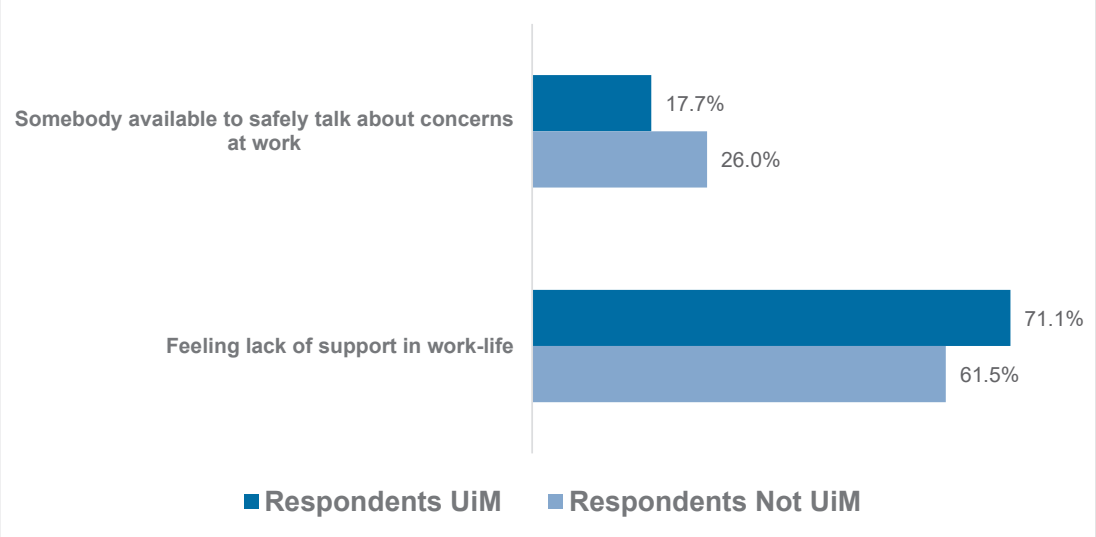
Figure 2: Dimensions associated with burnout in ESL compared to non-ESL



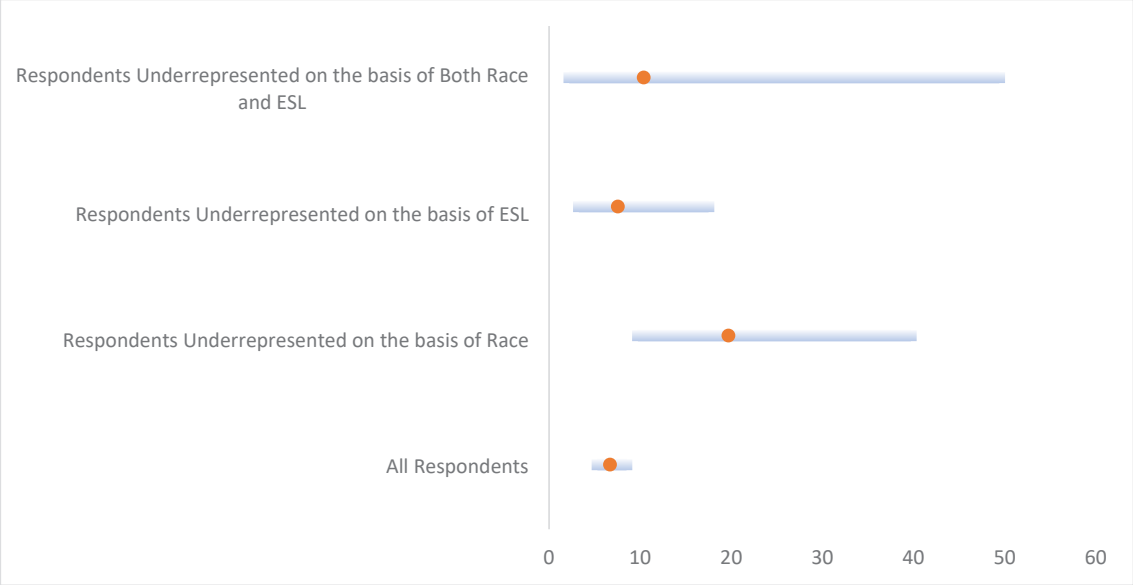
UiM vs Non-UiM



High Risk for Burnout: UiM vs Non-UiM



Adjusted Odds Ratio for Lack of Support in Work-Life Among High Risk for Burnout



ECONOMICS, EDUCATION AND POLICY 33

Practice Patterns and Knowledge Gaps of Anesthetic Gas Usage amongst Anesthesiology Departments in the University of California Hospital System: A Multi-Center Survey

Aalap C Shah[1], Aaron Przybysz[1], Kaiyi Wang[2], Solmaz P Manuel[2], Rakhi Dayal[1], Michael J Jung[3], Ian Jones[4], Seema Gandhi[5]

[1]University of California, Irvine Health, Orange, CA, [2]University of California, San Francisco Health, San Francisco, CA, [3]University of California, Davis Health, San Francisco, CA, [4]University of California, Irvine School of Medicine, Irvine, CA, [5]University of California San Francisco, San Francisco, CA

INTRODUCTION: Direct emission of inhaled volatile anesthetics (VA), while ubiquitously used to achieve general anesthesia, contribute up to up 1% of total global carbon dioxide emissions (eCO2)[1] and account for more than half of the eCO2 from medical perioperative services in a large healthcare system.[2] Adaptation of low fresh gas flows (FGF) to decrease eCO2 and consumption of sevoflurane VA has been proposed as a strategy to decrease greenhouse effect contributions and ozone layer depletion.[3] However, this adaptation with sevoflurane is currently considered 'off-label' given the original FDA recommendations for use of FGF > 2 L/min to prevent the formation of nephrotoxic Compound A, and thus its implementation has been variable. Nevertheless, numerous studies have corroborated the safe practice of low FGF with sevoflurane without renal toxicity.[4-7] In this study, we discern potential knowledge gaps and practice patterns related to CO2 absorbent usage and intraoperative delivery of FGF to target for future sustainability endeavors.

METHODS: A survey was administered anonymously to attending anesthesiologists, anesthesiology residents, and certified registered nurse anesthetists (CRNAs) in the anesthesiology departments of five University of California medical centers between January and March 2021. Institution-specific conservation and sustainability committees hosted hour-long educational presentations prior to survey distribution. In addition to practice volume and experience, respondents were queried regarding their awareness of the type of CO2 absorbent in use at their hospital, cost-effectiveness and environmental impact (eCO2) of sevoflurane, isoflurane, and desflurane VAs, and typical maintenance flows associated with these VAs. For knowledge assessment questions, responses such as 'unsure' and 'N/A' were grouped with incorrect answers. Chi square tests were used to analyzed categorical variables and results stratified by level of training. Statistically significant comparisons were entered into a post hoc analysis to calculate residuals for cell significance.

RESULTS: In total, 368 (44% physicians, 30% residents, and 26% nurse anesthetists) respondents completed and returned surveys. Seventy-six percent of all respondents were unaware or unsure about what type of CO2 absorbent they use without a statistically significant difference between groups based on level of training (79%% anesthesiologists, 67% nurse anesthetists, and 78% residents; p=0.07). Fifty-nine percent and 48% % of respondents used sevoflurane and desflurane with FGF ≥ 1 L/min, respectively, with a significantly greater proportion of anesthesiologists using lower FGF (<1 L/min) (p=.005). Most participants identified desflurane as the least environmentally friendly VA (89.9%) and a greater proportion of anesthesiologists correctly identified the most cost-effective VA (78.3%, p=0.02)

CONCLUSION: Significant knowledge gaps and variations in CO2 absorbent use and intraoperative fresh gas flow delivery exist within the anesthesia care team within a multi-institutional university system. Educational initiatives that improve awareness of our individual carbon footprints and integrated technical best practice advisories may address these knowledge deficits, decrease anesthetic consumption and associated costs, and ultimately benefit the environment through a sustainable change in practice.

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	UC Davis (N=89)	UCI (N=73)	UCLA (N=37)	UCSD (N=50)	UCSF (N=119)	Overall (N=368)
Level of Training						
Anesthesiologist	36 (40.4%)	33 (45.2%)	1 (2.7%)	20 (40.0%)	71 (59.7%)	161 (43.8%)
CRNA	33 (37.1%)	28 (38.4%)	0 (0%)	12 (24.0%)	24 (20.2%)	97 (26.4%)
Trainee	20 (22.5%)	12 (16.4%)	36 (97.3%)	18 (36.0%)	24 (20.2%)	110 (29.9%)
Gender						
Female	41 (46.1%)	32 (43.8%)	17 (45.9%)	25 (50.0%)	54 (45.4%)	169 (45.9%)
Male	47 (52.8%)	40 (54.8%)	20 (54.1%)	25 (50.0%)	62 (52.1%)	194 (52.7%)
Prefer not to say	1 (1.1%)	1 (1.4%)	0 (0%)	0 (0%)	3 (2.5%)	5 (1.4%)
Region of Training						
Midwest	2 (2.2%)	7 (9.6%)	0 (0%)	3 (6.0%)	2 (1.7%)	14 (3.8%)
NA	9 (10.1%)	4 (5.5%)	0 (0%)	3 (6.0%)	15 (12.6%)	31 (8.4%)
Northeast	7 (7.9%)	14 (19.2%)	0 (0%)	7 (14.0%)	19 (16.0%)	47 (12.8%)
Not specified	1 (1.1%)	2 (2.7%)	0 (0%)	1 (2.0%)	8 (6.7%)	12 (3.3%)
South/Southeast	9 (10.1%)	6 (8.2%)	1 (2.7%)	7 (14.0%)	9 (7.6%)	32 (8.7%)
West	61 (68.5%)	40 (54.8%)	36 (97.3%)	29 (58.0%)	66 (55.5%)	232 (63.0%)
Patient Population						
Mixed - both insured and uninsured	81 (91.0%)	64 (87.7%)	17 (45.9%)	41 (82.0%)	80 (67.2%)	283 (76.9%)
Mostly insured	2 (2.2%)	7 (9.6%)	20 (54.1%)	6 (12.0%)	23 (19.3%)	58 (15.8%)
Mostly uninsured/Medicaid	5 (5.6%)	2 (2.7%)	0 (0%)	0 (0%)	12 (10.1%)	19 (5.2%)
NA	1 (1.1%)	0 (0%)	0 (0%)	2 (4.0%)	2 (1.7%)	5 (1.4%)
Other	0 (0%)	0 (0%)	0 (0%)	1 (2.0%)	2 (1.7%)	3 (0.8%)
Numbers of GA Provided in a week						
0-10 patients	19 (21.3%)	16 (21.9%)	12 (32.4%)	12 (24.0%)	64 (53.8%)	123 (33.4%)
11-20 patients	36 (40.4%)	35 (47.9%)	22 (59.5%)	24 (48.0%)	36 (30.3%)	153 (41.6%)
More than 20 patients	34 (38.2%)	22 (30.1%)	3 (8.1%)	14 (28.0%)	19 (16.0%)	92 (25.0%)

Table 1

	Anesthesiologist (N=161)	CRNA (N=97)	Trainee (N=110)	P-value
Sevo_Maintainance				
Goal FGF < 1 L/min	73 (45.3%)	29 (29.9%)	40 (36.4%)	0.00507
Goal FGF >= 1 L/min	82 (50.9%)	63 (64.9%)	56 (50.9%)	
NA	6 (3.7%)	5 (5.2%)	14 (12.7%)	
Des_Maintainance				
Goal FGF < 1 L/min	61 (37.9%)	32 (33.0%)	41 (37.3%)	0.483
Goal FGF >= 1 L/min	48 (29.8%)	33 (34.0%)	42 (38.2%)	
NA	52 (32.3%)	32 (33.0%)	27 (24.5%)	

Table 2

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Interprofessional Anesthesia Simulation: Education of Resident Physicians and Student Anesthetists

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INTRODUCTION: Many anesthesia groups across the United States practice in an Anesthesia Care Team Model using medical direction or medical supervision. Few, if any, ACGME approved residency programs in anesthesiology include interprofessional training on how to work in an anesthesia team. We propose our innovative interprofessional simulation event as a way to close this educational gap in anesthesia resident physician training.

METHODS: Fifty three Clinical Anesthesia Year 2 and 3 anesthesia resident physicians participated in interprofessional simulations with a team of approximately ten Student Anesthesiologist Assistants (SAAs) over two years. Each resident physician was in the 'hot seat' for one simulation where they provided medical direction to two simulated operating room cases with SAAs playing the role of anesthetist as an embedded participant. Scenarios included every day situations where anesthesiologists need to prioritize which room, patient, and anesthetist demanded their clinical attention and presence. The simulation day also included a discussion, question, and answer period on anesthesia billing: medical supervision vs. medical direction vs. QZ.

RESULTS: Overall feedback from both resident physicians and SAAs was positive. In 2020, feedback from CA3s was to move the simulation to CA2 year when residents are looking for jobs, with the majority of residents noting they wish they had been told about anesthesia billing practices before they signed contracts for jobs. In 2021, only one third to one half of CA2s already had signed for jobs after residency graduation at the time of the simulation. This encouraged a robust and interactive conversation about anesthesia billing practices across our state of Indiana. Debriefing conversations were qualitatively themed across all groups. All debriefings included a discussion of how participants felt being needed in two places at the same time as well as the obstacles of the scenario. Topics discussed with every group also included how to communicate best, technology challenges with communication, how to plan for breaks, how to ask for help from colleagues, how to effectively use your circulating nurse, and how to maintain professionalism in stressful situations. Many participants noted how hard it was to both take care of a patient and send messages at the same time. We also discussed that relationships between anesthesiologists and anesthetists take time to develop and there is a balance in managing the art of an anesthetic versus asking someone to follow evidence based best practice. Topics such as errors in handoff communication, second victim, error disclosure, and best practices in use of a medical translator were covered as they arose in the simulated scenarios.

CONCLUSION: Interprofessional simulations with resident physician anesthesiologists and anesthetists in training are possible to run and can provide a psychological safe learning environment for the practice of the seven steps of medical direction. Education on anesthesia billing is well perceived by anesthesia residents and should take place at all training institutions.

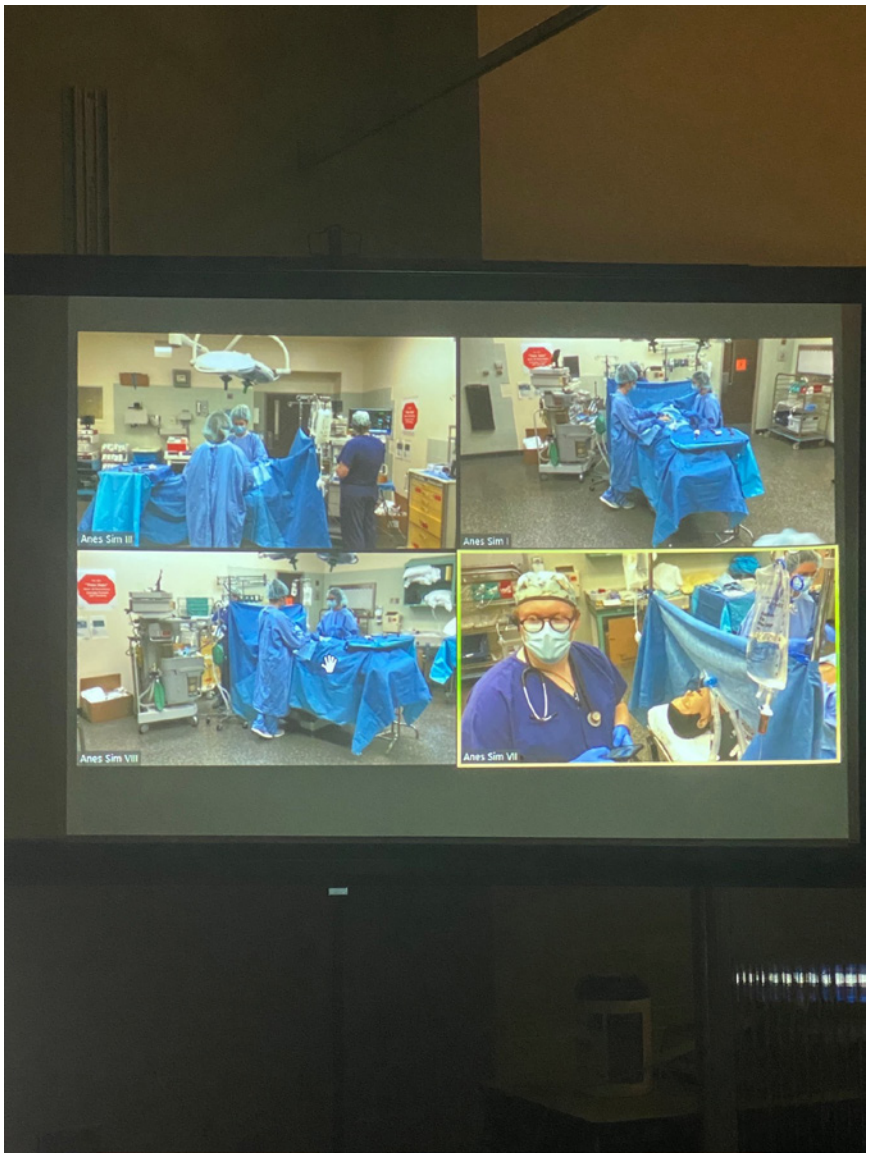

Figure 1

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The Purpose and Design of Pilot Studies in Anesthesia Research: Guidelines for Successful Planning of Larger Clinical Trials

Edward J Mascha[1]

[1]*Cleveland Clinic, Chesterland, OH*

INTRODUCTION: Far too often authors in perioperative and critical care medicine refer to small, underpowered and perhaps poorly designed and/or conducted studies as 'pilot' studies. Such studies might have little to no funding, have vague, poorly developed research proposals, and might simply be noted as possible helpful for a larger trial by future researchers. As well, it has been noted that many junior investigators can become entangled in a non-productive research strategy in which they design a series of small studies with 'negative' results (P>0.05) because they are not properly designing them as part of a larger goal. We clarify that a well done pilot study is not an exploratory or hypothesis-generating study of multiple exposures and outcomes, and is not an underpowered or poorly designed stand-alone study, or simply a smaller version of a larger study. Rather, a 'true' pilot study is well- designed and has clearly defined objectives that make it a useful planning tool for a larger clinical trial. We demonstrate these concepts by highlighting elements of published articles from Anesthesia & Anesthesia which bear the 'pilot study' label.

METHODS: In this presentation we therefore lay out the major functions that a well-done pilot studies might undertake: 1) estimating the variability and/or treatment effect in order to help power calculations for a subsequent larger study on the same topic (typically by the same researchers); 2) assessing the feasibility of various aspects of a clinical trial research protocol, including enrollment, details of the intervention, measuring the outcome variable, assessing compliance, achieving separation between groups on a mechanism variable, or training for investigational team, all for the purpose of planning and then conducting a larger trial on the same topic; 3) assessing the safety of a new intervention.[1,2] A pilot study thus needs to keep the next study in mind in its clearly stated objectives, with a study protocol specifically stating how the pilot study results will be used in planning that next larger study. As well, the sample size for a pilot study needs to be clearly justified based on the primary objectives. For example, if a primary objective is to estimate the variability (e.g., standard deviation) of the primary outcome for the future study, the pilot sample size can be justified as being large enough to estimate the standard deviation with sufficient precision. We further emphasize that a pilot study does not need to be powered to assess the efficacy of the intervention for the same primary outcome as planned for the larger trial, as that comparison will most likely be quite underpowered.

RESULTS: N/A

CONCLUSION: A pilot study is a very powerful tool for the planning of a larger clinical trial. In order to be successful the pilot study needs clearly stated objectives which keep the next larger study in mind, and might include estimating variability of the outcome, assessing feasibility of various aspects of the protocol, and assessing safety of the intervention. While many so-called pilot studies are currently not following these guidelines well, doing so in future studies should lead to better-designed clinical trials.

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Average relative effect versus standard multivariate tests for composite outcomes: extensions to count data and survival data

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INTRODUCTION: Biomedical researchers often assess the relationship between an exposure of interest and a composite endpoint consisting of multiple distinct components. Components are often a vector of binary events, such as distinct serious complications after surgery, but can represent counts, ordinal or even time-to-event outcomes. Guidelines for choosing components call for similar severity, frequency (for binary) and expected response to exposure. However, these are rarely all achieved. Thus, a key issue with standard analyses of binary-event composites is that components with the highest frequency dominate the overall treatment effect estimate, even though such components are often less serious. Mascha and Imrey (2010) introduced the average relative effect (ARE) test from a generalized Wald test as a solution for binary-event composites since it averages the distinct treatment effects across components, independent of their incidences.[1,2] The ARE test is more powerful than standard tests when smaller frequency components are most affected, and particularly appropriate when relative effects are at least as important as absolute effects.

METHODS: We consider extensions of the ARE test to count and survival data, since with standard multivariate methods the components with higher mean counts or baseline hazards, respectively, are also given disproportionate weight. Finally, we extend the ARE estimators to adjust for correlation between components. Applications use data from comparative effectiveness studies in perioperative medicine.

RESULTS: Extensions of the ARE test to count and survival data show that the tests protect against higher mean counts or higher baseline hazards from driving the composite outcome results (Table 1). As well, the correlation-adjusted ARE gives appropriate weights based on the inter-component correlations. Further, simulations show that power versus standard tests depends on heterogeneity of effects, correlation among components, and marginal means/hazards (Table 2).

CONCLUSION: The average relative effect estimator for composite outcomes is a marked improvement over traditional methods for binary, count and survival composite outcomes in regards to power when smaller components are more affected.

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DBS: multivariate results

Component	Mean (SD)		Negative binomial regression		
	Same Day N=22	Diff Day N=55	Beta (SE)	IRR (CI) [ratio of means]	P-value
# vaso meds	4.4 (4.0)	2.1 (2.1)	0.78 (0.26)	2.2 (1.3, 3.6)	0.002
# anti-hypertensives	0.18 (0.39)	0.34 (0.69)	-0.86 (0.67)	0.42 (0.11, 1.6)	0.198
Average relative effect	Mean of betas		-0.04(0.33)	0.96 (0.50, 1.8)	0.89
Common effect	Weighted towards #vaso		0.50(0.22)	1.6 (1.1, 2.6)	0.024
K-DF	Ignores directions				0.012
Interaction					0.011

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Table 1.

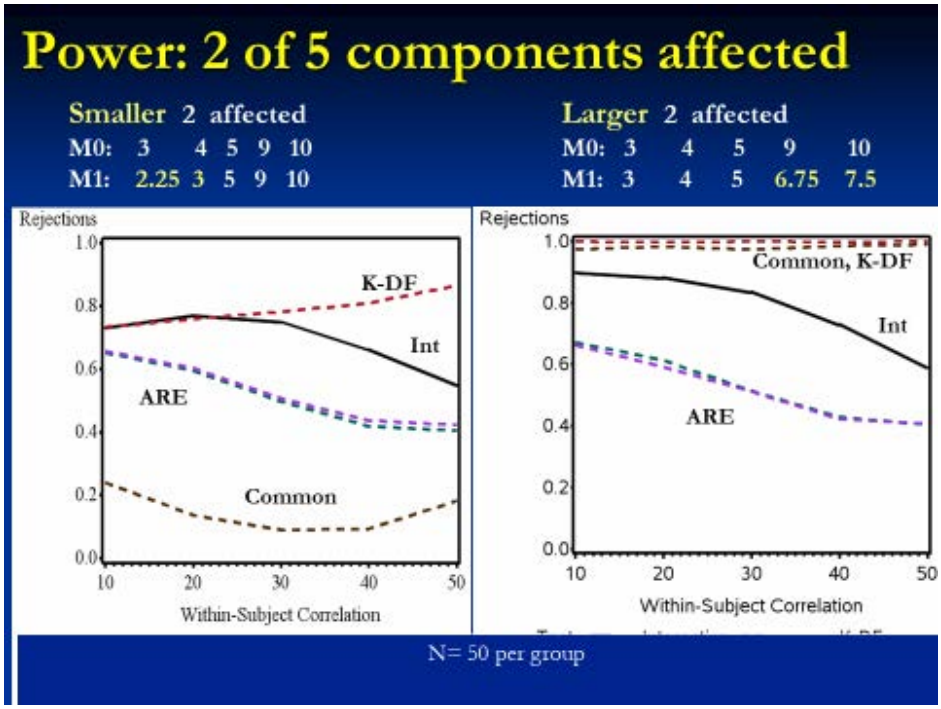

Fig. 1

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A Nudge in the Electronic Medical Record

Jennifer Yuan[1]

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INTRODUCTION: Behavioral economics has been gaining attention in recent years as a method to guide people to make 'better' decisions. Its toolkit for driving behavior with choice architecture as undeniably been impactful-the opt-in versus opt-out organ donation in European Countries, for instance, led the Netherlands to passing an organ donation law in 2020. However, as these nudges are being utilized more widely, it's apparent that some do not quite go as planned, and some may even backfire. Behavioral economics being deployed in the healthcare space is uniquely. Healthcare providers are highly educated people with sometimes strong individualistic qualities, often working under time pressure where any interruption of workflow can be perceived as extremely disruptive. A nudge, if utilized too obtrusively, may feel condescending or manipulative. A nudge that is too subtle may be overlooked altogether. As such, it is challenging to design a nudge for physicians and healthcare providers that is effective.

METHODS: In October 2019, University of Texas Southwestern Medical Centers deployed order sets with pricing symbols ($, $$, $$$) to signify cost of laboratory test and medications. These were embedded in order sets and were visible to ordering providers, with the goal that this would set up scenario in which people would make more economical decisions due to cost awareness. In October 2021, we surveyed the anesthesiology department to evaluate the perception and impact of the nudge.

RESULTS: In the survey responses of the UT Southwestern anesthesiology department (N = 122), only 60.7% of people noticed the price symbols in the order sets and 56.5% said the price symbols affected their order selection. However, 94.2% that delivering cost effective care was important for them. Looking at the responses more closely, of the attending anesthesiologists who responded (N = 49), 83.7% noticed the price symbols but only 59.2% said that the symbols affected their selection. Respondents who said that they noticed the price symbols but did not change behavior usually noted that they felt the medication or lab test they were selecting were not substitutable and necessary. Other people reported feeling unsure what the price symbols meant in actual prices, and thus continued to overlook them. However, despite these survey responses, 94.3% of all respondents and 93.9% of attending anesthesiologists reported that providing cost effective care was important to them.

CONCLUSION: Although people reported that providing cost effective care was important to them, their choices did not appear to be influenced by the price symbols. It may be that the price symbols embedded in order sets were too subtle to result in meaningful change in behavior, or the order sets themselves need to be revisited to provide more options. It is also possible that the actual monetary cost, rather than price symbols, would make a more impactful change. Moreover, upon discussion with some providers, we noted that there may be a misconception that cost effective care is not high-quality care; there may be an underlying bias that has not been fully explored. Overall, the survey was able to provide information on the user perception of the behavioral nudge and help guide in further iterations of this intervention.

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The Effect of Night Float Rotation on Resident Sleep, Activity, and Wellbeing: An Observational Study

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INTRODUCTION: Night float systems are becoming increasingly common at training programs with the goal of reducing fatigue related to sleep deprivation and sleep disturbance[1,2]. Prior studies have shown that trainees obtain less sleep during the night float rotation and have decreased sleep efficiency for several days after the rotation[3]. The impact on physical and emotional wellbeing has not been documented.

METHODS: Twenty-seven anesthesia resident trainees wore wearable activity trackers (Fitbit Alta HR) the week before, during, and after their night float rotation. Sleep hours and steps per day were captured. They also completed National Institutes of Health Patient Reported Outcome Measurement Information System (NIH PROMIS) surveys for Sleep Disturbance, Fatigue, and Positive Affect before, immediately after, and one week after completing a one-week night float rotation.

RESULTS: There was no difference in sleep hours or steps recorded on the wearable device when compared to baseline. Participants reported increased fatigue PROMIS scores (48.60[46.00,55.10] vs. 58.80[54.60,65.12], $p < 0.001$) immediately after the night float rotation that did not completely resolve one week later (51[48.6,58.8], $p=0.028$). Positive affect was reduced immediately after the night float rotation compared to baseline (44.80[40.12,49.60] vs. 39.60[35.00,43.50], $p<0.001$). Positive affect returned to baseline one week after the rotation (43.55[39.60,48.20].

CONCLUSION: The participants were a standard deviation more fatigued from their baseline at the end of their night float rotation despite no change in overall sleep hours, suggesting participants may need increased rest and recovery time when working at night. There may also be other emotional stressors associated with night work contributing to increased fatigue. More research is needed to identify optimal support to ameliorate fatigue and reduced affect to improve the night float rotation.

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Table 1. Demographic and Sleep Related Baseline Data
All data was self-reported before study onset. Participants have asked to report how much sleep they obtained on weekdays and weeknights, as well as estimate how much sleep they anticipated they would obtain per 24 hours while on a night float rotation, based on prior experience

Number of Participants	12
Age (years)	29.5 [29-31]
Female Gender	58%
Hours of Sleep - Weekday	6.5 [6-7]
Hours of Sleep - Weekend	8 [8-9]
Hours of Sleep - anticipated on night float	6 [5-6]
Non-prescription sleep aid use	30%
Caffeine Use	81%
Self-reported data before study onset Median [Interquartile Range]	

Figure 1: Sleep and Step Data from FitBit Alta HR

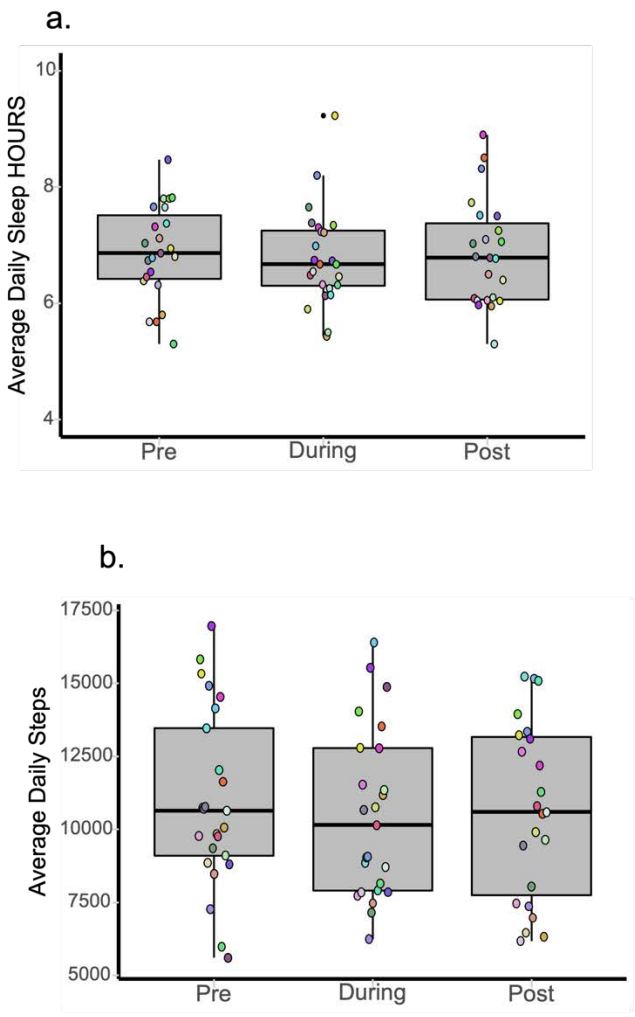

Figure 1a shows Total Sleep Hours per Day. Figure 1b shows Steps per day. The box and whisker plots present the median and interquartile ranges of the data. The whiskers extend to the most extreme values no further than 1.5 times the interquartile range. Each individual participant is identified by a distinct colored circle representing their median value for the week.

Figure 2: National Institutes of Health Patient-Reported Outcomes Measurement Information System Survey Results.

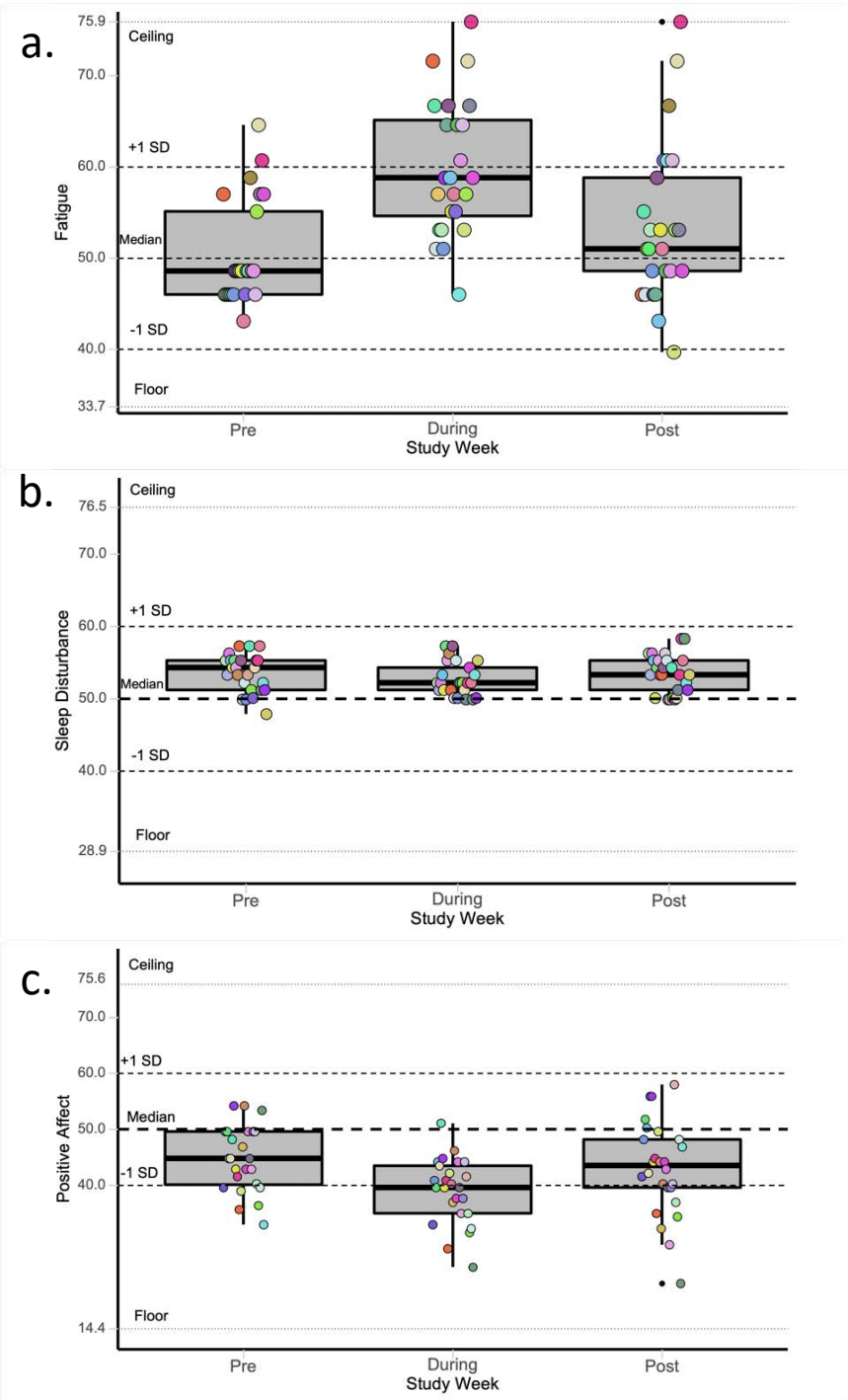

Figure 2a shows NIH PROMIS Fatigue. Figure 2b shows NIH PROMIS Sleep disturbance. Figure 2c shows NIH Promise Positive Affect. Lines identify the minimum (floor), -1 standard deviation, mean, +1 standard deviation, and maximum (ceiling) scores Each individual participant is identified by a distinct colored circle representing their median value for the week. Each increase or decrease of 10 represents 1 standard deviation noted with a fine dashed line. The ceiling and floor values for each instrument are noted with dotted lines.

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Buprenorphine Prescribing During the COVID-19 Pandemic: An Initial Disparities Analysis from the California Opioid Overdose Surveillance Dashboard

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INTRODUCTION: COVID-19 has exacerbated the opioid epidemic with about 100,000 opioid-related overdoses reported for 2020 alone. During this same interval, national data indicate that preexisting health care disparities may have worsened with poorer, Black, and Latino communities having markedly and disproportionately higher rates of opioid use disorder (OUD) and overdose.[1] Access to medication-assisted treatment, including buprenorphine and methadone, are key components of effective treatment for OUD and decrease risks for overdose. Prior to the epidemic, the Substance Abuse and Mental Health Services Administration (SAMHSA) was directed to geographically target its efforts to increase buprenorphine prescriptions for OUD treatment.[2] California maintains a near-real time opioid overdose surveillance dashboard that can give insight into these urgent public health issues. The dashboard includes a rich variety of metrics including buprenorphine prescribing rates and geographic markers like neighborhood socioeconomic status (nSES). As part of an ongoing disparities study on opioid treatment during the COVID-19 pandemic, we report interim analyses on whether SAMHSA's policies on buprenorphine prescribing were implemented in California during 2020.

METHODS: This study used publicly available, de-identified data and was exempt from IRB review. We included cross-sectional data at the zip code level for 2020 from the California Opioid Overdose Surveillance Dashboard 3 that integrates metrics for buprenorphine prescription; and 2) sociodemographic variables (including age, race, neighborhood socioeconomic status (nSES; using quintiles, 1st= lowest;5th =highest, wealthiest) from the University of California San Francisco Health Atlas. Our statistical analysis involved several steps: a) identified buprenorphine prescriptions per 1,000 residents by patient location, a measure of the relative number of prescriptions filled; b) categorized zip codes as potentially high risk for prescription disruption (yes/no if they were in the top 20% percentile of buprenorphine prescriptions); and c) used ordinary least squares and logistic regression models to analyze the association between nSES (using quintiles) and high-risk zip codes accounting for other factors including race and education. We used Python (version 3.10.0, Python Software Foundation) and Stata (version 17, Stata Corp.) for the statistical analyses. For all analyses, two-tailed nominal P-values of < 0.05 were considered significant.

RESULTS: Our study population was derived from 1,643 zip codes with complete data (i.e., 94.3% of 1741).The total number of unique buprenorphine prescriptions in California was n=132,626 in 2020. Overall, our population were nearly male (50.4%); between 18-64 years (60%); white (49.7%); with some college education (63.2%). For each nSES quintile group, the number of zip codes within each quintile are as follows: Q1(222); Q2(444); Q3(421);Q4(322); Q5(234). Notable characteristics of quintiles with highest rates of buprenorphine prescriptions (quintiles 2 and 3) were a plurality of white populations and high school degree education and were in highly rural counties like Sierra, Humboldt, and Shasta counties. The results of the linear and logistic regression models are displayed in Table 1. Variables associated with zip codes at higher risk for buprenorphine prescription disruption included poorer nSES quintiles (nSES 1-4); all age groups; women ; whites (OR=1.059;$p<0.05$); and those with less than high school education (OR=1.088, $p<0.05$).

CONCLUSION: Our analysis of the California Opioid Overdose Surveillance Dashboard in 2020 indicates that geographic areas of high buprenorphine prescriptions within California are characterized by low neighborhood socioeconomic status levels. Within these areas of high buprenorphine prescriptions, we found a higher percentage of white populations, patterns of lower education attainment, and were often in rural counties. SAMHSA's policies targeting lower socioeconomic status regions for buprenorphine prescribing were implemented in California during the pandemic. However, the beneficiaries were mostly white populations.[4] Our data suggest that further

improvement in effective treatment for OUD and decrease risks for overdose resources be directed to Black and Latino communities that often live in urban, lower socioeconomic status areas.

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ECONOMICS, EDUCATION AND POLICY 40

Race and Socioeconomic Status in Clinical Anesthesiology Research

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INTRODUCTION: Evidence Based Medicine (EBM), by definition, demands use of the best available evidence to make decisions about the care of individual patients. However, generalizability has been a long-standing concern when applying clinical research to real-world patients. Part of this discrepancy stems from recent research showing that racial/ethnic minorities and other disadvantaged populations bear a disproportionate burden of illness but are less likely to be included in clinical research samples. Recently, investigators have strived to better understand the impact of race and socioeconomic status (SES) on patient outcomes, but it is still unclear if these variables are consistently and effectively assessed. Specifically, there is a paucity of knowledge concerning the inclusion of race and SES in clinical anesthesiology research. Thus, we evaluated clinical anesthesiology publications to characterize the use of race and SES variables in anesthesiology research over a one-year period.

METHODS: Ten major, high impact anesthesiology journals were selected to include major anesthesiology subspecialties from a wide geographic origin (U.S.-based and international journals). Journals included were: Anesthesiology, British Journal of Anesthesiology, Anesthesia, Journal of Clinical Anesthesia, Intensive Care Medicine, Journal of Cardiothoracic and Vascular Anesthesia, International Journal of Obstetrics, Journal of Pain, Pediatric Anesthesia, and Regional Anesthesia and Pain Medicine. All articles published in 2019 were queried for review. Upon review of full text, all original human-participant clinical research studies were included in the analyses. Each article was manually analyzed to assess 1) if race and SES variables were collected and reported, 2) how race and SES variables (if specified) were defined, and 3) the extent to which race and SES were analyzed or discussed as variables of interest. Analyses of Means for Proportions and χ^2 tests were performed to detect differences between different anesthesia subspecialties in the frequency of reporting, analysis, and discussion of race and SES. χ^2 tests and Fisher's Exact Tests were performed to detect differences between geographic origin of study (i.e. United States-based studies vs. international studies).

RESULTS: Overall, 975 out of 3,090 (31.6%) articles met inclusion criteria. In total, 149 (15.3%) of studies specified race as a variable. Of the 149 studies that specified race, 29 (19.5%) defined race using racial and ethnic categories interchangeably. 143 (96.0%) reported data by race, 94 (63.1%) conducted analysis of race-based data, and 72 (48.3%) discussed race-based results. In total, 113 (11.6%) studies specified SES as a variable. Of the 113 studies that specified SES, 59 (52.2%) defined SES using education status, 31 (27.4%) using income level, 23 (20.4%) using health insurance (e.g. public vs. private), and 23 (20.4%) using employment status. 90 (79.6%) reported data by SES, 73 (64.6%) conducted analyses of SES-based data, and 65 (57.5%) discussed SES-based results. Lastly, sub-analysis by subspecialty revealed that compared to the average, 1) pain medicine articles reported/analyzed/discussed race ($p < 0.05$) and SES ($p < 0.05$) more, 2) cardiothoracic anesthesiology articles reported race ($p < 0.05$) and reported/analyzed/discussed SES ($p < 0.05$) less, 3) critical care anesthesiology articles analyzed race ($p < 0.05$) less, and 4) orthopedic/regional pain medicine articles analyzed SES ($p < 0.05$) more. Analysis of study location revealed that U.S.-based studies reported/analyzed/discussed race ($p < 0.05$) and SES ($p < 0.05$) more than international studies.

CONCLUSION: The inclusion of race and SES data in clinical anesthesiology research is low. Among studies that did specify race and SES data, the reporting and analyses of these data were even more limited. Although there was significant variation in rates of specification for race and SES data between different anesthesiology subspecialties, there remains a need to increase the specification of race and SES variables across all subspecialties. Thus, anesthesiology journals should emphasize increased reporting and analyses of race and SES data in order to improve the quality of anesthesiology research and care for all patients.

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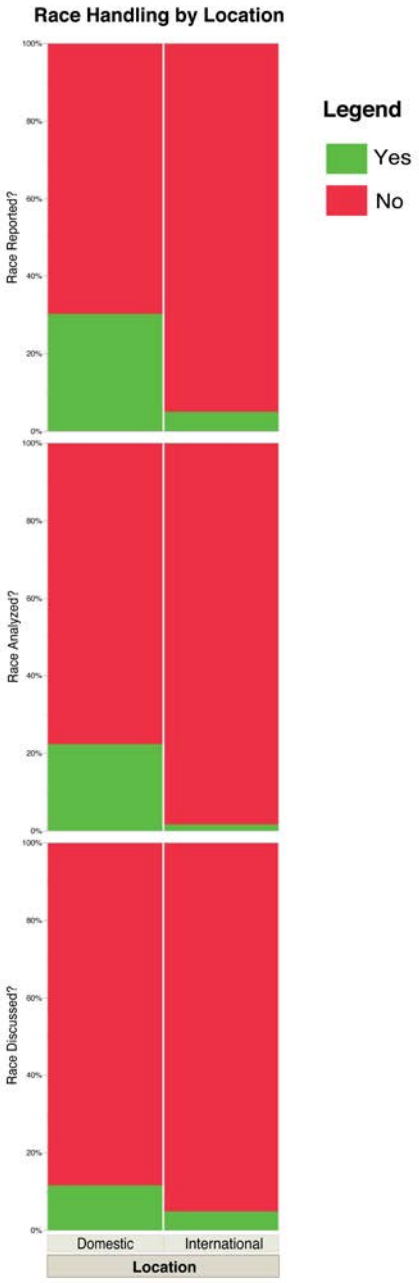

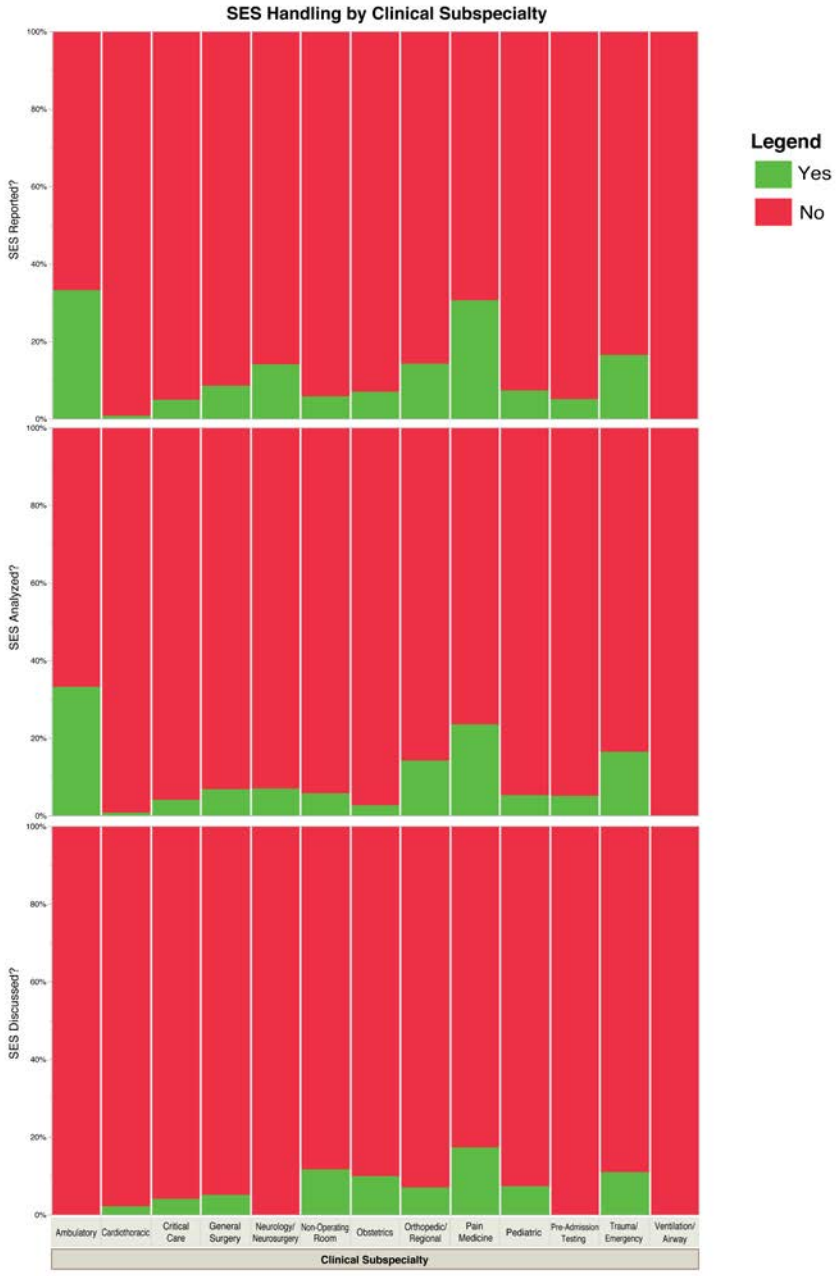

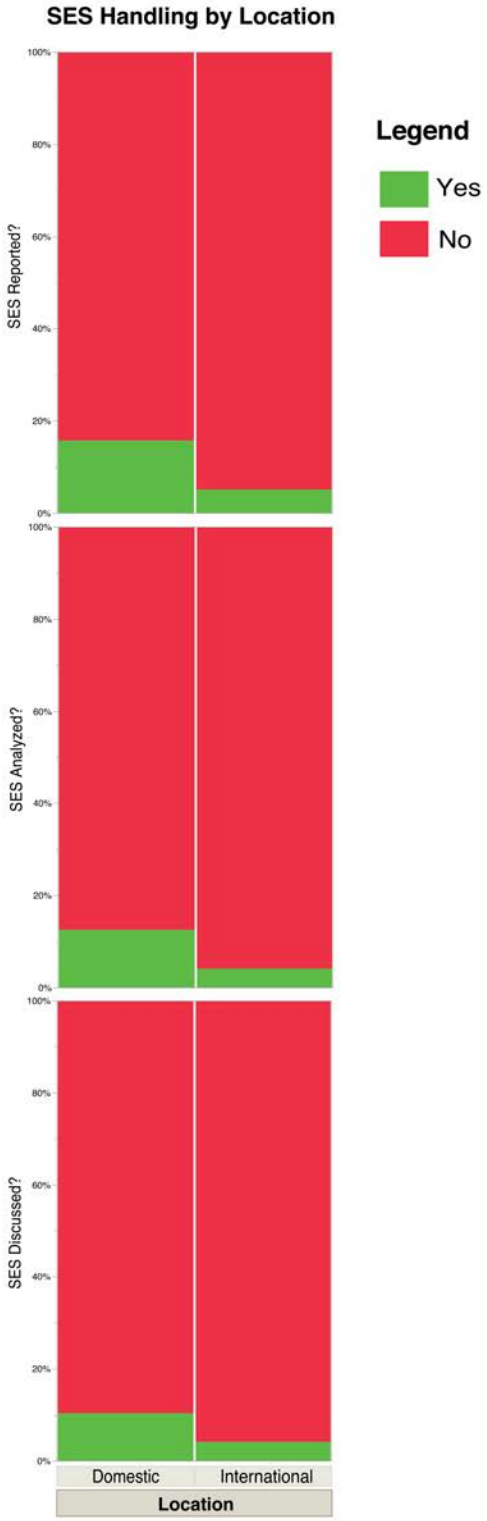

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Comparing the costs of Sugammadex vs. conventional muscle blockade reversal for laparoscopic cholecystectomy procedures

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INTRODUCTION: Laparoscopic cholecystectomy, the 3rd most commonly performed outpatient surgery, provides a model to examine outpatient Sugammadex utilization. Sugammadex can quickly and reliably reverse profound neuromuscular blockade. A study using the Multicenter Perioperative Outcomes Group database concluded that approximately 40% of cases receiving neuromuscular blockade utilized Sugammadex for reversal in 2018.[1] Conversely, the relatively high cost of Sugammadex compared to that of other conventional reversal drugs such as neostigmine is reported as a significant limitation in its routine use.[2] Therefore, our goal was to evaluate cost differences between Sugammadex and conventional reversal for laparoscopic cholecystectomies.

METHODS: We used the Premier Healthcare database to analyze cost data for outpatient laparoscopic cholecystectomy procedures performed at a large sample of hospitals in the United States, from January of 2016 to June of 2018. The sample was limited to procedures where patients received a neuromuscular blockade along with either Sugammadex or a conventional reversal drug (neostigmine, edrophonium, pyridostigmine, glycopyrrolate, or atropine). We then compared the mean total cost for procedures using Sugammadex (along or with other blockade drugs) versus any other used conventional reversal, without and with confounding adjustment including patient and hospital characteristics as well as time trends. We also performed the same comparison among Medicare patients, for whom we know the reimbursement rate for the procedure. Finally, we compared the change in costs between 2016 and 2018 among hospitals (a) switching from exclusively using conventional reversal to primarily using Sugammadex to (b) those that continued to exclusively use conventional blockade reversal.

RESULTS: We found an unadjusted difference in total costs per case of $5.89 (95% CI -$42.68 - $54.46), indicating no clinically meaningful difference in cost. However, the fully adjusted model identified that Sugammadex is associated with $42.25 (95% CI -$1.69 - $86.19) lower costs (Table 1). Among patients having Medicare, Sugammadex was associated with $87.67 (95% CI, -$7.84 - $183.18) in cost savings in the adjusted model (Table 2). Among the Medicare population, this increased 26.6% (95% CI -2.4% - 55.7%) on the average profit per procedure. We found no evidence that Sugammadex adoption is associated with increased costs at the hospital level (Table 3).

CONCLUSION: Numerous studies have demonstrated an increase in cost-effectiveness of outpatient surgery[3-5] making adoption of Sugammadex in the outpatient setting of particular interest, despite its higher costs when compared to neostigmine. Our results indicate that Sugammadex use is associated with cost reduction across different scenarios. Further investigation of complications and costs is recommended to assist institutions in developing policies regarding the optimal choice of neuromuscular blockade reversal. Supported in part by a research grant from Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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Table 1: Adjusted Cost Differences

	Model 1	Model 2	Model 3	Model 4
Sugammadex Use	5.89	-84.21***	-167.86***	-42.25
Standard Error	24.78	24.47	24.97	22.42
Controls				
Patient Characteristics	No	Yes	Yes	Yes
Year-Month Fixed Effects	No	No	Yes	Yes
Hospital Fixed Effects	No	No	No	Yes

Patient characteristics include sex, age, type of payer, race, the presence of each comorbidity used to calculate the van Walraven score, the use of IV acetaminophen, and the use of liposomal bupivacaine. Standard errors are heteroskedasticity-robust. * p<.05, ** p<.01 *** p<.001.

Table 2: Adjusted Cost Differences in Medicare Patients

	Model 1	Model 2	Model 3	Model 4
Sugammadex Use	-71.06	-172.78***	-262.21***	-87.67
Standard Error	52.10	51.71	53.08	48.73
Controls				
Patient Characteristics	No	Yes	Yes	Yes
Year-Month Fixed Effects	No	No	Yes	Yes
Hospital Fixed Effects	No	No	No	Yes

Sample is limited to patients with Traditional Medicare as their primary payer. Patient characteristics include sex, age, type of payer, race, the presence of each comorbidity used to calculate the van Walraven score, the use of IV acetaminophen, and the use of liposomal bupivacaine. Standard errors are heteroskedasticity-robust. * p<.05, ** p<.01 *** p<.001.

Table 3: Hospital-Level Cost Differences by Sugammadex Adoption Status

	Model 1	Model 2	Model 3	Model 4
Adopts Sugammadex	-178.10*	-105.86	-104.57	
	(88.09)	(57.68)	(86.96)	
After Potential Adoption	77.58***	70.45***		
	(12.68)	(12.45)		
Adoption x Post	-19.51	77.78	60.92	-292.10***
	(127.58)	(122.38)	(122.58)	(80.10)
Controls				
Patient Characteristics	No	Yes	Yes	Yes
Year-Month Fixed Effects	No	No	Yes	Yes
Hospital Fixed Effects	No	No	No	Yes

Sample is limited to patients treated from January to June in 2016 or 2018 at hospitals that adopted or did not adopt Sugammadex. Patient characteristics include sex, age, type of payer, race, the presence of each comorbidity used to calculate the van Walraven score, the use of IV acetaminophen, and the use of liposomal bupivacaine. Standard errors given in parentheses are heteroskedasticity-robust and clustered at the hospital level. * p<.05, ** p<.01 *** p<.001.

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Impact of the COVID-19 pandemic on gender authorship in critical care medicine

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INTRODUCTION: Data suggest that the COVID-19 pandemic has disproportionately affected the academic productivity of women.[1-8] In a specialty such as critical care medicine, where women are already under-represented,[9,10] understanding how and whether COVID-19 has affected the academic productivity of women is of particular importance. To address this question, we compared the proportion of women authors in abstracts presented at the Society of Critical Care Medicine (SCCM) Annual Congress in 2020 vs. 2021. This conference was chosen as it is the largest annual gathering of critical care providers in the US, with an abstract submission deadline and conference date in August and February respectively. As a result, the 2020 and 2021 conferences fall immediately prior to and immediately following the initial COVID-19 surges. We also conducted subgroup analysis, including proportion of women first and last authors in highlighted presentations, pediatrics abstracts, Covid-19 related work, and number of abstracts published per author. Based on trends in other medical subspecialties, we hypothesized that the proportion of women first and last authors would decrease from 2020 (pre-Covid-19) to 2021 (after the onset of the Covid-19 pandemic).

METHODS: To understand the effect of the COVID-19 pandemic on the academic productivity of women in critical care, a retrospective review of 3077 abstract publications for the 2020 and 2021 SCCM Annual Congress[11,12] was conducted. Data extracted included first author name, last author name, highlighted presentations ("Star Research Presentations"), and abstract subcategory. First and last author genders were estimated using the Genderize API.[13] Names with low incidence in the Genderize database were manually verified by online search. Names that could not be categorized using the Genderize database and which could not be manually verified were excluded from the analysis. Similarly, first/last author names on behalf of a consortium or group were excluded from the analysis (Figure 1). To account for the uncertainty in gender assignment introduced by use of the Genderize API, 10000 Monte Carlo simulations were run on the author name data. Summary statistics were applied to describe the proportion of men and women authors: parametric data were compared using Student's t-test adjusted for multiple comparisons, and non-parametric data were compared using the Kolmogorov-Smirnov test.

RESULTS: We found no difference in women first authorship in 2020 vs. 2021 (47.34% vs. 31.59%, $p > 0.2$) or in women last authorship in 2020 vs. 2021 (48.77% vs. 33.12%, $p > 0.2$). Similarly, there was no difference in the proportion of women authorship for abstracts designated "Star Research Presentations" (44.32% first authors in 2020 vs. 46.75% in 2021, $p > 0.4$; 28.28% last authors in 2020 vs. 34.8% in 2021, $p > 0.4$). However, a smaller proportion of COVID-19-related abstracts (2021 data only) had women first authorship (42.73% COVID-19 abstracts vs. 50.13% non-COVID-19 abstracts, $p < 0.0002$) and last authorship (22.57% COVID-19 abstracts vs. 35.51% non-COVID abstracts, $p < 0.0002$). Subgroup analysis in 25 research subcategories (Table 1) designated by the SCCM showed a significant difference in the proportion of women last authorship in abstracts related to administration (48.6% vs. 11.3%, $p < 0.005$); women first authorship in abstracts related to immunology (55.2% vs. 43.7%, $p < 0.03$); women first authorship in abstracts related to resuscitation (35.5% vs. 57.0%, $p < 0.005$); and women last authorship in abstracts related to patient/family (48.8% vs. 74.6%, $p < 0.03$). Finally, we found no difference in the distribution of abstracts published per unique author from 2020 to 2021, for men or women first or last authors (Figure 2).

CONCLUSION: Overall, we found no difference in the proportion of women first or last authors in 2020 vs. 2021. However, women were less likely to be the authors of COVID-19-related work, consistent with trends observed in other analyses. Future work will focus on following the proportion of women authorship over time and on understanding how Covid-19 has affected the proportion of women authorship in peer-reviewed critical care medicine publications to discern longer-term effects on the impact of the pandemic on academic productivity of women.

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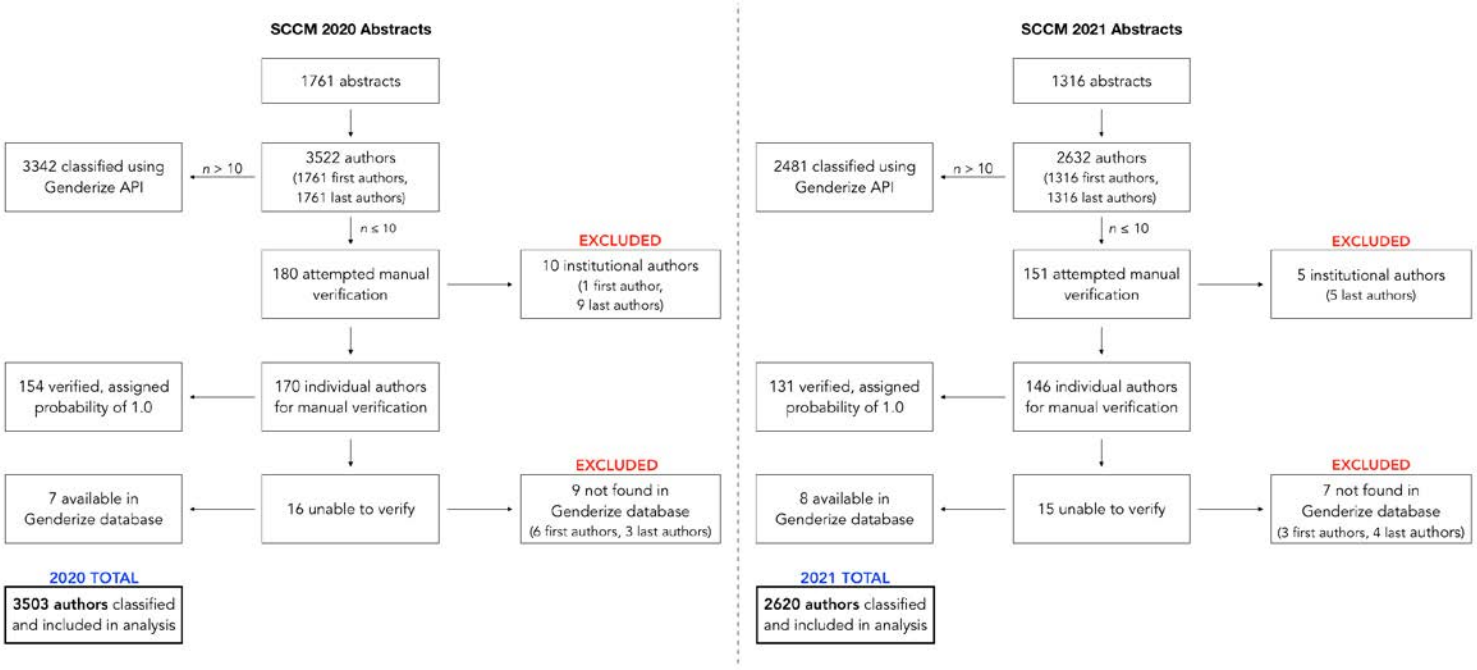

Figure 1. Data extraction process and exclusion criteria. From 1761 abstracts in 2020, we were able to extract 3522 non-unique authors (1761 first authors and 1761 last authors). Each author's first name was categorized using the Genderize API. Names with less than 10 instances in the Genderize database were manually verified. Institutional authors were excluded. If a name had less than 10 instances in the database but could not be manually verified, we reverted to the Genderize API output to classify the author's gender. Names that could not be manually verified and could not be found in the Genderize API were excluded. In total, 19 authors were excluded in 2020, and 12 were excluded in 2021.

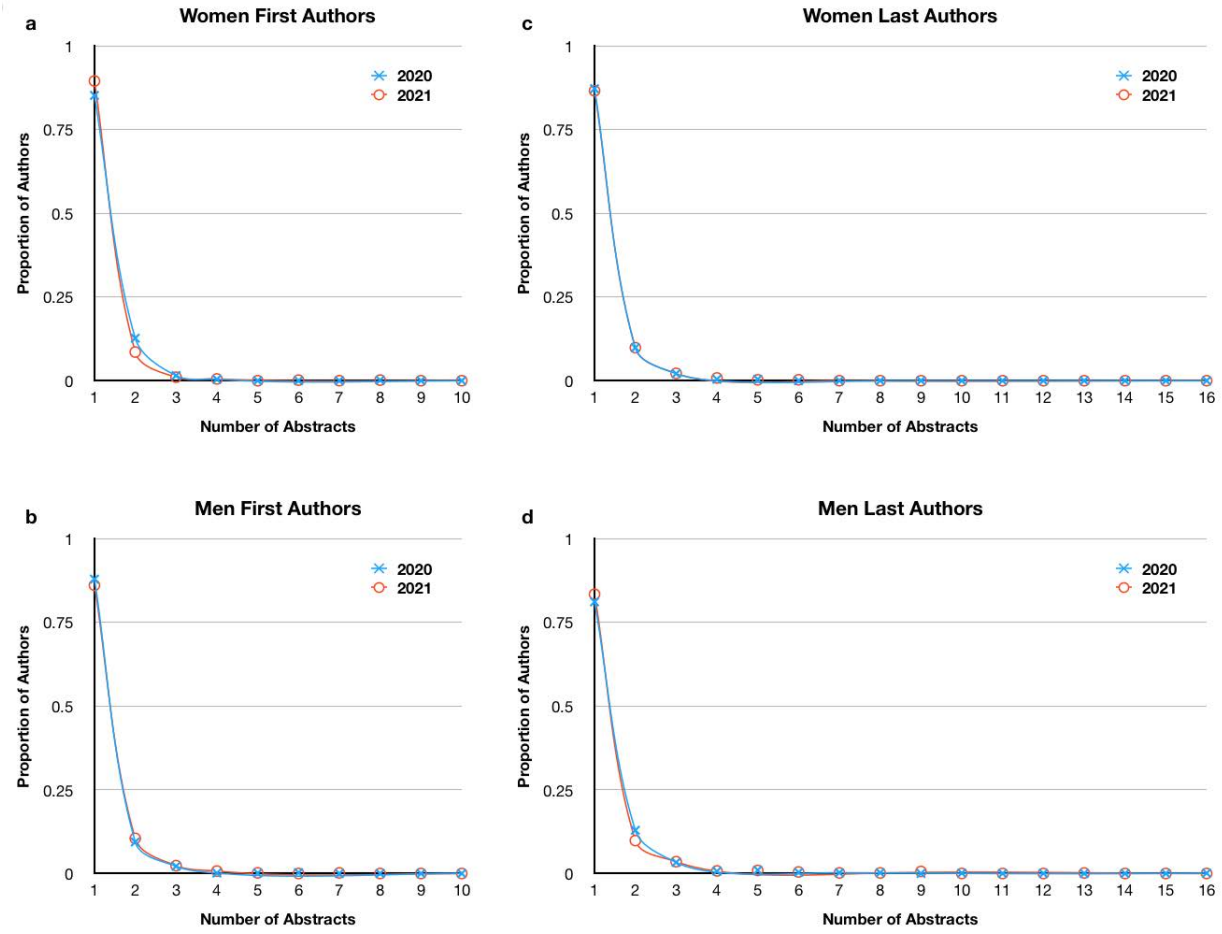

Figure 2. Distribution of abstracts per author, 2020 vs 2021. (a) Of women first authors, there was no significant difference between the proportion of authors with *n* abstracts, for *n* = 1 to 10. There were no women first authors who had published *n* > 10 abstracts. **(b)** Of men first authors, there was no significant difference between the proportion of authors with *n* abstracts, for *n* = 1 to 10. There were no men first authors who had published *n* > 10 abstracts. **(c)** Of women last authors, there was no significant difference between the proportion of authors with *n* abstracts, for *n* = 1 to 16. There were no women last authors who had published *n* > 16 abstracts. **(d)** Of men last authors, there was no significant difference between the proportion of authors with *n* abstracts, for *n* = 1 to 16. There were no men last authors who had published *n* > 16 abstracts.

Table 1. Change in proportion of female first and last authorship, 2020 to 2021: subgroup analysis

	First Author		Last Author	
	2020	2021	2020	2021
Administration	44.14 ± 4.17	47.67 ± 2.54	11.34 ± 3.41	48.59 ± 2.80 **
Cardiovascular	48.83 ± 2.29	42.56 ± 1.45	24.30 ± 1.55	26.97 ± 1.18
Dermatology	50.00 ± 4.79	55.55 ± 5.07	36.04 ± 13.43	55.92 ± 4.53
Disaster	26.07 ± 6.28	62.55 ± 6.81	0.46 ± 3.39	0.56 ± 2.80
Education	35.43 ± 6.08	40.37 ± 2.68	57.41 ± 5.51	51.25 ± 3.28
Endocrine	51.88 ± 5.02	46.66 ± 3.83	31.81 ± 3.75	41.84 ± 3.43
Epidemiology	53.27 ± 2.85	40.44 ± 2.11	35.96 ± 2.74	28.51 ± 2.00
Ethics	64.48 ± 6.40	52.77 ± 6.41	52.57 ± 5.12	69.34 ± 5.50
Gastrointestinal	44.84 ±3.56	47.61 ± 2.03	35.57 ± 3.24	27.75 ± 1.66
Hematology	66.36 ± 3.38	50.95 ± 2.28	33.53 ± 2.57	32.50 ± 2.23
Infectious Disease	43.72 ± 2.50	55.16 ± 2.33	44.31 ± 2.34	31.94 ± 1.50
Immunology	19.44 ± 4.20	56.10 ± 6.31 *	20.25 ± 5.24	29.10 ± 5.11
Neurology/Neuroscience	38.39 ± 1.94	46.34 ± 1.69	28.67 ± 2.02	31.70 ± 1.48
OBGYN	30.86 ± 13.85	39.39 ± 4.14	75.51 ± 15.50	20.28 ± 3.35
Patient/Family	77.98 ± 3.69	67.81 ± 3.98	74.64 ± 4.62	48.78 ± 2.87 *
Pharmacology	67.22 ± 1.79	57.61 ± 1.59	42.30 ± 1.52	40.72 ± 1.39
Procedures	42.99 ± 3.61	35.96 ± 2.84	17.29 ± 3.24	24.19 ± 3.24
Pulmonary	35.47 ± 1.90	39.06 ± 1.70	28.57 ± 2.15	27.22 ± 1.45
Quality Improvement	57.50 ± 2.08	55.72 ± 1.48	48.15 ± 2.02	38.91 ± 1.23
Renal	38.26 ± 3.71	28.31 ± 2.97	35.43 ± 4.78	24.50 ± 2.41
Resuscitation	56.95 ± 2.34	35.50 ± 1.81 **	33.69 ± 2.43	25.16 ± 2.07
Sepsis	44.74 ± 1.78	50.01 ± 1.68	27.08 ± 1.84	22.38 ± 1.19
Trauma	43.92 ± 2.52	54.21 ± 2.23	35.72 ± 2.17	29.41 ± 2.00
State of the Art/Future	54.24 ± 4.66	49.49 ± 3.02	36.87 ± 4.02	25.55 ± 4.30
Predictive Analytics/Machine Learning	3.06 ± 8.55	32.64 ± 4.75	25.26 ± 4.40	24.52 ± 4.88

*** $p < 0.03$** **** $p < 0.003$** **All others, $p > 0.05$**

ECONOMICS, EDUCATION AND POLICY 43

Use of Simulation in EEG Education for Anesthesiology Residents

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INTRODUCTION: Electroencephalography (EEG) is an important tool for monitoring, both for patients in the intensive care unit (ICU) and in the operating room. While neurologists and neurophysiologists are the ultimate domain experts in EEG, it is important for other health care professionals, particularly anesthesiologists, to have proficiency in reading and interpreting EEGs. The objective of this prospective cohort study was to evaluate performance of anesthesiology interns and residents on a web-based simulator to assess an EEG education curriculum. A secondary objective was to compare performance on the web-based simulator with that on a previously developed, 25-item EEG evaluation tool[1].

METHODS: Participants first completed a 25-item EEG evaluation (baseline) prior to an initial 50-minute EEG education podcast. Following podcast curriculum, they completed several 25-item EEG evaluations after performing 10, 15, and 20 EEG interpretations (pre-sim). Next, participants completed the web-based EEG simulator that included 10 different, clinically relevant ICU scenarios. Performance on the web-based EEG simulator was quantified as a percent (%) hint-based score, in which correct responses were weighted by the number of hints used to answer, then divided by the maximum possible points; higher % scores indicated more correct answers using fewer hints.

RESULTS: Fifty (n=50) were included in the analysis, with 65% at Intern level, 26% at CA-1 level, and 9% at CA-2/3 levels. Women comprised 21% of sample. Percent (%) hint-based score significantly differed across the 10 clinical scenarios ($F(9,504)=49.1$, $p<0.001$, Figure 1). Anesthesiology trainees had the highest performance on the non-convulsive status epilepticus scenario (87%) and the lowest performance on the focal epileptogenic potentials and showing scenario (37%).

Overall simulation performance (across all scenarios) demonstrated moderate correlation with scores on pre-sim (10 EEG) 25-item EEG evaluation ($r=0.28$, $p=0.054$), but not with 25-item EEG evaluation taken at baseline ($r=0.13$, $p=0.371$)). Scores on the pre-sim (10 EEG) 25-item EEG evaluation were correlated with performance on individual scenarios concerning sleep and sedative effects ($r=0.42$, $p=0.006$), brain death/isoelectric EEG ($r=0.40$, $p=0.009$), and cerebral ischemia ($r=0.37$, $p=0.015$). Performance on the web-based EEG simulation was not associated with training level ($p=0.679$) nor gender ($p=0.279$).

CONCLUSION: Our study demonstrates the feasibility of using a web-based simulator for EEG education in Anesthesiology trainees. Our study also provides insight into EEG-related areas in which Anesthesiology residents may need further training.

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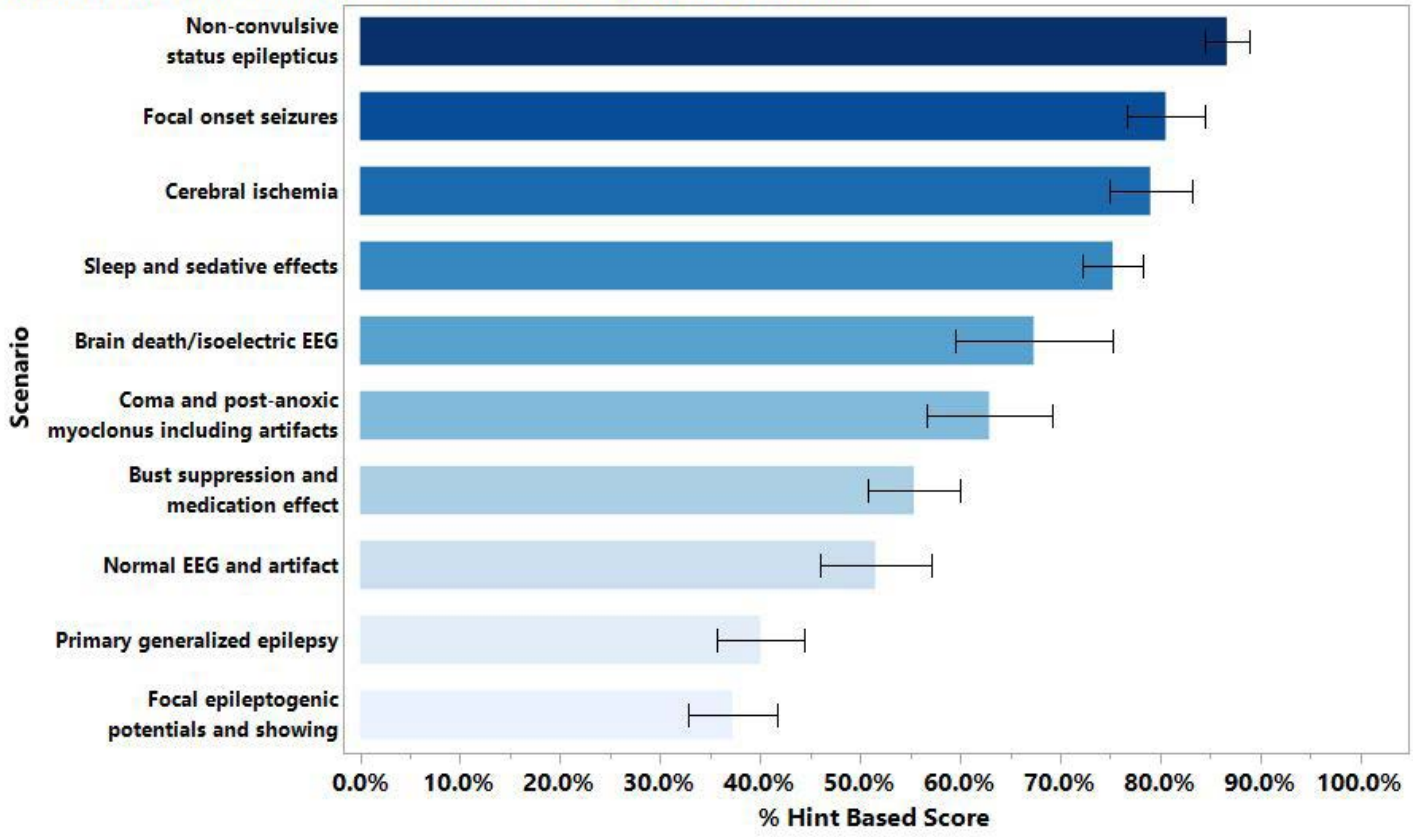
Figure 1. Mean percent hint-based scores across clinical scenarios of web-based EEG simulation. Higher scores indicate greater correct answers with fewer hints used. Error bars are 95% confidence intervals.



ECONOMICS, EDUCATION AND POLICY 44

Gender and Racial Representation in Anesthesiology

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INTRODUCTION: There have been significant efforts to improve gender and racial representation in anesthesiology, but gaps still exist in elucidating the current state of representation. In order to identify hotspot areas where diversity efforts should be targeted with the greatest impact, this study attempts to analyze the race and gender distributions of anesthesiologists--and the characteristics of the unique communities they serve--on a national scale using publicly available data from the American Community Survey, Center for Medicare Services, and the NPPES NPI Registry.

METHODS: Public data from the American Community Survey, Center for Medicare Services, and the NPPES NPI Registry were utilized to build a database of all 1307 counties that contained an anesthesiologist that had participated in the Medicare Quality Payment Program. 71 variables were tracked for each county that fully encompassed the quality scores and demographics of the anesthesiologists and the socioeconomic makeup of each county of practice. A race and gender diversity variable termed 'diversity index' was created for each county that represents the odds that two anesthesiologists randomly chosen would be of the same race and gender. This variable is scaled from 0-100 with 100 being the highest level of diversity. Using GeoDa, a geospatial analysis software, statistically significant hotspots and coldspots of diversity were identified and categorized into 4 groups using the Moran I algorithm: High-High, Low-Low, Low-High, and High-Low. The first 'High' or 'Low' represents a county's diversity compared to the national average. The second 'High' or 'Low' represents the average neighboring county's diversity compared to the national average. If both the county and the average of its neighbors are statistically significantly different than the national average, then that county is a hot/cold spot by Moran I. In Python, an ANOVA was then conducted between each of the 4 clusters to determine statistical differences in the chosen 71 variables of interest.

RESULTS: Hotspot (High-High) areas of diversity with $p < 0.05$ were located predominantly in the Mid-Atlantic, Pacific Southwest, Florida, Greater Houston, and Greater Chicago areas with average diversity index 60.8 +/- 11.85. Low-High designated counties flanked the edges of these areas with average diversity index 4.25 +/- 9.95. Coldspot (Low-Low) areas of diversity were in the Rocky Mountain West, Nebraska, and Deep South (excluding Georgia and Louisiana) with average diversity index 3.35 +/- 4.25. High-Low designated counties were evenly interspersed within Low-Low coldspots mostly representing high populations areas such as urban cities and metropolitan counties with average diversity index 51.25 +/- 10.45. Of the 71 chosen variables, 63 show statistically significant differences between the 4 clusters ($p < 0.05$). The average anesthesiologist MIPS score, a Medicare designation for physician quality, was found to have no statistically significant difference between diversity clusters ($p = 0.07$).

CONCLUSION: It is critical to document the current state of diversity in anesthesiology on a national scale if a more diverse workforce is to be achieved. Coldspot areas of diversity should be a focus of increased funding for hospital-level and national-level funding to decrease their gap from national averages. Mentorship programs and community outreach should be explored in these areas as well as many hotspot areas, which, despite being above the national average, are still not reflective of the communities they serve. Further analysis beyond community and physician metrics, such as hospital workplace atmosphere, childcare policies, and diversity programs, could advance this work in identifying potential causal factors.

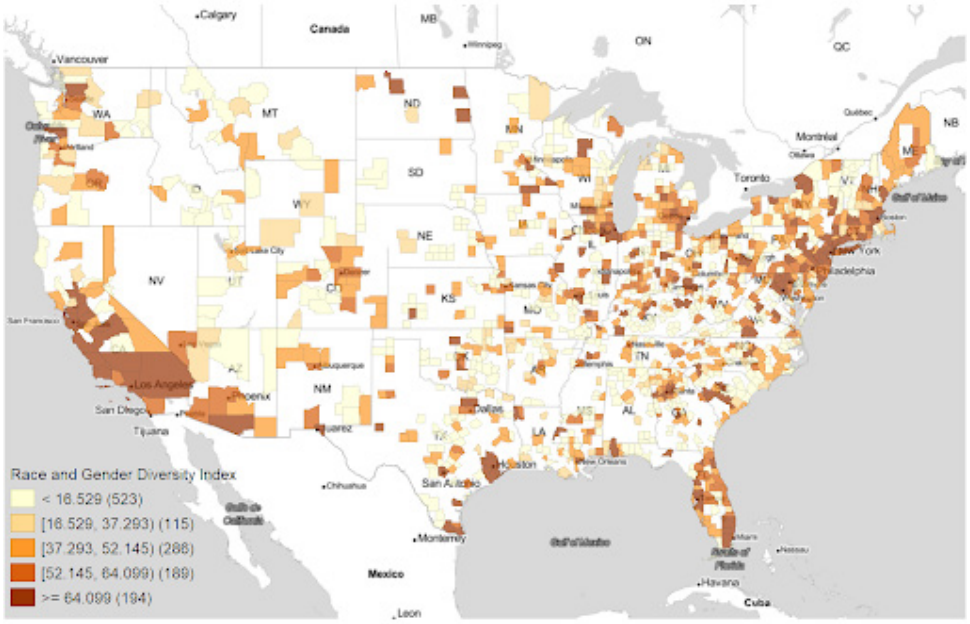

Figure 1

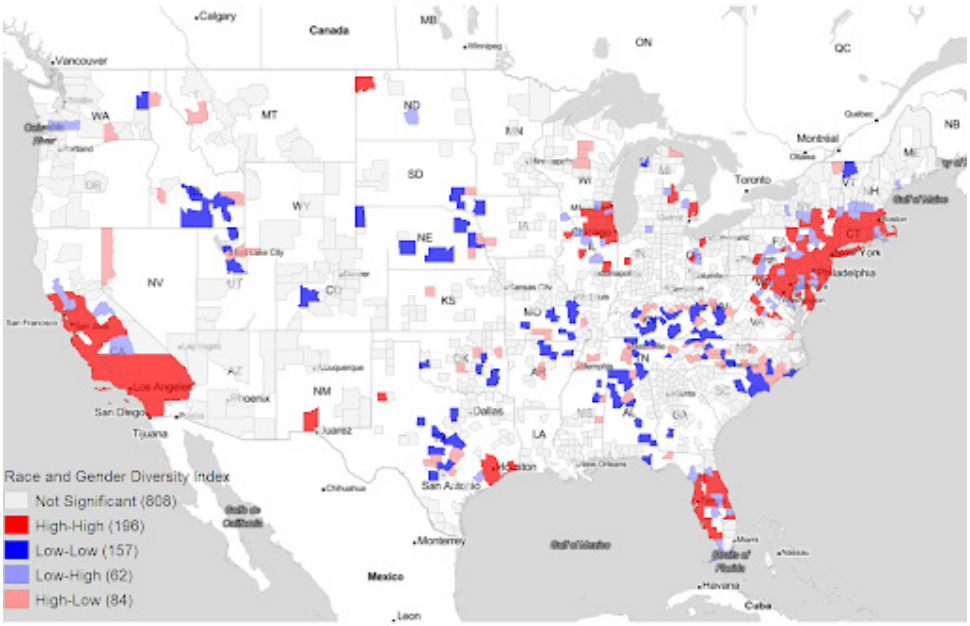

Figure 2

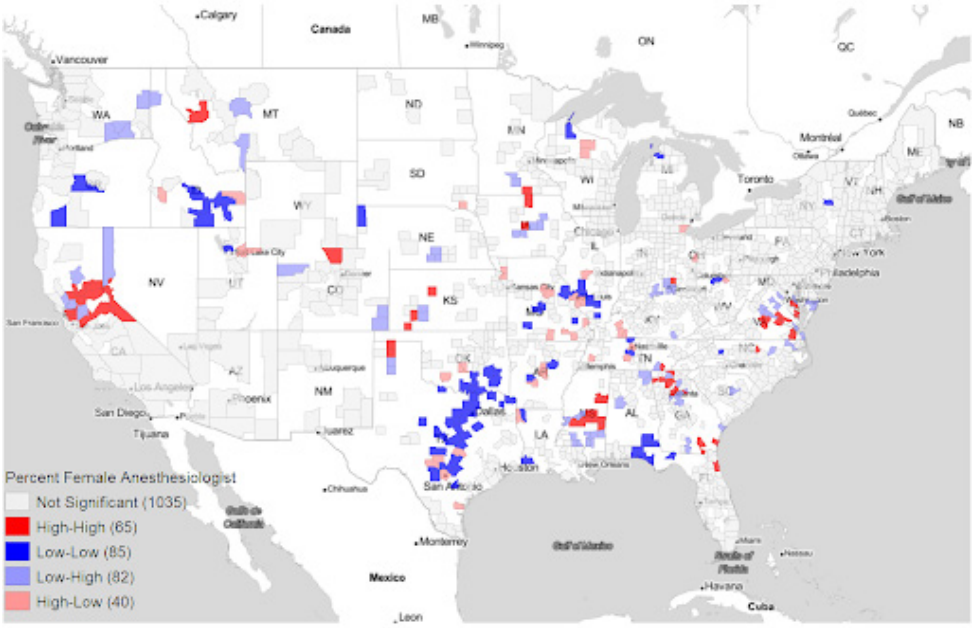

Figure 3

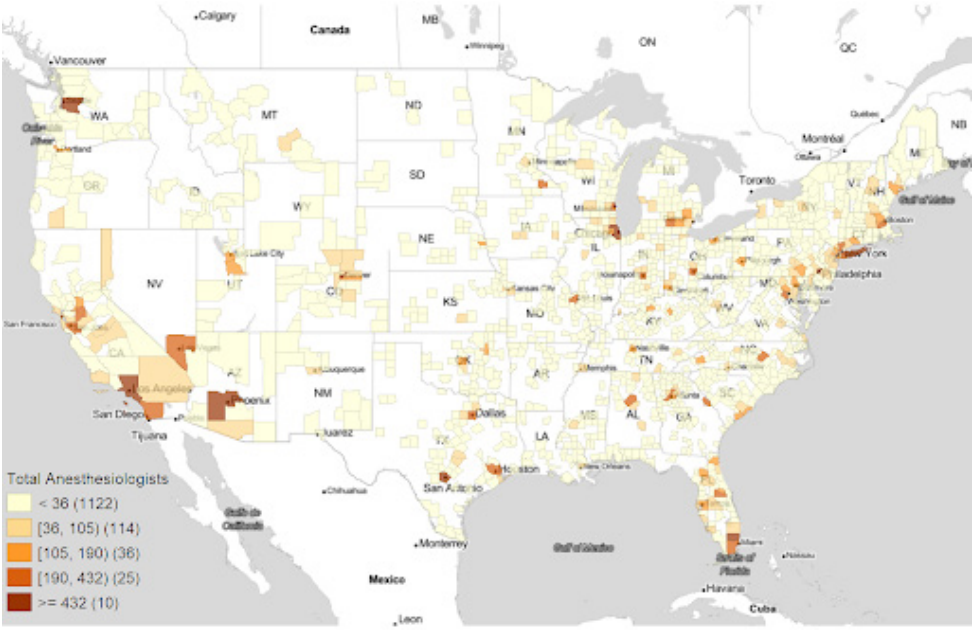

Figure 4

ECONOMICS, EDUCATION AND POLICY 45

Projecting Future Pediatric Post-Surgical Mortality in the United States: Current Trends and Racial/Ethnic Disparities

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INTRODUCTION: Despite advances in medical care, pediatric postoperative mortality varies across groups defined by race and ethnicity in the United States, with minority children bearing the highest burden. Forecasting changing trends is imperative to make essential adjustments to prevailing public health policies, priorities for health research, and fiscal investments. In this report, we evaluated trends in pediatric post-surgical mortality rates by race/ethnicity between 2000 and 2019 and projected these rates to 2029. We also estimated the impact of potential policy changes on mortality, quantifying the degree of mortality reduction needed to eliminate the disparities within the next decade.

METHODS: We performed a population-based study using a large, nationally representative sample of pediatric inpatient surgery patients between 2000 and 2019. We included children <18 years of age who were admitted for intermediate to high-risk surgery, as previously defined (n=265,440).[1] The primary outcome was risk-adjusted mortality rates across racial and ethnic groups. We estimated the annual risk-adjusted mortality rates for 2020-2029 by race/ethnicity using Age-Period-Cohort models, as used in previous studies.

RESULTS: Between 2000 and 2019, surgical mortality declined across racial categories, with Black children having the lowest rate of decline (Average annual percent changes [AAPCs]: -1.7% for White children, -0.9% for Black children, and -1.8% for Hispanics). Despite the overall decline, the risk-adjusted mortality rates trended consistently higher for Black and Hispanic children, compared to White children, with no evidence of narrowing of the disparity gap (Pairwise tests of parallelism of the AAPCs not statistically significant)- Figure 1. If Black and Hispanic children had post-surgical mortality rates comparable to their White peers, 3210 deaths would have been avoided in the last two decades. If the current trends continue, these disparities are projected to result in 1,493 excess deaths in children of minority race/ethnicity over the next 10 years. Mortality rates would need to decline by 6.4% per year for Black children and 1.9% per year for Hispanic children to eliminate the disparity gap by the end of 2029.

CONCLUSION: Despite a steady decline in pediatric post-surgical mortality across all groups, persistent racial/ethnic disparity existed over the past two decades. Pediatric post-surgical mortality rates need to decline 7-fold faster than the current rates if disparity gaps are to be eliminated within the next decade. Targeted, robust actions are imperative to ensure equitable pediatric surgical health.

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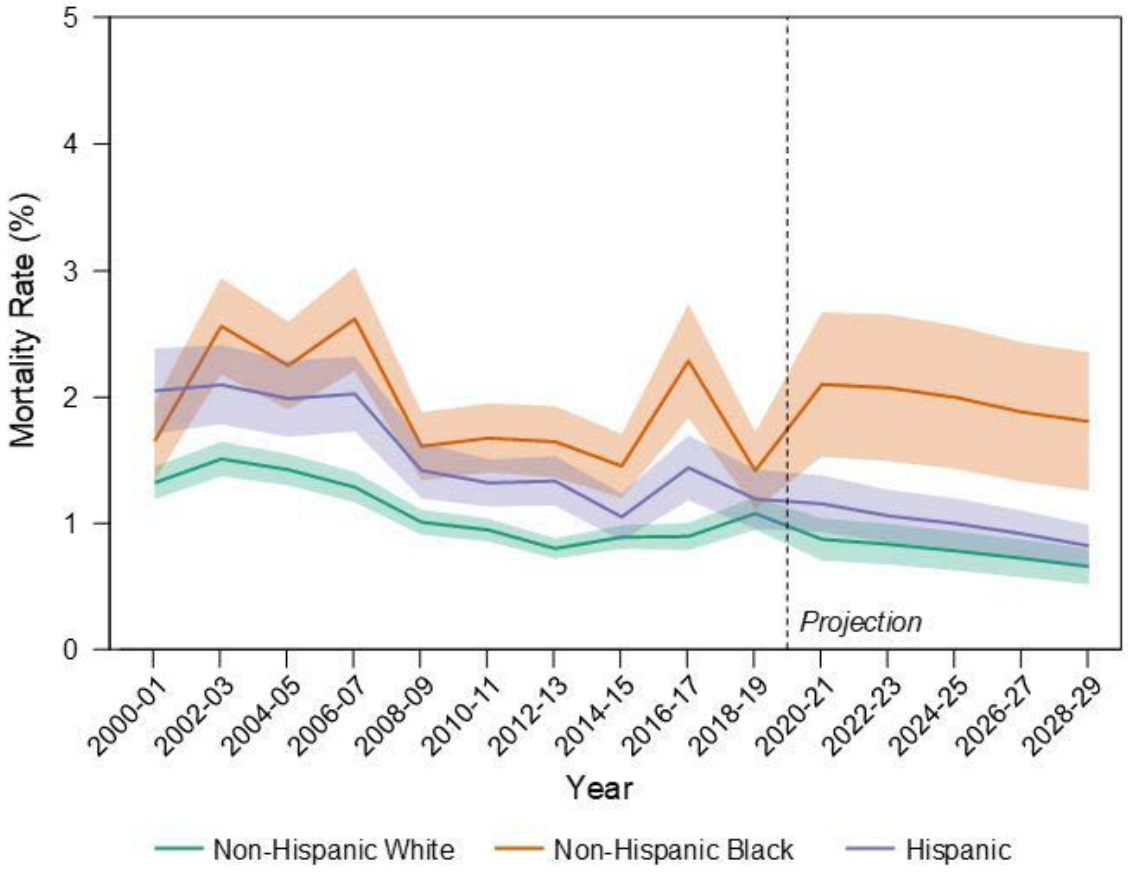

Figure 1. Observed and projected risk-adjusted postoperative mortality rates for children <18 years between 2000 to 2029(inclusive).

ECONOMICS, EDUCATION AND POLICY 46

Intraoperative Transthoracic Focus Cardiac Ultrasound: Feasibility and Focus for Training

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[1]*University of Virginia, Charlottesville, VA*

INTRODUCTION: Transthoracic FoCUS is a valuable diagnostic tool which has been shown to alter patient management throughout the perioperative period[1-5]. The majority of perioperative FoCUS literature describes utilization in the pre and post operative period with less prevalent descriptions of intraoperative feasibility, utility, and obtainable views[5-7]. Currently FoCUS, and other diagnostic ultrasound assessments, are being incorporated into formal anesthesiology graduate medical curriculum however intraoperative components do not appear common[8-10]. Given the increasing prioritization of formal GME FOCUS training, the significance of the intraoperative period for the anesthesiologist, and the apparent lack of formal intraoperative FOCUS training further attention in this area is warranted through curriculum adaptation and further research.

METHODS: Data presented was obtained in retrospective review of QI project seeking to improve resident education at Texas A&M/Baylor Scott and White. The pre-QI project FOCUS curriculum consisted of classroom lectures and one day of hands-on FOCUS classroom based practical portion. Pre-intervention a survey was sent to all residents assessing general comfort and their view on the feasibility of intraoperative FOCUS examinations. Subsequently, a 4th year elective rotation in perioperative ultrasound was made available in addition to above curriculum. The elective consisted of 5 post anesthesia care unit and 5 intraoperative FoCUS examinations under supervision. After this preliminary practical instructional the remainder of the elective required residents to independently attempt 40 intraoperative examinations and recording these attempts in a log book. The residents were instructed to attempt full standard FoCUS views consisting of parasternal long axis (PSLA), parasternal short axis (PSSA), apical 4 chamber (A4C), subcostal 4 chamber (SC4), and in addition the suprasternal (SS) view. Residents were instructed to only perform exams in intraoperative setting with an ongoing operation and not permitted to alter surgical field, drapes, or disrupt operation. Obtaining view was defined as ability to visualize all standard structures associated with view. At the completion of the elective the log books were retrospectively reviewed. Surgeries were identified as either thoracic, extremity, or abdominal with distinction of upper and lower abdominal with umbilicus as defining border between the two. Obtainable view by surgery was reported as a percentage. At completion of the elective participants took retook initial survey.

RESULTS: 36 surveys were sent to the 36 residents in the program years PGY1-PGY4 with 17 responses (47%). 0/17 responders stated they felt comfortable performing FOCUS examination independently. 10/17 (59%) stated they felt it was not feasible to perform a FoCUS examination given barriers and restrictions of intraoperative environment. 4/8 eligible (pgy-4) residents completed elective with remainder prevented by COVID-19 restrictions. PSLA views were obtained in 127/160 (79%) exams. PSSA views were obtained in 134/160 (84%) exams. A4C view was obtained in 69/160 (43%) exams. SC4 view was obtained in 31/160 (19%) exams. The suprasternal (SS) view was obtained in 125/160 (78%) cases. Abdominal surgery obtainable views were PSLA 83/108 (77%), PSSA 88/108 (81%), A4C 37/108 (34%), SC4 9/108 (8%), and SS 84/108 (78%). Thoracic surgery obtainable views were PSLA 6/11 (55%), PSSA 7/11 (64%), A4C 2/11 (18%), SC4 1/11 (9%), and SS 6/11 (55%). At completion of elective 100% of participants reported they felt comfortable performing the FOCUS examination and 100% participants felt intraoperative TTE is feasible.

CONCLUSION: The methods described above outline an effective method of incorporating intraoperative FoCUS examinations in a formal GME curriculum. The results suggest this may be a more effective manner of teaching FoCUS compared to classroom instruction alone. Further, incorporating intraoperative training effectively changed residents' views on the feasibility of intraoperative exams. The results support that intraoperative FoCUS is feasible even with minimal training. Finally, the results suggest that the parasternal views along with the suprasternal view are most obtainable and this should be considered for both the clinician in practice and educator in teaching.

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Table of obtainable view to surgery

	Total count	PSLA count	PSLA %	PSSA	PSSA %	A4C	A4C %	SC4	SC4 %	SS	SS %
Resident 1											
View count/percent	40	34	85%	35	88%	19	48%	10	25%	38	95%
Abd surgery	22	18	82%	20	91%	8	36%	3	14%	22	100%
Upper Abd surgery	15	12	80%	14	93%	3	20%	0	0%	15	100%
Lower Abd surgery	7	6	86%	6	86%	5	71%	3	43%	7	100%
Extremity surgery	14	14	100%	14	1	11	79%	7	50%	13	93%
Thoracic surgery	4	2	50%	1	25%	0	0%	0	0%	3	75%
Resident 2											
View count/percent	40	30	75%	30	75%	16	40%	5	13%	28	70%
Abd surgery	34	25	74%	25	74%	13	38%	1	3%	22	65%
Upper abd surgery	21	15	71%	15	71%	5	24%	0	0%	12	57%
Lower abd surgery	13	10	77%	10	77%	8	62%	1	8%	10	77%
Extremity surgery	6	5	83%	5	83%	3	50%	4	67%	6	100%
Thoracic surgery	0	na	na	0	na	0	na	0	na	0	na
Resident 3											
View count/percent	40	29	73%	32	80%	19	48%	13	33%	33	83%
Abd surgery	25	18	72%	19	76%	10	40%	5	20%	22	88%
Upper abd surgery	20	14	70%	15	75%	8	40%	3	15%	17	85%
Lower abd surgery	5	4	80%	4	80%	2	40%	2	40%	5	100%
Extremity surgery	12	10	83%	11	92%	9	75%	8	67%	10	83%
Thoracic surgery	3	1	33%	2	67%	0	0%	0	0%	1	33%
Resident 4											
View count/percent	40	34	85%	37	0.925	15	0.375	3	8%	26	65%
Abd surgery	27	22	81%	24	0.8889	6	0.2222	0	0%	18	67%
Upper abd surgery	14	11	79%	12	0.8571	2	0.1429	0	0%	7	50%
Lower abd surgery	13	11	85%	12	0.9231	4	0.3077	0	0%	11	85%
Extremity surgery	8	8	100%	8	1	6	0.75	2	25%	6	75%
Thoracic surgery	4	3	75%	4	1	2	0.5	1	25%	2	50%
Neuro	1	1	100%	1	100%	1	100%	0	0%	0	0%
Residents (1-4)											
View count/percent	160	127	79%	134	84%	69	43%	31	19%	125	78%
Abd surgery	108	83	77%	88	81%	37	34%	9	8%	84	78%
Upper abd surgery	70	52	74%	56	80%	18	26%	3	4%	51	73%
Lower abd surgery	38	31	82%	32	84%	19	50%	6	16%	33	87%
Extremity surgery	40	37	93%	38	95%	29	73%	21	53%	35	88%
Thoracic surgery	11	6	55%	7	64%	2	18%	1	9%	6	55%
Neuro	1	1	100%	1	100%	1	100%	0	0%	0	0%

SUBSPECIALTY ABSTRACTS

GERIATRIC ANESTHESIA

GERIATRIC ANESTHESIA 1

Development and validation of a risk assessment model for postoperative delirium based on artificial intelligence

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[1]University of Florida College of Medicine, Gainesville, FL, [2]St. Claraspital, Basel, Switzerland, [3]McMaster University, Hamilton, Canada, [4]University Medical Center Groningen, Groningen, Netherlands, [5]PIPRA AG, Zurich, Switzerland

INTRODUCTION: Postoperative delirium (POD) is recognized as the most frequent postoperative complication in the elderly, occurring in 10 to 50% of older patients after major surgical procedures. It is associated with postoperative cognitive decline and long-term dementia, poor functional recovery, prolonged hospitalization, increased nursing home admission, and increased mortality. Early identification of patients at risk for delirium is paramount, because adequate well-timed interventions could reduce the occurrence of POD and the related detrimental outcome. We have developed a prognostic tool aiming at predicting the risk of a patient to develop postoperative delirium (POD) based on individual patient data.

METHODS: This is an analysis of individual patient data originating from nine different observational cohort studies using systematic assessment of POD. The study met the criteria for waiver of ethical approval as defined by McMaster University Ethics Board as it used existing anonymized data. The dataset contained data from 2250 patients (1806 without POD, 444 with POD). The tool is based on statistical methods that avoid an overly optimistic estimation of the model performance.

RESULTS: The final model contained nine variables: age, body mass index, ASA status, history of delirium, cognitive decline, medications, C-reactive protein, surgical risk, and type of surgery. The result on the training data was an area-under-the-curve (AUC) of 0.8255 with a 95% confidence interval (CI) of 0.796 -0.854, with a cross-validation score AUC of 0.81. The test has been externally validated on a dataset from a ninth hospital with 293 patients (232 without POD, 61 POD). The validation data were missing two of the nine variables that had to be imputed. The performance on the external validation was an AUC of 0.75. Based on the predicted risk, patients can be divided into four sub-groups: low risk, medium risk, high risk, and very high risk. We propose three thresholds for this distinction based on sensitivity and specificity. The limit between low and medium risk is where we attain a 90% sensitivity. The limit between high risk and very high risk is where we attain 90% specificity, and the limit between medium and high risk is where sensitivity and specificity are equal.

CONCLUSION: We used individual patient data from different international studies to develop a robust test for predicting POD and performed an external validation of the model with good accuracy.

GERIATRIC ANESTHESIA 2

Rocuronium 0.3 mg/kg or 0.9 mg/kg comparing onset time, duration of action and intubating conditions in elderly patients. A randomized study

Matias Vested[1], Pernille Pape[1], Camilla Meno Kristensen[1], Felicia Dinesen[1], Malene Vang[1], Rasmus E Christensen[2], Cecilie Bjerring[1], Charlotte Albrechtsen[1], Lars S Rasmussen[2]

[1]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2]Rigshospitalet University of Copenhagen, Copenhagen, Denmark

INTRODUCTION: Tracheal intubation during anesthesia can be facilitated by neuromuscular blocking agents[1] such as rocuronium but there is limited data about the optimal dose in patients above 80 years of age[2,3]. We hypothesized that rocuronium 0.9 mg/kg would lead to a shorter onset time than 0.3 mg/kg in patients above 80 years.

METHODS: The study was approved by The Scientific Ethics Committee (February 27, 2020 - protocol number H-19079175), Danish Medicines Agency (EudraCT 2019-004343-76) and Data Danish Protection Agency (Videnscenter for Dataanmeldelser, November 6, 2018 - VD-2018-427). The study was registered at Clinicaltrials.gov (NCT04512313) prior to enrollment of patients. Informed consent was obtained from all patients and the trial was conducted in accordance with the Declaration of Helsinki. Thirty-four patients were randomized to either rocuronium 0.3 mg/kg or 0.9 mg/kg. Anesthesia was induced with fentanyl and propofol and maintained with remifentanil and propofol after intubation. Neuromuscular function was monitored with acceleromyography and the primary outcome was onset time defined as time from injection of rocuronium to train-of-four (TOF) count of 0. Other outcomes were duration of action (time to TOF ratio > 0.9), proportion of excellent intubating conditions using the Fuchs-Buder scale, tracheal intubating conditions using the Intubating Difficulty Scale (IDS), use of a stylet, use of a video laryngoscope, and time used for intubation.

RESULTS: Rocuronium 0.9 mg/kg resulted in shorter onset time compared to rocuronium 0.3 mg/kg; 108 sec (SD 40) vs. 228 sec (SD 140) (difference: 119 seconds (95% CI: 41-196), P=0.005)), respectively. However, in 66% of the patients receiving rocuronium 0.3 mg/kg a TOF count of 0 was not obtained. Duration of action was longer after rocuronium 0.9 mg/kg: 118 minutes (SD 43) vs. 46 minutes (SD 13) (difference: 72 minutes (95% CI: 49-95) P<0.0001)), and a greater proportion of excellent intubating conditions (Fuchs-Buder) was obtained; 11/16 (69%) vs 4/18 (22%) (P=0.006). No difference was found regarding IDS score 1 vs 2, employment of video laryngoscope 38% vs. 44% or use of a stylet 38% vs 50%.

CONCLUSION: Rocuronium 0.9 mg/kg resulted in a shorter onset time compared to rocuronium 0.3 mg/kg in patients above 80 years of age. In 66% of the patients receiving rocuronium 0.3 mg/kg a TOF count of 0 was not obtained. Rocuronium 0.9 mg/kg provided better intubating conditions but also a longer duration of action compared to rocuronium 0.3 mg/kg.

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Table 1 Baseline characteristics of patients above 80 years of age randomized to either rocuronium 0.3 or 0.9 mg/kg

	Rocuronium 0.3 mg/kg	Rocuronium 0.9 mg/kg
n	20	17
Age years	83 (1.9)	85 (3.3)
Sex M/F	10/10	4/13
BMI kg/m^2	25.4 (2.7)	25.1 (6.0)
ASA II/III	9/11	10/7
Daily medicine		
Diuretics	7 (35%)	8 (47%)
Magnesium	1 (5%)	1 (6%)
Comorbidity		
Renal disease	0	1 (6%)
Diabetes	3 (15%)	1 (6%)
Hypertension	12 (60%)	11 (65%)
Heart disease	4 (20%)	6 (35%)
Type of surgery Orthopedic Plastic/breast Gynecology	9 7 1 1	7 6 1 2
Continuous data presented as mean and standard deviation (SD)		

Table 2 Intraoperative data including onset time and duration of action for rocuronium 0.3 and 0.9 mg/kg in patients above 80 years of age

	Rocuronium 0.3 mg/kg	Rocuronium 0.9 mg/kg	Difference with 95%CI	P value*
n	18	16		
NMB reached TOF 0	6 (33%)	16 (100%)	66% (45% to 88%)	P<0.001
Onset time, seconds	227 (140) n=6	108 (40) n=16	119 (41 to 196)	0.005
Duration of action, minutes	46 (13) n=16	118 (43) n=11	72 (49 to 95)	<0.0001
Duration of anesthesia, minutes	205 (75)	209 (84)	-	-
Duration of surgery, minutes	121 (55)	126 (61)	-	-
Excellent intubating conditions (Fuchs-Buder) §	4 (22%)	11 (69%)	47 (17 to 77)	0.006
Use of video laryngoscope	8 (44%)	6 (38%)	6 (-26 to 40)	0.68
Use of stylet	9 (50%)	6 (38%)	12 (-20 to 46)	0.46
Intubating difficulty score (IDS) IDS>0 §	2 (1-3) 4 (22%)	1 (0-2) 6 (38%)	- 15 (-16 to 45)	0.18** 0.33
Time from administration of rocuronium until intubation, sec	385 (121)	188 (54)	196 (129 to 263)	<0.0001***

Continuous data presented as mean and standard deviation (SD).
§ Intubation performed at TOF 0 or at five minutes after rocuronium if TOF 0 was not obtained.
In seven patients the duration of action was not determined due to administration of a reversal agent, administration of supplemental doses of rocuronium or technical problems. Data presented as count and frequencies (%) or mean and standard deviation (SD) IDS presented as median and interquartile range (IQR)
*Chi square test
**Mann Whitney's rank sum test
***T-test
CI Confidence Interval

GERIATRIC ANESTHESIA 3

The Lidocaine Infusion for the Management of Postoperative Pain and Delirium (LIMPP) Trial

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INTRODUCTION: Postoperative delirium is a frequent adverse event following elective non-cardiac surgery. Older patients are at significant risk of postoperative delirium and while the problem is well documented and the risk factors well defined, there are few effective therapies for its prevention or treatment once it has developed. The occurrence of delirium increases the risk of functional impairment, placement to facilities other than home after discharge, cognitive impairment at discharge, as well as in-hospital and long-term mortality. Unfortunately, there is a dearth of efficacious strategies to minimize the risk from modifiable risk factors, including postoperative pain control and the analgesic regimen. Use of potent opioids, currently the backbone of postoperative pain control, alters cognition and may contribute to an increased risk of postoperative delirium. Literature supports the intraoperative use of lidocaine infusions to decrease postoperative opioid requirements, expedite return of bowel function, and decrease the risk of chronic post-surgical pain. However, whether the use of postoperative lidocaine infusions is associated with lower opioid requirements and subsequently a reduction in postoperative delirium has not been investigated.

METHODS: The LIMPP trial is a randomized, double-blinded clinical study of a postoperative 48-hour infusion of lidocaine at 1.33mg/kg/hr vs. placebo in older patients undergoing major reconstructive spinal surgery at UCSF. Patients will be randomized, and the study medication started upon arrival to the PACU/ICU. Our primary outcome is incident delirium (CAM) in the first 3 postoperative days. Secondary outcomes include delirium severity (MDAS), changes in cognition (TICS, digit symbol substitution test, timed verbal fluency test, and the word list learning task), pain scores, opioid use, incidence of opioid related side effects (respiratory depression, nausea vomiting) and functional benefits including time to discharge and improved recovery from surgery (SF-36, ODI). Lidocaine safety will be assessed with daily screening questionnaires and lidocaine plasma levels.

RESULTS: We have recently started recruiting patients for the pilot/feasibility phase and results will be forthcoming upon conclusion of the study.

CONCLUSION: Our study will be one of the few interventional studies to investigate the association between pain, postoperative delirium, and other postoperative opioid-related adverse effects. Although lidocaine has been used intraoperatively for years, with prior data supporting its efficacy and safety for improved analgesic and functional outcomes, the evidence supporting its postoperative use is scant. Our study will be one of the first to standardize the intraoperative anesthetic and separately investigate the potential postoperative benefits of a continuous postoperative lidocaine infusion. Data supporting our hypothesis that postoperative lidocaine is associated with a reduction in postoperative delirium will provide insight into the pathophysiology of postoperative delirium, particularly as to how delirium is associated with pain and opioids.

GERIATRIC ANESTHESIA 4

Cognitive Status: A predicator of preoperative instruction compliance?

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INTRODUCTION: The most common postoperative complication for older adults is the development of perioperative neurocognitive disorder (PNCD), which encompasses delirium and delayed neurocognitive recovery - 'brain fog' or difficulty with concentration and memory that may occur postoperatively.[1,2] The greatest risk factor for developing PNCD is the presence of preoperative cognitive impairment.[1-3] Preoperative cognitive impairment also predicts higher likelihood of postoperative complications.[3] While the cause of this disparity in outcomes is likely multifactorial, the ability to correctly follow perioperative instructions and recommendations may be one potentially modifiable component. The purpose of this study was to determine whether the presence of cognitive impairment led to reduced preoperative instruction compliance and if so, identify barriers and enact a tailored care plan to help close the gap.

METHODS: In line with societal recommendations,[2,4] our preoperative screening clinic implemented routine cognitive screening to identify older surgical patients at increased risk. All patients are given the same preoperative instructions with respect to NPO, how to use chlorhexidine gluconate (CHG) wipes, and which medications to continue or hold before surgery. On the day of surgery, patients age ≥65 were asked to participate in a 9-question survey (Figure 1) about the instructions they received. A documented Mini-Cog score of ≤2/5 was considered positive for cognitive impairment. Compliance was determined based on correctly following NPO instructions, demonstration of correct CHG wipe usage and correct medication management. The last dose of commonly prescribed and frequently altered medications - anti-hypertensives, blood thinners and diabetic medications - were recorded and compared to the instructions provided. Additionally, patients and family, if present, could provide further comment on specific issues with the instructions they received. Patients were excluded if they did not go to clinic prior to surgery or declined to participate. Data was stratified by cognitive status to evaluate whether the presence of impairment could predict incorrect execution of instructions. Feedback from patients and their families were compiled to identify compliance barriers.

RESULTS: Of 97 patients surveyed, 28 patients met exclusion criteria. Of the remaining 69 patients, 50 screened negative for impairment of which 68% correctly followed all preoperative instructions. Of the 19 patients with impairment, 84.2% struggled with one or more of the preoperative instructions leading to inadequate NPO status, incorrect usage of chlorhexidine wipes and/or preoperative medication management. Table 1 Patients with cognitive impairment were more likely to have difficulty correctly following preoperative instructions. (OR 10.5, p-value 0.001) While recognizing the limitation of a small sample size, we felt the number of our patients who struggled both without and especially with impairment did not warrant further data collection and instead required action - identifying targets for improvement and trialing solutions. For each of the identified barriers a team-based solution was proposed and enacted. Figure 2. The number of handouts were reduced from 15 to 3 and their format changed to become more infographic based. The perioperative committee reached consensus for institutional standardization of preoperative instructions to prevent differing instruction. Specific contact information (telephone, email) was provided - surgical coordinator and preoperative clinic nurse. For those with cognitive impairment, a patient appointed family member or friend was identified and included in all instructions and recommendations.

CONCLUSION: Despite the small sample size for this pilot study, we did find a clear difference in correct execution of preoperative instructions with respect to cognitive status. This study also revealed that as an institution changes needed to be made in the delivery of our instructions. Areas for change were identified through patient and family feedback. Actions were then implemented to address the identified barriers. Currently, we are analyzing the effect these changes have made on preoperative instruction compliance and patient satisfaction. Our aim is to improve the perioperative care of our older surgical patients by identifying the barriers they face and tailoring their care to bridge those gaps.

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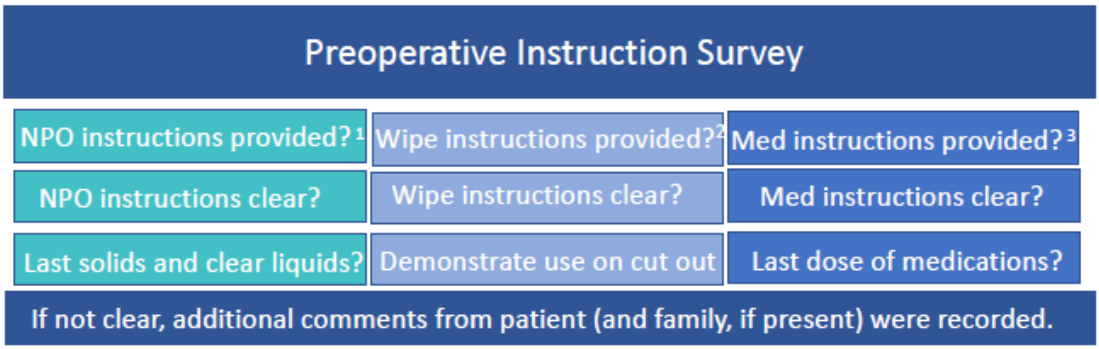

Figure 1. Preoperative Instruction Survey Questions. [1]NPO instructions: no solid food within 8hrs of scheduled surgical time, drink 16oz water at least 2 hours prior to scheduled surgical time. [2]CHG wipe instruction: handout was reviewed in clinic and provided to take home. [3]Medication instructions included in this study: antihypertensives, blood thinners and diabetic medications.

	Mini-Cog Pass	Mini-Cog Fail	p-value (OR)
Age	73.54	75.79	0.903
Correct	34	3	
Missed 1 or more	16 (32.0%)	16 (84.2%)	0.001 (10.5)

Table 1. Preoperative instruction compliance among patients with and without cognitive impairment.

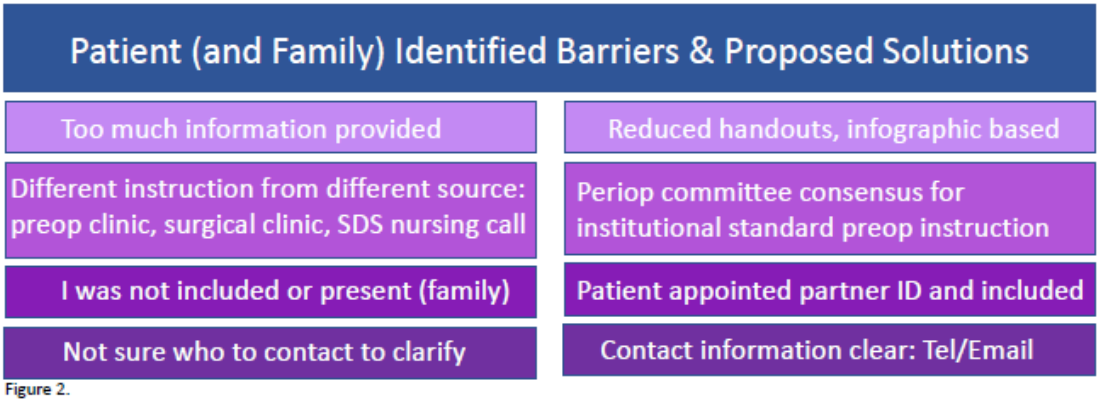

Figure 2.

GERIATRIC ANESTHESIA 5

Pre- and Postoperative CSF Proteomic Signatures of Postoperative Delirium

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INTRODUCTION: Up to 40% of older surgical patients will develop postoperative delirium (POD), a disorder of acute deficits in attention and level of consciousness. Interventions to prevent or treat POD are limited, since we understand little of its etiology. Changes in cerebrospinal fluid (CSF) proteins after surgery could inform our understanding of POD pathogenesis, since the CSF is in equilibrium with the brain's interstitial space. Prior CSF proteomic POD studies have characterized preoperative CSF proteomic signatures in hip fracture patients[1-3] but no studies have characterized postoperative CSF proteomic changes in patients with versus without POD.

METHODS: We selected 7 patients who had POD, 9 who had subclinical POD, and 7 without POD from two prospective cohort studies (INTUIT[4], and MARBLE[5]) that assessed for delirium in older non-cardiac surgery patients. For this case control study, patients with versus without POD were matched by age, race, sex, and surgical type (Table 1). The 3D-CAM delirium assessment was performed before surgery and twice daily after surgery for up to 5 days. Unbiased quantitative LC-MS/MS proteomics was performed on CSF samples obtained before and 24 hours after surgery. Differences in protein expression were analyzed by linear regression models using empirical Bayes corrected standard errors. P-values were corrected for multiple comparisons using the FDR method and considered significant if the adjusted p-value <0.05. Ingenuity Pathway Analysis was performed to examine postoperative changes in pathway expression and associations with POD severity.

RESULTS: Mass spectrometry quantified 8,746 peptides from 885 proteins in all patients at both time points. After adjusting for age and gender, proteins that showed the most significant change after surgery include SDF1, CO1A1, CO1A2, PROF1, SAA1, LEG1, WDR1, ACTB, PPIA, and 1433B, with significant alterations in the following coagulation, metabolism, and inflammation pathways (adj $p<0.05$; Figure 1). After adjusting for age, gender and comorbidities, preoperative CSF proteins associated with POD severity included immunoglobulin chains LV537, KVD42, KV139, and KVD39 (adj $p<0.05$; Figure 2), with nominally associated pathways involved in inflammation, metabolism, and coagulation ($p<0.05$; Figure 2). Postoperative CSF proteins associated with POD severity included LV537, KV139, and KVD39 (adj $p<0.05$; Figure 3) with nominally associated pathways involved in coagulation, inflammation, synapse formation, and metabolism ($p<0.05$).

CONCLUSION: These data demonstrate preliminary associations of pre- and postoperative CSF protein levels and pathway changes with POD severity (Figure 4). Further investigation of postoperative CSF proteomic changes in patients with delirium is warranted to clarify the molecular pathophysiology of POD and to identify potential therapeutic targets to prevent or treat POD.

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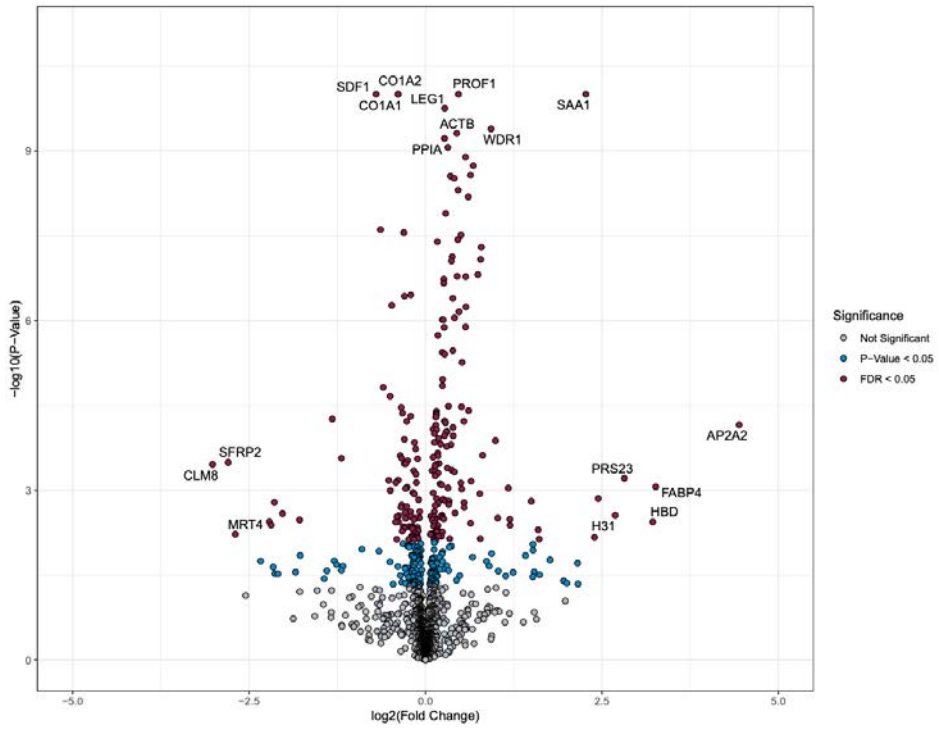
Table 1: Cohort Characteristics

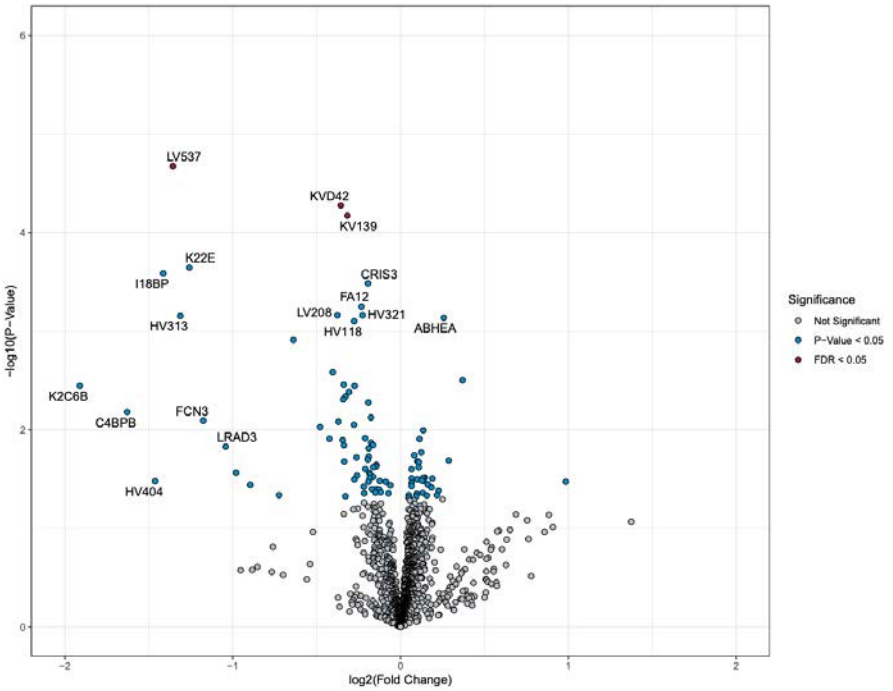
Demographics	
Number of Patients	23
AGE (SD)	71.57 years (4.54)
GENDER = Male	12 (52.2%)
RACE - Asian	1 (4.3%)
RACE - Black	4 (17.4%)
RACE - White	18 (78.3%)
BMI (SD)	26.86 (5.40)
Years of Education (SD)	14.61 (3.04)
Health Data	
APOE4 carrier	9 (39.1%)
Charlson Comorbidity Index (SD)	4.65 (1.72)
ASA Status – 2	7 (30.4%)
ASA Status – 3	14 (60.9%)
ASA Status – 4	2 (8.7%)
Surgery Duration [IQR]	3.43 hours [2.26, 4.29]
BL Delirium Severity Score [IQR]	1.00 [0.00, 1.00]
Surgical Service (%)	
Thoracic	4 (17.4%)
General Surgery	7 (30.4%)
Gynecology	2 (8.7%)
Orthopedics	4 (17.4%)
Otolaryngology Head and Neck	3 (13.0%)
Urology	3 (13.0%)
Outcomes	
Diagnosed with Delirium	7 (30.4%)
Worst Postop Delirium Severity Score [IQR]	2.00 [1.00, 3.50]
Change in Delirium Severity Score [IQR]	1.00 [0.00, 3.00]

Figure 1: Change in CSF proteins and pathway expression from before to after surgery



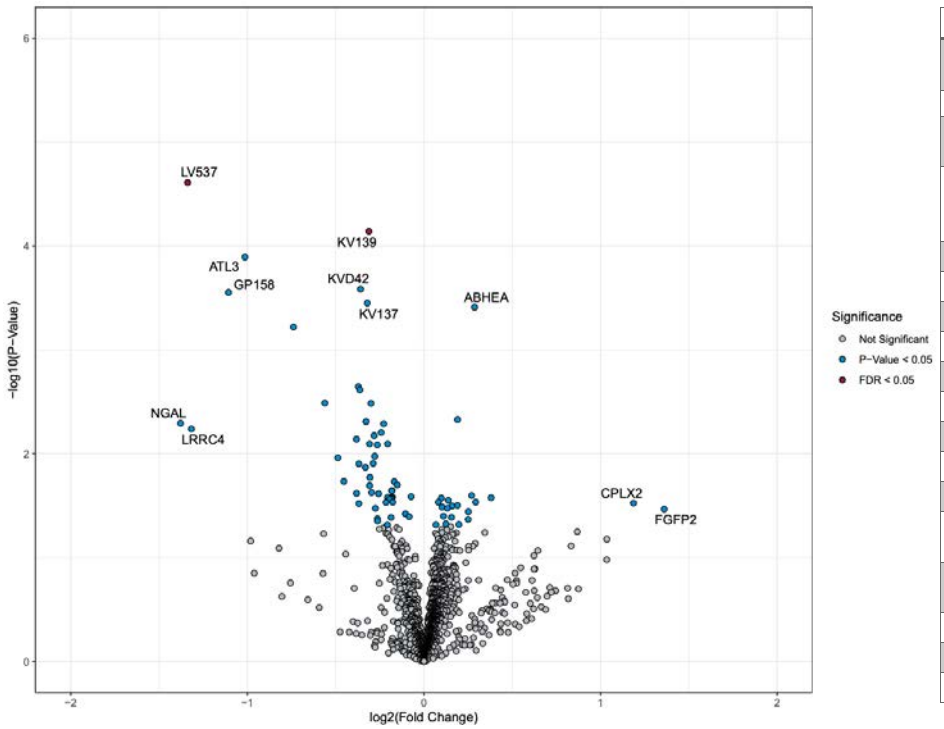
Ingenuity Canonical Pathway	Adjusted p-value
Intrinsic Prothrombin Activation Pathway	1.29E-07
GP6 Signaling Pathway	3.89E-07
MSP-RON Signaling in Cancer Cells Pathway	8.32E-07
Hepatic Fibrosis / Hepatic Stellate Cell Activation	2.63E-06
Glycolysis I	4.07E-06
Gluconeogenesis I	4.07E-06
Atherosclerosis Signaling	4.37E-06
IGF-1 Signaling	6.92E-06
Agrin Interactions at Neuromuscular Junction	5.37E-05
Apelin Liver Signaling Pathway	0.0001
Neuroprotective Role of THOP1 in Alzheimer's Disease	0.00013804
Complement System	0.00040738
NRF2-mediated Oxidative Stress Response	0.00045709
Leukocyte Extravasation Signaling	1.29E-07

Figure 2: Proteins and Pathways Nominally Associated with Postoperative Delirium Severity in CSF Before Surgery



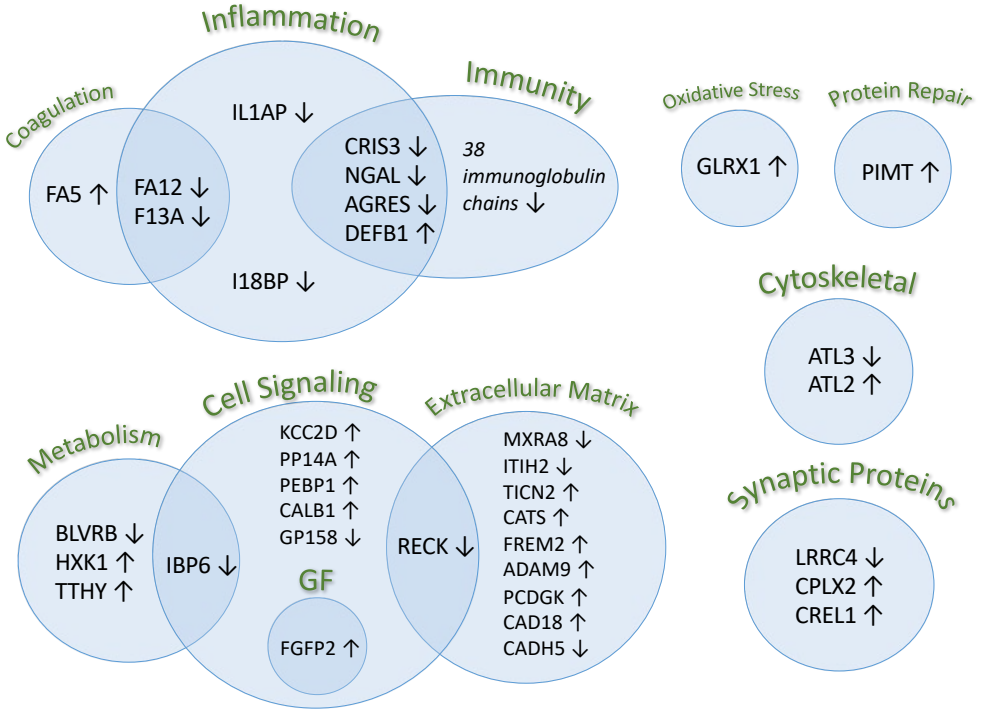
Ingenuity Canonical Pathways	p-value
Acute Phase Response Signaling	2.34423E-06
LXR/RXR Activation	5.01187E-05
Intrinsic Prothrombin Activation Pathway	0.000338844
FXR/RXR Activation	0.000758578
Extrinsic Prothrombin Activation Pathway	0.001202264
Coagulation System	0.005754399
Complement System	0.006456542
Iron homeostasis signaling pathway	0.010471285
Ascorbate Recycling (Cytosolic)	0.012882496
Glutathione Redox Reactions II	0.012882496
MSP-RON Signaling Pathway	0.015135612
Clathrin-mediated Endocytosis Signaling	0.024547089
Superoxide Radicals Degradation	0.025703958
Maturity Onset Diabetes of Young (MODY) Signaling	0.02630268
NRF2-mediated Oxidative Stress Response	0.041686938
Hepatic Fibrosis Signaling Pathway	0.046773514

Figure 3: Proteins and Pathways Nominally Associated with Postoperative Delirium Severity in CSF After Surgery



Ingenuity Canonical Pathways	p-value
Extrinsic Prothrombin Activation Pathway	6.91831E-06
Coagulation System	7.76247E-05
Intrinsic Prothrombin Activation Pathway	0.000134896
Differential Regulation of Cytokine Production in Intestinal Epithelial Cells by IL-17A and IL-17F	0.001348963
Synaptogenesis Signaling Pathway	0.006456542
Heme Degradation	0.009549926
Ascorbate Recycling (Cytosolic)	0.009549926
Glutathione Redox Reactions II	0.009549926
Acute Phase Response Signaling	0.009772372
IL-10 Signaling	0.012589254
VDR/RXR Activation	0.014791084
Trehalose Degradation II (Trehalase)	0.016595869
GDP-glucose Biosynthesis	0.025703958
Glucose and Glucose-1-phosphate Degradation	0.028183829
UDP-N-acetyl-D-galactosamine Biosynthesis II	0.030199517
LXR/RXR Activation	0.034673685
Synaptic Long-Term Potentiation	0.03801894
Gα12/13 Signaling	0.039810717

Figure 4: Conceptual Model of Postoperative Protein Differences Associated with Delirium Severity



GERIATRIC ANESTHESIA 6

Preoperative factors predict neurocognitive disorder after CABG or PCI in a population-based cohort of older adults

Elizabeth L Whitlock[1], L G Diaz-Ramirez[2], M. M Glymour[2], Sei J Lee[2], W J Boscardin[2], Alexander K Smith[2]

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INTRODUCTION: We recently found no population-average difference in long-term cognitive outcomes after coronary revascularization by coronary artery bypass grafting (CABG; including off-pump CABG [OPCAB]) versus percutaneous coronary intervention (PCI).[1] However, durable postoperative neurocognitive disorder (PND) remains a feared outcome of medical care, and occurred in both CABG and PCI recipients in our study. It is currently unknown whether individual PND risk can be predicted. We analyzed the cohort of older adults from our published study[1] to establish whether preoperative factors predict PND at 0-2 years after coronary revascularization.

METHODS: Older adults in the nationally-representative Health and Retirement Study (HRS) undergo biennial cognitive assessments throughout late life. We used Medicare billing records to identify 1,390 HRS participants (551 CABG, 839 PCI) who underwent CABG/PCI at age 65 or older between 1998 and 2015 and participated in at least one post-procedure HRS interview.[1] Using a summary measure of memory based on direct and proxy cognitive test responses,[2] we identified participants whose actual post-procedure memory performance was 1-2 ('mild NCD') or >2 ('major NCD') standard deviations lower than expected from pre-procedure memory assessment. After multiple imputation to address missing data, we modeled individual probability of mild or major NCD at the first postoperative cognition assessment using ordered logistic regression on a priori specified preoperatively-known factors including demographic and health factors, preoperative memory, and frailty.

RESULTS: Participants underwent CABG/PCI at 75±6 years old; 39.7% were women, and 16.6% were of nonwhite race/ethnicity. At a median of 1.1 [interquartile range 0.6-1.6] years after procedure, 1,035 had no NCD, 267 (19%) had mild NCD, and 88 (6%) had major NCD. Risk factors predicting any NCD included older age, male gender, nonwhite race/ethnicity, frailty, OPCAB, and, counterintuitively, higher memory score at preprocedure. Obesity was protective. Participants meeting 'high risk' criteria (11% of the cohort) had a 59% rate of any NCD, and 21% rate of major NCD. In contrast, 78% of those at 'low risk' were free of any NCD; 96% had either no or mild NCD only. The area under the receiver operator characteristic curve for any NCD was 0.753, which remained stable when the model was applied to PCI-only or CABG-only recipients. Calibration was excellent (slope 1.007, with expected:observed 0.999) in the whole cohort and CABG and PCI subgroups.

CONCLUSION: A model using preoperatively-known factors predicted durable NCD with discrimination and calibration suitable for clinical use. Figure 1. Discrimination and calibration for the prediction model. A, receiver operator characteristic curve. B, calibration plot.

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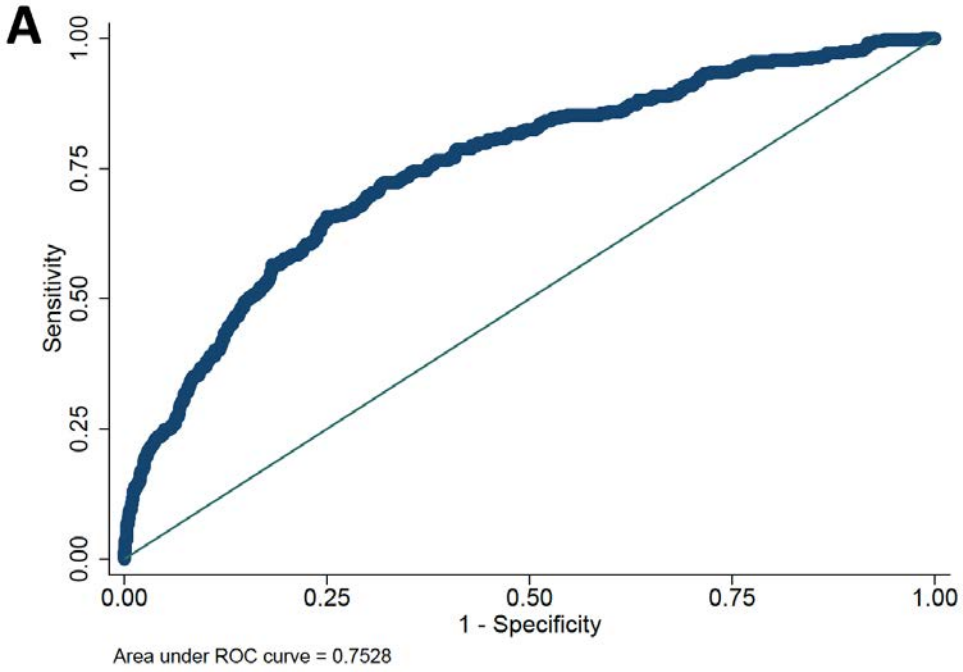

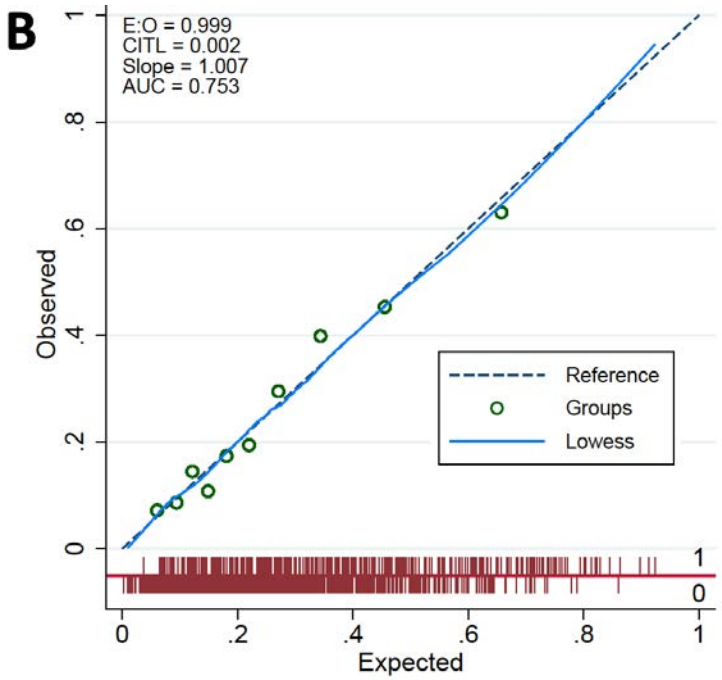

GERIATRIC ANESTHESIA 7

Post-operative Complications in Older Surgical Patients with Preoperative Cognitive Impairment: A Systematic Review and Meta-analysis

Emily Au[1], Lina Chen[1], Aparna Saripella[1], Paras Kapoor[2], Ellene Yan[1], Frances F Chung[3]

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INTRODUCTION: Cognitive impairment has been shown to be a risk factor for poor postoperative outcomes¬π. With the projected rise in the older population within the next few decades and the high prevalence of cognitive impairment in the older population, it will become increasingly important to understand the association between cognitive impairment and postoperative adverse outcomes. The objective of this systematic review and meta-analysis is to determine the association between preoperative cognitive impairment and postoperative complications in older patients undergoing elective and emergency non-cardiac surgery.

METHODS: Electronic databases including MEDLINE, PubMed, Embase, Cochrane CENTRAL, PsycINFO, Web of Science, Scopus, and clinicaltrials.gov were searched from their inception dates to March 30, 2021. Inclusion criteria were (1) patients ≥ 60 years undergoing elective or emergency non-cardiac surgery; (2) a preoperative cognitive impairment determined by a validated cognitive assessment tool; (3) at least one postoperative complication reported; (4) a comparator group with no preoperative cognitive impairment present; and (7) English language. The primary outcomes were postoperative delirium and mortality. Effect sizes were calculated as Odds ratio (OR) based on random effect model analysis using the Cochrane Review Manager Version 5.3.

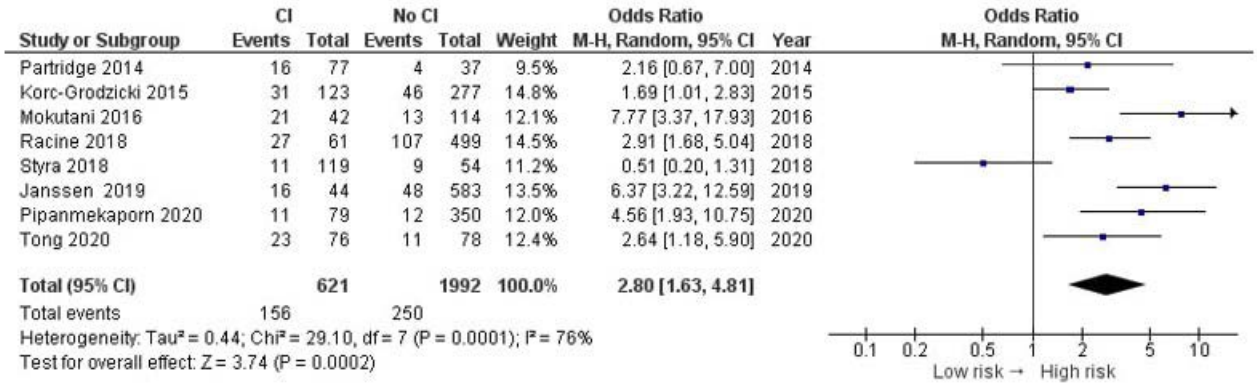
RESULTS: The search identified 9,491 studies, of which 40 studies with 15,957 patients were included. The most common study design was prospective cohort (n=29). Types of non-cardiac surgeries were cancer (abdominal), general, gynecologic, head and neck, neurosurgery, ophthalmologic, orthopedic, thoracic, urologic, vascular, and mixed. The mean age was 77.5 ± 11.9, of which 45.2% were male. The prevalence of cognitive impairment among elective and emergency non-cardiac surgery studies ranged from 7 to 80%. Overall, older patients with a preoperative cognitive impairment were more likely to experience postoperative delirium after elective non-cardiac surgery (25.1% vs. 12.6%; OR: 2.8; 95% CI: 1.6-4.8; I^2: 76%; p=0.0002) (Figure 1) and emergency non-cardiac (orthopedic) surgery (25% vs. 5%; OR: 9.0; 95% CI: 3.4-24.1; I^2: 65%; p < 0.0001). Preoperative cognitive impairment significantly increased risk for 1-year mortality after elective and emergency non-cardiac surgery (26.2% vs. 13.2%; OR: 2.3; 95% CI: 1.4-3.7; I^2: 73%; p =0.001). Subgroup analysis of emergency orthopedic surgery demonstrated an increased risk for 1-year mortality in older patients (33.8% vs.14.7%; OR: 3.0; 95% CI: 2.1-4.1; I^2: 8%; p < 0.00001).

CONCLUSION: Our systematic review and meta-analysis indicates that preoperative cognitive impairment in older surgical patients significantly increases risk for postoperative delirium and 1-year mortality after elective and emergency non-cardiac surgery.

REFERENCES:

1. Postoperative Outcomes in Primary Total Knee Arthroplasty Patients With Preexisting Cognitive Impairment: A Systematic Review. 2018;9:2151459318816482

Fig. 1 Forest plot displaying a meta-analysis of postoperative delirium in cognitively impaired and cognitively intact (control) elderly patients after elective non-cardiac surgery



GERIATRIC ANESTHESIA 8

Multidisciplinary Geriatric Care in the PACU: A Quality Improvement Initiative

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INTRODUCTION: This pilot project seeks to develop and assess an intervention for management of frailty in older Americans undergoing elective surgery, with intent of future testing of the intervention in a large multicenter trial. Frailty is common in older surgical patients and is associated with higher rates of postoperative delirium. Hospital based multidisciplinary geriatric care (MGC) plans include simple non-pharmacologic approaches developed to decrease delirium in geriatric populations and have demonstrated success in diverse settings. In the surgical setting, MGC care plans have been instituted postoperatively on the ward following post-anesthesia care unit (PACU) transfer. However, onset of postoperative delirium primarily occurs within the first 24 hours. Thus, the PACU provides an opportunity for earlier MGC implementation during the time of highest cognitive risk in frail surgical patients. The purpose of this pilot is two- fold: to fine tune our protocol which incorporates elements of hospital based MGC into current post-anesthesia recovery room (PACU) practice; to obtain preliminary data for a multicenter trial to determine whether implementing a PACU based MGC model of care will decrease postoperative delirium in frail older surgical patients.

METHODS: Following IRB approval, this performance improvement project occurred over 15 months and studied vulnerable subjects ≥ 65 years undergoing elective surgery not requiring ICU stay. Additional eligibility criteria included a preoperative Edmonton frailty score ≥ 6. The PACU-MGC model incorporates literature supported elements of hospital based MGC care for delirium prevention into current PACU practice[1]. Nurses in the preoperative holding area, PACU, and the surgical ward were trained to screen all patients ≥65 years for delirium using the 4 A's test (4AT; www.the4at.com). A 4AT total score of 0 indicates that delirium or cognitive impairment is unlikely; a score between 1 and 3 indicates possible cognitive impairment, and a score ≥ 4 is suggestive of delirium. The 4AT has been validated on the hospital ward[2] and in the PACU[3] as an excellent screening instrument for delirium with high specificity and sensitivity.

The study took advantage of clinical data routinely collected through EPIC to provide necessary preliminary data and test out the feasibility of the proposed PACU-MGC intervention. The primary outcome was binary: 4AT score of ≥4 at any time postoperatively on the surgical wards or 4AT score <4 at all postoperative assessments. Lowess smoothing was used to examine changes in delirium risk as determined by postoperative 4AT scores with ongoing development and implementation of the PACU-MGC model of care.

RESULTS: Current analysis included 99 patients studied from 7/20-10/21. Pertinent demographics are outlined in the table. During the 15 month study period the protocol was continuously developed and tweaked. Loess smoothing during that time period shows continuous improvement in delirium rates in this frail population. Postoperative delirium rates decreased from 14% during the first 5 months of the project to 5% in the last 6 months of instituting the PACU-MGC intervention (see figure)

CONCLUSION: Preliminary findings suggest that implementing a PACU-MGC program leads to a decrease in early postoperative 4AT scores. In addition, an MGC care program is feasible to implement in the PACU setting. Further study is warranted to determine the effects of the PACU-MGC program on outcomes in frail surgical patients.

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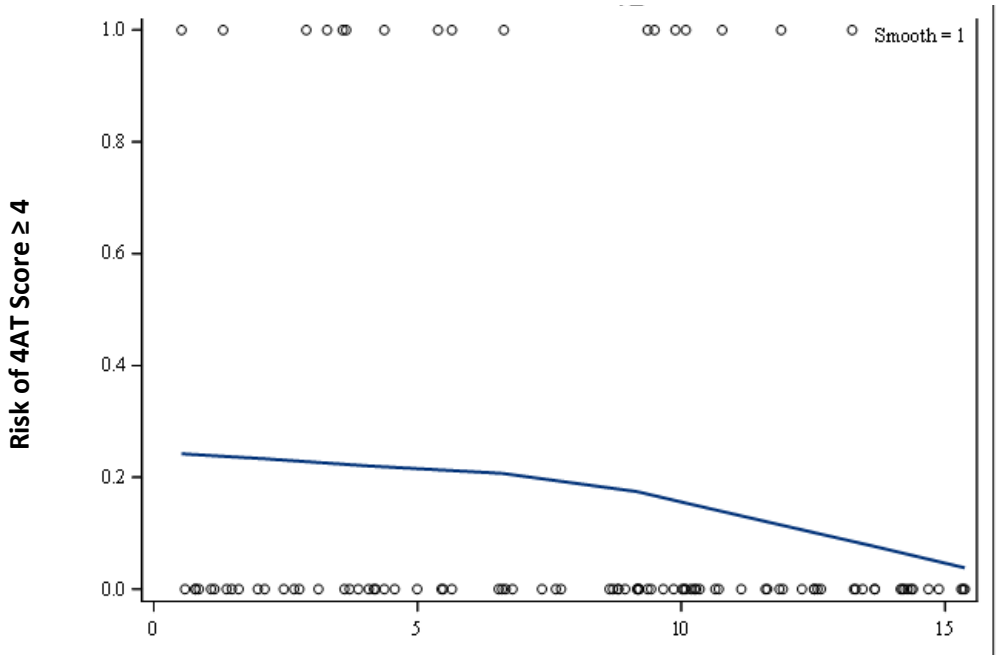
Age	80 ± 9			
Gender	Female (66%)			
race	Black (22%)	Caucasian (73%)		
Surgical service	General (27%)	Neurosurgery (11%)	Orthopedics (25%)	Vascular (25%)
ASA	II (15%)	III (74%)	IV (11%)	
Anesthetic technique	General (67%)	Spinal/epidural (22%)	MAC/regional (11%)	
Discharge disposition	Home (74%)	skilled nursing (23%)		
death	In-hospital (1%)	Following discharge (8%)		



GERIATRIC ANESTHESIA 9

Intraoperative frontal electroencephalographic preoperative frailty marker in patients ≥ 65 years old in elective non-cardiac surgery

Juan C Pedemonte[1], Gonzalo Boncompte[2], Maria F Elgueta[2], Javiera Benavides[2], Natalia Calderón[2], Victor Contreras[3], Trinidad Larraín[2], Maria I Morales[2], Marcela Carrasco[2], Ignacio Cortinez[3]

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INTRODUCTION: Frailty is a state of vulnerability that determines a lower capacity to recover from a stressful incident. It is associated with poorer postoperative outcomes, increased morbidity and mortality.[1] There are multiple instruments for preoperative frailty screening[2], with no agreement as to which is the best available tool. Alpha spectral power derived from frontal electroencephalography (EEG) has been associated with preoperative physical activity, preoperative cognitive level, comorbidities, and postoperative delirium.[3] Our aim was to evaluate alpha power as a possible EEG marker of preoperative frailty in patients ≥65 years undergoing general anesthesia with sevoflurane.

METHODS: Cohort, observational and prospective study (NCT04783662). Inclusion criteria: patients over 65 years of age undergoing elective non-cardiac surgery requiring general anesthesia, ASA Physical Status I-III. Exclusion criteria: neurosurgical patients, alcohol and/or drug abuse, or allergy to anesthetic drugs. Preoperative frailty screening was performed using the Fried phenotype, the FRAIL scale and the Clinical Frailty Scale. The intraoperative frontal electroencephalogram (SedLine) was recorded for 10 mins (maintenance). Alpha power (8-12 Hz) was quantified as median, mean, peak and 1/f oscillation-specific peak alpha power. We categorized patients into 3 frailty groups (Robust, Pre-frail, Frail) according to Fried's phenotype. Statistical analysis: continuous variables are presented as median and interquartile range. Categorical variables with count and percentage. Comparisons were made using the Kruskal Wallis test (with Dunn test for pairwise comparisons for boxplots) and Chi square or Fisher's test, respectively. Correlations between frailty measures and alpha power were conducted using Spearman's Rho, with Bonferroni correction. P <0.05 was considered significant. EEG analyses: empirical bootstrap approach was performed to enable statistical inferences (#bootstraps: 5000, 95%CI). Statistical significance was considered when the upper and lower CI of the median difference distribution did not border zero over a contiguous frequency range. Analyses were performed in Python and R.

RESULTS: 33/60 patients have been recruited. 31/33 EEG recordings were analyzed given an adequate signal quality. We found similar distribution between robust (11), pre-fragile 13) and fragile (9). Comparisons between groups according to Fried categories are shown in Table 1. As the level of frailty increases, the mean, median, peak, and 1/f oscillation specific of the median peak of the alpha spectral power decrease, without being statistically significant (Figure 1). There is a positive and significant correlation between the different EEG studied markers (Mean, Median, Peak, 1/f = Rho>0.79, p<0.05), as well as between the different frailty scales (Fried, FRAIL, CFS = Rho>0.59, p<0.05)(Figure 2). In spectral analysis, EEG power was significantly greater in the No-frail group between 3.30 to 9.57 Hz, when compared to Frail group (Figure 3).

CONCLUSION: Alpha spectral power markers present a decline as the level of frailty increases. The three measured frailty instruments showed high correlation between them. Recruitment completion and validation is required to determine if these measurements can be used as an intraoperative EEG marker of frailty.

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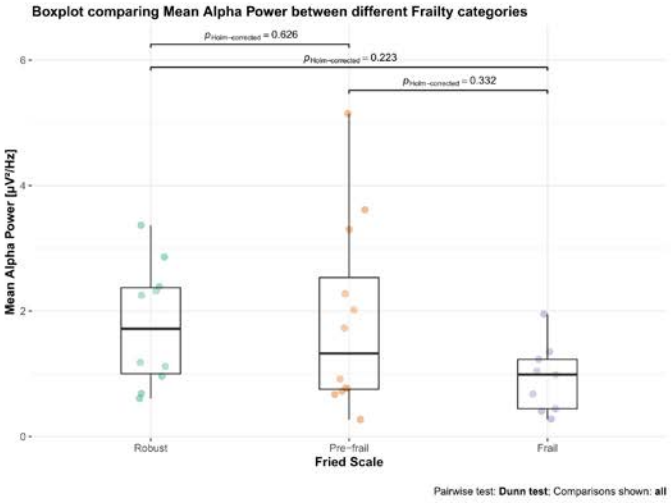
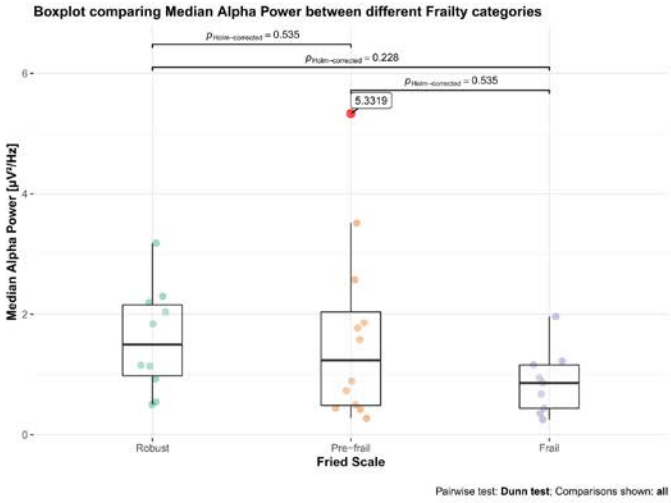
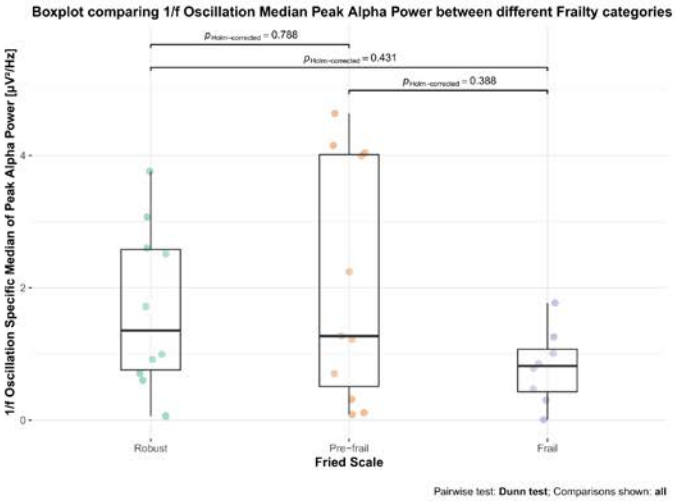
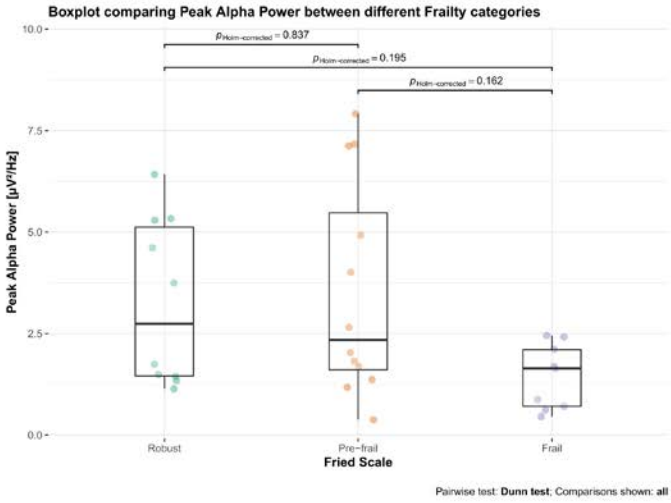
Table 1: Demographic data comparing groups according to Frailty category (Fried)

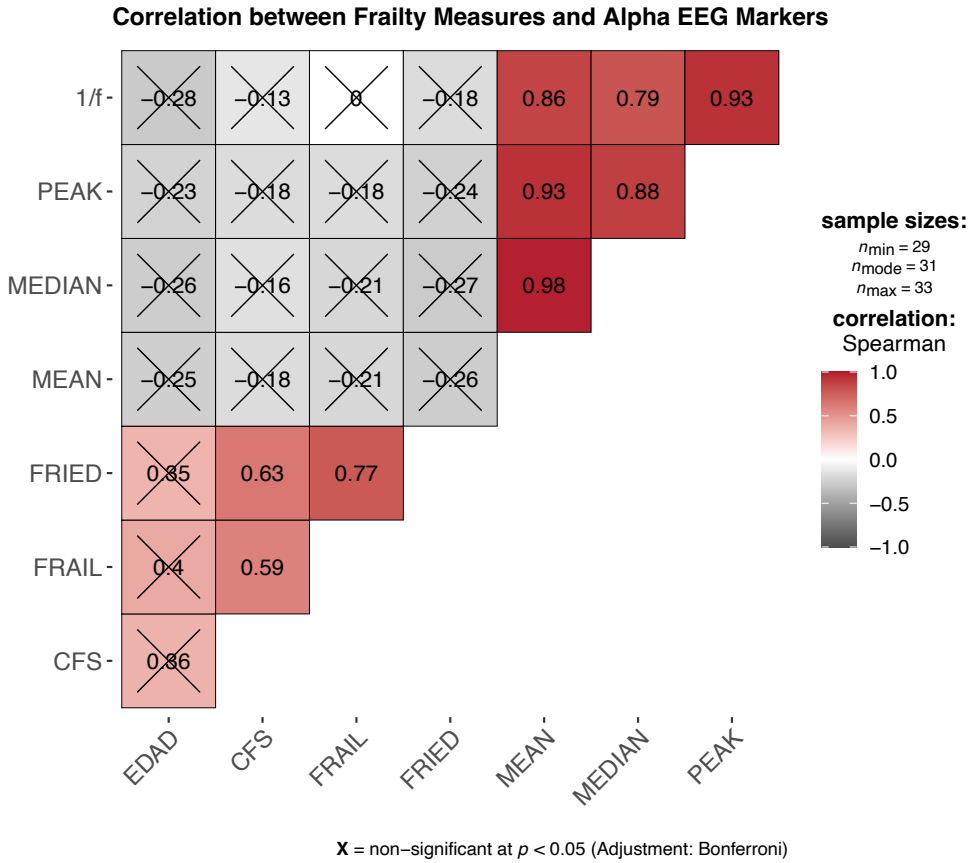
		Robust	Pre-frail	Frail	p
n		11	13	9	
Gender (%)	Female	4 (36.4)	6 (46.2)	2 (22.2)	0.518
	Male	7 (63.6)	7 (53.8)	7 (77.8)	
Age (median [IQR])		73.00 [70.50, 74.00]	75.00 [69.00, 78.00]	80.00 [75.00, 82.00]	0.127
Weight (median [IQR])		77.00 [72.50, 83.50]	70.00 [62.00, 76.00]	70.00 [66.00, 82.00]	0.187
Height (median [IQR])		165.00 [160.00, 170.00]	160.00 [159.00, 169.00]	170.00 [154.00, 173.00]	0.424
BMI (median [IQR])		29.00 [26.00, 31.00]	25.00 [24.00, 29.00]	26.00 [23.00, 30.00]	0.204
ASA Physical Status (%)	1	1 (9.1)	0 (0.0)	0 (0.0)	0.54
	2	10 (90.9)	12 (92.3)	8 (88.9)	
	3	0 (0.0)	1 (7.7)	1 (11.1)	
Educational Level (%)	Lower/Middle	4 (36.4)	6 (46.2)	4 (44.4)	0.392
	Highschool	1 (9.1)	5 (38.5)	3 (33.3)	
	College/University	5 (45.5)	2 (15.4)	2 (22.2)	
	Postgraduate	1 (9.1)	0 (0.0)	0 (0.0)	
Years of formal education (median [IQR])		15.00 [6.00, 17.00]	10.00 [8.00, 12.00]	8.00 [4.00, 12.00]	0.213
Hearing impairment (%)	Yes	4 (36.4)	5 (38.5)	5 (55.6)	0.643
	No	7 (63.6)	8 (61.5)	4 (44.4)	
Visual Impairment (%)	Yes	7 (63.6)	8 (61.5)	6 (66.7)	0.97
	No	4 (36.4)	5 (38.5)	3 (33.3)	
Depression (%)	Yes	0 (0.0)	1 (7.7)	0 (0.0)	0.452
	No	11 (100.0)	12 (92.3)	9 (100.0)	
Charlson Comorbidity Index (median [IQR])		0.00 [0.00, 0.50]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.451
Revised Cardiac Risk Index (median [IQR])		0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.485
Barthel Index for ADL (%)	Independent	11 (100.0)	13 (100.0)	6 (66.7)	0.012
	Low dependence	0 (0.0)	0 (0.0)	3 (33.3)	
Clinical Frailty Scale (%)	Very fit	5 (45.5)	4 (30.8)	0 (0.0)	0.003
	Fit	6 (54.5)	5 (38.5)	1 (11.1)	
	Managing well	0 (0.0)	4 (30.8)	5 (55.6)	
	Living with very mild frailty	0 (0.0)	0 (0.0)	3 (33.3)	
FRAIL Scale (%)	Robust	10 (90.9)	5 (38.5)	0 (0.0)	0.001
	Pre-frail	1 (9.1)	6 (46.2)	5 (55.6)	
	Frail	0 (0.0)	2 (15.4)	4 (44.4)	
Fried phenotype(%)	Robust	11 (100.0)	0 (0.0)	0 (0.0)	<0.001
	Pre-frail	0 (0.0)	13 (100.0)	0 (0.0)	
	Frail	0 (0.0)	0 (0.0)	9 (100.0)	
Minicog (%)	Possible Cognitive Impairment	1 (9.1)	2 (15.4)	0 (0.0)	0.467
	No Cognitive Impairment	10 (90.9)	11 (84.6)	9 (100.0)	
Mean Arterial Preassure [mmHg] (median [IQR])		86.00 [78.00, 87.50]	80.00 [75.00, 86.00]	89.00 [77.00, 95.00]	0.358
ETSevo [%] (median [IQR])		1.40 [1.30, 1.45]	1.40 [1.30, 1.50]	1.40 [1.40, 1.40]	0.756



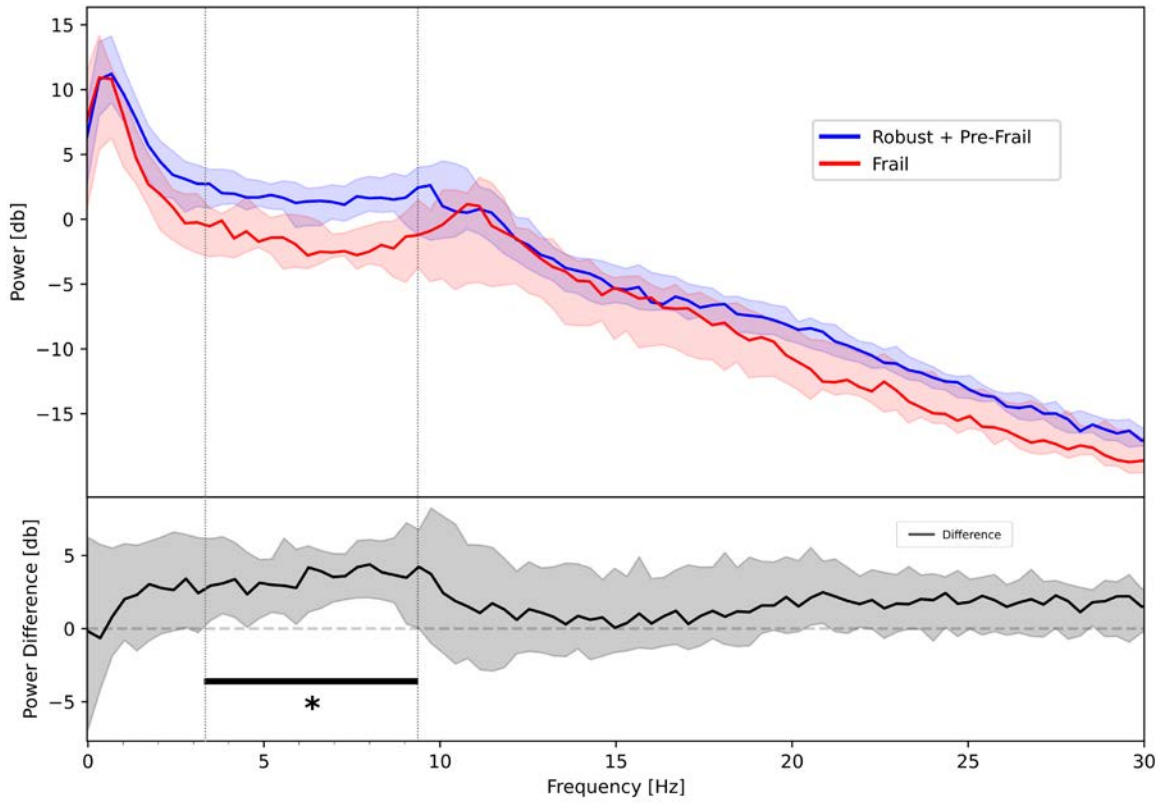








X = non–significant at $p < 0.05$ (Adjustment: Bonferroni)



GERIATRIC ANESTHESIA 10

Studying possible intraoperative EEG markers of postoperative delirium using standardized propofol induction: The roles of burst suppression and delta-band power

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INTRODUCTION: Postoperative delirium (POD) is the main cause of preventable postoperative morbidity and mortality in older population. Intraoperative markers that could reliably predict POD would be useful in identifying, managing, and reducing its adverse effects. The etiology of POD remains unknown but excessive anesthetic dosage has long been proposed as a risk factor. Burst suppression (BS), an electroencephalogram (EEG) activity pattern linked to anesthetic over-administration, has been associated with POD in observational studies[1, 2]. However, randomized controlled trials have produced controversial results[3, 4]. Here we studied the association of BS with POD, and explored spectral bands powers as possible POD markers, by analyzing intraoperative EEG of high POD risk geriatric patients after a standardized propofol induction.

METHODS: The present was a cohort, observational and prospective study (ClinicalTrials NCT04713644). Inclusion criteria: patients ≥65 years old undergoing elective cardiac surgery with CPB, ASA physical status II-III. POD was evaluated twice daily (AM-PM) during the first 72 postoperative hours with CAM-ICU and structured chart review. Standardized induction: Fentanyl 5-10ucg/Kg, Propofol 0.5mg/Kg (plus 0.5mg/Kg if necessary) and Vecuronium 0.1mg/Kg plus halogenated gas (Isoflurane or Sevoflurane; see Figure 1). 20 minutes of EEG signal, following propofol injection, were recorded (Sedline ®) and analyzed offline using R, Python and JASP. BS was estimated by the number of seconds in isoelectricity (amp < 10uV) per minute. We analyzed spectral power of canonical frequency bands by means of FFT using Welch method. Statistical analyses were conducted using Mann-Whitney U test. Power spectra differences were analyzed using bootstrapping (5000 iterations). Statistical differences between spectra were determined as frequency segments in which the value zero was not within the 95% confidence interval of the difference between conditions. A value of $p < 0.05$ was considered statistically significant.

RESULTS: 25 out of a total of 80 patients have been recruited so far. Data from 5 patients were rejected due to poor signal quality or incomplete POD evaluation. POD group was slightly older than no_POD (75 [73, 76] vs. 69 [66-73], $p = 0.028$; See table in Figure 2). We found no difference in BS between groups (0.00 [0.00, 0.03] vs. 0.01 [0.00, 0.02], $p = 0.533$, Figure 3). Patients that subsequently developed POD showed increased spectral power (5.79 [3.44, 6.94] vs. 2.58 [2.19, 3.97], $p = 0.017$) in the Low Delta range (0.1 - 2Hz; Figure 3). No other frequency band showed significant differences (Figure 4).

CONCLUSION: Isoelectricity during a standardized propofol induction was not associated with POD in older patients. Intraoperative Low Delta activity was enhanced in POD patients. Completion of recruitment is required to confirm these results, however Low Delta band appears as a promising candidate.

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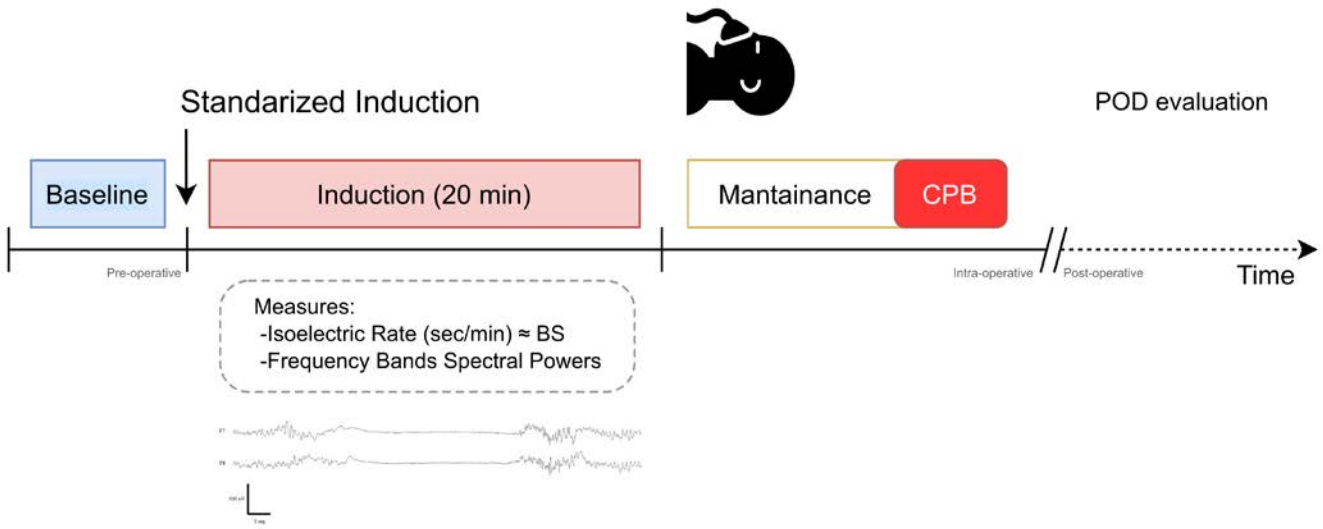
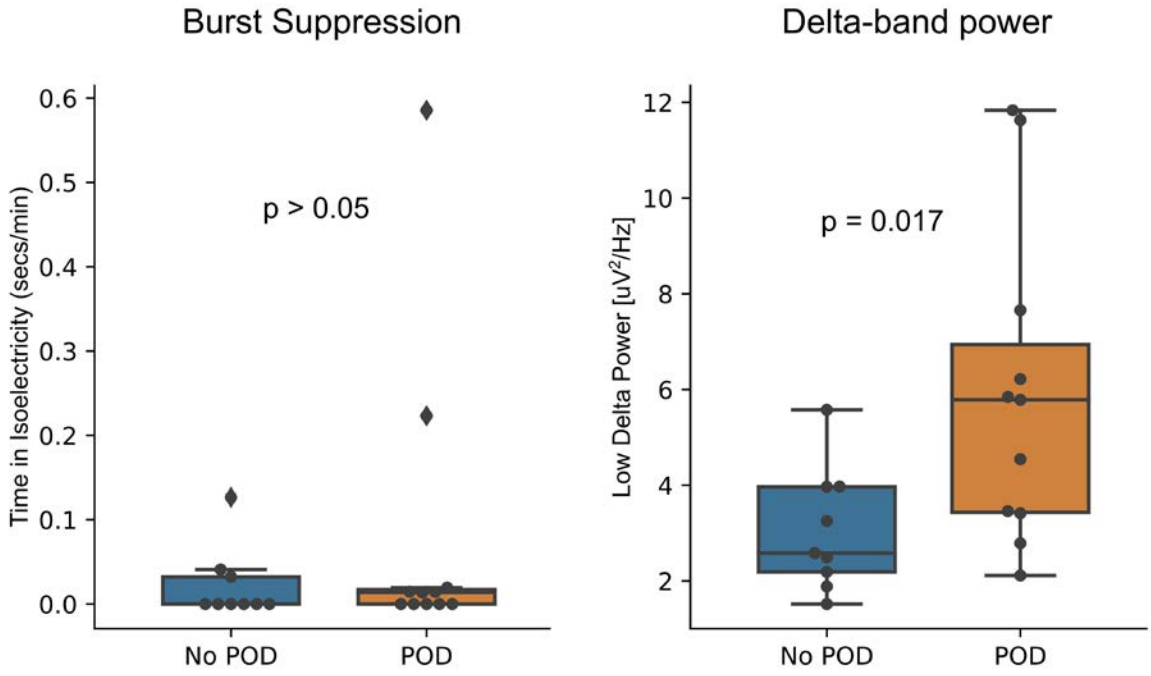
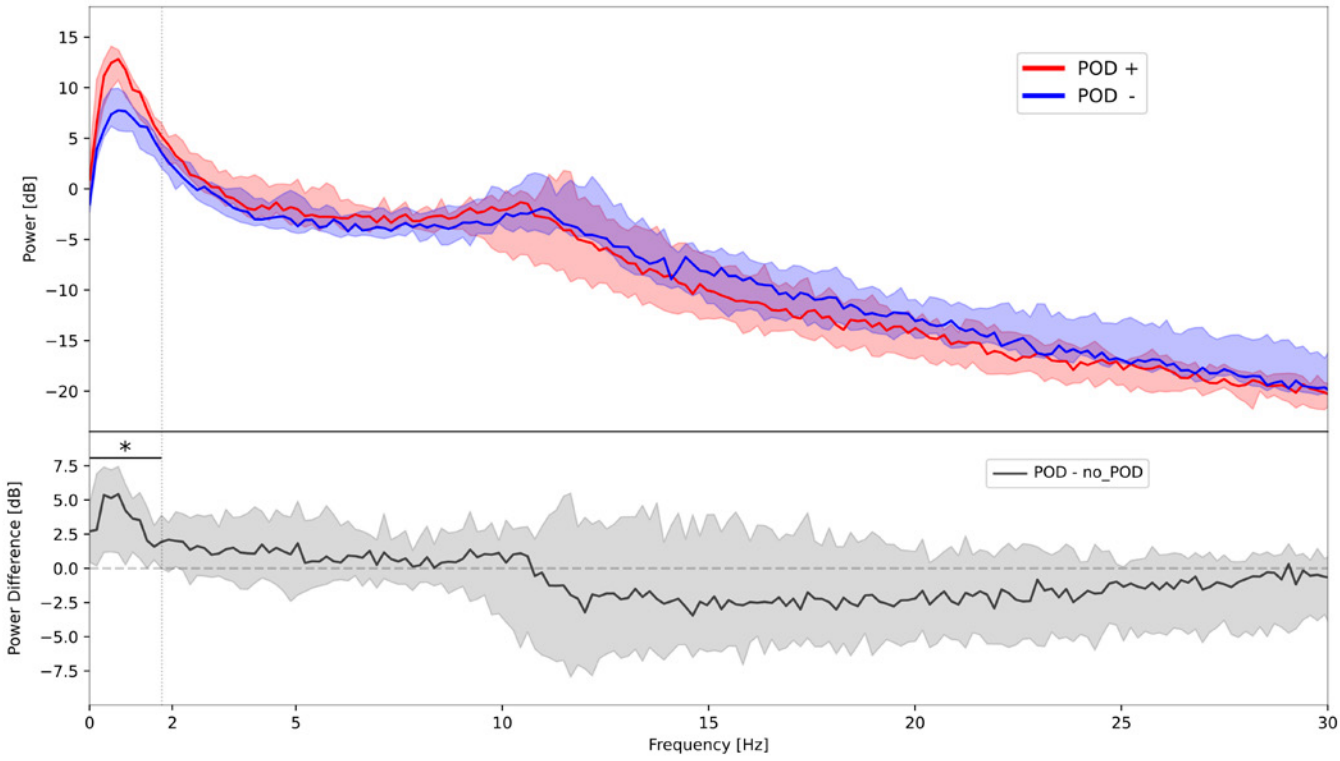


Figure 1: Schematic depiction of the experimental protocol

Table I: Demographic data for patients separated by POD diagnostic cardiac surgery. P-values correspond to pairwise comparisons using Mann-Whitney U-test (uncorrected)

	No_POD	POD	p-value
N	11	12	
Gender (% Female)	10 (90.9)	8 (66.7)	0.367
Age (median [IQR])	69 [66, 73]	75 [73, 76]	0.028
ASA Physical Status (% 2)	5 (45.5)	5 (41.7)	>0.99
(% 3)	6 (54.5)	7 (58.3)	
Educational Level (%) Lower/Middle School	2 (18.2)	4 (33.3)	0.59
Highschool	3 (27.3)	2 (16.7)	
College/University	5 (45.5)	6 (50.0)	
Postgraduate	1 (9.1)	0 (0.0)	
Years of formal education (median [IQR])	14 [9.50, 16.00]	11 [7.75, 14.75]	0.421
Depression	0 (0.0)	1 (8.3)	>0.99
Visual Impairment (% No)	3 (27.3)	6 (50.0)	0.491
Hearing impairment (% No)	11 (100.0)	12 (100.0)	
Dental prostheses (% No)	8 (72.7)	11 (91.7)	0.518
Charlson Comorbidity Index (median [IQR])	1.00 [0.00, 1.50]	1.00 [0.75, 2.00]	0.476
Alcohol Consumption Questionnaire (median [IQR])	0.00 [0.00, 2.00]	1.00 [0.00, 1.00]	0.897
Barthel Index for ADL (%)	8 (72.7)	11 (91.7)	0.518
Baseline hemoglobin (median [IQR])	12.90 [12.50, 13.90]	13.45 [12.43, 14.50]	0.774
Clinical Frailty Scale (median [IQR])	3.00 [2.00, 3.00]	3.00 [2.00, 3.25]	0.49
MiniCog – No Cognitive Impairment (%)	9 (81.8)	11 (91.7)	0.936
Baseline CRP (mg/L) (median [IQR])	0.14 [0.09, 0.34]	0.10 [0.07, 0.36]	0.563
CPB length (min) (median [IQR])	32.00 [28.77, 35.50]	35.20 [29.80, 36.00]	0.55
Dexmedetomidine dose (ucg) (median [IQR])	224.00 [158.00, 285.00]	152.00 [84.00, 156.38]	0.063
RBC Units transfused (median [IQR])	1.00 [0.00, 2.00]	2.00 [1.00, 2.00]	0.434





GERIATRIC ANESTHESIA 11

The effect of Age in measures of anesthesia hypnosis, comparison of BIS, Alpha Power, Lempel-Ziv Complexity and Permutation Entropy during propofol administration

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INTRODUCTION: Precise anesthetic titration is of particular importance in geriatric patients given their higher risk for complications. This is specially challenging because they require different dosages when compared to general population[1]. Intraoperative electroencephalographic (EEG) monitors, like the Bispectral Index (BIS), are strongly based on spectral EEG properties and have proven to be a valuable tool in reducing under and over-dosage of anesthetics. However, evidence has suggested that commercial monitors show a systematic bias in the values of their indexes given by age[2, 3]. Here we systematically analyzed the effect of age on four measures, previously proposed as indexes of anesthesia hypnosis, during propofol induction: BIS, Alpha power, Lempel-Ziv Complexity and Permutation Entropy.

METHODS: The present was an exploratory study in which we prospectively obtained EEG signals and BIS values, during intravenous propofol induction from 30 ASA I-II patients scheduled for elective surgery. Patients' age ranged from 18 to 86 years old. We separated patients in group 1 (<65) and group 2 (≥65) for statistical analysis. Continuous age-adjusted propofol infusion was delivered until the first appearance of suppression rate as indicated by the monitor. Five one-minute periods were selected for each patient between 2 minutes before LOC and the time when the maximal predicted propofol effect site (Schnider's) concentration (CeMax) was reached (LOC-2min, LOC-1min, LOC, midpoint between LOC-CeMax and CeMax). For each period we extracted the average BIS value and calculated total alpha power (8-12Hz), Lempel-Ziv Complexity and Permutation Entropy. Statistical analyses conducted for each measure were (1) a simple ANOVA analyzing measure value during each depth of anesthesia, (2) Mixed-effect ANOVA with depth of anesthesia as the within-patient variable and age group as the between-patient variable.

RESULTS: 1-way ANOVAs showed, for each measure, a main effect of depth of anesthesia (all $p < 0.05$), indicating that all measures were significantly modulated by depth of anesthesia in the general sample (Figure 1). We then included age group to this analysis, which showed, for all measures, a significant effect of age group (BIS $p<0.001$, $\omega2=0.297$; Alpha $p=0.028$, $\omega2=0.079$; Lempel-Ziv Complexity $p<0.001$, $\omega2=0.246$; Permutation Entropy $p<0.001$, $\omega2=0.198$), indicating that all measures analyzed here showed different values in young compared to elderly patients (Figure 2).

CONCLUSION: Our results characterize the age dependence of 4 measures of depth of anesthesia during propofol induction. They show that all measures were modulated by depth of anesthesia, but more importantly they also differed between age groups. These results show that the age of the patient is an important consideration when clinically interpreting BIS values, but also the values of other proposed measures of depth of anesthesia.

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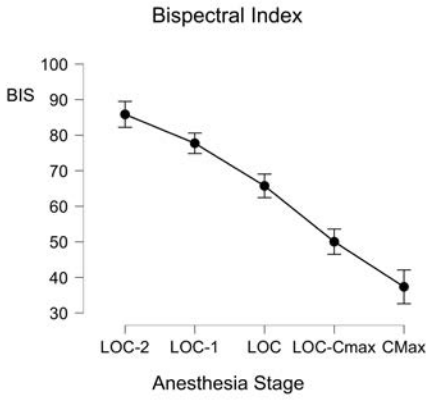

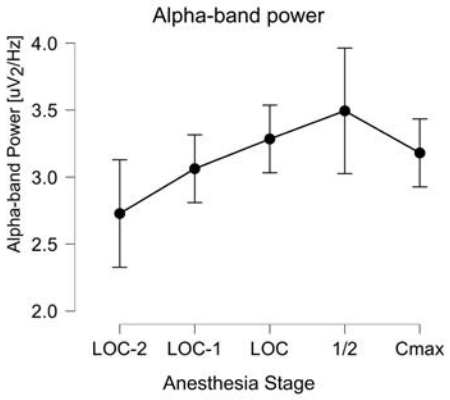

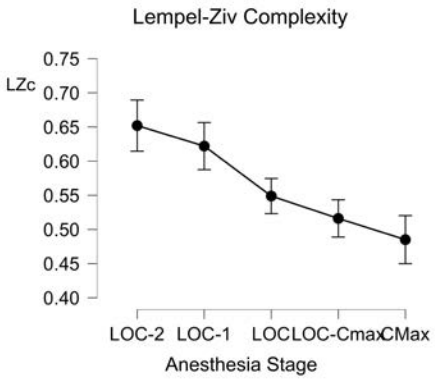

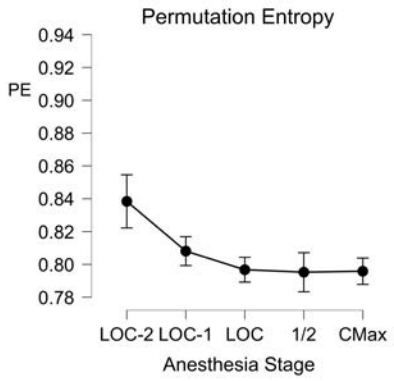

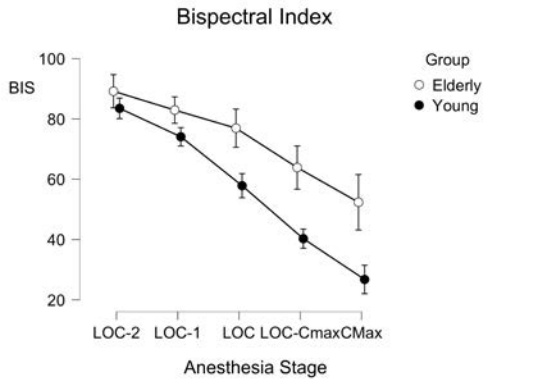

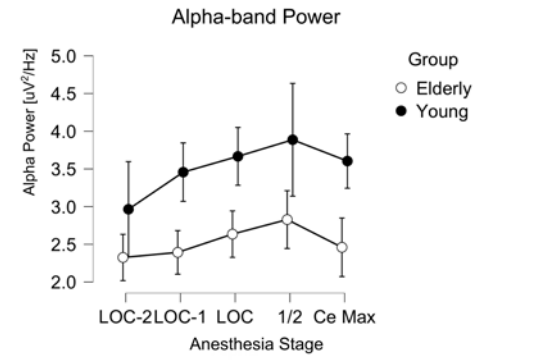

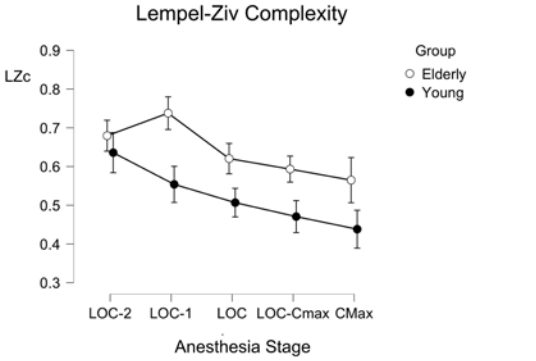

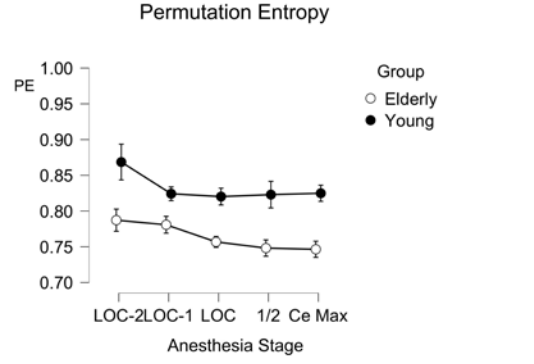

GERIATRIC ANESTHESIA 12

Dexmedetomidine is associated with a reduced postoperative increase in plasma p-tau181 in older patients undergoing spine surgery

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INTRODUCTION: Perioperative acceleration of neurodegeneration is thought to be an important contributor to the development of perioperative neurocognitive disorders (PND). Biomarkers of neuroinflammation, neuronal injury, and Alzheimer's disease (AD) are increased in patients postoperatively; however, the contribution of specific anesthetic agents, such as inhalational or intravenous, remains unclear. In this study, we focus on plasma levels of phosphorylated tau 181 (p-tau181), a relatively specific and predictive biomarker of AD.[1,2,3] We recently published data showing significant increases in plasma p-tau181 in cardiac and hip surgery patients throughout the perioperative period from preinduction to postoperative day 2.[4] Here, we sought to determine whether patients having a predominantly inhalational anesthetic (GAS) compared to patients having a predominantly intravenous anesthetic (IV) would have differences in the change of plasma p-tau181 levels from preoperative baseline to 3-months postoperatively. We also examined whether there were differences in p-tau181 in patients who received dexmedetomidine intraoperatively.

METHODS: In this prospective observational study of 70 patients (>= 65 years) having elective inpatient spine surgery under general anesthesia at a single academic center, we compared changes in plasma p-tau181 levels from preoperative baseline to 3-months postop in patients who received GAS (n=38) compared to IV (n=32). Plasma p-tau181 levels were measured using the fully automated immunoassay analyzer (Lumipulse G1200, Fujirebio) as previously described.[4] T-tests were used to compare 2 groups and 2-way ANOVA with Tukey's multiple comparisons test was used for dexmedetomidine analyses.

RESULTS: Plasma analysis revealed that, on average, p-tau181 levels increased in the GAS group (n=38) and decreased in the IV group (n=32, mean ± SD; 0.64 ± 2.46 pg/mL vs. -1.06 ± 3.24 pg/mL; p=0.014). This was despite the IV group having increased duration of surgery, blood loss, and hospital length of stay (Table 1). Examination of plasma p-tau181 levels in relation to intraoperatively-administered sedative agents revealed a greater postop increase in plasma p-tau181 in patients not administered dexmedetomidine (p=0.002, Fig. 1a). Patients who were not administered dexmedetomidine had a greater increase in postop plasma p-tau181 in both the GAS and IV groups (main effect of Dexmedetomidine, F(1, 66)=5.303, p=0.02, Fig. 1b).

CONCLUSION: Changes in plasma p-tau181 levels from preoperative baseline to 3-months postop were greater in older surgical patients who had GAS compared to IV maintenance of general anesthesia. Importantly, patients not receiving dexmedetomidine had a greater increase in plasma p-tau181 levels regardless of anesthesia type. Biomarkers have the potential to identify individuals at risk for PND by allowing early and accurate postoperative diagnoses. Such tests have the potential to revolutionize perioperative research, clinical trials, and clinical practice.

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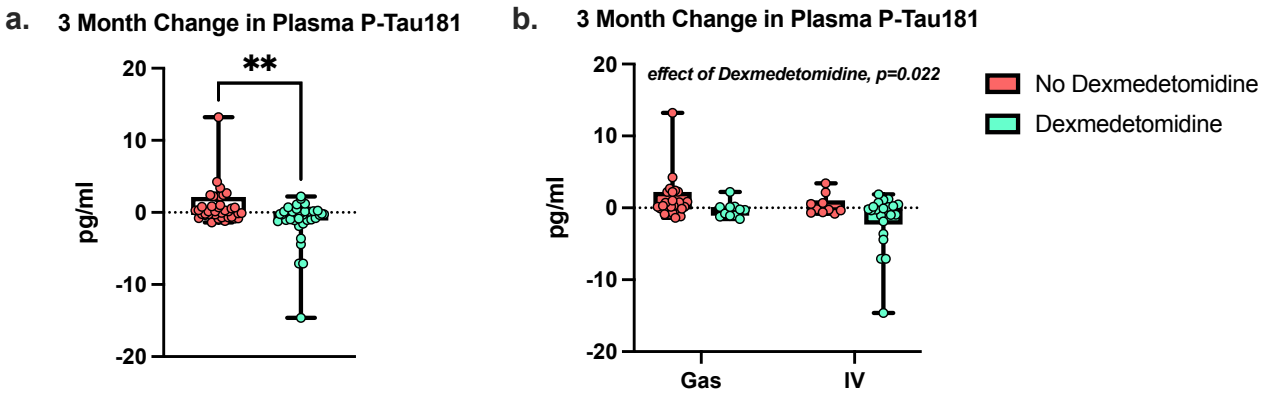
3. Longitudinal plasma phosphorylated tau 181 tracks disease progression in Alzheimer's disease. Transl Psychiatry 11, 356 (2021)
4. Plasma Biomarkers of Tau and Neurodegeneration During Major Cardiac and Noncardiac Surgery. JAMA Neurol (2021)

Table 1. Clinical characteristics IV vs. GAS			
	IV n=32	GAS n=38	Difference
	Mean	Mean	95% CI
Anesthesia duration (min)	402	272.5	[54.1, 209.1]
Estimated blood loss (mL)	876.3	371.7	[165.5, 1034.4]
Length of Stay (Days)	4.3	3.1	[0.2, 2.3]

Figure 1. Change in plasma P-Tau181 levels



Changes in plasma p-tau181 levels from preoperative baseline to 3-months postoperatively. **a)** Patients had a greater increase in p-tau181 if they did not receive intraoperative dexmedetomidine (red) compared to those who received intraoperative dexmedetomidine (green). **b)** Patients who were not administered dexmedetomidine had a greater increase in postoperative plasma p-tau181 in both the GAS and IV groups. (main effect of Dexmedetomidine, $F_{(1, 66)}$=5.303, p=0.02)

GERIATRIC ANESTHESIA 13

Perioperative neurocognitive and CSF Alzheimer's biomarker trajectories in older patients randomized to Isoflurane or Propofol for Anaesthetic Maintenance

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INTRODUCTION: Animal studies have suggested that isoflurane versus propofol have differential effects on Alzheimer's Disease (AD) - related neuropathological processes, such as amyloid beta[1] and tau pathology[2, 3], and on memory function[4]. Whether these drugs also have differential effects on cognition and AD neuropathology in actual patients is a clinically important question, since over 19 million older Americans undergo surgery each year[5] and are at risk for AD or other related dementias based on their age.[6]

METHODS: Patients age ≥ 60 undergoing non-cardiac, non-neurologic surgery were prospectively enrolled and randomized to receive isoflurane (N=54) or propofol (N=52) for anesthetic maintenance. We collected CSF samples before, 24 hours and 6 weeks after surgery (via lumbar punctures performed for research), to measure CSF AD - related biomarker levels (ie, Aβ42, tau, and p-tau 181p) and performed cognitive testing to assess the effect of anesthetic choice on cognitive function. Wilcoxon rank sum tests were used to compare CSF AD-related biomarkers between groups; univariable and multivariable linear regression was used to evaluate the relationship between anesthetic treatment group and cognitive outcomes.

RESULTS: There was no difference in the CSF tau/Aβ ratio between patients randomized to isoflurane vs propofol treatment groups before or 24 hrs after surgery (P = 0.186). All other CSF AD – related biomarkers (Aβ , tau, p-tau/ Aβ, and p-tau 181p) showed no significant difference between treatment groups before surgery, or 24 hours or 6 weeks after surgery. There was no significant difference in overall cognitive change from before to 6- weeks after surgery among propofol vs isoflurane treated patients (P = 0.881), nor were there any significant differences between anesthetic groups in individual cognitive domain changes over this time interval.

CONCLUSION: The results from this randomized controlled trial in over 100 older adults suggest that there is no reason to favor inhaled vs intravenous anesthesia for older adults concerned about their postoperative cognitive function and/or risk of developing Alzheimer's disease. These data suggest that the choice of anesthetic type (ie inhaled vs intravenous) should be made based on other patient, procedural or institutional factors.

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Of the 106 patients with complete cognitive data 14 (13.2%) were not treated as randomized. Hence, we conducted primary analysis according to the Intention To Treat principal. There was no evidence of a difference in rate of protocol deviations between groups (p=0.22).

Table 1

	Isoflurane (N=54)	Propofol (N=52)	p value
Age	67.5 [64, 71]	69.5 [64, 73]	0.502[1]
Race			0.079[2]
Black or African American	2 (3.7%)	8 (15.4%)	
Caucasian/White	51 (94.4%)	44 (84.6%)	
Not Reported/Declined	1 (1.9%)	0 (0.0%)	
GENDER (Male)	37 (68.5%)	29 (55.8%)	0.176[2]
BMI	28.0 [24.8, 31.3]	29.3 [24.5, 34]	0.259[1]
Years of Education	14.5 [12, 17.5]	16 [13.5, 18]	0.305[1]
Preop MMSE	29 [27, 29]	29 [28, 29]	0.122[1]
Pre-op Verbal Memory	0.40 (0.91)	0.60 (0.85)	0.248[3]
Pre-op Visual Memory	-0.10 (0.96)	0.07 (0.92)	0.365[3]
Pre-op Executive Function	0.02 (1.00)	0.30 (0.98)	0.155[3]
Pre-op Attention/Concentration	-0.17 (0.82)	-0.07 (0.80)	0.536[3]
PreOp Cognitive Index	0.04 (0.68)	0.22 (0.68)	0.167[3]
ASA			0.670[2]
1	1 (1.9%)	0 (0.0%)	
2	10 (18.5%)	13 (25.0%)	
3	42 (77.8%)	38 (73.1%)	
4	1 (1.9%)	1 (1.9%)	
SURGICAL SERVICE			0.598[2]
Thoracic	5 (9.3%)	5 (9.6%)	
General Surgery	14 (25.9%)	16 (30.8%)	
Gynecology	2 (3.7%)	0 (0.0%)	
Orthopedics	10 (18.5%)	9 (17.3%)	
Otolaryngology Head and Neck	0 (0.0%)	2 (3.8%)	
Plastic Surgery	2 (3.7%)	1 (1.9%)	
Urology	21 (38.9%)	19 (36.5%)	
Surgery duration (min)	131.5 [105, 191]	152 [92, 201]*	0.608[1]
CSF Biomarkers	N=48	N=49	
AB	358 [268.5, 399]	367 [298, 410]	0.521[1]
P-TAU 181P	27.5 [20.5, 30]	26.0 [21, 33]	0.989[1]
P-TAU/AB	0.08 [0.06, 0.10]	0.08 [0.06, 0.09]	0.711[1]
Tau	49.5 [44.5, 58.5]	47 [39, 59]	0.251[1]
TAU/AB	0.14 [0.12, 0.19]	0.13 [0.11, 0.18]	0.347[1]
Shaw Grouping			

[1]Wilcoxon [2]Chi-Square [3]Equal Variance T-Test [4]Unequal Variance T-Test
* Missing for 1

Table 2

CSF AD - related Biomarkers 24-hour change by treatment group

Grouping (N Iso/ N Prop)	Isoflurane median [Q1, Q3]	Propofol median [Q1, Q3]	Wilcoxon p-value
Intention To Treat (44/43)			
AB	-6 [-22, 18]	-1 [-25, 19]	0.879
P-TAU 181P	0 [-4, 6]	2 [-2, 6]	0.269
P-TAU/AB	0.00 [-0.01, 0.02]	0.01 [-0.01, 0.02]	0.339
Tau	-1 [-5, 2.5]	1 [-4, 4]	0.324
TAU/AB	-0.01 [-0.02, 0.02]	0.00 [-0.01, 0.02]	0.186

Table 3

CSF AD - related Biomarkers 6-Week change by treatment group

Grouping (N Iso/ N Prop)	Isoflurane median [Q1, Q3]	Propofol median [Q1, Q3]	Wilcoxon p-value
ITT (44/45)			
AB	-11 [-37, 18]	-3 [-13, 14]	0.512
P-TAU 181P	1 [-5, 6]	-2 [-7, 4]	0.248
P-TAU/AB	0.01 [-0.01, 0.02]	0.00 [-0.02, 0.02]	0.361
Tau	-2 [-4.5, 3.5]	-2 [-4, 3]	0.660
TAU/AB	0.00 [-0.02, 0.01]	0.00 [-0.01, 0.01]	0.575

Table 4

6-week Overall Cognitive Change

Domains	Isoflurane mean (SD)	Propofol mean (SD)	Univariable		Multivariable*	
			Mean Difference (95% CI)	p-value	Mean Difference (95% CI)	P-value
Overall	0.06 (0.27)	0.02 (0.34)	0.04 (-0.08, 0.16)	0.543	0.01 (-0.12, 0.13)	0.881

*Multivariable model adjusted for age, years education, APOE4 carrier, surgical service, surgery duration, baseline cognition

Table 5

6-week Cognitive Domain Change

Cognitive Domain	Univariable		Multivariable*	
	Mean Difference (95% CI)	p-value	Mean Difference (95% CI)	P-value
Verbal Memory	0.15 (-0.21, 0.51)	0.410	0.12 (-0.28, 0.52)	0.552
Visual Memory	-0.17 (-0.42, 0.07)	0.170	-0.25 (-0.50, 0.00)	0.051
Executive Function	0.09 (-0.07, 0.25)	0.257	0.08 (-0.08, 0.24)	0.318
Attention/Concentration	0.08 (-0.13, 0.28)	0.464	0.09 (-0.14, 0.31)	0.442

*Multivariable model adjusted for age, years education, APOE4 carrier, surgical service, surgery duration, baseline cognition

GERIATRIC ANESTHESIA 14

Rapid cognitive assessment tools for screening of mild cognitive impairment: A systematic review and meta-analysis

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INTRODUCTION: Mild cognitive impairment (MCI) can progress to depressive syndromes, delirium and dementia, with longer hospital stays, and higher risks of mortality[1,2]. Currently, there is an unmet need of a gold-standard, rapid MCI cognitive assessment tool that is suitable for busy, high-paced clinical environments including perioperative and emergency settings. We aimed to evaluate the predictive parameters of rapid MCI cognitive assessment tools in different clinical settings.

METHODS: Comprehensive literature search was conducted in the following databases: Medline (Ovid), Medline In-Process/ePubs, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and APA PsychINFO from 1946 to May 26, 2021. Our inclusion criteria were: (1) Older patients ≥ 60 years of age; (2) Patients from community, memory clinic, emergency, in-patient, preoperative, or long-term care clinical settings; (3) MCI screening tests with an average administration time ≤5 minutes; (4) Reference test as the Diagnostic and Statistical Manual of Mental Disorders (version III-V), the Mini-Mental State Examination, Petersen Criteria, and/or Montreal Cognitive Assessment; and (5) Predictive parameters were reported. Data was curated through a random-effects model and statistical analysis used R-software. The outcome variables were pooled predictive parameters (sensitivity, specificity, positive predictive value, and negative predictive value) of screening tests in older patients.

RESULTS: Twenty-three studies with 9,973 participants with eighteen screening tools were identified. In the community setting, the prevalence of MCI was 38.1%, the mean age for MCI was 73.3 ± 3.5 years with a 46.3% female population. In the memory clinic cohort, the prevalence was 40.2%, the mean age was 74.9 ± 1.85 years with a 47.4% female population. The emergency department had a prevalence of 25.5%, the mean age was 76.5 ± 7.7 with a 60% female population. The long-term care setting had a prevalence of 69.0% with unknown age and sex distribution. The prevalence of MCI among the Rapid Cognitive Screen (RCS), The Six-item Screener (SIS), Mini-Cog, and the Clock Drawing Test (CDT) studies were 24.6%, 28.3%, 40.9%, and 20.7% respectively. The RCS has 82% sensitivity and 79% specificity in detecting MCI. The SIS has 61% sensitivity and 89% specificity. Mini-Cog has 52% sensitivity and 80% specificity. CDT has 56% sensitivity and 59% specificity. Eight other index tools had high sensitivities of 97% – 82% and specificities of 90% – 73% but were studied only once.

CONCLUSION: Currently, there exists no universal recommendation for rapid cognitive assessment tools for MCI in community, memory clinic, emergency, in-patient, preoperative, or long-term care clinical settings. Despite growing credibility of certain tools, further work is needed to determine the generalizability and applicability of rapid MCI screening tools.

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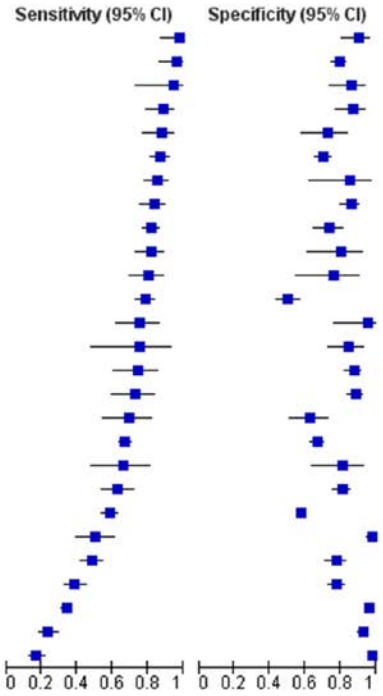
Figure 1: Coupled Forest Plots of screening test accuracy of all short screening tools

Study	TP	FP	FN	TN	Index test	Sensitivity (95% CI)	Specificity (95% CI)
Ghose, 2019	39	6	1	56	STMS	0.97 [0.87, 1.00]	0.90 [0.80, 0.96]
Rami, 2007	48	84	2	316	M@T	0.96 [0.86, 1.00]	0.79 [0.75, 0.83]
Wilber, 2005 a	17	8	1	48	SIS	0.94 [0.73, 1.00]	0.86 [0.74, 0.94]
Li, 2018	68	9	9	61	MINICOG	0.88 [0.79, 0.95]	0.87 [0.77, 0.94]
Yang, 2019	56	14	8	37	M- ACE	0.88 [0.77, 0.94]	0.73 [0.58, 0.84]
Malmstrom, 2015	157	132	23	308	RCS	0.87 [0.81, 0.92]	0.70 [0.65, 0.74]
Goring, 2004	99	3	17	17	OMC	0.85 [0.78, 0.91]	0.85 [0.62, 0.97]
Roalf, 2016	98	25	19	151	s-MoCA	0.84 [0.76, 0.90]	0.86 [0.80, 0.91]
Foran, 2021 community+Inpatients *	212	30	46	85	QUICKSORT	0.82 [0.77, 0.87]	0.74 [0.65, 0.82]
Mansbach, 2016	80	6	18	24	BCAT- SF	0.82 [0.73, 0.89]	0.80 [0.61, 0.92]
Takahashi, 2012	60	6	15	19	AQT	0.80 [0.69, 0.88]	0.76 [0.55, 0.91]
Petrazzuoli, 2020 b	203	103	55	105	AQT	0.79 [0.73, 0.84]	0.50 [0.43, 0.57]
Adachi, 2021	43	1	14	20	RDST-J	0.75 [0.62, 0.86]	0.95 [0.76, 1.00]
Wilber, 2005 b	12	9	4	50	MINICOG	0.75 [0.48, 0.93]	0.85 [0.73, 0.93]
Koc Okudur, 2019 B	40	27	14	190	RCS	0.74 [0.60, 0.85]	0.88 [0.82, 0.92]
Koc Okudur, 2019 A	43	28	16	209	RCS	0.73 [0.60, 0.84]	0.88 [0.83, 0.92]
Vyhnalek, 2017	34	33	15	55	CDT	0.69 [0.55, 0.82]	0.63 [0.52, 0.73]
Sebaldt 2009	565	219	278	445	AFT	0.67 [0.64, 0.70]	0.67 [0.63, 0.71]
Yavuz, 2017	23	6	12	26	qMCI-TR	0.66 [0.48, 0.81]	0.81 [0.64, 0.93]
Wilber, 2008	70	46	41	195	SIS	0.63 [0.53, 0.72]	0.81 [0.75, 0.86]
Ehreke, 2009	279	1161	200	1558	CDT	0.58 [0.54, 0.63]	0.57 [0.55, 0.59]
Callahan, 2002	43	6	42	238	SIS	0.51 [0.40, 0.62]	0.98 [0.95, 0.99]
Petrazzuoli, 2020 a	125	46	133	162	CDT	0.48 [0.42, 0.55]	0.78 [0.72, 0.83]
Holsinger, 2012 a	96	80	151	282	MINICOG	0.39 [0.33, 0.45]	0.78 [0.73, 0.82]
Liew, 2019	309	105	594	2342	Brief-Moca	0.34 [0.31, 0.37]	0.96 [0.95, 0.96]
Holsinger, 2012 c	59	25	188	337	MF2	0.24 [0.19, 0.30]	0.93 [0.90, 0.95]
Holsinger, 2012 b	42	7	205	355	MIS	0.17 [0.13, 0.22]	0.98 [0.96, 0.99]



Abbreviations: AFT, Animal Fluency Test; AQT, A Quick Test of Cognitive Speed; BCAT-SF, Brief Cognitive Assessment Tool- Short Form; CDT, Clock drawing test; FN, False negative; FP, False positive; M-ACE, Mini-Addenbrooke's Cognitive Exam; M@T, Memory Alteration test; MF2, Two-item functional memory screen; MIS, Memory Impairment Screen; MoCA, Montreal Cognitive Assessment; OMC, Orientation-Memory-Concentration; qMCI-TR, quick MCI test - Turkish; RCS, Rapid Cognition Screen; RDST-J, Rapid Dementia Screening Test- Japanese Version; s-MoCA, Short-MoCA; SIS, Six Item Screener; STMS, Short Test of Mental Status; TN, True negative; TP, True positive.

* Foran, 2021 study had combined sensitivity and specificity for the community and inpatient population.

GERIATRIC ANESTHESIA 15

Accelerated age-related cognitive decline after surgery in the Framingham Heart Study Cohort

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INTRODUCTION: The effects of surgery on cognitive trajectory remains controversial, with some studies suggesting no major long-term sequelae[1]. The sensitivity of the cognitive test batteries used in these studies, along with other variables such as the population's age and duration of the study could contribute to the observed discrepancies. In this pilot study, we examined the long-term effects of surgery through systematic assessment iof the cognitive trajectory in a large community-based cohort of elderly participants recruited into the Generation 1 of the Framingham Heart Study.

METHODS: This pilot study was approved by the Institutional Review Board at our institution.The incidence of cognitive decline and dementia as well as the longitudinal trajectory of the performance on a neuropsychological (NP) battery was examined in the original cohort of the Framingham Heart Study (FHS) participants with or without surgery (S and N groups, respectively). Repeated measures ANOVA was used to compare the NP trajectory between two groups over time, and linear mixed-effect model analyses were applied to control for differences in age, sex and education

RESULTS: Of the 5209 participants, 2508 underwent dementia evaluation and 1407 NP assessment, 839 with longitudinal scorings. Baseline characteristics were obtained from the NP cohort of participants (N= 839, Table 1). The mean age of participants in the S cohort at baseline was 80.7 ± 0.7 years and for the N cohort was 79.4 ± 0.7 years (p=0.006). The surgery cohort consisted of 31.5% participants who were identified as males (128/407) and the non-surgery cohort consisted of 38% (164/432) male identifying participants (p=0.048). While 48.2% of participants in the surgery group were widowed at the time of baseline tests, the non-surgery group consisted of 46.3% married individuals (p=0.044) (Table 1). The incidence of cognitive impairment as well as mild, moderate and severe dementia were significantly higher in the S group (p<0.001) (Figure 1). Participants who underwent surgery performed equal to their N counterparts on their initial NP battery. However, the S participants had a more significant decline in their performance after 8 years, performing at lower levels than their N counterparts on all NP tests except for the Digit Span tests (primary memory, p=0.86 and 0.19), Trail making test B (executive function, p=0.14) and Wechsler Similarities test (abstract reasoning, p=0.11)) (Table 2).

CONCLUSION: Cognitive deficits and dementia were more prevalent among the original cohort of the FHS participants who underwent surgery. Longitudinal follow-up of the NP testing revealed an escalated 8-year decline after surgery in most cognitive domains, suggesting a long-lasting effect on the cognitive trajectory of the elderly. Further analysis and studies are needed to examine the contributions of anesthesia, type and duration of surgery, the pathology of underlying diseases and other perioperative adverse events.

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Variables	Surgery (N= 407)	Non Surgery (N = 432)	P-value
Age	80.67 (6.78)	79.37 (6.97)	0.006
Biological Sex			0.048
Male	128 (31.5%)	164 (38%)	
Female	279 (68.5%)	268 (62%)	
Marital Status			0.044
Single	32 (7.8)	36 (8.3)	
Married	167 (41)	200 (46.3)	
Widowed	196 (48.2)	169 (39.1)	
Divorced	7 (1.7)	18 (4.2)	
Separated	1 (0.3)	2 (0.5)	
Unknown	4 (1)	7 (1.6)	
Type of NP test administered			0.66
Short form	67 (16.5)	76 (17.6)	
Long form	340 (83.5)	356 (82.4)	
Education			0.49
High school did not graduate	17(4.2)	23 (5.3)	
High school graduate	45 (11.1)	55 (12.7)	
Some college	29 (7.1)	23 (5.3)	
College graduate	17 (4.2)	23 (5.3)	
Employment Status			0.67
Works full time (≥ 30 hours)	3 (0.7)	1 (0.2)	
Works part time (< 29 hours)	5 (1.2)	6 (1.4)	
Retired	3 (0.8)	5 (1.2)	
Unemployed (expects to return to work)	98 (24.1)	112 (25.9)	
Missing	298 (73.2)	308 (71.3)	

Table 1: Baseline demographic details of participants with neuropsychological testing divided into surgery and non-surgery cohorts. All data are represented as either mean (SD) or count (%).

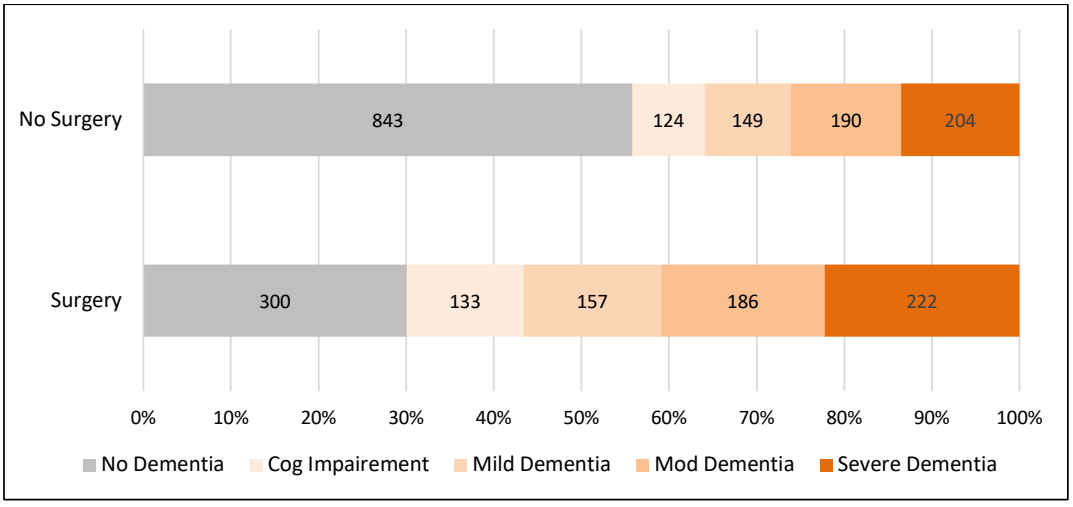

Fig 2: Reviewer assigned dementia diagnosis of dementia database patients for Surgery (N= 998) vs No-surgery (N=1510) participants.

		Surgery (S)		Non-Surgery (N)			
Testing for	Variable	NP at 81	NP at 89	NP at 79	NP at 87	Group P-value	Time P-value
Verbal Memory	Logical Memory Immediate Recall	7.64 (0.40)	5.17 (0.47)	7.97 (0.40)	6.34 (0.48)	0.0067	<0.0001
	Logical Memory Delayed Recall	6.07 (0.43)	3.83 (0.47)	6.72 (0.41)	5.38 (0.50)	0.0001	<0.0001
Learning	Paired Associate Immediate Recall	11.06 (0.35)	8.25 (0.45)	11.47 (0.36)	9.48 (0.43)	0.0007	<0.0001
	Paired Associate Delayed Recall	7.16 (0.32)	5.65 (0.34)	7.28 (0.28)	6.22 (0.32)	0.027	<0.0001
Visual Memory	Visual Reproduction Immediate Recall	4.66 (0.32)	2.72 (0.32)	4.76 (0.33)	3.60 (0.32)	0.033	<0.0001
	Visual Reproduction Delayed Recall	3.39 (0.31)	1.80 (0.28)	3.64 (0.31)	2.63 (0.30)	0.008	<0.0001
Working Memory	Digit Span Forward	5.99 (0.13)	5.48 (0.14)	5.99 (0.13)	5.51 (0.14)	0.87	<0.0001
	Digit Span Backward	4.13 (0.12)	3.47 (0.50)	4.20 (0.12)	3.62 (0.13)	0.19	<0.0001
Motor Speed	Weschler Similarities Test	11.61 (0.56)	8.55 (0.65)	11.80 (0.56)	9.63 (0.63)	0.11	<0.0001
Language/Naming	Boston Naming Test	8.72 (0.15)	7.00 (0.31)	8.73 (0.15)	7.76 (0.27)	0.004	<0.0001
Visuo-perception	Hooper Visual Test	18.57 (0.56)	15.47 (1.01)	19.21 (1.00)	16.78 (0.90)	0.081	<0.0001
Attention, Visual Processing and Processing Speed	Trail Making Test A	1.07 (0.20)	2.12 (0.32)	0.98 (0.11)	1.56 (0.21)	0.011	<0.0001
	Trail Making Test B	3.60 (0.56)	6.29 (0.60)	3.36 (0.48)	5.52 (0.51)	0.14	<0.0001
Verbal Fluency	FAS Test	27.41 (1.33)	19.91 (1.51)	28.58 (1.40)	25.26 (1.54)	0.0008	<0.0001

Table 2 (a): Results of repeated measures ANOVA for independent variable on all Neuropsychological Test receiving participants (N= 839). Values are represented as Mean (SD).

GERIATRIC ANESTHESIA 16

Preoperative EEG Inattention Signatures and Postoperative Delirium

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INTRODUCTION: Delirium is a syndrome of acute, fluctuating changes in attention and consciousness that increases mortality and that afflicts up to half of older adults after undergoing major surgery and anesthesia. Preoperative predictors of postoperative delirium are critically needed to target limited delirium-reduction resources. Delirium's cardinal feature-inattention-is reflected by lower power in the beta (14-20 Hz) and theta (4.5-7 Hz) bands of the awake, eyes closed electroencephalogram (EEG) of patients with attention deficit hyperactivity disorder (ADHD) compared with healthy control subjects. (Bresnahan and Barry 2002, Snyder and Hall 2006) Here, we sought to determine whether ADHD-associated EEG patterns of inattention were present preoperatively in older adults who went on to develop postoperative delirium.

METHODS: Fifty patients 60 and older underwent 32-channel whole head EEG collection for 3 minutes with eyes closed prior to elective non-neurological, non-cardiac surgery. Before surgery and twice daily during postoperative hospitalization, delirium presence and severity were measured using the 3-minute confusion assessment method (3D-CAM). Investigators blinded to 3D-CAM and demographic data performed the EEG processing. EEG spectral power in the beta and theta bands were calculated for the entire head.

RESULTS: Seven subjects (14%) developed postoperative delirium. Preoperative whole-head EEG beta (14-20 Hz) power comprised a significantly lower fraction of total EEG power in subjects who developed delirium compared with those who did not ($p < 0.05$, student's t-test). Neither preoperative EEG theta (4.7-7 Hz) power nor the ratio of theta to beta power differed significantly between the delirious and non-delirious groups. However, a greater fraction of preoperative whole-head EEG power in the theta band significantly correlated with baseline greater delirium severity ($p = 0.015$, Spearman's $\rho = 0.34$).

CONCLUSION: These results suggest that EEG features associated with inattention in ADHD-namely higher theta power and lower beta power-may be present in the preoperative EEG of older surgical patients having reduced baseline cognitive function and/or elevated risk of postoperative delirium.

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GERIATRIC ANESTHESIA 17

Implication Of Pre Operative Frailty On Post Operative Delirium And Cognitive Dysfunction In Elderly Patients Undergoing Non-Cardiac Surgery

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INTRODUCTION: Frailty is a geriatric syndrome thought to identify the most vulnerable older adults, who have reduced reserve when faced with stress[1]. It is defined as a state of decreased physiologic reserve due to multisystem decline[2]. Delirium is one of the most common postoperative complications among elderly patients with prevalence of 30-62%[3]. It is characterized by an acute fluctuating course of cognition and consciousness, inattention, and perceptual disturbance[3]. Post-operative cognitive dysfunction (POCD) is a syndrome defined by a drop in cognitive performance on a set of neuropsychological tests from before to after surgery[4]. In a recent study frail elderlies had 2.7 times odds of postoperative delirium after non cardiac major surgery. The post-operative cognitive dysfunction however was similar in both frail and non-frail groups[5]. The interaction between frailty and post-operative cognitive decline still needs to be explored further. We hypothesized that presence of preoperative frailty is associated with increased occurrence of post-operative delirium and cognitive dysfunctions in elderly after non cardiac.

METHODS: This prospective observational study was conducted after approval from Institute Ethics board and registering the trial in national registry. Consecutive consenting patients >65years of age, of either sex, with education up to middle school, undergoing noncardiac, non-neurological surgeries were enrolled. Patients with preexisting delirium, hearing impairment, neurological illness and undergoing emergency surgeries were excluded. Preoperatively, patients were assessed for frailty with Modified Fried Criteria (MFC) and were divided into Frail (MFC<3/7) and Nonfrail category (MFC>3/7)[2]. Postoperatively patients were assessed for delirium by Confusion assessment method(CAM) on days 1 and 3[5]. POCD was assessed by Montreal Cognitive Assessment (MoCA)[6] and Mini-Mental State Examination (MMSE)[7] on Days 1&3. A printed questionnaire of MoCA in native language was given to the patients to be completed in 10 minutes. A score ±26/30 was considered abnormal. MMSE had a maximum score of 30. For a patient with education status of middle school, score less than 24, with education till high school, score below 25 and for education till college a score below 26 was considered as POCD[7]. Cognitive dysfunction 1 and 3months after was assessed by T-MOCA. Four items were asked over the telephone in 5 mins.[8] The total score was 30 and patients having score less than 26 were said to have cognitive impairment. Continuous variables were presented in mean ± SD whereas categorical variables in frequency (%). Student-t test was used to compare the means and Fischer exact to compare categorical values. P-value <0.05 was considered significant. A regression analysis was performed to examine relationship of delirium and POCD to frailty adjusted for covariates. Statistical analysis was performed using software Statistical package for social sciences, version-26 (IBM, Chicago, USA).

RESULTS: 111 patients were considered for inclusion. Two did not give consent so 109 were enrolled. Preoperatively 98 patients were deemed frail as per MFC while 11 were categorized non-frail. The mean age of subjects was 71.45 ±6.11 years. 82(75.3%) males and 27 (24.7%) females participated. Post-operative delirium on Days 1&3 was seen in 9 (8.25%) and 1 patients. All belonged to frail category. Cognitive dysfunction as assessed by MOCA and MMSE on Day1 was seen in 85.7%(81/98) and 63.3%(62/98) in frail elderly which was significantly higher than 45.5%(5/11), and 27.3%(3/11) in non-frail elderlies. Similarly significantly greater cognitive dysfunction was seen in frail patients at Day 3 (MOCA <26: 77.6% in frail and 45.5% in non-frail and abnormal MMSE:59.18% in frail and 9.09% in non-frail). At one month 87.6%(86/98) in frail and 54.5% (6/11) in non-frail and at three months 77.6% (76/98) in frail versus 36.4% (4/11) in non-frail) had T MOCA <26, significantly less in frail patients. Binary logistic regression showed no significant association between frailty and delirium. Linear regression analysis showed association of frailty with MMSE and T MoCA (p<0.05)

CONCLUSION: Elderly with preoperative frailty had significantly increased post-operative cognitive dysfunction at days 1, 3 and one month and three months after non cardiac surgery. The incidence of postoperative delirium however was similar.

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Table1 : Preoperative characteristics of patients in Frail and Non Frail group

		Frail (n=98)	**Non frail** (n=11)	**pvalue**
	Age (Mean±S.D)	69±6.29	71±3.27	0.302*
	Gender (Male/Female)	74/24 (75.5%/24.4%)	6/3 (66.6%/33.3%)	0.689
Educational Status	**Graduation**	68 (69.40%)	10 (90.90%)	0.450
	High school	23 (23.46)	1 (9.10%)	
	Middle school	7 (7.14%)	0	
Type of Surgery	**Gastrointestinal** Oncological surgery Non oncological	30 (30.63%) 16 14	1(9.09%) 1 0	0.337
	Urology Oncological Non Oncological	48(48.97%) 24 24	6(54.54%) 3 3	
	ENDOCRINE (All cancerous)	14(14.28%)	3(27.27%)	
	Orthopedic surgery	1(1.02%)	0	
	Plastic surgery	5(5.1%)	1(9.09%)	
Type of Anesthesia	**General anaesthesia**	82 (83.67%)	7 (63.63%)	0.115
	Regional Anesthesia	16 (16.33%)	4 (36.36%)	
Duration of surgery in minutes	(Mean±S.D)	219.10±121.25	175.45±45.74	0.241*

*Independent student t test, Fisher exact test.

Table 2: Post-operative delirium and cognitive dysfunction in 'Frail' versus 'Non-frail' patients, as per various Criteria's.

NAME OF SCALE	Frail (n=98)	Non-Frail (n=11)	P value
CAM DAY 1 delirium present	9 (9.2%)	NONE	0.594
CAM DAY3 delirium present	1 (1.02%)	NONE	-
MOCA DAY1 <26	81 (82.65%)	5 (45.45%)	0.011*
MOCA DAY 3< 26	76 (77.55%)	5 (45.45%)	0.031*
Abnormal MMSE DAY 1	62 (63.26%)	3 (27.27%)	0.027*
Abnormal MMSE DAY 3	58 (59.18%)	1 (9.09%)	0.002*
T MOCA MONTH 1<26	86 (87.75%)	6 (54.54%)	0.013*
T MOCA MONTH 3<26	76 (77.55%)	4 (36.36%)	0.007*

Data presented in frequency. Fischer Exact test used**. ***p significant <0.05

SUBSPECIALTY ABSTRACTS

GLOBAL HEALTH

GLOBAL HEALTH 1

GPR68 inhibition enhances endothelial barrier function and protects against bacterial pathogens or acidosis-induced inflammation in lung endothelium

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INTRODUCTION: Endothelial dysfunction characterized by an increase in endothelial permeability and hyper-inflammatory responses is a pathological hallmark of a number of lung disorders including acute lung injury, acute respiratory distress syndrome, sepsis, and more importantly the current global pandemic COVID-19[1, 2]. Thus, drugs targeting the prevention and restoration of endothelial function is of great clinical interest to treat endothelial dysfunction-derived cardiopulmonary diseases. Recent findings have suggested a role of G protein-coupled receptors (GPCRs), especially a sub-family of proton-sensing GPCRs including GPR4 and GPR68, in modulation of endothelial function[3, 4]. In this study, we examined barrier protective and anti-inflammatory effects of two recently developed novel class of GPR68 inhibitors: ogremorphins OGM8345 and OGM-1[5] using cultured human pulmonary arterial endothelial cells (HPAECs) and mouse models of bacterial pathogen-induced acute lung injury.

METHODS: Endothelial barrier function was measured in HPAECs by monitoring transendothelial electrical resistance (TER) using an electric cell-substrate impedance sensing system, ECIS Z (Applied Biophysics, USA). The mRNA and protein expression analysis of inflammation markers was carried out by quantitative real time PCR and western blot, respectively. Cells were switched to low pH (6.5) media to examine the role of GPR68 in acidosis-induced inflammation. GPR68 activation was analyzed by luciferase-based tango assay described earlier[6]. Vascular leak and inflammation induced by lipopolysaccharide (LPS from Escherichia coli) or heat-killed Staphylococcus aureus (HKSA) in C57BL/6 mice was evaluated by extravasation of intravenously injected Evans blue tracer into lungs and total cells/protein count in bronchoalveolar lavage samples.

RESULTS: Both OGM8345 (1-5 μM) and OGM-1 (0.3-1.5 μM) robustly enhanced basal EC barrier function in a dose-dependent fashion by reaching an 150-200% increase in TER values. These inhibitors also effectively rescued LPS- and HKSA-induced EC hyperpermeability. RT-PCR analysis demonstrated that LPS or HKSA-induced expression of inflammatory cytokines/chemokines genes TNF-α, ICAM-1, VCAM-1, IL-6, IL-8, IL-1β, and CXCL5 in HPAECs was significantly attenuated by pre-treatment of cells with OGM8345 and OGM-1. Both OGMs suppressed LPS- and HKSA-induced protein expression of endothelial cell adhesion molecules VCAM-1 and ICAM-1. Although both OGMs were equally effective in enhancing/protecting EC barrier function, OGM8345 showed more potent anti-inflammatory effects. OGM8345 was also effective in suppressing acidic pH-mediated increased expression of inflammatory marker genes. In contrast, pharmacologic inhibition of GPR4 by NE 52-QQ57 failed to alleviate EC barrier dysfunction and inflammation caused by LPS and HKSA, thus ruling out GPR4 involvement in EC dysfunction in these settings. Importantly, LPS, HKSA or acidosis stimulation of HPAECs increased the mRNA expression of GPR68 that was inhibited by OGMs pre-treatment. OGMs inhibition of LPS- and HKSA-induced activation of GPR68 was further confirmed by luciferase assay. The beneficial effects of OGMs were recapitulated in vivo. Vascular leak and lung inflammation in C57BL/6 mice caused by intratracheal injection of LPS or HKSA was attenuated by both OGMs as illustrated by reduced Evans blue accumulation in the lungs. Furthermore, OGM8345 and OGM-1 significantly inhibited accumulation of inflammatory cells and increase in protein content in bronchoalveolar lavage samples collected from LPS- or HKSA-exposed mice. RT-PCR analysis of lung tissues showed that OGMs suppressed LPS-induced upregulation of TNF-α, IL-6, KC, and IL-1β mRNA transcripts.

CONCLUSION: This study shows a critical role of GPR68 in endothelial dysfunction and lung injury caused by bacterial pathogens. It provides a comprehensive analysis of novel GPR68 inhibitors in suppressing ongoing lung inflammation and barrier compromise. Overall, these results strongly suggest a therapeutic potential of GPR68-selective inhibitors in improving endothelial dysfunction caused by bacterial infections and acidosis associated with acute and chronic lung injury.

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GLOBAL HEALTH 2

A checklist instrument for hospitals in resource-limited settings to identify barriers to implementation of the Enhanced Recovery After Cesarean pathway in Mexico

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INTRODUCTION: Enhanced Recovery After Surgery (ERAS) pathways with standard evidence-based protocols have been developed for interdisciplinary teams responsible for the perioperative care of patients. The implementation of the ERAS pathways in more than 20 countries have resulted in better clinical outcomes at reduced costs.[1] ERAS guidelines for Cesarean deliveries were introduced in 2018,[2] and since then, the Enhanced Recovery After Cesarean (ERAC) protocols have been found to reduce the post-operative length of stay[3,4] and costs[4], and have been associated with improved analgesic and recovery outcomes[5] in the United States. While the ERAS guidelines have been made for all countries, the need for surgical and anesthesia care in low- and middle-income countries (LMICs) has been largely unrecognized, and the global burden of surgical disease continues to cost LMICs significant GDP.[6] The availability of the ERAS pathways creates an opportunity to proactively address surgical and anesthesia care in LMICs that can help improve clinical outcomes, reduce complications and costs, and scale up progress. In Mexico, the cesarean delivery rates are among the highest in the world[7] and women undergoing cesarean delivery face challenges of being postoperative as well as postpartum. Implementation of the ERAC protocol has the potential to improve overall clinical outcomes and reduce costs. However, the resources available in Mexico must first be considered to adapt the ERAC protocol accordingly. This project aims to develop a checklist instrument that could be used in LMICs to determine the available resources and identify any barriers that limit implementation of the ERAC pathway.

METHODS: A checklist instrument was developed using the core elements outlined by the Society for Obstetric Anesthesia and Perinatology in the ERAC Consensus Statement in 2019. After translation to Spanish, the checklist was sent to obstetrics and gynecology hospitals in resource-limited settings in Mexico to elucidate understanding of the barriers that currently exist to implementing the ERAC pathway.

RESULTS: Two hospitals (one public, one private) providing specialized obstetric and gynecologic care in urban Mexico, and serving an average of 133,631 women per year, completed the checklist instrument. We examined 19 preoperative, 17 intraoperative and 27 postoperative elements of the ERAC pathway in public (vs. private) hospitals and found that 47% (vs. 5.26%) of preoperative, 76% (vs. 0%) of intraoperative, and 67% (vs. 37%) of postoperative elements were not available or sometimes available.

CONCLUSION: This suggests that barriers exist in implementing the ERAC pathway in resource limited settings, with a greater impact on public (vs. private) hospitals, regardless of hospital size.

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GLOBAL HEALTH 3

Carbon pricing is an effective method to reduce environmental impact of the operating room

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INTRODUCTION: The World Health Organization has declared climate change as the greatest threat to global health in the 21st century.[1] All physicians should consider reducing their carbon footprint in their clinical settings. It is well established that volatile anesthetics are potent greenhouse gases (GHG) and that desflurane is responsible for a significant portion of the carbon footprint of the operating theatre.[2] We proposed to implement a strategy to make a tertiary care centre in Ontario (Health Sciences North [HSN], Sudbury, ON, Canada) desflurane-free to reduce the carbon footprint of the facility. We implemented an approach supporting the use of forcing functions according to a ''hierarchy of effectiveness'' as various studies have shown that relying on educational interventions to change clinicians' behaviours is predictably disappointing.[3] We also calculated the effect of the Canadian Carbon pricing mechanism on the costs of sevoflurane and desflurane based on current pricing and future pricing declared at COP26.

METHODS: The carbon footprint in CDE (carbon dioxide equivalents) was calculated using the Yale Gassing Greener program created by Yale Anesthesiology Media Lab.

RESULTS: The implementation of these measures was associated with a significant drop in carbon dioxide equivalents (CDE) from the HSN volatile gases use. The 2016 CDE were: sevoflurane, 31 tonnes vs desflurane, 744 tonnes; the 2019 CDE were: sevoflurane, 66 tonnes vs desflurane, 140 tonnes; and the 2020 CDE were: sevoflurane, 52 tonnes vs desflurane, 0 tonnes. It should be noted that the number of anesthesia cases dropped in 2020 because of the COVID-19 pandemic. Using the existing Canadian carbon price of 30 CAD/tonne CDE (price in 2020 at the time of study completion)5 if applied to volatile anesthetic gases would increase prices by 1.48 CAD per bottle of sevoflurane and by 26.82 CAD per bottle of desflurane. In 2030, the projected carbon price of 170 CAD/tonne CDE would increase the price of sevoflurane by 8.39 CAD and the price of desflurane by 151.98 CAD in our Canadian institution.

CONCLUSION: We proposed to implement a strategy to make a tertiary care centre in Ontario (Health Sciences North [HSN], Sudbury, ON, Canada) desflurane-free to reduce the carbon footprint of the facility. We implemented an approach supporting the use of forcing functions according to a ''hierarchy of effectiveness'' as various studies have shown that relying on educational interventions to change clinicians' behaviours is predictably disappointing.[3] This approach took years and significant effort from a few dedicated individuals. Interestingly, implementing carbon pricing is a well recognized effective strategy to reduce carbon pollution. We have calculated that applying the current Canadian pricing mechanism to the GHG emissions from volatile anesthetics would immediately make the purchase of desflurane difficult to justify and thus reduce the carbon footprint of the operating room as presented. Unfortunately, volatile anesthetics are currently not included in the GHG Canadian inventory and are not yet included in the carbon pricing. We have lobbied Canadian politicians to include volatile anesthetics in the inventory and pricing mechanism. Implementing a carbon price on anesthetic gases could be an immediate and effective strategy to further reduce the carbon footprint of operating rooms. An overwhelming message from the COP26 meetings was the need for urgency. A carbon price would be far more efficient in discouraging desflurane use than education and in-hospital advocacy.

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GLOBAL HEALTH 4

Spin and Distortion in Surgical Trials

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INTRODUCTION: Randomized trials are essential for generating evidence to inform safety and efficacy of interventions. However, publication bias and selective reporting may distort the evidence base, and threatens decision making. The objective is to describe registered surgical RCTs between 1997-2017, and to quantify distortion in the surgical evidence base including failure to publish, spin, and distortion.

METHODS: Studies registered on ClinicalTrials.gov were screened for the following inclusion criteria: randomized design, involving patients undergoing surgery, registered between 1997 - 2017. From this set, a stratified iterative sampling method was used to select studies for data extraction until saturation was observed for the main outcome measures (failure to publish, spin). To quantify failure to publish, a systematic search was performed for each registered RCT to identify whether it had been published as of July 2021. To quantify spin, the published conclusions were compared with supporting evidence within the study, and categorized using accepted definitions[1]: none (conclusion is consistent with the results and highlights adverse events), low (acknowledgement of statistically nonsignificant results for the primary outcome OR uncertainty and recommendations for further trials), medium (no acknowledgement of the statistically nonsignificant results for the primary outcome AND uncertainty or recommendations for further trials), or high (no acknowledgement of the statistically nonsignificant results for the primary outcomes AND no uncertainty AND no recommendations for further trials). Distortion was defined as declaring positive results when actual results were negative, mixed, or unavailable. Time to publication was defined as median (IQR) time from registration to publication date.

RESULTS: In total, 13,761 RCTs met the inclusion criteria. Data was extracted from 5,094 studies to reach saturation. Median sample size was 92 (IQR: 51-186). Most studies were from high income countries (96.4%). Most common surgical categories were orthopedic (20.5%), cardiac/vascular/thoracic (14.4%), and gastroenterology (14.2%). Only 33.7% of registered surgical RCTs were published (1,718/5,094). Positive conclusions were declared in 61.6% of studies. In total, 25.4% of conclusions were distorted (declared as positive, from results that were either negative, mixed, or unknown). Spin was found in 39.2% of studies, of which 7.2% had high spin, 11.2% had medium spin, and 20.7% had low spin. Studies with positive conclusions had shorter time to publication (46 (33-65) vs. 58 (40-86) months).

CONCLUSION: While a large volume of registered RCTs exists, most were small in size, conducted in high-income countries, and remain unpublished. The high proportion of spin and distorted conclusions raises issues of research integrity in the published evidence base. Further efforts are required to ensure all RCTs are published and that the outcomes are reported without bias.

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GLOBAL HEALTH 5

Chronic pain and associated factors in Monrovia, Liberia

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INTRODUCTION: Approximately one in three adults that live in low-and middle-income countries (LMICs) suffer from chronic pain (PMID: 27537761). Few studies characterized chronic pain in sub-Saharan Africa as a region, with the prevalence of chronic pain in Liberia being unknown.

METHODS: Utilizing a structured household survey known the Vanderbilt Global Pain Survey (VGPS), this was a community-based, cross-sectional study that included adults aged ≥18 years old who live in Monrovia, Liberia. This survey tool was previously administered in Mozambique, India, and Nepal. The VGPS includes multiple validated surveys on pain and disability, including the Brief Pain Inventory, World Health Organization Disability Schedule (WHODAS 2.0), Post-traumatic distress disorder Checklist-Civilian Version (PLC-C), Pain Catastrophizing Scale (PCS), and Widespread Pain Index (WPI) and Symptom Severity Scale (SSS) from the American College of Rheumatology 2010 Fibromyalgia diagnostic criteria.

RESULTS: Of the 325 persons approached, a total of 309 eligible surveys were collected in Caldwell (24.3%), New Kru Town (27.8%), Sinkor (25.6%), and West Point (22.3%). Each community was randomly chosen to represent the four neighborhood classifications per the Liberia Housing Profile. Chronic pain, defined as recurrent or persistent pain ≥3months, was found to be 81.9%, which is significantly higher than described in other LMICs ($P<0.05$). Of these, 37.2% of whom reporting pain persisting for ≥1year. Although participants reported having mild pain with minimum interference with their daily lives on the BPI, 35.9% scored ≥10 on the WHODAS2.0, suggesting clinically significant disability. Approximately one in five (22%) respondents screened positive for post-traumatic stress disorder. One in three (38.5%) reported catastrophic thinking about pain on the PCS. In addition to taking medication, almost all respondents would be willing to undergo a procedure or participate in group therapy for pain management.

CONCLUSION: The burden of chronic pain amongst Liberians is substantial. Having chronic pain was associated with disability and catastrophic thinking about pain ($P<.05$). To improve Liberia's capacity for pain treatment, a first step is to understand the impact of chronic pain in Liberia as a country by including questions on chronic pain on national health surveys.

GLOBAL HEALTH 6

Peri-operative Anesthesia Research Output from Low- and Middle-Income Countries: A Systematic Review

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INTRODUCTION: Research infrastructure and capacity for anesthesia in low- and middle-income countries (LMICs) remain scarce. Promoting academic scholarship through research will increase the practice of evidence-based medicine in low resource settings. This systematic review examines the peer-reviewed research output for adult peri-operative anesthesia conducted in LMICs.

METHODS: A systematic review of the medical literature was performed with search terms representing the following groups: 1) adult population aged ≥ 18 years, 2) peri-operative anesthesia (pre-, intra-, and post-operative anesthesia care), 3) LMICs as defined by the World Bank Atlas in 2020. The protocol included articles in all languages from journal inception to December 31, 2020 in the following databases: PubMed, CINAHL, Embase, Web of Science, PsycINFO, Cochrane and WHO Global Index Medicus. Non-human or basic science studies, studies of only pediatric subjects, dissertations and the grey literature were excluded. After export of citations and removal of duplicates via EndNote, articles titles and abstracts were screened using the Rayyan platform. Among the included studies, article title, year of publication, country of study, study design, journal of publication and impact factor were extracted. Temporal trend of publication counts globally and by WHO region, distribution of study designs, and impact factor of published journals were examined and analyzed in R. Geographical heat map for publication count based on study country was generated in Tableau Public.

RESULTS: The search yielded 10,121 articles across the databases. We included 3105 studies and excluded 7016. Among the 132 LMICs, 89 countries published at least one peri-operative anesthesia study (67%). The top five countries with the highest research output were China (744), India (349), Turkey (283), Iran (269), and Egypt (242). Moreover, 62 of 89 (70%) published countries had fewer than 10 studies conducted locally, and only one published peri-operative anesthesia study was observed in 19 countries.

CONCLUSION: This is the first comprehensive systematic review examining peri-operative anesthesia research conducted in LMICs. The findings of our systematic review demonstrate the dearth of anesthesia research and disparity in research output among LMICs. Forty-three countries have been neglected with no anesthesia studies – a focus on these is needed. The double-screening to follow and final analyses will provide an updated overview of the landscape of anesthesia research conducted in LMICs.

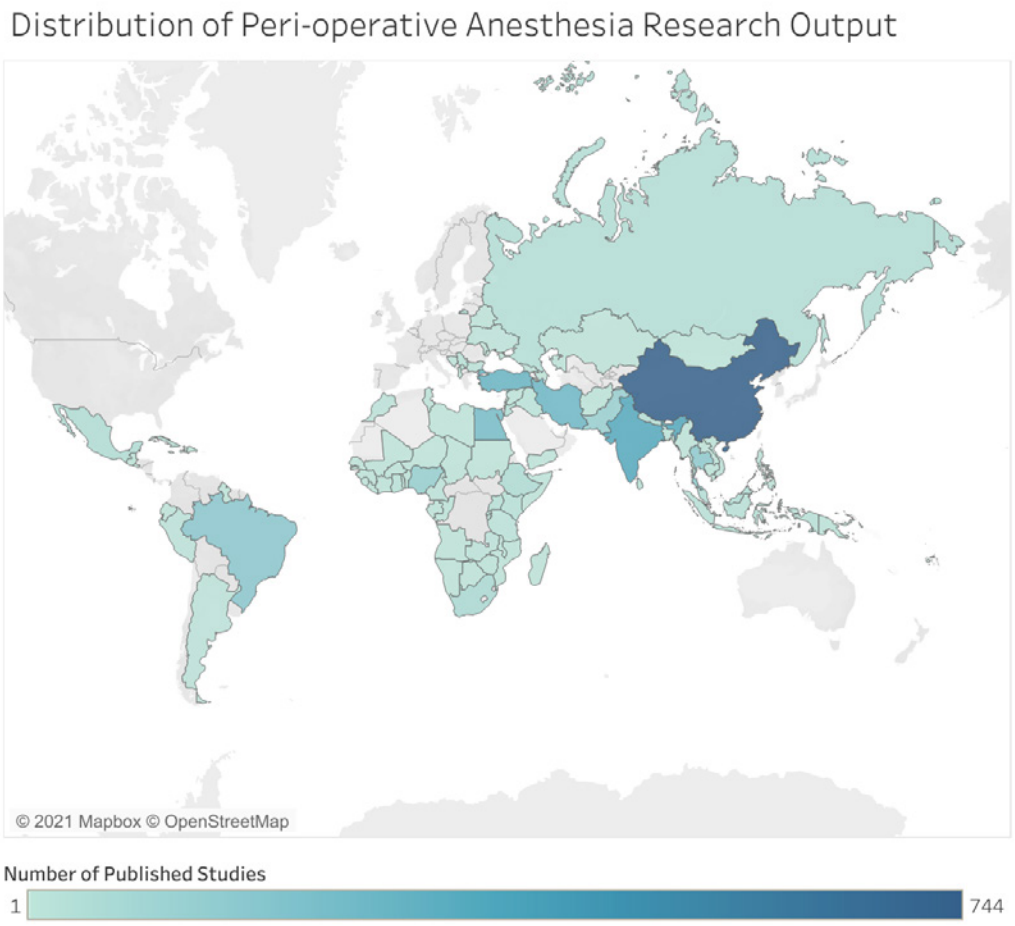

Fig. 1

SUBSPECIALTY ABSTRACTS

LIVER

LIVER 1

Association of Right Ventricular TAPSE with increased length of stay after liver transplant surgery

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INTRODUCTION: To evaluate the association between Right ventricular TAPSE (Tricuspid Annular Plane Systolic Excursion) and length of stay after liver transplant surgery.

METHODS: Retrospective cohort study accrued at the Johns Hopkins Hospital from July 1, 2016 through June 30, 2018. Patients who met the following criteria were eligible for inclusion: >18 yrs old, underwent liver transplant surgery with preoperative transthoracic echocardiography within 6 months of surgery.

RESULTS: The study sample consisted of 74 patients with mean age 45 year, 47% female. Mortality was 8% 6/74. After adjusting for MELD, baseline creatinine, and age, TAPSE was associated, in dose response fashion, with decreased hazard of prolonged hospital stay (HR 1.7, 1.07-2.3, $p < .023$).

CONCLUSION: Even though all transplant candidates must have normal left ventricular ejection fraction prior to transplant, heart failure and cirrhotic cardiomyopathy after transplant constitute significant amount of morbidity and mortality. Measures of right ventricular function may further elucidate this complex problem and provide further preoperative information for transplant candidacy. An increase in TAPSE may be a novel cardiovascular risk factor for bad outcome after liver transplant.

LIVER 2

Living Donor Liver Transplantation Anesthetic Management: Survey results from the United States and the Republic of Korea

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INTRODUCTION: Living donor liver transplantation (LDLT) is an emerging LT alternative for deceased donor liver transplantation (DDLT) to help alleviate the imbalance between the waitlist and the number of deceased donors. In the United States (US), 442 LDLTs were performed, which is growing but still a tiny fraction (5.3%) of the 8,345 adult patients (≥ 18 years) who received LT in 2019[1]. In the Republic of Korea, 1,118 LDLTs were performed, which represented a significant portion (74.8%) of the 1,579 adult LTs in 2019[2]. The authors conducted surveys of LDLT programs in these two countries to explore current anesthesiology practice patterns and patient management methods.

METHODS: Between May 2021 and October 2021, an electronic survey was distributed to the Directors of Liver Transplant Anesthesiology at LDLT programs in the US (n=37; identified via 2018 Scientific Registry of Transplant Recipients database) as well as in Korea (n=16). The survey looked for information on each institution's demographics and management practices for donors and recipients. The Quality & Standards Committee of the Society for the Advancement of Transplant Anesthesia (SATA) created the survey and performed the collection in the US, while the Korean Society of Transplantation Anesthesiologists (KSTA) surveyed in Korea. Bi-weekly reminders were sent to the directors until full participation was achieved.

RESULTS: The survey response rate was 100% (37/37 in the US and 16/16 in Korea). Recipient management: In both countries, there is no alteration from typical DDLT management. Most centers in the US selectively place a pulmonary artery catheter (PAC) while routinely using transesophageal echocardiography (TEE); in Korea, PAC and TEE are routinely used. In the US, LDLT recipients typically receive one arterial line and one central line, while centers in Korea frequently place two arterial lines and two central lines. Recipients in the US are routinely extubated in the operation room, while most recipients in Korea remain intubated at case end. Donor management: In the US, anesthesiologists participate in donor selection and pre-operative evaluation. They routinely utilize enhanced recovery after surgery (ERAS) protocols and regional anesthesia techniques. However, in Korea, anesthesiologists are not typically involved in donor selection, nor do they rely on ERAS protocols or regional anesthesia techniques. Most centers in each country will place invasive hemodynamic monitors (an arterial line and a central line) for donor hepatectomies and do not routinely utilize pre-operative autologous blood donation or intraoperative acute normovolemic hemodilution.

CONCLUSION: There are many similarities but also considerable differences in donor/recipient anesthetic management in LDLT between the US and Korea. These variations should be explored in more detail to assess their impact on patient outcomes.

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LIVER 3

Hyperoxemia During Organ Reperfusion is Associated with Worsened Graft Outcomes After Liver Transplantation

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INTRODUCTION: Ischemic reperfusion injury (IRI) is a paradoxical exacerbation of cellular dysfunction and death following restoration of blood flow to ischemic tissues. Reactive oxidative species (ROS) are one of the crucial players in the mechanism of IRI, producing oxidative stress that promotes endothelial dysfunction and eventually cellular death[1]. Hyperoxemia increases ROS production and may exacerbate tissue damage from IRI. Various studies have demonstrated that hyperoxemia (PaO2 > 300 mmHg) is associated with increased in-hospital mortality after a cardiac arrest, ischemic stroke or TBI - all events associated with significant IRI[2-7]. In liver transplantation, hepatic IRI following reperfusion is estimated to be responsible for approximately 10% of early graft failure. Efforts to mitigate hepatic IRI have primarily focused on medications that reduce oxidative stress, pre-ischemic conditioning or machine perfusion[8]. It is common practice among anesthesiologists to increase FiO2 prior to organ reperfusion in preparation for possible hemodynamic instability during this event. However, no literature investigating the effects of intraoperative hyperoxemia on graft function during liver transplantation exists. We investigated the relationship between PaO2 at organ reperfusion and graft function in patients undergoing deceased donor liver transplantation.

METHODS: We conducted a single-center retrospective cohort study of all adult and pediatric patients who underwent liver transplantation at our institution from 2012-2020. Institutional review board approval was obtained for the study. Patients who underwent combined liver-heart transplantation were excluded. For patients with multiple liver transplants during the study period, each transplant was included as its own independent event. Data was collected from UNOS and from the electronic medical record. PaO2 during reperfusion was estimated from FiO2 at time of reperfusion, assuming the same PaO2/FiO2 ratio as the first arterial blood gas measured after reperfusion. The primary outcome was post-operative graft function, represented by the L-GrAFT risk score at 7 and 10 days. L-GrAFT score is a validated model to predict three-month graft failure that has been shown to be superior to the MEAF and EAD scores[9]. The association between PaO2 at reperfusion and L-GrAFT score was evaluated using the Spearman's rank correlation coefficient.

RESULTS: Of the 1208 patients who underwent liver transplant, 929 were included in the analysis. A weak but statistically significant negative correlation was found between PaO2 at reperfusion and L-GrAFT score at both 7 and 10 days (R = -0.111 and -0.086, p = 0.001 and 0.008 respectively).

CONCLUSION: Among patients undergoing liver transplantation, the degree of hyperoxemia during reperfusion is associated with worsened graft function as represented by the L-GrAFT score. We theorize that hyperoxemia may play a role in exacerbating hepatic reperfusion injury, although further studies are needed to better demonstrate causal effect. While there are many other factors which contribute to postoperative graft dysfunction, reducing hyperoxemia at reperfusion is an easily modifiable adjustment within anesthetic practice which could have long term implications on graft function and survival.

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LIVER 4

An updated role of right heart echocardiography on early autograft dysfunction and other outcomes after orthotopic liver transplantation

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INTRODUCTION: Pre-operative testing is a vital component of patient risk evaluation prior to orthotopic liver transplantation. Since the incorporation of echocardiography, pre-operative assessments of the heart have focused on several key parameters, including ejection fracture, screening for pulmonary hypertension with pulmonary artery systolic pressure (PASP) estimation, valvular dysfunction, evidence of ischemia during dobutamine infusion, etc. Recently, researchers have looked at the role of the right heart in predicting outcomes after orthotopic liver transplantation (OLT)[1,2]. The goal of this presentation is to describe the experience and outcomes of several key right heart echocardiography variables at a single institution and their relationship with short-term and one-year outcomes of mortality and graft survival. A new area of research with this study incorporates the role of early allograft dysfunction, occurring seven days after OLT.

METHODS: From a sample of 214 patients from 1/1/2019 through 6/30/2020, data were collected on patients undergoing liver transplantation. Pre-operative workup included echocardiography assessment of estimated pulmonary artery systolic pressure (PASP), left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), and severity of tricuspid regurgitation (TR). A multivariate analysis was conducted on early allograft dysfunction and patient survival at one-year or graft survival at one-year.

RESULTS: From a sample of 214 patients, a multivariate analysis showed that MELD score at time of OLT, PASP, left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), and severity of tricuspid regurgitation (TR) with presence of tricuspid disease rated as mild or greater were not correlated with higher risk of patient survival at one-year or graft survival at one-year. With respect to early allograft dysfunction, PASP was shown to be a significant predictor of adverse outcomes ($p = 0.05$, OR = 1.05, 95 CI: 1.00 - 1.10) while other variables were not statistically significant predictors of adverse outcomes. On multivariate analysis, right heart echocardiography measurements were not statistically significant factors for length of stay (LOS).

CONCLUSION: On multivariate analysis, right heart echocardiography measurements were not statistically significant factors for length of stay (LOS), adding ambiguity to the discussion of PASP, TAPSE, or severity of TR in outcomes data[1,2]. This presentation provides an update to the continued discussion regarding right heart echocardiography measurements and outcomes of liver transplantation patients and introduces the concept of early allograft dysfunction and its prediction from these measurements.

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LIVER 5

A report of acetaminophen toxicity referrals and outcomes in National Liver Transplant Unit Ireland July 2010-July 2021

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INTRODUCTION: Acetaminophen was introduced in the 1950s with the first reported of toxicity occurring in 1966[1, 2]. In Ireland acetaminophen toxicity (AT) is the leading cause of drug induced acute liver failure requiring orthotopic liver transplant (OLT)[3]. In Ireland there is public health measures attempting to reduce the incidence of AT, however, significant interruption to these has occurred due to the covid-19 pandemic. The aim of this study was to characterize the referrals to intensive care at the Irish National Liver Transplant Unit (INLTU) over an 11-year period.

METHODS: Eighty-eight patients with AT were referred to the INLTU in the period from July 2010 until July 2021, baseline characteristics at referral were collected in a prospective database. Including laboratory and physiological parameters, psychiatric history, ingested dose, intentionality and requirement for extracorporeal therapies.

RESULTS: Twenty OLTs for AT were performed in the 11-year period representing 23% of the ICU referrals. Twenty-one patients died without receiving OLT and a further two died post transplantation accounting for 32% of ICU referrals. The mean SOFA score in the OLT group was 11 vs 12.3 in the non-survivor group and 7.8 in the Medically managed group (P <0.001). The mean INR in the OLT group was 7.86 vs 6.67 in the non-survivor group and 3.39 in the Medically managed group (P <0.001). The mean Lactate in the OLT group was 9.98 vs 8.63 in the non-survivor group and 3.12 in the Medically managed group (P <0.001). Mean Creatinine level in the OLT and non-survivor group combined was 224 compared to 152 in the medical managed group (p=<0.001), with RRT in the same groups 93% vs 44% (P<0.001). In the Period of January 2019 - July 2021 during the covid-19 pandemic there was six referrals to the intensive care unit for AT, of which one underwent transplant and two died, a significant reduction in referrals from pre-pandemic levels 0.33/month from 0.8/month (p=0.005).

CONCLUSION: In the 11-year period from July 2010 until July 2021 there was comparable rates of OLT for acetaminophen toxicity in Ireland compared to international data, 23% of patients referred. Internationally there has been stability in suicide rates reported during national lock-downs, this was not observed our data, although this may be accounted for by an increase in alternative mechanisms, with the reduced availability of acetaminophen from multiple vendors due to travel restrictions during lock-down[4]. Our patient cohort reflects the previously observed trends in hematological and biochemical parameters except for hyperbilirubinemia where no significant difference was observed between the groups[5]. However, a significant difference was noted for creatinine levels and requirement for renal replacement therapies when the non-survivors and OLT groups were combined compared with medically managed groups, and this was a strong predictor of transplant or mortality.

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SUBSPECIALTY ABSTRACTS

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 1

Chemogenetic activation of dopaminergic midbrain neurons accelerates cognitive recovery following dexmedetomidine- but not ketamine-induced loss of consciousness in rats

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INTRODUCTION: Dopaminergic midbrain neurons, specifically those in the ventral tegmental area, are likely involved in restoring consciousness following general anesthesia[1,2]. However, it is unknown whether these circuits contribute to cognitive recovery following emergence. Recently, a novel cognitive recovery testing paradigm for rodents using an adapted version of the 5-Choice Serial Reaction Time Task (5CSRTT) has been developed. In it, higher order neurocognitive processes, such as attention and working memory, are tracked in real-time following emergence to establish neurocognitive recovery trajectories. Importantly, young, healthy rats recover cognitive function rapidly following isoflurane, sevoflurane, and propofol, but have delayed cognitive recovery following dexmedetomidine- and ketamine-induced loss of consciousness (LOC). To assess whether neural circuits involved in re-establishing consciousness can be similarly exploited to hasten cognitive recovery, we employed chemogenetic techniques to activate midbrain dopaminergic neurons in rats following dexmedetomidine and ketamine-induced LOC. It has been previously reported that pharmacologic activation of dopaminergic neurotransmission with d-amphetamine hastens emergence from dexmedetomidine, but not ketamine-induced LOC[3]. Therefore we hypothesized that activating dopaminergic midbrain neurons would differentially affect cognitive recovery following dexmedetomidine and ketamine exposure.

METHODS: Eight adult Sprague Dawley rats (4 male, 4 female) were trained on the 5CSRTT until they achieved high accuracy (>80%) and low omissions (<20%). Once trained, midbrain neurons were targeted using a combinatorial adeno-associated viral (AAV) strategy to drive selective expression of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in dopaminergic neurons. The targeting virus, AAV9-rTH-Cre, induces expression of Cre recombinase in dopaminergic neurons that express tyrosine hydroxylase (TH). This was co-injected with an AAV that induces Cre-dependent expression of the excitatory DREADD, AAV2-DIO-hM3DGq-mCherry, into the midbrain (+/-0.9ML, -4.8AP, -8.3DV). After waiting three weeks for DREADDs expression, rats received dexmedetomidine (20 µg/kg, i.v. infused over 10 min) or ketamine (50 mg/kg, i.v. infused over 10 min). Following the anesthetic infusion, rats were administered either saline (control) or clozapine-N-oxide (CNO, 3mg/kg, i.p.), the designer ligand used to activate the excitatory DREADD, in a randomized order. Rats were placed supine in the testing chamber to recover. Following the return of the righting reflex (RORR), rats had three hours to perform the task. Recovery of working memory was measured as the time taken following RORR to achieve ≥80% accuracy in five consecutive trials. Recovery of attention was measured as the time taken following RORR to achieve ≤20% omissions in five consecutive trials. After all testing was completed, histological analysis was performed to confirm DREADDs expression in the targeted brain region. Recovery latency was compared between CNO and saline conditions by Mantel-Cox comparison.

RESULTS: DREADDs expression in the midbrain was confirmed by mCherry fluorescence (Fig 1). Recovery of a low omission rate, a metric of sustained attention, following dexmedetomidine was significantly faster in the CNO condition ($\chi2$=5.588, P=.0104) (Fig 2A). Following RORR from dexmedetomidine, the median latency to recover high accuracy, a metric of working memory, was 114.7 minutes with saline and 49.7 minutes with CNO, but this was not significantly different ($\chi2$=2.705, P=.1001) (Fig 2B). In contrast, CNO had no impact on cognitive performance following ketamine. Median recovery of low omissions was 70.5 min with saline and 68.5 min with CNO ($\chi2$=0.3793, P=.5380)(Fig 2C). Median recovery of high accuracy was 42.9 min with saline and 45.6 min with CNO ($\chi2$=0.9155, P=.3387)(Fig 2D).

CONCLUSION: Selective activation of midbrain dopaminergic neurons hastens neurocognitive recovery following dexmedetomidine-induced LOC in rats. Interestingly, activating these neural circuits has no impact on cognitive function following ketamine. These data suggest there are distinct mechanisms by which the brain recovers cognitive function following anesthetic-induced breaks in consciousness. Identifying these mechanisms will be key to designing effective strategies for facilitating neurocognitive recovery.

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Figure 1

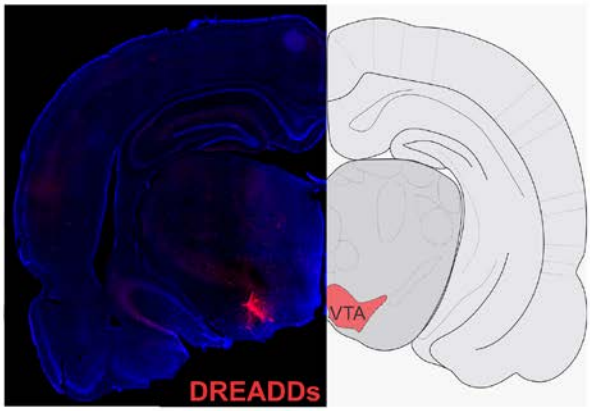
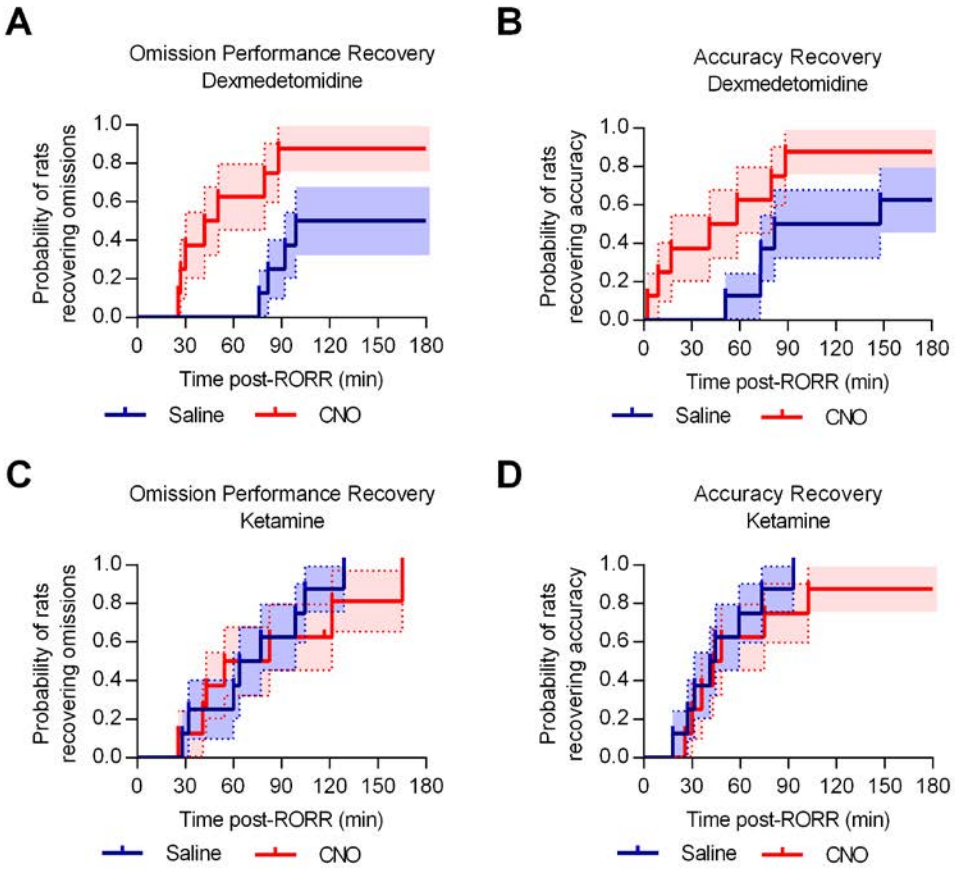


Figure 2



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 2

Volatile anesthetics inhibit presynaptic cGMP signaling to depress presynaptic excitability in rat hippocampal neurons

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INTRODUCTION: Volatile anesthetics alter essential presynaptic functions including Ca2+ influx and neurotransmitter release, with potential roles in producing unconsciousness and amnesia. Nitric oxide and cyclic guanosine monophosphate (NO/cGMP) signaling is implicated in several presynaptic mechanisms[1], and animal models of disrupted NO/cGMP signaling have altered sensitivity to volatile anesthetics.

METHODS: Volatile anesthetic effects on NO/cGMP signaling in rat hippocampal neurons was investigated using pharmacological approaches and genetically encoded biosensors for measuring cGMP levels.

RESULTS: Expression of the fluorescent biosensor cGull was used to measure activity-driven NMDAR-independent presynaptic cGMP transients in neurons. Isoflurane or sevoflurane depressed electrical stimulus-evoked increases in cGMP to 69.25 ± 11.31% and 76.15 ± 10.17% of a control stimulus, respectively ($p<0.0001$, both). Isoflurane and sevoflurane depression of action potential-evoked increases in presynaptic Ca2+ and synaptic vesicle exocytosis was blunted in neurons expressing the cGMP scavenger sponGee. This effect was recapitulated by ivabradine inhibition of HCN, a cGMP modulated ion channel.

CONCLUSION: Volatile anesthetics depress presynaptic cGMP signaling and downstream effectors like HCN channels which normally enhance presynaptic function and excitability, thereby reducing neurotransmission via second messenger signaling.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 3

Distinct effects of inhaled and intravenous anesthetics on presynaptic calcium dynamics in rodent hippocampal GABAergic neurons

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INTRODUCTION: Significant progress has been made in resolving the molecular targets of general anesthetics, but their cellular and circuit-level effects remain unclear. The volatile anesthetic isoflurane inhibits synaptic vesicle exocytosis to different degrees for various neuronal subtypes[1], but whether other common anesthetics also affect presynaptic function in a neuron-subtype specific manner is unknown.

METHODS: We used the genetically encoded Ca2+ sensor GCaMP6f expressed in mouse hippocampal neurons to compare the effects of isoflurane, sevoflurane, propofol, and ketamine on presynaptic excitability in glutamatergic neurons and in parvalbumin-, somatostatin-, and VIP-expressing (PV+, SST+, and VIP+) GABAergic interneurons.

RESULTS: Isoflurane and sevoflurane depressed electrical activity-evoked presynaptic Ca2+ transients in a cell-type specific manner, with greater potency for inhibition in glutamate and SST+ neurons compared with PV+ and VIP+ neurons. In contrast, propofol potentiated evoked Ca2+ entry in PV+ interneurones but only at a supraclinical concentration (3 μM). A clinical concentration of propofol (1 μM) or ketamine (15 μM) had no significant effect, with no neuronal subtype specificity.

CONCLUSION: Anesthetic agent-selective effects on presynaptic Ca2+ entry suggest that distinct changes in hippocampal circuit function occurs during intravenous or volatile anesthetic-mediated anesthesia. Hippocampal interneurons have distinct sensitivities to volatile anesthetic actions on action potential-evoked increases in presynaptic Ca2+, which are largely conserved between isoflurane and sevoflurane.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 4

Phase-Locked Acoustic Stimulation Increases Human Thermal Arousal Thresholds during Dexmedetomidine Sedation

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INTRODUCTION: States of deep sedation and general anesthesia are characterized by slow-delta oscillations (0.1-4Hz) in the electroencephalogram (EEG), and the relative power of these oscillations correlates with depth of unconsciousness[1]. Acoustic stimulation in-phase with the upslope of these slow oscillations enhances the expression of EEG slow waves during sleep states[2,3]. It is unknown whether this technique induces similar phenomena during pharmacological sedation. Modulating EEG slow oscillations using non-invasive neurostimulation could provide clinicians with a targeted method to non-pharmacologically manipulate brain states during sedation and general anesthesia. We hypothesized that acoustic stimulation in-phase with the upslope of EEG slow oscillations during dexmedetomidine sedation would lead to 'deeper' sedation states, incurring higher thresholds for arousal during noxious thermal stimulation.

METHODS: An interim analysis was performed on data acquired from healthy volunteers during the ongoing trial: Closed-Loop Acoustic Stimulation during Sedation with Dexmedetomidine (CLASS-D)[4]. Thermal arousal thresholds are a pre-specified secondary outcome of this trial. Each participant received phase-locked acoustic stimulation (60 dB pink noise) while sedated with a target-controlled infusion (TCI) of dexmedetomidine titrated to induce both slow-delta oscillations and loss of responsiveness to a behavioral task. A custom-built device incorporating an endpoint-corrected Hilbert Transform[5] (Elemind Technologies, Inc., Cambridge, MA) was used to phase-lock auditory stimuli to a 1 Hz central frequency (Figure 1): in-phase stimuli were delivered shortly before slow wave peaks (0°) while anti-phase stimuli were delivered shortly before slow wave troughs (180°). A standard quantitative sensory testing (QST) protocol with a Thermal Sensory Analyzer (TSA-II, Medoc, Israel) was employed by applying a Peltier thermode to the non-dominant forearm and increasing its temperature at a rate of 1°C per second (up to a maximum of 52°C) until participants either opened their eyes or withdrew from the thermode[6]. In this way, thresholds for behavioral arousals were determined at steady-state concentrations of dexmedetomidine across three conditions: in-phase, anti-phase and sham (silence). The order of in-phase, anti-phase and sham conditions was randomized across participants. For this preliminary analysis, paired parametric statistical testing was undertaken to compare arousal thresholds during in-phase and sham stimulation. A mixed effects model will be used to compare arousal thresholds across all three conditions at the conclusion of the trial.

RESULTS: Data were analyzed from the first eight participants, one of which was withdrawn early precluding analysis. Target dexmedetomidine effect site concentrations required to induce slow-delta EEG oscillations and achieve a state of unresponsiveness ranged from 1.5 – 2.5 ng/ml. Approximately 1000 in-phase stimuli (median phase -5.7°, resultant 0.76) and 1000 anti-phase stimuli (median phase 169.7°, resultant 0.72) were delivered to each participant (Figure 2). Thus, phase-locking of stimuli relative to the peak and trough of slow EEG oscillations was effective. The mean temperature required to induce a behavioral arousal was 48.8°C (95% CI, 47.8 – 49.8) during sham, 48.5°C (95% CI, 47.0 – 50.0) during anti-phase stimulation, and 50.6°C (95% CI, 49.9 – 51.3) during in-phase stimulation (Figure 3). Compared to the sham condition, thermal arousal thresholds were increased by 1.8°C (95% CI, 0.6 – 3.0, p = 0.02) during in-phase stimulation. (Figure 4)

CONCLUSION: Preliminary data from this ongoing trial suggests that in-phase acoustic stimulation may increase thresholds for arousal to noxious stimulation during dexmedetomidine sedation. Non-invasive, phase-locked neurostimulation methods such as closed loop acoustic stimulation could allow clinicians to quickly modulate patients' sedation states without the adverse effects of traditional pharmacological interventions. Future studies should investigate the effect of in-phase acoustic stimulation on nociceptive processing and seek to translate these findings into clinical settings.

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Figure 1. Schematic of phase-locked neurostimulation with inphase and antiphase conditions.

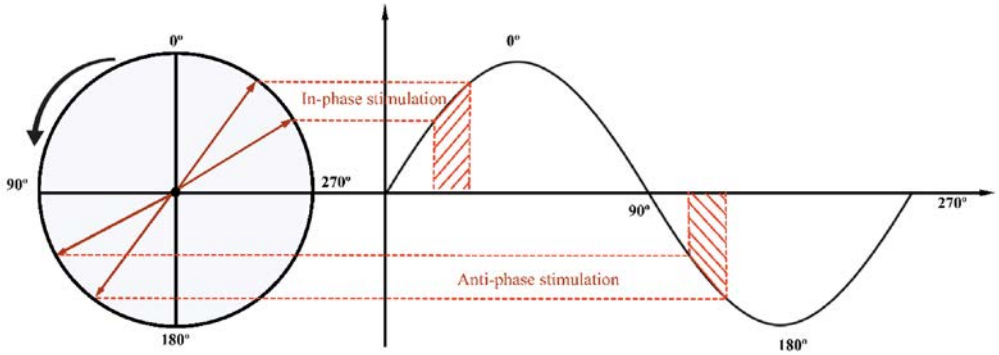


Figure 2. Phase histograms of inphase and antiphase stimulation, exhibiting accurate and precise phase-locking.

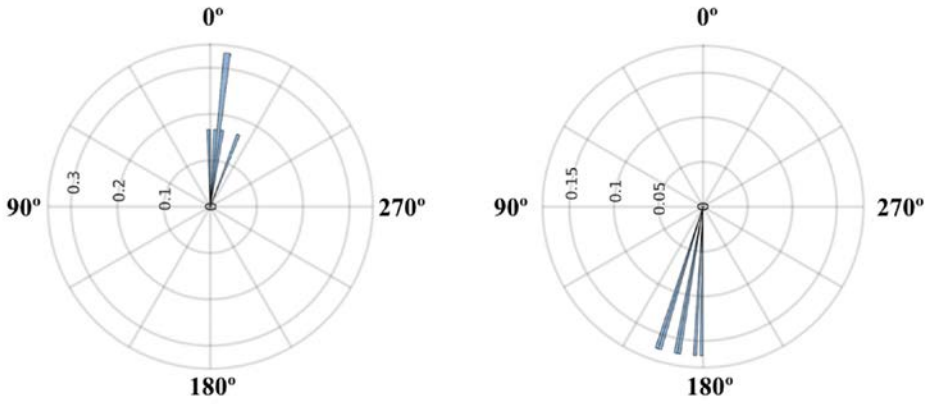


Figure 3. Thermal arousal thresholds during sham, antiphase and inphase stimulation.

Markers denote means and error bars represent 95% confidence intervals.

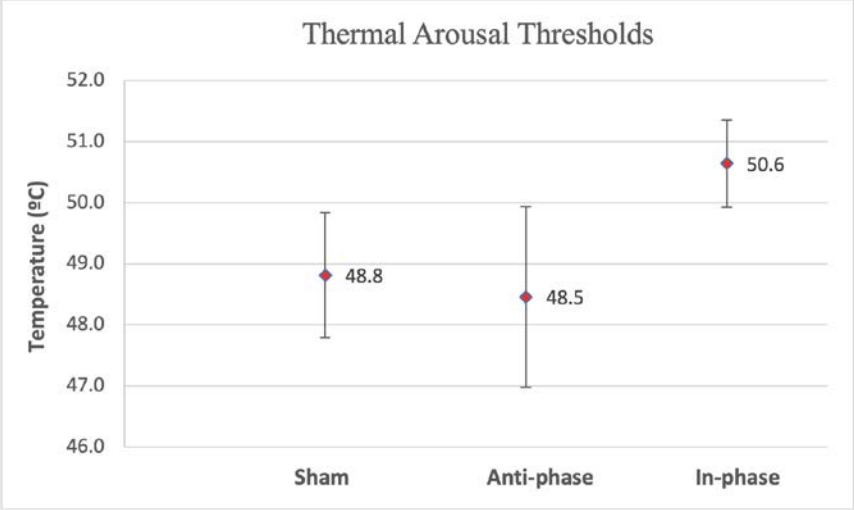
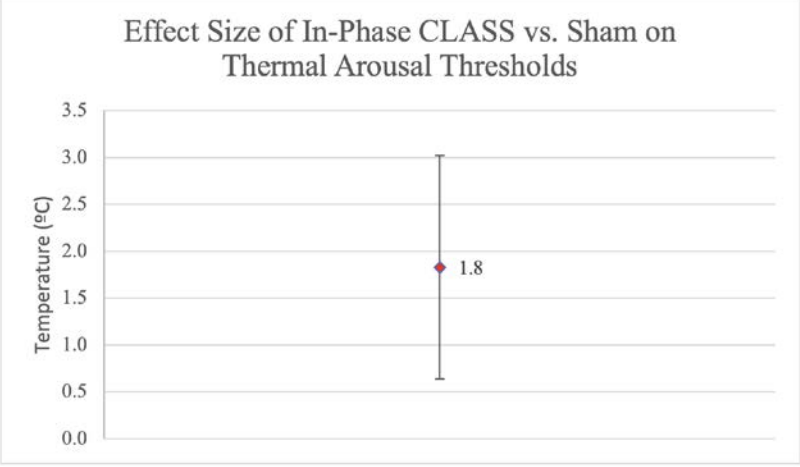


Figure 4. Effect sizes of inphase stimulation vs. sham on thermal arousal thresholds.

Marker denotes mean effect size and error bars represent 95% confidence intervals.



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 5

GABAA receptors in astrocytes are targets for intravenous and inhalational general anesthetic drugs in mice

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INTRODUCTION: Perioperative neurocognitive disorders (PNDs) occur commonly in older patients after anesthesia and surgery. Treating astrocytes with general anesthetic drugs that are frequently used in clinical practice stimulates the release of soluble factors that increase the cell-surface expression and function of GABAA receptors in neurons[1, 2]. Such crosstalk may contribute to PNDs[3]; however, the receptor targets in astrocytes have not been identified. GABAA receptors, which are the major targets of general anesthetic drugs in neurons, are also expressed in astrocytes[4, 5], raising the possibility that anesthetic drugs act on GABAA receptors in astrocytes to trigger the release of soluble factors. To date, no study has directly examined the sensitivity of GABAA receptors in astrocytes to general anesthetic drugs that are now used in clinical practice. Thus, the goal of this study was to determine whether the function of GABAA receptors in astrocytes was modulated by the intravenous anesthetic etomidate and the inhaled anesthetic sevoflurane.

METHODS: Whole-cell voltage-clamp recordings were performed in astrocytes in the stratum radiatum of the CA1 region of hippocampal slices isolated from C57BL/6 male mice. Astrocytes were identified by their morphologic and electrophysiologic properties: low membrane resistance (RM < 15 MΩ), a low resting membrane potential (VM < -70 mV), and a unique linear I-V relationship. Focal puff application of GABA (300 μM) was applied with a Picospritzer system to evoke GABA responses (Fig. 1A). Currents were studied before and during the application of the noncompetitive GABAA receptor antagonist picrotoxin (0.5 mM), or etomidate (100 μM) or sevoflurane (532 μM).
Data are represented as mean ± SD (Standard Deviation). All continuous variables were tested to determine whether they met conditions of normality (Shapiro-Wilk test) and homogeneity of variance (Levene's test). Paired Student's t-test was performed to compare paired data. A two-tailed hypothesis test was used, and statistical significance was set at $P < 0.05$.

