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TABLE OF CONTENTS

Continued on next page

TABLE OF CONTENTS, *continued*

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Subspecialty Abstracts

AIRWAY MANAGEMENT

AIRWAY MANAGEMENT 1

Fast and accurate automatic placement of pulse-wave Doppler ultrasound gate over air-tissue interface in the neck for a novel respiratory monitor

Amy J Weisman[1], Lin Qi[1], Humberto Rosas[1], Quinton W Guerrero[1], Irene Ong[1], Guelay Bilen-Rosas[1]

[1]University of Wisconsin School of Medicine and Public Health, Madison, United States of America

INTRODUCTION: During conscious sedation procedures, patients are at a high risk for airway obstructions. If not detected early, obstructions can lead to adverse respiratory events ranging from desaturation to severe apnea requiring intervention. This can increase procedure time, prolong hospital stays, and cause severe health complications [1,2]. Current monitoring technologies fail at detecting obstructions directly, instead monitoring downstream parameters which change seconds to minutes after an obstruction occurs. We have recently developed a novel respiratory monitoring method that uses B-mode and Pulse-wave Doppler ultrasound measurements of the air-tissue interface of the laryngo-tracheal structures for airflow estimation. Preliminary results suggest this device may be invaluable in detecting airflow obstructions immediately. However, widespread use of such a monitor would be hindered by the difficulty of manually placing the ultrasound probe on the correct air-tissue interface. In this work, we implement region-based convolutional neural networks (CNNs) to automate this process using the B-mode images.

METHODS: Healthy subjects were recruited as part of an IRB-approved feasibility study assessing the novel respiratory monitor. An experienced radiologist placed a Siemens 18L6 HD transducer on the neck of each subject, ensuring the cricothyroid membrane (CTM) was in view. A 2 mm Doppler gate was placed on the CTM at perpendicular incidence. Due to ultrasound system constraints, the gate location was fixed throughout data collection. Concurrent B-mode and Doppler data was collected during normal breathing for 5 minutes per subject at 13.7 frames per second. Raw radiofrequency data was transferred for offline processing. In each B-mode frame, the CTM was segmented using a semi-automatic image processing method followed by manual edits. Using the orientation and location of the final segmentation, a "moving" CTM box was assigned to each frame (Figure 1) to be used for training of a faster region-based CNN (R-CNN) with a Resnet-18 backbone [3]. Training was performed with 5-fold cross validation (28 subjects for training, 3 for validation, and 8 for testing per fold) until plateau of validation set loss. In testing, only a single box with the highest confidence score was considered for each frame. Only boxes with confidence scores over 50% were considered. To assess R-CNN performance, the accuracy, sensitivity, and precision of CTM identification was calculated for each subject. Identical values were extracted for the fixed Doppler gate used during data collection in order to benchmark performance. A paired Wilcoxon test was used to compare the R-CNN with the fixed gate approach.

RESULTS: A total of 109,074 B-mode image frames were captured in 39 subjects (range: 2,080-2,844 per subject). This includes 1,239 negative frames (range: 0-339 per subject), where the CTM was not present due to subject movement or a swallow. The faster R-CNN box placement took an average of 0.08 (range: 0.05-0.21) seconds per frame. Overall, the performance of the R-CNN showed a median (range) accuracy of 99.2% (83.3-100%), a sensitivity of 99.8% (83.3-100%), and precision of 99.8% (92.9-100%). For comparison, the median (range) performance of the static ROI showed an accuracy of 99.0% (58.7-100%), a sensitivity of 99.9% (59.1-100%), and precision of 99.4% (87.1-100%). The precision of the R-CNN was significantly greater than that of the static ROI approach ($p<0.001$), while there were no statistically significant differences in the accuracy or sensitivity (Figure 2).

CONCLUSION: A faster region-based convolutional neural network was able to quickly and accurately place a region of interest around the cricothyroid membrane in B-mode ultrasound images. This technique brings us closer to fully automating the placement of the ultrasound probe and collection of ultrasound measurements from human subjects without the guidance of an experienced radiologist.

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2. Saunders R, Davis JA, Kranke P, Weissbrod R, Whitaker DK, Lightdale JR. Clinical and economic burden of procedural sedation-related adverse events and their outcomes: Analysis from five countries. Ther Clin Risk Manag 2018;14:393–401.
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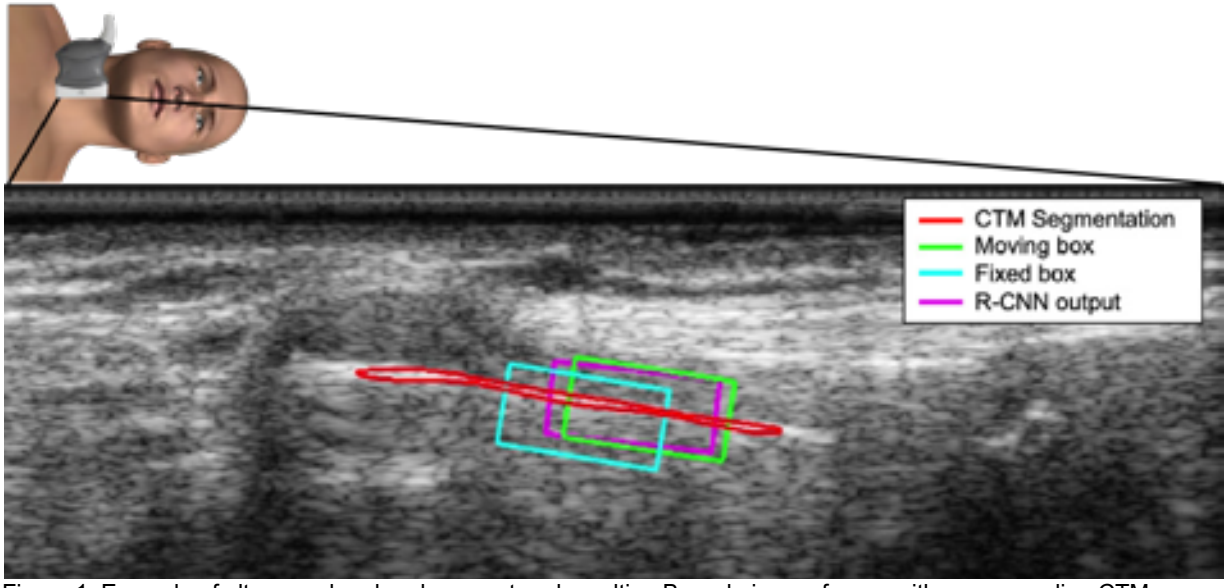


Figure 1: Example of ultrasound probe placement and resulting B-mode image frame, with corresponding CTM segmentation and boxes. Note that Doppler data is only collected from only a single ultrasound transducer element, though large boxes were used to ensure a large enough field of view for the R-CNN.

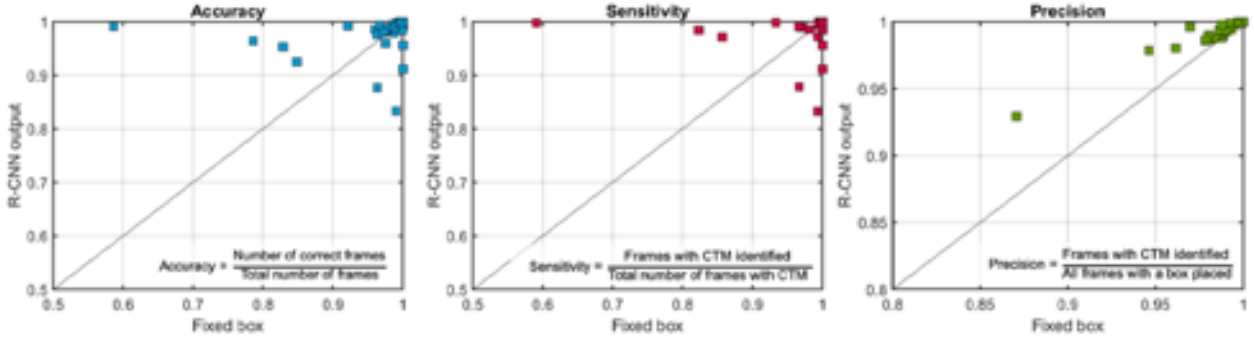


Figure 2: Performance of the R-CNN output (y-axis) compared to the fixed Doppler gate (x-axis) for all three assessed performance metrics.

AIRWAY MANAGEMENT 2

Effective protection from SARS-CoV-2 transmission during aerosol generating procedures: Experience from an intubation and tracheostomy team at a large urban safety net hospital

Nikhil Mikkilineni[1], Robert Canelli[2], Mark Stasaitis[3], Shivali Mukerji[4], Katherine Christopher-Dwyer[5], Elizabeth Ryan[5], Ala Nozari[2]

[1]Boston Medical Center, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Boston University Medical Center, Boston, MA, [4]Boston University, Boston, MA, [5]Boston Medical Center, Boston, United States of America

INTRODUCTION: Protecting health care workers from exposure to COVID-19 during aerosol generating procedures remains challenging. We examined the effectiveness of a CDC-based PPE protocol adapted for aerosol generating procedures in preventing transmission of SARS-CoV-2 to health care workers.

METHODS: We surveyed anesthesiologists, respiratory therapists, nurses, and surgeons who participated on the intubation and tracheostomy teams during the COVID-19 pandemic. The primary outcome was the total number of infected individuals, as defined by a positive RT-PCR assay, rapid antigen test, or serologic antibody test during the timeframe of the first surge at our institution. The secondary outcome was self-reported perceived PPE adherence.

RESULTS: Of the 64 heath care providers who performed 231 endotracheal intubations and 22 percutaneous tracheostomies, 57 were included in the final analysis. Twenty-one reported receiving either a RT-PCR assay or rapid antigen test and zero positive tests (0%) were reported. Twenty-five respondents reported receiving a serologic antibody test and zero positive tests (0%) were reported. The average self-reported perceived adherence to the institutional PPE protocol was 99.3% for the intubation team and 99.7% for the tracheostomy team.

CONCLUSION: Based on our findings of 0 positive test results among surveyed health care workers performing intubations and tracheostomies, our institution's CDC-based PPE protocol is effective in preventing the transmission of SARS-CoV-2 during aerosol generating procedures. Further studies are warranted to validate these findings.

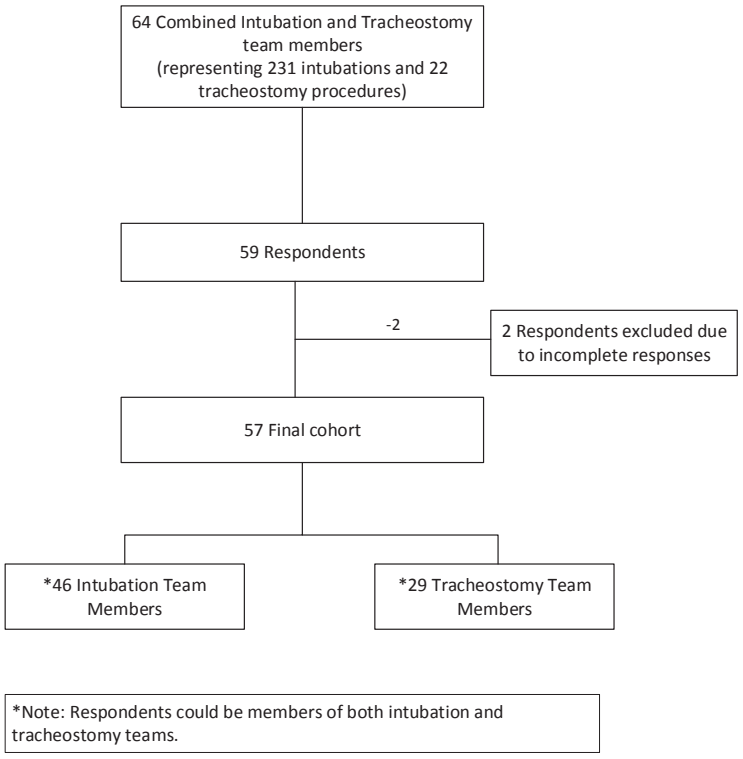


Fig. 1

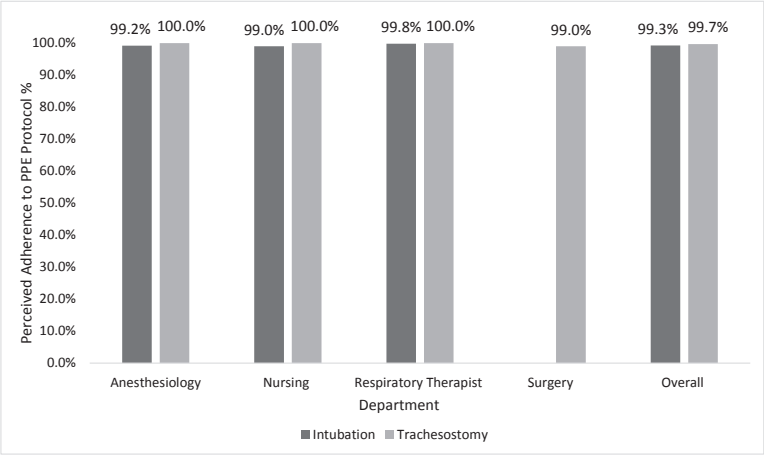


Fig. 2

Fig. 4

Table 2: Summary of self-reported COVID-19 RT-PCR assay and rapid antigen test results.

Survey Question	N	%
Did you receive a COVID-19 RT-PCR assay or rapid antigen test?	57	
Yes	21	36.8%
No	36	63.2%
How many times were you tested by RT-PCR assay or rapid antigen test?	21	
1	13	62.0%
2	7	33.3%
3	1	4.7%
How many RT-PCR assays or rapid antigen tests were positive?	21	
0	21	100%

Table 3: Summary of self-reported COVID-19 antibody test results.

Survey Question	N	%
Did you receive a COVID-19 antibody test?	57	
Yes	25	43.8%
No	32	56.2%
What was the result of the COVID-19 antibody test?	25	
Positive	0	0%
Negative	25	100%

AIRWAY MANAGEMENT 3

Assessment of ease of laryngoscopy at varying table heights

Kavya Goel[1], Alok B Roy[2], Rajiv Aggarwal[2]

[1]MAX Superspeciality Hospital, Vaishali, Ghaziabad, Uttar Pradesh, [2]Max Superspeciality Hospital, Vaishali, Ghaziabad, Uttar Pradesh

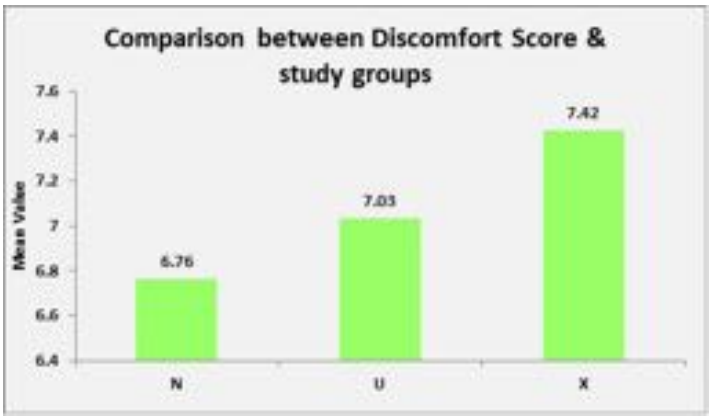
INTRODUCTION: In our study we aimed to evaluate discomfort to the anesthetist at varying table heights during laryngoscopy subjectively as well as objectively while also monitoring the head extension of the patient at each table height so as to determine the optimum extension required. Once an optimum table height is established in patients with a normal airway, this study can be applied upon patients with difficult airways to facilitate surer and smoother laryngoscopy, providing an answer to one of the most challenging aspects of a general anesthesia.

METHODS: A prospective randomized study was performed at the department of anesthesiology, Max Super Speciality Hospital, Vaishali over a period of one year including adult patients undergoing general anesthesia for elective surgeries without an anticipated difficult airway. The patients were divided into 3 groups depending on the operating table height at which the laryngoscopy was performed in relation to the anesthetist's anatomical landmarks into U (Umbilicus), X (Xiphoid Process) and N (Nipple) with a sample size of 38 in each group. After standard induction of general anesthesia, table was set at one of the three randomly allotted heights and patient ventilated in an initial posture assumed by the anesthetist, at the end of which they were asked to score ease of mask holding out of a scale of 0 to 10, 0 being most difficult and 10 the easiest. Laryngoscopy was done without changing posture and laryngeal view graded using the Cormack Lehane Grading. A person unaware of the details of the study took pictures of the process. The anesthetist was then allowed to adjust their posture to obtain the best laryngeal view and again pictures were taken and grading done. The pictures were then used to calculate the degree of deviation in the angles of wrist deviation, arm elevation, neck flexion and lower back flexion in the anesthetist and degree of head extension in the patient before and after change in posture. The observations were tabulated and analyzed through analysis of variance. Tukey test was used to find out which group is different from the others.

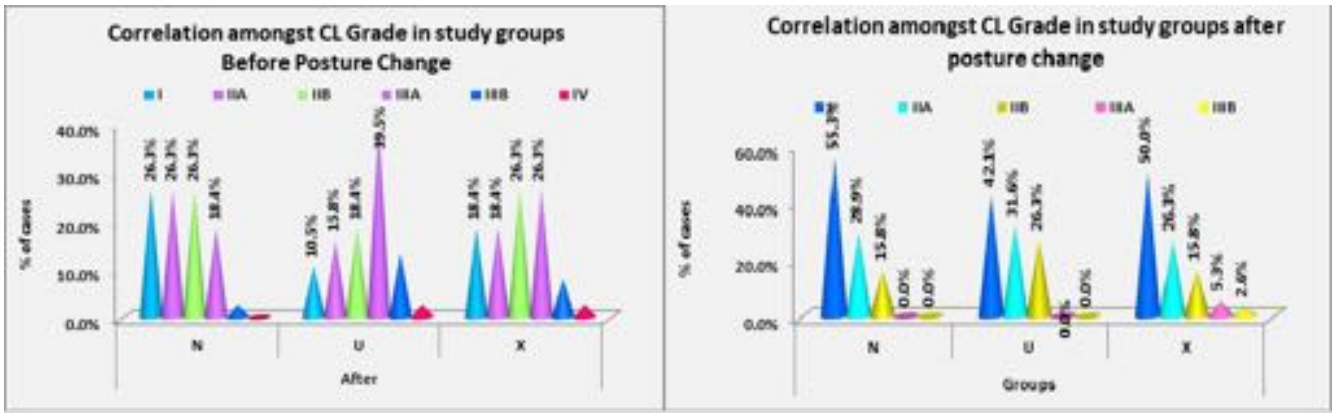
RESULTS: Initial laryngeal views were significantly better in N group (p value <0.001) along with lesser neck and back discomfort as was lesser head extension. However the presence of wrist and arm discomfort, subjectively uncomfortable mask holding and occasional difficulty in blade insertion make it unsuitable for routine intubations. At the umbilicus height, there was significantly less wrist and arm discomfort but initial laryngeal views were poorer as was an increased neck and lower back discomfort. The head extension required was also the most(p value 0.002). In the Xiphoid group, the initial laryngeal views were similar to Nipple height while there was a decreased incidence of neck and lower back discomfort. Subjective mask discomfort was least in this group though was not statistically significant (p value 0.303) making it the ideal height for routine laryngoscopies and intubations.

CONCLUSION: The ideal height of operating table while performing laryngoscopy based on our study is concluded to be at the level of xiphoid process of the anesthetist owing to better laryngoscopic views, lesser neck and back discomfort to the anesthetist, lesser head extension in the patient and lower mask holding discomfort. The nipple height while not best for routine intubations, may however be advantageous in patients with limited neck mobility, cervical spine injuries, anesthetists with lower back and neck discomforts and cases of difficult airway. The umbilicus height may be advantageous for anesthetists with wrist and arm morbidities and for patients with difficult bag and mask ventilation.

Depiction of a pilot case where the various angles are being measured according to the guidelines in the parent study using Adobe Photoshop CS6



Pic. 2



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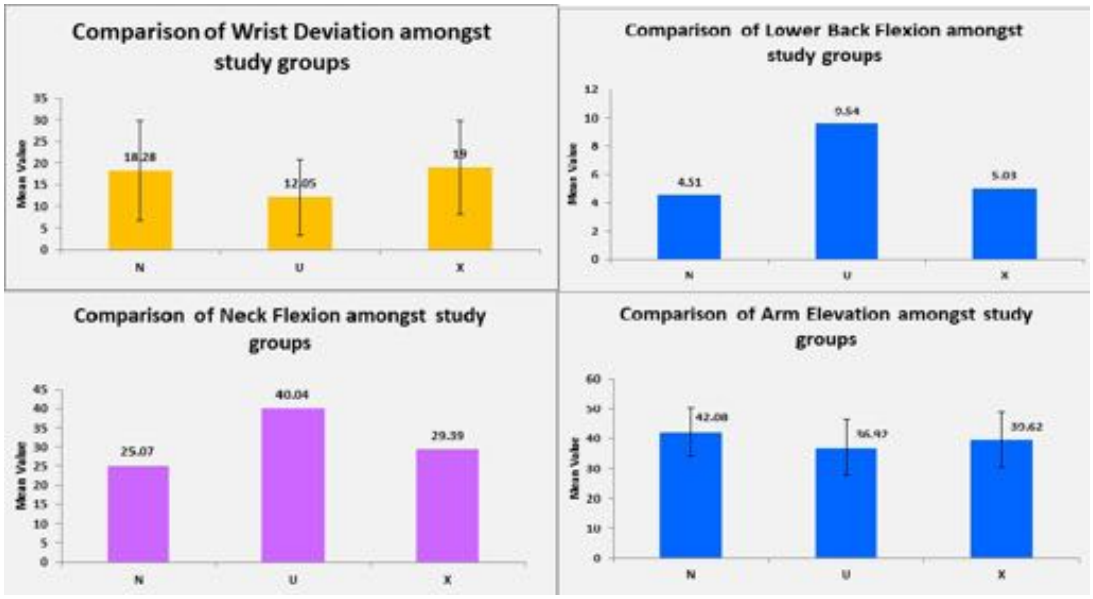

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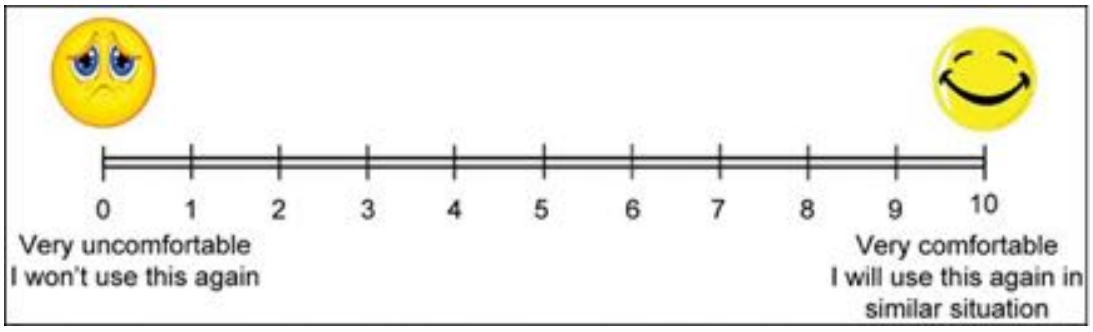

Pic. 5

AIRWAY MANAGEMENT 4

OMAN Score (Obesity, Mallampati and Neck Circumference) as a predictor of difficult intubation in obese patients: A prospective observational study

Salim A Jassasi[1], Rashid M Khan[1], Naresh k Kaul[1]

[1]Khoula Hospital, Muscat, Oman

INTRODUCTION: Individual predictors of identifying a difficult tracheal intubation in obese patients do not have a satisfactory predictive value (1). The aim of this study was to develop a cumulative score combining Obesity grade (BMI), Mallampati class and Neck circumference (OMAN Score) and to identify whether this cumulative score would give a better prediction of difficult tracheal intubation in obese patients as compared to its individual predictor.

METHODS: After obtaining permission from Ethical Issues Committee approval, 82 verbally consenting adult obese patients with BMI ≥ 30, between the ages range from 18-60 years and ASA physical status I-III requiring endotracheal intubation for elective surgery under a uniform general anesthetic technique were prospectively included in this observational study. Patients showing Cormack and Lehane (C & L) grade III and IV while using conventional Macintosh laryngoscope in the hand's of senior anesthesiologist were considered to represent difficult laryngoscopy and tracheal intubation. BMI, Mallampati class and neck circumference were recorded and scored.

RESULTS: OMAN score values >5 were found to better predict Grade III and IV C & L views to its individual components (P<0.0001) in obese patients. Though a higher Mallampati class, Neck circumference and BMI were also significantly correlated with C & L III & IV but neither was better than the cumulative OMAN score. OMAN score shows a higher area under the ROC curve (AUC= 0.779, 95% CI= 0.673 to 0.863, P<0.0001) compared to other variables.

CONCLUSION: Cumulative OMAN score gives a better sensitivity and specificity of difficult intubation in obese patients as compared to its individual predictors like BMI, Mallampati class and neck circumference.

REFERENCE(S):

Br J Anaesth 2018; 120 (5): 1110-1116.

BMI, Mallampati class and neck circumference were recorded and scored as:

Obesity (BMI) (kg/m^2)	Score	Mallampati Grade	Score	Neck Circumference (cm)	Score
30-35	1	I	1	40-45	1
36-40	2	II	2	46-50	2
41-45	3	III	3	51-55	3
>45	4	IV	4	>55	4

Variable	Sensitivity	Specificity	Significance level P (Area=0.5)	Area under the ROC curve (AUC)	95% Confidence Interval	Associated criterion (cut off Value)
BMI	82.61	45.76	0.0472	0.641	0.528 to 0.744	>34.1
Mallampati class	78.26	64.41	<0.0001	0.751	0.644 to 0.840	>2
NC	69.57	69.49	0.0005	0.721	0.611 to 0.815	>43
OMAN score	65.22	74.58	<0.0001	0.779	0.673 to 0.863	>5

AIRWAY MANAGEMENT 5

Role of thyromental distance, thyromental height, sternomental distance and their ratio with patient's height for prediction of difficult laryngoscopy in Omani patients

Noor G Al Dhahri[1], Rashid M Khan[1], Naresh k Kaul[1]

[1]Khoula Hospital, Muscat, Oman

INTRODUCTION: Preoperative airway assessment to predict patients with difficult laryngoscopy while using conventional Macintosh laryngoscope is crucial for the safe airway management as up to 30% of all anesthesia related death is attributed to mismanagement of the airway[1,2]. Unfortunately, most of the airway predictors come from studies done in non-Omani population. We conducted this study in adult Omani population with primary aim to evaluate the role of thyromental height (TMHT), thyromental distance (TMD), sternomental distance (SMD) and their ratios with patient height (RHTMHT, RHTMD, and RHSMD respectively) to note if anyone of these is superior to others as a single bedside screening test for predicting difficult laryngoscopy and tracheal intubation.

METHODS: This prospective, observational study was conducted in 134 patients of either sex aged >18 years scheduled for elective surgery under general anesthesia. Anesthetists in the clinic assessed the patients' airway preoperatively. TMHT is the height between the anterior borders of the mentum and thyroid cartilage, while the patient lies supine with her/his mouth closed. Standard uniform anesthetic technique was followed in all the patients. A senior anesthesiologist who is blinded from the measurements (TMHT, RHTMHT, TMD, RHTMD, SMD and RHSMD) graded the laryngoscopic view as per Cormack–Lehane scale. Grade I & II was considered easy while grades III & IV was considered as difficult laryngoscopy.

RESULTS: The incidence of difficult laryngoscopy in this study was 9.7%. Demographic factors seemed to play no role in the incidence of difficult laryngoscopy in this series. Of the six predictors that were studied (TMHT, RHTMHT, TMD, RHTMD, SMD and RHSMD) for predicting difficult laryngoscopy and tracheal intubation, only an SMD of 13.73 cm or less showed a significant correlation with difficult laryngoscopy (p=0.05).

CONCLUSION: A SMD of 13.73 cm or less was observed to be the single best predictor of difficult laryngoscopy in Omani patients.

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1. Benumof JL, Scheller MS. The importance of transtracheal jet ventilation in the management of the difficult airway. Anesthesiology. 1989;71:769–78.
2. Bellhouse CP, Doré C. Criteria for estimating likelihood of difficulty of endotracheal intubation with the Macintosh laryngoscope. Anaesth Intensive Care. 1988;16:329–37.

Table: Predicting difficult laryngoscopy and tracheal intubation

Variable	Mean (SD)	Easy Laryngoscopy (n=119) Mean (SD)	Difficult Laryngoscopy (n=13) Mean (SD)	P value
TMD (cm)	7.92 (1.50)	7.95 (1.43)	7.73 (2.11)	0.72
HT/TMD %	21.22 (4.02)	21.05 (3.74)	22.78 (6.04)	0.33
TMH (cm)	6.05 (1.44)	6.05 (1.40)	6.00 (1.84)	0.92
HT/TMH %	28.53 (7.65)	28.39 (7.54)	29.78 (8.81)	0.53
SMD (cm)	14.89 (2.30)	15.02 (2.23)	13.73 (2.66)	0.05
HT/SMD %	11.33 (2.28)	11.09 (1.74)	13.47 (4.65)	0.09

AIRWAY MANAGEMENT 6

Efficacy of a new scoring system to predict difficult ventilation through Classic Laryngeal Mask Airway vs Ambu Laryngeal Mask

Aziza Khalifa A Busaidi[1], Abdullah M Aljadidi[2], Rashid M Khan[1], Naresh K Kaul[1]

[1]Khoula Hospital, Muscat, Oman, [2]Khoula Hospital, Muscat, WY

INTRODUCTION: Saito et al in 2016 developed a new scoring system that could predict difficult ventilation via a Supraglottic Airway Device (SAD).[1] However, they did not analyze if the scoring system would work equally well for directional and non-directional SAD. The aim of the present study was to observe which of the two SAD devices, one from non-directional (Classic Laryngeal Mask Airway, CLMA) and another from directional (Ambu Laryngeal Mask, ALM), variety would correlate better with Saito et al's score predicting poor ventilation.

METHODS: Following Ethical Approval, 102 consenting adult patients of either gender were assessed for Saito's score that included male sex (1 point), age >45 yr (1 point), short thyromental distance (3 points) and limited neck movement (2 points). All patients underwent a standardized general anesthetic technique followed by placement of designated SAD i.e. CLMA or the ALM was placed as per group allotment via randomization number. Poor ventilation was interpreted by noting the loss of tidal volume to leaks exceeding >10% of the set TV (8 ml/kg). Likelihood Ratio Test and Fisher's Exact Test were used to analyze data. P value > 0.05 has been considered as insignificant in this study.

RESULTS: See Table.

CONCLUSION: Our results showed that Saito et al's scoring system[9] for predicting poor ventilation through SAD did not show any correlation either through ALM or CLMA. In addition, the incidence of poor ventilation was nearly identical through ALM or CLMA as assessed by loss of tidal volume >10%, non-rectangular $EtCO_2$ curve or peak airway pressure >25 cmH_2O.

REFERENCE(S):

Br J Anaesth 2016; 117: i83-i6.

Results & Conclusions

Parameter	Group	Saito et al's Score[1]							
		0		1-3		4-6		7	
		n	%	n	%	n	%	n	%
TV loss > 10%	ALM	2	25.0	4	50.0	2	25.0	-	
	CLMA	-		7	77.8	2	22.2	-	
	P value	0.170							

AIRWAY MANAGEMENT 7

Morbidity and mortality of Emergent versus Nonemergent Difficult Airway Management Team (DAMT) Activation

Michael Desciak[1], Juan Rango[1], Tara Zehrer[1], Abdullah Qureshi[1], Joshua Knight[1]

[1]University of Pittsburgh Department of Anesthesiology, Pittsburgh, PA

INTRODUCTION: Data regarding outcomes for patients for whom a Difficult Airway Team is emergently activated, versus activated in an anticipated or non-emergent manner, are lacking. The authors of this study sought to evaluate the difference in outcomes of these two patient groups at a large academic medical center. The primary outcome examined was mortality during hospitalization, with secondary outcomes being discharge destination and event mortality.

METHODS: The authors retrospectively analyzed the electronic medical records of 182 patients for whom the Difficult Airway Team was activated from June 2015 until December 2019. Of these 48 were activated non-emergently compared to 135 done so emergently. Data collected included patient demographics, intubation/airway management techniques, operator experience, site of DAMT activation, and whether the activation was classified as nonemergent, or emergent. Determination of the nature of the call was as recorded by the responding team in the airway documentation, with nonemergent being calls prior to induction for airway manipulation and emergent being in critically-ill patients and/or after initial airway manipulation.

RESULTS: There was a major trend towards increased event and in-hospital mortality in the emergent group however this difference did not achieve statistical significance. Patients with emergent calls had a statistically significant increased chance of discharge to a long-term acute care facility.

CONCLUSION: Most DAMT activations are done so in an emergent nature. Activating in a non-emergent situation trends toward decreased mortality. Emergently intubated patients are more likely to be discharged to a nursing facility. Further research is needed to evaluate the true impact of emergent vs. nonemergent difficult airway calls.

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Difficult airway response team: a novel quality improvement program for managing hospital-wide airway emergencies 2015;121(1):127-139.

Integration of a difficult airway response team into a hospital emergency response system 2015;33(2):369-379.

Development of a Multidisciplinary Pediatric Airway Program: An Institutional Experience 2019;9(6):468-475.

A novel role for otolaryngologists in the multidisciplinary Difficult Airway Response Team 2015;125(3):640-644.

Obstetric Anaesthetists' Association and Difficult Airway Society guidelines for the management of difficult and failed tracheal intubation in obstetrics 2015;70(11):1286-1306.

Table 1. Baseline patient and call characteristics of non-emergent versus emergent DAMT activation. SD = standard deviation, ICU = intensive care unit, ED = emergency department, OR = operating room

Demographics	Non-emergent (n=48)	Emergent (n=135)	*p*
Age, years (SD)	56.3 (17.6)	57.5 (14.8)	0.7
Gender, % male	56.3	63.7	0.39
Location of call, n (%)			0.117
ICU	28 (58.3)	87 (64.4)	
ED	8 (16.7)	14 (10.3)	
Inpatient Floor	8 (16.7)	26 (19.3)	
Radiology suite	2 (4.2)	3 (2.2)	
Procedure Suite	0 (0)	5 (3.7)	
Other	2 (4.2)	0 (0)	
Anesthesiology Resident Available, %	70.8	63	0.456
Previous Intubation Note in EMR, %	66.7	57.8	0.28
Different Intubation Method Used, %	43.8	44.4	0.7
Reason for DAMT call, n (%)			**0.001**
Concern before intubation attempt	26 (20.8)	30 (22.2)	
Unable to intubate	13 (27.1)	62 (45.9)	
Unable to ventilate (before/after intubation)	2 (4.2)	23 (17.0)	
Assistance with airway exchange	1 (2.1)	5 (3.7)	
Tracheostomy issue	4 (8.3)	11 (8.1)	
Issues following extubation	0 (0)	3 (2.2)	
Other	1 (2.1)	2 (1.1)	
Airway Secured, n (%)			**0.042**
Yes	43 (89.5)	132 (97.8)	
No	1 (2.1)	1 (0.7)	
Intervention Not Needed	4 (8.3)	2 (1.1)	
Service securing airway, n (%)			0.399
DAMT	22 (45.8)	66 (48.9)	
RRT	3 (6.3)	18 (13.3)	
Primary	16 (33.3)	39 (28.9)	
Other	7 (14.6)	12 (8.9)	
Training of airway sercuring, n (%)			0.436
Resident	12 (25.0)	21 (15.6)	
Fellow	12 (25.0)	30 (22.2)	
Attending	18 (37.5)	69 (51.1)	
CRNA	2 (4.2)	4 (3.0)	
Other	4 (8.3)	11 (8.1)	
Method to secure airway, n (%)			**0.043**
Direct laryngoscopy	5 (10.4)	27 (20.0)	

Table 2: Clinical outcomes of emergent versus non-emergent DAMT calls. OR = odds ratio, CI = confidence interval.

Variable	OR	CI	P-value
Event Mortality	6.008	[0.775, 46.571]	0.0861
Index admission mortality	2.389	[0.982, 5.812]	0.0549
LTAC / Skilled nursing admission post-discharge	2.227	[1.004, 4.941]	**0.0489**

AIRWAY MANAGEMENT 8

A Specialized Intubation Team for Airway Management during the COVID-19 Pandemic is Efficient and Has a Favourable Impact on Health Care Providers

Keziah W Magor[1], Tejinder Chhina[1], Bill I Wong[1], Hossam El Beheiry[1]

[1]Trillium Health Partners (THP), Mississauga, Ontario

INTRODUCTION: At the onset of the COVID-19 pandemic, the department of Anesthesia at THP decided to assemble a highly specialized intubation team. The intubation team comprised of an anesthesiologist, an ICU registered nurse, a respiratory therapist and a safety officer. The team provided 24-hour daily coverage. The intubation team performed all intubations requested outside the operating rooms. The underlying principle for assembling the team was that during COVID-19 pandemic all endotracheal intubations outside the operating rooms should be performed by experts in upper airway management to guarantee the highest probability of success in the shortest time possible[1].In order to evaluate our underlying assumptions, this study determined the effectiveness of the intubation team and its impact on health care providers during the COVID-19 crisis.

METHODS: The study was a retrospective chart review of patients who were intubated by the intubation team and a survey questionnaire targeting physicians who had the option to activate the intubation team. After ethics board approval, the study was conducted at a tertiary medical center (751 beds). The retrospective review that determined the efficiency of the team included 178 patients who required airway management by the team during the COVID-19 pandemic from March 28 to June 11, 2020. All charts reviewed showed that the intubation team was activated, patients intubated were ≥18 years of age, and intubation location was outside the operating room. The review was done using Electronic Medical Record applications. The analysis was performed by an investigator not involved in the data collection. The following outcome variables were extracted: a) Primary outcomes: intubation success, number of attempts for intubation, intubation time, time for team arrival at location, and team to patient contact time; b) Secondary outcomes: COVID-19 status, reason for intubation, intubating medications and technique, intubating complications, and breeches of team protocol; c) other confounders: patient demographics, co-morbidities, pre-intubation medications and O_2 therapy. The physicians' survey questionnaire established the impact of the intubation team. The questionnaire was e-mailed to 58 physicians who activated the team or who have had the option to activate the team. The questionnaire examined the relevance, performance, reasonableness, and clinical utility of the implementation of the intubation team program (Table 3). Continuous variables were expressed in means and standard deviation. Categorical data were presented with frequencies, proportions, or percentages.

RESULTS: There were 178 activations of the intubation team in the period from March 28 to June 11, 2020. During this period, the hospital was closed for elective cases because of the pandemic. The team intubated 152 adult patients mainly in the ICU and emergency rooms. The remaining 26 encounters represented mobilization of the team for acute airway management issues other than intubations. The intubated cohort included 14% COVOD-19 positive patients, 42% COVOD-19 negative patients, and 44% of patients had undetermined COVID-19 status at the time of intubation. The patients' average age was 65.7 +/- 15.3 years and 45.8% of patients were females. The indications for intubation in the cohort were respiratory failure (75%), Cardiac arrest (14%), and severely decreased level of consciousness (11%). The intubation team showed high efficiency in intubating high-risk patients (Table 1). The response time and the intubation time were short and the duration of patient contact were kept to a minimum (Table 2). The most common breech of the intubation team protocol was the presence of more than expected personnel in the room during intubation (Table 1). The physician survey responses (N=26 of 58) indicate that the impact of the intubation team was highly valued by most physicians. However, there was mixed opinions about forming a permanent intubation team to perform all out-of-operating room intubations (Table 3).

CONCLUSION: The formation of the intubation team at the time of COVID-19 pandemic was effective, and had a favourable impact on the responsible attending physicians. Therefore, assembling intubation teams during severe respiratory pandemics and mass causalities is essential to provide expertise in airway emergencies, protect other personnel from the virus, and free other teams to undertake the critical management of patients[2,3].

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Table 1. Performance of the intubation team (N indicates the number of charts that contained the information shown in table; DL indicates direct laryngoscopy; VL indicates Video-laryngoscopy).

Intubation success N=102		Complications of intubation N=48		Breech of PPE protocol N=152	
Awake	1 (.90%)	Hypotension	18 (36.8%)	Donning	10 (6.6%)
1st attempt	89 (87.3%)	Desaturation	6 (12%)	Doffing	12 (7.9%)
2nd attempt	7 (6.9%)	Bleeding	1 (2.6%)	Equipment	0 (0.0%)
3rd attempt	5 (4.9%)	Dental damage	1 (1.3%)	Personnel > 3	83 (54.6%)
DL	12 (11.2%)	Cardiac arrest	1 (0.65%)	Personnel > 5	28 (18.4%)

Table 2. Response and intubation time intervals in 152 activation of the intubation team

Time interval	Time (min)
Response time (paging of team to arrival at location)	10.9 ± 5.4
Intubation time (start of drug injection to ETCO2 detection)	2.8 ± 1.1
Time of patient contact (total time in patient's room)	15.8 ± 6.3

Table 3. Survey of attending responsible physicians who had the option to activate the intubation team (N=58 physicians responding to the survey)

Relevance of the intubation team:											
What is the degree to which the intubation team supports the hospital's mission during the COVID-19 pandemic?											
Very high	18	High	5	Average	1	Low	0	Very low	0	Don't know	2
Performance of the intubation team:											
What is the degree to which the intubation team is achieving its initially stated objective, that is: 'safe, timely and successful intubation'?											
Very high	14	High	8	Average	1	Low	0	Very low	1	Don't know	2
Reasonableness of intubation team:											
What is the degree to which the intubation team has been making satisfactory progress on response time and availability?											
Very high	11	High	10	Average	0	Low	0	Very low	1	Don't know	4
What is the degree to which the intubation team anesthesiologist has been assisting in taking the decision to intubate patients?											
Very high	3	High	8	Average	4	Low	2	Very low	4	Don't know	5
Clinical utility of the intubation team:											
Rate the clinical usefulness of the intubation team pertaining to emergent/urgent situations.											
Very high	14	High	7	Average	3	Low	0	Very low	1	Don't know	0
Rate the clinical usefulness of the intubation team pertaining to acute situations.											
Very high	10	High	12	Average	3	Low	0	Very low	1	Don't know	0
Rate the clinical usefulness of the intubation team pertaining to intubating COVID-19 patients regardless of the acuity of their medical condition.											
Very high	12	High	10	Average	1	Low	0	Very low	1	Don't know	2
What is the likelihood that you would recommend the establishment of an intubation team during a pandemic or mass casualty situation?											
Very high	16	High	7	Average	1	Low	1	Very low	1	Don't know	0

AIRWAY MANAGEMENT 9

Early diagnosis of esophageal intubation: first auscultation of the armpits versus epigastrium?

Medard B Isokuma[1], Raïs Nsinabau[2], Patricia Kabuni[1], Eric Amisi[3], Jean-Pierre Ilunga[3]

[1]University of Kinshasa, Kinshasa, Congo, The Democratic Republic Of The, [2]General Referral Hospital in N'djili, KINSHASA, Congo, The Democratic Republic Of The, [3]University of Kinshasa teaching hospital, KINSHASA, Congo, The Democratic Republic Of The

INTRODUCTION: Esophageal intubation is a common occurrence[1]. Because of anoxia, more than the hypoxia of selective intubation, its occurrence is an urgent emergency. The capnograph is expensive and the pulse oximeter does not allow rapid diagnosis[2]. This study is a contribution for its rapid clinical diagnosis.

METHODS: This is a cross-sectional observational study, carried out at the general referral hospital in N'djili from june 01 to september 31, 2020. The authorization of the hospital's ethics committee was obtained. By passive observation, the investigator counted the time starting from the moment when the stethoscope was placed at the level of the armpits to confirm the tracheal location of the tube for the control group or at the epigastrium to rule out esophageal intubation for the group of study. We would consider as time, the moment between the placement of the stethoscope and the diagnosis of an esophageal intubation.

RESULTS: Five cases of esophageal intubation were observe among the 42 patients in the study. The average time to diagnose esophageal intubation was 15±7,0 seconds for the study group and 26±3,8 seconds for the control group (X^2 = 3,67; p= 0,03).

CONCLUSION: The primary auscultation of the epigastrium allows a diagnosis of esophageal intubation much faster than that of armpits. In addition, taking Into account the urgency, the risk of anoxia, 'Bula-Bula's sign of cross' which prioritizes the primary exclusion of esophageal intubation by seeking in such a way:

- Vertical: the absence of esophageal intubation (1. presence of mist by compression of the thorax and 2. absence of rumbling by auscultation of the epigastrium)
- Horizontal : the symmetry of the ventilation (auscultation of the armpits : 3. left and 4. right), could improve the practice of endotracheal intubation.

- Keywords: intubation - esophageal - auscultation - armpits - epigastrium

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AIRWAY MANAGEMENT 10

Effect of Cricoid Pressure and Low Left Paratracheal Compression on the Airway

Xavier Hoang[1], nicolas gautier[1], benjamin javillier[2], Jean-françois Brichant[2], Philippe gautier[3]

[1]Catholic University of Louvain, Bruxelles, Belgium, [2]Centre hospitalier universitaire de Liège, liège, Belgium, [3]Saint Anne Saint Remi Clinic, Bruxelles, Belgium

INTRODUCTION: The efficacy of cricoid pressure (CP) in reduction of the risk of regurgitation and pulmonary aspiration is controversial. Moreover, CP may interfere with facemask ventilation and airway visualization. A low left paratracheal esophageal compression (LPEC)(1) has recently been proposed as an alternative to CP. This study compared the videolayngoscopic views between CP and LPEC.

METHODS: Thirty adult ASA I-II patients scheduled for elective general anesthesia were enrolled after approval and informed consent. After induction of general anesthesia in sniffing position and deep neuromuscular blockade (no response after a train-of-four stimulation), the videolaryngoscopy was performed using CMAC videolaryngoscope with a Macintosh curved blade size 3 and three pictures of the airway were successively recorded: one in neutral position one under a CP and one under a LPEC. One anesthesiologist, simulator-trained to perform the CP and the LPEC consistently using force of 30N, performed all the manoeuvres blinded to the laryngoscopyc view. The area of the rima glottides (RG) and its displacement during CP and LPEC were meassured on the acquired images; views data (RG area)were compared by an analysis of covariance. To assess RG mobilization, the displacement of the middle of the bisector of the angle made by the 2 vocal cords in the vertical and horizontal plane was measured using Image J software. (Figure 1). Pixels measures were converted in square surface, a tracheal intubation catheter markers placed in the esophagus prior to the intubation.

RESULTS: 20 women and 10 men were included. The mean (SD) age was 45.9 (18.04) years and the mean (SD) BMI of was 26.74 (6.01) kg.m -2 (Chart 1) There was no difference between the variation of the glottic area relative to the neutral position during the CP (95.6 % [49.0]) and the LPEC (111.1% [76.4]) (p=0.4). (Chart 2) The displacement of laryngeal structures was significantly greater with LPEC than with PC (13.8 (6.4) mm vs 8.9 (5.4) mm; p=0.012) (Chart3). There was no significant effect of Mallampati scores on laryngeal displacement by both maneuvers (p=0.86); however, there was a trend towards decreased laryngeal displacement with higher Mallampati scores for LPEC and towards increased laryngeal displacement with higher Mallampati scores for CP (Figure 3).

CONCLUSION: CP and LPEC maneuvers produce no significant change in RG area compared to the neutral position. LPEC displaces the laryngeal mass more than CP.

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FIGURE 1: Demographics data

Demographic data (all patients)								
	Gender M/F	Age (year)	Weight (kg)	Height (cm)	Mallampati score (1 / 2 / 3)	*Mouth opening* (cm)	Thyromental distance (cm)	Neck circumference (cm)
N (%)	10 (33.3%) / 20 (66.7%)	30	30	30	15(50%) / 13(43.3%)/ 2 (6.7%)	30	30	30
Mean ± SD		45.9 ± 18.0	75.7 ± 22.4	167.2 ± 9.9		4.7 ± 0.8	6.9 ± 1.5	37.8 ± 5.5
Median		45.5	71.5	164		4.5	7	37
Interquartile range		34 - 58	59.7 – 89.5	160 – 175.7		4.4 – 5.1	5.75 - 8	33.7 – 42.2

Chart 2 : % of area during cricoid compression versus % of area during paratracheal compression: p=0.40

	Percent of area during cricoid compression as compared to neutral position (%)	Percent of area during paratracheal compression as compared to neutral position (%)
Mean ± SD	95.6 ± 49.0	111.1 ± 76.4
Median	97.1	114.3
Interquartile range	61.9 – 111.5	53.9 – 145.4

CHART 3 : Sum of the absolute values of glottis displacements in the two planes (mm)

		Mallampati 1	Mallampati 2	Mallampati 3	All patients
Paratracheal compression	Mean ± SD	15.3 ± 7.2	12.5 ± 5.7	11.2 ±	13.8 ± 6.4
	Median	17.2	13.2	11.2	14.8
	Interquartile range	11.2 – 18.8	8.3 – 17.0	11.2 – 11.2	9.8 – 17.7
Cricoid compression	Mean ± SD	7.9 ± 3.5	9.7 ± 7.0	13.2 ±	8.9 ± 5.4
	Median	7.35	7.8	13.2	7.8
	Interquartile range	4.9 – 11.5	4.4 – 13.7	13.2 – 13.2	5.0 – 11.9

Results of the analysis of covariance : Cricoid pressure (CP) versus left paratracheal esophageal compression (LPEC): F=6.86, p=0.012 ; Mallampati value: F=0.03, p=0.86; interaction between Mallampati value and intervention (CP vs LPEC) : F=2.74, p=0.10.

Figure 1: illustration of the effect of LPEC and CP compared to the neutral position

AIRWAY MANAGEMENT 11

Negative Pressure Airway Chamber: A Clinical Simulation Trial of an Isolation Chamber

Stefan Kojic[1], Fabio Magistris[2], Alex Zheng[3], Matthias Görges[4], Andrew Poznikoff[4], Krystal Cardinal[2], Gurmaan Gill[2], Robert Purdy[2]

[1]University of British Columbia, Vancouver, British Columbia, [2]University of British Columbia, Vancouver, Canada, [3]University of British Columbia, Vancouver, BC, [4]The University of British Columbia, Vancouver, BC

INTRODUCTION: Aerosol generating medical procedures (AGMP) are a concern in the current COVID-19 pandemic [1-3]. One concern in the guidance for intubation of COVID+ patients is foregoing high flow oxygen therapy and bag-mask ventilation prior to a rapid sequence induction[4], favoring provider safety over patient safety. Several isolation chambers have been described that cover the patient's head and shoulders to provide a physical barrier between the patient and their provider[5]. Testing of these chambers in a simulated setting, with subsequent iterative improvements in design to address identified shortcomings, is necessary before initial clinical implementation. We developed a Negative Pressure Airway Chamber (NPAC) designed to answer many of the design concerns of its predecessors in the literature[5]. Preliminary results for the NPAC are promising in its capability of actively capturing aerosolized particles generated during simulated AGMPs with high efficiency, including bag-mask ventilation and preoxygenation prior to intubation. The aim of this study was to determine if the NPAC significantly impeded induction of anesthesia until the airway is secured.

METHODS: Ethics approval was obtained from our local institution. A within-subject, block-randomized, procedure evaluation study comparing intubation of a manikin by pediatric anesthesiologists both with and without the NPAC was conducted. Simulated intubation trials were set up as follows: a) participants practiced four intubations on an intubation manikin, twice in each condition, b) participants donned appropriately fitted PPE, including gown, gloves, surgical mask, and goggles, c) starting conditions, with the NPAC or without, were randomized, d) a nebulizer filled with saline was attached to one bronchus of the manikin, e) at TSTART, the aerosol generator was turned on and the participant and assistant placed their hands into NPAC's sleeves and gloves (if applicable), f) the participant then pre-oxygenated the manikin for 3 min, g) a rapid sequence induction was simulated by having the assistant depress a 20 mL syringe over 30 sec, after which aerosols were turned off, h) the participant performed intubation and secured the airway, i) once the airway was secured and taped, a desaturation event was called and the participant removed the NPAC (if in use) and listened to the airway for 10 sec. The primary outcome was intubation time. Secondary outcomes included time to endotracheal tube securement and time to diagnose an airway emergency. A pre- and post-simulation survey was conducted for subjective participant experience.

RESULTS: Twenty pediatric anesthesiologists were recruited. The randomized repeated measures study design controlled for participant differences. As seen in Figure 1, use of the NPAC prolonged intubation time by a median [95% confidence interval (CI)] of 8.5 [4.0-13.0] sec; p=0.002. Time to secure the endotracheal tube was prolonged by 5.2 [95%CI 1.3-9.2] sec; p=0.017. In the simulated desaturation emergency requiring removal of the NPAC, the time to diagnosis took an additional 17.0 [95%CI 15.1-19.0] sec; p<0.001. The majority of participants (12/20) did not think the NPAC made intubation more difficult. Comments from the debrief survey included obstructed video laryngoscope views, chamber ergonomics that could be improved, and concerns regarding feasibility of use in an awake COVID+ pediatric patient.

CONCLUSION: The use of the NPAC device delayed the time to intubation (8.5 sec), endotracheal tube securement (5.2 sec), and the diagnosis of an airway emergency (17.0 sec). Some interruption to procedure flow when performed inside a restricted environment is to be expected, yet these short delays may not be clinically significant. To mitigate delays, practice using the chamber, and team planning on how and when to move it in an emergency should be completed in advance of the procedure. Reducing aerosol exposure to health care providers is vitally important, as is the ability to deliver much-needed oxygen therapy and ventilation prior to intubation of a sick patient. This chamber may allow both of these considerations to be met in a safe manner and create improved intubating conditions where concerns for short delays are permissible.

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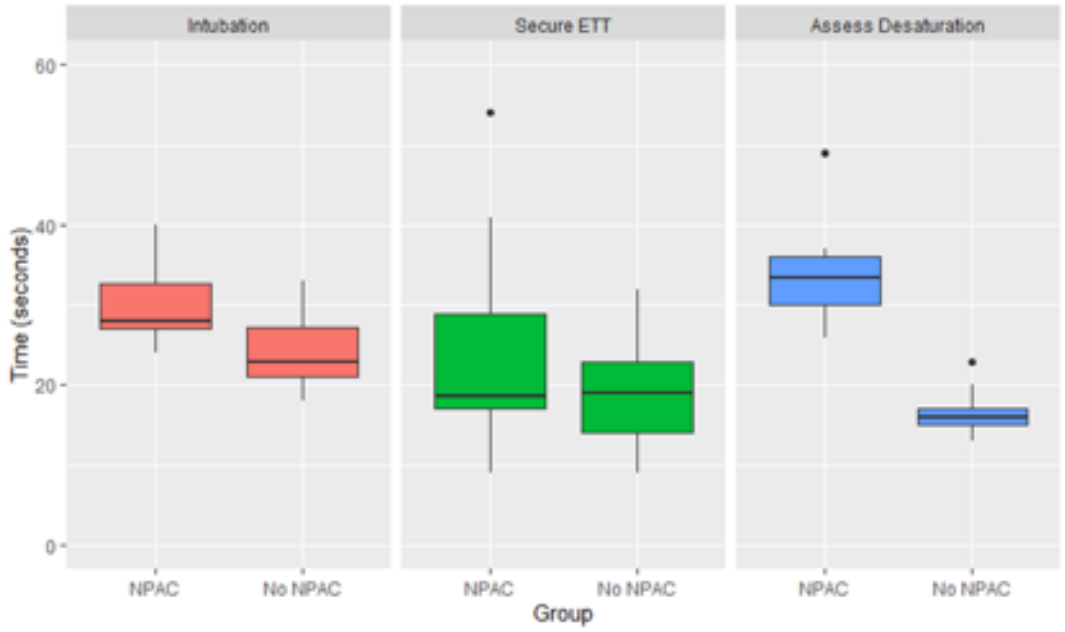

Figure 1: Box and whisker plot comparing time to complete intubation, secure endotracheal tube (ETT), and assess desaturation. Horizontal lines represents median with the box representing the interquartile range. One data point at 75 sec to intubate with the NPAC was censured for scaling.

AIRWAY MANAGEMENT 12

Incidence of Unanticipated Airway Events in Male-To-Female Transgender Patients Undergoing Facial Feminization Procedures

Deen Debryn[1], Eugene Kim[2], Shivali Mukerji[3], Ryan K Price[1]

[1]Boston University School of Medicine, Boston, MA, [2]Boston University School of Medicine, Boston, United States of America, [3]Boston University, Boston, MA

INTRODUCTION: Transgender individuals make up about 0.6% of the US population[1]. Studies have shown that every year more transgender patients are undergoing gender affirming surgeries (GAS)[2]. Although hospitals are seeing more transgender surgical patients, this unique population remains largely unstudied, and important perioperative considerations (such as the rate of airway difficulties) are currently unknown. In the general population, the incidence of unexpected airway difficulties is estimated to be within the realm of 1 – 2%[3,4,5]. The goal of this study is to better understand the perioperative considerations within a cohort of male-to-female (MTF) transgender patients undergoing GAS; in particular, we will examine the prevalence of unanticipated airway events in this population.

METHODS: Data was gathered retrospectively by reviewing the charts of all patients who underwent facial feminization procedures at an urban academic institution between the years of 2014 and 2020. A total of 282 patients met the selected inclusion criteria of MTF transgender individuals between the ages of 18 to 60 at the time of chart review. Basic demographic information and information on airway-related events were collected. Airway events were identified in cases during which the patient desaturated (oxygen saturation less than 92%) within 45 minutes of induction and/or if more than 1 attempt was required for endotracheal tube insertion. These events were stratified based on severity into mild (desaturation only), moderate (desaturation and one or more of the following: difficult bag mask ventilation, laryngoscope view grade of 3, 3 attempts at airway), and severe (desaturation to <80 and/or 4 or more attempts at airway). Statistical analysis was performed using multinomial logistic regression.

RESULTS: Of the 282 patients in our cohort, 97.2% were classified as ASA I or II, the remainder (8 patients) being ASA III. A total of 27 patients (9.6%) had a BMI that was greater than or equal to 30. Patients were predominantly young, with a mean age of 33.75 (further demographics in Table 1). The total rate of unanticipated airway events was 13.8%, occurring in a total of 39 procedures. Of these, 20 were considered mild and 15 moderate. Severe airway events occurred in 1.42% of procedures (4 cases total). There was no statistically significant association between the odds of airway event occurrence and the studied variables: BMI greater than or equal to 30, history of drug use, frequency of alcohol use, and ADHD.

CONCLUSION: Our calculated incidence of severe airway events (1.42%) is within the range of the suggested 1 – 2% incidence of unexpected airway difficulties in the general population. Thus, MTF transgender patients do not appear to have an elevated risk for severe airway difficulty. However, given the total airway event incidence of 13.8%, MTF transgender patients may be at greater risk for mild or moderate airway events during facial feminization procedures. Overall, in regard to anticipating significant airway difficulty, anesthesia providers should approach transgender patients as they would their cisgender counterparts; though, they may encounter increased minor airway difficulties in this population. More studies are needed on this topic, particularly to evaluate the rate of airway events in female-to-male transgender patients, because there are theoretical concerns for airway changes secondary to hormonal therapies used in this population.

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Table 1: Baseline characteristics for all patients (N=282) included in the study

Baseline Characteristics	Mean/N
Age at date of surgery (years)	33.75 ± 12.93
Height (m)	4.23 ± 20.74
Weight (kg)	72.43 ± 15.08
BMI (kg/m^2)	
Less than 30	255
Greater than or equal to 30	27
Race	
Asian	10
Native American/Alaska Native	1
Black/African American	8
White	154
Unknown	109
Hispanic or Latino	
Yes	21
No	252
Unknown	9
Marital Status	
Single	185
Married	27
Unknown	66
Other	4
Preferred Pronouns	
She/Her/Hers	254
He/Him/His	4
They/Them/Theirs	2
Unknown	22
ASA Status	
1	157
2	117
3	8
Hormone Therapy	
Yes	236
No	46
Was hormone therapy held?	
Yes	160
No	28
Unknown	48
Duration of withholding prior to surgery	
2 weeks or less	21
2-4 weeks	125
4 weeks	10
Unknown	4

AIRWAY MANAGEMENT 13

A comparison study of Powered Air Purifying Respirator and N95 use during intubation of COVID-19 patients

Esther Lee[1], Reem Q Al Shabeeb[2], Muhammad El Shatanofy[2], Collin F Mulcahy[2], Ivy Benjenk[2], David Yamane[3], Marian Sherman[4], Eric Heinz[5]

[1]George Washington University Medical Faculty Associates, Washington, DC, [2]The George Washington University School of Medicine & Health Sciences, Washington, DC, [3]George Washington University Hospital, Washington, DC, [4]The George Washington University Hospital, Washington, DC, [5]The George Washington University, Washington DC, United States of America

INTRODUCTION: Currently recommended personal protective equipment (PPE) during the COVID-19 pandemic is an N95 respirator, protective eyewear, gown, and gloves[1]. Since healthcare providers performing intubations (intubators) of confirmed COVID-19 patients are at particular risk of infection, many intubators utilize powered air-purifying respirator (PAPR) in addition to currently recommended PPE. Further, many institutions require its use in their protocols of airway management[2]. Our study aims to compare various demographic and exposure factors, as well as a feeling of adequacy on PPE usage between PAPR and only N95 use during intubation of suspected or confirmed COVID-19 patients.

METHODS: In this multicenter cross-sectional national study, electronic surveys were disseminated using a snowball sample approach to intubators between 9/2020 and 12/2020. Surveys were initially pilot-tested for reliability and validity. Various demographic and exposure factors, and feelings of the adequacy of PPE were collected. Respondents using PAPR with or without N95 (PAPR group) were compared to those using only N95 (N95 group) using the Mann-Whitney U test, Fisher's exact test, and Chi-square test of homogeneity. Statistical significance for these tests was declared at $p<0.05$.

RESULTS: A total of 182 complete surveys from 32 hospitals were analyzed after excluding surveys that reported no experiences with COVID-19 intubations and no use of PAPR or N95 during COVID-19 intubations. 37% of the intubators used PAPR and 63% of the intubators used only N95 during COVID-19 intubations. The median intubator age for the PAPR group was higher than the age for the N95 group (median= 37.5, IQR= 27-64 vs. 35, 27-71; p = 0.043). The median number of COVID-19 intubations for the PAPR group was higher than those in the N95 group (median=10, IQR=1-40 vs. 5, 1-100; p=0.006). PAPR group included 40 attending physicians [AtP] (58.8%), 21 resident physicians [RP] (30.9%), and 7 certified nurse anesthetist or physician assistants [CNA or PA] (10.3%). N95 group included 41 AtP (36.0%), 38 RP (33.3%), and 35 CNA or PA (30.7%). There was a greater proportion of AtP in the PAPR group compared to the N95 group (58.8% vs. 36.0%, p= 0.003). Additionally, there was a lower proportion of CNA or PA in the PAPR group compared to the N95 group (n=7, 10.3% vs. n=35, 30.7%, p < .0125). More providers who use PAPR felt that PPE was adequate during the majority of the intubation for COVID-19 patients compared to those who use N95 only (n=67, 98.5% vs. n=97, 85.1%, p=0.003).

CONCLUSION: More providers who use PAPR with or without N95 as a part of their PPE felt that PPE was adequate during COVID-19 intubations compared to providers who only use N95. This suggests that PAPR may provide an additional benefit to healthcare providers who feel that PPE is inadequate during the intubation for confirmed or suspected COVID-19 patients.

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AIRWAY MANAGEMENT 14

Level and Degree of Airway Collapse During Administration of Various Sedative Medications: A Systematic Review

Elizabeth Clark[1], Jordan Barton[1], Claude Abdallah[2]

[1]Goerge Washington University, Washington , DC, [2]Children's National Health System, Washington, DC

INTRODUCTION: Drug-induced sleep endoscopy (DISE), magnetic resonance imaging (MRI) and sedated upper airway electromyography (EMG), are valuable studies for assessment of the degree and level of airway collapsibility. The varying protocols and different medication regimens, including sedative and anesthetic medications, used in these studies have been shown to exert different effects on upper airway morphology, degree of airway obstruction, and vital signs. The aim of this study was to systematically review studies reporting morphological changes of the upper airway during DISE, sedated MRI and EMG under various sedative and anesthetic medications.

METHODS: This systematic review searched PubMed, Scopus, EMBASE, and Cochrane CENTRAL Register of Controlled Trials. Inclusion criteria were studies reporting the location of airway collapse under specified sedative and/or anesthetic regimens, availability in English Language, publication in the past 10 years. Articles were excluded if they involved animal studies, failed to disaggregate different medication regimens in upper airway morphology results, included less than three patients, or did not provide original data. Two investigators independently reviewed all search results through the Covidence systematic review title/abstract and full-text screening program.

RESULTS: A total of 421 article titles/abstracts were screened, and 57 of these articles were eligible for full text review. Ultimately, 23 studies met criteria for qualitative synthesis. Primary medications included in these studies were propofol, dexmedetomidine, midazolam, propofol-remifentanil, sevoflurane, lidocaine (4% topical), and pentobarbital. Study designs also varied widely, particularly in pre-medication regimens, sedation depths and scales utilized, drug administration protocols, sample demographics and outcomes.

CONCLUSION: Variables such as premedication regimens, sedation depth, drug administration protocols, and study populations are likely to influence the results of different studies included. Additional research is needed to determine the direct effects of sedative and anesthetic agents on upper airway morphology.

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AIRWAY MANAGEMENT 15

Effect of Low Left Paratracheal Compression on Carotid Blood Flow

Flavien Grandjean[1], Eric Deflandre[2], Benjamin Javillier[3]

[1]University of Liège, Liège, Belgium, [2]Clinique Saint-Luc, Bouge, Belgium, [3]University of Liège, Neuville en Condroz, Belgium

INTRODUCTION: For many years, cricoid pressure (Sellick maneuver) has been subject to debate. Recently, Gautier et al. demonstrated that a compression in the left paratracheal region could compress the esophagus. However, at this level, the left common carotid artery is closely located to the esophagus and could be affected during this manipulation. This study aims to assess the hemodynamic effects on the carotid blood flow during Left Paratracheal Esophagus Compression (LPEC).

METHODS: After IRB agreement and patient's written informed consent, we prospectively included 47 healthy adult volunteers. We excluded pregnant women and people with facial or oropharyngeal abnormalities and anomalies of the carotid arteries. Demographic data, neck circumference, history of vascular pathology, or hypercholesterolemia were registered. Patients were placed in a supine position for the ultrasonographic exam, with the head in a neutral position. Using the Philips Epiq5Q ultrasound machine, the radiologist performed an ultrasound examination of the neck using a linear ultrasound transducer. The common and bilateral internal carotid arteries were studied in cross-section and longitudinal axis to exclude atheromatous plaques or vascular malformation. We performed a planimetry of the common and internal carotid arteries. The radiologist performed A Doppler echography of the carotid artery, and recorded maximum systolic and telediastolic velocities in the common and internal carotid arteries. The ultrasound scanner automatically calculated the resistivity index. Then, all measurements were repeated while applying LPEC-maneuver for 15 to 20 seconds (duration).

RESULTS: Forty-seven (47) patients were enrolled, (68 F, 32 M; mean [SD] age : 42.36 [13.03]). For the overall cohort, the mean [SD] surface of the left common carotid was not significantly modified by LPEC 278.11 [64.56] mm2 versus 255,06 [73.66] mm2 during LPEC (P = 0.112). Using pulsed Doppler, maximum systolic velocity in left common carotid [SD] was similar without compression LPEC 133.83 [30.10] cm/s vs. 148.59 [62.30] cm/s with LPEC (P = 0.136, Fig 1). Resistivity index [SD] changes were nonsignificant between without and with LPEC 0.766 [0.057] versus 0.765 [0.095] with LPEC (P = 0.942). Of note, eight patients (17%) did show ultrasound significant changes with either a compression of the left common carotid artery or an acceleration of the blood flow downstream of the compression. We did not observe any clinical effect in these patients.

CONCLUSION: Our results suggest that left paratracheal esophagus compression (LPEC) does not significantly influence the left common carotid artery blood flow. Thus, it appears to be a safe technique of esophageal compression. A future study, on a larger scale with healthy and non-healthy patients, should confirm our results.

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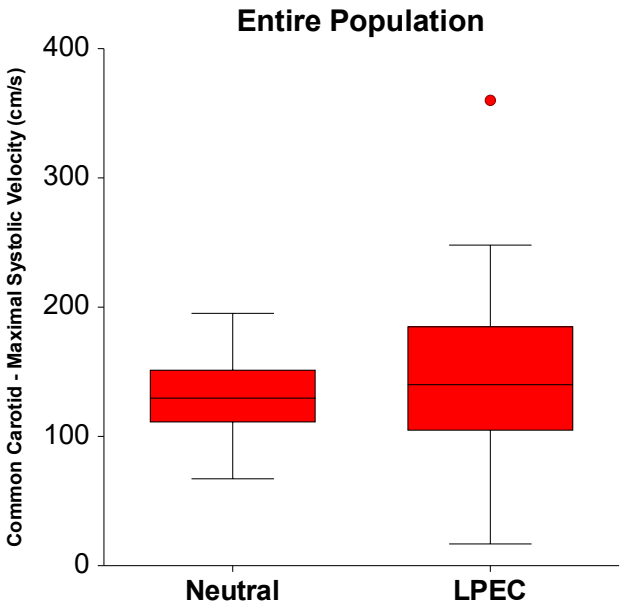

AIRWAY MANAGEMENT 16

Exploring the association between provider years in training and comfort and fear levels during primary and subsequent intubation attempts of COVID-19 patients

Muhammad El Shatanofy[1], Reem Q Al Shabeeb[1], Esther Lee[1], Collin F Mulcahy[1], Ivy Benjenk[1], David Yamane[1], Marian Sherman[1], Eric Heinz[1]

[1]The George Washington University School of Medicine & Health Sciences, Washington, DC

INTRODUCTION: The COVID-19 pandemic has highlighted comfort and safety concerns of intubating physicians across the world.[1, 2, 3] Given the risk of transmission, severe degrees of hypoxia, and PPE requirements, providers have encountered additional challenges while intubating COVID-19 patients. Several studies have demonstrated that senior physicians are more likely to achieve successful endotracheal intubations on the first attempt and show better confidence leading resuscitations.[1,2,4] The purpose of this study was to explore the association between provider age and years in training and comfort and fear levels during primary and subsequent intubations of COVID-19 patients.

METHODS: In this IRB-approved national multi-center, prospective, cross-sectional study, we used a snowball sampling approach to administer a 24-question survey to providers across different specialties, training levels, and geographic locations in the United States. This survey included questions about the provider's background, institutional training, and preparedness intubating COVID-19 patients. To gauge comfort and fear levels during intubations, providers were asked to rate, on a scale from 1 to 10, their comfort with intubation in general, comfort with intubation of suspected or confirmed COVID-19 patients, and fear of contracting COVID-19 during primary and subsequent intubations of confirmed or suspected COVID-19 patients. Data collected between September 2020 and December 2020 were analyzed using Pearson's chi-squared, Mann-Whitney U, and Wilcoxon rank tests.

RESULTS: We analyzed 186 responses from providers at 32 hospitals after excluding incomplete surveys and surveys that reported no experiences with COVID-19 intubations. Approximately half of providers were 25 to 35 years old (48.9%) and had 0 to 5 years of experience (55.4%). Providers were more comfortable with intubation in general than with intubation of COVID-19 suspected patients (median 10, IQR = 5-10, vs. 8, IQR = 1-10, $p < 0.0005$). Providers with more than 16 years of experience reported greater comfort with intubation in general and intubation of COVID-19 patients than providers with 0 to 5 years of experience (median 10, IQR = 6-10, vs. 9, IQR = 5-10, $p < 0.0005$ and median 9, IQR = 3-10, vs. 8, IQR = 1-10, $p = 0.006$). Between primary and subsequent intubation attempts of COVID-19 suspected patients, fear of contracting COVID-19 declined from a median rating of 7, IQR = 1-10, to 4, IQR = 1-10 ($p < 0.0005$). Across all age groups, there was no difference in fear level during the first intubation attempt of a COVID-19 suspected patient. During subsequent intubation attempts, however, providers aged 25 to 35 years old averaged a higher fear rating than providers older than 56 years old (median 5, IQR = 1-10, vs. 3, IQR = 1-9, $p = 0.048$).

CONCLUSION: This study demonstrated that older and more experienced providers felt more comfortable with intubations in general and intubations of suspected or confirmed COVID-19 patients. While all age groups experienced similar fear levels during initial intubations of COVID-19 patients, providers older than 56 years old encountered less fear than providers aged 25 to 35 years old during subsequent intubations. Despite the heightened risk of infection due to age, it is possible that older providers encountered less fear during subsequent intubations due to more practice managing airways in the past and greater confidence with leading resuscitations.[1,2,4] Future work should explore how confidence levels of intubating providers have been affected by the pandemic.

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AIRWAY MANAGEMENT 17

A single center retrospective cohort analysis of patients with systemic sclerosis: Preliminary data suggests increased mask ventilation but not intubation risk with modern airway management techniques

Manuel A Bohorquez[1], Luying Yan[1], Kunal Karamchandani[2], Zyad J Carr[1]

[1]Yale University School of Medicine, New Haven, CT, [2]Penn State Health Milton S. Hershey Medical Center, Hershey, PA

INTRODUCTION: Systemic sclerosis (SSc) is an autoimmune disease characterized by abnormal deposition of collagen in organ systems. Scleroderma is rare with an incidence of 2-10 per million population and is broadly characterized into diffuse, limited and overlap categories, although multiple organ systems may be affected in any category[1]. Few large-scale studies have examined the perioperative implications of SSc, and in this single-center study, we will analyze a retrospective cohort of patients with SSc to quantify perioperative complications and identify preoperative risk factors associated with this autoimmune disorder. In this sub-analysis, we analyzed the modern airway management of SSc patients due to the previously published reports of difficult airway management in this population[2,3].

METHODS: This IRB approved retrospective cohort study has aggregated 468 SSc patients with 1630 surgical encounters over a period of ten years (Jan. 2009-19). Inclusion criteria included age >18 years old, elective inpatient surgical procedure, ASA status I-IV with or without emergency status, and a historical diagnosis of systemic sclerosis (either diffuse, limited or overlap). Patients were categorized based on current rheumatological differentiation of SSc (Progressive/diffuse, Limited/CREST, Sine/Overlap). To quantify the airway risks associated with SSc, we analyzed the following outcome variables: Presence of microstomia, Mallampati score, cervical range of motion, ventilation grade (I-IV), direct and videolaryngoscopic (DL, VL respectively) attempts and McCormick grade. In these preliminary results, we present airway management characteristics for 13 individual SSc patients who underwent 19 surgical encounters under general endotracheal anesthesia.

RESULTS: Descriptive statistics were performed utilizing XLStat software (Addinsoft, Paris, France). 5/13 (38.4%) patients analyzed were noted to have diffuse SSc and accounted for 8/19 (42.1%) of the GETA encounters. 2/13 (15.3%) of patients had observed microstomia/ facial tightness, both with diffuse SSc. 6/13 (46.1%) patients had limited cervical extension; average Mallampati score was 2.15 with only 1 patient with a Mallampati Class IV grade. Rapid sequence intubation was performed in 6/19 (31.5%) encounters. Mask ventilation was Grade I (easy, single provider) in 7/11 (63.6%) mask ventilation events and Grade II (difficult, requiring an oral airway/adjuvant) in 4/11 (36.3%) events. No Grade 3 or 4 mask ventilations were observed. DL was performed in 12/19 (63.1%) encounters, with 100% first attempt success and mean McCormick view of 1.33. 1/12 patients (8.3%) were noted to be McCormick Grade III and they had a diagnosis of diffuse SSc. VL was performed in 4 encounters, with 100% first attempt success and grade 1 McCormick views. 1 patient had a preoperative difficult airway designation and received a fiberoptic bronchoscopic intubation. Among 19 encounters for GETA there were no failed intubations, airway injuries and only 1 instance of dental/soft tissue injury.

CONCLUSION: Previously published case reports would suggest that patients with SSc have a higher risk of difficult airway. Our findings in 19 occurrences of SSc related airway management with GETA suggest that modern airway management techniques have likely reduced the incidence of difficult airway. Nearly half the patients in our studied cohort had diffuse SSc, which carries the highest anticipated risk of difficult airway management. When compared to the incidence of difficult DL in the general population (4.9%), we did observe a moderate excess risk of difficult direct laryngoscopy in our small cohort (8.3%) but we suspect that much of that risk has been mitigated by the pre-emptive use of VL and fiberoptic bronchoscopy[4]. SSc patients appear to have an increased risk for Grade 2 mask ventilation compared to published data on normal population (36.3% compared to 20.0%) and may benefit from the early use of oral airway adjuvants to reduce the risk of gastric insufflation[5].

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AIRWAY MANAGEMENT 18

Dexmedetomidine use in awake fiber optic intubation is associated with improved patient satisfaction and comparable rates of adverse events

Timothy Shen[1], Craig Johnson[2], Michael Schiml[3], David Glick[4]

[1]University of Chicago Pritzker School of Medicine, Chicago, IL, [2]University of Chicago Pritzker School of Medicine, Chicago, United States of America, [3]Case Western Reserve University, Chicago, United States of America, [4]University of Chicago, Chicago, IL

INTRODUCTION: Dexmedetomidine, an α2 adrenergic receptor agonist, is a potentially useful adjunct to traditional sedatives used for awake fiber optic intubations (AFOI). Like traditional sedatives (opioids and benzodiazepines) dexmedetomidine can provide sedation and analgesia, with the potential advantage of not causing as much respiratory depression. We have previously shown that patients who receive dexmedetomidine for at least 21 minutes are more satisfied with their AFOI sedation regimen. In light of this, the current study assessed the rates of adverse events with dexmedetomidine use; if dexmedetomidine showed similar or lower rates of adverse events, this would support an overall benefit to its use.

METHODS: In this double-blind RCT, 75 narcotic-naïve patients were taken through the consenting process and enrolled in the study. In the preop holding area, patients were given midazolam (1-2 mg IV) and glycopyrrolate (0.2 mg IV) and started on IV administration of either a normal saline placebo or dexmedetomidine (0.7 mcg/kg/hr). The start time of the infusion was recorded as well as the patient's baseline heart rate (HR), blood pressure (BP), and oxygen saturation (SpO2). In the operating room patients with a Ramsay Sedation Score (RSS) of <2 were given fentanyl (1 mcg/kg, rounded to the nearest 25 mcg) until adequate sedation was achieved. Once adequately sedated, AFOI was performed. Patient HR, BP, and SpO_2 were measured and recorded every minute, starting when the patient was connected to the monitors in the OR and ending after completion of the intubation. Quantity of fentanyl titrated was recorded, which served as a proxy for the efficacy of the dexmedetomidine. The amount of fentanyl given was compared using a Mann Whitney U test. Fisher's exact tests were performed on adverse events to analyze rates of hyper/hypotension, tachy/bradycardia, and hypoxemia between placebo and dexmedetomidine receiving patients. Complications were identified, and patient satisfaction was recorded.

RESULTS: The dexmedetomidine group showed lower rates of tachycardia (13/38, 34.2% vs 23/37, 62.2%; $p<.05$), and higher rates of bradycardia (19/38, 50% vs 6/37, 16.2%, $p<.05$). Rates of hypoxemia, hypertension, and hypotension were similar between groups. No adverse events were life threatening. Patients in the dexmedetomidine group reported higher satisfaction (M=9.5) compared to patients who received placebo (M=8.1).

CONCLUSION: Dexmedetomidine was associated with comparable rates of adverse events when compared to the placebo group (more frequent bradycardia and less frequent tachycardia). In light of the previously observed increased patient satisfaction and decreased requirement of fentanyl, dexmedetomidine appears to be a valuable adjunct to traditional sedatives for awake fiberoptic intubations.

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Adverse Event	Placebo (n=37)	Dexmedetomidine (n=38)	Chi-Square Statistic	p-value
Hypertension n, (%)	21 (57)	16 (42)	1.61	.20
Hypotension n, (%)	22 (59)	29 (76)	2.45	.12
Tachycardia n, (%)	23 (62)	13 (34)	5.87	**.015***
Bradycardia n, (%)	6 (16)	19 (50)	9.63	**.002***
Hypoxemia n, (%)	3 (8)	3 (8)	.001	1

Table 1: Rates of adverse events between groups. Protocol-defined hypertension: SBP or MAP increased ≥15% from baseline values. Protocol-defined hypotension: SBP or MAP decreased ≥15% from baseline values. Protocol-defined tachycardia: HR increased ≥15% from baseline value. Protocol-defined bradycardia: HR decreased ≥15% from baseline value. Protocol defined hypoxemia: SpO2 ≤ 90%.

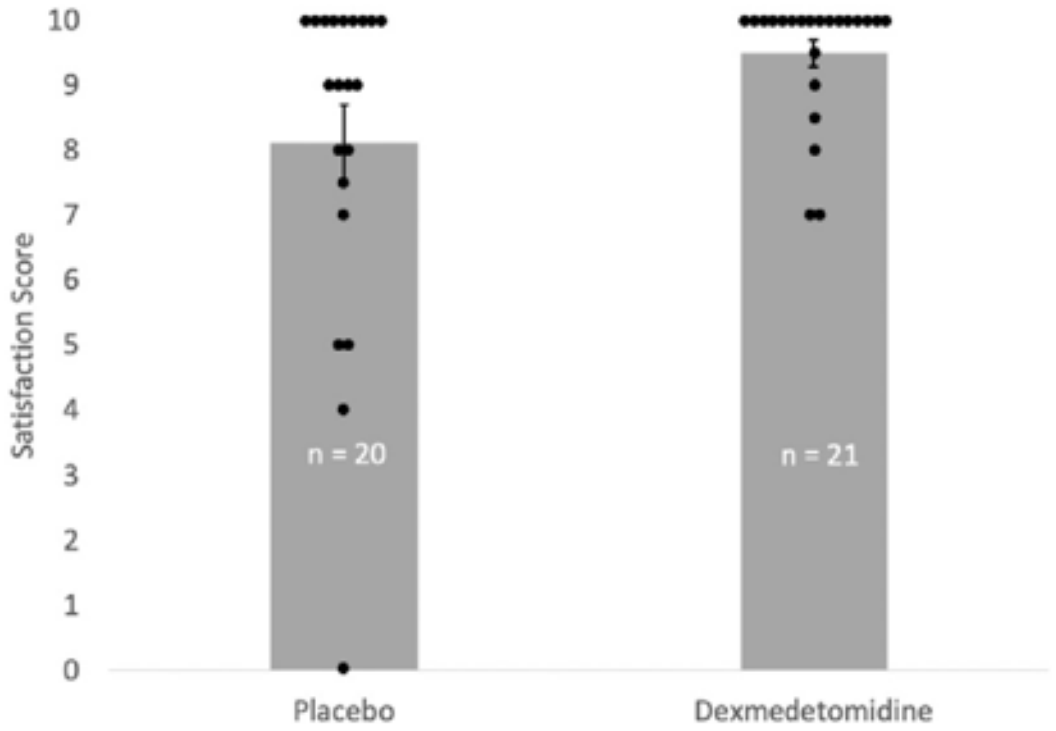

Figure 1. **Patient Satisfaction: Placebo vs. Dexmedetomidine.** Patients who received infusions of dexmedetomidine for >21 minutes reported higher satisfaction (M=9.5) compared to patients who received placebo (M=8.1) ($p<0.05$). Satisfaction was measured via survey and patients were asked to score their anesthetic on a scale from 0-10 (0 = worst, 10 = best).

AIRWAY MANAGEMENT 19

Investigation of Factors Affecting Providers' Fear of Contracting COVID-19 During Intubations: Results from a USA National Survey

Reem Q Al Shabeeb[1], Esther Lee[2], Muhammad El Shatanofy[1], Collin F Mulcahy[1], Ivy Benjenk[1], David Yamane[1], Marian Sherman[1], Eric Heinz[1]

[1]The George Washington University School of Medicine & Health Sciences, Washington, DC, United States of America, [2]The GW Medical Faculty Associates, Washington, DC, United States of America

INTRODUCTION: With more than 300,000 physicians infected with COVID-19, preserving the wellness of providers is essential[1,2]. Endotracheal intubation is a hazardous procedure risking contraction of SAR-CoV-2 due to airway proximity and aerosolization[3]. Since an estimated 8% of COVID-19 patients eventually require endotracheal intubations, there have been multiple studies addressing the safety concerns regarding COVID-19 intubations[3,4]. In our study, we seek to understand the factors affecting providers' fear of contracting COVID-19 during intubations.

METHODS: In this multi-center cross-sectional study, we disseminated an IRB-approved 24-question survey, pilot-tested for reliability and validity, to providers from different specialties, training levels, and geographic locations across the USA using a snowball sample approach to assess factors affecting providers' fear when intubating COVID-19 patients. A scale of 1-10, with 10 being the most fearful, was used to assess providers' fear of contracting COVID-19 by asking the following questions: 'On a scale from 1-10, how would you rate your fear of contracting COVID-19 during your FIRST intubation of a confirmed or suspected COVID-19 patient?' A similar question was asked for subsequent intubations. Data was analyzed using Pearson's chi-squared, Mann-Whitney U, and Wilcoxon rank tests.

RESULTS: We analyzed 186 responses from providers at 32 hospitals after excluding incomplete surveys and surveys that reported no experiences with COVID-19 intubations. While there were no significant differences in fear levels during the first COVID-19 intubation, providers with a history of quarantine for potential COVID-19 exposure reported more fear during subsequent COVID-19 intubations than those without a history of quarantine (p=0.021, median 5 vs 4). Factors that did not significantly affect the fear of contracting COVID-19 during first or subsequent intubations included having a designated intubation team, having children, being a primary caretaker for someone over the age of 80, and having friends or close relatives contract COVID-19.

CONCLUSION: Fear is a known psychological response to quarantine[5]. As the providers' fear levels during initial COVID-19 intubations were not significant, increased fear of contracting COVID-19 during subsequent intubations can be attributed to the negative psychological outcomes, financial loss, isolation, and stigma associated with quarantine[5]. This may also suggest that providers associated their personal infection with a prior intubation, leading to increased fear during future intubations. The cumulative risk of exposure from multiple COVID-19 intubations could explain why providers experienced more fear during repeat intubations. Educational interventions and psychological support have been shown to improve the mental health of physicians combating the COVID-19 pandemic[6-7]. Future work investigating these interventions among intubators would be beneficial.

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AIRWAY MANAGEMENT 20

A Comparison of the Compression and Relaxation Characteristics of Polyvinyl Chloride Versus Reinforced Endotracheal Tubes

Ryan Hoang[1], Sanjana Rao[1], Shreya Dhar[1], David Glick[1], P. Allan Klock[1], Philip J Griffin[2]

[1]University of Chicago, Chicago, IL, [2]The Pritzker School of Molecular Engineering at The University of Chicago, Chicago, IL

INTRODUCTION: Obstruction of endotracheal tubes can be caused by tube compression or kinking from extensive bite force. There are numerous case reports of ventilatory obstruction, requiring quick recognition and tube replacement to prevent desaturation and pulmonary edema related morbidities. Diagnostic indicators can include elevated airway pressure and low tidal volume.[1,2,3] The average adult can apply 295 newtons of pressure with their bite.[4] The effect of such pressure and the change in resistance to prolonged compression on polyvinyl chloride (PVC) and reinforced tubes remains largely unexplored. This study investigates these differences by measuring the tidal volume, inspiratory resistance, and diameter of standard PVC tubes and reinforced endotracheal tubes against the increasing and subsequently decreasing force applied by a hydraulic press.

METHODS: Increasing force was exerted on a PVC tube and on a reinforced (Fastrach–LMA America) tube by chisels mounted on a hydraulic press. Intermittent airflow was generated by a ventilator forcing air through the tubes as pressure was applied so that the inspiratory resistance (Rinsp) as well as the expiratory tidal volume (VTE) could be measured. Pressure exerted on the tubes began at 1 newton and increased in a slow stepwise fashion until no airflow through the tube could be achieved.

RESULTS: Our findings demonstrated an interesting difference between PVC and reinforced tubes in terms of resistance to indentation by force and recovery with relaxation. The reinforced tube displayed the greater resistance to indentation by force, with less indentation at 40 newtons compared to the PVC tube (Figure 1). On the other hand, the PVC endotracheal tube displayed the greater recovery after the force was removed, with an almost complete recovery, while the reinforced tube maintained a degree of persistent compression (Figure 2).

CONCLUSION: The reinforced tube is more effective in preventing abrupt compression from a large force, but is susceptible to prolonged indentation after the force subsides. The PVC tube proved to be more effective in recovering after the force is removed, but is susceptible to complete obstruction from a large force. The indentation of tubes with an applied force ranging from 40 to 100 newtons (only a fraction of the force applied by the bite of an adult) results in near complete obstruction.

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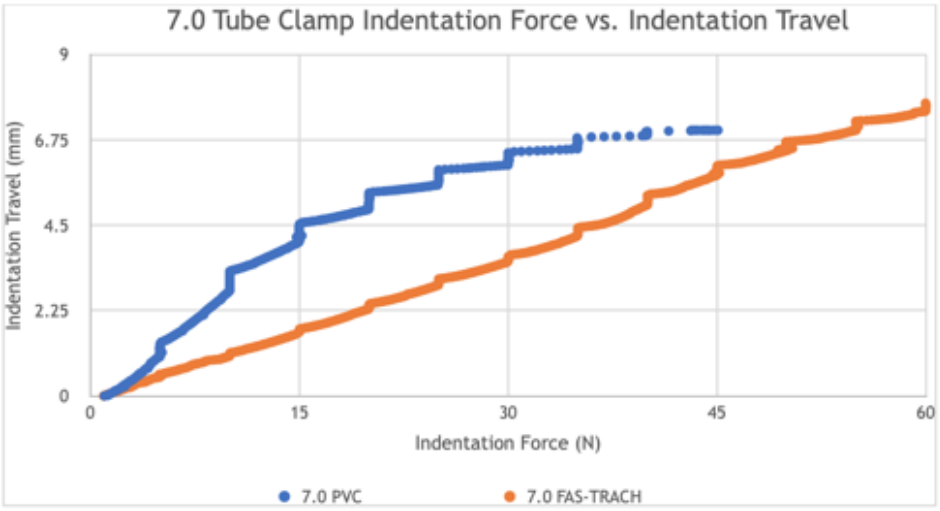

Fig. 1

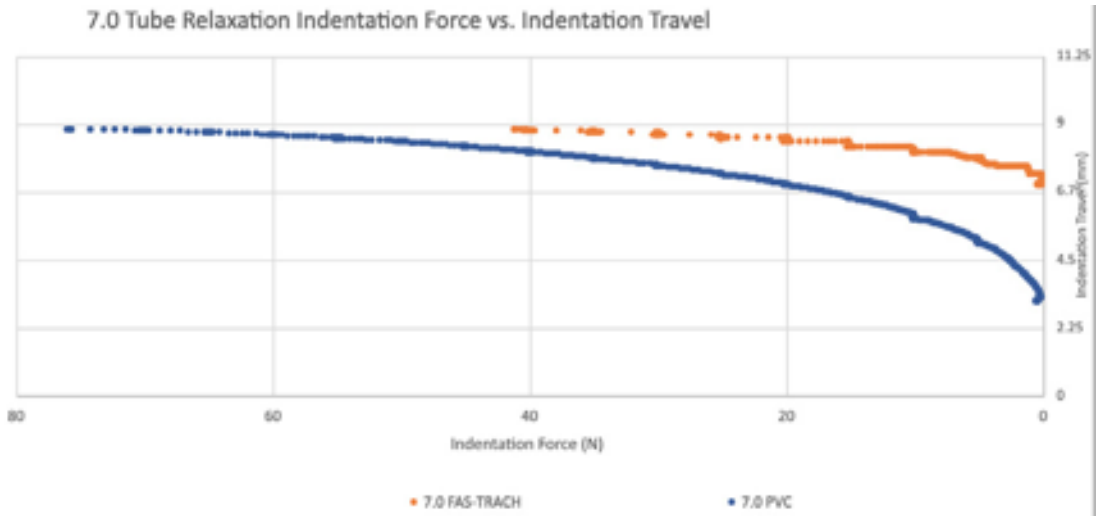

Fig. 2

AIRWAY MANAGEMENT 21

A Comparison of Compression and Relaxation Characteristics in 7.0mm Versus 8.0mm Polyvinyl Chloride Endotracheal Tubes

Shreya Dhar[1], Sanjana Rao[1], Ryan Hoang[1], P. Allan Klock[1], David Glick[1], Philip J Griffin[2]

[1]University of Chicago, Chicago, IL, [2]The Pritzker School of Molecular Engineering at The University of Chicago, Chicago, IL

INTRODUCTION: Pressure exerted on endotracheal tubes by the bite force of a patient's teeth has been shown to cause ventilatory obstruction by producing compression on the tube. Depending on a patient's bite force, endotracheal tubes have been reported to become punctured or even severed completely. Damage inflicted on endotracheal tubes has been shown to cause further complications such as irregular breathing patterns, or in extreme cases, the possibility of further injury such as lodging of sheared tubes in major airways.[1,2] While an adult can apply an average of 295 newtons of force with their bite, the ability of the various sizes of polyvinyl chloride (PVC) tubes to withstand bite force pressure as well as recover after the compressive force has been removed has not been determined.[3] In this study, the effectiveness of two different sized (7.0 and 8.0 mm) PVC tubes to resist and recover from compression is investigated by increasing and decreasing force applied to both tubes by a hydraulic press. Tidal volume and inspiratory resistance changes were measured as simulated breaths were delivered through the tubes by a ventilator.

METHODS: In order to compare the resistance of the 7.0 mm and 8.0 mm PVC endotracheal tubes, two chisels were attached to a hydraulic press to simulate the force applied by a patient's teeth. Once the respective tubes were in position, a ventilator generated simulated breaths through the endotracheal tubes during the compression and relaxation phases, allowing the inspiratory resistance (Rinsp) and the expiratory tidal volume (VTE) to be measured in addition to the diameter of the tube. The hydraulic press applied a gradually increasing force until airflow could no longer be achieved. The force was subsequently decreased back to 0 newtons to see how the tubes recovered.

RESULTS: Our results illustrate an inverse relationship with regards to resistance to indentation by force and recovery after relaxation between the 7.0 and the 8.0 PVC tubes (Figure 1, 2). At lower levels of force (0 -15N), both tubes displayed similar levels of resistance to indentation. At levels greater than 15 newtons, the 7.0 PVC tube demonstrated a greater resistance to indentation by force with a lesser indentation up until 45 newtons as compared with the 8.0 PVC tube. However, due to its greater initial internal diameter, forced air flow was still possible in the 8.0 PVC tube following applications of force greater than 45 newtons while no flow was possible through the 7.0 PVC tube. With increasing force, the 8.0 PVC tube experienced lower peak pressures, reaching a pressure of 100 cmH2O at 50 newtons while the 7.0 PVC tube reached a pressure of 100 cmH2O at a compressive force of 40 newtons (Figure 3). The 8.0 PVC tube also recovered from pressure sooner, with decreasing airway resistance pressures beginning at 10 newtons, compared to 5 newtons for the 7.0 PVC tube (Figure 4). With regards to relaxation, the 7.0 PVC tube displayed a slightly greater indentation recovery than the 8.0 PVC tube, however, neither retained prolonged compression.

CONCLUSION: While the 8.0 PVC tube can withstand slightly greater indentation force, the 7.0 PVC tube is more effective in both resisting compression and recovering after the force is removed. Both tubes were nearly completely obstructed by a force around 50 newtons, a small fraction of the force applied by the bite of an adult.

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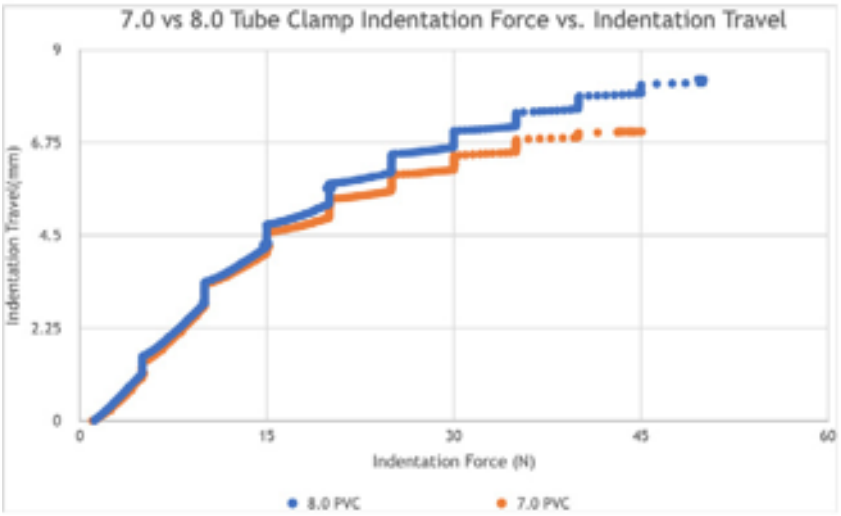

Fig. 1

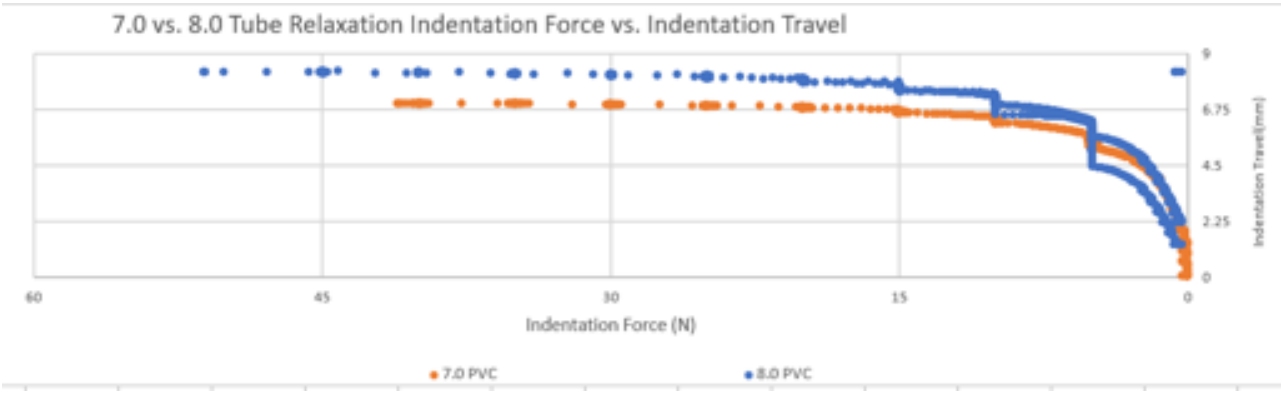

Fig. 2

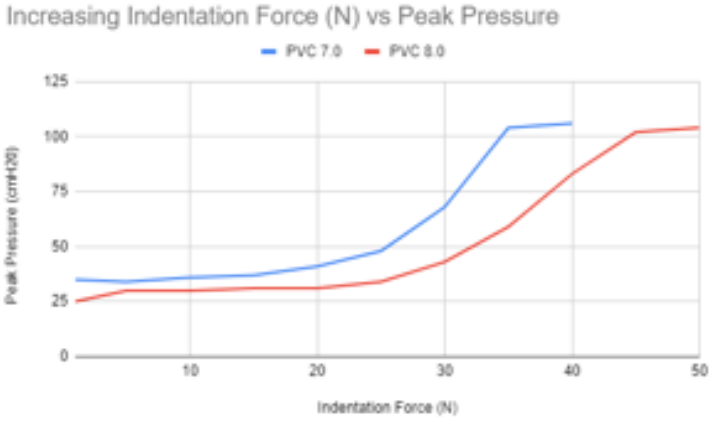

Fig. 3

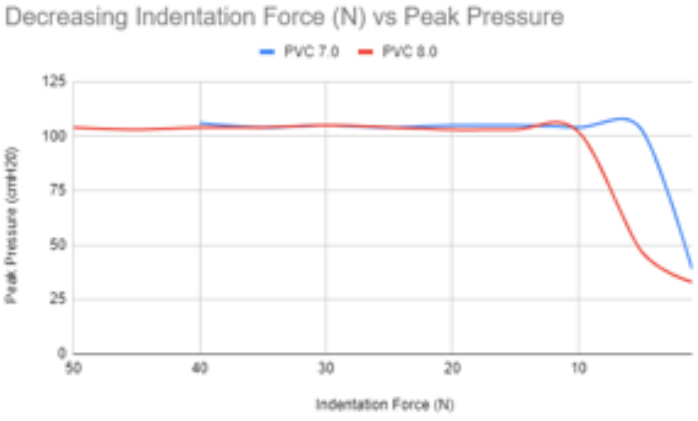

Fig. 4

AIRWAY MANAGEMENT 22

Investigation of Factors Affecting Providers' Comfort in Intubating COVID-19 Patients: Results from a USA National Survey

Reem Q Al Shabeeb[1], Esther Lee[2], Muhammad El Shatanofy[1], Collin F Mulcahy[1], Ivy Benjenk[1], David Yamane[1], Marian Sherman[1], Eric Heinz[1]

[1]The George Washington University School of Medicine & Health Sciences, Washington, DC, United States of America, [2]The GW Medical Faculty Associates, Washington, DC, United States of America

INTRODUCTION: As the COVID-19 pandemic strained the healthcare system with more than 300,000 physicians infected with SARS-CoV-2, preventing burnout is essential[1,2]. Endotracheal intubation is a hazardous aerosolizing procedure with a potential risk of contracting SAR-CoV-2 due to the proximity to the airway[3,4]. Since an estimated 3.2%-8% of COVID-19 patients eventually require endotracheal intubations[3,5], it is important to understand the factors affecting providers' comfort during intubation.