RESULTS: We first examined the effects of etomidate (100 μM) on GABAA receptor-generated currents in astrocytes (Fig. 2A). After obtaining an initial baseline current in response to GABA (300 μM), the slices were perfused for 2 minutes with aCSF containing etomidate and a second puff of GABA was applied. Etomidate increased the amplitude of the current by 35.0 ± 24.4% (Fig 2B; n = 7; P = 0.006). Etomidate did not alter the current rise time but did prolong the decay time by 27.2 ± 24.3% (Fig. 2B; n = 7; P = 0.037). The total charge transfer was also increased by 71.2 ± 45.9% (Fig. 2B; n = 7; P = 0.006). We next confirmed that GABA-evoked responses in the presence of etomidate were primarily generated by GABAA receptors by co-applying picrotoxin (0.5 mM), which reduced the peak current by 75.3 ± 5.5% (Figure 2C; n = 4; P = 0.001, paired t-test). In the next set of studies, sevoflurane (532 μM) was added to the bath solution for 2 minutes and the changes GABA-evoked currents were investigated (Fig. 3A). Sevoflurane did not increase the peak current nor did it increase the current rise time (Fig. 3B). However, sevoflurane prolonged the current decay by 28.3 ± 23.1% (Fig 3B; n = 7; P = 0.030) and increased the total charge transfer by 51.8 ± 48.9% (Fig 3B; n = 7; P = 0.029). Thus, sevoflurane increased the GABA-evoked currents. GABA-evoked currents in the presence of sevoflurane were also inhibited by 64.4 ± 12.5% with picrotoxin (0.5 mM) (Fig. 4C; n = 4; P = 0.003).

CONCLUSION: The function of astrocytic GABAA receptors in the hippocampus was increased by etomidate and sevoflurane. Future studies will determine whether these general anesthetic drugs act on astrocytic GABAA receptors to stimulate the release of soluble factors that may contribute to PNDs.

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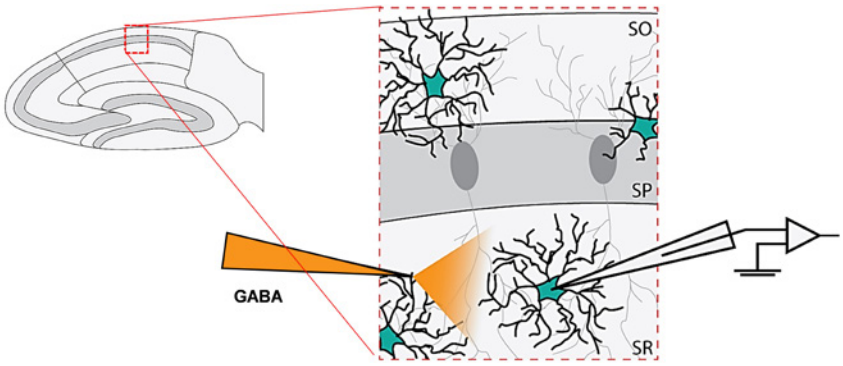

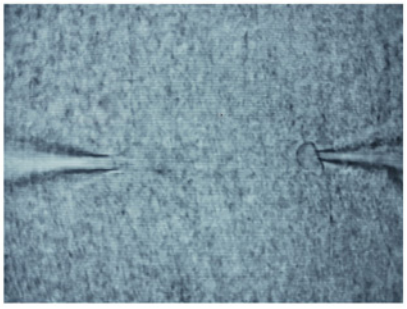

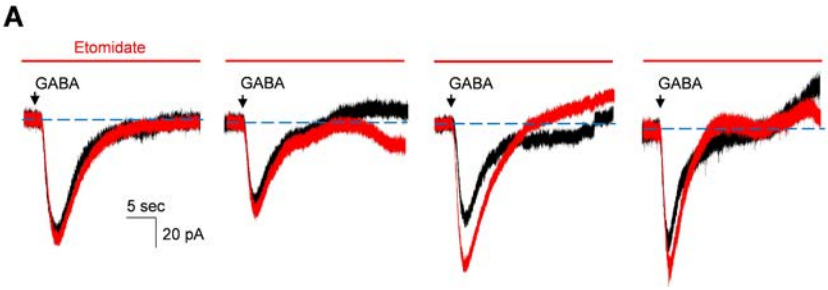

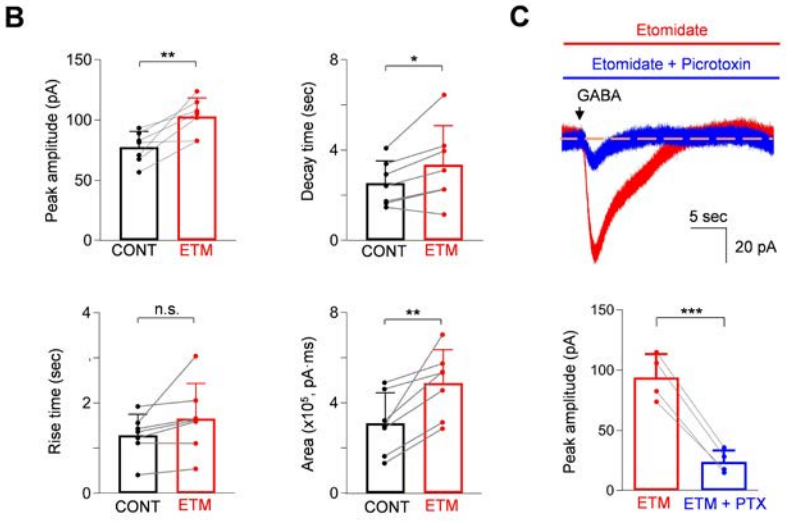

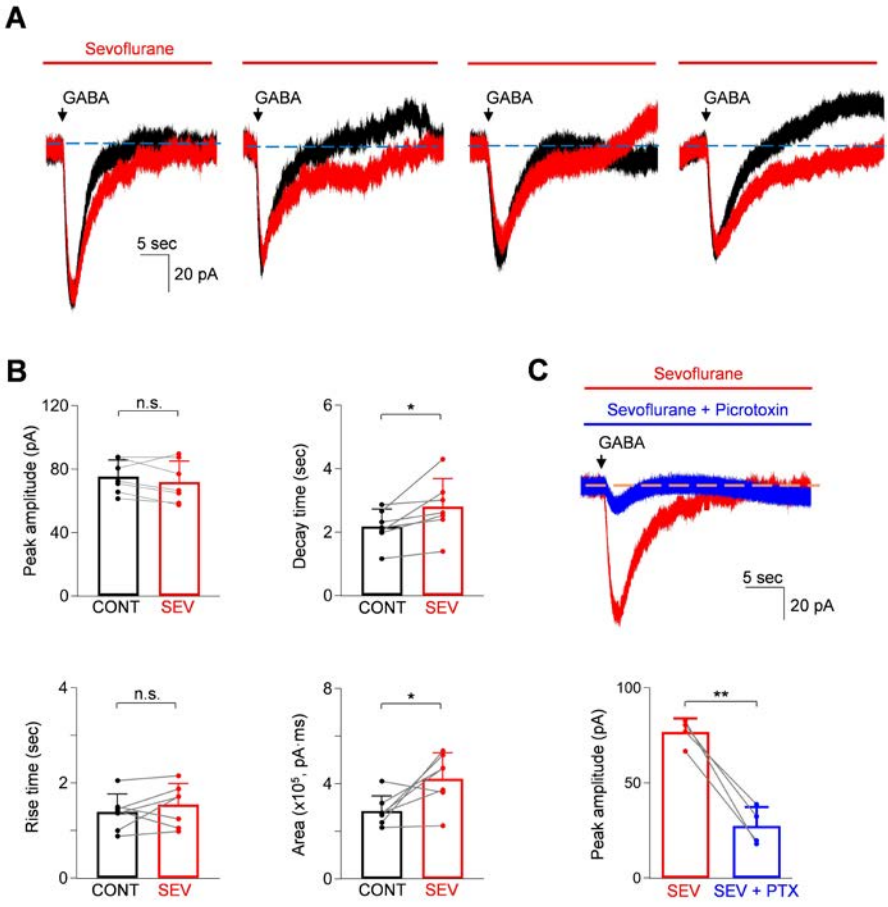

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 6

Effect of PPV Guided Fluid Management on Intra Operative Fluid Requirement in Supratentorial Tumour Surgery: A Randomized prospective trial

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INTRODUCTION: In neuro anaesthesia quality recovery is vital. Intra-operative fluid therapy is an integral part of anaesthetic management with significant potential to improve patient outcome[1]. Central venous pressure (CVP) is a conventionally used variable to guide fluid therapy, but found to be poorly reliable in various studies[2]. Pulse Pressure Variance (PPV) is a dynamic variable that can be used to assess fluid responsiveness. The aim of our study was to evaluate the efficacy of PPV guided fluid therapy on the intra-operative fluid requirement and postoperative recovery in patients who underwent supratentorial tumour surgery.

METHODS: This was a randomized, double blind, prospective, single centre trial. After IRB approval, 72 Patients planned for supra-tentorial tumour surgeries in supine position, were randomized using computer generated random number table into either CVP group or PPV group. Patients in CVP Group, received fluids to maintain a CVP of 8-12 mm Hg and patients in PPV Group received fluids to maintain PPV<13. The two groups were compared for intra-operative fluid requirement, incidence of intra-operative hypotension, brain relaxation score at the time of opening of duramater, serum lactate levels (at the end of surgery and 24 hours post operatively), incidence of conjunctival, peri-orbital oedema , nausea and vomiting postoperatively. In SPSS 20 software, to compare the means between the two groups (CVP vs PPV), independent t-test was used for normal distribution data. While for proportions, chi-square test was used. (p <0.05 significant)

RESULTS: Seventy two patients aged 18-60 years (ASA I and II), undergoing supratentorial tumor surgery electively in supine position were included in the study. Patients with features of sepsis, elevated baseline lactate levels (> 20 mg/dl), cardiac illness, peripheral vascular disease, tumours prone to precipitate diabetes insipidus, massive blood loss during surgery and those shifted on ventilatory support post operatively were excluded from the study. Baseline parameters like age, gender, comorbidities, serum lactate levels (mg/dl) and duration of surgery were comparable between the two groups. Urine output(ml) was higher in CVP group than PPV group (1283.75 ± 783.51 vs 1008.13 ± 477.59, p=0.04). During surgery, PPV group received significantly lesser crystalloids than CVP Group [CVP vs PPV (4.34 ±1.01 vs 3.54 ± 0.74, p<0.01)]. Incidence of intraoperative hypotension was more in CVP group than the PPV group (4:0, p=0.04). Other objectives like serum lactate levels, brain relaxation score, conjunctival and periorbital oedema and post operative nausea and vomiting were not statistically significant (Table 1).

CONCLUSION: PPV can be an effective guide to fluid therapy requiring lesser intra-operative fluids when compared to CVP, with no compromise in intra-operative and post-operative hemodynamic parameters.

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Table 1: Summary of outcomes

Patient characteristics	Group 1 (CVP) n = 36	Group 2 (PPV) n = 36	p value
Intraoperative fluid requirement in liters (mean± SD) #	4.34 ±1.01	3.54 ± 0.74	**< 0.01***
Baseline Sr. Lactate in mg/dl (mean± SD) #	11.61 ± 4.90	11.97 ± 5.22	0.77
Sr. Lactate (mg/dl) at the end of surgery (mean± SD) #	17.69 ± 8.90	16.74 ± 7.66	0.61
Sr. Lactate (mg/dl) 24 hours after surgery (mean± SD) #	17.52 ± 8.23	16.77 ± 9.38	0.70
Urine output in ml (mean± SD) #	1283.75 ± 783.51	1008.13 ± 477.59	**0.04***
Amount of blood loss during surgery in ml (mean± SD) #	629.17 ± 321.67	531.94 ± 219.14	0.14
Intraoperative hypotension (%) $	4 (11.1%)	0 (0%)	**0.04***
Vasopressor infusion requirement (%) $	1 (2.8%)	0 (0%)	0.31
Presence of conjunctival and periorbital edema (%) $	5 (13.9%)	3 (8.3%)	0.45
Brain relaxation score (Score 1: 2: 3: 4) $	2: 32: 2: 0	3: 32: 0: 1	0.36
Presence of post-operative nausea and vomiting (%) $	5 (13.9%)	4 (11.1%)	0.72

- independent t-test used, $ - chi square test used, p <0.05 significant, * - significant p value

CVP- central venous pressure, PPV- Pulse pressure variance, BRS- Brain relaxation score, BRS score (1- perfectly relaxed, 2- satisfactorily relaxed, 3- firm brain, 4- bulging brain)

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 7

Estrous cycle affects emergence latency from dexmedetomidine but not propofol, isoflurane, nor sevoflurane anesthesia in rats

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INTRODUCTION: While sex differences in anesthetic sensitivity have been reported in both human and animal studies, little is known about the mechanisms underlying these differences. It has been previously found that female rats show greater delay and variability in return of right reflex (RORR) latency following anesthetic doses of dexmedetomidine[1]. A commonly cited source of female variability is the estrous cycle, the reproductive cycle in rodents analogous to the menstrual cycle in humans. In rats, the cycle repeats every four to six days and includes four stages: proestrus (Pro), estrus (Est), metestrus or early diestrus (Di-I), and late diestrus (Di-II)[2]. During these stages, hormonal fluctuations impart broad physiological and neurochemical changes in the rat. To establish whether the changes associated with the estrous cycle impact sensitivity to commonly used general anesthetic agents, we measured RORR latency, gonadal hormone serum concentration, total body weight, and frontal electroencephalographic (EEG) signatures in female rats under multiple anesthetic agents across each of the four stages. We hypothesized that variability in RORR latency within female rats following general anesthesia is attributable to physiological fluctuations that occur across the estrous cycle.

METHODS: Sixteen female Sprague Dawley rats underwent stereotaxic surgery for intracranial EEG electrode placement. After a one-week postoperative recovery period, rats were divided into cohorts that received inhalational anesthesia (N=8) and intravenous anesthesia (N=8). The inhalational cohort was tested under isoflurane (2% for 1 hour, ISO) and sevoflurane (3% for 20 minutes, SEVO). RORR latency was measured as the time taken to flip from a supine to a prone position following their removal from the induction chamber. The intravenous cohort was tested under dexmedetomidine (50 µg/kg, infused over 10 minutes, DEX) and propofol (10 mg/kg, bolus, PROP). RORR latency was measured as the time taken to return to the prone position following the end of drug infusion. All rats were tested under the respective agents once per estrous stage with at least 72 hours between testing sessions. The estrous cycle was tracked by daily vaginal lavage for cytology assessment (Figure 1)[3]. Serum concentration of progesterone and 17β-estradiol was measured by enzyme linked immunosorbent assay (ELISA) from blood collected on each test day. The effect of estrous cycle stage on RORR latency was assessed by repeated measures ANOVA. The association between RORR latency and total weight and serum hormone concentration was tested by linear regression. Power spectral densities measured from frontal EEG electrodes were analyzed across estrous stages by repeated measures ANOVA.

RESULTS: Rat estrous cycle does not affect RORR latency following ISO, SEVO, or PROP (Figure 2A). When in the Di-I stage, rats emerge more rapidly from DEX than when in the Pro or Di-II stage (Fig 2A). Independent of estrous cycle, greater total body weight was associated with longer emergence latencies from PROP and DEX in female rats (Figure 2B). Surprisingly, 17β-estradiol and progesterone serum concentrations were unrelated to RORR latency for the anesthetics tested. Finally, frontal EEG spectral analysis revealed significantly reduced power under DEX anesthesia at both early (30 min, Fig. 2C) and late (90 min, Fig. 2D) time periods when rats were in Di-I compared with Pro and Di-II.

CONCLUSION: Overall, our data suggest that the effects of the estrous cycle on anesthetic sensitivity are anesthetic-dependent. Importantly, at high doses of dexmedetomidine sufficient to induce loss of righting, the rat estrous cycle significantly affects both RORR latency and anesthetic depth, but this effect is through an estradiol- and progesterone-independent mechanism. In contrast, sensitivity to isoflurane, sevoflurane, and propofol is not affected by the estrous cycle, though greater total body weight does contribute to prolonged RORR latency for propofol in female rats. By identifying when and how sex-specific

biophysiological processes interact with general anesthetics, better guidelines for patient care can be established.

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Figure 1

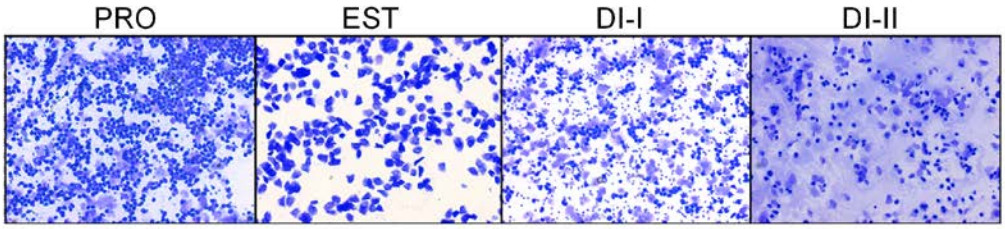
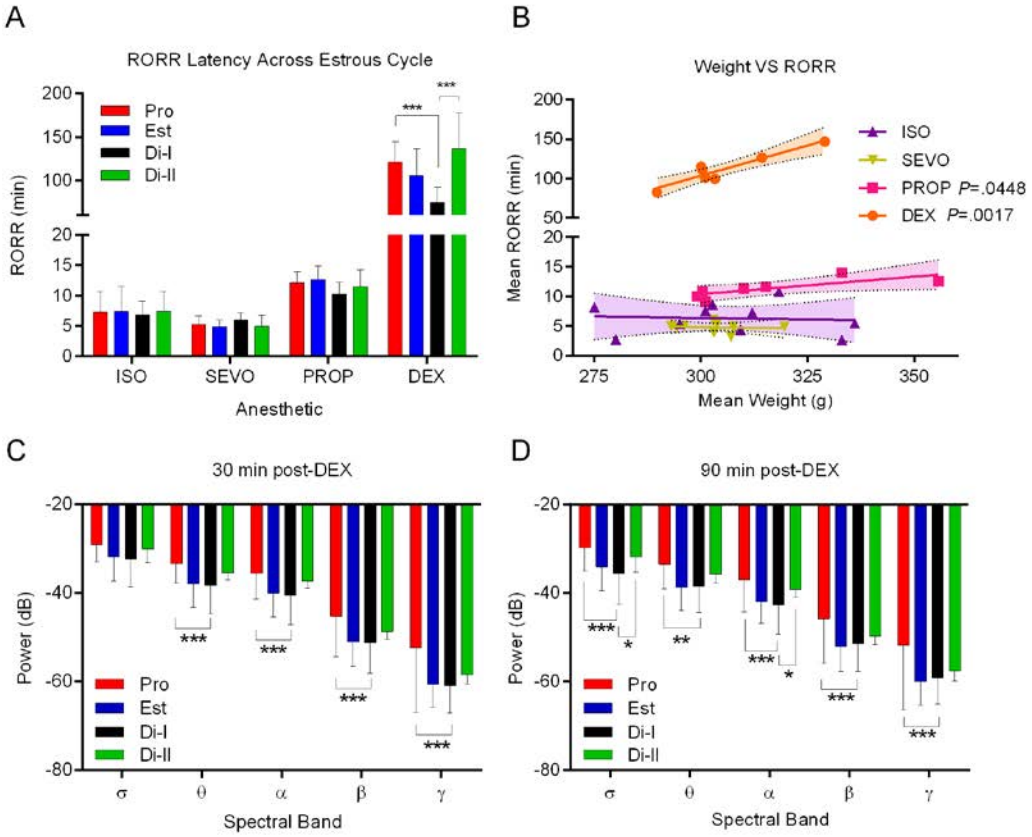


Figure 2



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 8

Exposure to Preeclampsia In Utero Leads to Cerebrovascular Dysfunction in Offspring

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INTRODUCTION: Preeclampsia (PE) is a devastating hypertensive disorder that affects 5-10% of pregnancies worldwide.[1] Aside from its acute effects during pregnancy, PE is known to have long-term effects on both the mother and baby.[3-5] While considerable research has focused on the maternal brain in PE, relatively little is known about how preeclampsia affects offspring, particularly with respect to cerebrovascular function and brain perfusion. In addition, though it is known that the cerebrovasculature matures over time in the developing brain, the effect of PE on cerebrovascular maturation is not known. The purpose of this study was to determine if in utero exposure to experimental PE (ePE) would lead to abnormal cerebrovascular maturation and if this would be associated with impaired cerebral blood flow autoregulation (CBFAR) in juvenile and/or adult offspring.

METHODS: To induce ePE, pregnant rats were fed a high-cholesterol diet from day 7 - day 20 of a 22 day gestation. Mothers were maintained on the high cholesterol diet until offspring were weaned. Offspring from ePE and normal pregnant (NP) rats were studied at p30 (postnatal day 30, approximating a 2-year-old child; n=9-11/group) or at 18-22 weeks of age (adult; n=5-7/group). To assess CBFAR, offspring were anesthetized with 3% isoflurane in oxygen, intubated, and mechanically ventilated on room air to maintain normoxia and normocarbia. Femoral arterial and venous catheters were placed to measure continuous arterial blood pressure (ABP) and administer compounds. A laser Doppler probe was placed on the skull in the territory of the middle cerebral artery (MCA) to measure relative cerebral blood flow (rCBF). Animals were transitioned to IV chloral hydrate to minimize the effects of vasodilating anesthesia on CBF. Then, ABP was increased in 10 mmHg increments via IV infusion of norepinephrine (NE) to assess the upper range of CBFAR and controlled hemorrhage was used decrease ABP and determine the lower range of CBFAR. Change in CBFAR at each pressure was calculated as % change from baseline. The amount of blood required to cause hypotension was also measured. Continuous recordings of blood pressure and heart rate were measured in separate groups of unanesthetized, freely moving adult rats using radio telemetry.

RESULTS: CBFAR curves were similar between p30 NP and ePE offspring, showing no difference in the upper or lower limits (Figure 1). However, in adult offspring from ePE animals, the upper limit of the CBFAR curve was shifted to the right compared to NP (Figure 1). The rightward shift was found to be significant at 130, 140, and 150 mmHg ($p<0.05$). When compared to p30 offspring, all adult offspring had CBFAR curves that were shifted to the right regardless of PE exposure in utero, demonstrating…. The total volume of hemorrhage required to decrease the blood pressure from baseline to 20 mmHg was significantly higher in the ePE group at p30 (1.44±0.2 vs. 2.25±0.16 mL, $p<0.01$), but not in adult animals (6.43±2.1 vs. 8.15±1.7 mL, $p<0.01$). Average diurnal heart rate (305±3 vs 349±4, $p<0.01$) and nocturnal heart rate (373±7 vs 417±5, $p<0.01$) were significantly higher in adult ePE offspring (Figure 2) without a difference in ABP (data not shown).

CONCLUSION: Our results showed no difference in CBFAR curves between NP and ePE offspring at a young age of p30. However, we found maturation was associated with a rightward shift in the upper limit of the CBFAR curve in adults from both groups that was more pronounced in offspring from ePE dams. We also found a resistance to hemorrhagic hypotension ePE p30 offspring and persistent tachycardia in adult offspring exposed to ePE, suggesting ePE offspring had enhanced sympathetic tone. Understanding how ePE affects CBFAR in offspring may be important when considering the effect of anesthesia on blood pressure and CBF.

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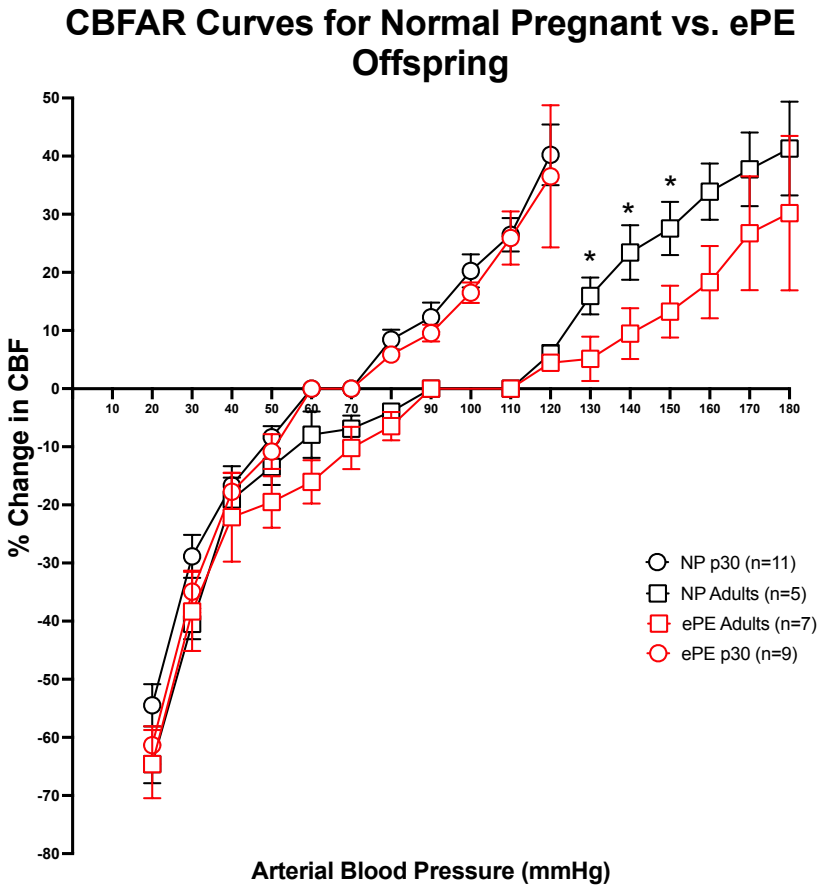

Figure 1. CBFAR curves for p30 (open circles) and adult (open squares) offspring of NP vs. ePE rats. CBFAR in p30 offspring CBFAR curves were found to be similar in both groups. In contrast, the CBFAR curve was shifted to the right in adult animals, and was significantly so at 130, 140, and 150 mmHg. *p<0.05, Student's t-test.

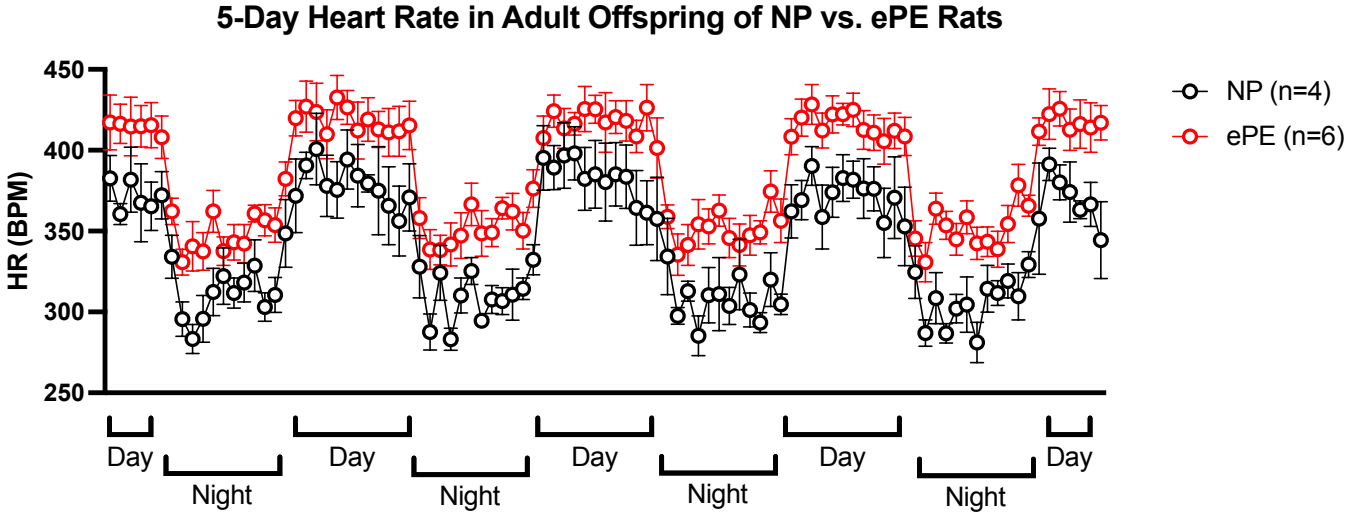

Figure 2. Implanted telemeter data from adult offspring of NP vs. ePE rats. This figure shows 5 days of continuous telemeter data in which each data point represents one hour of averaged data.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 9

Intergenerational perioperative neurocognitive disorder (PND) induced by surgery, traumatic brain injury and subsequent exposure to sevoflurane in young adult male rats

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INTRODUCTION: Stress, inflammation, and preexisting neurocognitive dysfunction are believed to play a role in accelerated neurocognitive disorder (PND) after general anesthesia (GA)/surgery. PND is most readily detectable and studied in older adults. Young adults with traumatic brain injury (TBI) also experience exacerbated stress, inflammation, and neurocognitive deficiencies. They often require GA/surgery orthopedic, abdominal, or thoracic injuries. Similarly, these patients may undergo long-term sedation, for example for increased intracranial pressure. Here we tested whether the effects of surgery, TBI, and subsequent repeated exposure to sevoflurane (SEVO) interact to induce neurobehavioral abnormalities in the exposed young adult males (F0 generation) and their future offspring (generation F1).

METHODS: All animal procedures were approved by IACUC. Male Sprague-Dawley rats in the TBI + SEVO group were subjected to a moderate TBI via a midline fluid percussion injury model on postnatal day 60 (P60) that involved craniectomy under 3% SEVO for 40 min. This group also had 2.1% SEVO for 3 h on P62, P64, and P66. The Control group had none of these procedures; the TBI group had only TBI on P60; the SEVO group had only SEVO exposure on P60, P62, P64, and P66; and the Sham + SEVO group had surgery, but not TBI, on P60 and exposure to SEVO on P62, P64, and P66. All F0 males were mated with control females on P90 to generate offspring. The F0 males and F1 males and females were sequentially evaluated in the elevated plus maze (EPM), prepulse inhibition (PPI) of acoustic startle, Morris water maze (MWM) and for resting and stress levels of serum corticosterone starting on ~P125 (F0) and ~P60 (F1).

RESULTS: When compared to controls, all F0 groups exhibited deficiencies in the EPM, PPI, and MWM tests. Abnormalities were more profound in the TBI + SEVO group. A statistically significant interaction between TBI and subsequent exposure to SEVO was found in the MWM and in resting and stress corticosterone levels. When compared to F1 males of control sires, all groups of F1 males exhibited deficiencies in the EPM, PPI, and MWM tests, with a trend towards greater abnormalities in F1 males of TBI + SEVO sires. Serum corticosterone levels 30 min after the PPI test were significantly increased only in F1 males of Sham + SEVO and TBI + SEVO sires, with a greater increase in the latter. The only behavioral abnormality in F1 females was reduced PPI of startle at a 3-dB prepulse intensity in F1 females of TBI + SEVO sires. The findings provide evidence for epigenetic mechanisms mediating the studied effects.

CONCLUSION: This is the first evidence of intergenerational neurobehavioral effects (intergenerational PND in a rodent model) of TBI + SEVO and surgery + SEVO in young adult males.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 10

Postoperative neurocognitive dysfunction after cardiac surgeries requiring hypothermic circulatory arrest

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INTRODUCTION: Cardiac surgery is associated with a significant risk of postoperative neurocognitive dysfunction (POND), with incidence as high as 60%[1]. POND is associated with increased healthcare costs, poorer patient experiences, and overall worse outcomes. In this retrospective study, we compared the occurrence of POND in patients undergoing cardiac surgery with and without hypothermic circulatory arrest (HCA).

METHODS: Five hundred and seventy-one patients who underwent cardiac surgery necessitating cardiopulmonary bypass from 7/1/2020-12/31/2020 at the Massachusetts General Hospital were evaluated. Patient baseline characteristics, surgical data, and outcomes were collected retrospectively from electronic medical records. Screening for POND was performed by nurses using the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) scores within the first 30 days of surgery or until the patient was discharged[2,3]. Logistic regression was performed to examine the association between HCA and POND while adjusting for other confounding factors.

RESULTS: Fifty-one (8.9%) of the study cohort underwent HCA. The HCA and non-HCA groups did not differ significantly on age, gender, BMI, and baseline comorbidities (Table 1). Seventeen (33.3%) patients from the HCA group had history of prior cardiac surgery compared to 83 (16%) of patients from the non-HCA group (p=0.006). Incidence of emergency surgery was higher for the HCA group (Table 2). Cardiopulmonary bypass times and aortic cross clamp times were significantly longer for the HCA group. Patients in the HCA group had higher rates of POND within the first 7 and 30 days postoperatively than the non-HCA group (Figure 1). After risk adjustment, HCA was not significantly associated with 30-day POND, whereas surgery status (urgent and emergency), history of prior cardiac surgery, and cardiopulmonary bypass times were (Table 3).

CONCLUSION: Patients who underwent surgery that required HCA experienced significantly higher risks of POND than patients without HCA. While HCA may contribute to an increased risk of POND, it was not identified as a significant predictor for POND.

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Figure 1. Postoperative neurocognitive dysfunction after cardiac surgery during the postoperative day 0-7 period or the postoperative day 0-30 (or until discharge) period. Gray bars represent patients who had not undergone hypothermic circulatory arrest; black bars represent patients who had.

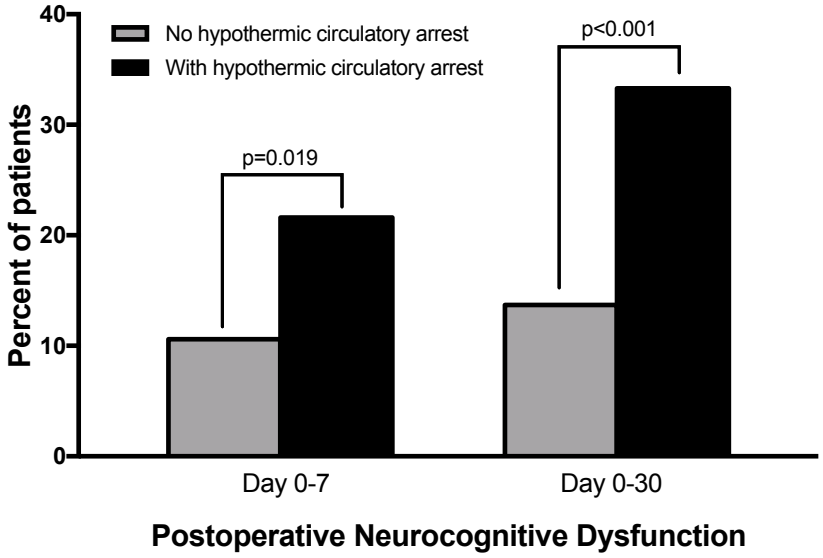

Table 1. Patient characteristics.

	Total (N=570)	Hypothermic circulatory arrest		p value
		No (N=519)	Yes (N=51)	
Age, mean (SD)	63.1 (12.6)	63.4 (12.2)	56.0 (15.7)	0.061
Female gender, N (%)	165 (28.9%)	148 (28.5%)	17 (33.3%)	0.469
Body mass index, mean (SD)	28.4 (5.8)	28.3 (5.7)	29.5 (6.9)	0.159
Prior cardiac surgery	99 (17.4%)	83 (16.0%)	17 (33.3%)	0.006
Diabetes, N (%)	153 (26.8%)	144 (27.7%)	9 (17.6%)	0.120
Renal failure requiring dialysis, N (%)	19 (3.3%)	18 (3.5%)	1 (2.0%)	0.567
Hypertension, N (%)	433 (76.0%)	397 (76.5%)	36 (70.6%)	0.346
Tobacco Use, N (%)	289 (0.5)	263 (0.5%)	26 (0.5%)	0.967
Chronic Lung Disease, N (%)				0.704
No	470 (82.5%)	427 (82.3%)	43 (84.3%)	
Mild	65 (11.4%)	61 (11.8%)	4 (7.8%)	
Moderate	25 (4.4%)	22 (4.2%)	3 (5.9%)	
Severe	5 (0.9%)	4 (0.8%)	1 (2.0%)	
Severity unknown	5 (0.9%)	5 (1.0%)	0 (0.0%)	
Peripheral Arterial Disease, N (%)	81 (14.2%)	72 (13.9%)	9 (17.6%)	0.461
Prior stroke, N (%)	71 (58.2%)	67 (58.3%)	4 (57.1%)	0.954

N, number; SD, standard deviation.

Table 2. Surgery characteristics.

	Total (N=570)	Hypothermic circulatory arrest		p-value
		No (N=519)	Yes (N=51)	
Surgery status, N (%)				< 0.001
Elective	302 (53.0%)	273 (52.6%)	29 (56.9%)	
Urgent	245 (43.0%)	234 (45.1%)	11 (21.6%)	
Emergent	23 (4.0%)	12 (2.3%)	11 (21.6%)	
Cardiopulmonary Bypass Time, mean (SD)	152.8 (73.7)	144.3 (67.6)	239.5 (77.9)	< 0.001
Cross Clamp Time (min), mean (SD)	111.8 (59.7)	108.1 (56.6)	153.2 (76.3)	< 0.001
Total Circulatory Arrest Time (min), mean (SD)			38.1 (37.1)	

Min, minute; N, number; SD, standard deviation.

Table 3. Predictors of postoperative neurocognitive dysfunction during the first 30 days after cardiac surgery

	Odds ratio (95% confidence interval)	p-value
Hypothermic circulatory arrest	1.50 (0.68-3.15)	0.301
Age	1.01 (0.99-1.03)	0.316
Male gender	1.07 (0.63-1.85)	0.808
Urgent surgery	1.74 (1.05-2.90)	0.032
Emergency surgery	5.99 (2.25-16.03)	<0.001
Prior cardiac surgery	1.88 (1.03-3.36)	0.035
Cardiopulmonary bypass time	1.01 (1.00-1.01)	0.003

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 11

Propofol Modulates the Stemness and Migration of Cancer Stem Cells Derived from Lung Tumor-Derived Brain Metastases and their Interaction with Glial Cells

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INTRODUCTION: Recent studies demonstrated the effects of anesthesia on tumor progression and patient survival in solid tumors.[1] Various mechanisms have been proposed, including direct effects on tumor cells and indirect effects via activation of the immune system.[2] However, there is less information on anesthetic effects in brain tumor patients. While some reports are conflicting or inconclusive, there is also evidence that propofol is beneficial in certain brain tumors.[3] Brain metastases (BM) are the most common brain tumors in adults and a major cause of cancer morbidity and mortality. Metastatic tumors develop following infiltration of the brain through the blood brain barrier of cells from primary tumors such as lung, breast, melanoma, and colorectal cancers. BM are treated with combination therapies, including surgery, radiotherapy, chemotherapy, and immunotherapy, however the prognosis of patients with BM remains dismal. In this report we investigated the effects of propofol on cancer stem cells derived from human lung cancer brain metastases and crosstalk with microglia.

METHODS: In this study we employed cancer stem cells derived from lung tumor-derived brain metastases (BM-CSCs) and analyzed the effects of propofol on the apoptosis, self-renewal, mesenchymal transition, and migration of these cells. Cell apoptosis was determined using LDH assay and caspase 3 activation; expression of mesenchymal transition was analyzed using qRT-PCR mesenchymal and cell migration by a transwell assay. One of the major factors that determine the establishment of new metastases depends on a complex interaction of the tumor and the microenvironment niche. We therefore also analyzed these effects of propofol on cancer stem cell self-renewal and apoptosis in co-culture with human microglia cells. We further examined the effects of propofol on the activation/polarization of microglia in co-culture with CSCs using qRT-PCR.

RESULTS: We found that propofol exerted a dose-dependent inhibitory effect on BM-CSCs self-renewal and proliferation. These effects were already observed at 25 microM propofol. At concentrations higher than 100 microM, propofol exerted a large degree of cell death (Figure). In addition, propofol decreased the expression of the stemness markers SOX2 and Nanog and those of mesenchymal transit, CD44 and ZEB1. At lower concentrations, propofol decreased BM-CSC migration. Co-culturing BM-CSCs with microglia increased the self-renewal and stemness of the CSCs, and propofol treatment abrogated this increase as well. Propofol also promoted the M1 phenotypes of co-cultured microglial cells and decreased the expression of TGF-beta, while increasing that of IL-1 beta.

CONCLUSION: Propofol exerted anti-tumor effects on BM-CSCs ranging from inhibition of cell renewal, proliferation, mesenchymal transition, and cell death. In addition, propofol abrogated the pro-tumor interaction of BM-CSCs and microglia. Inhibition of stemness and mesenchymal transit decreases the oncogenic phenotypes of the CSCs and is expected to inhibit tumor progression. The activation of microglia M1 phenotype promotes anti-tumor effects via activation of the immune system and by inhibiting tumor growth. The propofol effects we observed were obtained in a range of concentrations suggesting that its effects could be exploited as a GA of choice during tumor resection. Further studies are planned using tumor xenografts in mice to explore if propofol (in the correct dosage and interval) could be effective as an anti-tumor agent in sub-anesthetic doses, either alone or in combination with radiation or other treatments.

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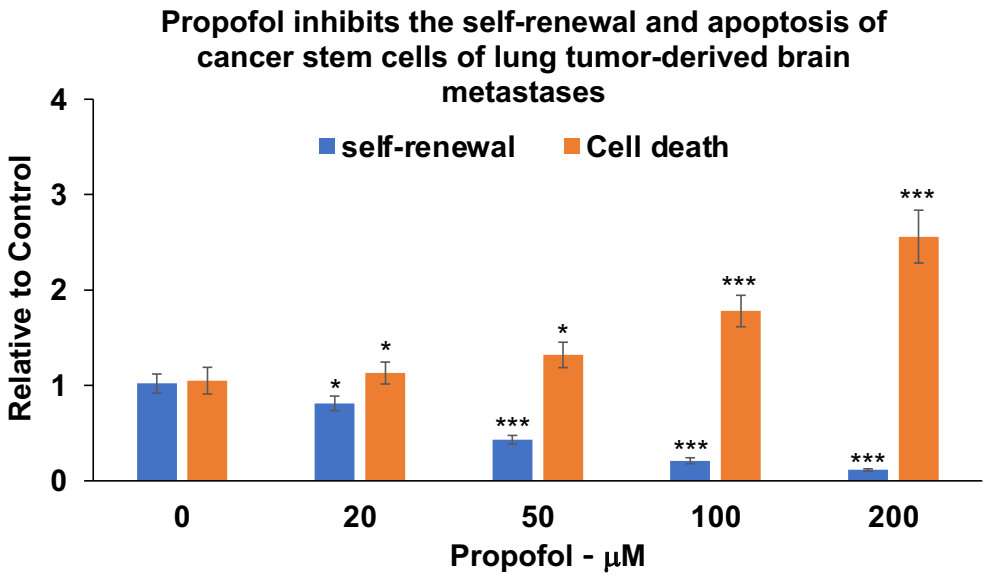

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 12

Altered complexity and network integration during anesthesia and sleep

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INTRODUCTION: We seek to understand the neural correlates of loss and recovery of consciousness by exploring common mechanisms during anesthesia and sleep[1]. Leading theories of consciousness predict that loss of consciousness (LOC) during anesthesia and sleep is precipitated by reorganization of brain networks critical for consciousness[2]. We used an analysis of resting state functional connectivity called diffusion map embedding (DME;[3]) to identify these organizational changes. DME maps data into a space in which distance represents similarity in connectivity to the rest of the sampled network, and has been used previously to demonstrate the hierarchical structure of cortical networks[4] and to track changes in that structure in response to treatments, disorders, and aging[5]. We investigated changes in cortical networks across arousal state using DME applied to functional connectivity derived from resting state intracranial electroencephalography (iEEG) recordings in neurosurgical patients.

METHODS: Resting state intracranial recordings were obtained during induction of propofol anesthesia or during sleep from adult neurosurgical patients implanted with electrodes (propofol: n = 15 total; sleep: n = 13 total) in temporal, parietal, and frontal cortex to identify epileptic foci. Three arousal states were compared during anesthesia [pre-drug wake (WA), sedated/responsive (S) and unresponsive (U), determined by OAA/S] and five in sleep [wake (WS), N1, N2, N3, and REM, determined by standard polysomnography]. During pre-processing, channels in the white matter or seizure foci were excluded, and artifact rejection used to excluded interictal spikes. Channel-by-channel adjacency matrices were computed as pairwise gamma (30-70Hz) orthogonalized power envelope correlations[6]. Adjacency matrices were thresholded (top 33%) and normalized to yield the transition probability matrix P, which was analyzed using DME. The eigenvalue spectrum of P ($|\lambda i|$) was used to calculate effective dimensionality (estimated as the quadratic entropy: $(\Sigma \lambda i)2/(\Sigma \lambda i2)$), a measure of network redundancy. Pairwise distances in the embedding space, a measure of network integration, were calculated and compared across states.

RESULTS: Embeddings in states involving reduced consciousness (U, N2, N3) had lower mean effective dimensionality but higher variability over time compared to corresponding states (S/WA and N1/WS). REM sleep had similar effective dimensionality to WS. The increased variability in U, N2 , and N3 was especially evident when the time resolution of the analysis was increased (using 10-sec rather than 60-sec data segments). In this case, some data segments exhibited 'wake-like' effective dimensionality while others had reduced values, suggesting fluctuating arousal or awareness states. No individual brain region was responsible for these changes, suggesting a global rather than centralized functional reorganization with LOC. However, specific inter-ROI embedding distances (PFC-auditory cortex; PFC-limbic) increased in U compared to WA/S, and in N2/N3 compared to WS/N1/REM, consistent with reduced network integration upon LOC.

CONCLUSION: Decreases in effective dimensionality reflect decreased network complexity (increased redundancy) associated with states of reduced levels of arousal and awareness (U, N2, N3). Increased variability may reflect behavioral state changes between dreaming (disconnected consciousness) and unconsciousness. Increases in inter-ROI distances in these states reflect impaired integration and information sharing that may be critical to normal waking consciousness.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 13

Orexin neurons regulate anesthesia arousal and analgesia through broad projections

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INTRODUCTION: Orexin (Ox) neurons are localized in the tuberal part of the lateral hypothalamus (LHA), and have widespread projections in the brain[1-3]. Ox was found to have a variety of roles in sleep-wake control, feeding, autonomic, and neuroendocrine homeostasis, thermoregulation, and memory formation[4,5]. We aim to systematically map the whole Ox projections in the mouse brain, which is essential for future studies of the functional role of Ox neurons. Anesthesia has advanced tremendously from the demonstration of ether as a general anesthetic drug in 1846, nevertheless, the mechanisms remain to be studied[6]. It has been shown in animal experiments that the Ox circuit is involved in anesthesia emergence speed, upper airway patency, autonomic tone, and gastroenteric motility, which are important aspects in anesthesia management[7,8]. We applied optogenetics tools to investigate the details of the involvement of Ox neurons in anesthesia. Optogenetics provides unparalleled spatial and temporal resolution. During the process, we found the expression of opsins in neurons through the infection by adeno-associated virus (AAV) provides an excellent tool to image the neuron projections due to the high level of cell membrane surface expression of the fluorophore coupled with the opsin. Here we report the structural projections of the Ox neurons in the mouse brain and the functional effects of activating Ox neurons with the optogenetic tools.

METHODS: We used the Ox-Cre transgenic mice to specifically express optogenetic opsins in the Ox neurons by injecting adeno-associated virus carrying the opsin and fluorophore genes. After validation of the expression, we systematically mapped the neuroanatomy of the orexin projections in detail in the mouse brain with confocal and light-sheet microscopy. To investigate the effects on anesthesia and analgesia, we implanted the optical fibers into the LHA and stimulated the fibers while testing the animal behaviors, including arousal, emergence and hotplate tests.

RESULTS: Our results showed that orexin cell bodies located in the lateral hypothalamus area (LHA) and the fibers projected broadly throughout the brain, particularly to the nuclei related to arousal and pain control. Optogenetic activation of orexin neurons in LHA consistently elicited arousal while the animals were under 0.75% isoflurane, and shortened the emergence time after the animals were exposed to 2% isoflurane, and increased the paw withdrawal latency to 55,ÑÉ hotplate for the ChR2-mCherry group but not the control mCherry group.

CONCLUSION: 1. Orexin cell bodies located in the lateral hypothalamus area (LHA) and the fibers projected broadly throughout the brain, particularly to the nuclei related to arousal and pain control. 2. Optogenetic manipulations of Ox neurons significantly affect anesthesia states and pain tolerance, which suggested a crucial role of Ox in anesthesia and analgesia, and a potential therapeutic value.

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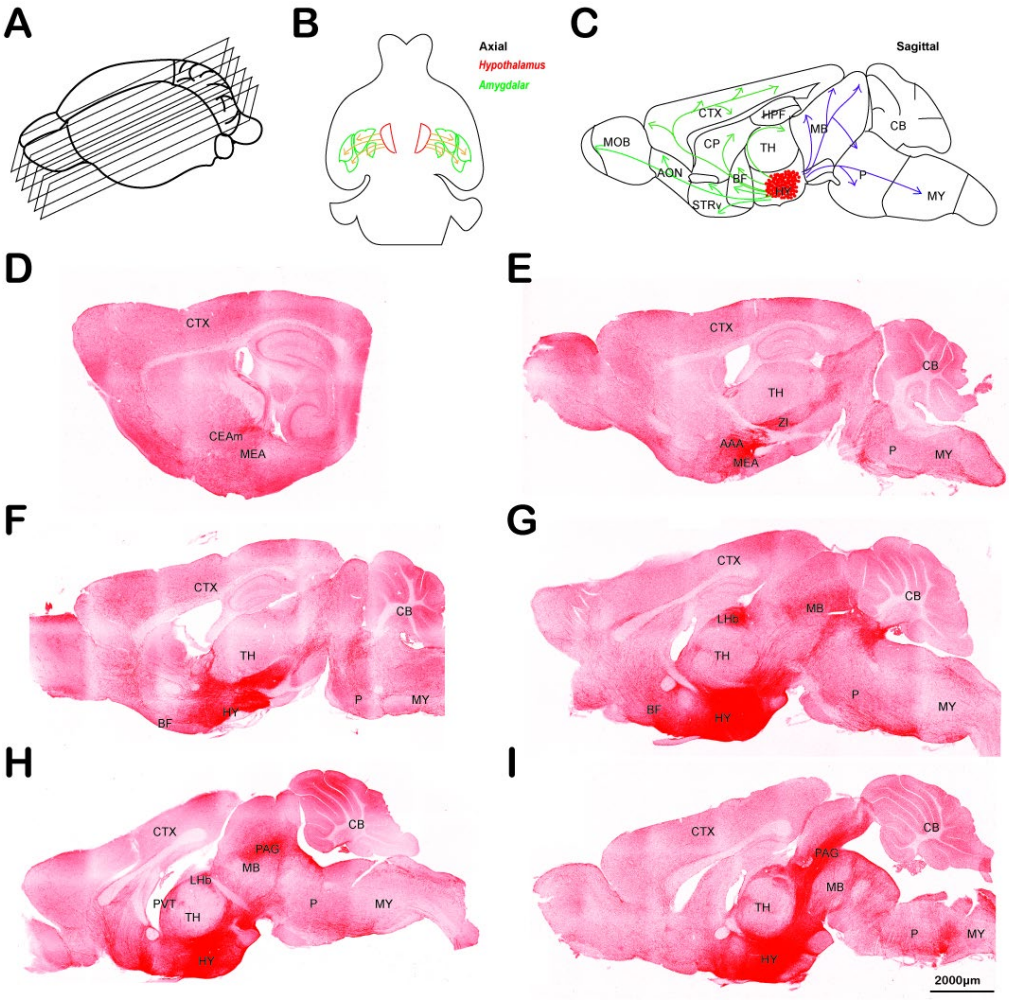

Fig. 1. Ox projections in sagittal planes. Ox-Cre mice were injected with AAV5-DIO-ChrimsonR-tdT into LHA. (A) Schematic diagram of the sagittal brain slices. (B and C) Schematic drawings of hypothalamic, lateral, rostral, and caudal projections of Ox neurons. (D-I) Representative confocal images (lateral to medial) showed projections of Ox neurons in sagittal planes. Scale bars: 2000 μm.

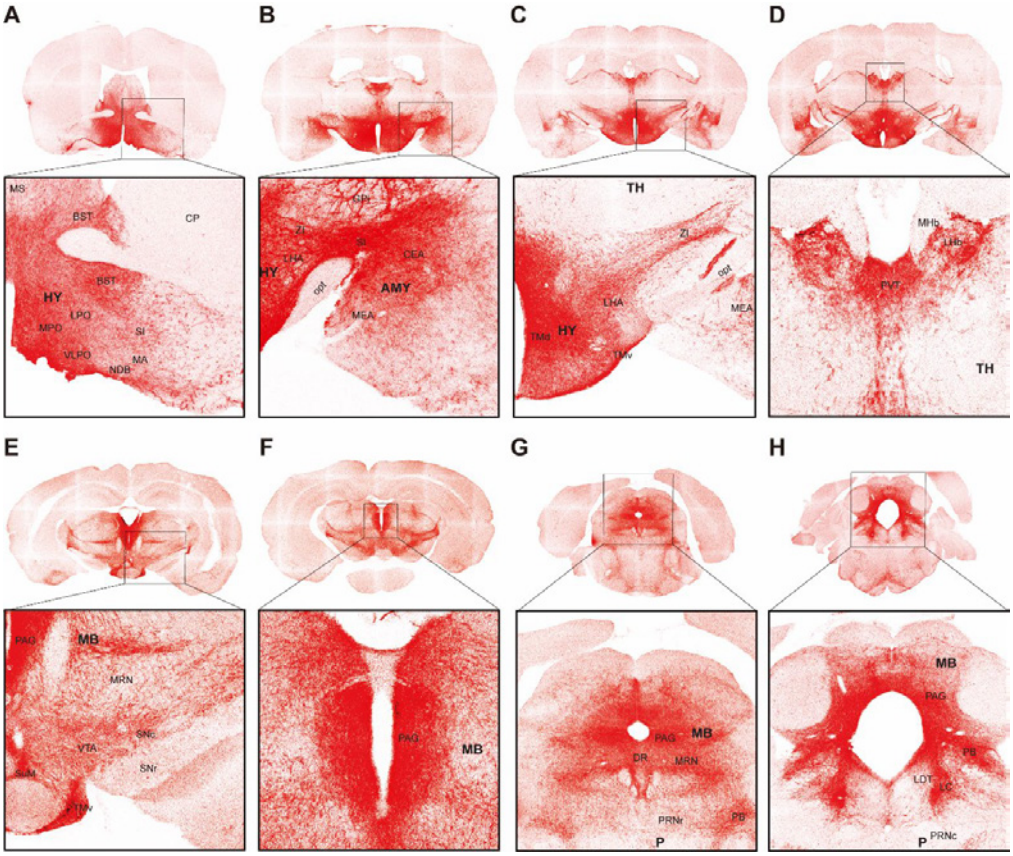

Fig. 2. Ox projections to the nuclei related to sleep-wake and pain control. Ox-Cre mice were injected with AAV_{retro}-DIO-ChR2-mCherry into LHA. The immunostaining of mCherry highlighted the projections of Ox fibers to the nuclei related to sleep-wake and pain control.

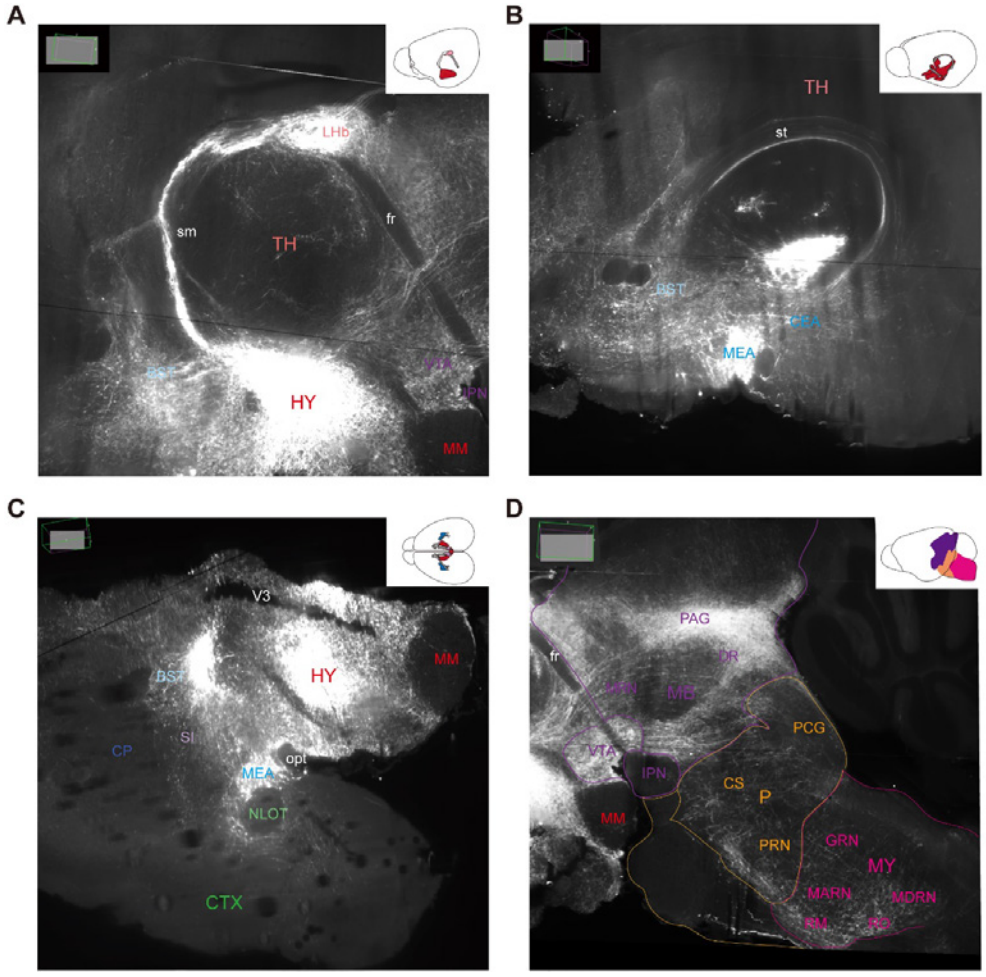

Fig. 3. Ox projection patterns revealed by the light-sheet microscope. Ox-Cre mice were injected with AAV_{retro}-DIO-ChR2-mCherry into the LHA. A brain hemisphere was used for light-sheet imaging after clarification and staining with anti-mCherry. The images here were chosen to show certain particular features of the Ox projections which were not easily identified on the confocal images. (A) At the view close to sagittal, along the anterior surface of the TH, a fiber bundle through sm was noted to project from HY to LHb. The fiber tract connecting LHb and IPN, fr, was clearly noted with negative staining. (B) Another fiber tract, st, was noted to connect BST to CEA and MEA. (C) On a transverse plane at the ventral hypothalamus level was noted the relative orientation of several structures, including v3, Ox cell bodies at HY, MM, BST, SI, MEA, NLOT, opt, CP, and CTX. (D) A sagittal plane highlighted the reticular pattern of Ox projections in the MB, P, and MY.

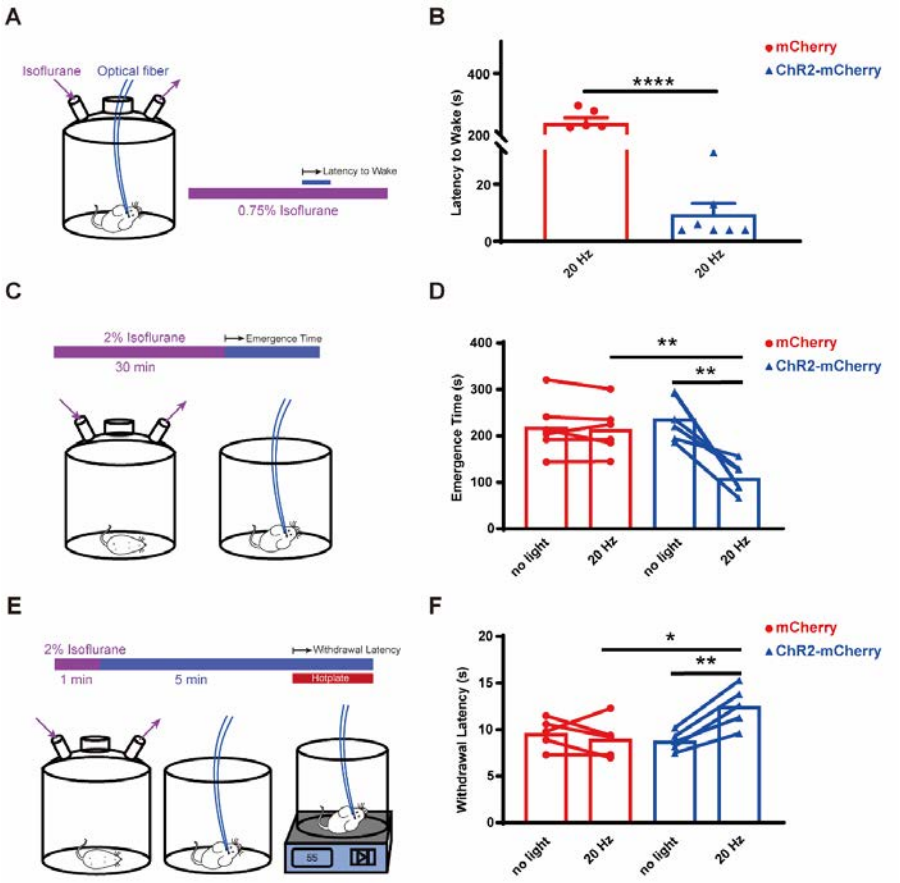

Fig. 4. Optogenetic activation of Ox neurons facilitated arousal and pain tolerance. (A) Schematic diagram showing the arousal test under 0.75% isoflurane. Blue light (473 nm) was applied after 10 minutes equilibration and latency to wake is recorded. (B) Optogenetic stimulation of LHA elicited early arousal, while the animals were still under 0.75% isoflurane, for the ChR2-mCherry group but not the mCherry group. (C) Schematic diagram showing the emergence test after 2% isoflurane. Blue light was started when isoflurane was turned off. (D) Optogenetic stimulation of LHA significantly shortened the emergence time, after 30 min exposure to 2% isoflurane, for the ChR2-mCherry group but not the mCherry group. Without stimulation, the ChR2-mCherry group has similar emergence time to the mCherry group. (E) Schematic of the hotplate test. (F) Optogenetic stimulation of LHA increased the withdrawal latency to 55°C hotplate for the ChR2-mCherry but not the mCherry group. Without stimulation, the ChR2-mCherry group has similar withdrawal latency to the mCherry group. All data are expressed as mean ± S.E.M. Significance was analyzed using paired t-test within the same group of animals with or without optogenetic stimulation, and unpaired t-test between different groups. **P* <0.05, ***P* < 0.01, *****P* <0.0001.

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Non-invasive MRI measurements of CSF secretion rate and choroid plexus tissue perfusion in rats during anesthesia with dexmedetomidine and low-dose isoflurane versus isoflurane only

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INTRODUCTION: Circulation of cerebrospinal fluid (CSF) in the central nervous system (CNS) is critical for normal brain function and nearly 80% of CSF production is being secreted by the choroid plexuses (CP). For decades the CSF production rate has been measured using the invasive tracer dilution method[1-3]. Recently, a non-invasive arterial spin labeling (ASL) MRI technique was applied to measure CSF barrier (BCSFB) mediated delivery of arterial blood water into ventricular CSF which is representative of choroidal CSF secretion[4, 5]. Here we used this novel non-invasive approach to characterize the effects of two anesthetics regimens on the choroidal the CSF production rate in rats.

METHODS: All the experiments were approved by the local Institutional Animal Care and Use Committee. A total N=12 of female Wistar Kyoto rats (9-12 months old) were used. The MRI study was designed so that each rat was randomly selected and scanned twice (1-week apart) under isoflurane (ISO) or dexmedetomidine with low dose ISO (DEXM-I) as described previously[6]. All imaging acquisitions were performed on a Bruker 9.4T/16 MRI equipped with a volume transmit/receive imaging coil interfaced with Paravision 6. The ASL sequence designed captured perfusion signals at two echo times (23ms and 150ms) and the net CP tissue perfusion signals was modeled as the sum of partial contributions from pure CP tissue perfusion and BCSFB mediated delivery of arterial blood water into ventricular CSF. Regions of interest were manually drawn to extract perfusion weighted signals and a standard single compartment model was implemented to calculate the CP apparent tissue perfusion, CP pure tissue perfusion, and BCSFB.

RESULTS: Irrespective of the anesthetics, pure CP blood perfusion was two to three folds higher than cortical blood flow and BCSFB was only 25% of the pure CP perfusion values. A paired t-tests with Bonferroni correction was performed to compare the effects of DEXM-I vs ISO and yielded significant differences between the two anesthetics in both CP perfusion and cortical perfusion ($P<0.001$). Arterial transit times (ATTs) were also significantly lower ($P<0.001$) in ISO compared to DEXM-I. Although Pearson's correlation analyses yielded significant correlations ($P<0.05$) between CP perfusion and BCSFB, there was no difference in BCSFB across the two anesthetic regimens.

CONCLUSION: Anesthetics effects on perfusion and BCSFB are of particular interest because CSF circulation in the glymphatic system plays a critical role for waste removal such as amyloid-beta and tau proteins and the glymphatic function is very sensitive to alpha2 adrenergic agonists (Dexmedetomidine)[7]. Reduced cortical and CP perfusion with DEXM-I compared to pure ISO anesthesia was an expected finding given that DEXM is potent and selective agonist of alpha2 adrenergic receptors and a vasoconstrictor[8, 9]. Although CP perfusion and BCSFB were linearly correlated, BCSFB was not significantly different between the two anesthetics indicating that the magnitude of water exchange from CP to CSF is not directly proportional to the magnitude of change in blood perfusion of the choroid plexus.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 15

Blood glutamate scavenging with pyruvate as a novel preventative approach for depressive-like behavior following traumatic brain injury in a rat model

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INTRODUCTION: Depression is a common and serious complication following traumatic brain injury (TBI). Both depression and TBI have independently been associated with pathologically elevated extracellular brain glutamate levels. These increased glutamate levels have been strongly correlated with poor outcomes. One method of eliminating excess brain glutamate is by utilizing the naturally occurring brain-to-blood glutamate efflux, known as blood glutamate scavenging. In the setting of TBI, blood glutamate scavenging with pyruvate has been widely shown as an effective method to provide neuroprotection by reducing blood glutamate and subsequent brain glutamate levels.

METHODS: Here we evaluated pyruvate as a novel approach in the prevention of post-TBI depression-like behavior in a rat model. Male rats were divided into four groups: 1) sham-operated control with pyruvate, 2) sham-operated control with placebo, 3) post-TBI with placebo, and 4) post-TBI given preventative pyruvate. Rats were assessed for depressive-like behavior, neurological status, and glutamate levels in the blood and brain.

RESULTS: Post-TBI neurological deficits with concurrent elevations in glutamate levels were demonstrated ($p<0.01$), with peak glutamate levels 24 h after TBI. Following TBI, the administration of prophylactic pyruvate led to reduced glutamate levels ($p<0.05$), improved neurologic recovery ($p<0.01$), and improved depressive-like behavior ($p<0.01$).

CONCLUSION: Glutamate scavenging with pyruvate may be an effective prophylactic option for post-TBI depression by reducing associated elevations in brain glutamate levels.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 16

Effects of Continuous Positive Airway Pressure (CPAP) in the Rat on Systemic Physiology, CSF Flow, and Glymphatic-Lymphatic Transport

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INTRODUCTION: Cerebrospinal fluid (CSF) circulation is required for brain waste disposal via the glymphatic system[1]. Aging is linked to cognitive dysfunction and associated with a decline in CSF production[2]. Hence, there has been a growing interest in therapies directed towards sustaining CSF flow to minimize life-long toxic brain waste accumulation. Spontaneous, deep inspiratory breathing is one of the driving forces of CSF flow in the human central nervous system (CNS)[3,4]. Obstructive sleep apnea (OSA) is associated with intermittent sleep, diminished functional residual capacity (FRC) and hypoxic episodes which may interfere with CSF flow. Further, OSA shares epidemiological overlap with Alzheimer's disease[5]. Here we designed a nasal continuous positive airway pressure (CPAP) device for rats. Our goal was to characterize the effect of improved oxygenation and FRC with CPAP in dexmedetomidine-sedated rats on CSF flow and glymphatic transport.

METHODS: Experiments were approved by the local Institutional Animal Care and Use Committee. A 3D printer created the MRI-compatible CPAP device (Fig. 1). Sprague Dawley rats (250-280g) were used to test the effect of CPAP device on vital signs and arterial blood gases (ABG) in comparison to a nose cone. The rats were fasted overnight and anesthetized with dexmedetomidine and low-dose-isoflurane and breathed spontaneously[6]. Six rats underwent the experiment without CPAP, and 6 were exposed to CPAP set at 3mmHg[7]. Invasive blood pressure was measured and ABGs were collected via a femoral arterial catheter, at 120min and 180min after induction of anesthesia while the CPAP pressure was 3mmHg.

RESULTS: We discovered that a rapid increase of the CPAP chamber pressure to 3mmHg resulted in apneic episodes and paradoxical labored breathing in rats similar to what has been reported in neonates[8]. To overcome this initial stress, we gradually increased the chamber pressure, starting at 0.5mmHg and then raising it in small increments of 0.5mmHg every 5 minutes until reaching 3mmHg. This procedure was well tolerated by the rats. Fig. 2 shows results from the non-CPAP vs CPAP groups. There were no statistical significances in the mean arterial PCO2 across groups. However, the mean PO2 was significantly higher in CPAP group ($p<0.05$). There were no differences in heart rate or respiratory rate across groups (Fig. 2).

CONCLUSION: We designed a CPAP device for anesthetized rats. The CPAP pressure was increased slowly to allow for a gradual increase in end-expiratory lung volume above the residual volume[9]. This allowed the compliant chest wall in the small rat to stabilize at each higher CPAP level, thereby reducing the energy needed to withstand the lung recoil. Our experiments showed that 3mmHg CPAP was well tolerated and increased oxygenation over the ~2-3 h long experiment. We have pre-tested the device in the MRI (Fig. 1) and studies to characterize the effect of CPAP on CSF flow dynamics and glymphatic transport are ongoing.

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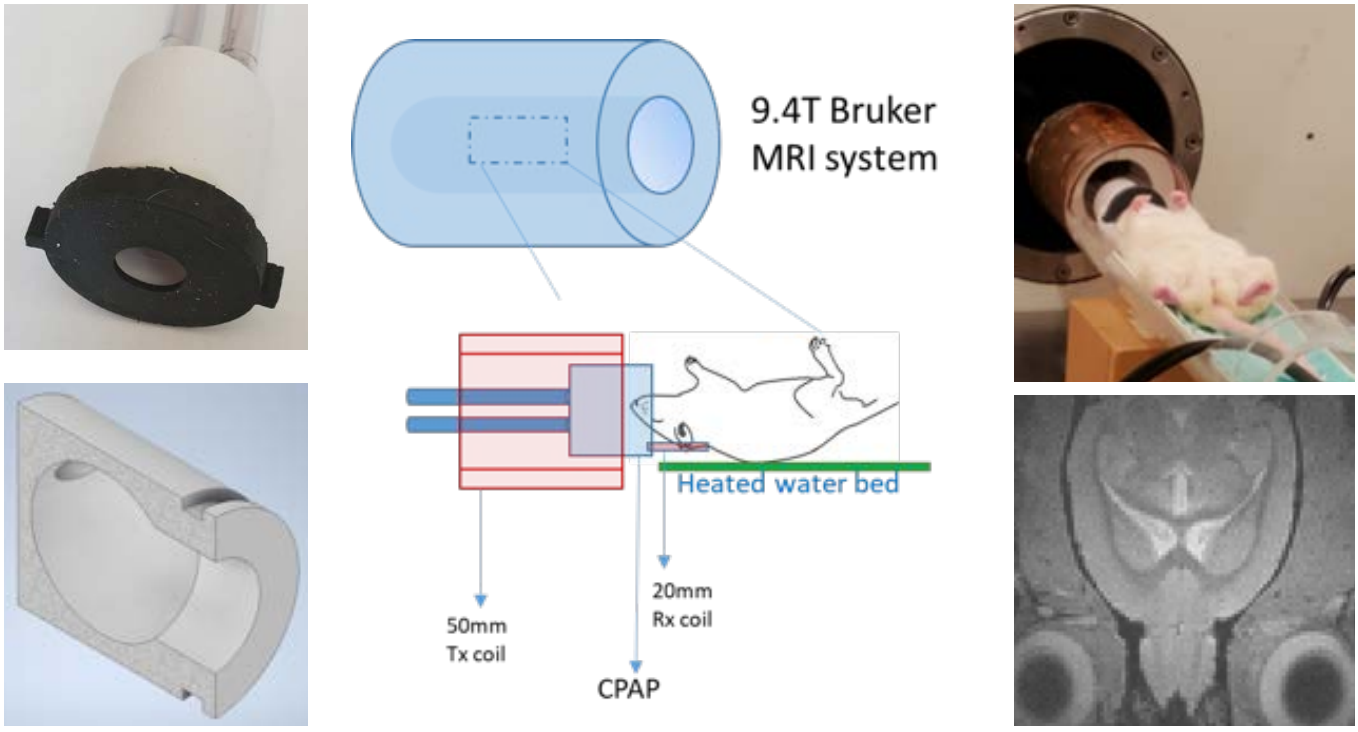

Fig.1 Top left: Photo of the nasal CPAP design with the soft rubber seal. Bottom left: Illustration of the CPAP design highlighting its spherical center. Center: Illustration of CPAP setup is inside the 9.4T Bruker MRI system. Top right: Photo of anesthetized rat positioned in the CPAP device before entering the MRI. Bottom right: Anatomical 2D proton density weighted MRI image at the level of the cerebral ventricles (horizontal section). Spatial resolution = 0.234 x 0.234 x 0.234 mm

Fig. 1

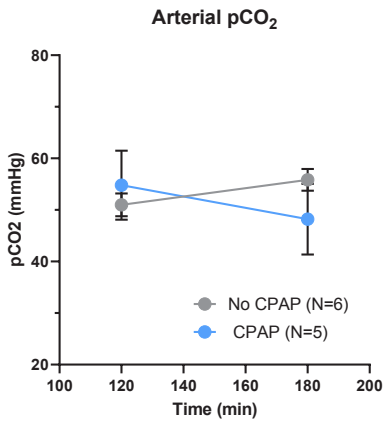

Fig 2A Changes in pCO_2 levels over 3 hours in non-CPAP vs CPAP groups (p-value > 0.05)

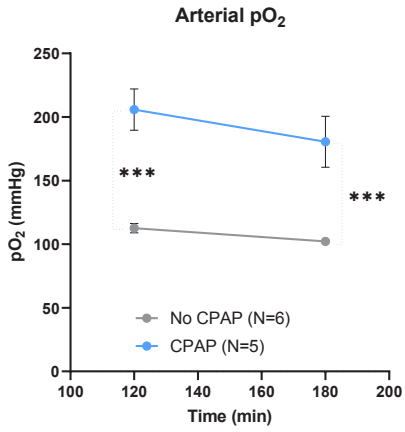

Fig 2B Statistically significant higher pO_2 levels in CPAP group vs non-CPAP group over 3 hours (***p-value < 0.001)

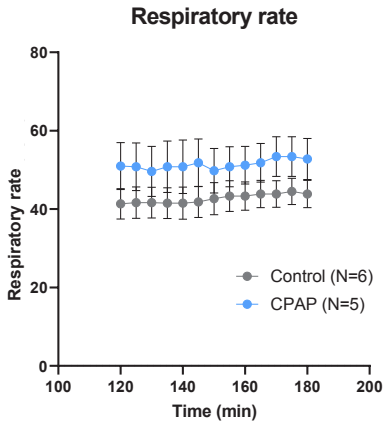

Fig 2C Respiratory rates trend slightly higher in CPAP group vs non-CPAP group (p-value > 0.05)

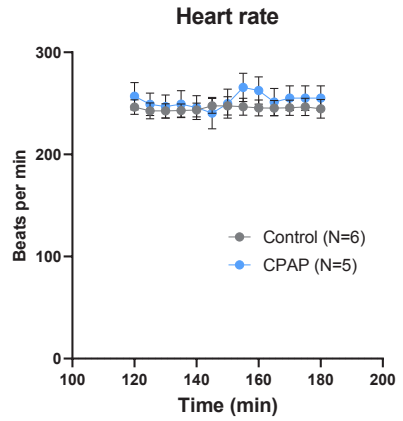

Fig 2D Comparable heart rates over 3 hours in non-CPAP vs CPAP groups (p-value > 0.05)

Fig. 2

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 17

Glutamatergic and Adrenergic Neurons Mediate Alpha-2-Agonist-Induced Sedation and Hypnosis in Mice

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INTRODUCTION: α2-adrenergic agonists induce hypnosis in part through their actions on the neural circuits regulating endogenous arousal[1,2] and produce a hypnotic state most similar to NREM sleep.[3] While downstream pathways involved in α2-agonist hypnosis have been characterized[4,5] the precise neuronal population(s) on which α2 agonists act to produce sedation and hypnosis are unknown.

METHODS: We generated knock-in mice with LoxP sites flanking the Adra2a gene (Adra2af/f) and crossed them with tissue specific Cre recombinase (CRE) driver mice under the control of the Snap25 (n=10), Dbh (n=18), or Vglut2 (n=10) promoters to create cell-specific knockouts of Adra2a or controls (n=9). Cell specific deletion of Adra2a was assessed using fluorescent in-situ hybridization. Hypnotic, sedative, and physiologic actions of 0, 300, or 1000 µg/kg dexmedetomidine IP (Dex) were determined using the righting reflex, rotarod assay, and spontaneous locomotion, as well as core body temperature. To assess motor-independent measures of dexmedetomidine, a subset of mice from each genotype (n=5-7) was chronically implanted with EEG and EMG leads . Following recovery, EEG/EMG mice were challenged with Dex. Signals were band-pass filtered from 1-100 Hz. Spectral power estimation over M1 was computed over 5s non-overlapping windows using previously published code.[6] All analyses used Matlab 2021a or Prism 9.2.

RESULTS: Adra2af/f controls showed expected changes in behavioral hypnosis (Fig 1), temperature (Fig 2), and sedation (rotarod distance and spontaneous movement, Fig 3) in response to Dex. The pan-neuronal knockout Adra2af/f:Snap25-Cre mice exhibited Dex resistance to all behavioral and physiologic endpoints. Mice with deletion of Adra2a in Vglut2 (primarily subcortical glutamatergic) and Dbh (adrenergic) neurons showed resistance to loss of righting equivalent to neuronal knockouts. While the Dbh-driven knockouts showed partial resistance to sedation and temperature change, mice missing Adra2a in Vglut2 neurons were indistinguishable from pan-neuronal knockouts. Spectral analysis of the EEG mirrored behavior, as Snap25-Cre and Vglut2-Cre showed high resistance to EEG changes and Dbh-Cre partial resistance to EEG changes after dexmedetomidine administration. (Fig 4, 5.)

CONCLUSION: The resistance to sedation and hypnosis shown by the glutamatergic and adrenergic Adra2a knockouts suggests that α2 agonists act through multiple neuronal subtypes to cause sedation and hypnosis. Additional glutamatergic sub-populations, beyond the previously-described NOS1 group, likely contribute to the sedative-hypnotic and theromregulatory actions of α2 adrenergic agonists. Adra2a knockout in adrenergic neurons produces a partial resistance to α2 sedative-hypnotic effects. Future studies will identify the glutamatergic population(s) responsible for sedation and whether and how adrenergic adrenergic neuronal pathways converge with those populations.

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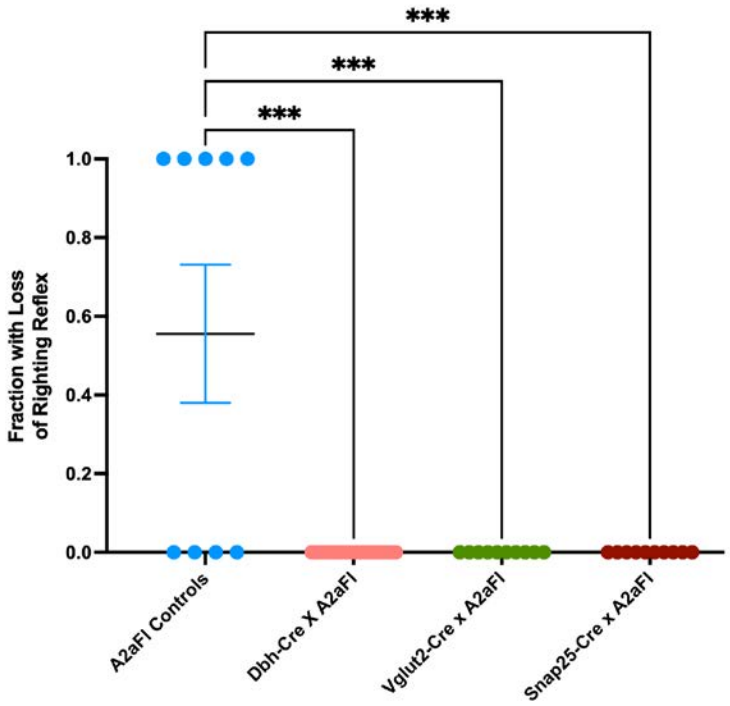

Figure 1. Behavioral Hypnosis Measured By Righting Reflex to IP Dexmedetomidine. Mice were given intraperitoneal saline, 0.3 mg/kg dexmedetomidine, or 1 mg/kg dexmedetomidine and righting reflex assessed 20 minutes after injection. No mice lost righting reflex at the 0.3 mg/kg dose, 1 mg/kg results shown here. Mean and SEM shown. One-way ANOVA. * p<0.05, ** p<0.01, *** p<0.001.

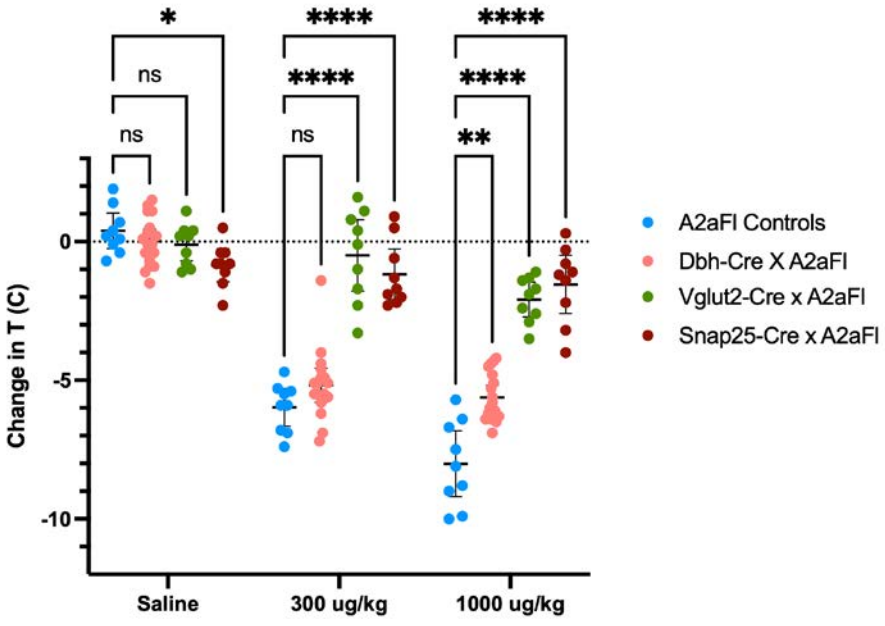

Figure 2. Temperature Change In Response to Dexmedetomidine. The Vglut2 cross and pan-neuronal knockout showed little temperature change 20 minutes after receiving dexmedetomidine, and significantly less change than controls. Adrenergic Adra2a knockouts show slightly less change than controls at the higest dose. 2-Way ANOVA with multiple comparrisons. * p<0.05, ** p<0.01, **** p<0.0001

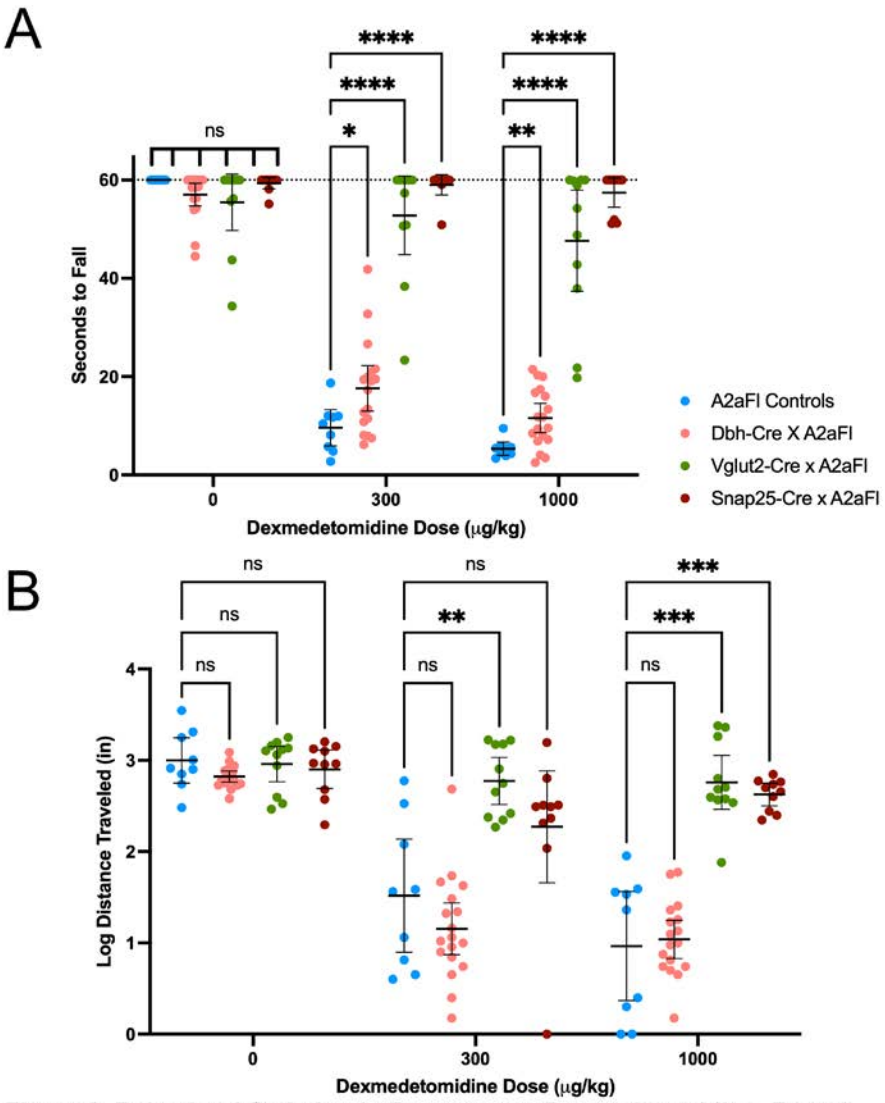

Figure 3. Behavioral Sedation in Response to Dexmedetomidine. Forced movement (rotarod, A) and spontaneous movement (beambreak measured over 1 hour, B) demonstrate profound resistance to sedation by pan-neuronal (Snap25) and Vglut2 Adra2a knockouts, while adrenergic (Dbh) Adra2a knockouts show partial resistance in the forced movement test. Individual values and means with 95% CI shown. 2-way ANOVA with multiple comparrisions, * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001.

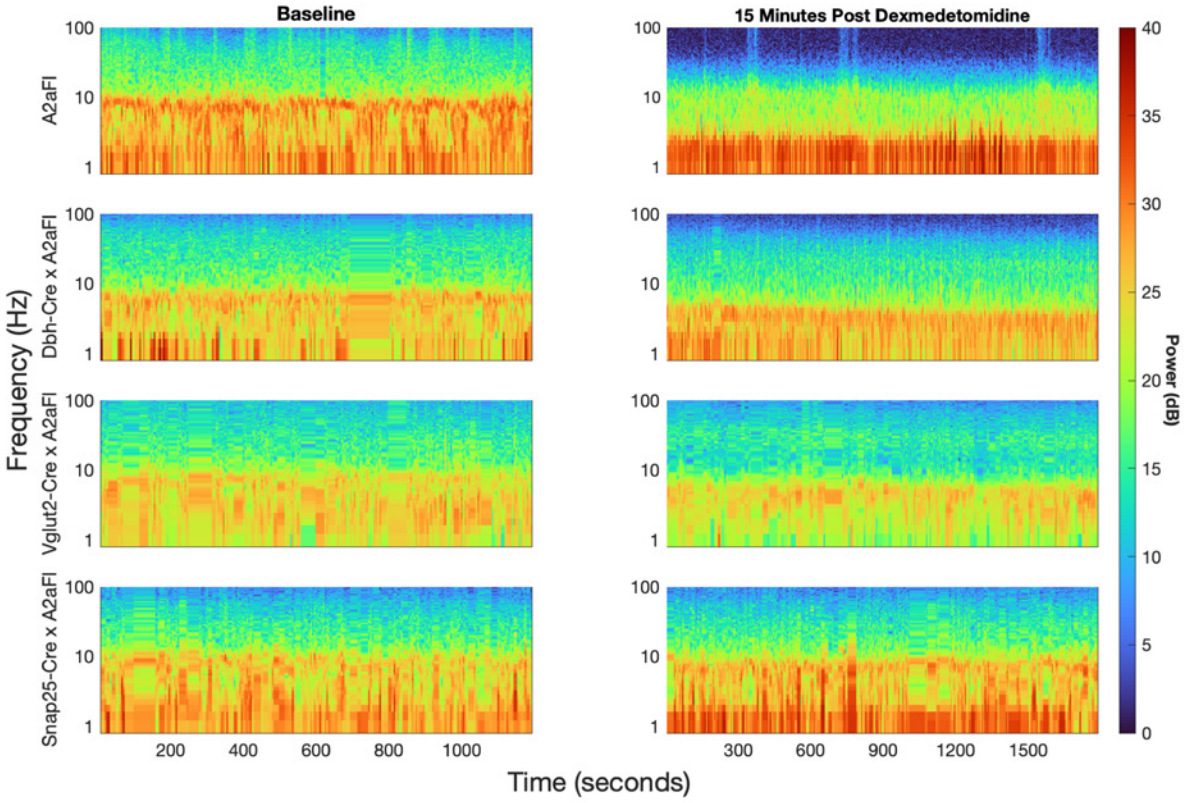

Figure 4. Representative Spectrograms of M1 Lead : 20 Minute Baseline and Minutes 15-45 Post 300 µg/kg IP Dexmedetomidine. Both pan-neuronal *Adra2a* knockouts (bottom) and Adra2a knockout in (the primarily subcortically-expressed) Vglut2 neurons produced profound resistance to spectral changes in EEG in response to dexmedetomidine. Adra2a deletion in adrenergic neurons produced a partial resistance to the effects of dexmedetomidine on EEG, with a decrease in alpha and high gamma power, as well as an increase in delta and theta power, though not to the degree seen in control animals.

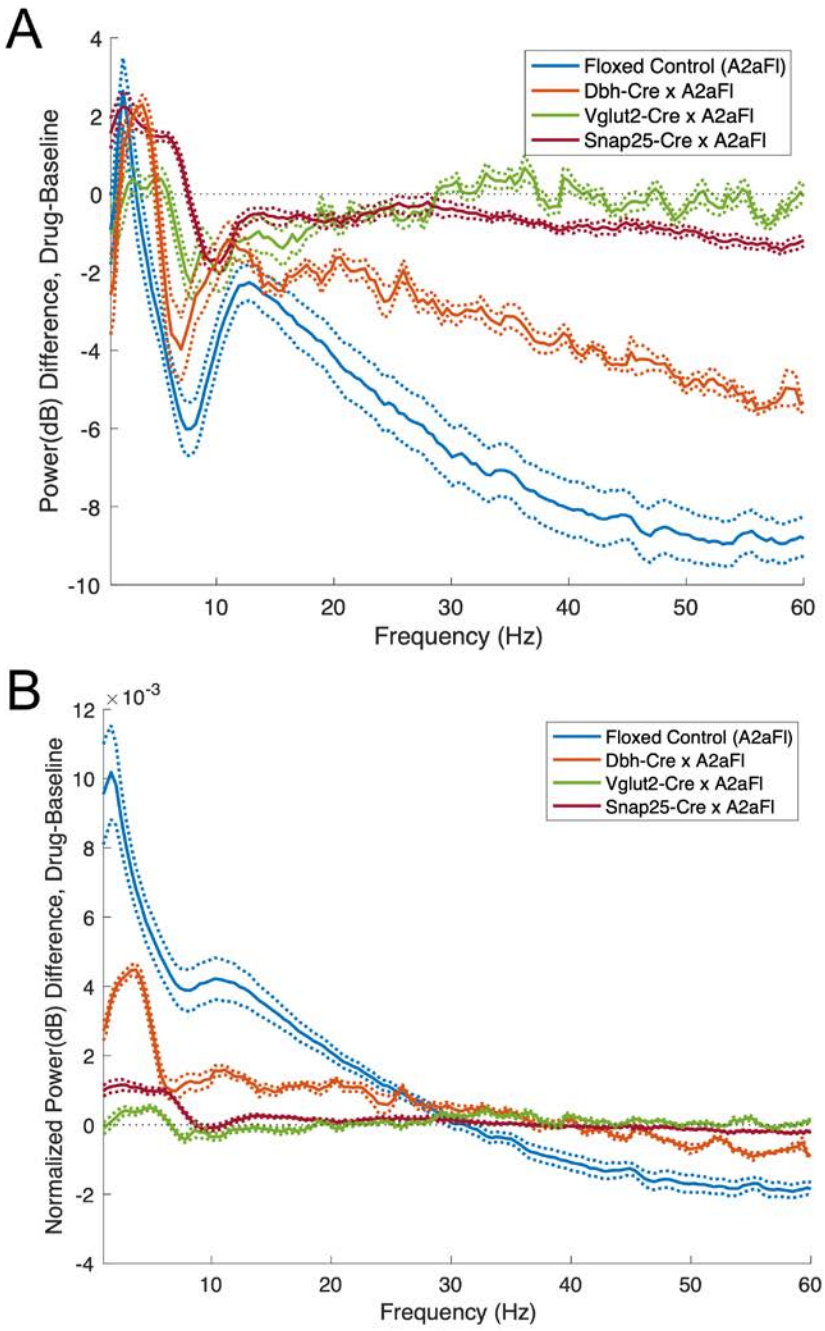

Figure 5. Mean Spectral Differences Between Pre- and Post-Dexmedetomidine Administration Mirror Degree of Sedation Seen in Behavior. The degree of difference from before to after dexmedetomidine in mean frontal spectra, non-normalized (A) and normalized to total power (B), corresponds to the relative level of sedation observed in each genotype. Floxed controls show the expected increase in delta power and supression of all other higher-frequency activity, while Vglut2 *Adra2a* knockouts and pan-neuronal *Adra2a* knockouts show only minor changes, and adrenergic *Adra2a* knockouts display intermediate changes between controls and pan-neuronal knockouts. Mean (solid) and 95% CI (dotted) spectra by genotype shown.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 18

A genetic variant causing alcohol intolerance leads to impaired recovery from propofol-induced general anesthesia in rodents

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INTRODUCTION: Alcohol has a major impact on an individual's sensitivity to general anesthetics. Chronic alcoholics require higher doses of general anesthetic agents, whereas acute intoxication increases sensitivity to anesthetics[1]. Over half a billion people are alcohol intolerant due to a genetic variant in the mitochondrial enzyme, aldehyde dehydrogenase 2 (ALDH2*2)[2]. This alcohol intolerance is due to the ALDH2*2 inactivating variant limiting the metabolism of the product of alcohol, acetaldehyde to acetic acid. However, little is known whether an intolerance to alcohol will alter general anesthetic sensitivity. Here we hypothesize that an inactivating genetic variant in ALDH2, known as ALDH2*2, will delay recovery from general anesthesia due to an alteration in the redox state at the mitochondria.

METHODS: ALDH2*2 knock-in mice are heterozygous for targeted insertion of the inactivating human ALDH2 point mutation into the native ALDH2 locus on a C57/BL6 background, which mimics the human phenotype[3]. Wild-type (WT) ALDH2 and ALDH2*2 male and female 12-18 week old mice were pair-wise placed in individual cages on heating pads. Baseline activity was recorded for 15 minutes followed by induction of general anesthesia by either propofol (200mg/kg, intraperitoneal) or 1.5% isoflurane in room air for 40 minutes. Open field activity was analyzed with Biobserve software by a blinded observer as an objective measure of recovery from general anesthesia. Primary astrocytes were cultured from the cerebellum of adult mice to assess mitochondrial function. The basal respiration, ATP-linked respiration, maximal and reserve capacities and non-mitochondrial respiration were measured using the Seahorse XF96 (Agilent). WT ALDH2 and ALDH2*2 primary astrocytes were incubated with 10 μM propofol for 60 minutes and cells were washed 3 times with assay medium prior to the assay. Liver homogenates from WT and ALDH2*2 mice and ALDH2 recombinant protein were used to quantify ALDH activity at baseline and in the presence of propofol or isoflurane. A two-way ANOVA with Bonferroni correction was used for multiple comparisons between WT and ALDH2*2 with statistical significance defined as p-value <0.05.

RESULTS: Representative open-field tracking images of WT ALDH2 and ALDH2*2 mice from the first 2.5 minutes following the return of the righting reflex (RR) from propofol-induced (Fig A) and isoflurane (Fig B) general anesthesia are shown. There was no significant difference between the two groups in the time to loss of RR (WT 177±17sec; ALDH2*2 234±22sec, n=8/group) or the duration of general anesthesia (WT 57±10min; ALDH2*2 75±15min, n=8/group). Importantly, there was a significant decrease in activity following the return of the RR in the ALDH2*2 compared to WT mice (Fig A, 53±7% vs 26±4%, respectively, n=8/group, p=0.03) that was specific to propofol. There was no significant difference in activity between WT and ALDH2*2 following emergence from isoflurane anesthesia (Fig B). At baseline, there was decreased ALDH2 activity from the liver of ALDH2*2 mice compared to WT ALDH2 mice (Fig E, 14.51±1.0, n=6 vs 26.4±1.8, n=4 [NADH] μM/μg/min, respectively, p=0.01). Isoflurane increased ALDH2 activity in WT recombinant protein (Fig D), as opposed to propofol which did not alter ALDH2 activity. Baseline cerebellar mitochondrial respiration was not different between WT and ALDH2*2, however, there was an increase in reserve capacity with and without propofol in the mitochondria of ALDH2*2 astrocytes (Fig E).

CONCLUSION: The ALDH2*2 genetic variant mice have delayed recovery from propofol-induced general anesthesia without altering emergence from isoflurane. Our results suggest that the mitochondrial activity of ALDH2 may impact the bioenergetic profile in the brain following general anesthesia. As isoflurane induces ALDH2 activity, this increased activity may compensate for the reduced activity of ALDH2*2, however this does not occur with propofol. Future work will delineate the differential bioenergetic profiles with altered aldehyde metabolism following post-operative recovery from isoflurane and propofol. In addition to mechanistic insights underlying general anesthetics, this work offers an opportunity to implement precision anesthetics for the growing East Asian population. Understanding the neurobiological effects of general anesthesia in ALDH2*2 variant patients will improve anesthetic management and unlock potential targets to accelerate recovery from general anesthesia.

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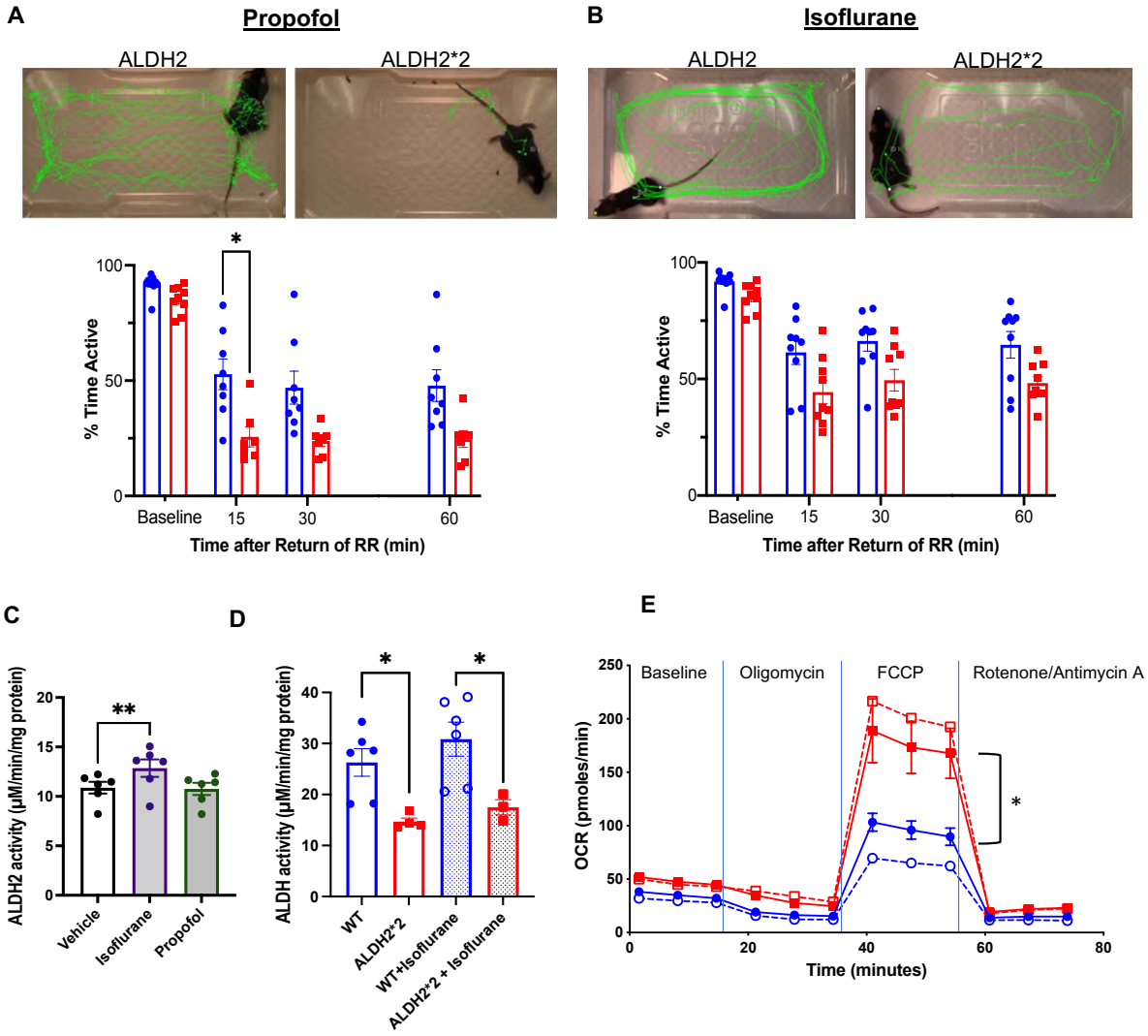

Figure. (A-B) Representative mouse tracking image for the first 2.5 minutes following return of the righting reflex (RR) after 200mg/kg intraperitoneal propofol (A) and 40 minutes 1.5% isoflurane (B) in WT (left) and ALDH2*2 mice (right). The percent time active in the one hour following return of the RR after propofol (A) and isoflurane (B) in WT (blue) and ALDH2*2 (red). (C) Quantification of ALDH2 activity from WT recombinant ALDH2 protein in the presence of DMSO vehicle (black), isoflurane (purple), and propofol (green). (D) ALDH activity at baseline in WT (blue, closed circles) and ALDH2*2 (red, closed squares) liver homogenates and in 1mM isoflurane in WT (blue, open circles) and ALDH2*2 (red, open squares). (E) Oxygen consumption rate (OCR) in primary cerebellar astrocytes in WT (solid, blue) and ALDH2*2 (solid, red) and following administration of 2µM oligomycin (ATP-linked respiration), 2µM FCCP (maximal respiration), and 0.5µM rotenone/antimycin A (non-mitochondrial). OCR following incubation for one hour in 10µM propofol in WT (dotted blue) and ALDH2*2 (dotted red). *p<0.05 WT vs ALDH2*2, **p<0.05 vehicle vs isoflurane.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 19

Frontal Electrocortical Activity and Respiratory Dynamics After Administration of Fentanyl in Humans

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INTRODUCTION: Opioid drugs are double-edged swords in medicine: They are an essential tool for pain management, yet their side effects are profound, difficult to manage, and potentially deadly [1,2]. Although it is well-known that opioid drugs influence multiple brain circuits to produce analgesia as well as its side effects[3,4], we are unable to directly measure how opioid drugs affect the brain in a clinical setting[5]. Here describe the results of a human study in which patients were administered increasing doses of fentanyl prior to induction of general anesthesia for surgery while measuring EEG, respiration, and reaction time in response to an auditory task. We report here a noninvasive EEG-based brain biomarker that is highly correlated with opioid predicted effect site concentration (ESC) and with opioid induced respiratory depression.

METHODS: The protocol consisted of recording EEG, respiratory inductance plethysmography (RIP) and sedation state during administration of fentanyl prior to induction of general anesthesia. We administered fentanyl gradually over a 4-minute period in doses of 2 µg/Kg of ideal body weight (IBW) every 2 minutes with a maximum dose of 6 µg/Kg IBW according to patient tolerance and level of consciousness. Subjects were administered oxygen and vital signs were closely monitored by the research anesthesiologist, keeping oxygen saturation above 95%. We collected data from a 4-channel SEDLine® frontal EEG sensor. RIP was measured using inductive elastic bands placed across each subject's chest and abdomen. The data from the RIP sensor was captured using a Neuroelectrics® NIC2 device. The auditory behavioral task was administered using a computer-driven script. The subjects were asked to listen to a series of sounds played every 4 seconds, and to respond via button press to identify the sound as either a train of clicks, or verbal stimuli. Auditory stimuli were delivered using Etymotic® ER-3C earphones. Button presses were recorded using a computer mouse strapped to the subject's hand. To analyze changes in respiration, we used a neural oscillator state-space model to estimate instantaneous time-varying respiratory amplitudes and frequencies, and derived an expression for an instantaneous minute ventilation index (MVI) based on those values. We estimated fentanyl effect site concentrations (ESC) using Stanpump in R. We analyzed relationships between the EEG and fentanyl ESC, MVI, and reaction time (RT) using mixed-effects models. We calculated the time lag between decreases in MVI and increases in RT using cross correlation and the bootstrap, and estimated the relative potency of fentanyl for respiratory depression compared to sedation based on these time lags.

RESULTS: We completed 25 data sets out of 31 subjects enrolled. From these participants 13 were female (52%), with a mean age of 54.4 years (range: 31 - 64 years) and a mean weight of 78.76 Kg (SD = 22.6). The mixed-effects analyses showed a strong positive association between EEG theta power and fentanyl ESC (Slope: 0.55 (0.25, 0.86), Marginal R^2 = 0.151, Conditional R^2 = 0.744; Fig. 1D) and a strong negative association between EEG theta power and MVI (Fig 2; Slope: -1.62 (-2.51, -0.73), Marginal R^2 = 0.054, Conditional R^2 = 0.248). The mean lag between changes in MVI and RT was 277 seconds (95% CI: 219.5 sec. - 332.5 sec)(Fig. 3 A and B). We also observed that MVI would decline by 51.4% (95% CI: 30.9 – 80.4 %) before noticeable increases in reaction time occurred (Fig. 3C). Finally, we estimated that the predicted ESC of fentanyl needed to induce a 10% drop in the MVI is roughly 1750-fold lower than the concentration present upon RT changes (95% CI: 839-2854-fold) (Fig. 3D).

CONCLUSION: The specific EEG signature of fentanyl we describe here and its unique associations with respiration, sedation, and unconsciousness have not, to our knowledge, been previously reported. We found that respiratory decline induced by fentanyl far outpaces any behavioral change, suggesting that in non-medical settings, fentanyl would induce apnea before any behavioral effects, and would be dangerous in any quantity. This novel biomarker of fentanyl drug effect could provide real-time feedback to enable opioid titration in the operating room, post-anesthesia care unit, intensive care unit and beyond.

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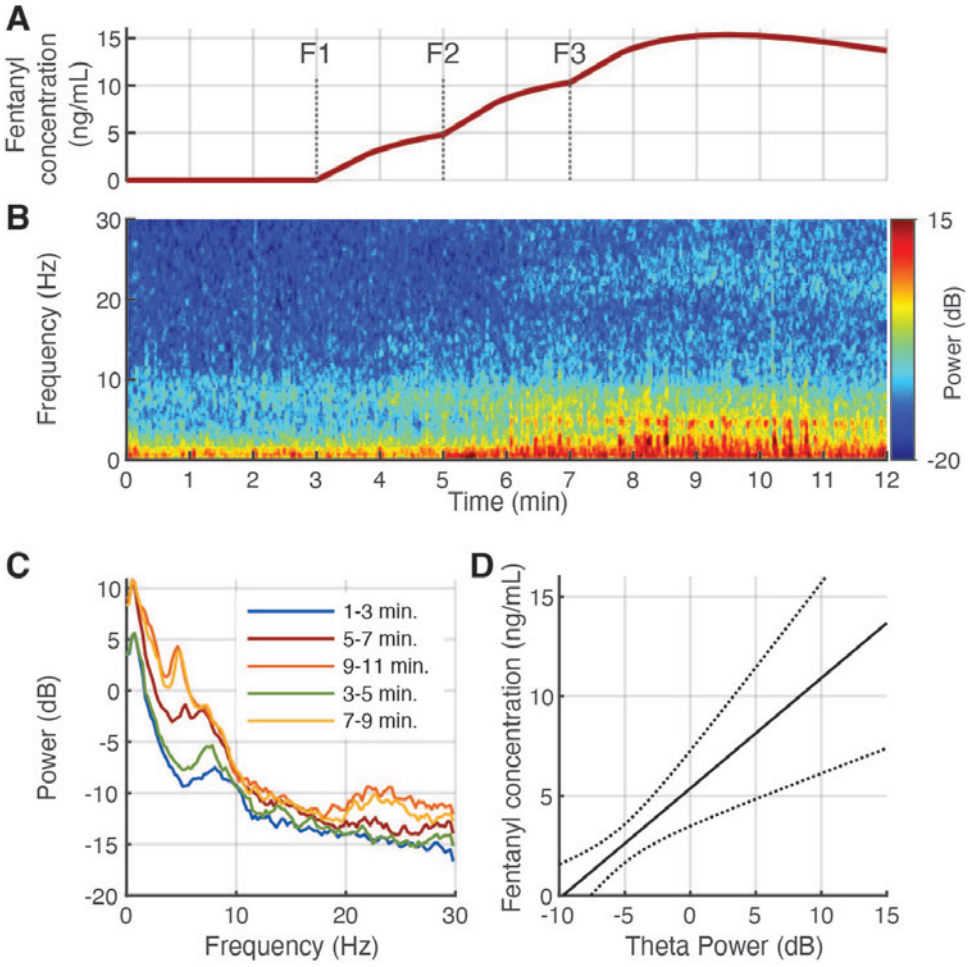

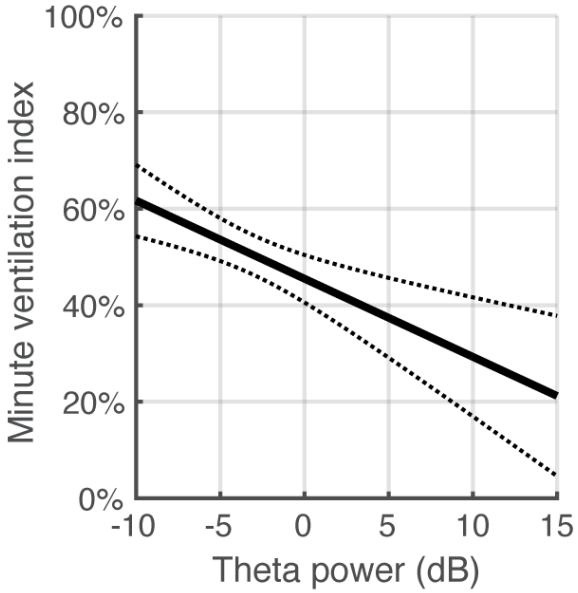

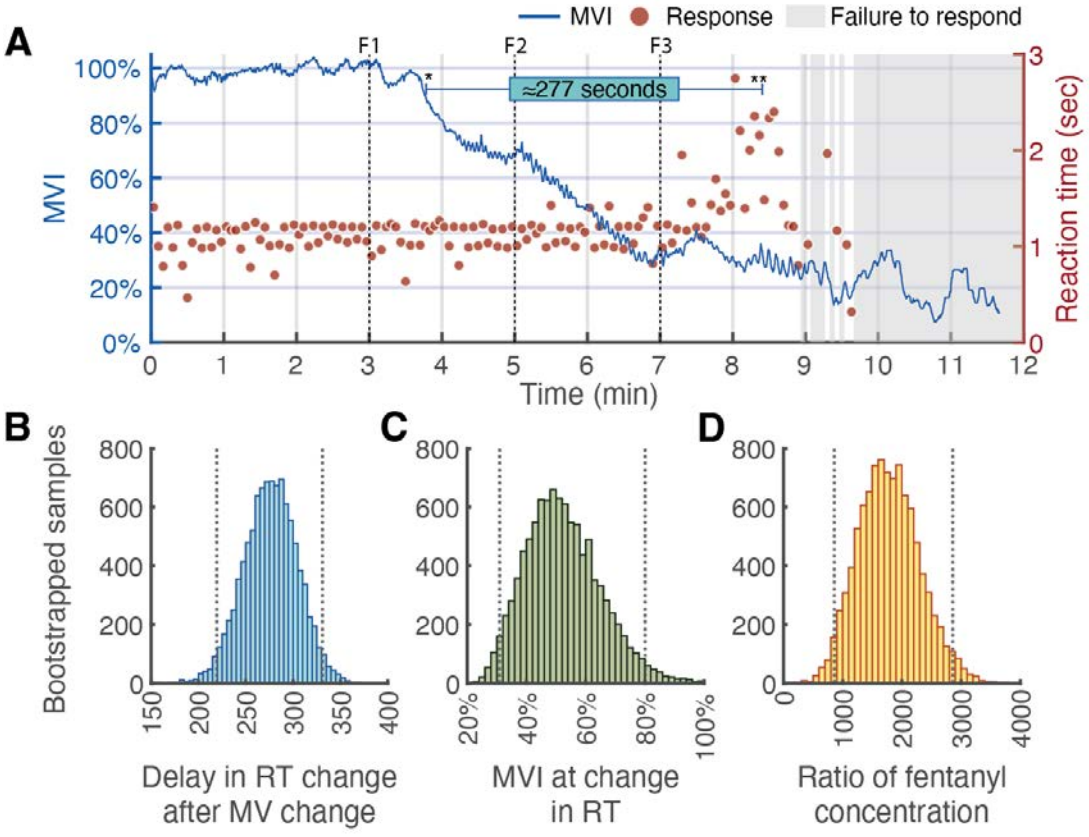

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 20

Case-control study evaluating serum biomarkers associated with in-patient status and the development of delirium following major cardiac surgery

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INTRODUCTION: Postoperative delirium is associated with prolonged impairments in cognition, memory, and functional recovery. The purpose of this study was to address whether in-patient status compared to same-day admission contributes to a differential serum profile that may be associated with delirium development following major cardiac surgery.

METHODS: A case-control study of 38 patients (aged ≥60 years old) undergoing cardiac surgery with cardiopulmonary bypass was developed. This study was an approved substudy of the Minimizing ICU Neurologic Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) trial[1]. All patients provided written, informed consent in accordance with institutional and federal guidelines. Patients with same-day admissions (control = 11, delirium = 8) and in-patient status (control = 11, delirium = 8) were matched based on age, sex, and baseline Telephone-Montreal Cognitive Assessment (T-MoCA) scores. Serum was collected preoperatively and on postoperative day 1 and analyzed using targeted proximity extension assays and enzyme-linked immunosorbent assays. Cognitive evaluations were performed preoperatively (T-MoCA) and postoperatively twice daily from postop days 1 through 3 (Confusion Assessment Method). Statistical comparisons were performed using the Mann-Whitney test with correction for multiple comparisons using the Holm-Šídák method.

RESULTS: No significant differences in body mass index or cardiopulmonary bypass time were associated with in-patient status/same-day admissions or control/delirium cohorts. A targeted protein screen of 173 proteins revealed elevated preoperative serum levels of carbonic anhydrase 5a (mean±stdev log2 relative abundance = 4.7±1.9, p=0.003) and interleukin-1 receptor antagonist (7.1±0.7, p=0.01) in subjects with in-patient status compared to same-day admissions (2.9±0.7 and 6.2±0.6, respectively). Elevated FGF-23 (5.8±1.5, p=0.02) and MMP-7 (12.7±0.3, p=0.03) were detected on postoperative day 1 in patients with delirium compared to the control group (3.7±1.4 and 12.2±0.4, respectively), independent of in-patient/same-day admissions status. Preoperative total 25-OH Vitamin D serum levels were found to be significantly lower in subjects with in-patient status (27±12 ng/mL) compared to same-day admissions (35±11 ng/mL, p=0.03) with a similar decrease in both groups by postoperative day 1 (18±10 ng/mL and 27±9 ng/mL, respectively). Subjects with in-patient status who later developed delirium showed lower Vitamin D levels (23±14 ng/mL) at preop, but not significantly different to subjects with same-day admissions who later developed delirium (34±9 ng/mL, p=0.2).

CONCLUSION: Higher postoperative FGF-23 and MMP-7 serum levels were detected in patients with delirium. Lower preoperative Vitamin D levels were associated with in-patient status. Further studies in larger cohorts are required to evaluate the role of nutritional status on patient-centered outcomes following surgery.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 21

Characterizing ketamine-induced dissociation using human intracranial neurophysiology: brain dynamics, network activity, and interactions with propofol

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INTRODUCTION: Ketamine is a widely used anesthetic. At higher doses, ketamine induces unconsciousness and immobility, whereas at lower or subanesthetic doses, it produces a dissociative state, which includes altered sensory perception and a sense of disembodiment. The mechanism whereby a subanesthetic dose of ketamine disrupts normal brain activity to produce the dissociated state remains unclear. It is also unknown how ketamine-induced EEG power changes relate to ketamine's actions at the receptor level. It is believed that at subanesthetic doses, ketamine has a more pronounced effect on NMDA receptors on GABAergic interneurons, leading to disinhibition of the downstream excitatory neurons. The objective of this study was to investigate in humans the effects of subanesthetic doses of ketamine on brain dynamics and network activity, as well as its interactions with a GABAa receptor agonist propofol. We hypothesized that ketamine would increase high-beta and gamma oscillations in prefrontal cortical structures, decrease alpha power in posterior cortical sensory areas, and that some subset of these effects would be reversed by propofol.

METHODS: Ten epilepsy patients were implanted with intracranial depth electrodes for detection of seizure foci. We recorded intracranial EEG (iEEG) during a ketamine infusion administered just prior to the electrode removal surgery. We recorded baseline signals for 5 minutes. We then administered an infusion of a subanesthetic dose of ketamine (0.5 mg/kg over 14 minutes). Patients completed an abbreviated version of the Clinician-Administered Dissociative States Scale (CADSS) questionnaire at the conclusion of the ketamine infusion. Propofol bolus was given to the patients to induce general anesthesia. Structural and functional network mapping analysis was conducted to investigate the iEEG power changes after ketamine and propofol.

RESULTS: The responses on the CADSS questionnaire confirmed that our subanesthetic ketamine administration paradigm induced a dissociative state. This state was associated with a remarkable increase of gamma power (25-55Hz) in frontal region of the brain, which includes superior frontal, middle frontal, orbitofrontal, and inferior frontal regions, as well as anterior and posterior cingulate cortex (Figure 1). While parietal and temporal cortices showed mild increase of gamma power, a decrease in gamma power was observed in occipital regions. A global reduction of iEEG power was detected at low frequency oscillations (0-25Hz) for nearly all brain regions studied. The presence of propofol largely reversed the iEEG power changes induced by ketamine (Figure 2). Meanwhile, propofol further intensified the alpha power (8-15Hz) decrease at occipital cortex and the gamma power increase at precentral, postcentral, isthmus cingulate, hippocampal, amygdala, and insula regions of the brain.

CONCLUSION: These results suggest that a subanesthetic dose of ketamine may induce dissociative states in distinct ways, first by disrupting posterior cortical alpha networks involved in sensory processing, and second by disrupting prefrontal gamma networks involved in arousal and attention. The iEEG power changes that could be reversed by propofol may be related to the NMDA antagonism of ketamine and the GABAa agonism of propofol. The additive effects of propofol on ketamine may be accounted by their shared inhibition at the hyperpolarization-activated cyclic nucleotide-gated potassium channel 1 (HCN1). This study could provide important insights into the neurophysiological mechanism of the subanesthetic ketamine-induced dissociative state.

Figure 1. Structural mapping (DKT40 atlas) for intracranial EEG power changes after ketamine infusion.

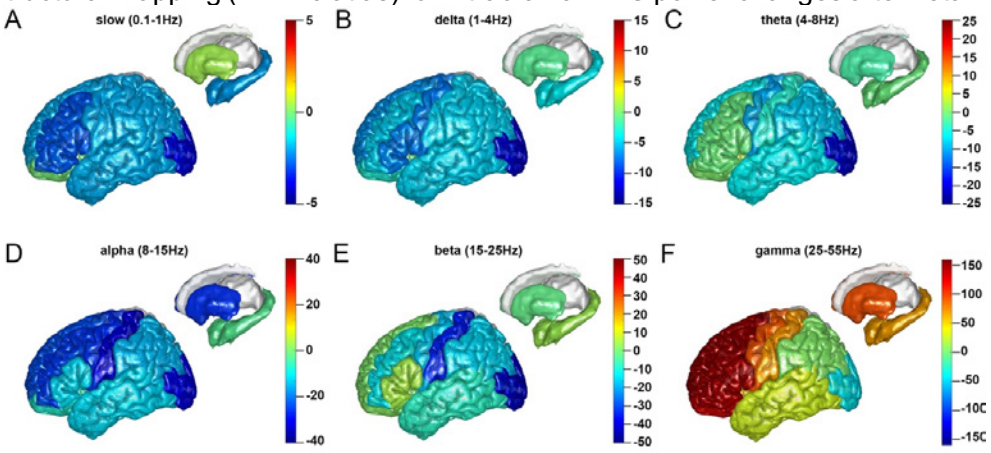
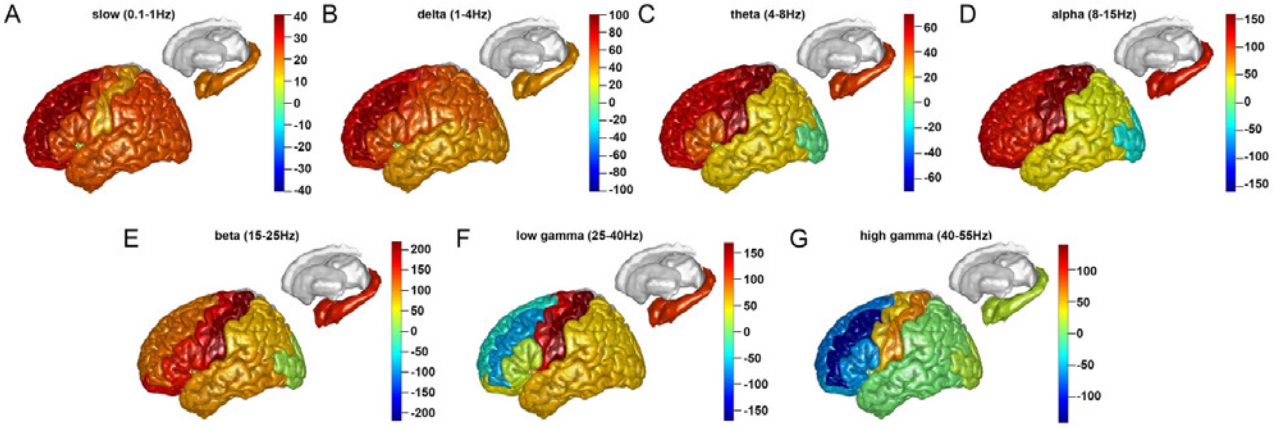


Figure 2. Structural mapping (DKT40 atlas) for intracranial EEG power changes after propofol infusion.



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 22

Cognitive deficits after general anesthesia: a systematic review of animal studies

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INTRODUCTION: Perioperative neurocognitive disorders (PNDs) are common postoperative complications that are associated with poor long-term outcomes and increased healthcare costs. While the mechanisms underlying PNDs are multifactorial, the contribution of general anesthetic drugs is controversial[1,2]. Some clinical studies report increased PND incidence with longer durations and greater depths of anesthesia, whereas others report no significant difference in cognitive outcomes between general and regional anesthesia[3-5]. In clinical studies, it is not possible to distinguish the relative contribution of general anesthesia from other contributing factors (such as tissue trauma, sepsis, or underlying surgical and medical conditions) on postoperative cognitive performance. Thus, preclinical studies are needed to provide definitive evidence for the persistent impact of general anesthetic drugs on cognition. The aim of the study was to review the preclinical literature to determine whether general anesthetic drugs cause cognitive deficits that persist after the drugs are eliminated from the brain.

METHODS: The Ovid MEDLINE database was systematically searched from inception to November 1, 2021. A pilot study was performed on the most recent 100 citations. We included studies that involved adult vertebrate animals undergoing a single exposure to general anesthesia (not ketamine or nitrous oxide). The main outcome was cognitive performance on behavioural tests after recovery from general anesthesia (> 24 hours) compared to non-exposed controls. Descriptive statistics were performed; the percentage of studies that reported cognitive deficits was calculated and subgroup analyses were conducted for age and drug treatment.

RESULTS: 378 reports were identified and the most recent 100 citations were used for the pilot study; 51 met inclusion criteria (Figure 1). All but one study used a rat or murine model and 82% (42/51) reported deficits in at least one cognitive domain. Deficits were reported more often in studies using aged animals (22/24; 92%) compared to younger adult animals (20/27; 74%). Regardless of age, studies that included a surgical group (n=4) only observed deficits associated with surgery but not with general anesthesia alone. The anesthetic drug treatment used did not impact the development of cognitive deficits (e.g. 21/23 or 91% deficit for sevoflurane vs 17/19 or 89% deficit for isoflurane).

CONCLUSION: General anesthetic drugs were associated with cognitive deficits in most studies that used vertebrate animal models; age and surgery may increase the risk. Analysis and inferential statistical testing of the entire dataset will further clarify the relationship between general anesthesia and cognitive outcomes in animal models and may inform the design of future clinical trials.

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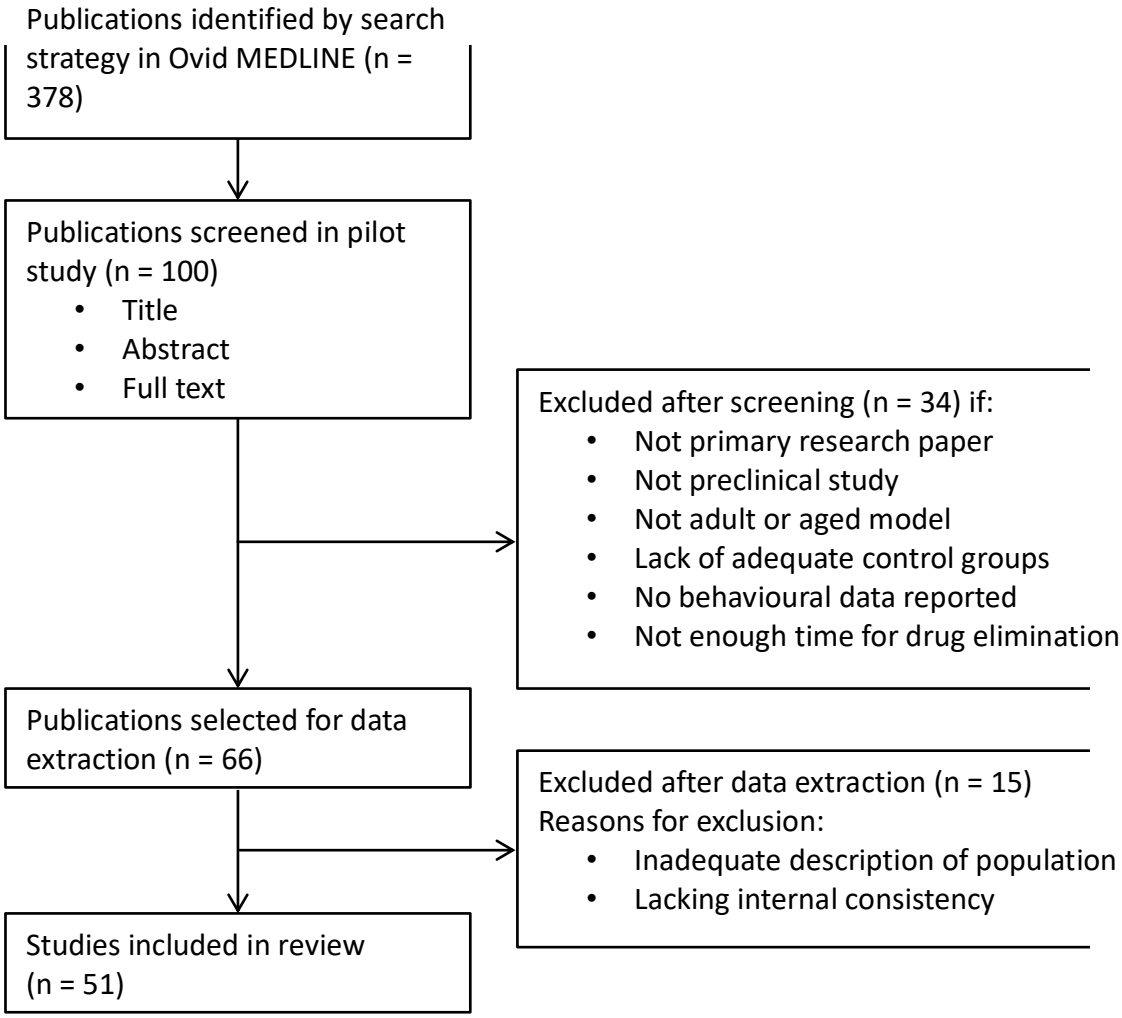

Figure 1. Consort flow diagram depicting the study selection process. Literature search, selection of publications, and data analysis for the pilot study (n = 100) is complete; study selection and data analysis for the full dataset (n = 378) is ongoing.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 23

Assessing the Analgesic Properties of Volatile Anesthetics Using High-Power Infrared Lasers in Mice

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INTRODUCTION: Many volatile general anesthetics (VGA) block the experience of pain by inducing unconsciousness, however, a select few can provide analgesia in responsive patients. What makes one VGA analgesic, and another non-analgesic, is currently unknown. As the ongoing inhalation of VGAs in awake, freely moving mice precludes the use of most widely used nociceptive sensory tests, it is technically challenging to quantitatively assess the analgesic properties of VGAs. Here, we develop a methodology for that allows for simultaneously assessing both the reflexive and non-reflexive measures of pain during inhalation of subanesthetic concentrations of VGAs in awake, freely moving mice. To demonstrate the utility of this method, we investigated the influence of non-analgesic (isoflurane [ISO]) and analgesic (nitrous oxide [N2O]) anesthetics on thermal sensory thresholds and on noxious stimulus-evoked behavioral responses.

METHODS: In adult mice, we monitored thermal noxious stimulus-evoked responses during inhalation of VGAs. Stimuli were generated by a high-power infrared laser (LASMED Inc.) targeted to the hindpaw. The Dixon Up/Down method was used to document thermal stimulus-response thresholds, and behavioral responses (no response, withdrawal, shake, lick) were recorded after each stimulus. Testing occurred within a modified anesthetic chamber with a high-transmittance glass floor. Mice were tested during inhalation of medical air, or equipotent, subhypnotic concentrations of ISO (0.26%) or N2O (60%), with equivalent concentrations of oxygen throughout (~21%).

RESULTS: We found that laser-evoked 50% response thresholds increase under ISO (+18%) and N2O (+28%) compared to air. Interestingly, however, ISO and N2O differentially alter laser-evoked behavioral responses. Thus, laser-evoked licking of the stimulated hindpaw was reduced by N2O (-75%), but not ISO, compared to air. In contrast, under ISO, but not N2O, laser-evoked hindpaw shaking increased (+37%), whereas hindpaw withdrawals decreased (-64%), compared to air.

CONCLUSION: We conclude that analgesic and non-analgesic VGAs differentially alter behavioral responses to noxious stimuli. In rodents, licking of the hindpaw following a noxious stimulus is indicative of the experience of pain; not merely a reflexive response. Therefore, our finding that N2O, but not ISO, decreases laser-evoked licking of the hindpaw is of particular interest, and indicates that N2O, but not ISO, provides relief from laser-evoked pain (i.e., analgesia). In fact, as ISO, but not N2O, increased the severity of laser-evoked behavioral responses (increasing shaking at the expense of withdrawals), our findings confirm that ISO is not analgesic at subhypnotic concentrations. In the future, to develop a circuit level understanding of the analgesic properties of VGAs, we plan to simultaneously monitor laser-evoked behavioral responses and record neural activity from pain processing regions of the brain.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 24

Ketamine Mitigates Sevoflurane-Induced Persistent Memory Deficits and Prevents Increased Activity of $GABA_A$ Receptors in Mice

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INTRODUCTION: The etiology of perioperative neurocognitive disorders is multifactorial, with exposure to general anesthetic drugs that target $GABA_A$ receptors, such as sevoflurane, being a potential contributing factor[1-2]. Ketamine, a dissociated anesthetic that primarily targets NMDA receptors, may be neuroprotective[3-4]; however, in some clinical studies, ketamine has had no cognition-sparing properties[5]. In preclinical studies, we have shown that general anesthetic drugs trigger a sustained increase in cell-surface expression and function of extrasynaptic $GABA_A$ receptors, which contributes to cognitive deficits[6-7]. The goals of this preclinical study were to test the hypotheses that ketamine 1) mitigates sevoflurane-induced sustained memory deficits in vivo and 2) prevents a sustained increase in tonic current in vitro.

METHODS: Studies were approved by the local ethics committee. C57BL/6 mice (8-15 weeks old) were anesthetized with sevoflurane (2.3% for 2 h) whereas control mice were exposed to medical air (30% O2/70% air for 20 min). Separate groups of mice were treated with ketamine (10 mg/kg, I.P.) or a vehicle 30 min before exposure to sevoflurane. The novel object recognition assay and object location recognition assay were used to study recognition memory and spatial memory, respectively, 24 h and 48 h later. Data were scored by an observer who was blinded to the treatment. For the in vitro studies, co-cultures of hippocampal neurons and cortical astrocytes were prepared from fetal mice (embryonic days 17-18). Co-cultures were treated with sevoflurane (266 μM; 1 h) or vehicle, in the absence and presence of ketamine (10 μM). Cultures were then washed, and $GABA_A$ receptor function was studied 24 h later by recording whole-cell tonic current from neurons.

RESULTS: Control mice demonstrated recognition memory and spatial memory, as evidenced by a preference for the novel and displaced objects, respectively. In contrast, sevoflurane-treated mice did not exhibit such preferences (Fig. 1). Mice co-treated with ketamine and sevoflurane showed recognition memory (Fig. 2). Notably, ketamine alone did not alter recognition memory or spatial memory. No sex-dependent differences were observed. Sevoflurane treatment increased the amplitude of the tonic current generated by $GABA_A$ receptors, and co-treatment with ketamine prevented this increase (Fig. 3).

CONCLUSION: Ketamine mitigated memory deficits after sevoflurane anesthesia. Ketamine also prevented the sevoflurane-induced persistent increase in extrasynaptic $GABA_A$ receptor function in hippocampal neurons. These studies identify a novel mechanism that may account for the cognition-sparing properties of ketamine. Further clinical studies are warranted to investigate the cognition-sparing properties of ketamine for the prevention of perioperative neurocognitive disorders.

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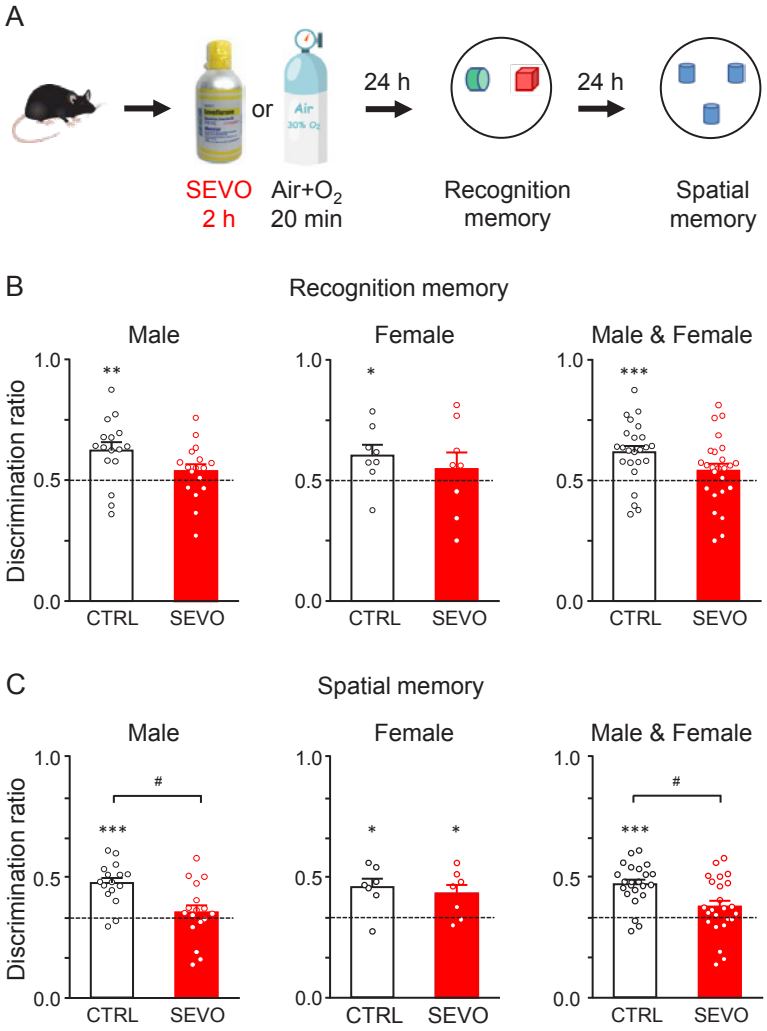

Fig. 1. Sevoflurane (SEVO) anesthesia resulted in sustained memory impairment. (A) A schematic of the experimental design. **(B)** Control (CTRL) mice had a higher discrimination ratio than chance value, but SEVO-treated mice did not. There were no sex-dependent differences. CTRL: n = 16 Male, 8 Female, 24 Total; SEVO: n = 17 Male, 8 Female, 25 Total. **(C)** Control mice showed a higher discrimination ratio than chance value, but SEVO-treated mice did not, except for female mice. The discrimination ratio of SEVO-treated mice was lower than control except for female mice. CTRL: n = 16 Male, 7 Female, 23 Total; SEVO: n = 17 Male, 7 Female, 24 Total. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, one-sample *t*-test; $^{\#}P < 0.01$, unpaired *t* test. Data are Mean ± SEM.

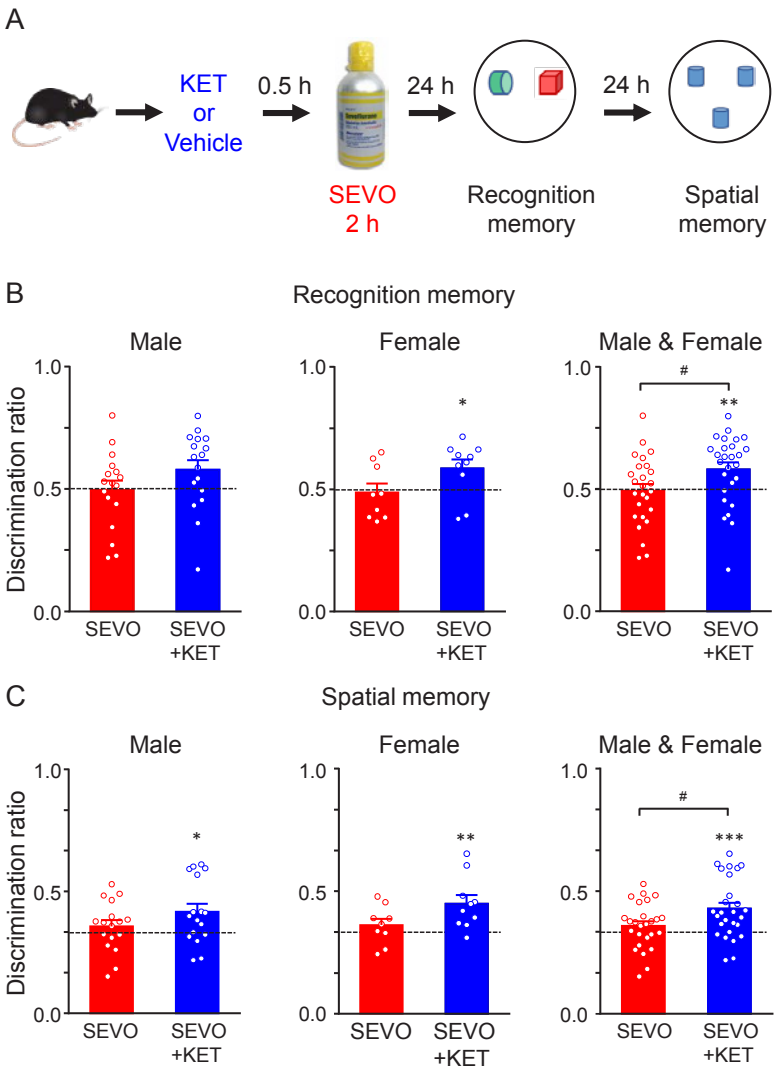

Fig. 2. Ketamine (KET) mitigated sustained memory impairment after sevoflurane (SEVO) anesthesia. (A) A schematic of the experimental design. **(B)** KET-treated mice had a higher discrimination ratio than chance value except for male mice, but those treated with only SEVO did not. SEVO: n = 17 Male, 9 Female, 26 Total; SEVO+KET: n = 17 Male, 10 Female, 27 Total. **(C)** KET-treated mice had a higher discrimination ratio than chance value, but those treated with only SEVO did not. There were no sex-dependent differences. SEVO: n = 17 Male, 9 Female, 26 Total; SEVO+KET: n = 17 Male, 10 Female, 27 Total. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, one-sample *t*-test; $^{\#}P < 0.05$, unpaired *t* test. Data are Mean ± SEM.

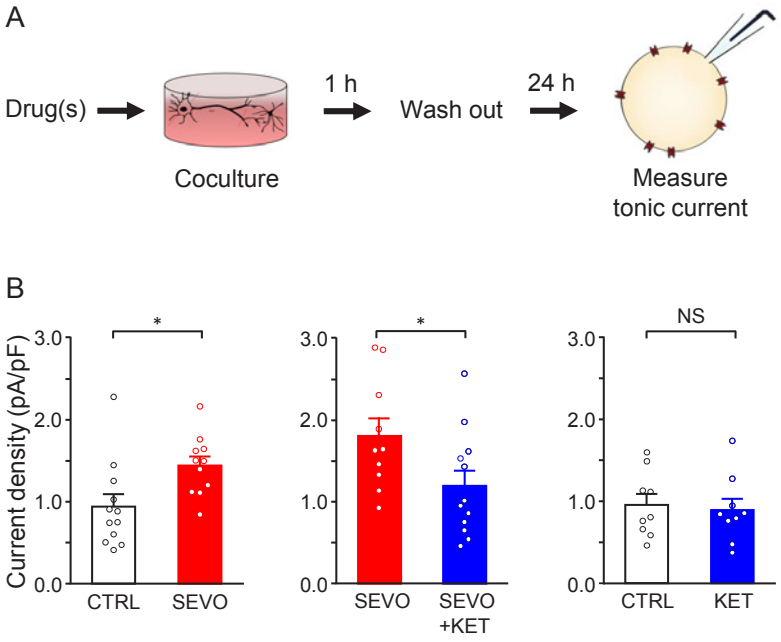

Fig. 3. Ketamine (KET) prevented the increase in tonic current induced by sevoflurane (SEVO) treatment. (A) A schematic of the experimental design. **(B)** Summarized data demonstrated that SEVO increased the tonic current mediated by $GABA_A$ receptors, whereas co-treatment with KET prevented the increase. KET alone did not modify the tonic current. n = 9-12 cells; **P* < 0.05, NS: no significance, unpaired *t*-test. Data are Mean ± SEM.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 25

Spectral electroencephalographic patterns of dexmedetomidine anesthesia in mice

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INTRODUCTION: In the last decade there has been increasing evidence that the perioperative application of the Œ±2-receptor agonist dexmedetomidine (DEX) improves patient outcome after anesthesia[1, 2]. Despite the established application in the clinical setting, the exact underlying neuronal mechanisms of the DEX-induced loss of consciousness (LOC) and its beneficial effects remain unclear. In order to perform in-depth analyses of DEX-mediated neuronal processes and to examine the role of subcortical non-rapid eye movement (NREM) -sleep promoting pathway during LOC, we established an intravenous administration of DEX combined with chronic electroencephalographic recordings (EEG) in freely behaving mice.

METHODS: All experimental procedures were approved by the Committee on Animal Health and Care of the State of Upper Bavaria. Eight adult male mice (C57BL6\N) were included. We established a chronic central venous access via the mice's right external jugular vein and then implanted nine epidural electrodes bilaterally on the frontal association, primary motor, primary somatosensory and visual cortex including a grounding electrode maintaining anesthesia with isoflurane[3]. After 14 days of recovery, we performed experimental DEX-anesthesia (0.05µg/µl) starting at a flow rate of 1µl/min, increased by 1µl/min every two minutes until a target dosage of 0.45µg/g body weight (BW) was reached. During the anesthesia the occurrence of loss or righting reflex (LORR) as marker for LOC was noted. We used the Wilcoxon-signed rank test to test for changes in the EEG band power and descriptive statistics (median [interquartile range]) to show the time to LORR.

RESULTS: LORR occurred 1310s [IQR: 449] after the start of anesthesia at a dosage of 0.262 µg/g BW [IQR: 0.158] and lasted for 24s (median, min.: 4s, max.: 8777s). 77.7% of mice experienced multiple LORR regaining righting reflex in between. All animals reached a state of persistent LORR (average duration: 6718s, min.: 2061s, max.: 9880s). We observed a continuous overall shift towards slower frequencies throughout the anesthesia (Fig.1). From an awake state to a post-LORR state, delta power (0.7 - 4.2 Hz) increased significantly in all cortices while beta power (12.5 – 25.1 Hz) decreased globally. We found a distinct decrease in alpha power (7.7 – 12.5 Hz) over somatosensory and visual cortices whereas no significant changes were found in motor and prefrontal cortices. (Fig. 2, 3)

CONCLUSION: Our analyses presented distinct changes in spectral EEG-features during DEX anesthesia. Especially the global increase in slow-wave delta power, the occipital decrease in alpha power as well as global decrease in beta power correspond with findings in human patients[4]. The results establish face validity and constructive validity for further studies investigating potential cortical/subcortical versus subcortical/cortical processes during LOC and recovery of consciousness (ROC) especially under DEX anesthesia.

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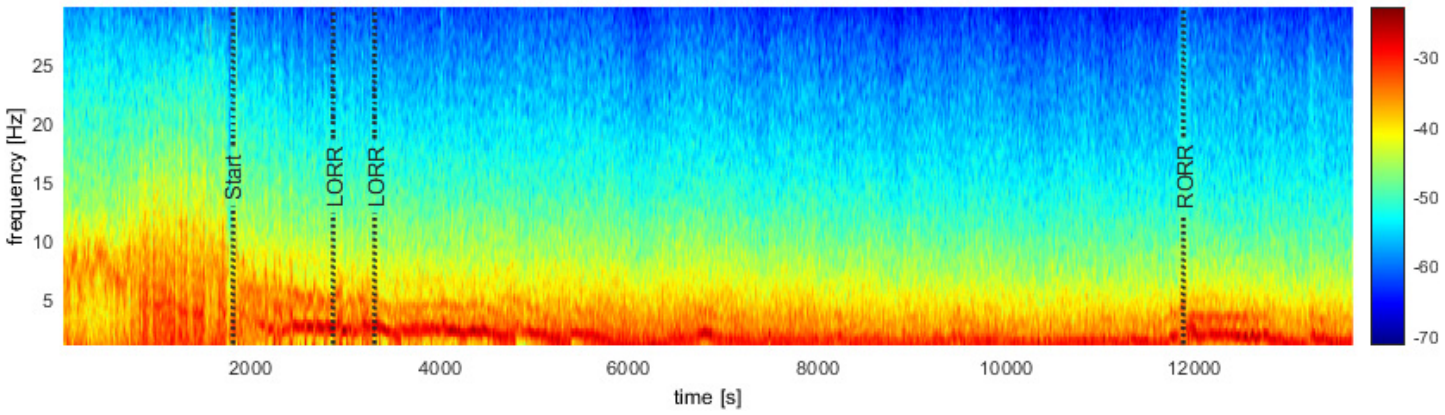

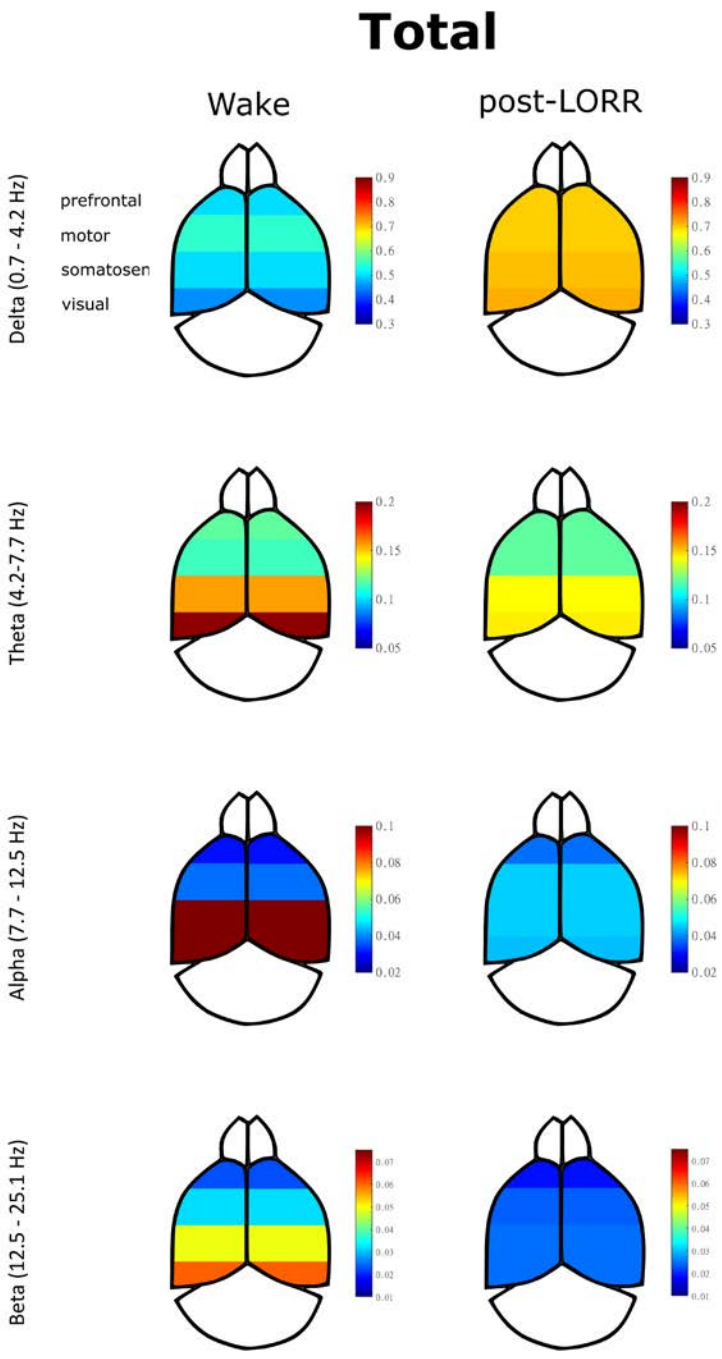

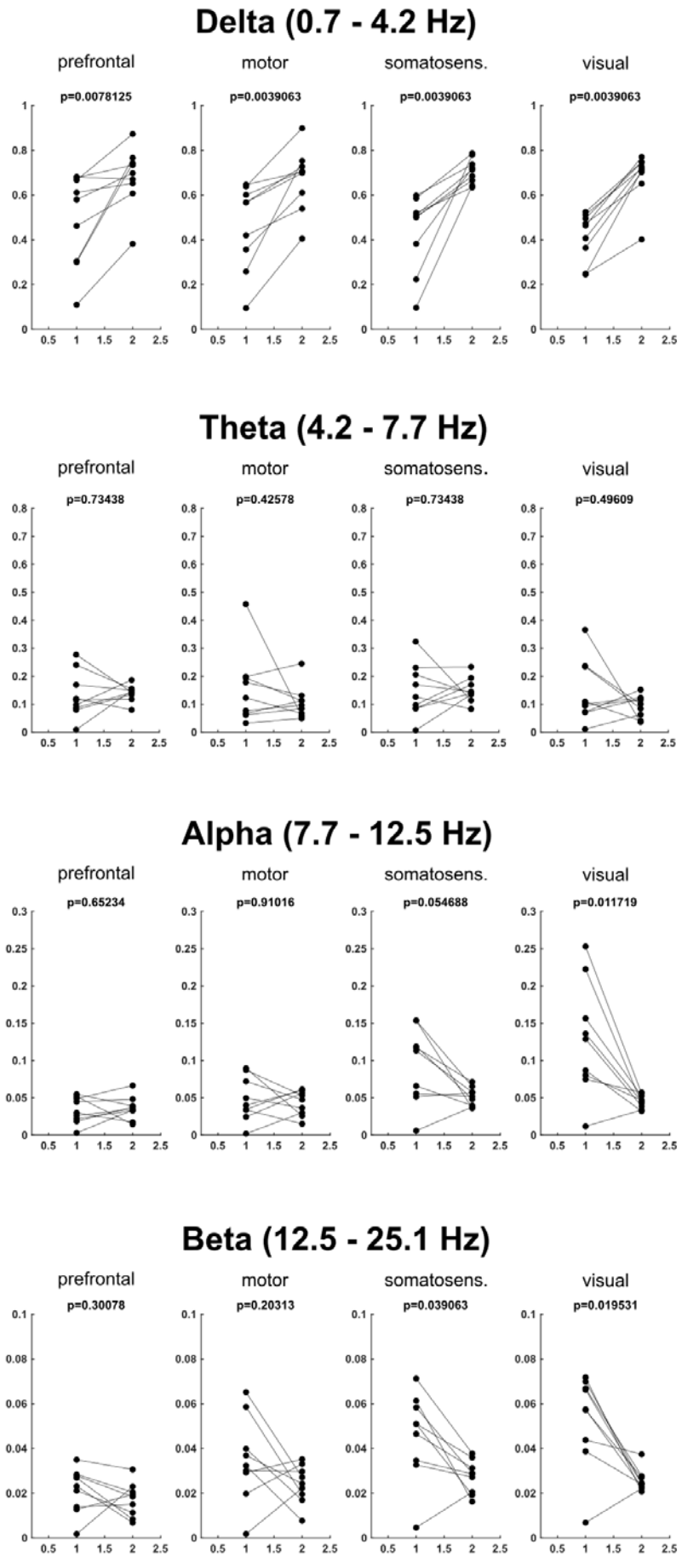

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 26

The impact of inflammation and general anesthesia on memory and executive function in mice

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INTRODUCTION: Perioperative neurocognitive disorders are complex, multifactorial conditions that are associated with poor long-term outcomes[1]. Inflammation and exposure to general anesthetic drugs are likely contributing factors[2]; however, the relative impact of these factors alone and in combination remains poorly understood. The goal of this study was to compare the relative impact of inflammation, general anesthesia, and the combination of inflammation and general anesthesia on memory and executive function - two cognitive domains that are commonly impaired in patients in the postoperative period[3].

METHODS: Mice were treated with lipopolysaccharide (LPS) or vehicle to induce inflammation, and one day later were anesthetized with etomidate (or vehicle). To assess neuroinflammation, levels of proinflammatory cytokines and markers of glial activation were measured in the hippocampus 24 and 72 h after LPS (Fig. 1A). Recognition memory was studied 24 h after anesthesia using the novel object recognition assay. Discrimination ratios were calculated as the time spent interacting with the novel object divided by total interaction time, whereby a discrimination ratio greater than 0.5 indicated intact memory. Executive function was assessed using the 3-day puzzle box assay, starting 48 h after anesthesia. Data are presented as mean ± standard deviation.

RESULTS: Levels of the proinflammatory cytokines IL-1β, TNF-α, and IL-6 were elevated 24 h after LPS injection, and recovered by 72 h (Fig. 1B). LPS also increased the expression of the microglial activation marker Iba1 for up to 72 h after treatment (Fig. 1C). In contrast, there was no change in astrocyte activation (Fig. 1D). These results indicate that LPS-induced neuroinflammation was present for at least 72 h after injection.
Recognition memory was impaired in mice treated with LPS, as evidenced by a lack of preference for the novel object, and a discrimination ratio no different from 0.5 (Fig. 2) Mice treated with etomidate alone showed intact recognition memory, whereas mice co-treated with both LPS and etomidate exhibited memory deficits. In the puzzle box, mice treated with either LPS or etomidate alone performed similarly to controls in all problem-solving tasks (Fig. 3). However, the combination of LPS and etomidate caused deficits in the Door Open and Plug tasks, indicating impaired executive function.

CONCLUSION: Impairments in recognition memory were driven by inflammation. Deficits in executive function were only observed in mice co-treated with etomidate, indicating that general anesthetic drugs may unmask or exacerbate latent cognitive deficits induced by inflammation. These results suggest that an interplay between inflammation and general anesthesia may be critical in the development of perioperative neurocognitive disorders.

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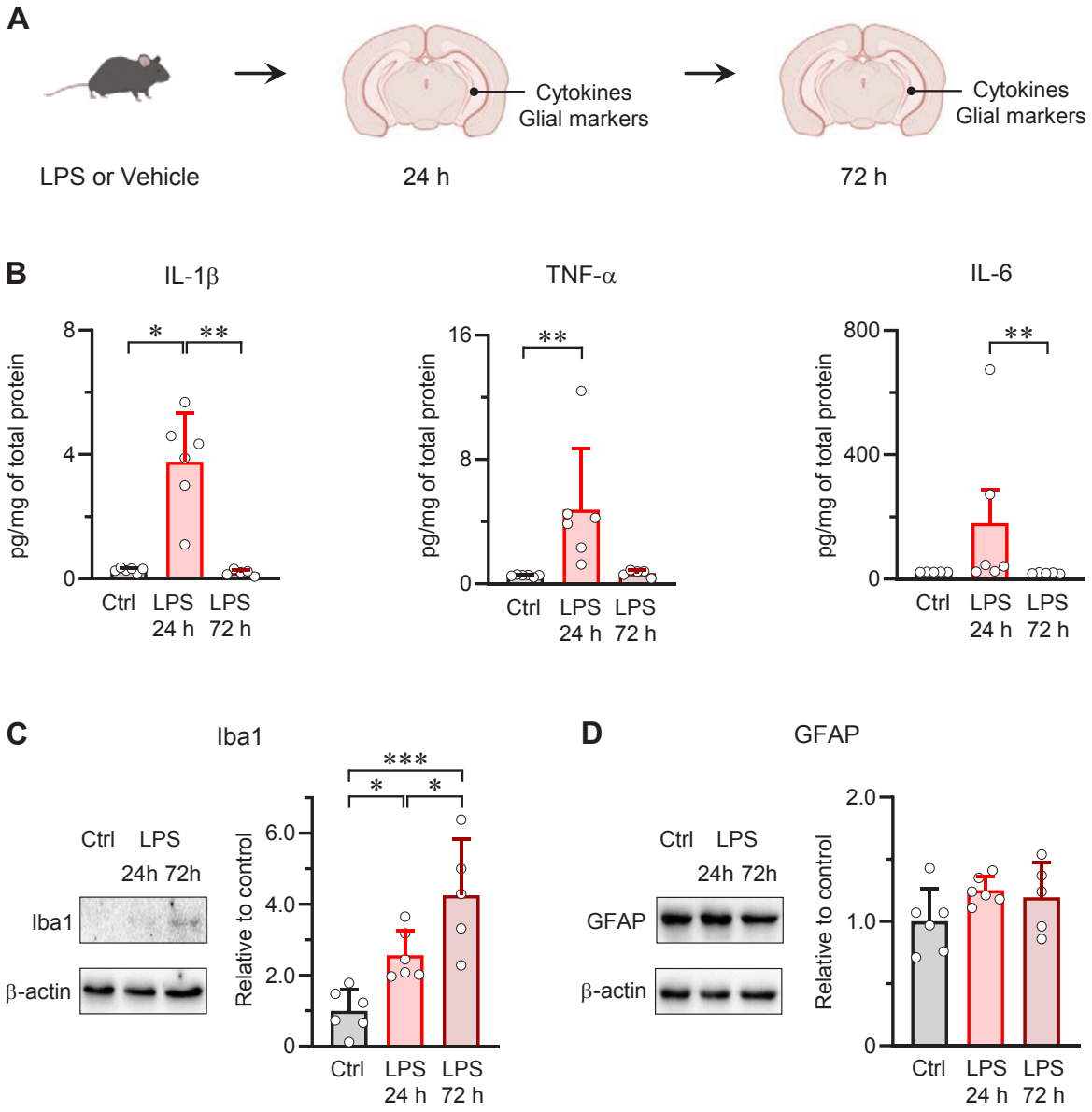

Fig. 1. Lipopolysaccharide (LPS) increased levels of proinflammatory cytokines and activated microglia in the hippocampus. (A) A schematic of the experimental design and timeline. Mice were injected with LPS or vehicle, and brains were collected after 24 h (Ctrl and LPS 24 h groups) and 72 h (LPS 72 h group). **(B)** Summarized data show that the levels of interleukin-1b (IL-1b), tumour necrosis factor-a (TNF-a), and IL-6 were elevated 24 h after LPS injection and recovered by 72 h. n=5–6. **P* < 0.05, ***P* < 0.01, Kruskal-Wallis test followed by Dunn's multiple comparisons test. **(C)** Representative western blot and summarized data show that Iba1 levels were increased for up to 72 h in the hippocampus. n=5–6. **P* < 0.05, ****P* < 0.001, one-way ANOVA followed by Tukey's multiple comparisons test. **(D)** Representative western blot and summarized data show the expression of GFAP was not altered by LPS injection. n=5–6. Data are mean ± SD. Ctrl, control; GFAP, glial fibrillary acidic protein; Iba1, ionized calcium-binding adaptor molecule 1.

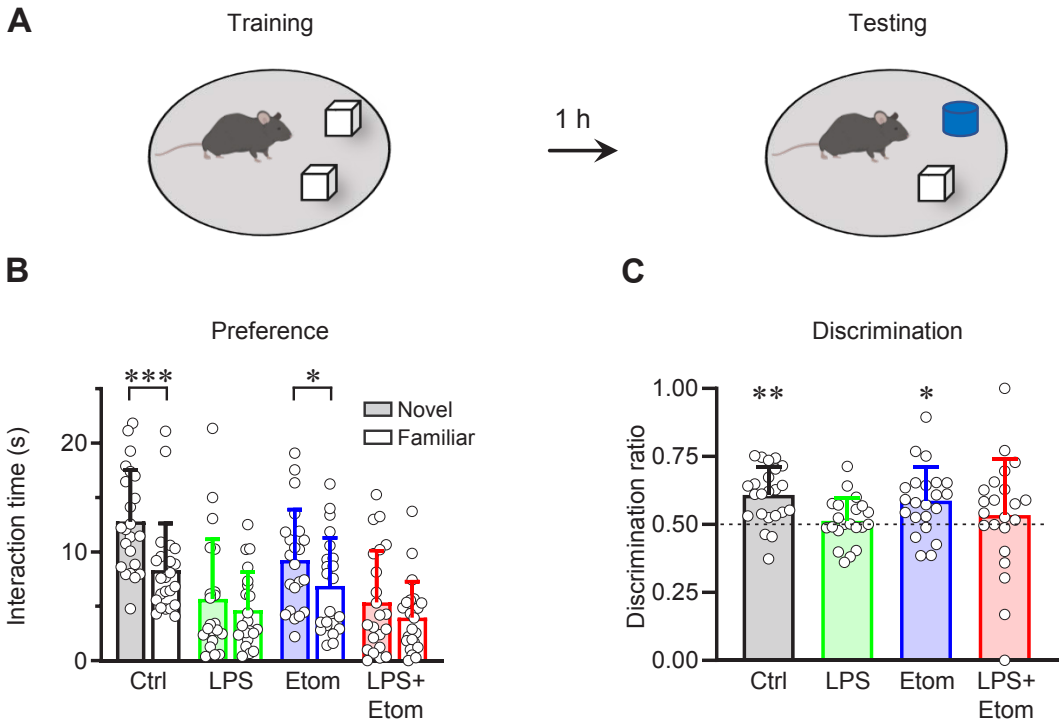

Fig. 2. Lipopolysaccharide (LPS) alone and the combination of LPS and etomidate impaired recognition memory in the novel object recognition assay. (A) A schematic of the novel object recognition assay. **(B)** (left) Both LPS alone and LPS + etomidate eliminated the preference for the novel object in the NOR assay. n= 21–23. **P* < 0.05, ****P* < 0.001, two-way repeated-measures ANOVA followed by Šidák's multiple comparisons test. (Right) Only mice in the control or etomidate alone groups showed a discrimination value significantly different from the theoretical chance level of 0.5. **P* < 0.01, ***P* < 0.001, one-sample t-test. Data are mean ± SD. Ctrl, control; Etom, etomidate.

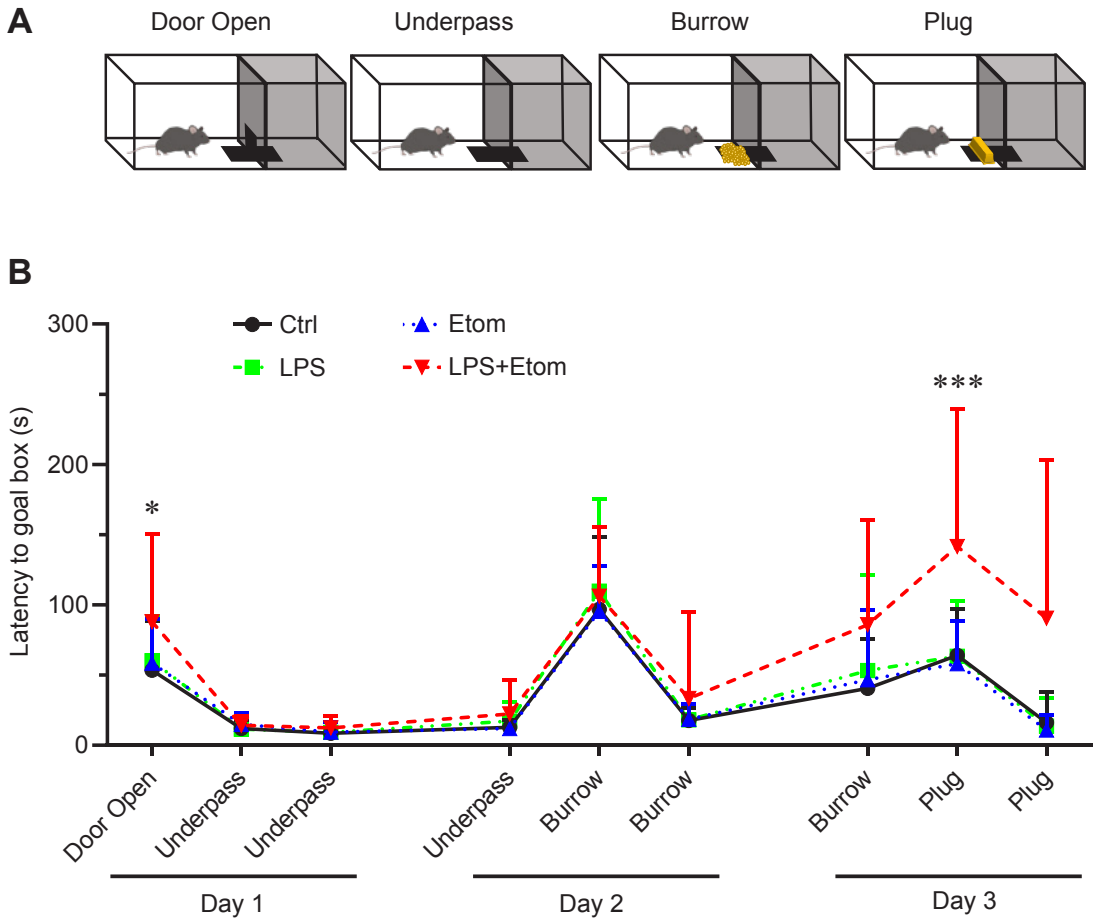

Fig. 3. The combination of lipopolysaccharide (LPS) and etomidate, but not single factors alone, impaired executive function in the puzzle box assay. (A) A schematic of the problem-solving tasks. **(B)** Only mice treated with the combination of LPS and etomidate exhibited a longer latency to enter the goal box in the Door Open and Plug tasks. n= 16–21. **P* < 0.05 LPS + etomidate versus control, ****P* < 0.001, LPS + etomidate versus all other groups, two-way ANOVA followed by Tukey's multiple comparisons test. Data are mean ± SD. Ctrl, control; Etom, etomidate.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 27

An immune signature of postoperative cognitive dysfunction (POCD)

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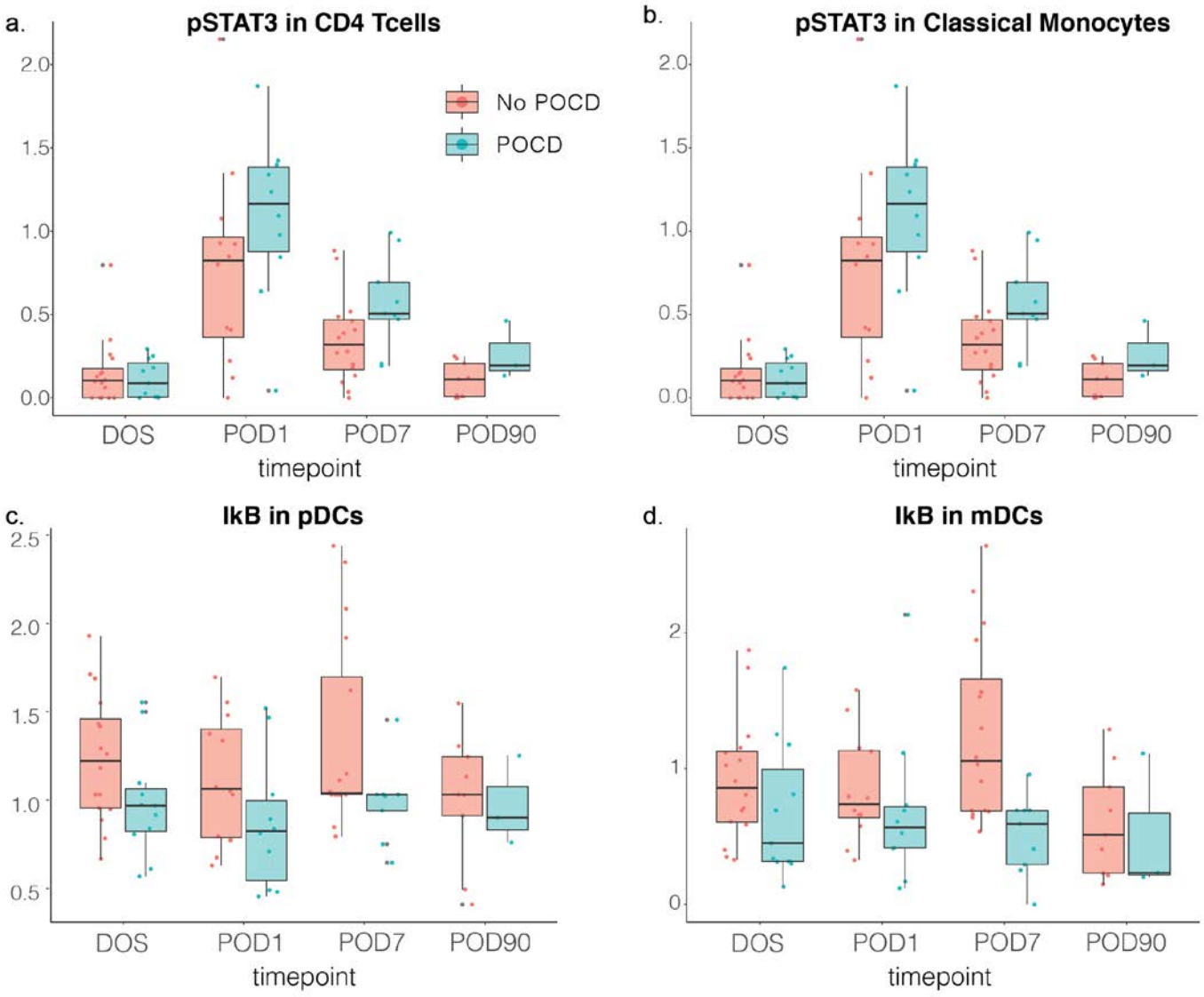
INTRODUCTION: Postoperative cognitive dysfunction (POCD) is a keystone complication of major surgeries and affects up to 41% of surgical patients aged over 60 years. POCD is associated with earlier retirement, greater use of social financial assistance, higher risk of developing dementia and higher mortality. However, there is no therapy to prevent or treat these cognitive disorders. A precise understanding of the complex neuro-immune mechanisms implicated in the pathophysiology of POCD is integral towards the development of targeted interventions to prevent POCD. We employed an integrated single-cell and plasma proteomic approach to comprehensively characterize immune system trajectories after major orthopedic surgery in patients with and without POCD. We hypothesized that 1) postoperative immune trajectories differ between patients with and without POCD and 2) that patient-specific preoperative immune states are predictive of POCD.

METHODS: 102 whole blood samples were obtained from a unique biobank of human perioperative samples collected over four time points before and after major orthopedic surgery: day of surgery (DOS) and postoperative days (POD) one, seven, and ninety. Samples were processed and analyzed using suspension mass cytometry (CyTOF) and plasma proteomics aptamer assays. The goal of this study was to identify inflammatory biomarkers associated with the occurrence of postoperative cognitive dysfunction defined as an absolute difference in Z-score >1 in at least one cognitive test (Montreal Cognitive Assessment (MoCA) or Trail Making Test A and B) between the presurgical (DOS) and postsurgical POD7 or POD90 timepoints. We employed a statistical framework to characterize the difference in the postoperative immune signature associated with the onset of POCD disorders using one-way ANOVA.

RESULTS: The high-dimensional analysis of the combined single-cell and plasma proteomic data identified a distinct immune signature of POCD. Examination of the most informative immune trajectories of the multivariate model revealed upregulated STAT3 response in CD4 T-cells (p=8e-3, Fig. 1a) and classical monocytes (p=1e-2, Fig. 1b) at postoperatively in patients with POCD. In addition, preoperative expressions of IkB in pDCs (p=4e-3, Fig. 1c) and mDCs (p=4e-3, Fig. 1d) differed between patients who developed POCD and those who did not.

CONCLUSION: Immunological trajectories differentiate patients who develop POCD from patients who do not highlight a key role of the peripheral immune system in the pathophysiology of POCD. The resulting immune signature of POCD points at cell-specific immune dysfunctions in patients with POCD (including JAK/STAT3 and NFκB signaling responses) and provides the basis for the development of a predictive test that may assist in the perioperative management of patients at risk for POCD.



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 28

The Mu opioid receptor gene does not impact survival in the MLL-AF9 murine model of acute myelogenous leukemia

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INTRODUCTION: The anesthetic care of cancer patients would benefit from further mechanistic understanding of cancer related perioperative processes. Preclinical and clinical studies have suggested opioids impair functions of immune cells, which could disrupt immune mediated clearance of cancer. However, in human cancer surgery, opioid dosing is confounded by tumor stage and burden, and retrospective studies are insufficient for justifying witholding of opioids during cancer surgery at this time. Indeed, retrospective studies have emerged suggesting that some cancer surgery patients may actually benefit from liberal opioid administration, while other patients may be negatively impacted by higher intraoperative opioid doses. Esophageal squamous cell carcinoma surgery patients given higher fentanyl doses enjoyed improved recurrence free survival (RFS) and overall survival (OS), though adenocarcinnoma patients did not[1]. We also recently reported significantly improved RFS of triple negative breast cancer patients with higher opioid doses[2]. In contrast, our lung adenocarcinoma cohort suffered worse OS with higher intraoperative opioid doses, though patients with genetic alterations in the Wnt and Hippo signaling pathways received RFS benefit from higher intraoperative opioid doses[3]. Understanding the molecular mechanisms underlying these observations could greatly improve preoperative determinations of anesthetic and analgesic strategies for cancer surgery, and preclinical modeling of these processes could be an important tool to such insights. Opioid effects on cancer could be mediated by neural control of immune system[4], through opioid effects on immune cells[5], or through opioid effects on cancer cells themselves[6]. Genetics represent a powerful way to disentangle these mechanisms[7]. We modeled acute myelogenous leukemia (AML) using wildtype versus opioid receptor (Oprm1) knockout lineage negative, Sca-1 positive, C-Kit positive (LSK) cells as the basis, usings the mixed lineage leukemia (MLL)-Af9 fusion oncogene model. Our investigations were motivated by the previous observation that bone marrow of Oprm1 KO mice are hyperproliferative and that proliferative hematopoietic progenitor cells are permissive for MLL-Af9 transformation.

METHODS: Lentivirus expressing the MLL-Af9 fusion protein and green fluorescent protein (GFP) was generated in HEK-293T cells, and viral supernatant used to transduce bone marrow progenitor cells enriched for lineage negative, Sca-1 positive, C-Kit positive (LSK) cells. Transduced progenitor cells were expanded ex vivo, then purified for GFP(+) cells by fluorescence activated cell sorting (FACS), and GFP(+) cells were transplanted into lethally irradiated CD45.1 congenic mice. These cohorts of mice were followed for cell-autonomous survival differences, analyzed by Log-rank (Mantel-Cox) testing with Prism. The bone marrow of a moribund Oprm1 KO derived MLL-Af9 AML was harvested, and transplanted into a secondary transplant into wt versus Oprm1 KO mice and followed for surivival differences, analyzed by Log-rank (Mantel-Cox) testing.

RESULTS: Figure 1: The survival analysis of female CD45.1 congenic mice transplanted with MLL-Af9 leukemia derived from LSK cells of female wt versus Oprm1 KO mice did not evidence survival differences (p=0.858). Figure 2: To examine whether MLL-Af9 AML generated in LSK cells of Oprm1 KO would demonstrate differences in AML kinetics, we subsequently transplanted MLL-Af9 Oprm1 KO AML into female wt versus Oprm1 KO recipient mice. MLL-Af9 Oprm1 KO AML did not demonstrate signifficant differences in growth in wt versus Oprm1 KO recipients (p=0.2687).

CONCLUSION: Though others have previously shown that Oprm1 KO mice have hyperproliferative hematopoietic progenitor cells in bone marrow, and that MLL-Af9 AML is reportedly licensed by proliferative status, our experiments indicate that the MLL-Af9 AML model is insensitive to Oprm1 genotype in cell autonomous (mutation in the leukemia) and cell-non-autonomous (mutation in the somatic tissues) contexts. We provide a model for the study of opioid receptor genetics and tumors, by independently mutating Oprm1 in tumor versus host. Future studies will examine drug effects.

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Figure 1

Survival kinetics of murine MLL-Af9 AML derived from wt vs *Oprm1* KO LSK cells in CD45.1 congenic transplant recipients

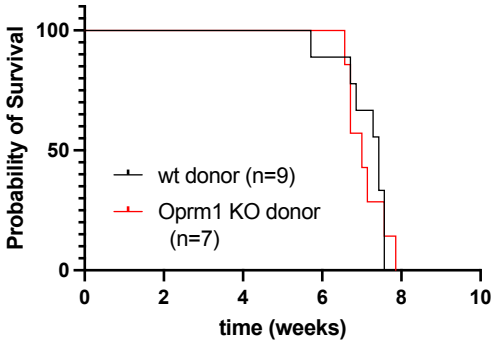
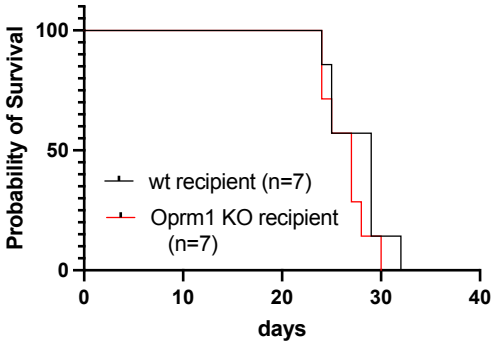


Figure 2

Survival kinetics of murine MLL-Af9 AML derived from *Oprm1* KO LSK cells in wt vs Oprm1 KO transplant recipients



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 29

Dopaminergic activity during emergence from isoflurane anesthesia in mice

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INTRODUCTION: Mechanisms of emergence from general anesthesia are poorly understood, and patients emerge passively without the use of targeted interventions to promote arousal. The dopaminergic system plays an important role in both arousal and emergence from anesthesia. Here we take advantage of genetically encoded sensor technology to record dopamine activity during emergence from isoflurane in mice in order to develop a greater mechanistic understanding of neural circuits engaged in emergence.

METHODS: The genetically encoded optical dopamine sensor dLight was expressed by stereotaxic viral delivery in nucleus accumbens of adult mice. Fiber photometry recording of dLight fluorescence was performed during restoration of the righting reflex (RORR), a behavioral marker of emergence in rodents, following isoflurane exposure.

RESULTS: We find that dLight activity increases immediately preceding emergence from isoflurane anesthesia, reflecting an increase in dopamine levels in nucleus accumbens prior to restoration of the righting reflex. Optogenetic stimulation of ventral tegmental area dopamine terminals within nucleus accumbens increases dLight activity and plays a modulatory role in changing righting behavior.

CONCLUSION: These data align with published studies showing dopamine receptor agonism in nucleus accumbens accelerates emergence from general anesthesia. Further studies are aimed at using genetically encoded biosensors and chemogenetic approaches to dissect relative contributions of ventral tegmental area to nucleus accumbens projections in emergence.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 30

A retrospective review of anesthetic management of EDAS surgery for Moya Moya disease with EEG and SSEP neuromonitoring

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INTRODUCTION: Encephaloduroarteriosynangiosis (EDAS) has been used to treat Moya Moya Disease in children. However its use in adult patients is uncommon. Several aspects make this case uniquely challenging for anesthesia management. Decisions regarding cerebral perfusion pressure, normocarbia, and information from intraoperative neurophysiologic monitoring must be considered throughout the procedure. Anesthestic management regarding maintenance with inhalational agents or intravenous agents and choice of narcotics are important decisions. No single regimen has been defined as optimum. Here we present a retrospective review of the anesthetic management of 15 adults who underwent EDAS surgery.

METHODS: A retrospective review of all EDAS cases performed at Columbia University Medical Center in New York City between October 2019 - August 2021 was performed. This single center experience, involved only one surgeon. Anesthesia records, charts and post-operative records were reviewed Pharmacologic specifics regarding induction, maintainance, use of vasopressors and anti-hypertensives, was recorded. The middle of surgery was used to determine anesthetic maintenance. The duration of anesthesia was also noted as well as the length of hospital stay after surgery.

RESULTS: A total of 15 patient records were identified (10 female, 5 male).The majority of patients had a preoperative ASA grade 3 (11). The mean BMI was 30. Average duration of anesthesia was 5.4 hours. All patients were extubated in the operation room. Propofol was used in all patients for anesthesia induction. In 11 patients fentanyl was used for induction and (4, received sufentanil during induction). Four patients received a sufentanil infusion during maintenance, whereas all 11 patients who received fentanyl for induction received reminfentanil infusion during maintenance. Two out of fifteen patients received total intravenous anesthesia for maintenance. The rest received volatile anesthesia (12 sevoflurane, 1 desflurane). A median number of 3.5 bolus doses were used for all patients of vasopressor and antihypertensive drugs. Of the four patients who received sufentanil, none required antihypertensive medicationduring the procedure. Themajority of patients who received remifentanil (8 out of 11) required at least 1 dose of antihyperstensives (esmolol, labetalol, nicardipine) during the procedure. All pateints had intraoperative EEG and SSEP monitoring. And the recordings were stable throughout the procedure. One patient suffered intracerebral hemorrhage in the postoperative period. This was the second EDAS for the patient. This patient had the longest duration of stay. Modified Rankin Score for all patients was < 2.

CONCLUSION: Encephaloduroarteriosynangiosis is an uncommon case that presents many unique challenges for anesthesiologists. Our retrospective review is limited in that it comes from a single center and only examined a small number of patients. Intraoperative neuromonitoring did not influence the anesthetic management. Although hemondynamic fluctuations are common for these procedures, of the patients that received sufentanil, antihypertensives were not required during the surgery.

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Table 1: Demographics and patient characterstics (15 patients)

Age (years, mean +/- sd)	52.73 +/- 6.69
Sex (male:female)	5:10
BMI (Mean +/- sd)	30.33 +/- 4.12
ASA grade (n = number of patients)	
Grade 2	1 (6.66%)
Grade 3	11 (20%)
Grade 4	3 (73.33%)

Table 2: Intraoperative Anesthesia management

Anesthesia Induction	
Anesthesia maintainance (n = number of patients)	
Inhalational: TIVA	13:2
Age adjusted MAC (13 patients, mean +/-sd)	0.6 +/- 0.1
Phenylephrine (mg, mean +/- sd)	14.3 +/- 9.04
Intraoperative EEG + SSEP monitoring (n = number of patients)	15
Intraoperative EEG changes (n = number of patients)	0
Other intraprocedure complications (n)	0
Duration of Anesthesia (hours, mean +/- sd)	5.4 +/- 0.59

Table 3: Postoperative course and follow up

Duration of hospital stay (days, mean +/- sd)	5 +/- 2.26
Postoperative complications during hospital stay	1 patient had stroke (ICH)

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 31

Aging delays emergence and recovery from general anesthesia in mice genetically modified to knockout the alpha-4 subunit of the GABA-A receptor

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INTRODUCTION: It is well known that anesthetic agents can disrupt thalamo-cortical function to induce anesthesia. However, recovery of the conscious state is partially mediated by inactivation of sleep pathways and activation of sub-cortical arousal networks. Clinical experience suggest that aging lengthens recovery from general anesthesia. Extra-synaptic alpha-4 containing GABA-A receptors are highly expressed in the somatosensory thalamus and regulate the firing mode of thalamo-cortical neurons. We have shown that deletion of the gabra4 gene hastened emergence from isoflurane anesthesia in mice.

METHODS: We used young adult (3-4 months) and middle-aged (11-13 months) GABRA-4 knock-out (KO) and wild-type (WT) mice to test the hypothesis that age-related changes in specific GABA-A receptors can alter emergence/recovery after isoflurane anesthesia. Following the administration of isoflurane (1.5%, 90 min), minimal alveolar concentration (MAC), emergence (return of righting reflex; RORR) and recovery (sticky dot notice) were recorded. Cognitive performance was also evaluated using spontaneous Y-maze alternation test.

RESULTS: MAC (immobility) of isoflurane, a response primarily involving reflex loops in the spinal cord, was not changed by GABRA-4 deletion in young mice, while in middle-aged mice, this marker was significantly decreased only in KO mice. Further, although genetic ablation of GABRA-4 in young mice can hasten emergence (decrease time to RORR), delays in RORR were significantly increased in both WT and GABRA-4 middle-aged mice. Additionally, aging delayed recovery after anesthesia measured by sticky-dot regardless of the genotype. Pharmacologic studies with gaboxadol (a selective GABRA-4 agonist) showed that time to RORR was significantly increased in both young and middle-aged WT mice but had minimal effects on GABRA-4 KO mice. Further, gaboxadol delayed time to sticky dot notice in both young and middle-aged mice regardless of the genotype. In respect to cognitive performance, genetic ablation of GABRA-4 receptors had no effects on the Y-maze correct alternations.

CONCLUSION: These findings suggest that the in vivo effects of isoflurane on knockout mice depends on age. Further, we confirm age-associated delays in recovery from general anesthesia. We tentatively conclude that this is due to impaired coordination of cortical signaling involving the thalamus. Future investigations into regional distribution of extra-synaptic GABA-A receptors will be necessary to reveal these mechanisms at the systems neuroscience level.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 32

Evaluation of systemic α-klotho protein levels in patients pre- and post-cardiac surgery with cardiopulmonary bypass

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INTRODUCTION: α-Klotho (klotho) is a multifunctional protein found in circulation that is highly expressed by the kidneys and choroid plexus of the brain and has reported neuroprotective and anti-aging properties[1, 2]. This study evaluated klotho serum levels in older patients before and after cardiac surgery with cardiopulmonary bypass to identify any potential associations with postoperative cognitive dysfunction. The a priori hypothesis was that lower preoperative levels of klotho are associated with the development of postoperative delirium following surgery.

METHODS: Serum samples were collected preoperatively and on postoperative day 1 from patients enrolled in the Minimizing ICU Neurologic Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) trial[3]. Written and informed consent was obtained from all patients prior to enrollment in accordance with the Institutional Review Board protocol. Inclusion criteria included patients aged ≥60 years who were undergoing cardiac surgery with an expected same-day admission to the Cardiac Surgery Intensive Care Unit for >24 hours. Exclusion criteria included patients with renal or liver failure or severe neurocognitive damage, as well as patients admitted in the intensive care unit for >2 days during the month before surgery. The 3D Confusion Assessment Method (CAM) and/or Telephone-Montreal Cognitive Assessment (T-MoCA) were performed preoperatively to establish baseline cognitive function. The long- and short-form CAM was performed twice daily from postoperative day 1 through 3 to identify the presence of delirium. Serum samples from an approved substudy of n=38 patients were analyzed (n=22 non-delirium control cohort and n=16 delirium cohort). Enzyme-linked immunosorbent assays were used to determine klotho serum concentrations preoperatively and on postoperative day 1.

RESULTS: Preoperative klotho serum levels were similar between patients who developed delirium compared to patients who did not develop delirium following major cardiac surgery (median, 95% confidence interval (CI), 468 pg/mL, 95% CI [264-2038] vs 431 pg/mL, 95% CI [272-660], respectively, p=0.5). Interestingly, higher CAM scores on postoperative day 1 positively correlated with preoperative klotho serum levels (Spearman r = 0.43, 95% CI [0.07-0.7], p=0.02). Postoperative klotho serum levels were not significantly different between control and delirium groups (552 pg/mL, 95% CI [320-798] vs 255 pg/mL, 95% CI [216-713], respectively, p=0.2), with no correlation observed between CAM scores at the same timepoint as sample collection (Spearman r = -0.18, 95% CI [-0.5-0.3], p=0.4).

CONCLUSION: Preoperative and postoperative serum klotho concentrations were not associated with the development of postoperative delirium following major cardiac surgery in this small cohort study. The broad range of the klotho concentration detected in human serum suggest a larger prospective study may be required to detect any potential associations with delirium.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 33

Probability of alpha oscillation presence during emergence from volatile based general anesthesia: an observational study.

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INTRODUCTION: It is known that the frequency of the alpha oscillation (7-17 Hz) in the frontal electroencephalogram (EEG) slows with increases in volatile anesthetic concentration during maintenance of general anesthesia. Alpha frequency (together with theta power) has consequently been suggested as a biomarker to possibly decrease the risk of unintended awareness during ongoing general anesthesia[1]. However, little is understood about the development and dynamics of the alpha oscillation during emergence i.e., the process of return of consciousness (RoC) following surgery. In particular, the relationship between alpha power, alpha frequency, and the bandwidth of the alpha oscillation has not been well characterized.

METHODS: From a single-center South-Korean open-access database (VitalDB) we analyzed 456 patients under the age of 46 undergoing emergence from sevoflurane and desflurane-based general anesthesia. 307 patients were included in the final analysis, the rest being excluded (78 due to noise or missing data and an additional 71 due to absent alpha oscillations prior to emergence). Using a method recently suggested to enhance detection of oscillations (first derivative of the EEG[sup]2[/sup]), we created a binary measure of oscillation presence [0,1] depending on if the peak power of the EEG first derivative was greater than a value of 6 dB and within the alpha frequency range. We then fitted a logistic regression to model the probability of an alpha oscillation being present over time. We compared minimum alveolar concentration (MAC), peak alpha power, oscillatory alpha power, alpha frequency and full width at half maximum (FWHM) of the oscillation (a measure of oscillation bandwidth) at oscillation probabilities of 1.0, 0.8, 0.6 & 0.4 to values immediately prior to emergence begin. We used the Mann-Whitney-U test to compare medians, and p-values adjusted for multiple comparisons using the Bonferroni method.

RESULTS: Median MAC values decreased from 0.9 to 0.3 over the time period of interest ($p < 0.05$). See Figure 1. Median peak alpha frequency increased from 9.66 Hz before emergence to 11.6 and 12.6 Hz at 0.8 and 0.4 oscillation probabilities respectively (for all comparisons $P < 0.05$). Median peak alpha power decreased from 9.34 dB prior to emergence to 8.24 & 7.01 dB at the same oscillation probabilities ($P < 0.001$). Median oscillatory alpha power increased at the same comparisons from 8.64 dB prior to emergence to 10.24 and 10.08 dB ($P < 0.001$). Median FWHM did not increase from prior to emergence to 0.4 oscillation probability ($P = 0.271$).

CONCLUSION: Peak alpha frequency and both power measures (peak and oscillatory) all showed clear changes during the emergence process, but clear differences in full-width at half-maximum (FWHM) were not observed in this dataset. Using the first derivative of the EEG enabled us to detect the alpha oscillation in a computationally efficient manner. Using this procedure, the changing alpha oscillation characteristics in response to decreasing MAC could be easily described and analyzed across different patients with different speeds of volatile flushing. This study suggests that measures of both alpha frequency and power in the frontal spectrogram may be able to act as a biomarker of the ongoing emergence process.

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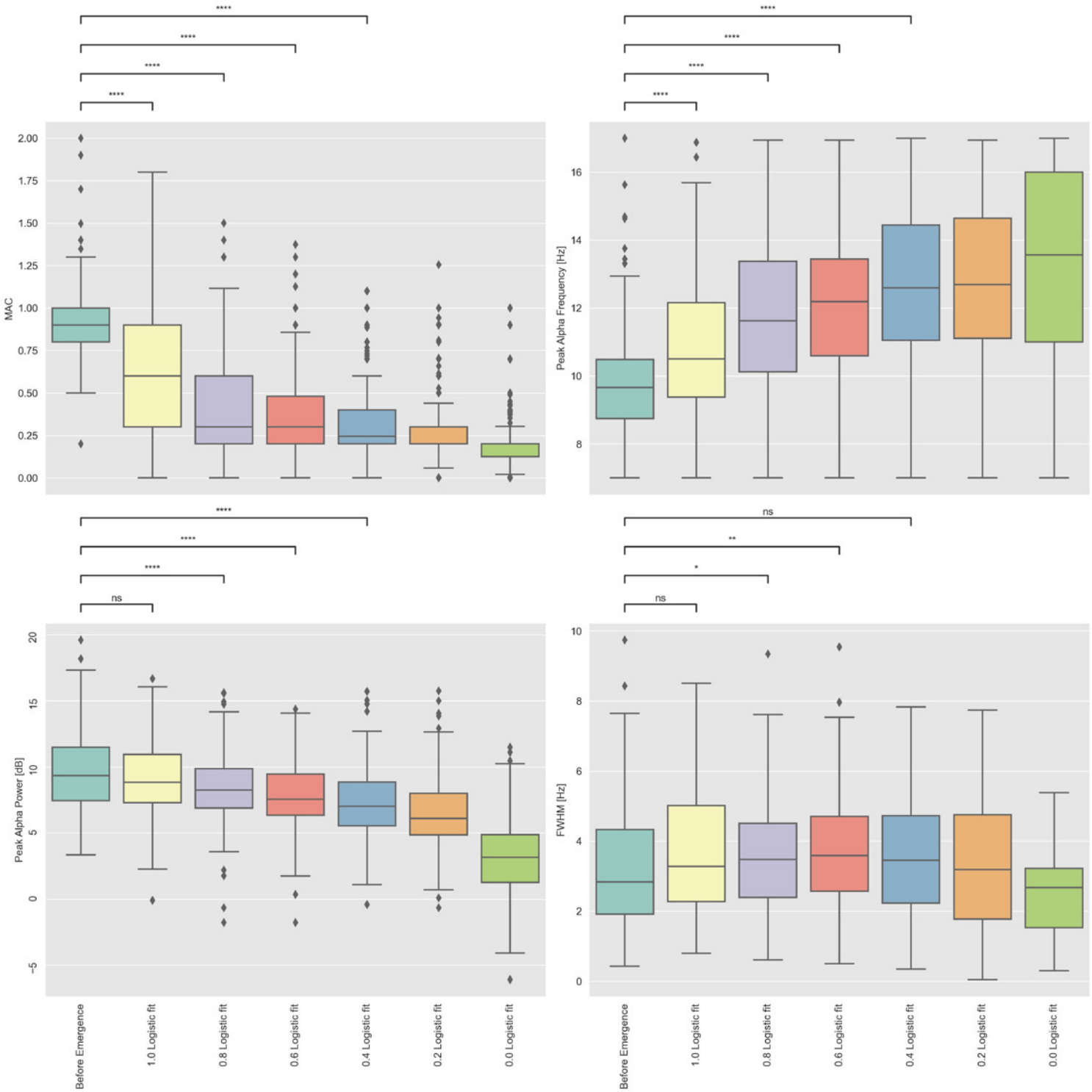

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 34

Weak, layer- and region-dependent pairwise coupling of cortical sites underlies globally synchronous state transitions during fixed isoflurane in rats.

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INTRODUCTION: During recovery from anesthesia, cortical activity states defined by the power spectra of electrophysiological recordings have been observed to transition abruptly between several characteristic patterns in rodents[1], non-human primates[2], and humans[3]. These transitions often appear synchronized between regions; furthermore, the full state obtained by combining the time-frequency spectrograms of several regions is low-dimensional[1]. The circuit mechanism that produces such state transitions is unknown. Modulation from the brainstem and basal forebrain is known to coordinate uniform changes in oscillatory activity across the thalamocortical network[4], but changes in activity may also propagate through the network in a decentralized manner. To test the uniformity of transitions and distinguish these possibilities, we directly measure transition synchrony and state correspondence between cortical sites.

METHODS: Rats were implanted with linear silicon probes in either visual (V1) and motor (M1) cortices or left and right V1. They were held at 1% isoflurane while local field potential (LFP) was recorded for up to 7 hours. Spectrograms were created by the multitaper method. Nonnegative matrix factorization (NMF) was used to compress each spectrogram, and discrete state labels were assigned based on the NMF component with the largest loading at each time. For each pair of recording sites, state transitions, normalized mutual information (NMI) of states, and canonical correlation (CC) of NMF scores were computed. Each of these measures was compared to a null model that shuffled each site's transitions using a Markov chain, with Bonferroni correction over pairs. Coupling measures for different groups of site pairs were compared using permutation tests.

RESULTS: Three M1/V1 and 4 bilateral V1 rats were included. Transitions were more synchronized than chance in 57.0% of site pairs in M1/V1 recordings and 80.2% of pairs in bilateral V1 recordings. Discrete state NMI was greater than chance in 81.9% and 96.9% of pairs in the two recording types respectively, and NMF score CC was greater than chance for all pairs in all recordings. Within-region site pairs had higher coupling by all three measures than across-region pairs ($p < 10^{6}$, permutation tests). In V1 recordings, site pairs that included a channel in layer 4 (L4) had lower coupling by all measures than those that did not ($p < 0.05$, permutation tests).

CONCLUSION: Pairs of recording sites in M1 and V1 did not consistently transition synchronously. Also, both transition synchrony and state correspondence varied depending on whether the pair mixed brain regions and whether one of the sites was in L4; sites that are expected to receive more differing input had less coupling. While the global synchrony of state transitions may emerge even from weak pairwise coupling[5], these results suggest that modulation from subcortical structures may not be responsible for synchrony.

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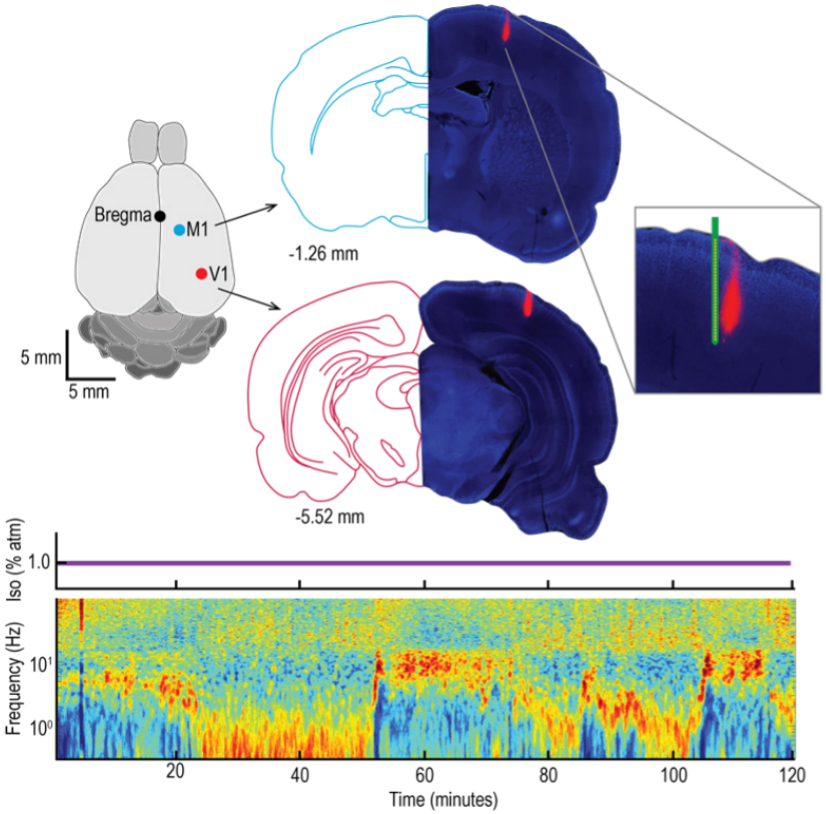

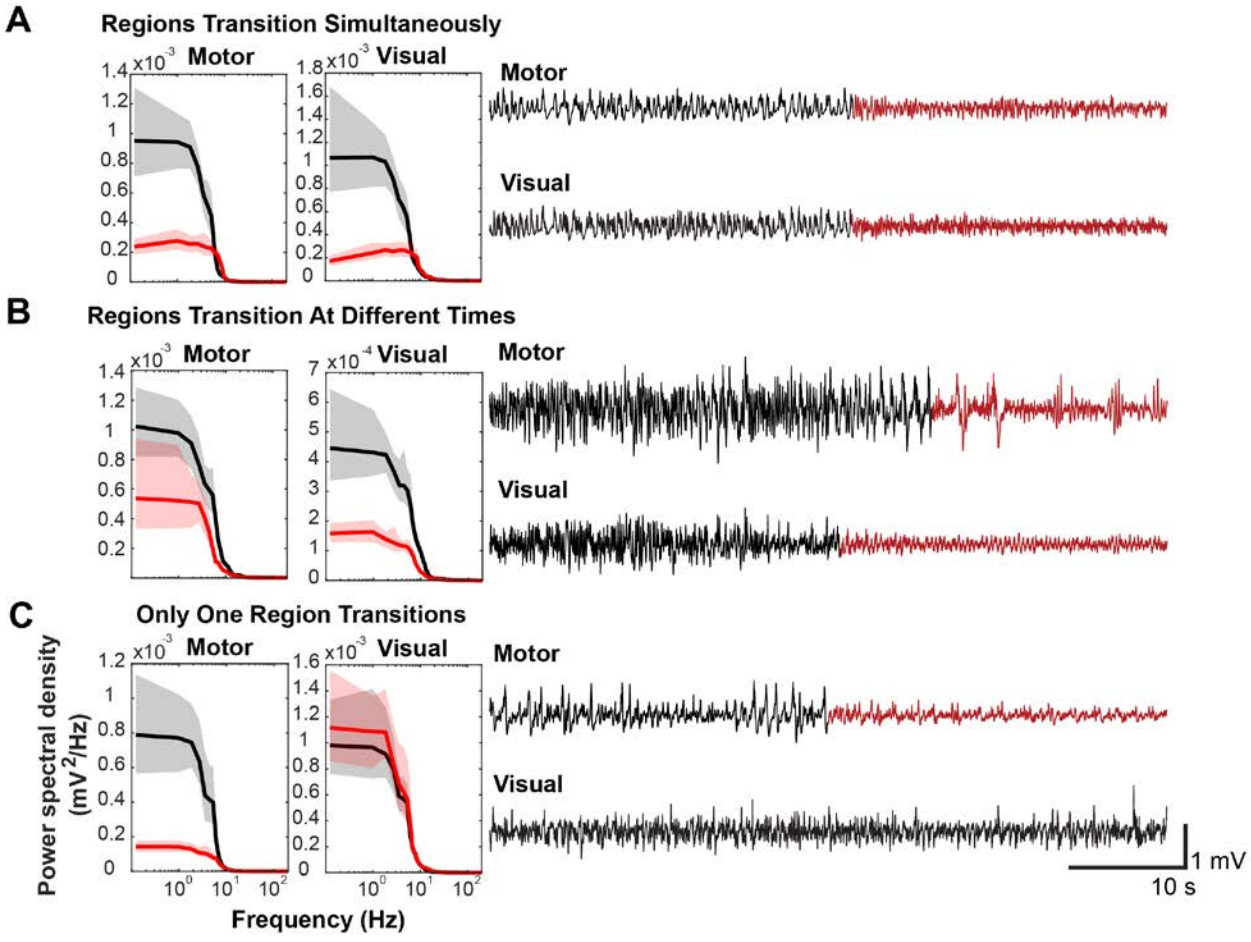

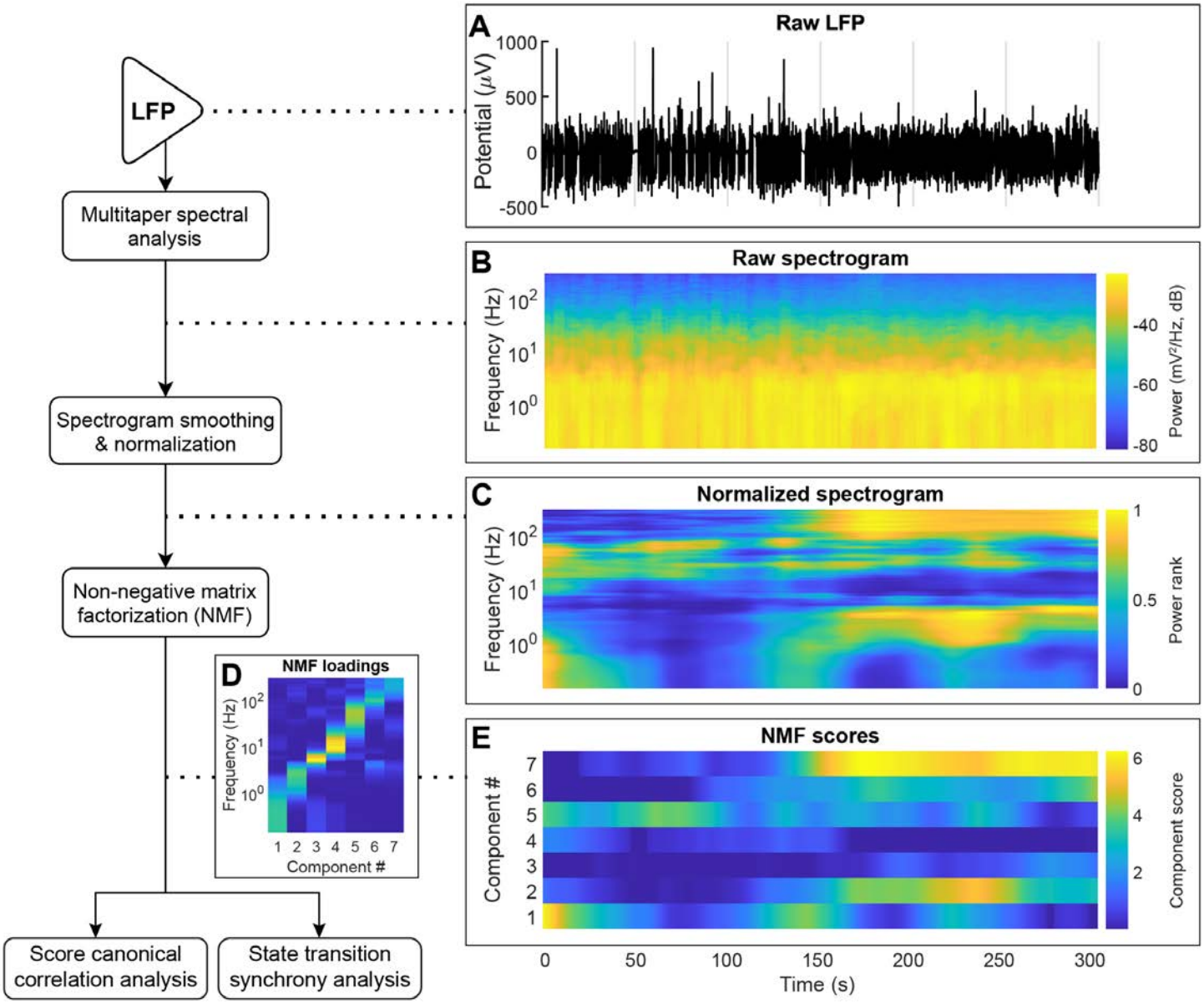

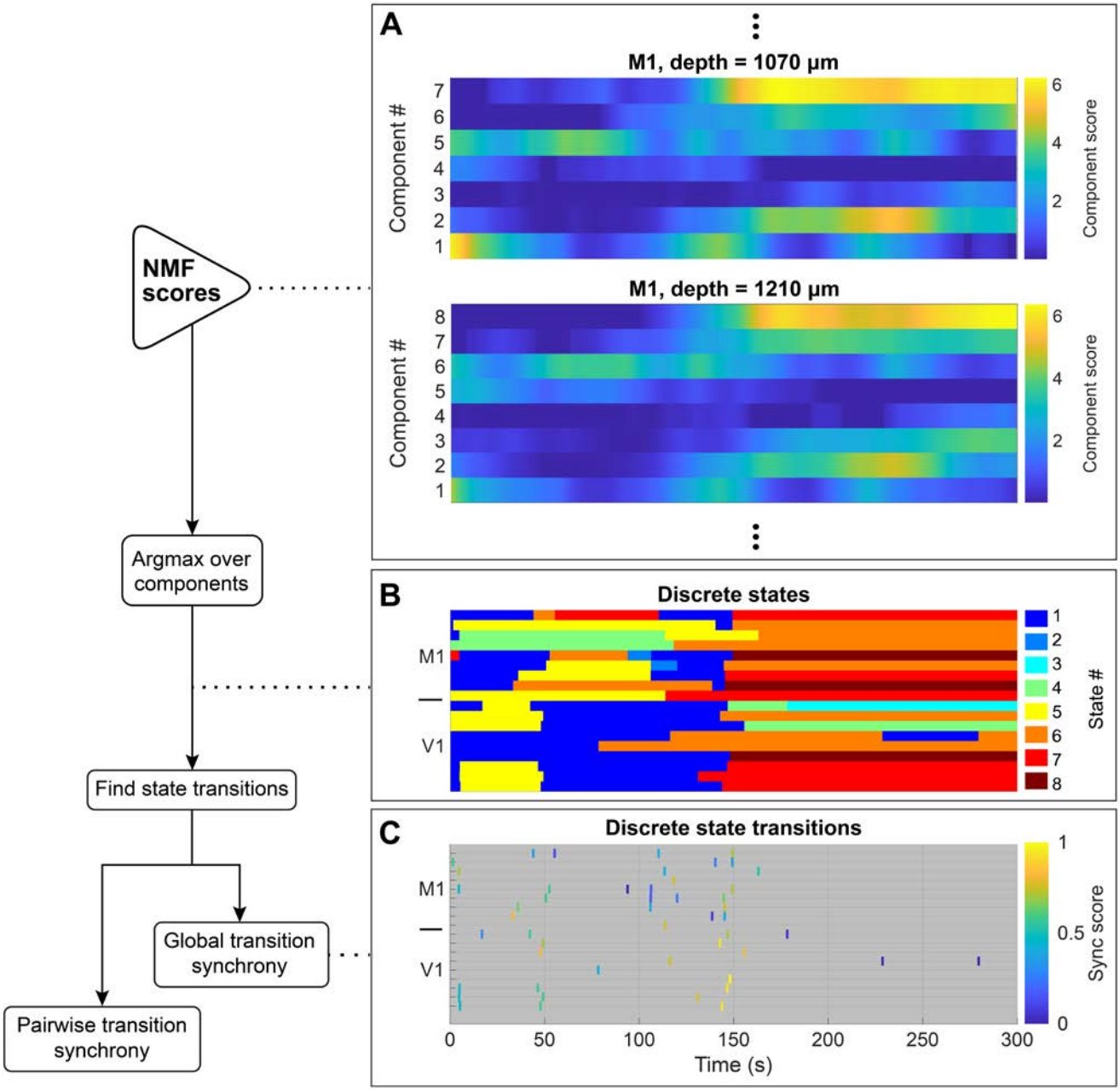

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 35

Performance of the SedLine Monitor: Age dependency and time delay

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INTRODUCTION: The use of intraoperative neuromonitoring is recommended by the European Society of Anaesthesiology as well as by the American Society for Enhanced Recovery and Perioperative Quality[1, 2]. The main purpose of these devices is to avoid excessive administration of anesthetics on one and to prevent intraoperative awareness on the other hand. However, previous publications demonstrated certain limitations and drawbacks of these devices, of which the attending anesthesiologist should be aware. For example, the processing of the EEG and the calculation of the index hinders the real time detection of sudden changes in anesthetic level[3]. Also the patient's age seems to have a significant influence on the processed EEG parameters[4]. In the present study we evaluated the performance of the SedLine monitor -one of the most commonly used monitoring systems - regarding the influence of the patient's age on the index value and analyzed the time delay caused by index calculation.

METHODS: For the analyses of the influence of the patient's age on the patient state index (PSI) we evaluated the electroencephalogram (EEG) of 141 patients undergoing general anesthesia either maintained with propofol, sevoflurane or desflurane. We selected 2 minutes of EEG recordings (free of artefacts and burst suppression) in the time period of 10 minutes before surgical stimulation. These recordings were replayed to the SedLine monitor using an EEG player[5] and we then calculated the median of the last 3 index values before the end of the recording. To analyze the correlation of the PSI and the patient's age we performed a linear regression. In addition, we randomly chose 5 patients and selected 30 seconds EEG recordings of stable awake and anesthetic states. We looped these recordings to a length of 5 minutes and replayed the various transitions. All recordings were replayed 3 times and we used the median value to calculate the time delays.

RESULTS: The PSI increased significantly with patient's age ($p<0.001$, one-sided t test). For every decade the index value increased by about 2 index points (Fig. 1). The time delay of the SedLine monitor ranged from 56.0 to 104.0 seconds depending on the transition between the different levels (Tab. 1). It has a longer delay for the transitions from either adequate anesthesia or awake/sedation to suppression with about 90 seconds and a shorter delay from adequate anesthesia to awake/sedation and vice versa with about 56 seconds.

CONCLUSION: Our results demonstrated that the PSI changed significantly with the patient's age. This fact should be taken into account when using the index value for intraoperative pharmacologic decision-making as an excessive administration of anesthetics in older patients is possible. Furthermore, the PSI showed a considerable time delay, which may hinder the prevention of adverse events such as intraoperative awareness.

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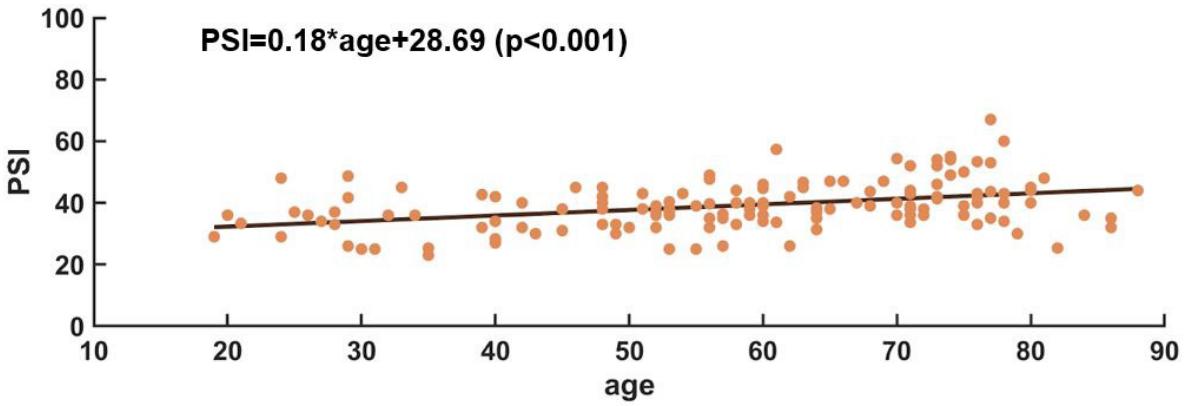
Transition	Target PSI range	Time delay median[s]	Time delay range [s]
Suppression → adequate anesthesia	≥ 25	69.33	67.33 – 76.78
Suppression → awake/sedation	≥ 70	104.00	83.33 – 108.67
Adequate anesthesia → awake/sedation	≥ 70	56.00	46.00 – 60.67
Awake/sedation → adequate anesthesia	≤ 60	56.67	50.00 – 67.33
Adequate anesthesia → suppression	= 0	90.67	89.33 – 91.33
Awake/sedation → suppression	= 0	91.33	90.67 - 95



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 36

Distinct neural firing patterns are observed in unit recordings from the rat prefrontal cortex during anesthetic-induced unconsciousness

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INTRODUCTION: The prefrontal cortex (PFC) is thought to be critically involved in the regulation of consciousness. It has been reported that administering a cholinergic agonist in the PFC restores consciousness during continuous sevoflurane anesthesia in rats.[1] Furthermore, the medial PFC is involved in thalamocortical and corticocortical interactions that modulate both induction and emergence from propofol anesthesia.[2] However, it is not known how various anesthetics and sedatives with distinct molecular targets modulate single unit activities in the rat PFC during the transition into unconsciousness and subsequent recovery.

METHODS: All experiments were approved by our Institutional Animal Care and Use Committee. One female Sprague Dawley rat (29 weeks old) was used for this pilot study, and experiments were conducted between 9am to 5pm. A central venous catheter was surgically placed in the femoral vein by Charles River Laboratory prior to arrival in our animal housing facility. The rat underwent stereotaxic neurosurgery under isoflurane anesthesia to implant a 64-channel Neuronexus microelectrode in the PFC. The 4-shank microelectrode contains 16 channels in each shank separated by 50 μm spaces. Analgesia was provided with ketoprofen after surgery, and the animal recovered for at least one week before conducting the following experiments. IV anesthetics (Propofol: 1.6mg/kg/min over 10 min; Dexmedetomidine (DEX): 3.0 μg/kg/min over 10 min; Ketamine: 5 mg/kg/min over 10 min; or Fentanyl: 3.67 μg/kg/min over 15 min) were administered via the central venous catheter. At least three days of rest were provided between experiments. After all IV anesthetic experiments were completed, additional experiments were performed with volatile anesthetics (2% isoflurane over 60 min; 3% sevoflurane over 60 min). Neural activity was continuously recorded during the awake state (before anesthetic administration), anesthetized state, and recovery state. These states were behaviorally defined by loss and recovery of the righting reflex (LORR and RORR, respectively). The neural firing frequencies were compared with the awake state, and if the firing frequency was higher or lower than the mean ±2 standard deviations, the neural firing frequencies were defined as significantly increased or decreased, respectively.

RESULTS: Three distinct neural firing patterns were identified with propofol, isoflurane, and sevoflurane. The first type exhibited a brief increase in firing frequency immediately before LORR (Figure 1). The second type exhibited a decrease in firing frequency during the anesthetized state and recovered to baseline after RORR. The third type exhibited an increase in firing frequency during the anesthetized state which decreased after RORR. DEX, ketamine and fentanyl did not significantly change the neural firing frequencies despite inducing LORR.

CONCLUSION: Three distinct firing patterns were identified in the rat PFC during propofol, isoflurane, and sevoflurane anesthesia. The neurons that increased their firing frequency immediately before LORR may be involved in producing paradoxical brain excitation during the transition to unconsciousness with these drugs. However, these changes were not observed with DEX, ketamine, or fentanyl despite inducing LORR, suggesting that anesthetics and sedatives with distinct molecular targets produce unconsciousness by distinct neural circuit mechanisms. These results encourage additional experiments to confirm these findings, and additional analysis to characterize the specific neuron types that exhibit these distinct firing patterns.

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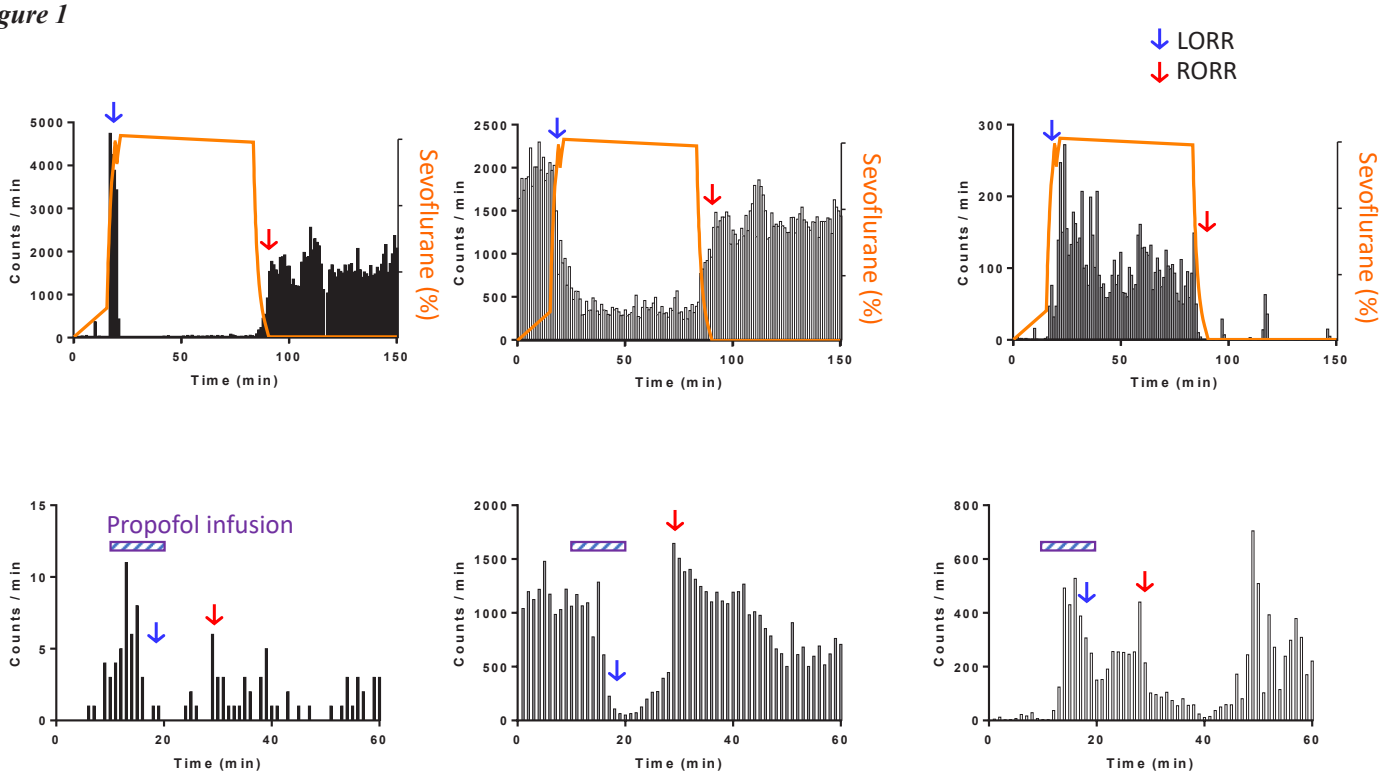
Figure 1



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 37

Performance in distinct domains of cognition may be differentially impacted by light sedation with diverse anesthetics

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INTRODUCTION: The effect of sedation with distinct anesthetics on specific cognitive domains has not been rigorously studied. Prior studies have demonstrated that different aspects of cognition may be impaired during sedation[1, 2] or emergence from general anesthesia[3]. Understanding the changes in arousal and memory formation under anesthesia is important for tailoring sedation to patient needs. To further investigate, we developed a short battery of cognitive tasks to quantify performance in the cognitive domains of attention, executive function, and memory, with motor responses. These tasks were deployed in a larger functional neuroimaging trial comparing 3 anesthetics. Results from a preliminary cohort are presented.

METHODS: Data was collected from healthy volunteers during a randomized saline-controlled, parallel-arm within-subject study (NCT04062123) comparing propofol, dexmedetomidine, and fentanyl (IRB #19030183). Three tasks were included in a 3.5 min battery. First was a psychomotor vigilance task, for which subjects were asked to respond as quickly as possible to a series of unpredictable tones, measuring motor response and attention. A serial object recognition paradigm (Fig. 1) then employed a 3-back task (measuring attention and executive function) and also assessed long-term memory[1,4]. The proportion of correct recognitions and false-positive identifications were calculated, separately, for the 3-back and memory tasks. The difference in Z-scores for correct vs. false identifications were used to quantify performance in standard deviation units. The task battery was repeated 3 times with unique images, under steady-state drug concentrations.

RESULTS: Data from 21 subjects (10 male) were analyzed; age (mean, SD) was (24.2, 5.7), drug-group sample sizes are listed in Figures 2 & 3. Small cohorts in this preliminary dataset precluded formal statistical comparisons between drug conditions. Response times to the psychomotor vigilance task are displayed in Fig. 2, with an indication that dexmedetomidine resulted in slower responses. Performance on the 2 tasks in the object recognition paradigm are shown in Fig. 3. Different profiles suggest that the drugs have distinct cognitive effects on each performance metric relative to saline.

CONCLUSION: We have successfully implemented a brief testing battery that can be used to periodically profile distinct cognitive impairments in studies of anesthetic action. Our preliminary findings suggest that dexmedetomidine may cause more pronounced slowing of motor response to auditory stimuli. Early data also suggest that propofol and dexmedetomidine may have a greater impact on attention, executive function, and memory than fentanyl. We plan to confirm if these preliminary trends persist in the full study cohort.

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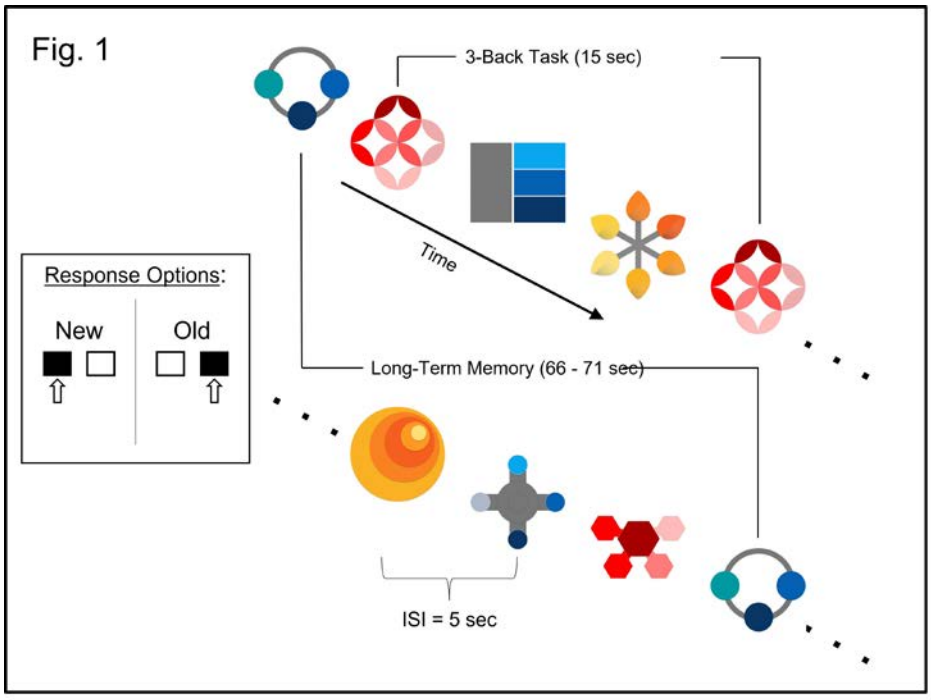

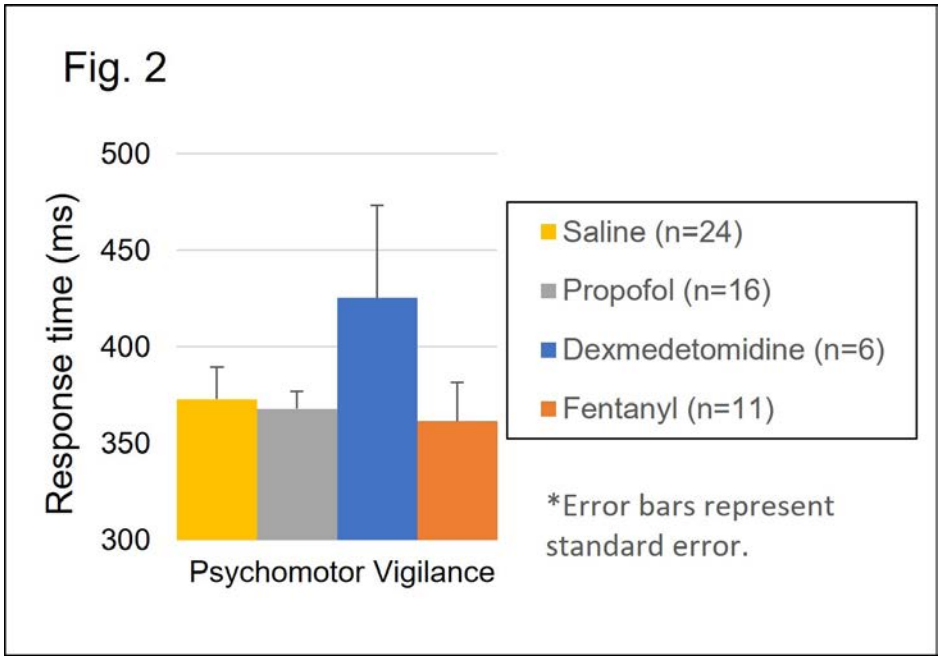

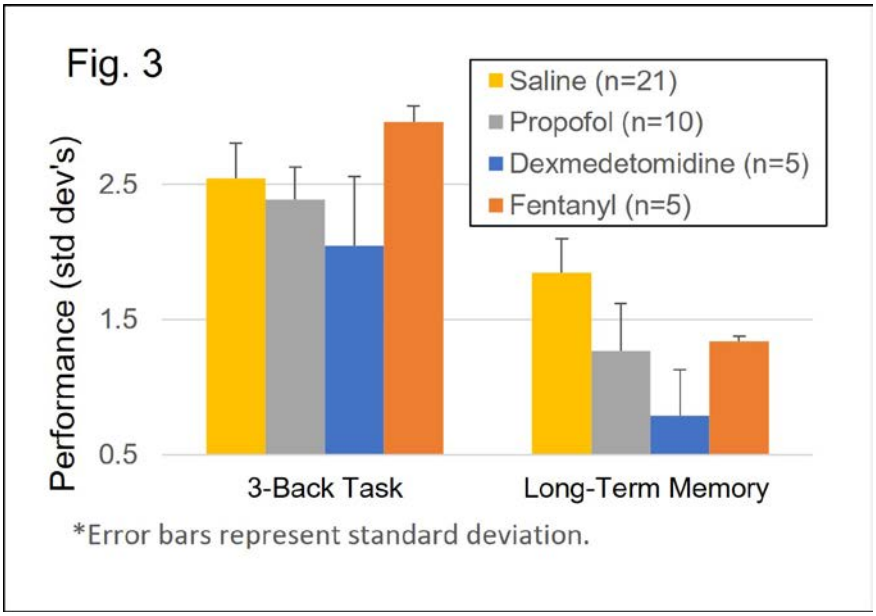

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 38

Chemogenetic activation of GABAergic neurons in the rostromedial tegmental nucleus reduces arousal and increases sensitivity to general anesthetics in mice

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INTRODUCTION: The rostromedial tegmental nucleus (RMTg) in the midbrain sends inhibitory GABAergic projections to the ventral tegmental area (VTA) to inhibit wakefulness and increase non-rapid eye movement (NREM) sleep.[1,2] We hypothesized that activating GABAergic neurons in the RMTg decreases wakefulness and increases sensitivity to anesthetic-induced unconsciousness. In this study, designer receptors exclusively activated by designer drugs (DREADDs) were used to selectively activate GABAergic RMTg neurons in transgenic Vgat-ires-cre mice. The behavioral effects on arousal and sensitivity to anesthetic-induced unconsciousness were measured.

METHODS: All experiments were approved by our Institutional Animal Care and Use Committee. Adult Vgat-ires-cre mice (4 males and 4 females) were used for all experiments. These mice express Cre recombinase under the transcriptional control of the vesicular GABA transporter (Vgat), thus limiting expression to GABAergic neurons. Stereotaxic surgery was performed to inject AAV2-hSyn-DIO-M3Dq-mCherry bilaterally (60 nL/side) into the RMTg (AP: -3.8 mm, ML: +/- 0.55 mm, DV: -4.8 mm). This adeno-associated virus (AAV) induces Cre-dependent expression of the excitatory DREADD M3Dq, which is a modified M3 muscarinic receptor that has low affinity for the native ligand acetylcholine, and high affinity for the synthetic ligand clozapine-N-oxide (CNO). On the day of behavioral experiments, mice were injected intraperitoneally (IP) with 3 mg/kg clozapine-N-oxide hydrochloride (CNO-HCl) or saline (vehicle) 30-45 minutes prior to conducting the open field test. The order of CNO-HCl and saline was randomized, and the experimenter was blinded to the condition. For the open field test, mice were placed in a 40 cm x 40 cm opaque box for 5 minutes. Activity was recorded by video and analyzed using ANY-maze software (Stoelting). To measure the effect of activating GABAergic RMTg neurons on anesthetic sensitivity, mice were anesthetized with isoflurane (2.5% for 50 minutes) or propofol (100 mg/kg, IP) and placed in the supine position. Return of the righting reflex (RORR), defined as returning to the prone position, was used as a surrogate measure for return of consciousness.

RESULTS: When GABAergic neurons of the RMTg were activated using excitatory DREADDs, mice travelled significantly shorter distances (CNO-HCl: 10.1 ± 9.5 m; Saline: 17.1 ± 4.0 m) and spent more time immobile (CNO-HCl: 126.0 ± 72.1 s; Saline: 27.3 ± 12.3 s) in the open field test after receiving CNO-HCl compared to saline ($p < 0.05$, n=8). These mice also showed a trend of taking more time for RORR after 2.5% isoflurane after receiving CNO-HCl (12.3 ± 4.9 min) compared to saline (5.6 ± 2.5 min). After propofol, mice showed a trend of increased time to return of righting with CNO-HCl (55.4 ± 27.8 min) compared to saline (8.6 ± 17.3 min). Four mice that did not lose the righting reflex after saline + propofol, did lose righting for over 50 minutes after receiving CNO-HCl + propofol.

CONCLUSION: These results suggest that activating GABAergic RMTg neurons reduces overall motor activity and makes the brain more susceptible to isoflurane- and propofol-induced unconsciousness. The RMTg may play an important role in actively suppressing arousal during states of unconsciousness induced by general anesthetics that potentiate GABAA receptors such as halogenated ethers and propofol.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 39

Patients' Ability to Participate in Telehealth Appointments for Preoperative Assessments

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INTRODUCTION: Telehealth has been shown to increase access, decrease cost[1], alleviate travel time and decrease the amount of time patients spend away from work[2]. Preoperative assessments for appropriately triaged cases in our clinic can be done via telehealth to provide timely and high-quality assessments for patients to enhance perioperative surgical outcomes. This paper investigates the feasibility of adopting telehealth in a preoperative assessment clinic in a metropolitan academic medical center.

METHODS: In fall 2021, a survey was designed to collect patient demographics, preference for in-patient versus telehealth encounters, and type of smart and medical devices owned. Medical students collected 146 surveys from a random, convenience sampling of patients who came into our clinic. Verbal consent was obtained and results were analyzed using descriptive and chi-squared statistics.

RESULTS: Our study included 146 patients, 65 males and 81 females, from three age categories with 54% of participants (79 patients) falling into the 65 and older category. No survey participants were excluded from our study. Forty-seven percent of participants (69 patients) preferred in-person appointments, among which 51% (35 patients) were categorized as having 'communication' concerns. This was defined as the inability to fully understand what was happening via a telehealth appointment (Figure 1). Among the 35 patients, 15 were age 65 and older while 20 were below age 65 (Table 1). Thirty percent of patients who preferred in-person appointments (21 patients) were categorized as having 'technology' issues, defined as having limited access to smart devices (Figure 1). Fourteen of these patients were age 65 and older and 7 were below age 65 (Table 1). Thirty-five percent of patients (51 patients) preferred telehealth appointments for the following reasons: 'location and commute' and 'ease of use' (Figure 2). Participants in the 'location and commute category' either lived far away from the clinic or liked that telehealth encounters alleviate commute time. Those who felt comfortable using smart devices for telehealth appointments were placed in the 'ease of use' category. With respect to access, 86% of patients either had at least one smart device and/or could use someone else's smart device while 14% (21 patients) could not (Figure 3). Only 12 patients could not participate in telehealth at all due to lack of access. Most patients own medical devices for vital sign measurements, such as a thermometer (75%), a scale (71%), a blood pressure machine (66%), a glucometer (29%), and a pulse oximeter (28%) (Figure 4).

CONCLUSION: Most participants (47%) prefer in-person appointments even though many possess both smart devices and medical devices. Many patients feared decreased access to higher level health care providers as well as a reduced quality of care. Surprisingly, most patients who preferred in-person appointments due to 'communication' issues were less than 65 years old. However, age had no significant influence on patients who had 'technology' concerns, meaning patients in all age groups are equally as comfortable using technology for telehealth encounters (Table 1). Taking this into consideration, we recommend that an educational component be developed to compel patients to accept telehealth services and realize healthcare quality and the level of communication will be just as effective with these services. Further studies are needed to determine how social, cultural, and economic factors affect participation in telehealth encounters in a major metropolitan academic center.

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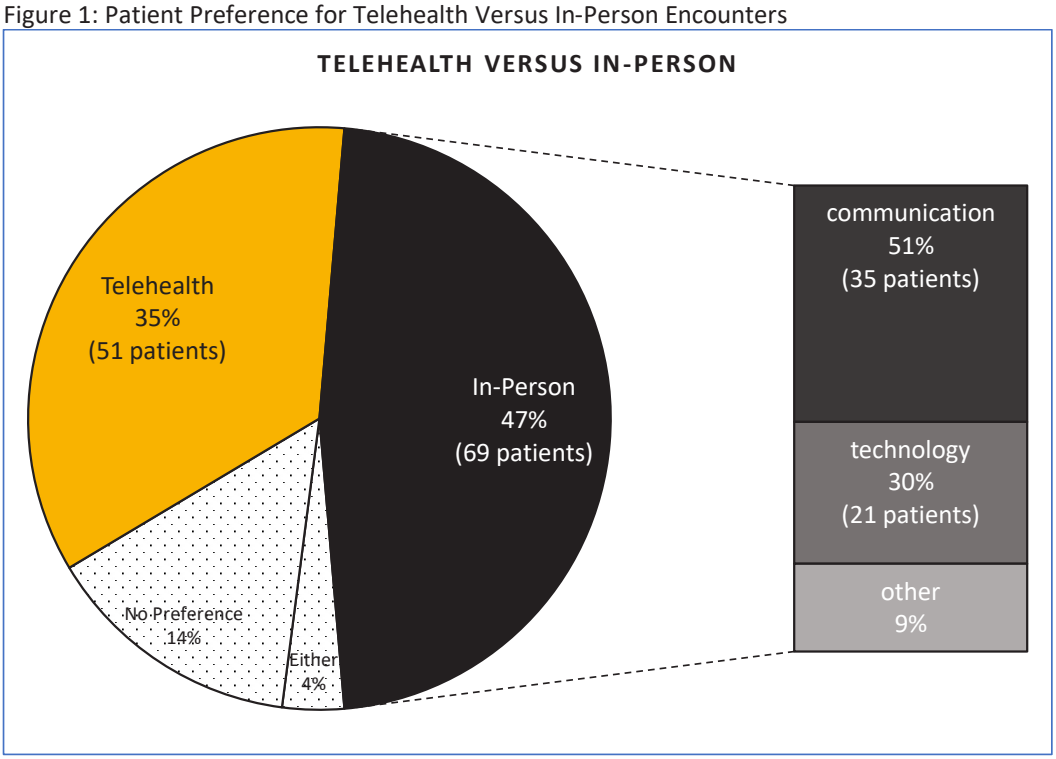
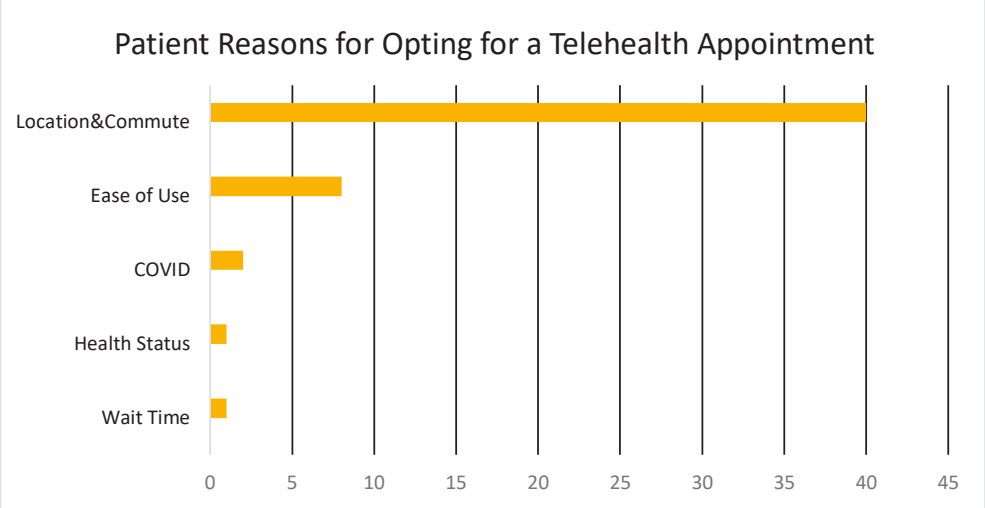
Figure 1: Patient Preference for Telehealth Versus In-Person Encounters



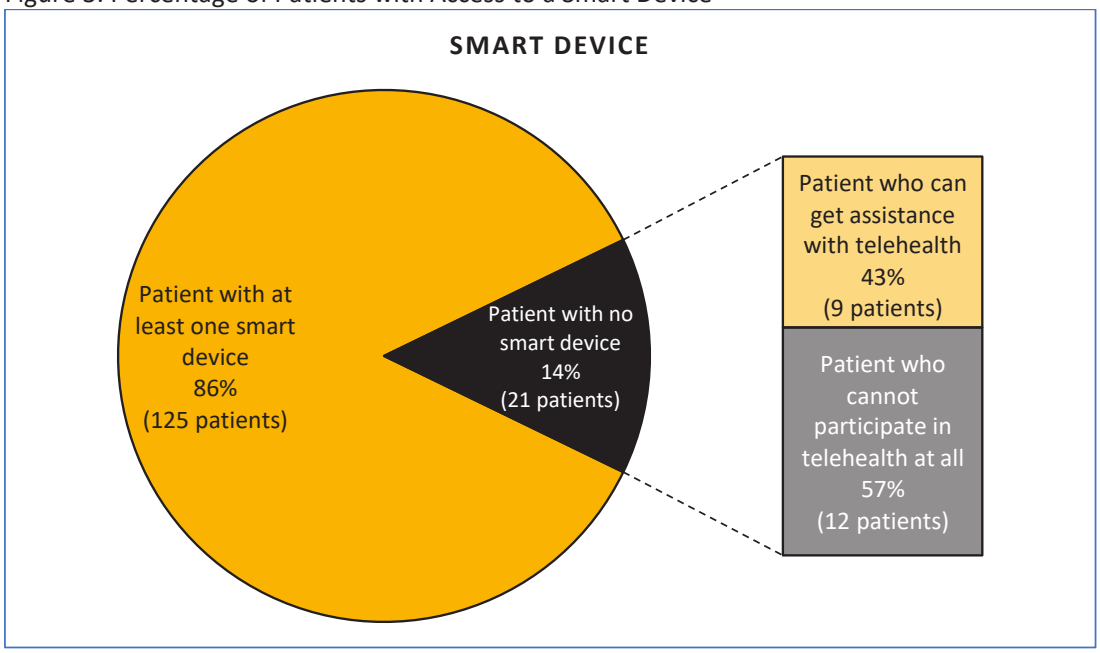
Among the patients who participated in our survey, 47% preferred in-person appointments due to experienced or feared communication and/or technological issues via telehealth.

Figure 2: Patient Reasons for Opting for a Telehealth Appointment



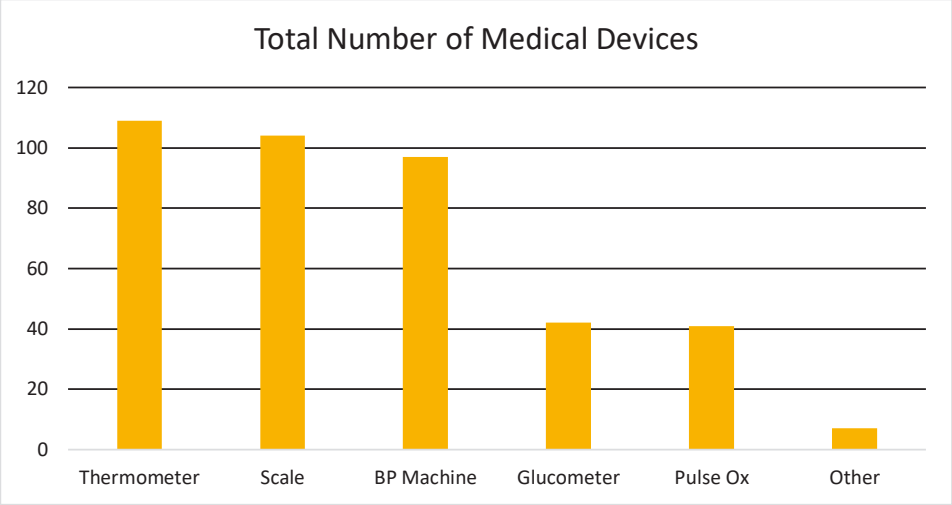
The most popular reason for choosing telehealth appointments fell into the "Location & Commute" category because patients lived far away from the clinic and liked that telehealth appointments decreased commute time. Patients also liked how easy it was to attend a telehealth appointment.

Figure 3: Percentage of Patients with Access to a Smart Device



Out of the 146 patients who participated in our survey, 86% own at least one smart device while 14% percent do not own any smart devices. However, only 8% (12/21 patients) of study participants are unable to participate in a telehealth encounter at all due to issues with access, meaning they did not own a smart device and were unable to find someone who owned a smart device to assist them with their appointment.

Figure 4: Number of Patient-Owned Medical Devices



The thermometer, owned by 109 patients, is the most popular medical device. This is followed closely by a scale, owned by 104 patients, and a BP machine which is owned by 97 patients.

Table 1: Preference for In-Person Encounters by Age Group and Reason

	Prefer In-person Encounters due to Reasons Categorized as "Communication"	Prefer In-person Encounters due to Reasons other than "Communication"
Age 65 and older	15	23
Age 64 and younger	20	11
Age group, especially among those below 65, had a significant influence on patient's listing "communication" as a reason for preferring in- person appointments over telehealth appointments (p = 0.04).		
	Prefer In-person Encounters due to Reasons Categorized as "Technology"	Prefer In-person Encounters due to Reasons other than "Technology"
Age 65 and older	14	24
Age 64 and younger	7	24
Age group had no significant influence on choosing "technology" as a reason for preferring in-person vs telehealth appointments.		

Age group had a significant influence on choosing "communication" concerns as the reason for preferring in-person encounters, especially among patients less than 65 years old. On the other hand, age group had no significant influence on choosing "technology" as a reason for preferring in-person encounters, meaning that patients in all age categories are equally likely to have technological concerns.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 40

The impact of the EEG emergence trajectory on commercial indices monitoring the hypnotic component of anesthesia

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INTRODUCTION: Patients receiving general anesthesia seem to be at higher risk of developing postoperative delirium (POD) when presenting with certain electroencephalographic EEG patterns during emergence[1]. These results were based on the analysis of the spectral composition of frontal EEG whilst emerging. However, in daily clinical routine anesthetists are provided rather with indexed processed EEG data than the visualized EEG spectrum over time. Hence, we evaluated if the most commonly used neuromonitoring devices with their corresponding indices (Entropy Module / state entropy (SE), Conox / qCON, the bispectral index (BIS), SedLine / the patient state index (PSI)) are able to differentiate between the various emergence trajectories allowing an intraoperative screening for patients with higher odds of developing POD.

METHODS: For our analyses we selected the EEG of 30 patients recorded in the initial study[1]. Ten of these patients showed the most favorable trajectory (T1), while the other 20 patients showed the least favorable trajectories (T4, n=10 or T5, n=10). T1 was characterized by a delta (0.5-4 Hz) dominant EEG pattern at the beginning of emergence, followed by an alpha (7-17 Hz) dominant slow wave anesthesia (SWA) period and eventually showing non-slow-wave patterns before waking up (lowest odds of developing POD). T4 was defined by an abrupt change from a delta dominant SWA to wake patterns (4-fold increased risk to entail POD). The third trajectory - T5 - presents early non-slow-wave activity with dominating power in higher frequencies (8-fold increased risk). In order to evaluate the performance of the neuromonitoring devices we replayed the patients' EEG to the monitors using an EEG player[2]. Subsequently, we compared the index values for T1, T4 and T5 for each monitoring device.

RESULTS: As described earlier[1], the particular trajectories showed significant differences in their spectral composition (Fig. 1). SE and PSI were able to resolve significant differences between T1 and T4. T1 showed an almost linear increase of index values, whereas T4 led to an episode of low index values followed by a sudden increase (Fig. 2). Comparing T1 vs. T5, however, qCON and BIS were the indices showing significant differences, especially in the beginning of emergence. Patients representing T1 patterns had significantly lower index values than those depicting T5 (Fig. 2). Due to the T5 cases starting in non-slow-wave anesthesia, their indices were already high at the start of emergence.

CONCLUSION: Our analysis revealed that spectral EEG patterns during emergence from general anesthesia do influence the course of the different indices as well. Considering certain emergence trajectories being associated with higher risk of developing POD our approach might enable the anesthetist to identify patients particularly susceptible to POD by observing the course of index values before admission to the postanesthesia care unit.

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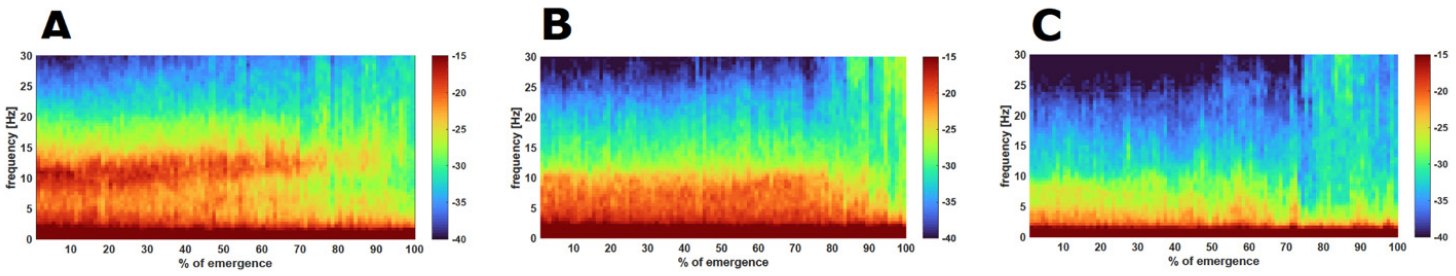

Fig. 1 Density spectral array of raw frontal EEG resembling trajectories **T1(A)**, **T4(B)** and **T5(C)**, respectively.

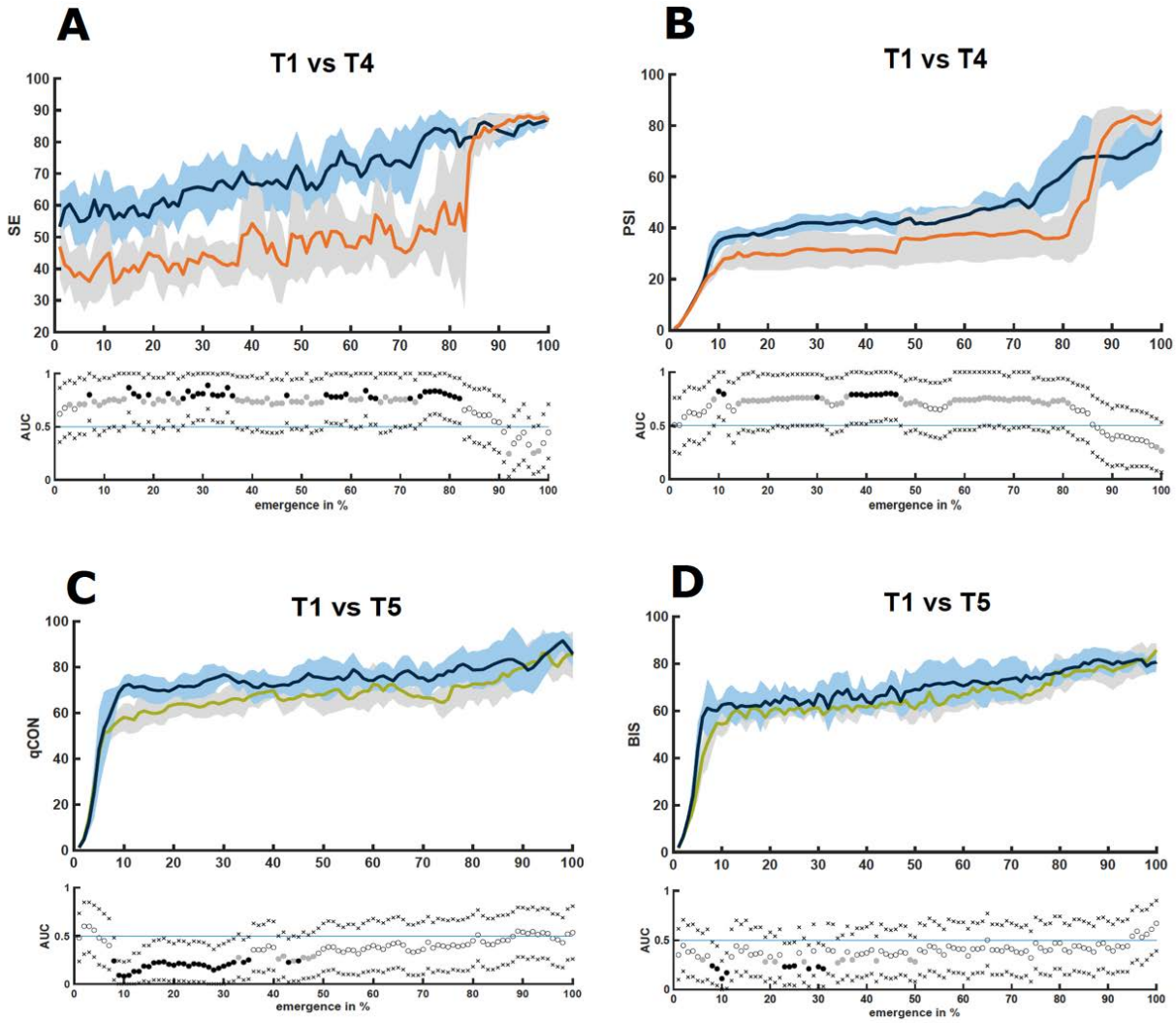

Fig. 2 Course of respective indices during emergence from anaesthesia. Trajectories **T1** (blue) ,**T4** (orange) and **T5** (green) displayed for **SE (A)**, **PSI (B)**, **qCon (C)** and **BIS (D)**. Below AUC (black dots resembling significance, grey ones clinical relevance).

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 41

Modeling pupillary reflex dilation and feature extraction for the estimation of remifentanil effect under general anesthesia

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INTRODUCTION: In previous studies[1,2] a relation between the amplitude of dilation in the pupillary reflex dilation (PRD) curve and the remifentanil effect-site concentration (RemiEC) was observed. In this study we aim to model the PRD curve and determine which features, in addition to the amplitude of dilation, are best to discriminate the pharmacodynamic effect of remifentanil.

METHODS: PRD measurements were obtained using Algiscan (IDMED, France) in patients undergoing general anesthesia with remifentanil and propofol (Target Controlled Infusion). This data was then modeled using an ordinal differential equation model, considering a 5 seconds tetanic stimulus, and one second step stimuli to account for observed time varying properties of the PRD, resulting in a model of nine transfer constants (k1 to k9). Model parameters were obtained minimizing the error between original and modeled data, using the simplex search method, constraining the search to a maximum of iterations in case of divergence. Features extracted from the modeled curve consisted of baseline pupil diameter, maximum pupil reflex diameter, delay between stimulus onset and peak dilation, percentage of dilation from baseline, maximum pupil diameter variation (first differences) and delay, minimum pupil diameter variation (fastest descent) and delay, area under the curve (AUC), AUC with baseline removal (AUCb). Correlation analysis was applied to reduce dimension, and the extracted features introduced in a neural network to estimate the analgesic dose according to RemiEC classes 0, 0-2ng/ml and >2ng/ml. The NN was trained in 70%, and tested in 30% of the data. Data analysis was performed using IBM SPSS Statistics.

RESULTS: 1294 PRD measurements from 86 patients were initially included. Due to data loss, a final set of 1264 PRD records were analyzed. An example of a modeled curve is shown on Figure 1. Table 1 presents dataset summary. Figure 2 and Table 2 present the results for the classification of RemiEC groups, using the trained NN and features extracted from the modeled PRD. We obtained a correct classification in 72,3% of data points in the training set, with best results for the extreme groups, remifentanil 0ng/ml (80,0%) or remifentanil>2ng/ml (88,1%), showing the difficulty in differing intermediate effects that are constrained by interpatient variability regarding drugs' effect-site concentration.

CONCLUSION: Conclusions: We were able to produce a robust model of the PRD while extracting features from this curve. Our data suggests these features can be used to better predict the remifentanil effect. Besides, these results also corroborate PRD as an useful measurement to detect the remifentanil dose-dependent blunting effect to nociceptive stimuli such as a tetanic stimulation. The classification results are limited since effect-site concentrations were used as estimates of effect, which may be hindered by interpatient variability and PKPD models' limitations.

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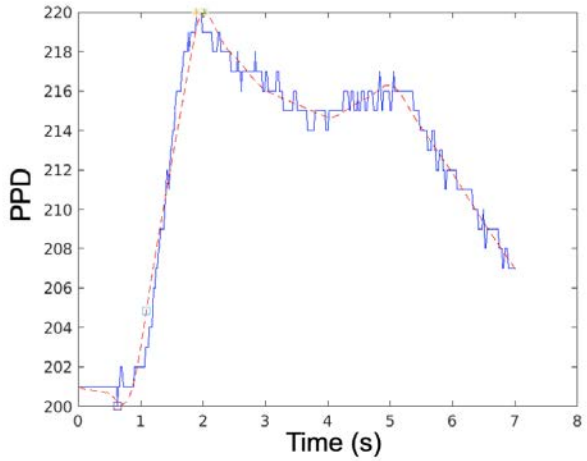

Figure 1. Example of modeled curve and extracted features from one PRD segment in the study.

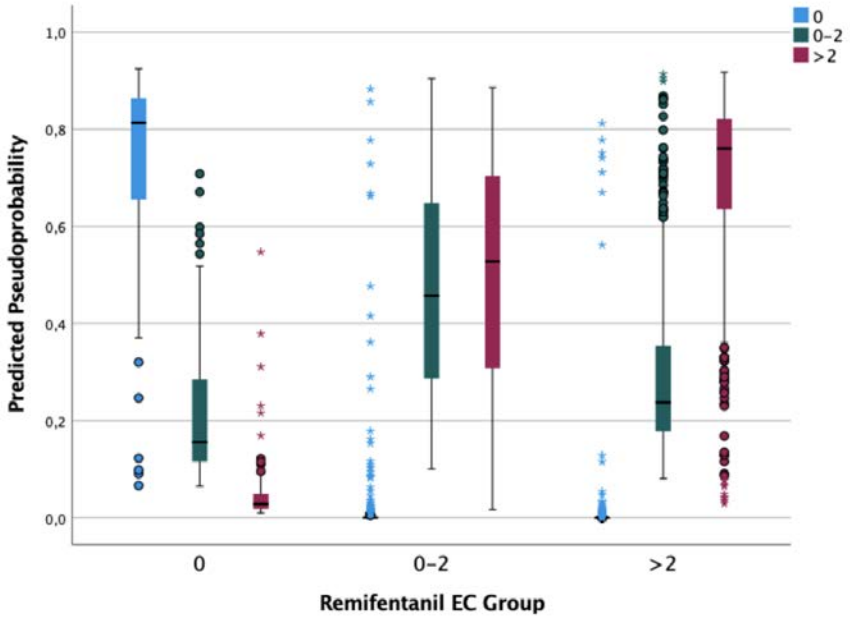

Figure 2: Results of the classification of RemiEC groups, using the trained NN and features extracted from the modeled PRD.

	Remifentanil EC Groups (ng/ml)		
	0 (N = 74)	**0-2 (N = 408)**	**>2 (N = 782)**
Remifentanil EC (ng/ml)**	0	1,33 ± 0,42	3,32 ± 2,37
Propofol EC (ug/ml)**	6,35 ±1,32	3,32 ± 1,75	3,32 ± 1,33
Baseline**	386,65 ± 80,42	222,49 ± 37,76	208,45 ± 38,30
Maximum**	532,97 ± 93,00	269,10 ± 55,16	235,70 ± 53,86
Maximum Delay**	5,28 ± 1,29	3,78 ± 1,78	3,09 ± 1,60
Maximum Derivative**	5,53 ± 15,00	1,77 ± 3,64	0,45 ± 0,61
Maximum Derivative Delay**	1,89 ± 1,52	0,82 ± 1,28	1,17 ± 0,94
AUC (10^3)**	224,33 ± 37,90	117,54 ± 21,14	104,92 ± 20,82
AUC-Baseline (10^3)**	42,61 ± 24,30	12,98 ± 9,43	6,95 ± 7,22
Dilation**	146,32 ± 81,25	46,62 ± 34,96	27,24 ± 31,45
Dilation (%)**	41,14 ± 27,40	21,10 ± 15,45	13,18 ± 14,74
Minimum Derivative	-4,80 ± 15,29	-1,59 ± 3,74	-0,42 ± 2,40
Minimum Derivative Delay**	2,98 ± 2,39	1,43 ± 2,27	3,38 ± 2,37

Table 1. Average and standard-deviation of drugs' effect site concentrations (EC) and extracted features from the original pupil reflex dilation to a tetanic stimulus. AUC, AreaUnder de Curve for the three groups (RemiEC 0, 0-2 and >2ng/ml).

		Predicted			
	Observed	**0**	**0-2**	**>2**	**Correct %**
Training	0	44	5	0	89.8%
	0-2	6	127	147	45.4%
	>2	4	58	476	88.5%
	Global	6.2%	21.9%	71.9%	**74.6%**
Testing	0	20	3	2	80.0%
	0-2	2	52	74	40.6%
	>2	3	26	215	88.1%
	Global	6.3%	20.4%	73.3%	**72.3%**

Table 2: Results of the training and testing set. We obtained a correct classification in 72,3% of data points in the training set, with best results for the extreme groups, remifentanil 0ng/ml (80,0%) or remifentanil>2ng/ml (88,1%).

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 42

Machine learning XGBoost classification of postoperative delirium by intraoperative EEG metrics

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INTRODUCTION: Postoperative delirium (POD) occurs in up to 50% of older adults undergoing major surgery with anesthesia[1] and is associated with long-term cognitive impairment[2-4] and increased risk of 1-year mortality[5] and Alzheimer's disease.[6] As the number of older adults undergoing surgery increases each year, there is an increasing need for clinical prediction tools and research on delirium mechanisms.[7] Neurophysiological measures like electroencephalography (EEG) are a logical target for researching clinical prediction and mechanisms of POD, since they can identify brain abnormalities before impairment is detectable with cognitive tests. Because EEG requires a reference channel to eliminate ground-related noise, and the choice of reference can bias outcomes, we investigate the influence of intraoperative EEG features and referencing methods on POD classification with gradient boosted decision trees.

METHODS: Data come from 3 prospective studies measuring intraoperative EEG during major surgeries with general anesthesia.[8-10] Enrollment criteria required patients to be ≥60 years old, English-speaking, with a scheduled non-cardiac, non-neurologic surgery, and planned surgical duration of ≥2 hours. EEG data was collected from custom 32-channel BrainVision EASYCAPs (Morrisville, NC) offline filtered from 0.5-55Hz. Delirium incidence was determined from 3-Minute Diagnostic Confusion Assessment Method (3D-CAM) or CAM scores through postoperative day 5 or hospital release. Data was selected for analysis if the patient had inhaled gas anesthetic for ≥80% of surgery and EEG data with ≥30 minutes of usable data after artifact removal. 46 patient datasets met criteria for analyses.

XGBoost in Python 3.8 was used to fit a classification model with delirium incidence as the outcome. Features included intraoperative EEG metrics (average case power, phase lag index, coherence, burst suppression, and global field synchrony) from delta (1-4Hz) through gamma (30-55Hz) frequency bands by region of interest (left and right frontal and parietal, whole-head) and referencing method (system reference, local, current source density (CSD), and average mastoid). Connectivity metrics were calculated from pairwise regions of interest as well as whole-head, inter-hemispheric, and intra-hemispheric variations. 473 intraoperative EEG features split by referencing method were used to identify the optimal feature set for classifying POD. A 60-40 training-test split was used to perform feature selection, hyperparameter tuning, and classification of POD. Referencing models were compared by area under the curve (AUC), and feature importance was recorded to find the top 3 intraoperative metrics contributing to classification of POD for each referencing model.

RESULTS: 6 subjects (13%) experienced POD. CSD referencing had the highest AUC value of the 4 referencing models. For additional results, see Figures 1-4.

CONCLUSION: Results suggest that POD is best classified from CSD referenced right frontal-right parietal theta phase lag index and left parietal alpha power. Future analysis will include the full dataset (isoflurane and propofol cases) to determine whether anesthetic type influences feature selection or classification. If results generalize to other datasets, then these measures may guide development of improved clinical prediction tools as well as future research on POD brain mechanisms. Future studies may extend this technique to categorical cognitive criteria that may be impaired after surgery with anesthesia in a subset of surgical patients.

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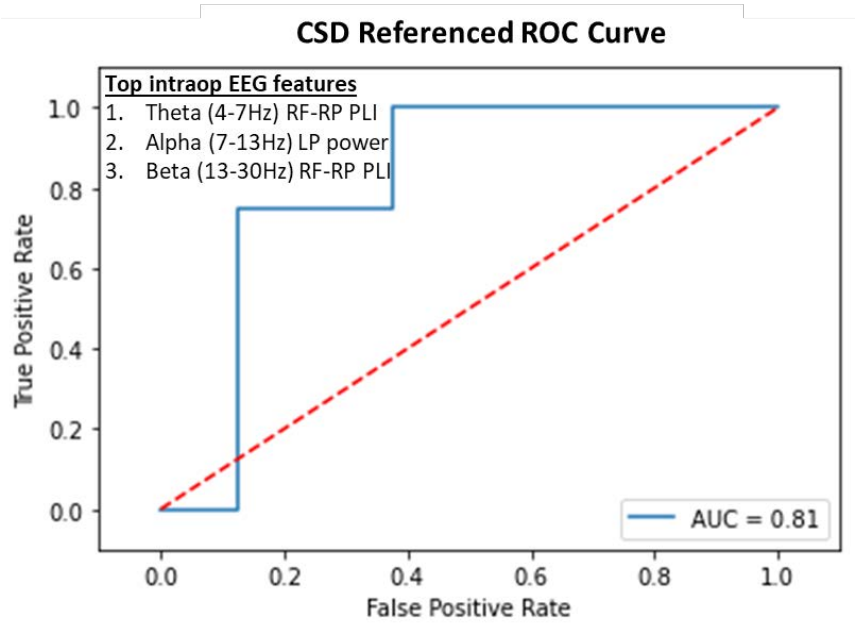

Figure 1. RF = right frontal, RP = right parietal, LP = left parietal, PLI = phase lag index.

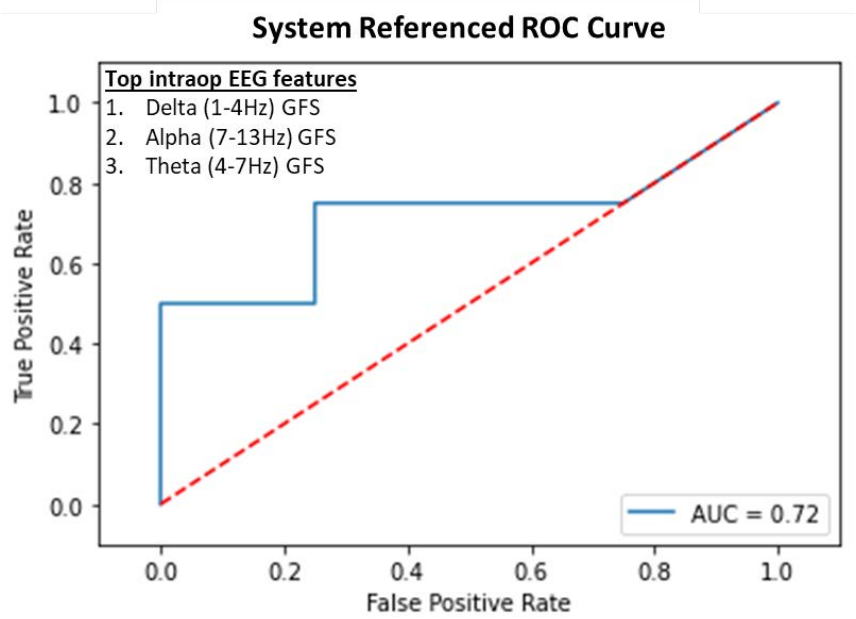

Figure 2. GFS = global field synchrony.

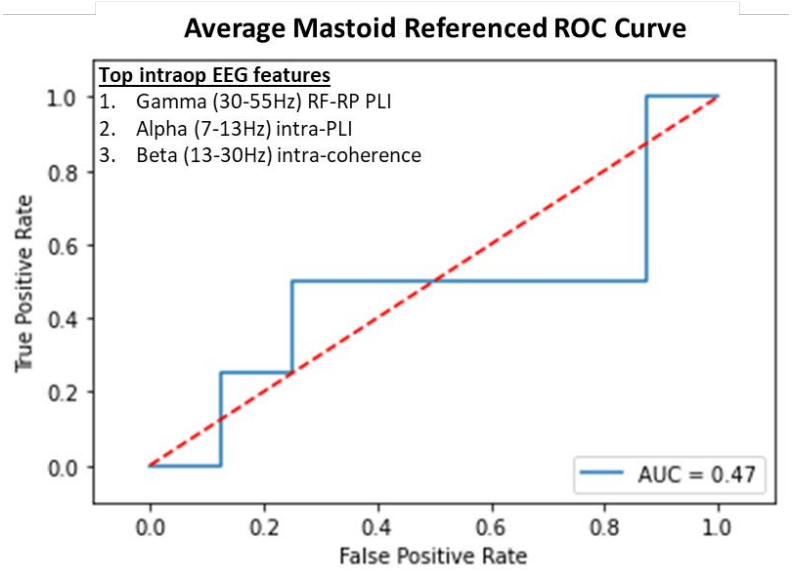

Figure 3. RF = right frontal, RP = right parietal, PLI = phase lag index, intra = intrahemispheric.

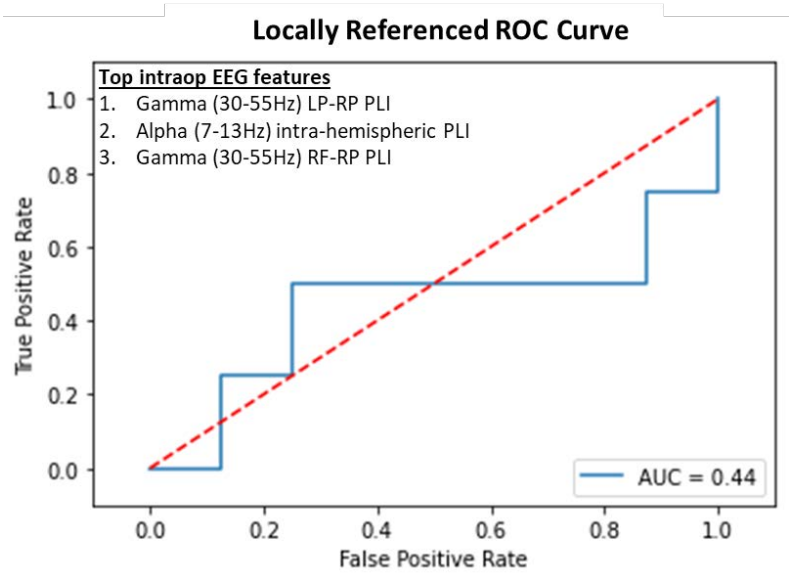

Figure 4. LP = left partietal, RP = right parietal, RF = right frontal, PLI = phase lag index.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 43

QTc Interval Evaluation in Naïve Methylphenidate Users: A Double-Blind Placebo-Controlled Analysis

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INTRODUCTION: Prolonged QTc interval has been linked to adverse outcomes for chronic methylphenidate users.[1-3] We intended to investigate if naïve methylphenidate users receiving a single dose of methylphenidate extended-release formula experienced a prolongation of QT interval as seen on 12 lead ECG recorded at 4.5 hour after administration.

METHODS: This is a sub-study using data obtained from a placebo-controlled double-blind trial. Fifty-four adult naïve methylphenidate participants (18-65 years old) received methylphenidate extended-release formula or matching placebo suspension. Pre- and post-operative QTc intervals were calculated. We included in our analysis only participants with a pre-operative QTc less than 450 ms (the normal QT interval is considered between 400 - 440 ms).

RESULTS: Of the fifteen study participants in the placebo group, only one experienced a QTc above 500 ms post-op, seven ranged between 450-500ms, and seven below 450 ms. In the methylphenidate group, two participants were above 500 ms, two between 450-500, and eight were below 450 ms.

CONCLUSION: Our team found no conclusive evidence to suggest that a single dose of methylphenidate extended-release formula results in QTc interval prolongation. In fact, a weak negative correlation was noticed and should be further investigated.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 44

Modulation of hippocampal contextual memory, place cells, and spatial engrams by (R)-CPP, a potent NMDAR antagonist

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INTRODUCTION: N-methyl-D-aspartate receptors (NMDARs) are strongly linked to memory, learning and other higher cognitive functions. We recently reported an interesting mismatch between the dose and brain concentration of CPP (a potent NMDAR antagonist) that suppresses contextual fear conditioning (IC50 = 2.3 mg/kg -> 53 nM) versus the concentration needed to block NMDARs and LTP in the hippocampus (361 - 464 nM)(1). To test whether this mismatch occurs because of CPP actions at extrahippocampal sites or within the hippocampus, we used a variant of fear conditioning that separates the contextual (hippocampal) and other (e.g. amygdaloid) components of learning temporally. We also imaged hippocampal CA1 pyramidal neuron activity in awake behaving mice to assess effects of CPP on place cell formation and spatial engram stability.

METHODS: All experiments were carried out with institutional IACUC approval. CPFE - Context Preexposure Facilitation Effect: On day1 (context pre-exposure), mice (n=12/group) were placed explored a novel arena freely for 10 minutes. On day2 (aversive conditioning), mice were replaced into the arena and after 15sec administered foot shock. On day3 (recall), mice were placed in the same arena, and their freezing behavior (an innate fear response) was quantified. Saline or (R)-CPP (1mg/kg, 3mg/kg, and 10mg/kg IP) was administered on either day1 or day2. Ca2+ imaging: A miniature endoscopic camera (Inscopix nVoke) was used to capture the activity of underlying CA1 pyramidal neurons expressing GCaMP6f, in mice (n=4) repeatedly exposed to a novel context on day1, then the same or an alternate context on day2. Saline or (R)-CPP (1mg/kg, 3mg/kg, and 10mg/kg) was injected prior to day1 or day2 imaging.

RESULTS: In CPFE experiments, CPP given before pre-exposure (day1) induced a dose-dependent reduction in fear memory, with IC50=3.2 mg/kg (Figure 1). CPP given pre-shock (day2) similarly blocked freezing (IC50 4.4mg/kg). In Ca2+imaging experiments, CPP given on day 1 dose-dependently reduced place cell formation (Figure 2) and suppressed the formation of stable engrams (Figure 3), as shown by reduced rate map correlations between day1 and day2 (RMcorr:d1->d2). CPP given on day2 (pre-recall 10mg/kg (R)-CPP) did not significantly reduce RMcorr:d1->d2, showing that CPP blocked learning but not recall.

CONCLUSION: CPP suppresses hippocampus-specific memory (CPFE behavioral experiments) and the neural correlates of memory (place and engram cell formation) at doses that do not block LTP or NMDAR-mediated field potentials in brain slices. These findings indicate that CPP acts within the hippocampus to impair learning, but that acts on elements (e.g. interneurons) that are not reflected in commonly employed measures (i.e. LTP and EPSPs). The lack of effect of CPP on recall indicates that CPP also can suppress the association of context and shock by acting outside of the hippocampus.

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1. (authors redacted) (2021). CPP impairs contextual learning at concentrations below those that block pyramidal neuron NMDARs and LTP in the CA1 region of the hippocampus. Neuropharmacology, 202, 108846. https://doi.org/10.1016/j.neuropharm.2021.108846

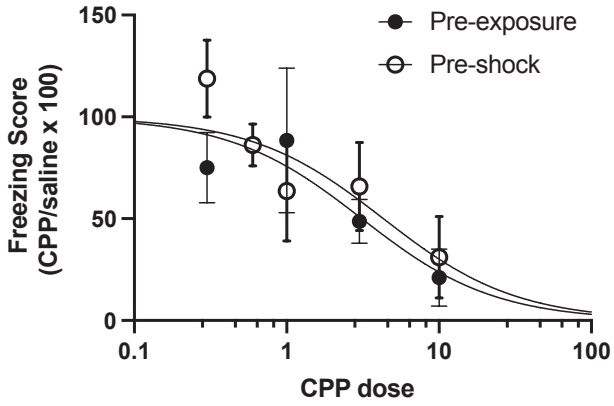

Figure 1. Dose-dependent reductions in fear memory expression by pre-exposure and pre-shock administration of (R)-CPP, as measured by CPFE learning paradigm.

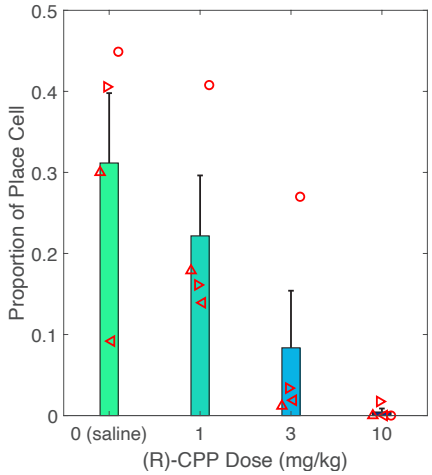

Figure 2. Dose-dependent reductions of hippocampal place cell formation, as measured by mutual information.

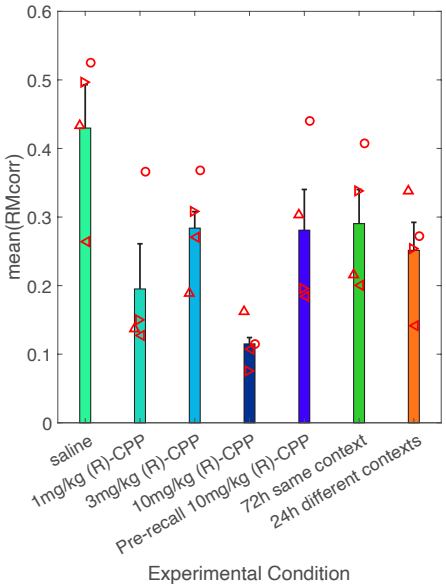

Figure 3. Dose-dependent reduction of rate-map (RM) correlation as a measure of spatial engram stability, as well as some control experiments.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 45

Hypoxia-triggered O-GlcNAcylation in the brain drives glutamate-glutamine cycle and reduces sevoflurane anesthesia sensitivity

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INTRODUCTION: General anesthesia, its nature, and how exactly it works are still elusive. Hypersensitivity to general anesthetics predicts adverse postoperative outcomes in patients. However, the biological underpinnings that determine anesthesia sensitivity remain poorly understood.

METHODS: To investigate whether hypoxia regulates anesthesia sensitivity, mice were acclimated to hypoxia condition (HA, 10% oxygen [O2] for 8 hours/day) for 28 days and anesthetized with sevoflurane; the effective concentrations for 50% of the animals (EC50) showing loss of righting reflex (LORR) and loss of tail-pinch withdrawal response (LTWR) were determined and quantified. Moreover, Western blotting and mass spectrometry were conducted to analyze the brain O-GlcNAcylation level and O-glycoproteomic landscape. Seahorse analysis, carbon 13 (13C) tracing experiment, coimmunoprecipitation, and site-specific mutagenesis technique were also used to explore the mechanisms by which hypoxia regulates sevoflurane anesthesia sensitivity.

RESULTS: As compared to the control group, the HA-exposed mice required higher doses of sevoflurane to present LORR and LTWR, and the dose-response curves of both tests were right-shifted. Interestingly, the HA-blunted sevoflurane sensitivity was correlated with an elevation of protein O-linked N-acetylglucosamine (O-GlcNAc) modification in the brain, and could be abolished by 6-diazo-5-oxo-l-norleucine (DON), a glutamine fructose-6-phosphate amidotransferase (GFAT) inhibitor, and mimicked by thiamet-G (TMG), a selective O-GlcNAcase (OGA) inhibitor. Mechanistically, O-GlcNAcylation drives de novo synthesis of glutamine from glucose in astrocytes and promotes the glutamate-glutamine cycle, partially via remodeling of glycolytic flux and activation of glutamine synthetase (GS).

CONCLUSION: Hypoxia promoted the glutamate-glutamine cycle in the brain in an O-GlcNAc-dependent fashion, which decreased mouse sensitivity to sevoflurane anesthesia. Our results, therefore, reveal an unappreciated critical role of O-GlcNAcylation in neurotransmitter homeostasis and anesthesia sensitivity, and highlight the potential of HA as a simple remedy for the anesthetic-vulnerable populations.

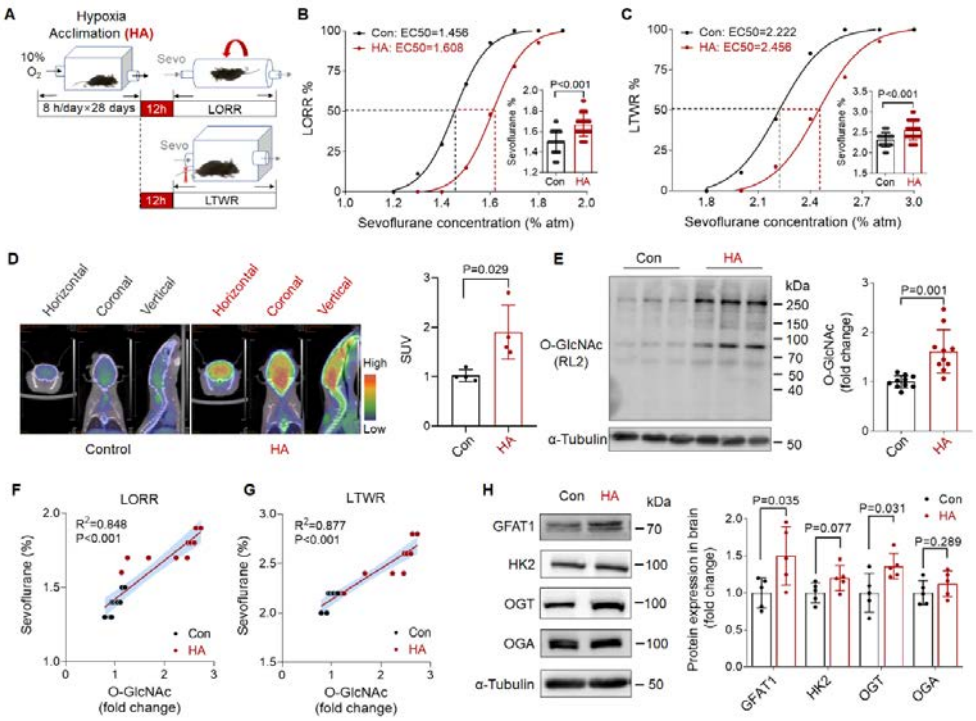

Figure 1. HA boosted O-GlcNAcylation in mouse brain and reduced sensitivity to sevoflurane anesthesia.

(A) A schematic representation of the experimental protocol.

(B-C) Dose-response curves showing the percentages of mice exhibiting LORR (B) or LTWR (C) in response to incremental sevoflurane concentrations for the control and HA groups. Insets: the sevoflurane concentrations at which each mouse exhibited LORR (B) or LTWR (C) are shown (n=27 per group).

(D) Representative 18F-FDG PET-CT images of the control and HA brains. The color bar applies to all images, with warmer colors represent greater 18F-FDG uptake (left). The SUV in the control and HA brains (right, n=4 per group).

(E) Representative blots (left) and a quantitation graph of O-GlcNAc-modified protein (right) in the control and HA brains (n =10 per group).

(F-G) The linear regression analysis between the protein O-GlcNAcylation levels and sevoflurane concentrations at which each mouse exhibited LORR (F) or LTWR (G).

(H) Representative blots (left) and average protein levels (right) of HK2, GFAT1, OGT, and OGA in the control and HA brains (n = 5 per group).

Data are presented as mean±SD. Statistical comparisons were conducted using Unpaired 2-tailed Student t-test (B, C, D, E, H) or linear regression analysis (F, G). The exact P-values are reported for indicated comparisons and P<0.05 is considered statistically significant. 18F-FDG, 18F-labeled fluoro-2-deoxyglucose; Con, Control; GFAT1, glutamine:fructose 6-phosphate aminotransferase 1; HA, hypoxia acclimation; HK2, hexokinase 2; LORR, loss of righting reflex; LTWR, loss of tail-pinch withdrawal response; OGA, O-GlcNAcase; OGT, O-GlcNAc transferase; PET-CT, positron emission tomography-computed tomography; SUV, standardized uptake values.

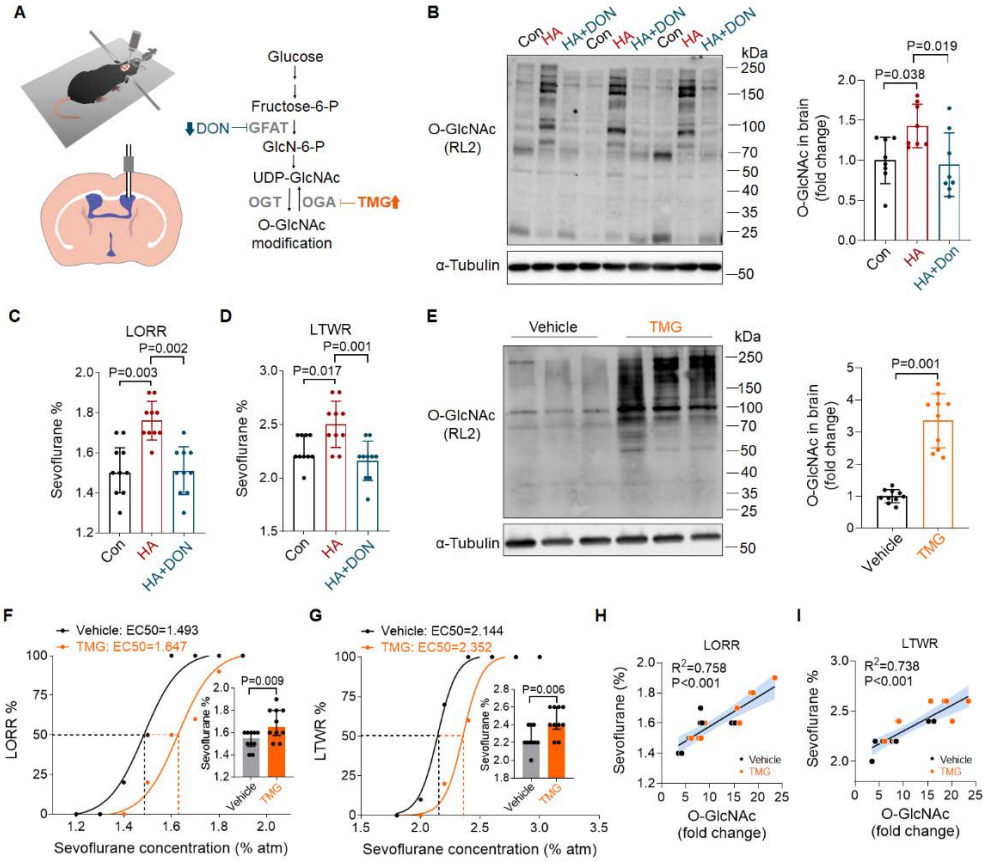

Figure 2. Sevoflurane sensitivity was modulated by O-GlcNAcylation in the brain.
(**A**) A schematic diagram showing the injection of DON or TMG into the lateral ventricle of mice (left). The DON and TMG were used for inhibition of hexosamine biosynthesis pathway enzymes GFAT and OGA, respectively (right).
(**B**) Immunoblot analysis of protein O-GlcNAc modification in mouse brains after indicated treatments (n=8 per group).
(**C-D**) The sevoflurane concentrations at which each mouse exhibited LORR (**C**) or LTWR (**D**) (n=10 per group).
(**E**) Immunoblot analysis of protein O-GlcNAc modification in mouse brains after Vehicle or TMG treatment (n=10 per group).
(**F-G**) Dose-response curves showing the percentages of mice exhibiting LORR (**F**) or LTWR (**G**) in response to incremental sevoflurane concentrations of the mice after Vehicle or TMG treatment. Insets: the sevoflurane concentrations at which each mouse exhibited LORR (**F**) or LTWR (**G**) are shown (n=10 per group).
(**H-I**) The linear regression analysis between the protein O-GlcNAcylation levels and sevoflurane concentrations at which each mouse exhibited LORR (**H**) or LTWR (**I**).
Data are presented as mean±SD. Statistical comparisons were conducted using One-way ANOVA (**B, C, D**), Unpaired 2-tailed Student *t*-test (**E, F, G**), or linear regression analysis (**H, I**). The exact *P*-values are reported for indicated comparisons and $P<0.05$ is considered statistically significant. Con, Control; DON, 6-diazo-5-oxo-l-norleucine; HA, hypoxia acclimation; LORR, loss of righting reflex; LTWR, loss of tail-pinch withdrawal response; TMG, Thiamet-G.

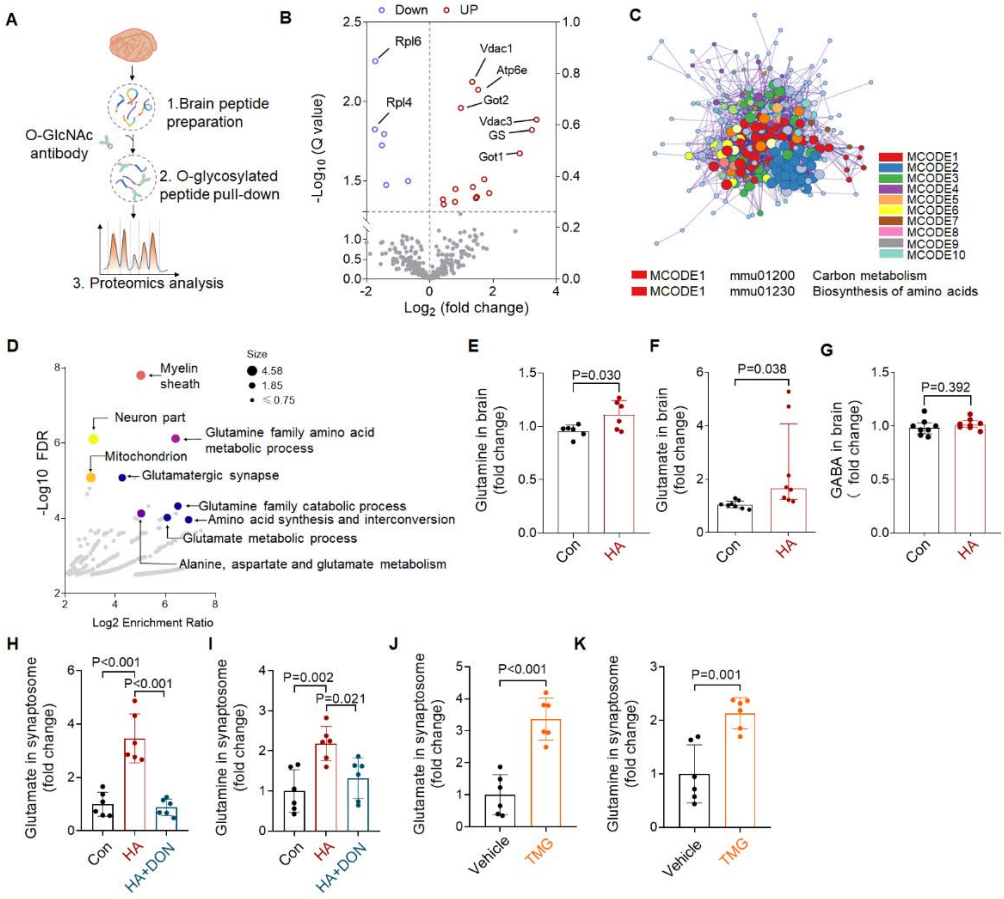

Figure 3. HA promoted the glutamate-glutamine cycle in brain via O-GlcNAcylation.
(**A**) A schematic view of the O-glycoproteomics analysis.
(**B**) Volcano plot of O-GlcNAc-proteome analysis for HA versuse control brains. Significantly increased O-glycosylated proteins are indicated in red color (n=3 per group).
(**C**) Metascape visualization of the interactome network formed by the 477 proteins bearing O-GlcNAc modification, where the MCODE complexes are colored according to their identities.
(**D**) Bubble chart showing Gene Ontology (GO) annotation results.
(**E-G**) The levels of glutamine (**E**), glutamate (**F**) and γ-aminobutyric acid (GABA; **G**) in the control and HA brains (n=6-8 per group).
(**H-I**) The levels of glutamate (**H**) and glutamine (**I**) in synaptosomes isolated from the control, HA and HA+DON brains (n=6 per group).
(**J-K**) The levels of glutamate (**J**) and glutamine (**K**) in synaptosomes isolated from the Vehicle and TMG-treated brains (n=6 per group).
Data are presented as mean±SD. Statistical comparisons were conducted using Unpaired 2-tailed Student *t*-test (**E, F, G, J, K**) or One-way ANOVA was used for (**H, I**). The exact *P*-values are reported for indicated comparisons and *P*<0.05 is considered statistically significant. Con, Control; DON, 6-diazo-5-oxo-l-norleucine; GABA, γ-aminobutyric acid; GO, Gene Ontology; HA, hypoxia acclimation; MCODE, Molecular Complex Detection; TMG, Thiamet-G.

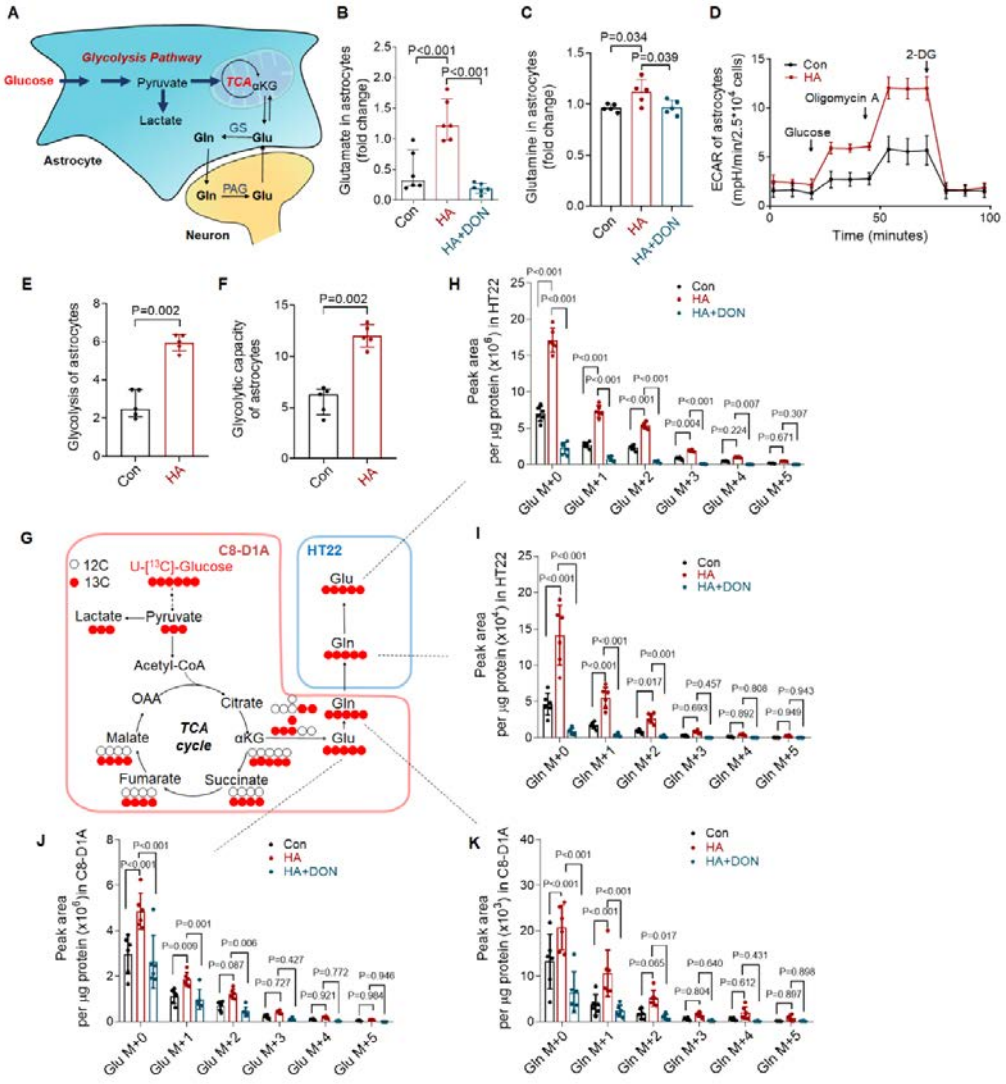

Figure 4. O-GlcNAcylation directed glucose carbon to replenish the glutamate-glutamine cycle.

(**A**) A schematic diagram of the *de novo* synthesis of glutamine.

(**B-C**) The levels of glutamate (**B**) and glutamine (**C**) in primary mouse cortical astrocytes with indicated treatments (n=5-6 per group).

(**D-F**) The extracellular acidification rates (ECAR; **D**) of primary mouse cortical astrocytes with control or HA treatment. The calculated glycolysis levels (**E**) and glycolytic capacity (**F**) (n=5 per group).

(**G**) Schematic view of [U-^{13}C] glucose-originated ^{13}C incorporation into the glutamate-glutamine cycle.

(**H-I**) ^{13}C incorporation of [U-^{13}C] glucose into glutamate (**H**) and glutamine (**L**) in HT22 neurons with indicated treatments (n=6 per group).

(**J-K**) ^{13}C incorporation of [U-^{13}C] glucose into glutamate (**J**) and glutamine (**K**) in C8-D1A astrocytes with indicated treatments (n=6 per group).

Data are presented as mean±SD. Statistical comparisons were conducted using One-way ANOVA (**B, C, H, I, J, K**) or Unpaired 2-tailed Student *t*-test (**E, F**). The exact *P*-values are reported for indicated comparisons and $P<0.05$ is considered statistically significant. 2-DG, 2-deoxyglucose; DON, 6-diazo-5-oxo-l-norleucine; Gln, glutamine; Glu, glutamate; GS, glutamine synthetase; HA, hypoxia acclimation; PAG, phosphate-activated glutaminase.

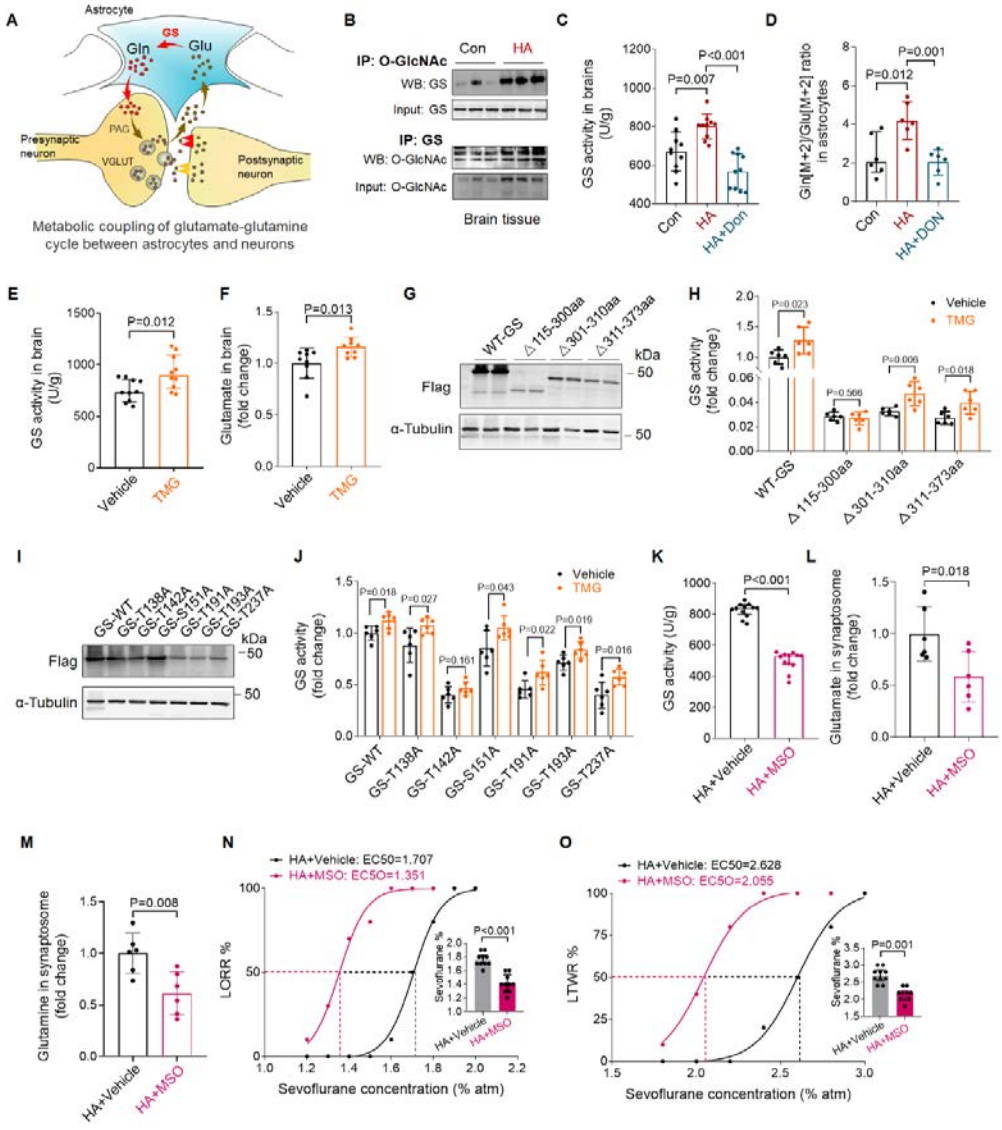

Figure 5. O-GlcNAcylation-mediated activation of glutamine synthetase (GS) enhanced glutamate-glutamine cycle and reduced sevoflurane anesthesia sensitivity.

(**A**) Schematic representation of the glutamate-glutamine cycle.
(**B**) Representative blots of O-GlcNAc-modified GS in the control and HA brains (n=10 per group).
(**C**) The GS activity in mouse brains after indicated treatments (n=10 per group).
(**D**) The ratio of Glutamine[M+2]/Glutamate[M+2] in C8-D1A astrocytes with indicated treatments (n=6 per group).
(**E**) The GS activity in mouse brains after Vehicle or TMG treatment (n=10 per group).
(**F**) The glutamate levels in mouse brains after Vehicle or TMG treatment (n=10 per group).
(**G**) Overexpression of different truncated mutants of Flag-GS in HEK293T cells were determined by immunoblotting.
(**H**) The GS activity of wild-type GS and its mutants in HEK293T cells (n=6 per group).
(**I**) Overexpression of S/T-to-A mutants in indicated amino acids of GS were determined by immunoblotting.
(**J**) The GS activity of wild-type GS and its point mutants in HEK293T cells (n=6 per group).
(**K**) The GS activity in mouse brains after HA+Vehicle or HA+MSO treatment (n=10 per group).

(**L-M**) The levels of glutamate (**L**) and glutamine (**M**) in synaptosomes isolated from mouse brains after HA+Vehicle or HA+MSO treatment (n=6 per group).
(**N-O**) The dose-response curve showing the percentages of mice exhibiting LORR (**N**) or LTWR (**O**) in response to incremental sevoflurane concentrations for the HA+Vehicle and HA+MSO groups. Insets: the sevoflurane concentrations at which each mouse exhibited LORR (**N**) or LTWR (**O**) are shown (n=10 per group).
Data are presented as mean±SD. Statistical comparisons were conducted using One-way ANOVA (**C, D**). Unpaired 2-tailed Student *t*-test was used for (**E, F, H, J, K, L, M, N, O**). The exact *P*-values are reported for indicated comparisons and $P<0.05$ is considered statistically significant. DON, 6-diazo-5-oxo-l-norleucine; Gln, glutamine; Glu, glutamate; GS, glutamine synthetase; HA, hypoxia acclimation; LORR, loss of righting reflex; LTWR, loss of tail-pinch withdrawal response; MSO, methionine sulfoximine; PAG, phosphate-activated glutaminase; TMG, Thiamet-G.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 46

Reactive astrocytes contribute to post surgical cognitive decline via release of Complement C3 in young WT mouse.

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INTRODUCTION: Functioning astrocytes are crucial in the CNS and are involved in neuroinflammation but can become pathologically reactive and contribute to cognitive deficits by releasing complement factors[1]. Complement C3 is an essential component for the complement pathway and its excessive levels in adult brains correlates with cognitive dysfunction in neurodegenerative diseases. However, whether reactive astrocytes and C3 contribute to post-operative cognitive decline remains unknown. Here, we investigate the role of reactive astrocytes and complement C3 in post-operative cognitive decline using a murine WT mouse surgical model.

METHODS: Adult male C57BL/6N mice were subjected a laparotomy under sevoflurane anesthesia. Novel objective recognition and forced Y-maze tests were used to assess cognitive function. Expression of cytokines and activation of astrocyte in the hippocampus were evaluated by immunofluorescent staining and RT-PCR. Astrocytes from post-surgical hippocampi samples were extracted and purified by FACS, followed by RNA-seq. Cerebral C3 was knocked down by administration of AAV9-C3shRNA in the lateral ventricle

RESULTS: We showed a significant decline in postoperative cognitive performance, along with increase in neuroinflammatory markers as well as A1 reactive astrocyte. Furthermore, astrocytes extracted from post-operative hippocampal samples were subjected to transcriptomal profiling. The enrichment of KEGG pathway analysis indicated complement system is elevated by surgical stimuli and C3 is the central molecule in the complement activation. Finally, cerebral C3 knocked down by AAV9-C3shRNA was able to alleviate post-operative cognitive impairment.

CONCLUSION: Our study demonstrated that surgery induced increase of reactive astrocyte and its C3 are associated with cognitive deficits, which could be alleviated by knockdown of C3. It indicates the potential of C3 to be one of therapeutic target of for post-operative cognitive decline.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 47

Effect of deep versus light general anesthesia on postoperative pain and cognitive function: a meta-analysis with trial sequential analysis of randomized controlled trials

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INTRODUCTION: The association between the depth of general anesthesia and postoperative outcomes remains controversial. This meta-analysis was conducted to determine the effects of deep vs. light anesthesia on postoperative pain, cognitive function, recovery from anesthesia, and postoperative complications[1-4].

METHODS: PubMed, EMBASE, and Cochrane library databases were searched until February 20, 2021 for eligible randomized controlled trials. The co-primary outcomes were postoperative visual analog scale (VAS, 0-10) pain scores and the incidence of postoperative cognition dysfunction (POCD). Meta-analyses were performed using a random-effect model. Publication bias was assessed using Egger's and Begg's tests. Trial sequential analysis (TSA) and Grading of Recommendations Assessment, Development and Evaluation (GRADE) were utilized to assess the reliability and level of evidence.

RESULTS: A total of 23 trials with 10262 patients were included. Deep anesthesia was associated with lower VAS pain scores at rest within 1 hour postoperatively (weighted mean difference = -0.72 points, 95%CI = -1.25 to -0.18 points, P = 0.009, I2 = 33%) and at 8 and 24 hours postoperatively, as well as on movement at 8 hours postoperatively. The incidence of POCD during 1-7 days (risk ratio = 1.37, 95%CI = 0.82 to 2.28, P = 0.23, I2 = 65%) or 1-3 months postoperatively did not differ between the two groups. No publication bias was detected. The TSA suggested sufficient evidence for VAS pain scores, but not for the incidence of POCD. The GRADE level of evidence was rated as moderate to low for the primary outcomes. In addition, deep anesthesia was associated a delayed recovery profile, without affecting postoperative complications or 1-year mortality.

CONCLUSION: Deep anesthesia was associated with reduced postoperative pain during the first 24 hours after surgery. The depth of general anesthesia itself may not influence cognitive function, postoperative complications, or long-term mortality.

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3. Minerva Anestesiol 2020; 86(9):965-973
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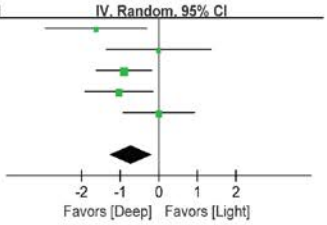
A

Study or Subgroup	Deep anesthesia Mean	SD	Total	Light anesthesia Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Faiz 2017	4.07	2.74	30	5.7	2.44	30	13.1%	-1.63 [-2.94, -0.32]
Law 2014	4	4	66	4	4	69	12.6%	0.00 [-1.35, 1.35]
Quan 2019	3.8	2.4	52	4.7	1.1	53	29.2%	-0.90 [-1.62, -0.18]
Sahni 2012	3.15	1.83	40	4.18	2.15	40	23.3%	-1.03 [-1.90, -0.16]
Short 2014	3.4	2.75	61	3.4	2.5	64	21.8%	0.00 [-0.92, 0.92]
Total (95% CI)			249			256	100.0%	-0.72 [-1.25, -0.18]

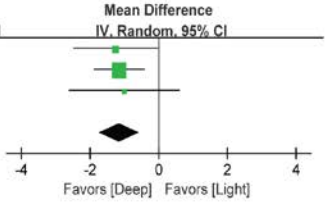
Heterogeneity: Tau² = 0.12; Chi² = 6.00, df = 4 (P = 0.20); I² = 33%
Test for overall effect: Z = 2.61 (P = 0.009)



B

Study or Subgroup	Deep anesthesia Mean	SD	Total	Light anesthesia Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Faiz 2017	2.57	1.7	30	3.83	2.95	30	22.9%	-1.26 [-2.48, -0.04]
Sahni 2012	3	1.4	40	4.15	1.89	40	63.9%	-1.15 [-1.88, -0.42]
Soumpasis 2010	1	2	30	2	4	30	13.3%	-1.00 [-2.60, 0.60]
Total (95% CI)			100			100	100.0%	-1.16 [-1.74, -0.57]

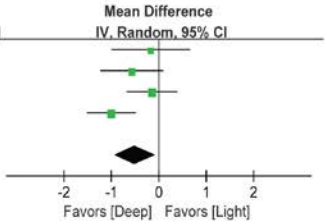
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 3.89 (P = 0.0001)



C

Study or Subgroup	Deep anesthesia Mean	SD	Total	Light anesthesia Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
An 2011	0.73	1.8	40	0.9	1.93	40	18.1%	-0.17 [-0.99, 0.65]
Faiz 2017	1.13	1.22	30	1.7	1.37	30	23.3%	-0.57 [-1.23, 0.09]
Hou 2018	3.56	0.86	30	3.7	1.18	30	28.9%	-0.14 [-0.66, 0.38]
Soumpasis 2010	0	1	30	1	1	30	29.6%	-1.00 [-1.51, -0.49]
Total (95% CI)			130			130	100.0%	-0.50 [-0.94, -0.06]

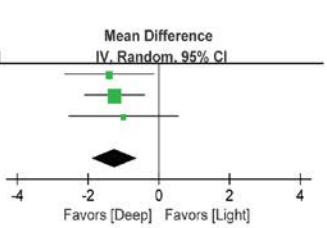
Heterogeneity: Tau² = 0.10; Chi² = 6.21, df = 3 (P = 0.10); I² = 52%
Test for overall effect: Z = 2.24 (P = 0.03)



D

Study or Subgroup	Deep anesthesia Mean	SD	Total	Light anesthesia Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Faiz 2017	3.73	2.09	30	5.13	2.82	30	25.7%	-1.40 [-2.66, -0.14]
Sahni 2012	4.18	1.68	40	5.43	2.14	40	57.1%	-1.25 [-2.09, -0.41]
Soumpasis 2010	1	2.5	30	2	3.5	30	17.1%	-1.00 [-2.54, 0.54]
Total (95% CI)			100			100	100.0%	-1.25 [-1.88, -0.61]

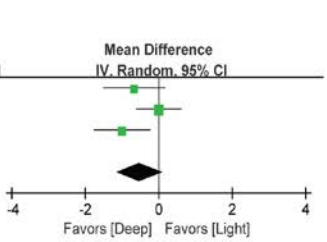
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 2 (P = 0.92); I² = 0%
Test for overall effect: Z = 3.83 (P = 0.0001)



E

Study or Subgroup	Deep anesthesia Mean	SD	Total	Light anesthesia Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Faiz 2017	1.7	1.75	30	2.37	1.5	30	29.3%	-0.67 [-1.49, 0.15]
Law 2014	3	2	66	3	1.5	69	38.8%	0.00 [-0.60, 0.60]
Soumpasis 2010	0	1.5	30	1	1.5	30	31.9%	-1.00 [-1.76, -0.24]
Total (95% CI)			126			129	100.0%	-0.52 [-1.14, 0.11]

Heterogeneity: Tau² = 0.17; Chi² = 4.46, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 1.62 (P = 0.11)



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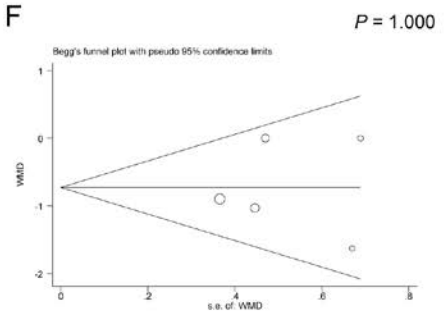

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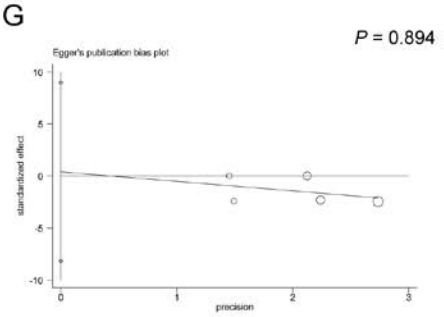

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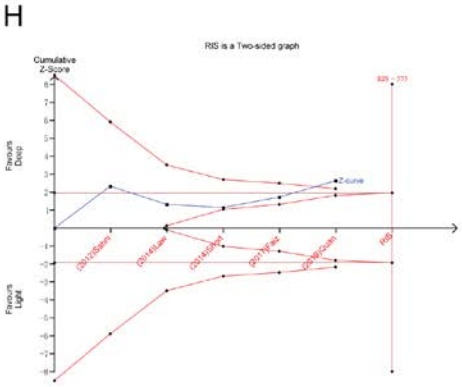

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 48

Electroencephalographic features in the cardiothoracic intensive care unit following intraoperative aminocaproic acid administration

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INTRODUCTION: Tranexamic acid (TXA) and the less-potent[1] aminocaproic acid (ACA) are commonly used antifibrinolytic agents in the perioperative setting to reduce allogenic transfusion and decrease hemorrhage-associated mortality.[2] Despite potential benefits, there is concern that antifibrinolytic administration may confer an increased risk of convulsive seizures in humans,[3] which is corroborated by animal data.[4] These studies point to a potential mechanism for cortical hyperexcitability as TXA and ACA can antagonize both gamma-aminobutyric acid (GABA) and glycine receptors.[5] Indeed, recent large human trials studying TXA have shown a strong association with postoperative seizures.[3,6] However, meta-analyses have not corroborated this finding.[7,8] This may be partially because seizure is not a consistent secondary outcome in many studies, and when seizure is reported, it is largely based on the clinical presentation and not electrographic findings. Moreover, the potential association between ACA and seizure activity is not well-studied. This gap in knowledge is underscored in cardiothoracic (CT) surgery patients who are routinely administered antifibrinolytics and at high seizure risk from neurological complications. Here, we performed a retrospective analysis of electrographic findings of patients receiving continuous electroencephalographic (EEG) monitoring in our hospital's CT surgery intensive care unit (CT-ICU). Our primary outcome was electrographic evidence of seizure activity in patients receiving ACA.

METHODS: After Institutional Review Board approval, we obtained electronic medical records of patients admitted to our hospital's CT-ICU who underwent continuous EEG (cEEG) monitoring from January 01, 2015 to December 31, 2019. Demographic information, diagnosis and procedure codes, operation type, dose history, laboratory results, and cEEG reports were collected. We included patients with a cEEG monitoring start date within seven days of their date of surgery or CT-ICU admission (Figure 1). We compared demographic characteristics, cEEG findings, and dose dependency with respect to ACA administration. Categorical variables were compared via Fisher's Exact test. Continuous variables were compared via Student's t, Welch's t, and Mann-Whitney U tests where appropriate. P-value < 0.05 was considered significant.

RESULTS: Of 124 patients with cEEG monitoring in the CT-ICU, 83 met inclusion criteria. 41 received ACA; 42 did not receive antifibrinolytic (AF). Within the non-AF group, 21 underwent surgery prior to admission to the CT-ICU. There were no significant differences in demographics between the ACA and non-AF groups (Table 1). However, there was a significant association between surgery and ACA administration ($p < 0.001$), reflecting perioperative AF administration practices. There was a significant association between ACA administration and electrographic seizure on cEEG monitoring (Table 2, $p = 0.006$). Among those with seizures on cEEG, the majority were subclinical (not associated with motoric activity). Moreover, a greater proportion of patients receiving ACA exhibited generalized seizures (Table 2, $p = 0.03$) and markers of cortical hyperexcitability (Table 2, $p = 0.0486$). We further observed a trend toward electrographic seizure and markers of cortical hyperexcitability with increasing ACA dose (Figure 2, $p = 0.1$). Patients with seizures on cEEG monitoring had significant associations with advanced age, CT surgery, cardiopulmonary bypass, and acute neurologic injury (Table 3).

CONCLUSION: We found an increased incidence of electrographic seizure and markers of cortical excitability in patients receiving ACA, and a trend toward seizure and markers of cortical excitability with increasing ACA dose. Our results suggest that patients receiving ACA, known to be less potent for anti-fibrinolysis than TXA, may still be vulnerable to hyperexcitable cortical states. Thus, patients receiving AF therapy may warrant a lower threshold for cEEG monitoring during and after AF administration. However, the retrospective and exploratory nature of this study posits limitations, including a lack of a control group, a small sample size, and selection bias, as most patients undergoing cEEG monitoring had a witnessed clinical event suspicious for seizure. Future prospective studies should be designed to more fully elucidate the relationship of ACA administration and hyperexcitable cortical states.

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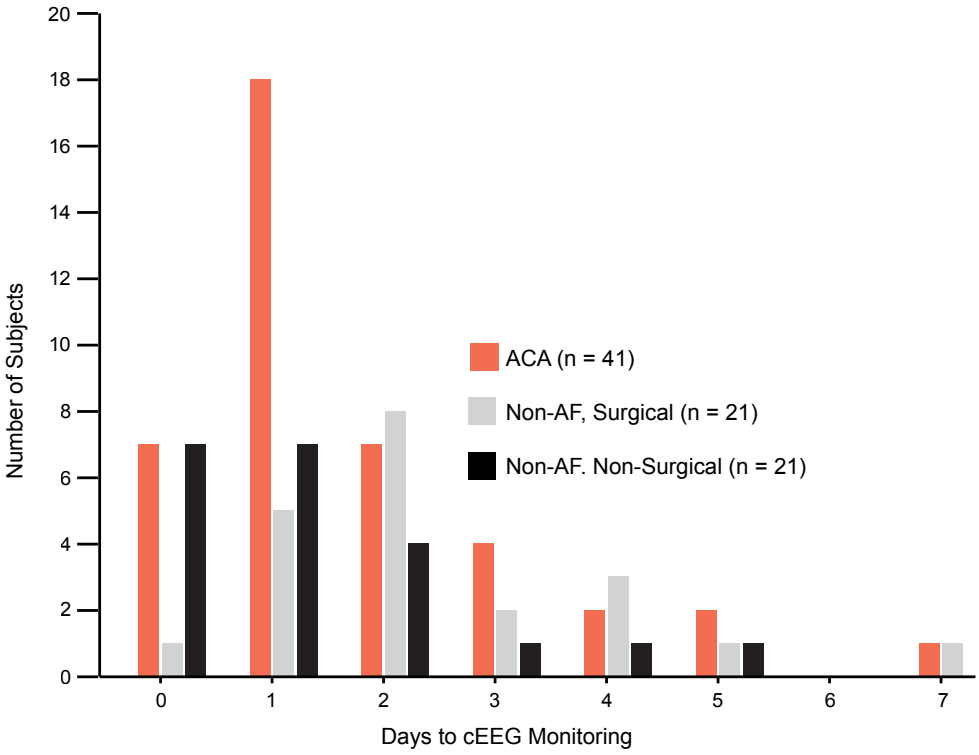
Figure 1. Histogram of patients undergoing cEEG monitroing with respect to surgery or CT-ICU admission



Abbreviations: ACA, aminocaproic acid; AF, antifibrinolytics.

Table 1. Baseline characteristics of patients undergoing cEEG

	Total (n = 83)	Non-AF (n = 42)	ACA (n = 41)	P
Demographics				
Mean age – years	65.4	64.0	66.9	0.2
Female gender – no. (%)	34 (41)	14 (33)	20 (49)	0.2
History of epilepsy – no. (%)	3 (4)	2 (5)	1 (2)	1.0
Primary Operation Type – no. (%)				
Valvular repair	28 (34)	5 (12)	23 (56)	**< 0.001**
CABG	3 (4)	0 (0)	3 (7)	0.1
CABG + valvular repair	7 (8)	0 (0)	7 (17)	**0.005**
Great vessel repair	11 (13)	6 (14)	5 (12)	1.0
LVAD/device placement	4 (5)	2 (5)	2 (5)	1.0
ECMO cannulation	2 (2)	2 (5)	0 (0)	0.5
Non-cardiac	28 (35)	27 (64)	1 (2)	**< 0.001**
Thoracic	4 (5)	3 (7)	1 (2)	
Neuro	2 (2)	2 (5)	0 (0)	
General	1 (1)	1 (2)	0 (0)	
N/A	21 (25)	21 (50)	0 (0)	
Reason for cEEG – no. (%)				
Witnessed event suspicious for seizure*	39 (47)	17 (40)	22 (54)	0.3
Unexplained encephalopathy**	32 (39)	16 (38)	16 (39)	1.0
Other***	12 (14)	9 (21)	3 (7)	0.1

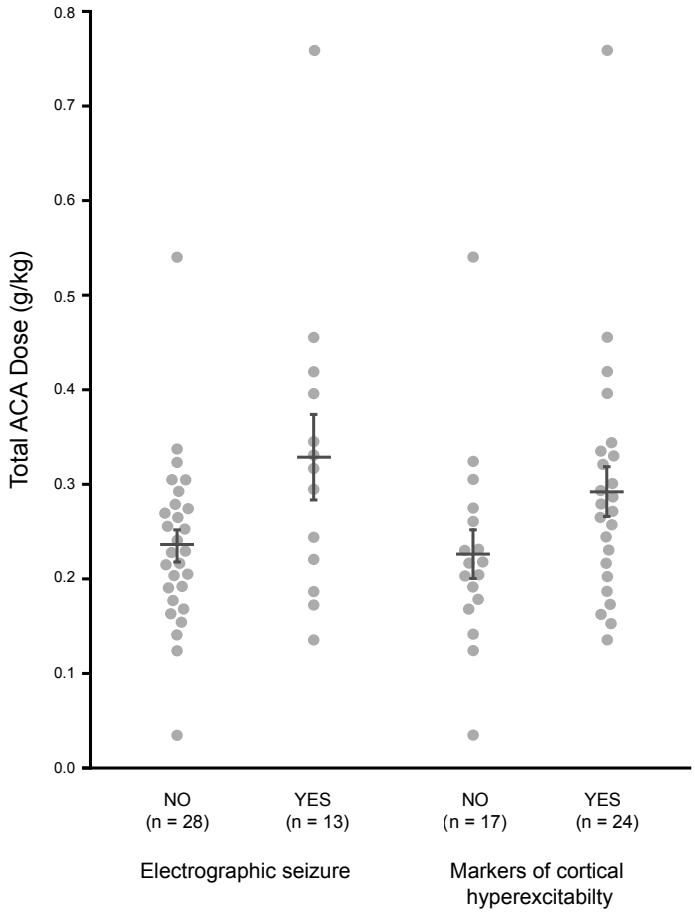
Percentages reported are proportion of total number of patients in group. *Witnessed event suspicious for seizure defined as clinically witnessed convulsion, twitching, and abnormal, involuntary body movement. **Unexplained encephalopathy defined as clinically witnessed altered mental status, unresponsiveness, aphasia, weakness, and dysconjugate gaze. ***Other defined as prognostication status post pulseless electrical activity (PEA) arrest, prognostication status post cardiac arrest, safety of discontinuation of automated external defibrillator (AED), and subarachnoid hemorrhage (SAH) management. Abbreviations: ACA: aminocaproic acid; AF: antifibrinolytics; CABG, coronary artery bypass surgery; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; N/A, not applicable.

Table 2. Electrographic findings among patients undergoing cEEG monitoring

	Total (n = 83)	Non-AF (n = 42)	ACA (n = 41)	P
Electrographic seizure (any type) – no. (%)	16 (19)	3 (7)	13 (32)	**0.006**
Subclinical seizure	12 (14)	3 (7)	9 (22)	0.07
Status epilepticus (any type)	4 (5)	0 (0)	4 (10)	0.06
Subclinical status	3 (4)	0 (0)	3 (7)	0.1
Onset location – no. (%)				
Generalized/non-localizing	5 (6)	0 (0)	5 (12)	**0.03**
Focal	3 (4)	1 (2)	2 (5)	0.6
Unknown/undocumented	9 (11)	2 (5)	7 (17)	0.09
Epileptiform and/or periodic discharges – no. (%)	39 (47)	15 (36)	24 (59)	**0.0486**
Sporadic (sharp waves, spikes)	37 (45)	15 (36)	22 (54)	0.1
Periodic discharges	9 (11)	4 (10)	5 (12)	0.7
Lateralized (LPDs)	5 (6)	2 (5)	3 (7)	0.7
Generalized (GPDs)	4 (5)	2 (5)	2 (5)	1.0
Bilateral independent (BIPDs)	2 (2)	0 (0)	2 (5)	0.2

Subclinical seizure defined as electrographic seizures not associated with witnessed evidence of convulsions or rhythmic motor activity. Epileptiform discharges defined as generalized spike-and-wave complexes, lateralized spike-and-wave complexes, bilateral independent spike-and-wave complexes, multifocal spike-and-wave complexes, and triphasic waves. Periodic discharges defined as generalized periodic discharges, lateralized periodic discharges, and bilateral independent discharges. Abbreviations: ACA, aminocaproic acid; AF, antifibrinolytics.

Figure 2. Effect of aminocaproic acid dose on electrographic seizure and markers of cortical hyperexcitability



Dots represent individual patients with weight-normalized aminocaproid acid dose. Crosshairs represent mean and standard error. Markers of cortical hyperexcitability include sporadic discharges, generalized spike-and-wave complexes, lateralized spike-and-wave complexes, bilateral independent spike-and-wave complexes, multifocal spike-and-wave complexes, triphasic waves, generalized periodic discharges, lateralized periodic discharges, and bilateral independent discharges. Abbreviations: ACA, aminocaproic acid; g, gram; kg, kilogram.

Table 3. Risk factors associated with electrographic seizure on cEEG monitoring

	Total (n = 83)	Electrographic Seizure (n = 16)	No Electrographic Seizure (n = 67)	P
Baseline characteristics				
Age ≥ 65	52 (63)	14 (88)	38 (57)	**0.02**
Female gender	34 (41)	9 (56)	25 (37)	0.26
History of epilepsy	3 (4)	0 (0)	3 (4)	1.0
Clinical course				
Cardiothoracic surgery	59 (71)	15 (94)	44 (66)	**0.03**
Cardiopulmonary bypass	44 (53)	15 (94)	29 (43)	**0.0002**
Induced circulatory arrest	6 (7)	2 (13)	4 (6)	0.3
ACA use	41 (49)	13 (81)	28 (42)	**0.006**
Reason for monitoring				
Witnessed event suspicious for seizure	39 (47)	13 (81)	26 (39)	**0.004**
Unexplained encephalopathy	32 (39)	3 (19)	29 (43)	0.09
Other	12 (14)	0 (0)	12 (18)	0.1
In-hospital Diagnoses				
Acute renal injury	39 (47)	8 (50)	31 (46)	0.8
Acute hepatic failure	6 (7)	1 (6)	5 (7)	1.0
Acute myocardial infarction	9 (11)	1 (6)	8 (12)	1.0
Acute neurologic injury*	47 (57)	12 (75)	25 (37)	**0.01**
Lab Values				
Peak AST (U/L), mean	672.8	495.5	718.5	0.5
Peak AST (U/L), median	167.5	184	152	0.9
Peak ALT (U/L), mean	414.2	236.6	460.0	0.3
Peak ALT (U/L), median	81.5	119.5	76	0.6
Peak Creatinine (mg/dL), mean	2.5	2.1	2.7	0.2
Peak Creatinine (mg/dL), median	1.8	1.5	1.8	0.3
Markers of cortical Hyperexcitability				
Epileptiform and/or periodic discharges	39 (47)	15 (94)	24 (36)	**< 0.001**
Sporadic discharges	32 (39)	14 (88)	18 (27)	**< 0.001**
Periodic discharges	9 (11)	2 (13)	7 (10)	1.0
Lateralized (LPDs)	5 (6)	1 (6)	4 (6)	1.0
Generalized (GPDs)	4 (5)	0 (0)	4 (6)	1.0
Bilateral independent (BiPDs)	2 (2)	1 (6)	1 (1)	0.3

*Acute brain injury was determined by review of neuroimaging reports and is defined as cerebral infarcts, intracerebral brain hemorrhage, restriction diffusion, stroke, posterior reversible encephalopathy syndrome (PRES), air emboli, ischemia, diffuse loss of cerebral gray-white differentiation, severe global anoxic brain injury, hypodensities, and aneurysm. Epileptiform discharges defined as generalized spike-and-wave complexes, lateralized spike-and-wave complexes, bilateral independent spike-and-wave complexes, multifocal spike-and-wave complexes, and triphasic waves. Periodic discharges defined as generalized periodic discharges, lateralized periodic discharges, and bilateral independent discharges. Abbreviations: ACA, aminocaproic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; dL, deciliter; mg, milligram; L, liter; U, units.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 49

Inter-patient vs intra-patient variability in spectral EEG information during critical illness

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INTRODUCTION: Bifrontal electroencephalography (EEG) montages are commonly used intraoperatively to observe spectral EEG changes during transitions in consciousness. They are placed easily and facilitate timely interventions, such as the modification of sedation strategies[1,2]. Despite the routine use of analgosedation regimens among mechanically ventilated patients, bifrontal EEG monitoring is not commonly used in the critical care setting. It is well understood that the complexity of EEG signals is associated with varying anesthetic states[3], thus, the goal of this study was to describe the variability in EEG waveforms among mechanically ventilated, critically ill, adult patients receiving intravenous analgosedation.

METHODS: Eligible patients underwent EEG monitoring via Sedline Root™ (Masimo Corp., Irvine, CA). Four channels of EEG information were obtained through adhesive electrodes configured on a disposable sensor applied across the forehead (electrodes Fp1/2,F7/8, common reference, Fz). Daily sensor checks were conducted to ensure integrity and appropriate impedance. MATLAB (Mathworks, Inc. Natick, MA) was used to calculate the 95th percentile of spectral edge frequency (SEF95) and relative logarithmic β-ratio-degree of high frequency activation-for each patient. The first 6 hours of continuous EEG data (free from artifacts) was used for analysis. Patient demographics and factors that could influence the patients' EEG findings were collected via retrospective chart review.

RESULTS: Forty-eight patients were enrolled over the course of the study. At time of EEG placement, the majority of patients (45/48) were receiving intravenous analgosedation and most (34/48) had a RASS (Richmond Agitation Sedation Scale) score of -4, or lower (Table 1). The interquartile range for the SEF95 varied from 6.3 - 16.7 Hz (median 8.9 Hz), suggesting heterogeneity in traditional α band activity in this population (Figure 1a). The median logarithmic β ratio was -3.2 (IQR: -3.6 - -2.6), which is consistent with reduced activity at cortical synapses. The intra-patient median interquartile range for SEF95 only varied by 4.1 Hz (IQR: 2.1 - 6.2, median variability, 3.0 Hz) (Figure 1b).

CONCLUSION: Over the course of a six-hour monitoring period, most critically ill patients exhibit EEG patterns dominated by low-moderate frequency activity, which could be explained by the patients' illness, excessive sedation drug effect, or poor pre-existing neurologic substrate. There was a wide-range of interpatient variability when compared with intra-patient variability, suggesting that the underlying patients' underlying neurologic function could be more relevant than differences in analgosedative regimens. Ongoing studies will focus on the relationship between the quantitative EEG parameters derived from these abbreviated montages and critically ill patient outcomes.

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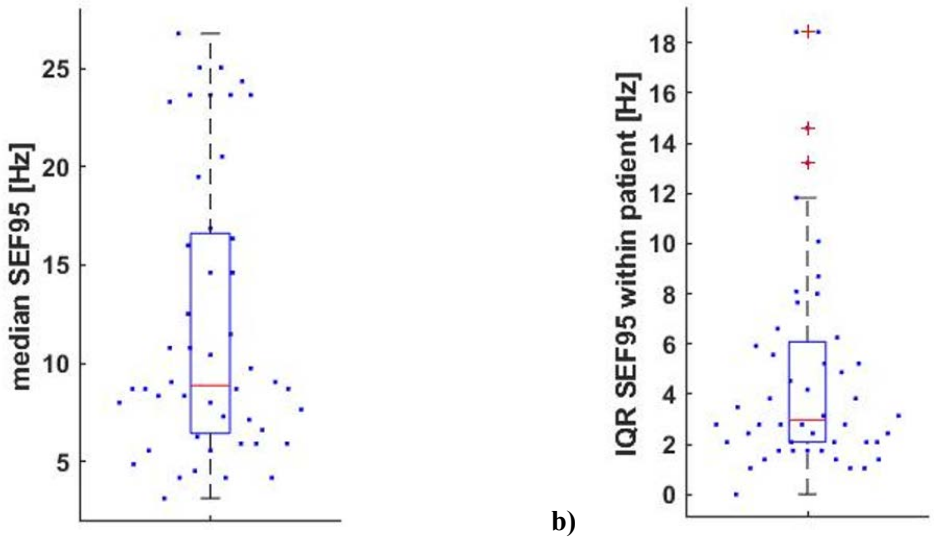
Figure 1: Inter-patient and intra-patient variability of median SEF95 over a 6-hour monitoring in period in critically ill patients



a) **b)**

Legend:

SEF95: 95th percentile of spectral edge frequency

Figure a: The interquartile range for the SEF95 in the entire study population varied from 6.3 – 16.7 Hz (median: 8.9 Hz).

Figure b: The intra-patient median interquartile range for SEF95 varied from 2.1 – 6.2 Hz (median: 3.0 Hz)

Table 1. Patient Charactertistics

	N = 48
Age (y)	59.6 ± 16
Sex (%)	
M	38 (77.6)
F	11 (22.4)
RASS Score (IQR)*	-4 (-3 to -4)
Patient Comorbidities	
Neurologic history[±]	
Y	10 (20.8)
N	38 (79.2)
Uremia [┼]	
Y	20 (40.8)
N	28 (59.2)
Requiring dialysis	
Y	7 (14.6)
N	41 (85.4)
Liver dysfunction[‡]	
Y	15 (31.3)
N	33 (68.7)
Cardiac arrest	
Y	7 (14.6)
N	41 (85.4)
Drug Exposure	
Analgosedation[†]	
Y	45 (93.7)
N	3 (6.3)
Fentanyl (mcg/hr)	105.5 ± 93.1
Propofol (mcg/kg/min)	34.9 ± 21.7

*Richmond Agitation Sedation Scale score at time of Sedline placement
[±]Neurologic history included: history of stroke, seizures, and dementia
[┼]Uremia: BUN >30mg/dL
[‡]Liver failure: AST > 80U/L and ALT > 110U/L
†Analgosedation: Any documentation of patients receiving continuous infusions of opioids, propofol, midazolam, dexmedetomidine, or ketamine

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 50

Inhaled anesthetics for hypnosis in critical care patients: Evaluating neurocognitive and mental health outcomes.

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INTRODUCTION: The use of inhaled volatile anesthetic agents to provide sedation and hypnosis in critically ill general medical and postoperative patients who require invasive ventilation has been well described.[1-3] Available evidence suggests there may be potential benefits on neuropsychiatric outcomes after discontinuation of drug delivery, but the study of cognitive and mental health outcomes remains understudied. We conducted a systematic review and meta-analysis to assimilate studies that evaluated the short-term in-hospital and longer-term post-hospital discharge neurological outcomes in adult mechanically ventilated intensive care unit (ICU) patients.

METHODS: We searched key databases MEDLINE, EMBASE, and PsychINFO between the time period of 1970 to 2021 for case series reports, observational studies and prospective clinical trials of postoperative and general medical-surgical patients who received inhaled anesthetic drugs in the ICU. We studied cognitive (i.e., delirium) and psychiatric (i.e., anxiety, depression, posttraumatic stress disorder) neurocognitive outcomes.

RESULTS: We identified 5 postoperative and 3 general medical-surgical ICU studies that included a total of 564 patients. The studies included 5 single centre trials, 1 multicentre trial and 2 cohort studies that compared the effect of inhaled (sevoflurane, isoflurane or desflurane) to intravenous sedative drugs (propofol or midazolam). Variation in the parameters of patient outcome assessments, measurement tools and quality of the data limited metanalytic-review. Delirium was reported by 5/8 (63%) studies (n=344) during ICU or hospital stay using varied tools. Pooling of 4 trials (n=258) showed no difference in delirium (risk ratio 0.90, 95% CI 0.5-1.56). A single trial (n=60) assessed attention and concentration using psychometric tests in ICU and showed no significant difference. One trial (n=40) evaluated anxiety/depression (using Hospital Anxiety and Depression Scale) and post-traumatic stress disorder (using Impact Event Scale) at 6-months and showed no significant difference (60% volatile vs. 33% IV). One trial evaluated cognition at 3-months using a telephone interview (TICS) assessment and showed no difference in sedation arms (78% volatile vs. 67% IV).

CONCLUSION: The study of neurocognitive recovery among mechanically ventilated ICU patients who received inhaled general anesthetic drugs for hypnosis and sedation is limited. Current data are suggestive of equivalent cognitive and psychiatric outcomes between inhaled and injectable sedative and anesthetic drugs, but further in-depth and adequately powered studies using standardized measurement tools are needed.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 51

Anesthesia, Surgery and Intensive Care environment impair hippocampal BDNF-Arc signaling and dendritic arborization in aged mice

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INTRODUCTION: We recently reported impaired expression of brain-derived neurotrophic factor (BDNF)-dependent proteins critical for synaptic plasticity in aged mice with delirium like-behaviors induced by anesthesia, surgery and Intensive Care environment (A/S/I). Importantly, it has been shown that BDNF activates the tyrosine kinase B (TrkB) receptor, which in turn phosphorylates extracellular kinases (Erk 1/2), activating cAMP responsive element-binding protein (CREB) and ultimately promoting expression of Arc, an activity-regulated cytoskeleton-associated protein that is a master regulator of dendritic development, synaptic plasticity and memory consolidation. In light of this, we aimed to test whether BDNF-Arc signaling plays a role in A/S/I-induced delirium-like cognitive dysfunction. Our hypothesis was that A/S/I would impair the hippocampal BDNF-Arc pathway, as well as hippocampal dendritic arborization, in aged mice.

METHODS: Eighteen-month-old C57BL/6J mice were randomized to insult (A/S/I) or control group. A/S/I mice received laparotomy under sevoflurane anesthesia (3 h), sedation with propofol (2 h) and Intensive Care Unit (ICU) conditions, i.e., intermittent lights, sounds and cage shaking (12 h). Controls did not receive A/S/I. Mouse hippocampi were collected at the end of ICU conditions for gene and protein expression studies and for rapid Golgi staining. This study was approved by the Institutional Animal Care and Use Committee at the University of Virginia.

RESULTS: Expression of several BDNF gene exons was differentially regulated in A/S/I mice compared to controls (fold change 'F'=1) (Fig.1: BDNF-I (0.69 F, *p=0.01), BDNF-IIa (0.57 F, p=0.001**), BDNF-IIb (0.84 F, p=0.01*), BDNF-IV (0.84 F, p=0.006**), BDNF-VI (1.24 F, p=0.005**), BDNF-VII (0.78 F, p=0.004**)). BDNF exons IIc, III, V, VIII, IXA, and nerve growth factor (NGF) gene expression levels were not significantly modulated by A/S/I. Protein expression of total BDNF (-22.1± 8.1%, p=0.02*), TrkB (-24.4± 7.9%, p= 0.01*), Erk1/2 (-5.8 ± 3.0%, p= 0.09), pErk1/2 (-33.8± 9.5%, p= 0.007**), Elk1 (-28.2± 11.9%, p=0.04*), pElk1 (-42.6± 11.6%, p=0.007**), CREB (-13.1± 3.7%, p=0.007**), pCREB (-35.1± 14.2%, p=0.03*) and Arc (-33.1± 8.1%, p=0.003**) were also decreased in A/S/I mice, relative to controls (Fig.2). A/S/I mice displayed impaired dendritic arborization, as measured by a decrease in the mean length of the longest dendrite originating from CA-1 neurons (-82.0±17.1, p=0.0002***) and the number of its branches (-1.69±0.4, p=0.0010**), compared to controls (Fig.3 a,b).

CONCLUSION: Surgery, Anesthesia and Intensive Care environment impair BDNF-induced expression of Arc and dendritic arborization in the hippocampus of aged mice. Given Arc's critical role for synaptic plasticity, memory and cognitive function, BDNF-mediated decrease in Arc expression may be important in triggering and supporting cognitive impairment in delirium evoked by anesthesia, surgery and ICU environment.

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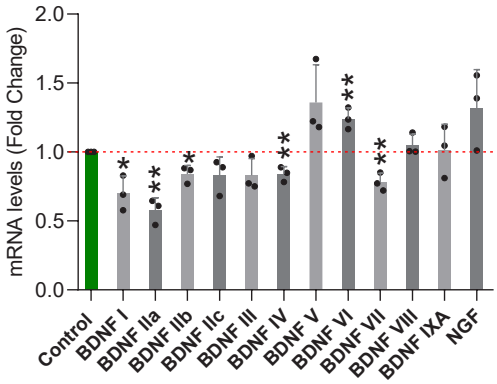


Fig 1. mRNA expression levels of Brain Derived Neurotrophic Factor (BDNF exons I-IXA) and Nerve Growth Factor (NGF) profiling in mouse hippocampus of control vs ASI (N=3). Two-tailed unpaired t-test ∗P < 0.05 and ∗∗P < 0.01, respectively and data represented as mean ± SEM.

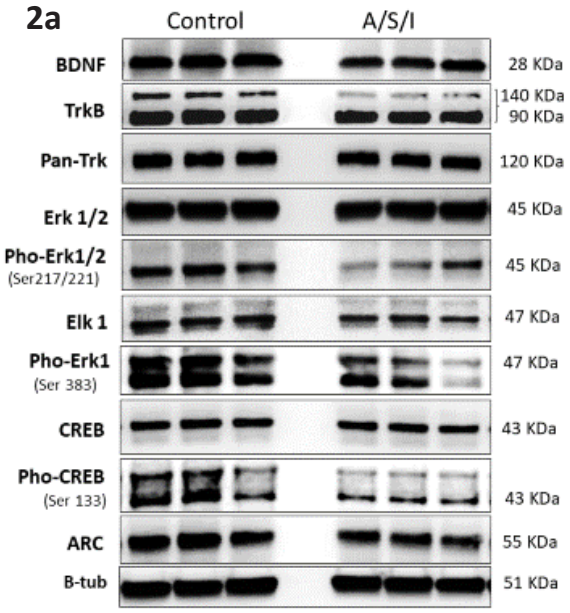
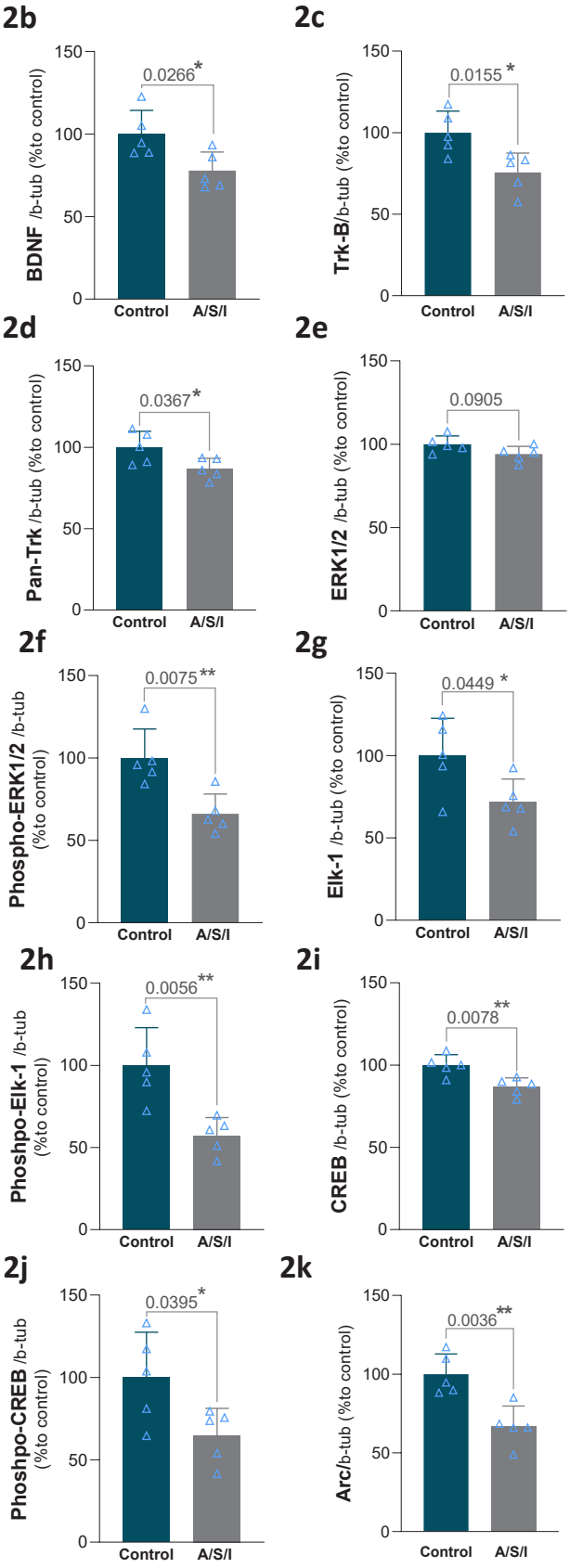


Fig 2. (2a) Representative immunoblots displaying protein expression patterns and β-tubulin (loading control). The quantified protein expression levels shown in graphs are (2b) BDNF, (2c) TrkB, (2d) Pan-Trk, (2e) Erk1/2, (2f) phospho-Erk1/2, (2g) Elk1, (2h) phospho-Elk1, (2i) CREB, (2j) phospho-CREB and (2k) Arc. Protein densities were quantified using Syngene – Gene Tools analysis software and expression levels were normalized with β-tubulin. Data is presented as percent change to controls. N=5 Control and 5 A/S/I mice. Two-tailed unpaired t-test ∗P < 0.05 and ∗∗P < 0.01, respectively and data represented as mean ± SEM.



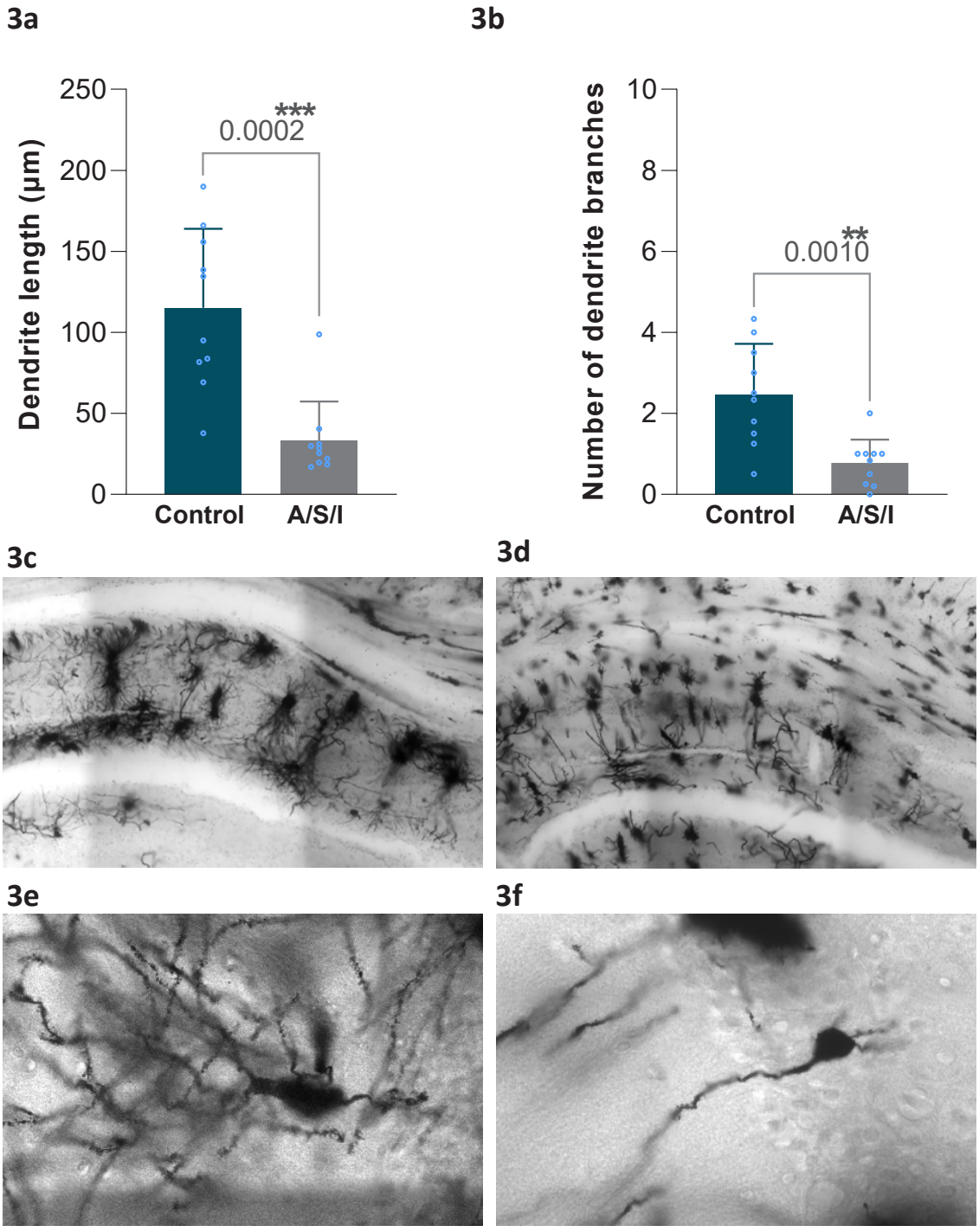


Fig 3. (3a) Mean length of the longest dendrite originating from CA-1 neurons and (3b) average number of its branches. Representative microscopy images from one control (3c, 10X magnification and 3e, 63X magnification) and one A/S/I (3d, 10X magnification and 3f, 63X magnification) animal. N=10 neurons/group. Two-tailed unpaired t-test ***P < 0.001 and **P < 0.01, respectively and data represented as mean ± SEM.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 52

Surgery, Anesthesia and Intensive Care Environment induce delirium-like disruption of sleep and circadian rhythm in aged mice

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INTRODUCTION: To date, the pathophysiology of postoperative Intensive Care Unit (ICU) delirium remains poorly understood. The lack of adequate experimental animal models is a major barrier to advancing the understanding of the neurobiological mechanisms underpinning delirium. Dysregulated sleep and circadian rhythm are a very common symptom in delirious ICU patients. Thus, we set out to test the face validity of our recently published mouse model of postoperative ICU delirium by assessing sleep quantity, fragmentation and circadian rhythm in aged mice subjected to anesthesia, surgery and ICU conditions (ASI). We hypothesized that ASI would induce disturbances in mouse sleep and circadian rhythm consistent with those of delirious patients and alter the expression of genes that are important for normal sleep-wake behavior and circadian function.

METHODS: Eighteen-month-old C57BL/6J mice (N=31) were implanted with electroencephalographic (EEG) and electromyographic electrodes. After two weeks, they were randomized to insult (ASI) or control group. ASI mice received laparotomy under sevoflurane anesthesia (3 h), sedation with propofol (2 h) and ICU conditions, i.e., intermittent lights, sounds and cage shaking (12 h). Controls did not receive ASI. Twenty-eight hour-long EEG recordings were obtained at the end of ICU conditions. Mice hippocampi were collected upon completion of the EEG recordings and processed for gene and protein expression analysis of sleep and circadian markers by qPCR and western blot. Two-tailed unpaired t-test and repeated measures analysis of variance were used for statistical analysis. Sleep data are presented as mean ± S.D. Gene and protein data are expressed as fold change relative to controls and mean ± S.E.M, respectively.

RESULTS: ASI significantly altered Rapid Eye Movement (REM) and Non-Rapid Eye Movement (NREM) sleep during the dark 1 (D1) and dark 2 (D2) phases (Fig.1, A REM: D1,**; D2,*; B NREM: D1, ***; D2,**) relative to controls. ASI mice spent more time asleep during dark, at a time when they should be more awake (Fig. 1C,**), and experienced greater numbers of wake bouts in between sleep, and shorter wake bout duration, compared to controls (Fig.2, A,*; B,**). ASI impaired gene expression of Cry 1 (-1.495 fold change), Cry 2 (-1.200), Per 1 (-1.250), Per 2 (-1.412) and Per 3 (-1.369) (Fig.3). Additionally, protein levels of BMAL1 and CLOCK were down-regulated (Fig. 4, A: 25.7 ± 9.1%,*; B: 28.9 ± 9.1%,*) in ASI mice relative to controls.

CONCLUSION: ASI caused sleep fragmentation and impaired sleep quantity and circadian rhythm in aged mice. Mice with ASI-induced sleep-wake disruption exhibited decreased expression of key genes that regulate sleep-wake activity and circadian function. The sleep and circadian rhythm changes evoked by ASI in aged mice closely recapitulate those of delirious human subjects and thus support the use of our preclinical model for future mechanistic studies of postoperative delirium.

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Fig. 1

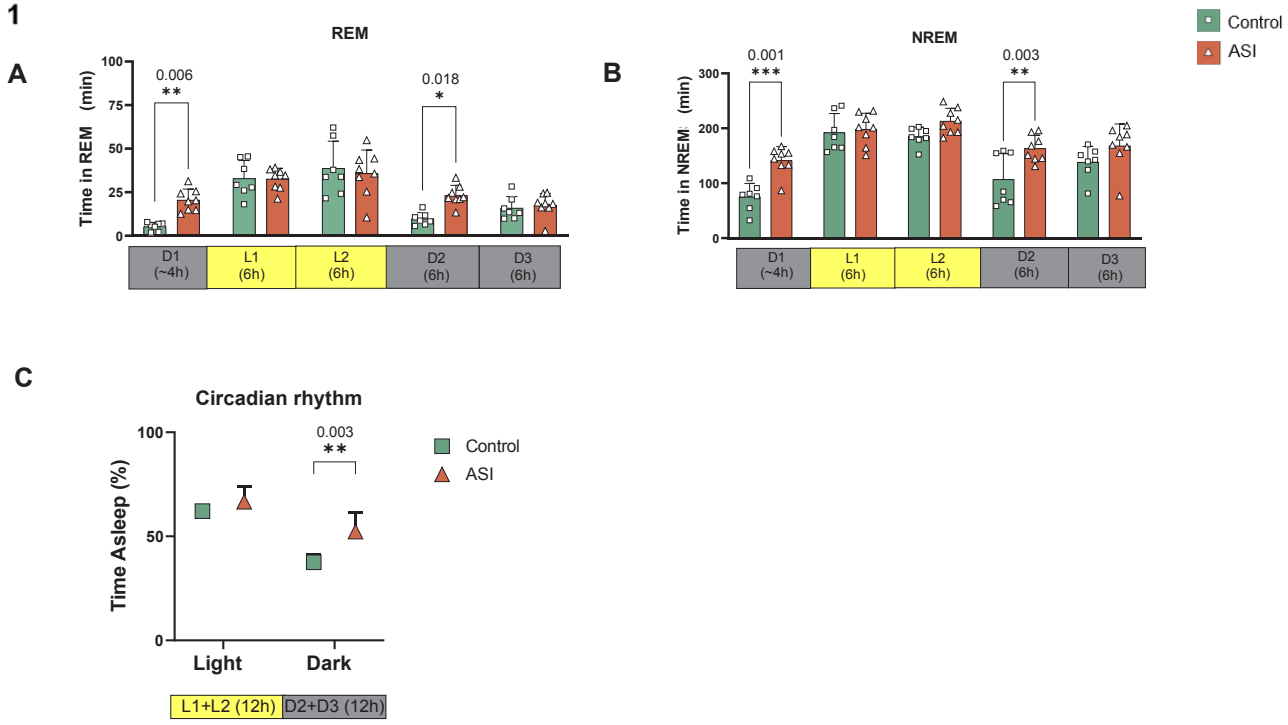


Fig. 2

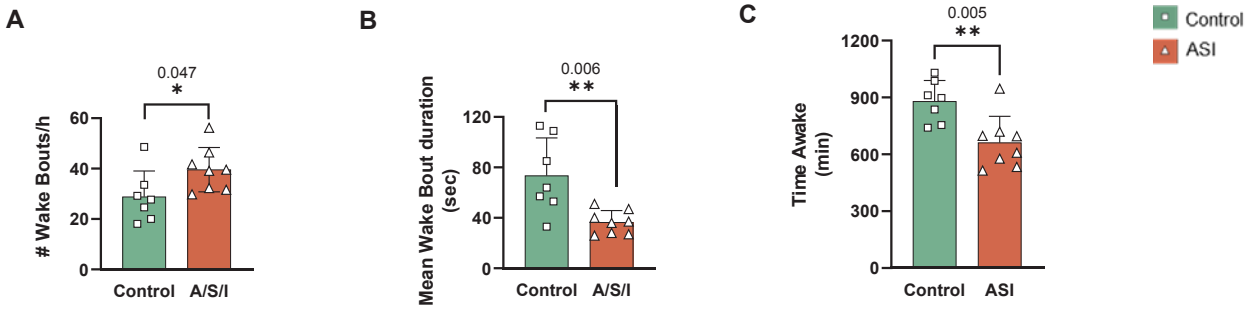


Fig. 3

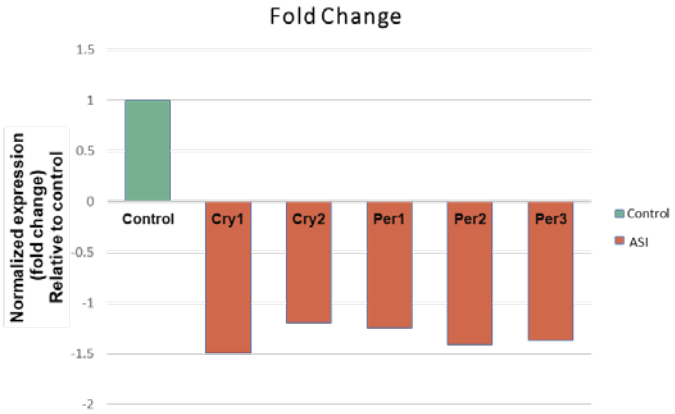
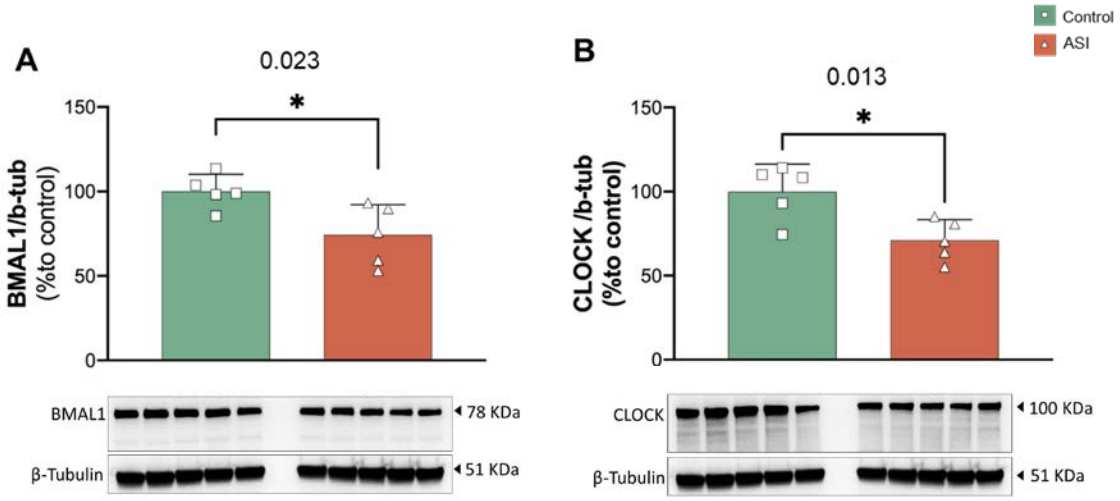


Fig. 4



SUBSPECIALTY ABSTRACTS

OBESITY

OBESITY 1

Varying cardiometabolic disease patterns with or without obesity are associated with differential increases in acute kidney injury following joint replacement procedures

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INTRODUCTION: Total joint arthroplasty is the most common elective surgery performed in the United States[1]. There is a paucity of information describing cardiometabolic disease patterns, obesity, and associations with postoperative acute kidney injury (AKI). This study aims to describe the co-occurrence of cardiometabolic diseases with and without obesity and analyze associated risks of postoperative AKI following total knee and hip arthroplasty procedures.

METHODS: This retrospective analysis examined 81,871 patients ≥18 years of age undergoing primary non-emergent total knee or hip arthroplasties across academic and community health systems within the Multicenter Perioperative Outcomes Group between 2008 and 2019. Exclusion criteria are described in Figure 1. AKI was defined based upon pre- and postoperative creatinine values using modified KDIGO criteria[2,3]. The primary outcome was any AKI stage ≥1. Cardiometabolic diseases were defined using ICD 9/10 codes, preoperative vital signs and labs, and preoperative history and physical data. Latent classes were constructed from cardiometabolic diseases (Table 1). Following latent class construction, the data were split 70/30 into derivation and validation datasets at the institution level. A mixed-effect logistic regression model was constructed, adjusting for random effect of institution, the AKI outcome, and the interaction between latent class membership and obesity status, adjusting for additional known risk factors for AKI. Model fixed effects were then applied in the validation cohort and model area under the curve (AUC) c-statistics compared.

RESULTS: Of the 81,871 cases meeting study inclusion criteria, 4,023 (4.9%) developed AKI. Compared to those without AKI, those with AKI were more commonly older and with higher BMI and ASA physical classification scores (Table 2). A latent class model selected three groups of cardiometabolic disease patterns, labeled as 'Hypertension (HTN)', 'Metabolic Syndrome (MetS)', and 'MetS+Cardiovascular Disease (CVD)' (Figure 2). There was no significant difference in class membership by AKI status between derivation and validation cohorts. After model adjustment, varying combinations of latent classes and obesity status yielded differential risk of AKI compared to those in 'HTN'/Non-obese (Figure 3). Those 'HTN'/Obese had 1.7-fold increased odds of AKI compared to 'HTN'/Non-obese (95%CI: 1.5-2.0). Compared to 'HTN'/Non-obese, those 'MetS+CVD'/Obese had the highest odds of AKI (OR 3.6, 95%CI: 3.1-4.3), while 'MetS+CVD'/Non-obese had 2.5 times the odds of AKI (95%CI: 2.0-3.0). The model performed well in both cohorts (AUC 0.748 derivation, 0.732 validation).

CONCLUSION: There exists significant heterogeneity in the odds of AKI given the presence of comorbid cardiometabolic disease with or without obesity. The use of latent classes intersected with obesity can prove a useful tool for clinicians to determine who is most at risk for AKI following elective joint replacement.

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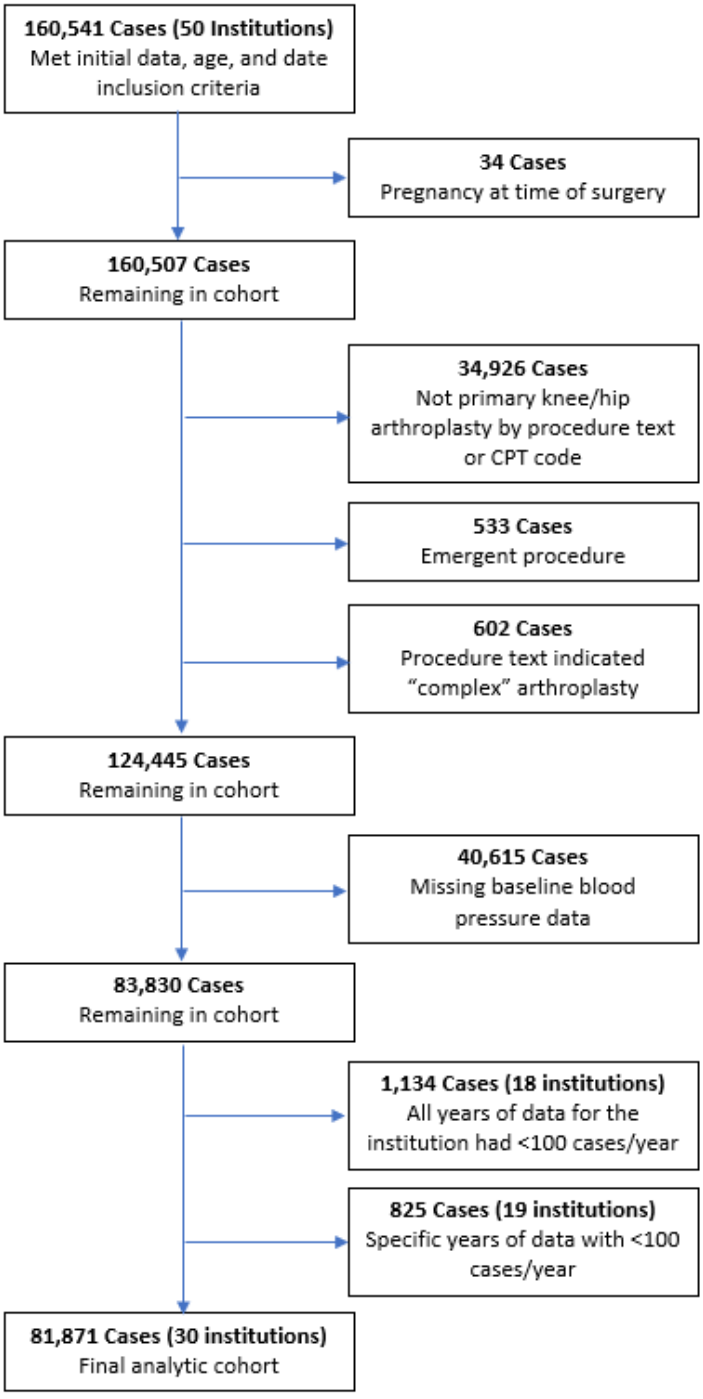

Figure 1. Study population flow chart

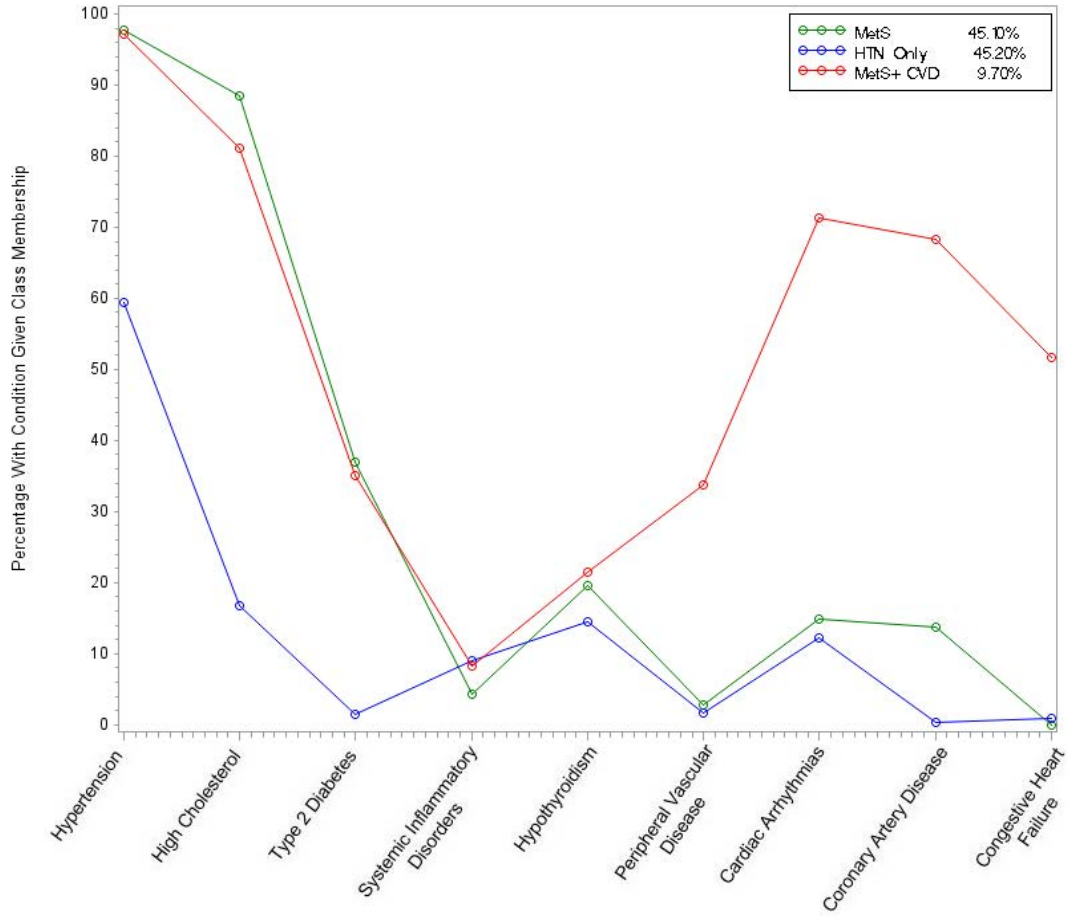

Figure 2. Percentage of each cardiometabolic disease by class membership. Abbreviations: MetS – Metabolic Syndrome, HTN – Hypertension, CVD – Cardiovascular Disease

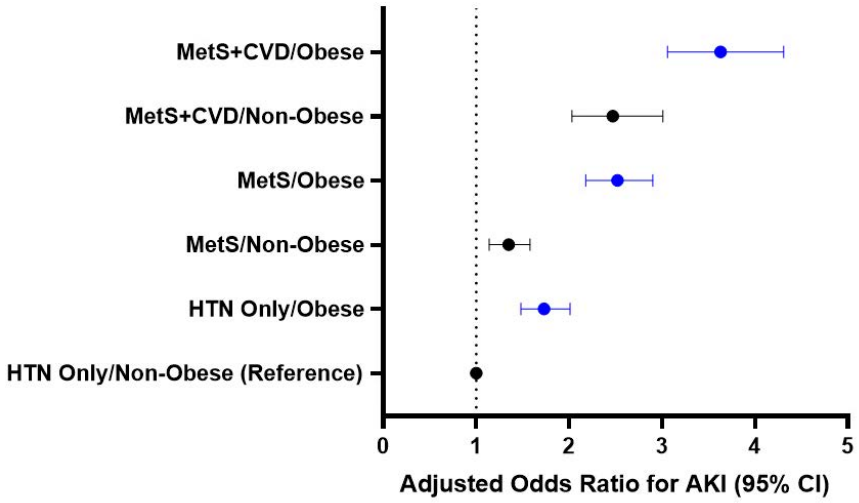

Figure 3. Forest plot of results of fully adjusted model within the derivation dataset (N = 55,798) for the interaction of latent class membership and obesity, with the reference group of "HTN"/Non-obese. Odds ratios for obese individuals are in blue. Model was adjusted for the random effect of institution, and additionally adjusted for fixed effects of age, sex, race, procedure type (knee versus hip), ASA classification, smoking category, general anesthesia use, packed red blood cell use, crystalloid equivalents given, minutes of mean arterial hypotension <65mmHg, preoperative hypotension, intraoperative nephrotoxic medication use, tranexamic acid use, and case year. Abbreviations: MetS – Metabolic Syndrome, CVD – Cardiovascular Disease, HTN - Hypertension

Table 1. Cardiometabolic diseases included in latent class construction

Condition	Overall Prevalence	MetS Class (N = 36,889)	HTN Class (N = 37,032)	MetS+CVD Class (N = 7,950)
Hypertension	80.4% (65,791)	97.7% (36,046)	59.5% (22,026)	97.1% (7,719)
High Cholesterol	55.3% (45,304)	88.5% (32,659)	16.7% (6,191)	81.2% (6,454)
Type 2 Diabetes	20.7% (16,925)	37.0% (13,629)	1.4% (505)	35.1% (2,791)
Peripheral Vascular Disease	5.3% (4,355)	2.8% (1,031)	1.7% (637)	33.8% (2,687)
Systemic Inflammatory Disorders	6.8% (5,593)	4.3% (1,596)	9.0% (3,341)	8.3% (656)
Hypothyroidism	17.5% (14,292)	19.6% (7,224)	14.5% (5,367)	21.4% (1,701)
Cardiac Arrhythmias	19.3% (15,760)	14.9% (5,512)	12.3% (4,570)	71.4% (5,678)
Congestive Heart Failure	5.4% (4,429)	0.0% (0)	0.9% (325)	51.6% (4,104)
Coronary Artery Disease	12.9% (10,594)	13.7% (5,041)	0.4% (135)	68.2% (5,418)

Data are presented as percentage (frequency). Abbreviations: MetS – Metabolic Syndrome, HTN – Hypertension, CVD – Cardiovascular Disease

Table 2. Demographic characteristics of total knee and hip arthroplasty patients, overall analytic cohort

	Overall (N = 81,871)	No Acute Kidney Injury (N = 77,848)	Any Acute Kidney Injury (N = 4,023)	Absolute Standardized Differences
Demographics				
Age				0.239
18-29	519 (0.6)	505 (0.7)	14 (0.4)	
30-39	1,100 (1.3)	1,079 (1.4)	21 (0.5)	
40-49	4,321 (5.3)	4,199 (5.4)	122 (3.0)	
50-59	16,467 (20.1)	15,816 (20.3)	651 (16.2)	
60-69	29,363 (35.9)	27,954 (35.9)	1,409 (35.0)	
70-79	22,770 (27.8)	21,497 (27.6)	1,273 (31.6)	
80+	7,331 (9.0)	6,798 (8.7)	533 (13.3)	
Body Mass Index	31.4 ± 6.8	31.2 ± 6.7	34.1 ± 7.6	0.397
Gender				0.107
Male	32,758 (40.0)	30,946 (39.8)	1,812 (45.0)	
Female	49,113 (60.0)	46,902 (60.2)	2,211 (55.0)	
Race				0.299
Non-Hispanic White	61,888 (75.6)	59,243 (76.1)	2,645 (65.8)	
Non-Hispanic Black	11,019 (13.5)	10,038 (12.9)	981 (24.4)	
Hispanic	840 (1.0)	797 (1.0)	43 (1.1)	
Other	8,124 (9.9)	7,770 (10.0)	354 (8.8)	
ASA Class				0.568
1	1,525 (1.9)	1,510 (1.9)	15 (0.4)	
2	39,013 (47.7)	37,989 (48.8)	1,024 (25.5)	
3	39,717 (48.5)	37,012 (47.5)	2,705 (67.2)	
4	1,616 (2.0)	1,337 (1.7)	279 (6.9)	
Smoking Status				0.027
Current Smoker	7,544 (9.2)	7,074 (9.1)	470 (11.7)	
Former Smoker	1,962 (2.4)	1,858 (2.4)	104 (2.6)	
Never Smoker	9,739 (11.9)	9,375 (12.0)	364 (9.1)	
Unknown	62,626 (76.5)	59,541 (76.5)	3,085 (76.7)	
Cardiometabolic Conditions for Latent Class Analysis				
Hypertension	65,791 (80.4)	62,001 (79.6)	3,790 (94.2)	0.443
High Cholesterol	45,304 (55.3)	42,716 (54.9)	2,588 (64.3)	0.194
Peripheral Vascular Disorders	4,355 (5.3)	3,929 (5.1)	426 (10.6)	0.208
Diabetes	16,925 (20.7)	15,436 (19.8)	1,489 (37.0)	0.388
Systemic Inflammatory Disorders	5,593 (6.8)	5,321 (6.8)	272(6.8)	0.003
Hypothyroidism	14,292 (17.5)	13,470 (17.3)	822 (20.4)	0.080
Cardiac Arrhythmias	15,760 (19.3)	14,562 (18.7)	1,198 (29.8)	0.261
Congestive Heart Failure	4,429 (5.4)	3,794 (4.9)	635 (15.8)	0.364
Coronary Artery Disease	10,594 (12.9)	9,629 (12.4)	965 (24.0)	0.305
Additional Comorbidities				
Obesity	45,214 (55.2)	42,404 (54.5)	2,810 (69.9)	0.321
Preoperative Hypotension	16,347 (20.0)	15,208 (19.5)	1,139 (28.3)	0.207
Estimated Glomerular Filtration Rate	78.3 ± 22.4	78.8 ± 22.0	68.9 ± 27.1	0.402
Intraoperative Characteristics				
Procedure Type				0.027
Knee	46,662 (57.0)	44,420 (57.1)	2,242 (55.7)	
Hip	35,209 (43.0)	33,428 (42.9)	1,781 (44.3)	
Use of General Anesthesia	30,721 (37.5)	28,684 (36.9)	2,037 (50.6)	0.281
Packed Red Blood Cell Transfusion	531 (0.7)	450 (0.6)	81 (2.0)	0.127
Total Fluid Volume, Crystalloid Equivalents	1559.5 ± 1277.2	1559.5 ± 1289.9	1558.2 ± 998.2	0.001
Minutes of MAP <65	3.0 [0.0 to 13.0]	3.0 [0.0 to 13.0]	3.0 [0.0 to 12.0]	0.048
Tranexamic acid use	54,461 (66.5)	52,079 (66.9)	2,382 (59.2)	0.160
Nephrotoxic Medication Use	72,738 (88.8)	69,133 (88.8)	3,605 (89.6)	0.026
Diuretic	67 (0.1)	57 (0.1)	10 (0.3)	0.044
Antibiotic	71,998 (87.9)	68,427 (87.9)	3,561 (88.5)	0.019
NSAID	9,569 (11.7)	9,184 (11.8)	385 (9.6)	0.072

Data are presented as means ± standard deviations, medians [25th percentile to 75th percentile], or frequency (percentage) as appropriate. A standardized difference >0.20 indicates the potential for heterogeneity between those with and without AKI. Abbreviations: MAP – mean arterial pressure, NSAID – non-steroidal anti-inflammatory drugs

OBESITY 2

Multimodal Anesthesia Protocol Implementation and Perioperative Outcomes in Bariatric Surgery

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INTRODUCTION: Opioids are frequently used in the perioperative period to manage pain and reduce the intraoperative sympathetic response. 5.9-6.5% of patients persistently use opioids after both minor and major surgeries, compared to 0.4% of people that do not have surgery.[1] Surgery is often patients' initial exposure to opioids and likely a major contributing factor to the opioid epidemic. Multimodal opioid sparing anesthesia has increasingly gained prominence as a method to potentially reduce opioid use and opioid-associated complications. Opioid free anesthesia (OFA) is not clinically inferior to opioid-inclusive anesthesia in postoperative pain outcomes and associated with a 20% reduction in postoperative nausea and vomiting.[2]

Patients undergoing bariatric surgery are at particularly high risk of opioid-associated complications. The primary immediate risk is for opioid-induced ventilatory impairment (OIVI) due to high BMI and obstructive sleep apnea (OSA). Patients with obesity are also at increased risk for poorly controlled postoperative pain and chronic opioid dependance.[3] A number of opioid-sparing techniques have been explored in bariatric surgery, including intraoperative lidocaine infusions and dexmedetomidine infusions with mixed results.[4,5] This is a study of a multi-modal opioid-sparing anesthetic protocol for bariatric surgery implemented at a high volume tertiary referral center.

METHODS: This is a retrospective study of 1,555 patients over 18 years old who underwent elective laparoscopic gastric bypass or gastrectomy surgeries at tertiary referral center between 8/1/2018 and 12/31/2019. A multimodal intraoperative anesthetic protocol for bariatric surgery was implemented 7/15/2019. The protocol consisted of intraoperative administration of ondansetron, dexamethasone, propofol infusion, dexmedetomidine infusion, acetaminophen and ketorolac. Intra-operative opioid administration was up to discretion of supervising anesthesiologist. Data was obtained from the electronic medical record (EMR). Outcomes of interest included compliance with protocol after implementation, intraoperative opioid use, pain scores, post-operative opioid use and complications. Comparisons of medication utilization was tested with Fisher exact test. Two-sample t-tests were used to compare intraoperative opioid administration.

RESULTS: Prior to implementation of this protocol, multimodal anesthesia was utilized in some bariatric cases at our institution. 36% of cases utilized at least 4 out of 6 medications and 22% were done with at least 5. After implementation of the protocol, utilization increase significantly ($P<0.0001$), with 66% of cases utilizing at least 4 medications and 46% used at least 5. Doses of intraoperative opioids were converted to morphine equivalents, with no significant differences in average dose given pre and post protocol (22.5mg vs. 23.5mg, $P=0.1635$).[6]

CONCLUSION: Preliminary analysis suggests that the protocol implementation increased utilization of multimodal anesthesia, but gaps in utilization remain. Overall morphine dose equivalent administration did not change after protocol implementation. Further analysis will include data from 2020, post-operative outcome comparisons and comparisons of protocol-adherent and non-adherent surgeries.

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OBESITY 3

Association between High Preoperative Body Mass Index and Mortality after Cancer Surgery

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INTRODUCTION: Despite an association between obesity and increased mortality in the general population, obesity has been paradoxically reported with improved mortality of surgery and some types of cancer. However, this has not been fully investigated in patients undergoing cancer surgery.

METHODS: Methods: From March 2010 to December 2019, 87,567 adult patients undergoing cancer surgery were divided into three groups according to body mass index (BMI): 53,980 (61.6%) in the normal (18.5-25 kg/m2), 2,787 (3.2%) in the low BMI (<18.5 kg/m2), and 30,800 (35.2%) in the high BMI (>25 kg/m2) groups. The high BMI group was further stratified into overweight (25-30 kg/m2) and obese (>30 kg/m2) groups. The primary outcome was mortality during three years after surgery.

RESULTS: Following adjustment by inverse probability weighting, mortality during three years after surgery was significantly lower in the high BMI group than the normal (4.8% vs. 7.0%; hazard ratio [HR], 0.69; confidence interval [CI], 0.64-0.77; $p < 0.001$) and low BMI (4.8% vs. 13.0%; HR: 0.38; CI: 0.35-0.42; $p < 0.001$) groups. The mortalities of the overweight and obese groups were lower than that of the normal group (7.0% vs. 5.0%; HR: 0.72; CI: 0.67-46 0.77; $p < 0.001$ and 7.0% vs. 3.3%; HR: 0.57; CI: 0.50-0.65; $p < 0.001$, respectively). This association was not observed in female patients and those undergoing surgery for breast and gynecological cancers.

CONCLUSION: High BMI may be associated with decreased mortality after cancer surgery. Further investigations are needed for clinical application of our finding.

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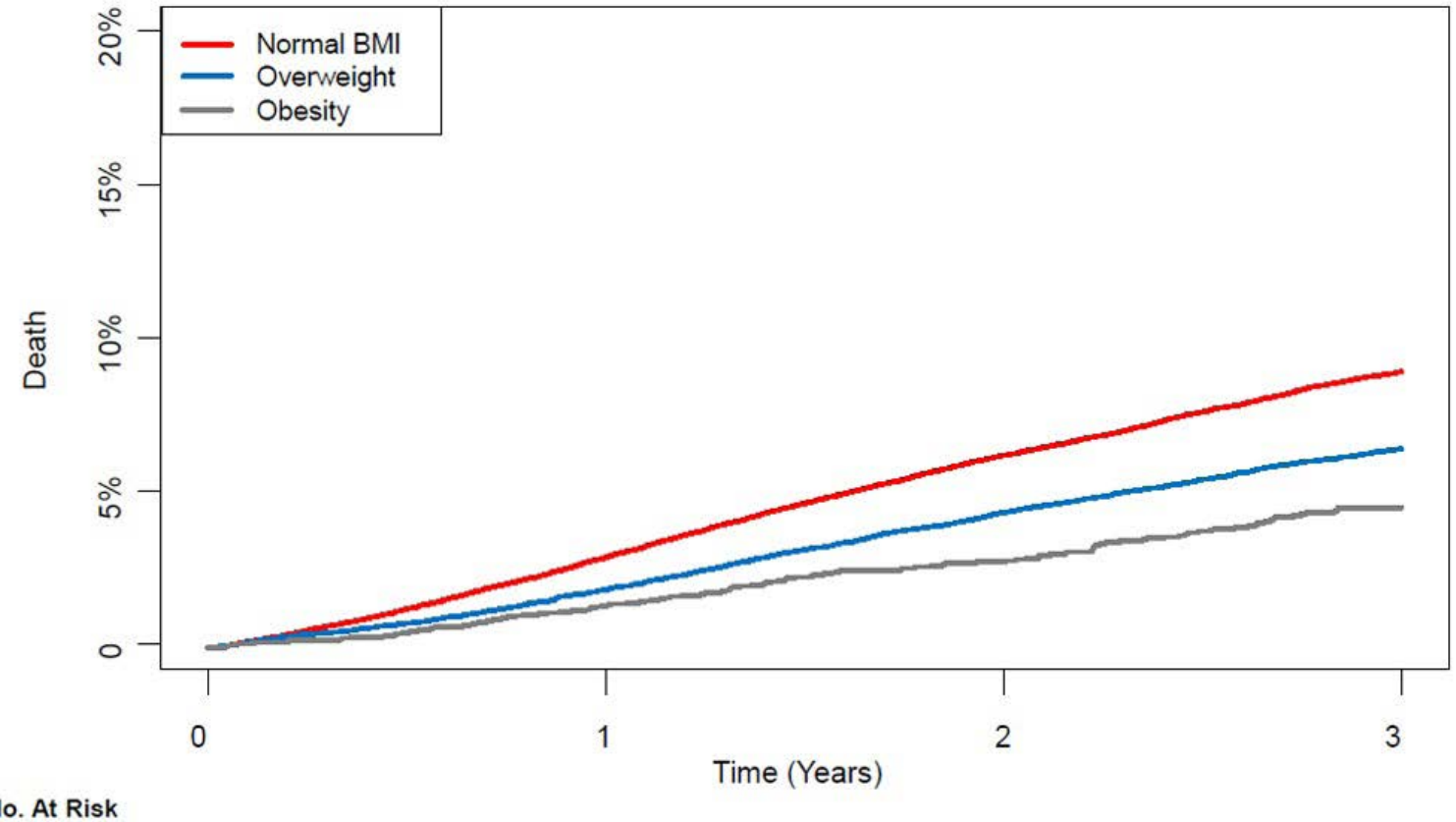

No. At Risk				
Normal BMI	53980	44553	35639	28687
Overweight	27002	22472	17867	14195
Obesity	3798	3062	2392	1862

SUBSPECIALTY ABSTRACTS

OBSTETRIC ANESTHESIOLOGY

OBSTETRIC ANESTHESIOLOGY 1

The effect of remifentanil infusion on respiratory status in pregnant women undergoing fetoscopic surgeries in mid pregnancy

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INTRODUCTION: Since remifentanil undergoes extensive placental transfer, maternal administration has been used for fetal immobilization and/or maternal sedation during fetal therapies[1]. Generally, remifentanil is known to induce respiratory depression in proportion to the concentration of remifentanil[2] and the time required to achieve a plasma steady-state by starting a continuous infusion without the administration of boluses is around 15 minutes in adults[3]. However, pharmacokinetics (PK) and pharmacodynamics (PD) of remifentanil in pregnant women is not well known. The aim of this study was to evaluate the safety and effect of remifentanil on maternal respiratory status during fetal surgeries.

METHODS: We retrospectively examined obstetric and anesthetic data in pregnant women with twin-to-twin transfusion syndrome (;TTTS) who underwent fetoscopic laser coagulation (FLP) in our hospital between November 2018 and June 2021. The patient received combined spinal-epidural anesthesia with intrathecal injection of hyperbaric bupivacaine 7.5 mg, and local anesthetics were administered epidurally as necessary to obtain an adequate sensory block level. After confirming fetal conditions and position by obstetricians, the infusion of remifentanil was initiated at 0.1 μg/kg/min prior to surgical procedure. When the fetal movement was observed by obstetricians, the infusion rate of remifentanil was increased to attain optimal operative conditions. 2 /min oxygen was supplied via nasal cannula, and maternal respiratory condition was monitored by CapnostreamTM 20P (Medtronic, Minneapolis, MN, USA), which can continuously measure the approximate value of end-tidal carbon dioxide (ETCO2) intubated, and respiratory rate (RR) during the surgery.

RESULTS: Seventy-five patients underwent FLP during the period; 16 patients were excluded due to lack of respiratory monitoring or insufficient respiratory data, and 59 patients were enrolled in this analysis. The mean (SD) age, body mass index, and gestational weeks at the procedure were 32.0 ± 4.7, 22 ± 5.1 and 20.8 ± 22.3, respectively. The median (IQR) sensory block level prior to the procedure was Th8 (6 - 10). Maternal RR gradually decreased until 10min after the initiation of remifentanil infusion and then remained constant level (Fig.1). Serious respiratory depression (RR <7 /min) was not observed in any patient during the procedure. Maternal EtCO2 gradually increased until 15 mins after the initiation of remifentanil infusion and then remained constant level (Fig.2). In this period, no significant change in hemodynamic parameters (HR, BP) was observed.

CONCLUSION: In this study, no serious respiratory complications were observed using remifentanil infusion. Maternal RR and ETCO2 were decreased until 10 and 15 minutes respectively after the initiation of remifentanil infusion, and then they remained constant. They suggest that respiratory response reflects the PK/PD of remifentanil. Further investigations about PK/PD in pregnant women is required.

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Fig.1 The changes of RR

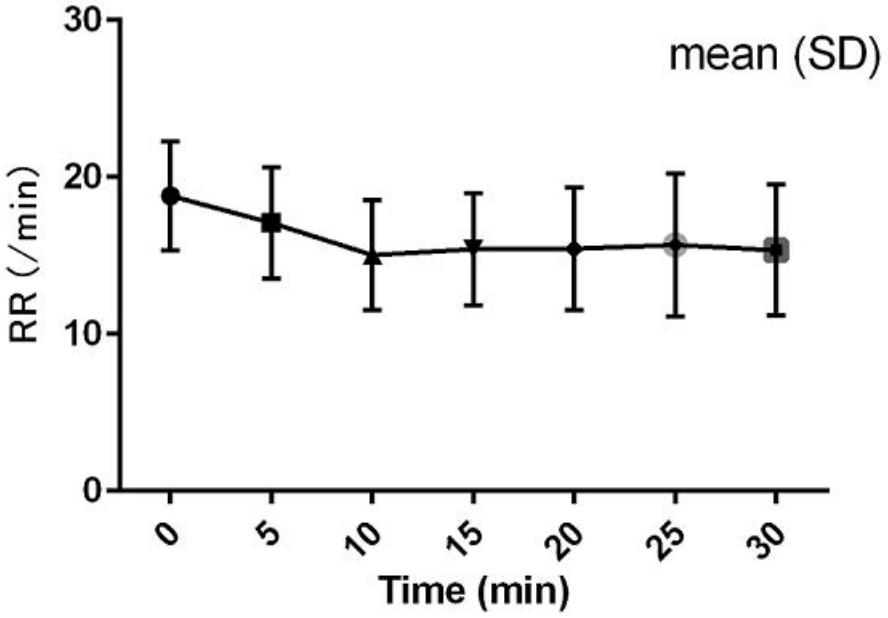
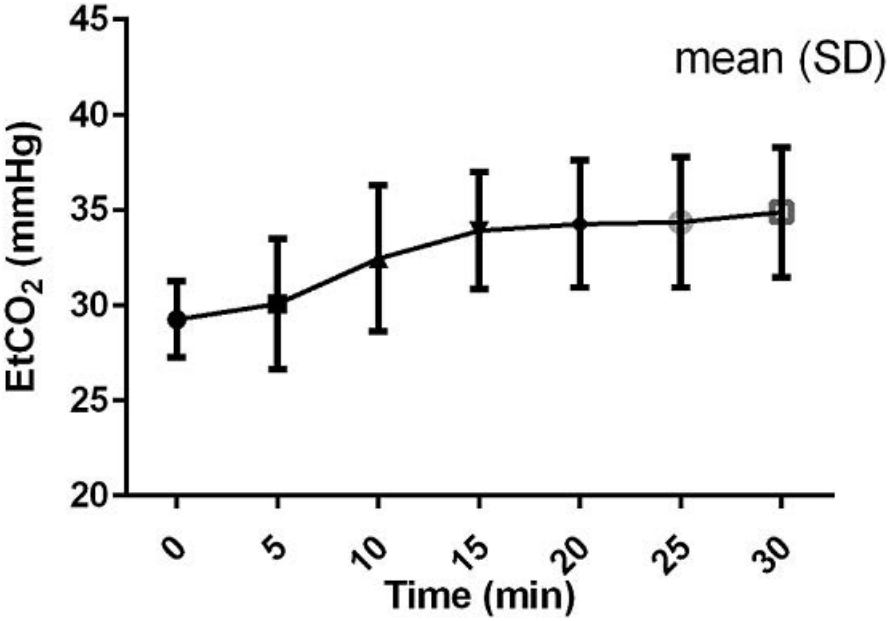


Fig.2 The changes of $ETCO_2$



OBSTETRIC ANESTHESIOLOGY 2

Assisted reproductive technology does not increase bleeding risk associated with cesarean section: a cohort study

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INTRODUCTION: In the past few decades, the number of women who conceived using assisted reproductive technology (ART) has increased worldwide because of rising incidence of infertility. Several studies and meta-analyses indicate that ART pregnancies carry increased risk of complications including postpartum hemorrhage (PPH). As PPH is the leading cause of maternal mortality, anesthesiologists need to understand the bleeding risk associated with ART. However, the association between ART and the bleeding risk particularly in cesarean section has not been systematically assessed. The aim of this study was to evaluate bleeding risk during and after cesarean section in parturients who conceived using ART.

METHODS: This is a retrospective observational study analyzing data from a cohort of parturients who underwent cesarean section at our institution from 2014 to 2019. We defined ART as having conceived with intracytoplasmic sperm injection and in vitro fertilization. For each ART case, we selected a control from among parturients who had conceived spontaneously, matching the ART case patient's age and year of delivery. Matched cases selected as explained above were designated the control group. The primary outcome measure was the amount of blood loss during and within 24 hours after cesarean section, which was compared using Student's t-test. Secondary outcome measure was the incidence of severe PPH defined as blood loss greater than 1,500 ml, which was compared using chi-squared test. The independent effect of ART on the primary and secondary outcomes were evaluated using multiple linear regression and multivariable logistic regression, respectively. With 132 parturients in each group, we had 90% power to detect a 200 ml difference in the bleeding amount, at a 0.05 two-sided significance level.

RESULTS: 155 parturients in each group were analyzed. The amount of bleeding in the ART group was 1234 ± 669 mL, which was 124 mL (11.2%) greater than that in the control group. The difference was not statistically significant (95% CI: −34 to 282; P = 0.12). The incidence of severe PPH in the ART group and in the control group was 23.9% and 16.8% respectively, and the difference was not statistically significant (P = 0.16). No significant independent effect of ART on the bleeding amount and the incidence of severe PPH was observed in multivariable regression analyses (P = 0.27, P = 0.61).

CONCLUSION: ART was not associated with increased blood loss and risk of severe PPH. The results were consistent through univariable and multivariable analyses. In particular, the upper limit of 95% CI of the mean difference was 282 ml, which, in our opinion, is small enough to exclude as a clinically relevant increase. It is unlikely for a 282 ml increase of blood loss contaminated with substantial amount of amniotic fluid to affect clinical management or outcomes, such as blood transfusion requirement or length of hospitalization. ART does not increase risk of bleeding in cesarean section.

OBSTETRIC ANESTHESIOLOGY 3

Decision Analysis for Evaluating Ante-Partum Risk Prediction of Pre-Eclampsia: Minimum Test Tradeoff

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INTRODUCTION: Pre-eclampsia complicates 2-8% of pregnancies worldwide, and in the US such hypertensive disorders are associated with 16% of maternal deaths. The prevalence of pre-eclampsia is higher at centers specializing in the care of high-risk patients and significantly influences anesthetic management. As anesthesiologists become increasingly involved in prenatal care of obstetric patients, it is important to recognize the potential value of pre-eclampsia screening. Because accurate early prediction of the later development of pre-eclampsia leads to changes in obstetrical management, a number of studies have evaluated biomarkers, clinical factors, and other tests by using receiver-operating characteristic curve analysis and area under the curve (AUC). A recent study[1] compared a model that included clinical factors plus the biochemical marker Inhibin-A with a model adding the biophysical parameter of uterine artery pulsatility index (UtA PI) to the first model. The results showed an improvement (higher AUC) with the latter. That study, as well as numerous other studies in this area, failed to consider the costs of data acquisition to improve the model. We therefore questioned whether the addition of the UtA PI was worthwhile to improve risk prediction. We investigated the cost of UtA PI measurement to decide whether improvements in risk prediction are sufficient to justify data collection costs.

METHODS: We used decision analysis to compare two models predicting in early (12-14 weeks) pregnancy the risk of late-onset (>34 weeks gestation) pre-eclampsia (LO PE), based on published data[1]. The methodology is based on recent work by Baker[2,3], who developed a useful decision-analytic metric, the test tradeoff, and a simple approximation of its minimum value. For a given ratio of the benefit of a true positive to the cost of a false positive, the test tradeoff is the minimum number of data collections per true positive to yield a positive net benefit. Data were not available for a detailed test tradeoff analysis. We used Baker's formula applied to model comparisons to compute an approximate minimum test tradeoff (over benefit-cost ratios) for an added predictor, MTT. Formula for MTT is in Figure. Formula inputs included published AUC's[1] that used models incorporating clinical background factors plus measurements of inhibin A with (AUC 0.824) or without (AUC 0.815) the addition of uterine artery pulsatility index (UtA PI). The formula also includes the probability of developing LO PE disease. We compared the MTT for the general US population (5% prevalence) with the MTT for a high risk group of subjects with a history of PE (40% prevalence). We obtained cost data from CPT codes used at our institution. For UtA PI, we assumed that patients already undergo screening doppler studies in the first trimester, and therefore the additional cost of UtA PI would not include the doppler cost.

RESULTS: For the low risk, general US population, we found that MTT = 1250 for comparing a model using clinical background factors plus Inhibin A with a second model using clinical background factors plus Inhibin A and UtA PI. For the high risk group, MTT = 156. There were no costs of data collection of clinical background factors, as this information was included in each patient's history and physical exam. Cost per measurement of Inhibin-A (CPT 86336) is $53.00. UtA PI (CPT93976) costs $1395.30 ($720.30 facility fee + $675 pro fee) per measurement.

CONCLUSION: A recent study[1] evaluated two models to predict the development of LO by comparing AUC's, without considering whether additional costs of UtA PI data collection for improved risk prediction were worthwhile. In this study, we found that for a positive net benefit, we would need to trade 1250 UtA PI measurements for every true positive prediction of LO PE in the general US obstetrical population. This number is significantly lower (156) in women with PE in the past. Data collection costs are low for the model that incorporates baseline clinical data with Inhibin-A levels. Based on MTT, costs of adding UtA PI are relatively high compared to the anticipated benefit of a true positive that prompts intervention, especially in the general US group. Implications of a true positive include prophylactic administration of aspirin and frequent monitoring of maternal blood pressure and fetal condition. In summary, MTT can assist with medical decision-making when risk prediction alters clinical management.

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MTT = minimum test tradeoff

AUC_1 = AUC for Model 1 (clinical risk factors with inhibin A)

AUC_2 = AUC for Model 2 (clinical risk factors with inhibin A and UtA PI)

P = probability of developing late onset pre-eclampsia (LO PE) in the population

$$\text{MTT} = \frac{1}{\{(h(\text{AUC}_2) - h(\text{AUC}_1)\} \text{ x P}}$$

$$h(\text{AUC}) = \text{AUC} - \sqrt{\frac{1-\text{AUC}}{2}}$$

Fig. 1

OBSTETRIC ANESTHESIOLOGY 4

Anesthesia-Associated Racial Disparities in Severe Maternal Morbidity After Cesarean Delivery

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INTRODUCTION: Severe maternal morbidity (SMM) is an unexpected complication of childbirth that poses risk for significant immediate and life-long adverse health effects[1]. Black people have a higher risk for SMM than Whites, and the disparity persists even after accounting for comorbidities and mode of delivery[2]. Published literature suggest that Black people have higher odds of receiving general anesthesia (GA) for cesarean delivery (CD)[3] and that GA increases the risk of SMM[4]. However, it is unknown if the association between the mode of the anesthesia and SMM outcomes vary by race. We hypothesized that Black people will have higher risk of SMM compared to Whites when receiving GA for CD.

METHODS: A retrospective cohort design was chosen. Cesarean (CD) deliveries from a single institution over 2008-2018 were reviewed. SMM events were defined as the presence of at least 1 out of 23 conditions: 1) any of the 21 Centers for Disease Control SMM indicators[5]; 2) Postpartum intensive care unit admission during delivery; and 3) Prolonged postpartum length of stay. Self-reported race was categorized into Black and White groups. Baseline characteristics between groups were compared using chi-square, Student t-test, or Wilcoxon rank-sum where appropriate. Generalized linear and mixed models adjusted for multiple deliveries during the study period and clinical and socioeconomic variables defined based on prior published work[3,4]. To assess the potential effect of unmeasured confounding on results, E-scores were calculated. A P-value of <0.05 was considered statistically significant.

RESULTS: 27,918 CD with complete anesthesia records were included and 1,614 (5.5%) experienced SMM. Black people with and without SMM outcomes had higher incidence of hypertensive disorders, food and health care assistance, and less than high school education (Table 1). Univariate analysis showed Blacks with neuraxial anesthesia were more likely than Whites to experience SMM (OR 1.04, 95% CI, 1.03-1.04 P<0.001), and no racial differences were seen among recipients of GA (OR 1.03, 95% CI, 0.97-1.09 P=0.39). After adjusting for clinical and socioeconomic variables, the risk of SMM among Black people receiving neuraxial anesthesia persisted (OR 1.02, 95% CI, 1.02-1.03 P<0.001). However, E-value for the relationship between SMM and neuraxial anesthesia among Black people was 1.18 (95% CI, 1.14-1.22) which represents the strength of association of unmeasured confounders.

CONCLUSION: In our large single-center cohort, no racial disparities were observed when Black people received GA for CD. Black people were found to be at higher risk of experiencing SMM after receiving neuraxial anesthesia for CD, but this finding could be explained by unmeasured confounding factors such as social determinants of health. Future work to eliminate disparities in SMM should focus on addressing these important non-anesthesia factors that influence SMM.

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Table 1. Cohort baseline characteristics, stratified by the presence of SMM.

	No SMM			**SMM**		
	White	Black	*P*-value	White	Black	*P*-value
	n=20,453	*n=4,966*		*n=1,010*	*n=480*	
Age	31 (27, 34)	26 (22, 31)	**<0.001***	31 (27,35)	27 (22,32)	**<0.001***
Nulliparous	11012 (54.0%)	2987 (60.3%)	**<0.001***	497 (49.3%)	298 (62.7%)	**<0.001***
Gestational Age	38.2 (2.6)	37.9 (3.0)	**<0.001***	35.8 (4.1)	35.7 (4.3)	0.68
Preterm	3061 (15.0%)	857 (17.3%)	**<0.001***	466 (46.1%)	220 (45.8%)	0.91
Hypertensive disorder of pregnancy	3976 (19.4%)	1232 (24.8%)	**<0.001***	454 (45.0%)	260 (54.2%)	**<0.001***
Pre-existing Diabetes	554 (2.7%)	147 (3.0%)	0.33	80 (7.9%)	48 (10.0%)	0.18
Depression	220 (1.1%)	28 (0.6%)	**<0.001***	16 (1.6%)	3 (0.6%)	0.12
Substance Abuse	768 (3.8%)	243 (4.9%)	**<0.001***	58 (5.7%)	26 (5.4%)	0.8
Smoking	2157 (12.3%)	787 (18.5%)	**<0.001***	139 (15.8%)	67 (16.0%)	0.91
Food assistance	3933 (20.7%)	2828 (61.4%)	**<0.001***	238 (25.9%)	259 (58.2%)	**<0.001***
Medicaid	5050 (24.7%)	3602 (72.5%)	**<0.001***	371 (36.7%)	366 (76.2%)	**<0.001***
Mother education: High school or less	3894 (20.5%)	2318 (50.3%)	**<0.001***	283 (30.8%)	239 (53.7%)	**<0.001***
Mode of Anesthesia:						
General Anesthesia	560 (2.9%)	199 (4.2%)	**<0.001***	205 (21.4%)	83 (18.5%)	0.21
Neuraxial	19010 (97.1%)	4527 (95.8%)		754 (78.6%)	366 (81.5%)	

Results are reported as median (interquartile range), mean (standard deviation) or frequency (percent).
* *P*<0.05
SMM, severe maternal morbidity.

OBSTETRIC ANESTHESIOLOGY 5

Racial, Ethnic & Language Disparities in Labor Epidural Analgesia Utilization

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INTRODUCTION: Labor epidural analgesia (LEA) is the most effective pain treatment modality for childbirth. In the United States, >70% of delivering women use LEA. However, significant racial and ethnic disparities have been reported with Black and Hispanic/Latinx women being less likely to utilize LEA compared to non-Hispanic White women. Our objectives were to identify labor epidural disparities across a large urban healthcare system in the northeast and to identify a need for standardized labor analgesia education.

METHODS: Retrospective chart review was performed to determine LEA rates across our institution's delivery sites between January 2019 and August 2021. Delivering women did not receive standardized labor analgesia education prior to delivery. Differences in labor epidural rates among Black, Hispanic/Latinx, and non-Hispanic White women were assessed using Chi-squared and Fisher's exact tests when appropriate.

RESULTS: The study population included 18,860 women across delivery sites. 61.5% of women identified as White, 11.3% Black, 10.5% Asian, and 17% other races. 17.6% of women identified as Hispanic/Latinx. 8.8% of women were non-English speaking. 78.5% of all women utilized LEA. LEA was significantly lower for Black women (74.6%) and Hispanic/Latinx women (75.3%) compared to non-Hispanic White and non-Hispanic Asian women (79.9%), p=0.000. LEA was also significantly lower for non-English speaking women (71.3%) compared to English speaking women (79.2%), p=0.000, and even lower for non-English speaking Hispanic/Latinx women (66.9%). In a subgroup analysis for women undergoing Cesarean section, general anesthesia was more commonly used in place of neuraxial anesthesia for Black women (3.2%) compared to White women (1.6%), p=0.016.

CONCLUSION: Significant racial, ethnic and language disparities were identified for LEA across our institution. Racial disparities for neuraxial anesthesia during Cesarean section were also identified. The latter finding is concerning given the increased morbidity associated with general anesthesia during Cesarean section compared to neuraxial anesthesia. Reported contributors to these disparities include lack of knowledge and familiarity with LEA as well as fears and misconceptions about LEA. At least one peripartum education program has been shown to reduce LEA misconceptions and improve LEA utilization for vulnerable populations. We have created a language-concordant, standardized, prenatal LEA education program to reduce LEA disparities within our institution.

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Table 1. Labor Epidural Analgesia Utilization among 18,860 Delivering Women, January 2019 to August 2021

Variable	Total (N=18,860)	Epidural (N=14,432)	No Epidural (N=3,953)	P Value
Race, no. (%)				
White	11,605 (61.5)	9,042 (79.9)	2,280 (20.1)	0.000‡
Black	2,129 (11.3)	1,543 (74.6)	526 (25.4)	
Asian	1,988 (10.5)	1,558 (79.9)	392 (20.1)	
Other	3,138 (16.6)	2,289 (75.2)	755 (24.8)	
Ethnic group, no. (%)				
Non-Hispanic/Latinx	15,035 (82.4)	11,600 (79.1)	3,061 (20.8)	0.000‡
Hispanic/Latinx	3,220 (17.6)	2,360 (75.3)	774 (24.7)	
Language, no. (%)				
English Speaking	17,136 (91.2)	13,230 (79.2)	3,473 (20.8)	0.000‡
Non-English Speaking	1,653 (8.8)	1,152 (71.3)	463 (28.7)	

‡Chi squared test

Table 2. Labor Epidural Analgesia Utilization by Language Strata, January 2019 to August 2021

	Epidural	No Epidural	P Value
White, no. (%)			
English Speaking	8,784 (80.0)	2,198 (20.0)	0.171‡
Non-English Speaking	246 (76.9)	74 (23.1)	
Asian, no. (%)			
English Speaking	1,385 (79.6)	354 (20.4)	0.523§
Non-English Speaking	171 (81.2)	38 (18.2)	
Black, no. (%)			
English Speaking	1,430 (74.9)	479 (25.1)	0.253§
Non-English Speaking	111 (70.7)	46 (29.3)	
Other Race, no. (%)			
English Speaking	1,631 (78.7)	442 (21.3)	0.000‡
Non-English Speaking	624 (67.2)	305 (32.8)	
Hispanic, no. (%)			
English Speaking	1,672 (79.3)	436 (20.7)	0.000‡
Non-English Speaking	684 (66.9)	338 (33.1)	

§ Fisher's exact test

‡Chi squared test

Table 3. Neuraxial Analgesia Utilization among 5,612 Delivering Women undergoing C-Section, January 2019 to August 2021

Variable	Neuraxial Anesthesia (N=5,519)	General Anesthesia (N=93)	P Value
Race, no. (%)			
White	3,418 (98.6)	48 (1.4)	0.016§
Black	705 (96.8)	23 (3.2)	
Asian	546 (98.6)	8 (1.4)	
Other	850 (98.4)	14 (1.6)	
Ethnic group, no. (%)			
Non-Hispanic/Latinx	4,467 (98.3)	78 (1.7)	0.385§
Hispanic/Latinx	864 (98.7)	11 (1.3)	
Language, no. (%)			
English Speaking	5,005 (98.3)	86 (1.7)	0.854§
Non-English Speaking	490 (98.6)	7 (1.4)	

§ Fisher's exact test

OBSTETRIC ANESTHESIOLOGY 6

Baseline parameters for rotational thromboelastometry in healthy pregnant American women Population: a retrospective study

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INTRODUCTION: The early recognition of hypofibrinogenemia is critical to minimize bleeding during postpartum hemorrhage (PPH).[1] Unfortunately, the gold standard reading of Clauss fibrinogen takes an hour to obtain. Research in pursuit of new technology for the early detection and correction of hypofibrinogenemia highlights the benefits of Point of Care Viscoelastic Testing (POCVT) for PPH management due to its rapid run time (10 minutes).[2] Baseline parameters must be established to identify treatment triggers as recommended by both the manufacturer and by the International Federation of Clinical Chemistry.[3] While baseline studies using rotational thromboelastrometry (ROTEM®) has been conducted[3,4], there is a lack of literature representing our United States obstetric population. When comparing baseline parameters, some variations are expected secondary to sample size, genetic composition, and geographic differences. For instance, some studies have excluded patients with a body mass index (BMI) >30 kg/m2. Such exclusion criterion would misrepresent our U.S. population. Our primary aim is to create a representative baseline ROTEM parameters. A secondary aim is to evaluate the effect of obesity on ROTEM parameters.

METHODS: After institutional review board approval, we obtained data from 681 patients presenting for labor at Yale New Haven Hospital from 2017- 2021. All charts were reviewed by two obstetric anesthesiologists, with any discrepancies resolved by a third. Exclusion criteria included receiving medications affecting coagulation, tranexamic acid, or blood products before conduction of ROTEM and having inherited or acquired thrombophilia. Patients were sorted into 4 groups by BMI and age-adjusted mean differences of all ROTEM parameters were found for the BMI cutoff of 30 kg/m2. (Table 1and 2)

RESULTS: A total of 466 charts were reviewed. FIBTEM A10 by BMI is summarized in Table 1. After adjusting for age, patients with a BMI >30 kg/m2 demonstrated higher ROTEM parameters, when compared to their counterparts as shown in Table 2. The average values of ROTEM parameters by BMI group are presented in Table 3.

CONCLUSION: Our study demonstrates that patients with BMI ≥30 kg/m2 exhibit a hypercoagulable profile. These alterations in addition to venous stasis, may result in an increased risk of postpartum hemorrhage[5] and clotting disorders such as venous thromboembolism (VTE)[6] . As the most common comorbidity in women of reproductive age,[7] obesity is known to increase thromboembolism risk, potentially due to increased factors like adipokines, fibrinogen, factor VII, plasminogen activator inhibitor,[8] and LDL-C.[9] Given these pathophysiologic risk factors in obese patients, consideration of this baseline state is essential for proper coagulation assessment and hemorrhage management with the ROTEM. Particularly, given the postpartum risk of VTE in the obese patient, should the American College of Obstetricians and Gynecologists consider pregnancy BMI >30 kg/m2 as an important determinant for thromboprophylaxis?

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OBSTETRIC ANESTHESIOLOGY 7

The Effect of Obesity on Opioid Consumption Following Quadratus Lumborum Block After Cesarean Delivery: A Retrospective Review

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INTRODUCTION: Obesity plays a significant role in anesthetic management during the peri-operative period. Specifically, it has been shown to be related to complications of regional anesthesia, with reports suggesting that obesity results in reduced ultrasound visibility of target structures, inadequate needle positioning, and altered drug distribution.[1,2] Such difficulties may lead to increased failure rates of multiple regional anesthetic blocks.[3] However, studies analyzing the impact of obesity on quadratus lumborum block (QLB) after cesarean delivery is lacking, in part because trials of QLBs exclude patients with higher body mass indexes (BMI). The purpose of this study is to analyze the effect of obesity on opioid consumption following QLB after cesarean delivery.

METHODS: Charts of patients who received a QLB after cesarean delivery during 2017-2021 were reviewed. Patients were divided into a control group with BMI < 30 kg/m^2 and a study group with BMI ≥ 30 kg/m^2. In addition to baseline demographics, outcome variables studied were opioid request rate, time to first rescue opioid analgesia, and opioid consumption measured as morphine milligram equivalents (MME). Statistical analysis was performed using ANOVA, Fischer's exact test, or χ^2 test when appropriate. $P< 0.05$ was considered significant.

RESULTS: Of the 175 patients who received a QLB after cesarean delivery, 144 patients (82.3%) met inclusion criteria. Exclusion criteria included patients who were < 16 years old, received intrathecal morphine intraoperatively, or continuous epidural postoperatively. 45 patients (31.2%) had a BMI < 30 kg/m^2 and 99 patients (68.8%) had a BMI ≥ 30 kg/m^2. Patient demographics were comparable between the two groups, except for age (29.7 ± 6.3 vs. 31.9 ± 4.8, p=0.022) and duration of cesarean delivery, in min (60.6 ± 19.6 vs. 71.5 ± 27.0, p=0.017) between patients with a BMI < 30 kg/m^2 and BMI ≥ 30 kg/m^2, respectively. There was no significant difference in the opioid request rate between the control and study groups (84.4 % vs. 83.8 %, p=0.93) after receiving a QLB. Additionally, the difference between median time to rescue opioid analgesia (376.5 [178.75 – 1137.25] min in women with a BMI < 30 vs. 512 [177.0 – 1485.0] min in women with a BMI ≥ 30) was not statistically significant ($p = 0.232$). Analysis of median MME consumed within the first 24hrs of receiving a QLB revealed no significant difference between the control and study groups (15.0 [7.5 – 30.0] vs. 15.0 [0.0 – 30.0], p=0.445). No difference was also observed between 24-48hrs and 48hrs+.

CONCLUSION: Our results suggest that obesity does not result in significantly increased opioid consumption following QLB for women who have undergone cesarean delivery. Quadratus lumborum blocks should be encouraged in obese patients and future clinical trials studying QLB should include patients with greater BMI.

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Table 1. Baseline demographics of patients who received quadratus lumborum block after cesarean delivery.

Characteristic	BMI < 30 kg/m^2 (n=45)	BMI ≥ 30 kg/m^2 (n=99)	*p*-value
Age (years)	29.7 ± 6.3	31.9 ± 4.8	0.022*
Race			0.691
Black/African American	40 (88.9)	92 (92.9)	
Caucasian	4 (8.9)	6 (6.1)	
Undisclosed	1 (2.2)	1 (1.0)	
Hypertension			0.272
Yes	8 (17.8)	23 (23.2)	
Prior pregnancies	2 (4.4)	11 (11.1)	
No	35 (77.8)	65 (65.7)	
Diabetes			0.320
Yes	6 (13.3)	19 (19.2)	
Prior Pregnancies	0 (0)	3 (3.0)	
No	39 (86.7)	77 (77.8)	
ASA Class			0.155
I	0 (0)	2 (2.0)	
II	39 (86.7)	72 (72.7)	
III	6 (13.3)	25 (25.3)	
Prior Cesareans	0.98 ± 0.8	0.86 ± 0.8	0.907
Current Cesarean Type			0.846
Elective	32 (71.1)	67 (67.7)	
Emergent	12 (28.9)	32 (32.3)	
Anesthetic Technique			0.476
Combined Spinal Epidural	44 (97.8)	93 (93.9)	
Spinal	1 (2.2)	3 (3.0)	
General	0 (0)	3 (3.0)	
Operative Duration (min)	60.6 ± 19.6	71.5 ± 27.0	0.017*
Sedative Prior to QLB			0.354
Yes	14 (31.1)	40 (40.4)	
No	31 (68.9)	59 (59.6)	

Data is expressed as mean ± SD or n (%)

Table 2. Post-QLB opioid request rates and use measured in oral milligram morphine equivalents (MME).

	BMI < 30 kg/m^2 (n=45)	BMI ≥ 30 kg/m^2 (n=99)	*p*-value
Opioid Requested			0.93
Yes	38 (84.4)	83 (83.8)	
No	7 (15.6)	16 (16.2)	
Time to first rescue analgesia (min)	376.5 [178.75 – 1137.25]	512 [177.0 – 1485.0]	0.232
MME Consumed			
0-24hrs	15.0 [7.5 – 30.0]	15.0 [0.0 – 30.0]	0.445
24-48hrs	15.0 [0.0 – 31.875]	15.0 [7.5 – 30.0]	0.489
48hrs +	7.5 [0.0 – 22.5]	7.5 [0.0 – 22.5]	0.677

Data is expressed as n (%) or median [interquartile range]

OBSTETRIC ANESTHESIOLOGY 8

Rates of Severe Pruritus with Combined Spinal Epidural Labor Analgesia

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INTRODUCTION: Combined spinal epidural (CSE) labor analgesia provides rapid onset analgesia during labor. The intrathecal component often consists of local anesthetic, opioid, or a combination of both. Frequently used opioids include fentanyl and sufentanil, but these can be associated with pruritus. At our institution we often perform CSE with intrathecal 1.25mg bupivacaine and 15mcg fentanyl in parturients believed to be in the active phase of labor, or with severe pain based on clinician judgement. We performed this study to determine the incidence of severe pruritus requiring treatment with butorphanol among self-identified African American parturients compared to non-African American patients.

METHODS: We retrospectively reviewed the charts of patients who received intrathecal 1.25mg bupivacaine and 15mcg fentanyl as part of CSE labor analgesia. We noted demographic data and butorphanol administration during labor or within two hours after delivery. Patients were excluded if either they delivered within 60 minutes of intrathecal medication, or if the decision to perform a cesarean delivery was made within 60 minutes. A convenience sample of two years from February 2019 to February 2021 was used to gather patients.

RESULTS: A total of 1548 patients met the inclusion criteria (1193 African American, 200 White, 90 Hispanic and 65 Asian). African American patients had a higher incidence of severe pruritis requiring butorphanol than other patients (P=0.0003) (Table).

CONCLUSION: Our data demonstrates a significant difference in rates of severe pruritus as defined by butorphanol use among African American compared to non-African American patients. Further study is required to assess variations among non-African American populations, as well as determining a mechanism for these differences in pruritus severity. Providers may want to consider these findings when tailoring an analgesic plan for their patients.

African American	White non-Hispanic	Hispanic	Asian	Combined non-African American
12%	4%	3%	6%	4%

Data presented as n(%) requiring butorphanol for pruritus

Fig. 1

OBSTETRIC ANESTHESIOLOGY 9

Assessment of benefits and accuracy of a handheld ultrasound device for neuraxial placement

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BACKGROUND: Although the use of ultrasound (US) guided neuraxial anesthesia was described over two decades ago, its use remains scarce. The lack of adoption of this non-invasive technique persists despite its known benefits of better identification of the lumbar interspace level, optimal needle insertion site, diagnosis of associated scoliosis and estimated depth of epidural space. The causes for its limited use may relate to cost, technical expertise, difficulty interpreting images, access to, and space for storage of ultrasound equipment.[1,2]

METHODS: After institutional review board approval, we have started this prospective observational study for epidural placement utilizing handheld US (Butterfly iQ+) guidance and landmark technique. We evaluated time to perform epidural placement (the time from needle insertion till loss of resistance), number of insertion attempts (needle in and out of skin), number of needle redirections (needle adjustments without removal of needle from insertion point), and -for cases in which US was utilized we compared the estimated depth by US and actual depth of epidural space. Intergroup differences were assessed for significance using Mann-Whitney test. Values are presented as mean and standard deviation (SD)

RESULTS: A total of 125 of epidural placement were evaluated, 82 of which were placed with US guidance. The average number of needle insertion attempts [US 1.0 (0.6) versus landmark 2(1.3); $p = 0.29$[and number of needle redirection [US 1.0 (0.8) versus landmark 3.0 (1.3); $p < 0.001$[was lower in the US group. The duration of the procedure was also lower in the US groups versus the landmark groups with average duration of 3.1 min (3.2) versus 6.3 (7.5); $p = 0.009$, respectively. In terms of accuracy, our handheld US underestimated measurements by -0.15 (0.37) 95% confidence interval [-0.07, -0.23].

CONCLUSION: Conclusion: In a cohort of patients with a mean (SD) body mass of 33.3 (6.9), the use of US helped reducing the number of needle insertion attempts and adjustments in a statistically significant manner when compared to landmark-guided technique. Our results are in agreement with previously reported accuracy, with some authors reporting an accuracy within 0.8 cm. The use of the portable Butterfly iQ+, obviates some of the limitations related to cost and real state. More importantly, the use of this device resulted in procedure performance in half the time when compared to a landmark technique. the authors think that the additional information obtained improves patient satisfaction and may potentially decrease the risk of complications, such as accidental dural puncture.

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OBSTETRIC ANESTHESIOLOGY 10

Obstetric pain management for women with opioid use disorder: A longitudinal, QUalitative mixed-methods Evaluation of patientS and provider perspecTives (QUEST)

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INTRODUCTION: Patients with opioid use disorder (OUD) often have inadequate pain management due to hyperalgesia and a fear of recurrence of opioid misuse that is associated with opioid analgesia exposure[1]. Yet poorly treated pain can also trigger treatment noncompliance and return to use. Women are particularly susceptible to suboptimal therapies during pregnancy and lactation[2]. A knowledge gap exists on patient-centered priorities for pain management among pregnant people with OUD and their providers. This study assessed patient and provider perspectives on labor and postpartum analgesia in pregnant people with OUD.

METHODS: This prospective mixed-methods study included semi-structured interviews with third-trimester pregnant people with a history of OUD on medication for opioid use disorder, and clinical providers. Interviews were supplemented by quantitative validated self-report instruments, including childbirth experience, pain management preferences, analgesia satisfaction, perceived social support (MSPSS), mental health surveys, and personal attitudes and beliefs towards pain (PROMIS inventories). Interviews were independently coded and qualitatively analyzed for major themes in patient and provider groups.

RESULTS: A total of 32 participants (17 patients and 15 providers) were included. 299 quantitative surveys were completed. Table 1 notes demographic and birth characteristics: 88% of patients had a history of anxiety or depression, 58% were using buprenorphine monotherapy, 35% were on a combination of buprenorphine and naloxone, and one was using methadone therapy. Table 2 and 3 note the support systems and mental health issues among patients, and obstetric delivery variables. Four major interview themes emerged regarding patient prenatal attitudes and beliefs toward pain: (1) women believe childbirth pain to be an independent and unavoidable experience; (2) their personal history of opioid use will inevitably limit analgesia options and the ability to control their pain; (3) women with OUD prefer non-opioid pain management options with a multimodal approach; and (4) their interactions with providers sometimes act as barriers to adequate pain management. Full analysis of provider interviews and postpartum patient interviews is underway and will be presented.

CONCLUSION: There is an opportunity and need to expand multidisciplinary prenatal consultation, including potentially with anesthesiologists, for pregnant people with OUD. Such consultation should provide information, eliminate fears and misunderstandings, and create individualized pain management plans prior to labor and delivery. These early interventions can be evaluated in future studies for outcomes of improved pain management, postpartum treatment adherence, and reduced risk for return to opioid use.

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Table 1: Study Population Characteristics. The population consisted of pregnant women enrolled in the 3rd trimester with a history of opioid use disorder on medication for opioid use disorder (MOUD)

Characteristics	Patients (N = 17)
Mean Age (95% CI)	28.9 (21- 34)
Race – no./total no. (%)	
White	17/17 (100)
Black/African American	0/17 (0)
Asian	0/17 (0)
Pacific Islander	0/17 (0)
American Indian/Alaskan	0/ 17 (0)
Ethnicity – no./total no. (%)	
Hispanic	0/17 (0)
Non-Hispanic	17/17 (100)
Mean Body Mass Index (IQR)	28.8 [20.4- 47]
History of Anxiety/ Depression (%)	15/17 (88)
History of Mental Illness (%)	9/17 (52)
Education Level– no./total no. (%)	
Highschool Graduate or Equivalent	11/17 (64)
Trade/ Technical/ Vocational Training	1/17 (5)
Some College Credit, No Degree	4/17 (23)
Associate Degree	1/17 (5)
Income Level– no./total no. (%)	
Less than $10,000	5/16 (31)
$10,000 to $19,999	4/16 (25)
$20,000 to $29,999	3/16 (18)
$30,000 to $39,999	3/16 (18)
$100,000 to $149,999	1/16 (6)
Median Gravidity (IQR)	4 [1- 12]
Median Parity (IQR)	2 [0- 10]
Median Prior Cesareans (IQR)	0 [0- 2]
MOUD Type– no./total no. (%)	
Methadone	1/17 (5)
Buprenorphine- Naloxone	6/17 (35)
Buprenorphine	10/17 (58)

IQR, interquartile range
No, number
MOUD, medication for opioid use disorder

Table 2. Patient self-reported quantitative instrument results for the study cohort. The study cohort was within normal scale ranges for measured elements, except for low scores on PCS helplessness: the cohort reported lower than normal scores for a sense of helplessness as it relates to real or anticipated pain experiences.

Characteristic		Result (N = 17)
Perceived Social Support	**PSS- Total** *Mean (SD)*	63.8 (15.5)
	PSS- Family *Mean (SD)*	21.5(6.0)
	PSS- Significant Other *Mean (SD)*	24.1 (5.1)
	PSS- Friends *Mean (SD)*	18.2(7.2)
Pain Catastrophizing Scale	**PCS- Total** *Mean (SD)*	11.5 (10.9)
	PCS- Rumination *Mean (SD)*	4.1 (4.2)
	PCS- Magnification *Mean (SD)*	2.5 (2.6)
	PCS- Helplessness *Mean (SD)*	**4.9 (4.6) ****
Anxiety or Depression	**Anxiety** *Mean (SD)*	15.1 (6.1)
	Depression *Mean (SD)*	15.41 (6.4)
Fear of Pain	**FOP- Total** *Mean (SD)*	17.8 (6.2)
	FOP- Severe *Mean (SD)*	8 (3.6)
	FOP- Minor *Mean (SD)*	4.4 (1.7)
	FOP- Medical *Mean (SD)*	5.5 (2.1)

PSS, perceived social support
PCS, pain catastrophizing scale
FOP, fear of pain
SD, standard deviation

Scale Ranges:

PSS Total	*[12-84]*
PSS Subscales	*[7-28]*
PCS Total	*[0-52]*
PCS Rumination	*[0-16]*
PCS Magnification	*[0-12]*
PCS Helplessness	*[0-24] ***
FOP Total	*[9- 45]*
FOP subscales	*[3- 15]*
Anxiety Total	*[7-35]*
Depression Total	*[8-40]*

Table 3. Obstetric, Labor & Delivery Outcomes

Characteristic	Result (N = 17)
Median Duration of labor (minutes) *median (IQR)*	435 [174.5 – 1347.**0**]
Median Sterile Vaginal Exam at the time of epidural labor analgesia request (centimeters) *median (IQR)*	4.0 [3.5 – 5.5]
Mean Neonatal Apgar 1 minute *mean (SD)*	8.0 (1.0)
Mean Neonatal Apgar 5 minute *mean (SD)*	8.8 (0.6)
Mode of Delivery – no./total no. (%)	
NSVD	9/17 (53)
Cesarean	7/17 (41)
Assisted Vaginal Delivery	1/17 (5)
Reasons for Cesarean – no./total no. (%)	
Non reassuring fetal heart tracing	1/7 (14)
Elective Repeat	3/7 (43)
Breech/ Malpresentation	2/7 (26)
Abnormal placenta	1/7 (14)
Anesthesia Type for Cesarean– no./total no. (%)	
Spinal	6/7 (86)
Epidural	1/7 (14)
Median Surgery Time (minutes) *median (IQR)*	64 [48- 72]
Median EBL (mL) *median (IQR)*	500 [500- 700]
Labor Analgesia Type– no./total no. (%)	
Epidural analgesia	10/16 (62)
Other (nitrous oxide, systemic analgesia)	6/16 (36)

IQR, interquartile range
SD, standard deviation
NSVD, normal spontaneous vaginal delivery
EBL, estimated blood loss
mL, milliliters

OBSTETRIC ANESTHESIOLOGY 11

Acute Postpartum Pain and Anxiety Influence Long-term Postpartum Pain, Maternal-Infant Attachment and Parenting Self-Efficacy

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INTRODUCTION: Pain and depression are bi-directionally related in chronic pain settings, and worse labor pain has been linked to postpartum depression symptoms[1-3]. These findings raise questions about whether improving pain and mood after delivery can improve maternal parenting function. However, few studies have examined relationships between postpartum pain and negative mood, and their effects on parent-infant relationship outcomes. We aimed to assess the relationships between postpartum pain, depression, parent-infant attachment, and parenting self-efficacy.

METHODS: This was a prospective longitudinal observational study of healthy, adult, nulliparous women, at term gestation presenting for labor and delivery at ≥38 weeks gestational age. Baseline self-reported outcome assessments included validated inventories of depression (Edinburgh postnatal depression screen, EPDS), anxiety (state trait inventory, STAI), pain (brief pain inventory short, BPI). Demographic and labor variables were recorded. At 6 weeks and 3 months postpartum, self-reported assessments included EPDS, STAI, BPI, maternal infant attachment (MPAS), and parenting self-efficacy (PMPSE). Pain severity scores were calculated as the average of items 2-5 on the BPI and pain interference scores were averaged on items 8-14 from the BPI. Linear regression was used to estimate the effects of 6-week pain scores on 3-month pain scores. A P-value less than 0.05 was considered statistically significant.

RESULTS: 187 subjects participated; 87 subjects had complete data on parent-infant attachment and 85 had complete parenting self-efficacy data. Cohort demographic and labor and delivery characteristics are in Table 1. Worse postpartum anxiety scores were associated with lower parenting self-efficacy scores (Table 2). Higher pain severity at 3 months was associated with lower parent-infant attachment and parenting self-efficacy scores (Table 3) Pain severity scores at 6 weeks postpartum were significantly associated with pain severity at 3 months (Parameter Estimate 0.25, 95% CI 0.07 to 0.43, P=0.01) (Table 4). The potential strength and dose-responsiveness of these relationships will be assessed and reported.

CONCLUSION: We observe trends that associate worse postpartum anxiety and pain with worse parenting outcomes. The potential relationships between postpartum anxiety, pain, and parenting self-efficacy deserve scrutiny, because reducing both postpartum pain and improving mood can potentially improve long-term postpartum parenting outcomes.

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Tables

Table 1. Demographic Labor & Delivery Characteristics among the cohort.

Characteristic	Result (N = 187)
Epidural labor analgesia utilization rate – no./total no. (%)	116/187 (62.0%)
Race – no./total no. (%)	
White	142/187 (75.9%)
Black/African American	41/187 (21.9%)
Asian	14/187 (7.4%)
Hawaiian	1/187 (0.5%)
American Indian/Alaskan	4/187 (2.13%)
Other	2/187 (1%)
Ethnicity – no./total no. (%)	
Hispanic	179/187 (95.7%)
Non-Hispanic	8/187 (4.3%)
Outcome of labor (n=147)	
NSVD	103/144(71.5%)
Cesarean delivery – Arrest of dilation or descent	15/144(10.4%)
Cesarean delivery – other reason	9/144(6.25%)
Cesarean delivery – non-reassuring fetal status	7/144(4.8%)
Assisted vaginal delivery	5/144(3.74%)

Data are presented as mean (SD), median (IQR), frequency (percentage)
NSVD, normal spontaneous vaginal delivery.

Table 2. Parent survey responses by depression (EPDS) and anxiety (STAI) measures.

	MPAS (N=87)	*P*-value	Parent self-efficacy (N=85)	*P*-value
EPDS < 25	34.9 ± 2.6 (N=38)	0.11	32.6 ± 5.9 (N=36)	0.35
EPDS ≥ 25	35.8 ± 2.6 (N=49)		33.9 ± 5.9 (N=49)	
STAI state < 69	35.2 ± 2.6 (N=46)	0.35	31.8 ± 5.6 (N=44)	**0.01 ***
STAI state ≥ 69	35.7 ± 2.7 (N=41)		35.0 ± 5.4 (N=41)	
STAI trait < 69	35.3 ± 2.8 (N=42)	0.63	31.8 ± 6.4 (N=40)	**0.03 ***
STAI trait ≥ 69	35.5 ± 2.4 (N=45)		34.7 ± 5.2 (N=45)	

** P < 0.05*
MPAS, maternal parent infant attachment scale. STAI, state trait anxiety inventory. EPDS, Edinburgh postnatal depression scale.
Results reflect T-test statistic. EPDS score calculated by summing responses to 10 EPDS items. Score ranged from 16-29, with median score of 25 which was used to categorize into low and high values. The 40 item STAI questionnaire assesses State and Trait anxiety. Median scores for both State and Trait were 69.0 which was used to categorize patients into lo/hi categories (State: range 11.0-80.0 and mean 66.8 ± 10.4; Trait: 24.0-80.0 and mean 67.1 ± 9.6).

Table 3. Parent survey responses by postpartum Pain Severity and Pain Interference.

BPI: postpartum (N=78)	MPAS (N=87)	*P*-value	Parent self-efficacy (N=85)	*P*-value
Pain Severity: mild	35.8 ± 2.4 (N=43)	0.40	33.7 ± 5.5 (N=43)	0.68
Pain Severity: moderate-severe	35.3 ± 2.9 (N=35)		33.1 ± 6.3 (N=35)	
Pain Interference: mild	35.4 ± 2.2 (N=40)	0.64	33.2 ± 5.8 (N=40)	0.73
Pain Interference: moderate-severe	35.7 ± 3.0 (N=38)		33.7 ± 6.0 (N=38)	

Results reflect T-test statistic. Note: Pain Severity score = average of items 2-5 and Pain Interference score = average of items 8-14 from the Brief Pain Inventory short form.

Table 4. Unadjusted linear regression models estimating the effect of postpartum pain score on 6-week pain score and on 3-month pain score (postpartum pain severity score used to predict pain severity; postpartum pain interference score used to predict pain interference).

Outcome	Parameter estimate of postpartum pain score	95% confidence interval	*P*-value
Pain Severity 6 week	0.19	-0.002 – 0.38	0.06
Pain Interference 6 week	0.12	-0.03 – 0.26	0.13
Pain Severity 3 months	0.25	0.07 – 0.43	**0.01** *
Pain Interference 3 months	0.12	-0.03 – 0.26	0.12

** P < 0.05*

Note: Pain Severity score = average of items 2-5 and Pain Interference score = average of items 8-14 from the Brief Pain Inventory short form.

OBSTETRIC ANESTHESIOLOGY 12

Variation in postpartum hemorrhage prevalence based on hospital of delivery in California

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INTRODUCTION: In the United States, postpartum hemorrhage (PPH) is a leading cause of preventable maternal death and morbidity[1-3]. However, few studies have examined the extent to which PPH prevalence varies between US hospitals and factors that contribute towards such variability.

METHODS: We performed a population-based, cross-sectional study of livebirths that occurred in 247 hospitals in California between 2011-2014. Our primary outcome - PPH - was classified using ICD-9 diagnosis codes 666.x. ICD9 coding was used to obtain maternal characteristics from this data set and included maternal comorbid conditions, delivery associated factors, and hospital based factors. Based on knowledge of PPH risk factors in the literature, we adjusted for the following covariates in logistic models: sociodemographic factors, chronic hypertension, diabetes, trimester when prenatal care commenced, pre-eclampsia, previous cesarean delivery, placenta previa, polyhydramnios, plurality, fibroids, gestational age at delivery, trial of labor, prolonged labor, induction of labor, chorioamnionitis, placental abruption, delivery mode, hospital teaching status and annual hospital delivery volume (in quartiles). The crude hospital PPH prevalence was calculated for each hospital. We performed multilevel logistic regression and fit five sequential models which accounted for a null model with hospital as a random effect (Model 1), patient sociodemographic factors (Model 2), pre-existing medical and pregnancy-related covariates (Model 3), peripartum covariates (Model 4), and hospital-level factors (Model 5). In each model, between-hospital variation was assessed with the median odds ratio (MOR) and the intraclass coefficient (ICC)[4,5].

RESULTS: Our analytic cohort comprised 1,904,479 women, of whom 62,830 (3.3%) women experienced PPH. A Caterpillar plot is presented for the adjusted hospital-level prevalence of PPH. Table 1 presents the findings of our multilevel models. The MOR in Model 1 was 2.10 which means that a woman's odds of PPH varied by hospital i.e., if a woman moved to a hospital with a high probability of PPH, the odds of experiencing PPH would increase by 210%. The ICC was relatively low (15.7%) indicating that a low proportion of the variance is explained by hospitals. Only a modest decrease in the MOR and ICC occurred after adjustment for patient-level factors and adding hospital-level covariates.

CONCLUSION: Findings from this study suggest that, after accounting for patient-level and hospital-level factors, substantial variation was present in the prevalence of PPH among hospitals in California between 2011 and 2014. Further research is needed to assess the impact of a state-wide hemorrhage bundle on the PPH prevalence in high-prevalence hospitals as well as the extent of the PPH variability across all California hospitals.

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SUBSPECIALTY ABSTRACTS

PAIN MECHANISMS

PAIN MECHANISMS 1

The encoding of peripheral stimuli by superficial dorsal horn excitatory and inhibitory networks in vivo

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INTRODUCTION: The superficial dorsal horn (SDH) of the spinal cord represents the first site of integration between innocuous and noxious somatosensory stimuli. According to gate control theory, diverse populations of excitatory and inhibitory interneurons within the SDH are activated by distinct sensory afferents, and their interplay determines the net nociceptive output projecting to higher pain centers. Although specific SDH cell-types are ill-defined, numerous classifications schemes find that excitatory and inhibitory neurons fundamentally differ in their morphology, electrophysiology, neuropeptides, and pain-associated plasticity; yet little is known about how these neurons respond over a range of 'natural' innocuous and noxious stimuli.

METHODS: We applied an in vivo imaging approach where the genetically encoded calcium indicator GCaMP6s was expressed either in vGluT2-positive excitatory or vIAAT-positive inhibitory neurons. Neuronal activity was imaged in vivo, using a custom-made imaging window. Fluorescence traces were analyzed offline and inferred spiking rates were deconvolved using CaImAn, an established image analysis software.

RESULTS: We found that inhibitory neurons were markedly more sensitive to innocuous touch than excitatory neurons but still responded dynamically over a wide range of noxious mechanical stimuli. In a capsaicin model of acute pain sensitization, the responses of excitatory neurons were significantly potentiated to innocuous and noxious mechanical stimuli, whereas inhibitory neurons were only depressed to noxious stimuli.

CONCLUSION: Our in vivo studies in anesthetized animals suggest that excitatory and inhibitory superficial dorsal horn neurons are activated by fundamentally different stimuli, and therefore inhibition may serve to contrast between somatosensory channels rather than sharpen the resolution within-contrary to what is typically observed in other sensory systems. Future in vivo studies characterizing more refined neural subtypes and their responses to natural stimuli will aid in identifying dorsal horn cell-types based on their function, in addition to their variety of forms.

PAIN MECHANISMS 2

Mapping neuronal activity provoked by analgesic and non-analgesic general anesthetics in mice

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INTRODUCTION: Nitrous oxide (N_2O) is a fast-acting general anesthetic that produces analgesia without loss of consciousness. Previous studies suggest that N_2O induces analgesia by engaging midbrain periaqueductal gray (PAG)-mediated descending inhibitory controls. Importantly, as N_2O is increasingly used for treatment-resistant major depressive disorder, N_2O anesthesia presents a unique opportunity to concurrently study the sensory-discriminative and the affective components of the pain experience. Based on its analgesic properties and on previous reports, we predicted that N_2O would decrease neuronal activity in the anterior cingulate cortex (ACC), which is implicated in pain's affective component. Surprisingly, however, N_2O exposure rapidly and robustly activates ACC neurons (unpublished data). As the ACC provides excitatory input to the PAG, we hypothesized that N_2O-mediated analgesia involves cortically-derived activation of PAG-to-spinal cord descending inhibitory controls.

METHODS: In adult male and female double transgenic TRAP2-Ai14 mice, we captured and compared brain-wide activity patterns in response to subanesthetic doses of N_2O and isoflurane, a sedating, non-analgesic general anesthetic that induces unconsciousness. To permanently label neurons that are transiently activated during anesthesia, mice were injected with 4-hydroxytamoxifen and exposed to one hour of N_2O or isoflurane. Two weeks later, mice were exposed to one hour of a different gas and perfused one hour later for Fos immunostaining. We collected fluorescent microscopy images of the whole brain and used Imaris for cell counting and quantification.

RESULTS: In both anesthesia experiences, we observed robust Fos+ labeling throughout the brain, including in the ACC. This dose-dependent effect of anesthesia-induced activity is consistent with our calcium imaging data. We observed Fos+ labeling in several pain-associated areas downstream of the ACC (e.g. PAG). Downstream regions with higher N_2O-Fos+ labeling included the somatosensory cortex; regions with higher isoflurane-Fos+ labeling included the bed nucleus of the stria terminalis.

CONCLUSION: Our findings suggest that the canonical understanding of ACC encoding of pain aversion ignores a differential contribution of cell type, layer specificity, and most importantly, projection target of the ACC neurons (e.g. PAG, but not BNST). Ongoing work includes identifying the cell types and projection targets of Fos+ neurons in the ACC and characterizing the contribution of these neurons in response to noxious stimuli.

PAIN MECHANISMS 3

Technical Considerations for Approaches to Ultrasound-Guided Posterior Tibial Nerve Peripheral Nerve Stimulation

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INTRODUCTION: Neuromodulation of the posterior tibial nerve has potential to be an effective tool in the treatment of dorsal and midfoot pain. We sought to describe the approach to ultrasound-guided posterior tibialis peripheral nerve stimulator implantation in a case series of four subjects.

METHODS: Four subjects with chronic foot pain and positive diagnostic posterior tibial nerve (PTN) blocks underwent ultrasound-guided PNS implantation. In each case, the posterior tibialis nerve was localized with an ultrasound probe in the long axis at the border of the gastrocnemius-soleus muscle complex approximately six inches above the medial malleolus (anterior to the gastrocnemius muscle to avoid intramuscular entry). After making a small incision at the cephalad end of the ultrasound probe, an introducer was advanced caudally at a 10-degree angle to the skin toward the medial malleolus in the subcutaneous tissue near the PTN. At this point, the bevel of the introducer needle was turned lateral to the PTN. After removing the introducer stylet, an electrode array was inserted through the introducer to cross the PTN (two contact points cross the nerve). After confirmation of placement via stimulation, the leads were secured, and the receiver coil was placed under the skin with a fixation suture. The Stimwave 'StimQ' system was used for this procedure. As the case report is devoid of patient identifiable information, it is exempt from IRB review requirements as per Northwestern University's policy.

RESULTS: At subsequent follow-up, all four subjects reported satisfactory pain relief (>50%), functional improvements, and no adverse advents. Two subjects reported pain relief at two-month follow-up while the remaining two subjects reported sustained pain relief through one year follow up.

CONCLUSION: The PTN is a terminal branch of the sciatic nerve (L4 to S3 nerve roots). Proximally, the PTN travels between the two heads of the gastrocnemius in the deep posterior leg compartment. More caudally, the nerve is located between the posterior tibial and flexor digitorum longus muscles. Before approaching the medial malleolus, the nerve courses between the flexor digitorum longus and flexor hallicus longus muscles. The PTN becomes the medial calcaneal nerve, the medial plantar nerve, and the lateral plantar nerves after passing under the flexor retinaculum. These nerves innervate the heel, medial and lateral plantar foot. The course of the PTN is variable relative to the posterior tibial artery, though the medial plantar nerve (the largest terminal PTN branch) crosses the lateral surface of the posterior tibial artery. While the literature has highlighted external PTN stimulation, tibial nerve stimulator implantation at the thigh, and surgical PTN stimulator implantation for urinary incontinence[1], no study to date has described an ultrasound-guided approach to PTN PNS implantation to treat pain. These cases demonstrate the feasibility, efficacy, and ease of this procedure as an approach to address fore and midfoot pain.

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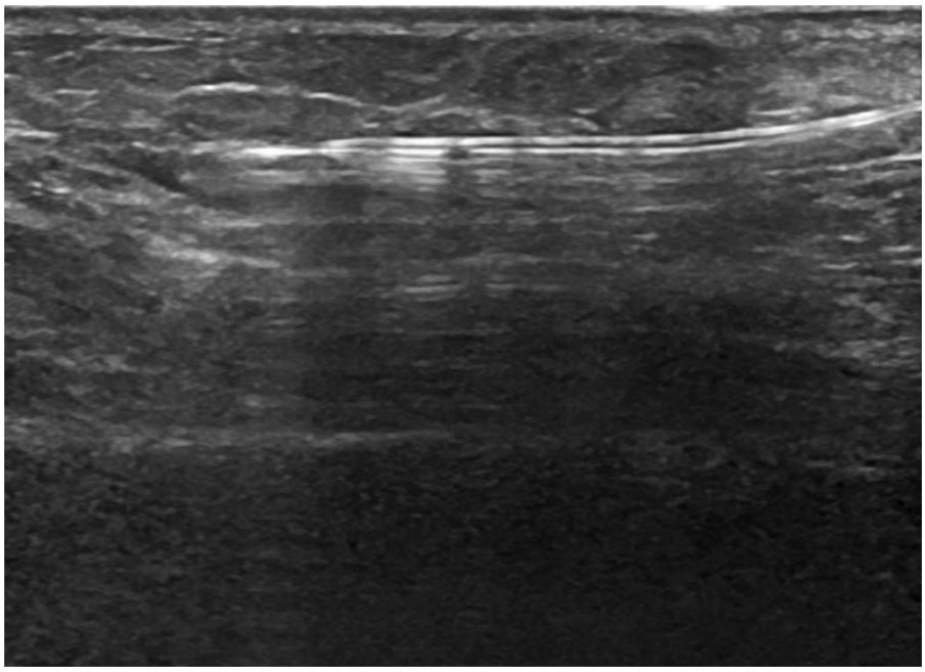

Figure 1

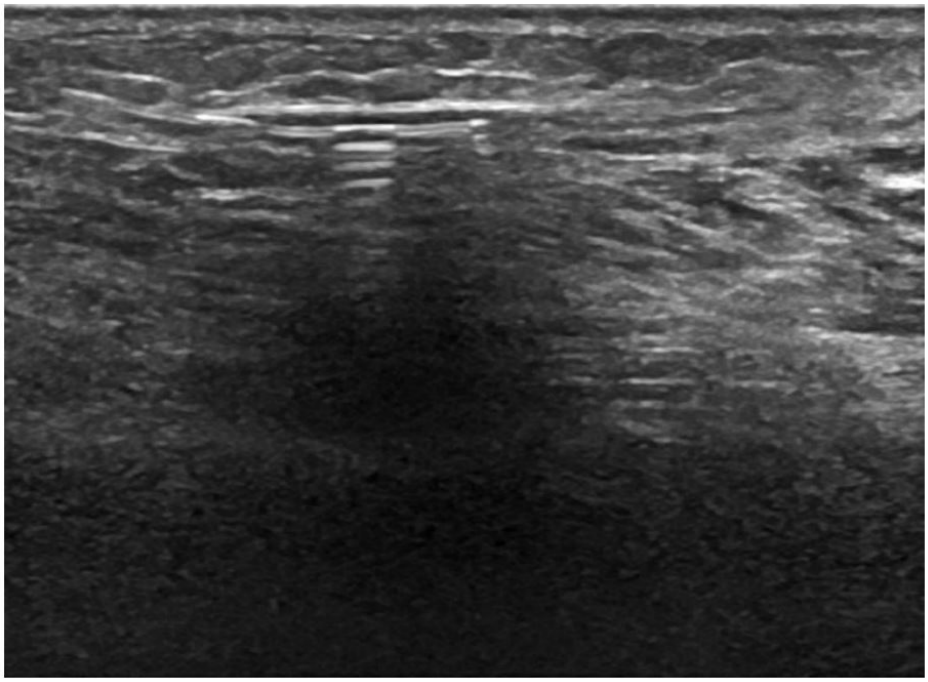

Figure 2

PAIN MECHANISMS 4

A Pain in the Neck: A Population Study of Cervical Axial Pain in the COVID-19 Era

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INTRODUCTION: The field of pain management in the era of the COVID-19 pandemic is a growing area of interest to anesthesiologists. In this study we aim to evaluate how the COVID-19 pandemic has impacted neck pain and depression rates among the general United States (US) population.

METHODS: This was an Institutional Review Board approved study. A questionnaire was created where respondents were asked demographic questions regarding their race, gender, as well as questions from the Neck Disability Index (NDI) and the Patient Health Questionnaire (PHQ-9) to assess the severity of functional impairment from their neck pain and depression. The NDI is a validated and reliable method which assesses activities of daily living that are affected by neck pain.[1] The PHQ-9 is a validated and reliable self-administered survey that measures depression severity.[2]

Respondents were asked about their COVID-19 status, family members who had COVID-19, and their neck pain following COVID-19. Finally, they were asked about their chronic pain conditions, pain interventions that they would be interested in pursuing, and interest in seeing a pain specialist. Only survey respondents who were 18 years or older and living in the United States were able to participate in this study and were screened for in advance by Amazon MTurk. Two Way Analysis of Variance (ANOVA), Fisher's Exact Test, and Pearson's Correlation Coefficient were used to compare the mean scores, predict associations, and determine correlations. Microsoft Excel (Microsoft, Redmond) and Prism's Graph Pad (Prism, San Diego) were used for data analysis.

RESULTS: A total of 2,859 responses were recorded (1,327 female respondents (46%) and 1,532 male respondents (54%)); 57% were Caucasian, and 45% were between the ages of 25-34. Not surprisingly, a positive COVID-19 diagnosis was associated with worsened neck pain among all respondents ($p<.0001$). Self-reported increased screen time was also associated with worsened neck pain among COVID-19 positive respondents ($p<.0001$). When comparing relative screen time usage, COVID-19 positive patients who spent 2-4 hours, 4-8 hours, 8-12 hours had significantly worse NDI scores compared to COVID-19 negative patients ($p=.0333$, $p<.0001$, and $p<.0001$ respectively); additionally, COVID-19 positive patients across all screen times had significantly increased PHQ-9 scores when compared to COVID-19 negative patients ($p<.0001$). Respondents who had a COVID-19 positive family member also had higher NDI and PHQ-9 scores ($p<.0001$); they also demonstrated a greater interest in seeing a pain specialist ($p<.0001$). Overall, COVID-19 positive respondents had higher NDI and PHQ-9 scores when compared to respondents without COVID-19 ($p<.0001$); they also had a greater interest in seeing a pain specialist ($p<.0001$) and had a greater number of chronic pain conditions ($p=.0004$).

CONCLUSION: The growing interest in axial cervical pain and the ever-evolving changes of the COVID-19 pandemic with its variants makes the need to investigate neck pain increasingly important. The results of our study support that neck pain is correlated with depression, a positive COVID-19 diagnosis, and increased screen time. There are multiple mechanisms in which pain can be worsened due to COVID-19.[3,4] Physical inactivity associated with COVID-19 infection and hospitalization has been associated with muscle atrophy, which commonly contributes to neck pain.[5,6] Additionally, hospital bed comfort and the mechanics of proning patients may also cause neck pain. COVID-19 has been documented to cause cytokine storms, which can contribute to the morbidity and mortality seen with the infection. The resulting inflammation can increase the chance of developing neck pain; specifically increases in C-Reactive Protein (CRP), TNF-alpha, IL-Beta are associated with acute and chronic neck pain. Increased screen time is also associated with neck pain due to excessive neck flexion and forward inclined cervical column. This places an excessive load on the cervical spine leading to changes in the anatomy which contribute to neck pain. Our specialty should recommend encouraging physical activity, physical therapy, decreasing screen time, and counseling on proper posture to decrease risk of severity of neck pain in patients affected by COVID-19.

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PAIN MECHANISMS 5

Comparison of efficacy of Erector Spinae plane block and Transversus Abdominus plane block for post-operative analgesia in laparoscopic donor nephrectomy

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INTRODUCTION: Laparoscopic approach to donor nephrectomy has greatly reduced postoperative travails of an altruistic voluntary kidney donor[1]. However, even this procedure is associated with significant postoperative pain. Port site, incision to retrieve the kidney, pelvic organ nociception, diaphragmatic irritation from residual pneumoperitoneum, contribute to the total pain experience[2]. Ubiquitous use of ultrasound guided Fascial Plane blocks have gained wide acceptance in anesthesiologist's armamentarium[3]. Fascial plane blocks of interest in laparoscopic nephrectomy are Transversus abdominis plane block (TAP Block), Quadratus Lumborum Block (QL Block) and Erector Spinae block (ES Block) [3] There are studies which have found the benefit of TAP block in urological surgeries[4]. ES block has evinced a lot of interest lately as a more potent fascial plane block in alleviating postoperative pain[5]. A comprehensive literature review yielded scant research on comparing these two blocks and found absolutely no study specifically comparing these two blocks for a laparoscopic donor nephrectomy. Hence, we decided to compare the effect of TAP and ES block in alleviating postoperative pain and meeting Enhanced Recovery after surgery (ERAS) postoperative goals[6]. We hypothesized that ES block due to its proximity to neuraxial axis will be have more potent and lasting analgesic effect.

METHODS: This is a randomized parallel study where consenting consecutive adults, undergoing laparoscopic donor nephrectomy under general anesthesia were included. Exclusion criteria involved patients allergic to local anesthetics. Sample size was estimated using software power analysis and sample size version 8. Assuming an effect size convention of 0.3 at 2 sided minimum 95% confidence interval and 5% margin of error the estimated sample size came out to be 25. We planned to include 30 patients in each group. Patients were randomly allocated into 2 groups based on computer generated random table and sealed envelope technique. After completion of surgery and before extubating 1 group was administered TAP block and 2nd ES block with 30 ml of 0.5% ropivacaine. Both the blocks were given under ultrasound guidance. Post operatively patients received Patient controlled analgesia pump (PCP) with fentanyl. It was set with 25ug boluses, maximum 4 doses allowed in an hour and no background infusion. The primary outcome was 48 hours postoperative fentanyl consumed. Secondary outcome was Static and dynamic pain scores as assessed by Visual Analogue scale (VAS) of 0 to 100, at different time points till 48 hours. Presence of nausea and vomiting (PONV) at same intervals, time to first ambulation and passage of flatus were also noted. At discharge, patients were asked if they had less than or more pain than expected by them. Continuous variables were presented as Mean±Standard deviation and categorical values as frequencies. Student t test was used for continuous parametric data and Mann Whitney U for VAS pain scores. Frequencies were compared using chi-square / Fischer's Exact test.

RESULTS: 69 voluntary kidney patients were assessed for inclusion and randomized in 2 groups. Surgery was converted to open in 5, 4 had PCP malfunction. Hence eventually 60 donors were analyzed. Both groups were comparable with regards to demographic data, duration of surgery and intraoperative fentanyl given. There was significant reduction in fentanyl consumption in ES group compared to TAP at both 24 (429 mcg vs 537.33 mcg) and 48 hours (280 mcg vs 367.33 mcg). Static pain scores were significantly reduced in ES group at all time points apart from 48-hour. ES group donors reported lower Dynamic pain scores at all time points, however the difference was significant less only at 30min, 6hour and 48hour time points. Similarly, need for rescue analgesic (Tramadol) in postoperative period was less in ES group however the difference was not significant. The incidence of PONV, ambulation time and time to pass flatus was comparable in both groups. There was no incidence of adverse effects like local anesthetic toxicity, injection site infection or hematoma. The number of donors who felt that the pain experienced by them was more than expected was also similar in both groups.

CONCLUSION: ES block provided greater sparing of postoperative opioids and better pain scores as compared to TAP block in patients undergoing laparoscopic donor nephrectomy.

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Table 1. Demographic Data, Intraoperative Fentanyl Requirement and Duration of Surgery.

	Group TAP (n=30)	Group ES (n =30)	P value
Age (years)*	42.1 ± 7.83	42.4±9.01	0.915
Gender (M/F) †	3/27	5/25	0.706
BMI (kg/m^2)*	26.4 ± 4.11	25.77±2.74	0.509
Intraop Fentanyl (µg)*	210.0±26.75	203.3 ± 26.17	0.360
Duration of Surgery(minutes)*	264.17± 36.09	255.33± 31.18	0.314

BMI: Body Mass Index .Values are presented as Mean ± S.D or Number of patients.

*Independent student t test. †chi-square test/ Fischer's Exact test

Table 2. Primary & Secondary objectives.

	Group TAP (n=30)	Group ES (n =30)	P value
PCA Fentanyl Consumption 0-24hrs.*	537.33±187.97	429.00±103.	**0.008**
PCA Fentanyl Consumption 24-48hrs.*	367.33±170.01	280.00±104.79	**0.020**
Rescue Analgesic (yes/no) †	11/19	5/5	0.072
Avg. Rescue Analgesic consumption *	163.64±67.42	120.00 ± 44.72	0.212
Less than expected pain (yes/no) †	7/23	11/19	0.260
Ambulation time (hr) *	19.30±3.31	19.50±2.16	0.783
Flatus Time (hr) *	10.77±3.87	12.40±3.91	0.110
PONV (yes/no) †	4/26	7/23	0.506

PCA: Patient controlled analgesia. PONV: Postoperative Nausea and Vomiting. Values are presented as Mean ± S.D or Number of patients. *Independent student t test. †chi-square test/ Fischer's Exact test.

Fig 1. Mean Static Pain scores

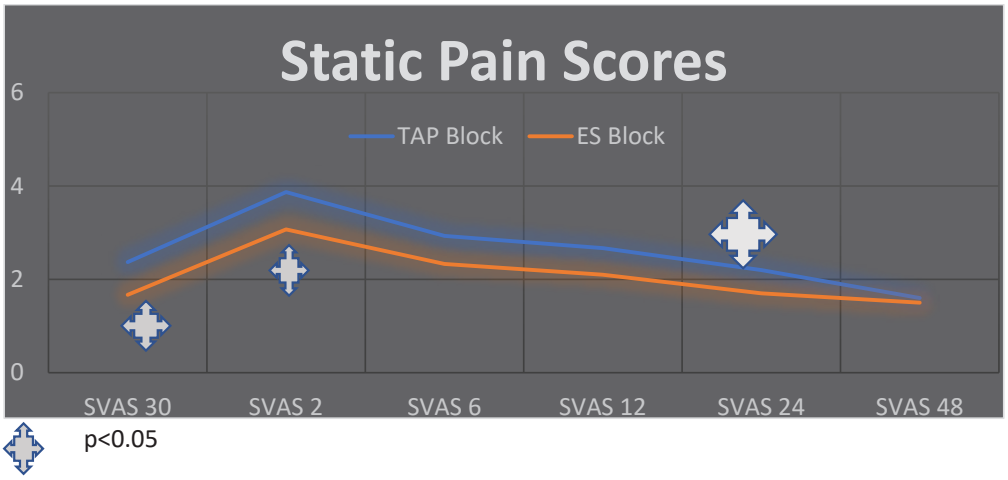
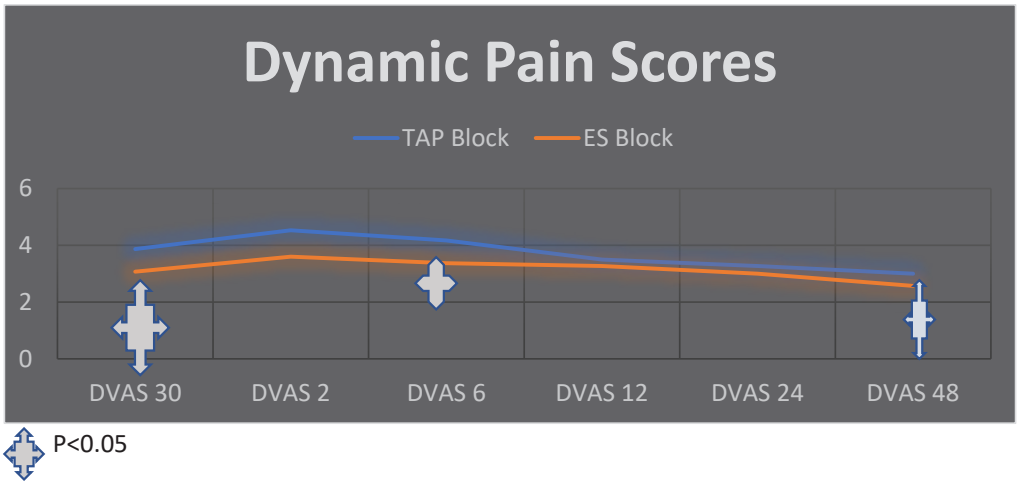


Fig 2. Dynamic Pain Score



PAIN MECHANISMS 6

Association between aesthetic satisfaction and chronic postsurgical pain in breast cancer patients treated with one stage prosthesis implantation

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INTRODUCTION: Chronic post-surgical pain (CPSP) is reported to be one of the most serious problems for patients who have survived breast cancer. Post-mastectomy pain has been estimated to affect 20-50% of patients. In our previous study, we found that the rate of chronic pain after mastectomy is about 40-50%. It was reported that for patients receiving single-stage implant-based breast reconstruction (IBBR), no more incidence of CPSP was found. However, studies on CPSP in patients with single-stage IBBR have often had a very small sample size, and there has been no separate analysis of patients who received a tissue expander and those who had an implant. Apparently, it is not precise to calculate the incidence of CPSP of these two different surgical procedures together. This study retrospectively studied the incidence of CPSP following single-stage IBBR and evaluated the possible risk factors.

METHODS: This was a retrospective cohort study, involving all patients who underwent single-stage IBBR between January and December 2019. The female patients, aged between 18 and 60, were identified for inclusion in the study and attended follow-ups between January and March 2021. Patients' details were collected, including history of psychological disorders, history of preoperative chronic pain, the severity of postoperative pain (PP), type of surgery, whether a biological matrix was used, and the size of implant. The scores for satisfaction (SS) were based on the BREAST-Q, while the pain burden index (PBI) was used to assess the degree of CPSP. Statistical analysis was performed using SPSS version 21.0. Risk factors for the development of CPSP were compared using logistic regression. Patients were divided into the SS ≥12 vs SS< 12 groups, the unilateral vs bilateral groups, the severe acute PP vs non-severe acute PP groups, and the history of chronic pain vs no history of chronic pain groups. The PBIs of those subgroups was compared using a Mann–Whitney U test.

RESULTS: The study involved 182 patients. One patient, who died from metastasis, was excluded from the final analysis. The questionnaires were completed by 159 patients, where there were 2 cases of metastasis, 2 cases of local relapse, and 13 cases of postoperative complications, including 3 cases of nipple necrosis, 8 cases of implant retraction due to infection, and 2 cases of implant displacement. 9 of them received bilateral single-stage IBBR plus a mastectomy. CPSP occurred in 48.43% of the patients, 2.52% of them being severe cases. Significant predictors for the development of CPSP in the univariate analysis included severe acute PP, a history of preoperative chronic pain, psychological disorders, SS with the reconstructed breasts, and whether there were any regrets about having had the reconstruction. Multivariate analysis identified severe acute PP (odds ratio (OR) = 2.80, 95 % confidence interval (CI) = 1.16-6.79, p = 0.023), a history of preoperative chronic pain (OR = 3.39, 95 % CI = 1.42-8.10, p = 0.006), and the SS (OR =0.86, 95 % CI = 0.75-0.99, p = 0.034) as being independently associated with the development of CPSP. In subgroup analysis, the PBI of the patients in the SS <12 group (p <0.001), the bilateral group (p <0.01), and the severe acute PP group (p <0.005) was significantly higher than the PBI of those in the control groups.

CONCLUSION: This study demonstrated a significant incidence of CPSP following single-stage IBBR. It was possible to identify patient-specific characteristics associated with an increased risk of CPSP. Patients who have a lower SS developed more CPSP, and it is clear that lower SS, bilateral procedures, and severe acute PP are predictors of higher PBI. Although nearly half of the patients in this study experienced CPSP, none of them had ever pursued treatment. Both anesthesiologists and surgeons should be encouraged to counsel patients on the course and risks of CPSP following single-stage IBBR, and they should be made more aware of the potential need to solicit aggressive CPSP management for symptomatic women.

Table 1. The incidence of CPSP, the amount of pain originating from different locations, and the different PBI levels and VAS scores.

The total incidence of CPSP	48.43% (77/159)
Location (n, %)	
Breast	48 (30.19%)
Chest wall	34 (21.38%)
Axillary	26 (16.35%)
Arm	11 (6.92%)
Intensity (n, %)	
VAS 0	82 (51.57%)
VAS 1–3	37 (23.27%)
VAS 4–6	36 (22.64%)
VAS 7–10	4 (2.52%)
PBI (n, %)	
0	82 (51.57%)
1–20	55 (34.59%)
21–50	19 (11.95%)
51–100	2 (1.26%)
>100	1 (0.63%)

CPSP chronic post-surgical pain; VAS visual analogue scale; PBI Pain Burden Index.

Table 2. The univariate analysis of risk factors for CPSP.

Variables	CPSP	No CPSP	Odds ratio (95 % CI)	P value
Age (years)	40.7 ± 6.4	41.4 ± 7.5	0.99 (0.95–1.04)	0.560
Type of surgery				0.104
With SLNB	55	53	0.84 (0.69–1.03)	
With ALND	15	27	1.58 (0.92–2.71)	
Biological matrix				1.000
Yes	62	65	0.98 (0.84–1.15)	
No	15	17	1.06 (0.57–1.98)	
Unilateral or bilateral				0.091
Unilateral	70	80	1.07 (0.99–1.16)	
Bilateral	7	2	0.27 (0.06–1.25)	
Psychological problems				0.027
Yes	44	32	0.68 (0.49–0.95)	
No	33	50	1.42 (1.04–1.94)	
History of preoperative chronic pain				0.002
Yes	25	10	0.38 (0.19–0.73)	
No	52	72	1.30 (1.09–1.55)	
Acute PP				0.004
Non-severe	53	72	1.28 (1.08–1.51)	
Severe	24	10	0.39 (0.20–0.76)	
Postoperative complications				0.392
Yes	8	5	0.59 (0.20–1.72)	
No	69	77	1.05 (0.95–1.15)	
Regretted having single-stage IBBR				0.034
Yes	12	4	0.31 (0.11–0.93)	
No	65	78	1.13 (1.01–1.26)	
The size of implant	222.4 ± 51.8	232.7 ± 57.9	1.0 (0.99–1.0)	0.238
SS	11.0 ± 2.7	12.5 ± 2.7	0.8 (0.71–0.91)	0.001

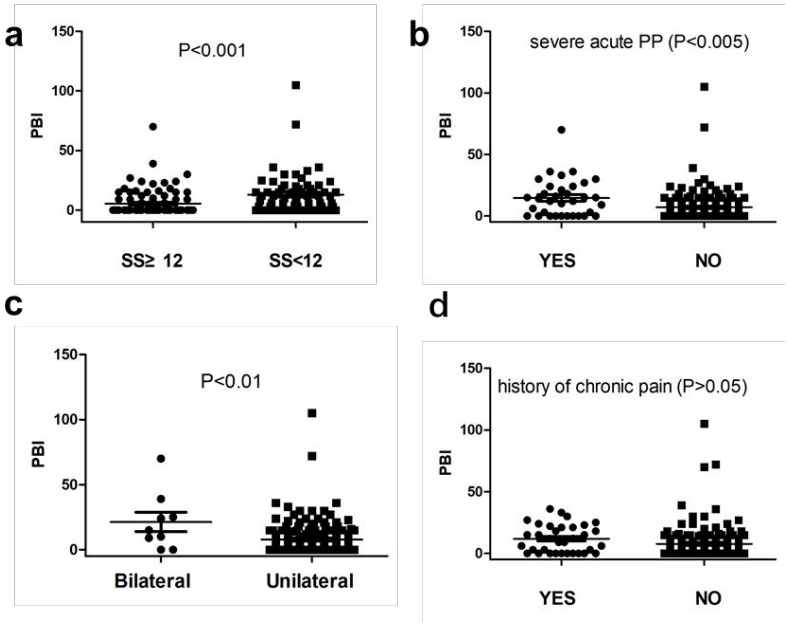
CPSP chronic post-surgical pain; ALND axillary lymph node dissection; SNLB sentinel lymph node biopsy; PP postoperative pain; IBBR implant-based breast reconstruction; SS satisfaction score.

Table 3. The multivariate analysis of risk factors for CPSP.

Variables	Odds ratio (95 % CI)	P value
Psychological disorders	1.70 (0.85–3.40)	0.135
History of preoperative chronic pain	3.39 (1.42–8.10)	0.006
Severe acute PP	2.80 (1.16–6.79)	0.023
SS	0.86 (0.75–0.99)	0.034
Regretted having single-stage IBBR	3.20 (0.90–11.43)	0.073

PP postoperative pain; IBBR implant-based breast reconstruction; SS satisfaction score.

Fig 1



SUBSPECIALTY ABSTRACTS

PAIN MEDICINE

PAIN MEDICINE 1

Synthetic Amphipathic Helical Peptide L37pA Alleviates Chronic Inflammatory Pain Independently on Its Anti-inflammatory Properties

Kamoltip Promnares[1], Yunbo Ke[2], Anna Birukova[3], Cynthia Renn[4], Alexander V Bocharov[5], Konstantin Birukov[2]

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INTRODUCTION: Apolipoprotein A-I (apoA-I) is a major protein constituent of high-density lipoprotein (HDL), which plays an important role in reverse cholesterol transport, but possesses anti-inflammatory and tissue-protecting properties[1-4] by virtue of blocking receptors sensing danger-associated molecular patterns (DAMPs) and pathogen associated molecular patterns (PAMPs)[5,6]. Synthetic amphipathic helical peptides (SAHPs) with apoA-I mimetic features antagonize apoA-I binding receptors[7-9] and exhibit anti-inflammatory properties in several models[3,10-11]. Based upon apoA-I and SAHPs anti-inflammatory effects, novel SAHP-based therapies are being currently developed to control serious inflammatory conditions[12]. We examined anti-inflammatory properties of SAHP member, L37pA, in the model of human pulmonary artery endothelial cells (HPAEC) exposed to bacterial wall lipopolysaccharide (LPS). We also examined effect of L37pA on chronic inflammatory pain caused by injection of complete Freund's adjuvant (CFA) to mouse paw.

METHODS: HPAEC monolayers were challenged with 100 ng/ml LPS, with or without 30 min pretreatment with L37pA, and measurements of transendothelial electrical resistance as reflection of changes in EC permeability were performed with an electrical cell substrate impedance-sensing system over 20 hrs as we previously described[13]. C57BL/6 mice were CFA challenged into the plantar surface of left hind paw, with or without 30 min pretreatment with L37pA. Thermal hyperalgesia test was performed at 3, 24, and 72 hours post challenge. Results are presented as mean ± SEM. A p value < 0.05 was considered significant.

RESULTS: Our results show that L37pA, but not control inactive peptide L3DL37pA significantly attenuated EC barrier disruption caused by EC treatment with LPS (Fig.1) suggesting potent anti-inflammatory effects of L37pA in innate immune response. Given its anti-inflammatory properties potential role of L37pA in attenuation of chronic inflammatory pain was further evaluated in mouse model. Plantar surface of left hind paw in mice was injected with CFA and saline. L37pA, L3DL37pA, and vehicle was administered as an intramuscular injection or as a topical application in the form of hydrogel every consecutive day 30 min prior to behavioral test. CFA-injected mice developed inflammatory sign in the form of increased paw thickness within 3 hrs after CFA injection which peaked within 1 day. Contralateral (non-injected) hind paw thickness remained unchanged (Fig.2). Pain was further accessed as a decreased paw withdrawal temperature. Altered paw withdrawal effect in inflamed paws developed within 3 hrs post-injection. Importantly, topical application of L37pA hydrogel formulation or local intramuscular injection of peptide returned the withdrawal temperature of inflamed paws to control levels measured in non-injected paw within 30 min after peptide application. This rapid analgesic effect of L37pA peptide application was observed in inflamed paws within 3 days post-CFA (Fig.3), while negative control L3DL37pA peptide was without effect. In contrast to pain relief, the inflammation sign (paw thickness) was not recovered to normal level upon short-term peptide application (Fig.2).

CONCLUSION: These exciting findings demonstrate for the first time rapid and potent analgesic effect of L37pA SAHP that alleviated CFA-induced chronic inflammatory pain. Analgesic effect was reached 30 min post peptide treatment at different time points of CFA challenge. Despite potent anti-inflammatory effects of L37pA observed in HPAEC cell culture, its analgesic effect is likely independent on anti-inflammatory properties. This finding suggests L37pA as a promising new therapeutic molecule for non-opioid treatment of chronic pain.

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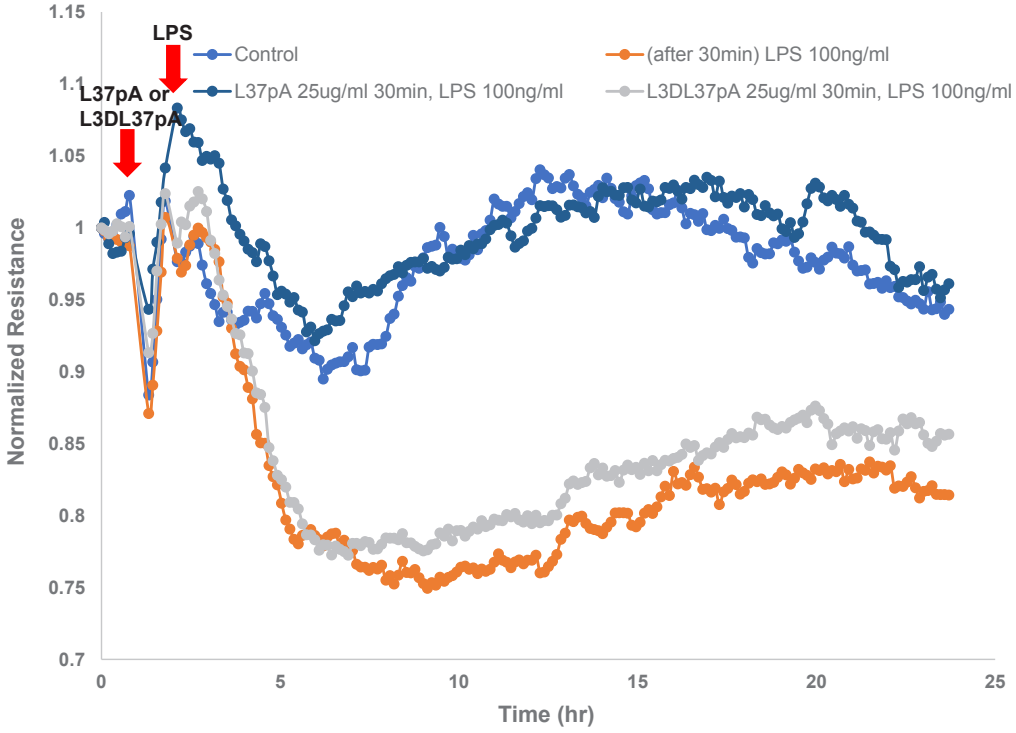

Figure 1 Effect of L37pA and L3DL37pA on endothelial barrier function in vitro.

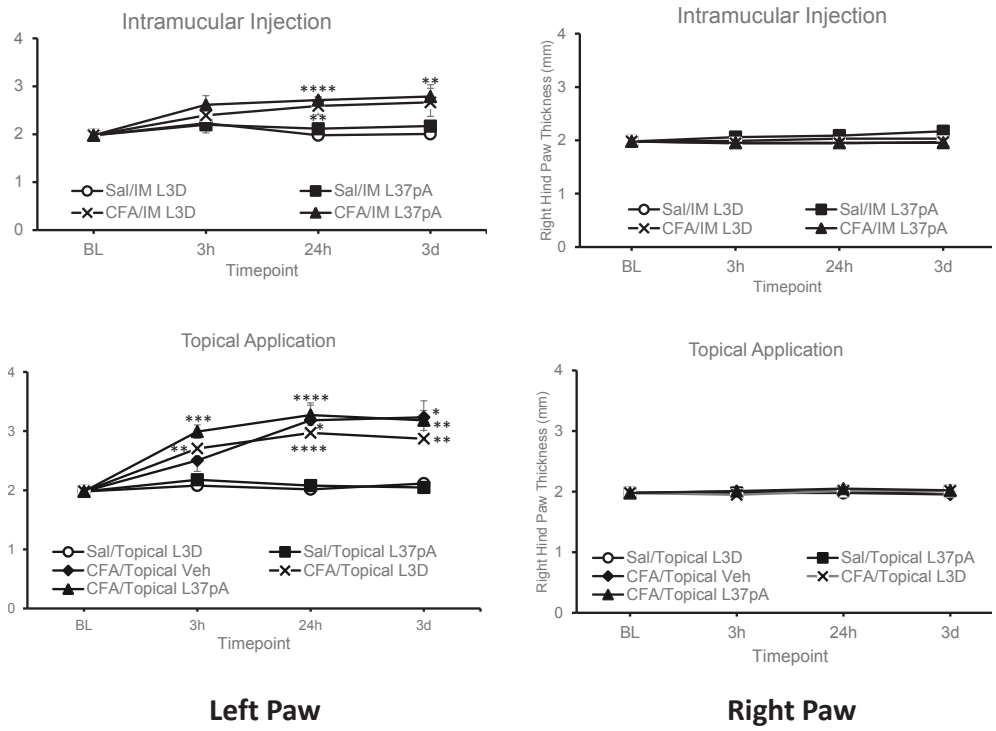

Figure 2 Effect of L37pA and L3DL37pA on paw thickness after CFA challenge.

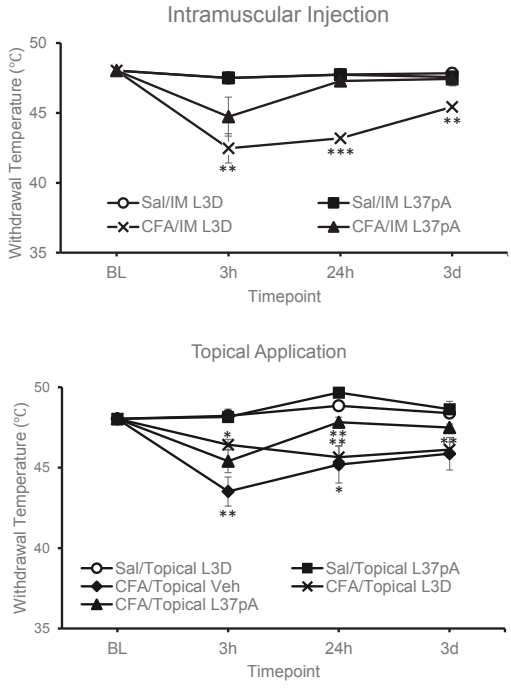

Figure 3 Effect of L37pA and L3DL37pA on paw withdrawal temperature after CFA challenge.

PAIN MEDICINE 2

It's lonely at the top (of the pandemic): Depression mediates the impact of loneliness on pain-related catastrophizing during COVID-19

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INTRODUCTION: Feelings of loneliness increased during the pandemic-related social distancing, potentially exacerbating negative cognitions about pain. Individuals with chronic pain may have been more at risk of isolation as a result of social distancing guidelines, and consequently worsen pain. Chronic pain is often comorbid with depression, and thus, depression may link feelings of loneliness and negative cognitions about pain. Because pain catastrophizing is a modifiable risk factor, it is important to identify factors related to increased catastrophic pain-related cognitions as a means of indirectly reducing pain.

METHODS: Participants (n=93) living with chronic pain (pain for ≥3 months) completed two sets of electronic questionnaires.
The initial set of questionnaires was completed from April 28-June 17, 2020 (Time 1, T1) and the follow-up survey a year later from May 21-June 7, 2021 (Time 2, T2).

The 3-item UCLA Loneliness Scale Version 3 assessed feelings of loneliness at T1.

The 13-item Pain Catastrophizing Scale assessed negative cognitions about pain at T1 and T2.
The 8-item depression short form from the Patient Reported Outcome Measurement Information System was used to measure depressive symptoms at T2.
Spearman correlations and Mann-Whitney U test were used to explore associations between psychosocial, pain, and demographic characteristics.

A mediation analysis investigated whether depression (T2) mediated the relation between loneliness (T1) and pain catastrophizing (T2).

Covariates from T1 included average pain intensity and pain interference, pain medication use, (patients indicated whether or not ('yes' or 'no') they typically take any medications for their pain),and baseline pain catastrophizing.

RESULTS: Greater feelings of loneliness (T1) were associated with higher levels of pain catastrophizing (T2) (Figure 1). Pain catastrophizing (T2) was associated with greater depression, pain severity and pain interference, pain medication use, and baseline catastrophizing (T1). A mediation analysis investigated whether depression (T2) mediated the relation between loneliness (T1) and pain catastrophizing (T2). The model was significant, $F(6, 85) = 18.85$, $p < 0.001$, $R2 = 0.562$, and there was a significant indirect effect of loneliness on pain catastrophizing through depression ($b = 0.57$, 95% CI [0.15, 1.31]). This mediation analysis demonstrated that there was a significant indirect effect of loneliness on pain catastrophizing through depression. The direct effect of loneliness on pain catastrophizing was no longer significant when depression was included in the model.

CONCLUSION: The longitudinal design of this study allowed identification of early loneliness as a unique predictor of subsequent pain catastrophizing. Greater severity of depression during the pandemic year partially mediated this relationship. Findings suggest feeling lonely may contribute to depressed mood, leading to more maladaptive cognitions about pain. Future studies may benefit from investigating the temporal associations among these variables over the course of empirically-supported treatments that can improve cognitive and affective outcomes.

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PAIN MEDICINE 3

Do Mechanically Ventilated Covid-19 Patients on Prolonged Opioid Infusions Require Opioids upon Hospital Discharge?

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INTRODUCTION: Intubated COVID-19 patients often require opioid infusions to combat pain and facilitate synchronization with mechanical ventilation. In addition, chronic pain can develop after both surgical and medical ICU care, with one study showing 44% of patients reporting chronic pain 6 months to 1 year after ICU stay.[1-6] Therefore, critically ill COVID-19 patients are at a theoretical risk of developing chronic pain and opioid dependence. We evaluated a cohort of COVID-19 intubated patients treated with opioid infusions to compare those who were discharged with opioids to those who were not.

METHODS: A retrospective case control analysis was performed on 42 COVID-19 intubated patients treated with opioid infusions from February 1, 2020 to May 1, 2020 at a large New York City hospital. The electronic medical record was queried to identify 56 patients who were discharged with opioids after COVID-19 intubation. Of those, 21 were selected at random for chart review and compared to 21 controls. Variables included duration of ventilator use and opioid infusion, opioid dosages, history of substance abuse and basic demographics such as gender, age, and comorbidities. Data was analyzed using Stata v17. Descriptive statistics were calculated, and continuous variables were evaluated using students t-test. Logistic regression was used to look for covariables associated with the use of opioids at discharge.

RESULTS: There were no significant differences in the demographic data and baseline clinical characteristics between the cases (patients discharged with opioid) and controls (patients not discharged with opioid) (Table 1). The mean age of the cases and control groups were 55.8 and 58, respectively. There was no significant differences between the cases and controls for mean number of days on the ventilator (26.6 and 16.6, respectively), number of days on opioid infusions (10.16 and 5.16, respectively), or maximum dosages of fentanyl (150 mcg/hr and 137 mcg/hr, respectively) and hydromorphone (0.87 mg/hr and 1.7 mg/hr, respectively) (Table 2). None of the variables evaluated were significantly associated with opioid use at discharge (Table 3).

CONCLUSION: In a small study of 42 intubated COVID-19 patients, there was no statistically significant association between the duration or dose of opioid administration while mechanically ventilated and the incidence of opioid use at discharge. This finding is consistent with other recent studies.[7-13] Although this study is limited by a small sample size, the results add to the evidence that in COVID-19 intubated patients, high dose opioid infusions may not increase the risk of later opioid use.

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Demographic Categories		CASES	CONTROLS	P Value
Gender				
	Male	7	10	
	Female	8	17	NS
Age				
	25-34	2	5	
	35-44	3	1	
	45-54	3	4	
	55-64	2	4	
	>64	5	13	NS
	(Mean ± SD)	55.9 ± 17.6	58. ± 16.3	NS
Clinical Characteristics		N		
	Hx of Pulm Dz	3/15	10/25	NS
	Hx CV Dz	6/15	7/25	NS
	HTN	5/15	16/25	NS
	DM	2/15	9/25	NS
	Tobacco	0/15	4/25	NS
	Alcohol	0/15	5/25	NS
	Illicit Drug Use	3/15	3/25	NS
	Prior Opioid Use	2/15	2/25	NS

Table 1. Clinical Characteristics between Cases and Controls: Percent of patients based on gender, age, and clinical characteristics or comorbidities. Hx (History), Pulm (pulmonary), CV (cardiovascular), Dz (disease), HTN (hypertension), DM (diabetes), NS (not significant).

Results		CASES	CONTROLS	P Value
Days on Vent	(Mean ± SD)	26.6 ± 37.6	16.6 ± 24.6	0.84
Days on Opioids	(Mean ± SD)	10.16 ± 15.3	5.16 ± 9.6	0.89
Max Dose of Fentanyl (mcg/hr)	(Mean ± SD)	150.0 ± 198.2	137.0 ± 192.5	0.58
Hydromorphone (mg/hr)		.87 ± 2.9	1.7 ± 3.3	0.18

Table 2. P-Value > 0.05, No Statistical Significant Difference in Days on Ventilator, Days on Opioids, and Maximum dosages on Fentanyl and Hydromorphone Between Cases and Controls.

Discharged with opioids	Odds ratio	Std. err.	z	P>|z|	[95% conf.	interval]
Ventilator days	1.007697	.021169	0.37	0.715	.9670496	1.050054
Opioid days	1.045182	.0526096	0.88	0.380	.9469918	1.153552
Fentanyl	0.9935767	.0083709	-0.76	0.444	.9773048	1.01012
Hydromorphone	.8771579	.1202525	-0.96	0.339	.6704767	1.147551
Fentanyl by dosage	2.211459	3.085065	0.57	0.569	.1436223	34.05146

Table 3. Logistics Regression Model: P-Value > 0.05, Odds Ratio of Different Independent Predictors (i.e. ventilator days, opioid days, fentanyl infusion only, hydromorphone infusion only, fentanyl by dosage) Versus Dependent Binary variable (i.e. Discharged with Opioids). Std. err. (standard error), Z (z- score), P (p-value), 95% conf. interval (95% confidence interval).

PAIN MEDICINE 4

A Double-Blinded Prospective Randomized Clinical Trial of Use of Venlafaxine in Reducing Post-surgical Pain and Opioid Consumption in Primary Total Knee Arthroplasty

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INTRODUCTION: According to the Agency for Healthcare Research and Quality, more than 600,000 knee replacements are performed each year in the United States and the demand is projected to increase every year due to the aging population. The goal of total knee replacement is to alleviate patients' chronic pain and improve functional ability. However, there is over 20% of patients experience chronic postsurgical pain despite utilizing regional anesthesia, and multimodal approach in treating pain in the perioperative period. Serotonin-norepinephrine reuptake inhibitors have been widely used in treating chronic neuropathic pain, but their role in acute and transitional pain is less well known. Our study is the first study to our knowledge to examine the effect of perioperative administration of venlafaxine in reducing acute and chronic postsurgical pain in patients undergoing total knee arthroplasty.

METHODS: This project is a double-blinded prospective randomized clinical study examining the temporal effect of Venlafaxine vs. placebo for reducing pain intensity, opioid consumption and perceived function in patients undergoing TKA. 100 patients of adult patients (male and female) aged from 18 to 75, English speaking scheduled for primary total knee arthroplasty are consented for the study. Study patients will be those who planned to have regional anesthesia including spinal and adductor canal block. Exclusion criteria include planned general anesthesia (GA or converted to GA from failed spinal block), hepatic failure, renal failure, a history of diabetes with diagnosed neuropathic pain, chronic opioid use (e.g. slow release preparations of opioids as it may compromise one of the primary study result). Current use of other antidepressants (TCAs, SNRIs, SSRIs, and MAOIs), anticonvulsants (gabapentoids), triptans or linezolid that may significantly increase the level of serontonin, will be excluded from this study. Allergy to the study medications, prior knee surgery, a body mass index greater than 40kg/m2 or American Society of Anesthesiologists physical status greater than IIIa will result in exclusion. Here, we outline the experimental design of a prospective randomized clinical trial whereby study subjects are randomized to receive a 7-day course of venlafaxine 37.5mg or placebo pill starting on the day of total knee arthroplasty. The primary outcome of interest is total opioid consumption on postoperative day 1. In addition, pain severity and interference, and functional outcomes are measured at 1-week and three months after surgery.

RESULTS: We are currently recruiting our patients into our studies and have 1/3 of patients completed the studies.

CONCLUSION: The results from this study may help us determine whether neuropathic agents have a role as part of a multimodal approach in treating acute postoperative pain and preventing the development of persistent postsurgical pain.

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Patient Centered Outcomes	Baseline evaluation	After 1 week	After 3 months
Primary Outcomes			
KOOS, JR (joint pain, stiffness and function in daily living)	x	x	x
NPRS score at rest and with movement	x	x	x
MME	x	x	
Secondary Outcomes (patient reported outcomes)			
PROMIS 10 (physical health, mental health, social health, pain, fatigue, and overall perceived quality of life)	x		x
VR 12 (patient's overall perspective of their health).	x		x
KOOS, JR (joint pain, stiffness and function in daily living)	x	x	x

Table 2: Patient Centered Outcomes to be Assessed for Specific Aim 1 and 2.

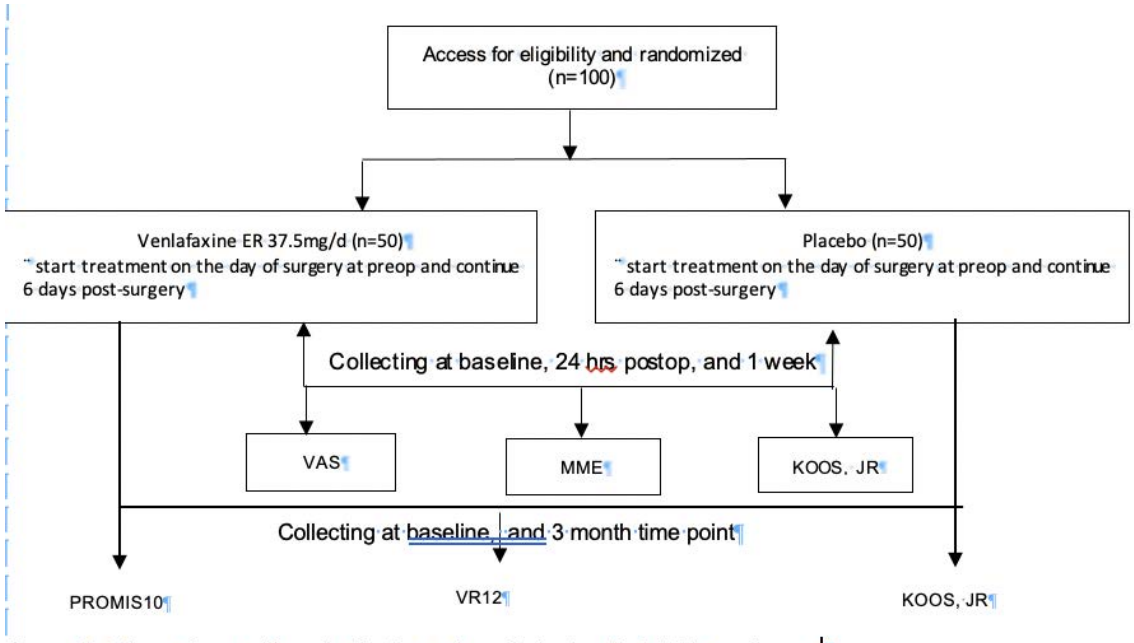

Figure 1: Flow chart of study design of venlafaxine in TKA patients.

PAIN MEDICINE 5

Pain on top of pain: The impact of longstanding chronic non-cancer pain on the management of acute pain in patients with cancer

Kristin L Schreiber[1], Meghan Beck[2], Desiree Azizodin[2]

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INTRODUCTION: Pain is a central symptom for postsurgical patients who present to the emergency department (ED) after cancer surgery. Acute pain exacerbation is often even more complex and challenging to manage among those with a history of chronic pain (CP). The current study aimed to compare pain-related outcomes and ED and hospital length of stay, between cancer patients with and without a history of chronic pain.

METHODS: Cancer patients presenting to the ED with a complaint of acute pain (> 4/10 NRS) completed validated self-report measures assessing socio-demographics, cancer diagnosis and treatment, pain severity (BPI-SF), medication use, and psychosocial wellbeing (depression, anxiety, pain catastrophizing, sleep disturbance), as well as length of time since most recent surgery. Pain scores, opioid administration, length of stay were abstracted from the medical record. Groups were defined according to whether they endorsed having other chronic pain (>3 months) prior to cancer diagnosis. Mann-Whitney U, t-tests, and chi-square tests were used to compare groups on several pain-related outcomes.

RESULTS: About 30% (50/173) of the participants reported having chronic pain before cancer. Metastatic disease was common (76%), and 42% were using opioids, which did not differ between groups(p=0.40). However, patients with historical CP were more likely to receive opioids in the ED (70% vs 53%) and as inpatient (97% vs 71%) compared to those without historic CP. Similarly, patients with historical CP received a higher total dose of opioids (Morphine Mg Equivalents, MMEs) during their ED stay (27.0±40.1 vs 20.4±48.8, p=0.034) and during their inpatient stays (m=446.8± 655.3 vs 263.2±604.1, p=0.006; also when normalized per hour of admission (3.4±3.3 vs 1.5±2.2, p<0.001). Despite receiving more opioids, patients with historical CP had higher average pain scores in the ED (6.1±1.9 vs 5.1±2.1, p=0.003) and during their inpatient stay (4.6±1.9 vs 3.0±1.8, p<0.001). However, there was no difference in stay duration in ED (12.5 ±13.3 vs 10.5±9.2 hours, p=0.17) or hospital (146.4± 151.9 vs 148.6±157.4, p=0.65), or differences in psychological well-being.

CONCLUSION: Pain and opioid consumption during ED stay and hospital admission were higher in cancer patients with a history of other CP. These findings underscore the challenge of managing pain while preventing post-discharge dose escalation in cancer patients who has a history of chronic pain, and highlight the importance of implementing multimodal pain management strategies.

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PAIN MEDICINE 6

Liposomal bupivacaine compared to conventional bupivacaine in transversus abdominis plane blocks for elective lower abdominal surgery

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INTRODUCTION: Transversus abdominis plane (TAP) blocks, using local anesthetic infiltration, are an established method for providing postoperative analgesia for abdominopelvic surgeries.[1-6] Liposomal bupivacaine (LB) is an extended-release formulation of bupivacaine reported to provide up to 72 hours of analgesia, significantly longer than conventional bupivacaine (CB).[7] The purpose of our study is to examine institutional experience of liposomal bupivacaine for TAP blocks in patients undergoing elective lower abdominal surgery. We investigated if LB was associated with reduced opioid consumption and pain scores compared to CB.

METHODS: This is a retrospective cohort study of patients who underwent TAP blocks with either LB or CB for post-surgical anesthesia following elective lower abdominal surgery between 12/1/2020 and 8/31/21 at a single institution. Patients who had a second surgery within 48 hours of the original surgery were excluded from analysis. After institutional review board approval, data was collected on demographic information, surgical type, average and maximum pain scores and total opioid consumption in Morphine Milligram Equivalent (MME). Data presented as means (SD), medians [IQR], or frequency counts (%) as appropriate; $p < 0.05$ considered significant.

RESULTS: A total of 144 patients were included in our analysis: 81% (117) were female and 95.1% (137) white. The most common procedures involved were hysterectomy 37.5 % (54), pelvic mass resection 20.1% (29), ileostomy closure 12.5% (18), nephrectomy 11.1% (16), cesarean section 6.9% (10), and herniorrhaphy 6.3 (9). Most of the procedures, 92.4% (133), were performed under general anesthesia. There was no statistically significant difference in average dose of opioid consumption on postoperative days (POD) 0, 1, 2 in LB TAP block compared to CB TAP block (Table 1).

Additionally, there was no statistically significant difference between the average pain scores and maximum pain scores between LB and CB TAP block groups. Patients who underwent TAP block with LB received opioids less frequently than those with CB TAP block, but this did not reach statistical significance.

CONCLUSION: LB TAP block following lower abdominal surgeries did not show a statistically significant difference in opioid consumption or pain scores compared to conventional bupivacaine, however our findings were limited by a small sample size in the LB TAP group. There were no differences in pain scores at the time points investigated. A larger sample size may be required to detect significant differences in these outcomes.

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Table 1: Patient outcome measures, stratified by use of TAP block with liposomal bupivacaine

Variable	TAP block with liposomal bupivacaine			
	Yes		No	
	Measurement		Measurement	p-value
N	32		112	
Local anesthetic dose (mg)	-		106	120 [88.5-120.0]
MME				
POD 0	40.5 [23.1-79.9]		63.0 [27.0-107.5]	0.26
POD 1	16.0 [10.0-67.5]		38.8 [18.4-60.0]	0.15
POD 2	74.4 [61.9-273.8]		56.0 [22.5-101.7]	0.35
Average pain score				
POD 0	4.7± 1.9		5.2 ± 1.7	0.15
POD 1	4.7 ± 1.6		4.9 ± 1.4	0.38
POD 2	4.6 ± 2.5		4.3 ± 1.5	0.79
Maximum pain score				
POD 0	7.1 ± 1.8		7.7 ± 1.8	0.15
POD 1	6.6 ± 1.9		7.0 ± 1.7	0.48
POD 2	5.4 ± 3.4		5.9 ± 2.7	0.68

Abbreviations: POD, post-operative day; calculated as 24-hour periods after anesthesia stop time
Data are shown as mean ± standard deviation or as median [interquartile range]

PAIN MEDICINE 7

Examining the Efficacy of Lumbar Epidural Steroid Injections (ESI) for Lumbosacral Radiculopathy in Patients with Obesity

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INTRODUCTION: The goal of lumbar ESI is to improve pain and function while delaying the need for operative interventions. Obese patients undergoing lumbar spine surgery suffer greater intraoperative and postoperative complications including increased blood loss, longer operative times, higher complication, and reoperation rates[1]. Obese patients undergoing ESI require longer fluoroscopy times[2]. This study sought to compare pain, function and disability scores in obese vs non-obese patients three months following lumbar ESI.

METHODS: This study is an IRB approved retrospective analysis of 343 patients who have undergone lumbar ESIs for lumbosacral radiculopathy at a single academic center from 2016-2021. Patients underwent assessment using validated measurement scales of Visual Analogue Scale (VAS), Oswestry Disability Index (ODI), and PROMIS 29 v1.0 (P29) scores at baseline and 3 months post ESI. Patients were stratified into two groups: obese (BMI ≥30) and non-obese (BMI <30) which was further stratified by class of obesity: class 1 (BMI 30 to <35), class 2 (BMI 35 to <40), class 3 (BMI 40 or higher). Frequency counts were determined for all categorical measurements overall and by BMI category. Means and standard deviations were calculated for all time periods, BMI categories, and for each of 44 differences scores. Student t tests for paired observations were made for all difference scores. Each difference score was compared by BMI category to determine if BMI affected that particular outcome. Analysis of variance was conducted to analyze the differences among the means stratified by classes of obesity. No adjustment for multiple comparisons was made. Statistical significance was set at 0.01.

RESULTS: 343 patients took part in the study (age M(SD) = 64.25(14.48); Female N(%) = 193(56.27); Non-Hispanic N(%) = 308(89.80); Hispanic N(%) = 25(7.29). Inclusion criteria were all patients who received a lumbar ESI for lumbosacral radiculopathy. Patient comorbidities are displayed in Table 1. Table 2 depicts no significant difference in mean levels of ODI, VAS, or P29 scores when comparing values from baseline to 3 months in groups stratified by a BMI of <30 vs a BMI of ≥30. Table 3 depicts no significant difference in mean levels of ODI, VAS, or PROMIS-29 v1.0 scores when comparing values from baseline to 3 months in groups further stratified by class of obesity.

CONCLUSION: The results of this study mirror the results of prior studies[3,4]. This study was unique due to a large sample size, comprehensive evaluation of disability, pain, and function. No significant difference was discovered in outcomes when stratified by BMI or by BMI class. These results have indicated that obesity should not be a strict contraindication to lumbar ESI, thus it is prudent to explore this approach prior to surgery.

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Table 1: Patient Comorbidities

COMORBIDITIES N(%)	
HYPERTENSION	146 (42.57)
DIABETES	73 (21.28)
DEPRESSION	52 (15.16)
CANCER	47 (13.70)
ANXIETY	41 (11.95)
CHF	12 (3.50)
CVA	11 (3.21)
COPD	9 (2.62)

Table 2: Changes in mean levels of disability, pain and function in patients receiving ESI from baseline to 3-months stratified by BMI

OUTCOME	N (BM<30)	N (BMI≥30)	M ± SD BMI<30	M ± SD BMI≥30	Δ M ± SD	P-VALUE
ODI	133	123	-5.7444 ± 15.4947	-7.3333 ± 18.6049	1.5890 ± 17.0595	0.4572
VAS BACK	154	147	-1.7013 ± 2.9197	-1.8027 ± 3.2258	0.1014 ± 3.0730	0.7749
PROMIS PAIN	158	148	-1.5759 ± 2.6235	-1.6757 ± 2.6270	0.0997 ± 2.6252	0.7401
PROMIS SATISFACTION	158	148	0.7848 ± 5.7555	1.5473 ± 5.6932	-0.7625 ± 5.7254	0.2453
PROMIS SLEEP	158	148	-0.4494 ± 3.6056	-0.7973 ± 3.9157	0.3479 ± 3.7588	0.4190
PROMIS FATIGUE	158	148	-1.0380 ± 3.8240	-1.0068 ± 4.1148	-0.0312 ± 3.9673	0.9452
PROMIS DEPRESSION	158	148	-0.5823 ± 3.2987	-0.5068 ± 2.6688	-0.0755 ± 3.0106	0.8266
PROMIS ANXIETY	158	148	-0.8038 ± 3.4484	-0.4459 ± 2.8339	-0.3579 ± 3.1662	0.3239
PROMIS PHYSICAL FUNCTION	158	148	1.0949 ± 4.1589	1.3986 ± 3.9996	-0.3037 ± 4.0826	0.5160

Table 3: ANOVA comparing mean levels of disability, pain and function in patients receiving ESI from baseline to 3-months stratified by class of BMI

OUTCOME	P-VALUE
ODI	0.8915
VAS BACK	0.9684
PROMIS PAIN	0.4615
PROMIS SATISFACTION	0.4677
PROMIS SLEEP	0.7836
PROMIS FATIGUE	0.3554
PROMIS DEPRESSION	0.9954
PROMIS ANXIETY	0.8024
PROMIS PHYSICAL FUNCTION	0.7348

PAIN MEDICINE 8

RCT to compare analgesia property of USG-guided fascia iliaca block, IV Fentanyl & sublingual tablet buprenorphine for positioning and postoperatively in fracture femur surgery under spinal anesthesia

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INTRODUCTION: Fracture Femur causes severe pain and distress as periosteum has lowest pain threshold. Regional anaesthesia is preffered for lower limbs procedures as it provides good perioperative pain relief,early ambulation,avoids airway manipulation,reduces total analgesic requirements,poly pharmacy & deep vein thrombosis. Overriding of bone ends during movement worsens pain,delays positioning-increases pain further. Alleviating pain increases patient comfort,provides better positioning for subarachnoid block. Buprenorphine-semi-synthetic opioid agonist-antagonist is 25-40 times potent analgesic than morphine,ceiling effect for respiratory depression not for analgesia,high clinical safety-Prolonged duration of action,well absorbs sublingually,used for opioid detoxification,cancer-related pain,postoperative pain control. Fentanyl-phenylpiperidine synthetic opioid agonist is 50-80 times potent analgesic than morphine,little hypnotic or sedative activity,rapid onset of action. In USG guided Fascia Iliaca Compartment Block-local anesthesia is injected beneath fascia iliaca superficial to iliopsoas muscle having femoral nerve medially and Sartorius muscle laterally to block the femoral nerve,obturator nerve and lateral cutaneous nerve of thigh simultaneously.

METHODS: Ethical approval was taken from college ethical committee before starting this Prospective, Randomized, Double-blind, Controlled study. Oral and informed written consent was taken from all participants and informed that they can leave the study at any time during the study and assured that it won't affect their further treatment.60 ASA(American society of anaesthesiology) grade I and II of either sex,age 18-55 years posted for fracture femur surgery under subarachnoid block were selected(120days).Based on reference data: at confidence interval 95%, estimated margin of error +/-0.80,with Standard deviation(SD) & z value3.09 & 1.96 respectively,type I error 0.05,type II error 0.20,asuming80% power of study,minimum sample size required for the study calculated to be 60 and 20 for each. Randomisation: Random number table.Patients, anaesthesiologist and staff were blinded to allotment. In the operation theatre, all patients received standard anesthesia monitors. Baseline vitals: pulse rate, NIBP, oxygen saturation, ECG were recorded.Intravenous access was obtained with 18G IV cannula and IV fluids started. Group I(n=20) received USG guided Fascia Iliaca compartment block(FICB)with 30ml of 0.25% Ropivacaine 15 minutes before the subarachnoid block with linear array transducer probe(6-15Mhz).Group II(n=20) received 2 tablets(200mcg/tablet) sublingual buprenorphine(SLBUP) 1hr before the subarachnoid block GroupIII(n=20)received Inj.Fentanyl(IVFEN) 2mcg/kg I.V.15 minutes before subarachnoid block. Sub-arachnoid block was performed in sitting posture under strict aseptic precautions in L3-L4 space using 25G Quincke needle with 3ml of 0.5%Bupivacaine (hyperbaric,dextrose 80mg/ml). The analgesia provided by either of modes was assessed by using Visual analogue scale (VAS) scores at time of positioning. Quality of patient positioning(QOPP) for subarachnoid block was recorded with scores of 0-3.0-Not satisfactory, 1-satisfactory, 2-good, 3-optimal. Patient satisfaction was recorded with 1-satisfactory,0-non satisfactory. Time to perform subarachnoid block(time from beginning of positioning to end of spinal). Post-operative analgesia was standardized in all three groups with Inj.Tramadol 2mg/kg I.V; first dose (Rescue analgesia) to be given whenever patient complained pain or vas >= 4.SPSS version 25 software & openepi application was used. Demographic data were analysed by Anova test.

RESULTS: VAS for positioning for FICB (1.1 +/- 1.20), SLBUP (1.4 +/- 1.31),IVFEN(2.5+/-1.70) with P-value 0.073.QOPP for FICB(2.4+/-0.68),SLBUP(2.2+/-0.69),IVFEN(1.75+/-0.85) with P value 0.024.Patient satisfaction is significant with P value 0.043.Time to perform SAB for FICB(5.025+/-0.57),SLBUP(5.195+/-0.75),IVFEN(5.96+/-0.79) with P value 0.0002.Time for rescue analgesia for FICB(348+/-48.07),SLBUP(258+/-41.75),IVFEN(96+/-39.65) with P value <0.0001. Analgesic property was found to be successor in following manner- FICB> SLBUP >IVFEN. No statistical significant difference for hemodynamics.

CONCLUSION: Fascia Iliaca compartment block is more efficacious than sublingual buprenorphine which in turn is more efficacious than IV fentanyl for both positioning during spinal anaesthesia and postoperatively. No statastical significant difference for hemodynemics is found.

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VAS DURING PATIENT POSITIONING						
VAS DURING PATIENT POSITIONING-GROUPS	**FICB GROUP**	**%**	**SUBLINGUAL BUPRENORPHINE**	**%**	**IV FENTANYL**	**%**
VAS 0	10	50	8	40	3	15
VAS 2	9	45	10	50	11	55
VAS 4	1	5	2	10	4	20
VAS 6	0	0	0	0	2	10
TOTAL	20	100	20	100	20	100
P value 0.07 as per ANOVA test, significant.						

QUALITY OF PATIENT POSITIONING						
QUALITY OF PATIENT POSITIONING (QOPP)-GROUPS	**FICB GROUP**	**%**	**SUBLINGUAL BUPRENORPHINE**	**%**	**IV FENTANYL**	**%**
QOPP 0	0	0	0	0	2	10
QOPP 1	2	10	3	15	4	20
QOPP 2	8	40	10	50	11	55
QOPP 3	10	50	7	35	3	15
TOTAL	20	100	20	100	20	100
P value 0.024 as per ANOVA test, significant.						

PATIENT SATISFACTION (P value- 0.043,significant)						
PATIENT SATISFACTION-GROUPS	**FICB GROUP**	**%**	**SUBLINGIAL BUPRENORPHINE**	**%**	**IV FENTANYL**	**%**
YES(1)	19	95	17	95	13	65
NO(0)	1	5	3	15	7	35
TOTAL	20	100	20	100	20	100

TIME TO PERFORM SUBARACHNOID BLOCK						
TIME TO PERFORM SAB-GROUPS (minutes)	**FICB – GROUP**	**%**	**SUBLINGUAL BUPRENORPHINE**	**%**	**IV FENTANYL**	**%**
</= 5	12	60	10	50	2	10
5.01 – 6.00	8	40	8	40	11	55
6.01- 7.00	0	0	2	10	5	25
7.01- 8.00	0	0	0	0	2	10
TOTAL	20	100	20	100	20	100
P value 0.0002 as per ANOVA test, significant.						

Figure 1

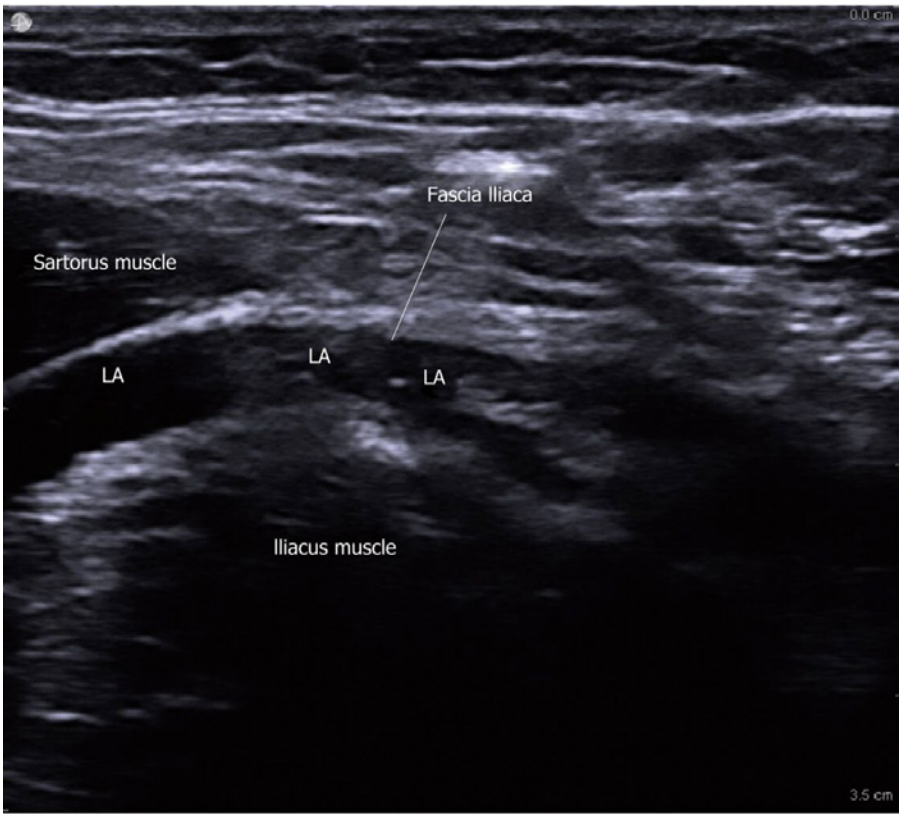

Figure 2

PAIN MEDICINE 9

Machine Learning Can Identify Geographic Disparities in Opioid Overdose Before and After the COVID-19 Pandemic

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INTRODUCTION: New data suggest that COVID-19 has exacerbated the opioid epidemic.[1] Unexpected increases in overdose mortality have highlighted potential weaknesses in our nation's approach to prevention and treatment of opioid related adverse outcomes. California, with its robust data collection history in this domain, may provide helpful insights on the geographical patterns and potential associations between the opioid epidemic and COVID-19 pandemic. The objective of this study was to compare the opioid overdose risks in different rural/urban regions within California before and after the start of the COVID-19 pandemic and identify sociodemographic risk factors.

METHODS: This study used publicly available, deidentified data and was exempt from IRB review. We included cross-sectional data from 2018 to Dec. 2020 from 1) the California Opioid Overdose Surveillance Dashboard that integrates metrics for thirty opioid-related adverse outcomes (including overdoses and deaths) across California's 58 counties; 2) demographic variables (age, race, gender, socioeconomic status, education, county) from the University of California San Francisco Health Atlas; and 3) urban-rural classifications at the county level from the National Center for Health Statistics (large central metropolitan, large fringe metropolitan, medium metropolitan, small metropolitan, micropolitan, noncore region). The period prior to March 2020 (statewide shelter in place order in effect) was designated as the pre-Covid era. Our statistical analysis involved several steps. First, we evaluated trends in overall opioid adverse outcomes from 2019-2020 within California and studied the opioid overdose risks across all counties within California. Second, we used affinity propagation clustering techniques to group the counties a) based on their sociodemographic and geographic features; and b) based on thirty opioid-related adverse outcomes between the pre-Covid and Covid eras. Features were selected after testing to build models. We used Python (version 3.10.0, Python Software Foundation) and Stata (version 17, Stata Corp.) for the statistical analyses. For all analyses, two-tailed nominal P-values of < 0.05 were considered significant.

RESULTS: From 2019 to 2020, California experienced increases across 3 key opioid-related adverse outcomes: deaths, emergency department visits, and hospitalizations (Fig. 1). Large central metropolitan counties experienced the largest absolute increase in any opioid-related death rate (median 7.76 to 13.76 deaths/100,000). The six-level urban-rural classifications (e.g., large central metropolitan, micropolitan,.) were strongly associated with clustering labels based on the various opioid overdose metrics, the Pearson Chi-2 statistic is 77.79($p<0.001$) (Fig 2). Clustering results show that after the pandemic started, opioid-related deaths and emergency department admission risks were higher in the micropolitan counties relative to small metropolitan and non-core counties.

CONCLUSION: After the COVID-19 pandemic began, many regions in California experienced increases in opioid-related adverse outcomes. Micropolitan counties (geographic areas of 10-50,000 people) experienced disproportionate increases in opioid-related deaths and emergency department risks relative to their opioid prescription rates. These data suggest a worsening of healthcare disparities regarding the opioid response in micropolitan areas compared to larger cities, and additional resources may be needed in these areas to mitigate opioid deaths as the pandemic continues.

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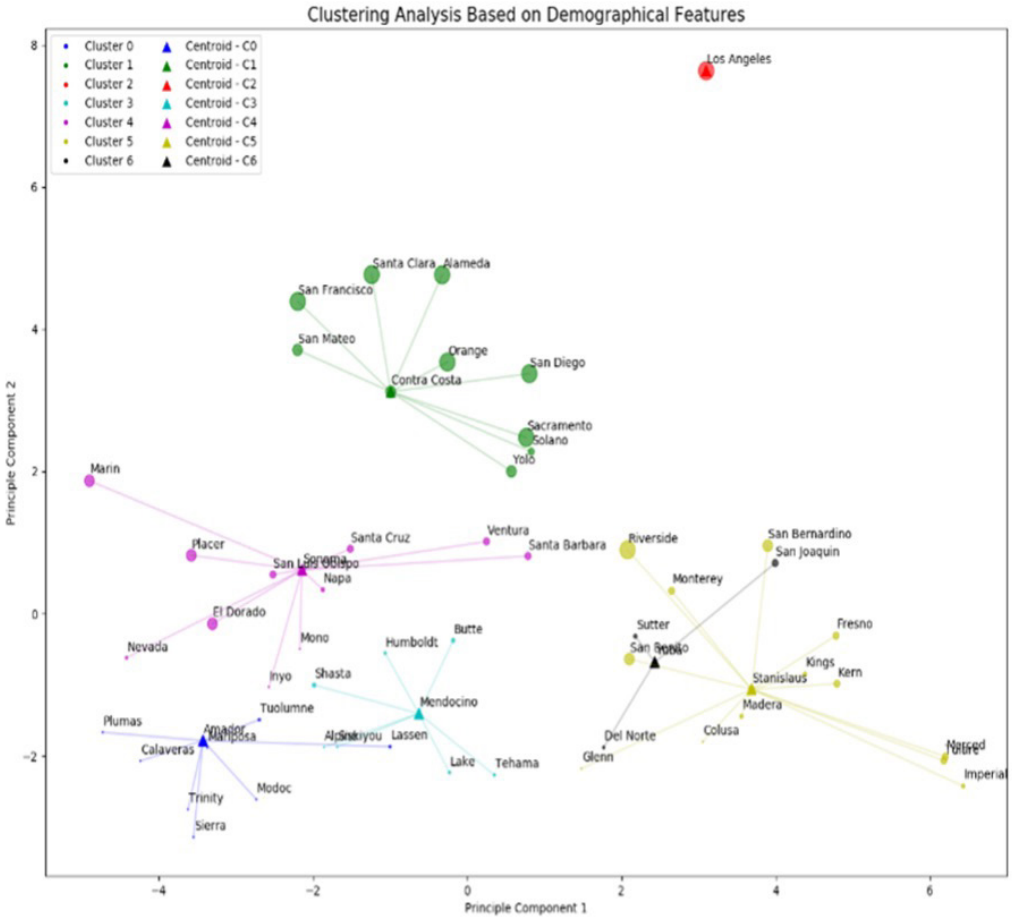

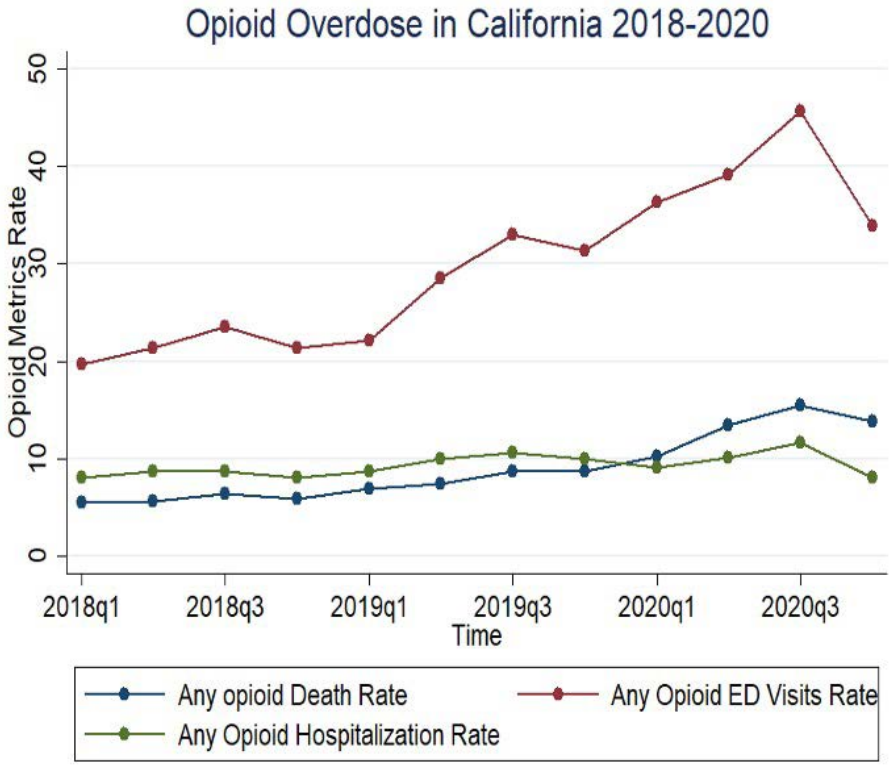

PAIN MEDICINE 10

Dideiodo amiodarone provides long-lasting anesthesia and analgesia in mice

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INTRODUCTION: Local anesthetics play significant roles in various clinical settings, including the management of perioperative and chronic pain.[1] However, current local anesthetics cannot entirely fulfill the demand for long-lasting anesthesia and analgesia.[2] Amiodarone, a multiple ion channel blocker, has been shown to have long-lasting anesthetic and analgesic effects.[3] However, amiodarone contains approximately 37% iodine by weight, which often raises concerns regarding tissue and organ complications.[4] In this study, we tested dideiodo amiodarone - a benzofuran derivative of amiodarone that does not contain iodine (Figure 1), for its potential as a long-acting local anesthetic.

METHODS: The experimental protocol was reviewed and approved by the internal review board.
First, the anesthetic effects of dideiodo amiodarone were tested using a mouse model of sciatic nerve block. Briefly, 24 adult C57BL/6J mice were randomly assigned into the following three groups (n = 8 each, 4 males and 4 females): 1% dideiodo amiodarone, 1% bupivacaine, and vehicle (5% DMSO in normal saline). Under isoflurane anesthesia, the left sciatic nerves of the mice were visualized, and 20 μL of the drug solution was administered by bolus peri-sciatic injection. Sensory and motor blockade were assessed using the pinprick, von Frey, and toe spread tests at baseline, 10 min, 20 min, 30 min, 45 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, and 24 h after drug injection.

Second, the analgesic effects of low-dose dideiodo amiodarone were assessed using a mouse model of inflammatory pain. In another set of 16 mice, inflammatory pain was induced in the left hind paw by injecting 10 μL of zymosan (5 μg/μL). Consequently, either 0.2% dideiodo amiodarone or vehicle was injected in the left hind paw at a volume of 10 μL (n = 8 each). The mechanical and thermal sensitivity and paw thickness were assessed at 1, 2, 4, 6, 8, 12, and 24 h after the zymosan injection.

Statistical analysis was conducted using the Prism 8 software (GraphPad Software, San Diego). Pinprick and toe spread scores, mechanical withdrawal threshold, thermal withdrawal latency, and paw thickness over 24 h were analyzed by two-way analysis of variance followed by the Sidak test. $P < 0.05$ was considered statistically significant. Experimental sample size was determined to detect a difference in the responses of 15% while providing 80% power with an α level of 0.05 (G*Power 3.1.9.3).

RESULTS: In the sciatic nerve model, dideiodo amiodarone produced considerably longer-lasting sensory and motor blockade, compared with bupivacaine (sensory: 248 ± 18 min vs. 30 ± 5 min, $P < 0.001$, motor: 112 ± 21 min vs. 21 ± 1 min, $P < 0.001$)(Figure 2A and 2B). Dideiodo amiodarone and bupivacaine achieved complete nerve block at 10 min after injection.

In the inflammatory pain model, low-dose dideiodo amiodarone reversed the mechanical and thermal hypersensitivity induced by zymosan for up to 8 h [50% withdrawal threshold (g): 0.75 ± 0.12 vs. 0.48 ± 0.13 at 8 h, $P < 0.05$, withdrawal latency (s) 9.0 ± 1.1 vs 5.9 ± 1.0 at 4 h, $P < 0.01$] (Figure 3A and 3B). Dideiodo amiodarone did not influence the paw thickness. (Figure 3C).

CONCLUSION: Dideiodo amiodarone produced robust anesthesia and analgesia in the mouse models of sciatic nerve block and zymosan-induced inflammatory pain. Thus, dideiodo amiodarone may have a potential of being a long-acting local anesthetic and activity in both the naïve and inflamed tissue.

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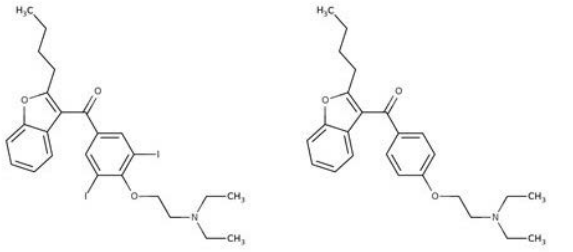
Figure 1



Amiodarone Dideiodo amiodarone

Figure 2

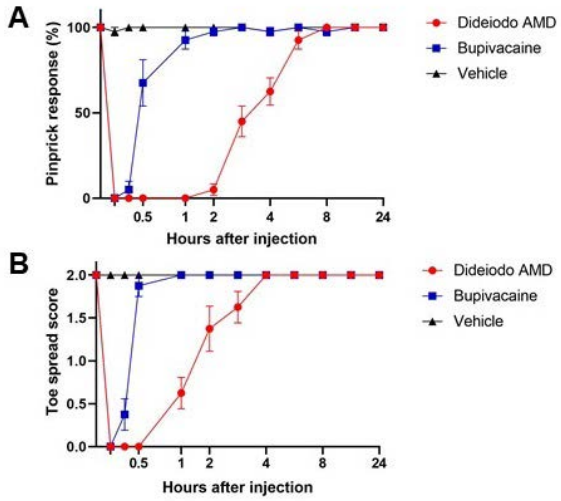
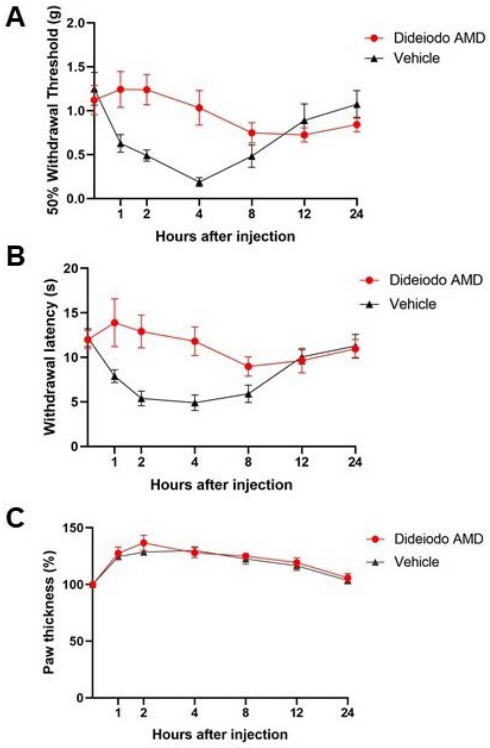


Figure 3



PAIN MEDICINE 11

Impact of U.S. Opioid Drug Overdose by Race/ Ethnicity and State in 2005-2017

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INTRODUCTION: In 2017, the increasing prevalence of opioid-related deaths across the United States prompted the U.S. Department of Health and Human Services to declare the opioid epidemic a 'public health crisis'[1,2]. Understanding what communities are vulnerable and affected by opioid-related mortality would hone public health interventions and policies to address this growing issue[3]. In our study, we compared opioid-related overdose mortality prevalence rates between racial/ethnic populations by U.S. states from years 2005 to 2017 to determine communities most affected by the opioid epidemic.

METHODS: We conducted an observational, cross-sectional study utilizing death certificate data from the U.S. National Vital Statistics System dataset containing vital events from 2005 to 2017 and considered not-human subjects research by the Stanford University Institutional Review Board (Protocol #53429). Specifically, opioid-related deaths among the Non-Hispanic White, Black, Hispanic/Latinx, and Asian/Pacific Islander populations were analyzed. We analyzed the mean crude 13-year overdose prevalence rates per 100,000 people, based on estimated state populations from the U.S. Census Bureau American Community Survey (ACS). Additionally, underlying causes of death due to opioid-related overdose were determined using codes from the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) [2]. We also computed proportions of opioid overdose by age, sex, and overdose intention for each racial/ethnic group. Statistical analysis was performed by using Pearson's Chi-squared test with Yates' continuity correction and the Mann Whitney U Test.

RESULTS: We identified 330,217 opioid-related deaths among Non-Hispanic Whites (274,378), Blacks (28,145), Hispanic/Latinx (25,657), and Asians/Pacific Islanders (2,037) in the United States from 2005 to 2017. West Virginia is the state with the highest prevalence of opioid overdoses among Non-Hispanic White [26.5, 95% CI (26.4, 26.5)] and Black [23.7, 95% CI (22.1, 25.7)] populations, and New Mexico is the state with the highest prevalence among the Hispanic/Latinx [16.0, 95% CI (15.8, 16.1)] population. When considering ethnicity, states with the highest rates of opioid-related deaths drastically varied by ethnicity (Figure 1). Additionally, although Asian/Pacific Islanders have nearly a five-fold lower prevalence of opioid overdose deaths relative to other ethnicities ($\chi 2 = 13716$, df = 1, p-value <0.001), opioid overdose deaths in Asians are two-fold more likely to be caused by intentional self-harm (Figure 2: $\chi 2 = 141.05$, df = 1, p-value < 0.001). When considering the age distribution of opioid related deaths separated by ethnicity, sex, and age, those who overdosed on opioids among the Black population also tend to be older with a median age group of 45-54 versus other ethnicities [Asian = 25-34 (W = 18534063, p-value < 0.001), Non-Hispanic Whites = 35-44 (W = 4537351760, p-value < 0.001), Hispanic = 35-44 (W = 269369823, p-value < 0.001)] (Figure 3).

CONCLUSION: Our study identifies that opioid overdose death rates vary between ethnic groups, with Non-Hispanic Whites having the highest overall opiate deaths, and Asians having the highest intentional opiate overdoses. Classifying opioid overdose deaths by ethnicity, as we did for this study, may improve strategies for precision-based approaches to reach communities within the United States most affected by the opioid epidemic.

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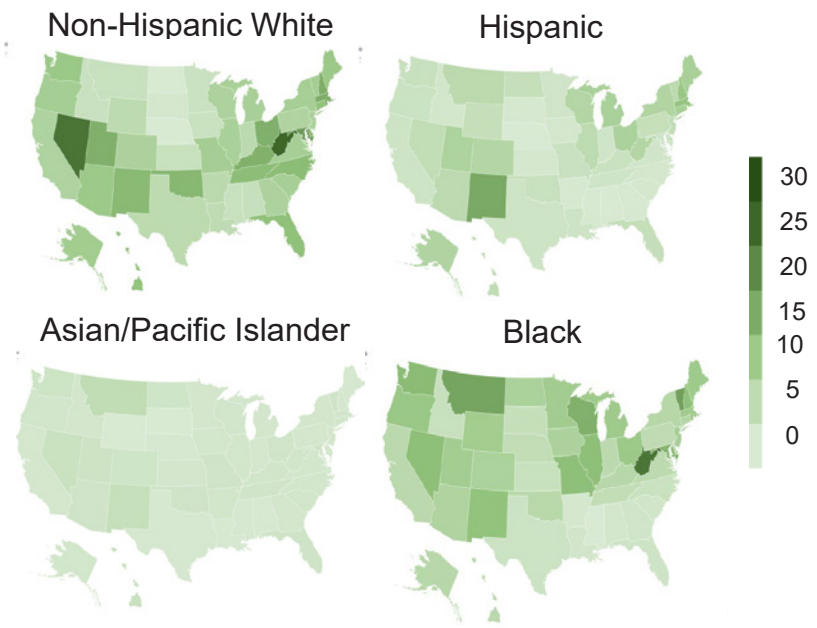

Figure 1. Opioid overdose deaths from NVSS database 2005-2017. Prevalence of opioid overdose deaths per 100,000 per state by ethnicity.

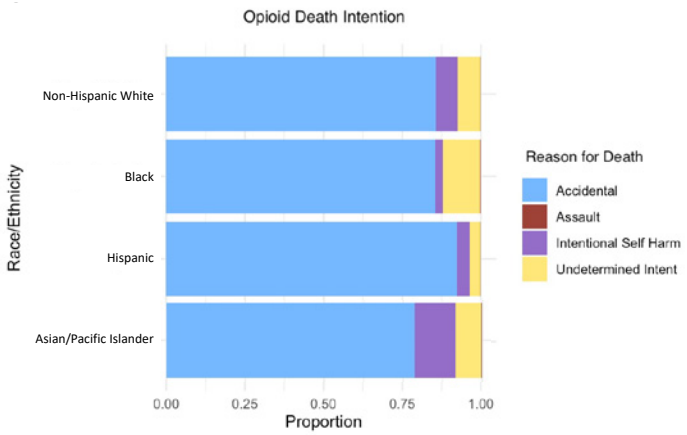

Figure 2. Reason for opioid overdose deaths from NVSS database 2005-2017. Proportion of opioid overdose deaths separated by race/ethnicity and intention. ICD-10 codes X40-X44 constitute "Accidental" opioid overdoses, X85 constitute "Assault" opioid overdoses, X60-X64 constitute "Intentional Self Harm" opioid overdoses, and Y10-Y14 constitute "Undetermined Intent" opioid overdoses.

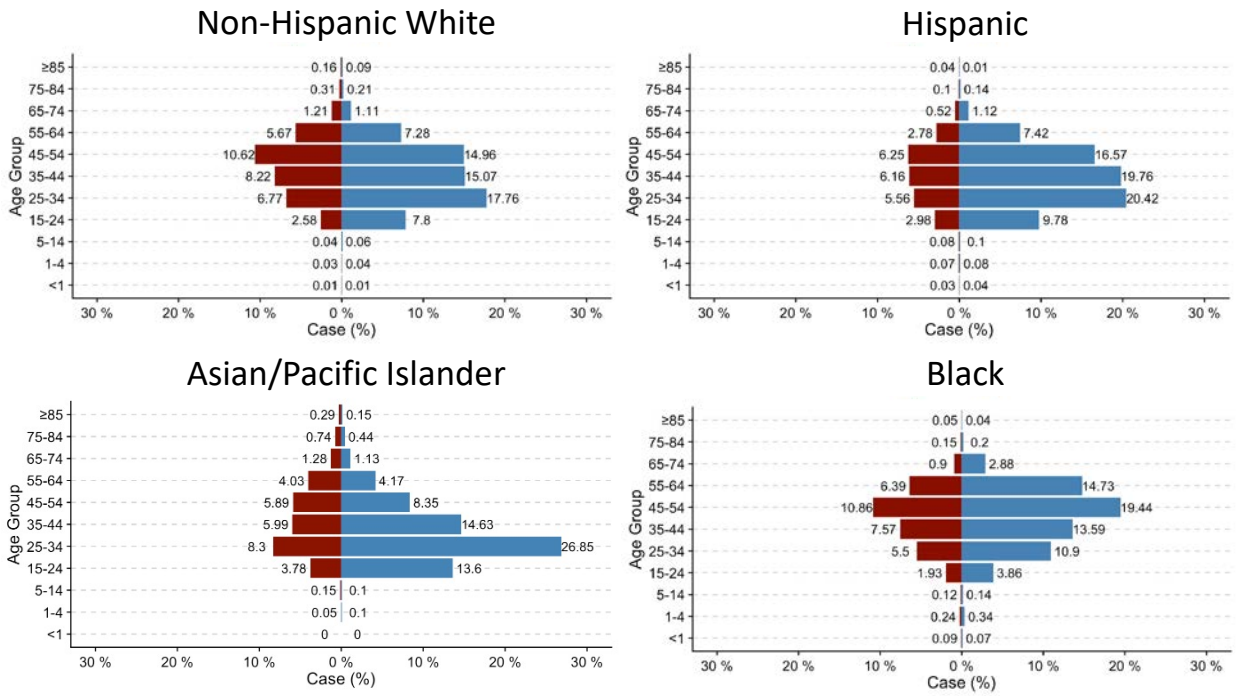

Figure 3. Ethnic, gender, and age distributions for total opioid overdose deaths in the United States from 2005-2017 (red bar = female, blue bar =male).

PAIN MEDICINE 12

Acute postoperative pain control predicts persistent pain trajectories across the six months following surgery

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INTRODUCTION: Persistent postsurgical pain is associated with increased pain in the acute postoperative period[1-2]. Recent work by our research team demonstrated that there is heterogeneity in acute postoperative pain trajectories in the first seven days following surgery[3]. The primary aim of this current study was to 1) determine different patterns or trajectories of persistent pain in the first six months following surgery and 2) to examine the association between acute postoperative pain trajectories with these persistent pain trajectories. A secondary aim was to examine the association between pre-, intra-and acute post-operative sociodemographic, clinical, and behavioral factors with persistent pain trajectories.

METHODS: This was a prospective cohort using a mixed surgical sample which included n=428 patients who were followed for both the first seven days following surgery (POD 1-7) and every month for the first six months following surgery. Pain was assessed with the Brief Pain Inventory. Group-based trajectory modeling was used to estimate trajectories/patterns of persistent postoperative pain. Chi-square tests and ANOVAs were used to examine associations between persistent postoperative pain trajectories and acute daily postoperative pain trajectories and other factors.

RESULTS: Three persistent postoperative pain trajectories were identified (Figure 1). Sixteen percent (15%) of patients were in moderate pain trajectory; 33% were in low to moderate pain trajectory; and 52% of patients were in the low pain trajectory. Acute postoperative pain trajectories were strongly associated with persistent postoperative pain trajectories ($\chi 2=95.6$, df=10, $p < 0.001$, Figure 2). Ninety percent (90%) of the patients in the persistent moderate pain trajectory group were in the high and moderate-high acute postoperative pain trajectory groups. No patients in decreasing, low, or low-moderate acute postoperative pain trajectories went on to be in the persistent moderate pain trajectory. Additionally, age, race, income, surgical service, intraoperative ketamine use, preoperative pain, and intra- and post-operative opioids were associated with persistent postoperative pain trajectories ($p < 0.05$). Interestingly, patients in the persistent moderate pain trajectory had higher preoperative anxiety, depression, pain behaviors, and pain catastrophizing (all $p < 0.001$).

CONCLUSION: Poor acute postoperative pain control was strongly associated with persistently elevated pain during the first six months following surgery. Combined with important perioperative sociodemographic, clinical, and behavioral factors, clinicians may be able to use acute postoperative pain control as a way to predict which patients are at risk of persistent postoperative pain and, hopefully, to be able to devise individualized management plans to reduce likelihood, or magnitude of persistent pain following surgery.

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3. Anesthesiology. 2021 Mar;134(3):421-34

Figure 1. Group-based pain trajectories during the first 6 months following surgery, with % of patients (n=428) in each group. Error bars indicate 95% confidence intervals.

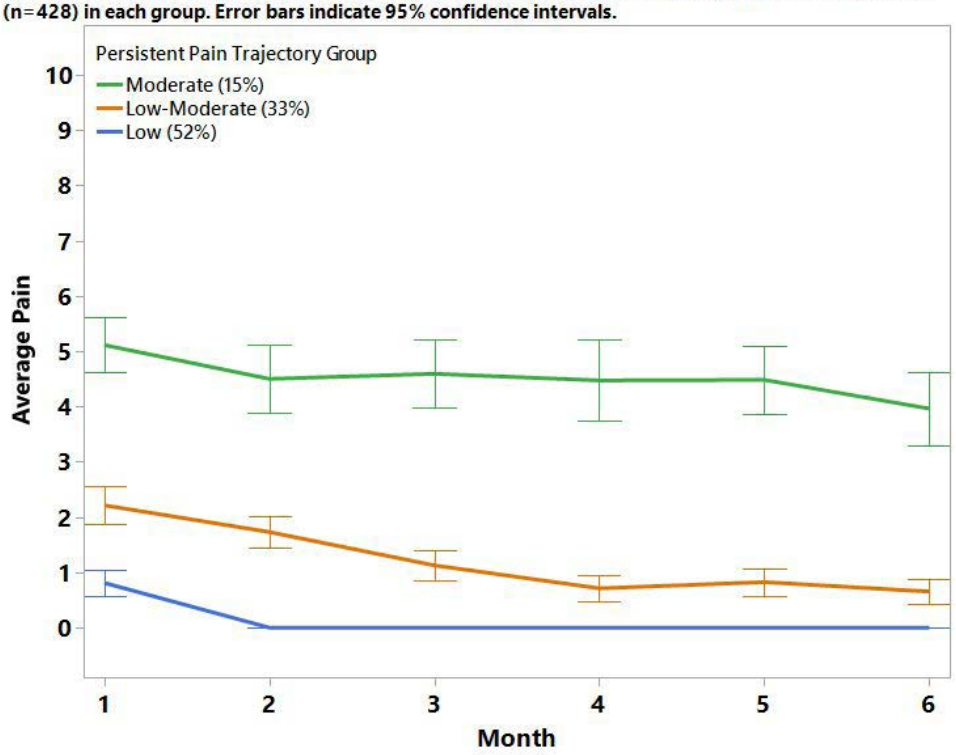
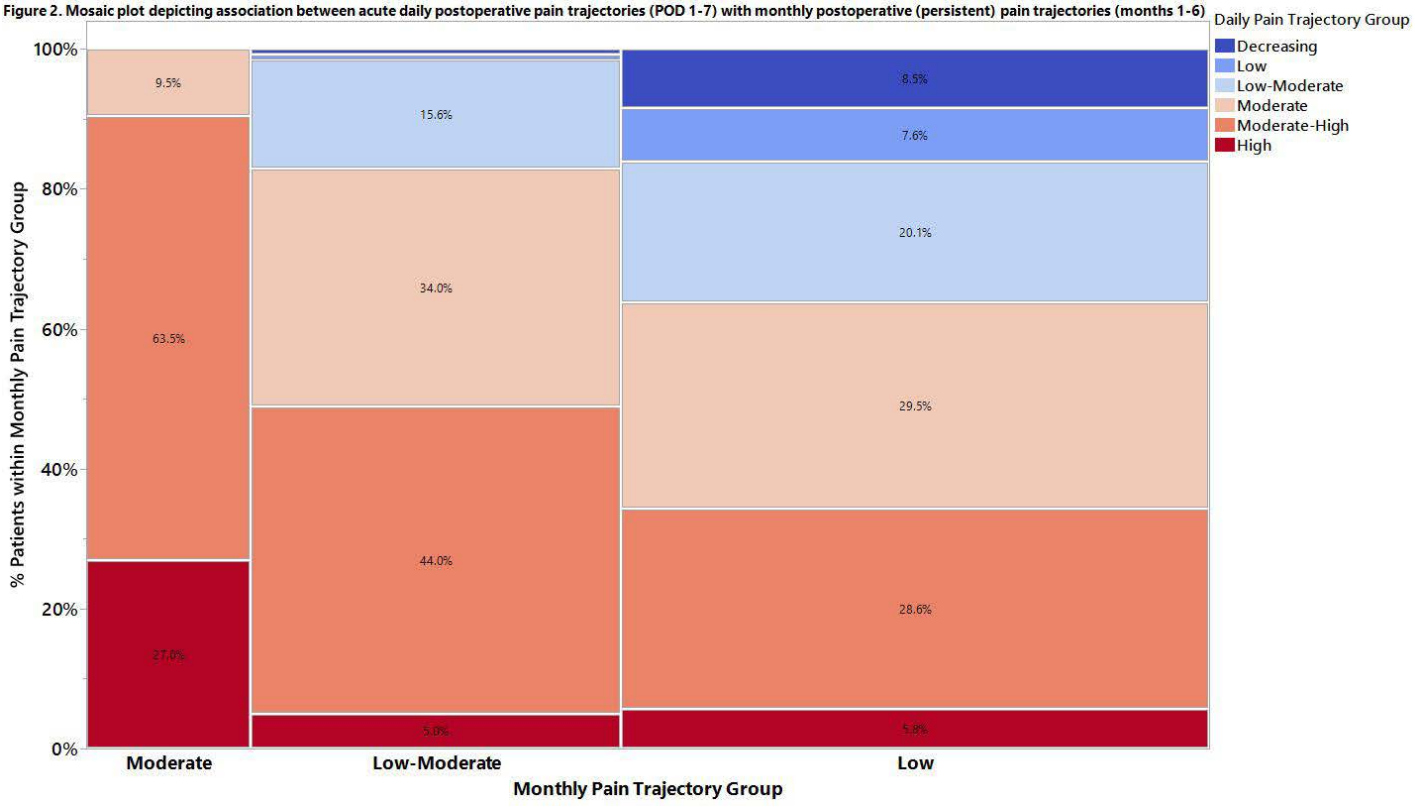


Figure 2. Mosaic plot depicting association between acute daily postoperative pain trajectories (POD 1-7) with monthly postoperative (persistent) pain trajectories (months 1-6)



PAIN MEDICINE 13

Retrospective review of transversus abdominis plane and rectus sheath blocks with liposomal bupivacaine for postoperative pain control following minimally invasive partial and total nephrectomy

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INTRODUCTION: Despite being minimally invasive, laparoscopic and robotic surgery can cause moderate to severe postoperative pain. Little to no data exists on the ability of abdominal fascial plane blocks to improve pain in this patient population and there is a further paucity of data investigating the effect of adding liposomal bupivacaine (LB)1-3. We hypothesized that patients undergoing minimally invasive partial and total nephrectomy surgery receiving bilateral transversus abdominis plane (TAP) and rectus sheath (RS) blocks with LB would require less opioids after surgery than patients that did not receive a block. Secondary endpoints were postoperative pain scores and hospital length of stay.

METHODS: Following Institutional Review Board approval, we conducted a retrospective observational study reviewing patients that underwent robotic and/or laparoscopic partial and/or total nephrectomy performed between May 1, 2015 and June 21, 2021 at a single institution. American Society of Anesthesiology Classification I-IV patients greater than 18 years of age who received TAP and RS blocks with LB were eligible for inclusion. Patients with a history of opioid dependence, those undergoing emergent or urgent procedures, or had a nerve block other than a TAP and RS with LB were ineligible (Figure 1). Data were collected by chart review and included oral morphine equivalents (OMEs) used in post anesthesia care unit (PACU), OMEs used each postoperative day, hospital length of stay, and both average and median pain scores on each postoperative day. We tested for differences between patients using two-tailed Mann Whitney U tests.

RESULTS: Data were collected and analyzed on 140 patients; 76 receiving no block and 64 receiving the block (Table 1). There was no significant difference in opioid use on any postoperative day between patients who received the block and those that did not (Table 2). There was no significant difference in opioid use in PACU or postoperative pain scores (Table 2). Patients who received the block had a significantly longer hospital length of stay (days) then those that did not receive the block (3.1 vs 1.9, p=0.003).

CONCLUSION: This retrospective review provides evidence that TAP and RS blocks with LB do not decrease the use of postoperative opioids, improve pain scores, or decrease hospital length of stay for patients undergoing minimally invasive nephrectomy. Limitations to this study include the retrospective nature, the small sample size, and it took place at a single center.

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Table 1. Baseline, intraoperative, and postoperative patient characteristics.

Patient Characteristic	No Block (n =76)	Block (n=64)	P-value
Age, years	64.0 (57.8-68.3)	67.5 (59.0-74.0)	0.02
Female gender	5.3%	6.3%	0.80
Surgery type			0.001
Partial nephrectomy	71.1%	28.9%	
Nephrectomy	51.6%	48.4%	
ASA Class			0.15
1	0	0	
2	13.2%	7.8%	
3	80.2%	81.3%	
4	6.6%	10.9%	
Charlson co-morbidity index	2.6	3.4	0.01
Myocardial infarction	5.3%	4.7%	0.88
Congestive heart failure	70%	7.8%	0.16
Peripheral vascular disease	2.6%	3.1%	0.86
CVA or TIA	6.6%	10.9%	0.36
Dementia	0%	0%	N/A
COPD	10.5%	15.6%	0.37
Connective tissue disease	5.3%	0%	0.06
Peptic ulcer disease	1.3%	0%	0.36
Liver disease	3.9%	20.3%	0.05
Diabetes Mellitus	34.2%	43.8%	0.30

Moderate to severe CKD	23.7%	53.1%	0.06
Solid tumor	100%	100%	0.12
Leukemia	3.9%	0%	0.11
Lymphoma	3.9%	0%	0.11
AIDS	5.2%	3.1%	0.54
Premedication			
Tylenol	0%	0.02%	0.28
Gabapentin	0%	0%	N/A
OR OME, mg	62 (50-82)	55 (45-74)	0.06
OR non-opioid analgesia			
Ketamine	20%	6.3%	0.02
Dexmedetomidine	5.2%	9.4%	0.35
Lidocaine infusion	0%	0%	N/A
Tylenol	64.5%	70.3%	0.47
Toradol	0%	0%	N/A
Postoperative non-opioid analgesia			
Tylenol	47.4%	65.6%	0.03
Gabapentin	14.5%	26.6%	0.08
NSAID	4%	6.3%	0.53

Categorical variables are reported as percent, and continuous variables are reported as median (interquartile range).

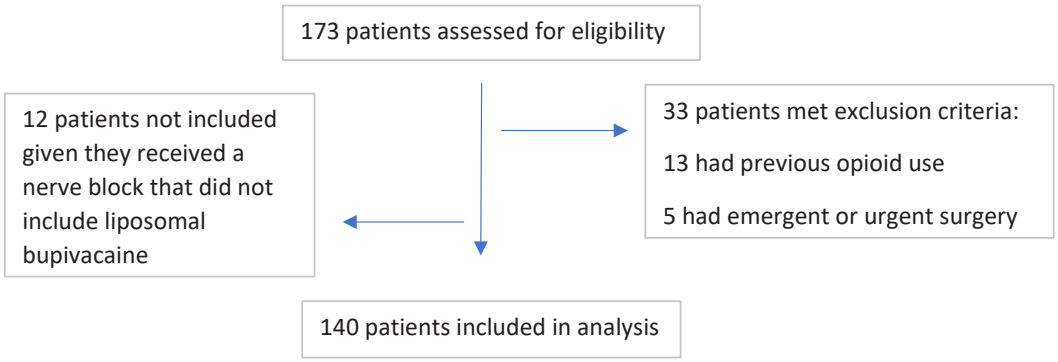

Table 2. Postoperative Analgesia

Outcome	No Block (n =76)	Block (n=64)	P-value
PACU OME, mg	4.5 (0 – 20)	4 (0 – 20)	1
Hospital Length of stay, days	1 (1 – 2)	2 (1 – 3.3)	0.003
Postoperative OME, mg			
Day 0	10 (5 – 20)	10 (5 – 20)	0.98
Day 1	15 (8.75 – 30)	25 (10 – 30)	0.67
Day 2	15 (0 – 30)	10 (0 – 10)	0.055
Day 3	10 (0 – 30)	7.5 (0 – 10)	0.13
Day 4	10 (0 – 30)	5 (0 – 20)	0.40
Day 5	0 (0 – 0)	0 (0 – 5)	n/a
Postoperative pain scores, median			
Day 0	4 (1 – 5.6)	4 (2 – 6)	0.38
Day 1	4 (2 – 5.5)	4 (2 – 5.6)	0.86
Day 2	3 (0 – 5.5)	3 (0 – 5.5)	0.98
Day 3	3.25 (0 – 5)	2 (0 – 5)	0.43
Day 4	4 (0.75 – 5)	0 (0 – 3)	0.26

Primary outcomes table of postoperative opioid consumption in patients who received a TAP block with liposomal bupivacaine and patient who received no block. All continuous variables are reported as a median (interquartile range). PACU= post-anesthesia care unit.

PAIN MEDICINE 14

A Randomized Control Study Evaluating Smoking Cessation at a Pain Clinic

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[1]Montefiore Medical Center, Bronx, NY

INTRODUCTION: Smoking cessation has been shown to improve clinical outcomes by reducing the risk for many adverse health effects. However, patients are rarely provided with individualized counseling and resources to aid with cessation while being treated at pain clinics. Furthermore, they are not advised on the association of smoking with chronic pain. We hypothesize that smoking cessation counseling by a pain medicine physician will lead to a decrease in smoking habits in patients with chronic pain. The primary objective is to compare the patients that received smoking cessation counseling or not at baseline, 4 weeks, and 8 weeks. The secondary objective is to evaluate the utilization of Smoking Cessation Programs (SCPs) by the patients.

METHODS: We are conducting a randomized control study on patients visiting the Montefiore Multidisciplinary Pain Program with an active history of smoking. Patients that were screened as actively smoking were then randomized into three groups. The first group received counseling from their physician through an informational diagram detailing the association of smoking with chronic pain. The second group received a flyer on smoking cessation from front desk personnel, and the third group received neither intervention. After obtaining consent, a questionnaire survey was administered electronically by the research associate and a follow-up survey will be conducted after 4 weeks and 8 weeks. In this interim analysis, we are presenting the preliminary descriptive results.

RESULTS: During the study period, 509 patients attending the pain clinic were screened. Among those, 102 had a history of active smoking (20.0%), and 47 were enrolled. The median age in our cohort was 57 years and was predominantly females (76.6%). In our interim analysis, 97.9% of the patients in the study have considered quitting smoking, however, 74.5% reported never having participated in an SCP (Figure 1). Additionally, 55.3% stated never having been offered an SCP by their providers (Figure 2). Finally, 91.5% reported not receiving support with cessation in preparation for a pain management procedure. A full analysis will be provided at the time of the conference.

CONCLUSION: Smoking is a modifiable lifestyle risk factor that is directly related to several chronic diseases. Although the adverse relationship between smoking and chronic pain has been established, pain physicians seldom initiate smoking cessation discussions. In our study cohort, although the majority of patients have considered smoking cessation, many have never participated in a structured SCP, nor have they been offered one by their current healthcare providers. Providing actively smoking patients with information and assistance regarding obtaining smoking cessation resources can prove beneficial in decreasing rates of smoking. Additionally, we believe that when patients are educated about the strong relationship between their chronic condition and smoking, the probability of quitting could be higher.