METHODS: In this multi-center cross-sectional study, we disseminated a pilot-tested, IRB-approved 24-question survey to providers from different specialties, training levels, and geographic locations across the USA using a snowball sample approach to assess factors affecting providers' comfort when intubating COVID-19 patients. A scale of 1-10, with 10 being the most comfortable, was utilized when asking: 'How comfortable are you with intubation in general?' and 'How comfortable are you with intubating suspected or confirmed COVID-19 patients?' Data was analyzed using an ordinal logistic regression test.

RESULTS: We analyzed 185 responses from providers at 32 hospitals after excluding incomplete surveys and surveys that reported no experiences with COVID-19 intubations. Comfort levels with intubation were lower in COVID-19 positive patients as compared to those who had a negative test (median 8 vs 10, $p<0.0005$). Residents felt less comfortable than attending physicians when intubating COVID-19 patients (adjusted odds ratio [AOR]=0.214, p=0.001). Factors associated with higher comfort levels when intubating COVID-19 patients included a higher number of COVID-19 intubations performed by the provider (AOR=3.764, 16-20 vs 1-5 intubations, p=0.015). Providers who had friends or close relatives contract COVID-19 were found to have lower comfort levels (AOR=0.47, p=0.028). Factors that did not significantly affect comfort when intubating COVID-19 patients were age, race, gender, specialty, parental status, and being a primary caretaker of someone > 80 years old.

CONCLUSION: Our study demonstrated that performing more COVID-19 intubations led to increased comfort during subsequent intubations, which is reflected in attending physicians' increased comfort compared to residents. Simulation training can be utilized to potentially increase the providers' comfort by increasing the number of intubations performed under COVID-19 settings. While family structure such as having children or being a primary caretaker of someone > 80 years old did not affect the comfort, having friends or close relatives who have contracted COVID-19 decreased comfort. Known contractions could have increased the psychological pressure to save the patient's life decreasing the provider's comfort. Future work investigating the relationship between educational interventions on these factors and provider comfort would be beneficial.

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AIRWAY MANAGEMENT 23

Comparison of "ETT cuff inflation technique" for Nasotracheal intubation (NTI) with Standard Macintosh laryngoscope versus C-MAC® video laryngoscope in adult patients undergoing elective surgery

Kriti Singh[1], Sonia Kasaudhan[2], Madhu Gupta[2]

[1]ESI Hospital, Basaidarapur, New Delhi, Delhi, 110075, [2]ESI Hospital, Basaidarapur, New Delhi, Delhi, India

INTRODUCTION: Airway management is an integral component of anaesthesia practice. Nasotracheal Intubation (NTI) is most common method used for giving anaesthesia in patients undergoing oropharyngeal and maxillofacial surgeries.[1,2] In NTI, a lubricated endotracheal tube (ETT) is inserted into the nostril. Once it reaches the oropharynx, laryngoscopy is done which allows optimal visualization of glottis and lifts the larynx away from the tip of the advancing ETT, which generally lies along the posterior pharyngeal wall. This necessitates the need of bringing the tip of ETT anteriorly to glottis. There are various techniques available to bring ETT towards glottis including external laryngeal manipulation, inflation of ETT cuff and use of Magill forceps.[3,4,5] Macintosh direct laryngoscope is Gold standard, however due to several significant advantages video laryngoscope is widely use to access difficult intubation for definitive airway management. C-MAC® is non-channeled video laryngoscope which provide optimal intubating condition with improved rate of success and less incidence of complications.[6] The present study was planned to compare the intubating conditions for NTI between Macintosh laryngoscope and C-MAC® video laryngoscope with modality of ETT cuff inflation technique to bring the ETT anteriorly in line of glottis.

METHODS: This prospective randomized study was carried out in Department of Anaesthesia, ESI PGIMSR and Hospital, New Delhi. A total of 50 patients randomized into two group (VL-Cmac Videolaryngoscope vs ML- Macintosh laryngoscope) by sealed number opaque slips. Patients' nostrils were decongested and induction of anaesthesia was done as per standard institutional protocol. Lubricated appropriate size ETT was introduced nasally till the oropharynx and then laryngoscopy was performed. In first instance, ETT cuff inflation was done with 15 cc air to bring ETT anteriorly up to glottis. If the ETT could not be navigated up to the glottis with 15 cc of cuff inflation, an additional 5cc of air was added to the cuff. Maximum amount of air for ETT cuff inflation permitted was 20 cc. If it was not possible to intubate by ETT cuff inflation technique, ETT tube was brought anteriorly up to the glottis with the help of Magill forceps. Total time taken for NTI was recorded in both the groups (T=T1+T2), where TIME (T1): time taken for ETT introduction from nostril till oropharynx and TIME (T2): time taken to introduce the laryngoscope at the level of incisor till the tube was navigated into the glottis. The number of patients requiring assistance with Magill forceps for navigation of ETT from oropharynx to glottis, number of attempts taken to achieve successful NTI, hemodynamic effects, and complications were also recorded. Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS, Chicago, Illinois).

RESULTS: A total of 50 subjects were enrolled for the study. Both the study groups had similar demographic profile and baseline characteristics. Gender distribution, ASA status and CL grade of the patients between two groups was comparable. Comparison of T, T1 and T2 between the two groups is given in Table 1 Comparison of Frequency of modality used for intubation between the two groups is given in Table 2. Complications like sore throat was lesser with C-MAC® video laryngoscope in comparison to Macintosh laryngoscope however, the difference was not statistically significant.

CONCLUSION: The cuff inflation technique, which facilitates passage of ETT from oropharynx till the glottis for NTI, with C-MAC® video laryngoscope had more success rate, required lesser time and had minimal post-operative complications as compared to Macintosh Laryngoscope.

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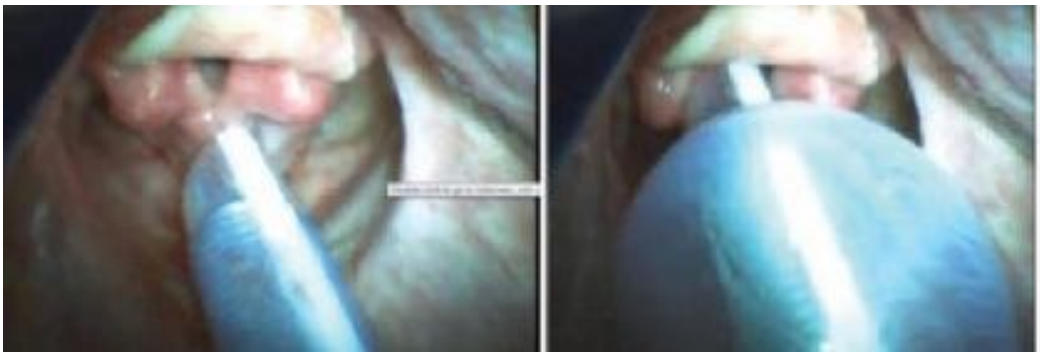

Table 1: Time taken for nasotracheal intubation (seconds)

Time taken for nasotracheal intubation (seconds)	VL GROUP Mean ± SD	ML GROUP Mean ± SD	P Value
T1 (Time taken for ETT introduction from selected nostril till oropharnyx)	13.08 ± 1.68	12.80 ± 1.56	0.544
T2 (Time taken for ETT navigation froml oropharnyx till the glottis)	19.60 ± 10.53	33.08 ± 13.43	<0.001
T (Time taken for ETT introduction from selected nostril till the glottis)	31.48 ± 10.72	45.88 ± 13.47	<0.001

	VL group n	VL group Frequency %	ML group n	ML group Frequency %	P Value
Successful intubation using cuff inflation	25	100.0%	19	76.0%	0.022
15ml of cuff inflation	22	88.0%	8	32.0%	<0.001
20 ml of cuff inflation	3	12.0%	11	44.0%	0.026
Magill forceps	0	0.0%	6	24.0%	0.022

Table 2: Frequency of modality used for intubation

AIRWAY MANAGEMENT 24

Inhibition of endothelial barrier dysfunction and acute lung injuries by peptides targeting CD36

Yunbo Ke[1], Yue Li[2], Pratap Karki[2], Alexander V Bocharov[3], Anna Birukova[2], Konstantin Birukov[1]

[1]Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, MD, [2]Dept of Medicine, University of Maryland School of Medicine, Baltimore, MD, [3]National Institutes of Health, Bethesda, MD

INTRODUCTION: CD36 belongs to scavenger receptor class B and is a fatty acid translocase. Previous studies have suggested that the receptor may be involved in regulation of responses to endotoxin and inflammation of the lungs. We have tested a group of helical peptides that interact with and modulate the activities of CD36 and tested their activities against endothelial barrier dysfunction and acute lung injuries in mice.

METHODS: We have employed ECIS, WB analysis, qPCR and mouse models to study the activities of the peptide in regulation of endothelial barrier function and acute lung injuries.

RESULTS: Peptides that inhibit CD36 activities including L37pA, ELR-B and ELR-BP reversed or mitigated the barrier disruptive activities induced by LPS, truncated phospholipids and histone H3 as measured by TER (trans-endothelial electric resistance). In consistence with these results, the peptides also enhanced the barrier protective activities of OxPAPC. The same set of peptides inhibited LPS-induced expression of inflammatory markers including ICAM-1 and VCAM-1 through down-regulation of NFκB and State3 mediated signaling pathways in cultured endothelial cells. The peptides were delivered intravenously to mice treated with LPS to induce acute lung injury. It has been observed that among peptides that antagonize the activities of CD36, L37pA, ELR-B and ELR-BP have demonstrated inhibitory effects on parameters of acute lung injury induced by LPS which were characterized by reduced extravasation of inflammatory cells from circulation to bronchoalveolar lavage (BAL) fluid and a decrease in protein concentration in the BAL in peptide-treated mice.

CONCLUSION: These results demonstrate for the first time the utility of CD36 antagonistic amphipathic helical peptides L37pA, ELR-B and ELR-BP as a novel strategy to ameliorate acute lung injury.

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AIRWAY MANAGEMENT 25

Self Reported Loss of Voice and Hoarseness at Post-Operative Day 1 in Outpatient Surgery Patients

Hunter Perela[1], sean runnels[2], lauren Knecht[3], Ashka Shah[3]

[1]University of Utah Department, Saltlake, UT, [2]University of Utah, saltlake, UT, [3]University of Utah, Saltlake, UT

INTRODUCTION: Sore throat is a common source of patient pain affecting patient satisfaction after surgery. Less is known about the incidence or impact of vocal changes after surgery. The incidence of sore throat after general anesthesia is well described with rates of up to 50%.[1,2] Several studies have described hoarseness after endotracheal intubation,[3,4] however little is known about hoarseness with other airway techniques. Little is known about loss of voice. We retrospectively analyzed an outpatient surgery dataset to explore vocal changes after outpatient surgery.

METHODS: The study was approved by the University of Utah IRB. Design: Retrospective EMR review Outpatient surgical cases at the University of Utah routinely receive a Nursing follow up call on POD 1. The questions: 1) Do you have hoarseness? 2) Did you have a loss of voice? were asked at that time. We performed a retrospective data analysis including all outpatient surgery call back notes and corresponding airway note from our EMR. These cases were analyzed for reported hoarseness and loss of voice for different airway management techniques as well as for temporal variation. Any patient who had an outpatient surgery was included. No Cases were excluded. 18905 cases met our inclusion criteria.

RESULTS: 18905 patients were identified who underwent out patient surgery at the University of Utah voer a 5 year period. The number of patients managed with airway management technqiue was Number of airways managed by technique: ETT(12944); LMA(4947); DL(7135); VL(1231); Lighted Stylet(39); FOB(24); MAC(209). The overall self reported hoarseness or loss of voice on Post Op Day #1 was 12.54% and 2.67% respectivly, for any patinet who had an outpatinet surgery. Self reprted hoarseness or loss of voice on Post Op Day #1, respectivly, by airway management catagory is as follows: ETT(15.02%, 3.04%); LMA(6.54%, 1.60%); DL(14.85%,2.80%); VL(16.57%,3.33%); Lighted Stylet(25.64%, 10.26%); FOB(19.65%, 3.28%). Patients who were listed as a MAC had a self reported hoarseness rate of 2.44% and a loss of voice rate of 1.03%.

CONCLUSION: Patient reported hoarseness and loss of voice are common after outpatient surgeries across a wide variety of airway management techniques. Hoarseness occurs at a higher rate than loss of voice for all forms of airway management studied. Further studies are needed to understand the incidence and mechanisms of vocal changes. We find evidence of vocal changes with LMA interesting as it is described as a 'supraglottic airway' technique which in theory, has little contact with the vocal cords themselves. The high rates of hoarseness and loss of voice with the use of a light wand warrants further study. Caution should be used in drawing conclusions from this data as it is retrospective from a single institution.

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AIRWAY MANAGEMENT 26

Comparison between Rocuronium and Succinylcholine for onset of action during rapid sequence induction: a systematic review and meta-analysis of randomized clinical trials at patient level

Ana Beatriz S de souza[1], Clístenes C de Carvalho[2], Danielle M da Silva[3], Stéphanie L Regueira[4], Caroline O Rego[2], Isabella B Ramos[5], Jayme M Santos Neto[6]

[1]Universidade Federal de Campina Grande, João Pessoa, 58.071-141, [2]Universidade Federal de Campina Grande, Campina Grande, Paraíba, [3]Hospital da Clínicas da UFPE, Recife, Pernambuco, [4]Universidade Federal de Campina Grande, Cabedelo, Brazil, [5]Universidade Federal de Campina Grande - UFCG, Serra Talhada, Pernambuco, [6]Universidade Federal de Pernambuco - UFPE, Recife, Brazil

INTRODUCTION: A swift neuromuscular blockade is crucial for rapid sequence induction (RSI), so long as we need to quickly place tracheal tube in order to avert oxygen desaturation as well as aspiration of gastric content. Rocuronium (Roc) and succinylcholine (Scc) are currently the choices in such context due to their rapid onset of action. We thus conducted this systematic review (SR) and network meta-analysis to evaluate which dose of which drug has the shortest time for neuromuscular blockade.

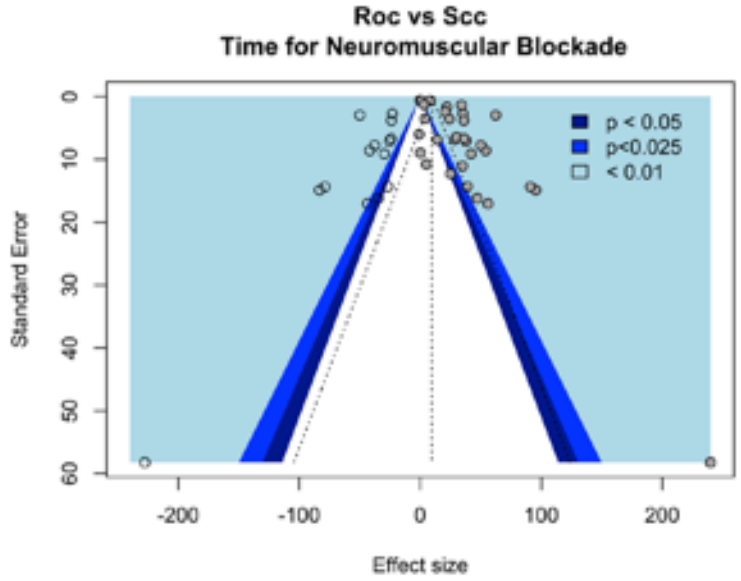
METHODS: This is part of a more comprehensive ongoing SR of multiple outcomes. We conducted a search in PubMed, LILACS, Scielo, Embase, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 6) in June 2020. We included randomized clinical trials fully reported with patients at all ages. Here we present the results of included studies comparing rocuronium and succinylcholine during RSI for time for neuromuscular blockade. Measures of neuromuscular blockade were performed either by single twitch or TOF T1, from different nerve stimuli such as ulnar, facial, and recurrent laryngeal. Maximal stimulus depression (19 studies) as well as depressions of 90% (3 studies) and 95% (2 studies) were considered for this outcome. One paper reported an inaccurate definition. Article screening and data extraction were conducted in duplicate by 2 independent reviewers with ability to resolve conflict with supervising author. Pooled effects were estimated by both fixed and random-effects models and presented according to qualitative and quantitative heterogeneity assessment. Sensitivity analyses were performed as well as a priori subgroup, meta-regression and multiple meta-regression analyses. Additionally, we assessed the risk of selective publication by funnel plot asymmetry.

RESULTS: Twenty-five randomized trails (1708 subjects) were analyzed for time for neuromuscular blockade (Figure 1). Five studies were regarded at 'high risk' of overall bias, whereas 20 at 'some concerns' according to ROB 2 tool. Significant heterogeneity was present (: I2=98.1%; Chi2-p<0.0001). When not accounting for doses, Roc appears as taking longer than Scc to accomplish muscle relaxation (MD [Roc - Scc]=32.04 s; 95% CI: 20.59 to 43.48; p<0.0001); For subgroup analyses, population, dose of Roc and clinical scenario (elective vs urgency) were associated with significant changes in effect sizes and may be responsible for the large heterogeneity found. Only Roc 0.3 mg.kg-1 (MD=38.99 s; 95% CI: 29.07 to 48.90) and 0.6 mg.kg-1 (MD=240 s; 95% CI: 125.85 to 354.15) presented significant difference as compared to Scc. In the meta-regression analysis, getting doses of Roc and Scc as numerical variables, linear association was found between dose of Roc and effect size (p=0.0003). For the multiple meta-regression analysis, including doses of Roc and Scc, the model was significant and accounted for 53% of the correspondent heterogeneity (p=0.0008), with dose of Roc as the only significant variable included – negatively associated (p=0.0003). Egger's test showed significant asymmetry (p=0.0005), suggesting possible publication bias (Figure 2). When controlling the pooled effects for selective publication, statistical significance was missed (MD=9.55 s; 95% CI: -6.27 to 25.36; p=0.2302). Evidence was judged as of very low quality according to GRADE assessment recommendations.

CONCLUSION: Current available evidence is not enough to reliably support the assumption of relevant difference in onset time between Roc and Scc. Difference found was present only when pooling together diverse doses of both Roc and Scc - with lowest doses of Roc being summarized. Subgroup analyses did not show significant difference between drugs where Roc was administered in doses above 0.6 mg.kg-1. Moreover, evidence was judged as of very low quality and confidence intervals do not allow us to ensure clinically relevant differences.

Study	Roc Mean	Roc SD	Roc Total	Scc Mean	Scc SD	Scc Total	Weight	Mean Difference IV, Random, 95% CI
Abdulatif 1996	56.00	12.00	12	57.00	17.00	12	3.4%	-1.00 [-12.77; 10.77]
Abu-Halweh 2007	65.80	3.20	60	66.00	3.20	60	3.5%	-0.20 [-1.35; 0.95]
Ajeet 2004	87.94	5.90	20	65.89	4.63	20	3.5%	22.05 [18.76; 25.34]
Alvarez 1997	96.00	46.00	20	61.00	18.00	20	3.2%	35.00 [13.35; 56.65]
Barve 2002	101.50	29.47	20	63.75	11.57	20	3.4%	37.75 [23.87; 51.63]
Chavan(1) 2016	115.50	11.11	30	53.25	8.31	15	3.5%	62.25 [56.46; 68.04]
Chavan(2) 2016	74.00	6.19	30	53.25	8.31	15	3.5%	20.75 [16.00; 25.50]
Cooper 1992	88.90	36.90	40	60.40	22.40	40	3.4%	28.50 [15.12; 41.88]
Dubois 1995	130.00	46.00	12	74.00	37.00	12	2.8%	56.00 [22.60; 89.40]
Hemmerling(1) 2000	92.00	42.00	30	38.00	15.00	15	3.3%	54.00 [37.16; 70.84]
Hemmerling(2) 2000	52.00	31.00	30	38.00	15.00	15	3.4%	14.00 [0.56; 27.44]
Kumar 2015	95.15	9.40	40	59.80	14.30	40	3.5%	35.35 [30.05; 40.65]
Labrada 2019	90.60	2.48	32	82.35	2.54	32	3.5%	8.25 [7.02; 9.48]
Le Corre 1999	99.00	47.00	30	57.00	17.00	30	3.3%	42.00 [24.12; 59.88]
Magoriam(1) 1993	89.00	33.00	10	50.00	17.00	3	3.0%	39.00 [10.92; 67.08]
Magoriam(2) 1993	75.00	28.00	10	50.00	17.00	4	3.1%	25.00 [0.94; 49.06]
Magoriam(3) 1993	55.00	14.00	10	50.00	17.00	3	3.2%	5.00 [-16.10; 26.10]
Naguib 1994	90.00	9.70	10	54.00	7.14	10	3.5%	36.00 [28.53; 43.47]
Nelson 1997	72.00	25.04	20	42.00	15.24	22	3.4%	30.00 [17.31; 42.69]
Puhringer 1992	72.00	15.30	20	48.00	3.06	10	3.5%	24.00 [17.03; 30.97]
Shukla(2) 2004	80.10	5.42	40	46.05	4.70	20	3.5%	34.05 [31.39; 36.71]
Stevens 1996	83.70	34.90	30	47.40	6.50	10	3.4%	36.30 [23.18; 49.42]
Stoddart 1997	92.00	41.00	30	42.00	11.00	30	3.3%	50.00 [34.81; 65.19]
Stourac 2016	65.00	25.00	120	61.00	29.00	120	3.5%	4.00 [-2.85; 10.85]
Sutradhar 2017	43.41	5.32	72	42.51	2.56	72	3.5%	0.90 [-0.46; 2.26]
Tang 1996	158.00	76.00	27	62.50	19.00	48	2.9%	95.50 [66.33; 124.67]
Tripathi 2012	53.00	7.82	50	50.08	3.98	50	3.5%	2.92 [0.49; 5.35]
Venkateswaran(1) 2012	305.00	258.25	20	65.00	24.00	10	0.9%	240.00 [125.85; 354.15]
Venkateswaran(2) 2012	156.00	54.50	20	65.00	24.00	10	3.0%	91.00 [62.86; 119.14]
Vianna(1) 1997	121.87	55.29	15	74.80	20.26	7	2.8%	47.07 [15.32; 78.82]
Vianna(2) 1997	74.93	20.97	15	74.80	20.26	8	3.3%	0.13 [-17.47; 17.73]
Total (95% CI)			**925**			**783**	**100.0%**	**32.04 [20.59; 43.48]**
Prediction interval								**[-36.43; 100.51]**

Heterogeneity: Tau^2 = 1089.3395; Chi^2 = 1541.73, df = 30 (P < 0.01); I^2 = 98%



AIRWAY MANAGEMENT 27

Comparison between Rocuronium and Succinylcholine for poor intubating conditions during rapid sequence induction: a systematic review and network meta-analysis of randomized clinical trials

Stéphanie L Regueira[1], Clístenes C de Carvalho[2], Danielle M da Silva[3], Jayme M Santos Neto[4], Ana Beatriz S de souza[5], Caroline O Rego[2], Isabella B Ramos[6]

[1]Universidade Federal de Campina Grande, Cabedelo, Brazil, [2]Universidade Federal de Campina Grande, Campina Grande, Paraíba, [3]Hospital da Clínicas da UFPE, Recife, Pernambuco, [4]Universidade Federal de Pernambuco - UFPE, Recife, Brazil, [5]Universidade Federal de Campina Grande, João Pessoa, 58.071-141, [6]Universidade Federal de Campina Grande - UFCG, Serra Talhada, Pernambuco

INTRODUCTION: Appropriate intubating conditions are crucial for rapid sequence induction (RSI) in order to get early intubation and curb the occurrence of complications such as hypoxia and bronchoaspiration. To quickly attain such appropriate conditions, two blocking agents are widely used for RSI: rocuronium (Roc) and succinylcholine (Scc).1,2 We performed this systematic review (SR) and meta-analysis aiming to evaluate current evidence about the risk of getting poor intubating conditions during RSI using Roc as compared to Scc.

METHODS: This is part of a more comprehensive ongoing SR of multiple outcomes. We conducted a search in PubMed, LILACS, Scielo, Embase, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 6) in June 2020. We included randomized clinical trials fully reported with patients at all ages. Here we present the results of included studies comparing rocuronium and succinylcholine during RSI for poor intubating conditions. Article screening and data extraction were conducted in duplicate by 2 independent reviewers with ability to resolve conflict with supervising author. Pooled effects were estimated by both fixed and random-effects models and presented according to qualitative and quantitative heterogeneity assessment. Sensitivity analyses were performed as well as a priori subgroup, meta-regression and multiple meta-regression analyses. Additionally, network meta-analyses were applied to rank the different doses of rocuronium and succinylcholine. We also assessed the risk of selective publication by funnel plot asymmetry.

RESULTS: Forty-three randomized trails (4613 subjects) were analyzed for poor intubating conditions (Figure 1). Five studies were regarded at 'high risk' of overall bias, 37 at 'some concerns' and only one at 'low risk' according to ROB 2 tool. No quantitative heterogeneity was present (I2=17.5%; Chi2-p=0.1846). When not accounting for doses, Roc was at higher risk of having poor intubating conditions (RR=1.82; 95% CI: 1.29 to 2.55; p=0.0011); For subgroup analyses, only dose of Roc significantly changed effect sizes and only two different doses of Roc were at higher risk than Scc: Roc 0.6 mg.kg-1 (RR=1.92; 95% CI: 1.07 to 3.44; 29 studies; 1768 participants) and 0.9 mg.kg-1 (RR=3.05; 95%CI: 2.34 to 3.98; 9 studies; 390 participants). Egger's test found significant asymmetry (p=0.0118), suggesting possible publication bias. When controlling the pooled effects for selective publication, statistical significance was missed (RR=1.32; 95% CI: 0.89 to 1.95; p=0.1620). By dose, only Roc 0.6 mg.kg-1 increased the risk of poor intubating conditions as compared to Scc 1 mg.kg-1 (Figure 2). Evidence was judged as of very low quality according to GRADE assessment recommendations.

CONCLUSION: Current available evidence does not support the assumption of any advantage of either Roc or Scc to avoid poor intubating conditions. Differences found were only present when pooling together different doses of both Roc and Scc - with lowest doses of Roc being summarized. When drugs were ranked by dose, Scc 1mg.kg-1 did not show significant difference as compared to highest doses of Roc such as 1 and 1.2 mg.kg-1. Moreover, evidence was judged as of very low quality and confidence intervals do not allow us to ensure clinically relevant differences.

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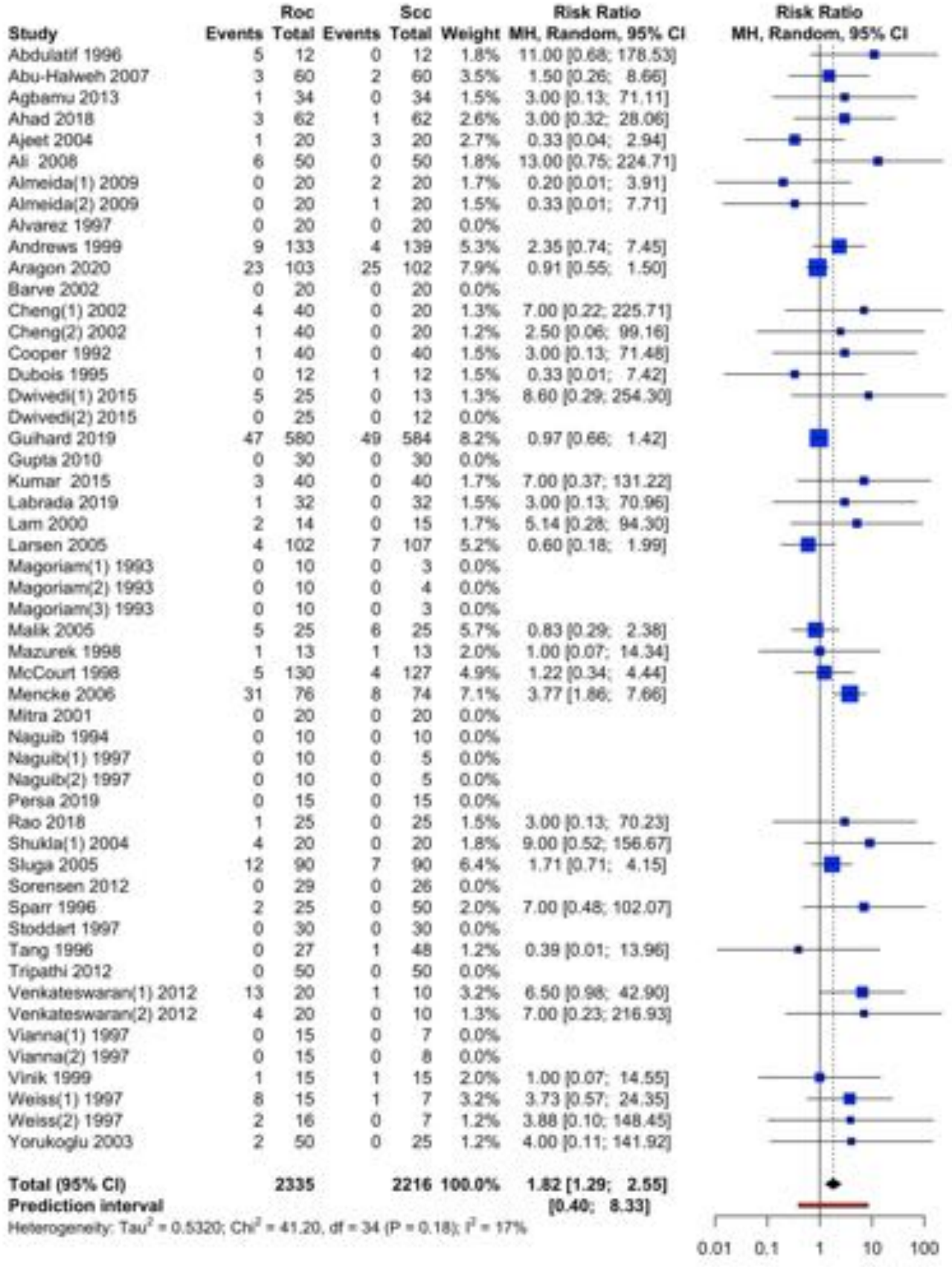

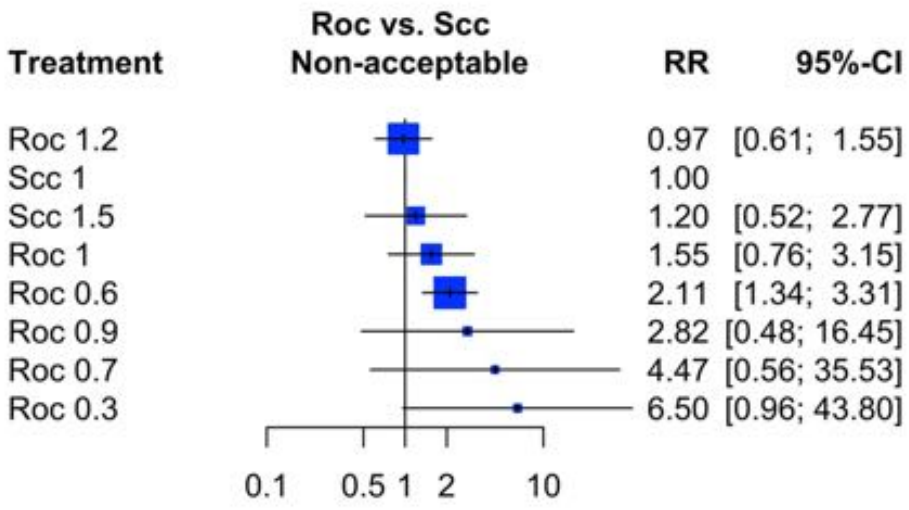

AIRWAY MANAGEMENT 28

Neck circumference for prediction of difficult laryngoscopies: a prospective cohort

Ana Beatriz S de souza[1], Clístenes C de Carvalho[2], Stéphanie L Regueira[3], Caroline O Rego[2], Isabella B Ramos[4], Danielle M da Silva[5]

[1]Universidade Federal de Campina Grande, João Pessoa, 58.071-141, [2]Universidade Federal de Campina Grande, Campina Grande, Paraíba, [3]Universidade Federal de Campina Grande, Cabedelo, Brazil, [4]Universidade Federal de Campina Grande - UFCG, Serra Talhada, Pernambuco, [5]Hospital da Clínicas da UFPE, Recife, Pernambuco

INTRODUCTION: Airway prediction still remains challenging and further approaches are worth investigating.[1,2] We evaluated the predictive values of the neck circumference (NC) for prediction of difficult laryngoscopies based on diverse statistic models.

METHODS: A prospective cohort was conducted with patients undergoing general anesthesia for surgical procedures. We preoperatively collected data on sex, age, weight, height, ASA physical status, and NC. The main outcome was difficult laryngoscopies defined as Cormack and Lehane's classes 3 or 4. Uni and multivariable analyses were performed to evaluate association between variables and build predictive models.

RESULTS: From a total of 130 patients, 9 (6.9%) presented difficult laryngoscopies. Sex (p=0.008) and NC (p=0.008) were associated with difficult laryngoscopies. Age (p=0.306), weight (p=0.090), height (p=0.156), and ASA (p=0.624) did not present significant difference between the 2 groups. NC was weakly correlated with Cormack and Lehane's classification modified by Cook (r=0.271; p=0.001). Six predictive models were built including only NC. The ROC curves for the predictive models are presented in Figure 1 and their AUC were as follows: Logistic Regression model - LR (81.86%; 95% CI: 70.97-92.76%); Linear Discriminant Analysis - LDA (81.86%; 95% CI: 70.97-92.76%); Classification and Regression Trees – CART (50%; 95% CI: 50-50%); k-Nearest Neighbors – kNN (88.93%; 95% CI: 81.71-96.16%); Random Forest – RF (93.2%; 95% CI: 87.11-99.3%); Generalized Boosted Model – GBM (87.14%; 95% CI: 77.66-96.63%). The optimal cut-off point for NC according to Youden index was 39.1 cm. For such threshold, the predictive values were sensitivity of 88.88%, specificity of 74.38%, PPV of 20.51, NPV of 98.90%, overall accuracy of 75.38%, and balanced accuracy of 81.63%. Positive likelihood ratio and negative likelihood ratio were 3.46 and 0.14 respectively.

CONCLUSION: NC is associated with difficult laryngoscopies and demonstrated helpful predictive performance. Therefore, it might be useful into multivariable models. Notwithstanding, the ability to segregate easy and difficult laryngoscopies remains cripple.

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AIRWAY MANAGEMENT 29

Predictive performance of thyromental height for prediction of difficult laryngoscopies in adults: a systematic review and meta-analysis

Isabella B Ramos[1], Clístenes C de Carvalho[2], Stéphanie L Regueira[3], Ana Beatriz S de souza[4], Caroline O Rego[2], Jayme M Santos Neto[5]

[1]Universidade Federal de Campina Grande - UFCG, Campina Grande, Paraíba, Brazil, [2]Universidade Federal de Campina Grande, Campina Grande, Paraíba, Brazil, [3]Universidade Federal de Campina Grande, Cabedelo, Paraíba, Brazil, [4]Universidade Federal de Campina Grande, João Pessoa, Paraíba, Brazil, [5]Universidade Federal de Pernambuco - UFPE, Recife, Pernambuco, Brazil

INTRODUCTION: Thyromental height (TMH) was first reported as a great single test for prediction of difficult laryngoscopies. However, further studies have been performed and shown variable estimates of the test accuracy. We thus performed this meta-analysis to summarize the predictive values of TMH mainly for prediction of difficult laryngoscopies.

METHODS: A search in PubMed, EMBASE, LILACS, and Scielo was conducted from database inception to June 2020. We included prospective cohorts fully reported with patients ≥ 16 years, providing data on predictive values of TMH for prediction of either difficult laryngoscopies or difficult intubations. Article screening, data extraction, and summarization were conducted by 2 independent reviewers with ability to resolve conflict with supervising authors. Diagnostic properties and association between TMH (index test) and Cormack and Lehanes's classification by direct laryngoscopy (reference standard) were evaluated. A random-effects meta-analysis using hierarchical models was performed.

RESULTS: Of the initial 26 screened articles, 8 studies evaluating 2844 patients were included. All included studies had high risk of bias and low concern regarding applicability. There was significant heterogeneity among the studies (Figure 1). The pooled diagnostic odds ratio (DOR) and positive (LR+) and negative (LR-) likelihood ratios were as follows: DOR, 57.94 (95% CI: 18.19-184.55); LR+, 11.32 (95% CI: 4.28-29.92); and LR-, 0.23 (95% CI: 0.15-0.35). Summary sensitivity and specificity for studies with common threshold were 82.6 (95% CI: 74-88.8%) and 93.5 (95% CI: 79-98.2%), respectively. The estimated AUC was 81.1%.

CONCLUSION: TMH shows up as a very good predictor of difficult laryngoscopies in adult patients from diverse populations presenting better predictive values than most previously reported bedside tests. However, the high risk of bias throughout the studies may have skewed the results of the individual researches as well as the summary points of the present meta-analysis.

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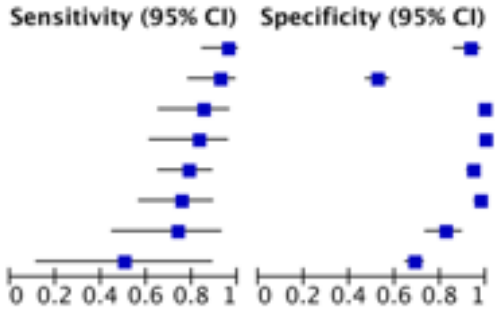
2. Reliability of the thyromental height test for prediction of difficult visualisation of the larynx: A prospective external validation. Indian J Anaesth. 63:270–6. 2019.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nurullah 2018	41	7	2	89	0.95 [0.84, 0.99]	0.93 [0.86, 0.97]
Selvi 2017	34	198	3	216	0.92 [0.78, 0.98]	0.52 [0.47, 0.57]
Rao 2018	22	3	4	287	0.85 [0.65, 0.96]	0.99 [0.97, 1.00]
Etezadi 2013	19	2	4	289	0.83 [0.61, 0.95]	0.99 [0.98, 1.00]
Panjiar 2019	43	30	12	465	0.78 [0.65, 0.88]	0.94 [0.91, 0.96]
Jain 2017	24	9	8	304	0.75 [0.57, 0.89]	0.97 [0.95, 0.99]
Mostafa 2020	11	19	4	86	0.73 [0.45, 0.92]	0.82 [0.73, 0.89]
Yabuki 2019	3	191	3	412	0.50 [0.12, 0.88]	0.68 [0.64, 0.72]



AIRWAY MANAGEMENT 30

Machine learning and regular logistic regression predictive models for prediction of difficult laryngoscopies: a prospective cohort

Stéphanie L Regueira[1], Clístenes C de Carvalho[2], Ana Beatriz S de souza[3], Caroline O Rego[2], Isabella B Ramos[4], Danielle M da Silva[5]

[1]Universidade Federal de Campina Grande, Cabedelo, Brazil, [2]Universidade Federal de Campina Grande, Campina Grande, Paraíba, [3]Universidade Federal de Campina Grande, João Pessoa, 58.071-141, [4]Universidade Federal de Campina Grande - UFCG, Serra Talhada, Pernambuco, [5]Hospital da Clínicas da UFPE, Recife, Pernambuco

INTRODUCTION: Machine learning (ML) algorithms have been deemed to improve predictive performance as compared to regular logistic regression (LR) models.1,2 We compared the AUC for multiple predictive models including ML algorithms and LR for prediction of difficult laryngoscopies.

METHODS: A prospective cohort was conducted with patients undergoing general anesthesia for surgical procedures. We preoperatively collected data on sex, age, weight, height, ASA physical status, modified Mallampati test (MMT), mouth opening (MO), and sternomental distance (SMD). The main outcome was difficult laryngoscopies defined as Cormack and Lehane's classes 3 or 4. Uni and multivariable analyses were performed to evaluate association between variables and to build the predictive models. Only variables with p-values<0.2 were included into the models.

RESULTS: From a total of 453 patients, 29 (6.4%) presented difficult laryngoscopies. Sex (p=0.015), weight (p=0.009), height (p=0.001), MMT (p<0.001), MO (p<0.001), and SMD (p<0.001) were associated with difficult laryngoscopies. Age (p=0.212) and ASA (p=0.070) did not present significant difference between the 2 groups. Six predictive models were built including sex, weight, height, ASA, MT, MO, and SMD. The ROC curves for the predictive models are presented in Figure 1 and their AUC were as follows: Logistic Regression model - LR (82.58%; 95% CI: 67.25-97.91%); Linear Discriminant Analysis - LDA (82.58%; 95% CI: 70.7-94.46%); Classification and Regression Trees – CART (58.32%; 95% CI: 41.89-74.74%); k-Nearest Neighbors – kNN (58.32%; 95% CI: 37.53-79.11%); Random Forest – RF (69.05%; 95% CI: 44.22-93.87%); Generalized Boosted Model – GBM (84.35%; 95% CI: 73.85-94.85%).

CONCLUSION: ML algorithms did not improve airway prediction as compared to regular LR model.

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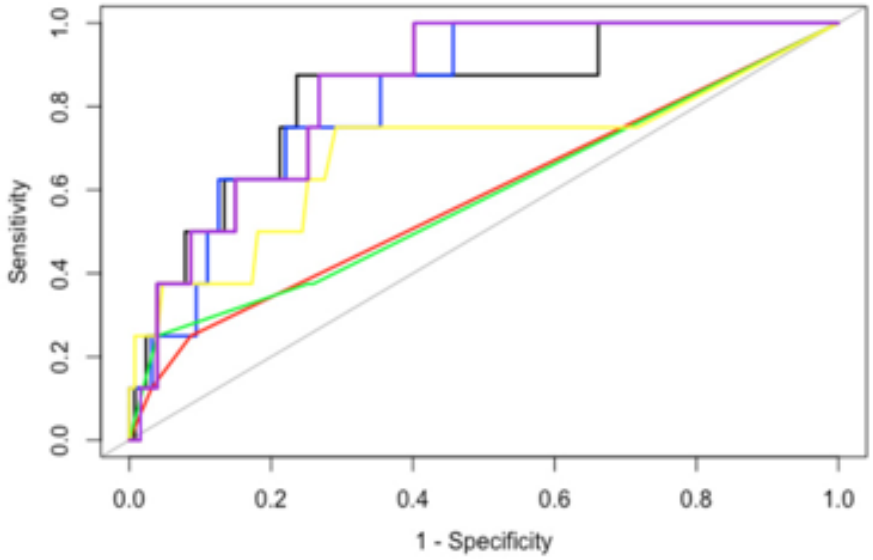

AIRWAY MANAGEMENT 31

Upper airway angle: a prospective cohort to evaluate the association between a new feature and difficult laryngoscopies

Isabella B Ramos[1], Clístenes C de Carvalho[2], Marina S Leite[3], Stéphanie L Regueira[4], Ana Beatriz S de souza[5], Caroline O Rego[2]

[1]Universidade Federal de Campina Grande - UFCG, Campina Grande, Paraíba, Brazil, [2]Universidade Federal de Campina Grande, Campina Grande, Paraíba, Brazil, [3]Universidade Federal de Pernambuco - UFPE, Recife, Pernambuco, Brazil, [4]Universidade Federal de Campina Grande, Cabedelo, Paraíba, Brazil, [5]Universidade Federal de Campina Grande, João Pessoa, Paraíba, Brazil

INTRODUCTION: Predicting difficult airways still remains challenging in clinical practice and advances are needed in this field. The present study then aimed at observing whether a new tool—the angle formed between mentum, mandibular angle, and anterior border of the thyroid cartilage (upper airway angle)—would be associated with difficult laryngoscopies.

METHODS: A prospective cohort was conducted with 125 patients – based on a sample size estimation - undergoing general anaesthesia for surgical procedures. We collected preoperatively data on sex, age, weight, height, body mass index (BMI), ASA physical status, modified Mallampati test (MMT), sternomental distance (SMD), thyromental distance (TMD), upper lip bite test (ULBT), and upper airway angle (UAA). The main outcome was difficult laryngoscopy defined as Cormack and Lahane's classes 3 or 4. Bivariate analyses were performed to investigate mainly the association between variables and alternatively calculate their predictive values.

RESULTS: Difficult laryngoscopy was presented by 9 patients (7.2%). Three features presented significant association with difficult laryngoscopies: sex (p=0.009); modified Mallampati test (p=0.020); and upper airway angle (0.000). The AUC for the 5 evaluated predictors were as follows (Figure 1): UAA=92.4% (95% CI: 85.3-99.6%); MMT=68.9% (95% CI: 59-78.7%); TMD=60.2% (95% CI: 38.3-82.1); SMD=45.9 (95% CI: 17.4-74.4); and ULBT=38.7% (95% CI: 26.7-50.7).

CONCLUSION: The upper airway angle is a new feature found to be associated with difficult laryngoscopies. It presented the best predictive performance among the 5 assessed predictors and may help us more accurately predict the occurrence of difficult airways in daily clinical practice.

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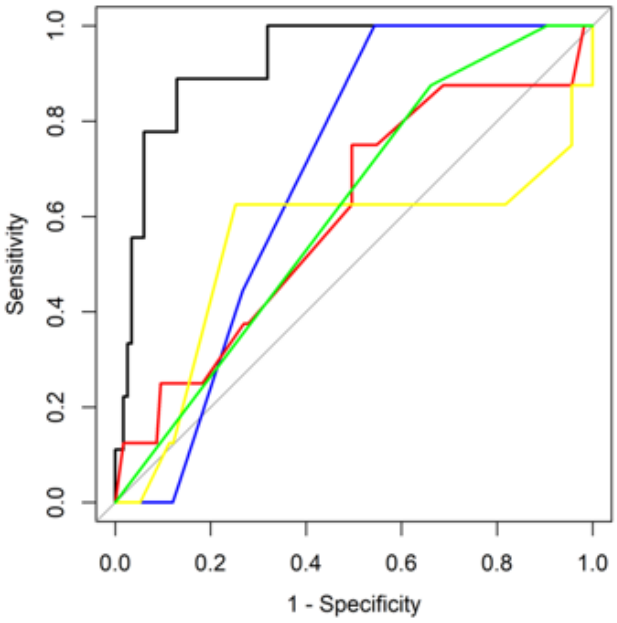

Fig. 1

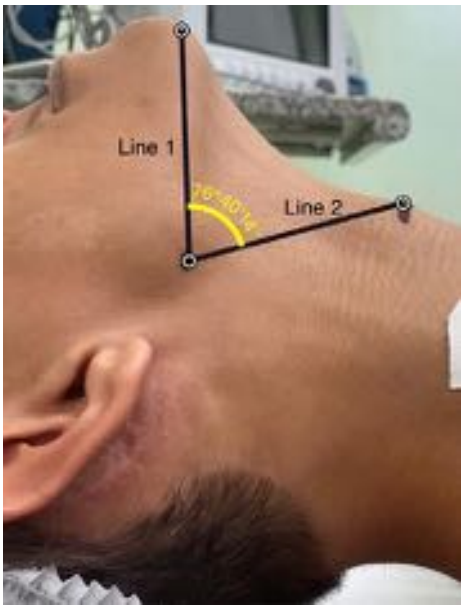

Fig. 2

AIRWAY MANAGEMENT 32

Clinical Characteristics of COVID-19 Patients Requiring Endotracheal Tube Exchange

Tazeen Beg[1], Cindy A Punta[1], Ana Mavarez Martinez[1], Jamie Romeiser[1], Jerry A Rubano[1], Sergio D Bergese[1]

[1]Renaissance School of Medicine, Stony Brook University, Stony Brook, NY, USA

INTRODUCTION: The novel coronavirus disease (COVID-19) has been shown to cause a wide range of symptoms from asymptomatic infection or mild disease to severe respiratory distress with an ARDS-like picture requiring intubation and ventilation support for prolonged periods of time in the ICU.[1] In a previous study, Rubano, et.al[2] described an acute partial or complete obstruction of the airway due to the presence of tracheobronchial slough impeding ventilation and oxygenation leading to desaturation and hemodynamic instability after a week post intubation. They suggested that endotracheal tube (ETT) exchange would make a difference in these patients. Following up on that study we identified a subset of patients who had an ETT exchange and retrospectively studied their characteristics. As per our knowledge to date, no other study has examined critically ill, ventilated, COVID-19 patients to identify possible reasons for requiring ETT exchange. The aim of this observational study was to describe the clinical characteristics of COVID-19 positive intubated patients in the ICU who required ETT exchange and to determine the characteristics associated with higher mortality.

METHODS: With institutional IRB approval, we performed a retrospective review of 59 intubated patients with COVID-19 admitted at our teaching hospital between March 2020 and June 2020 who required an ETT exchange and were followed till August 2020. Demographics, comorbidities, ETT exchange dates, number of exchanges, oxygen saturation, ventilation parameters and final outcomes were collected. Categorical variables are presented as frequencies (%), whereas continuous variables are presented as either means (SD) or medians (IQR) depending on their distribution. Determinants were compared between survivors and non-survivors using Chi-square, Fisher's exact, Student's T-tests, or Wilcoxon Rank Sum tests. Oxygenation and ventilation parameters prior to the exchange were compared to parameter values at 30 minutes and 24 hours after exchange for all patients using paired tests. The magnitude of change at each time point was then compared across survival groups. All statistical analyses were performed at the 95% confidence level using SAS 9.4© software (Cary, NC).

RESULTS: Patients requiring ETT exchanges had a mean age of 59.2 years (SD, 13.2). Most patients were male (71.7%), and mean BMI was 29.2 (SD, 7.1). Among the different ethnic groups, 30% were Hispanics or Latino though there are only 17-20% Hispanics compared to 67-69% white population in the area. The three most common primary comorbidities identified were hypertension (37, 62.7%), obesity (24, 40.7%) and diabetes (21, 35.6%). The reason for intubation in all patients was acute respiratory distress syndrome (ARDS). The median time to first ETT exchange from intubation was 8 days (IQR, 6, 12). Main reasons for ETT exchanges included: increased peak inspiratory pressures (PIP) (16, 27.1%), acute respiratory failure (15, 25.4%) and clogging/obstruction (15, 25.4%). The median number of ETT exchanges was 2 (IQR, 1, 3) (Table 1). Approximately half of the patients survived (30, 50.8%) and were discharged to home or a rehabilitation facility. We found no significant differences in ETT exchange details between survivors and non-survivors (Table 2), but weight, BMI, and obesity rates were all significantly higher in non-survivors. Most oxygenation and ventilation parameters significantly improved after the ETT exchange. PAW, CO2, FiO2 and PEEP, all significantly decreased, whereas SpO2 and TV significantly increased after the ETT exchange (Table 3). However, the magnitude of these changes were not significantly different between survivors and non-survivors, with the exception of PAW at 24 hrs.

CONCLUSION: Critically ill patients with COVID-19 requiring prolonged mechanical ventilation are predisposed to problems with oxygenation and ventilation and may require ETT exchange. In our study, mortality rates were significantly higher in those who were more obese. Most of these ETT exchanges were non-elective, therefore, further research is necessary to determine if early elective ETT exchange may improve survival outcomes in obese patients. Indeed, endotracheal tube (ETT) exchange has become a necessary component in the management of our intubated COVID-19 patients in the ICU.

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	Total (N= 59)	Survivors (n = 30 [50.85%])	Non-Survivors (n = 29 [49.2%])	P-value
Age (years) [*], mean (SD)	59.2 (13.2)	57.2 (12.2)	61.4 (14.1)	0.22
Gender[+] N (%)				
Male	42 (71.2%)	20 (66.7%)	22 (75.9%)	0.44
Female	17 (28.8%)	10 (33.3%)	7 (24.1%)	
Height (cm) [*], mean (SD)	170.1 (8.5)	169.1 (9.6)	171.1 (7.3)	0.38
Weight (kg) [*], mean (SD)	84.9 (22.8)	76.9 (22.4)	93.2 (20.5)	0.005
BMI (kg/m^2) [*], mean (SD)	29.2 (7.1)	26.7 (6.5)	31.7 (6.9)	0.006
Race[#] N (%)				
Caucasian	41 (69.5%)	22 (73.3%)	19 (65.5%)	0.12
African American	2 (3.5%)	2 (6.7%)	0 (0%)	
Asian	7 (11.9%)	1 (3.3%)	6 (20.7%)	
Other	9 (15.3%)	5 (16.7%)	4 (13.8%)	
Ethnicity[+] N (%)				
Not Hispanic or Latino	41 (69.5%)	20 (66.7%)	21 (72.4%)	0.63
Hispanic or Latino	18 (30.5%)	10 (33.3%)	8 (27.6%)	
Comorbidities N (%)				
Obesity[+]	22 (37.3%)	7 (23.3%)	15 (51.7%)	0.02
Hypertension[+]	37 (62.7%)	19 (63.3%)	18 (62.1%)	0.92
Diabetes[+]	21 (35.6%)	11 (36.7%)	10 (34.5%)	0.86
Asthma[#]	6 (10.2%)	2 (6.7%)	4 (13.8%)	0.42
COPD[#]	4 (6.8%)	2 (6.7%)	2 (6.9%)	1

Table 1: Demographics
BMI: Body Mass Index; COPD: Chronic obstructive pulmonary disease; [*] Student's T-Test with equal variance; [+] Chi-Square Test; [#] Fisher's Exact Test

	All (N=59)	Survivors (n= 30)	Non-Survivors (n= 29)	P-value
Time to **first intubation** from admission (days) [@], median [IQR]	3 (1, 6)	3 (2, 6)	2 (1, 5)	0.17
Time to **first ETT exchange** from intubation (days) [@], median [IQR]	8 (6, 12)	7 (6, 13)	9 (5, 12)	1
Time to discharge/death from **admission** (days) [@], median [IQR]	34 (24, 58)	42 (30, 85)	27 (19, 36)	0.0004
Time to discharge/death from **intubation** (days) [@], median [IQR]	29 (21, 51)	38 (28, 29)	24 (17, 32)	0.0003
Time to discharge/death from **first tube exchange** (days) [@], median [IQR]	18.5 (12, 42)	29 (17, 73)	14 (10, 19)	0.0003
Reason for intubation (ARDS), N (%)	59 (100%)	30 (100%)	29 (100%)	-
Reason for ETT exchange[#], N (%)				
Increased PIP	16 (27.1%)	7 (23.3%)	9 (31%)	0.44
Air leak	9 (15.3%)	3 (10%)	6 (20.7%)	
Acute respiratory failure	15 (25.4%)	10 (33.3%)	5 (17.2%)	
Clogging/obstruction	15 (25.4%)	7 (23.3%)	8 (27.6%)	
Other	4 (6.8%)	3 (10%)	1 (3.5%)	
ETT size for ETT exchange[#], N (%)				
Decreased 0.5	3 (5.1%)	1 (3.3%)	2 (6.9%)	0.71
Same size	36 (61%)	18 (60%)	18 (62.1%)	
Increased 0.5	19 (32.2%)	11 (36.7%)	8 (27.6%)	
Increased 1	1 (1.7%)	0 (0%)	1 (3.4%)	
Number of ETT exchanges[@], median [IQR]	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.74
(Categorical)[#], N (%)				
1	24 (40.6%)	13 (43.3%)	11 (37.9%)	0.59
2	15 (25.4%)	8 (26.7%)	7 (24.1%)	
3	10 (17%)	3 (10%)	7 (24.1%)	
4+	10 (17%)	6 (20%)	4 (13.8%)	
Paralysis medication use				
From intubation to ETT exchange, N (%)	50 (84.6%	27 (90%)	23 (79.3%)	0.3
From ETT exchange to 24h after, N (%)	8 (13.6%)	2 (6.7%)	6 (20.7%)	0.15

Table 2: Differences in time to intubation, first exchange and death or discharge in survivors versus non-survivors.
ARDS: Acute Respiratory Distress Syndrome; PIP: Peak Inspiratory Pressure; [@]Wilcoxon Rank Sum test; [#] Fisher's Exact Test. *Note: at the time of analysis, one person in the survivor group is still admitted and does not have a discharge date.*

	All	Paired P-Value[+] (vs. Baseline)	Survivors	Non-Survivors	p-value
			N= 30	N= 29	
PAW (mmHg)[@], median (IQR)					
Before ETT exchange	38 (30, 44)		38 (30, 45)	36 (29.5, 43)	0.37
Change after 30m	-4 (-12, 0)	<0.001	-5 (-13, -3)	-3 (-10.5, 0.5)	0.18
Change after 24h	-6.5 (-14, -0.5)	<0.001	-13 (-15, -4)	-3 (-8, 1)	0.01
SpO_2 (%)[*], mean (SD)					
Before ETT exchange	91.6 (4.0)		92.5 (3.9)	90.6 (3.9)	0.07
Change after 30m	5.0 (3.7)	<0.001	4.9 (3.5)	5.0 (3.9)	0.92
Change after 24h	4.7 (4.7)	<0.001	4.0 (4.6)	5.3 (4.8)	0.3
CO_2 (mmHg)[@], median (IQR)					
Before ETT exchange	58 (47, 65)		56.5 (47, 63)	58 (48.6, 66)	0.73
Change after 30m	-5 (-11, 0)	0.0001	-4.5 (-13, -2)	-5 (-8, 3)	0.21
Change after 24h	-4 (-11, 4)	0.03	-3 (-11, 1.7)	-4 (-11, 8)	0.47
PP (cmH_2O)[*], mean (SD)					
Before ETT exchange	25.7 (7.9)		26.4 (7.3)	24.8 (8.7)	0.47
Change after 30m	-4.7 (13)	0.01	-7.2 (12.5)	-1.9 (13.2)	0.16
Change after 24h	-0.9 (6.4)	0.47	-3.5 (4.1)	1.1 (7.2)	0.06
FiO_2 (%)[@], median (IQR)					
Before ETT exchange	80 (60, 100)		60 (50, 90)	90 (60, 100)	0.04
Change after 30m	0 (-10, 0)	0.0006	0 (-10, 0)	0 (-7, 0)	0.41
Change after 24h	0 (-20, 0)	0.006	-2.5 (-20, 0)	0 (-15, 7.5)	0.24
PEEP (cmH_2O)[@], median (IQR)					
Before ETT exchange	10 (5, 10)		10 (5, 10)	10 (5, 12)	0.74
Change after 30m	0 (-2, 0)	0.01	0 (-2, 0)	0 (0, 0)	0.18
Change after 24h	0 (-2, 0)	0.008	0 (-2, 0)	0 (-2, 0)	0.64
TV (ml)[@], median (IQR)					
Before ETT exchange	479 (431, 524)		485 (437, 521)	475 (426, 532)	0.69
Change after 30m	31 (-4, 70)	<0.001	12 (-6, 68)	36 (1, 70)	0.31
Change after 24h	18.5 (-20, 87)	0.008	9.5 (-19, 43)	48.5 (-29.5, 123.5)	0.35

Table 3: **Oxygenation and Ventilation patterns in the critically ill COVID-19 patients.**
PAW: Peak Airway Pressure; SpO_2: Oxygen saturation; CO_2: Carbon dioxide (From Arterial Blood Gases); PP: Plateau pressure; FiO_2: Fraction of inspired oxygen; PEEP: Positive end-expiratory pressure; TV: Tidal volume. [+] Comparisons between baseline and both follow up measurement time points were examined for all study patients using Paired T-Tests or Wilcoxon Sign Rank tests. [@]Wilcoxon Rank Sum test; [*] Student's T-Test with equal variance

AIRWAY MANAGEMENT 33

Effect of cricoid pressure and left paratracheal compression in obese patients: An international survey on the quality of laryngeal visualization in videolaryngoscopy

Lydie Gody[1], Cyril Fabbro[1], Nicolas Thiry[1], Jean-françois Brichant[1], Eric Deflandre[2], Benjamin Javillier[1]

[1]University of Liège, Liège, Belgium, [2]Clinique Saint-Luc, Bouge, Belgium

INTRODUCTION: Obese patients exhibit a higher risk during rapid sequence intubation than non-obese patients. Cricoid pressure (CP), recommended to decrease the risk of inhalation of gastric contents, may disrupt the intubation process by altering anatomical landmarks. Gautier et al recently demonstrated that a compression of the esophagus into the left low paratracheal cavity (LPEC) could be an interesting alternative to CP[1]. The purpose of this study is to compare the influence of CP and LPEC on glottic surface visualization.

METHODS: In another study comparing displacement and surface modification of the glottic surface under CP and LPEC, we prospectively included (after IRB agreement and written patient consent) 91 adult patients with a body mass index (BMI) greater than or equal to 35 kg m-2 admitted for elective surgery. We randomized the patients into two groups according to their position on the operating table. Forty-seven patients were placed in the supine position (DD) and 44 patients were placed in the Rapid Airway Management Positioner (RAMP). Of the 91 patients, we took 3 images during video laryngoscopy, one without compression (Neutral Position, NP), one with a CP, and one with an LPEC. In total, 273 (3 * 91) images were recorded for the original study (results are presented separately). In the present study, with the help of the French Society of Anesthesia and Intensive Care (SFAR), we handed out these 273 images to anesthesiologists, in a randomized order to be classified on a scale ranging from 1 (glottic visualization indicating easy intubation) to 3 (glottic visualization indicating difficult intubation).

RESULTS: The survey conducted by the SFAR gathered the opinions of 340 anesthesiologists and resuscitators. There was no difference between the groups in terms of demographics. In the dorsal decubitus group (n=47):
- The glottic visualization is considered to be easy in 57.84% in NP, in 38.98% ($P < 0.001$ relative to PN) with CP and in 46.23% with LPEC ($P < 0.001$ relative to PN).
- The intubation is considered difficult in 11.17% of cases in NP, 31.22% ($P < 0.001$ relative to NP) with CP and 18.27% with LPEC ($P < 0.001$ relative to NP). In the 'RAMP' group (n=44): - The intubation is rated as easy in 53.42% with NP, in 45.90% with CP ($P < 0.001$ relative to NP) and in 44.02% with LPEC ($P < 0.001$ relative to NP).
- The intubation is labeled difficult in 17.04% of cases in NP, 24.93% in CP ($P < 0.001$ relative to NP) and 22.44% in LPEC ($P < 0.001$ relative to NP).

CONCLUSION: Visualization of an obese patient's glottic surface in videolaryngoscopy is considered easier in the supine position, than the RAMP position if an LPEC or no esophageal compression is applied. In patients of a similar category, intubation in videolaryngoscopy is considered easier in the RAMP position, than the supine position if cricoid pressure is applied. To the best of our knowledge, this is the first study in which these different intubation conditions have been evaluated concomitantly. A future validation of our results under real intubation conditions is mandatory before considering a possible modification of the rapid sequence induction guidelines.

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1. Gautier N, Danklou J, Brichant JF, Lopez AM, Vandepitte C, Kuroda MM, et al. The effect of force applied to the left paratracheal oesophagus on air entry into the gastric antrum during positive-pressure ventilation using a facemask. Anaesthesia.2019;74(1):22-8.

AIRWAY MANAGEMENT 34

Effect of Cricoid Pressure and Left Paratracheal Compression on Obese Patients: A study on the visualization quality of the larynx using videolaryngoscopy

Nicol Emmanuel[1], Nicolas Thiry[1], Jean-françois Brichant[2], Eric Deflandre[3], Benjamin Javillier[1]

[1]University of Liège, Liège, Belgium, [2]centre hospitalier universitaire de Liège, Liège, Belgium, [3]Clinique Saint-Luc, Bouge, Belgium

INTRODUCTION: The interest of using cricoid pressure (CP) during rapid sequence inductions has always been disputed, and still is nowadays. The pressure applied on the cricoid cartilage produces a shift of the glottic axis and a modification of the surface which could worsen the intubation conditions. Authors such as Gautier and al. focused on a different approach and suggested the left paratracheal esophagus compression (LPEC)[1]. This study aims to compare, within obese patients, the differences between the shifts and surface of the glottic axis when CP and LPEC are applied.

METHODS: We prospectively included (after IRB agreement and written patient consent) 100 adult patients with a body mass index 35 kg.m² or higher, admitted for an elective surgery. They were randomised into two groups depending on their position on the operating table. The first one involved 50 patients installed in supine postion and the second, in « Rapid Airway Management Positioner » (RAMP). 3 pictures were taken while using videolaryngoscopy, one without any maneuvers (REF group), another while applying cricoid pressure (CP group) and last, with left paratracheal esophagus compression (LPEC group). After defining the height and width's center of the glottic axis, we measured using pixels the vertical and horizontal shifts according to the different esophagus compression techniques used.

RESULTS: The demographic data were similar between the different groups. 56 women and 44 men were included. Mean age was (SD) 53,10 (15,91) and mean (SD) body mass index (BMI) was 39,17 (3,90) Kg.m-2. The percentage of glottic surface variation, compared with the reference group (SD) was higher in the CP group 34,8 (46,6) % than in the LPEC group 19.8 (41.3) %, (P = 0.018). The glottic horizontal displacement distance (SD), relative to its neutral position, was identical in RAMP position 46,47 (27,05) pixels or in supine position 48,90 (31,42) pixels, regardless which compression technique was used. The glottic vertical displacement distance was identical in RAMP position 60,04 (37,20) pixels or in supine position 69,58 (43,38) pixels regardless which compression technique was used.

CONCLUSION: The intubation of a patient with a BMI > 35 is considered potentially difficult. To facilitate the process, installing the patient in RAMP position is a possibility.[2] Cricoid pressure alters the intubation maneuver by shifting and reducing the surface of the glottic axis.[3] No matter the patient's installation, the glottic's surface of obese subjects observed with videolaryngoscopy was greater using LPEC than CP. In addition, this setup does not bring about any change in the surface and shifts whether applying an external pressure or not while using videolaryngoscopy. Intubation could be less influenced by LPEC than CP. Finally, the patient's position may not have an impact on the larynx's mobility during these external esophagus compression techniques.

REFERENCE(S):

1. Gautier N, Danklou J, Brichant JF, Lopez AM, Vandepitte C, Kuroda MM, et al. The effect of force applied to the left paratracheal oesophagus on air entry into the gastric antrum during positive-pressure ventilation using a facemask. Anaesthesia. 2019;74(1):22-8.
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AIRWAY MANAGEMENT 35

Transmission Rates of COVID-19 between Patients and Healthcare Workers Performing Airway Management

Pooja Senthil[1], Amir Abrishami[2], Jean Wong[3]

[1]McMaster University, Hamilton, Canada, [2]McMaster University, Niagara Health, St. Catherine's , Canada, [3]University of Toronto, University Health Network, Toronto, Ontario

INTRODUCTION: With COVID-19 cases at their highest point in countries across the globe, there is an increasing number of patients who required hospitalization and mechanical ventilation. Due to the contagious nature of the virus, this brings an increased risk of transmission to healthcare workers (HCW), primarily to the anesthesiologists and those who perform airway management. We performed a systematic review of the literature to assess this risk and investigate which preventative measures can effectively limit the spread.

METHODS: Two databases, Embase and Medline, were searched electronically using the 'index terms' and 'free-text words' related to 'coronavirus,' 'healthcare personnel,' and 'airway management.' The literature search was performed from January 2019- February 2021. All observational studies that reported the rate of symptomatic and/or clinically proven COVID 19 (positive test result) among HCWs who were involved in airway management (e.g. tracheal intubation) of a COVID 19 patient were considered eligible for inclusion.

RESULTS: A total of 823 citations were screened and 5 studies met our inclusion criteria. This included a total of 2,143 health care personnel, all of whom worked closely with covid-19 patients during airway management. The data was primarily collected from China, Singapore and the USA, and one international study (17 countries). The duration, personal protective equipment (PPE), and infection rates of each study were complied (Table I). The overall rate of infection was 0-10.7%. When the healthcare personnel were equipped with adequate quantities of respiratory masks (N95 or surgical mask), gowns, eye protection, and gloves, the infection transmission rate was minimal. With additional shoe and hair covers (hoods), as well as an air-purifying respirator (25-43.5%), no transmission was reported. In hospitals that could not provide healthcare personnel with appropriate protection or those with staff who chose not to wear PPE reported greater positive test results.

CONCLUSION: Overall, these findings suggest that the use of appropriate PPE (mask, gloves, gown, and eye protection) is associated with decreased rate of transmission of COVID-19 between patients and healthcare workers performing airway management. More studies are needed to further evaluate the transmission risk specific to different type of PPE (e.g. N95 vs. surgical masks or air-purifying respirators)..

REFERENCE(S):

The COVID-19 intubation experience in Wuhan, 125, e25-e27, 2020. COVID-19 and the risk to health care workers: a case report, 172, 766-767, 2020. Acquired infection after intubating patients with COVID-19: A retrospective pilot study, 67, 110006, 2020.

Anesthesiologists' and intensive care providers' exposure to COVID-19 infection in a New York City academic center: a prospective cohort study assessing symptoms and COVID-19 antibody testing, 13, 669-676, 2020. Risks to healthcare workers following tracheal intubation of patients with COVID-19: a prospective international multicentre cohort study, 75, 1437-1447, 2020.

Transmission of COVID-19 to health care personnel during exposures to a hospitalized patient — Solano County, California, February 2020, 69,472-476, 2020.

Table I: Summary of collected data from all included studies.

Study ID	Country-Time	Follow up Duration	Setting	Type	No. of Infected HCWs (Rate%)	PPE
Yao et al. 2020	China (Wuhan) February - March 2020	14 days	hospital	retrospective case series	0/52 (0%)	Inner and outer gown with hood and shoe cover, double gloving, N95 respirator and standard surgical mask over N95, eye goggles and face shields, powered air- purifying respirator (25%)
Heinzerling et al. 2020	USA (California) February 2020	14 days	hospital	case report (index patient)	3/121 (2.48%)	**no** use of gowns, N95 respirators, powered air-purifying respirators (PAPRs), or eye protection some used gloves and masks
Ng et al., 2020	Singapore February 2020	14 days	hospital	case report	0/41 (0%)	N95 (15%) or surgical mask (85%)
Zhand et al., 2020	China (4 provinces)	n/a	hospital	retrospective survey	10/211 (4.74%)	n/a
Boghdadly et al., 2020	International (17 countries) March-June 2020	32 days (18-48 days)	hospital	prospective cohort	184/1718 (10.7%)	87.9% followed WHO-recommended PPE (N95 or equivalent mask, gown, gloves, eye protection, and powered air-purifying respirator (43.4%)

AIRWAY MANAGEMENT 35

Transmission Rates of COVID-19 between Patients and Healthcare Workers Performing Airway Management

Pooja Senthil[1], Amir Abrishami[2], Jean Wong[3]

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Subspecialty Abstracts

AMBULATORY ANESTHESIA

AMBULATORY ANESTHESIA 1

Postoperative Rescue Antiemetics in Adult Strabismus Surgery Under Combined Inhalational/ Intravenous vs Inhalational Anesthesia

Renan Ferrufino[1], Amr Jijakli[1], Adriana C Paz Mancia[1], Roman Schumann[2]

[1]Tufts Medical Center, Boston, MA, [2]VA Boston Healthcare System, Boston, MA

INTRODUCTION: Postoperative nausea and vomiting (PONV) approaches > 40% after strabismus surgery. The surgery type and extent are independent risk factors [1]. Anesthesia PONV risk factors are inhalational anesthetics, duration of anesthesia, postoperative opioid use, and nitrous oxide. Patient risk factors are female gender, PONV/motion sickness history, non-smoking and younger age[2]. To reduce PONV, a combination of inhalational anesthesia (IA) with a propofol infusion (CIIVA) may be beneficial because of propofol's antiemetic properties and a reduced IA dose while avoiding the higher cost of a total intravenous anesthetic. We hypothesized that CIIVA would reduce postoperative recovery room rescue antiemetic administration (PRAA) in patients undergoing strabismus surgery.

METHODS: Following IRB approval, we performed a retrospective study of adults undergoing outpatient strabismus surgery under general anesthesia with supraglottic airway management. Patients receiving CIIVA were compared to case matched IA controls. Matching included age, sex, BMI, ASA and tobacco use, type of strabismus surgery, intraoperative fluids, and nitrous oxide use. PRAA was the outcome of interest. Intra- and postoperative factors relevant to PONV were extracted. Analysis for categorical and continuous data was performed using the t-test, Chi-square test, Fisher's exact test, and the Wilcoxon rank sum test as appropriate.

RESULTS: Seventy IA patients were case matched with 55 CIIVA patients for study inclusion. Table 1 shows the patients' characteristics. A history of PONV was significantly more prevalent in the CIIVA compared to the IA group. The median Propofol infusion rate was 68 mcg/kg/min (range 5 – 175) with significantly less sevoflurane during longer anesthesia compared to controls. PRAA occurred in 7.2% of all patients. Significantly more intra- but fewer postoperative antiemetic administrations occurred in the CIIVA group (Table 2 and 3).

CONCLUSION: Antiemetic administration after strabismus surgery was infrequent (7.2%). Patients receiving a propofol infusion and inhalational anesthetic combination received significantly less postoperative antiemetics compared to controls. Intra- and postoperative MME administration was not different. Considering a higher PONV history prevalence and a longer anesthesia time in the CIIVA group, their Propofol infusion combined with a lower inhalational anesthesia dose and more intraoperative antiemetic administration was associated with less postoperative antiemetic administration compared to controls. A larger prospective study is justified to confirm these results, determine the most effective propofol infusion rate, and better control for confounding factors.

REFERENCE(S):

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Table 1: Baseline Characteristics

PARAMETER	IA n=70 n (%)	CIIVA n=55 n (%)	p-value
Age, years, mean (± SD)	48.33 (8.09)	48.55 (19.74)	0.95
Sex, n (%)			0.73
Female	49 (70)	36 (65)	
Male	21 (30)	19 (35)	
BMI (kg/m^2), mean (± SD)	25.9 (4.2)	27.5 (5.2)	0.064
Surgery Type, n (%)			0.67
Complex	28 (40)	25 (45)	
Simple	42(60)	30 (55)	
Surgery Side, n (%)			0.58
Bilateral	21 (30)	20 (36)	
Unilateral	49 (70)	35 (64)	
ASA Status, n (%)			>0.99
1	18 (26)	14 (25)	
2	38 (54)	30 (55)	
3	13 (19)	10 (18)	
4	1 (1.4)	1 (1.8)	
Smoking Status (+), n (%)	27 (39)	22 (40)	>0.99
History of Nausea/ Vomiting, n (%)	5 (7.1)	13 (24)	**0.019**

IA: Inhalational anesthesia, **CIIVA**: Combined inhalational and intravenous anesthesia, **SD:** standard deviation, **BMI:** body mass index

Table 2: Intraoperative PONV Factors

PARAMETER	IA n=70	CIIVA n=55	p-value
Anesthesia duration, minutes (range)	48 (22 – 169)	70 (22-196)	**0.025**
Sevoflurane maintenance, ET%, median (range)	1.25 (0.56 – 1.81)	0.95 (0.3-1.83)	< **0.001**
Number of antiemetics administered, median (range)	2 (1 – 4)	4 (2-6)	< **0.001**
N_2O, n (%)	23 (33)	21 (39)	0.67
$N_2O \geq$ 30 min, n (%)	19 (27.3)	13 (24)	0.25
Crystalloids, ml, mean (± SD)	660 (242)	677 (266)	0.86
MME mg, median (range)	10 (0 – 20)	10 (5-20)	0.99

PONV: Postoperative nausea and vomiting, **IA:** Inhalational anesthesia, **CIIVA**: Combined inhalational and intravenous anesthesia, **N_2O:** Nitrous oxide, **ml:** milliliters, **SD:** standard deviation, **MME:** Morphine milligram equivalents

Table 3: Postoperative

PARAMETER	IA n=70	CIIVA n=55	p-value
Antiemetic administered, yes, n (%)	8 (5.6)	1 (0.55)	0.076
Number of antiemetics administered, median (range)	0 (0-2)	0 (0-1)	**0.04**
MME mg, median (range)	0 (0-13.3)	0 (0-7.5)	0.16

IA: Inhalational anesthesia, **CIIVA**: Combined inhalational and intravenous anesthesia,
MME: Morphine milligram equivalents

AMBULATORY ANESTHESIA 2

Tonsillar hypertrophy is associated with perioperative complications in pediatric dental procedures under general endotracheal anesthesia

Audra Webber[1], Cynthia Wong[2], Cheol Choi[2], Changyong Feng[1], Stephen Brenemen[1], Shan Gao[1], Jennifer Gewandter[1]

[1]University of Rochester School of Medicine and Dentistry, Rochester, NY, [2]Eastman Institute for Oral Health, Rochester, NY

INTRODUCTION: General anesthesia (GA) is used in children undergoing comprehensive dental care when office based dentistry is not appropriate[1]. In our institution this is performed at both a freestanding ambulatory surgery center (ASC) and at the main hospital as an outpatient procedure. Appropriate patient selection for the ambulatory surgery center is vital to maintain both patient safety and workflow[2]. In general, American Society of Anesthesiologists (ASA) 1 and 2 patients are scheduled for the freestanding ambulatory center and ASA 3 and 4 patients for outpatient procedures at the main hospital. In addition to ASA status, patients with large tonsils (Brodsky Classification 3 or 4) are thought to have an increased risk of perioperative complications secondary to possible undiagnosed obstructive sleep apnea[3] and are excluded from the ambulatory center. These exclusion criteria led to a significant backlog of dental cases at the main hospital of more than 9 months. In contrast, the ASC had only a 3 month backlog. We undertook this analysis to determine what, if any, patient comorbidities were associated with adverse outcomes in our pediatric dental population. In doing so, we aimed to determine whether our exclusion criteria could be safely modified to allow more GA dental procedures to be scheduled at the ASC.

METHODS: A retrospective review of the electronic medical records of all ASA 1-3 pediatric patients (ages 2-17) having general anesthesia for dentistry at either the ambulatory surgery center or main hospital between June 2015 and March 2018 was undertaken. Age, race/ethnicity and gender distributions are shown in Table 1. All patients underwent inhalation induction and general endotracheal anesthesia with nasal intubation. Children with ASA 4 status or those who were undergoing extractions in preparation for cardiac surgery or who required a pediatric cardiac anesthesiologist were excluded from the analysis as they would be ineligible for the ASC regardless of outcome.

A patient was considered to have an adverse outcome if at least one of the following occurred:

1) documented laryngospasm,

2) documented bronchospasm

3) three or greater intubation attempts

4) intraoperative hypoxia SpO2 <90% lasting more than one minute

5) respiratory complications requiring intervention in the post anesthesia care unit (PACU) or

6) escalation of care/unplanned admission.

Independent variables analyzed included: age, sex, race/ethnicity, history of asthma, recent upper respiratory infection obesity (defined by BMI percentile >95% for age and sex), ASA status, and Brodsky tonsil size (0-2 versus 3-4).

RESULTS: Results: 1,777 patients were analyzed. 55 composite adverse outcomes were identified (3.1%). 41 patients experienced hypoxia, bronchospasm, and/or laryngospasm– 26 during induction/intubation, 12 during extubation and 3 intra-procedurally. Fourteen patients requiring 3 or more intubation attempts were identified. There were no PACU respiratory complications requiring intervention and no escalation of care/unplanned admissions. Univariate analyses and logistic regressions demonstrated tonsil size 3-4 (p=0.006), asthma (p=0.047), and recent URI (p=0.035) increased the risk of an adverse outcome. Of note, younger age, higher ASA status, and obesity/morbid obesity were not associated with the composite adverse outcome.

CONCLUSION: Asthma and upper respiratory infections have been previously demonstrated to be associated with perioperative complications during anesthesia and sedation[4,5]. While an association exists between tonsil size and obstructive sleep apnea[6], there has not been a study demonstrating an association between enlarged tonsils and increased risk of adverse outcome in pediatric dentistry performed under general endotracheal anesthesia. These data support the risk stratification of patients according to tonsillar hypertrophy when assessing likelihood of perioperative complications. However, it should be noted that while statistically significant, all of the composite adverse outcomes were managed without the need for escalation of care or admission, and no patient had respiratory issues in PACU.

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Categorical Variables	Category	Total N(%)
Age Categories	2-3yo	314 (17.67%)
	4-6yo	1135 (63.87%)
	7-17yo	328 (18.46%)
Sex	Female	790 (44.46%)
	Male	987 (55.54%)
Race Ethnicity	White	690 (38.83%)
	Black	465 (26.17%)
	Other	416 (23.41%)
	Hispanic/Latino	206 (11.59%)
Tonsil size	...missing	264
	Tonsil Size 0-2	1170 (77.33%)
	Tonsil Size 3-4	343 (22.67%)
ASTHMA	No	1438 (80.92%)
	Yes	339 (19.08%)
URI	No	1547 (87.06%)
	Yes	230 (12.94%)
Obese	0-94%	1440 (81.04%)
	95%-98%	186 (10.47%)
	99%+	151 (8.50%)
ASA_STATUS	1	929 (52.28%)
	2	727 (40.91%)
	3	118 (6.64%)

Table 1. Independent variables

AMBULATORY ANESTHESIA 3

Early Outcomes of Super Morbid Obese compared to Morbid Obese Patients after Ambulatory Surgery under General Anesthesia: A Propensity Matched Analysis of a National Database

Sherine Hajmohamed[1], Deeran Patel[1], Gildasio S DeOliveira[1], Mark C Kendall[1], Patricia Apruzzese[2]

[1]Alpert Medical School of Brown University, Providence, RI, [2]Lifespan Hospital, Providence, RI

INTRODUCTION: Obesity has become increasingly common in the United States affecting more than 35% of American adults.[1] Patients with BMI greater than 50 kg/m^2, defined as super morbid obesity, represent the fastest growing segment of patients with obesity in the United States.[2,3] Several studies have demonstrated that obese patients are at a greater risk of poor surgical outcomes compared to non-obese patients including: (1) wound infection, (2) longer operative time, and (3) postoperative cardiopulmonary complications.[4,5] Nonetheless, few studies have evaluated postoperative outcomes in patients with super morbid obesity. It is currently unknown if super morbid obese patients are at greater risk than morbid obese patients for poor outcomes after outpatient surgery. The main objective of the current investigation is to determine if super morbid obese patients are at increased risk for postoperative complications after outpatient surgery when compared to morbid obese patients. We hypothesized that super morbid obese patients would be at significantly greater risk of postoperative complication. In addition, we sought to determine if the risk varied across different specialties.

METHODS: The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database from 2017-2018 was queried to extract patients defined as super morbid obese (BMI ≥50 kg/m2) who underwent outpatient surgery. Body mass index (kg/m2) was the primary independent variable of interest and it was categorized as morbid obesity (BMI ≥ 40kg/m2 and less than 50 kg/m2) or super morbid obesity (BMI≥50 kg/m2).12,13 The primary outcome was any early (72 hours) medical complications or surgical complication. Medical complications included: (1) deep vein thrombosis, (2) pulmonary embolism, (3) unplanned intubation, (4) failure to wean from ventilator, (5) renal insufficiency, (6) renal failure, (7) stroke/CVA, (8) cardiac arrest, (9) myocardial infarction, (10) pneumonia, (11) urinary tract infection, (12) systemic sepsis or (13) septic shock, (14) bleeding, and (15) death. Surgical complications included: (1) surgical site infection (superficial SSI, deep incisional SSI, organ space SSI), (2) wound dehiscence, Mortality, readmissions, and return to the operating room were also evaluated as separate outcomes of interest. A propensity matched analysis was used to evaluate the association of BMI ≥50 kg/m2 and the outcomes.

RESULTS: A total of 661,729 outpatient surgeries were included in the 2017-2018 NSQIP database. Of those, 7160 with a BMI ≥50 kg/m2 were successfully matched to 7160 with a BMI <50 kg/m2 and ≥ 40 kg/m2. After propensity matching, 29 out of 7160 super morbid obese patients had any three-day complication compared to 27 out of 7160 morbid obese patients, P=0.86. The rate of three day medical and surgical complications in super morbid obese patients was very similar to morbid obese patients. 35 out of 7160 super morbid obese patients were readmitted within 3 days, compared to 33 out of 7160 morbid obese patients, P=0.86. When evaluated in a multivariate analysis, BMI ≥ 40 kg/m2 was not significantly associated with any complication, OR (95% CI) of 1.00 (0.98 to 1.03), P= 0.47, overall surgical complication, OR (95% CI) of 1.02 (0.98 to 1.06), P=0.23 and readmissions, OR (95% CI) of 0.99 (0.97 to 1.02), P=0.8.

CONCLUSION: The most important finding of the current investigation was the lack of differences in early surgical and medical complications when super morbid obese patients undergoing outpatient surgery were compared to morbid obese patients. Specifically, early pulmonary complications were very low after outpatient surgery. After propensity matching to adjust for imbalances in potential covariates, we did not detect any outcome difference between the two groups. In addition, BMI ≥40 kg/m2 was not a significant independent predictor for early adverse outcomes in a multivariate analysis. Taken together, our results suggest that BMI alone should not be used as a cutoff for selection of patients undergoing ambulatory surgery.

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Table1. Patient Outcomes following procedure
MATCHED COHORT
BMI>50 vs BMI 40-50 (events in 3 days)

	BMI 40-50	BMI >50	Difference (95% CI)	Odds Ratio (95% CI)	P-value	False Discovery Rate
Any 3-day complication	0.38% (2/T160)	0.41% (2/T160)	0.03%[-0.18%,0.23%]	1.07[0.64,1.82]	0.709	0.8649
Overall surgical complication	0.17% (1/2/T160)	0.21% (1/5/T160)	0.04%[-0.10%,0.18%]	1.25[0.58,2.67]	0.564	0.8643
SSI	0.14% (1/0/T160)	0.15% (1/1/T160)	0.01%[-0.11%,0.14%]	1.10[0.47,2.59]	0.827	0.8649
Superficial SSI	0.06% (0/T160)	0.15% (1/T160)	0.01%[-0.08%,0.11%]	1.17[0.39,3.47]	0.782	0.8649
Deep incisional SSI	0.03% (2/T160)	0.06% (4/T160)	0.03%[-0.04%,0.09%]	2.00[0.37,10.93]	0.414	0.7326
Organ/space SSI	0.03% (2/T160)	0.00% (0/T160)	-0.03%[-0.07%,0.01%]	–	0.157	0.6635
Wound dehiscence	0.03% (2/T160)	0.06% (4/T160)	0.03%[-0.04%,0.09%]	2.00[0.37,10.93]	0.414	0.7326
Overall medical complication	0.21% (1/5/T160)	0.24% (1/7/T160)	0.03%[-0.13%,0.18%]	1.13[0.57,2.27]	0.724	0.8649
Pneumonia	0.06% (4/T160)	0.07% (5/T160)	0.01%[-0.07%,0.10%]	1.25[0.34,4.66]	0.739	0.8649
Unplanned intubation	0.01% (1/T160)	0.00% (0/T160)	-0.01%[-0.04%,0.01%]	–	0.317	0.6635
VTE	0.03% (2/T160)	0.00% (0/T160)	-0.03%[-0.07%,0.01%]	–	0.157	0.6635
Deep vein thrombosis	0.03% (2/T160)	0.00% (0/T160)	-0.03%[-0.07%,0.01%]	–	0.157	0.6635
Pulmonary embolism	0.01% (1/T160)	0.00% (0/T160)	-0.01%[-0.04%,0.01%]	–	0.317	0.6635
Failure to wean	0.00% (0/T160)	0.00% (0/T160)	0.00%[...]	–		
Progressive renal insufficiency	0.01% (1/T160)	0.00% (0/T160)	-0.01%[-0.04%,0.01%]	–	0.317	0.6635
Acute renal failure	0.01% (1/T160)	0.00% (0/T160)	-0.01%[-0.04%,0.01%]	–	0.317	0.6635
Urinary tract infection	0.07% (5/T160)	0.07% (5/T160)	0.00%[-0.09%,0.09%]	1.00[0.29,3.46]	1.000	1.0000
Stroke/cerebrovascular accident	0.00% (0/T160)	0.00% (0/T160)	0.00%[...]	–		
Cardiac arrest	0.00% (0/T160)	0.03% (2/T160)	0.03%[-0.01%,0.07%]	–	0.157	0.6635
Myocardial infarction	0.00% (0/T160)	0.00% (0/T160)	0.00%[...]	–		
Bleeding	0.01% (1/T160)	0.07% (5/T160)	0.06%[-0.01%,0.12%]	5.00[0.58,42.83]	0.102	0.6635
Sepsis/Septic shock	0.01% (1/T160)	0.04% (3/T160)	0.03%[-0.03%,0.08%]	3.00[0.31,28.86]	0.317	0.6635
Sepsis	0.01% (1/T160)	0.04% (3/T160)	0.03%[-0.03%,0.08%]	3.00[0.31,28.86]	0.317	0.6635
Septic shock	0.00% (0/T160)	0.00% (0/T160)	0.00%[...]	–		
Death	0.01% (1/T160)	0.03% (2/T160)	0.01%[-0.03%,0.06%]	2.00[0.18,22.06]	0.564	0.8643
Readmission	0.48% (3/T160)	0.49% (3/T160)	0.01%[-0.29%,0.25%]	1.00[0.66,1.71]	0.888	0.8649
Return to the operating room	0.13% (0/T160)	0.15% (1/T160)	0.02%[-0.08%,0.15%]	1.22[0.51,2.89]	0.655	0.8649

AMBULATORY ANESTHESIA 4

Intrathecal morphine does not increase POUR in joint Arthroplasty surgeries. A double blind RCT

Naveed Siddiqui[1], Muhammad Imran Khan[2], Yehoshua (Josh) Gleicher[2], Shiva Khandadashpoor[2], David Backstein[2], Ashok Kumar Jayaraj[2]

[1]University of Toronto, Toronto, Ontario, [2]Mount Sinai Hospital, Toronto, Canada

INTRODUCTION: The changing health economy has driven the need for greater patient throughput, rapid turnover, and shorter hospital stays whilst retaining high-quality medical care. The use of intrathecal opioids has become a widely accepted technique for providing effective postoperative pain relief in joint arthroplasty surgeries[1]. However, intrathecal morphine (ITM) has its own adverse effects including urinary retention and delayed respiratory depression[2]. Postoperative urinary retention (POUR) is one of the main reasons for the delayed discharge following hip and knee arthroplasties. Early removal is important, as a risk of UTI is reported to rise 5% for each day a urinary catheter remains in situ[3]. Avoiding intrathecal morphine would benefit patients by decreasing complications associated with prolonged catheterization such as urinary tract infection and improve cost-effectiveness through the early discharge of patients[4]. Our aim was to evaluate, whether removing the intrathecal morphine would facilitate early removal of urinary catheters and earlier discharge from the hospital.

METHODS: A prospective, double-blind, randomized controlled trial of 134 patients who are 18 to 85 years old, with BMI 18 to 40 and undergoing elective primary as well as revision knee and hip arthroplasty under regional anesthesia was conducted. Patients were excluded if they had a language barrier, prior history of urinary retention, or BPH. Intra-operatively, patients received intrathecal morphine 100 mcg (group A) or saline (group B) in addition to the standard dose of bupivacaine and 15 mcg of fentanyl. None of these patients were catheterized. If they were unable to urinate, an in and out was performed according to preset ultrasound bladder residual volumes. Post-operatively, data collection includes the time of in and out catheterization, Post-op pain, opioids side effects, and hospital length of stay.

RESULTS: 112 out of 134 patients were recruited, with 99 completing the study, of which 66 underwent knee surgery and 33 underwent hip surgery. Both groups; A (ITM) and B (Non-ITM) were similar at baseline. The use of ITM was found to significantly reduce the length of hospital stay at 48 hours post-operatively (with the Difference (95%CI) in the median of -15.3 (-29.9, -0.71) and p-value of 0.04). There was no significant difference in the incidence of opioid-related side effects, duration of bladder catheterization, and the requirement for In & Out catheterizations, pain score, and patient satisfaction between the two groups.

CONCLUSION: The results of our study show that the traditional use of ITM in joint arthroplasties significantly reduces hospital length of stay. It does not increase the incidence of opioid-related side effects, duration of bladder catheterization, and the requirement for In & Out, patient satisfaction, and pain score measured at rest and movement. The use of Intrathecal Morphine in the context of Fast Track Knee and Hip Arthroplasty is still a useful modality.

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Intrathecal morphine does not increase POUR in joint Arthroplasty surgeries. A double blind RCT.

Table 1. Baseline characteristics

Characteristics	ITM	Non-ITM
# Patients	48	51
Age, median (IQR)	67 (60, 74)	68 (60, 74)
BMI, mean (SD)	29.8 (4.3)	31.8 (5.4)
Male, %(n)	52.1 (25)	52.9 (27)
ASA, %(n)	52.1 (25)	60.8 (31)
Surgery type (TKA), %(n)	75.0 (36)	58.8 (30)
Highest Bupivacaine, %(n)	37.5 (18)	33.3 (17)
Pain score at rest on screening day, median(IQR)	2.0 (0, 4)	1 (0, 3)
Pain score at movement on screening day, median (IQR)	6 (4, 8)	6 (5, 8)

Table 2(a). Comparison of outcomes

Outcomes	ITM	Non-ITM	Difference (95%CI)*	p-values*
# Patients	48	51	(ITM vs Non-ITM)	
Length of hospital stay (hrs.), median(IQR)	28 (23.4, 48)	43 (23.2, 68.5)	-15.3 (-29.9, -0.71)	0.04
Satisfaction, median (IQR)	6 (5, 6)	6 (5, 6)	0 (-0.47, 0.47)	0.99
First In&out Catheterization needed (hrs.) %(n)	37.5 (18)	35.3 (18)	2.2 (-16.8, 21.2)	0.81
Second In&out Catherization needed, %(n)	8.3 (4)	3.9 (2)	4.4 (-5.1, 13.9)	0.36
Catheter duration, (hrs.) %(n/N)	16.7 (3/18)	27.8 (5/18)	-11.1 (-38.0, 15.8)	0.41
VASm24	4.5 (3, 8)	6 (3, 7)	-1.0 (-3.10, 1.10)	0.35
VASm36	6 (5, 8)	6 (5, 7)	0.0 (-1.44, 1.44)	0.99
VASm48	7 (5, 8)	6 (5, 7)	1.0 (-1.32, 3.32)	0.39
VASr24	3 (1, 5)	3 (1, 5)	0.0 (-1.70, 1.70)	0.99
VASr36	4.5 (2, 6)	3 (2, 4)	1.0 (-0.98, 2.98)	0.32
VASr48	4 (3, 6)	2 (1, 3)	2.0 (0.73, 3.27)	0.002

Table 2(b)

Outcomes	ITM	Non-ITM	Difference (95%CI)*	p-values*
# Patients	18	18	(ITM vs Non-ITM)	
Time to first in&out Catheterization (hrs.), median (IQR)	6.48 (4.80, 9.75)	6.03 (5.0, 6.80)	0.33 (-1.69, 2.35)	0.74

Intrathecal morphine does not increase POUR in joint Arthroplasty surgeries. A double blind RCT.

Table 3. outcomes

	Baseline (at Screening day)			Post surgery period		
Side-effect	ITM (48)	Non-ITM (51)		ITM (48)	Non-ITM (51)	p-value
Nausea, %(n/N)	0 (0/48)	0 (0/51)		18.75 (9/48)	17.65 (9/51)	0.89
Vomiting, %(n/N)	2.08 (1/48)	0 (0/51)		4.17 (2/48)	0 (0/51)	0.23
Constipation, %(n/N)	6.25 (3/48)	5.88 (3/51)		14.58 (7/48)	7.84 (4/51)	0.29
Difficulty passing urine, %(n/N)	2.08 (1/48)	0 (0/51)		12.5 (6/48)	11.76 (6/51)	0.91
Concentration difficulty, %(n/N)	4.17 (2/48)	0 (0/51)		6.25 (3/48)	7.84 (4/51)	0.99
Drowsiness, %(n/N)	4.17 (2/48)	0 (0/51)		8.33 (4/48)	5.88 (3/51)	0.71
Dizziness, %(n/N)	0 (0/48)	0 (0/51)		22.92 (11/48)	27.45 (14/51)	0.6
Confusion, %(n/N)	0 (0/48)	1.96 (1/51)		6.25 (3/48)	1.96 (1/51)	0.35
Fatigue, %(n/N)	4.17 (2/48)	9.8 (5/51)		25 (12/48)	15.69 (8/51)	0.25
Itchiness, %(n/N)	4.17 (2/48)	5.88 (3/51)		39.58 (19/48)	23.53 (12/51)	0.08
Dry mouth, %(n/N)	12.5 (6/48)	11.76 (6/51)		45.83 (22/48)	47.06 (24/51)	0.9
Headache, %(n/N)	6.25 (3/48)	3.92 (2/51)		10.42 (5/48)	13.73 (7/51)	0.61
Any side-effect, %(n/N)	33.33 (16/48)	29.41 (15/51)		75 (36/48)	68.63 (35/51)	0.48

Subspecialty Abstracts

ANESTHETIC PHARMACOLOGY

ANESTHETIC PHARMACOLOGY 1

Association between administration of gabapentin or pregabalin before surgery and 30-day hospital readmission: A retrospective hospital registry study

Luca J Wachtendorf[1], Maximilian S Schaefer[2], Peter Santer[3], Omid Azimaraghi[4], Salameh S Obeidat[5], Sabine Friedrich[6], Liana Zucco[3], Albert Woo[5], Sarah Nabel[3], Eswar Sundar[5], Matthias Eikermann[7], Satya Krishna Ramachandran[8]

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [2]Beth Isreal Deaconess Medical Center, Boston, United States of America, [3]Beth Israel Deaconess Medical Center, Boston, MA, [4]Beths Israel Deaconess Medical Center, Harvard Medical School, Boston, United States of America, [5]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, United States of America, [6]Massachusetts General Hospital, Boston, MA, [7]Beth Israel Deaconess Medical Center, Boston, United States of America, [8]Harvard Medical School, Boston, MA

INTRODUCTION: Equivocal data is presented on the use of gabapentinoids before surgery. We hypothesized that gabapentinoid administration before surgery is associated with decreased hospital readmissions due to lower intraoperative opioid utilization.

METHODS: 111,008 adult patients undergoing non-cardiac surgery between 2014 and 2018 at Beth Israel Deaconess Medical Center (Boston, MA, USA) were included. The primary exposure was gabapentinoid administration (gabapentin/pregabalin) before surgery. The primary outcome was hospital readmission within 30 days after surgery. We tested the co-primary hypothesis that lower intraoperative opioid utilization mediated the effect of gabapentinoid administration on readmission.

RESULTS: Gabapentinoid administration was associated with lower odds of readmission (adjusted odds ratio [ORadj] 0.80; 95%CI 0.75–0.85;p<0.001). This effect was mediated by lower intraoperative opioid utilization in patients receiving gabapentinoids (8.15%; 95% CI 2.40–11.47%;p=0.012). Readmissions for gastrointestinal disorders (ORadj 0.74; 95%CI 0.60–0.90;p=0.003), neuro-psychiatric complications (ORadj 0.66; 95%CI 0.49–0.87;p=0.004), non-surgical site infections (ORadj 0.68; 95%CI 0.52–0.88;p=0.004) and trauma or poisoning (ORadj 0.25; 95%CI 0.16–0.41; p<0.001) occurred less frequently in patients receiving gabapentinoids. The risk of postoperative respiratory complications was lower in patients receiving gabapentinoids (ORadj 0.77; 95%CI 0.70–0.85;p<0.001). In contrast to low and moderate doses, high-dose gabapentinoids were not associated with lowered readmission rates (ORadj 0.88; 95%CI 0.76–1.01;p=0.069) and decreased risks of postoperative complications (ORadj 0.87; 95%CI 0.72–1.07 p=0.185).

CONCLUSION: Administration of low and moderate gabapentinoid doses before surgery is associated with decreased hospital readmission. This effect was in part mediated by lower intraoperative opioid utilization.

ANESTHETIC PHARMACOLOGY 2

Ideal Body Weight - Based Remimazolam Infusion Is Sufficient in Mildly Obese Patients

Hiroshi Sakamoto[1]

[1]*Shin Sapporo Orthopaedic Hospital, Sapporo, Hokkaido*

INTRODUCTION: A long-awaited ultra-short acting benzodiazepine, Remimazolam (RZ), was marketed last August in Japan. Its recommended maintenance dose is 1 mg/kg/h based on total body weight (TBW). In most anesthetics, dosing for obese patients should not be based on their TBW.[1] We compared the effect of RZ in mildly obese patients based on ideal body weight (IBW) with that based on TBW.

METHODS: After obtaining IRB and patients' informed consent, 32 patients undergoing scheduled orthopedic surgery with body mass index (BMI) > 25 were enrolled in this study. Patients were randomly divided into 2 groups. In TBW group, RZ maintenance dose, 1 mg/kg/h, is calculated based on TBW. In IBW group, it is calculated based on IBW. IBW = 45.4+0.98×(height(cm)-152.4) and if male add 4.5.

General anesthesia was maintained with RZ and remifentanil 0.1 μg/IBW/min and nerve blocks were performed. 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 RZ infusion. Patients' demographic data were compared using unpaired t-test and PSI was compared using Mann - Whitney's U-test. A *p*-value < 0.05 was considered statistically significant.

RESULTS: Results are shown in tables. Patients' demographic data showed no significant difference. PSI showed significant difference. In this study, mild obese patients were involved. BMI of TBW group ranges from 25.1 to 34.2 and that of IBW group ranges from 25.3 to 36.6. PSI was significantly different between TBW group and IBW group. But PSI ranges from 24 to 51 in TBW group and from 24 to 50 in IBW group. That means anesthesia.

CONCLUSION: Anesthesia with RZ maintenance dose based on IBW is sufficient in obese patients.

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

group	Demographic data				
	M/F	age (y.o.)	height (cm)	TBW (kg)	BMI (kg/m²)
TBW	11 / 8	59.7 ± 15.0 [21 – 74]	164.8 ± 10.3 [147 – 184]	76.4 ± 7.6 [65 – 89]	28.2 ± 2.5 [25.1 – 34.2]
IBW	8 / 5	50.6 ± 15.9 [19 – 72]	163.8 ± 9.6 [148 – 175]	77.9 ± 11.3 [60 – 102]	29.0 ± 3.6 [25.3 – 36.6]
p		0.116	0.793	0.685	0.485

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

group	Demographic data			PSI during Remimazolam Infusion
	Duration of Anesthesia (minute)	Duration of Surgery (minute)	Duration of Remimazolam Infusion (minute)	
TBW	119 ± 48 [52 – 201]	76 ± 41 [22 – 144]	88 ± 41 [35 – 158]	38.0 ± 7.2 [24 – 51]
IBW	119 ± 54 [41 – 213]	71 ± 50 [10 – 149]	93 ± 55 [21 – 200]	37.0 ± 6.2 [24 – 50]
p	0.976	0.766	0.753	**0.000**

ANESTHETIC PHARMACOLOGY 3

Intravenous vs volatile anesthesia and colorectal cancer surgery outcome—a systematic review and meta-analysis

Zhaosheng Jin[1], Ru Li[1], Jun Lin[2]

[1]Stony Brook Medicine, Stony Brook, NY, [2]Stony Brook University Health Sciences Center, Stony Brook, NY

INTRODUCTION: Colorectal cancer is common in the US and contributes to a significant proportion of cancer related mortality. Several in vitro studies in recent years have suggested that anesthetic agent can alter the cancer cell phenotype or the immune system handling of cancer cells[1-5]. In this systematic review we will investigate if the choice of intravenous anesthesia (TIVA) or volatile anesthesia (VA) during surgery affects the outcome after colorectal cancer surgery.

METHODS: We systematically searched PubMed, Central, EMBASE, CINAHL, Google Scholar, Web of Science citation index for clinical studies comparing the two anesthesia techniques. From each included study, we extracted the mortality, recurrence and recurrence free survival rate.

RESULTS: The last search was conducted on Jan 10th, 2021. We identified a total of 4 studies comparing TIVA to VA in colon cancer surgery. All 4 studies reported the mortality rate (after 2-5 year follow up), meta-analysis did not report significant difference in all-cause mortality between TIVA and VA [Hazard ratio 0.76 (0.54-1.08)] (Fig. 1). Two studies reported the rate of recurrence, with no significant difference between TIVA and VA: 0.80 (0.58-1.09). Two studies reported the rate of recurrence free survival, which also showed no significant difference: 1.02 (0.91-1.15) (Fig. 2).

CONCLUSION: Our systematic review suggests that the choice of anesthesia does not appear to affect the outcome after colorectal surgery. This contrasts with earlier studies which showed a protective effect of TIVA in other surgery types. The reliability of the conclusion is limited by the number of included studies. More studies are needed for more reliable evidence, and the difference between cancer sites should be investigated.

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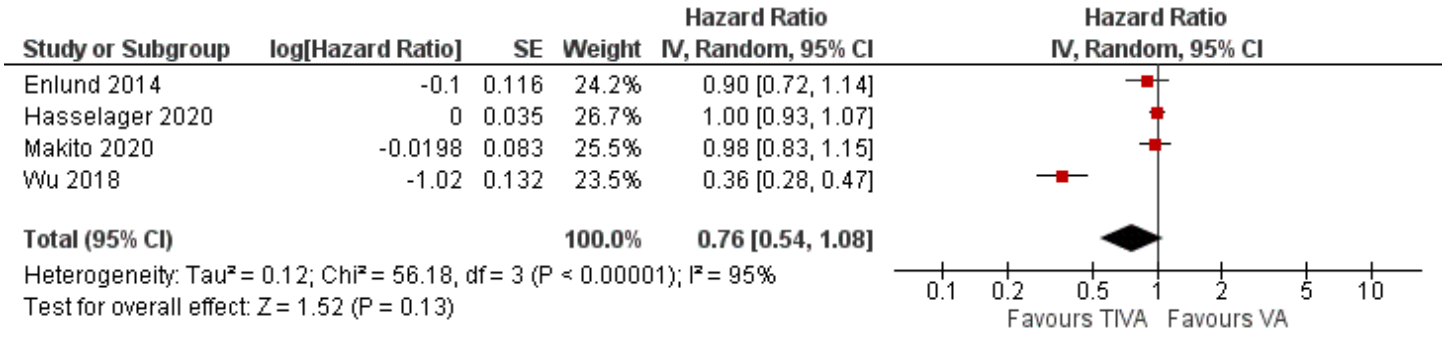

Fig. 1

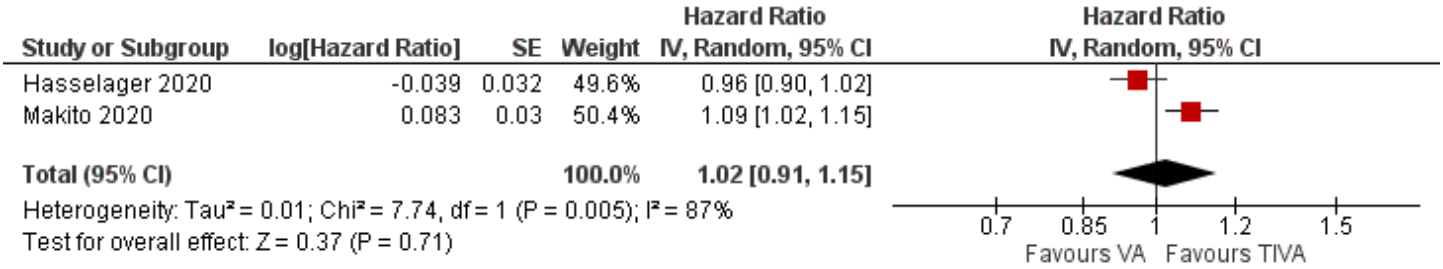

Fig. 2

ANESTHETIC PHARMACOLOGY 4

Pursuing the Next Generation of Anesthetic and Anticonvulsant Compounds

Edward J Bertaccini[1], Frances Davies[2], Alam Jahangir[3], Hilary McCarren[4], Rachel K Lam[5], Mehrdad Shamloo[6], Noelie Cayla[5], Bruce Maciver[2]

[1]Stanford University School of Medicine and Palo Alto VA HCS, Palo Alto, CA, [2]Stanford University School of Medicine, Stanford, CA, [3]Stanford Univeristy, Stanford, CA, [4]United States Army, Kennett Square, PA, [5]Stanford University, stanford, CA, [6]Stanford University, Stanford, CA

INTRODUCTION: All currently used intravenous anesthetic agents are associated with an entire spectrum of undesirable side effects, most notably cardiovascular and respiratory depression. Such effects are poorly tolerated in many patients without expert intervention, but especially in very young children who possess immature physiologic compensatory mechanisms, as well as in the elderly with confounding comorbidities and otherwise exhausted physiologies. In light of this, we have pursued the development of new lead compounds to produce the next generation of safer anesthetic agents. We have additionally tested their antiepileptic action against seizures produced by the nerve gas soman (180 mg/kg) for potential battlefield applications as not only a stable anesthetic for trauma but also as an antidote to seizures induced by organophosphate-based chemical weapons.

METHODS: Due to space constraints Method details are merely outlined here. The details of the Methods for in silico molecular screening, tadpole in vivo testing, rat in vivo testing for loss of righting reflex and physiologic measurements, hippocampal slice electrophysiology are as noted in references 2 and 4. Specific ion channel profiling was carried out by the Eurofins Corporation according to published Fluxion protocols. The protocols for experimentation involving soman gas as a chemical weapon were carried out by the United States Army Medical Research Institute and are officially classified information that is not available for public viewing.

RESULTS: Our methodologies of in silico screening and prediction of compounds which bind to our validated model of the gamma amino butyric acid type A receptor (GABAAR) have now identified a novel class of lead compounds which demonstrate overt anesthetic and anticonvulsant activity (Figure 1).[1,2,3] The most recent within our series is KSEB 01-1 which anesthetizes both tadpoles (EC50= 0.96 μM) and male Sprague Dawley rats (ED50= 2.2 mg/kg) with a potency greater than that of propofol, the current intravenous anesthetic standard. KSEB 01-1 also increases Cl- flux in cells transfected with alpha1/beta2/gamma2 receptor subunits (Figure 2). These structures are devoid of the imidazole nitrogen known to produce adrenal suppression which commonly occurs with etomidate (Figure 1). In hippocampal slice preparations, KSEB 01-1 shows potent paired-pulse inhibition which is consistent with its unique suppression of the GABAAR 'slow' receptor subtype (Figure 3). Of even greater importance is the fact that our new class of compounds shows minimal to no suppression of blood pressure, respiratory rate (Figure 4), or other respiratory parameters (O2, CO2, pH), in stark contrast to the deleterious effects of propofol on these parameters. Further, IV administration (Figure 5) suppresses seizures tin rats exposed to chemical weapons at a dose between 2.5-5 mg/kg. While much higher doses of KSEB 01-1 can be proconvulsant, this effect can be successfully blunted with co-administration of midazolam (Figure 6) at a dose that also does not suppress breathing.

CONCLUSION: We have now refined the latest lead compound in our new class of agents to enhance its solubility while maintaining the desirable anesthetic and anticonvulsant characteristics without significant hemodynamic or respiratory suppression. These compounds are derived from novel chemical structures not previously associated with or known to produce significant anesthetic effect.[3] This class of compound will have ready application as an anesthetic in any patient with the potential for such physiologic instabilities and, through its GABAAR mechanism, provide a stable means of acute and possibly chronic seizure suppression especially as related to chemical weapons and other battlefield scenarios.

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4. Davies MF, Jahangir A, Shamloo M, Lam RK, McCarren HS, Barker BS, Bertaccini EJ, "Development of a next generation of GABAergic compounds for anesthesia and epilepsy," 2019 Annual Meeting of the Society for Neuroscience, poster 645.02 / B43.

Pursuing the next Generation of Anesthetic and Anticonvulsant Compounds

Edward J. Bertaccini[1,2,5], M. Frances Davies[1,2], Alam Jahangir[4], Hilary S.Mccarren[3], Bryan Barker[3], Rachel K. Lam[4], Mehrdad Shamloo[4,5] , Noelie S. Cayla[2], M Bruce MacIver[2]

[1]*Department of Anesthesia, Stanford University School of Medicine, Stanford, CA, USA*
[2]*Palo Alto VA Health Care System, Palo Alto, CA, USA*
[3]*USAMRICD, US Army Medical Research Institute of Chemical Defense*
[4]*Department of Neurosurgery, , Stanford University School of Medicine, Stanford, CA, USA*
[5]*SPARK Drug Discovery Scholars Program and Child Health Research Institute at Stanford*

Introduction: All currently used intravenous anesthetic agents are associated with an entire spectrum of undesirable side effects, most notably cardiovascular and respiratory depression. Such effects are poorly tolerated in many patients without expert intervention, but especially in very young children who possess immature physiologic compensatory mechanisms, as well as in the elderly with confounding comorbidities and otherwise exhausted physiologies. In light of this, we have pursued the development of new lead compounds to produce the next generation of safer anesthetic agents. We have additionally tested their antiepileptic action against seizures produced by the nerve gas soman (180 mg/kg) for potential battlefield applications as not only a stable anesthetic for trauma but also as an antidote to seizures induced by organophosphate-based chemical weapons.

Methods and Results: Our methodologies of in silico screening and prediction of compounds which bind to our validated model of the gamma amino butyric acid receptor ($GABA_AR$) have now identified a novel class of lead compounds which demonstrate overt anesthetic and anticonvulsant activity (Figure 1).[1,2,3,4] The most recent within our series is KSEB 01-1 which anesthetizes both tadpoles (EC_{50}= 0.96 µM) and male Sprague Dawley rats (ED_{50} = 2.2 mg/kg) with a potency greater than that of propofol, the current intravenous anesthetic standard. KSEB 01-1 also increases Cl^- flux in cells transfected with alpha1/beta2/gamma2 receptor subunits (Figure 2). These structures are devoid of the imidazole nitrogen known to produce adrenal suppression which commonly occurs with etomidate (Figure 1). In hippocampal slice preparations, KSEB 01-1 shows potent paired-pulse inhibition which is consistent with its unique suppression of the $GABA_AR$ "slow" receptor subtype (Figure 3). Of even greater importance is the fact that our new class of compounds shows minimal to no suppression of blood pressure, respiratory rate (Figure 4), or other respiratory parameters (O_2, CO_2, pH), in stark contrast to the deleterious effects of propofol on these parameters. Further, IV administration (Figure 5) suppresses seizures in rats exposed to chemical weapons at a dose between 2.5-5 mg/kg. While much higher doses of KSEB 01-1 can be proconvulsant, this effect can be successfully blunted with co-administration of midazolam (Figure 6) at a dose that also does not suppress breathing.

Conclusion: We have now refined the latest lead compound in our new class of agents to enhance its solubility while maintaining the desirable anesthetic and anticonvulsant characteristics without significant hemodynamic or respiratory suppression. These compounds are derived from novel chemical structures not previously associated with or known to produce significant anesthetic effect.3 This class of compound will have ready application as an anesthetic in any patient with the potential for such physiologic instabilities and, through its $GABA_AR$ mechanism, provide a stable means of acute and possibly chronic seizure suppression.

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3. Bertacccini EJ, Davies MF: Methods, Compounds and Compositions for Anesthesia. Edited by Office USP. United States of America, The Board of Trustees of the Leland Stanford Junior University and The United States Government as represented by the Department of Veterans Affairs, 2019
4. Davies MF, Jahangir A, Shamloo M, Lam RK, McCarren HS, Barker BS, Bertaccini EJ, "Development of a next generation of GABAergic compounds for anesthesia and epilepsy," 2019 Annual Meeting of the Society for Neuroscience, poster 645.02 / B43

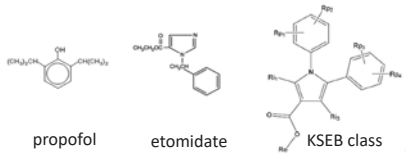


Fig. 1: Chemical structures of two commonly used anesthetics, propofol and etomidate, in comparison to our new agent class.

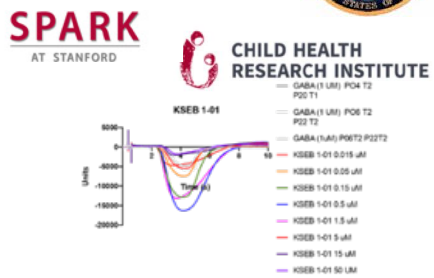


Fig. 2: In HEK 293 cells transfected with $GABA_AR$ ($\alpha1\beta2\gamma2$) KSEB 01-1 potentiated the maximal GABA response and lengthened its duration. Higher concentrations of KSEB 01-1 suppressed the GABA response but did not eliminate it.

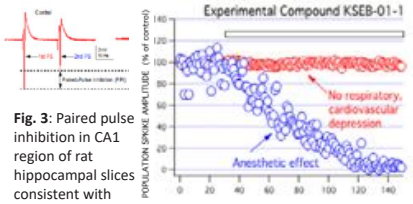


Fig. 3: Paired pulse inhibition in CA1 region of rat hippocampal slices consistent with $GABA_AR$ slow subtype potentiation.

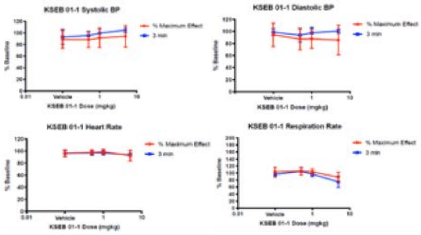


Fig. 4: Hemodynamic profiling for KSEB 01-1 in rats. Note the ED_{50} for LORR is 0.2.2 mg/kg and the lack of significant effects on hemodynamics or respiration.

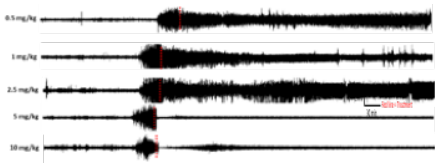


Fig. 5: Varied doses of KSEB 01-1 in combination with standard atropine/midazolam for seizure (induced by soman gas) cessation in rats after ***intravenous*** injection and its antiepileptic action against seizures produced by soman (180 µg/kg). Note that its ED_{50} for LORR is 2.2 mg/kg and seizure cessation occurred between 2.5 and 5 mg/kg.

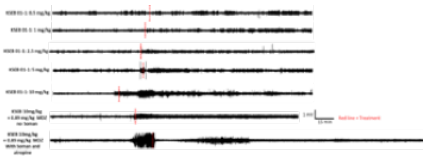


Fig. 6: The effect of KSEB 01-1 on EEG activity in rats given IV KSEB 01-1 in varied doses. By itself KSEB 01-1 induced tonic-clonic EEG spike activity at doses around 10mg/kg. When combined with 0.89 mg/kg midazolam the 10 mg/kg KSEB 01-1 induced tonic-clonic activity subsides and EEG spike activity is blunted.

ANESTHETIC PHARMACOLOGY 5

Determinants for reversal versus spontaneous recovery of neuromuscular blockade following general anesthesia in a university center in the Netherlands: a retrospective observational study

Chris Martini[1], Martijn Boon[1], Erik Olofsen[1], Lori D Bash[2], Albert Dahan[3]

[1]Leiden University Medical Center, Leiden, Netherlands, [2]Merck and Co., Inc., Kenilworth, NJ, [3]Leiden University Medical Center, Leiden, NL

INTRODUCTION: In Leiden University Medical Center, a single-center tertiary care academic center, sugammadex slowly replaced neostigmine for reversal of a rocuronium-induced neuromuscular block since its introduction in 2008. Still, the majority of our patients are not reversed after surgery. We identified determinants for reversal versus spontaneous recovery of patients that received rocuronium for relaxation during general anesthesia.

METHODS: After approval of the protocol by the local IRB anonymized data from patients that received general anesthesia since April 1, 2016 were retrieved from the patient data monitoring system HiX (Healthcare Information X-change, Chipsoft, the Netherlands). Adult patients receiving general anesthesia with endotracheal intubation and were treated with rocuronium for any type of elective procedure by using HiX specific queries were included. Exclusion criteria included age < 18 years, diagnostic procedures, no intubation, both sugammadex and neostigmine administered, degenerative muscle disease, renal failure (eGFR <30 mL/min). The following data were extracted from HiX: age (age, gender, weight, ASA-state, type of surgery, duration of surgery, type of anesthesia (volatile or total intravenous anesthesia, TIVA). Data analysis was by stepwise logistic regression in SPSS.

RESULTS: We retrieved records from 23,373 patients of which 9.726 were discarded because exclusion criteria were met. In the final cohort (n = 13,647; mean age 55 ± 18 years (mean ± SD); 55% men; mean weight 78 ± 18 kg; mean body mass index 26 ± 5 kg/m2), 77% of patients were not reversed, while 23% were reversed with sugammadex. The percentage of patients reversed increased with increasing age from 19% (18-29 years) to 72% (80+ years), increasing ASA class from ASA 1 (20%) tot ASA 3 (32%) while patients at higher ASA class had much lower reversal rates. Among patients that received volatile anesthesia 19% were reversed, while among those receiving TIVA 24% were reversed. More than 20% reversal was observed in patients following general surgery (29%), ENT surgery (28%), Eye surgery (35%) and Urology (30%). Procedures which were actively reversed were significantly shorter in duration compared to those which were spontaneously reversed (97±59 min vs 172±130 min, respectively ($p < 0.001$). See Fig. 1 for results of the logistic regression analyses.

CONCLUSION: Sugammadex reversal of muscle relaxation with rocuronium given during either volatile or total intravenous anesthesia was observed in 23% of patients and depended on patient age, ASA state, type of anesthesia and type and duration of surgery. Younger patients with lower ASA class, receiving TIVA and longer surgery times were preferentially not reversed. Logistic regression analysis shows the complex relationship between patient and procedural characteristics and choice of reversal.

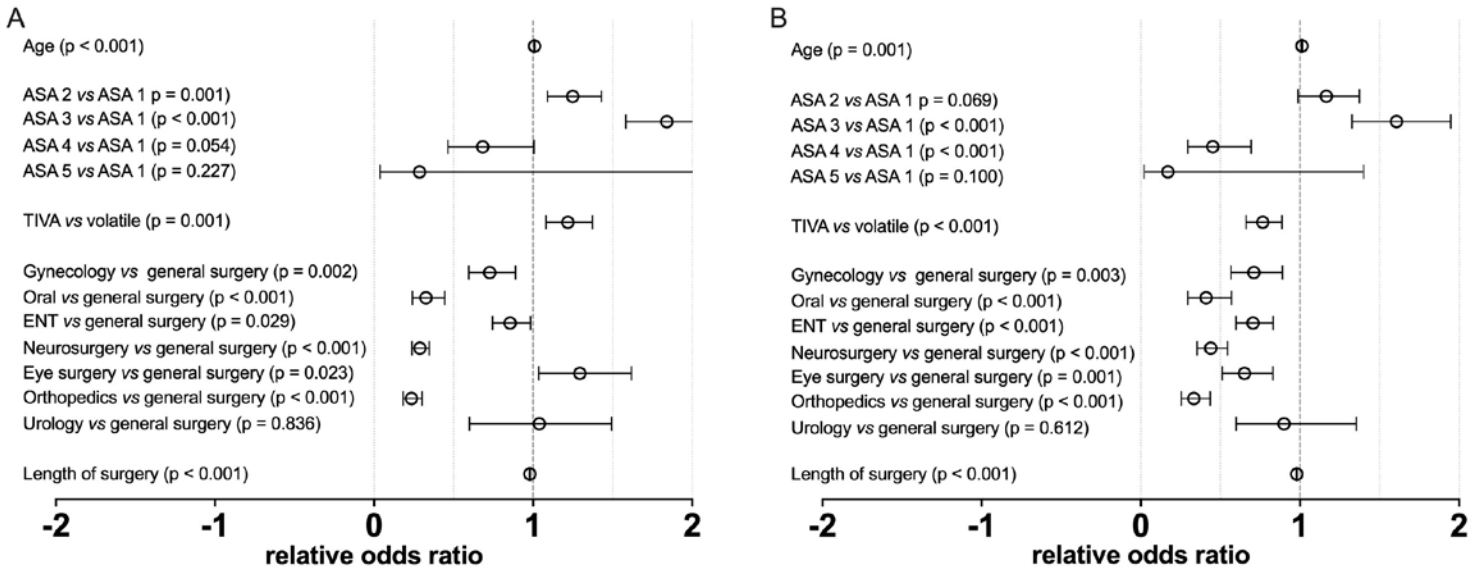


Figure 1. Relative odds ratio of reversal with sugammadex *versus* spontaneous recovery. A. Univariate analysis. B. Multivariate analysis. Covariates are relative to age = 50 years, ASA = 1, anesthesia = volatile, surgery = general surgery, and duration of surgery = 160 min.

ANESTHETIC PHARMACOLOGY 6

Structural mechanism of lipid modulation of a pentameric ligand-gated ion channel

Wayland W Cheng[1], John T Petroff[1], Noah Dietzen[1]

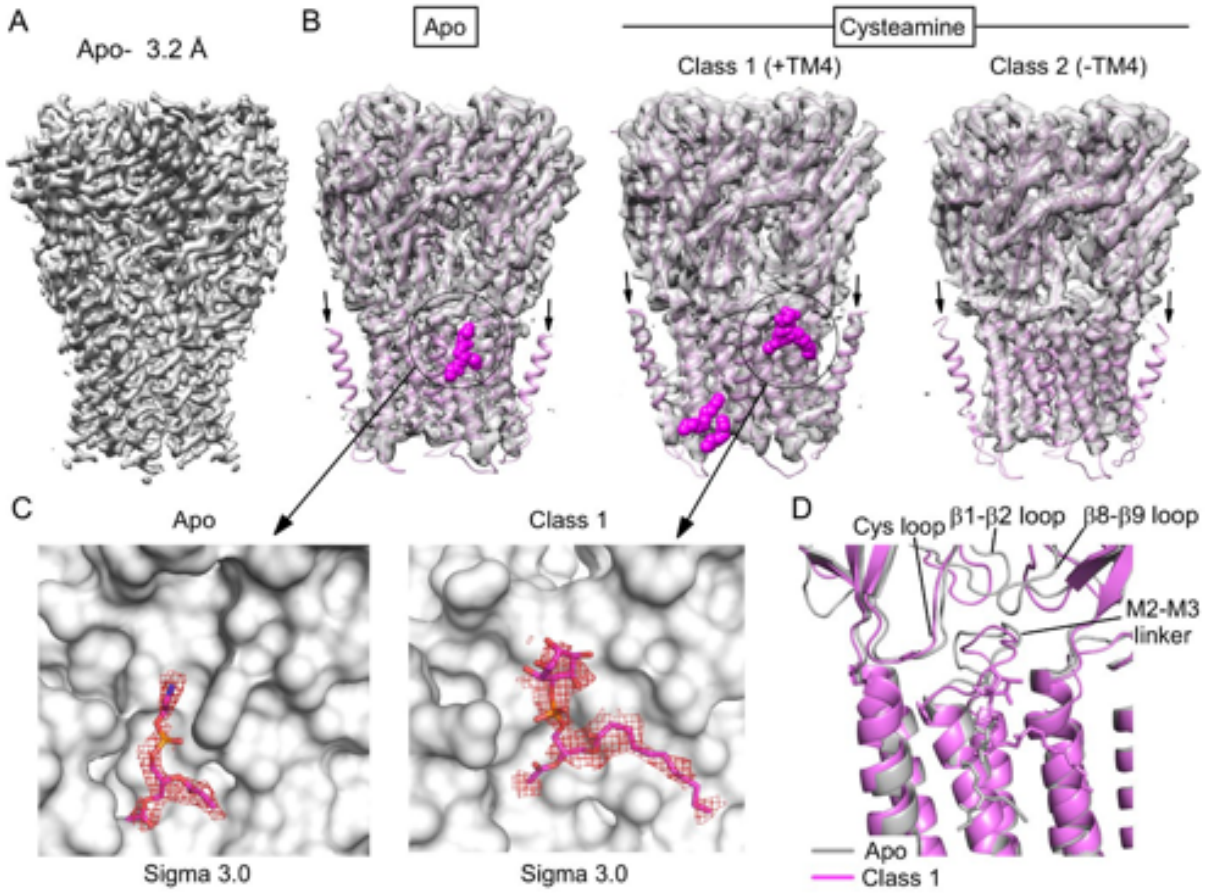
[1]Washington University, Saint Louis, MO

INTRODUCTION: Pentameric ligand-gated ion channels (pLGICs) such as the GABA(A) receptor and glycine receptor are essential determinants of synaptic neurotransmission and primary targets of anesthetics. Rational design of drugs that specifically target these ion channels requires a high resolution structural understanding of channel activation and allosteric modulation. pLGICs are allosterically modulated by lipids, and lipid modulators likely share binding sites with anesthetics. Despite recent landmark discoveries of pLGIC structure using cryo-EM, the structural mechanism of lipid modulation of pLGICs, including the binding sites of functionally-important lipids and the impact of these lipids on channel structure, is not known.

METHODS: We studied the mechanism of lipid modulation of the model pLGIC, ELIC, by combining cryo-electron microscopy (cryo-EM), stopped-flow measurements of channel activity in liposomes, and native mass spectrometry. ELIC was reconstituted in lipid nanodiscs consisting of three different lipid compositions (POPC, 2:1:1 POPC:POPE:POPG, and asolectin) and high resolution structures were determined using single particle cryo-EM on a 300kV Titan Krios Cryo-TEM. ELIC function in liposomes with different lipid composition was assessed using a fluorescence stopped-flow assay of thallium influx. The stoichiometry and affinity of phospholipid binding to ELIC was measured using native mass spectrometry on an QExactive EMR mass spectrometer.

RESULTS: Structures of ELIC with and without the agonist, cysteamine, were determined by cryo-EM in MSP lipid nanodiscs composed of POPC, 2:1:1 POPC:POPE:POPG, and asolectin. The six structures ranged from 2.9-3.4 Angstrom resolution. Cysteamine-containing structures show bound cysteamine and agonist-dependent conformational changes consistent with channel activation. The structures in 2:1:1 POPC:POPE:POPG and asolectin lipid environments reveal lipid densities at two distinct sites, located in the outer and inner regions of the transmembrane domain (TMD) (see attached Figure). The presence of bound lipids is associated with agonist-dependent conformational changes. Functional experiments show that POPE increases ELIC gating efficacy, while POPG slows channel desensitization. Native mass spectrometry and mutagenesis experiments reveal that the outer TMD site selectively binds POPE mediating its effect on gating efficacy, while the inner TMD site selectively binds POPG mediating its effect on desensitization.

CONCLUSION: Using a combination of structural and biochemical approaches, we show that binding of different lipids to two distinct sites mediates allosteric modulation of gating efficacy and desensitization in the pLGIC, ELIC. The inner TMD site has been reported to be a volatile anesthetic binding site while the outer TMD site is not a known anesthetic binding site, although other lipids such as neurosteroids and fatty acids have been shown to bind to this site. Our results reveal conserved binding sites for allosteric modulators in pLGICs, and provide a structural mechanism of how direct binding of lipids to these sites stabilize specific conformations of the ion channel.



Structures of ELIC in asolectin nanodiscs (**A**) Cryo-EM map of apo ELIC in MSP1E3D1 nanodiscs with asolectin at overall 3.2 Å resolution. (**B**) Structures of ELIC in asolectin nanodiscs with (10 mM cysteamine) and without agonist (apo) showing cryo-EM density maps, cartoon representation of the structural model, and bound phospholipids (magenta spheres). Arrows indicate TM4. For the upper TMD site, only the phospholipid headgroup and partial acyl chains could be modeled. For the lower TMD site, only two partial acyl chains could be modeled. (**C**) Surface representation of the upper TMD site with bound phospholipid. Non-protein densities (σ level 3.0) in the apo and class 1 structures were best fit with PE and PI headgroups, respectively. Both PE and PI are phospholipids present in asolectin. (**D**) Comparison of the apo and class 1 structures in the ECD-TMD interface showing bound phospholipids adjacent to major structural changes in the interfacial loops and M2-M3 linker.

ANESTHETIC PHARMACOLOGY 7

Ketamine Produces a Long-Lasting Enhancement of CA1 Neuron Excitability

Grace Jang[1], Bruce Maciver[1]

[1]Stanford University School of Medicine, Stanford, CA

INTRODUCTION: Ketamine has recently been shown to improve major depressive disorder in patients who are unresponsive to other forms of treatment. The antidepressant effect occurs rapidly, often following a single exposure, and can outlast the presence of the drug for days or even weeks. Current evidence suggests that the mechanisms for this effect involve actions in addition to NMDA receptor antagonism. Little is known about other molecular targets for ketamine. The present study examined the effects of ketamine on synaptic transmission at glutamate and GABA synapses to determine whether changes in activity at these synapses contribute to the long-lasting effects produced by this drug.

METHODS: All procedures were approved by the Stanford University Animal Use Committee. Male C57BL/6J mice weighing between 25-30 grams were used to prepare 400 μM thick coronal brain slices. We studied the effects of ketamine and its major metabolites (2R, 6R & 2S, 6S)-hydroxynorketamine, NMDA receptor antagonists DL-2-Amino-5-phosphonovaleric acid (APV) and MK-801, and a potassium channel blocker tetraethylammonium (TEA) by electrically stimulating Shaffer-collateral axons while recording evoked responses from CA1 pyramidal neurons. We also studied GABA inhibitory responses using GABA-A receptor antagonist bicuculline and a paired-pulse paradigm.

RESULTS: Concentration-dependent effects were observed at clinical concentrations (10 μM for antidepressant and 350 μM for anesthetic). Ketamine produced three effects: 1) an acute depression of population spike amplitudes, 2) an enhancement of GABA-mediated inhibition, and 3) a long-lasting increase in population spike amplitudes. The long-lasting increase in amplitudes was observed following drug washout and lasted for up to 4 hours (longest duration of recording). While the acute effects of ketamine were blocked by bicuculline, the washout increase was not altered by bicuculline, nor was it produced by any anesthetics we have previously studied (halothane, isoflurane, desflurane, sevoflurane, ethanol, pentobarbital, phenobarbital, thiopental, propofol, dexmedetomidine, or urethane). A long-lasting effect was not observed for EPSP responses, indicating a postsynaptic site for ketamine's action. Ketamine's effects were mimicked by the NMDA receptor channel blocker MK-801, but only partially mimicked by the NMDA receptor antagonist APV and a broad spectrum potassium channel blocker TEA.

CONCLUSION: Our results agree with previous studies showing that ketamine produces an acute depression of population spike amplitudes with an increase in GABA-mediated inhibition. This is the first report to demonstrate a long-lasting increase in excitability following washout of ketamine from brain slices. An increase in excitability following washout was also seen with MK-801 but only partially evident with APV, demonstrating the importance of channel block downstream of NMDA receptors. Additionally, the results with TEA indicate a potential for potassium channel block in ketamine's long-lasting effect. We suggest that the long-lasting effect produced following washout of ketamine could be related to the long-lasting antidepressant effects produced by ketamine.

ANESTHETIC PHARMACOLOGY 8

Impact of polymorphisms in the pharmacokinetic pathway for ondansetron on PONV treatment efficacy

Yvette N Martin McGrew[1], Jason P Sinnwell[2], Krishna R Kalari[2], Timothy B Curry[2]

[1]Mayo Clinic, Rochester, Minnesota, [2]Mayo Clinic, Rochester, MN

INTRODUCTION: Despite the tools for predicting post-operative nausea and vomiting (PONV) and the guidelines for prevention and treatment, there remain a proportion of individuals who experience PONV despite receiving prophylaxis. The incidence of failed post-operative nausea and vomiting (PONV) treatment can be as high as 35% after receiving the 5HT3 antagonist, ondansetron[1]. There is the potential for substantial morbidity associated with any episode of PONV; therefore, every attempt must be made to further reduce this adverse anesthetic complication. Many factors may influence and contribute to the variable PONV prophylaxis drug efficacy, including genetic variability in the pharmacokinetic pathway including metabolism and transport. Previous genetic association studies on ondansetron have focused on single gene-drug interaction, focusing on the main drug metabolizing enzyme CYP2D6 to explore the pharmacogenetics of PONV. There are limited studies on the contribution of other drug metabolizing enzymes for ondansetron (CYP1A2, CYP3A4, CYP3A5) or proteins responsible for ondansetron transport such as ABCB1. We hypothesize that polymorphisms in the pharmacokinetic pathway of the commonly used anti-nausea medication ondansetron are responsible for the rate of PONV treatment failure in patients undergoing general anesthesia.

METHODS: After IRB approval, surgical patients with preemptive sequencing performed by the RIGHT10K protocol were identified[2]. From that group, we performed a retrospective, genotype –phenotype association study in 982 patients who had general anesthesia and received ondansetron as the only PONV prophylaxis with polymorphisms in the following genes: CYP2D6, CYP1A2, CYP3A4, CYP3A5 and ABCB1. The five genes studied were selected based on their role in metabolism and transport of ondansetron. All clinical outcomes such as PACU length of stay, length of surgery, and opioids used were obtained retrospectively from the electronic health record. PONV was defined as requiring rescue antiemetic in the PACU setting, and/or nursing documentation of nausea/vomiting in the PACU. Single SNP and multi SNP genotype-phenotype association analyses were performed.

RESULTS: Of the 982 patients, 232 had PONV (24%). Univariate analysis for CYP2D6, CYP3A5, and CYP3A5 was not significant. CYP1A2 normal (extensive) metabolizers were higher in the no PONV group [44(5.9%) vs 21 (9.1%) p 0.110] however it did not reach statistical significance. Three polymorphisms in ABCB1 (rs2032582, rs1128503, rs10276036) were higher in those with no PONV, however only the rs2032582 reached statistical significance (p 0.03). Multivariate analysis after adjusting for gender, age, and intraoperative opioids showed ABCB1 genotype rs2032582 as protective [OR 0.814 (0.663, 1.0), p=0.05]. Haplotype analysis was performed with the multiple polymorphisms in ABCB1 and one haplotype was found to be protective and was statistically significant when compared with the baseline haplotype [OR 0.81 (0.63, 1.0), p=0.05].

CONCLUSION: Our retrospective study set out to identify the association of polymorphisms in the pharmacokinetic pathway of ondansetron with PONV treatment failure. This is one of the largest PONV pharmacogenomic studies performed to date with 982 patients. In contrast to previous studies we did not find that the CYP2D6 phenotype explains PONV treatment failure. We identified a haplotype in the ABCB1 gene that is associated with decreased PONV after ondansetron treatment. Our data suggests that the variability of ondansetron efficacy is more dependent on transport as opposed to metabolism. This is a step towards using genotypic data to better understand PONV treatment efficacy and to evaluate the benefit and utility of pharmacogenomics to guide post-operative nausea and vomiting treatment in the anesthesia practice.

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3. Hum Hered, 2003. 55(1): p. 56-65.

ANESTHETIC PHARMACOLOGY 9

Characters of Rapid Eye Movement Sleep rebound after sevoflurane anesthesia

Elzbieta Dulko[1], Joanna Klos[2], Jaideep Kapur[1], Zhiyi E Zuo[3], Nadia Lunardi[1]

[1]University of Virginia, Charlottesville, VA, [2]University of Virginia, Charlottesville , VA, [3]University of Virginia School of Medicine, Charlottesville, VA

INTRODUCTION: Rapid Eye Movement Sleep (REMS) rebound is a common clinical problem following anesthesia and surgery, and is associated with severe physiological derangements that greatly increase morbidity and mortality in postoperative patients[1]. It typically manifests between the first and fourth postoperative night in the form of increased REMS duration and shortened latency to REMS. REMS rebound has been linked to postoperative hyperalgesia[2], delirium[1] and a number of respiratory complications[1,3], and is identified as an independent risk factor for heart failure, myocardial infarction, stroke and death[3]. Recent experimental evidence indicates that commonly used anesthetics disrupt REMS circuits[4-6], and that REMS rebound occurs in both mice and rats after sevoflurane (SEVO) exposure[4,5]. However, the specific REMS-associated neural populations impacted by anesthetics remain elusive. We now aim to resolve how SEVO, the most common clinically used anesthetic, affects REMS networks in the adult brain.

METHODS: This study was approved by the Institutional Animal Care and Use Committee at the University of Virginia. Three-month-old male and female Sprague-Dawley rats were surgically implanted with electroencephalographic (EEG) and electromyographic (EMG) electrodes, as described previously[6], and were allowed a minimum of 12 days of recovery. Next, they were randomized to receive 2.8% SEVO in 45% O_2 for 3 h, or control conditions (45% O_2 for 3h). A concentration of 2.8% SEVO was chosen because in pilot experiments we determined that it is the minimum alveolar concentration that prevents movement to pain in 50% of rats at age 3 months (MAC EC_{50}). Twenty-four h-long EEG/EMG recordings were obtained immediately after SEVO emergence, and again one week later in SEVO-exposed and control rats (Fig. 1A). EEG signals were processed with SleepSign software and manually scored by two independent scorers blinded to experimental conditions. A Targeted Recombination in Active Populations (TRAP) approach was used to identify the neuronal populations involved in the REMS changes observed after SEVO (Fig. 2). Briefly, transgenic TRAP mice use the activity-dependent immediate early gene c-Fos to drive the expression of tdTomato, an easily-imaged fluorescent protein. The c-Fos locus is linked to a tamoxifen-dependent recombinase, CreER. This approach allows visualization of active neurons, permanently tagged by tdTomato, in the presence of the short-acting tamoxifen metabolite 4-hydroxytamoxifen (4-OHT). Subcutaneous injection of 4-OHT allows tagging of active neurons in a 1- to 2- hour window preceding the time of injection[7]. Thus, three-month-old transgenic TRAP mice were subjected to 2.8% SEVO in 45% O_2 for 3 h, or control conditions. They were injected with 4-OHT (50 mg/kg, subcutaneous) at 8.5 h after SEVO emergence, as this was the time when the REMS rebound was most pronounced. Brains were transcardially perfused 7 days after 4-OHT injection to allow for maximal expression of the tdTomato. Next, brains were processed using a CLARITY clearing technique[7] and Z-stack images were taken at 15 µM intervals with a confocal microscope.

RESULTS: SEVO-exposed rats exhibited a significant 30% increase in REMS duration during the 24 h following SEVO anesthesia compared to controls (**, $p<0.005$, Fig. 1B). No differences were found in the amount of wakefulness and non-REMS (data not shown). Moreover, SEVO-exposed rats took less than half the time of age-matched controls to enter REMS at lights off (*, $p<0.05$, Fig. 1C). In addition, the ventrolateral periaqueductal gray (vlPAG), a midbrain region that suppresses REMS through tonic inhibition of REMS-generating nuclei, appeared to have more tdTomato-tagged active neurons in control mice compared to SEVO-exposed mice (Fig. 3).

CONCLUSION: Adult rodents exhibit acute increase in REMS duration and shortened latency to REMS following SEVO anesthesia. These REMS changes are short-lived and do not persist beyond one week. Hypo-activity of the REMS-off neurons in the vlPAG may be a mechanism for the REMS adaptations observed after SEVO.

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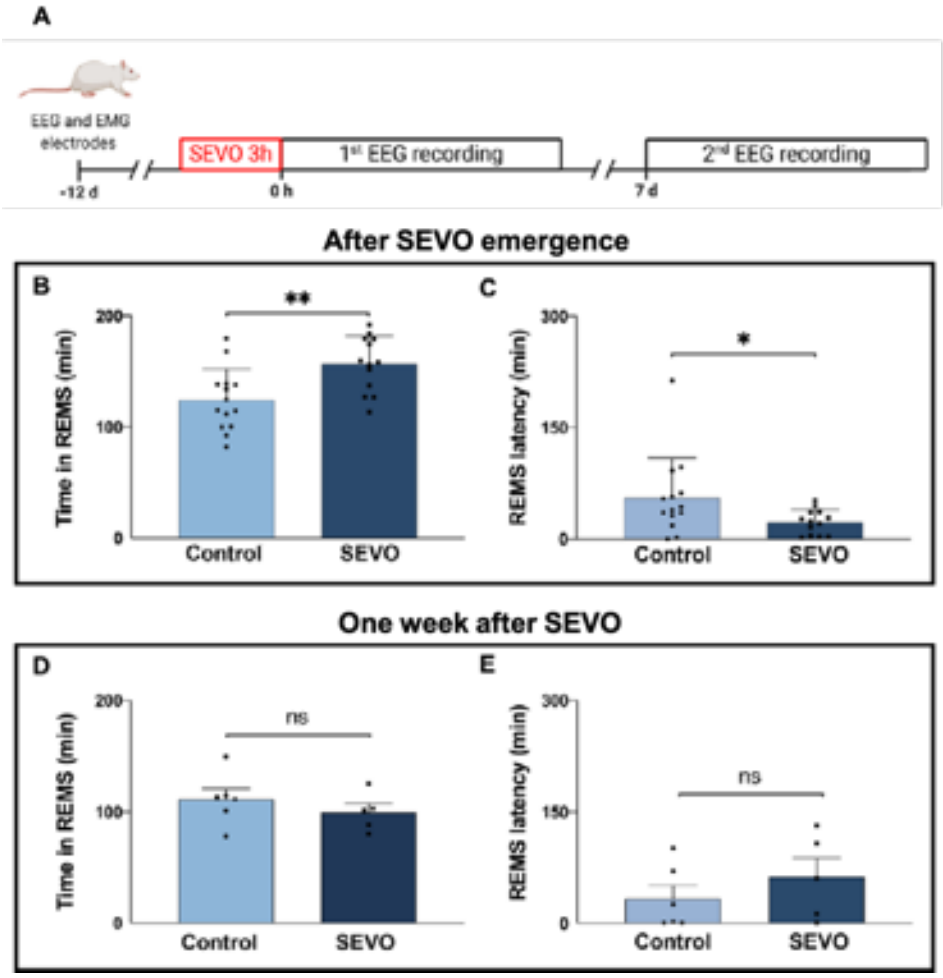

Fig. 1: A- Schematic of EEG/EMG experiments. **B-** Adult rats exhibit increased REMS duration in the 24 h following SEVO emergence. **C-** Time to REMS onset is significantly shorter in adult rats after emergence from SEVO than controls. **D, E-** There are no differences in REMS duration or latency one week after SEVO in SEVO-exposed rats relative to controls. B, C: N=14 Control and 13 SEVO-exposed rats. D, E: N=6 Control and 5 SEVO-exposed rats. Data expressed as mean ± S.E.M. Unpaired t-student's test. Created with BioRender.com.

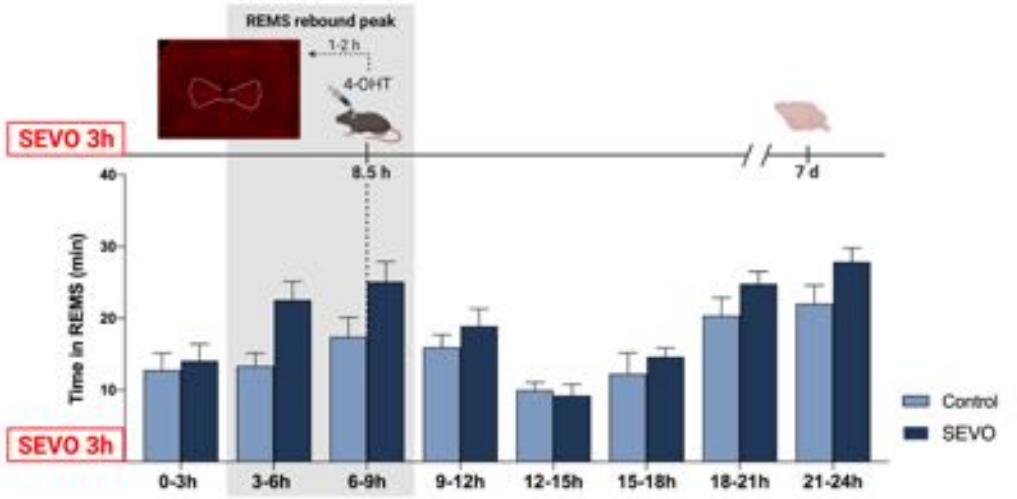

Fig. 2: Schematic of TRAP experiments. SEVO-exposed and control TRAP mice were injected with 4-OHT at 8.5 h after SEVO emergence. Injection of 4-OHT allowed tagging of active neurons in a 1- to 2- h window prior to the injection. Brains were collected 7 days after 4-OHT injection. Data expressed as mean ± S.E.M. Created with BioRender.com.

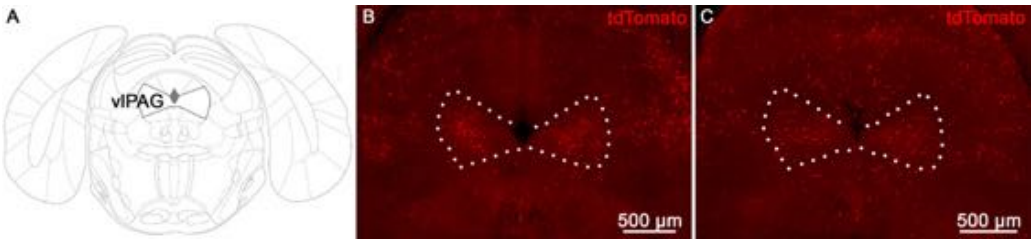

Fig. 3: A- Representative coronal map through the vlPAG adapted from the mouse brain atlas of Paxinos and Watson. **B-** Representative vlPAG image from a control TRAP mouse. **C-** Representative vlPAG image from a SEVO-exposed TRAP mouse. Red: tdTomato. Abbreviations: vlPAG: ventrolateral periaqueductal gray.

ANESTHETIC PHARMACOLOGY 10

Comparison of the Effectiveness of Ascorbic Acid and Magnesium in Renal Ischaemia Reperfusion Model in Rats

Ural C Ekmekci[1]

[1]*Dokuz Eylul University, Izmir, Turkey*

INTRODUCTION: Background: This study aims to determine the effectiveness of ascorbic acid and magnesium administration separately or combined before ischaemia in the rat renal ischaemia and reperfusion damage of the model. Objective: To test the antioxidant and protective effects of ascorbic acid and magnesium. Design: A randomized, comparative, experimental study. Participants: Thirty-five Wistar albino male rats ranging in weight from 250-300 g were divided into five groups. Interventions: Group 1 received only laparotomy, whereas 45 min ischaemia, and 240 min reperfusions were applied to the other groups. No drugs were applied to Group 2. One hour before ischemia, 250 mg/kg ascorbic acid to Group 3, 200 mg/kg magnesium sulfate to Group 4, and both drugs at the same doses to Group 5 were administered intraperitoneally. Main outcome measures: Malondialdehyde and glutathione levels were determined in the renal tissues received, serum blood urea nitrogen and creatine levels were measured in blood samples. Hematoxylin & eosin and periodic acid Schiff paintings for histological examinations. TUNEL immunohistochemical staining for apoptotic cell examinations. Results: The blood urea nitrogen value was found significantly lower in Group 5 compared to Group 2 (p:0.021). Malondialdehyde value was found significantly lower in Group 3 (p:0.034) and Group 5 (p<0.001) compared to Group 2. Glutathione value of Group 4 (p<0.001) and Group 5 (p<0,001) were significantly higher than the other groups. TUNEL counts of the Group 5 was significantly lower than the Group 2 counts (p:0,005). Conclusion: It was concluded that before ischaemia, pre-treatment of 250 mg/kg ascorbic acid or 200 mg/kg magnesium sulfate or their combination reduce the kidney damage in the rat renal IR model. Trial registration: No 47/2018, Dokuz Eylul University Local Ethics Board of Animal Experiments
Keywords: Kidney, Ischaemia Reperfusion Injury, Ascorbic Acid, Magnesium, Rat.

METHODS: A randomized, comparative, experimental study. Participants: Thirty-five Wistar albino male rats ranging in weight from 250-300 g were divided into five groups. Interventions: Group 1 received only laparotomy, whereas 45 min ischaemia, and 240 min reperfusions were applied to the other groups. No drugs were applied to Group 2. One hour before ischemia, 250 mg/kg ascorbic acid to Group 3, 200 mg/kg magnesium sulfate to Group 4, and both drugs at the same doses to Group 5 were administered intraperitoneally. Main outcome measures: Malondialdehyde and glutathione levels were determined in the renal tissues received, serum blood urea nitrogen and creatine levels were measured in blood samples. Hematoxylin & eosin and periodic acid Schiff paintings for histological examinations. TUNEL immunohistochemical staining for apoptotic cell examinations.

RESULTS: The blood urea nitrogen value was found significantly lower in Group 5 compared to Group 2 (p:0.021). Malondialdehyde value was found significantly lower in Group 3 (p:0.034) and Group 5 (p<0.001) compared to Group 2. Glutathione value of Group 4 (p<0.001) and Group 5 (p<0,001) were significantly higher than the other groups. TUNEL counts of the Group 5 was significantly lower than the Group 2 counts (p:0,005).

CONCLUSION: It was concluded that before ischaemia, pre-treatment of 250 mg/kg ascorbic acid or 200 mg/kg magnesium sulfate or their combination reduce the kidney damage in the rat renal IR model.

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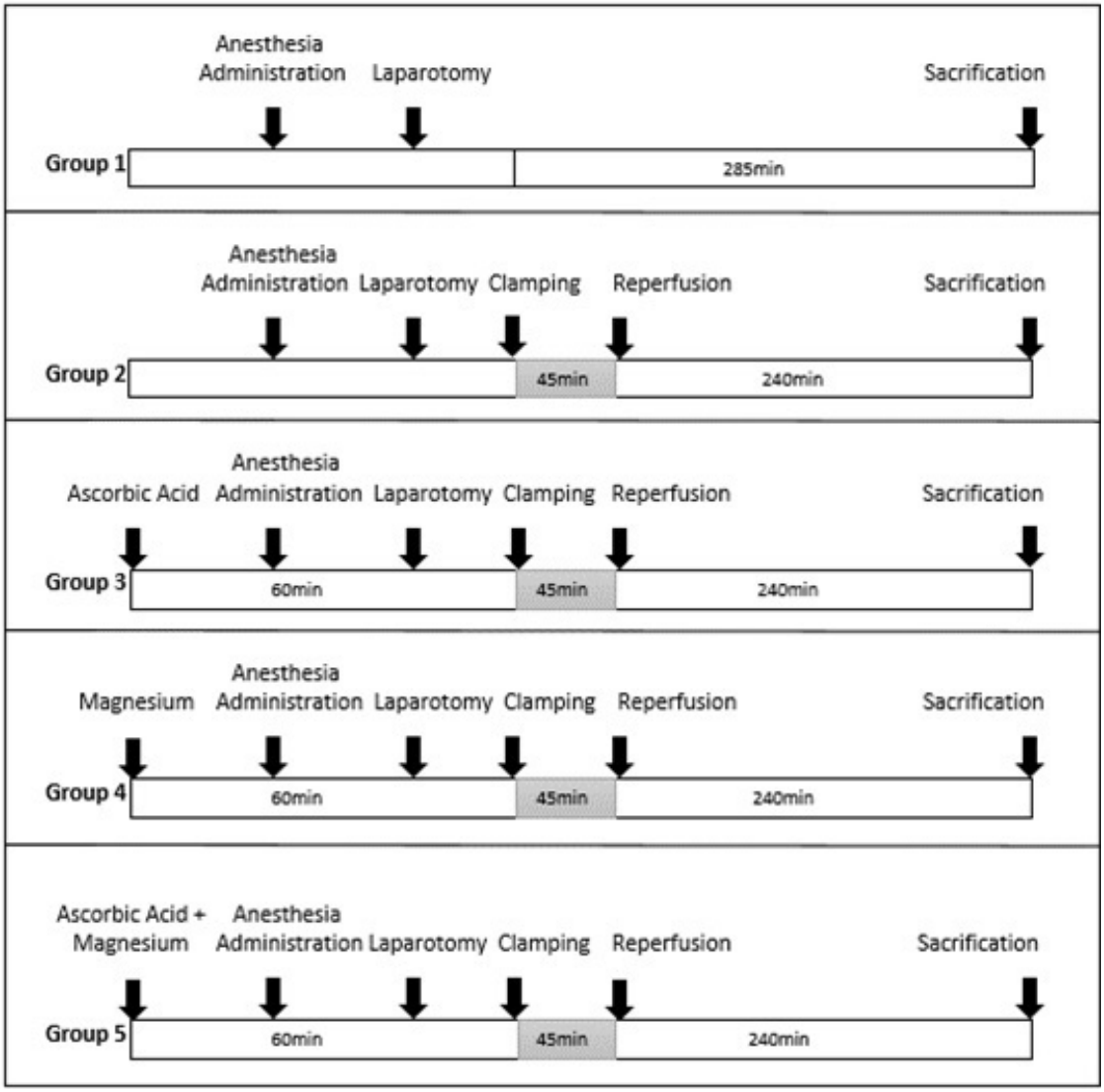

Fig. 1

ANESTHETIC PHARMACOLOGY 11

A propofol binding site on ryanodine receptor 1

Thomas T Joseph[1], Weiming Bu[1], Kellie Woll[2], Omid Haji-Ghassemi[2], Filip van Petegem[2], Grace Brannigan[3], Roderic G Eckenhoff[4]

[1]University of Pennsylvania, Philadelphia, PA, [2]University of British Columbia, Vancouver, BC, [3]Rutgers University, Camden, NJ, [4]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

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 such 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 AziPm[2], a photolabel analog of propofol. The RyR1 protein was incubated with AziPm and irradiated. This causes the formation of a reactive carbene version of AziPm and its covalent bonding to RyR1. 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 (PDB: 5GKY) with a) a single AziPm molecule and b) a single propofol molecule placed in one putative binding site on the tetrameric RyR1. 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 both AziPm and propofol were stable in the site. FEP MD simulations predicted binding affinities of AziPm and propofol that corresponded to dissociation constants KD of 80 nM and 10-20 μM respectively.

CONCLUSION: Our data shows that propofol binds RyR1 at a clinically relevant concentration in the L4827 site on RyR1. 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.

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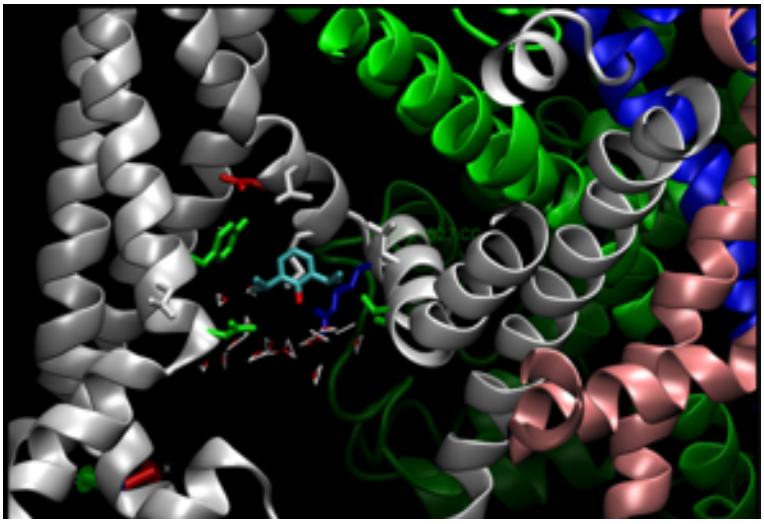

ANESTHETIC PHARMACOLOGY 12

Substituted Cysteine Modification with Alkyl-MTS Reagents Suggests Bulk Mutations on Alpha M1 Domain Sterically Impact MTS Modification on M3 Domain

Kieran Bhave[1], Stuart A Forman[2]

[1]Massachusetts General Hospital, Boston, United States of America, [2]Massachusetts General Hospital, Boston, MA

INTRODUCTION: Potent intravenous anesthetics act in part through sites in the transmembrane β+/α- inter-subunit interfaces of typical synaptic α1β3γ2L $GABA_A$ receptors. Previous studies showed that stable disulfide linkages can form between α1L232C and β3M286C mutations on alpha M1 and beta M3 transmembrane helices respectively of GABA-activated receptors[1], suggesting that these residues are located near each other on opposing faces of the inter-subunit pocket. Cryo-EM studies suggest that these two residues may be as close as 5.1Å in desensitized receptors[2]. We have used a series of n-alkyl-MTS reagents to precisely probe spatial relationships between the β3M286C mutation and bound etomidate, but it is uncertain whether the biphasic size-dependent pattern of functional effects (Fig 1) is due to modifier access, length, volume, or other factors. Presuming the proximity of α1L232 to β3M286C, we hypothesized that adding bulk to the α1L232 sidechain would sterically restrict alky-MTS access and possibly alter the functional effects of modification at β3M286C. We tested this idea using a tryptophan mutation at α1L232 in α1L232Wβ3M286Cγ2L $GABA_A$ receptors.

METHODS: *Xenopus laevis* were kept in a veterinarian-supervised facility with IACUC approval (protocol #2020N000002) and in line with ARRIVE guidelines. Oocytes were harvested via mini-laparotomy from frogs anesthetized in 0.2% tricaine, and injected with a messenger RNA mixture encoding **α**1(L232W), β3(M286C), and γ2L $GABA_A$ receptor subunits at 1α:1β:5γ ratios. Two-electrode voltage-clamp electrophysiologic experiments were conducted in oocytes. Covalent modification by n-alkyl-MTS reagents at β3M286C residues was detected as changes in the low:high GABA current response ratio, elicited with respective applications of 1 μM GABA (~ EC_3) and 10 mM GABA (maximal). Low:high ratios were measured twice before and twice after exposure to 9 mM*s n-alkyl-MTS + 10mM GABA, with all procedures separated by 5 minute wash in electrophysiology buffer. The GABA modification ratio was calculated as the post-modification low:high ratio normalized to the pre-modification low:high ratio in the same oocyte. GABA modification ratios (n=5, per alkyl-MTS reagent) were compared to controls (10mM GABA without modifier) and significance was determined using single variable ANOVA analysis and Dunnett's post-hoc tests, with $p < 0.05$ as a significance threshold. Anesthetic protection was tested by adding 300 μM Etomidate (ETO) during alkyl-MTS + 10mM GABA modification exposure. Comparisons to control modification effects were assessed using unpaired two-tailed Student's t-tests with n=5 oocytes per condition.

RESULTS: Low:high GABA response ratios were unaffected by methyl-MTS, n-hexyl-MTS, and n-octyl-MTS modification. Ethyl-MTS, n-propyl-MTS, n-butyl-MTS, and n-pentyl-MTS all enhanced low:high GABA response ratios ($p=0.0091$, $p<0.0001$, $p<0.0001$, $p<0.0001$, respectively). ETO at 300 μM significantly reduced modification effects for ethyl-MTS, n-propyl-MTS, n-butyl-MTS, and n-pentyl-MTS ($p=0.0003$, $p=0.0012$, $p=0.0001$, $p<0.0001$, respectively).

CONCLUSION: Persistent GABA sensitivity effects of n-alkyl-MTS reagents in both α1L232Wβ3M286Cγ2L and α1β3M286Cγ2L receptors were inhibited by ETO, suggesting that β3M286C modified by these n-alkyl-MTS reagents overlaps ETO sites. In α1L232Wβ3M286Cγ2L $GABA_A$ receptors, persistent increases in GABA sensitivity were observed following exposures to ethyl-MTS through n-pentyl-MTS (Fig 1, right). In comparison, persistent increases in GABA sensitivity in α1β3M286Cγ2L GABAA receptors were seen after exposure to n-propyl-MTS through n-hexyl-MTS (Fig 1, left). Thus, both "cut on" and cut off" modifier sizes are shifted down by one methyl group for α1L232Wβ3M286C receptors vs. α1β3M286Cγ2L receptors. This is consistent with the length increase from leucine to tryptophan (2.3 Å) compensating for loss of one methyl from -S-n-alkyl modification (1.3 Å). The dramatic loss of effect of n-hexyl-MTS exposure associated with the α1L232W mutation suggests that steric obstruction accounts for loss of modifier effects for the longer n-alkyl-MTS modifiers, and thus the approximate distance from α1L232 to β3M286 is about 6-7Å in the open state. At the same time, the unexpected enhancement of GABA sensitivity following ethyl-MTS modification suggests that contraction of the anesthetic binding pocket enhances the efficacy of small modifiers.

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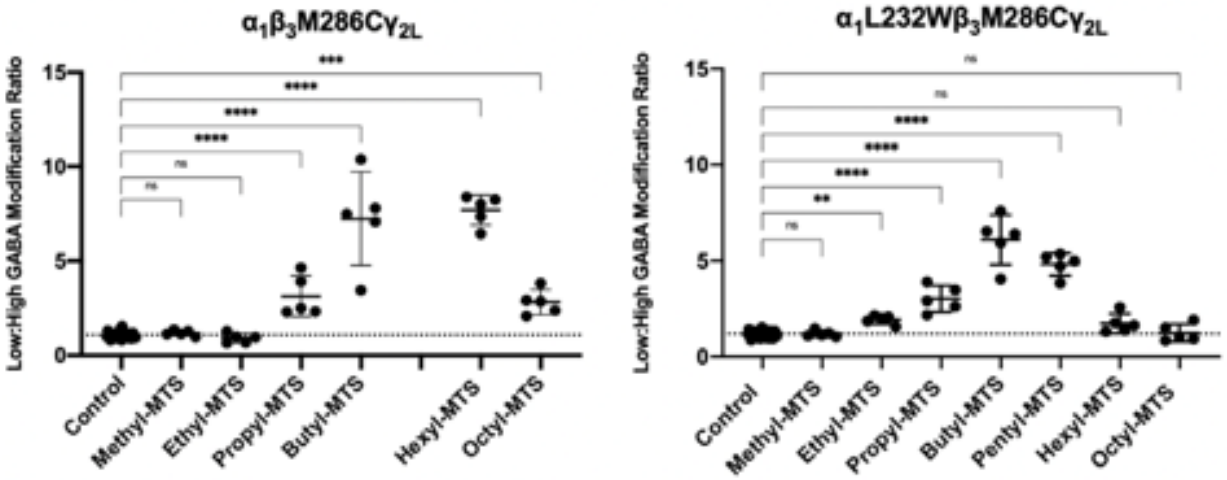

Figure 1. GABA sensitivity changes after exposure to 9 mM*s n-alkyl-MTS + 10mM GABA in $\alpha_1\beta_3M286C\gamma_{2L}$ and $\alpha_1L232W\beta_3M286C\gamma_{2L}$ receptors. Symbols represent individual oocyte results. Error lines indicate mean ± SD (n=5, per alkyl-MTS reagent). Dotted line indicates mean value of control cells (n=35). P-values were calculated using single variable ANOVA analysis and Dunnett's post-hoc tests, with $p < 0.05$ as a significance threshold (****=p<0.0001, ***=p<0.001, **=p<0.01, *=p<0.05).

Subspecialty Abstracts

BLOOD MANAGEMENT

BLOOD MANAGEMENT 1

Over-Transfusion in Pediatric Patients Intra-operatively. A Retrospective Observational Study at a Tertiary Pediatric Hospital

Timothy R Walsh[1], Anna Kordun[2], Steven Staffa[3], Joseph Cravero[4], Susan Goobie[5]

[1]Boston Children's Hopsital, Boston, MA, [2]Children's Hospital Boston, Boston, MA, [3]Children's Hospital Boston, Boston , MA, [4]Boston Children's Hospital, Boston, MA, [5]Harvard Medical School, Boston, MA

INTRODUCTION: Pediatric patients may be particularly sensitive to the negative sequalae of transfusion including allergic reactions, volume overload, and acute lung injury[1, 2]. Red blood cell (RBC) transfusion is associated with increased postoperative infections and 30-day mortality in pediatric surgical patients[3]. High quality prospective studies support restrictive over liberal transfusion strategies in a wide variety of patient populations including pediatric patients; most recently expanded to neonates[4, 5]. Expert consensus recommendations for RBC transfusion in critically ill children also endorse a restrictive strategy[6]. Additionally, patient blood management (PBM) is more important than ever as the COVID-19 pandemic has led to critical shortages of blood components[7, 8]. The question remains; how well do transfusion practices cohere to evidence based guidelines? The primary aim of this retrospective observational study is to determine the incidence of intraoperative over-transfusion at a single center in patients presenting for surgery or invasive procedures requiring anesthesia. The secondary aims are to identify if factors such as age, weight, pre-operative anemia, surgery type, emergent cases, ASA classification, length of case and postoperative ventilation are associated with over-transfusion and to examine if there are specific associated patient-centered outcomes present in over-transfused patients.

METHODS: This retrospective observational study received IRB approval. Data was collected from PowerChart, SurgiNet and the Anesthesia Electronic Medical Record (AIMS). A de-identified blood management database was created for patients ages 0-21 years from 2017 to 2019. Based on the TRIPICU trial metrics, over-transfusion was defined a priori liberally as post-operative hemoglobin (Hb) value >9.5 g/dL [4]. Univariate analysis of the primary outcome of intra-operative over-transfusion is performed using Chi-square test or Fisher's exact test for categorical variables, and Wilcoxon rank sum test for continuous variables. Univariate risk factors with $P<0.05$ are included in a multivariable logistic regression model. Adjusted analysis of the association between intra-operative over-transfusion and postoperative outcomes is performed using multivariable logistic regression for dichotomous complications and adverse outcomes, and using multivariable median regression for continuous outcomes. A two-tailed $P<0.05$ is considered statistically significant. Following data collection and exclusion of patients with missing data, a total sample size of 898 patients was reached. This is estimated to provide 80% power to detect an odds ratio of 1.3 for a given risk factor using logistic regression analysis and assuming a two-tailed 5% alpha.

RESULTS: The database totals 47469 patients with 3227 who received a peri-operative allogeneic RBC blood transfusion; 30% of those transfusions were intra-operative. Of these patients, a Hb value within the 24-hour period post-operatively was available for 898. As per Table 1, 78% surpassed an initial post-operative Hb level of 9.5 g/dL with 27% meeting extreme over-transfusion criteria of Hb ≥ 12 g/dL. Neonates surpassed the over-transfusion threshold of Hb 9.5 g/dL by 93% with 55% exceeding extreme over-transfusion threshold (Figure 1). Using a multivariate logistic regression analysis, weight (OR 0.97 P=0.004 95 % CI 0.96-0.99) and surgical duration (OR 1.0013 P=0.014 95% CI 1.0003-1.0024) were both found to be significant independent predictors of over-transfusion adjusting for age, procedure type, emergent status, and ASA physical status classification (Table 2). A significant independent association with extreme intra-operative over-transfusion and post-operative ventilation risk (OR 1.95 P=0.002 95% CI 1.29-2.95), pulmonary infections (OR 1.70 P=0.021 95 % CI 1.08-2.67) and heart failure (OR 2.00 P= 0.02 95% CI 1.11-3.595) is reported.

CONCLUSION: Pediatric patients undergoing anesthesia for surgery and/or invasive procedures are frequently over-transfused. Neonates have the highest rates of intraoperative over-transfusion. Pediatric PBM initiatives should be established to decrease exposure of children to unnecessary blood products[9]. Given the association with blood transfusion and adverse outcomes, we plan future prospective studies to determine the relationship between transfusion practice and perioperative outcomes.

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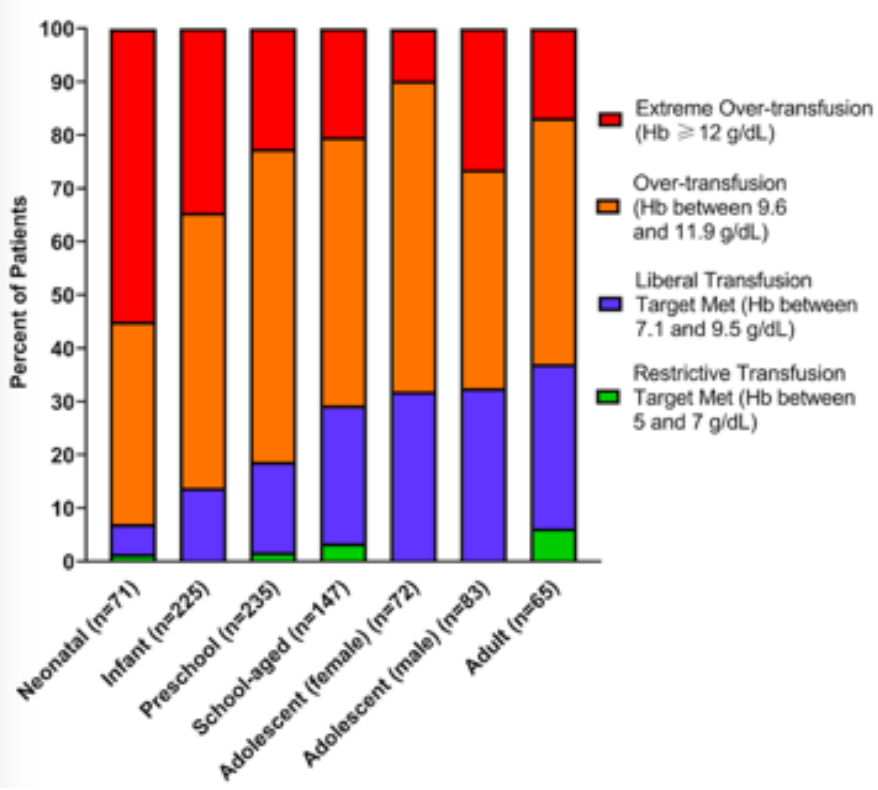

Fig. 1

Table 1: Univariate Analysis of Intraoperative Over-transfusion based on 24-hour Hemoglobin Postoperatively (N=898)

Variable	Restrictive Transfusion Target Met (Hb between 5 and 7 g/dL)	Liberal Transfusion target met (Hb between 7.1 and 9.5 g/dL)	Over-transfusion (Hb between 9.6 and 11.9 g/dL	Extreme Over-transfusion (Hb ≥ 12 g/dL)	P value
Number of Patients	**14**	**183**	**461**	**240**	
Age Category					
Neonatal	1 (1.4%)	4 (5.6%)	27 (38%)	39 (54.9%)	
Infant	0 (0%)	31 (13.8%)	116 (51.6%)	78 (34.7%)	
Preschool	4 (1.7%)	40 (17%)	138 (58.7%)	53 (22.6%)	
School-aged	5 (3.4%)	38 (25.9%)	74 (50.3%)	30 (20.4%)	**<0.001***
Adolescent (female)	0 (0%)	23 (31.9%)	42 (58.3%)	7 (9.7%)	
Adolescent (male)	0 (0%)	27 (32.5%)	34 (41%)	22 (26.5%)	
Adult	4 (6.2%)	20 (30.8%)	30 (46.2%)	11 (16.9%)	
Sex					
Male	9 (1.7%)	106 (20.3%)	259 (49.6%)	148 (28.4%)	0.541
Female	5 (1.3%)	77 (20.5%)	202 (53.7%)	92 (24.5%)	
Weight (kg)	24.5 (16.4, 60)	21.4 (10.1, 45.9)	12.6 (7.6, 27.9)	8.8 (3.9, 20.2)	**<0.001***
Pre-operative anemia					
Yes (n=513)	9 (1.8%)	141 (27.5%)	253 (49.3%)	110 (21.4%)	**<0.001***
No (n=321)	4 (1.3%)	33 (10.3%)	180 (56.1%)	104 (32.4%)	
Procedure Type					
General/GI	3 (0.7%)	75 (16.9%)	211 (47.6%)	154 (34.8%)	
Ortho	1 (0.6%)	47 (25.8%)	103 (56.6%)	31 (17%)	
Neuro	2 (2.3%)	12 (13.8%)	48 (55.2%)	25 (28.7%)	
Plastics & Maxillary	4 (5.2%)	18 (23.4%)	45 (58.4%)	10 (13%)	**<0.001***
Transplant	0 (0%)	17 (28.3%)	31 (51.7%)	12 (20%)	
GU	0 (0%)	8 (38.1%)	9 (42.9%)	4 (19.1%)	
ORL	1 (7.1%)	3 (21.4%)	7 (50%)	3 (21.4%)	
Other	3 (21.4%)	3 (21.4%)	7 (50%)	1 (7.1%)	
Emergent					
Yes (n=258)	7 (2.7%)	63 (24.4%)	100 (38.8%)	88 (34.1%)	**<0.001***
No (n=577)	6 (1%)	110 (19.1%)	324 (56.2%)	137 (23.7%)	
ASA-PS					
I	0 (0%)	4 (57.1%)	2 (28.6%)	1 (14.3%)	
II	2 (2.5%)	25 (31.7%)	41 (51.9%)	11 (13.9%)	
III	8 (1.5%)	112 (20.4%)	292 (53.2%)	137 (25%)	**0.005***
IV	4 (1.7%)	38 (16%)	118 (49.6%)	78 (32.8%)	
V	0 (0%)	4 (16.7%)	8 (33.3%)	12 (50%)	
VI	0 (0%)	0 (0%)	0 (0%)	1 (100%)	
Surgery Duration (minutes)	194 (72, 285)	292 (159, 452)	378 (238, 529)	310 (178, 489)	**<0.001***
Total Perioperative RBC Transfused (ml)	571 (366, 607)	312 (240, 610)	270 (120, 480)	224 (90, 463)	**<0.001***
Total Perioperative RBC Transfused (ml/kg)	20.5 (16.6, 37)	16.9 (9.9, 29.5)	16.2 (10.8, 24.6)	21.1 (14.8, 33.6)	**<0.001***
Perioperative administration of autologous RBC (cell saver)					
Yes	1 (0.7%)	26 (17.9%)	91 (62.8%)	27 (18.6%)	**0.019***
No	13 (1.7%)	157 (20.9%)	370 (49.1%)	213 (28.3%)	
Perioperative administration of yellow blood products					
Yes	7 (2.5%)	75 (26.5%)	129 (45.6%)	72 (25.4%)	**0.005***
No	7 (1.1%)	108 (17.6%)	332 (54%)	168 (27.3%)	

Categorical data are presented as n (row percent) and continuous data are presented as median (interquartile range).

Sample sizes are shown to indicate variables with missing data.

P values were calculated using the Chi-square test, Fisher's exact test or the Kruskal-Wallis test, as appropriate.

*Statistically significant.

Table 2: Analysis of Postoperative Outcomes by Intraoperative Over-transfusion using 24-hour Hemoglobin Postoperatively (N=898)

Postoperative Outcome Variable	Restrictive Transfusion Target Met (Hb between 5 and 7 g/dL) [n=14]	Liberal Transfusion target met (Hb between 7.1 and 9.5 g/dL) [n=183]	Over-transfusion (Hb between 9.6 and 11.9 g/dL [n=461]	Extreme Over-transfusion (Hb ≥ 12 g/dL) [n=240]	Univariate P value	Adjusted Coefficient or Odds Ratio for Extreme Over-transfusion	95% CI	Multivariable P value
Length of Hospital Stay (days)	9 (5, 19)	12 (7, 39)	18 (8, 56)	26 (10, 70)	**<0.001***	1.07	(-6.1, 8.2)	0.768
Length of ICU stay (days)	2 (0, 4.7)	1.5 (0, 5.4)	2 (0.8, 7.7)	2.2 (0.7, 11.3)	**0.02***	0.51	(-1.23, 2.25)	0.568
Postoperative intubation and/or mechanical ventilation	4 (28.6%)	73 (39.9%)	248 (53.8%)	179 (74.6%)	**<0.001***	1.95	(1.29, 2.96)	**0.002***
Allergic Reaction	0 (0%)	6 (3.3%)	5 (1.1%)	2 (0.8%)	0.169			
Cardiac Arrest	0 (0%)	1 (0.6%)	8 (1.7%)	7 (2.9%)	0.346			
Heart Failure	1 (7.1%)	12 (6.6%)	30 (6.5%)	31 (12.9%)	**0.028***	2.0	(1.11, 3.59)	**0.02***
Neonatal Cardiac Failure	0 (0%)	0 (0%)	2 (0.4%)	1 (0.4%)	0.999			
Pulmonary Infection	8 (57.1%)	108 (59%)	335 (72.7%)	198 (82.5%)	**<0.001***	1.7	(1.08, 2.67)	**0.021***
Renal Failure	2 (14.3%)	21 (11.5%)	32 (6.9%)	26 (10.8%)	0.105			
Sepsis	1 (7.1%)	24 (13.1%)	46 (10%)	40 (16.7%)	0.075			
Transfusion Reaction	0 (0%)	14 (7.7%)	18 (3.9%)	11 (4.6%)	0.243			
Wound Infection	0 (0%)	8 (4.4%)	22 (4.8%)	7 (2.9%)	0.688			
30-day mortality	1 (7.1%)	5 (2.7%)	10 (2.2%)	4 (1.7%)	0.395			

Data are presented as n (column percent) or median (interquartile range).
Univariate P values were calculated using the Chi-square test, Fisher's exact test or the Kruskal-Wallis test, as appropriate.
Multivariable median and logistic regression models were adjusted for age, ASA, procedure type, emergent status, and weight.

*Statistically significant.

BLOOD MANAGEMENT 2

Should we protect or prevent COVID-19 coagulopathy in a time-dependent fashion? The role of anesthesiologist does matter

Dimitar G Tonev[1], Svilen A Alexov[2], Zlatan S Tsonchev[2]

[1]Medical University of Sofia, Bulgaria, Sofia, NY, [2]Medical University of Sofia, Bulgaria, Sofia, Sofia - City

INTRODUCTION: COVID-19 is a complex multisystem inflammatory vasculopathy with significant mortality implication for those admitted to intensive care [1]. Disseminated intravascular coagulopathy (DIC) and severe bleeding events are uncommon in COVID-19 patients. The currently available evidence suggests that COVID-19 coagulopathy represents a combination of localized pulmonary platelet consumption, low-grade DIC (only rarely meeting the International Society on Thrombosis and Hemostasis (ISTH) DIC criteria), and variably a thrombotic microangiopathy[2]. In the context of ongoing controversies about the use of noninvasive ventilation (NIV) versus invasive mechanical ventilation (IMV), as well as intubation timing and criteria[3], a few reports exist regarding bleeding outcomes for in-hospital COVID-19 intensive care patients receiving either prophylactic or therapeutic anticoagulation[4], which is the aim of this study.

METHODS: Data were obtained retrospectively from 90 intensive care patients treated for COVID-19 pneumonia (type L phenotype – not typical of pneumogenic ARDS; type H phenotype – corresponding to pneumogenic ARDS[5]) at 2 healthcare institutions, by manual chart review of the electronic medical records with a data cutoff date of 31 December 2020. Severe illness was defined throughout the study as a hypoxic respiratory failure requiring noninvasive respiratory support (oxygen therapy via a mask with a reservoir, or continuous positive airway pressure (CPAP), or high-flow nasal canula (HFNC)), whereas critical illness was defined as a requirement for endotracheal intubation and lung protective mechanical ventilation, escalated if patient deteriorate rapidly in order to achieve the target SpO2 92-95% without chronic lung disease (COPD) and SpO2 88-92% with COPD. The anesthesiologists with PPE performed all nonoperating room intubations classified as early (within 24 h, on the day of meeting ARDS criteria [6]) and delayed (not intubated on that day). Epidemiology, demographics, medical history, comorbidities (including CCI score[7]), laboratory findings (platelet count, fibrinogen, D-dimer and prothrombin time to calculate ISTH DIC score[8]), treatments (antibiotics, antivirals, proton pump inhibitors or histamine receptor blockers, corticosteroids, prophylactic low-molecular weight heparins [LMWH in therapeutic doses in all intubated on IMV], interventions (noninvasive/invasive oxygen support, intubations) as well as major bleeding medical events[9] during ICU stay were collected accordingly.

RESULTS: IMV was performed on 70 intensive care patients with proven Covid-19 infection and severe bilateral pneumonia, 30% of whom were intubated within 24 hours (early intubation) and 70% after 24 hours (delayed intubation). The remaining 20 non-intubated patients received only non-invasive oxygen support (via mask with a reservoir, HFNC or CPAP). Non-invasive oxygen support was administered to all intensive care patients before being placed on the IMV, within 24 hours (21/70), within 5 days (27/70) and after day 5 (16/70). = 0.001). IMV was performed on all patients meeting the ISTH criteria for overt DIC (≥ 5 points) (15/70), as well as on some of those not meeting the ISTH criteria for overt DIC (<5 points) (55/70, p = 0.020). All non-intubated patients had no overt DIC. Of the intubated patients with overt DIC, there were 2 times more with delayed intubation than early one (p = 0.034). As a complication of coagulopathy, 2 early intubated patients developed major GI bleeding (one survived), and another 2 with delayed intubation were complicated by major GI bleeding and tracheal bleeding (both died). The presence of DIC leads to prolongation of the stay in the intensive care unit and the in-hospital stay of all critically treated patients, as well as the time from admission to the fatal outcome in the non-survivors (p = 0.008).

CONCLUSION: COVID-19 associated coagulopathy(CAC) is an early manifestation in the evolution of DIC[10]. Since CAC is not commonly associated with a bleeding phenotype, anticoagulation is recommended[11]. According to ISTH a change of anticoagulant regimen from prophylactic LMWH can be considered in patients without establishing venous thromboembolism, but deteriorating pulmonary status or acute respiratory distress syndrome [12]. Our findings suggest the growing role of anesthesiologists in the management of bleeding risk in Covid-19 patients under prophylactic or therapeutic anticoagulation in a time-dependent fashion.

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BLOOD MANAGEMENT 3

Acute Normovolemic Hemodilution Decreases Blood Product Utilization in Reoperative Cardiac Surgery

Joseph B Norman[1], Jacob Enslin[1], Benjamin Leahy[1], Luz A Padilla[2], James Davies[2], Kyle Eudailey[2], Domagoj Mladinov[1]

[1]Department of Anesthesiology and Perioperative Medicine, University of Alabama at Birmingham, Birmingham, AL, [2]Division of Cardiothoracic Surgery, Department of Surgery, University of Alabama at Birmingham, Birmingham, AL

INTRODUCTION: Cardiac surgery carries a high risk for blood product transfusion; with major specialties recommending several blood conservation strategies.[1] Acute normovolemic hemodilution (ANH) is one of such strategies that consists of intraoperative removal of whole blood before initiation of cardiopulmonary bypass (CPB), volume replacement with crystalloid or colloid solutions, and its return after separation from CPB.[2,3] The reported variable success may be attributed to lack of standardization and heterogeneity across patient populations and procedure types.[3] In this study we hypothesized that ANH decreased allogeneic blood transfusion in high-bleeding risk cardiac surgeries. Our secondary hypothesis was that transfusion rates were different between various cardiac surgical procedures.

METHODS: Following institutional review board approval, a single-center retrospective case-control study was conducted comparing ANH vs standard institutional practice (control) during 2019-2020. Patients who underwent re-operative cardiac surgery (repeat sternotomy) were included. Exclusion criteria were hemodynamic instability, severely reduced left ventricular function, and hematocrit less than 30%. The ANH protocol consisted of intraoperative removal of whole blood prior to heparin administration and initiation of CPB, and its return after separation from CPB and protamine administration. Primary outcome was allogeneic blood product transfusion rate. ANH and control patient characteristics and outcomes were described and compared using x^2, Fisher's exact, Wilcoxon rank sum, Student's and paired t-test where appropriate. A secondary analysis similar to the primary analysis but stratified by surgical procedure (aortic aneurysm/dissection repair, valve plus coronary artery bypass grafting (CABG), valve only, CABG only) was performed. Lastly, logistic regression was used to identify the association of transfusion across all surgical procedures. All statistical tests of a two-sided <0.05 p-value were considered significant.

RESULTS: A total of 176 patients were included, of which 60 received ANH and 116 controls. The two groups were compared by demographic characteristics, past medical history, preoperative laboratory values and type of performed surgery (Table 1). The ANH group had higher average weight and higher proportion of chronic kidney disease compared to controls ($p \leq 0.02$). The average volume of removed ANH blood was 924mL (± 230, SD). In the ANH group following separation from CPB, coagulation labs were obtained before and after transfusion of the autologous blood demonstrating increased platelet count (from 117 ± 48 to 138 ± 52; 10^3/cmm), increased fibrinogen (from 223 ± 82 to 240 ± 78; mg/dL), and decreased INR (from 1.9 to 1.6), all with a $p < 0.0001$ (Table 2). The proportion of patients who required transfusions (at least one unit of any blood product) was lower in the ANH group vs controls (53.3% vs. 69.8%, $p = 0.03$). The ANH group had also a statistically significant ($p<0.05$) lower average number of transfused fresh frozen plasma (1.2 ± 1.6 vs. 1.8 ± 2.0; units) and cryoprecipitate (0.2 ± 0.6 vs. 0.6 ± 1.0; units); reduction in other blood products was not significant. There was no difference in incidence of postoperative kidney injury between the ANH groups (Table 3). The subgroup analysis by surgical procedure type showed that ANH patients who underwent aortic repair surgery received significantly ($p<0.05$) less fresh frozen plasma (2.2 ± 1.6 vs. 3.8 ± 2.8; units), platelets (1.2 ± 1.1 vs. 2.1 ± 1.5), and cryoprecipitate (0.6 ± 0.9 vs. 1.5 ± 1.4) units compared to controls (Table 4). ANH associated reduction in blood transfusion showed no difference among those with valve only and valve plus CABG repairs.

CONCLUSION: Acute normovolemic hemodilution is a safe blood conservation strategy for high-bleeding risk cardiac surgeries, including repairs of thoracic aortic aneurysms or dissections, operations on multiple valves, CABG, and the combination of those. Laboratory data suggests improved coagulopathy with ANH after separation from CPB. Our study demonstrates reduced incidence of allogeneic blood product transfusion, as well as reduced number of transfused products when ANH is utilized. A decrease in blood transfusion was more pronounced in aortic repairs compared to other procedures. This study highlights the importance of patient and procedure selection, and may contribute to standardization of ANH practice.

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Table 1. Comparison of patients who undergo high risk cardiac surgery and received either Acute Normovolemic Hemodilution (ANH) or Standard Institutional Practice without ANH

	ANH N=60 (34.1%)	No ANH N=116 (65.9%)	*P* value
Age (years)	62.6 ± 11.5	61.1 ± 12.6	0.44
Male (%)	44 (73.3)	74 (63.8)	0.20
Weight (kg)	97.3 ± 21.1	86.1 ± 18.6	0.0004
Past Medical History			
CAD/MI	43 (71.7)	64 (55.2)	0.03
HTN	56 (93.3)	96 (82.8)	0.05
CVA	12 (20.0)	19 (16.4)	0.55
COPD	8 (13.3)	22 (18.9)	0.34
DM	12 (20.0)	21 (18.1)	0.76
CKD	15 (25.0)	14 (12.1)	0.02
Tobacco use (yes)	11 (18.3)	19 (16.3)	0.74
BMI (kg/m^2)	31.7 ± 6.6	28.8 ± 5.6	0.002
STS (%) score*	2.5 ± 3.1	2.5 ± 1.6	0.95
EuroSCORE (%)*	6.8 ± 4.0	9.1 ± 6.6	0.07
Procedure type			0.12
Aortic Aneurysm/Dissection Repair^	21 (35.0)	27 (23.3)	
Valve repair only (one or more)	17 (28.3)	54 (46.5)	
Valve repair + CABG	8 (13.3)	12 (10.3)	
CABG only	14 (23.3)	23 (19.8)	
DHCA (yes)	6 (10.0)	8 (6.9)	0.55
Pre-Operative Creatinine Clearance (abnormal %)	21 (35.0)	28 (24.1)	0.12
Pre-Operative Laboratory values			
Hematocrit (%)	39.1 ± 5.1	38.8 ± 5.2	0.71
Hemoglobin (g/dL)	13.1 ± 1.8	13.0 ± 1.8	0.95
Platelets (10^3/cmm)	206.5 ± 61.0	200.1 ± 68.0	0.53
INR	1.05 [1-1.1]	1.06 [1-1.1]	0.69

Key: CAD=Coronary Artery Disease, MI=Myocardial Infarction, HTN=Hypertension, CVA=Cerebrovascular Accident, COPD=Chronic Obstructive Pulmonary Disease, DM=Diabetes Mellitus Type 2, CKD=Chronic Kidney Disease, DHCA=Deep Hypothermic Circulatory Arrest, CABG=Coronary Artery Bypass Graft, INR=International Normalized Ratio
N (%); mean ± SD; median [Q1-Q3]; ^Some patients may also have undergone a CABG and/or valve repair; * ≥50% of data is missing

Table 2. Coagulation factors among patients who received Acute Normovolemic Hemodilution (ANH) during high risk cardiac surgery (N=60)

	After CPB	After ANH	*P* value
Platelets (10^3/cmm)	116.8 ± 48.1	138.1 ± 52.1	<.0001
Fibrinogen (mg/dL)	222.7 ± 81.6	239.66 ± 78.3	<.0001
INR	1.9 [1.7-2.2]	1.6 [1.5-1.8]	<.0001

Key: CPB=Cardio Pulmonary Bypass; mean ± SD; median [Q1-Q3]

Table 3. Comparison of patients who undergo high risk cardiac surgery and received either Acute Normovolemic Hemodilution (ANH) or Standard Institutional Practice without ANH

	ANH N=60 (34.1%)	No ANH N=116 (65.9%)	*P* value
Transfused during surgery (any product)	32 (53.3)	81 (69.8)	0.03
Packed Red Blood Cell	0.5 ± 1.0	0.7 ± 1.4	0.25
Fresh Frozen Plasma	1.2 ± 1.6	1.8 ± 2.0	0.04
Platelet packs	0.7 ± 1.0	1.0 ± 1.2	0.09
Cryoprecipitate	0.2 ± 0.6	0.6 ± 1.0	0.01
24 hours after surgery			
Chest tube output (ml)	488.3 ± 307.6	473.0 ± 261.3	0.73
Creatinine (mg/dL)	1.1 [0.8-1.4]	1.0 [0.8-1.3]	0.11
Blood Urea Nitrogen (mg/dL)	21.4 ± 8.2	20.6 ± 8.1	0.54
Creatinine Clearance (% abnormal)	27 (45.0)	40 (34.8)	0.18

N (%); mean ± SD; median [Q1-Q3]

Table 4. Comparison of transfusion products for patients who received Acute Normovolemic Hemodilution (ANH) or Standard Institutional Practice without ANH stratified by type of high risk cardiac surgery

	Aortic repair N=48			Valve only repair N=71			Valve + CABG N=20			CABG only N=37		
	ANH 21 (44%)	No ANH 27 (56%)	*P* value	ANH 17 (24%)	No ANH 54 (76%)	*P* value	ANH 8 (40%)	No ANH 12 (60%)	*P* value	ANH 14 (38)	No ANH 23 (62)	*P* value
Transfused (any product)	17 (81)	23 (85)	0.71	9 (53)	33 (61)	0.55	4 (50)	10 (83)	0.16	2 (14)	15 (65)	**0.002**
Packed Red Blood Cell	1.0±1.5	1.7±2.3	0.23	0.2±0.5	0.3±0.7	0.33	0.3±0.5	0.5±0.8	0.43	-	-	-
Fresh Frozen Plasma	2.2±1.6	3.8±2.8	**0.01**	1.2±1.5	1.1±1.2	0.81	1.1±1.6	2.0±1.4	0.17	-	-	-
Platelet packs	1.2±1.1	2.1±1.5	**0.03**	0.5±0.7	0.4±0.6	0.79	0.9±1.1	1.1±0.8	0.51	-	-	-
Cryoprecipitate	0.6±0.9	1.5±1.4	**0.01**	-	-	-	-	-	-	-	-	-

Key: CABG=Coronary Artery Bypass Graft; N (%); mean ± SD; - Unable to compute due to small/non-existent values

BLOOD MANAGEMENT 4

A retrospective study of the off-label Use of Activated 4-Factor Prothrombin Complex Concentrate in Neonates after Cardiac Surgery

Kati A Miller[1], Nina Guzzetta[2], Laura A Downey[1]

[1]Children's Healthcare of Atlanta, Atlanta, GA, [2]Emory University School of Medicine, Atlanta, GA

INTRODUCTION: Postoperative bleeding in patients requiring congenital cardiac surgery is associated with increased morbidity and mortality[1-2]. Immature coagulation systems, cardiopulmonary bypass (CPB) effects, and complex surgery result in postoperative bleeding, necessitating blood product transfusions[3]. While blood transfusions are often needed to restore post-CPB hemostasis, some patients have refractory bleeding despite maximal standard hemostatic therapy. Activated Four Factor Prothrombin Complex Concentrates (4F-PCCs), such as Factor Eight Inhibitor Bypass Activator (FEIBA, Baxter Healthcare Corp. Westlake Village, CA), are being used off-label to treat refractory bleeding and reduce transfusions in adult cardiac surgery patients after CPB[4-5]. There is a paucity of data the safety and efficacy of the off-label use of the activated 4F-PCC as rescue therapy for children undergoing cardiac surgery. Here we compare neonates who underwent cardiac surgery with CPB who received a 4F-PCC for rescue therapy with those who did not.

METHODS: After IRB approval, we queried our institutional database between January 1, 2017 and April 8, 2020 for patients undergoing cardiac surgery requiring CPB who received a 4F-PCC. We also queried our database during the same time period for neonates undergoing cardiac surgery with CPB who did not receive 4F-PCC to provide a control group for comparison. Our primary outcome was total blood products (ml/kg) after CPB. Secondary outcomes included component blood products (ml/kg), intensive care unit (ICU) and hospital length of stay (LOS), mechanical ventilation time, 24hr chest tube output (CTO), ICU arrival lab values, and adverse events (AE).

RESULTS: Patient demographics and intraoperative data are shown in Table 1. Patients receiving 4F-PCC were older (8 v 5 days, $p<0.05$), had a lower preoperative hemoglobin (12.8 v 14.4 mg/dL, $p<0.05$), and higher STAT scores (100% 4 or 5 v 72% of non-FEIBA). Intraoperative variables were similar between groups. Table 2 shows the 4F-PCC group had more total transfusions post-CPB (87.6 v 35.0 ml/kg, $p<0.001$), as well as more component transfusions post-CPB. ICU LOS and mechanical ventilation time were longer, and 24hr CTO was higher in the 4F-PCC group (14.7 v 5.4 ml/kg, $p<0.02$). The 4F-PCC group had more normalized coagulation labs on ICU arrival than control patients (fibrinogen 347 v 280 mg/dl, $p=0.025$), INR 1.2 v 1.4, $p=0.003$) (Table 3). AE were similar between groups, though there were more arrythmias in the 4F-PCC group (36.4% v 0, $p=0.004$) (Table 4). In patients who received 4F-PCC as a rescue therapy for bleeding, significantly less platelets and cryoprecipitate (cryo) were given after 4F-PCC administration (Table 5).