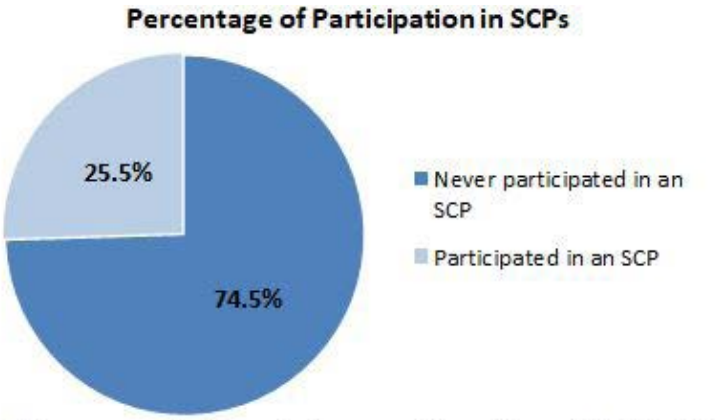

Figure 1: Percentage of patients that have participated in an SCP (N = 47).

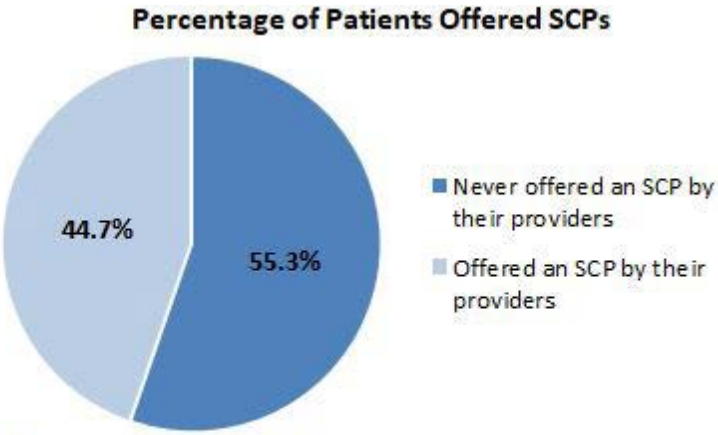

Figure 2: Percentage of patients that have been offered an SCP by their healthcare providers (N = 47).

PAIN MEDICINE 15

Effect of postoperative single dose of ketamine on pain after mastectomy

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INTRODUCTION: Ketamine, as a perioperative infusion, has been demonstrated to reduce opioid consumption and pain scores after surgery.[1,2] However, an alternative to ketamine infusion is a single dose of ketamine, which is simpler to administer. We previously found that a single dose of ketamine in the recovery room at a dose of 0.4 mg/kg reduced the affective component of pain for 7 days after bariatric surgery.[3] Based on this prior study, we are conducting a single-blinded, randomized controlled trial (RCT) of single dose ketamine in patients undergoing mastectomy with immediate reconstruction for breast cancer. We hypothesize that a single ketamine dose of 0.6 mg/kg, in the range of the therapeutic dose for mood disorders and pain in the emergency department[3,4] after surgery, may relieve postoperative pain, improve mood, and decrease opioid requirements. Due to the COVID-19 pandemic, we used this study to gauge the feasibility of using remote methods to facilitate enrollment and retention in the study. Cancer patients are more vulnerable to COVID-19 due to the progression of cancer and immunocompromising treatments, therefore it is especially vital to provide safer options for cancer patients to participate in research.

METHODS: This study was approved by our institution's institutional review board. This is a single-blind, placebo-controlled RCT of adult women undergoing mastectomies with immediate reconstruction. All recruitment for the study and informed consent was done remotely. Patients were contacted either through phone or through secure e-mails and were consented over the phone and through e-consent. Following surgery, patients are randomized to receive either ketamine 0.6mg/kg or saline intravenously over a 45-60 minute time period. The primary outcome is postoperative mastectomy pain measured by the Brief Pain Inventory (BPI) pain subscale on postoperative days (POD) 1 and 2. Secondary outcomes include assessing the effect of ketamine on pain severity and interference, mood, recovery, and opioid use. Baseline assessments are done prior to surgery. Outcomes are measured on POD 0, 1, 2, and 7 through patient-reported outcome measure surveys. Outcomes were assessed in person during hospitalization. Once discharged, outcomes were assessed through online electronic surveys sent to their e-mail, with telephonic option as well.

RESULTS: We have enrolled a total of 25 patients from thus far. Out of all eligible patients that were contacted, there was a 48% conversion rate to enrollment. The administration of a single dose (0.6 mg/kg) of ketamine, after patients underwent mastectomy for breast cancer, was generally overall well-tolerated. 42% of patients that received ketamine reported side effects, compared with 38% of patients that received the saline control. 100% of patients have completed the study infusion, and have successfully completed all follow-ups and reached the end of the study utilizing remote survey methods outside of their hospital admission.

CONCLUSION: Administering a single-dose administration of ketamine after surgery is well-tolerated in patients undergoing mastectomy for breast cancer. Remote recruitment and survey administration is a feasible method for enrolling patients and maintaining retention.

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PAIN MEDICINE 16

Improving Anesthesia Resident Knowledge of the Preoperative Management of Buprenorphine/Naloxone Therapy Through the Use of OSCE Teaching

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[1]The University of Kentucky, Lexington, KY

INTRODUCTION: Buprenorphine has been available since the 1970s and after passage of DATA 2000 it has been utilized for outpatient detoxification, addiction therapy and chronic pain treatment.[1] Buprenorphine prescriptions in Kentucky increased from the first quarter of 2015 to the fourth quarter of 2017 from 30.8 to 46.6 per 1000 persons.[2] Clearly, there is a growing need to address the specialized needs of patients on a Buprenorphine/Naloxone regimen. Buprenorphine/Naloxone contains a combination of buprenorphine and naloxone in different doses depending upon the prescription. Naloxone, an opioid antagonist, is added to the drug compound to ensure the drug is not abused by intravenous means. Managing intraoperative and postoperative pain in patients on a Buprenorphine/Naloxone regimen is complicated due to the complex pharmacology of the medication. All of these factors contribute to the complexity of developing a safe and effective treatment plan for patients on a Buprenorphine/Naloxone regimen. Given the increasing number of patients on Buprenorphine/Naloxone therapy, as well as the complexity of the medication, there is a clear need for further education on the perioperative management of patients on this medicateon in residency training programs. Simulation training has shown to be useful tool for the evaluation of resident performance within training programs.[3] In this study, we attempted to develop an OSCE scenario to focus on this need for further education in the perioperative management of Buprenorphine/Naloxone in our anesthesia residents. The overall aim of this study is to evaluate the University of Kentucky Anesthesiology residency program training in intraoperative and postoperative pain management for patients with a history of Buprenorphine/Naloxone use by comparing OSCE scores each year of training.

METHODS: This is a prospective study of the University of Kentucky Anesthesia residents from their PGY1 year through the PGY4 year of training. It is a cross-over study in that PGY-1 residents are fairly naïve to opioid management in patients undergoing treatment for opioid addiction, whereas, the same residents, in their third year, will be expected to have experienced some intervention for opioid management techniques for patients with opioid use disorder in the pain clinic, CAS, and inpatient surgical rotations. We did this by creating several OSCE stems. A case script was developed for each standardized patient that highlighted the major aspects of patient discussion including the anesthesia plan, patient's beliefs regarding pain, patient's coping strategies, post procedure pain control, and details regarding possible effects to their Buprenorphine/Naloxone therapy. A 20 point grading rubric was then developed to evaluate each anesthesia resident. After each OSCE session, a debriefing and teaching session was conducted. Scores from each year were then compared to each other to evaluate the effectiveness of OSCE teaching.

RESULTS: Through this study, a 30% improvement was seen in overall OSCE scores from the PGY1 year to the PGY4 year.

CONCLUSION: Through this study, we found that PGY1 anesthesia residents had a limited knowledge base of the management of Buprenorphine/Naloxone therapy in the preoperative period. Our initial results show an overall improvement in OSCE scores over the residency training period. Limiting factors in this study include: multiple evaluators, the inability of certain residents to participate due to clinical responsibilities, and the inability to evaluate Group E in the 2020 period due to the COVID 19 Pandemic. Our future plans include development of a more complex OSCE scenarios to continue to present to the University of Kentucky residents. Further data points are needed to clearly show the relationship between OSCE teaching and anesthesia resident education.

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PAIN MEDICINE 17

Potential Value of a Survey of Treatment Expectations on Patient Satisfaction with Chronic Pain Management: Preliminary Results from a Prospective Study

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INTRODUCTION: Patient satisfaction improves patient adherence to treatment and is needed for quality improvement in healthcare.[1] It can be defined in context of the degree of congruency between the individual's expectations and actual clinical experiences.[2] Prior studies in the Pain Medicine literature have focused on identifying factors associated with patient satisfaction, such as the level of provider engagement.[3] The objective of this study is to determine if an expectation survey, administered prior to initial clinical evaluation, would lead to enhanced patient satisfaction regarding treatment planning and outcomes within the scope of chronic pain management.

METHODS: This was an IRB-approved, prospective study at an outpatient chronic pain management clinic at an academic teaching hospital. 66 patients naïve to the Pain Medicine Department at the Multidisciplinary Pain Center were enrolled into the study. Participants were administered questionnaires in the waiting room prior to first visit with the provider. Primary outcome measures were pain rating and locations, prior treatments, expected degree of functionality, expected quality of life, opioid misuse and willingness to participate in treatment planning. Secondary outcome measures were satisfaction with treatment, satisfaction with meeting goals and expectations and satisfaction with overall experience. Statistical analysis was done using two tailed t-tests and ANOVA to define patient improvement.

RESULTS: 66 patients, ages ranging from 21 to 87, naïve to the Pain Medicine Center were each administered a survey prior to the first visit with the provider. Based on a numerical pain rating scale of 0-10, the participants reporting pain rating > 0 were divided into three categories, participants with pain rating of 1-3 (n=4), participants with pain rating of 4-6 (n=5), and participants with pain rating of 7-10 (n=57) (Tables 1 & 2). Participants with a pain rating of 7-10 reported that improvement in Quality of Life (QoL) was extremely important in treatment planning compared to participants with pain ratings of 1-3 and 4-6 (65% vs 60% vs 50%) (Table 3). Participants with a pain rating of 4-6 reported that they expected QoL to be significantly improved compared to participants with pain ratings of 1-3 and 7-10 (60% vs 25% vs 56%) (Table 4).

CONCLUSION: Based on initial surveys, expectations of participants with a pain rating of 7-10 were that it was extremely important to have most significant improvement in QoL compared to expectations of participants with pain ratings of 1-3 and 4-6. The participants with a pain rating of 7-10 had the highest expectations for some sort of improvement in QoL, when compared to the other participants with pain ratings of 1-3 and 4-6. This study presents some preliminary results on expectations from participants undergoing initial evaluations in a Pain Management Clinic. Further data must be collected to determine true improvement in outcomes correlating with initial survey results.

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Table 1. Pain categories based on patient-reported numerical pain rating of 0-10

Average Pain Rating	Pain Category (Based on Average Pain in past 30 days)
0	0
1 to 3	1
4 to 6	2
7 to 10	3

Table 2. Number of patients in each pain category

Pain Category	Number of patients
0	0
1	4
2	5
3	57

Table 3. Number (percentage) of patients by degree of importance of quality of life improvement

Pain Category	Improvement of QoL not at all important	Improvement of QoL is not so important	Improvement of QoL is some what important	Improvement of QoL is very important	Improvement of QoL is extremely important
1	0	0	0	2 (50.0%)	2 (50.0%)
2	0	0	1 (20.0%)	1 (20.0%)	3 (60.0%)
3	1 (1.8%)	1 (1.8%)	7 (12.3%)	11 (19.3%)	37 (64.9%)

Table 4. Number (percentage) of patients by degree of expectations of quality of life improvement

Pain Category	Expect QoL to be mildly improved	Expect QoL to be moderately improved	Expect QoL to be fully improved
1	0	3 (75.0%)	1 (25.0)
2	1 (20.0%)	1 (20.0%)	3 (60.0%)
3	11 (19.3%)	14 (24.6%)	32 (56.1%)

PAIN MEDICINE 18

Development and Validation of Machine Learning Model to Predict Postoperative, Post-Discharge Opioids Refills as a Screening Tool for Referral to a Transitional Pain Service Clinic

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INTRODUCTION: Transitional Pain Service (TPS) clinics have recently been proposed as a way to reduce persistent postoperative opioid use, by providing acute pain care for recently post-surgical patients at elevated risk of new persistent opioid use or chronic post-surgical pain.[1,2] Identifying which patients may benefit from TPS evaluation within 2 months postoperatively is a challenge, however, because there are no validated models for predicting who is at risk of prolonged postoperative opioid use prior to pain chronification at ~3 months postoperatively. To identify opioid-naïve patients who might benefit from a TPS approach at our institution, so that surgeons may refer them to the TPS clinic, we leveraged local data available in the electronic medical record (EMR) to predict post-operative, post-discharge opioid refills during a transitional period, defined as between 30 - 89 days after surgery.

METHODS: This is a retrospective, observational study of 39,231 opioid- naïve patients aged 18 and older who had surgical procedures at University of California, San Francisco (UCSF) Medical Center from June 2012 to December 2019. This study was approved by our institutional review board with waiver of patients' consent for acquisition of data (IRB #18-26728). We used the eXtreme Gradient Boosting (XGBoost) machine learning algorithm to train a decision tree-based model on the training dataset. Specific hyperparameters of the algorithm were: learning rate=0.01, maximum tree depth=4, minimum child weight=2, number of estimators=1000, scaled positive weight=1. We calculated a confidence interval of the ROC-AUC with 6-fold cross-validation.

RESULTS: We achieved a ROC-AUC of 0.75 [0.74,0.76] in predicting the outcome of opioid refills 30-90 days after the surgery (Figure 1A). Our model also showed a promising calibration curve (Figure 1B), suggesting robustness of the algorithm at varying decision thresholds. Important variables in the model included receiving an opioid prescription during days 0-30, total number of oral morphine equivalents (OME) needed on the day prior to discharge, discharge disposition, postoperative length of stay in the hospital, total OME ordered at discharge, age, and total length of surgical case (Figure 2).

CONCLUSION: A machine learning model using local EMR data predicts transitional opioid prescription with sufficient discrimination and calibration to facilitate referral of high-risk patients to our local TPS clinic within 2 months after surgery.

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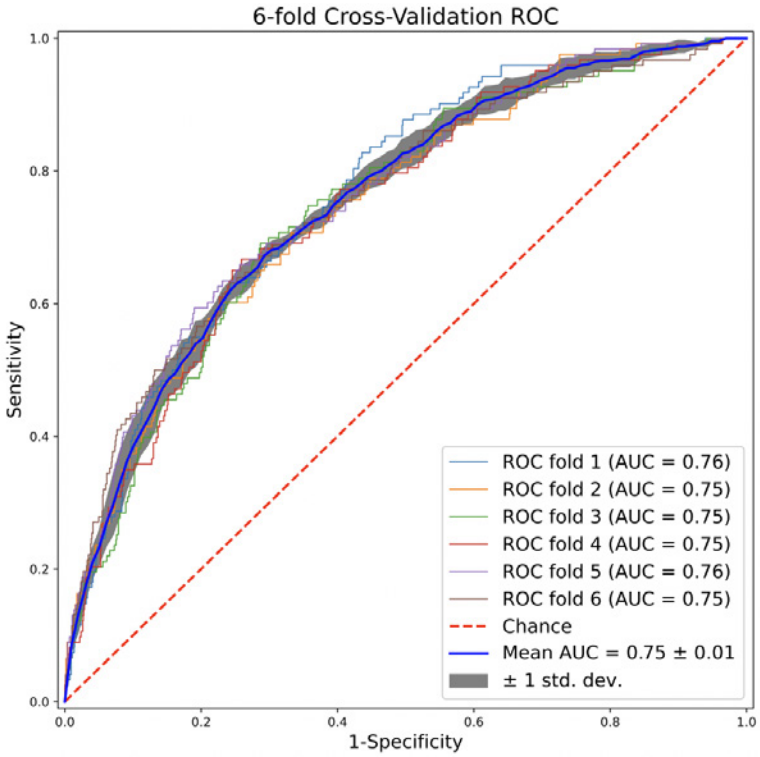

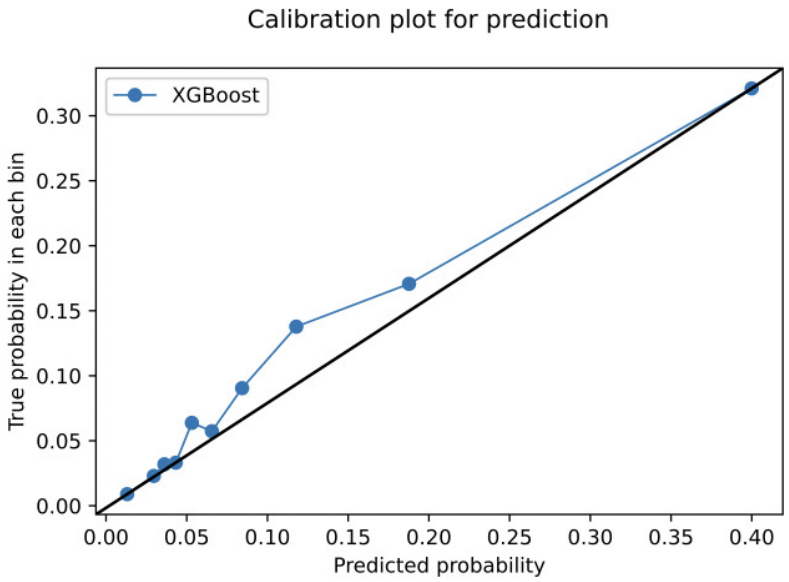

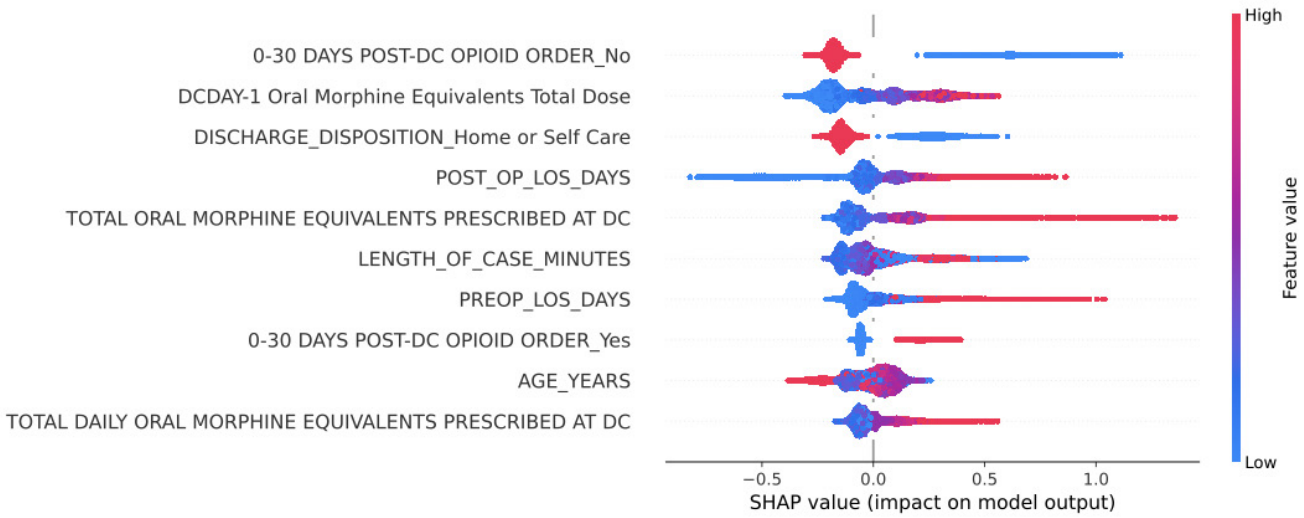

PAIN MEDICINE 19

Prevalence of Fatal and Non-fatal Overdose After Prescribing Opioids for Chronic Pain: A Systematic Review and Meta-analysis of Twenty Cohort Studies

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INTRODUCTION: Long-term opioid use is associated with serious harms, including fatal and non-fatal overdose. We conducted a systematic review and meta-analysis to explore the overall prevalence of nonfatal and fatal overdose of opioids when prescribed for chronic pain.

METHODS: We searched MEDLINE, EMBASE, CINAHL, and PsycINFO from inception to November December 2021, for observational cohort studies reporting fatal or non-fatal overdose of prescribedfollowing prescription of opioids for chronic pain. Paired reviewers independently extracted study characteristics, patient demographic information, clinical conditions and comorbidities, use of opioids and other medications, and fatal and non-fatal overdose. We assessed the risk of bias of all eligible studies, including representativeness of study population, validity of outcome measures, and missing data. and used We used random-effects models to pool data for prevalence of fatal and non-fatal overdose across studies, and a Freeman-Tukey Double Arcsine transformation to stabilize the variancerandom-effects meta-analysis with Freeman-Tukey Double Arcsine transformation to pool prevalence across studies. We explored for small study effects by visual assessment of asymmetry of funnel plots and calculation of Egger's test, when there were at least 10 studies in a meta-analysis. We generated the following a priori hypotheses to explain variability between studies assuming a higher prevalence of fatal or non-fatal overdose is associated with 1) high-risk population; 2) chronic non-cancer pain vs cancer-related chronic pain; 3) intentional vs unintentional overdose; and 4) higher risk of bias. We used logit transformation as sensitivity analysis.

RESULTS: Twenty cohort studies were eligible, including with 22,452,480 patients prescribed opioids for chronic pain were eligible for review. Ten cohort studies with 723,374 patients reported the prevalence of opioid-related death (fatal overdose) ranginged from 0.2 – 17.5 ‰ (median 2 ‰, IQR 0.6 – 3 ‰), and the pooled prevalence of fatal opioid overdose was 1.6 ‰ (95%CI 0.6 – 2.9 ‰), Figure 1. Ten cohort studies with 328,632 patients reported the prevalence of non-fatal opioid overdose ranginged from 0.02 – 14.9 ‰% (median 2.3 ‰, IQR 0.5 – 4.7 ‰), and the pooled prevalence of non-fatal opioid overdose was 2.7 ‰ (95%CI 1.6 – 4.1 ‰), Figure 2. Among 6,824 patients who reported a previous non-fatal opioid overdose in four cohort studies, the pooled risk of fatal overdose was 38 ‰ (95%CI 6 – 92 ‰), Figure 3. We did not detect significant subgroup effects and small study effects among eligible studies. And the sensitivity analysis using logit transformation showed similar results.

CONCLUSION: Our review suggests that for every 10,000 patients prescribed opioids for chronic pain, 23 will overdose and survive and 16 will experience a fatal opioid overdose. Among patients who had previous non-fatal overdose, the risk of fatal overdose increases to 380 per 10,000 patients.

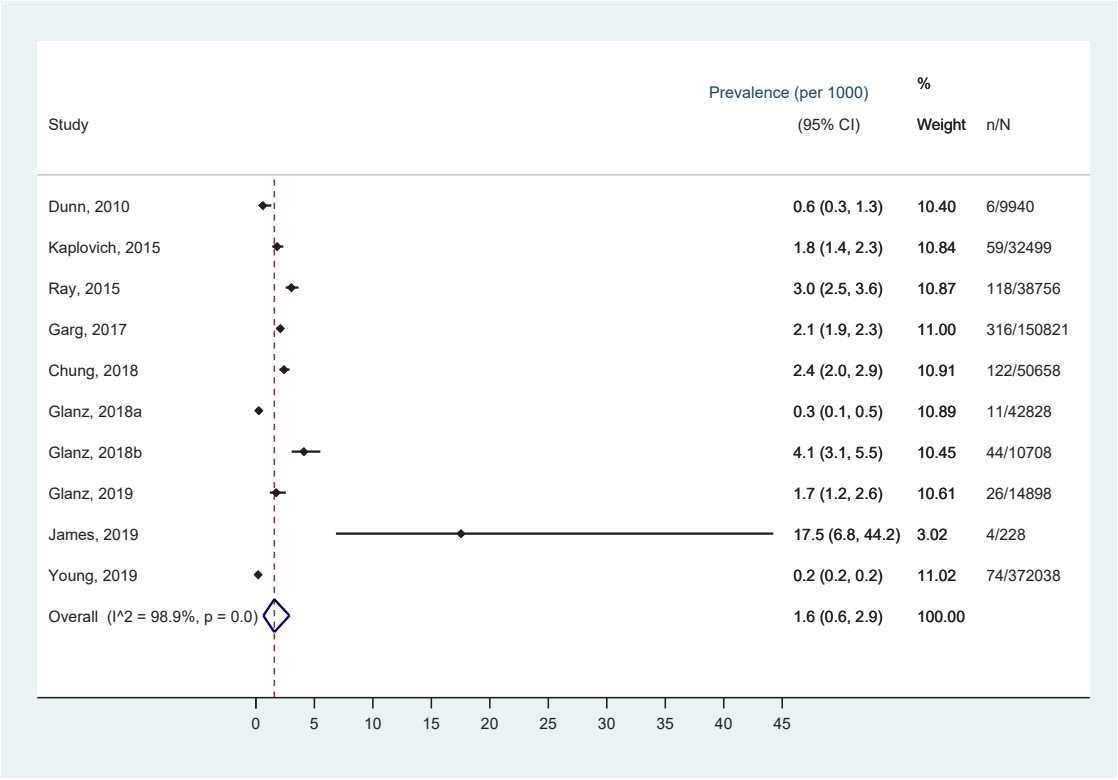

Figure 1 prevalence of fatal opioid overdose (per 1000)

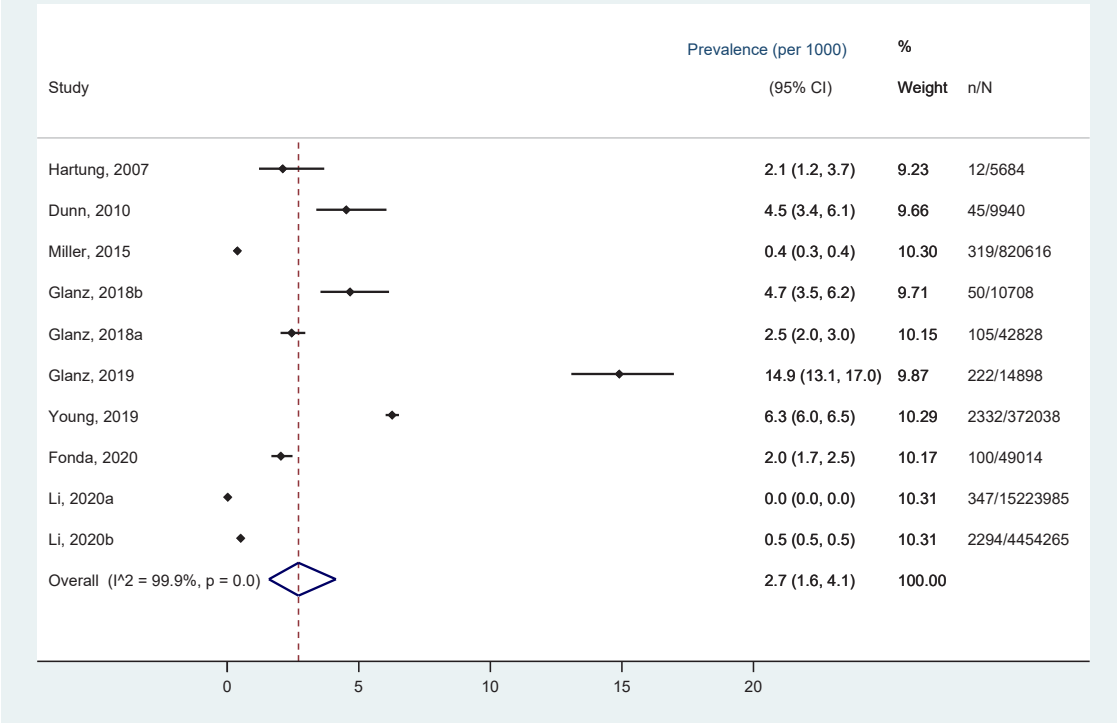

Figure 2 prevalence of non-fatal opioid overdose (per 1000)

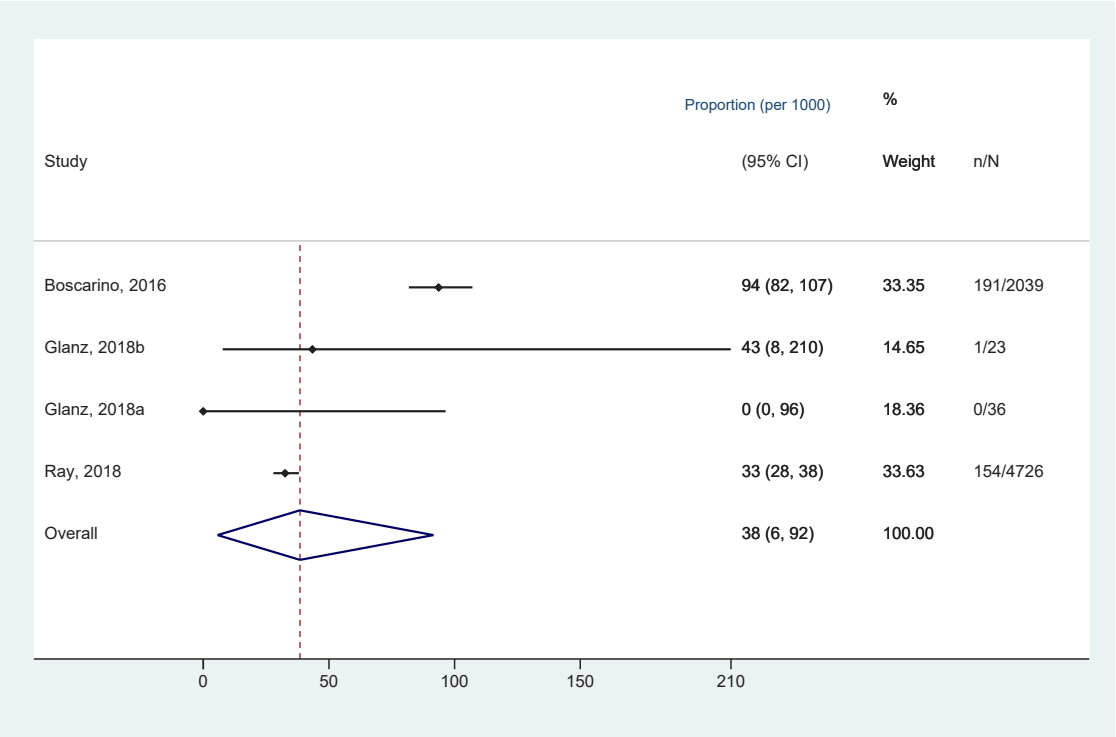

Figure 3 proportion of fatal overdose among previous non-fatal opioid overdose (per 1000)

PAIN MEDICINE 20

Preliminary Study of Vocacapsaicin for Treatment of Pain Following Open Laparotomy Repair of Ventral Hernia

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INTRODUCTION: Significant multi-day postoperative pain following ventral hernia repair (VHR) and other open laparotomy procedures remains an important unmet medical need. The increased focus on postoperative mobilization requires effective management of pain with movement. Vocacapsaicin (formerly CA-008) is a water-soluble prodrug of capsaicin, a well-characterized TRPV1 agonist, that provides durable c-fiber mediated analgesia without numbness or motor weakness. A single treatment with vocacapsaicin via intraoperative injection has been shown to provide post-operative analgesia and reduce opioid consumption (OC) for two weeks following total knee arthroplasty[1] and bunionectomy[2]. We evaluated the safety and efficacy of vocacapsaicin in a randomized, double-blind, pilot study of patients undergoing open laparotomy for VHR.

METHODS: The study was conducted in patients undergoing elective, open VHR with mesh (Rives-Stoppa technique or equivalent) under general anesthesia with full standard-of-care perioperative analgesia including a bilateral rectus block with bupivacaine 75 mg, plus peri-incisional, local anesthetic infiltration with bupivacaine 100 mg and preoperative acetaminophen and celecoxib. (ClinicalTrials.gov: NCT04774328). Eligible patients were aged 18-80 years with BMI up to 40 kg/m2. Patients were excluded if opioid tolerant, allergic to capsaicin, or had a concurrent painful condition. Following IRB approval and written informed consent, patients were randomized 1:1 to placebo or 24 mg of vocacapsaicin delivered in 80 mL (0.3 mg/mL) of aqueous solution. Prior to surgical closure, the test article was infiltrated into (a) the deep midline, peritoneal layer, (b) the mesh/fascia layer (including the virtual space created for the mesh) and (c) the anterior layer. Patients remained in the hospital for 4 days for assessments and collection of blood samples for pharmacokinetic analysis. After discharge, all patients received celecoxib twice daily and acetaminophen or acetaminophen with oxycodone as needed. The primary outcome measures were pain and opioid consumption. Pain was measured using a numerical rating score (NRS) with activity (coughing and ambulation) and at rest. NRS scores were integrated over 96 hours and over 8 days. Cumulative opioid consumption was calculated at 96 hours and at 8 days. Safety endpoints were measured until post-operative day 29, and included vital signs, physical examination, surgical site assessments, neurosensory testing, adverse events, and clinical laboratory evaluations.

RESULTS: A total of 24 patients (mean age 45 years, 71% men, mean BMI 31 kg/m2) were enrolled. Groups were well-matched at baseline. Over the first 4 days, vocacapsaicin 24 mg reduced pain on coughing by 46% (p=0.02, ANOVA) and pain on ambulation by 35% (p=0.07) compared to placebo. Pain at rest was reduced by 21% and cumulative opioid consumption was reduced 26% compared to placebo, but neither result reached statistical significance. There was a trend toward improved analgesia through day 8 in patients receiving vocacapsaicin, but this did not reach statistical significance. There was no difference between vocacapsaicin and placebo in the safety analysis through day 29.

CONCLUSION: This preliminary study suggests that a single dose of vocacapsaicin infiltrated during surgery provides safe, durable and clinically meaningful pain reduction when added to a standard-of-care analgesic regimen that includes a regional block and local anesthetic infiltration with bupivacaine. The results are consistent with previous results in total knee arthroplasty[1] and bunionectomy[2], suggesting that the prolonged analgesic effects of vocacapsaicin injection may prove useful in both soft-tissue and bone surgery. These results provide guidance for additional studies of vocacapsaicin for postoperative analgesia after open laparotomy and other soft tissue procedures.

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PAIN MEDICINE 21

Intraoperative continuous lidocaine infusion for chronic post-surgical pain after breast cancer surgery: a meta-analysis of randomized clinical trials and trial sequential analysis

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INTRODUCTION: Chronic post-surgical pain (CPSP), defined as pain that develops or increases after operation and lasts at least 3 months by the International Association for the Study of Pain (IASP), which is a prevalent and complex clinical issue.[1] Studies have reported that general CPSP prevalence was about 10% to 50% among patients after breast cancer surgery.[2-4] For patients, CPSP has become a major humanitarian and socioeconomic burden because it can lead to poorer sleep quality, more anxiety or depression, and greater healthcare costs, which will reduce the overall quality of life of patients.[5,6] Many studies have explored the possible prevention techniques including regional block (local anesthetic infiltration, intercostal or paravertebral block, and thoracic epidural anesthesia, etc.), oral or intravenous analgesics.[7] Existing evidences showed that I.V. lidocaine may offer a convenient and beneficial strategy.[8] Lidocaine, as an effective and economical local anesthetic, has been commonly used in clinical practice. Although a meta-analysis[9] published in 2017 revealed that lidocaine seemed to attenuate the risk of chronic pain after breast surgery, the evidence was insufficient for the small participant numbers (n=97). Therefore, we conducted this meta-analysis with new RCTs added to assess the effect of perioperative I.V. lidocaine for CPSP in breast cancer patients. The trial sequential analysis (TSA) was applied to determining whether the evidence was reliable and conclusive.

METHODS: Registration We have prospectively registered this meta-analysis on the website of International Prospective Register of Systematic Reviews (PROSPERO: CRD42021272208). The review was reported in accordance the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 2020. Literature search and selection criteria We searched the databases including PubMed, Embase, Cochrane Library, the trial registry database clinicaltrials.gov (up to 3rd September, 2021) with no language restrictions. Search strategies were based on the combination of the following terms: lidocaine, breast cancer surgery, and pain. In addition, we searched Google Scholar, and reference lists of included articles to obtain additional studies. Inclusion criteria were: (1) RCTs; (2) women undergoing breast cancer surgery; (3) patients in the intervention group received I.V. lidocaine, and patients in the placebo group received saline or no treatment; (4) Outcomes include postoperative pain. Studies in which target outcome data could not be extracted were excluded. Outcome The primary outcome was the incidence of CPSP, which was assessed at 3 months after surgery with the binary 'Yes/No' criteria. Statistical methods Data analysis were performed with Review Manager 5.4.1 software and STATA 15.1 software. We pooled dichotomous data using the Inverse Variance method and reported risk radios (RRs) with 95% CIs. Heterogeneity among studies was quantified by the I2 statistic. The fixed effect model was used. All tests were two tailed and $P < 0.05$ was statistically significant. Publication bias was assessed with the Egger's funnel plot and Egger's test. Sensitivity analysis was performed to assess the robustness of the results. Moreover, we performed TSA to calculate the required information size (RIS) using the TSA software v0.9 Beta and construct the monitoring boundaries, aiming to evaluate the validity of evidence.

RESULTS: We identified 341 records and a total of 9 RCTs[10-18] were included in review, and 6 RCTs[10-12,15,16,18] with 544 participants (277 in the lidocaine group, 267 in the control group) contributed to the qualitative analysis of the primary outcome CPSP. Compared with that in the placebo group (37.8%), the incidence of CPSP in the lidocaine group (22.7%) was lower (RR 0.61, 95% CI 0.47 - 0.78; I2 = 14%; P = 0.001). (Fig. 1) The results of TSA showed that the Z curve had crossed both the traditional boundary and TSA boundary. (Fig.2)

CONCLUSION: Intravenous lidocaine infusion in patients undergoing breast cancer surgery could help reduce the incidence of postoperative chronic pain. However, a more precise conclusion should be confirmed by multi-center, large-sample and high-quality studies.

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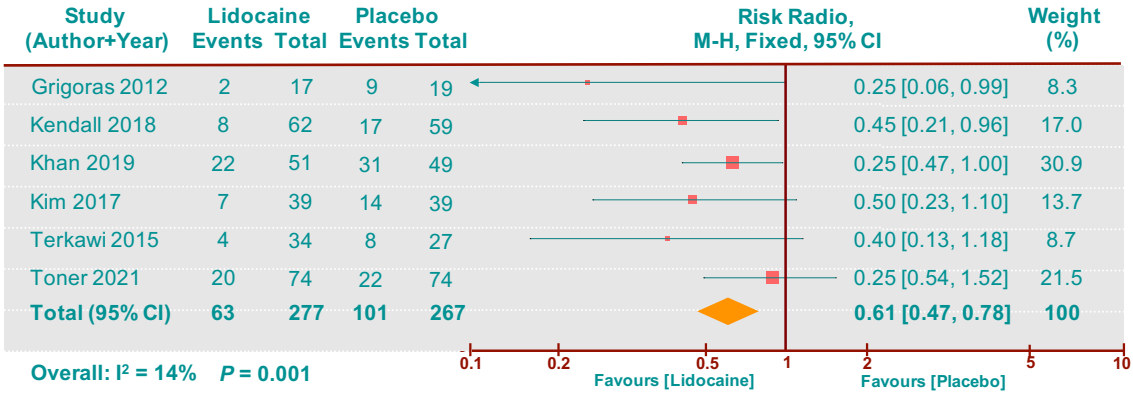

Figure 1

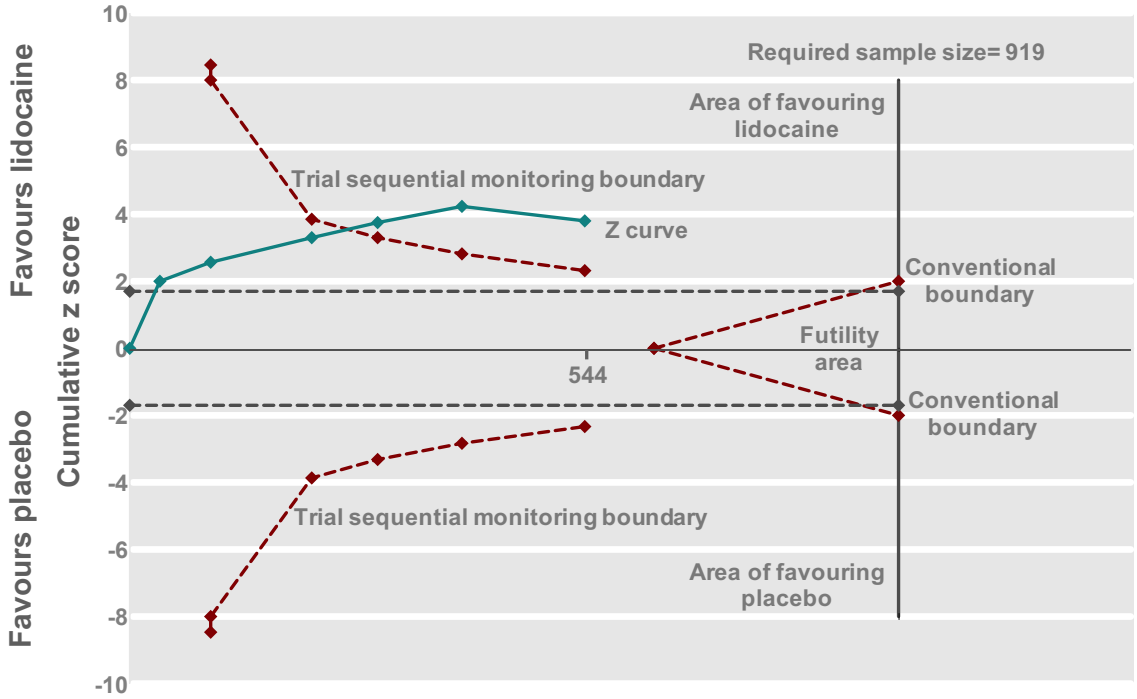

Figure 2

PAIN MEDICINE 22

Dysfunction of the descending pain-modulation system is involved in the augmented pain response after traumatic brain injury

QiLiang Chen[1], David Clark[2]

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INTRODUCTION: Individuals with histories of traumatic brain injury (TBI) exhibit high rates of acute and chronic pain. Such patients may be susceptible to persistent pain after peripheral injuries. Recent laboratory and clinical data suggest dysregulated endogenous pain-modulating circuits could also be involved. Brainstem output nodes of this pain-modulating system, such as rostral ventromedial medulla (RVM) and locus coeruleus (LC), play an important role in regulating pain-related behaviors and nociceptive processing via their projections to the dorsal horn. The pain-modulating function of these descending projections can be controlled by the endogenous opioid tone in the brainstem. Interestingly, endogenous opioid concentration in brainstem regions is altered after TBI, rising the possibility that the dysfunction of brainstem pain-modulating system after TBI is opioid-mediated.

METHODS: These studies employed a recently developed mouse closed head model of TBI and a well-established model of incisional pain. Pain sensitization was quantified using mechanical pain thresholds in cohorts of mice from 1 to 100 days after injuries. Immunohistochemical staining of c-fos was used to identify nuclei involved in the observed pain-related behaviors after naloxone administration.

RESULTS: We observed pain sensitization bilaterally in the hindpaws of mice with TBI lasting up to 10 days. When hindpaw incisions were made in control and TBI mice after recovery of normal pain thresholds, mechanical thresholds in control mice returned to baseline after 7 days, while those animals with prior TBI experienced prolonged sensitization lasting up to 38 days. Furthermore, blockade of central but not peripheral mu opioid receptors (MORs) led to mechanical sensitization in both hindpaws in animals recovered from TBI. Control animals and those with incision alone did not experience changes in their pain thresholds after MOR blockade. Increased neuronal activation, marked by c-Fos staining, was observed in brain regions important for descending pain-modulation, such as rostral ventrolateral medulla and locus coeruleus, in animals recovered from TBI after MOR blockade.

CONCLUSION: Collectively, these data suggest that dysfunctional descending pain-modulation is responsible for the slow resolution of pain after peripheral injury in the setting of TBI. The endogenous opioid system is important for the subsequent recovery of pain sensitivity after TBI but not after peripheral injury alone. Identifying ways to enhance endogenous pain control mechanisms may help those with pain after TBI.

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PAIN MEDICINE 23

Nocturnal Hypoxemia and Sickle Cell Crisis – Oxygen, the Common Factor

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INTRODUCTION: Sickle cell disease is characterized by chronic hemolytic anemia as well as recurrent and extremely painful vaso-occlusive crisis (VOC), the latter of which may lead to acute chest syndrome, avascular necrosis, and organ damage. The VOC phenomenon is considered to occur as the result of capillary blockade at low oxygen saturations, followed by an activation of inflammation and adhesion phenomena further increasing the damage. These painful crises often require medical attention and hospitalization. Pathophysiological triggers that may contribute to VOC include: hypoxia, daytime exertion, waking up earlier with a shortened duration of sleep, daytime exertion, stress, fatigue, exercise, exposure to cold, ingestion of alcohol, airline travel, altitude that exceeds 2,000 ft, infection, malaria, or pregnancy. In patients with SCD, VOC tends to occur most often at night, due to the relative hypoxia as a result of varying degrees of sleep apnea, or due to a trigger the patient may have been exposed to during the day. During sleep, minimum oxygen saturation is significantly lower. This nocturnal hypoxemia is a prelude to VOC.

METHODS: A review of the pathophysiology of sickle cell anemia and triggers of sickle cell pain crisis.

RESULTS: Sickle cell disease is characterized by chronic hemolytic anemia as well as recurrent and extremely painful vaso-occlusive crisis (VOC), the latter of which may lead to acute chest syndrome, avascular necrosis, and organ damage. The VOC phenomenon is considered to occur as the result of capillary blockade at low oxygen saturations, followed by an activation of inflammation and adhesion phenomena further increasing the damage. These painful crises often require medical attention and hospitalization. Pathophysiological triggers that may contribute to VOC include: hypoxia, daytime exertion, waking up earlier with a shortened duration of sleep, daytime exertion, stress, fatigue, exercise, exposure to cold, ingestion of alcohol, airline travel, altitude that exceeds 2,000 ft, infection, malaria, or pregnancy. In patients with SCD, VOC tends to occur most often at night, due to the relative hypoxia as a result of varying degrees of sleep apnea, or due to a trigger the patient may have been exposed to during the day. During sleep, minimum oxygen saturation is significantly lower. Castele, et al,22 performed 5 full-night and 7 daytime studies to examine this further. According to the findings: 'For all patients the mean (+/- SEM) of the median oxygenation values was 93.3% +/- 0.4% during wakefulness and 91.4% +/- 0.8% during sleep. During wakefulness the lowest saturation was 90% +/- 0.5%; during sleep there was a fall in the lowest oxygen saturation to 86.5% +/- 0.9%. In all patients a fall in oxygen saturation was associated with a decrease in respiratory depth without a change in respiratory frequency.' This nocturnal hypoxemia is a prelude to VOC. Another study found that low nocturnal oxygen saturation was 'highly significantly associated with a higher rate of painful crisis.' Other triggers of crises that involve varying degrees of tissue hypoxia may include exercise, fatigue, infection, and exposure to cold. Exposure to cold results in vasoconstriction and delayed transit time, which can trigger a crisis. Subsequent to commercial airline flights, and due to prolonged desaturation at high altitudes, patients with SCD are known to experience complications such as bone pain, splenic infarction, osteonecrosis (avascular necrosis) of the hip, and, in some cases, prolonged crisis resulting in death.

CONCLUSION: Prior to sleep or at bedtime, and especially in the presence of VOC triggers such as daytime exertion, shortened duration of sleep, stress, fatigue, exercise, exposure to cold, ingestion of alcohol, airline travel, altitude that exceeds 2,000 ft, infection, and malaria, Oxygen should be administered by nasal canula at a rate of 1.5-2 liters/minute. This should be delivered by an oxygen cylinder or preferably by a home or portable oxygen concentrator, to maintain an oxygen saturation of > 95%. This can result in a decrease by 85% to 90% in the frequency of nocturnal vaso-occlusive crises. Oxbryta (voxelotor) medication results in a shift of the oxy-hemoglobin dissociation curve and an endogenous increase of oxygenated sickle cell hemoglobin. Patients on Oxbryta whose oxygen saturation is above 93% do not need supplemental oxygen at bedtime. Oxygen should however be utilized in the presence of VOC triggers.

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PAIN MEDICINE 24

Buprenorphine ordering patterns during and after critical illness

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INTRODUCTION: Buprenorphine (BUP) is a partial opioid agonist administered for induction and maintenance treatment of opioid use disorder (OUD).[1] The 2018 PADIS clinical practice guideline did not include recommendations for managing prior to admission (PTA) BUP use during critical illness.[2] The objectives of this study were to describe the clinical characteristics of patients receiving BUP prior to intensive care unit (ICU) admission, characterize BUP and opioid dosing patterns during critical illness, and to evaluate the incidence of BUP prescribing upon hospital discharge and at 3 and 12 months post-hospital discharge.

METHODS: We performed a retrospective electronic medical record review of all patients requiring ICU admission between December 1, 2014 and May 1, 2019 at a single institution after obtaining Institutional Review Board approval. Patients were included if they were ≥18 years of age and were receiving BUP prior to hospital admission. Patients were excluded if they transferred to a different hospital, had a hospital length of stay <24 hours, did not survive to hospital discharge, or were prescribed BUP for chronic pain. Only the first ICU admission for each patient was used. Opioid dosing in the ICU and post-ICU was obtained from a computer-generated report and post-hospital discharge opioid data came from the state-maintained Prescription Monitoring Program. Opioid doses were converted to fentanyl-equivalents (FE). Data are reported as median (IQR) or frequency (%).

RESULTS: A total of 34 patients were included with a median age of 38 [32-46] years and an ICU length of stay of 3 [2-6] days. Most patients (23/34, 68%) required invasive mechanical ventilation for 2 [1-7] days and were admitted to the trauma service (15/44, 44%). The median PTA BUP dose was 16 (12-16) mg/day. BUP was ordered in the ICU for 12/34 (35%) patients who received it PTA, increasing to 24/34 (70%) after transfer to a non-ICU floor. BUP patients received 921 [329-1469] FE/day while in the ICU, decreasing to 168 [19-278] FE/day after ICU discharge to a non-ICU floor. A total of 56% patients were discharged from the hospital on their PTA BUP, while 29% received opioids other than BUP. Among patients receiving an opioid prescription post-hospital discharge, BUP use was 27/30 (87%) at 3 months and 25/26 (96%) at 12 months.

CONCLUSION: 35% of ICU patients prescribed BUP prior to admission received it during their ICU course. Approximately half of patients received a BUP prescription for upon hospital discharge and 25/26 (96%) of patients receiving an opioid prescription were using BUP again at 12 months. Further study is needed to determine the clinical implications of continuing or withholding premorbid buprenorphine in the ICU and to determine the rationale for doing so for differing patient characteristics.

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Table 1: Demographics and ICU Characteristics

Variable	N=34
Age, years	37.5 [32.3-45.8]
Male, no. (%)	17 (50.0)
Race	
White	30 (88.2)
African American	1 (2.9)
Asian	2 (5.9)
Other	1 (2.9)
BMI (kg/m^2)	25.6 [22.9-29.2]
Reason for admission	
Trauma	15 (44.2)
Sepsis	6 (17.6)
Respiratory failure	5 (14.7)
Endocarditis/soft tissue infection/ osteomyelitis	4 (11.8)
Cardiac arrest	2 (5.9)
Overdose	2(5.9)
Home buprenorphine dose (mg)	16 [12-16]
ICU LOS, days	3.0 [2.0-6.2]
Hospital LOS, days	14.0 [6-34.7]
Mechanical ventilation, n (%)	23 (67.6)
Mechanical ventilation, days	2.2 [1.0-6.6]
Discharge disposition, n (%)	
Home or self-care	26 (76.5)
Acute rehabilitation facility	6 (17.6)
Skilled nursing, intermediate care, long-term care	2 (5.9)
Self directed discharge	1 (2.9)

Continuous variables reported as median (IQR) and proportions as number (%)

BMI= body mass index ICU = intensive care unit; LOS = length of stay

Table 2: ICU, Post-ICU, Hospital and Post-discharge Opioid Exposure Data

Variable	N=34
ICU opioid fent equiv (mcg)	2173 [689-8471]
ICU fent equiv/day (mcg)	921 [329-1469]
ICU buprenorphine given n(%)	12/34 (35%)
ICU buprenorphine (mg)	7.5 [3.2-25]
ICU methadone given n(%)	10 (29%)
ICU methadone (mg)	132.5 [31.2-262.5]
post ICU opioid fent equiv	1345 [166-3430]
post ICU fent equiv/day	168 [19.4-277.8]
post ICU buprenorphine given n(%)	24/34 (70%)
post ICU buprenorphine (mg)	16.5 [6.0-75.2]
Post ICU methadone given n(%)	12(35%)
post ICU methadone (mg)	213.8 [160-392.5]
Hospital total fent equiv, mcg	5062 [2192-13,208]
Hosp total buprenorphine (mg)	14.5 [6.2-67.0]
Hosp total methadone (mg)	437.5 [236.2-572.5]
Survival at 3 months	34 (100.0)
Opioid at 3 months post-discharge, n (%)	30 (88.2)[4]
% receiving buprenorphine	26/30 (86.7)
Survival at 6 months	33 (97.1)
Opioid at 6 months post-discharge, n (%)	30/33 (90.9)
% receiving buprenorphine	27/30 (90.0)
Survival at 12 months	33 (97.1)
Opioid at 12 months post-discharge, n (%)	26/33 (78.8)
% receiving buprenorphine	25/26 (96.2)

Continuous variables reported as median (IQR) and proportions as number (%)

Fent equiv =fentanyl equivalents

PAIN MEDICINE 25

Identification of Foramen Ovale with H-figure Fluoroscopic Landmark Improves Treatment Outcomes in Idiopathic Trigeminal Neuralgia

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INTRODUCTION: Radiofrequency thermocoagulation (RFT) of trigeminal ganglion through foramen oval (FO) is an effective way to manage idiopathic trigeminal neuralgia (ITN),[1,2] one of the most common causes of persistent intense orofacial pain with an incidence of 12.6 per 100,000 persons per year.[3] However, the ambiguous fluoroscopic visualization of FO by existing approaches often lead to prolonged procedure time and suboptimal distance between the active RFT needle tip and target branches of trigeminal ganglion. This ambiguity can also lead to inadvertent puncture of the jugular foramen and/or foramen spinosum that causes injury to the internal carotid artery or middle meningeal artery - both can be fatal complications.[4-6] Recently, we developed the 'H-figure' approach as a novel and easily-recognizable fluoroscopic landmark that significantly facilitates the visualization of FO with less fluoroscopic shots and shorter procedure time.[7,8] The H-figure landmark composes of two vertical lines from the medial border of mandible and lateral edge of maxilla, and one horizontal line from the Superior line of Petrous ridge of Temporal bone (S-P-T line). With H-figure fluoroscopic landmark, the FO fluoroscopic view can be easily optimized above the S-P-T line at the center of the H-figure when the medial end of the temporomandibular joint is located midpoint between the lateral and medial borders of mandible.[7] Compared to the classical approach, RFT needle inserted by H-figure method required lower electrical stimulation to elicit paresthesia in affected area after FO puncture,[7] suggesting that the needle tip from H-figure approach is closer to the target trigeminal ganglion branches. However, it remains unclear if RFT performed with H-figure has better clinical outcomes. We now report a 12-month follow-up retrospective cohort study to show that RFT with H-figure fluoroscopic approach is associated with better long-term therapeutic efficacy in managing idiopathic trigeminal neuralgia than the classical approach.

METHODS: In a 12-month follow-up retrospective cohort study, patients with ITN had fluoroscopy-guided RFT of trigeminal ganglion via either classical approach (n=100) or H-figure approach (n=136) to identify FO. The primary outcome was the facial pain measured by Visual Analogue Scale (VAS) at one year after the treatment. The secondary outcomes included the quality of the fluoroscopic FO views, the threshold voltage to provoke paresthesia, the procedure time, the number of fluoroscopic images, and the facial numbness VAS.

RESULTS: Compared with the classical approach group, the H-figure approach group was associated with better long-term pain relief after the procedure, with significantly lower pain VAS scores at 6 months (0.5±0.1 vs. 1.3±0.2, p=0.029) and 12 months (1.0±0.2 vs. 2.0±0.3, p<0.0001). Importantly by 12 months, while the analgesic effect from RFT in the classical group started to wear off (1.1±0.2 at 1 week vs. 2.0 ±0.3 at 12 months, p=0.0013), the analgesic effect was sustained in H-figure group (0.7±0.1 at 1 week vs. 1.0 ±0.2 at 12 months, p=0.5670). Moreover, compared to the classical approach, the H-figure approach provided better fluoroscopic view of FO, lower threshold voltage to elicit paresthesia (0.23±0.01 vs. 0.46±0.01 V, p<0.0001), with shorter procedure time (7.8±0.2 vs. 14.7±0.5 min, p<0.0001), and required less number of fluoroscopic images (4.2 ±0.1 vs. 8.0±0.3 p<0.0001).

CONCLUSION: RFT of the trigeminal ganglion using the H-figure approach is associated with superior longer term clinical pain relief than the classical approach in treating ITN.

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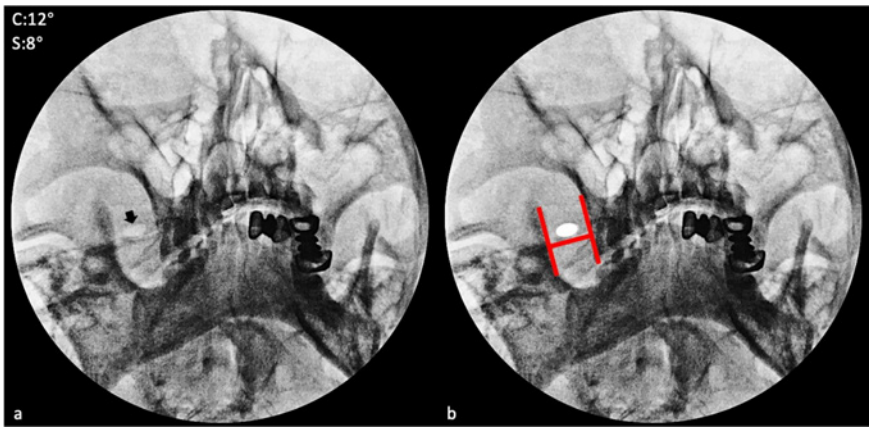

FIGURE 1. The fluoroscopic landmark of the H-figure to identify foramen ovale (FO).

a. The fluoroscopic view of FO, which is indicated by the black arrow. **b.** The H-figure composes of two vertical lines which are the medial border of mandible and lateral edge of maxilla, and one horizontal line which is the Superior line of Petrous ridge of Temporal bone (S-P-T line). The FO marked by the white ovale. C: coronal angle; S: sagittal angle.

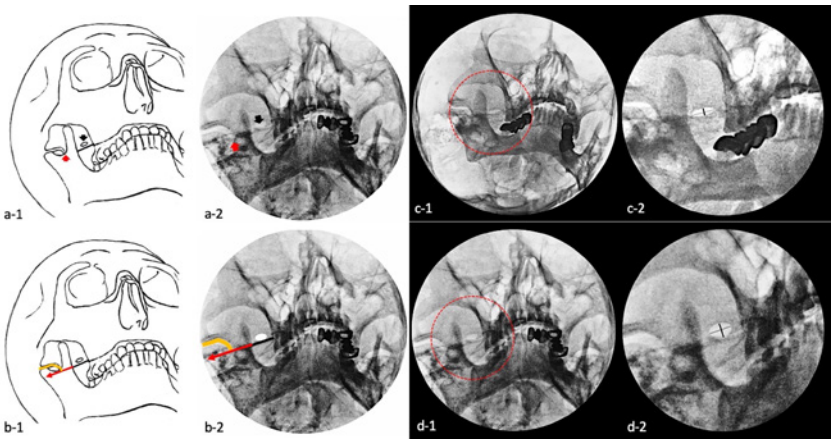

FIGURE 2. Identification of foramen ovale (FO) with medial end of temporomandibular joint and S-P-T line and the grades of FO view with different width to length ratio.

a-1 and a-2 FO is at the center between the medial border of mandible and lateral edge of maxilla when the medial end of temporomandibular joint at the midpoint between lateral and medial borders of mandibular ramus. The red arrow indicates the medial end of temporomandibular joint, the black arrow indicates FO. **b-1 and b-2** The medial end of the temporomandibular joint is on the on the lateral extension of S-P-T line. The red arrow indicates the lateral extension of S-P-T line, the yellow arc marked the medial end of temporomandibular joint, and the white ovale marked FO. **c.** Grade 1 FO view (**c-1**) with width to length ratio of 1/3, and **c-2** is the amplified image of red circle in **c-1**. **d.** Grade 2 FO view (**d-1**) with width to length ratio of 2/3, and **d-2** is the amplified image of red circle in **d-1**. The black line indicates width, and the grey line indicates length.

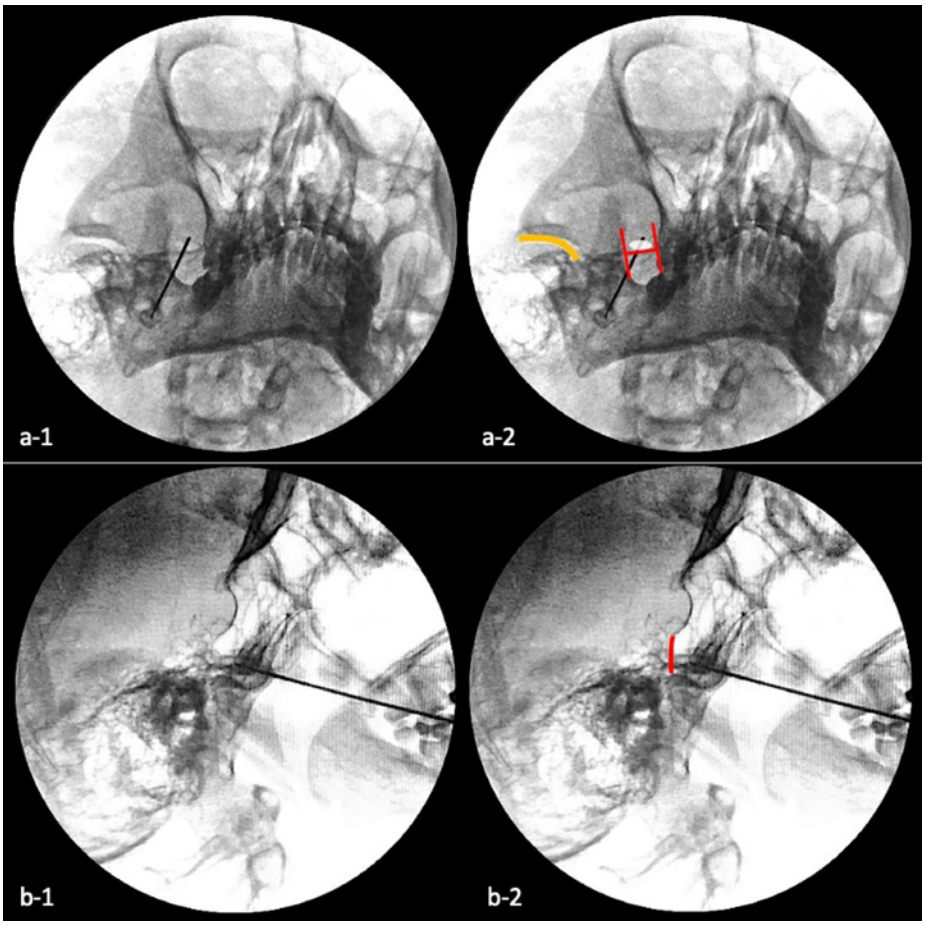

FIGURE 3. Punctuation of foramen ovale (FO) with H-figure approach.

a. The image of FO punctuation (**a-1**) with highlighted H-figure (**a-2**) in oblique projection. The white ovale marked FO, the yellow arc shape indicates the temporomandibular joint, and the red arrow indicates the midpoint between lateral and medial borders of mandibular ramus. **b.** The image showing the position of the needle tip (**b-1**) with highlighted clivus (**b-2**) in lateral projection. The red vertical line indicates the clivus.

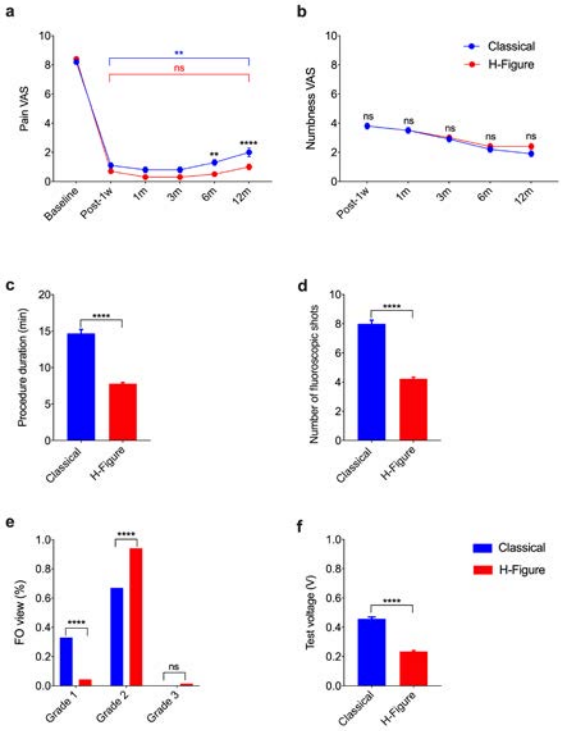

FIGURE 4. H-figure method is superior to classical method in treating ITN with RFT. Compared with to the classical method, H-figure method provided better long-term facial pain alleviation (**a**) without significant difference in facial numbness (b) through taking about half the procedure time (**c**), with approximately half number of fluoroscopic shots (**d**), better view of FO (**e**), and roughly half testing voltage to evoke paresthesia (**f**). Data were presented as mean ± SEM. Analyses were performed using two-way ANOVA with post-hoc Sidak's multiple comparison test (**a**-**b**), unpaired two-tailed Student's *t* tests (**c, d, f**), and two-tailed Chi-square test (**e**). ***p<0.01*, *****p*<0.0001. FO: foramen ovale, RFT: Radiofrequency thermocoagulation, ITN: idiopathic trigeminal neuralgia

SUBSPECIALTY ABSTRACTS

PATIENT SAFETY

PATIENT SAFETY 1

Tumor recurrence following postoperative infection – a systematic review

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INTRODUCTION: The role of post-operative infection on tumor recurrence following tumor resection is not well established in the literature. This is an especially important area to explore as surgical resection remains the mainstay of treatment for many types of solid tumors, such as breast, colorectal, gastric, and ovarian carcinoma. In general, postoperative infection (POI) has been associated with worse morbidity and mortality in patients.[1] The introduction of prophylactic antibiotics has greatly reduced the risk of POI, though rates still vary from 1% to 5% in the month following surgery.[2] We performed this systemic review to investigate the relationship between POI and recurrence of tumors following operative removal.

METHODS: We systematically searched PubMed, EMBASE, and Google Scholar using keywords such as 'cancer', 'tumor', 'neoplasm', 'recurrence', 'surgical site infection', 'sepsis', 'pneumonia', and 'postoperative infection'. We identified twelve articles suggesting a link between postoperative infection and cancer recurrence for breast, colorectal, gastric, and head and neck tumors. We included articles only if the patient had undergone surgical removal of their tumor, and if postoperative infection was identified in patients. Hematologic malignancies were not included in our review. Subjects were patients who underwent surgical removal of their tumor. Exposure was a postoperative infection, including surgical site infection, sepsis, or pneumonia. Controls were patients who have undergone surgical removal of their tumor, but did not develop a postoperative infection. Outcome was recurrence of the tumor.

RESULTS: There were several studies suggesting a positive correlation between postoperative infection and cancer recurrence compared with controls who did not develop a postoperative infection. Three studies suggested a relationship between postoperative infection with breast cancer recurrence and three suggested a relationship with colorectal cancer recurrence. Two studies found that infectious complications following gastric cancer were significantly associated with local and hematologic recurrences of the tumor. Studies for head and neck cancer were more conflicting. One study for head and neck cancer suggested that postoperative infection was associated with a lower recurrence rate, while another suggested no change, and two others suggested a higher recurrence rate.

CONCLUSION: Overall, our systematic review found that infectious complications following surgical resection of a tumor were associated with an increased risk of recurrence of the primary tumor, either local recurrence or systemic recurrence, or both local and systemic recurrence. This association was particularly seen with breast, colorectal, and gastric tumors, with conflicting evidence on head and neck tumors. Overall, however, the morbidity and mortality rate for patients was higher for patients who developed a postoperative infection. Possible explanations include increased local and systemic inflammatory mediators following infection, but cancer-independent mechanisms also need to be considered. Clinical considerations for managing infective complications after cancer surgery include risk stratification (including comorbidities, neoadjuvant and adjuvant therapies), risk-based optimization of perioperative antibiotics, and surveillance of patients after infective complications. More research are needed in this field.

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Author	Cancer Type	Number of patients	Infection number (percentage)	Summary of findings
Indelicato 2007	Breast cancer	580	7.20%	Acute infections were associated with increased local recurrence
Beecher 2016	Breast cancer	229	19.20%	Recurrence increased; HR: 4.94; 95% CI: 2.72-8.95; p<0.001
Murthy 2007	Breast cancer	1065	8.70%	Recurrence increased; HR: 2.52; 95% CI: 1.69-3.77; p<0.0001
Wang 2016	Colorectal cancer	11353	4-29.5%	Recurrence increased; HR: 1.71; 95 % CI: 1.22-2.38; p=0.002
Mirnezami 2011	Colorectal cancer with rectal anastamoses	N/A	N/A	Recurrence increased; HR: 2.05; 95% CI: 1.51-2.8; p=0.0001
Mirnezami 2011	Colorectal cancer with both colon and rectal anastamoses	N/A	N/A	Recurrence increased; HR: 2.90; 95% CI: 1.78-4.71; p=0.001
Han 2020	Gastric cancer	6585	6.20%	Infection → Increased local recurrence (p = 0.044), LN recurrence (p = 0.038) and hematologic recurrence (p = 0.033)
Hayashi 2015	Gastric cancer	502	10.40%	5 year recurrence free survival (RFS) 83% without infection, 58% in infection group; p=0.0000
Ramadan 1992	Head and neck cancer	N/A	N/A	Recurrence rate decreased with POI
Sturgis 1997	Head and neck cancer	144	25%	No difference; p=0.9
Jackson 1990	Head and neck cancer	60	26%	Recurrence 45% with POI and 26% without POI; p>0.05
Rodrigo 1998	Head and neck cancer	158	8.80%	Recurrence 57% with POI and 27% without; p=0.041
Grandis 1992	Head and neck cancer	134	22%	Recurrence increased in patients with POI; p=0.008

Figure 1

PATIENT SAFETY 2

The Impact of a Wellness Intervention on the Burnout Potential of Urm and Female Anesthesiology Residents

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INTRODUCTION: It has been well established through many studies that burnout remains a national issue among U.S physicians with anesthesiologists among those specialities reporting higher than average rates[1]. Furthermore, many studies have established a link between burnout and how targeted wellness interventions can help mitigate feelings of burnout[2]. However, while women and underrepresented minorities (URM) physicians face unique challenges, there has been a paucity of research evaluating burnout rates and mitigating wellness interventions amongst these populations especially in the field of anesthesiology[3]. Thus our objective seeks to investigate whether burnout rates are higher in women and URM anesthesiologists at an academic anesthesiology residency program. We aim to investigate whether an organization-led intervention such as extending morning break time would have any impact on feelings of burnout and/or wellness on residents, as well as the impact that the intervention had on the attendings.

METHODS: After obtaining IRB approval, we implemented phase 1 of our uncontrolled experimental study which involved administering a modified and validated 37 item pre-intervention survey addressing burnout and wellness to anesthesiology residents (n= 49) over a period of 2 months. After this period, a department-wide policy of extending morning breaks from 15 to 25 mins for residents went into effect for six months at the Montefiore Anesthesia Department. Residents were subsequently administered a 47 item post-intervention survey to determine whether feelings associated with burnout and wellness improved. Additionally, we administered a 15 item survey to Montefiore Anesthesiology attendings to assess their feelings on burnout as well as their adjustment to the intervention.

RESULTS: Subjects included in this study were CA-1 (class of 2023) , CA-2 (class of 2022), and CA-3 residents (class of 2021); CA-0 (class of 2024) were excluded since they had not began their clinical anesthesia rotations yet. Results: Baseline n= 49 (98%); F - 33%; M - 67%; URM - 14% | Post intervention n = 41 (82%); F - 37%; M - 63%; URM - 17.5% | Attendings n = 41 (50%); F - 56% M - 44% Pre-intervention, all residents reported higher rates of burnout (55%), job frustration (61%), and job emotional drain (59%). Female residents reported higher levels of burnout (69%) compared to URM students (42.9%). Post-intervention, work burnout decreased in female residents (69% vs 60%); job satisfaction increased in all residents (80% vs 88%) including URM residents (57% vs 86%). Lastly, inadequate break reports decreased (73% vs 63%), and 88% of residents favored the 25 minute morning break extension compared to 36% of the attendings. Nevertheless, both residents (90%) and attendings (66%) reported well above average adjustment to the intervention.

CONCLUSION: Burnout is an important issue that plagues many physicians including Anesthesiologists. Our study showed that, pre-intervention all residents reported higher than average rates of burnout with female anesthesiology residents reporting the highest rates even when compared to URM students. Post-intervention, burnout associated with work decreased in female residents, and ratings of job satisfaction improved among URM residents. Overall, Anesthesiology attendings were less supportive of the concept of extended breaks compared to residents, but did report that a 20 minute break would be acceptable. We hope that this study may shed some light on how specific targeted institutional interventions may mitigate some aspects of burnout and improve wellness. Ultimately, by promoting a culture and environment of compassion and support that can help reduce the negative consequences associated with burnout for physicians, we can advance quality patient care to new levels.

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3. Incidence and Factors Associated with Burnout in Anesthesiology: A Systematic Review. Biomed Res Int, vol. 2017; ID:8648925, 10 pages

THE IMPACT OF A WELLNESS INTERVENTION ON THE BURNOUT POTENTIAL OF URM AND FEMALE ANESTHESIOLOGY RESIDENTS

Pre - intervention	All n= 49 (98%)	F n= 16 (33%)	URM n= 7 (14%)	Post - intervention	All n= 41 (82%)	F n= 15 (37%)	URM n= 7 (17.5%)	Att n= 41 (50%)
Job frustration	61%	75%	42.8%	Job frustration	71%	80%	86%	N/A
Job emotional drain	59%	69%	57.1%	Job emotional drain	59%	67%	57%	N/A
Job burnout	55%	69%	42.9%	Job burnout	59%	60%	43%	41%
Job satisfaction/ fulfillment	80%	87.5%	57.1%	Job satisfaction/ fulfillment	88%	80%	86%	N/A
Healthy coping mechanism	84%	87.5%	87.5%	Healthy coping mechanism	90%	93%	100%	N/A
Healthy work balance	85%	100%	100%	Healthy work balance	85%	80%	86%	N/A
Satisfaction with current wellness initiatives	47%	25%	29%	Satisfaction with current wellness initiatives	32%	40%	29%	24%
Break inadequacy	73%	75%	57.1%	Break inadequacy	63%	53%	71%	N/A
				Favor AM break extension	88%	80%	86%	36%
				AM break extension adjustment	90%	85%	81%	66%
				Preferred break time 20/25/30min	20% 42.5% 37.5%	27% 33% 40%	29% 29% 43%	61% 28% 11%
				Best type of wellness intervention	17% 27% 49% 7%	20% 27% 53% 0%	29% 14% 43% 14%	23% 21% 39% 18%

PATIENT SAFETY 3

When in Rome, speak as the Romans do: determinants of language preference at emergence in non-native English speakers

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INTRODUCTION: In a range of clinical settings, patients with limited English proficiency are at increased risk of experiencing medical complications due to inadequate communication with healthcare providers[1]. This communication gap can present itself in the perioperative setting as there have been cases in which general anesthesia inhibited one language in bilingual patients and prevented proper responses to English commands during anesthetic emergence[2]. Current evidence suggests that hearing a language from multiple different speakers is better for language acquisition than hearing the language from a single source, thus English learners could have better language acquisition in countries where English is the primary language spoken compared to English learners in a non-English speaking environment[3]. In this study we examined whether having a non-English language as the predominant language in the country where English was learned is predictive of a preferential response to a patient's native language rather than to English upon emergence from general anesthesia.

METHODS: After IRB approval, 106 patients scheduled to undergo a general anesthetic for whom English was a second language were enrolled in the study. A questionnaire was given to all participants to collect the following demographic data: age, sex, native language, what age and where English was learned, languages spoken at home, languages that they dream in, self-assessed English proficiency from a scale from 1-10, self-assessed native language proficiency on a scale from 1-10, the planned procedure, and anesthetic gas used. During emergence from anesthesia, the patients were given verbal commands in alternation in their native language and in English to determine any differences in response rates to the two languages. Logistic regression was used to identify whether or not multilingual patients who learned English in an English-speaking country would have a lower rate of preferential responses to their native language during emergence from anesthesia when compared to patients who learned English in non-English speaking countries.

RESULTS: A total of 177 responses were collected from 77 participants who were included in the study. Of the 77 participants included in the study, 39 participants learned English in an English-speaking country and 38 participants learned English in a non-English speaking country. Twenty-nine percent of the responses from participants who learned English in English speaking countries were exclusively to commands in their native language, compared to 44% from participants who learned English in non-English speaking countries (Figure 1). Univariate analysis determined 'where English was learned' to be a statistically significant predictor of preferential response to native language (OR = 1.93, 95% CI = 1.03-3.61). Multivariate analysis was performed to elucidate the contributions of possible covariates which could influence language acquisition: age when English was learned and the language spoken at home (Table 2). Results from the multivariate analysis identified 'where English was learned' to still be a significant factor (OR = 2.05, 95% CI = 1.04-4.04).

CONCLUSION: This study demonstrated that participants who learned English in countries where English is not the primary spoken language have a greater preferential response to their native language during emergence from general anesthesia than subjects who learned English in an English-speaking country.

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Table 1

Summary of demographic information. Note n = sample size.

	n
Participants[a]	77
Non-English languages	21
Countries of origin	25
Sex	
Male	53
Female	50
N/A	3
Where English was learned	
English-speaking country	45
Non English-speaking country	32

[a]106 participants were enrolled, but 77 completed protocol and were included for analysis

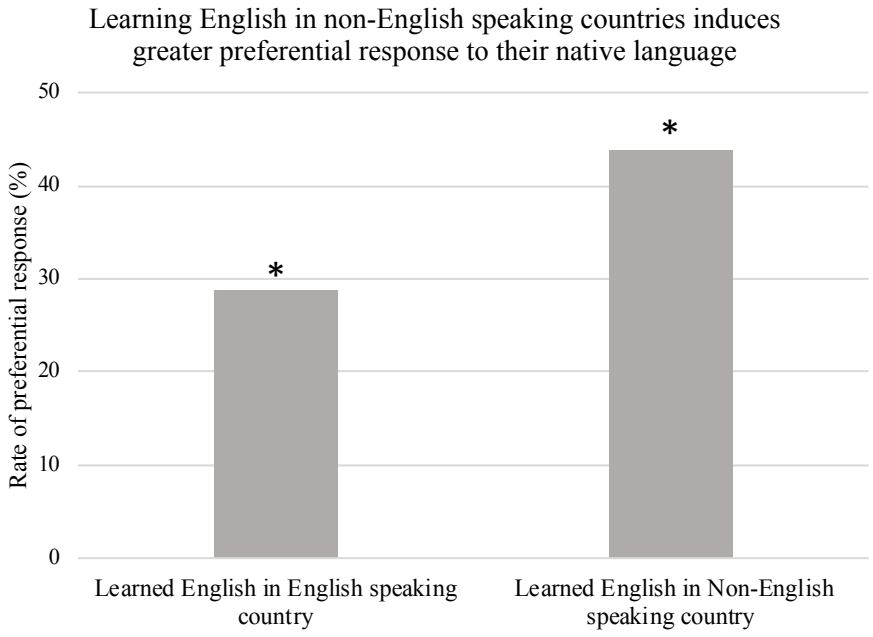
Table 2

Logistic regression for predictors of response to English only or both languages[a].

	Univariate Analysis		Multivariate Analysis	
Factor	p value	O.R. (95% CI)	p value	O.R. (95% CI)
Where English was learned	0.04	1.92 (1.03-3.61)	0.04	2.05 (1.04-4.04)
Age learned English			0.25	1.55 (0.73-3.28)
Language spoken at home			0.0003	3.93 (1.87-8.26)

[a]Response to English only or both languages = 0, Native only = 1. Learned English in an English-speaking country = 0, non-English-speaking country = 1. Age learned English was treated as a binary so that <18 = 0, >18 = 1. Language spoken at home was also treated as a binary so English spoken at home = 0, non-English spoken at home = 1.

Figure 1



PATIENT SAFETY 4

Focused financial incentives to drive quality improvement amongst anesthesiologists: a report on 15 years' experience

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INTRODUCTION: Implementation of best practices to improve quality and safety (Q&S) remains a challenge in healthcare. Focused financial incentives are one approach to nudge clinicians into desired behavior changes, when combined with physicians' professionalism and internal drive to 'do the right thing.' They have been shown to decrease testing in ICUs,[1] increase trainee engagement with quality improvement (QI) initiatives,[2] and decrease the time for finalizing radiology reports.[3] Considerations for using such incentives include incentive size, maintaining clinicians' intrinsic motivation, and considering a reward versus penalty system.[4] We report participation and some results of 15 years of incentives in an anesthesia department as part of a hospital-wide quality incentive program.

METHODS: The design of the Massachusetts General Physicians Organization (MGPO) quality incentive program has been described previously.[5] The incentive system was designed around the framework of prospect theory,[6] starting with a guaranteed reward to all eligible clinicians in the first year before making the reward contingent on meeting specific metrics. Incentives were set at no more than 2% of annual salary. Metrics are selected semiannually and divided into system-wide and department-specific metrics.

Departmental metrics were selected by QI leadership based on organizational quality and safety goals. Some chosen metrics are shown in Figure 1. Metrics were sometimes used to encourage continued improvement over several measurement periods. For example, the target for difficult airway documentation was initially set at 50%, then at 80%, and finally at 90%. Targets were set based on baseline data whenever possible and to be attainable as stretch goals with clinician behavior change.

RESULTS: Participation amongst anesthesia clinicians from the start of the program to now has remained high. Recent individual metrics (e.g., training in time-outs or disclosure of medical errors) reached 96% completion, suggesting high levels of engagement. Metrics repeated to promote continued improvements were successful in doing so; difficult airway documentation improved from 82% to 100% over 3 measurement periods. Intraoperative glucose monitoring showed improvement from 57% to 73% of appropriate cases over 2 periods. Other results are in Figure 1.

CONCLUSION: A quality incentive program is a sustainable way to increase engagement with Q&S goals. By setting small incentives on easily measured and applicable metrics, behavior can be changed. These financial incentives supplement educational efforts, workflow changes, and system changes to create safer practices. The attainable goals and meaningful financial incentives have maintained a high level of clinician engagement. The flexibility of designing new metrics semiannually allows the program to remain relevant. QI metrics have brought awareness to clinical practice changes and provided an avenue for educational initiatives, improving our healthcare system.

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Figure 1: Select metrics and results

Individual Metrics			
Year	**Metric**	**Eligible Clinicians (#)**	**Engagement (%)**
2010	Glucose Monitoring Training	123	100%
2015	Emergency Manual Training	164	79.1%
2017	Defibrillator Training	154	95%
2018	EEG Monitor Training	154	100%
2021	Emergency Manual Training	167	96%
2021	OR Timeout Audit	167	96%
2021	Apology and Disclosure Training	167	96%
Departmental Metrics			
Year	**Metric**	**Target (%)**	**% Cases Meeting Metric**
2011	Intraoperative Glucose Monitoring	57% (baseline)	73.1%
2011	Airway Documentation for General Anesthesia Cases	75%	84%
2012	Repeat Airway Documentation for General Anesthesia Cases	90%	90%
2011	Difficult Intubation Documentation	50%	82.5%
2012	Repeat Difficult Intubation Documentation	80%	97%
2013	Anesthesia Procedure Time Out	75%	88.7%
2014	Intraoperative Handoff Checklist Documentation	70%	74.7%
2015	Blood Transfusion Documentation	85%	94.4%
2017	Median Tidal Volume <10mL/kg ideal body weight	75%	96%
2018	Post-Operative Nausea/Vomiting Prophylaxis	70%	84%
2018	Hyperglycemia Treatment and Re-Check	80%	93%
2018	Multimodal Analgesia in ERAS Patients	70%	85%
2019	Intraoperative Handoff Documentation	40%	46%
2019	Hemoglobin Monitoring in Blood Transfusion Patients	60%	80%

PATIENT SAFETY 5

Crisis training in non-operating room anesthesia (NORA) locations: What do front-line staff need?

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INTRODUCTION: More than 30% of anesthetic cases take place in non-operating room anesthesia (NORA) settings,[1,2] which are often managed by interprofessional care teams with highly specialized roles (e.g., radiology technicians, anesthesia clinicians). Lack of familiarity between teams and diverging expectations about roles and responsibilities can make the management of adverse events and crises especially challenging in NORA.[3,4] Following an adverse event involving a pediatric patient undergoing a computed tomography (CT) scan, our institution recognized the need for urgent intervention, and interprofessional education on emergency preparedness was requested by the hospital safety leadership. This needs-assessment was developed to encourage front-line staff to weigh in on needs and preferences prior to designing a team training module.

METHODS: A questionnaire was developed in an iterative process by anesthesia providers with expertise in NORA. We asked about respondents' personal experience with adverse events affecting NORA patients and preferences for education relevant to NORA events. The final questionnaire contained eight closed questions and two free-text questions. It was distributed via email to the Anesthesiology and Radiology departments at Dartmouth-Hitchcock Medical Center. A descriptive analysis of the data collected was performed.

RESULTS: A total of 64 responses were received (36 anesthesia, 28 radiology, see Table 1). The most witnessed adverse events affecting NORA patients involved airway/ventilation problems (56%) and cardiac arrest/hemodynamic instability (28%). Only 21 (33%) respondents had not experienced an adverse event. Airway/ventilation adverse events were reported as the most worrisome by both types of providers. The most frequently cited challenges of NORA reported by anesthesia clinicians were remote location (42%), infrequent exposure and unfamiliarity (31%), and lack of NORA staff support (25%) (Figure 1). When asked what resources and/or curricula would be most helpful in improving safety of anesthetized patients in non-OR locations, on-site crisis simulation was favored by respondents (44%) over cognitive aids (38%), written hand-outs (33%) and video tutorials (31%). The preferred way of learning differed by department, with radiology personnel most often choosing simulation (50%) and anesthesia clinicians most often choosing cognitive aids (50%). Very few participants were in favor of no changes needed (11%). Eighteen (28%) of respondents provided additional comments, which provided further insight into preferred educational content (Table 1).

CONCLUSION: Results from this survey support a need to train healthcare personnel in NORA crisis management, especially for airway events. Given an overall favorable view of simulations at our institution and recent evidence supporting their effectiveness,[5] we prioritized creation of a "lost airway" scenario for in situ simulation training. Taking into consideration that the preferred mode of learning differed among groups, we are simultaneously developing cognitive aids and a tutorial video. With NORA procedures becoming more prevalent and increasingly complex,[4] interprofessional team education and collaboration is important to proactively address common crisis scenarios and to achieve the best possible outcomes for our patients.

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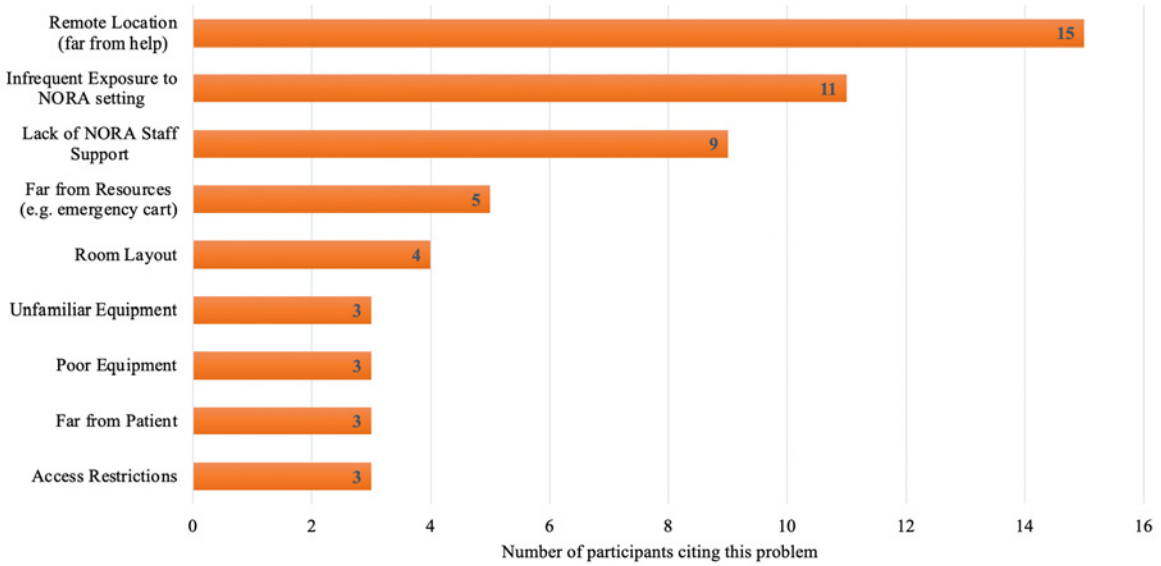
Table 1: Cross-departmental questionnaire results

	Anesthesia **N = 36**	Radiology **N = 28**	Total **N = 64**
Adverse Event Experienced in NORA			
Airway/ventilation	23 (64%)	13 (46%)	36 (56%)
Cardiac arrest, hemodynamic instability	12 (33%)	6 (21%)	18 (28%)
Anaphylaxis, allergy, drug reaction	2 (6%)	1 (4%)	3 (5%)
Other	3 (8%)	3 (11%)	6 (9%)
None	11 (31%)	10 (36%)	21 (33%)
Most worrisome adverse event in NORA			
Airway/ventilation	24 (67%)	9 (32%)	33 (52%)
Cardiac arrest, hemodynamic instability	9 (25%)	7 (25%)	16 (25%)
Anaphylaxis, allergy drug reaction	1 (3%)	3 (11%)	4 (6%)
Other	1 (3%)	1 (4%)	2 (3%)
None	2 (6%)	9 (32%)	11 (17%)
Preferences for new curriculum			
1–2-page written summary	11 (31%)	10 (36%)	21 (33%)
5-minute video orientation	7 (19%)	13 (46%)	20 (31%)
On-site crisis simulation	14 (39%)	14 (50%)	28 (44%)
Cognitive aids	18 (50%)	6 (21%)	24 (38%)
No change	4 (11%)	3 (11%)	7 (11%)
Example quotes from respondents	“It's imperative for the staff in all NORA locations to be educated in anesthesia emergencies” - Anesthesia		
	“As non-anesthesia providers/non-RN's in during a crisis, it would be good to know how we can help (run for supplies, call for help) or just get out of the way" - Radiology		
	“Having a dedicated NORA team for various sites and requiring mock codes every few months would be best” - Anesthesia		
	“The more frequently we can run scenarios in NORA locations, the better! There are many unique things about each department that are useful to know” - Anesthesia		
	Most MRI/CT Techs get minimal training on airway issues when anesthesia is involved. [Provide] training on basic airway management more than every two years” - Radiology		

Figure 1: Factors that make NORA locations stressful for Anesthesia clinicians



*Answers from free response questions were assigned to appropriate categories, listed above

PATIENT SAFETY 6

Non-OR Anesthesia (NORA) Quality Improvement and Patient Safety: Assessment of Cognitive Aid Need Amongst Anesthesiology and Non-Anesthesiology Professional Staff in a High Volume Academic Center

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[1]Massachusetts General Hospital, Boston, MA

INTRODUCTION: As procedural volume continues to increase in the Non-Operating Room Anesthesia (NORA) space there has been concomitant increase in critical crisis and Quality assurance (QA) events.[1,2] In recognition of the benefits provided by cognitive aids in the perioperative setting, Emergency Manuals (EMs) are highly integrated in our operating rooms and associated perioperative areas.[3-6] As part of a quality improvement (QI) initiative EMs were more recently introduced into our NORA procedure rooms and recovery areas and have not yet had a formal familiarization campaign. As the motto for cognitive aid implementation is "create, familiarize, use, and integrate"[7] we sought to assess baseline familiarity with and need for training across role groups in NORA.

METHODS: As part of a QI project to increase patient safety we have rolled out EMs in NORA. While our anesthesia department was made aware that EMs had became available in NORA through email, large-scale education for non-anesthesiology role groups has not yet been incorporated. We sought to evaluate baseline familiarity through survey (REDCap) of anesthesia staff as well as proceduralist attendings, advanced practice providers and trainees, nursing staff and technologists from the areas with the highest patient volume: Interventional Radiology and Endoscopy departments. We surveyed data regarding use of, familiarity with, and feelings towards EMs as well as individual experience with self-reported emergencies in NORA. Baseline data is presented, and chi-square analysis used.

RESULTS: 122 staff members completed the survey for a response rate of 15.2%. 41.8% of respondents reported experiencing at least one emergency in NORA in the last 12 months. Though 79.5% of respondents agreed or strongly agreed that cognitive aids are helpful during emergencies, only 11.6% (25.4% of those experiencing an emergency) reported using EMs during an offsite emergency. There was no difference in perceived usefulness of EM between anesthesiology clinicians and offsite staff (76.6% vs. 81.3%, p=0.53); however, anesthesia clinicians were more likely to use EMs in an emergency (40% vs 11.5%, p=0.020). Anesthesia clinicians were more aware of EM presence in NORA (72.3% vs 40%, p=0.0005) and were more likely to be trained in EM use (66.0% vs 30.7%, p=0.0001). Non-anesthesia clinical staff was more likely to agree or strongly agree with the usefulness of formal EM presentation in NORA (52.2% vs 77.0%, p=0.005).

CONCLUSION: Though most clinical staff in NORA recognize cognitive aids as useful during emergencies, EMs are not routinely used in NORA. To increase EM familiarity and use, formal education should include all role groups as they are key members of a crisis management team. There is an understandable lag in familiarization and use of EMs among non-anesthesia staff and therefore a pilot program to spread awareness of and familiarize those staff members represents an important, and desired, future direction.

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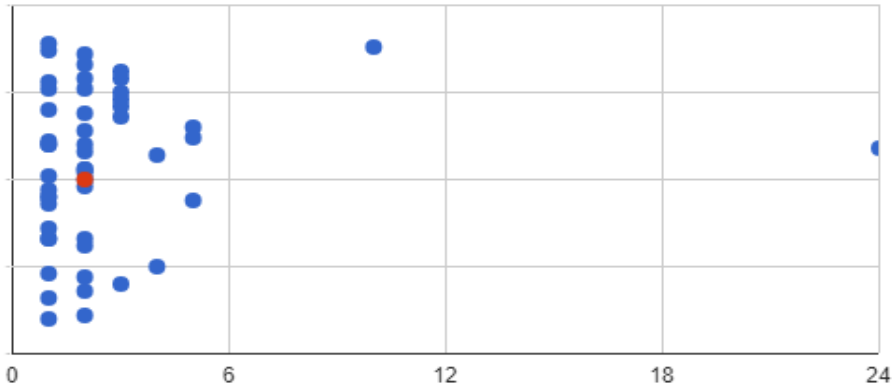
Table 1: Respondent breakdown by role group

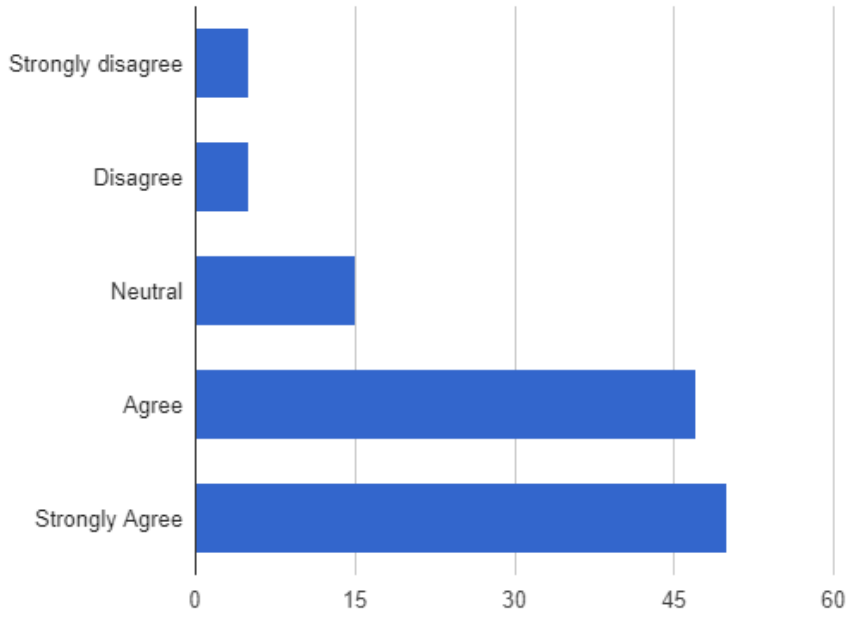
Role Group	Number (%)
Anesthesia Attending	32 (26.2)
Nurse	27 (22.1)
Anesthesia Resident/Fellow	19 (15.6)
Anesthesia CRNA	13 (10.7)
Technologist	12 (9.8)
Proceduralist Attending	11 (9.0)
Proceduralist Resident/Fellow	2 (1.6)
Total	122 (100)

Figure 1: Self-reported emergencies per respondent experienced in the last 12 months.



*Staff only included if they had experienced at least one emergency (N=51, mean =2.61).

Figure 2: Response distribution to "Cognitive aids/written reminders, such as an emergency manual, are helpful resources are useful during times of crisis/emergencies."



PATIENT SAFETY 7

A comparison of two different foreign language interventions for non-native English-speaking patients during emergence from general anesthesia

Ryuji Arimoto[1], David Glick[2]

[1]The University of Chicago Pritzker School of Medicine, Chicago, IL, [2]University of Chicago, Chicago, IL

INTRODUCTION: Verbal commands are often used to determine the timing of extubation following a general anesthetic. Case reports suggest that bilingual patients can experience temporary inhibition of a language from general anesthesia[1,2]. Previous work from our lab has demonstrated that when native language commands are given using either voice recordings from family members or translation software (Google Translate), patients showed a preferential response to their native language compared to English commands in both scenarios. In this study we compare the relative efficacy (response rates) of these two language interventions.

METHODS: After obtaining informed consent, 96 bilingual patients receiving general anesthesia were enrolled for the first study using commands recorded by family members, and 106 patients were enrolled in the second study where the Google Translate app was used to deliver the commands. In the first study, the family members of patients recorded the following commands in their native language: 'open your eyes', 'squeeze my finger', and 'wiggle your toes'. During anesthetic emergence, verbal commands were given in alternation every thirty seconds between English by a research assistant and the participants' native language from the recordings. In the second study, both native language and English commands were given in the same alternating fashion using the translation software. The response rates to native language commands and the mode in which they were given were compared using logistic regression.

RESULTS: Of the 202 enrolled participants, 166 provided responses and were included in the study. Univariate analysis predicting which mode of communication would elicit a native language response to at least one of the three commands showed the family member voice recordings elicited a response from patients more frequently than the computer-generated commands delivered using the translation app (p=0.02). When comparing the response rate to all three commands, the response rate to the family recordings was higher as well (p=0.001).

CONCLUSION: During anesthetic emergence, recordings of commands made by patient family members were shown to be more effective at eliciting a response to native language commands than computer generated instructions in the patients' native tongue. Although voice recordings have higher response rates, it can be challenging to obtain these recordings from family members in the preoperative area for every bilingual patient. Further work is needed to develop an approach that optimizes response rate and efficiency.

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Table 1

Summary of demographic information.

	Study 1	Study 2
Participants[a]		
Total	96	106
Included for analysis	89	77
Countries of origin	29	25
Non-English languages	20	21

[a]Participants that were transported to the PACU (post-anesthesia care unit) before commands could be given were excluded from analysis

Table 2

Summary of native command response rates. Note. Study 1 and 2 investigated use of voice recordings and Google Translate respectively.

	Study 1	Study 2
Participants that responded to native commands	87	67
Participants with no response	2	10
Total native commands with response	222	127
Total native commands with no responses	45	104

Table 3

Univariate analyses predicting which foreign language intervention would elicit a native language response.[a]

Target of analysis	p value	Odds Ratio (95% CI)
Response to at least 1 of 3 commands	0.001	4.04 (2.68-6.10)
Response rate for all commands	0.02	6.49 (1.38-30.63)

[a]Response to commands (dependent variable) was coded as 0 = no response, 1 = response to native command. Foreign language intervention (independent variable) was coded as 0 = Google Translate, 1 = voice recordings.

Figure 1

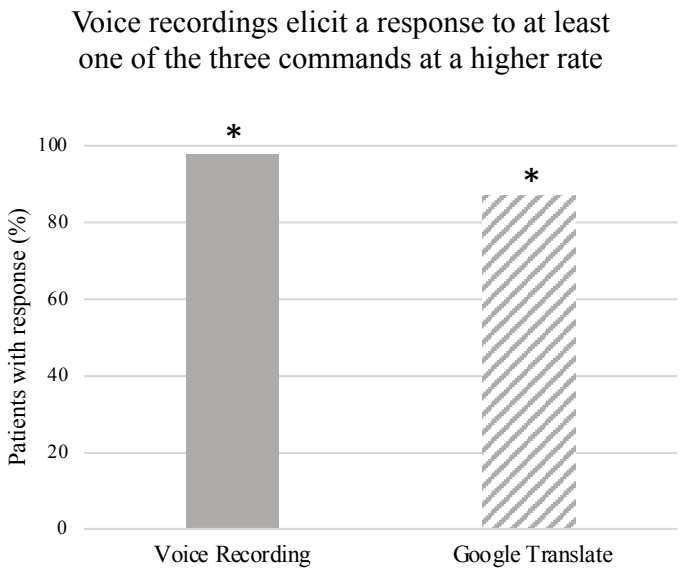
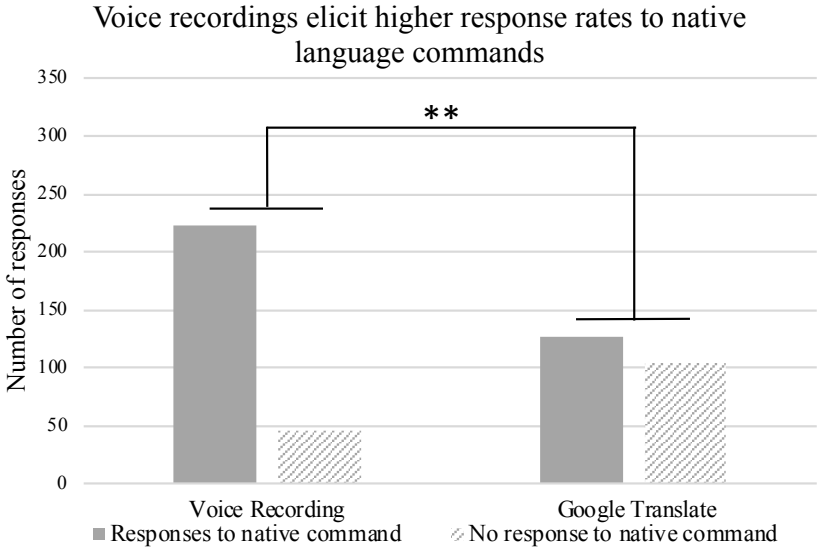


Figure 2



PATIENT SAFETY 8

Continuous Operating Room Patient Vital Signs Enhance the Prediction Power for Postoperative Complications

Megan Anders[1], Shiming Yang[1], Peter F Hu[1], Miranda Gibbons[1], Yi-Mei Kuo[1], Peter Rock[1]

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INTRODUCTION: An improved ability to predict postoperative complications (POC) would allow clinicians to target interventions to improve outcomes. Machine-learning methods using high fidelity intraoperative vital signs (VS) might facilitate development of robust predictive analytics. The authors hypothesized that VS analysis would enhance prediction of the risk of POC.

METHODS: The University of Maryland Department of Anesthesiology maintains a 'Perioperative Data Warehouse (PDW)' that contains anesthesia-specific data, relevant data from patients' electronic patient record, and high fidelity VS. After IRB approval, data from the PDW was extracted for adult patients undergoing surgery at the University of Maryland Medical Center from 2016-19 with admission on day of procedure, excluding cardiac and liver transplant surgery. We analyzed the last hour of operating room high-resolution VS (VS: HR, SpO2, RR, BP collected at a rate of 0.5Hz and ECG, PPG waveform collected at 240Hz), patient demographics, and preoperative laboratory values (DEMO: age, ASA class, BMI, albumin, bilirubin, and creatinine). Models were developed for prediction of POC using VS and DEMO and the Gradient Boosting Tree technique. POCs included: 7-day post OR Mortality (MORT); postoperative Ventilation Support (VENT); postoperative acute kidney injury (AKI), anemia (ANEM) and return to the OR (RtOR). Highly linearly correlated variables were removed. 10-fold cross-validation and the area under the receiver operating characteristic curve (AUROC) with a 95% confidence interval (CI) were used to assess a model's performance. The SHAP (SHapley Additive exPlanations) value was used to quantify variables' importance in models.

RESULTS: The rate of POCs were (%=Incident/Total): MORT (0.11%=15/14,100), VENT (0.4%=51/12,838), AKI (5.2%=156/3,019) ANEM (1.77%=120/6795) and RtOR (0.32%=45/14,100). AUROCs of three types of models (DEMO, VS, DEMO+VS) were MORT (0.65, 0.87, 0.89), VENT (0.76, 0.87, 0.90), AKI (0.95, 0.78, 0.94), ANEM (0.73, 0.66, 0.77) and RtOR (0.56, 0.68, 0.69) respectively (Table 1). The SHAP values show that VS variables rank top contributions in those predictions. For example, higher entropy (instability) of pulse pressure has a higher impact on the odds of VENT than other DEMO variables such as ASA class (Figures 1 and 2). In general, for VS models, more than 400 VS related features were evaluated and 20-30 variables were selected in the final model.

CONCLUSION: High fidelity analysis of VS can enhance the prediction of POCs. For some outcomes (MORT, VENT and RtOR), the high resolution VS model achieved a better prediction power than the DEMO only model, which shows the feasibility of real-time machine-learning models for predictive analytics in the field of anesthesiology. Some complications, such as ANEM, are better predicted by DEMO+VS than by either set alone. Heterogeneity of etiology for some complications, such as for RtOR, may limit predictability as a single outcome.

Table 1. AUROCs with 95% CI of models using variables from DEMO, VS and DEMO+VS for five outcomes. * Indicate the significant difference between VS and Demo based model AUROCs and + indicate the significant difference between Demo + VS and Demo based model AUROC results

	DEMO	VS	DEMO+VS
MORT	0.65 (0.59-0.70)	0.87 (0.82-0.92)*	0.89 (0.86-0.92)$^{+}$
VENT	0.76 (0.73-0.79)	0.87 (0.84-0.89)*	0.90 (0.88-0.91)$^{+}$
AKI	0.95 (0.94-0.96)	0.78 (0.76-0.80)	0.94 (0.93-0.96)
ANEM	0.73 (0.71-0.75)	0.66 (0.63-0.69)	0.77 (0.75-0.80)
RtOR	0.56 (0.51-0.60)	0.68 (0.63-0.72)*	0.69 (0.65-0.73)$^{+}$

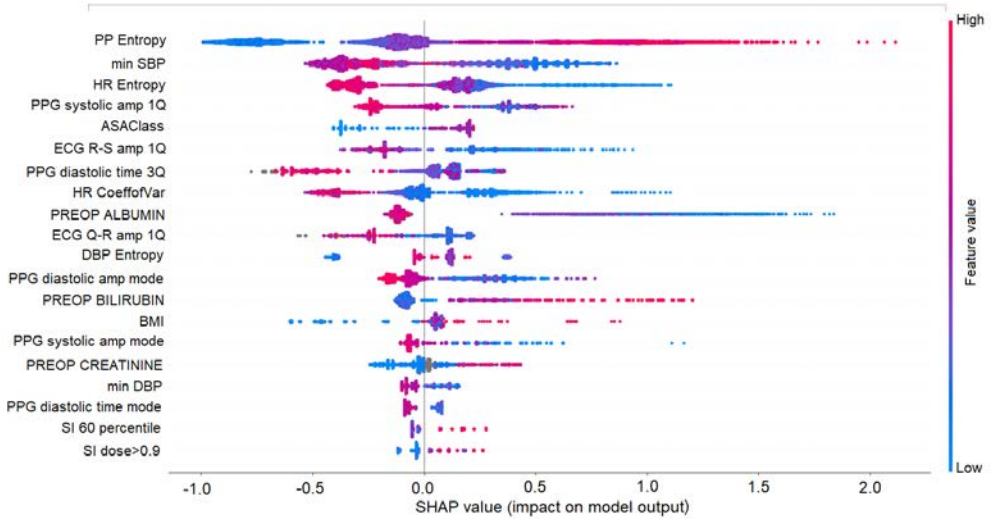

Figure 1. Rank of DEMO and VS variables showing their impact on the model output in predicting VENT. Each feature's values are represented in color ranging from red to blue (high to low). The x axis shows their corresponding SHAP values. A larger SHAP value stands for higher log odds ratio that a variable's value added to the prediction.

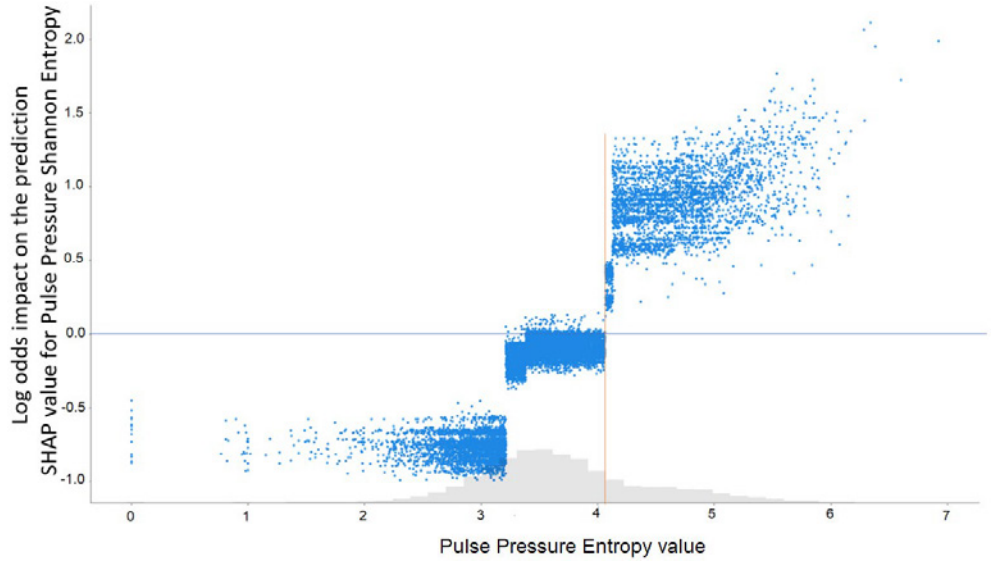

Figure 2. Scatter plot of each pulse pressure entropy value and its impact on the prediction of VENT. Higher PP entropy has higher impact in predicting positive VENT outcome.

PATIENT SAFETY 9

Evolution of Opioid-Free Anesthesia Practice Using Real World Data

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INTRODUCTION: Most surgical patients in the US receive opioids perioperatively[1]. Opioids have side effects and are variably associated with increase postoperative opioid requirements[1-5]. Persistent opioid use after surgery in opioid naïve patients is more frequent than previously believed[6-8]. Based on this and evidence of benefits from enhanced recovery programs[9], Seattle Children's has pursued a multiyear effort to reduce opioids. Initial efforts at opioid-free anesthesia were focused on the ambulatory surgery center[10], but have now evolved to encompass higher acuity surgery at the hospital.

METHODS: This prospective, observational cohort quality improvement (QI) project was deemed to not be research by Seattle Children's IRB. Seattle Children's practices lean principles (standardized practice, waste minimization, visual tracking, staff engagement, and continuous improvement). Plan-Do-Study-Act (PDSA) cycle speed was enhanced by (1) rapid adherence to standards via protocol insertion into electronic anesthesia records and (2) immediate access to electronic perioperative data and analytics through AdaptX® (Seattle, WA). Multimodal analgesia including regional anesthesia replaced opioids. Data for statistical process control (SPC) chart analyses were extracted from Seattle Children's Data Warehouse for all surgeries at the main campus hospital (10/1/15-10/31/21). Standard SPC rules were used to identify special cause variation[11]. The primary outcome was the incidence of opioid-free anesthesia. Secondary outcomes included mean maximum post anesthesia care unit (PACU) pain score, PACU rescue rates of opioids and antiemetics, and mean PACU length of stay (LOS). Observational periods were divided into 4 phases based on significant changes in opioid-free anesthesia incidence. Phase 1 (10/1/15-3/31/18) was pre-intervention baseline. Phase 2 (4/1/18-2/28/19) was observation with no active intervention (spread by socialization only). Phase 3: (3/1/19-12/31/20) involved public communication and data display (passive replication). Phase 4 (1/1/21-10/31/21) included launching serial multidisciplinary QI teams completing PDSA cycles using real-time data monitoring and electronic implementation of opioid-free protocols (active replication).

RESULTS: A total of 57,453 surgeries occurred (phase 1: 26,732; phase 2: 10,190; phase 3: 13,792; phase 4: 6,739). Primary and secondary outcomes are displayed (see figure). The incidence of opioid-free anesthetic increased (phase 1: 14.9%, phase 2: 26.2%, phase 3: 39.7%, phase 4: 51.2%). There was no change in maximum PACU pain score. PACU rescue opioid (phase 3 &4) and antiemetic rates (phase 3) improved. Mean PACU LOS initially increased (phase 2) and then decreased (phase 4).

CONCLUSION: Opioid-free anesthesia is possible for high acuity surgeries without adversely impacting post-operative pain. Work to expand opioid-free protocols to additional higher acuity surgeries and procedures continues.

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Fig. 1

PATIENT SAFETY 10

Optimizing neuromuscular Blockade management for Improving Patient Safety and Perioperative Outcomes (OBISPO): quality improvement initiative - pilot experience

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INTRODUCTION: Residual neuromuscular blockade (NMB) is an independent risk factor for postoperative pulmonary complications¬π, to a great extent preventable by avoiding residual NMB after general anesthesia¬≤. Patients with preserved muscle strength may foreseeably experience an enhanced recovery after major surgery, with fewer respiratory complications. Avoiding residual paralysis after general anesthesia warrants: judicious administration of muscle relaxants, quantitative NMB monitoring and pharmacological reversal as required. However, blind administration of paralytic and reversal drugs and subjective assessments are still a widespread practice despite their lack of sensitivity to rule out residual paralysis.¬≥ The OBISPO initiative intends to address this practice gap procuring interventions to facilitate the adoption of safer standards based on evidence.

METHODS: OBISPO consist of interventions aimed to enhance patients recovery after major surgery by improving the current management of NMB at our institution. The pilot phase focused in all patients destined to fast-track extubation in the postoperative care unit (PACU) after elective cardiac surgery. Practice change implementation and its impact are periodically assessed following outcome, process, and balancing measures in Plan-Do-Study-Act (PDSA) cycles.¬‚ The main outcome is the incidence of residual NMB after general anesthesia, defined as a train-of-four ratio TOFR < 0.9 by electromyography or acceleromyography on arrival to PACU. The process measured is the percentage patients per cycle who had a TOFR assessed and recorded in PACU; TOFR assessments in at least 70% of patients was convened as minimum acceptable level of adherence (fidelity). Balancing measures are the dosing of NMB and reversal agents, PACU length-of-stay, time-to-extubation, incidence of adverse respiratory events, and staff perceptions. Run charts of the outcome and process measures are analyzed monthly by the OBISPO team for adjusting interventions, which consist of: 1) Educational sessions for anesthesia staff, trainees and nurses; 2) Cognitive aids (Fig. 1, visual guide for proper use of quantitative NMB devices; Fig. 2, reversal management flowchart displayed at PACU fast-track bays); 3) Improvement of charting (e.g., modification of PACU nursing chart and electronic anesthesia record for TOF documentation); 4) Progress dashboards (run charts) displaying outcome and process measures as incentives. An internal survey of provider's perceptions about quantitative monitoring and perioperative NMB management was sent for root cause analysis. By adopting TOFR assessment in PACU as standard of care after elective cardiac surgery, we anticipate <10% patients will be affected by residual NMB by December 2021.

RESULTS: From February to September 2021, 592 patients underwent elective cardiac surgery at Toronto General Hospital, among which 214 patients were fast-tracked for early extubation in PACU (Fig. 3). Since the launch of our initiative, 74% patients after cardiac surgery had TOFR assessed and documented in PACU. Residual neuromuscular blockade was detected in 48% of patients. The rate of quantitative NMB assessments performed and recorded in PACU increased from 0 to 90% the first after implementation, whereas the incidence of residual neuromuscular blockade after cardiac surgery decreased steadily from 66% to 24% after the first three months. However, the number of elective surgeries decreased dramatically between May and June 2021 during COVID-19's third wave in Ontario. This disruption represented a major drawback in adherence to implementing the practice changes proposed by OBISPO. Nevertheless, leading efforts for reengage providers have recently restored a decreasing incidence of residual NMB in PACU after elective cardiac surgery.

CONCLUSION: OBISPO has achieved an acceptable adherence to adopting quantitative NMB monitoring in PACU after elective cardiac surgery as standard practice. Reducing residual paralysis before extubation after major surgery will require sustained educational efforts, technical improvements and policy changes. Pedagogic strategies should emphasize on the necessity of adopting quantitative NMB monitoring to rule out residual paralysis, and on the impact that preserving muscle strength has on preventing adverse postoperative outcomes.

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Figure 1. Visual aid for electromyography electrodes placement

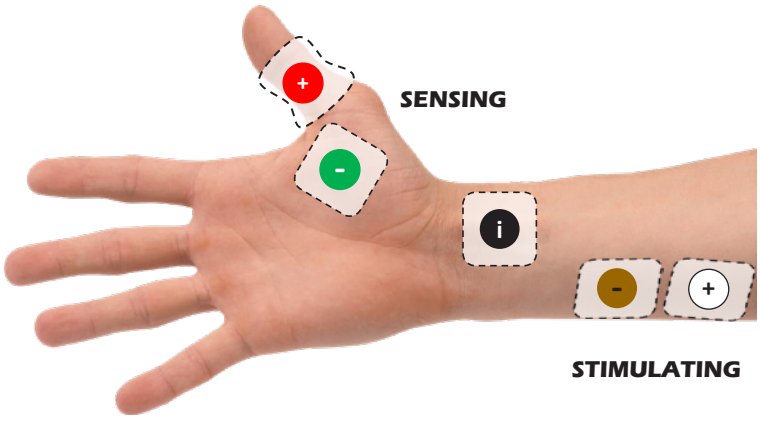


Figure 2. Reversal strategy flowchart

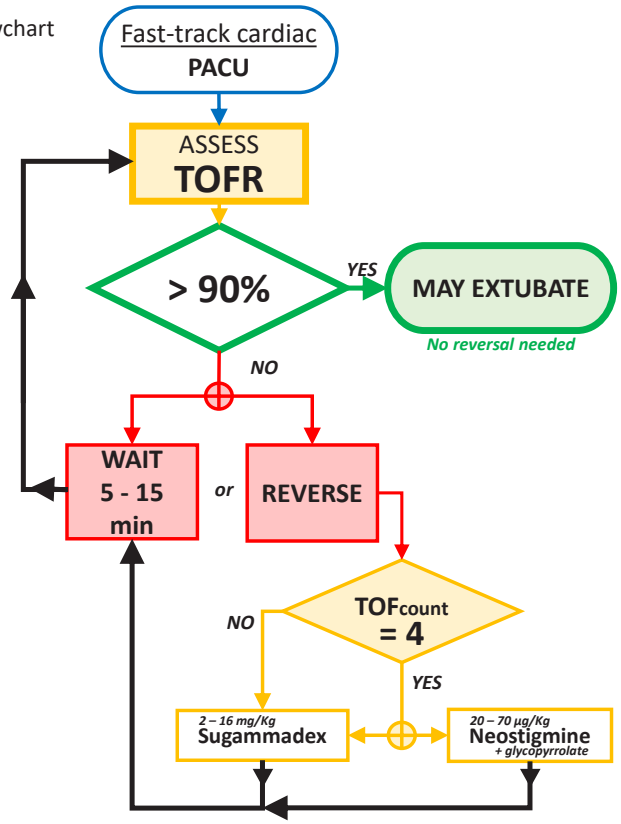
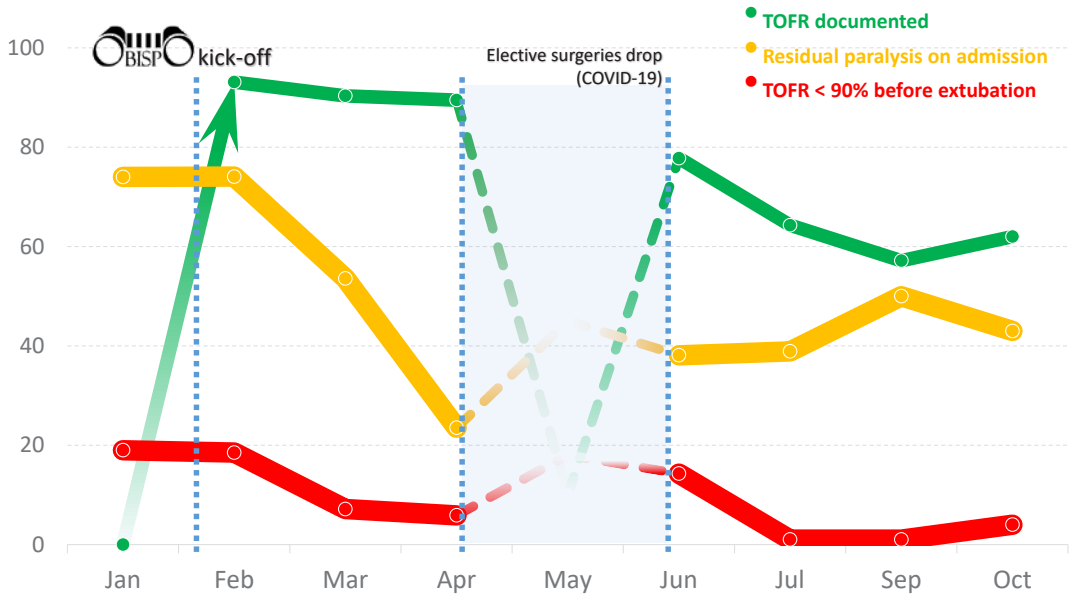


Figure 3. **OBISPO quality improvement initiative pilot phase in fast-track elective cardiac surgery. Monthly percentage of patients assessed by quantitative NMB monitor in PACU**



PATIENT SAFETY 11

Risk of aspiration with shortened NPO duration compared to aspiration risks in standard NPO groups

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INTRODUCTION: There is mounting evidence that shorter fasting times may have beneficial metabolic and hemodynamic effects during anesthesia[1]. This is combined with the patient discomfort that prolonged preoperative fasting times cause[2]. In a medical climate where reimbursements are tied to patient satisfaction, it's not only ethically good practice to reevaluate treatment standards with respect to patient comfort but also financially prudent. Pulmonary aspiration remains relatively uncommon. The APRICOT study showed the incidence to be 10 per 10,000 cases[3]. New studies have been conducted which have shown that clear fluids with fasting times decreased to 1 hour did not increase the risk of regurgitation or pulmonary aspiration[4]. Similar results have been shown in critical care research which has shown benefits of decreased hypoglycemic events without increased incidence of aspiration[5]. Similar protocols were adopted at Children's Hospital of Philadelphia in a 2017 protocol where clear fluid fasting times were decreased to 1 hour. 16,000 children were studied in the protocol. The results did not show an increase in aspiration events. The resulting guidelines have since been endorsed by the European Society for Pediatric Anesthesiology[3]. While there continues to be much interest in this topic as of late, much has been focused in pediatric populations. It is not enough to assume that similar mechanisms can be extrapolated across all age spectrums. Varying metabolic rates and anatomic size variations account for just several of the reasons why more research into the post-operative outcomes of shortened fasting times in adult patient populations is needed.

METHODS: Data was obtained via retrospective chart review across all HCA facilities between January 1, 2016 and June 30, 2020. Inclusion criteria was defined as patients undergoing scheduled elective surgery necessitating intubation aged 18-89. Exclusion criteria was defined as recent intubation within the previous 30 days. The study attempted to determine if a statistically significant variation in aspiration events exists in mechanically ventilated elective surgical patients without an NPO order when controlling for age, sex, race, BMI, pre-operative vitals, and co-morbidities including Diabetes Mellitus, cognitive impairment, GERD, apnea, vomiting or bowel obstruction. (figure 2)

RESULTS: Summary of inclusion, exclusion criteria and resulting patient population data sets are detailed in figure 1. Of the variables controlled for in the study, BMI and cognitive impairment were statistically significant. Logistic regression was obtained for a one-unit increase in Body Mass Index (BMI). The difference in log-odds for aspiration risk was determined to be -0.026 when all other variables remain constant ($p=0.045$). Cognitive impairment was also found to be statistically significant as a predictive variable for aspiration events ($p<0.001$). Patients with a prior diagnosis of cognitive impairment were determined to be 3.139 times as likely to experience an aspiration type event as those without a diagnosis of cognitive impairment. Of particular note, NPO status was not determined to be a statistically significant predictive factor of aspiration risk when all variables were held constant during statistical modeling. ($p=0.240$). Chi-square analysis comparing the risk of aspiration in NPO group to the non-NPO group did not show a statistically significant difference in the rate of aspiration between the two groups ($p=0.110$) (figure 3).

CONCLUSION: Retrospective chart review across all HCA facilities was conducted between 1/1/16-6/30/20. The study purpose was to determine if a statistically significant variation in aspiration events exists in mechanically ventilated elective surgical patients with and without an NPO order when controlling for age, sex, race, BMI, pre-operative vitals, and co-morbidities. Statistical analysis was conducted including logistic regression and chi-square analysis did not reveal a statistically significant difference in the rate of aspiration. Study limitations included a small sample size in the non-NPO group. Due to the findings and implications for increased patient satisfaction, the authors advocate for further prospective research with a larger sample size.

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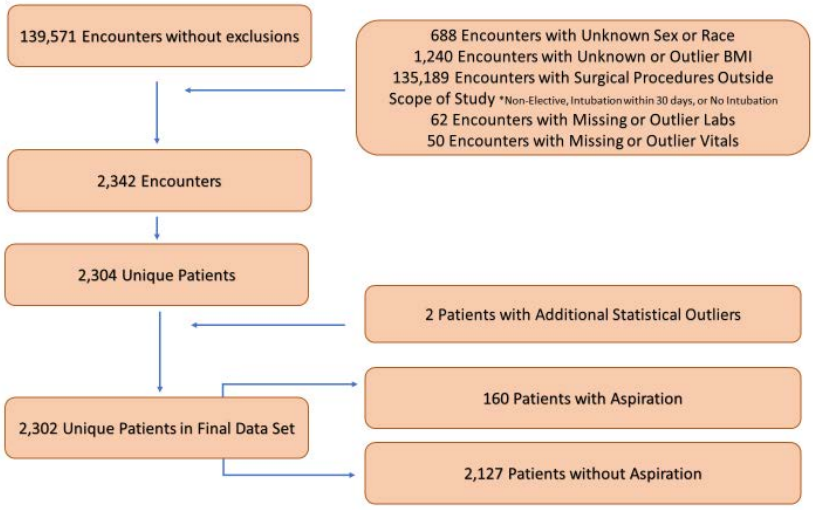

Fig. 1

Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
NPO	.471	.401	1.383	1	.240	1.602	.731	3.512
Age	.007	.006	1.389	1	.239	1.007	.996	1.018
Sex1	.345	.179	3.700	1	.054	1.412	.993	2.006
Race (Black)	.370	.261	2.008	1	.156	1.447	.868	2.413
Race (Other)	.106	.184	.332	1	.564	1.112	.775	1.594
BMI	-.026	.013	4.016	1	.045	.974	.949	.999
DM	.328	.177	3.428	1	.064	1.389	.981	1.966
Cognitive Impairment	1.144	.348	10.836	1	<.001	3.139	1.589	6.204
GERD	-.059	.261	.051	1	.822	.943	.565	1.573
Apnea	.227	.350	.420	1	.517	1.255	.632	2.492
Vomiting or Obstruction	-.482	.733	.432	1	.511	.618	.147	2.599
Preoperative WBC	.006	.008	.654	1	.419	1.006	.991	1.022
Preoperative Respiratory	.030	.016	3.501	1	.061	1.031	.999	1.064
Preoperative Temp (F)	.098	.067	2.132	1	.144	1.103	.967	1.259
Constant	-13.603	6.616	4.228	1	.040	.000		

Fig. 2

		Aspiration 0	1	Total
NPO	0	168_a	7_a	175
	1	1974_a	153_a	2127
Total		2142	160	2302

Figure 3

PATIENT SAFETY 12

Near Miss Events in NORA: A Current Literature Review

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INTRODUCTION: While adverse events that result in patient harm are required to be reported to institutional QI committees, near miss (NM) events are often not captured well. Near miss events represent an opportunity to identify and correct errors that jeopardize patient safety. Since no prior study has focused on identifying risk factors for evaluating NM events in NORA locations we conducted an extensive literature search of NM events in NORA locations.

METHODS: A literature review was conducted in 2021 using the following databases: PubMed, Embase, Web of Science, and Google Scholar. Two separate reviewers used a combination of the following keywords: 'NORA,' 'non-operating room anesthesia,' 'anesthesia,' 'near miss,' and 'adverse event.' Librarian assistance was requested to further help expand the search results. Reference chaining from search results was used to find and retrieve additional related articles. Any previously omitted articles were reviewed and validated. Results were limited to English, and no time limits were applied to the date of publication; articles reviewed, however, were primarily published within the 2006-2021 timeframe. Exclusion criteria included studies that were pediatric only (patient age < 18 years old), set in the Intensive Care Unit (ICU) only, set in the Operating Room (OR) only and/or set in the Post Anesthesia Care Unit (PACU) only. Any duplicates were omitted and any discrepancies were resolved by consensus amongst the two reviewers.

RESULTS: A total of 117 articles were identified, of which 53 were excluded. NORA settings were identified in 46 results. Among these results, 41 mentioned adverse events and only 9 mentioned NM events. Out of these 9 results, only 3 studies attempted to measure NM events in NORA locations. All three studies examined NM events in both NORA and OR; none of them specified which NORA location the NM event were being recorded in but were rather labeled 'off-site' or 'out of operating room'. Only one study, an abstract from 2012, presented a breakdown of the type of NM events collected from the NORA setting-the top three being: failure to execute a skill, equipment malfunction, and poor culture of safety.

CONCLUSION: Our systematic search reveals that there is a paucity in studies that evaluate NM events in NORA locations. Our results suggest that a prospective cohort study to systematically evaluate the incidence and characteristics of NM in NORA locations is indicated. As NORA cases increase and evolve, it is imperative for anesthesiologists to examine NM events to optimize for NORA patient safety both currently and in the future.

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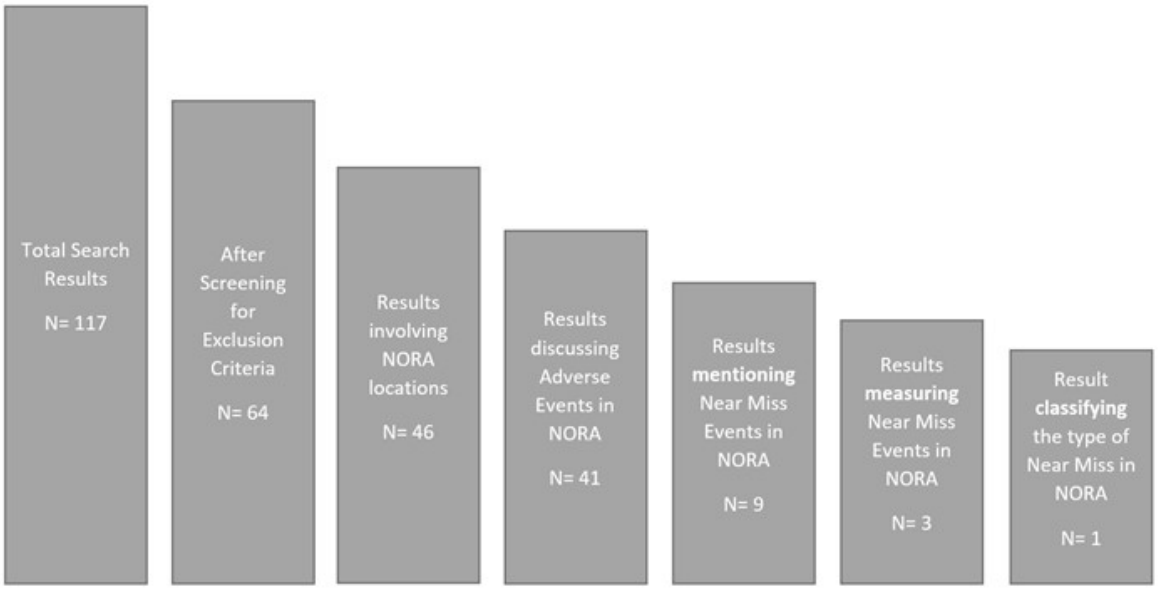

Figure 1

PATIENT SAFETY 13

Key Audit-At a Tertiary Care Teaching Hospital

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INTRODUCTION: The proper functioning of anesthesia machine is of utmost importance for safe delivery of anesthesia care, including an uninterrupted supply of oxygen to avoid delivery of hypoxic gas mixture[1]. In modern hospitals, a central supply of oxygen is used as the main source of oxygen. In addition to this central supply, an oxygen cylinder attached to the back of anesthesia machine acts as another essential safety feature, per the latest guidelines by American Society of Anesthesiologists (ASA) published in 2008[2]. In the same guidelines, ASA mandates availability of a device for opening the cylinder for use[2]. Therefore, presence of a mechanical key to open the oxygen cylinder in case of need is mandatory per ASA safety guidelines. This mechanical key is always secured to the anesthesia machine by a metal cord, preventing its removal from the machine. At a tertiary care large medical center, we hypothesized that 'every machine has a key attached to it by a metal cord per protocol'. A safety audit was conducted to confirm this hypothesis.

METHODS: After IRB approval (study deemed exempt), an anesthesia resident visited all 44 (forty-four) anesthetizing locations at main operating suite, free standing surgery center, and all offsite locations including Cath lab, GI-suite, Radiology, and all other locations. Using a pre-approved excel sheet, data was collected for machine make/model, number of gas tanks attached to the back of the machines, number of attached oxygen tanks, nitrous tanks, and air tanks, number of mechanical keys, status of presence of the keys, and whether the keys are secured via metal cord. The data was analyzed by the PI and co-PIs together.

RESULTS: As shown in Fig. 1, out of the 44 locations or machines, all machines had at least 1 key. 2 had more than one key on the back of the anesthesia machines. According to Fig. 2, 30/44 keys were secured to the back of the machines via metal cord, and the rest, 14/44 had a key but the key was not secured via a metal cord. Therefore, there was no safety breach at any of the anesthetizing locations but 14/44 were not compliant with the safety protocol of being attached via a metal cord. As shown in Fig. 3, all machines had cylinders attached to their backs. 17/44 machines use 2 gas cylinders, 20/44 use 3 gas cylinders, and 7/44 machines have 4 cylinders attached to their backs. 7/44 machines had 2 oxygen tanks attached to their backs. 36/44 machines had 1 air tank attached, and 35/44 had a nitrous oxide tank attached.

CONCLUSION: Cooper et al in a multi-center retrospective analysis concluded that equipment failure was the second cause of adverse events in anesthesia management[3]. Failure of the fresh gas supply was one of the top equipment failures after circuit disconnection. Anesthesia practice relies heavily on the use of machines and electronic equipment (both delivery/execution and monitoring); therefore, quality and safety review of anesthesia equipment plays an integral part of practicing improvement. Our audit has shown that although all the machines evaluated at our institution had the appropriate back-up oxygen supply and associated keys available, however not every key was properly secured to the machine as required per guidelines. This increases the risk of the key being lost or stolen, and as a result this poses a potential safety concern in the event of an emergency that would require the use of the back-up oxygen tanks.

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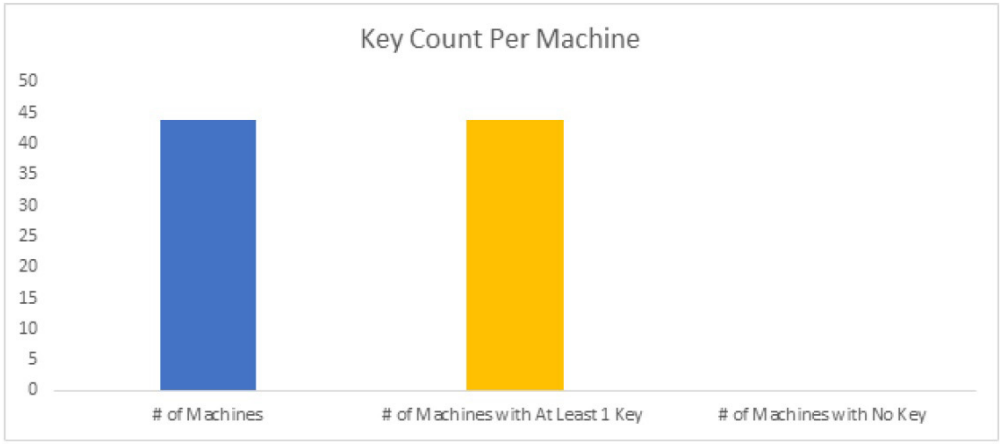

Figure 1. The figure shows the number of machines with keys. All machines have at least 1 key.

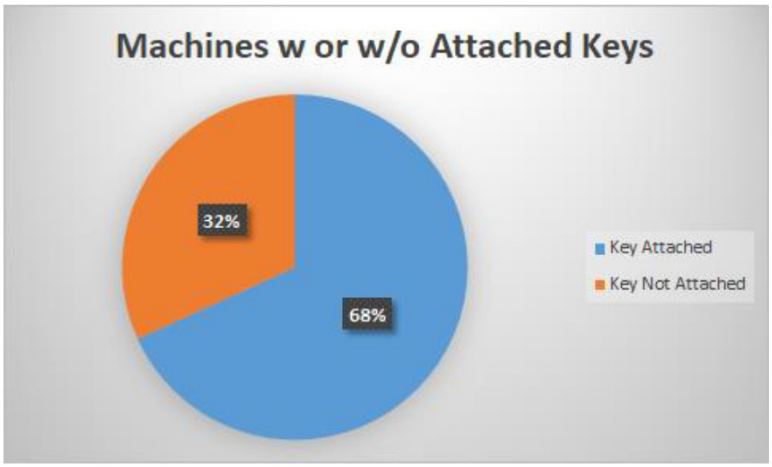

Figure 2. The figure shows the number of machines with secured (attached) keys vs no attached keys.

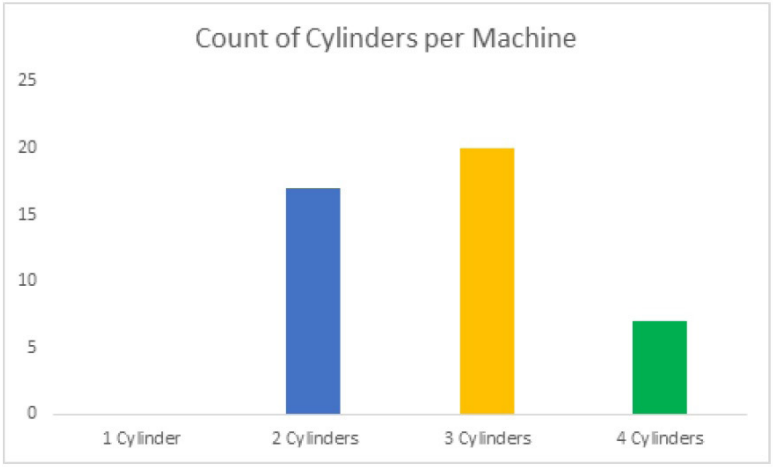

Figure 3. The figure shows the number of cylinders used per machine.

PATIENT SAFETY 14

Low incidence of postoperative delirium at one urban, academic hospital

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INTRODUCTION: Postoperative delirium (POD) is defined as an acute change in the state of mind that is associated with memory loss and behavioral changes after an operation. Although it may not be clear how or why postoperative delirium develops, there are many established risk factors associated with this altered mental state such as an older age, prior history of drug or alcohol abuse and pre existing cognitive impairments[1]. Delirium is usually identified and monitored through the Confusion Assessment Method (CAM) score conducted routinely by nurses or trained staff every 8 to 12 hours[2]. Previous literature has reported that the average rate of POD is above 10% depending on the type of procedure and patient population[3]. Considering an urban ACO which provides healthcare to a major metropolitan uninsured population that includes a high number of patients with chronic disease and substance abuse disorders, this study reports the rate of post-operative delirium at one large, urban, academic center[4].

METHODS: This study was approved by the Institutional Review Board at our institution on 3/21/2021. Eligible patients were screened prior to the day of procedure and approached for HIPAA authorization on the day of procedure in the pre-op area. Eligibility criteria included patients between the ages of 65-89 and undergoing a procedure (not neuro or cardiac) under general anesthesia which required at least 3 days of hospital stay. Chart reviews were performed after the patient had been admitted to the hospital for 3 days following their procedure. Information such as demographic data, comorbidities, use of antipsychotics, and CAM scores collected by nurses for every day the patient was admitted following their procedure (up to 5 days).

RESULTS: A total of 44 patients were enrolled in the study. Average age of participants was 71.71 years with an average BMI of 28.69. Male and female participants were equally represented (50% each). Majority of participants were white (56.82%) followed by 29.6% African-Americans participants. ASA Status of 3 was the most common (70.45%) (Table 1). The average hospital length of stay was 7 days. Only one participant scored 'Yes' on the delirium scale on all 3 post-operative days of study observation. A second participant scored 'Yes' only on post-operative day 2. The total rate of post-operative delirium observed in this was hence 4.45% (2/44) (Fig. 1).

CONCLUSION: The delirium rate of 4.45% reported in this prospective observational study is much lower than the national and international averages reported in other studies ranging from 10-13%. Based on our results, we will further investigate the use of the CAM scoring system by nurses at our institution and design PDSA (Plan-Do-Study-Act) cycles to improve the assessment of delirium at our institution.

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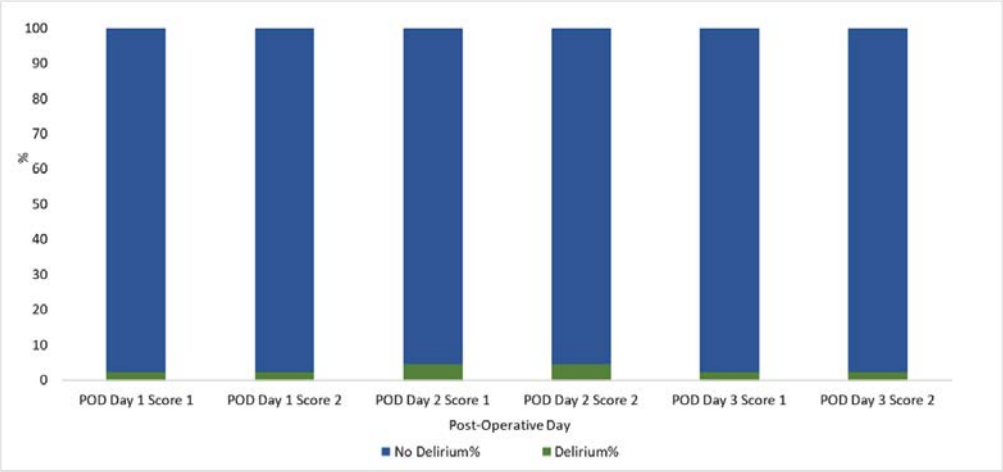

Fig 1: Delirium scores for participants enrolled in the study represented as % of total scores for each day. Two scores were collected for each post-operative day.

Baseline Characteristics	N = 44
Age at date of surgery (years)	71.71 (5.52)
Patient's Height (m)	1.66 (0.12)
Patients Weight (kg)	79.58 (19.66)
Patient's BMI	28.69 (6.38)
Biological Sex	
Male	22 (50.00)
Female	22 (50.00)
Race	
Asian	1 (2.27)
Native American/Alaska Native	1 (2.27)
Black/ African American	13 (29.55)
White	25 (56.82)
More than 1 race	1 (2.27)
Unknown	3 (6.82)
ASA Status	
1	0
2	6 (13.64)
3	31 (70.45)
4	7 (15.91)
Risk Factors (count)	
Hearing Loss	3 (6.81)
Visual impairment	16 (36.26)
Hyponatremia	9 (20.45)
Hypernatremia	2 (4.54)
Diabetes Mellitus	21 (47.72)
Frailty	14 (31.81)
On anticholinergic drugs (count)	8 (18.18)

Table 1: Baseline characteristics of all participants enrolled in the study. Data is represented as mean (SD) or count (%).

PATIENT SAFETY 15

Systematic review of OR to ICU handoff standardization interventions highlights need for focus on sustainability and patient outcomes

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INTRODUCTION: Operating room (OR) to the intensive care unit (ICU) handoff standardization is a well-studied intervention to decrease preventable patient harm. We conducted a systematic review to synthesize findings about OR-to-ICU handoff intervention sustainability and their impact on patient outcomes, attributes of these interventions that are not well described in recent reviews of OR-to-ICU handoff studies.

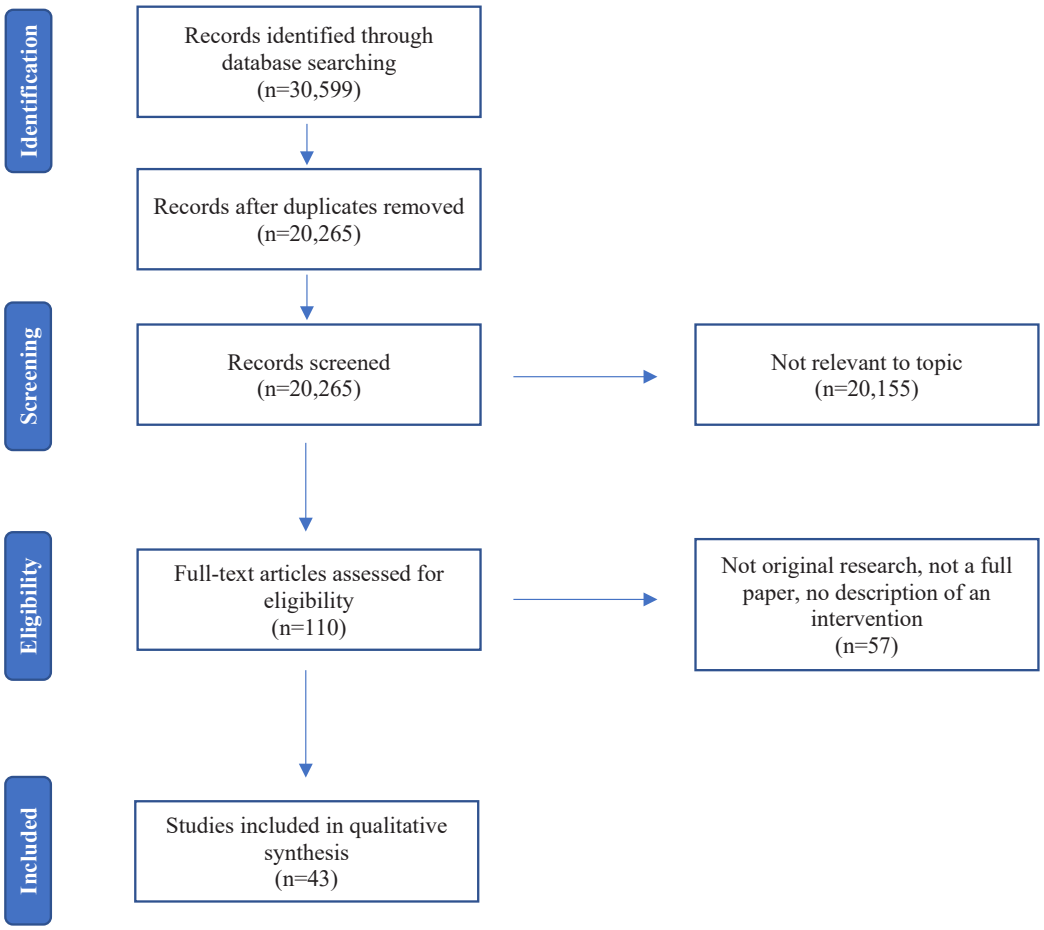
METHODS: We searched 10 electronic bibliographic databases (including PubMed, Scopus, and eight others) for studies published between 1995 and October 2021 describing OR-to-ICU handoffs. Search terms included synonyms of 'operating room,' 'intensive care unit,' and 'patient handoff,' using both natural language terms and controlled vocabulary. Inclusion criteria included full papers (i.e., not abstracts) describing original research with intervention descriptions. We used the Cochrane Consumers and Communication Review Group Study Quality Guide to evaluate each study using the criteria pertaining to the study format and PRISMA guidelines for reporting.

RESULTS: The initial search yielded 30,599 combined results [Fig. 1]. De-duplication, abstract review, and full text review yielded 43 papers published between 2007-2021. Ten countries were represented, with the largest number from the U.S. (n=19). ICU types included cardiac (n=18), surgical (n=8), neurologic (n=2), neonatal (n=1), pediatric (n=1), general (n=4), and unspecified (n=12). Study designs included quasi-experimental before-and-after studies (n=42) and one randomized controlled trial. Methods included surveys, interviews/focus groups, observations, and chart reviews. Outcomes were clinician-, patient-, or process-related. Of 35 using observations, 31 studies (88.6%) had a pre-intervention period and 34 (97.1%) had a post-intervention period. Thirteen (32.6%) of the studies described a sustainability period following the initial implementation phase that lasted 6 months to 2.5 years.

All studies with a sustainability period showed continued improvement of at least one study outcome. Nine studies measured patient outcomes, including unplanned or early extubations, delayed dosing of antibiotics, unspecified post-surgical complications, ICU-level patient mortality, length of stay, duration of mechanical ventilation, and vasopressor or inotrope treatment duration. Of these, 7 (77.8%) reported statistical significance improvement of patient outcomes, but none were able to establish causation. Two studies reported no difference in any outcomes.

CONCLUSION: Current research in OR-to-ICU handoff interventions focuses primarily on improving provider satisfaction and information exchange, with less known about how these interventions affect patient outcomes or how to enact lasting improvements to the handoff process. Future research should focus on longer term studies of interventions and evaluation of patient outcomes.

Figure 1. PRISMA Chart



PATIENT SAFETY 16

Sensitivity and Specificity of 5 lead ECG ST analysis for major adverse cardiac events in non-cardiac surgical patients

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INTRODUCTION: The 5 lead electrocardiographic (ECG) monitoring is one of the standard American Society of Anesthesiologists (ASA) monitors.[1] The V5 is the most sensitive lead for detecting myocardial ischemia.[2-4] The V5 lead is frequently not placed in the correct position due to the surgical site preparation of the patient with further reduction in its sensitivity for myocardial ischemia detection. The highest risk of myocardial ischemia occurs in vascular surgery patients where ECG ST changes occur in 3%.[4-6] The 'Gold Standard' for ECG ST analysis is a 12 lead ECG. The pathophysiology of myocardial infarction (MI) is classified by the World Health Organization as type 1 if it results from atherosclerotic plaque rupture and intraluminal thrombosis in the coronary artery, or as type 2 if it results from an imbalance between myocardial supply and demand.[7] Non-cardiac surgery increases the risk for both type 1 and 2 MI, by producing a prothrombotic state, and increased heart rate, blood pressure and stress hormones.[8,9] Anesthesia related deaths are now extremely rare.[13,14] Yet, almost 1% of non-cardiac surgical patients in the United States die within a month of their surgery.[15,16] The deaths are most strongly associated with major bleeding and myocardial injury.[17] Perioperative myocardial infarctions are usually silent, without symptoms.[18] The diagnosis of myocardial infarction after surgery is usually accomplished by an elevation in the cardiac enzyme troponin.[7,19,20] In non-cardiac surgery patients in the VISION trial the peak postoperative troponin level during the first postoperative days was significantly associated with 30-day mortality.[21] We hypothesize that ECG ST analysis has low sensitivity and specificity for MACE in non-cardiac surgery, but this can be improved when patient co-morbid factors are incorporated.

METHODS: Following institutional review board (IRB) approval a retrospective study of adult patients undergoing non-cardiac surgery at Mayo Clinic Rochester, between January 1, 2016 to May 4, 2018. The electronic medical record 'EPIC' was started at Mayo May 5, 2018. The information from the intraoperative electronic medical records (intraoperative anesthesia medical record and postoperative data recorded in the medical record), we reviewed and collected for all patients who underwent elective non-cardiac surgical procedures during the study period. To identify all patients who had a possible MACE event the charts of all patients who had a post-operative 12 lead ECG or troponin level, a cardiology consult, myocardial infarction diagnosis, cardiac catheterization with or without coronary intervention, and coronary artery bypass grafting within one week following non-cardiac surgery were reviewed. Those patients who had a ST segment depression of elevation of greater or equal to 0.2 millivolt in one lead or greater than or equal to 0.1 millivolt in two contiguous leads that lasts greater than 10 minutes with the measurement occurring 60 milliseconds after the J point. Any measurement of 12 lead ECG and/or troponin levels within 24 hours of the index surgery was noted along with consultation by cardiology and use of cardiac angiography with or without and coronary stenting. The death database was used to determine any death within 31 days and 365 of the index surgeries.

RESULTS: Complete data was collected on 69,951 patients. The charts of 1130 patients were reviewed in detail. The indication for the chart review were: 12 lead ECG and/or cardiac consult 975, Acute MI 233, Cardiac catheterization 87 and CABG following non-cardiac surgery 3. There were 54 patients who had an MI diagnosed with elevated troponins prior to non-cardiac surgery. Every one of these surgeries were emergency surgeries. Intraoperative MI was diagnosis in 7 patients (1.0 events per 10,000 patients). Post-operative MIs occurred in 142 patients. All MIs occurred within 3 days of surgery and were associated with new onset of atrial fibrillation with rapid rate response or sepsis resulting in a type 2 MI. The predictive value of the intraoperative 5 lead ECG monitor for lead V5 ST changes for all perioperative MACE events are presented on Table 1. The results of only intraoperative MACE are presented in Table 2.

CONCLUSION: We have found intraoperative MI to be rare with an incidence of 1 per 10,000 anesthetics. The 5 lead ECG had a poor positive predictive value of 0.1.

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Table 1. Predictive value of Lead V changes using cut-off of 0.2

Lead V change from baseline	No MACE (N=69748)	MACE (N=203)	NPV	PPV	Timing of MACE events: Pre-op (N=54)	Intra-op (N=7)	Post-op (N=142)
Maximum Increase							
< 0.20	39675 (56.9*)	92 (45.3)	99.8		26 (48.1)	1 (14.3)	65 (45.8)
≥ 0.20	30073 (43.1)	111 (54.7**)		0.4	28 (51.9**)	6 (85.7**)	77 (54.2**)
Maximum decrease							
< 0.20	44209 (63.4*)	103 (50.7)	99.8		32 (59.3)	4 (57.1)	67 (47.2)
≥ 0.20	25539 (36.6)	100 (49.3**)		0.4	22 (40.7**)	3 (42.9**)	75 (52.8**)
Maximum absolute change							
< 0.20	17226 (24.8*)	34 (16.7)	99.8		10 (18.5)	1 (14.3)	23 (16.2)
≥ 0.20	52482 (75.2)	169 (83.3**)		0.3	44 (81.5**)	6 (85.7**)	119 (83.8**)

*Specificity
**Sensitivity
NPV=negative predictive value
PPV=positive predictive value

Table 2. Predictive value of Lead V changes using cut-off of 0.2 excluding patients with pre-op MACE and not counting postop MACE as events

Lead V change from baseline	No Intra-op MACE (N=69890)	Intra-op MACE (N=7)	NPV	PPV
Maximum absolute change				
< 0.20	17289 (24.7*)	1 (14.3)	99.99	
≥ 0.20	52601 (75.3)	6 (85.7**)		0.01

*Specificity

PATIENT SAFETY 17

Subanesthetic Sevoflurane Concentration during Low Flow Gas Delivery: A Retrospective Single Center Registry Study

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INTRODUCTION: Due to reduced delivery of anesthetic agent, we hypothesized low fresh gas flow (FGF) anesthesia to be associated with exposure to low minimum alveolar concentrations (MAC), therefore increasing the risk of accidental awareness particularly during the early phase of general anesthesia when surgical incision occurs. Depending on the methodology used, the incidence of accidental awareness under general anesthesia is reported as between 1 in 19 000 cases in large retrospective studies[1] to around 1 in 600[2-4] when prospectively assessed. We focused on the risk state of low MAC rather than patient-reported or elicited outcomes, using automated capture to explore a generalizable data-driven method to evaluate the latent hazard of low MAC in a cohort of patients anesthetized at a large academic medical center.

METHODS: This retrospective hospital registry study comprised patients who underwent general anesthesia from 2014 to 2018 and used deidentified data from the institutional Anesthesia Research Data Repository. Adult non-cardiac surgical patients were included if they received general anesthesia with sevoflurane via an endotracheal tube. Exclusion criteria were: median age-adjusted MAC of sevoflurane less than 0.34, use of isoflurane, desflurane, nitrous oxide or propofol infusion, ASA 6, or transfer to or from the ICU intubated. Low flow anesthesia was defined as median FGF less than or equal to 1 l/min. We selected the outcomes of age adjusted MAC less than 0.6 at the surgical start time, and cases with more than 10 minutes below age adjusted MAC 0.6 within the first 30 minutes of the case. For our analysis, we conducted a multivariable logistic regression, adjusted to a priori defined confounders of patient demographics, comorbidities and markers of procedural severity.

RESULTS: There were 30 569 available cases for the outcome of age adjusted MAC less than 0.6 at the surgical start time. Of those receiving low flow anesthesia, 5.9% experienced this outcome in comparison with 3.7% of those receiving non-low flow anesthesia (Table 1). After adjusting for covariates the low flow group had increased odds (OR 1.54, CI 1.26 - 1.89, $p < 0.001$) of experiencing this outcome. Of 30 852 records, 12.7% in the low flow group and 10.4% in the non-low flow group had more than 10 minutes of MAC less than 0.6 in the first 30 minutes of the case. When adjusting for potential confounding the low flow group had increased odds of this outcome (OR 1.22, CI 1.06 - 1.40, $p = 0.007$).

CONCLUSION: While the observed difference between low flow and non-low flow groups may not be clinically significant, we report frequent occurrence of low MAC exposure at the time of surgical incision amongst all patients. This finding may not just be a local problem,[5] and suggests the need for updated minimum monitoring standards that include end tidal agent concentration, reflecting the importance of this latent hazard and the subsequent potential for accidental awareness.

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Table 1 Unadjusted and adjusted analysis for the proportion of patients with an end tidal age adjusted MAC < 0.6 at the surgical start time, and having greater than 10 minutes of age adjusted MAC < 0.6 in the first 30 minutes of the case. Comparison is made between the low flow and non-low flow groups.

Outcome	Low flow	Non-Low flow	Adjusted analysis		
			Adjusted absolute difference (95% CI)	OR (95% CI)	p value
End-tidal age-adjusted MAC < 0.60 at surgical incision (n = 30 569)	124 / 2104 (5.89%)	1063 / 28 465 (3.73%)	1.78% (0.81 - 2.75)	1.54 (1.26 - 1.89)	< 0.001
Greater than 10 minutes with age adjusted MAC < 0.60 during the first 30 minutes of the case (n = 30 852)	270 / 2128 (12.69%)	2979 /28 724 (10.37%)	1.84% (0.44 - 3.25)	1.22 (1.06 - 1.40)	0.007

PATIENT SAFETY 18

Bag-Valve-Mask (BVM): A performance Evaluation Report

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INTRODUCTION: Bag-valve-mask (BVM) devices, also known as manual resuscitators, are critical equipment in acute care. BVMs are used for short-term manual ventilation; pre-oxygenation prior to short procedures under anesthesia (e.g. elective cardioversion) or endotracheal intubation and initiation of mechanical ventilation. Unanticipated results during an unrelated experiment raised concerns regarding the performance of new BVM models in use at our centre during the COVID-19 pandemic. We sought to evaluate the inspiratory resistance and competence of the inspiratory-expiratory control valve in three common BVM models: Ambu Bag Spur II, CAREstream CARE-BVM, and Laerdal LSR.

METHODS: We evaluated inspiratory resistance and competence of the inspiratory-expiratory valve in 3 samples of each model. Inspiratory flow and resistance were measured with expiratory ports open vs. blocked. If device valves are competent the state of the expiratory port should have no impact on inspiratory flow resistance. In the event of significant changes in inspiratory resistance with obstruction of the expiratory port, flow through the expiratory port during simulated inspiration was directly measured. Testing was consistent with procedure outlined in CSA-Z10651-4-08 (R2018): Lung ventilators - Part 4: Particular requirements for operator-powered resuscitators, section A.4.8 (CSA revision of ISO 10651-4:2002), with the addition of testing under blocked expiratory port condition that is not included in the CSA/ISO standard.

RESULTS: All samples from two of the three models (Laerdal LSR, Ambu Spur II) showed anticipated behavior with no effect of expiratory port blockage on inspiratory flow and resistance, though several of the samples from these two models had inspiratory pressure drops that measured as much as 10% above the maximal limit of 5 cm H2O prescribed by CSA-Z10651-4-08(R2018). All three samples of CARE-BVM showed lower values of inspiratory pressure drop [mean (SD)= 3.0(0.26) cm H2O] but showed consistent and significant increases in inspiratory resistance when the expiratory port was blocked, with pressure drops of 7.8(0.72) cm H2O, significantly exceeding the 5 cm H20 limit. This suggests significant entrainment of outside air during negative pressure inspiration, via a leaking expiratory valve. To confirm this, we directly measured entrained air flow from the expiratory port. At 50 L/min of inspiratory flow 43-74% of inspiratory gas consisted of room air from the expiratory valve instead of flowing through the self-inflating reservoir of the BVM. This corresponds to a calculated delivered oxygen fraction of 40-60% assuming a perfect face seal and 100% oxygen flow from the BVM reservoir.

CONCLUSION: Our results raise a significant safety concern regarding the performance of CARE-BVM devices in spontaneously breathing patients suggesting that these patients may often be receiving a significantly lower concentration of oxygen than assumed by care providers. However, the technical standard (ISO/CSA-Z 10651-4-08) required by Health Canada and FDA does not explicitly mandate competence of the valves and only requires delivery of 35% oxygen at an external oxygen flow of 15 L/min into the device, meaning that the CARE-BVM devices meet the explicit requirements regarding inspiratory resistance and oxygen provision. There is significant inconsistency between clinician expectations, device performance, and regulatory requirements for BVM devices.

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PATIENT SAFETY 19

Opioid Disposal Preferences For Surgery Outpatients, Preliminary Responses

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INTRODUCTION: The nation-wide opioid crisis has drawn widespread media attention for many years. The principle attempts to address the opioid crisis have focused on reducing the opioid supply to the community by campaigns to reduce over prescribing. A neglected part of the opioid supply equation is the rate of elimination of opioid from the community. Reverse distribution is a concept wherein opioids could be taken to drug disposal locations for collection and eventual destruction. Reverse distribution of controlled substances was not possible until legislation was enacted to allow this. Even after changes in legislation with the Secure and Responsible Drug Disposal Act of 2010, barriers to participation in drug disposal programs continue to exist due to confusion in the community regarding which disposal options are best, which are discouraged, and perhaps lack of appreciation by regulators as to which disposal options would be likely to be used by patients in the practice. It is hypothesized: Patients have little of knowledge of proper opioid disposal methods. Patients will have a preference for opioid disposal options that are more readily accessible on a daily basis.

METHODS: A survey is conducted of outpatient surgery patients, ages 18 and older. The survey is administered on electronic format using an iPad webform to enter data directly into REDCap for anonymous collection. The survey is designed to take 2 minutes or less. The patients are read a script by the pre-operative nurse for uniform instructions. The patients are expected to be able to fill out the form themselves while waiting in the preoperative area. Consent is implied by participation. The IRB approved this study.

RESULTS: A greater than expected proportion of patients estimated their knowledge of opioid disposal to be very high (69% reported knowing how to dispose). Of these respondents, 27% supplied a proposed location for opioid disposal. Of the proposed locations only 57% were locations that were likely to be successful based upon cross-referencing known drug disposal locations and calling the proposed disposal sites. It was revealed that there is poor cross-referencing between municipal government or law enforcement-sponsored drug disposal locations and drug disposal locations predominantly within pharmacies as found on the DEA Diversion drug disposal site finder. Discussion: Outpatient surgery survey respondents at our institution report unexpectedly high estimates of self-knowledge of proper opioid disposal techniques. Respondents overwhelmingly preferred using opioid disposal locations that were permanent in location and available through the year. (93% reported permanent disposal locations as a proper method, whereas 67% reported that they were likely to use this method) Of the respondents who would use a permanent disposal locations only 16% supplied a viable location. Some viable locations for drug disposal could not be identified on any database of disposal locations but could be validated by contacting the locations directly.

CONCLUSION: There is a disconnect between public perception of the need to dispose of unused opioid medications, the knowledge of disposal locations, and the availability of disposal locations.

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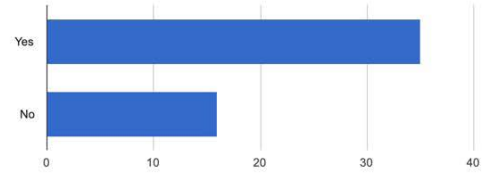
Do you know how to properly dispose of extra pain pills?

Total Count (N)	Missing*	Unique
51	5 (8.9%)	2

Counts/frequency: Yes (35, 68.6%), No (16, 31.4%)

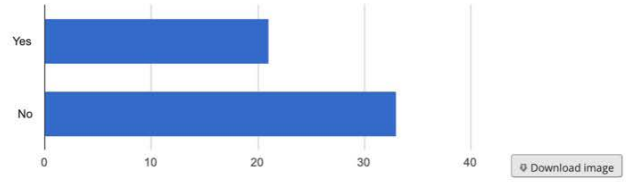


Do you know where the nearest drug disposal location to your home is? *(ods*

View as Bar Chart

Total Count (N)	Missing*	Unique
54	2 (3.6%)	2

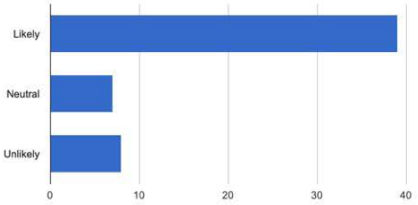
Counts/frequency: Yes (21, 38.9%), No (33, 61.1%)



Store in a safe place? *(ods_6a)* Refresh Plot | View as Bar Chart

Total Count (N)	Missing*	Unique
54	2 (3.6%)	3

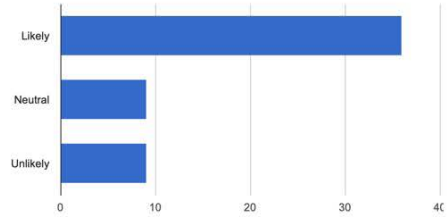
Counts/frequency: Likely (39, 72.2%), Neutral (7, 13.0%), Unlikely (8, 14.8%)



Take to an approved drug disposal location? *(ods_6f)* Refre:

Total Count (N)	Missing*	Unique
54	2 (3.6%)	3

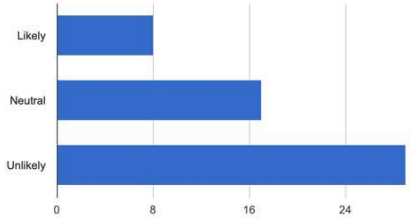
Counts/frequency: Likely (36, 66.7%), Neutral (9, 16.7%), Unlikely (9, 16.7%)



Participate in a mail-back program? *(ods_6i)* Refresh Plot

Total Count (N)	Missing*	Unique
54	2 (3.6%)	3

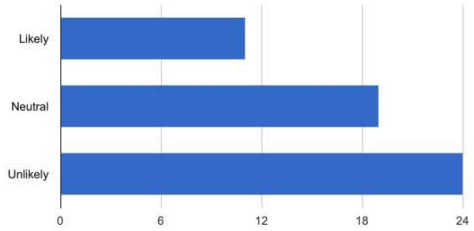
Counts/frequency: Likely (8, 14.8%), Neutral (17, 31.5%), Unlikely (29, 53.7%)



Save them for a later need? *(ods_6c)* Refresh Plot | View as Bar Chart

Total Count (N)	Missing*	Unique
54	2 (3.6%)	3

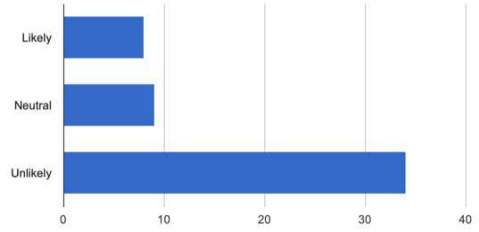
Counts/frequency: Likely (11, 20.4%), Neutral (19, 35.2%), Unlikely (24, 44.4%)



Use a neutralizing chemical disposal bag at home? *(ods_6j)*

Total Count (N)	Missing*	Unique
51	5 (8.9%)	3

Counts/frequency: Likely (8, 15.7%), Neutral (9, 17.6%), Unlikely (34, 66.7%)



PATIENT SAFETY 20

Concise Out of OperatiNg room Interprofessional in-Situ Exercises (CONcISE): Novel simulation allows the detection of amendable patient safety issues in procedural units - Interim report

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INTRODUCTION: In consideration of the increasing patient safety and malpractice risks posed by procedural care out-of-the-operating room[1-3], we implemented a novel training method that utilizes the strengths of in-situ simulation, focused debriefing and active identification of latent hazards. The Concise Out of operatiNg room Interprofessional in-Situ Exercises (CONcISE) project is designed to address the factors which increase the risk of adverse events, by improving technical and non-technical skills of interprofessional teams. The CONcISE methodology identifies site-specific latent hazards by embedding identification tools into the focused debrief and promoting greater visibility of hazards through repetitive drills.

METHODS: Procedural units within our organization (gastrointestinal endoscopy, interventional radiology, interventional cardiology) were recruited and randomized to receive CONcISE drills at either a high, medium or low frequency (9-12, 4-8, and 1-3 drills per year, respectively). A preliminary assessment of the culture of safety and implementation readiness within each unit was conducted through validated surveys and interviews. Using a high-fidelity mannequin, we created training environments to mimic the real working atmosphere within each unit. Exercises simulated a procedure under anesthesia, routinely performed within that specific unit, with a full local interprofessional team. Soon after the start of each mock case, an emergency cascade was triggered, and the team was allowed to perform the necessary steps to rescue the patient before more 'help' arrived. The drill was stopped after 5-7 minutes, and a debrief was performed immediately afterward, focusing on latent hazards and barriers to optimal patient management within the unit. Identified hazards were categorized according to severity and frequency using the Root Cause Analysis (RCA2) matrix[4], and shared with the unit leadership for further action.

RESULTS: We recruited eleven procedural units across four different hospitals within our network to participate in this study. Of these, ten units completed the baseline assessment process and three units withdrew their participation due to staffing shortages. Over a seven-month period, we executed 20 out of 23 scheduled CONcISE drills with full procedural teams. Reasons for cancelling drills included the inability to gather a complete interprofessional team (e.g.: absent proceduralist, n=2) and an unexpected scheduling conflict (n=1). Focused debriefings resulted in the identification of 87 hazards, of which 65 were distinct and 22 were repeatedly identified. Most hazards detected were environment/equipment issues (43/65) such as clutter preventing access during emergency or distance between the patient to the anesthesia machine. Communication and teamwork issues accounted for 15/65 detected hazards. Frequency and severity are reported in Table 1.

CONCLUSION: We report the successful implementation of a novel team training program aimed at improving teamwork and identifying latent hazards within procedural, out of operating room units. The overwhelming number of hazards identified demonstrate the need for ongoing review, improvement and re-assessment of the working environment and interprofessional communication, to help mitigate the risk of latent hazards that are clearly present.

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Table 1. Hazards Categories and frequencies as detected during CONcISE drills

Hazard Category / Frequency	Frequent	Occasional	Uncommon	Remote	Total
Environment/equipment	**26**	**9**	**6**	**2**	**43**
Catastrophic	5	-	-	-	
Major	7	4	2	1	
Moderate	12	2	3	1	
Minor	2	3	1	-	
Communication	**8**	**4**	**1**	**2**	**15**
Catastrophic	1	-	-	-	
Major	4	2	-	-	
Moderate	1	-	1	2	
Minor	2	2	-	-	
Rules/policy	**3**	**-**	**2**	**-**	**5**
Catastrophic	-	-	1	-	
Major	1	-	1	-	
Moderate	-	-	-	-	
Minor	2	-	-	-	
Training / technical skills	**1**	**-**	**1**	**-**	**2**
Catastrophic	-	-	-	-	
Major	1	-	1	-	
Moderate	-	-	-	-	
Minor	-	-	-	-	
	38	**13**	**10**	**4**	**65**

PATIENT SAFETY 21

Increased incidence of PONV in patients undergoing neovaginoplasty

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INTRODUCTION: Postoperative nausea and vomiting (PONV) is an undesirable but common self-reported patient outcome after general anesthesia with an estimated overall incidence of 20-30%[1]. Risk factors for PONV such as sex, BMI, type of anesthetic, and age have been extensively studied. It is thought that female sex is associated with higher rates of PONV due to estrogen as there is a higher incidence of PONV among patients in the periovulatory phase of their menstrual cycle[2,3]. The incidence of PONV among transgender patients, however, is still not thoroughly understood. While estrogen therapy is common among transgender women, there is a lack of data on PONV after gender-affirming surgeries and minimal understanding on whether there is a link between hormone therapy for transgender women and PONV. Neovaginoplasties are rapidly increasing in incidence with an 11% increase from 2019 to 2020 in the number of procedures performed nationally[4]. It is vital for providers to gain a better understanding of this patient population and procedure. This study aims to assess the incidence of PONV in transgender women after undergoing neovaginoplasty.

METHODS: This study was approved by the Institutional Review Board at our institution. Retrospective chart review was conducted and all patients over the age of 18 at the time of chart review who underwent neovaginoplasty procedures between 2014-2019 were included. Data collected from the charts included demographics, history of hormone use, comorbidities, and history of PONV, which was defined as any episode of nausea or emesis in the PACU. Severity of PONV was stratified by the amount of antiemetics utilized in treatment.

RESULTS: 154 transgender patients fit the eligibility criteria for this study. The mean age of patients was 39.01 (+14.67) years and mean BMI was 26.32 (+5.16). ASA status of 2 was the most common at 83.12% (128/154) and 49.35% patients spent 2-4 hours in the PACU. Over 90% of patients (141/154) reported using hormone therapy with 70% reporting oral administration of their medications. PONV was experienced by 32.54% (50/154) of the patients in this study. When stratified by severity the majority of patients, 86% (43/50) were categorized as having none to mild nausea (one medication was administered for nausea at most). 6% (3/50) of patients experienced moderate nausea (two or more medications administered for the treatment of nausea). 8% (4/50) of patients were reported to have significant nausea overnight.

CONCLUSION: Our study finds a PONV rate of 32.54% in a population of transgender patients undergoing neovaginoplasty, which is higher than the incidence of PONV in the general population. These rates are consistent with those observed by our team in other studies of transgender women for outpatient surgery. No association of nausea incidence was found with type of anesthesia, prior hormone use, or tobacco usage. Further studies are needed to conclusively demonstrate these results.

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PATIENT SAFETY 22

Epidural Infusions for Trans-Women undergoing Neo-vaginoplasty: A case for central sensitization

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INTRODUCTION: Neovaginoplasty, is a gender affirming surgery provides a way for transfeminine persons to remove masculine appearing genitalia and replace with a more gender congruent appearance. As of 2019 "bottom" surgery was reported in transgender and non-binary persons at a rate of 4-13% with prevalence increasing rapidly.[1] The benefits of combined general and epidural anesthesia for neovaginoplasty has been well described.[2] In this study we examined dosing strategies for epidural infusions at our institution for patients undergoing neovaginoplasty.

METHODS: This study was approved by the Institutional Review Board at our institution. Non-experimental retrospective chart reviews were conducted and all trans-gender patients who underwent neovaginoplasty procedures between 2014-2019 and were over the age of 18 at the time of chart review were included. Patient demographics including age, ethnicity, BMI were collected as well as comorbidities, history of hormone use, DVT, and nausea. Lumbar Epidurals were placed preoperatively and dosed after incision. Epidural start and stop times were collected along with pain scores measured on a visual analogue scale, and blood loss was recorded.

RESULTS: The final cohort consisted of 154 cases that matched the eligibility criteria of this study. About half of these patients, 49.3%, spent 2-4 hours in the PACU after their procedures. The most common ASA status was 2. As expected, an overwhelming number of patients, 141 of 154 (91.6%) reported using hormone therapy. Epidural infusion duration prior to first pain score assessment was 0 to 701 minutes. Median epidural infusion duration was 285 minutes. Patients whose epidural was begun early had an average pain score of 5.06/10 (+2.11). Epidurals which were started late had an average pain score of 5.16/10 (+3.04). Maximum EBL noted for all cases was 450 mls.

CONCLUSION: Overall, pain score was not significantly impacted by epidural start time post incision. Average initial pain scores were high in both cohorts, despite good pain relief on postoperative day 1. Observed EBL for these procedures was low at our institution, with no patients requiring blood transfusion. Central sensitization may play a large role in the initial pain scores and PACU length of stays for neovaginoplasty patients. Our future protocols will move towards dosing epidurals prior to incision for these procedures.

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PATIENT SAFETY 23

Epidural Infusions for Trans-Women undergoing Neo-vaginoplasty: A case for central sensitization

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INTRODUCTION: Patients with preexisting neurocognitive decline are at greater risk for postoperative neurocognitive decline (PND) and dementia, possibly through an accelerated progression of neuroinflammation and neurodegeneration[1,2]. While many studies have documented early PND following cardiac and non-cardiac surgeries, controversy remains regarding the incidence and pathophysiology of persistent PND or postoperative dementia[3,4]. We analyzed a subset of participants from the Framingham Heart Study (FHS) Gen 1 cohort who underwent non-cardiac surgeries to examine differences in their long-term trajectory of neurocognitive function.

METHODS: This study was approved by the Institutional Review Board at our institution. From the original 5209 participants, a cohort of 1063 were followed longitudinally with screening neuropsychological examinations (NP) and assessed for the development of dementia. Our final cohort consisted of 200 participants with surgical data (S-group) and 201 sex- and age-matched controls (Ctl). We examined the age-related decline in multiple cognitive domains (Table 2). A Cognitive Composite Score (CCS) was calculated based on 5 cognitive tests, as described by Dokkedal et al (4). These tests included immediate and delayed logical memory, digit span forward and backward (primary memory) and the FAS phonemic verbal fluency. The score of each participant for the individual test was standardized to the average score of the first cognitive testing in the cohort, and was then added to compute the CCS. The neurocognitive trajectory of participants with or without surgery was assessed by comparing the initial NP test scores and their performance after 8-years.

RESULTS: A majority of participants were female (155/200, 77.5%) and 30% (60/200) underwent only one surgery over the span of their lifetime (Table 1). Stroke was reported in 19% (38/200) of participants in the S cohort and 26.4% (53/201) in controls. Common procedures included appendectomy (20), hysterectomy (29), cholecystectomy (13), hemorrhoidectomy, and thyroidectomy (4 each). As compared to their non-surgical counterparts, the CCS score was significantly lower in S participants, indicating an increased incidence of cognitive decline (3.34+/-0.38 versus 4.00+/-0.30 respectively, p=0.008). Analysis of the individual NP scores revealed an accelerated decline in logical and verbal memory, paired associate learning and Hooper's visual organization test over the 8-year period in the S-participants as compared to controls (Table 2).

CONCLUSION: Non-cardiac surgery is associated with an increased incidence of persistent PND and dementia. An accelerated age-related decline in multiple cognitive domains is consistent with the hypothesis of an intensified neuroinflammation and neurodegeneration after surgery. Further studies are warranted to examine the role of anesthesia, duration of surgery and inciting factors such as perioperative hypotension and hypoxia.

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Baseline Characteristics	Non-cardiac	Controls
Total	200	201
Age at fist NP test (years)	81 ± 7	81 ± 3.2
Age at last NP test (years)	89 ± 6	88 ± 4.9
Female	155 (77.5%)	162 (80.6%)
Male	45 (22.5%)	39 (19.4%)
white	192 (96%)	
Alcohol Use	20 (10%)	
Tobacco Use	102 (51%)	
Stroke	38 (19%)	53 (26.4%)
Number of Procedures over lifetime		
1	60 (30%)	
2	43 (21.5%)	
3	27 (13.5%)	
4	10 (5%)	
5	13 (6.5%)	
6	11 (5.5%)	
7	12 (6%)	
8	7 (3.5%)	
9	8 (4%)	
10	9 (4.5%)	

Table 1: Baseline characteristics for participants that underwent non-cardiac surgeries vs age and gender- matched controls. Data is represented as mean ± sd and count (%).

	Non Cardiac		Control			
	First NP test	Last NP test	First NP test	Last NP test	P value (first)	P value (last)
Logical Memory Immediate Recall	7.68 ± 0.81	4.83 ± 0.96	8.19 ± 0.58	6.52 ± 0.74	0.301	0.007
Logical Memory Delayed Recall	6.1 ± 0.83	3.69 ± 0.92	6.83 ± 0.61	5.48 ± 0.75	0.162	0.004
Visual Reproduction Immediate Recall	4.99 ± 0.65	2.36 ± 0.58	4.81 ± 0.49	3.51 ± 0.47	0.663	0.003
Visual Reproduction Delayed Recall	3.42 ± 0.62	1.33 ± 0.44	3.57 ± 0.45	2.43 ± 0.43	0.692	0.001
Paired Associate Immediate Recall	11.1 ± 0.69	7.93 ± 0.84	11.54 ± 0.51	9.48 ± 0.61	0.311	0.003
Paired Associate Delayed Recall	7.14 ± 0.79	5.12 ± 0.74	7.51 ± 0.36	6.52 ± 0.42	0.321	<0.001
Digit Span Forward	6.13 ± 0.29	5.67 ± 0.27	5.85 ± 0.18	5.52 ± 0.19	0.084	0.367
Digit Span Backward	4.32 ± 0.26	3.49 ± 0.27	4.14 ± 0.18	3.55 ± 0.19	0.266	0.720
Trail Making Test A	0.81 ± 0.15	1.84 ± 0.61	0.95 ± 0.14	1.69 ± 0.34	0.299	0.663
Trail Making Test B	2.94 ± 0.92	6.48 ± 1.36	3.02 ± 0.56	5.55 ± 0.76	0.884	0.205
Wechsler Similarities Test	12.17 ± 1.03	9.09 ± 1.20	12.03 ± 0.82	9.55 ± 0.76	0.842	0.558
Hooper Visual Test	19.43 ± 2.06	14.37 ± 2.04	19.93 ± 1.26	17.58 ± 1.21	0.683	0.006
Boston Naming Test	8.72 ± 0.30	7.04 ± 0.59	8.64 ± 0.24	7.68 ± 0.40	0.706	0.070
FAS Test	29.65 ± 2.66	20.98 ± 3.14	28.76 ± 1.99	24.22 ± 2.15	0.598	0.087

Table 2: Neuropsychological test scores at first test vs last for both non-cardiac and control participants. Data is represented as mean ± sd.

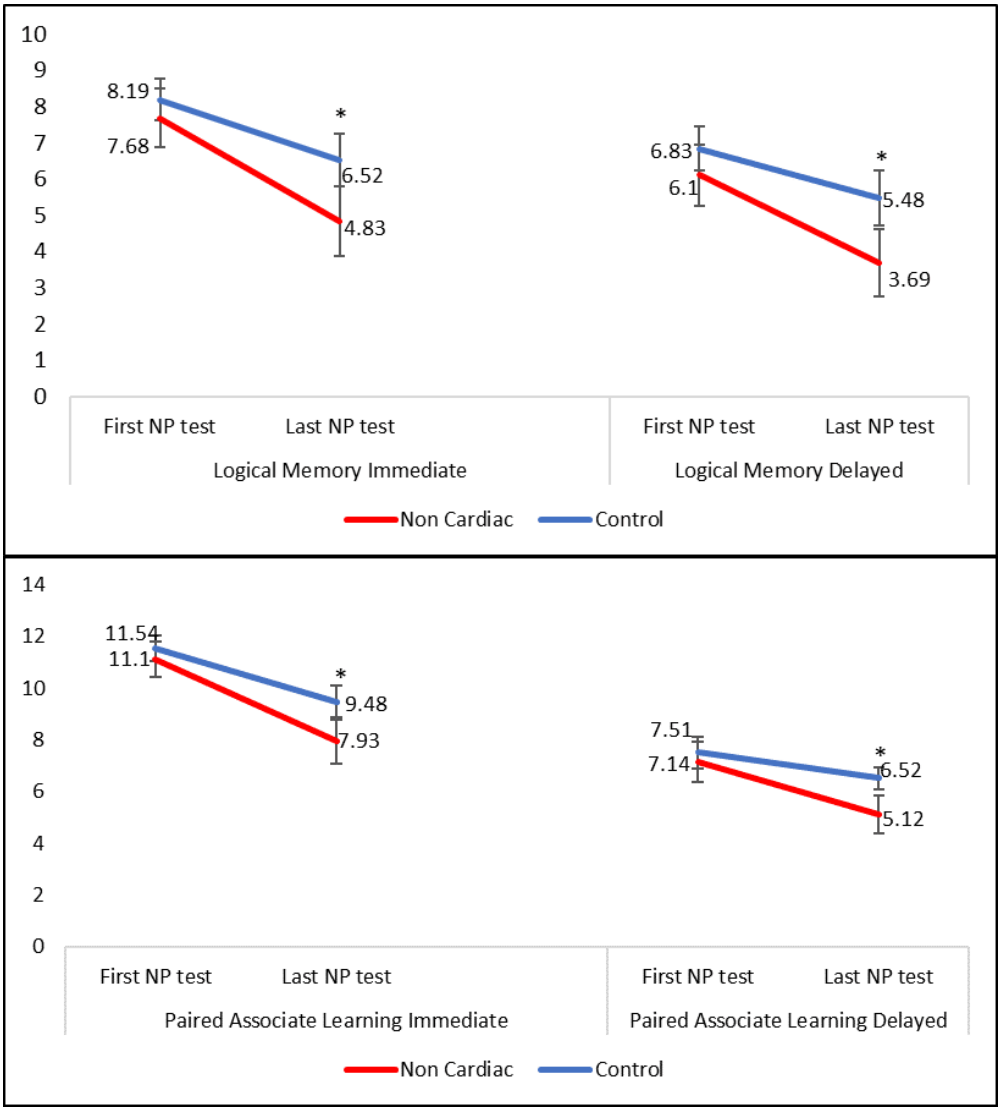

Fig 1: Neuropsychological test scores for the logical memory (immediate and delayed) and Paired Associate Learning (immediate and delayed) tests for non cardiac vs control participants at first vs last test. *P<0.010

PATIENT SAFETY 24

No incidence of VTE amongst transgender patients undergoing neo-vaginoplasties

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INTRODUCTION: One of the most life threatening conditions that anesthetists have to be at caution for is deep vein thrombosis/pulmonary embolism (DVT/PE)[1]. It has been well documented in prior literature that the general risk for DVT/PE is markedly increased in female patients taking oral contraceptives of levonorgestrel, ethinylestradiol, etc, with one study estimating a relative risk of 3.5[2]. This increase in risk has also been documented in both post-menopausal females and male-to-female (MTF) transgender individuals who are taking estrogen hormone replacement therapy (HRT)[3,4]. However, there is minimal literature outlining the risk of DVT/PE in MTF transgender patients taking HRT during the perioperative period of gender affirming procedures, and therefore this study aims to evalulate this risk in patients who are undergoing neo-vaginoplasty procedures.

METHODS: This study was approved by the Institutional Review Board at our institution. Non-experimental retrospective chart reviews were conducted and all trans-gendered patients who underwent neo-vaginoplasty procedures between 2014-2019 and were over the age of 18 at the time of chart review were included. Patient demographics including age, ethnicity, BMI etc were collected as well as the history of hormone use, comorbidities, history of PONV, DVT and airway issues. Caprini scores were calculated from information in the patient's charts and were compared to score reported by PACU nurses. Notes were reviewed for DVT incidence immediately, 1 week, 1 month, and upto 6 months after admission.

RESULTS: A total of 154 cases met the eligibility criteria for the study and were included in analysis. Average age of patients was relatively young at 39.01 (+14.67) years with a mean BMI of 26.32 (+5.16). Majority of the patients, 74.03% were white (114/154). The most common ASA status was 2 (83.12% or 128/154). PACU length of stay was 2-4 hours for most patients (49.4% or 76/154) followed by 1-2 hours for 30.52% (47/154) patients. An overwhelming number of patients, 141/154 or 91.6% also indicated that they were prescribed hormone therapy. Of these patients, most indicated that they took their medication orally (69.5%) followed by transdermal use (20.6%), and very few took it intramuscularly (10%) (Table 1). Interestingly, while the Caprini score recorded in the PACU notes categorized 55.2% (85/154) of the patients as having a Caprini score between 0-5 and 40.9% (63/154) with Caprini scores 6-10, the numbers differed from the self-calculated Caprini scores by RAs of the study. For these latter scores, 75.3% (116/154) of patients were categorized as 0-5 and only 24% (38/154) patients with Caprini scores 6-10. However, zero of the 154 cases developed VTE at any time point following surgery.

CONCLUSION: In this cohort of transgender patients undergoing neovaginoplasties, none developed VTEs despite approximately 92% of patients indicating they were prescribed hormone therapy. At this time there are no formal recommendations for withholding or continuing hormone therapy during the perioperative period. Additional studies are needed but future recommendations may favor continuing estrogen based therapies during the perioperative period.

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PATIENT SAFETY 25

Incidence and Analysis of Opioid Induced Respiratory Depression in Post-Operative Patients

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INTRODUCTION: The risk of opiate induced respiratory depression (OIRD) is alarmingly high in post operative patients. In our previous work[5], we investigated the use of the Masimo Safety Net System to validate tools used for proactive identification of patients at high risk of developing OIRD. We found that our Henry Ford Health System (HFHS) Opioid Predictive Risk Assessment Tool (HFHA-OPRAT) to be superior in predicting ORID in a post-operative patient population. Our current study is a subset analysis to determine OIRD incidence and specific risk factors predictive of opioid induced respiratory depression.

METHODS: Masimo SafetyNet system was initially implemented in October 2018 for post-operative arthroplasty patients and then expanded to all admitted post-operative patients on a particular orthopedic nursing floor. Post-operative patients admitted to Henry Ford Main Hospital (HFH) in January - December 2019 were assigned a MOSS and a HFHS OPRAT score. Retrospective data analysis was performed from patients during this time period. Based on literature review, an algorithm was established for post-operative monitoring of patients using Masimo SafetyNet system. Patients with HFHS OPRAT score greater than 10 and requiring supplemental oxygen were considered high risk, therefore they were subjected to continuous pulse oximetry with either acoustic respiratory rate monitor or end-tidal carbon dioxide monitor. Data were collected from Masimo SafetyNet monitoring system and analyzed to determine the predictive value of individual factors contained within the risk assessment tools. OIRD was defined as RR<10 breaths/minute and oxygen saturation less than 82%. These values were set as cut off limits for alarms in the Masimo SafetyNet monitoring system (critical events). The incidence of OIRD was defined as 2 or more critical events and severe OIRD was defined as 10 or more critical events during the hospital stay.

RESULTS: The incidence of OIRD was 65.9% and severe OIRD was 29.1%. Retrospective data analysis from Masimo SafetyNet monitoring system showed that the HFHS OPRAT score was superior in predicting Opioid Induced Respiratory Depression compared with other tools. On individual risk factor analysis, patients with COPD and age greater than 75 years were 2.15 times as likely to have 2 or more critical events in comparison to participants not displaying either of these characteristics, $p < 0.05$. The type of surgery did not significantly affect the likelihood of having 2 or more critical events.

CONCLUSION: The HFHS OPRAT score has good predictability for OIRD as compared with other tools. In a subset analysis it was found that patients with a history of COPD and age >75 years could especially benefit from continuous monitoring in postoperative period for early recognition and intervention of OIRD.

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MHA Keystone Center

Michigan Opioid Safety Score (MOSS)

Roy Soto, M.D.

RISK STRATIFICATION

MOSS= Health Risk (maximum of 2 points) + RR Score +/- mPOSS STOP modifier
(Possible score 0 – 4 with possible STOP modifier)

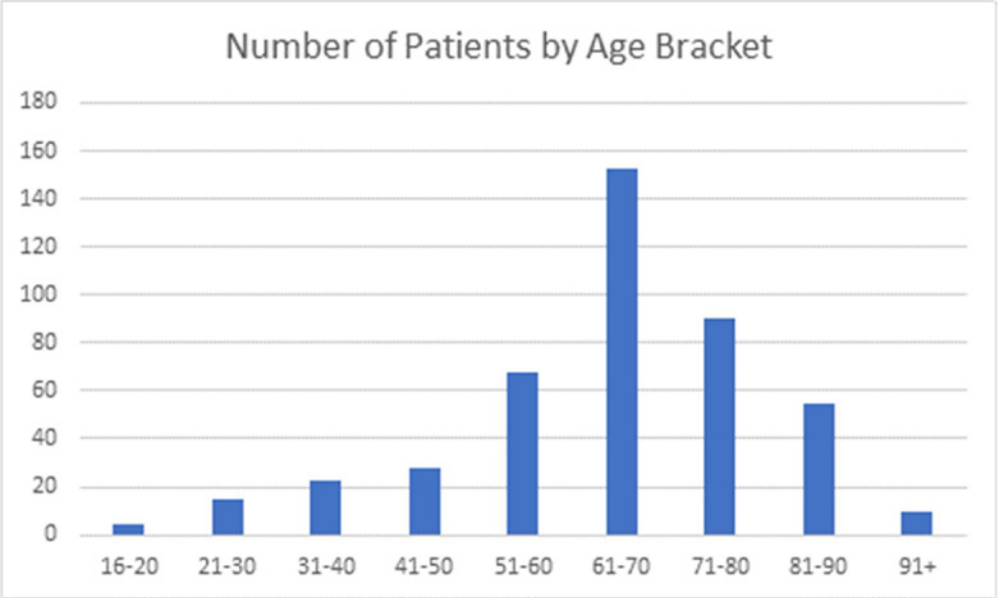
		Circle point score if any criteria apply to patient	MOSS Score (Total Points)
A) Health Risk			
Group 1	• OSA • Snoring • BMI>40	1	
Group 2	• Abd/Thor surgery • Anesthesia time >3hr (within 24hr of assessment)	1	
Group 3	• Concomitant sedatives received within 2 hours	1	
Group 4	• Age > 75 • Smoker	1	
If points total for this section is >2, enter "2" for MOSS Score here:			
B) Respiratory Rate			
Respiratory Rate ≥ 10		0	
Respiratory Rate < 10		2	
Add points from this section to MOSS Score above and enter here:			
C) Modified Pasero Opioid-Induced Sedation Scale (mPoss): STOP Modifier			
Excessively sedated, drifts off to sleep, difficult to arouse or unarousable		STOP	
If STOP is circled for this section, enter "STOP" for MOSS Score and follow guidelines below			

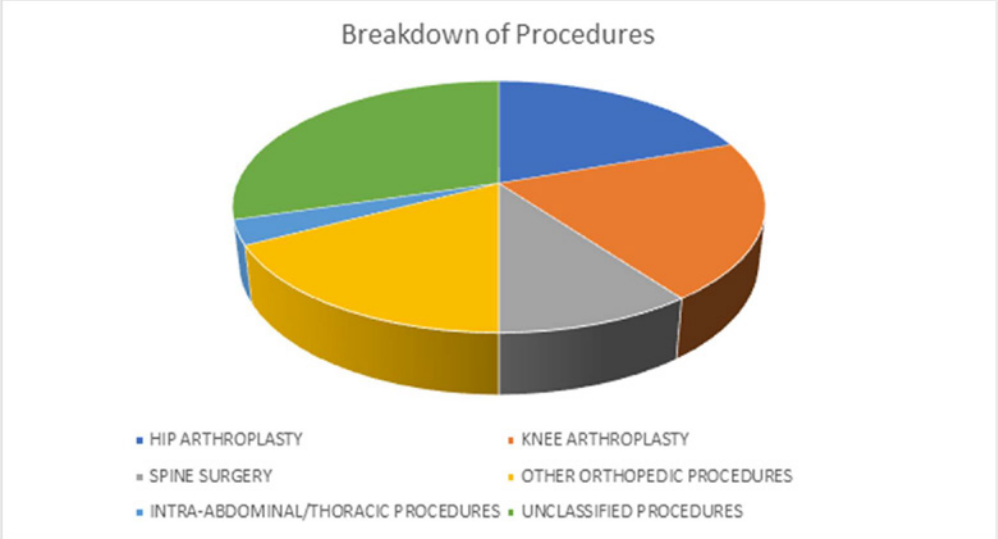
MOSS INTERPRETATION

STOP	STOP	Stop all opioids Notify primary physician Institute increased levels of monitoring Consider anesthesia/pain consultation Ensure multimodal analgesia delivered Consider reversal agents (naloxone or flumazenil as appropriate)
4 3	CAUTION	Decrease opioid dose Increase levels of monitoring Ensure multimodal analgesia delivered
2	CONCERN	Increase opioids as needed with special attention Consider increased levels of monitoring Ensure multimodal analgesia delivered
1 0	SAFE	Safe to proceed with further opioid dosing Ensure multimodal analgesia delivered

HFHS Opioid Predictive Risk Assessment Tool

Risk Factor		Points
Age		
	60 – 70	2
	71 – 80	6
	>80	8
Concurrent sedating medications (including benzodiazepines, gabapentin, muscle relaxants, sleep aids)		4
PCA Use (containing opioid)		
	With continuous basal rate	10
	Without basal rate	4
Surgery or procedure within 24 hours		4
Obstructive Sleep Apnea (OSA)		4
BMI >= 30		2
COPD		2
Congestive heart failure		2
Renal impairment (GFR <60)		2
Duration of anesthesia > 3 hours		2
History of smoking		2
Total		





PATIENT SAFETY 26

Hemodynamic safety of sub-anesthetic ketamine therapy in an out-of-hospital setting

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INTRODUCTION: Positive outcomes continue to emerge from clinical trials of ketamine delivered at sub-anesthetic doses for patients with major depressive disorder (MDD), treatment-resistant depression, post-traumatic stress disorder (PTSD), and a range of anxiety disorders[1,2]. In contrast to a formal clinical setting, a retreat environment provides comfort, context, and community for patients and may augment ketamine's therapeutic benefit[3]. Anesthesiologists may be asked to consult on medical comorbidities, as well as physiologic monitoring and management, during and after ketamine administration. As ketamine evokes a known sympathomimetic response, there is concern regarding hemodynamic stability when treating these patients in a non-hospital location. This retrospective study evaluates potential risk factors for a hypertensive response in patients receiving sub-anesthetic ketamine in an out-of-hospital setting. This information will improve clinicians' ability to identify appropriate patient populations for therapeutic treatment and in the development of safety and monitoring protocols.

METHODS: Data was collected retrospectively from patient charts (Osmind; San Francisco, CA). Patients received three ketamine sessions, each flanked by individual and group integrative counseling. Comprehensive medical intake was performed for each participant. Vital signs were collected before and after each retreat session per protocol. Participation in the ketamine session was not allowed for any patient with BP over 160/95. Per protocol, clonidine 0.2 mg po was offered to these patients prior to ketamine treatment. Hypertensive response to ketamine was defined as SBP greater than 160 torr and/or DBP greater than 95 torr. Per protocol, patients with a hypertensive response after ketamine were offered an oral clonidine 0.2 mg, and blood pressure was re-checked in 30 minutes. All statistical methods were performed using Graphpad Prism 9 (GraphPad Software, LLC). Categorical data were analyzed using Fisher's exact test and continuous data using student's T-test.

RESULTS: Ninety-one patients participated in four retreats using sub-anesthetic ketamine as off-label treatment for psychiatric diagnosis between October 8, 2021- January 2, 2022. The vast majority of patients 83 (91%) were classified as ASA 1/2 and 8 (9%) as ASA 3. Twenty-nine (32%) were male. Average patient age was 46.8 +/- 12.0 years, and average weight was 158.2 +/- 29.1 lbs. Six (6.6%) patients had a history of hypertension, 21 carried a diagnosis of PTSD, 46 of MDD, 18 of dysthymia, adjustment disorder, or mood disorder, 47 of generalized anxiety disorder (GAD), 20 of anxiety NOS, and 8 with a history of headache. Average ketamine dose was 74.8 +/- 25.4 mg. Thirty-two (35.2%) patients developed a hypertensive response (SBP>160 and/or DBP>95) and no patients developed hypertensive urgency (SBP>180 and/or DBP>110) or symptoms related to hypertension. Male gender, higher weight, elevated blood pressure prior to ketamine administration, and pre-treatment with clonidine were risk factors for elevated blood pressure after ketamine session ($p=0.034$, $p=0.001$, $p=0.047$, $p=0.016$, respectively). Of the patients who developed a hypertensive response, 7 (22.0%) received oral clonidine with resolution of their hypertension. Of patients who exhibited a hypertensive response, 56.3% experienced it after the first session. Interestingly, dose was not associated with post-ketamine hypertensive response. Other variables not independently associated with post-session hypertensive response were ASA status, age, retreat date, past medical history of hypertension, psychiatric diagnosis, and headache.

CONCLUSION: Administering sub-anesthetic doses of ketamine in a retreat setting is safe for patients given pre-treatment assessment, adequate monitoring, and management by experienced medical practitioners. Factors that increase the odds of post-session hypertensive response are male, higher weight, and blood pressure measurement prior to ketamine administration. Notably, neither a past medical history of hypertension, nor higher ketamine doses appear to increase the risk of hypertensive response in this cohort. The role of the anesthesiologist in ketamine-assisted psychotherapy continues to evolve. Important considerations regarding patient selection, comorbid conditions, and acute pharmacologic treatment highlight the importance of consultation with an anesthesiologist before initiating treatment in the out-of-hospital setting.

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Demographics and Results

	(-) Sympathetic Response	(+) Sympathetic Response	P-value
Total (%)	59 (64.8%)	32 (35.2%)	
ASA 3	3 (5.1%)	5 (15.6%)	0.124
Gender: Male	14 (23.7%)	15 (26.9%)	0.034*
Age (Years)	45.4 (12.4)	49.4 (10.9)	0.129
Weight (Lbs)	151.0 (10.9)	171.4 (33.2)	0.001**
History of HTN	2 (3.4%)	4 (12.5%)	0.179
History of Psych dx			
PTSD	11 (18.6%)	10 (31.3%)	0.199
MDD	31 (52.5%)	15 (46.9%)	0.664
GAD	27 (45.8%)	20 (62.5%)	0.187
Anxiety NOS	13 (22.0%)	7 (21.9%)	> 0.999
Dysthymia/Adjust	12 (20.3%)	4 (12.5%)	0.403
Headache	4 (6.8%)	7 (12.5%)	0.445
Pre-ket HTN	4 (6.8%)	7 (21.9%)	0.047*
Pre-ket Clonidine	2 (3.4%)	6 (20.0%)	0.016*
Dose (mg)	76.5 (25.5)	71.7 (25.2)	0.391

Categorical data displayed as N (%). Continuous data displayed as Avg (St Dev).

Figure 1

PATIENT SAFETY 27

The Trainee Experience with Quality Improvement: Standardization Of OR To ICU Handoff (SOOTH)

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INTRODUCTION: The ACGME outlines expectations for residents to participate in activities that address patient safety and specifically participating in Quality Improvement (QI) activities[1]. Published attitudes on QI participation in a small cohort of residents found that the generally negative trainee perspectives could impede the future of the learning health care system[2]. Further, there is a large body of evidence promoting resident involvement in QI as well as implementing a QI curriculum[3]. However, the experience of trainees in QI projects has not been well described and the aim of this paper is to share the experience of a trainee in developing and implementing a QI initiative.

METHODS: As part of the University of Utah Department of Anesthesiology's QI training, the CA-1 residents participate in an online 6 week QI primer course through the University of Minnesota. QI principles are taught through modules with weekly assignments wherein faculty facilitate discussions among learners as they define a problem, detail specific measurement tools and interpret data. Additionally, there is a dedicated 4 week QI rotation away from clinical responsibilities which has a structured curriculum including: literature search, faculty mentorship matching, weekly meeting with value engineer and faculty mentor(s), project planning, and a project presentation at the monthly research meeting to solicit feedback. This resident QI experience is focused on the standardization of OR to ICU Handoff.

RESULTS:

PROBLEM DEFINITION

After the online primer course the first week of the QI month is focused on problem definition. A fishbone analysis of current workflow and thorough literature search for precedent and the salient data points in a handoff were conducted. It quickly became clear that understanding of implementing lasting cultural change in a healthcare system was requisite to the project's success. The in-depth publication and availability of resources from the HATRICC[4] trial, including speaking with primary investigator Dr Meghan Lane-Fall, proved to be invaluable to the development of the project plan.

STRATEGIC PLANNING

Through combining previously acquired healthcare strategy training along with the peer-reviewed published processes[5] to implement healthcare change, an effective strategic analysis of the ICU handoff was performed. This analysis demonstrated a need for project champions from several departments and involvement of high-level stakeholders such as departmental chairs, ICU nursing administrators, ICU directors, and program directors. It was also evident from the analysis that this was a longitudinal project and early recruitment of additional residents and medical students would improve success. Three aims of the project were then defined: Needs Assessment, Implementation of Handoff and Evaluation of Implementation and Effectiveness.

NEEDS ASSESSMENT

During the needs assessment, observations of handoffs were used to collect pre-intervention data and stakeholders' feedback were used to gauge feasibility and appropriateness of a new protocol.

IMPLEMENTATION

Several planning meetings were held with relevant stakeholders and the multidisciplinary champions to refine the workflow and protocol. Educational and promotional presentations were held in department M&M conferences, resident didactics and nursing in-service trainings. Implementation also included re-structuring the environment through visual aids and bedside forms created to streamline the workflow and communication of salient info during handoff. Input from project champions facilitated strategic placement of the visual aids as well as bedside forms to enhance buy-in of the protocol.

EVALUATION

Effectiveness will be evaluated through handoff observations post intervention for 1 month to be compared to pre-intervention data. The observations will then continue for the period of one year to evaluate the longevity of the change.

CONCLUSION: QI training is an excellent way to empower trainees to enact change and further the learning health care system. Providing trainees with foundational QI training in addition to structured and supported time away from clinical responsibilities led to a constructive and efficacious experience developing and implementing a QI project. Moreover, early recruitment of additional residents and medical students

facilitated project progress as the developing resident returned to clinical responsibilities.

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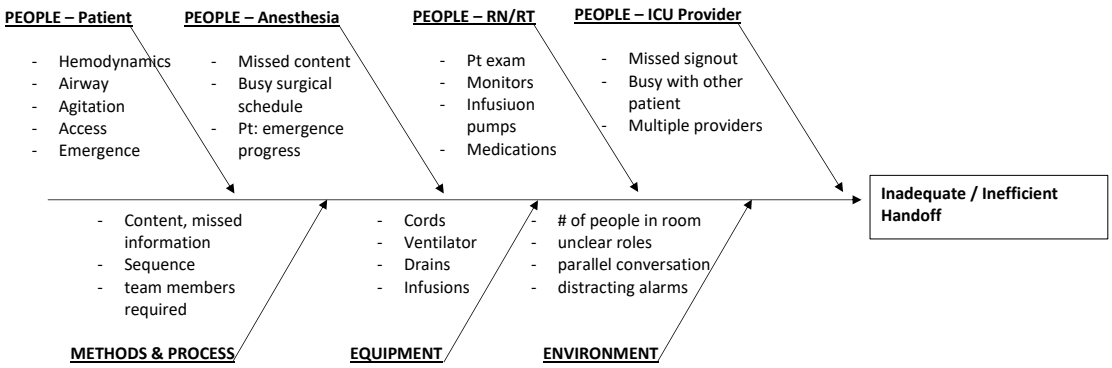
What we know: University of Utah



HEALTH
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What we know: SWOT Analysis

HEALTH
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Pt Name_____ Time: arrive_____start_____complete_____
MRN_____ RN ☐ Anesthesia☐ Surgery☐ ICU ☐

HANDOFF CONTENT				
Hands on exam by receiving team?	Y☐	N☐	UNK☐	Exam
Past Medical history	Y☐	N☐	UNK☐	PHist
Reason for ICU admission	Y☐	N☐	UNK☐	HPI
Allergies	Y☐	N☐	UNK☐	Allergies
Airway	Y☐	N☐	UNK☐	Airway
Breathing	Y☐	N☐	UNK☐	Breathing
Circulation	Y☐	N☐	UNK☐	Circulation
Inputs	Y☐	N☐	UNK☐	Ins
Outputs	Y☐	N☐	UNK☐	Outs
Drains/lines	Y☐	N☐	UNK☐	lines
Complications (or absence of)	Y☐	N☐	UNK☐	Course/Comps
Plan	Y☐	N☐	UNK☐	Plan
Team Contact Info	Y☐	N☐	UNK☐	Contact

Exam: including alaris pump sign out

PHist: Medical history

HPI: Name ● Diagnosis ● Procedure ● Reason for ICU admit

Allergies

Airway: (Difficult, Easy, Fiberoptic, Glidescope)

Breathing: vent settings ● neuromuscular blockade (blocker: rocuronium, succinylcholine, cisatracurium; reversal agents: sugammadex, neostigmine, glycopyrrolate)

Circulation: hemodynamic stability ● Vasoactives (levophed, nor-epi, epi, vaso, phenylephrine)

Ins: IV fluids administered ● Blood products (type and amount)

Outs: Estimated blood loss ● Urine output ● drain output

Drains/Lines: IV, arterial lines, central lines, surgical drains, chest tubes, NG, dobhoff

Course/Comps:
Type of anesthesia ● Anesthesia complications ● Intraoperative & transport medications, including dose ● Surgical complications and interventions ● Surgical course

Plan: Anticipated recovery and problems ● Clear postoperative management plan ● Postoperative orders and investigations ● Monitoring plan and range for physiological variables

Observer Name:_____

Handoff Observer Scoresheet

ICU Hand-off Checklist

I. Intraoperative Report Circulator name:_____

Name _____ DOB_____/_____/_____ Wt _____kg PMH_____
ICU admit reason_____ Procedure _____
Allergies _____ COVID Status_____ (PCR/rapid) ☐ Intubated ☐ Vasopressor infusions
PIV x ____. Arterial Line Central Line Chest Tubes x_____ Drains x_____

II. Anesthesia Sign Out Anesthesia Attending/Resident

Diagnosis _____ Procedure _____
Relevant PMH: _____

Anesthetic: ___GETA ___TIVA ___Regional

Meds:
Fent _____ (mcg)
Dilaudid _____ (mg)
Midaz _____ (mg)
_____
Paralytic:_____
Last dose:_____ (mg)
_____ (time)
☐ Reversal
Ancef _____ (g)/_____(time)
_____
_____
_____

Prop _____ mcg/kg/min
Fent _____mcg/kg/min
Insulin _____unit/hr
_____
Epi _____mcg/kg/min
Norepi _____mcg/kg/min
Vaso _____unit/hr
Phenyl _____ mcg/kg/min

Access:
PIV_____(g)/_____(site)
PIV_____(g)/_____(site)
_____
A-line _____(site)
Central _____(fr)/_____(lumen)/_____site
_____

Airway: ☐ Easy ☐ Difficult:_____ ETT size _____ Vent Settings _____

I/O: Crystalloid _____mL Colloid:_____mL UOP_____mL EBL _____mL

Transfusions: ____ Units PRBC ___Units FFP ___Units Platelets ___Units Cryo
☐ TXA ☐ Amicar

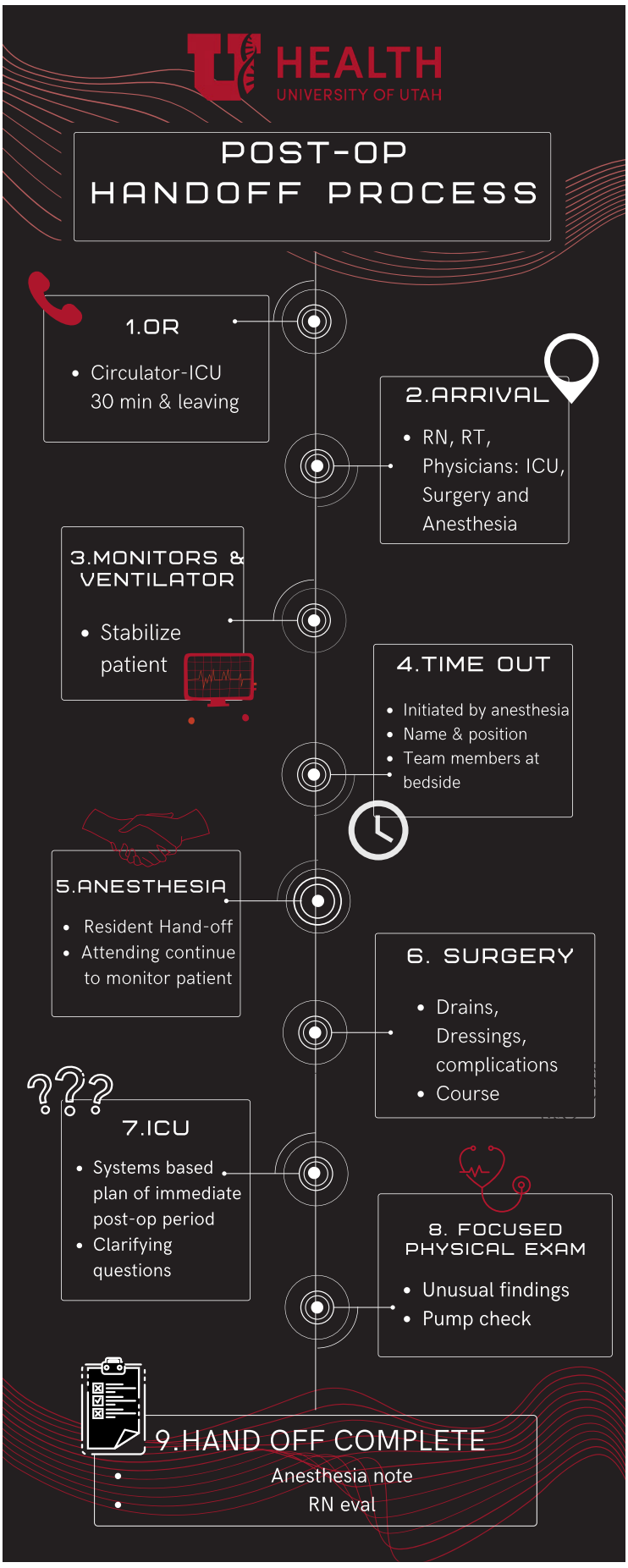
Most Recent labs: ☐ Blood Gas ☐ Rotem
Complications:

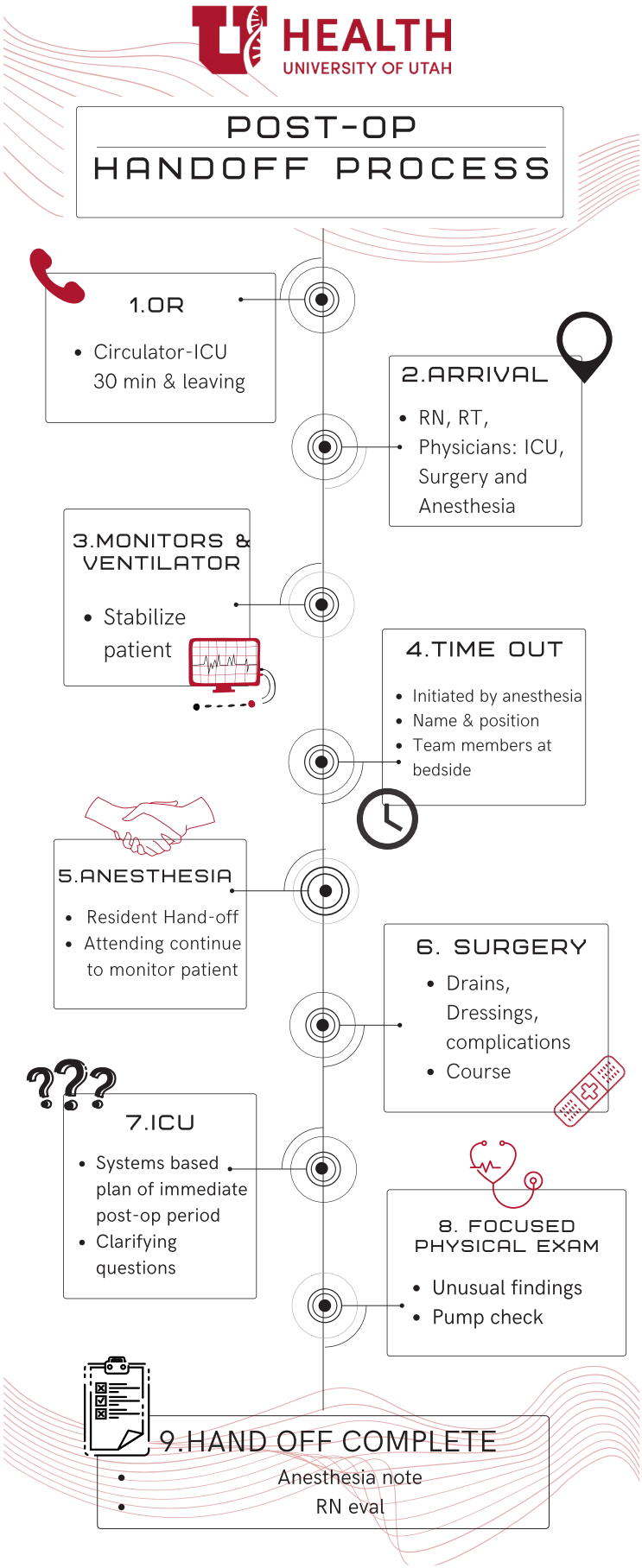
III. Surgery Sign Out Surgical Attending/Resident

Surgical site: Tubes_____ drains_____
Dressing _____ packing_____
Surgical complications _____ ☐ Bowel discontinuous
Operative Plan: _____

IV. Patient-specific Concerns/Treatment Goals ICU Attending/Resident

☐ **Family Contacted**





SUBSPECIALTY ABSTRACTS

PEDIATRIC ANESTHESIOLOGY

PEDIATRIC ANESTHESIOLOGY 1

Effect of a controlled fluid bolus on hemoglobin and hematocrit in anesthetized pediatric patients

Jenna Helmer Sobey[1], Bret Alvis[2], Kyle Hocking[1]

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INTRODUCTION: The effect of crystalloid fluid boluses on hematocrit levels is highly debated in perioperative medicine. How a singular fluid bolus affects one's hematocrit has been studied in adults; however, the literature is limited in pediatrics. One key study demonstrated that in healthy, non-bleeding adult patients, hematocrit drops by 4.8 points following a 20ml/kg crystalloid bolus given over 45 minutes with no other interventions.[1] In another adult study, the hemoglobin and hematocrit decreased by a maximum of 1.5 +/- 0.1 g/dL and 4.1 +/- 0.3% at 1 hour.[2] Neither of these studies are on pediatric patients undergoing anesthesia. We sought to determine whether a controlled fluid bolus of crystalloid causes a significant change in the hemoglobin or hematocrit in pediatric patients undergoing complex cranial vault reconstructive surgery.

METHODS: Following approval by the University of Alabama-Birmingham Institutional Review Board, pediatric patients undergoing elective complex cranial vault reconstruction (CCVR) or revision cranioplasty were included in this study. After an inhalational induction of general anesthesia, a peripheral intravenous catheter was placed and saline locked. No medications or fluids were administered. The patient was intubated and placed on controlled ventilation with tidal volumes of 8 ml/kg. An arterial line was placed, and a baseline arterial blood gas was obtained, to specifically evaluate starting hemoglobin and hematocrit. A controlled fluid bolus of 10 ml/kg of Lactated Ringer's crystalloid solution was then administered to each patient and immediately following the bolus, another arterial blood gas was sent, to evaluate hemoglobin and hematocrit following a controlled fluid bolus. Statistical analysis of the change in hemoglobin and hematocrit values was then performed using a paired t-test.

RESULTS: Seven patients ages 2 months to 22 months undergoing CCVR or cranioplasty revision were enrolled in the study. Following a controlled fluid bolus of 10 ml/kg prior to the start of the procedure, there was a statistically significant drop in the hemoglobin and hematocrit levels when measured by arterial blood gas ($p<0.05$). The mean change in hemoglobin was 1.5 +/- 0.2 g/dL and the mean change in hematocrit of 4.6 +/- 0.8%.

CONCLUSION: Crystalloid administration is the mainstay of fluid resuscitation in pediatric patients under anesthesia. Currently there is a lack of knowledge and evidence supporting the idea that there is a dilution of hematocrit following fluid administration in pediatric patients. We present the effect of a 10ml/kg controlled crystalloid fluid bolus on the hemoglobin and hematocrit of pediatric patients under anesthesia. Larger studies are needed in the future to further investigate the effect of hemodilution in pediatric patients in the perioperative setting.

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PEDIATRIC ANESTHESIOLOGY 2

Inflammatory Biomarkers of Congenital Heart Disease-Associated Pulmonary Arterial Hypertension: A Prospective Cohort Study

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INTRODUCTION: Pulmonary arterial hypertension associated with congenital heart disease (CHD-PAH) is a devastating pediatric condition resulting in significant morbidity and mortality. Gold standard diagnosis and follow-up of these patients currently involves right heart catheterization, which itself carries significant peri-operative risks to the patient. As such, the identification of a circulating biomarker of CHD-PAH could potentially limit the number of children requiring this invasive and high-risk procedure. It is widely accepted that PAH has a large immunological component, with significant pulmonary vascular inflammation present. We therefore sought to assess the ability of circulating biomarkers of inflammation to predict the presence of PAH in children with CHD.

METHODS: Our study was approved by our institutional research ethics board. Children with CHD presenting for cardiac catheterization were approached for consent to participate. Transplant recipients, patients with significant inflammatory disease, active malignancy, or infection were excluded from the study. Patients were stratified into 2 groups based on hemodynamic definitions, either CHD alone or CHD-PAH (n=25 each). A third group served as a control, and was comprised of otherwise healthy children presenting for outpatient urological and dental procedures (n=10). Blood was collected (femoral vein, CHD and CHD-PAH, peripheral intravenous, controls) and plasma was analyzed for levels of HMGB1, NT-proBNP, and other inflammatory markers. Analysis included mean analyte level within each group, as well as correlations of analyte levels to pulmonary hemodynamics.

RESULTS: Mean age was 6.7 years, mean pulmonary artery pressure was 14.7 mmHg in the CHD alone group and 36.0 mmHg in the CHD-PAH group and pulmonary vascular resistance index was 1.5 and 8 Woods Units•m^2, respectively. HMGB1 levels were not significantly different between CHD and CHD-PAH (3.2 vs 3.1 ng/ml, p=0.22), nor were NT-pro-BNP levels (43.2 vs 93.5 ng/ml, p=0.11). No significant correlations existed for any analyte versus pulmonary hemodynamics (HMGB1 vs mPAP r=0.097, p=0.55; NT-pro-BNP vs mPAP r=0.22, p=0.35).

CONCLUSION: Unlike previous reports in adult populations, inflammatory biomarkers were not predictive of the presence or absence of PAH in children with CHD in our institution. This observed difference may reflect a difference in disease pathogenesis or duration in our population. Further studies will seek to assess other non-invasive biomarkers of disease in children with PAH.

PEDIATRIC ANESTHESIOLOGY 3

Natural airway as a safe alternative to intubation for pediatric endoscopic foreign body removal

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INTRODUCTION: Pediatric foreign body (FB) ingestions occur frequently, with an annual estimated 116 000 patients presenting to emergency departments[1]. However, there are no clearly defined guidelines for airway management during anesthesia for endoscopic FB removal procedures. Specifically, it is unclear as to when intubation is indicated over noninvasive airway management. The primary aim of this study was to evaluate pre-, intra-, and post-operative factors associated with planned intubation during FB removal among pediatric patients. We hypothesized that pre-, intra- and post-operative outcomes including duration and type of retained FB, total operating time, and hospital admission rates were significantly different among intubated patients in comparison to non-intubated patients.

METHODS: This retrospective cohort study included pediatric patients ages 0-18 years presenting to Johns Hopkins All Children's Hospital from July 2013 to September 2020 who were assigned an ICD-9 or ICD-10 code indicating esophageal FB and underwent endoscopic removal. Patients with foreign bodies in the airway, those that underwent surgical removal, or in whom the FB moved to the stomach prior to intervention were excluded. Descriptive statistics summarized patient, object, and provider variables by intubation status while Chi-square and Fisher's exact tests determined unadjusted associations.

RESULTS: The sample included 281 patients, 53 (18.9%) who were initially managed for their endoscopy with intubation and 228 (81.1%) initially managed with natural airway and nasal cannulae for oxygen supplementation. Eleven non-intubated natural airway patients (3.9%) required intra-procedural 'rescue' intubation. Nearly half (45.3%, n=24) of intubated patients had a history of foreign-body-related drooling, compared to under a third (31.1%, n=71) of non-intubated patients. Among intubated patients, 11.3% (n=6) had fasted for <6 hours compared to 1.8% (n=4) of non-intubated patients (p =0.004). The median duration of retained foreign body was also lower in intubated patients (13.3 hours) vs. non-intubated (16.0, p=0.02). There was a higher proportion of food bolus ingestions among intubated patients (15.1%, n=8) than non-intubated patients (1.8%, n=4; p<0.001). The proportion of patients admitted to the hospital (intubated 20.8%, n=11; non-intubated: 4.8%, n=11; p<0.001) and median total operating time (intubated: 26.0 minutes; non-intubated: 11.0 minutes; p<0.001) were also increased for intubated patients.

CONCLUSION: This study is one of the first to compare airway management techniques for foreign body ingestion procedures. Patients' airways for endoscopic removal of esophageal foreign body were managed without intubation in 81% of this cohort. Only 3.9% of patients managed without intubation were subsequently intubated during the procedure. Intubation was associated with history of drooling and a food bolus FB; intubated patients were less likely to have met pre-operative fasting requirements and had a shorter duration of FB retention. Intubated patients were more likely to require postoperative hospital admission. This study shows that anesthetic management of selected patients undergoing endoscopic removal of esophageal foreign body is safe and possible without the need for intubation. Further confirmatory studies are necessary. However, the median total operating time for patients managed with natural airway was only 11 minutes, which may limit generalizability of these findings at institutions with slower perioperative times.

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PEDIATRIC ANESTHESIOLOGY 4

Combined Spinal Caudal Anesthesia is a Safe and Effective Technique for Longer-Duration Urological Day Surgery

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INTRODUCTION: Spinal anesthesia (SA) is a safe and effective technique for infants undergoing infraumbilical surgery. It avoids endotracheal intubation and systemic sedation while maintaining hemodynamic stability[1]. It is shown to improve operating room (OR) and post-anesthesia recovery unit (PACU) utilization[2] and reduce postoperative pain scores[3]. Applications of SA in infants are limited however by its fixed time duration. To overcome this, we piloted a case series to study the novel technique of Combined SA and Caudal catheter (CSC) to assess its feasibility, safety, and effectiveness for infants undergoing urological day surgery over 90 minutes.

METHODS: Eight infants underwent CSC for hypospadias repair. SA was performed using a previously described protocol[2]. Following SA onset, the infant was positioned laterally and a 20-gauge angiocatheter was inserted into the caudal space under ultrasound guidance and confirmation. Sixty minutes following SA onset, the caudal catheter was activated with chloroprocaine 2% with epinephrine at a dose of 1 ml/kg over 10 minutes, followed by an infusion of 1ml/kg/hr4. The infusion was stopped 15 minutes before procedure end to allow for chloroprocaine metabolism. Ropivacaine 0.2% 1ml/kg was given for postoperative analgesia before catheter removal.

To compare CSC to the standard of care general anesthesia (GA), we retrospectively matched 8 patients who had GA to the 8 who had CSC by age, weight, ASA status, and surgical procedure (Table 1). The GA cohort underwent inhalational induction with sevoflurane, intravenous insertion, endotracheal intubation, and a caudal single shot block with ropivacaine 0.2% 1ml/kg with epinephrine for postoperative analgesia. Opioids were administered at the discretion of the anesthesiologist. We compared the length of induction time, procedure end to OR exit time, and PACU recovery time between the cohorts using paired t-tests.

RESULTS: The mean age of CSC patients was 6.8 months. All 8 CSC patients remained under regional anesthesia for the entire duration of surgery. Four CSC patients received intravenous dexmedetomidine, all at a dose ≤1 mcg/kg. Mean surgery length under CSC was 110 minutes, with the longest length of 138 minutes (Table 1).

None of the CSC patients received opioids, while 4 of the 8 GA patients (50%) received intraoperative opioids. Induction lengths and PACU times were not significantly different ($p=0.15$ and $p=0.52$ respectively, Figure 1). Procedure end to OR exit times were significantly shorter in CSC patients (one-tailed paired t-test, $p=0.04$).

CONCLUSION: Our case series demonstrated the feasibility, safety, and effectiveness of the novel CSC technique for urologic day surgery in infants. CSC allowed for surgeries as long as 138 minutes. Patients in the CSC group were spared intubation and systemic opioids, adding to the safety of the technique. Furthermore, all were able to be discharged on the day of surgery with shorter emergence periods and without incurring longer PACU recovery times.

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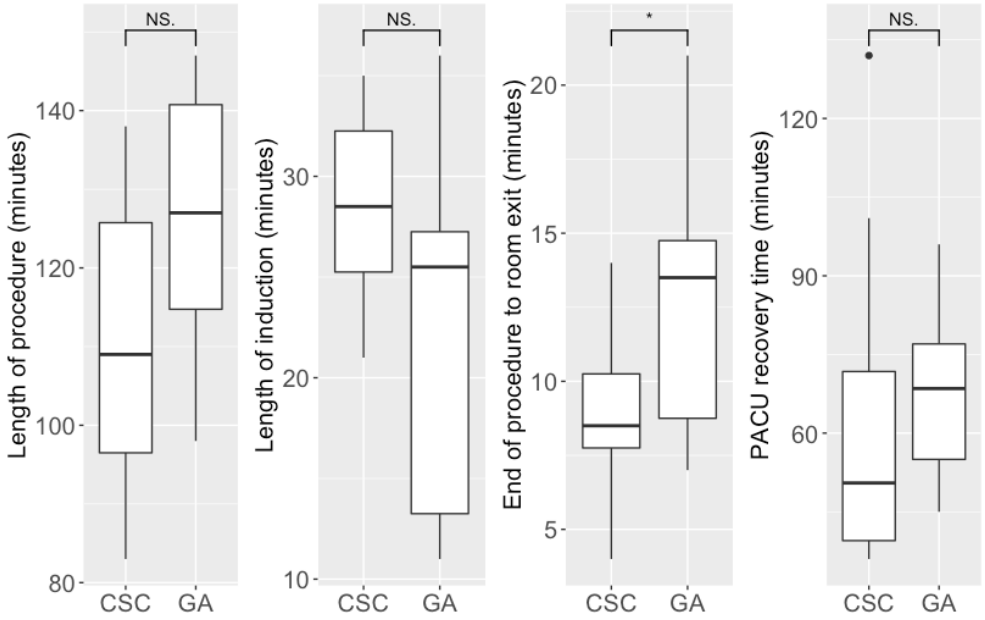

Figure 1. Differences between CSC and GA cases in perioperative efficiency. The end of procedure to room exit time was found to be significantly shorter in CSC cases (p=0.04), while other comparisons remained insignificant.

	CSC (n=8)	GA (n=8)	p-value
Chronological age (months)[a]	6.8 (range 3.3-9.6)	6.8 (range 3.6-9)	0.64[1]
Weight (kg)[a]	8.5 (range 6.8-10.3)	8.2 (range 6.9-9.5)	0.46[1]
ASA status (I, II)	I (7), II (1)	I (7), II (1)	--
Length of induction (min)[b]	28.5 (IQR 25-32)	26 (IQR 13-27)	0.15[1]
Length of surgery (min)[b]	109 (IQR 97-126)	127 (IQR 115-141)	0.08[1]
End of procedure to room exit (min)[b]	9 (IQR 8-10)	14 (IQR 9-15)	0.04[1]*
Length of PACU stay (min)[b]	51 (IQR 40-72)	69 (IQR 55-77)	0.68[1]
Use of intraoperative dexmedetomidine ≤1 mcg/kg (n, %)	4 (50%)	N/A	--
Use of intraoperative opioids (n, %)	0 (0%)	4 (50%)	0.08[2]

Table 1. Demographic and intraoperative data for CSC and GA patients. [a]=mean, range, [b]=median, interquartile range (IQR). *=p<0.05, **=p<0.01. [1]=paired t-test, [2]=Fisher's exact test.

PEDIATRIC ANESTHESIOLOGY 5

Anapod™ Humi-Therm Heated Humidification System Breathing Circuit vs Bair Hugger™ Warming Blanket for Intraoperative Maintenance of Body Temperature in Pediatric Patients Undergoing Dental Surgery

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INTRODUCTION: Perioperative maintenance of body temperature falls under the purview of the anesthesiologist. Perioperative hypothermia is associated with adverse patient outcomes including morbid cardiac events, hypertension, increased blood loss, increased allogenic transfusion requirements, coagulopathy, reduced immune response and surgical wound infections. Multiple warming methods are in clinical use, with forced-air warming blankets being the most common. However, heating of anesthetic gases via the breathing circuit is another option to influence patient body temperature perioperatively. This modality not only helps with temperature maintenance, it also adds humidity to the breathing gases which might have beneficial effects on the respiratory tract. The Anapod™ Humi-Therm Heated Humidification System Breathing Circuit has successfully been used in adult patients.(1,2) Its safety in pediatric patients has also been confirmed, but so far, no studies have evaluated its efficacy in this patient population. Our study aimed at evaluating whether the Anapod™ Humi-Therm Heated Humidification System Breathing Circuit is non-inferior compared to the Bair Hugger™ Forced-Air Warming Blanket when used in pediatric patients undergoing dental procedures under general anesthesia.

METHODS: The study was approved by the Institutional Review Board (IRB) at the University of Minnesota (IRB ID# STUDY00005616). We included patients aged 18 years and younger who underwent dental exams with restorations under general endotracheal anesthesia. Patients were excluded if parents refused consent, if additional procedures involving parts of the patient's body other than the oral cavity were planned and if the patient had a history of diseases associated with temperature dysregulation such as active hyperthyroidism, dysautonomia, osteogenesis imperfecta and history of malignant hyperthermia. Informed consent was obtained from parents. The patients were randomized at the time of induction to temperature maintenance with either 1) the Bair Hugger™ blanket or 2) the Anapod™ Breathing Circuit (both systems were present for all cases). Anesthetic care was determined by the attending pediatric anesthesiologist. Temperature measurements were obtained from a rectal temperature probe. The primary outcome for this study was the last measured core temperature obtained from the rectal temperature probe at conclusion of the procedure prior to removal of the probe. The secondary outcome included the need for hypothermic or hyperthermic rescue in each group. The study was designed as a non-inferiority study with a predefined non-inferiority boundary of 0.3°C.

RESULTS: Patient characteristics are displayed in table 1 while table 2 shows the primary and secondary outcomes. The final rectal temperature was 0.5°C higher in the Bair Hugger™ group compared to the Anapod™ group (37.2 +/- 0.38°C versus 36.7 +/- 0.47°C). The 95% confidence interval for the difference in the final rectal temperature was (-0.709, -0.371) Celsius and excluded the non-inferiority margin of -0.3. The Bair Hugger™ group required more rescue interventions compared to the Anapod™ group (44.0% versus 22.0%; p=0.033), but those were most commonly due to hyperthermia (21 patients). Only one patient in the Bair Hugger group required a rescue intervention for hypothermia. Conversely, most interventions in the Anapod™ group were for hypothermia (8 patients), while 3 patients required hyperthermic rescue.

CONCLUSION: Both warming modalities resulted in intraoperative increases in body temperature. Based on the predefined non-inferiority margin, the results showed that the Anapod™ Humi-Therm Heated Humidification System Breathing Circuit was NOT non-inferior to the Bair Hugger™ Forced-Air Warming Blanket. A superiority analysis based on the pre-defined O'Brien-Fleming stopping boundaries confirmed that the Bair Hugger™ Forced-Air Warming Blanket was superior in warming pediatric patients during dental procedures under general anesthesia, although this statistical difference was largely because the Bair Hugger™ system frequently "overheated" patients. When examining the individual patient temperature curves in figures 1 and 2, it becomes apparent that both devices are successful in warming patients after the initial drop in temperature due to induction of general anesthesia

resulting in vasodilation and redistribution, although the Bair Hugger™ system achieves a quicker and steeper temperature rise as compared to the Anapod™ system.

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Table 1: Patient Characteristics

	Bairhugger (N=50)	**Anapod** (N=50)
Age (years)	5.1 (4.2 – 6)	5.3 (4.1 – 6.3)
Sex (male/female)	30/20	28/22
Height (m)	1.13 (0.27)	1.1 (0.12)
Weight (kg)	19.96 (4.93)	21.6 (8.99)
ASA I	27	22
ASA II	19	21
ASA III	4	7
Total anesthesia time (min)	172.5 (29.69)	173.68 (30.85)

Values are mean (SD), median (interquartile range [range]), or number (proportion) as appropriate

Table 2: Primary and Secondary Outcomes

	Overall (N=100)	**Bairhugger** (N=50)	**Anapod** (N=50)
Rescue Intervention Needed	34 (34.0%)	23 (46.0%)	11 (22.0%)
Reason for Intervention:			
None	67 (67.0%)	28 (56.0%)	39 (78.0%)
Hypothermic	9 (9.0%)	1 (2.0%)	8 (16.0%)
Hyperthermic	24 (24.0%)	21 (42.0%)	3 (6.0%)
Post-Induction Rectal Temp (C)	36.6 (0.57)	36.5 (0.74)	36.6 (0.34)
Final Rectal Temp (C)	37.0 (0.5)	37.2 (0.38)	36.7 (0.47)
Min Rectal Temp (C)	36.1 (0.66)	36.0 (0.84)	36.1 (0.4)
Max Rectal Temp (C)	37.1 (0.44)	37.3 (0.33)	36.9 (0.44)

Figure 1: Anapod Rectal Temperature Curve

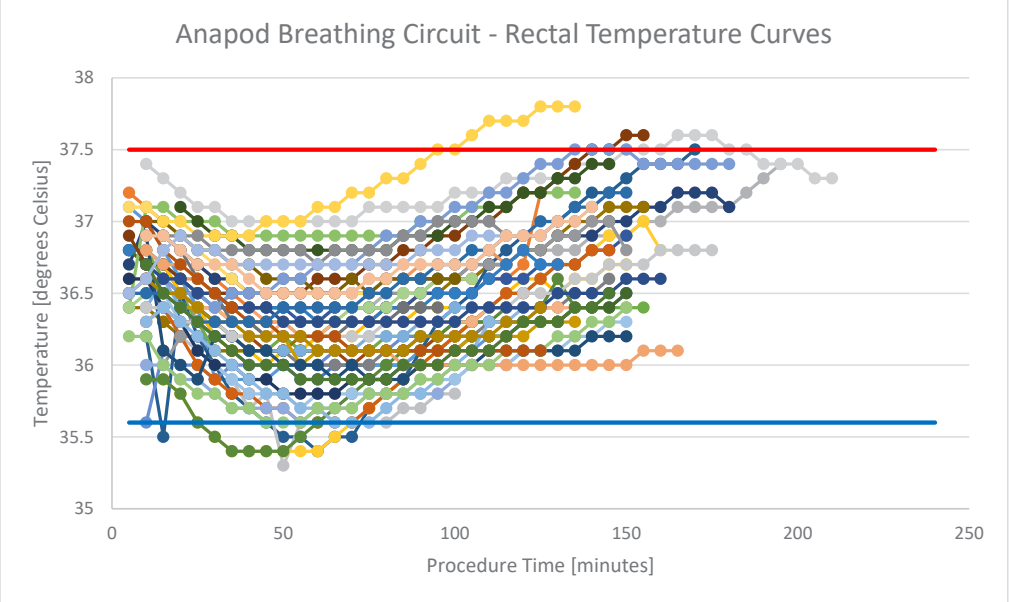
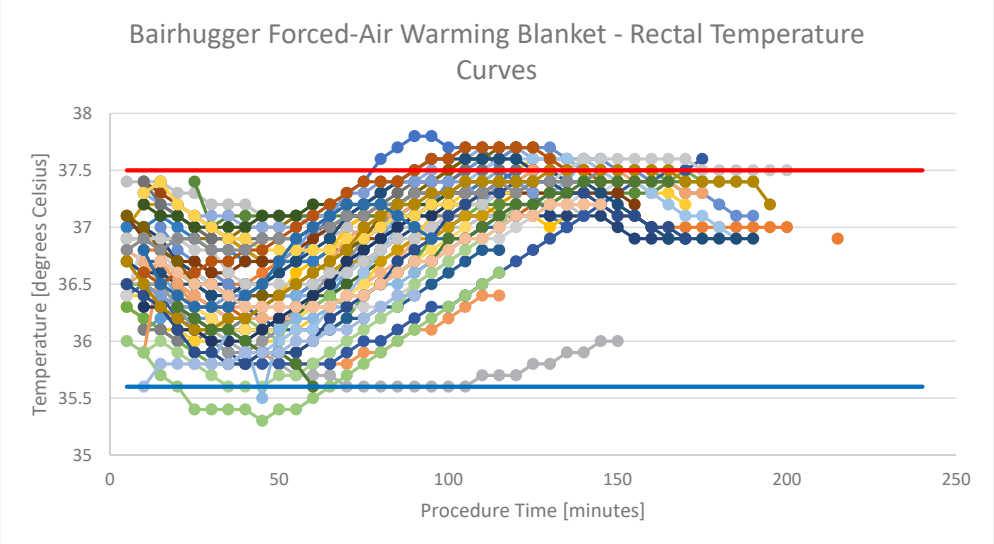


Figure 2: Bairhugger Rectal Temperature Curve



PEDIATRIC ANESTHESIOLOGY 6

Carotid peak flow velocity variation as a surrogate of aortic peak flow velocity variation in a pediatric population. Preliminary results.

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INTRODUCTION: Guiding resuscitation in pediatric population is still a challenge. Intravenous fluids and vasoactive agents are the most commonly administered therapies for the critically ill and are the cornerstone of hemodynamic management. Invasive dynamic indexes demonstrated to be good predictors of fluid responsiveness. Still, they require invasive monitoring, which is difficult to establish in children. A practical less invasive approach, as Transthoracic echocardiography (TTE), can be helpful for volume status assessment. Echocardiographic indexes have been used to estimate intravascular volume and predict fluid responsiveness. A recent systematic review suggested that the Aortic peak flow velocity variation (ΔVpeak) is the only dynamic preload variable capable of predicting fluid responsiveness in children. However, surgical patients often have inadequate cardiac windows, making transthoracic echocardiography examination challenging. An easier alternative proposed is the common carotid Doppler ultrasonography (CDU).

We hypothesize that measuring carotid peak flow velocity variation (ΔVpeakCar) can be used to surrogate ΔVpeak in children. The aim was to compare ΔVpeak with ΔVpeakCar in mechanical ventilated pediatric patients and establish their interchangeability.

METHODS: A prospective, transversal and observational study was performed. Pediatric patients under 12 years old, scheduled for superficial minor surgery with general anesthesia and mechanical ventilation, were included. Before surgery started and after anesthesia induction, a TTE and CDU were performed by a pediatric cardiologist using a Sonosite MicroMaxx (Fujifilm, USA) equipped with a phased array transducer (1–5 MHz) and a linear transducer (6–13 MHz), respectively. Maximum and minimum flow velocity were determined from pulsed Doppler waves of blood flow at the left ventricle outflow tract (LVOT) and the left common carotid artery (CCA) during the respiratory cycle. Flow variation at each level was calculated as ΔVQ=Qmax-Qmin/Qmean, where Q=Vpeak at LVOT and CCA.

Continuous variables are expressed as mean±SD. Pearson correlations and Linear regression were used to determine the product-moment relationship and the coefficient of determination of ΔVpeakCar. Paired Sample t-Test was used to compare means. Bland-Altman was used to describe the interchangeability between them. The concordance rate was assessed with an X-Y 4-quadrant plot with a 15% exclusion zone. $p<0.05$ was considered significant.

RESULTS: Forty-one patients (66±49 months, 1-130 months; 28±21 Kg, 3.8-72 Kg) were included. No significant difference was found between ΔVpeak and ΔVpeakCar (Table 1). Data showed a significative correlation ($r=0.92$; $p<0.05$) with a coefficient of determination of $r2=0.85$ (ΔVpeakCar= 0.29 + 0.87 ΔVpeak) (Figure 1). Bland Altman's analysis showed a bias of 0.5% (SD=2.4%; 95% CI, -0.2-1.3) with a limit of agreement of 4.8% (Figure 2). The X-Y 4-quadrant concordance rate was 90% (Figure 3).

CONCLUSION: In this group of patients, the measurement of the peak velocity at the CCA level showed a good correlation with that measured at the LVOT, having a high coefficient of determination and a high concordance rate. The interchangeability between them had a low bias with just an acceptable clinical limit of agreement. In conclusion, ΔVpeakCar could be used with precaution as a surrogate of ΔVpeak in children when clinical decisions are needed.

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Table 1. Ultrasound hemodynamic flow parameters registered at different sites.

	LVOT (mean±SD)	CCA (mean±SD)	Significance
PFv Variation (%)	6.3±6.2	5.8±5.7	NS
Maximun PFv (cm/s)	88.0±19.3	129.4±36.8	$p<0.05$
Minimun PFv (cm/s)	80.5±18.2	118.9±35.4	$p<0.05$

PFv: peak flow velocity. LVOT: left ventricle outflow tract. CCA: common carotid artery. NS: non-significative.

Figure 1. Scatter plot ΔVpeak vs $\Delta Vpeak_{Car}$.

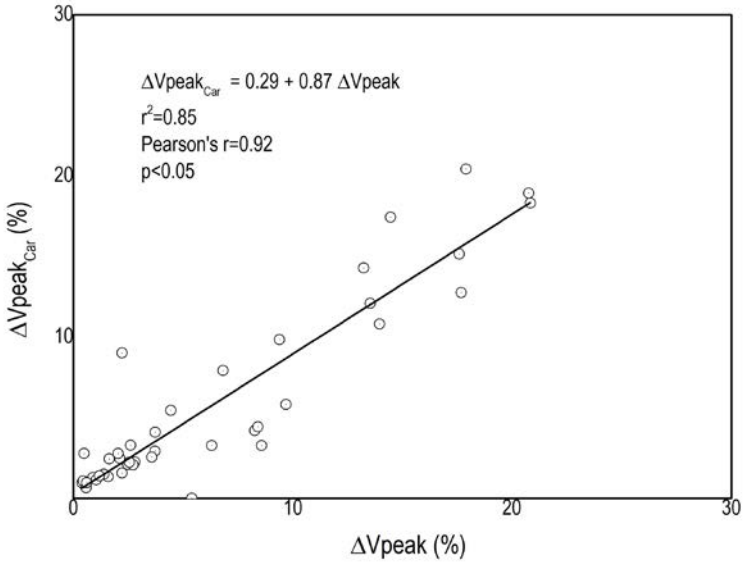


Figure 2. Bland-Altman analysis between ΔVpeak and $\Delta Vpeak_{Car}$.

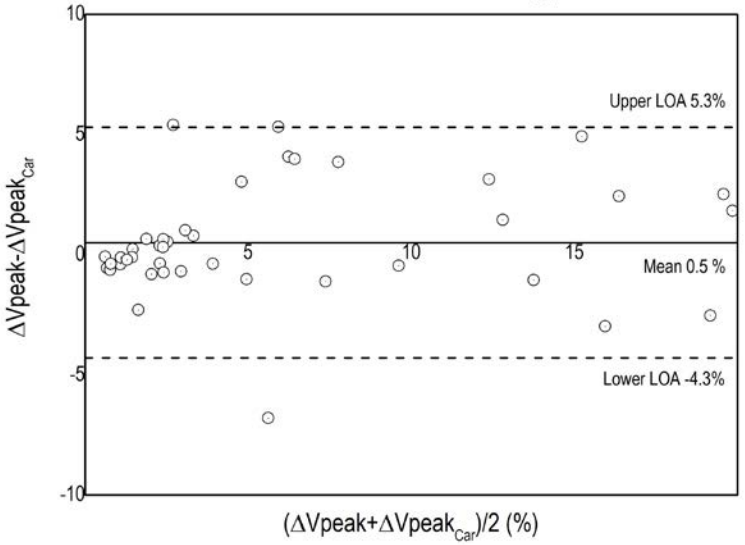
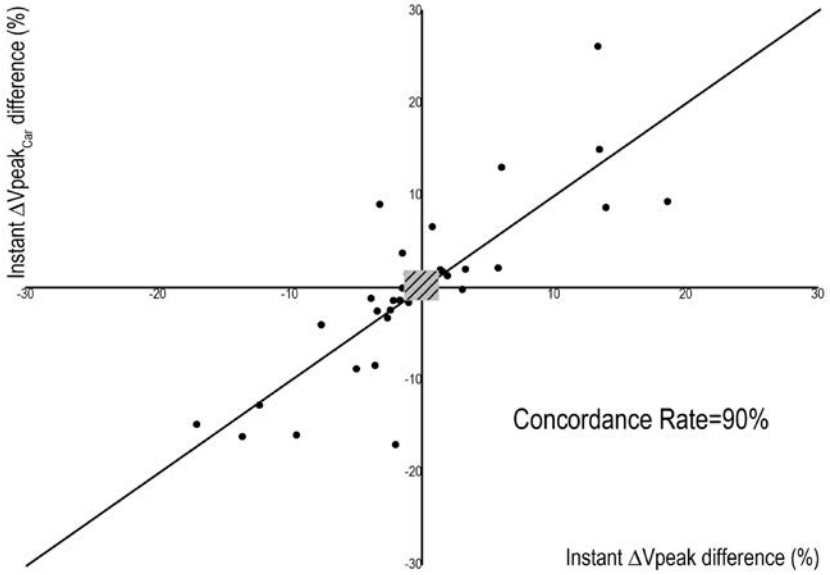


Figure 3. X-Y 4-quadrant plot of instant difference betwen ΔVpeak and $\Delta Vpeak_{Car}$.



PEDIATRIC ANESTHESIOLOGY 7

Spinal anesthesia as an alternative to general anesthesia in infants undergoing urologic day surgery

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INTRODUCTION: The use of spinal anesthesia (SA) in infants avoids endotracheal intubation and use of systemic sedatives[1]. Additionally, SA can reduce the risk of early postoperative apnea[2] and improve hemodynamic stability in infants[3]. Besides being a safe alternative to GA, SA can expedite the operative workflow[4]. We hypothesized that in the urologic day surgery setting, SA is an alternative to GA that avoids intubation and intraoperative opioids and reduces OR and PACU time.

METHODS: Eighty-three patients underwent SA at our hospital for urologic day surgery following a previously published infant protocol[4] (2019P002042), 10 of whom were planned inpatients and thus excluded from analysis. Patients <10 months and <10 kg were candidates for SA. Demographic and intraoperative variables were recorded from the electronic medical record (Table 1). As a pilot study, a subset of our SA database (n=19) was matched to GA patients by age, weight, ASA status, and procedure length. Primary outcomes were overall OR time as defined by in-room to room exit, and PACU recovery time between groups. The secondary outcome was use of intraoperative opioids. Matched comparisons were performed in R using one-sided Wilcoxon signed rank tests. Here, we report overall database statistics as well as preliminary results from the matched cohort analysis.

RESULTS: Demographics of 73 patients are outlined in Table 1. Two cases started under SA were converted to GA due to intolerance of laparoscopic insufflation and continued leg movement following spinal placement, respectively. Intrathecal clonidine (ITC) was administered in 44 cases (60.2%), and a novel combined spinal/caudal catheter anesthesia technique[5] was used in 9 (11.8%). Intraoperative airway changes occurred in 7 patients (5 received ITC, 2 did not), with 4 patients requiring chin lift and 3 resolving spontaneously. All patients were brought awake and ready to feed to the PACU without need for additional interventions, and were discharged after feeding. In our pilot study, 19 GA-SA pairs (38 patients) were closely matched (Table 1). Overall OR time was significantly shorter in the SA group ($Z=1.89$, $p=0.03$, effect size $r=0.43$, Figure 1a), despite no significant differences in operative time ($Z=1.59$, $p=0.06$). PACU recovery time was also significantly shorter in the SA cohort ($Z=2.13$, $p=0.016$, effect size $r=0.49$, Figure 1b). SA patients received no opioids whereas 63.1% of GA patients did (n=12, Figure 2).

CONCLUSION: In this study, we show that SA reduces total OR and PACU time compared to GA while avoiding intraoperative opioids. Our experience demonstrates that SA is a viable alternative to GA in infants undergoing urologic day surgery.

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Overall database (n=73)	**Chronological age (months)[a]**			5 (IQR 3.7-6.1)
	Sex			
	Male (n, %)			71 (97%)
	Female (n, %)			2 (3%)
	Born at term (%)			65 (93%)
	Weight (kg)[a]			7.3 (IQR 6.5-8.6)
	ASA status (I, II)			I (60), II (13)
	Length of surgery (min)[a]			75 (IQR 66-90)
	<=60 min			15 (21%)
	61-90 min			41 (56%)
	>90 min			17 (23%)
	Conversion to GA (%)			2 (2.7%)
	Use of adjunctive intravenous sedation (%)			16 (22%)
	Time required for placement of spinal (min)[a]			9 (IQR 7-13)
	Surgery type (n, % of cases)			
	Inguinal hernia repair			15 (21%)
	Hypospadias repair			14 (19%)
	Correction of webbed penis/hidden penis/scrotoplasty			24 (33%)
	Chordee correction			11 (15%)
	Orchiopexy			6 (8%)
	Hydrocelectomy			1 (1 %)
	Circumcision			2 (3%)
Matched analysis (n=38)		**GA (n=19)**	**SA (n=19)**	**Mean pairwise difference**
	Weight (kg)	7.7 (IQR 7-8.7)	7.7 (IQR 7-8.4)	0.38 kg
	Age (days)[a]	184 (IQR 156-227)	198 (IQR 165-229)	5 days
	ASA status (I, II)	I (16), II (3)	I (16), II (3)	N/A
	Surgery length (min)[a]	57 (IQR 44-85)	72 (IQR 61-94)	14.5 min

Table 1. Demographic data for patients in overall database (n=73) and matched cohort analysis. [a]=median, interquartile range (IQR)

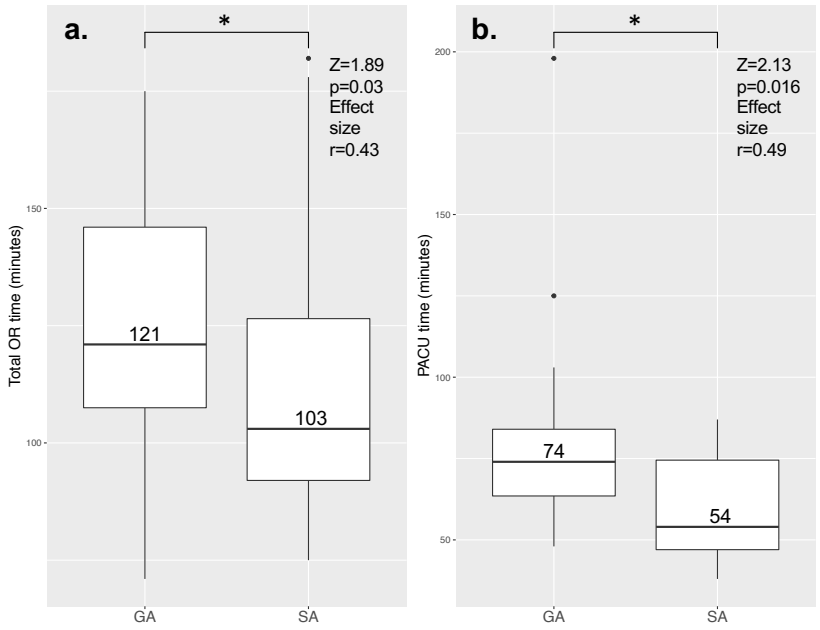

Figure 1. Comparison of total OR time and PACU time between patients undergoing urologic day surgery under general anesthesia (GA) and spinal anesthesia (SA). *=p<0.05. One-sided Wilcoxon signed-rank tests were used to compare total OR and PACU time.

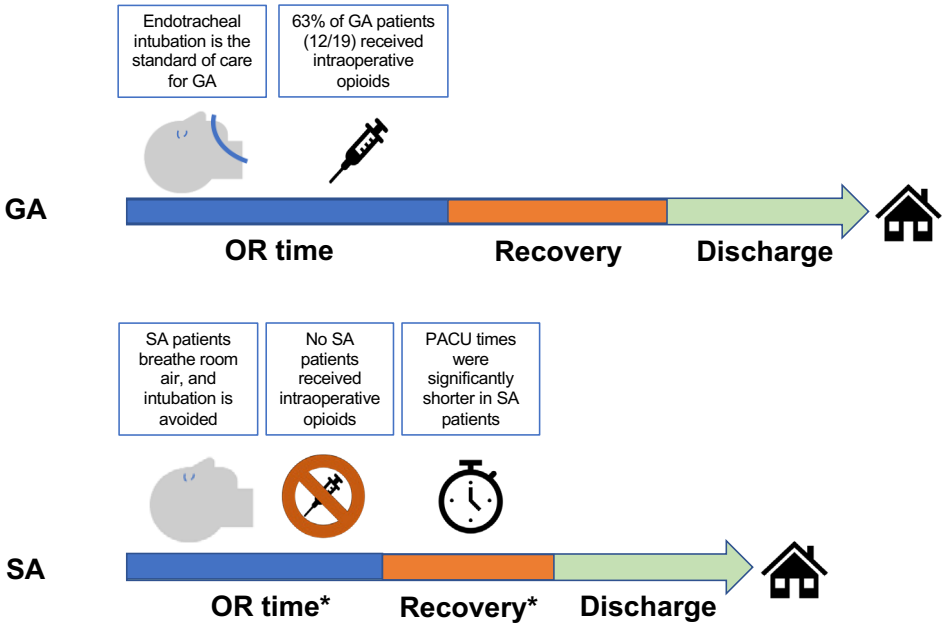

Figure 2. Our pilot study of 19 matched GA-SA pairs shows that SA allows for shorter OR time and faster PACU recovery time in patients undergoing urologic day surgery while avoiding intubation and intraoperative opioid medications. *=statistically significant differences as found by Wilcoxon signed-rank tests ($p<0.05$)

PEDIATRIC ANESTHESIOLOGY 8

Predictors of early extubation after pediatric liver transplant

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INTRODUCTION: Liver transplantation is the life-saving treatment for many end-stage pediatric liver diseases with significant perioperative physiologic derangements. Despite this, early extubation after surgery has been proposed in small studies with a positive safety signal and potential for improved outcomes.[1-3] The purpose of our study was to investigate the rate of intra-operative extubation at a single high-frequency transplant institution, to delineate outcomes and identify predictors of early extubation.

METHODS: After obtaining ethics approval, the records of 192 children who underwent liver transplantation between 2013 to 2020 were retrospectively analysed. We classified the patients in two groups; those who were extubated intra-operatively and those who remained intubated in the intensive care unit (ICU). We recorded multiple pre-operative, intra-operative and post-operative variables (Table 1,2). We used student t-test to analyse continuous data and Chi square test to analyse categorical data. A p-value of < 0.05 was considered significant.

RESULTS: All patients that underwent liver transplant between 2013 and 2020 were included in the study. 23/192 children (12%) were extubated intra-operatively. 82.6% of those extubated underwent liver transplant after 2017. Younger patients were more likely to remain intubated (Table 1). There was no statistical difference between the 2 groups in regards to: preoperative disposition, preoperative INR and bilirubin, quantity of crystalloid or colloid administered and peak lactate (Table 1). Criteria which were statistically significant for successful extubation included: older age, shorter length of stay (LOS) in hospital preoperatively, shorter duration of surgery, less red blood cell (pRBC) and fresh frozen plasma (FFP) transfusion and the presence of regional anesthesia (Table 1). None of the patients who were extubated had to be reintubated in the ICU. Our data also demonstrates that the early extubation group had a shorter ICU LOS, shorter hospital LOS, and less graft complications (Table 2). Furthermore, the non-extubation group had a ventilator induced pneumonia (VAP) rate of 10.7% and reintubation rate of 12.4% (Table 2).

CONCLUSION: Our data demonstrates that 12% of patients were extubated intraoperatively and did not require reintubation in the ICU; however, 82.6% of these occurred after 2017 indicating a temporal trend towards extubation in more recent years. Pre-operative and intra-operative predictors of extubation included shorter LOS in hospital prior to transplant, older age, shorter length of surgery, smaller volume of pRBC and FFP transfused and utilization of regional anesthesia. Furthermore, the extubation group demonstrated a favourable clinical profile with decreased ICU and hospital LOS. These parameters can potentially guide decision making towards predicting early extubation candidates after pediatric liver transplantation.

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Table 1 – Demographic and Clinical Characteristics in Children Extubated and not Extubated Intraoperatively after Liver Transplantation

Variables	Extubated	Not Extubated	p value
	n=23 (12%)	n=169 (88%)	
Demographics			
Age (months)	108 (22.5-174)	19 (8-73.5)	0.0038
Weight (kg)	30.7 (11.4-45.3)	11.3 (8-21.3)	0.0125
Preoperative			
Preop disposition			0.1490
Home	17 (73.9%)	93 (55%)	
Ward	6 (26.1%)	62 (36.7%)	
PICU	0 (0%)	14 (8.3%)	
Days in hospital preop (days)	2 (2-3)	3 (2-29)	0.0203
Preop INR	1.2 (1.1-1.4)	1.2 (1.1-1.6)	0.9830
Preop bilirubin	22 (5-174)	89 (11-201)	0.5291
Intraoperative			
Duration of surgery (hours)	510 (465-653)	610 (508-689)	0.0471
Crystalloids (mL/kg)	85 (56.0-128.0)	63.2 (42.7-88.5)	0.2595
Colloids (mL/kg)	20.9 (15.6-43.1)	36.5 (20.8-53.1)	0.1103
Blood (mL/kg)	9.6 (0-17)	31.2 (16.5-51)	0.0000
FFP (mL/kg)	8.5 (0-22.4)	30.8 (13-62.2)	0.0000
Highest lactate	4.6 (3.5-5.3)	5.4 (4.3-7.4)	0.0564
Regional Block	10 (43.5%)	3 (1.8%)	0.0000

NB: Continuous variables are reported as median and interquartile range (IQR) and categorical variables are expressed as number and percentages.

Table 2 - Clinical outcomes and complications in children extubated and not extubated intraoperatively after liver transplant.

Variables	Extubated	Not Extubated	p value
Postoperative			
Duration of Mechanical Ventilation (hours)	0 (0-0)	26 (15.2-114.9)	0.0000
Ventilator Acquired Pneumonia (VAP)	0 (0%)	18 (10.7%)	0.1043
Reintubation	0 (0%)	21 (12.4%)	0.0767
Graft complications	0 (0%)	34 (20.1%)	0.0194
PICU Length of Stay (hours)	26.6 (22.3-45.6)	92.89 (49-224.2)	0.0000
Hospital Length of Stay (hours)	432 (317-564)	732 (456-1632)	0.0000

NB: Continuous variables are reported as median and interquartile range (IQR) and categorical variables are expressed as number and percentages.

PEDIATRIC ANESTHESIOLOGY 9

Early Extubation in Pediatric Liver Transplantation Associated with Improved Post-Operative Outcomes

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INTRODUCTION: Early extubation after liver transplantation has been utilized in adult anesthesia since the late 1990s. Initial studies showed that by extubating patients in the early post-operative period, patients required shorter Intensive Care Unit (ICU) stays, decreased hospital length of stay and reduced costs with no increase in respiratory failure and reintubation rates[1,2]. Although this method of 'fast-track' liver transplantation has gained popularity, it is still not standard of practice at many pediatric institutions and anesthesiologists facilitating pediatric liver transplantation have only recently begun to adopt early extubation. There are many reasons why pediatric anesthesiologists are concerned about immediate post-operative extubation: graft function, vessel patency, graft-recipient mismatch, pre-existing malnutrition, depressive effects of analgesics and emotional difficulties among children. To date there have been a few manuscripts describing single-center experience in pediatric hospitals with immediate post-operative extubation, but there is scarce data on the post-operative impact this technique confers[3,4]. Over the last 6 years, we have actively attempted immediate extubation after pediatric liver transplantation in the majority of our patients and tracked the post-operative course to evaluate if this technique offers similar benefits to that in adult transplantation.

METHODS: After IRB approval, we performed a retrospective analysis of all pediatric liver transplantation cases performed at our hospital from January 2014 to June 2021. We collected baseline demographic data and information on the intra-operative management including intravenous fluid, blood product and medication administration. We then collected data on any events that may be related to extubation including need for re-intubation, high flow nasal cannula requirements, issues with graft function (including arterial thrombus, venous thrombus, need for re-exploration, graft failure requiring re-transplantation), PICU length of stay (LOS) and hospital LOS.

RESULTS: 173 patients were included in our analysis with a median age of 3 years (range:15 days-21 years) and weight 14.4kg (range: 3.5-102.2kg). 69.9% (121 patients) were extubated in the OR post-transplant. Average ICU stay in the early extubation group was 4.7 days vs 11.4 days in the delayed extubation group. Average hospital length of stay was 13.1 days in the early extubation group vs 22.8 days in the delayed extubation group. The percentage of patients requiring high flow nasal cannula was 10.7% for the early extubation group and 23.1% for the delayed extubation group. Graft function issues such as arterial or venous thrombus, decreased arterial or venous flow requiring re-exploration and graft failure necessitating re-transplantation occurred in 15.7% of patients in the early extubation group vs 21.2% of patients in the delayed extubation group.

CONCLUSION: This data shows that our institution's experience with immediate post-operative extubation following liver transplantation has not only been successful, but it has led to improved outcomes in the form of shorter ICU and hospital LOS, decreased high flow requirements and decreased incidence of graft malfunction. This is important because while there have been reports of the ability to successfully extubate pediatric patients post liver transplant, there has been minimal data on if this practice actually improves outcomes. Future research looking at pain scores, analgesic requirements and time to first bowel movement between the two groups may further delineate the improved outcomes seen from early extubation.

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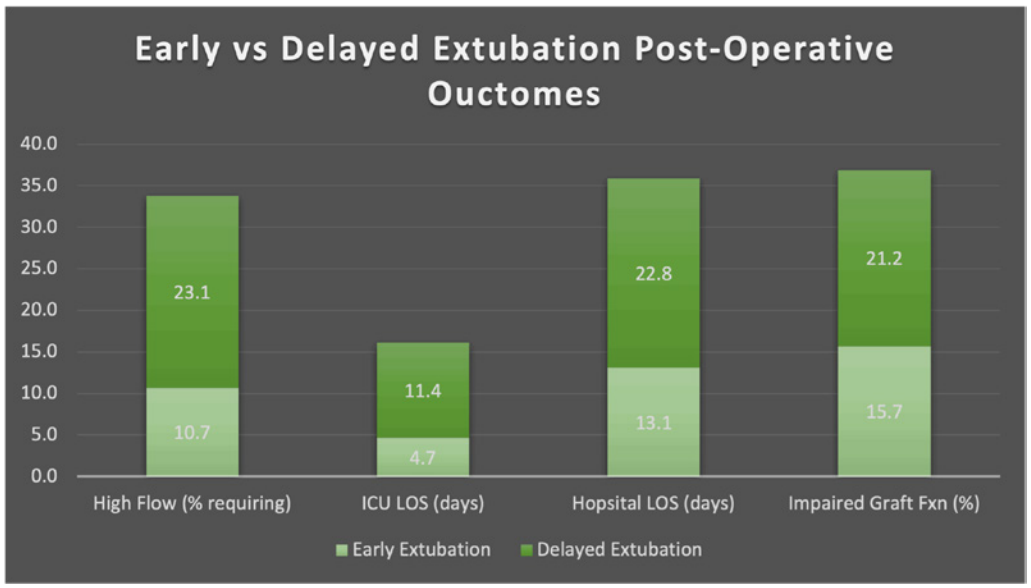

PEDIATRIC ANESTHESIOLOGY 10

Racial/Ethnic Variability in Use of General Anesthesia for Pediatric Magnetic Resonance Imaging

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INTRODUCTION: Children increasingly undergo diagnostic imaging procedures, sometimes with general anesthesia (GA). It is unknown whether or not the use of GA differs by race/ethnicity among children undergoing magnetic resonance imaging (MRI) scans.

METHODS: This is a retrospective cohort study of GA use for pediatric patients from 0 to 21 years of age who underwent MRIs from January 1, 2004 to May 31, 2019. The study sample was stratified into five age groups: 0 to 1, 2 to 5, 6 to 11, 12 to 18, and 19 to 21. Analysis was performed separately for each age group and the entire sample.

RESULTS: Among the 525,986 MRI encounters by 457,948 pediatric patients, 33,001 encounters had GA (6.3%). In the all-age sample, after adjusting for confounders and repeated observations, Asian (adjusted odds ratio [aOR], 1.14, 95% confidence interval [CI], 1.05-1.23; P = 0.001), Black (aOR, 1.16, 95% CI, 1.09-1.24; P < .001), and Hispanic (aOR, 1.08, 95% CI, 1.03-1.14; P = 0.004) patients were more likely to receive GA for MRIs than White patients. This finding remained in age-stratified analysis for Black patients 2 to 18 years old, Asian patients 0 to 5 years old, and Hispanic patients aged 0 to 1.

CONCLUSION: Children of color were more likely to receive GA during MRI scans than White children. Future research is warranted to delineate whether this phenomenon signifies disparate care for children based on their race/ethnicity.

PEDIATRIC ANESTHESIOLOGY 11

Low-dose intraoperative opioids and its association with PACU outcomes: a retrospective equivalence study

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INTRODUCTION: Opioids are a mainstay of intraoperative and postoperative analgesia in pediatric surgical patients, but also have significant dose-dependent side-effects. Significant variation in intraoperative dose administered occurs, but the relationship between intraoperative opioid administration and postoperative outcomes is unclear. We examined the relationship between intraoperative opioid dose among children and PACU outcomes; we hypothesized that pediatric patients receiving the lowest amounts of opioids intraoperatively would have higher pain scores, more opioid administrations, and less antiemetic administrations than those receiving the highest amounts.

METHODS: We performed a retrospective cohort study of eleven select procedures at a single pediatric quaternary care institution. Patients <19 years of age, American Society of Anesthesiologists physical status classification I-III, who underwent one of 11 procedures under general anesthesia, without regional anesthesia, and were admitted to the post-anesthesia care unit (PACU) afterwards at Stanford University Children's Hospital between May 4th, 2014 and August 31st, 2019 were eligible for inclusion. The exposure of interest was total intraoperative opioid dose. It was analyzed as quartiles, comparing each higher quartile to the lowest quartile. The primary outcome of interest was the first conscious pain score in the PACU. Secondary outcomes of interest included mean PACU pain score; PACU opioid use; and PACU antiemetic use. Linear regression models were fitted for continuous outcomes and logistic regression models were fitted for binary outcomes, controlling for confounders. To further explore the effects of opioid-free anesthetics, an exploratory analysis was also performed, categorizing intraoperative opioid dose as none (0 MEU/kg) or any (>0 MEU/kg), and analyzing the same outcomes for procedures where >=5% of cases received no intraoperative opioids.

RESULTS: 2583 patients were included, with mean (standard deviation [SD]) age of 8.10 (5.06) years, 1587 (61.4%) of whom were male. After adjusting for confounders, none of the higher opioid-dose quartiles had CIs for the difference in first conscious pain score or mean PACU pain score that crossed the specified boundaries of -1 or +1. After adjusting for confounders, the ORs (95% CI) for receiving opioids in the PACU were 1.24 (0.96 - 1.59), 1.09 (0.8 - 1.44) and 1.11(0.80 - 1.55) for the second, third and fourth (highest) quartiles respectively. After adjusting for confounders, the OR for antiemetic use in the second quartile compared to the lowest quartile was 1.73 (95% CI: 1.01 - 2.98); for the third quartile compared to the lowest was 2.11 (95% CI: 1.05 - 4.25), and for the highest quartile compared to the lowest it was 1.90 (95% CI: 0.89 - 4.06). Under a post hoc superiority analysis, the second and third quartiles were associated with significantly higher odds of receiving antiemetics than the lowest. The adjusted OR (95% CI) associated with receiving intraoperative opioids was 1.21 (0.86 - 1.70). After adjustment, the estimated mean (95% CI) increase in total PACU opioid dose for patients who received intraoperative opioids was 0.021 (-0.005 - 0.048) MEU/kg.

CONCLUSION: In this retrospective analysis of the association between total intraoperative opioid dose and PACU outcomes in children who underwent general anesthesia for one of 11 surgeries at a single center, the lowest quartile was not associated with worse PACU pain outcomes. However, higher intraoperative opioid administration was associated with increased odds of receiving antiemetics in the PACU. These results suggest that reducing intraoperative opioid dose may not be detrimental to pediatric patient outcomes. While optimal dosing and combinations of opioid and non-opioid analgesics are not apparent for many surgeries, future investigations may focus on opioid dosing threshold effects on patient outcomes.

PEDIATRIC ANESTHESIOLOGY 12

The effects of intravenous dexamethasone in analgesic quality of pudendal nerve block in children undergoing hypospadias surgery

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INTRODUCTION: Administration of intravenous (IV) dexamethasone is known to increase duration of neuraxial block and improve quality of analgesia. Pudendal nerve block is commonly used in pediatrics undergoing hypospadias surgery and known to be safer and more effective than caudal block. In this study, we aimed to investigate the effect of IV dexamethasone on enhancing pudendal block for postoperative analgesia in children undergoing hypospadias surgery.

METHODS: In this prospective, double-blinded, and randomized study, we hypothesized that administration of 0.5 mg/kg of IV dexamethasone would increase the duration of pudendal nerve block by 20%, and a total of 46 patients were planned to be enrolled. From May to October 2021, 29 children under the age of 3 with American society of anesthesiology physical status (ASA PS) I-II were enrolled and analyzed. All patients were randomly allocated to either the control group (C group) or the dexamethasone group (D group). Pudendal block was conducted before the surgery, and patient controlled analgesia (PCA) was connected to patients 30 minutes before the end of the surgery. PCA regimen was 10 mcg/kg of fentanyl and 0.1 mg/kg ondansetron mixed with 0.9 % normal saline to 100 ml in total. Basal infusion rate was set at 0.1ml/hr, and the bolus analgesia for breakthrough pain was set at 0.2 mcg/kg of fentanyl and did not exceed 1mcg/kg per hour. Caregivers were educated to press the bolus button when the pain score was over 4 points. The primary outcome was the time of the first PCA bolus dose was administered. The secondary outcomes were the pain score, the number of PCA bolus attempts, the number of rescue analgesia at each time period, total amount of fentanyl administered, and overall parents' satisfaction. Pain score was assessed by FLACC scale, VAS, or Wong-Baker FACES pain scale, as appropriate. Comparisons between the groups were performed with Student's t-test, the Mann-Whitney rank-sum test, and Fisher's exact test as appropriate. The first PCA bolus administered time was estimated by the Kaplan-Meier survival curves and was compared using the log-rank tests. A P -value of 0.05 was considered significant.

RESULTS: A total of 35 patients were screened, and 6 of them were excluded for the following reasons: foreigner caregiver (2), refusal (2), failed block (2). A total of 29 patients were analyzed. Our primary outcome, the first PCA bolus administered time, did not show statistically significant difference between the two groups (5.35 hr vs. 6.5 hr, P = 0.568). The pain score, the number of PCA bolus attempts, the number of rescue analgesia at each time period, the total amount of fentanyl administered (50 mcg vs. 39.6 mcg, P = 0.365), and overall parents' satisfaction (3.0 vs. 3.0, P = 0.602) also did not show any difference between the two groups.

CONCLUSION: In present study, administration of IV dexamethasone did not present statistically significance in terms of the duration of pudendal nerve block and the quality of the block in children undergoing hypospadias surgery. The adequate number of patients should be enrolled to confirm these results.

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Table 1. Patients' baseline characteristics and perioperative data

	C group (N = 16)	D group (N = 13)	*P* -value
Patients characteristics			
Age (D)	418.0 ± 73.5	327.5 ± 77.1	0.845
Height (cm)	76.4 ± 2.1	74.6 ± 2.7	0.517
Weight (kg)	10.1 ± 2.0	9.3 ± 2.1	0.966
ASA PS			0.897
I	9 (56.3)	7 (53.8)	
II	7 (43.8)	6 (46.2)	
Perioperative data			
Anesthesia duration (min)	98.4 ± 6.1	91.9 ± 6.9	0.485
Operation duration (min)	67.0 ± 6.2	62.3 ± 7.4	0.629
Intraoperative fluid (ml)	108.4 ± 8.6	103.1 ±13.0	0.724
PONV in PACU	0	0	NA
Heart rate in PACU (min^{-1})	138.6 ±6.8	134.6 ±6.5	0.682
PACU duration (min)	32.8 ± 1.0	33.3 ± 1.1	0.677

Data were presented as mean ± SD, median [interquartile range] or n (%).