CONCLUSION: Given the increased morbidity and mortality associated with blood transfusions, finding safe and effective blood product alternatives to restore post-bypass hemostasis in pediatric patients is paramount. Our retrospective study suggests that neonatal patients who receive 4F-PCC for refractory bleeding receive significantly less platelets and cryoprecipitate after 4F-PCC administration. However, this study demonstrates that while low dose 4F-PCC administration used as a rescue therapy may achieve hemostasis in the operating room and treats coagulopathy assessed by ICU arrival laboratory values, CTO at 24h is significantly higher in the 4F-PCC group. These patients also had significantly longer mechanical ventilation times, and hospital and ICU LOS. However, severe AE were significantly lower in patients who received a 4F-PCC. It is important to note the limitations of this small retrospective investigation. At our institution, 4F-PCC is primarily used as rescue therapy, which introduces a bias in patient selection that may not be captured in our demographic data. In order to answer questions regarding safety and efficacy, a randomized trial will be required to determine is 4F-PCC may be a safe and effective hemostatic agent for rescue therapy in neonates with refractory bleeding after CPB.

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Table 1. Patient Demographics and intraoperative data between 4 Factor-PCC Group and Control group

		N	Overall N=40	4F-PCC Group N=11	Control Group N=29	P-Value	SMD
Gender[a]	Female	40	14 (35.0%)	4 (36.4%)	10 (34.5%)	0.911	-0.039
	Male		26 (65.0%)	7 (63.6%)	19 (65.5%)		
Weight (kg)[b]		40	3.1 (2.7, 3.4)	3.2 (2.5, 3.6)	3.1 (2.7, 3.4)	0.796	-0.014
Height (cm)[b]		40	49 (47.3, 51)	51.0 (45.0, 52.5)	49.0 (47.5, 50.5)	0.474	0.094
Age (days)[b]		40	6 (4, 8.5)	8 (6, 13)	5 (3, 7)	**0.019**	0.611
Prematurity[a]	No	40	35 (87.5%)	9 (81.8%)	26 (89.7%)	0.503	0.226
	Yes		5 (12.5%)	2 (18.2%)	3 (10.3%)		
Race[a]	Black	40	15 (37.5%)	2 (18.2%)	13 (44.8%)	0.120	0.599
	White		25 (62.5%)	9 (81.8%)	16 (55.2%)		
Preoperative Hemoglobin (gm/dL)[b]		40	14.1 (12.7, 16)	12.8 (12.4, 14.5)	14.4 (13.1, 16)	**0.033**	0.814
Baseline Saturation[b]		40	93 (90, 95)	94.0 (88.0, 95.0)	93.0 (90.0, 95.0)	0.761	0.103
STAT Score[a]	2	38	2 (5.3%)	0 (0.00%)	2 (6.9%)	0.135	1.059
	3		6 (15.8%)	0 (0.00%)	6 (20.7%)		
	4		22 (57.9%)	5 (55.6%)	17 (58.6%)		
	5		8 (21.1%)	4 (44.4%)	4 (13.8%)		
Anesthesia Time (min)[b]		40	508.5 (461, 582)	585.0 (463.0, 705.0)	507.0 (459.0, 535.0)	0.282	0.453
Procedure Time (min)[b]		40	354.5 (316, 429)	393.0 (323.0, 530.0)	351.0 (312.0, 374.0)	0.126	0.262
CPB Time (min)[b]		40	191 (127.5, 228.5)	218.0 (105.0, 282.0)	189.0 (129.0, 212.0)	0.296	0.409
Aortic Cross Clamp[a]	No	40	4 (10.0%)	1 (9.1%)	3 (10.3%)	0.906	0.042
	Yes		36 (90.0%)	10 (90.9%)	26 (89.7%)		
Aortic Cross Clamp Time (min)[b]		36	124.5 (70, 160.5)	125.5 (73, 180)	124.5 (67, 154)	0.525	0.295
Regional Perfusion[a]	No	40	26 (65.0%)	8 (72.7%)	18 (62.1%)	0.528	0.229
	Yes		14 (35.0%)	3 (27.3%)	11 (37.9%)		
Circulatory Arrest[a]	No	40	25 (62.5%)	5 (45.5%)	20 (69.0%)	0.170	0.489
	Yes		15 (37.5%)	6 (54.5%)	9 (31.0%)		
Circulatory Arrest Time (min)[b]		15	25 (9, 44)	22.5 (5, 72)	25.0 (14.0, 42.0)	1.000	0.277
Lowest Temperature (C)[b]		40	19 (18, 28)	18.0 (18.0, 31.9)	20.0 (18.0, 28.0)	0.847	0.038

[a] = Number (%)
[b] = Median (25%, 75%)
PCC = Prothrombin Concentrate Complex; CPB = Cardiopulmonary Bypass
SMD guideline (Effect Size): 0.20 = small effect size; 0.50 = medium effect size; 0.80 Large effect size

Table 2. Comparison of Blood Product Transfusions between 4Factor-PCC Group and Matched Controls

Variable	N	Overall N=40	4F-PCC Group N=11	Control Group N=29	P-Value
Total PRBCs (ml/kg)[a]	40	89.1 (68.1, 126.6)	112.1 (87.6, 154.0)	79.4 (65.4, 103.3)	**0.034**
Total FFP (ml/kg)[a]	40	35.8 (29.9, 44.2)	40.0 (30.3, 50.8)	34.5 (29.4, 41.7)	0.422
Total Platelets (ml/kg)[a]	39	26.6 (19.1, 37.6)	44.4 (30.9, 57.9)	21.2 (16.2, 32.4)	**0.003**
Total Cryoprecipitate (ml/kg)[a]	38	13.9 (11.5, 17.1)	17.1 (15.2, 24.4)	11.9 (10.0, 15.3)	**0.002**
Total Blood Products (ml/kg)[a]	40	170.8 (139.6, 214.4)	207.9 (182.5, 255.6)	149.6 (123.1, 184.1)	**0.002**
Total PRBCs post-bypass (ml/kg)[a]	40	0 (0, 16)	26.0 (10.0, 45.5)	0 (0, 11.111111111)	**0.002**
Total FFP post-bypass (ml/kg)[a]	40	0 (0, 0)	0 (0, 20.588235294)	0 (0, 0)	**0.019**
Total Platelets post-bypass (ml/kg)[a]	39	26.6 (19.1, 37.6)	44.4 (30.9, 57.9)	21.2 (16.2, 32.4)	**0.003**
Total Cryoprecipitate post-bypass (ml/kg)[a]	38	13.9 (11.5, 17.1)	17.1 (15.2, 24.4)	11.9 (10.0, 15.3)	**0.002**
Total Blood Products post-bypass (ml/kg)[a]	40	50.7 (30.2, 85.1)	87.6 (77.1875, 121.17647059)	35.0 (25.0, 61.3)	**<.001**

[a] = Number (%)
PCC = Prothrombin Concentrate Complex; CPB = Cardiopulmonary Bypass, PRBCs = Packed Red Blood Cells
SMD guideline (Effect Size): 0.20 = small effect size; 0.50 = medium effect size; 0.80 Large effect size

Table 3. Patient Outcomes between patients who received 4 Factor-PCC and Control

	N	Overall N=40	FEIBA patients N=11	No FEIBA N=29	P-Value
FEIBA (units/kg)[a]	11	10.6 (9.4, 20.5)	10.6 (9.4, 20.5)	- (-, -)	-
24h CTO (ml/kg)[a]	40	7.2 (4.4, 20.2)	14.7 (6.7, 28.8)	5.4 (3.8, 10.4)	**0.017**
Mechanical Ventilation Time (min)[a]	40	98.4 (51.8, 157.3)	123.7 (98.1, 267.0)	63.6 (35.6, 105.7)	**0.009**
ICU LOS (days)[a]	40	10 (6, 23.5)	21.0 (10.0, 42.0)	7 (5, 18)	**0.021**
Hospital LOS (days)[a]	40	26.5 (15.5, 51.5)	35.0 (28.0, 51.0)	19.0 (14.0, 52.0)	0.054
ICU Hemoglobin level[a]	40	14.2 (13, 15.1)	14.7 (12.7, 16)	13.6 (13, 15)	0.422
ICU Hematocrit level[a]	40	41.4 (37.8, 44.2)	42.0 (38.1, 44.3)	40.4 (37.7, 44.1)	0.694
ICU Platelet Count[a]	40	196.5 (178, 250.5)	211.0 (195.0, 302.0)	193.0 (152.0, 223.0)	0.069
ICU Fibrinogen level[a]	40	295.5 (235, 347.5)	347.0 (279.0, 389.0)	280.0 (223.0, 310.0)	**0.025**
ICU INR[a]	40	1.4 (1.3, 1.5)	1.2 (1.1, 1.3)	1.4 (1.3, 1.5)	**0.003**
ICU PTT[a]	40	37.6 (35.9, 43)	39.2 (31.9, 77.8)	37.5 (36.2, 41.1)	0.832
ICU PT[a]	40	16.8 (15.9, 17.6)	15.8 (14.6, 17.7)	17.0 (16.4, 17.5)	0.092

[a] = Median, 25% percentile, 75% percentile
PCC = Prothrombin Concentrate Complex, CTO = Chest Tube Output; ICU = Intensive Care Unit; PTT = Partial Thromboplastin Time; PT = Prothrombin Time

Table 4. Adverse Events in Neonates between 4-PCC Group and Control group

		N	Overall N=40	4-PCC Group N=11	Control Group N=29	OR (95% CI)	P-Value
Thrombosis requiring intervention (within 7 days)?[a]	No	40	37 (92.5%)	11 (100.0%)	26 (89.7%)	0.65 (0.00 - 4.57)	0.370
	Yes		3 (7.5%)	0 (0.00%)	3 (10.3%)		
Requiring ECMO within 24 hrs?[a]	No	40	39 (97.5%)	11 (100.0%)	28 (96.6%)	2.64 (0.00 - 50.09)	0.725
	Yes		1 (2.5%)	0 (0.00%)	1 (3.4%)		
Repeat Surgery[a]	No	40	31 (77.5%)	9 (81.8%)	22 (75.9%)	0.70 (0.12 - 4.03)	0.688
	Yes		9 (22.5%)	2 (18.2%)	7 (24.1%)		
Chest Exploration[a]	No	40	34 (85.0%)	9 (81.8%)	25 (86.2%)	1.39 (0.22 - 8.93)	0.729
	Yes		6 (15.0%)	2 (18.2%)	4 (13.8%)		
Arrhythmia requiring treatment[a]	No	39	35 (89.7%)	7 (63.6%)	28 (100.0%)	17.88 (2.80 - Unestimable)	**0.004**
	Yes		4 (10.3%)	4 (36.4%)	0 (0.00%)		
Infection[a]	No	40	36 (90.0%)	11 (100.0%)	25 (86.2%)	0.46 (0.00 - 2.92)	0.260
	Yes		4 (10.0%)	0 (0.00%)	4 (13.8%)		
Stroke[a]	No	40	39 (97.5%)	11 (100.0%)	28 (96.6%)	2.64 (0.00 - 50.09)	0.725
	Yes		1 (2.5%)	0 (0.00%)	1 (3.4%)		
Death[a]	No	40	34 (85.0%)	8 (72.7%)	26 (89.7%)	3.25 (0.54 - 19.38)	0.196
	Yes		6 (15.0%)	3 (27.3%)	3 (10.3%)		
Death less than 24 hrs[a]	No	40	40 (100.0%)	11 (100.0%)	29 (100.0%)		-
Death less than 30 days[a]	No	40	37 (92.5%)	9 (81.8%)	28 (96.6%)	6.22 (0.50 - 76.96)	0.154
	Yes		3 (7.5%)	2 (18.2%)	1 (3.4%)		

[a] = Number (%)
PCC = Prothrombin Concentrate Complex

Table 5. Blood products before and after 4-Factor PCC in neonates who receive 4F-PCC

Variable	N	Before 4-F PCC	After 4F-PCC	P-Value
PRBCS (ml/kg)	11	13.2 (0.0, 30.8)	0 (0, 17.65)	0.461
FFP (ml/kg)	11	0 (0, 1.92)	0 (0, 14.74)	0.250
Platelets (ml/kg)	11	26.6 (19.6, 45.2)	8.3 (0.0, 15.3)	**0.019**
Cryo (ml/kg)	11	16.4 (11.94, 24.4)	0 (0, 0)	**0.005**

PCC = Prothrombin Concentrate Complex; PRBCs = Packed Red Blood Cells
[a] = Median, 25 percentile, 75 percentile

BLOOD MANAGEMENT 5

The Wash-Out Effect of Intravenous Iron by Cell Savers: A prospective, single center pilot study in patients

Roman M Olivier[1], Marcel Macke[2], Deniz Y Dogan[1], Uwe Karst[2], Andrea U Steinbicker[3]

[1]University Hospital Muenster, Muenster, Germany, [2]University of Muenster, Muenster, Germany, [3]University Hospital Muenster, Department of Anesthesiology, Intensive Care and Pain Medicine, Muenster, Germany

INTRODUCTION: Iron deficiency anemia is an ongoing global health burden. As part of Patient's Blood Management (PBM), Cell Saver (CS) usage is considered international standard in surgery of patients with expected high blood loss without inflammation or cancer to retransfuse patient's own red blood cells. CS has positive hematological effects and can reduce the need of allogenic red blood cell concentrates (RBCs). In iron-deficient patients, who undergo major surgery in less than 6 weeks, intravenous (IV) iron supplementation is strongly recommended[1,2], for example with a single dose of 500 milligrams (mg) ferric carboxymaltose (FCM), showing a terminal elimination half-life of 7.4 to 12.1 hours[3]. Frequently, FCM is given only 1-2 days prior to surgery. The first hypothesis of this trial is that FCM will still remain within the patient's blood preoperatively, if substituted less than 48 hours prior to surgery. The second hypothesis is that FCM will be washed-out from the patient's blood by using CS, which has to be elucidated in the ongoing trial.

METHODS: With approval of the ethical committee and written informed consent, adult patients undergoing elective cardiac surgery were screened for anaemia and iron deficiency defined as haemoglobin (Hb) < 12/13 g/dL (women/men), transferrin saturation < 20%, ferritin serum levels < 200 Mg/L. The trial was registered at clinical trials.gov (NCT04631679). So far, a total of 20 patients (10 anaemic, 10 non-anaemic) were included in this clinical, prospective pilot study. Patients were recruited between 11/2019 – 07/2020 at one University hospital in Germany. Anaemic patients received 500 mg FCM 1-4 days prior to surgery. Non-anaemic patients remained untreated. Seven heparinised samples were drawn from each patient as follows: directly prior to surgery, intraoperatively from CS red blood cell concentrate (CS-RBC), heart-lung machine (HLM), CS disposal bag (CS-DB), patient's blood postoperatively on day 0, 3 and 7. Analytical Chemistry Samples were centrifuged and the collected blood plasma was filtered and diluted for further analysis. Determination of FCM levels was carried out using hyphenation of size-exclusion chromatography (SEC) and inductively coupled plasma-mass spectrometry (ICP-MS). The application of SEC enabled a successful separation of FCM and the iron-containing protein fraction of holo-transferrin. Furthermore, ICP-MS allowed for a sensitive element-specific quantification of iron with detection limits in low ng/mL range. Statistical analysis Data were analysed using GraphPad Prism 9 and Microsoft Excel. Amount of FCM in CS-DB or CS-RBC in anaemic patients treated with FCM was tested against FCM in CS-DB in non-anaemic non FCM treated controls and against the value '0' (for CS-DB). Anaemic patients were split into 2 subgroups with 5 participants each: 1.) IV iron substitution < 48 h ('< 48 h') and 2.) > 48 h ('> 48 h') prior to surgery. Nonparametric Mann-Whitney U tests were performed.

RESULTS: FCM could be discriminated by means of SEC-ICP-MS from body's own iron. Blood of non-anaemic patients (controls) showed FCM levels of < 0.1 µg/mL (= below level of quantification), as required for internal validity. IV iron substitution '< 48 h' resulted in higher preoperative FCM serum levels compared to '> 48 h'. Despite a wide individual range, FCM levels in HLM and CS-DB were higher in '< 48 h' than in '> 48 h' (***p < .0001).

CONCLUSION: The timeframe of FCM substitution less than 48 hours prior to surgery resulted in higher values of FCM in patient's serum and in the CS-DB compared to longer than 48 hours prior to surgery. FCM treatment longer than 48 hours prior to surgery seem beneficial to incorporate administered iron into body iron stores. The data suggest a wash-out effect by CS. Future trials will have to investigate the wash out effect further. Funding The study was funded by Innovative Medical Research Funding, Medical Faculty of Muenster University, Muenster, Germany (AUS). Figure legend: FCM levels [Mg/mL] in the following compartments: Patient's blood in Heart-Lung machine (HLM), Cell Saver red blood cell concentrate (CS-RBC) and Cell Saver disposal bag (CS-DB). Values split by '< 48 h' (black) and '> 48 h' (magenta) subgroups and control group (teal, Group B). *** p < .0001; n.s., not significant.

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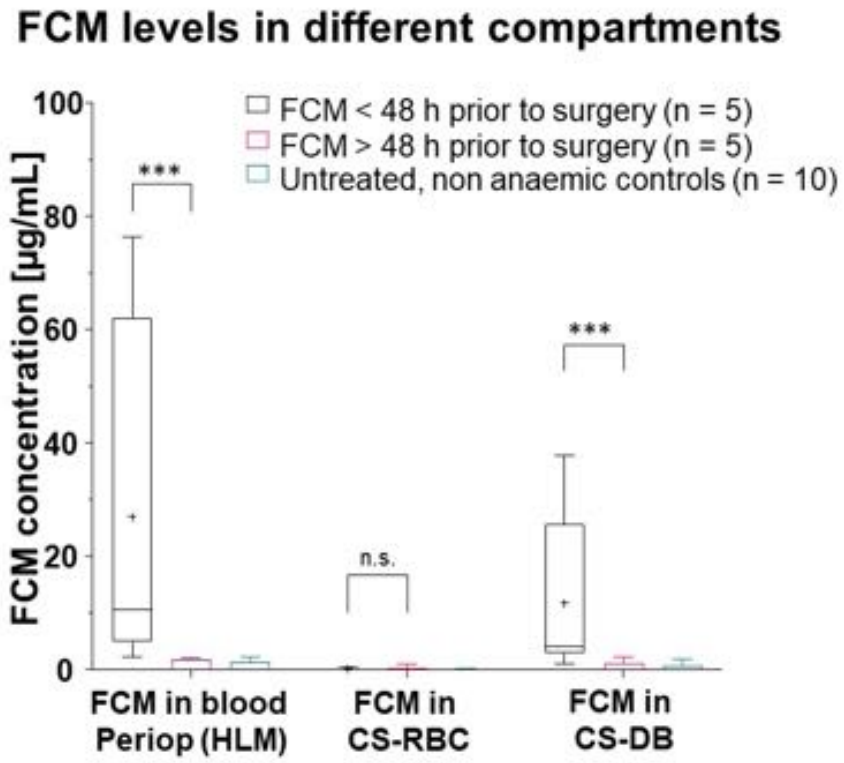

BLOOD MANAGEMENT 6

Reliability and Waste Reduction in Perioperative Blood Management: A Failure Modes and Effects Analysis

Megan Dewey[1], Mara Bollini[1], Troy Wildes[1], Tracey W Stevens[1], Derek Harford[1], Renata Slayton[2], Cindy Ingold[2], Brenda Grossman[1], Jackie Martin[2], Ivan Kangrga[1]

[1]Washington University School of Medicine, St. Louis, MO, [2]Barnes-Jewish Hospital, St. Louis, MO

INTRODUCTION: Blood product waste strains healthcare system, increasing costs and compromising transfusion capabilities. While acceptable rates of blood waste have not been determined, conservation efforts remain a focus of continuous improvement in academic centers worldwide. At this large academic institution, historically high rates of blood product ordering, return, and waste may reflect inadequate trust in current processes, lack of standardization, and poor inter-team communication.

METHODS: A multidisciplinary quality improvement initiative targeted the surgical suite with the highest utilization of blood products, which includes the cardiothoracic, vascular, and transplant surgery operating rooms. The primary aim was to design and implement a standardized, reliable process for blood delivery and administration that would ensure safe handling and minimize waste measures. Target outcomes of this project were reduction in red blood cell unit waste, reduction in packed red blood cell (PRBC) unit return, and improvement in reliability and satisfaction survey scores. The method of Failure Modes and Effects Analysis (FMEA), performed among a diverse group of physicians and staff involved in the blood management process, served as a foundation for advancement beginning in April 2019. This methodology allowed for close scrutiny of every step in the process of obtaining and using blood in the operating room in order to best target areas of improvement.

RESULTS: Multiple improvements were successfully implemented to target areas of weakness. The highest-yield interventions included mandatory educational modules, rapid-turnover audits of waste with the clinical team, and a modified blood tracking application in the EMR. As of December 2020, waste of PRBC units in target operating rooms was reduced by 55%. This effect was mirrored across all operating rooms, with reduction in total blood product waste achieved through the same educational and process improvement initiatives. Results also demonstrate reduction in units returned to the blood bank and improved satisfaction and reliability scores.

CONCLUSION: The FMEA process effectively prioritized the areas most in need of improvement and incorporated multidisciplinary input to address all points of failure. This encouraging progress serves as a starting point for ongoing initiatives, which target both longer-term endpoints and the maintenance of improved perioperative blood management.

BLOOD MANAGEMENT 7

Blood Product Utilization for Severe Anemia and Acute Kidney Injury at a Tertiary Hospital in Malawi

Meghan Prin[1], Alex Kaizer[2], Onias Mtalimanja[3], Ernest Eugene Moore[4], Adit Ginde[5]

[1]University of Colorado School of Medicine, Aurora, CO, [2]University of Colorado School of Public Health, Aurora, CO, [3]Kamuzu Central Hospital, Lilongwe, Malawi, [4]Denver Health Trauma Surgery, Denver, CO, [5]University of Colorado, Aurora, CO

INTRODUCTION: Blood products are an essential component of quality surgical care. This is especially relevant in sub-Saharan Africa, where endemic conditions increase the prevalence of pre-operative anemia. Over half of the world's blood donations occur in high-income countries, while >60% of the global population lives in low-income countries. In 2000, the WHO recognized the global blood crisis and developed a strategy focused on centralizing blood transfusion services. Despite this effort, blood product shortages persist. It is not clear if there are differences in the utilization of blood products between different surgical populations. This study aimed to evaluate how the use of blood products in Malawi differs between critically ill general surgery and obstetric patients, and the association of anemia and transfusion with acute kidney injury.

METHODS: This was a secondary analysis of data collected prospectively in the adult intensive care unit (ICU) at a tertiary referral hospital in the capitol of Malawi, a small country in southern Africa, from 2016-18. This database describes the demographics, clinical status and course (e.g. vital signs, use of mechanical ventilation, use of blood products), laboratory measurements, and hospital outcomes for patients admitted to the ICU. We included all patients admitted to the ICU from either the Department of Obstetrics & Gynecology (OBGyn) or General Surgery (GS) who received a urinary catheter, and excluded all readmissions. We stratified the cohort by admitting service and ICU admission hemoglobin (using a common cutoff value for blood transfusion: <7.0g/dL versus ≥7.0g/dL), and performed descriptive analyses with a focus on enumerating the proportion of patients for whom blood was ordered and given in a timely manner. We looked for differences in these variables between the OBGyn and General Surgery groups. The primary outcome was acute kidney injury, defined using the Acute Kidney Injury Network oliguria criteria which were most feasible in our low-resource setting. (Figure 1) Other outcomes of interest included hospital mortality. Summary statistics are presented as mean (standard deviation, SD) and frequency (%). Regression analyses examine unadjusted and adjusted models, with ordinal logistic and logistic regression models applied to ordinal and binary outcomes, respectively. All analyses used R v3.6.3 (Vienna, Austria).

RESULTS: After exclusions, 279 patients (114 OBGyn and 165 GS) were included for analysis. OBGyn patients had a mean age of 28 years (SD 8, all female) and the GS group had a mean age of 37 years (SD 19) and was 41% female. The vast majority of patients in both groups had surgery within the index hospitalization. In the OBGyn group, 30% of patients were admitted to ICU with plasma hemoglobin <7.0g/dL compared to 11% of GS patients. Blood products were ordered for 67% and 62% of OBGyn and GS patients, respectively, with 54% and 50% of patients in each group receiving blood within 24 hours of ordering it. Almost all blood transfusions were whole blood. Acute kidney injury occurred in 53% of OBGyn patients and 35% of General Surgery patients. In ordinal logistic regression, OBGyn patients were not more likely than GS patients to develop acute kidney injury. In both the unadjusted and adjusted models, OBGyn patients had a significantly lower odds of death compared to General Surgery. Holding other variables in the adjusted model constant, the odds of death for OBGyn patients are 0.38 (95% CI: 0.22 to 0.67) times those of general surgery (p<0.001).

CONCLUSION: A better understanding of the supply and demand of blood products is imperative to improving quality surgical care in the sub-Saharan African region. This study shows that whole blood is the predominant product used in a tertiary hospital of Malawi, where a large proportion of ICU patients are admitted with severe anemia but blood products are not available on a timely basis. Although acute kidney injury was common in both groups, there was no difference groups. Further research may focus on evaluation of different hemoglobin thresholds for severe anemia and/or improving the timely provision of blood products in this region.

Figure 1. Acute Kidney Injury Network Definitions

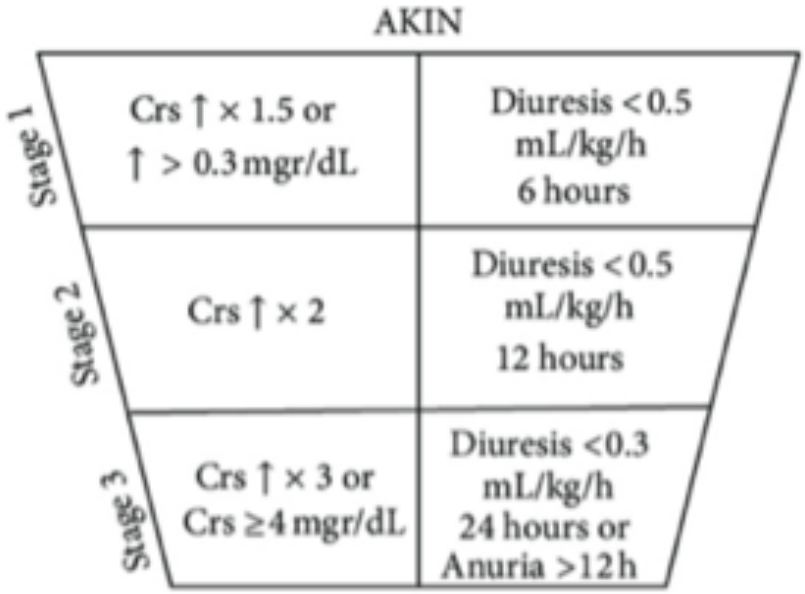

Table 1. Clinical traits of Obstetric and General Surgery Patients Admitted to the ICU of a tertiary hospital in Malawi, 2016-18			
	Overall (n=279)	**OBGyn (n=114)**	**General Surgery (n=165)**
Female	182 (65)	114 (100)	68 (41)
Age (years)	33 (16)	28 (8)	37 (19)
Admit From:			
High-Dependency Unit	57 (20)	43 (38)	14 (9)
Operating Theater	198 (71)	56 (49)	142 (86)
General Ward	14 (5)	7 (6)	7 (4)
Other	10 (4)	8 (7)	2 (1)
Surgery during index hospitalization	252 (90)	95 (83)	157 (95)
Vital Signs at ICU Admission			
Heart Rate at Admit	122 (27)	126 (26)	120 (27)
Systolic BP (mmHg)	113 (29)	117 (27)	110 (30)
Diastolic BP (mmHg)	69 (22)	72 (21)	67 (22)
Respiratory Rate	21 (9)	23 (9)	20 (8)
Temperature, C	36 (2)	36 (2)	36 (2)
Laboratory Measurements at ICU Admission			
Anemia (Hemoglobin<7)	52 (19)	34 (30)	18 (11)
Hemoglobin	9.3 (3.1)	8.2 (3.1)	10.1 (2.7)
Mean Corpuscular Volume	84 (9)	85 (7)	83.0 (10)
Red Cell Distribution Width	13.3 (4)	13.7 (4)	13.0 (4)
Platelet Count	184 (125)	168 (119)	195 (130)
Sodium	145 (10)	145 (10)	145 (10)
Potassium	4.7 (1.4)	4.6 (1.4)	4.8 (1.4)
Serum Bicarbonate	17 (13)	15 (7)	18 (15)
Blood Urea Nitrogen	39.3 (43)	27.6 (21)	46.6 (51)
Creatinine	2.22 (3.1)	1.63 (1.8)	2.6 (3.7)
HIV	29 (10)	10 (9)	19 (12)
Malaria	15 (5)	10 (9)	5 (3)
Blood Product Utilization			
Blood products ordered	179 (64)	76 (67)	103 (62)
Blood products given within 24 hours	144 (52)	61 (54)	83 (50)
Blood products ever given	154 (55)	66 (58)	88 (53)
Whole blood utilization	143 (51)	60 (53)	83 (50)
Outcomes			
Acute Kidney Injury			
Stage 1	31 (11)	18 (16)	13 (8)
Stage 2	78 (28)	28 (25)	50 (30)
Stage 3	45 (16)	14 (12)	31 (19)
Duration of mechanical ventilation, days	4.42 (5)	4.47 (5)	4.38 (5.5)
ICU Length of Stay, days	3.78 (5)	3.85 (5)	3.73 (5)
Hospital Length of Stay, days	13.9 (17)	14.4 (20)	13.6 (15)
ICU mortality	134 (48)	41 (36)	93 (56)
Hospital mortality	153 (55)	49 (43)	104 (63)

ICU: intensive care unit; OBGYN: Obstetrics & Gynecology; BP: blood pressure; mmHg: millimeters of Mercury; C: Celcius; HIV: Human immunodeficiency virus

Table 2. Ordinal logistic regression for outcome of Acute Kidney Injury						
	Unadjusted			***Adjusted***		
Covariate	OR	95% CI	p-value	OR	95% CI	p-value
None | Stages 1-3	0.62		0.003	0.68		0.075
None - Stage 1 | Stages 2-3	0.99		0.961	1.10		0.661
None - Stage 2 | Stage 3	4.25		<0.001	4.95		<0.001
OBGyn (vs. General Surgery)	0.69	(0.44, 1.08)	0.103	0.84	(0.50, 1.38)	0.486
Anemia (Hemoglobin < 7)				0.70	(0.37, 1.32)	0.277
Blood Given within 24 Hours				1.52	(0.93, 2.50)	0.093

BLOOD MANAGEMENT 8

The Incidence and Etiology of Perioperative Anemia in Infants and Children Undergoing Surgery for Craniosynostosis at a Single Tertiary Care Hospital

Janice Davis[1], Karina Lukovits[2], Steven Staffa[3], Mark Proctor[2], John Meara[2], Susan Goobie[4]

[1]Boston Children's Hospital, Boston, MA, [2]Boston Children's Hospital, Boston, MA, [3]Children's Hospital Boston, Boston , MA, [4]Harvard Medical School, Boston, MA

INTRODUCTION: Craniosynostosis is defined as premature fusion of cranial sutures. Surgical intervention depends on age at presentation. If diagnosed early, infants (typically ages 2-5 months) undergo endoscopic suturectomy (ES) whereas older children (generally ages 9-48 months) undergo cranial vault restructuring (CVR). Despite ES minimizing operative time and reducing blood loss, infants typically present with anemia pre-operatively, making them particularly vulnerable to blood loss and increasing the likelihood of requiring a blood transfusion[1]. High rates of blood loss and blood transfusion are reported in children undergoing CVR[2]. An important patient blood management intervention is early diagnosis and treatment of anemia[3]. The primary aim of this study was to determine the incidence of perioperative anemia in children with craniosynostosis presenting for ES or CVR surgery. The secondary aim was to determine the etiology of perioperative anemia. We hypothesized that the rate of preoperative anemia in our cohort was at least 20% based on our preliminary work and World Health Organization data[4,5].

METHODS: This retrospective observational study received local IRB approval. Data was collected from Powerchart, Surginet, and the Anesthesia Electronic Medical Record (AIMS). A de-identified database was created for patients ages 0-18 who underwent endoscopic suturectomy or cranial vault restructuring from 2017 to 2020. Preoperative labs were observed for anemia, iron depletion (ID), iron deficiency erythropoiesis (IDE), and iron deficiency anemia(IDA). Anemia was defined as Hemoglobin or hematocrit (Hb/Hct) less than the accepted pre-defined age specific cutoff thresholds as follows: 1-2 months (9.4/28); 2-6 months (10/31); 6 months – 2 years (10.5/33) and 2-4 years (11/34). Iron depletion (ID) was defined as plasma ferritin <10 ng/mL or iron <30 mcg/dL with normal Hb/Hct. IDE is defined as total iron binding capacity (TIBC) > than 420 mcg/dL or transferrin iron saturation <20% with a reticulocyte count > 2% and normal (Hb/Hct). IDA is defined as TIBC >420 mcg/dL or transferrin saturation <20%. Continuous data are presented as medians and interquartile ranges (IQR), and categorical data are presented as frequencies and percentages. Rates are presented as percentages with binomial exact 95% confidence intervals.

RESULTS: A total of 235 infants and children were included. The median age was 3.1 months (IQR: 2 – 10.4). The majority of patients were male; 68.9% and 71 % underwent ESC, and 29 % underwent CVR. Among patients 48 months of age or younger, the anemia rate was 53/235 (23.6%; 95% CI: 17.4% to 28.4%) of which the IDA rate was 20/152 (13.2%; 95% CI: 8.2% to 19.6%). Among non-anemic patients 48 months of age or younger, the ID rate is 3/112 (2.7%; 95% CI 0.6% to 7.6) and the iron deficiency erythropoiesis rate is 61/106 (57.6%; 95% CI: 47.6% to 67.1%). Among patient 6 months of age or younger, the anemia rate was 38/161 (23.6%: 95% CI: 17.3% to 30.9%) of with the IDA rate was 10/100 (10%: 95% CI: 4.9% to 17.6%). Among non-anemic patient 6 months of age or younger, the ID rate was 2/73 (2.7%: 95% CI: 0.3% to 9.6%) and the iron deficiency erythropoiesis rate was 35/70 (50%: 95% CI: 37.8% to 62.2%).

CONCLUSION: Up to 24% of infants and children presenting for craniosynostosis corrective surgery have preoperative anemia, with >10% being the result of iron deficiency. Furthermore, in those not yet anemic, iron deficiency erythropoiesis is evident with an incidence of 58%. There is a strong independent association between preoperative anemia and postoperative morbidity and mortality in infants and children[(6)]. Early identification of iron deficiency anemia may benefit from a simple intervention such as iron supplementation prior to surgical procedures. Targeted preventative and therapeutic strategies to improve hematologic status of anemic infants and children prior to surgery could reduce blood transfusions and morbidity, improve safety, and decrease costs.

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Subspecialty Abstracts

CARDIOVASCULAR ANESTHESIOLOGY

CARDIOVASCULAR ANESTHESIOLOGY 1

Iron Supplementation for Patients Undergoing Cardiac Surgery: a systematic review and meta-analysis of randomized-controlled trials

Stephen Yang[1], Latifa Al Kharusi[2], Anissa Chirico[1], Pouya Gholipour Baradari[2], Adam Gosselin[1], Matthew Cameron[2]

[1]McGill University, Montreal, Canada, [2]McGill University, Montréal, Canada

INTRODUCTION: Iron supplementation has been evaluated in several randomized controlled trials (RCTs) for the potential to increase baseline hemoglobin and decrease the incidence of red blood cell (RBC) transfusion during cardiac surgery. This study's main objective was to evaluate the evidence for iron administration in cardiac surgery patients, for its effect on the incidence of perioperative RBC transfusion.

METHODS: This systematic review protocol was registered with PROSPERO (CRD42020161927) on Dec. 19th, 2019, and was prepared as per the PRISMA guidelines. MEDLINE, EMBASE, CENTRAL, Web of Science databases, and Google Scholar were searched for RCTs evaluating perioperative iron administration in adult patients undergoing cardiac surgery. Each abstract was independently reviewed by two reviewers using predefined eligibility criteria. The primary outcome was perioperative RBC transfusion, with secondary outcomes of the number of RBC units transfused, change in ferritin level, reticulocyte count, hemoglobin, and adverse events, after iron administration. The risk of bias was assessed with the Cochrane Collaboration Risk of Bias Tool, and the primary and secondary outcomes were analyzed with a random-effects model.

RESULTS: Out of 1556 citations reviewed, five studies (n = 554 patients) met the inclusion criteria. The use of iron demonstrated no difference in transfusion incidence (RR 0.86; 95% CI 0.65 to 1.13). There was a low heterogeneity between studies (I2=0%). The trial sequential analysis suggested an optimal information size of 1,132 participants, which the accrued information size did not reach.

CONCLUSION: The current literature does not support the routine use of iron supplementation before cardiac surgery; however, insufficient data is available to draw a definite conclusion. A critical knowledge gap has been identified, and more robust RCTs are required on this topic.

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CARDIOVASCULAR ANESTHESIOLOGY 2

Protective Effects of Hydrogen Gas against Spinal Cord Ischemia–Reperfusion Injury: A Microdialysis Study in the Spinal Ventral Horn

Aya Kimura[1], Koichi Suehiro[1], Takashi Mori[1]

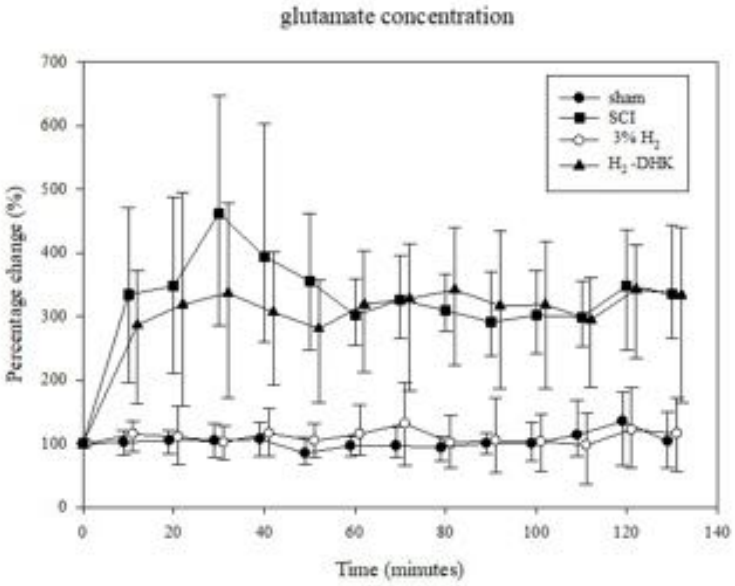
[1]Osaka City University Graduate School of Medicine, Osaka, Japan

INTRODUCTION: This experimental study aimed to assess the efficacy of hydrogen gas (H_2), as a novel neuroprotective gas, against spinal cord ischemia-reperfusion injury (SCI) and reveal its mechanism by measuring the glutamate concentration in the ventral horn of the spinal cord using an in vivo microdialysis method.

METHODS: Thirty-six male Sprague-Dawley rats were included and divided into 6 groups (n = 6 in each group) as follows: sham (sham operated); SCI (only SCI); 3% H_2 (SCI + treatment with 3% H_2 inhalation); 2% H_2 (SCI + treatment with 2% H_2 inhalation); 1% H_2 (SCI + treatment with 1% H_2 inhalation); and H_2-DHK (SCI + DHK [a selective inhibitor of glutamate transporter-1 (GLT-1)] + treatment with 3% H_2 inhalation). SCI was performed by direct descending aortic clamping for 12 min. Treatment with H_2 inhalation was given 10 min before the clamping until 130 min after aortic clamp (total 140 min). For H_2-DHK group, DHK was administered 30 min before the clamping. The glutamate concentration in the ventral horn was measured by microdialysis for 130 min after SCI. Motor-evoked potential (MEP) amplitude in the left hind limb was also measured at each 10min. Immunofluorescence to assess the expression of GLT-1 in the ventral horn was performed in the sham, SCI, and 3% H_2 groups. Data of the glutamate concentration and MEP amplitude were analyzed using two-way repeated ANOVA with Turkey post-hoc test. One-way repeated ANOVA with Tukey post-hoc test was performed to evaluate the mean intensity of luminance in immunofluorescence. Statistical significance was set at $p < 0.05$.

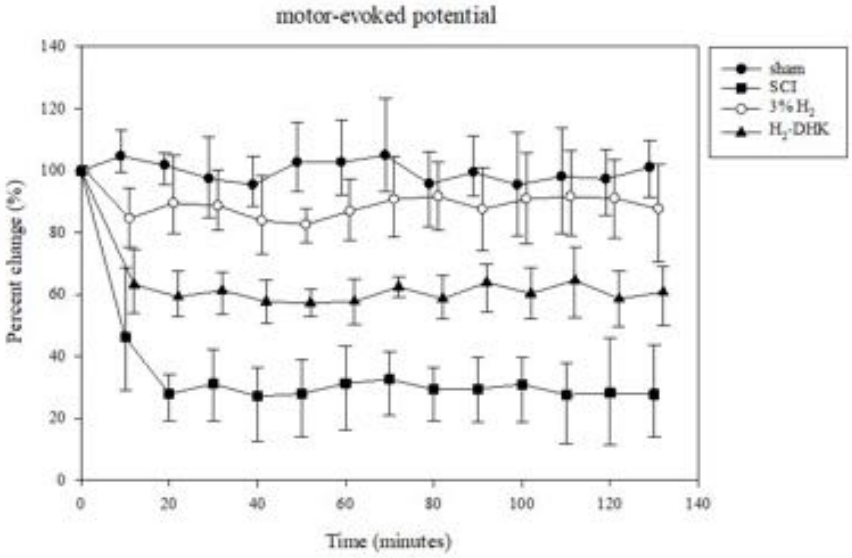
RESULTS: The results of the two-way repeated-measures ANOVA showed significant differences in glutamate concentration and MEP amplitude among the groups (glutamate concentration: $F [3,260] = 23.2$, $p < 0.001$, MEP amplitude: $F [3,260] = 42.2$, $p < 0.001$). In the 3% H_2 group, the glutamate concentration was significantly lower, and the MEP amplitude was significantly higher compared with those in the SCI group at each time point ($p < 0.05$, respectively). In contrast, pre-administration of DHK induced an increase in the glutamate concentrations and a decrease in the MEP amplitude even under H_2 inhalation ($p < 0.05$, respectively) (Fig. 1, 2). H_2 inhalation had a concentration-dependent effect to attenuate the increase in glutamate concentration and the decrease of MEP amplitude induced by SCI (Fig. 3, 4). Immunofluorescence indicated a significantly decreased expression of GLT-1 in the SCI group compared with that in the sham group, which was attenuated by 3% H_2 inhalation ($p < 0.05$, respectively) (Fig. 5).

CONCLUSION: Our study demonstrated that H_2 inhalation shows a protective and concentration-dependent effect against SCI, and the GLT-1 plays an important role in this preventive mechanism.



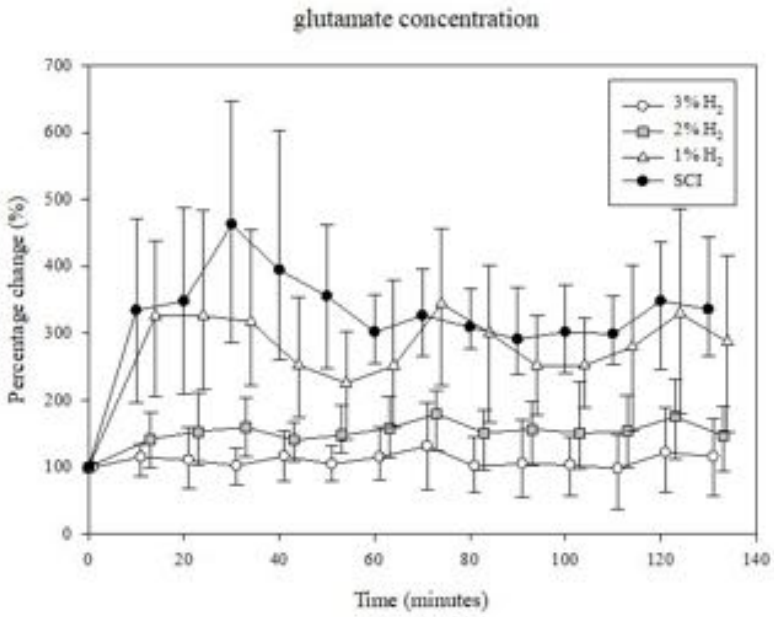
Time (minutes)	0	10	20	30	40	50	60	70	80	90	100	110	120	130
sham vs SCI	-	*	**	**	**	**	*	*	**	*	*	*	*	*
sham vs 3% H_2	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SCI vs 3% H_2	-	*	*	**	**	**	*	*	*	*	*	*	*	*
3% H_2 vs H_2-DHK	-	*	*	*	*	*	*	*	**	*	*	*	*	*

Fig. 1



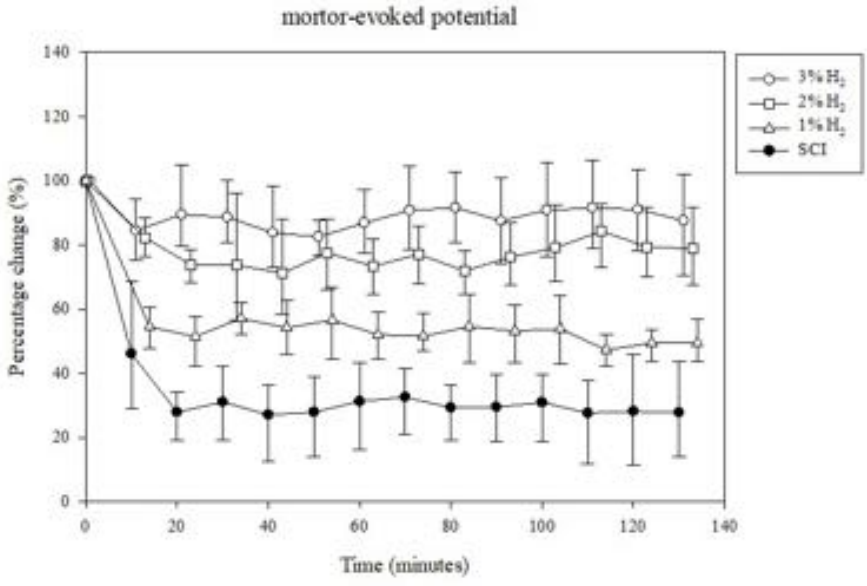
Time (minutes)	0	10	20	30	40	50	60	70	80	90	100	110	120	130
sham vs SCI	-	**	**	**	**	**	**	**	**	**	**	**	**	**
sham vs 3% H_2	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SCI vs 3% H_2	-	**	**	**	**	**	**	**	**	**	**	**	**	**
3% H_2 vs H_2-DHK	-	*	*	*	*	*	*	*	*	*	*	*	*	*

Fig. 2



Time (minutes)	0	10	20	30	40	50	60	70	80	90	100	110	120	130
3% H_2 vs SCI	-	*	*	**	**	*	*	*	*	*	*	*	*	*
2% H_2 vs SCI	-	*	*	**	**	*	-	-	-	-	-	-	*	*
1% H_2 vs SCI	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Fig. 3



Time (minutes)	0	10	20	30	40	50	60	70	80	90	100	110	120	130
3% H_2 vs SCI	-	**	**	**	**	**	**	**	**	**	**	**	**	**
2% H_2 vs SCI	-	*	**	**	**	**	**	**	**	**	**	**	**	**
1% H_2 vs SCI	-	-	-	-	*	-	-	-	-	-	-	-	-	-

Fig. 4

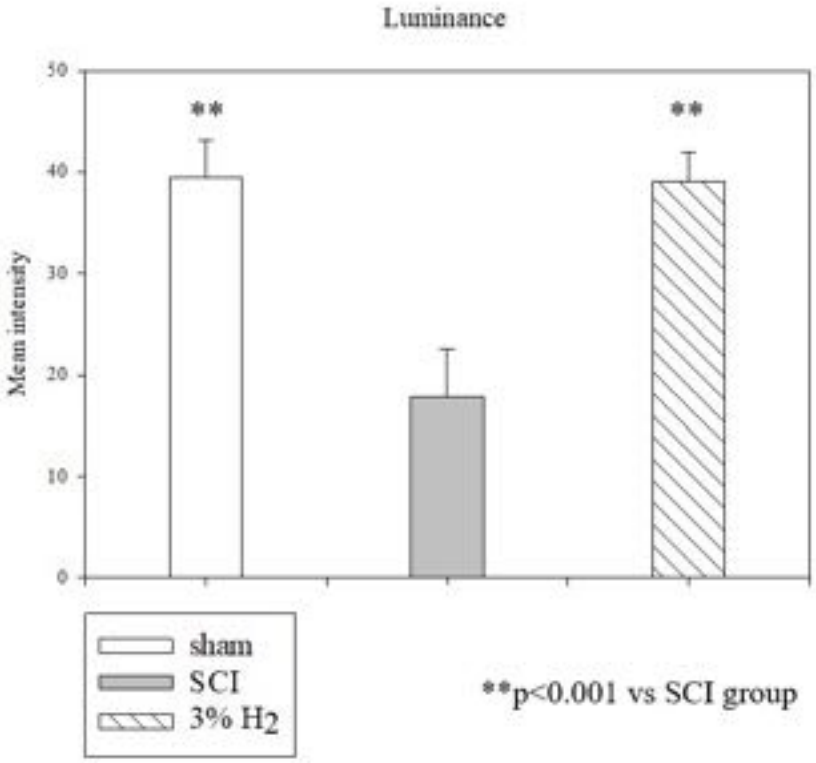


Fig. 5

CARDIOVASCULAR ANESTHESIOLOGY 3

Effect of Exogenous Nitric Oxide Given During Cardiopulmonary Bypass on the Incidence of Postoperative Kidney Injury in Children

Andrew J Matisoff[1], Thoai Vuong[2], Nina Deutsch[3], Jessica Cronin[4], Sohel Rana[2], Brenna Moore[5]

[1]Children's National Hospital, Washington, DC, [2]Children's National Hospital, Washington, DC, [3]Children's National Medical Center, Washington, DC, [4]Children's National Health System, Washington, DC, [5]George Washington University School of Medicine, Washington, DC

INTRODUCTION: In children undergoing cardiopulmonary bypass (CPB), there is an increased risk of postoperative renal dysfunction due to the systemic inflammatory response to the cardiopulmonary bypass machine[1,2]. In recent years there have been a number of trials published reporting the benefits of administering exogenous inhaled nitric oxide (iNO) directly into the CPB circuit during bypass for adult cardiac surgeries[3,4]. This includes promising data that suggests improved renal outcomes with decreased rates of acute kidney injury and chronic kidney disease after its administration[3]. In this single-center, retrospective cohort study we compared the incidence and severity of acute kidney injury (AKI) following open heart surgery in children less than 18 years after administration of exogenous inhaled nitric oxide into the cardiopulmonary bypass circuit.

METHODS: Following approval by The Children's National Hospital (CNH) Institutional Review Board, a retrospective review of the medical records of all children less than 18 years of age who underwent surgery with cardiopulmonary bypass at CNH between January 2017 and June 2019 was conducted. Only patients with complete perioperative data recordings were included in the study. Patients were divided into two groups based on whether they received iNO into the CPB circuit. From January 2017 until the beginning of March 2018, iNO was not administered during CPB. Due to a change in CPB protocol at CNH, all patients after 3/7/2018 received iNO 20 ppm directly into the circuit during CPB. In order to assess the renal effects of iNO given during CPB, several outcome variables were chosen. The primary outcome variable to assess renal outcome was change in serum creatinine levels, defined as the difference between the preoperative creatinine (CrPre) and peak postoperative creatinine (CrmaxPost). In addition, the incidence of acute kidney injury within the first 48 hours after surgery as defined by Acute Kidney Injury Network (AKIN Table 1) scores was compared between the cohorts. AKIN criteria are considered an excellent measure of acute kidney injury in children after open heart surgery as compared to other criteria[4]. The demographic and baseline data between the control and intervention group were compared using Mann-Whitney U test and Chi-square test respectively for continuous and categorical data and summarized as median with interquartile range and frequencies with percentages respectively. Difference in maximum serum creatinine changes (from CrPre to CrmaxPost) between the control and intervention group was analyzed using a multiple linear regression analysis adjusting for the potential confounder variable CPB time (above or below 120 minutes). We also compared the incidence of acute kidney injury between two groups using a Chi-square test. A separate sub-analysis was done to assess the same outcomes but in patients less than 6 weeks of age.

RESULTS: A total of 617 patients were included in the analysis, 321 (52%) in the control group (without iNO) and 296 (48%) in the intervention group (with iNO). Control and intervention groups didn't vary significantly in terms of demographic characteristics. After adjusting for the potential confounding variable of CPB times (above and below 120 minutes) there was no statistically significant difference in increase in serum creatinine between the control and the intervention groups (0.01 [95% CI: 0.02, 0.04], p= 0.535). There was also no statistically significant difference found between cohorts in patients under 6 weeks old (-0.05 (-0.13, 0.02) p=0.18). The incidence of AKI in the control and intervention groups by AKIN score were 12.6% (36 out of 285) and 12.5% (36 out of 288) respectively.

CONCLUSION: In this single center retrospective cohort study, we found no change in the incidence and severity of postoperative acute kidney injury after the administration of exogenous nitric oxide into the cardiopulmonary bypass circuit in children.

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Table 1

Demographic factors	Overall (N=617)	Control (N=321)	Intervention (N=296)	P value
	Median (IQR) or n (%)			
Age in year	0.6 (0.2, 4.3)	0.5 (0.2, 4.0)	0.8 (0.3, 4.5)	0.34
Weight in kg	14.6 (17.4)	6.9 (4.3, 16.3)	7.4 (4.5, 16.1)	0.63
Gender (Female)	272 (44.2%)	148 (46.3%)	124 (41.9%)	0.28
Premature	99 (18.2%)	60 (19.7%)	39 (16.3%)	0.31
CPB time				
<120 minute	383 (67.8%)	223 (72.6%)	160 (62.0%)	**0.007**
≥120 minute	182 (32.2%)	84 (27.4%)	98 (38.0%)	

*IQR= Interquartile range

** P values were obtained from Mann–Whitney U test for continuous data and Chi-square test for categorical data.

CARDIOVASCULAR ANESTHESIOLOGY 4

Peri-Bypass Ascorbic Acid Administration and Vasodilation in Cardiothoracic Surgery: A Pilot Feasibility Study

Patrick M Wieruszewski[1], Misty Radosevich[1], Scott D Nei[1], Kianoush Kashani[1], Hartzell V Schaff[1], Erica D Wittwer[1]

[1]Mayo Clinic, Rochester, MN

INTRODUCTION: Vasoplegia – the presence of persistent hypotension despite adequate circulatory volume and cardiac output – is a common complication of cardiothoracic surgery utilizing cardiopulmonary bypass (CPB) that leads to excessive vasopressor exposure and poor outcomes.[1] Ascorbic acid (vitamin C) is an essential cofactor in the biosynthetic pathway of endogenous catecholamine production.[2] It also plays a role in the function of the vascular endothelium and the preservation of microcirculatory flow.[3] Critically ill patients are known to be ascorbate-deficient, and cardiothoracic surgical patients have a significant reduction in plasma ascorbic acid concentrations following CPB.[2,4] Most perioperative cardiothoracic care interventions are aimed at treating vasoplegia once it occurs (i.e., vasoconstrictors).[1] Since ascorbic acid is not a vasoconstrictor, we hypothesize early administration around the pathologic insults leading to vasodilation (i.e., CPB) may reduce the incidence and severity of postoperative vasoplegia. Therefore, we aimed to assess the feasibility and possible hemodynamic effects of ascorbic acid administration in the peri-CPB setting.

METHODS: This single-center, single-arm, pilot feasibility study enrolled patients aged ≥ 18 years presenting for a non-emergent cardiothoracic surgical procedure requiring the use of CPB and involving septal myectomy or valve intervention. After written informed consent was obtained, patients received ascorbic acid 1500 mg i.v. 1) at the beginning of the case before initiation of CPB, 2) immediately after successful CPB separation, and 3) every 6 hours thereafter for a total of 12 doses. Postoperative vasoplegia was defined as requiring a continuous i.v. vasoconstrictor to maintain mean arterial pressure ≥ 65 mmHg in the setting of cardiac index ≥ 2.2 L/min/m^2. The primary feasibility endpoint was successful and timely ascorbic acid administration across the multiple phases of care. The secondary endpoints included physiologic signals of response and adverse events. Descriptive statistics were used to summarize the results.

RESULTS: Eleven patients were enrolled in this pilot study. The median (IQR) age was 60 (57, 68) years and 7 (64%) were male. The surgical procedures included septal myectomy alone (n = 5) and in combination with valve repair (n = 1) or valve replacement (n = 1), and isolated valve replacement (n = 4). Two of the patients underwent a repeat sternotomy. The median pre-CPB plasma ascorbic acid concentration was 0.7 (0.5, 0.9) mg/dl. The median CPB and aortic cross-clamp times were 53 (37, 84) and 41 (23, 74) minutes, respectively. One patient received high-dose hydroxocobalamin early after separation from CPB. No rescue methylene blue was used in any patients. The left ventricular ejection fraction following separation from CPB was 60 (60, 65) %. For the primary feasibility endpoint, all patients successfully received ascorbic acid at the pre-specified times in the operating room and intensive care unit. The cardiac index post-CPB on arrival to the intensive care unit was 2.95 (2.30, 3.04) L/min/m^2. Nine patients required vasopressors for postoperative vasoplegia, with a maximum dosage of 0.1 (0.04, 0.13) mcg/kg/min norepinephrine-equivalent in the first 24-hour postoperative period. The cardiac index around the time of highest vasopressor dosing requirement was 3.12 (2.79, 4.10) L/min/m^2. Among the nine patients with vasoplegia, the median duration of overall postoperative vasopressor use was 12 (8, 19) hours. All patients were free of vasopressors by postoperative day 1, without the use of oral midodrine at any time. All patients were discharged alive and the duration of the intensive care unit and hospital lengths of stay were 26 (22, 45) hours and 5 (5, 7) days, respectively. No adverse events were documented at any time during or after ascorbic acid treatment.

CONCLUSION: A pilot study of ascorbic acid administration across the operative and postoperative environments in cardiothoracic surgery utilizing CPB was feasible and no adverse drug events were reported. Larger comparative studies are necessary to determine the role of peri-CPB ascorbic acid administration on the development and treatment of vasodilation following cardiothoracic surgery.

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CARDIOVASCULAR ANESTHESIOLOGY 5

Single value of Nephrocheck™ performed at 4 hours after surgery does not predict Acute Kidney Injury in Off-pump Coronary Artery Bypass Surgery

Muralidhar Kanchi[1]

[1]*Narayana Institute of Cardiac Sciences, NH health city, Bangalore, Karnataka*

INTRODUCTION: The Nephrocheck™ (NC) is a rapid biomarker expressed in urine in kidney injury. The Nephrocheck™ (NC) is a combination of tissue inhibitor of metalloproteinases and an insulin-like growth factor-binding protein. This study was performed to determine if one single Nephrocheck™ (NC) performed 4 hours after off-pump coronary artery bypass grafting.

METHODS: After IRB approval, ninety adult patients undergoing elective OPCABG were included. Urine samples were collected preoperatively and at 4 hours after surgery for the Nephrocheck™ test. Urine output, serum creatinine, estimated glomerular filtration rate (eGFR) were also measured. The patients were followed to determine the occurrence of AKI using the KDIGO criteria.

RESULTS: Thirteen patients developed AKI in the study cohort (14.4%) out of which 6 patients (6.6%) developed stage 1 AKI and the remaining 7 (7.8%) developed stage 2/3 AKI. Baseline renal parameters were similar between AKI and non-AKI group. The 4 hour post-operative Nephrocheck™ as compared to the preoperative NC, did not predict AKI. There were no significant differences in duration of mechanical ventilation, length of intensive care stay and hospital stay between the two groups (P>0.05). The Nephrocheck™ test performed at 4 hours after surgery did not identify patients at risk for developing AKI following OPCABG surgery. NC-Nephrocheck™ value, S Cr- serum creatinine, eGFR-estimated glomerular filtration rate, LVEF-left ventricular ejection fraction, EuroSCORE- European System for Cardiac Operative Risk Evaluation, PA -pulmonary artery, MI-myocardial infarction, DM-diabetes mellitus, HTN-hypertension. Data are expressed as mean±SD. or number (percentage).

CONCLUSION: The postoperative Nephrocheck™ test performed at 4 hours after surgery did not predictAKI in our study population (P =0.24).

REFERENCE(S):

Table 1: Demographic and clinical data of patients who developed AKI as compared to no AKI following OP-CABG.

Variable name	AKI (N= 13)	Non-AKI (N= 77)	P value
Age (years)	55.38±11.6	53.17±8.6	0.52
Gender (Male) (%)	10 (76.9%)	71 (92.2%)	0.08
Height (cm)	157.5±7.1	162.5±6.6	0.01
Weight (kg)	59.5±10.6	67.8±9.8	0.007
Preoperative S Cr (mg/dl)	0.98±0.17	0.99±0.14	0.92
Preoperative eGFR (ml/min/1.73m)	76.92±15.89	78.99±13.42	0.61
LVEF (%)	52.3±9.3	52.7±7.9	0.86
EuroSCORE	3.46±3.01	3.58±1.92	0.84
PA pressure (mm Hg)	28.3±6.3	29.0±5.0	0.67
No of grafts	2±0.4	2.1±0.7	0.68
Duration of surgery (minutes)	420.4±128.1	353.3±109.2	0.04
Recent MI (%)	4 (30.8%)	8 (10.4%)	0.04
Re-exploration (%)	3 (23.1%)	2 (2.6%)	0.02
DM (%)	5 (38.5%)	54 (70.1%)	0.02
HTN (%)	7 (53.8%)	55 (71.4%)	0.20
Pre-operative NCV	0.45±0.91	0.43±0.59	0.23
Post-operative NCV	0.42 ± 0.42	0.28 ±0.34	0.79

CARDIOVASCULAR ANESTHESIOLOGY 6

Off-Pump Technique May Prevent Deterioration of Renal Function in Patients with Chronic Kidney Disease Undergoing Coronary Artery Bypass Grafting

Sujani Kola[1], Muralidhar Kanchi[2]

[1]Narayana institute of Cardiac Sciences, Banglore, Karnataka, [2]Narayana Institute of Cardiac Sciences, NH health city, Bangalore, Karnataka

INTRODUCTION: Cardiovascular disease (CVD) is a major cause for a significant proportion of all deaths and disability worldwide. Post-operative renal dysfunction following cardiac surgery is not an uncommon complication of cardiac surgery which has serious implications with regard to morbidity, mortality, financial expenditure and resource utilization. We conducted a cohort review to compare outcomes of patients with pre-operative renal dysfunction with those having normal renal function undergoing off pump coronary artery bypass grafting (OPCABG).

METHODS: Patients were divided into two categories depending on their pre-operative serum creatinine and glomerular filtration rate (GFR). Pre-operative renal dysfunction was defined as serum creatinine > 1.3mg/dl and/or estimated GFR of <60ml/min/1.73m2. The category A patients had normal renal function defined as serum creatinine ≤1.3mg/dl and/or estimated GFR of ≥60ml/min/1.73m2 while the category B patients had pre-operative renal dysfunction but did not necessitate renal dialysis. Blood samples were collected from both the category patients for serum creatinine prior to surgery and postoperatively on days 1, 2, 3, 4, 5 and on the day of discharge. The occurrence of acute kidney injury (AKI) was defined as an increase in the serum creatinine levels of ≥0.3 mg/dl within 48 hours postoperatively, or an increase of ≥1.5 mg/dl above baseline known or presumed to have occurred within the previous 7 days postoperatively based on KDIGO criteria. The anaesthetic care in both groups was standardized and aimed at maintaining renal perfusion and avoiding nephrotoxic agents.

RESULTS: There were 242 patients in the study, 121 in each of the categories. AKI occurred in 7.4% of patients with normal renal function and worsening of renal function occurred in 10.74% of patients with renal dysfunction. This difference was not statistically significant. None of the patients in either groups needed renal replacement therapy. There were no differences in other outcome measures.

CONCLUSION: Based on the results, we conclude that OPCABG surgery may not worsen the renal dysfunction in patients with pre-existing chronic kidney disease if meticulous attention is paid to perioperative management.

Table 1. Demographic and clinical data

		Category A(Normal renal function)	Category B (Renal dysfunction)	P Value
Age (years) (mean ± SD)		55±9.6 (30-73 years)	60.71±8.1 (44-82 years)	< 0.001
Gender(F/M)		11/110	8/113	0.473
Diabetes(Y/N)		62/59	73/48	0.155
Hypertension (Y/N)		73/48	89/32	0.029
Pre-op CVD (Y/N)		0/121	1/120	0.316
Smoking status (Y/N)		41/80	44/77	0.686
Pre-Op Serum Creatinine (mg %)		0.96 ± 0.1	1.46 ± 0.3	<0.001
Pre-Op eGFR ml/min (mean ± SD)		81.13 ± 13.95	51.07 ± 9.02	<0.001
Pre-Op eGFR(ml/min) (categorized)	**>60**	120	4	
	60-45	1	93	
	45-30	0	23	
	<30	0	1	
Euro Score Risk (±SD)		1.83 (±1.7)	2.98 (±1.9)	< 0.001
LVEF (%)		47.40 (±7)	47.40(±7)	1
Number of Grafts		1.92 (±0.7)	1.92(±0.7)	1
Incidence of AKI		9(7.5%)	13(10.7%)	0.37
IABP requirement (Y/N)		2/119	0/121	0.156
Re-exploration (Y/N)		4/117	0/121	0.044
Post-op stroke (Y/N)		2/119	0/121	0.156
ICU stay(days)		2.11 (±0.4)	2.11 (±0.4)	1
Mortality		0	0	0

Table 2. Mean serum creatinine values in two groups till the 5th postoperative day

Serum Creatinine mg%	Category A(Normal Renal Function)	Category B(Renal Dysfunction)	P Value
POD-1	0.96 ± 0.2	1.64 ± 0.3	<0.001
POD-2	0.96 ± 0.2	1.62 ± 0.4	<0.001
POD-3	0.99 ± 0.4	1.74 ± 0.4	<0.001
POD-4	0.96 ± 0.4	1.66 ± 0.4	<0.001
POD-5	0.96 ± 0.3	1.66 ± 0.4	<0.001

CARDIOVASCULAR ANESTHESIOLOGY 7

Outcomes and Risk Factors for Cardiovascular Events in Hospitalized COVID-19 Patients

Jiapeng Huang[1], Qian Xu[2], Harideep Samanapally[2], Pavani Nathala[2], Vidyulata Salunkhe[3], Lynn Roser[2], Maiying Kong[2]

[1]University of Louisville, Louisville, KY, [2]University of Louisville, Louisville , United States of America, [3]Medicine, Louisville , United States of America

INTRODUCTION: Cardiovascular injuries are prevalent and carry high mortality rate in COVID-19 patients[1-3]. In addition, outcomes and risk factors of cardiovascular events in African American COVID-19 patients are unknown. In all cited studies, cardiac injury has been defined as serum levels of cardiac biomarkers above the 99th percentile reference limit, regardless of abnormalities on electro and/or echocardiography. However, critically ill patients could have elevated cardiac markers from mismatch between myocardial oxygen supply and demand without structural cardiovascular abnormalities. Currently, there is not enough data on detailed risk factor analysis in COVID-19 patients who suffered a new clinically diagnosed cardiovascular event. In addition, minority ethnic groups are reported to experience a higher burden of severe COVID-19 than white individuals, but there is uncertainty about the underlying factors and where risk lies during the disease trajectory[4, 5]. We have established a large COVID-19 database in a US metropolitan city in a midwestern state which takes into account the local population and individual level co-morbidities[6]. In this study, our primary objectives are to analyze outcomes and risk factors of cardiovascular events in a metropolitan COVID-19 database. Our secondary objectives are to perform a subgroup analysis in African American populations to determine whether outcomes and risk factors are influenced by race.

METHODS: Design: Retrospective cohort analysis from March 9, 2020 to June 20, 2020. Setting: population-based study in Louisville, KY, USA Participants: 700 adult inpatients hospitalized with COVID-19. Inclusion criteria for the study included all hospitalized inpatients with a diagnosis of COVID-19. This study excluded any COVID-19 patient that was not admitted as a hospital inpatient. Exposures: COVID-19 infection Main Outcomes and Measures: Mortality, length of stay for survivors, days to mortality for non-survivors. Statistical Methods: Comparison between the groups (e.g., patients without cardiovascular events versus patients with cardiovascular events) was performed using Mann-Whitney U test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. Pearson's correlation coefficients were used to evaluate the correlation between different variables. Multiple logistics regression analyses were conducted to examine which variables (i.e., laboratory data, demographic data, and co-morbidities) predict cardiovascular event.

RESULTS: Our cohort consisted of 126 patients (18%) with cardiovascular events and 574 patients without cardiovascular events. Patients with cardiovascular events had a much higher mortality rate than those without cardiovascular events (45.2% vs. 8.7%, P<0.001). There was no difference between African American and white groups in terms of mortality (43.9% vs. 46.3%, P=0.958) and length of stay for survivors (IQR 9(5.5, 6) vs. 11 (7.5,23.5), P=0.257). Multiple logistics regression analysis suggested that male (OR 1.737, 95% CI 1.003-3.01), race (OR 4.888, 95% CI 1.01-23.66), lower SaO2/FiO2 (OR 0.995, 95% CI 0.993-0.997), higher serum potassium (OR 1.557, 95% CI 1.056-2.296), lower serum albumin (OR 0.623, 95% CI 0.411, 0.945), and number of cardiovascular co-morbidities (OR 1.297, 95% CI 1.106-1.521) were highly associated with the occurrence of cardiovascular events in COVID-19 patients. Subgroup multiple logistics analysis demonstrated lower serum albumin (OR 0.165, 95% CI 0.06-0.454) and neoplastic/immune compromised diseases count (OR 5.157, 95% CI 1.074-24.77) were highly associated with cardiovascular events for African American COVID-19 patients. SaO2/FiO2 ratio (OR 0.994, 95% CI 0.991-0.997) and cardiovascular comorbidity count (OR 1.326, 95% CI 1.069-1.645) were significantly associated with cardiovascular events for white patients.

CONCLUSION: Cardiovascular events were prevalent and associated with worse outcomes in hospitalized patients with COVID-19. Outcomes of cardiovascular events in African American and white COVID-19 patients were similar except days to mortality. There were common and unique risk factors for cardiovascular events in African American COVID-19 patients when compared with white patients.

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Table 1. Demographics, comorbidities, and biomarkers analysis of COVID-19 Patients with and without cardiovascular (CV) events (N=700).

Variables	Cases without CV Events (n=574)	Cases with CV Events (n=126)	P-values
Death	50 (8.7%)	57 (45.2%)	<0.001
LOS for survivors (Days) (IQR)[#]	5 (3,11)	9(6,18)	<0.001
Days to mortality for non-survivors (Days) (IQR)[#]	8(5,11)	10(6,15)	0.088
Demographics Morphometrics			
Age	57.8±19.37	66.8±15.2	<0.001
Female	330 (57.5%)	54(42.9%)	0.004
Male	244 (42.5%)	72(57.1%)	
Hispanic	77(13.4%)	4(3.2%)	<0.001
Non-Hispanic African American	179(31.2%)	41(32.5%)	
Non-Hispanic white	267 (46.5%)	76(60.3%)	
Non-Hispanic other	51(8.9%)	5(4.0%)	
Comorbidities			
Pulmonary comorbidity	256 (44.6%)	80 (63.5%)	<0.001
Pulmonary comorbidity count			
0	318(55.4%)	46(36.5%)	<0.001
1	174(30.3%)	50(39.7%)	
2-4	82(14.3%)	30(23.8%)	
Cardiovascular comorbidity	338(58.9%)	104(82.5%)	<0.001
Cardiovascular comorbidity count			
0	236(41.1%)	22(17.5%)	<0.001
1	125(21.8%)	21(16.7%)	
2-4	178(31.0%)	63(50.0%)	
5-8	35(6.1%)	20(15.9%)	
Renal disease	86(15.0%)	39(31.0%)	<0.001
Renal disease count			
0	488(85.0%)	87(69.1%)	<0.001
1	48(8.4%)	25(19.8%)	
2	38(6.6%)	14(11.1%)	
Diabetes	164(28.6%)	60(47.6%)	<0.001
Neoplastic/immune compromised diseases	47(8.2%)	20(15.9%)	0.013
Neoplastic/immune compromised diseases count			
0	527(91.8%)	106(84.1%)	0.026*
1	39(6.8%)	17(13.5%)	
2	8(1.4%)	3(2.4%)	

Table 1, continued

Variables	Cases without CV Events (n=574)	Cases with CV Events (n=126)	P-values
Laboratory Tests			
AST/ALT Ratio	1.5±0.77	1.7±0.83	0.003
Neutrophil/lymphocyte Ratio	6.4±7.69	9±10.74	<0.001
SaO2/FiO2 ratio	382.1±105.22	282.4±136.89	<0.001
WBC ($10^3/mm^3$)	7.4±4.43	8.6±5.72	0.026
Neutrophil percentage	71.5±13.53	75.4±14.24	0.002
Lymphocyte percentage	18.5±10.75	15.2±10.53	0.001
Neutrophil ($10^3/mm^3$)	7.8±13.03	8±9.63	0.013
Lymphocyte ($10^3/mm^3$)	1.7±3.3	1.5±2.92	0.001
Serum potassium (mmol/liter)	3.8±0.62	4.1±0.73	<0.001
Glucose (mg/dl)	145.7±80.01	165.3±91.96	0.001
BUN (mg/dl)	21±18.28	32.5±24.82	<0.001
Creatinine (mg/dl)	1.4±1.8	1.7±1.26	<0.001
Albumin(g/dl)	3.6±0.63	3.3±0.68	0.001
Bilirubin (mg/dl)	1±4.05	1.1±3.14	0.002
AST (units/liter)	55.7±64.38	83.6±168.01	0.033
INR	1.3±0.8	1.4±0.95	0.009
Procalcitonin (ng/ml)	2.3±22.06	2.2±6.15	<0.001
D-dimer (μg/ml fibrinogen equivalent units)	1729.9±4686.23	4741.5±13169.36	<0.001
Interleukin-6 (pg/ml)	95.7±131.58	190.8±266.21	0.001
CRP (mg/liter)	40.2±95.65	53.2±72.17	0.001
ABG FiO2 (%)	49.5±30.54	60.5±33.08	0.016
BNP (pg/ml)	1098.6±9406.06	823.5±1072.37	<0.001
NT-proBNP (pg/ml)	3374.8±17423.69	6168.1±15115.23	<0.001

Note: P-values for continuous variables were obtained using Mann-Whitney U test, and P-values for categorical variables were obtained using Chi-square test or Fisher's exact test indicated by *.

# indicates that median and interquartile range were reported.

Table 2. Demographics, comorbidities, and laboratory biomarkers comparison between African Americans and Whites COVID-19 patients with and without cardiovascular events. (N=644)

Variables	African American Patients (N=220)			White Patients (N=424) (Non-Hispanic White and Hispanic)			African American vs. White Patients	
	Without CV events	With CV events	P-values	Without CV events	With CV events	P-values	P-values without CV events	P-values with CV events
Sample Size	179 (81.4%)	41 (18.6%)		344 (81.1%)	80 (18.9%)		1	
Death	14 (7.8%)	18 (43.9%)	**<0.001**	31 (9.0%)	37 (46.3%)	**<0.001**	0.767	0.958
LOS for survivors (Days) (IQR)[#]	5(2,11)	11(7.5,23.5)	**<0.001**	5(3,12)	9(5.5,16)	**<0.001**	0.419	0.257
Days to mortality for non-survivors (Days) (IQR)[#]	8.5(5.25,13.75)	6(5,10)	0.391	7(4,10.5)	12(8,15)	**0.004**	0.32	**0.031**
Age	57.2±17.67	68.5±12.26	**<0.001**	59±20.22	66±15.58	**0.003**	0.318	0.667
Sex: Female	107 (59.8%)	16(39.0%)	**0.025**	189(54.9%)	36(45.0%)	0.139	0.334	0.664
Male	72 (40.2%)	25(61.0%)		155(45.1%)	44(55.0%)			
Comorbidities								
Pulmonary comorbidity	93 (52.0%)	23 (56.1%)	0.760	147 (42.7%)	57(71.3%)	**<0.001**	0.055	0.143
Pulmonary comorbidity count								
0	86(48.0%)	18(43.9%)	0.7607	197(57.3%)	23 (28.8%)	**<0.001**		
1	59(33.0%)	16(39.0%)		102(29.7%)	34 (42.5%)		0.082	0.182
2-4	34(19.0%)	7(17.1%)		45(13.1%)	23 (28.8%)			
Cardiovascular comorbidity	120(67.0%)	36(87.8%)	**0.014**	194(56.4%)	64 (80.0%)	**<0.001**	**0.024**	0.413
Cardiovascular comorbidity count								
0	59(33.0%)	5(12.2%)	**<0.001***	150(43.6%)	16 (20.0%)	**<0.001***	**0.024**	0.741
1	44(24.6%)	6(14.6%)		71 (20.6%)	12 (15.0%)			
2-4	68(38.0%)	23(56.1%)		97 (28.2%)	39 (48.8%)			
5-8	8(4.5%)	7(17.1%)		26 (7.6%)	13 (16.3%)			
Renal disease	39(21.8%)	13(31.7%)	0.2523	46 (13.4%)	26 (32.5%)	**<0.001**	**0.019**	1
Renal disease count								
0	140(78.2%)	28(68.3%)	0.3647*	298 (86.6%)	54 (67.5%)			
1	20(11.2%)	7(17.1%)		28 (8.1%)	18 (22.5%)	**<0.001***	**0.030**	0.638*
2	19(10.6%)	6(14.6%)		18 (5.2%)	8 (10.0%)			
Diabetes	62(34.6%)	24(58.5%)	**0.008**	90 (26.2%)	36 (45.0%)	**0.001**	0.054	0.223
Neoplastic/immune compromised diseases	14(7.8%)	8(19.5%)	**0.039***	31 (9.0%)	11(13.8%)	0.214*	0.767	0.575
Neoplastic/immune compromised diseases count								
0	165(92.2%)	33(80.5%)	**0.021***	313 (91.0%)	69 (86.3%)	0.194*	0.813*	0.208*
1	11(6.2%)	8(19.5%)		26 (7.6%)	8 (10.0%)			
2	3(1.7%)	0(0.0%)		5 (1.5%)	3 (3.8%)			

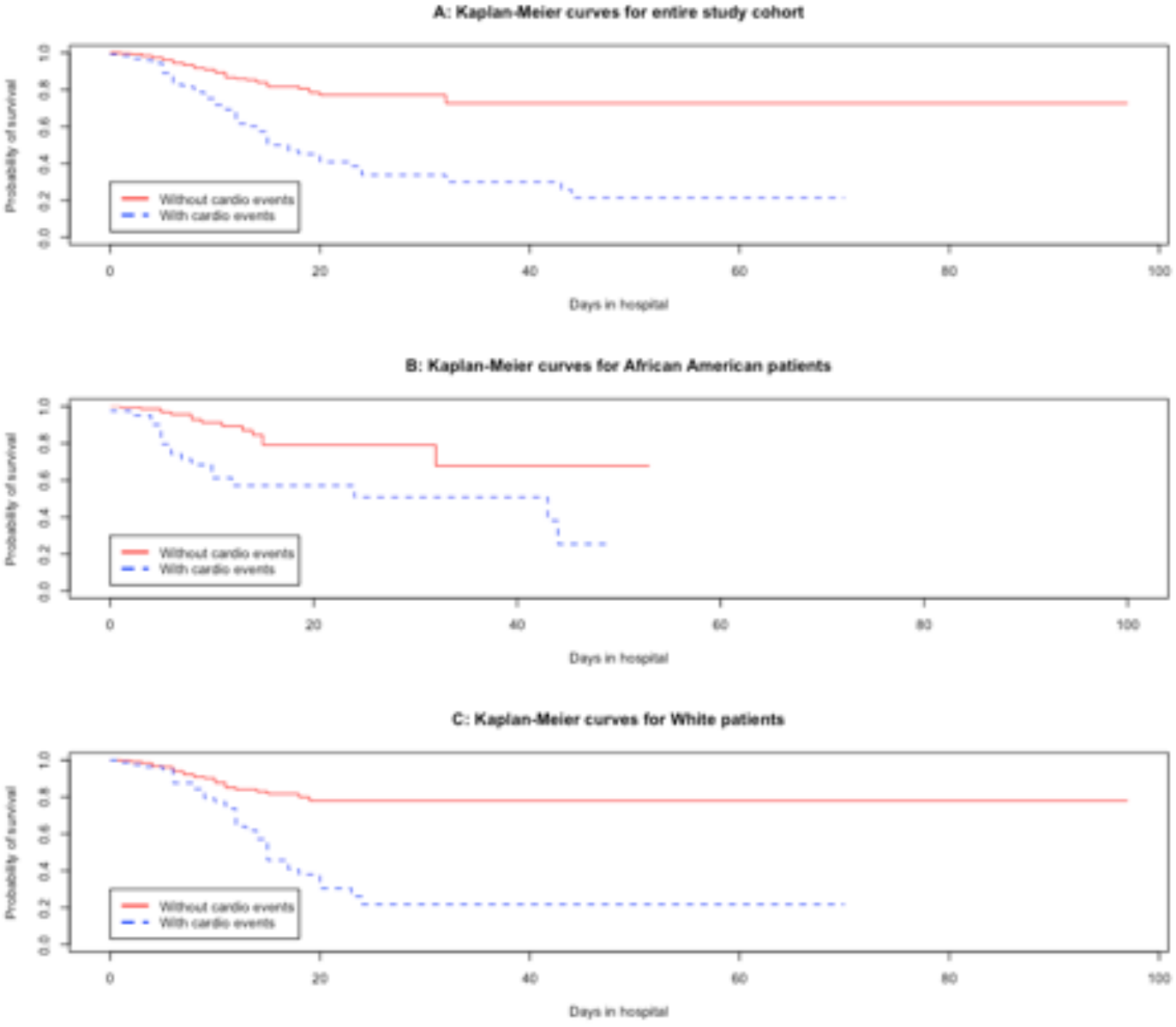

Fig. 1

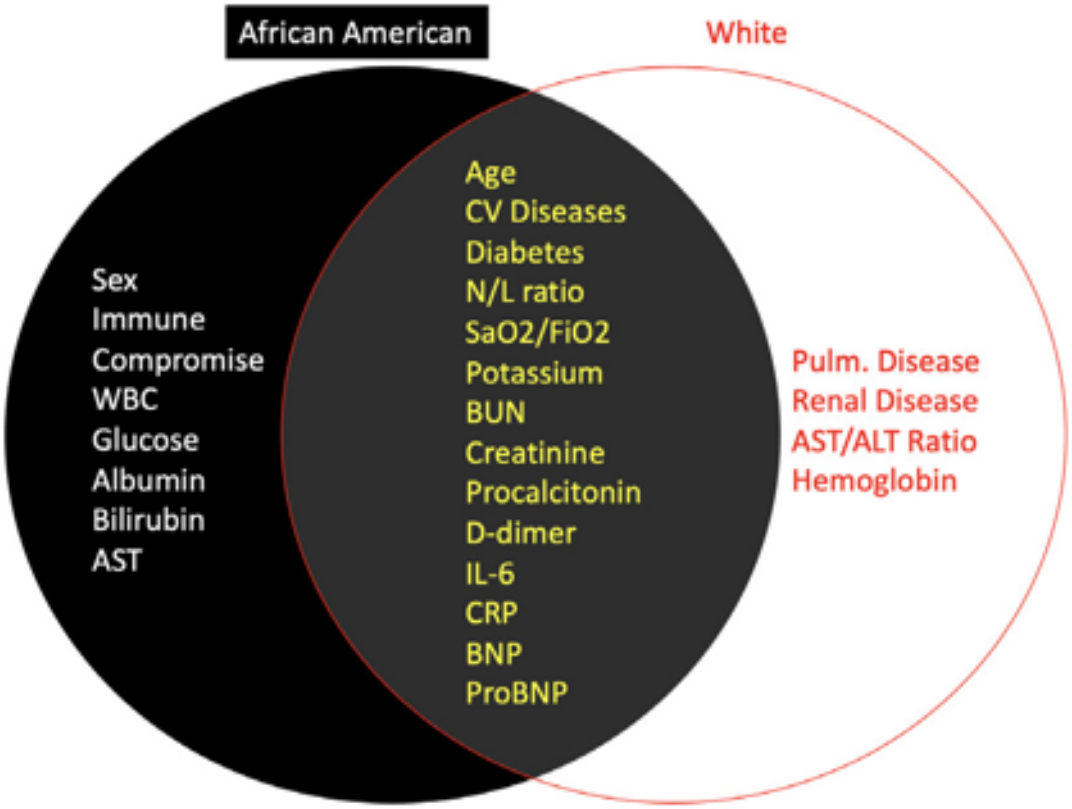

Fig. 2

CARDIOVASCULAR ANESTHESIOLOGY 8

The Effects of Phenylephrine and Haemorrhage on the Porcine Gut Mucosal Microcirculation

Constance Sturgess[1], Monty Mythen[2], Simon J Davies[3]

[1]University College London, London, United Kingdom, [2]University College London, London, England, [3]York Hospitals NHS Trust, York, Yorkshire

INTRODUCTION: Reduced microcirculatory perfusion of the gut is an early manifestation of hypovolaemia[1] This is associated with surgical post-operative complications mediated through ischaemic damage to the mucosa[2]. These microcirculatory disturbances are not always reflected by the systemic haemodynamic variables commonly measured in clinical practice[3]. Vasopressors are often given as a pharmacological intervention to restore mean arterial pressure and thus perfusion of the vital organs by increasing systemic vascular resistance. Their effect on gut microcirculation however, is not clear. This study investigated the effects of incremental haemorrhage and phenylephrine administration on the porcine gut mucosal microcirculation and systemic haemodynamic variables.

METHODS: Six anaesthetised pigs were bled in stages relating to an estimation of 5%, 10%, 15% and 20% of total blood volume. The blood was then re-transfused and crystalloid fluids infused. Phenylephrine was given after baseline and following each haemorrhage stage. Gut mucosal microcirculation was assessed using sidestream dark-field imaging of the small intestine through a midline laparotomy. Microcirculation recordings were scored and a wide range of haemodynamic variables were measured at baseline and following each stage of the procedure. The facility used is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International and is registered with the USDA to conduct research with laboratory animals. Statistical analysis was performed using one-way repeated measures ANOVA with Greenhouse-Geisser correction across all stages for each variable. For the variables demonstrating significance, post-hoc analysis with Bonferroni correction was carried out. The significance level was set at $P<0.05$.

RESULTS: Mean arterial pressure, stroke volume, stroke volume variation and hypotension prediction index were the only variables that showed any significant difference from baseline following haemorrhage. Following administration of phenylephrine, the great majority of variables did not differ significantly from baseline at all haemorrhage stages. Gut microcirculation scores decreased from 5% haemorrhage, reaching significance at 15% and 20% haemorrhage ($P=0.003$ and $P=0.008$ respectively). Gut microcirculation scores did not change significantly before and after phenylephrine administration at all haemorrhage stages (all $P>0.999$).

CONCLUSION: Gut microcirculation deteriorated from the early stages of haemorrhage. The majority of haemodynamic variables did not reflect this gut hypoperfusion or intravascular deficit. Phenylephrine rapidly restored these variables but gut microcirculatory disturbances persisted. This study emphasises the shortcomings of these commonly used haemodynamic variables, particularly following the use of vasopressors. A clinically applicable method of determining any dissociation between systemic haemodynamics and the microcirculation would be invaluable in guiding appropriate, early intervention choices.

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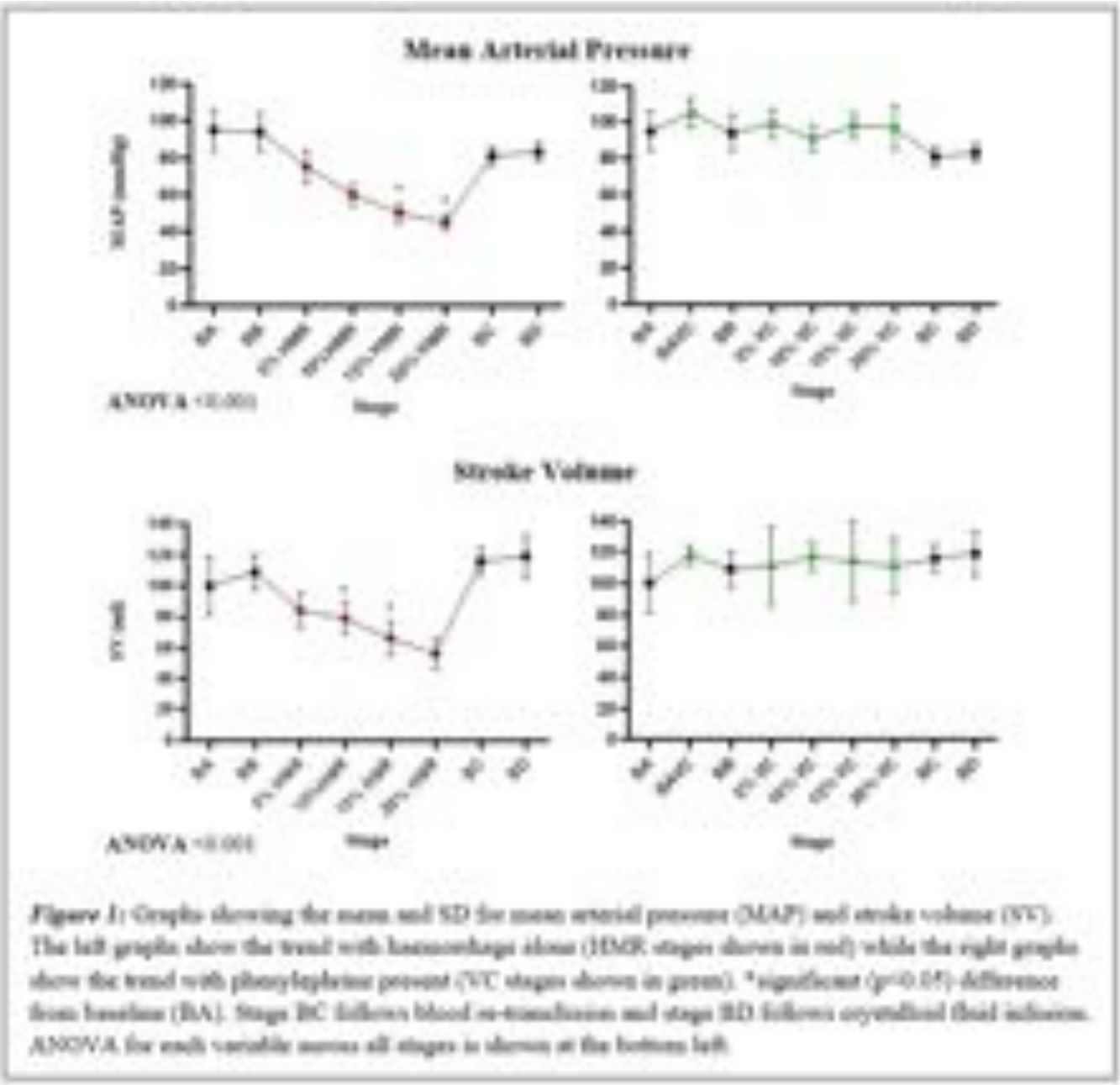

Figure 1: Graphs showing the mean and SD for mean arterial pressure (MAP) and stroke volume (SV). The left graphs show the trend with hemorrhage alone (HMR stages shown in red) while the right graphs show the trend with phenylephrine present (VC stages shown in green). *significant ($p<0.05$) difference from baseline (BA). Stage BC follows blood re-transfusion and stage RD follows crystalloid fluid infusion. ANOVA for each variable across all stages is shown at the bottom left.

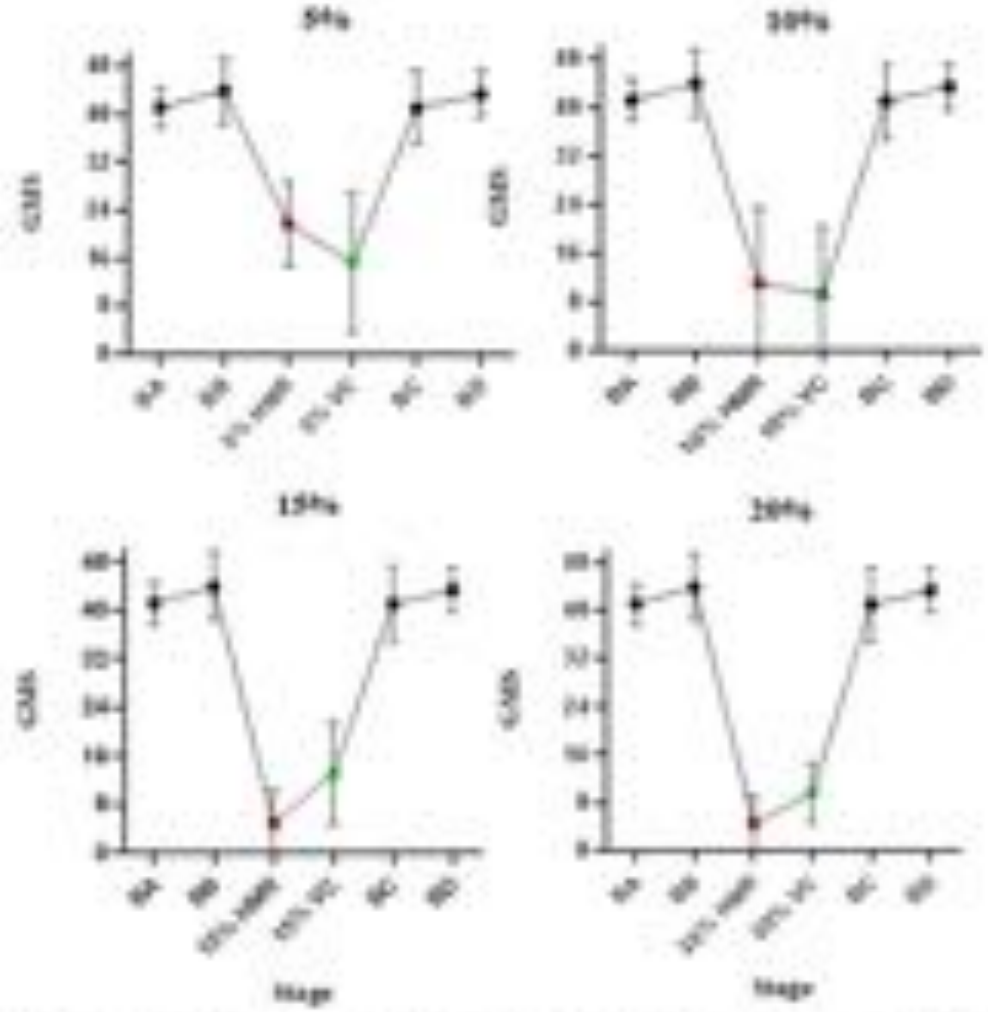

Figure 2: Graphs showing gut microcirculation scores (GMS) before and after phenylephrine administration at each percentage haemorrhage. Red points show haemorrhage slows (HMR stages) and green points are with phenylephrine present (VC stages). Stage BC follows blood re-transfusion and stage BD follows crystalloid fluid infusion.

CARDIOVASCULAR ANESTHESIOLOGY 9

Perioperative Myoclonus in Heart Transplant Patients on Calcineurin Inhibitors

Tyler Dunn[1], Ricardo Verdiner[2]

[1]Mayo Clinic, Phoenix, AZ, [2]Mayo Clinic Arizona, Phoenix, AZ

INTRODUCTION: Calcineurin inhibitors play a pivotal role in antirejection therapy for transplant patients. Neurotoxicity is a common side effect. Perioperative myoclonus as a manifestation of neurotoxicity, has clinical implications that are not well defined.

METHODS: In this retrospective study, patients undergoing heart transplants (HT) were compared to a control group undergoing coronary bypass grafts. The objective was to: 1) identify if the heart transplant patients receiving calcineurin inhibitors would be at a greater risk for myoclonus than the coronary bypass graft (CABG) patients who did not receive calcineurin inhibitors. 2) determine what clinical impact perioperative myoclonus had on mortality and length of stay. The NIS database from January 2011 to December 2014 was the source for the analysis. Patients with underlying epilepsy or hypo-ischemic encephalopathy based on ICD-9-CM codes were excluded from the study.

RESULTS: 147 HT cases had evidence of perioperative myoclonus. This was a statistically significant 6.5-fold difference in the incidence of myoclonus between HT and CABG group. For the HT group, myoclonus was associated with an increased length of stay and approached statistical significance for increased mortality.

CONCLUSION: Calcineurin inhibitors may increase the incidence of perioperative myoclonus. Perioperative myoclonus may be a neuronal indicator of poor global endothelial health. If the endothelium of the blood brain barrier can be compromised by chronic disease and inflammatory states, it is likely that the endothelium of other organ systems will also be compromised. The observation that myoclonus was associated with increased mortality in both groups supports this conclusion.

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Table 1: Incidence of Myoclonus in HT and CABG			
	Heart transplant N: 56423	**CABG N :** 786339	**P value**
With Myoclonus	147 (0.26%)	338 (0.04%)	<.0001
Without Myoclonus	56276 (99.74%)	786000 (99.96%)	
With Myoclonus (renal failure excluded)	(0.18%)	(0.036%)	0.012

Table: 2, Comparing Basic CABG Demographics			
	CABG with myoclonus N: 338	CABG without myoclonus N: 786000	**P value**
Age (mean ± SD)	65.2± 14.4	66.1± 10.6	0.50
Age ≥65 yrs	190 (56.2%)	453855 (57.7%)	0.79
Female	77 (23.0%)	210623 (26.8%)	0.45
Medical Comorbidities			
Diabetes Mellitus	153 (45.3%)	338597 (43.1%)	0.70
Congestive Heart Failure	0	9619 (1.22%)	-
Hypertension	264 (78.0%)	623500 (79.3%)	0.79
Hyperlipidemia	168 (49.6%)	497390 (63.3%)	0.03
Atrial Fibrillation	131 (38.8%)	262069 (33.3%)	0.36
Renal Failure	96 (28.4%)	125667 (15.9%)	0.03
Hypercoagulable State	103 (30.6%)	157019(20.0%)	0.05
Chronic Lung Disease	84 (0.24%)	176121 (22.4%)	0.64
In-hospital complications			
Acute Kidney Injury	132 (39.1%)	147998 (18.8%)	0.001
Myocardial Infarction	142 (42.0%)	237641 (30.2%)	0.05
Pneumonia	40 (11.8%)	37105(4.72%)	0.08
Urinary Tract Infection	28 (8.41%)	53923(6.86%)	0.64
Sepsis	18 (5.55%)	18369(2.33%)	0.24
Outcomes			
Prolonged length of stay	275 (81.2%)	515605 (65.6%)	0.001
Discharge disposition of alive patients to nursing home	128 (43.4%)	168470 (22.0%)	0.002
In-hospital mortality	41 (12.3%)	19298 (2.45%)	0.02

Table: 3, Comparing Basic HT Demographics			
	Heart transplant with myoclonus N: 147	**Heart transplant without myoclonus N: 56271**	**P value**
Age (mean ± SD)	64.8± 10.3	55.4± 20.4	.01
Age ≥65 yrs	83 (56.8%)	23644 (42.0%)	0.12
Female	34 (23.2%)	16130 (28.3%)	0.48
Medical Comorbidities			
Diabetes Mellitus	89 (60.6%)	23625 (41.2)	0.04
Congestive Heart Failure	24 (16.0%)	6552 (11.6%)	0.47
Hypertension	94 (63.7%)	35523 (63.1%)	0.94
Hyperlipidemia	83 (56.9%)	23394 (41.6%)	0.11
Atrial Fibrillation	9 (6.5%)	4883 (8.67%)	0.63
Renal Failure	94 (64.0%)	27520 (48.9%)	0.08
Hypercoagulable state	0	3905 (6.93%)	-
Chronic Lung Disease	19 (13.0%)	8225 (14.6%)	0.78
In-hospital complications			
Acute Kidney Injury	98 (66.8%)	20843 (37.0%)	0.01
Pneumonia	19 (13.2%)	5776 (10.3%)	0.63
Urinary Tract Infection	4.5 (3.11%)	4939 (8.77%)	0.09
Sepsis	29 (19.8%)	4145 (7.36%)	0.15
Outcomes			
Prolonged length of stay	83 (56.5%)	14647 (26.0%)	0.002
Discharge disposition of alive patients to nursing home	39 (30.7%)	6267 (11.4%)	0.05
In-hospital mortality	19 (13.5%)	1167 (2.07%)	0.08

Table 4: Comparing HT vs CABG Demographics			
	Heart transplant with myoclonus N: 147	**CABG with myoclonus N:** 338	**P value**
Age (mean ± SD)	64.8± 10.3	65.2± 14.4	0.90
Age ≥65 yrs	83 (56.8%)	190 (56.2%)	0.93
Female	34 (23.2%)	77 (23.0%)	0.98
Medical Comorbidities			
Diabetes Mellitus	89 (60.6)	153 (45.3)	0.123
Congestive Heart Failure	24 (16.0)	0	-
Hypertension	94 (63.7)	264 (78.0)	0.215
Hyperlipidemia	83 (56.9)	168 (49.6)	0.463
Atrial Fibrillation	9 (6.5)	131 (38.8)	<.0001
Renal Failure	94 (64.0)	96 (28.4)	0.0002
Hypercoagulable state	0	103 (30.6)	-
Chronic Lung Disease	19 (13.0)	84 (0.24)	0.086
In-hospital complications			
Acute Kidney Injury	98 (66.8)	132 (39.1)	0.011
Pneumonia	19 (13.2)	40 (11.8)	0.819
Urinary Tract Infection	4.5 (3.11)	28 (8.41)	0.231
Sepsis	29 (19.8)	18 (5.55)	0.103
Outcomes			
Prolonged length of stay	83 (56.5)	275 (81.2)	0.008
Discharge disposition of alive patients to nursing home	39 (30.7)	128 (43.4)	0.192
In-hospital mortality	19 (13.5)	41 (12.3)	0.87

Table 5: Comparing Mortality with and without Myoclonus		
	Heart Transplant	**CABG**
Mortality without Myoclonus	2.07%	2.45%
Mortality with Myoclonus	13.6%	12.3%
P value	0.08	0.02

CARDIOVASCULAR ANESTHESIOLOGY 10

Atrial Fibrillation and Alcohol Intake, Do Patients Know About This Relationship? - A Questionnaire Survey Study

Seung Mi Oh[1], Patrick O'Connor[2], Juan Pablo Forero[2], Christina Lee[3], Singh Nair[3], Jonathan Leff[3]

[1]Albert Einstein College of Medicine, Bronx, NY, [2]Albert Einstein College of Medicine, Bronx, United States of America, [3]Montefiore Medical Center, Bronx, NY

INTRODUCTION: Atrial fibrillation (AF) is one of the most frequently diagnosed cardiac arrhythmias with significant adverse outcomes[1]. Excessive alcohol consumption is detrimental to the development of AF and increases the risk of triggering atrial arrhythmias, which has led to the term 'holiday heart syndrome[2].' Given the well-established dose-response relationship between alcohol intake and the incidence of AF[3], patient education materials advise patients to limit alcohol intake[4]. However, the effectiveness of patient education in reducing alcohol intake in AF patients is not well-established. The aim of this study was to evaluate the effectiveness of patient education and the patient's understanding of the link between alcohol intake and AF incidence.

METHODS: All patients who were admitted between Jan 2019 – Jan 2020 with a diagnosis of atrial fibrillation were identified using a data repository. Using ICD-10 diagnosis code, patients with a history of alcoholism and a history of atrial ablation were identified and grouped. We randomly selected 125 patients each from the AF only group, AF and alcoholism group, and atrial ablation group. We conducted a phone survey using a standardized questionnaire adapted from the AUDIT alcohol screening questionnaire totaling 7 questions. Baseline demographic information was reviewed. Descriptive statistics was used to report all data points. Continuous variables are reported medians and interquartile ranges. Categorical variables are reported as frequencies and percentages. Chi-square test or Fisher exact test were performed as appropriate for the analysis of association between variables.

RESULTS: In total, 112 patient responses were collected. The median age of respondents was 65 years (IQR:57 – 74), with majority male (64.3%). Overall, 50 (44.6%) patients reported current alcohol use and 62 (55.4%) patients reported no current drinking, of which 35 (31.3%) patients were non-drinkers prior to AF diagnosis. To a True/False question, 83 (74.1%) patients responded that alcohol affects AF, but only 59 (52.7%) patients reported receiving education on the negative effects of alcohol on AF at their time of diagnosis. 25 (22.3%) patients reported they were offered counseling for alcohol use at the time of AF diagnosis. There was a strong association (p=0.005) between the patient's knowledge of whether alcohol affects atrial fibrillation and whether the patient received education from his/her physician on the negative effects of alcohol on AF.

CONCLUSION: Our survey results suggest that there is still a lack of patient understanding on the association of alcohol use and AF, with 10.7% reporting that alcohol does not affect AF and 15.2% reporting uncertainty. Almost half of the total respondants (47.3%) reported their physicians gave no education on the negative impact of alcohol use on AF, but it should be taken into consideration that physicians may omit education on alcohol use to patients who reported no drinking (n=35). Furthrmore, 52% of patients who currently drink after AF diagnosis reported no recollection of the physician educating them on the relationship between alcohol and AF. The diagnosis of AF is perhaps a missed opportunity to engage patients in their lifestyle choices and alcohol cessation.

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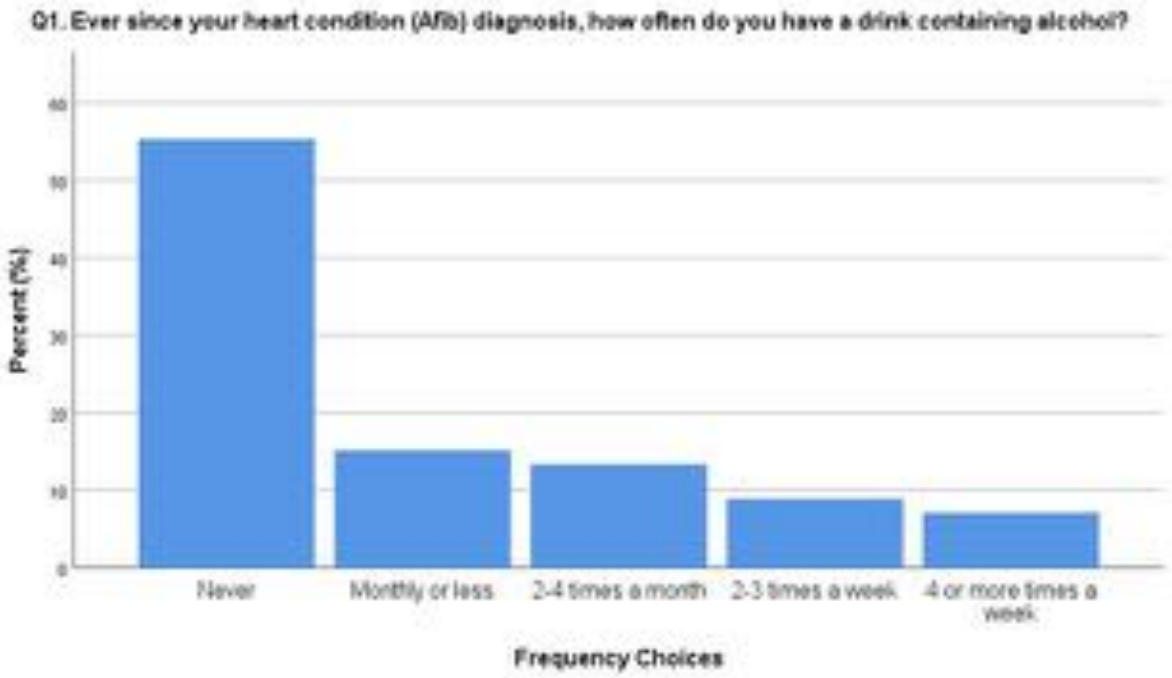
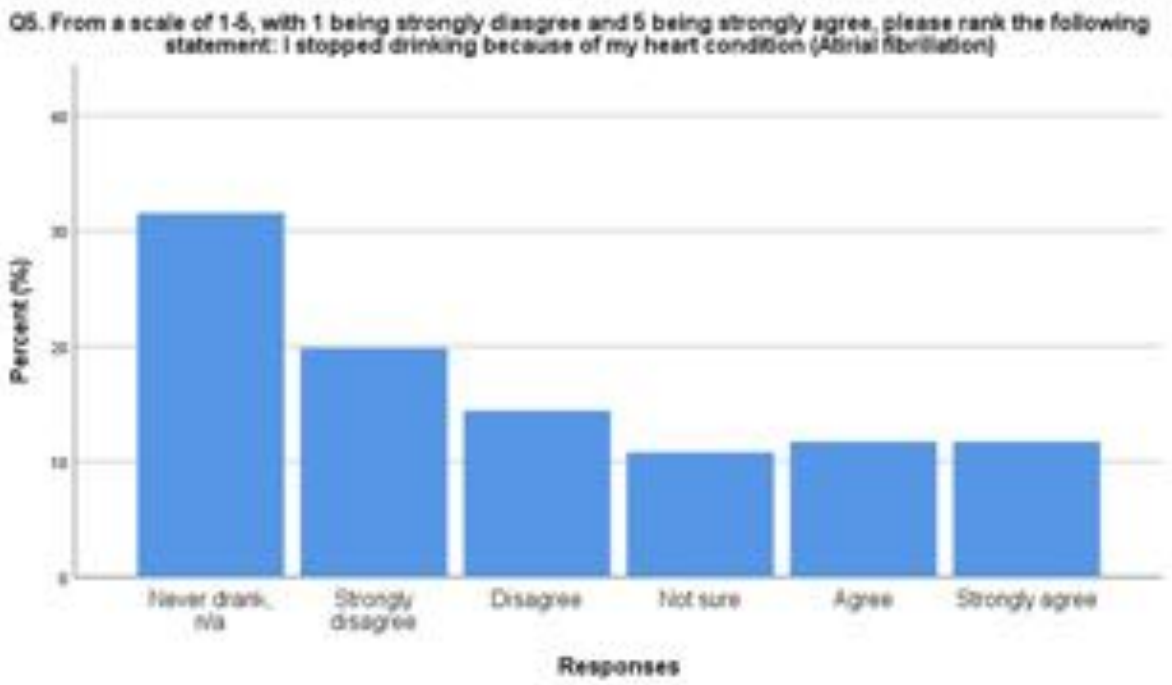
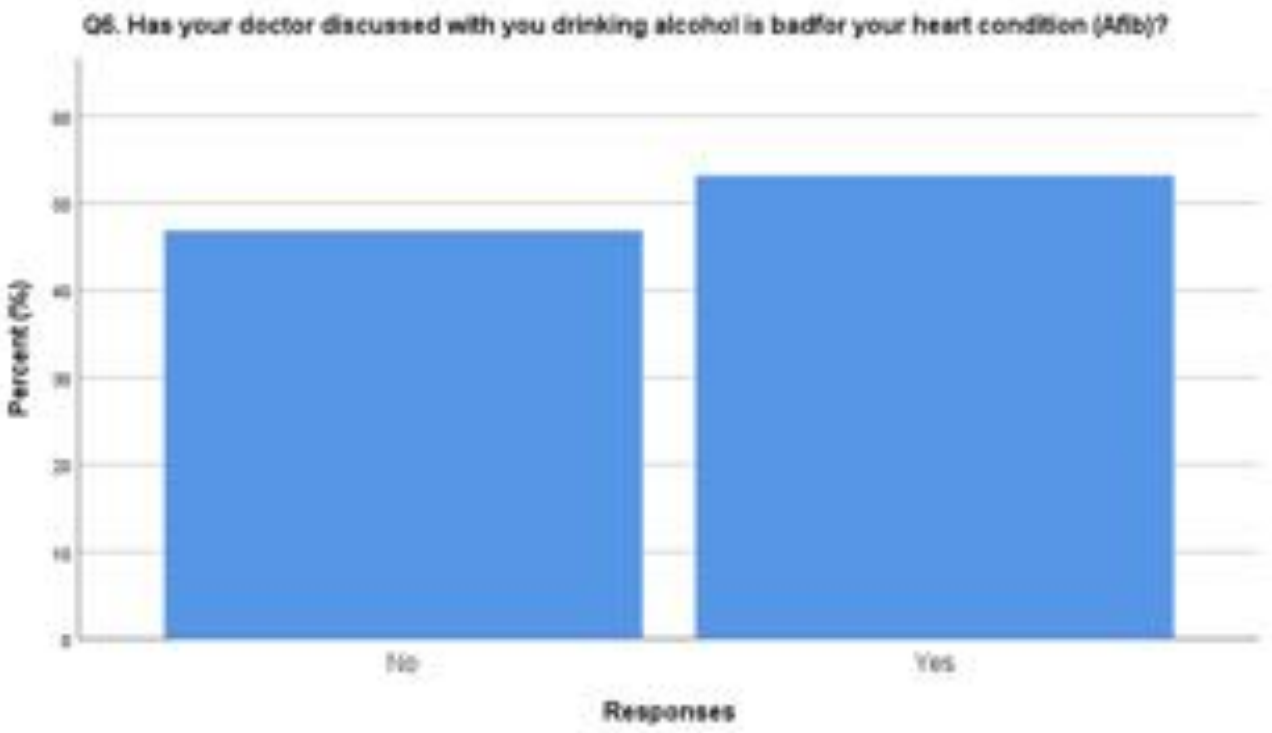
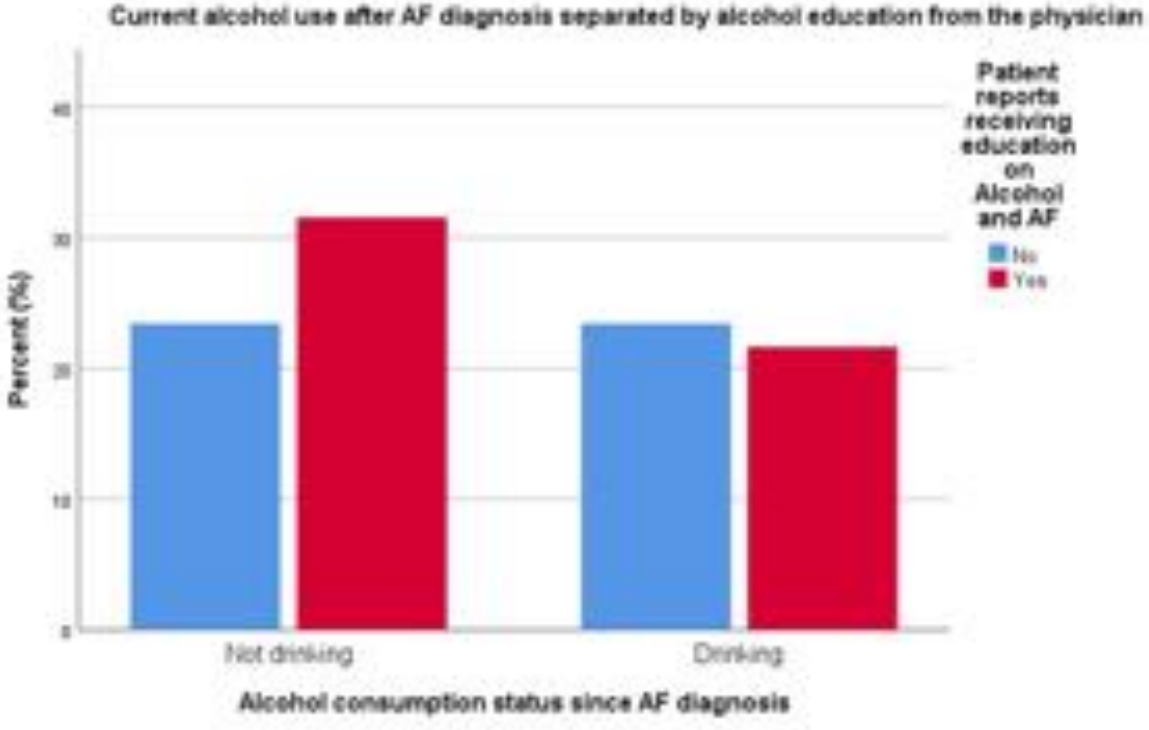
Table 1. Baseline Demographics and Clinical Characteristics of Respondents

	Median (IQR) or n (%)
Demographics	
Age	65 (57 – 74)
Male Gender	72 (64.3%)
Clinical Characteristics	
Ablation	77 (68.8%)
Alcoholism	21 (18.8%)









CARDIOVASCULAR ANESTHESIOLOGY 11

Echocardiography as an Aid to Tracheal Extubation in Cardiac Surgical Patients

Roshini s simon[1], Muralidhar Kanchi[2]

[1]Narayana institute of Cardiac Sciences, Banglore, India, [2]Narayana Institute of Cardiac Sciences, NH health city, Bangalore, Karnataka

INTRODUCTION: Weaning failure can result in significant morbidity & mortality. There is increasing evidence to support the use of transthoracic echocardiography (TTE) to identify the cardiac origin of weaning failure. The aim of the study is to determine the sensitivity of echocardiography parameters in predicting weaning failure.

METHODS: All adult patients for elective cardiac surgery between April 2020 to September 2020 were selected for the study. Ethical clearance was obtained prior to the study (NHH/AEC-CL-2020-504). Informed consent was taken for all patients. Sequential sampling of 390 elective cardiac surgical patients of the age group 18 – 65 years were done. Peri -op management was as per standardized institutional protocol. Echocardiography was performed prior to spontaneous breathing trial and after tracheal extubation for all patients by an experienced sonographer who was blinded to the study. Patients were categorised into three groups: short ventilation group (SV) if extubated within 6 hours of surgery, interim group (IV) if extubated between 6 to 12 hours and delayed extubation group (DE) if extubated after 12 hours. The following parameters were assessed: left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), pulmonary artery systolic pressure (PASP), E/A, E/e', inferior venacava (IVC) collapsibility index and right atrial pressure (RAP).

RESULTS: There were 400 patients who underwent elective cardiac surgery during the study period. The demographic, clinical and echocardiographic data are shown in the table. Amongst the echocardiographic parameters, EF and E/e' were significantly different in the short ventilation (SV) and delayed extubation (DE) group. The sensitivity of EF and E/e' in predicting weaning failure were found to be 85% and 87.5% respectively while the specificity of E/e' was 97.6% and that of LVEF was found to be only 55.4%. There was no significant difference in other echocardiographic parameters.

CONCLUSION: Echocardiography has a significant role in diagnosing and monitoring patients in intensive care units and provides information regarding patient suitability for extubation following cardiac surgery. Based on our findings in this study in patients undergoing elective cardiac surgery, echocardiography can be used to benefit the patient in terms of predictability of weaning the patient from ventilator. E/e' has extreme sensitivity and predictability regarding extubation success. Ejection fraction also helps in predicting weaning failure, but specificity is less compared to E/e'. Thus, we recommend the use of echocardiography to aid extubation in cardiac surgical patients as it helps in identifying difficult to wean patients which helps in better decision making and post-operative management in these patients which further improves the outcome of the surgery and benefit the patient.

Table 1: Demographic and preoperative data

Baseline Variables			**Short Ventilation, SV (N=83)**	**Interim Ventilation, IV (N=235)**	**Delayed extubation, DE (N=80)**	**P value**
Age (years)		Mean ± SD	54.67 ± 7.69	54.77 ± 7.69	56.19 ± 4.49	0.271
Gender	Males	Number (Percentage)	52 (62.7)	147 (62.6)	54 (67.5)	0.716
	Females		31 (37.3)	88 (37.4)	26 (32.5)	
Weight (kg)		Mean ± SD	63.13 ± 5.64	65.37 ± 9.25	63.85 ± 5.13	0.055
Height (cms)			161.25 ± 4.89	160.77 ± 6.49	160.03 ± 3.65	0.383
Hypertension		Number (Percentage)	33 (39.8)	124 (52.8)	35 (43.8)	0.084
Diabetes			33 (39.8)	101 (43)	24 (30)	0.122
Thyroid issues			13 (15.7)	36 (15.3)	18 (22.5)	0.316
Other	Nil		83 (100)	227 (96.6)	79 (98.8)	0.64
	Seizures		0 (0)	4 (1.7)	1 (1.3)	
	Stroke		0 (0)	1 (0.4)	0 (0)	
	Rheumatoid Arthritis		0 (0)	3 (1.3)	0 (0)	
Euro score		Median (IQR)	1.45 (1 - 2.1)	1.48 (1.13 - 1.9)	1.48 (1.07 - 2)	0.904

Table 2: Echocardiographic data

Echo Variables		**Short ventilation (SV) (N=83)**	**Interim ventilation (IV) (N=235)**	**Delayed extubation (DE) (N=80)**	**P value (between SV and DE)**
LVEF (%)	Mean ± SD	53.19 ± 4.06	52.68 ± 1.95	38.69 ± 9.37	<0.001
TAPSE (mm)	Mean ± SD	15.49 ± 1.06	15.72 ± 1.95	15.38 ± 1.29	0.568
PASP (mm hg)		26.28 ± 3.21	27.54 ± 4.24	27.05 ± 2.1	0.07
E/A	Median (IQR)	1.2 (0.8 - 1.2)	0.9 (0.7 - 1.2)	0.7 (0.6 - 2.1)	0.128
E/e'	Mean ± SD	6.78 ± 0.84	7.61 ± 3.31	9.8 ± 1.49	<0.001
IVC Collapsibility Index (<50%)	Number (Percentage)	8 (9.6)	16 (6.8)	12 (15)	0.297
RAP	Mean ± SD	3.48 ± 1.48	3 ± 0	3.63 ± 1.04	0.564

CARDIOVASCULAR ANESTHESIOLOGY 12

Influence of Hyperglycemia and Diabetes on Cardioprotection by Humoral Factors released after Remote Ischemic Preconditioning

Carolin Torregroza[1], Lara Gnägy[1], Annika Raupach[1], Martin Stroethoff[1], Katharina Kristina Feige[1], André Heinen[2], Markus W Hollmann[3], Ragnar Huhn[1]

[1]Department of Anesthesiology, Medical Faculty and University Hospital Duesseldorf, Duesseldorf, Germany, [2]Institute of Cardiovascular Physiology, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany, [3]Department of Anesthesiology, Amsterdam University Medical Center, Amsterdam, The Netherlands

INTRODUCTION: Ischemic preconditioning (IPC) leads to significant reduction of ischemia and reperfusion (I/R) injury. Remote ischemic preconditioning (RIPC) is less invasive and hence, much more practical in everyday clinical practice. Nevertheless, current clinical multicenter trials could not detect any protective benefit of RIPC. This discrepancy could be caused by a loss of cardioprotection due to comorbidities in patients, including diabetes mellitus along with acute hyperglycemia. Hyperglycemic conditions are common risk factors for myocardial infarction and have been shown to negatively influence cardioprotection by several pharmacological conditioning strategies. RIPC is discussed to confer protective properties by release of different humoral factors activating cardioprotective signaling cascades in cardiomyocytes. In the present study we investigated whether diabetes mellitus type 1 and/or hyperglycemia (1) inhibit the release of humoral factors after RIPC and/or (2) block the cardioprotective effect directly at the myocardium.

METHODS: Animals were treated in compliance with institutional and national guidelines. All experiments were performed on 2-3 months old male Wistar rats. The study is comprised of two parts. In part 1 rats were randomized into 6 groups for in vivo experiments followed by plasma sampling for further investigations. Animals included in part 1 of the study were either healthy normoglycemic (NG), type 1 diabetic (DM1) or received glucose solution for induction of acute hyperglycemia (HG). RIPC was implemented by 4 cycles of 5 min bilateral hind-limb ischemia and reperfusion (RIPC). Control (Con) animals were not treated. Cardioprotective properties of blood plasma from part 1 was further investigated in isolated hearts of male Wistar rats (6 groups, each group n=7-9). Hearts were mounted on a Langendorff system and were perfused with Krebs-Henseleit buffer. Plasma from diseased animals (DM1 or HG) was administered onto healthy (NG) hearts as preconditioning (PC) for 10 minutes before 33 minutes global ischemia followed by 60 minutes of reperfusion. Part 2 of the study was performed vice versa – plasma taken in in vivo experiments with or without RIPC from healthy rats was transferred to DM1 and HG hearts in vitro (4 groups, each group n=8-9). Infarct size was determined by TTC-staining. Statistics: t-Test. Data are expressed as mean±SD.

RESULTS: Part 1: RIPC plasma from NG animals reduced infarct size from 49±8% to 29±6% ($P<0.05$ vs Con). RIPC plasma from DM1 rats showed a similar effect (DM1 Con: 47±7% vs. DM1 RIPC: 38±7%; $P<0.05$). Interestingly, transfer of HG plasma showed similar infarct sizes independent of prior treatment (HG Con: 34±9% vs. HG RIPC 35±9%; ns). Part 2: No infarct size reduction was detectable when transferring RIPC plasma from healthy rats to DM1 (DM1 Con: 54±13% vs. DM1 RIPC 53±10%; ns) or HG hearts (HG Con: 60±16% vs. HG RIPC 53±14%; ns).

CONCLUSION: These results suggest that: 1) RIPC under NG and DM1 induce release of a humoral factor with cardioprotective impact, 2) HG plasma might own cardioprotective properties per se and 3) RIPC does not confer cardioprotection in DM1 and HG myocardium. These findings indicate that comorbidities, like DM1 and HG, possibly negatively influence the myocardium itself while having no effect on release of humoral factors after RIPC.

CARDIOVASCULAR ANESTHESIOLOGY 13

Effect of neuraxial anaesthesia on left ventricular diastolic function assessed by transthoracic echocardiography

Muralidhar Kanchi[1]

[1]*Narayana Institute of Cardiac Sciences, NH health city, Bangalore, Karnataka*

INTRODUCTION: Abnormal ventricular diastolic function may lead to clinical heart failure (HF) in 40 to 50% of patients despite their having normal systolic function. Left ventricular (LV) diastolic function plays a major role in determining the overall cardiovascular performance, and heart failure resulting from diastolic dysfunction may occur in the absence of or precede the development of abnormalities in systolic function. Unrecognized and untreated diastolic dysfunction may increase perioperative mortality and morbidity. The incidence of diastolic dysfunction is increasing alarmingly due to age and increase in comorbidities such as hypertension, diabetes mellitus, thyroid diseases, chronic kidney disease and others. This study was performed to evaluate the effect of neuraxial anaesthesia on left ventricular (LV) diastolic function in clinical setting using transthoracic echocardiography (TTE).

METHODS: This prospective observational study was performed in 50 adult patients undergoing elective orthopaedic surgical procedure using neuraxial anaesthesia. TTE was performed before, 20, 40 and 60 minutes after neuraxial anaesthesia. Heart rate and mean arterial pressure were recorded. Pulsed wave Doppler of the transmitral flow (TMF), pulmonary venous flow (PVF), deceleration time (DT) and propagation velocity (Vp) were measured. Mitral (E', A') annulus velocities which includes both lateral and septal wall were assessed by tissue Doppler imaging (TDI). The maximum diameter of left atrium (LA), LA volume index, left ventricular (LV) end-diastolic volume (EDV), end-systolic volume (ESV), end-diastolic area (EDA), end-systolic area (ESA) and LV FAC were measured from apical 4-chamber view (A4CV) view. The maximum diameter of the right atrium (RA), right ventricular (RV) end-diastolic area (EDA), end-systolic area (ESA), fractional area change (FAC) and RV systolic pressure was obtained from the A4CV. Similarly, Assessment of diastolic dysfunction was graded as per the American Society of Echocardiography (ASE).

RESULTS: There were 50 patients in the cohort of whom 48 had normal diastolic function preoperatively. Following neuraxial anaesthesia, mean arterial pressure decreased ($P<0.001$) while heart rate remained unchanged ($P=0.436$). None of the measured dimensions and volumes of various cardiac chambers changed significantly after neuraxial anaesthesia. Similarly, LV FAC and RV FAC remains unchanged. Transmitral pulse wave doppler, DT, Vp, PVF and mitral annulus TDI did not vary after neuraxial anaesthesia. There was no significant change in the LV diastolic function.

CONCLUSION: In patients with normal diastolic function, neuraxial anaesthesia does not alter diastolic function indices and grading. It is recommended that the study be performed in patients with documented diastolic dysfunction to demonstrate beneficial or detrimental effects of central neuroaxial blockade, if any.

Table 1: Study patients demographics, characteristics, laboratory values and outcomes.

Variable	Descriptive statistics
Age in years (Mean ± SD)	41.30± 11.76
Gender Male/Female (n %)	37/13 (74/26)
Weight in kilogram (Mean ± SD)	68.16± 13.31
Height in centimeters (Mean ± SD)	166.32± 7.06
BSA (Mean ± SD)	1.71±0.23
ASA 1/2/3 (n)	36/12/2
Coronary artery disease: Yes/No (n, %)	1/49 (2/98)
Hypertension: Yes/No (n, %)	6/44 (12/88)
Diabetes mellitus Yes/No (n, %)	9/41 (18/82)
Hypothyroidism Yes/No (n, %)	1/49 (2/98)
Hyperthyroidism Yes /No (n, %)	1/49 (2/98)
Hemoglobin in g/L (Mean ± SD)	11.78± 1.76
Serum creatinine in mg/dl (Mean ± SD)	0.91±0.23
Spinal/Epidural	x/y
Postoperative ICU stay in days Yes/No (n, %)	1/49 (2/98)

Table 2: Hemodynamic changes after neuraxial anaesthesia. HR- Heart rate, SBP- Systolic blood pressure, DBP- Diastolic blood pressure, MAP- Mean arterial pressure. Data are represented as mean±SD.

Parameters	Baseline	20 minutes	40 minutes	60 minutes	*p*
HR (/min)	84.4±16.6	85.3±15.0	83±12.3	81±11.1	0.436
SBP (mm Hg)	144.6±16.7	122.6±17.9	125.3±11.2	130.1±12.4	<0.001
DBP (mm Hg)	81.6±12.6	71.6±71.6	75.0±9.7	76.7±10.3	<0.001
MAP (mm Hg)	96.6±1.5	83.7±0.3	87.6±0.2	88.9±0.1	<0.001

Table 3: Chamber dimensions, volumes and functions. LA- left atrium, LVEDA- Left ventricular end-diastolic area, LVESA- Left ventricular end-systolic area, LVFAC- left ventricular fractional area change, LVEDV- left ventricular end-diastolic volume, LVESV- Left ventricular end-systolic volume, LVEF- Left ventricular ejection fraction, RA- right atrium, RVEDA- Right ventricular end-diastolic area, RVESA- Right ventricular end-systolic area, RVFAC- right ventricular fractional area change. Data are mean±SD.

Parameters	Baseline	20 minutes	40 minutes	60 minutes	P value
LA Maximum Diameter (cm)	3.03±0.39	3.11±0.45	3.03±0.37	3.04±0.38	0.7
LVEDA ($cm^{2)}$	19.46±4.06	19.53±3.61	19.49±3.49	19.95±3.88	0.9
LVESA ($cm^{2)}$	10.68±3.44	10.43±2.92	10.15±2.76	10.33±2.77	0.8
LVFAC (%)	45.14±6.91	49±7.54	46.30±7.46	45.92±7.67	0.6
LVEDV (ml)	98.46±19.66	98.04±15.71	96.34±15.90	97.38±15.46	0.9
LVESV (ml)	42.30±9.23	43.3±7.65	42.37±7.69	42.10±6.96	0.8
LVEF (%)	56.76±6.74	54.90±6.56	56.04±6.30	55.84±5.84	0.5
RA Maximum Diameter	3.28±0.5	3.26±0.47	3.22±0.39	3.25±0.4	0.9
RVEDA ($cm^{2)}$	21.42±2.44	21.83±2.31	22.04±1.99	21.71±2.16	0.9
RVESA ($cm^{2)}$	11.70±1.68	11.48±1.66	11.30±1.59	11.25±1.48	0.4
RVFAC (%)	47.32±5.77	47.15±8.96	48.96±5.99	49.00±5.87	0.3

Table 4: Left ventricular diastolic function parameters. E- transmitral E wave, A- transmitral A wave, E/A- transmitral E/A ratio, PVF S- pulmonary vein flow systolic wave, PVF D- pulmonary vein flow diastolic wave, PVF S/D ratio- pulmonary vein flow systolic/diastolic

ASE grading of DD	Baseline n (%)	20 minutes n (%)	40 minutes n (%)	60 minutes n (%)	*p*
No DD	48 (96%)	48 (96%)	48 (96%)	48 (96%)	0.238
Yes DD	0	0	0	0	
Indeterminate	2 (4%)	2 (4%)	2 (4%)	2 (4%)	

CARDIOVASCULAR ANESTHESIOLOGY 14

Novel Opioid-Free Anesthesia Protocol for Cardiac Surgery Utilizing Dexmedetomidine: A Retrospective Review

Lindsay Pharmer[1], Tiffany Morandi[2], Alexander Nguyen[2], Jessica Lee[2], Vikas O'Reilly-Shah[3], Carli Hoaglan[2], James Helman[4], Sarah Bain[2]

[1]Matrix Anesthesia at Evergreen Health Medical Center, Kirkland, WA, [2]Virginia Mason Medical Center, Seattle, WA, [3]University of Washington, Seattle, WA, [4]Sunnybrook Health Sciences Center and University of Toronto, Toronto, Canada

INTRODUCTION: Opioids have been a mainstay in cardiac anesthesia due to their ability to provide a hemodynamically stable anesthetic that predictably blunts sympathetic response to laryngoscopy, sternotomy and post-operative pain. However, there are many compelling reasons to minimize opioid usage in the perioperative setting including the numerous adverse effects of opioids and risk of habituation.[1] Opioid-free anesthetic (OFA) techniques have been successfully introduced for several types of non-cardiac surgery.[2,3] Since 2018, cardiac anesthesia practice at our institution has gradually evolved with the use of progressively smaller doses of opioids replaced by larger doses of dexmedetomidine. To our knowledge, OFA using dexmedetomidine has not been studied in cardiac anesthesia for cardiopulmonary bypass. Our objective is to present a retrospective review of cardiac opioid anesthesia (OA) versus OFA, using dexmedetomidine as the primary adjunct.

METHODS: Following IRB approval, we retrospectively analyzed 86 patients undergoing open cardiac surgery with cardiopulmonary bypass from March 2018 to December 2019. Patients who were included were managed either by our institutional OFA pathway (Chart 1) or by a more traditional opioid-based anesthetic according to anesthesiologist preference. Patients who received pectoralis nerve blocks were not included. The OA group utilized a low dose dexmedetomidine infusion (no bolus) for maintenance and transport to the ICU. Hemodynamic stability with induction was analyzed based on the change in mean arterial blood pressure (MAP) and heart rate (HR) compared to baseline during the first 15 minutes post-induction. The use of vasopressors prior to going on cardiopulmonary bypass was also recorded. Opioid usage (using oral morphine equivalents, MED) and antiemetic treatment for the first 24 hours post-surgery were reported, as was time to extubation, length of intensive care unit (ICU) and hospital stay. Statistical analysis was conducted with the R software package utilizing the Wilcoxon Rank Sum Test and Fisher's Exact Test.

RESULTS: Demographic data is presented in Table 1. The median intraoperative fentanyl usage in the OA group was 650mcg (range 300-1000mcg). No clinically significant differences were observed between groups with respect to change in MAP or HR after induction, vasopressor use, postoperative MED, or rescue antiemetic medications (Table 2). There was also no difference in time to extubation, length of ICU stay, or length of hospitalization. There was one in-hospital mortality among the OA group (p=0.209).

CONCLUSION: This study found no difference between OA and OFA groups with respect to hemodynamic stability with induction or postoperative outcomes. These findings suggest OFA is a viable alternative to OA and high dose opioids at induction for cardiothoracic surgical procedures involving CPB. Our OFA cardiac pathway would benefit from a larger prospective trial to fully evaluate its benefits and any potential risks. Of particular interest is an analysis of preoperative versus post-induction left ventricular systolic and diastolic function.

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Chart 1: Cardiac Opioid-Free Anesthesia Pathway

- Premedication:
  - Midazolam 2mg IV as needed
- Induction:
  - Dexmedetomidine 1mcg/kg IV bolus over 9 min
  - Propofol 1-3 mg/kg IV
  - Paralytic
- Maintenance:
  - Isoflurane
  - Dexmedetomidine 0.8 – 1.0 mcg/kg/hr IV infusion
- Emergence/ICU transfer:
  - Acetaminophen 1000mg IV
  - Patients transported to the ICU intubated with infusions of dexmedetomidine 0.4 – 1.0 mcg/kg/hr and propofol 25-75mcg/kg/min for sedation.

Variable	OA (n=18)	OFA (n=68)	P-value
Age (median, IQR)	66 (62, 69)	69 (63, 75)	0.068
Gender (% male)	83.3 (n=15)	73.5 (n=50)	0.542
BMI (median, IQR)	30 (28.0, 33.0)	28 (24.7, 32.3)	0.092
Type of surgery (n, %)			
AVR	5 (27.8)	17(25.0)	0.872
MVR	0 (0.0)	4 (5.9)	
CABG	11 (61.1)	41 (60.3)	
CABG + AVR	2 (11.1)	6 (8.8)	
Pre-operative EF (median, IQR)	60.5 (57.1, 65.3)	57.3 (52.0, 64.0)	0.331

Table 1: Demographic data
OA – opioid anesthesia, OFA – opioid-free anesthesia, IQR – interquartile range, BMI – body mass index, AVR – aortic valve replacement, MVR – mitral valve replacement, CABG – coronary artery bypass graft, EF – ejection fraction.

Variable	OA (n=18)	OFA (n=68)	P-value
Change in MAP (median, IQR)	-4.00 (-18.25, 4.25)	0.00 (-6.25, 12.00)	0.07
Change in HR (median, IQR)	-4.00 (-9.75, -0.25)	0.50 (-5.00, 7.25)	0.023
Vasopressor use pre-CPB			1.00
Not given (%)	1 (5.6)	6 (8.8)	
Given (%)	17 (94.4)	62 (91.2)	
24-hr postoperative MED (median, IQR)	91.50 (47.00, 108.75)	60.00 (26.88, 96.62)	0.243
Postoperative antiemetic			0.298
None given (%)	10 (55.6)	28 (41.2)	
Rescue given (%)	8 (44.4)	40 (58.8)	
Time to extubation, min (median, IQR)	197.00 (151.50, 248.50)	191.50 (153.50, 309.25)	0.97
Length of ICU stay, hours (median, IQR)	33.15 (25.12, 46.82)	27.55 (23.28, 46.50)	0.432
Hospital stay, days (median, IQR)	6.00 (5.00, 7.75)	6.00 (5.00, 7.25)	1.00
In-hospital mortality (%)	1 (5.6)	0 (0.0)	0.209

Table 2: Outcomes

OA – opioid anesthesia, OFA – opioid-free anesthesia, MAP - mean arterial pressure, HR - heart rate, CPB – cardiopulmonary bypass, MED - morphine equivalent dose, IQR - interquartile range, ICU - intensive care unit

CARDIOVASCULAR ANESTHESIOLOGY 15

Mannitol induced cardioprotection in the isolated rat heart – more than just Hyperosmolarity?

Katharina Feige[1], Janine Rubbert[1], Martin Stroethoff[1], Annika Raupach[1], André Heinen[2], Markus W Hollmann[3], Ragnar Huhn[1], Carolin Torregroza[1]

[1]Department of Anesthesiology, Medical Faculty and University Hospital Duesseldorf, Duesseldorf, Germany, [2]Institute of Cardiovascular Physiology, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany, [3]Department of Anesthesiology, Amsterdam University Medical Center, AUMC, Amsterdam, Netherlands

INTRODUCTION: Cardiac preconditioning (PC) and postconditioning (PoC) are powerful measures against the consequences of myocardial ischemia and reperfusion injury. Mannitol (Man) – a hyperosmolar solution – is clinically used for treatment of intracranial and intraocular pressure, promotion of diuresis in renal failure and as perioperative neuroprotection. Next to these clinical indications, different organprotective properties are described. However, whether Man also confers cardioprotection via PC and/or PoC is unknown. Therefore, in the present study we investigated whether (1) Man-induced PC and/or -PoC induces myocardial infarct size reduction and (2) activation of mitochondrial ATP-sensitive potassium (mKATP) channels is involved in cardioprotection by Man.

METHODS: Experiments were conducted in compliance with institutional and national guidelines in male Wistar rats in vitro. Hearts were mounted on a Langendorff system and were perfused with Krebs-Henseleit buffer (KHB) at a constant pressure of 80 mmHg. All hearts underwent 33 minutes of global ischemia followed by 60 minutes of reperfusion. At the end of experiments infarct size was determined by TTC staining. Animals were randomized into seven groups (each group n=6-7). Control animals (Con) received KHB as vehicle only. PC and PoC was induced by 11 mmol/L Man for 10 minutes before ischemia (Man-PC) or immediately at the onset of reperfusion (Man-PoC), respectively. Additionally, the mKATP-channel blocker 5HD was applied with and without Man-PC or Man-PoC for 10 minutes (5HD-PC+Man-PC, 5HD-PC, 5HD-PoC+Man-PoC, 5HD-PoC).

RESULTS: Man-PC and Man-PoC significantly reduced infarct size (Man-PC: 31±4%; Man-PoC: 35±6%, each $P<0.05$ vs. Con: 57±9%). The mKATP-channel inhibitor 5HD completely abrogated the cardioprotective effect of Man-PC (5HD-PC+Man-PC: 59±8%; $P<0.05$ vs. Man-PC) and Man-PoC (5HD-PoC+Man-PoC: 59±10%; $P<0.05$ vs. Man-PoC). 5HD itself did not influence infarct size (5HD-PC: 60±14%, 5HD-PoC: 54±14%; ns vs. Con).

CONCLUSION: These results demonstrate that Mannitol (1) induces myocardial pre- and postconditioning and (2) confers cardioprotection via activation of mKATP-channels.

CARDIOVASCULAR ANESTHESIOLOGY 16

Pulmonary artery pulsatility index is outperformed by mean pulmonary artery pressure and mean arterial pressure in predicting one-year mortality in cardiac surgery patients

Ziyad O Knio[1], Robert H Thiele[1], Matthew Hulse[2]

[1]University of Virginia Health System, Charlottesville, VA, [2]University of Virginia, Charlottesville, VA

INTRODUCTION: There exist many studies demonstrating the value of right heart hemodynamics in risk stratifying individuals. Recently, the pulmonary artery pulsatility index (PAPi) has been investigated as a potential marker of right heart dysfunction and poor outcomes, primarily in heart failure patients. This study aimed to investigate the predictive ability of the PAPi, among other hemodynamic indices, in assessing morbidity and mortality in a heterogenous sample of cardiac surgery patients.

METHODS: This retrospective analysis examined all cardiac surgery patients at a single academic medical center from January 2017 through March 2020 (n=1510). The primary outcome was one-year mortality. Peak increase in serum creatinine from baseline was investigated as a secondary outcome. Right heart hemodynamic parameters sampled continually in the immediate (one-hour) post-operative period included central venous pressure (CVP), mean pulmonary artery pressure (mPAP), PAPi, and a novel index: the gradient between mPAP and CVP. Mean arterial pressure (MAP) was sampled continually from arterial catheter pressure tracings. Cardiac index (CI) was routinely calculated with less frequency. Univariate and multivariate analyses were performed to test for the association between the one-year mortality and post-operative hemodynamic indices, among other potential predictors. Univariate tests included Student's t-test and Pearson's Chi-square test, with an exploratory $p < 0.10$ identifying potential predictors. Multivariate testing utilized backwards stepwise logistic regression model selection and receiver operating characteristic analysis, providing adjusted odds ratios (AOR) and model area under the curve (AUC). The relationship between serum creatinine and post-operative hemodynamic indices was investigated visually and with Pearson's correlation coefficient at alpha = 0.05.

RESULTS: Of the 1133 patients with hemodynamic recordings, one-year mortality was observed in 66 (5.8%). On univariate analysis, mortality was associated with mPAP (25.16 ± 5.92 vs. 22.44 ± 5.08, $p < 0.001$), the novel index (12.47 ± 6.07 vs. 10.35 ± 4.66, $p = 0.007$) and MAP (72.51 ± 10.56 vs. 75.25 ± 9.56, $p = 0.067$) but not CVP (12.82 ± 5.24 vs. 12.07 ± 4.52, $p = 0.261$), PAPi (1.44 ± 0.73 vs. 1.40 ± 0.78, $p = 0.682$), or CI (2.55 ± 0.81 vs. 2.66 ± 0.79, $p = 0.322$). Model selection during multivariate analysis revealed that the only hemodynamic parameters independently predictive of mortality were mPAP (AOR = 1.096 [1.042 - 1.151]) and MAP (AOR = 0.966 [0.934 - 0.997]), with model AUC = 0.716. Of the 1104 non-end stage renal disease patients, serum creatinine was recorded in 935. Peak increase in serum creatinine from baseline demonstrated a weak ($|r| < 0.3$) but non-zero ($p < 0.05$) linear relationship with CVP, mPAP, the novel index, and MAP, while demonstrating no relationship with PAPi or CI.

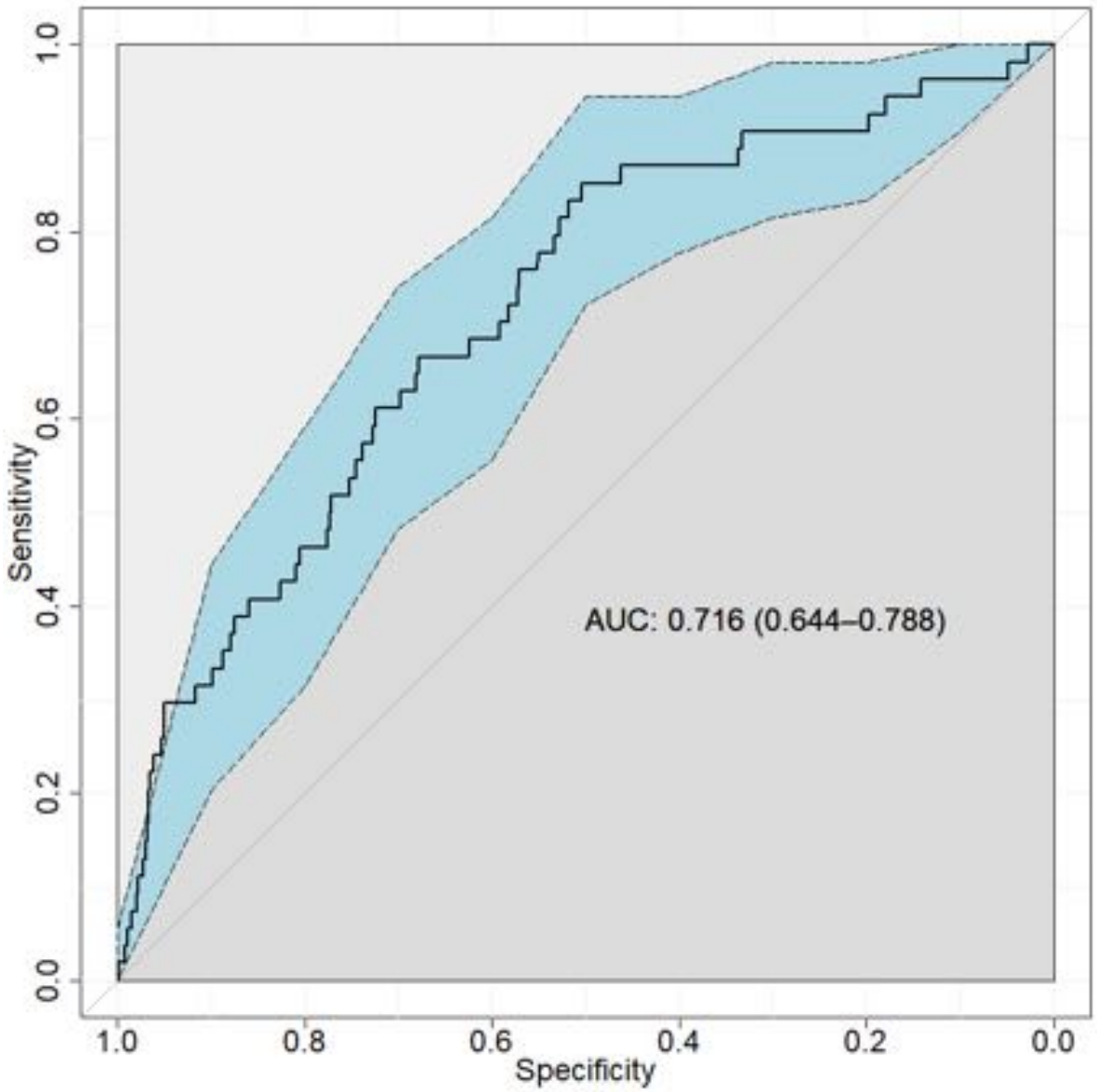
CONCLUSION: In this heterogenous sample of all cardiac surgery patients, mortality and serum creatinine were not associated with the immediate post-operative PAPi. Mortality was, however, independently predicted by mPAP and MAP and associated with a novel index.

Table 1. Demographic, hemodynamic, and outcome data.

Variable	Mean ± SD, or Frequency (%)	n
Demographic		
Age (years)	66.12 ± 10.52	1133
Body Mass Index (kg/m^2)	30.15 ± 6.49	1133
Sex (Female)	364/1133 (32.1%)	1133
Race (White)	1016/1133 (89.7%)	1133
Current Smoker	219/1133 (19.3%)	1133
Diabetes	495/1132 (43.7%)	1132
Previous Cardiac Intervention	405/1133 (35.7%)	1133
Systolic Heart Failure	255/1133 (22.5%)	1133
Prior Myocardial Infarction	536/1132 (47.3%)	1132
Re-operation	83/1133 (7.3%)	1133
Urgent/Emergent Surgery	493/1133 (43.5%)	1133
Hemodynamic		
Central Venous Pressure	12.11 ± 4.57	1133
mPAP	22.60 ± 5.17	1132
PAPi	1.40 ± 0.78	1133
Novel Index	10.47 ± 4.78	1132
Mean Arterial Pressure	75.11 ± 9.63	1059
Cardiac Index	2.65 ± 0.79	1128
Outcome		
Mortality	66/1133 (5.8%)	1133
Peak Serum Creatinine Increase	0.41 ± 0.60	935

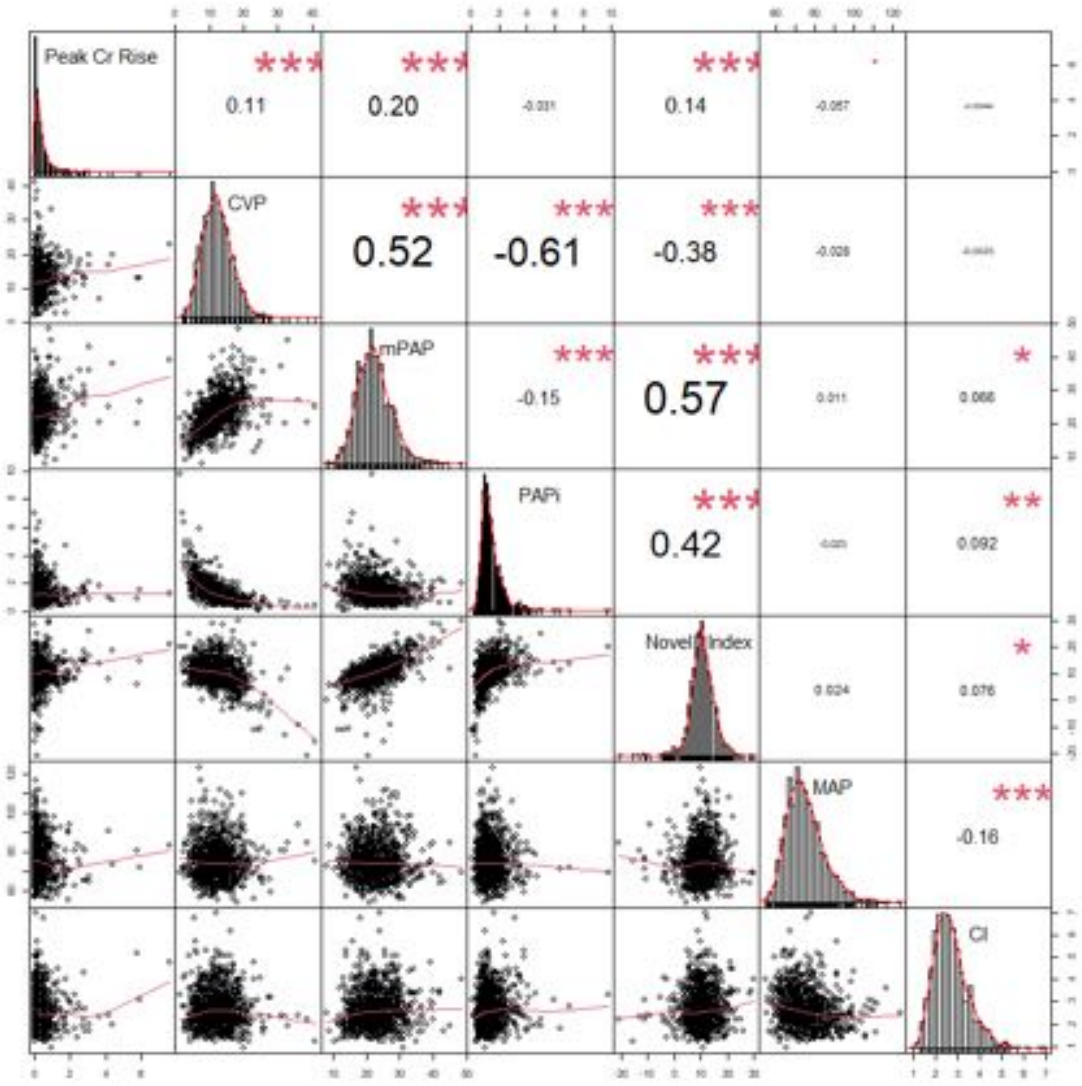
Abbreviations: mPAP, mean pulmonary artery pressure; PAPi, pulmonary artery pulsatility index.

Figure 1. Receiver operating characteristic analysis applied to one-year mortality regression.



Abbreviations: AUC, area under the curve.

Figure 2. Pearson's correlation between peak serum creatinine increase from baseline (mg/dL) and hemodynamic indices.



Abbreviations: CI, cardiac index; Cr, creatinine; CVP, central venous pressure; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PAPi, pulmonary artery pulsatility index.

CARDIOVASCULAR ANESTHESIOLOGY 17

Higher preoperative high-density lipoprotein concentration is associated with a lower risk of acute kidney injury after endovascular aortic repair

Jordan T Patrick[1], Loren Smith[2], Derek K Smith[2]

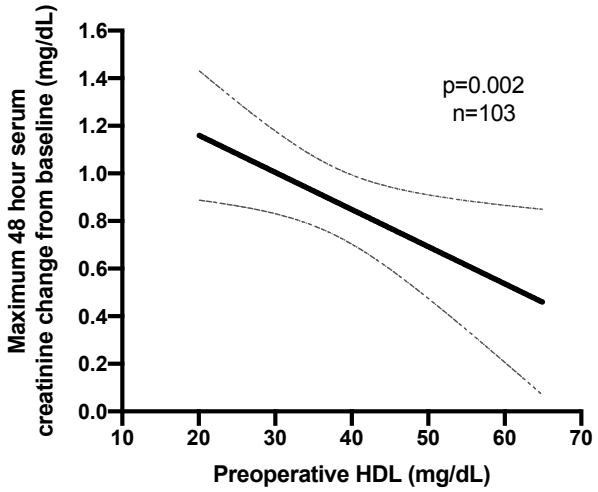
[1]Meharry Medical College, Nashville, TN, [2]Vanderbilt University Medical Center, Nashville, TN

INTRODUCTION: Acute kidney injury (AKI) after endovascular aortic repair occurs in up to 20% of patients and is an independent predictor of death. Patients undergoing endovascular aortic repair have unique risk factors for AKI including exposure to radiocontrast, aortic clamping, and the potential for renal microembolization. A higher high-density lipoprotein (HDL) concentration before revascularization of chronic limb ischemia is associated with a lower risk of AKI, and our group has shown that a higher preoperative HDL cholesterol concentration is associated with a lower risk of AKI after major cardiac surgery. HDL exhibits anti-inflammatory and anti-oxidant properties. These molecules also serve as a systemic signaling mechanism facilitating rapid inter-organ communication during times of physiologic stress. We hypothesized that a higher preoperative HDL cholesterol concentration is inversely associated with a lower risk of developing AKI in patients who undergo endovascular aortic repair.

METHODS: After IRB approval, data were obtained from a database of de-identified patient electronic health records developed by our medical center for research purposes. Charts from patients over 18 years of age that underwent thoracic endovascular aortic repair (TEVAR) or endovascular aortic repair (EVAR) were selected using the ICD9 codes of 39.71 or 39.73 or ICD10 codes of 02VW3DZ or 04V03 (n=253). These charts were manually reviewed for basic demographic and medical information, preoperative and postoperative serum creatinine concentrations, and preoperative HDL concentration. One hundred and three patients had available serum creatinine and HDL concentrations and were included in our final analysis. The association between HDL level and maximum serum creatinine change from baseline in the first 48 postoperative hours was assessed using a multivariable linear regression model, adjusted for other known risk factors for acute kidney injury.

RESULTS: There were no significant differences in age, sex, history of hypertension or diabetes, baseline preoperative serum creatinine concentrations, or maximum serum creatinine change from baseline in the first 48 postoperative hours in patients that did and did not have preoperative HDL concentrations available. There were also no significant differences in these variables or in preoperative HDL concentration in patients that did and did not have postoperative serum creatinine measurements available. Median (10th, 90th percentile) preoperative HDL was 39 (25, 60) mg/dl and postoperative creatinine change 0.78 (-0.29, 1.77) mg/dl. Lower HDL levels were independently associated with increased postoperative serum creatinine rise (p=0.002, Figure).

CONCLUSION: Higher preoperative HDL levels are associated with decreased changes in postoperative creatinine levels. Future work involves identifying the biological mechanism underlying these associations as a first step toward HDL supplementation in patients at increased risk for developing AKI following endovascular surgery.



Partial effects plot adjusted for age, diabetes, baseline serum creatinine concentration, and volume of red blood cells transfused during surgery. Dashed lines denote 95% confidence interval.

CARDIOVASCULAR ANESTHESIOLOGY 18

Intraoperative Use of Methylene Blue for Vasoplegia in Cardiac Surgery Not Associated With Decreased Vasopressor Requirement

Audrey E Spelde[1], Emily J Mackay[2], Jeremy D Kukafka[3], Jacob Gutsche[1], Warren J Levy[3]

[1]University of Pennsylvania, Philadelphia, PA, [2]The University of Pennsylvania Health System, Philadelphia, PA, [3]The University of Pennsylvania, Philadelphia, PA

INTRODUCTION: Vasoplegic syndrome (VS) is a condition of low vascular tone causing refractory hypotension despite use of pressors. VS occurs in up to 25% of cardiac surgical patients and is associated with increased morbidity and mortality[1]. Associated mortality typically ranges from 5-10%, however VS persisting more than 48 hours is associated with mortality as high as 28%[2,4]. There currently exists no consensus on risk factors or treatment approach, however methylene blue (MB) is commonly used as a rescue medication and may reduce the risk of vasoplegia when given prophylactically[3-5]. Methylene blue has been associated with decreased pressor requirements in patients with postcardiotomy VS[2,6]. We hypothesized that patients receiving MB intraoperatively would have lower pressor requirements.

METHODS: We retrospectively identified all cardiac surgical cases from 7/1/2013 through 7/1/2020 at two tertiary care centers within one health system. A total of 9616 cases were analyzed, of which 288 (3%) received MB. We included patient demographics, preoperative and intraoperative variables for analysis. Continuous variables were analyzed by Student's t test. Categorical variables were tested by chi squared analysis. Following unadjusted analysis using simple linear regression, adjusted outcome analysis was accomplished using multiple linear regression and adjusted for variables such as age, sex, ASA status, emergency and reoperation status, CPB duration, and endocarditis, among others. An additional, adjusted analysis used multiple linear regression on a propensity score-matched (nearest neighbor, 1:1, without replacement) cohort. Matches were evaluated by standardized differences (SD) with a SD < 0.20 indicating an acceptable match.

RESULTS: Among 9,616 patients 288 (3%) received MB and 9,328 (97%) did not receive MB. Overall, those that received MB were younger, but demonstrated higher comorbid conditions such as endocarditis, more likely to be a reoperation, and more likely to undergo longer duration surgery and CPB (Table 1). All analyses revealed that those who received MB demonstrated higher NE equivalents compared to those who did not receive MB. The unadjusted analysis using simple linear regression demonstrated higher NE equivalents among the MB group (16.74 [95% CI 15.11-18.38] vs 7.32 [95% CI 7.20-7.44]; p<0.001). Following adjusted analysis using multiple linear regression, those receiving MB still demonstrated higher NE equivalents of 6.84 mcg/min (95% CI: 6.12 – 7.56; p<0.0001) despite adjusting for baseline characteristics. Among a propensity score-matched cohort of 566 patients (283 MB vs 283 control), adjusted analysis using multiple linear regression demonstrated higher pressor requirement among the MB group (7.30 mcg/min [95% CI: 5.42 – 9.19; p=0.002). These findings prompted a prediction model, which found endocarditis (OR 4.48 [95% CI 3.20 – 6.27]; p<0.0001) to be highly predictive of methylene blue receipt (Table 2).

CONCLUSION: We unexpectedly found a higher pressor requirement associated with MB despite adjusting for baseline characteristics. Propensity score matching was performed to account for confounding factors which resulted in acceptable matches among all covariates (Figures 1 and 2). However, despite matching, the MB group still demonstrated higher pressor requirements. Given that these results conflict with existing literature, we think this is likely due to residual unobserved confounding by indication. For this reason, we elected to undertake an analysis to determine which covariates were most predictive of MB receipt. Prior studies have failed to identify a single or combination of factors as robust predictors of post-CPB VS and few cite endocarditis. Few studies have prospectively evaluated MB administration, though retrospective data suggests earlier (in the OR) vs. late administration (in the ICU) is protective for mortality and major adverse events[7]. Only two studies have evaluated prophylactic MB in cardiac surgery. These found benefit to MB but utilized weak predictive factors for VS and included small sample sizes[4,5]. Importantly, not all studies, including our analysis, have found benefit to MB[8]. Given our findings, we believe these data provide compelling preliminary results for a future randomized trial of MB use among endocarditis patients undergoing cardiac surgery. Further, the development of a more robust risk stratification profile may help in patient selection for further prospective studies.

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Table 1. Patient and procedural characteristics for patients receiving methylene blue compared with those not administered methylene blue.

Characteristic (n = 9,616)	No MB Use (n = 9328)	MB Use (n = 288)	P value
Age (years)	62.55 (± 13.65) [95% CI 62.27-62.83]	56.68 (± 16.36) [95% CI 54.79-58.57]	<0.0001†
Sex - Female	3,029 (32.5%)	62 (21.5%)	<0.0001*
Male	6,299 (67.5%)	226 (78.5%)	
ASA Status 1	1 (<1%)	0 (<1%)	<0.0001*
Status 2	122 (1.3%)	0 (<1%)	
Status 3	4,928 (52.8%)	76 (26.4%)	
Status 4	4,153 (44.5%)	209 (72.6%)	
Status 5	124 (1.3%)	3 (1.0%)	
Hospital - University hospital	6,549 (70.2%)	224 (77.8%)	0.0056*
Satellite hospital	2,779 (29.8%)	64 (22.2%)	
Preoperative hemoglobin (g/dL)	13.12 (± 1.98) [95% CI 13.08-13.16]	11.63 (± 2.44) [95% CI 11.35-11.91]	<0.0001†
Endocarditis	395 (4.2%)	76 (26.4%)	<0.0001*
Preoperative ACE inhibitor	2,317 (24.8%)	66 (22.9%)	0.4567*
Preoperative ARB	1,634 (17.5%)	54 (18.8%)	0.5881*
Reoperation	1,310 (14.0%)	90 (31.2%)	<0.0001*
Emergency	774 (8.3%)	45 (15.6%)	<0.0001*
Case duration (minutes)	411.65 (± 123.53) [95% CI 409.14-414.16]	533.49 (± 178.63) [95% CI 512.86-554.12]	<0.0001†
Bypass duration (minutes)	131.18 (± 68.28) [95% CI 129.79-132.56]	189.59 (± 103.99) [95% CI 177.58-201.60]	<0.0001†
Circulatory arrest	1,377 (14.7%)	51 (17.7%)	0.7318*
Mean NE equivalents (mcg/min)	7.32 (± 5.89) [95% CI 7.20-7.44]	16.74 (± 14.17) [95% CI 15.11-18.38]	<0.0001†
Mechanical circulatory support	636 (6.8%)	68 (23.6%)	<0.0001*

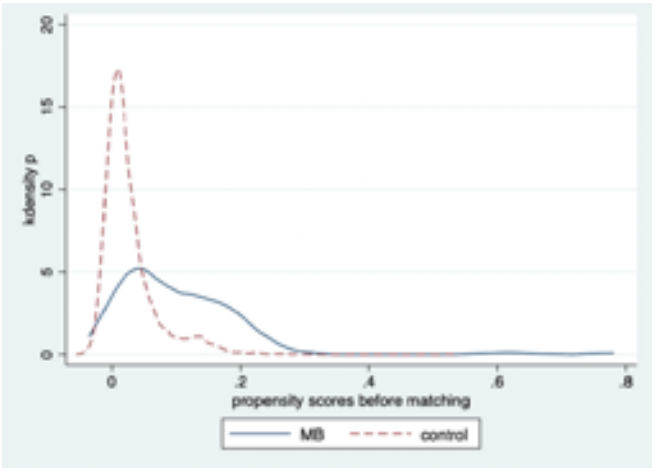
† Indicates Student's t test analysis
* Indicates chi squared analysis

Table 2. Prediction model for methylene blue use.

Variable	Odd Ratio	95% Confidence Interval	P value
Age	0.98	0.97-0.99	0.002
Male	1.61	1.20-2.17	0.001
*ASA Status 3	1.72	0.47-6.32	0.411
Status 4	3.34	0.94-11.91	0.062
ACE inhibitor	0.89	0.66-1.19	0.445
Endocarditis	4.93	3.58-6.80	<0.001
Reoperation	1.40	1.05-1.88	0.022
Emergency	1.09	0.75-1.60	0.636
Mechanical circulatory support	3.07	2.24-4.20	<0.001
Bypass duration	1.006	1.005-1.007	<0.001

* ASA status 1,2 omitted – no patients in these categories received MB
* ASA status 5 omitted due to collinearity

A.



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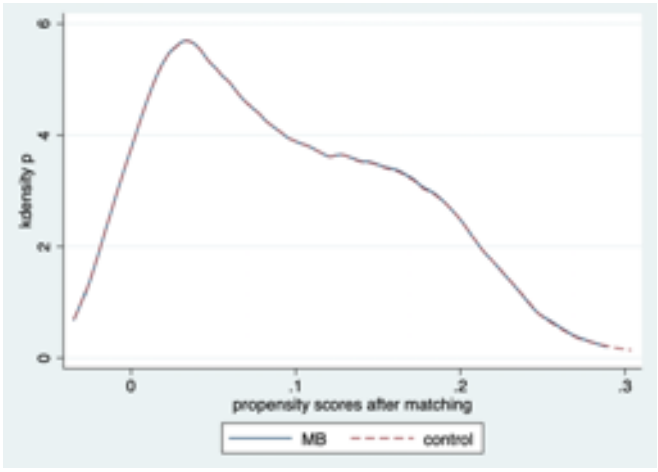


Figure 1. Kernel density plots demonstrating propensity scores of both cohorts before and after matching. A) Propensity scores before matching show a large difference in scores between MB and control cohorts. B) Matching resulted in similar scores between MB and control cohorts.

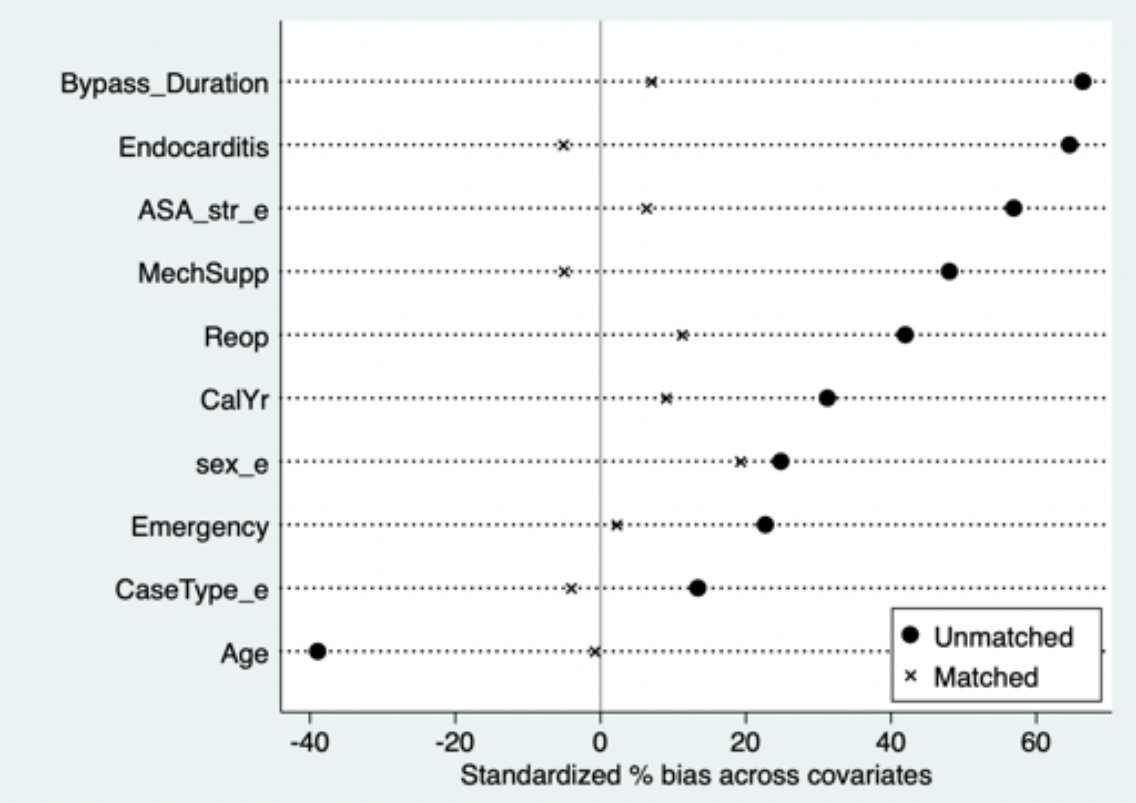


Figure 2. Standardized differences before and after propensity score matching comparing covariate values for patients receiving MB and controls. Balance can be judged as acceptable as imbalance for all variables was less than 20%. (ASA_str_e, ASA physical status; MechSupp, mechanical circulatory support; Reop, reoperation; CalYr, calendar year).

CARDIOVASCULAR ANESTHESIOLOGY 19

4D flow MRI analysis improved perioperative management in a patient with severe pulmonary regurgitation and pulmonary artery aneurysm

Koichi Akiyama[1], Yurie Obata[2], Yu Hirase[2], Teiji Sawa[3]

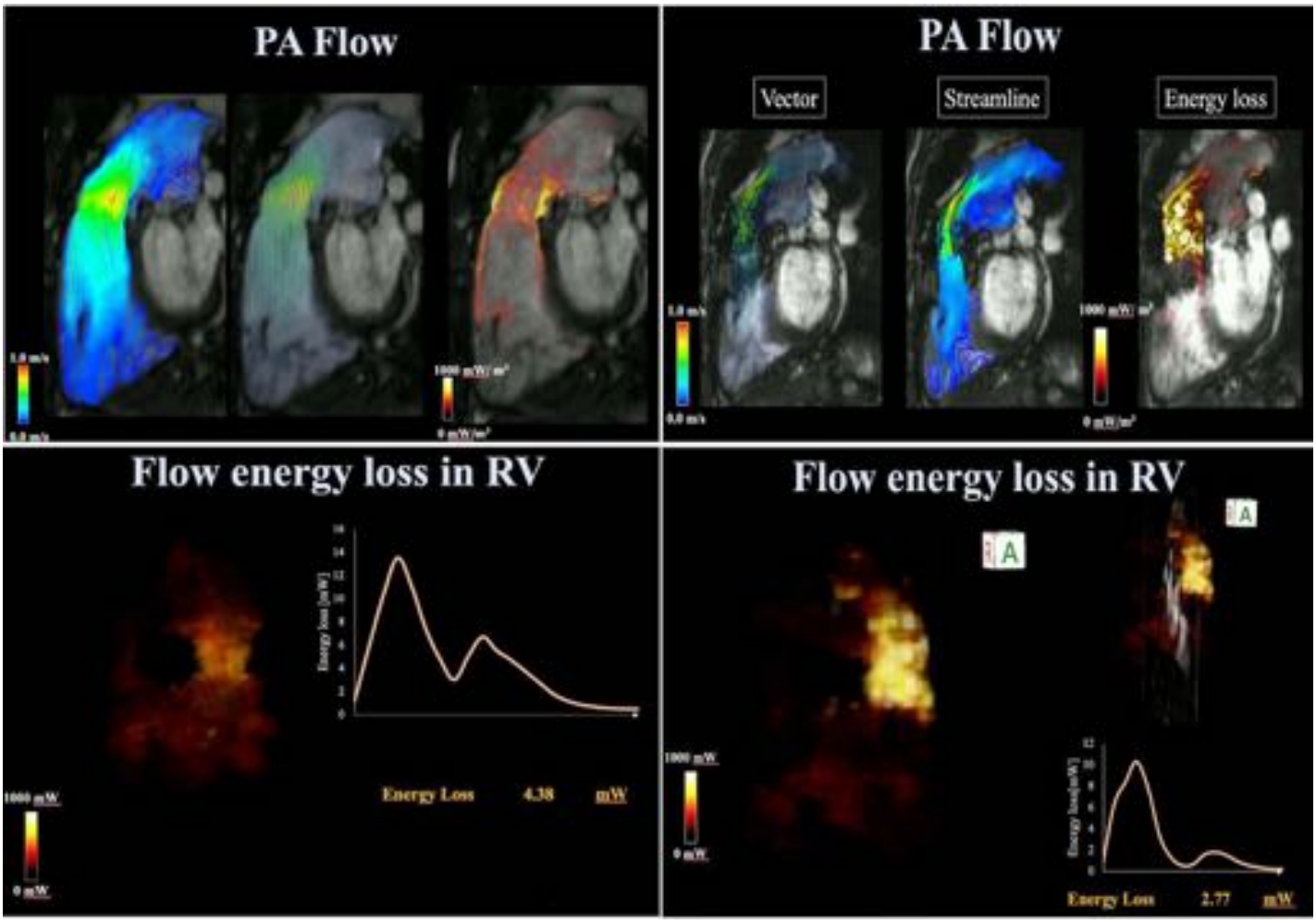
[1]Yodogawa Christian Hospital, Osaka, Osaka, [2]Yodogawa Christian Hospital, Osaka city, Japan, [3]Kyoto Prefectural University of medicine, Kyoto city, Kyoto prefecture

INTRODUCTION: A patient who had undergone pulmonic valvotomy 5 years after birth was scheduled to undergo pulmonic valve replacement and pulmonary artery plasty at the age of 40. We treated this patient successfully by both preoperative and postoperative evaluation of 4D flow MRI.

METHODS: Time-resolved three-dimensional phase contrast magnetic resonance has emerged tool to provide valuable hemodynamics with 3D visualization of blood flow. We applied the tool to the patient to evaluate hemodynamics and novel energy parameters both before and after the surgery.

RESULTS: Severe pulmonary regurgitation flow and dilated pulmonary artery were confirmed before the procedure. After the procedure, those flows were improved. Hemodynamics parameters and energy loss were also improved (RV EDV; 180.26 to 88.61 ml, RV ESV 77.28 to 38.41 ml, cardiac output; 3.14 to 3.43 L/min, energy loss 4.38 to 2.77 mW). There was no event in clinical course of anesthesia, and the patient was extubated in the ICU 5 hours after the surgery.

CONCLUSION: 4D flow MRI is extremely helpful tool for the whole perioperative term. Especially, for adult congenital patients, the complex anatomy and blood flow are difficult to understand. However, the emerging blood flow visualization tools enable us to comprehend. For anesthesiologists, the precise hemodynamic information is useful for both induction and maintenance of anesthesia.



CARDIOVASCULAR ANESTHESIOLOGY 20

Life impact of extracorporeal life support due to primary graft dysfunction in patients after orthotopic heart transplantation

Rene M'Pembele[1], Sebastian Roth[1], Giovanna Lurati Buse[1], Udo Boeken[1], Ragnar Huhn[1]

[1]University Hospital Duesseldorf, Duesseldorf, Germany

INTRODUCTION: Primary graft dysfunction (PGD) is a feared complication after orthotopic heart transplantation (HTX). These patients frequently receive veno-arterial extracorporeal membrane oxygenation devices (VA-ECMO) to overcome cardiac failure until graft recovery. Long-term survival of VA-ECMO survivors after HTX is comparable to non-ECMO patients. However, impact on life quality and hospitalization of these patients is unknown. This study investigates days alive and out of hospital (DAOH) as patient-centered outcome in these patients at 1 year after HTX.

METHODS: This retrospective single-center cohort study enrolled 144 HTX patients from 2010-2020 from the University hospital Duesseldorf HTX database. Study groups were divided in 98 patients without mechanical support and 46 patients with VA-ECMO due to PGD after HTX. A subgroup of 37 patients survived VA-ECMO. As primary outcomes mortality and DAOH were assessed in all patients at 1 year after HTX.

RESULTS: Mortality was significantly lower in non-ECMO patients [Non-ECMO 14,3% (14/98) vs. VA-ECMO 34,8% (16/46), HR: 0.32, 95% CI: 0.15-0.74; p=0.002]. However, mortality did not differ between VA-ECMO survivors and non-ECMO patients at 1-year after HTX [Non-ECMO 14,3% (14/98) vs. VA-ECMO survivors 18,9% (7/37), HR: 0.72, 95% CI: 0.27-1.90; p=0.48). DAOH were significantly higher in non-ECMO patients compared to VA-ECMO patients and VA-ECMO survivors (non-ECMO vs. VA-ECMO: 266.5 ± 102.9 days vs. 177.1 ± 132.4 days; p=<0.0001; non-ECMO vs. VA-ECMO survivors: 266.5 ± 102.9 days vs. 220.2 ± 110.3 days; p=<0.0001).

CONCLUSION: VA-ECMO after HTX showed no difference in mortality between VA-ECMO survivors and non-ECMO patients. However, Impact on life quality and hospitalization was higher.

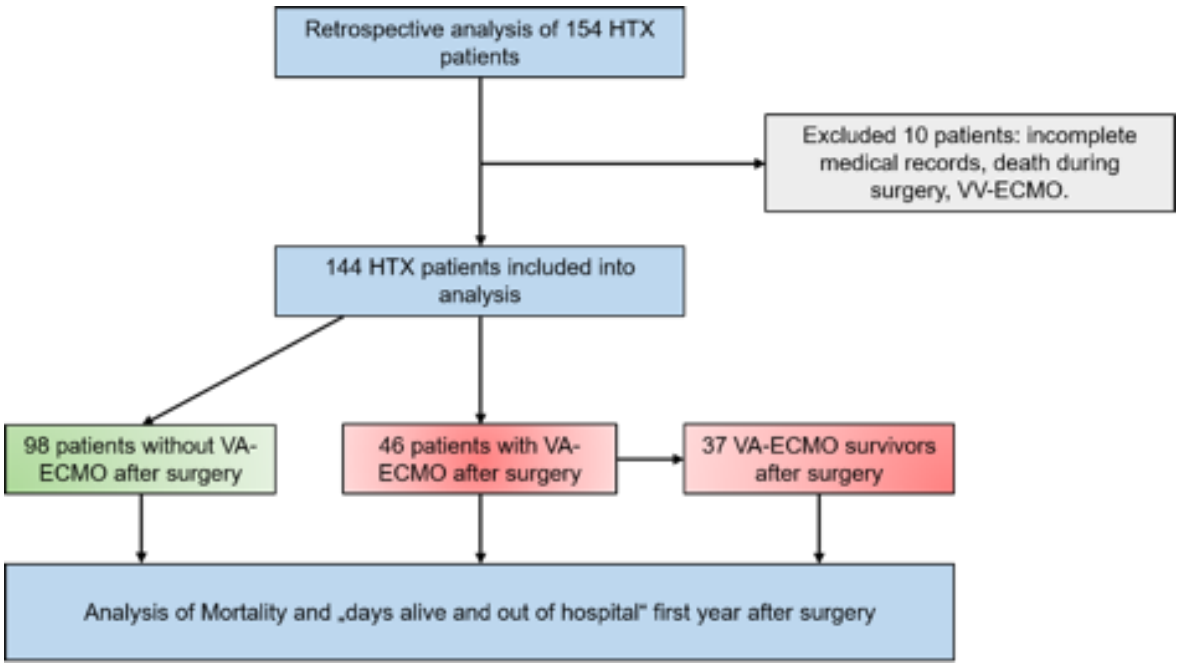


Fig. 1

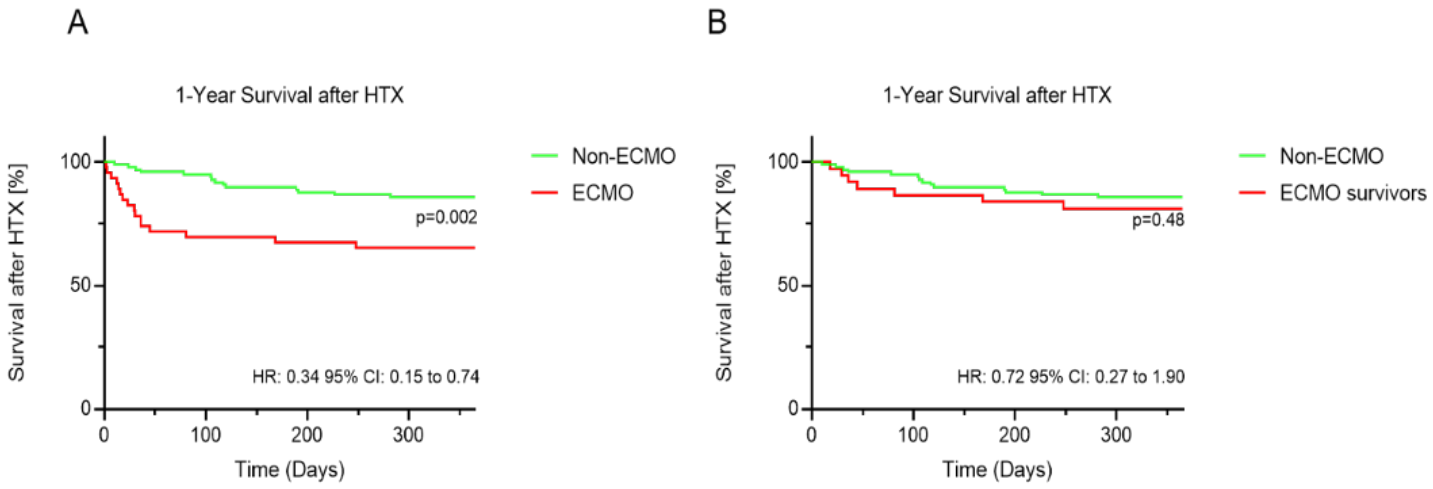


Fig. 2

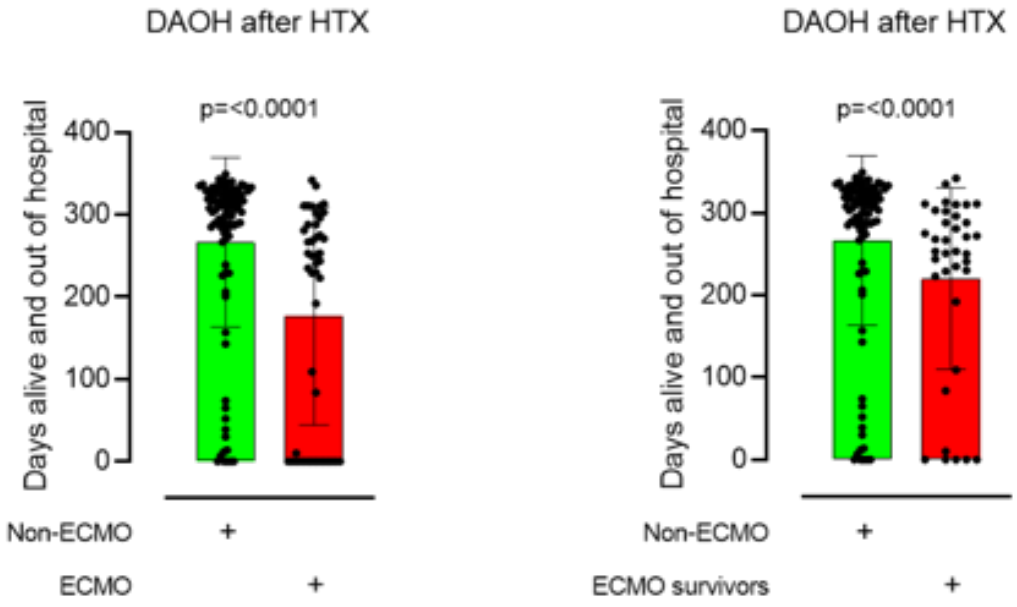


Fig. 3

CARDIOVASCULAR ANESTHESIOLOGY 21

Nasal intubation is not associated with "smoother" emergence from general anesthesia for carotid endarterectomy

Christopher R Parrino[1], Ashanpreet Grewal[2], Miranda Gibbons[2], Shahab A Toursavadkohi[3], Peter Rock[2], Megan Anders[2]

[1]University of Maryland School of Medicine, Baltimore, MD, [2]Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, MD, [3]Department of Surgery, University of Maryland School of Medicine, Baltimore, MD

INTRODUCTION: Hemodynamic swings, particularly hypertension, are undesirable after carotid artery surgery due to risk of bleeding from the incision site. Perioperative cardiovascular instability and hypertension occur in up to 20% of patients undergoing carotid endarterectomy (CEA)[1]. Coughing occurs in between 70 and 96%[2-4] of patients emerging from general anesthesia, and associated hemodynamic changes can promote the oozing of blood from surgical sites[5]. We sought to determine if nasotracheal intubation for CEA would be associated with smoother emergence from general anesthesia as defined by elevation of systolic blood pressure (SBP) and need for antihypertensive medications during emergence.

METHODS: Data for this retrospective study were obtained from an institutional review board-approved perioperative data warehouse. Patients who underwent CEA at our tertiary academic medical center between 12/2015 and 10/2020 were included. Patients were excluded if they were intubated prior to arrival in the operating room (OR), did not have endotracheal tube (ETT) type documented, or if no intubation or extubation event was documented in the electronic anesthesia record. The primary outcome measure was the highest SBP in the 10 minutes prior to extubation. Secondary outcomes included the median SBP in the 10 minutes prior to extubation, 'stormy' qualitative assessment of extubation, use of antihypertensive medications, and need for takeback to the OR. Parametrically distributed data were described using means and standard deviations, and nonparametric data with medians and interquartile ranges. Qualitative data were described using frequencies and percentages. Quantitative variables were analyzed using the Welch's t-test or Mann-Whitney U test, and qualitative variables with the chi-square test or Fisher's exact test, as appropriate.

RESULTS: Three hundred and three (303) patients met inclusion criteria. Three patients were excluded for presence of in-situ airway. Nineteen patients were excluded for absent documentation of an intubation or extubation event. Analysis was performed on the 281 remaining patients. Two patients were excluded from primary outcome analysis due to artifact blood pressure values. An additional 8 patients had artifact blood pressure values manually removed but were included in primary outcome analysis. Average age was 66 years (SD, 11), and 59 percent were male (Table 1). ASA physical status classifications were as follows: 1 (0%), 2 (4%), 3 (69%), 4 (27%), and 5 (0%). Oral ETTs were used in 258 (92%) of patients, with 23 (8%) receiving a nasal ETT. Demographic and medical characteristics were similar between our cohorts except for length of surgery, which was significantly decreased for the patients who received nasal ETTs. Median time from surgery end to extubation was 8.5 minutes and was similar between the groups (9 min for oral ETT vs. 8 min for nasal ETT, P = 0.999; Figure 1). Our analysis revealed no significant differences in maximum, minimum, average, median, or standard deviation of SBPs in the 10 minutes prior to extubation (Figure 2; Table 2). A larger proportion of patients with a nasal ETT received antihypertensive medications in the 10 minutes before extubation compared to the patients with an oral ETT (65.2% vs. 36.0%, P = 0.006). No patients required takeback to the operating room due to a postoperative complication.

CONCLUSION: In our cohort of patients undergoing CEA with either an oral or nasal ETT, we observed no difference in the primary outcome of maximum SBP in the 10 minutes prior to extubation. Secondary analyses also revealed no advantage to nasal intubation. Our data suggest that when a hemodynamic parameter such as SBP is used as a surrogate for the smoothness of extubation, use of a nasal ETT is not associated with smoother emergence. Interestingly, a higher proportion of patients with a nasal ETT received antihypertensive medications than did patients with an oral ETT from 10 minutes before extubation until 5 minutes after extubation. Limitations of this study include a relatively small cohort of patients receiving a nasal tube and possible confounding by surgeon preference regarding ETT type and emergence SBP goals. Our results do not support recommending routine insertion of a nasal ETT for the provision of general anesthesia for patients undergoing CEA. Future studies may examine other methods of quantifying and achieving a 'smooth' extubation for this patient population.

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Table 1 – Patient characteristics

	Oral ETT (n = 258)	Nasal ETT (n = 23)	*P* value
Age in years, mean (SD)	66 (10.7)	64 (10.5)	0.290
Male sex (%)	155 (60.1)	10 (43.5)	0.121
ASA physical status, mean (SD)	3.2 (0.5)	3.3 (0.6)	0.766
HTN history (%)	195 (75.6)	16 (69.6)	0.523
Left-sided procedure (%)	121 (46.9)	11 (47.8)	0.932
Propofol infusion (% receiving)	109 (42.2)	13 (56.5)	0.186
Length of surgery in minutes, mean (SD)	170 (48.6)	142 (46.2)	**0.018**
Estimated blood loss in mL, median (IQR)	100 (50-200)	100 (80-200)	0.448

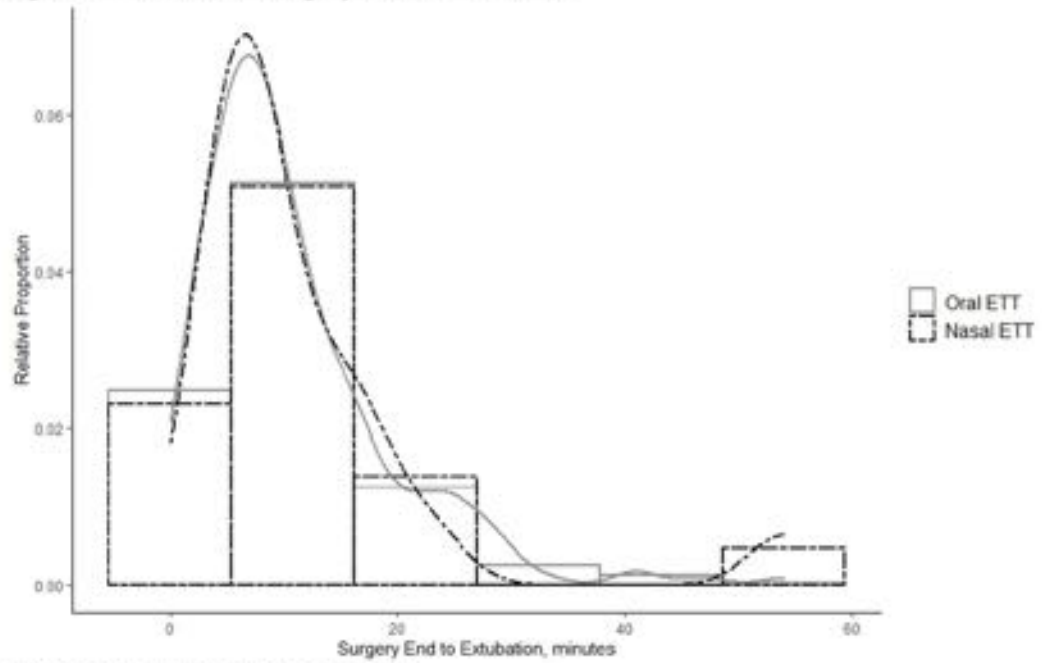
Abbreviations: ETT, endotracheal tube; ASA, American Society of Anesthesiologists; HTN, hypertension.

Table 2 – Outcomes

	Oral ETT (n = 258)	Nasal ETT (n = 23)	*P* value
Time to extubation after surgery in minutes, median (IQR)	9 (5-14)	8 (6-14)	0.999
"Stormy" extubation (%)	9 (3.5)	0 (0.0)	1.000
Any antihypertensive given 10 minutes before extubation to 5 minutes after extubation (%)	93 (36.0)	15 (65.2)	**0.006**
In the 10 minutes before extubation:			
Maximum SBP in mmHg, mean (SD)	169 (30.8)	176 (39.3)	0.410
Minimum SBP in mmHg, mean (SD)	118 (23.1)	123 (26.0)	0.239
Average SBP in mmHg, mean (SD)	140 (23.3)	145 (28.4)	0.498
Standard deviation SBP in mmHg, mean (SD)	16.8 (9.0)	17.5 (10.4)	0.764
Median SBP in mmHg, mean (SD)	139 (24.3)	140 (28.2)	0.871

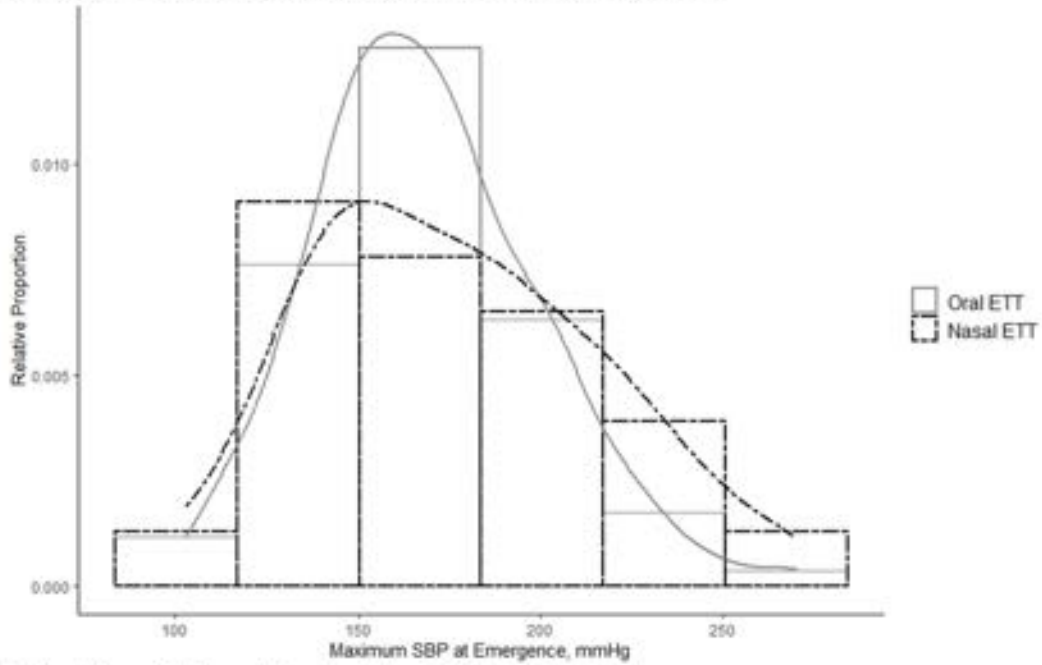
Abbreviations: ETT, endotracheal tube; SBP, systolic blood pressure.

Figure 1 – Time from Surgery End to Extubation



Abbreviations: ETT, endotracheal tube.

Figure 2 – Maximum Systolic Blood Pressure at Emergence



Abbreviations: ETT, endotracheal tube; SBP, systolic blood pressure.

CARDIOVASCULAR ANESTHESIOLOGY 22

Use of Factor and fibrinogen concentrate in Adult cardiac surgery- A Single center retrospective cohort study

Sathappan Karuppiah[1], Kyleen Grissom[1], Andrew W Shaffer[2], Ranjith John[1], Ryan Knoper[3], Stephen Huddleston[2], Andrew Wilkey[2], Megan Lanigan[1], Tjorvi Perry[1]

[1]University of Minnesota, Minneapolis, MN, [2]University Of Minnesota, Minneapolis, MN, [3]University 0f Minnesota, Minneapolis, MN

INTRODUCTION: The acquired coagulopathy associated with cardiac surgery and cardiopulmonary bypass (CPB) has been associated with increased perioperative transfusion requirements, morbidity, and mortality.[1] As the COVID-19 pandemic put significant strain on blood bank resources,[3] our institution implemented recommendations to utilize prothrombin complex concentrate (PCC) and fibrinogen concentrate[4,5] to either replace or supplement intraoperative FFP and cryoprecipitate administration, respectively during cardiac surgery. Herein, we describe the transfusion patterns when FFP, cryoprecipitate, PCC and fibrinogen concentrate are available to the intraoperative care team.

METHODS: On March 4, 2020, the Division of Cardiothoracic Anesthesia in collaboration with the Department of Cardiac Surgery recommended the use of PCC and Fibrinogen concentrate 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 Fibrinogen concentrate 1 gram up to 4 grams in divided doses until the TEG R value and alpha angle, respectively returned to normal or bleeding in the surgical field stopped. We collected patient demographic information, clinical variables and outcomes retrospectively from the electronic medical record. Data are described as a means (± SD) and percentages.

RESULTS: From March 4, 2020 to October 30, 2020, we analyzed 224 patients. The mean age was 58 years ±14.4 and 79 (35.7%) were women. Three patients were excluded, as they had cardiac surgeries without CPB. The majority of patients had the CABG and/or valve surgery; 29 (13.1%) patients had complex surgery, 37 (16.7 %) had heart or lung transplantation surgery, and 26 (11.7%) an LVAD placed. One hundred and eighteen (53.3%) patients received no blood product or concentrates (NP Group), 40 (18%) patients received factor concentrates with or without platelets (FC Group), 33 (14.9%) patients received FC and allogeneic blood product (FC+ABP Group), and 30 (13.3%) patients received only APB (ABP Group). There was no meaningful difference in platelet administration or chest tube output between groups. Group 2 patients who received both FC and ABP received more RBCs (Table 1). There was no clinically meaningful difference between the baseline static and viscoelastic test results (Table2).

CONCLUSION: In this single-academic center experience, we demonstrate that non-surgical coagulopathy can be managed safely and effectively with factor and fibrinogen concentrates, allogeneic blood products and combinations thereof in consecutive patients undergoing varying complexities of cardiac surgery. Future analysis will focus on stratifying surgical procedures to identify patterns of administration as they relate to operational and clinical outcomes.