ASA PS (American society of anesthesiology physical status); PONV (postoperative nausea/vomiting); PACU (post anesthesia care unit); NA (not available)

Table 2. Primary and secondary outcomes

	C group (N = 16)	D group (N = 13)	*P* -value
Pain score			
In PACU	1.0 [0.75, 3.25]	1.0 [1.0, 2.0]	0.714
0~6hr	3.0 [1.75, 5.25]	0 [0, 4.0]	0.216
6hr~24hr	6.0 [4.0, 7.25]	5.0 [4.0, 6.0]	0.545
24hr~48hr	3.0 [1.75, 4.0]	3.0 [2.0, 4.0]	0.563
48hr~72hr	4.0 [2.0, 4.25]	3.0 [0, 4.0]	0.128
PCA bolus			
0~6hr attempt	2.0 [0.0, 4.3]	1.0 [1.0, 3.0]	0.562
6hr~24hr attempt	7.0 [2.8, 17.3]	7.0 [3.0, 12.0]	0.809
24hr~48hr attempt	6.0 [3.0, 8.0]	3.0 [2.0, 13.0]	0.611
48hr~72hr attempt	5.0 [2.0, 8.0]	3.0 [1.0, 8.3]	0.459
Total attempt	23.5 [13.0, 39.3]	14.0 [7.0, 43.0]	0.456

Table 2 continued

Real given	20.0 [13.5, 31.8]	16.5 [6.8, 40.3]	0.583
Total administered fentanyl (mcg)	50.0 ± 8.03	39.6 ± 7.65	0.365
Rescue analgesia			
In PACU	2 (12.5)	2 (15.4)	0.823
within 48hr	6 (37.5)	2 (15.4)	0.185
after 48hr	7 (43.8)	2 (15.4)	0.101
Total rescue	1.5 [1.0, 4.5]	1.0 [1.0, 2.0]	0.263
Other complications			
Fever within 48hr (>37.5)	5 (31.3)	3 (23.1)	0.624
PONV	2 (12.5)	0 (0)	0.186
Wound dehiscence	0	0	NA
Hospital stay (d)	10.0 [9.0, 10.3]	10.0 [10.0, 11.0]	0.629
Parents' satisfaction	3.0 [2.5, 4.0]	3.0 [3.0, 4.0]	0.602

Data were presented as mean ± SD, median [interquartile range] or n (%).

PCA (patient controlled analgesia); PACU (post anesthesia care unit); PONV (postoperative nausea/vomiting); NA (not available)

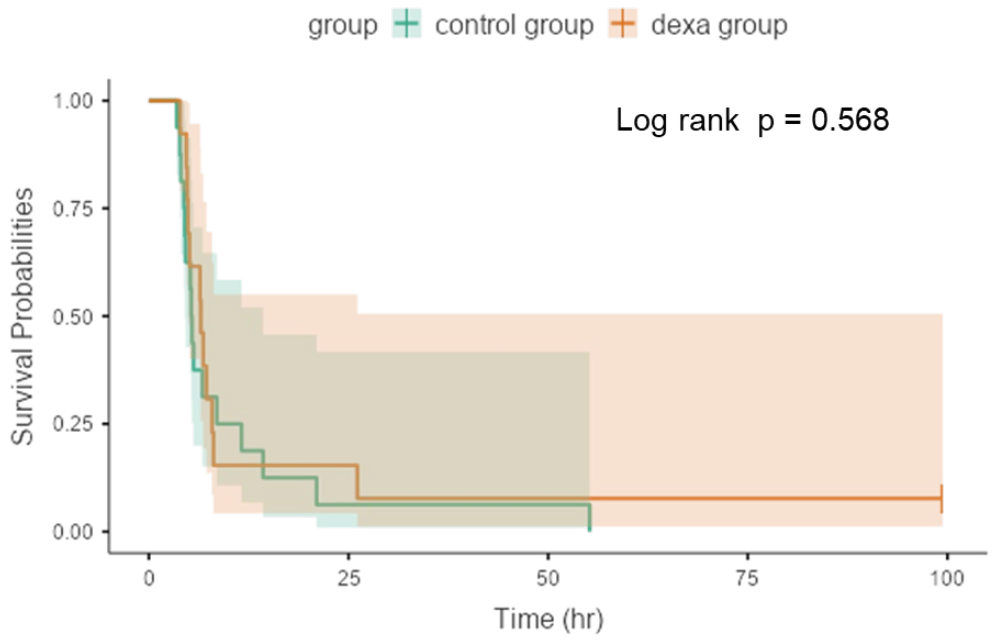

Figure 1. Comparison of PCA first bolus time between two groups

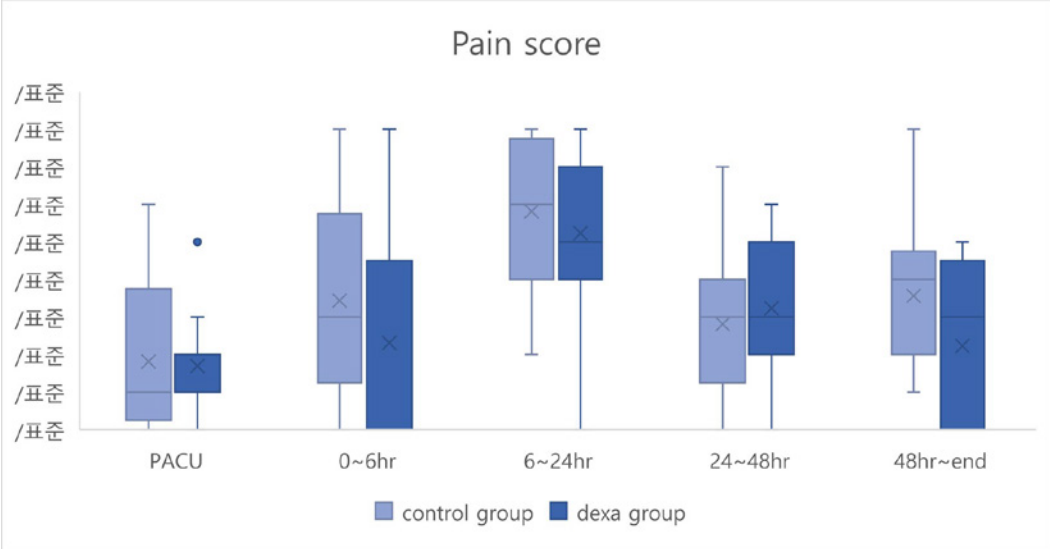

Figure 2. Pain score at each time period.

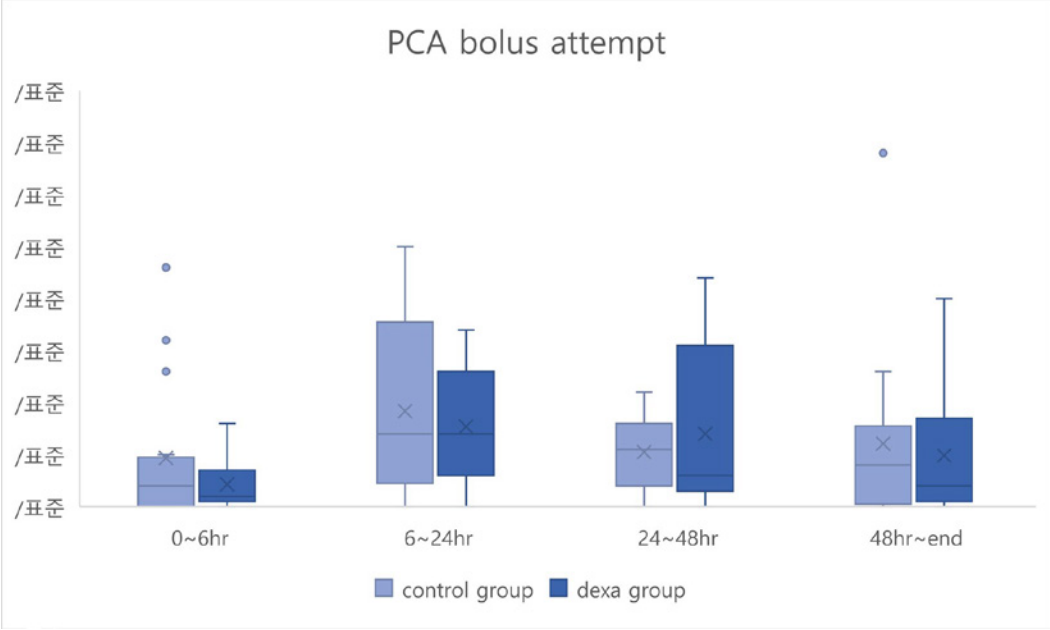

Figure 3. PCA bolus attempt by caregiver after surgery at each time period.

PCA (patient controlled analgesia)

PEDIATRIC ANESTHESIOLOGY 13

Age-Dependent EEG Signatures in Infants Receiving Spinal Anesthesia

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INTRODUCTION: Infants under spinal anesthesia appear to be sedated despite the absence of systemic sedative medications. In this study, we investigated the electroencephalogram (EEG) of infants under spinal anesthesia and hypothesized that we would observe EEG features similar to those seen during physiologic sleep.

METHODS: Continuous 4-channel frontal EEG data were recorded using the SedLine monitor after the administration of spinal anesthesia in infants undergoing infraumbilical surgeries (n = 34). We computed the power spectra and spectrogram for each subject using multitaper spectral estimation methods, and visually scored the data for episodes of EEG discontinuity or spindle oscillations. We characterized the relationship between EEG discontinuity or spindle activity and gestational age (GA), postmenstrual age (PMA), or chronological age using logistic regression analyses.

RESULTS: The predominant EEG patterns observed in infants under spinal anesthesia were slow oscillations, spindles, and EEG discontinuities (Figure 1). We observed spindles in infants under spinal anesthesia starting at about 8 weeks chronological age. The presence of spindle activity was best described by PMA ($p<0.05$), with spindles being more likely in infants with higher PMA (Figure 2). We also observed EEG discontinuities in infants under spinal anesthesia (Figure 3), the presence of which was best described by GA ($p<0.05$), with EEG discontinuities being more likely in infants with lower GA (Figure 4). These age-related changes in the presence of spindle activity and EEG discontinuities in infants under spinal anesthesia appeared to generally correspond to developmental changes in the sleep EEG in infants.

CONCLUSION: This work illustrates two key age-dependent transitions in EEG dynamics during spinal anesthesia in infants that may reflect the maturation of underlying brain circuits. Despite similarities between the EEG during spinal anesthesia and sleep in infants, the sedative state under spinal anesthesia is distinct in that this sedative state remains largely sustained throughout the duration of the neuraxial anesthetic. This tendency for infants to remain sedated under spinal anesthesia could reflect a shift in the balance between sleep and wakefulness that favors sleep.

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Table 1. Patient Characteristics (n = 34)

Chronological Age (weeks)	11.5 (9,17)
Postmenstrual Age (weeks)	49 (43, 56)
Gestational Age (weeks)	38 (35.2, 39)
Term	24 (71%)
Pre-term	10 (29%)
Gender	
Male	30 (88%)
Female	4 (12%)
ASA	
I	18 (53%)
II	13 (38%)
III	3 (9%)
Weight (kg)	5.3 (1.7)
Type of Procedures	
Inguinal Hernia Repair (Bilateral)	18 (53%)
Circumcision	9 (26%)
Inguinal Hernia Repair (Unilateral)	5 (15%)
Other procedures	2 (6%)

*Variables were reported as mean and standard deviation, median and interquartile range, or count and percentage.
*Spinal anesthesia was performed in the sitting position with maximal hip flexion, midline approach at L4–L5 interspace using a 25-gauge pediatric, Quincke type spinal needle. When free flow of CSF was identified, a mixture of 1 mg/kg of bupivacaine 0.5% (PF) alone or in combination with 1 mcg/kg of clonidine was administered

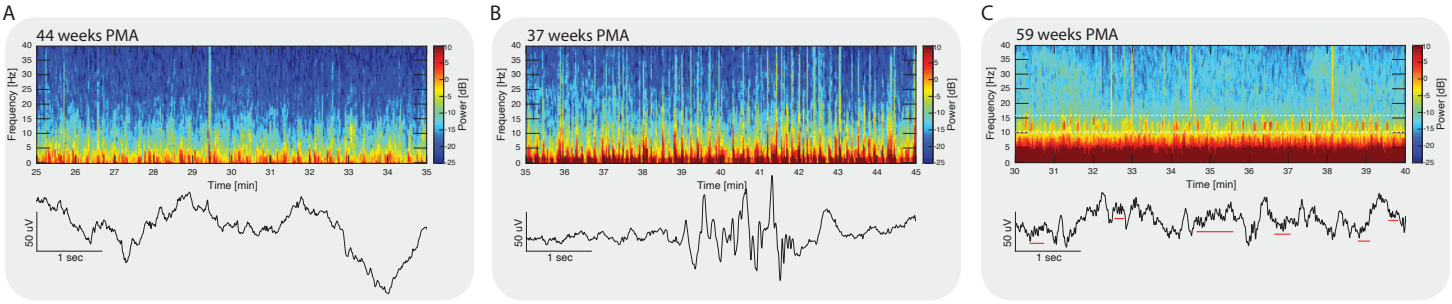

Figure 1. Illustrative spectrograms and time domain waveforms of infants under spinal anesthesia. A. The spectrogram and time domain waveform of a 11-week-old premature infant (33 weeks GA, 44 weeks PMA) under spinal anesthesia for bilateral inguinal hernia repair. The spectrogram shows a dominant low-frequency (slow/delta – 0.1 – 4 Hz) activity. A corresponding ten-second electroencephalogram trace recorded at minute 26 featuring slow-delta oscillations is shown. **B.** The spectrogram and time domain waveform of a 11-week-old premature infant (26 weeks GA, 37 weeks PMA) under spinal anesthesia for bilateral inguinal hernia repair and circumcision. The spectrogram shows an alternating pattern of burst events lasting a few seconds followed by periods of discontinuity of variable duration and amplitude. A corresponding ten-second electroencephalogram trace recorded at minute 44 shows alternating discontinuity events and high frequency bursts. **C.** The spectrogram and time domain waveform of a 20-week-old infant (38 weeks GA, 59 weeks PMA) under spinal anesthesia for chordee repair and circumcision. The spectrogram shows spindles (~10 to 16 Hz oscillations) and slow-delta oscillations (0.1 – 4 Hz). A corresponding ten-second electroencephalogram trace recorded at minute 32 from the spectrogram shows slow waves and spindles (red underlines).

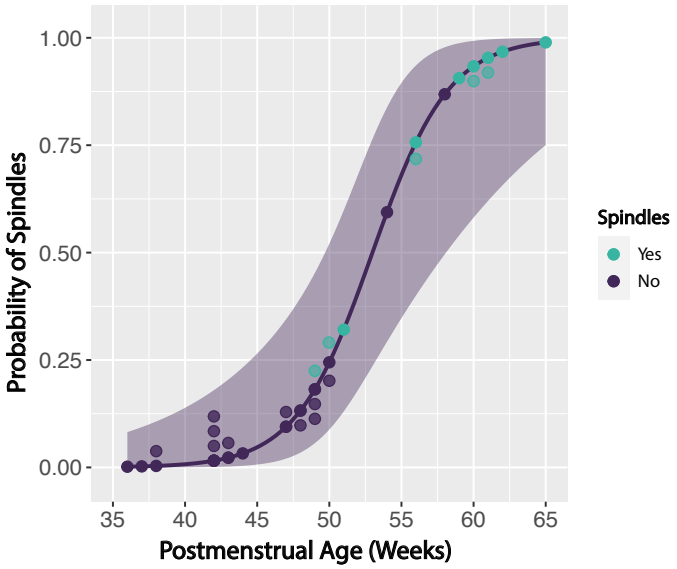

Figure 2. Logistic regression analysis of spindle probability as a function of postmenstrual age (PMA). The central bolded line represents the estimated probability of observing spindle activity as a function of PMA. The shaded bounds represent the 95% confidence interval for this regression model. The individual circles along the central line represent individual subjects, which were filled in green if spindles were observed or purple if spindles were not observed under spinal anesthesia. Model 1 shows that the probability of spindles under spinal anesthesia increases with increasing PMA, especially after approximately 50 weeks PMA.

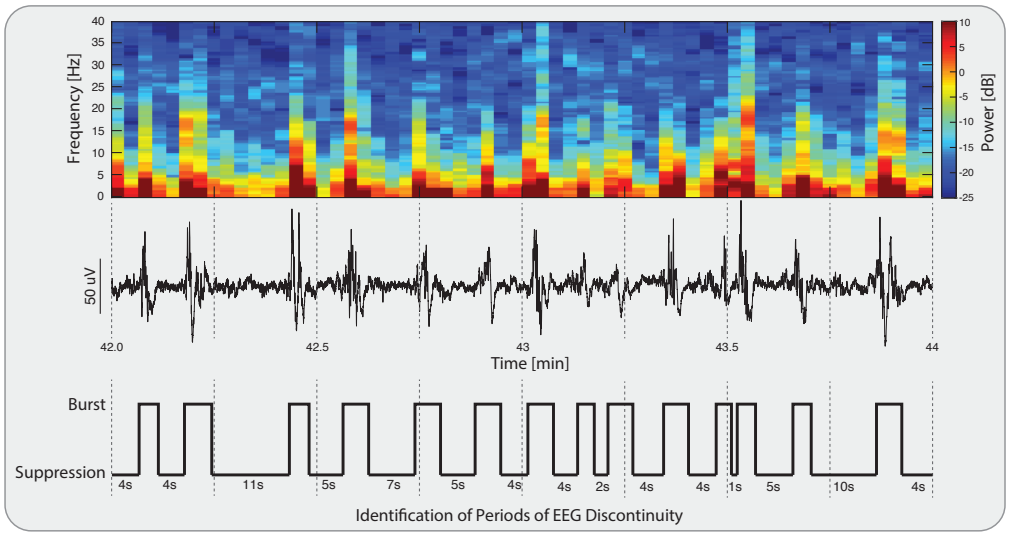

Figure 3. Example of EEG discontinuity in an infant. A two-minute EEG spectrogram and time domain waveform from a 9-week-old premature infant (29 weeks GA, 38 weeks PMA) under spinal anaesthesia for inguinal herniorrhaphy. The spectrogram and time domain waveform above show discontinuous activity characterised by an alternating pattern of burst events lasting a few seconds followed by periods of suppression of variable duration and amplitude. The bottom panel shows the discontinuities identified by visual scoring.

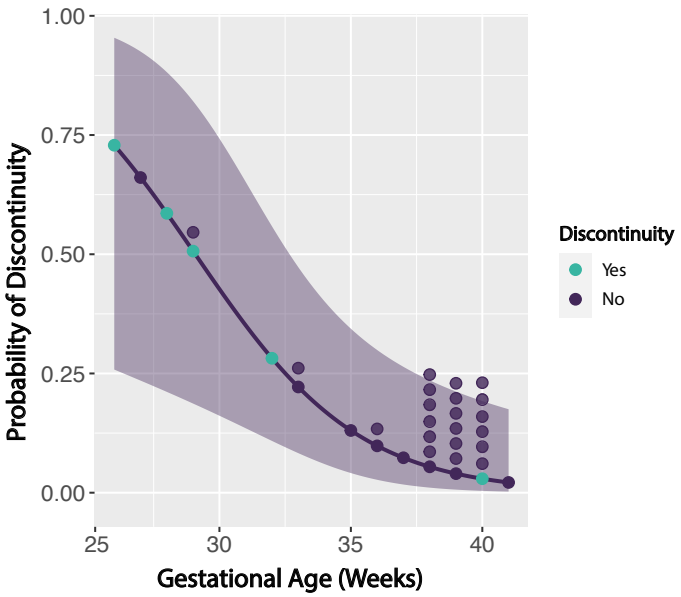

Figure 4. Logistic regression analysis of EEG discontinuity probability as a function of gestational age (GA). The central bolded line represents the estimated probability of observing EEG discontinuity as a function of GA. The shaded bounds represent the 95% confidence interval for this regression model. The individual circles along the central line represent individual subjects, which were filled in green if EEG discontinuities were observed or purple if EEG discontinuities were not observed under spinal anesthesia. This model shows that the probability of EEG discontinuity events under spinal anesthesia increases with decreasing GA, with an increased likelihood of observing EEG discontinuity in infants who were pre-term.

PEDIATRIC ANESTHESIOLOGY 14

Environmental and Socioeconomic Influences on Perioperative Complications

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INTRODUCTION: Children undergoing anesthesia and surgery can be at risk for perioperative respiratory adverse events (PRAEs). Our previous work validated the COLDS score, which integrates risk factors for PRAE into a prediction tool. The predictive ability of the COLDS score was modest, suggesting that additional unaccounted factors may contribute to PRAEs. Lower socioeconomic status has been historically associated with worse health outcomes, which may influence rates of PRAEs. Our study focuses on how socioeconomic factors may affect the risk of PRAEs, and has not been well-studied.

METHODS: Data was collected prospectively on patients 6 years and under who were scheduled to receive sedation or general anesthesia. Patients with artificial airways in place, or those with cyanotic heart lesions were excluded. The following factors were collected: any current URI symptoms and onset, underlying pulmonary disease (including second-hand exposure to smoke), procedure type, and airway device. We recorded any respiratory complications occurring during induction, maintenance, emergence from anesthesia, and in the PACU. Zip codes were collected for each patient, converted into census tracts and then cross-walked with geo-data from the CDC/ATSDR's Social Vulnerability Index (SVI). There are 4 major categories in the SVI: Socio-economic status, Household Composition and Disability, Minority Status & Language, Housing Types & Transportation. Each category was considered as an individual factor. Univariate and multivariable logistic regression were used to test the association between these factors and occurrence of PRAEs.

RESULTS: There were 1767 cases for analysis. Of those, 26 cases had zip codes outside of California, and were excluded. We found that 'Housing Types & Transportation' category was significantly correlated with increased risk of PRAEs (OR=1.88, p-value=0.045). After controlling for known patient and case factors associated with PRAE, we found that living in a zip code with a high prevalence of multi-unit structures was independently associated with PRAEs (OR=1.99, p-value=0.036).

CONCLUSION: It is known that lower socioeconomic status may be associated with worse health outcomes. Using zip code as a marker for socioeconomic status, we found a significant correlation between increased housing density with the incidence of perioperative respiratory events. Further investigation is planned to explain this association and evaluate other potential environmental factors contributing to PRAEs.

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PEDIATRIC ANESTHESIOLOGY 15

Intrathecal clonidine is associated with intraoperative BP, HR, and respiratory changes without affecting postoperative course in infants receiving spinal anesthesia for urologic day surgery

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INTRODUCTION: Spinal anesthesia (SA) for infants undergoing infraumbilical surgeries avoids systemic sedatives, airway instrumentation, reduces the risk of early postoperative apnea[1], and improves hemodynamic stability compared to general anesthesia[2]. A caveat of SA is its limited surgical duration. Clonidine is an adjunct that prolongs SA in infants[3], allowing for more complex procedures to performed; however, the safety and efficiency of intrathecal clonidine in infants undergoing day surgery is not well studied. In this study, we compared bupivacaine only SA (bSA) to SA with adjunctive clonidine (cSA) for infants undergoing urologic day surgery. We examined the intra- and postoperative courses of bSA vs. cSA patients.

METHODS: Sixty-two infants undergoing urologic day surgery under SA using a previously described protocol[4] were studied. Clonidine was used as an adjunct on a need-to-treat basis as decided by the surgeon and anesthesiologist during the preoperative huddle. Demographic, intraoperative, and postoperative data were collected from electronic medical records (Table 1). We compared vital signs, airway events, need for additional intraoperative sedation, and PACU length of stay between bSA and cSA groups. Continuous data were analyzed using t-tests or Mann-Whitney U tests based on data normality, whereas Z-tests or Fisher's exact tests were used for categorical data. Analysis was conducted in R.

RESULTS: Twenty-four bSA and 38 cSA patients were studied. Intraoperatively, average mean arterial pressure (MAP) was 59 mmHg in the bSA group and 53 mmHg in the cSA group (t=-2.84, df=46.7, p=0.003, Figure 1a). Mean heart rate (HR) was 135 bpm in the bSA group and 124 bpm in the cSA group (t=-2.69, df=41, p=0.005, Figure 1b). No differences were seen for oxygen saturation (SpO2) between groups (U=467, p=0.88, Figure 1c). In regards to intraoperative airway events, patients in the cSA group had significantly more hiccup-like short shallow inspirations (n=10, p=0.005, Fisher's exact test) and mild airway obstruction relieved by chin-lift (n=8, p=0.02, Fisher's exact test) compared to bSA patients. Additional sedatives were used in 29.2% and 10.5% of bSA and cSA cases, respectively, though this did not reach significance (p=0.09). Mean surgical duration was significantly longer in the cSA (59 min) than the bSA group (52 min, U =574.5, p=0.04). Interestingly, there was no significant difference in the mean length of PACU stay between cSA (69 min) and bSA groups (65 min). No patients required additional medications or interventions in the PACU.

CONCLUSION: Our study shows that while clonidine is associated with reduced intraoperative MAP and HR, and transient and observable airway changes requiring minimal or no interventions to resolve, PACU course was not affected in infants undergoing urologic day surgery. Additionally, clonidine can prolong surgery length, allowing for more complex procedures to take place.

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		bSA (n=24)	cSA (n=38)	p-value
Demographic	Chronological age (days)[a]	144 (range 55-339)	149 (range 37-250)	0.18
	Sex			
	Male (n, %)	23 (96%)	37 (97.4%)	--
	Female (n, %)	1 (4%)	1 (2.6%)	--
	Prematurity (gestational age<37 weeks, %)	3 (12.5%)	4 (10.5%)	1
	Weight (kg)[a]	7 (range 3.2-9.8)	7.4 (range 4.6-9.8)	0.36
	ASA status (I, II)	I (19), II (5)	I (31), II (7)	1
Intraoperative	Length of surgery (min)[b]	50 (IQR 41-64)	57 (IQR 53-65)	0.04*
	Surgery type (n, % of cases)			
	Inguinal hernia repair	8 (33.3%)	6 (15.8%)	--
	Chordee correction/repair	4 (16.7%)	7 (18.4%)	--
	Correction of webbed penis/hidden penis/scrotoplasty	8 (33.3%)	15 (39.5%)	--
	Orchiopexy	1 (4.2%)	5 (13.2%)	--
	Hypospadias repair	2 (8.3%)	3 (7.9%)	--
	Hydrocelectomy	0	1 (2.6%)	--
	Circumcision	1 (4.2%)	1 (2.6%)	--
	Vitals			
	Mean MAP (mmHg)[a]	59 (range 38-73)	53 (range 36-71)	0.003**
	Mean SpO2 (%)[a]	99 (range 96-100)	99 (range 96-100)	0.88
	Mean HR (bpm)[a]	135 (range 98-164)	124 (range 96-148)	0.005**
	Transient airway changes			
	Hiccup-like short shallow inspirations (n, %)	0 (0%)	10 (26.3%)	0.005**
	Mild airway obstruction relieved by chin lift (n, %)	0 (0%)	8 (30.7%)	0.02*
	Use of additional systemic sedatives (n, %)	7 (29.2%)	4 (10.5%)	0.09
Postoperative	Length of PACU stay (min)[a]	65 (range 31-109)	69 (range 33-175)	0.74

Table 1. Demographic and intraoperative data for bSA and cSA patients. [a]=mean, range, [b]=median, interquartile range (IQR). *=p<0.05, **=p<0.01. T-tests or Mann-Whitney U tests were used to compare continuous data depending on normality as determined by the Shapiro-Wilk test, whereas Z-tests and Fisher exact tests were used to compare categorical data (Fisher test used when x^2 expected frequencies in any cell was <5).

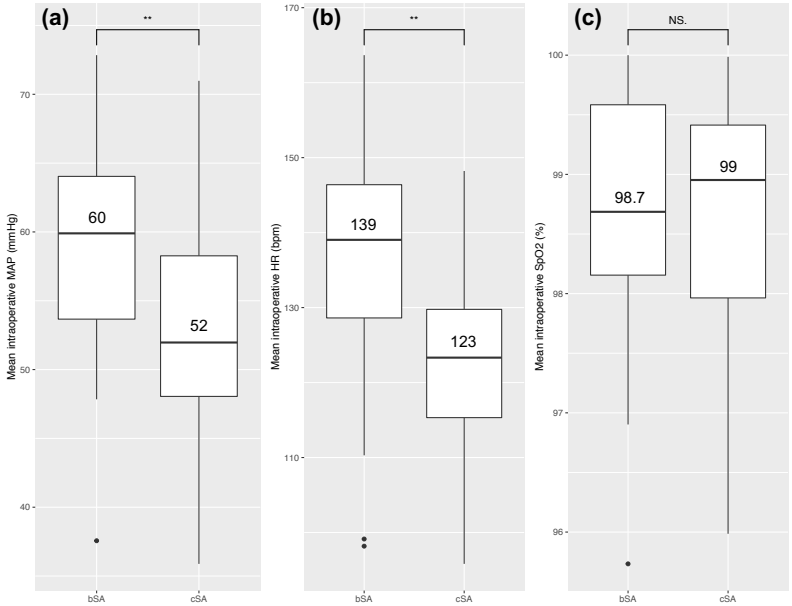

Figure 1. Comparison of intraoperative MAP (a), HR (b), and SpO2 (c) between patients who received bupivacaine only spinal anesthesia (bSA) and spinal anesthesia with adjunctive clonidine (cSA). MAP and HR were compared using one-sided t-tests, whereas SpO2 was compared using a Mann-Whitney U test as the data were not normally distributed. **=p<0.01, NS denotes non-significant differences.

PEDIATRIC ANESTHESIOLOGY 16

Sedation vs. General Anesthesia For Tracheal Intubation in Children with Difficult Airway

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INTRODUCTION: General anesthesia (GA) is the most common approach in children with difficult airways, however, some anesthesia providers elect to use intravenous sedation with spontaneous ventilation to secure the airway[1]. Previous data suggest that controlled ventilation with or without neuromuscular blockade is associated with a lower incidence of complications when compared to spontaneous ventilation in children with difficult airway, possibly due to a link between anesthetic depth and the incidence of complications during tracheal intubation[2]. The primary aim of our study is to establish if sedation with spontaneous ventilation has a different rate of first-attempt success of tracheal intubation (TI) and a different rate of complications as compared to GA.

METHODS: Using data from an international observational registry which prospectively collects data from pediatric patients with a difficult airway (PeDI registry), we evaluated the association of sedation versus GA with outcomes of children with difficult tracheal intubation. The primary outcome was first-attempt success of tracheal intubation. Secondary outcomes included number of intubation attempts, non-severe and severe complications. We used propensity score matching (PSM) to control for treatment selection bias and adjust for baseline characteristics. Generalized Estimating Equation models were conducted for both unmatched and matched data, and baseline characteristics found to be imbalanced after matching were included as covariates in post-matching models to establish the association between treatment (Sedation vs. GA) and outcomes.

RESULTS: Data from 34 hospitals between 2012 and 2020 was collected. A total of 1848 patients with anticipated difficult airway met inclusion criteria for the study. 75 patients received sedation and 1773 patients received GA, which resulted in 56 patients in the sedation group and 505 patients in the GA group after PSM. The rate of first-attempt success of tracheal intubation was 48.2% the sedation group and 48.5% GA-group (OR 0.9, 95% CI 0.5 - 1.6; p=0.81); The median number of intubations attempts was 2 [IQR 1, 3] in the sedation group and 2 [IQR 1, 2] in the GA group; with an incidence rate ratio of 1.2 (95% Confidence Interval 0.9-1.5 p=0.16). Complications overall where higher in the sedation group than in the GA group (26.8% vs. 15.3%; OR 2.1, 95%CI 1.1-4.0; p=0.023). Severe complications were higher in the sedation group as compared to the GA group (3.6% vs. 0.8%, OR 7.5, 95%CI 1.1-50.1; p=0.038). The rate of conversion from sedation to GA was 24% (18/75 cases).

CONCLUSION: Sedation and GA had a similar rate of first-attempt success of tracheal intubation in children with difficult airway in this cohort. However, patients receiving sedation were more likely to experience complications and severe complications than those who received GA.

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PEDIATRIC ANESTHESIOLOGY 17

In Vivo Effects of Fibrinogen Concentrate (FC) versus Cryoprecipitate on the Neonatal Fibrin Network Structure after Cardiopulmonary Bypass (CPB)

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INTRODUCTION: Bleeding is a serious complication of cardiopulmonary bypass (CPB) in neonates and is associated with substantial morbidity and mortality.[1] To adequately restore hemostasis, transfusion is often a necessity. However, given the risks associated with blood product transfusion, neonates would benefit from other effective, and safe, therapies to augment hemostasis after CPB. Our prior studies suggest that adult fibrinogen does not seamlessly integrate with neonatal fibrinogen and may result in prolonged clot degradation, thus increasing the risk of thrombotic events in neonates post-operatively. However, it is unclear if this is a direct result of the adult fibrinogen molecule or the other clot stabilizing factors (von Willebrand Factor (vWF) and Factor XIII (FXIII)) in cryoprecipitate.[2] An alternative to cryoprecipitate, fibrinogen concentrate (FC; RiaSTAP®, CSL Behring, Marburg, Germany) contains purified fibrinogen with a low volume of administration. The use of FC has been growing in popularity, but it has not been adequately studied in pediatric cardiac patients and the limited experience in adults may not be relevant to pediatric practice. Our study in infants undergoing cardiac surgery suggests that FC may be most beneficial in reducing post-CPB bleeding and transfusions in neonates when compared to cryoprecipitate when used as part of a post-CPB transfusion algorithm.[3] In this randomized control trial, we sought to compare clot structure, clot degradation rates, and post-CPB blood transfusions in neonates who are randomized to receive either FC or cryoprecipitate as part of a post-CPB transfusion algorithm.

METHODS: After IRB approval, 36 neonates were block randomized 1:1 to receive either FC (FC group) or cryoprecipitate (control group) as part of a post-CPB transfusion algorithm. Inclusion criteria for neonates included: 36-42 weeks gestational age, age < 30 days, APGAR score >6 at 5 minutes, non-emergent surgery, parental consent. Blood samples were collected from neonates undergoing cardiac surgery at four time points: 1) baseline; 2) after either FC or cryoprecipitate; 3) arrival to ICU; 4) 24h after ICU arrival. All samples were centrifuged to yield platelet poor plasma Clots were formed ex vivo from each time point. We then analyzed clots for fiber density (FD), clot degradation rates, and levels of thrombin, fibrinogen, FXIII, and vWF. Demographic information, post-CPB blood transfusions, and adverse events (AE) were collected. Based on our previous data, to detect a difference in degradation times between clots formed with neonatal fibrinogen and clots formed with adult fibrinogen with 80% power, we will enroll at total of 36 patients, with 18 in patients in each arm. All quantitative data will be analyzed using a paired t-test or Wilcoxon rank-sum test to determine differences between the two groups. Significance will be defined by a p-value less than or equal to 0.05.

RESULTS: Eighteen neonates were enrolled in each group. Demographics, intraoperative data, and post-CPB transfusion of packed red blood cells (pRBCs), fresh frozen plasma (FFP), and platelets were not different between groups (Table 1). Preoperative and post-operative coagulation values on ICU arrival were similar between groups. Three patients received prothrombin complex concentrate (PCC) as part of rescue hemostatic therapy: 2 in control group and 1 in FC group. Patients in the FC group received less cryoprecipitate (p=<0.001). There were two deaths within 30 days (controls) and 4 thrombotic events, 2 in each study group. Representative images of clots are shown in Figure 1. Clots from both groups had similar FD and 24-h degradation rates (Figure 2A-C). Procoagulant levels were lower in the FC group, but not statistically significant (Figure 3A-C).

CONCLUSION: This study suggests that while cryoprecipitate contains additional factors required for clot strength and stabilization, there is no significant difference in clot parameters in neonates who receive either cryoprecipitate or FC. Clinically, patients receiving FC appear to have adequate hemostasis with similar post-operative ICU labs and outcomes. FC may result in less post-CPB allogenic transfusions. Our data shows no significant differences in adverse events, including thrombotic events, between groups. FC may provide an alternative strategy to achieve hemostasis and reduce overall allogenic transfusions in neonates undergoing cardiac surgery without increased risk of adverse events.

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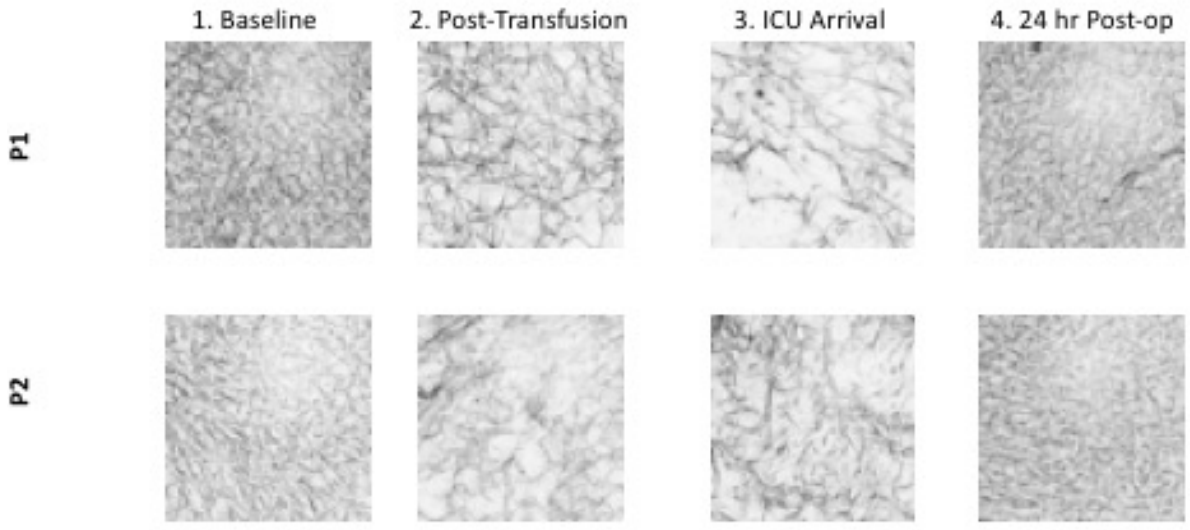

Figure 1. Representative images of electron microscopy of neonatal clot formed from platelet poor plasma at 1) Baseline, 2) Post-Transfusion, 3) On ICU arrival, and 4) 24-hours post operatively. Patient 1 received cryoprecipitate and Patient 2 received fibrinogen concentrate.

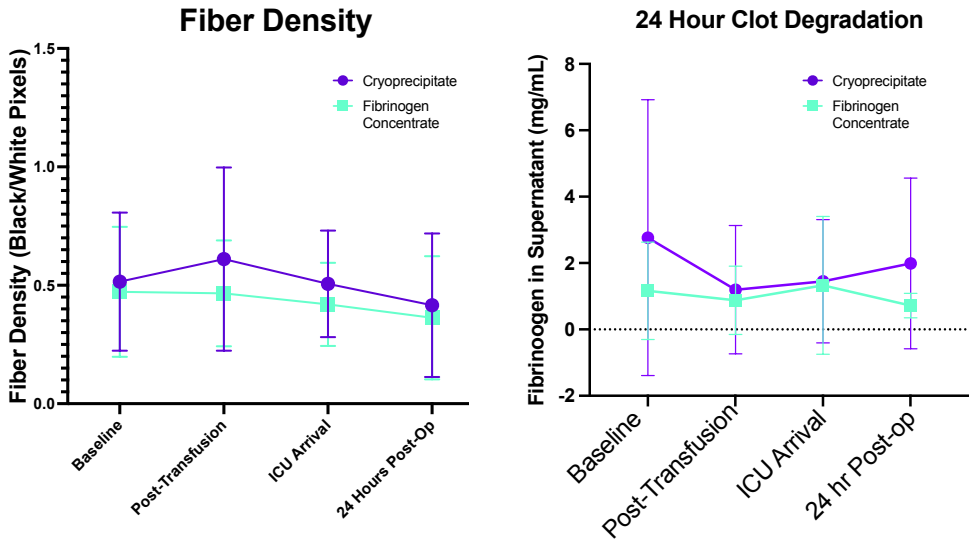

Figure 2. Clots were formed ex vivo from 36 neonates undergoing cardiac surgery with cardiopulmonary bypass (CPB) at four times points. Patients received either cryoprecipitate (control group) or fibrinogen concentrate (study group) after CPB. We show no significant differences in fiber density (A) and clot degradation rates (B) at each time point.

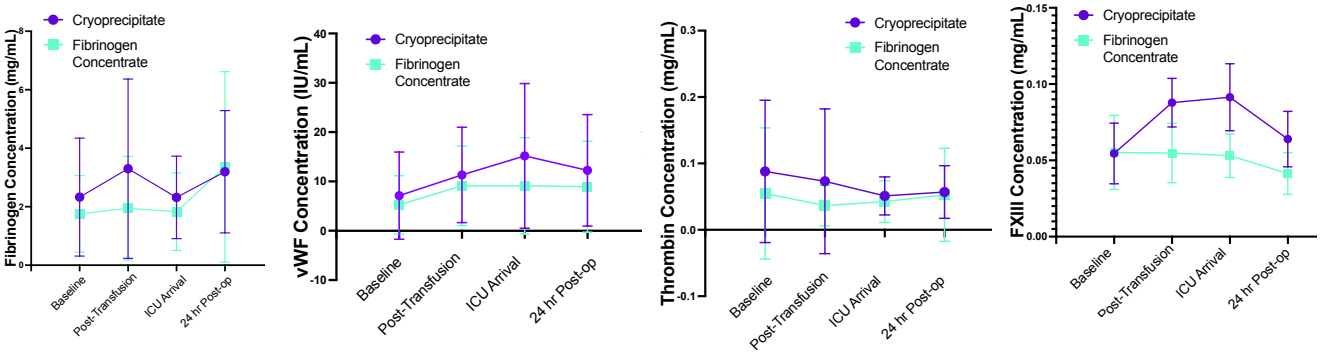

Figure 3. ELISAs were performed from 36 neonates undergoing cardiac surgery with cardiopulmonary bypass (CPB) at four times points to ELISA studies demonstrating different procoagulation levels between control group (cryoprecipitate) and study group (fibrinogen concentrate). A) Fibrinogen levels B) Von Willebrand levels C)Thrombin levels and D) FXIII levels.

Table 1. Demographics and clinical data for neonates enrolled in the study.

	All Patients (n=36)	*Cryoprecipitate (n=18)*	*Fibrinogen Concentrate (n=18)*	*P-value*[a]	*SMD*[b]
Demographics					
Male (%)	23 (63.9%)	14 (77.8%)	9 (50.0%)	0.164	0.604
Age (days)	6.00 [4.00, 11.25]	6.00 [5.00, 12.75]	5.00 [4.00, 7.00]	0.232	0.545
Weight (kg)	3.40 [2.68, 3.69]	3.50 [2.92, 3.69]	3.10 [2.66, 3.58]	0.311	0.286
Prematurity	10 (28.6%)	3 (17.6%)	7 (38.9%)	0.264	0.485
Baseline Saturation (%)	93.50 [90.75, 98.00]	94.50 [89.25, 98.00]	93.00 [91.00, 95.75]	0.886	0.038
Lowest Temperature	26.15 [18.00, 28.00]	28.00 [19.00, 28.00]	21.00 [18.00, 28.00]	0.416	0.256
Anesthesia Time (hours)	6.75 [6.21, 7.78]	7.38 [6.32, 9.22]	6.50 [5.94, 6.81]	0.065	0.628
Surgery Time (hours)	4.27 [3.40, 4.87]	4.42 [3.67, 6.07]	4.04 [3.18, 4.46]	0.109	0.721
CPB time (min)	146.50 [112.75, 162.50]	143.50 [112.25, 174.25]	146.50 [115.00, 157.50]	0.629	0.289
Aortic CxClamp (min)	81.00 [58.00, 97.00]	92.50 [79.25, 128.00]	74.00 [57.00, 82.00]	0.025	0.768
Pre-Op labs					
Hemoglobin	13.80 [12.88, 14.90]	14.00 [12.93, 16.05]	13.60 [12.53, 14.43]	0.367	0.312
Hematocrit	41.05 [38.53, 45.17]	41.35 [38.78, 48.85]	40.25 [38.38, 42.95]	0.438	0.262
Platelets	271.50 [232.00, 383.75]	261.50 [230.00, 318.50]	281.00 [236.00, 391.25]	0.343	0.262
Fibrinogen	236.50 [199.25, 286.00]	236.50 [190.25, 278.25]	239.00 [200.50, 292.75]	0.569	0.241
ICU Arrival labs					
Hemoglobin	14.10 [12.40, 14.88]	12.50 [12.00, 14.30]	14.40 [13.50, 15.20]	0.048	0.574
Hematocrit	40.50 [36.10, 42.98]	36.90 [35.10, 42.40]	41.50 [39.20, 44.50]	0.109	0.469
Platelets	206.50 [165.00, 266.75]	187.00 [149.00, 268.00]	213.00 [176.00, 263.00]	0.469	0.087
Fibrinogen	311.00 [270.00, 363.00]	355.00 [325.00, 397.00]	276.00 [264.50, 305.00]	0.001	1.026
Post-CPB Blood Products (ml/kg)					
RBCs	0.00 [0.00, 13.92]	0.00 [0.00, 14.16]	0.00 [0.00, 11.88]	0.565	0.192
FFP	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.713	0.033
Platelets	19.58 [13.95, 28.56]	16.08 [13.57, 26.93]	23.13 [14.53, 28.84]	0.486	0.239
Cryoprecipitate	9.93 [0.00, 12.82]	12.56 [10.80, 16.62]	0.00 [0.00, 0.00]	<0.001	2.043
Cell Saver	0.00 [0.00, 13.25]	0.00 [0.00, 7.93]	0.00 [0.00, 15.97]	0.805	0.345
Fibrinogen Dose (total)	---	---	299.10 [230.75, 350.25]	---	---
Fibrinogen Dose (ml/kg)	---	---	96.14 [86.86, 104.15]	---	---

[a] two-groups comparisons were conducted using Fisher exact/Chi-square test for categorical variables, and Wilcoxon rank-sum test for continuous variables.
[b] Effect sizes were additionally calculated, as standardized mean differences (SMDs), and interpreted using Cohen's d thresholds, 0.2 (small), 0.5 (moderate), and 0.8 (large).

PEDIATRIC ANESTHESIOLOGY 18

Association of obesity in children with serious postoperative infections

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INTRODUCTION: Childhood obesity is increasingly prevalent even among the surgical population. Obesity in children is a risk factor for many acute perioperative complications.[1] Similarly, emerging data in adult subjects suggests that obesity may increase the risk of serious infections including pneumonia, urinary tract infections, and deep surgical space infections (SSI).[2-4] To date, whether obesity in children is a risk factor for serious post-surgical infections has not been characterized. Therefore, we assembled a cohort of children who underwent elective, in-patient, non-cardiac surgical procedures between 2012-2019 to determine the role of obesity in the incidence of serious postoperative infections.

METHODS: Using the National Surgical Quality Improvement Program dataset, we identified a retrospective cohort of children (<18 years) who underwent inpatient surgery between 2012 and 2019. We estimated the 30-day incidence of serious postoperative infections defined as the occurrence of either deep wound infection, organ-space infection, or wound dehiscence. Serious infection rates were compared across body mass index (BMI) categories defined according to Centers for Disease Control and Prevention criteria as normal weight (NW), overweight (OVW), and obese (OBS). Present analysis excluded underweight children.

RESULTS: The study cohort included 185,380 children of whom 62.4% were normal weight, 15.8% were overweight and 21.8% were obese. Overall, 3086 (1.7%) children developed serious postoperative serious postoperative infections (NW = 1.5%; OVW = 1.7% and OBS = 2.1%). A similar pattern was observed across the components of the composite variable (Fig. 1). Multivariable analysis adjusted for baseline covariates showed that the incidence of serious SSI was higher among overweight and obese patients compared to healthy-weight patients (OVW odds ratio [OR] 1.14, 95% confidence interval [CI] 1.02 - 1.27, p=0.02; OBS OR=1.41, 95% CI 1.29 - 1.54, p<0.001).

CONCLUSION: Childhood overweight and obesity were associated with a higher risk of serious postoperative surgical site infections. Future studies to determine the mechanistic basis of these associations are needed.

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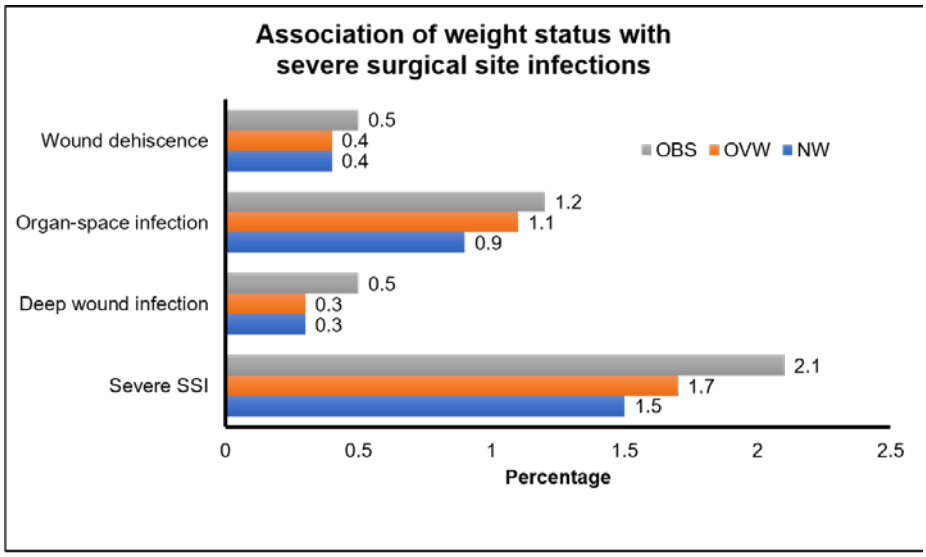

Fig. 1. Obese children were more likely to develop severe surgical site infection, organ space infection and wound disruption. Abbreviations: NW =normal weight; OVW = overweight; OBS= obese; SSI: surgical site infection

PEDIATRIC ANESTHESIOLOGY 19

Type 2, alternatively activated macrophages present during alveolar lung development are not dependent upon the IL-4Rα chain of the IL-4 Receptor

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INTRODUCTION: The discovery of different subtypes of macrophages has revolutionized our understanding of this vital immune cell. Macrophages can adopt a variety of phenotypes based on the tissue environment which includes the presence of cytokines and chemokines[1]. Recently, our research group demonstrated the presence of Type 2 alternatively activated macrophages during allergic lung inflammation[2]. Unlike conventional Type 1 macrophages, Type 2 macrophages have less anti-bacterial, phagocytic activity and assume a pro-asthmatic phenotype and protect the host from parasitic infection. M2 macrophages are activated by the presence of T helper cell type 2 cytokines IL-4 and IL-13. These M2 macrophages proceed to also secrete IL-4 and IL-13 once activated. Our research group has shown that in a Respiratory Syncytial Viral (RSV) infection model and during allergic lung inflammation, the induction of M2 macrophages requires signal transduction through the IL-4Rα[2-4].

Increased numbers of M2 macrophages have also been observed during normal alveolar lung development[5], which corresponds to mouse pups day 5-36 of life and humans at gestational age 36 weeks through 2-3 years of life. The function of these M2 cells during lung development is not well understood. Additionally, the dependence of these M2 macrophages on IL-4 signal transduction has not been investigated. To test the hypothesis that M2 macrophages are IL-4 dependent during alveolar lung development, we examined mouse pups during lung alveolarization for the expression of M2 macrophage genes in mice who were sufficient or deficient in IL-4 signal transduction. All IL-4 receptors share an IL-4Rα chain that is pivotal to IL-4 signal transduction. Therefore, we used IL-4Rα-/- mice to represent the experimental group that has deficiency of IL-4 signal transduction.

METHODS: We isolated RNA from lung samples of wildtype (WT) and IL-4Rα-/- Balb/c mice (3-4 mice/group) at p14 and p21 pups ages. Complementary DNA was generated, and quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) was performed with primer sets from Life Technologies.

RESULTS: We observed no significant difference in the expression of transcripts for the following M2 macrophage genes Chi3L3/4 (transcript for YM1), Arg1 (transcript for arginase-1), and Retnla (transcript for Fizz1). Additionally, lung immunohistochemistry staining of the M2 cell marker, YM1, encoded by Chi3L3 was comparable in WT and IL-4Rα-/- pups.

CONCLUSION: In conclusion, we discovered that unlike the M2 macrophages present during RSV infection and allergic lung inflammation, M2 macrophages associated with lung alveolar development do not require signal transduction via the IL-4 receptor. This suggests an alternative pathway to stimulate the M2 macrophage phenotype during physiologic lung development.

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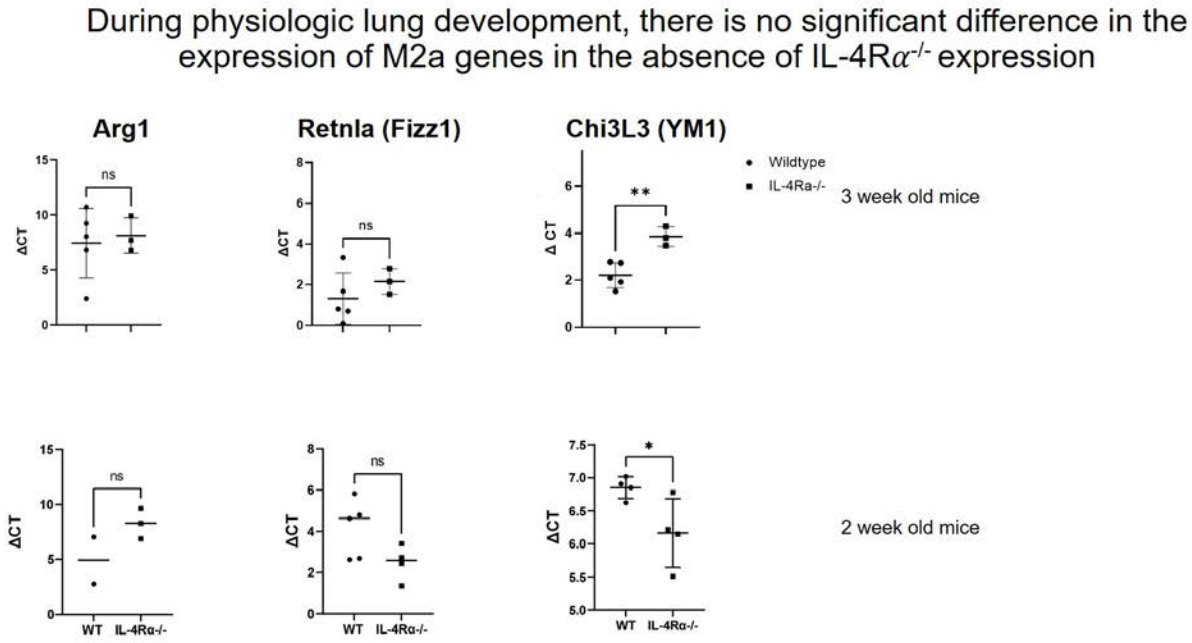

Fig. 1

PEDIATRIC ANESTHESIOLOGY 20

Effect of the COVID-19 Pandemic on Incidence of Upper Respiratory Tract Infections and Perioperative Respiratory Adverse Events

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INTRODUCTION: In the past year, the COVID-19 pandemic has resulted in multiple lockdowns with a concomitant decrease in pediatric viral upper respiratory infections (URIs).[1] Further, it has been reported that active COVID-19 infection in patients undergoing general anesthesia is associated with greater risk of perioperative respiratory adverse events (PRAE).[2] The optimal length of time to delay elective surgery for COVID-19 positive pediatric patients to decrease the risk of respiratory complications has not been determined.[3] In this study, we sought to quantify the difference in URI and PRAE rates before and after the start of the COVID pandemic. Additionally, we sought to evaluate whether patients with a history of COVID-19 positivity experienced more PRAEs compared to patients without known history of COVID-19.

METHODS: After obtaining IRB approval, data was collected prospectively on 4269 pediatric patients aged 6 years and younger at 3 institutions. Patients who were already intubated prior to anesthesia start, those with a pre-existing tracheostomy or cyanotic heart disease were excluded from the study. The following variables were recorded: age, gender, ASA status, recent/currently active URI, date of onset of symptoms, history of pulmonary disease (including secondary smoke exposure), airway device, type of surgery, current COVID-19 status and history of COVID-19 positivity. Intraoperative and postoperative respiratory complications of laryngospasm, bronchospasm, oxygen desaturation <90%, prolonged coughing and need for bronchodilator therapy were recorded. Chi-square was used to evaluate for differences between groups, except when there were cell counts of less than 5, when Fisher's Exact Test was used.

RESULTS: Prior to the start of the COVID-19 pandemic, the incidence of upper respiratory tract infection on the day of surgery was relatively high at 20.7% (410/1978 cases). There was a 67% ($p<0.001$) reduction in patients presenting with URI during the COVID-19 pandemic (6.9%, 159 cases with URIs out of 2291 cases) after institution of lockdowns, with a 29% reduction in patients experiencing PRAE (Pre-pandemic PRAE rate was 10.7% vs. 7% Post-Pandemic, $p<0.001$) (Figure 1). Additionally, a history of COVID-19 positivity without current symptoms did not seem to be associated with an increase in PRAE. In patients with history of COVID-19, 8.4% (3/36) experienced PRAE versus 8.2% (167/2035) without previous COVID-19 positivity ($p= 0.75$).

CONCLUSION: There was a significant reduction in both pediatric URIs and PRAEs during the pandemic and subsequent lockdowns. We found that a history of COVID-19 positivity in patients without active COVID-19 was not significantly associated with an increase in PRAEs. Further research is needed to evaluate the association of COVID-19 positivity and anesthesia in pediatric patients.

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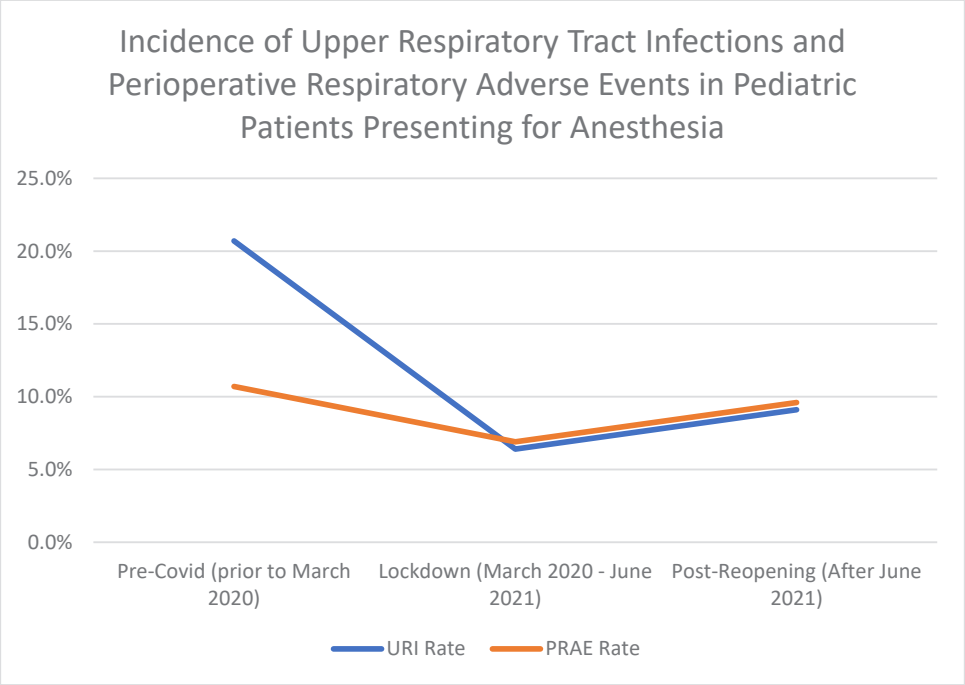

Fig. !

PEDIATRIC ANESTHESIOLOGY 21

ECMO requirements after pediatric cardiac surgery: the who, what, when and why

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INTRODUCTION: Timely initiation of ECMO in appropriately selected patients has been associated with improved survival and decreased morbidity in pediatric patients undergoing cardiac surgery[1]. This review aims to describe the incidence and outcomes of patients who require ECMO within 24 hours of cardiac surgery.

METHODS: A retrospective review was performed on patients requiring ECMO after cardiac surgery 2008-2020 at a tertiary center, divided into 3 cohorts: in the OR, between OR and first 24 postoperative hours, and >24 hours postoperatively. The <24 hours cohort was selected for analysis to better understand the perioperative factors leading to ECMO.

RESULTS: Among 262/12846 (2%) patients, 62 (24%) were placed on ECMO in the OR 86 (33%) patients were placed on ECMO within the first 24 hours post cardiac surgery and 114 (43%) after 24 hours. The median time to ECMO was 6 (range 0.5-23.5) hours in the study cohort. Hypoplastic left heart syndrome (HLHS) (22%) and Heterotaxy syndrome (21%) were common. 66 (77%) patients experienced a cardiac arrest prior to ECMO initiating and 20 (23%) were placed on ECMO for low cardiac output. 28% required re-exploration for bleeding. Complications included stroke (21%), dialysis (16%) and multi-organ failure (27%) with rates being higher in non-survivors.. Survival to discharge was 50%.

CONCLUSION: Single ventricle physiology and the presence of syndromes, particularly heterotaxy, was identified in a high proportion of patients and additional analysis is planned to develop a prediction tool based on these findings. 55% of patients survived to discharge which is higher than previously reported[2,3], likely indicating that timely ECMO support improves outcomes. These findings indicate that timely ECMO support in high-risk patients may improve survival with decreased morbidity in survivors.

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Table1 *Demographic of the study population*

Demographics	Median [range] or n (%)
Median age (years)	0.125 [0-16]
Median weight (kilogram)	3.705 [1.56-53]
Male gender	52/86 (60%)
Prematurity	20/86 (23%)
Syndromes other than Heterotaxy	12/86 (14%)
Heterotaxy	18/86 (21%)
Single-ventricle physiology	35/86 (41%)
HLHS	19/86 (22%)

Table2 *Intraoperative descriptors*

Intraoperative variables	Median [range] or n (%)
Median CPB time (minutes)	178 [14-796]
Median cross-clamp time (minutes)	98.5 [0-369]
Median circulatory arrest (minutes)	0 [0-76]
Redo sternotomy	25/86 (29%)
Sternum left open	55/86 (64%)
Post-CPB echo: ventricular dysfunction	22/86 (26%)
Post-CPB echo: valvular dysfunction	14/86 (16%)
Median VIS score	15 [0-227]

Table3 *Overall outcomes*

Outcomes	Median [range] or n (%)
Median time to ECMO (hours)	6 [0.5-23.5]
Median ICU LOS (days)	23.9 [2.8-510.7]
Median hospital LOS (days)	31.5 [2.92-512.1]
Same-admission mortality	39/86 (45%)

Table4 *Complications*

	All (86)	Survivors (47)	Non-survivors (39)
Re-exploration for bleeding (%)	24/86 (28%)	10/47 (21%)	14/39 (39%)
Re-exploration for low cardiac output (%)	44/86 (51%)	20/47 (43%)	24/39 (62%)
Stroke (%)	18/86 (21%)	9/47 (19%)	9/39 (23%)
Renal failure (%)	14/86 (16%)	2/47 (0.04%)	12/39 (31%)
Cardiac arrest (%)	66/86 (77%)	36/47 (77%)	30/39 (77%)
Multi-organ failure (%)	23/86 (27%)	3/47 (0.06%)	20/86 (51%)

PEDIATRIC ANESTHESIOLOGY 22

Unsupervised Machine Learning Models for Characterization of Risk for Pediatric Severe Critical Events from Anesthesia Using the Wake-Up Safe Registry

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INTRODUCTION: Despite improvements in anesthesia safety, patients continue to experience unintended harm related to anesthesia and surgical care.[1] Characterization of these serious adverse events in children remains an ongoing challenge due to their relative infrequency. Wake Up Safe (WUS), a national pediatric anesthesia collaborative supported by the Society of Pediatric Anesthesia launched in 2008, with the goal to make anesthesia safer for children.[2] The registry represents one effort to better understand and reduce the incidence of serious adverse events. This study applies unsupervised machine learning methods to help characterize risks for severe critical events from anesthesia and provide useful tools for clinical decision making and risk stratification. These tools help facilitate better use of the WUS registry in the clinical setting.

METHODS: Two datasets are made available from WUS, one for billing data and one for critical events data. The billing dataset has relatively few features collected (Age, ASA Score, ICD, CPT, ASA Emergency Status), while the events dataset contains detailed information on each critical event. The absence of a direct link between the events dataset and the billing dataset, as well as the substantial discrepancy in the features contained in each dataset, prohibit directly combining them into a single dataset for predictive modeling. To overcome this issue, a novel strategy to indirectly link the two together is devised. The approach is as follows: first the billing dataset is clustered using the k-prototypes algorithm.[3] The algorithm requires initial selection of a number of clusters. To find the optimal number of clusters, the algorithm is tested over multiple values. The elbow of the curve visually indicates the optimal number of clusters. Once the optimal number of clusters is selected, a fuzzy record matching algorithm is then applied to match the entries from the events dataset to clusters in the billing dataset. Then, the probability of different events is calculated for each cluster. This can be used to predict patient risk given diagnosis, procedure and demographics.

RESULTS: Table 1 shows cluster statistics. Four clusters were identified as optimal (data not shown). Cluster 1 had young, complex patients (ASA IV/V majority), with majority male. Cluster 2 contained older, moderately complex patients (ASA III majority). Cluster 2 contained the highest number of ASA emergency designations. Cluster 3 was composed of preschoolers who were medically stable (ASA I majority), predominantly nonemergency ASA status and female. Cluster 4 was composed of grade-schoolers who were moderately stable (ASA II majority). Matched critical events are shown in Table 2. The largest number of critical events occurred in Cluster 1, with Airway complications, Cardiac Arrest, Cardiovascular Support, Malignant Hyperthermia, Perioperative death and Respiratory events found most frequently in this group out of all groups. Cluster 2 had the second highest number of events, with the highest number of Airway Injury, Cutaneous/Musculoskeletal, Eye Injury, Medication Event, Nervous System Injury, Other Injuries, Under General Anesthesia and Wrong Side Sites occurring in this group. Cluster 3 had the second lowest number of events, with Blood Transfusion complications occurring with the highest frequency in this cluster. Cluster 4 had the lowest number of events. Respiratory events represented the most commonly occurring critical events, while Malignant Hyperthermia was the least common.

CONCLUSION: Application of unsupervised ML techniques along with matching facilitated development of a model with clinical utility from a dataset not amicable to advanced data use. Patient characteristics were identified from the clusters, while the type and frequency of several critical events was determined using matching. Young, medically complex patients were most likely to suffer from Respiratory events. Older, moderately complex patients undergoing emergency procedures were most likely to suffer from medication events when compared to all patient groups. This work provides insight into leveraging a complex dataset for better characterization of patient groups suffering from severe critical adverse events.

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Table 1.

Cluster	Age	ASA					Emergency Status		Gender	
		I	II	III	IV	V	Non.	Emerg.	Male	Female
1	1.26 (0.89)	24.71	39.20	26.61	**9.15**	**0.32**	95.02	4.98	**64.91**	35.09
2	14.79 (1.90)	22.56	45.02	**29.27**	3.02	0.13	93.15	**6.85**	53.07	46.93
3	4.85 (1.17)	**25.74**	45.20	26.46	2.54	0.07	**95.43**	4.57	43.66	**56.34**
4	9.07 (1.35)	23.00	**46.65**	27.83	2.43	0.09	93.21	6.79	62.18	37.82

Table 2. Critical events matched to each cluster.

Event Category	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Total
Airway Injury	38	39	37	23	137
Airway Management	135	63	75	73	346
Blood Transfusion	15	13	16	4	48
Cardiac Arrest	396	241	275	170	1082
Cardiovascular Support	195	160	159	91	605
Cutaneous/Musculoskeletal	29	37	30	23	119
Eye Injury	4	19	7	4	35
Malignant Hyperthermia	5	1	1	3	10
Medication Event	174	197	164	123	658
Nervous System Injury	47	71	29	20	167
Other Injuries	37	52	38	31	158
Perioperative Death	111	57	70	41	279
Respiratory Event	455	339	385	298	**1477**
Under Gen. Anesth.	2	8	0	3	13
Wrong Side Sites	1	11	3	7	22
Total Events	**1645**	1308	1289	914	5156

PEDIATRIC ANESTHESIOLOGY 23

A Systematic Review of Clinical Practice Guidelines for Perioperative Management of Tonsillectomy in Children

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INTRODUCTION: Tonsillectomy is one of the most common surgical procedures performed in children. Recently, obstructive sleep apnea has become the most common indication of pediatric tonsillectomy[1], posing additional challenges for anesthesiologists. When searching the literature for the latest trends in the perioperative management of these patients, most guidelines are designed to support surgical decisions, including diagnostic criteria and surgical techniques. The purpose of this systematic review is to identify and analyze the existing Clinical Practice Guidelines (CPG) for the perioperative management of children undergoing Tonsillectomy.

METHODS: The current systematic review followed PRISMA guidelines[2] and registered at PROSPERO (CRD42021253374).

Data sources: We searched databases including EMBASE, Medline, Ovid Medline (ePub Ahead of Print) and CINAHL via EBSCOhost, to identify eligible guidelines on April 8, 2021. We also searched grey literature on the TRIP database.

Study selection: Two reviewers independently screened articles according to inclusion criteria; 1) CPG of perioperative recommendations for tonsillectomy under general anesthesia in children, 2) CPG that include at least one evidence-based recommendation, 3) CPG published after the year 2000 and available in English. We excluded CPG exclusively focused on adults or surgical management or not peer-reviewed before publication. Perioperative management was defined as any pharmacological or non-pharmacological intervention by healthcare team members; during the preoperative, intraoperative, or postoperative period. Data extraction and synthesis: We conducted a quality assessment of eligible CPG using the AGREE II and AGREE REX tools for methodological robustness and clinical credibility, respectively [3,4]. Final scores of AGREE tools decided through a consensus approach.

RESULTS: We only found 5 CPGs eligible for the current study[5-9]. The search identified 4725 articles in databases and 96 in gray literature; after the title and abstract screening, 25 articles underwent full-text assessment, and 20 were ineligible. The table summarized characteristics of eligible CPGs and areas of clinical recommendations.

AGREE II revealed just two out of the five CPGs were High-Quality: AAO-HNSF 2019 and PROSPECT 2020; AGREE REX recommended only the former to implement without modifications. Of the other three CPGs, NTSRS 2015 and SFORL-AFCA-SFAR 2012 were Moderate-Quality and SFORL 2014 was Low-Quality. Most of the recommendations are for pain management. Acetaminophen is the only one that all 5 CPGs consistently recommend. Except the oldest CPG (SFORL-AFCA-SFAR 2012), the other four CPGs are all aligned in their support for the use of NSAIDs and steroid. While SFORL 2014 supports the use of Tramadol, NTSRS 2015 and AAO-HNSF 2019 are against it.

CONCLUSION: We found existing CPGs show inconsistent recommendation for the use of NSAIDs and Tramadol in pediatric tonsillectomy.

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Table: Characteristics of Clinical Practice Guidelines & Relevant Perioperative Recommendations for Tonsillectomy

			Recommendations made:		
Source CPG	Publishing Body (Country of Origin)	Funding Body	Pain Management	Perioperative Complications	Other Perioperative Management
Clinical Practice Guideline: Tonsillectomy in Children (Update)	AAO-HNSF 2019 (United States)	AAO-HNSF	✓	✓	✓
Swedish guidelines for the treatment of pain in tonsil surgery in pediatric patients up to 18 years	NTSRS 2015 (Sweden)	NA	✓	✓	✓
PROSPECT guideline for tonsillectomy: systematic review and procedure-specific postoperative pain management recommendations	PROSPECT 2020 (United Kingdom)	European Society of Regional Anaesthesia and Pain Therapy	✓	✓	
Pediatric tonsillectomy: Clinical practice guidelines	SFORL- AFCA-SFAR 2012 (France)	NA	✓	✓	✓
How to replace codeine after tonsillectomy in children under 12 years of age?	SFORL 2014 (France)	NA	✓	✓	

Abbreviations: AAO-HNSF: American Academy of Otolaryngology–Head and Neck Surgery Foundation; NTSRS: National Tonsil Surgery Register in Sweden; PROSPECT: Procedure-Specific Postoperative Pain Management; SFORL: French Oto-Rhino-Laryngology – Head and Neck Surgery Society; AFCA: French Association for Ambulatory Surgery; SFAR: French Society for Anaesthesia Intensive Care

Perioperative complications: Postoperative Nausea and Vomiting (PONV), agitation, delirium & adverse events (such as hemorrhage or respiratory events)

Other perioperative management: Antibiotics, steroids for airway management, postoperative pain assessment and postoperative monitoring.

PEDIATRIC ANESTHESIOLOGY 24

Pediatric Anesthesia Simulation Innovation: High Frequency Oscillatory Ventilation in Micropremies: A Case of NEC in the NICU

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INTRODUCTION: Pediatric Anesthesia Bootcamps were started in Philadelphia in fall of 2012.[1] Since then, both fall and spring (advanced) simulation bootcamps have been held across the US.[2] The hallmark of these bootcamps are well-designed simulations that provide hands on training in realistic conditions and a psychologically safe learning environment. Study Aims: To examine a new high-fidelity simulation added to the Midwest Pediatric Anesthesia Fellow Bootcamp (PAFB) that included a novel way to simulate High Frequency Oscillatory Ventilation (HFOV). Fellows learn how to perform a micropreemie case in the NICU setting on an oscillator.

METHODS: Eleven pediatric anesthesia fellows from three institutions participated in the fall 2021 Midwest PAFB; less than prior years due to the Covid-19 pandemic. Pre- and Post-simulation surveys were solicited, asking a series of qualitative and quantitative questions regarding the participant's confidence level with the clinical scenario (micropreemine with Necrotizing Enterocolitis (NEC) in the NICU on HFOV) and confidence in their skill level for managing the case. The simulation operation and technical set up included a real oscillator, respiratory therapist, low-fidelity mannequin, and approximately ten faculty members as observers and debriefers.

RESULTS: Pre-simulation survey results showed only one out of eleven participants had experience managing oscillator settings before. Six out of eleven participants had no prior experience managing anesthetic for an extremely premature baby (defined as birth during 26-28 weeks' gestation or birthweight < 700-800 grams). Eight out of eleven participants reported no prior experience with managing anesthetic for a baby with Necrotizing Enterocolitis (NEC). Eight out of eleven participants reported less than ten pediatric anesthetic cases performed outside of the OR. Participant responses regarding confidence levels pre- and post-simulation are shown in Table 1.

CONCLUSION: This simulation was designed to expose pediatric anesthesia fellows to a NICU case involving a micropreemie with NEC on HFOV for pediatric anesthesia fellows early in training that will increase their preparedness and confidence. The pre-simulation survey showed our simulation participants had very little experience with oscillators, and management of anesthetic for micropreemies and patients with NEC. Post-simulation survey results show a marked increase in confidence, knowledge, and practical skills among the participants. The collective growth in ability and knowledge reported after undergoing the simulation indicates that our simulation was well-timed in their fellowship year, needed, and successful.

HFOV can be successfully simulated with a micropreemie mannikin and can improve confidence and knowledge of fall pediatric anesthesia fellows participating in the Midwest PAFB.

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Question	Pre-simulation		Post simulation	
	yes	no	yes	no
Are you confident in your knowledge of oscillator settings and physiology?	1	10	9	2
Are you confident in your ability to manage an oscillator during and anesthetic	3	8	8	3
Are you confident in your knowledge of what drugs and equipment to bring to an out of OR case in NICU	7	4	10	1
Are you confident in your ability to keep a micropreemie warm during a NICU anesthetic	6	5	9	2

Figure 1

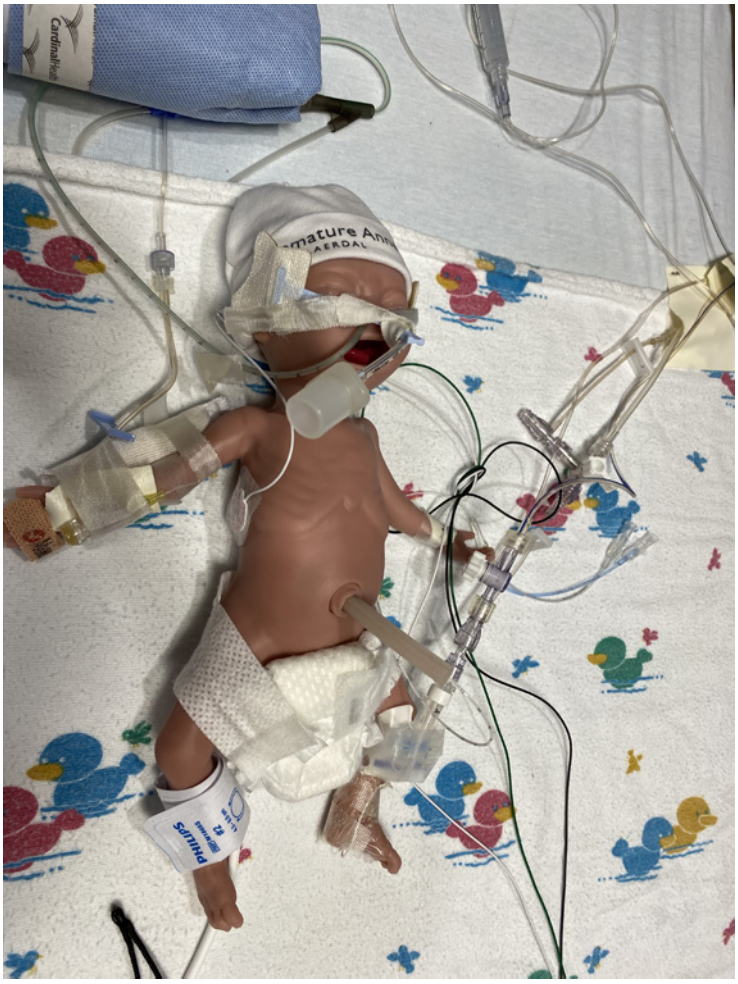

Figure 2

PEDIATRIC ANESTHESIOLOGY 25

Intraoperative use of neuromuscular blocking agents at an academic pediatric hospital after the introduction of Sugammadex

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INTRODUCTION: Sugammadex has been widely adopted in pediatric anesthesia practice for reversal of neuromuscular blockade since it was approved for use in adults in 20151. While use of neuromuscular blocking medications (NMBs) may improve surgical and intubating conditions, large doses in children have been associated with post operative respiratory failure2-4. Anecdotal evidence at one institution raised concerns regarding increased dosing of steroidal NMBs in the post-sugammadex era. Institutional changes in the anesthesia drug tray from cisatracurium to rocuronium in 2016 may have influenced NMB selection during this time. We hypothesize that choice of NMB medication has changed since the introduction of sugammadex, and that dosing of NMB medications has increased in the time period following the adoption of sugammadex.

METHODS: We performed a retrospective cohort study on children <18 years receiving general anesthesia with an endotracheal tube and neuromuscular blockade at a single large academic pediatric hospital 1/1/2014 - 12/31/2020. NMB agent used was plotted over time. Total case NMB dose administered was calculated using medication appropriate ED95s, normalized to patient weight and case duration. Total median NMB ED95s administered were plotted separately to illustrate dosing changes over time. A Wilcoxon Rank-Sum test was used to compare administered ED95s across years.

RESULTS: In the pre-sugammadex era, the primary NMB used was cisatracurium, which was largely replaced by rocuronium in the post-sugammadex era (Table 1, Figure 1). Additionally, succinylcholine use declined. Median administered ED95 decreased dramatically 2014-2016 vs. 2017-2020 from 2.1 ED95s per case to 1.7 ED95s per case ($p<0.001$). A small, statistically significant increase in ED95 administered occurred 2019-2020 from 1.5 to 1.7 ED95s ($p <0.001$).

CONCLUSION: Choice of NMB agent changed from primarily cisatracurium to rocuronium, accompanied by a decrease in total NMB dose administered, likely due to differences in methods of administration and pharmacokinetics. In the past year, a small but significant increase in NMB dose occurred, of unclear clinical significance. This may represent an unintended consequence of widespread sugammadex utilization. Continued attention to appropriate NMB dosing and monitoring of neuromuscular blockade remain crucial to ensuring patients are fully reversed and to prevent post-operative complications in the post-sugammadex era.

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	Cisatracurium		Rocuronium		Vecuronium		Succinycholine	
Year	N	%	N	%	N	%	N	%
2014	2716	75.5	183	5.1	73	2.0	907	25.2
2015	2848	77.6	182	5.0	72	2.0	913	24.9
2016	3143	77.6	130	3.2	111	2.7	1050	25.9
2017	3211	78.6	177	4.3	79	1.9	997	24.4
2018	2350	57.5	1071	26.2	38	0.9	901	22.0
2019	130	3.1	3672	86.9	1	0.0	585	13.8
2020	36	0.9	3955	93.0	2	0.1	365	8.6

Table 1

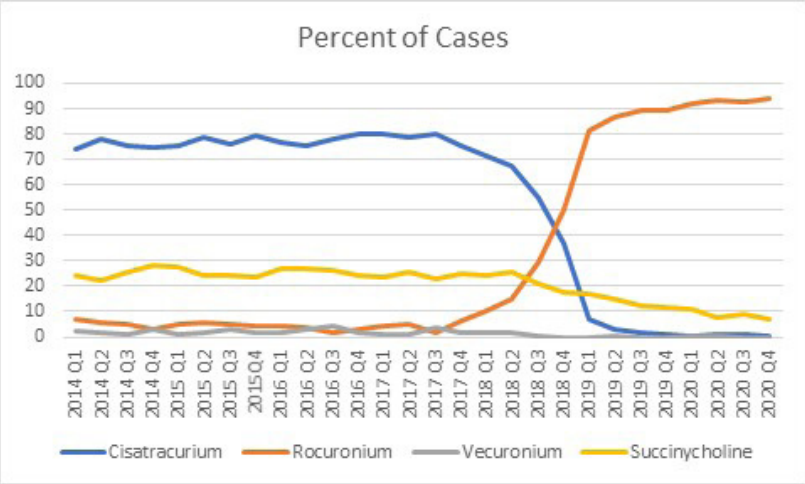

Figure 1

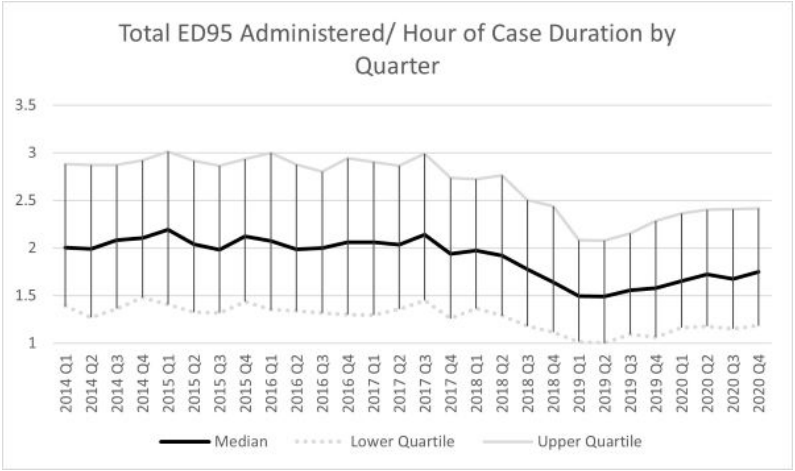

Figure 2

PEDIATRIC ANESTHESIOLOGY 26

Intra-Operative Hyperglycemia in Pediatric Liver Transplantation Associated with Prolonged Hospitalization, Increased Infection Rates and Graft Dysfunction

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INTRODUCTION: Alterations in glucose metabolism are frequently seen in patients undergoing surgery and are associated with increased morbidity and mortality[1]. End-stage liver disease itself is associated with altered glucose homeostasis, and patients undergoing liver transplantation experience large fluctuations in blood glucose[2]. Hyperglycemia is frequently seen following reperfusion in liver transplantation. In adult liver transplantation, hyperglycemia in the early post-transplant period has been associated with liver allograft rejection, surgical site infection and death. A retrospective study revealed improved outcomes in adult orthotopic liver transplant patients when the mean intraoperative blood glucose was kept below 150mg/dL[3]. In the pediatric intensive care unit, elevated blood glucose has been found to be associated with increased morbidity and mortality[4]. However, there is limited data on the effect of hyperglycemia on post-operative outcomes in pediatric liver transplantation. In this retrospective study, we aim to evaluate the effect of perioperative hyperglycemia on the post-operative outcomes in pediatric liver transplant patients. We hypothesize that perioperative hyperglycemia during pediatric liver transplantation has similarly deleterious consequences as seen in adults including prolonged hospitalization, increased infection rate and increased incidence of graft failure.

METHODS: Following IRB approval, we evaluated the records of all patients who underwent a liver transplantation at our institution from January 2014 to June 2021. Hyperglycemia was defined as an intra-operative glucose value greater than or equal to 200mg/dL. Hospital length of stay (LOS) was measured as time from anesthesia end to transfer out of the intensive care unit (ICU) and to discharge from the hospital. Graft issue was defined as the need for a re-transplantation or patient death within 2 weeks of the transplant and/or need for re-exploration due to arterial/venous thrombosis, decreased arterial/venous flow, or increased liver indices. Post-operative infection was defined as infection requiring additional antibiotic coverage and/or fever of unknown origin.

RESULTS: 173 patients were included in our analysis with a median age of 3 years (range:15 days-21 years) and weight 14.4kg (range: 3.5-102.2kg). Mean ICU and hospital LOS was 5.45 and 13.76 days in the normoglycemia group vs 7.74 and 17.78 days in the hyperglycemia group. Incidence of infection was 7.89% in the normoglycemia group vs 20.62% in the hyperglycemia group. Incidence of graft dysfunction was 15.79% in the normoglycemia group vs 19.59% in the hyperglycemia group.

CONCLUSION: Pediatric liver transplant patients experience large fluctuations in blood glucose levels, with hyperglycemia frequently seen after reperfusion. Often, these episodes of intra-operative hyperglycemia are not treated aggressively. This study demonstrates that the presence of intra-operative hyperglycemia is associated with poor outcomes. A single intra-operative glucose value greater than or equal to 200mg/dL is associated with increased hospital length of stay and increased infection rate. Interestingly, this study also finds a correlation between intra-operative hyperglycemia and graft dysfunction. Further studies looking at tight glucose control are needed to better determine an appropriate intra-operative glucose target in pediatric liver transplant patients.

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PEDIATRIC ANESTHESIOLOGY 27

Incidence and Risk Factors of Perioperative Respiratory Adverse Events in Children Undergoing Elective Surgery Employing Logistic Regression and Machine Learning Cluster Analysis

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INTRODUCTION: Perioperative Respiratory Adverse Events (PRAE) are a common causes of paediatric morbidity and mortality during the perioperative epoch, accounting for over three-quarters of adverse incidents. Complications of PRAE include laryngospasm, bronchospasm, hypoxia, airway obstruction, stridulous breathing, persistent coughing and atelectasis. There currently remains a paucity of the use of advanced data-analytical techniques within the PRAE literature, such as multivariate logistic regression and machine learning (ML). Aims and objective: We aimed to ascertain which risk factors are predictive of PRAE in children undergoing anaesthesia with a laryngeal-mask-airway (LMA), comparing and contrasting whether a data-driven epistemological approach using ML yields analogous findings to classical hypothesis-driven research employing logistic regression.

METHODS: Data was sourced from existing datasets previously collected (2015/2019) for quality improvement exercises. Our strategy for data-analysis and wrangling to ascertain and rank predictors, included pre-processing, data visualisation, dimensionality reduction (to reduce input variables), exploring the underlying mechanism-of-missingness, univariate analysis, multivariate clinical risk prediction modelling (CRPM) using logistic regression and unsupervised ML cluster-analysis (K-medoids)

RESULTS: The overall frequency of complications of PRAE was 12% . The predictors of PRAE (in order of significance) included fever, younger age, coughing (during LMA insertion), the presence of a productive cough, secretions and the absence of oropharyngeal suctioning prior to LMA removal, rhinorrhoea, a history of respiratory co-morbidities (i.e. asthma), otolaryngology dental surgery and the removal of the LMA asleep (Table. 1). Missing data were handled with multivariate imputation by chained equations (MICE). The missingness was diagnosed by creating dummy variables and testing whether the missingness was related to any of the candidate variables collected (using t-tests and chi-squared as appropriate) as well as using logistic regression where missingness was the outcome measure. These tests found that the mechanism underlying the missingness in the datasets was MAR and not MCAR. This was further supported by Little's test for MCAR which was significant ($p=0.00182$). From multivariate logistic regression stepwise (AIC) selection, our final model performed strongly having an AUCROC be 0.892 ($p<0.001$) and an accuracy of 0.9375 (95% CI: 0.8689, 0.9767) (Table 2). Results from ML cluster analysis was consistent with that of logistic regression (Table 3 and Figure. 2). the silhouette, elbow and gap statistic method for determining the optimal number of clusters (k) was found to be k=6.

CONCLUSION: The importance of identifying risk factor for developing PRAE can allow anaesthesiologists to risk assess children during the preoperative assessment, to delineate fitness for anaesthesia, as well as tailoring the anaesthetic technique to help ameliorate the risk of developing PRAE, as an application of precision medicine. Moreover, we introduced a new dimension to analysing data from retrospective, quality improvement datasets, by meticulously addressing data quality and completeness. This underscored how a data-driven epistemological approach can work synergistically with classical a priori, hypothesis-driven research.

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Table 1 - Adjusted Odds Ratio and Outcome from Multivariate Logistic Regression

Variable	Coefficient	p-value (Significance)	OR (95% CI)
Age	-0.249	0.000263 ***	0.76 (0.510, 0.920)
Weight	-0.341	0.021598 *	0.776 (0.626, 0.964)
Cough: Dry	0.311	0.017630 *	1.364 (1.190, 1.565)
Productive	1.143	0.002350 **	3.135 (2.757, 3.565)
Rhinorrhoea: Present	0.449	0.006509 **	1.567 (1.156, 1.700)
Fever: Present	-0.225	0.000263 ***	3.215 (2.668, 3.875)
Asthma: Present	0.196	0.0471 *	*1.216 (1.006, 1.472)*
OSA: Present	-0.076	0.263876	0.927 (0.811, 1.059)
Other past medical history			
Respiratory	0.116	0.012133 *	1.123 (1.051, 1.204)
Cardiac	0.073	0.082861	1.013 (0.872, 1.177)
Gastro	0.071	0.166331	1.073 (0.869, 1.245)
Neuro / other	0.095	0.362143	1.250 (0.868, 1.801)
Anticholinergics:	-0.189	0.009419 **	0.828 (0.678, 0.918)
Atropine	0.090	0.4768	1.094 (0.864, 1.387)
Glycopyrrolate			
No. of attempts:	0.275	0.0002	1.316
Other Issues:	0.300	6.63e-06 ***	1.762 (1.397, 2.222)
Coughing	-0.075	0.4284	0.927 (0.556, 1.547)
Laryngospasm	-0.006	0.9731	0.994 (0.693, 1.425)
Obstruction	0.242	0.0984	1.274 (0.146, 1.658)
Reposition			
Removal of LMA:	0.009	0.791180	1.009 (0.944, 1.079)
Deep	2.605	0.04891 *	13.532 (1.070, 26.162)
Awake			
Suctioning prior to LMA removal:	0.479	0.003589 **	1.614 (1.552, 1.701)
No	-0.163	0.000354 ***	0.850 (0.802, 0.899)
Yes			
Other Problems: Secretions	0.7524	0.000721 ***	2.1221 (1.1626, 3.9192)
Bleeding	0.4208	0.0026273 **	1.5231 1.0266, 1.8691
Other	0.4212	0.990509	1.5238 (0.2769, 8.9155)

Legend. Note: Pr(>|t|) –p-value, Wald test; significant codes: '***' 0.001, '**' 0.01, '*' 0.05, '-'not significant

Table 1 - Confusion Matrix for Model Appraisal

Test	Full Model	Reduced Model	Null Model
Sensitivity	0.9882	0.7143	0.5000
Specificity	0.8182	0.9663	0.9894
PPV	0.9767	0.6250	0.5000
NPV	0.9000	0.9773	0.9894
Prevalence	0.8854	0.0729	0.0208
Detection Rate	0.8750	0.0521	0.0104
Detection Prevalence	0.8958	0.0833	0.0208
Balanced Accuracy	0.9032	0.8403	0.7447

Note: PPV - positive predative value; NPV - negative predative value. Overall statistics: found an accuracy of 0.9375 (95% CI: 0.8689, 0.9767), no information rate : 0.8854; Kappa : 0.688; Mcnemar's test p-value: 0.0000189. ANOVA (between full and reduced model) was 0.2163 – i.e. non-significant.

Table 2 - Summary of Characteristics for ML k -Medoids Cluster Analysis

Characteristic	Cluster					
	1	2	3	4	5	6
Sex	M	F	M	M	M	M
Age (years)	6	7	10	1.9	7	8
Duration (mins)	25	28	19	15	20	22
Weight (Kgs)	20.0	31.0	53.0	14.5	22.0	35.4
Procedure	Dental	Orthopaedics	Urology	ENT	Urology	Other
Cough	0	0	0	Productive	0	0
Runny Nose	0	0	0	Yes	0	0
Fever	0	0	0	0	0	0
Asthma	0	0	0	0	0	0
OSA	0	0	0	Yes	v	No
Other PMHx	No	No	No	Respiratory	No	No
Anaesthesia	Sevoflurane	Sevoflurane	Sevoflurane	Sevoflurane	Sevoflurane	Sevoflurane
Anticholinergics	0	0	0	Atropine	0	0
Pre-medication	0	0	0	Midazolam	0	0
Size	2.5	2.5	3.0	2.0	2.5	3.0
Type	fLMA	uLMA	uLMA	fLMA	uLMA	uLMA
No. of attempts	2	1	1	2	1	1
Change size	0	0	0	Size-up	0	0
Leaks	0	0	0	Leak	0	0
Other issues	0	0	0	Nil	0	0
Time LMA in recovery	11	10	9	18	17	15
Position pre	Lateral	Lateral	Supine HU	Lateral	Lateral	Supine
Position during	Lateral	Lateral	Supine HU	Lateral	Lateral	Supine
Position after	Lateral HU	Lateral	Supine HU	Supine HU	Lateral HU	Supine
LMA removal	Awake	Awake	Awake	Deep	Awake	Awake
Suction prior	0	0	0	No	0	Yes
Biting	0	0	0	Nil	0	0
Other problems	0	0	0	Yes *A	0	0
De-saturation	0	0	0	Yes *B	0	0
Coughing	0	0	0	Yes	0	0
Laryngospasm	0	0	0	Yes	0	0
Bronchospasm	0	0	0	Nil	0	0
Number of complications	0	0	0	2	0	0

*Note: *A coughing and reposition; *B Desaturation requiring airway intervention such as head-tilt, chin-lift or jaw thrust; HU – head-up.*

Figure 1 - Correlation Matrix for Univariate Analysis

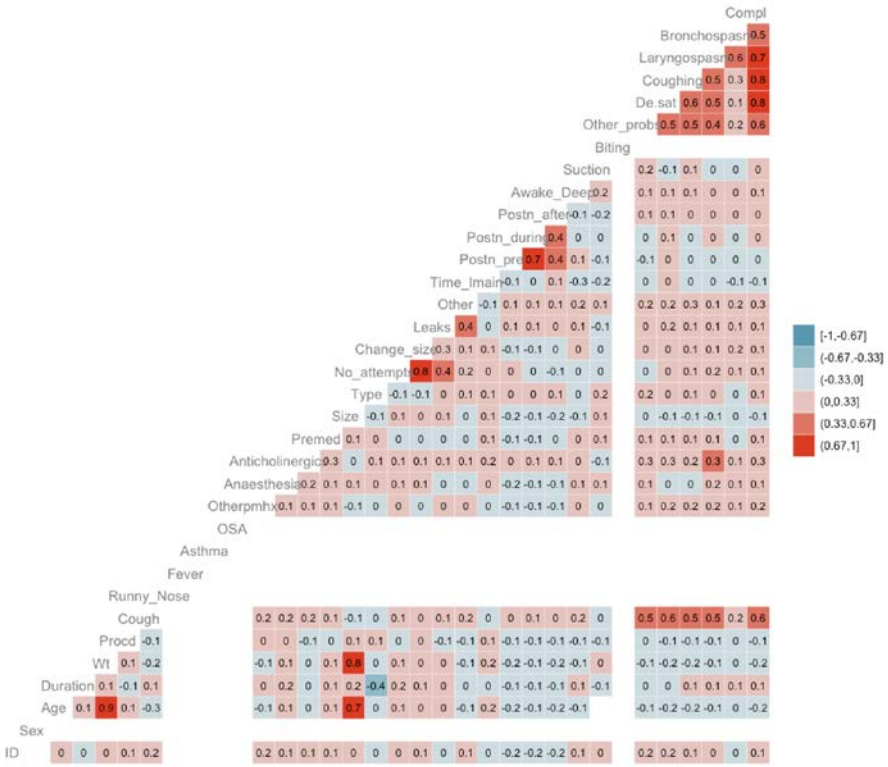
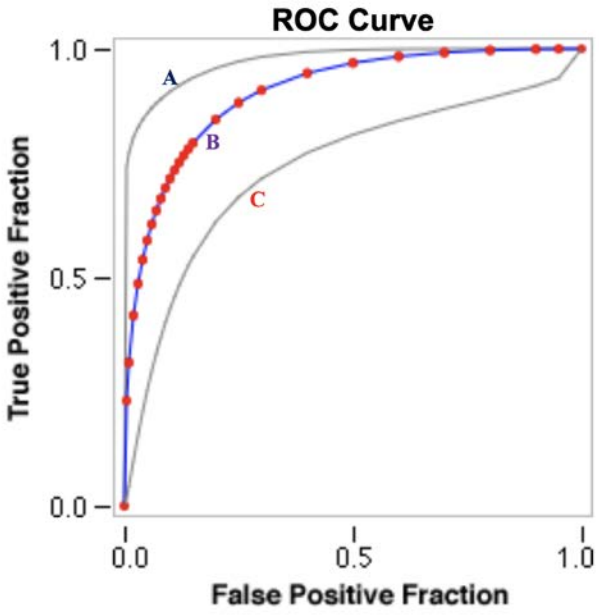


Figure 1 exhibits a correlation matrix disapplying the relationship between the predictors and the outcome measure (complications). this was an important endeavour to undertake since in multivariate regression analysis, multicollinearity (i.e. lack of) is an important assumption made. From critically scrutinizing the matrix, one can observe that the child's age and weight were strongly correlated (r=0.9), as well as age and weight with the size of LMA. These factors would be in keeping with what is expected as an older child would weigh more and require a larger sized LMA. Additionally, the number of attempts and changing the size of the LMA would also be related (r=0.8) since if on the first attempt the LMA was deemed to be of the incorrect size, a larger (and far less commonly a smaller) LMA is then sited. Finally, bronchospasm, laryngospasm, coughing, oxygen desaturation were all examples of complications (PRAE) and as such for multivariate analysis, these were collapsed into a single binary variable of having complications or not.

Figure 2 - ROC Curve for Model Performance



Note: Curve A represents the full model, curve B represents the reduced model and curve C represents the null model. Fitted ROC_B Area: 0.905; Empiric ROC_B Area: 0.892.

PEDIATRIC ANESTHESIOLOGY 28

Institutional Experience with Regional Anesthesia in Pediatric Renal Transplantation with Comparison to No Regional Anesthesia: A Retrospective Review of 68 Patients

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INTRODUCTION: Pain management in pediatric kidney transplant surgery is an under reported topic. Current modalities include patient-controlled analgesia, oral narcotic regimens, and regional anesthesia techniques with significant heterogeneity between institutions, anesthesia, and surgical providers. Despite comparative trials describing favorable, but controversial, efficacy of TAP blocks in adults[1], and emerging case reports describing use of Erector Spinae Plane Blocks (ESPB)[2], characterization of RA use in pediatrics is lacking. Our tertiary pediatric center began routinely employing RA techniques in late 2018. The objective of this retrospective case series was to analyze institutional specific data in order to highlight patient selection for RA, types of RA interventions provided, and assess for potentially related complications as well as pain management and opioid-related side effect profiles.

METHODS: We identified pediatric patients who underwent initial renal transplantation and with or without RA at our institution from 12/2018 through 10/2021. Kidney-liver transplantation combination and bring-back procedures were excluded from the analysis. The type of regional was identified. Patients without RA were reviewed for the primary reason for omittance. Patient/procedure characteristics, intraoperative management, and initial Pain Team rounding notes on POD 0 or 1 were reviewed. Data collected included perioperative analgesic administration, provider satisfaction with postoperative analgesia, management, and adjuncts and subsequent changes. The primary outcome measure was the percentage of patients with analgesia deemed 'Satisfactory' per the first available Pain Team Rounding note on POD 0/1. Secondary outcome measures included opioid-related side effects (nausea, vomiting, pruritis) requiring treatment, as well as Satisfactory analgesia between no-RA, TAP, and ESPB groups.

RESULTS: 68 patients underwent renal transplantation with 54 (79%) received RA, or which 33 received a TAP block, 12 ESPBs (2 catheters), 2 rectus sheath, 1 quadratus lumborum, as well as 3 lumbar and 3 thoracic epidural blocks (2 catheters each), of which 1 also received an ESPB. There were no differences in patient/procedure characteristics between no-RA and RA groups (Table 1). Intraoperatively, almost all patient received fentanyl (97%) and propofol (97%), acetaminophen (51%), lidocaine (51%), hydromorphone (25%), dexmedetomidine (21%), and ketamine (18%) or ketamine infusion (12%). However not statistically significantly, more no-RA patients had continuous PCA infusions postoperatively (78.6% vs. 57.4%, P=0.146), (Table 2). Pain management was deemed 'Satisfactory' in 44/54 (81.5%) of patients who received RA, and 13/14 (92.9%) in those who did not (P=.303). There were no difference in opioid-related side effects (29 vs. 24%, P=0.729) or regimens requiring changes (14 vs. 33%, P=0.163). There were no difference between no-RA, ESPB, and TAP block groups (Table 3).

CONCLUSION: Upon preliminary analysis, there were no significant differences between patients receiving RA and those not receiving RA during the time period when RA was instituted for renal transplant patients. These results are at odds with prospective, randomized trials in the adult literature demonstrating superiority of RA techniques in this population. We demonstrated significant heterogeneity in the management of renal transplantation patients. Subsequent analyses will characterize and adjust for potential confounders including intraoperative management, RA technique, PCA settings, and patient complexity. Future studies will aim to identify optimal management and design prospective evaluations.

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Table 1: Patient, Pre-, and Peri-Operative Characteristics

	Without RA (n=14)	With RA (n=54)	P-value
Patient Characteristics			
Sex			
Female	4 (28.6)	23 (42.6)	0.339
Age	10 (4-16)	13.5 (9-16)	0.283
Weight	29.2 (15.9-47.3)	39.8 (25.7-58.6)	0.234
BMI	18.2 (15.7-20.2)	18.8 (15.5-22.5)	0.638
BMI Percentile	33.7 (13.2-75.6)	45.4 (9.5-82.1)	0.987
ASA			
2	0	1 (1.9)	0.837
3	12 (85.7)	47 (87.0)	
4	2 (14.3)	6 (11.1)	
Preoperative CBC			
Hemoglobin			
Normal	4 (28.6)	16 (30.2)	0.906
Low	10 (71.4)	37 (69.8)	
Platelets			
Normal	13 (92.9)	41 (77.4)	0.326
Low	0	7 (13.2)	
High	1 (7.1)	5 (9.4)	
PT/INR:			
Normal	14 (100)	53 (100)	1.000
PTT			
Normal	6 (46.2)	37 (68.5)	0.252
Low	5 (38.5)	14 (25.9)	
High	2 (15.4)	3 (5.6)	
Perioperative Management			
Surgical Time	212 (175-273)	192 (161-243)	0.481
Anesthesia Time	333 (282-419)	343 (308-390)	0.645
Block Type:			
TAP	-	33	
ESPB	-	12 [2]	
Thoracic Epidural	-	3 [3]	
Lumbar Epidural	-	3 [3]	
Rectus Sheath	-	2	
Quadratus Lumborum	-	1	

Table 2: Initial Patient Transfer and POD 0/1 Note Evaluations

	Without RA (n=14)	With RA (n=54)	P-value
Initial Postop Note			
Initial Postop Note Unremarkable	2 (14.3)	8 (14.8)	0.960
Postoperatively Intubated (Yes, %)	1 (7.1)	2 (3.7)	0.577
Hemodynamic Support (Yes, %)	0	3 (5.6)	0.367
Agitation (Yes, %)	0	2 (3.7)	0.465
Pain Control Inadequate (Yes, %)	1 (7.1)	3 (5.6)	0.822
PONV (Yes, %)	1 (7.1)	0	0.048
POD 0/1 PCA, Oxygen, and Sedation			
Continuous Infusion	11 (78.6)	31 (57.4)	0.146
Operator			
Patient	4 (28.6)	16 (29.6)	0.995
Proxy	3 (21.4)	11 (20.4)	
Patient or Proxy	7 (50)	27 (5000)	
PCA Requests Filled (%)	100 (90-100)	93.2 (77.9-100)	0.028
Adjunct – Acetaminophen (yes, %)	11 (78.6)	39 (72.2)	0.631
Adjunct – Diazepam (yes, %)	1 (7.1)	16 (29.6)	0.083
Supplemental Oxygen			
None	12 (85.7)	44 (81.5)	0.762
Low Flow	2 (14.3)	8 (14.8)	
High Flow/ CPAP-BiPAP	0	2 (3.7)	
Sedation Level			
Sleeping	3 (21.4)	9 (16.7)	0.415
Awake and Alert	11 (78.6)	39 (72.2)	
Moderately Sedated	0	6 (11.1)	

Table 3: POD 0/1 Pain Team Rounding Note Evaluations

	Without RA (n=14)	With RA (n=54)	P-value
Provider Analgesia Evaluation			
Satisfactory	13 (92.9)	44 (81.5)	0.303
Unsatisfactory	1 (7.1)	10 (18.5)	
Opioid-Related Side Effect			
No	10 (71.4)	41 (75.9)	0.729
Yes	4 (28.6)	13 (24.1)	
Side Effect Profile			
None	10 (71.4)	41 (75.9)	0.241
PONV	0	4 (7.4)	
Pruritus	3 (21.4)	8 (14.8)	
Myoclonus	0	1 (1.9)	
Hypotension	1 (7.1)	0	
Treatment for Side Effect			
No	10 (71.4)	33 (61.1)	0.476
Yes	4 (28.6)	21 (38.9)	
Pain/Side Effect Regimen Change			
No Change/Positive Change	12 (85.7)	36 (66.7)	0.163
Regimen Change Addressing Issue	2 (14.3)	18 (33.3)	

PEDIATRIC ANESTHESIOLOGY 29

Morphine Induced Myoclonus with Sleep Disturbance in Young Children: An Under-Recognised and Distressing Side Effect

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INTRODUCTION: Myoclonus is an uncommon side effect of morphine[1]. With a paucity of clear delineation of frequency, incidence and prevalence rates in children having not been established. Morphine induced myoclonus is an under-recognised side effect in children that is frequently associated with sleep disturbance - especially in younger children. This is commonly misinterpreted as pain which leads to further increases in morphine administration, further aggravating this side effect. A review of morphine induced myoclonus in children has not been published in the literature. We have evaluated the incidence and recognition of morphine induced myoclonus with or without sleep disturbance in young children in our institution.

METHODS: A prospective cohort review was undertaken as part of a service evaluation in 200 children under the age of 8 years (median age 2 years) in whom morphine infusion was used to treat their acute pain. Parents were asked to report any 'jumpiness' or 'sleep disturbance' which they considered to be abnormal behaviour for their child. If their child experienced any abnormal behaviour, they were then asked to quantify the frequency as either once, two or three times per hour or every 5 minutes. The incidence of morphine induced sleep disturbance myoclonus (SDM) was also recorded following any reduction or cessation of the morphine infusion. Demographic data, morphine dosage, pain scores and heart rate changes were recorded. Statistical analysis: All tests undertaken were two-sided, and a p value <0.05 was considered as statistically significant, with (bootstrapped) 95% confidence intervals (CI) calculated. For univariable and multivariable logistic regression modelling was undertaken with logit function, along with a robust error variance and age and sex adjustment were fitted to identify the potential risk factors associated with the endpoint. Multivariable analyses were carried out via generalised linear models, with stepwise AIC (Akaike information criterion) in the backwards direction to ground the final model. Clinically relevant continuous variables were included in the multivariable model. Adjusted relative risks (RRadj) with bootstrapped 95% CIs were calculated and reported for the logistic regression model.

RESULTS: 53 children experienced myoclonus: morphine induced SDM was reported in 33 out of 200 children (16.5%) and a further 20 children (10%) experience morphine induced myoclonus without sleep disturbance (Figures 1&2; Table 1); 25/33 children (76%) with morphine induced SDM were under two years of age with a mean maximum infusion rate of morphine was 15.4 mcg/kg/h. The other eight children with morphine induced SDM were aged between two-six years with a morphine infusion rate between 5 to 35mcg/kg/h. From multivariate analysis, age under two years of age significantly increased the risk of developing myoclonus (RR 2.21 95%CI 1.32, 3.71; p<0.001) (Figure 3). The mean morphine infusion rate (in mcg/kg/h) was higher in children with morphine induced SDM (15.09 [95%CI 13.05,17.13; SD 7.33) than in children who did not experience myoclonus (15.15 [95%CI 14.06,16.24; SD 7.33) and was found to be statistically non-significant (two-tailed t-test p=0.95; 95%CI -2.12, 2.24). Myoclonus was recognised as a side effect of morphine in 19/53 children by parents or nurses and by the pain nurse specialist in the remaining 34 children. Morphine induced myoclonus was not recognised as a side effect of morphine in 63% of children by the nursing or medical staff. Morphine infusion rate was reduced or stopped in 12 out of 19 children recognised to have myoclonus and unchanged or increased in the other seven. In the 34 children not initially identified to have myoclonus, the morphine infusion rate was increased in 7 and 2 were given either chloral hydrate or diazepam to treat their myoclonus. Myoclonus stopped completely in 13 children following reduction of the morphine infusion, and a further 11 children had a noticeable improvement. Two children had no improvement following a reduction in morphine. Pain scores remained unchanged despite a reduction in the morphine infusion rate (ANOVA: p=0.313, adjusted R2 0.0209)

CONCLUSION: Morphine induced sleep disturbance myoclonus is common in young children, 76% occurring in those under 2 years of age and appears to be more common in female and is dose dependant. This side effect of morphine from our assessment appears to be under recognised and misinterpreted as pain by health professions.

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PEDIATRIC ANESTHESIOLOGY 30

Pain Control Following the Nuss Procedure in Pediatric Patients: A single center experience

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INTRODUCTION: Pectus excavatum repair by Nuss bar placement results in severe post-operative pain[1]. Poor pain control prolongs hospital discharge and can result in chronic post-surgical pain[2]. Prior literature has described comparative approaches to reduce acute pain including epidurals, multi-modal analgesia, chest wall catheters, and more recently, erector spinae plane blocks (ESBPs) and cryoablation[3,4]. Following concerns about the safety of thoracic epidurals in this population[5], we stopped performing neuraxial procedures for pain control, resulting in a significant change in our practice. The purpose of this study is to describe the evolution and compare pain-related outcomes of various post-surgical pain management strategies.

METHODS: We performed a retrospective chart review of all pediatric patients (<18 years) who underwent Nuss bar placement by a single surgeon at Duke Children's Hospital from July 2018 to July 2021. Patients were divided into 3 groups by intraoperative intervention, representing the chronologic change in our practice over the study period. Demographic and clinical data collected included: age, sex, race/ethnicity, ASA classification, and Haller Index. Intraoperative data collected included: use of multi-modal analgesics (methadone, ketamine), bilateral regional catheters (ESPBs or PVBs), and cryoablation (bilaterally T4-T8). Post-operative data collected included: opioid requirements at 24, 48, 72 and 96 hours post-op, average daily pain scores, length of stay, opioid refills after discharge, and complications.

RESULTS: 17 patients were included and analyzed by the following groups: no block (n=6), regional catheters (n=7), and cryoablation (n=4). All patients were male; mean age was 15.5 years (SD 1.44). The average operative time was an average of 61 minutes longer in the cryoablation patients than the other groups (158 vs. 97, p<0.0001). All patients received scheduled acetaminophen and a non-steroidal anti-inflammatory postoperatively. Total mean (+/- SEM) oral morphine equivalents (OMEs) were as follows: no block 269.5 (72), regional catheters 276.5 (82), and cryoablation 66.6 (20). Patients with cryoablation had a reduction in OMEs at 24 hours (p=0.074), 48 hours (p=0.076), 72 hours (p=0.039), and total (p=0.055) compared to the other two groups (Figure 1). Daily pain scores were not significantly different between groups at any period (Figure 2). 2 patients (1 no block, 1 regional) required a post-discharge opioid refill. All cryoablation patients were discharged by post-operative day 3; 6 patients in the other groups stayed an extra day. There were no reported complications with regional blocks, 1 cryoablation patient reported chest wall tingling on follow up.

CONCLUSION: Cryoablation was associated with longer operative times but decreased in-hospital OMEs when compared to bilateral regional block catheters and multi-modal analgesia alone.

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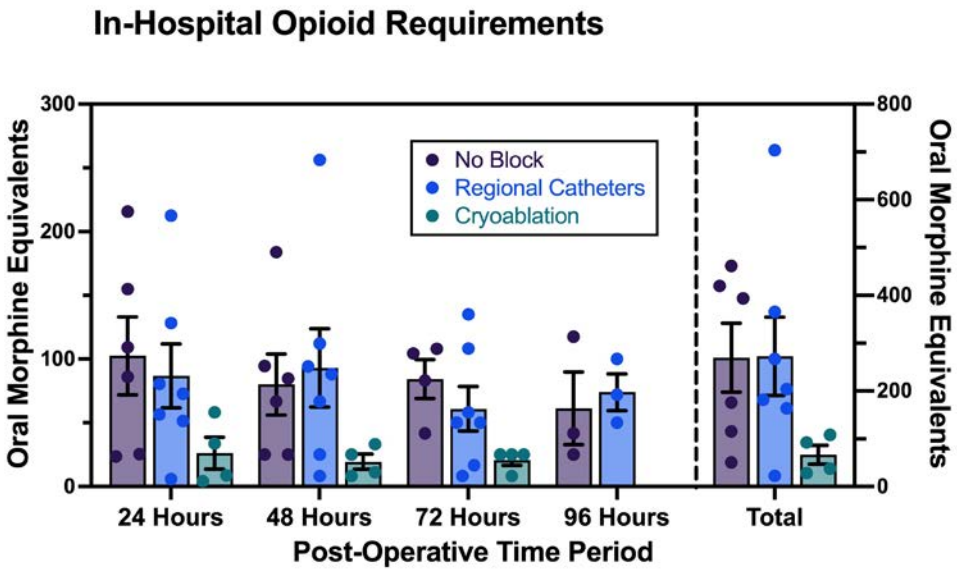

Fig. 1

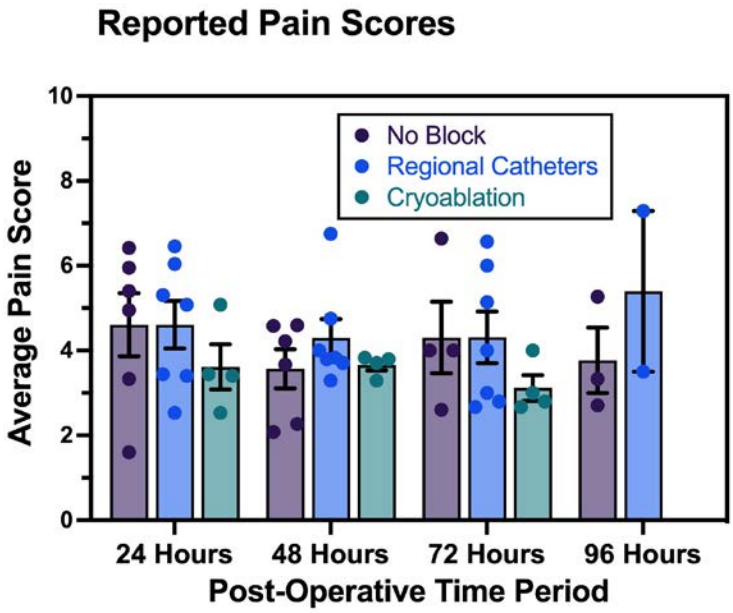

Fig. 2

PEDIATRIC ANESTHESIOLOGY 31

Evaluation of Stress Response and Anxiety Scores of Paediatric Patients Sedated with Intranasal Dexmedetomidine vs. Placebo: A Randomised Controlled Trial

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INTRODUCTION: Dexmedetomidine has been described for use in paediatric populations for over a decade.[1] The use of dexmedetomidine has widen into the perioperative setting not only because of its favourable physiological properties, but also due to its limited adverse effects.[1] Nonetheless, before administering dexmedetomidine in paediatric patients, its contraindications and biphasic effects on blood pressure need to be thoroughly understood.[2] There are a number of adverse clinical outcomes associated with the incidence of perioperative anxiety in paediatric patients.[3] The common ones include increased analgesic requirement, emergence delirium, and maladaptive behavioural changes, namely separation anxiety, enuresis, sleep disturbance, and eating disorders.[4] Salivary cortisol level was found to be decreased with maternal presence during the induction of anaesthesia in paediatric patients.[5] The level was found to be significantly decreased during the induction of anaesthesia and recovery, reflecting a reduced stress response to anaesthetic induction with maternal presence.[5] We conducted a prospective randomised controlled trial assessing the stress response and anxiety scores of paediatric patients who underwent elective surgeries. Baseline and post induction of anaesthesia serum cortisol levels were compared. Recruited patients were either sedated with intranasal dexmedetomidine or intranasal normal saline (placebo; NS).

METHODS: This is a prospective randomised controlled trial, and the study was approved by the Institutional Ethical Board . Paediatric patients aged 1–12 years old underwent elective surgery in various surgical disciplines were recruited. A total of 60 patients with American society of Anesthesiologists I and II weight between 10 and 60 kg were recruited. The exclusion criteria included patients with allergy to study drugs, underlying congenital heart disease, neuromuscular disorder, and neurological disease. Patients with metabolic disorders, on steroid therapy, and difficult airway cases and special need children (cerebral palsy, down syndrome, attention deficit hyperactive disorder, and autism spectrum disorder) were also excluded.

Baseline serum cortisol level was taken a day before surgery during the preoperative visit. On the day of the surgery, the patients received either 1 mcg. kg-1 intranasal DEX (undiluted 100 mcg.kg-1) or an equivalent volume of intranasal 0.9% NS using an intranasal Mucosal Atomization Device. Post induction serum cortisol level was taken within first 10 minutes of anaesthesia.

Assessment tools consisted of SBS and m-YPAS. m-YPAS is an observational checklist with four response categories, each consisting of four to six distinct behavioural descriptions. Four categories of behaviour were assessed: activity, vocalizations, emotional expressivity, and state of arousal. A total score of 23 indicated low anxiety levels, and 100 indicated high anxiety levels. On the other hand, SBS has two major categories: sedation and behavioural components. Scores are considered satisfactory when rated between 3 and 4, indicating that the patients either have minimal or no reaction to external stimuli.

RESULTS: Both NS and DEX groups showed a significant increase in serum cortisol levels when compared with the baseline. Pairwise comparisons between the groups showed no significant difference in serum cortisol levels (95%CI 1.77(−2.18,5.71); p = 0.374). Both NS and DEX groups showed significant improvement for SBS post sedation administration. There was a significant increase in post induction of anaesthesia heart rate level in the NS group (95%CI −10.23(−15.57, −4.90) p < 0.001); however, it was not significant in the DEX group (95%CI −7.17(−15.405,1.07); p = 0.090). (Table 1)
Table 2 shows the overall mean for cortisol, heart rate, m-YPAS, and SBS within each treatment group based on time (time effect) with adjustment for multiple comparisons (Bonferroni). Table 3 shows the comparison of mean cortisol, MAP, HR, mYPAS and SBS among two groups based on time (time-treatment interaction) for baseline and post induction of anaesthesia.

CONCLUSION: We conclude that 1 mcg.kg-1 intranasal DEX provides satisfactory levels of sedation for paediatric patients undergoing general anaesthesia. However, the dose may not be adequate to obtund the stress response to the induction of anaesthesia based on baseline and post induction of anaesthesia serum cortisol levels.

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Table 1:

Comparison of mean cortisol, MAP, HR, mYPAS and SAS within each treatment group based on time (time effect)

Parameters	Control		Intervention	
	MD (95% CI)	P value	MD (95% CI)	P value
Cortisol (nmol/L)	-125.39(-179.18,-17.60)	<0.001	-63.27(-108.48,-18.05)	0.008
MAP (mmHg)	2.40(-2.12,6.92)	0.286	4.40(-0.29,9.09)	0.650
HR (beats perminute)	-10.23(-15.57,-4.90)	<0.001	-7.17(-15.41,1.07)	0.090
mYPAS	-0.77(-1.95,0.41)	0.580	0.43(-0.76,1.63)	0.470
SBS	-1.97(-2.517,-1.42)	<0.001	-2.20(-2.90,-1.50)	0.001

Table 2:

Comparison of mean cortisol, MAP, HR, mYPAS and SBS among two groups based on time (time-treatment interaction)

Time	Parameters	MD (95% CI)	P value
Baseline			
	Cortisol (nmol/L)	-29.33(-86.84,28.19)	0.312
	MAP (mmHg)	0.77(-3.71,5.24)	0.733
	HR (beats perminute)	-0.17(-7.58,7.25)	0.964
	mYPAS	0.43(-1.56,2.43)	0.665
	SBS	-0.63(1.26,-0.01)	0.047
Post induction of anaesthesia			
	Cortisol (nmol/L)	32.79(-44.81,110.38)	0.312
	MAP (mmHg)	2.77(-2.83,8.37)	0.330
	HR (beats perminute)	2.90(-7.67,13.47)	0.585
	mYPAS	1.63(-.027, 3.53)	0.091
	SBS	-0.87(-1.51,-0.23)	0.009

PEDIATRIC ANESTHESIOLOGY 32

The Incidence of Residual Neuromuscular Blockade in Pediatrics: A Prospective, Multi-institutional Cohort Study

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INTRODUCTION: Despite evidence that residual neuromuscular blockade (NMB) is common, the incidence in adults remains high [1,2]. This incidence is not well studied in pediatric patients who face the same, if not greater, challenges to appropriate monitoring and reversal of neuromuscular blocking agents (NMBAs)[3]. We hypothesized the incidence of residual NMB in children is greater when neostigmine versus sugammadex is used as the antagonist.

METHODS: We conducted a prospective, multi-institutional study to evaluate the incidence of residual neuromuscular blockade in children, defined as a train-of-four ratio (TOFR) less than 0.9 by quantitative electromyography monitoring. Following IRB approval and an appropriate consent and assent process, a total of 74 children between 2 and 18 years old receiving general anesthesia with the use of the non-depolarizing NMBA, rocuronium, were enrolled. Thirty-seven children were enrolled at each of two study sites [Children's Hospital Colorado (CHCO) and Children's Healthcare of Atlanta (CHOA)]. Anesthesia was administered according to usual care and per institutional standards. NMBA antagonism was determined by the anesthesiologist; children at CHCO received primarily sugammadex while those at CHOA received primarily neostigmine. Residual NMB was assessed in the post-anesthesia care unit (PACU) quantitatively using the TwitchView® monitor (Blink Device Company, Seattle WA). Patients with measured train-of-four ratio (TOFR) <0.9 indicating an incomplete return of muscle strength received sugammadex, and their TOFR was monitored until TOFR ≥0.9 was achieved.

Statistical Analysis: Univariate analyses used Wilcoxon Rank Sum test, Fisher's exact test, or simple Firth's logistic regression as appropriate for the distributions. Since there appeared to be an association between residual NMB and patient weight within the neostigmine group, a subset analysis was performed in which a Firth's logistic regression model was produced in which "residual NMB" was the response, and the "interaction between reversal agent (sugammadex vs neostigmine) and patient weight" was the explanatory variable. All analyses were performed using the R statistical software package (Version 4.1.2) with the 'logistf' package used for the regression analyses. All p values were two-tailed and p values of < 0.05 were considered statistically significant.

RESULTS: Seventy-four patients met inclusion criteria with 37 consecutive patients in each cohort. Age, sex, weight, BMI and ASA status of these two cohorts were similar. There was a statistically significant increase in the incidence of residual NMB in the neostigmine group (OR 32.5, 95% CI: 3.9 to 4,244.8, p-value <0.001, Table 1) relative to the sugammadex cohort. This increase occurred despite the sugammadex cohort having more rocuronium administered and quantitative monitoring used less often intraoperatively (Table 1). Residual NMB was also seen to occur in this group despite achieving adequate spontaneous recovery (train of four count = 4) prior to administration of neostigmine and appropriate dosing of this agent (0.05 mg/kg, Table 1). On subset analysis, there was a correlation between patient weight and residual NMB in the neostigmine cohort (OR 1.02, 95% CI: 1.02 to 1.07, p-value <0.001, Figure 1).

CONCLUSION: NMBA reversal with neostigmine is associated with an increased risk of residual NMB when compared to sugammadex. Increased patient weight may be a risk factor for residual NMB in pediatric patients who received neostigmine antagonism. This finding may be due to the fixed maximum dose of neostigmine administered to heavier pediatric patients. Further randomized research would clarify the association between the incidence of residual NMB and neostigmine reversal.

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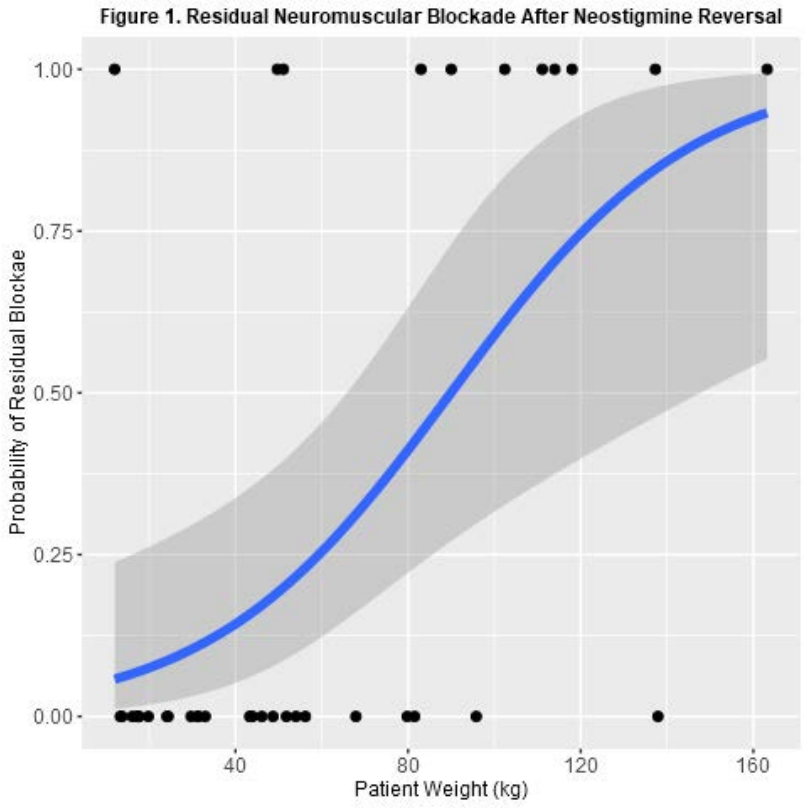
Table 1. Demographics and Perioperative Variables*

	CHC/Sugammadex (n = 37)	CHOA/Neostigmine (n = 37)	*P*-value
Sex (M/F)	24 (64.9%) / 13 (35.1%)	18 (48.6%) / 19 (51.4%)	0.24
Age (years)	13 [6, 16]	12 [8, 15]	0.57
Weight (kg)	42.4 [22.4, 62.1]	48.7 [24.4, 83.0]	0.27
BMI (kg/m^2)	19.5 [16.5, 22.7]	21.1 [16.0, 32.4]	0.19
ASA Classification			0.26
1	11 (29.7%)	6 (16.2%)	
2	18 (48.6%)	18 (48.6%)	
3	8 (21.6%)	13 (35.1%)	
Total Rocuronium Administered (mg/kg)	1.1 [0.9, 1.9]	0.6 [0.5, 0.8]	<0.001
Sugammadex Dose (mg/kg)	2.5 [2.0, 4.0]	---	
Neostigmine Dose (mg/kg)	---	0.05 [0.04, 0.07]	
Residual NM Blockade in PACU	0 (0.0%)	11 (29.7%)	<0.001

CHC = Children's Hospital of Colorado; CHOA = Children's Hospital of Atlanta; NM = Neuromuscular; PACU = Postoperative Care Unit.

*Nominal variables expressed as count (percentage) while continuous variables expressed as median [interquartile range (IQR)]. Univariate analyses were conducted utilizing the Wilcoxon rank-sum test or Fisher exact test as appropriate for the distribution.



PEDIATRIC ANESTHESIOLOGY 33

Prophylactic strategies to target post-operative nausea and vomiting in pediatric patients undergoing general anesthesia: a scoping review

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INTRODUCTION: Background: Post-operative nausea and vomiting (PONV) is a common occurrence in pediatric patients undergoing general anesthesia, impacting 33% to 82% of patients[1]. Clinicians seek prophylactic interventions to prevent not only its ill effect on patients, but also its ramifications on perioperative care. Objectives: To assess the body of evidence around prophylactic strategies, both pharmacologic and non-pharmacologic, targeting pediatric PONV. Further information such as demographic data, secondary outcomes, and concurrent pain assessment can help inform the robustness of the prophylactic strategies studied.

METHODS: A scoping review was designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Scoping Review (PRISMA-ScR) Extension guideline[2]. Eligibility criteria included a study population less than or equal to eighteen years of age undergoing general anesthesia. The primary outcome was the incidence of PONV or post-operative vomiting (POV). Randomized clinical trials assessing various prophylactic strategies for PONV in pediatric patients undergoing general anesthesia were identified using 10 databases from their inception to September 19, 2021. Ancillary data collected includes the type of surgery patients underwent, measurement tools used to assess PONV, secondary outcomes, whether pain was concurrently assessed to PONV, and whether dose-dependent effects were studied.

RESULTS: Of 188 trials, 157 (83.5%) investigated pharmacologic interventions, 25 (13.3%) investigated non-pharmacologic interventions, and 6 (3.2%) investigated mixed pharmacologic and non-pharmacologic interventions. Of 224 total prophylactic strategies studied in trials using pharmacologic or mixed interventions, the most common modalities were ondansetron (44 trials, 19.6%), droperidol (24 trials, 10.7%), and dexamethasone (28 trials, 12.5%). Of 36 total prophylactic strategies studied in trials using non-pharmacologic or mixed interventions, the most common modalities were acupuncture/acupressure (17 trials, 47.2%) and gastric aspiration (3 trials, 8.3%). Of the 44 trials investigating ondansetron as a pharmacological intervention, the doses used ranged from 0.01 mg/kg to 0.2 mg/kg, with the most common dose studied being 0.15 mg/kg (22 trials, 18.5%). Of the 24 trials investigating droperidol as a pharmacological intervention, the doses ranged from 0.005 to .3 mg/kg, with the most frequent being 0.075 mg/kg (11 trials, 9.2%). Of the 28 trials investigating dexamethasone as a pharmacological intervention, the doses ranged from 0.0625 to 1 mg/kg, with the most frequent being 0.5 mg/kg (13 trials, 10.9%). Ondansetron was the most common pharmacologic prophylactic intervention studied in the years spanning 1996-2005, followed by dexamethasone from 2006-2021 (Figure 1). Of the 188 trials, the most common surgeries investigated for pediatric PONV were strabismus surgery (68 trials, 36.2%) and tonsillectomy or tympanoplasty (45 trials, 23.9%). Of a total 4 measurement tools used to assess PONV in the included trials, the most common was clinical judgement (170 trials, 90.4%); the validated Baxter Animated Retching Faces (BARF) Scale was utilized in 4 of 188 trials (2.1%). Of the 188 trials, the most common secondary outcomes assessed included the need for rescue medication (46 trials, 24.5%), adverse events (39 trials, 20.7%), and pain (39 trials, 20.7%). Of the 188 trials, 46 (24.5%) measured and addressed pain in the recovery room as part of their study protocol. 16 (8.5%) of 188 trials investigated dose-dependent adverse effects. Of the 188 trials, 175 (93.1%) were single centre, 7 (3.7%) were multi-centre but single country, and 6 (3.2%) were multi-country. Of the 188 trials, the most common countries of origin were United States of America (58, 30.9%), Canada (19, 10.1%), and Turkey (17, 9.0%) (Figure 2).

CONCLUSION: The majority of data in pediatric PONV prophylaxis is based on pharmacologic interventions, with a paucity of research in non-pharmacologic or mixed interventions. Assessing and documenting PONV using validated tools such as the BARF scale may aid in standardizing pediatric PONV prophylaxis research moving forward. In addition, a more thorough impact of PONV prophylaxis may be gleaned from concurrently measuring related metrics such as adverse events. In particular, assessment and treatment of pain can bolster our understanding of its impact on nausea and vomiting in the post-operative recovery period.

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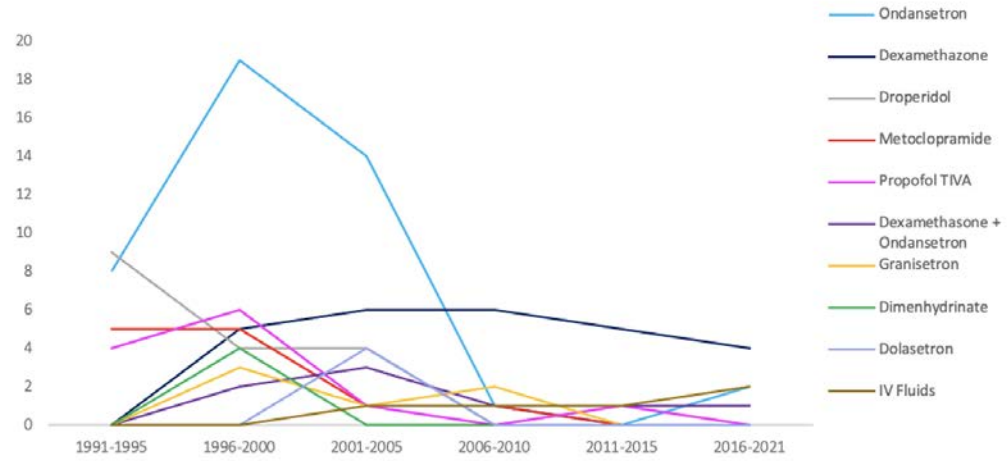

Figure 1. Temporal trend of pharmacologic interventions studied over time. Within each 5-year span beginning in 1991 to present, the number of studies investigating each pharmacologic intervention listed in the legend are shown.

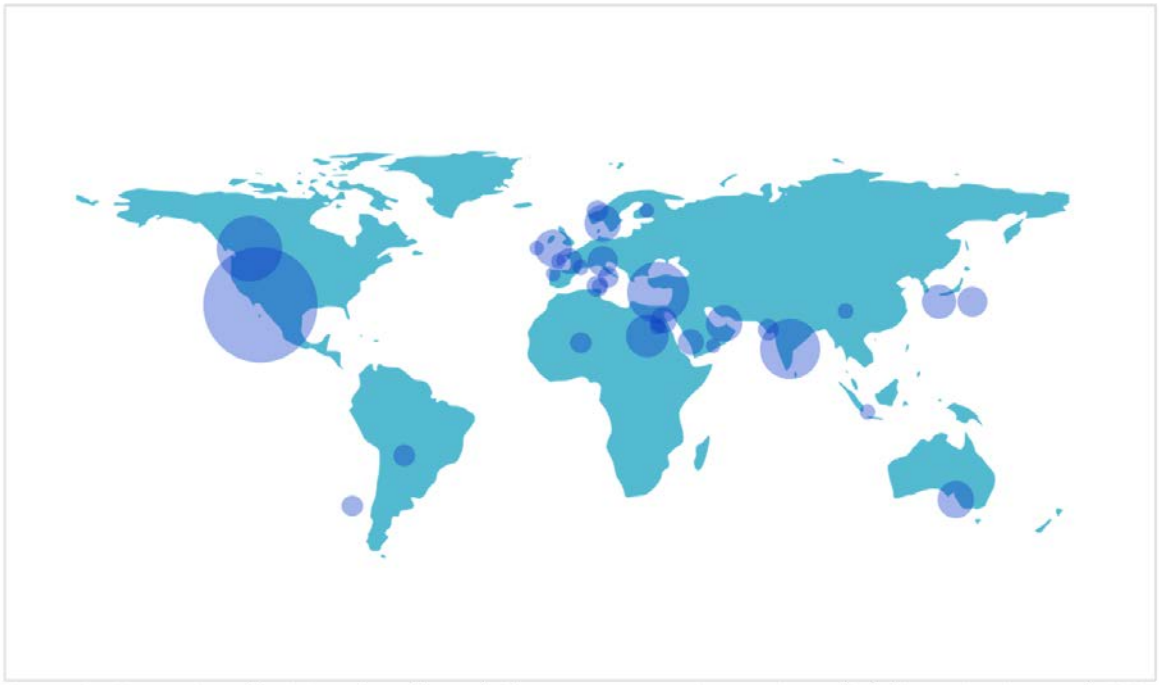

Figure 2. Countries of origin of studies which met our scoping review eligibility criteria, total 188. The size of sphere reflects the relative number of studies.

PEDIATRIC ANESTHESIOLOGY 34

A Systematic Review of Epileptiform Changes During Sevoflurane Anesthesia in Infants and Children

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INTRODUCTION: Sevoflurane is the most commonly used potent volatile agent for inhalation induction of general anesthesia in pediatric patients. Early clinical case reports have described involuntary movements, seizure-like behaviors, and incidental findings of epileptiform changes during brain monitoring. Subsequent studies recording the electroencephalogram (EEG) have demonstrated epileptiform activity, defined as abnormal patterns reflecting underlying neurophysiologic dysfunction. The objective of this study was to perform a systematic review of the literature describing epileptiform activity during pediatric anesthesia using sevoflurane. A secondary aim was to begin to classify the heterogeneous reporting of EEG changes in the literature to determine the feasibility of a meta-analysis.

METHODS: A targeted clinical question was crafted using the PICO framework and registered a priori on PROSPERO on 3/19/21 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=237719). Under the guidance of a librarian from the Gottesman Library at Albert Einstein College of Medicine, a boolean search string was generated to search for articles and gray literature focusing primarily on 'pediatric', 'sevoflurane' and 'electroencephalogram' in PubMed, OVID, the Cochrane Library, Google Scholar, etc. We utilized the COVIDENCE software platform (Cochrane Collaborative Group, UK) to manage our literature review. We selected English language articles only. 495 references were imported for initial screening. After title and abstract screening, 56 full-text studies were included for further assessment. The final systematic review included 13 references. A PRISMA flow chart of the data extraction is shown in Figure 1. A preliminary screening of the extracted literature was conducted by three researchers (JC, MT, AF) with the addition of two research members (DI, LG) for data extraction and bias assessment. An assessment for risk of bias was made using the Newcastle-Ottawa Quality Assessment Scale. Data extraction and assessment of bias were discussed as a group during weekly meetings. The characteristics of the studies and their primary outcomes were collected (Table 1) and strategies for data synthesis were discussed with the larger team.

RESULTS: A total of 13 studies were included. The incidence of epileptiform changes reported in individual studies ranged from 0 - 95%. There were a total of 649 subjects ranging in age from neonate to 18 years of age with EEG abnormalities reported in 204 (31.4%). EEG data were acquired using a variety of recording systems with variable number of leads and heterogeneous outcomes reported. The majority of studies utilized less than 16 channels of EEG (10/13, 76.9%) with five utilizing processed monitors or 2 channels or less. Three studies (23.1%) utilized 16 or more channels of unprocessed EEG taking into account activity over the entire head. There was variability in sevoflurane dosing as well as premedication practices with midazolam or hydroxyzine. The periods of anesthesia monitoring were also heterogeneous. Characteristics of the studies are presented in Table 1.

CONCLUSION: There was heterogeneity in the reported incidences of epileptiform changes during pediatric anesthesia using sevoflurane. Clinical studies varied in the age range assessed, study design, phases of anesthesia under investigation, number of EEG leads recorded, and adjuvant anesthetics administered. Methods of ventilation also varied. Next steps would be the development of a process to classify study outcomes based on the quality and comprehensiveness of EEG data with the eventual goal of performing a meta-analysis.

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Figure 1

	Reference Age (Sample Size)	Phase of anesthesia Sevoflurane Dose	EEG - Number of Channels	Abnormal EEG Outcomes
1	Chao. et al 2020 0-3 yrs (n= 54)	Induction Up to 8% sevoflurane	26 channels	5/54 patients
2	Gibert. et al 2012 3-11 yrs (n=76)	Maintenance 6% sevoflurane in 50% N_2O)	1 channel	12/76 patients
3	Vakkuri et al 2000 6±2 yrs (n=32)	Induction 8% sevoflurane	4-channel	27/32 patients
4	Rigouzzo et al 2018 5- 18 yrs (n=36)	Maintenance Randomized between 1%, 2%, 3%, 4%, 5% sevoflurane	1-channel BIS monitor	17/52 trials
5	Nieminen et al 2002 3-8 yrs (n=30)	Maintenance 2% sevoflurane in air/oxygen	5 channel EEG	---
6	Kreuzer et al 2014 4.6 ± 3.0 yrs (n=100)	Induction sevoflurane 8% or 6%	2-channel Narcotrend EEG	64/100
7	Constant et al 1999 2-12 yrs (n=32)	Induction 7% sevoflurane OR incremental 2%, 4%, 6%, 7% sevoflurane in 100% oxygen OR 7% sevo in oxygen and nitrous oxide 50:50	16 channels	---
8	Koch et al 2018 0.5-8 yrs (n=18)	Induction Average induction dose: 6.2%	4 channels	12/18
9	Schultz et al 2012 7 months- 8 yrs (n=70)	Induction 8% induction, 4% maintenance	3 channel narcotrend	14/70
10	Sonkajärvi et al 2009 4-10 yrs (n=20)	Induction 8% sevoflurane in 50:50 oxygen:nitrous oxide	21 leads according to the International 10–20 system	19/20
11	Stolwijk et al 2017 Neonatal period- average agee 38.28 weeks (n=111)	Induction Absolute dose: 1.26% (0.04-2.5)	2 channels	11/111
12	Moran et al 2011 36 to 54 weeks post-conceptual age (n=23)	Induction Sevoflurane concentrations from 0.16 to 4.25	8-channel referential EEG montage	6/23
13	Vakkuri et al 2001 2 to 12 years old (n=31)	Induction Sevoflurane (8% in N_2O/O_2 2:1)	bipolar 4-channel EEG	17/31

Figure 2

PEDIATRIC ANESTHESIOLOGY 35

Allostatic Load of Cumulative Anesthesia and Sedation Exposure on Infant Brain Following Esophageal Atresia Repair: Retrospective Analysis

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INTRODUCTION: Esophageal atresia (EA) is a congenital malformation that was previously thought to have no neurological component, except when associated with syndrome[1]. Recent reports implicated that EA may be associated with clinically significant brain findings[2] and long-term neurological consequences[3]. We quantitatively examined anesthesia and sedation exposure as possible early indirect markers of underlying disease complexity in relation to neurological findings in infants born with EA.

METHODS: Institutional Review Board approved a retrospective cross-sectional cohort study of term-born (n=44) and preterm infants (28-37 weeks of gestation; n=26) that underwent primary surgical repair of EA at a single institution (2009-2020). Exclusion encompassed infants with chromosomal and genetic abnormalities known to be associated with neurologic findings (n=14). Demographic and clinical data were obtained from the electronic medical record, Powerchart (Cerner, London, UK). Patients were categorized by (i) sex, (ii) gestational age at birth (viz. term-born vs. preterm), (iii) incidence of neurologic findings (viz. vertebral/peripheral nervous system and those of the cranium/brain), (iv) severity of disease (viz. American Society of Anesthesiologists (ASA) and Pediatric Risk Assessment (PRAm) scores), and (v) type of surgical repair (primary anastomosis for short-gap vs. Foker process for long-gap EA). We collected length of postoperative intubation, weaning of sedation medications, and total sedation time at the time of the first surgery, and the number of anesthesia events and cumulative monitored anesthesia care (MAC) hours in the first year of life. Data were presented as numerical sums and percentages while associations were measured using Spearman's Rho.

RESULTS: Vertebral/spinal abnormalities are more common than cranial/brain findings in the settings of 100% (70/70) spinal ultrasound diagnostics, in comparison to brain diagnostics performed only when clinically indicated (47%; 33/70). Of those infants that underwent diagnostics, 41% (29/70) had clinically significant vertebral/spinal and 45% (15/33) had cranial/brain findings. The incidence of neurological findings was not dependent on the gestational age, or ASA status. We noted a trend for higher incidence of cranial/brain findings in term-born and premature infants with higher PRAm scores. Infants with long-gap EA had approximately double the number of anesthesia events in their first year of life and more than twice as many anesthesia MAC hours exposure than short-gap EA patients. Long-gap EA infants also had approximately ten times more total sedation exposure than short-gap EA patients for preterm and term-born cohorts. No significant positive associations between anesthesia and sedation end-point measures with incidence of neurologic findings were found.

CONCLUSION: Our data implicate that cranial/brain findings might be underestimated in a cohort of infants born with EA. Neither anesthesia nor sedation exposure proved valuable as an individual indicator of early brain findings in selected cohort of infants undergoing EA repair. Future research should aim to evaluate neurologic development of EA patients undergoing complex perioperative critical care.

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SUBSPECIALTY ABSTRACTS

PERIOPERATIVE ANESTHESIA

PERIOPERATIVE ANESTHESIA 1

Anesthetic management of patients undergoing tracheal resection and reconstruction A retrospective observational study

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INTRODUCTION: Tracheal resection and reconstruction (TRR) is the preferred treatment for residual tracheal stenosis after dilation and primary tracheal tumors.[1] Recommendations for the perioperative management of TRR are primarily based on clinical experience and observational surgical studies with a short description of perioperative anesthetic interventions.[2] Moreover, this surgery presents many challenges to the anesthesiologist; the risk of losing the airway is lingering throughout the surgery, the airway is shared with the surgeon during surgical resection, and at the end of the intervention, extubation with cervical flexion and adequate pain management are paramount to prevent Valsalva maneuvers (i.e., cough or nausea) that could cause tracheal anastomoses rupture.[1] Therefore, anesthetic interventions can be a concealed factor in perioperative outcomes of patients undergoing TRR.

METHODS: After approval of the Ethics and Research Committee and the Department of Anesthesiology of the Hospital Universitario San Ignacio, a retrospective analysis of the medical records was performed to identify patients over 18 years of age with tracheal stenosis undergoing TRR in the last ten years (June 1, 2009, to May 31, 2020). Exclusion criteria were patients on mechanical ventilation, surgical reintervention, carinal resection, and cases where the anesthesia record in the electronic or physical medical records was not available. Our primary objective is to describe the perioperative anesthetic management of patients with tracheal stenosis undergoing TRR. Secondary objectives are to describe the demography, preoperative condition, and postoperative complications after TRR. Finally, we did a post-hoc analysis to identify possible risks factors for postoperative complications after TRR procedures; the analysis was performed between postoperative complications and the following variables: previous balloon dilation, laser resection, severity of the stenosis, preoperative tracheostomy, duration of surgery, number of rings resected, cervical flexion, airway approach, and anesthetic induction. For the statistical analysis, categorical variables were presented as percentages and continuous variables as mean and standard deviation. For the post-hoc analysis, we did a bivariate analysis with Student t-test, chi-squared test, and Fisher's exact test. Statistical significance was set for a p-value less than 0.05.

RESULTS: Forty-three patients undergoing TRR were analyzed; prolonged intubation was the primary cause (72%) for tracheal stenosis, which was found to be of variable degrees of severity. Thirty percent of patients had been tracheostomized approximately 36 months (SD ± 34) before TRR. The post-hoc analysis did not find an association of postoperative surgical reintervention for patients who had undergone preoperative tracheostomy ($p = 1.000$). The induction anesthetic technique was either intravenous (70%) or inhalational (18%), and 2% of patients required awake intubation. Endotracheal intubation (either pre-stenosis or trans-stenosis) was performed in 39% of cases, an LMA approach was used in 37% of patients, and stoma site intubation was done in 23% of patients undergoing TRR. In a post-hoc analysis, we did not find an association between airway management and reoperation ($p = 0.556$). In 71% of cases, sevoflurane and intravenous infusion of remifentanil were used for anesthesia maintenance. In the intensive care unit (ICU), 49% of patients received an infusion of dexmedetomidine for sedation and analgesia, without reports of respiratory depression. Major postoperative complications were vocal cord paralysis (25.6%), postoperative ventilatory support (20.9%), and the need for surgical reintervention (20.9%). One patient died in the postoperative period due to massive hemoptysis and neck hematoma. We did not find a statistical association between the severity of the stenosis and reintervention ($p = 0.478$).

CONCLUSION: Perioperative management of TRR at our hospital has a low mortality rate. We did not find an association between perioperative anesthetic interventions with postoperative complications. Additional studies are needed to evaluate if anesthetic interventions (airway management, anesthetic induction, early extubation or postoperative sedoanalgesia) may be associated with better outcomes.

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PERIOPERATIVE ANESTHESIA 2

Association of Anesthesiologist Staffing Ratio with Postoperative Morbidity and Mortality

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INTRODUCTION: While anesthesia staffing research has focused on provider type (independent nurse anesthetist versus anesthesiologist), little attention has been paid to evaluating the impact of varying staffing ratios of anesthesiologists across multiple operating rooms. Literature suggests no difference in quality based on anesthesia provider type[1,2] yet improved patient outcomes with anesthesiologist involvement[3]. Anesthesiologists may operate as (1) a solo provider in a procedural room, or (2) in anesthesia care teams – overseeing multiple procedural rooms concurrently, each continuing a single nurse anesthetist, anesthesia assistant, or resident. There are presumed benefits of working in care teams, including cost reduction efforts targeting high fixed-cost anesthesiology services. These efforts assume increasing anesthesiologist responsibilities are non-inferior to lower staffing ratios[1]. Understanding potential effects of these efforts on patient care is necessary to inform clinical care staffing decisions. In this study, we used multicenter data from a national electronic perioperative health record registry to evaluate the association between varying anesthesiologist staffing ratios and operative patient morbidity and mortality.

METHODS: Participants: Data was obtained from the Multicenter Perioperative Outcomes Group (MPOG) database, a comprehensive perioperative patient registry from over 50 hospitals[4]. Cases were selected for patients greater than 18 years of age who underwent surgery between 1/1/2010 and 10/31/2017. The ratio of anesthesiologist to the number of rooms covered is called their 'staffing ratio'. It can reach to 1:4 without resident involvement, above which care is considered medical supervision. For that reason, staffing ratios are commonly less than or equal to 1:4. Electronic health record anesthesiologist sign in/out times were used to determine staffing ratios. Cases with invalid data, including irreconcilable concurrencies, were excluded from analysis, as were cases with historically fixed staffing ratios: cardiac, liver transplant, cataract, organ procurement, and labor epidural procedures. Exposure measure (Staffing Ratio): Sign in/out times between anesthesia start and end were used to calculate a single staffing ratio for each operative case, using the time-weighted average of the individual staffing ratios as a continuous variable. This staffing ratio was categorized into 4 levels used in our regression models: 1, 1< Staffing Ratio <=2, 2< Staffing Ratio <=3 and 3< Staffing Ratio <=4. Primary Outcome: A composite of six major morbidities and in-hospital mortality. Morbidities are composed of cardiac, respiratory, gastrointestinal, urinary, bleeding, and infection ICD-9 groupings based on the U.S. Agency for Healthcare Research and Quality's single-level Clinical Classifications Software categories for International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes and manually crosswalked to ICD-10 codes within MPOG5. Statistical Analysis: Propensity score matching methods were applied to create a balanced sample with respect to patient, procedure, and hospital level confounders. A sequential modeling approach used logistic regression in which propensity scores were estimated for two staffing ratio levels at a time, using 1<staffing ratio<=2 as the reference group. Cases were matched on propensity scores, using a radius method with radius of 0.016. After matching, the association between staffing ratio group and the collapsed composite primary outcome was assessed using a multivariable conditional logistic regression modeling.

RESULTS: Propensity matched samples consisted of 578,815 patients across 23 institutions. Compared to patients receiving care from an anesthesiologists covering between 1-2 cases, those exposed to an anesthesiologist covering between 2-3 and 3-4 overlapping cases showed a 5% and 13% increase in risk adjusted mortality/morbidity (5.27% vs 5.50%, aOR 1.05 [95% CI 1.01-1.08], p=0.005) and an observed composite rate of 5.27% vs 5.93%, aOR 1.13 [95% CI 1.08-1.19], p-value <0.001).

CONCLUSION: Increasing anesthesiologist staffing ratios was associated with an increase in risk-adjusted morbidity and mortality. These findings should be considered when considering clinical coverage efforts. These data quantify a potential patient and safety risk associated with increasing staffing ratio and highlight effects of anesthesiologist responsibilities in perioperative team models.

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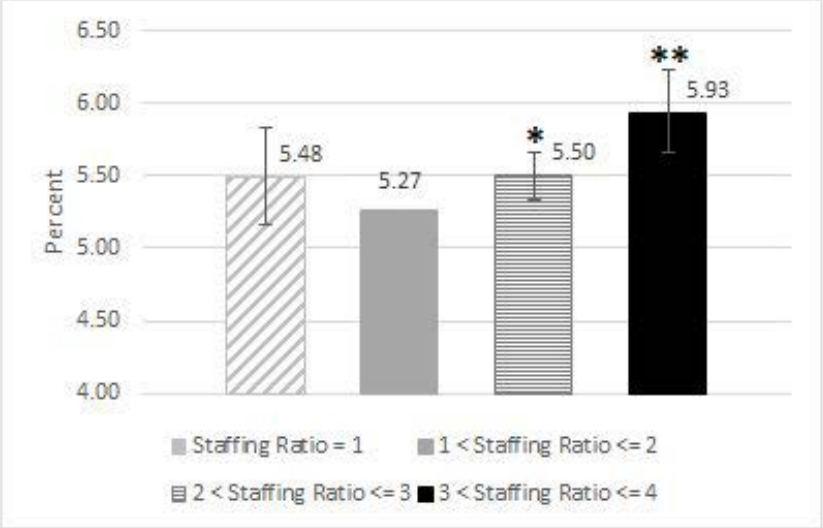

Figure: Adjusted Composite Morbidity/Mortality Rate. Values are shown composite morbidity/mortality percentage for four time-weighted average staffing ratio groups. *p-value=0.005. **p-value<0.001.

PERIOPERATIVE ANESTHESIA 3

Intraoperative low driving pressure ventilation and loss of independent living after surgery in older patients: A retrospective multicenter cohort study

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INTRODUCTION: Loss of independent living after surgery is dreaded by older patients and their families. While comprehensive instruments to identify patients at risk of loss of independent living have been established[1,2], few interventions are known to prevent this unfavorable outcome. In this study, we hypothesized that intraoperative ventilation maintaining lower driving pressures is associated with a lower risk of a patient's loss of previous independent living after surgery through a reduction in postoperative respiratory complications[3].

METHODS: Patients aged 60 years or older who lived at home prior to elective, non-cardiothoracic surgery at two tertiary academic healthcare networks in Massachusetts, USA between 2006 and 2018 were included in this hospital registry study. The primary exposure was the median driving pressure (plateau pressure - positive end-expiratory pressure) during general anesthesia and the primary outcome was the loss of independent living, defined as postoperative discharge to a skilled nursing facility, long-term nursing home or hospice. Multivariable logistic regression analysis adjusted for a priori defined factors including patient demographics, comorbidities and intraoperative factors was applied. Path mediation analysis was conducted to examine whether the association between lower driving pressure ventilation and loss of independent living after surgery was mediated by a reduction in postoperative respiratory complications, defined as reintubation within 7 days or hemoglobin oxygen saturation below 90% within 10 minutes after extubation.

RESULTS: Among 87,407 patients (Figure 1), 12,584 (14.4%) lost the ability to live independently after surgery. Patient characteristics are provided in Table 1. The median (interquartile range) driving pressure during general anesthesia was 16.0 cmH2O (13.0-19.5) in patients who lost the ability to live independently after surgery and 14.7 cmH2O (12.0-18.0) in patients who did not. There was variability for using low (<15 cmH2O) driving pressures among individual anesthesia providers (Figure 2). In adjusted analyses, a lower driving pressure was associated with a reduced risk of postoperative loss of independent living (adjusted odds ratio [aOR] 0.91 per every 10 cmH2O decrease [95% confidence interval [CI] 0.88 to 0.96]; p<0.001; Figure 3). This association was in part mediated by a reduction in postoperative respiratory complications (7.8% mediation [95% CI 5.5 to 38.3%]; p<0.001). A high baseline risk to lose the ability to live independently after surgery, defined as a Discharge Prediction for Patients Undergoing Inpatient Surgery (DEPENDENSE) [2] score ≥41, magnified this association (aOR 0.80 per every 10 cmH2O decrease [95% CI 0.76 to 0.84]; p<0.001; p-for-interaction<0.001), while there was no association in patients with a low baseline risk (aOR 1.05 per every 10 cmH2O decrease [95% CI 0.96 to 1.16]; p=0.29). The primary findings were confirmed through instrumental variable analysis in a homogeneous subgroup of patients undergoing general or orthopedic surgery, using the hospital network as instrument (coefficient -0.71 [95% CI -0.85 to -0.58]; p<0.001).

CONCLUSION: A lower intraoperative driving pressure is associated with a decreased risk of losing independent living after surgery in high-risk patients of advanced age. These results support preoperative risk assessment and targeted intraoperative ventilation strategies utilizing low driving pressures to avoid postoperative respiratory complications and improve discharge disposition.

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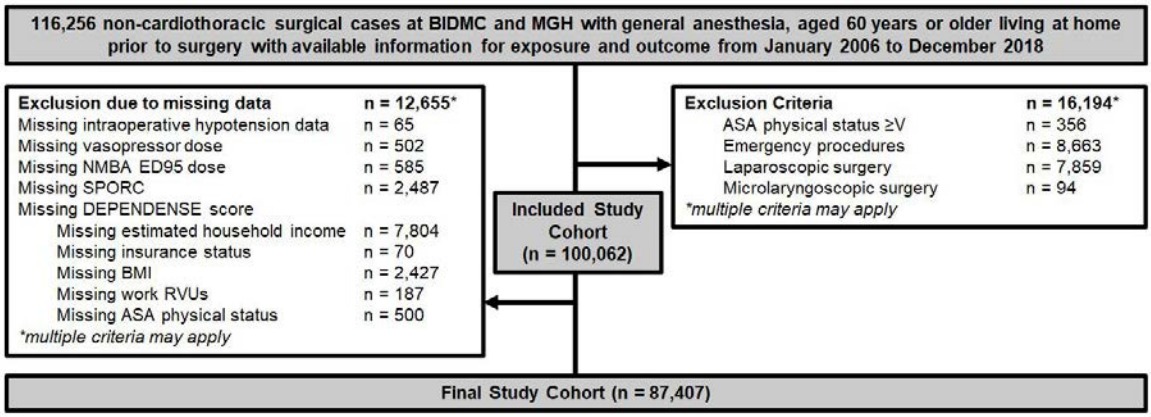

Figure 1. Study flow diagram.

ASA: American Society of Anesthesiologists; BIDMC: Beth Israel Deaconess Medical Center; BMI: Body Mass Index; DEPENDENSE: Discharge Prediction for Patients Undergoing Inpatient Surgery score; ED95: median effective dose required to achieve a 95% reduction in maximal twitch response from baseline; MGH: Massachusetts General Hospital; NMBA: neuromuscular blocking agents; SPORC: Score for Prediction of Postoperative Respiratory Complications; work RVUs: work Relative Value Units.

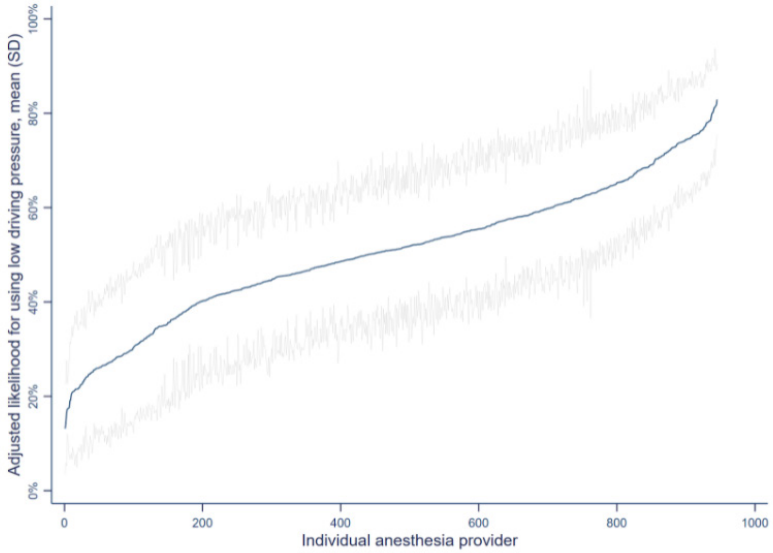

Figure 2. Adjusted likelihood for using mean low driving pressures.

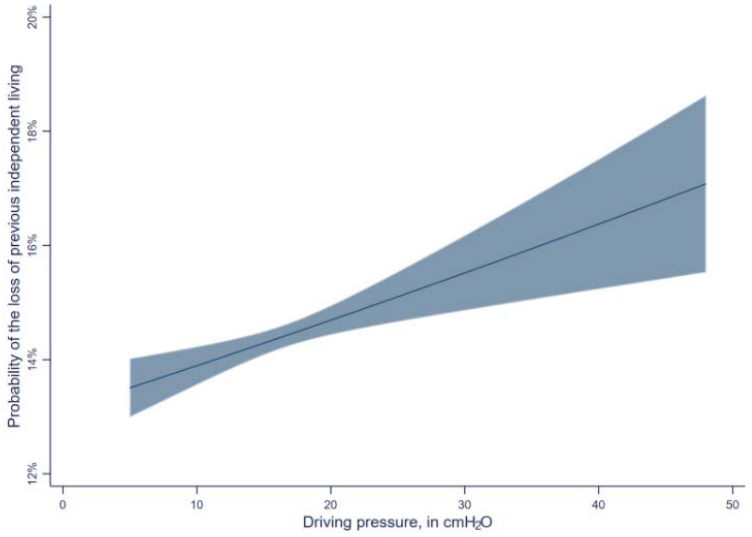

Figure 3. Intraoperative driving pressure and the probability of the loss of previous independent living.

Table 1. Patient characteristics and distribution of variables.

	Driving pressure ≥15 cmH_2O N = 44,921	Driving pressure <15 cmH_2O N = 42,486	Standardized difference
Demographics			
Age, years	68.0 (64.0 - 74.0)	69.0 (64.0 - 75.0)	-0.093
Sex (female)	25,107 (55.9%)	20,048 (47.2%)	0.175
BMI, kg/m^2	29.3 (25.8 - 33.7)	25.8 (23.1 - 28.8)	0.695
ASA physical status	3.0 (2.0 - 3.0)	2.0 (2.0 - 3.0)	0.234
Admission type			
Ambulatory admission	9,752 (21.7%)	14,761 (34.7%)	-0.293
Comorbidities			
DEPENDENSE score*	39.0 (28.0 - 51.0)	35.0 (25.0 - 45.0)	0.237
SPORC ≥7	1,718 (3.8%)	1,235 (2.9%)	0.051
Intraoperative factors			
Duration of surgery, min	159.0 (109.2 - 231.0)	126.7 (80.8 - 196.0)	0.280
Mean arterial pressure below 55 mmHg, min	1.0 (0.0 - 4.0)	0.0 (0.0 - 3.0)	0.091
Vasopressor dose, mg norepinephrine equivalents	0.0 (0.0 - 0.3)	0.0 (0.0 - 0.2)	0.002
Crystalloid and colloid infusion, ml	1250.0 (900.0 - 2000.0)	1000.0 (700.0 - 1700.0)	0.193
Short acting opioid dose, mg OME	37.5 (25.0 - 62.5)	37.5 (25.0 - 62.5)	0.008
Long acting opioid dose, mg OME	8.5 (0.0 - 17.0)	3.2 (0.0 - 15.0)	0.199
Non-depolarizing NMBA, ED95	2.1 (0.9 - 3.2)	1.8 (0.0 - 3.1)	0.130
Age-adjusted mean alveolar concentration of inhalational anesthetics	1.0 (0.9 - 1.2)	1.0 (0.8 - 1.1)	0.195
Neostigmine dose, mg/kg	2.0 (0.0 - 3.0)	0.0 (0.0 - 3.0)	0.315
Units of packed red blood cells	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.047
Ventilatory parameters			
Tidal volume, ml/kg predicted body weight	9.1 (8.0 - 10.3)	7.5 (6.5 - 8.5)	0.949
Positive end-expiratory pressure, cmH_2O	4.1 (2.0 - 5.0)	5.0 (2.0 - 5.0)	-0.084
Standardized compliance, (ml/kg)/cmH_2O	29.0 (24.5 - 33.6)	40.8 (35.2 - 47.5)	-1.418
Plateau pressure, cmH_2O	22.0 (20.0 - 25.5)	16.0 (13.5 - 18.0)	2.027

Data are expressed as frequency (prevalence in %), mean ± standard deviation, or median (interquartile range [25th-75th percentile]).

ASA: American Society of Anesthesiologists; BMI: Body Mass Index; ED95: median effective dose required to achieve a 95% reduction in maximal twitch response from baseline; NMBA: neuromuscular blocking agents; OME: oral morphine equivalents; SPORC: Score for Prediction of Postoperative Respiratory Complications.
**DEPENDENSE (Discharge Prediction for Patients Undergoing Inpatient Surgery) score. Patients with emergency surgery were excluded. Therefore, emergency surgery was not considered as part of the DEPENDENSE score.*

PERIOPERATIVE ANESTHESIA 4

Impact of Exercise Training on Survival in Rats Exposed to Sepsis

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INTRODUCTION: Preoperative fitness, as measured by VO2 max, is highly predictive of outcomes after major surgery[1]. Small trials have demonstrated that a short pre-surgical training program can increase physical activity and exercise tolerance (6 min walk test) before surgery[2]. Whether or not these regimens impact important outcomes (e.g. survival) and how they modify the biological response to stress are not fully understood. The purpose of this study was to test the ability of exercise training in rats to improve survival after surgery, as well as explore some of the mechanistic changes that occur following pre-surgical exercise training.

METHODS: This study was approved by our IACUC. Exercise training consisted of 3 weeks of treadmill running for 90 minutes (800-1500m/day) for 5 days/ week (15 total sessions). Cecal ligation and puncture (CLP) was performed using 100% ligation and with two punctures using a 16 ga. needle. For part one of our study (survival), 50 three month old Sprague-Dawley (SD) rats (both male and female) were randomized to two groups - trained and untrained. Other than training, they lived in identical conditions. After three weeks, all rats received CLP under isoflurane anesthesia and were monitored for 5 days. For part two (mechanistic) of the study, we randomized 60 three month old SD rats to six groups: sedentary (no exercise), exercise training, exercise training with sham surgery (celiotomy), sepsis (cecal ligation and puncture), exercise training and sepsis (sacrificed at 12 hours), and exercise training and sepsis (sacrificed at 24 hours). After three weeks, all rats received CLP under isoflurane anesthesia and were sacrificed at 24 hours (except for group 5, at 12 hours). Survival data was analyzed using the log rank test. Means between groups were compared using the t-test for normally distributed data and the Mann-Whitney test for non-parametric data.

RESULTS: Trained animals survived exposure to sepsis longer than untrained animals ($p < 0.05$). Hepatic tissue revealed the following: exposure to exercise lead to a significant increase in hepatic superoxide dismutase (SOD) activity as well as concentration of SOD1 and SOD3 (extracellular [ec]SOD). Following sepsis, SOD1 and SOD3 protein expression was reduced compared to controls, but in animals exposed to exercise and sepsis, SOD1 and SOD3 protein expression was greater than controls (but less than trained animals not exposed to sepsis). Sepsis lead to a profound increase in HIF-1a expression, and exercise lead to an increase in HIF-1a in males (in females, the increase did not reach statistical significance). Following exposure to sepsis after exercise training, HIF-1a levels were almost identical to trained animals not exposed to sepsis. Exercise training lead to an increase in Nrf2 in male and female rats, and sepsis lead to a significant decrease in Nrf2, particularly in male rats. Trained rats exposed to sepsis maintained normal Nrf2 levels. Exercise training produced a subtle increase in iNOS expression (statistically significant in females), sepsis lead to a substantial increase in iNOS expression, and this increase was attenuated in trained animals. eNOS was increased in sepsis and this increase was also attenuated in trained animals. Exercise training had no impact on haptoglobin in healthy animals. Sepsis lead to a significant increase in haptoglobin expression, which was amplified in trained animals exposed to sepsis. Exercise training had no impact on heme oxygenase 1 (HO-1) in healthy animals.

CONCLUSION: Exercise training increases survival in sepsis, likely due to induction of anti-oxidant mechanisms. This work is novel in that it demonstrates an impact following a treatment regimen of only three weeks. While confirmatory inhibitor studies are needed, SOD1 and SOD3 appear to be implicated given their clear increase in exercise training, which persisted in the setting of sepsis. Interestingly, septic, trained animals showed substantial increases in haptoglobin expression at 24 hours, a finding worth additional investigation given its prominent role as a free hemoglobin scavenger and anti-oxidant agent. The role of Nrf2, which clearly increases with exercise training, also deserves further investigation given its role as a 'master regulator' of the antioxidant response and its downstream effects on HO-2, iNOS, SOD1 and SOD3.

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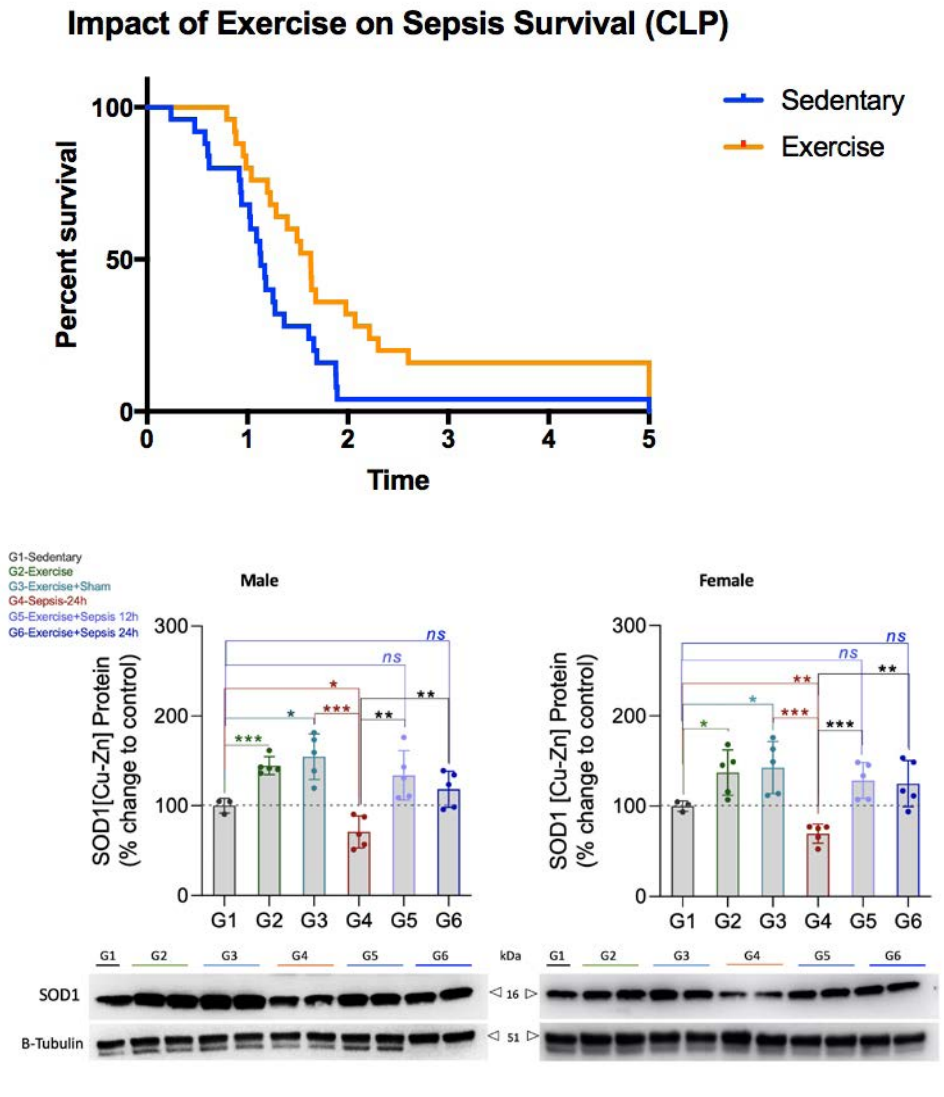

Figure 2

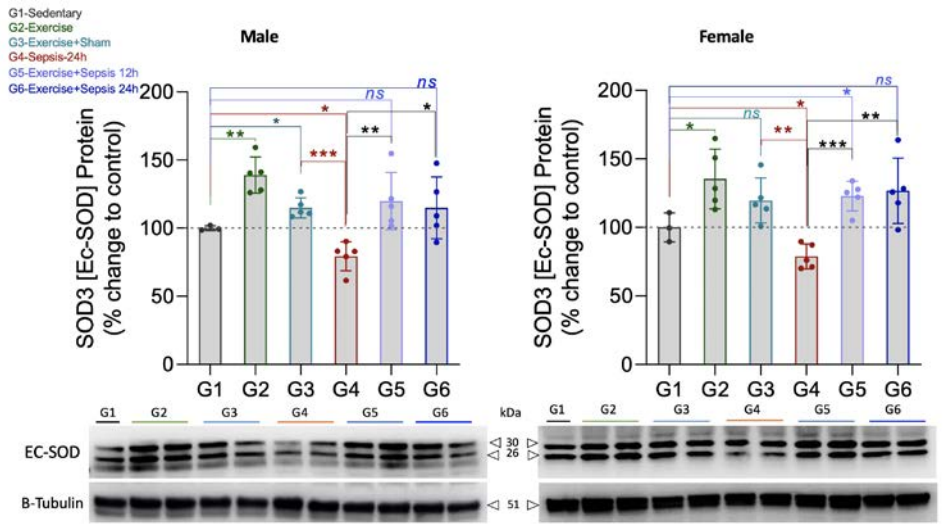

Figure 3

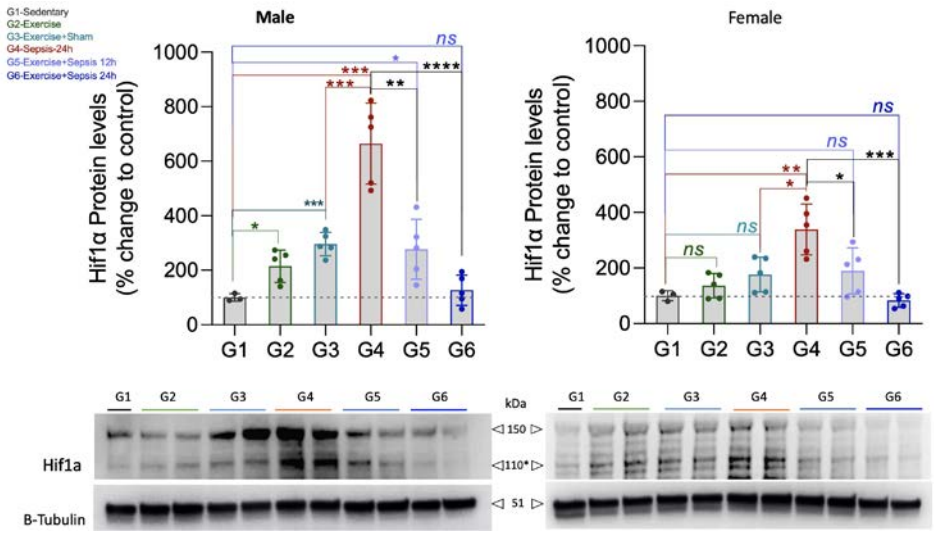

Figure 4

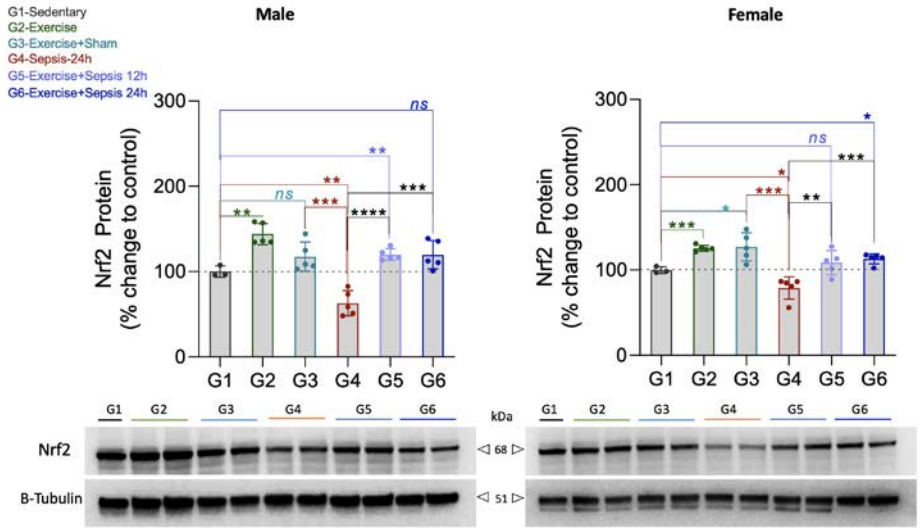

Figure 5

PERIOPERATIVE ANESTHESIA 5

Association of preoperative diagnosis of migraine and postoperative delirium: A retrospective multicenter cohort study

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INTRODUCTION: Migraine is the second most disabling disease in the world, and the top cause of years lived with disability in adults under 50[1,2]. Migraine is associated with an increased stroke risk after surgery[3] - its effect on postoperative, transitory, acute brain injury has not been examined. Postoperative delirium is a common complication, associated with increased health care utilization, longer hospital stays, and mortality[4,5]. In this study, we hypothesized that a diagnosis of migraine is associated with increased risk of delirium after surgery.

METHODS: We studied data from a large cohort of patients who underwent surgery between 2005 and 2021 at three tertiary academic healthcare networks in Boston, Massachusetts, and in the Bronx, New York, USA. The primary exposure variable was defined as a diagnosis of migraine with or without aura prior to surgery. The primary outcome was defined as a new diagnosis of delirium within 30 days after surgery. The respective diagnoses of the primary exposure and outcome were identified through the International Classification of Diseases, Ninth/Tenth Revision (ICD-9/10), diagnostic codes.(4) Diagnoses derived from ICD-9/10 diagnostic codes were additionally validated through chart review.[4] To assess the primary association between migraine and delirium, multivariable logistic regression analysis adjusted for a priori defined patient demographics, comorbidities, and procedure-related factors based on available literature and clinical plausibility were applied. With an exploratory intent, we investigated the effects of age and sex on the association between preexisting migraine and delirium in the study cohort, and after exact matching for sex and age ± 2 years with a 1:3 ratio for patients with and without migraine. Effect modification analysis was used to assess the interaction between migraine and age by including the interaction term 'age*migraine' into the primary model. To assess a potential non-linear relationship for age in this interaction, a second-degree fractional polynomial modeling for age in interaction with migraine adjusted for all confounders was performed.

RESULTS: A total of 764,232 adult patients who underwent surgery during the study period were included in the final study cohort (Figure 1). Baseline characteristics of the study cohort by the occurrence of migraine are presented in Table 1. 5.63%(n=42,996) of patients had a previous diagnosis of migraine with or without aura. The incidence of postoperative delirium was 0.72% (n = 5,530)(Figure2). In adjusted analysis, patients with a prior diagnosis of migraine had a lower risk of a new diagnosis of delirium within 30 days after surgery compared to patients with no history of migraine (adjusted odds ratio [ORadj] 0.83; 95%CI 0.72–0.97; p=0.017). (P for interaction with age=P<0.001, Figure 3). After exact matching for sex and age ± 2 with a 1:3 ratio for patients with and without migraine, the primary association remained robust (ORadj 0.81; 95%CI 0.70–0.98; 0.021). The association of migraine on postoperative delirium remained robust when incorporating the second-degree fractional polynomial modeling for age in interaction with migraine into the model (ORadj 0.81; 95%CI 0.67–0.98; p=0.038).

CONCLUSION: Based on data from a large cohort of patients undergoing surgery, prior diagnosis of migraine is associated with a lower incidence of delirium after surgery and this effect is magnified by age. Our data support the view that assessment of migraine status should be included in the risk assessment for postoperative delirium in patients undergoing surgery. Future studies may investigate the underlying mechanisms and potential mediators of the differential effects of migraine on delirium after surgery.

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Tables:

Table 1. Cohort characteristics

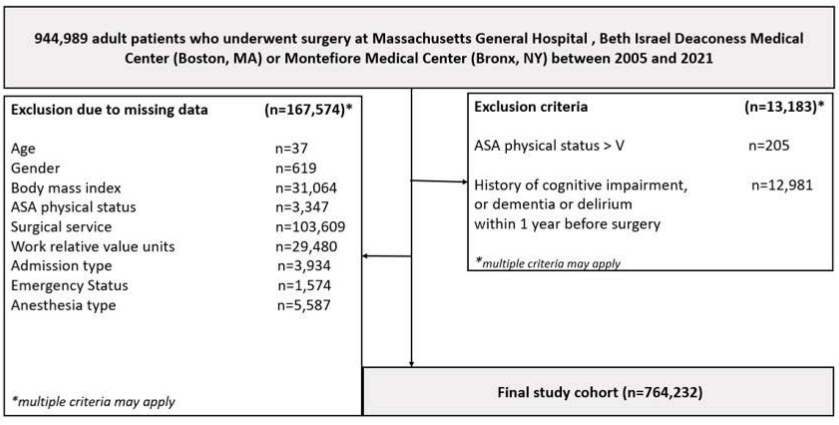
ASA, American Society of Anesthesiologists; ENT, Ear nose and throat.

Characteristic	No Migraine (n = 721,236)	Prior Migraine (n = 42,996)
Demographics		
Age, years	55.399 ± 16.902	50.540 ± 14.428
Sex, female	359,939 (49.9%)	23,696 (55.1%)
Body mass index, kg/m^2	28.76 ± 6.95	30.07 ± 7.76
ASA physical status	2 (2–3)	2 (2–3)
Admission Type		
Same-day admission	375,195 (52.0%)	20,352 (47.3%)
Emergency surgery	44,774 (6.2%)	2,008 (4.7%)
Surgical service		
ENT	23,630 (3.3%)	1,496 (3.5%)
Cardiac	18,415 (2.6%)	520 (1.2%)
Gastroenterology	64,773 (9.0%)	4,854 (11.3%)
General Surgery	138,352 (19.2%)	8,542 (19.9%)
Gynecology	87,914 (12.2%)	6,693 (15.6%)
Neurosurgery	30,442 (4.2%)	2,221 (5.2%)
Orthopedic	129,952 (18.0%)	7,595 (17.7%)
Plastic	36,944 (5.1%)	2,697 (6.3%)
Thoracic	29,155 (4.0%)	1,217 (2.8%)
Transplant	13,634 (1.9%)	618 (1.4%)
Urology	47,179 (6.5%)	1,850 (4.3%)
Vascular	27,697 (3.8%)	1,029 (2.4%)
Others	73,149 (10.1%)	3,664 (8.5%)
Comorbidities		
Atrial Fibrilation	52,720 (7.3%)	2,024 (4.7%)
Congestive heart failure	57,089 (7.9%)	3,110 (7.2%)
Stroke	12,436 (1.7%)	1,135 (2.6%)
Schizoaffective disorders	29,385 (4.1%)	4,857 (11.3%)
Depression	70,069 (9.7%)	11,033 (25.7%)
Alcohol abuse	19,672 (2.7%)	1,023 (2.4%)
Drug abuse	18,186 (2.5%)	2,239 (5.2%)
Prior benzodiazepine use	119,667 (16.6%)	13,504 (31.4%)
Prior antipsychotics	23,740 (3.3%)	3,005 (7.0%)
Prior opioid use	121,046 (16.8%)	10,827 (25.2%)
Intraoperative factors		
Duration of surgery, min	102 (56-176)	96 (51-161)
Work relative value units	12.71 (6.41–21.79)	9.53 (5.32–17.40)
General anesthesia	572,293 (79.3%)	33,909 (78.9%)

Data are expressed as frequency (prevalence in %), mean ± standard deviation, or median (interquartile range (25th-75th percentile).

Figure 1. Study flow diagram

ASA, American Society of Anesthesiologists



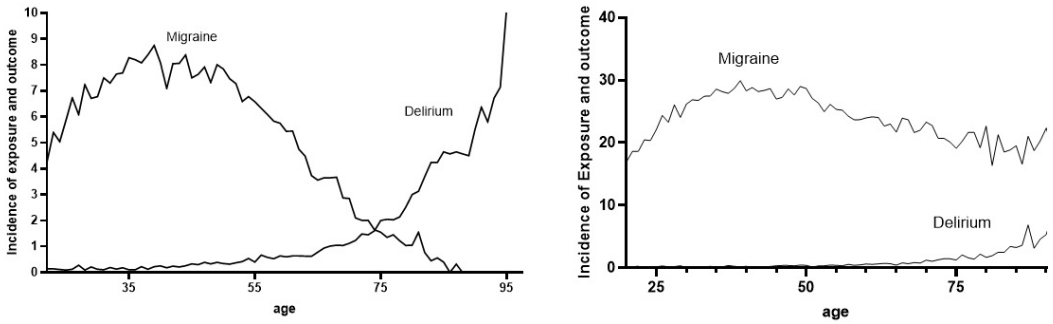


Figure2. Incidence of prior diagnosis of migraine and postoperative delirium within 30 days after surgery in the primary(left) and the exact matched cohort for sex and age ± 2 with a 1:3 ratio for patients with and without migraine(right).

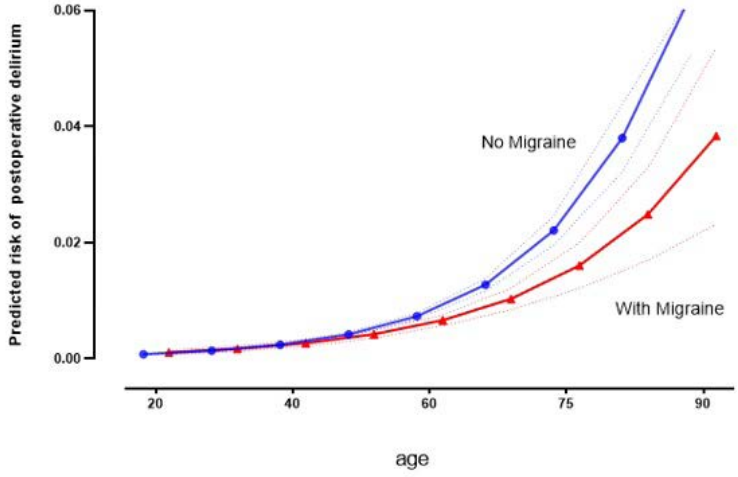


Figure 3: Predicted risk of postoperative delirium between patients with and without a prior diagnosis of migraine

PERIOPERATIVE ANESTHESIA 6

Preoperative oral carbohydrate and post-operative hyperglycemia in patients undergoing hip fracture surgery under combined spinal epidural anesthesia: Preliminary results

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INTRODUCTION: Preoperative fasting leads to a catabolic state further aggravated by surgical stress.[1] Preoperative oral carbohydrate (POC) administration mitigates the development of postoperative hyperglycemia, insulin resistance and may improve patient outcome.[2,3] This study explores the effect of POC administration on postoperative hyperglycemia in patients undergoing hip fracture surgery under combined spinal epidural anaesthesia (CSEA).

METHODS: This prospective, randomized study was done on 60 consenting adult ASA I/II patients between 18-65 years of age scheduled for hip fracture fixation under CSEA after obtaining institutional ethical committee clearance. Patients with diabetes mellitus, pheochromocytoma, carcinoid tumor, pancreatitis, alcoholism, jaundice or liver disorders, obesity, gastro-esophageal reflux, gastric outlet/ intestinal obstruction, pregnancy, contraindications to CSEA, on continuous steroid therapy for >5 days in the last one year were excluded. As per a computer generated random number table, patients were randomized to either group F (n=30, nil per orally for both solids and liquids for at least 6 h before surgery) or group C (n=30, nil per orally for solids for at least 6 h and received 200 ml oral carbohydrate solution 2 h before surgery). An independent anesthesiologist, not involved with the further conduct of the study, administered the carbohydrate drink. Under all aseptic precautions CSEA was given at L2-L3/L3-L4 intervertebral space. After adequate subarachnoid block level, the surgery was allowed to proceed. Blood samples were drawn at baseline (T0: before CSE), immediately after surgery (T1) and 24hrs after surgery (T2). Primary outcome measure was blood glucose and secondary outcomes included serum insulin, blood urea, anxiety, hunger, thirst, postoperative complications, length of hospital stay, 30-day readmission and 3-month mortality. Descriptive statistics were reported as mean ± S.D. or median [IQR]. Repeated measure ANOVA followed by Dunnett's test was used for repeatedly measured variables. Qualitative parameters were compared using Chi-square/Fisher's test. Statistical analysis was carried in SPSS v.20.0 and STATA v.15.0. Relative risk was calculated using the MedCalc from www.medcalc.org. A p-value<0.05 was taken as significant.

RESULTS: A total of 49 patients have been assessed for eligibility so far (study ongoing). Five of these did not meet the inclusion criteria and another four did not give consent to participate. Results of the first 40 patients is being presented. The two groups were demographically comparable. Blood glucose values increased from T0 to T2 in both groups and the rise was significantly more in group F than in group C (group F: 112.80 ± 21.04 mg/dl vs 143.20 ± 33.90 mg/dl, p=0.007; group C: 109.70 ± 24.88 mg/dl vs 136.05 ± 23.58 mg/dl, p=0.002). In group F, insulin was significantly higher than T2 compared to T0 (p=0.012) and T1 (p=0.001). In group C, insulin was comparable at T0 and T1 (p= 0.149) and T0 and T2 (p=0.178), but T2 value was significantly higher than T1 (p=0.017). Blood urea was comparable between groups. Hunger scores were comparable in the preoperative (p=0.379) and postoperative (p=0.769) time point. Preoperative thirst score (4.30 ± 2.87 vs 6.50 ± 3.66, p=0.041) and anxiety was lower in group C than group F (p=0.035). The chance of having postoperative hyperglycemia and anxiety at T2 was 1/4th in group C compared to group F. (RR: 0.025, 95% CI: 0.030 to 2.045; p=0.196). There was a significantly lower risk of having pre-operative anxiety in group C compared to group F (RR: 0.222, 95% CI: 0.054 to 0.902, p=0.035). Incidence of postoperative complications and the length of hospital stay (p=0.206) was comparable.

CONCLUSION: Administration of POC reduces the chances of developing postoperative hyperglycemia by 1/4th when compared to fasting from midnight. The consumption of POC increases patient comfort by considerably decreasing the preoperative thirst and anxiety level.

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PERIOPERATIVE ANESTHESIA 7

Quantitative Physical Activity Measures within 48 hours after Major Abdominal Surgery are Associated with Complications and Clinical Outcomes

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INTRODUCTION: Physical activity is important for recovery after major abdominal surgery, but the specific relevance of the highest level of mobility and the timing, frequency, duration, and intensity of physical activity on postoperative outcomes is not well understood[1,2]. This study aims to investigate the effect of early postoperative physical activity, measured using a wearable research-grade accelerometer, on clinical outcomes.

METHODS: In this prospective cohort study, patients undergoing elective open abdominal procedures at the University of Colorado Hospital wore a research-grade accelerometer to measure physical activity continuously, starting immediately after surgery until discharge or up to 7 days postoperatively. Daily step counts, duration of upright position, sit-to-stand frequency, and time to first mobility events were recorded from the accelerometer data. The primary clinical outcome was a composite of postoperative complications including ileus, pulmonary complications, venous thromboembolism, delirium, and major adverse cardiac events within 30 days after surgery. Postoperative complications were defined adjusting from previously published criteria[3]. Physical activity measures were compared between patients with and without any complication using Wilcoxon rank sum test. Fisher's exact test was used to compare proportions.

RESULTS: Data from 28 analyzable patients were available at the time of this abstract preparation. Patients wore the monitor for a median of 4 days. Patient characteristics are shown in Table 1. The incidences of the primary outcome and individual complication components are shown in Table 2. Compared with patients with any complication, patients without complication took more steps on postoperative day (POD) 1 (92 vs. 0, p = 0.046) and POD 2 (754 vs. 22, p = 0.003) and spent longer time in upright position on POD 1 (9 min vs. 5 min, p = 0.088) and POD 2 (34 min vs. 9 min, p = 0.038). Sit-to-stand frequency was not different between the two groups. Patients who got out of bed within 24 hours after surgery had fewer overall complications (relative risk, 0.25; 95% confidence interval [CI], 0.13-0.50; p = 0.010) and shorter length of stay (6 days vs. 11 days, p = 0.010). Similarly, patients who achieved greater than 50 steps in one session (out-of-room ambulation) within 48 hours after surgery had fewer complications (relative risk 0.18; 95% CI, 0.05-0.69; p = 0.006) and were more likely to be discharged home (prior living situation) (100% vs. 50%, p = 0.008).

CONCLUSION: In this preliminary data, accelerometer-measured physical activity within 48 hours after major abdominal surgery was associated with complications, length of stay, and discharge destination. Quantitative analysis using an accelerometer can help understand the impact of specific physical activity measures on postoperative outcomes.

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Table 1. Patient Characteristics

Patient Characteristics	No complication (n = 18)	Any complication (n = 10)
Age (yr), mean ± SD	59 ± 10	65 ± 9
Sex (Female), n (%)	11 (61%)	6 (60%)
BMI (kg/m2), mean ± SD	26.5 ± 5.1	22.8 ± 3.5
ASA, n (%)		
1	2 (11%)	0
2	6 (33%)	3 (30%)
3	10 (56%)	7 (70%)
Charlson Comorbidity Index, median (IQR)	4 (2-5)	5 (4-7)
Procedures by Specialties, n (%)		
General Surgery	9 (50%)	7 (70%)
Gynecology	5 (28%)	2 (20%)
Urology	4 (22%)	1 (10%)
Surgery duration (min), median (IQR)	308 (287-400)	418 (316-607)

ASA, American Society of Anesthesiologists physical status classification;
BMI, body mass index

Table 2. Outcomes

Outcomes	n = 28
Any complication, n (%)	10 (36%)
Delayed return of gastrointestinal function (ileus), n (%)	6 (21%)
Postoperative pulmonary complication, n (%)	7 (25%)
Venous Thromboembolism, n (%)	1 (4%)
Delirium, n (%)	1 (4%)
Major adverse cardiac events, n (%)	0
Length of stay (days), median (IQR)	6 (3-8)
Discharged home, n (%)	24 (86%)

PERIOPERATIVE ANESTHESIA 8

Preoperative guideline adherent treatment of diabetes and hypertension mitigates the effects of race on adverse discharge

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INTRODUCTION: Diabetes mellitus and arterial hypertension are more prevalent among Black compared to White patients in the United States[1-3] and are associated with adverse outcomes after surgery[4-5]. The effect of a patient's self-identified race on the postoperative loss of the ability to live independently through adverse discharge to a nursing home after surgery is mediated by severe diabetes mellitus and arterial hypertension[6]. In this study, we tested the research hypothesis that adequate preoperative treatment of diabetes mellitus and arterial hypertension adherent to published guidelines mitigates the association between a patient's race and the loss of the ability to live independently after surgery.

METHODS: Adult patients of self-identified non-Latinx White and non-Latinx Black race with preoperatively diagnosed severe diabetes mellitus or arterial hypertension who lived at home prior to undergoing surgery at two competing tertiary academic healthcare networks in Boston (Massachusetts, USA) between January 2007 and February 2020 were included in this multicenter hospital registry study. The primary exposure was a patient's self-identified non-Latinx Black compared to non-Latinx White race. The primary outcome was the loss of the ability to live independently after surgery, defined as postoperative adverse discharge to a nursing home or skilled nursing facility[7]. To test the primary hypothesis of a modifying effect of adequate guideline adherent treatment on the association between a patient's self-identified race and the primary outcome, we defined guideline adherent treatment of diabetes mellitus and arterial hypertension as prescriptions of medications included in the 2020 American Heart Association and International Society of Hypertension guidelines for these diseases[8-9]. We then calculated the proportion of guideline adherent treatment, defined as the number of months with a prescription within 12 months before surgery. This variable was subsequently categorized into no guideline adherent treatment as well as a low (≤ 2 months with prescriptions) and a high (> 2 months with prescriptions) proportion of guideline adherent treatment based on the median number of months with prescriptions in the study cohort. Multivariable logistic regression analysis adjusted for a priori defined patient demographics, comorbidities and intraoperative factors was used to assess the interaction term 'self-identified race*proportion of guideline adherent treatment' on the primary outcome.

RESULTS: Among 129,747 patients who underwent surgery (Figure 1), 17,639 (13.6%) patients identified themselves as non-Latinx Black and 112,108 (86.4%) as non-Latinx White. 13.0% (n=16,852/129,747) of patients lost the ability to live independently after surgery. In adjusted analysis, patients of non-Latinx Black race were at a higher risk of losing the ability to live independently after surgery compared to non-Latinx White patients (adjusted odds ratio [ORadj] 1.27; 95%CI 1.19-1.35; p<0.001). 30.2% of patients received no guideline adherent treatment while 44.3% received a low proportion and 25.5% received a high proportion of guideline adherent treatment. Guideline adherent treatment before surgery modified the association between a patient's race and the loss of the ability to live independently after surgery (p-for-interaction<0.001 for no versus a low proportion of guideline adherent treatment and p-for-interaction<0.001 for no versus a high proportion of guideline adherent treatment) towards a more pronounced effect in patients who did not receive guideline adherent treatment before surgery (ORadj 1.59; 95%CI 1.43-1.78; p<0.001; Figure 2). By contrast, in patients who received a low proportion of guideline adherent treatment, the effect was mitigated (ORadj 1.20; 95%CI 1.09-1.32; p<0.001; Figure 2) and in patients who received a high proportion of guideline adherent treatment, the effect of self-identified race on the loss of the ability to live independently was insignificant (ORadj 1.07; 95%CI 0.97-1.19; p=0.20; Figure 2).

CONCLUSION: Adequate preoperative treatment adherent to published guidelines mitigated the effect of a patient's self-identified race on the loss of the ability to live independently after surgery towards a complete effect attenuation. These findings emphasize the value of preoperative treatment in the prevention of racial disparities in perioperative medicine.

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Table 1. Cohort characteristics

ASA, American Society of Anesthesiologists; USD, United States Dollar; ENT, Ear Nose and Throat; MAP, Mean Arterial Pressure; OME, Oral Morphine Equivalent dose.

Characteristic	Non-Latinx White (n = 112,108)	Non-Latinx Black (n = 17,639)
Demographics		
Age, years	64.99 ± 12.71	60.56 ± 13.08
Sex, female	5,3465 (47.7%)	11,057 (62.7%)
Body mass index, kg/m^2	30.79 ± 12.74	31.58 ± 8.10
ASA physical status	3 (2–3)	3 (2–3)
Federal Insurance	58,780 (52.4%)	8,055 (45.7%)
Estimated household income, USD	85,191 (66,556–105,380)	55,333 (49,048–73,034)
Admission Type		
Ambulatory surgery	34,475 (30.8%)	8,193 (46.5%)
Same-day admission	50,456 (45.0%)	5,562 (31.5%)
Inpatient surgery	27,177 (24.2%)	3,884 (22.0%)
Emergency surgery	6,725 (6.0%)	1,143 (6.5%)
Surgical service		
Dent / Oral / ENT	1,993 (1.8%)	271 (1.5%)
Cardiac	4,844 (4.3%)	380 (2.1%)
Gastroenterology	4,442 (4.0%)	1,001 (5.7%)
Interventional Radiology	925 (0.8%)	103 (0.6%)
Ophthalmology	3,974 (3.5%)	1,605 (9.1%)
General Surgery	16,640 (14.8%)	2,152 (12.2%)
Gynecology	7,916 (7.1%)	1,751 (9.9%)
Neurosurgery	6,569 (5.9%)	595 (3.4%)
Orthopedic	22,057 (19.7%)	3,579 (20.3%)
Plastic	3,485 (3.1%)	557 (3.2%)
Podiatry	2,560 (2.3%)	635 (3.6%)
Surgical Oncology	3,760 (3.4%)	664 (3.8%)
Thoracic	7,646 (6.8%)	678 (3.8%)
Transplant	2,992 (2.7%)	980 (5.6%)
Trauma / Surgical Critical Care	5,941 (5.3%)	762 (4.3%)
Urology	9,483 (8.5%)	1,223 (6.9%)
Vascular	6,881 (6.1%)	703 (4.0%)
Comorbidities		
Charlson Comorbidity Index	2 (1–4)	2 (1–5)
Non-severe diabetes mellitus	32,382 (28.9%)	7,650 (43.4%)
Severe diabetes mellitus	15,672 (14.0%)	4,595 (26.1%)
Moderate to severe renal disease	16,608 (14.8%)	4,166 (23.6%)
Arterial hypertension	107,729 (96.1%)	16,701 (94.7%)

Figure 1. Study flow diagram

ASA, American Society of Anesthesiologists.

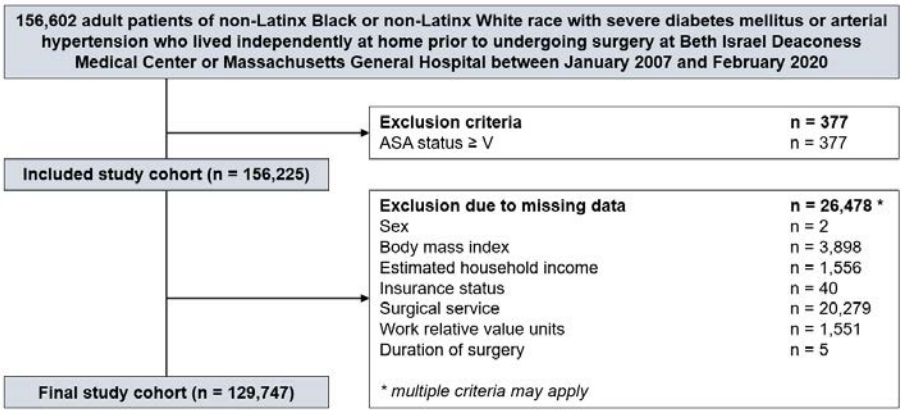
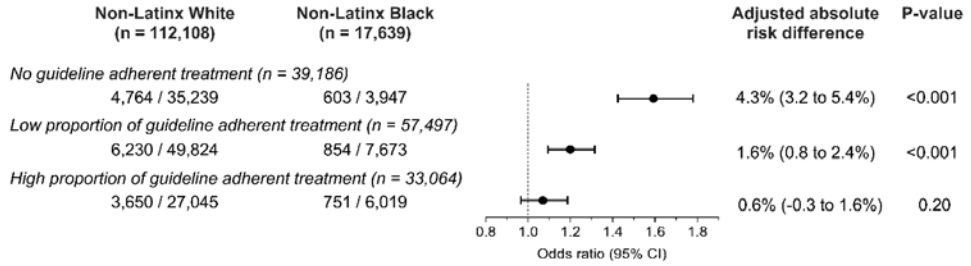


Figure 2. Effect modification by guideline adherent treatment before surgery

The results of the effect modification and subgroup analyses are shown. Preoperative guideline adherent treatment significantly modified the association between a patient's self-identified race and the loss of the ability to live independently after surgery. If patients did not receive guideline adherent treatment before surgery, the adverse effect in non-Latinx Black compared to non-Latinx White patients was magnified. By contrast, in patients who received a low proportion of guideline adherent treatment, the effect was mitigated and in patients who received a high proportion of guideline adherent treatment, the effect of self-identified race on the loss of the ability to live independently was insignificant.



PERIOPERATIVE ANESTHESIA 9

Analysis of Attending Cardiac Anesthesiologists' Physiological Arousal While Taking Over Trainee Tasks in the Operating Room

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INTRODUCTION: While academic medicine is essential to provide clinical experience for trainees, intraoperative teaching activities may also introduce unintentional burden on senior team members. Sensor data, including heart rate variability (HRV), affords objective monitoring for physiological arousal analysis, representative of cognitive burden. Previous work has explored the role of cognitive burden according to HRV metrics among perfusionists,[1] surgeons,[2] and surgical teams,[3-7] but anesthesiologists have received less attention. This preliminary, descriptive study sought to characterize attending anesthesiologists' physiological arousal 1) during trainees' poor performance on discrete tasks and 2) after task takeover.

METHODS: The anesthesia induction phase (including induction, intubation and acquisition of lines and invasive access) of non-emergent open cardiac surgery procedures (N=27) was analyzed to identify takeover episodes, marked by times when an individual task transferred from the trainee (resident or SRNA) to the attending anesthesiologist. Using audio-video recordings collected as part of an NIH-funded, IRB-approved research study, episodes were specifically defined as times when the trainee started a task, took their hands off the patient, and the attending took over the task. The subset of cases with takeover episodes (N=6) were further analyzed by calculating HRV values for the attending anesthesiologist over the course of the episodes identified. The low-frequency to high-frequency (LF/HF) ratio HRV component, an indicator of physiological arousal, was calculated for each consecutive minute of the episodes identified. Under resting conditions, reference LF/HF ratio values range from 1.86 to 2.01 units,8 and higher values represent higher levels of physiological arousal.

RESULTS: Seven takeover episodes were identified. Tasks included intubation (N=1), IV placement (N=1), central venous line (CVL) placement (N=2), and arterial line (a-line) placement (N=3). Episodes were categorized into: trainee attempted the task for < 5 minutes (N=2) and > 5 minutes (N=5) before the attending took over. For episodes in the latter category, the attending anesthesiologists' physiological arousal was notably higher during periods when observing the trainee's attempt (average LF/HF ratio=7.06 units), and reduced after taking over (average LF/HF ratio=6.28 units). In each episode, the height of physiological arousal was observed preceding the attendings' takeover, evidenced by elevated peaks in LF/HF ratio (Figure 1).

CONCLUSION: This novel study demonstrated for the first time that objective markers of physiological arousal, including the LF/HF ratio, may be reflective of cognitive burden states during task management with trainees. Accordingly, this study demonstrates that when trainees displayed prolonged difficulty in critical tasks (> 5 minutes), attending anesthesiologists' arousal tended to be higher compared to the time periods corresponding to when they were physically completing the task(s) themselves.

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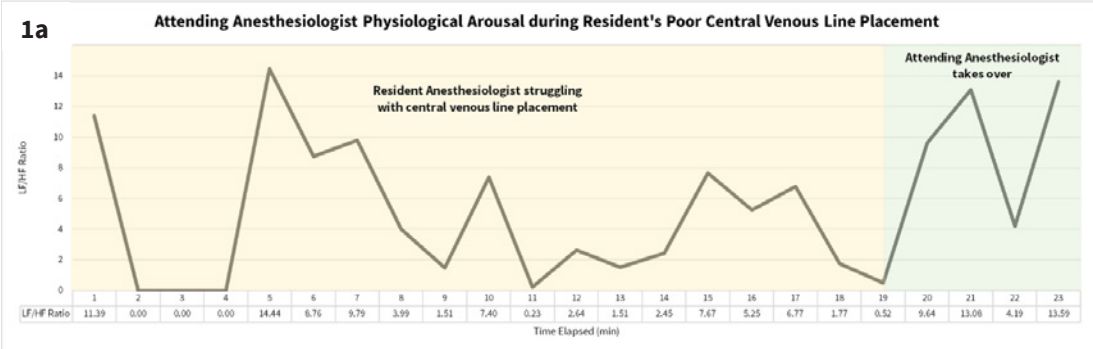

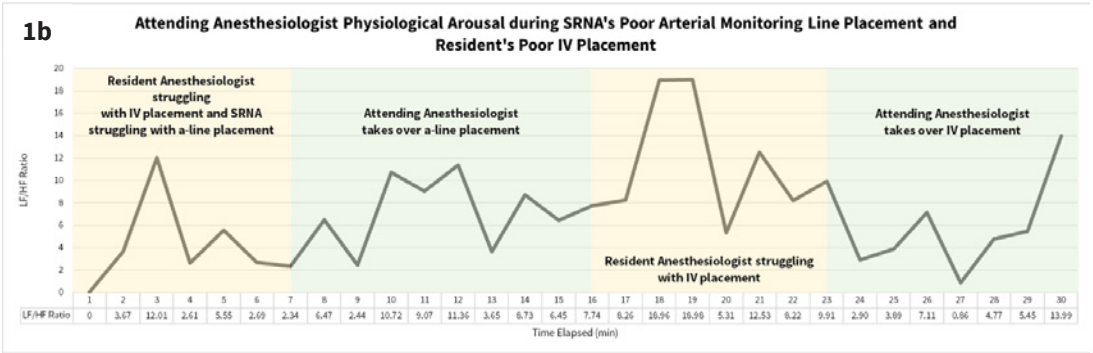

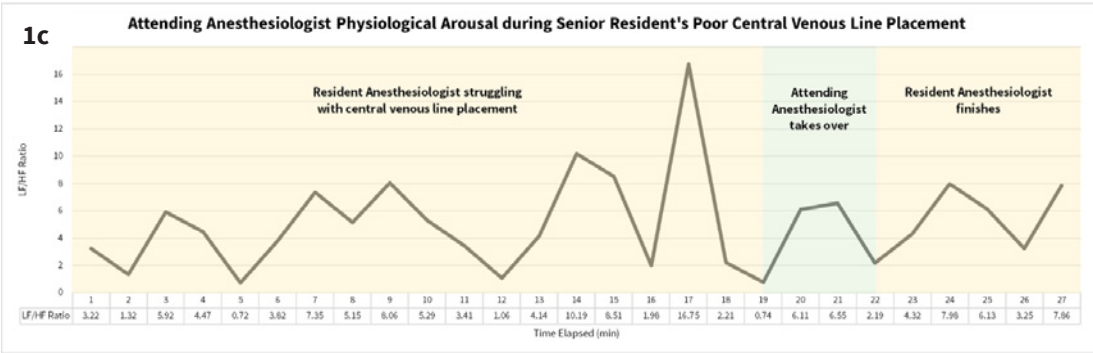

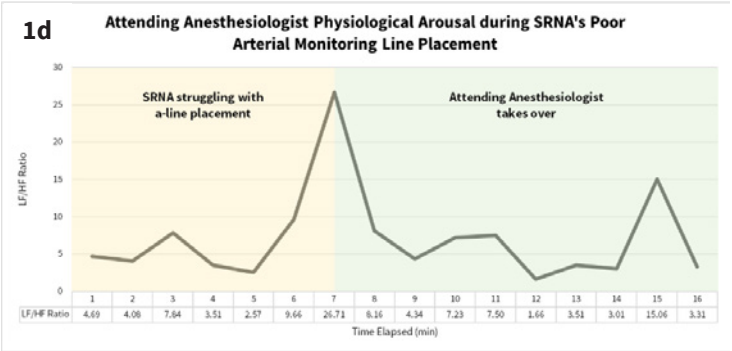

Figure 1. Episodes in which the trainee began a task and persisted for more than 5 minutes (yellow panels), followed by the attending anesthesiologist taking over the task completely (green panels). **1a** demonstrates the attending anesthesiologists' minute-by-minute physiological arousal during a resident's attempted central venous line (CVL) placement; **1b** shows the same data during a resident's attempted IV placement and simultaneously a SRNA's attempted arterial monitoring line (a-line) placement; **1c** represents a resident's attempted CVL placement; and **1d** represents a SRNA's a-line placement.

PERIOPERATIVE ANESTHESIA 10

CPL-01, a novel ropivacaine formulation, demonstrates safety and extended-release characteristics in abdominoplasty

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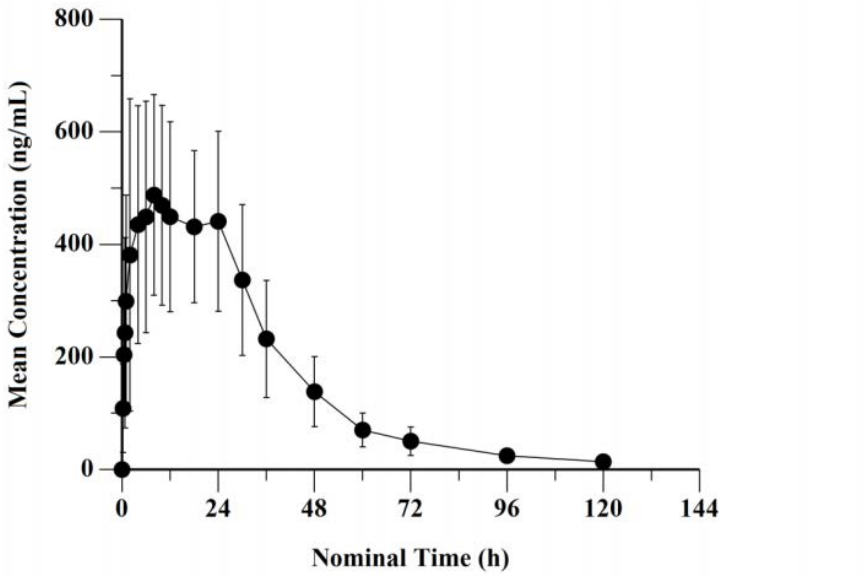
INTRODUCTION: There is continued concern that postoperative pain and consequent perioperatively administered opioids may contribute to chronic opioid use and opiod use disorder, feeding the opioid crisis. Bupivacaine is a useful local anesthetic (LA) for providing extended analgesia but is associated with potential cardiotoxicity. A number of bupivacaine-based extended release LA formulations have been recently approved; others are in development. We present results from an initial pharmacokinetic (PK) and safety study of a long-acting phospholipid-based formulation of ropivacaine given intra-operatively during abdominoplasty by infiltration into the surgical wound.

METHODS: After obtaining IRB approval, consented patients were randomized to receive either CPL-01 (2% ropivacaine phospholipid depot, 200 mg) or placebo (10 mL) by infiltration and instillation into the surgical site. Study drug was administered near the end of the procedure, and subjects were required to stay in the facility through 72 hours then had further visits on days 5, 6, 7-10, and 28. Assessments included PK, adverse events (AEs), serious adverse events (SAEs), local anesthetic systemic toxicity (LAST), labs, vital signs (VS), ECGs, wound healing, pain scores, and rescue medication.

RESULTS: A total of 20 subjects were enrolled over 10 weeks, 15 received CPL-01 and 5 received placebo; 100% were female. The mean (standard deviation [SD]) age was 48.5 (11.26) years in the CPL-01 group and 41.0 (12.06) years in the placebo group; the mean (SD) BMI was 27.8 (2.39) kg/m^2 and 26.4 (4.00) kg/m^2, respectively. All subjects completed the study except one who discontinued due to pregnancy. Administration of 200 mg CPL-01 by wound infiltration and instillation demonstrated a mean tmax of 13.0 ± 8.83 hours and t1/2 of 25.4 ± 5.44 hours. The mean Cmax was 573 ± 258 ng/mL, and AUC0-∞ was 20,400 ± 6,480 ng * h/mL. The mean (SD) ropivacaine plasma concentration curve is presented in Figure 1. A total of 73% of CPL-01 subjects and 80% of placebo subjects reported at least one treatment-emergent AE; the majority of these were commonly seen with surgery. In the CPL-01 group, 10 (66.7%) subjects had a maximum AE severity of mild, and 1 (6.7%) subject had a maximum AE severity of moderate; in the placebo group, 2 (40.0%) were mild, 1 (20.0%) moderate, and 1 (20.0%) severe. Only 1 AE was considered by the investigator to be related to study drug: metallic taste in a CPL-01 subject; this resolved on the same day and was accompanied by a Cmax of 224 ng/mL. No serious adverse events (SAEs) were observed in the study. No subject was assessed as having LAST by the investigator. Review of clinical laboratory data and vital sign values did not reveal any abnormalities suggestive of a negative impact of CPL-01. No subject experienced a clinically meaningful ECG change. There were no meaningful differences in wound healing results between CPL-01 and placebo. Despite being underpowered to assess pain relief, the mean (SD) SPI1-24 was numerically lower for the CPL-01 group (122.4 [30.87]) than the placebo group (140.4 [43.17]); p=0.3. A total of 60% of subjects in both the CPL-01 and the placebo groups received opioids, amounts were generally similar through the first 24 hours (9 mg vs 8 mg, respectively) with a median time to first opioid use of 17 vs 12 hours, respectively.

CONCLUSION: CPL-01 is a novel formulation of ropivacaine intended to have extended release characteristics. In this first-in-human study, CPL-01 demonstrated the ability to provide LA effect and analgesia with safety similar to placebo. Further studies are warranted to determine if CPL-01 can safely provide prolonged analgesic effects following incisional infiltration, and thus become an available long-acting ropivacaine formulation for the management of postoperative pain that may reduce on the need for opioids.

Figure 1
Mean (SD) Ropivacaine Plasma Concentration-Time Profiles in Human Subjects Following a Single Local Administration by Wound Infiltration and Instillation at a 2% CPL-01 (200 mg Ropivacaine in 10 mL) After Mini-Abdominoplasty Surgery (Linear Scale)



PERIOPERATIVE ANESTHESIA 11

Comparing the predictive accuracy of frailty instruments applied to preoperative electronic health data for adult patients undergoing non-cardiac surgery: a retrospective cohort study

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INTRODUCTION: Frailty before surgery is associated with increased risk of post-operative mortality, complications, and healthcare resource utilization[1]. Despite multiple guideline recommendations, routine preoperative frailty assessment is under-performed[2,3,4,5]. Automation of preoperative frailty assessment using electronic health data could improve adherence to guideline-based care if an accurate instrument is identified. Our aim was to measure and compare predictive accuracy of frailty instruments operationalizable in electronic data for prognosticating outcomes and resource use in older adults undergoing surgery.

METHODS: We conducted a retrospective cohort study utilizing linked healthcare administration data for adults >65 undergoing elective non-cardiac surgery or emergency general surgery (EGS) from 2012-2018. Four frailty instruments were compared: the Frailty Index (FI), Hospital Frailty Risk Score (HFRS), Risk Analysis Index-Administrative (RAI), and ACG Frailty-defining diagnoses indicator (ACG). We estimated and compared the added predictive performance of each instrument beyond the baseline model (age, sex, American Society of Anesthesiologists' score, procedural risk) using discrimination, calibration, explained variance, net reclassification index (NRI) and Brier score for binary outcomes, and using explained variance, root mean squared error and mean absolute prediction error for continuous outcomes. The primary outcome was 30-day mortality. Secondary outcomes included 365-day mortality, non-home discharge, days alive at home, hospital length of stay, and 30- and 365-day health systems cost.

RESULTS: We identified 171,576 elective surgery and 121,095 EGS patients who met inclusion criteria, of which 1,370 (0.8%) and 11,422 (9.4%) died at 30-days, respectively. Compared to the baseline model predicting mortality at 30-days for the elective cohort (area under curve [AUC], 0.85; R2, 0.08), addition of HFRS lead to greater improvement in discrimination (AUC, 0.87), explained variance (R2, 0.09), and net reclassification (NRI, 0.65) than FI, RAI or ACG; Compared to the baseline model predicting death at 30-days among EGS patients (AUC, 0.68, R2, 0.08), addition of RAI demonstrated greater improvement in discrimination (AUC, 0.74), explained variance (R2, 0.10), and net reclassification (NRI, 0.53) than FI, HFRS, or ACG. Brier scores and calibration curves did not differ appreciably between models in either cohort.

CONCLUSION: All four frailty instruments improved baseline model performance for predicting postoperative outcomes and resource use. The HFRS and RAI showed the greatest improvement amongst all measures of predictive performance for 30-day mortality within elective and EGS cohorts, respectively. Clinicians and health system planners may consider these findings in guiding selection of the most prognostically accurate instrument for development of automated preoperative frailty assessment.

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PERIOPERATIVE ANESTHESIA 12

Use of intravenous fat emulsion to suppress 18F-fluorodeoxyglucose uptake in non-ischemic myocardium for cardiac positron emission tomography

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INTRODUCTION: Determining need for definitive care following post-operative myocardial injury remains challenging.[1] We aim to determine whether intravenous fat emulsion suppresses physiological metabolic uptake of 18F-fluorodeoxyglucose (18F-FDG) in non-ischemic myocardium for enhanced cardiac positron emission tomography (PET) imaging. Optimal imaging of ischemic myocardium via 18F-FDG PET imaging requires suppression of background carbohydrate metabolism in normal non-ischemic myocardium. Administration of intravenous lipid emulsion has not previously been used to rapidly prepare unfasted patients, such as during emergent postoperative care.[2-4] We assess whether intravenous lipid emulsion as the single preparatory step in unfasted, hyperglycemic patients suppresses non-ischemic myocardial uptake of 18F-FDG.

METHODS: We conducted an ethics-approved, single-blind, randomized-crossover trial of 10 healthy volunteers selected via convenience sampling. Participants were unfasted and rendered hyperglycemic before being administered either intravenous lipid emulsion or saline prior to 18F-FDG injection and subsequent cardiac PET/CT imaging, before alternating to the other intervention of either intravenous lipid emulsion or saline. Two blinded nuclear medicine physicians undertook image analysis for maximum standard uptake value (SUVmax), minimum standard uptake value (SUVmin) and qualitative assessment, and groups were compared using univariate analysis. Baseline patient characteristics were summarized using descriptive statistics and were reported for continuous variables as the number of patients, mean, standard deviation, median, inter-quartile range, minimum and maximum, depending on data distribution. Categorical variables were reported as counts and percentages. All patients who completed the 18F-FDG PET study were included in the feasibility analysis. Endpoints of quantitative SUV measurements and the quantitative visual scale for cardiac 18F-FDG PET imaging quality were compared between groups with a Wilcoxon signed rank at $\alpha = 0.05$.

RESULTS: All 10 participants completed the study. The study population age was 44.5 years [IQR 32.5-56.5], with 50% male and a median BMI of 22.75 [IQR 25.0-28.5] kg/m2. The study was feasible and there were no adverse side effects from the interventions. In these participants with normal myocardium, 18F-FDG uptake was significantly reduced by intravenous lipid emulsion as assessed by SUVmax and qualitative assessment ($p = 0.042$, $r = 0.454$ and $p = 0.009$, $r = -0.581$, respectively). There were no significant differences between SUVmin assessments.

CONCLUSION: We provide proof-of-concept evidence that intravenous lipid emulsion suppresses physiological uptake of 18F-FDG in non-ischemic myocardium of healthy volunteers. Our findings suggest the possibility of future applications for cardiac 18F-FDG PET in acute settings, such as evaluating for myocardial ischemia and establishing the area of myocardium that is at-risk.

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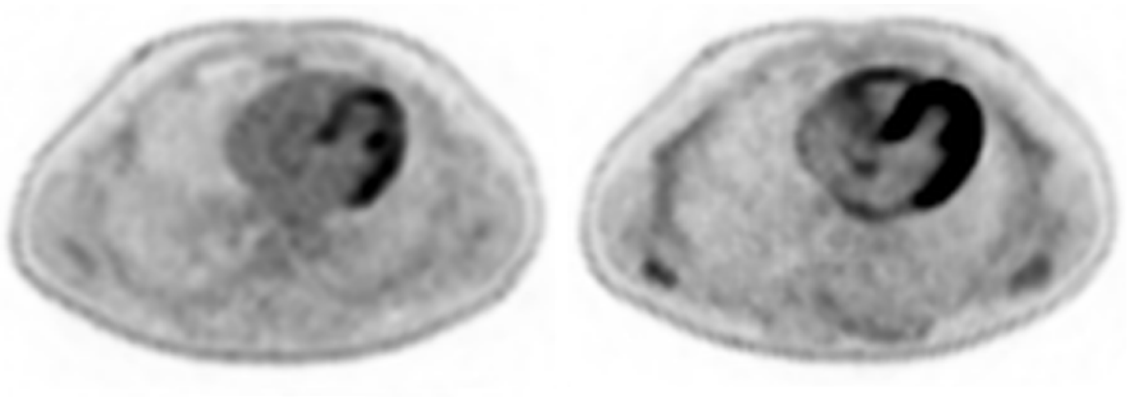

Figure 1

PERIOPERATIVE ANESTHESIA 13

Validation of the modified DASI in the non-cardiac surgical population

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INTRODUCTION: The original 12-question Duke Activity Status Index (DASI) has recently been suggested to predict post-operative 30 mortality or adverse myocardial infarction.[1] A further sub-study has suggested that a modified 4 or 5 question DASI (4M-DASI and 5M-DASI, respectively) is equally predictive of peak oxygen uptake (peak VO2) compared to the original DASI.[2] This study also recalibrated the DASI to predict peak VO2, which was shown to predict in-hospital complications in the METS study. We examined a non-cardiac surgery population using these version of DASI to ascertain their ability to predict composite 30-day mortality and post-operative myocardial infarction.

METHODS: We conducted a single-center, retrospective study in patients undergoing elective major non-cardiac surgery with hospital stay of greater than 24 hours from January 2018 to August 2021, with a completed DASI within 90-days preoperatively and at least one cardiac risk factor, comprising a prior diagnosis of coronary artery disease, heart failure, cerebral vascular disease, diabetes mellitus, chronic kidney disease, peripheral vascular disease, hypertension, smoking and age greater than 70 years. Our primary outcome was to assess the predictive capacity of the original, recalibrated, the 4M-DASI and 5M-DASI for 30-day mortality and suspected or proven myocardial infarction.

RESULTS: The total patient cohort included 4204 patients, with a median of 66 years [IQR 57-73], 47.5% male, 71.4% Caucasian/white, and 21.4% black or African American. While the predominance of patients were American Society of Anesthesiology (ASA) score 3 or above (73.3%), the predicted peak VO2 (mL/kg) was 22.59 [IQR 17.59-27.96] for the original DASI and 39.61 [IQR 26.63-32.42]. The median 4M-DASI score was 2 [IQR 1-3] and 5M-DASI score was 2 [IQR 1-4]. The proportion of the composite outcome was 2.5% (107 patients) in comparison to the total population. We found the unadjusted versions to the DASI to be weakly predictive of our primary outcome. (Table 1) When adjusting for ASA score 3 or greater and patients with 3 or more risk factors, we found an improvement in the predictive value of all the each of the respective DASI versions (Table 2).

CONCLUSION: The DASI is weakly predictive of 30-day mortality and confirmed or suspected myocardial infarction in the broader non-cardiac surgery cohort, but its predictive capacity is increased in ASA equal or greater than 3 or for patients with 3 or more cardiac risk factors. The 5M-DASI and 4M-DASI were equally predictive compared to the original 12-question DASI.

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Table 1: Univariate logistic model results describing the predictive impact of each DASI variant on the composite mortality and MI outcome.

Model	OR (95% CI)	p-value	AUC (95% CI)
DASI (per 5 units)	0.85 (0.793, 0.904)	<0.0001	0.63 (0.59, 0.69)
Recalibrated DASI (per 5 units)	0.88 (0.834, 0.933)	<0.0001	0.63 (0.58, 0.68)
M-DASI (Four question)	0.70 (0.603, 0.829)	<0.0001	0.62 (0.57, 0.67)
M-DASI (Five question)	0.74 (0.652, 0.841)	<0.0001	0.63 (0.58, 0.68)

Table 2: Results of multivariable logistic regression models describing the predictive impact of each DASI variant on the composite mortality and MI outcome with covariate adjustments. All models were adjusted by binary covariates describing a patient having an ASA score of 3 or greater, and having 3 or more risk factors.

Model	OR (95% CI)	p-value	AUC (95% CI)
Covariates only	---	---	0.72 (0.68, 0.76)
DASI (5 units) + **Covariates**	0.91 (0.846, 0.970)	0.0048	0.75 (0.70, 0.79)
Recalibrated DASI (5 units) + **Covariates**	0.92 (0.875, 0.974)	0.0036	0.72 (0.68, 0.76)
M-DASI (Four question) + **Covariates**	0.83 (0.700, 0.972)	0.0212	0.74 (0.69, 0.79)
M-DASI (Five question) + **Covariates**	0.84 (0.739, 0.962)	0.0092	0.75 (0.70, 0.79)

PERIOPERATIVE ANESTHESIA 14

Epidural anesthesia is associated with improved insulin sensitivity during liver resection: a case-control study

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INTRODUCTION: Neuraxial block of afferent and efferent signals using epidural administration of local anesthetic, i.e. epidural anesthesia, has been shown to attenuate hyperglycemia during surgery, presumably mediated through its inhibitory effect on the hypothalamopituitary-adrenal response and, presumably, decreased insulin resistance. Intraoperative insulin sensitivity, however, in the context of epidural anesthesia and major abdominal surgery has never been measured in humans. Using the gold standard for the assessment of insulin sensitivity, i.e. the hyperinsulinemic-normoglycemic clamp (HNC) technique, we tested the hypothesis that epidural anesthesia would be associated with improved insulin sensitivity during liver resection.

METHODS: This study is a post hoc exploratory analysis of the first 100 patients participating in an unblinded, randomized-controlled trial in surgical patients receiving HNC as a potential intervention to reduce the incidence of postoperative infections (ClinicalTrials.gov NCT01528189). Following approval from the institutional ethics review board, written informed consent was obtained from patients scheduled for elective hepatobiliary surgery including Whipple's procedures and liver resection. Patients <18 years, with diabetes mellitus, liver disease (Child-Pugh grade B or C) or on dialysis were not eligible. We identified 18 patients that underwent elective liver resection receiving the HNC. Seven patients had general anesthesia alone, while 11 patients had combined general and epidural anesthesia. Epidural catheters were inserted at a thoracic level between Th7 and Th10 and segmental sensory block established between T4 and L1. Epidural anesthesia during surgery was maintained by boluses of bupivacaine. General anesthesia in both groups was provided by volatile anesthetics supplemented with fentanyl and rocuronium for complete muscle paralysis. The HNC was initiated by insulin at rate of 2mU/kg/min followed by dextrose (20%) infusion titrated to maintain blood glucose between 4 and 6 mmol/L. Blood glucose levels were measured at 5-30 min intervals to ensure normoglycemia during the clamp. Insulin sensitivity was expressed as the dextrose infusion rate (mg/kg/min) during steady-state conditions (90-120 min after starting the HNC). Continuous data were analyzed by unpaired t test, Mann-Whitney U test or Wilcoxon test and proportions were analyzed by Fisher's exact test.

RESULTS: We analyzed seven patients in the GA group (reason for no epidural catheter placement: one refusal, one coagulation disorder, one accidental intravascular placement and four technical difficulties) and 11 patients in the EDA group. Patient characteristics are shown in Table 1. Mean insulin sensitivity in the EDA group (2.3±1.1mg/kg/min) was almost three times higher than in the GA group (0.8±0.6mg/kg/min, P=0.004, Table 1).

CONCLUSION: Epidural anesthesia was associated with significantly improved insulin sensitivity during liver resection.

Table 1: Patient characteristics and clinical outcomes

	GA (n=7)	EDA (n=11)	P value
Age (y)	58.4 ± 12.4	60.8 ± 12.4	0.70
Female-n (%)	1 (14)	5 (45)	0.32
BMI (kg/m^2)	27.5 ± 3.9	25.1 ± 5.2	0.32
Hypertension-n (%)	3 (43)	3 (27)	0.63
Dyslipidemia-n (%)	1 (14)	5 (45)	0.32
HbA1c (%)	5.5 ± 0.4	5.6 ± 0.4	0.54
Fasting time before surgery (h)	14.3 ± 2.6	13.5 ± 1.0	0.71
No. of segments resected	1.6 ± 0.5	2.0 ± 1.1	0.35
Duration of surgery (min)	187.3 ± 109.5	188.9 ± 79.0	0.97
Estimated blood loss (mL)	628.6 ± 275.2	704.5 ± 671.7	0.74
Crystalloids (mL)	1600.0 ± 939.9	1845.5 ± 751.5	0.55
Artificial colloids (mL)	142.9 ± 244.0	90.9 ± 202.3	0.63
5% albumin (mL)	250.0 ± 250.0	336.4 ± 258.9	0.50
RBC (units)	0.0 ± 0.0	1.1 ± 3.6	>0.99
FFP (units)	0.0 ± 0.0	0.7 ± 2.4	>0.99
Insulin sensitivity (mg/kg/min)	0.8 ± 0.6	2.3 ± 1.1	0.004

Data are expressed as mean ± standard deviation, n (%). Insulin sensitivity was expressed as the dextrose infusion rate (mg/kg/min) during steady-state conditions (90-120 min after starting the HNC). BMI, body mass index; EDA, epidural anesthesia; FFP, fresh frozen plasma; GA, general anesthesia; HbA1c, glycated hemoglobin A1c; HNC, hyperinsulinemic-normoglycemic clamp; RBC, red blood cells

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Utilizing Buprenorphine in Multimodal Pain Control for Robotic Assisted Laparoscopic Prostatectomy: A Quality Improvement Comparison to Conventional Opioid Management

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INTRODUCTION: Buprenorphine, a partial mu receptor agonist and kappa receptor antagonist, has been used for acute and chronic pain management since U.S FDA approval in 1981. Administration of buprenorphine may present with potentially lower opioid-related side effects including constipation, respiratory depression, dysphoria, and substance abuse compared to full mu receptor opioids. Prolonged opioid use in the treatment of postoperative pain can result in overprescribing and lead to opioid tolerance and substance abuse, contributing to complications after surgery. Clinicians have responsibilities to provide adequate pain relief while minimizing harmful side effects of opioid treatments. By developing alternative analgesic pathways utilizing buprenorphine instead of full mu agonist opioids in managing postoperative pain, perioperative providers can decrease surgical patient's utilization of opioids while simultaneously attempting to improve postoperative outcomes such as length of stay, length of surgery, and incidence of ileus. However, few studies have tested buprenorphine's utilization and efficacy in perioperative administration. The purpose of this multidisciplinary quality improvement study (urology, anesthesiology and surgical home) is to examine outcomes in patients who received full mu agonist opioids versus buprenorphine for perioperative pain control while undergoing robotic assisted laparoscopic prostatectomy (RALP).

METHODS: Two perioperative analgesic pathways were designed for patients undergoing RALP. A quality improvement study with retrospectively collected data in a single institution over a 10-month period was performed. The control group (n=40) used standard mu opioid agonists (like fentanyl, hydromorphone, oxycodone, tramadol or hydrocodone) and the intervention group (n=40) used buprenorphine. The patients were surveyed five days after surgery regarding post-operative complications, pain level at discharge, and at-home analgesics used at five days post-op to monitor pain control. The primary endpoints were pain scores at discharge and total morphine equivalent dosage (MED). The secondary endpoints included length of stay (LOS), subjective pain control, ileus and patient satisfaction using a Likert scale of 1 (strongly agree) to 5 (strongly disagree). Statistical analysis included Mann-Whitney U and Chi-square, with $p<0.05$ considered significant.

RESULTS: The buprenorphine and control group were similar in mean age (65.95 vs. 64.78, p=0.504), BMI (28.8 vs. 29.1, p=0.730) and race distribution (p=0.851). There was no difference between buprenorphine and the control groups in LOS (1.43 vs. 1.23 days, p=0.158) and length of surgery (271 vs. 260 mins, p=0.476). Buprenorphine had lower reported pain scores at discharge (4.7) compared to the control (5.4) although this did not reach significance (p=0.242). While 74.7% of buprenorphine strongly agreed that their pain was adequately controlled in the hospital, this was 57.5% in the control (p=0.261). There was no difference in overall satisfaction at postoperative day 5 (p=0.313). When analyzing the primary endpoint of MED, buprenorphine received significantly less MED compared to control (15.19 vs. 47.53, p=0.012). There was no significant difference in incidence of ileus between buprenorphine and control (40% vs. 33%, p=0.485).

CONCLUSION: The use of buprenorphine reduced MED by 68% compared to the use of standard mu opioid agonists. Our study demonstrates buprenorphine's analgesic capabilities to maintain non-inferior levels of LOS, length of surgery, pain score at discharge and patient satisfaction comparable to patients on opioid-inclusive analgesia during RALP while decreasing post-surgical and home opioid use. By markedly decreasing post-surgical opioid prescriptions, we can hope to reduce the risk of opioid addiction and associated harm to patients. This study provides evidence that buprenorphine use for perioperative analgesia during RALP is an alternative to traditional opioid-inclusive analgesic pathways. We believe such a strategy will decrease the incidence of opioid use disorder and have benefits including less associated healthcare spending by reducing hospital stay, improved patient health and reduced social harm.

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PERIOPERATIVE ANESTHESIA 16

Decreasing Emergence Agitation with Personalized Music (DEAP Music): A Pilot Trial

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INTRODUCTION: In the perioperative setting, music has been shown to decrease anxiety and perceived pain, each of which independently increases the risk for emergence agitation (EA).[1-8] Personalized music (PM), or selected music that is familiar and meaningful to each patient, has been shown to be a particularly effective adjunct to medical treatment in a variety of settings.[9,10] Played intraoperatively, auditory stimulation with maternal voice and standardized music have shown promise in decreasing EA.[11,12] There is no research to date studying the perioperative impact of PM. The primary aim of the present study is to assess the effect of PM on EA in pediatric patients recovering from elective procedures under general anesthesia (GA). Secondary aims include assessment of the impact of PM on preoperative anxiety and parental satisfaction with perioperative care. The purpose of this pilot trial was to evaluate implementation feasibility and to test the overall study design before expanding enrollment necessary for adequately powered data analysis.

METHODS: This was a prospective, 1:1 parallel-group, superiority randomized controlled pilot trial in children 3-9 years of age undergoing myringotomies at a tertiary level care center in the United States. Six patients were enrolled in this pilot study, divided between two groups: a PM group and a standard care (SC) group. Patient eligibility was determined prior to surgery (Fig 1a) based on inclusion and exclusion criteria (Fig 1b). Patients enrolled in this study were randomly assigned to receive SC or SC + PM during the perioperative period (Fig 1c). A standardized anesthetic regimen was utilized for study subjects (Fig 1d), consistent with common practice for simple myringotomies at the University of Vermont Medical Center (UVMMC). The Pediatric Anesthesia Emergence Delirium (PAED) scale was used as the primary outcome measure to assess for EA, collected at 10-minute intervals following discontinuation of the anesthetic (Fig 1e). Secondary measures included the modified Yale Preoperative Anxiety Scale (mYPAS), induction approach (used as a surrogate for mask acceptance), and parent satisfaction surveys. Potential confounders were tracked to assess for an even distribution of patient characteristics in each study group (Table 1). Descriptive statistics were used to analyze our pilot data.

RESULTS: From March through October 2021, seven patients met eligibility criteria for this pilot study, of which six patients were enrolled. No major feasibility issues were encountered in implementing perioperative PM or in the overall study design. Comments recorded by research staff were positive, finding that perioperative teams generally welcomed the integration of PM during their care (Fig 2a). PM intervention was consistent among study patients and never paused, despite reassurance that any staff member was welcome to stop it if it was felt to interfere with patient care. Minor issues were identified during the pilot which prompted adjustments to study processes and slight modifications to the RCT design (Fig 2b). Case volume was also lower than anticipated as projected case numbers were estimated prior to the COVID-19 pandemic; however, enrollment was high (Fig 2c). No patients were withdrawn after enrollment. Patients assigned to receive music did well in all measures of assessment (Fig 3). A PAED score of greater than 12 was considered to be diagnostic of EA, which served as the primary outcome measure.[13,14] In this pilot study, no patients in the music group developed EA compared to 66% of patients in the control group (Fig3a). Parent satisfaction was also high in the music group (Fig 4). Study groups were not large enough to evaluate for statistical significance. The methods for data collection and plans for analysis serve as the foundation for beginning the randomized controlled trial.

CONCLUSION: The results of this pilot show proof-of-concept and proved essential in assessing the feasibility of implementation for a broader randomized controlled trial. Though this initial cohort did not allow in-depth analysis and no conclusions can be drawn at this time, this pilot revealed results that suggest that PM may be a safe and easy non-pharmacologic intervention to decrease EA. The insights gained from the planned multi-center expanded randomized controlled trial present a unique opportunity to improve perioperative care for children, particularly those at high risk for EA.

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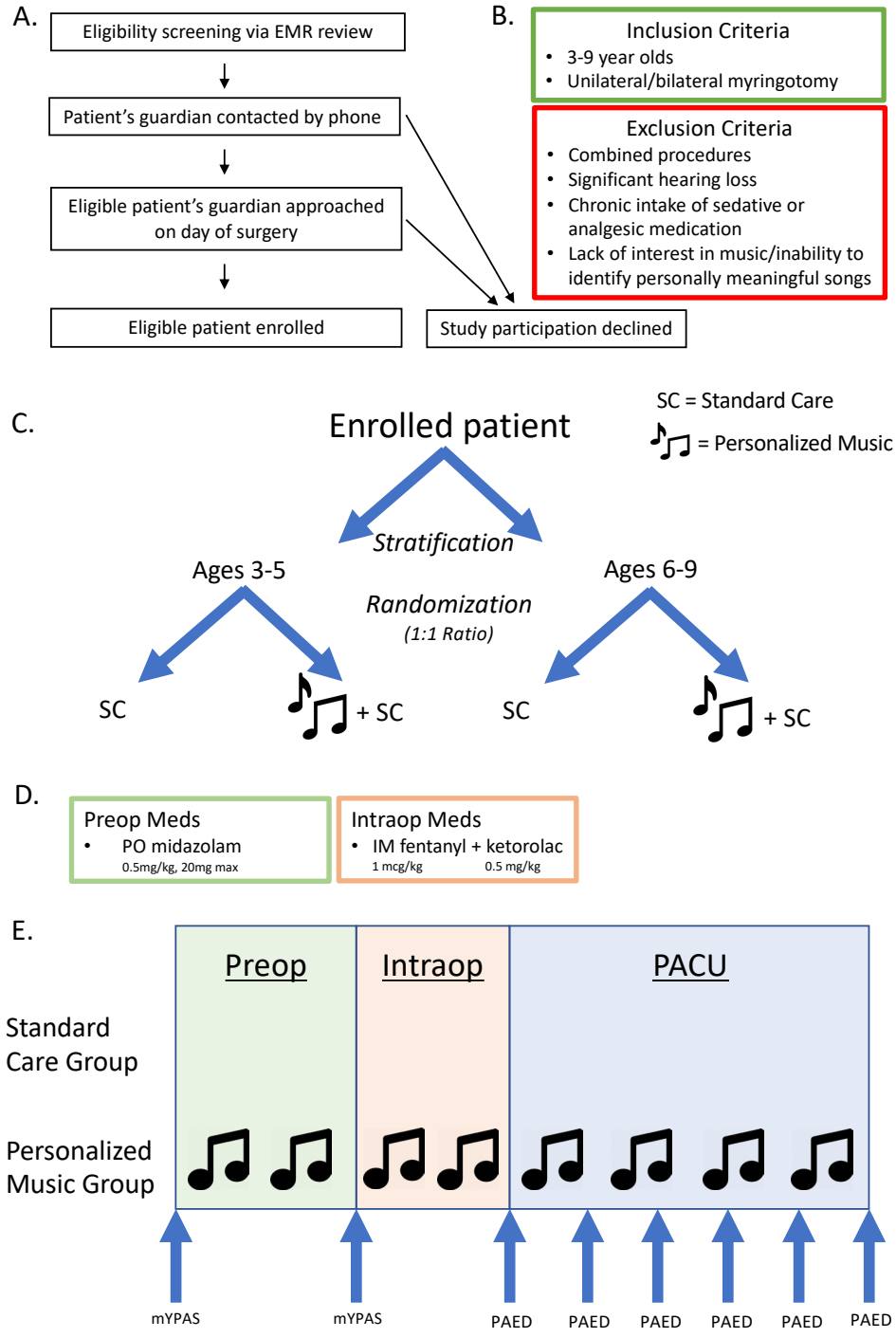
Figure 1: Enrollment/Eligibility, Randomization, Meds, and Assessment Timepoints



Legend: After eligibility screening and enrollment (A and B), patients were randomized to receive institutional standard care +/- personalized music in a 1 to 1 ratio, divided between two age groups (C). Once assigned to a study arm, patients were assessed for baseline anxiety and anxiety on parental separation (mYPAS). A standardized anesthetic regimen was planned, consistent with common practice at UVMMC (D). Following the procedure, patients were assessed for emergence delirium (PAED) at 10 minutes intervals (E).

Table 1: Comparison of Study Groups

	Control (n=3)	Music (n=3)
Patient Characteristics		
Age in years, mean (range)	3.5 (3.1-3.8)	6.8 (4.4-9.1)
BMI, mean (range)	18.33 (17.0-20.0)	21.00 (17.0-28.0)
Sex, M:F	2	0.5
PMH related to procedure, % pts	0%	33%[1]
PMH unrelated to procedure, % pts	33%[2]	0%
Anesthetic Factors (% of patients)		
Preop analgesia given	0%	0%
Preop midazolam given	66%	66%
Parental presence	0%	0%
Intraop analgesia (any)	100%[3]	33%
Intraop analgesia per protocol	66%	33%
Perioperative complications (minor)[4]	33%	33%
Perioperative complications (major)[5]	0%	0%
Surgical Factors		
Tympanostomy Tubes Placed, % pts	100%	100%
Ear Drops placed, % pts	100%	33%
Number of tubes places, mean (range)	1.33 (1-2)	2
Number of Ears Receiving Ear Drops, mean (range)	1.33 (1-2)	.33 (0-1)
Surgical Time in minutes, mean (range)	10 (6-15)	8.33 (5-12)
Social Factors		
Parental State Anxiety (STAI-S), mean (range)	43.5 (43-44)	43.67 (40-47)
Parental Trait Anxiety (STAI-T), mean (range)	43.50 (43-44)	44.00 (41-50)

Legend: A difference in mean age and sex is seen in comparing the two study groups. More patients were given intraoperative analgesia and ear drops in the control group compared to the music group. All other patient characteristics and perioperative factors is similar between study groups.

1. Pt w/ hx of 5 prior myringotomies in music group
2. Pt w/ hx of skull fx in control group, no major sequelae
3. IN fentanyl given to 1 pt in control group instead of IM fentanyl+ketorolac per protocol
4. Pt w/ cough in control group, pt with PONV in music group
5. Major complications would include cardiorespiratory compromise requiring intervention (intubation, CPR, overnight admission)

Figure 2: Assessment and Analysis of Feasibility

A.

Comments recorded by research staff related to music intervention:

- *"Surgical resident and med student dancing, smiling, and singing in OR"*
- *"Patient singing in PACU"*
- PACU RN*: "I think he's listening! This is cool."*

B.

Logistical Issue	Pilot Resolution	Plan for RCT
Crowding in preop room during consent	Consent moved to preop holding	Same
Mask acceptance difficult to assess	Used method of induction (gentle vs rapid) as measure of mask acceptance	Add Induction Compliance Checklist (ICC) to assessment measure
Speaker in way during myringotomy	Speaker moved from IV pole to bedrail	Same
Case volume less than anticipated	Extended duration of pilot trial	Expand eligibility criteria to include tonsillectomies (>5x myringotomy case volume) with standardized anesthetic regimen
Uneven distribution of ages seen in study groups	n/a	Decrease size of block randomization to facilitate mid-study analysis

C.

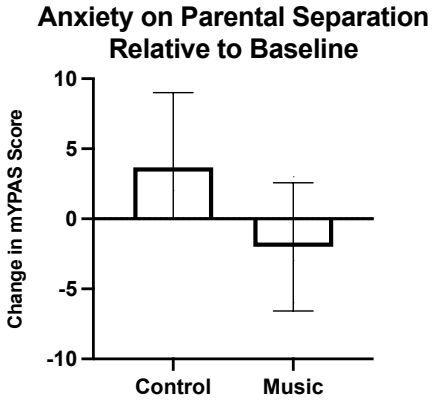
Case Volume fitting Selection Criteria during Enrollment (05-10/2021)	Eligible Case Volume during Enrollment (05-10/2021)	Patients Enrolled	Eligible : Enrolled %	Dropout %
9	7[1]	6[2]	86%	0

Legend**:** Review of pilot implementation is encouraging for initiating RCT. Perioperative care team comments (A) are positive regarding implementation of PM. Logistical issues (B) encountered allowed for minor revisions to pilot and design modifications for RCT. Low case volume during enrollment was attributed to changes in patient needs following COVID-19 pandemic, which prompted addition of tonsillectomies to inclusion criteria for RCT. Despite low case volume in pilot, enrollment was high relative to eligibility, and dropout was low (C).

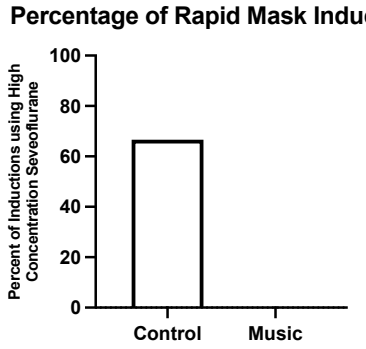
1. Two patients ineligible due to degree of hearing loss/lack of interest in music
2. One patient not enrolled due to research staff availability

Figure 3: Comparison of Perioperative Outcomes

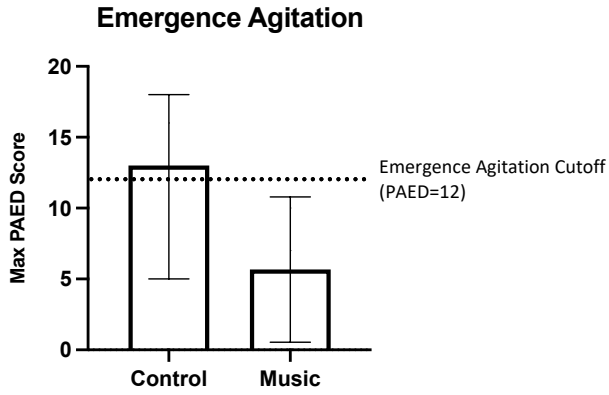
A.



B.

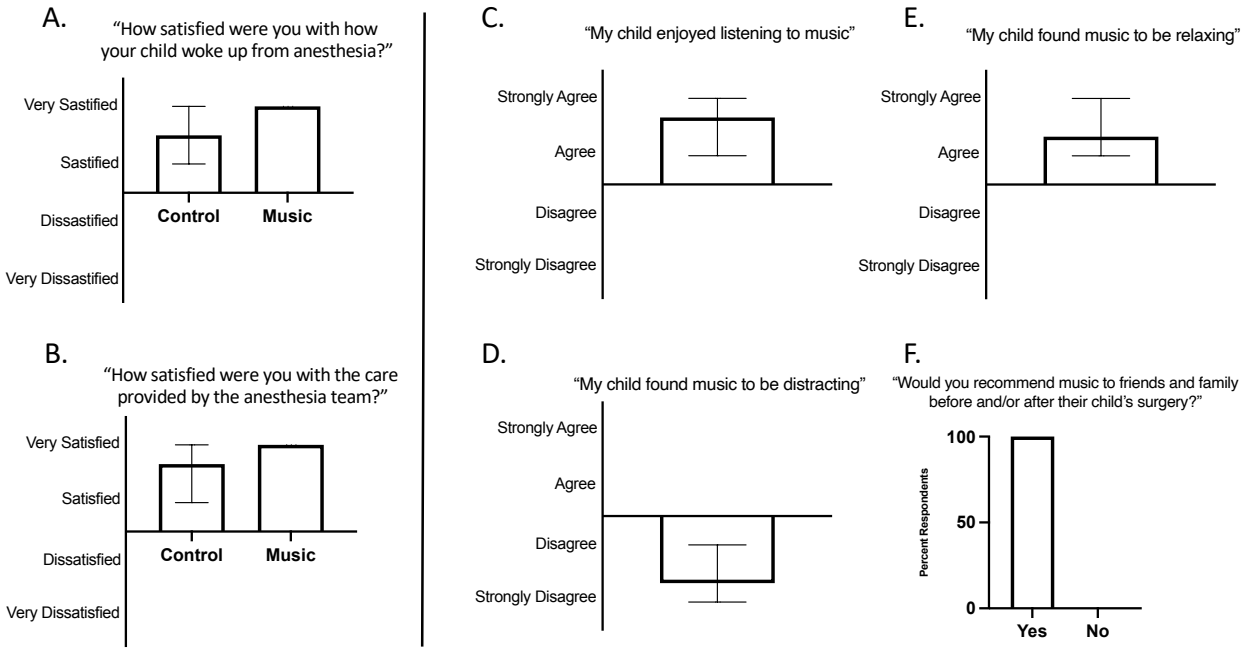


C.



Legend: Pilot data comparing patient anxiety on parental separation (A), percentage of rapid mask inductions (B), and emergence agitation (C), between control and music groups. Data are reported as means with brackets showing range within each set. Percentage of rapid mask indications (B) is reported as a surrogate for mask acceptance, as it indicates the anesthesiologist's decision to slowly vs rapidly titrate inhalational agent on mask induction. Dotted line (C) indicates a PAED score of 12, which is the study's cutoff for emergence agitation.

Figure 4: Parent Satisfaction



Legend: Parental satisfaction in the music group was especially high, with 100% reporting "very high" satisfaction regarding their child's emergence (A) and overall anesthetic care (B). Parents of patients assigned to the music group also reported favorable opinions towards perioperative music (C-E), with 100% of parents stating that they would recommend music for children before/after surgery (F).

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Postoperative Hyponatremia in Oncologic Orthopedic Patients: Incidence, risk factors, and outcomes

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INTRODUCTION: Hyponatremia is the most common electrolyte abnormality encountered in the hospital associated with poorer outcomes and increased economic burden. The purpose of this study is to determine the incidence of hyponatremia among cancer patients undergoing orthopedic procedures, to characterize associated risk factors and outcomes, and determine which outcomes are associated with hyponatremia.

METHODS: This retrospective cohort analysis included all adult patients who underwent surgery with a minimum of two hours of anesthesia time and with post-surgical sodium labs within 30 days at an academic cancer center in 2019 (N = 24,137). Of these, 1445 patients underwent orthopedic surgery. We assessed incidence of post-operative hyponatremia (serum [Na+] < 133 mEq/L) with age, sex, race, BMI, admission service, ASA physical status, Elixhauser comorbidity index, drug intake, GFR, glucose concentration, length of surgery, and post-operative complications. Univariable and multivariable logistic regression models were used to assess associations between hyponatremia and secondary outcomes: 30-day all-cause mortality and length of stay (LOS). A subgroup analysis of hip vs. knee procedures within orthopedic surgery was also conducted.

RESULTS: Post-operative hyponatremia was noted in 217 out of 1445 orthopedic patients (15%) and 3061 out of 22692 other surgical service patients (13.5%). Post-operative hyponatremia (OR = 2.58 [95% confidence interval (CI), 2.01 - 3.30], p < 0.001) and orthopedic surgery (1.85 ([95% CI, 1.28 - 2.66], p=.001) were independently associated with higher 30-day mortality. Post-operative hyponatremia was also associated with longer hospital LOS [7.0 (4.0 - 13.0) vs. 3.0 (2.0 - 7.0); P < 0.001]. Multivariate analysis showed a 32% increase in LOS for hyponatremia patients (exp(estimate)= 1.32, estimate=0.28, [95% confidence interval (CI), 0.26 - 0.30], p < 0.001) and 20% increase for the orthopedic patients compared to all other services (exp(estimate)= 1.20, estimate=0.18, [95% confidence interval (CI), 0.15 - 0.21], p < 0.001). Subgroup analysis within the orthopedic patient population showed higher prevalence of developing post-operative hyponatremia in hip procedures compared to knee (21.5% vs 11.4%, p = 0.042). Within orthopedic patients, multivariable analysis of LOS showed a 27% increase in hyponatremic patients (exp(estimate)= 1.27, estimate=0.24, [95% confidence interval (CI), 0.11 - 0.36], p < 0.001). However, there was no difference in LOS between knee and hip procedures.

CONCLUSION: Post-operative hyponatremia, especially in orthopedic cancer patients, is associated with longer hospital stay and higher mortality. There is higher prevalence of developing post-operative hyponatremia in hip procedure compared to knee procedures.

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PERIOPERATIVE ANESTHESIA 18

Rectus femoris measurement by ultrasound is a valid and reproducible metric of muscle mass in patients undergoing kidney transplantation

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INTRODUCTION: Low skeletal muscle mass predicts increased morbidity and mortality in various surgical populations.[1,2] Kidney transplant patients represent a unique population as chronic kidney disease and dialysis accelerate protein catabolism and muscle wasting.[3] However, quantification of muscle mass often requires exposure to radiation via computed tomography (CT) or other invasive or resource intensive modalities.[1] Herein we aim to evaluate an easy-to-perform, non-invasive, bedside ultrasound technique for assessing muscle mass specifically in patients immediately prior to kidney transplantation.

METHODS: Eligible patients undergoing deceased-donor kidney transplant were prospectively enrolled at our center between 2019-2020. The cross-sectional area (CSA) of the rectus femoris muscle was measured by a skilled ultrasonographer at two different time points ≥10 minutes apart but before transplant. Measurements were taken using a wide linear-array transducer with patients in Semi-Fowler's position and legs in passive extension. Reproducibility was assessed by performing the replicate measurement on the muscle of same laterality. The validity of rectus femoris ultrasound as a metric of muscle mass was evaluated by comparing the mean CSAs measured by ultrasound with the CSA of a psoas muscle of same laterality in the same patient evaluated by abdominal CT at the L3-L4 disc space and read by a qualified radiologist.

RESULTS: Of the 38 patients who had a first rectus femoris muscle CSA measurement performed (median 4.88 cm2 [interquartile range 3.82-6.29]), 37 patients also had a repeat CSA available (median 4.89 cm2 [interquartile range 4.42-5.94]). Replicate ultrasound measurements of the rectus femoris CSA at the two different timepoints were highly correlated (r=0.94, p<0.0001), Figure 1. The intraclass correlation coefficient (ICC) was calculated for the first and repeat rectus femoris muscle CSAs and demonstrated excellent reproducibility (ICC=0.93, 95% CI 0.89-0.98). Reproducibility between the first and repeat rectus femoris muscle CSAs was further substantiated by Bland-Altman analysis. Only 1 of 37 CSA observations fell outside of the respective limits of agreement (mean difference -0.24 cm2, SD 0.84, 95% limits of agreement -1.89-1.40), Figure 2. Of the 37 patients, 14 patients had psoas muscle CSA measurements by CT available (median 10.62 cm2 [interquartile range 9.36-15.55]). Bland-Altman analysis was performed with all resulting observations falling within the respective limits of agreement (95% limits of agreement 5.00-19.49).

CONCLUSION: The ultrasound measurement of the rectus femoris muscle CSA is a highly reproducible and valid method of evaluation in patients undergoing kidney transplant. Further research should investigate whether the estimated limits of agreement are clinically acceptable and whether this measurement is suitable to predict outcomes after kidney transplantation.

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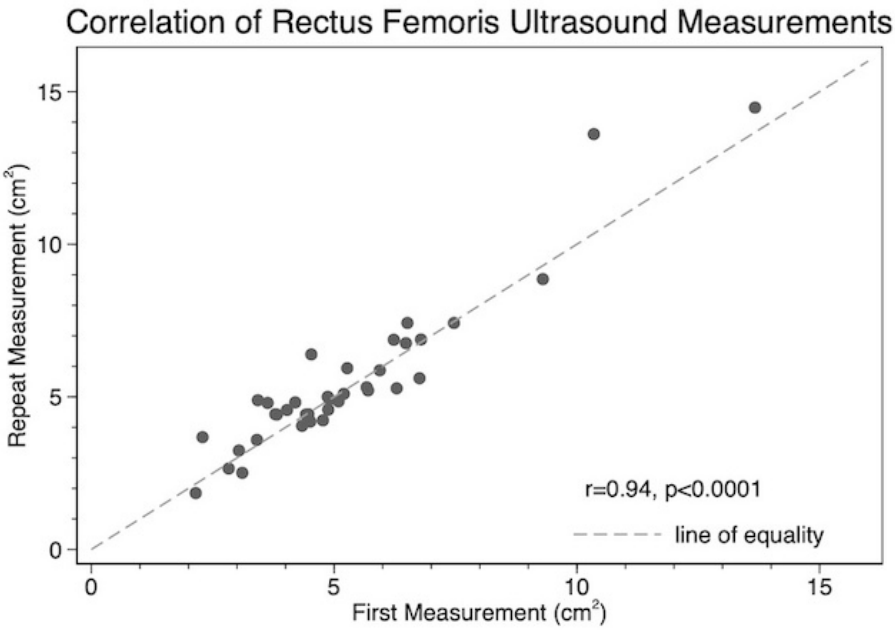

Figure 1: Correlation between first and repeat rectus femoris muscle cross-sectional area measurements by ultrasound (r=0.94, p<0.0001).

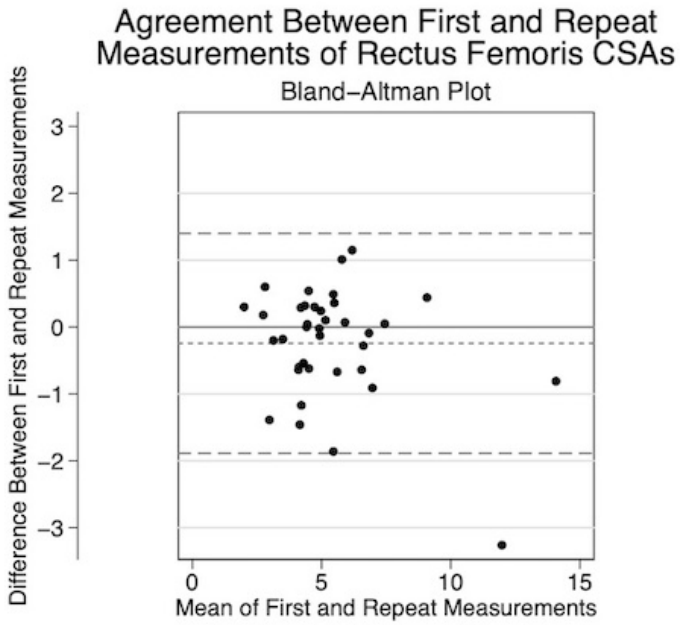

Figure 2: Bland-Altman plot evaluating the reproducibility between the first and repeat rectus femoris muscle CSAs measured by ultrasound with only 1 of 37 CSA observations falling outside of the respective limits of agreement (mean difference -0.24 cm^2, SD 0.84, 95% limits of agreement -1.89-1.40).

PERIOPERATIVE ANESTHESIA 19

Association between Preoperative Anemia Optimization and major complications after noncardiac surgery

Federico Almonacid-Cardenas[1], Moises Auron[1], Dong Wang[1], Edward J Mascha[1], Andrea Kurz[1], Beborah Tolich[1], Eva Rivas[2], Alparslan Turan[3]

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INTRODUCTION: Anemia is a common preoperative finding in patients undergoing non-cardiac surgery, with a prevalence of 5-75% that has been associated with 30-day mortality, acute kidney injury, and infection.[1,2] Moreover, the complications associated with blood transfusions intraoperative, such as renal and pulmonary dysfunction increase mortality, prolong of stay, and infections.[3] Thus, hemoglobin optimization reduces the need for blood transfusions improving outcomes postoperatively.[4] Our goal is to examine the association between preoperative anemia optimization and a composite of all-cause mortality and major complications after non-cardiac surgery in adult patients.

METHODS: We included adult patients who underwent elective non-cardiac surgeries from 2014 to 2019 and had documented preoperative anemia defined as a hemoglobin concentration below 12.0 g/dL in women and 13.0 g/dL in men within 6 months before surgery. Our exposure variable was preoperative anemia optimization (AO) according to Patient Blood Management (PBM) protocol, and the primary outcome was a composite of all-cause in-hospital mortality and major in-hospital postoperative cardiovascular, renal, and pulmonary complications. We assessed the association between AO (versus not) and the primary outcome using a generalized estimating equation (GEE) distinct effects model to estimate the average odds ratio across components while controlling confounding using the inverse probability of treatment weighting (IPTW) propensity score method.

RESULTS: 2,295 out of 15,104 patients received preoperative AO treatment. Patient baseline characteristics were well balanced after IPTW was applied (Table 1). The median [quartiles] of preoperative hemoglobin concentration measured on the available closest date before surgery was 11.1 [9.9, 12.2] g/dL for AO (N= 2,082), and 11.8 [10.8, 12.9] in non-AO (N=12,762). For AO patients, the change of hemoglobin concentration after anemia optimization was 0.0 [-0.2, 1.2] g/dL, while median [quartiles] length between these two values was 35 [4, 102] days. Preoperative anemia optimization was not associated with the composite outcome, with an estimated average relative effect odds ratio of 1.02 (95% CI, 0.85, 1.23) for AO versus non-AO, P=0.80. Similar results were found for each component, with no evidence of treatment-by-component interaction, P=0.17.

CONCLUSION: Preoperative anemia optimization does not appear to be associated with a composite outcome of all-cause in-hospital mortality and major in-hospital postoperative cardiovascular, renal, and pulmonary complications.

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PERIOPERATIVE ANESTHESIA 20

Personalized Scrub Caps for Improved Communication and Professional Wellness

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INTRODUCTION: Effective communication in perioperative settings at an academic institution can be challenging. Team members change frequently and each residency matriculation cycle brings new resident members to the operating room. While standard name badges are mandatory, they are likely printed in small font, may flip backwards, and may be covered by PPE. Communication problems were identified as the root cause of approximately 70% of adverse events reported to the Joint Commission and it has been shown that communication failures in the OR occur in approximately 31% of team exchanges[1]. Personalized scrub caps with visible name and role have been proposed as a potential method of improvement[2]. In 2021 at Stanford Healthcare a three-stage project was completed with an attempt to demonstrate whether the introduction of personalized scrub caps can improve perioperative communication among OR team members and decrease depersonalization among anesthesiology residents, fellows, and attendings.

METHODS: The research design of the Personalized Scrub Caps quality improvement project was a three-part design. All information gathered was subjective, anonymous, and collected via online surveys. The Stanford IRB considered this project to be part of quality improvement and non-human subject research with no written consent required, though all participation was voluntary. 1) Small Group Resident Pilot Project; six representative resident volunteers over 14 day work period. 2) Departmental Implementation; eight week trial period utilizing personalized embroidered scrub caps within Stanford general OR locations. 3) Follow-up and Feedback Collection; survey from those electively wearing personalized embroidered scrub caps. Small Group Resident Pilot Project Goal: Assess effectiveness of a simple, visible name sticker (Image 1) on increasing appropriate use of anesthesia resident names and the impact on resident wellness, specifically feelings of depersonalization in perioperative settings. First week: resident volunteers completed a pre-survey, no cap name stickers worn. Second week: cap name stickers worn, completed post-survey. Survey responses indicated that appropriate name use during perioperative communication was an area that necessitated significant improvement. The responses also demonstrated a positive response to name visibility on scrub caps. Departmental Implementation Personalized embroidered scrub caps were provided at no cost to all residents, fellows, and attendings within the general OR pool. Name and role, cap color (solid), embroidery color (contrasting color), and cap style were included as customizable options (Image 2). Four caps were provided at no cost to each individual. Total of 80 anesthesia professionals requested caps. Follow-Up and Feedback Collection After eight weeks of voluntary personalized scrub cap use, survey data was collected with a total of 17 anonymous responses collected including attendings, fellows, and residents.

RESULTS: Small Group Resident Pilot Project (Survey results displayed in Image 3) Given the positive response from the representative resident cohort, survey data was presented to department leaders who proceeded with the approval process for funding of personalized embroidered scrub caps. Post-Implementation Follow-Up and Feedback (Survey results displayed in Image 4 and Image 5). Overwhelmingly positive feedback from voluntary users of the personalized scrub caps. Improvements of 52% to 88% were seen across nine separate areas of perioperative/intraoperative communication and workplace-related wellness. Voluntary follow-up survey response rate of 22% may decrease the representative accuracy of survey findings.

CONCLUSION: The simple implementation of name and role displayed on surgical scrub caps can improve multiple areas of perioperative communication and professional wellness for anesthesia attendings and trainees. Further areas of data collection could potentially include feedback collection from patients, study of the effect on communication and efficiency in simulated critical OR crises scenarios, and mixed-methods studies including interprofessional colleagues i.e. surgeons, OR nursing, technicians, and other staff.

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Image 1

Image 2

Small Group Resident Pilot Project Results

During the surgical timeout I feel that other OR team members are attentive to my introduction.

Always	0%
Usually	17%
Sometimes	17%
Rarely	67%
Never	0%

I feel that other members of the OR team take a personal interest in me.

A great deal	0%
A lot	0%
A moderate amount	17%
A little	67%
None at all	17%

I prefer to be called by my name rather than "anesthesia", etc.

Yes I prefer my name	84%
Slight preference for my name	16%
No preference	0%
I prefer that other team members do not know my name	0%

In general, do you feel more comfortable speaking to other OR team members if you know their name?

Yes, I am more likely to speak to members if I know their name	100%
No, it doesn't make a difference	0%

In the main OR I feel included as a valuable member of the OR team.

Pre		Post	
Always	0%	Always	0%
Usually	33%	Usually	75%
Sometimes	50%	Sometimes	25%
Rarely	17%	Rarely	0%
Never	0%	Never	0%

I feel that I am treated respectfully by non-anesthesia team members in the OR.

Pre		Post	
Strongly agree	0%	Strongly agree	25%
Agree	67%	Agree	50%
Neither agree nor disagree	17%	Neither agree nor disagree	25%
Disagree	17%	Disagree	0%
Strongly disagree	0%	Strongly disagree	0%

How often do (non-anesthesia) OR team members refer to you by name?

Pre		Post	
Always	0%	Always	0%
Usually	0%	Usually	25%
Sometimes	33%	Sometimes	50%
Rarely	67%	Rarely	25%
Never	0%	Never	0%

How often do pre-op and post-op RNs refer to you by name?

Pre		Post	
Always	0%	Always	0%
Usually	0%	Usually	50%
Sometimes	33%	Sometimes	0%
Rarely	50%	Rarely	50%
Never	17%	Never	0%

In the event of an OR emergency (i.e. code situation, unstable patient, large-scale resuscitation) do you feel that knowing the name and role of other OR team members is beneficial to communication?

Yes, this information is beneficial	100%
It likely does not make a difference	0%
No, there is no benefit in this information	0%

I noticed an increased use in my name when it was visible on my scrub cap.

Yes, some increased use	100%
No change	0%

When my name was used I felt more included as a part of the care team.

Yes	100%
No difference	0%

If made available to me, I would choose to wear a scrub cap with my name visible more frequently.

Yes	100%
No	0%

Do you feel that wearing personalized scrub caps has the potential to increase anesthesia resident inclusion and improve work-related wellness?

Yes	100%
No	0%

Comments volunteered by participating residents:

"When I started this study, I had no idea how much I'd like having my name on my scrub cap! During the week when I had my name sticker on my cap, I found that a greater number of team members called me by name, including surgical attendings and residents. Before using the name tag, I might have days where my name was used a lot, but it was generally because one circulator or resident knew me and reliably called me by name. This may have skewed the results somewhat if looking at only numbers. What matters to me is that MORE members of the team use my name in the OR when I have my name visible. Furthermore, there were several instances when members of the OR team specifically commented on how great it was to have my name visible, and several circulators/scrub nurses mentioned that more people should do this. I believe that caps with names would be well received, and having my name displayed made me feel more like an actual member of the team."

"I wish everyone in the OR had a personalized scrub cap! Would be so easy to identify people's roles and call them by their name instead of sneakily using the log navigator."

"Overall helped with name use a bit but it seems very dependent on the culture of the room."

"I LOVE this idea. I've noticed your name on scrub cap and have copied it occasion when I have a case I really want the team to communicate with me during (liver transplant etc)."

"Many people commented on how having my name visible was a clever idea. I've started wearing a name sticker on my cap more frequently after receiving such positive feedback."

Interdepartmental Personalized Scrub Caps Follow-Up and Feedback

Survey data (subjective, anonymous) collected 8 weeks after caps distributed.
Respondents: 17 Total (8 attendings, 2 fellows, 7 residents)
Representative selected responses below.

Q1: What was your motivation for utilizing personalized scrub caps?
15 Total responses

"So that everyone involved during the pre-, intra- and post-op process will know what role I play."
"Wanting to identify as an MD to patients and provide an alternative to being called 'anesthesia' in the OR."
"Making myself less anonymous in a big OR suite where one can be assigned to work with a team they don't know on any given day."
"Free scrub cap and ease of communication."
"Helping create a more friendly environment in the OR"

Q2: Have you noticed improvements in intra/perioperative communication aided by personalized scrub caps?
(16/16 respondents said YES)

"Yes - people have used my name far more often than they had in the past. Several people have told me that it is easier to communicate when seeing my name on the cap."
"Yes! The other day I took over a case in a location I rarely work. The surgeons wanted the table moved and politely called me by my name to move the table. It was so civilized and made me feel appreciated, part of the team, and respected."
*"*Yes, people know my name more when they see my cap. It's easier to identify others as well, particularly when wearing lead."
*"*Yes. I can call the nurses by name and we notice each other more when we see someone who is wearing the scrub caps."

Q3: Will you continue electively wearing personalized scrub caps in the OR?
(16/16 respondents said YES)

*"*Definitely and beyond residency."
*"*Yes! And I want more colors!"
"Definitely - I enjoy wearing them and I think that have been a great addition to the interventional platform setting."
"Yes on/off. I do like my scrub caps with other designs as well. Would be open to having them embroidered if covered by the department."

Have you noticed improvements in any of the specific areas listed below?

ANSWER CHOICES	RESPONSES	
None of the above	11.76%	2
Communication with pre-op nursing staff	64.71%	11
Communication with patient	52.94%	9
Recognition of role (ie resident, attending, physician, anesthesia member)	76.47%	13
Communication with intra-operative nursing staff	76.47%	13
Intraoperative communication with residents and surgeons	70.59%	12
Increase in use of name	88.24%	15
Improved communication during emergent or critical scenario	47.06%	8
Improved wellness in the workplace	70.59%	12
More team-centered OR	52.94%	9
Total Respondents: 17		

PERIOPERATIVE ANESTHESIA 21

Tracking Case Cancellations: A Review of Same Day Cancellation Causes and Areas for Perioperative Anesthesia Clinic Intervention

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[1]Virginia Commonwealth University, Richmond, VA, [2]VCU Health System, Richmond, VA

INTRODUCTION: Elective OR case cancellation has significant implications on hospital resources, financial profit, workflow efficiency, as well as patient satisfaction, and health outcomes. The Office of the Director at one major university health system quotes a cost of approximately $3600 per hour of unused operative time per operating room in 2011[1]. Medical centers across the United States have been able to find causes of inefficiency within their system and reduce their case cancellation rate through interventions such as the perioperative surgical home that has been shown to lead to better outcomes, better service to patients, and reduced costs[2]. The perioperative surgical home consists of a team of anesthesiologists who work with a patient and their surgeon to optimize and standardize care across patients in the pre-, intra-, and postoperative phases. The purpose of this study is to identify common reasons for elective case cancellations within our health system and identify areas where the perioperative anesthesia clinic may be a point of intervention.

METHODS: To identify the reasons behind elective case cancellations at our health system, we queried a convenience sample of elective cases scheduled to occur >24 hours or more from posting and where canceled within 24 hours of the scheduled operating time from March 1, 2021 to April 30, 2021. A total of 85 cases were identified across both main and ambulatory ORs and across all surgical service lines. Chart review was completed by reviewing the patient's chart on an electronic database and results from the chart review were broadly cataloged into COVID-19 related, medical concern, patient-related, or reason not clearly documented.

RESULTS: Results show that of the 46 operating days in the period, there were 29 days with cancellations less than 24 hours before the scheduled surgery and a total of 84 elective case cancellations within our time frame. 40% of these canceled cases were related to inappropriate medical optimization in the patient, 17% were due to COVID-19 related reasons, 21% due to patient-related concerns and 23% of cases were canceled without clarifying documentation.

CONCLUSION: At the current moment, our operating room schedule may not be as efficient, financially productive, and as patient-centered as it could be with respect to its rate of elective case cancellations. A small sample size suggests that there may be financial loss suffered by the health system on a daily basis. Furthermore, these data suggest that a larger barrier to making the OR schedule more efficient is determining what is causing the suboptimal rate of cancellations. An unexpected area of perioperative anesthesia improvement is the lack of a standardized documentation system or process to track the underlying reasons for cancellations, which equates to in-depth chart review as the only means for potentially determining causes of cancellations. Additionally, it is unclear how many patients, particularly those who had medical reasons for cancellation or unknown causes for cancellation, were evaluated in the preoperative anesthesia clinic because this information is not routinely tracked through our informatics design. With optimizing a perioperative surgical home model of care in our institution as a departmental goal for Anesthesiology, these data suggest a need for a simple, yet more structured data tracking process along the continuum of a patient's surgical experience with multiple endpoints to record reasons for case cancellations. These endpoints ideally would allow users to recognize patterns of cancelations and streamline improvements. Future directions for this quality improvement project include using PDSA cycles to pilot a process design that includes a standardized case cancellation form in the electronic record. This would be utilized to gather more data points across a longer timeline and stratify case cancellations by service line, then propose areas where the perioperative anesthesia clinic would have highest utility.