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Table 1. Factor, Fibrinogen and Allogeneic Blood Product Dosing Between Groups

	Overall Median (IQR) N=221	Group 1(FC) Median (IQR) N=40	Group 2 (FC+ABP) Median (IQR) N=33	Group 3 (ABP) Median (IQR) N=30	Group 4 (NP) Median (IQR) N=118
PCC (Units)	1103 (1076)	776.5(1104.5)	1103 (597)	-	-
Fibryga (mgs)	1050 (55)	1000 (60)	1050 (50)	-	-
Factor VII (Units) (n=8)	3000 (2750)	4000 N=2	3000(2500) N=6	-	
FFP (Units)	2(2)	-	2(1.25)	1(1)	-
Cryoprecipitate (Units)	1(1)	-	1(1)	1(1)	
RBCs (Units)	2 (3)	2(1)	4(4)	1(1)	1 (1.25)
Platelets (Units)	2 (1)	2(1)	2(1.25)	2(1)	-
Chest Output-24 hours	410 (410)	540 (573.25)	550 (890)	455 (490)	350 (341.25)

Table 2. Perioperative Static and Viscoelastic Test Results Between Groups

	Overall Mean (SD) N=221	Group 1 (FC) Mean (SD) N=40	Group 2 (FC+ABP) Mean (SD) N=33	Group 3 (ABP) Mean (SD) N=30	Group 4 (NP) Mean (SD) N=118
Static Tests					
Pre-Op INR	1.22(0.3)	1.33(0.32)	1.35(0.5)	1.22(0.3)	1.12(0.15)
Post Protamine INR	1.8(0.5)	1.8(0.35)	2.2(0.8)	1.8(0.5)	1.68(0.49)
ICU INR	1.54(0.49)	1.49(0.22)	1.68(0.55)	1.52(0.20)	1.53(0.58)
ICU fibrinogen	234.7(95)	221.2(77.8)	200.3(109)	266.1(89.6)	248.1(92.3)
Viscoelastic Tests					
Baseline R	6 (2.3)	6.1(2.41)	5.9(6.1)	6.7(3.9)	5.7(1.7)
Baseline K	1.6 (1.1)	1.55(0.5)	2.02(1.8)	1.88(1.2)	1.5(0.8)
Baseline Alpha angle	68.7(8.4)	68.65(7)	66.58(11.4)	65.9(11.5)	70.1(6.3)
Baseline MA	70(8.8)	69.6(8.7)	67.5(11.5)	68.3(6.7)	71.4(8.5)
Post Protamine R	5.6 (2.5)	5.9 (2.9)	6.4 (2.7)	5.5 (2.7)	5.3 (2.1)
Post Protamine K	1.8(1.5)	2(1.5)	2.9(2.6)	1.7(0.8)	1.5(0.7)
Post Protamine Alpha angle	66.1(9.7)	65.16(10.1)	58.3(10.8)	66.2(9.3)	69.15(7.7)
Post Protamine MA	64.2(10)	63.34(9.09)	54.3(11.6)	64.3(6.7)	67.75(8.28)

CARDIOVASCULAR ANESTHESIOLOGY 23

Detection of blood volume changes utilizing Peripheral Venous Pressure (PVP) waveform analysis

Abubakr El Sobky[1], Mohamed Y Elgamal[2], Ahmad Ibrahim[3], Kirk Shelley[4], Aymen Alian[4]

[1]Student Organization, New London, CT, [2]Yale University, NEWHAVEN, CT, [3]Yale University, New Haven, CT, [4]Yale University School of Medicine, New Haven, CT

INTRODUCTION: Passive leg raise (PLR) is commonly used to evaluate preload fluid responsiveness and may be considered more reproducible than the fluid bolus technique[1]. The PLR test has the same effect as mobilization of 300 cc of blood from the lower body into the cardiac chambers. The peripheral venous catheter is the most commonly used method of vascular access, and the peripheral venous pressure (PVP) reflects 'downstream' pressure to the right atrium. In this experiment, we utilized PVP waveform analysis to assess blood volume status and fluid responsiveness during mild blood volume changes, autotransfusion of 300 cc of blood (PLR test), and the loss of 600 cc of blood at -30 mmHg of Lower Body Negative Pressure (LBNP), mild hypovolemia.

METHODS: With IRB approval, 38 healthy subjects underwent a PLR test for 2 minutes followed by LBNP induced mild hypovolemia of -30 mmHg. Each subject was connected to EKG, BP monitor, and NICOM (Cheetah Medical, MA, USA) to measure Thoracic Fluid Content (TFC). The Intravenous catheter was transduced and PVP waveforms were recorded at 100 Hz with a data acquisition system (Collect 5/S, GE). PVP waveform was analyzed using time domain analysis (mean PVP value) and frequency analysis (spectrum,2K, Hamming, Amplitude Density (AD), 93.75% overlap) with LabChart 7.3.7 (ADInstruments). The frequency domain analysis of the PVP waveform included measuring the amplitude density of PVP DC (at the respiratory frequency) and cardiac frequency (PVP cardiac) and calculating the PVP DC% (the ratio of AD at respiratory to cardiac frequencies) at baseline, PLR, and -30 mmHg.

RESULTS: According to the PVP waveforms analysis, from the baseline to the PLR test, the mean PVP and TFC significantly increased by 48% and 1% respectively, while the DC% PVP decreased significantly by 2%. However, from the PLR test to -30 mmHg, the mean PVP and TFC significantly decreased by 50% and 6% respectively, while the DC% PVP significantly increased by 109%, as shown in figure 1 and 2.

CONCLUSION: Transient PLR testing resulted in increased preload, which led to an increase in total fluid content and was reflected as an increase in Mean PVP at the peripheral and a reduction in the PVP DC%. During mild hypovolemia, then PVP DC% increased, while mean PVP and TFC decreased. These results have demonstrated the potential of using the PVP waveform as a clinical tool for monitoring changes in blood volume.

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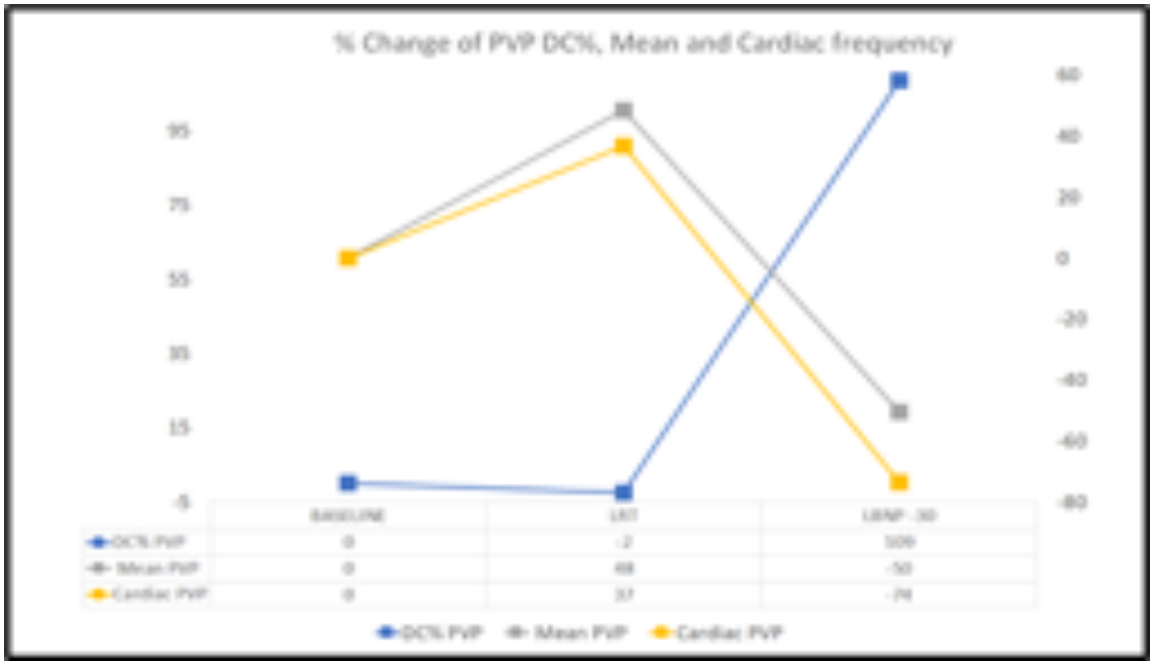

Fig. 1

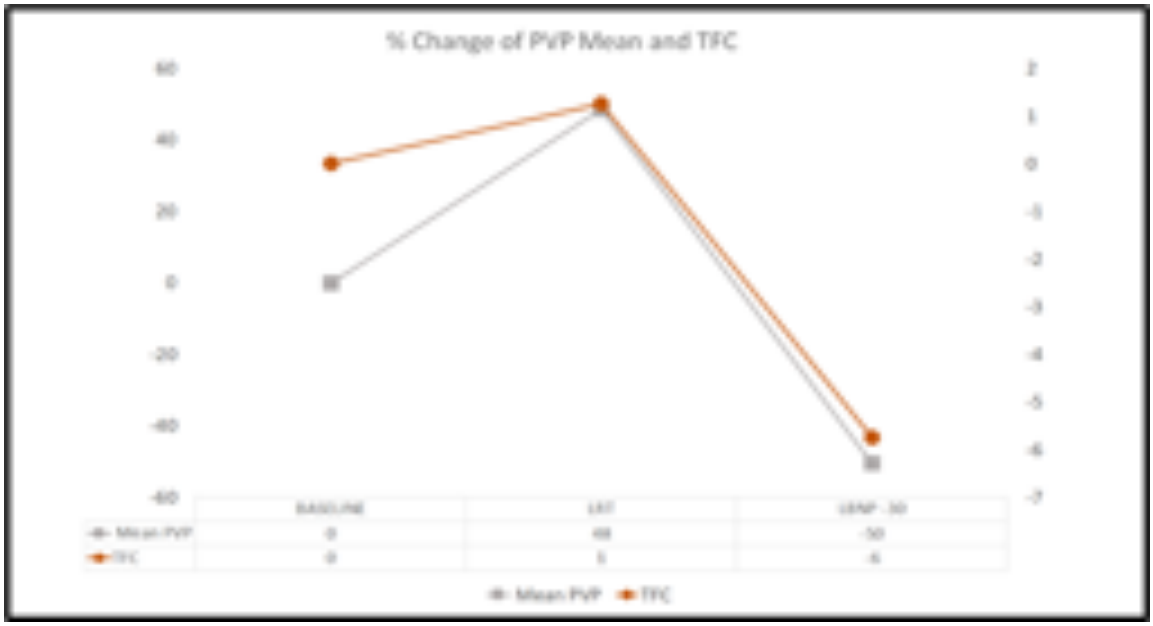

Fig. 2

CARDIOVASCULAR ANESTHESIOLOGY 24

Trained Immunity with Synthetic Toll-like Receptor 4 Agonist Protects Against Acute Kidney Injury in a Model of Ischemia-Reperfusion Injury

Antonio Hernandez[1], Lauren Scarfe[1], Rachel Delgado[1], Naeem K Patil[1], Lauren E Himmel[1], Julia K Bohannon[1], Edward Sherwood[1], Mark P de Caestecker[1]

[1]Vanderbilt University Medical Center, Nashville, TN

INTRODUCTION: Monophosphoryl lipid A (MPLA) is an FDA-approved TLR4 vaccine adjuvant with potent immunomodulatory properties that enhance innate immunity and protects against infection-induced kidney dysfunction. However, MPLA is unavailable as a standalone immunotherapeutic drug for patients. Phosphorylated hexaacyl disaccharides (PHADs) are synthetic TLR4 agonists that are structurally similar to MPLA and are available for clinical development. We hypothesized that pretreatment with 3D (6-Acyl) PHAD would reduce acute kidney injury secondary to ischemia-reperfusion. To test our hypothesis, we employed a model of ischemia-reperfusion induced acute kidney injury (IRI-AKI) in mice pretreated with 3D (6-Acyl) PHAD.

METHODS: 10-week old male BALB/c mice received intravenous treatment with vehicle (Lactated Ringers solution) or 2 µg, 20 µg and 200 µg 3D (6-Acyl) PHAD at 48 and 24 hours prior to IRI-AKI. Mice then underwent unilateral renal pedicle clamping for 28 minutes to induce IRI-AKI along with a simultaneous contralateral nephrectomy to allow monitoring of injury and renal function. Blood was drawn for BUN and serum creatinine (measured by mass spectrometry) pre-operatively, 24 and 72 hours after IRI-AKI to assess renal function. Tissue injury was evaluated by a renal pathologist blinded to the treatment groups on Periodic Acid Schiff stained kidney sections (tubular injury scores, TIS: 0-5 arbitrary units, with 5 being assigned to the most injured kidneys).

RESULTS: Treatment with 20 and 200 µg of 3D (6-Acyl) PHAD attenuated renal injury as determined by lower BUN and serum creatinine concentrations at 72 hours after IRI-AKI compared to vehicle-treated controls. Tubular injury scores were reduced in mice treated with 200µg 3D (6-Acyl) PHAD at 72 hours after IRI-AKI. Survival was increased in mice treated with 20 µg 3D (6-Acyl) PHAD 72 hours after IRI-AKI.

CONCLUSION: Pretreatment with 3D (6-Acyl) PHAD significantly preserved renal function and morphology after IRI-AKI in a dose-dependent manner. 3D (6-Acyl) PHAD has been shown to train the innate immune system and enhance leukocyte antimicrobial function, develop endotoxin tolerance, and attenuate the inflammatory response. Further studies are underway to evaluate the role of trained immunity in organ protection from ischemia-reperfusion injury.

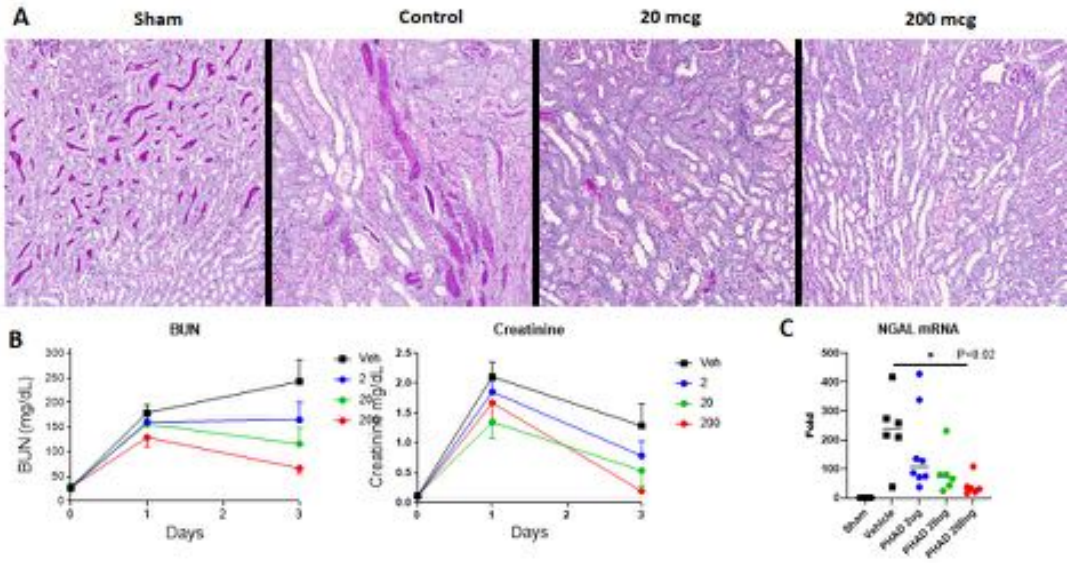

Figure. Kidney sections taken 3 days post 28-minute kidney ischemic insult and pretreated with 3D (6-Acyl) PHAD (**Panel A**). BUN and Creatinine change from baseline to 3 days post ischemic insult (**Panel B**). Day 3 NGAL mRNA post ischemic insult (**Panel C**).

CARDIOVASCULAR ANESTHESIOLOGY 25

Perioperative hyperglycemia is an independent risk factor for surgical mortality in patients undergoing ascending aorta and arch repair

ShaoFeng Zhou[1], Shaodi F Yan[2], Harleen F Sandhu[3], Warren F Choi[2], Medea F Mshvildadze[2]

[1]UT Medical School at Houston, Houston, TX, [2]UT Medical school at Houston, Houston, TX, [3]McGovern Medical School, Houston, TX

INTRODUCTION: As the metabolic consequences of surgical stress and anesthesia, hyperglycemia is reported in up to 60-90% of patients undergoing cardiac surgery[1]. Previous studies have shown that perioperative hyperglycemia is closed related to poor outcomes in cardiac surgical patients . However, all evidence available so far was based on studies involving patients who underwent coronary artery bypass graft (CABG), congenital heart surgery, or a broad spectrum of non-selective cardiac surgery, and few studies have specifically focused on ascending aorta repair (AAR). AAR is one of the most challenging cardiac procedures, and in clinical practice, perioperative hyperglycemia, which always caused by severe symptoms, cardiopulmonary bypass (CPB), hypothermic circulatory arrest (DHCA), et al, is very common in patients undergoing AAR. Therefore, it is highly necessary to investigate the impact of patients' blood glucose on AAR. To further elucidate the relationship between blood glucose and AAR, the objective of this study was to evaluate the prognostic value of perioperative glucose on the in-hospital outcomes of patients who underwent AAR.

METHODS: We retrospectively reviewed 1338 cases of AAR, patients ages 18-80, from 2003 to 2019. Patients were stratified according to the level of preoperative (<110mg/dl, 110-139mg/dl, and ≥140mg/dl) and postoperative (<140mg/dl, 140-200mg/dl, and ≥200mg/dl) blood glucose. Chi-Square test was used to compare categorical variables and t-test was used for the comparison of normally distributed variables between two groups. Multiple groups were compared by using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, as appropriate. Multivariate logistic regression analysis was used for the analysis of the correlation between perioperative glucose and patients' outcomes. A P value <0.05 was considered statistically significant.

RESULTS: Among all patients, 8.3% died in-hospital, 69.1% discharged to home, and the rest 22.6% discharged to long-term care/rehabilitation facility (Table 1). With an increasing level of glucose before and after surgery, in-hospital mortality increases and discharge home rate decreases gradually (Figure 1). Higher preoperative (≧ 140mg/dl) and postoperative (≧ 200mg/dl) glucose are independent predictors for in-hospital mortality (HR = 2.23, 95% CI = 1.30-3.80, p = 0.003 and HR = 2.11, 95% CI 1.10-4.02, p = 0.024, respectively) after adjusting for demographic factors, diabetes mellitus history, creatinine clearance and surgical variables (Figure 2). Additionally higher preoperative glucose levels (110-139 mg/dl and ≧ 140 mg/dl) are also significantly related to lower incidence of discharging home compared to preoperative glucose < 110mg/dl (HR = 0.57, 95% CI = 0.42-0.79, p < 0.001 and HR = 0.50, 95% CI = 0.34-0.72, p < 0.001, respectively) (Figure 2).

CONCLUSION: Higher perioperative glucose is an independent risk factor for poor in-hospital outcomes in patients undergoing ascending aorta repair (AAR). Further well-designed studies are necessary to confirm this finding and determine the causality..

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Table 1. Characteristics of overall patients and patients stratified by preoperative and postoperative glucose respectively.

Characteristics of patients and surgery	All Patients n=1338	Groups based on Preoperative Glucose Level				Groups based on Postoperative Glucose Level			
		<110mg/dl n=803	110-139mg/dl n=317	>=140mg/dl n=218	p-value	<140mg/dl n=409	140-199mg/dl n=899	>=200mg/dl n=210	p-value
Age (years)	57.9±14.8	56.9±15.2	58.9±14.2	60.3±13.8	0.005	53.1±15.9	59.2±14.3	61.7±12.8	<0.001
Gender (Male)	67.0%	66.5%	69.7%	65.1%	0.475	36.8%	31.7%	31.4%	0.214
BMI[a]	28.9±6.5	28.0±6.3	29.7±6.6	30.7±7.0	<0.001	27.6±5.8	29.2±6.8	29.7±6.4	<0.001
Ccr[b] (ml/min)	92.6±40.2	96.8±45.5	90.6±42.4	80.0±44.2	<0.001	95.5±47.4	91.5±43.2	92.4±42.5	0.367
Medical history									
Diabetes mellitus	12.4%	8.1%	11.0%	30.3%	<0.001	6.6%	12.1%	24.3%	<0.001
Hypertension	70.4	71.6%	68.5%	68.8%	0.496	68.1%	71.8%	69.2%	0.417
Coronary heart disease	20.4%	20.0%	19.9%	22.5%	0.707	14.1%	21.5%	28.1%	<0.001
COPD	16.4%	17.1%	18.3%	11.5%	0.084	17.5%	16.6%	14.1%	0.584
End stage renal disease	5.2%	4.0%	6.0%	8.7%	0.016	3.7%	5.5%	7.0%	0.237
Smoke	37.6%	38.1%	39.1%	33.5%	0.373	38.2%	38.0%	35.7%	0.825
Operation details									
Type A dissection	47.1%	35.1%	60.3%	72.0%	<0.001	46.0%	45.3%	56.2%	0.025
Emergency/Urgent	32.5%	18.1%	48.9%	61.9%	<0.001	32.2%	31.5%	36.8%	0.380
DHCA	89.6%	87.7%	93.4%	91.3%	0.013	84.2%	91.5%	93.0%	<0.001
Operation time (hours)	5.0±1.6	4.9±1.4	5.1±2.1	5.2±1.7	0.012	5.1±1.5	4.9±1.4	5.3±2.4	0.001
Pump time (minutes)	156.6±54.6	154.4±55.8	160.0±54.0	160.1±50.4	0.187	162.1±51.4	154.1±55.6	157.4±55.2	0.083
Clamp time (minutes)	96.2±40.6	94.8±41.7	96.7±39.4	100.7±37.4	0.178	100.7±42.3	93.9±39.2	97.4±42.3	0.032
Cooling time (minutes)	18.1±7.7	17.8±7.7	18.1±7.1	19.2±8.6	0.057	17.7±7.9	17.9±7.4	19.3±8.4	0.057
Warming time (minutes)	76.8±23.0	74.6±23.6	79.5±22.2	81.2±21.1	<0.001	76.4±25.2	76.7±22.8	77.7±19.9	0.830
Extubated within 24 hours[c]	64.5%	69.6%	60.1%	45.8%	<0.001	62.5%	67.2%	54.8%	0.020
Length of stay[c]	12.8 (8.6, 19.3)	11.9 (8.3, 17.8)	14.2 (9.3, 20.9)	14.7 (9.4, 22.0)	<0.001	12.3 (8.3, 20.0)	12.8 (8.7, 19.0)	13.9 (9.0, 19.0)	0.803
ICU Length of stay[c]	5.5 (3.1, 10.9)	5.0 (2.7, 9.2)	6.6 (3.4, 13.1)	7.2 (3.9, 14.0)	<0.001	5.4 (2.9, 10.7)	5.4 (3.1, 10.7)	6.2 (3.1, 11.6)	0.366
Discharged Position									
Home	69.1%	76.6%	62.1%	51.8%	<0.001	74.4%	68.7%	62.7%	0.016
Long term care	22.6%	18.2%	28.4%	30.3%	<0.001	19.3%	24.5%	21.1%	0.131
Deceased	8.3%	5.2%	9.5%	17.9%	<0.001	6.3%	6.9%	16.2%	<0.001

Abbreviations: BMI: body mass index; Ccr: creatinine clearance; COPD: chronic obstructive pulmonary disease; DHCA: deep hypothermic circulatory arrest

a. BMI is the weight in kilograms divided by the square of the height in meters.

b. Ccr (Creatinine clearance) was calculated using the Cockcroft-Gault equation: Ccr = ([140-age] × weight in kg × 0.85 if female)/(serum creatinine × 72).

c. Statistical analysis was performed in discharged patients (n=1227).

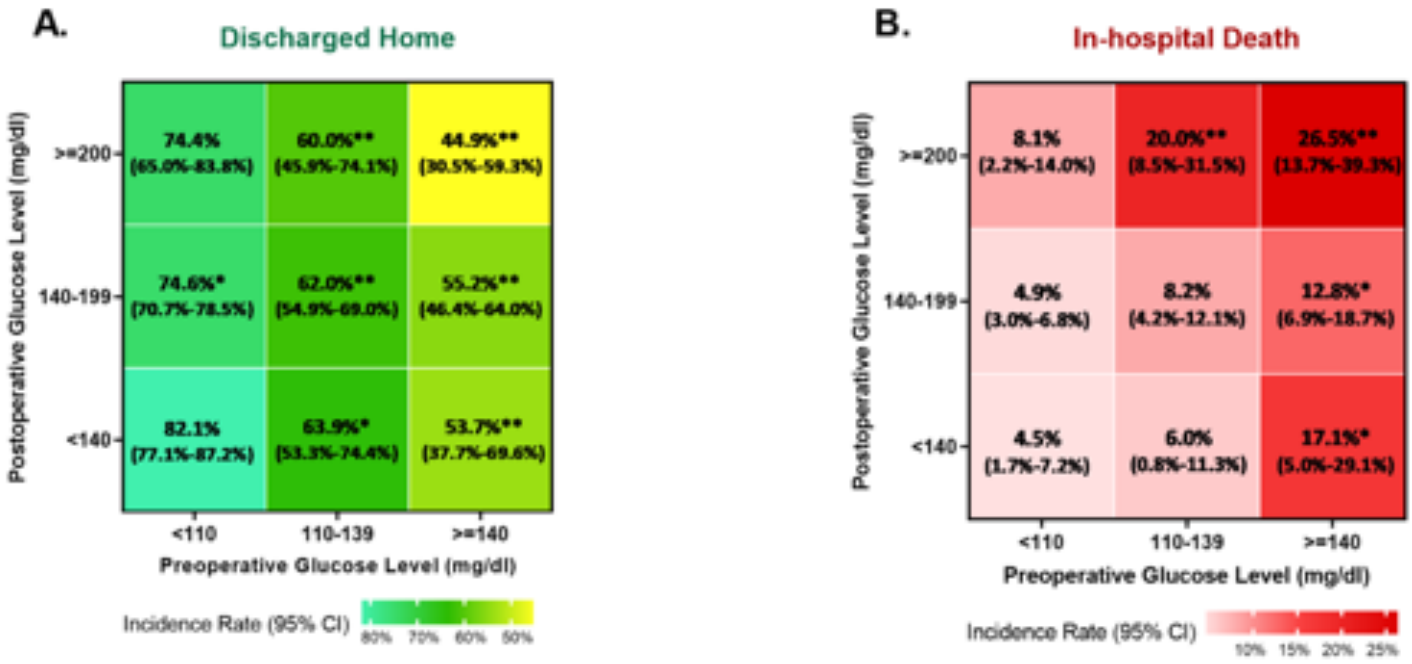

Figure 1: The joint effect of preoperative glucose (X axis) and preoperative glucose (Y axis) on the rates of discharged home (A) and in-hospital death (B). * p-value < 0.05 and ** p-value < 0.001 compared to the group with preoperative glucose < 110 mg/dl and postoperative glucose < 140 mg/dl.

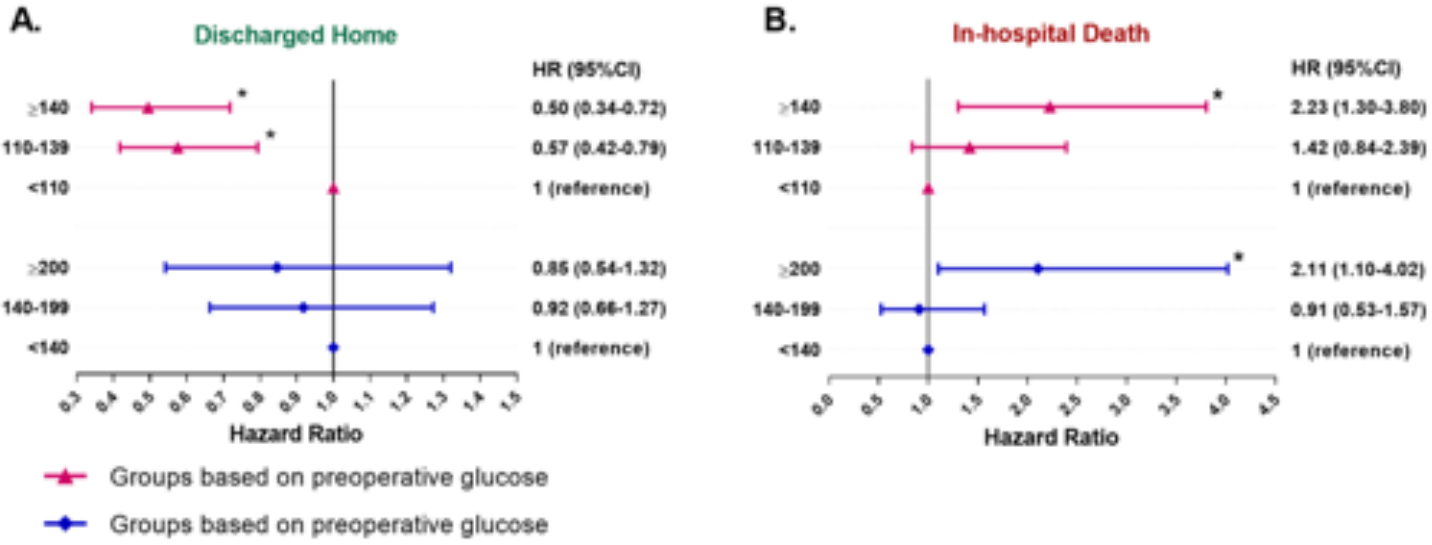

Figure 2 Results of multivariate logistic regression analysis for the in-hospital mortality (A) and discharged home (B) in patients stratified by preoperative and postoperative glucose respectively. Odds ratios (ORs) were adjusted for demographic factors (age, gender, body mass index), diabetes mellitus history, creatinine clearance and surgical variables (emergency/urgent operation, operation time, pump time and clamp time). * p-value < 0.05

CARDIOVASCULAR ANESTHESIOLOGY 26

Lipid Emulsion Improves Left Ventricular Function in Rats with Lipopolysaccharide Endotoxemia-Induced Cardiac Dysfunction through STAT3 Activation

Michael Zargari[1], Hanzi L Russino[2], Somanshu Banerjee[1], Natalie Koons[3], Lejla Medzikovic[1], Matthew Mikhael[4], Siamak Rahman[5], Tristan Grogan[6], Mansoureh Eghbali[7], Soban Umar[1]

[1]University of California Los Angeles, Los Angeles, CA, [2]Kaiser Permanente, Panorama City , CA, [3]University of New England College of Osteopathic Medicine, Biddeford , ME, [4]Vanderbilt University School of Medicine, Nashville , TN, [5]Ronald Regan UCLA Medical Center, Los Angeles , CA, [6]University of California at Los Angeles, Los Angeles, CA, [7]University of California, Los Angeles David Geffen School of Medicine, Los Angeles, CA

INTRODUCTION: Sepsis-induced cardiomyopathy contributes to significant morbidity and mortality. Despite decades of research on myocardial dysfunction in sepsis, a dearth of novel therapeutic targets still remains. Lipid emulsion (LE) has been demonstrated to mitigate the cardio-depressant effects of local anesthetics and ischemia-reperfusion injury, however, its potential role in sepsis-induced cardiac dysfunction has yet to be elucidated. In this study, we tested the hypothesis that LE improves left ventricular dysfunction secondary to lipopolysaccharide (LPS)-endotoxemia in rats, specifically through STAT3 activation.

METHODS: Adult female Sprague-Dawley rats (n=12) received a single intraperitoneal injection of LPS (20 mg/kg). 6h later, rats were randomly divided to receive either intravenous 20% lipid emulsion (LE group; n=6) or PBS (Control; n=6) as a 5 ml/kg bolus followed by a 0.5 ml/kg/min infusion over 10-min. Echocardiography was performed to assess left ventricular ejection fraction (LVEF) at baseline prior to injection of LPS, 6h post-LPS, and 5 and 10 min after LE administration. GSK-3β and STAT3 phosphorylation were assessed in LV using Western blots. In a follow-up experiment, female rats (n=7) were given an intravenous injection of Stattic (10 mg/kg), a STAT3 inhibitor, 4h after LPS. At the 6h time point, Stattic treated rats received LE and echocardiography was performed. STAT3 phosphorylation was assessed by Western blots. Values are expressed as mean±SD followed by p-value. $P<0.05$ is considered statistically significant.

RESULTS: LVEF at the baseline in the control group was 76±1% and 6h after LPS injection, LVEF was significantly decreased to 51±4%, $p<0.0001$. Similarly, baseline LVEF in the LE group was 74±1% and 6h after LPS, LVEF was significantly decreased to 50±3%, $p<0.0001$. In the LE group at 10-min after LE, LVEF increased to 76±4%, $p=1.0$ compared to baseline. Conversely, in the control group at 10-min after PBS, LVEF was 51±5%, $p=0.0008$ compared to baseline. Western blot analysis demonstrated increased phosphorylation of STAT3 (~2-fold) in LE treated rats compared to control rats, $p=0.042$, whereas GSK-3 phosphorylation was unchanged. Baseline LVEF in the LE+Stattic group was 74±2% and 6h after LPS, LVEF was significantly decreased to 50±3%, $p<0.0001$. At 10-min, LVEF was only 57±2%, $p<0.0001$ compared to baseline, similar to the change in control rats. Western blot analysis confirmed significantly decreased phosphorylation of STAT3 in the LV of LE+Stattic rats compared to the LE alone group, $p=0.001$.

CONCLUSION: Acute administration of LE significantly improves LV function in rats with LPS-induced cardiac dysfunction, mediated via STAT3 phosphorylation. Our data highlights the possible translation of LE as a novel treatment modality in the setting of sepsis-induced cardiac dysfunction.

CARDIOVASCULAR ANESTHESIOLOGY 27

Autonomic Control of Cardiovascular Function: Group III/IV Muscle Afferents Regulate the Hemodynamic Response to Locomotor Exercise

Taylor S Thurston[1], Joshua C Weavil[1], Hsuan-Yu Wan[1], Nate Birgenheier[1], Jacob E Jessop[1], Candice Morrissey[1], Markus Amann[1]

[1]University of Utah Health Care, Salt Lake City, United States of America

INTRODUCTION: Group III/IV muscle afferents respond to mechanical and chemical stimuli occurring in skeletal muscle during exercise and contribute, via their feedback to cardiovascular control centers in the brainstem, to the circulatory response to physical activity. In healthy young individuals, feedback from these afferents facilitate leg blood flow during single-joint exercise. However, their exact role in determining peripheral hemodynamics during locomotor exercise (large active muscle mass), which is characterized by larger sympathetically-mediated vasoconstriction compared to single-joint exercise (small active muscle mass), has yet to be investigated.

METHODS: Separated by 2 h of rest, 6 healthy males (Age 23 ± 3 yrs) completed three 4-min bouts of cycling exercise [75 W: ~45% of VO2max, 100 W: ~55% VO2max, and 80% of peak power output (246 ± 37.4 W): ~98% VO2max] under both control conditions (CTRL) and with lumbar intrathecal fentanyl (FENT) blocking -opioid receptor-sensitive group III/IV muscle afferents. To avoid different respiratory muscle metaboreflex and/or chemoreflex effects on leg vascular resistance (LVR) and blood flow, subjects' breathing (VE) during FENT (usually characterized by hypoventilation and asphyxia) was guided to be similar to that in CTRL. Femoral arterial blood flow (QL; Doppler Ultrasound), LVR, and leg perfusion pressure (PP; intravascular catheter, arterial – venous blood pressure) were continuously determined; cardiac output (CO), stroke volume (SV), heart rate (HR), femoral arterial and venous blood samples were collected during the final minute of each workload.

RESULTS: There were no hemodynamic differences between conditions at rest. Arterial blood gases and VE were, per design, not different between conditions. During FENT exercise, PP was, compared to CTRL, significantly lower at all intensities (up to 26%). Without affecting HR ($P = 0.41$), CO and SV were significantly lower during FENT compared to CTRL at 75 and 100 W (~10%), but not at 80% Wpeak. QL was, however, not different between conditions ($P = 0.43$) as LVR was up to 25% lower during FENT compared to CTRL ($P < 0.05$). Additionally, arterial oxygen content, leg oxygen uptake and leg oxygen delivery were similar in both conditions ($P > 0.15$).

CONCLUSION: The current findings obtained from humans during leg cycling suggest that group III/IV-mediated afferent feedback from locomotor muscle facilitates blood pressure, LVR and CO during whole body exercise. These effects of group III/IV muscle afferents are likely secondary to their role in regulating autonomic control of the heart and vasculature. Interestingly, the effect of these sensory neurons on leg vascular resistance differs between exercise characterized by large vs small active muscle mass. While afferent blockade decreases leg vascular resistance and MAP (with no changes in QL) during locomotor exercise, it increases leg vascular resistance (relatively larger fall in QL compared to fall in MAP) during single-joint exercise.

CARDIOVASCULAR ANESTHESIOLOGY 28

On the circulatory interaction of the chemoreflex and the muscle mechanoreflex

Hsuan-Yu Wan[1], Joshua C Weavil[1], Taylor S Thurston[1], Vincent P Georgescu[1], Russell S Richardson[1], Markus Amann[1]

[1]University of Utah and Veterans Affairs Medical Center, Salt Lake City, United States of America

INTRODUCTION: Although the chemoreflex (CR) and the muscle mechanoreflex (MR) are recognized as strong, independent sympatho-excitatory feedback mechanisms, the interaction of these reflexes and the resulting effect upon the circulatory response remains unclear. This study evaluated the cardiovascular consequence of the interaction of the CR and MR in healthy men.

METHODS: We administered a hypoxic and a hypercapnic inspirate to activate the CR at rest and during passive leg movement (PLM) activating the MR. Eight male volunteers completed 2 experimental sessions. With subjects at rest, one session included normoxic control conditions ($Norm^{Rest}$; S_pO_2 ~98%, $P_{ET}O_2$ ~84 mmHg, $P_{ET}CO_2$ ~34 mmHg), isocapnic hypoxia ($Hypo^{Rest}$; S_pO_2 ~85%, $P_{ET}O_2$ ~46 mmHg, $P_{ET}CO_2$ ~35 mmHg), and hyperoxic hypercapnia ($Hyper^{Rest}$; S_pO_2 ~100%, $P_{ET}O_2$ ~527 mmHg, $P_{ET}CO_2$ ~45 mmHg). In the other session, PLM was performed for 1 min under the same conditions of normoxia ($Norm^{PLM}$), isocapnic hypoxia ($Hypo^{PLM}$), and hyperoxic hypercapnia ($Hyper^{PLM}$). $Norm^{Rest}$ was considered the condition with no reflexes activated. $Hypo^{Rest}$ and $Hyper^{Rest}$ were considered to activate the CR alone; $Norm^{PLM}$ was considered to activate the MR alone; $Hypo^{PLM}$ and $Hyper^{PLM}$ were considered to simultaneously activate the CR and the MR. All sessions and conditions were conducted in a randomized order. Mean arterial blood pressure (MAP), cardiac output (CO), and femoral blood flow (Q_L) were continuously quantified using finger photoplethysmography and Doppler ultrasound.

RESULTS: CR activation via hypoxia (i.e., $\Delta Hypo^{Rest}$-$Norm^{Rest}$) and CR activation via hypercapnia (i.e., $\Delta Hyper^{Rest}$-$Norm^{Rest}$) significantly, but similarly, increased CO (~0.7 $L \cdot min^{-1}$). MR activation by PLM (i.e., $\Delta Norm^{PLM}$-$Norm^{Rest}$) decreased MAP (~7 mmHg; $p < 0.05$), but significantly increased CO (~1.6 $L \cdot min^{-1}$, Q_L ~1.4 $L \cdot min^{-1}$), and leg vascular conductance (LVC, ~14 $ml \cdot min^{-1} \cdot mmHg^{-1}$). During co-activation of the CR via hypoxia and the MR (i.e., $\Delta Hypo^{PLM}$-$Norm^{Rest}$), the observed Q_L and LVC responses were significantly lower compared to the summated responses evoked by each reflex alone (Q_L: 1.1 ± 0.1 vs. 1.5 ± 0.1 $L \cdot min^{-1}$; LVC: 11 ± 1 vs. 15 ± 2 $ml \cdot min^{-1} \cdot mmHg^{-1}$); there were no differences between the observed and summated responses of MAP and CO. During co-activation of the CR via hypercapnia and the MR (i.e., $\Delta Hyper^{PLM}$-$Norm^{Rest}$), only the observed LVC response was significantly lower than the summation of the responses to each reflex alone (LVC: 12 ± 1 vs. 14 ± 1 $ml \cdot min^{-1} \cdot mmHg^{-1}$), whereas the observed MAP, CO, and Q_L did not differ from the summated responses.

CONCLUSION: With CR activation by hypoxia, the CR:MR interaction is additive in terms of MAP and CO, but hypo-additive in terms of Q_L and LVC (i.e., impeded leg muscle perfusion). By contrast, with CR activation by hypercapnia, the CR:MR interaction is additive in terms of MAP, CO, and Q_L, but hypo-additive in terms of LVC. These outcomes indicate that the different modes of the chemoreflex engaged and interacting with the MR result in different impacts on the peripheral hemodynamic regulation. Taken together, despite different cardiovascular consequences, the LVC-based findings suggest that the interaction between the CR and the MR further augments sympathetically-mediated vasoconstriction in healthy men.

CARDIOVASCULAR ANESTHESIOLOGY 29

Differential Impact of Percutaneous and Surgical Mitral Repair on Mitral Annular Remodeling as Assessed by Three-Dimensional Transesophageal Echocardiography

Lisa Q Rong[1], Alexandra Lopes[2], Hannah Mitlak[3], Maria C Palumbo[3], Stephanie Mick[3], Mario Gaudino[3], Jonathan W Weinsaft[3]

[1]Weill Cornell Medicine, NEW YORK, NY, [2]Weill Cornell Medicine, New York, NY, [3]Weill Cornell Medicine, New York, United States of America

INTRODUCTION: Mitral repair can be performed via open surgical or percutaneous (MitraClip) methods, each of which impact mitral annular remodeling. Three-dimensional (3D) transesophageal echocardiography (TEE) is widely used to guide surgical and procedural decision-making for mitral repair - relative impact of surgical repair and MitraClip on annular remodeling is unknown, and may provide mechanism behind differential rates of recurrent mitral regurgitation (MR).

METHODS: The study population comprised patients with >moderate mitral regurgitation undergoing MitraClip or surgical mitral valve repair with annuloplasty and/or leaflet resection. Comprehensive mitral annular geometry including planar (mitral annular area, annular circumference, anterior-posterior and anterolateral-posteromedial diameters), and nonplanar (annular height, tenting height, tenting volume, anterior and posterior leaflet angle and non-planar angle) indices were quantified on intra-procedural 3D TEE; 3D TEE was used to measure surgical and MitraClip-induced changes in annular geometry.

RESULTS: Patients with advanced MR (69±11 years old, 61% male) undergoing elective cardiac surgery [9 (33%) isolated mitral valve repair (MVR), 10 (37%) MVR/CABG, 8 (30%) MVR/other) and 27 MitraClip (mean 1.61±0.58 clips, 57% with multiple clips), Figure 1, Table 1. Leaflet morphology was similar in terms of prolapse and thickening (P> 0.27) but there was increased annular calcification in the MitraClip group and trend for more flail pathology in the surgical group (P=0.03, 0.18 respectively). (Table 1) Baseline left ventricular indices were similar (P=NS) while left atrial dimensions, areas and volumes were larger for the MitraClip population (P<0.05). Baseline echo characteristics of mitral annular area, annular circumference, and anterior-posterior and anterolateral-posteromedial diameters were similar (Table 2). While both MitraClip and undersized annuloplasty induced mitral annular remodeling, the surgical population had greater reductions in mitral annular area, annular circumference, and anterior-posterior and anterolateral-posteromedial diameters than MitraClip. There was also a significant change in the non-planar angle of the valve (135.4 ± 16.0 to 122.3±11.9, P<0.001) in the surgical group whereas MitraClip preserved all other non-planar measures of annular geometry except tenting volume (3.67±1.86 to 2.95±1.58, P<0.001). (Table 3) Despite similar baseline indices, magnitude of annular remodeling was greater with surgical vs. percutaneous repair, including non-planar indices for the surgical group (Figure 2).

CONCLUSION: Surgical mitral valve repair and MitraClip both alter mitral annular geometry, but pattern of repair-induced remodeling alterations differs between methods: Surgical repair induced greater annular reduction than did MitraClip, and also altered non-planar annular geometry: Differential impact on annular remodeling may provide a mechanism for recurrent MR after surgical and percutaneous mitral repair. Figure Legend: Figure 1: Representative examples of mitral valve pathology of surgical patients pre and post-mitral valve repair Figure 2: Bar Plots of the difference (delta Δ) between the post-procedural – pre-procedural indices of annular geometry. P-value denotes paired Student's t-test between MitraClip and surgical patients.

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Table 1. Clinical Characteristics

	Overall (n=54)	Surgical (n= 27)	MitraClip (n=27)	p
Age (year)	69 ± 11	64 ± 9	74 ± 12	**0.002**
Male gender	63% (34)	63% (17)	63% (17)	>0.99
Atherosclerosis Risk Factors				
Hypertension	74% (40)	70% (19)	78% (21)	0.54
Hypercholesterolemia	59% (32)	56% (15)	63% (17)	0.58
Diabetes mellitus	22% (12)	15% (4)	30% (8)	0.19
Tobacco use	50% (27)	33% (9)	67% (18)	**0.01**
Coronary Artery Disease	50% (27)	48% (13)	52% (14)	0.79
Prior Myocardial Infarction	20% 11)	7% (2)	33% (9)	**0.02**
Prior Revascularization	24% (13)	11% (3)	37% (10)	**0.03**
Prior CABG	28% (15)	37% (10)	19% (5)	0.13
Number of Clips Implanted				
Mean	--	--	1.70 ± 0.69	--
Multiple (>1)	--	--	32% (17)	--
Ring type	--		--	--
Duran*/Physio**/Cosgrove*	--	26%(6)/26%(6)/ 48%(11)	--	--
Type of Surgery MVr isolated/MVr CABG/MVr other	--	--	33% (9)/37% (10)/30%(8)	--
Mitral Valve Morphology				
Mitral Valve Prolapse	61% (33)	63% (17)	59% (16)	0.78
Mitral Valve Flail	19% (10)	27% (7)	11% (3)	0.18
Mitral Annular Calcification	24% (14)	37% (10)	11% (3)	**0.03**
Mitral Valve Thickening	30% (16)	23% (6)	37% (10)	0.27

Table Legend: MVr, mitral valve repair; CABG, coronary artery bypass graft

*incomplete ring, ** complete ring

Table 2. Baseline Echocardiographic Indices

	Overall (n=54)	Surgical (n= 27)	MitraClip (n=27)	p
Mitral Valve Geometry				
Mitral Annular Area (cm^2)	13.11 ± 3.55	12.96 ± 4.42	13.25 ± 2.47	0.77
Annular Circumference (cm/m^2)	13.33 ± 1.73	13.20 ± 2.14	13.47 ± 1.120	0.57
Antero-Posterior Diameter (cm)	3.66 ± 0.58	3.48 ± 0.67	3.83 ± 0.42	**0.03**
Anterolateral-Posteromedial Diameter (cm)	4.29 ± 0.59	4.29 ± 0.75	4.30 ± 0.40	0.94
Annular Height (cm)	0.68 ± 0.22	0.59 ± 0.18	0.77 ± 0.21	**0.001**
Tenting Volume (cm^3)	2.35 ± 1.96	1.13 ± 1.06	3.67 ± 1.86	**<0.001**
Tenting Height (mm)	6.93 ± 3.44	4.67 ± 2.20	9.19 ± 2.94	**<0.001**
Anterior Leaflet Angle (°)	28.56 ± 14.81	20.31 ± 7.72	36.81 ± 15.69	**<0.001**
Posterior Leaflet Angle (°)	23.09 ± 9.44	24.86 ± 10.48	21.33 ± 8.09	0.17
Nonplanar Angle (°)	142.88 ± 16.20	135.36 ± 15.97	150.40 ± 12.75	**<0.001**
Left Ventricle				
LV Ejection Fraction (%)	52.48 ± 15.36	54.27 ± 16.88	50.69 ± 13.75	0.40
LV Mass Indexed (g/m^2)	108.01 ± 33.27	101.39 ± 34.14	112.42 ± 32.57	0.28
LV End Diastolic Volume (mL/m^2)	93.02 ± 27.38	88.85 ± 34.00	95.64 ± 22.57	0.43
LV End Systolic Volume (mL/m^2)	46.65 ± 24.43	44.88 ± 25.97	47.82 ± 23.82	0.70
Left Atrium				
LA dimension (cm)	4.71 ± 1.12	4.26 ± 0.87	5.01 ± 1.18	**0.03**
LA Area 2-Chamber (m^2)	28.89 ± 11.97	24.64 ± 6.58	31.57 ± 13.82	0.06
LA Area 4-Chamber (m^2)	28.10 ± 9.46	23.13 ± 4.78	31.05 ± 10.36	**0.002**
LA Volume Indexed (mL/m^2)	57.44 ± 28.68	46.93 ± 10.74	65.61 ± 35.21	**0.02**

Table 3. MitraClip and Surgical Induced Annular Remodeling

	Pre	Post	Δ	p
Overall				
Mitral Annular Area (cm^2)	13.11 ± 3.55	8.91 ± 3.90	-4.20 ± 3.87	**<0.001**
Annular Circumference (cm/m^2)	13.33 ± 1.73	10.98 ± 2.46	-5.39 ± 11.73	**<0.001**
Antero-Posterior Diameter (cm)	3.66 ± 0.58	2.88 ± 0.75	-1.69 ± 3.51	**<0.001**
Anterolateral-Posteromedial Diameter (cm)	4.2 ± 0.59	3.57 ± 0.84	-1.68 ± 3.89	**<0.001**
Annular Height (cm)	0.68 ± 0.22	0.61 ± 0.21	-0.18 ± 0.58	**0.01**
Tenting Volume (cm^3)	2.35 ± 1.96	1.67 ± 1.71	-0.69 ± 0.94	**<0.001**
Tenting Height (mm)	6.93 ± 3.44	5.93 ± 3.15	-1.00 ± 2.31	**0.002**
Anterior Leaflet Angle (°)	28.56 ± 14.81	28.01 ± 13.79	-0.55 ± 10.74	0.71
Posterior Leaflet Angle (°)	23.09 ± 9.44	29.45 ± 10.63	6.36 ± 10.76	**<0.001**
Nonplanar Angle (°)	142.88 ± 16.20	135.12 ± 16.20	-7.76 ± 16.04	**<0.001**
Surgical				
Mitral Annular Area (cm^2)	12.96 ± 4.42	5.75 ± 2.03	-7.21 ± 3.23	**<0.001**
Annular Circumference (cm/m^2)	13.20 ± 2.14	8.97 ± 1.55	-10.26 ± 15.20	**<0.001**
Antero-Posterior Diameter (cm)	3.48 ± 0.67	2.29 ± 0.48	-3.02 ± 4.62	**<0.001**
Anterolateral-Posteromedial Diameter (cm)	4.29 ± 0.75	2.85 ± 0.39	-3.35 ± 5.00	**<0.001**
Annular Height (cm)	0.59 ± 0.18	0.51 ± 0.15	-0.31 ± 0.78	**0.02**
Tenting Volume (cm^3)	1.13 ± 1.06	0.47 ± 0.57	-0.66 ± 1.05	**0.003**
Tenting Height (mm)	4.67 ± 2.20	3.46 ± 1.74	-1.21 ± 2.19	**0.008**
Anterior Leaflet Angle (°)	20.31 ± 7.72	21.25 ± 8.05	0.93 ± 10.60	0.65
Posterior Leaflet Angle (°)	24.86 ± 10.48	36.59 ± 9.07	11.73 ± 11.35	**<0.001**
Nonplanar Angle (°)	135.36 ± 15.97	122.28 ± 11.89	-13.08 ± 15.60	**<0.001**
MitraClip				
Mitral Annular Area (cm^2)	13.25 ± 2.47	12.06 ± 2.51	-1.19 ± 1.13	**<0.001**
Annular Circumference (cm/m^2)	13.47 ± 1.120	12.95 ± 1.30	-0.52 ± 0.57	**<0.001**
Antero-Posterior Diameter (cm)	3.83 ± 0.42	3.47 ± 0.43	-0.36 ± 0.27	**<0.001**
Anterolateral-Posteromedial Diameter (cm)	4.30 ± 0.40	4.30 ± 0.45	-0.01 ± 0.29	0.95
Annular Height (cm)	0.77 ± 0.21	0.72 ± 0.22	-0.05 ± 0.20	0.20
Tenting Volume (cm^3)	3.67 ± 1.86	2.95 ± 1.58	-0.72 ± 0.83	**<0.001**
Tenting Height (mm)	9.19 ± 2.94	8.39 ± 2.13	-0.80 ± 2.46	0.10
Anterior Leaflet Angle (°)	36.81 ± 15.69	34.78 ± 15.69	-2.03 ± 10.87	0.34
Posterior Leaflet Angle (°)	21.33 ± 8.09	22.31 ± 6.48	0.98 ± 6.87	0.47
Nonplanar Angle (°)	150.40 ± 12.75	147.96 ± 17.97	-2.45 ± 14.92	0.40

Figure 1:

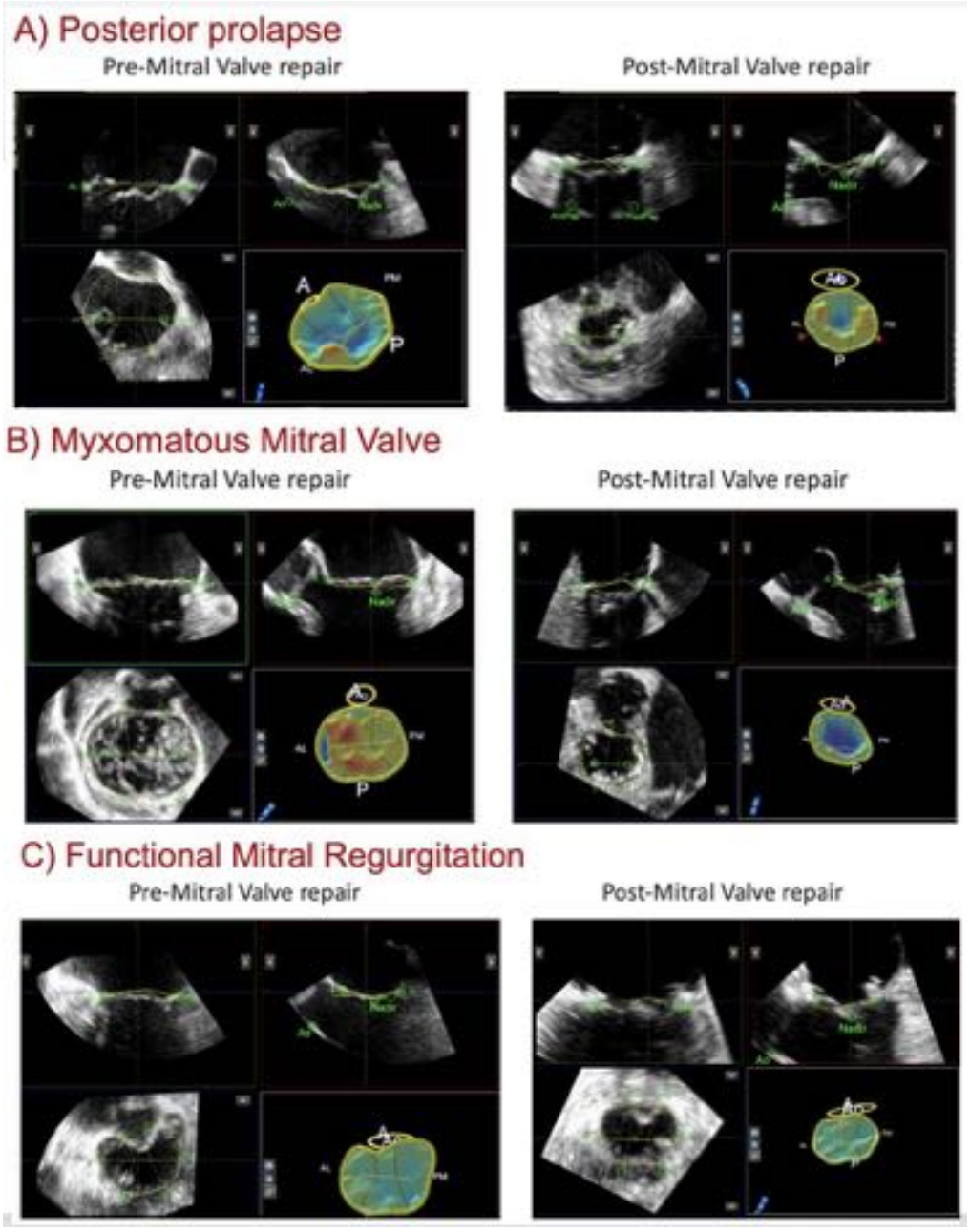
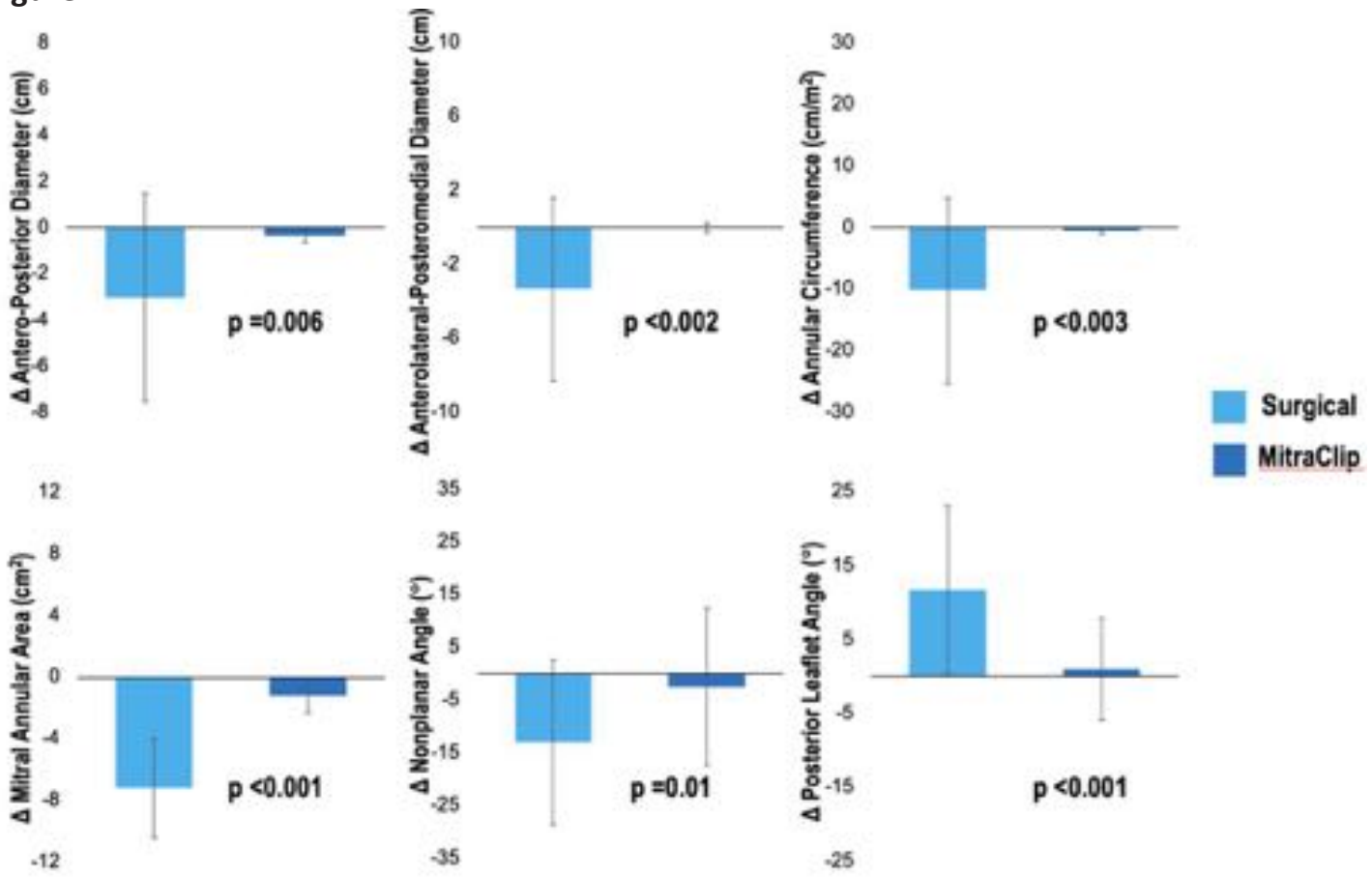


Figure 2:



CARDIOVASCULAR ANESTHESIOLOGY 30

Monitored Anesthesia Care, When Compared to General Anesthesia, Is Associated With a Higher Risk of Postoperative Permanent Pacemaker Placement Following Transcatheter Aortic Valve Replacement

Brendan Feehan[1], Luz A Padilla[1], James Davies[1], AHMED ZAKY[1], Matthew G Broyles[1]

[1]University of Alabama at Birmingham, Birmingham, AL

INTRODUCTION: Transcatheter aortic valve replacement (TAVR) is the recommended treatment for patients with severe, symptomatic aortic stenosis who are at high operative risk and is gaining a growing number of new indications[1]. Choice of anesthetic for TAVR has been a matter of a debate between general anesthesia (GA) and monitored anesthesia care (MAC), which appears to be largely based off institutional and regional practices[2], with a recent trend towards MAC[3], and some regions performing 100% of TAVRs under MAC[3]. MAC for TAVR is largely safe[2], and is associated with several benefits, such as shorter procedure time and hospital stays[4], but a number of studies have identified a possible association with MAC and a higher incidence of permanent pacemaker (PPM) placement postoperatively. Initially identified as a trend,[2,5,6] a recent meta-analysis reached statistical significance (28.2% vs 20.8%, p < 0.0001)7. STS data demonstrated no significant difference in new PPM implantation after falsification end point analysis adjustment[8]. These studies face a number of limitations, including small sample size for the single site studies and varying institutional practices for the multi-site studies. Causal factors for the association between anesthesia type and postoperative PPM placement have been unelucidated. Proposed mechanisms include differences in valve type (despite a positive association in a cohort of patients who only received one valve type[9]), impaired or altered valve positioning during MAC[7], surgical technique differences, attributed to residual confounding[10], and anesthetic agents. Dexmedetomidine, in particular, could play a role given the rapid adoption in its use for the procedure, and as it has been found to have prolonged hemodynamic effects, particularly bradycardia[11,12,13], including in a study which compared MAC using propofol to dexmedetomidine in patients undergoing TAVR[14]. In this study we take advantage of our large volume of TAVR procedures and dexmedetomidine-based MAC protocol to compare postoperative PPM and other outcomes between patients who undergo MAC and GA for TAVR. We hypothesize that patients who underwent MAC anesthesia for TAVR will have a significantly increased incidence of postoperative PPM placement.

METHODS: This is a single center retrospective study. A query of electronic medical records was conducted to identify all patients who underwent TAVR from 2011-2018. Exclusion criteria were the presence of a preoperative PPM, other preoperative pacing, and crossover from MAC to GA. Baseline demographics and perioperative data were extracted from medical records and dichotomized by anesthesia type. The MAC and GA groups were compared using x2, Fisher's exact, Wilcoxon rank sum, and Student's t-test where appropriate. Our primary endpoint was postoperative PPM placement, with secondary endpoints of temporary pacemaker requirement, and ICU and hospital length of stays. Logistic regression was used to identify the association of MAC and PPM. All data analysis was performed using SAS, and a two-sided <0.05 p-value for all statistical tests were considered significant.

RESULTS: 698 patients were included; 476 underwent GA and 222 underwent MAC. There were no statistically significant differences between the groups at baseline. The rate of postoperative PPM was significantly higher in the MAC group when compared to the GA group (13.1% vs 7.3%, p 0.01). There was no difference in rate of temporary pacemaker between groups (p 0.18). Patients undergoing MAC had shorter ICU and hospital length-of-stays (p 0.04, p 0.01). Logistic regression showed a significant association between PPM and anesthesia type; those who underwent MAC were 89% more likely to require a PPM compared to those who underwent GA (OR 1.89, CI 1.12-3.18, p 0.01).

CONCLUSION: Our large single center study shows that MAC is independently associated with PPM placement when compared to GA in patients undergoing TAVR, and confirms previous findings of shorter lengths of stay. The association of MAC and PPM requires consideration, as identifying those at-risk or altering treatment could decrease the need for postoperative PPM placement. Our study is limited by its design as a retrospective cohort study, and the lack of an association between a specific factor, such as a medication, and the outcome of increased rate of PPM. Future studies are needed to identify factors that may better explain the association between anesthetic type and postoperative PPM placement for TAVR.

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CARDIOVASCULAR ANESTHESIOLOGY 31

Volatile anesthetics loading of the sonoparticles; preparation for future clinical application

Amir Teimouri Dereshgi[1], Paul R Knight[1], Bruce A Davidson[1], Siavash Sedghi[1], Hilliard Kutscher[1], Nader D Nader[1]

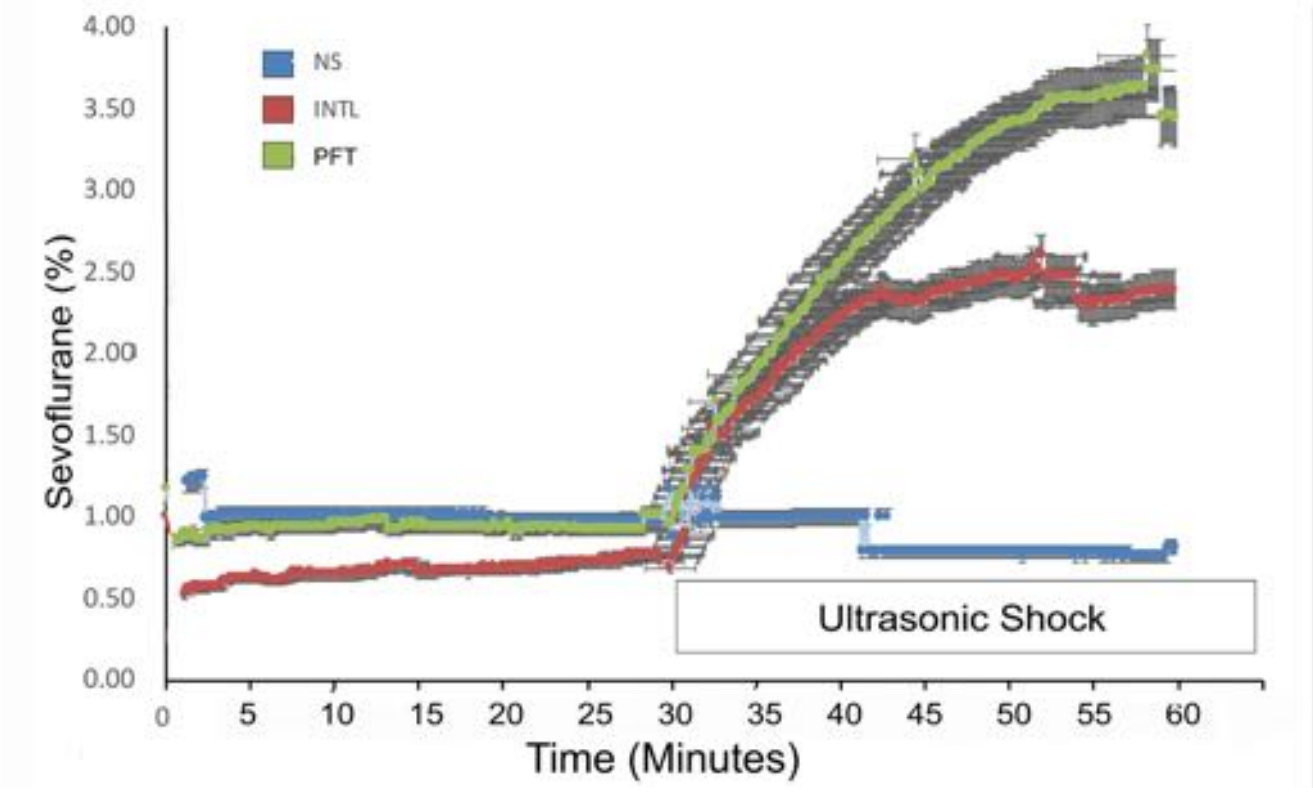
1University at Buffalo, Buffalo, NY

INTRODUCTION: Volatile anesthetics in clinical medicine are generally administered through inhalation. Intravenous administration of these agents requires emulsification or phospholipid particle loading due to their hydrophobic chemical structure. We have taken initial steps toward testing the feasibility and stability of sevoflurane-loaded sonoparticles. Perflutren is used as a contrast material in echocardiographic assessment of coronary perfusion, where the microspheres are ruptured under high mechanical index (> 0.8). This targeted release of sevoflurane could be used to precondition the ischemic myocardium to limit subsequent ischemia-reperfusion injury.

METHODS: Sevoflurane 100ul was added to 1.7 mL microtubes containing 1.5 mL of normal saline (NS0.9%), intralipid 20% (INTL) or perflutren (PFT) vial and vigorously agitated for 45 seconds. The activation (loading) was confirmed with a milky appearance of the perflutren vial. Sealed glass tubes (10-mL) were attached to the gas analyzers (to measure the concentrations of sevoflurane) were primed with 4.5 mL NS0.9%. Following the initial mix of loaded samples, 500 uL from each sevoflurane containing solution was added to the measurement chamber. Sevoflurane concentration was analyzed in two phases lasting 30 minutes each. The initial phase of measurement was carried out without sonification, followed by 30 minutes of sonification. Measurements were taken every 5 seconds for a total duration of 60 minutes.

RESULTS: Sevoflurane concentration had a decremental pattern in NS0.9% solution and continued to decrease after initiation of sonification. INTL and PFT solutions had relatively lower levels of sevoflurane compared to NS0.9% solution indicating a lower free vapor during the initial phase. On the other hand, both solutions released sevoflurane vapor in a stepwise fashion to a higher extent than that of NS0.9% solution during the sonification phase. (Figure 1)

CONCLUSION: Perflutren sonoparticles held sevoflurane contained and were able to release the vapor on demand when the particles were destroyed by ultrasonic energy. This observation may pave the road for targeted delivery of volatile anesthetic to organs like the myocardium under ultrasound guidance.



Subspecialty Abstracts

CRITICAL CARE

CRITICAL CARE 1

Compassion and Humanism Play a Greater Role in Mitigating the Stress of COVID 19 Amongst ICU Staff than Wellness Programs

Shahla Siddiqui[1]

[1]*Beth Israel Deaconess Lahey Medical Center, Boston, MA*

INTRODUCTION: The COVID 19 pandemic gripped the world at the beginning of this year and very quickly it was clear that ICU staff would have to take the major brunt of managing thousands of critically ill and dying patients. By March 2020 Boston was in the midst of its first surge and our hospital like others was dealing with hundreds of patients in all ICUs, as well as in surge ICUs that were staffed by nurses, CRNAs and physicians deployed from non-ICU settings. Even before the pandemic the rate of anxiety, depression as well as ethical and moral distress amongst staff was high in the critical care environment, however, since the pandemic began, multiple reports of work in the ICU significantly affecting the mental health of healthcare workers (HCWs), who stand in the frontline of this crisis have come forth. Several studies have shown that the pandemic has led to extraordinary amounts of stress on healthcare workers (HCWs). Some of the reasons for this include increased workload, physical exhaustion, inadequate personal equipment (PPE), risk of nosocomial transmission, and the need to make ethically difficult decisions on the rationing of resources may have dramatic effects on their physical and mental well-being. Their strength can be further compromised by isolation and loss of social support required for infection control, risk or infections of family and friends as well as new sudden changes to work locations and hours. HCWs are, therefore, especially vulnerable to mental health problems, including fear, anxiety, depression and burnout. Hospitals and organizations have added a multitude of wellness programs during the pandemic to provide staff with coping techniques, including online yoga sessions, meditation programs, stress hotlines and other virtual group activities whilst maintaining social distancing. The objective of this study was to evaluate the prevalence of anxiety, depression, ethical and moral distress among ICU HCWs based on job categories during the COVID-19 pandemic surge in our hospital, and to assess the value of wellness programs offered in mitigating this stress.

METHODS: This study was approved as exempt by the Institutional review board. Between the months of March and May 2020, we conducted an online cross-sectional, mixed method survey across all ICUs of the Beth Israel Deaconess Medical center in Boston, USA. The survey link was advertised in all ICUs and weekly reminders were sent to all ICU staff. A cross-sectional online survey composed of 26 multiple choice and open-ended questions was administered between March and May 2020. We invited physicians, nurses, and respiratory technicians as well as certified nurse anesthetists who were deployed to work in ICUs due to the COVID 19 surge. A letter of information was attached to the link for the survey and completion of the questionnaire implied their consent. The survey instrument was developed using validated questions from the generalized anxiety disorder (GAD) screening tool and the depression screening tool developed by the Anxiety and depression association of America (Fig 1). In addition, other open-ended questions were tailored to focus on how respondents dealt with fear, anxiety, loss of control and stress of working in the front lines. A specific question was asked about how much wellness focused programs offered by their respective departments provided relief to HCWs.

RESULTS: Our results show that although stress and anxiety were high among the HCW in the ICU, almost 70 % felt that the wellness resources being offered were not useful. The qualitative analysis revealed that compassionate interactions with the leadership and managers proved very useful and morale building for the nurses and doctors.

CONCLUSION: The stress of COVID 19 among frontline ICU health care workers is significant and can be mitigated by compassionate peer interaction and caring emotionally intelligent and mindful leadership. This may result in reduction of Burnout of the workforce and building resilience for future pandemic surges.

Stress Survey Analysis

Baseline Characteristics

Characteristic	N=67
Role, No. (%)	
Resident	15 (22.4)
Fellow	0 (0.0)
Attending	3 (4.5)
Respiratory Therapist	3 (4.5)
Nursing Professional	44 (65.7)
Other	2 (3.0)
Gender, No. (%)	
Female	56 (84.9)
Ethnicity, No. (%)	
Hispanic or Latino	4 (6.1)
Not Hispanic or Latino	58 (87.9)
Prefer not to answer	4 (6.1)
Race, No. (%)	
White	54 (81.8)
Black or African American	0 (0.0)
Asian	3 (4.6)
Native Hawaiian or other Pacific Islander	0 (0.0)
American Indian or Alaskan Native	0 (0.0)
Multi-Racial	0 (0.0)
Other	2 (3.0)
Prefer not to answer	7 (10.6)

Are you troubled by any of the following since the COVID-19 pandemic started?

Characteristic	(n=67) No. (%) of those who are troubled
Experience excessive worry	(n=60) 33 (54.1)
Worry excessive in intensity, frequency, or amount of distress it causes	(n=59) 27 (45.0)
Find it difficult to control the worry (or stop worrying) once it starts	(n=59) 28 (46.7)
Worry excessively or uncontrollably about minor things	(n=59) 20 (33.3)
Bothered by excessive worries more days than not, During the COVID-19 pandemic	(n=60) 24 (39.3)

During the past few weeks have you often been bothered by any of the following symp
select one option.

Symptom	N=67 No. (%)
Restlessness or feeling keyed up or on edge	(n=58)
Not at all	3 (5.1)
A little bit	18 (30.5)
Moderately	13 (22.0)
Quite a bit	18 (30.5)
Extremely	7 (11.9)
Irritability	(n=58)
Not at all	7 (11.9)
A little bit	15 (25.4)
Moderately	13 (22.0)
Quite a bit	20 (33.9)
Extremely	4 (6.8)
Difficulty falling/staying asleep or restless/unsatisfying sleep	(n=58)
Not at all	9 (15.3)
A little bit	7 (11.9)
Moderately	9 (15.3)
Quite a bit	22 (37.3)
Extremely	12 (20.3)
Being easily fatigued	(n=58)
Not at all	5 (8.5)
A little bit	12 (20.3)
Moderately	16 (27.1)
Quite a bit	16 (27.1)
Extremely	10 (17.0)
Difficulty concentrating or mind going blank	(n=57)
Not at all	12 (20.7)
A little bit	16 (27.6)
Moderately	9 (15.5)
Quite a bit	17 (29.3)
Extremely	4 (6.9)
Muscle tension	(n=58)
Not at all	11 (18.6)
A little bit	12 (20.3)
Moderately	9 (15.3)
Quite a bit	18 (30.5)
Extremely	9 (15.3)
How much do worry and physical symptoms interfere with your life, work, social activities, family, etc.?	(n=58)
Not at all	7 (11.9)
Mildly	22 (37.3)
Moderately	21 (35.6)
Severely	7 (11.9)
Very Severely	2 (3.4)
How much are you bothered by worry and physical symptoms (how much distress does it cause you)?	(n=58)
Not at all	6 (10.2)
Mildly bothered	20 (33.9)
Moderately bothered	21 (35.6)
Severely bothered	8 (13.6)
Very severely bothered	4 (6.8)

Over the last two weeks, how often have you been bothered by any of the following problems?

Problem	N=67 No. (%)
Little interest or pleasure in doing things	(n=58)
Not at all	21 (35.6)
Several days	23 (39.0)
More than half of the days	13 (22.0)
Nearly everyday	2 (3.4)
Feeling down, depressed or hopeless	(n=58)
Not at all	15 (25.4)
Several days	26 (44.1)
More than half of the days	14 (23.7)
Nearly everyday	4 (6.8)
Trouble falling or staying asleep, or sleeping too much	(n=58)
Not at all	10 (17.0)
Several days	21 (35.6)
More than half of the days	15 (25.4)
Nearly everyday	13 (22.0)
Feeling tired or having little energy	(n=58)
Not at all	7 (11.9)
Several days	24 (40.7)
More than half of the days	18 (30.5)
Nearly everyday	10 (17.0)
Poor appetite or overeating	(n=58)
Not at all	17 (28.8)
Several days	18 (30.5)
More than half of the days	15 (25.4)
Nearly everyday	9 (15.3)
Feeling bad about yourself - or that you are a failure or have let yourself or your family down	(n=58)
Not at all	31 (52.5)
Several days	16 (27.1)
More than half of the days	7 (11.9)
Nearly everyday	5 (8.5)
Trouble concentrating on things such as reading the newspaper or watching television	(n=58)
Not at all	34 (57.6)
Several days	14 (23.7)
More than half of the days	6 (10.2)
Nearly everyday	5 (8.5)
Moving or speaking so slowly that other people could have noticed? Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual	(n=58)
Not at all	47 (79.7)
Several days	8 (13.6)
More than half of the days	3 (5.1)
Nearly everyday	1 (1.7)
How difficult have the problems you experienced made it for you to do your work, take care of things at home, or get along with other people?	(n=54)
Not difficult	17 (30.9)
Somewhat difficult	30 (54.6)
Very difficult	6 (10.9)
Extremely difficult	2 (3.6)

In your opinion are the Wellness Resources being offered to you through your work helpful?

15 (30%) said yes, 35 (70%) said no

Comparing Genders

Are you troubled by any of the following since the COVID-19 pandemic started?

Characteristic	**(n=56) No. (%) of women who are troubled**	**(n=11) No. (%) of men who are troubled**	**P-Value**
Experience excessive worry	(n=51) 30 (58.8)	(n=9) 2 (22.2)	0.069
Worry excessive in intensity, frequency, or amount of distress it causes	(n=50) 25 (50.0)	(n=9) 2 (22.2)	0.16
Find it difficult to control the worry (or stop worrying) once it starts	(n=50) 27 (54.0)	(n=9) 1 (11.1)	0.027
Worry excessively or uncontrollably about minor things	(n=50) 19 (38.0)	(n=9) 1 (11.1)	0.148
Bothered by excessive worries more days than not, During the COVID-19 pandemic	(n=51) 18 (35.3)	(n=9) 6 (66.7)	0.137

During the past few weeks have you often been bothered by any of the following symptoms? Please select one option.

Symptom	(n=56) No. (%) of Women	(n=11) No. (%) of Men	P-Value
Restlessness or feeling keyed up or on edge	(n=50)	(n=8)	
Not at all	1 (2.0)	2 (25.0)	
A little bit	15 (30.0)	2 (25.0)	0.183
Moderately	11 (22.0)	2 (25.0)	
Quite a bit	17 (34.0)	1 (12.5)	
Extremely	6 (12.0)	1 (12.5)	
Irritability	(n=50)	(n=8)	0.421
Not at all	5 (10.0)	2 (25.0)	
A little bit	12 (24.0)	2 (25.0)	
Moderately	12 (24.0)	1 (12.5)	
Quite a bit	17 (34.0)	3 (37.5)	
Extremely	4 (8.0)	0 (0.0)	
Difficulty falling/staying asleep or restless/unsatisfying sleep	(n=50)	(n=8)	0.332
Not at all	6 (12.0)	3 (37.5)	
A little bit	7 (14.0)	0 (0.0)	
Moderately	7 (14.0)	1 (12.5)	
Quite a bit	19 (38.0)	3 (37.5)	
Extremely	11 (22.0)	1 (12.5)	
Being easily fatigued	(n=50)	(n=8)	0.535
Not at all	2 (4.0)	3 (37.5)	
A little bit	11 (12.0)	0 (0.0)	
Moderately	15 (30.0)	1 (12.5)	
Quite a bit	14 (28.0)	2 (25.0)	
Extremely	8 (16.0)	2 (25.0)	
Difficulty concentrating or mind going blank	(n=50)	(n=7)	0.206
Not at all	7 (14.0)	4 (57.1)	
A little bit	16 (32.0)	0 (0.0)	
Moderately	8 (16.0)	1 (14.3)	
Quite a bit	15 (30.0)	2 (28.6)	
Extremely	4 (8.0)	0 (0.0)	
Muscle tension	(n=50)	(n=8)	0.414
Not at all	8 (16.0)	3 (37.5)	
A little bit	10 (20.0)	1 (12.5)	
Moderately	8 (16.0)	1 (12.5)	
Quite a bit	16 (32.0)	2 (25.0)	
Extremely	8 (16.0)	1 (12.5)	
How much do worry and physical symptoms interfere with your life, work, social activities, family, etc.?	(n=50)	(n=8)	0.002
Not at all	3 (6.0)	4 (50.0)	
Mildly	19 (38.0)	3 (37.5)	
Moderately	19 (38.0)	1 (12.5)	
Severely	7 (14.0)	0 (0.0)	
Very Severely	2 (4.0)	0 (0.0)	
How much are you bothered by worry and physical symptoms (how much distress does it cause you)?	(n=50)	(n=8)	0.21
Not at all	3 (6.0)	3 (37.5)	
Mildly bothered	19 (38.0)	1 (12.5)	
Moderately bothered	17 (34.0)	3 (37.5)	
Severely bothered	7 (14.0)	1 (12.5)	
Very severely bothered	4 (8.0)	0 (0.0)	

Over the last two weeks, how often have you been bothered by any of the following problems?

Problem	(n=56) No. (%) of Women	(n=11) No. (%) of Men	P-Value
Little interest or pleasure in doing things	(n=50)	(n=8)	0.658
Not at all	17 (34.0)	4 (50.0)	
Several days	21 (42.0)	2 (25.0)	
More than half of the days	10 (20.0)	2 (25.0)	
Nearly everyday	2 (4.0)	0 (0.0)	
Feeling down, depressed or hopeless	(n=50)	(n=8)	0.048
Not at all	10 (20.0)	5 (62.5)	
Several days	23 (46.0)	2 (25.0)	
More than half of the days	13 (26.0)	1 (12.5)	
Nearly everyday	4 (8.0)	0 (0.0)	
Trouble falling or staying asleep, or sleeping too much	(n=50)	(n=8)	0.272
Not at all	7 (14.0)	3 (37.5)	
Several days	18 (36.0)	2 (25.0)	
More than half of the days	13 (26.0)	2 (25.0)	
Nearly everyday	12 (24.0)	1 (12.5)	
Feeling tired or having little energy	(n=50)	(n=8)	0.414
Not at all	3 (6.0)	4 (50.0)	
Several days	23 (46.0)	0 (0.0)	
More than half of the days	16 (32.0)	2 (25.0)	
Nearly everyday	8 (16.0)	2 (25.0)	
Poor appetite or overeating	(n=50)	(n=8)	0.071
Not at all	12 (24.0)	5 (62.5)	
Several days	16 (32.0)	1 (12.5)	
More than half of the days	13 (26.0)	2 (25.0)	
Nearly everyday	9 (18.0)	0 (0.0)	
Feeling bad about yourself - or that you are a failure or have let yourself or your family down	(n=50)	(n=8)	0.26
Not at all	25 (50.0)	6 (75.0)	
Several days	14 (28.0)	1 (12.5)	
More than half of the days	6 (12.0)	1 (12.5)	
Nearly everyday	5 (10.0)	0 (0.0)	
Trouble concentrating on things such as reading the newspaper or watching television	(n=50)	(n=8)	0.246
Not at all	30 (60.0)	4 (50.0)	
Several days	12 (24.0)	1 (12.5)	
More than half of the days	5 (10.0)	1 (12.5)	
Nearly everyday	3 (6.0)	2 (25.0)	
Moving or speaking so slowly that other people could have noticed? Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual	(n=50)	(n=8)	1.0
Not at all	40 (80.0)	6 (75.0)	
Several days	6 (12.0)	2 (25.0)	
More than half of the days	3 (6.0)	0 (0.0)	
Nearly everyday	1 (2.0)	0 (0.0)	
How difficult have the problems you experienced made it for you to do your work, take care of things at home, or get along with other people?	(n=48)	(n=6)	0.082
Not difficult	13 (27.1)	4 (66.7)	
Somewhat difficult	27 (56.3)	2 (33.3)	
Very difficult	6 (12.5)	0 (0.0)	
Extremely difficult	2 (4.2)	0 (0.0)	

Interpretation of results: Over the last two weeks, 20% of female participants never felt down, depressed or hopeless, 46% felt down depressed or hopeless several days, 26% more than half of the days, and 8% nearly every day, compared to male survey participants where 62.5% never felt down, depressed or hopeless, 25% several days, 12.5% more than half of the days, and none nearly every day. There is a statistically significant difference in the amount that males and females felt down, depressed or hopeless (females felt this more often than males) (p=0.048).

All questions with ordinal responses can be interpreted similarly

In your opinion are the Wellness Resources being offered to you through your work helpful?

	(n=56) No. (%) Women	**(n=11) No. (%) Men**	**P-Value**
Wellness resources being offered are helpful No. (%) Yes	10/42 (23.8)	4/7 (57.1)	0.091

Comparing Profession (nurses versus not nurses)

Are you troubled by any of the following since the COVID-19 pandemic started?

Characteristic	**(n=23) No. (%) of non-nurses who are troubled**	**(n=44) No. (%) of Nurses who are troubled**	**P-Value**
Experience excessive worry	(n=20) 12 (60.0)	(n=41) 21 (51.2)	0.518
Worry excessive in intensity, frequency, or amount of distress it causes	(n=19) 9 (47.4)	(n=41) 18 (43.9)	0.802
Find it difficult to control the worry (or stop worrying) once it starts	(n=19) 9 (47.4)	(n=14) 19 (46.3)	0.941
Worry excessively or uncontrollably about minor things	(n=19) 7 (36.8)	(n=41) 13 (31.7)	0.695
Bothered by excessive worries more days than not, During the COVID-19 pandemic	(n=20) 8 (40.0)	(n=41) 16 (39.0)	0.942

During the past few weeks have you often been bothered by any of the following symptoms? Please select one option.

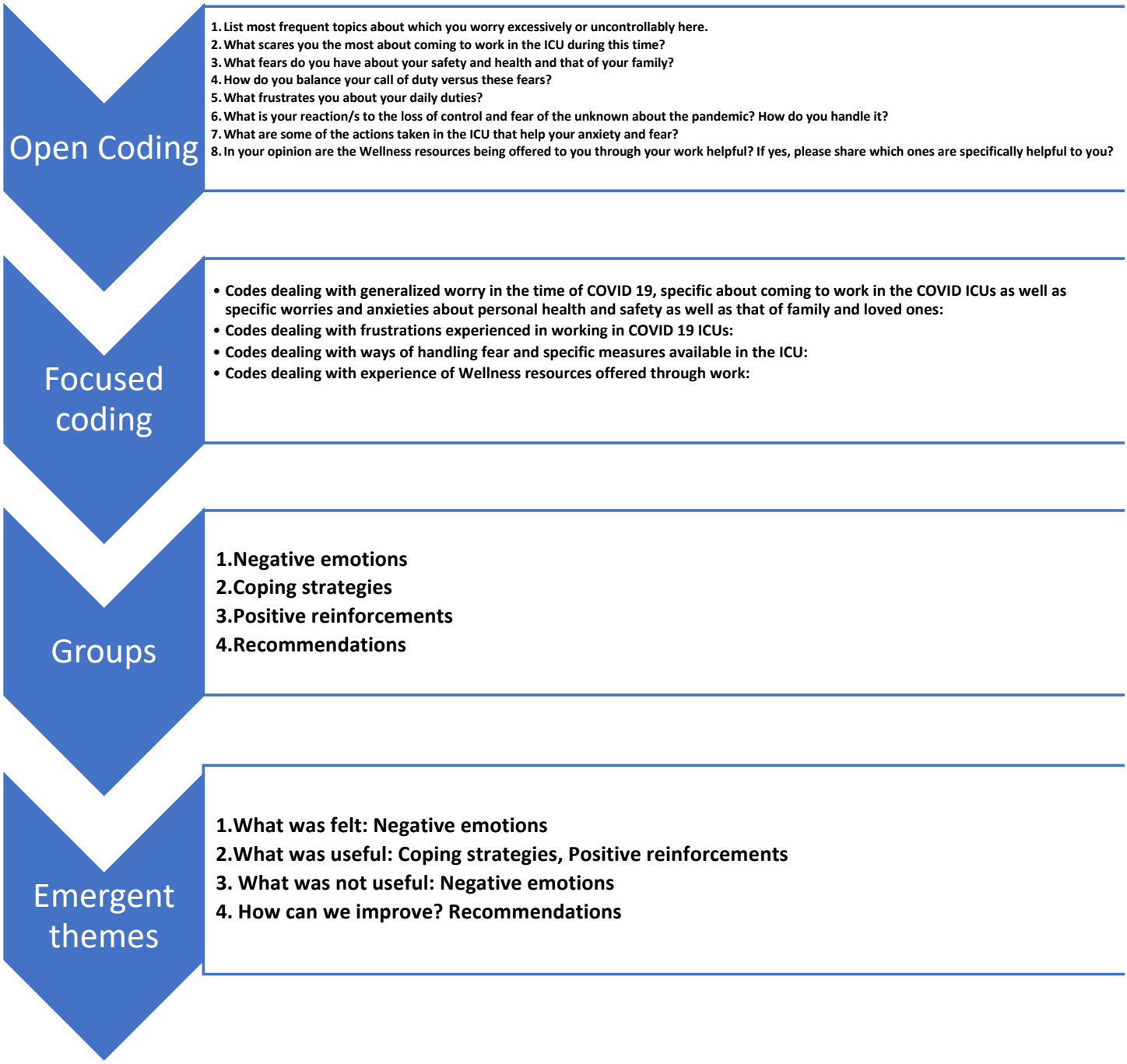
Symptom	(n=23) No. (%) of non-nurses	(n=44) No. (%) of Nurses	P-Value
Restlessness or feeling keyed up or on edge	(n=18)	(n=41)	
Not at all	3 (16.7)	0 (0.0)	
A little bit	6 (33.3)	12 (29.4)	0.136
Moderately	2 (11.1)	11 (26.8)	
Quite a bit	6 (33.3)	12 (29.3)	
Extremely	1 (5.6)	6 (14.6)	
Irritability	(n=18)	(n=41)	0.905
Not at all	2 (11.1)	5 (12.2)	
A little bit	6 (33.3)	9 (22.0)	
Moderately	2 (11.1)	11 (26.8)	
Quite a bit	7 (38.9)	13 (31.7)	
Extremely	1 (5.6)	3 (7.3)	
Difficulty falling/staying asleep or restless/unsatisfying sleep	(n=18)	(n=41)	0.02
Not at all	6 (33.3)	3 (7.3)	
A little bit	2 (11.1)	5 (12.2)	
Moderately	3 (16.7)	6 (14.6)	
Quite a bit	5 (27.8)	17 (41.5)	
Extremely	2 (11.1)	10 (24.4)	
Being easily fatigued	(n=18)	(n=41)	0.102
Not at all	4 (22.2)	1 (2.4)	
A little bit	4 (22.2)	8 (19.5)	
Moderately	4 (22.2)	12 (29.3)	
Quite a bit	3 (16.7)	13 (31.7)	
Extremely	3 (16.7)	7 (17.1)	
Difficulty concentrating or mind going blank	(n=18)	(n=40)	0.659
Not at all	5 (27.8)	7 (17.5)	
A little bit	4 (22.2)	12 (30.0)	
Moderately	3 (16.7)	6 (15.0)	
Quite a bit	5 (27.8)	12 (30.0)	
Extremely	1 (5.6)	3 (7.5)	
Muscle tension	(n=18)	(n=41)	0.003
Not at all	8 (44.4)	3 (7.3)	
A little bit	4 (22.2)	8 (19.5)	
Moderately	1 (5.6)	8 (19.5)	
Quite a bit	4 (22.2)	14 (34.2)	
Extremely	1 (5.6)	8 (19.5)	
How much do worry and physical symptoms interfere with your life, work, social activities, family, etc.?	(n=18)	(n=41)	0.385
Not at all	4 (22.2)	3 (7.3)	
Mildly	5 (27.8)	17 (41.5)	
Moderately	8 (44.4)	13 (31.7)	
Severely	0 (0.0)	7 (17.1)	
Very Severely	1 (5.6)	1 (2.4)	
How much are you bothered by worry and physical symptoms (how much distress does it cause you)?	(n=18)	(n=41)	0.059
Not at all	4 (22.2)	2 (4.9)	
Mildly bothered	6 (33.3)	14 (34.2)	
Moderately bothered	6 (33.3)	15 (36.6)	
Severely bothered	2 (11.1)	6 (14.6)	
Very severely bothered	0 (0.0)	4 (9.8)	

Over the last two weeks, how often have you been bothered by any of the following problems?

Problem	(n=23) No. (%) of non-nurses	(n=44) No. (%) of Nurses	P-Value
Little interest or pleasure in doing things	(n=18)	(n=41)	0.409
Not at all	8 (44.4)	13 (31.7)	
Several days	6 (33.3)	17 (41.5)	
More than half of the days	4 (22.2)	9 (22.0)	
Nearly everyday	0 (0.0)	2 (4.9)	
Feeling down, depressed or hopeless	(n=18)	(n=41)	0.107
Not at all	6 (33.3)	9 (22.0)	
Several days	10 (55.6)	16 (39.0)	
More than half of the days	1 (5.6)	13 (31.7)	
Nearly everyday	1 (5.6)	3 (7.3)	
Trouble falling or staying asleep, or sleeping too much	(n=18)	(n=41)	0.026
Not at all	7 (38.9)	3 (7.3)	
Several days	5 (27.8)	16 (39.0)	
More than half of the days	4 (22.2)	11 (26.8)	
Nearly everyday	2 (11.1)	11 (26.8)	
Feeling tired or having little energy	(n=18)	(n=41)	0.029
Not at all	6 (33.3)	1 (2.4)	
Several days	5 (27.8)	19 (46.3)	
More than half of the days	6 (33.3)	12 (29.3)	
Nearly everyday	1 (5.6)	9 (22.0)	
Poor appetite or overeating	(n=18)	(n=41)	0.079
Not at all	10 (55.6)	7 (17.1)	
Several days	3 (16.7)	15 (36.6)	
More than half of the days	2 (11.1)	13 (31.7)	
Nearly everyday	3 (16.7)	6 (14.6)	
Feeling bad about yourself - or that you are a failure or have let yourself or your family down	(n=18)	(n=41)	0.887
Not at all	9 (50.0)	22 (53.7)	
Several days	6 (33.3)	10 (24.4)	
More than half of the days	2 (11.1)	5 (12.2)	
Nearly everyday	1 (5.6)	4 (9.8)	
Trouble concentrating on things such as reading the newspaper or watching television	(n=18)	(n=41)	0.774
Not at all	10 (55.6)	24 (58.5)	
Several days	5 (27.8)	9 (22.0)	
More than half of the days	0 (0.0)	6 (14.6)	
Nearly everyday	3 (16.7)	2 (4.9)	
Moving or speaking so slowly that other people could have noticed? Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual	(n=18)	(n=41)	0.681
Not at all	14 (77.8)	33 (80.5)	
Several days	4 (22.2)	4 (9.8)	
More than half of the days	0 (0.0)	3 (7.3)	
Nearly everyday	0 (0.0)	1 (2.4)	
How difficult have the problems you experienced made it for you to do your work, take care of things at home, or get along with other people?	(n=15)	(n=40)	0.431
Not difficult	5 (33.3)	12 (30.0)	
Somewhat difficult	9 (60.0)	21 (52.5)	
Very difficult	1 (6.7)	5 (12.5)	
Extremely difficult	0 (0.0)	2 (5.0)	

In your opinion are the Wellness Resources being offered to you through your work helpful?

	(n=23) No. (%) of non-nurses	(n=44) No. (%) of Nurses	P-Value
Wellness resources being offered are helpful	8/17 (47.1)	7/33 (21.2)	0.059



CRITICAL CARE 2

Postoperative Acute Kidney Injury is Associated with Progression of Chronic Kidney Disease Independent of Severity

Jamie Privratsky[1], Vijay Krishnamoorthy[1], Karthik Raghunathan[2], Tetsu Ohnuma[1], Mohammed Rasouli[3], Thorir E Long[4], Martin I Sigurdsson[5]

[1]Duke University, Durham, NC, [2]Duke University School of Medicine, Durham, NC, [3]Stanford University, Palo Alto, CA, [4]Landspitali–The National University Hospital of Iceland,, Reykjavik, Iceland, [5]Duke University Hospital, Durham, NC

INTRODUCTION: Both postoperative acute kidney injury (AKI) and preoperative chronic kidney disease (CKD) are associated with significantly worse short- and long-term outcomes following surgery. The relationship of both of these conditions to each other and to CKD progression after surgery remains poorly studied impeding efforts to reduce risk. The objective of our study was to determine whether postoperative AKI is independently associated with CKD progression within one year of surgery, in groups stratified by preoperative estimated glomerular filtration rate (eGFR), and to determine if a dose-response relationship exists. We hypothesized that AKI would be dose-dependently associated with an increased risk of CKD progression within one year of surgery, which would be exacerbated by preoperative kidney dysfunction.

METHODS: Our study was a retrospective cohort study at the University Hospital in Iceland which serves about 75% of the population. Adults receiving their first major anesthetic between 2005–2018 were included in the initial cohort. Patients with end stage renal disease (ESRD); undergoing major urologic procedures; or having missing creatinine values for follow-up of GFR stage were excluded from analysis. Our primary exposure was postoperative AKI stage within 7 days after surgery classified by the kidney disease improving global outcomes (KDIGO) criteria. Our primary outcome was progression of CKD by at least one GFR category within 1-year following surgery. Multivariable Cox proportional hazards models were used to estimate hazards.

RESULTS: A total of 7499 patients were studied. Patients who experienced postoperative AKI displayed faster time to CKD progression than patients who did not develop postoperative AKI; though, there did not appear to be additional risk based on severity of AKI (Figure 1). When plotted against time, patients with GFR category > 2 (eGFR < 90ml/min per 1.73m2) displayed faster progression to higher GFR category within 1 year of surgery (Figure 2). When stratified by both AKI stage and preoperative GFR category, patients with either postoperative AKI or GFR category > 2 were both at increased risk of progression to higher stage of CKD within 1 year following surgery; however, it again should be noted that there was not a dose response based on either variable (Figure 3). In the multivariable model adjusting for relevant risk factors including preoperative GFR category, post-operative AKI stage 1 (HR 2.76, 95% CI 2.19-3.48, p<0.001), stage 2 (HR 2.58, 95% CI 1.48-4.50, p<0.001), and stage 3 (HR 4.17, 95% CI 2.27-7.64, p<0.001) were all independently associated with GFR stage progression within 1 year following surgery. There was no dose-response relationship. Preoperative GFR category was found to be a confounder as it was independently associated with postoperative CKD progression (G2 60-89 ml/min/m2 [HR 4.33, 95% CI 2.82-6.67, p<0.001], G3a 45-59 [HR 4.37, 95% CI 2.76-6.93, p<0.001], and G3b 30-44 [HR 2.61, 95% CI 1.58-4.34, p<0.001]).

CONCLUSION: The development of postoperative AKI was independently associated with CKD progression within the year following surgery irrespective of AKI severity or baseline kidney function. Further, the presence of preoperative kidney dysfunction (increased GFR category) itself poses increased risk for postoperative CKD progression. These data suggest that the adoption of kidney protective practices is necessary whenever possible.

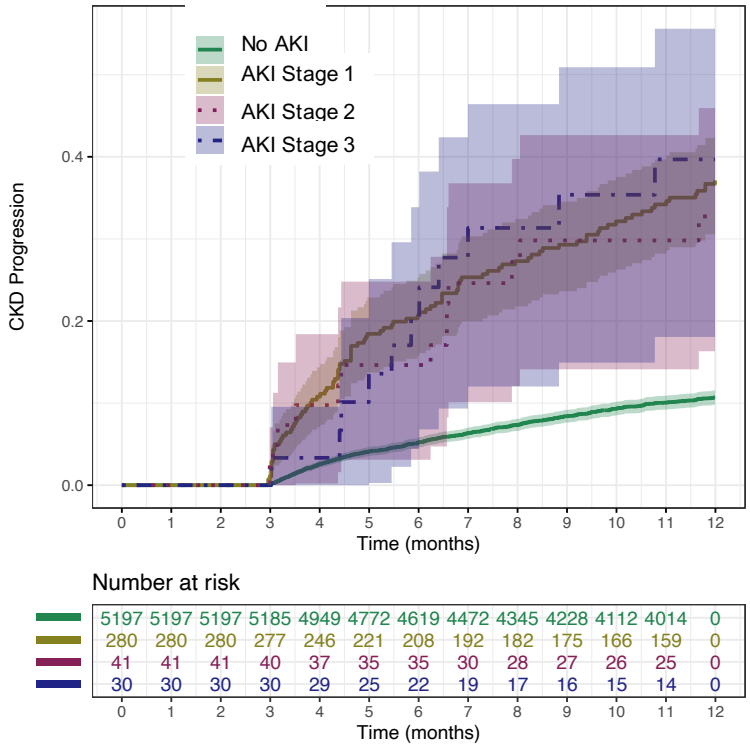


Figure 1: Unadjusted risk of GFR category after surgery versus time for patients who did or did not develop postoperative AKI. All AKI stages demonstrate increased risk of GFR category, though there is not a dose response relationship.

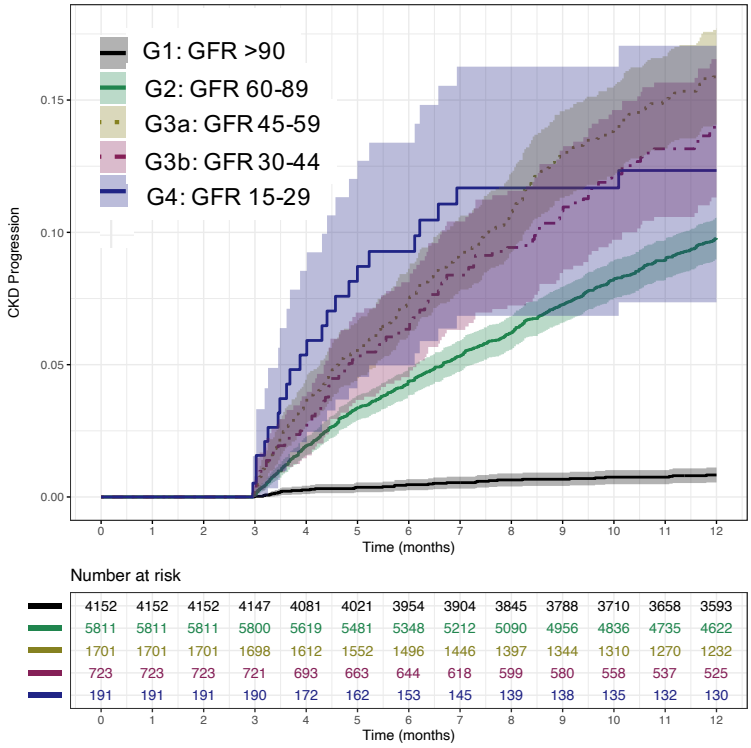


Figure 2: Unadjusted risk of GFR category after surgery versus time for GFR categories 2-4. All stages demonstrate increased risk of GFR category, though there is not a dose response relationship.

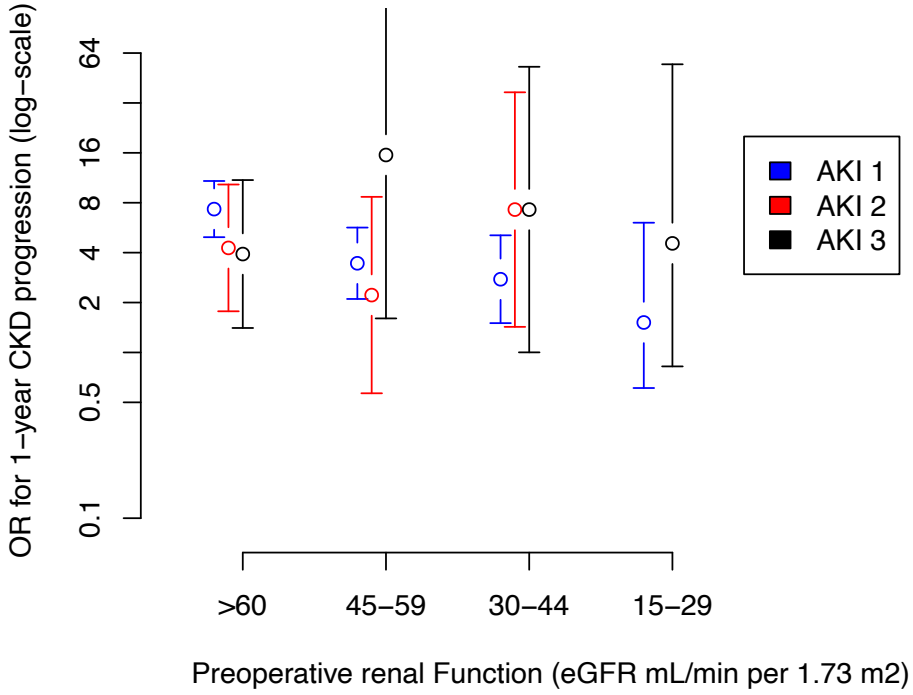


Figure 3: Unadjusted odds ratio for GFR category after surgery based on preoperative GFR category (eGFR) and postoperative AKI stage.

CRITICAL CARE 3

Initiation of SMOFLipid in Single Health System affects Hospital Length of Stay among Critically Ill Adults Requiring Total Parenteral Nutrition

Osamudiamen Obanor[1], Krista L Haines[2], Vijay Krishnamoorthy[3], David G Williams[4], Karthik Raghunathan[5], Tetsu Ohnuma[3], Paul E Wischmeyer[5]

[1]Duke University Hospital, Durham, NC, [2]Duke University, Durham, United States of America, [3]Duke University, Durham, NC, [4]Duke University Medical Center, Durham, United States of America, [5]Duke University School of Medicine, Durham, NC

INTRODUCTION: Previous research has suggested that in patients receiving parenteral nutrition (PN), the use of a balanced lipid emulsion containing Soybean oil, Medium-chain Triglycerides (MCT), Olive Oil, and Fish Oil (SMOF) may improve clinical outcomes. The Duke University Health System made a full change to SMOF in May 2017. We examined patient characteristics and length of stay in critically ill patients pre- and post- health system change from a pure soybean oil emulsion to SMOF as part of PN.

METHODS: We conducted a retrospective study using electronic health record data from 2016-2018, one year prior to the switch to SMOF (SMOFlipid) and one year following the switch to SMOF among 505 adults admitted to the Intensive Care Unit (age ≥ 18 years) patients requiring PN. Our primary exposure was SMOF (post-switch) and the comparison was Intralipid, a soybean oil based lipid emulsion (pre-switch). The outcome was hospital length of stay. We used the multivariable Poisson model to examine the association between SMOF and length of hospital stay.

RESULTS: Our patient cohorts were relatively equal with regards to demographic, clinical, and nutrition delivery characteristics. 129 (26%) patients were hospitalized pre-switch and 376 (74%) were hospitalized post-switch. Similar proportions of female patients (44% pre-switch and 40% post-switch), and similar proportions of race/ethnicities were treated pre- and post-switch. The median (IQR) body mass index was 26.8 (22.0-30.8) pre-switch and 26.7 (22.3-30.9) post-switch. More patients post-switch had diagnoses of intestinal malabsorption (9% versus 6%) and malnutrition (65% versus 57%). The median (IQR) daily total calorie delivery was higher in the post-switch group [1590 (1372.8 – 1815.6) calories pre-switch versus 1710 (1491.6 – 1908.0) calories post-switch, p=0.005]. Cumulative total calorie delivery was similar between time periods [median (IQR) 21,305 (10,126-33,436) calories pre-switch versus 19,218 (10,426-39,328) calories post- switch, p=0.68]. Compared with the pre period (Lipid), SMOF was associated with a 5% shorter LOS (0.95, 95% CI 0.92 to 0.98, p=0.0017), with a multivariable Poisson regression model.

CONCLUSION: A switch to SMOF was successfully implemented among critically ill adult patients at Duke University Health System in 2017. Despite treating patients with more nutritional co-morbidities during the time period, the switch to SMOF showed a significant decrease in hospital length of stay while patients received similar amounts of cumulative calories, potentially related to the higher daily caloric delivery seen in the post-switch group. More studies are needed but our study shows that there may be a benefit to LOS when using SMOF as part of PN.

	SMOF			
	No (pre)	Yes (post)	Total	P Value
	(N = 129)	(N = 376)	(N = 505)	
Demographics				
Female	57 (44.19%)	151 (40.16%)	208 (41.19%)	
Age at Encounter				
Median (IQR)	59.0 (47.0 – 70.0)	61.0 (48.0 – 69.0)	61.0 (48.0 – 69.0)	0.76
Race				
Black or African American	42 (32.56%)	111 (29.52%)	153 (30.30%)	0.18
Other	7 (5.43%)	41 (10.90%)	48 (9.50%)	
White/Caucasian	80 (62.02%)	224 (59.57%)	304 (60.20%)	
Hispanic	0 (0.00%)	13 (3.46%)	13 (2.57%)	
Median BMI				
Median (IQR)	26.8 (22.0 – 30.8)	26.7 (22.3 – 30.9)	26.8 (22.3 – 30.9)	0.97
LOS [days]				
Median (IQR)	34.3 (23.0 – 47.3)	29.1 (17.3 – 48.0)	30.8 (18.6 – 47.8)	0.038**
Emergency Department	41 (31.78%)	142 (37.77%)	183 (36.24%)	0.22
Comorbidities				
Malnutrition	74 (57.36%)	243 (64.63%)	317 (62.77%)	
Intestinal Malabsorption	8 (6.20%)	35 (9.31%)	43 (8.51%)	
Acute Pancreatitis	11 (8.53%)	33 (8.78%)	44 (8.71%)	
Peritonitis	26 (20.16%)	64 (17.02%)	90 (17.82%)	
Gastrointestinal fistula	2 (1.55%)	3 (0.80%)	5 (0.99%)	
Malignancy	31 (24.03%)	104 (27.66%)	135 (26.73%)	
Cirrhosis/chronic liver failure	19 (14.73%)	64 (17.02%)	83 (16.44%)	
Renal Failure	79 (61.24%)	179 (47.61%)	258 (51.09%)	
Diabetes	21 (16.28%)	65 (17.29%)	86 (17.03%)	
Pneumonia	14 (10.85%)	44 (11.70%)	58 (11.49%)	
Bacteremia/Septicemia	61 (47.29%)	179 (47.61%)	240 (47.52%)	
All Cause Infection	68 (52.71%)	200 (53.19%)	268 (53.07%)	
TPN Data				
Total Days On TPN				
Median (IQR)	12.0 (6.0 – 19.0)	11.0 (6.0 – 21.0)	11.0 (6.0 – 21.0)	0.97
Total Days receiving Lipids: Median				
Median (IQR)	9.0 (6.0 – 14.0)	10.0 (5.0 – 19.0)	10.0 (5.0 – 17.0)	0.46
Calorie Summary Data				0.37
Median Daily Protein Based Calories				
Median (IQR)	452.4 (385.2 – 514.8)	475.2 (399.6 – 550.8)	475.2 (396.0 – 540.0)	0.13
Cumulative Protein Based calories				
Median (IQR)	5446.8 (2952.0 – 9558.0)	5401.2 (2908.8 – 10786.8)	5424.0 (2914.8 – 10641.8)	0.61
Median Daily Lipid Based Calories				
Median (IQR)	504.0 (496.8 – 504.0)	504.0 (499.2 – 504.0)	504.0 (499.2 – 504.0)	0.11
Cumulative Lipid Calories				
Median (IQR)	4550.4 (3019.2 – 7083.6)	5028.0 (2520.0 – 9777.6)	5012.8 (2520.0 – 8585.4)	0.23
Median Daily Dextrose Based Calories				
Median (IQR)	742.8 (595.0 – 936.0)	842.4 (676.8 – 939.0)	833.1 (672.0 – 937.8)	0.11
Cumulative Dextrose Calories				
Median (IQR)	10202.4 (4194.0 – 15774.0)	8666.4 (4550.4 – 18230.4)	9045.4 (4469.9 – 17398.1)	0.91
Median Daily Total Calories				
Median (IQR)	1590.0 (1372.8 – 1815.6)	1710.0 (1491.6 – 1908.0)	1692.0 (1449.9 – 1887.6)	0.005**
Cumulative Total Calories				
Median (IQR)	21304.8 (10125.6 – 33435.6)	19218.8 (10425.6 – 39327.6)	19545.8 (10329.0 – 37358.3)	0.68

CRITICAL CARE 4

Canadian Emergency Medicine and Critical Care Physician Perspectives on Pandemic Triage in COVID-19

Blair Bigham[1], Ali Mulla[2], Michael Christian[3]

[1]Stanford U, Palo Alto, CA, [2]McMaster U, Hamilton, Ontario, [3]Barts Health Trust, London, United Kingdom

INTRODUCTION: Local and regional policies to guide the allocation of scarce ritical care resources have been developed, but the views of prospective users are not understood. We sought to investigate the perspectives of Canadian acute care physicians towards triaging scarce critical care resources in the COVID-19 pandemic.

METHODS: We rapidly deployed a brief survey to Canadian emergency and critical care physicians in April 2020 to investigate current attitudes towards triaging scarce critical care resources and identify subsequent areas for improvement. Descriptive and between-group analyses along with thematic coding were used.

RESULTS: The survey was completed by 261 acute care physicians. Feelings of anxiety related to the pandemic were common (65%), as well as fears of psychological distress if required to triage scarce resources (77%). Only 49% of respondents felt confident in making resource allocation decisions. Both critical care and emergency physicians favored multidisciplinary teams over single physicians to allocate scarce critical care resources. Critical care physicians were supportive of decision making by teams not involved in patient care (3.4/5 vs 2.9/5 p=0.04), whereas emergency physicians preferred to maintain their involvement in such decisions (3.4/5 vs 4.0/5 p=0.007). Free text responses identified five themes for subsequent action including the need for further guidance on existing triage policies, ethical support in decision making, medico-legal protection, additional tools for therapeutic communications, and healthcare provider psychological support.

CONCLUSION: There is an urgent need for collaboration between policymakers and frontline physicians to develop critical care resource triage policies that wholly consider the diversity of provider perspectives across practice environments.

CRITICAL CARE 5

Association between Cerebral Autoregulation as Estimated by Diffuse Correlation Spectroscopy and Neurologic Injury among Children on Extracorporeal Life Support

Ethan L Sanford[1], Isabel Miller[2], Rufai Akorede[3], Giezi Contreras[4], Michael C Morris[1], Lakshmi Raman[3], David Busch[5]

[1]UTSouthwestern Medical Center, DALLAS, TX, [2]UTSouthwestern, DALLAS, TX, [3]UT Southwestern Medical Center, DALLAS, TX, [4]University of Chicago, Chicago, IL, [5]University of Texas Southwestern, Dallas, TX

INTRODUCTION: Extracorporeal Life Support (ECLS) is used in extreme physiologic shock states to support cardiopulmonary function and augment oxygen delivery. ECLS alters hemodynamics at the macro and micro circulatory levels and requires systemic anti-coagulation which may contribute to the risk of neurologic injury which occurs in ~13% of children. As post-ECMO neurological imaging is not widespread,[1] this neuroinjury incidence is likely much higher (45-62%), as suggested by retrospective studies.[2,3] Current neurologic monitoring modalities (NIRs, clinical exam) are not able to accurately determine risk or occurrence of neurologic injury. Imaging confirmation of injury with MRI, CT, or transcranial doppler are limited to single timepoint measurements, require advanced training to interpret, and are often not feasible during ECLS. Diffuse correlation spectroscopy (DCS) is a recently developed interferometric optical technique capable of dynamic measurement of microvascular regional cerebral blood flow through application of a simple, small light source and detector applied to the forehead. The correlation between DCS-measured cerebral blood flow and mean arterial pressure has been utilized as an autoregulatory index termed DCSx. Elevated DCSx measurement indicate disrupted cerebral autoregulation. We hypothesized disruption of cerebral autoregulation as indicated by increased DCSx is associated with neurologic injury among children on ECLS.

METHODS: After obtaining IRB approval, we conducted a prospective cohort study of children under 18 years old on ECLS to assess the relationship between DCSx and neurologic injury. After obtaining consent, DCS measurement of regional cerebral blood flow data old was collected for a minimum of 1 hour daily unless precluded by clinical complexity, staff concerns, or parental request. Each unilateral (right or left sided) application of DCS was assessed as an independent measurement. DCSx was determined from Pearson correlation of cerebral blood flow and mean arterial blood pressure as previously described.5 Clinical vital signs including mean blood pressures measured by arterial line were recorded using medicollector data acquisition software. All relevant laboratory, ventilator, and type of ECLS were recorded. Head imaging including head US, head CT, and brain MRI were assessed by a blinded neuroradiologist to determine previously established pediatric neuroinjury scoring.[4,5] The association between all DCSx measurements and neurologic injury was established through Spearman correlation. Spearmen correlation for the highest DCSx measurement and neurologic injury score was also calculated. Neuroimaging scores were dichotomized at a value of 10 as scores of 10 or greater signify more severe injury. DCSx was dichotomized at 0.5 as DCSx greater than 0.5 has been associated with cerebral dysregulation.[6,7] Logistic regression defined the odds ratio for significant neurologic injury for patients with DCSx measures greater than 0.5.

RESULTS: DCS data for 20 patients were collected. Imaging data were not available for 3 patients and there were incomplete clinical or DCS data for another 3 patients. Among the 14 patients included for analysis, 55 distinct DCS measurement episodes occurred. Descriptive statistics for baseline characteristics were calculated (Table 1). The Spearman correlation coefficient between all DCSx measures and neurologic injury was 0.55, $P<0.001$ (Figure 1). The Spearmen correlation for the highest DCSx measures for each patient and neurologic injury was 0.46, $P=0.15$. There was a significant difference in the odds of severe neurlogic injury for patients with a DCSx measurement greater than 0.5 (OR 13, 95% CI 2.66-63.6, $P=0.002$).

CONCLUSION: We identify a significant association between disruption in cerebral autoregulation measured by DCSx and neurologic injury. The odds of severe injury was higher for those patients with a DCSx measure>0.5. These results should be interpreted with caution as measures are limited to 1-hour time frame among relatively few patients. Our results may also be skewed by discrepancies in the number of measurements taken in individual patients. Despite limitations, these data suggest that dynamic measurement of DCSx may lead to earlier recognition of risk or occurrence of neurologic injury which could prompt changes in clinical management to ameliorate neurologic injury.

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Table 1: Baseline Characteristics

CHARACTERISTIC	N=14 (%)
SEX	
MALE	8 (55.6)
FEMALE	6 (44.4)
AGE	2 (1.25,10)[a]
WEIGHT	11.6 (10.0, 56.5)[a]
ECPR OR CPR PRIOR TO ECMO	
YES	6 (44.4)
NO	8 (55.6)
ECMO CANNULATION	
VV	1 (11.1)
VA	13 (88.9)
MORTALITY WITHIN STUDY TIME FRAME	
YES	5 (38.9)
NO	9 (61.1)
HIGHEST LACTIC ACID	6.6 (3.7,10.1)
MEAN XA LEVEL	0.33 (95% CI 0.24-0.43)
HIGHEST OI	24.9 (95% CI 16.5-33.3)
IMAGING NEUROINJURY SCORE	7 (3,13)[a]

[a] Median values with interquartile ranges

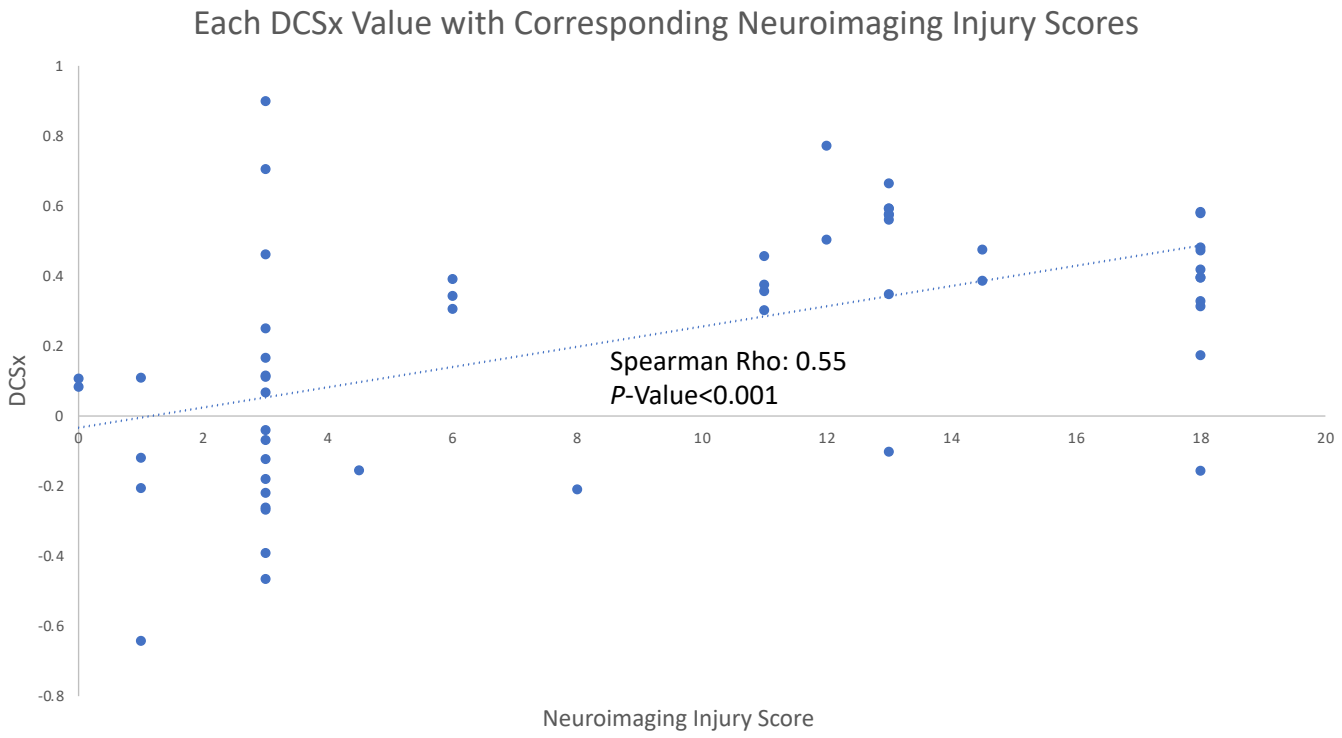

Fig. 1

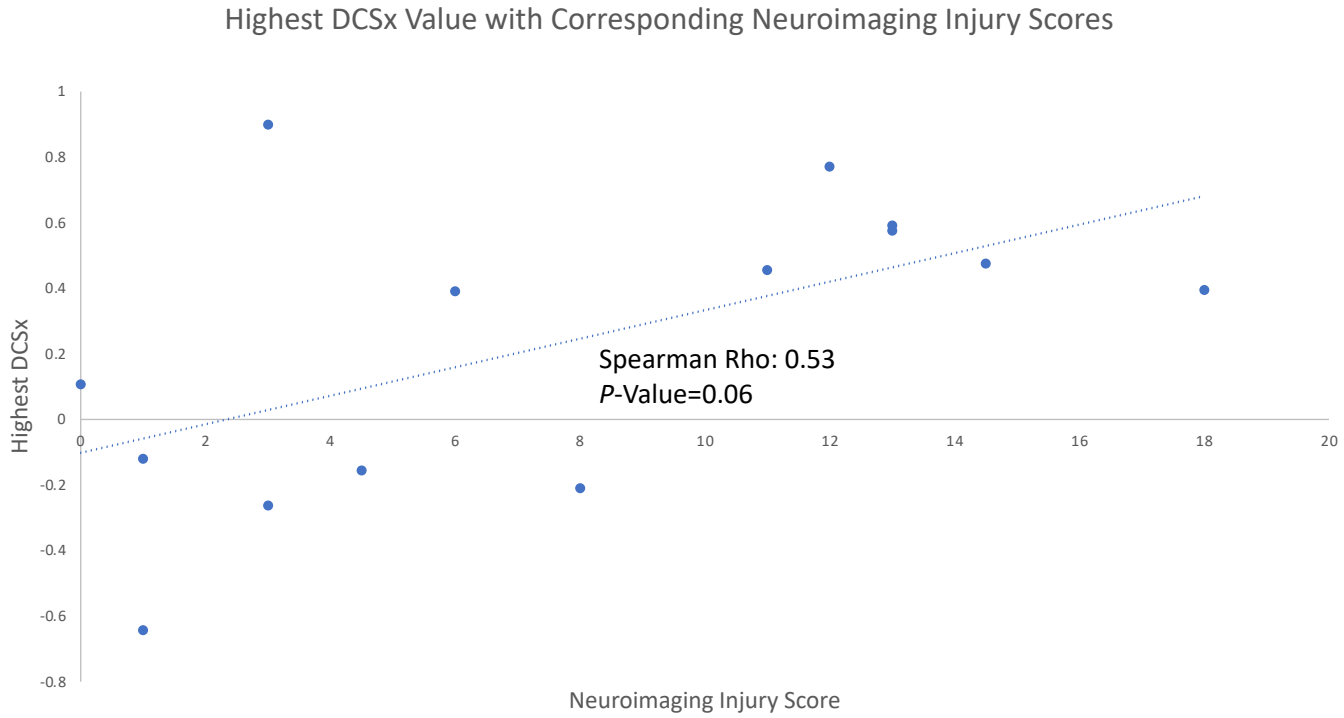

Fig. 2

CRITICAL CARE 6

Pressure Support Ventilation in COVID-19 Patients

Tammar Al-Ani[1], Euan Black[1], Robert Docking[1], Chris Wright[1]

[1]NHS Greater Glasgow and Clyde, Glasgow, United Kingdom

INTRODUCTION: Vigorous spontaneous inspiratory efforts during mechanical ventilation can result in patient self-inflected lung injury and diaphragm injury[1]. We studied the characteristics and the effects of the duration of Pressure Support Ventilation (PS) on COVID19 patients.

METHODS: We performed retrospective analysis of twenty-two ventilated patients with confirmed COVID-19 between March and April 2020. The total hours of PS during ICU stay was recorded, excluding PS episodes that led to patient extubation or tracheostomy insertion. For each PS episode the following data were collected: (A) Timeline from the start of COVID-19 respiratory symptoms to the initiation of PS after intubation and ventilation, (B) PaO2/FiO2 ratio at the start and end of PS, (C) Respiratory rate, (D) Tidal volume, (E) Minute ventilation, (F) Pressure support, (G) PEEP and, (H) Peak airway pressure. Using correlation statistical analysis we measured the correlation between total hours PS versus five outcomes (1) Length on ventilator (days), (2) Total paralysis hours, (3) Total proning hours, (4) The need for tracheostomy and, (5) ICU mortality.

RESULTS: (A) COVID-19 symptoms to first PS: 7-14 days for 27% and >14 days for 73% patients (B) PaO2/FiO2 (P/F) ratio: Mean of medians start P/F ratio of 21.5 and end P/F ratio of 14.1 (C) Respiratory rate: Mean of medians 22 cycles/min (D) Tidal volume: Mean of medians 613 mL (E) Minute ventilation: Mean of medians 13.2 L/min (F) Pressure support: Mean of medians 7.9 cmH2O (G) PEEP: Mean of medians 11.3 cmH2O and, (H) Peak airway pressure: Mean of medians 19.8 cmH2O. (1) Duration of PS vs. length on the ventilator: Positive correlation of 0.47 (2) Duration of PS vs. total paralysis hours: Negative correlation of 0.12 (3) Duration of PS vs. total proning hours: Negative correlation of 0.17 (4) Duration of PS vs. the need for tracheostomy: Positive correlation of 0.359 and, (5) Duration of PS vs. ICU mortality: Positive correlation of 0.151.

CONCLUSION: Longer duration of PS is associated with increased length on ventilator and the need for tracheostomy with a weak positive correlation with ICU mortality. High minute ventilation could be injurious to the lungs and this may be reflected in the deterioration of P/F ratio at the end of each PS episode even in patients who were switched to PS two weeks after the start of COVID-19 respiratory symptoms.

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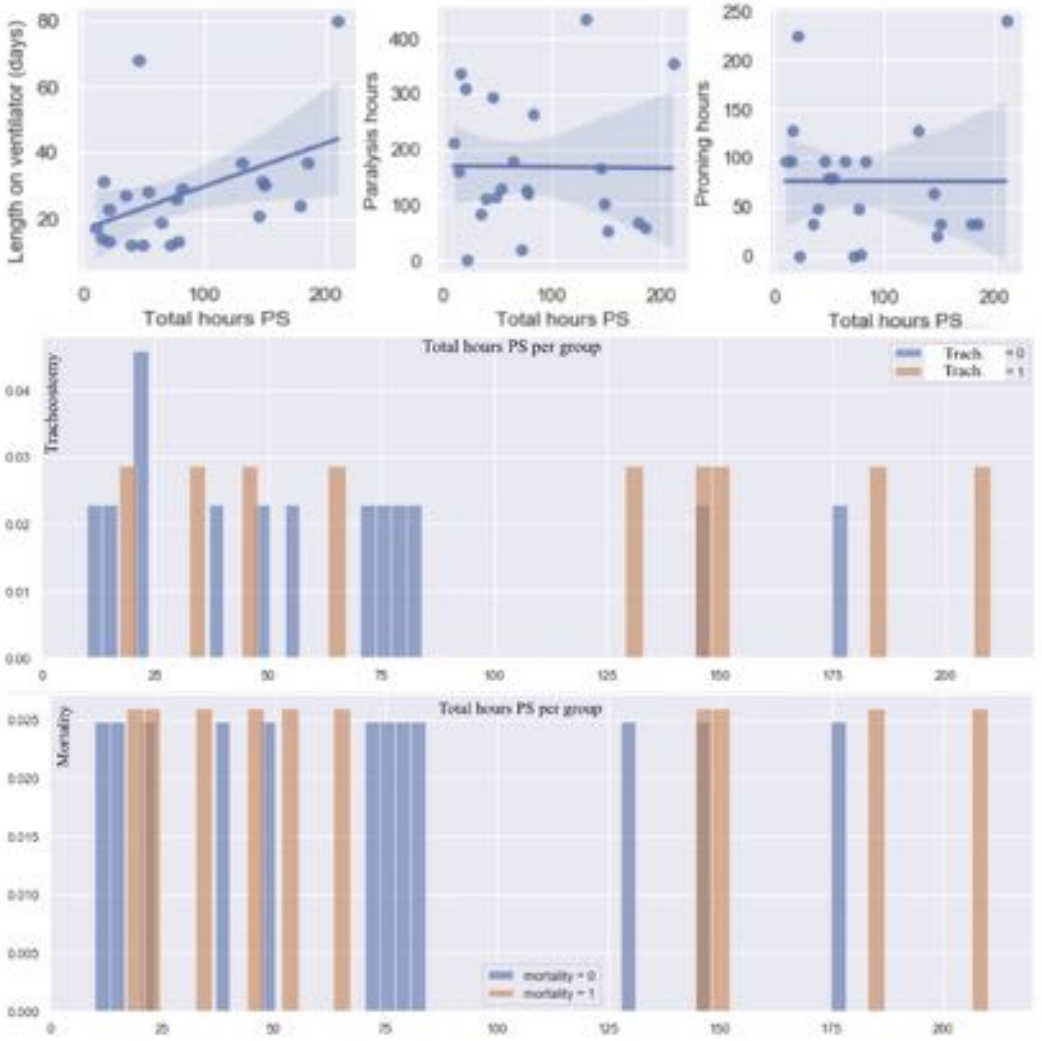

CRITICAL CARE 7

Concomitant Administration of Dantrolene and Nimodipine Significantly Improves Cerebral Blood Flow Perfusion in a Rat Model of Cerebral-Induced Vasospasm

Marie Roman[1], Javier Morales[1], Henrique Martins[1], Yancy Ferrer[2], Maria J Crespo[3]

[1]University of Puerto Rico-School of Medicine, San Juan, Puerto Rico, [2]Universidad Central del Caribe-School of Medicine, San Juan, Puerto Rico, [3]Univeristy of Puerto Rico-School of Medicine, San Juan, Puerto Rico

INTRODUCTION: A cerebral vasospasm (CVSP) is a potent vasoconstriction of the cerebral vasculature, and the primary cause of morbidity and mortality following a hemorrhagic stroke. The middle cerebral artery (MCA) is one of the most common vessels affected by CVSPs. Experimental evidence shows that concomitant administration of dantrolene (a ryanodine receptor blocker) and nimodipine (a Ca+2 channel blocker) has synergistic effects in reducing vasospasms in aortic rings from Sprague Dawley rats.

METHODS: To determine if the effects observed in the systemic vasculature extend to the cerebral circulation, we investigated the effect of intravenous administration of dantrolene (2.5 mg/kg) and nimodipine (1 mg/kg and 2 mg/kg) on MCA blood flow velocity (BFV). Using a PeriFlux 5000 Laser Doppler System, we measured BFV before and after administration of the drugs 7 days after induction of cerebral vasospasms in Sprague Dawley rats. A reduction in blood flow velocity indicates that vascular reactivity decreases and blood perfusion increases. Mean blood pressure (MBP) and heart rate (HR) were also measured.

RESULTS: Individual administration of these drugs resulted in similar reductions in BFV (34% with dantrolene, n=6, $p<0.05$; 32% with nimodipine 2 mg/kg, n=6, $p<0.05$). Moreover, dantrolene combined with 1mg/kg of nimodipine decreased BFW by 48% (from 435.70 ± 21.50 to 284.30 ± 26.10 perfusion units, n=6, $p<0.05$). Similarly, dantrolene combined with 2 mg/kg of nimodipine, reduced BFW by 54% (from 536.00 ± 32.60 to 367.80 ± 40.90 perfusion units, n=6, $p<0.05$). Although when combined with 2 mg/kg of nimodipine, dantrolene significantly increases HR, the combination of dantrolene and 1mg/kg of nimodipine, did not alter MBP or HR.

CONCLUSION: Thus, our results indicate that concurrent administration of 2.5 mg/kg dantrolene and 1 mg/kg nimodipine significantly reduce BFV in the MCA without altering systemic hemodynamic parameters. By reducing vascular reactivity synergistically, these drugs may improve cerebral blood perfusion. Therefore, adding dantrolene to current standard pharmacological therapies with calcium channel blockers (CCB) may allow a dosage reduction of CCB and minimize the systemic secondary effects of these drugs. Furthermore, if our findings with rats are applicable to humans, the combined use of dantrolene and nimodipine at optimal doses may be effective in reducing CVSPs. This work was supported by Grants from the National Institute of Health (MBRS-RISE Grant R25GM061838), the NIMHD-CCRHD-RCMI Program (U54-MD007600), and the Anesthesiology Department of the University of Puerto Rico-School of Medicine.

CRITICAL CARE 8

Incidence of Atrial Fibrillation in Single vs Bilateral Lung Transplantation Patients

Natan Hekmatjah[1], Michael Zargari[1], Tristan Grogan[1], Sumit Singh[1]

[1]Department of Anesthesiology & Perioperative Medicine, University of California, Los Angeles, Los Angeles, CA

INTRODUCTION: Lung transplantation (LTx) is an important treatment option for patients with end-stage lung diseases such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis (IPF). Though LTx improves patient outcomes, the most frequent complications, such as infection and acute rejection, contribute to increased mortality in the immediate postoperative period[1]. LTx has also been associated with the development of atrial fibrillation (AF)[2], however, the relationship between LTx type and AF development postoperatively has been understudied. In this preliminary study, we assessed the incidence of AF development in unilateral and bilateral LTx patients.

METHODS: A retrospective chart review was conducted on adult patients (≥18 years old) who underwent right, left, or bilateral LTx between April 2013 and June 2018 at our home institution. The outcome variables measured were the type of LTx (right, left, or bilateral) and whether or not the patient developed AF postoperatively during their hospital stay before discharge or death. The incidence of AF was compared between LTx type using the chi-squared test.

RESULTS: A total of 431 patients that underwent right, left, or bilateral LTx were screened. Of those patients, 113 (26.2%) were diagnosed with AF. Left LTx had AF incidence of 30.1%, right LTx of 33.3%, and bilateral LTx of 22.5% (p=0.103) (Table 1). Results did not show a significant difference in the incidence of AF development between left vs right LTx (30.1% vs 33.3%, p=0.646). Incidence of AF development was lower in bilateral vs left LTx (22.5% vs 30.1%, p=0.133) and bilateral vs right LTx (22.5% vs 33.3%, p=0.058), indicating a trend in AF development in regard to LTx type. However, in comparing bilateral vs single (right and left) LTx, we found a statistically significant reduction in the incidence of AF development (22.5% vs 31.5%, p=0.038).

CONCLUSION: Preliminary data analysis showed a decreased incidence of AF in bilateral vs unilateral LTx. Haissaguerre et al. identify the critical role pulmonary veins play in the development of AF[3]. LTx involves the Cox Maze ('cut and sew') procedure in order to achieve pulmonary vein electrical isolation. This has been shown to mitigate AF in four vein (bilateral LTx) but not two vein (unilateral LTx) pulmonary isolation. Although the exact mechanism is not certain, the lower incidence of AF in bilateral LTx may be attributed to the prevention of pulmonary vein reconnection[2]. Known risk factors for AF include older age, IPF, coronary disease, enlarged left atrium, and use of postoperative vasopressors[4]. Though our study did not take into account these risk factors, future studies should control for them in order to help elucidate the relationship between AF and LTx type. A comprehensive understanding of the underlying mechanisms leading to AF development with respect to LTx type can help improve patient postoperative outcomes.

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Table 1: Incidence of Atrial Fibrillation Development by Lung Transplantation Type

		Left LTx	Right LTx	Bilateral LTx
AF Development	No	72 (69.9%)	50 (66.7%)	196 (77.5%)
	Yes	31 (30.1%)	25 (33.3%)	57 (22.5%)

CRITICAL CARE 9

Intestinal Macrophages Incorporate Microbiome Signals to Promote Wound Healing

Jim Castellanos[1]

[1]*Weill Cornell Medical College, New York, NY*

INTRODUCTION: Inflammatory bowel disease (IBD) results from a dysregulated interaction between the microbiota and a genetically susceptible host. Genetic studies have linked TNFSF15 polymorphisms and its protein TNF-like ligand 1A (TL1A) with IBD, but the functional role of TL1A in linking tissue homeostasis and intestinal inflammation is not known. Here, using cell-specific genetic deletion models, we show an essential role for the gut microbiome in directing intestinal macrophages to promote wound healing at the intestinal epithelium via TL1A.

METHODS: Mice. C57BL/6, Itgax-cre, Rorc-cre, OT-II, Il1r-/-, Cx3cr1-GFP, Cx3cr1-CreER mice were purchased from The Jackson Laboratory. All mouse models were on C57BL/6 background. CX3CR1-DTR mice (Longman et al., 2014) were previously described. Il23rGFP mice were obtained from M. Oukka (Awasthi et al., 2009). Myd88-/- were obtained from J. Blander. MHCII–ILC3 mice were obtained from G. Sonnenberg (Hepworth et al., 2015). Tnfsf4flox were provided by T. Vyse and M. Botto (Cortini et al., 2017). Tnfrsf25-/- mice were obtained from Cancer Research UK (Wang et al., 2001). Generation of Tnfrsf25flox/flox mice is previously described (Shih et al., 2014). Tnfsf15flox/flox mice were generated at Cedars-Sinai by D. Shih and S. Targan. All experiments were performed with 6-8 week old littermates. Male and female mice were used with random and equal assignment of same sex to each experimental group. All vertebrate work was approved by the IACUC at Weill Cornell Medicine. Human IBD subjects. Endoscopic biopsies were obtained under an Institutional Review Board–approved protocol (1103011578) and informed consent was obtained at Weill Cornell Medicine (WCM) including patients >18 years of age. Active inflammation was defined by an endoscopic score of >2 and inactive disease was defined by an endoscopic score of 0. The age and gender of subjects included are as follows: Healthy controls-22, 38, 53, 55, 71, 72, 79 year old males and 36 year old female; Crohn's inactive-30, 52, and 57 year old males; Crohn's active-32, 36 year old males and 27, 44, 55, 55, 62, and 68 year old females. Statistical analysis. Statistical analysis was performed in GraphPad Prism or R software. Results represent mean ± s.e.m. and were analyzed by unpaired Student's t-test, Mann-Whitney test, one-way ANOVA, Log-rank (Mantel-Cox) test. Given that mouse experiments required littermate controls and complex genotyping, experimental group allocation was not blinded. No relevant exclusion criteria were applied.

RESULTS: Using cell-specific genetic deletion models, we report an essential role for CX3CR1+ mononuclear phagocyte (MNP) TL1A in signaling through its cognate receptor death receptor 3 (DR3) on group 3 innate lymphoid cell (ILC3) to promote IL-22-dependent protection during acute colitis. Induction of intestinal MNP TL1A by IBD-associated adherent microbes confers TL1A-dependent protection from acute colitis. However, in contrast to this protective role in acute colitis, colitis-induced DR3-dependent expression of OX40L enables MHCII+ ILC3 to co-stimulate antigen-specific T cell proliferation and exacerbate chronic T cell-dependent colitis. Colonic biopsies from IBD patients revealed increased TL1A expression on MNPs and OX40L on ILC3 compared to healthy controls, highlighting the conserved TL1A-OX40L ILC3 axis in IBD. These results identify the mechanistic contributions of this IBD-linked pathway as a central regulator of ILC3 function in tissue homeostasis and wound healing.

CONCLUSION: Here we show a protective role for microbial induction of the IBD-linked protein TL1A in promoting ILC3-driven wound healing and uncover a pathogenic role for TL1A-induced expression of OX40L on ILC3s in driving chronic T cell colitis. A more thorough understanding of TL1A and group 3 innate lymphoid cell biology will lead to novel therapeutic approaches to wound healing in IBD and the preoperative environment.

CRITICAL CARE 10

Prone Positioning is Associated with Improved Intensive Care Unit Survival Among Critically Ill Obese Patients with COVID-19

Nicholas Rizer[1], Blake Mergler[1], Benjamin Smood[1], Alexandra Sperry[1], Federico Sertic[1], Andrew Acker[1], Christian Bermudez[1], Jacob Gutsche[1], Asad A Usman[1]

[1]University of Pennsylvania, Philadelphia, PA

INTRODUCTION: The use of prone positioning has been widely reported in patients with coronavirus disease 2019 (COVID-19).[1] While prone positioning has been shown to have mortality benefit in patients with acute respiratory distress syndrome (ARDS), its specific benefit in obese patients is less clear.[2] For obese patients with ARDS, supine positioning has been shown to be particularly detrimental to respiratory status; however, there is also concern that prone positioning can lead to hepatic and renal derangements.[3–7] Here we present a retrospective cohort study among critically ill COVID-19 patients who received prone positioning in order to compare intensive care unit (ICU) mortality between obese and non-obese cohorts.

METHODS: We designed a retrospective cohort study of all patients admitted to our center's ICU from 3/9/2020 to 4/19/2020 and underwent prone positioning. Patients were divided into two cohorts: body mass index (BMI) ≥ 30 kg/m2 and < 30 kg/m2. Cohorts were compared on survival to ICU discharge, secondary outcomes, demographic and clinical features. Univariate logistic regression was performed on pre-specified demographic features to test their association with survival at ICU discharge. Any variables with statistically significant associations with ICU survival were planned to be included in a multivariate logistic regression analysis. Data was manually extracted from the electronic medical record at our center by a trained team of physicians and researchers using a protocolized Case Record Form developed by the COVID-19 Critical Care Consortium and International Severe Acute Respiratory and Emerging Infection Consortium (CCCC/ISARIC) previously published elsewhere.[8]

RESULTS: Demographic characteristics and initial vital signs for our patients are presented in Table 1. No significant demographic differences, aside from BMI, were noted between groups. There was no significant difference observed in the frequency of severe ARDS or SOFA scores among cohorts. Primary and secondary outcomes for patients with and without obesity are presented in Table 2. Proned obese patients were more likely to survive to ICU discharge than their non-obese counterparts (79% vs 33%, p = 0.03). ICU length of stay, duration of mechanical ventilation, time to initial proning, and duration of proning were similar between both groups. Univariate logistic regressions were performed on a set of pre-specified variables to test their association with survival to ICU discharge. The only covariates with a significant association were obesity (OR = 7.5, p = 0.03) and age (OR = 0.91, p = 0.03). Multivariate logistic regression revealed a significant mortality association with age (OR = 0.91, p = 0.04) and a trend towards survival among patients with obesity (OR = 8.5, p = 0.06).

CONCLUSION: Among patients who were proned for COVID-19 ARDS, obese patients were more than twice as likely to survive than non-obese patients, despite similar cohort composition and severity of illness. Improved survival among patients with obesity is concordant with prior non-COVID-19 literature suggesting unique detrimental effects with supine positioning in obese patients.[3,5] Proning is thought to be particularly effective in obese patients, given the substantial compressive effects of body habitus on the lung in obese patients.[9] Prior work has shown proning to improve ventilation in obese COVID-19 patients, however our study is the first to show a mortality beneifit to our knowledge.[10] Taken together with our work, proning may offer substantial therapeutic benefit in COVID-19 patients with obesity.

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	Obese	Non-obese	p-value
Total (n)	19	9	
BMI (kg/m^2)[a]	38.8 (32.9 – 52.4)	26.4 (21.6 – 27.7)	$1.6x10^{-4}$
Age (years)	63 (47 – 68)	74 (52 – 75)	0.32
Sex			
Male (n)	10	5	1.0
Female (n)	9	4	-
Self-Reported Race			
White (n)	7	3	1.0
Black (n)	10	4	-
Asian (n)	0	2	-
Other (n)	2	0	-
Chronic Cardiac Disease[a] (n)	8	1	0.20
Hypertension[a] (n)	16	6	0.35
Chronic Pulmonary Disease (Not Asthma)[a] (n)	11	4	0.69
Asthma [a] (n)	5	2	1.0
Chronic Kidney Disease [a] (n)	3	1	1.0
Temperature (°F)[a]	99.7 (99.0 – 101.3)	100.5 (98.3 – 102.0)	0.58
Mean Arterial Pressure (mmHg)[a]	99.7 (89.7 – 117.3)	92.3 (76.0 – 108.0)	0.89
Heart Rate (min^{-1})[a]	106.0 (92.0 – 110.5)	93.0 89.0 – 117.0)	0.91
Respiratory Rate (min^{-1})[a]	28.0 (23.0 – 33.5)	32.0 (21.0 -36.0)	0.63
Pulse Oxygen Saturation (%)[a]	86.0 (75.0 – 92.0)	88.0 (83.0 – 93.0)	0.92
Severe ARDS (n)	16 (84%)	7 (78%)	1.0
SOFA Score[b]	9.0 (7.3 – 10.0)	6.0 (6.0 – 8.0)	0.24

Table 1: Demographic and Clinical Signs for Patients With and Without Obesity.

BMI : Body mass index. ARDS: Acute Respiratory Distress Syndrome. SOFA: Sequential Organ Failure Assessment. [a] - Data recorded at first presentation to facility. [b] – Data recorded at admission to ICU.

	Obese (n=19)	Non-obese(n=9)	
Survival to ICU Discharge	15 (79%)	3 (33%)	0.03
Length of ICU Stay (days)	30 (22 -44)	38 (20 – 46)	0.50
Duration of Mechanical Ventilation (days)	26 (17.5 – 42.0)	32 (20 -44)	0.46
Time to Proning From ICU Admission (days)	1 (0 – 6)	3 (0 – 6)	0.24
Duration of Proning (days)	4 (2 – 5)	4 (2 – 6)	0.29
Use of ECMO	0 (0%)	1 (11%)	0.32
Use of vasopressors or inotropes	19 (100%)	9 (100%)	1.0

Table 2: Mortality and Secondary Outcomes in Patients With and Without Obesity.

ICU : Intensive care unit. ECMO : Extra-corporeal membrane oxygenation.

CRITICAL CARE 11

Effectiveness of a Just in Time Educational Course Blending Remote Asynchronous Standardized Video Didactics and Live Simulation Scenario on Mechanical Ventilation for Non-Intensivist Training (VENT)

Brooke Albright-Trainer[1], Paul Miller[2], James Lavelle[3], Jonathan Nguyen[4], Jessica Feinleib[5]

[1]University of Virginia, Charlottesville, VA, [2]Veterans Health Administration, Orlando, FL, [3]VA Eastern Colorado Health Care System, Aurora , CO, [4]Central Virginia VA Health Care System, Richmond, VA, [5]Yale School of Medicine, New Haven, CT

INTRODUCTION: In anticipation of predicted ICU surges[1], the Veterans Health Administration sought novel methods of providing training for Non-Intensivists to better prepare them for managing critical patients with Acute Respiratory Distress Syndrome (ARDS)[2] requiring mechanical ventilation utilizing current evidence-based best practices[3,4]. As multiple studies demonstrate the efficacy of simulation-based mechanical ventilation education[5], a standardized video didactic, cognitive aids (Fig 5), and live simulation scenario were developed to meet social distancing requirements and reduce travel. To evaluate this educational product, we designed and conducted a pilot study.

METHODS: A multi-center prospective cohort study was designed to evaluate three outcomes of the VENT course: 1) feasibility; 2) educational effectiveness; and 3) clinical relevance. Multidisciplinary Non-Intensivists with varying levels of experience managing ventilators from high acuity hospital centers were recruited over three months. If study participants failed to complete any portion of the course curriculum and/or assessment tools they were eliminated from the analysis.The feasibility of the study was assessed at two study sites utilizing similar faculty and high-fidelity patient simulators. Each participant received the same video lecture, simulation scenario, and assessment tools at similar time intervals. The only difference between the sites was the type of advanced lung simulator and ICU ventilator used. The educational effectiveness was assessed by testing participants' baseline knowledge of mechanical ventilation concepts and management goals for ARDS and comparing it to an identical post course exam. Clinical relevance of the course was assessed using a Kirkpatrick's level 1 and 2 survey.[6] Analysis between individual cohorts as well as between learners with varying experience in managing ventilators was performed using a univariate and multivariate statistical analysis of variance.

RESULTS: Of thirty participants, twenty-six completed the study and were included in the analysis. (Fig 1) Outcome #1: Feasibility The pilot study revealed that advanced mechanical ventilation scenarios, including breath stacking and/or Auto-PEEP, were difficult to reliably reproduce with the QuickLung® simulator but was reliably reproduced with the IngMar ASL 5000™ lung simulator. Sixty-five percent of participants reported completing the video lecture in first sitting and most (92%) completed the entire video. All participants completed the live simulation scenario within one week of viewing the video and within 4 +/- 3 days from completion of the Pre-Test. On average, the Post-Test and Level 1-2 survey were completed 3 to 5 (+/- 7) days from the date of simulation performance. Outcome #2: Educational Effectiveness Despite the learners' difference in experience managing ventilators, all cohorts scored similarly on the post-test (76-78%). (Fig 2) Pre- to post-test scores improved (16%) in all cohorts. First and second-year residents improved the most (26 +/- 17%), followed by ICU Nurse Practitioners (23 +/- 17%). (Fig 3) Outcome #3: Clinical Relevance and Appropriateness All participants found the course relevant to their level of clinical training. Most participants found the video lecture (91%) and simulation scenario (100%) engaging. Although all participants believed they could apply the techniques and principles to their clinical practice, only 26% of participants strongly agreed they fully understood the materials and techniques after completing the entire course. Overall, 91% of participants believed that the training would enhance their ability to perform their clinical duties. (Fig 4)

CONCLUSION: VENT course pilot data supports that remote asynchronous standardized video education paired with face-to-face high-fidelity simulation is feasible, educationally effective, and relevant. VENT is useful just-in-time training for a wide range of Non-Intensivist healthcare providers prior to entrance into critical care environments. Even the most experienced providers find this program useful in reviewing evidence-based best practices for managing complex and challenging concepts associated with mechanical ventilation of patients with ARDS. Though educationally effective, VENT learners reported not fully grasping some concepts and post-tests revealed persistent knowledge gaps. Therefore, authors strongly recommend ICU Physician supervision of all VENT-trained Non-Intensivists.

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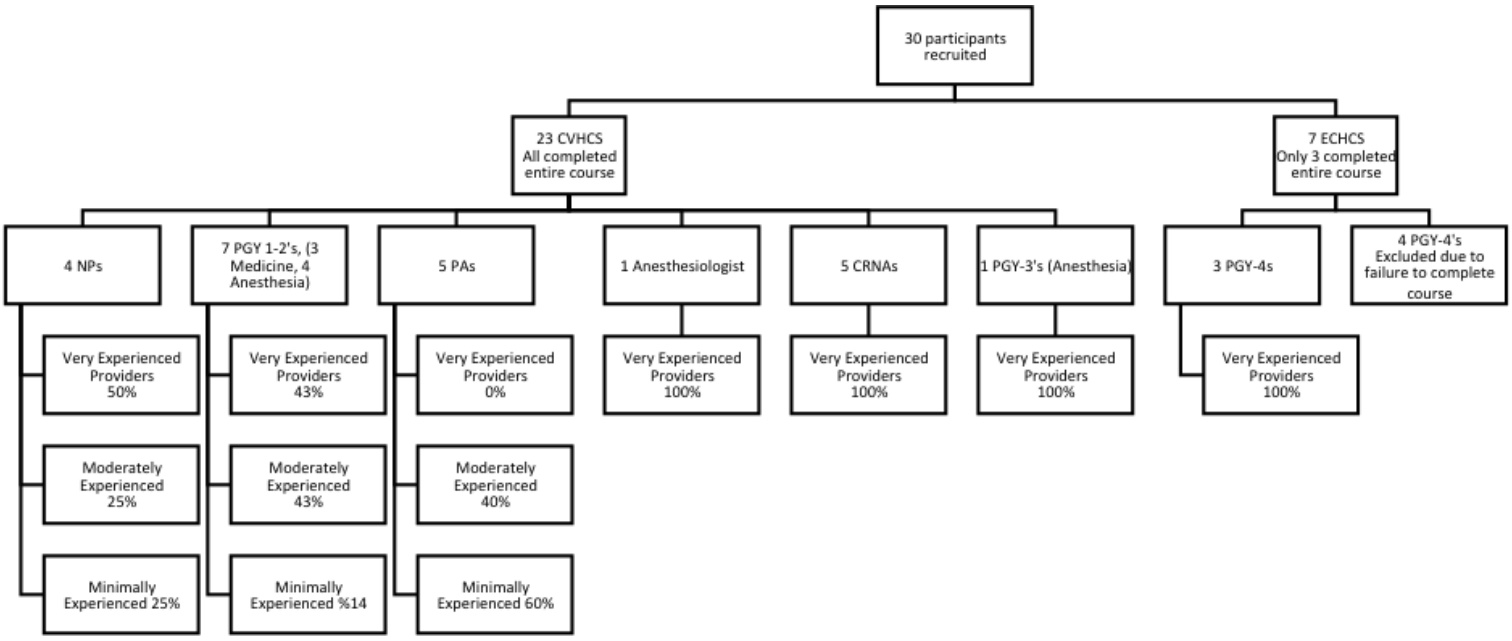

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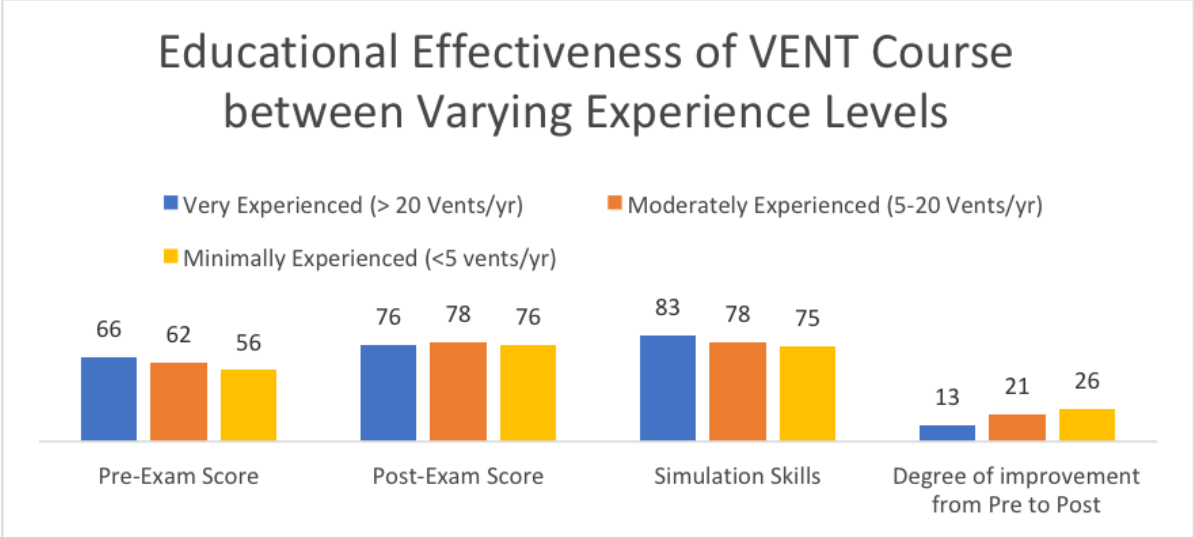

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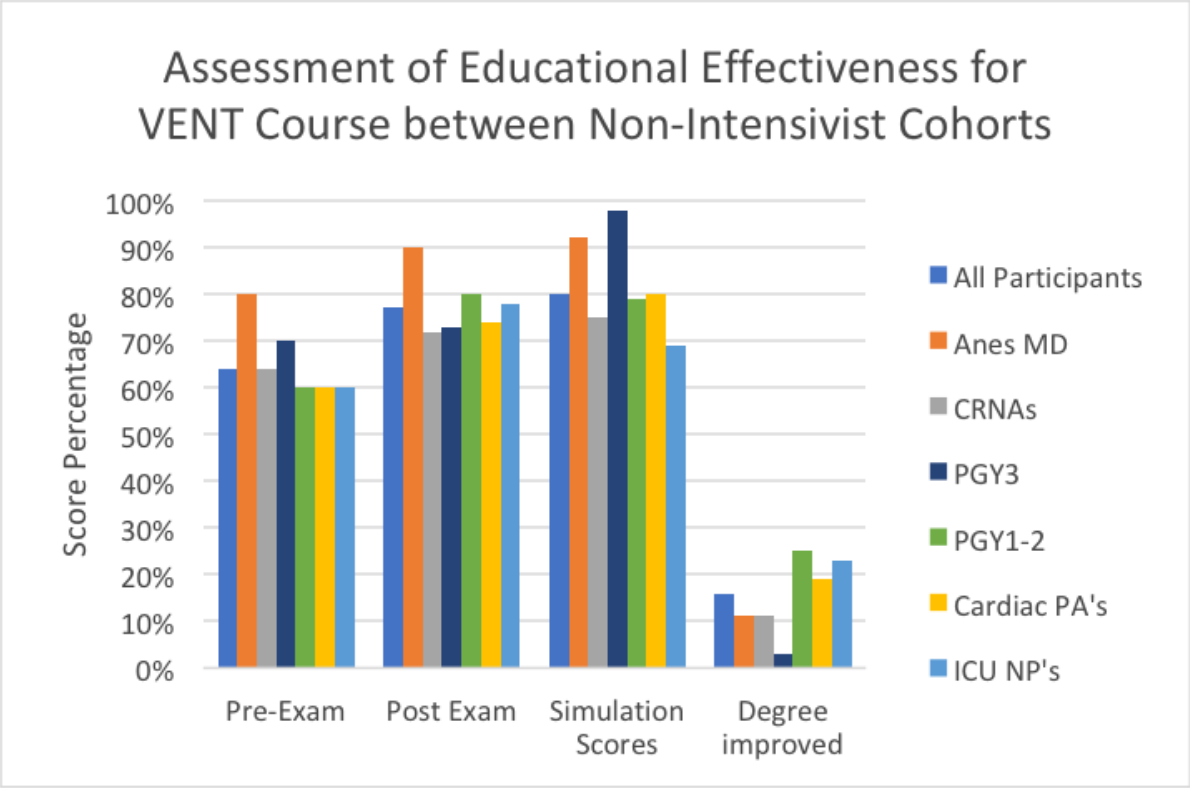

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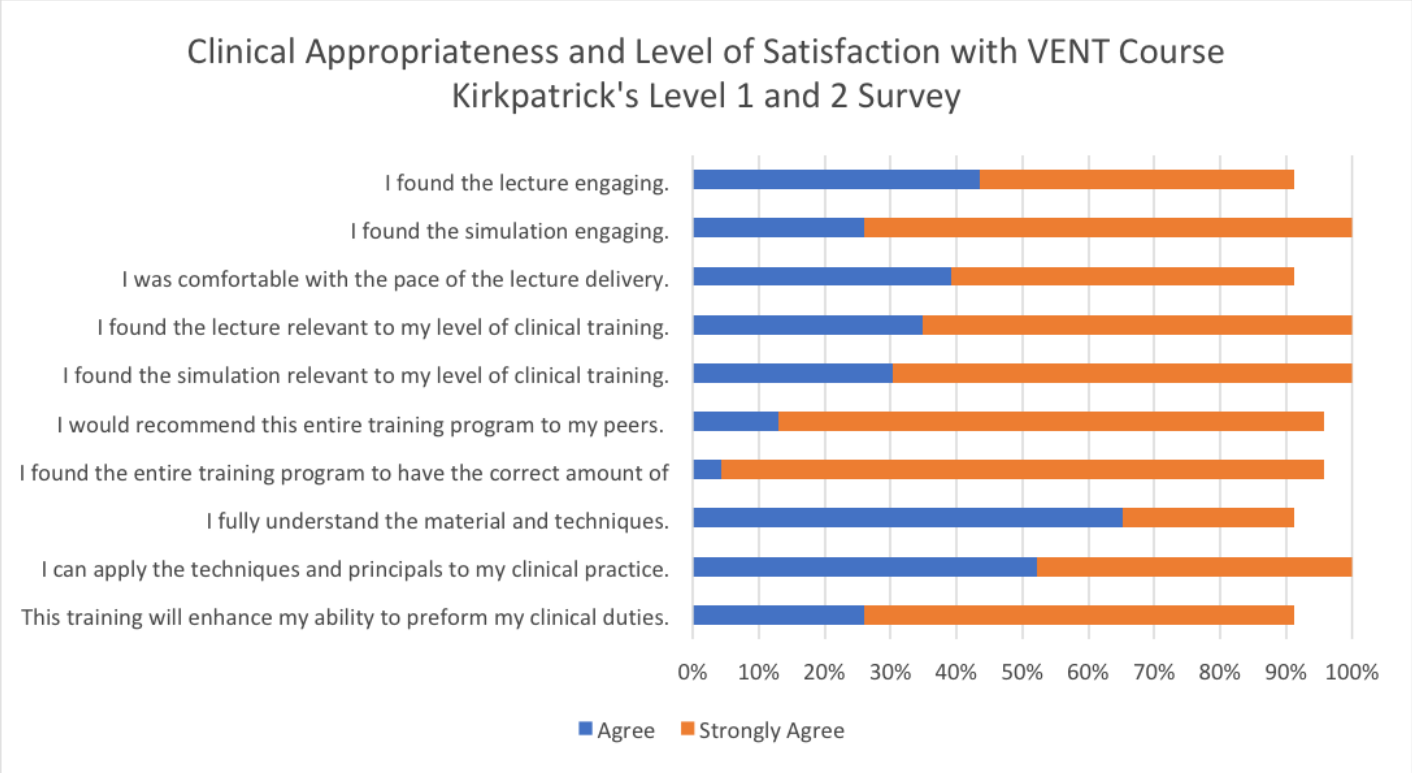

Fig. 4

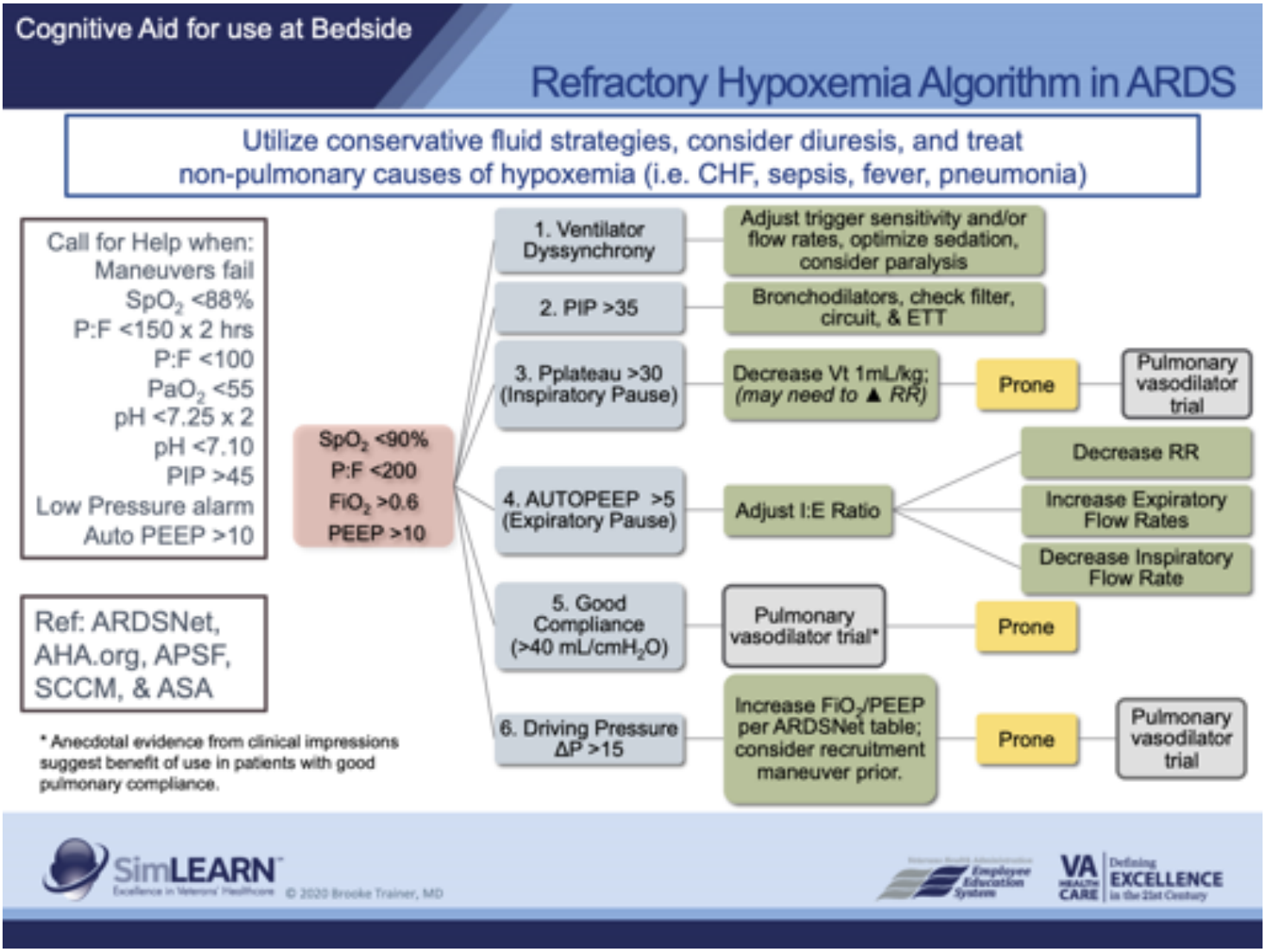

Fig. 5

CRITICAL CARE 12

The Neuroprotective Effects of Metformin: Insights from Rodent Cardiac Arrest and in Vitro Ischemia-Reperfusion of Neurons and Astrocytes

Santiago J Miyara[1], Muhammad Shoaib[2], Judith Aronsohn[3], Ernesto P Molmenti[4], Stacey Watt[5], Tai Yin[6], Linda Shore-Lesserson[3], Ata M Kaynar[7], Lance B Becker[6], Rishabh C Choudhary[6]

[1]Elmezzi Graduate School of Molecular Medicine / Feinstein Institutes for Medical Research, Manhasset, NY, [2]Feinstein Institutes for Medical Research / Donald and Barbara Zucker School of Medicine, Manhasset, NY, [3]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell / Department of Anesthesiology, Manhasset, NY, [4]North Shore University Hospital / Department of Surgery, Manhasset, NY, [5]University at Buffalo, Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, [6]Feinstein Institutes for Medical Research / Department of Emergency Medicine, Manhasset, NY, [7]U. of Pittsburgh / Departments of Critical Care Medicine and Anesthesiology & Perioperative Medicine, Pittsburgh, PA

INTRODUCTION: Brain damage due to ischemia-reperfusion injury (IRI) is an important challenge in post cardiac arrest syndrome (PCAS). Metformin is a widely available drug with numerous properties beyond its role in insulin resistance, including purported benefits in cardio and neuroprotection. Metformin's mechanisms of action are still under investigation, however, compelling evidence has shown the plurality and diversity of these mechanisms, which include modulation of oxidative stress and cell death in a cell-phenotype dependent fashion. Herein, we studied the effects of metformin on a rodent model of cardiopulmonary arrest. Furthermore, we explored the effects of metformin in vitro on single-cultures of astrocytes and neurons.

METHODS: Adult male Sprague–Dawley rats experienced 10 min asphyxial cardiac arrest (CA) followed by resuscitation and received intravenously either metformin (100 mg/Kg in saline; n=16), or vehicle (saline; n=16) immediately following return of spontaneous circulation (ROSC). Survival and modified neurological deficit scores were monitored until 72 h post-ROSC with brains harvested from the surviving rats for histological evaluation. Brain protein carbonyl concentration was determined in both groups as a surrogate marker of reactive oxygen species (ROS) production. Nissl's staining was performed on the hippocampus CA1 region and dentate gyrus to determine neuronal morphology in both groups. Cell viability assay (WST-8) was assessed after 6 h of oxygen-glucose deprivation (OGD) and 20 h of reperfusion in single-cultures of neurons (mouse cell line HT-22) and astrocytes (mouse cell line C8-D1A).

RESULTS: In the rodent model of CA, metformin treatment demonstrated an improved survival at 72 h from 43.8% to 68.8% (p= 0.0692; Kaplan-Meier Analysis with Gehan-Breslow-Wilcoxon test) (Fig.1). Metformin also significantly improved the neurological status at 72 h assessed by modified neurological deficit score when compared with vehicle (p= 0.0103) (Fig. 2). Metformin preserved neuron body integrity in both hippocampal CA1 and dentate gyrus regions observed by Nissl's staining, when compared with the noticeable neuronal body degeneration in the vehicle group (Fig. 3). Metformin treatment was associated with significantly lower protein carbonyl concentration, revealing significantly lower ROS production versus vehicle group (p= 0.0152). CA resulted in increased ROS production versus sham, determined by protein carbonyl concentration (p= 0.0012). Metformin significantly improved the cell viability of HT-22 neurons after 6 h of OGD and 20 h of reperfusion in a dose dependent manner [10 umol Metformin (p= 0.0425); 50 umol Metformin (p= 0.0336)] (Fig. 5A), but without significant impact on C8-D1A astrocytes (Fig. 5B).

CONCLUSION: Our results suggest that metformin improves survival and cell viability outcomes in both in vivo and in vitro models, respectively. Metformin treatment demonstrated increased neurological function and improved brain-cytologic morphology as well as decreased ROS production in our rodent CA model. Furthermore, metformin improved cell viability in single-cultures of HT-22 neurons, with no effect on C8-D1A astrocytes, after OGD and reperfusion, which was observed in a dose dependent fashion. Overall, albeit at a very high dose, metformin could be a potential therapeutic intervention for improving survival and preventing neuronal death after cardiac arrest.

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Fig. 1

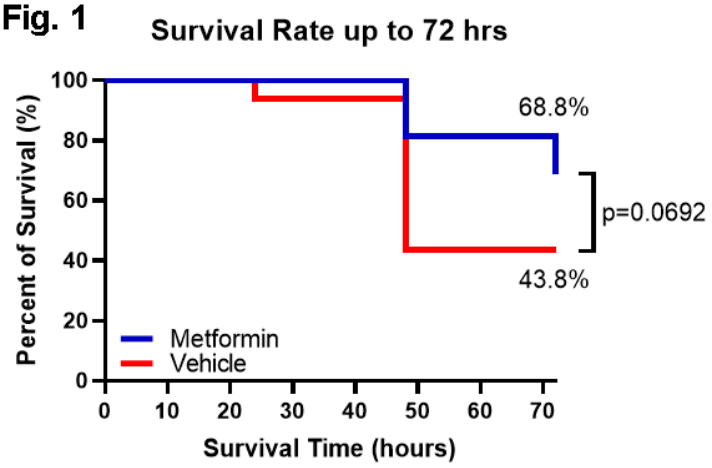


Fig. 2

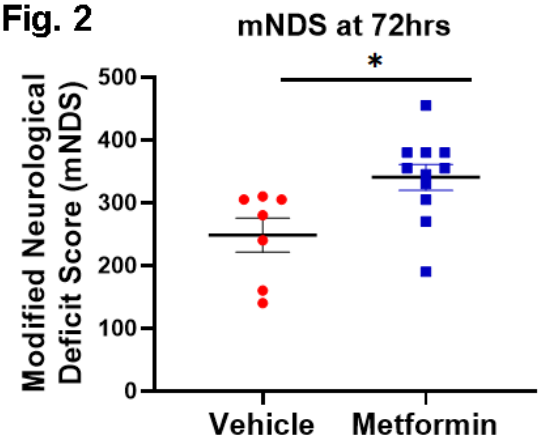


Fig. 3

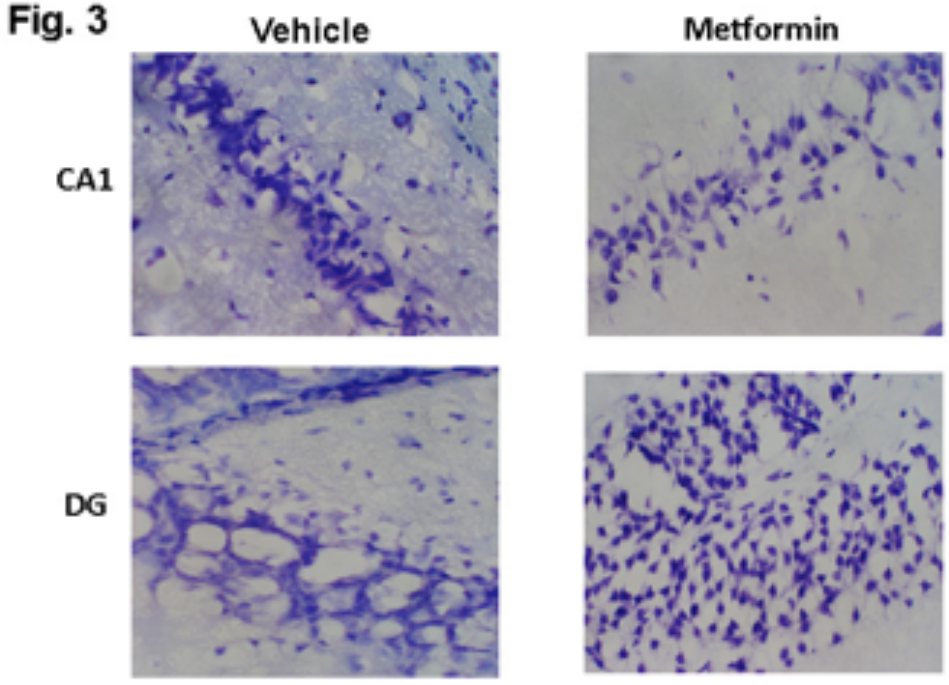


Fig. 4

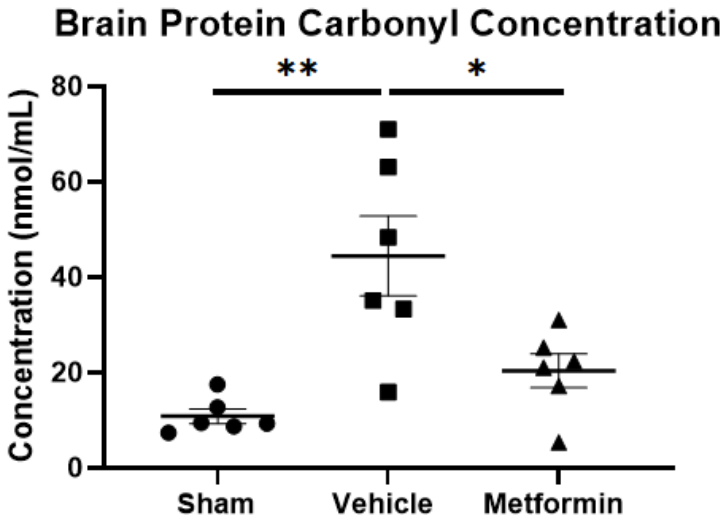


Fig. 5A

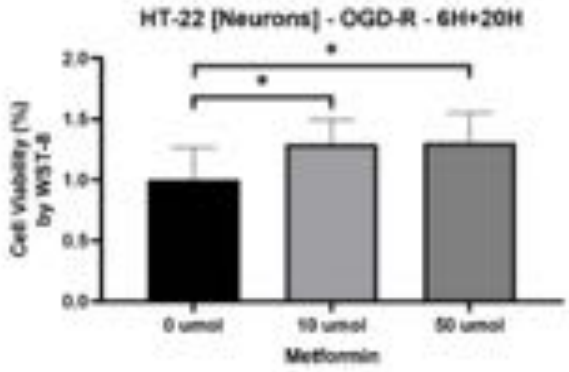
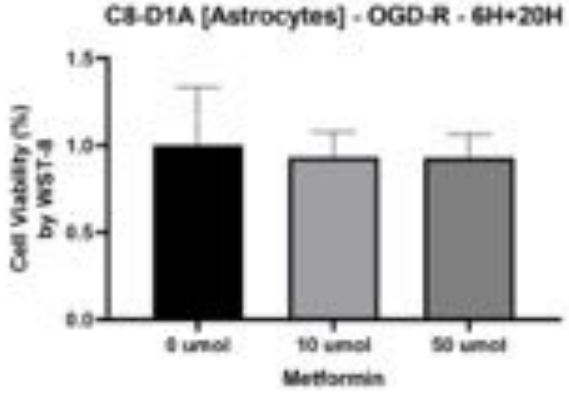


Fig. 5B



CRITICAL CARE 13

Hypoxanthine is a Biomarker of Cerebral Ischemia

Lynne C Gehr[1], Todd Gehr[1], Lorin M Machman[1], Sarah Tensen[1]

[1]VCU, Richmond, VA

INTRODUCTION: We previously demonstrated that hypoxanthine (HX) a metabolite of ATP, can accumulate during ischemia, such that it can be used to determine myocardial ischemia prior to infarction associated with troponin elevation[1]. As a biomarker of ischemia, we hypothesize that HX can also be used to detect cerebral ischemia in patients presenting acutely with concern for a stroke. We examined the plasma of 15 patients for HX presenting to the VCU emergency room for a stroke alert.

METHODS: In a retrospective manner we examined residual plasma for HX in 15 patients presenting to the emergency room for a stroke alert with blood samples drawn as per routine clinical practice. Patients presenting for a stroke alert had a range of 1 to 15 on the NIH stroke Scale Score (SSS). Plasma samples from 13 healthy volunteers were also examined for HX levels and served as the control group. The plasma HX levels were quantitatively determined with HPLC-DAD(diode array detector) equipment, and using a gradient mobile phase and monolithic C18 analytical column.

RESULTS: Our results show a significant different between the 2 groups with a p value of <.0001 using both a Welch two sampled t-test and Mann-Witney U-test. The mean HX level of patients presenting for a stroke alert was 23.4 (+/-12.40) micromolar compared to 4.1 (+/-1.3) micromolar in the control group. In the Welch two sampled U-test the mean HX levels were 18.6 (11.4 min, 51.9 max) for the stroke alert group and 4.2 micromolar (2.1 min, 6.3 max) for the control group. Stroke scale score (SSS) for the stroke alert patients ranged from 1 to 15 with average score of 5.5(+/-5.0)

CONCLUSION: HX is elevated in patients presenting to the emergency room for a stroke alert with stroke scale scores from 1 to 15 compared to normal control patients. Detecting ongoing ischemia may be difficult with traditional testing and preclude further investigation of some patients that could benefit from more clinical followup before discharge and/or additional diagnostic testing. Following serial hypoxanthine levels during the ER/hospital course may prove helpful in determining when it is safe to discharge a patient or consider further examinations of the patient for an ischemic source.

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Patient Characteristics

Characteristics, mean (sd)	Overall	Stroke Alert (N= 15)	Control (N= 13)	p-value
Hypoxanthine (μM)				
Mean (STD)	14.5 (13.29)	23.4 (12.40)	4.1 (1.13)	<.0001[a]
Median [Min, Max]	11.7 [2.1, 51.9]	18.6 [11.4, 51.9]	4.2 [2.1, 6.3]	<.0001[b]

[a] Welch's Two Sample t-test used for p-value [b]Mann-Witney U-test

Fig. 1

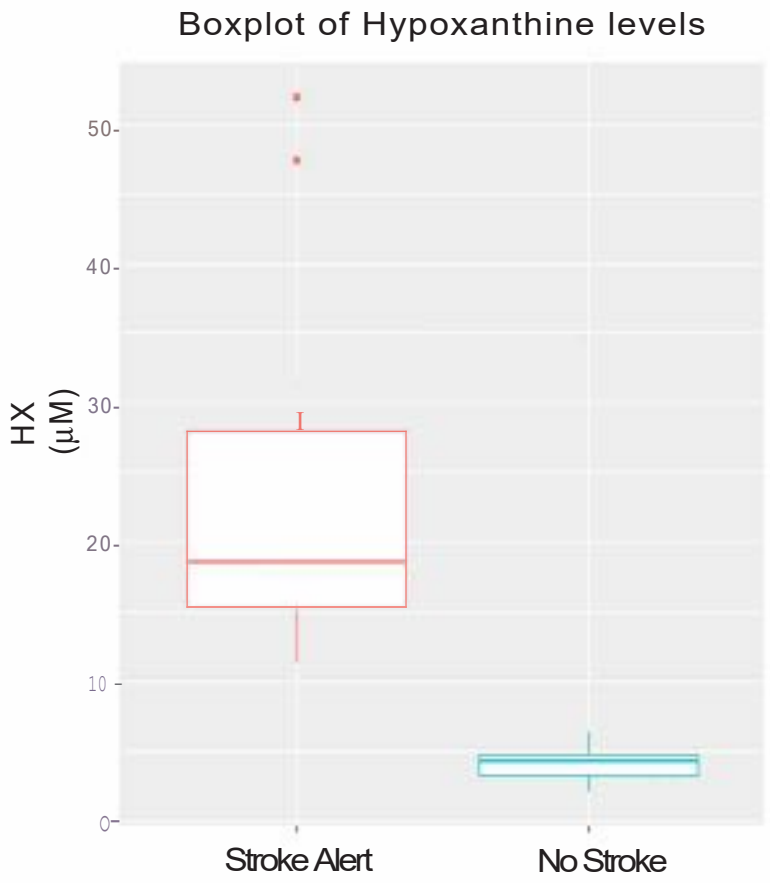

Fig. 2

CRITICAL CARE 14

Clinical Course of Critically Ill COVID-19 Patients with Tube Thoracostomy

Nicholas Rizer[1], Blake Mergler[1], Benjamin Smood[1], Alexandra Sperry[1], Federico Sertic[1], Andrew Acker[1], Christian Bermudez[1], Jacob Gutsche[1], Asad A Usman[1]

[1]University of Pennsylvania, Philadelphia, PA

INTRODUCTION: COVID-19 can cause acute respiratory failure requiring admission to the intensive care unit (ICU), mechanical ventilation, and potential ventilator associated complications. Notable among these, pneumothorax has been described in several reports of COVID-19 patients, with one case series from China reporting an incidence of 5.4% shortly after intubation.[1–4] Pneumothorax is known to cause significant morbidity and mortality, even necessitating tube thoracostomy. While tube thoracostomy has been reported in COVID-19 patients with pneumothoraces, there is limited information on the incidence and clinical course of critically ill COVID-19 patients with pneumothoraces requiring tube thoracostomy. We present here a case series of 4 critically ill COVID-19 patients necessitating 8 chest tubes.

METHODS: We described a series of patients admitted to an intensive care unit at our center requiring tube thoracostomy for pneumothorax. Our center's electronic medical record was queried for all laboratory confirmed COVID-19 patients with tube thoracostomies admitted to the Intensive Care Unit (ICU) between March 9th, 2020 to April 19th, 2020. Data was manually extracted from the electronic medical record by a trained team of physicians and researchers using a protocolized Case Record Form developed by the COVID-19 Critical Care Consortium and International Severe Acute Respiratory and Emerging Infection Consortium (CCCC/ISARIC).[5] Additional information on tube thoracostomy technique, complications, and mechanical ventilation parameters prior to the procedure were obtained. Radiographic and clinical notes were reviewed for improvement of pneumothorax. Data collection was stopped on August 10th, 2020.

RESULTS: We identified 69 patients admitted to an intensive care unit with COVID-19 from March 9th to April 19th 2020, with 8 chest tubes being placed between 4 patients (5.8%). Demographic information and clinical signs and symptoms at presentation are shown in Table 1. There was a prolonged duration of chest tubes in our patients (range 3-24 days; interquartile range: 18-20 days). 3 patients (75%) developed their initial pneumothoraces after 23 days, and all of these patients went on to develop contralateral pneumothoraces (See Table 2). Furthermore, all patients that developed delayed bilateral pneumothoraces, expired in the ICU (See Table 3). Patient 2 likely had an underappreciated hydropneumothorax at time of his first tube thoracostomy and necessitated a subsequent ipsilateral chest tube. 1 patient (25%) developed a ventilator associated pneumonia following chest tube placement. No patients (0%) developed significant bleeding or hemothorax following chest tube placement despite all patients being on therapeutic anti-coagulation.

CONCLUSION: Tube thoracostomy for pneumothorax appears to be a common and safe procedure in critically ill COVID-19 patients. The development of bilateral pneumothoraces after prolonged ICU admission appears to be a negative prognostic sign. This case series suggests that there may be a poor healing phenotype among critically ill COVID-19 patients with pneumothoraces and could inform management and prognosis in these patients.

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Patient	1	2	3	4
Age	44	73	52	59
Sex	F	M	M	F
Race	White	White	White	Black
Body Mass Index (kg/m^2)	51.62	33.82	25.87	16.24
Admission Temperature (°F)	98.2	102.6	102	98.3
Admission Heart Rate (min^{-1})	155	125	87	144
Admission Blood Pressure (mmHg)	180/108	199/131	112/74	222/139
Admission Respiratory Rate (min^{-1})	16	39	30	42
Admission Oxygen Saturation	92%	64%	55%	85%
Initial Oxygen Therapy	Room Air	Room Air	Room Air	Room Air
Comorbidities	Hypertension	None	Hypertension, coronary artery disease, asthma, Hodgkin's Lymphoma (remote)	Scleroderma, chronic kidney disease, autoimmune hepatitis, interstitial lung disease
Presenting Symptoms	Fever, dyspnea, chest pain, fatigue, diarrhea, nausea, vomiting,	Non-productive cough, dyspnea, fatigue, altered mental status	Non-productive cough, dyspnea, fatigue, anorexia, abdominal pain	Cough, dyspnea

Table 1. Demographics and Clinical Signs and Symptoms on Presentation.

Patient	Chest Tube Number	Side	Indication	Time from Start of Mechanical Ventilation to Indication Diagnosis (Days)	Technique	Duration of Chest Tube (Days)	Chest Tube Output in First 24 hours (mL)	Chest Tube Total Output (mL)
1								
	1.1	R	PTX†	11	Surgical	3	140	150
2								
	2.1	R	PTX	25	Percutaneous	21	2100	3573
	2.2	R	Hydro-PTX	26	Surgical	20	690	4100
	2.3	L	Hydro-PTX	26	Surgical	20	430	2411
3*								
	3.1	R	PTX†	25	Percutaneous	24	350	2220
	3.2	L	PTX	28	Percutaneous	21	370	590
4								
	4.1	L	PTX	23	Percutaneous	12	45	217
	4.2	R	PTX	29	Percutaneous	20	120	1445

Table 2. Patient and Chest Tube Clinical Course.

PTX = Pneumothorax; Hydro-PTX = Hydropneumothorax

* Patient was transferred to our facility for ECMO and started on Veno-Venous ECMO on hospital day 2.

† Tension physiology.

Patient	Duration of ICU Stay	Duration of Mechanical Ventilation (Days)	Disposition
1	30	19	Acute Rehabilitation
2	46	46	In Hospital Death – respiratory failure due to bronchopulmonary fistula
3	49	49	In Hospital Death – multi-organ system dysfunction
4	108	108	In Hospital Death – acute on chronic hypoxemic respiratory failure

Table 3. Patient Outcomes.

CRITICAL CARE 15

Clinical Characteristics of Recovered COVID-19 Inpatients after Hospital Discharge: An Observational Descriptive Study

Alberto A Uribe[1], Luis Periel[2], Carmen Skinner[1], Juan Fiorda-Diaz[1], Tristan Weaver[1], Marco Echeverria-Villalobos[1], Haixia Shi[1], Barbara Rogers[2]

[1]The Ohio State University Wexner Medical Center, Columbus, OH, [2]The Ohio State University Wexner Medical Center, Columbus , OH

INTRODUCTION: At the end of December 2019, authorities from Wuhan, Hubei Province, China reported cases of patients with atypical pneumonia of unknown cause. The pathogen was identified as the novel COV (SARS-CoV-2, a beta coronavirus with 79% genetic similarity to SARS-CoV). Consequently on January 30th, 2020, the World Health Organization declared the Coronavirus Disease-2019 (COVID-19) as a new rapidly emergent disease of pandemic proportions. SARS-CoV-2 reaches the lower respiratory tract after aerosolization, affecting cells with high angiotensin-converting enzyme 2 (ACE2) expression, such as the alveolar type 2 cells. However, SARS-CoV-2 affinity to the ACE2 receptors may be higher than the one described for SARS-CoV. Furthermore, the incidence of hypoxic respiratory failure in patients with COVID-19 is 19%, where 14% of them require hospitalization for oxygen therapy (high flow nasal cannula or non-invasive positive pressure ventilation) and 5% required ICU admission for invasive mechanical ventilation (MV). Despite that, the majority of infected individuals develop mild symptoms; some individuals can progress to fulminant pneumonitis, multi-organ failure, ARDS or death. Fever, dry cough, dyspnea, headache, muscle and joint pain, dizziness, diarrhea, nausea and bloody sputum has been reported in COVID-19 patients requiring hospitalization. Moreover, recent reports suggest that COVID-19 inpatients may experience a similar clinical progression after hospital discharge based on advanced age, presence of more than one comorbidity (e.g. hypertension, lung disease and heart disease), dyspnea, oxygen desaturation, leukocytosis, lymphocytopenia and C-reactive protein elevation. We collected relevant information from recovered COVID-19 patients that have been admitted at The Ohio State University Wexner Medical Center (OSUWMC) since the beginning of the current pandemic (April 2020) in order to determine the clinical evolution after hospital discharge.

METHODS: This is a single center retrospective/prospective descriptive observational study in COVID-19 inpatients that were discharged and followed-up at The OSUWMC. Data was collected from hospital admission up to 60 days after hospital discharge. The primary objective of the study was to assess the clinical progression during hospitalization and clinical outcomes after hospital discharge in recovered patients treated for COVID-19 at OSUWMC. Patient demographics and clinical characteristics were summarized as frequencies (percentage) for categorical variables and means (standard deviation) or medians (inter-quartile range) for continuous variables. All statistical analyses will be conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS: A total of 59 patients were included in the study (31 males and 28 females). The mean age is 52 ± 13.3 years. The mean BMI is 34.8 ± 9.3 kg/m2. The mean length of stay was 8.7 ± 6.9 days and the mean length of ICU stay was 7.8 ± 6.6 days. The five most common symptoms were history of fever (59.3%), cough (54.2%), shortness of breath (47.6%), gastrointestinal symptoms (35.6%) and headache (8.5%). The five most common comorbidities were hypertension (40.7%), diabetes (30.5%), heart disease (20.3%), chronic kidney disease (16.9%) and asthma (10.2%). The mean number of days of treatment with corticoids, antibiotics, antiviral and hydroxichloroquine were 5 ± 5.4, 5 ± 3.4, 7 ± 1.9 and 9 ± 15.3 days, respectively. The observed complications documented after hospital discharge were ARDS (47.5%), septic shock (15.3%), acute kidney failure (15.3%) and invasive mechanical ventilation (13.6%). The most common chest X-ray findings at baseline were bilateral pneumonia (69.5%), multiple mottling and grounded glass opacity (49.2%) and unilateral pneumonia (8.5%). In addition, a chest CT scan for 23 subjects was requested at baseline and the most common findings were grounded glass changes (25.4%), bilateral opacities (25.4%) and atelectasis (5.1%).

CONCLUSION: The most common onset symptoms in subjects admitted to the hospital due to COVID-19 infection were fever, cough, shortness of breath, gastrointestinal symptoms and headache. Women are less likely to require hospital admission. The most common complications were ARDS, septic shock, acute kidney failure and invasive mechanical ventilation. There were relevant changes in laboratory tests and improvement of chest x-rays and CT scan findings.

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Table 1. Demographic characteristics

Demographic characteristics	N = 59
Age, years, mean (SD)	52.4 (13.3)
Sex, N (%)	
Male	31 (52.5)
Female	28 (47.5)
Height, meter, mean (SD)	1.7 (0.1)
Weight, kilogram, mean (SD)	99.6 (29.3)
BMI, units, mean (SD)	34.8 (9.3)
Race, N (%)	
White	23 (39.0)
Black	21 (35.6)
Asian	1 (1.7)
Other	14 (23.7)
Ethnicity, N (%)	
Hispanic	14 (23.7)
Not hispanic	45 (76.3)

Table 2. Clinical and Key time variables

Clinical and key time variables	N= 59
ICU admission, N (%)	14 (23.7)
Length of Stay, days, mean (SD)	8.7 (6.9)
Length of ICU Stay, days, mean (SD)	7.8 (6.6)
Time from onset of symptoms to first consultation, days, mean (SD)	6.2 (4.0)
Time from onset of symptoms to hospitalization, days, mean (SD)	8.0 (5.5)
Onset symptoms, N (%)	
Fever	35 (59.3)
Cough	32 (54.2)
Shortness of breath	44 (47.6)
Gastrointestinal symptoms	21 (35.6)
Headache	5 (8.5)
Nasal congestion	2 (3.4)
Sore throat	2 (3.4)
Expectoration	3 (5.1)
Comorbidities, N (%)	
Hypertesion	24 (40.7)
Diabetes	18 (30.5)
Heart disease	12 (20.3)
Chronic kidney disease	10 (16.9)
Asthma	6 (10.2)
COPD	3 (5.1)
Connective tissue disease	2 (3.4)
Chronic liver disease	1 (1.7)
Active malignancy	1 (1.7)
Treatment	
Anticoagulants, N (%)	56 (94.9)
Antibiotic, N (%)	38 (64.4)
Convalescent plasma, N (%)	18 (30.5)
Antiviral, N (%)	11 (18.6)
Corticoids, N (%)	13 (22.0)
Corticoids, days, mean (SD)	5 (5.4)
Antibiotic, days, mean (SD)	5 (3.4)
Antiviral, days, mean (SD)	7 (1.9)
Hydroxychloroquine, N (%)	9 (15.3)
Complications, N (%)	
ARDS	28 (47.5)
Septic shock	9 (15.3)
Acute kidney failure	9 (15.3)
Invasive mechanical ventilation	8 (13.6)
Others	6 (10.2)
Time from discharge to first FU, days, median (IQR)	5.4 (3.1, 7.3)
Time from discharge to second FU, days, median (IQR)	8.5 (5.8, 13.5)
Time from discharge to third FU, days, median (IQR)	18.5 (13.8, 23.9)

Table 3. Laboratory and image outcomes

Laboratory and image outcomes	Baseline	First Follow-up
Hematology, median (IQR)		
WBC	6.4 (5.0, 9.1)	6.4 (5.2, 7.7)
Hematocrit	39.5 (36.4, 41.9)	37.5 (32.7, 39.4)
Hemoglobin	13.2 (11.6, 14.1)	12.0 (10.5, 13.1)
Platelets	**218 (180,261)**	**309 (213.0, 382.5)**
Neutrophils	87.2 (73.9, 88.2)	
Lymphocytes	18 (11.6, 24.6)	25.7 (20.4, 31.6)
Coagulation, median (IQR)		
INR	1.0 (1.0, 1.1)	1.1 (1.0, 1.2)
PT	13.5 (13.2, 14.3)	13.9 (13.3, 14.7)
PTT	33.5 (29.4, 36.1)	33.7 (30.2, 39.2)
Chemistry, median (IQR)		
BUN	14.0 (11.0, 20.0)	14.0 (11.0, 19.0)
Albumin	3.5 (3.3, 4.0)	3.3 (3.1, 3.5)
ALT	23.5 (16.8, 52.3)	31.0 (17.0, 55.0)
AST	35.5 (22.0, 61.5)	26.0 (20.0, 46.0)
Total bilirubin	0.5 (0.4, 0.8)	0.4 (0.4, 0.6)
Sodium	135 (133, 137)	137.0 (136.0, 140.0)
Potassium	3.9 (3.5, 4.0)	3.9 (3.6, 4.2)
Creatinine	0.9 (0.7, 1.3)	0.8 (0.6, 1.0)
Creatine Kinase (CK)	**108.5 (60.5, 266.0)**	**76.0 (47.0, 118.0)**
LDL cholesterol	**127 (104.0, 153.0)**	**100.0 (79.0, 158.0)**
Bilirubin direct	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)
Urea	0.2 (0.2, 1.5)	0.2 (0.2, 1.0)
Lactate	**1.7 (1.6, 1.8)**	**1.2 (1.1, 1.3)**
Troponin I	0.02 (0.01, 0.04)	0.02 (0.01, 0.10)
C-reactive protein	**110.1 (41.7, 158.2)**	**54.9 (19.6, 123.3)**
LDH	32.5 (20.3, 180.5)	34.0 (28.5, 42.5)
D-dimmer	1.0 (0.6, 2.2)	1.2 (0.5, 2.1)
Ferritin	**845.3 (353.1, 1667.3)**	**678.1 (436.1, 1174.1)**
IL-6	**38.9 (19.9, 83.1)**	**22.4 (9.4, 66.8)**
Procalcitonin	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)
Chest x rays, N (%)	48 (81.4)	28 (47.5)
Bilateral pneumonia	41 (69.5)	18 (30.5)
Multiple mottling and grounded glass opacity	29 (49.2)	17 (28.8)
Unilateral Pneumonia	5 (8.5)	1 (1.7)
Chest CT scan requested, N (%)	23 (39.0)	10 (16.9)
Grounded glass changes	15 (25.4)	3 (5.1)
Bilateral opacities	15 (25.4)	3 (5.1)
Atelectasis	3 (5.1)	2 (3.4)

CRITICAL CARE 16

The Evolving Role of Extracorporeal Membrane Oxygenation (ECMO) in Patients Undergoing Lung Transplantation: A Single-Center Experience

Annandita Kumar[1], Jayanta Mukherji[2], Stella Duong[2]

[1]Loyola University Medical Center, Chicago, IL, [2]Loyola University Medical Center, Maywood, IL

INTRODUCTION: The role of Extracorporeal Membrane Oxygenation (ECMO) for perioperative support of deteriorating patients with end-stage lung disease undergoing lung transplantation has greatly expanded over the past two decades. In most clinical scenarios ECMO is offered as a semi-elective procedure to deteriorating patients rather than as an acute rescue therapy thereby improving its chances of success. Increased demands for donor lungs and prolonged time on the waiting list have prompted the use of ECMO as a bridge to lung transplantation (LT) to severely hypoxic and hypercarbic patients. The ventilatory and hemodynamic support provided by veno-venous (VV) and veno-arterial (VA) ECMO has helped support patients with primary graft dysfunction following LT. However, there is a paucity of data regarding how ECMO support will affect survival and complications after LT.