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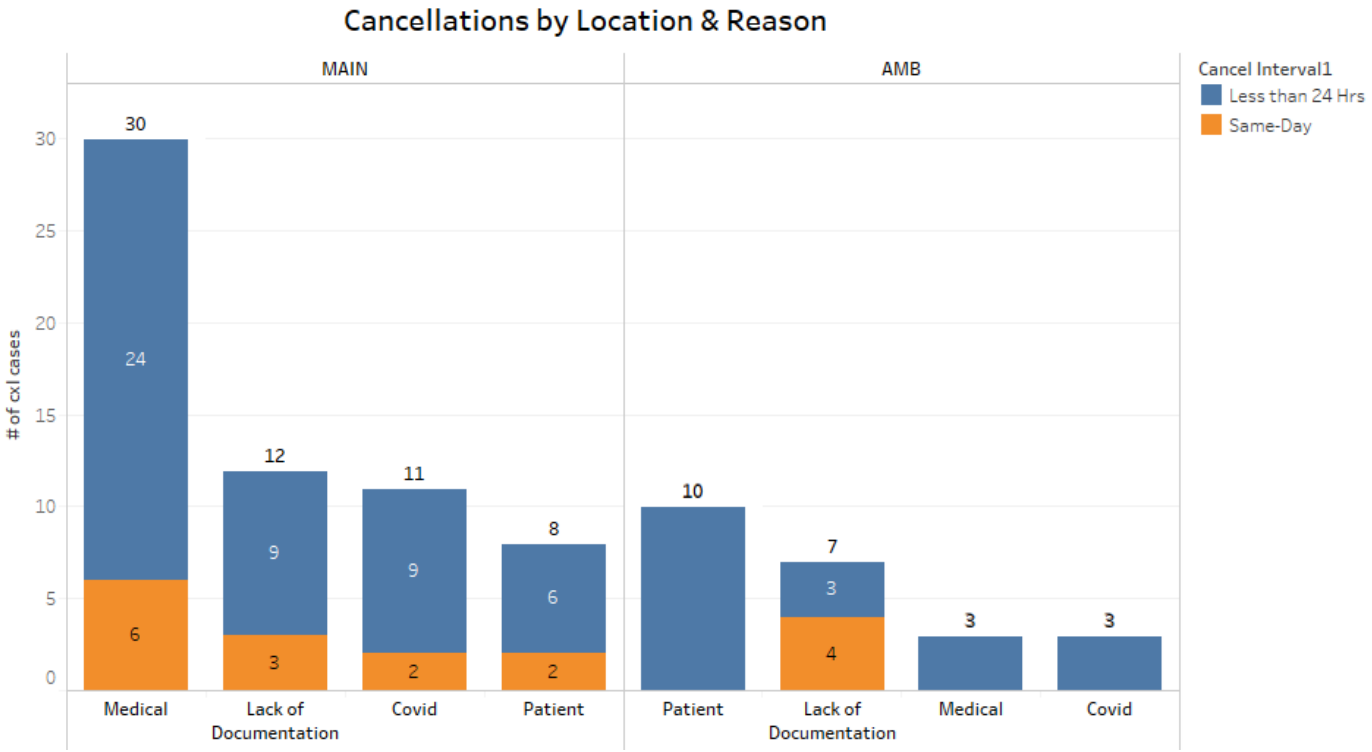

Figure 1

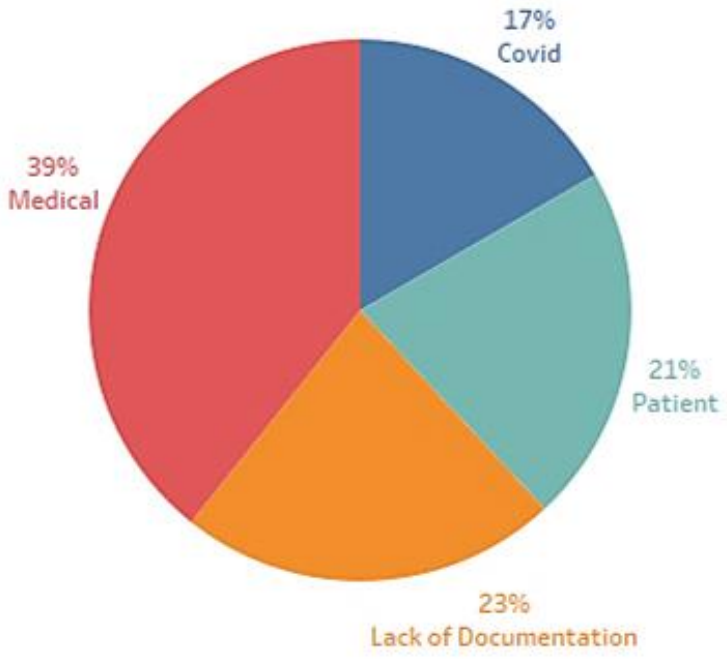

Figure 2

PERIOPERATIVE ANESTHESIA 22

Retrospective Analysis Investigating Intraoperative Opioid Administration and Anesthetic Recovery with a Focus on Identifying Risk and Protective Factors

Melat Gebre[1], David W Boorman[1], Addison Jones[1], Grant Lynde[1], Anna Woodbury[1]

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INTRODUCTION: Increased use of intraoperative opioids can lead to delayed arousal, respiratory depression, acute opioid tolerance, and increased postoperative pain[1,2]. These undesirable effects can lead to increased length of stay in the postoperative care unit (PACU) and increased costs[3]. This study aims to identify both risk and protective factors that affect intraoperative opioid administration and PACU length of stay (LOS). Our goal is to improve patient outcomes, efficiency, and reduce costs.

METHODS: Subjects: Patients over age 18 who have undergone surgical procedures under general anesthesia at Emory University Hospital and Emory University Hospital Midtown from 1/1/2014 through 12/31/2018.

Exclusion Criteria: ICU patients, patients that did not have a documented PACU stay duration, surgical procedures completed under sedation, and PACU durations deemed to be out of range. Total of 103,778 patients were included.

Analysis: Charts were reviewed, and data was collected on patient demographics, type of surgery, intraoperative opioids administered, PACU length of stay, use of opioid sparing medications and regional/neuraxial anesthesia. Log-transformed PACU minutes data were analyzed with the General Linear Model. Intraoperative MME data were analyzed with Multinomial Logistic Regression.

RESULTS: We found that female sex increased the odds of receiving more opioids when compared to males on average by 1.25x (CI 1.19-1.47; p <0.0001) ; Temp < 36 C decreased the odds of receiving more opioids by 1.5x (CI 0.44-0.86; p <0.0001); White patients were 1.2x more likely to receive more opioids than AA patients (CI 0.78-0.96; p<0.001). Patients who received one opioid sparing agent intraoperatively had 4.7x increased odds of receiving more intraoperative opioids than those who received none and patients who received two or more opioid sparing agents intraoperatively had a 2.6x increased odds of receiving more intraoperative opioids (p<0.0001). We also found that giving up to 25 MME intraoperatively increased PACU LOS by 2 mins (CI 1.3-2.7; p <0.0001), giving up to 50 MME increased PACU LOS by 4.5 mins (CI 3.6-5.4; p<0.0001), and giving up to 100 MME increased PACU LOS by 6 mins (CI 5.1-7.1; p<0.0001). Females have 3 min longer PACU LOS than males (CI 2.5-3.3; p<0.0001). AAs had longer PACU LOS by 2.5 mins than Whites (CI 2-2.9; p<0.0001). Temperature: being <36 C increased PACU LOS by about 5.5 mins (CI 4.0-6.9; p<0.0001). The utilization of intraoperative opioid sparing drugs increased PACU LOS (1 min for 1 drug (CI 0.4-1.5; p<0.0001), 2 min for 2 drugs (CI 1.4-2.8; p<0.0001). For all results, we controlled for 16 different variables including American Society of Anesthesiologists (ASA) physical classification, length of time under anesthesia, type of surgery, gender, race, age, and chronic opioid use.

CONCLUSION: This study has identified both risk and protective factors that affect intraoperative opioid administration and PACU LOS. We discovered an unanticipated significant effect of sex and race/ethnicity on opioid administration in the peri-operative period, with African Americans receiving significantly less intraoperative opioids (37.5 MME) on average than other races/ethnicities including Asians (47.5 MME), non-Hispanic Whites (50 MME), and 'other' (47.2 MME) p<0.0001. We also found that females received significantly more intraoperative opioids on average (45 MME) than males (37.5 MME) p<0.0001. These results warrant further investigation into the reasons behind these variations, and whether they have a biologic basis or are related to provider biases. Intra-operative and pre-operative utilization of opioid sparing adjuncts may not be as impactful as we had hoped, as we did not find reduction in PACU LOS nor intraoperative opioid administration related to these techniques.

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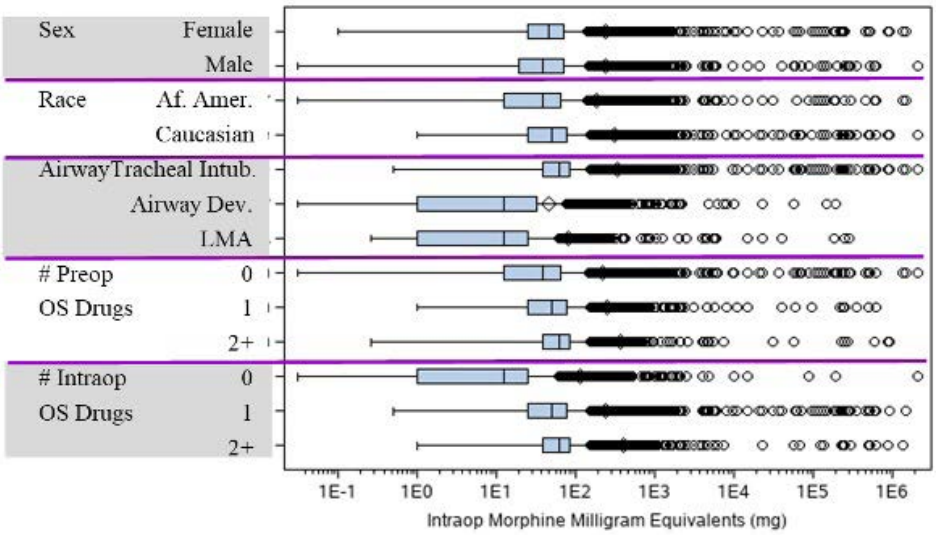

Figure 1

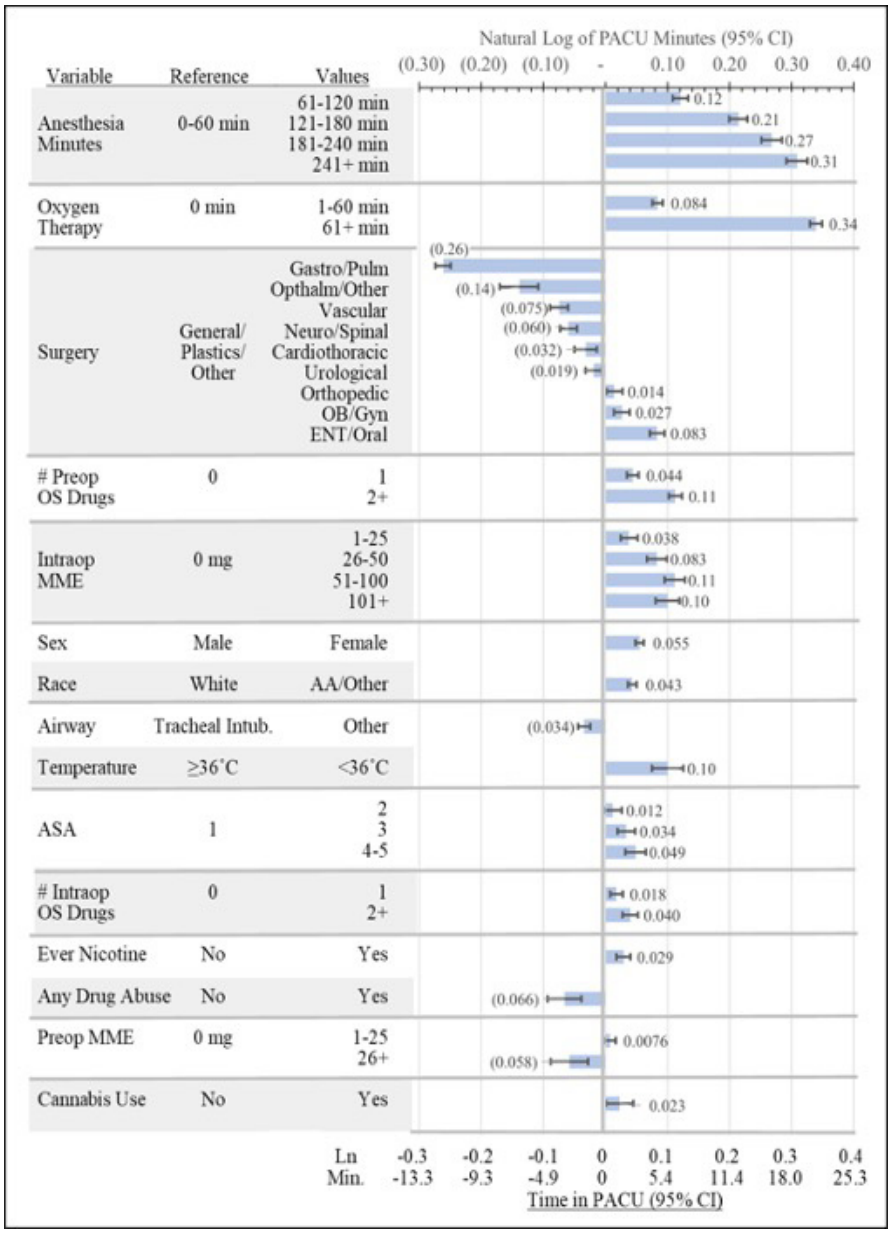

Figure 2

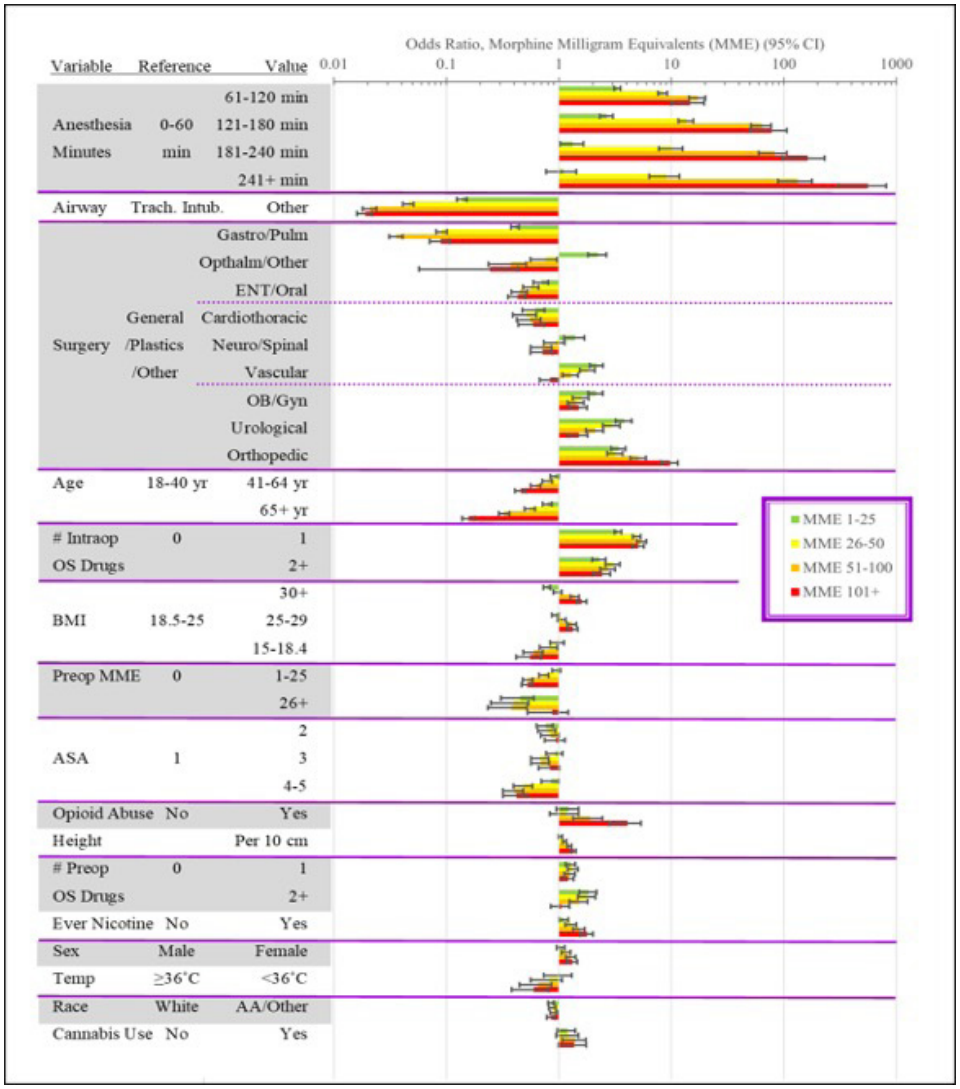

Figure 3

Variable	Values	N (%)	Grouping	N (%)
Sex	Male	42,577 (59.0%)	NA	NA
	Female	61,201 (41.1%)		
Race	White	47,610 (45.9%)	White	47,610 (45.9%)
	Af. Amer.	50,421 (48.6%)	Af. Amer.	50,421 (48.6%)
	Asian	1,679 (1.6%)	Other	5,747 (5.5%)
	Multiple	1103 (1.1%)		
	Am. Indian	1269 (1.2%)		
	Hawaiian	114 (0.1%)		
	Unknown	1582 (1.5%)		
Ethnicity	Hispanic	2,500 (2.6%)	NA	NA
	Other	92,433 (97.4%)		
ASA Class	1	6,320 (6.1%)	1	6,320 (6.1%)
	2	29,833 (28.8%)	2	29,833 (28.8%)
	3	52,449 (50.5%)	3	52,449 (50.5%)
	4	15,155 (14.6%)	4-5	15,176 (14.6%)
	5	21 (0.02%)		

Abbreviations: IQR: Interquartile Range; AA: African American; ASA: Amer. Society of Anesthesiologists Physical Status Classification

Figure 4

PERIOPERATIVE ANESTHESIA 23

Implementation of Point-of-Care Ultrasound Curriculum in an Anesthesiology Residency Program

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INTRODUCTION: Point-of-care ultrasound (POCUS) has become the standard of care for many anesthesia procedures, including diagnostic evaluation to guide therapy. In response to the growing application of ultrasound studies, the ACGME has acknowledged the need for POCUS training and testing by incorporating this skillset into required curriculums. Our goal was to implement a POCUS curriculum for trainees at an anesthesiology residency program at a large academic institution and to highlight rotation quality by measurable improvement in POCUS performance.

METHODS: We used a Plan, Do, Study, Act cycle as our model. In collaboration with our critical care and emergency departments, we developed a pilot curriculum consisting of four, 3-hour online modules for self-education, and five, 8-hour days of one-on-one ultrasound practice sessions on volunteer patients with assigned faculty members. Based on the pilot's success, we plan to incorporate a POCUS curriculum into the core academics for all anesthesiology residency trainees. Baseline surveys and knowledge assessment quizzes were given during orientation and repeated at the end of the rotation. Comparison of the results before and after the POCUS curriculum, as well as time spent working through POCUS online modules, were the primary outcomes evaluated.

RESULTS: Twenty-two trainees attended a full POCUS curriculum with online modules and five days of in-person sessions in the 2021 academic year. The primary outcome measures of our study were the pre- and post-test assessment scores and time spent on each assessment, in addition to fine-tuning the curriculum based on Plan, Do, Study, Act cycles and feedback from residents. We will also use analysis of POCUS-based ITE questions as a marker for longitudinal improvement in POCUS knowledge.

CONCLUSION: A successful POCUS training and educational program for anesthesiology residents at a large academic institution is feasible as demonstrated by improved confidence in POCUS performance, retention of knowledge, and increased interest in using POCUS in everyday practice. While developing this curriculum, we were able to ascertain several areas for improvement crucial to long-term success of the program. Identifying faculty with expertise, training, and time to dedicate to the rotation was our priority. Identifying the number of ultrasound interpretations each resident should complete in each POCUS area remains a gray area. There is currently no minimum number needed to successfully complete an anesthesiology residency. Trainees were encouraged to keep a record of the number of scans completed while on rotation. An area of future development will include maintenance of expertise through a combination of POCUS continuing medical education, a minimum number of personally performed examinations per year, and a method of maintaining quality assurance.

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PERIOPERATIVE ANESTHESIA 24

Association of Preoperative Cannabinoid Use with Postoperative Cardiac Complications: A Retrospective Cohort Study

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INTRODUCTION: An increasing number of patients present for surgery who use cannabinoids for recreational or medical purposes, which has been augmented by legislature changes in various states of the United States between 2012 and 2016. (1) Previous retrospective studies have raised concerns about an increased risk of cardiovascular events including myocardial infarction (2, 3) in patients who abuse cannabis. However, there is little data on whether surgical patients who consume cannabinoids are at higher risk of postoperative cardiac events. We investigated the association of recreational and medical cannabinoid use with adverse cardiac outcomes in a large hospital network in New England.

METHODS: Adult patients undergoing non-cardiac surgery under general anesthesia at a tertiary academic healthcare network in Boston, MA, USA, between 2006 and 2020 with available pre-admission or pre-procedural notes were included in this hospital registry study. Recreational use of cannabinoids was identified based on physician and nursing notes from structured patient interviews during pre-admission or pre-procedural testing, prescriptions of medical cannabinoids, or ICD-9/10 diagnostic codes of cannabinoid abuse. The primary outcome was major adverse cardiac events (MACE) (4), which included myocardial infarction, cardiac arrest, acute heart failure or revascularization procedures within 30 days after surgery. Multivariable logistic regression analyses adjusted for a priori defined factors including patient baseline characteristics, socioeconomic factors, concomitant substance abuse, markers of procedural severity and comorbidities including the Revised Cardiac Risk Index (RCRI) (5) were fitted. In secondary analyses, we differentiated the risk of postoperative MACE by types of cannabinoid use (recreational use, medical use, and abuse of cannabinoids) and investigated whether a high perioperative cardiovascular risk based on the RCRI modified the association between cannabinoid use and postoperative MACE. Exact matching for age (± 2 years) and sex at a 1:3 ratio was performed in sensitivity analyses. Standardized differences and odds ratios with 95% confidence intervals are reported. A p-value <0.05 was considered as statistically significant. All analyses were performed in Stata (Versions 15 and 16, StataCorp, TX, USA).

RESULTS: In the primary cohort of 308,330 patients, 25,219 (8.2%) reportedly used cannabinoids before surgery for recreational or medical purposes (Figure 1). 8,583 (2.8%) patients experienced MACE within 30 days after surgery. 516 (2.1%) of those who reportedly used cannabinoids experienced MACE, whereas 8,067 (2.8%) of those who did not reportedly use cannabinoids experienced MACE (odds ratio [OR], 0.71 [95% confidence interval [CI], 0.65-0.79]; p<0.001). The incidence of postoperative MACE increased with patient age (Table 1, Figure 2).
After confounder adjustment, preoperative cannabinoid use was not significantly associated with MACE (adjusted OR [aOR], 1.02 [95% CI, 0.92-1.13]; p=0.77). These findings were independent from recreational, medical, or abuse of cannabinoids (Table 2). A high perioperative cardiovascular risk profile defined as an RCRI class of 3 or more did not significantly modify these findings (p-for-interaction=0.07). There was no significant association between cannabinoid use and postoperative myocardial infarction within 30 days alone (aOR, 1.11; 95% CI 0.90-1.39; p=0.33). Sensitivity analyses after exact matching for sex and age (± 2 years) confirmed the results (aOR, 1.04; 95% CI 0.92–1.17; p=0.57 and p-for-interaction = 0.49).

CONCLUSION: Cannabinoid use for recreational or medical purposes was not associated with an increased risk of postoperative cardiac complications within 30 days after non-cardiac surgery.

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Figure 1. Study flow

ASA, American Society of Anesthesiologists; RCRI, Revised Cardiac Risk Index.

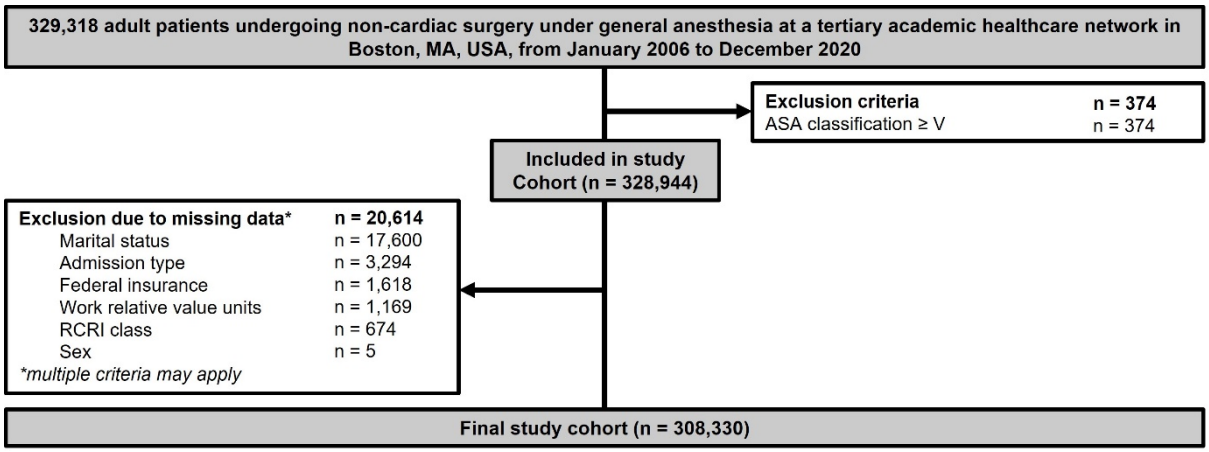

Figure 2. Cannabinoid use and MACE by age and sex

Prevalence of cannabinoid use before surgery and incidence of MACE within 30 days after surgery by patient age and sex.

MACE, major adverse cardiac events.

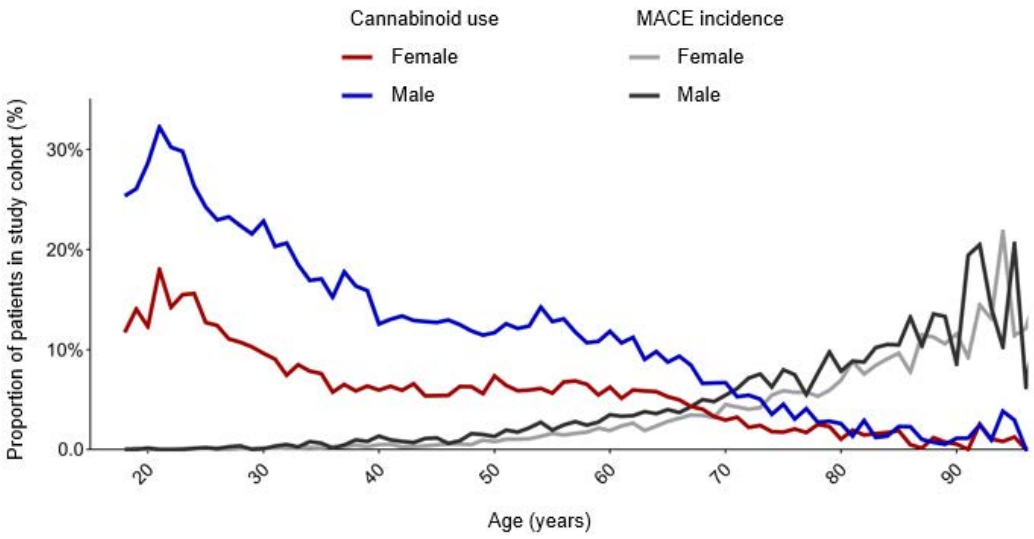

Table 1. Patient Baseline Characteristics and Covariates by MACE

MACE, major adverse cardiac events; SD, standard deviation; ASA, American Society of Anesthesiologists; IQR, interquartile range; USD, United States Dollar; ENT, ear, nose, and throat, RCRI, Revised Cardiac Risk Index.

Characteristics	No MACE within 30 postoperative days n=299,747	MACE within 30 postoperative days n=8,583	Standardized difference
Demographics			
Mean age ± SD, y	54.9 ± 16.3	69.6 ± 12.4	-1.013
Sex (female), n (%)	174,066 (58.1)	3,978 (46.3)	0.236
Median body mass index (IQR), kg/m2	27.1 (23.6 – 31.5)	28.8 (24.7 – 34.4)	-0.259
ASA classification, n (%)			-1.336
I	37,971 (12.7)	13 (0.2)	
II	148,350 (49.5)	608 (7.1)	
III	103,000 (34.4)	6,257 (72.9)	
IV	10,426 (3.5)	1,705 (19.9)	
Race/ ethnicity, n (%)[a]			-0.021
White	191,577 (73.9)	5,778 (75.1)	
Black	28,770 (11.1)	1,117 (14.5)	
Hispanic	15,623 (6.0)	395 (5.1)	
Asian	11,847 (4.6)	171 (2.2)	
Other	11,084 (4.3)	230 (3.0)	
Two or more	409 (0.2)	3 (0.0)	
Socioeconomic factors			
Estimated median household income (IQR), USD[b]	70163 (43919 – 91597)	67028 (43532 – 89451)	0.066
Federal insurance, n (%)	94,317 (31.5)	5,496 (64.0)	-0.690
Education level n (%)[c]			0.210
No education	246 (0.4)		
Attended high school	4,352 (6.9)		
Graduated high school	20,497 (32.3)		
Attended college	12,737 (20.1)		
Graduated college	25,559 (40.3)		
Marital status, n (%)			-0.090
Divorced	20,240 (6.8)	739 (8.6)	
Life partner	372 (0.1)	12 (0.1)	
Married	159,780 (53.3)	4,167 (48.5)	
Separated	3,889 (1.3)	168 (2.0)	
Single	96,998 (32.4)	2,025 (23.6)	
Widowed	18,468 (6.2)	1,472 (17.2)	
Preoperative factors			
Admission type, n (%)			-0.290
Ambulatory	176,479 (58.9)	3,657 (42.6)	
Same-day admission	87,698 (29.3)	3,538 (41.2)	
Inpatient	35,570 (11.9)	1,388 (16.2)	
Emergency surgery, n (%)	17,999 (6.0)	865 (10.1)	-0.150
Intraoperative factors			
Median duration of surgery (IQR), min	92 (52 – 153)	91 (51 – 152)	0.007
Median work relative value units (IQR)	8.5 (5.0 – 15.6)	8.5 (5.0 – 15.9)	-0.063
Surgical service, n (%)			-0.308
Colorectal	8,023 (2.7)	145 (1.7)	

Table 2. Results of multivariable logistic regression with categorized exposure

MACE, major adverse cardiac events; OR, odds ratio; aOR, adjusted odds ratio.

Cannabinoid use	No MACE within 30 postoperative days (n = 299,747)	MACE within 30 postoperative days (n = 8,583)	Unadjusted Analysis		Adjusted Analysis	
			OR 95% CI	P-value	aOR 95% CI	P-value
No use	275,044 (97.15%)	8,067 (2.85%)	Reference		Reference	
Recreational use	17,985 (98.41%)	291 (1.59%)	0.55 0.49–0.62	<0.001	1.02 0.89–1.16	0.82
Abuse	2,728 (96.81%)	90 (3.19%)	1.12 0.91–1.39	0.28	1.20 0.94–1.53	0.15
Medical use	3,990 (96.73%)	135 (3.27%)	1.15 0.97–1.37	0.11	0.93 0.76–1.12	0.44

Data are expressed as frequency (incidence in %). Statistical analyses were conducted using multivariable logistic regression. Unadjusted odds ratios (OR) and adjusted odds ratios (aOR) are reported from multivariable logistic regression analyses.

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The effect of tidal volume on postoperative respiratory complications is dependent on patients' respiratory system elastance: A multicenter hospital registry study

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INTRODUCTION: Trials investigating the effects of intraoperative low-tidal volume ventilation have been equivocal, with some studies[1,2] reporting lowered postoperative respiratory complications (PRC), while others found no effects[3]. A retrospective study even indicated harmful effects of using very low tidal volumes[4]. In patients with Acute Respiratory Distress Syndrome (ARDS), the mortality benefit of using lower tidal volumes varied with the patients' respiratory system elastance[5]. However, the clinical significance of this interaction in surgical patients is unclear. We hypothesized that the association between tidal volume during mechanical ventilation and PRC is modified by the patient's respiratory system elastance.

METHODS: In this multicenter retrospective hospital study, we analyzed adult patients with American Society of Anesthesiologists (ASA) class < V undergoing non-cardiothoracic surgery under general anesthesia between January 2006 and December 2018 at two competing healthcare networks in Boston, MA. We excluded emergency surgeries, laparoscopic surgeries and microlaryngoscopies. The primary exposure was an interaction term between tidal volume per kilogram ideal body weight (IBW) and standardized respiratory system elastance (SEl) (expressed in cmH2O/[ml/kg]). Patients were categorized into two groups according to the tidal volume: >8 ml/kg IBW (high tidal volume group) and ≤8 ml/kg IBW (low tidal volume group). The primary outcome was PRC, defined as the need for mechanical ventilation within seven days after surgery or post-extubation desaturation (SpO2) <90% within the first 10 minutes[6-9]. In the primary analysis, we tested whether the association between tidal volume and PRC was modified by the patient's SEl using multivariable logistic regression with interaction term analysis, adjusted for patient demographics, comorbidities and markers of procedural severity. In the secondary analyses, we examined the association between driving pressure (DP) and PRC, and investigated whether the association between tidal volumes and PRC was mediated by the resulting DP.

RESULTS: 197,474 cases were included (Figure 1). 10,821 patients suffered PRC (5.5%). Baseline characteristics and distribution of variables are shown in Table 1. The median (IQR) SEl was 1.77 (1.46-2.18) cmH2O/(ml/kg). The intraoperative tidal volume was associated with PRC, and was modified by a patient's SEl (p-for-interaction<0.001, Figure 2A): In patients with a high SEl (>1.65 cmH2O/[ml/kg], poor compliance), the risk of PRC was higher if patients received high (>8 ml/kg) tidal volumes. Risk differences between high and low tidal volumes in this group ranged from 0.3% ([0.0-0.5], p=0.030) in patients with a SEl of 1.7 cmH2O/[ml/kg] to 5.8% ([3.8-7.8], p<0.001) in patients with an SEl of 5.0 cmH2O/[ml/kg] (red part, Figure 2B). By contrast, patients with a very low SEl (<0.8 cmH2O/[ml/kg], good compliance) showed a decreased risk of PRC by as much as -0.6% ([-1.03 to -0.24], p<0.001) when high compared to low tidal volumes were applied (green part, Figure 2B). There was no effect of high versus low tidal volumes in patients with a moderate SEl (blue part, Figure 2B). The median (IQR) DP in our study population was 15 (12-19) cmH2O. Higher DPs were associated with an increased risk of PRC ('adjusted odds ratio' aOR 1.04 [1.03-1.04], p<0.001 per 1 cmH2O increase). Mediation analysis revealed that increased DP completely mediated adverse effects of high tidal volumes on PRC in patients with SEl >1.65 cmH2O/[ml/kg] (indirect effect: 100%, p<0.001 (Figure 3)). The DP that was associated with the average risk in the study population ('adjusted relative risk' RRadj=1) was 14.1 cmH2O. DPs exceeding

this threshold increased the predicted risk of PRC (Figure 4A). 2nd-order fractional polynoms supported the linear model with slightly corrected estimations of predicted PRC at extreme values of DP (Figure 4B).

CONCLUSION: The effects of intraoperative tidal volume on PRC depend on patients' respiratory system elastance. Physicians should consider assessing the individual patients' lung mechanics and apply low tidal volumes in patients with high elastance (i.e. poor compliances), with the goal to limit the application of high driving pressures.

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Table 1. Patient characteristics and distribution of variables.

Characteristics	No PRC (n= 186,653)	PRC (n= 10,821)
Centre		
BIDMC	94,745 (50.8%)	5,772 (53.3%)
MGH	91,908 (49.2%)	5,049 (46.7%)
Age, years	54.6 ± 16.1	56.5 ± 16.1
Gender		
Male	82,138 (44.0%)	5,140 (47.5%)
Female	104,515 (56.0%)	5,681 (52.5%)
Body mass index	28.3 ± 6.6	30.1 ± 7.8
ASA class		
1	21,133 (11.3%)	764 (7.1%)
2	105,387 (56.5%)	4,824 (44.6%)
3	56,841 (30.5%)	4,713 (43.6%)
4	3,292 (1.8%)	520 (4.8%)
Type of surgery		
Acute care surgery	4,270 (2.3%)	374 (3.5%)
Burn	1,510 (0.8%)	141 (1.3%)

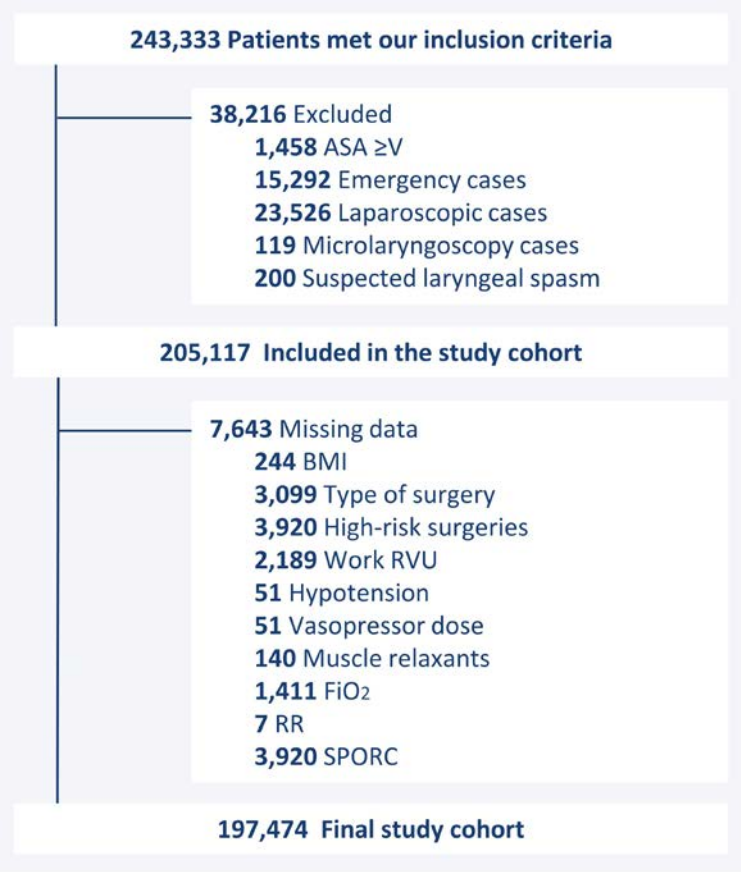

Figure 1. Study flow diagram.
ASA: American Society of Anaesthesiologists; BMI: body mass index; RVU: relative value units; FiO2: fraction of inspired oxygen; RR: respiratory rate; SPORC: Score for Prediction of Postoperative Respiratory Complications. Multiple exclusion criteria may apply.

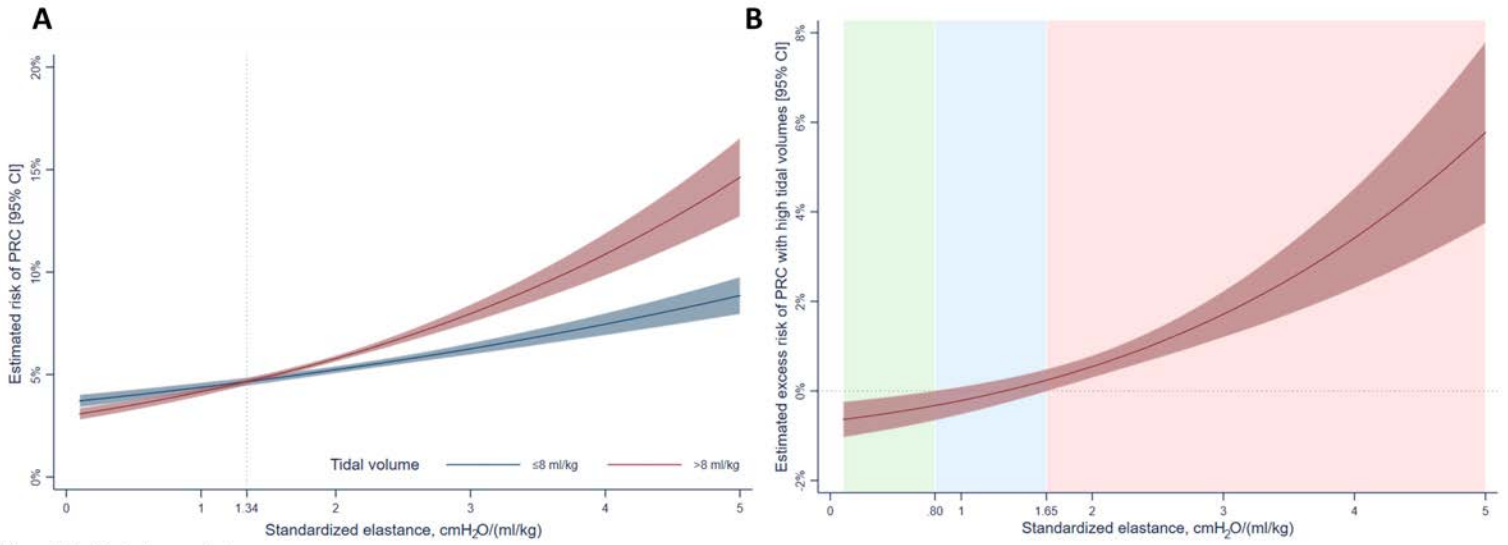

Figure 2. Results of primary analysis
2A. Estimated risk of postoperative respiratory complications (PRC) in patients who received high (>8ml/kg predicted body weight, maroon) and low (≤8ml/kg predicted body weight, navy) tidal volumes, stratified by the patient's standardized respiratory system elastance (cmH2O/[mL/kg]). Contingent on the interaction (p<0.001) between tidal volume and standardized respiratory system elastance, the adjusted risk estimates with corresponding 95% confidence intervals (CI) for PRCs are presented. The two curves cross at a lung elastance of 1.34 cmH2O/(ml/kg).
2B. Estimated excess risk (95% Confidence Interval) of postoperative respiratory complications in patients who received high (>8ml/kg predicted body weight) compared to low (≤8ml/kg predicted body weight) tidal volumes stratified by the patient's standardized respiratory system elastance (cmH2O/[mL/kg]). In patients with a standardized respiratory system elastance of >1.65 cmH2O/(ml/kg) (red), the estimated risk was higher (up to 5.8%; 95% CI 3.8 to 7.8%; p<0.001) if patients received a high tidal volume compared to a low tidal volume. No significant association was found between high tidal volumes and PRCs in patients with a lung elastance between 0.8 and 1.65 cmH2O/(ml/kg) (blue). Patients with a standardized respiratory system elastance of <0.8 cmH2O/(ml/kg) (green) had a significantly decreased estimated risk of PRCs by as much as -0.6% (95% CI -1.0 to -0.2%; p<0.001), when using high tidal volumes compared to low tidal volumes.

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Trends in Daily Heart Rate Variability among Anesthesia Providers

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INTRODUCTION: Heart rate variability (HRV) is closely linked to cognition, memory, attention, and executive function.[1,2,3] These functions allow us to focus, remember instructions, plan, and multitask, and are critical to the practice of anesthesia. Decreased HRV has been described following physical, emotional, and mental fatigue. Aims: The aim of this study is to observe and report trends in HRV among anesthesia providers from baseline (pre-shift) to end-of-shift. Secondary aims include analyzing the impact of provider characteristics such as age, sex, BMI, smoking/drinking/caffeine consumption on HRV trends as well as trends in additional biophysical markers such as pulse rate variability (PRV), body temperature, and oxygen saturation (SpO2).

METHODS: A total of 61 unique anesthesia providers were randomly selected based upon availability for this prospective, observational study. Each provider underwent, at a minimum, a five-minute baseline recording at the beginning of their shift and an additional 5-minute recording in the afternoon following a minimum 30-minute lunch break. A total of 177 recordings were taken for a total of 546 hours of biophysical monitoring. All baseline and afternoon recordings were taken while the provider was seated, at rest, without cognitive distraction using a TigerTech™ armband monitor consisting of a single limb electrocardiogram (EKG), three photoplethysmography sensors (PPGs), a temperature sensor, and a 9 degree of freedom (9-DOF) inertial measurement unit (IMU), which was used to control for physical movement.

RESULTS: Demographics are presented in Table 1. Providers were a median of 33.5 years old. 45% were male, 77.5% were Caucasian. The median BMI was 24. 49% of providers self-reported regular caffeine consumption, 53% reported alcohol consumption, and the median self-reported nightly sleep duration was 6 hours. HRV analysis is reported in Table 2. Overall, HRV decreased significantly from the morning to the afternoon measurement across all measures of HRV. Age >35 and sleep <6 hours per day were most strongly linked to a decrease in HRV. Surprisingly, BMI and caffeine consumption had little effect on change in HRV. Overall, providers maintained minimal physical exertion and there were no statistically significant changes in SpO2 or temperature.

CONCLUSION: Anesthesia providers displayed statistically significant reductions in HRV from morning to afternoon recording across all measures. Providers over the age of 35 or who slept fewer than 6 hours per night displayed greater reductions in HRV, which may suggest a reduced physiological reserve. These findings may have important scheduling implications such as the need for protected duty-free hours between shifts for providers and perhaps an indication to book complex procedures as first-start cases to maximize cognitive function.

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Table 1. Participant Demographics

Participant Demographics							
Male (%)	Age Med (IQR)	Caucasian (%)	Hispanic (%)	BMI Med (IQR)	Caffeine (%)	Alcohol (%)	Sleep Med (IQR)
45	33.5 (38.5-28.5)	77.5	30	24.05 (26.75-21.35)	48.72	53.11	6 (6.9 – 5.1)

Table 2. Biophysical Monitoring Analysis

			Morning		Afternoon			
			Median	IQR	Median	IQR	%Change	p-value
ECG	**SDNN (ms)**	All	147	(123-189)	138	(95-167)	6.122449	0.003921
		Male	161	(127-197)	143	(98-180)	11.18012	0.044935
		Female	140	(119-178)	121	(85-151)	13.57143	0.03602
		Age < 35	169	(136-206)	150	(126-184)	11.2426	0.013023
		Age > 35	127	(109-150)	98	(80-139)	22.83465	0.038186
		BMI > 25	134	(116-173)	111	(85-157)	17.16418	0.034277
		BMI < 25	164	(136-197)	143	(102-179)	12.80488	0.043737
		Sleep < 6	136	(115-169)	107	(85-142)	21.32353	0.046989
		Sleep > 6	167	(132-205)	154	(114-180)	7.784431	0.02442
	rMSSD (ms)	All	43	(22-61)	31	(21-52)	27.90698	0.003023
		Male	49	(24-68)	43	(22-55)	12.2449	0.029064
		Female	37	(22-52)	26	(21-38)	29.72973	0.034132
		Age < 35	56	(28-68)	43	(28-55)	23.21429	0.043207
		Age > 35	37	(21-43)	24	(20-31)	35.13514	0.015251
		BMI > 25	37	(22-56)	27	(21-36)	27.02703	0.039823
		BMI < 25	49	(28-66)	44	(22-54)	10.20408	0.025283
		Sleep < 6	33	(20-50)	24	(20-39)	27.27273	0.018178
		Sleep > 6	53	(33-69)	43	(27-56)	18.86792	0.043917
	PNN50 (%)	All	17	(9-30)	9	(6-24)	47.05882	1.49E-05
		Male	23	(12-35)	15	(8-24)	34.78261	0.00042
		Female	16	(9-21)	8	(6-16)	50	0.006586
		Age < 35	22	(14-34)	17	(8-24)	22.72727	0.003861
		Age > 35	12	(8-18)	7	(5-9)	41.66667	0.000509
		BMI > 25	14	(9-23)	8	(6-22)	42.85714	0.000139
		BMI < 25	22	(12-38)	14	(6-24)	36.36364	0.023633
		Sleep < 6	23	(9-24)	7	(5-17)	69.56522	0.001093
		Sleep > 6	22	(13-32)	16	(8-24)	27.27273	0.002303
PPG	**SDNN (ms)**	All	147	(125-186)	138	(95-165)	6.122449	0.005171
	rMSSD (ms)	All	43	(23-65)	31	(20-54)	27.90698	0.002864
	pNN50 (%)	All	18	(9-29)	8	(7-24)	55.55556	1.62E-05
Other	**SPO2 (%)**	All	98	(96-100)	98	(96-100)	0	0.795321
	Temp (F)	All	98.6	(97.3-99.4)	98.8	(97.8-99.48)	-0.20284	0.222017

PERIOPERATIVE ANESTHESIA 27

How do you take your coffee before anesthesia? A randomized controlled crossover study comparing gastric emptying with black coffee vs coffee with half and half vs coffee with non-dairy creamer

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INTRODUCTION: An important component in the pre-operative patient evaluation is to determine fasting status to reduce the risk of pulmonary aspiration.[1] The American Society of Anesthesiologists guidelines recommend a minimum fasting period of 6 hours for nonhuman milk and 2 hours for clear liquids including black coffee. The European Society of Anaesthesiology states tea or coffee with some milk could be considered clear fluid but there is not a consensus.[2] About 68% of adults in the United States consume coffee with add-ins such as cream or sugar.[3] This study aims to assess the effects that dairy or sugar additives to coffee will have on gastric emptying via serial ultrasound of the gastric antrum in healthy adults.

METHODS: This randomized controlled crossover study with 3 arms received institutional review board approval and was registered at ClinicalTrials.gov (NCT04786691). One arm was the consumption of 355 ml black coffee. The second was 355 ml coffee with 30 ml of half and half and the third arm was 355 ml coffee with 30 ml of liquid non-dairy coffee creamer. Study volunteers participated in all 3 arms of the study, the order of which was randomized, with a minimum 2-day washout period between each arm (Fig. 1).

A total of 24 volunteers were screened between the ages of 18 and 65. Study participants were excluded if they had a history of diabetes, delayed gastric emptying, previous gastric surgery, lactose intolerance, or current pregnancy (Table 1).

After informed consent, participants were instructed to consume nothing by mouth for 6 hours. The cross-sectional area (CSA) of the gastric antrum was measured using ultrasound with the participant in the right lateral decubitus position which served as the baseline measurement. The participant then consumed one of the 3 coffee options according to the randomization sequence and returned in 2 hours to repeat the gastric antrum ultrasound measurement.

The primary outcome was the difference between gastric volume post coffee consumption compared to the baseline gastric volume which was calculated using the participant's age and CSA (Fig. 2).[4] Descriptive statistics were used for data analysis.

RESULTS: 18 participants completed the study. The mean gastric volume difference was 13 ml (95% CI, -0.6 to 26.6) after black coffee alone, 5 ml (95% CI, -8.6 to 18.6) with half and half, and -1.5 ml (95 CI%, -15 to 12.1) with non-dairy creamer (Table 2, Fig. 3).

CONCLUSION: This pilot study demonstrated no significant difference in gastric volume 2 hours after consumption of black coffee, coffee with half and half, and coffee with non-dairy creamer. These results are consistent with other studies performed in Europe demonstrating no difference in gastric volume with the addition of milk to coffee or tea.[5,6] We used half and half and non-dairy creamer as additives in our study as this is more representative of an American demographic. Further studies with larger sample sizes would be beneficial to determine its applicability to the general population.

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Figure 1. Consort Diagram

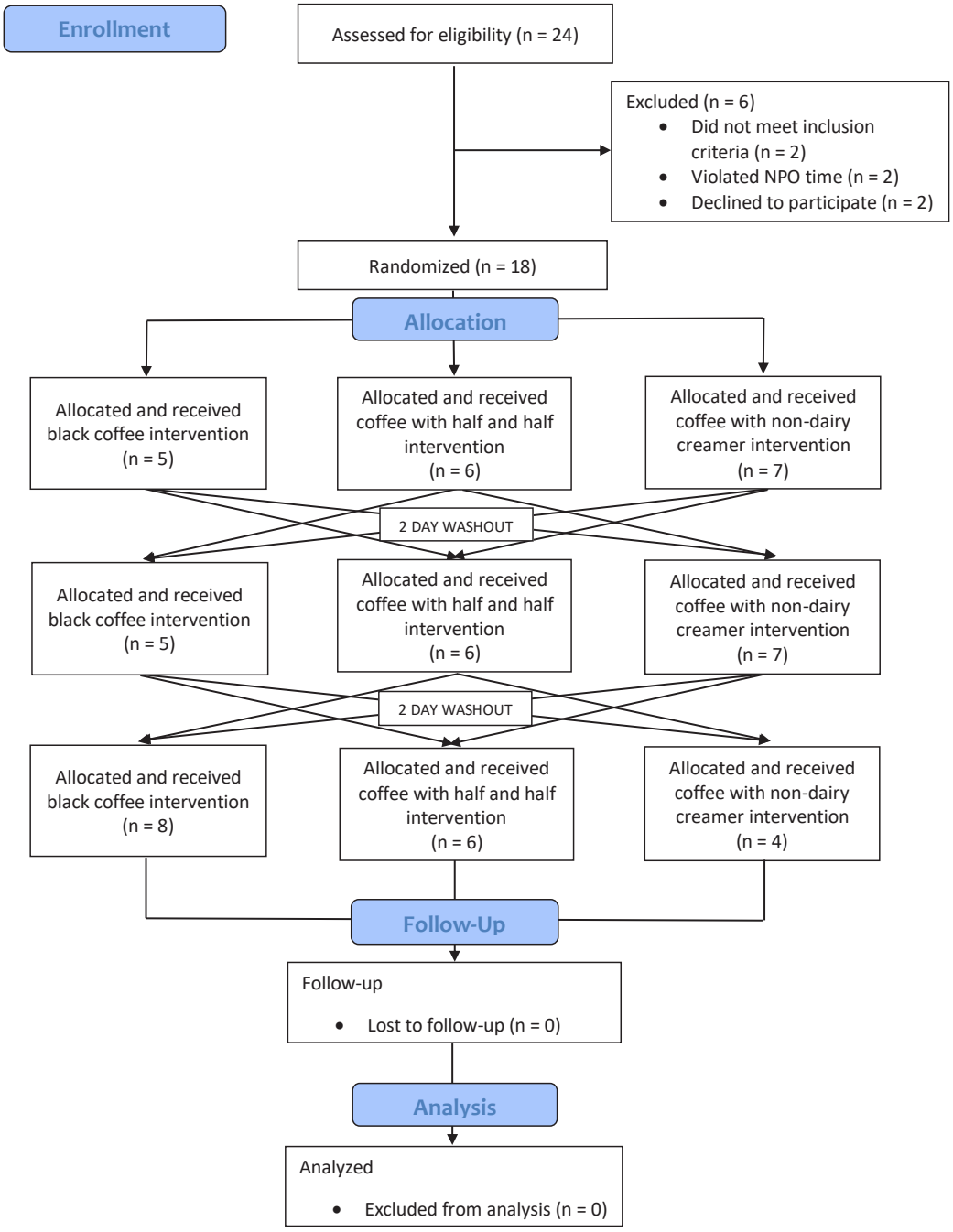


Figure 2. Predictive model equation used to estimate gastric volume

Predictive model used to assess gastric volume using cross-sectional area (CSA) of gastric antrum in the right lateral decubitus position and age. Applicable to non-pregnant adults for gastric volumes up to 500 ml.[4]

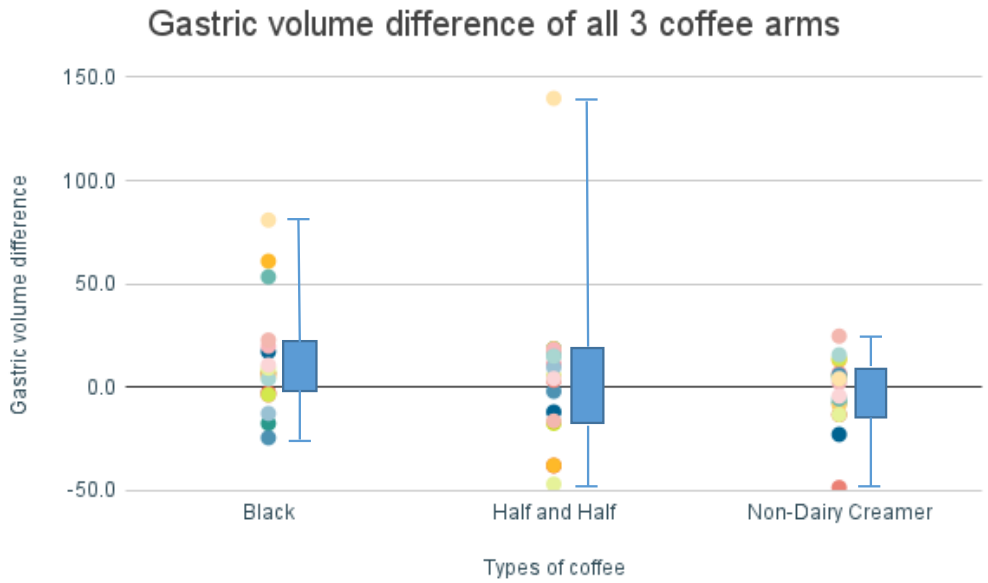
$$\text{GASTRIC VOLUME (ML)} = (27.0 + 14.6 * \text{CSA}) - (1.28 * \text{AGE})$$

Table 1. Characteristics of Participants

	Total Number	Median	Minimum	Maximum	Interquartile Range
Gender (male/female)	7 / 11				
Age (years)	18	34	28	55	30 - 42
Height (cm)	18	166	150	191	165 - 182
Weight (kg)	18	72	50	100	62 - 81
BMI (kg / m^2)	18	24	20	34	23 - 26

Table 2. Difference in gastric volume between all 3 coffee arms

	Mean Difference Gastric Volume (95% CI)	Standard Deviation	Minimum	Maximum
Black coffee	13 (-0.6 to 26.6)	27.4	-24.4	80.9
Half and half	5 (-8.6 to 18.6)	39.6	-46.8	139.8
Non-dairy creamer	-1.5 (-15.1 to 12.1)	16.7	-48.5	24.8



PERIOPERATIVE ANESTHESIA 28

Cognitive and cerebrospinal fluid Alzheimer's Disease biomarker changes over time in older surgical patients and matched nonsurgical controls

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INTRODUCTION: Some older patients have lasting cognitive impairment after anesthesia/surgery,[1,2] though it remains unclear if this cognitive decline is caused by anesthesia/surgery versus whether it simply reflects the natural cognitive trajectory due to other patient risk factors.[2,5,6] Some human studies have found that older adults have altered postoperative CSF levels of AD-related biomarkers, such as tau and p-tau, raising the possibility that perioperative care could contribute to long term cognitive decline by accelerating AD pathogenesis.[6-8] Yet, to our knowledge, no prior study has compared CSF AD-related biomarker and cognitive trajectories over time in surgical patients and matched non-surgical controls.

METHODS: We prospectively enrolled 140 patients age ≥60 years old undergoing major non-cardiac, non-neurologic surgery under general anesthesia for >2 hours, and 51 non-surgical controls who were matched to the surgical cohort based on age, sex, and education via strata-based matching. CSF samples were obtained by lumbar puncture at baseline, 24 hrs, 6 weeks after surgery in surgical patients and at the same time intervals in controls. CSF levels of Aβ42, tau, and phosphorylated tau (p-tau) were measured at according to established methods.[9,10] Cognitive testing was administered at baseline and 6 weeks postoperatively and the cognate time intervals in the control group. Cognitive performance was measured by the continuous cognitive index (CCI),[3] a weighted average of multiple individual tests in our test battery. AD biomarker and CCI trajectories and were compared overall via Friedman's test, and at each time point by Wilcoxon Rank Sum tests.

RESULTS: The surgical and non-surgical groups were well-matched on age, gender, and years of education, yet a higher percentage of the non-surgical controls had baseline CSF biomarker evidence of AD pathology (p=0.002) even though there was no difference in baseline MMSE scores between groups (p=0.577) (Table 1). There was no significant difference between the surgical and control groups in median CSF Aβ42, tau, p-tau, tau/Aβ42, or p-tau/Aβ42 change from baseline to 24 hours, 6 weeks (p>0.05 for all). There was also no difference in CCI change from baseline to 6 weeks later (p>0.05) between the surgical and matched non-surgical control groups (Figure 1). In a multivariate analysis for predictors of CCI change at 6 weeks, there was a significant effect of baseline CCI (p=0.009) but no effect of group (surgical vs non-surgical p=0.159).

CONCLUSION: These findings suggest that non-cardiac, non-neurological surgery does not cause acceleration of AD pathology or cognitive decline. However, accurate comparison of cognitive decline or CSF biomarker changes between surgical and non-surgical patients selected based on demographic matching (i.e. rather than randomization) remains challenging given our finding that groups with matching demographic information may nonetheless have significant differences in preclinical AD pathology.

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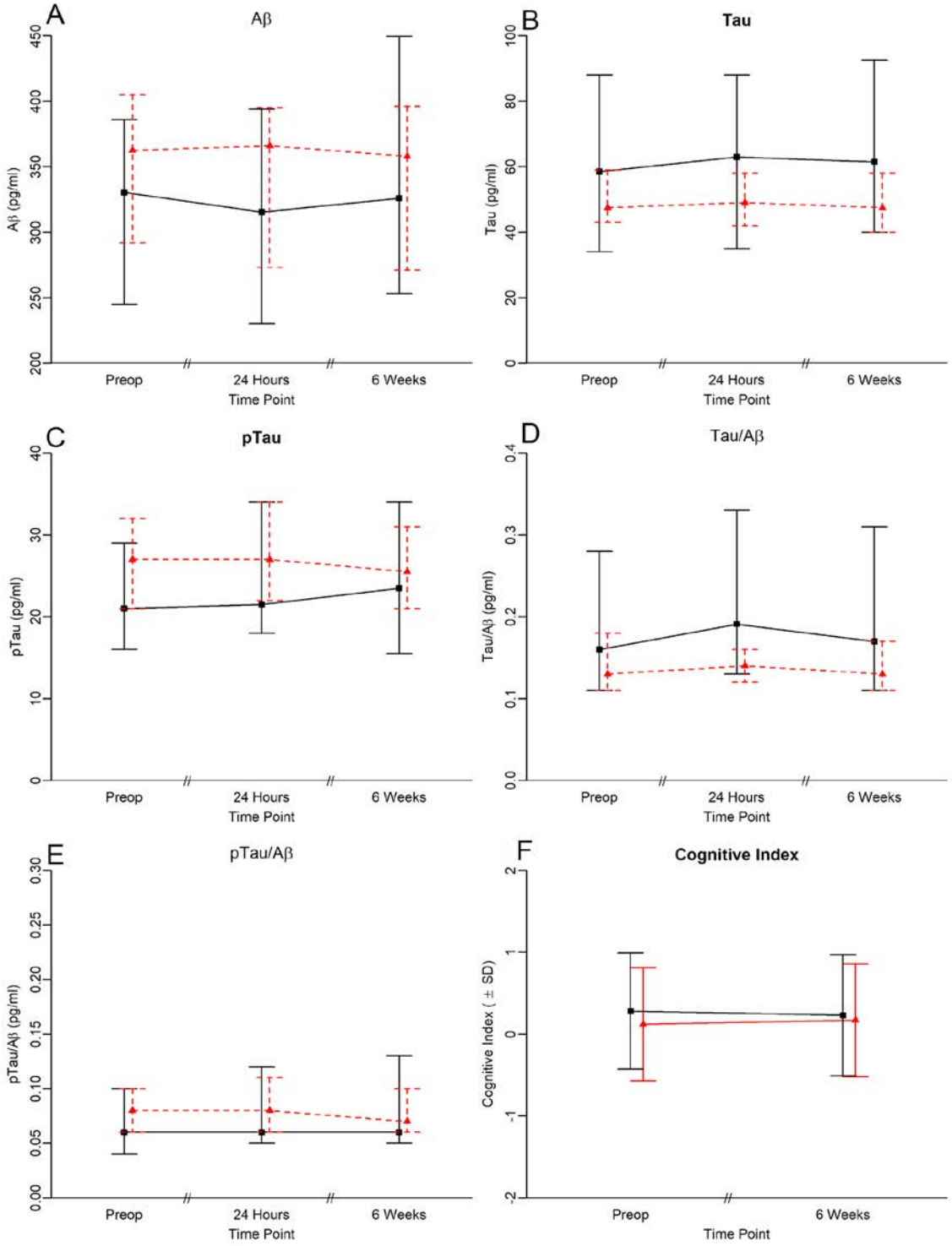
Table 1. Patient Summary

	Surgical (N=107)	Control (N=46)	p value
Patient Demographics			
Age	68 [64, 73]	68 [64, 73]	0.921[1]
White/Caucasian Race	96 (89.7%)	36 (78.3%)	0.059[2]
Male Sex	67 (62.6%)	28 (60.9%)	0.838[2]
Years of Education	16 [13, 18]	16 [14, 18]	0.214[1]
Baseline Cognitive Performance			
BL MMSE	29 [28, 29]	29 [28, 30]	0.577[1]
BL MMSE <25	5 (4.7%)	1 (2.2%)	0.669[4]
Baseline Cognitive Index	0.12 (0.69)	0.28 (0.71)	0.205[3]
Baseline Biomarkers			
APOE4 Positive*	34 (32.1%)	12 (27.9%)	0.618[2]
BL Tau**	47.5 [43.0, 59.0]	58.5 [34.0, 88.0]	0.239[1]
BL p-Tau**	27 [21, 32]	21 [16, 29]	0.006[1]
BL AB**	362.5 [292.0, 405.0]	330.5 [245.0, 386.0]	0.166[1]
BL Tau/AB**	0.13 [0.11, 0.18]	0.16 [0.11, 0.28]	0.306[1]
BL p-Tau/AB**	0.08 [0.06, 0.10]	0.06 [0.04, 0.10]	0.052[1]
Shaw Group**			0.002[4]
A+ | T+	2 (2.0%)	3 (6.5%)	
A+ | T-	15 (15.3%)	10 (21.7%)	
A- | T+	1 (1.0%)	6 (13.0%)	
A- | T-	80 (81.6%)	27 (58.7%)	

[1]Wilcoxon [2]Chi-Square [3]Chi-Square [4]Fisher Exact
*Missing for1 Surgical patient, 3 Control patients
**Missing for 9 Surgical patients

Figure 1. Trends in CSF AD biomarkers and cognitive function



PERIOPERATIVE ANESTHESIA 29

Total Intravenous Anesthesia (TIVA) vs. Inhalational Anesthesia for Cancer Resection: The Anesthesiologist's Perspective

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INTRODUCTION: TIVA and volatile anesthetics are two common techniques used for induction and maintenance of general anesthesia. Strong evidence has shown that TIVA, compared to inhalational anesthesia, offers a more favorable side effect profile in adult patients, including a lower risk of postoperative nausea and vomiting (PONV) by as much as 38%[1], as well as a rapid recovery profile[2]. Some in vitro studies have revealed anti-metastatic effects of the intravenous anesthetic propofol[3]; however conflicting results have been found in clinical studies[4-7]. TIVA is more burdensome to setup and manage by the anesthesiologist, especially in the US where automated TIVA pumps/targeted controlled infusion (TCI) systems have not been approved for perioperative use[8]. Inhalational anesthesia is much more commonly used because of greater familiarity and its ease of setup and monitoring[9]. Inhalational anesthesia, compared to TIVA, has also been shown to offer improved cardiac, pulmonary, and cerebral protection[2,10]. As more evidence begins to emerge on TIVA's indications for use within oncologic surgery, it is crucial to understand anesthesiologists' current landscape of use of TIVA compared to inhalational anesthetics. Information on the factors influencing TIVA's use remains limited. A study conducted by Lim et al. of 275 anesthesiologists conducted in Australia assessed practice patterns and perspectives comparing TIVA and inhalational anesthetics[11]. Another international study of 763 anesthesiologists in Australia, Asia, and Europe assessed factors influencing use of TIVA[9], but no such studies to date have been conducted in the US. There is little insight on the frequency of use of TIVA among anesthesiologists in the US and specifically within oncologic surgery. Our study aims to address this gap in knowledge and investigate TIVA – its practices, perceived benefits, and barriers – compared to inhalation anesthetics among anesthesiologists in designated cancer centers in the US. Ultimately, identifying anesthesiologists' understanding, indications for use and barriers for TIVA will help inform future guidelines and increase TIVA uptake in the profession.

METHODS: Data for this study was collected from a survey conducted between September 2019 and February 2020 and between May 2021 and August 2021. The survey consisted of 21 questions based on the 18-question survey by Lim et al. that was used in a study previously conducted among Australian anesthesiologists.[2] This survey assessed the practice patterns and perspectives of inhalational anesthesia versus TIVA among US anesthesiologists at 10 institutions within the Alliance of Dedicated Cancer Centers. Statistical analyses were performed with R (version 4.1.0, R Foundation).

RESULTS: 281 anesthesiologists were contacted by email. 78 completed the entire survey and were included in the analysis, yielding an overall 27.8% response rate. Physician characteristics are shown in Table 1. Respondents were from the following US regions: New England, Middle Atlantic, East North Central, South Atlantic, West south Central, and Pacific. 1 respondent does not primarily practice in the US. 87.2% of participants practice at a designated cancer center, and 12.8% practice at a university hospital. 84% of respondents practice in an impatient setting, and 16% practice in an outpatient setting. Only 16% of respondents use TIVA for >50% of the cases.

CONCLUSION: Given that evidence remains uncertain if TIVA is the anesthetic of choice for oncologic surgery, anesthesiologists among cancer centers in the US are generally slow to uptake TIVA. The results from this survey also show that patterns of practice among anesthesiologists in the US are like those previously explored among anesthesiologists around the world, but familiarity levels with TIVA may be lower in the US. Given the results of this study, we infer that the usage of TIVA among all US hospitals, considering all surgical cases beyond cancer resections, is even lower than what we have found. Therefore, broadly increasing TIVA uptake poses an even greater challenge and requires more evidence-driven understanding of the benefits of TIVA versus inhalational anesthetics and addressing TIVA's barriers to use. As variations in practice and perspectives remain, prospective randomized control trials would provide stronger evidence to inform a preferred anesthetic method for oncologic surgery and provide improved treatment for cancer patients worldwide.

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Table 1. Demographic Characteristics of Respondents

Characteristic	N = 90
Location of Practice (Within United States)	
New England (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut)	2 (2.5%)
Middle Atlantic (New York, New Jersey, Pennsylvania)	30 (38%)
East North Central (Ohio, Indiana, Illinois, Michigan, Wisconsin)	10 (13%)
West North Central (Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, Kansas)	0 (0%)
South Atlantic (Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida)	8 (10%)
West South Central (Arkansas, Louisiana, Oklahoma, Texas)	23 (29%)
Mountain (Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada)	0 (0%)
Pacific (Washington, Oregon, California, Alaska, Hawaii)	5 (6.3%)
N/A (I do not work in the US)	1 (1.3%)
Unknown	11
Gender	
Female	26 (32%)
Male	51 (64%)
Other (please specify)	3 (3.8%)
Unknown	10
Percentage of Cancer Resection Cases	
Less than 25%	3 (3.8%)
25-50%	11 (14%)
50-75%	6 (7.5%)
More than 75%	60 (75%)
Unknown	10
Institution Type	
Cancer Center	70 (88%)
University Hospital	10 (12%)
Unknown	10
Workplace Setting	
Inpatient	68 (85%)
Outpatient	12 (15%)
Unknown	10
Year of Anesthesia Training Completion	
Prior to 1980	2 (2.5%)
1980-1984	4 (5.0%)
1985-1989	3 (3.8%)
1990-1994	10 (12%)
1995-1999	8 (10%)
2000-2004	10 (12%)
2005-2009	13 (16%)
2010-2014	21 (26%)
2015 or later	9 (11%)
Unknown	10

Figure 1. Percentage of Cancer Resection Cases using TIVA

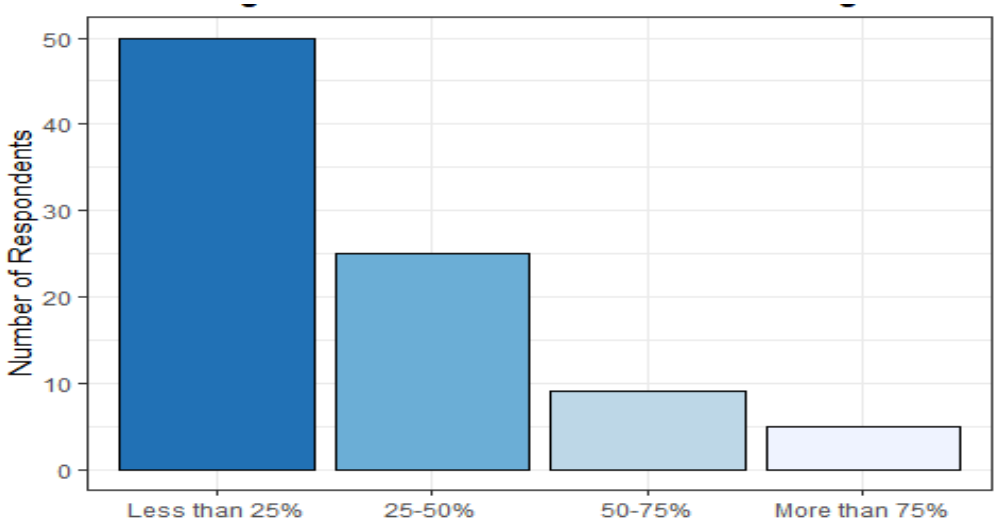


Figure 2. Technical Aspects of TIVA vs Inhalational Anesthetics

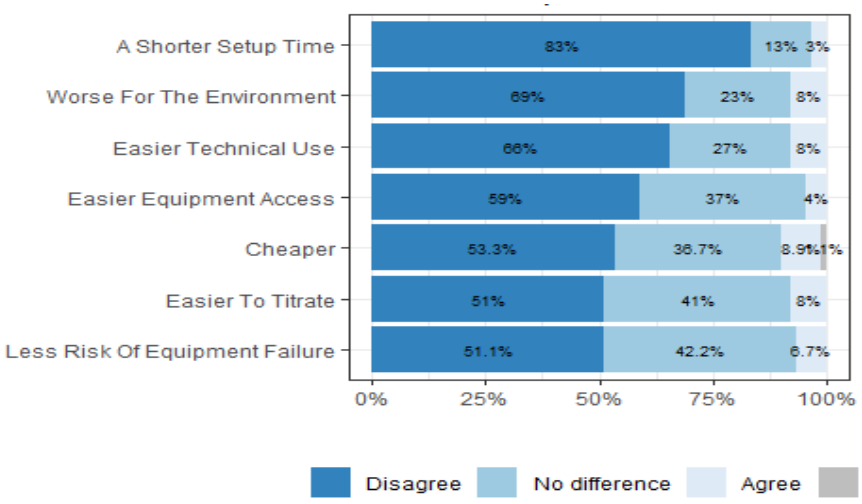


Figure 3. Barriers to TIVA use

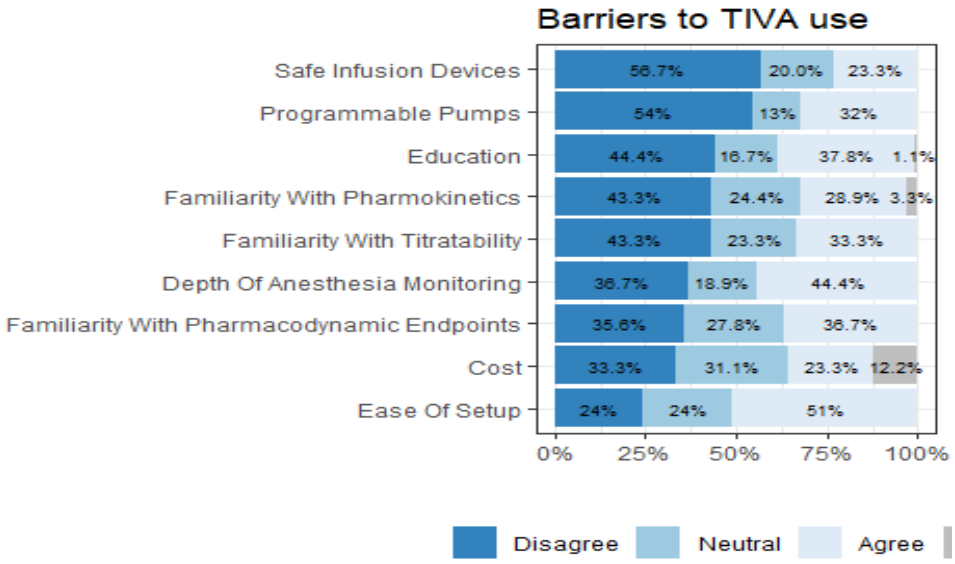


Figure 4. TIVA Usage in Clinical Settings

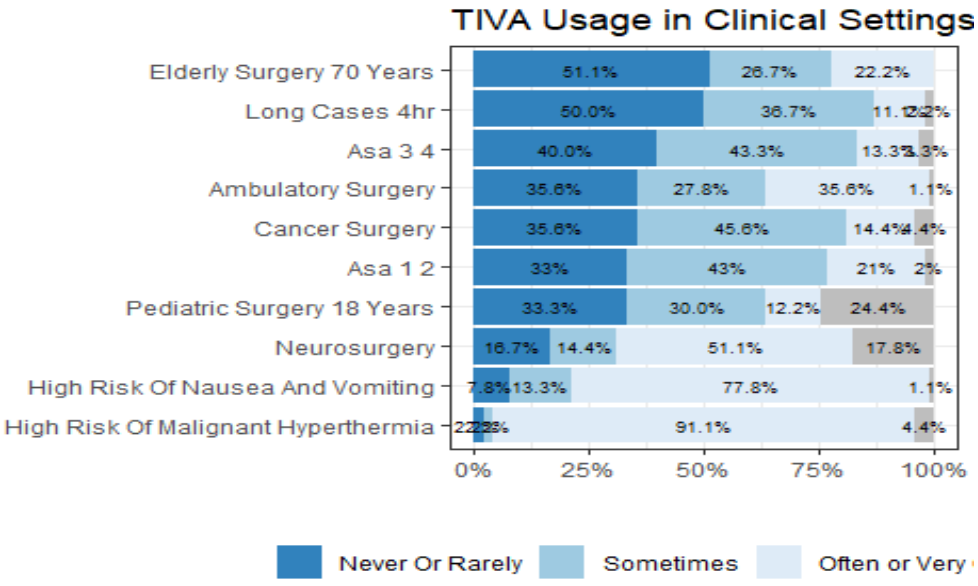


Figure 5. Clinical Impact of TIVA vs. Inhalational Anesthetics

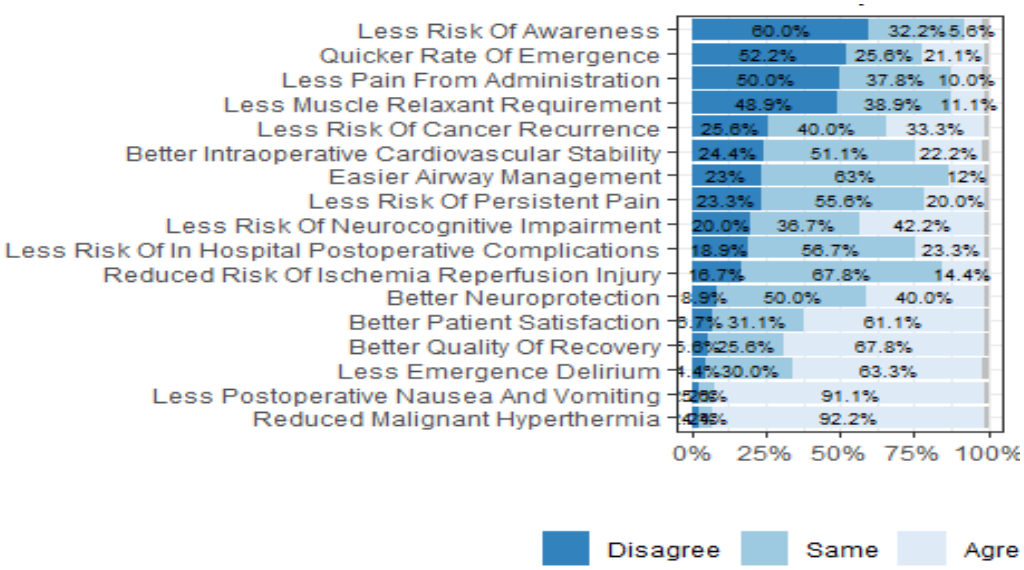
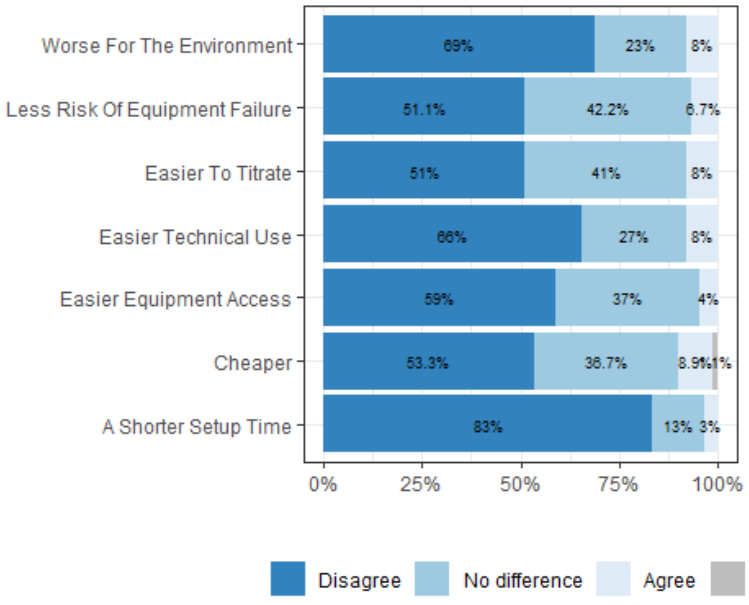


Figure 6. TIVA Perspectives



PERIOPERATIVE ANESTHESIA 30

Socioeconomic factors, psychiatric disorders and substance abuse associated with cannabinoid use in surgical patients

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INTRODUCTION: Recreational and medical use of cannabinoids has steadily increased over the past decade and was accelerated by the legalization of medical cannabinoids in 2012 and for recreational purposes in 2016 in Massachusetts[1]. Previous studies in non-surgical populations suggested that the use of cannabinoids is associated with an increased incidence of psychiatric disease, neuropsychological decline, and a higher risk of adverse cardiovascular and cerebrovascular events[2-4]. There is little information about relevant other factors including socioeconomic variables associated with cannabinoid use in patients undergoing surgery. We tested the hypothesis that use of cannabinoids in surgical patients is associated with household income, psychiatric disease, and concomitant substance abuse. We further investigated whether the prevalence of cannabinoid use in surgical patients increased in the period after legislative changes in Massachusetts in 2012 and again after 2016.

METHODS: Adult patients undergoing anesthesia care at a tertiary academic healthcare network in Boston (Massachusetts, USA) between 2006 and 2020 with available procedural data and pre-admission or pre-procedural notes were included in this study. Cannabinoid use before surgery was defined as recreational use of marijuana and other cannabinoids identified based on physician and nursing notes from structured patient interviews during pre-admission or pre-procedural testing, abuse was identified through International Classification of Disease Ninth and Tenth revision diagnostic codes, or prescription of medical cannabinoids. In the primary analysis, we compared estimated household income[5], disorders of the schizoaffective spectrum based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) classification and concomitant substance abuse of alcohol, medications, as well as intravenous and other drugs between patients with and without cannabinoid use[6]. We then investigated whether the prevalence of cannabinoid use increased in the period between 2012 and 2016, and 2017 to 2020 as compared to before 2012 in a multivariable logistic regression model encompassing the aforementioned variables as well as patient demographics, other socioeconomic factors and comorbidities. Standardized differences and odds ratios with 95% confidence intervals are reported with alpha set to 0.05. A standardized difference ≥ 0.1 was considered as clinically relevant threshold. All analyses were performed in Stata (Version 16, StataCorp, TX, USA).

RESULTS: Among 338,839 patients undergoing surgery included in this study, 27,462 (8.1%) patients were identified who consumed cannabinoids. Most of these patients used non-medical cannabinoids (Figure 1). Patients with reported cannabinoid abuse had a 15.5% lower estimated household income ($p<0.001$), a higher prevalence of psychiatric disorders (30.21% versus 19.6%; $p<0.001$) and a higher incidence of concomitant substance abuse (9.7 % versus 3.0%; $p<0.001$, Table 1). Compared to recreational cannabinoid users, patients with medical cannabinoid prescriptions were on average older, more often female with a higher comorbidity load, including higher rates of cancer and psychiatric disorders (Table 2). The preoperative use of cannabinoids increased steadily throughout the study period (Figure 2). In the period of 2006 to 2011, 6.0% of patients consumed cannabinoids, as opposed to 7.7% in the period after legislation of medical cannabinoids between 2012 and 2016, and 11.7% between 2017 and 2020 after legislation of recreational cannabinoids. The increase of cannabinoid use between 2017 and 2020 remained robust in adjusted analyses in a subgroup of patients with available data for all variables (n = 62,864, ORadj 1.65; 95% CI 1.48-1.83; $p<0.001$ for the period after 2017-2020; (ORadj 1.31; 95% CI 1.20-1.43; $p<0.001$ for 2012-2016, both compared to before 2012).

CONCLUSION: Based on our data, patients presenting for surgery and anesthesia who use cannabinoids have a higher prevalence low household income and more often present with concomitant substance abuse and schizoaffective spectrum disorders comorbidities including depression and anxiety. Studies investigating the implications of cannabinoid use on postoperative outcomes should consider these factors to substantiate potential effects of cannabinoids.

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Figure 1. Study Cohort.

ASA, American Society of Anesthesiologists.

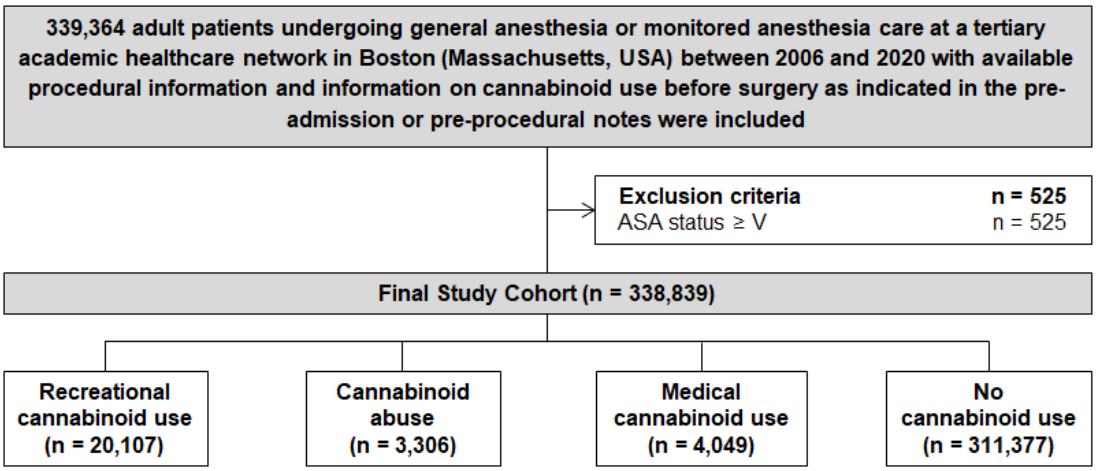

Figure 2. Cannabinoid use over time.

Cannabinoid use over time. Vertical line depicts legalization of medical and recreational cannabinoids in the state of Massachusetts.

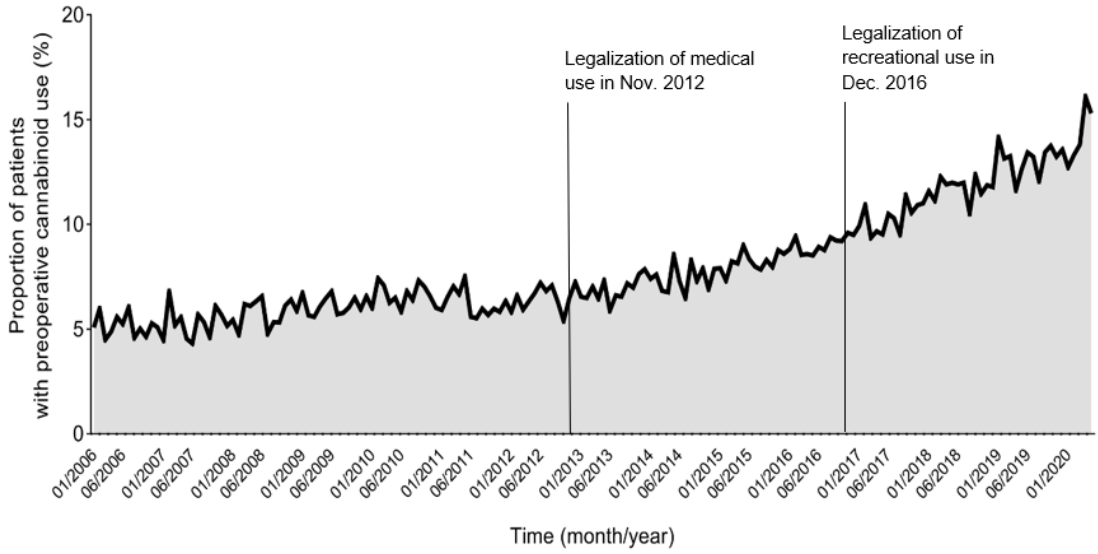

Table 1. Cohort Characteristics compared between patients who used and did not use cannabinoids.

ASA, American Society of Anesthesiologists; USD, United States Dollar; ENT, Ear, Nose, and Throat.

Characteristics	No cannabinoid use (n = 311,377)	Cannabinoid use (n = 27,462)	Standardized difference
Demographics			
Age	56.0 ± 16.5	47.6 ± 15.9	0.519
Sex, female	181,390 (58.3%)	11,318 (41.2%)	0.346
Body mass index, kg/m^2	28.4 ± 6.78	27.9 ± 6.74	0.073
ASA physical status			-0.015
I	39,139 (12.6%)	3,385 (12.3%)	
II	146,415 (47.0%)	12,553 (45.7%)	
III	107,567 (34.5%)	10,093 (36.8%)	
IV	18,256 (5.9%)	1,431 (5.2%)	
Ethnicity and Race*			-0.048
Asian	12,252 (4.7%)	211 (1.0%)	
Black	27,775 (10.7%)	3,115 (14.3%)	
Hispanic	15,595 (6.0%)	1,115 (5.1%)	
Other	11,117 (4.3%)	904 (4.1%)	
Two or more	380 (0.1%)	45 (0.2%)	
White	191,737 (74.1%)	16,451 (75.3%)	
Socioeconomic factors			
Estimated household income*, USD	68,932 (39,051)	58,274 (38,883)	0.273
Federal Insurance	101,271 (32.7%)	8,362 (30.6%)	0.044
Education Level*			0.084
No education	271 (0.4%)	6 (0.1%)	
Attended high school	4,660 (7.0%)	420 (5.9%)	
Graduated high school	21,458 (32.4%)	2,656 (37.1%)	
Attended college	12,919 (19.5%)	1,661 (23.2%)	
Graduated college	26,924 (40.7%)	2,414 (33.7%)	
Marital Status*			-0.252
Divorced	19,930 (6.8%)	1,928 (7.4%)	
Life Partner	346 (0.1%)	64 (0.2%)	
Married	162,118 (55.0%)	9,164 (35.1%)	
Separated	3,817 (1.3%)	387 (1.5%)	
Single	88,105 (29.9%)	13,864 (53.1%)	
Widowed	20,459 (6.9%)	686 (2.6%)	
Preoperative Factors			
Admission type*			-0.063
Ambulatory	177,169 (57.5%)	14,862 (69.0%)	
Same-day admission	91,797 (16.7%)	8,243 (18.7%)	
Inpatient	38,404 (1.0%)	3,995 (1.3%)	
Emergency surgery	19,165 (6.2%)	2,060 (7.5%)	-0.053

Table 2. Cohort characteristics compared between medical versus non-medical cannabinoid use.

ASA, American Society of Anesthesiologists; USD, United States Dollar; ENT, Ear, Nose, and Throat.

Characteristics	Medical cannabinoid use (n = 4,308)	Non-medical cannabinoid use (n = 23,154)	Standardized difference
Demographics			
Age	57.7 ± 14.3	45.7 ± 15.5	0.800
Sex, female	2,392 (55.5%)	8,926 (38.6%)	0.345
Body mass index, kg/m^2	26.6 ± 6.4	28.1 ± 6.8	-0.221
ASA physical status			0.674
I	75 (1.7%)	3,310 (14.3%)	
II	1,356 (31.5%)	11,197 (48.4%)	
III	2,453 (56.9%)	7,640 (33.0%)	
IV	424 (9.8%)	1,007 (4.3%)	
Ethnicity and Race*			0.107
Asian	81 (2.1%)	130 (0.7%)	
Black	432 (11.4%)	2,683 (14.9%)	
Hispanic	117 (3.1%)	998 (5.5%)	
Other	117 (3.1%)	787 (4.4%)	
Two or more	4 (0.1%)	41 (0.2%)	
White	3,023 (80.1%)	13,428 (74.3%)	
Socioeconomic factors			
Estimated household income*, USD	66,044 (40,317.6)	56,838 (38,441.8)	0.233
Federal Insurance	1,787 (41.7%)	6,575 (28.6%)	0.277
Education Level*			0.225
No education	1 (0.1%)	5 (0.1%)	
Attended high school	64 (4.9%)	356 (6.1%)	
Graduated high school	423 (32.2%)	2,233 (38.2%)	
Attended college	238 (18.1%)	1,423 (24.3%)	
Graduated college	586 (44.7%)	1,828 (31.3%)	
Marital Status*			
Divorced	323 (7.6%)	1,605 (7.3%)	-0.228
Life Partner	8 (0.2%)	56 (0.3%)	
Married	2,084 (49.2%)	7,080 (32.4%)	
Separated	56 (1.3%)	331 (1.5%)	
Single	1,482 (35.0%)	12,382 (56.6%)	
Widowed	280 (6.6%)	406 (1.9%)	
Preoperative Factors			
Admission type*			0.239
Ambulatory	2,007 (47.1%)	12,855 (56.3%)	
Same-day admission	1,308 (30.7%)	6,935 (30.4%)	
Inpatient	948 (22.2%)	3,047 (13.3%)	
Emergency surgery	343 (8.0%)	1,717 (7.4%)	0.020

PERIOPERATIVE ANESTHESIA 31

Association between cannabinoid use and stroke after surgery: A retrospective cohort study

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INTRODUCTION: An increasing number of patients who present for surgery reports use of cannabinoids for recreational or medical purposes, which was accelerated by its legalization in various states throughout the United States[1]. Retrospective studies in non-surgical patients who consume cannabinoids for recreational purposes suggested neurotoxic effect of cannabis on the adolescent brain[2] and an increased risk of acute ischemic stroke requiring hospitalization[3]. It is unclear whether patients with cannabinoid use are also at higher risk of stroke after surgery. Previous studies were limited to patients with cannabinoid abuse identified by International Classification of Disease Ninth and Tenth revision (ICD-9/10) diagnostic codes, as well as in their ability to control for important demographic and socioeconomic confounding variables[4]. In this study, we evaluated whether cannabinoid use for medical or recreational purposes is associated with postoperative ischemic stroke within 1 year after surgery using data from a large hospital network in New England.

METHODS: Adult patients undergoing non-cardiac surgery at a tertiary academic healthcare network in Boston (MA, USA) between 2006 and 2020 with available pre-admission or pre-procedural notes were included in this hospital registry study. Recreational use of cannabinoids was identified based on physician and nursing notes from structured patient interviews during pre-admission or pre-procedural testing, ICD-9/10 diagnostic codes of cannabinoid abuse, or prescriptions of medical cannabinoids. The primary outcome was a diagnosis of ischemic stroke within 1 year after surgery. Multivariable logistic regression analysis adjusted for a priori defined factors including patient demographics, socioeconomic factors, concomitant substance abuse, markers of procedural severity and comorbidities including patient's baseline risk of stroke based on the STRoke After Surgery (STRAS) prediction score (5) was applied. In secondary analyses, we differentiated the risk of postoperative ischemic stroke by types of cannabinoid use (recreational use, medical use, and abuse of cannabinoids) and investigated whether a high baseline stroke risk based on the STRAS prediction model modified the association between cannabinoid use and postoperative ischemic stroke. Exact matching for age (± 2 years) and sex at a 1:3 ratio was performed in sensitivity analyses. Standardized differences and odds ratios with 95% confidence intervals are reported. A P-value <0.05 was considered as statistically significant. All analyses were performed in Stata (Version 16, StataCorp, TX, USA).

RESULTS: Among 308,077 included patients (Figure 1), 25,264 (8.9%) used cannabinoids for recreational or medical purposes. 2,651 (0.8%) patients had a diagnosis of stroke within one year after surgery, of which 197 (0.8%) used cannabinoids and 2,454 (0.9%) did not. The incidence of postoperative stroke increased with patient age (Table 1, Figure 2). After adjusting for confounding factors, cannabinoid use was not significantly associated with postoperative ischemic stroke (adjusted OR [ORadj] 0.91; 95% CI 0.77–1.06; p=0.25; Table 2), independent of as to whether the patients used the drug recreationally or based on a medical indication (Table 3). This finding was not modified by the predicted risk of postoperative stroke (P-for-interaction=0.31). Sensitivity analyses conducted in a sub-cohort matched for sex and age (± 2 years) confirmed the primary findings (ORadj 0.96; 95% CI 0.79–1.16; p=0.69).

CONCLUSION: Cannabinoid use is not associated with an increased risk of ischemic stroke within one year after surgery.

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Figure 1. Study cohort.

ASA, American Society of Anesthesiologists. STRAS, STRoke After Surgery.

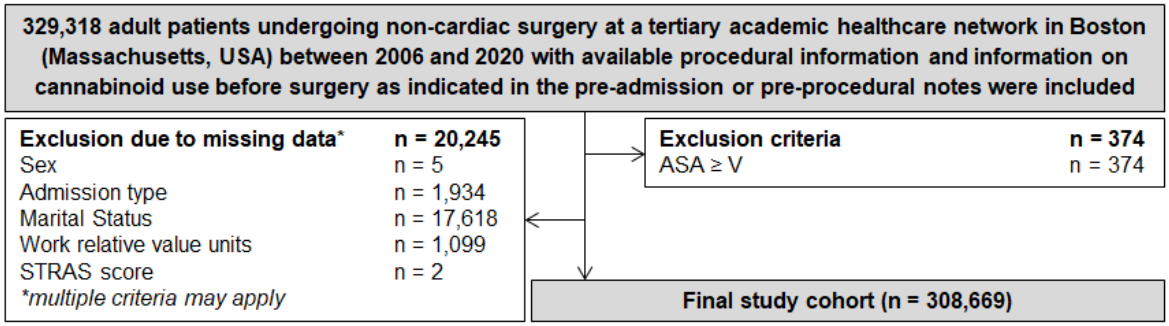

Figure 2. Cannabinoid use and stroke by age and sex.

Prevalence of cannabinoid use (left y-axis) and stroke within 1 year after surgery (right y-axis) by patient age and sex.

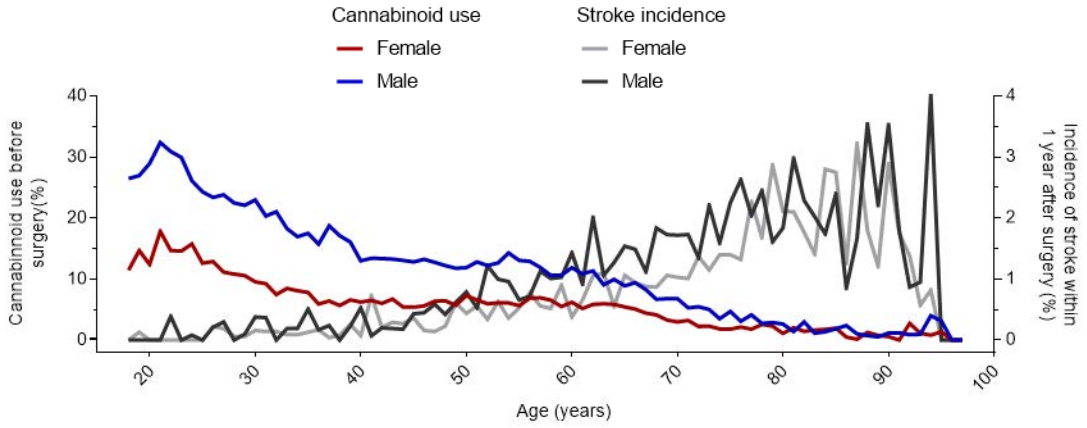

Table 1. Baseline characteristics.

ASA, American Society of anesthesiologists; USD, United States Dollar; ENT, Ear, Nose, and Throat.

Characteristics	No Stroke (n = 306,681)	Stroke within 1 year (n= 25,264)	Standardized difference
Demographics			
Age, years	55.24 ± 16.42	66.52 ± 12.84	-0.765
Sex, female	176,817 (57.8%)	1,227 (46.3%)	0.232
Body mass index (BMI), kg/m^2	28.34 ± 6.83	27.99 ± 6.03	0.055
ASA physical status			-1.014
I	37,974 (12.4%)	10 (0.4%)	
II	148,509 (48.6%)	449 (16.9%)	
III	107,465 (35.2%)	1,794 (67.7%)	
IV	11,733 (3.8%)	398 (15.0%)	
Ethnicity and race			0.053
Asian	11,933 (4.5%)	85 (3.6%)	
Black	29,546 (11.2%)	341 (14.5%)	
Hispanic	15,856 (6.0%)	162 (6.9%)	
Other	11,245 (4.2%)	69 (2.9%)	
Two or more	412 (0.2%)	0 (0.0%)	
White	195,664 (73.9%)	1,691 (72.0%)	
Socioeconomic factors			
Estimated household income, USD	68,413 ± 39,074	64,043 ± 39,977	0.110
Federal Insurance	98,345 (32.2%)	1,470 (55.5%)	-0.482
Education Level			0.157
No education	241 (0.4%)	12 (1.2%)	
Attended high school	4,493 (6.9%)	87 (8.4%)	
Graduated high school	21,121 (32.6%)	386 (37.2%)	
Attended college	12,965 (20.0%)	202 (19.5%)	
Graduated college	26,000 (40.1%)	350 (33.8%)	
Marital Status			-0.001
Divorced	20,727 (6.8%)	252 (9.5%)	
Life Partner	382 (0.1%)	2 (0.1%)	
Married	162,612 (53.2%)	1,337 (50.4%)	
Separated	4,009 (1.3%)	48 (1.8%)	
Single	98,336 (32.2%)	687 (25.9%)	
Widowed	19,615 (6.4%)	325 (12.3%)	
Preoperative factors			
Admission type			-0.557
Ambulatory	179,225 (58.6%)	911 (34.4%)	
Same-day admission	90,274 (29.5%)	964 (36.4%)	
Inpatient	36,182 (11.8%)	776 (29.3%)	
Emergency surgery	18,586 (6.1%)	278 (10.5%)	-0.160
Intraoperative factors			
Duration of surgery, min	118.85 (98.24)	127.77 (98.96)	-0.090
Work relative value units	11.23 (8.88)	13.78 (11.19)	-0.251

Table 2. Results of the primary analysis.

	No Cannabinoid use (n = 280,113)	Cannabinoid use (n = 25,219)	Unadjusted Analysis		Adjusted Analysis	
			OR 95% CI	P-value	OR 95% CI	P-value
Stroke within 1 year	2,245 (0.9%)	197 (0.8%)	0.90 0.78–1.04	0.158	0.91 0.78–1.07	0.25

Data are expressed as frequency (prevalence in %). Statistical analyses were performed using multivariable logistic regression. Odds ratios (OR) are reported for multivariable logistic regression analyses.

Table 3. Results of multivariable logistic regression with categorized exposure.

Cannabinoid use	No stroke (n = 305,681)	Stroke within 1 year (n = 2,651)	Unadjusted Analysis		Adjusted Analysis	
			OR 95% CI	P-value	aOR 95% CI	P-value
No use	280,659 (99.1%)	2,454 (0.9%)	Reference		Reference	
Recreational use	18,160 (99.4%)	116 (0.6%)	0.73 0.61–0.88	0.001	0.91 0.74–1.11	0.35
Abuse	2,795 (99.2%)	23 (0.8%)	0.94 0.62–1.42	0.77	0.73 0.47–1.14	0.16
Medical use	4,067 (98.6%)	58 (1.4%)	1.63 1.25–2.12	<0.001	1.20 0.90–1.58	0.22

Data are expressed as frequency (incidence in %). Statistical analyses were performed using multivariable logistic regression. Unadjusted odds ratios (OR) and adjusted odds ratios (aOR) are reported from multivariable logistic regression analyses.

PERIOPERATIVE ANESTHESIA 32

Metabolic flexibility in patients undergoing Radical Cystectomy

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INTRODUCTION: Aerobic fitness predicts the development of postoperative complications[1]. Preoperative cardiopulmonary exercise testing (CPET) is used to stratify patients' ability to handle the physiological demands of surgery and post-operative recovery. A preoperative ventilatory anaerobic threshold (AT) of <11 mL/min/Kg in patients listed for radical cystectomy predicts an increased length of stay and the development of postoperative morbidity[2,3]. The underlying mechanisms linking reduced aerobic fitness to the development of postoperative morbidity are not well described. Aerobic exercise capacity hinges on mitochondrial function, and efficiency of substrate usage. Lipid oxidation during exercise is a surrogate of mitochondrial function and is increasingly being proposed as a marker of metabolic and cellular health[4,5]. Whole body fat oxidation during exercise has been associated with insulin sensitivity, metabolic flexibility, and reductions in factors associated with metabolic risk[6]. The relationship between established metabolic inflexibility and the metabolic response to surgery is unknown. The primary objective of this pilot study was to describe the relationship between lipid and carbohydrate oxidation derived from metabolic cart data during CPET and aerobic fitness in patients with bladder cancers listed to undergo radical cystectomy. The secondary objective was to establish if any relationship exists between preoperative and postoperative lipid and carbohydrate oxidation in higher and low fitness individuals.

METHODS: In this prospective observational study 18 patients underwent fasted CPET on a bicycle ergometer preoperatively and within 12 weeks after radical cystectomy at Duke University Medical Centre, Durham, NC. CPET consisted of a 5-minute warmup followed by a 5,10, 15 or 25 watt/minute ramp protocol dependent on gender, age and activity level to peak oxygen consumption (VO2 peak). Oxygen consumption and CO2 production were measured by metabolic cart (COSMED Quark). Fat and glucose oxidation (FATox, CHOox) were calculated using stoichiometric equations up to ventilatory anaerobic threshold (VAT) [7]. Cohorts were separated according to perioperative risk by ventilatory anaerobic threshold (< 12 mls/O2/kg and > 12 mls/O2/kg)[3]. Comparison between before and after surgery and between AT groups was carried out using Student's t-test and one- way ANOVA/MANOVA as appropriate. Significance was set at $P < 0.05$.

RESULTS: 10 patients had an VAT of ≥ 12 mls/O2/kg (higher fitness) and 8 had an VAT of < 12 mls/O2/kg (lower fitness). Demographic data is presented in Table 1. Peak VO2 did not change in either group from pre to post surgery, higher fitness group (1290 mL/min vs 1219 mL/min p =0.4502) and lower fitness group (842mL/min vs 975 mL/min p=0.0860). Longitudinal FATox and CHOox were different between higher and lower fitness groups both pre and postoperatively (p=<0.05) Figure 1. Maximal fat ox in the higher fitness group increased from pre to post operatively (0.264 ± 0.013 gram/min vs. 0.272 ± 0.017 gram/min, p=<0.0001). This was also the case in the lower fitness group (0.112 ± 0.01 gram/min vs 0.128 ± 0.009 gram/min, p=<0.0001).

CONCLUSION: While overall fuel utilization as determined by stoichiometric equations did not differ significantly pre to one month post operatively in either the low or higher fitness cohorts, significant differences in terms of FATox were observable at both time points between cohorts. Importantly, the lower fitness group appeared to demonstrate metabolic inflexibility, with both an abnormal pattern of fat oxidation with increasing metabolic demand and reduced maximal fat oxidation. This has important potential implications for this population's ability to respond to conditional changes in metabolic demand, such as those expected in the perioperative period and raises a novel paradigm to be investigated in terms of unpicking the relationship between fitness and surgical outcome. The improvement in MFO postoperatively in both cohorts may reflect systemic metabolic changes consequent to removal of the tumor [8] and may also have important implications for tumor free survival. Importantly, targeted nutritional and exercise interventions have, in other contexts, been demonstrated to ameliorate metabolic inflexibility and improve outcomes and may therefore be applicable to the perioperative space.

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	Ventilatory Anaerobic threshold >12 group	Ventilatory Anaerobic threshold <12 group
Age, Median (IQR)	67 (63 - 73)	75 (68 - 82)
Sex		
Male	10	7
Female	0	1
BMI, Median (IQR)	27.7 (26.4 – 33.2)	30.2 (23.6 – 38.1)

Table 1. Demographic data of higher fitness group <12 mls/O_2/kg and lower fitness group VAT >12 mls/O_2/kg

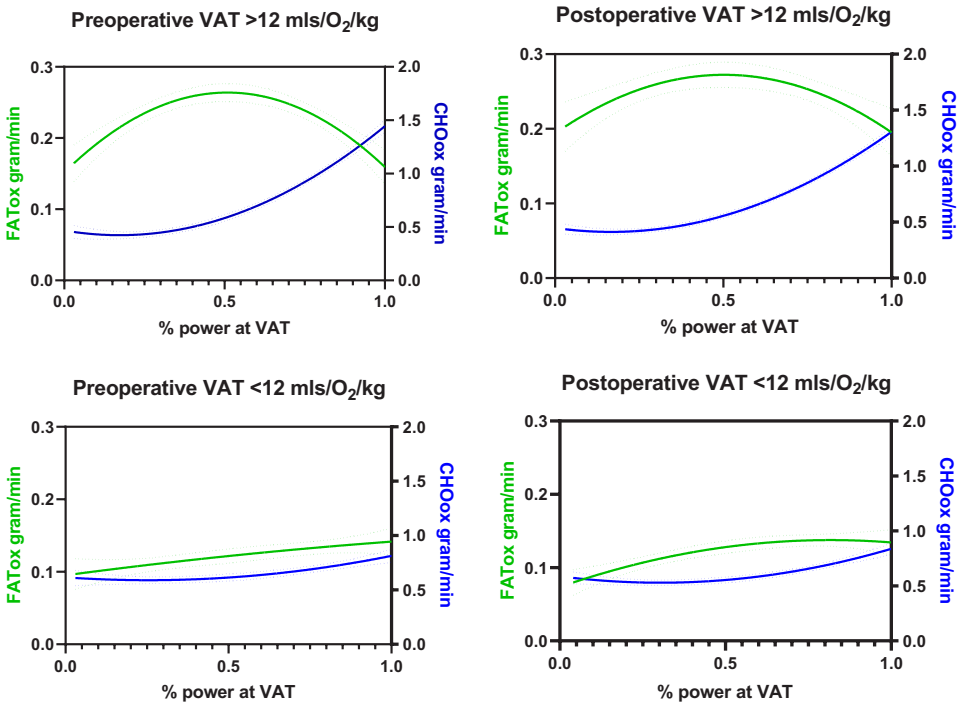

Figure 1. Relationships between fat oxidation (FATox) and Carbohydrate oxidation (CHOox) as a function of power output during ramped cardiopulmonary exercise testing in surgical patients around radical cystectomy. Longitudinal data for FATox & CHOox are presented as fitted regression curves (locally weighted scatter plot smoothing, with a 10-point smoothing window, mean,sd). AT = Ventilatory anaerobic threshold

PERIOPERATIVE ANESTHESIA 33

Oxygen Administration during Surgery and Postoperative Organ Injury

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INTRODUCTION: Patients undergoing surgery frequently receive a greater amount of supplemental oxygen than required to maintain normal oxygen levels in the blood.[1] Whether the administration of excess supplemental oxygen is associated with organ injury is uncertain. We examined whether excess oxygen administration during surgery is associated with postoperative kidney, heart, and lung injury.

METHODS: We conducted an observational cohort study of patients drawn from 42 medical centers across the United States participating in the Multicenter Perioperative Outcomes Group data registry. Eligible patients included adults undergoing surgery of 120 minutes or longer, with general anesthesia and endotracheal intubation, and who were admitted to the hospital after surgery between January 2016 and November 2018. Minute-to-minute data for the fraction of inspired oxygen (FIO2) and non-invasively measured hemoglobin oxygen saturation (SpO2) data were used to calculate excess oxygen administration, defined as the area under the curve of the FIO2 above air (21%) during minutes when the SpO2 was greater than 92% (AUC FIO2). Co-primary endpoints were acute kidney injury, myocardial injury following noncardiac surgery, and lung injury. The association between excess oxygen administration (AUC FIO2) and each of the co-primary endpoints was evaluated using multivariable logistic regression, adjusting for pre-specified baseline covariates and other potential confounding variables. A detailed pre-specified sensitivity analysis was undertaken, redefining the exposure variable (AUCFIO2), restricting the cohort, and conducting an instrumental variable analysis.

RESULTS: The cohort comprised 350,647 cases (median [interquartile range] age, 59 [46-69] years; 51.5% women; duration of surgery, 205 [158-279] minutes). Acute kidney injury was diagnosed in 19,256 cases (5.8%), myocardial injury in 10,323 (2.9%), and lung injury in 14,430 (4.1%). The median FIO2 was 54.0 (47.5-60.0) %, and the area under the curve of the fraction of inspired oxygen was 7,951 (5,870-11,107) %•minutes. After accounting for baseline covariates and other potential confounding variables, greater excess oxygen administration was independently associated with a higher risk of acute kidney injury, myocardial injury, and lung injury: compared to patients at the 25th percentile for the area under the curve of the fraction of inspired oxygen patients at the 75th percentile had 26% greater odds of acute kidney injury (95% CI: 21-30%), 11% greater odds of myocardial injury (95% CI: 6-16%), and 13% greater odds of lung injury (95% CI: 12-16%) [Figure 1]. Our findings were generally robust to a detailed, pre-specified sensitivity analysis.

CONCLUSION: Greater excess oxygen administration during surgery was independently associated with a higher incidence of renal, cardiac, and pulmonary injury. A large clinical trial to detect small but clinically significant effects on organ injury and patient-centred outcomes is needed to guide oxygen administration during surgery.

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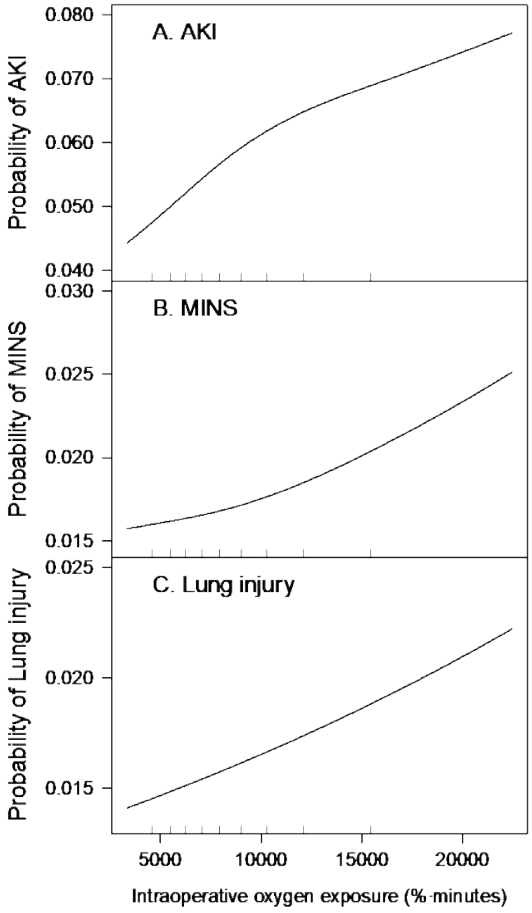
Figure 1. Independent association between intraoperative oxygen exposure and **A**. acute kidney injury (AKI), **B**. myocardial injury following non-cardiac surgery (MINS), and **C**. lung injury. Tick marks on the x-axis identify each decile of cases.



PERIOPERATIVE ANESTHESIA 34

Pain Management As An Element Of Enhanced Recovery After Surgery (ERAS) In Bariatric Surgery: A Systematic Review Of Randomized Control Trials

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INTRODUCTION: Perioperative pain management is instrumental to enhanced recovery, prevention of post-surgical complications, reduction in length of hospital stay and improved patient comfort[1]. Pain is the most common reported problem by patients after bariatric surgery[2]. Adequate pain control perioperatively in patients with obesity is vital albeit challenging. The addition of opioid-sparing multimodal approaches and regional blocks are possible solutions[3]. This study aims to explore the evidence surrounding various pain management modalities as part of enhanced recovery after surgery (ERAS) protocols for patients undergoing bariatric surgery.

METHODS: A systematic search of PubMed, Scopus and Cochrane Central Register of Controlled Trials until November 2021 was conducted. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed. Studies assessing pain management interventions as part of ERAS protocols for bariatric surgery were included. Two reviewers independently screened articles. Sixty-seven papers were screened of which six papers were accepted into this study.

RESULTS: Six studies contained a total of 714 patients. All articles were double-blinded RCTs. Study characteristics are found in Table 1. The primary outcomes for the articles revolved around the evaluation of postoperative pain at varying timestamps and using different measures. Secondary outcomes included length of hospital stay, postoperative nausea or vomiting (PONV), additional analgesic use. Outcomes are described in Table 2. A wide variety of pain management modalities were implemented across the studies. The use of intraperitoneal local anesthesia with ropivacaine, IV lidocaine, and transversus abdominus plane (TAP) bupivacaine in comparison to control groups was investigated by Jarrar A et al., Plass F et al. and Saber AA et al, respectively. Ma P et al. investigated the effect of liposomal bupivacaine compared to bupivacaine at port-site infiltration. Ruiz Tovar J et al. looked at laparoscopic guided TAP block compared to port site infiltration. Narejo AS et al. investigated the effect of dexmedetomidine compared to remifentanil on postoperative pain. Ruiz Tovar J showed that the use of laparoscopy guided TAP was associated with reduced pain at 24 hours. Narejo et al. revealed a significant reduction in pain with remifentanil while PONV was increased. The remaining articles did not report significant reduction in post-operative pain. As for complication rates, Plass et al. reported statistically significant intraoperative hypotension with the use of IV lidocaine.

CONCLUSION: Articles in this systematic review did not show clear benefit in outcomes such as pain score. When there were improvements in pain levels, there was also an increased risk of adverse events such as hypotension. We propose that one reason why results did not show clear benefit is due to the robust analgesia patients were already receiving as part of ERAS protocols. More research is needed to determine the risk-to-benefit ratio of these interventions.

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Table 1: Study Characteristics

#	First Author	Location	Length	Intervention Groups and # per group	Type	Primary Outcome	Secondary Outcomes
1	**Jarrar A 2021**	Canada	8 mo.	#1: IPLA Ropivacaine: 46 patients #2: IPLA NS: 46 patients	LRY GB	Postoperative pain (0-10)	Opioid analgesic use, Peak expiratory flow, 6MWT, QoL and perioperative complications
2	**Ma P 2019**	USA	10 mo.	#1: Liposomal bupivacaine: 89 patients #2: Bupivacaine: 90	Both	Opioid use in hospital	LOS, pain score, adverse events, home opioid use
3	**Narejo AS 2021**	Saudi Arabia	3 mo.	#1: Dexmedetomidine: 20 patients #2:Remifentanil: 20	LSG	Postoperative pain	Morphine consumption, PONV, LOS, time of awakening, time of extubation, shivering
4	**Plass F 2021**	France	8 mo.	#1: IV Lidocaine: 88 #2: IV NS: 88	Both	Oxycodone use till day 3	LOS recovery ward, LOS, PONV, bowl function, pain, lidocaine use.
5	**Ruiz-Tovar J 2018**	Spain	10 mo.	#1: TAP-lap: 69 patients #2: Port site infiltration: 68 patients	LRY GB	Postoperative pain	LOS, morphine consumption
6	**Saber AA 2019**	USA	6 mo.	#1: TAP bupivacaine: 31 #2: TAP bupivacaine and epinephrine: 27 patients #3: Placebo: 32 patients	LSG	Postoperative pain	LOS, PONV, time to get back to work, ambulation, 30-day complications, Questionnaire recovery

IPLA: Intraperitoneal local anesthesia, LSG: laparoscopic sleeve gastrectomy, LRYGB: laparoscopic Roux-en-Y gastric bypass surgery, 6MWT: Six-minute walk test, QoL: Quality of Life, LOS: length of stay, TAP: Transverse abdominis plane

Table 2: Study outcomes

#	First Author	Length of Stay	PONV	Postoperative Pain	Analgesic Use
1	**Jarrar A 2021**	NA	NA	8, 24, 48 hrs No significant difference	No significant difference
2	**Ma P 2019**	No significant difference	Antiemetic use No significant difference	First 24 hrs No significant difference	Mobilization: No significant difference
3	**Narejo AS 2021**	No significant difference	PACU: No significant difference Ward: D Group had significant reduction of PONV	PACU: No significant difference Ward: R group had significant reduction of pain score	NA
4	**Plass F 2021**	No significant difference	No significant difference	No significant difference	Total IV oxycodone higher in the control group. Significant result
5	**Ruiz-Tovar J 2018**	Significant reduction	NA	First 24 hrs: Significant reduction with TAP-lap	Morphine rescue higher in PSI group. Significant result
6	**Saber AA 2019**	No significant difference	No significant difference	Pain score at 3 hrs: Significant reduction. All others times no significant difference.	No significant difference

LOS: length of stay, PONV: postoperative nausea or vomiting, LP: liposomal, PACU: post-anesthesia care unit, D group: Dexmedetomidine group, R group: Remifentanil group

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Guideline-Concordant Perioperative Antibiotic Prophylaxis in Routine Clinical Practice

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INTRODUCTION: Surgical site infections (SSIs) are a significant postoperative complication associated with increased morbidity, mortality, healthcare costs and length of stay[1,2]. Anesthesiologists play a critical role in SSI prevention by directly managing a patient's modifiable risk factors. Current guidelines for SSI prevention suggest that timely administration of the initial antibiotic dose may be the most impactful intervention in an anesthesiologist's arsenal[3,4]. For prophylaxis to be effective, the antibiotic should be administered with adequate time to achieve minimum inhibitory concentration (MIC) against targeted organisms at the surgical site prior to incision. While current guidelines recommend dosing 0-60 minutes pre-incision, recent studies have suggested superior outcomes in patients who received antibiotic prophylaxis 15-60 minutes prior to surgical incision[5,6,7]. We examined the timing of antibiotic administration to investigate potential process improvement opportunities for timely antibiotic administration.

METHODS: Timing of antibiotic administration relative to surgical incision across all surgical service lines (except neurosurgery and cardiac surgery) was reviewed over a 12-month period from July 2020 to June 2021. Information on surgical team, surgery, preoperative holding room time, administration time and incision time were recorded and tabulated for all main operating room surgeries.

RESULTS: Over 2988 surgeries were observed with the median time to pre-incision antibiotic administration of 18 minutes, with 39% of cases administering antibiotics within 15 minutes of surgical incision.

CONCLUSION: Our median time for pre-incision antibiotics may not allow adequate time to achieve MIC at the surgical site prior to incision. Furthermore, interquartile calculation found 39% of antibiotics were administered within 15 minutes of incision. Upon review, there were several process steps for potential improvement. Among these were potential clinical decision support systems to promote earlier antibiotic administration, encouraging providers to administer antibiotics with or prior to induction rather than post-induction, ensuring patients roll to the operating room with appropriate surgical prophylaxis in-hand, and reducing reliance on the intraoperative team to provide the desired antibiotic.

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PERIOPERATIVE ANESTHESIA 36

Intraprocedural hypoxemia, delirium and effect modification by obstructive sleep apnea: A hospital registry study

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INTRODUCTION: Postoperative delirium (POD) increases hospitalization and is associated with a 1.5-fold higher one-year-mortality[1]. Previous studies reported an association between the occurrence of perioperative hypoxemia and postoperative cognitive dysfunction[2]. Further, perioperative hypoxemia is a common complication in patients suffering from obstructive sleep apnea (OSA)[3]. At the same time, chronic, recurrent episodes of hypoxemia, which occur frequently in patients with OSA, might have protective effects on POD through hypoxic preconditioning[4]. We hypothesized that intraprocedural desaturation is associated with POD. Contingent on this association, we hypothesized that this association is modified by a diagnosis or high susceptibility for OSA.

METHODS: Inpatients aged 60 years or older who underwent general anesthesia or monitored anesthesia care (MAC) for surgery and interventional procedures between 2009 and 2020 at a tertiary academic healthcare network in Boston, Massachusetts, United States of America, were included in this retrospective cohort study. Patients with an American Society of Anesthesiologists physical status classification ≥V or with a pre-existing diagnosis of dementia, delirium or cognitive impairment were excluded (Figure 1).
The primary exposure was the occurrence of intraprocedural hypoxemia, defined as a recording of an intraprocedural peripheral oxygen saturation of less than 90% for an episode of more than two consecutive minutes. The co-primary exposure was a diagnosis of OSA based on International Classification of Diseases (9th/10th Revision, Clinical Modification [ICD-9/10-CM]) codes, pulmonary and anesthesia alert notes and standardized nurse assessment notes prior to the procedure, or high susceptibility for OSA according to the BOSTN-score[5]. The primary outcome was the occurrence of POD within 30 days, identified based on ICD-9/10-CM codes[6] and available Confusion Assessment Method[7] assessments in the intensive care unit. We applied multivariable logistic regression analysis adjusted for a priori defined factors including patient demographics, comorbidities, procedural severity and anesthesia-related factors. Linear combinations of the main effect and interaction terms were performed to assess effect modification of the association between intraoperative hypoxemia and POD by a diagnosis or high susceptibility for OSA. Adjusted odds ratios with 95% confidence intervals with alpha set to 0.05 are reported.

RESULTS: The study cohort consisted of 84,568 patients (Figure 1), among which 4,900 (5.8%) experienced intraoperative hypoxemia. 27,175 (32.1%) patients had a diagnosis or high susceptibility for OSA. 2,835 patients (3.4%) developed POD, 354 (7.2%) of patients with and 2,481 (3.1%) of patients without intraoperative hypoxemia. Patient characteristics are provided in Table 1.
In adjusted analysis, the occurrence of intraprocedural hypoxemia was associated with an increased risk of POD (aOR 1.34 [95% CI 1.17-1.53]; p<0.001). This association was characterized by a dose response (Figure 2) and was modified by a diagnosis or high susceptibility for OSA: A diagnosis or high susceptibility for OSA magnified the risk of POD associated with desaturation (aOR 1.68 [95% CI 1.35-2.09]; p<0.001 in patients with OSA, compared to aOR 1.20 [95% CI 1.02-1.41]; p=0.024 in patients without OSA, p-for-interaction=0.011) (Table 2). Episodes of desaturation in patients with a diagnosis or high susceptibility for OSA were comparable to patients without OSA with regard to their duration (mean 24.1 ± 36.8 min, median 11 [IQR 5.5-22.5] min versus 26.6 ± 41.2 min, median 10.5 [IQR 5-26.3] min, p=0.97). The association between intraprocedural hypoxemia and POD was not modified by MAC versus general anesthesia (p-for-interaction=0.61).

CONCLUSION: Patients who experience intraprocedural hypoxemia are at higher risk of POD. Our results do not support the hypothesis that patients with OSA are less vulnerable to hypoxemia-associated delirium. Rather, physicians should aim to avoid oxygen desaturation particularly in patients with OSA.

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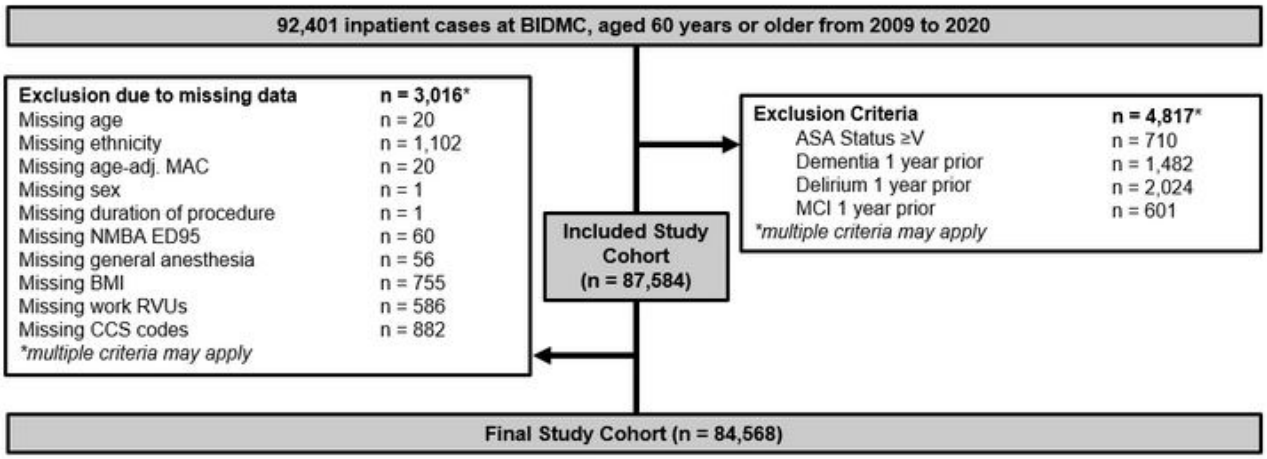

ASA: American Society of Anesthesiologists; BIDMC: Beth Israel Deaconess Medical Center; BMI: Body Mass Index; ED95: median effective dose required to achieve a 95% reduction in maximal twitch response from baseline; NMBA: neuromuscular blocking agents; work RVUs: work Relative Value Units; CCS: Clinical Classifications Software; MCI: mild cognitive impairment; age-adj. MAC: age-adjusted mean alveolar concentration of inhalational anesthetics.

Figure 1. Study flow diagram.

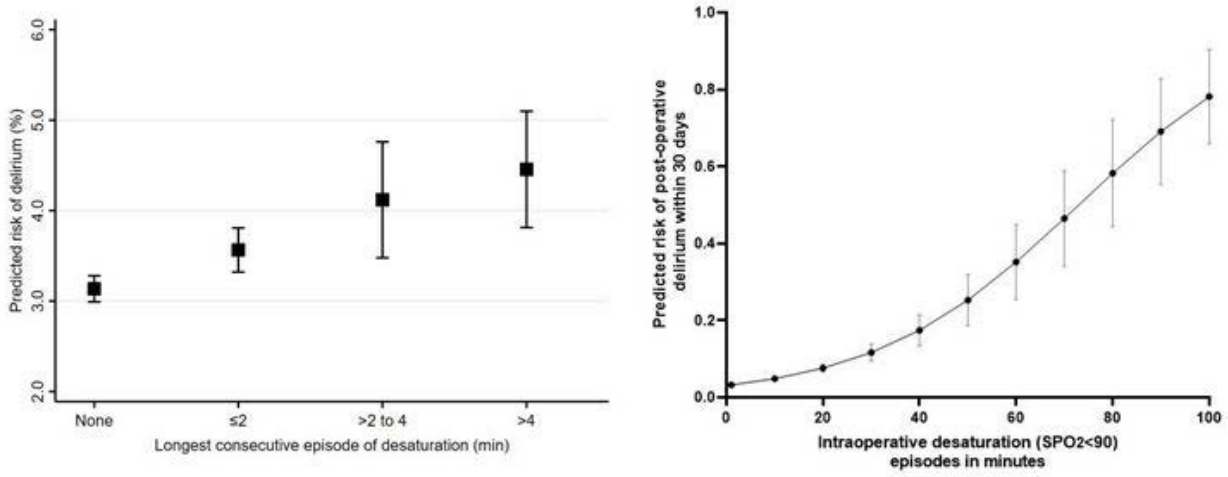

Figure 2. Adjusted, estimated risk of postoperative delirium (%) by duration of desaturation, defined as peripheral oxygen saturation <90%.

Table 1

	No intraprocedural desaturation	Intraprocedural desaturation	Standardized difference
	N=79,668	**N=4,900**	
Demographics			
Age, years	70.0 (65.0 - 78.0)	70.0 (65.0 - 77.0)	0.041
BMI, kg/m^2	27.3 (23.8 - 31.4)	28.6 (25.1 - 33.3)	-0.226
Sex			0.213
Male	40,175 (50.4%)	2,987 (61.0%)	
Female	39,493 (49.6%)	1,913 (39.0%)	
Ethnicity			-0.111
Asian	2,165 (2.7%)	89 (1.8%)	
Black	6,092 (7.6%)	275 (5.6%)	
Hispanic	2,363 (3.0%)	130 (2.7%)	
Other	199 (0.2%)	10 (0.2%)	
Two or more	32 (0.0%)	1 (0.0%)	
White	58,236 (73.1%)	3,664 (74.8%)	
Unspecified	10,581 (13.3%)	731 (14.9%)	
Comorbidities			
Smoking	15,082 (18.9%)	1,210 (24.7%)	-0.140
Alcohol abuse	2,611 (3.3%)	154 (3.1%)	0.007
Drug abuse	1,103 (1.4%)	56 (1.1%)	0.022
Anemia	24,125 (30.3%)	1,826 (37.3%)	-0.148
Schizoaffective disorders	8,330 (10.5%)	380 (7.8%)	0.094
BOSTN-score	1.0 (0.0 - 1.0)	1.0 (0.0 - 2.0)	-0.165
High susceptibility for OSA	11,754 (14.8%)	966 (19.7%)	-0.132
Diagnosis of OSA	16,243 (20.4%)	1,145 (23.4%)	-0.072
Procedural characteristics			
Duration of surgery, min	139.0 (78.0 - 217.0)	243.0 (125.0 - 318.0)	-0.621
Emergency surgery	10,674 (13.4%)	661 (13.5%)	-0.003
Work relative value units	15.4 (7.2 - 23.5)	27.3 (12.1 - 44.8)	-0.765
Crystalloid and colloid infusion, ml	1000.0 (500.0 - 1740.5)	2000.0 (900.0 - 3000.0)	-0.568
Units of packed red blood cells	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	-0.293
Age-adjusted mean alveolar concentration of inhalational anesthetics	0.9 (0.0 - 1.1)	0.8 (0.6 - 1.0)	-0.032
Short acting opioid dose, mg OME	25.0 (0.0 - 50.0)	100.0 (25.0 - 250.0)	-0.624
Long acting opioid dose, mg OME	0.0 (0.0 - 13.6)	0.0 (0.0 - 0.0)	0.266
Non-depolarizing NMBA, ED95	1.7 (0.0 - 3.1)	3.4 (1.1 - 5.5)	0.622
Neostigmine dose, mcg/kg	0.0 (0.0 - 3.0)	0.0 (0.0 - 2.0)	0.153
Vasopressor dose, mg norepinephrine	0.0 (0.0 - 0.3)	0.4 (0.0 - 0.9)	-0.117
Mean arterial pressure below 55 mmHg, min	1.0 (0.0 - 3.0)	8.0 (0.0 - 36.0)	-0.786

Data are expressed as frequency (prevalence in %), mean ± standard deviation, or median (interquartile range [25th-75th percentile]).

OSA: obstructive sleep apnea; BMI: body mass index; ED95: median effective dose required to achieve a 95% reduction in maximal twitch response from baseline; NMBA: neuromuscular blocking agents; OME: oral morphine equivalents.

Table 2. Estimated risk of delirium in %.

	Obstructive sleep apnea	No obstructive sleep apnea	p-value
Desaturation	4.64 (3.82-5.46)	4.00 (3.47-4.54)	<0.001
No desaturation	2.93 (2.69-3.16)	3.40 (3.24-3.55)	<0.001

Table 2. Adjusted, estimated risk of postoperative delirium (%) for patients experiencing intraprocedural hypoxemia (peripheral oxygen saturation of less than 90% for an episode of more than two consecutive minutes) with and without a diagnosis or high risk of obstructive sleep apnea.

PERIOPERATIVE ANESTHESIA 37

Incidence of PONV, VTE, and airway events in patients undergoing rhinoplasty procedure

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INTRODUCTION: Rhinoplasty procedures have historically been some of the most sought after cosmetic procedures with a 2020 survey by the American Society of Plastic Surgeons rating it as the fifth most common procedure amongst women and an estimated 350,000+ procedures performed annually[1]. Despite the frequency of this procedure, not much has been added to the scientific literature in regards to anesthesia techniques and perioperative outcomes for this population. In this present study, we aim to report the incidence of three commonly reported perioperative outcomes: postoperative nausea and vomiting (PONV), deep venous thrombosis (DVT), and airway issues in a population of biological males and females who underwent rhinoplasty procedures at one urban, academic institution.

METHODS: This study was approved by the Institutional Review Board at our institution. Non-experimental retrospective chart reviews were conducted and all cis-gendered patients who underwent any facial feminization procedures performed by the same surgeon between 2014-2019 and were between the ages of 18-89 at the time of chart review were included. Patient demographics including age, ethnicity, BMI etc were collected as well as the history of hormone use, comorbidities, and history of PONV. PONV was defined as any episode of nausea and/or vomiting in the PACU. Airway incidents were recorded when a patient's saturation dropped to below 92 or more than one attempt at airway insertion was made. Notes from the patient's chart were analyzed for a period of 6 months post-procedure for any incidents of DVT. For the purpose of analysis, patients were divided by biological sex due to the prevalance of PONV being higher in women[2] and airway issues higher in men[3].

RESULTS: The final cohort consisted of 375 unique patients who fit the eligibility criteria for the study. Of these 375 patients, 123 were biological men and 252 were women. The average age was relatively similar in both groups at 34.3 + 11.8 and 33 + 12.1 years respectively for both groups. The majority of patients in both groups were relatively healthy with 82.1% (101/123) of men and 88.4% (221/252) women with BMIs of less than 30 (Table 1). The rate of PONV was reported to be 5.7% (7/123) in men and 13.9% (32/252) in women. No DVTs were reported in either cohorts upto 6 months post procedure. Airway events were recorded in 7.3% (9/123) of men and 3.6% (9/252) women. Multinomial regression analysis revealed that the type of anesthetic used, inhaled with propofol vs inhaled only vs intravenous only, did not impact the PONV rate in either cohort.

CONCLUSION: Our study found a 13.9% incidence of PONV in women undergoing rhinoplasty procedures and 7.3% rate of intraoperative airway events in men undergoing the same procedure. While rhinoplasties have a well documented history and practice, not much is known about perioperative patient outcomes. Our study shows that type of anesthesia did not determine incidence of PONV in this population. Further studies are needed to confirm treatment and management of PONV/ airway events experienced during this procedure.

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Table 1

Baseline Characteristics	Cis Men	Cis Women
Total	123	252
Age at date of surgery	34.3 ± 11.8	33 ± 12.1
Patient's Height (m)	3.1 ± 14.7	4.6 ± 21.4
Patients Weight (kg)	79.5 ± 14.4	63.2 ± 14.2
Patients BMI		
Less than 30	101 (82.1%)	221 (88.4%)
Equal to or more than 30	22 (17.9%)	29 (11.6%)
Race		
Asian	4 (3.3%)	11 (4.4%)
Native American/ Alaska/ Pacific Islander	4 (1.7%)	2 (0.8%)
Black/ African American	13 (10.6%)	12 (4.8%)
white	61 (49.6%)	153 (60.7%)
Unknown	43 (35%)	73 (29%)
Marital Status		
Single	89 (74.2%)	164 (66.1%)
Married	23 (19.2%)	57 (23%)
Tobacco Use		
Former	14 (11.4%)	23 (9.1%)
Current	11 (8.9%)	15 (5.9%)
Never	98 (79.7%)	214 (85%)
Comorbidities		
ADHD	2 (1.6%)	12 (4.8%)
Depression	12 (9.8%)	31 (12.3%)
Anxiety	13 (10.6%)	51 (20.2%)
Asthma	9 (7.3%)	23 (9.1%)
GERD	15 (12.2%)	18 (7.1%)
Hypertension	10 (8.1%)	7 (2.8%)
PONV	7 (5.7%)	35 (13.9%)
Airway Events	9 (7.3%)	9 (3.6%)
DVT	0 (0.0%)	0 (0.0%)

PERIOPERATIVE ANESTHESIA 38

Association of Post-operative ICU Delirium and Intraoperative Triple Low State

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INTRODUCTION: Post-operative delirium (POD) is a common complication, occurring in up to 52% of non-cardiac surgical patients, and is a significant cause of increased mortality and morbidity[1,2]. While general risk factors for POD have been identified, such as age, surgical duration, and pre-operative cognitive function, potential modifiable risk factors are less established[3]. The triple low state (TLS) is a period of concurrent low bispectral index (BIS), minimum alveolar concentration (MAC), and mean arterial pressure (MAP) values, associated with increased postoperative mortality and a hypothesized indicator of poor physiologic reserve[4]. This preliminary study aimed to determine whether intraoperative TLS is associated with POD.

METHODS: This retrospective study included non-cardiac and non-liver transplant surgical patients within a multi-hospital health system from 2016 - 2018 who had Intensive Care Delirium Screening Checklist (ICDS) scores documented during a post-operative ICU stay (ICDS >3 was considered positive for delirium). Patients were excluded if there was evidence of pre-operative delirium or did not have intraoperative values for BIS, MAC and MAP. TLS was defined as simultaneous BIS < 45, MAP < 75 mmHg and MAC < 0.7. Logistic regression was performed to determine the association between TLS events and the development of POD. Covariates included age, gender, ASA physical status, emergency surgery, surgical specialty, hospital site, and the presence of a TLS during the procedure. Multiple comparisons were accounted for using Benjamani-Hochberg correction to calculate the False-Discovery Rate (FDR).

RESULTS: Of the 259 patients that met inclusion criteria, 95 patients had TLS events and 164 did not. Demographic and clinical variables are in Fig. 1. Average cumulative TLS duration within the TLS cohort was 30.7 min [6 min (Q1), 38.75 min (Q3)]. POD occurred more often in the TLS subgroup (28.4%) compared to patients without TLS events (11.6%). Logistic regression analysis demonstrated a trend towards TLS being associated with POD, OR 3.0 (1.35 - 6.69), FDR-adj p=0.06 (Figure 2).

CONCLUSION: In a multihospital surgical population with post-operative ICU care, TLS was common and prolonged. TLS may be associated with post-operative ICU delirium, however, the sample size limited our analysis including the ability to account for all confounders (e.g. with propensity matching). This study demonstrates how intraoperative data may be used to identify patients at elevated risk for postoperative delirium, and should motivate larger studies evaluating the relationship between TLS and POD.

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Characteristics	Delirium	No_Delirium	p value
Total Patients	46	213	
Patients with TLS	27 (58.7 %)	63 (29.6 %)	< 0.001
Surgical_Site:			< 0.001
MUH	7 (15.2 %)	12 (5.6%)	
PUH	39 (84.8 %)	201 (94.4%%)	
Year:			< 0.001
2016	21 (45.7 %)	67 (31.5%)	
2017	15 (32.6 %)	112 (16.0%)	
2018	10 (21.7 %)	34 (16.0%)	
Age	71.2 +/- 15.8	62.4 +/- 15.3	< 0.001
Gender:			< 0.001
Female	26 (56.5 %)	91 (42.7%)	
Male	20 (43.5 %)	122 (57.3%)	
ASA:			< 0.001
5	3 (6.5 %)	1 (0.5%)	
4	19 (41.3 %)	59 (27.7 %)	
3	21 (45.7 %)	132 (60.2%)	
2	3 (6.5 %)	20 (9.4%)	
1	0 (0.0 %)	1 (0.5%)	
Emergency	19 (41%)	53 (25%)	
Procedure_Length	211.6 +/- 150.6	239 +/- 159.4	0.273
Surgical_Specialty:			< 0.001
General	16 (34.8 %)	70 (32.9%)	
Vascular	8 (17.4 %)	21 (9.9 %)	
Thoracic	7 (15.2 %)	80 (37.6%)	
Orthopaedic	9 (19.6 %)	30 (14.1%)	
Other	6 (13%)	12 (5.6 %)	

Table 1

Characteristic	Odds Ratio (95% CI)	p value	FDR
Surgical Site	3.31 (0.90 – 12.2)	0.071	0.142
Emergency	2.37 (0.99 – 5.69)	0.053	0.13
ASA Physical Status	1.35 (0.75 – 2.41)	0.316	0.379
TLS	2.74 (1.26 – 5.96)	0.011	0.066
Year	1.08 (0.64 – 1.85)	0.771	0.771
Age	1.03 (1.00 – 1.06)	0.024	0.096
Procedure Length	1.00 (0.99 – 1.00)	0.254	0.38
Gender	0.7 (0.36 – 1.57)	0.440	0.48
Surgical Specialty:			
General	0.27 (0.07 – 1.02)	0.054	0.13
Vascular	0.34 (0.07 – 1.57)	0.167	0.286
Thoracic	0.12 (0.02 – 0.59)	0.010	0.066
Orthopaedic	0.45 (0.1 – 1.96)	0.290	0.38

Table 2

PERIOPERATIVE ANESTHESIA 39

Could AI improve perioperative handoffs? A qualitative study of AI use cases with perioperative nurses

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INTRODUCTION: In the postoperative environment, a well-conducted handoff from the operating room to PACU and PACU to ward provides key situational awareness and anticipatory guidance for bedside nurses. Inadequate handoffs remain a source of medical errors and patient harm[1] despite numerous attempts to improve handoffs, predominantly by adopting checklists.[2] Our hypothesis was that artificial-intelligence (AI) based risk predictions incorporated into a handoff report-sheet could steer handoff to focus on problems and data pertinent to the patient's trajectory.

METHODS: As part of an implementation program for perioperative risk prediction using AI, we observed 58 handoffs of patients with planned admission to a general surgery service or the surgical step-down unit at a single center. We recruited 11 postoperative nurses for in semi-structured interviews regarding handoff practices and how they approach existing and future AI risk prediction in the electronic health record. Mixed inductive-deductive thematic analysis extracted major themes and subthemes for the role of AI supporting postoperative nursing.

RESULTS: OR providers largely followed the institutional handoff-report-sheet at arrival to PACU. However, neither PACU nor ward participants were aware of the handoff protocol for transfer out of PACU, and information transfer at this stage was much less consistent. Most ward nurses were not able to identify topics on which they had received anticipatory guidance from the PACU handoff. Four themes emerged from the interviews: (1) All participants recognized that understanding of the adverse events likely for a patient is critical for identifying relevant changes in patient condition and timely initiation of rescue therapies. (2) Most PACU and ward participants felt that too much time is spent in handoff on irrelevant information and that handoffs lack a problem-focus. Almost all participants said that they would likely use flagged risks to organize handoffs or ask pertinent questions. AI-identified predictors of adverse events were felt to be beneficial because of the complexity of the electronic health record. (3) AI may augment nurse – physician team communication. All ward participants said that they would call out to the physician team about the plan for flagged risks, but most PACU participants said that they would rather address flagged risks at OR-PACU handoff. (4) User experience and information overload are likely barriers to using AI. Participants did not converge on a single best interface point or presentation for AI. Participants were also concerned that excessive false-positives or information-overload related to too many alerts would cause them to be ignored.

CONCLUSION: Most research on postoperative handoff communication relies on structured checklists. Our results suggest that AI can facilitate postoperative handoff communication for nurses by adapting the content to the risks faced by a specific patient and assisting with more general situational awareness.

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PERIOPERATIVE ANESTHESIA 40

Mechanical power during one-lung ventilation and postoperative respiratory failure: A hospital registry study

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INTRODUCTION: Patients who require one-lung ventilation (OLV) for thoracic surgery are at high risk of developing postoperative respiratory failure (PRF)[1]. PRF can be exacerbated by inappropriate mechanical ventilation, aggravating ventilator-induced lung injury due to pulmonary strain and stress[2]. These can be markedly increased during OLV due to nonphysiologic ventilation and loss of normal functional residual capacity[3]. Mechanical power unifies ventilatory parameters of tidal volume (Vt), respiratory rate (RR) and driving pressure (DP) and yields a single value that may depict appropriateness of mechanical ventilation[4]. There is little evidence as to what is a favorable mechanical power with regard to PRF in patients undergoing OLV[5,6]. We investigated whether intraoperative mechanical power is associated with PRF in patients undergoing OLV and explored individual effects of each component of MP.

METHODS: Adult patients with American Society of Anesthesiologists physical status (ASA) ≤ IV who underwent general anesthesia for thoracic surgery requiring OLV between 2006 and 2020 at an academic hospital were included in this retrospective cohort study. The primary exposure was the median mechanical power during OLV, calculated from the previously validated formula 0.098 * RR * Vt * [PEEP + ½ DP + (Ppeak−Pplat)] [4]. The primary outcome was PRF, defined as unplanned reintubation or the need for noninvasive ventilation within 7 days after surgery. Within a Bayesian framework, we estimated the dose-response association of mechanical power and PRF through adjustment for a generalized propensity score, which incorporated patient demographics, baseline characteristics and intraoperative factors (Table 1).

Contingent on a dose-response relationship between mechanical power and PRF, we conducted an Influential variable analysis (DFBETAS) to investigate the effect of the individual components of mechanical power (DP, Vt and RR) on PRF. We assessed the relative predictive strength of each component in our estimation model using dominance analysis.

RESULTS: 880 patients were included in the primary analysis (Figure 1), among which 106 (12.1%) experienced PRF. Patient demographics and intraoperative factors stratified by the occurrence of PRF are provided in Table 1. The median (IQR) mechanical power was 8 J/min (7-10) and the median duration of OLV was 102 min (54-181). After confounder adjustment, there was a significant association between mechanical power and PRF (p=0.017). Figure 2 depicts the dose-response function curve of mechanical power and PRF as well as the treatment effect function. In general, OLV with a mechanical power of 6.5 J/min was associated with the lowest risk of PRF (7.8%), which increased with higher and lower values. Among the individual components, DP had the highest contribution to predicting PRF when stratified to data density with respiratory rate becoming increasingly relevant at very high mechanical powers (Figure 3). This was further corroborated in our exploratory dominance analysis which showed that driving pressure had the strongest dominance when compared to Vt and RR (Figure 4).

CONCLUSION: Patients who experience higher mechanical power during OLV are at greater risk of PRF requiring reintubation or non-invasive ventilation. These effects are mainly driven by a high DP. Based on our findings, clinicians should adjust mechanical ventilation during OLV to maintain mechanical power between 4 and 10 J/min.

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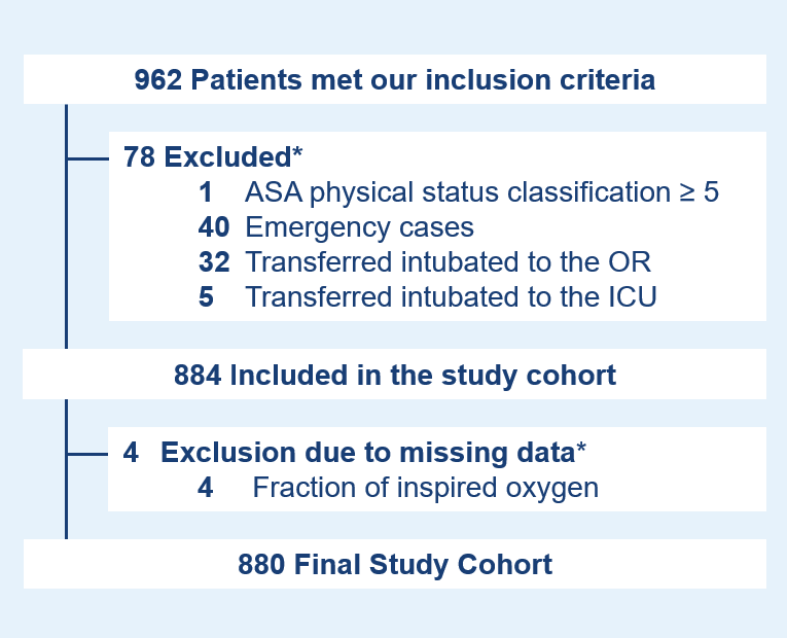
Figure 1. Study flow



*Multiple criteria may apply

ASA: American Society of Anesthesiologists; OR: Operation room; ICU: Intensive care unit

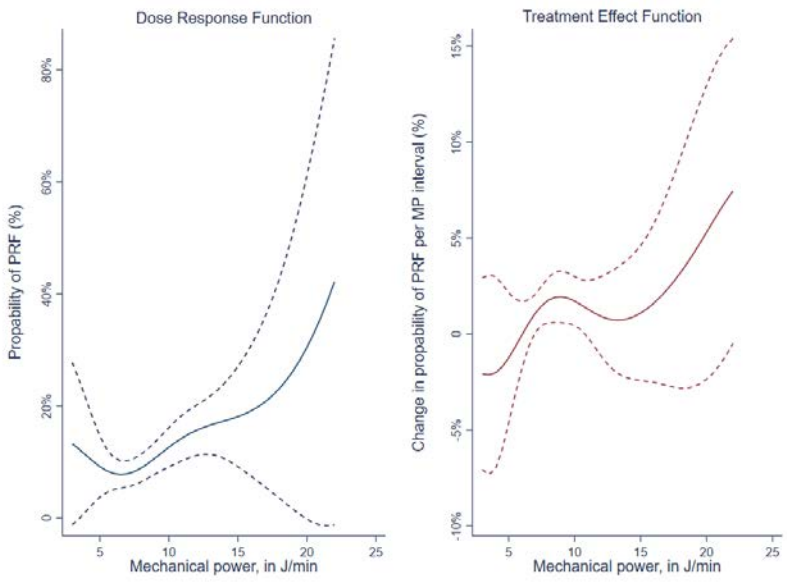


Figure 2. Dose response and treatment effect functions.

Dose response curve (solid line) with corresponding 95% confidence interval (dotted line) between mechanical power during one-lung ventilation and postoperative respiratory failure (PRF) (left side). The treatment effect function (right side) reflects the effect of a change in mechanical power on a patient's risk of PRF, depending on the respective mechanical power level. For example, in a patient ventilated with a mechanical power of 8 J/min, the probability of experiencing PRF is 9%. If the MP value is increased by 1 J/min, the probability of PRF will increase by 1.7%.

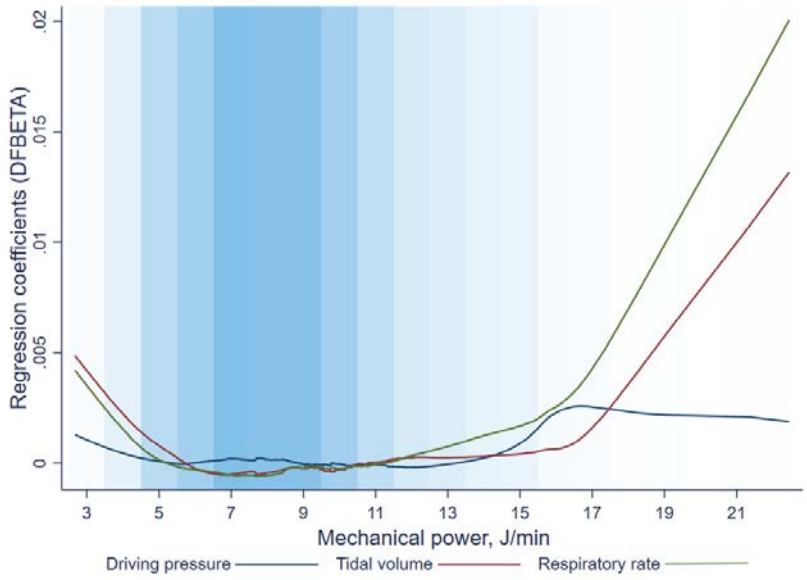


Figure 3. Influential observation analysis.

The individual regression coefficients (DFBETA) represent the influence of each component of mechanical power (driving pressure, tidal volume and respiratory rate) over each level of mechanical power. The background opacity reflects the density of observations (highest density of patients between MP 6-10 J/min; n= 581 patients [66%]).

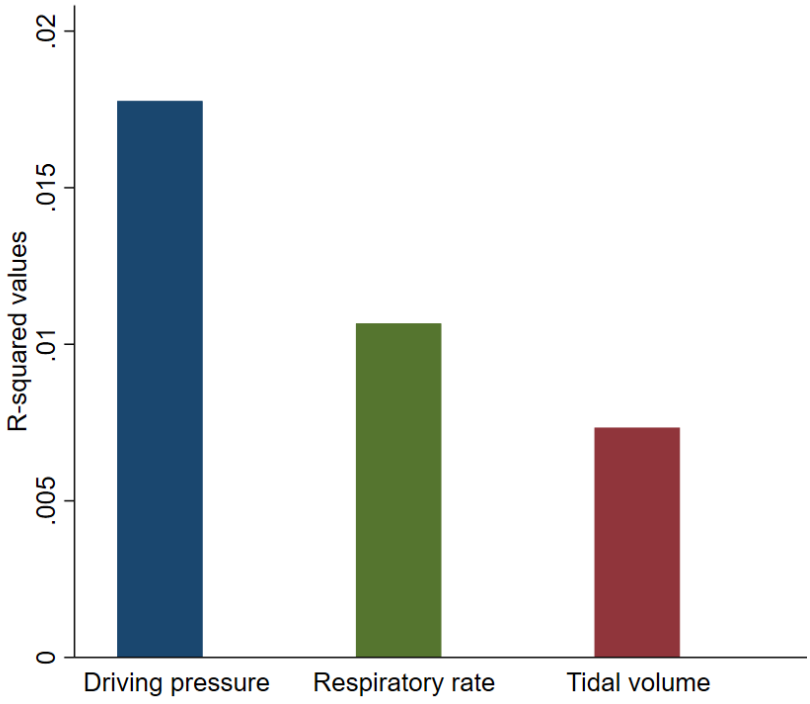


Figure 4. Dominance analysis.

This analysis represents the predictive strength of each component of mechanical power with regard to postoperative respiratory failure. The results indicate that driving pressure has the highest incremental contribution to our estimates (r^2= 0.018) with the strongest dominance when compared to tidal volume and respiratory rate.

Table 1. Patient characteristics and distribution of variables

	No postoperative respiratory failure N = 774	Postoperative respiratory failure N = 106
Demographics		
Age, years	63 (53 - 71)	66.5 (58 - 71)
Female	410 (53%)	44 (41.5%)
Body Mass Index, kg/m^2	27.3 ± 5.8	31.1 ± 7.5
Comorbidities		
Smoking	204 (26.4%)	36 (34%)
Obstructive sleep apnea	8 (1.0%)	14 (13.2%)
Obstructive lung disease	242 (31.3%)	41 (38.7%)
Restrictive lung disease	142 (18.3%)	24 (22.6%)
Chronic heart failure	41 (5.3%)	12 (11.3%)
Charlson Comorbidity Index	2 (0 - 4)	3 (2 - 5)
SPORC ≥ 7	38 (4.9%)	12 (11.3%)
Procedural characteristics		
Type of surgery		
Lobectomy	142 (18.3%)	19 (17.9%)
Thymectomy or other mediastinal	113 (14.6%)	11 (10.4%)
Pneumonectomy	8 (1%)	2 (1.9%)
Wedge resection	320 (41.3%)	30 (28.3%)
Esophagogastrectomy	59 (7.6%)	14 (13.2%)
Pulmonary decortication, pleuradesis, other pleural/chest wall procedures	114 (14.7%)	18 (17%)
Tracheoplasty/ bronchoplasty	18 (2.3%)	12 (11.3%)
Thoracoscopy approach	588 (76%)	55 (51.9%)
Duration of surgery, min	177.5 (117 - 269)	270 (168 - 406)
Duration of one lung ventilation, min	97 (52 - 177)	150.5 (81 - 250)
Work relative value units	16.9 (14.5 - 25.5)	24.6 (15 - 27.9)
ASA physical status classification		
I	7 (0.9%)	0
II	213 (27.5%)	10 (9.4%)
III	515 (66.5%)	86 (81.1%)
IV	39 (5%)	10 (9.4%)
Epidural analgesia	125 (16.1%)	36 (34%)
MAP below 55 mmHg, min	1 (0 - 4)	2 (0 - 4)
Packed red blood cell units	0	0
Crystalloid and colloid infusion, ml	1000 (750 - 1500)	1425 (900 - 2000)
Vasopressors, mg norepinephrine equivalents	0.1 (0 - 0.4)	0.3 (0.1 - 1)
Age-adjusted MAC	1 ± 0.2	1.1 ± 0.3
Non-depolarizing neuromuscular blockers, ED_{95}	3.2 (2.3 - 4.7)	3.7 (2.6 - 5.7)
Neostigmine dose, mg	2.5 (0 - 4)	2 (0 - 3)
Sugammadex application	292 (37.7%)	37 (34.9%)
Intraoperative opioids, mg OME	44.3 (33.5 - 63.6)	50 (36.3 - 71.5)
Respiratory rate, min	14 (12 - 16)	14.8 (12 - 16)
Tidal volume, ml/kg	6.8 ± 1.5	6.8 ± 1.6
Fraction of inspired oxygen, %	92 (78 - 96)	94.5 (87.5 - 96)
Peak inspiratory pressure, cmH_2O	26.9 ± 5.6	29.6 ± 5.8
Positive end expiratory pressure, cmH_2O	5.1 (4.1 - 5.1)	5.1 (4.1 - 6.1)
Standardized compliance, cmH_2O/ml/kg	0.3 ± 0.1	0.3 ± 0.1
Standardized elastance, cmH_2O/ml/kg	3.3 (2.7 - 4)	3.8 (3.2 - 4.5)
Driving pressure, cmH_2O	22.3 ± 5.6	24.5 ± 5.8
Mechanical power, J/min	8.2 (6.6 - 10.2)	9.7 (7.5 - 11.8)

NIV: Non- invasive ventilation; ASA: American Society of Anesthesiologists; MAP: mean arterial pressure; ED95: median effective dose required to achieve 95% reduction in maximal twitch response from baseline; MAC: mean alveolar concentration; OME: oral morphine equivalents; IBW: ideal body weight.

Data is expressed as frequency (prevalence in %), mean ± standard deviation or median (interquartile range [25th-75th percentile]) for continuous measures, and n (%) for categorical measures.

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The Duke Activity Status Index and its Simplified Version (m-DASI) Predict Hospital Length of Stay and Short and Long-Term Mortality Following Surgery

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INTRODUCTION: Functional capacity (FC) assessments are a critical part of the pre-anesthesia evaluation prior to major surgery. Both the Duke Activity Status Index (DASI) and a recently published simplified version (m-DASI) have been shown to discriminate with reasonable accuracy between patients with and without satisfactory functional capacity (defined as an anaerobic threshold >11 ml/kg/min and VO2 peak >16 ml/kg/min) as measured by CPET.1 How DASI and mDASI correlate with outcomes in a surgical cohort has not been described.

METHODS: We conducted a retrospective cohort study to evaluate the association between FC (as measured through DASI and m-DASI-5Q) and a series of clinical outcome measures (hospital length of stay [LOS], 30-day Emergency Department visits, 30-day all-cause readmissions, and 30-day and one-year mortality). The study was conducted during the perioperative period in a population of US veterans scheduled for elective procedures at a tertiary VA hospital (Durham, NC). We included patients undergoing in-person assessments in a pre-anesthesia evaluation clinic between June 2019 and August 2021. For the analysis of one-year mortality, we only included patients who had a one-year follow-up. We made use of generalized linear models (multiple linear and logistic) for continuous and categorical forms of outcomes to assess their association with their DASI and m-DASI scores.

RESULTS: A total of 4,017 patients completed the DASI questionnaire. Of these, 3,408 underwent an index surgical procedure and were included in our analysis (our study sample), with 1,656 of these surgeries being inpatient procedures (our sample for the analysis of LOS). First, we created a composite outcome measure that included ED visits or readmissions within 30 days or death within 30 or 365 days and created ROC curves for the DASI and m-DASI questionnaires (Figure 1). The thresholds of DASI and m-DASI scores that would determine a low vs high FC were estimated using a non-parametric optimization of the Youden's Index.2 A DASI score ≤34 (AUC = 0.761, sensitivity of 86.6% and specificity of 55.3%) and an m-DASI score of ≤2 (AUC = 0.724, sensitivity of 75.8% and specificity of 60.5%) were identified as the optimal thresholds. Table 1 presents the proportion of outcomes in the surgery sample stratified by DASI and m-DASI thresholds, respectively. Patients below the DASI threshold had longer LOS and an increased odds of 30-day and one-year mortality following surgery when compared to patients above that DASI threshold. Conversely, we found no significant associations between a low DASI score (≤34) and 30-day Emergency Department visits or 30-day all-cause readmissions. Using the composite outcome measure, we found that patients with a DASI score below the threshold presented 2.1 (95% CI: 1.66-2.65; $p < 0.001$) times the odds of developing an adverse clinical outcome when compared to those above the threshold. When performing the same analysis using the m-DASI ≤2 threshold, we found similar results. Patients below the m-DASI threshold had longer LOS and an increased odds of 30-day Emergency Department visits and 30-day and one-year mortality following surgery when compared to patients above that m-DASI threshold. Conversely, we found no significant association between a low m-DASI score (≤2) and 30-day all-cause readmissions. Using the composite outcome measure, we found that patients with a m-DASI score below the threshold presented 2.32 (95% CI: 1.83-2.93; $p < 0.001$) times the odds of developing an adverse clinical outcome when compared to those above the threshold.

CONCLUSION: We found that preoperative DASI and m-DASI scores correlate moderately with hospital length of stay and short and long-term mortality but not 30-day ED visits or hospital readmissions in a population of patients scheduled for surgery. A DASI threshold of 34 (or 7 METS as derived from the DASI score) and a m-DASI threshold of 2 are able to identify patients who may be at risk for postoperative adverse outcomes with good sensitivity but modest specificity, making DASI and m-DASI good screening tools in the preoperative period. Further research is needed to understand how these tools may be incorporated into perioperative preoperative risk assessment algorithms.

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Figure 1: The ROC curves for DASI and m-DASI models used to estimate their optimal thresholds.

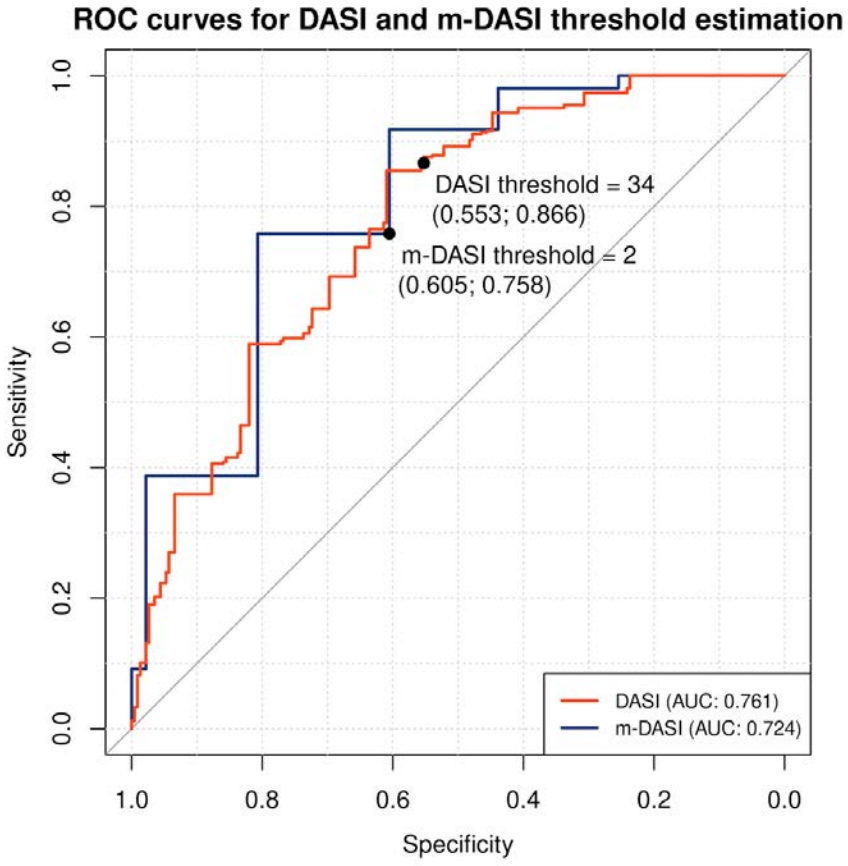

Table 1: The proportions of outcomes occurrences in the surgery sample stratified by DASI and m-DASI thresholds (Low FC: DASI ≤34.3, m-DASI≤2; not-Low FC: DASI >34.3, m-DASI >2)

		DASI score			m-DASI score		
Variable	**Total (3,408)**	≤34.3 (1,247)	>34.3 (2,161)	p	≤2 (1,240)	>2 (2,168)	p
Length of stay (days)	3.35 (±4.24)	3.69 (±4.48)	3.16 (±4.09)	0.017	3.72 (±4.52)	3.14 (±4.07)	0.009
30-day ED visit	273 (8.01%)	108 (8.66%)	165 (7.64%)	0.319	116 (9.35%)	157 (7.24%)	0.034
30-day readmission	134 (3.93%)	54 (4.33%)	80 (3.7%)	0.414	57 (4.6%)	77 (3.55%)	0.156
30-day mortality	18 (0.528%)	13 (1.04%)	5 (0.231%)	0.004	13 (1.05%)	5 (0.231%)	0.003
One-year mortality	152 (4.46%)	101 (8.1%)	51 (2.36%)	<0.001	96 (7.74%)	36 (1.66%)	<0.001
Composite outcome	324 (9.51%)	175 (14%)	149 (6.89%)	<0.001	181 (14.6%)	143 (6.6%)	<0.001

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Impairment of NAD+ Synthesis During Major Vascular Surgery and Acute Kidney Injury

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INTRODUCTION: Acute kidney injury (AKI) occurs in up to 40% of patients after major vascular surgery and is associated with an increased risk of morbidity and mortality. In animal models, inhibition of renal nicotinamide adenine dinucleotide (NAD+) synthesis due to reduced quinolinate phosphoribosyltransferase activity promotes ischemic AKI. A marker of reduced quinolinate phosphoribosyltransferase activity and NAD+ synthesis inhibition is elevated urinary quinolinate. In one study, urinary quinolinate concentration and the ratio of urinary quinolinate to tryptophan were elevated in critically ill patients that developed AKI, suggesting impaired NAD+ synthesis may play a role in the development of human AKI. Further, in a small study of on-pump coronary artery bypass graft (CABG) patients, urinary quinolinate concentrations before and shortly after surgery were higher in patients that later developed AKI compared to patients that did not, as were urinary quinolinate to tryptophan ratios measured shortly after surgery[1]. Importantly, preoperative administration of nicotinamide, an NAD+ precursor, to CABG patients has been associated with less AKI. Currently, phase II and III clinical trials of nicotinamide to prevent AKI in cardiac surgery and sepsis patients, respectively, are ongoing. It is unclear if impaired NAD+ synthesis plays a role in the development of postoperative AKI in other high-risk patient populations. We measured the urinary quinolinate concentrations in patients undergoing major vascular surgery to determine if impaired NAD+ synthesis was associated with AKI after major vascular surgery.

METHODS: After obtaining IRB approval, we measured the concentrations of quinolinate and tryptophan in urine collected from 9 non-emergent major vascular surgery patients who developed postoperative AKI and nine patients who did not develop postoperative AKI, matched on age, sex, BMI, baseline eGFR, and past medical history of hypertension and diabetes. Urine samples were collected at anesthetic induction and on the morning of postoperative day one. Two-sided Mann-Whitney-U tests were used to compare urine quinolinate and quinolinate to tryptophan ratios between patients that did and did not develop AKI. Multivariate linear regression modeling was used to estimate the relationship between urine quinolinate and quinolinate to tryptophan ratios and maximum change in serum creatinine from baseline 48 hours after surgery. The model was adjusted for age, sex, baseline estimated glomerular filtration rate, and diabetes using the first two principle components of these factors in order to avoid model overfitting.

RESULTS: There was no difference in the preoperative or postoperative urine quinolinate concentrations between patients that did and did not develop postoperative AKI ($p=0.07$ and 0.93 respectively). Similarly, there was no difference in the preoperative urine quinolinate to tryptophan ratio between patients that did and did not develop postoperative AKI ($p=0.32$). However, there was a difference in the quinolinate to tryptophan ratio on the morning of postoperative day one between patients that did and did not develop AKI ($p=0.04$). Further, higher preoperative urine quinolinate concentrations were associated with higher maximum changes in serum creatinine from baseline to 48 hours after surgery ($p=0.04$). Additionally, higher urinary quinolinate to tryptophan ratios measured on the morning of postoperative day one were also associated with higher maximum changes in serum creatinine from baseline 48 hours after surgery ($p=0.04$). Logistic models of KDIGO AKI demonstrated similar relationships (data not shown).

CONCLUSION: Consistent with previous observations in on-pump CABG and sepsis patients, higher preoperative urine quinolinate concentrations, a marker of impaired renal NAD+ synthesis, are associated with an increased risk of AKI after major vascular surgery. Higher urinary quinolinate to tryptophan ratios the morning after surgery are also associated with increased AKI after major vascular surgery. These data and previous data suggest that impaired NAD+ synthesis before and during surgery may play a role in the development of postoperative AKI in high-risk patient populations. Compounds which can overcome perioperative NAD+ synthesis impairment, such as nicotinamide, should be further studied in these patient populations.

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Association Between Two Versions of the Duke Activity Status Index and Gait Speed in a Surgical Population

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INTRODUCTION: Functional capacity (FC) assessments are a critical part of the pre-anesthesia evaluation prior to major surgery. Gait speed (GS) is an objectively measured indicator of FC that has been shown to predict disability, morbidity and mortality in a broad range of populations.[1] A slow GS is also associated with worse postoperative outcomes in cardiac and non-cardiac surgical patients.[2,3] The Duke Activity Status Index (DASI) is a 12-item questionnaire that may be administered remotely and is a valid indicator of cardiopulmonary fitness.4 The DASI - and its derived metabolic equivalent tasks (METs) - have been used for preoperative risk stratification.[5,6] Simultaneous measurement of DASI score and GS can shed light on the concordance between subjective and objective assessments of FC. Here, we examine associations between DASI and GS in a surgical population.

METHODS: We conducted a retrospective cohort study to evaluate the association between the 4-meter gait speed (4MGS) test and DASI among veterans scheduled for elective surgery at a tertiary VA hospital (Durham, NC). We included patients undergoing in-person assessments in a pre-anesthesia evaluation clinic between June 2019 and August 2021. We made use of a series of locally estimated scatterplot smoothing (LOESS) splines for graphic exploratory analyses, which were then coupled with generalized linear models (multiple linear and logistic) for continuous and categorical forms of 4MGS to assess its association with DASI, and an abbreviated version of the score termed the modified DASI (m-DASI-5Q). Given that a GS <1m/s is a well established threshold for low FC,7 we estimated the equivalent thresholds for DASI and m-DASI using a non-parametric optimization of the Youden's Index.8 To further validate our DASI threshold predictions, we categorized DASI scores as low (≤34.3), medium (>34.3 and ≥45.5), and high (>45.5, where the second cut-point is defined as the median above the first cut-point) and calculated the mean GS and odds ratios for each of the 3 DASI categories.

RESULTS: A total of 4,017 patients completed the DASI questionnaire, with 655 also completing the 4MGS test. We found a moderate correlation between DASI and m-DASI and 4MGS scores. Figure 1 presents scatterplots with linear regression lines and corresponding Pearson's correlation coefficients for 4MGS and DASI ($R = 0.41$, $p < 0.001$) (a), and 4MGS and m-DASI ($R = 0.38$, $p < 0.001$), (b). In order to establish a DASI threshold that would predict low FC we used the Youden's Index analysis and found that a DASI score of ≤34.3 identifies patients with low FC (AUC = 0.761, sensitivity of 86.6% and specificity of 55.3%). This threshold corresponds to an m-DASI of 2 (AUC = 0.724, sensitivity of 75.8% and specificity of 60.5%) and an estimated METs = 7. The receiver-operating-characteristic (ROC) curves for the DASI and m-DASI models are presented in Figure 2. Once we categorized DASI scores as low, medium and high, we found that, compared to a low DASI score, patients in the medium and high categories presented a 21% (95% CI: 0.127-0.335; $p < 0.001$) and 8% (95% CI: 0.043-0.124; $p < 0.001$) probability of having a GS<1m/s, respectively. In the same way, a low DASI score predicted a mean gait speed of 0.8m/s (95% CI: 0.758-0.84), while medium and high DASI scores predicted a mean GS of 1.12m/s (95% CI: 1.02-1.21; $p < 0.001$) and 1.28m/s (95% CI: 1.19-1.37; $p < 0.001$) respectively.

CONCLUSION: We found that DASI scores correlate moderately with measured GS in a population of patients scheduled for surgery. A DASI threshold of 34 (or 7 METS as derived from the DASI score) and an m-DASI threshold of 2 are able to distinguish patients with low (GS<1 m/sec) versus high (GS≥1 m/sec) FC with good sensitivity but modest specificity, making DASI and m-DASI good screening tools in the preoperative period.

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Figure 1: Scatterplots with regression lines and Pearson's correlation coefficients (R) showing the association between 4MGS and DASI (a), and 4MGS m-DASI (b).

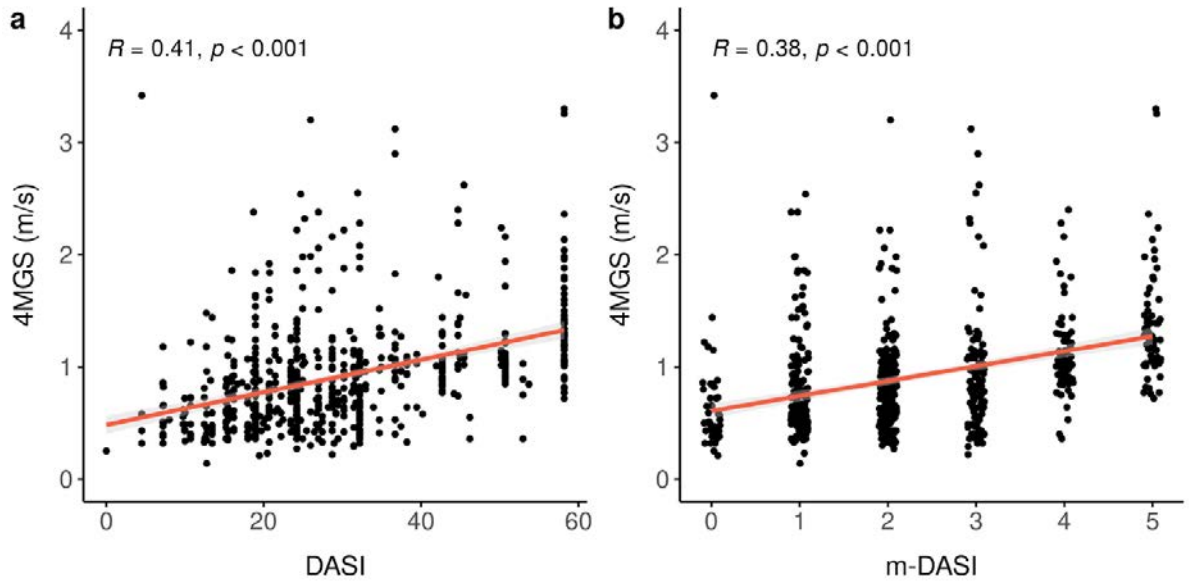


Figure 2: The ROC curves for DASI and m-DASI models used to estimate their optimal thresholds.

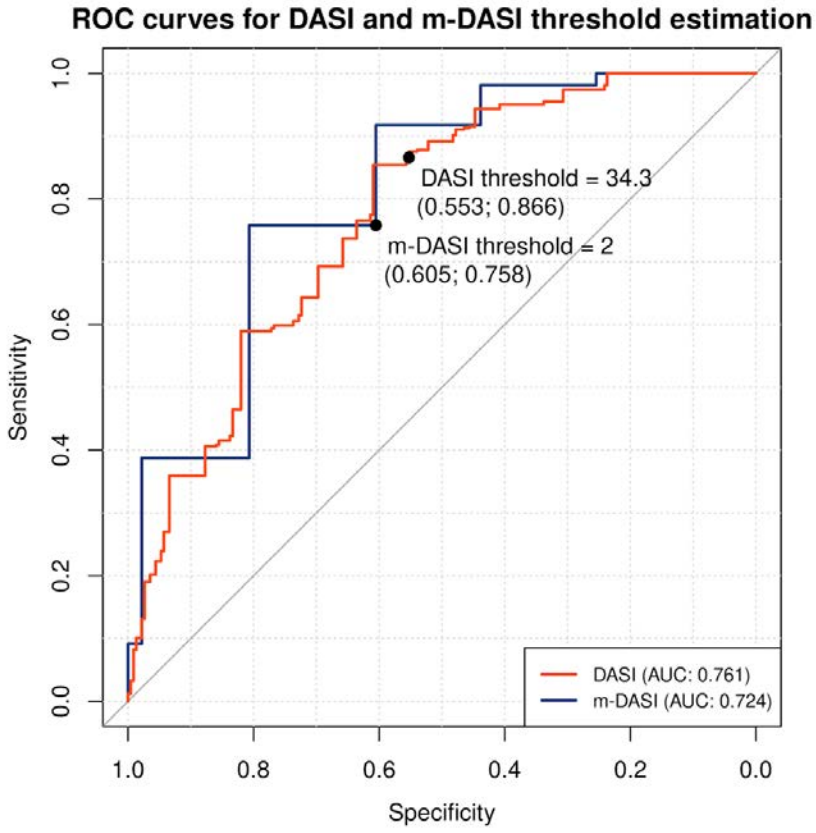
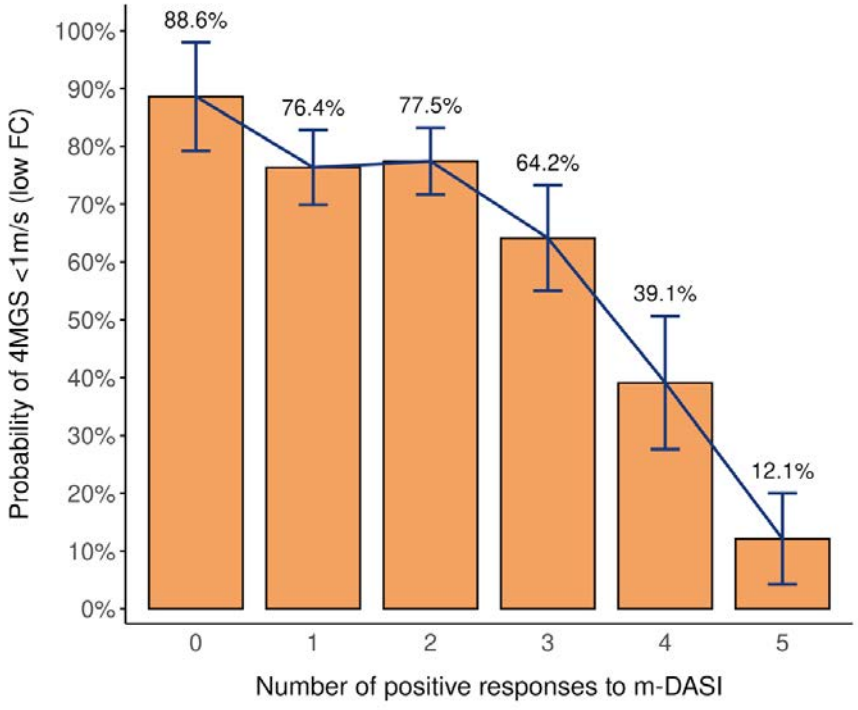


Figure 3: Probabilities (with error bars showing 95% confidence interval) of estimating a low FC (GS <1m/s) in relation to the number of positive responses to the m-DASI questions.



PERIOPERATIVE ANESTHESIA 44

Perioperative Point-of-Care Ultrasound Use by Anesthesiologists

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INTRODUCTION: Point-of-Care ultrasound (POCUS) is the bedside utilization of ultrasound, in real-time, to aid in the diagnosis and treatment of patients. Image acquisition from POCUS utilization by anesthesiologists involves the assessment of multiple organs in different perioperative situations. POCUS can be utilized to enhance clinical decision-making in a variety of perioperative situations due to its ability to assess endotracheal tube placement, cardiac function, pulmonary function, aspiration risk, hemodynamics, vascular access, and nerve visualization for regional procedures. The mounting clinical evidence for the value of POCUS in perioperative settings, its growing affordability, and its low associated risks are responsible for the nationwide movement across many anesthesiology residency programs to increase the focus on perioperative ultrasound training. The purpose of this review is to present to current anesthesiologists and anesthesiology trainees, a broad discussion regarding the diverse utility and importance of POCUS in perioperative settings.

METHODS: We reviewed point-of-care ultrasound studies by conducting a keyword search on the PubMed database. The search keywords included: 'ultrasound', 'POCUS' combined with 'anesthesiologist', 'anesthesia', or 'perioperative'. Publications were screened by title and abstract.

RESULTS: POCUS is a valuable bedside tool that is increasingly utilized in perioperative settings due to its reliability, accuracy, speed, and ease of use. POCUS can be utilized to confirm correct endotracheal tube placement and be utilized in complex airway situations. Cardiac POCUS provides invaluable information that aids in assessing challenging hemodynamically unstable situations. Pulmonary POCUS can identify numerous pulmonary conditions including pneumothorax, pulmonary edema, pleural effusion, and lung consolidation. POCUS is also utilized for the assessment of aspiration risk, vascular access, and ultrasound-guided nerve blocks.

CONCLUSION: The diverse utility of POCUS by anesthesiologists enriches the quality of healthcare patients receive in perioperative settings. Thus, the current and growing clinical evidence supporting the value of POCUS will continue to increase its utility in perioperative settings and its significance in aiding in perioperative clinical decision-making.

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VIEW	PROBE POSITION	ASSESSMENT
Parasternal long-axis	Probe at 3rd- 4th intercostal space with indicator directed to 10 o'clock position	Assesses EF, ventricular size, mitral valve, aortic stenosis or regurgitation, hypertrophic obstructive cardiomyopathy, and congestive heart failure
Parasternal short-axis	Probe at 3rd- 4th intercostal space with indicator directed to 2 o'clock position	Assesses volume status, RV volume overload, coronary ischemia
Apical four chamber	Probe at 6th midclavicular line intercostal space with indicator directed to 3 o'clock position	Assesses valvular function, atrial sizes, ventricular sizes, systolic function
Subcostal four chamber	Probe at subxiphoid space with indicator directed to 3 o'clock position	Assesses pericardial effusions, RV, tricuspid valve

Table 1: Transthoracic cardiac POCUS views, probe position, and assessment.

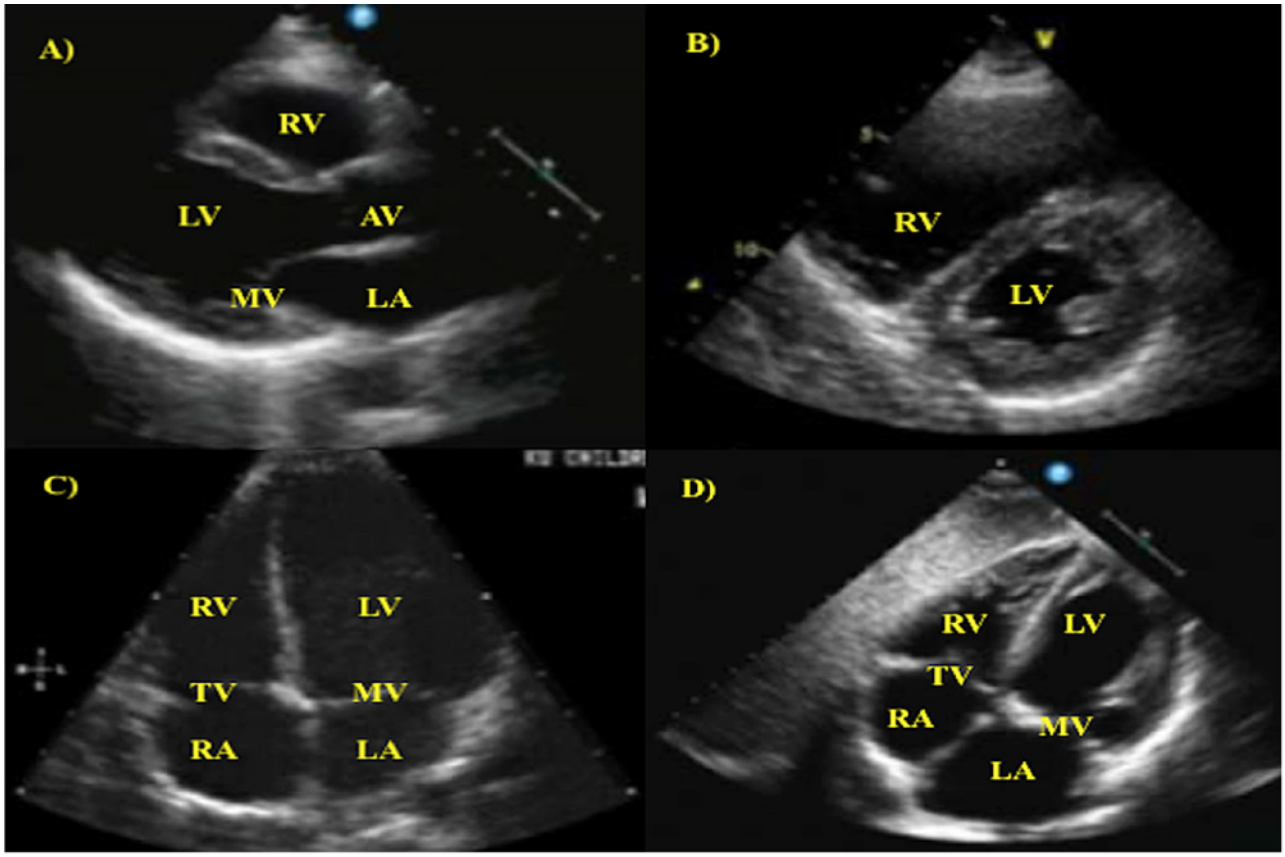

Figure 1: Transthoracic echocardiogram images from four cardiac views. A) parasternal long-axis view. B) parasternal short-axis view. C) apical four chamber view. D) subcostal four chamber view.

PERIOPERATIVE ANESTHESIA 45

Implementation and Evaluation of Point-of-Care Ultrasound OSCEs Amongst CA3 Residents across Multiple Residency Programs

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INTRODUCTION: POCUS educational curriculums across anesthesiology residencies are currently variable in structure. To aid curriculum development, we proposed a multi-institutional study during which each participating program performed a standardized POCUS OSCE on their graduating Clinical Anesthesiology-3 residents. Each program followed standardized scripts, POCUS OSCE scenarios, and grading rubrics to evaluate resident POCUS capabilities with a focus on the cardiopulmonary system. Our primary goal of this study was to describe how to implement a POCUS OSCE and evaluate anesthesia residents on their POCUS skills in their last 6 months of training to prepare them for their upcoming OSCE board examinations. Objectives included resident satisfaction surveys and resident OSCE scores.

METHODS: Nine institutions participated in the study (Albany Medical Center, University of Colorado, UCLA-Harbor, Loma Linda University, University of Oklahoma, University of California-Davis, University of California-Irvine, University of Washington, University of Southern California). Each site obtained individual institutional review board approval and signed a data-sharing agreement with the primary site (UC-Irvine). Examine Site Preparation The primary site distributed testing preparation materials to each site prior to examination to ensure standardized OSCE setup and grading. The test preparation materials included the following: 1. A OSCE demonstration video demonstrating room setup, time structure, and various instructions. 2. An OSCE POCUS views scoring rubric which included examples of views and their corresponding scores. 3. A 7-criteria general competency Likert scoring scale to aide in scoring the general competency question. OSCE Examination Study participants were pre-randomized to receive one of three test forms to ensure normalized distribution. Each test form contained 2 sections; Section 1 focused on cardiac ultrasound and Section 2 focused on pulmonary ultrasound. Emulating the structure of the current ABA Applied Examination, subjects were given an introduction prompt to read prior to entering the testing room for 4 minutes. Subjects then had 8 minutes in the testing room. Each section of the test contained 4 questions with a time limit of three minutes per section. This allowed 1 minute for setup and 1 minute for examiner grading. Thus, each OSCE examination totaled 12 minutes. Each section of the exam had the general format of:

1. Obtain specific ultrasound view
2. Identify relevant structures
3. Identify relevant structures
4. Question on topic Images and answers from the exam were saved and were graded according to the pre-defined scoring rubric with 1=Yes, 0.5=somewhat, 0=None which is structured similarly to the ABA Applied Exam matrix.

RESULTS: 36 Subjects took Test Form A, 38 took Test Form B, 36 took Test Form C. Scores for obtaining the A4C view were the lowest (Mean 0.731, SD 0.36), compared to PSAX (Mean 0.833, SD .316) and PLAX (Mean 0.806, SD 0.344). Mean scores for identifying structures were overall high > 0.7 with the notable exception of identifying the left ventricular inferior wall on PSAX (mean 0.611, SD 0.494), and where to measure Fractional Shortening on PLAX (mean 0.472, SD 0.506). In addition, subjects positioned the patients well (mean > 0.9) Scores for the lung portion were more variable. Subjects who took the pneumothorax exam scored well (> 0.8) all questions except how to describe what a pneumothorax would like in M-Mode (Mean 0.609 SD 0.492). The most difficult test for the subjects was the pleural effusion exam; approximately 1/3 of the subjects did not choose the correct probe for the exam, choosing a linear probe over the phased array or curvilinear probe. This likely led to overall low scores in structure identification and interpretation. The mean total score for this exam was 2.95/5 with a SD 1.5 which was below a passing score.

CONCLUSION: This is first study to evaluate the impact of a practice POCUS OSCE exam in graduating anesthesiology residents. The pre- and post-examination

survey demonstrated positive feedback from graduating residents regrading POCUS OSCEs. The scores on the OSCE examination highlighted areas to improve resident POCUS education in preparation for the ABA Applied Examination. Additional in-depth analysis on program POCUS education and scoring are on-going.

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4. Ramsingh D, Rinehart J, Kain Z, et al. Impact Assessment of Perioperative Point-of-Care Ultrasound Training on Anesthesiology Residents. Anesthesiology 2015;123(3),670-682
5. Epstein RM. Assessment in medical education. N Engl J Med. 2007;356:387-396
6. Sloan D, Donnelly MB, Schwartz R, Strodel W. The objective structured clinical examination – the new gold standard for evaluating postgraduate clinical performance. Ann Surg. 1995;222(6):735-742

OSCE Cardiac Views Scoring Guidelines

Scoring Guidelines
≥6.5 (≥80%) of Listed Structures = Yes (1)
6-5 (≥60%) of Listed Structures = Somewhat (0.5)
≤4.5(<60%) of Listed Structures = No (0)
Incomplete views of structures can be counted as 1/2 structures (ie two incomplete views can be counted as 1 structure)

Parasternal Long Axis View Structures

1. LA
2. LV
3. RV
4. IV Septum
5. Aortic Valve
6. Aortic Root/Ascending Aorta
7. LVOT
8. Mitral Valve

Parasternal Short-Axis View Midpapillary Level Structures

1. LV Anterior Wall
2. LV Inferior Wall
3. LV Lateral Wal
4. LV Septal Wall
5. 1 Papillary Muscle
6. 2 Papillary Muscles
7. RV
8. Pericardium

Apical 4 Chamber View Structures

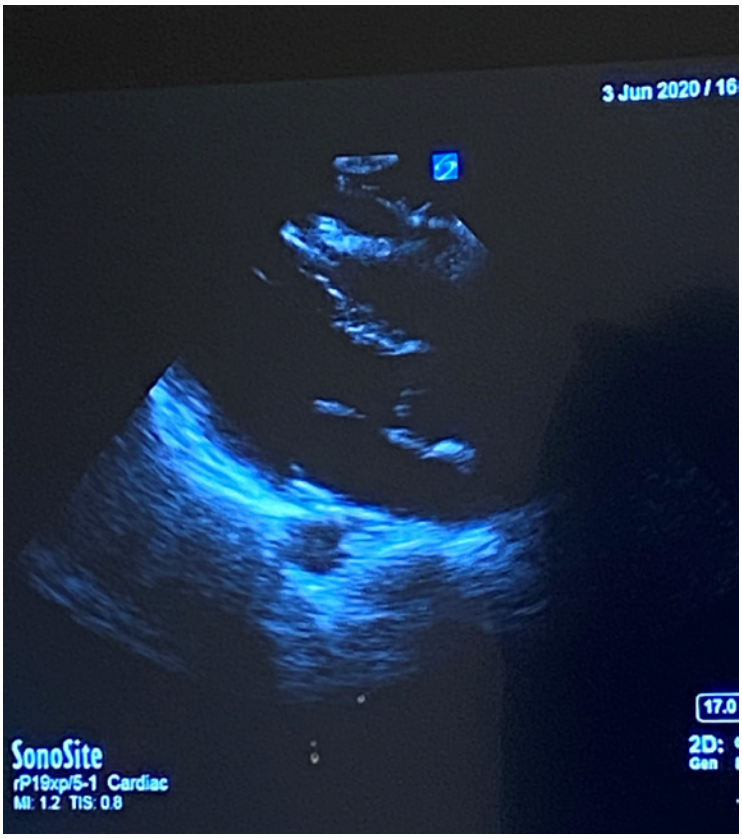
1. LA
2. LV
3. RA
4. RV
5. Mitral Valve
6. Tricuspid Valve
7. IV Septum
8. Inter-atrial Septum

Disclaimer: Due to the fact that not all aspects of the ultrasound exam can always be captured in one image, examiners are allowed to make on the spot decisions regarding image scoring. The comments section should be used to justify captured image discrepancies that deviate from standard scoring.

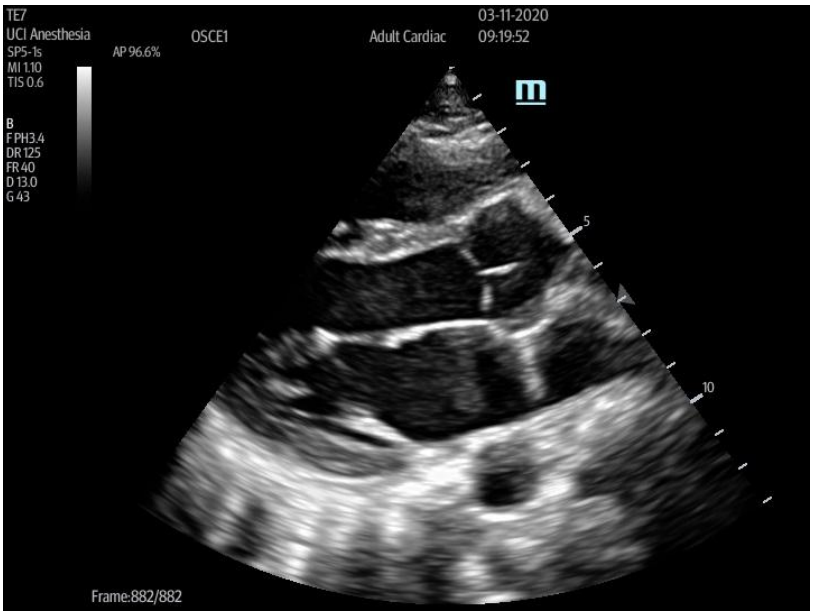
Cardiac Image Scoring Examples

Parasternal Long Axis Examples

Examples of Yes (1) views:

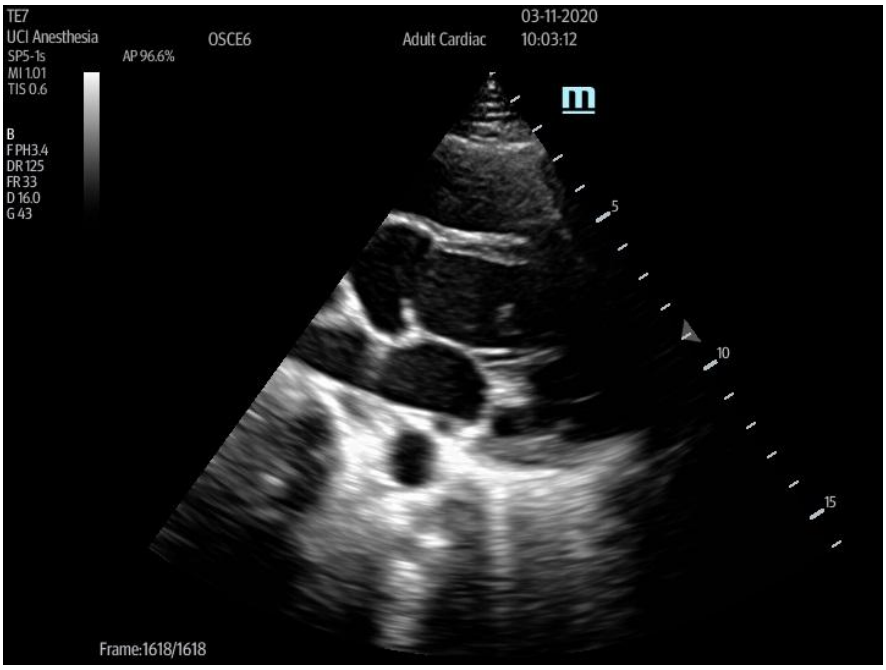


Comment: Good View



Comment: Incomplete view of LA but still good

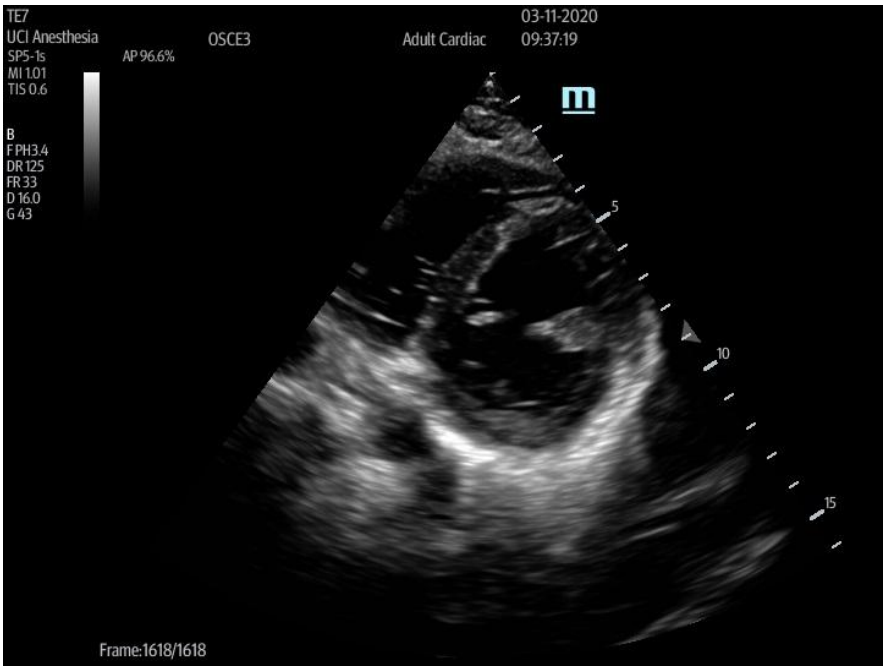
Examples of Somewhat (0.5) views:



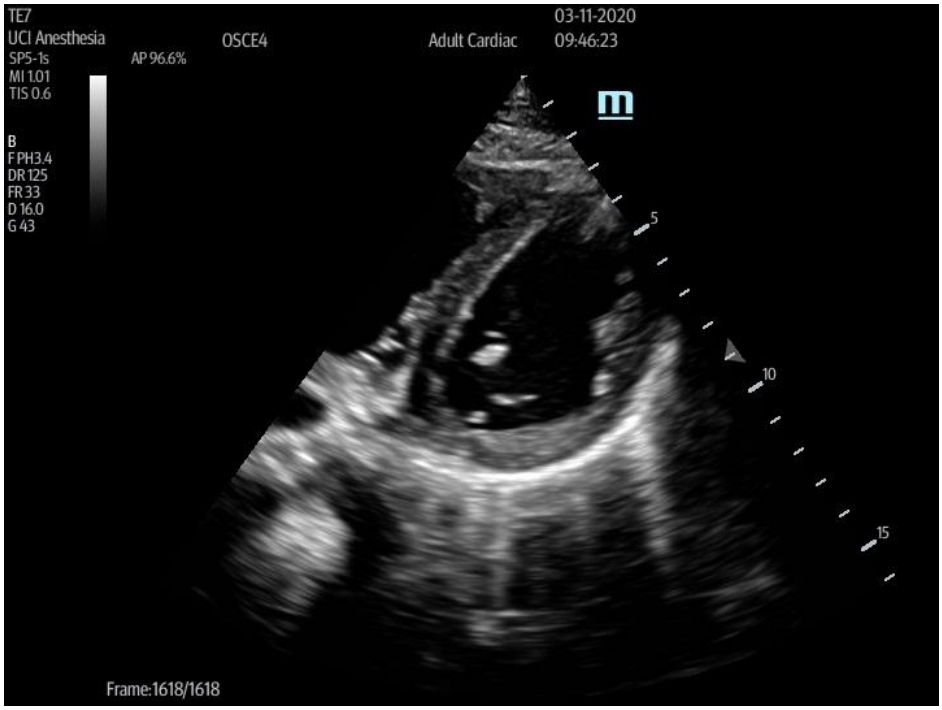
Comment: Incomplete view of LA, LV, IV Septum, Mitral Valve

Parasternal Short Axis Examples

Examples of Yes (1) views:

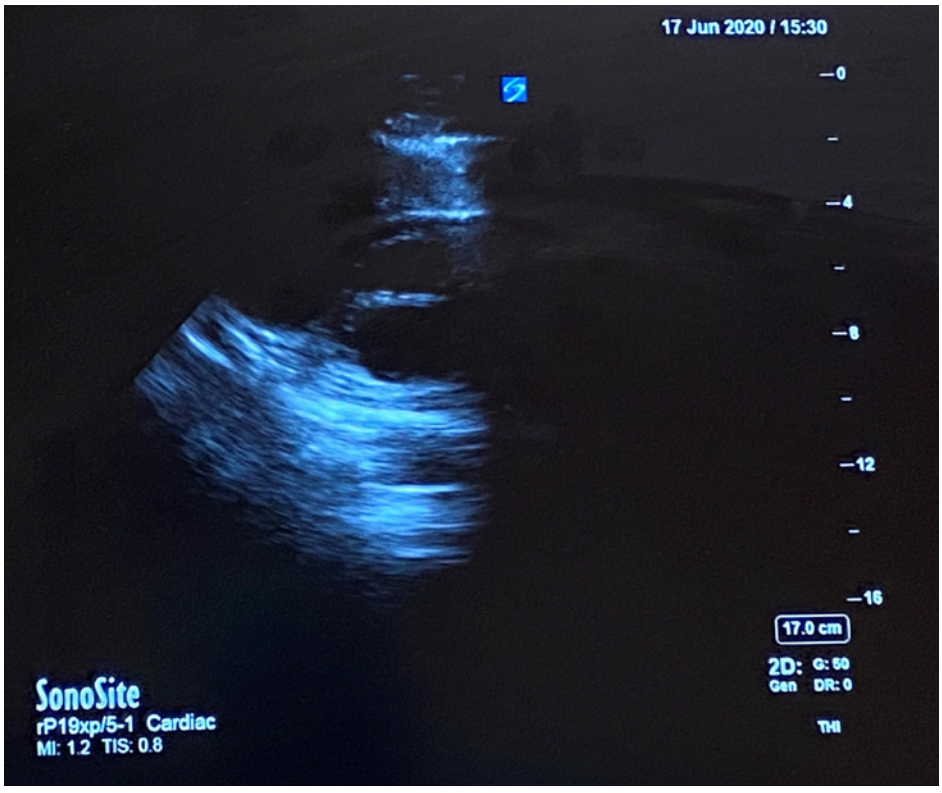


Comment: Good view, both papillary muscles seen in short axis.

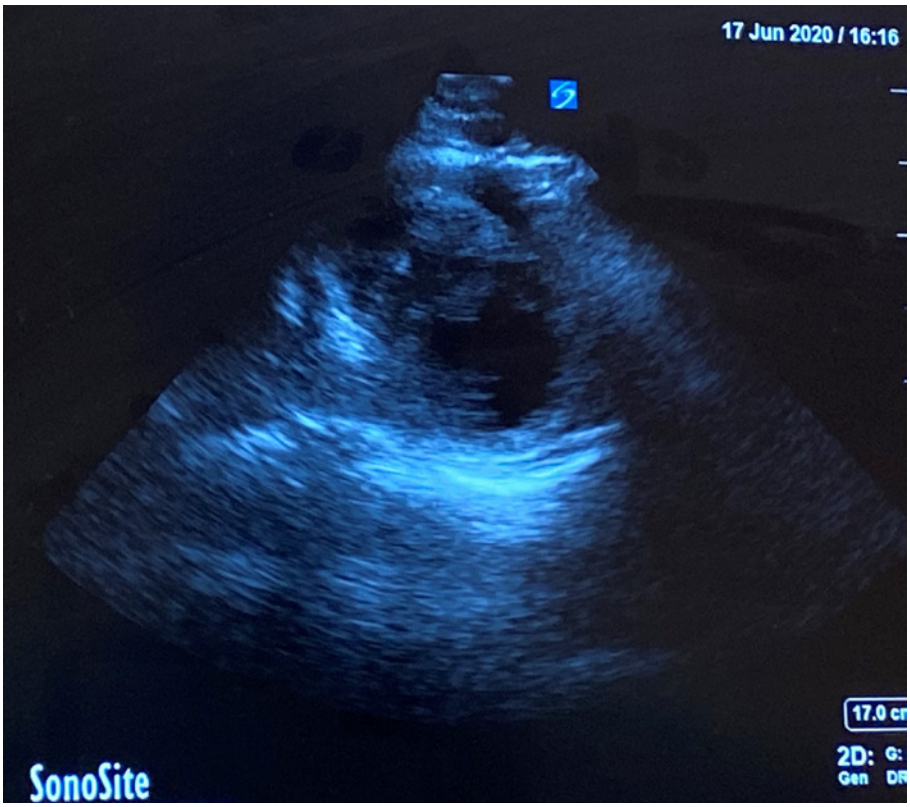


Comment: We see One papillary muscle in short axis, but still acceptable.

Examples of Somewhat (0.5) views:



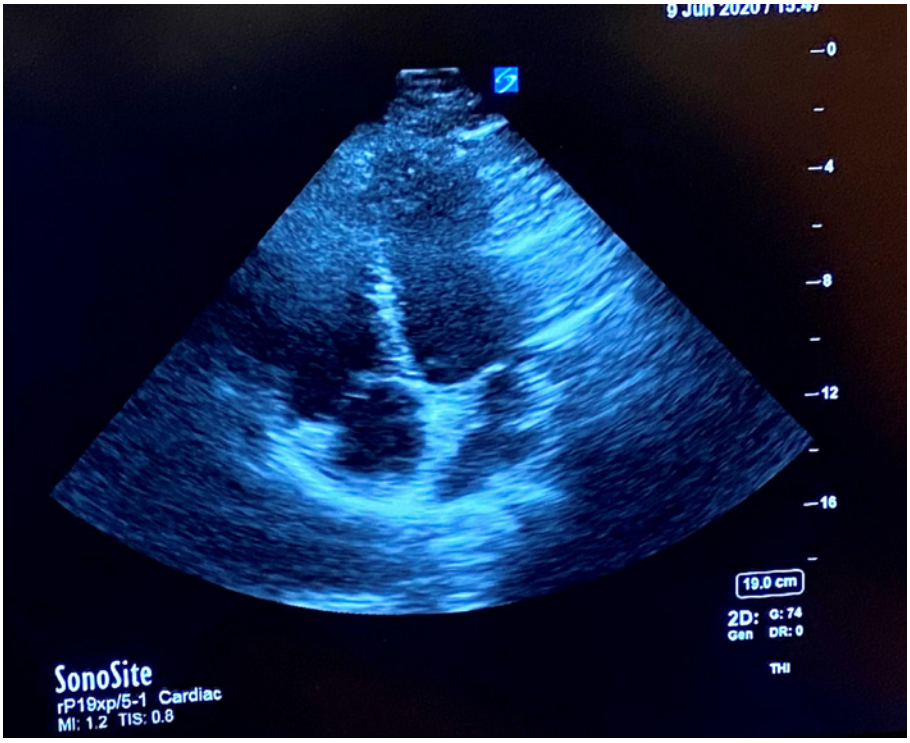
Comment: More of a short axis basal (lvl of mitral valve view)



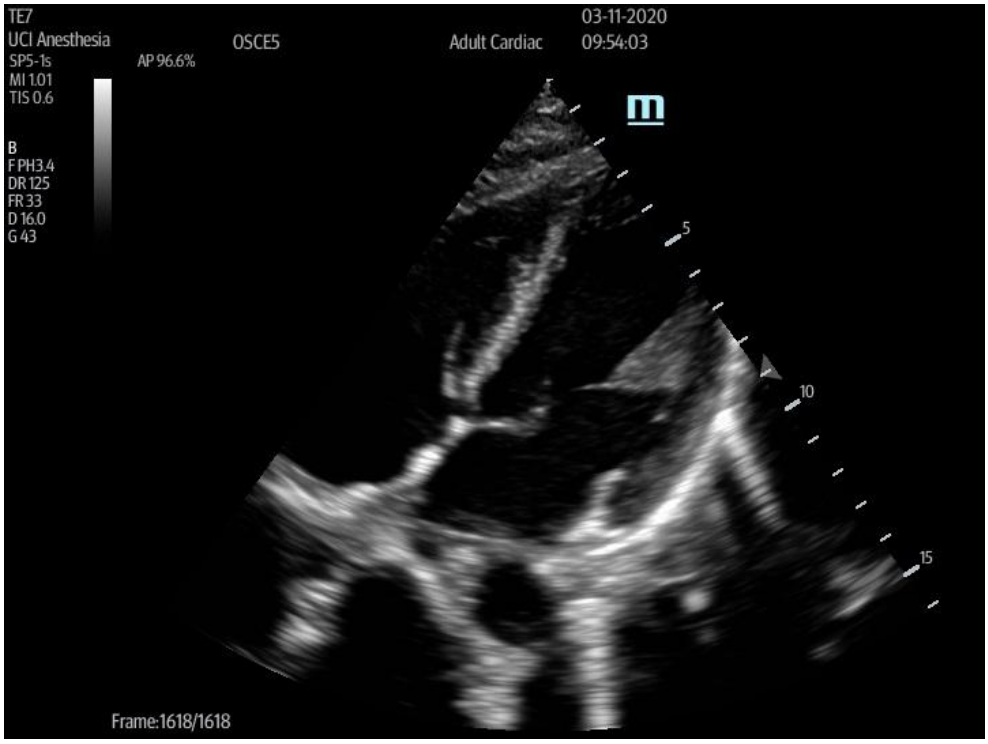
Comment: Short axis towards apex (no papillary muscles seen)

Apical 4 Chamber Examples

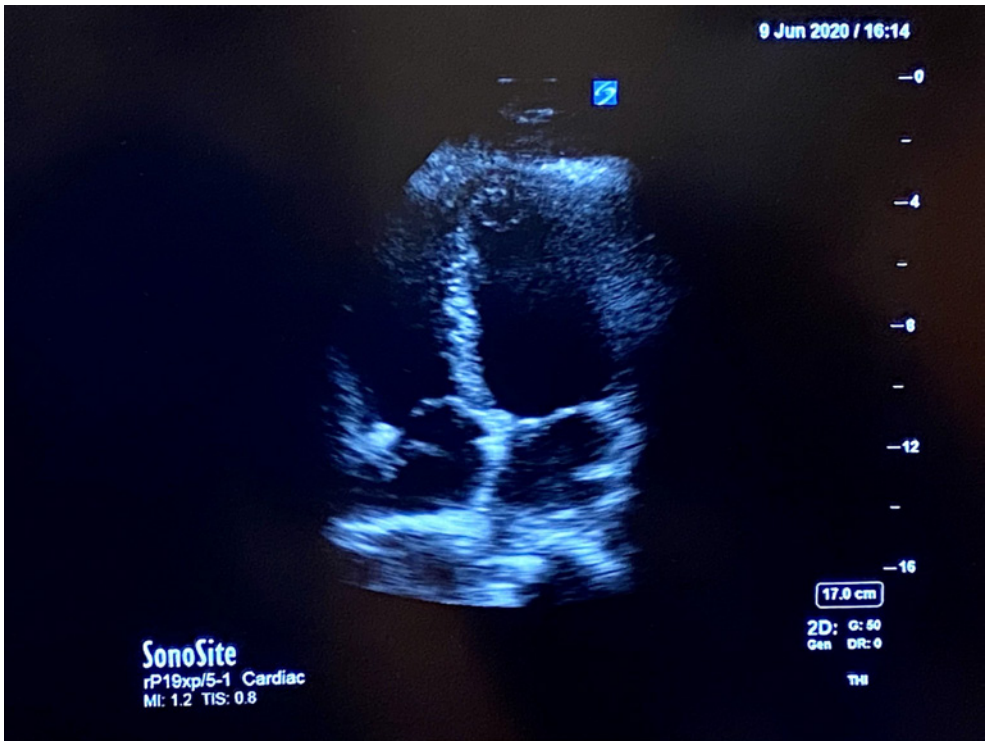
Examples of Yes (1) views:



Comment: All 4 chambers visualized although 3 partially incomplete

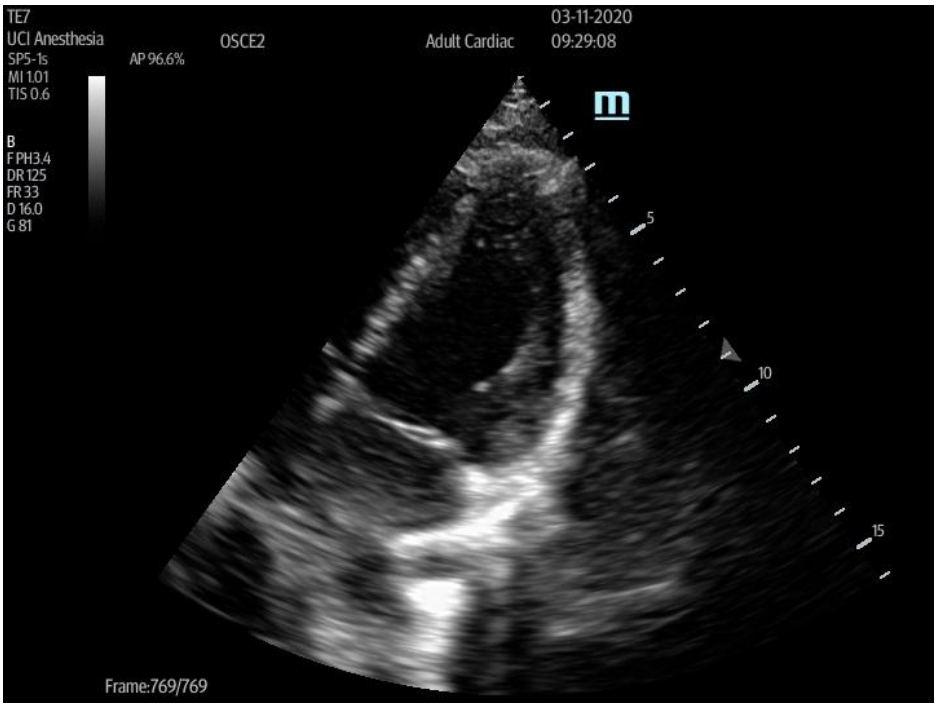


Comment: All 4 chambers visualized, but too zoomed in.

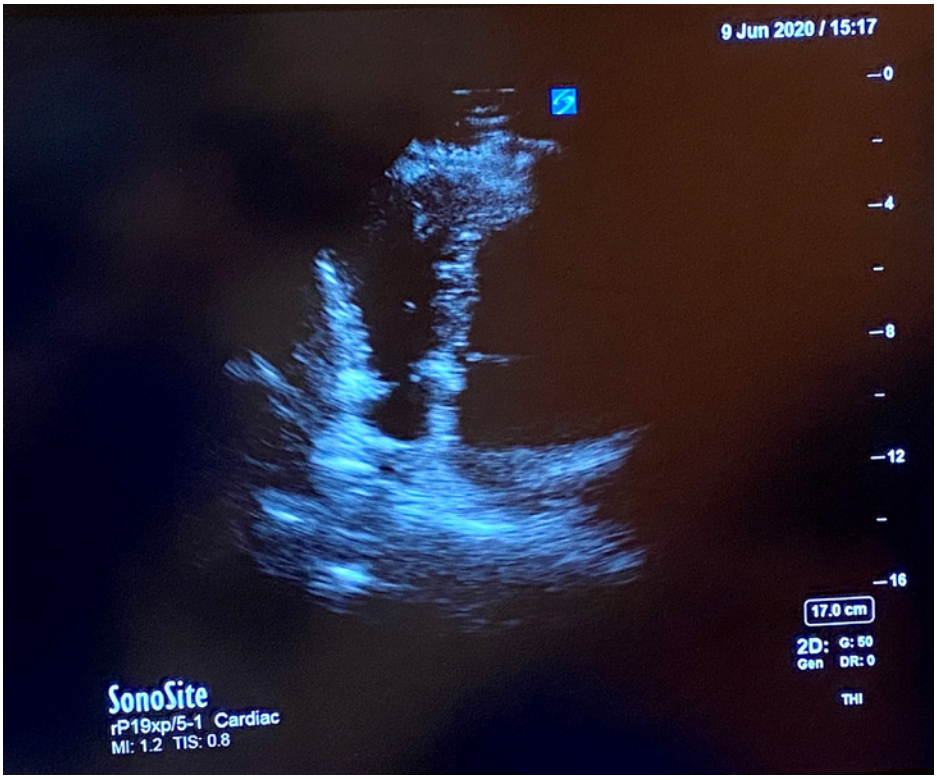


Comments: All 4 chambers visualized

Examples of Somewhat (0.5) views:



Comment: Incomplete views of RV, RA, TV, Atrial Septum (Total = 6 Structures)



Comment: Incomplete views of LV, LA, RV, RA, TV, MV. (Total = 5 structures)

OSCE Pulmonary Views Scoring Guidelines

Scoring Guidelines
≥4 (≥80%) of Listed Structures = Yes (1)
3 (≥60%) of Listed Structures = Somewhat (0.5)
≤2 (<60%) of Listed Structures = No (0)
All or none, no ½ structures

Lung view for PTX Structures

1. 1 Rib
2. 2 Ribs
3. Lung Parenchyma
4. Pleural Line
5. Intercostal Muscles

Lung view for Pleural Effusion Structures

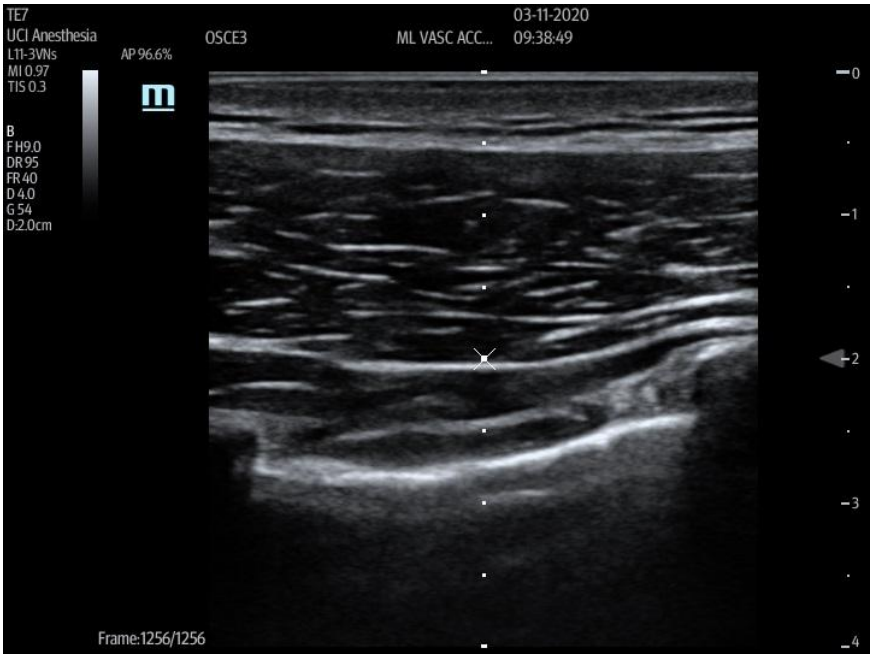
1. Liver
2. Diaphragm
3. Lung Parenchyma
4. Pleural Line
5. A Lines

Disclaimer: Due to the fact that not all aspects of the ultrasound exam can always be captured in one image, examiners are allowed to make on the spot decisions regarding image scoring. The comments section should be used to justify captured image discrepancies that deviate from standard scoring.

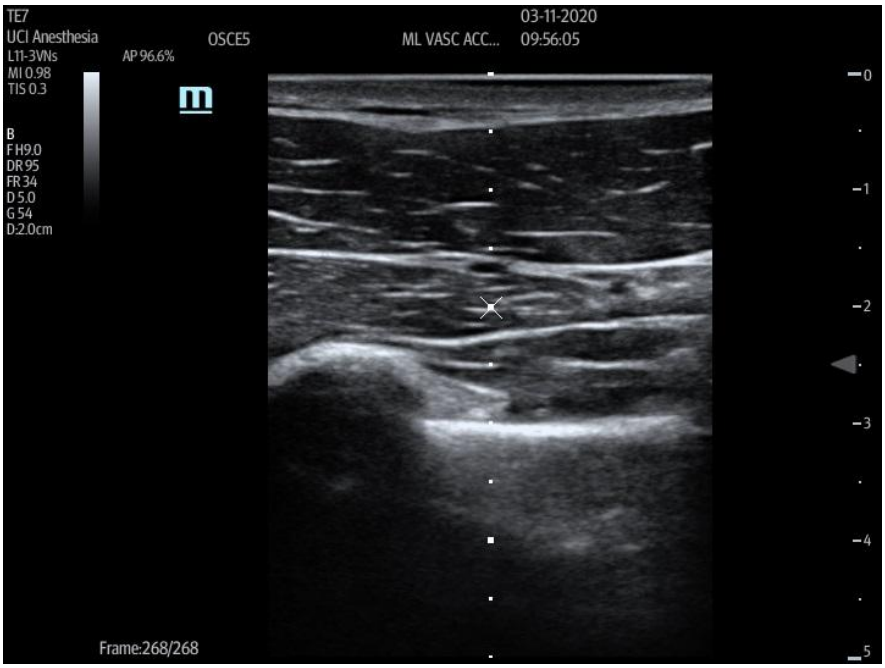
Pulmonary Image Scoring Examples

PTX Examples:

Examples of Yes (1) views:

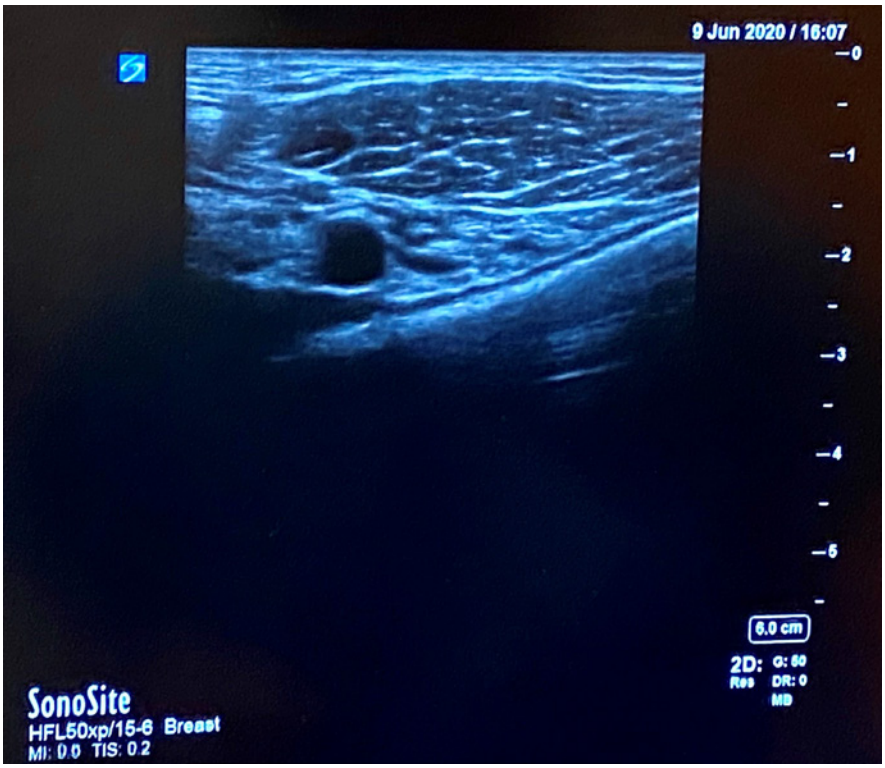


Comments: Excellent view with 2 rib shadowing



Comments: Acceptable view with 1 rib shadowing

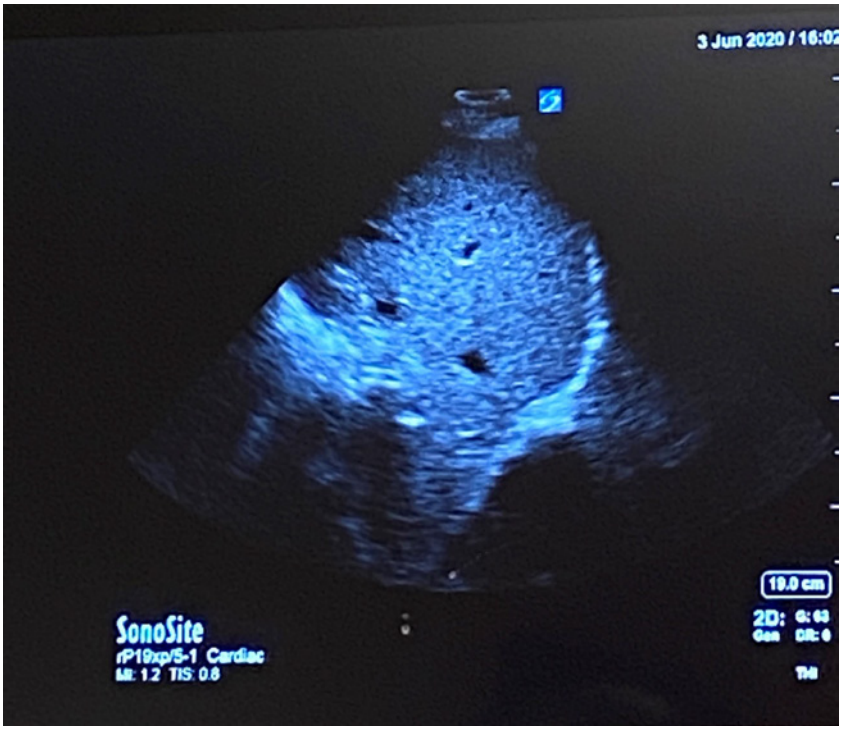
Examples of Somewhat (0.5) views:



Comments: No Rib shadowing but does have pleura and parenchyma in view

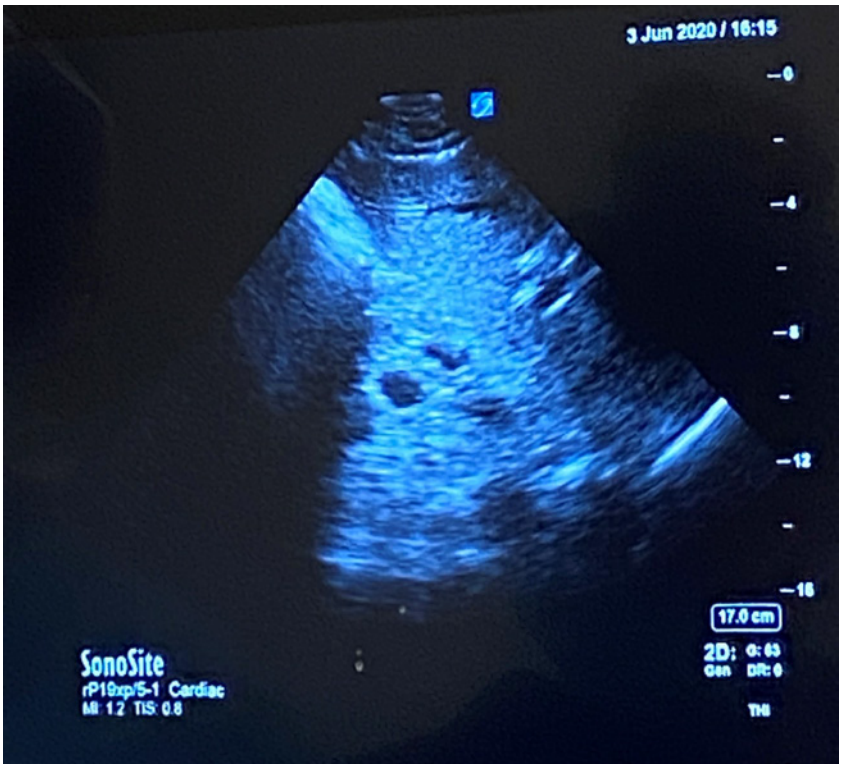
Pleural Effusion Examples:

Examples of Yes (1) views:



Comments: Acceptable view with Liver, Diaphragm, and lung parenchyma in view but no Pleural Line

Examples of Somewhat (0.5) views:



Comments: No Diaphragm or Pleural Line.

POCUS OSCE Pre-Survey

	Strongly Disagree 1	Disagree 2	Undecided 3	Agree 4	Strongly Agree 5
1. I feel that POCUS is an important aspect of my training.					
2. I feel that a structured POCUS Curriculum is important to anesthesia resident education					
3. I feel that practicing on live models and patients is helpful to learning POCUS					
4. I feel that consistent assessment of my POCUS skills would be helpful to my training.					
5. I have had prior experience with OSCE examinations.					
6. I feel that OSCE Examinations are helpful to skills assessment.					
7. I feel that skills assessment through OSCEs would be helpful to me in learning POCUS.					
8. Having scheduled OSCE examinations would encourage me to practice my POCUS skills.					

PERIOPERATIVE ANESTHESIA 46

The Preoperative Skin Microbiome is Associated with Causes of Surgical Site Infection in Spinal Fusion Surgery and Varies by Operative Level

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[1]University of Washington, Seattle, WA, [2]Harborview Medical Center, Seattle, WA, [3]University of California, San Francisco, San Francisco, CA, [4]Harborview Medical Center, Seattle , WA

INTRODUCTION: Surgical site infection (SSI) is a devastating outcome of instrumented spine surgery, occurring in as many as 1 in 30 procedures with adverse impacts on patient satisfaction, pain, functional outcomes, and healthcare costs[1,2]. Quality improvement in this arena is limited by a poor fundamental understanding of the pathogenesis of these infections. We and others have previously described an anatomic gradient in the pathogens causing SSI following spinal fusion, transitioning along the length of the back from gram-positive infection at cervical levels to gram-negative infection at lumbosacral levels[3,4]. These observations suggest that the patient skin microbiome may be a primary source for SSI in modern spine surgery; however, the back is a poorly characterized region of the human skin microbiome. The objective of this study was to determine whether observed anatomic differences in the causes of SSI are associated with differences in the preoperative skin microbiome at various operative levels.

METHODS: Adult patients undergoing posterior spinal fusion surgery at a single, high-volume academic medical center between September 2019 and August 2020 were included. Preoperative swabs from skin overlying the intended surgical site were obtained on the day of surgery, immediately prior to surgical skin preparation. Multiple samples spanning 10 positions from C2 to coccyx were also collected prior to the day of surgery among a subset of enrolled patients. Standard processes for DNA extraction, 16S PCR, and amplicon sequencing were followed5. Analysis of sequence data was performed using QIIME 2[6] and R[7].

RESULTS: Among 209 enrolled patients, adequate specimens were obtained from 204 (97%). A subset of 110 samples from cases confined to only cervical (21%) or lumbosacral (79%) operative levels and further stratified by patient sex (to provide balanced representation within each region) were selected for sequencing and analysis. The relative abundance of potentially pathogenic gram-positive flora was greater in cervical skin regions while gram-negative organisms predominated in preoperative lumbosacral skin regions (Fig 1). This anatomic gradient persisted at the individual patient level, with most patients showing a graded transition in skin flora along the length of the back (Fig 2). Marked differences in the anatomic distribution of several specific taxa were observed. Staphylococci demonstrated the greatest enrichment in preoperative skin samples collected at cervical levels whereas Escherichia, Pseudomonas, Enterobacter, and anaerobes were more abundant at lumbosacral levels. (Fig 3).

CONCLUSION: Anatomic differences in the preoperative skin microbiome are closely correlated with the causative bacteria identified in postoperative wound cultures from cases of spinal fusion SSI. Future infection prevention research in spine surgery should prioritize strategies targeting perioperative control of the patient skin microbiome. The efficacy of alternative or personalized prophylactic antibiotic regimens that account for anatomic and individual differences in preoperative skin colonization should be evaluated.

REFERENCES:

1. Clinical outcomes after lumbar fusion complicated by deep wound infection: a case-control study. Spine 2012; 37:1370-4
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7. R Foundation for Statistical Computing, Vienna, Austria., 2021 at <https://www.R-project.org/>

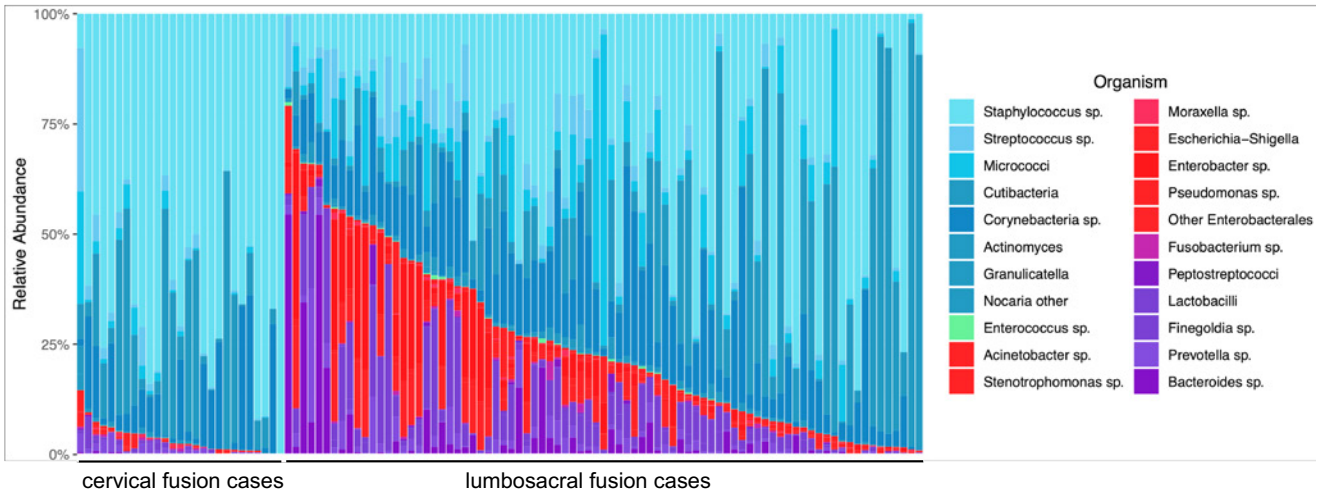

Figure 1. Skin microbiome overlying cervical vs. lumbar surgical sites. Each column along the horizontal axis contains 16S microbiome data from the skin of a single patient, sampled immediately prior to the application of surgical antisepsis. The relative abundance of all potentially pathogenic bacteria (isolated from more than one spine SSI during the study period) is shown as stacked bar plot for each patient on the vertical axis. Blue shades indicate gram-positive organisms (e.g. Staphylocci, Streptococci, etc), which predominate skin communities at cervical levels. Red and purple shades indicate gram-negative and anaerobic organisms, respectively, which are significantly enriched in the skin microbiome of the back at lumbosacral levels.

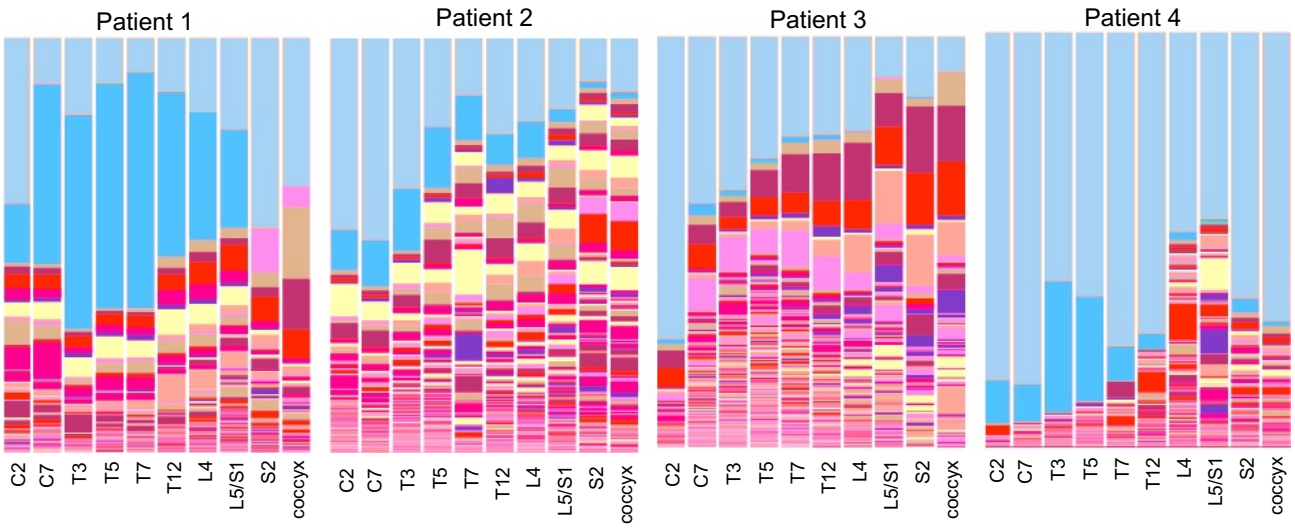

Figure 2. Anatomic gradients in the skin microbiome along the length of the back in individual patients. As in Figure 1, the relative abundance of preoperative skin flora is shown on the vertical axis with bars shaded to discriminate key gram-positive (blue) vs. gram-negative (red/purple) organisms. However, in this analysis, multiple samples from four patients were collected at ten points along the length of the back (stratified along the horizontal axis from C2 to coccyx). These results indicate that the shift from gram-positive (cervical) to gram-negative (lumbosacral) skin colonization represents true gradient across anatomic space, rather than a population-level phenomenon arising from generalized differences in the skin microbiomes of patients undergoing cervical vs. lumbar fusion.

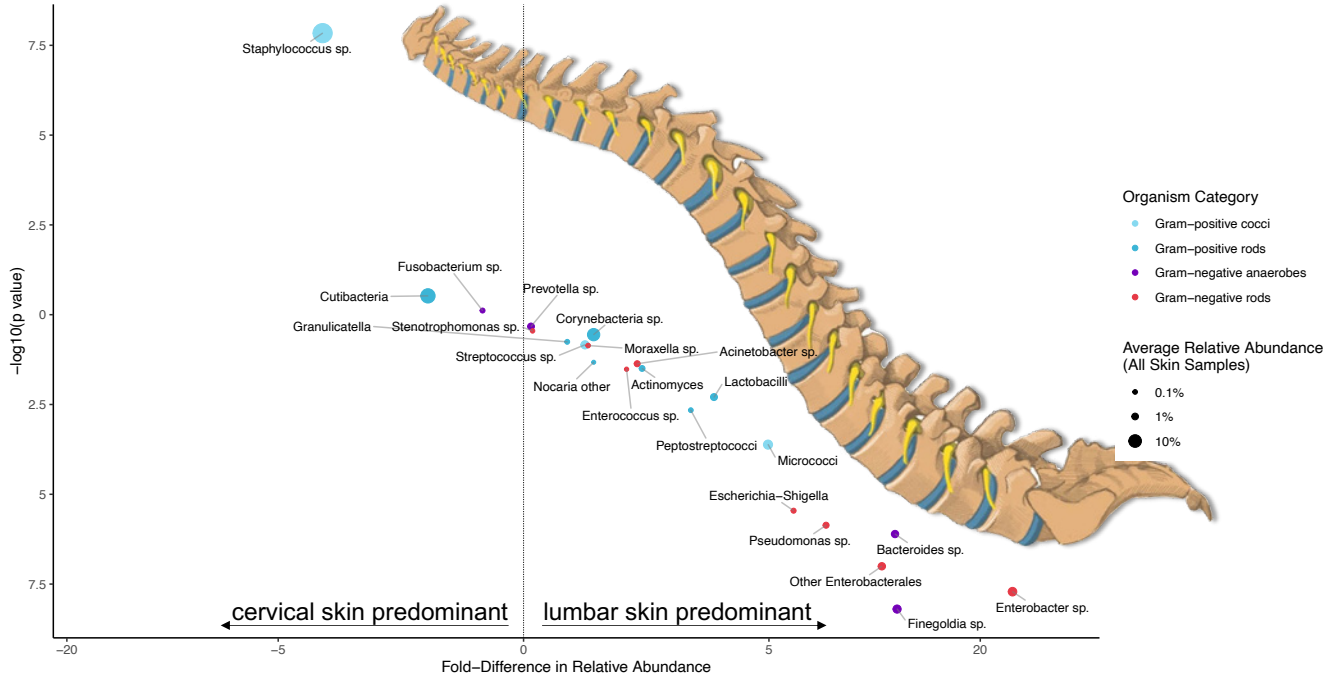

Figure 3. Relative distribution of potential pathogens colonizing preoperative skin along the length of the back. This "volcano plot" is vertically mirrored at the mid-point of the horizontal axis to visually convey the anatomic polarization of individual taxonomic groups. Staphylococci demonstrate the greatest enrichment in samples collected from preoperative skin samples at cervical levels. Anaerobes and enteric gram-negative flora are significantly over-represented in the preoperative skin microbiome at lumbosacral levels. Color shading scheme is comparable to Figures 1 and 2, dot area is proportional to overall organism abundance.

PERIOPERATIVE ANESTHESIA 47

Failure of Sugammadex to Improve Operating Room Discharge Times following Laparoscopic Cholecystectomy

Danielle Esnard[1], Christian Lee[1], David Broussard[2], Stuart Hart[3], Alex Allain[2], Brittany Bond[2], Eric Busch[2], Preya Jhita[2], Melissa Matte[2], Robin Stedman[4], Jacob Lessing[2], Bobby D Nossaman[3]

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INTRODUCTION: Studies examining perioperative time savings with sugammadex have been limited to small group analyses,[1,2] meta-analysis,[3] or in hypothetical time efficiency models.[4-6] The purpose of this study was to determine the clinical effectiveness of sugammadex when compared to neostigmine under real-world, non-Hawthorne effect[7] conditions on operating room discharge times in patients following laparoscopic cholecystectomy.

METHODS: Following institutional review board approval, data from 1,614 consecutive surgical records for laparoscopic cholecystectomy were electronically abstracted from May 2020 to May 2021. Patient characteristics, type of primary neuromuscular blocking reversal agent, and operating room (OR) discharge times were the measures of interest. Categorical variables were presented as counts and percentages with 95% confidence intervals (CI) with group differences assessed using chi-square (œá¬≤) tests. Continuous variables with skewed distributions were presented as medians with 25%-75% interquartile range [IQR] with differences between the two groups assessed by the Wilcoxon rank sum test. Geometric means were expressed with associated CI.

RESULTS: Patient demographics are shown in Table 1. There were no statistically significant differences in age, gender, or in the ASA PS scores between the two neuromuscular blocker reversal agents (Table 1). The OR discharge times for the two neuromuscular blocking agents are shown in Figure 1. Box-plots for OR discharge times for sugammadex and for neostigmine are shown in the left panel and when the OR discharge times are expressed as Normal Quantile plots on the right panel (Fig. 1). The median and 25-75% interquartile (IQR) times for sugammadex was 9.0 min IQR 7.0-13 min and neostigmine 8.0 min IQR 6.0-11 min. Geometric mean times for sugammadex were 9.1 min CI 9.1-9.2 min and 8.0 min CI 8.01-8.03 min for neostigmine. A discernable difference in the slopes of the OR discharge times for the two neuromuscular blocking reversal agents begins to declare at the .64 quantile (green line, right panel) with the slope of the OR discharge times progressively increasing more for sugammadex when compared to neostigmine. The OR discharge times slope for neostigmine (blue line) was less acute when compared to the OR discharge times slope for sugammadex (right panel).

CONCLUSION: These results suggest no benefit of sugammadex when used as a primary neuromuscular blocking reversal agent to improve OR discharge times when compared to neostigmine following laparoscopic cholecystectomy.

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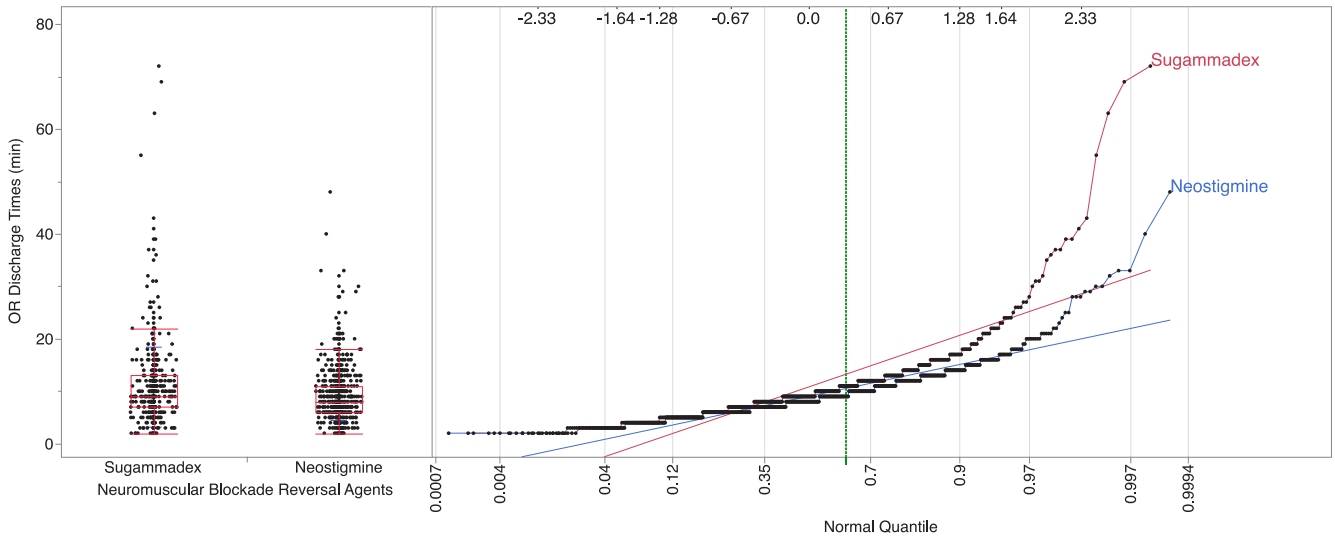
Table 1: Baseline Characteristics in 1,614 Patients with Sugammadex or Neostigmine as the Primary Neuromuscular Blocking Reversal Agent following Laparoscopic Cholecystectomy

	Sugammadex	Neostigmine	P Value
Age, yrs median [IQR]	49 [35-62]	47 [33-61]	0.2778
Gender, m (%)	151 (26.7)	294 (29.9)	0.1658
ASA PS, counts (%)			
I	28 (4.7)	63 (6.2)	
II	331 (55)	613 (61)	0.0196
III	229 (38)	322 (32)	
IV	14 (2.3)	14 (1.8)	

IQR: 25-75% interquartile range; Gender, m: male; ASA PS: American Society of Anesthesiologists' Physical Status Score; P values <0.005 are statistically significant.

Figure 1



PERIOPERATIVE ANESTHESIA 48

Impact of tranexamic acid use on perioperative blood transfusion in pediatric cranioplasty: a retrospective review

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INTRODUCTION: Cranioplasty is the surgical reshaping of the skull. It may be required due to several pediatric conditions usually involving the early fusion of one or more suture lines between bony skull plates resulting in asymmetric skull growth and deformity. If left uncorrected, this deformity can result in raised intracranial pressure, cognitive and neurodevelopmental delay, including feeding and speech, as well as psychosocial effects[1]). A wide range of surgical procedures can be performed at varying ages involving different surgical complexities. Minimal access techniques are being developed; however, most of the surgery performed at our institution involves open repair. The main intraoperative hazards specific to these procedures are hemorrhage and venous air embolism: blood loss may be massive and sudden, principally from the periosteum and venous sinuses[1]. Tranexamic acid (TXA) is an antifibrinolytic drug that has been shown to reduce blood loss in several situations[2]. Its use in cranioplasty procedures has been previously described[3]. However, evidence of benefit in this group has yet to be established. Our study retrospectively investigated perioperative records for the last six years. We hypothesized that the use of TXA reduced perioperative blood loss and red cell transfusion requirements, while also reducing the length of stay in critical care (LOS). The primary outcome measure looked at the effect of TXA use on the volume of red cells transfused perioperatively. The secondary outcome measures looked at the lowest recorded postoperative hemoglobin, LOS, and the estimated perioperative blood loss (EBL).

METHODS: After obtaining IRB approval we performed a retrospective observational investigation on the electronic pediatric patient charts of all those from 0-8 years of age who underwent cranioplasty procedures from 2015 to 2021 at our institution. A data collection form in Excel (Microsoft 365) was designed to collect de-identified patient data. The accessed fields were patient demographics (age, gender, and weight), type of surgery, lowest postoperative hemoglobin, perioperative receipt of TXA, EBL, intraoperative hematocrit, the volume of transfused blood per kilogram of body weight, and LOS. A secondary data sheet was then created to filter and separate those patients that received tranexamic acid (TXA group) from those that did not (non TXA group) to test our study hypothesis. We performed a comparative statistical analysis using the Mann Whitney U test on: the volume of red cells transfused per kilogram body weight; EBL; LOS; and the lowest postoperative hemoglobin. The level of significance used was 0.05.

RESULTS: A total of 71 pediatric patient records were analyzed. Our study included all those aged 0-8 years who underwent cranioplasty procedures between 2015 and 2021. All other patients were excluded. Table 1 lists the median values for the various parameters with the interquartile ranges (IQR) mentioned within brackets. The median age of the TXA group was younger than that of the non TXA group. The median weight of the TXA group was less heavy than that of the non TXA group. The median volume of transfused blood per kg body weight in the TXA group was more than the non TXA group. The median value for the lowest postoperative hemoglobin was similar amongst both groups. The median EBL in the TXA group was less than the non TXA group. The median LOS for the TXA group was less than the non TXA group. The p-value was more than 0.05 for the red cell transfusion volumes, EBL, and lowest postoperative hemoglobin. The p-value was less than 0.01 for the LOS. Figure 1 shows a graphical representation from 2015 to 2021 of the medians and IQRs for the LOS amongst both TXA and non TXA groups.

CONCLUSION: Our study found no difference in the volume of red cells transfused per kilogram body weight between the two groups. However, there was a significant clinical and statistical difference in the LOS between the TXA and non TXA groups. The reduction in LOS over time in the TXA group could be a direct effect of the drug; however, other possible confounders were not controlled for in our study. Surprisingly, the TXA group was smaller and younger than their counterparts which might be expected to result in longer critical care stay. We believe our study justifies a prospective controlled investigation of the effect of TXA on LOS and recovery after surgery.

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Figure 1. Line plot of the TXA vs Non TXA groups. Points are Median (whiskers represent the IQR)

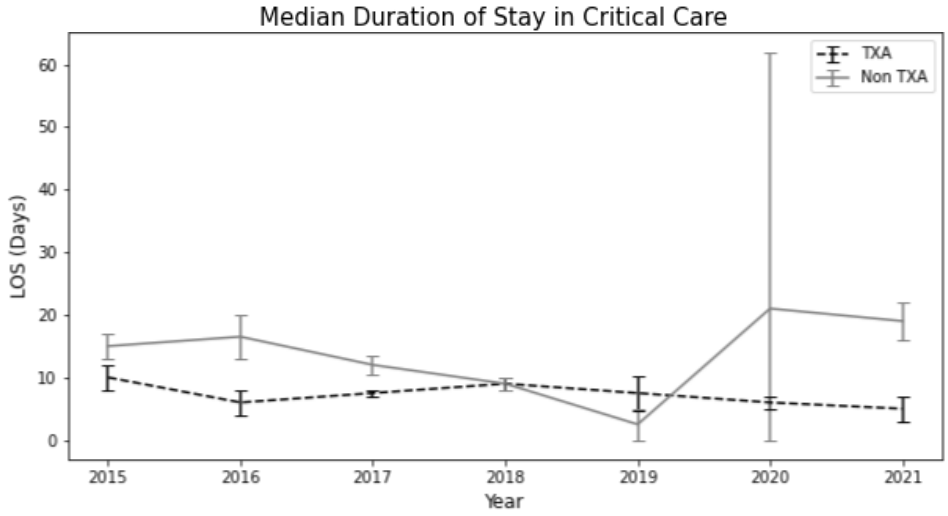

Table 1. Variable parameter values in the TXA vs Non TXA groups. Numbers are Median (IQ range)

	Age (months)	Weight (kg)	Red cell transfusion volumes (ml/kg)	EBL (ml)	Lowest postoperative Hb (g/L)	LOS (days)
TXA	14 (9-21)	10 (8-12)	26 (21-36)	225 (150-300)	96 (86-111)	6 (5-8) *
Non TXA	23 (16-36)	12 (10-14)	23 (9-39)	250 (140-400)	98 (91-114)	12 (9-15) *

*$p < 0.01$

PERIOPERATIVE ANESTHESIA 49

Leveraging MPOG ASPIRE quality metrics for assessment of disparities in perioperative care and postoperative outcomes: an exploratory quality improvement analysis

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INTRODUCTION: Identifying and mitigating racial and ethnic disparities in healthcare are critical to ensuring the provision of equitable care, a core pillar of quality care (O'Kane 2021). A promising approach to identifying these disparities is to stratify existing high-quality metrics of process and outcome measures according to race and ethnicity and other markers of vulnerability such as language of care and rurality, and adjusting for potential confounders and effect modifiers. The Multicenter Perioperative Outcomes ASPIRE team has developed detailed, evidence-based definitions and business logic for a large number of these metrics.

METHODS: A local implementation of 5 ASPIRE metrics (intraoperative hypotension avoidance; intraoperative use of lung protective ventilation; intraoperative hyperglycemia treatment; postoperative acute kidney injury; postoperative troponinemia) had previously been deployed using data from the University of Washington Medicine perioperative electronic medical record. Success at the case level was calculated for appropriately included cases performed between January 2017 and March 2021. Patient ZIP codes were used to retrieve and stratify median income and rurality using publicly accessible US Census data. A safe-harbor deidentified dataset was generated including the following data elements: age, sex, body mass index (BMI), race, ethnicity, insurance, rurality, median income by ZIP, ASA relative value guide base units, ASA physical status, emergency case, anonymized facility. Race and ethnicity were combined into a single multilevel categorical variable using previously described logic (Groenewald 2021). Due to differences in underlying inclusion and exclusion criteria, the final case count for each ASPIRE metric varied. Using R v4.1.1 and RStudio v1.4.1717, multiple variable logistic regression models were developed and assessed using c-statistic and Hosmer-Lemeshow tests. Because different subgroups were tested, no adjustment for multiple comparisons was deemed necessary.

RESULTS: The full data set encompassed 125,518 cases, with (as indicated) variable subsets for each metric examined. For ASPIRE process metrics, adjusted analysis revealed substantial disparities in care for use of lung protective ventilation (Fig 1a; N = 81,145 with 33,069 failures) but not for hypotension avoidance (Fig 1b; N = 113,392 with 8,495 failures) or treatment of hyperglycemia (Fig 1c; N = 7,044 with 1,074 failures). For outcome metrics, significant disparities were observed for acute kidney injury (Fig 2a; N = 104,485 with 3,347 events) but not for troponinemia (Fig 2b; N = 116,271 with 246 events).

CONCLUSION: Our adjusted analysis of a selection of ASPIRE process and outcome metrics suggested significant disparities in care and outcomes. Next steps in this project will be confirmation of these findings through sensitivity analyses, assembly of prediction models, multicenter implementation of this analysis, and identification of modifiable factors that could drive improvements in these disparities.

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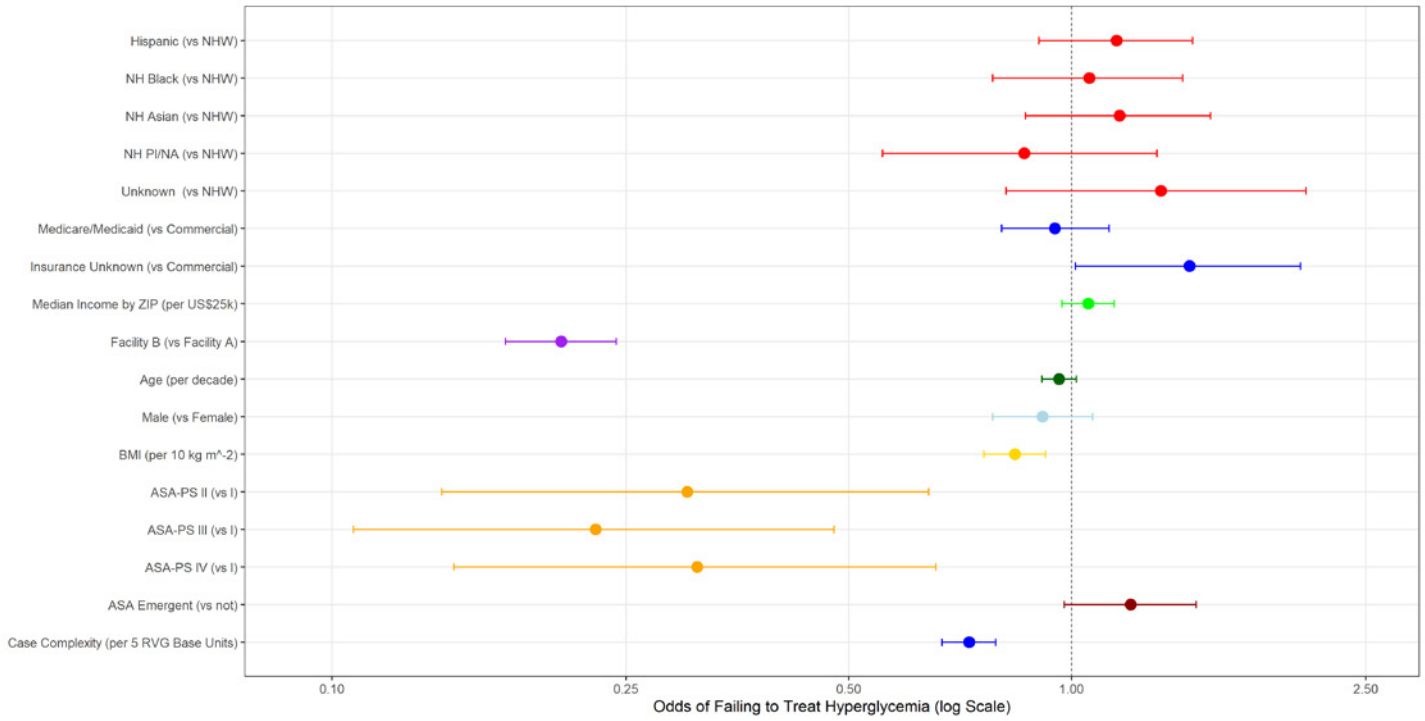

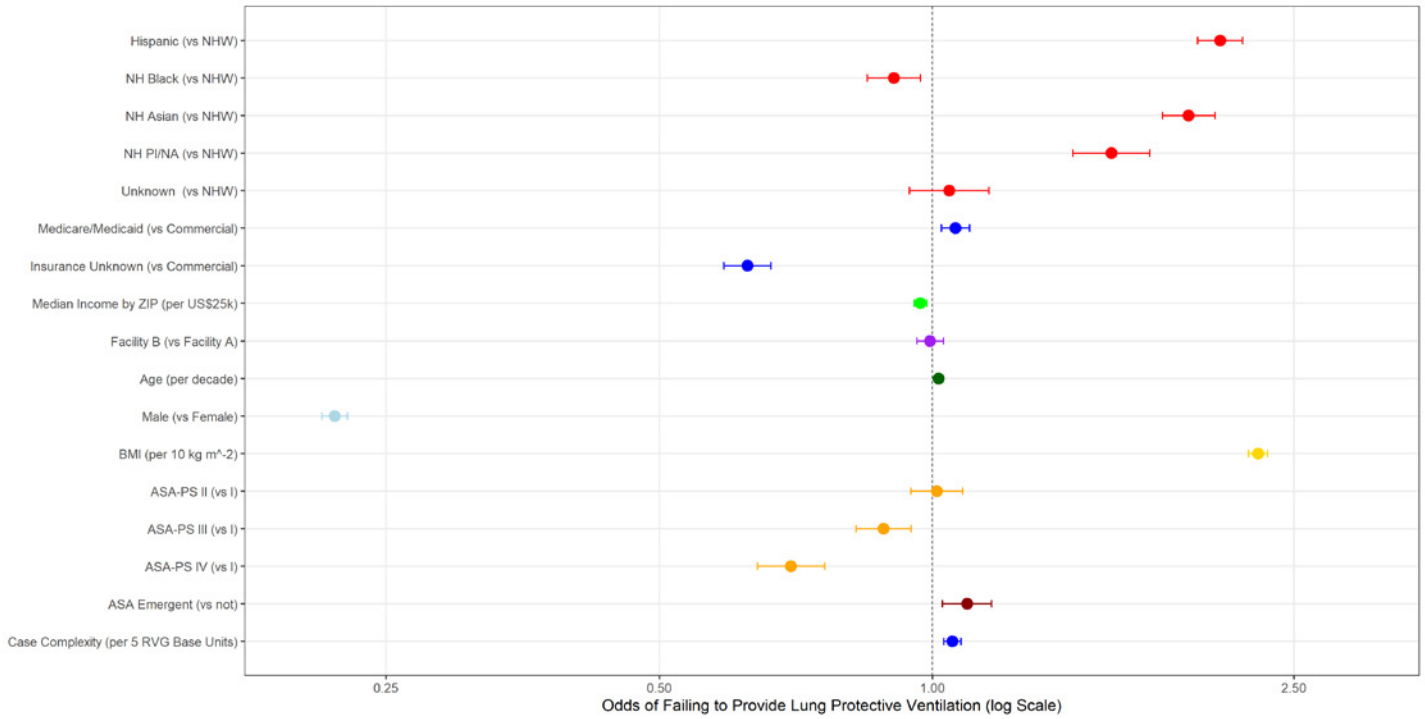

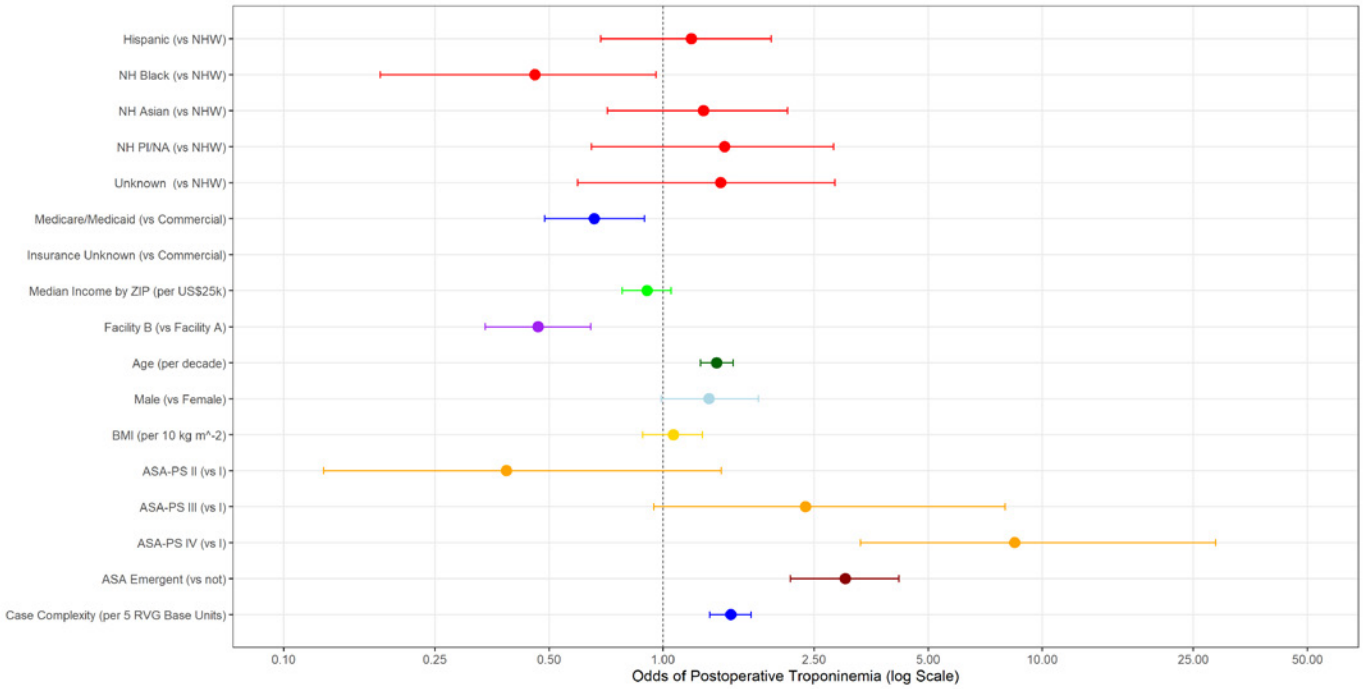

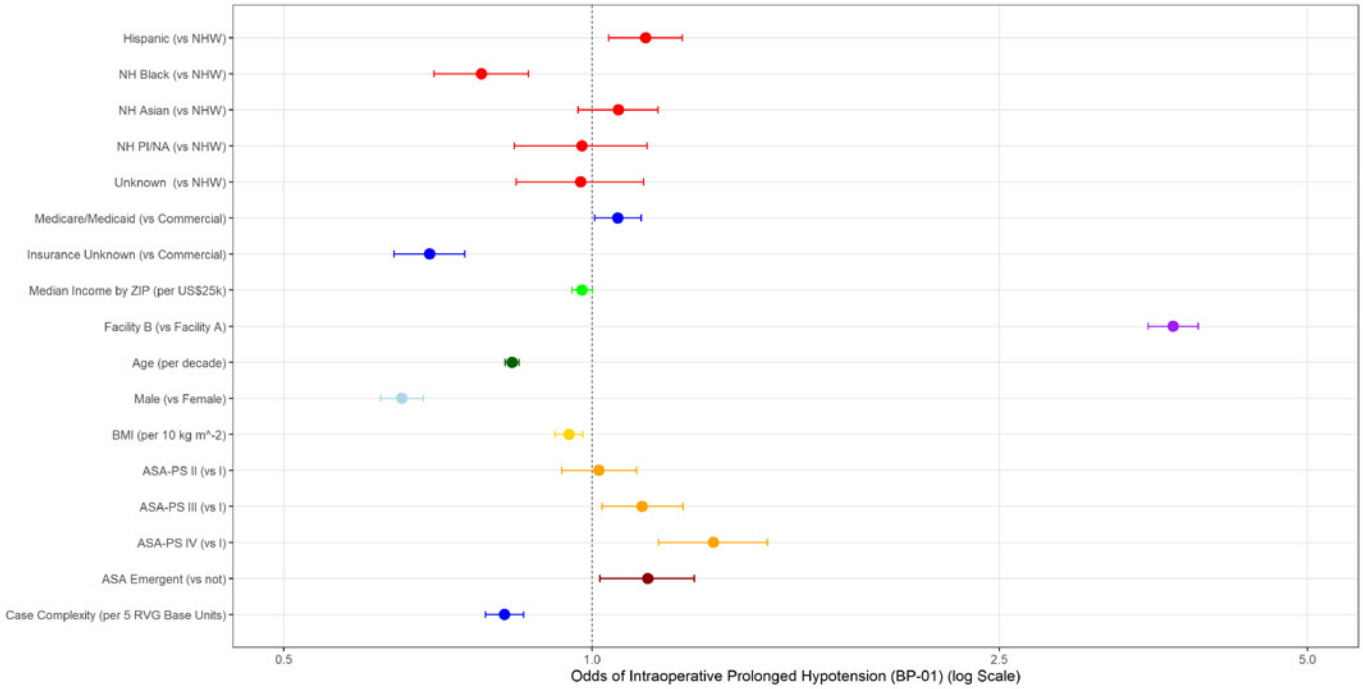

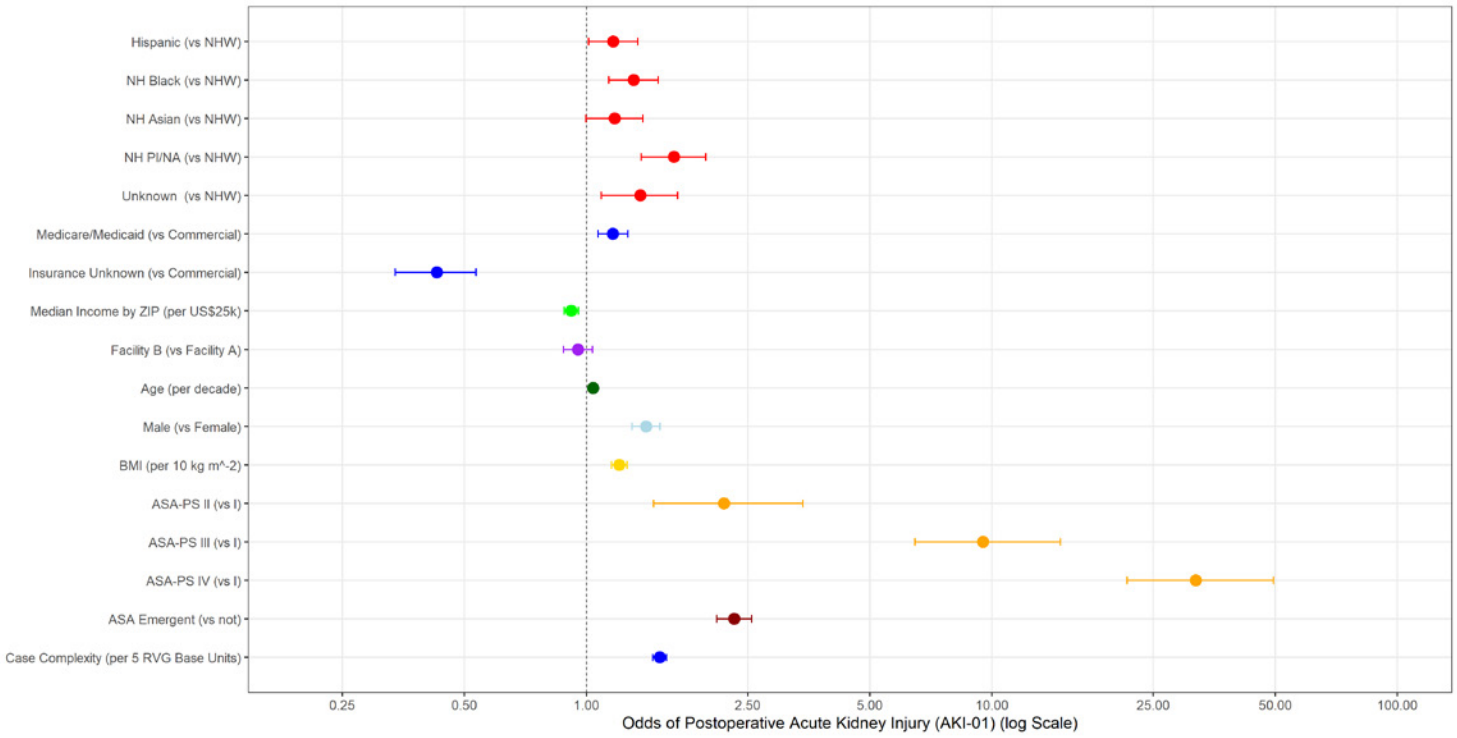

PERIOPERATIVE ANESTHESIA 50

Perioperative hypothermia in the presence of poor glycemic control nearly triples the risk of surgical site infection

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INTRODUCTION: Surgical site infection (SSI) is the leading cause of nosocomial infections among surgical patients in the U.S[1]. Currently, there is compelling evidence suggesting temperature regulation in surgical patients may be a risk factor for the development of SSI[2-7]. We believe that if an association between perioperative hypothermia (PH) and SSI exists, it would be more apparent, and potentially compounding in a population already at increased risk such as patients with diabetes mellitus (DM).

METHODS: This retrospective chart review was conducted of patients with a history of DM undergoing elective orthopedic surgery at our teaching institution between May 1, 2018, and June 9, 2021. Surgeries were performed within a single hospital. Included patients were over the age of 15 with a history of DM or a recent HbA1c level ≥6.5% and receipt of general anesthesia for an elective orthopedic operation at least 60 minutes in duration. Poor glucose control was defined as a HbA1c level ≥6.5% or a serum glucose >200 at the time of surgery. T-tests, Chi-squared analysis, and univariate logistic regression were used to compare demographic data and outcomes between the normothermic and hypothermic cohorts and infection and non-infection cohorts.

RESULTS: One hundred and eighty-nine patients were included in the final analysis. Seventy-one (38%) patients became intraoperatively hypothermic. The overall incidence of SSI was 6.87%. Among the seventy-one patients who experienced PH, poor glycemic control was associated with nearly a two-fold increased risk of SSI (OR = 2.7, 95% CI = 1.09-6.69, p-value = 0.032).

CONCLUSION: Poor glycemic control in the presence of perioperative hypothermia increased the risk of surgical site infection nearly two-fold. These results suggest that in patients at increased risk of SSI, the presence of PH may confer a substantial additive risk. Fortunately, there exist effective interventions for reducing the incidence of PH.

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Risk of Surgical Site Infection Among PH Cohort		
Factor	**OR (95% CI)**	**p-value**
Poor glycemic control (HbA1c ≥6.5%; serum glucose >200)	2.697 (1.087-6.688)	0.0322

Figure 1

PERIOPERATIVE ANESTHESIA 51

A 5-year, 830,528 Patient, Multi-Center Study of Inpatient Post-Surgical Morbidity (Pre and Post COVID-19)

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[1]Envision Healthcare (University of Arizona, University College London), Nashville, TN, [2]Envision Healthcare, Phoenix, AZ, [3]Envision Healthcare, Dallas, TX, [4]Envision Healthcare, Plantation, AZ, [5]Envision Healthcare, Nashville, TN, [6]Envision Physician Physician Services, Plantation, FL, [7]University of California, Berkeley, Oakland, CA, [8]Amazon Logistics, Oakland, CA

INTRODUCTION: Annually, 234 million major operations are performed worldwide,[1] 48 million of which are performed in the United States. Of these, between 5% and 45% will suffer post-surgical complications[2,3,4,5] that increase physical and psychosocial suffering[6], hospital length of stay[7], increased level of care at discharge,[7,8] cost,[9,10] and decreased long term survival.[11,12] It is also known that variation in post-surgical complication rates exist between surgical service lines and between specific procedures within a service line.[13] Furthermore, older patients following non-cardiac surgery have been shown to experience higher postoperative complication rates.[14,15] The primary purpose of this large, 830,528 patient, multi-center, 5-year, retrospective database study was to validate the findings of several smaller trials showing that major inpatient surgery is associated with high post-surgical complication rates. Secondary findings include type of complication, day on which the complication occurs, and associations with both age and gender. Pre and post COVID-19 pandemic post-surgical complications rates are described. This study offers a more accurate picture of perioperative morbidity than is provided by self-reported event data, and, thus, better informs perioperative shared-decision making and the development of best-evidence pathways and protocols to mitigate these complications.

METHODS: This is a retrospective, 35-center, administrative database study including patients who were selected based on inpatient surgical status between October 1, 2017 and November 10, 2021 who were cared for by Envision Medical Group's anesthesiology and hospital medicine service lines. Current Procedural Terminology (CPT) codes for specific surgical procedures were bucketed into surgical service lines, such as cardiac surgery, thoracic surgery, general surgery, neurosurgery, urology, gynecology, orthopedics, etc. Post-surgical morbidities were defined and bucketed into categories, such as pulmonary, cardiac, renal, neurologic, hemorrhagic, and septic complications using International Classification of Diseases, Tenth Revision (ICD-10) codes. Age, gender, and postoperative day that a complication was reported were abstracted from the database. The proportion of post-surgical complications was defined as the total number of complications divided by the total surgical inpatient population, which was further stratified by service line, procedure type, and the post-operative day on which the complication was noted. (Figure 1)

RESULTS: *Study Dates:* 10/1/2017 - 11/10/2021

Surgical Inpatients: n= 830,528

Total Complications: n= 71,513

Proportion of Complications: Average 8.61% Range [0.45% - 26.55%].

Proportion of Complications for Specific Surgical Service lines: Cardiac Surgery: 26.55%; Neurosurgery: 24.13%; Thoracic Surgery: 20.1%; Vascular Surgery: 13.78%; General Surgery: 11.61%; Orthopedic Surgery: 10%; Urology: 8.45%; Gynecology: 2.4%; Ophthalmology: 0.45%.

Most Frequent Major Complications within 7 days of surgery per 1000 patients (Figure 2): Acute Kidney Injury: 6; Post-operative pulmonary complications: 6.7; Post surgical sepsis: 5.1; Acute Coronary Syndrome: 1.07; Stroke and new neurologic deficit: 0.8; Cardiac Arrest: 0.63.

Complications occurred more often in males than in females (10% vs 7.31% respectively), and increased with age (Figure 3):

Age Group: *Proportion of Complications* 0-10: 0.67%; 11-20: 2.75%; 21-30: 4.06%; 31-40: 5.75%; 41-50: 8.52%; 51-60: 9.93%; 61-70: 9.67%; 71-80: 9.84%; 81-90: 13.36%; 91-100: 16.98%.

Influence of COVID-19 on Post-Surgical Complication Rates: Pre-COVID-19 (10/1/2017 - 3/31/2020) overall complication rate: 8.27% [n= 549,192]; Post-COVID-19 (4/1/2020- 6/1/2020) overall complication rate: 10.44% [n=24,701]; (Period of emergency cases only) Post-COVID-19 (6/2/2020 - 11/10/2021) over all complication rate: 8.96% [n= 262,570].

CONCLUSION: Our study confirms prior findings that complications following major inpatient surgery occur in up to 1:4 patients. Pulmonary, renal, and post-surgical sepsis occur more frequently than cardiac or neurologic events, and increase with age and male gender. Post-pandemic surgical complication rates remain higher than pre-pandemic.

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Figure 1. Data Curation Along the Continuum of Care.

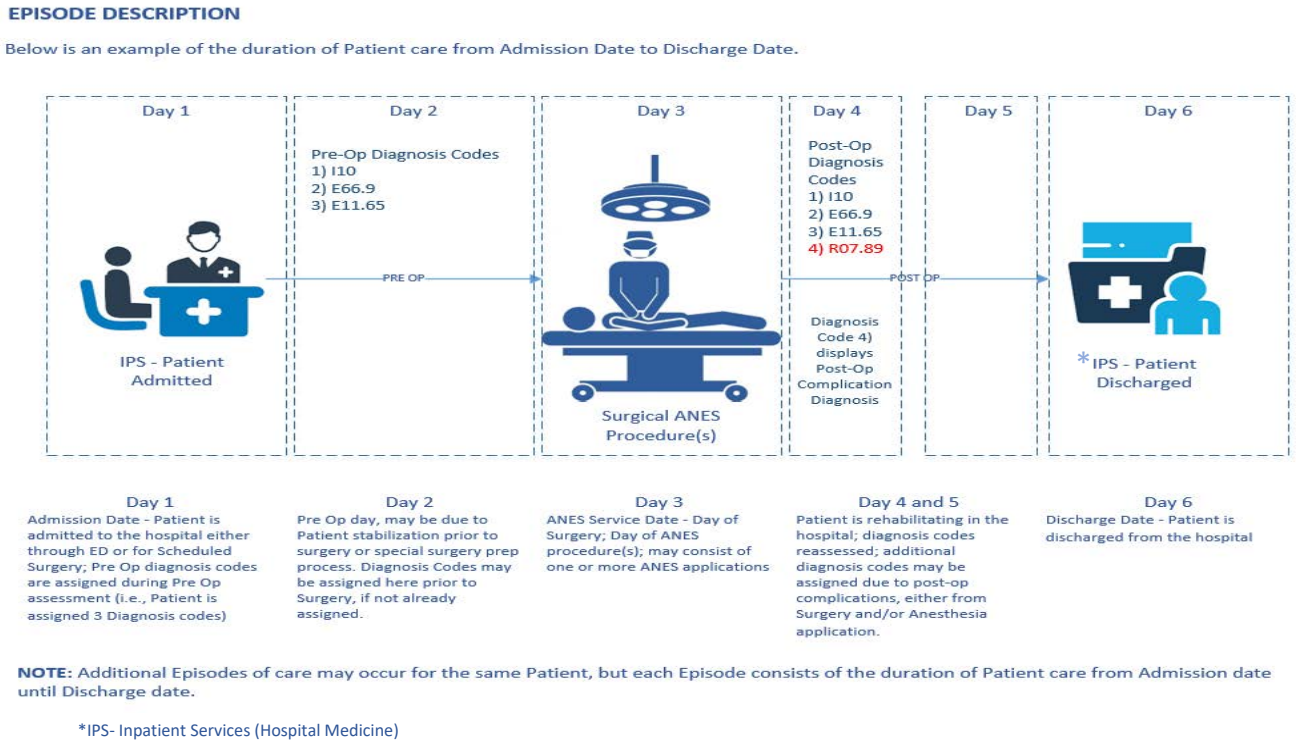


Figure 2. Post-Surgical Complication Type by Day per 1000 Patients.

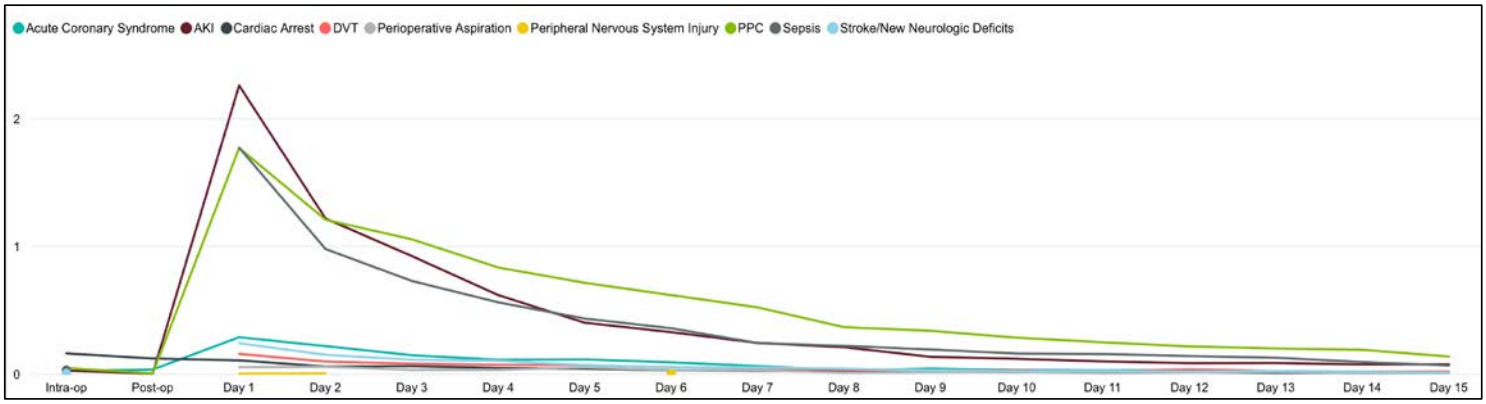
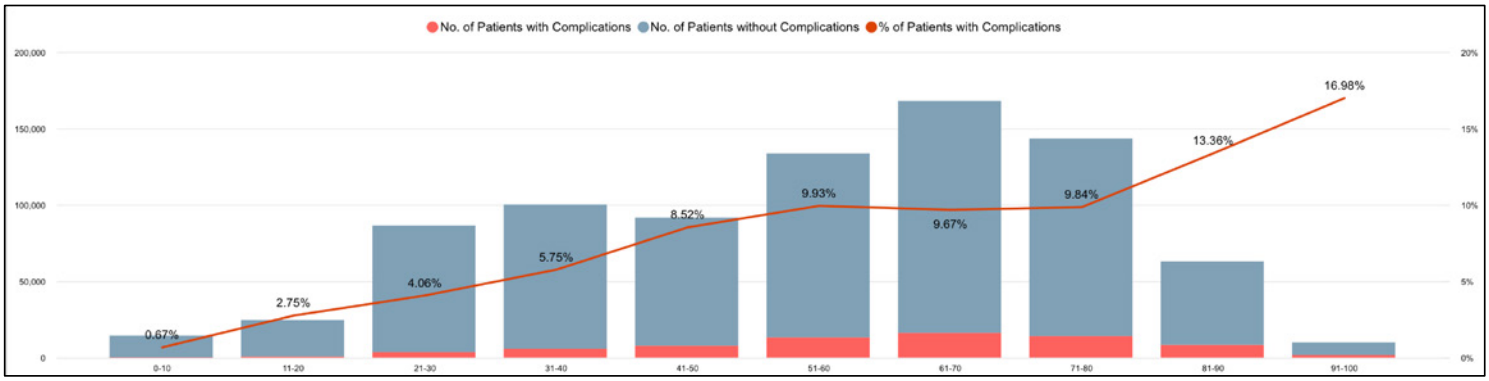


Figure 3. Post-Surgical Complications by Age-Group.



PERIOPERATIVE ANESTHESIA 52

Telemedicine improves Anesthesia Pre-operative Evaluation Appointment Adherence: A Retrospective Analysis

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INTRODUCTION: Amidst the COVID-19 pandemic, the sudden demand for virtual medical visits drove the drastic expansion of telemedicine across all medical specialties[1]. Current literature demonstrates limited knowledge on the impact of telehealth on appointment adherence particularly in preoperative anesthesia evaluations[2-4]. We hypothesized that there would be increased completion of preoperative anesthesia appointments in patients who received telemedicine visits.

METHODS: We performed a retrospective cohort study of adult patients at UCLA who received preoperative anesthesia evaluations by telemedicine or in-person within the Department of Anesthesiology and Perioperative Medicine from January to September 2021 and assessed appointment adherence. The primary outcome was incidence of appointment completion. The secondary outcomes included appointment no show and cancellations. Patient demographic characteristics including sex, age, ASA physical status class, race, ethnicity, primary language, interpreter service requested, patient travel distance to clinic, and insurance payor were also evaluated. Patient reported reasons for cancellations were also reviewed and categorized into thematic groups by two physicians. Statistical comparison was performed using independent samples t test, Pearson's chi-square, and Fischer's exact test.

RESULTS: Of 1332 patients included in this study, 956 patients received telehealth visits while 376 patients received in-person preoperative anesthesia evaluations. Compared to the in-person group, the telemedicine group had more appointment completions (81.38% vs 76.60%, $p = 0.0493$). There were fewer cancellations (12.55% vs 19.41%, $p = 0.0029$) and no statistical difference in appointment no-shows (6.07% vs 3.99%, $p = 0.1337$) in the telemedicine group (Table 1, Figure 1). Compared to the in-person group, patients who received telemedicine evaluations were younger (55.81 ± 18.38 vs 65.97 ± 15.19, $p < 0.001$), less likely Native American and Alaska Native (0.31% vs 1.60%, $p = 0.0102$), more likely of LatinX ethnicity (16.63% vs 12.23%, $p = 0.0453$), required less interpreter services (4.18% vs 9.31%, $p = 0.0003$), had more private insurance coverage (53.45% vs 37.50%, $p < 0.0001$) and less Medicare coverage (37.03% vs 50.53%, $p < 0.0001$) (Table 2). Main reasons for cancellation included patient request, surgery rescheduled/cancelled/already completed, and change in method of appointment (Table 3).

CONCLUSION: In 2021, preoperative anesthesia evaluation completion was greater in patients who received telemedicine appointments compared to those who received in-person evaluations at UCLA. We also demonstrate potential shortcomings of telemedicine in serving patients who are older, require interpreter services, or are non-privately insured. Knowledge of these factors can provide feedback to improve access and equity to telehealth for patients from all backgrounds, particularly during the COVID pandemic as virtual evaluations increase.

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	Telemedicine	In-Person Clinic	P-Value
Total Patients	956	376	0.0029**
Cancelled	120 (12.55%)	73 (19.41%)	0.0014**
No-Show	58 (6.07%)	15 (3.99%)	0.1337
Completed	778 (81.38%)	288 (76.60%)	0.0493**

Table 1. Comparison of cancellation, no-show, and completion of appointments between patients who received telemedicine or in-person preoperative evaluation appointments. Data presented as n (%). **P values < 0.05 were considered significant.

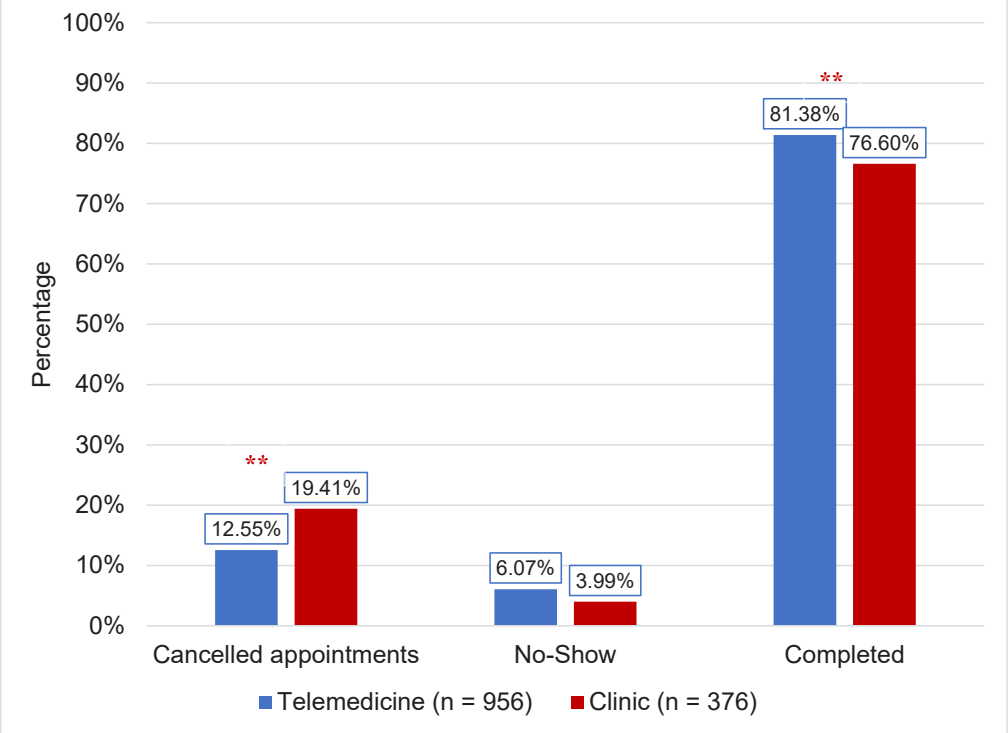

Figure 1. Comparison of cancellation, no-show, and completion of appointments between patients who received telemedicine or in-person preoperative evaluation appointments. **P values < 0.05 were considered significant.

	Telemedicine	In-Person Clinic	P-Value
Sex			0.0435**
Male	309 (32.32%)	148 (39.36%)	
Female	646 (67.57%)	228 (60.64%)	
Age	55.81 (18.38)	65.97 (15.19)	<0.001**
ASA			0.3804
I	12 (1.26%)	3 (0.80%)	
II	302 (31.59%)	110 (29.26%)	
III	598 (62.55%)	238 (63.30%)	
IV	44 (4.60%)	25 (6.65%)	
Race			
Native American and Alaska Native	3 (0.31%)	6 (1.60%)	0.0102**
Asian	72 (7.53%)	30 (7.98%)	0.7823
Black or African American	84 (8.79%)	31 (8.24%)	0.7513
Declined	29 (3.03%)	9 (2.39%)	0.5278
Other	172 (17.99%)	58 (15.43%)	0.2647
White	588 (61.51%)	236 (62.77%)	0.6701
Native Hawaiian and other Pacific Islander	1 (0.10%)	2 (0.53%)	0.1387
Unknown	7 (0.73%)	4 (1.06%)	0.5472
Ethnicity			
LatinX	159 (16.63)	46 (12.23%)	0.0453**
Not LatinX	742 (77.62%)	309 (82.18%)	0.066
Declined	9 (2.39%)	25 (2.62%)	0.8176
Unknown	30 (3.14%)	12 (3.19%)	0.9600
English as Primary Language	903 (94.46%)	324 (86.17%)	<0.001**
Interpreter Required	40 (4.18%)	35 (9.31%)	0.0003**
Distance to Clinic	99.84 (343.09)	91.55 (503.21)	0.7693
Insurance Coverage			
Medicaid	57 (5.96%)	30 (7.98%)	0.18
Medicare	354 (37.03%)	190 (50.53%)	<0.0001**
Private	511 (53.45%)	141 (37.50%)	<0.0001**
Self-Pay	1 (0.10%)	0 (0%)	0.5304
Other	8 (0.84%)	6 (1.60%)	0.2215
Unknown	25 (2.62%)	9 (2.39%)	0.8176

Table 2. Demographic Characteristics between patients who received telemedicine and in-person Clinic Preoperative Evaluations. Data presented as n (%) or mean (SD). **P values < 0.05 were considered significant.

Reasons for Cancellation	Percentage
Patient request/reason	45 (32.61%)
Surgery rescheduled/cancelled/already completed	23 (16.67%)
Change of method of appointment	17 (12.32%)
Time conflict with another medical appointment	10 (7.25%)
Other	8 (5.8%)
System error	8 (5.8%)
Team request	8 (5.8%)
Appointment no longer needed	7 (5.07%)
Patient no show/late	6 (4.35%)
Appointment Rescheduled	3 (2.17%)
Technology Issue	3 (2.17%)

Table 3. Patient reported reasons for cancellations. Data presented as n (%).

PERIOPERATIVE ANESTHESIA 53

Use of a novel Relative Index to estimate changes in volume status after non-cardiac surgery

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INTRODUCTION: Accurate perioperative fluid assessment remains a challenge.[1] We present the first clinical use of a non-invasive patient fluid monitor being investigated to improve perioperative assessment of patient fluid status. This technology simplifies patient fluid monitoring by continuously monitoring five parameters and outputting a single value, the Relative Index (RI). The RI is a unitless parameter calculated with a proprietary algorithm from changes in the measured parameters (bioelectrical impedance, heart rate, ECG amplitude, PPG amplitude, and skin temperature), reflecting respective fluid volume change. An RI of 100 represents the patient's baseline volemic state, and deviations indicate relative fluid changes. This descriptive analysis utilized the RI to monitor relative fluid status of patients after major non-cardiac surgery.

METHODS: Adult patients undergoing laparoscopic or open abdominal surgery were consecutively enrolled in this prospective observational study. Patients were connected to the fluid monitor upon entering the PACU, and user-blinded monitoring continued until patients left the PACU. Perioperative fluid balances were recorded. Subjects with a RI change of ± 5 from baseline were examined further for adverse events. Data was evaluated using descriptive statistics. From 160 monitored subjects, those with one or more irregular parameters during monitoring and those with a monitoring session < 1hr were excluded from the final analysis, leaving 98 evaluable subjects. Final RI values and minimum (min), median (med), and maximum (max) RI values were correlated with total fluid changes during subjects' time in the PACU and OR/PACU combined.

RESULTS: Mean patient age (years) was 61.2 ± 13.7 for open abdominal surgery subjects and 54.8 ± 12.8 for laparoscopic. The mean BMI for open surgery was 28.6 ± 7.4 kg/m2 and 33.8 ± 7.6 kg/m2 for laparoscopic. The min and max RI values for subjects with a net fluid change <200mL trended between 95 and 109, with a med RI of 99 ± 2.3. For net fluid changes >200mL, the lowest min RI value observed was 80, and the highest max RI value observed was 113. The med RI values continued to trend at 100 ± 2.4. Of the patients analyzed, no post-operative adverse events were observed, which correlates with the med RI for all patients remaining close to 100.

CONCLUSION: This novel, non-invasive method of monitoring utilizes an algorithm which simplifies patient fluid monitoring through the Relative Index (RI). Additional studies are necessary to further validate the significance of this device on improving clinical outcomes.

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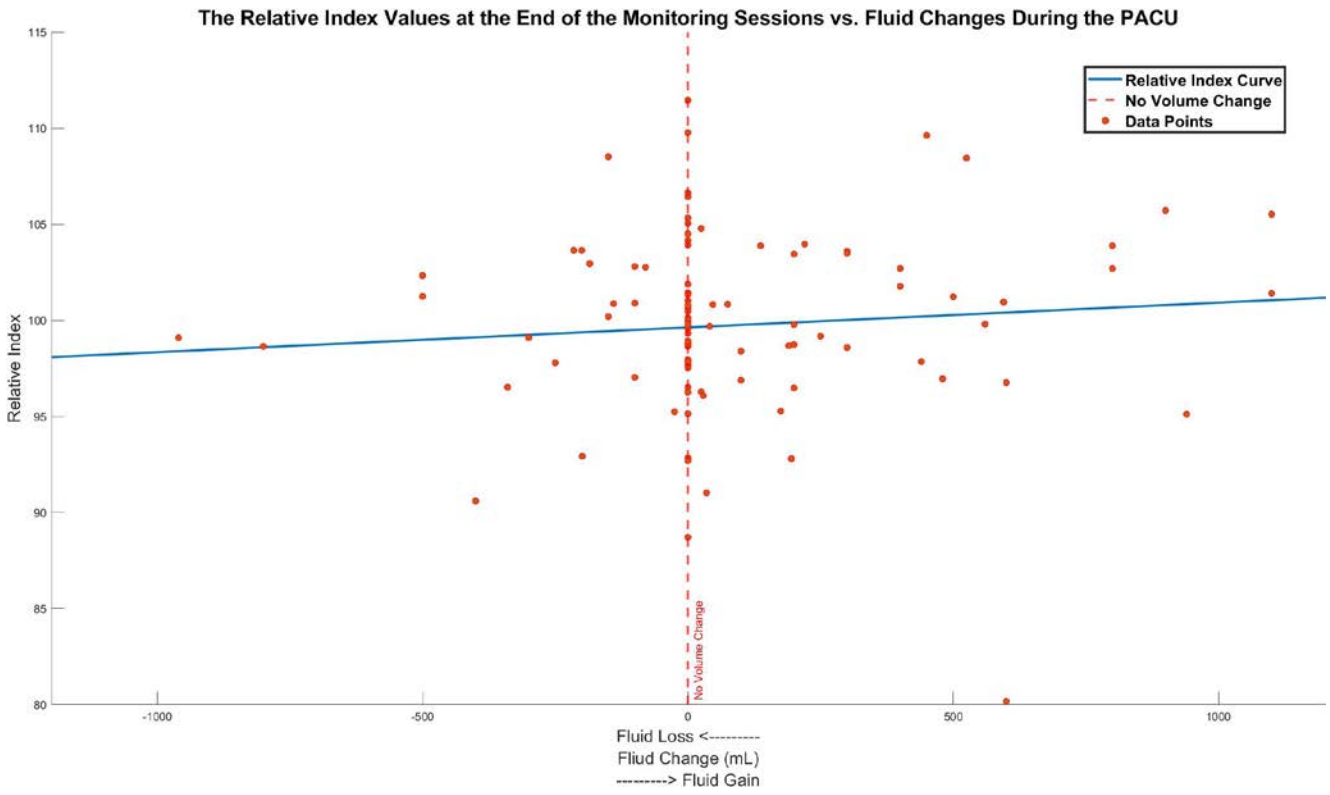

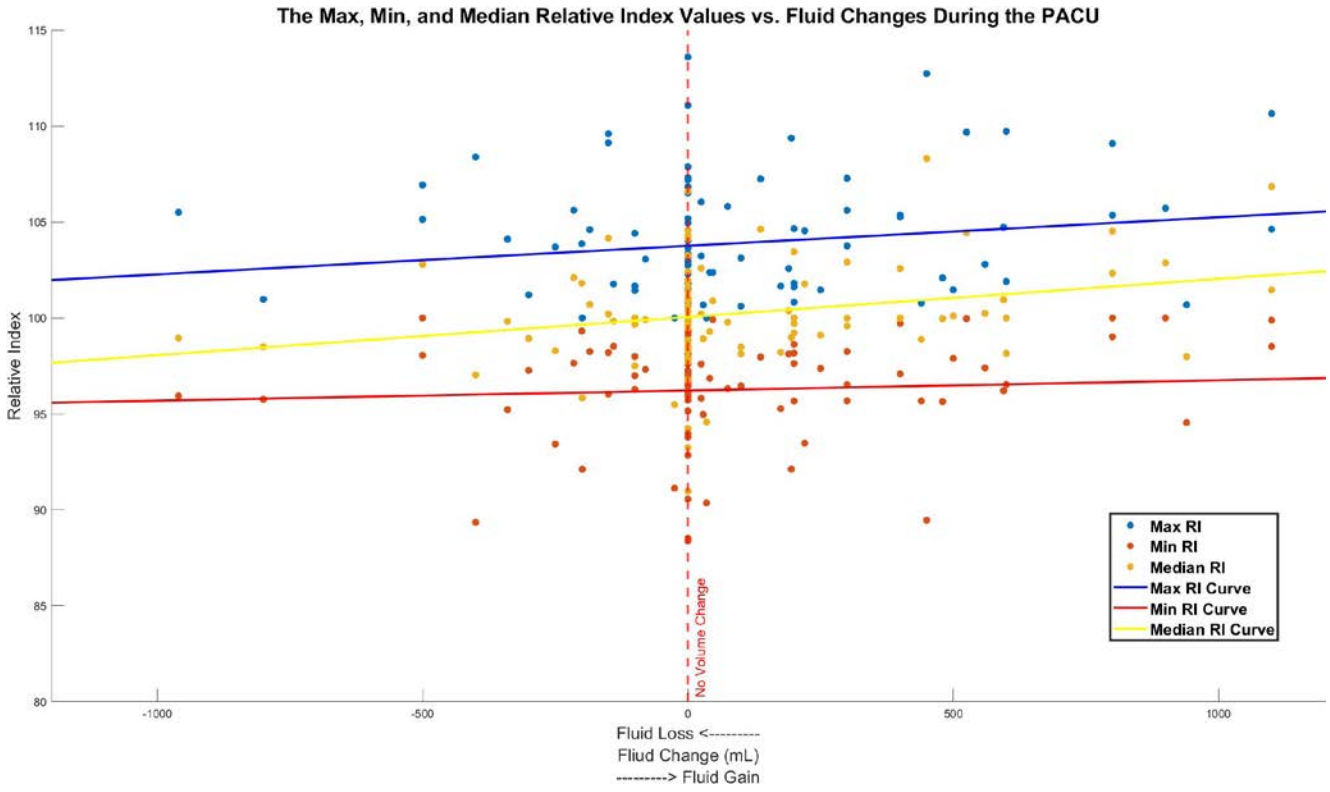

PERIOPERATIVE ANESTHESIA 54

Intraoperative Spinal Cord Stimulation Mitigates Pain after Spine Surgery in Mice

Chengrui Hu[1], Satoshi Yamamoto[1], Blaine Wiemers[1], Jigong Wang[1], Jin Mo Chung[1], Jun-Ho La[1]

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INTRODUCTION: Managing postoperative pain after spine surgery is challenging; up to 40% of patients develop failed back surgery syndrome resulting in intractable back and/or leg pain. While spinal cord stimulation (SCS) has been shown to effectively alleviate such chronic pain, it is unknown if SCS during spine surgery can mitigate the development of intense postoperative pain after spine surgery. In this study, we modeled spine surgery-induced pain hypersensitivity in mice and then examined if intraoperative SCS inhibits the development of such hypersensitivity.

METHODS: Unilateral T13 laminectomy was performed in mice to expose the dorsal part of L4-5 spinal segments that receive sensory inputs from the hind limb. After the laminectomy, a group of mice received intraoperative SCS (0.2 ms biphasic pulse at 50 Hz frequency and 50% motor threshold intensity) epidurally applied to the exposed side of dorsal column for an hour under anesthesia before closing the surgical wounds. Mechanical pain sensitivity in hind paws was measured using von Frey assay one day before and at predetermined times after surgery.

RESULTS: Mice that underwent unilateral T13 laminectomy developed mechanical hypersensitivity in both hind paws, which gradually resolved in 1-2 weeks. The extent of the hypersensitivity was less in the contralateral hind paw (relative to the laminectomy) than in the ipsilateral hind paw. Intraoperative SCS applied to the exposed side of dorsal column significantly inhibited the development of hind paw mechanical hypersensitivity only in the SCS-applied side. This inhibition of hypersensitivity was more pronounced in males than in females on the first 2 days post-laminectomy.

CONCLUSION: These results demonstrate that spine surgery for unilateral laminectomy induces central sensitization that results in bilateral postoperative pain hypersensitivity. Intraoperative SCS after laminectomy can mitigate the development of this hypersensitivity in the SCS-applied side and the effects are more profound in males than in females.

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Figure 1

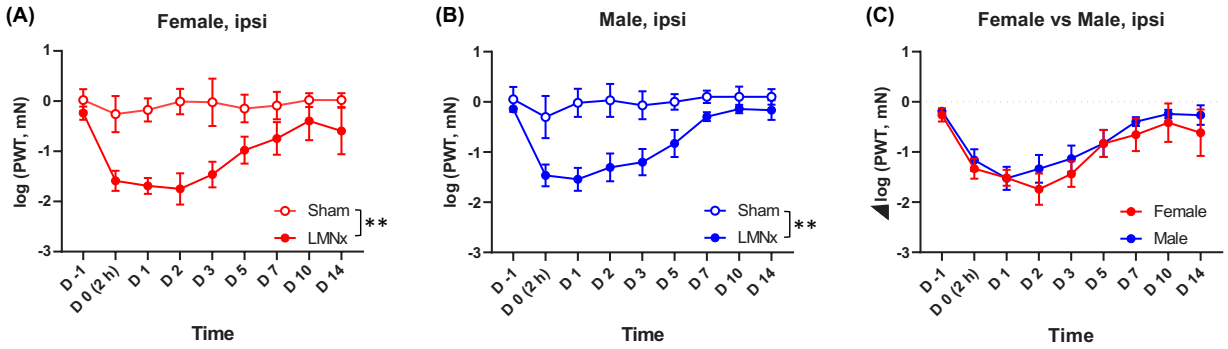


Figure 2

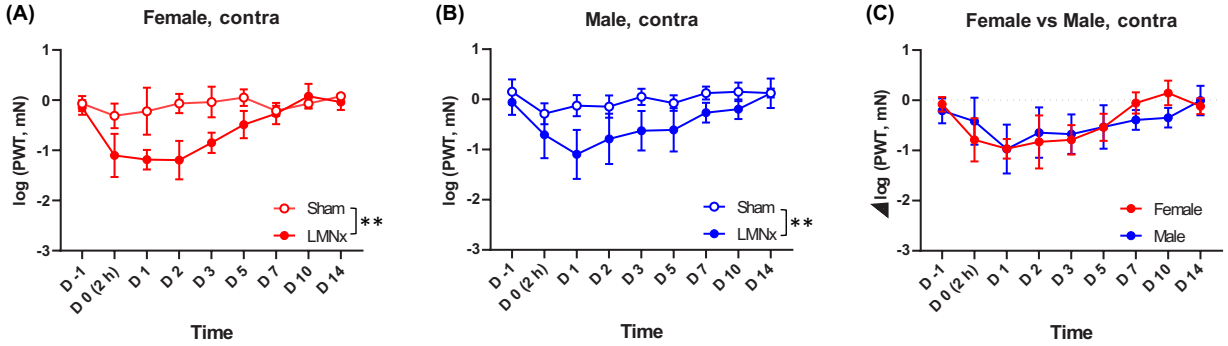


Figure 3

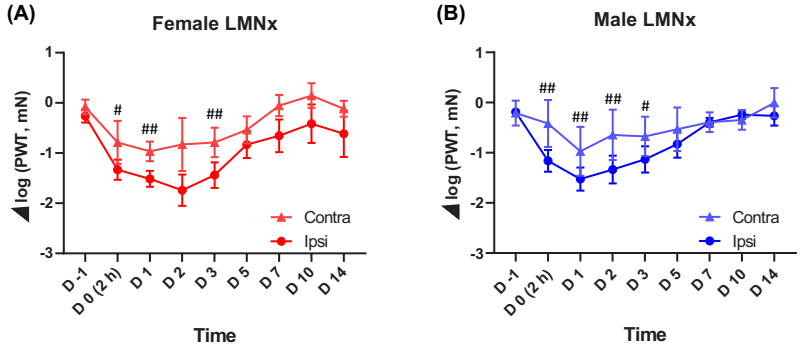
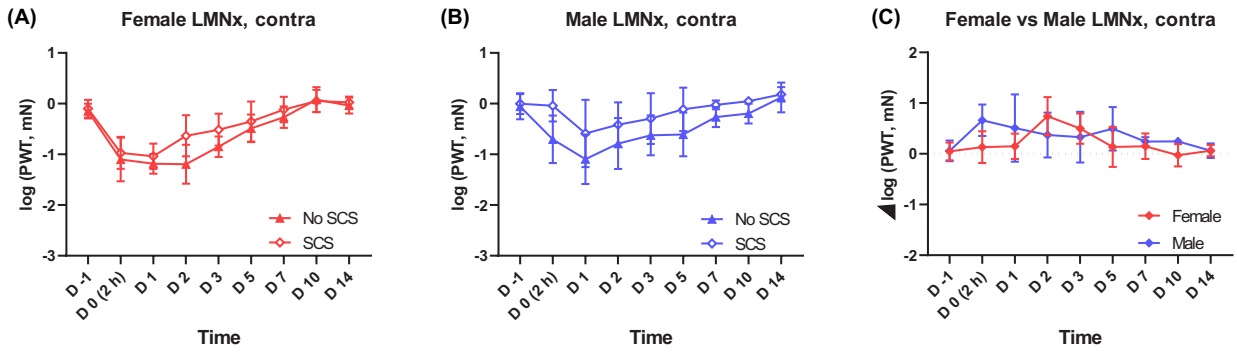


Figure 5



SUBSPECIALTY ABSTRACTS

REGIONAL ANESTHESIA

REGIONAL ANESTHESIA 1

Thoracolumbar interfascial plane block as part of PI project decreasing pain and speeding discharge after thoracolumbar interbody fusion surgery

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INTRODUCTION: Four multidisciplinary interventions were chosen for this performance improvement (PI) project aiming to reduce narcotic use, and speed discharge from hospital after TLIF surgery at a community hospital. Figure 1. Measures 3 & 4 required a second cycle of Plan-Do-Study-Act in a second phase. Routine care prior to implementation included hospital admission status > 24 hour, overnight Foley catheter drainage, and discharge home afternoon of POD#1 after physical therapy (PT) evaluation. Preoperative adjuvant analgesic medications were not utilized, and regional analgesia was not employed. First described in 2015[1] the TLIP block has been studied for discectomies[2].

METHODS: Patients were selected as a sequential convenience sample of approximately 20 in baseline and phase 1 & 2 groups, over 2 years. Exclusion criteria included preoperative daily oral narcotics, and previous spine surgery. Intraoperative and PACU narcotics were converted to hydromorphone equivalents using fentanyl 50 mcg = 0.5 mg hydromorphone. Floor narcotic PO and IV doses were tallied separately.

RESULTS: One and two patients were discharged on day of surgery in phase1 & 2 respectively. Phase 2 patients tended to be more complex due to restrictions on elective surgery coincident with the COVID pandemic. Four patients in phase 2 required more than 65 hours to discharge which greatly skewed time to discharge data. They all had significant preexisting neurologic deficits, which were not an exclusion criterion. Time to ambulation was nearly halved from 14.8 hours pre-implementation, to 8.7 and 8.8 for phase 1 and phase 2. By the start of phase 2 Foley catheters were being removed in operating room. Two patients in phase 2 did not receive indicated blocks due to staffing. We saw a decrease in hydromorphone equivalents in phase 1 in all care areas. This trend was slightly reversed from phase 1 to phase 2 due to confounding by 2 patients who required > 10 narcotic doses postop. It is clinically significant that 11 patients in phase 2 required no IV narcotics postop compared 2 patients in phase 1.

CONCLUSION: Real-world implementation necessitated a second phase for which a new electronic orderset was built, and collaborative education cycles with PT and nursing staff conducted. Surgical scheduling places more complex patients at the start of the day. It is possible that scheduling more complex cases later in the day might reveal patients meeting discharge criteria sooner during daylight hours. A recent RCT of an ERAS protocol not employing regional analgesia blocks reported not reaching clinical significance.[3] Since completing data collection, an ERAS consensus statement rates use of 'locoregional analgesia' as having high evidence level support and strong recommendation grade.[4] We were able to use our data internally to explore change to 23-hour observation status for TLIF patients at our institution.

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1. Oral gabapentin 600 mg and acetaminophen 1,000 mg preoperatively
2. Bilateral thoracolumbar interfacial plane (TLIP) Blocks.
3. Assessment by Physical Therapy 2 hours after floor admission
4. Foley catheter removal at the end of surgery

FIGURE 1. Multidisciplinary interventions incorporated

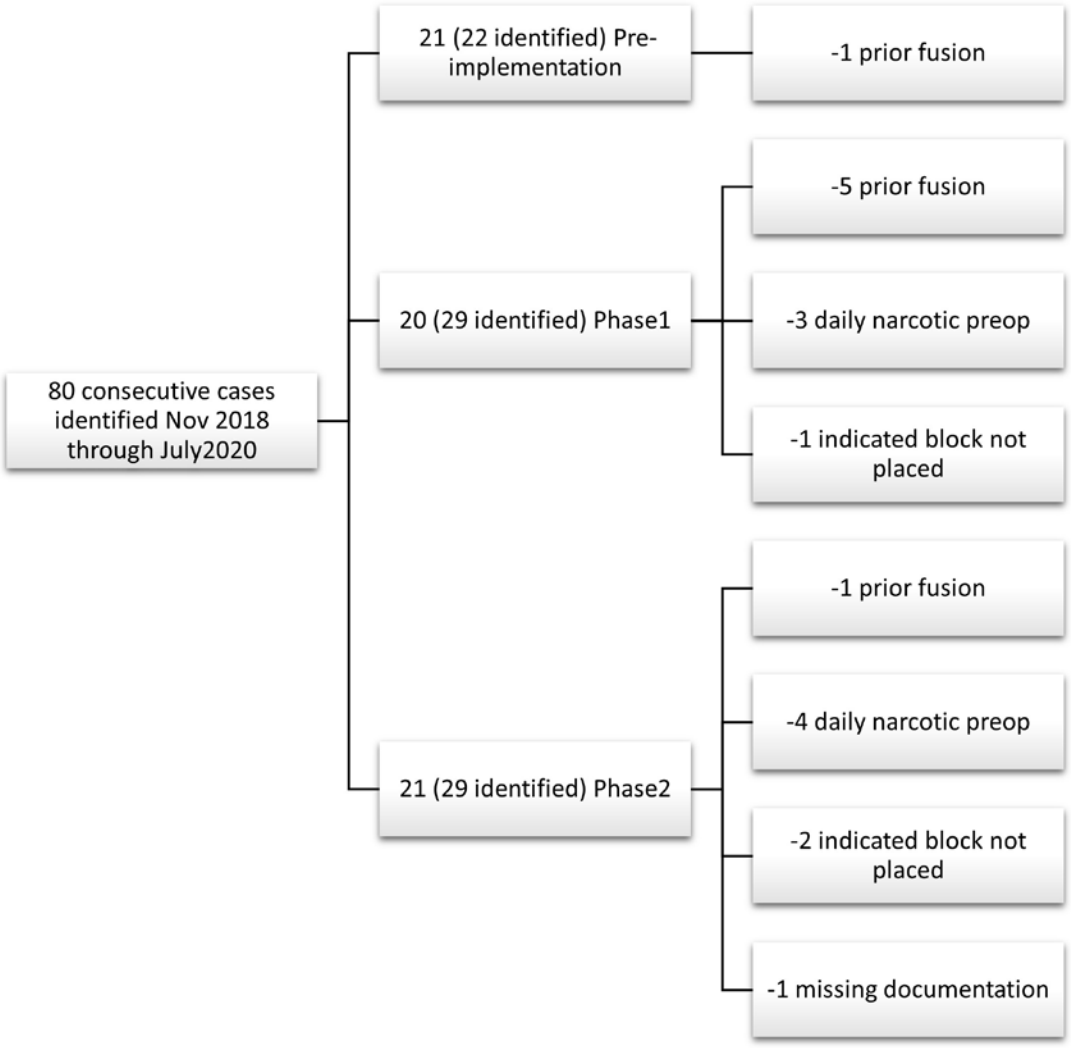
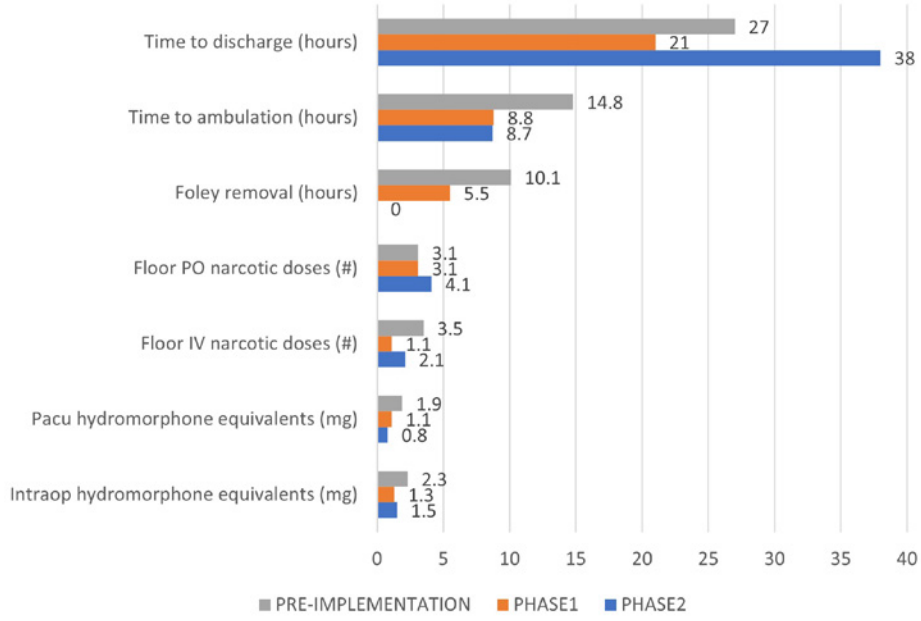


Figure 2

Figure 3. Project average data trends



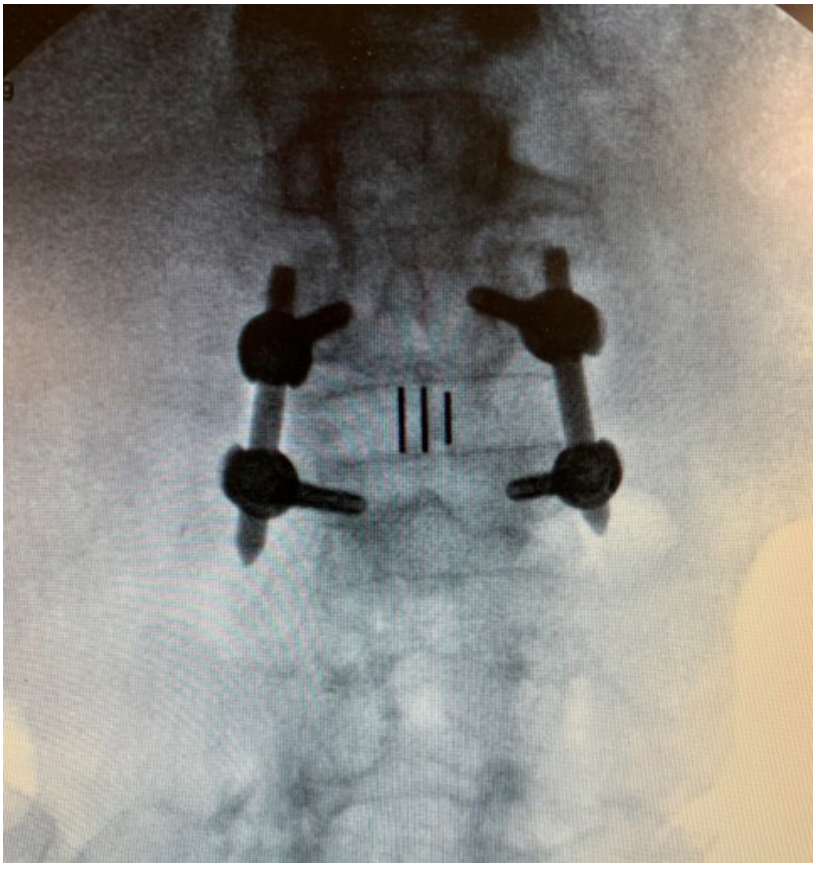


Figure 4

REGIONAL ANESTHESIA 2

Social Determinants of Regional Anesthesia Use for Patients Undergoing Hemodialysis Vascular Access Procedures

Agustin Oneto[1], Rafael Vazquez[2]

[1]Harvard Medical School, Boston, MA, [2]Massachusetts General Hospital, Boston, MA

INTRODUCTION: Healthcare disparities exist in access to regional anesthesia (RA) in pediatric and obstetric anesthesiology.[1,2] To date there has been no investigation on whether these disparities persist in the end-stage renal disease population, which is disproportionately composed of patients from marginalized backgrounds.[3] RA is suggested to improve the success of hemodialysis (HD) vascular access surgeries via venodilation and improved fistula patency, blood flow, and maturation time.[4,5] This study aims to determine whether disparities in the use of RA for HD vascular access surgeries exist based on patient factors at a single academic hospital.

METHODS: We performed a retrospective review of anesthetics for HD vascular access surgeries including arteriovenous (AV) fistula creation, AV graft, and AV transposition. Data was collected from one academic hospital in northern Boston from April 2016 to August 2021. 250 patients were reviewed. Associations between the use of RA and patient factors including race/ethnicity, language, estimated income, substance use disorder, chronic pain, and anticoagulation were determined via multiple logistic regression.

RESULTS: The study cohort was made up of 250 patients, of which 42.4% received RA, 40.0% were minorities (non-white and/or Hispanic), 14.8% required interpreters, and 28.4% had low estimated incomes (median household income ≤ $65,000 for their zip code). Within subgroups, the percentages that received RA were 58.7% of minorities versus 85.2% of non-minorities, 68.2% of non-English speakers versus 74.5% of English speakers, and 77.4% of low-income versus 72.1% of high-income patients. Multiple logistic regression adjusting for confounders did not find statistically significant associations between the use of RA and language or income, but did find a lower odds ratio based on minority status (adjusted odds ratio = 0.35, 95% confidence interval = 0.14 – 0.86, p = 0.03). Findings were validated by sensitivity analyses. Review of platelet and coagulation parameters did not suggest any difference in subgroup eligibilities for RA, and the disparity was observed after controlling for anticoagulant use.

CONCLUSION: This study identifies a racial/ethnic disparity in the use of RA in HD vascular access surgeries at one academic hospital, with minority patients being less likely to receive RA. There was no significant difference in the use of RA based on language or income. The lack of language-based disparities may represent the success of institutional use of in-person and videophone interpreters. Given no observed physiologic differences between subgroups, differences in education on RA (e.g., regarding the need to hold anticoagulant drugs) may be a factor leading to the observed disparity. Quality improvement initiatives regarding RA education should be pursued. Further studies are needed to clarify the etiology of the racial/ethnic disparity and determine whether these trends persist among additional samples.

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Table 1: Measured Factors Stratified by Procedure Type

	Procedure type				
	AV Fistula (n=166)	AV Graft (n=58)	AV Transposition (n = 26)	%*	P-Value†
Age (yr)					
< 45	13 (7.8%)	10 (17.2%)	3 (11.5%)	10.4%	0.429
45-64	61 (36.7%)	23 (39.7%)	11 (42.3%)	38.0%	
65-74	47 (28.3%)	15 (25.9%)	6 (23.1%)	27.2%	
≥ 75	45 (27.1%)	10 (17.2%)	6 (23.1%)	24.4%	
Sex					
Male	112 (67.5%)	29 (50.0%)	21 (80.8%)	64.8%	0.0111
Female	54 (32.5%)	29 (50.0%)	5 (19.2%)	35.2%	
Race					
White	107 (64.5%)	33 (56.9%)	17 (65.4%)	62.8%	0.0274
Black	19 (11.4%)	16 (27.6%)	6 (23.1%)	16.4%	
Asian	20 (12.0%)	2 (3.4%)	0 (0.0%)	8.8%	
Other	20 (12.0%)	7 (12.1%)	3 (11.5%)	12.0%	
Ethnicity					
Hispanic	25 (15.1%)	7 (12.1%)	3 (11.5%)	14.0%	0.793
Non-Hispanic	141 (84.9%)	51 (87.9%)	23 (88.5%)	86.0%	
Primary Language					
English	138 (83.1%)	51 (87.9%)	24 (92.3%)	85.2%	0.378
Non-English	28 (16.9%)	7 (12.1%)	2 (7.7%)	14.8%	
Estimated Income‡					
≤$65,000	47 (28.3%)	17 (29.3%)	7 (26.9%)	28.4%	0.974
>$65,000	119 (71.7%)	41 (70.7%)	19 (73.1%)	71.6%	
BMI					
<18.5	1 (0.6%)	4 (6.9%)	2 (7.7%)	2.8%	0.0387
18.5-24.9	45 (27.1%)	18 (31.0%)	8 (30.8%)	28.4%	
25.0-29.9	70 (42.2%)	15 (25.9%)	7 (26.9%)	36.8%	
>30.0	50 (30.1%)	21 (36.2%)	9 (34.6%)	32.0%	
ASA Class					
2	7 (4.2%)	2 (3.4%)	0 (0.0%)	3.6%	0.443
3	140 (84.3%)	47 (81.0%)	20 (76.9%)	82.8%	
4	19 (11.4%)	9 (15.5%)	6 (23.1%)	13.6%	
Substance Use Disorder					
Yes	11 (6.6%)	1 (1.7%)	3 (11.5%)	6.0%	0.182
No	155 (93.4%)	57 (98.3%)	23 (88.5%)	94.0%	
Diabetes Mellitus					
Yes	96 (57.8%)	33 (56.9%)	14 (53.8%)	57.2%	0.928
No	70 (42.2%)	25 (43.1%)	12 (46.2%)	42.8%	
Chronic Pain					
Yes	22 (13.3%)	11 (19.0%)	5 (19.2%)	15.2%	0.483
No	144 (86.7%)	47 (81.0%)	21 (80.8%)	19.2%	
Use of anticoagulants					
Yes	29 (17.5%)	12 (20.7%)	2 (7.7%)	17.2%	0.34
No	137 (82.5%)	46 (79.3%)	24 (92.3%)	82.8%	
Use of Nerve Block					
Yes	41 (24.7%)	41 (70.7%)	24 (92.3%)	42.4%	<0.0001
No	125 (75.3%)	17 (29.3%)	2 (7.7%)	57.6%	

Data presented as n (%). BMI = Body mass index.
*Chi-square test for categorical variables, t test for continuous variables.
†Estimated by median income for a household of 4 within the patient's zip code.

Table 2: Models of Correlations Between Patient Factors and Use of Regional Anesthesia

	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Race/Ethnicity*								
Non-minority	Reference		Reference		Reference		Reference	
Minority	0.69 (0.41—1.15)	0.160	0.52 (0.24—1.09)	0.0899	0.44 (0.18—1.01)	0.0598	0.35 (0.14—0.86)	0.0272
Language								
English	Reference		Reference		Reference		Reference	
Non-English	0.91 (0.44—1.85)	0.817	2.10 (0.80—5.58)	0.134	2.26 (0.77—6.70)	0.141	2.28 (0.76—6.99)	0.147
Income†								
High	Reference		Reference		Reference		Reference	
Low	1.07 (0.61—1.87)	0.812	NA	NA	1.08 (0.46—2.48)	0.868	1.23 (0.51—2.96)	0.661
Age (yr)								
	1.01 (0.99—1.03)	0.381	1.02 (0.98—1.05)	0.193	1.01 (0.98—1.03)	0.533	1.01 (0.98—1.04)	0.515
Sex								
Female	Reference		Reference		Reference		Reference	
Male	0.95 (0.56—1.61)	0.864	0.98 (0.51—1.88)	0.947	0.93 (0.46—1.92)	0.863	0.85 (0.41—1.77)	0.674
BMI								
	0.98 (0.95—1.02)	0.450	NA	NA	0.98 (0.93—1.03)	0.456	0.99 (0.93—1.05)	0.734
ASA Class								
2	Reference		Reference		Reference		Reference	Reference
3	0.82 (0.21—3.40)	0.792	0.39 (0.09—1.78)	0.216	0.52 (0.10—2.82)	0.443	0.50 (0.09—1.05)	0.860
4	1.79 (0.40—8.38)	0.463	0.71 (0.14—3.89)	0.703	1.11 (0.18—7.35)	0.917	1.28 (0.19—8.85)	0.812
Substance Use Disorder‡								
No	Reference		Reference		Reference		Reference	
Yes	0.32 (0.07—1.04)	0.0952	NA	NA	NA	NA	0.15 (0.02—0.86)	0.0575
Diabetes Mellitus								
No	Reference		Reference		Reference		Reference	
Yes	1.02 (0.62—1.71)	0.931	NA	NA	NA	NA	1.02 (0.48—2.14)	0.970
Chronic Pain								
No	Reference		Reference		Reference		Reference	
Yes	0.76 (0.37—1.53)	0.465	NA	NA	NA	NA	0.41 (0.13—1.16)	0.106
Use of anticoagulants								
No	Reference		Reference		Reference		Reference	
Yes	0.77 (0.38—1.50)	0.462	NA	NA	NA	NA	0.68 (0.26—1.70)	0.424

OR = Odds Ratio. CI = Confidence Interval.

* Non-minority defined as non-Hispanic white. Minority defined as non-white race and/or Hispanic ethnicity.

† Income estimated by median income for a household of 4 within the patient's zip code. High income is defined as cases where this value is ≥$65,000. Low income is defined as cases where this value is <$65,000.

‡ Substance use disorder defined as a diagnosis of any substance use disorder including alcohol, opiate, and polysubstance use disorders.

[a]Model 1: Unadjusted.

[b]Model 2: Adjusted for race/ethnicity, language, age, sex, ASA physical status, and procedure.

[c]Model 3: Adjusted for race/ethnicity, language, income, age, sex, ASA physical status, procedure, BMI, and surgeon.

[d]Model 4: Adjusted for race/ethnicity, language, income, age, sex, ASA physical status, procedure, BMI, surgeon, substance use disorder, chronic pain, diabetes mellitus, and anticoagulant prescription.

REGIONAL ANESTHESIA 3

Perioperative Pain Management in Staged Osseointegration Procedures: A Retrospective Study

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INTRODUCTION: Transdermal bone anchored implants provide an innovative alternative to conventional prosthetic limb attachment shown to improve physical function and quality of life relative to conventional limb attachment.[1-5] Known as 'osseointegration,' the procedure involves placement of an intraosseous implant, as well as a transdermal component that emerges from the skin, and becomes the prosthetic attachment site.[2] Many patients with both upper and lower limb amputations have undergone osseointegration procedures at Walter Reed National Military Medical Center (WRNMMC). However, research regarding the perioperative pain management requirements of patients undergoing osseointegration has been limited to small case series describing pain management.[6] This study provides greater detail of the pain management procedures and prescriptions for osseointegration procedures.

METHODS: Design and Record Selection This retrospective, descriptive study was approved by the WRNMMC Institutional Review Board. Patient records were included if they underwent at least one osseointegration procedure for a lower or upper limb amputation between 2016-2021 at WRNMMC. Variables of Interest Data included demographic variables such as age, chronic pain history, and mental health comorbidities. Pain management variables included pre- and postoperative outpatient opioid prescriptions, intraoperative opioid utilization, preoperative pain and acute (24-hour) pain scores, perioperative regional/neuraxial interventions and medications, post-anesthesia care unit (PACU) entry and exit pain scores, and PACU opioid utilization. Analytic Plan Pain management variables were aggregated for the following time periods: 6-months prior to stage I, perioperative stage I, postoperative stage I (defined as duration between surgeries if two stages occurred, or 3-months after stage I if no stage II), perioperative stage II, and 1-year postoperative stage II. Pain intensity scores (range 0-10) recorded within the first 24 postoperative hours were transformed into a summed pain intensity (SPI24) score, calculated as the area under the curve using the trapezoidal rule. The worst 24-hour postoperative pain score was also extracted. Descriptive statistics (e.g., means (SD), medians (interquartile ranges), and frequencies (percentages)) were reported for patient- and pain-related characteristics by time period. Paired samples tests (Wilcoxon signed-rank and McNemar's tests) were used to compare outcomes by stage. Unadjusted linear regression models were used to estimate associations of characteristics with SPI24 at each stage. Significance was considered $p < 0.05$ and no corrections were made for multiple tests.

RESULTS: Overall, the sample included 41 patients who underwent 75 staged osseointegration procedures from 2016 to 2021. Patients had a median age of 34.5 years [IQR 29.0, 39.8]. Most patients had a diagnosis of preoperative chronic pain (stage I 83%, stage II 82%), but not mental health conditions (stage I 20%, stage II 5%). Intraoperative (stage I median 60.0 [IQR 30.0, 95.0], stage II median 65.0 [IQR 45.0, 91.0], $p = 0.51$) and PACU (stage I median 4.50 [IQR 1.0, 13.5], stage II median 4.0 [IQR 1.0, 14.5], $p = 0.71$) morphine equivalent doses were similar between stages, as were PACU entry (stage I median 0 [IQR 0.0, 4.0], stage II median 2 [IQR 0.0, 7.0], $p = 0.08$) and PACU exit (stage I median 3.0 [IQR 0.0, 4.0], stage II median 2.0 [IQR 0.0, 4.0], $p = 0.85$) pain intensity scores. SPI24 values were similar between stage I (median 88.0 [IQR 51.0, 114.0]) and stage II (median 83.0 [IQR 38.0, 113.0], $p = 0.18$). The proportion of patients receiving a postoperative opioid prescription was greater after stage II (94%) relative to stage I (22%, $p < 0.01$). In linear regression models of predictors of pain intensity after each surgery, presence of preoperative chronic pain was significantly associated with higher SPI24 in stage I (beta = 44.0, $p = 0.02$) and in stage II (beta = 56.3, $p = 0.01$).

CONCLUSION: In the present study, most preoperative factors, pain management interventions, and pain-related outcomes were statistically similar across stage I and II osseointegration procedures. In the linear regression predicting SPI24 values, chronic pain was a significant predictor of higher SPI24. Future work is needed to optimize perioperative pain management pathways, to include longitudinal functional outcomes and pain management satisfaction.

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REGIONAL ANESTHESIA 4

The effect of peripheral nerve block anaesthesia on postoperative opioid use in ankle fracture surgery: a retrospective cohort study

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INTRODUCTION: Orthopaedic procedures are associated with significant postoperative pain and over-prescription of opioids, increasing the risk of persistent opioid use[1]. Peripheral nerve blocks (PNB) are commonly used at the time of surgery following injuries such as ankle fracture to reduce perioperative pain and opioid consumption[2,3]. Limited standards exist to guide analgesia during and after traumatic lower extremity surgery[4]. The purpose of this study is to determine the impact of PNBs on postoperative opioid use in patients undergoing acute, traumatic ankle fracture surgery.

METHODS: Following ethical and hospital locality approval, all patients who underwent acute unilateral post-traumatic open reduction and internal fixation (ORIF) of the distal fibula and/or tibia at our institution, between 1st January-31st December 2019, were retrospectively identified. Patients with unilateral ankle mortice fractures, which were uni-, bi- or tri-malleolar were eligible for inclusion. Surgeries exceeding 4 hours in duration and patients with multiple injury sites were excluded. Eligible patients were stratified into two groups by use or avoidance of PNB at the time of surgery (PNB or reference group). Linked data from departmental and institutional health databases was used to obtain demographic, anaesthetic, surgical and pharmaceutical data. The primary outcome was cumulative opioid consumption during the first 48 hours postoperatively. In addition, we compared the proportion of patients dispensed strong opioids, either morphine or oxycodone, at 30-day intervals until 3 months post-discharge. All opioid doses were converted to Oral Morphine Equivalents (OMEs). Ancillary secondary outcomes included postoperative length of hospital stay, and Days Alive and Out of Hospital at 30-days (DAOH-30). Data was analysed using Chi Square and Mann Whitney U tests. A two-tailed p-value of <0.05 defined statistical significance.

RESULTS: Two-hundred and eleven patients were eligible for inclusion. The PNB group were older (42.5 vs 35.0 years) and had a greater Charlson score when compared to the reference group, although neither were statistically significant. Patients receiving PNBs had more bi- or tri-malleolar fractures (p=0.023). Māori and Pacific patients were disproportionately overrepresented in our sample, compared to the ethnic composition of our hospital's catchment. Cumulative opioid consumption measured at 6-hourly intervals postoperatively showed the PNB group consumed significantly less opioid at 24 hours (p=0.002), and continued to consume less opioid at 36 and 48 hours although this was not statistically significant (p=0.06; p=0.11 respectively). Postoperatively during hospital stay, the PNB group had significantly lower daily average opioid use (23.8 [IQR 8.7–53.4] vs 40.2 mg OME [11.3–62.3], p=0.049). After discharge, there was no significant difference in opioid dispensing between the two groups. Dispensing of tramadol and codeine was greater in the PNB group at two-months (p=0.045; p=0.055 respectively). Overall, the incidence of outpatient strong opioid use in our sample was low, with all patients ceasing morphine or oxycodone use after 60 days following discharge. The PNB group had a longer hospital stay following surgery by 4.8 hours (1.20 [IQR 0.92-2.12] vs 1.00 days [0.88-1.87] , p=0.007) and had reduced DAOH-30 (p=0.0003).

CONCLUSION: Single-shot peripheral nerve blocks can provide opioid-sparing analgesia up to 48 hours following surgery for acute traumatic ankle fractures. PNBs alone are unlikely to impact persistent opioid use. Although, the reduction of inpatient opioid consumption may decrease long-term opioid dispensing (5). Further studies are needed to explore the effects of perioperative pain interventions on hospital length of stay and persistent opioid use following lower extremity procedures.

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Figure 1: Postoperative cumulative median opioid consumption over 48 hours since patients' arrival to the operating room

Abbreviations: OME, Oral Morphine Equivalents; PNB, Peripheral Nerve Block

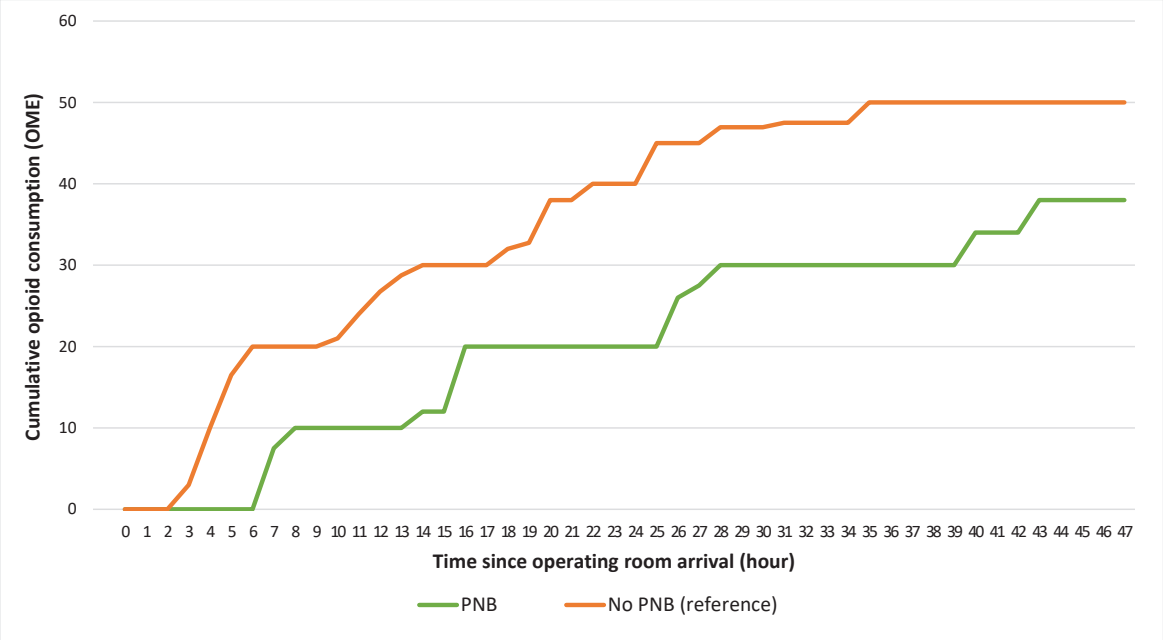

Table 1: Comparison of perioperative opioid consumption

	Total (n=211)	**PNB group (n=132)**	**Reference group (n=79)**	**p-value**
Intraoperative opioid use (OME)	50 (35-70)	40 (30-55.5)	70 (46-80)	**<0.0001**
Cumulative postoperative opioid use (OME)				
6 hrs	10 (0-26)	0 (0-20)	16.5 (0-36)	**0.0004**
12 hrs	20 (0-33)	10 (0-28)	24 (6.8-52.8)	**0.0001**
18 hrs	20 (0-46)	20 (0-40)	30 (14-60)	**0.0007**
24 hrs	30 (0-60)	20 (0-49.75)	40 (10-70)	**0.0096**
36 hrs	39.5 (10-72)	30 (10-72)	50 (20-73)	0.056
48 hrs	40 (15-82.5)	38 (10-81)	50 (21.3-86)	0.11
PACU opioid consumption in 48 hrs (OME)	0 (0-20)	0 (0-20)	6 (0-30)	**0.022**
Postoperative opioid use (OME)				
POD 0	30 (0-60)	20 (0-49.75)	40 (10-70)	**0.0096**
POD 1	10 (0-30)	10 (0-35)	0 (0-22.5)	0.17
POD 2	10 (0-37.5)	7.5 (0-35)	15 (0-37.5)	0.54
POD 3	10 (0-30)	10 (0-30)	5 (0-38.5)	0.81
Average inpatient postoperative opioid use (up to POD 7) (OME/day)	28.9 (9.0-57.0)	23.8 (8.7-53.4)	40.2 (11.3-62.3)	**0.049**

Results expressed as median (interquartile range).
p-values are two-tailed with a threshold of <0.05 used to define significance.
Abbreviations: OME, Oral Morphine Equivalents; PNB, Peripheral Nerve Block; PACU, Post Anaesthetic Care Unit; POD, Postoperative Day

REGIONAL ANESTHESIA 5

Perfusion Index as an indicator of successful ultrasound-guided supraclavicular block placement in orthopedic oncosurgical patients under general anesthesia: A prospective cohort study

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INTRODUCTION: Supraclavicular brachial plexus blocks (SCBPB) suffice as sole anesthetic for short orthopedic surgery. As postoperative pain relief for prolonged orthopedic oncosurgery under general anesthesia (GA), SCBPB routinely precedes anesthetic induction since sensorimotor evaluation of the block is not possible under GA. This causes significant patient discomfort, sympatholysis induced intraoperative blood loss and wastage of that duration of SCBPB which overlaps GA. If the window after surgery but before anesthesia-reversal is employed for administering SCBPB, it bestows the quadruple advantage of being painless, not augmenting surgical bleed, longer post-operative analgesia and reduced opioid-related side-effects[1,2]. The problem spot is assessing SCBPB under GA. Pin-prick, cold sensation and motor effect are impossible to test under GA, skin temperature gives a delayed result, thermographic imaging while more objective is cumbersome and requires specialized equipment not normally a part of the OT milieu.[3,4] Our solution is serial co-oximetric monitoring of perfusion index (PI) in the blocked limb (BL).[5]

METHODS: This prospective, single-centric, observational cohort study enrolled 30 patients undergoing upper limb oncosurgery under GA with SCBPB for post-operative pain relief. The primary outcome measure was PI recorded at 10 successive time points, simultaneously in both upper limbs, using two separate Radical-7 finger pulse co-oximeter units. PI-ratios were calculated. The secondary outcome measures were post-SCBPB serial skin temperature, postoperative Numeric Rating Scale score, time to first analgesic, and degree of sensory/motor block. The paired sample t-test/Mann-Whitney U test were utilized for normally distributed/skewed continuous variables, respectively. A p-value < 0.05 was considered statistically significant. To statistically regulate intra-individual variability, and account for non-independence among paired observations, repeated measures correlation (rmcorr) was utilized to analyse covariance. Data is presented as multiple comparison graphs and serial dotted box-whisker plots.

RESULTS: Thirty ASA I-III patients of either sex, aged 15-80yrs, weighing 30-90kg, undergoing upper limb orthopedic oncosurgery under GA were included. Exclusion criteria comprised patient refusal, local anesthetic (LA) allergy, infection/tumour at SCBPB-site, hand-amputation, arrhythmias and peripheral vascular disease. After a successful block, PI in BL abruptly rose after 5mins, progressively rising for next 10mins, whereas PI failed to increase beyond that attained post anesthetic-induction in the unblocked limb. PI in BL was 4.32, 4.49, 4.95, 7.25, 7.71, 7.90, 7.94, 7.89 and 7.93 at 0, 2, 3, 5,10 and 15min post block-institution, at reversal and 2min, 5mins post-reversal, respectively. PI-ratios at 2,3,5,10 and 15min post block-administration in BL, taking PI at LA injection as denominator, were 1.04, 1.15, 1.67, 1.78 and 1.83, respectively. Correlation between PI and skin temperature in BL gave an rmcorr coefficient of 0.79.

CONCLUSION: Co-oximeters constitute an inseparable part of the modern OT milieu. Monitoring trends in PI and PI-ratios in the blocked limb is a quantitative, non-invasive, inexpensive, simple, effective technique to assess SCBPB in patients under GA enabling utilization of the window between end-surgery and reversal of GA for successful SCBPB placement. The utility of PI in assessment of success of other regional blocks needs further prospective studies.

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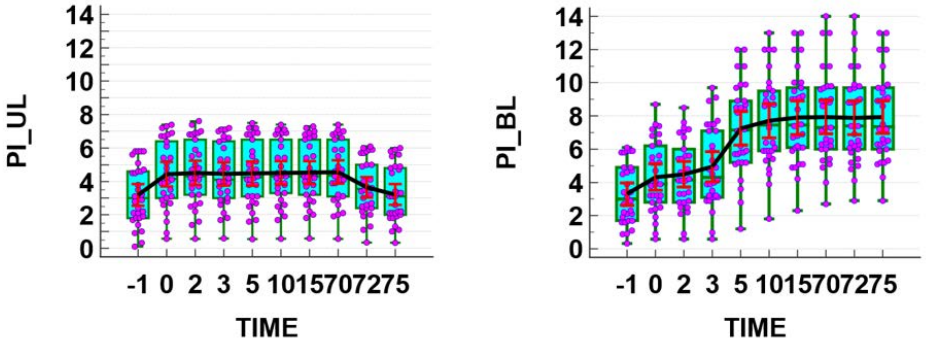

Figure 1

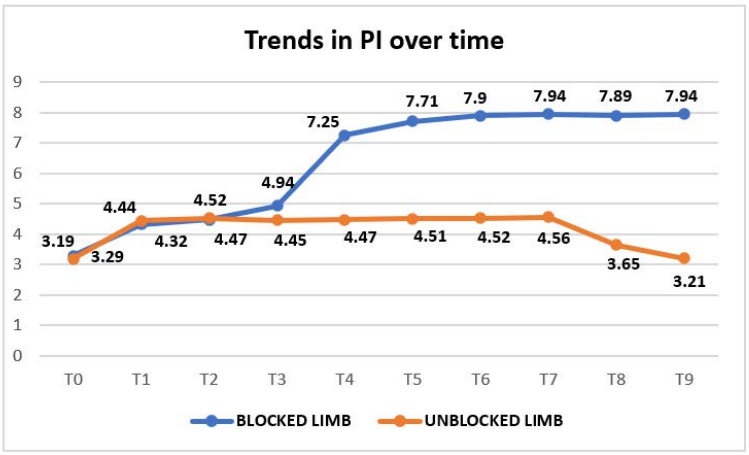

Figure 2

Figure-3: Trends in skin temperature over time for Blocked Limb (BL=blocked limb)

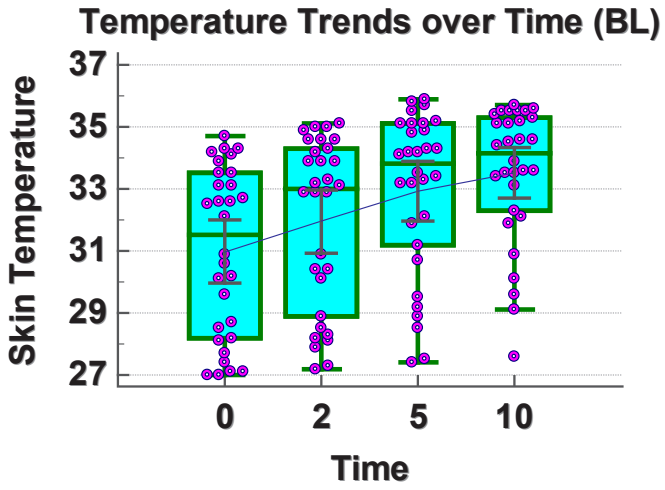

Figure-4: Correlation between PI and skin temperature in the blocked limb

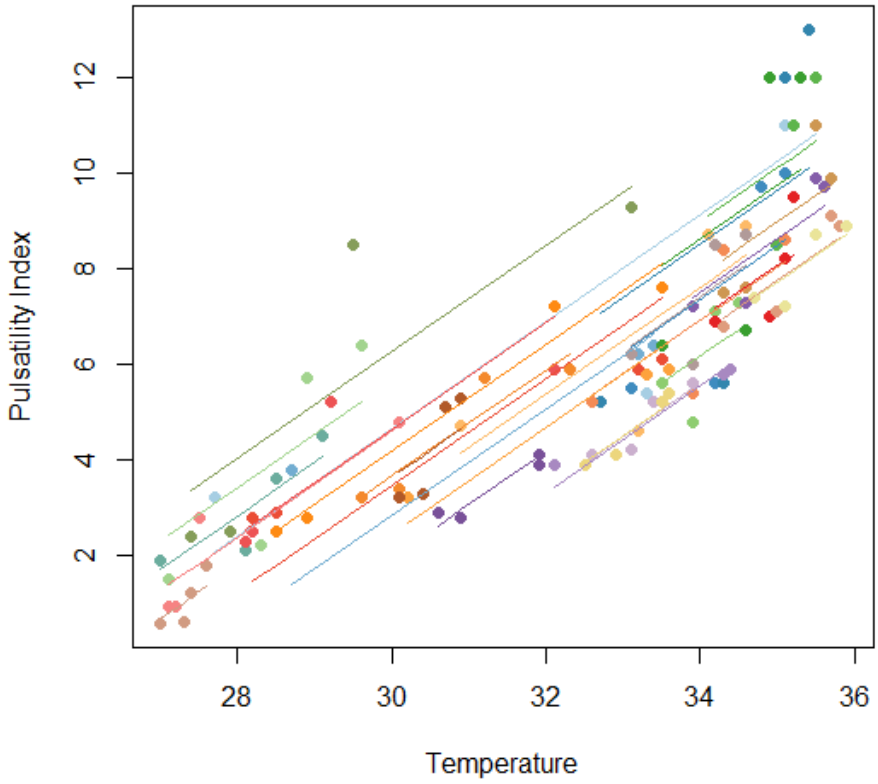

Table-1: Demographic and surgical profile (F=female; KS test= Kolmogorov Smirnov Test; LAE=Left arm above elbow; LBE=Left arm below elbow; M=male; RAE=Right above elbow; RBE=Right arm below elbow)

Parameter	Mean	SD	95% CI for mean	Lowest	Highest	KS test for normal distribution
Age (years)	42.77	18.42	35.9 to 49.7	15	79	D=0.13
Weight (kg)	63.93	13.77	58.8 to 69.1	31	90	D=0.13
Height (cm)	161.97	11.10	157.8 to 166.1	146	185	D=0.14
Gender (M:F)	17:13					
Site of lesion RAE/RBE/LAE/LBE	9(30%)/9(30%)/7(23%)/5(17%)					
Time to first analgesic (h)	8.73	1.75	8.08 to 9.38	3.42	11.67	D=0.17

Table-2: PI values and PI-ratios in blocked and unblocked limbs (BL=blocked limb; CI=confidence interval; PI=perfusion index; SD=standard deviation; UL=unblocked limb)

Time	Limb	PI ratio	Mean PI	SD	95% CI	P-Value
Baseline	BL	1	3.29	1.81	2.62 to 3.97	0.038
	UL	1	3.19	1.76	2.54 to 3.85	
Post- Induction Block just given	BL	1.31	4.32	2.14	3.52 to 5.12	0.375
	UL	1.39	4.44	1.96	3.70 to 5.17	
2 min post-block	BL	1.04	4.49	2.08	3.71 to 5.26	0.847
	UL	1.02	4.52	1.95	3.79 to 5.24	
3 min post-block	BL	1.15	4.95	2.40	4.05 to 5.84	0.085
	UL	1.00	4.45	1.86	3.75 to 5.14	
5 min post-block	BL	1.67	7.25	2.72	6.23 to 8.26	<0.0001
	UL	1.01	4.47	1.93	3.75 to 5.19	
10 min post-block	BL	1.78	7.71	2.74	6.68 to 8.73	<0.0001
	UL	1.02	4.51	1.89	3.81 to 5.22	
15 min post-block	BL	1.83	7.90	2.72	6.89 to 8.92	<0.0001
	UL	1.02	4.52	1.84	3.83 to 5.21	
Reversal	BL	1.84	7.94	2.74	6.91 to 8.97	<0.0001
	UL	1.03	4.56	1.85	3.87 to 5.25	
2 min post-reversal	BL	1.82	7.89	2.70	6.88 to 8.90	<0.0001
	UL	0.87/1.21	3.85	1.64	3.04 to 4.27	
5-min post-reversal	BL	1.84	7.93	2.63	6.96 to 8.92	<0.0001
	UL	0.72/1.01	3.21	1.66	2.60 to 3.83	

REGIONAL ANESTHESIA 6

Retrospective Review of Transversus Abdominis Plane Nerve Blocks with Liposomal Bupivacaine for Post-Operative Pain Control in Patients Undergoing Open Prostatectomy

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INTRODUCTION: Transversus abdominis plane (TAP) blocks have been studied in open prostatectomy surgery and have failed to find a significant benefit[1-3]. Liposomal bupivacaine (LB) is a long-acting bupivacaine that has been approved for use in interscalene nerve blocks and infiltration in fascial nerve blocks[4]. No significant work has been done investigating the effect of the use of LB in TAP blocks for patients undergoing open prostatectomy[5]. We hypothesized that patients undergoing open prostatectomy receiving a TAP block with LB would require less opioids after surgery than patients who did not receive a block. Secondary end points were to measure the effect of this block on post-operative pain scores and hospital length of stay.

METHODS: We conducted a retrospective observational study reviewing patients that underwent open prostatectomy from May 1, 2015 to June 21, 2021 at our institution. A total of 55 patients were assessed for eligibility. American Society of Anesthesiology (ASA) Classification I-IV patients greater than 18 years of age who received a TAP block with LB were eligible for inclusion. Patients with a history of opioid dependence, those undergoing emergent or urgent procedures, or those with a nerve block other than a TAP with LB were ineligible. 31 patients met these criteria (Figure).

Data was collected by chart review and included oral morphine equivalents (OMEs) used in PACU, OMEs used during each post-operative day, hospital length of stay, and both average and median pain scores on each post-operative day. We used two-tailed Mann Whitney U tests to test for differences between our patient groups (α=.05) (Table 2). Patient characteristics including ASA classifications, co-morbidities, operating room OMEs, and pre/post-operation non-opioid medications were tabulated and analyzed using two-tailed Student's t-tests (Table 1).

RESULTS: Data were collected and analyzed on 31 patients; 11 in the control group and 20 in the TAP group (Figure). Patients who received the TAP block with LB required less median (interquartile range) opioids (20mg [10mg-26.25mg]) than patients not receiving the block (35mg [17.5mg-49mg]) on postoperative day one (P-value .07). No large differences in OMEs administered in PACU or any other postoperative day were detected. There was no significant difference in hospital length of stay or postoperative pain scores. (Table 2).

CONCLUSION: This retrospective review does not provide evidence that the TAP block with LB can decrease opioid usage in the postoperative period, decrease hospital length of stay or improve pain scores. Though there was a large decrease in opioid use with an LB TAP block, it did not meet our threshold of significance. Limitations of this study include its retrospective nature, patient data which came from a single center, and its small sample size. This study supports the initiation of larger, prospective studies to measure the effect of TAP blocks with LB on this patient population.

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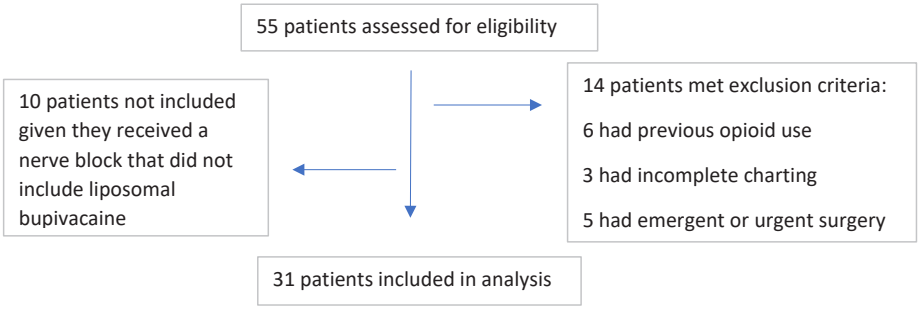

Figure. Flow diagram of the patient selection process. Initial eligibility included >18-year-old patients with an American Society of Anesthesiology Class I-IV who underwent open prostatectomy.

Table 1. Patient Demographics

Patient Characteristic	No Block (n =11)	Block (n=20)	P-value
Age, years	66.0 (63.0-68.0)	67.5 (65.5-69.5)	0.38
ASA Class			0.47
1	0	0	
2	0%	0%	
3	100%	90.9%	
4	0%	9.1%	
Charlson co-morbidity index	2.4	1.4	0.12
Myocardial infarction	36.4%	0%	0.002
Congestive heart failure	0%	5.0%	0.47
Peripheral vascular disease	9.1%	0%	0.18
CVA or TIA	0%	10%	0.29
Dementia	0%	0%	
COPD	27.2%	5.0%	0.67
Connective tissue disease	9.1%	5.0%	0.78
Peptic ulcer disease	0%	0%	
Liver disease	9.1%	15.0%	0.78
Diabetes Mellitus	63.6%	25.0%	0.01
Moderate to severe CKD	0%	0%	
Solid tumor	100%	100%	1
Leukemia	0%	0%	
Lymphoma	0%	0%	

Table 1 continued

AIDS	9.1%	0%	0.18
Premedication			
Tylenol	9.1%	5.0%	0.67
Gabapentin	0%	0%	
OR OME, mg	82 (60-113.5)	62 (38.75-70.5)	0.03
OR non-opioid analgesia			
Ketamine	0%	10.0%	0.32
Dexmedetomidine	9.1%	0%	0.18
Lidocaine infusion	0%	0%	
Tylenol	45.5%	50.0%	0.82
Toradol	0%	0%	
Postoperative non-opioid analgesia			
Tylenol	63.6%	70.0%	0.73
Gabapentin	18.1%	15.0%	0.83
NSAID	9.1%	10.0%	0.94

Baseline, intraoperative, and postoperative patient characteristics. Categorical variables are reported as percent, and continuous variables are reported as median (interquartile range).

Table 2. Primary and Secondary Outcomes of Patients Following Open Prostatectomy

Outcome	No Block (n =11)	Block (n=20)	P-value
PACU opioids	5 (0-20)	10 (0-20)	0.53
Postoperative opioid analgesia			
Day 0	20 (10.5-24.5)	10 (0-15.5)	0.16
Day 1	35 (17.5-49)	20 (17.5-26.3)	0.07
Day 2	20 (7.5-33)	20 (0-20)	0.29
Day 3	10 (0-18.5)	7.5 (0-20)	1.00
Day 4	0 (0-3.8)	0 (0-16.3)	0.83
Hospital length of stay	4 (3-5)	3 (3-5)	0.53
Postoperative pain scores (mean)			
Day 0	4.4 (3.4-5.6)	3.5 (1.2-4.7)	0.16
Day 1	3.4 (2.6-3.7)	3.3 (2.8-4.2)	0.62
Day 2	3.3 (1.1-4.1)	2.9 (2.1-3.8)	0.83
Day 3	2.6 (2.3-3)	2.5 (0.3-3.9)	0.82
Day 4	3.1 (1.5-3.5)	3.4 (2.2-4.5)	0.47
Postoperative pain scores (median)			
Day 0	4 (3-6)	3.25 (0.8-5)	0.13
Day 1	4 (3-4)	3 (1-4.1)	0.73
Day 2	4.3 (0.8-5.8)	3 (1-3.8)	0.32
Day 3	1.5 (0-3)	2.5 (0-5)	0.22
Day 4	3 (0-4.5)	3.5 (1.8-4.5)	0.66

Primary outcomes table of postoperative opioid consumption (mg) in patients who received a TAP block with liposomal bupivacaine and patient who received no block. All continuous variables are reported as a median (interquartile range). PACU= post-operative care unit.

REGIONAL ANESTHESIA 7

Efficacy and Safety of Erector Spinae Blocks for Lumbar Spine Surgery: A cohort retrospective multi-institutional study

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INTRODUCTION: Lumbar spine fusions are painful surgeries with opioids as the mainstay of perioperative analgesia. Given the ongoing opioid epidemic and the risk of opioid-related adverse drug events, it is critical to identify and implement opioid-sparing clinical pathways. We report the results of a retrospective case series during which patients undergoing lumbar spine surgery in two large community hospitals (St. Vincent's Medical Center [SVMC], Midstate Medical Center [MMC]) received a multimodal anesthetic regimen including ultrasound-guided erector spinae plane (ESP) blocks was used to provide robust opioid-sparing postoperative analgesia. Our main question was how (1) whether this multimodal regimen would impact postoperative pain and opioid requirements in patients undergoing lumbar spine surgery surgery, and (2) if this protocol caused similar improvements in pain and opioid requirements at both hospitals that received the multimodal analgesia protocol. In addition to pain and opioid consumption we also looked at the length of hospital stay, time to first opioid, and as well as the safety profile of erector spinae blocks for lumbar spine surgery..

METHODS: In this study, we performed a retrospective, observational study of patients undergoing lumbar spine surgery at two hospitals in Connecticut. This study was reviewed by Hartford Hospital Institutional Review Board. The study involved three cohorts of patients, (1) a control cohort of patients who underwent lumbar spine surgery without ESP blocks St. Vincent's Medical Center from from January 2020 - February 2020, (2) a case cohort of patients who underwent lumbar spine surgery with ESP blocks at St. Vincent's Medical Center from August - September 2020 and (3) a case cohort of patients who underwent lumbar spine surgery with ESP blocks at Midstate Medical Center from August - September 2020. The sample was comprised of men and women, aged 18-89 who underwent elective lumbar spine surgery. Those with a preoperative BMI >50 and those using more than 20 morphine milligram equivalent (MME)/ day preoperatively were excluded. Cumulative opioid requirements were tabulated in MME for the first 72 hours after surgery. Records were identified through the hospital electronic health record (EHR) based on type of procedure, using an ICD code consistent with lumbar pain, radiculopathy, disc degeneration, disc herniation, foraminal stenosis, or 1-2 level spondylolisthesis or deformity. STATA was used for statistical analysis. Outcome measures were compared between groups using analysis of variance for continuous variables and Fisher's exact test for categorical data. Results yielding $p<0.05$ were deemed statistically significant.

RESULTS: A total of 21 patients were identified in the control group, 28 patients were identified in the SVMC case group, and 28 patients were identified in the MMC case group. At 24 hours after surgery, the mean (and SD) MME was 377.6 (351.7), 73.86 (129.6) and 32.85 (29.21) for control, SVMC ESP, and MMC ESP groups respectively -- significant difference was found between means (F 16.10, $p<0.0001$). At 48 hours after surgery, the mean (and SD) MME was 431.4 (353), 127.1 (164.2) and 52.4 (49.7) for control, SVMC ESP, and MMC ESP groups respectively -- significant difference was found between means (F 17.02, $p<0.0001$). At 72 hours after surgery, the mean (and SD) MME was 442.4 (350.1), 151.1 (179.3) and 63.7 (70.3) for control, SVMC ESP, and MMC ESP groups respectively -- significant difference was found between means (F 16.15, $p<0.0001$). Mean time to first opioid was also analyzed, but no significant difference was found between means (F 2.024, $p = 0.13$). Post-hoc analysis between SVMC ESP vs MMC ESP cohorts found no significant difference ($t=1.6$, $p= 0.128$).

CONCLUSION: A statistically significant decrease in opioid requirement in the ESP block group, as compared to the historical control group, was noted up to 72 hours after lumbar spine surgery. The effectiveness of this protocol was demonstrated at both institutions in our study, with slightly more significant results at MMC. The data from this study supports ESP blocks as an effective method of postoperative pain management. Additional investigation will help to determine the role of the ESP in terms of other outcome measures (rehabilitation metrics, quality of recovery, and cost-benefit analysis analysis) as well as gauge its relative efficacy with minimally invasive surgical approaches.

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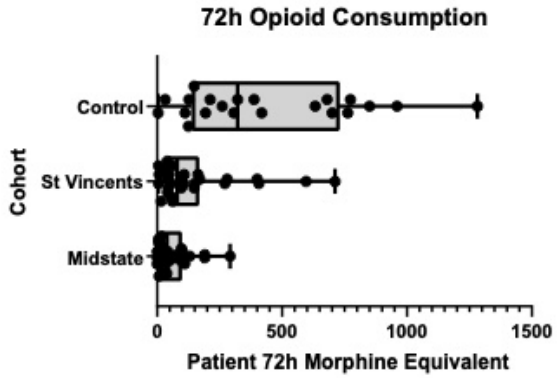

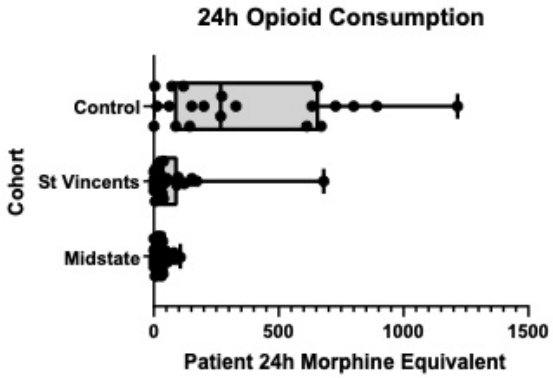

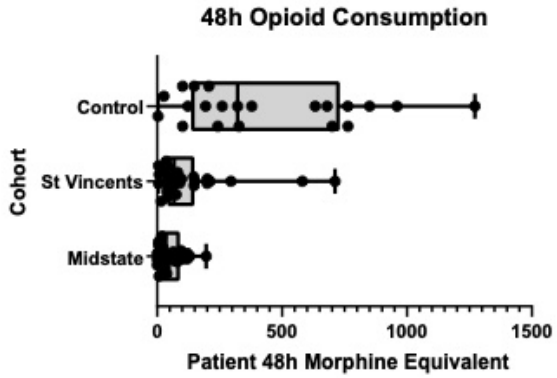

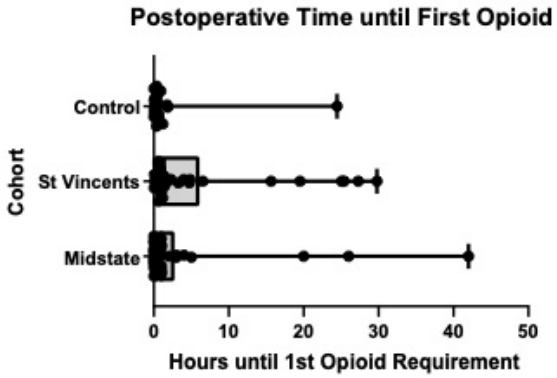

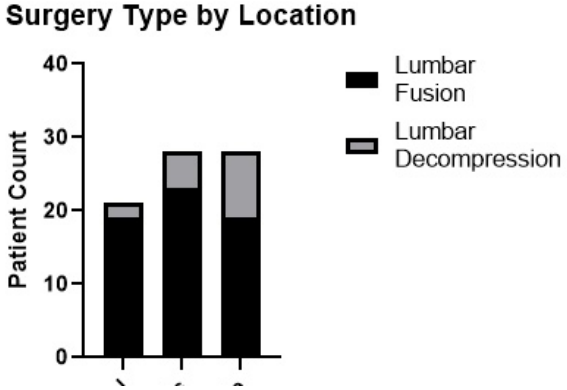

REGIONAL ANESTHESIA 8

Transversus abdominis plane and rectus sheath blocks with liposomal bupivacaine does not improve postoperative pain control following minimally invasive prostatectomy

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INTRODUCTION: The current standard of practice is not to perform a regional anesthesia block for patients undergoing minimally invasive prostatectomy. There is little knowledge about the effectiveness of transversus abdominis plane (TAP) blocks in combination with rectus sheath (RS) blocks to help improve postoperative pain in these patients[1]. Liposomal bupivacaine (LB) is a long acting bupivacaine that has been approved for use in infiltration in fascial nerve blocks[2]. There are no current studies investigating the effect of LB in TAP and RS blocks for minimally invasive prostatectomy. We hypothesized that patients undergoing robotic and laparoscopic prostatectomy receiving bilateral TAP and RS blocks with LB would require less opioids after surgery than patients that did not receive the blocks. Secondary endpoints were to measure the effect of this block on post-operative pain scores and hospital length of stay.

METHODS: Following Institutional Review Board approval, we conducted a retrospective observational study reviewing patients that underwent robotic and/or laparoscopic prostatectomy performed between May 1, 2015 and June 21, 2021 at the Central Virginia VA Medical Center in Richmond, VA. American Society of Anesthesiology Classification I-IV patients greater than 18 years of age who received TAP and RS blocks with LB were eligible for inclusion. Patients with a history of opioid dependence, those undergoing emergent or urgent procedures, or had a nerve block other than a TAP with LB were ineligible (Figure 1). Data were collected by chart review and included oral morphine equivalents (OMEs) used in post anesthesia care unit (PACU) and each postoperative day, hospital length of stay, and both average and median pain scores on each postoperative day. We tested for differences between patients using two-tailed Mann Whitney U tests.

RESULTS: Data were collected and analyzed on 134 patients; 81 receiving no block and block 53 receiving the block (Table 1). Patients who received the blocks with LB required less median [interquartile range] opioids (5 mg [0 mg - 20 mg]) than patients not receiving the block (10 mg [0 mg - 20 mg]) on postoperative day one, however, the difference was not significant. There was no difference in OMEs administered in PACU or any other postoperative day (Table 2). There was no difference in hospital length of stay or postoperative pain scores (Table 2).

CONCLUSION: This retrospective review provides evidence that TAP and RS blocks with LB does not decrease the use of postoperative opioids, improve pain scores, or decrease hospital length of stay for patients undergoing minimally invasive prostatectomy. Limitations to our study include sample size and single-center study.

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Table. Baseline, intraoperative, and postoperative patient characteristics.

Patient Characteristic	No Block (n =81)	Block (n=53)	P-value
Age, years	65.0 (60.0-69.0)	62.0 (57.0-70.0)	0.36
ASA Class			0.67
1	0	0	
2	9.8%	7.5%	
3	90.2%	90.5%	
4	0%	1.9%	
Charlson co-morbidity index	2.89	2.94	0.81
Myocardial infarction	4.9%	7.6%	0.54
Congestive heart failure	4.9%	7.6%	0.54
Peripheral vascular disease	4.9%	11.3%	0.17
CVA or TIA	2.4%	3.7%	0.66
Dementia	4.9%	0%	0.10
COPD	22.2%	9.4%	0.06
Connective tissue disease	1.2%	0%	0.42
Peptic ulcer disease	7.4%	11.3%	0.44
Liver disease	9.9%	9.4%	0.95
Diabetes Mellitus	19.8%	33.9%	0.30
Moderate to severe CKD	0%	0%	
Solid tumor	100%	100%	1
Leukemia	0%	0%	
Lymphoma	0%	0%	
AIDS	1.2%	0%	0.42
Premedication			
Tylenol	2.5%	7.6%	0.17
Gabapentin	1.2%	0%	0.42
OR OME, mg	45 (38-70)	45 (38-62)	0.06
OR non-opioid analgesia			
Ketamine	11.1%	3.8%	0.13
Dexmedetomidine	18.5%	15.1%	0.61
Lidocaine infusion	13.5%	0%	0.004
Tylenol	86.4%	90.6%	0.47
Toradol	23.4%	7.6%	0.02
Postoperative non-opioid analgesia			
Tylenol	85.2%	90.6%	0.36
Gabapentin	27.2%	47.2%	0.02
NSAID	33.3%	39.6%	0.46

Categorical variables are reported as percent, and continuous variables are reported as median (interquartile range).

Table 2.

Outcome	No Block (n =81)	Block (n=53)	P-value
PACU OME, mg	0 (1 – 16)	0 (0 – 10)	0.33
Hospital Length of stay, days	1 (1 – 1)	1 (1 – 1)	0.20
Postoperative OME, mg			
Day 0	5 (0 – 10)	5 (0 – 10)	0.77
Day 1	10 (0 – 20)	5 (0 – 20)	0.26
Day 2	10 (5 – 20)	5 (5 – 20)	0.37
Day 3	0 (0 – 7.5)	0 (0 – 0)	n/a
Postoperative pain scores, median			
Day 0	4 (2 – 5)	3.5 (2 – 5)	1
Day 1	3.75 (1.5 – 5)	3 (1 – 5)	0.36
Day 2	4.5 (3 – 6)	4 (2 – 6)	0.97
Day 3	3 (0 – 5.5)	4 (4 – 4)	n/a

Primary outcomes table of postoperative opioid consumption in patients who received a TAP block with liposomal bupivacaine and patient who received no block. All continuous variables are reported as a median (interquartile range). PACU= post-anesthesia care unit.

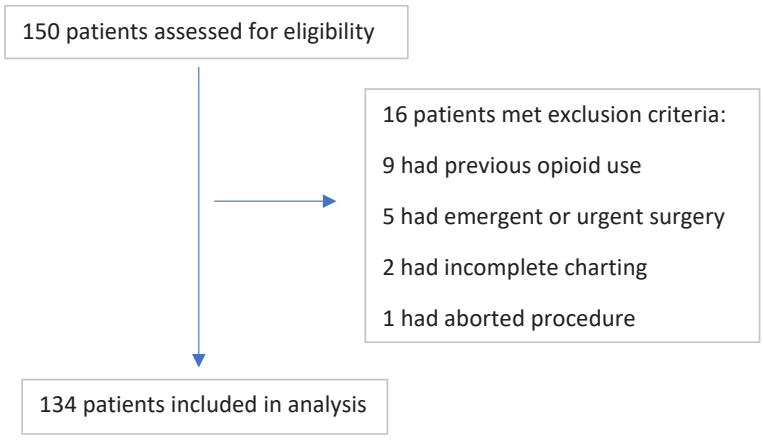

Figure 1

REGIONAL ANESTHESIA 9

The Efficacy of Serratus Anterior Plane Block for Postoperative Analgesia after Video Assisted Thoracoscopic Surgery

Giacomo Scorsese[1], Yujie Jiang[2], Seth H Greenspan[2], Zhaosheng Jin[1], Christopher Seiter[1], Jun Lin[3]

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INTRODUCTION: Pain is the most common adverse event after surgery. While thoracic epidural anesthesia has been the gold standard for postoperative analgesia after undergoing video assisted thoracoscopic surgery (VATS), it is also associated with risks of dura and pleura injury, as well as technical difficulty in placement. The serratus anterior plane block (SAPB) is a fascial plane block which could be done quickly under ultrasound guidance and yield comprable pain reduction. In this meta-analysis, we evaluate the analgesic efficacy of SAP block in VATS.

METHODS: We systematically searched PubMed for both prospective and retrospective studies using the following criteria: adult patients undergoing VATS under general anesthesia. The intervention of interest is serratus anterior plane block (SABP) and control is general anesthesia with systemic analgesia. The primary outcomes included 24-hour opioid requirement, 24-hour area under the curve (AUC) of pain score. The secondary outcome was PONV and incidence of other complications.

RESULTS: The last literature search was conducted on Sep 28, 2021 . We identified a total of 7 studies which fulfilled the inclusion criteria. Three studies reported 24-hour opioid requirement, pooled data significantly favored SAPB [mean difference (MD)= 10.52 mg, 95% confidence interval (CI) (8.02 to 13.01)]. Six studies reported the AUC of pain score over the 24 hours after surgery, which again favored SAPB (standardized MD= 3.26, 95% CI 2.07 to 4.46). SAPB arm also trended towards less PONV, but was not statistically significant (Risk ratio=0.57, 95% CI 0.33 to 1.00).

CONCLUSION: Serratus anterior plane block is potentially an effective alternative mode of analgesia for VATS during the first 24 hours after surgery. Compared to epidural anesthesia and paravertebral block, it has the advantage of lower risk of dura and pleura injury. Further studies are needed in comparing the analgesic efficacy of different regional anesthesia options, as well as the potential of catheter-based techniques.

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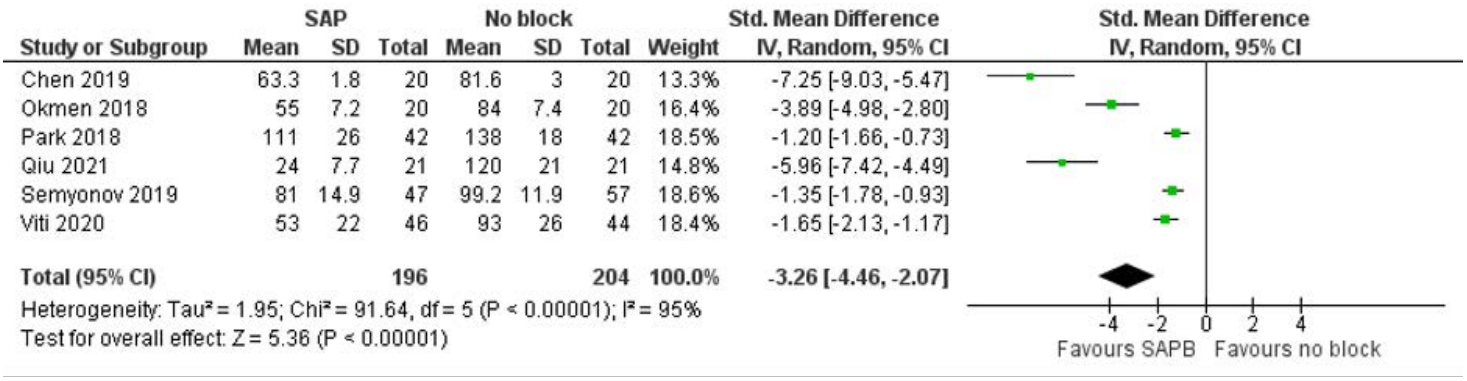

Figure 1

REGIONAL ANESTHESIA 10

Programmed intermittent bolus via a thoracic paravertebral catheter provides greater dermatomal spread compared to a continuous infusion in video assisted thoracic surgery: A randomized control trial

Elird Bojaxhi[1], Alberto Ardon[2], Christopher Robards[1], Steven Porter[3], Ilana Logvinov[4]

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INTRODUCTION: Video assisted thoracic surgery (VATS), though less invasive than open thoracotomy, can still be associated with significant pain in the early post-operative period. A paravertebral blockade and catheter use can significantly reduce acute pain after a thoracic procedure. While continuous infusions (CI)have traditionally been utilized to deliver local anesthetic via peripheral nerve catheters, programed intermittent bolus (PIB) has shown promise as an alternative mechanism to deliver analgesia. Paravertebral catheters (PVC) are routinely used in our institution for VATS and other thoracic surgeries. In this prospective double-blinded randomized control trial, we compare a PVC delivering local anesthetic via a PIB setting vs CI. Our primary outcomes include pain and opioid use on post-op day 1, and dermatomal coverage between the two different pump settings. Our secondary outcomes were a difference in the patient's quality of recovery (QoR-15), use of local anesthetic, post-operative nausea and vomiting (PONV), and hospital length of hospital stay (hLOS).

METHODS: After IRB approval, 50 opioid na√Øve patients were approached, and 46 agreed to participate in the study. The patients were randomized on a 1:1 ratio between PIB and CI. All catheters were placed pre-operatively at the T5 level and the block was confirmed via lack of sensation to cold over the corresponding dermatome. The pump was programed to PIB or CI and connected to the catheter by an acute pain nurse not participating in the data collection. All pumps were also programed with a patient-controlled bolus dose. All patients received standardized perioperative multimodal analgesia (acetaminophen 1000mg PO every 6 hours and ketorolac 30 mg IV every 8 hours) and PONV prophylaxis (dexamethasone 10mg IV and ondansetron 4 mg IV prior to emergence). Opioid administration included intraoperative IV fentanyl (titrated at the discretion of the in-room provider), and postoperative oxycodone 5-10 mg PO every 4 hours for moderate pain and hydromorphone 0.2-0.5 mg IV every 4 hours for severe pain. Data collection and patient assessment was conducted by a member of the acute pain service that was blinded to the pump setting and randomization schedule. The primary timeframe of interest was the morning of POD 1 since the initial injection of the PVB would have worn off and the difference between the two pump settings could be best assessed. Data collection was stopped on the evening of POD 1 since most PVC and chest tubes were discontinued in the evening of POD 1 or morning of POD 2. QoR-15 was assessed pre-op and evening of POD1.

RESULTS: Patient demographics and intra-operative characteristics are show in Table 1 with the average body mass index being slightly higher in the PIB group. As shown on table 2, there was no significant difference in pain scores (with rest or cough) or opioid use between the PIB and CI groups. However, there was a significant difference between the average dermatome coverage of the block on POD1 between the PIB and CI [5 vs 3 respectively (p=0.03)]. Figure 1 illustrates the differences in dermatomal coverage of the block on POD1 between the PIB and CI groups. There was no difference between the two groups with regards PONV, change in the QoR-15, hLOS, and total volume of local anesthetic use through either pump.

CONCLUSION: Delivery of local anesthetic via PIB through a thoracic PVC provides greater dermatomal spread of the block when compared to a CI. However, the increased efficacy of the block did not translate to a significant improvement in analgesia between the two groups in patients undergoing VATS.

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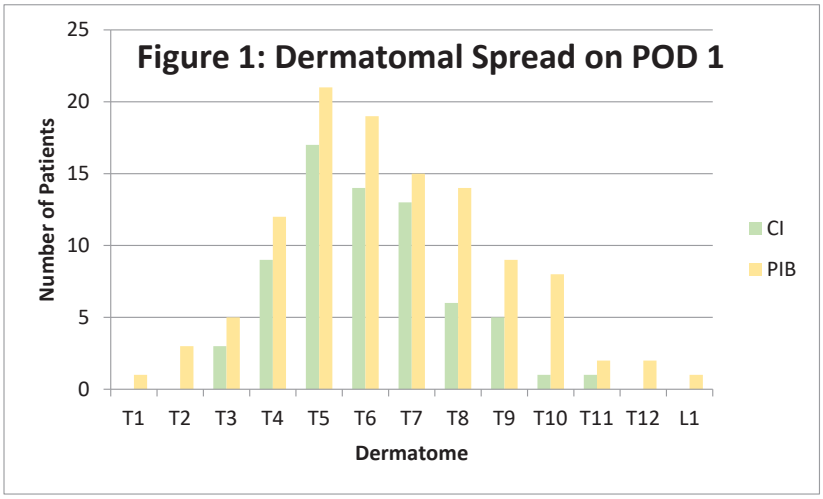

Table 1: Perioperative Characteristics				PONV		hLOS (median)
Group:	Age (mean)	% Male	BMI (kg/m^2)	PACU	POD 1	
CI	69.5 years	43.5%	25.8	4.2%	16.7%	2
PIB	63.9 years	43.5%	29.2	8.3%	12.5%	2
P - value	0.09	1.00	0.03	0.55	0.68	1.00

Table 2: Pain, Opioid Use, and Dermatomal Deficit

	Pain Scores (median)								Opioids (OME)				Deficit (median)	
Group:	Preop - Rest	Preop - Cough	PACU - Rest	PACU - Cough	POD 1 am - Rest	POD 1 am - Cough	POD 1 pm - Rest	POD 1 pm - Cough	Intra-op	PACU	Day 0	Day 1	PACU	Day 1
CI	0.0	0.0	1.2	3.2	1.61	4.17	1.32	3.77	73.49	10.52	6.20	10.54	3	3
PIB	0.0	0.2	1.9	4.5	2.13	5.26	1.65	4.13	70.54	9.74	7.94	15.65	3	5
P-Value	1.00	0.10	0.28	0.18	0.36	0.19	0.55	0.65	0.76	0.86	0.55	0.37	0.94	0.03

REGIONAL ANESTHESIA 11

Intrathecal Hydromorphone for Analgesia after Partial Hepatectomy: A Double-Blind Randomized Controlled Trial

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INTRODUCTION: Over 841,000 cases of liver cancer are diagnosed worldwide each year.[1,2] Partial hepatectomy is currently the major surgical procedure to treat liver cancer and other hepatic benign tumors, but the optimal postoperative analgesic strategy has not been determined. There is tremendous interest in intrathecal opioids as part of a multimodal pain strategy. Hydromorphone is a middle lipid-soluble opioid with faster onset of action, stronger analgesic effect, and shorter half-life, which is considered an alternative opioid for intrathecal block.[3] No prospective studies have evaluated the effectiveness and safety of intrathecal hydromorphone as part of a multimodal analgesic regimen for partial hepatectomy. The authors hypothesized that intrathecal hydromorphone would decrease the incidence of moderate to severe pain after partial hepatectomy.

METHODS: In this single-center, double-blinded randomized trial, 126 adult patients with ASA I-III for partial hepatectomy under general anesthesia were randomly allocated to received intrathecal hydromorphone or no block. Both groups received standard care with protocolized multimodal analgesia including systematic nonsteroidal anti-inflammatory drugs and wound infiltration. The primary outcome was the incidence of moderate to severe pain with movement at 24 h after surgery. Secondary outcomes included the incidences of moderate to severe pain at rest (30 min, 24 h, 48 h, 72 h) and with movement (30 min, 48 h, 72 h), pain scores at rest and with movement within 72 h, analgesics use, adverse events, postoperative recovery outcomes. Differences in the primary outcome, the incidence of moderate to severe pain during movement at 24 h after surgery, were assessed for significance using a chi-squared test. NRS scores at 30 min, 24 h, 48 h, and 72 h after surgery were evaluated using a linear mixed model to take into account repeated measurements in the same patient.

RESULTS: We assessed 563 patients who underwent elective partial hepatectomy for eligibility, and we ultimately enrolled and randomized 126 patients to receive either intrathecal hydromorphone or no block (n = 63 each; Figure 1). Two patients were later excluded because their surgeries were cancelled, so 124 patients were included in the final intention-to-treat analysis. The incidence of moderate to severe pain with movement in 24 h after surgery was lower in the intrathecal hydromorphone group compared with the control group (29.0% vs. 50%; relative risk, 0.58; 95% CI, 0.37, 0.92; P = 0.017)(Table 1). In 30 min after surgery, the incidence of moderate to severe pain at rest (8.1% vs. 29.0%; P = 0.003) and with movement (50.0% vs. 77.4%; P = 0.001) were significantly lower in intrathecal hydromorphone group. While, there was no significant difference on the incidence of moderate to severe pain between two groups in 48 h and 72 h after surgery. The NRS recorded for up to 72 h is shown in figure 3. In both groups, the pain scores at rest and during movement changed significantly over time. Patients in the intrathecal hydromorphone group showed significantly lower NRS at rest and during movement at all time points examined (Figure 2). In addition, pruritus was more common in the intrathecal hydromorphone group (19.4% vs. 4.8%; P = 0.013) within 24 h after surgery.

CONCLUSION: This randomized controlled trial provides strong evidence that adding intrathecal hydromorphone to conventional multimodal analgesia can improve postoperative analgesia for at least 24 h after partial hepatectomy, without increasing risk of clinically important complications. Thus, intrathecal hydromorphone could be considered as a part of multimodal analgesia in patients undergoing partial hepatectomy.

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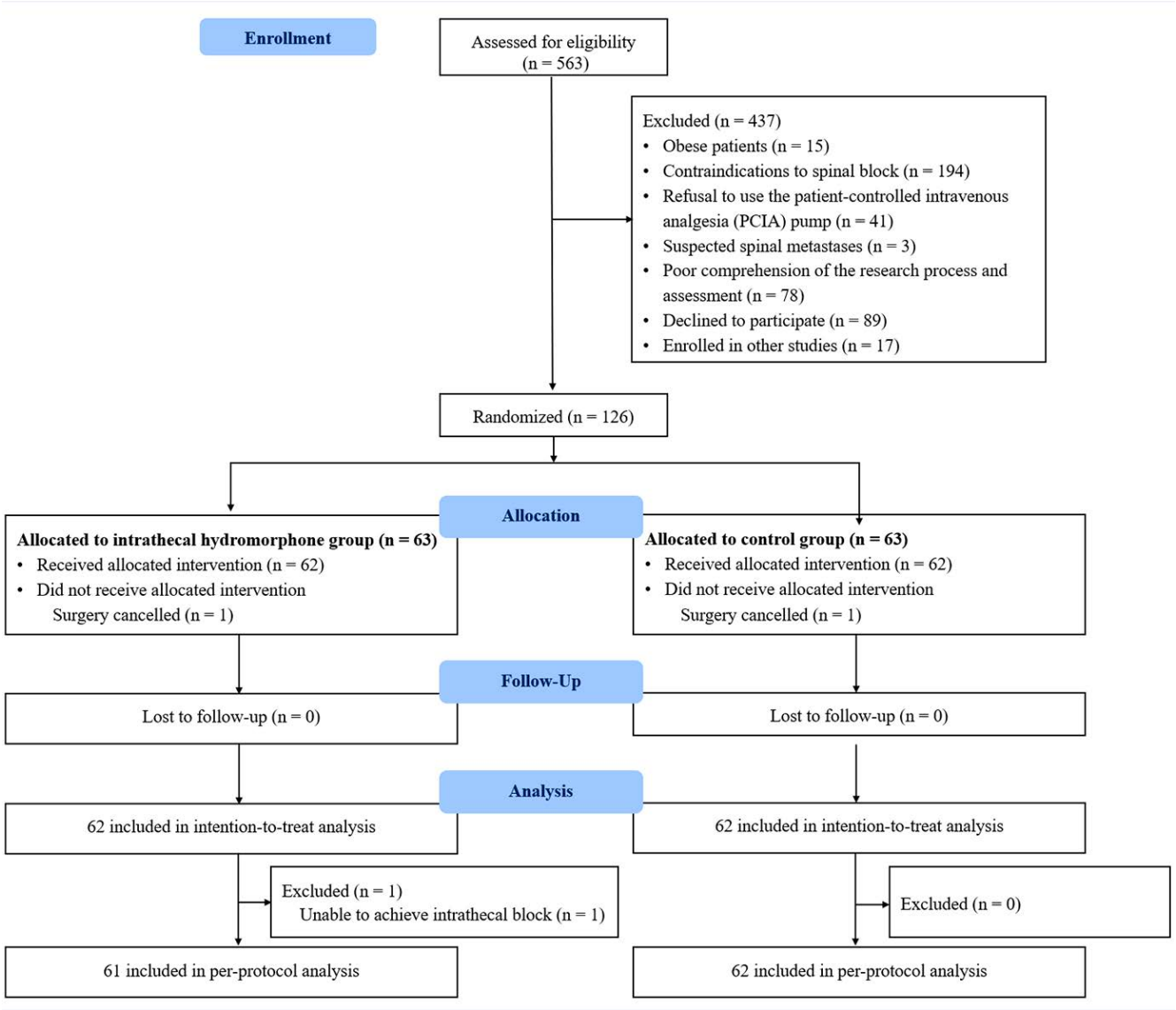

Figure 1

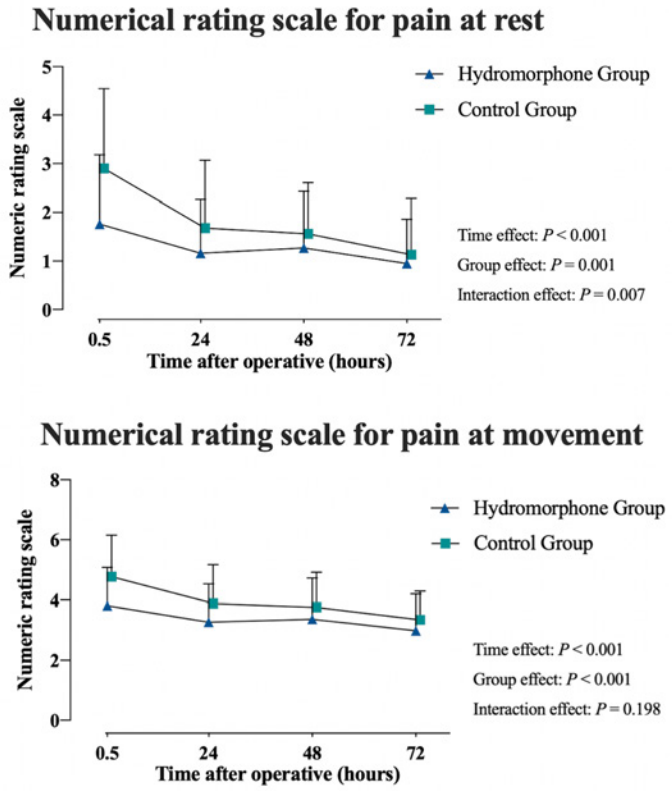

Table 3. Incidence of moderate to severe pain during rest and movement.

Outcome and time point	Hydromorphone group (N=62)	Control group (N=62)	Relative Risk (95% CI)	*P* value
Incidence of moderate to severe pain at rest				
30 min after surgery	5 (8.1)	18 (29.0)	0.28 (0.11, 0.70)	0.003 [a]
24 h after surgery	2 (3.2)	4 (6.5)	0.50 (0.10, 2.63)	0.403 [b]
48 h after surgery	2 (3.2)	1 (1.6)	2.00 (0.19, 21.49)	0.500 [b]
72 h after surgery	1 (1.6)	3 (4.8)	0.33 (0.04, 3.12)	0.309 [b]
Incidence of moderate to severe pain during movement				
30 min after surgery	31 (50.0)	48 (77.4)	0.65 (0.49, 0.86)	0.001 [a]
24 h after surgery	18 (29.0)	31 (50.0)	0.58 (0.37, 0.92)	0.017 [a]
24 h after surgery (per-protocol analysis)	17 (27.9, n = 61)	31 (50.0)	0.55 (0.35, 0.90)	0.012 [a]
48 h after surgery	24 (38.7)	34 (54.8)	0.71 (0.48, 1.04)	0.072 [a]

REGIONAL ANESTHESIA 12

Clonidine Prolongs Pediatric Spinal Blockade but May Increase the Risk of Airway Obstruction, Hiccups, and Apnea

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INTRODUCTION: Spinal anesthesia (SA) allows anesthesia providers to avoid general anesthesia (GA) during pediatric urological or lower abdominal surgery. Avoiding general anesthesia has implications for future neurological development, post-anesthesia apnea, and PACU length of stay. Adoption of SA has been limited by concerns for inadequate duration of blockade and spinal adjuvants like clonidine (SAC) have been increasingly used to prolong neuraxial blockade[1]. However, clonidine may impact intraoperative breathing mechanics.

METHODS: This is a single institution, prospective cohort study. All patients aged ≤10.0 months receiving spinal anesthesia as their primary anesthetic were considered for inclusion in the present study (n=57). Patients received intrathecal bupivacaine (1mg/kg) with or without clonidine (1mcg/kg) at the anesthesia provider's discretion. Patients receiving alternative intrathecal dosing (n=4) or combined spinal and caudal epidural anesthesia (n=6) were excluded.

RESULTS: 47 patients are included in the present analysis. Demographics including age, weight, ASA classification, and rate of prematurity were similar in the two groups (Table 1). A chi square test was performed for categorical variables. Intraoperatively, SAC patients had higher rates of hiccups (SAC: 30%, SA: 0.0%, p=0.01) and mild airway obstruction (SAC: 33.3%, SA: 0.0%, p<0.01). SAC patients also trended towards higher rates of apnea (SAC: 30.0%, SA: 11.8%, p=0.16) and oxygen desaturation (SAC: 26.7%, SA: 5.9%, p=0.08) though these outcomes did not reach significance. Rates of conversion to GA were similar in both groups (SAC: 3.3%, SA: 5.9%, p=0.68) (Table 2). Spinal to end-of-procedure times and PACU lengths of stay were not normally distributed and had unequal independent sample sizes and variances. Therefore, Mann-Whitney U-tests were performed for these outcome variables. SAC patients experienced longer times from spinal-placement to end-of-procedure (W=360.5, p=0.02) but had shorter PACU lengths of stay (W=128.5, p=0.02) (Table 2). The PACU time analysis included 44 patients, as 3 patients were planned inpatients. Analyses were conducted in R (R Core Team, 2018).

CONCLUSION: Results from this analysis demonstrate that SAC patients experienced longer spinal to end-of-procedure times without prolonging PACU length of stay. SAC patients also experienced a higher rate of hiccups and mild airway obstruction than patients receiving SA and trended towards higher rates of apnea and oxygen desaturation. These findings confirm that the addition of clonidine to spinal anesthesia impacts breathing mechanics within our study population. However, these findings did not result in an increased rate of conversion to general anesthesia.

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Table 1: Patient Demographics

Classification	Without Clonidine (n=17)	With Clonidine (n=30)
Post-Menstrual Age (days) mean (+/-SD)	398.3 (78.2)	391.4 (72.7)
ASA Classification		
Mean	1.4 (0.57)	1.4 (0.58)
ASA 1 (n, %)	n=12 (70.6%)	n=19 (63.3%)
ASA 2 (n, %)	n=5 (29.4%)	n=8 (26.7%
ASA 3 (n, %)	n=0 (0.0%)	n=3 (10%)
Prematurity (y/n) (%)	n=3 (17.6%)	n=5 (16.7%)
Weight (kg) mean (SD)	6.4 (2.0)	6.4 (2.0)

Table 2: Procedure Outcomes

Outcome	Without Clonidine	With Clonidine	p-value
Apnea (n, %)	n=2 (11.8%)	n=9 (30.0%)	0.16
Desaturation (n, %)	n=1 (5.9%)	n=8 (26.7%)	0.08
Hiccups (n, %)	n=0 (0.0%)	n=9 (30.0%)	**0.01**
Airway Obstruction (n, %)	n=0 (0.0%)	n=10 (33.3%)	**0.007**
Conversion to General Anesthesia (n, %)	n=1 (5.9%)	n=1 (3.3%)	0.68
Time: Spinal Placement to Procedure End (min) mean (SD)	61.9 (17.8)	77.2(22.3)	0.02
PACU Time (min) mean (SD)	43.5 (29.7)	27.4 (42.5)	0.02

SUBSPECIALTY ABSTRACTS

RESPIRATION

RESPIRATION 1

Amelioration of acute lung injury by peptides targeting scavenger receptor CD36

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INTRODUCTION: CD36 is a fatty acid translocase belonging to a scavenger receptor class B family. We have previously demonstrated involvement of CD36 in endotoxin binding and propagation of lung injury in mice[1]. This study tested effects of amphipathic alpha helical peptides that interact with CD36 as potential inhibitors of LPS-induced lung endothelial cell barrier dysfunction and acute lung injury in mice challenged with bacterial wall lipopolysaccharide (LPS) or heat-killed S. aureus (HKSA).

METHODS: Measurement of transendothelial electrical resistance (TER) across confluent human pulmonary artery endothelial cell monolayers was performed with an electrical cell substrate impedance-sensing (ECIS) system (Applied Biophysics, Troy, NY), as previously described[2]. Cell monolayers were challenged with LPS (200 ng/ml), with or without pretreatment with CD36i peptides, and TER measurements were performed over 6-20 h.
Animal studies: All animal care and treatment procedures were approved by the Animal Care and Use Committees of the National Heart, Lung, and Blood Institute and the University of Maryland, Baltimore. Animals were handled according to the National Institutes of Health's Guide for the Care and Use of Laboratory Animals. C57BL/J male mice (8–10-wk old), with an average weight of 20–25 g, were obtained from The Jackson Laboratory (Bar Harbor, ME). Animals were anesthetized by i.p. injection of ketamine (75 mg/kg) and Xylazine (15 mg/kg). Bacterial LPS or sterile water was infused intratracheally in a small volume (20–30 µl). CD36i peptides were injected i.v. 30 min after LPS intratracheal instillation. Peptide and saline solutions were essentially LPS free. After 20 h, animals were sacrificed by exsanguination under anesthesia. Bronchoalveolar lavage was performed using 1 ml sterile PBS buffer, and measurements of cell count, protein concentration were conducted as previously described[3].
Statistical analysis: Results are presented as mean ± SEM. One-way ANOVA with a Bonferroni multiple-comparison test or two-way ANOVA with a Bonferroni posttest test was calculated using GraphPad Prism, version 8.0a (GraphPad, La Jolla, CA). A p value < 0.05 was considered significant.

RESULTS: Peptides that inhibit CD36 activity including L37pA, ELR-B and ELR-BP reversed or mitigated lung endothelial cell barrier dysfunction caused by LPS, HKSA, truncated phospholipids and histone H3, which was monitored by measurements of trans-endothelial electric resistance (TER). Moreover, these peptides also enhanced barrier protective activity of oxidized phospholipids (OxPAPC) in cultured human pulmonary endothelial cells. In the mouse model of acute lung injury, LPS or HKSA were delivered intranasally, and the peptides were delivered intravenously. The results showed that L37pA, ELR-B and ELR-BP exhibited potent protective effects against acute lung injury induced by LPS and HKSA, which were reflected by significant reduction of inflammatory cell accumulation in bronchoalveolar lavage (BAL) fluid and decrease in protein concentration in BAL samples from peptide-treated mice.

CONCLUSION: This study strongly suggests that inhibition of CD36 activity by a new group of synthetic peptide inhibitors may be a novel strategy to confront acute lung injury caused by pro-inflammatory agents of endogenous and exogenous origin.

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RESPIRATION 2

Serum from rats subjected to traumatic brain injury and hemorrhagic shock induces profound endothelial barrier dysfunction

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INTRODUCTION: Traumatic brain injury (TBI) has been associated with development of indirect acute respiratory distress syndrome (ARDS). However, the causative relationship between TBI and lung injury remains unclear. To explore potential mechanism linking TBI with development of ARDS, we characterized effects of serum factors released during TBI and hemorrhagic shock (HS) in a rat model on the pulmonary endothelial cell (EC) barrier dysfunction, a key feature of ARDS.

METHODS: The adult male rat polytrauma model consisted of controlled cortical impact (CCI)-induced TBI followed by 30 minutes of hemorrhage shock (HS) induced by blood withdrawal. The HS phase was followed by a 1-hour 'prehospital' Hextend fluid resuscitation phase and then a 1-hour 'hospital phase' when shed blood was reinfused. 48 hours after the TBI, blood was drawn from right ventricle and serum samples were obtained[1]. Serum was collected from the TBI or sham rats, and its effects on barrier properties of pulmonary endothelial cell culture were assessed by measurements of transendothelial electrical resistance (TER) using the electrical cell impedance sensor[2, 3] and visualization of fluorescent tracer penetration through EC monolayer using XPerT assay.

RESULTS: We found pronounced barrier-disruptive effects of serum samples from animals exposed to controlled cortical impact (CCI) and HS, but not from sham operated rats. Rapid and sustained decrease in EC monolayer transendothelial resistance was observed within minutes after serum addition and remained below basal TER levels after incubation with CCI-HS sera. Thrombin has been implicated in the early-phase barrier disruptive activity of CCI-HS serum, as both thrombin inhibitor and thrombin receptor antagonist attenuated the acute phase of serum-induced TER decline, but did not affect TER decline at later time points. These findings suggest that thrombin elevation may play a role in early-phase barrier disruptive activity of CCI-HS serum. However, both the early and late phases of CCI-HS-induced EC permeability were inhibited by heparin. The late phase barrier disruptive effect of CCI-HS was also prevented by serum preincubation with heparin-sepharose. Pulmonary EC treated with serum from CCI-HS rats for 3 hours have demonstrated significant decline in expression of EC junctional protein, VE-Cadherin, and disassembly of peripheral EC adherens junction complexes monitored by immunostaining with VE-cadherin antibody.

CONCLUSION: These results suggest that exposure to CCI-HS leads to production of humoral factors causing early and late-phase barrier disruptive effects in lung vascular endothelium. While thrombin-PAR1 signaling has been identified as mechanism of acute EC permeability increase by CCI-HS serum, the factor(s) defining long-term EC barrier disruption in CCI-HS model remain to be determined.

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RESPIRATION 3

CD36 Inhibition by Synthetic Amphipathic Helical Peptides Protect Human Pulmonary Endothelial Barrier Dysfunction and Inflammation

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INTRODUCTION: Cluster of differentiation 36 (CD36), also known as scavenger receptor class B member 3 (SR-Bs), binds fatty acids and participates in lipid metabolism. CD36 is also one of the most important receptors mediating bacterial uptake[1]. Our previous study has identified two synthetic amphipathic helical peptides (SAHPs): L37pA, and ELK-B selected from 23 SAHP candidates which significantly reduced lung inflammation caused by Gram-negative bacterial wall lypopolysacharide from Klebsiella pneumoniae (LPS-KP) in vitro and in vivo through CD36 pathway[2]. In this study, we expanded analysis of anti-inflammatory SAHPs and investigated their effects on pulmonary endothelial cell dysfunction caused by bacterial and host-generated inflammatory agonists.

METHODS: Effects of agonists and inhibitory peptides on human pulmonary artery endothelial cell (HPAEC) permeability were assessed by measurements of transendothelial electrical resistance (TER) across EC monolayers using electrical cell impedance sensor system (ECIS, Applied Biophysics) as described[3]. Coimmunoprecipitation and Immunoblotting assay studies were performed as described previously[4]. Protein expression was quantified by using Image Quant software. Pre-designed human CD36-specific siRNA or nonspecific RNA were transfected into EC by using Lipofectamine RNAiMAX transfection reagent 72hr before ECIS or immunoblotting experiments. Results are expressed as means ± SD. Experimental samples were compared to controls by unpaired Student's t-test.

RESULTS: Six SAHPs (ELR-BP, L37pA, ELR-B, ELR-P, ELK-B and L3D), targeting CD36, were designed; and their properties were screened in various models of lung endothelial dysfunction. All peptides we tested in a dose range 2 μg/mL to 100 μg/mL. Among 6 peptides tested, L37pA and ELR-BP exhibited the most potent protective effects against hyper-permeability caused by endogenous (Histone 3.1) and exogenous (LPS-KP) danger signals. L37pA and ELR-BP alone did not affect basal TER levels at the full range of doses tested and efficiently suppressed agonist-induced permeability at minimal effective concentration of 5 μg/mL. Both peptides were also protective in models of EC barrier-disruption caused by truncated oxidized phospholipids (PON-PC, KOdiA-PC, Paz-PC POVPC, PGPC, Lyso-PC). Interestingly, L37pA and ELR-BP peptides further augmented EC barrier enhancement caused by barrier-protective phospholipid OxPAPC.
Barrier-protective effect of peptides on LPS-KP-challenged EC monolayers was associated with preservation of cell junction integrity and preventing the dissociation of adherens junction and tight junction protein complexes formed by VE-Cadherin, p120-catenin and ZO-1.

Effects of CD36 inhibitory peptides were further examined in co-immunoprecipitation studies with antibody to VE-Cadherin, the protein involved in formation of cell junctions and participating in the maintenance of EC barrier. In agreement with the previous observations, LPS-KP induced dissociation of a complex consisting of adherens junction proteins VE-Cadherin and p120-catenin, and tight junction protein ZO-1. The data also showed that while L37pA, ELR-BP, ELK-B and ELR-P reversed the LPS-KP-induced disassembly of cell junctions, ELR-B was without effect. Analysis of EC inflammatory signaling revealed strong inhibitory effects by all CD36 inhibitory peptides with L37pA and ELR-BP being most effective. Both peptides even at low dose (2 μg/mL) suppressed mRNA expression of cytokines (TNFα, IL1β, IL-6, IL-8) and EC adhesion molecules (ICAM1, VCAM1, E-Selectin) caused by LPS-KP or Histone 3.1 challenge. In agreement with these data, CD36 inhibitory peptides attenuated LPS- and histone-induced NFkB activation and expression of ICAM1 and VCAM1. Similar effects were observed in pulmonary EC with siRNA-based CD36 knockdown.

CONCLUSION: This study demonstrates the barrier-protective and anti-inflammatory effects of ELR-BP and L37pA in pulmonary EC exposed to exogenous (LPS-KP) and endogenous (histone 3.1) inflammatory agents. Both peptides also augmented the EC barrier enhancing effects induced by low dose OxPAPC and reversed barrier disruptive effects of fragmented phospholipids. Thus, the research of CD36 pathway regulation in human pulmonary endothelial cell function may lead to discovery of efficient treatment for ALI and lung inflammation diseases.

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RESPIRATION 4

Mechanical power in ventilated patients - Agreement between calculations from bedside formulae and continuous recordings

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INTRODUCTION: Mechanical Power (MP) unifies physical forces exerted on the respiratory system during positive pressure ventilation[1] under the postulation that the applied energy is a primary driving factor of ventilator-induced lung injury. A high MP is associated with increased mortality in the intensive care unit (ICU).[2,3] MP is ideally calculated from continuous measurements of inspiratory flow and pressures, however, an abbreviated formula has been proposed for use in epidemiological studies and daily clinical use.[4] There is, however, a paucity of evidence with regard to the granularity of the surrogate formula to reflect MP calculated from continuous recordings based on 'real-world' clinical data.

METHODS: We investigated the agreement between mechanical power calculated either based on the surrogate formula 0.098*RR*VT*[PEEP + ½(Pplat−PEEP) + (Ppeak−Pplat) or continuous recordings of inspiratory pressure and flow from data recorded in mechanically ventilated patients with acute respiratory distress syndrome during the EPVent study.(5) From continuous recordings, MP in J/min was derived from inspiratory work, calculated for each breath as the area under the inspiratory limb of the pressure/volume curve multiplied with the respiratory rate, and application of a conversion factor (0.098).(5) In a secondary analysis, we compared driving power after exclusion of the static (PEEP) component. Paired t-tests, Standard difference of means, Pearson's correlation, and Bland Altman analyses were used to evaluate agreement between measured and calculated MP. Alpha was set to 0.05. Julia (v1.6.3) within Microsoft Visual Studio Code (v1.61.2) and R (v4.1.1), "Kick Things", 2021-08-10 in RStudio 1.4.1106 were used.

RESULTS: Continuous flow and pressure recordings were available in 54 patients with an average sampling rate of 18.6 +-6.4Hz. The average MP was 40.3 +- 18.3J/min, calculated from continuous recordings versus 35.3 +-16.5J/min, calculated from the surrogate formula ($p<0.001$). There was a strong correlation between both methods (Fig 1, R=0.98, 95%CI 0.96-0.99, $p<0.001$). Bland-Altman analysis (Fig 2) revealed an overall bias of 4.97 J/min (95% CI 3.87- to 6.06 $p<0.001$) and evidence of proportional bias with aggravation at MP>50J/min. Driving power displayed similar agreement (Fig 3) with a bias of -2.06 (95% CI -4.10 to -0.02), though aggravation of bias was noticed at DP>25J/min, suggesting aggravation of underestimation through the surrogate formula.

CONCLUSION: While MP calculated from continuous recordings and estimated from an abbreviated formula correlate closely, MP may be underestimated when the abbreviated formula is applied. Calculations of MP should be attempted based on continuous recordings in patients ventilated with high MP, for example through high respiratory rates or driving pressures.

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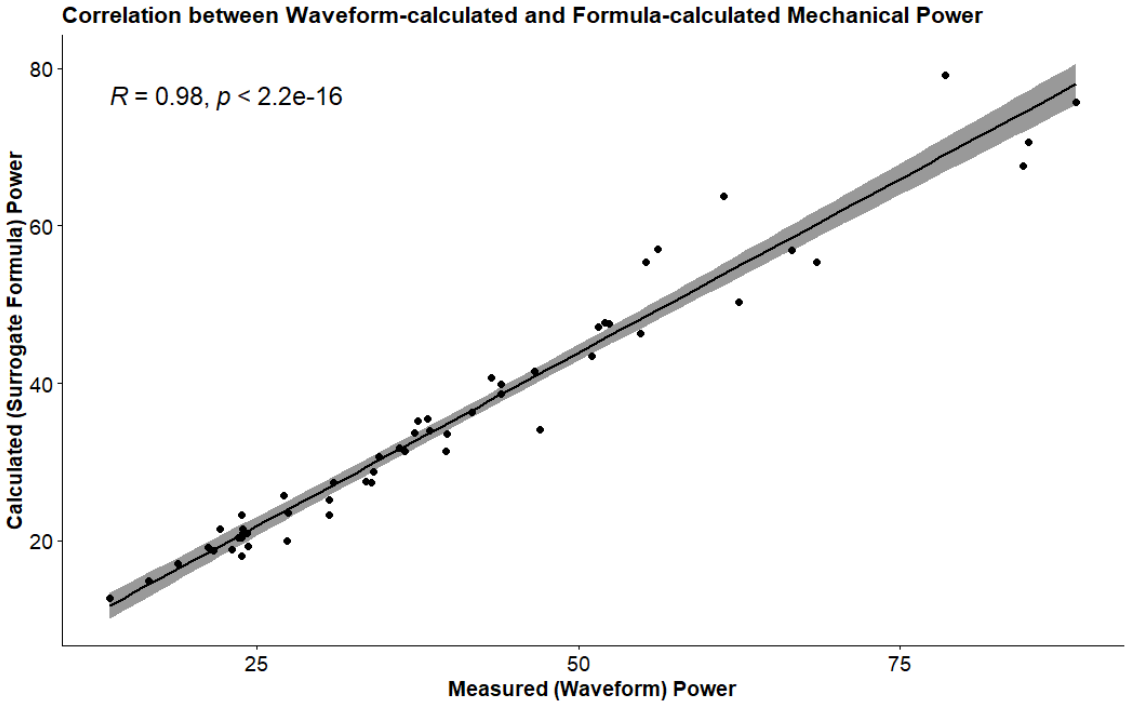

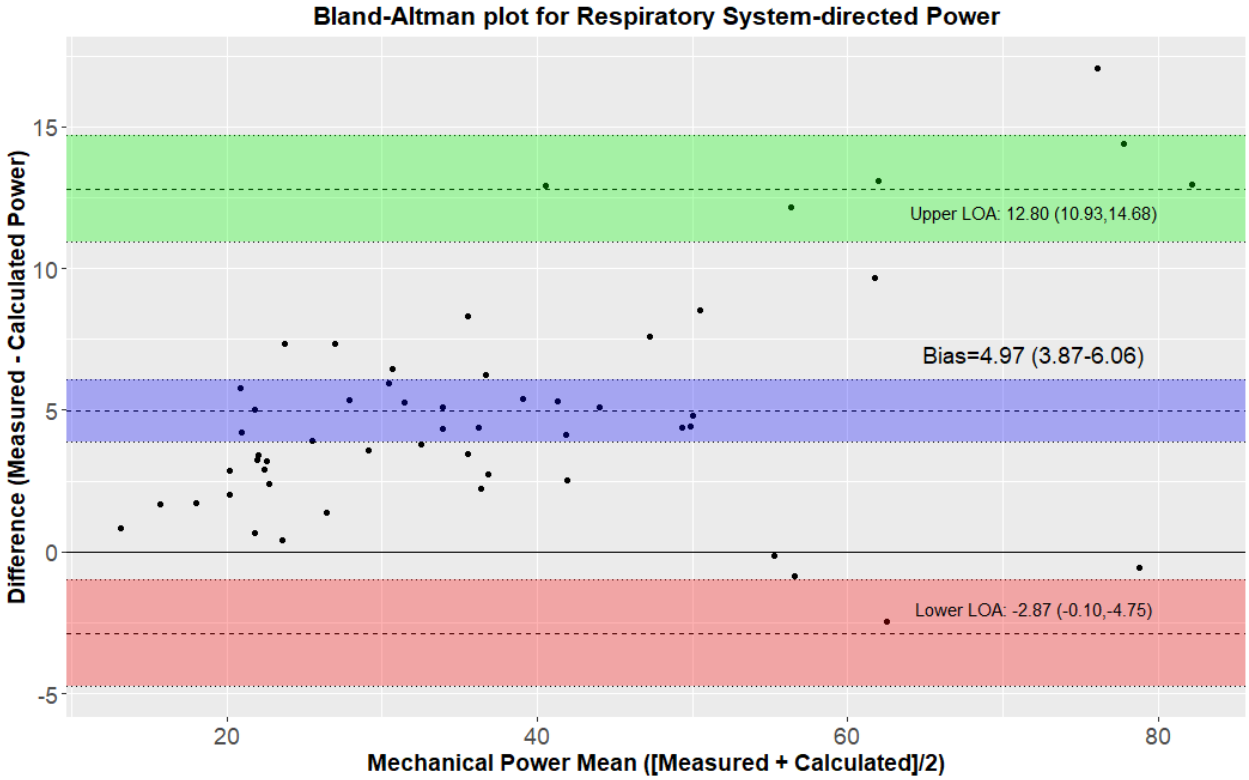

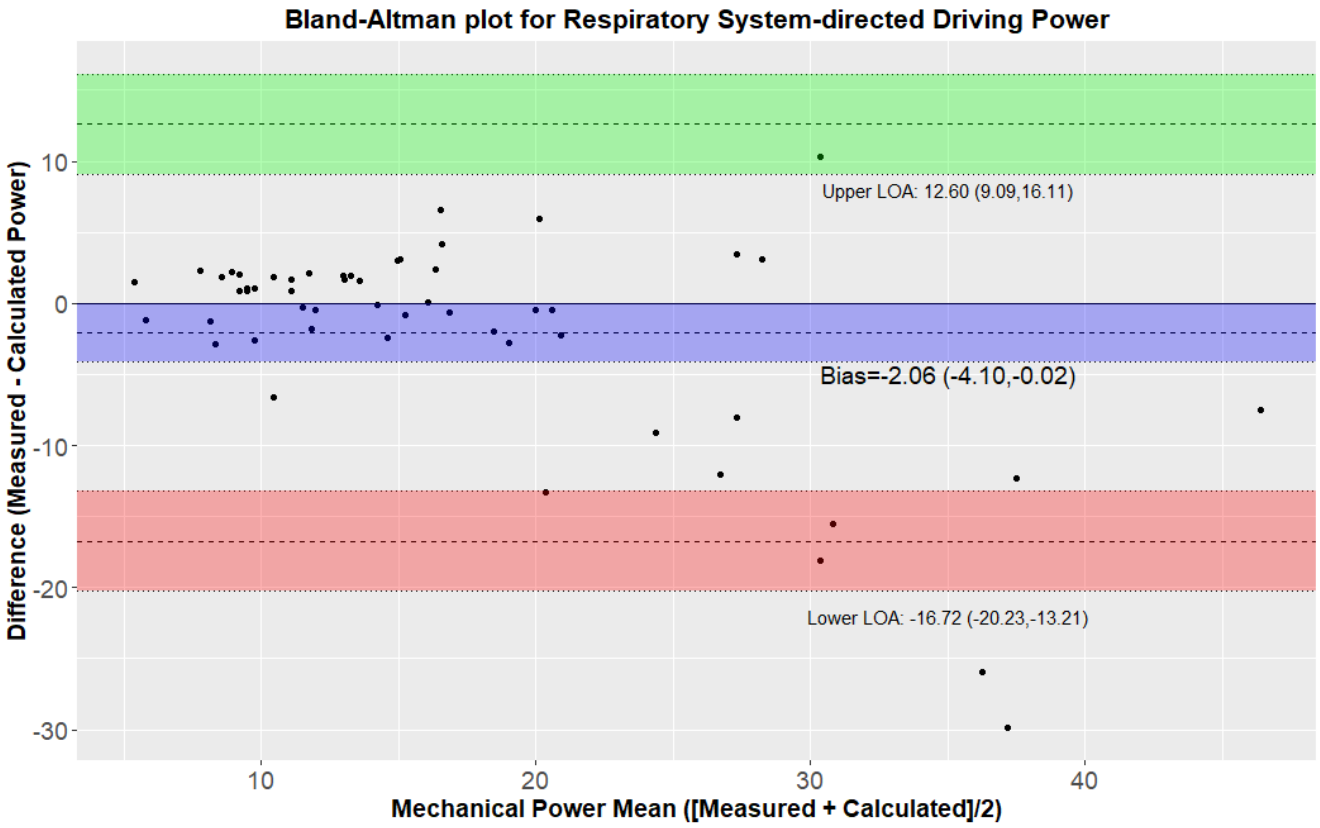

RESPIRATION 5

Oxygen Administration Practices during Surgery in the United States

Frederic T Billings[1], David R McIlroy[2], Matthew S Shotwell[3], Marcos Lopez[2], Shelley Housey[4], Jonathan Wanderer[5], Matthew Semler[2], Hannah M Wunsch[6], Sachin Kheterpal[7]

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INTRODUCTION: Anesthesiologists administer supplemental oxygen to nearly all patients during surgery. Determinants of intraoperative oxygen administration practice patterns are unclear. We sought to describe current intraoperative oxygenation practices and characterize the relative contributions of patient, procedure, medical center, and anesthesia provider factors.

METHODS: In 42 medical centers across the United States participating in the Multicenter Perioperative Outcomes Group data registry, we analyzed surgical cases of 120 minutes or longer in adult patients who received general anesthesia with endotracheal intubation and were admitted to the hospital after surgery between January 2016 and November 2018. We measured patient, procedure, medical center, anesthesiologist, and in-room anesthesia provider factors and compared these factors to the median intraoperative fraction of inspired oxygen.

RESULTS: The cohort comprised 367,841 cases (median age [interquartile range], 59 [47-69] years; 51.1% women) managed by 3,836 anesthesiologists and 15,381 in-room anesthesia providers (nurse anesthetists, residents, fellows). Median fraction of inspired oxygen was 0.55 (interquartile range, 0.48-0.61) and the median pulse oximetry hemoglobin saturation was 99% (interquartile range, 98-100)(Figure 1). Multivariable linear mixed-effects regression revealed significant heterogeneity in oxygen administration among medical centers, anesthesiologists, and in-room providers. For example, independent of patient and procedure factors the median fraction of inspired oxygen ranged from 0.41 (95% confidence interval, 0.40-0.43) to 0.80 (0.79-0.82) across medical centers and from 0.27 (0.22-0.32) to 0.87 (0.83-0.92) across anesthesiologists (Figure 2). Patient factors explained 3.5% (95% confidence interval, 3.5-3.5) of the variability in oxygen administration, procedure factors 4.4% (4.3-4.6), medical center 23.3% (22.8-23.8), anesthesiologist 7.7% (7.3-8.1), and in-room provider 8.1% (7.6-8.5)(Figure 3). Individual patient factors independently associated with higher oxygen administration included age (0.05 % higher per year [95% confidence interval, 0.04-0.05]), female sex (0.36 [0.24-0.49]), body mass index (0.11 % per kg/m2 [0.10-0.11]), cardiac and pulmonary comorbidities, preoperative measurement of troponin (2.19 [1.93-2.45]), and American Society of Anesthesiology physical classification 4 or greater (4.11 [3.90-4.33]). Dominant procedural factors included emergency surgery (0.78 [0.61-0.95]), open heart surgery (10.18 [9.69-10.66]), and intraoperative transfusion (0.87 [0.65-1.08]).

CONCLUSION: Among adults undergoing surgery with general anesthesia in the United States, oxygen administration varied significantly, with more of the variability explained by the medical center and anesthesia provider than by patient or procedure factors.

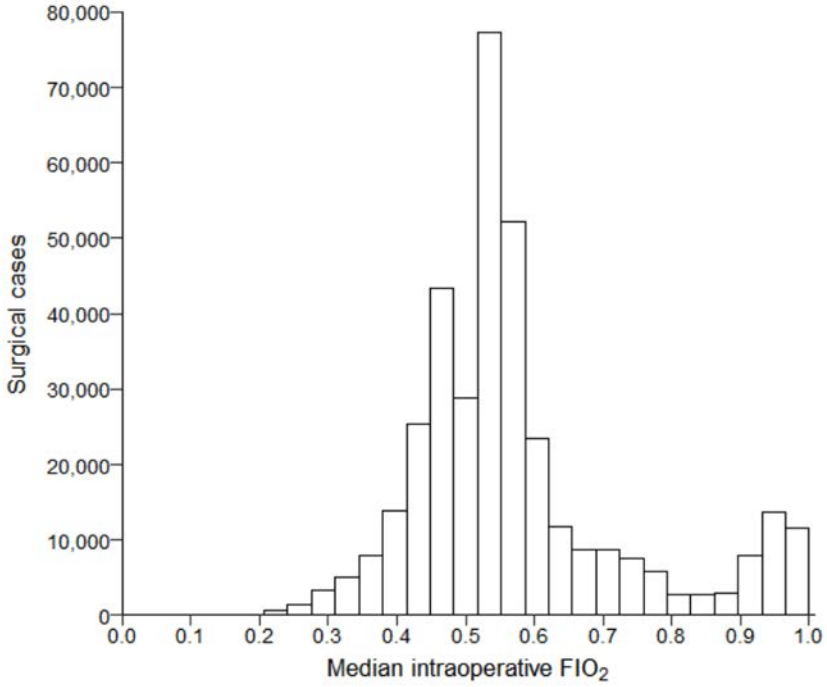

Figure 1

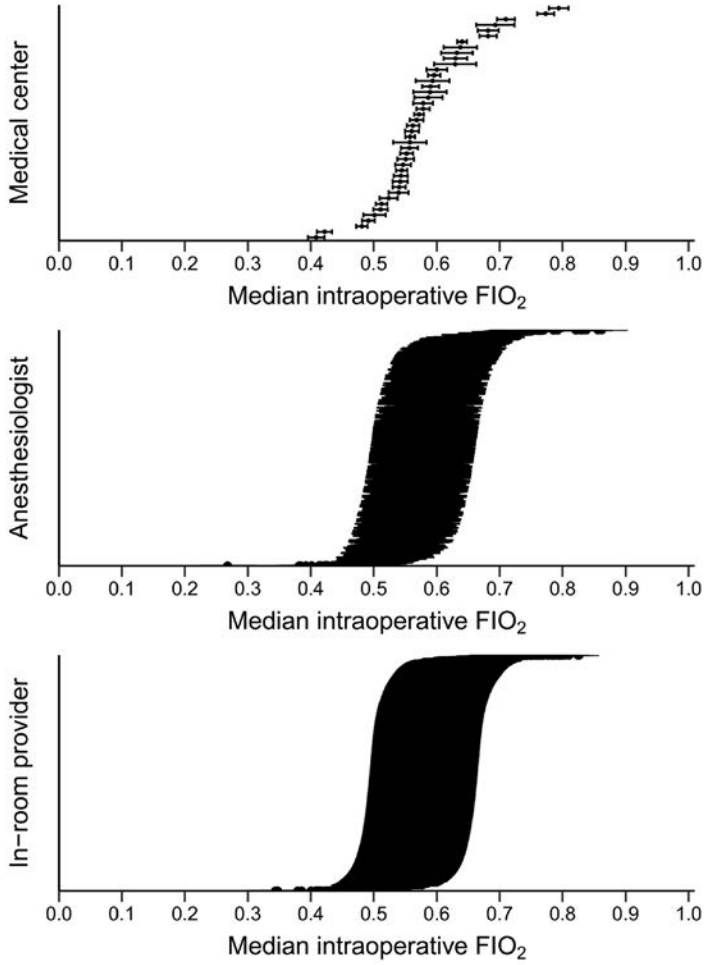

Figure 2

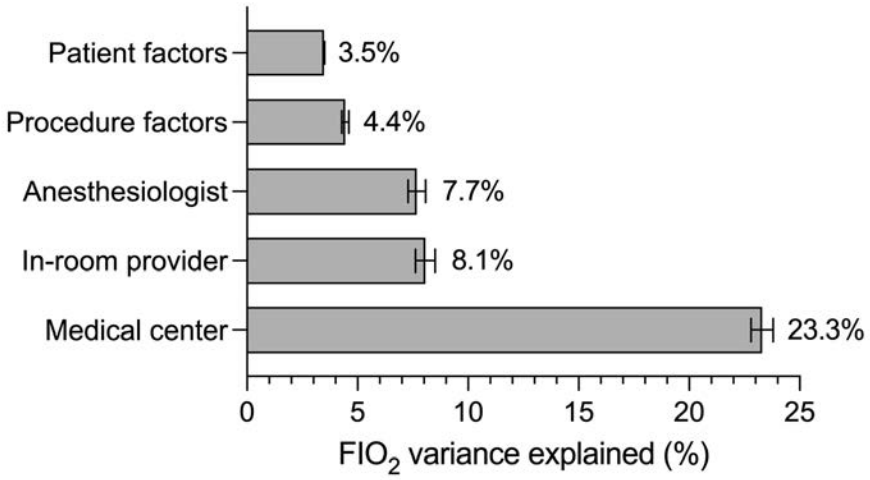

Figure 3

RESPIRATION 6

Impact of supplemental oxygen during renal ischemia and reperfusion in mice

Melissa Kimlinger[1], Eric H Mace[2], Frederic (Josh) Billings[3]

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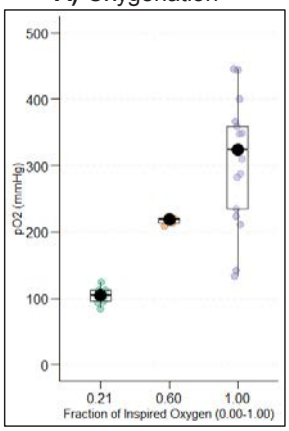
INTRODUCTION: Ten percent of patients undergoing major surgery suffer from postoperative acute kidney injury (AKI), and AKI is independently associated with increased length of stay, multi-organ complications, increased cost, and death. Perioperative renal ischemia and reperfusion (IR) contribute to AKI. During the ischemic phase, loss of oxygen and blood flow lead to depletion of ATP and nutrients and can cause cell death. Reperfusion causes additional cellular damage via reactive oxygen species (ROS) production, oxidative stress, and inflammation. The differential impact of oxygen on renal outcomes during IR injury is unclear, as oxygen modulates tissue oxygenation, vascular reactivity, oxidative damage, and inflammation. Supraphysiologic oxygen (hyperoxia) may protect against ischemic insults but accelerate ROS-production and inflammation during reperfusion. We hypothesized that the fraction of inspired oxygen (FiO2) administered to mice during renal IR impacts tissue oxygenation, oxidative stress, and inflammation, renal damage, and renal function.

METHODS: We divided 27 eight-week-old male FVB/N mice into normoxic, mild hyperoxic, and hyperoxic groups. Mice were anesthetized with an intraperitoneal injection of 100 mg/kg ketamine, 10 mg/kg xylazine, and 1 mg/kg subcutaneous sustained-release buprenorphine prior to intubation and initiation of mechanical ventilation with an FiO2 of 0.21 (normoxia), 0.60 (mild hyperoxia), or 1.00 (hyperoxia), a tidal volume of 0.25 mL, and respiratory rate 110 breaths/minute. We performed a right unilateral nephrectomy followed by dissection of the left kidney. In 22 of the animals a vascular clamp was placed across the renal artery and vein for 30 minutes, followed by 30 minutes of reperfusion. In 5 animals, we performed sham IR and did not place the vascular clamp. At 30 minutes of reperfusion, mice were extubated to air. To confirm efficacy of oxygen treatment during IR, an arterial blood gas (ABG) was measured via left cardiac puncture at the end of reperfusion in a separate cohort of animals. At 24 hours we sacrificed the animals via terminal bleed and collected blood for BUN measurement and kidney for histology and immunohistochemistry. Kidney sections were stained with periodic acid-Schiff (PAS) to score for histological injury on the basis of tubular vacuolization, cast formation, tubular dilatation, loss of brush border, and necrosis. Additional sections were stained for pimonidazole (marker of cellular hypoxia), F4/80 (macrophages), kidney injury molecule 1 (KIM-1, a marker of proximal tubule damage), and neutrophil gelatinase-associated lipocalin (NGAL, a marker of distal tubule damage). BUN was measured using an infinity urea assay. We performed a Kruskal Wallis test for significance for all continuous data. Pairwise comparisons were performed using the Dunn test with Holm adjustment.

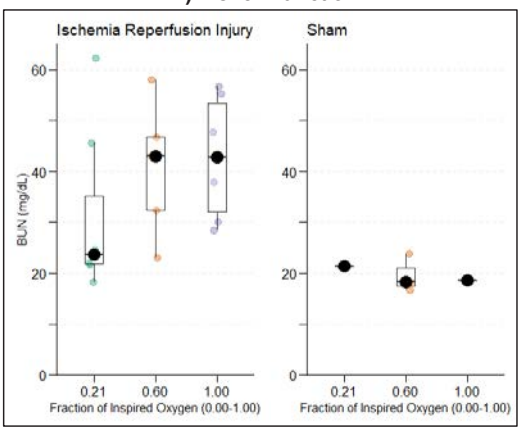
RESULTS: The median pO2 was 104 mmHg, 218 mmHg, and 324 mmHg in the 0.21, 0.60, and 1.00 FiO2 groups, respectively (Figure, Panel A). Median BUN was 23.67 mg/dL, 42.98 mg/dL, and 42.83 mg/dL in the 0.21, 0.60, and 1.00 oxygen groups for those mice who had IR (p=0.20) and 21.33 mg/dL, 18.33 mg/dL, and 18.67 mg/dL for those who had sham IR (p=0.77; Panel B). The median histological injury scores were 1.43, 2.22, and 1.95 for IR surgery (p=0.15), and 1.12, 1.00 and 0.67 for sham surgery (p=0.67; Panel C). Analysis of pimonidazole-stained kidneys revealed similar degree of corticomedullary ischemia in the IR kidneys of all oxygen groups (Panel D). F4/80 macrophage staining was minimal and also was similar between groups. KIM-1 and NGAL expression were increased in mice in the FiO2 1.00 oxygen group compared to the 0.60 and 0.21 groups.

CONCLUSION: Hyperoxia may increase renal injury and BUN compared to normoxia following IR but does not appear to affect tissue hypoxia or macrophage recruitment. Although we were underpowered to detect a difference in BUN, mice exposed to 0.60 and 1.00 FiO2 had nearly twice the BUN 24 hours after IR as mice ventilated with 0.21 FiO2. These findings also corresponded to greater histological injury score in the 0.60 and 1.00 oxygen groups compared to the 0.21 group. In ongoing subsequent studies we will quantify the extent of renal injury and function and determine the impact of oxygen administration during renal IR.

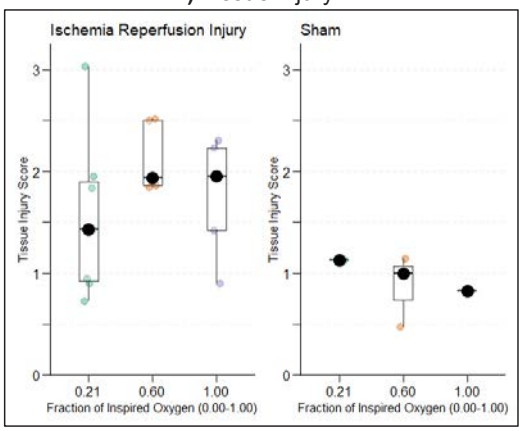
A) Oxygenation



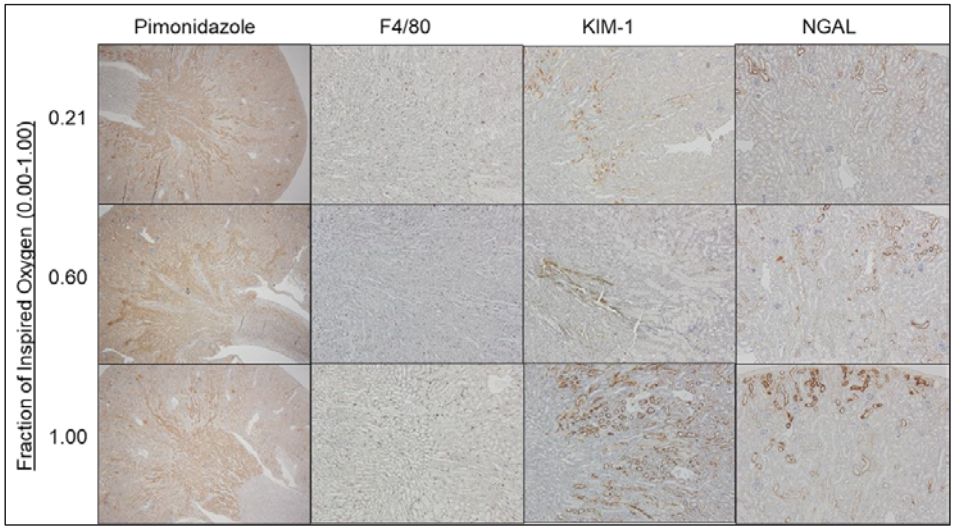
B) Renal Function



C) Tissue Injury



D) Immunohistochemistry



SUBSPECIALTY ABSTRACTS

SLEEP MEDICINE

SLEEP MEDICINE 1

Spinal Cord Stimulation translates to improvements in sleep health in Neuropathic pain patients

Hannah J Coyle-Asbil[1], Anuj Bhatia[2], Andrew Lim[3], Jamal Kara[4], Mandeep Singh[5]

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INTRODUCTION: The bidirectional relationship between chronic pain and difficulties pertaining to sleep has been a point of contention in previous literature[1], with pain leading to sleep disturbances and poor sleep[1]. Currently, numerous techniques are utilized to treat neuropathic pain, for instance cognitive behavioural therapy, physical therapy, and pharmacological interventions; however, for many patients, the inadequate pain relief and negative side effects render these approaches insufficient[2]. Given this information, other avenues of treatment, such as neuromodulation techniques like spinal cord stimulation (SCS) have been implemented[3]. Moreover, there is previous research to support the concept that the positive effects of SCS translate to sleep[4]. Using raw acceleration based actigraphy, this study sought to investigate the effect of short-term SCS on the sleeping patterns of males and females suffering from NP.

METHODS: Prior to enrolment, the hospital research ethics board approved the study protocol and participants provided written consent. One hundred and forty-nine individuals between the ages of 18 to 80 years, with NP in their back and/or lower limbs were eligible to participate in the study. At enrolment, participants were asked to complete a series of questionnaires which included the Pain Disability Index (PDI), Oswestry Disability Index (ODI) and the Pain and Sleep Questionnaire - 3 items (PSQ-3). Furthermore, they were asked to provide baseline demographics and pain related information such as previous diagnoses, opioid intake (OMED; mg), alcohol and smoking habits. For a minimum of 7 days, participants received percutaneous SCS. Simultaneously, they were asked to wear an Actigraphy device (GENEActiv) on their wrist. The sampling frequency of the devices was set to measure at 50 Hz. Upon return on the devices, the data was downloaded, and sleep metrics were computed using previously validated algorithms[5]. Variables of interest included sleep efficiency (SE; as a %), wake after sleep onset (WASO; in minutes) and total sleep time (TST; in minutes). The SCS was deemed successful if the intensity of pain achieved a 50% reduction and the ODI and PSQ-3 scores were decreased by 25% compared to baseline. For the statistical analyses, the sleep metrics of the successful and unsuccessful participants were compared using univariate analyses to determine whether there were significant differences in their sleep outcome measures. Subsequently, a mixed-model ANOVA was performed to compare the sleep metrics in males and females at baseline (night 1) and follow-up (night 7); when appropriate Bonferroni adjustments were used.

RESULTS: From the original 149 participants that were enrolled, 43 participants (mean age = 55.41 ± 11.91 years; 22 M) were excluded due to missing or invalid actigraphy data. As such, 106 participants were included in the analyses; details regarding the population characteristics are highlighted in table 1. The SCS was found to be successful in 34 out of the 49 females (49.96 ±12.74 years) and 38 out of the 57 (54.81 ± 13.32 years) males. With respect to the sleep metrics, no significant differences were found between the successful and unsuccessful trial participants according to the univariate analyses. The mixed-model ANOVA revealed a significant main effect of sex was found for TST $F(1.00, 104)= 4.322$ ($p=0.040$; Figure 1A) and SE $F(1.00, 104)= 4.10$ ($p=0.038$; Figure 1B). The pairwise comparison revealed that females had a greater TST and SE. Additionally, a significant main effect of time-point for TST $F(1.00, 104)= 15.522$ ($p<0.001$; Figure 2A) and WASO $F(1.00, 104)= 4.001$ ($p=0.048$; Figure 2C). Subsequently, the pairwise comparison revealed that both TST and WASO were significantly reduced at follow-up. No interaction effects were found.

CONCLUSION: As demonstrated by the reduction in WASO after 7 nights, this study suggests that he findings from this study suggest short-term SCS significantly improves the sleep of individuals suffering from NP. Furthermore, our study suggests that compared to males, females have improved sleep. It remains unclear whether these improvements in sleep will be maintained long-term and will subsequently translate to improvement in functional and quality of life outcomes accordingly. Further investigation is required.

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Table 1. Baseline demographic information of included patients (n=106).

Variable	**Males (n = 57)**	**Females (n = 49)**
Age (yrs, mean ± SD)	54.81 ± 13.32 years	49.96 ± 12.74 years
PSQ3 score	193.10 ± 76.55	201.43 ± 81.66
PDI score	46.41 ± 13.84	44.22 ± 14.23
ODI score	28.11 ± 8.92	26.46 ± 7.29
Opiod (converted to morpone/day)	75.83 ± 109.50	29.19 ± 44.86
Alcohol	25 (43.86%)	19 (38.78%)
Smoke	10 (17.54%)	10 (20.41%)
Successful SCS trial outcome	38 (66.67%)	34 (69.39%)
ODI Categorization		
minimal disability: 1 (0-10)	1 (1.75%)	1 (2.04%)
moderate disability: 2 (11-20)	7 (12.28%)	6 (12.24%)
severe disability: 3 (21-30)	20 (35.09%)	27 (55.10%)
crippled: 4 (31-40)	13 (22.81%)	10 (20.41%)
Bed-bound or exaggerating symptoms: 5 (>40)	2 (3.51%)	1 (2.04%)
Not reported	14 (24.56%)	4 (8.16%)
Diagnosis		
Failed back surgery	21 (36.8%)	21 (42.86%)
CRPS Type 1,2	2 (3.51%)	6 (12.24%)
Neuropathic pain, post-traumatic	12 (21.1%)	5 (10.20%)
Neuropathic pain, diabetic	1 (1.75%)	0
Neuropathic pain, postherpetic neuralgia	0	1 (2.04%)
Neuropathic pain, other	1(1.75%)	0
Neuropathic pain, unclear etiology	3 (5.26%)	4 (8.16%)
Lumbar spinal stenosis	1(1.75%)	1(2.04%)

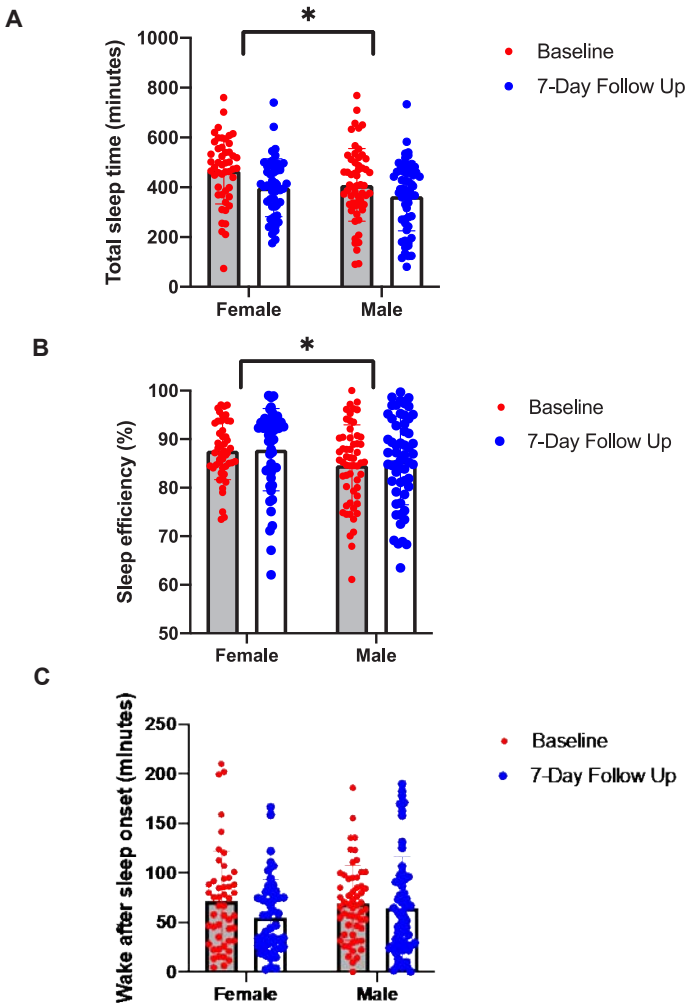

Figure 1. Total sleep time (TST; **A**), sleep efficiency (SE; **B**), wake after sleep onset (WASO; **C**) at baseline and follow-up divided by sex. Individual values are in red and blue, the population means and standard deviations are shown in the bar graph. Mixed-model ANOVA revealed a significant main effect of sex for TST and SE. The pairwise comparisons revealed that compared to males, females had significantly greater TST and SE.

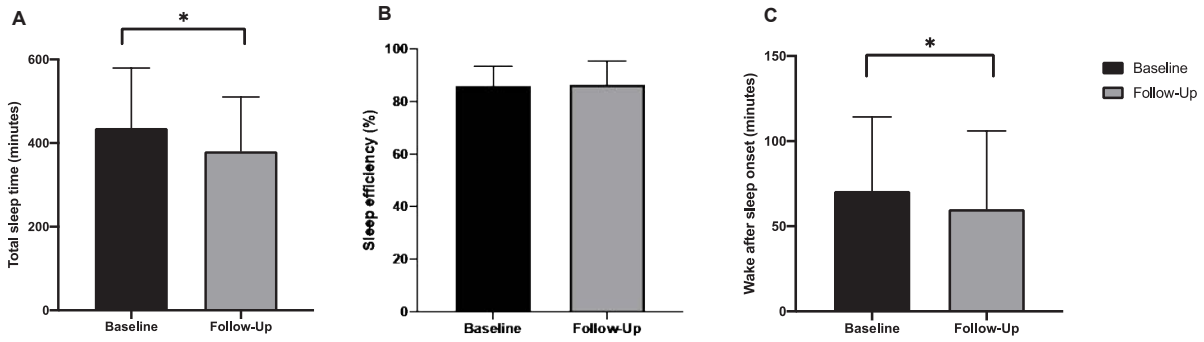

Figure 2. Mean (SD) of TST (A), SE (B) and WASO (C) of the population at baseline and follow-up. Mixed-model ANOVA (Timepoint x Sex) revealed a significant main effect of Time-point for TST (A) and WASO (C). Pairwise comparisons revealed that both TST and WASO were reduced at Follow-Up compared to Baseline.

SLEEP MEDICINE 2

Dexmedetomidine Sedation with Closed Loop Acoustic Stimulation Alters Sleep Macrostructure in Healthy Volunteers

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INTRODUCTION: General anesthesia, deep sedation, and stage 3 of non-rapid eye movement sleep (N3) are characterized by slow-delta oscillations (0.5 - 4Hz) in the electroencephalogram (EEG)[1]. The reduction in the power of these oscillations (termed slow wave activity, SWA) over successive cycles of N3 sleep putatively reflect dissipation of homeostatic sleep pressure[2]. Decreases in SWA and the proportion of total sleep time (%TST) spent in N3 during nocturnal sleep also occur following daytime naps[3]. Promotion of slow-delta EEG oscillations using pharmacological and non-pharmacological approaches offers the potential for enhancing perioperative outcomes given the ubiquity of perioperative sleep disruption and N3 deficiency[4]. Data have accumulated that the alpha-2 agonist dexmedetomidine induces states of biomimetic sleep[5,6], but are lacking on whether these states fulfill homeostatic sleep needs and there are no reports of pre- vs. post-sedation sleep studies in human volunteers receiving dexmedetomidine. We hypothesized that altered overnight dissipation of N3 sleep pressure would occur following a daytime intervention of dexmedetomidine.

METHODS: An interim analysis was performed on data acquired from healthy volunteers during the ongoing trial: Closed-Loop Acoustic Stimulation during Sedation with Dexmedetomidine (CLASS-D)[7]. Changes in sleep measures are pre-specified secondary outcomes of this trial. Participants were trained and provided with a wireless, dry-electrode EEG headset (Dreem, New York, NY)[8] to record their EEG during sleep on the nights prior to, and following, a sedation session. Participants were instructed not to nap between the end of the sedation session and their regular evening bedtime. Each participant received phase-locked acoustic stimulation (60 dB pink noise) while sedated with a target-controlled infusion of dexmedetomidine titrated to induce both slow-delta oscillations and loss of responsiveness to a behavioral task. Sleep EEG records were scored by a registered polysomnographic technologist in 30 second epochs as either wake, N1, N2, N3, REM or non-scorable, using the modified American Association of Sleep Medicine (AASM) criteria[9].

RESULTS: Data were considered for eight participants, two of which did not record sleep data on the immediate post-sedation night, precluding analysis. The mean (SD) age of the remaining six participants (2 females) was 29.1 (5.2) years old. The mean (SD) duration of dexmedetomidine infusion was 183.6 (41.4) minutes. The mean (SD) absolute and weight-adjusted dexmedetomidine infused per participant was 447.2 (80.2) mcg and 6.0 (1.4) mcg/kg, respectively. Dexmedetomidine targeted effect site concentrations ranged from 1.5 - 2.5 ng/ml. On the night preceding sedation, mean (SD) total sleep time (TST) was 263.1 (48.3) minutes, N1 was 8.9 (4.7) minutes, N2 was 146.9 (46.0) minutes, N3 was 49.7 (27.8) minutes, and REM was 57.6 (21.1) minutes (Figure 1). Subtracting each participant's pre-sedation from post-sedation sleep yielded a mean reduction of TST by 80.5 minutes (CI 95%, -23.7 - -137.3, p = 0.03). Furthermore, we observed an attenuation of duration of both N2 (mean difference -36.8 minutes, CI 95%, -5.7 - -67.9, p = 0.04) and N3 (mean difference -26.8 minutes, CI 95%, -12.5 - -41.1, p = 0.01). In contrast, no significant changes were observed for durations of N1 (mean difference -1.5 minutes, CI 95%, -6.0 - 3.0, p = 0.29) or REM (mean difference -15.3 minutes, CI 95%, -47.7 - 17.1, p = 0.22) (Figure 2). Changes in %TST were also evaluated by subtracting values during pre-sedation sleep from post-sedation sleep. A reduction of %TST of N3 was observed (mean difference -8.0%, CI 95%, -4.1 - -12.0, p = 0.007). In contrast, there were no significant differences in the %TST of N1 (mean difference -1.5%, CI 95%, -5.3 - 2.2, p = 0.25), %TST of N2 (mean difference -9.7%, CI 95%, -22.6 - 3.1, p = 0.12), or %TST of REM (mean difference -3.2%, CI 95%, -11.3 - 17.7, p = 0.35) (Figure 3).

CONCLUSION: Preliminary data from this ongoing trial suggest that healthy volunteers exhibit altered sleep structure following sedation with dexmedetomidine and closed loop acoustic stimulation, titrated to achieve induction of slow-delta oscillations. The reduction of TST reflected shorter durations of N2 and N3 sleep, with the

latter reduced out of proportion to TST. These results support the hypothesis that dexmedetomidine-induced slow-delta oscillations relieve homeostatic requirements for N3 sleep.

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Figure 1. Sleep macrostructure during pre- and post-sedation sleep. Bars denote means and error bars represent standard deviations.

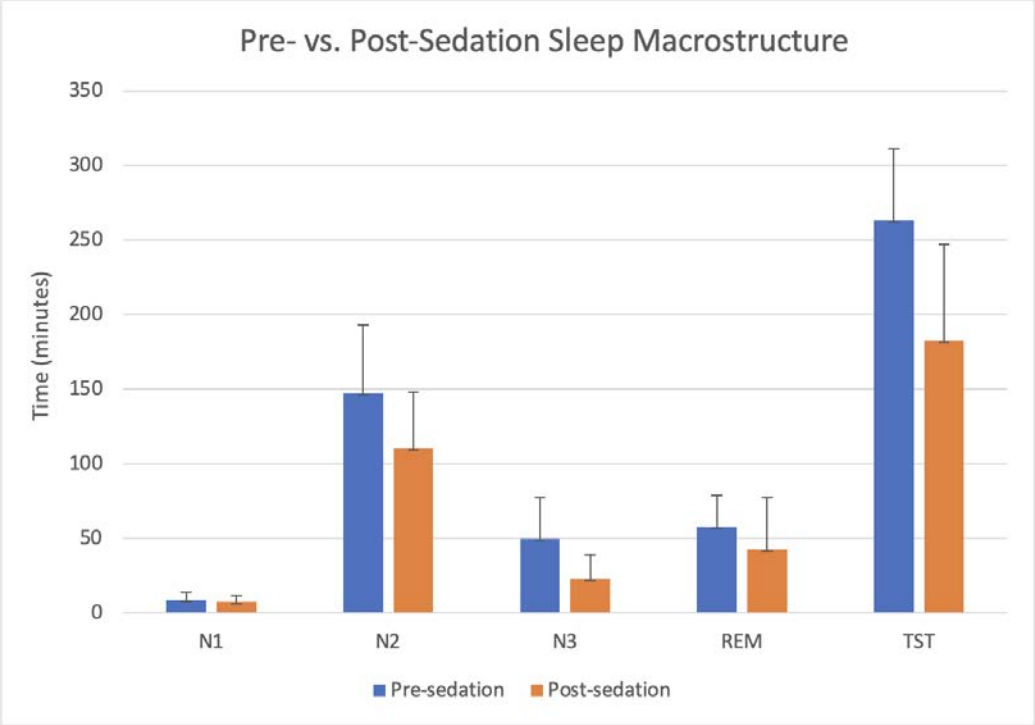


Figure 2. Differences in absolute time spent in each sleep stage, computed by subtracting pre-sedation from post-sedation values for each participant. Markers denote means and error bars represent 95% confidence intervals.

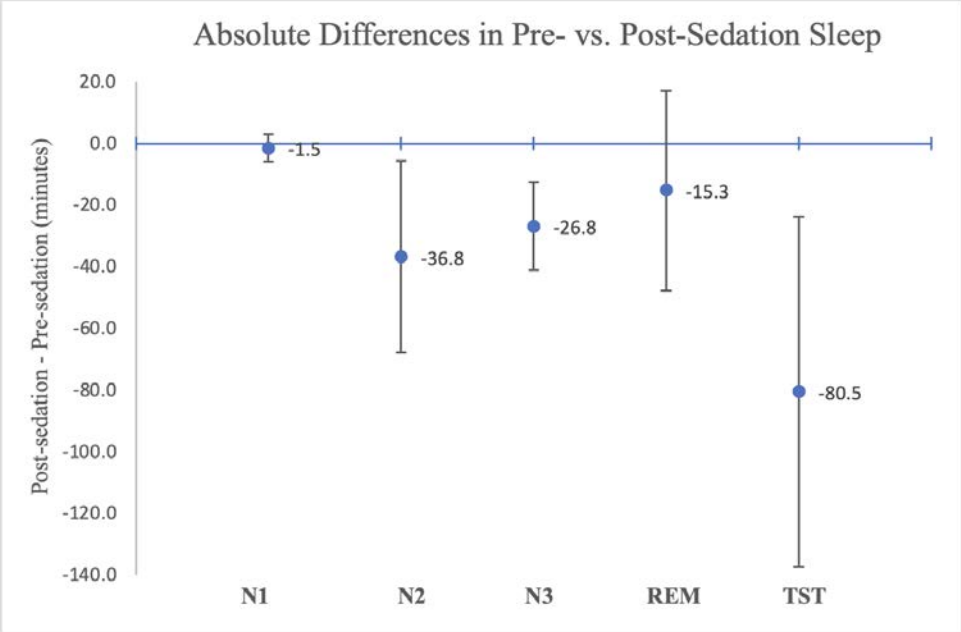
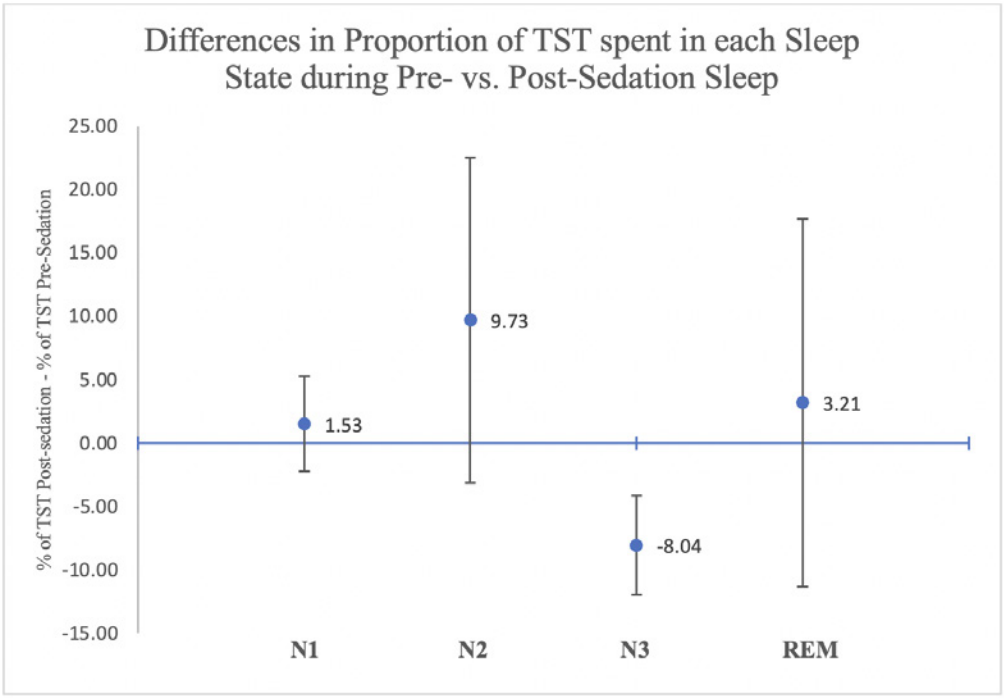


Figure 3. Differences in the proportion of total sleep time (%TST) spent in each sleep stage, computed by subtracting pre-sedation from post-sedation values for each participant. Markers denote means and error bars represent 95% confidence intervals.



SLEEP MEDICINE 3

Validation of the STOP-Bang Questionnaire as a Preoperative Screening Tool for Obstructive Sleep Apnea: A Systematic Review and Meta-analysis

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INTRODUCTION: Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder, characterized by frequent episodes of hypopnea and apnea. Up to 68% of patients undergoing surgery with OSA can be undiagnosed, resulting in increased risk of postoperative cardiovascular and pulmonary complications.[1] The STOP-Bang questionnaire is a simple, rapid, and reliable tool used to screen for OSA.[2] The objective of this systematic review and meta-analysis is to evaluate whether the STOP-Bang questionnaire is a valid screening tool for unrecognized OSA in the surgical population.

METHODS: Electronic databases were systematically searched from 2008 to May 2021. The inclusion criteria were: 1) the study evaluated the STOP-Bang questionnaire as a screening tool for OSA in patients undergoing surgery; 2) polysomnography or home sleep apnea testing (HSAT) was performed to confirm OSA diagnosis; 3) OSA was defined by an Apnea-Hypopnea Index (AHI) or Respiratory Disturbance Index (RDI) cut-offs ≥ 5, ≥ 15, and ≥ 30 events per hour; and 4) data on predictive parameters of the STOP-Bang questionnaire were provided. To address heterogeneity, a bivariate random-effects model was used to obtain pooled predictive parameters (sensitivity, specificity, positive (PPV) and negative predictive value (NPV), and area under the curve (AUC) to assess the validity of the STOP-Bang questionnaire for different AHI cut-offs: AHI ≥ 5, ≥ 15, and ≥ 30 events per hour.

RESULTS: The systematic search identified 4,641 articles, from which 10 studies (n=3,247) were included in the final analysis. The mean age of the surgical population was 57.3 ± 15.2 years, the mean BMI was 32.5 ± 10.1 kg/m2, and 47.4% were male. Surgical procedures included bariatric surgery (n=4), non-cardiac elective surgery (n=3), non-vascular abdominal surgery (n=1), coronary artery bypass grafting (n=1), and total joint arthroplasty (n=1). The pooled predictive parameters of the STOP-Bang questionnaire are presented in Figure 1 and Table 1. The STOP-Bang questionnaire has high pooled sensitivities of 85% (95%CI: 82-88%), 88% (95%CI: 85-89%), and 90% (95%CI: 87-93%) to screen for all (AHI ≥ 5), moderate-to-severe (AHI ≥ 15), and severe (AHI ≥ 30) OSA, respectively. The specificities were lower at 47% (95%CI: 42-52%), 29% (95%CI: 27-32%), and 27% (95%CI: 25-29%) for all, moderate-to-severe, and severe OSA, respectively. The PPV was highest at 74.9% (95%CI: 71.8-77.7%) to detect all OSA. With a NPV of 93.2% (95%CI: 90.9-95.1%), STOP-Bang is most effective in ruling out severe OSA. The AUC was 0.84, 0.67, and 0.63 respectively for all, moderate-to-severe, and severe OSA.

CONCLUSION: The STOP-Bang questionnaire is a valid tool to screen for OSA in surgical patients, with high sensitivity and high discriminative power to exclude severe OSA with negative predictive value (NPV) of 93.2%.

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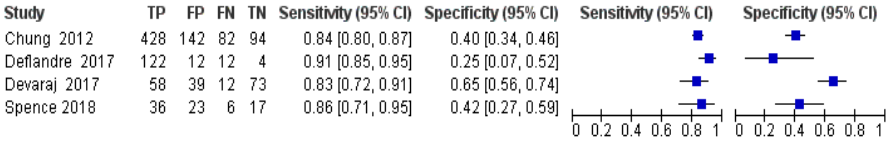
2. STOP-Bang questionnaire: a practical approach to screen for obstructive sleep apnea. 149, 631-638 (2016)

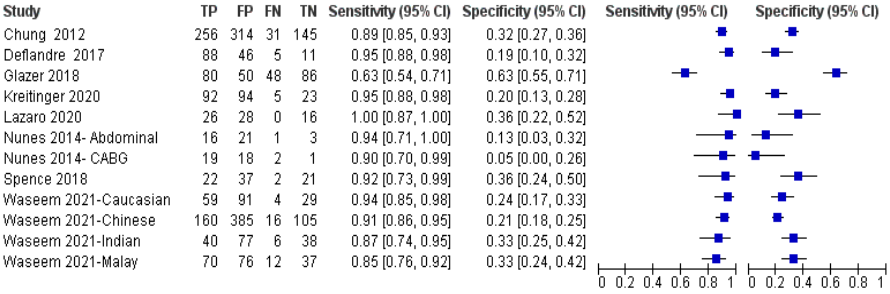
Figure 1. Forest Plot for Combined Sensitivity and Specificity for Obstructive Sleep Apnea for All Included Studies in the Surgical patients

All OSA (AHI ≥ 5)



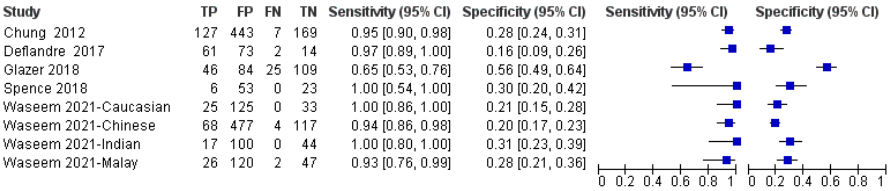
Pooled Sensitivity = 0.85 (0.82 – 0.88); Chi-squared = 5.08; df = 3 (p= 0.1661); Inconsistency (I-square) = 40.9%
Pooled Specificity = 0.47 (0.42 – 0.52); Chi-squared = 23.46; df = 3 (p= 0.0000); Inconsistency (I-square) = 87.2%

Moderate-to-Severe OSA (AHI ≥ 15)



Pooled Sensitivity = 0.88 (0.85 – 0.89); Chi-squared = 77.08; df = 11 (p= 0.0000); Inconsistency (I-square) = 85.7%
Pooled Specificity = 0.29 (0.27 – 0.32); Chi-squared = 108.53; df = 11 (p= 0.000); Inconsistency (I-square) = 89.9%

Severe OSA (AHI ≥ 30)



Pooled Sensitivity = 0.90 (0.87 – 0.93); Chi-squared = 53.25; df = 7 (p= 0.0000); Inconsistency (I-square) = 86.9%
Pooled Specificity = 0.27 (0.25 – 0.29); Chi-squared = 101.55; df = 7 (p= 0.000); Inconsistency (I-square) = 93.1%

Values are presented as means with 95% CI in parentheses. AHI, Apnoea–Hypopnea index; Bang, BMI, age, neck circumference and gender; OSA, obstructive sleep apnoea; STOP, snoring, tiredness, observed apnea and high blood pressure.

Table 1. Pooled predictive parameters of STOP-Bang ≥3 as cut-off for surgical patients

Predictive parameters	All OSA AHI ≥5	Moderate-to-Severe OSA AHI ≥15	Severe OSA AHI ≥30
	(4 studies, n = 1160)	(8 studies, n = 2812)	(5 studies, n = 2447)
Prevalence	65.2 (62.3 – 67.9)	37.7 (35.9 – 39.5)	17 (15.5 – 18.6)
Sensitivity	85 (82 – 88)	88 (85 – 89)	90 (87 – 93)
Specificity	47 (42 – 52)	29 (27 – 32)	27 (25 – 29)
Positive predictive value	74.9 (71.8 – 77.7)	42.9 (40.8– 45.0)	20.3 (18.5 – 22.2)
Negative predictive value	62.7 (56.9 – 68.1)	79.6 (76.2 – 82.6)	93.2 (90.9 – 95.1)
Diagnostic odds ratio	4.63 (2.76 – 7.75)	3.36 (2.67 – 4.21)	4.17 (2.74 – 6.35)
AUC	0.8437 SE= 0.0531	0.6729 SE= 0.0351	0.6302 SE= 0.0488

Data presented as means with 95% confidence interval in parentheses. Abbreviations: AUC, Area under the curve; AHI, Apnea–Hypopnea Index; OSA, Obstructive sleep apnea; SE, Standard error

SLEEP MEDICINE 4

Postoperative outcomes in polysomnography diagnosed obstructive sleep apnea patients undergoing non-cardiac and cardiac surgeries: A meta-analysis of prospective cohort studies

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INTRODUCTION: Identifying surgical patients with obstructive sleep apnea (OSA) may assist with risk stratification, anesthetic management, and monitoring to minimize postoperative complications.[1] Our aim was to investigate the effect of OSA, diagnosed by objective measures such as polysomnography (PSG) or home sleep apnea testing (HSAT), on postoperative outcomes in cardiac and non-cardiac surgical patients. Therefore, we designed this systematic review and meta-analysis (SRMA) of prospective cohort studies using trial sequential analysis to minimize the risk of type 1 error in evaluating the impact of OSA on postoperative outcomes in surgical patients.

METHODS: Multiple databases were systematically searched to identify prospective studies related to OSA patients undergoing surgery and postoperative outcomes. OSA patients were diagnosed by PSG or HSAT. Outcomes included: (1) total postoperative complications; (2) systemic complications: cardiovascular, respiratory, neurological, renal, and infectious; and (3) specific complications: atrial fibrillation, myocardial infarction, ICU admission, and mortality. The SRMA was conducted to examine pooled odds ratios (OR) of postoperative complications using inverse-variance random-effects model.

RESULTS: The systematic search resulted in 12,717 articles and 20 prospective cohort studies, enrolled from 11 different countries, were included for meta-analysis (non-cardiac surgeries n=9; cardiac surgeries n=11). Total of 3,756 patients were screened for OSA using PSG or HSAT with 2,127 patients diagnosed with OSA and 1,629 control patients without OSA. Mean age of patients with OSA: 63.7±9.5 years; BMI of 29.5±9.1 kg/m^2; 65.0% male. Mean age of non-OSA patients: 58.5±10.3 years; BMI of 26.5±3.1kg/m^2; 49.1% male. Overall, postoperative complications were higher in the OSA than in the non-OSA group, with OR of 1.92 (95%CI: 1.52 - 2.42, P<0.05) and an absolute risk increase of 6.97% in OSA patients. For non-cardiac surgeries: OR of 1.97 (95%CI: 1.31 - 2.96, P<0.05) and absolute risk increase of 7.34% in OSA patients. For cardiac surgeries: OR of 1.89 (95%CI: 1.43 - 2.49, P<0.05) and absolute risk increase of 7.80% in OSA patients. There was also a significant increase in postoperative cardiovascular OR of 1.56 (95%CI: 1.20-2.02, P<0.05) and respiratory OR of 1.91 (95%CI: 1.39-2.62, P<0.05) complications in OSA patients. Other findings include increased neurological complications, hospital readmissions, atrial fibrillation and arrhythmia postoperatively.

CONCLUSION: OSA was associated with a nearly two-fold increased risk of total postoperative complications in patients undergoing either non-cardiac or cardiac surgeries compared with patients without OSA. This increased risk emphasizes the importance of preoperative screening of OSA, especially with newly diagnosed OSA patients. Future investigation needed to assess whether interventions can modify risk of OSA for cardiac and non-cardiac surgeries.

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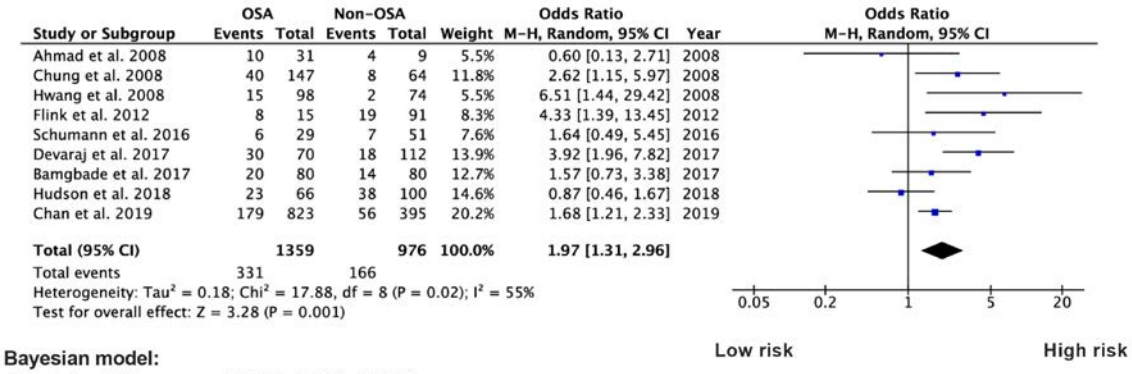
A) Postoperative complications: non-cardiac surgeries

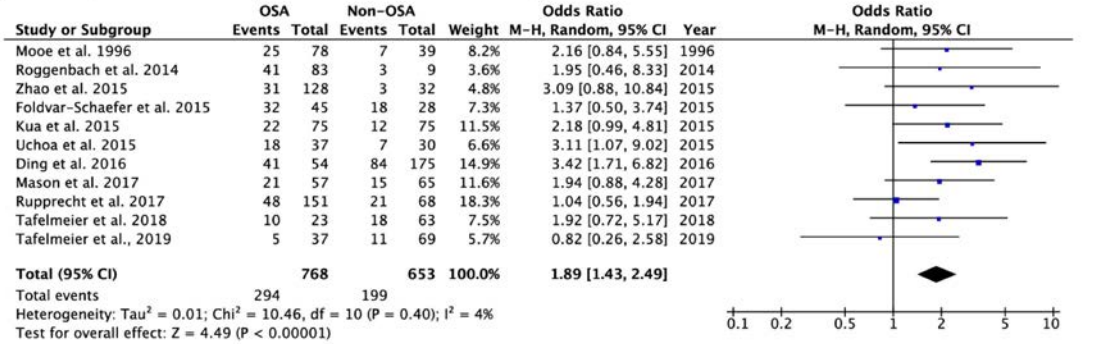


Study or Subgroup	OSA Events	OSA Total	Non-OSA Events	Non-OSA Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Ahmad et al. 2008	10	31	4	9	5.5%	0.60 [0.13, 2.71]	2008
Chung et al. 2008	40	147	8	64	11.8%	2.62 [1.15, 5.97]	2008
Hwang et al. 2008	15	98	2	74	5.5%	6.51 [1.44, 29.42]	2008
Flink et al. 2012	8	15	19	91	8.3%	4.33 [1.39, 13.45]	2012
Schumann et al. 2016	6	29	7	51	7.6%	1.64 [0.49, 5.45]	2016
Devaraj et al. 2017	30	70	18	112	13.9%	3.92 [1.96, 7.82]	2017
Bamgbade et al. 2017	20	80	14	80	12.7%	1.57 [0.73, 3.38]	2017
Hudson et al. 2018	23	66	38	100	14.6%	0.87 [0.46, 1.67]	2018
Chan et al. 2019	179	823	56	395	20.2%	1.68 [1.21, 2.33]	2019
Total (95% CI)		**1359**		**976**	**100.0%**	**1.97 [1.31, 2.96]**	
Total events	331		166				

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 17.88$, df = 8 (P = 0.02); $I^2 = 55\%$
Test for overall effect: Z = 3.28 (P = 0.001)

Bayesian model:
Absolute risk increase: 24.35 - 17.00 = 7.34%
Predictive intervals: 0.64 to 6.01

B) Postoperative complications: cardiac surgeries



Study or Subgroup	OSA Events	OSA Total	Non-OSA Events	Non-OSA Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Mooe et al. 1996	25	78	7	39	8.2%	2.16 [0.84, 5.55]	1996
Roggenbach et al. 2014	41	83	3	9	3.6%	1.95 [0.46, 8.33]	2014
Zhao et al. 2015	31	128	3	32	4.8%	3.09 [0.88, 10.84]	2015
Foldvar-Schaefer et al. 2015	32	45	18	28	7.3%	1.37 [0.50, 3.74]	2015
Kua et al. 2015	22	75	12	75	11.5%	2.18 [0.99, 4.81]	2015
Uchoa et al. 2015	18	37	7	30	6.6%	3.11 [1.07, 9.02]	2015
Ding et al. 2016	41	54	84	175	14.9%	3.42 [1.71, 6.82]	2016
Mason et al. 2017	21	57	15	65	11.6%	1.94 [0.88, 4.28]	2017
Rupprecht et al. 2017	48	151	21	68	18.3%	1.04 [0.56, 1.94]	2017
Tafelmeier et al. 2018	10	23	18	63	7.5%	1.92 [0.72, 5.17]	2018
Tafelmeier et al., 2019	5	37	11	69	5.7%	0.82 [0.26, 2.58]	2019
Total (95% CI)		**768**		**653**	**100.0%**	**1.89 [1.43, 2.49]**	
Total events	294		199				

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 10.46$, df = 10 (P = 0.40); $I^2 = 4\%$
Test for overall effect: Z = 4.49 (P < 0.00001)

Bayesian model:
Absolute risk increase: 38.28 - 30.47 = 7.80%
Predictive intervals: 1.27 to 2.79

SLEEP MEDICINE 5

The use of waist circumference instead of neck circumference in the STOP-Bang questionnaire and B-APNEIC score to screen for severe obstructive sleep apnea

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INTRODUCTION: We have previously shown that neck circumference (NC) is the most important parameter to screen for severe obstructive sleep apnea (OSA) when using the STOP-Bang questionnaire or B-APNEIC score.[1] However, NC is seldom measured during routine medical care. While more common anthropometric measures, such as waist circumference (WC), have been proposed as an alternative to NC for OSA screening tools, their validity has remained underexplored. Therefore, our goal was to compare the utility of WC to NC when using the STOP-Bang questionnaire and B-PANEIC score to screen for severe OSA.

METHODS: Following Institutional Review Board approval, we retrospectively assessed data from a prospective cohort of patients referred for overnight polysomnography (PSG). Severe OSA was diagnosed based on criteria set by the American Academy of Sleep Medicine.[2] We measured WC using 3 different methods: 1) at the level of the umbilicus; 2) the National Institutes of Health (NIH) method;[3,4] and 3) the World Health Organization (WHO) method.[4] First, locally weighted scatterplot smoothing (LOWESS) curves were generated to graphically represent the relationship between NC as well as all 3 WC measurements and the likelihood of severe OSA. Then, receiver operating characteristic (ROC) curves were generated for the STOP-Bang questionnaire as well as B-APNEIC score using NC and WC, and their areas under the curve (AUC) were compared using the DeLong method.

RESULTS: Of the 275 patients in the main study cohort, 239 patients had complete data points for the present analysis. 33% (n=78) of patients were diagnosed with severe OSA. LOWESS curve analysis demonstrated a near linear relationship between NC as well as all 3 WC measurements and likelihood of severe OSA (Figure 1). Pearson correlation between NC and WC were: 1) Umbilicus, r=0.54; 2) NIH, r=0.46; and 3) WHO, r=0.62. Since NC and WC-WHO demonstrated the highest correlation, STOP-Bang questionnaire and B-APNEIC scores were tabulated using these two measurements. The traditional cut-off value for NC (40 cm) is in the center of the distribution of measurements and therefore we used similar approach to derive a cutoff value of 125 cm for WC-WHO (Figure 1). ROC curves (Figure 2) demonstrated that AUC for the original vs modified STOP-Bang questionnaire were 0.75; 95%CI 0.68-0.81 vs 0.74; 95%CI 0.68-0.80 (p=0.55), respectively. Similarly, AUC for the original vs modified B-APNEIC score were 0.75; 95%CI 0.68-0.81 vs 0.72; 95%CI 0.66-0.78 (p=0.27), respectively. Sensitivity, specificity, and accuracy data for the original and modified screening tools are shown in Table 1.

CONCLUSION: Our data suggest that WC-WHO may be an acceptable substitute for NC when screening for severe OSA using either the STOP-Bang questionnaire or B-APNEIC score. Further studies are needed to validate our findings and to prospectively assess the accuracy of OSA screening using alternative anthropometric measures such as WC.

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Figure 1. Locally weighted scatterplot smoothing curves to graphically represent the relationship between: (A) NC = neck circumference; (B) WC-Umbilicus = waist circumference - umbilicus method; (C) WC-NIH = waist circumference - National Institutes of Health method; as well as (D) WC-WHO = waist circumference - World Health Organization method and the likelihood of severe obstructive sleep apnea (OSA). Dotted line in (A) represents the original cut-point (<40cm vs ≥40cm) for NC in the STOP-Bang questionnaire and B-APNEIC score. Dotted line in (D) represents the proposed cut-point (<125cm vs ≥125cm) for WC-WHO for the STOP-Bang questionnaire and B-APNEIC score.

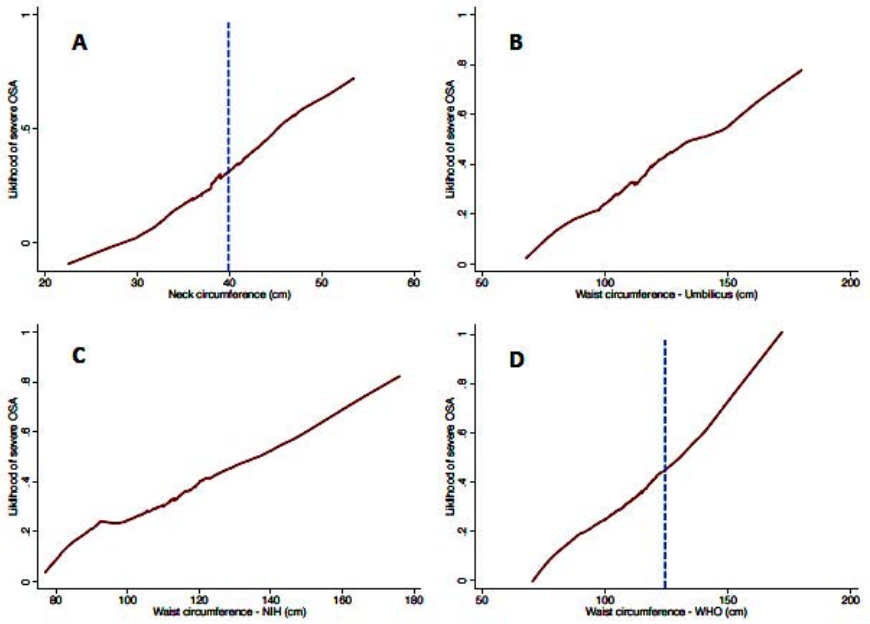

Figure 2. Receiver operating characteristic curves comparing: (A) original STOP-Bang questionnaire using neck circumference versus modified tool using waist circumference for severe obstructive sleep apnea (AUC 0.75; 95%CI 0.68-0.81 vs 0.74; 95%CI 0.68-0.80: p=0.55, respectively), and (B) original B-APNEIC score using neck circumference versus modified tool using waist circumference for severe obstructive sleep apnea (0.75; 95%CI 0.68-0.81 vs 0.72; 95%CI 0.66-0.78: p=0.27, respectively).

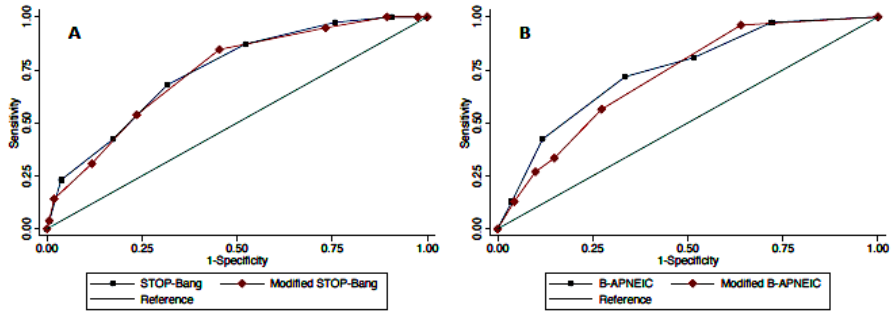

Table 1. Sensitivity, specificity, and accuracy of the STOP-Bang questionnaire and B-APNEIC score using neck circumference versus modified screening tools using waist circumference.

Screening Tool	Sensitivity (%)	Specificity (%)	Accuracy (%)
STOP-Bang (<5 vs ≥5)	68	68	68
Modified STOP-Bang (<5 vs ≥5)	54	76	69
B-APNEIC (<3 vs ≥3)	72	67	68
Modified B-APNEIC (<3 vs ≥3)	56	73	67

SLEEP MEDICINE 6

Examination of EEG Sleep Patterns in Post-Operative Cardiac Surgery Patients

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INTRODUCTION: Post-operative sleep alterations have been shown to play a role in the development of postoperative cognitive dysfunction and delirium[1,2,3]. Recently, postoperative delirium has been shown to be an independent predictor for the development of dementia within 5 years following cardiac surgery[4,5]. To date, few studies have examined continuous EEG monitoring in the post-operative period and its association with delirium with fewer studies examining patients in the postoperative intensive care unit or following cardiac surgery[1,6]. We designed a study that utilized a user-friendly single-lead EEG device to monitor sleep at home and also post-operatively in the ICU after cardiac surgery in the same group of patients. We aimed to determine the prevalence and severity of sleep disturbance following cardiac surgery using EEG data as well as qualitative sleep questionnaires to determine how these changes were associated with the development of postoperative delirium. We hypothesized that following cardiac surgery, total sleep and quality of sleep (measured by time in deep sleep and REM sleep) would be significantly decreased and that patients with sleep disturbances would be more likely to develop postoperative delirium. As a secondary aim of this study, we analyzed the raw EEG waveforms in our patient population pre-operatively while sleeping at home and compared them to post-operative EEG sleep data to determine whether we could uncover any changes in EEG signatures between baseline sleep and post-operative sleep.

METHODS: This was a prospective observational study of adult patients (≥18 years of age) who were scheduled for cardiac surgery utilizing cardiopulmonary bypass. Any patients with a pre-existing sleep disorder, adhesive allergy, or inability to consent were excluded. EEG data was collected using ZMachine Insite [General Sleep, Cleveland, OH], an FDA-approved device that uses single-channel EEG to determine sleep state information including sleep stages. In patients able to use the device at home, a total of up to 5 consecutive nights of baseline sleep at home were collected to determine a representative sample of baseline sleep patterns. Following cardiac surgery, discontinuation of sedation, and extubation, patients underwent EEG monitoring with the same ZMachine device for the duration of their post-operative hospital stay up to a total of 5 consecutive postoperative nights. Light sleep, deep sleep, REM sleep, total sleep time, and sleep efficiency were collected for each day. Data from patient's who had significant sleep disturbances, did not use the EEG device correctly at home, had poor EEG data, or had significant amount of data missing were excluded from the final analysis.

RESULTS: A total of 91 patients were included in the analysis. Baseline data for 15 patients were obtained. EEG data are described in Table 1. Self-reported questionnaire data suggest the postoperative period is associated with a reduction in the perceived amount of sleep. This perceived sleep disturbance is associated with post-operative EEG findings consistent with a reduction in sleep quality (reduced deep and REM sleep) as opposed to actual time spent sleeping (light sleep and total sleep) which was increased in the post-operative period. Our results revealed that although patients appeared to have an adequate amount of sleep post-operatively, most of their time sleeping was in light sleep and deep sleep and REM sleep were actually decreased from baseline. EEG spectrograms in these patients were analyzed pre and post-operatively to identify specific changes in EEG patterns post-operatively from baseline and will be displayed at the time of presentation.

CONCLUSION: Our data suggests that overall, patients have perceptibly poorer quality sleep in the post-operative period following cardiac surgery compared to cohort baseline which was confirmed with quantitative EEG data. The novelty of our study was in that we were able to observe direct changes in each individual patient's post-operative sleep from baseline sleep patterns and plan to evaluate individual EEG patterns with the objective to identify changes in EEG patterns in these patients. We hope that our study can improve the understanding of post-operative sleep disturbances using quantitative EEG as well as qualitative data and help pave the way to uncovering the effects of surgery and anesthesia, in particular cardiac surgery, on postoperative delirium.

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Table 1. Average amount of REM, deep, light and total sleep for baseline sleep and postoperative days 1 -5 (POD1 - POD5) sleep, p values comparing postoperative sleep to the baseline sleep.

Days	REM Sleep		Deep Sleep		Light Sleep		Total Sleep	
	Mean ± SD (hours)	p value	Mean ± SD (hours)	p value	Mean ± SD (hours)	p value	Mean ± SD (hours)	p value
Baseline Sleep	1.51± 0.78		1.98± 0.67		2.10± 0.85		5.59± 1.49	
POD1	0.91± 1.11	0.011	0.51± 0.76	<0.001	6.55± 2.14	<0.001	7.97± 2.71	<0.001
POD2	0.99± 1.25	0.021	0.91± 0.78	<0.001	6.14± 2.39	<0.001	8.04± 2.84	<0.001
POD3	1.05± 1.01	0.02	0.83± 0.71	<0.001	5.14± 2.56	<0.001	7.02± 2.75	<0.001
POD4	0.91± 0.98	<0.001	0.75± 0.61	<0.001	4.51± 2.01	<0.001	6.17± 2.61	<0.001
POD5	1.01± 0.96	0.004	0.69± 0.54	<0.001	4.61± 2.01	<0.001	6.31± 2.22	<0.001

SLEEP MEDICINE 7

The SANDMAN Study: Sleep Apnea, Neuroinflammation, and Cognitive Dysfunction Manifesting After Non-cardiac surgery

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INTRODUCTION: Up to 40% of older surgical patients develop postoperative delirium (POD) and/or postoperative cognitive dysfunction (POCD)-objective cognitive deficits occurring 1-12 months after surgery. Although POCD and POD are both associated with decreased quality of life, increased mortality, and long-term cognitive decline, there are few interventions to prevent them. One potentially modifiable POD and POCD risk factor is poor sleep quality, due to obstructive sleep apnea (OSA), a frequently undiagnosed disorder characterized by repetitive breathing interruptions and hypoxia during sleep. Although OSA has been connected to long-term cognitive decline and earlier dementia onset, it is unknown whether untreated OSA is associated with POD, POCD, or increased neuroinflammation-a potential mechanism underlying POD and POCD. SANDMAN aims to determine the relationship between untreated OSA, POD, POCD, and neuroinflammation.

METHODS: SANDMAN is an IRB-approved sub-study of the NIH-funded INTUIT study, in which 200 patients age>60 undergoing non-cardiac surgery complete blood and cerebrospinal fluid sampling before, 24 hours, and 6 weeks after surgery. POD is assessed up to 5-days postoperatively with 3D-CAM, and a cognitive testing battery is performed before, 6-weeks, and 1-year after surgery. SANDMAN patients underwent preoperative home sleep apnea testing (HSAT) to diagnose OSA and quantify its severity by measuring the apnea-hypopnea index (AHI). Preoperative subjective sleepiness, a marker of sleep quality, was assessed with the Epworth Sleepiness Scale (ESS), categorized as normal, mild, and moderate/severe excessive. The relationship of OSA severity and ESS scores with POD incidence and severity change was assessed in multivariable models adjusting for age, sex, and baseline POD severity score.

RESULTS: 145 INTUIT patients were screened for SANDMAN inclusion, and 101 eligible patients underwent preoperative HSAT (Figure 1). We obtained valid HSAT data on 97 subjects, of whom 91 completed POD assessments. 60% of the SANDMAN patients who completed HSAT were diagnosed with OSA, of whom 36% had mild OSA, 14% had moderate OSA, and 9% had severe OSA (Table 1). There was no significant relationship between OSA severity (AHI) and POD incidence (OR 0.99; 95% CI 0.93-1.04, p=0.97) or severity (OR 0.98, 95% CI 0.95-1.01, p=0.32; Figure 2). ESS was not associated with POD incidence, but moderate-severe sleepiness (ESS≥13) was associated with increased POD severity (OR 3.98; 95% CI 1.10-14.37, p=0.035; Figure 3).

CONCLUSION: These results suggest no relationship between OSA and POD incidence or severity, although increased preoperative subjective sleepiness was associated with POD severity. This suggests that sleep deficits, perhaps unrelated to OSA, could play a role in POD. Future work is warranted on the role of perioperative sleepiness and sleep dysfunction in POD.

Table 1. Baseline summary table by physician diagnosis of OSA severity. Variables summarized with mean (SD) or median [Q1, Q3] and compared with ANOVA or Kruskal Wallis tests

	None (N=39)	Mild OSA (N=35)	Moderate OSA (N=14)	Severe OSA (N=9)	p value
Age	67.54 (6.21)	68.17 (5.17)	70.71 (6.94)	68.78 (4.52)	0.377
Gender (Male)	14 (35.9%)	14 (40.0%)	7 (50.0%)	9 (100.0%)	0.005
AHI	2.19 (1.49)	9.68 (4.27)	18.56 (2.84)	48.97 (16.79)	<0.001
ODI					<0.001
Mean (SD)	3.08 (1.98)	11.50 (5.27)	18.96 (7.69)	49.72 (23.79)	
Median	2.70	10.80	18.45	41.90	
Q1, Q3	1.40, 4.50	8.50, 15.50	15.10, 21.30	37.10, 59.90	
HSAT days to surgery	-4 [-6, -2]	-3 [-8, -3]	-4 [-7, -3]	-3 [-7, -1]	0.782
Duration of Recording (min)	439 [356, 544]	438 [360, 508]	455 [387, 532]	403 [357, 420]	0.341
Baseline Delirium	0	0	0	0	--
Baseline 3D-CAM severity Score	0 [0, 0]	0 [0, 1]	0 [0, 1]	0 [0, 0]	0.318
Epworth Sleepiness Score	8 [5, 9]	6 [4, 8]	6 [3, 10]	7 [5, 13]	0.366

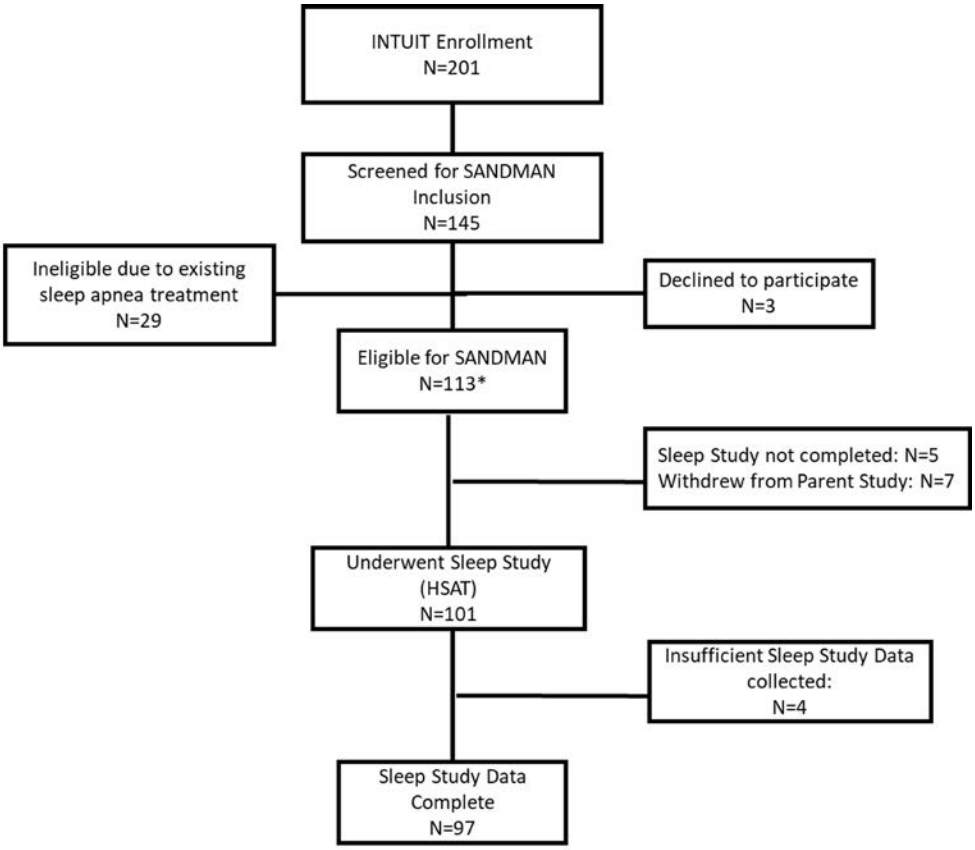

Figure 1. SANDMAN Consort Diagram

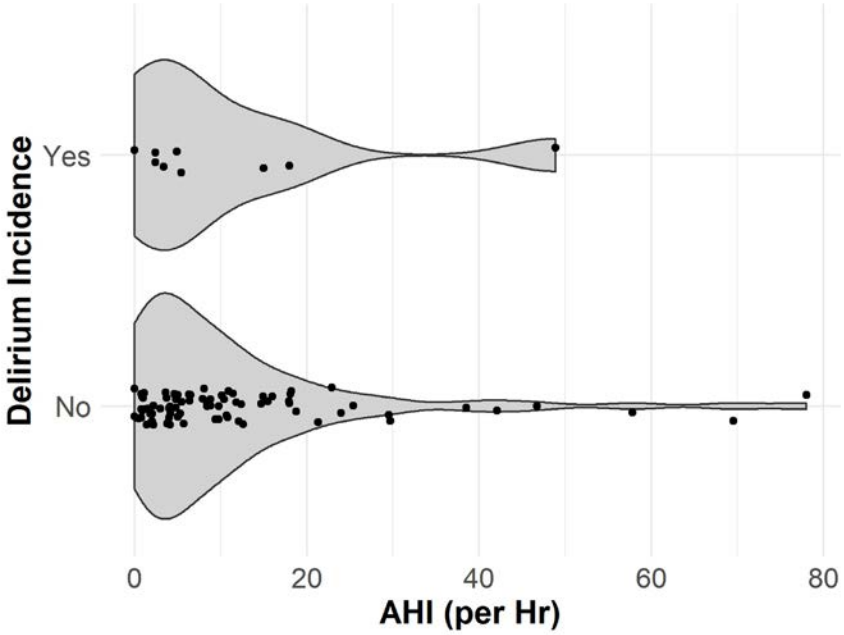

Figure 2. Relationship between OSA Severity (AHI) and POD

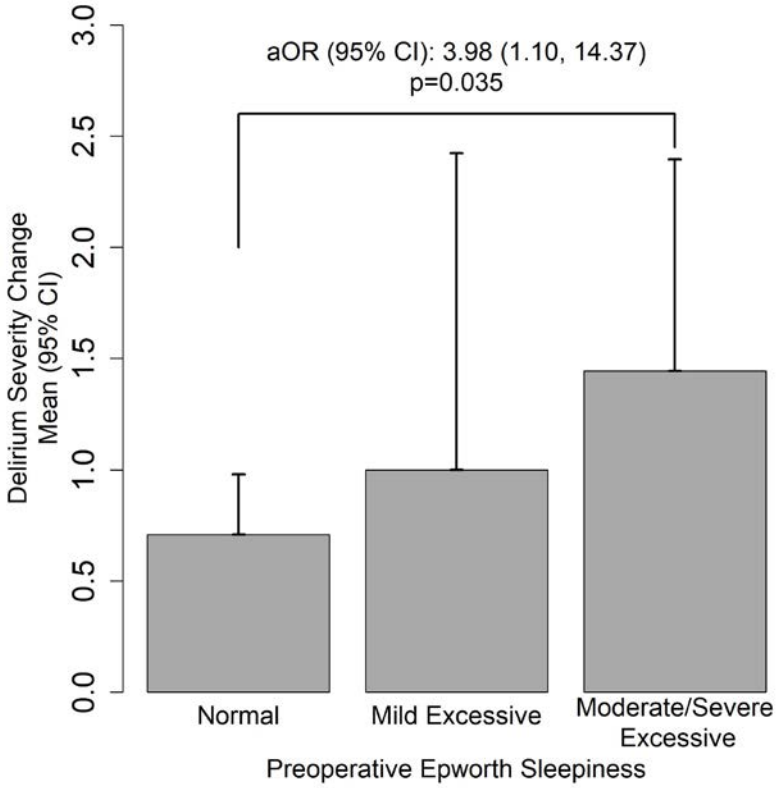

Figure 3. Relationship between sleepiness (ESS score) and POD severity

SUBSPECIALTY ABSTRACTS

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 1

Development of interprofessional crisis simulation for a hybrid magnetic resonance imaging operating-room suite.

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INTRODUCTION: Intraoperative magnetic resonance imaging (MRI) is a technology increasingly used for neurosurgical and other procedures[1,2]. Operating in close proximity to a mobile magnetic field requires multiple changes and adaptations to normal equipment and workflow, making it a highly complex environment with potential for significant adverse events[3,4]. In addition, the MRI operating room (MRI-OR) is often isolated from the regular operating rooms, either because it is located in a different part of the hospital, or because entry into the MRI-OR requires adherence to time-consuming MRI safety protocols[5]. Our institution experienced several incidents in which corrective actions were delayed because external help arrived many minutes after a call for help. This resulted in an institutional review of our crisis response for the MRI-OR and the request to create mock code training. The intent was to define distinctive features of crisis management in the MRI-OR and to develop a realistic location-specific crisis simulation module for the MRI-OR.

METHODS: An initial group of experts and stakeholders, including anesthesia, nursing, and MRI personnel, convened and discussed MRI-OR related barriers to effective crisis management and explored potential solutions. Next, a series of mock code scenarios were conducted over several months by a volunteer group of personnel directly involved in MRI-OR procedures, including anesthesia personnel, perioperative nurses and scrub technicians, and MRI technologists (Figure 1A). In an iterative process, we identified problems experienced during resuscitation efforts and addressed them, trialing various solutions. This effort led to a low-fidelity code simulation training that was offered to about 100 anesthesia and perioperative personnel over the course of 1 year as part of mandatory orientation training to the MRI-OR. Feedback from participants prompted minor adjustments to the training content as well as to organization of emergency equipment. In light of rising case volumes and increasing complexity of procedures in the MRI-OR, we subsequently developed several high-fidelity scenarios with a customized MRI-safe mannequin, to be able to realistically present a larger variety of crisis situations during neurosurgical procedures (Figure 1 B-D).

RESULTS: The following areas of crisis management were identified as uniquely affected by the MRI-OR environment (see table 1): Calling for help, providing positive pressure ventilation and effective chest compressions, and accessing the code cart. Standard operating procedures and cognitive aids for these areas were then created, tested, and subsequently modified as needed. MRI-safe 'airway grab bags' and 'code medication trays' were assembled and are now available in the room at all times. Creation of a high-fidelity simulation required several workarounds. The following 2 were most significant: 1) Metal-containing simulation equipment cannot enter the MRI-OR. Therefore, simulation technicians customized an adult (upper body) mannequin by removing any metal screws and 3D printing them in plastic, resulting in an MRI-safe mannequin capable of being ventilated, intubated, auscultated, and to receive intravascular medication. 2) The computer/device on which the simulation software is controlled cannot be brought in the MRI-OR, nor can wireless signals be transmitted due to radio frequency shielding of MRI rooms. This made it initially difficult to project vital signs (and their dynamic changes) in the operating room. We ultimately positioned the simulation computer in the control room, hardwiring the 'anesthesia vital sign screen display' and the sounds of vital signs and alarms to equipment in the MRI-OR. Our final simulation module has several variations including lost airway or lost vascular access scenarios, with options to mimic intraoperative status (head in pins) and supine or prone positioning.

CONCLUSION: Creating realistic simulation scenarios for complex environments such as the MRI-OR is very resource-intensive, but feasible with several modifications to normal simulation set-ups[6]. While simulation training has become established in multiple different healthcare fields[7], the effectiveness and acceptance of this highly specific simulation training will need to be evaluated. If found to be useful, this training could be modified for multiple other complex non-operating room environments, including diagnostic MRI settings and cardiac hybrid operating rooms.

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Table 1

Key feature of crisis management	Problem in MRI-OR setting	Solutions and workarounds	Discarded suggestions
Call for help	• remote • no personal cell/devices in MRI-OR • not every responder MRI-OR trained	• group page with cognitive aid • portable phone for covering attending for non-emergent communication	• overhead page system • phone call to main OR front desk • code blue button
Positive-pressure ventilation (PPV)	• head of patient inaccessible while in scanner • far away from machine - single provider can either be at head or ventilate	• Airway grab bag • Training of PST/circulator to “squeeze the bag”	• circulator obtaining specific airway equipment as per directions
Chest compressions (CPR)	• OR table swings, needs stabilizer • table too high for CPR	• Stabilizer pole • designated step stools	
General resuscitation	• Code cart is not MRI-safe	• Airway grab bag • Code drug kit	• MRI safe code cart

Abbreviations: CPR: cardiopulmonary resuscitation; MRI-OR: magnet resonance imaging operating-room suite; OR: operating room; PPV: positive pressure ventilation; PST: periprocedural services technologist.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 2

Assessment of the Pulmonary Gas Exchange Efficiency and Cardiac Output by an Online Volumetric Capnography in Anesthetized Rabbits

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INTRODUCTION: Assessment of exhaled CO2 has evolved into an essential component of patient monitoring in different clinical scenarios[1]. Volumetric capnography (Vcap) allows a complete analysis of the global V/Q efficiency by comparing Bohr versus Enghoff approaches to physiologic dead space measurements (VDB and VDE, respectively), as it should also monitor cardiac output (CO) non-invasively (if minute ventilation and cellular metabolism are stable)[2-4]. We developed a wireless online capnograph to determine the correlation between the intrapulmonary shunt fraction (Qs/Qt) and (VDE-VDB) and the correlation between pulmonary flow (PF) and minute expiratory CO2 (VCO2)[5] during normobaric acute global hypoxia (Hx) in a rabbit model.

METHODS: Five female New Zealand rabbits (3.1 ¬± 0.2 Kg) were anesthetized and mechanically ventilated. A left thoracotomy was performed. Central venous (CVP) left atrial (LAP); and femoral arterial (AoP) pressures (fluid column catheter); and pulmonary arterial pressure (PAP, Millar); and PF (Transonic) were monitored (LabChart, 1KHz). Blood gas samples from central venous; arterial; and left atrial; and hemoglobin content were obtained. The Qs/Qt (Berggren equation) and HPV stimulus (PsO2, Marshall equation) were estimated[6,7]. Vcap was obtained by an infrared mainstream CO2 sensor (QuRe, Treaton) clipped onto a neonatal digital flow meter (SFM3400, Sensirion) and airway pressure transducer (HSC series, Honeywell) (200 Hz). We designed dedicated hardware and software (Samay S24) (Fig. 1) which communicates via Wifi on a cell phone or tablet screen to display in real-time the temporal signals with Vcap and estimated parameters (minute VCO2, mean-expired PCO2 -PECO2-, end-tidal PCO2 -PetCO2-, and VDE) (Fig. 2). The S24 does not need the installation of any specific software, just a web browser, and it supports up to four monitors connected in simultaneously mode with a storage capacity of 1536 hours of registration. We estimated dead airway space (VDaw, Fowler), alveolar PCO2 (PACO2), VDB, and alveolar dead space (VDalv) off-line (Fig. 3). The animals were subjected to a FiO2 0.1 for 5 min.

RESULTS: HPV stimulus obtained during Hx was 26 ± 3 mmHg. Hypoxic pulmonary vasoconstriction determined a significant increase in mean PAP and pulmonary vascular resistance without a significant change of the AoP (Table). VDaw was 4.6 ± 1 mL, and minute ventilation (MV) was 539 ± 101 (Basal) and 459 ± 86 mL/min (Hx) (NS). The PF correlated with the minute expired VCO2 normalized for the MV ($r = 0.56$; $P < 0.05$) (Fig. 3). Hx increases the VDE-VDB difference at the expense of the increase of VDE, coinciding with the increase in Qs/Qt ($P < 0.05$) (Table). Both, VDE-VDB and Qs/Qt were correlated ($r = 0.79$; $P < 0.01$) (Fig. 4).

CONCLUSION: We present the Samay S24 designed in our laboratory to monitor online expired CO2 parameters (wireless communication and web browser). Generalized HPV could impair circulatory efficiency, increasing the intrapulmonary shunt associated with the significant increase in VDE-VDB. Under stable CO2 metabolism conditions, PF was correlated with normalized minute expiratory VCO2.

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Figure 1. Volumetric capnograph SAMAY 24 (S24)

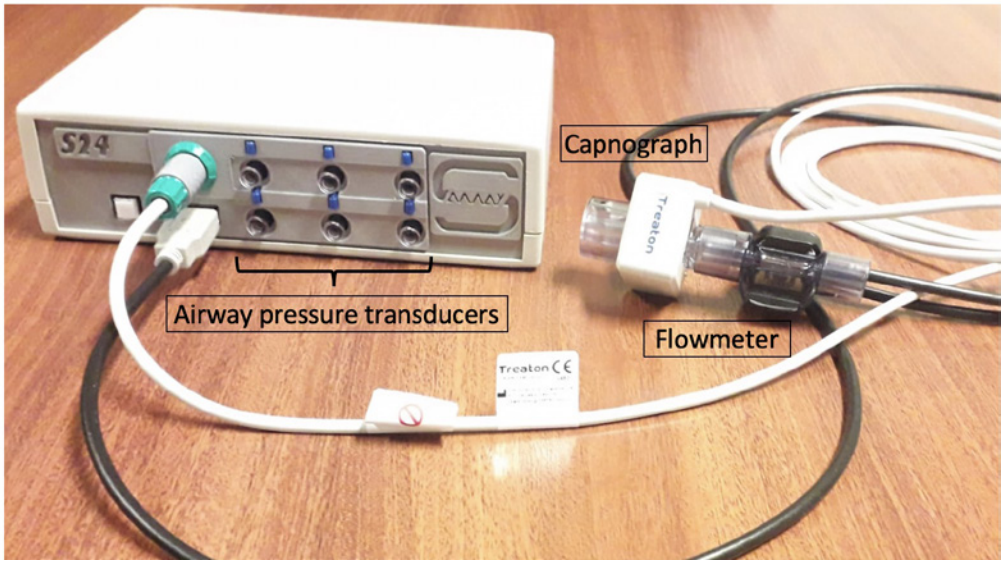


Table: Changes in hemodynamic, gasometric and capnographic data values during hypoxia

	Basal	Hx
Mean AoP, mmHg	55±12	56±15
Mean PAP, mmHg	7.2±1.3	8.8±1.7*
PF, mL/min	214±56	208±69
PVR, Wu	22.4±5	43±14*
pH	7.40±0.06	7.36±0.06
PaO_2, mmHg	371±34	33±6
$PaCO_2$, mmHg	34±1.4	34±3
Lactate, mEq/L	1.7±0.4	1.7±0.9
VCO_2, mL/min	11.2±2.2	11.8±2.0
$PetCO_2$, mmHg	31±5	33±5
VD_B, %	26.9±6.6	27.7±5
VD_E, %	31.8±9.8	38±7.5
VD_E-VD_B, %	3.0±3.9	12±5*
VDalv, mL	1.3±0.9	1.6±1.5
Qs/Qt, %	4.2±3	14.8±9*

Mean ± SD. P <0.05 *vs. Basal (n = 5).

Figure 2. Online variables monitored by the SAMAY 24 (S24) on a cell phone screen. VCI, VCE: inspiratory and expiratory volume; TI, TE: inspiratory and expiratory time; FR: respiratory rate; $EtCO_2$: end-tidal CO_2; VCO_2: minute expiratory CO_2; $PECO_2$: mean-expired CO_2; VD/VT: Enghoff dead space; AwP: airway pressure; left loop: volumetric capnography; right loop: tidal volume-AwP loop (Temporal variables were subjected to a compression algorithm).

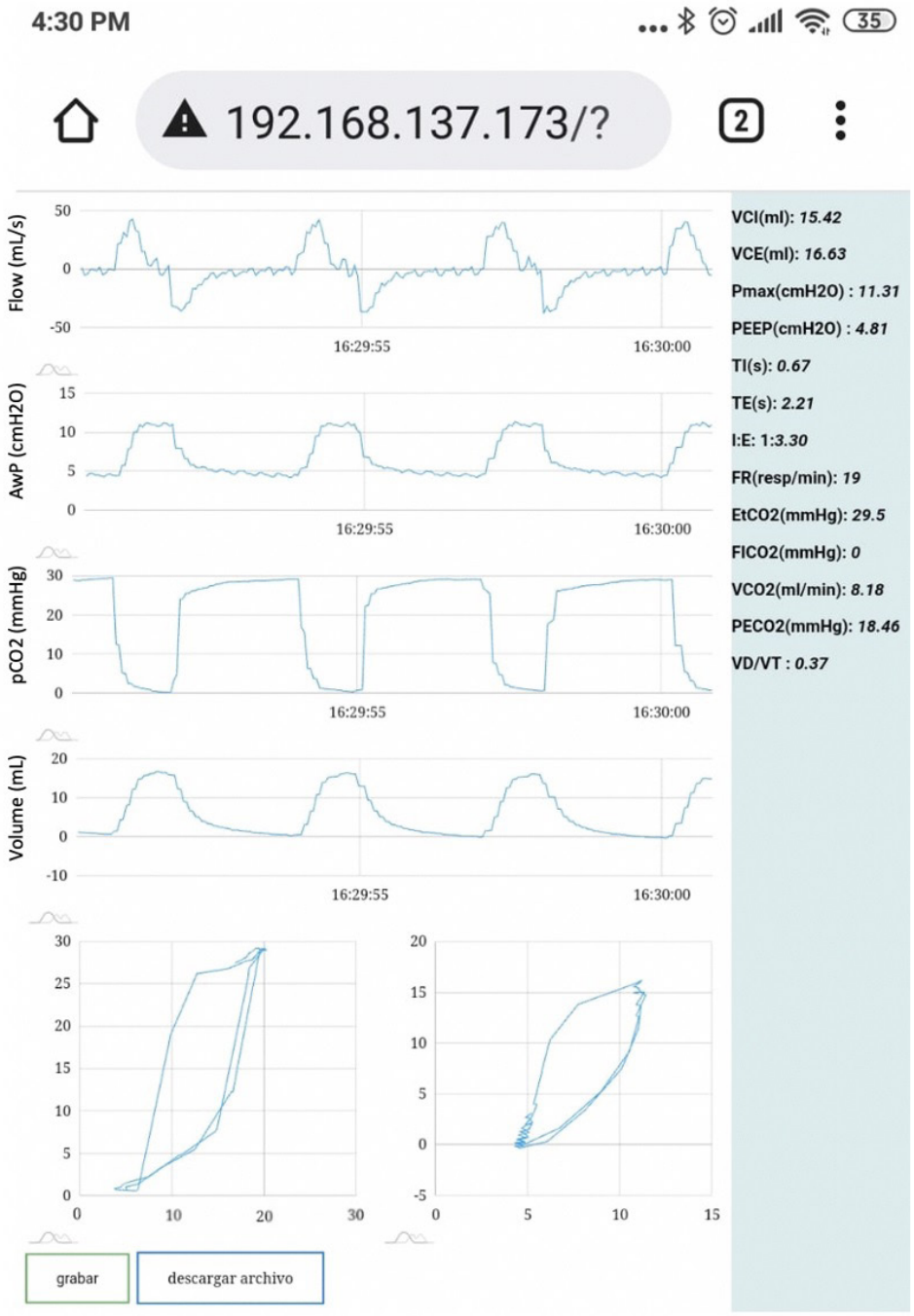


Figure 3: Representative volumetric capnogram (left) and temporal tracings of the online variables (right). Off-line estimated parameters in red italic font (PACO2, PaCO2, PECO2, and PetCO2: alveolar, arterial, mean-expired, and end-tidal PCO2, respectively; VD_{Alv}, VD_{AW}, VD_B, and VD_E: alveolar, airway, Bohr and Enghoff volume dead spaces; I: Inspiration; E: Expiration).

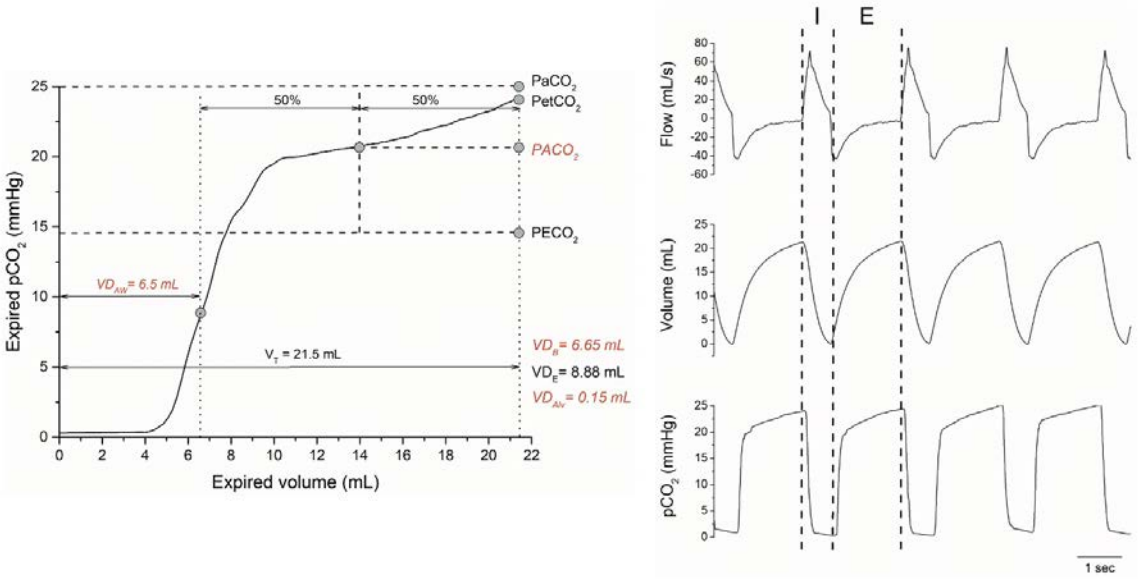
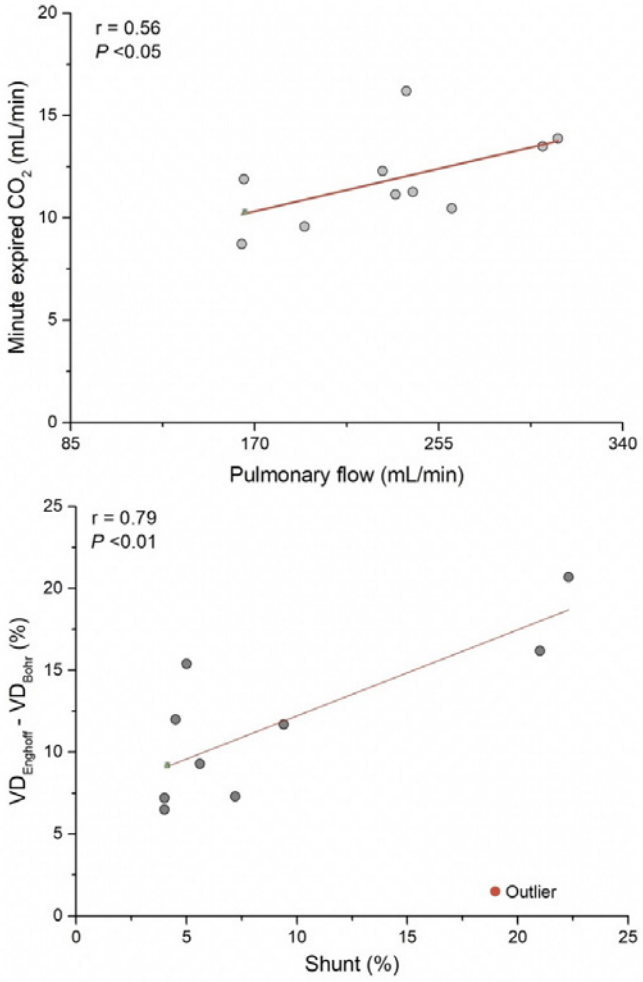


Figure 4: Scatter plots between the intrapulmonary shunt fraction and (VD_E-VD_B), and between pulmonary flow and minute expiratory CO_2



TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 3

Initial Adoption and Use of a Novel Learning Management System and Implications for Standardizing Performance Assessment of Anesthesia Residents

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INTRODUCTION: Although the potential for individualized/personalized learning is mentioned as a benefit of simulation-based training[1], this is currently not standard practice. There is a critical need for a system or capability to recommend appropriate training that is required to acquire or maintain knowledge/skills and avoid skill decay. The purpose of this initial study was to evaluate the impact of the initial adoption and use of a novel learning management system (LMS) platform on anesthesia resident education. The LMS platform is designed to standardize creation of training curriculum and underlying performance assessments. The LMS provides advanced assessment capabilities including measurement of neurophysiological data from learners around measured 'learning events' to serve as a more objective marker of performance and proficiency. For this study we seek to evaluate the utility of the platform in advancing resident education and identification of patterns and relationships that exist between learner physiological responses and performance evaluations made by clinical faculty. The study identified how the LMS platform can be used as a data-driven platform to improve education across multiple professional programs at our institution.

METHODS: All anesthesia residents participated in numerous simulation scenarios and had performance and physiological data measured throughout all simulation sessions across a period of 15 months by the LMS platform. All residents enrolled in the study had their physiological data monitored by a commercially available wearable device (Empatica E4 Wristband). The wearable device and a custom built application derived measures of heart rate, electrodermal activity (i.e., skin conductive response), skin temperature, and motion via a 3-axis accelerometer. Curriculum was developed by faculty using the LMS Platform which consisted of 'learning events' where faculty evaluated performance against predefined standardized anesthesia-specific learning objectives. The platform was used to debrief residents following participation and all data and measures were used to provide a more intelligent and focused debriefing. Physiological measures collected by the platform were standardized across subjects by calculating a percentage deviation from algorithm-derived baseline/resting states. Data analysis was focused on identifying relationships existent between physiological responses and performance using symmetric analysis windows around 'learning events' that were evaluated by faculty using the LMS.

RESULTS: Based on prior work[2] our thought was that there would be a relationship between physiological responses and performance data. We hypothesized that physiological responses indicating stress (e.g. increased heart rate relative to baseline state) would be associated with reduced performance ratings amongst residents as this could represent potential lack of knowledge or comfort level with an evolving patient care scenario due to inexperience. While this pattern was seen across residents it was not consistent or prevalent across the dataset. We hypothesize lack of consistency in patterns/trends in LMS data is related to timeliness of assessments made by faculty who were making assessments and simultaneously driving and participating in the training scenarios. Hence, we believe symmetrical analysis windows did not always capture physiological responses at the time of each learning event. Numerous patterns and trends were identified at the resident-specific level as well as globally across all residents. Figures 1 and 2 which includes screen shots from the LMS for an anesthesia resident during year 1 to year 2 of the residency program respectively. Similar global patterns across multiple residents (N=26) are shown in Figures 3 & 4. Figures 3 & 4 demonstrate clusters of residents identified based on physiological responses and performance relationships that were found to be consistent with our hypothesis.

CONCLUSION: Lessons learned from this initial adoption and roll-out are being incorporated across other professional programs as the LMS platform is being adopted at our academic institution. Improved data collection and analysis processes will result from this effort. The platform provides a unique potential in the future to support the development of machine learning-based models that may lead to the personalization of education and training across many different groups of healthcare providers.

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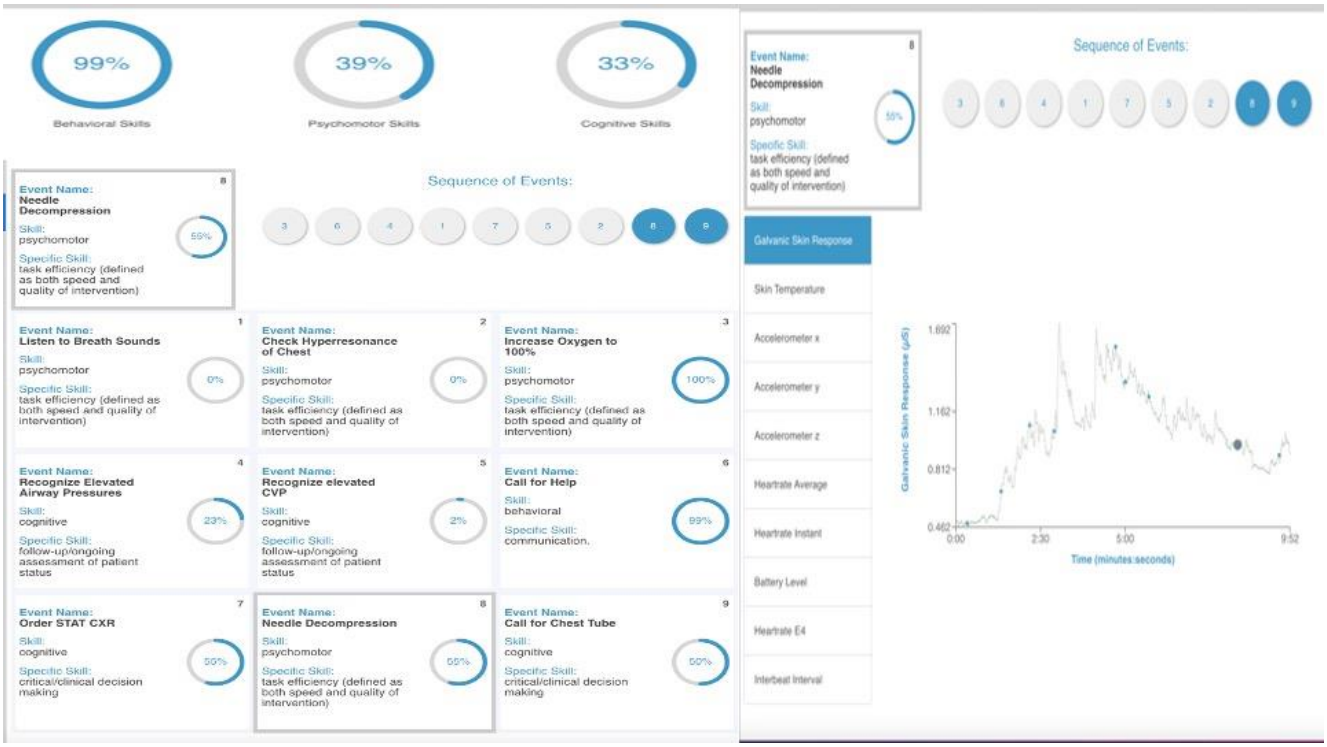

Figure 1. Screenshots from PREPARE for a first-year anesthesia resident (intern), which demonstrates increased stress response (increased skin conductive response or electrodermal activity) throughout pneumothorax scenario. Resident performance for representative learning event or psychomotor task (needle decompression) was evaluated as a score of 55 out of 100 or 55%. Trends in physiology and reduced performance may be correlated with lack of clinical experience and knowledge as hypothesized.

Figure 2. Screenshots from PREPARE for a second-year anesthesia resident (CA1) from Figure 1, which demonstrates improved performance and reduction of physiological response for psychomotor skill (hyperventilate) evaluated by faculty. Note skin conductance is reduced 2x from initial year which is likely related to acquiring clinical experience and increased education from Year 1 to Year 2 of residency. Data was collected 7 months apart.

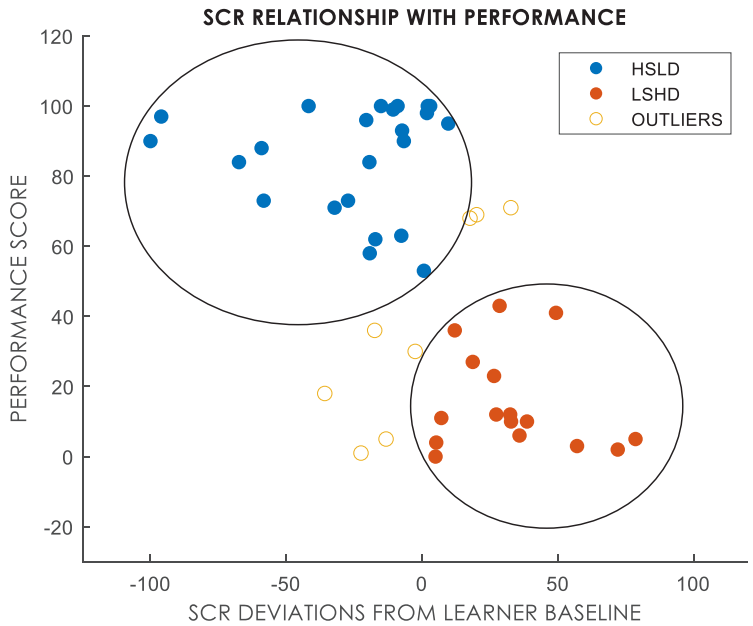

Figure 3. Clusters and patterns identified between skin conductive response (i.e. galvanic skin response or sweat) and performance data collected across multiple anesthesia residents. Two primary clusters or groups were identified, those with a higher performance rating/score and lower deviation from baseline/resting state (HSLD) and those with a lower performance rating/score and a lower deviation from baseline/resting state (LSHD). These groups represent expected trends based on our hypothesis where the HSLD group contained 23 ratings and the LSHD had a total of 17 ratings. The HSLD represents a non-stress state where the resident was comfortable and did not exhibit a stress response while achieving higher performance achieving higher performance (Mean = 85.2 SD = 15.4), the LSHD indicates a potentially stressed state where the resident achieves a lower performance score (mean = 15.9 SD = 14.0).

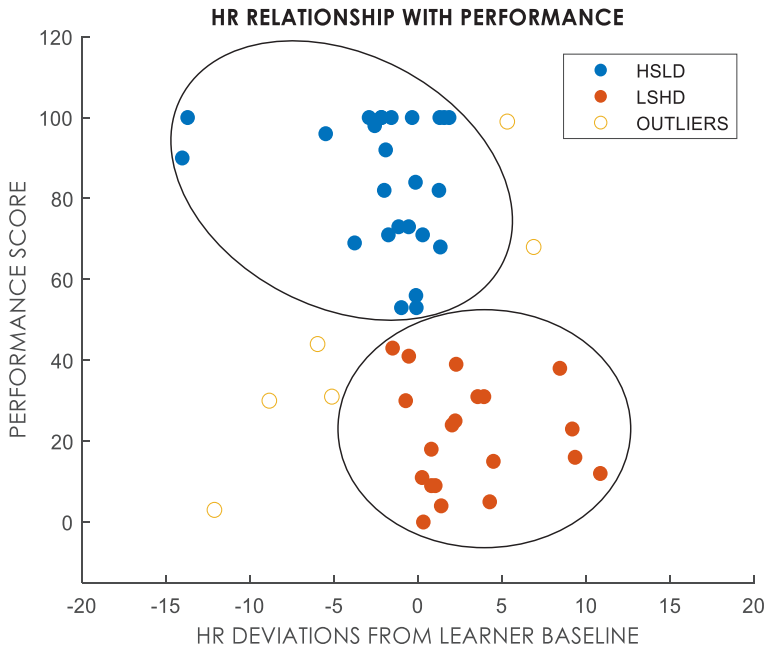

Figure 4. Clusters and patterns identified between heart rate and performance data collected across multiple anesthesia residents. Two primary clusters or groups were identified, those with a higher performance rating/score and lower deviation from baseline/resting state (HSLD) and those with a lower performance rating/score and a lower deviation from baseline/resting state (LSHD). These groups represent expected trends based on our hypothesis where the HSLD group contained 25 ratings and the LSHD had a total of 20ratings. The HSLD represents a non-stress state where the resident was comfortable and did not exhibit a stress response while achieving higher performance (Mean = 84.4 SD = 16.5), the LSHD indicates a potentially stressed state where the resident achieves a lower performance score (Mean = 21.2 SD = 13.2).

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 4

Implementation of a High-Fidelity Intraoperative Data Acquisition System in Operating Rooms for Anesthesia-Related Research

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INTRODUCTION: Rapid access to and analysis of high-fidelity intraoperative data constitute an important element in improving anesthesia-related patient outcomes, but the current Anesthesia Information Management System (AIMS) only provides low-fidelity data for bookkeeping purposes. However, collecting perioperative high-fidelity data can be obtrusive, require high levels of technical expertise, and is often cost-prohibitive, limiting its use and scalability for research applications and clinical care. Lee and Chung (2018) have described a real-time, intraoperative physiological data acquisition system (i.e., Vital Recorder) that was developed for the study of disease dynamics in the operating room (OR) that captures physiological signals and parameters (i.e., numerical data and waveforms) from multiple anesthesia devices simultaneously on a continuous basis-ideal for blinded data analysis.[1] We have described and implemented a laptop-based, real-time, high-fidelity data acquisition system (DAS) based on Vital Recorder for the existing AIMS environment for synchronous recording of intraoperative physiological data and clinical events for anesthesia research.

METHODS: We installed 10 completed DASs in 10 ORs primarily for cardiac, thoracic, neurological surgeries and other surgeries at UPMC Presbyterian and Shadyside Hospital. We targeted the high-risk surgeries that required general anesthesia (GA) and invasive monitoring (e.g., arterial blood pressure). Table 1 outlines the three essential anesthesia devices used at UPMC Presbyterian and Shadyside Hospital and the parameters of interest measured by those devices. Figure 1 depicts (1) the configurations of DAS in UPMC Presbyterian and Shadyside Hospital and (2) the structure of and data flow in DAS. The core of the system is a laptop-based archiving unit installed with Vital Recorder. The laptop computer needs the principal investigator's account to open. The DASs are only deployed to locations where need authorized access inside UPMC systems for patient data security. Once deployed, the DAS automatically records numerical and waveform data from the anesthesia devices and stores all data; however, the DAS neither stores nor transmits any data containing patient identifiers. Those data were encrypted and transferred to secure computers behind the UPMC firewall each day.

RESULTS: From October 2020 to September 2021, we recorded intraoperative high-fidelity data from around 2,000 high-risk surgeries with invasive monitoring. Figure 2 shows the proportion of different surgical cases among those 2,000 cases. Figure 3 is a screenshot of the DAS main data acquisition screen with the acquired physiologic signal waveforms and parametric values displayed in real time. These three anesthesia devices are used for all GA cases and record as many as 37 numerical parameters and 14 waveforms for fully monitored patients. The waveforms have sampling frequency up to 500hz and the numerical data has sampling frequency up to 1hz. The 2,000 cases also exhibited a median anesthesia duration of 4.4 hours and the median .vital file size was 9.1 MB. The recorded high-fidelity physiological data were synchronized with the minute-to-minute physiological data from anesthesia records. During analysis, error-free data collection was confirmed with the comparison between our recorded data and the data in the anesthesia record. Any inconsistency was due to a channel of the anesthesia devices failing to transmit data to either AIMS or our DAS during surgeries.

CONCLUSION: The study described herein has established a networked real-time intraoperative physiological signal acquisition system for multiple anesthesia devices, targeting easy access and low-cost standard data collection for anesthesia-perhaps even for other specific research categories. The DAS aims to set a preliminary standard anesthesia data collection infrastructure with little interruption to regular hospital work to overcome data heterogeneity for the benefit of research. The DAS also offers a gateway to the synthesis of clinical research and the complexities of anesthesia management. Over 12 months, high-fidelity intraoperative physiological data from 2000 GA cases of high-risk surgeries. Generally, it promotes high-fidelity anesthesia-related data acquisition for research purposes. More subsequent research about data security and storage, network encryption, data mining on high-fidelity intraoperative data, and real-time processing should be conducted.

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Figure 1: Data transmission from anesthesia devices and AIMS to data acquisition system.

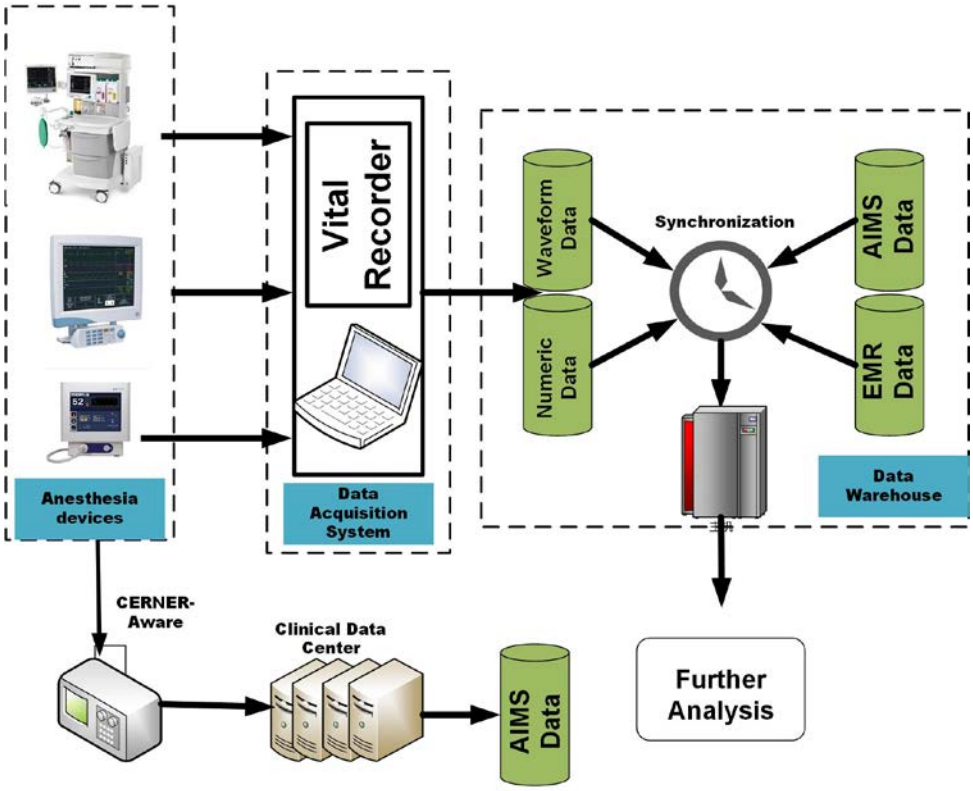

Figure 2: Surgical procedure statistics for the data from DAS.

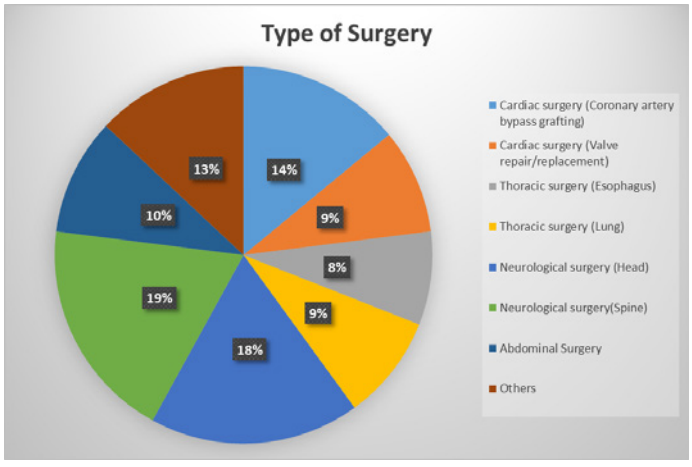

Figure 3: The completed numerical and waveform data for a 10-hour surgical case.

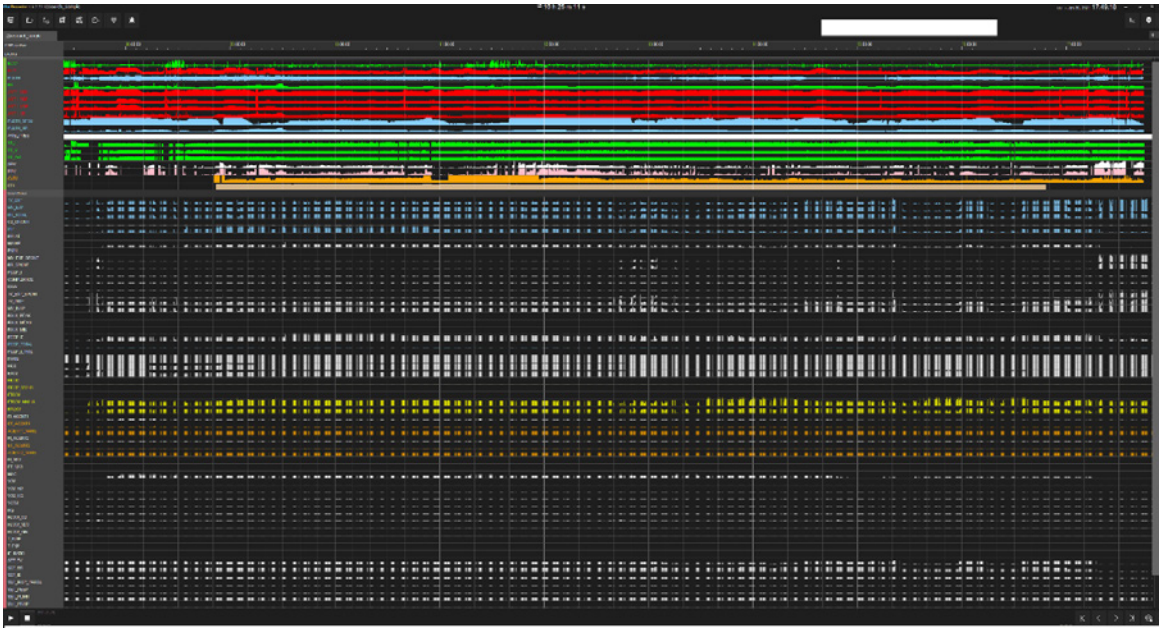

Table 1. Parameters of Interest from the physiological Monitors and aesthesia machines at UPMC Presbyterian and Shadyside Hospital

Device	Model	Manufacture	Parameters of Interest		Sampling Rate		1-Minute Data Points	
			Numerical	Wave	Numerical (Hz)	Wave (Hz)	Numerical	Wave
Physiological Monitor	B850	GE Health	16*	10**	0.5	125~500	30	30,000
Anesthesia Machine	Datex-Ohmeda	GE Health	20***	2****	0.2	25	12	1,500
Bispectral Monitor	BIS™ VISTA	Covidien	BIS index	EEGs	1	128	60	7,680

*Heart rate;[1] peripheral capillary oxygen saturation;[2] non-invasive blood pressure (systolic, diastolic, and mean);[3,4,5] temperature;[6] ST segment elevation (I, II, III, V5, AVF, AVR, and AVL);[7,8,9,10,10,11,12] invasive blood pressure (systolic, diastolic, and mean);[13,14,15] central venous pressure.[16]
**ECG (I, II, III, V5, AVF, AVR, and AVL);[1,2,3,4,5,6,7] plethysmography waveform;[8] invasive blood pressure;[9] central venous pressure.[10]
*** Fraction of inspired oxygen;[1] fraction of expired oxygen;[2] inspiratory carbon dioxide;[3] end-tidal carbon dioxide;[4] inspiratory sevoflurane pressure;[5] expiratory sevoflurane pressure;[6] fraction of inspired N_2O;[7] flow rate of air;[8] flow rate of N_2O;[9] flow rate of oxygen;[10] minimum alveolar concentration of volatile;[11] mean airway pressure;[12] peak airway pressure;[13] minute volume;[14] tidal volume (set and actual);[15,16] respiratory rate;[17] positive end expiratory pressure (PEEP);[18] positive end expiratory pressure (PEEP);[19] plateau pressure.[20]
**** Airway pressure wave;[1] capnography wave.[2]

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 5

The Impact of COVID-19 on Utilization of Telemedicine in Pain Management Clinics

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INTRODUCTION: The COVID-19 pandemic presented unique challenges on the healthcare system and required alternatives to the traditional face-to-face in person medical module[1]. These challenges have been difficult for patients with chronic pain who require frequent clinic visits for treatment and management[2]. Chronic pain remains the most common reason patients seek medical care and ranks among the ten most prevalent diseases worldwide with years lost to disability[3,4]. Untreated pain adversely affects quality of life and is linked to increased anxiety and depression[5]. In this pandemic, this problem has been compounded by lockdowns or other restrictions and fear of exposure to the virus. To circumvent some of these challenges, telemedicine has been rapidly and widely incorporated into the existing healthcare module[5]. Telemedicine eliminates travel-related costs, reduces travel time, and has the convenience of patients interacting with their providers in the comfort of their homes. However, impact of telemedicine on different population with differences in healthcare access remains to be elucidated. Also, key barriers to wider adoption such as lack of comfort with telemedicine technologies by patients and providers, as well as the impact of socio-economics factors that may influence access to telemedicine and its associated technology is yet to be fully explored. This study aims to identify disparities in telemedicine use at an urban, academic pain center.

METHODS: This retrospective study examines utilization of telemedicine at several pain management clinics catering to a diverse population during the COVID-19 pandemic within a large healthcare system (NYU Langone Health). During the COVID-19 pandemic lockdown (03/2020-06/2020), only telemedicine visits were available. In-person visits resumed in July 2020, however, telemedicine visits remain as an option. This study compared demographic information of patients that utilized in-person pain management visits (N= 10290) in the year prior to the pandemic (03/2019-02/2020), to that of patients who utilized telemedicine visits (N= 5819) during the COVID-19 pandemic (03/2020-6/2021). Telemedicine was not utilized prior to the COVID-19 pandemic in these clinics. We used SPSS statistical software to compare age, sex, visit type (new visit vs follow-up), race, ethnicity, zip code and insurance (private vs Medicare/Medicaid) distribution between the two cohorts. Data analysis is limited to purely descriptive summary statistics and inferential tests given that this is strictly an observational study.

RESULTS: Telemedicine visits were mostly utilized for follow-up (Follow-up:80.6% vs new visits:19.4%) compared to in-person visits prior to the pandemic (Follow-up:65.3% vs New visits: 34.7%). Average age± SD of patients who utilized pre-covid in-person visits vs telemedicine visits were (60.7 ± 16.3 years versus 55.5 ±15.8 years) respectively. Majority of pain management visits were by females (59.9% vs 62.6%) in the pre-COVID and telemedicine cohorts respectively. Majority of telemedicine visits were utilized by whites (Telemedicine: 66.5% vs pre-covid in-person visits 56.7%). In addition, fewer Hispanics utilized telemedicine visits as compared to in-person visits from the year prior (Telemedicine visit: 6.3% versus in-person pre-covid in person visit:14%). Majority of patients that utilized pain medicine had private insurance (73.6% private insurance vs 25% Medicare/Medicaid). There was no association between zip-code, insurance coverage type and telemedicine utilization.

CONCLUSION: This study shows that most telemedicine visits were used for follow-up visits. Telemedicine users were younger and white. Hispanics were less likely to utilize telemedicine, a possible reason could be due to language barriers. Majority of telemedicine users have private insurance, and Medicare/Medicaid patients were less likely to utilize telemedicine even though all insurance types (public and private), cover telemedicine visits. The result of this study suggests discrepancies in access to telemedicine. This could possibly be due to socioeconomic factors such as lack of access to reliable internet access, technological cost of devices and technological know-how. Future studies should be aimed at elucidating these factors.

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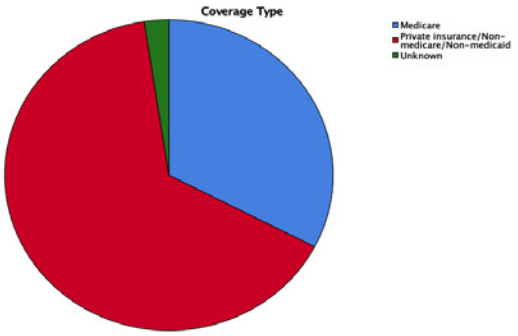
Insurance Coverage

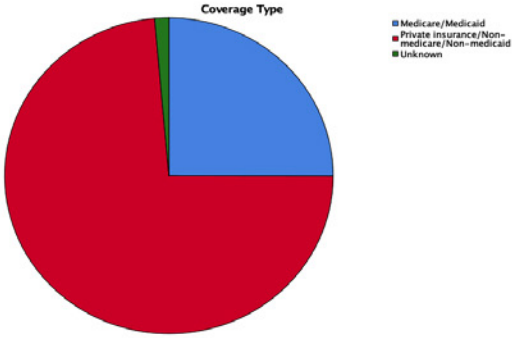
Pre-Covid visit: Insurance Coverage Type

	N	Percent
Medicare	3357	32.6
Private insurance	6685	65.0
Unknown	248	2.4
Total	10290	100.0



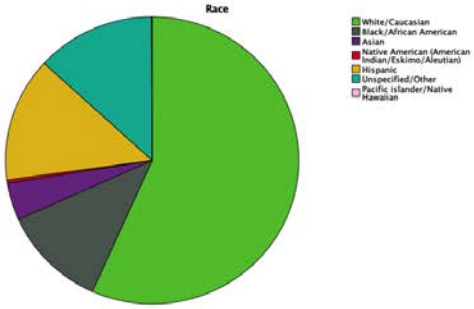
Telemedicine Insurance Coverage Type

	N	Percent
Medicare/Medicaid	1457	25.0
Private insurance/Non-medicare/Non-medicaid	4281	73.6
Unknown	81	1.4
Total	5819	100.0



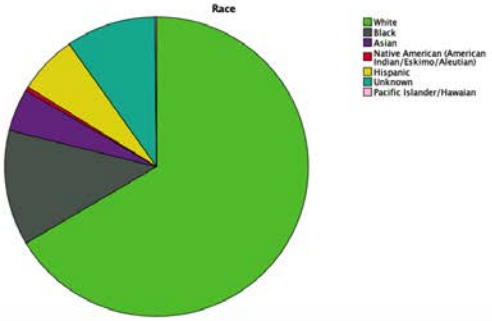
Race Distribution

Pre-Covid Race Distribution	N	Percentage
White/Caucasian	5833	56.7
Black/African American	1191	11.6
Asian	431	4.2
Native American (American Indian/Eskimo/Aleutian)	38	0.4
Hispanic	1440	14
Unspecified/Other	1350	13.1
Pacific islander/Native Hawaiian	7	0.1



Telemedicine Visit Race Distribution

	N	Percent
White	3868	66.5
Black	723	12.4
Asian	266	4.6
Native American (American Indian/Eskimo/Aleutian)	26	.4
Hispanic	368	6.3
Unknown	559	9.6
Pacific Islander/Hawaiian	9	.2
Total	5819	100.0



TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 6

Satisfaction with Telemedicine Among Anesthesiologists During the COVID-19 Pandemic

Uchenna O Umeh[1], Fiona Roediger[1], Germaine Cuff[1], Yevgeniy Romanenko[1], Ansara M Vaz[1], Arthur C Hertling[1]

[1]NYU Langone Health, New York, NY

INTRODUCTION: The COVID-19 pandemic has rapidly changed the way that health care providers interact with patients, particularly through the widespread implementation of telemedicine. Previous studies in other medical specialties have examined the role of telemedicine and physician satisfaction with the modality, but no such studies have been reported in the field of anesthesia. The purpose of the study was to evaluate the scope of use and satisfaction with telemedicine among anesthesiologists who were ASA and ESAIC members.

METHODS: We developed a survey that was sent out to anesthesia providers through the European Society of Anaesthesiology and Intensive Care (ESAIC) on 5/30/21 and the American Society of Anesthesiology (ASA) on three consecutive Saturdays (8/7/21, 8/14/21 and 8/21/21). The survey comprised three major sections and examined, (1) the characteristics of the anesthesia providers, (2) the settings within which they were using telemedicine, and (3) their satisfaction with the experience. We performed a two-sample t-test assuming unequal variances to determine if there was a significant difference in satisfaction for those who used telemedicine prior to COVID-19 compared to those who started using it during the pandemic.

RESULTS: Responses with inappropriately entered values were omitted from the analysis of those questions. Out of 708 responses received, 35.5% of the respondents utilized telemedicine, and of those 69.2% did not use it prior to the COVID-19 pandemic. 97.9% were physicians, with 55.6% from the United States and 35.2% from Europe. 52.1% practiced in an academic medical center, 33.0% practiced in a non-teaching hospital, 8.5% practiced in a Surgicenter, and 4.4% were in an office-based practice. 84.6% of respondents specialized in anesthesiology, 3.7% specialized in pain medicine, 9.0% practiced both anesthesiology and pain medicine, 1.3% were specialized in ICU/critical care, and 1.0% were specialized in both anesthesiology and ICU/critical care. 51.9% of providers were using telemedicine primarily preoperatively, 5.3% postoperatively, 31.6% in a pain clinic/office, and 3.2% in the ICU. The average duration of visits was 11-15 minutes in 29.1% of respondents and 16-20 minutes for 28.6%. Telemedicine visits were conducted through a wide variety of platforms, including 32.9% through the hospital EMR, 25.0% through Zoom, 11.0% using FaceTime or a smartphone, and 7.5% using Doximity. The overall satisfaction with telehealth visits was 70.4% +/- 25.3%. Satisfaction with developing patient rapport was 68.6% +/- 24.9%. Satisfaction with conducting a physical exam and airway exam was 34.5% +/-30.4% and 43% +/- 33.1%, respectively. We found that providers who were using telemedicine before the pandemic had higher rates of satisfaction across all the subcategories. Overall satisfaction for providers who used telemedicine before COVID-19 was 76.2% +/- 22.8% compared to 67.7% +/- 26.4% for those who did not ($p = 0.029$). 86.3% intend to continue using telemedicine after the COVID-19 pandemic.

CONCLUSION: Physician implementation of telemedicine increased rapidly since the onset of the COVID-19 pandemic. Among anesthesia providers, it was used in a broad range of practice settings. Overall satisfaction among users was high, especially with rapport building. Anesthesiologists were less likely to be satisfied with the ability to perform physical exams and airway exams through this modality. Providers who were using telemedicine before the pandemic have consistently higher rates of satisfaction across all subcategories than those who were not using it before the pandemic. This could be due to multiple reasons, including more familiarity with the software and the fact that they chose to use telemedicine instead of being required to do so by outside circumstances. Overall, satisfaction among users was high and the majority of practitioners plan to continue to use telemedicine in their practice.

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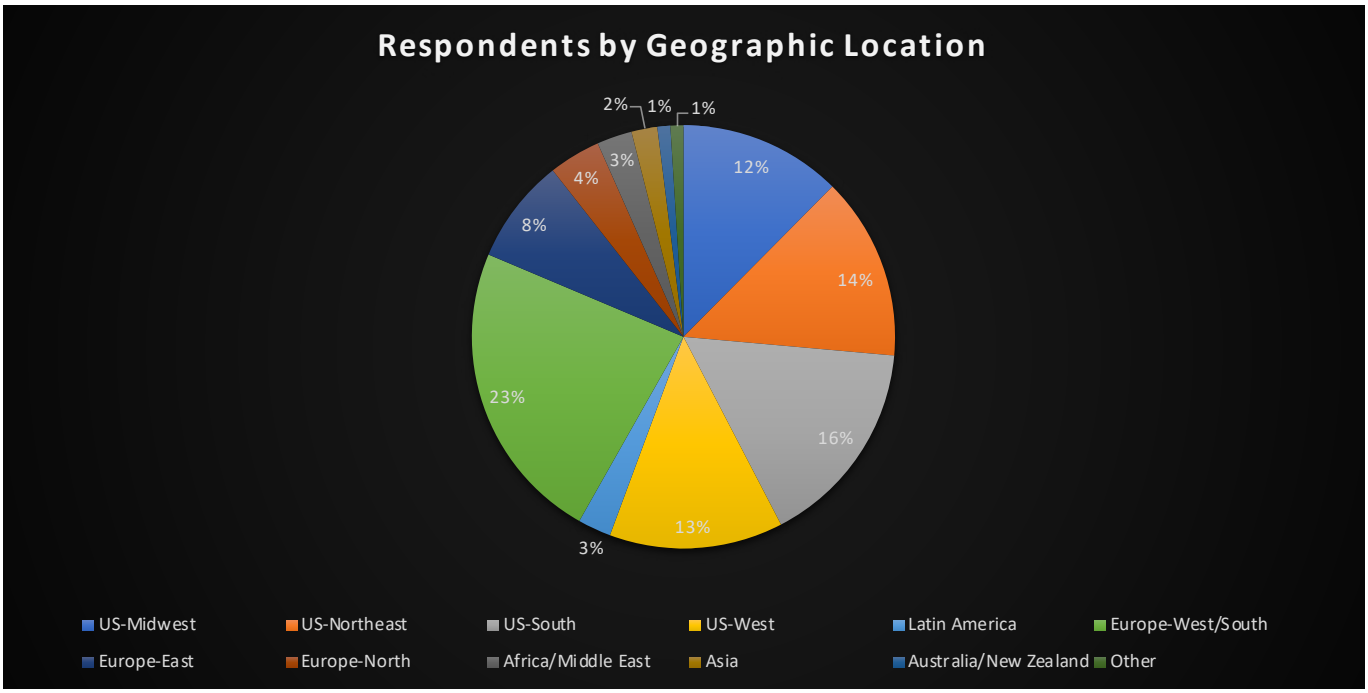

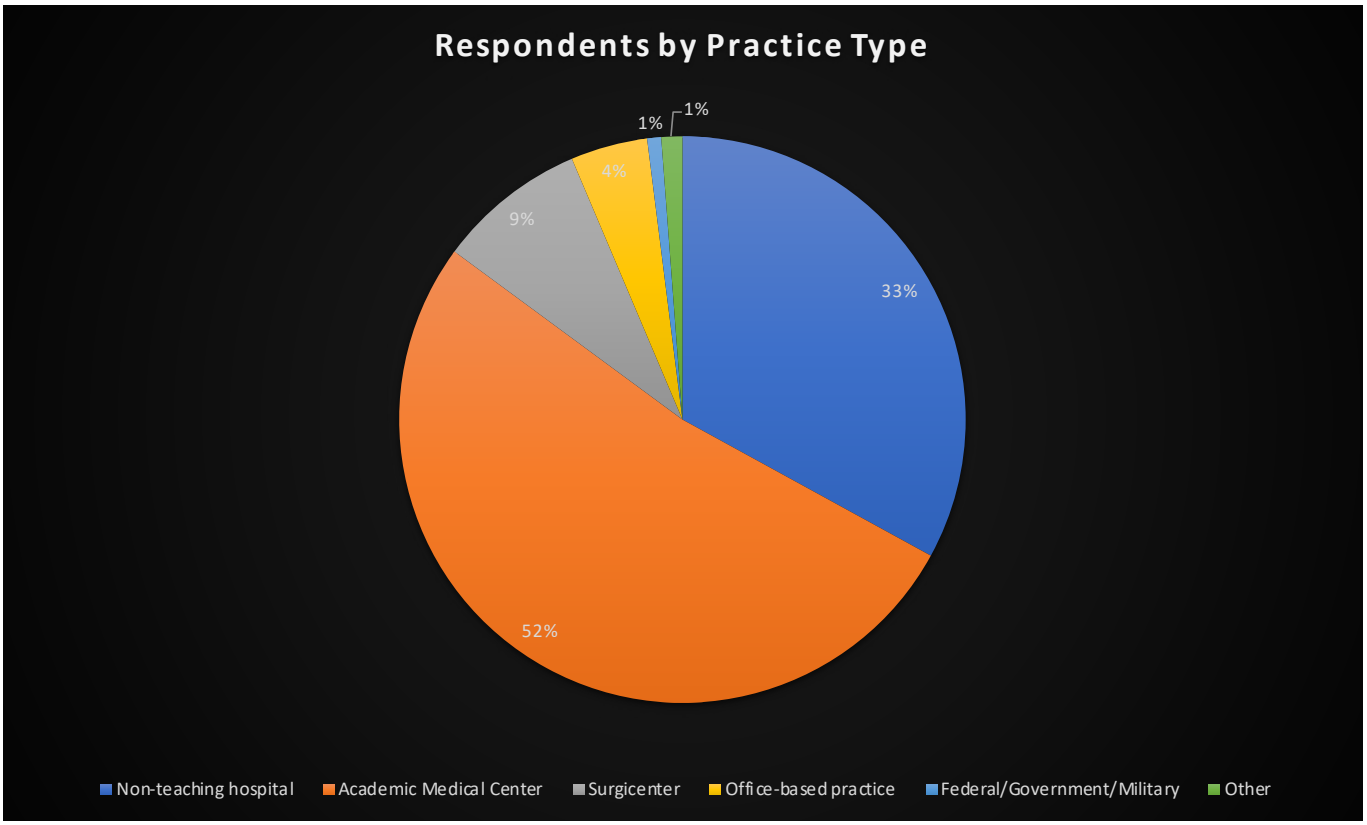

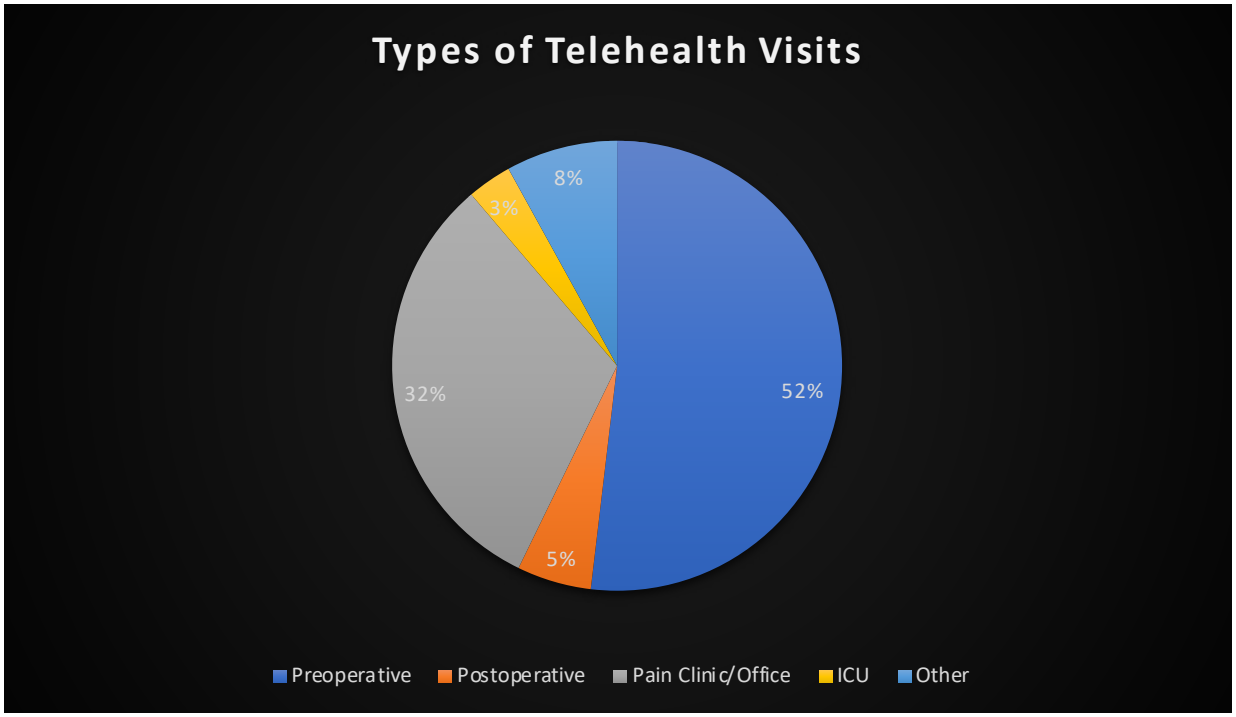

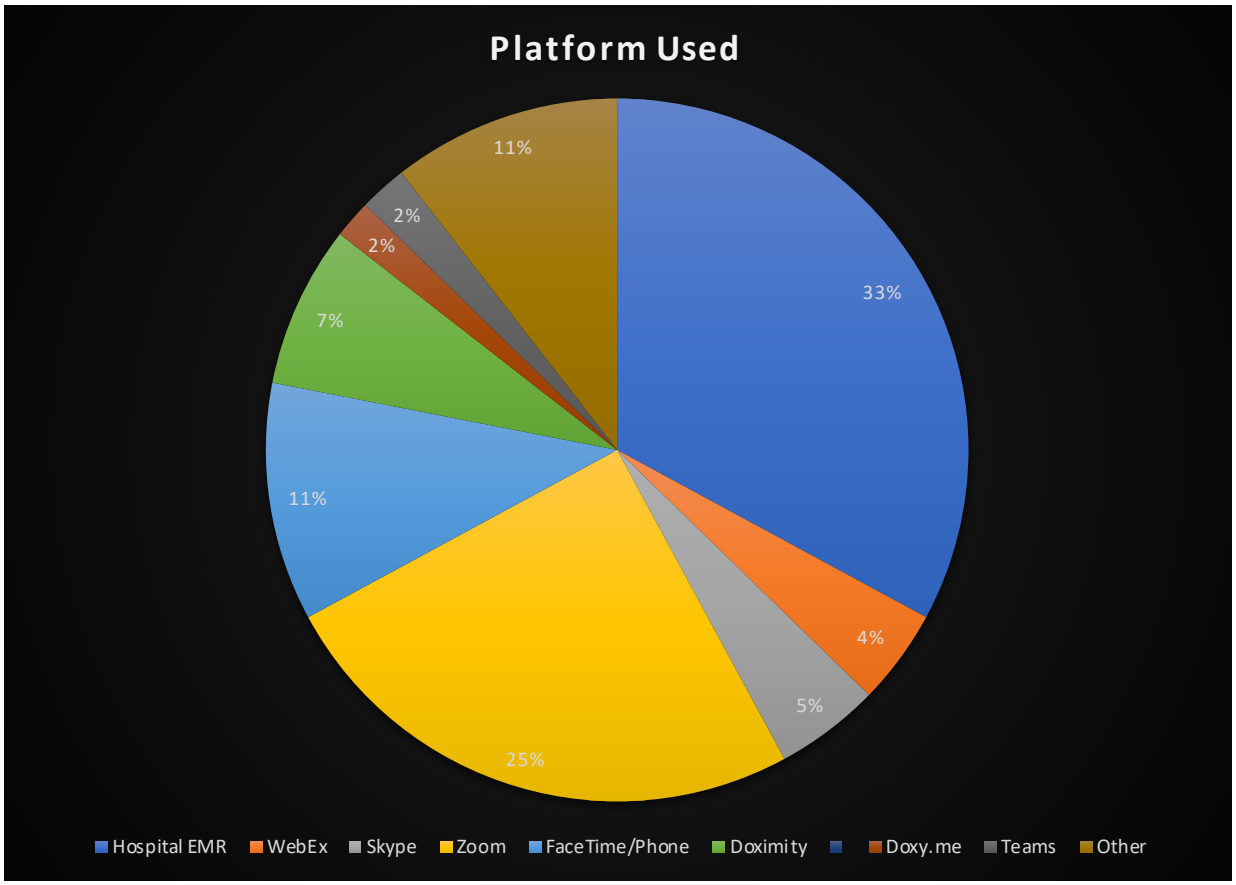

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 7

Generalizing Machine Learning Models from Medical Free Text

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INTRODUCTION: Research of medical applications using machine learning (ML) models have become increasingly common, but investigation into optimal methods of development for use outside of the institution on which they were trained is sparse[1]. Generalizability can theoretically improve with higher quality and more standardized model inputs. As medical free text data is often fraught with spelling, translational, grammatical, and copy-forward errors, improvement of this data's quality is considered critical for optimal ML model performance. While medical free text may contain 10% spelling error rates[2], studies of pre-processing are limited in both scope and size[3]. Understanding data discrepancy could help guide ML adoption at outside institutions. In this study, we investigate generalizing ML models using medical free text for anesthesiology Current Procedural Terminology (CPT) code prediction. First, we analyze the utility of text preprocessing using the medically focused preprocessing method cSpell[4]. Second, we use probability distributions and clustering techniques to group and predict ML performance at external institutions prior to expanded model implementation. Finally, we evaluate optimal pathways for implementing models at new sites with considerations on when to retrain on new data.

DATA: Utilizing data from the Multicenter Perioperative Outcomes Group, we identified all operative cases from 44 participating U.S. institutions[5-6]. Text Processing: Misspelled words were identified using context insensitive word correction by NIH Unified Medical Language System (UMLS) cSpell. 'Minimal' cleaning consisted of lowercasing, stripping excess white space, normalizing numbers, and removing punctuation and special characters. 'Maximal' cleaning included all of minimal cleaning and in addition included replacing identified misspelling with tool automated suggestions. 'Acronym' cleaning consisted of expanding physician-validated medical acronyms identified by the UMLS Specialist lexicon tool. Machine Learning (ML) Models: We created deep neural network ML models to predict anesthesiology CPT codes using procedural text[7]. Five-fold cross validation was used and models were evaluated with holdout testing data accuracy. A composite Kullback-Leibler Divergence (KLD) value was created for each institution using CPT code and procedural text distributions. K-medioid clustering and multidimensional scaling were then used to create a comparative 2-dimensional representation of KLD between institutions (Figure 1). Generalization by Institution: Independent ML models were trained and tested using each cleaning method by training on one or more institutions and testing on one or more remaining institutions.

RESULTS: From an initial 3,564,947 cases, 48 anesthesia CPT codes were shared across all 44 institutions, resulting in a final dataset of 1,607,393 cases. Within this dataset, approximately 64,248 unique terms were used in procedural texts, 10% of which were identified as misspelled. Nine percent of cases contained text with at least one misspelled word. Vocabulary varied considerably between institutions with an average overlap of 44.2% (9.0 - 93.2%, median 45.0%) (Figure 2). Preprocessing using 'maximal' cleaning reduced vocabulary size by 20% with a 7% increase in vocabulary match between any two institutions, though ML model accuracy was not substantially affected (+0.2%, IQR [-0.35%, 0.71%] average improvement). 'Maximal' + 'Acronym' preprocessing showed a pairwise ML performance improvement of +0.5% (IQR [-0.32%, 1.06%]).There was a negative correlation between accuracy and KLD for 100% of institution pairs (-3.5% average accuracy per KLD distance from the training institution, +/- 1.5%), with an overall trend of -5.0% (Figure 3). Adding institutional data to training improved accuracy 12.7% +/- 6.8% at that site, while adding other sites showed minimal change (0.1% +/- 0.3%).

CONCLUSION: Cleaning medical free text prior to ML model development may not yield significant improvement in model performance. Single institution ML models show greatest generalizability to external institutions by retraining with data from that external site. When retraining is infeasible or prohibitive, the strong correlation between KLD and accuracy suggests that measures of probability distributions and clustering techniques can aid identifying model performance apriori and provide a path for creating ML models with aspirations of expansion to external sites.

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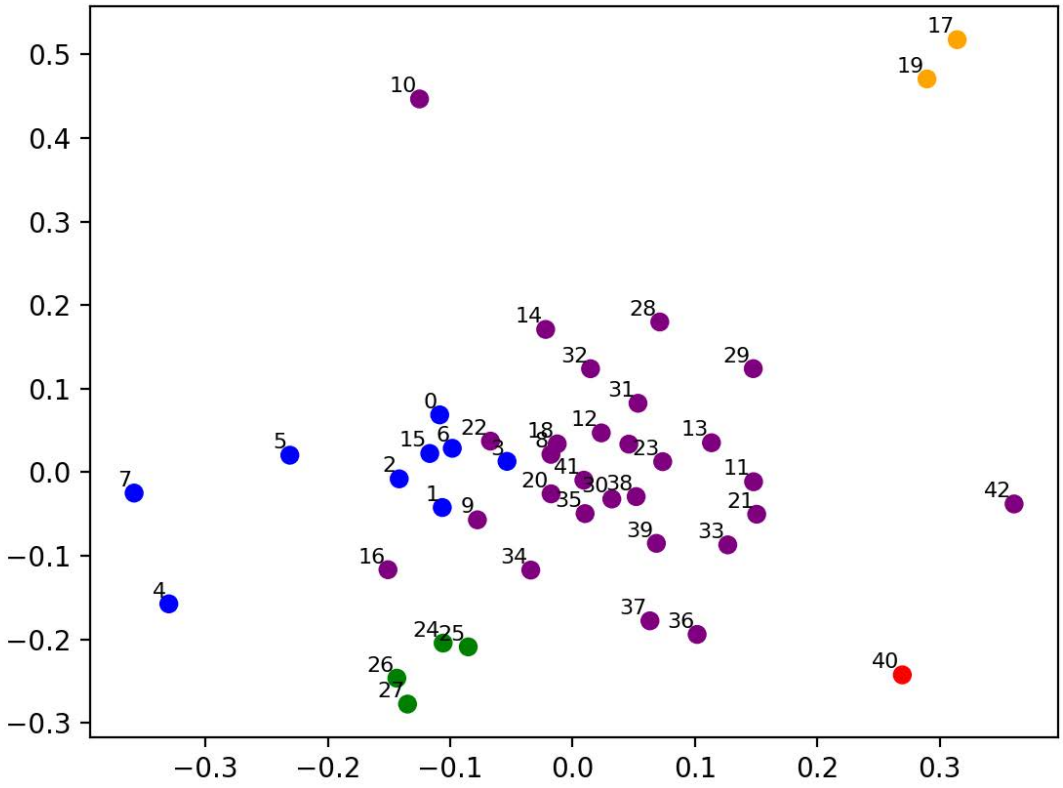

Figure 1: K-medioid Institutional Clustering. Each dot represents a single institution. The composite KLD score between institutions is represented in a 2D-cartesian plane utilizing multidimensional scaling. K-medioid clustering yields 5 distinct clusters identified by color. Institutions that are far apart have a large KLD indicating significant anesthesiology CPT and/or vocabulary differences.

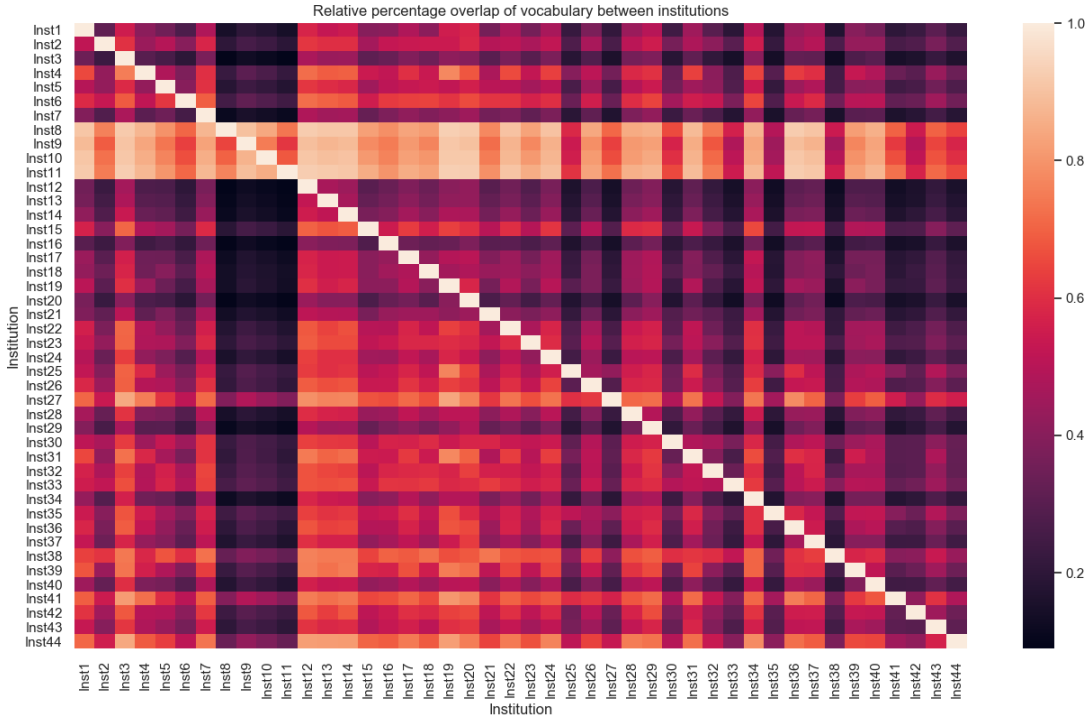

Figure 2: Institutional Vocabulary Overlap. Heat map showing vocabulary overlap between individual institutions (x and y axes). Intersections depict a heat map translation of the % overlap in vocabulary between institutions as: (number unique vocabulary in x-axis institution that matches to y-axis institution vocabulary) / y-axis institution vocabulary.

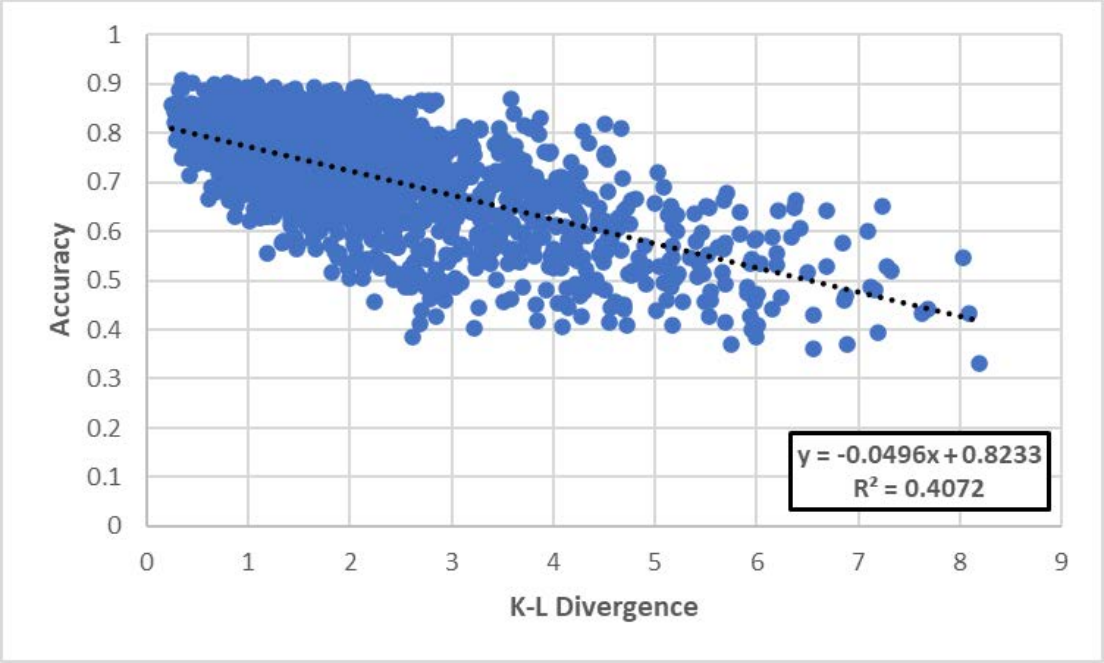

Figure 3: Single Institution Pairwise Comparison vs KLD. Each dot represents the performance of an ML model trained on an institution A and tested on a different institution B. This process was repeated for all pairs of institutions (except where A = B). This figure shows a negative correlation between performance and KL-Divergence between the institution pairs.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 8

Comparison of Onset of Neuromuscular Blockade with Electromyographic and Acceleromyographic Monitoring: A Prospective, Randomized Trial

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INTRODUCTION: Neuromuscular blocking agents (NMBAs) are a group of medications used in anesthesia to facilitate endotracheal intubation and optimize surgical conditions[1]. Reliable devices that quantitatively monitor the level of neuromuscular blockade (NMB) are crucial. Electromyography (EMG) and acceleromyography (AMG) are the two monitoring modalities used in the clinical practice. TetraGraph (Senzime AB, Sweden) is an EMG-based quantitative monitor that measures electrical activity within the muscle following stimulation. In comparison, TOFScan (Draeger Medical Inc., Telford, PA) is an AMG-based quantitative monitor that measures the muscle group of interest[2]. This study compares the onset of action of NMB, defined as a train-of-four count (TOFC) equal to 0, between the two devices while evaluating intubation conditions.

METHODS: After IRB approval, 15 adult patients scheduled for elective surgery requiring NMB were screened and enrolled after written informed consent. Prior to induction of anesthesia, TetraGraph and TOFScan electrodes were placed separately over the ulnar nerve and the thumb randomly assigned to their dominant or non-dominant hand. Intraoperative NMBA dose was standardized to 0.5 mg/kg of rocuronium. After baseline measurements were obtained, objective measurements were recorded every 20 seconds and intubation was performed using GlideScope only either device displayed a TOFC=0. The anesthesia provider was then surveyed about intubating conditions. Shapiro-Wilk statistics were used to conduct normality test. Results showed that data was not normally distributed, for that reason non-parametric tests were performed. The mean time difference between devices was determined with Wilcoxon rank sum test and chi-square statistic was performed for intubating conditions.

RESULTS: Eight males and seven females (58 ± 9 yr) (Table 1) were enrolled in the study. The onset time of NMB was 164 ± 54 (SD=98) seconds in TetraGraph, and 152 ± 34 (SD=61) seconds in TOFScan (p=0.563). TetraGraph displayed a TOFC=0 in 4 patients (26.7%) before TOFScan, while TOFScan displayed a TOFC=0 first in 7 patients (46.7%). Both devices reached TOFC=0 at the same time in 4 patients (26.7%) (p=0.549) (Table 2). During intubation, jaw relaxation was easy in 12 patients (80%) and fair in 3 (20%) (p=0.020). Vocal cord position was abducted in 14 patients (93.3%) and intermediate in 1 (6.7%) (p=0.001). Vocal cord movement was seen only in 1 patient (6.7%) (p=0.001). We did not detect patients with airway reaction or movement of the limbs during intubation (Table 3).

CONCLUSION: This study demonstrated that TOFScan measured a TOFC=0 in more patients before TetraGraph, however there was no significant difference between them. Significant variability exists between patients following a standardized dose of rocuronium, demonstrating the need for quantitative monitoring. A TOFC=0 in either device was a useful indicator for intubating conditions.

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Table 1. Demographics.

Variables	Categories		
Gender	Male	8	53.3%
	Female	7	46.7%

	Mean	Std. Dev.
Weight	84.08 ±8.95	16.15
BMI	28.13 ±2.88	5.20
Wrist Circumference	18.27 ±1.52	2.75
Age	58.67 ±9.51	17.17

Table 2. Number of times each device first reached zero.

	Frequency	%	p-value
TG	4	26.7	0.549
TS	7	46.7	
Both Devices	4	26.7	

TG: TetraGraph; TS: TOFScan.

Table 3. Intubating conditions assessment.

	Easy	Fair	Difficult	p-value
Jaw relaxation	12 (80%)	3 (20%)	0 (0%)	0.020
	Abducted	Intermediate	Closed	p-value
Vocal cord position	14 (93.3%)	1 (6.7%)	0 (0%)	0.001
	None	Moving	Closed	p-value
Vocal cord movement	14 (93.3%)	1 (6.7%)	0 (0%)	0.001
	None	Diaphragm	Sustained	p-value
Airway reaction	15 (100%)	0 (0%)	0 (0%)	0.000
	None	Slight	Vigorous	p-value
Movement of the limbs	15 (100%)	0 (0%)	0 (0%)	0.000

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 9

Train of Four Hysteresis, Assessed by Electromyography, Following Spontaneous Recovery from Neuromuscular Blockade with Rocuronium

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INTRODUCTION: Following administration of a neuromuscular blocking agent, the ratio of the amplitudes of the fourth to the first twitch (TOFR) following train of four stimulation is considerably higher during onset of neuromuscular blockade (NMB) than during spontaneous recovery, when measured at the same level of depression of the first twitch (T1) relative to the control value of T1 (Tc).[1,2] This pattern of hysteresis, assessed via mechanomyography, has been observed for atracurium, cisatracurium, and pancuronium.[2,3] The phenomenon can be explained by modeling the non-equilibrium state of diffusion of the neuromuscular blocking agent from the capillaries into the muscle.[4] In other words, because diffusion takes time, there is a lag in the concentration of the neuromuscular blocking agent at neuromuscular junctions that are at greater distances from the capillaries than those closer. There is increasing clinical use of quantitative monitoring of the neuromuscular blockade. However, nearly all of the focus has been on recovery of the TOFR to ≥90% before tracheal extubation.[5] We conducted this study to quantitate TOF hysteresis following administration of rocuronium. We also compared the results (obtained using electromyography [EMG]) to previous studies that used mechanomyography (MMG). Such information might be useful to interpret the TOFR values that these monitors display during block onset. We chose to conduct the study using EMG rather than acceleromyography (AMG) because the AMG often exhibits reverse fade (TOFR >1.0) and is less reliable when assessing recovery,6 and MMG devices are not clinically available.

METHODS: We obtained the raw monitor output files for N=14 patients who received a single dose of rocuronium from a recent intraoperative study comparing the TOFR from an EMG device (TetraGraph, Senzime AB, Sweden) to an AMG device (TOF-Watch SX, Organon Teknika BV, The Netherlands).[6] Full spontaneous recovery of the TOFR was intended by protocol, resulting in a wide range of TOFR values. The control T1 (Tc) was obtained immediately before rocuronium administration; the amplitudes of the first twitch (T1) and fourth twitch (T4) were determined at 15-sec intervals. Onset data were analyzed from 0 to 10 minutes following the first dose of rocuronium. Recovery data were analyzed from the return of the T1/Tc to 0.025 until the end of monitoring. We calculated the corresponding values of the TOFR (T4/T1) during onset and recovery at fixed values of the T1/Tc between 0.95 and 0.05 using linear interpolation.

RESULTS: TOF hysteresis for a typical patient is shown in Figure 1. During the onset of NMB, the TOFR lagged behind the decrease in the T1/Tc. In contrast, during recovery, the opposite pattern was observed. Differences between the TOFR during onset and the TOF during recovery at the same levels of T1/Tc are shown in Figure 2. Although there was heterogeneity among patients, on average, the degree of hysteresis initially was fairly constant, but as the depth of NMB increased (decreasing T1/Tc), the magnitude of the hysteresis decreased modestly. Hysteresis following rocuronium (mean[standard error]) was similar to that for vecuronium at various levels of T1/Tc (Table)

Figure 1. TOFR hysteresis from a typical study patient. The green circles represent the TOFR during onset and the red circles the TOFR during spontaneous recovery at the indicated level of T1/Tc.

Figure 2. TOFR hysteresis for all study patients. The dotted lines represent the difference between the TOFR during onset - recovery for the same T1/Tc. The blue line is the mean with error bars indicating the standard error of the mean.

CONCLUSION: The pattern of TOFR hysteresis seen with rocuronium, as assessed by EMG, is similar to that previously observed for vecuronium. During onset of neuromuscular blockade, the T1/Tc should be relied on to assess the extent of neuromuscular blockade to guide the timing of laryngoscopy, not the TOFR, as the latter lags considerably behind. Because of the wide differences in hysteresis among patients, we cannot provide a quantitative recommendation to guide the interpretation of the TOFR during the onset of NMB. In contrast, interpretation of the TOFR during recovery is straightforward. TOFR hysteresis assessed using AMG may differ from our findings because that technique

overestimates the extent of recovery of the TOFR, and inverse fade may be observed.[6]

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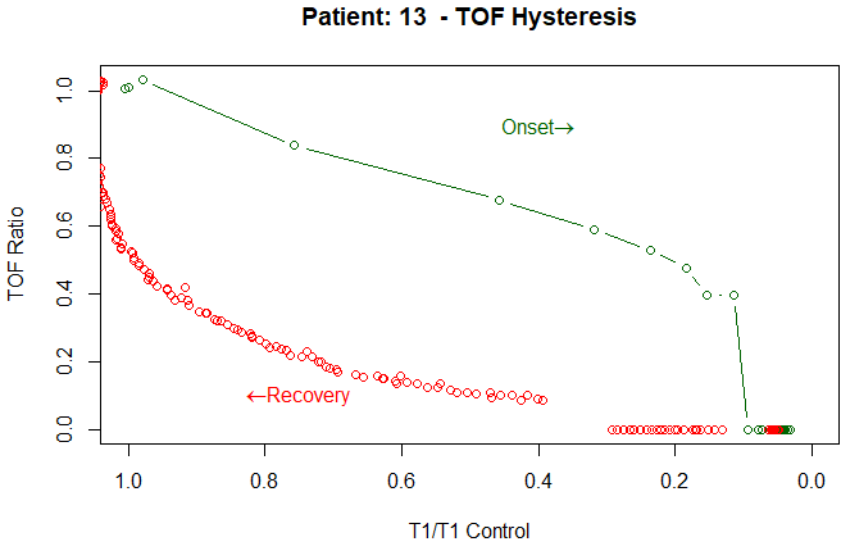

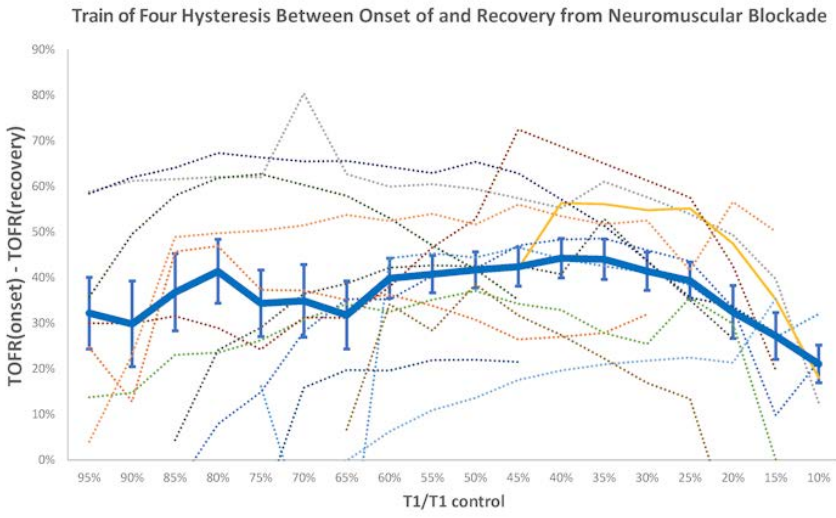

Table. Comparison of the differences between the TOFR during onset – recovery at various levels of T1 depression (T1/Tc).

T1/Tc	Atracurium[2]	Vecuronium[2]	Rocuronium
75%	35%	43%	34.3% (7.0%)
50%	31%	46%	41.6% (3.9%)
25%	20%	42%	39.3% (4.1%)

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 10

SecuriTEE™ A securement device for transesophageal echocardiography probes

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INTRODUCTION: Our cardiovascular anesthesia (CVA) team identified a need for a transesophageal echocardiography (TEE) probe handle securement device during cardiovascular operating room (CVOR) and cardiac catheterization (Cath) lab cases. Historically, we used a stylet to secure the TEE probe on the OR custom made rack (See image 1). The stylet was not an ideal product for securing the TEE probe and limited the ability to adjust the position of the probe. We sought to improve the current TEE securement solution by following a user-centered innovation process to help discover, develop, and validate a versatile and safe solution to create securiTEE™ (See Image 2 and 3). Background Based on concerns from CVA for a reliable and safe TEE probe securement solution during cardiac cases, the CVA team began the user-centered innovation process to discover a universal solution to secure all models of TEE probes in both the cath lab and CVOR settings. Literature supports incorporating frontline clinicians familiar with the 'need' and workspace during the innovation process to ensure design goals are met.[1-3] Following a stepwise approach to innovation, we first identified design goals based on CVA user feedback on an ideal securement solution. Next we searched for available products to fit the 'need' which yielded the Brooker Probe Holder and CIVCO TEE Transducer Holder.[4,5] Neither would fit our design goals as they are not universal to all TEE probes, nor did they fit on the CVOR rack or anesthesia tree. Based on these findings the team decided to create our own solution to fit our design goals utilizing frontline feedback throughout the entire design process.

METHODS: The project team incorporated a user-centered innovation process which included prototyping, 3D printing technology, interdisciplinary collaboration, user feedback, and quality improvement tools to develop the securiTEE™ (See Figure 1).

RESULTS: The securiTEE™ was surveyed (N30) by anesthesia providers and cardiologists who used it in either the CVOR or the cath lab. The results showed:
1. 100% found no safety issues
2. 100% recommended to their colleagues
3. 93.3% felt the securiTEE™ provided more flexibility for probe positioning in the CVOR and cath lab
4. 100% felt the device was easy to load, unload, and properly secure the TEE probe handle in the cath lab and CVOR
5. 100% felt the device was durable and easy to clean

We have a patent pending and are partnering with a medical supply company to make the design available for other institutions.

CONCLUSION: We used the innovation process to create our own solution to the need for a safe TEE securement device. We worked with frontline clinicians to validate the device design and received appropriate legal steps to implement the securiTEE™ into the clinical setting. We learned there is high value in incorporating user-centered design when developing a viable solution. (2) Following a step wise approach to innovation has led to a well-received design that we are now using in our CVORs and cardiac cath labs daily.

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Image 1

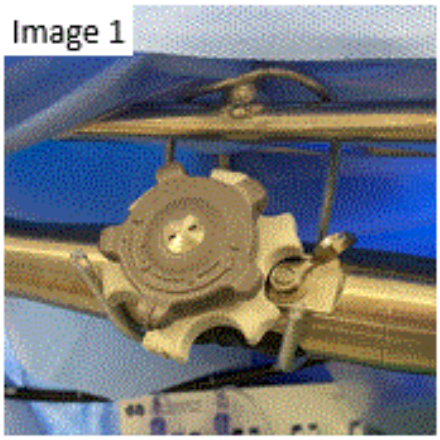


Image 2

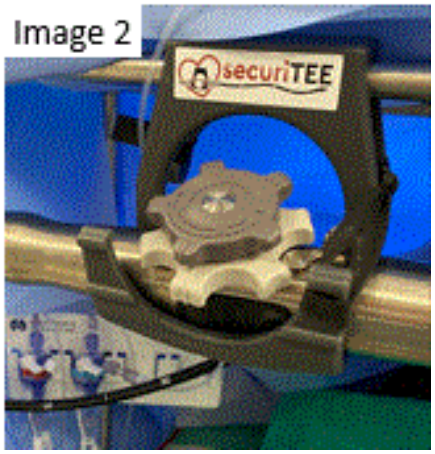


Image 3

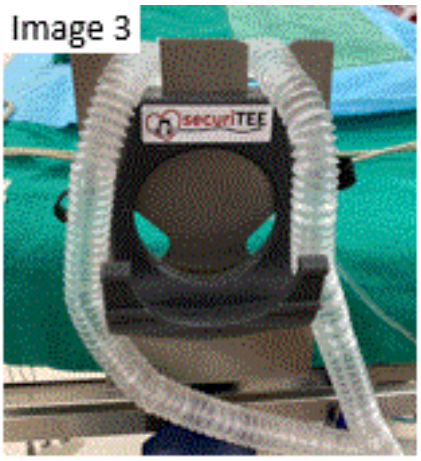


Image 4

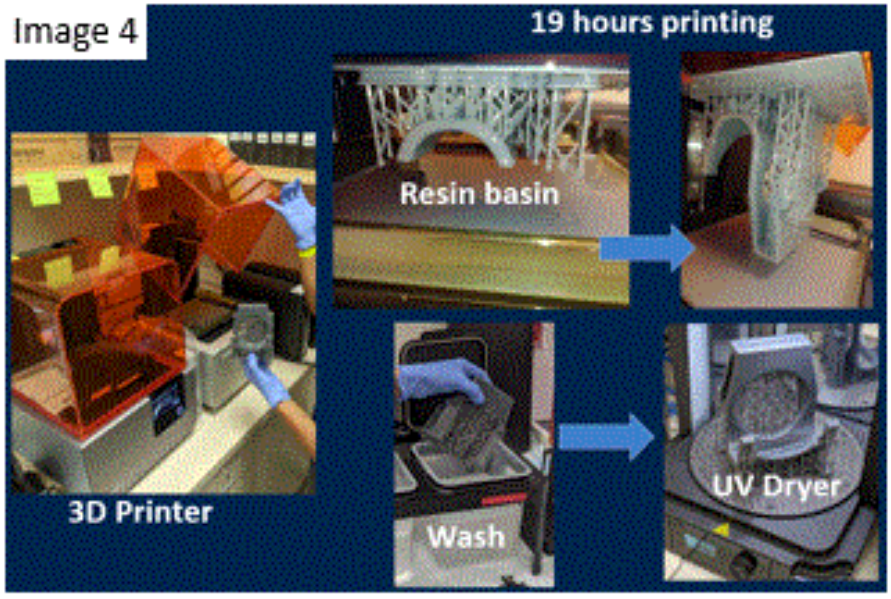
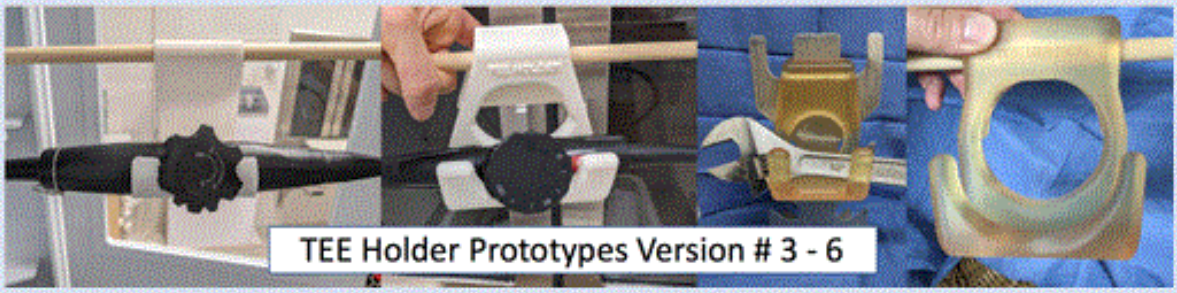


Figure 1: The Innovation Process

Phase 1: Discover and validate the "need"
CVA Identified new design goals and Quality indicators:

- Safe, durable, easy to clean, simple attach/detach for emergencies
- One device that works in the CVOR rack and on the anesthesia tree for cardiac catheter lab

Phase 2: Investigate available product to solve identified new design goals:
Project design goals not readily available on the market



Phase 3: New product development with user feedback
The goal in this stage is creating prototypes to **test different materials, shape, size, and fit** for ALL TEE control handles at TCH.

- Create mock ups and evaluated "rough" prototypes in simulated environment
- Began collaboration with TCH Radiology Research to develop 3D printed prototypes (see Image 4)
- Received funding and created name and logo in preparation for new product pilot
- With the seventh iteration, we felt we hit all our design goals
- Submitted "Indications for Use" to TCH legal(compliance, regulatory) to gain approval to pilot the design in our institution which was approved
  - IRB/FDA registration not required as it does not touch a patient
- Anesthesia research core created redcap survey
  - QR code on back of securiTEE™
- 3D Printed 8 to be used in the pilot, one for each CVOR and cath lab

Phase 4: New Product Pilot and Redcap Survey
The goal of the Pilot was to evaluate if we met our design goals, identify any safety issues, establish workflow using the device, storage and cleaning, and identify any unexpected outcomes.

- Surveyed one month of securiTEE™ data in CVOR and cath labs
- Established Anesthesia tech team leads to help implement pilot and ensure prototypes are available for clinicians
- Established workflow, cleaning and storage

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 11

Integrated, Immersive, and Interactive Printed Human Heart for Learning Transesophageal Echocardiography

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INTRODUCTION: Perioperative transesophageal echocardiography (TEE) has become an essential tool during the management of operative patients. Recently, digital 2D heart models and hands-on TEE simulators have emerged as popular teaching tools[1]. However, these educational tools remain limited as flat images built from idealized human hearts with limited visualization of intracardiac structures and associated anatomies[2]. Therefore, as an initial step towards creating an integrated, immersive, and interactive mixed realities platform in which physical and virtual models are merged, we describe the computational modeling and printing of a 3D human heart sliced to mimic the ASE-recommended intraoperative TEE views.

METHODS: Following consent, a human heart was explanted during organ recovery, perfusion-fixed in an end-diastolic state and gelled to maintain chamber integrity. MRI was performed using a T1 weighted protocol with 100μm resolution. Anonymized datasets were imported into post-processing software (Mimics® Innovation Suite, Materialise NV, Leuven, Belgium) for segmentation and generation of computational 3D models. Resulting models were exported to Meshmixer (Autodesk Inc, San Rafael, CA) for further editing and then to 3-Matic (Materialise NV, Leuven, Belgium) where the heart was sliced into echo planes corresponding to 10 of the 28 ASE views and printed on a Ultimaker 3 Extended printer using clear polycarbonate. Magnets were inserted to hold reciprocal pieces together.

RESULTS: We successfully developed a 3D model of a heart from a 44 year-old female patient. Five hearts were printed, each with 2 of the 28 ASE recommended views for a total of 10 views as follows; four chamber matched (Figure 1) with two chamber (Figure 2); long-axis (LAX) matched with aortic valve short-axis (SAX), transgastric (TG) mid papillary SAX (Figure 3) matched with bicaval; TG right ventricle inflow matched with deep transgastric five chamber; mitral commissural matched with trans-atrio-ventricular groove. Models are portable and currently being used for didactic purposes in the cardiac operating rooms.

CONCLUSION: Herein, we describe a viable and reproducible way of scanning, segmenting and printing a human heart in 10 of the 28 recommended ASE views for TEE. In so doing, we have created value by developing 3D models of a human heart with detailed intracardiac structures and the ability to define relative anatomy. We consider this a foundational step toward developing an integrated, immersive, and interactive mixed realities platform for educating medical students, residents, fellows and junior faculty caring for cardiac surgical and procedural patients. In the future, we will generate detailed models for additional human hearts that represent the inherent anatomic and pathologic variability we see in our patients.

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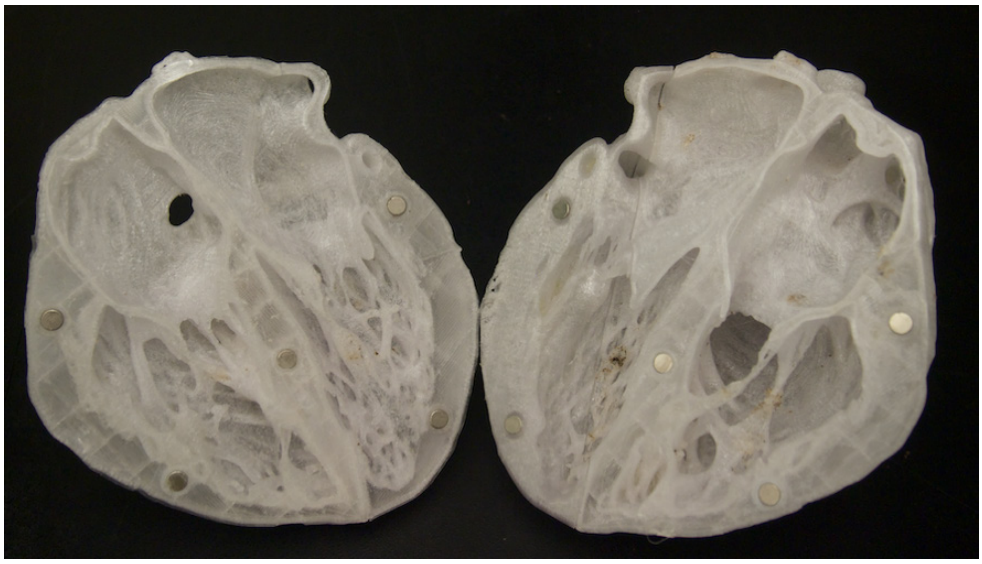

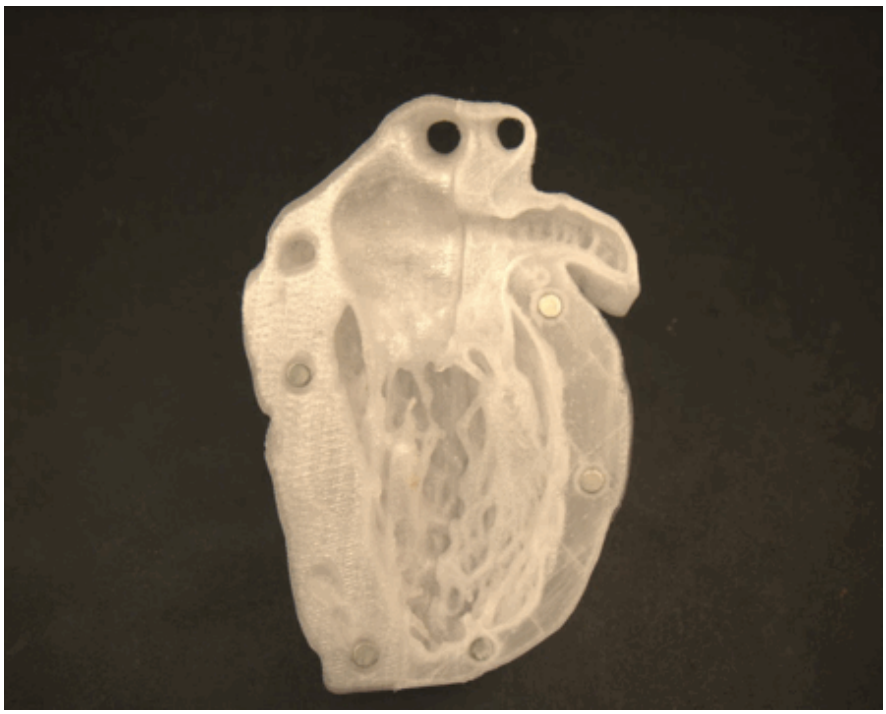

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 12

Is the Eleveld PK Model better than the Schnider and Schuttler PK Models in Capturing the Inter-individual Variability?

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INTRODUCTION: The performance of Target Controlled Infusion relies on the accuracy of Pharmacokinetics (PK) and Pharmacodynamics (PD) models for administering an appropriate amount of anesthetic drug. These models vary across different populations and have a different response from one individual to another. The Eleveld PK model was claimed to capture the inter-individual variability for all patient demographics[1]. The predictive precision of the Eleveld PKPD model is shown to be no worse than other models[2]. We examine this claim for the purpose of closed-loop control of Depth of Hypnosis (DoH), where a controller mitigates the variability using feedback from an EEG signal. We hypothesize that, as the Eleveld PK captures more inter-individual variability, if this PK model is used to predict the plasma concentration, there is less uncertainty in the identified PD models compared to the PD models identified based on the Schuttler[3] or Schnider[4] model.

METHODS: Propofol infusion rates and recordings of DoH of 118 individuals in three demographic groups, elderly (age>70), obese (BMI>30), and adult, were available[5]. Through visual inspection, data from 55 subjects with obvious response to stimulation in their DoH during the induction phase are excluded from the analysis. For the remaining subjects, plasma concentrations are predicted using three PK models: Eleveld, Schnider, and Schuttler, and corresponding PD models are identified employing the two-step method[6]. PD models were validated if the RMS error was < 5.3 for all three PK models for the same subject. PD models were validated for 45 subjects, and Varvel predictive performance indexes are computed and compared with the Mann-Whitney U-test, where $P < 0.05$ is significant. The uncertainty of the identified PD model sets is evaluated using multiplicative uncertainty in the frequency domain[7]. This measure reflects uncertainty relevant to feedback control, where the performance and speed of response are limited by the frequency at which the multiplicative uncertainty > 1.

RESULTS: There is no difference in the variability of MdAPE and Wobble for the validated PKPD models for the Schuttler PK model compared to the Eleveld PK model (p-values of MdAPE and Wobble are (0.7, 0.9, 0.5) and (0.7, 0.8, 0.5), respectively (elderly, obese, adults)), nor for the Schnider model compared to the Eleveld model (p-value of MdAPE and Wobble are (0.5, 1, 0.8) and (0.6, 1, 0.8)). The uncertainty of the PD model set using the Eleveld PK model is not smaller than the set identified using the Schuttler PK model, whose uncertainty is less than one for a larger range of frequencies than the Eleveld and Schnider PK models, (Figure 1).

CONCLUSION: The uncertainty in the PD model set identified using the Eleveld PK model is not smaller than the uncertainty in the model set identified using the Schuttler model. The Eleveld PK model provides no advantage for feedback control design for anesthesia.

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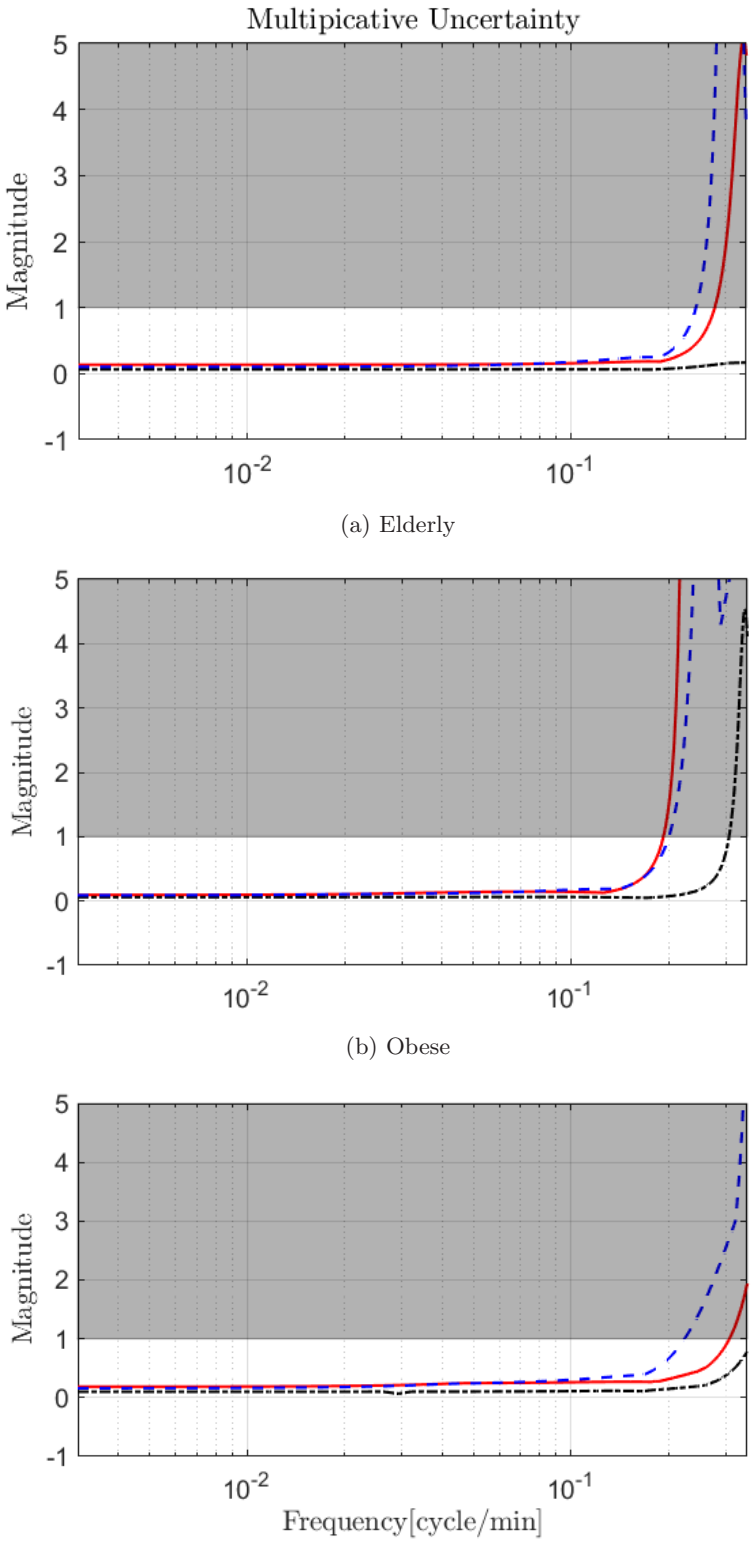

(a) Elderly

(b) Obese

(c) Adult

Figure 1: Dash-dotted black, red, and dashed blue lines indicate the multiplicative uncertainty of PD model sets identified based on the Schuttler, Eleveld, and Schnider PK models as a function of frequency. This measure reflects uncertainty relevant to feedback control. The performance and speed of response are limited by the frequency at which the multiplicative uncertainty > 1. The PD model sets with higher frequency at which the multiplicative uncertainty > 1 have smaller control-relevant uncertainty and better achievable performance.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 13

Is Total Intravenous Anaesthesia (TIVA) the way forward, is it time to abandon volatile anaesthesia?

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INTRODUCTION: This study was conducted in one of the largest multi-centre tertiary teaching institute which has the largest anaesthesiology and peri-operative medicine department in United Kingdom(UK). With improved peri-operative neuroendocrine/immune response,patient outcome and satisfaction,in addition to environmental sustainability(20years global warming potential of Desflurane 3700, isoflurane 1400, Sevoflurane 350, Nitrous Oxide 290[1] and benefits in cancer patients compared to volatile anaesthetics[2] popularity of TIVA in UK has increased significantly with Guidelines for the safe practice of total intravenous anaesthesia (TIVA)[3]. After approval from hospital clinical governance and audit committee, we explored the practice of routine use of TIVA & BIS, staff competency and requirement of TIVA/BIS training and awareness guidelines/recommendations at our hospital. Previous nation-wide surveys in UK and Ireland including National Audit Project(NAP) 5 study[4] showed that training in TIVA is currently inconsistent and often inadequate, many anaesthetists do not feel confident when using the technique, awareness is more common when TIVA was used & most of the cases were preventable, commonest contributory factor was inadequate education and training. Royal College of Anaesthetist(RCoA) and Society of Intravenous Anaesthesia(SIVA)[5] have following recommendations for trainees 1) Training in TIVA/TCI should begin during basic training for all anaesthetic and intensive care trainees and should continue into intermediate and higher training. 2) Trainees should be competent in the use of TIVA/TCI prior to unsupervised practice in this technique, including transfer of patients anaesthetised with an intravenous propofol infusion. 3) The Society for Intravenous Anaesthesia recommends 25 cases (10 consultant-led, 10 with close supervision and 5 solo cases) before basic trainee competence has been achieved.

METHODS: Study/Survey - TIVA / BIS Questionnaire - https://www.smartsurvey.co.uk/s/TIVAandBIS 1. Grade of Anaesthetist 2. Do you use TIVA in your clinical practice? 3. How often do you use TIVA? 4. Are you aware of any Departmental / National guidelines for the use of TIVA? 5. Are you member of any National or International society for TIVA? 6. Have you attended any workshops/courses or formally trained to use TIVA? 7. Do you routinely use BIS monitoring when using TIVA? If no, could you comment why? 9. Have you attended any workshops/courses or formally trained to use BIS?

RESULTS: Study/Survey revealed

- Nearly 90% use TIVA in clinical practice but around only 40% are trained or attended relevant courses
- Nearly 70% said they didn't have any formal training in BIS
- Only few are members of TIVA society

CONCLUSION: We achieved following things on the basis of above results.

- Teaching and Training/Educational Programme
- TIVA/BIS Study Day and BIS workshops
- Environmental Sustainability
- Implemented hospital wide TIVA/BIS Recommendations
- Improved perioperative outcomes
- Improved patient satisfaction
- Way above UK National average in TIVA/BIS usage (National average 6.6%, our practice 88%)
- No incidence of awareness under general anaesthesia in our practice with TIVA
- Efficient turnover of theatre time and optimal use of resources
- Implemented Basic, Intermediate and Higher TIVA/BIS training modules for trainees in anaesthesiology as per Royal College of Anaesthetists (RCoA) new curriculum
- TIVA can reduce length of stay and is cost effective in comparison to volatile anaesthetics, we are currently prospectively collecting the data
- Successful business plan and procured more BIS monitors and TIVA infusion devices

Based on this study, authors indicate that there is increased use of TIVA, however authors believe that there is ongoing need for safe and adequate training and teaching. Although. studies have shown effects of volatile on environmental sustainability , further evidence needed to completely abandon the volatile anaesthesia.

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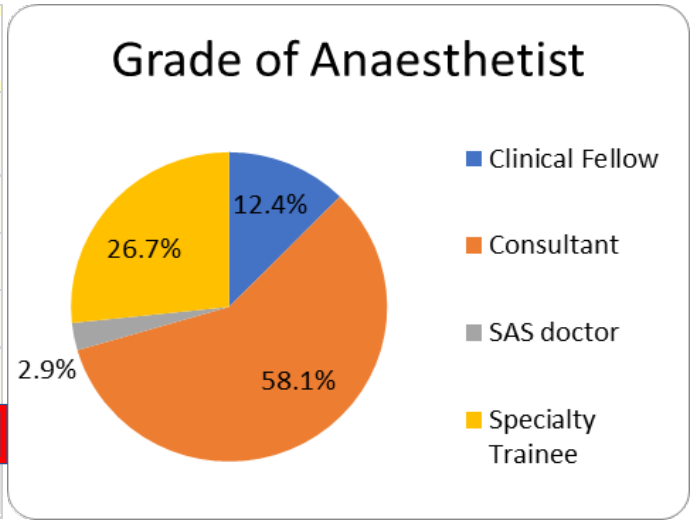
4. Pandit JJ, Andrade J, Bogod DG, et al. The 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. Anaesthesia 2014; 69: 1089-1
5. TIVA Education Tools (siva.ac.uk)

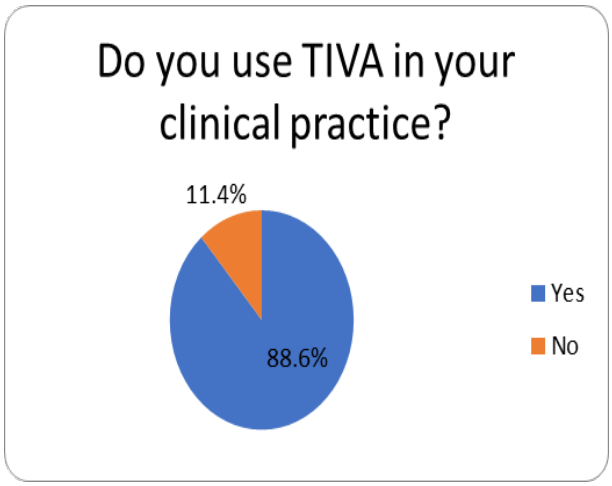
1. Grade of Anaesthetist

		Response Percent	Response Total
1	Clinical Fellow	12.38%	13
2	Consultant	58.10%	61
3	SAS doctor	2.86%	3
4	Specialty Trainee	26.67%	28
		answered	105
		skipped	0



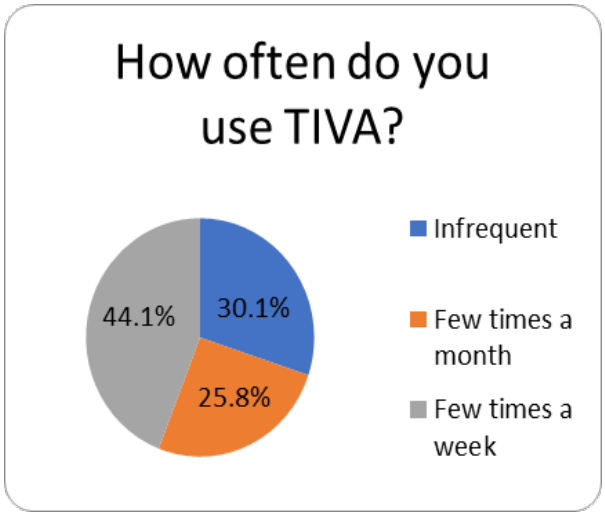
2. Do you use TIVA in your clinical practice?

		Response	Response Total
1	Yes	88.57%	
2	No		12
		answered	105
		skipped	0



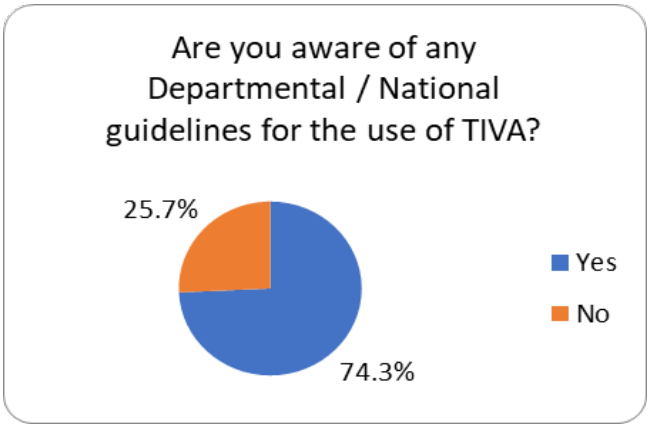
3. How often do you use TIVA?

		Response Percent	Response Total
1	Infrequent	30.11%	28
2	Few times a month	25.81%	24
3	Few times a week	44.09%	41
		answered	93
		skipped	12



4. Are you aware of any Departmental / National guidelines for the use of TIVA?

		Response Percent	Response Total
1	Yes	74.29%	78
2	No	25.71%	27
		answered	105
		skipped	0



Anaesthesia 2018 doi:10.1111/anae.14428

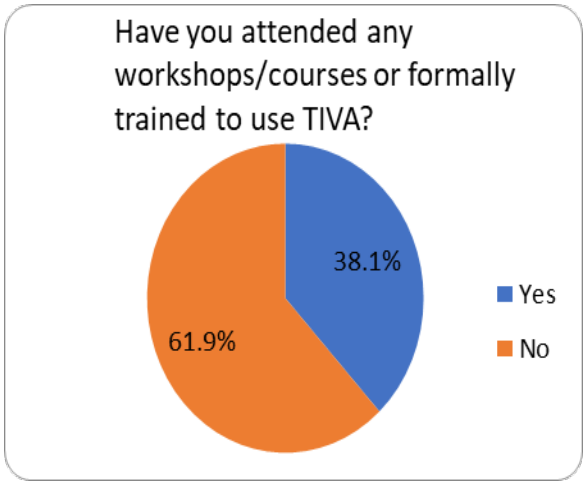
Guidelines

Guidelines for the safe practice of total intravenous anaesthesia (TIVA)

Joint Guidelines from the Association of Anaesthetists and the Society for Intravenous Anaesthesia

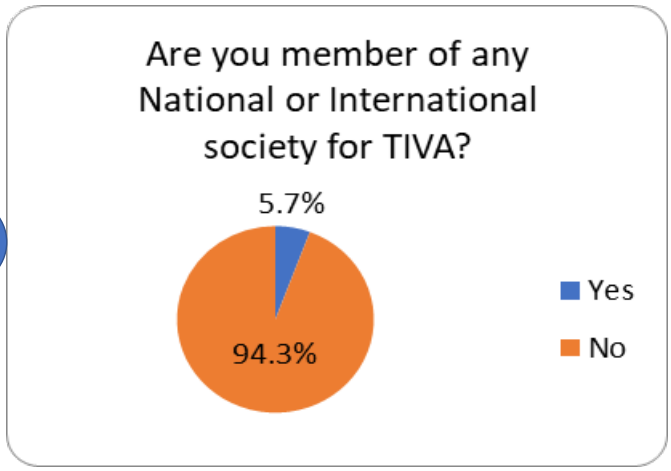
5. Have you attended any workshops/courses or formally trained to use TIVA?

		Response Percent	Response Total
1	Yes	38.10%	40
2	No	61.90%	65
		answered	105
		skipped	0



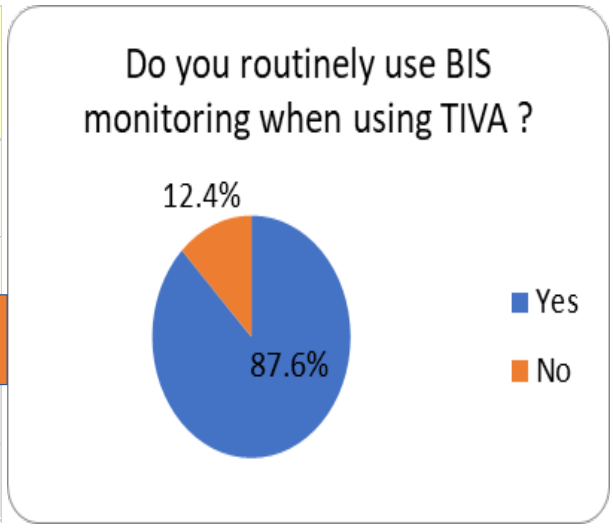
6. Are you member of any National or International society for TIVA?

		Response Percent	Response Total
1	Yes	5.71%	6
2	No	94.29%	99
		answered	105
		skipped	0



7. Do you routinely use BIS monitoring when using TIVA ?

		Response Percent	Response Total
1	Yes	87.62%	92
2	No	12.38%	13
		answered	105
		skipped	0



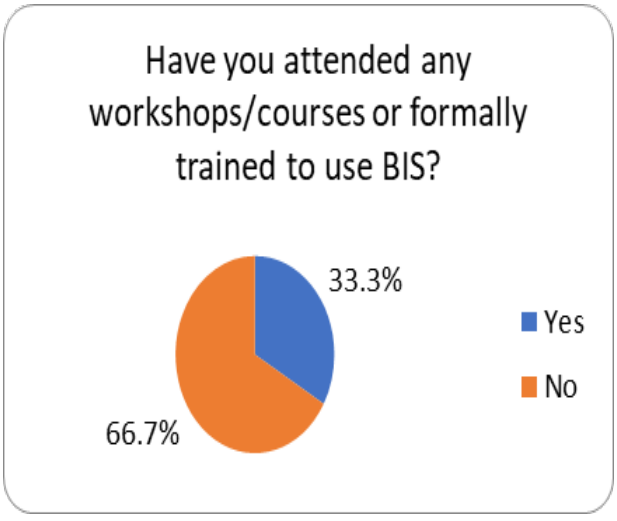
8. If you do not routinely use BIS monitoring when using TIVA, please state why?

Open-Ended Question

1		Not reliable
2		Don’t frequently use and when I do the cases do not need muscle relaxant
3		I don't use TIVA
4		Never really thought about using BIS
5		Don’t use TIVA
6		I do not use NMBDs with TIVA, all my patients are non-paralysed and spontaneously breathing
7		Lack of familiarity/training.
8		Routinely use if NMBA given. If LMA SV case don't use routinely but might in certain patient groups.
9		not experienced in TIVA and BIS
10		Rarely used TIVA
11		don't do TIVA
12		I often do not use muscle relaxants especially for lower abdominal surgery. If I do use muscle relaxants, I use BIS
13		Surgery in remote areas

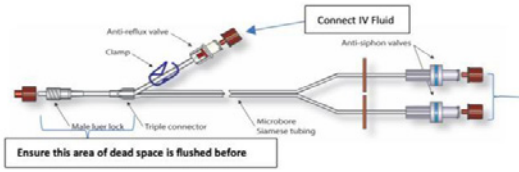
9. Have you attended any workshops/courses or formally trained to use BIS?

		Response Percent	Response Total
1	Yes	33.33%	35
2	No	66.67%	70
		answered	105
		skipped	0



Manchester University NHS Foundation Trust

TIVA Recommendations



Connect the Propofol and Remifentanyl syringes to the parallel ports and manually flush to the end

Both syringes should then be mechanically purged though the pump to take up the slack in the pumping system

The dead space beyond where the IV fluid line joins should now be flushed with the IV fluid

TIVA should only be used by an anaesthetist trained and competent with using this technique.

Always Ensure

Equipment and Monitoring:

- Infusion pumps are adequately charged and power cables connected
- Use syringes with Luer-lock connectors only
- Label syringes after drugs are prepared
- Syringe order – Propofol on top and Remifentanyl infusion below
- Infusion pumps (PK) to be programmed after loading syringes
- Infusion set with anti-reflux/anti-syphon valves
- Establish suitable IV Access and drip is running freely, cannula site should be visible and easily accessible
- It is suggested to use BIS/pEEG monitor when using TIVA. Always use if using neuromuscular blockade (NMB) and attach BIS prior to administration of NMB and continue until NMB recovery is confirmed with peripheral nerve stimulator (PNS) or tetragraph

Drug Administration:

- Cannula and any extension flushed with twice dead space volume at the end of procedure
- Use correct algorithm, patient age / weight / height
- In addition to TCI infusion rate, checking the pump infusion rate in ml/hr will guide to deliver manual infusion in the event of pump failure

Propofol targets:

Healthy young or middle-aged patients:

- Induction: 5-6 mcg/ml
- Maintenance: 3-6 mcg/ml (without opioids – provided analgesia is covered by other modalities), 2.5-4.0 mcg/ml(with opioids)
- Higher initial levels may be appropriate in 'robust' patients

Elderly / unwell patients:

- Target lower initial propofol concentrations (e.g., 3-4 mcg/ml) and use small incremental doses

Remifentanil targets:

- When administered with propofol, concentrations of 2-6 ng/ml can be used

Propofol requirements may be reduced with the addition of:

- Opioids, Benzodiazepines, Ketamine, 2-Adrenoreceptor Agonists, Magnesium, Nitrous Oxide, Regional Anaesthesia

FGF:

- Make sure the fresh gas flow is 4 - 6L /min which reduces running cost compared with lower FGFs, with minimal impact to the environment

Obesity:

- Depth of anaesthesia monitoring highly recommended due to altered pharmacokinetics
- The maximum actual body weight (AW) accepted by Marsh model is150 kg
- The Schnider model can only accept variables with a BMI < 35 for females and < 42 for males
- BMI >35 kg/m2 (females) or >42 kg/m2 (males): use 'Adjusted body weight' (ABW) if BMI more than 35
- ABW = Ideal body weight (IBW) + 0.4(AW-IBW)
- IBW (kg) for Males = height (cm) minus 100, Females = height (cm) minus 105

Note: For remote site anaesthesia: same standardsof practice and monitoring should apply to TIVA

References: SIVA/AAGBI joint guidelines for safe practice of total intravenous anaesthesia (TIVA)- Anaesthesia 2018 - doi:10.1111/anae.14428, SOBA,doi.org/10.1016/j.bja.2020.07.043

Created by - Dr A.Patil, Dr M.Swamy, Dr U.Panchagnula

Audit Number: 9529
08/2021

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 14

Telemedicine-based at-home postoperative vital signs monitoring: A systematic review and meta-analysis

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INTRODUCTION: The novel coronavirus disease 2019 (COVID-19) has tasked surgical teams with the challenge of retaining the quality and timeliness of postoperative care while keeping virus transmission to a minimum[1, 2]. Healthcare systems are actively implementing tools that replace in-person interactions between patients and healthcare providers for at-home virtual care interventions, commonly referred to as telemedicine or telehealth[3, 4]. The objective of this systematic review and meta-analysis is to evaluate the effectiveness of telemedicine-based at-home postoperative vital signs monitoring in comparison to usual care, defined as patients monitored without telemedicine technology or not monitored at all. This study will focus on outcomes such as readmission, complication rates, patient adherence, and patient preference.

METHODS: MEDLINE (Ovid), MEDLINE InProcess/ePubs, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov were searched to identify articles. Furthermore, forward and backward citation searching was completed using Google Scholar. Literature surveillance was continued through August 2021. Full-text articles were selected based on the following inclusion criteria: the study assessed telemedicine technology to relay vital signs recorded remotely in postoperative adult patients aged 18 years and older. Odds ratios were calculated for readmission and postoperative complication rates between telemedicine-based remote monitoring and usual care groups using RStudio 1.4.1717. Pooled estimates for readmission, postoperative complications, patient adherence, and patient experience was also calculated using a random effects meta-analysis.

RESULTS: Thirty-one studies (n = 2,748) were included in the review and twenty-six were included in the meta-analyses. The average age was 61±11 years and 61% of patients were male. Telemedicine-based at-home postoperative vital signs monitoring reduced readmission rates by 28% (odds ratio [OR]: 0.72; 95% confidence interval [CI]: 0.36 - 1.44) and increased postoperative complications by 48% (OR: 1.48; 95% CI: 1.02 - 2.14) when compared to the usual care group. This was attributed to telemedicine's high sensitivity to minor disturbances, allowing complications to be discovered before they progressed and required readmission. The pooled readmission, complication, and patient adherence estimates at 30 days were 10% (95% [CI]: 7 - 16%], 10% (95% CI: 6 - 15%), and 86% (95% CI: 72 - 93%) respectively. The pooled proportion of patients with positive patient experience was 88% (95% CI: 80 - 94%). Additionally, two studies reported substantial cost reductions in the range of 60-97% per patient when comparing telemedicine-based monitoring to discharge without monitoring and one study found that telemedicine-based monitoring was associated with 55% reduced mortality risk.

CONCLUSION: This systematic review and meta-analysis demonstrates the effectiveness and feasibility of telemedicine-based at-home monitoring with vital signs reporting. We found that remote telemedicine technology resulted in lower readmission rates, good adherence, and high patient preference. The effectiveness of remote monitoring was attributed to convenient access to a healthcare team and rapid identification of abnormal vital signs. Alert systems allowed for healthcare providers to automate the process of detecting and relaying information, enabling efficient interactions for both patients and physicians. Although more postoperative complications were detected, they were often minor abnormalities that rarely corresponded to serious events. The constant monitoring of relevant vital signs generated more alerts but helped curb complications at an earlier stage before they progressed further. High patient adherence was attributed to the integration of monitoring technology into common devices such as smartphones and tablets in combination with patient-friendly platforms. In addition, telemedicine technology was easy to use and helped remove barriers to care such as cost, travel, and wait time further supporting its use in postoperative care.

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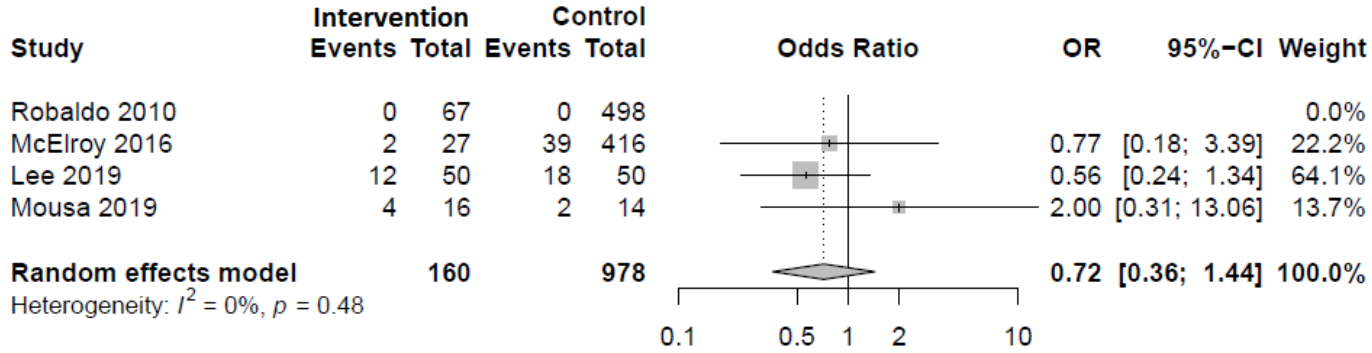
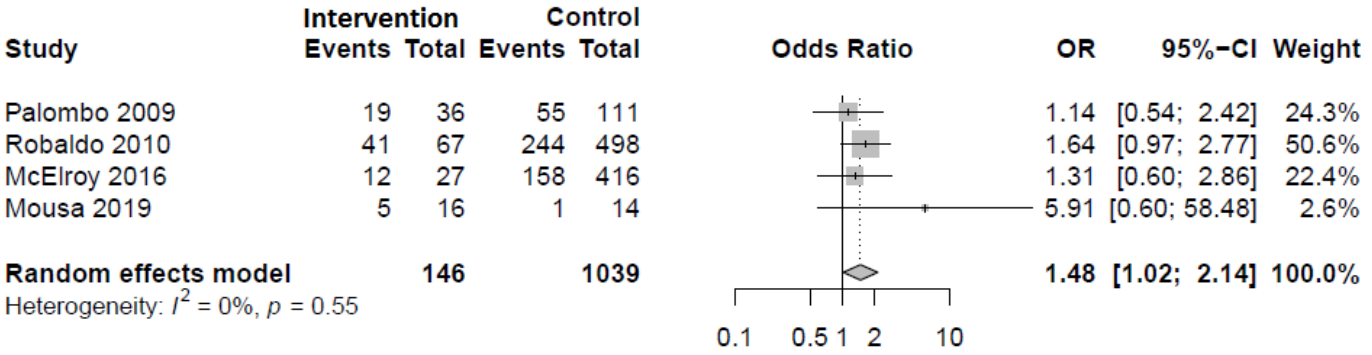
A. Comparison of ≤30-day readmission rate of at-home monitoring with telemedicine versus usual care



B. Comparison of ≤30-day postoperative complications rate of at-home monitoring with telemedicine versus usual care



TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 15

Hemorrhage increases renal sympathetic vasomotion in conscious rabbits

Alicia M Schiller[1], Peter Pellegrino[2], Irving H Zucker[3]

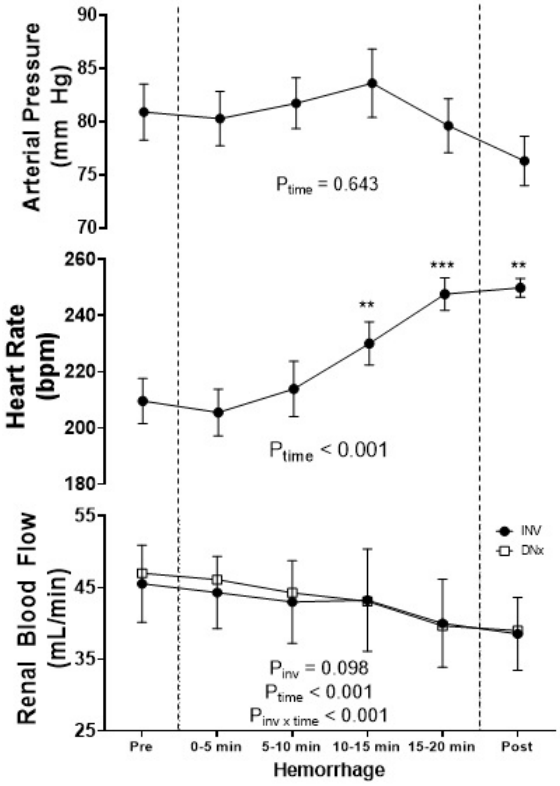
[1]Univeristy of Nebraska Medical Center, Omaha, NE, [2]UNMC, Omaha, NE, [3]University of Nebraska Medical Center, Omaha, NE

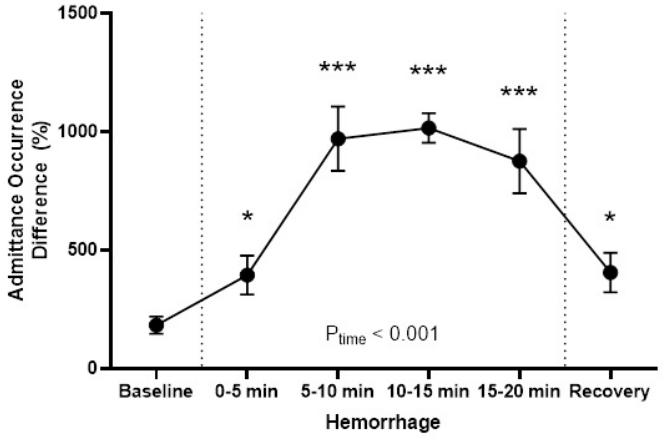
INTRODUCTION: Hemorrhagic shock causes 1.8 million deaths and results in 85 million years of life lost globally each year. The median time from onset to death is only two hours, and early recognition and prompt action form the cornerstone of management. The sympathetic nervous system is the principal hemodynamic response system for the body and measures of sympathetic activation could facilitate earlier detection of hemorrhagic shock, thereby improving patient care in the perioperative and critical care settings. We developed a novel, clinically implementable marker of rhythmic sympathetic vascular control called sympathetic vasomotion which is decreased by spinal anesthesia, ganglionic blockade, and sympathetic denervation, but its responsiveness to increases in sympathetic outflow like those that occur during hemorrhage has not been studied. We hypothesized that renal sympathetic vasomotion would increase in response to hemorrhage.

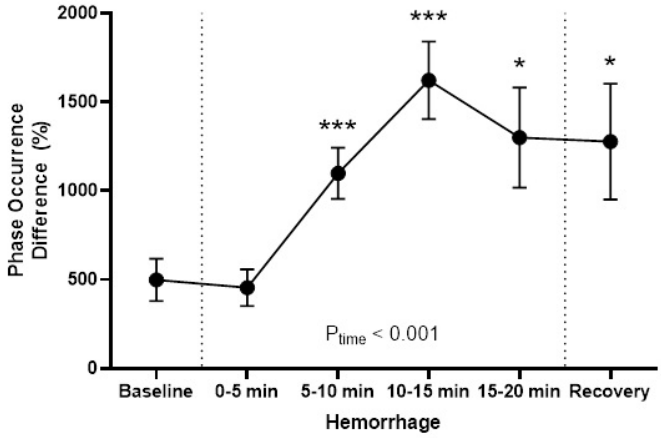
METHODS: To test this hypothesis, six rabbits underwent unilateral renal denervation and chronic instrumentation with bilateral renal arterial flow probes and an abdominal aortic pressure telemeter. After a two-week recovery, the rabbits underwent a controlled blood draw of 1% of their estimated blood volume per minute for twenty minutes via an ear arterial catheter. Blood pressure and bilateral renal arterial blood flow were measured, and mean hemodynamics as well as renal vasomotion profiles were calculated by creating occurrence histograms of the pressure-resistive flow time-varying transfer functions for both innervated (INV) and denervated (DNx) kidneys.

RESULTS: This paradigm resulted in a normotensive hemorrhage with an increase in heart rate after 10 minutes of hemorrhage; mean renal blood flow decreased over the course of the hemorrhage but did not differ between kidneys (Figure 1). The differences in the renal vasomotion admittance gain profiles between the INV and DNx kidneys increased above baseline by 116%, 430%, 455%, and 379% between minutes 0-5, 5-10, 10-15, and 15-20 of hemorrhage, respectively (Figure 2). The difference in the renal vasomotion phase shift profile also showed significant increases between minutes 5-10, 10-15, and 15-20 of hemorrhage (Figure 3).

CONCLUSION: These results show that increases in renal sympathetic vasomotion occur both earlier and to a much greater degree than canonical hemodynamic changes in hemorrhage. Further studies on sympathetic vasomotion in the context of hemorrhagic shock are needed to develop a clinically useful early detection tool that could improve patient outcomes.







TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 16

Clinical evaluation of Two-Way Machine Interpreter Applications for Non-Critical Communication

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INTRODUCTION: Language barriers in health care have been associated with decreased patient comprehension, increased length of hospital stay, poor adherence to treatment recommendations, and diminished patient satisfaction. Although using professional interpretation service remains the gold standard for communicating with patients with limited English proficiency (LEP), in some circumstances it is not feasible nor practical to use an interpreter service. Two-way machine interpretation tools have the potential to fill these necessary gaps of communicating with LEP patients, but their clinical utility has not been evaluated. This study aims to evaluate these applications for patient-provider communication in Spanish, Mandarin Chinese, and English.

METHODS: This was a non-inferiority study evaluating three machine interpretation tools (Google Translate [GT], Microsoft Translator [MT] and Apple iTranslate [AT]) to the gold standard, a professional interpretation, for its ability to interpret two-way conversation between English and Spanish, and between English and Mandarin Chinese. We developed communication contents that are based on frequently used between providers and patients. Assessors fluent in Spanish and Mandarin Chinese assessed quality of interpretation using evaluation metrics of accuracy, fluency, meaning and severity of errors using 5-point Likert scale. Logistic regression was performed based on Likert score of 4 (very good) and 5 (excellent) as acceptable quality of interpretation.

RESULTS: Total 105 provider-to-patient and 105 patient-to-provider communication contents were developed for the study. Most contents were either one or two sentences long (98.2%) with average word count of 12.2 and did not contain did not contain medical phrases or abbreviations (95.8%). In general, all three machine interpreters scored better interpreting from English to either Spanish or Mandarin than vice versa. For English to Spanish interpretation. acceptable rate for GT's fluency (0.81; 95% CI: 0.72 - 0.88) and meaning (0.85; 95% CI: 0.76 - 0 .91) and MT's meaning (0.81; 95% CI: 0.72 - 0.88) were above the non-inferiority threshold. For English to Mandarin interpretation, only the AT's accuracy (0.88; 95% CI: 0.80-0.93), GT's fluency (0.86; 95% CI: 0.78 - 0.92) and accuracy (0.88; 95% CI: 0.80 -0.93) and MT's fluency (0.86; 95% CI: 0.78 - 0.92), accuracy (0.91; 0.83 - 0.95) and meaning (0.77; 95 CI: 0.68 - 0.85) were above the non-inferiority threshold. For both Spanish to English and Mandarin to English interpretation, all three machine interpretations failed to meet the non-inferiority threshold for any evaluation criteria. The accuracy of interpreting Mandarin to English for AT (.46; 95% CI: 0.36 - 0.56), GT (0.43; 95% CI: 0.33 - 0.53) and MT (0.49; 95% CI: 0.39 - 0.59) were significantly lower than the accuracy of interpreting Spanish to English.

CONCLUSION: On application versions tested, all three machine interpretation applications were inferior compared to professional human interpreter. Moreover, applications had more difficulty accurately interpreting non-English language into English. This suggest that even for non-critical communication use, machine interpretation applications are significantly inferior to the professional interpretation and use in clinical setting is not recommended.

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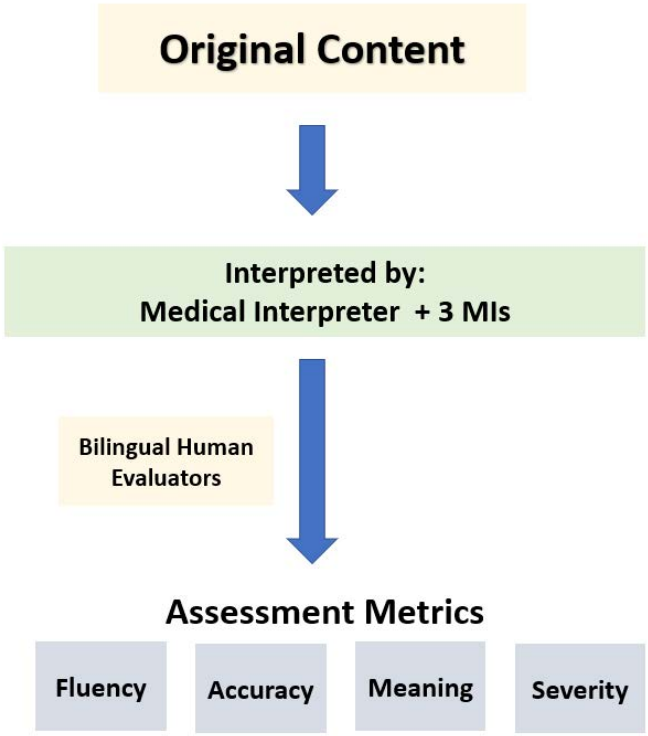
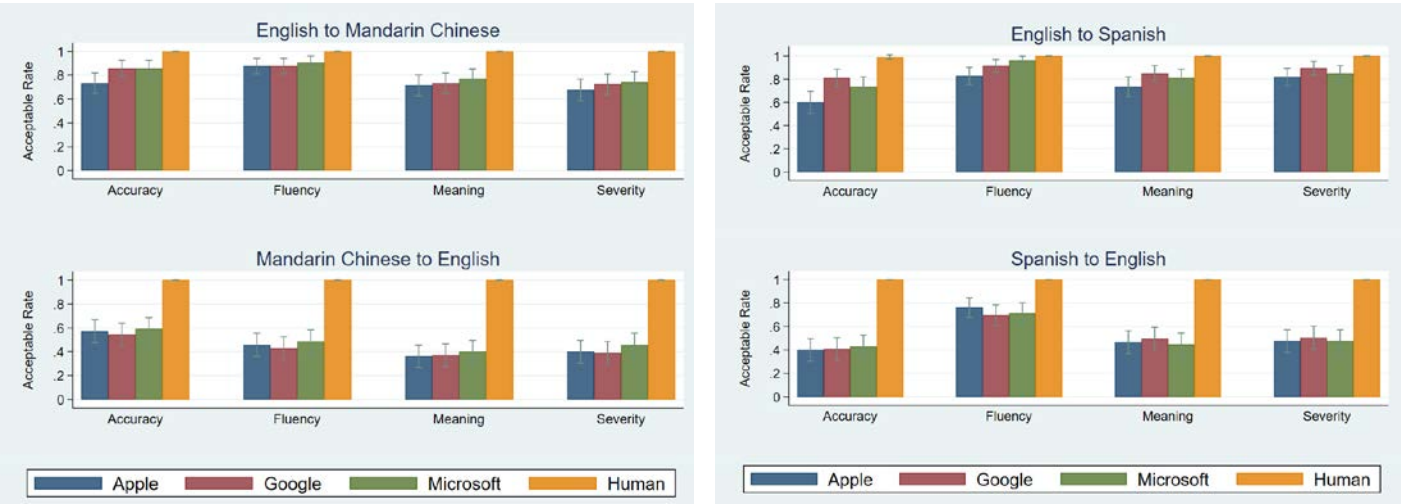


Figure 1. The audio-recording of original communication contents were provided to professional medical interpreters as the "gold standards". The three-machine interpreter (MI) tools interpreted same recordings. The original English contents were interpreted to either Spanish or Mandarin. The original Spanish or Mandarin contents were interpreted to English. Bilingual evaluators assessed the quality of interpretations on 4 categories using a 5-point Likert scale: fluency, accuracy, meaning and severity.



TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 17

Accuracy of Pulse Oximeters in Measuring Oxygen Saturation in Patients with Poor Peripheral Perfusion: A Systematic Review

Chi Pham[1], Khashayar Poorzargar[2], Jennita Ariaratnam[3], Matteo Parotto[1], Kang Lee[1], Frances F Chung[4], Mahesh Nagappa[5]

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INTRODUCTION: Pulse oximetry is used for continuous monitoring of oxyhemoglobin saturation (SpO2) and plays an important role in clinical practice as an alert for patient's deterioration. Poor perfusion is a factor which may limit pulse oximeter accuracy[1]. Patients can experience poor perfusion during perioperative care, in the emergency departments, and intensive care units. Inaccuracies in pulse oximetry can compromise patient safety and increase the cost of care. This systematic review aims to determine the accuracy of pulse oximetry measurement in various poor perfusion conditions.

METHODS: multiple database search was conducted from inception to December 2020. The inclusion criteria were studies with: (1) adults (≥18 years) with explicitly stated conditions that cause poor peripheral perfusion (conditions localized at the oximeter placement site; or systemic conditions, including critical conditions such as hypothermia, hypotension, hypovolemia, and vasoconstricting agents use; or experimental conditions) and (2) a comparison of arterial oxygen saturation (SpO2) and arterial blood gas (ABG) values. Twenty-two studies were included and assessed for reliability and agreement using a modified Guidelines for Reporting Reliability and Agreement Studies (GRRAS) tool. We extracted bias and precision values of individual oximeters from those studies and calculated their respective accuracy root mean square (Arms) error. Oximeters were deemed accurate if they had an Arms of less than 3%[2].

RESULTS: Most oximeters (75%,) were deemed accurate in patients with poor perfusion (Arms < 3). A visual analysis Arms values shows that the accuracy of oximeters improved over the past 20 years in measuring SpO2 under poor perfusion. Out of the 32 oximeter models, three (9%) were produced after 2000 and almost all were accurate in patients with poor perfusion (Arms<3.0). Measurement from oximeters placed on the earlobes were more sensitive with greater accuracy compared to fingertip placement. Poor perfusion factors included arterial hypotension (45%), hypothermia (32%), vasoactive drug use (23%) and a few studies (23%) stated 'poor perfusion' without stating specific factors. The FDA guidelines for the assessment of pulse oximeters requires testing to be performed in a diverse population, with various sex, age and 15% of participants must have dark skin tone. Of the 15 studies that reported patient population size and sex, almost all studies had a male population of greater than 50% and only one study controlled for skin pigmentation.

CONCLUSION: We found that oximeters are accurate in poorly perfused patients, especially newer oximeter models and those placed on earlobes. Further studies are needed that examine multiple oximeter models on a diverse selection of patients especially those with pigmentation.

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TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 18

Using Computer Vision To Identify Syringes During Low- versus Regular-Light Conditions In The Operating Room

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INTRODUCTION: Manual entry of medications administered intra-operatively is often inaccurate, and potentially detracts from patient monitoring, particularly during such periods as induction and emergence.[1] Additionally, most medications are recorded after delivery, making it hard to intervene if an inappropriate drug is selected. One potential solution involves real-time detection and recording of drug administration using smart eyewear and computer vision. We have developed a neural network trained to identify syringes in an anesthesia providers hand using a head mounted camera.[2] The aim of this study is to expand on these capabilities for real time syringe identification during low-light conditions. Given the increasing number of minimally invasive surgeries performed in the US each year, employing a neural network capable of detecting objects under low-light conditions (as might be seen in these surgeries) is necessary for this first of its kind advanced warning system.

METHODS: IRB approval was obtained for intra-operative recordings using a head-mounted camera worn by anesthesiology providers. Images were collated and labelled by a group of trained annotators. A dataset was compiled based on 28 clips from 5 days of recordings, sampling 6 frames per second for a total of 3200 images. Data included images captured under regular-light and low-light conditions (Figures 1 and 2). The images were tiled to 1/8th the original size and only those where a bounding box contained at least 75% of the syringe were included in the training and validation. The YOLOv5 algorithm was selected given its speed and real-time object analysis capabilities. Training and validation were performed on both low-light and regular-light tiled images for 200 epochs per case (as no further improvement was observed beyond this). Training was initially done with default YOLOv5 settings (image size 640 and pre-trained weights) on full-size and tiled images. Three additional training scenarios were trialed on full-size and tiled images: 1. Image size 640 without pre-trained weights, 2. Image size 416 with pre-trained weights, 3. Image size 416 without pre-trained weights. Testing of the neural network was completed on tiled low- and regular-light images and full-sized low-light images.

RESULTS: The average precisions at 0.5 for full-sized and tiled images are listed in Table 1. Full-sized low-light images tested against the trained full-sized dataset had an average precision at 0.5 of 0.583 (not shown in the table). Lastly, adjusting the brightness of full-sized low-light images by a factor of 1.5 did not significantly improve the precision of the neural network (average precision at 0.5: 0.587, not shown). Figures 3 and 4 show a selection of regular-light and low-light tile 8 testing images demonstrating 8/9 syringes were correctly identified under regular-light conditions compared to 6/9 identified under low-light conditions.

CONCLUSION: Our neural network is capable of real-time syringe identification during low light and regular-light conditions. Dividing images and tiling them, as well as using pre-trained weights significantly improved the average precision of tested images. Training on full-sized low-light images and adjusting their brightness, however, did not significantly increase precision of tested images and required a longer computation time compared to tiled images. To date, this is the largest data set we have tested on our neural network and the most accurate results for all light conditions. Future directions include using edge-detection filtering or sharpening tools to improve accuracy under low-light conditions.

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Figure 1. Sample regular-light image

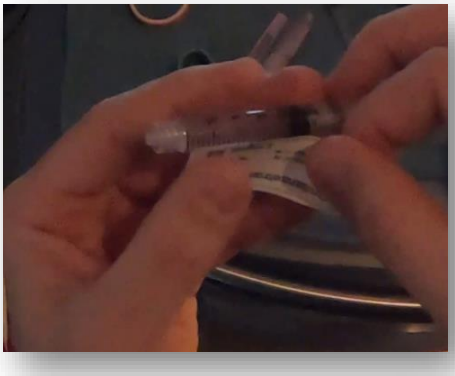

Figure 2. Sample low-light image

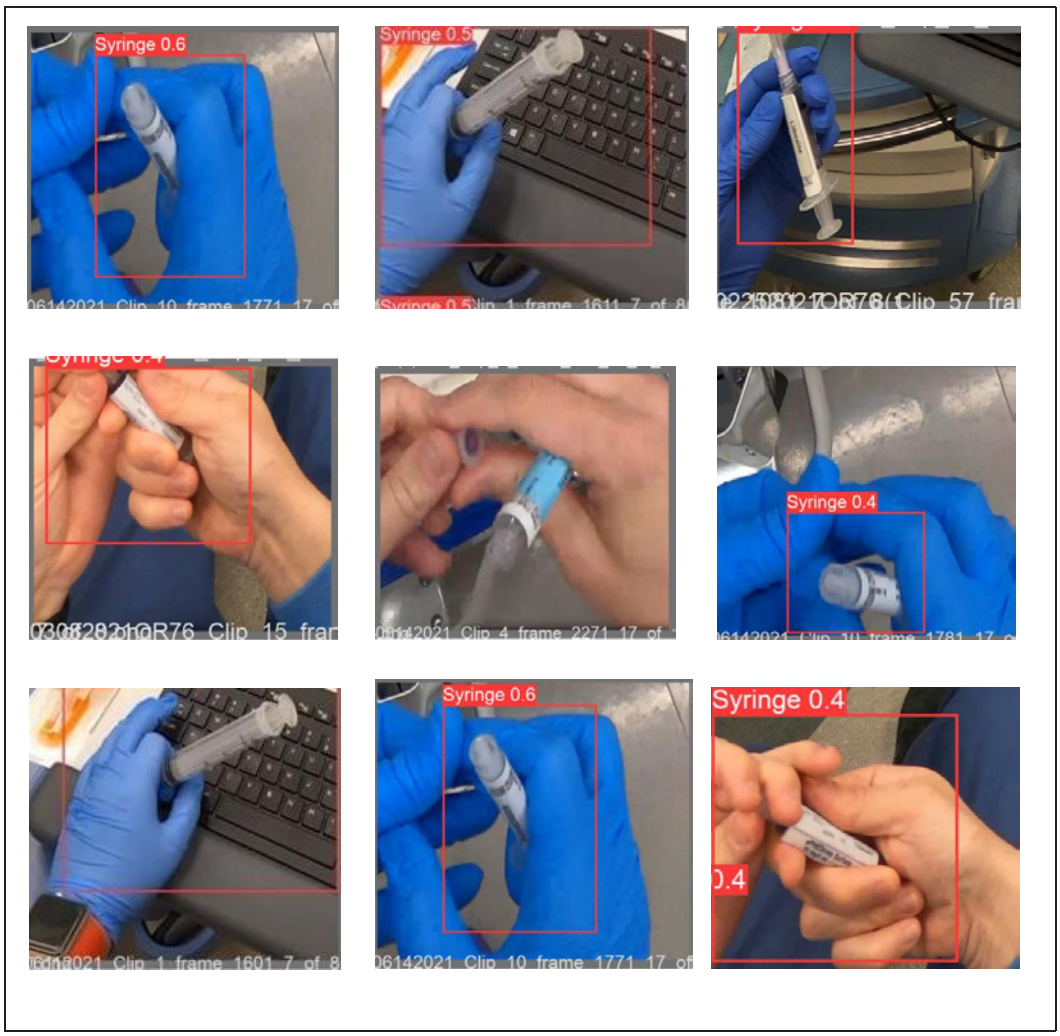

Figure 3. Sample of tiled regular-light condition images trained using image size 640 and pre-trained weights

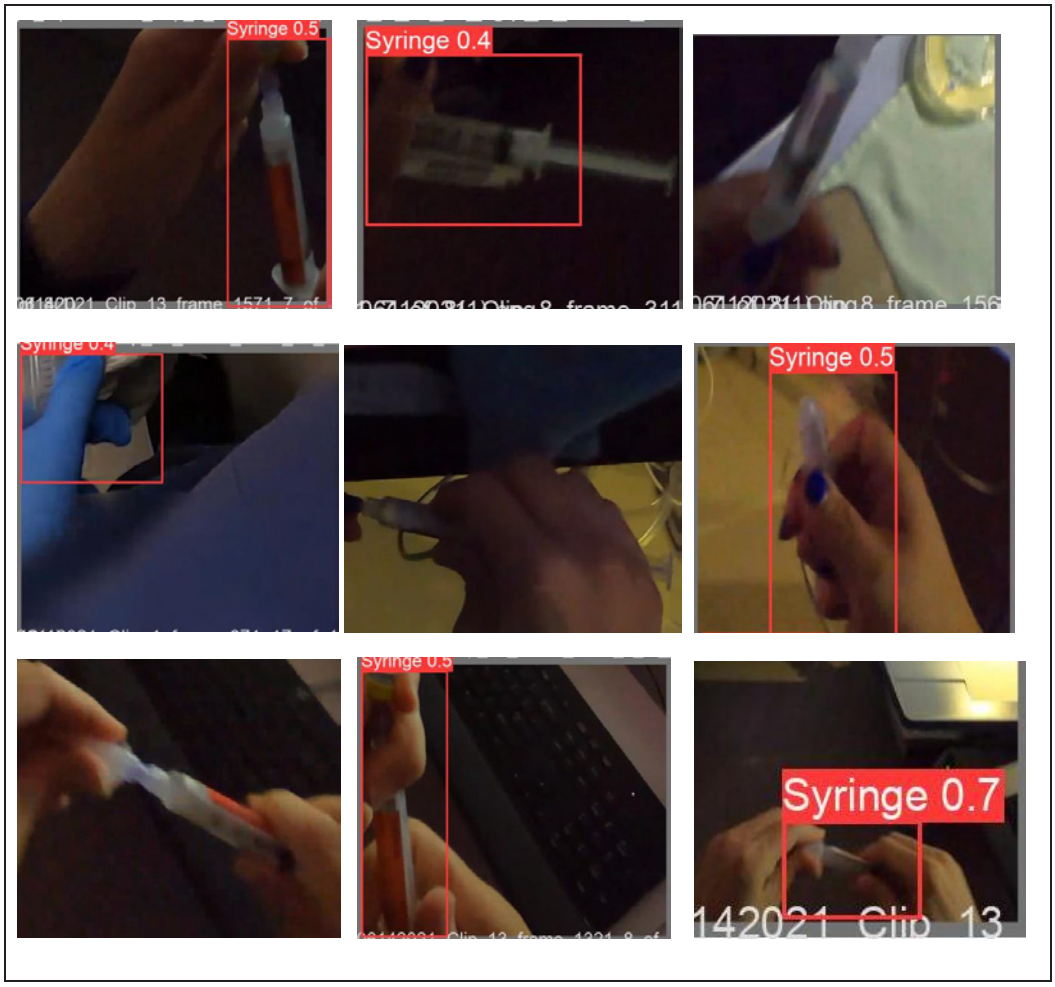

Figure 4. Sample of tiled low-light condition images trained using image size 640 and pre-trained weights

Table 1

Trained and Validated Images	Average Precision at 0.5		
	Full-Size Low Light	Tile 8[3] Regular light	Tile 8 Low light
Image size 416, PTW[1]	0.2	0.878	0.566
Image size 416, no PTW	0.0749	0.777	0.468
Image size 640[2], PTW	0.178	0.865	0.61
Image size 640, no PTW	0.073	0.662	0.407

[1]PTW, Pre-Trained Weight (default)
[2]Image size 640 (default)
[3]Tile 8, Image cropped to 1/8th

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 19

Using Motion Analysis to Assess Skill Acquisition in Anesthesiology Interns Practicing Central Venous Catheter Placement

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[1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

INTRODUCTION: Motion analysis involves the recording of hands and medical instruments using sensors. These recordings allow for objective comparison of certain metrics, including total distance travelled (path length), movements performed (translational motions) and time[1]. These metrics can be analyzed further to establish thresholds of performance, and potentially track skill acquisition in clinical procedures such central venous catheter (CVC) placement. We hypothesized that a combination of previously used and novel (rotational sum) motion metrics could be used to analyze performance trends of anesthesiology interns practicing central venous catheter placement in the simulation setting. We also hypothesized that segmentation of motion recordings would identify specific areas either exhibiting significant improvement or requiring deliberate practice.

METHODS: Twelve anesthesiology interns (novices) underwent a two-day training course in which they performed a total of nine central venous catheter placements each. They were equipped with motion sensors on the dorsum of their dominant hand and ultrasound probe (Figure 1). An additional five attending anesthesiologists (experts) performed 3 trials each in order to establish metric thresholds for comparison. Trials were recorded in order to precisely segment the motion recordings and assess metrics by procedural checkpoint (Figure 2). We analyzed the trend of each metric (path length, translational motions, rotational sum and time) for each sensor (dorsum of dominant hand and ultrasound probe) across all trials using generalized estimating equations (GEE). We also calculated the Pearson correlation coefficient between rotational sum and each other metric.

RESULTS: On average, novices exhibited a negative trend in path length, translational motions, rotational sum, and time ($p \leq 0.001$) with the exception of translational motions of the ultrasound probe (Figures 3, 4). Interns reached within one standard deviation of the expert average by trials 7-8 for most metrics. Rotational sum exhibited a moderate to strong positive correlation with previously explored metrics ($p < 0.001$). Segmentation revealed significant improvement in all metrics for each checkpoint describing the novice average, except for the path length of the dorsum in checkpoint 3 ($p = 0.130$).

CONCLUSION: It was determined that a comprehensive series of motion metrics, including path length, translational motions, rotational sum, and time, is able to track progression in novice performance of CVC placement in the simulation setting. Rotational sum may be used as a supplementary metric to assess performance in CVC placement. Segmentation provides detailed insight into skill acquisition in particular checkpoints of CVC placement, and can inform deliberate practice.

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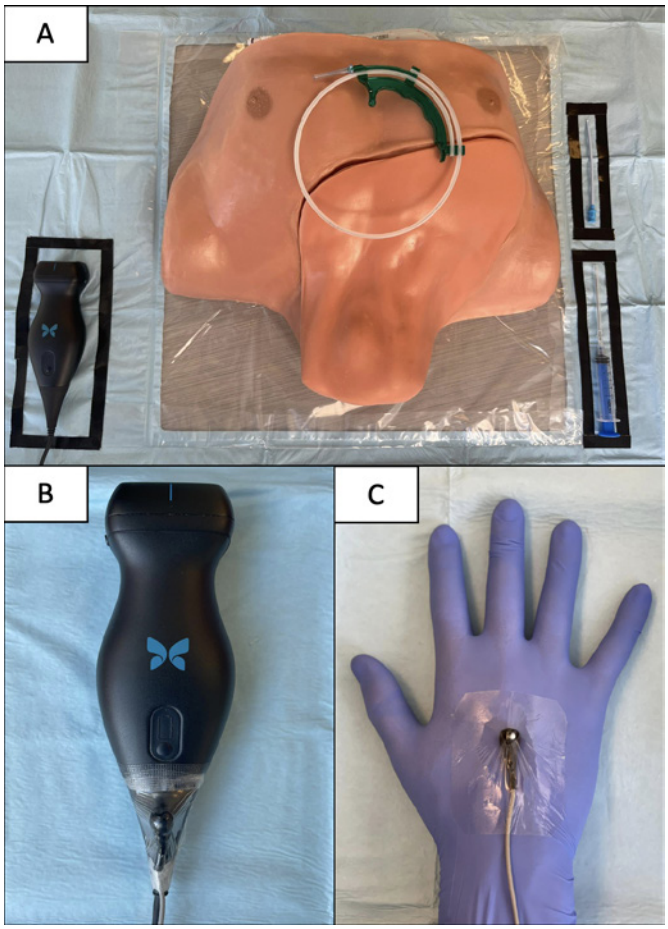

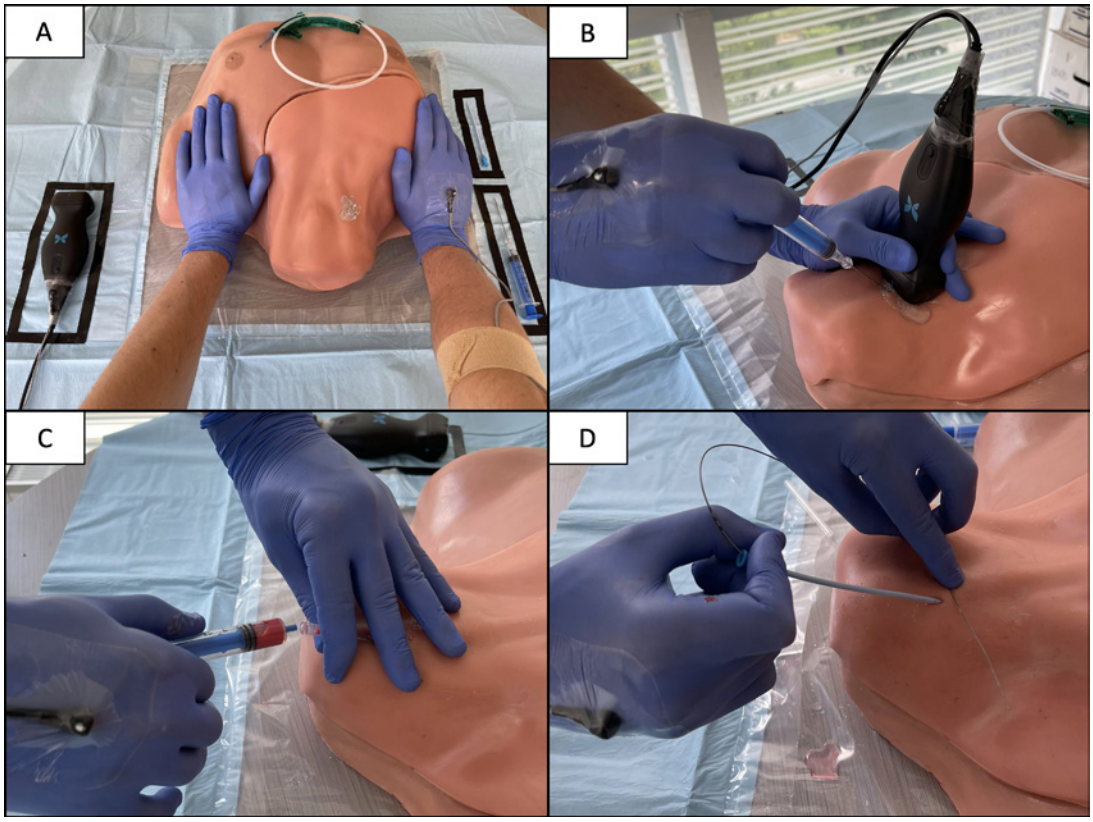

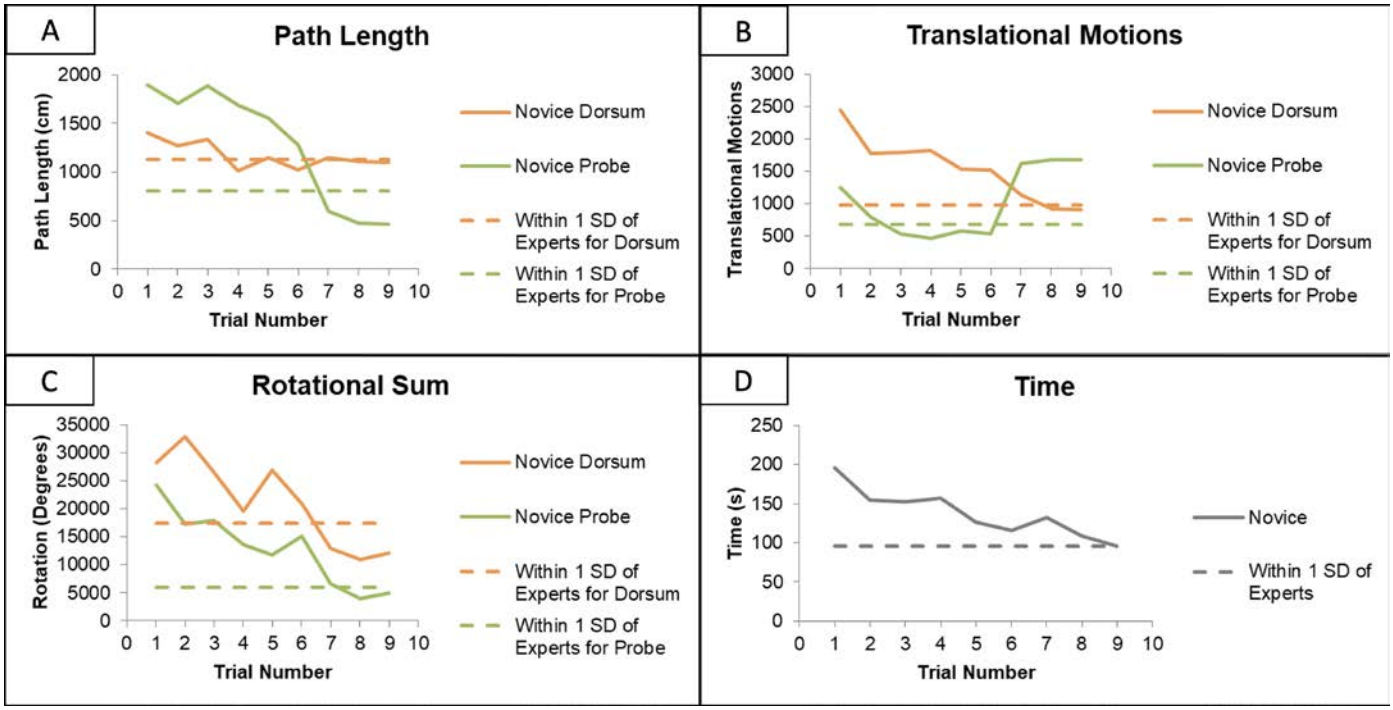

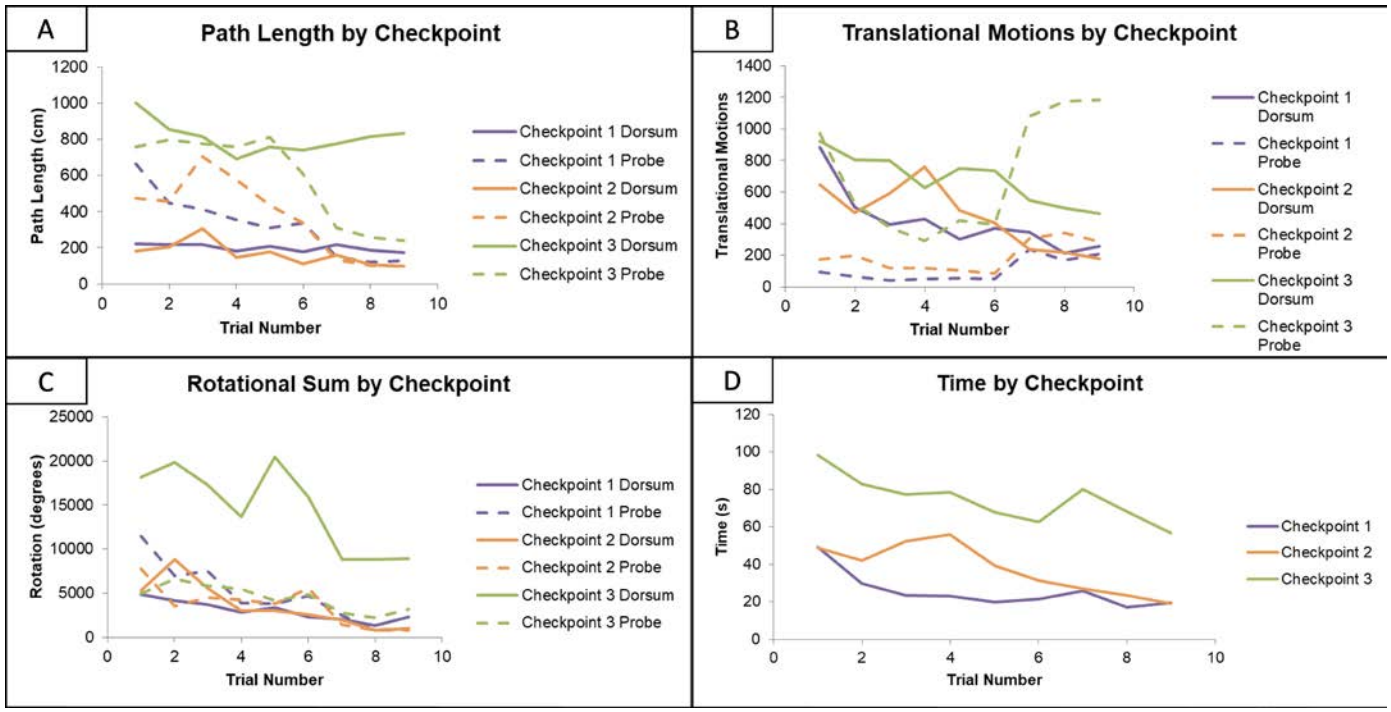

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 20

Demonstration of Artificial Intelligence Enabled Personalized Control of Hemodynamics (PCH) for High-Risk Surgery Patients in a Rat Model

Jinyoung Brian Jeong Jeong[1], Michael Zargari[2], Daniel Garcia[1], Chih-Ming Ho[1], Jacques Neelankavil[1], Maxime Cannesson[3], Jure Marijic[1], Soban Umar[2]

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INTRODUCTION: In surgery, even short periods of hypotension have been linked with increased incidence of complications such as acute kidney injury and myocardial infarction, leading to increased mortality and hospitalization. Despite substantial diversity among the 42 million surgery patients in the United States each year, management of hemodynamics currently uses a dose titration method, which is unable to precisely account for this diversity[1] (Fig. 1). An artificial intelligence (AI) platform, which is personalized based on a response surface of phenotypic variables and does not require large training datasets (AI-PRS), has been successfully used in the therapeutic intervention of organ transplants, cancers and infectious diseases[2-4]. By analyzing patients' unique hemodynamic response to medications with this platform, our AI-enabled Personalized Control of Hemodynamics (PCH) system can quickly customize drug dosing for a specific patient based on their individual physiology and biochemical profile[5,6]. Using this tool, hemodynamics such as blood pressure (BP) can be guided within a narrow and appropriate range. Here, we describe the preclinical testing and validation of the automated PCH in controlling BP of a rat model.

METHODS: Rats were anesthetized with isoflurane and placed on mechanical ventilation via a tracheostomy. Venous access for drug administration was obtained via femoral vein, and the left ventricular systolic pressure (LVSP) was continuously measured with a catheter that was placed directly into the left ventricle after sternotomy. Cardiac events were simulated by increasing the concentration of isoflurane to lower BP, or administering phenylephrine (PE) to raise it. LVSP was noted at baseline, and following bolus doses of medications to increase (with PE) or decrease (with nitroglycerin: NG) it, and analyzed to determine a population-averaged sensitivity. Syringe pumps and a pressure monitoring catheter were interfaced with a computer, and software was programmed to automate the system. AI-guided partial doses of PE and NG based on previously determined population-averaged profiles were given to dynamically calibrate individualized sensitivities, which were used to determine dosing to target LVSP (Fig. 2). LVSP readings were collected with PowerLabs from ADInstruments and all code was written in MATLAB. All experiments were conducted with IRB approval.

RESULTS: The preclinical PCH experiments were successful in controlling LVSP, from both hypotensive and hypertensive situations. The rats had varying responses to PE and NG, but by utilizing the calibrated individualized sensitivities, PCH brought the LVSP into target range with two boluses for most cases. Changing sensitivities to the medications, due to effects such as tachyphylaxis, were accounted for by the AI.

CONCLUSION: The emergence of AI has created a new paradigm for personalized and data-driven patient management. PCH greatly improves and simplifies BP management by utilizing dynamic personalized dosing. Our proof-of-concept experiments and analysis served as an initial step in validating the PCH for clinical use (patent pending). Ultimately, we will aim to develop the PCH platform to assist anesthesia providers in maintaining tight hemodynamic control with speed and precision.

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6. "Artificial Intelligence Assisted Control of Hemodynamics and Anesthesia in Surgery Patients", U.S. Provisional Patent Application No. 63/214,476 (2021)

Figure 1. Mean Arterial Pressure (MAP) management during surgery. *This retrospective data of a MAP recording during a coronary artery bypass graft illustrates that with current practices, keeping a patient's BP within a narrow range is a major challenge for anesthesiologists. The green area shows the safest range of MAP. Red boxes mark periods of time where the patient is hypotensive, which can increase the likelihood of complications.*

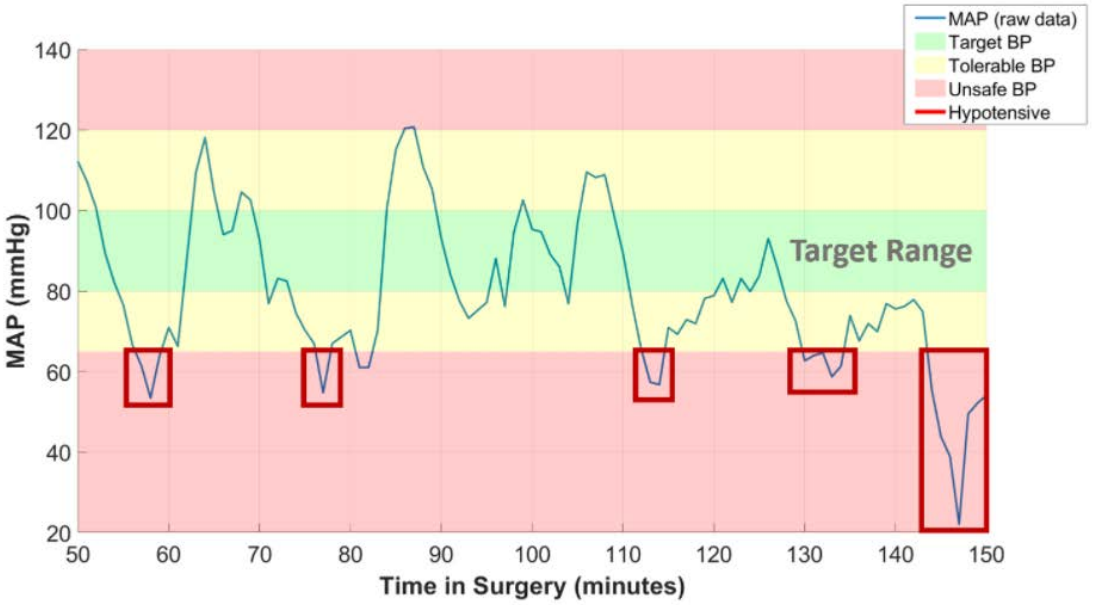
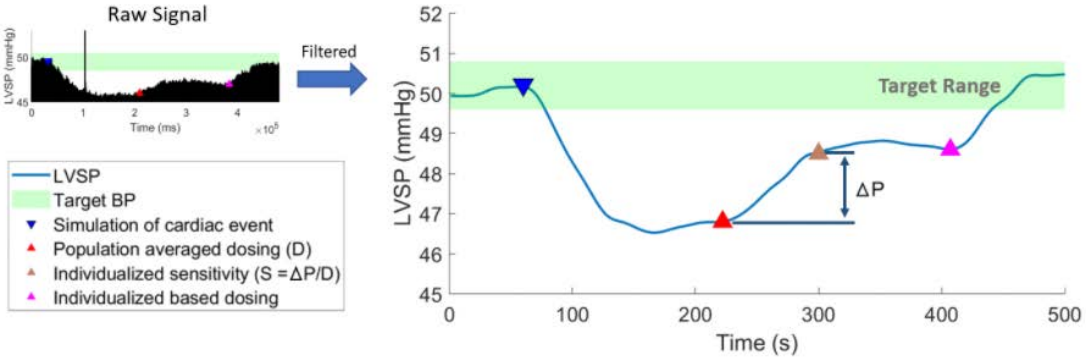


Figure 2. PCH system brings the LVSP of a rat into target range. *After decreasing LVSP by increasing isoflurane concentration (blue triangle), the rat is dosed with a partial dose of phenylephrine based on the population average (red triangle). Feedback is used to calculate an individualized sensitivity (brown triangle), which determines the remaining dose to target (pink triangle). Following the total dose, LVSP is in target range (green area).*



TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 21

A Sim Ops Guide to Setting Up Pediatric Anesthesia Oscillator Training Simulations

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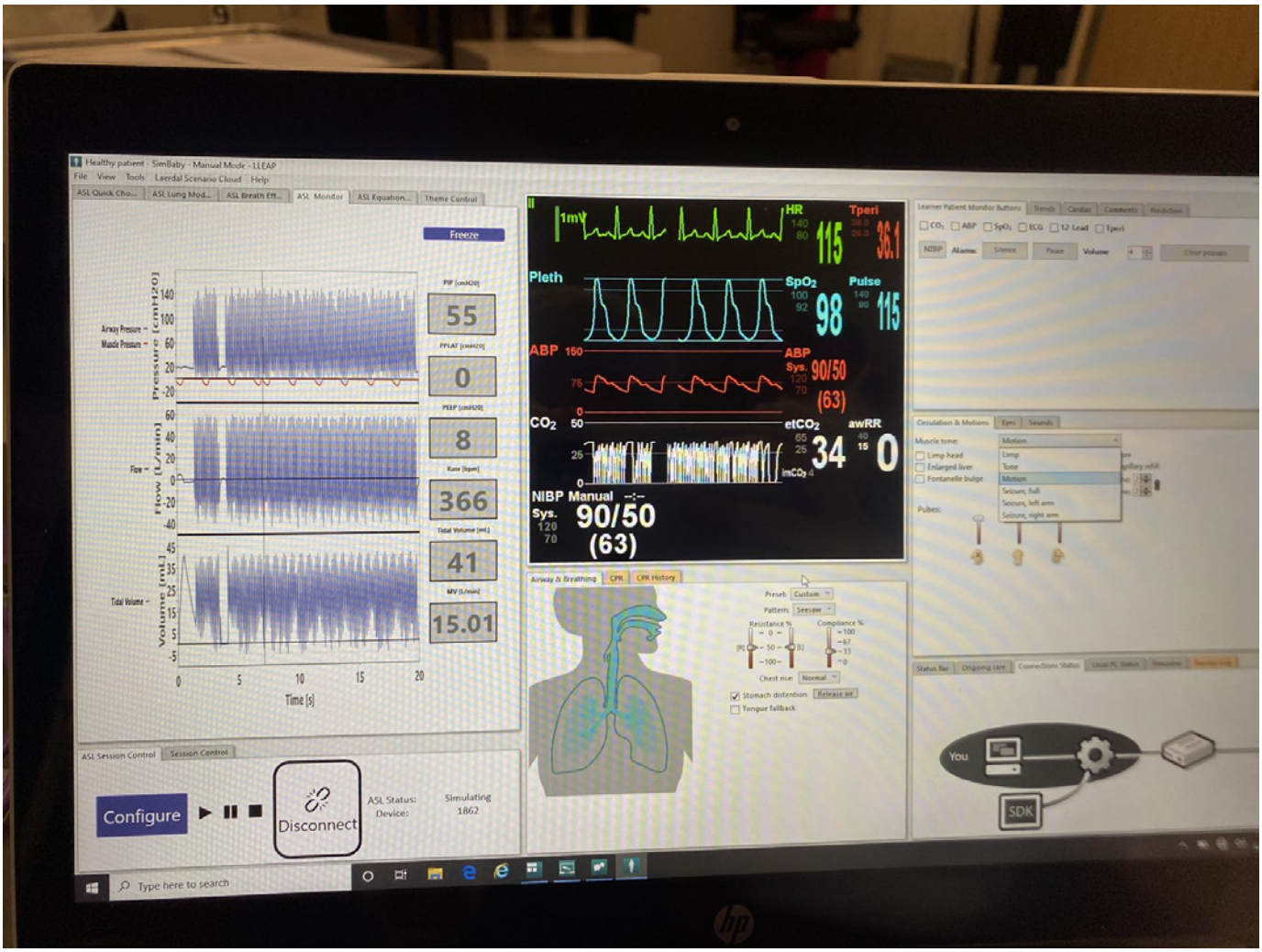
INTRODUCTION: High Frequency Oscillatory Ventilation (HFOV) is often used in Pediatric and Neonatal Intensive Care Units across the United States. Unfortunately, pediatric anesthesia fellows tend to have limited experience and education on how to manage HFOV. We present a new way to simulate HFOV in a micro-preemie for high-fidelity simulation scenario training for pediatric anesthesia fellows. This simulation could also be useful in the training of pediatricians, neonatologists, and pediatric intensivists.

METHODS: We have successfully used a micro-preemie low-fidelity mannequin with a real oscillator, and a high-fidelity lung simulator, for interprofessional simulations with our pediatric anesthesia fellows, faculty, and respiratory therapy for the past three years. Training groups have included three to five fellows per year with two to three faculty and a respiratory therapist each year. The micro-preemie mannequin can be connected directly to the oscillator via a 2.5 uncuffed endotracheal tube or via a high-fidelity lung simulator. Vital signs including heart rate and rhythm, blood pressure, SpO2, temperature, and FiO2, can be viewed via the patient monitor function on simulation platform.

RESULTS: With this setup, the mannequin is able to display chest wiggle similar to a real premature neonate and the settings on the oscillator can be changed appropriately for the case. Picture one shows our respiratory therapist teaching the group about HFOV and how to use an oscillator. Picture two shows the micro-preemie mannequin with the 2.5 endotracheal tube and the oscillator tubing connected. Picture three shows the output seen on the high-fidelity lung simulator when used in conjunction with the micro-preemie mannequin, 2.5 endotracheal tube, and oscillator.

CONCLUSION: HFOV can be effectively simulated using a micro-preemie mannequin, which opens many opportunities in HFOV training for pediatric anesthesia fellows, pediatric residents, neonatology fellows, and pediatric intensive care fellows. In theory, this same simulation set up would work with a toddler, child, or adult-sized mannequin as well.



TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 22

Human Demonstration of a Closed-loop, Wearable Naloxone Injector System

Jacob Sunshine[1]

[1]*University of Washington School of Medicine, Seattle, WA*

INTRODUCTION: Unwitnessed, fatal opioid overdose remains a substantial public health concern in the United States. Naloxone can readily reverse opioid toxicity but requires timely intervention from a bystander, yet most fatal overdoses occur when someone is alone. Within a harm reduction paradigm, people who use opioids for non-medical purposes endorse a willingness to take actions that keep themselves safe, including use of technologies that can sense and reverse an opioid overdose.[1] We report a human demonstration of a closed-loop wearable injector system that measures respiration and apneic motion associated with opioid toxicity using a pair of on-body accelerometers, and administers naloxone subcutaneously upon detection of persistent apnea.

METHODS: Our proof-of-concept system, comprising an accelerometer-based sensor patch coupleded to a wearable injection element (Figure 1), was developed and evaluated in two environments: (i) an approved supervised injection facility (SIF, InSite--Vancouver, BC), where people self-inject non-medically indicated opioids under clinical supervision and (ii) a lab environment with healthy participants who simulate persistent apnea and are automatically injected with naloxone subcutaneously. In the SIF, participants wore the system (without naloxone injection capabilities) and a respiratory impedance monitor (ground truth) to measure the accuracy of the system's respiratory monitoring capability during real-world, high-risk opioid self-injection events. Once fitted with the equipment, participants prepared their opioids, self-injected them, and their respiration was measured for 5 minutes. Bland-Altman analysis was performed to measure the system's accelerometer-based respiratory monitoring performance compared to ground truth. In the lab setting, the end-to-end system's performance (detection of apnea and automated administration of naloxone) was characterized on healthy volunteers. Participants were fitted with the wearable injection system, a ground truth respiratory monitor, and received an intravenous catheter for serial blood draws. Participants were instructed to engage in tidal breathing for 2 minutes, followed by breathing to a metronome at 8 breaths/minute and then to perform a breath hold for a minimum of 15 seconds, leading to subcutaneous administration of naloxone 1.2 mg (3 ml); blood draws were taken at baseline, 3 and 8 minutes post-injection initiation. Samples were analyzed using mass spectrometry (Xevo-TQs (Milford, MA)). The studies were approved by the Institutional Review Boards (IRBs) of the University of Washington, Vancouver Coastal Health, the University of British Columbia and registered with clinicaltrials.gov.

RESULTS: In the supervised injection facility, we recruited 25 participants over the course of two visits with a mean age of 48 ± 13 years, and female-to-male ratio of 0.14. Bland-Altman analysis showed a bias error of − 0.018 breaths per minute with 166 of 170 samples falling within the 95% agreement limits. The mean absolute breathing rate error computed over 30-s epochs was 1.7 ± 1.3 breaths per minute across all the participants (Figure 2). After injection of non-medically indicated opioids, 2 (8%) participants experienced at least one apnea event. In these participants, a decrease in respiratory rate of 3-4 breaths per minute during the monitored post-injection period was detected by our algorithm. During the SIF study, none of the participants experienced an overdose event requiring resuscitation. In the lab setting, the injector system detected apnea in 20/20 participants, with complete actuation of the injector element and successful delivery of naloxone in 18/20 subjects. Of these 18, fifteen participants triggered the injector on their first breath hold, while 3 of the remaining participants took between 2 to 6 attempts. All 18 participants had detectable plasma levels of naloxone by the 8 minute blood draw (Figure 3).

CONCLUSION: In this proof-of-concept work, we demonstrate the initial feasibility of a closed-loop, wearable naloxone injector system capable of accurately measuring real-world, opioid-affected respiration as well as opioid-induced bradypnea and, in healthy volunteers, administering naloxone in the setting of simulated apnea. Further work is needed to refine the automated algorithm to ensure acceptable injection performance in the setting of persistent apnea, in addition to feedback from system end-users to ensure it meets their needs, values and preferences.

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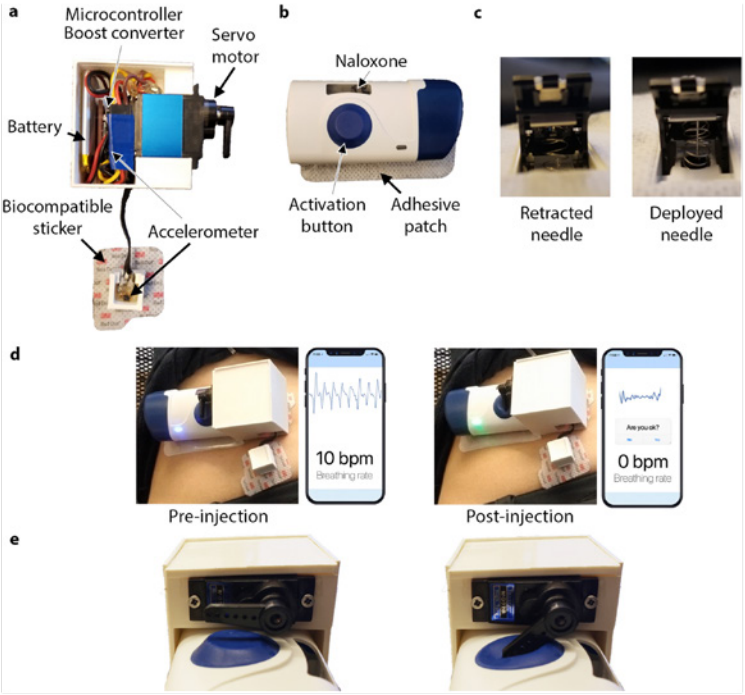

Figure 1. Overview of wearable auto-injector. (**a**) Sensor patch consists of two accelerometers to detect respiration and apneas, as well as a servo motor to activate the injector in the event of an overdose. (**b**) Wearable injector element (West Pharma, West Whiteland, PA) delivers naloxone subcutaneously when activation button is pressed. (**c**) The injector needle in a retracted and deployed state. After injection, the needle-shield locks out over the sharp end of the needle to prevent possible injury. (**d**) The device as placed on the subject's abdomen prior to and after activation of the injector. (**e**) Close-up view of servo motor pressing the injector button.

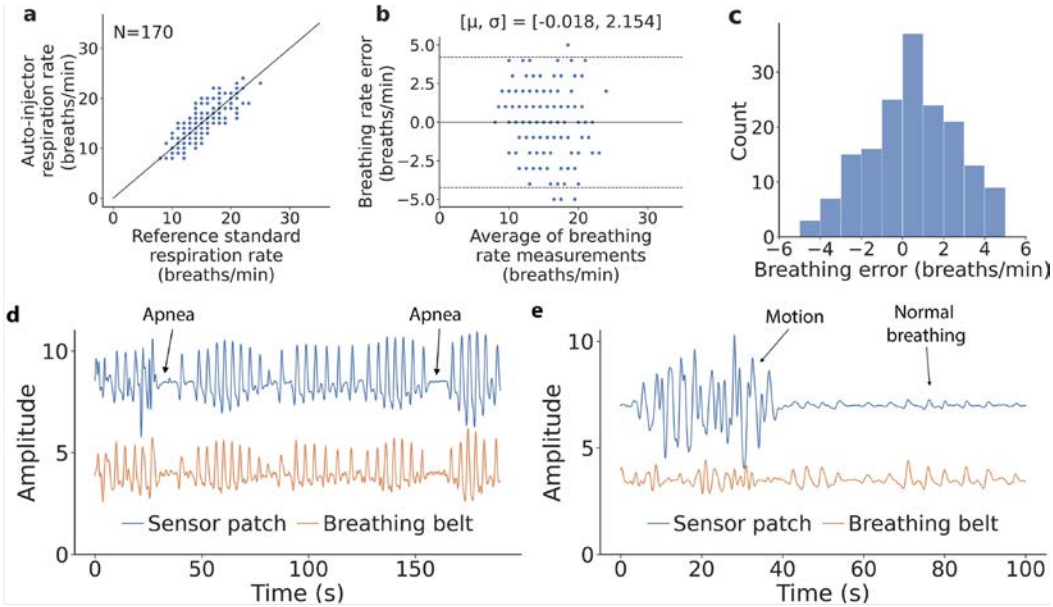

Figure 2. Measurement of non-medically indicated opioid use events in the supervised injection facility. (**a**) Correlation and (**b**) Bland–Altman plots comparing breathing rate from respiration belt (ground truth) and wearable sensor patch. In the Bland–Altman plot μ is the mean error and σ is the standard deviation (SD) of the errors; the solid line represents the mean error and the dotted lines represent the 95% limits of agreement. (**c**) Histogram of breathing rate error. (**d**) Example of raw breathing signal from sensor patch and breathing belt showing normal breathing, post-injection apneas and (**e**) human motion events at the supervised injection facility.

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Validation of a Research Mechanomyograph for Quantitative Twitch Assessment in Patients Receiving Neuromuscular Blocking Drugs

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INTRODUCTION: The gold standard assessment tool for measuring neuromuscular blockade (NMB) has traditionally been mechanomyography[1], despite the lack of commercially available testing systems. Studies on recent advances in pharmacologic reversal as well as new commercialized electromyographic measurement tools have been hampered by a lack of access to this gold standard. We previously demonstrated a novel mechanomyography device for assessment of quantitative train of four (TOF) ratio[2,3]. However, this device has never been externally validated through comparison with one of the original, commercial mechanomyography systems due to a lack of access[4]. Having recently obtained an original mechanomyography system and performed modifications to the hardware and software to allow the device to work with modern computers, we present the first in patient comparison testing with our new compact, inexpensive mechanomyography device.

METHODS: Five patients were enrolled in an IRB approved study of the research MMG, original MMG and clinical EMG systems in December 2021. Design and attachment of all the devices are shown in Figure 1. Patients were treated with neuromuscular blocking agents and reversal drugs at the discretion of the anesthesia provider. TOF ratio was assessed throughout the case with EMG and original MMG obtained simultaneously (EMG stimulus was used to measure the original MMG) and research MMG obtained on the opposite hand, all measurement pairs were obtained within a five second timespan. Data was obtained every minute when four distinct peaks were visualized in the raw data, more frequently, up to every 20 seconds when reversal drugs were given to maximize data collection across a range of TOF values. Over 600 individual measurements yielding more than 200 research vs. original MMG comparison data points and more than 200 MMG vs. EMG comparison data points. Data post processing included steps to remove electrocautery noise, ensuring sufficient signal strength relative to noise floor, data smoothing using a median filter approach and calculation of a train of four ratio using both the peak value as well as the area under the curve. A screenshot of data collection during a patient study showing peaks for both the original MMG (white) and research MMG (red), as well as post processing results of measured peaks is shown in Figure 2.

RESULTS: Substantial agreement was found between both the MMG devices, as well as when comparing the MMG devices to the clinical EMG with r squared values between 0.87 and 0.96. Figure 3 shows the values obtained over time from a single patient during recovery of neuromuscular blockade and administration of reversal agents over time for all three modalities. The right hand side shows a scatter plot of MMG values for all patients. Figure 4 shows comparisons between each MMG measurement technique and the clinical EMG technique. Table 1 shows differences in two different methods for calculating TOF, the first using maximum value of a peak and the second using area under the curve. Using peak value provided slightly better correlations than area under the curve calculations. Other measured outcomes including setup time, space constraints and frequency of recalibration were much worse for the original EMG device when compared to the research device.

CONCLUSION: These results demonstrate good correlation between the original MMG, research MMG system and EMG. The research MMG system has several benefits over the original in that it is much smaller, easier to apply and maintain within the desired calibration range. It is made up of low-cost components which could be put together in less than a day by someone with undergraduate level engineering expertise. The original MMG is much larger, comprised of mechanical parts which decay with age, components which cannot be easily replaced as they are no longer being manufactured and larger baseline signal noise and drift (data not shown). The original MMG correlated slightly better with EMG than the research MMG (r squared 0.96 vs 0.93), likely because they were always measured on the same arm, using the same electrodes for stimulation while research MMG was measured on the opposite arm. Prior work has shown some variation in measurements taken on different arms2. Future work will focus on collecting additional patient data with the EMG and research MMG measured on the same arm.

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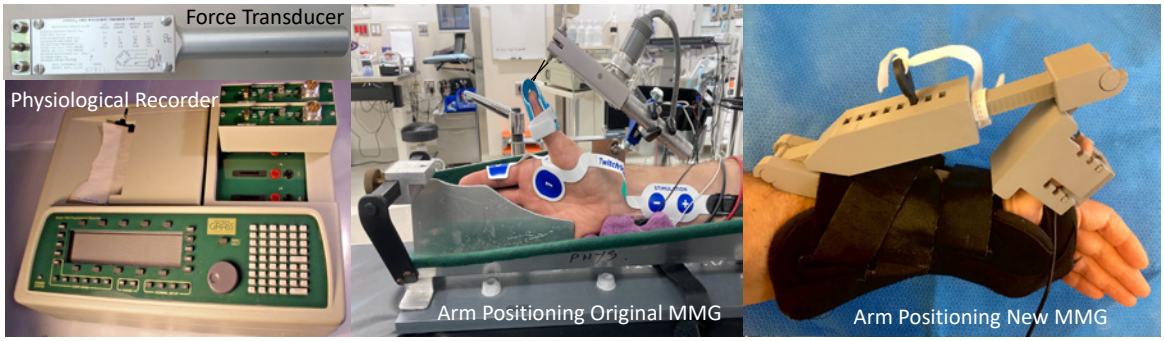
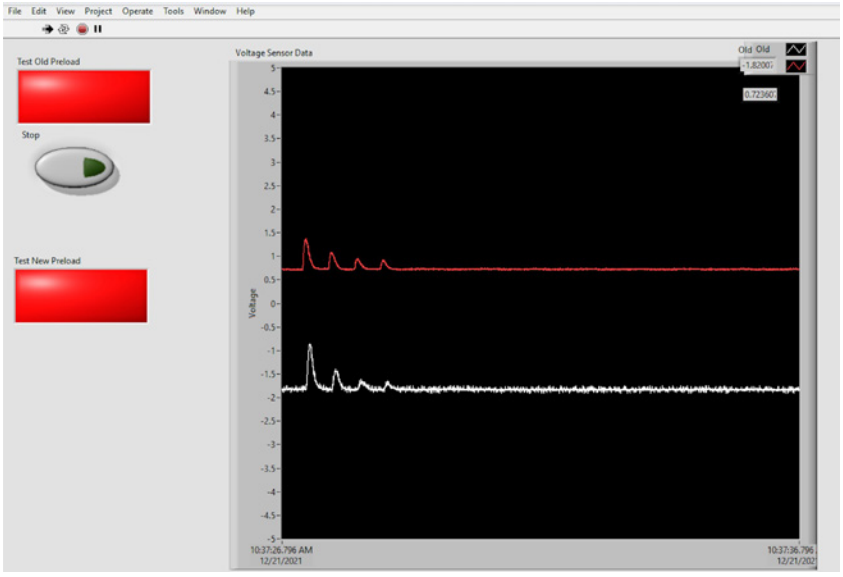


Figure 1



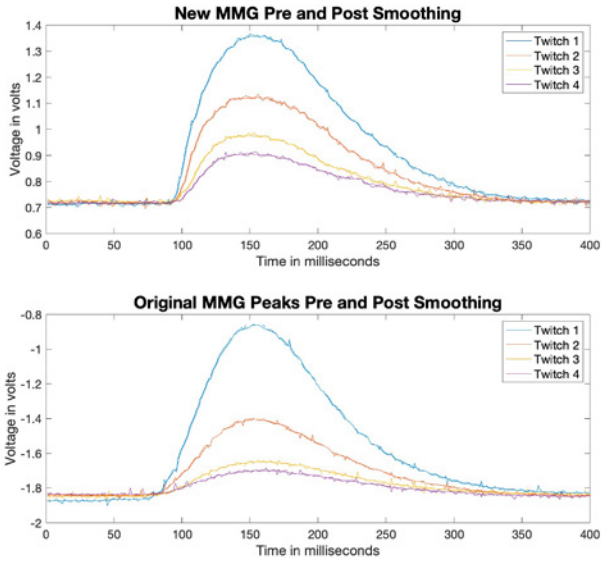


Figure 2

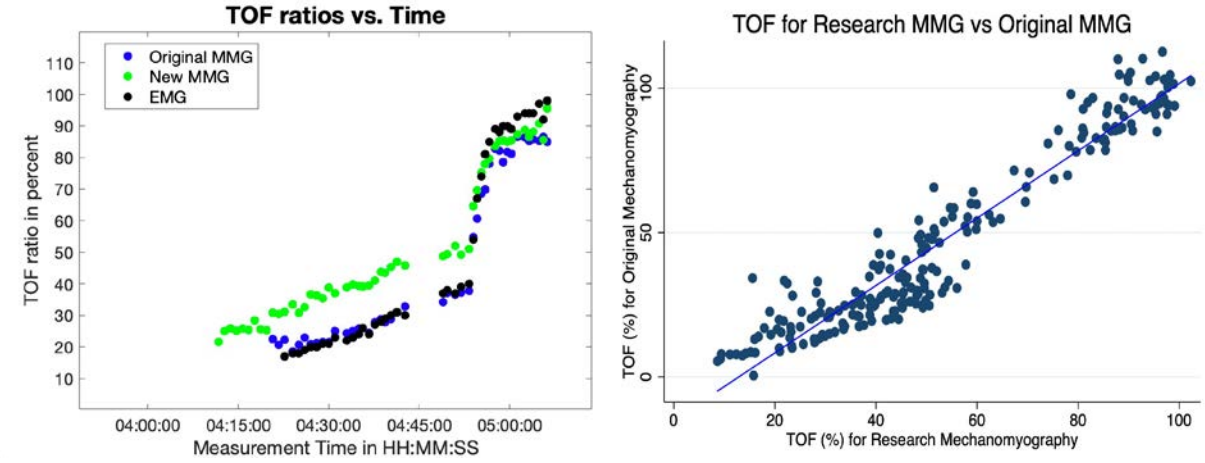


Figure 3

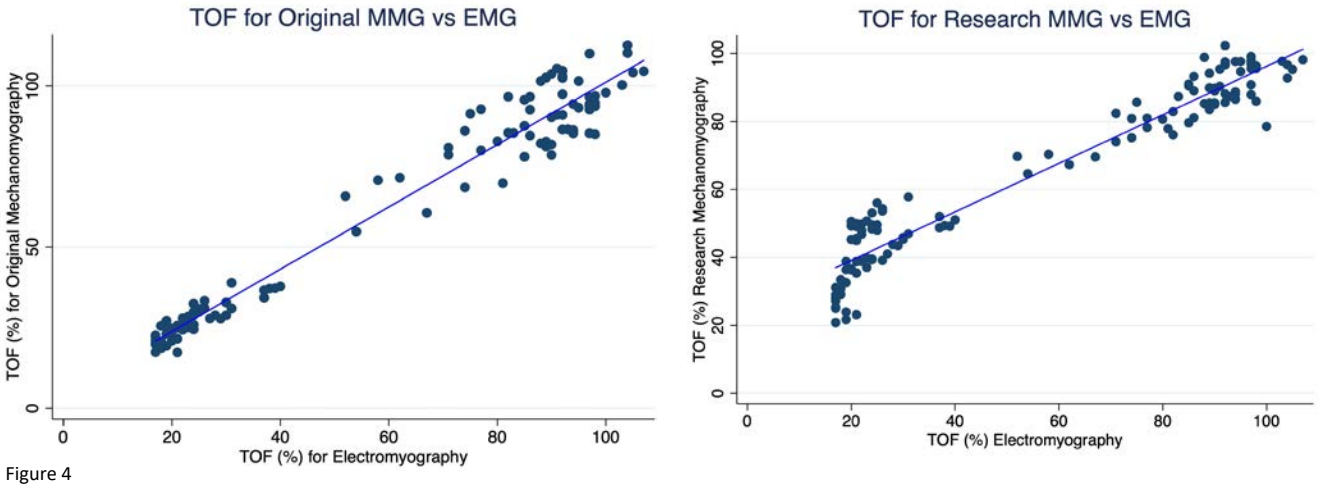


Figure 4

Table 1

R^2 Value for different TOF Calculation Methods	Peak	AUC
Original MMG vs Research MMG	0.91	0.88
Original MMG vs EMG	0.96	0.94
Research MMG vs EMG	0.93	0.87

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A novel model for massive pulmonary hemorrhage management training - demonstration of training utility in pediatric anesthesiologists

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INTRODUCTION: Massive pulmonary hemorrhage (MPH) is an airway emergency that requires immediate intervention, such as with bronchial blockade. Although bleeds of this magnitude are uncommon,[1] the associated mortality is reported to be as high as 38%.[2] The management of low frequency high acuity events, such as MPH, may benefit from simulation whereby critical care practitioners can safely develop and retain airway skills in low-consequence environments. However, a physical model of MPH for use in simulation has not been previously described. Therefore, the purpose of this project was two-fold: 1) to develop a model of MPH; 2) to apply the model in simulation with attending pediatric anesthesiologists and evaluate its utility.

METHODS: The model of MPH (Fig. 1) and the simulation environment were created in consultation with experts in anesthesiology, pulmonology, and human factors/simulation. A 20 mL bolus of artificial blood (Ben Nye, California, USA) is injected into each the oropharynx and the left bronchioles of a carbon fibre AirSim Advance Bronchi X manikin (TruCorp, Lurgin, Northern Ireland), which features internally accurate respiratory anatomy. Next, the artificial blood is pumped at a rate of 600 mL/hr via a catheter into the base of the left bronchial tree. Balloons located at the end of each bronchial tree serve as "lungs" and are used to indicate whether bronchial blockade and unilateral ventilation has been successfully achieved. The model has the capacity to elicit coughs, which reproduce the expected physiological response to airway stimulation. To evaluate the model, trials took place in an operating room in the hospital. Twenty attending pediatric anesthesiologists were recruited. Following written informed consent, participants completed a pre-study demographic questionnaire and a practice intubation trial. Next, they were instructed to perform left-sided single lung isolation of the manikin using four techniques in a stratified random order. Single use disposable bronchoscopes (Ambu Inc., Maryland, USA) were cleaned and reused between trials. A member of the research team served as an anesthesia assistant during the trials. Following the simulation, participants rated an adapted series of affirmative statements,[3] using a REDCap survey: five statements regarding the present MPH simulation, and four statements regarding simulation in general. Five-point Likert scales ranging from strongly disagree, to strongly agree were used. The primary outcome was the average rating across participants for each statement. Open-ended feedback regarding the experience was also collected. Each simulation concluded with a participant-tailored debrief session.

RESULTS: Data from 20 participants with an average (±SD) number of 13.89 (± 8.02) years of clinical practice, including fellowship, were available for analysis. Six participants had previous experience managing or assisting with the airway in an MPH case. Moderate agreement (3.85 ± 0.93 of 5) that the simulation provided a realistic model of MPH was reported. A high level of agreement amongst the participants on the utility of the simulation in improving their knowledge of devices (4.35 ± 0.59), practical skills (4.25 ± 0.72), and confidence in managing MPH (4.1 ± 0.72) was reported. Importantly, the statement most strongly agreed with was interest in participating in future simulations related to low-frequency airway emergencies (4.8 ± 0.41). A summary of Likert survey responses is presented in Figure 2.

CONCLUSION: A model of MPH was developed and demonstrated to have high utility for ongoing training in critical care airway management. The high acuity low frequency nature of MPH highlights its suitability for simulation training, even for senior anesthesiologists with extensive clinical practice. Future work will evaluate the utility of the simulation model in resident trainees, who have less experience with the various methods of single lung isolation in this difficult airway scenario.

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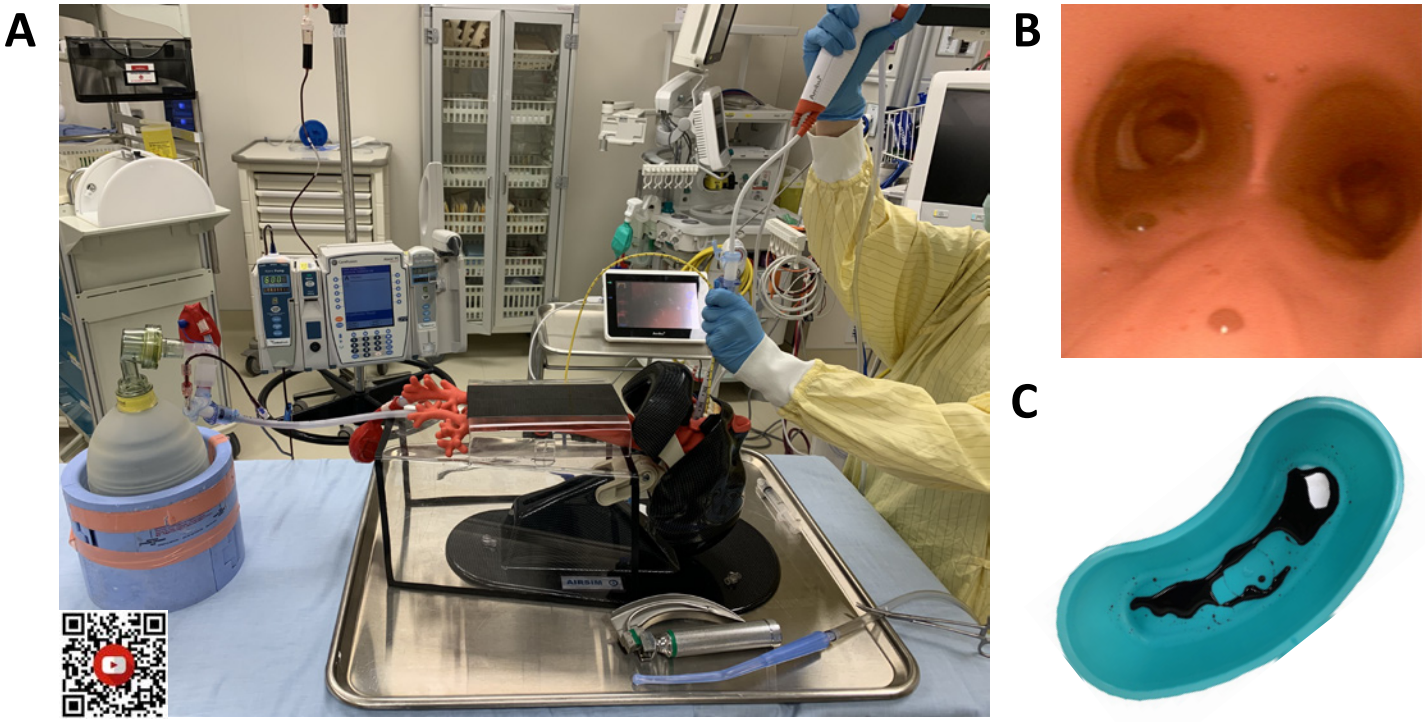

Figure 1. Massive pulmonary hemorrhage (MPH) simulation. (A) Equipment is set-up in the operating room. The TruCorp AirSim Advanced Bronchi X mannikin used in the model has an anatomically accurate internal respiratory tract. (B) The carina and main bronchi as seen on the portable monitor. To simulate MPH during the trial, (C) artificial blood is pumped into the base of the left bronchial tree at 600ml/hr. Vigorous pressure on the Ambu bag produces a cough, viewable via the QR code.

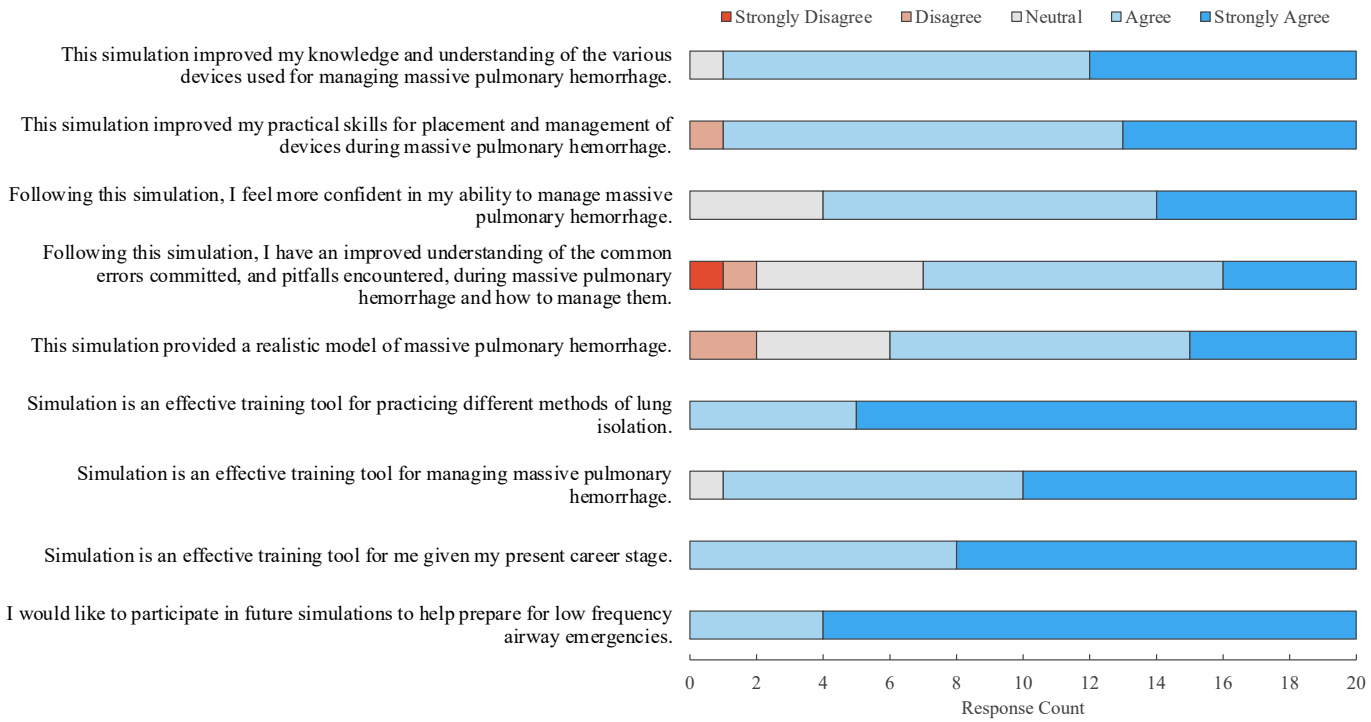

Figure 2. Summary of participant survey responses following massive pulmonary hemorrhage simulation.

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Absence of Racial Bias In Pulse Oximetry Saturation Measurement

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INTRODUCTION: Pulse oximetry is a critical monitor for assessing oxygenation status and guiding oxygen therapy. A retrospective comparison of arterial oxygen saturation (SaO2) with peripheral pulse oximetry (SpO2) found a nearly 3-fold increase in in the incidence of hypoxemia undetected by pulse oximetry in Black patients compared to White patients.[1] This report triggered an FDA Safety Communication emphasizing the limitations and potential inaccuracies of pulse oximetry in certain situations including home monitoring of patients with COVID-19. This possible racial bias in measurement could contribute to inequities in healthcare. However, race is not binary. Furthermore, the variable of interest is actually skin color. Race does not uniquely characterize skin color. There is a wide range of graded colors within any group of individuals with a common racial identity. A subsequent study focused on SpO2 measurements in ethnically diverse patients hospitalized with COVID-10 pneumonitis failed to demonstrate any effect of ethnicity on SpO2 accuracy.[2] Our study reported here retrospectively examined SpO2 accuracy using data from unrelated clinical trials that included a standardized, graded assessment of skin color in addition to racial identity.

METHODS: Following Human Subjects Research Committee approval, electronic medical records and previous clinical trial data were used to collect basic demographic information, including reported race and ethnicity as well as skin color assessed using the NIS Massey and Martin Skin Color Scale.[3] This scale ranges from 1 (very light skin) to 10 (very dark skin) and was recorded at the time of enrollment by trained personnel who referred to a standardized color image of the scale values. Arterial blood gas (ABG) PaO2 and SaO2 values and the corresponding SpO2 values were extracted from clinical laboratory reports and vital signs flowsheets. For all PaO2 values ≤125 mmHg, the corresponding SaO2 and SpO2 values were compared. Differences were grouped by the patient's Massey score. Group comparisons were performed with the Kruskal-Wallis test using GraphPad Prism version 9.2.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com.

RESULTS: Massey skin color assessments were available from 742 patients. Within this group, patients who identified as Black had Massey scale vales ranging from 5 to 9 and those who identified as White had values ranging from 1 to 5. For each patient, all ABG values for the initial and any subsequent hospitalizations were extracted from the medical records. 579 patients had ABG PaO2 values ≤125 mmHg. A total of 4,030 individual comparisons were available for analysis. The number of measurements at each Massey scale rating is summarized in Table 1. The average errors for each group are presented as a violin plot in Figure 1. There was a statistically significant difference among the groups ($p<0.0001$).

CONCLUSION: The potential for a clinically significant influence of skin tone on the accuracy of SpO2 measurements merits careful evaluation. These differences are better characterized using a standardized graded scale of skin color rather than patient identified race. This review failed to demonstrate any bias due to race or skin color in this measurement. Despite statistical significance, the observed errors are all within the stated and expected accuracy of the SpO2 monitor. Two limitations must be highlighted. The distribution of Massey scores is skewed to lower values. In this data set, the statistical differences are driven by the values for the Massey scale 8 which includes only 5 measurements from 3 patients. Second, the retrospective design in this review limits the confidence in the SpO2 measurements, especially at lower PaO2 values. These frequently occur in clinically dynamic periods that may not be as accurately captured by the lower time resolution data stored in the available vital signs flowsheets. These results do, however, demonstrate the need, and provide a template for subsequent prospective evaluations of skin color as a confounding influence in SpO2 measurement.

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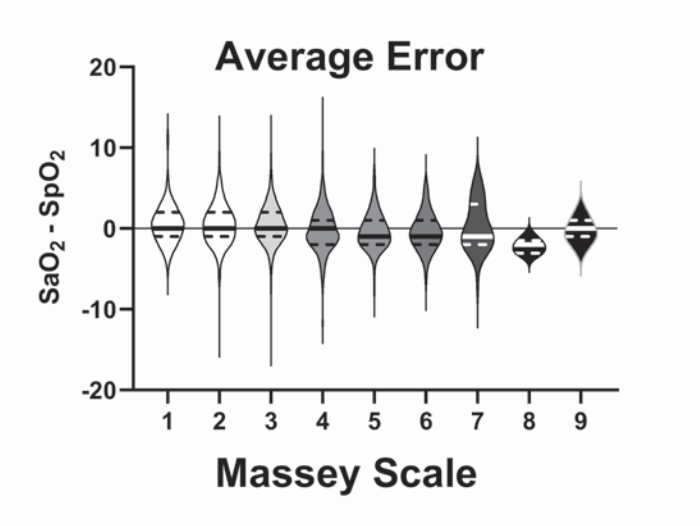
Massey Score	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Number of patients	27	221	196	80	30	14	7	3	1
Number of values	123	1471	1281	764	184	137	38	5	27
Median Error	0.00	0.00	0.00	0.00	-1.00	-1.00	-1.00	-2.00	0.00
Mean Error	0.53	0.46	0.38	-0.2	-0.35	-0.39	0.21	-2.2	-0.3
Std. Deviation	2.5	2.6	2.6	2.9	2.3	2.3	3	0.86	1.6



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Mask Ventilation Grip Device: A manikin study comparing the efficacy of a novel device to standard two-handed mask ventilation technique

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INTRODUCTION: During bedside airway emergencies, the nearest provider may have limited experience with delivering mask ventilation (MV) compared to anesthesiologists.[1, 2] Therefore, investigating strategies to make MV easier to deliver for inexperienced providers is warranted. In challenging cases, two-handed techniques are required over one-handed techniques.[3-7] The mask ventilation grip (MVG) device was designed to facilitate two-handed MV (Figure 1.)[8] This study investigates whether use of the MVG device improves two-handed MV. Our primary objective was to test the hypothesis that performing two-handed MV with the MVG device in a manikin simulation setting results in greater average expired tidal volumes (TVavg) than standard two-handed MV technique (Standard;) and that if this effect is present, it is more pronounced in novice providers versus experts. Secondarily, we also investigated the perceived task load and fatigue of providers when performing two-handed MV with and without the MVG device.

METHODS: This study has a repeated-measures cross over design and is powered sufficiently with a sample size of 32 subjects (16 novices and 16 experts) (Figure 2.) Novices were subjects without experience performing MV and consisted of interns and medical students; experts were subjects with more than 2 years of experience performing MV. Recruitment was conducted via email to University of Miami (UM) Miller School of Medicine clerkship directors and the Department of Anesthesiology. After obtaining written informed consent, subjects were randomized into order groups (Standard->MVG versus MVG->Standard) that indicated the order in which they would employ the techniques. TVavg values were obtained from subjects delivering two-handed MV to a manikin during separate sessions with each technique) in accordance with their order groups. Our primary outcome of interest, differences in mean TVavg, was analyzed for significance with respect to technique, expertise level, and order of techniques. Following each MV session, subjects completed the NASA-Task Load Index (NASA-TLX) and the Swedish Occupational Fatigue Inventory (SOFI,) instruments as a measure of subjective experience of task load and fatigue perceived with each technique. Differences in mean scores of items within both forms were analyzed with respect to technique, expertise, and order. All statistical analyses were performed with SPSS version 28. To test for the effect of within-subjects variables (Technique,) between-subjects variables (Order and Expertise) and their interactions, hypothesis testing was completed with a general linear model in the form of a mixed design with repeated measures. In addition to the calculated P values for each pairwise comparison, point estimation, and 95% confidence interval (CIs) were also calculated. Effect size is reported as the absolute difference between the means for each dependent variable across experimental conditions.

RESULTS: The final dataset consisted of 16 novices and 13 experts after 3 experts were excluded due to technical issues. Performing two-handed MV with the MVG device increased TVavg compared to Standard technique (MD = +17.058 mL; P = 0.004; Table 1.) No significant effect was observed with respect to order or expertise (Table 1.) Mean scores for NASA-TLX items were overall higher with Standard technique than with the MVG device (MD = +9.161; P = 0.022; Figure 3.) Specifically, the mean item scores of 'Physical Demand' (MD = + 3.420; P = 0.0004) and 'Effort' (MD = + 0.2470; P = 0.011) were greater with Standard technique than with the device (Figure 3.) Similarly, mean scores for SOFI items, 'Lack of Energy' (MD = + 2.417; P = 0.002) and 'Physical Exertion' (MD = + 1.323; P = 0.015) were greater with Standard technique than with the device (Figure 4.) Expertise had an effect on scores in both psychometric instruments. Amongst NASA-TLX items, novices' mean scores for self-assessed 'Performance' (MD = +4.028; P = 0.0008; Figure 3) and 'Frustration' (MD = +4.143; P = 0.010; Figure 3) were higher than experts' respective scores. Within the SOFI items, novices' mean scores for 'Physical Exertion' were higher than experts' (MD = +1.719; P = 0.039; Figure 4.)

CONCLUSION: The results demonstrate that the MVG device is an objective and subjective improvement of standard two-handed MV technique. This study also shows that gaps in expertise level may not present as objective differences but as subjective differences in perceived task load and fatigue.

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Table 1: TVavg

Independent factors	Observed Effect		Significance ($P < 0.05$)
	*Non-Standardized (mL)**	*Standardized (Partial Eta Squared)*	
Within-subjects			
Technique	**+17.058**	0.292	$P = 0.004$
Technique*Expertise		0.050	$P = 0.263$
Technique*Order		0.021	$P = 0.473$
Technique*Expertise*Order		0.002	$P = 0.846$
Between-Subjects			
Expertise	**-3.439**	0.002	$P = 0.822$
Order	**+21.787**	0.077	$P = 0.162$
Expertise*Order		0.015	$P = 0.543$

Footnote: Non-Standardized observed effect values are reported from the following perspectives.

Technique: MVG compared to Standard technique; I.E.: A value of +3 indicates that subjects obtained TVavg values with the MVG device that were 3mL greater than their obtained TVavg values using Standard technique.

Expertise: Novice compared to Expert; I.E.: A value of -3 indicates that novice subjects' mean TVavg values were 3mL less than experts' TVavg values.

Order: (Standard→MVG) compared to (MVG→Standard); I.E.: A value of +3 indicates that subjects who started the experiment with the Standard technique before switching to the MVG device demonstrated mean TVavg values that were 3mL greater than subjects who started the experiment with the MVG device before switching to the Standard technique.

Figure 1

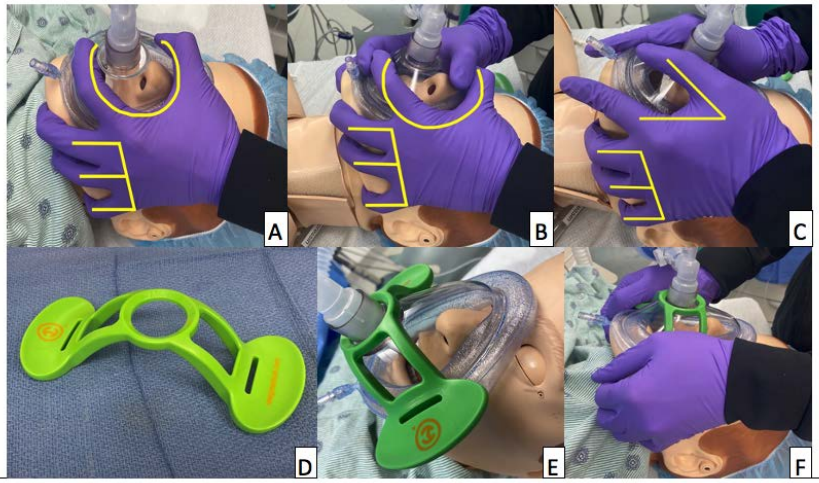

Figure 1: The one-handed C-E grip (E-C clamp) consists of the thumb and index finger of one hand forming a "C" shape as they hold the mask and apply downward pressure, as the the third, fourth, and fifth fingers (E) pull the mandible into the mask, collectively forms an air-tight seal (A.)[3] This one-handed grip technique enables the provider's free hand to squeeze a reservoir bag or perform other functions. In the 2-handed C-E technique, the thumb and index finger of each hand form a "C" shape as they grasp the mask from each side while while pushing down onto the face as the remaining fingers (the E) on both hands lift the mandible toward the mask (B.) In the 2-handed V-E technique, the thumb and thenar eminence of each hand are placed on the sides of the mask, forming a "V" with the second finger, which in addition to the remaining fingers is available to pull the mandible up into the mask. (C)* In both two-handed techniques, gas flow is supplied by mechanical ventilation or another provider.[3] The MVG grip device (D) is an add-on device that fits onto most anesthesia masks (E.) The "wings" of the device are designed to provide more lateral and lower-set leverage points for the provider to place their thumbs/thenar eminences, which creates a shorter distance for their other fingers to traverse and more comfortably grasp the mandible (F.)

Footnote: The index fingers of the provider in Figure 1C are extended outwards to demonstrate the potential to provide support over the mental protuberance in comparison to the 2-handed C-E grip.

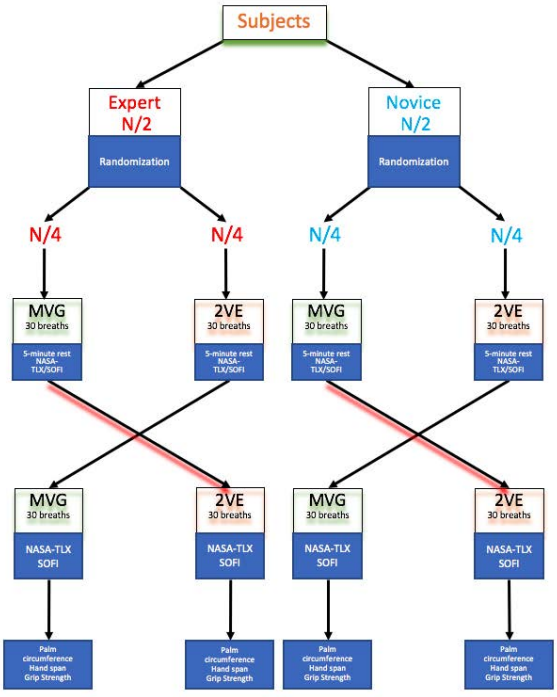

Figure 2: A schematic representation of the repeated-measures mixed-model design. Equal numbers of expert subjects and novice subjects were recruited for the study. Each expertise group was then further randomized to groups indicative of the order of exposure to both grip techniques. As such, grip technique (Technique) was our repeated independent variable and order of exposure to grip techniques (Order) and expertise level (Expertise) were our non-repeated fixed factors.

Figure 3

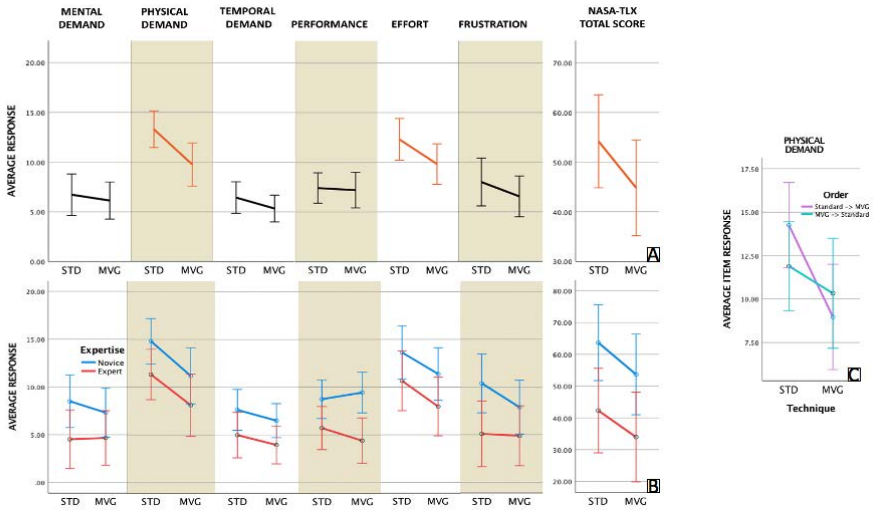

Figure 3: The difference in mean scores of "Physical Demand," "Effort," and "Nasa-TLX Total Score" were statistically significant with respect to Technique; this is highlighted in orange. Providing two-handed MV with MVG was perceived as less physically demanding and requiring less effort than Standard technique (A.)

Although only difference in mean scores of "Performance," "Frustration," and "NASA-TLX Total" demonstrated statistical significance with respect to Expertise, there were noticeable differences in mean scores between the expertise groups observed in all the items within the NASA-TLX assessment, which fell short of statistical significance (B.)

Subjects who belonged to the Order group "Standard→MVG," averaged "Physical demand" scores of 14.250 for MV with the Standard technique and 8.973 for MV with the MVG technique. Subjects belonging to the group "MVG→Standard" had average scores of 11.896 for the Standard technique and 10.333 for the MVG device (C.)

Figure 4

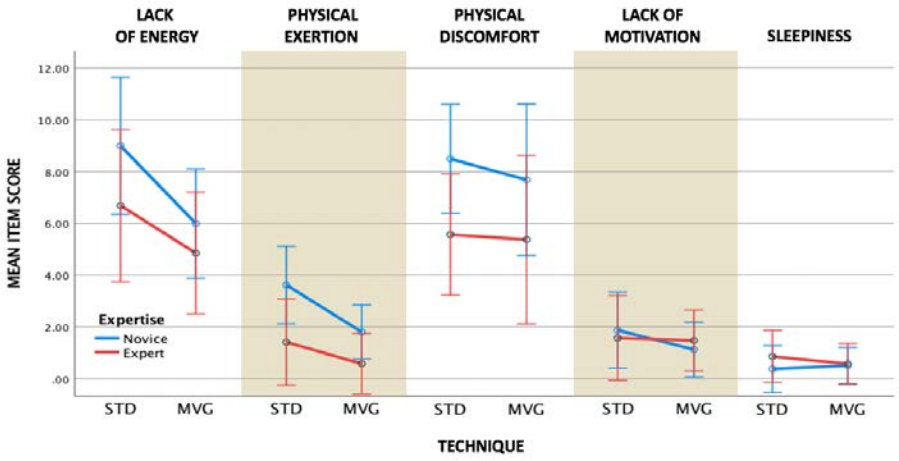

Figure 4: Average SOFI item scores for each expertise group with respect to Technique. Mean item scores are displayed with 95% confidence intervals. Technique had a significant effect on mean scores for the items "Lack of Energy" and "Physical Exertion." While there was no statistical difference with respect to Technique in the remaining items, the magnitudes of the "Physical Discomfort" item scores were high for both techniques, indicating that both techniques were uncomfortable to use. While Expertise had a statistically significant effect in mean scores for only the "Physical Exertion" item, there is a clear difference in novice score distributions and expert score distributions within the "Lack of energy" and "Physical discomfort" items as well.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 27

Using 'Plan, Do, Study, Act' (PDSA) Cycles to Improve an Ultrasound Guided Vascular Access Course

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INTRODUCTION: Establishing vascular access is a critical skill for anesthesiologists. With an increasing overweight patient population in the United States, ultrasound guidance is imperative for obtaining expedient arterial or venous access. Traditionally, trainees were only able to develop these proficiencies in the operating room which can limit skill acquisition. To address this, we developed and hosted a workshop focused on furthering the technical skill of ultrasound to establish vascular access. The ultrasound simulator was a mold made from ballistics gel and a 'Plan, Do, Study, 'Act model of process improvement was used to rapidly evaluate effects of the changes made in the simulator mold. The workshop consisted of two-parts the first being short 20-minute multi-media lecture that reviewed the basics of POCUS machines, discussed the advantages and disadvantages of short axis and long axis cannulation, and reviewed catheter length and target vessel depth. This was followed by approximately 70 minutes of unstructured time to allow learners to use various types and sizes of peripheral intravenous catheters, arterial catheters, and central lines on the homemade simulators made using ballistics gel. After each workshop, a survey was sent to the learners to solicit feedback about the workshop, the simulator molds, and the learning materials. Rapid changes to the workshop and simulator were rapidly implemented based on feedback from the learners.

METHODS: Six workshops were held between July 2018 and December 2021 for incoming CA-1 residents and anesthesiologist assistant students. A total of 57 trainees filled out the post-course evaluation survey. 12 ranked questions and 3 free text questions were answered.

RESULTS: There was a gradual improvement in the quality of the ultrasound simulator molds. This was expected due 'Plan, Do, Study, Act' process improvement model used for the simulator mold. Improvements over the study period include but not limited to changing the melting techniques to reduce the amount of air bubbles in the ballistics gel, changing the diameter of the vessels, trialing out different types of tubing, and adding dye to color the gel. The ultrasound models worked well (LIkert Scale 1=Strongly Disagree, 2=Disagree, 3=Neutral, 4=Agree, 5=Strongly Agree) 3.10 4.33 4.17 3.83 4.76 4.33 I would recommend this workshop to a colleague. 4.30 4.83 4.67 4.33 5.00 5.00

CONCLUSION: A 'Plan, Do, Study, Act' model of rapid process improvement can be an effective method in the development of ultrasound simulators for vascular access workshops. Future directions of the workshop would include the use of Butterfly iQ+ which allows for imaging in both long-axis and short-axis views at the same time. In addition, creation of the simulator mold that is longer in length to allow for full cannulation of the central venous catheters.

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TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 28

Arterial line: how accurate is it?

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INTRODUCTION: Variability exists between accuracy of arterial line transducers that can create inconsistencies in the management of intraoperative, postoperative and ICU blood pressure through invasive measurements; especially when reusable transducers are used. The Philips Intellivue MX800 monitors allow for a correction factor to be applied to invasive blood pressure measurements to compensate for this (ranging from 180 to 220). We have discovered that this value was being incorrectly modified within our institution. This value can be easily changed by any healthcare personnel or be locked to an incorrect value by engineering departments. The purpose of this study was to identify the ideal settings for obtaining the most accurate blood pressure readings and to assess the prevalence of incorrect monitor configurations within our institution.

METHODS: The validity of measurements from a monitor can be easily verified by using a sphygmomanometer connected to the transducer to raise the pressure to a desired level and confirming the reading on the screen. A monitor was calibrated with four disposable transducers at 200 mmHg of pressure; per instructions from the Phillips manual. A pressure reading was also tested in a Datex-Ohmeda monitor, which had no option for calibration. Furthermore, the settings of 52 monitors in the post anesthesia care unit (PACU) and preoperative holding area was verified.

RESULTS: The mean calibration factor obtained from new disposable transducers was 205; all values we're within a 204.5 to 205.5 range. The Datex-Ohmeda monitor confirmed a reading consistent with one from a Phillips monitor with a calibration factor of 200. In the PACU and preoperative holding area, 10 monitors had inappropriately low calibration factors ranging from 180-195. A monitor set to a callibration factor of 180 showed readings about 12% lower than expected; with 200 as the factor, the results were 2% lower.

CONCLUSION: When the calibration factor in the Phillips monitor for the transducer is too low, the blood pressure reading is lower than the actual patients blood pressure; this can make an adequate mean arterial pressure appear too low and cause delays in discontinuation of supportive therapy and invasive monitoring. The converse happens when the value is too high. A hypotensive patient may therefore not receive adequate supportive therapy for maintenance of end organ perfusion; which can result in worse outcomes over the treatment of a large patient population. Therefore, inconsistencies in invasive blood pressure readings due to the configuration of monitors is worrisome. A value of 205 as a calibration factor seems to result in the most accurate readings for the transducers used in our institution. Considering that there are small variations in between transducers of the same model, using a value slightly lower, such as 200, could be appropriate. If a change in transducer model or monitor is made institutionally, confirmation of accuracy should be performed in a small sample size of disposable transducers to determine the correct monitor settings for these transducers and reliability of readings.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 29

Use of Simulation-based Mastery Learning Curriculum to Improve Breaking Bad News Skills Amongst Pediatric Anesthesiologists: A Pilot Study

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INTRODUCTION: Breaking bad news is one of the most stressful duties that a physician must undertake. Unfortunately, pediatric anesthesiologists must often disclose bad news with very little training during residency or fellowship. Anesthesiologists who lack the necessary communication skills required for such a task may suffer from increased burnout after a bad event. We developed a breaking bad news simulation-based mastery learning (SBML) curriculum to determine whether the communications skills of pediatric anesthesiologists could be improved.

METHODS: Using the modified Delphi technique, an expert panel consisting of ten board-certified physicians (six pediatric anesthesiologists, one pediatric anesthesiologist/intensivist, one pediatric intensivist, and two internists) reached consensus on a 16-item skills checklist (Table 1). The minimum passing standard (MPS) was set at 13 out of 16 (81%) using the modified Angoff method. A pre-test/post-test study design was used to evaluate pediatric anesthesiologists' performance using the skills checklist. Participants completed a two-hour curriculum consisting of a pre-test, didactic session, deliberate practice with immediate feedback, and a post-test. The pre-test and post-test were simulated scenarios where the participant had to inform a parent actor that their child died in the operating room. Participants were required to meet or exceed the MPS to pass the course. Prevalence and bias adjusted Kappa (PABAK) coefficients were calculated to determine inter-rater reliability. We report descriptive summaries of collected data as medians with interquartile ranges for continuous data and counts and frequencies for categorical data. The Wilcoxon rank sign test was used to test whether there was a significant difference between pre-test and post-test scores and pre-course and post-course confidence, scored from 1 to 5.

RESULTS: Approval for this study was granted by the Institutional Review Board of the Ann & Robert H. Lurie Children's Hospital of Chicago (IRB # 2020-3469). Five pediatric anesthesiology attending physicians and five pediatric anesthesiology fellows were enrolled at a tertiary care children's hospital between February and September 2021. A summary of participants' demographic data is presented in Table 2. The median years of clinical experience was 6.5 (IQR 5-12.5) with approximately 70% of participants reporting breaking bad news in the past. The skills checklist inter-rater reliability was substantial with a PABAK of 0.76. At pretest, 2/10 (20%) of participants were able to meet or exceed the minimum passing standard. The median score on the pretest was 12/16 (75%) skills checklist items correct, which improved to 15/16 (94%) at post-test, p=0.02. All study participants achieved the MPS on their first post-test (Figure 1). Confidence improved from 3/5 to 4/5, p=0.02. Course satisfaction was high among participants.

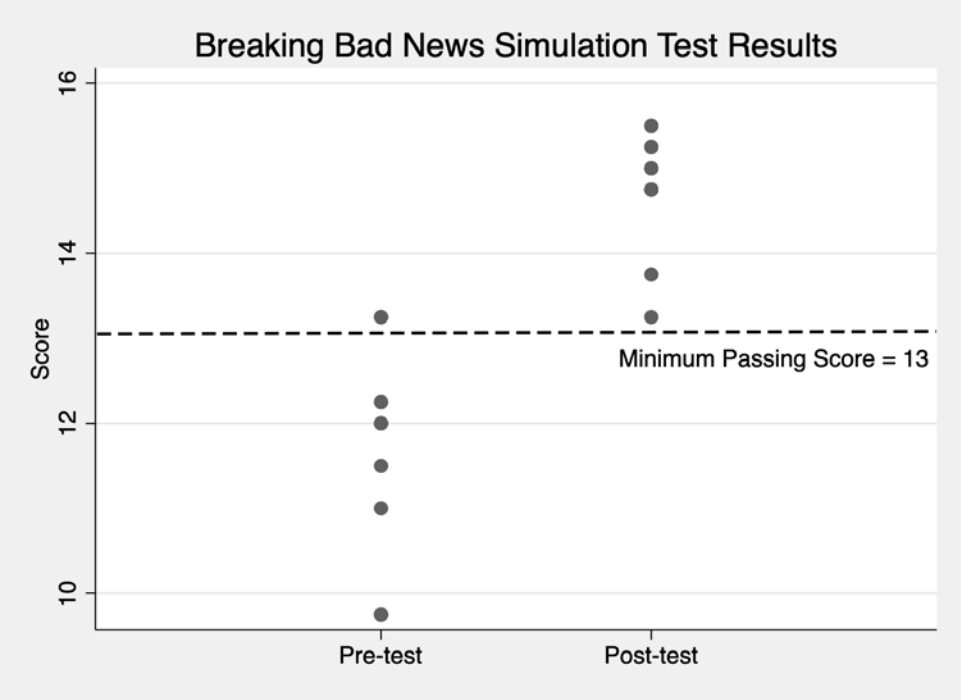
CONCLUSION: Our pilot study demonstrates that a breaking bad news SBML curriculum for pediatric anesthesiologists significantly improved communication skills and confidence in a simulated environment. Since only two participants met the minimum passing score prior to training, our results suggest pediatric anesthesiologists could benefit from further education to gain effective communication skills and SBML training may be effective to achieve this result.

	Yes	No
Creates initial rapport when first walking into room (e.g. introduces self/introduced by someone)		
Sits down		
Assumes a comfortable interpersonal distance		
Assesses family's perception or understanding of medical situation before breaking news (e.g. "tell me what you understand")		
Asks permission before giving the news (e.g. "I would like to discuss what happened")		
Gives a clear and concise "warning shot" (e.g. "I have some serious news")		
Pauses after delivering bad news		
Delivers bad news within the first minute of the conversation		
Delivers an empathic statement (e.g. "I know this is not what you expected to hear today")		
Suggests a plan for the next step		
Ensures family understanding (e.g. "It sounds like …")		
Avoids medical jargon (uses technical language without clarifying what it means)		
Gives information in small chunks (e.g. no more than 1 chunk of information before allowing family to process)		
Avoids giving information while family very emotional		
Avoids providing reassurances to family's emotion (e.g. avoid saying something like "it's ok")		
Listens attentively		

Table 1

	Fellow (n=5)	Attending (n=5)	Overall (n=10)
Clinical Experience (yrs, IQR)	5 (5-5)	13 (11-36)	6.5 (5-12.5)
Experience breaking bad news (%)	2 (40%)	5 (100%)	7 (70%)
# of times breaking bad news			
Never	3 (60%)	0	1 (10%)
<3	2 (40%)	0	3 (30%)
3-8	0	2 (40%)	2 (20%)
>10	0	3 (60%)	3 (30%)
Formal training in difficult conversations	2 (40%)	3 (60%)	5 (50%)
When did you receive education?			
None	3 (60%)	2 (40%)	5 (50%)
Medical School	2 (40%)	0	2 (20%)
Residency	1 (20%)	2 (40%)	3 (30%)
Attending	N/A	1 (20%)	1 (20%)
Pre-course Confidence (IQR)	2 (1-2)	3 (3-4)	3 (2-4)
Post-course Confidence (IQR)	4 (3-4)	4 (4-4)	4 (3.25-4)
Overall satisfaction (IQR)	5 (4-5)	5 (4-5)	5 (4.25-5)

Table 2



TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 30

Differences Between Pulse Oximetry Readings from Finger vs. Ear Probe Locations in Anesthetized Patients

Preshita Date[1], Gabriela Samayoa[2], Sakina Nayaz[3], Jeremy Dennis[4], Jacob Esquenazi[5], Malka Stohl[6], Sheldon Goldstein[1]

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INTRODUCTION: Pulse oximetry (PO) is a standard of care during the administration of anesthesia. During anesthesia, oxygen saturation (SpO2) sometimes decreases to levels that require diagnostic and/or therapeutic interventions by the anesthesiologist. When SpO2 decreases unexpectedly, the anesthesia provider will often place a second PO probe in a different location. During desaturation, we have seen ear probes placed that read higher SpO2 than finger probes placed initially. If the second probe confirms a higher saturation, it is usually interpreted as confirmation that the reading from the first location is falsely low. The goal of this study is to determine if there are significant differences between SpO2 readings obtained with PO probes on a finger vs. the ear.

METHODS: With IRB approval and informed consent, we studied 99 adults receiving general anesthesia or MAC for non-cardiac diagnostic or surgical procedures. A disposable PO probe (Nellcor Max-N) was placed on a finger and an ear. It was placed on a finger in the standard fashion. To reinforce connection on the ear, a layer of silk tape was applied to supplement the band-aid design of the probe. Readings were recorded with a Phillips 1020a PO module. Paired saturation readings for the finger and ear probes were recorded every five minutes. We analyzed pairs with differences of 5% or more between SpO2 as this can be clinically significant. We assumed the higher SpO2 to better reflect safety of a patient's status (no reason to suspect carboxyhemoglobin or methemoglobin in study subjects), and therefore labeled the higher SpO2 the correct reading. We hypothesized there would be no difference in readings between the probes. One sample test of proportions was applied with p-value < 0.05 significant.

RESULTS: 12,409 paired readings were recorded (see Table 1). The mean number (range) of paired readings per patient was 125.4 (19 - 456). A difference of 5% or more between SpO2 of the two probes occurred in 1,372/12,409 (11.06%) of paired readings. Of 1,372 paired SpO2 with differences of 5% or greater, the ear probe reported a higher SpO2 214/1,372 (15.6%) of the time, while the finger probe reported a higher SpO2 1,158/1,372 (84.4%) of the time; $p < 0.0001$. The data indicate a higher SpO2 is measured significantly more often on the finger vs. the ear, so we reject the null hypothesis.

CONCLUSION: When probes placed on the finger and ear provided SpO2 that differed by 5% or more, the higher SpO2 was generated on the finger 84.4% of the time. Still, 15.6% of the time the ear probe measured a higher SpO2. If SpO2 decreases, and stable vital signs and end-tidal carbon dioxide suggest no need for rapid or urgent measures, a reasonable course of action is to apply an SpO2 probe in a second location. One intriguing possibility remains; that both probes read accurately at their respective locations. A possible future study designed to determine if this is so will be described in a poster. A limitation of our work is that we used the same type of probe, one designed for the finger on the ear as well, with a layer of silk tape reinforcing the application, as we have found this better maintains this probe on the ear. Although not designed for the ear the PI has practiced at several centers that apply the finger probe to the ear in this manner, because these sites have not stocked probes designed for the ear. This data is representative of our clinical practice, but sites that have dedicated ear probes might repeat this work with the dedicated ear probe on the ear. Recent work suggests SpO2 may be elevated by 4% or more in Black patients with hypoxemia[1], thereby performing less well to detect hypoxemia. Additional analyses will be performed to assess paired SpO2 differences between finger and ear locations in Caucasian vs. Black patients, in patients with vascular disease, and during periods of hypotension.

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Paired SpO2 Data of Finger and Ear Locations				
	Frequency	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
I) SpO2 difference 7 % or greater, very large, clinically relevant, ear SpO2 higher	85	0.68	85	0.68
II) SpO2 difference 5 or 6 %, large, clinically relevant, ear SpO2 higher	129	1.04	214	1.72
III) SpO2 difference 3 or 4 %, moderate, may be clinically relevant, ear SpO2 higher	942	7.59	1156	9.32
IV) SpO2 difference 1 -2 %, "minimal, not clinically relevant	2805	22.60	3961	31.92
V) SpO2 difference of 0%	5874	47.34	9835	79.26
VI) SpO2 difference (-) 1% – (-) 2 %, "minimal, not clinically relevant	934	7.53	10769	86.78
VII) SpO2 difference (-) 3% - (-) 4 %, "moderate, may be clinically relevant, finger SpO2 higher	482	3.88	11251	90.67
VIII) SpO2 difference (-) 5% - (-) 6 %, "large, clinically relevant, finger SpO2 higher	332	2.68	11583	93.34
IX) SpO2 difference - 7 % or greater, very large, definitely clinically relevant, finger SpO2 higher	826	6.66	12409	100.00

Fig. 1

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 31

Effectiveness of a Covid-19 Aerosol Box in protecting healthcare workers - A Computational Fluid Dynamic Study (CFD)

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INTRODUCTION: Many variations of the COVID-19 Aerosol Box have been theorized and produced.[1,2] However, there is a paucity of scientific evidence regarding the effectiveness of such design alternatives. In light of this, we assess the effectiveness of a variation of the aerosol box using Computational Fluid Dynamics.[3]

METHODS: An aerosol box designed by the Medical Pantry was used in this simulation. This open source design incorporated a trapezoid shape whereby the cranial aspect was more narrow Using OpenFOAM (OpenCFD Ltd) and basing our equations on previously validated data by Bourouiba et al, we tested a trapezoidal shaped aerosol box and examined the fate of particles from a single a cough over 120 seconds. We examined the fate of particles from a cough in a supine patient in the following scenarios: no aerosol box, aerosol box with an open foot-facing side, and a sealed aerosol box while varying the number and position of wall suction ports. Variations on suction included 1 or 3 suction holes, and positions at either the cranial, center, or caudal aspect of the box. Particle fate at any given timepoint was classified as having collided with the box interior, having been suctioned, having remained floating inside the box, or having escaped the box. Finally, confederates, representing healthcare workers were placed cranially, to the right and the foot-end, and their particle exposure was assessed.

RESULTS: We found that the closed design with the drape on the foot-facing side reduced the number of escaped particles. Regardless of suction port outlet positioning, escaped or floating particles ranged from 4.6% to 5.6% by 30 seconds post-cough and this proportion remained the same by 100 seconds post-cough. Increasing the number of suction outlets significantly improved the efficiency of the aerosol box at clearing floating particles. Confederate exposure to particles was significantly reduced, with the exception of those positioned lateral to the patient in scenarios with aerosol box with an open foot-facing side.

CONCLUSION: We conclude that a modified, enclosed aerosol box with a trapezoid shape reduces the probability of floating or escaped particles in a simulated software environment and suggest further examination in a practical environment before widespread use in the COVID-19 environment.

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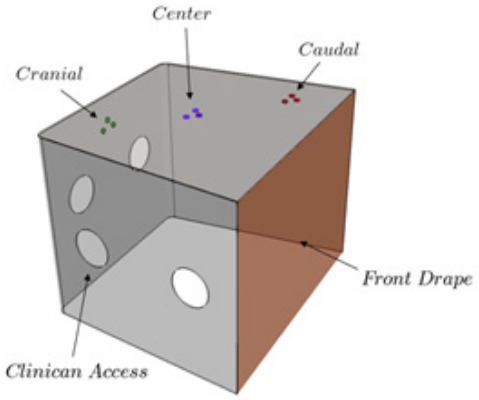

Figure 1

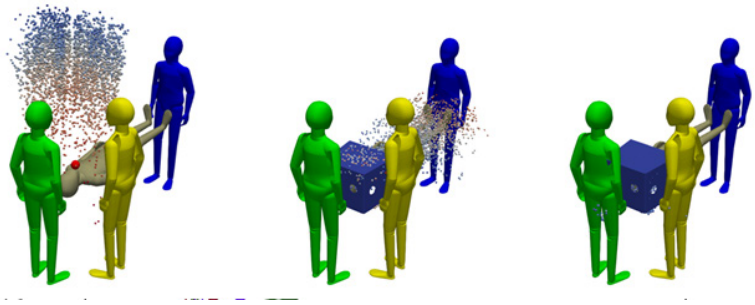

Figure 2

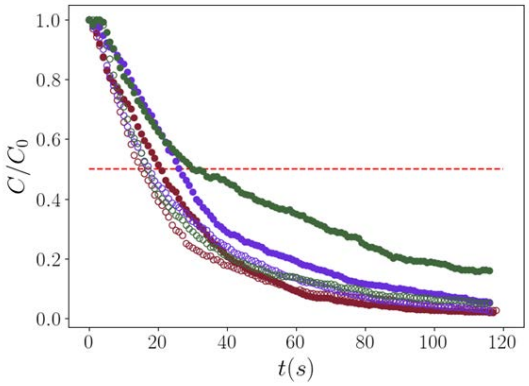

Figure 3

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 32

Target Controlled Infusion of Propofol: A Comparative prospective observational study of the Conventional TCI pump and the novel smartphone based application iTIVA

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INTRODUCTION: The current practice in anaesthesiology is the administration of intravenous agents using standard doses that are empirically adjusted. Propofol infusion is commonly used as it is antiemetic, environment friendly and gives a clear headed recovery. Computer technology of Target Controlled Infusion (TCI) has enabled the adoption of theoretical models for the pharmacokinetic simulation of these drugs. TCI has facilitated the administration of intravenous drugs, allowing for rapid titration to achieve desired therapeutic goals. However, TCI devices are far from ideal and need to be checked as thoroughly as anaesthesia machine.[1] 'iTIVA Anesthesia' is 'Interactive Total Intravenous Anesthesia' software designed for smartphones that simulates TCI for eleven intravenous agents including propofol. Developed as a possible alternative to TCI pumps, it is coupled with basic volumetric infusion pumps to enable target controlled delivery.[2,3] We used iTIVA for guiding propofol infusion. A practical feature of the app is a section that lists physiologic variables, medications, airway equipment, and fluids based on patient age.[3,4] Our study assesses the agreement and interchangeability between iTIVA and Conventional TCI pump (CTP ; B Braun) for the Schnider pharmacokinetic model for the anaesthetic drug propofol. Propofol was chosen as the study drug. Remifentanil the only other drug option available in the conventional monitor is unavailable in India.

METHODS: This prospective, interventional, single centric, cohort study enrolled 30 adult ASA I-III patients at a tertiary care cancer centre. Sample size was calculated based on a manuscript by Lu et al [5]. The minimum required number of pairs came out to be 109 after feeding these assumptions into Medcalc statistical software. Allowing for dropouts we compared 124 paired readings in 30 patients undergoing oncosurgery lasting 2-3h.

After application of standard monitors including the BIS monitor, the age, sex, weight and height of the patient was inputted into the smartphone. The TCI mode was selected, the target effect site concentration (3µg/ml for induction; 2µg/ml for maintenance) was entered followed by selection of the Schnider model. Under the hypnotic section propofol 10mg/ml was entered. The time periods in minutes (eg 3,11,12,17,51 etc) and the expected volume in ml of propofol infused during the corresponding time period (eg 4.9, 8.1, 7.9, 10.5, 29 etc.) were displayed by iTIVA in response. The CTP was set at identical effect site concentrations. Propofol was infused by the CTP and the readings for volume of propofol infused/given time period (primary outcome measure) obtained in iTIVA were compared with the actual volume delivered by the CTP during the same time period. "Real Time Tool" was utilized to run a stopwatch with audiovisual alarms at the same time as the start of infusion in the volumetric pump. Bias, precision, and limits of agreement (LOA) between the two methods was calculated using Bland and Altman analysis and the mountain plot.

RESULTS: All patients of either sex, aged 18-70 years scheduled to undergo onco-surgery lasting 2- 3 hours were included in the study. Patients not giving consent /allergic to propofol were excluded. The descriptive statistics are summarized in Table-1. Duration of comparison was shorter than the duration of surgery since after the 4th reading the time period displayed by iTIVA exponentially increased. Bias / mean of differences was -0.02. LOA (1.96 standard deviation above and below the mean) were 0.58 and -0.63. The maximum allowed difference of 2 was much larger than the 95% confidence intervals for LOA (Figure-1) The Mountain Plot was short tailed (-1.28 to 1.55) and centered over zero (0.01) indicating that the two methods are unbiased with respect to each other with very small differences.

CONCLUSION: The two devices (iTIVA and CTP) showed good agreement. Thus, one can convert any ordinary volumetric infusion pump into a TCI pump using iTIVA app. Use of conventional TCI pumps requires procurement of additional equipment at some cost, its regular maintenance, space for storage and need to be shifted to the OT wherever required to be used. The use of propofol is likely to increase in future as it is more environment-friendly than volatile anaesthetics. TCI will ensure predictable and safe use. An app based system like iTIVA is likely to go popular in view of its easy accessibility, cost effectiveness, versatility, and convenience to use.

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	Min	Max	Arithmetic Mean	95%CI for Mean	SD	Kolmogorov-Smirnov test (with Lilliefors significance correction) for Normal distribution
AGE	30	76	50.43	45.9635 to 54.9031	11.97	D=0.1024 accept Normality (P>0.10)
WEIGHT	43	90	61.73	57.7201 to 65.7466	10.75	D=0.0828 accept Normality (P>0.10)
HEIGHT	136	177	157.07	154.1894 to 159.9439	7.71	D=0.1554 accept Normality (P=0.0624)
SEX	6 Male:24Female					
Type of Surgery	8 Others: 22 breast surgery					
Duration of Sx	1-3h					
Duration of comparison	29	152	72.13	60.41 to 83.86	31.41	D=0.1265 accept Normality (P>0.10)

Table-1: Demographic and surgical profile of patients

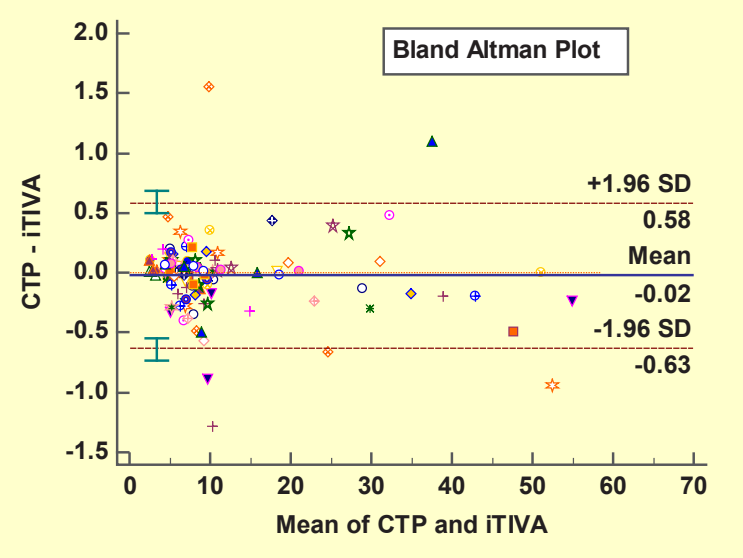

Figure-1: Bland-Altman Plot

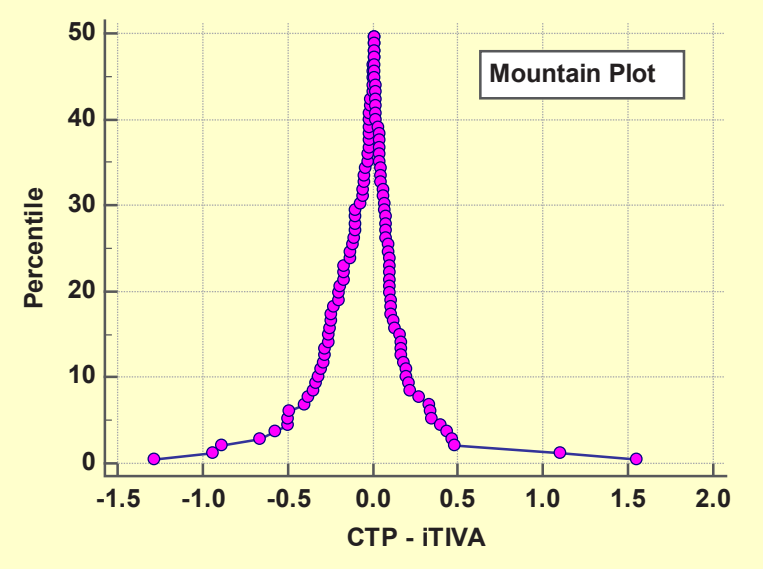

Figure 2

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 33

Development and Deployment of a ROTEM Clinical Decision Support App

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INTRODUCTION: At busy Trauma 1 Centers, there is a critical need for coagulation assays to delivery timely and accurate results during early trauma to improve the treatment of coagulopathies and allow for directed therapies to correct sources of bleeding in critically ill patients. This need has prompted the use of thromboelastography (TEG ®) and rotational thromboelastometry (ROTEM®)[1,2], respectively, in order to better classify the hemostatic process and status in individual patients. At the University of Utah School of Medicine we routinely utilize ROTEM in the perioperative and intraoperative period to direct therapies, however knowledge of ROTEM and confidence in result interpretation is limited by user frequency. This has thus limited the uptake and utilization of ROTEM by non-cardiac specialist faculty even during Trauma 1 activations. In order to realize the benefits of ROTEM in a broader set of physicians and care teams at our institution and others, we developed a smartphone app to ease the interpretation of ROTEM and assist in guiding therapy. We describe, herein, the development and deployment of the ROTEM Clinical Decision Support (RCDS) App.

METHODS: The RCDS app was developed through an iterative process in collaboration with Anesthesiology faculty, Information Technology management, Clinical Informatics, and anesthesia technicians. The process to develop the app took part in stages, including a literature review, review of current apps available in the Apple iOS App Store and Android Google Play stores, informal end user consultations, and beta testing with both clinical experts and ROTEM technicians. Our further plans include usability testing, an iterative development process planned in iOS TestFlight for Winter 2021, and solicitation of formal user ratings on usability and clinical relevance of the app. Given the infrequent and sporadic need for ROTEM in trauma situations, we will undertake a formal monitoring process to determine adequate length of testing prior to public availability.

RESULTS: At the time of submission we have developed a beta version of the RCDS app, which includes a clinical algorithm to interpret ROTEM in a step-wise visual manner (Figure 1). Our review of the iOS App store yielded n=3 apps, with one app having not been updated for five years, one app based on Australian guidelines, and one app that covered TEG but not ROTEM. The review of Android Play Store only yielded n=1 app that similarly covered TEG and not ROTEM, and had not been updated since 2018. Early feedback suggests the App is clinically useful and easy to use. The incorporation of Anesthesia Technicians in our test group has also been well received. Ongoing iterations are being tested from December 2021 - February 2021 in TestFlight, prior to publishing the app to the public via the iOS App Store.

CONCLUSION: The use of smartphones for clinical decision support is a feasible manner to simplify complex decision making and improve patient care. In addition, our search of the Android and iOS app stores found there is a dearth of clinical decision support for both TEG® and ROTEM®. The cost of smartphone app development continues to fall, making it a worthwhile investment for institutions. It is also worth mentioning that the incorporation of staff and technicians in the development process has both encouraged use and increased uptake of the app as well as improved the design and usability.

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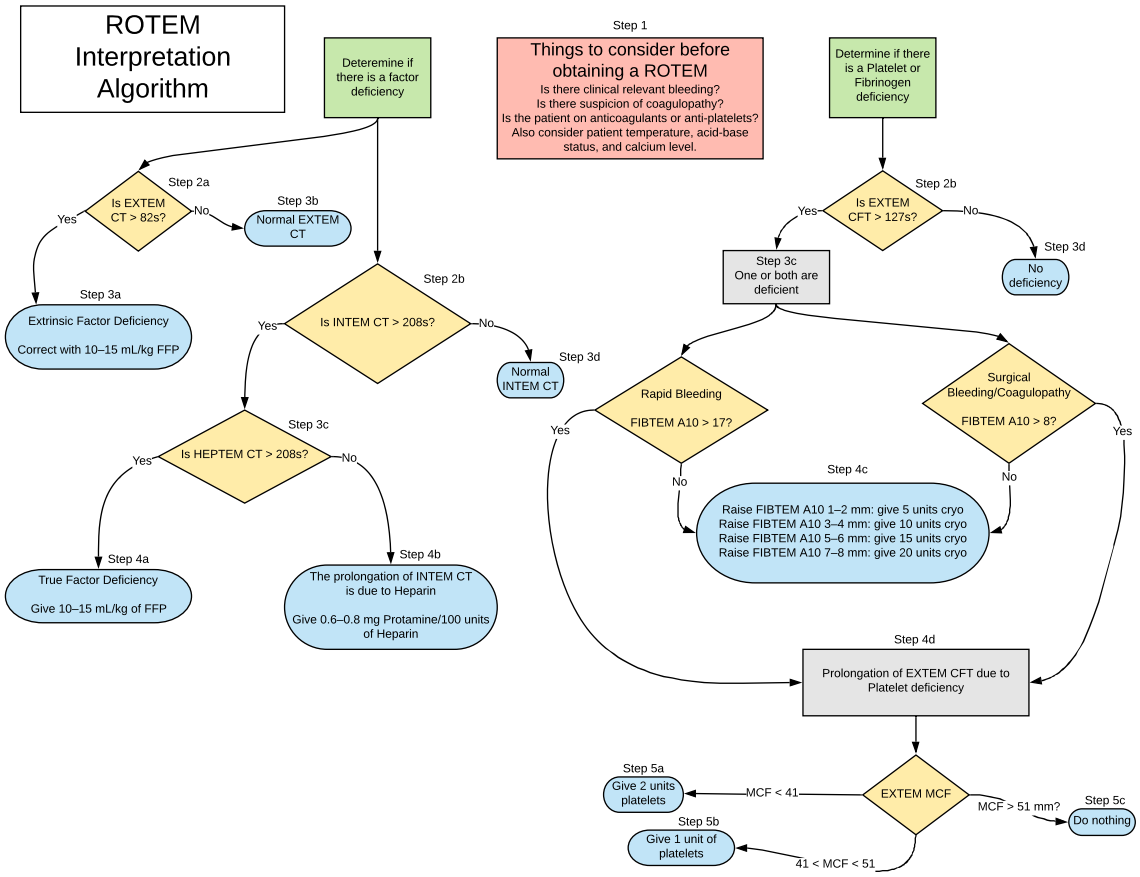

Fig. 1

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 34

A prospective, observational study of Non-Invasive Venous waveform Analysis (NIVA) for the detection of low volume blood loss in humans

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INTRODUCTION: Accurate non-invasive monitoring for early diagnosis of hemorrhage is an unmet need in the acute care setting.[1,2] Heart rate (HR) and blood pressure (BP) are the most common data points used to clinically diagnose acute hemorrhage.[1-3] However, they have routinely been shown to be unreliable requiring approximately 25-35% of blood loss before alteration in HR and BP occur.[1-3] Non-invasive Venous waveform Analysis (NIVA) has demonstrated significant sensitivity in detecting acute hemorrhage of only 8-10% blood volume loss.[3] In this prospective observational study, using a more optimized NIVA device prototype than prior studies[3], we hypothesize that a quantifiable change in the venous waveform would be associated with less than 8% blood loss in healthy adult subjects donating whole blood.

METHODS: 55 human blood donors were enrolled at an American Red Cross (ARC) donation center, of this data 39 subjects had waveforms clean enough for analysis. An optimized venous waveform capturing prototype with improved signal processing was secured to the volar aspect of the wrist in human subjects prior to the initiation of blood removal. Waveforms were recorded for the duration of the whole blood donation and then transformed from the time to the frequency domain. The ratio-metric power contribution of the cardiac frequencies were used to calculate a representative of volume status value- the NIVA score. The volume of whole blood removed was measured by an ARC digital flow device per ARC protocol.

RESULTS: A significant average change in the NIVA score was observed after 200 mL (3-4% blood volume) of whole blood donation (0.4, SD 1.8, $p < 0.05$). A ROC curve for the ability of the change in the NIVA score to detect 200 mL of blood loss demonstrated an area under the curve (AUC) of 0.65.

CONCLUSION: There remains a large unmet need in accurate and timely detection of acute hemorrhage. This study supports the potential application of NIVA in detection of low volume human blood loss. NIVA is a novel technology that uses previously undetectable, low frequency signals of the cardiac pulse that may prove useful for more accurate and early detection of acute hemorrhage.

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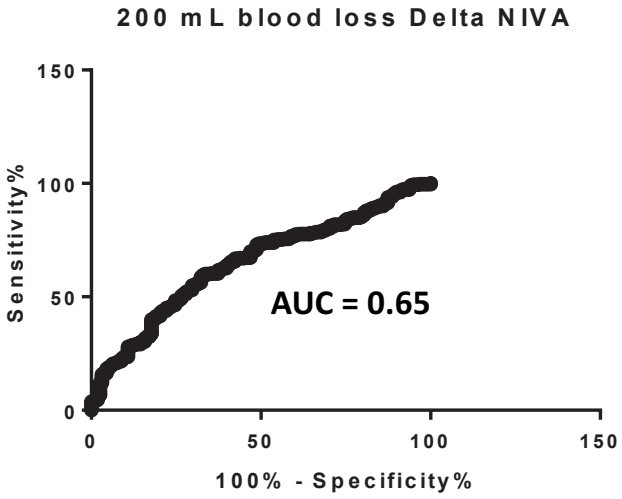

Fig. 1

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 35

High Fidelity CRISPR Libraries to Interrogate Anesthetic Genetic Susceptibilities

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INTRODUCTION: High-throughput CRISPR screens accelerate the discovery of novel genetic susceptibilities pertinent to human health. The ease and effectiveness of CRISPR screens derives from the technology's simplicity in requiring only two components for its use: an enzyme that cleaves double stranded DNA (CRISPR endonuclease) and a targeting element (Guide RNA) that directs the endonuclease to its target. Genome-wide collections of Guide RNAs (gRNAs) form CRISPR libraries that allow for highly customizable and robust interrogation of a genome. Importantly, the accuracy of CRISPR libraries depends on the ability of gRNAs to precisely direct a CRISPR endonuclease to its intended target. Non-precise gRNAs are capable of generating complex genomic rearrangements that can disrupt the organization and regulation of a genome. This consideration takes on added importance when CRISPR libraries are used to investigate genomic regulatory elements. Many current genome-wide CRISPR libraries contain non-specific gRNAs that contribute noise to screen results. This noise confounds the output of CRISPR screens and creates false positive and false negative hits. At present, no CRISPR gRNA libraries exist that guarantee high fidelity gRNAs against all coding and non-coding elements in both the human and mouse genomes. Here we utilized our GuideScan and CSC softwares to design ultra-specific CRISPR gRNA libraries to interrogate genome-wide coding and non-coding elements in both the human and mouse genomes[1,2]. Recent studies have highlighted the importance of genomics in suggesting new avenues of anesthetic discovery and therapeutic involvement[3]. We developed our high-fidelity CRISPR gRNA libraries to prospectively interrogate how anesthetic exposure affects human cell proliferation following coding gene or non-coding element knockout. Overall, CRISPR screens, using high fidelity gRNA libraries, promise to accelerate the development of anesthetic genomics.

METHODS: Enumeration of Guide RNA (gRNA) Targets Retrieval trees (tries) were constructed consisting of all possible 20mer Cas9 gRNA target sites in the mouse and human genomes[1]. To determine the mismatch neighborhood of each gRNA in the library, we traversed every library gRNA through its genome specific trie to exhaustively determine all neighbors up to and including Hamming and Levenshtein distances of 3. Specificity scores for each gRNA was computed using Hamming distance neighbors as previously described[1]. Potential off-target effects were assessed using CSC software to ensure gRNA specificity to target[2]. Cutting Efficiency Determination The cutting efficiency of gRNAs was done through computing Rule Set 2 scores for all gRNAs in the human and mouse libraries[4]. Rule Set 2 is a gradient boosted regression tree model that quantifies gRNA cutting efficiency with higher scores being indicative of more pronounced cutting efficiency[4]. Guide RNA Library Design Guide RNA libraries were constructed for all coding genes and a select subset of non-coding elements in the mouse and human genomes. Guide RNA specificity was determined by using the GuideScan software to select gRNAs that were maximally unique to their target feature. After determining each feature's set of maximally unique gRNAs, we selected for the final libraries those gRNAs with the highest Rule Set 2 scores as well as lowest self-complementarity. In this manner we designed genome-wide libraries against mouse and human coding and non-coding features that are maximally specific and efficient at cutting their genomic targets. We use these libraries to prospectively interrogate how anesthetic exposure affects human cell proliferation following coding or non-coding element knockout.

RESULTS: CRISPR libraries containing non-specific gRNAs limit screen utility (Fig 1d-e) as non-specific gRNAs confound screen readout. Utilizing our GuideScan and CSC softwares we design genome-wide CRISPR-Cas9 libraries that eliminate non-specific gRNAs and are designed to be maximally specific and efficient at cutting target loci (Fig 1a-c).

CONCLUSION: CRISPR-Cas9 genome-wide libraries designed with the GuideScan and CSC softwares contain maximally specific and efficient gRNAs capable of targeting coding genes and non-coding elements in both the human and mouse genomes. These libraries demonstrate an advance in the specificity of genome-wide CRISPR gRNA libraries and are prerequisite for CRISPR screens of anesthetic genetic susceptibilities.

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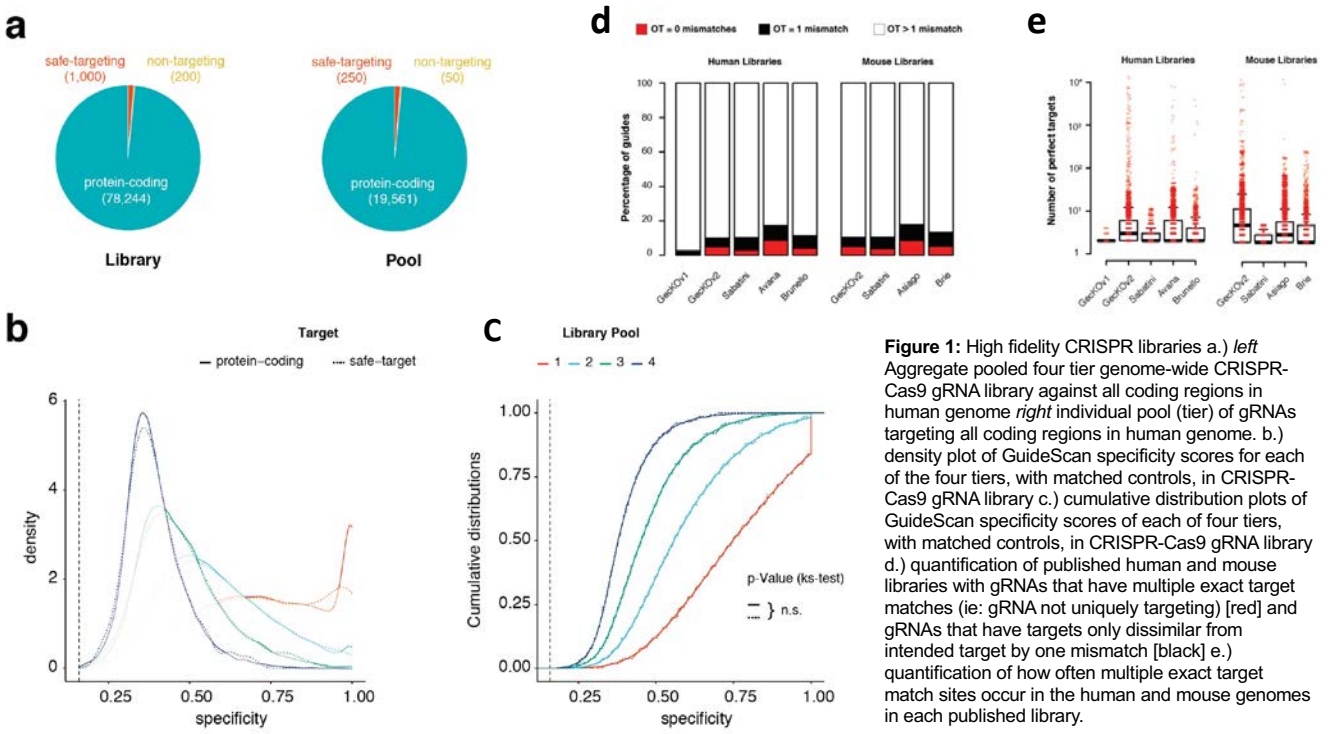

Figure 1: High fidelity CRISPR libraries a.) *left* Aggregate pooled four tier genome-wide CRISPR-Cas9 gRNA library against all coding regions in human genome *right* individual pool (tier) of gRNAs targeting all coding regions in human genome. b.) density plot of GuideScan specificity scores for each of the four tiers, with matched controls, in CRISPR-Cas9 gRNA library c.) cumulative distribution plots of GuideScan specificity scores of each of four tiers, with matched controls, in CRISPR-Cas9 gRNA library d.) quantification of published human and mouse libraries with gRNAs that have multiple exact target matches (ie: gRNA not uniquely targeting) [red] and gRNAs that have targets only dissimilar from intended target by one mismatch [black] e.) quantification of how often multiple exact target match sites occur in the human and mouse genomes in each published library.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 36

Validation of an Intensive Care Unit Data Mart for Research and Quality Improvement

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INTRODUCTION: The acceptance and adoption of findings from observational studies based on data derived from the electronic health record (EHR) is frequently limited by the perception that these data are inadequately validated and inherently inferior to data collected through more traditional means. We sought to create a structured, rigorously validated intensive care unit (ICU) data mart based on data automatically and routinely derived from the EHR, inclusive of data elements commonly used for quality improvement and research purposes, including high-quality outcomes data.

METHODS: Key variables were identified by study investigators and faculty critical care physicians. Physicians worked closely with analysts using a structured approach. First, the presence of data in routine clinical practice was confirmed using chart review. Next, algorithmic definitions were created for complex data elements, including most outcomes, leveraging existing literature, when available. Data analysts worked to identify the location of variables within the data architecture underlying the EHR. Test patients were extracted and algorithms were iteratively refined. Once shown to be reproducible in a broad cohort of patients, structured query language (SQL) was used to extract, transform, and load data from the EHR into a relational database housed on a departmental server. The sensitivity and specificity of algorithmic definitions was formally assessed.

RESULTS: A total of 459,465 patient ICU encounters were identified and included within the ICU data mart. These patients include over 460,000,000 individual laboratory results and 4,610,776 vital signs (with q1 minute fidelity in the first 24-hours of admission). We currently have 26 validated outcomes, structured within 19 tables, all of which have a sensitivity and specificity of greater than 95%. These data can be joined to 215 validated variables included within 125 tables comprising an existing anesthesiology perioperative data warehouse (PDW) for perioperative patients.

CONCLUSION: We propose a methodology for building a robust and highly granular ICU data mart, leveraging the synergistic expertise of clinicians and data analysts. Work to further identify and validate additional patient variables remains a core component of future quality improvement and research processes.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 37

Rapid manufacturing of mechanical ventilators for the COVID-19 pandemic using crowdsourced global innovation: results of the anesthesiology resident directed CoVent-19 Challenge

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INTRODUCTION: With the rapid spread of COVID-19 in early 2020, there was an overwhelming burden of critical illness throughout the world, resulting in a severe depletion of medical supplies and a lack of capacity for critical care and mechanical ventilation. In response to worldwide ventilator shortages, the CoVent-19 Challenge was a 12-week crowdsourced global innovation challenge that was hosted by anesthesiology residents to develop rapidly deployable mechanical ventilators at the start of the COVID-19 pandemic.

METHODS: The CoVent-19 Challenge launched on April 1, 2020 with a request for design submissions on social media. All participants were provided with a design brief that included minimum ventilator functional requirements and specifications developed by a committee of anesthesiology residents and faculty, intensivists, respiratory therapists, biomedical engineers, and medical device experts. Crowdsourcing of ventilator designs was performed on GrabCAD (Stratasys, Cambridge, MA) in two rounds. In the first 'open entry' round, any team could submit a ventilator design that included a CAD assembly, project abstract, and a product development plan. Initial designs were reviewed by an independent panel of clinical and technical respiratory therapy experts, and scored for safety, reliability, rapid manufacturability, cost, and design complexity. In the second 'invitation only' round, the highest scoring teams received access to additional resources for completing their ventilator design and support in developing functional prototypes, including rapid prototyping services, test lungs, and testing protocols. The ventilator prototypes were evaluated by each team using a loaned data acquisition system with a spirometry module and pneumotach flow head (ADInstruments, Colorado Springs, CO) to measure ventilator performance, safety, and reliability, and a final test report was provided to the expert panel.

RESULTS: The open entry round resulted in 213 ventilator design entries from 43 countries. Following expert scoring, 7 teams were invited to participate in the invitation only round. The winning design (SmithVent) was a pneumatic desktop ventilator with a proportional-integral-derivative (PID)-controlled proportional inspiratory flow valve developed by a team of engineering students, faculty and alumni from Smith College. The SmithVent prototype met all functional and system requirements during benchtop testing with a calibrated test lung. During verification testing, SmithVent demonstrated proper functioning of spontaneous pressure support and assist/control ventilation modes, and delivered tidal volumes with less than 2% error for the entire operating range of 200mL to 600mL. The 2nd-place design was a pneumatic, pole-mounted ventilator developed by a San Francisco-based product design firm.

CONCLUSION: As we have seen with COVID-19, global healthcare systems must be capable of rapid expansion of critical care capacity to accommodate large segments of the population during pandemics. Existing strategies for pandemic readiness, including national stockpiles and dependence on the conventional manufacturing sector, have proven unsustainable, inefficient, and inaccessible to both developed and developing countries. As demonstrated by CoVent-19 Challenge, crowdsourced innovation can rapidly harness global innovation capacity and manpower to solve urgent and complex healthcare challenges. The 1st place SmithVent design has continued to be developed at Smith College as a senior engineering student capstone project, and has been updated to include an electronic positive end expiratory pressure (PEEP) valve and a proportional air-oxygen blender.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 38

Pilot Validation of Airway Hemorrhage Simulation Scenarios

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INTRODUCTION: Airway hemorrhage is a challenging clinical situation faced by rapid response teams and emergency physicians, with an incidence of difficult airway intubation of 9-12% and complications that range from 4-28%. Simulation offers a teaching modality to facilitate education for high-risk, low frequency clinical situations. Creation of a simulator with airway hemorrhage capabilities in high fidelity airway scenarios (expanding post-surgical neck hematoma, oropharyngeal hemorrhage, posterior nasopharyngeal epistaxis) for interprofessional management with deliberate practice would lead to ability to discriminate between performance after debriefing and formative feedback.

METHODS: We recruited trainees in Emergency Medicine and Critical Care Medicine. We had 2 confederates (ME, DS, or AA) serving as RT and RN during all scenarios, which ran 5 minutes. Each subject underwent 3 versions of a simulation scenario within in one of our 3 types of airway hemorrhage cases (either hematoma, oropharyngeal hemorrhage or posterior nasopharyngeal epistaxis) in 1 hour, with no debriefing after scenario 1 (baseline), formative debriefing after scenario 2 (learning), and summative debriefing after scenario 3 (assessment). Post-simulation feedback was obtained for confidence, key learning point, and feedback for our scenario fidelity. Two anesthesiology-critical care (TD, SA) expert raters rated scenario 1 and 3 to look for performance difference in global rating (pass/ low pass/ fail) and items derived from previously validated NOTSS/ ANTS rating scales of non-technical skills. Interrater reliability, percent agreement, and intraclass coefficient were calculated for each type of scenario and overall between scenario 1 (pre) and scenario 3 (post).

RESULTS: A total of 11 trainees participated, with high ratings (5-point Likert) of overall clarity (4.9), realism (4.7), and usefulness (4.9). Interrater reliability (IRR) of entire rating scale by expert raters varied per scenario, with nasopharyngeal at 0.78, oropharyngeal at 0.78, and neck hematoma at 0.65. Majority of trainees were Pass or Low Pass for all scenarios, with only 4 instances of a global rating of Fail (out of 36 total assessments).

CONCLUSION: We piloted 3 airway hemorrhage simulation scenarios to determine the ability of the scenarios to discriminate between performance before and after formative debriefing feedback. We found for even highly complicated advanced airway simulation the benefit of deliberate practice and reflection on key cognitive, skills, and team performance related to airway hemorrhage. This pilot study validates these airway hemorrhage simulation scenarios as a modality for improving resident and fellow skills for complicated airway hemorrhage management through deliberate practice and reflection.

SUBSPECIALTY ABSTRACTS

TRAUMA

TRAUMA 1

Age-related dysregulation of autophagy contributes to microglial dysfunction and long-term neurological outcome after traumatic brain injury

Rodney Ritzel[1], Yun Li[2], Zhuofan Lei[1], Junyun He[3], Jordan Carter[1], Harry Choi[1], Niaz Khan[1], Hui Li[1], Samantha Allen[1], Marta Lipinski[1], Alan I Faden[1], Junfang Wu[1]

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INTRODUCTION: Elderly patients with traumatic brain injury (TBI) have higher mortality and poorer long-term outlook compared to younger individuals. This may contribute to the assumption that aggressive management of geriatric TBI is futile. The present study examined the long-term recovery potential and underlying mechanisms associated with advanced age in male C57BL/6 mice using a controlled cortical impact (CCI) model of TBI.

METHODS: Young (12 weeks) and old (aged at 18 months) male C57BL/6 mice were subject to sham or CCI surgery and evaluated for behaviorally recovery following repeated testing over four months for motor function (rotarod, grip strength, gait dynamics), cognition (novel object recognition, y-maze), and depressive-like phenotype (novelty suppressed feeding, social recognition). Autophagy and microglial activation were examined by NanoString gene analysis, flow cytometry, and histology. A follow-up study evaluated the efficacy of an established autophagy activator, trehalose, on long-term recovery in a group of aged mice at two months post-TBI. Trehalose or sucrose control was administered continuously in drinking water starting at d1 post-injury. Mice were randomly assigned to one of four groups based on surgery and treatment. Behavioral testing was performed by a blinded investigator. Two-way ANOVA with Tukey's post hoc test for multiple comparisons was implemented to determine the interaction between group effects of age and chronic TBI.

RESULTS: Aged mice had a higher mortality rate compared to young mice at 12 weeks post-injury (Fig. 1A). While aging alone had a significant impact on behavioral ability, the recovery slope in some, but not all, neurobehavioral tests were relatively similar between young and old mice. By 12 weeks, however, aged mice displayed significant cognitive deficits and depression (Fig. 1B). Histopathology revealed larger lesion volumes and microglia activation in aged TBI mice at 16 weeks post-injury (Fig. 1C-D). Nanostring analysis identified several age- and injury-specific genes that were differentially expressed in the injured brain, including those involved with the complement, phagocytosis, and autophagy pathways. Flow cytometry demonstrated temporal dysregulation of autophagic function in microglia from injured mice which was exacerbated with age and accompanied by increased inflammation and lymphocyte infiltration. Old TBI mice treated with trehalose exhibited either delayed deficits or enhanced recovery in cognitive and motor tasks (Fig. 1E). Trehalose treatment modified expression of autophagy markers and reprogrammed the microglial response to chronic TBI.

CONCLUSION: Taken together, our data indicate that microglia undergo chronic changes in autophagic regulation with both normal aging and TBI that are associated with poorer functional outcome. Boosting autophagy may be a promising therapeutic strategy for older TBI patients.

TRAUMA 2

HDAC inhibitor Romidepsin attenuates neuroinflammation and improves neurological deficits after traumatic brain injury

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INTRODUCTION: Traumatic brain injury (TBI) triggers delayed molecular and cellular responses, including neuroinflammation, that contribute to neuronal loss and neurological dysfunction. Microglia transcriptome changes are central to chronic neurodegeneration and cognitive decline. Post-traumatic activation of histone deacetylases (HDAC) is an important epigenetic regulatory mechanism that may underpin changes in the microglia transcriptomic signatures promoting activated phenotypes with a neurotoxic profile. Conversely, HDAC inhibitors (HDACi)-induced changes in the chromatin at key promoter regions, may favor the gene expression that facilitate microglia reparative phenotypes and lower the expression of pro-inflammatory gene. Romidepsin (RMD) is a potent HDACi that increases histone acetylation and improves cognitive outcomes in models of autism. The current study tests the efficacy of RMD to attenuate neuroinflammation and improve functional outcomes following TBI.

METHODS: All procedures were approved by the University of Maryland Institutional Animal Care and Use Committee. Mice received a controlled cortical impact (CCI) using our custom CCI-injury device fitted with a 3.5mm diameter tip. Mice were anesthetized with isoflurane and mounted into a stereotaxic device. The scalp was incised followed by a 5mm craniotomy over the left parietal cortex. Moderate injury was induced at a velocity of 6m/s and deformation depth of 2mm. Following CCI, the incision was closed and animals were allowed to recover. Sham animals underwent the same procedures without craniotomy or impact. Intraperitoneal injections of RMD were given every day for 3 days starting post-injury day (PID) 0. Animals underwent motor and cognitive tasks beginning at PID 1 to determine neurological outcomes. Animals were euthanized at PID 8 and the hippocampus and cortex were taken for mRNA analysis.

RESULTS: TBI animals showed significant motor impairments compared to sham animals at PID 1, 3, and 7; no differences were observed between RMD and vehicle animals. In the novel object recognition task, TBI animals spent less time with the novel object compared to sham animals. RMD treated animals spent significantly more time with novel object compared to vehicle animals; no significant differences were observed between RMD and sham animals. In a 2-trial y-maze test, vehicle animals displayed a deficit while RMD animals performed similar to shams spending significantly more time in the novel arm. Hippocampal expression of pro-inflammatory genes CD68 and NOX2 was significantly increased in vehicle animals that were attenuated in RMD animals.

CONCLUSION: RMD significantly improves cognitive outcomes in the first week after TBI. RMD also reduces expression of genes that are modulators of neurotoxic microglia phenotypes after TBI including NOX2 and CD68. Thus, RMD may be a promising therapeutic intervention that attenuates neuroinflammation and neurodegeneration after TBI.

TRAUMA 3

Impairment of autophagy in microglia/ macrophages exacerbates neuroinflammation after spinal cord injury in mice

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INTRODUCTION: Autophagy is a catabolic process that degrades cytoplasmic constituents and organelles in the lysosome, thus serves an important role in cellular homeostasis and protection against neurodegeneration. We have previously reported that defects in autophagy contribute to neuronal cell damage and are part of the secondary injury mechanism in traumatic spinal cord injury (SCI)[1,2]. Recent data implicate autophagy in regulation of immune and inflammatory responses, with high levels of autophagy flux associated with anti-inflammatory, and low levels with pro-inflammatory phenotypes[3,4]. The present study assessed if autophagy is involved in modulation of neuroinflammation after SCI.

METHODS: Young adult male C57BL/6, autophagy hypomorph Becn1+/- mice and their wildtype (WT) littermates were subjected to moderate/severe thoracic spinal cord contusion. Neuroinflammation and autophagy flux in the injured spinal cord were examined by flow cytometry, immunohistochemistry (IHC), and NanoString technology. Motor function was evaluated using the Basso Mouse Scale (BMS) and Horizontal ladder test. Lesion volume and spared white matter were evaluated by unbiased stereology. To stimulate autophagy, trehalose or sucrose control was administered continuously in drinking water starting at 1d post-injury.

RESULTS: Flow cytometry demonstrated temporal dysregulation of autophagic function in both microglia and infiltrating myeloid cells from injured spinal cord at 3d post-injury which was accompanied by increased pro-inflammatory cytokines. IHC in transgenic Cx3cr1-GFP mice confirmed accumulation of autophagosomes and inhibition of autophagy flux specifically in the activated microglia/macrophages. NanoString analysis with the neuroinflammation panel demonstrated increased pro-inflammatory genes and decreased expression of molecules related to neuroprotection in the Becn1+/- mice compared to WT at 3d SCI. These findings were further validated by qPCR, in which we observed significantly higher levels of pro-inflammatory cytokines. Western blot analysis showed higher protein expression levels for microglia/macrophages marker Iba-1 and autophagosome marker LC3 in Becn1+/- mice at 1d SCI, along with increased levels of the inflammasome marker NLRP3. Locomotor function showed poorer recovery in Becn1+/- mice, which correlated with increased tissue damage. Trehalose treatment significantly reduced expression levels of p62, accompanied by reduced expression of NOX2, Iba-1, NLRP3, and cell death marker α-Fodrin at 3d post-injury. Finally, C57BL/6 mice treated with trehalose showed better recovery at 6 weeks post-injury.

CONCLUSION: Our data indicates that inhibition of autophagy in microglia/macrophages potentiates pro-inflammatory activation that is associated with poorer functional outcome following SCI. These findings highlight the importance of autophagy in resident immune cells of the CNS and further elucidates its role in secondary injury after SCI.

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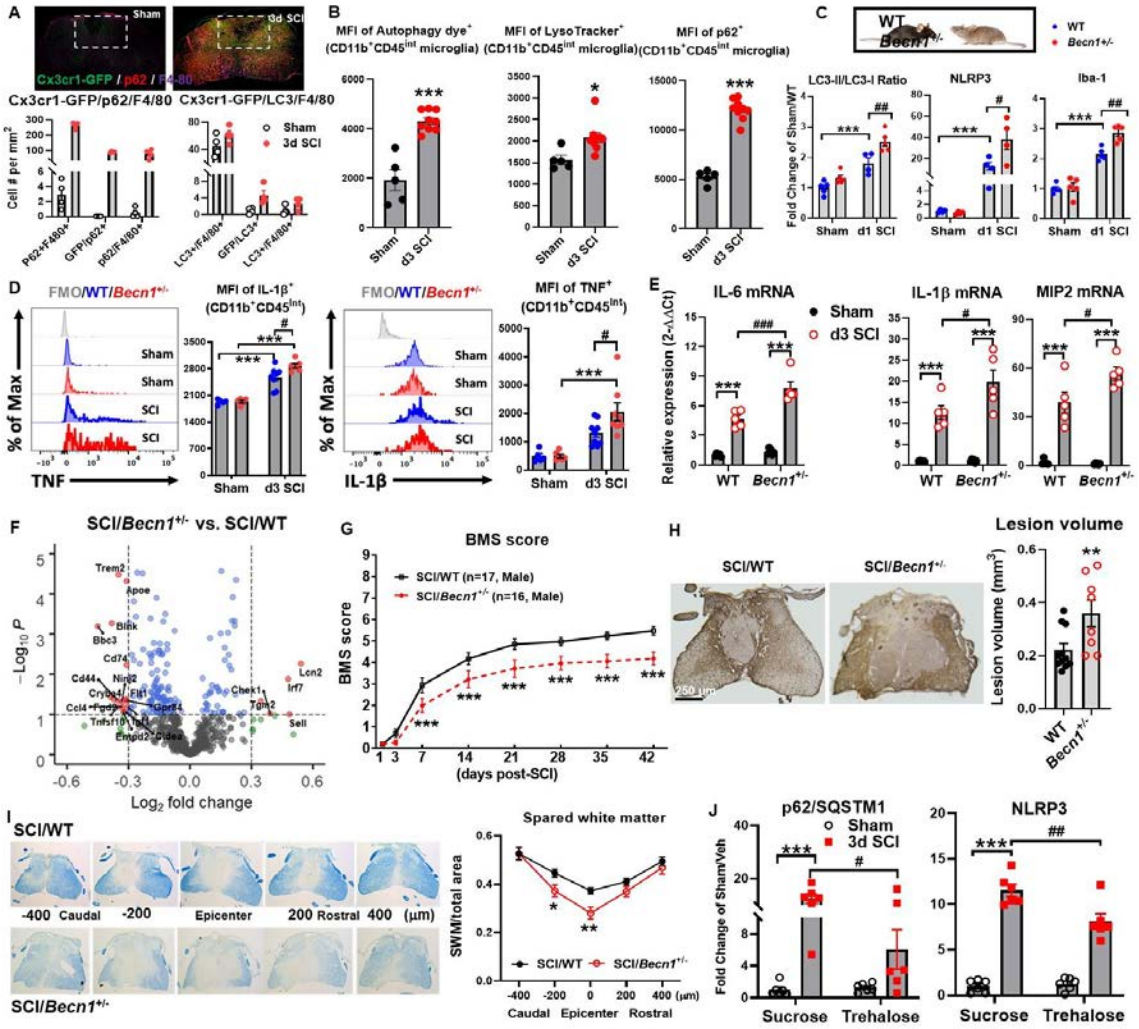

Figure. Impairment of autophagy in microglia/macrophages potentiates neuroinflammation after spinal cord injury (SCI). A) IHC staining of Cx3cr1-GFP mice showed LC3 and p62 accumulating in activated microglia and infiltrating macrophages at 3d post-injury. n=5 mice/group. **B)** Flow cytometry analysis showed increased autophagic marker in CD11b^{+}CD45^{int+} microglia at 3 d post-injury. n=5 (Sham) and 9 (SCI). **C)** Western blot analysis showed level of LC3-II/LC3-I ratio in autophagy hypomorph *Becn1*$^{+/-}$ mice at 1d post-injury, along with increased levels of inflammasome marker NLRP3 and Iba-1. n=5/group. **D)** Flow cytometry showed higher levels of IL-1β and TNF-α in *Becn1*$^{+/-}$ mice at 3d post-injury. n=5 (Sham/WT), 6 (Sham/*Becn1*$^{+/-}$), 9 (SCI/WT), and 8 (SCI/*Becn1*$^{+/-}$). **E)** qPCR analysis demonstrated higher levels of pro-inflammatory genes, IL-6, IL-1β and MIP2 in *Becn1*$^{+/-}$ mice at 3d post-injury. n=5/group. **F)** NanoString Assay showed robust changes of genes related to neuroinflammation in the injury site between SCI/WT and SCI/*Becn1*$^{+/-}$ at 3d post-injury**.** n=5/group. **G)** BMS score showed significantly worse locomotor functional recovery for *Becn1*$^{+/-}$ mice. n=16-17/group. **H)** GFAP-DAB staining showed significantly higher lesion volume after SCI for *Becn1*$^{+/-}$ mice. n=11 (SCI/WT) and 8 (SCI/*Becn1*$^{+/-}$). **I)** Luxol fast blue staining showed significantly lower levels of spared white matter in *Becn1*$^{+/-}$ mice. n=11 (SCI/WT) and 8 (SCI/*Becn1*$^{+/-}$). **J)** After treatment with 5% Trehalose (w/v), Western blot analysis showed restoration of autophagy flux and decreased inflammasomes at 3 d post-injury. n=6/group. *p<0.05, **p<0.01, ***p<0.001 vs Sham using Mann Whitney test or unpaired t test (B, H). *p<0.05, **p<0.01, ***p<0.001 vs WT/Sham, ##p<0.01, ###p<0.001 vs WT/TBI using 2-way ANOVA group analysis with Tukey's test for multiple comparisons (C-E, I-J) or repeated measurement (G).

TRAUMA 4

Olfactory function is impaired after traumatic brain injury in mice through Hv1/NOX2-mediated inflammation

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INTRODUCTION: Approximately 20-68% of traumatic brain injury (TBI) patients exhibit trauma-associated olfactory deficits (OD) which can compromise not only the quality of life but also cognitive and neuropsychiatric functions. Although post-traumatic anosmia has been documented in the medical literature for more than a century, few studies to date have examined the impact of experimental TBI on OD. While increased glial reactivity has been observed in the post-TBI olfactory bulb (OB), a site remote to non-contusive brain injury, neither the underlying mechanisms nor treatment remain clear. The present study examined the inflammatory changes in the OB and the underlying mechanisms associated with OD in mice using a controlled cortical impact (CCI) model of TBI.

METHODS: Young adult (10-12 weeks) male C57BL/6 mice were subjected to mild/moderate-level CCI. Flow cytometry, qPCR, and immunohistochemistry were used to examine inflammation in the OB after TBI. Transgenic mice with ablation of the voltage-gated proton channel Hv1 or NADPH oxidase (NOX2) as well as a specific NOX2 inhibitor were used to determine the effects of Hv1 and NOX2 activity on TBI-mediated OD. Olfactory function was assessed for up to 6 months post-injury, including buried food, two-bottle odor discrimination, and odor memory. Mice were randomly assigned to one of four groups based on surgery and treatment. Behavioral testing was performed by investigators blinded to surgery, genotype, and treatment.

RESULTS: Cortical contusion TBI without direct damage of the OB caused a rapid inflammatory response in the OB as early as 24 h post-injury, including elevated mRNA levels of proinflammatory cytokines, increased numbers of microglia and infiltrating myeloid cells, and increased IL1β and IL6 production. Microglial activation in the OB was sustained for up to 90 days after TBI. Moreover, we observed significant upregulation of Hv1 and NOX2 expression levels at 1 d and 3 days post-injury, which were predominantly localized in Iba1+ microglia/macrophages. Genetic ablation of Hv1 in mice significantly attenuated the production of NOX2-mediated production of reactive oxygen species (ROS) and cytokines. In a battery of olfactory behavioral tests, WT/TBI mice displayed significant OD. In contrast, Hv1 KO/TBI or NOX2 KO/TBI mice did not display significant deficits in any olfaction tests, indicating improved olfactory function. Finally, intranasal delivery of a NOX2 inhibitor (NOX2ds-tat, 1.4 mg/kg/day, once daily) for 7 days after TBI preserved post-traumatic olfactory function as evidenced using the buried food and two-bottle discrimination tests.

CONCLUSION: Our data indicate that Hv1/NOX2-mediated proinflammatory changes in the OB are associated with poorer olfactory function late after TBI. Targeting Hv1/NOX2 may be a promising intervention for improving post-traumatic anosmia.

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TRAUMA 5

Cardiovascular dysfunction following traumatic brain injury in male and female rats

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INTRODUCTION: Traumatic brain injury (TBI) has high mortality, reduced life expectancy, and persistent disability[1,2]. Despite the heterogeneity of TBI, autonomic nervous system (ANS) dysfunction (dysautonomia) is pervasive in mild to catastrophic injuries[3] and is associated with morbidity and mortality[3,4]. The reason TBI increases long-term mortality rates by 1.5 to 3 times is unknown, but dysautonomia could be a contributing factor[5,6] so ANS parameters could be biomarkers and therapeutic targets. The objective of this study is to quantify ANS parameters following TBI using a validated, rotational injury device (RID) rat model[7,8]. ANS function is quantified by heart rate variability (HRV), which is associated with poor neurological outcomes[3] and death[4]. As stress can be a frequent challenge during rehabilitation, this study also explores how exposure to the elevated-plus maze (EPM) affects TBI-induced dysautonomia.

METHODS: This study was approved by the Institutional Animal Care and Use Committee (IACUC). Male and female 8-week-old Sprague-Dawley rats were implanted with telemetry devices (DSI) into a femoral artery to record blood pressure (BP) from which HRV was derived[9]. Resting BP was recorded during undisturbed, home cage conditions. For stress conditions, BP was recorded immediately after TBI and the EPM. TBI was induced using the RID to administer a coronal plane rotational acceleration of the head (Figure 1)[7]. The EPM quantifies rats' time spent and entries into open arms, closed arms, and the center during a 15-min session[7]. Testing timeline is illustrated in Figure 2. Frequency-domain analysis of HRV[9], allows computation of the relative contributions of the sympathetic (LF power) and parasympathetic (HF power) nervous systems (SNS and PNS). As such, the LF/HF ratio is considered to reflect sympathovagal balance[10]. Rats were randomly assigned to TBI or Control groups. TBI was performed under isoflurane anesthesia after endotracheal intubation and confirmation of normal acid-base status. Rats were exposed to 5 - 10 TBI events in as fast succession as possible. Statistical analysis was completed with Graphpad Prism 8.4.3 using one-way and two-way repeated measures ANOVA.

RESULTS: The RID delivers accurate, precise, and reproducible biomechanical parameters (Figure 3) representing concussion with brief loss of consciousness[11]. Results indicate a main effect of TBI to decrease HF power at rest ($p<0.01$; Figure 4a) indicative of a decrease in PNS tone. There is also an increase in the LF/HF ratio ($p<0.01$; Figure 4b) at rest suggesting a relatively higher SNS versus vagal cardiac modulation. Both the HF power and LF/HF ratio normalize by post-injury day (PID) 8. On PID 8, EPM stress unmasked an increase in LF/HF ratio in TBI rats, that was not present in the TBI group at rest, or in control animals either at rest or after EPM ($p<0.05$; Figure 4c).

CONCLUSION: These data demonstrate that the RID induces a reproducible TBI that alters ANS function in male and female rats. Resting state data demonstrate prominent ANS dysfunction that is partially mediated by the PNS. The contribution of the SNS is unclear because the magnitude of change in the LF/HF ratio is disproportionately larger than HF power alone. This suggests a complex change in the ANS that is yet to be fully elucidated in terms of the involved brain region(s), neurocircuitry, and biomechanisms. Avoiding secondary insults after TBI, including excessive stress that could delay recovery or worsen outcomes is clinically important. Together, these findings support the hypotheses that TBI causes autonomic dysfunction and post-injury exposure to stress unmasks ANS dysfunction that is not detectable at rest or in controls. Thus stressors could be a diagnostic tool for detecting occult dysautonomia[12]. These data provide the foundation for future studies to a) understand central mechanisms underlying dysautonomia after TBI and b) identify potential ANS signatures that could be targeted to develop novel treatments and biomarkers for recovery or prognostication, which could transform the way athletes or veterans are evaluated for 'return to play' or 'return to service.'

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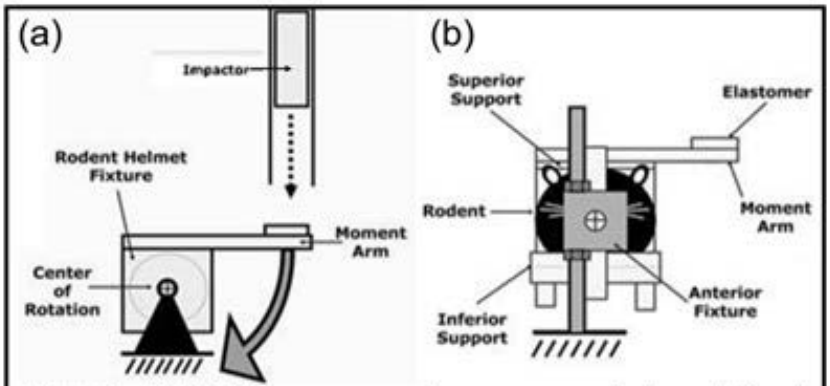

Figure 1. RID. (a) Rats are exposed to a pure coronal plane rotational acceleration of only the head to induce a TBI. The moment arm is displaced by a pressure ejected impactor with rotation limited to 90 degrees that avoids skull fracture. (b) The rat helmet fixture and moment arm are rotating elements, the body harness and anterior fixture are fixed elements. Modified from Fijalkowski et al. 2007.

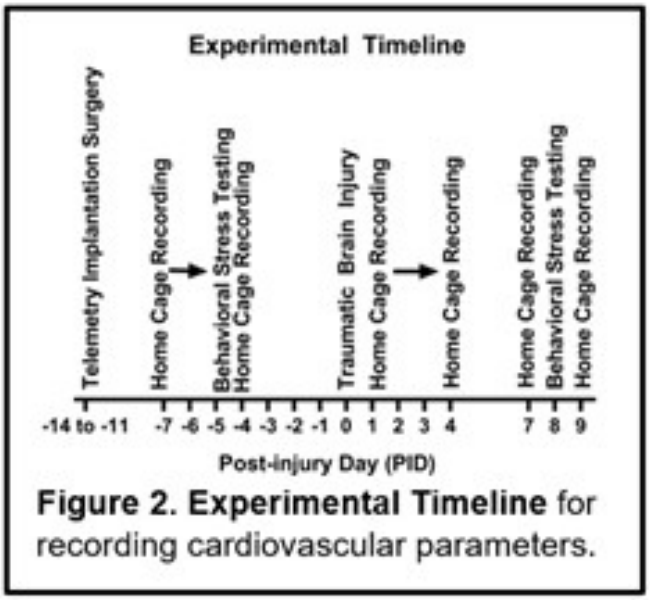

Figure 2. Experimental Timeline for recording cardiovascular parameters.

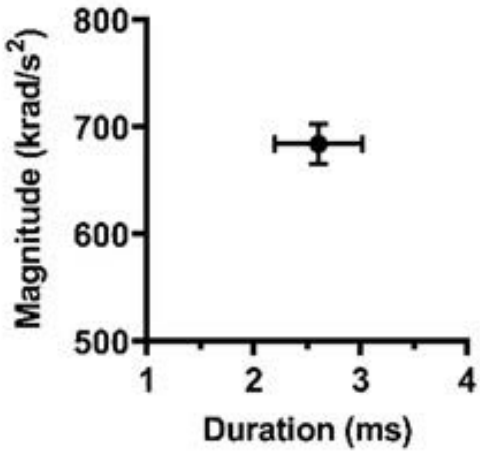

Figure 3. RID Biomechanical Reproducibility. Targeted peak acceleration magnitudes of 700 krad/s² and durations of 2.5ms (mean+/-SD) were reproducible with coefficient of variations of 9.9% and 15.6%, respectively in 10–12 wk-old Sprague-Dawley rats (5 males, 8 females).

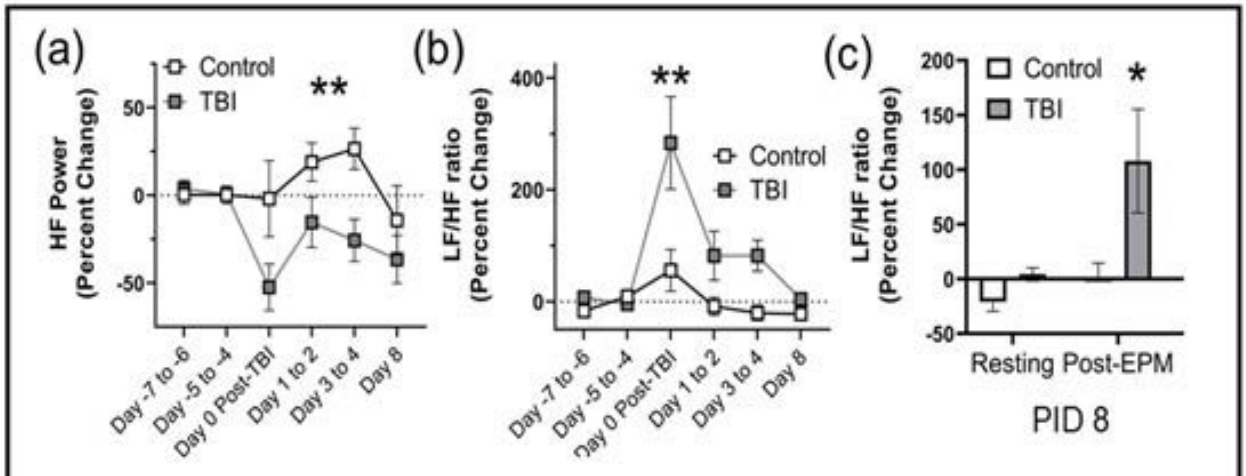

Figure 4. TBI-induced HRV changes in 10–12 wk-old Sprague-Dawley rats (5 female; 11 male; n=8/group). Significance denoted as *p<0.05; **p<0.01 with data shown as mean +/- SEM.

TRAUMA 6

Trauma-Induced Massive Transfusion Effect on Mortality: A Systematic Review

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INTRODUCTION: Massive transfusion (MT) is defined as transfusion of ten or more units of packed red blood cells (pRBCs) in a 24-hour period.Trauma remains a major cause of hemorrhage often necessitating MT. In this review, we aim to investigate the literature on MTs in order to determine the relationship between number of blood units and patient mortality in the setting of trauma with the ultimate goal of identifying a point when additional units of blood could be harmful.

METHODS: We performed a systematic review with a comprehensive search of Scopus, Cinahl Complete, Medline Complete, and PubMed databases from years 2000 to 2021 using a combination of keywords such as transfusion, blood, massive, mortality, etc. Inclusion criteria for studies was U.S. adult population, trauma as mechanism of injury, published in the English language, and includes information on the number of blood products administered and mortality rates.

RESULTS: The review identified 2763 studies. 1133 were duplicates. Of the remaining 1630 studies, 166 studies underwent full-text review. Twelve studies met inclusion criteria, which analyzed an aggregate of 6717 patient records. Eight of the studies were retrospective, four were prospective, and zero were randomized controlled trials (RCTs). Quality assessment yielded four low quality studies, six moderate-low quality studies, and two moderate quality studies. We identified zero high quality studies. There was a broad range of patient populations, process indicators, and outcomes utilized by the different authors, including using acute respiratory distress syndrome (ARDS) as the primary outcome, plasma deficit versus plasma ratio as predictors of mortality, defining poor outcomes by hemoglobin oxygen saturation, among a few others. In addition, each of the studies defined a myriad of blood product use ranges as well as different proportions of trauma patients, rendering the systematic review inconclusive. Due to the limitations, no study was able to isolate the ceiling of blood transfusion that causes patient mortality without introducing significant confounders.

CONCLUSION: There is currently no comprehensive analysis on the number of blood units transfused and patient mortality when removing confounding variables. Further research on this topic is necessary to limit mortality and promote lifesaving interventions in trauma care.

TRAUMA 7

Non-Coding RNA within Extracellular Vesicles in Trauma-Associated Pneumonia

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INTRODUCTION: Trauma predisposes to acute lung injury, pneumonia and ARDS, even in the absence of direct chest and pulmonary involvement. The incidence of pneumonia, in the setting of trauma, has held constant from 2007 to 2012, (~40%); hence new approaches are required. The molecular basis for this important complication not been identified but likely involves systemic inflammatory responses to local injury and danger signals. Such signals may be delivered by extracellular vesicles (EVs). These are small (100-1,000 nm) lipid bilayer membrane packets released by inflammatory cells that contain danger molecules e.g. extracellular ATP; transmembrane and cytosolic proteins; as well as mRNA and non-coding RNAs. Levels of EV-associated microRNAs such as miR-146a, miR-27a, miR-126, and miR-155 may predict ARDS in setting of community-acquired pneumonia. miR-155 has been shown to cause endothelial dysfunction linked to severity of sepsis via post-transcriptional changes in ENTPD1/CD39 expression, an immune and vascular ectonucleotidase. We have studied the role of EV-associated non-coding RNAs and ascertain impacts on CD39 and purinergic signaling in trauma patients with pulmonary complications. Manipulation of EVs, associated microRNA and the demonstration of linked pathogenetic roles drive not only studies of biomarkers predictive of post-trauma lung injury but may indicate future therapeutic targets.

METHODS: In this pilot study, exosomal non-coding RNAs from the plasma of trauma patients (n=10) admitted to the ICU, who were diagnosed with pneumonia were examined. The plasma exosomal non-coding RNA expression patterns were compared between the time of diagnosis of pneumonia relative to admission levels. Clinical parameters were explored to further define trauma severity (ISS), RBC transfusion requirement, and vasopressor usage in this context.

RESULTS: We discovered 85 non-coding RNAs, which were differentially expressed between admission and time of pneumonia diagnosis. Of these, the down-regulated miRNAs included miR-19b-3p, 19a-3p, 29b-3p, 331-3p, 191-3p, 133a-3p, 93-5p, 1306-5p, and 15b-3p; up-regulated miRNAs included miR-320b and 132-3p. miR-19b-3p was found to be down regulated in this population. ISS score was not correlated to the expression level of miR-19b-3p at admission or at time of pneumonia diagnosis. Changes in miR-19b have been linked previously to hemorrhagic shock. This was not observed in this cohort, as determined by the number of RBC units transfused, pressors utilized at admission or at time of diagnosis of pneumonia.

CONCLUSION: Levels of miR-19b-3p significantly decreased in those trauma patients, who were diagnosed with pneumonia in the ICU. This change was not related to hemorrhagic shock and did not appear to be correlated to the severity of trauma. Levels of miR-19b-3p may provide biomarkers for predicting onset of pneumonia in these critically ill, injured patients and may provide insights into pathogenesis.

TRAUMA 8

Integrated single-cell and plasma proteomic modeling to predict surgical site complications, a prospective cohort study

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INTRODUCTION: Surgical Site Complications (SSCs) may occur in up to 25% of patients undergoing bowel resection, resulting in significant morbidity and economic burden[1,2]. However, the accurate prediction of SSCs remains clinically challenging. Leveraging high-content proteomic technologies to comprehensively profile patients' immune response to surgery is a promising approach to identify predictive biological factors of SSCs. The objective of this study is to determine whether single-cell and plasma proteomic elements of the host's immune response to surgery accurately identifies patients who develop a SSC after major abdominal surgery.

METHODS: Forty-one patients undergoing non-cancer bowel resection at a major university hospital were prospectively enrolled. Blood samples collected before surgery and on post-operative day one (POD1) were analyzed using a combination of single-cell mass cytometry and plasma proteomics (Fig. 1a, 1b). The primary outcome was the occurrence of an SSC, including surgical site infection, anastomotic leak, or wound dehiscence within 30 days of surgery. We employed a stacked generalization (SG) predictive modeling approach[3,4] to determine whether differences in immune responses between patients with or without an SSC can be detected on POD1, which is before SSCs become clinically apparent. This approach integrates individual data layers into a single multivariate model (Fig. 1c). The SG model classified patients with high accuracy (AUC = 0.86, p = 2.5e-04, unpaired Mann-Whitney rank-sum test on the SG model cross-validated values, Fig. 1d). Additionally, single cell and plasma proteomic relationships were identified and explored (Fig. 1e).

RESULTS: A multiomic model integrating the single-cell and plasma proteomic data collected on POD1 accurately differentiated patients with (n=11) and without (n=30) an SSC (AUC = 0.86). Model features included co-regulated pro-inflammatory (e.g. IL-6- and MyD88- signaling responses in myeloid cells) and immunosuppressive (e.g. JAK/STAT signaling responses in M-MDSCs and Tregs) events preceding an SSC. Importantly, analysis of the immunological data obtained before surgery also yielded a model comprising 17 features that accurately predict SSCs (AUC = 0.82, Fig. 2).

CONCLUSION: The multiomic analysis of patients' immune response after surgery and immune state before surgery revealed systemic immune signatures preceding the development of SSCs. Our results suggest that integrating immunological data in perioperative risk assessment paradigms is a plausible strategy to guide individualized clinical care.

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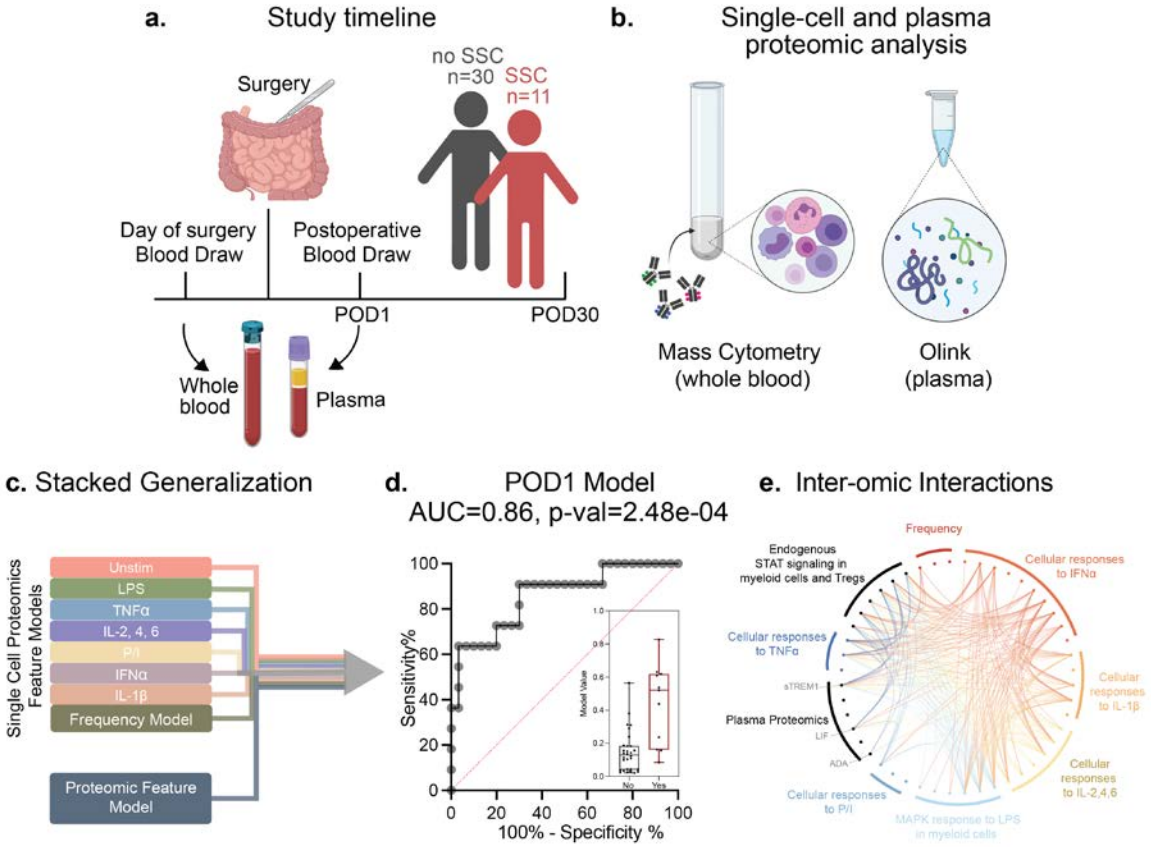

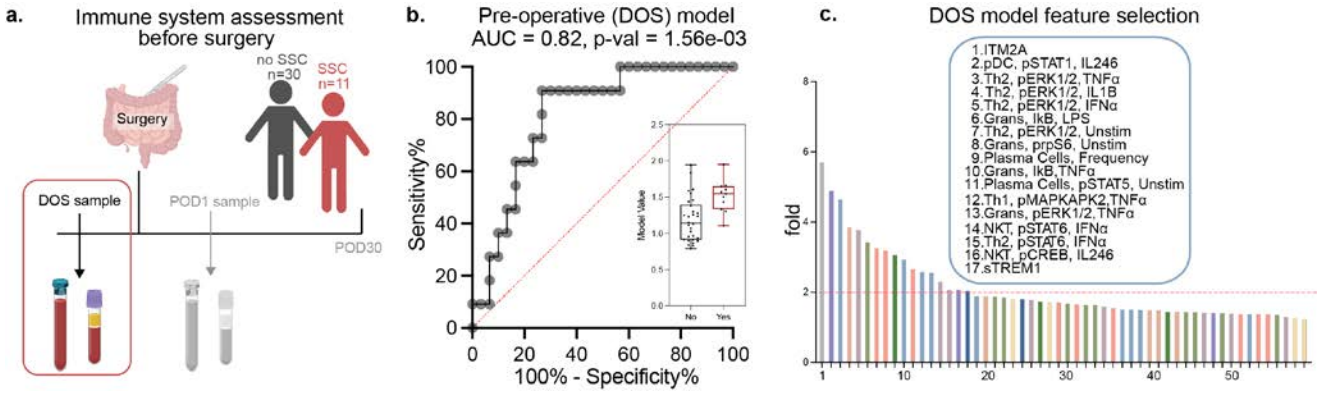

TRAUMA 9

Effects of air-evacuation-relevant hypobaria on ferrets following traumatic brain injury combined with hemorrhagic shock

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INTRODUCTION: Rats exposed to aeromedical evacuation (AE) relevant hypobaria within seven days after traumatic brain injury (TBI) alone or in combination with hemorrhagic shock (HS) exhibit greater neurologic injury and mortality than those maintained under normobaria[1-4]. The applicability of these results to humans may be limited, however, by differences in brain neuroanatomy. Like humans, ferrets have a gyrencephalic brain. We therefore developed a ferret polytrauma (PT) model consisting of controlled cortical impact TBI (CCI) of moderate severity combined with mild HS. The objective was to determine if the deleterious effects of AE-relevant hypobaria observed in rats after TBI are also observed in a distinctly different species with a gyrencephalic brain.

METHODS: The protocol was reviewed and approved by the U.S. Air Force Surgeon General's Office of Research Oversight and Compliance (AFOSR-2017-0017A) and by the University of Maryland, Baltimore Institutional Animal Care and Use Committee. Animal activities were conducted in compliance with all federal regulations governing the protection of animals and research. Anesthetized adult male ferrets (n=18) received CCI at a depth of 4 mm followed immediately by HS induced by withdrawing blood to maintain MAP 35-45 mm Hg for 30 minutes. Shams (n=4) received a craniotomy with no impact. Resuscitation with Hextend was followed one hr later by blood re-infusion. At 24 hr, ferrets were placed in a 'flight' chamber for 6 hr and exposed to normobaria (NB) (sea level, n=9) or to hypobaria (HB)(=8000 ft altitude, n=9) under normoxic conditions of 21-28% O2. MRI and MRS measurements were performed before injury and 2 days later. Cortical areas on T2 images appearing bright white were classified as 'hyperintensities' (HI) and areas appearing matte gray were classified as 'healthy'. Areas quantified with ImageJ from 1mm thick sections were summed to calculate cortical volumes (mm3). Spatial memory was evaluated with novel object location test before and 6 days after injury. Ferrets first spent time in an arena with two objects and then reintroduced to the arena once one object had been moved. Brains were perfusion-fixed on day 7, immunostained for IBA-1(microglia) and used for stereologic quantification of lesion volume and activated microglia near the site of cortical impact.

RESULTS: Data was analyzed by t test (behavior) or ANOVA (all other data) with Fishers LSD post hoc test. In contrast to our rat PT model that results in 30–60% mortality, no ferret deaths occurred. Polytrauma impaired spatial memory in ferrets at 6 dpi. Sham ferrets explored the moved object significantly more than the unmoved object whereas PT ferrets showed no preference for either object. Hypobaria exposure did not exacerbate this deficit. The total cortical lesion volume (11.9 ± 3.7 vs 98.4 ± 8.3 mm3) induced by PT was not affected by HB (98.4 ± 8.3 vs 108.0 ± 9.6 mm3). MRS results obtained at 48hr indicate reduced cortical levels of creatine, N-acetyl aspartate, GABA and glutamate after PT which was not affected by HB. T2 image quantification revealed increased HI volume representing cortical edema at the site of impact following PT (4.6 ± 1.6 vs 149.5 ± 38.2 mm3). Hypobaria did not exacerbate this focal edema but did result in an overall decrease in cortical volume in both ipsilateral (27%) and contralateral (34%) hemispheres.

CONCLUSION: To our knowledge this is the first ferret polytrauma model combining TBI plus hemorrhagic shock. Although the extent of total cortical injury was similar in rats and ferrets, neuroinflammation was more extensive in the gyrencephalic species. Results indicate that hypobaria exposure in ferrets does not further exacerbate the impairment of spatial memory, the reduction in several key brain metabolites, or the increase in cortical edema and neuropathology, induced by polytrauma. Hypobaria after injury does, however, result in the acute reduction of cortical volumes in both injured and uninjured hemispheres. The lack of any improvement in neuroinflammation or behavior by exposure to hypobaria indicates that flying within a few days after polytrauma should be avoided, if possible, for TBI patients. The views and opinions presented herein are those of the author(s) and do not necessarily represent the views of DoD or its Components. Supported by US AF FA8650-15-2-6D21.

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TRAUMA 10

Flight Relevant Hypobaria Worsens Neuropathologic and Behavioral Outcomes in Rats Following the Combination of Under-Vehicle Blast plus Controlled Cortical Impact

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INTRODUCTION: US warfighters exhibit a very high incidence of traumatic brain injury (TBI) that often results in long term neurologic impairment. Most injuries are caused by exposures to blasts, either as an unmounted soldier or present within a vehicle targeted by a land mine. A small-scale model of 'under-vehicle' blast was developed for studying the effects of this blast paradigm on TBI alone, or in combination with other trauma[1-5]. The current study utilized a new rat blast polytrauma model consisting of under-vehicle blast (B) followed by controlled cortical impact (CCI). This BCCI model extends our characterization of how exposure to aeromedical evacuation-relevant hypobaria can worsen neurologic outcomes[1-5]. Hypothesis 1: Exposure to hypobaria (=8000 ft) one day following BCCI worsens cerebral cortex inflammation compared to no hypobaria or to 4000 ft hypobaria. Hypothesis 2: Exposure to moderate hyperoxia (50% O2) during hypobaria worsens outcomes compared to rats maintained normoxic. Hypothesis 3: Exposure to BCCI damages the cerebellum which is exacerbated by exposure to hypobaria.

METHODS: The animal protocol was approved by the University of Maryland, Baltimore Institutional Animal Care and Use Committee (IACUC) and the U.S. Air Force Surgeon General's Office of Research Oversight and Compliance as protocol number FWR-2018-0002A. These studies were conducted in a facility accredited by AAALAC, in accordance with the Guide for the Care and Use of Laboratory Animals (NRC, 2011) and were performed in compliance with DODI 3216.1. The views and opinions presented herein are those of the author(s) and do not necessarily represent the views of DoD or its Components. Adult male rats were secured within restraints secured to a metal plate, simulating a vehicle. An explosive under the plate was detonated, causing 1800G acceleration. Rats were then anesthetized and subjected to the CCI model of TBI, thus simulating blast polytrauma caused by the combination of acceleration and head impact. At 24 hr after sham surgery or BCCI, rats were placed inside an altitude chamber under normobaric (sea level) or hypobaric (4000 or 8000 ft) pressures in the presence of either normoxic (21-28% O2) or hyperoxic (50% O2) conditions for 6 hr. Anxiety-like behavior was tested using time spent in the open zone of the elevated plus maze at 2, 7, and 14 days post injury (dpi). Anesthetized rats were euthanized by perfusion with paraformaldehyde at 2 or 14 dpi. Cortical inflammation was stereologically quantified using immunostained sections for activated macrophages (ED-1) or myeloperoxidase positive (MPO) neutrophils and astrocytes. Cerebellar injury was assessed in calbindin immunostained sections where Purkinje neurons were morphologically classified as healthy or injured.

RESULTS: All data were analyzed by ANOVA or Repeated Measures ANOVA with Fishers LSD post hoc test. A single under-vehicle blast followed immediately by moderate CCI resulted in acute neutrophil activation (MPO) in the cortex which was not further exacerbated by exposure to hypobaria. Blast CCI injury resulted in a two-fold increase in MPO positive neutrophil populations at 2 days, returning to sham levels by 14 dpi. Peri-lesional astrocyte volumes increased acutely by 7-fold and were not significantly different from shams at 14 dpi. Post injury exposure to 8000 ft hypobaria increased both anxiety-like behavior and inflammation (ED1) in the potentially salvageable penumbra near the site of cortical impact at 14 dpi. Increased anxiety behavior and cortical inflammation were neither further exacerbated by hyperoxia, or alleviated by a change in ambient pressure to 4,000 ft. Although cerebellar injury increased following exposure to BCCI, as reflected by an increase in numbers of injured Purkinje neurons, it was not further exacerbated by exposure to hypobaria. BCCI rats exposed to hypobaria under 50% oxygen had fewer injured Purkinje neurons compared to when hypobaria was performed under 28% O2.

CONCLUSION: 1. Hypobaria exposure after BCCI increases post-acute cortical inflammation and anxiety behavior in rats. 2. Blast polytrauma induces an acute increase in cortical activated neutrophils and long term cerebellar injury which are not further exacerbated by hypobaria or moderate hyperoxia. These results raise further concern that exposure of trauma patients to hypobaria during aeromedical transport can worsen neurologic outcomes. Supported by US Air Force FA8650-17-2-6H13.

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