METHODS: We reviewed charts of all patients requiring ECMO and who were listed for lung transplantation. Data reviewed included demographics, lung disease, timing and duration of ECMO, complications and 30-day survival. Patients were allotted into 4 groups based on the timing of ECMO placement in relation to LT. I. ECMO performed as a bridge to LT. II. ECMO performed within 24-hour following LT. III. ECMO performed after 24 hours following LT IV. ECMO performed with the intention to receive LT but could not be bridged to LT. A multivariate analysis was performed to determine the association, if any, between diagnosis and variables related to ECMO cannulation and complications.

RESULTS: A total of 51 patients listed for LT received ECMO support. The most common diagnosis was interstitial lung disease. VV ECMO was the predominant support provided with the most common indication being severe refractory hypoxemia. Majority of patients underwent a double LT. The overall 30-day survival in LT patients receiving ECMO support was 60.7%. No association was present between patient preexisting comorbidities and survival. Vasoplegia and AKI were the common complications of ECMO and there were no association between ECMO complications of ECMO and survival. Thirty-day survival was highest in patients who received ECMO as a bridge to lung transplant, however these patients also averaged a higher number of days of ECMO cannulation likely due to delay in lung procurement.

CONCLUSION: ECMO placed as a bridge to lung transplant (Group 1) showed significant 30-day survival advantages with severe hypoxemia in patients with CF representing the majority (see Table 1). Gastrointestinal and other bleeding were the most common complications encountered in this group. The prolonged mean duration of ECMO experienced by this group likely reflects delays in lung procurement. When ECMO was utilized to improve perfusion following lung transplant (Group II and III), it was most commonly placed for severe hypoxemia. Patients in whom ECMO was placed within 24 hours following transplant experienced decreased survival rates compared to patients who received ECMO greater than 24 hours following transplant. Although RV dysfunction with perioperative hypoxemia is expected, 90% of patients were salvageable with VV ECMO. The shorter duration of ECMO in Group II, when compared to group III, suggests an earlier resolution of hypoxemia in patients who are cannulated earlier following lung transplantation. The major complications encountered by patients who required postoperative ECMO were vasoplegia and AKI. Thirteen patients in group IV who received ECMO support as bridge to lung transplantation did not receive LT due to delays in donor lung procurement and deterioration of their underlying condition. The most common pulmonary diagnosis in these patients was ILD (5/13) and IPF (5/13). The mean duration of ECMO was 18.50 days with a low 30-day survival of 2/11 (18%) The most noteworthy complication in this group was AKI (25%) with 11.54% of patients requiring hemodialysis.

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Relationship of ECMO to LT	Diagnosis	Major Comorbidities	Indication for ECMO	Duration of ECMO (Days)	Complications of ECMO	30-Day Survival
Group 1 (17 patients): ECMO performed as a bridge to LT	CF (41%) IPF (29%) ILD (24%)	Hyperglycemia (47%) Pancreatic/Liver Insufficiency (41%)	Hypoxia (65%) Hypercapnia (36%) Hypercapnia & Hypoxia (12%)	15.4	Non-GI Bleeding (12%) GIB (6%)	100%
Group 2 (11 patients): ECMO performed during immediate 24 hours following LT	ILD (64%) IPF (18%)	Hypertension (55%) Coronary Artery Disease (45%) Hyperglycemia (45%)	Hypoxia (100%)	3.6	AKI (55%) Vasoplegia (9%)	72%
Group 3 (10 patients): ECMO performed > 24 hours following LT	IPF (30%) CF (20%) Pulmonary Hypertension (20%)	Hypertension (60%) Hyperglycemia (50%) Coronary Artery Disease (40%)	Hypoxia (70%) Hypercapnia (20%) Hypercapnia & Hypoxia (10%)	7.9	AKI (40%) Vasoplegia (20%) GIB (20%)	40%
Group 4 (13 patients): ECMO performed but patients were unable to be bridged to LT	IPF (34%) ILD (29%) CF (15%)	Acute Kidney Injury (46%) Hypertension (46%) Hyperglycemia (46%)	Hypoxia (55%) Hypercapnia (15%) Hypercapnia & Hypoxia (8%)	18.5	AKI (46%) Vasoplegia (46%) GIB (15%)	15%

Table 1. Summary of primary lung diagnosis, most common comorbidities and complications, and treatment course. The 51 patients included were divided into four groups based on the relationship of ECMO placement to lung cannulation. The percentages in parentheses reflect prevalence within each group.

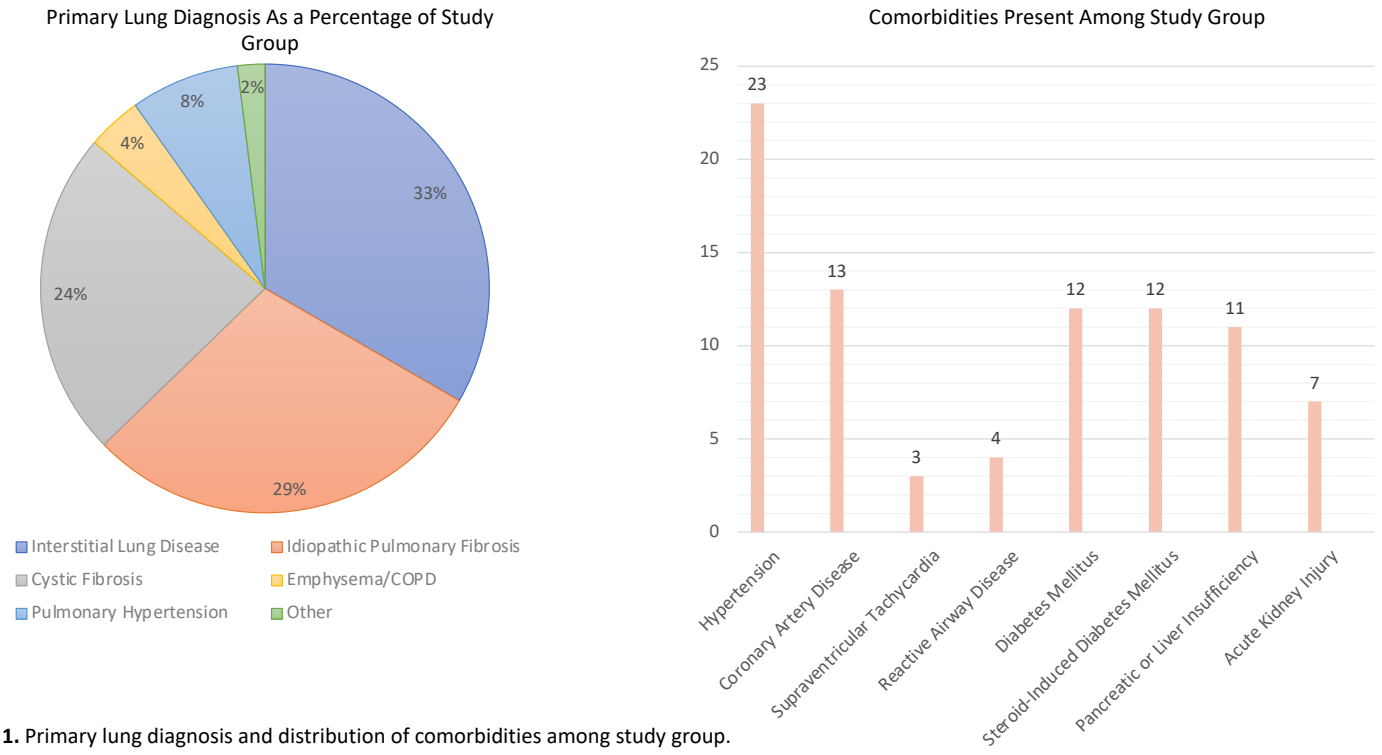

Figure 1. Primary lung diagnosis and distribution of comorbidities among study group.

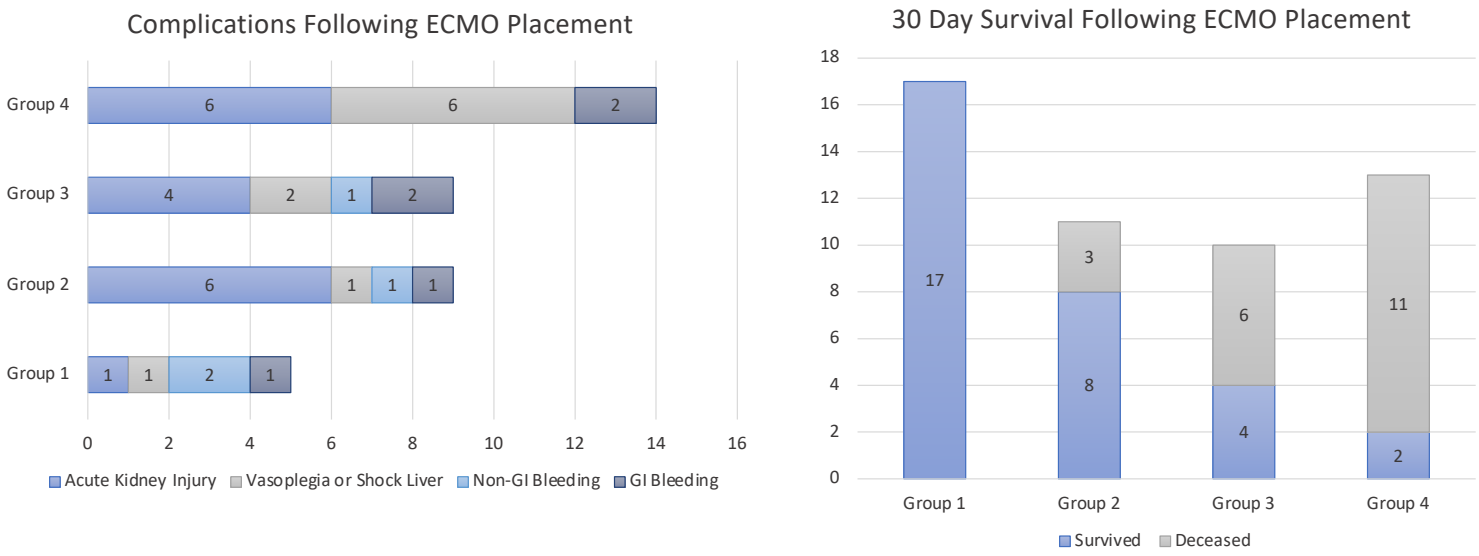

Figure 2. Summary of complications and 30-day survival following ECMO placement.

CRITICAL CARE 17

Time Course of Histidine-Rich Glycoprotein as a New Prognostic Biomarker for Sepsis: A Multicenter Prospective Observational Study

Naoya Kawanoue[1], Kosuke Kuroda[1], Masahiko Oiwa[1], Satoshi Suzuki[1], Hidenori Wake[2], Masahiro Nishibori[3], Hiroshi Morimatsu[4]

[1]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, [2]Faculty of Medicine, Kindai University, Osakasayama, Japan, [3]Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan, [4]OKAYAMA UNIVERSITY HOSPITAL, Okayama, Okayama

INTRODUCTION: Histidine-rich glycoprotein (HRG) is a plasma glycoprotein produced in a liver. It is thought that decreased HRG in septic conditions is associated with the uncontrolled activation of neutrophils, vascular endothelial damage, and immunothrombus formation, which leads to acute respiratory distress syndrome, disseminated intravascular coagulation, and multiple organ dysfunction syndrome. In a basic study, our group reported that plasma HRG levels decreased in septic mice and replenishment of HRG significantly improved the survival rate[1]). In a clinical study, we found that plasma HRG levels within 24 hours of the ICU admission in infective systemic inflammatory response syndrome (SIRS) patients were lower than in non-infective SIRS patients, and those in non-survivors were lower than in survivors[2]). In this study, we focused on time-dependent changes of plasma HRG levels in septic patients and evaluated the difference of time courses of plasma HRG levels between survivors and non-survivors.

METHODS: This was a multicenter prospective observational study. We studied the ICU patients who were newly diagnosed as sepsis. We collected blood samples within 24 hours of the ICU admission (day 1), and on day 3, 5, and 7. To determine whether time courses of plasma HRG levels differ between survivors and non-survivors, we measured plasma HRG levels by a quantitative enzyme-linked immunosorbent assay, analyzed using generalized linear mixed models and Cox proportional-hazards model.

RESULTS: We studied 200 septic patients from August 2018 to September 2019 in 16 Japanese hospitals. Figure 1 shows time courses of plasma HRG levels which compared survivors and non-survivors using generalized linear mixed models. Plasma HRG levels in non-survivors (n = 23) were significantly lower than those in survivors (n = 177) on day 1. Although plasma HRG levels in survivors were on a recovery trend over time, there was no significant difference in their time courses between survivors and non-survivors ($P = 0.34$). However, plasma HRG levels in non-survivors remained consistently lower than those in survivors ($P < 0.001$). In a Cox proportional-hazards model with plasma HRG levels as a time-dependent covariate, plasma HRG levels were significantly associated with mortality (hazard ratio, 0.85 [95% confidence interval, 0.78-0.92]; $P < 0.001$).

CONCLUSION: We evaluated the time courses of HRG levels in septic patients. We found that plasma HRG levels in non-survivors were consistently lower than those in survivors. These finding suggested that decreased HRG levels could be a new prognostic biomarker for sepsis.

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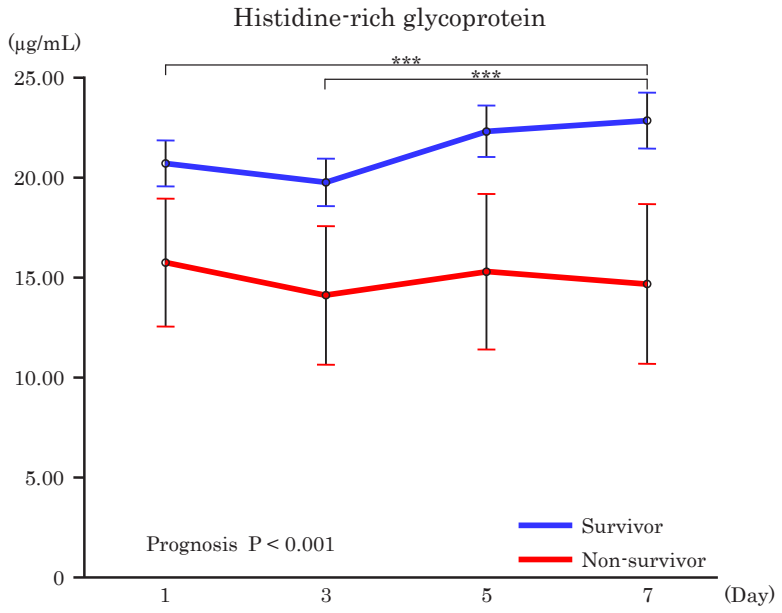
Figure 1. Time courses of plasma HRG levels which compared survivors and non-survivors

***P < 0.001



CRITICAL CARE 18

Awake Prone Position in Acute Hypoxemic Respiratory Failure secondary to COVID-19 Pneumonia: A Preliminary Systematic Review and Meta-Analysis

Miguel T Teixeira[1], Susannah F Empson[1], Braynt C Shannon[1], Fredrick Mihm[1]

[1]Stanford, Palo Alto, CA

INTRODUCTION: The use of prone position (PP) in moderate to severe ARDS requiring invasive mechanical ventilation improves oxygenation and reduces mortality. More recently, during the COVID-19 pandemic, use of high flow nasal cannula oxygen delivery has become commonplace with many experts recommending patients to self-prone. However, efficacy on awake PP is based on indirect evidence from mechanically ventilated patients, limited direct evidence and anecdotal observations. Whether PP results in reduced intubation rates, accelerated recovery, or a reduction in mortality remains largely unanswered. We conduct a systematic review and meta-analysis of the available evidence on the utility of awake PP in the management of the hypoxic non-intubated patient with COVID-19 pneumonia. Studying PP in the awake patient is complex, and it is imperative to elucidate how to effectively measure and monitor duration, continuity and positioning in order to elucidate meaningful clinical outcomes such as changes in intubation rates or mortality.

METHODS: We searched databases including MEDLINE and Cochrane Library from December 1, 2019 to January 5, 2021 for studies describing the use of PP in the management acute hypoxemic respiratory failure from COVID-19 pneumonia. We selected for full review comparative studies, feasibility studies, and qualitative studies in hospitalized patients with COVID-19 requiring supplemental oxygenation who underwent awake self-prone positioning and abstracted oxygenation markers, intubation rates, ICU and hospital length of stay, mortality and adverse events..

RESULTS: We abstracted data from 39 studies and 1,353 hospitalized adult patients with COVID-19 PNA who underwent non-invasive oxygen therapy managed with awake prone positioning. Observational data accounted for 95% (37/39) of studies and ubiquitously demonstrated improvement in oxygenation markers during PP with significant variability in sustained effects once re-supinated. There was limited non-comparative data on patient centered outcomes. 378 patients from 7/39 studies had a mean intubation rate of 23%. There was significant heterogeneity as to how standardized PP protocols were followed with a mean duration and overall continuity of PP being significantly shorter than in the reported literature pertaining to mechanically ventilated patients (16hrs). Only one randomized study was found with low adherence to prone position protocol being a major barrier to conclusive findings. We found an additional 29 ongoing clinical trials with only 5 of those being observational studies. The interventional arms of the remaining studies do not report or appear to lack a reliable way to monitor compliance to PP protocols. There was significant variability regarding initiation time, duration, continuity and type of prone position recorded.

CONCLUSION: In hospitalized non-intubated patients with hypoxemic respiratory failure secondary to COVID 19, prone position appears to temporarily improve oxygenation markers with low adverse events. Whether it results in more durable and meaningful outcomes such as a reduction in length of hospital stay, intubation rates and mortality remains unanswered. Fortunately, there is an abundance of ongoing interventional trials, some of which are intending to report comparative outcomes. However, we hypothesize that the heterogeneity in how prone position is being carried out among different groups and the lack of reliable monitoring to assess adherence to prone protocols may make it difficult to provide evidence-based recommendations on the role of awake self-prone position in respiratory failure.

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CRITICAL CARE 19

Palliative Care Delivery Amongst Critically Ill Patients with COVID-19

Selby Johnson[1], Matthew Fuller[2], Kathryn Pearson[3], Julien Cobert[4], Galen Royce-Nagel[5], Yi-Ju Li[5], Raquel R Bartz[6], Zachary Frere[6], Tetsu Ohnuma[6], Vijay Krishnamoorthy[6], Karthik Raghunathan[1], Krista L Haines[7]

[1]Duke University School of Medicine, Durham, NC, [2]Duke University Hospital, Durham, United States of America, [3]Johns Hopkins School of Medicine, Baltimore, MD, [4]University of California San Francisco, San Francisco, United States of America, [5]Duke University Medical Center, Durham, NC, [6]Duke University, Durham, NC, [7]Duke University, Durham, United States of America

INTRODUCTION: COVID-19 has disproportionately affected older, comorbid adults with crucial implications on end-of-life decisions and necessity of Palliative Care delivery. Limited access to staff and services[1] have impacted the quality of these two. COVID-19 has necessitated notable palliative care needs for symptom managements such as long-term dyspnea, isolation and the fear of dying alone[2], advanced care planning, and prognostication. The benefits of palliative care in critically ill patients have been well-described[3]. Utilization of PC consultation in ICU patients with COVID-10 has been reported ~40%[4, 5]. However, these reports of PC have been single center and limited by small patient samples and local practices and/or capabilities. To Understand the variation of PC use amongst critically ill COVID-19 patients, we studied the use of palliative care in a large nationally representative dataset.

METHODS: We analyzed data from the Premier Healthcare Database (Premier Inc., Charlotte NC), which is a hospital-based dataset of over 1000 US hospitals and nearly 10 million patients. Adults aged 18 years and older with an International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) were included. Only patients with a billing code for an ICU room for at least one day were included. A patient's first hospitalization for COVID-19 was included. Among this cohort, we examined the utilization of palliative care during the hospital encounter, using ICD-10 code Z51.5. Among patients exposed and unexposed to inpatient palliative care, we described demographic and clinical characteristics, facility characteristics, and the use of life-sustaining therapies such as cardiopulmonary resuscitation (CPR), hemodialysis, mechanical ventilation, and tracheostomies that are defined using ICD-10 codes and hospital charges.

RESULTS: Among 14,745 ICU patients with a diagnosis of COVID-19, 3619 patients (24.5%) received a PC consultation. Of those who received a PC encounter, only 15.7% were 85 years or older. The majority of patients receiving a PC encounter were between 65-74 years old. Among patients exposed to PC utilization during hospital encounter, patients were predominantly male (57.8%), white (51.3%), non-Hispanic (59.3%), and those using Medicare (70.1%). PC encounters were most frequent in urban and teaching hospitals. In general, patients had a higher median vanWalraven scoare at baseline in the PC group (9 IQR 5-15) compared to the non-PC group (5 IQR 0-11). Life-sustaining therapies were higher in patients who had a PC encounter at some point in their hospitalization. Mortality was higher in the PC group compared to the non-PC group (76% vs. 24.3%) and ICU length of stay was longer (7 days [IQR 3, 14] vs. 5 days [IQR 2, 10]). Overall hospital length of stay was similar.

CONCLUSION: There is wide variation in the use of PC amongst COVID-19 patients admitted to the ICU. More than half of ICU patients older than 85 years did not have a coded PC encounter despite a recently published study showing a substantially higher odds of dying in this age group. Patients who underwent PC, had more comorbidities at baseline and had a much a higher in-hospital mortality. However, the majority of patients in the ICU with COVID-19 who had respiratory failure requiring mechanical ventilation (68.9%) and with renal and respiratory failure requiring dialysis and mechanical ventilation (64.7%) did not have a palliative care encounter code. This suggests an important and possibly large unmet need of palliative care in critically ill patients with COVID-19. Limitations include data-base specific limitations, including the inability to review individual medical records given the deidentified nature of the dataset, possibly missing data and the lack of granular level (e.g. laboratory, radiologic) data. While charge/billing codes may not fully or accurately code for patient data compared to ICD codes, our previous work demonstrated improved data capture when using charge codes in addition to ICD codes. It is also possible that many hospitalized patients with COVID-19 are receiving PC consultations early in their hospital course and may not be transferred to the ICU based on advanced care plans. Also, while the ICD code for palliative care typically refers to specialized PC consultations, our results may not capture the majority of primary palliative care delivery (e.g. delivered by the primary ICU team).

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Table 1: Baseline Patient Characteristics and Presence or Absence of Palliative Care Consult

	Total ICU Patients (n= 14,745)	PC Consult (n= 3,619)	No PC Consult (n= 11,126)
Age Group			
18-64	7,377 (50.0%)	1,001 (27.7%)	6,376 (57.3%)
65-74	3,691 (25.0%)	1,060 (29.3%)	2,631 (23.6%)
75-84	2,513 (17.0%)	991 (27.4%)	1,522 (13.7%)
85+	1,164 (7.9%)	567 (15.7%)	597 (5.4%)
Gender			
Male	8,646 (58.6%)	2,092 (57.8%)	6,554 (58.9%)
Female	6,079 (41.2%)	1,525 (42.1%)	4,554 (40.9%)
Unknown	-------	2 (< 1%)	18 (< 1%)
Race			
Asian	511 (3.5%)	119 (3.2%)	392 (3.5%)
Black	3,421 (23.2%)	768 (21.2%)	2,653 (23.8%)
Other	3,043 (20.6%)	688 (19.0%)	2,355 (21.2%)
Unknown	862 (5.9%)	189 (5.2%)	673 (6.0%)
White	6,908 (46.9%)	1,855 (51.3%)	5,053 (45.4%)
Ethnicity			
Hispanic	2,906 (19.7%)	528 (14.6%)	2,378 (21.4%)
Non-Hispanic	8,409 (57.0%)	2,147 (59.3%)	6,262 (56.3%)
Unknown	3,430 (23.3%)	944 (26.1%)	2,486 (22.3%)
Insurance			
Managed Care	2,407 (16.3%)	294 (8.1%)	2,113 (19.0%)
Medicaid	2,572 (17.4%)	461 (12.7%)	2,111 (19.0%)
Medicare	7,477 (50.7%)	2,537 (70.1%)	4,940 (44.4%)
Other	2,289 (15.5%)	327 (9.0%)	1,962 (17.6%)
VW Score at Baseline	6 [1, 11]	9 [5, 15]	5 [0, 11]

Table 2: Presence or Absence of Palliative Care Consult by Hospital Category

	Total ICU Patients (n= 14,745)	PC Consult (n= 3,619)	No PC Consult (n= 11,126)
Rural	1,415 (9.6%)	270 (7.5%)	1,145 (10.3%)
Urban	13,330 (90.4%)	3,349 (92.5%)	9,981 (89.7%)
Teaching	8,427 (57.2%)	2,260 (62.4%)	6,167 (55.4%)
Non-teaching	6,318 (42.9%)	1,359 (37.6%)	4,959 (44.6%)

Data presented as n (%)

Table 3: Presence of Absence of Palliative Care Consult by Method of Life-Sustaining Treatment

	Total ICU Patients (n= 14,745)	PC Consult (n= 3,619)	No PC Consult (n= 11,126)
CPR	1,136 (7.7%)	300 (8.3%)	836 (7.5%)
Hemodialysis	2,334 (15.8%)	749 (20.7%)	1,585 (14.2%)
Mechanical Ventilation	8,358 (56.7%)	2,599 (71.8%)	5,759 (51.8%)
Hemodialysis AND Mechanical Ventilation	1,945 (13.2%)	686 (19%)	1,259 (11.3%)
Tracheostomy	647 (4.4%)	184 (5.1%)	463 (4.2%)

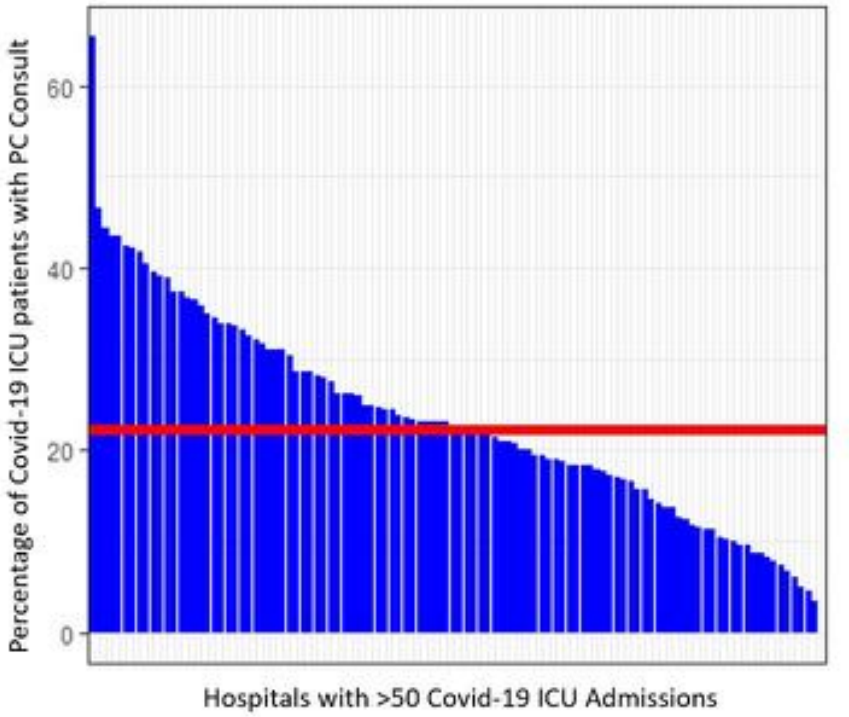
Data presented as n (%)

Table 4: Presence or Absence of Palliative Care Consult by Outcome

	Total ICU Patients (n= 14,745)	PC Consult (n= 3,619)	No PC Consult (n= 11,126)
Hospital LOS	11 [6, 19]	11 [6, 20]	11 [6, 19]
ICU LOS	5 [2, 11]	7 [3, 14]	5 [2, 10]
In-Hospital Mortality	5,449 (37.0%)	2,749 (76.0%)	2,700 (24.3%)
Discharge to Hospice	Missing data?		

Data for Hospital and ICU LOS are presented as median, Q1, and Q3 whereas mortality and discharge to hospital data are presented as n (%)

Figure 1- Percentage of Covid-19 Patients with PC Consult by Hospital



CRITICAL CARE 20

Seasonal Variability of the Incidence Rate of Healthcare-Associated Respiratory Tract Infections in a Neurosurgical ICU

Ksenia Ershova[1], Ivan Savin[2], Oleg Khomenko[3], Olga Ershova[2]

[1]University of Washington, Seattle, WA, [2]Burdenko Neurosurgery Institute, Moscow, Russian Federation, [3]Skolkovo Institute of Science and Technology, Moscow, Russian Federation

INTRODUCTION: Healthcare-associated respiratory tract infections in non-ventilated patients (NVA-HARTI) in neurosurgical intensive care units (ICUs) are an overlooked condition where preventive protocols are virtually non-existent. Meanwhile, ventilator-associated respiratory tract infections (VA-HARTI) have well-established evidence-based prevention protocols. Therefore, universal measures such as hand hygiene, cross-infection prevention, nursing care, physical therapy, and early mobilization become of particular importance in preventing NVA-HARTI. During the months of January, May, June, July, and August resources to perform these universal measures are arguably limited due to reduced staffing related to prolonged state holidays and vacation season. It presumably may lead to an increased nurse-to-patient ratio and the deficit of some auxiliary personnel. The goal of the study was to evaluate the rate of healthcare-associated respiratory tract infections with and without established preventive protocols during 'holiday' vs 'non-holiday' months in a neurosurgical ICU.

METHODS: This observational study included neurosurgical patients admitted to the Burdenko Neurosurgery Institute in Moscow from 2011 to 2018 who stayed in the ICU for >48h. We designated five months (January, May, June, July, and August) as a group of 'holiday months'. January and May are the months with the highest number of Russian federal holidays (9-11 days per month). From interviewing nursing staff, we found that June, July, and August are the months when most nurses take their vacation, including physical therapists who are off duty for most of this period making early mobilization very limited. Regarding other personnel changes, the introduction of new staff or trainees was minimal, and the ICU team remained stable over time. We compared the median incidence rate of NVA-HARTI and VA-HARTI during 'holiday months' to the rest of the year. Mann-Whitney test and Wilcoxon signed-rank test for yearly data were used to compare combined monthly incidence.

RESULTS: 2918 patients were included; 528 cases of VA-HARTI and 220 cases of NVA-HARTI occurred. The median incidence rate of NVA-HARTI during 'non-holiday months' was 3.0 [Q1, Q3: 1.8; 6.1] per 1000 patient-days in the ICU. During the 'holiday months', the incidence rate increased by 78.6%, to 5.4 [Q1, Q3: 3.3; 7.7] per 1000 patient-days. The difference was statistically significant with a Mann-Whitney test p-value of 0.0066 and Wilcoxon test p-value of 0.016 (Figure 1). However, for VA-HARTI such a difference was not observed: the median incidence rate was 9.8 vs 8.6 per 1000 patient-days constituting a non-significant 12.3% decrease, with a p-value of 0.46 (Figure 2).

CONCLUSION: This study demonstrated that in neurosurgical ICU patients, the incidence of NVA-HARTI is higher during 'holiday months' than 'non-holiday months'. It might be related to insufficient staffing leading to increased workload and resulting in the reduced use of universal preventive measures and early mobilization during this period. However, there may be other contributing factors responsible for the seasonal variability of incidence rates. Additionally, we did not find holiday-related seasonal variability of VA-HARTI incidence rate. One of the reasons for this can be that the incidence of healthcare-associated infections with well-established evidence-based prevention protocols is less susceptible to disruption in nursing care, early mobilization, and the use of universal infection prevention measures. This study has design limitations and its findings need to be confirmed by prospective interventional studies.

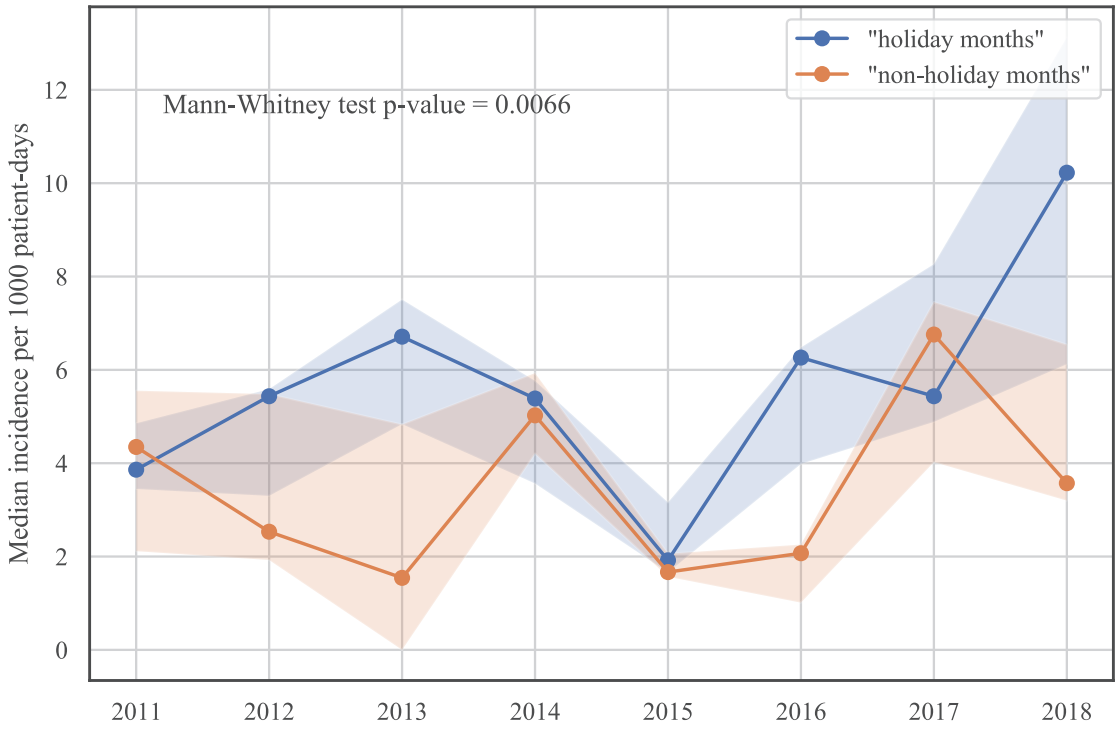


Figure 1. The median incidence rate of healthcare-associated respiratory tract infections in non-ventilated patients (NVA-HARTI) during"holiday months" (January, May, June, July, August) vs "non-holiday months" by year in a neurosurgical ICU. Incidence rate is shown as median number of cases per 1000 patient-days in the ICU with 1st and 3rd quartile.

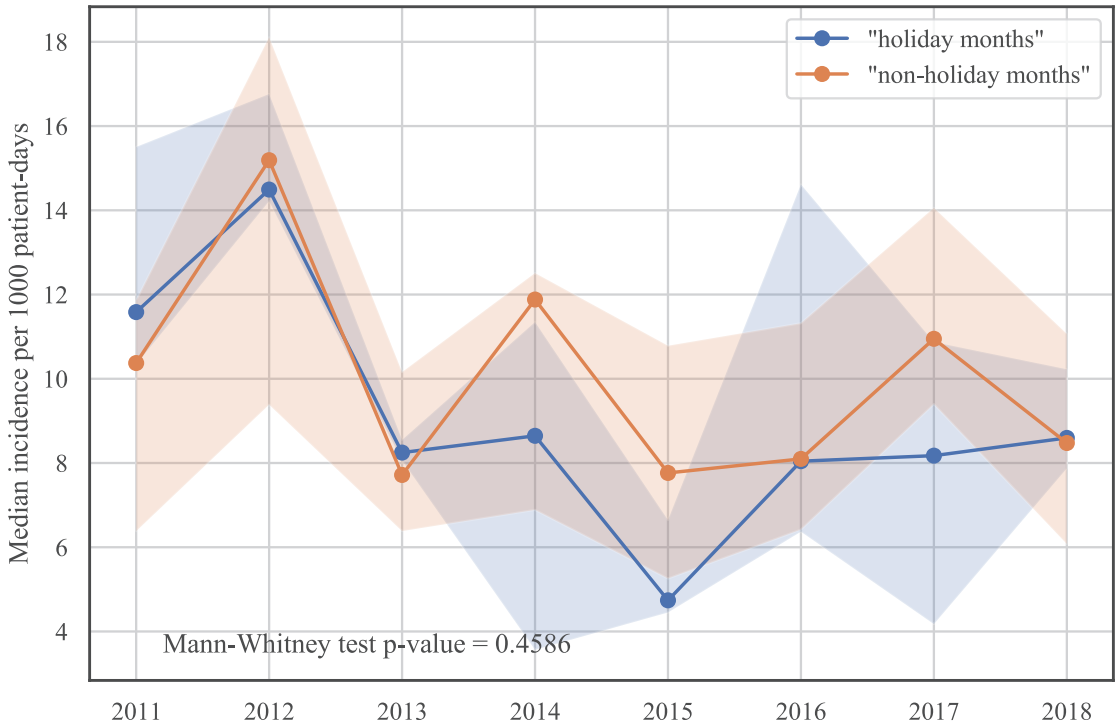


Figure 2. The median incidence rate of ventilator-associated healthcare-associated respiratory tract infection (VA-HARTI) during"holiday months" (January, May, June, July, August) vs "non-holiday months" by year in a neurosurgical ICU. Incidence rate is shown as median number of cases per 1000 patient-days in the ICU with 1st and 3rd quartile.

CRITICAL CARE 21

Effects of Blood Product Administration on Oxygen Dissociation Physiology of Patients Undergoing Cardiac Surgery

Karl Kristiansen[1], Ian Welsby[2], Nazish Hashmi[3], Dan Weikel[4]

[1]Duke University, Durham, NC, [2]Duke University School of Medicine, Durham, NC, [3]Duke University Medical Center, Durham, NC, [4]Duke University, Durham, United States of America

INTRODUCTION: Despite advances in blood conservation, cardiac surgery remains as one the primary consumers of blood products with estimates that 40-95% of cardiac surgery patients receive at least one transfusion; this accounts for 20-25% of all transfusions yearly.[1,2] Acute reduction in red cell mass has been historically treated aggressively via transfusions but concerns with cost, side effects, blood supply, and more recently lack of efficacy has trended towards a more restrictive practice.[3,4] To help elucidate the curious marginal benefit/deleterious effects of PRBC transfusion, we theorized that the reduced P50 value in PRBCs would negatively affect cardiac surgery patients' post-transfusion P50 value, reflecting impaired oxygen delivery to end-organ tissues. Although there are small data sets regarding global P50 changes in infants who have undergone transfusion[5] and trauma patients[6], this is the first study to our knowledge designed to examine global P50 changes in adult cardiac surgery patients.

METHODS: This was an IRB-approved retrospective study that included 1595 patients that underwent cardiac surgery Duke University Hospital, received intraoperative PRBCs, and had a pulmonary artery catheter placed. Point of care P50 analyzers have a high cost burden. Fortunately, P50 has been able to be calculated off of single mixed venous blood sample with an equation originally derived by Hill and has been examined by via sensitivity analysis to determine the error between P02 10-100, with the minimum errors between P02 20-45.[6] The number of PRBC transfused intraoperatively was recorded and then a P50 value was calculated at 12 hours and 24 hours post operating room. We assumed all patients initial P50 value was 27mmHg.

RESULTS: Of the 1595 patients initially included in our study, 477 had the mixed venous blood gas we parsed for to calculate P50 and were ultimately included. [Table 1] The average number and standard deviation of PRBC, FFP, PLT, and cryoprecipitate given was 1.10 (2.74), 1.19 (2.48), 1.82 (1.45) and 1.35 (1.36) respectively. The average and standard deviation of P50 at 12 hours was 26.16 (2.19) mmHg and 26.28 (2.07) mmHg at 24 hours. Univariate analysis for blood products relation to P50 at 12 hours [n=256) and 24 hours (n=123) was performed. [Table 2] Although no statistical significance was found at 12 hours, the relationship between PRBC administration and PRBC was significant at 24 hours: -0.14 per PRBC given (sd=0.05) with a p-value of 0.0056.

CONCLUSION: Assuming that the initial P50 value of patients was 27mmHg initially, these results support our initial hypothesis that PRBC transfusion lowered the P50 value of postoperative cardiac surgery patients at the 24-hour measurement by -0.14mmHg per units of PRBC given. For platelets and cryoprecipitate, the effect was also significant with a larger effect size: -0.24 (sd=0.103) and -0.26 (sd=0.112) respectively; which may be a function that these products are usually only given after multiple PRBC transfusions. Further work to examine clinical outcomes with regards to P50 is needed, particularly with therapeutics on the horizon.[7]

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Table 1: Patient demographics, baseline characteristics, intra-op and post-op data [mean (sd) or median [IQR]; N (%)]

	N = 477
Demographics	
Age	59.98 (13.98)
Gender (M)	324 (67.9%)
BMI, n = 474	29.85 (6.95)
Race	
African American/Black	138 (28.9%)
White	306 (64.2%)
Asian	7 (1.5%)
American Indian/Alaskan Native	10 (2.1%)
Other	16 (3.4%)
Smoking status (Y)	38 (8.0%)
Baseline Characteristics	
ASA Status	
3	33 (6.9%)
4	428 (89.7%)
5	16 (3.4%)
Starting Hb, n = 458	12.00 (2.02)
Emergent (Y)	75 (15.7%)
Intra-op Data	
PRBC, units, n = 357	1.10 (2.74)
FFP, units, n = 357	1.19 (2.48)
Plt, units, n = 357	1.82 (1.45)
Cryo, units, n = 357	1.35 (1.36)
Post-op Data	
SvO2 – 12 hr, n = 339	66.94 (7.84)
SvO2 – 24 hr, n = 172	65.39 (2.07)
PO2 – 12 hr, n = 339	34.44 (4.99)
PO2 – 24 hr, n = 339	33.78 (5.07)
p50 – 12 hr, n = 339	26.16 (2.19)
p50 – 24 hr, n = 172	26.28 (2.07)
pH – 12 hr, n = 338	7.39 (0.05)
pH – 24 hr, n = 124	7.40 (0.05)
Hospital LoS, days	30.44 (26.40)
ICU LoS, hours	8.66 (2.22)

Table 2: Univariate model results

	12 Hr Model, n = 256		24 Hr Model, n = 123	
	Estimate	**p-values**	**Estimate**	**p-values**
PRBC	-0.04 (0.054)	0.4300	-0.14 (0.050)	0.0056
FFP	0.03 (0.055)	0.6470	-0.05 (0.062)	0.3450
Platelets	-0.01 (0.102)	0.8850	-0.24 (0.103)	0.0217
Cryoprecipitate	-0.03 (0.107)	0.7720	-0.26 (0.112)	0.0245

CRITICAL CARE 22

Association of Initial Vasopressor Choice with Clinical and Functional Outcomes Following Moderate-Severe Traumatic Brain Injury: a TRACK-TBI study

Camilo Toro[1], Jason Barber[2], Nancy Temkin[2], Tetsu Ohnuma[3], Michael L James[4], Vijay Krishnamoorthy[3]

[1]Duke University School of Medicine, Durham, NC, [2]University of Washington, Seattle, WA, [3]Duke University, Durham, NC, [4]Duke University, Durham, United States of America

INTRODUCTION: Early hypotension following moderate-severe traumatic brain injury is associated with increased mortality and worse long-term outcomes. Current guidelines support the use of intravenous vasopressors to maintain optimal blood pressure control and improve outcomes for patients; however, guidelines do not specify vasopressor type, resulting in variation in clinical practice. Existing studies comparing the utilization and efficacy of different vasopressors vary in their results. Therefore, we conducted a multicenter study to examine utilization patterns of different vasopressors in the management of early hypotension following TBI and their association with long-term clinical and functional outcomes.

METHODS: In this retrospective cohort study of patients enrolled in the TRACK-TBI study, we examined adults with moderate-severe TBI (defined as Glasgow Coma Scale score <13) who were admitted to the ICU and received an intravenous vasopressor within 48 hours of admission. We excluded patients who received more than vasopressor in the first hour of admission (Figure 1). The primary exposure was initial vasopressor choice (phenylephrine versus norepinephrine) and the primary outcome was 6-month Glasgow Outcomes Scale Extended (GOSE) with secondary outcomes of length of hospital stay, length of ICU stay, in-hospital mortality, requirement of dialysis, and 6-month Disability Rating Scale (DRS). Descriptive statistics were used to examine the utilization patterns of initial vasopressors and demographic, clinical and facility characteristics of the cohort. Regression analysis was used to assess differences in outcome between norepinephrine and phenylephrine, with propensity-weighting to address selection bias due to both the non-random allocation of the treatment groups and subject drop-out.

RESULTS: The final study sample included 157 patients, of whom 79 (50%) received norepinephrine and 66 (42%) received phenylephrine as their initial vasopressor (Table 1). 121 (77%) of patients in the study population were male, with a mean age of 43.1 years and arrival GCS of 5.0. Only 12 (8%) individuals received an initial vasopressor other than norepinephrine and phenylephrine. Of all subjects, 73 (54%) received a second vasopressor after at least one hour following administration of the first vasopressor, most commonly phenylephrine (Figure 2). Utilization of norepinephrine versus phenylephrine differed significantly only by clinical site; there was no association of initial vasopressor choice with demographic or clinical characteristics. For the 145 subjects with complete outcomes data, we found a mean (SD) 6-month GOSE of 3.4 and 3.8 for norepinephrine and phenylephrine, respectively. Choice of norepinephrine versus phenylephrine was not significantly associated with improved 6-month GOSE (weighted odds ratio 1.38, 95% CI 0.72-2.64, p=0.37) or any secondary outcome (Table 2).

CONCLUSION: Most patients with moderate-severe TBI commonly receive either phenylephrine or norepinephrine as first-line agents for hypotension following brain injury, with significant variability among hospitals. Initial choice of norepinephrine, compared to phenylephrine, was not associated with improved clinical or functional outcomes.

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Figure 1: Study population with inclusion and exclusion criteria

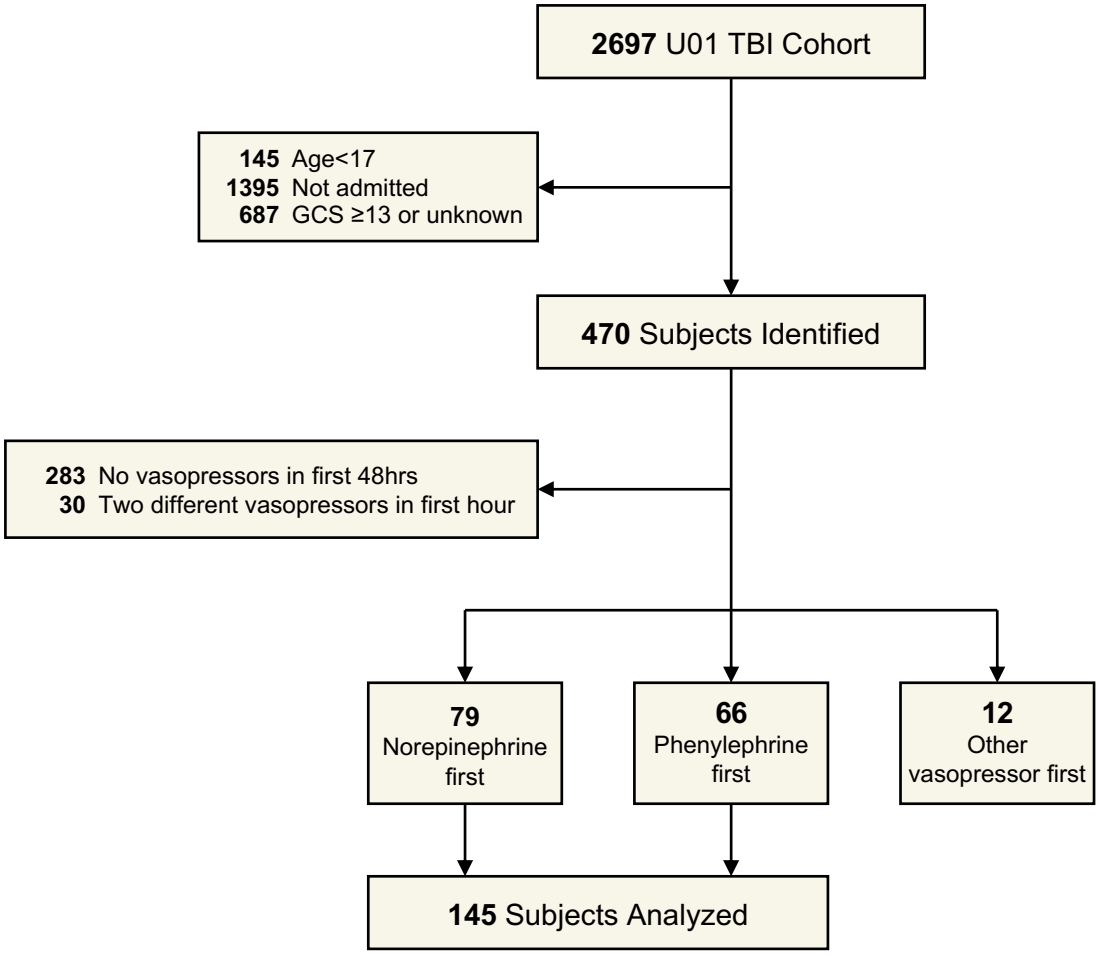

Table 1: Patient demographic, clinical, and facility characteristics

Variable		First IV Vasopressor		
	Total	Norepinephrine	Phenylephrine	Other
Subjects	**157**	**79 (50%)**	**66 (42%)**	**12 (8%)**
Had Second Vasopressor Type				
No	84 (46%)	54 (64%)	25 (30%)	5 (6%)
Yes	73 (54%)	25 (34%)	41 (56%)	7 (10%)
Mean (SD) hours	26.5 (38.9)	33.4 (43.9)	25.4 (38.3)	7.7 (8.3)
0-4 hours	26 (17%)	6 (23%)	16 (62%)	4 (15%)
4-24 hours	28 (18%)	11 (39%)	14 (50%)	3 (11%)
24+ hours	19 (12%)	8 (42%)	11 (58%)	0 (0%)
Site				
1	37 (24%)	30 (81%)	5 (14%)	2 (5%)
2	8 (5%)	3 (38%)	4 (50%)	1 (13%)
3	31 (20%)	7 (23%)	24 (77%)	0 (0%)
4	12 (8%)	11 (92%)	1 (8%)	0 (0%)
7	39 (25%)	18 (46%)	19 (49%)	2 (5%)
9	1 (1%)	0 (0%)	1 (100%)	0 (0%)
10	9 (6%)	5 (56%)	3 (33%)	1 (11%)
11	2 (1%)	1 (50%)	1 (50%)	0 (0%)
12	4 (3%)	1 (25%)	3 (75%)	0 (0%)
14	1 (1%)	0 (0%)	0 (0%)	1 (100%)
15	1 (1%)	0 (0%)	0 (0%)	1 (100%)
16	1 (1%)	0 (0%)	0 (0%)	1 (100%)
17	11 (7%)	3 (27%)	5 (45%)	3 (27%)
Age				
Mean (SD)	43.1 (17.3)	43.3 (17.8)	43.0 (17.1)	41.9 (15.5)
<20	9 (6%)	6 (67%)	3 (33%)	0 (0%)
20-29	38 (24%)	17 (45%)	17 (45%)	4 (11%)
30-39	29 (18%)	16 (55%)	12 (41%)	1 (3%)
40-49	26 (17%)	12 (46%)	10 (38%)	4 (15%)
50-59	27 (17%)	11 (41%)	14 (52%)	2 (7%)
60-69	13 (8%)	9 (69%)	4 (31%)	0 (0%)
70-79	13 (8%)	7 (54%)	5 (38%)	1 (8%)
80+	2 (1%)	1 (50%)	1 (50%)	0 (0%)
Sex				
Male	121 (77%)	63 (52%)	50 (41%)	8 (7%)
Female	36 (23%)	16 (44%)	16 (44%)	4 (11%)
Race				
White	123 (81%)	60 (49%)	54 (44%)	9 (7%)
Black	15 (10%)	10 (67%)	5 (33%)	0 (0%)

CRITICAL CARE 23

AI-guided Prediction of Need of ICU Admission

Martin Graessner[1], Bettina Jungwirth[1], Elke Frank[2], Jochen Vasold[1], Stefan J Schaller[3], Kurt Ulm[4], Manfred Blobner[5], Bernhard Ulm[2], Simone M Kagerbauer[2]

[1]School of Medicine, University of Ulm, Ulm, Germany, [2]Technical University of Munich, Munich, Germany, [3]Charité - Universitätsmedizin Berlin, Berlin, Germany, [4]School of medicine; Technical University of Munich, Munich, Germany, [5]Klinikum Rechts der Isar der TUM, Munich, MA

INTRODUCTION: Intensive care beds are a scarce resource in healthcare. However, neither experienced clinicians nor surgical risk scores such as ASA classification[1] validly predict which surgical patients require intensive care. Therefore, this exercise creates a machine learning algorithm to predict the postoperative probability of admission to an ICU on a personalized level.

METHODS: After ethical approval, prediction models of data of 94839 patients undergoing a first non-cardiac surgery between June 2014 and March 2020 were created with extreme gradient boosting[2,3] to estimate the need of ICU admission. Possible predictors were extracted from tabular and free-text sources of the clinic information system (CIS), the laboratory information system (LIS) and the preoperative section of the patient data management system (PDMS), which work independently from each other. The final dataset was split in a training (n=67344), testing (n=16809), and validation (n=10686) cohort. Model development included a random hyperparameter search followed by 3-fold cross validation for 10000 random combinations. AUROC of 63 models (any combination of 6 parent categories) were compared using Bayesian hyperparameter tunings. Top 10 features providing information gain were identified and used for a classification tree. Waterfall diagrams for index patients were created.

RESULTS: The full model including 1627 features proved high accuracy (AUROC, testing: (0.939 [0.930-0.948]), validation: (0.932 [0.919- 0.945]). Data of sources in tabular format performed better than free-text. The highest information gain had preoperative order for red cell concentrate (10.4%), order for fresh frozen plasma (2.6%), and C-reactive protein (2.4%). Personalized probabilities for ICU admission were calculated. within narrow borders.

CONCLUSION: We created a highly accurate and partly explicable machine learning algorithm to predict ICU admission on a personalized level. Most factors are not modifiable by preoperative optimization measures. Therefore, the patient's probability of ICU admittance has to be taken for granted but can be used to adjust clinical capacities.

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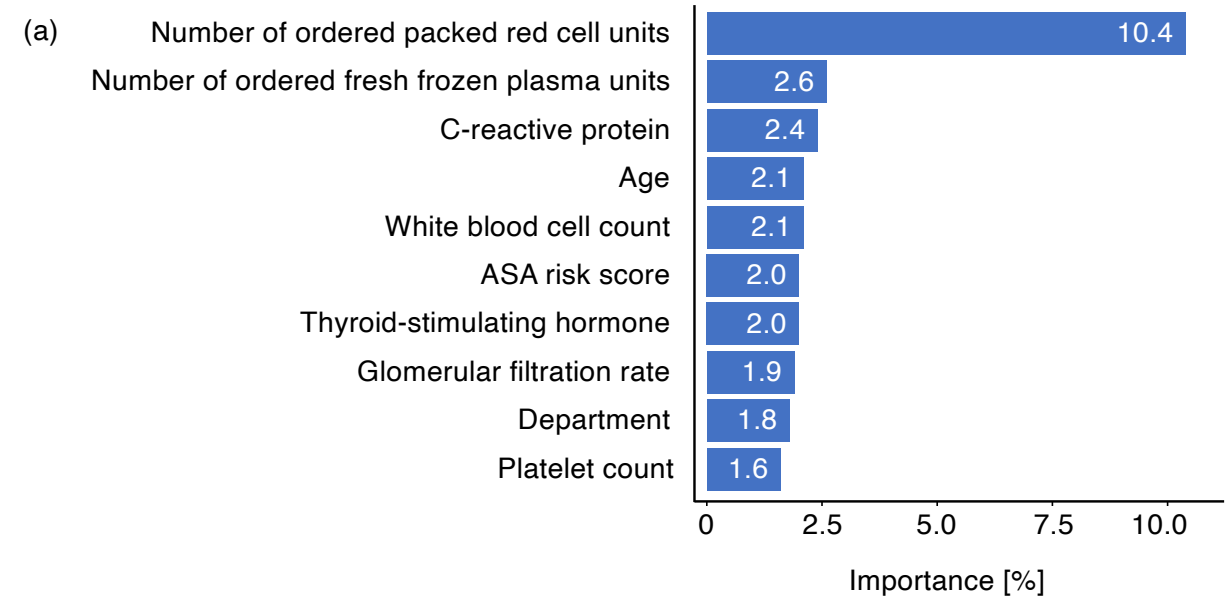

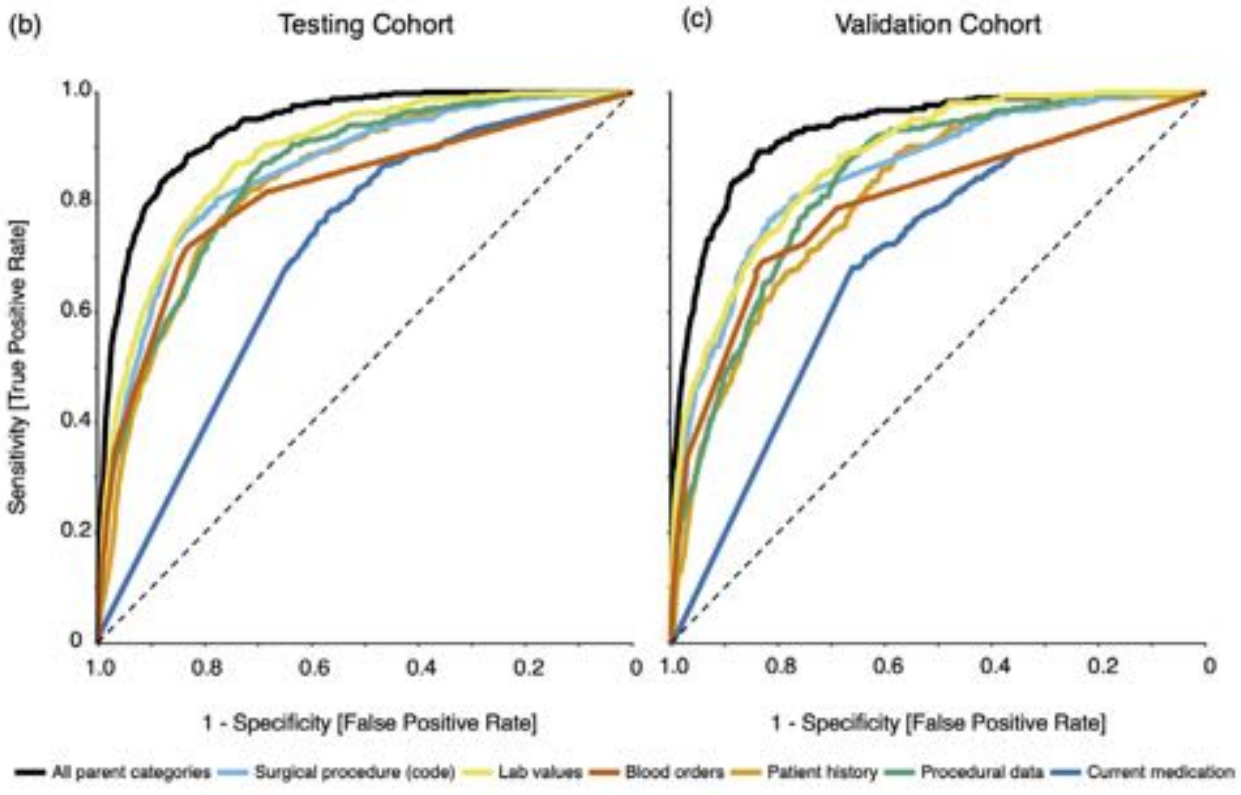

Top 10 variables and their predictive power within the model in the training cohort (a). Receiver operating characteristic of the full model and the models of the six parent categories (patient history, surgical procedure (code), procedural data, lab values, current medication and blood orders) in the testing (b) and the validation cohort (c).

CRITICAL CARE 24

Feasibility of Remote EEG Neuromonitoring in the ICU

Brian A Chang[1], Tuan Cassim[1], Esther Goldstein[1], Sagar R Navare[1], Harry Wanar[1], Matthias Kreuzer[2], Aaron Mittel[1], Paul S Garcia[1]

[1]Columbia University Medical Center, New York, NY, [2]Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

INTRODUCTION: Cerebral dysfunction in the intensive care unit (ICU) is an under-diagnosed complication, despite its association with poor short and long-term outcomes[1]. Clinicians can monitor patients' cerebral function with the use of continuous electroencephalography (cEEG). However, routine cEEG is resource intensive. As an alternative, EEG monitoring can be performed using reduced electrode montages. Recently, it has become possible to remotely monitor frontal EEG devices intended for titration of anesthetic medications. The value of these devices in the ICU is not known. Thus, we undertook a feasibility study to evaluate their utilization.

METHODS: We performed a prospective observational study in a sample of mechanically ventilated, critically ill, adult patients. Eligible patients underwent cEEG monitoring via Sedline Root™ in combination with the KiteTM system (Masimo Corp., Irvine, CA). Bi-frontal EEG information was obtained through adhesive electrodes configured on a disposable sensor applied across the forehead. EEG data were collected for at least 24 hours using this abbreviated electrode montage (Fp1/2, F7/8, reference Fz). Daily sensor checks were conducted to ensure integrity and appropriate impedance. Using the Masimo KiteTM system, raw continuous EEG waveforms were viewed and interpreted in real-time by a neuroanesthesiologist. EEG data were subsequently downloaded onto a secure device for off-line quantitative analyses using custom software scripts written in MATLAB (Mathworks, Inc. Natick, MA). These data were evaluated for EEG quality including data acquisition failures and artifact detection. Additional clinical data were extracted via retrospective chart review. A brief descriptive analysis was conducted to characterize the study population.

RESULTS: Twelve patients were enrolled over the course of a 2-week period. The majority of patients were male (83%) and were admitted to the ICU after surgical intervention (83%). Patients were monitored for a median of 50 hours [IQR: 25 - 74 hours]. Real-time remote analysis of one of the patient's resulted in a neurology consult and subsequent full montage cEEG. In two patients, sedating medications were adjusted based on real-time feedback from the neuromonitoring team. No adverse events were reported. Several factors contributed to a reduction in quantitative EEG analysis. Overall, 9/12 patients had at least 90% of their EEG data of high enough quality for analysis (Table 1). This was determined after removing artifacts due to poor electrode contact or disconnection (Figure 1). As we have previously reported, 'clipping' artifacts occur with this data acquisition system[2]. The average contribution to loss of EEG data was less than 2% (Table 1).

CONCLUSION: These preliminary findings suggest that remote bifrontal EEG neuromonitoring is feasible in the ICU. We demonstrated that a commercial device can be used to acquire data appropriate for quantitative analysis. In the future, decision-support systems may utilize this technology to aid in diagnosis and/or treatment planning. Additionally, this approach may increase accessibility to advanced neuromonitoring, particularly in low-resource environments. While the purpose of this study was to evaluate feasibility of remote bifrontal EEG neuromonitoring, clinical care was modified for several patients based on EEG data obtained. Future studies may consider the implications of a remote neuromonitoring EEG team on clinical outcomes.

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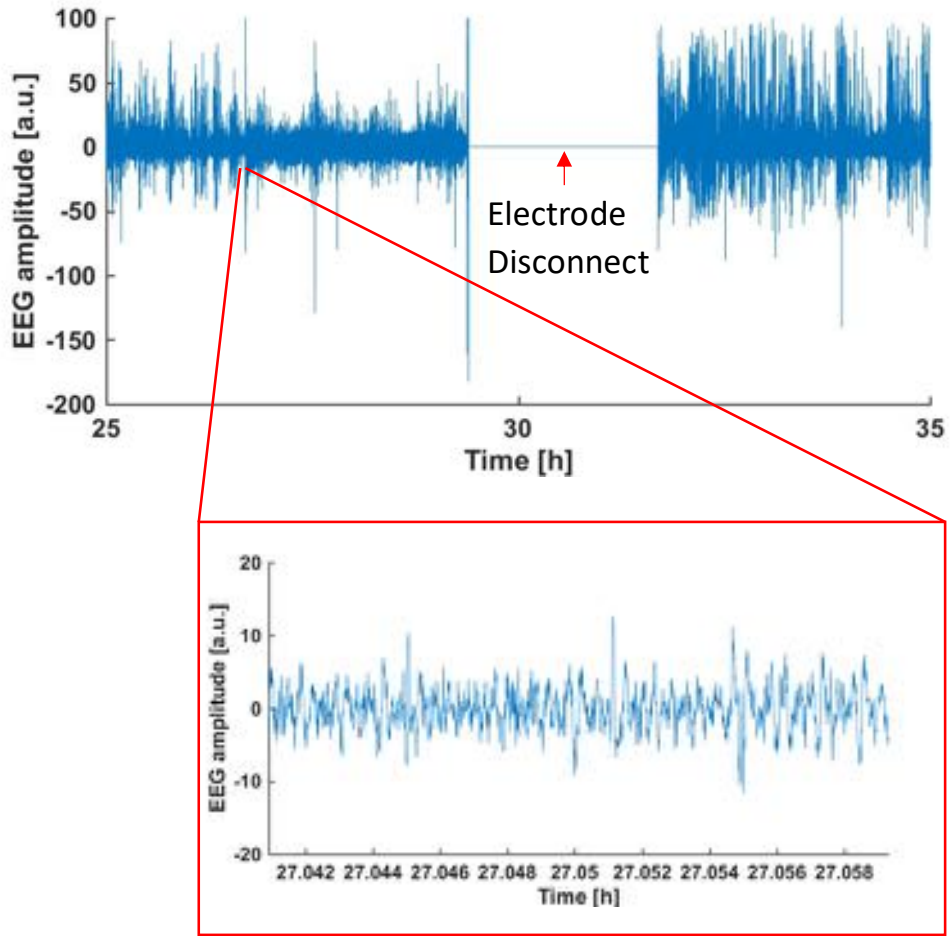
Table 1: Assessment of EEG data quality

Patient	Age (y)	Sex	Total EEG Duration (h)	Duration with connected electrodes (h)*	Proportion of EEG data with "clipping" artifact (%)±	Proportion of analyzable data over entire duration (%)
1	70	M	22.5	22.1	3.2	94.8
2	56	M	52.7	47.8	0.6	90.0
3	73	M	73.4	50.5	0.4	68.4
4	39	F	70.1	68.6	1.3	96.6
5	41	F	74.6	71.5	0.3	95.6
6	54	M	77.2	75.2	0.9	96.4
7	73	M	26.3	26.2	0.1	99.5
8	46	M	74.6	73.6	4.3	94.3
9	68	M	19.7	17.1	0.3	86.2
10	88	M	28.9	27.4	0.8	94.1
11	78	M	47.3	46.9	0.3	98.7
12	43	M	7.4	1.9	5.4	21.0

***** Total time (h) of EEG monitoring after removing periods of electrode disconnection or poor contact

± Proportion of EEG data that contained artifact secondary to issues with data acquisition settings on the SedLine device, commonly described as "clipping" (2)

Figure 1: EEG waveform after filtering and demonstration of electrode disconnect



CRITICAL CARE 25

Predicting Poor Outcome of COVID-19 Patients on the day of Admission with the COVID-19 Score

Luke Tseng[1], Erin Hittesdorf[2], Mitchell Berman[2], Desmond Jordan[2], Nina Yoh[2], Katerina Elisman[2], Katherine Eiseman[1], Yuqi Miao[3], Shuang Wang[3], Gebhard Wagener[2]

[1]Columbia University Vagelos College of Physicians and Surgeons, New York, NY, [2]Columbia University Irving Medical Center, New York, NY, [3]Columbia University Mailman School of Public Health, New York, NY

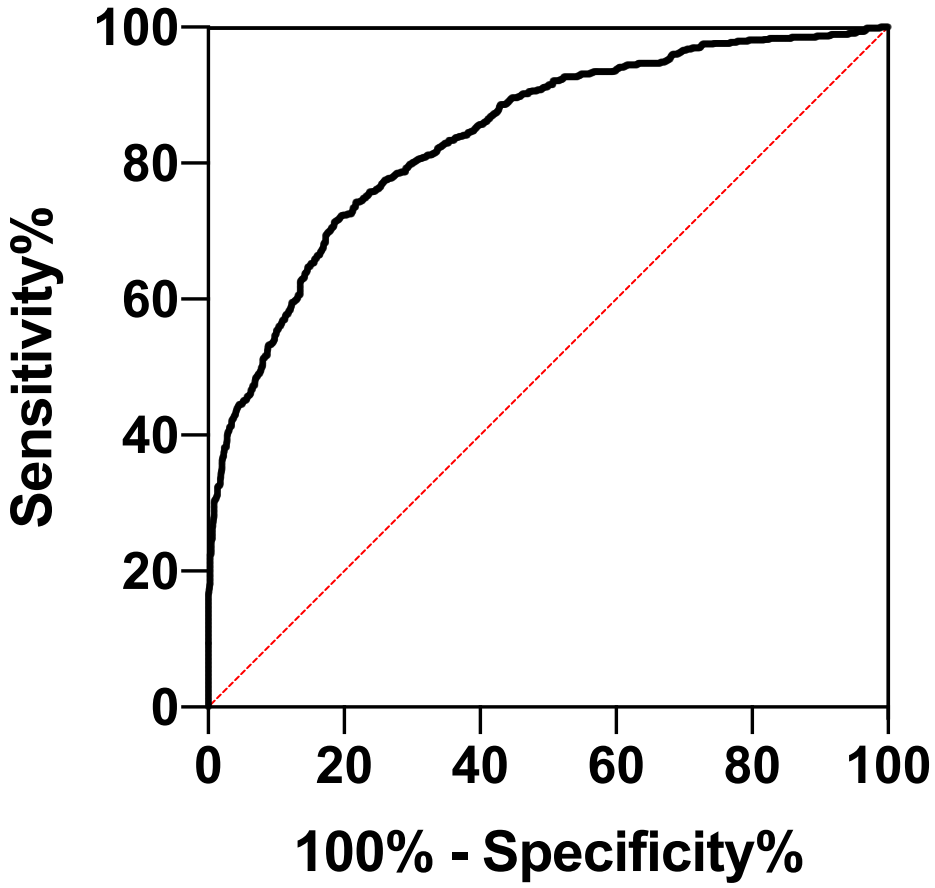
INTRODUCTION: From March to May 2020, New York City experienced a severe crisis of COVID-19 cases that resulted in a surge of patients who required hospital-level care. Although many patients recovered quickly, some progressed to develop severe COVID-19 characterized by multi-organ failure and death. There is an urgent need for objective clinical tools that can identify patients at risk for severe COVID-19 during admission to aid in triage. Laboratory tests are a promising source of easily obtained, objective data, and there is evidence that inflammatory laboratory markers and markers of cardiac, liver, and renal dysfunction may be associated with severe disease. The aim of this study is to determine which laboratory values on hospital admission can predict poor outcome in COVID-19 patients and to create a predictive COVID-19 score that can help practitioners triage patients on admission to the hospital.

METHODS: This retrospective cohort study included all 2545 patients admitted to Columbia University Irving Medical Center, a tertiary academic medical center, with COVID-19 from March to May 2020. The primary combined endpoint was either intubation, stage 3 acute kidney injury (AKI) defined by Kidney Disease Improving Global Outcomes (KDIGO) criteria (increase in serum creatinine to 3 times baseline or to ≥4 mg/dL within seven days after admission), or death during hospitalization. Data were retrieved from electronic medical record systems. Laboratory tests available on admission in at least 70% of patients (and age) were included for univariate analysis. Tests that were statistically or clinically significant were then included in a multivariate binary logistic regression model using step-wise exclusion. 70% of all patients were used to train the model, and 30% were used as an internal validation cohort.

RESULTS: Out of 2545 patients, 537 patients (21.1%) died, 309 patients (12.1%) were intubated, and 324 patients (12.7%) experienced stage 3 AKI. The primary combined endpoint was observed in 833 patients (32.7%). For the univariate analysis, 53 out of 99 laboratory tests (as well as race, sex and age) were available for ≥70% of patients on admission, and of these, 47 tests (and age) were significantly different between patients with and without the endpoint. For the multivariate analysis, we removed patients who were missing any of these variables, which yielded a final cohort of 1492 patients. The final multivariate model included age, albumin, creatinine, C-reactive protein (CRP) and lactate dehydrogenase (LDH). The area under the ROC curve was 0.850 (CI[95%]: 0.813, 0.889) (Figure 1), with a sensitivity of 0.800 and specificity of 0.761. The probability of experiencing the primary endpoint (i.e. the COVID-19 score) can be calculated as: $P = [\exp(-2.4475 \times \text{age} - 0.6504 \times \text{albumin} + 0.81926 \times \text{creatinine} + 0.00388 \times \text{CRP} + 0.00143 \times \text{LDH})] / \{1 + [\exp(-2.4475 \times \text{age} - 0.6504 \times \text{albumin} + 0.81926 \times \text{creatinine} + 0.00388 \times \text{CRP} + 0.00143 \times \text{LDH})]\}$.

CONCLUSION: Our study demonstrated that poor outcome in COVID-19 patients can be predicted on the day of admission with good sensitivity and specificity using age and a handful of laboratory tests (albumin, creatinine, C-reactive protein, lactate dehydrogenase). The COVID-19 score is potentially very useful for early identification of patients who are at risk for severe disease.

Figure 1. Receiver operating characteristic (ROC) curve of the admission COVID-19 score to predict the primary combined endpoint (either stage 3 acute kidney injury, intubation or death) in the internal validation cohort (n=447):



CRITICAL CARE 26

Do-Not-Resuscitate Orders in Patients with COVID-19 Admitted to ICUs in the US

Galen Royce-Nagel[1], Karthik Raghunathan[2], Julien Cobert[3], Daryl Kerr[4], Nathaniel Erskine[5], Matthew Fuller[5], Zachary Frere[6], Yi-Ju Li[7], Tetsu Ohnuma[6], Vijay Krishnamoorthy[6], Raquel R Bartz[6], Krista L Haines[8]

[1]Duke University Hospital, Durham, NC, [2]Duke University School of Medicine, Durham, NC, [3]University of California San Francisco, San Francisco, United States of America, [4]Rush University Medical Center, Chicago, IL, [5]Duke University Hospital, Durham, United States of America, [6]Duke University, Durham, NC, [7]Duke University Medical Center, Durham, NC, [8]Duke University, Durham, United States of America

INTRODUCTION: The COVID-19 pandemic has disproportionately impacted elderly, and frail patients with increased comorbidities. The need for goal-oriented and goal-concordant care in critically ill patients has been highlighted by the mortality associated with COVID-19 and the limitations on staffing, supplies and beds that occurs during surges. Prior analyses of hospitalized COVID-19 patients in the US have been limited to evaluating ICU admission rates, comorbidities, organ dysfunction frequency, and overall mortality. In these reports, broad differences are noted in absolute mortality rates and risk-standardized event rates (RSERs) (composite outcome of in-hospital mortality and hospice). No prior report has sought to define rates of Do Not Resuscitate (DNR) in COVID-19 patients which would likely effect how previously published ICU mortality and morbidity outcomes are interpreted. Variations in DNR orders contribute significantly to care delivered, in-hospital mortality, and hospice discharge rates. This study aims to examine the prevalence of DNR orders in COVID-19 patients and associated clinical outcomes.

METHODS: Following IRB approval, Premier, a large, geographically diverse, hospital-based database was examined. We conducted a retrospective study of patients admitted to ICUs with a diagnosis of COVID-19 between April and June 2020 using ICD-10-CM code U07.1 which has previously been validated. To reduce heterogeneity we only included hospitals with a minimum of 50 COVID ICU patient admissions. The exposure of interest was DNR status ascertained using ICD-10 codes. Among patients with and without DNR orders, descriptive statistics were used to examine demographic and clinical patient characteristics, hospital characteristics, use of life-sustaining treatments (LSTs), and clinical outcomes, including hospice utilization, hospital mortality, hospital length of stay (LOS), ICU LOS, and discharge disposition.

RESULTS: Of the 14,745 patients admitted to the ICU, 4,962 (34%) were identified as DNR. Among DNR patients, 1,732 (35%) had this status on admission. The presence of DNR orders varied significantly between hospitals from less than 10% to greater than 60% (Figure 1). There were no significant differences between DNR rates in urban vs rural or teaching vs non-teaching institutions. Rates of DNR status increased with age. 75% of patients aged 85 and above had a DNR order. No significant differences were noted in DNR rates between races; however, there were lower rates of DNR among patients who identified as Hispanic ethnicity when compared to non-Hispanic or unknown.When considering insurance status, higher rates of DNR status were noted among Medicare patients. Compared to full code patients, DNR patients were less likely to receive LSTs such as mechanical ventilation, renal replacement therapy, and cardiopulmonary resuscitation (CPR). Only 67% of ICU patients with in-hospital mortality or discharge to hospice had a DNR order. Of those patients with a DNR order, 81% died in hospital or were discharged to hospice. Among full code patients, 21% died in the hospital or were discharged to hospice.

CONCLUSION: This analysis showed significant variation in utilization of DNR status with up to a 10-fold rate difference between hospitals. Lower rates of DNR status historically observed in minority communities was only seen in our data when comparing Hispanic to non-Hispanic whites. When evaluating insurance status, Medicare patients had higher rates of DNR; however, this is similar to other literature. This analysis showed that most patients, including those with advanced care planning (65% with a DNR), died in the hospital. This information is challenging to interpret based on the difficulties of transferring patients to hospice in the COVID-19 era with either Covid positive status or patient instability. Differences in outcomes could reflect diversity in fundamental quality of care, different admission thresholds, differences in medical comorbidities of the patients presenting to these hospitals (data not captured in the RSER), and/or variations in the presentation of the COVID-19 disease itself. On the other hand, differences in DNR rates could reflect hospital and physician comfort with end-of-life planning, presence of a strong palliative care team, community sentiments toward goals of care discussions, and/or distrust of the medical community as a whole.

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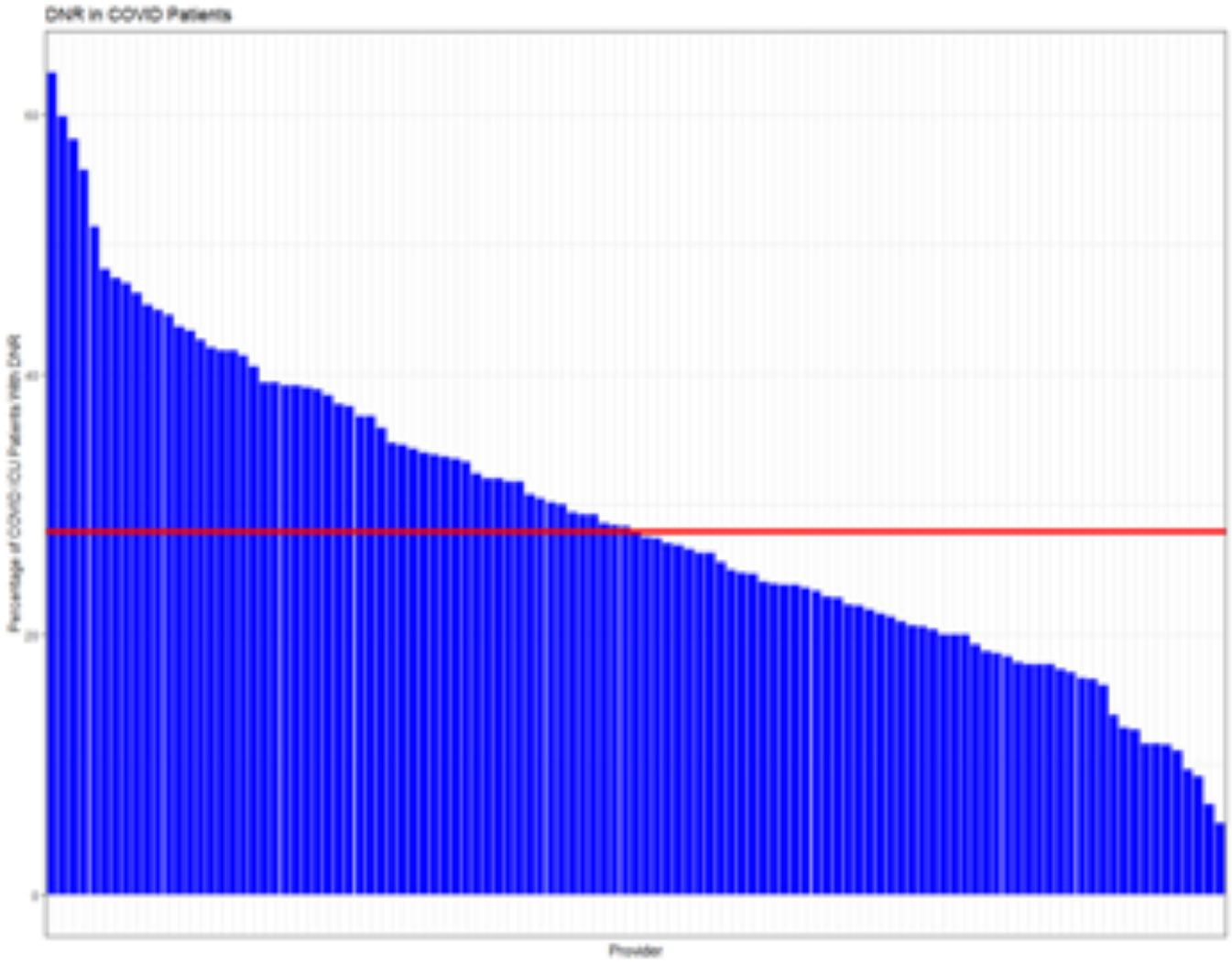

Fig. 1

Table 1: Patient Characteristics

	Total ICU pts	DNR	Full Code
Sample Size	14745	4962 (33.6%)	9783 (66.4%)
Age Median IQR	64 [54, 74]	73 [64, 81]	60 [49, 70]
Age group			
18-64	7377 (50.0%)	1305 (17.7%, 26.3%)	6072 (82.3%, 62.1%)
65-74	3691 (25.0%)	1430 (38.7%, 28.8%)	2261 (61.3%, 23.1%)
75-84	2513 (17.0%)	1399 (55.7%, 28.2%)	1114 (44.3%, 11.4%)
85+	1164 (7.9%)	828 (71.1%, 16.7%)	336 (28.9%, 3.4%)
Gender			
Male	8646 (58.6%)	2854 (33.0%, 57.5%)	5792 (67.0%, 59.2%)
Female	6079 (41.2%)	2103 (34.6%, 42.4%)	3976 (65.4%, 40.6%)
Race			
Asian	511 (3.5%)	157 (30.7%, 3.2%)	354 (69.3%, 3.6%)
Black	3421 (23.2%)	1041 (30.4%, 21.0%)	2380 (69.6%, 24.3%)
Other	3043 (20.6%)	889 (29.2%, 17.9%)	2154 (70.8%, 22.0%)
Unknown	862 (5.9%)	228 (26.5%, 4.6%)	634 (73.5%, 6.5%)
White	6908 (46.9%)	2647 (28.3%, 53.3%)	4261 (61.7%, 43.6%)
Ethnicity			
Hispanic	2906 (19.7%)	640 (22.0%, 12.9%)	2266 (78.0%, 23.2%)
Non-Hispanic	8409 (57.0%)	3011 (35.8%, 60.7%)	5398 (64.2%, 55.2%)
Unknown	3430 (23.3%)	1311 (38.2%, 26.4%)	2119 (61.8%, 21.7%)
Insurance			
Managed Care	2407 (16.3%)	393 (16.3%, 7.9%)	2014 (83.7%, 20.6%)
MedicAid	2572 (17.4%)	574 (22.3%, 11.6%)	1998 (77.7%, 20.4%)
Medicare	7477 (50.7%)	3585 (47.9%, 72.2%)	3892 (52.1%, 39.8%)
Other	2289 (15.5%)	410 (17.9%, 8.3%)	1879 (82.1%, 19.2%)
vW Score at Baseline			
Min	-16	-13	-16
First Quartile	1	5	0
Median	6	9	5
Third Quartile	11	15	10
Max	43	43	41

Table 2: Hospital Characteristics

	Total ICU patients	DNR	Full Code
Rural	1415 (9.6%)	384 (27.1%, 7.7%)	1031 (72.9%, 10.5%)
Urban	13330 (90.4%)	4578 (34.3%, 92.3%)	8752 (65.7%, 89.5%)
Teaching	8427 (57.2%)	3011 (35.7%, 60.7%)	5416 (64.3%, 55.4%)
Non-teaching	6318 (42.9%)	1951 (30.9%, 39.3%)	4367 (69.1%, 44.6%)
East North Central	1934 (13.1%)	601 (31.1%, 12.1%)	1333 (68.9%, 13,6%)
East South Central	654 (4.4%)	179 (27.4%, 3.6%)	475 (72.6%, 4.9%)
Middle Atlantic	5737 (32.1%)	1644 (28.7%, 33.1%)	3093 (53.9%, 31.6%)
Mountain	957 (6.5%)	359 (37.5%, 7.2%)	598 (62.5%, 6.1%)
New England	697 (4.7%)	401 (57.5%, 8.1%)	296 (42.5%, 3.0%)
Pacific	688 (4.7%)	232 (33.7%, 4.7%)	456 (66.3%, 4.7%)
South Atlantic	3069 (20.8%)	970 (31.6%, 19.5%)	2099 (68.4%, 21.5%)
West North Central	685 (4.7%)	224 (32.7%, 4.5%)	461 (67.3%, 4.7%)
West South Central	1324 (9.0%)	352 (26.6%, 7.1%)	972 (73.4%, 9.9%)

Table 3: Life Sustaining Therapies

	Total ICU patients	DNR	Full Code
CPR (Use Charge and ICD)	1136 (7.7%)	373 (32.8%, 7.5%)	763 (67.2%, 7.8%)
Hemodialysis (Use Charge and ICD)	2334 (15.8%)	1022 (43.8%, 20.6%)	1312 (56.2%, 13.4%)
Mechanical ventilation (Use Charge and ICD)	8358 (56.7%)	3341 (40.0%, 67.3%)	5017 (60.0%, 51.3%)
Hemodialysis AND Mechanical Ventilation	1945 (13.2%)	920 (47.3%, 18.5%)	1025 (52.7%, 10.5%)
Tracheostomy	647 (4.4%)	180 (27.8%, 3.6%)	467 (72.2%, 4.8%)

Table 4: Outcomes

	Total ICU patients	DNR	Full Code
Discharged to Hospice	549 (3.72%)	462 (84.2%, 9.3%)	87 (15.8%, 0.9%)
Composite of either Discharged to Hospice or In-Hospital Mortality	5998 (40.7%)	3995 (66.6%, 80.5%)	2003 (33.4%, 20.5%)
Hospital LOS	11 [6, 19]	11 [5, 19]	11 [6, 19]
ICU LOS	5 [2, 11]	6 [2, 12]	5 [2, 10]
In-Hospital Mortality	5449 (37.0%)	3533 (64.8%, 71.2%)	1916 (35.2%, 19.6%)
Discharge to Home in patients admitted from Home	2998/10989 (27.3%)	86/3390 (2.5%)	2912/7599 (38.3%)

CRITICAL CARE 27

The Immune Response of Nasal PcrV Vaccination Against Pseudomonas Aeruginosa in Rabbits

Keita Inoue[1], Junya Ohara[2], Toshihito Mihara[2], Atsushi Kainuma[3], Yoshifumi Naito[4], Mao Kinoshita[3], Masaru Shimizu[5], Teiji Sawa[3]

[1]Kyoto Prefectural University of Medicine, Kyoto city, Kyoto prefecture, [2]Kyoto Prefectural University of Medicine, Kyoto, Japan, [3]Kyoto Prefectural University of medicine, Kyoto city, Kyoto prefecture, [4]University of California San Francisco, San Francisco, CA, [5]Uji-Tokushukai Medical, Kyoto city, Kyoto prefecture

INTRODUCTION: Among the recent spread of multidrug-resistant bacteria, outbreaks of multidrug-resistant *Pseudomonas aeruginosa* (MDRP) are a serious concern not only making treatment difficult but also worsening the prognosis of infected patients. The development of an effective vaccine against *P. aeruginosa* as an alternative to conventional antimicrobial therapy has been highly anticipated. We have focused on the V antigen (PcrV), which inhibits the type III secretion system involved in the pathogenicity of virulent *P. aeruginosa*. In our previous studies, we examined the efficacy of PcrV vaccines by intraperitoneal and intranasal administration in mice[1,2]. In this study, we examined the immunity of nasal administration of PcrV vaccine in rabbits. As a formula of PcrV vaccine, we used CpG-oligodeoxynucleotide (ODN), K3 (5'-ATC GAC TCT CGA GCG TTC TC-3', synthesized by GeneDesign, Ibaraki, Japan) as an adjuvant, which induces Th1 type immune response by stimulating Toll-like receptor (TLR) 9.

METHODS: Eleven-week-old rabbits (Japanese white species) were divided into four groups as follows, (1) PcrV alone 500Mg, n=3, (2) PcrV 500Mg + CpG-ODN 500Mg, n=3, (3) CpG-ODN alone 500Mg, n=1, (4) saline alone 2ml, n=1. The vaccines were intranasally administered on days 0, 7, and 14. The serum was obtained by collecting blood from the auricular vein of rabbits, and titer increases against PcrV were evaluated by ELISA.

RESULTS: In rabbits vaccinated with either PcrV or PcrV + CpG, the anti-PcrV titers increased on day 30 (group 1:1.22±0.15, group 2: 1.12±0.08), in comparison with the titers in the control rabbits vaccinated with CpG alone or saline alone (group 3: 0.09, group 4: 0.08). Fig. 1 Time-series data on changes in antibody titer in the course of vaccination (Mean±SD).

DISCUSSION: While, in our previous study, a PcrV CpG ODN vaccine, which was administered either intraperitoneally or intranasally, successfully induced a significant increase of anti-PcrV titers in mice[1,2]. On the other hand, in this study, PcrV vaccine alone increased anti-PcrV titer in rabbits.

CONCLUSION: The nasal administration of PcrV vaccine demonstrated the specific anti-PcrV titer increases, regardless of with or without the CpG-ODN adjuvant. Nasal administration of PcrV vaccine is attractive to induce specific immunity against a major virulence factor of *P. aeruginosa*.

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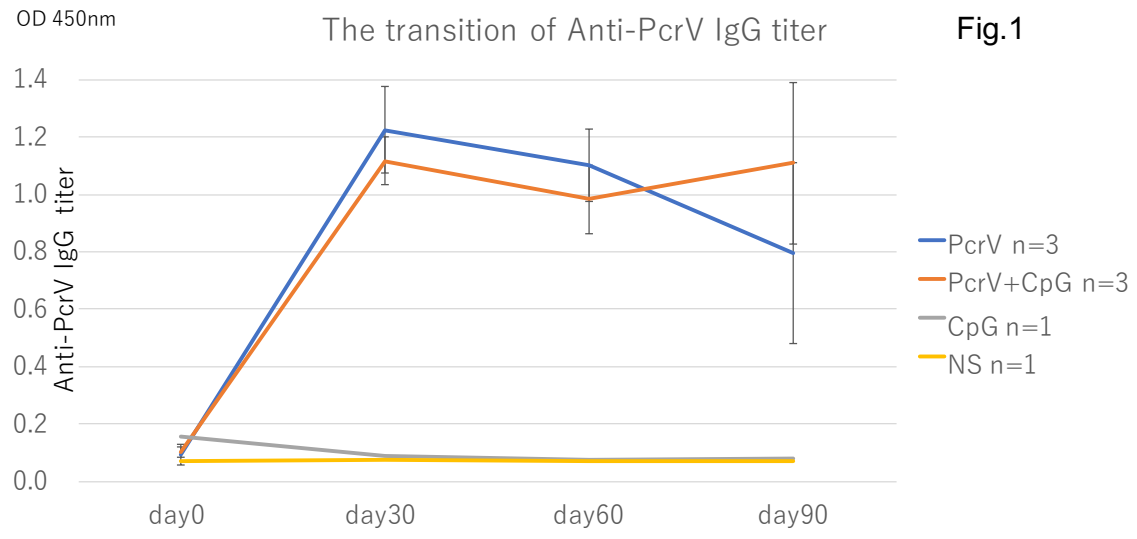
Fig.1



CRITICAL CARE 28

Randomized Controlled Trial of the Efficacy and Safety of Sugammadex on Time-to-Extubation Following Cardiac Surgery

Amit Bardia[1], Miriam Treggiari[1], Chanel Johnson[2], Feng Dai[1], Mayanka Tickoo[2], Kim Kunze[2], Hossam Tantawy[2], Arnar Geirsson[2], Robert B Schonberger[3]

[1]Yale University, New Haven, CT, [2]Yale University, New Haven, United States of America, [3]Yale University School of Medicine, New Haven, CT

INTRODUCTION: Residual neuromuscular blockade (NMB) represents a key factor leading to prolonged intubation after cardiac surgery[1] and has been associated with postoperative pulmonary complications[2,3]. Sugammadex rapidly reverses NMB without adverse cardiovascular effects commonly seen with traditional NMB reversal agents[4]. However, its use in the post cardiac surgery setting has not been investigated. We designed a randomized, controlled trial to determine the effectiveness of sugammadex in reducing time to extubation in mechanically ventilated patients admitted to the ICU after cardiac surgery.

METHODS: This was a single center, randomized, double-blind, placebo-controlled trial. The study was approved by the institutional IRB, and all patients gave written informed consent preoperatively. Eligible participants were adult patients with preoperative left ventricular ejection fraction (LVEF) ≥45% undergoing elective aortic valve replacement (AVR), coronary artery bypass grafting (CABG) or a combination of the two. Exclusion criteria were: BMI>40, moderate to severe right ventricular dysfunction, estimated GFR <30 mL/min, home oxygen, chronic opioid use, neuromuscular disorders, cognitive impairment, emergency procedures, known allergy to rocuronium or sugammadex, anaphylactoid reaction intraoperatively, intraoperative hypoxia, cardiac arrest, sudden arrhythmia, postoperative ST changes postoperative bleeding (chest tube output >100cc/hr), temperature<35.5 or >38.3 degree C at ICU admission, or anticipated need for prolonged mechanical ventilation as determined by the treating team. Postoperatively, all patients were transferred to the ICU intubated and on a propofol and/or dexmedetomidine infusion. 30 minutes after the ICU admission, propofol was discontinued, and the participants were randomized to receive either sugammadex or placebo. Ten minutes after drug administration, if the patient was able to perform a head lift and remained hemodynamically stable, a spontaneous breathing trial (SBT) was initiated for 30 minutes. The patient was extubated if he/she was not hypoxic/ hypercapnic, had RSBI300 ml. The clinical decision to remove the endotracheal tube was determine by the treating team. If a patient failed the SBT, every attempt was made to correct the underlying reversible causes and the SBT was repeated once the cause was corrected or otherwise the patient was continued on mechanical ventilation. The primary study endpoint was time from study drug administration to extubation. Secondary endpoints were pulmonary function tests including negative inspiratory force (NIF), vital capacity (VC) at the time of extubation, and adverse events. The analysis was based on intention-to-treat. For the analysis of the primary endpoint, a two-sample Student's t-test was used to compare the time to extubation between the two groups. Frequency of adverse events were compared between the two groups using chi-square test.

RESULTS: A total of 90 patients were randomized on an intention to treat basis of which 83 patients (Sugammadex=40, placebo=43) received sugammadex or placebo. The two groups were comparable with respect to demographic characteristics including age [sugammadex: 67 ± 8.45 vs. placebo: 64.4 ± 11.18 years], sex [women- sugammadex: 17.8% vs. placebo: 11.1%] and BMI [sugammadex: 29.39 ± 4.61 vs. placebo: 29.55 ±4.83 kg/m2]. Patients in sugammadex group had reduced time to extubation compared with the placebo group [sugammadex: 178 ± 130 minutes vs. placebo: 250.9 ± 201.9 minutes, difference 72.8 [95% CI:1.63-144.0] minutes, p=0.04]. There were no differences in NIF [sugammadex: -31.06 ± 15.90 vs. placebo: -29.22 ± 12.98, p=0.59] and VC [sugammadex:425 ± 466 ml vs. placebo: 470.7 ± 513.9 ml, p=0.68]. There were no difference in postoperative blood product requirements [sugammadex: 0.13 ± 0.76 vs. placebo: 0.04 ± 0.21 pRBC units, p=0.45] or dysrhythmias [sugammadex: 6.82% vs. placebo:13.33%, p=0.31] between the two groups. There were no serious adverse events in either group.

CONCLUSION: This randomized trial in patients undergoing cardiac surgery showed that Sugammadex administration decreased time to extubation by over one hour, without detectable difference in measures of pulmonary function. Larger trials may be required to confirm these findings and determine the clinical implications.

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CRITICAL CARE 29

The Burden of Organ Failure in United States Surgical Patients from 2008-2018

Julien Cobert[1], Zachary Frere[2], Matthew Fuller[3], Yi-Ju Li[4], Galen Royce-Nagel[4], Krista L Haines[5], Raquel R Bartz[2], Vijay Krishnamoorthy[2], Karthik Raghunathan[6]

[1]University of California, San Francisco, San Francisco, CA, [2]Duke University, Durham, NC, [3]Duke University Hospital, Durham, United States of America, [4]Duke University Medical Center, Durham, NC, [5]Duke University, Durham, United States of America, [6]Duke University School of Medicine, Durham, NC

INTRODUCTION: The epidemiology of organ failure in preoperative patients carries important implications in how resources for research, policy and clinical interventions are allocated. Identifying organ failure helps risk stratify patients, discuss goals of care with patients and families and place outcomes of epidemiologic research in their proper contexts. Notably, having dysfunction in multiple organ systems in the surgical intensive care unit has been proposed as a trigger or flag for possible palliative care interventions[1, 2]. Measures of organ failure on a national-scale largely stem from studies on sepsis and septic shock and rely on the use of claims-based codes when studying administrative data. However, few studies have documented the evolution and trends in organ dysfunction in surgical patients, particularly at time of admission. In this study, we use a large hospital database to determine trends in comorbidity and organ dysfunction at time of presentation, among patients undergoing inpatient surgery in the United States.

METHODS: We conducted a retrospective cohort study using the Premier Healthcare Database (Premier Inc., Charlotte, NC, USA). Patients ≥18 years old who had a surgical procedure during their hospitalization were included. We defined acute organ dysfunction from the International Classification of Diseases (ICD), 9th and 10th Revisions, Clinical Modification based on expert consensus and adapted from from the literature[3-8]. All ICD-9 codes were cross-referenced to ICD-10 using source data from the Centers for Medicare and Medicaid Services General Equivalence Mapping[9]. Only acute organ dysfunction was used in our definition. Table 1 shows definitions of organ failure based on ICD-9/10 codes. Patient-level demographic and clinical data, hospital-level data and procedures (including surgical interventions, mechanical ventilation, hemodialysis, and tracheostomy) were collected using either ICD codes, hospital billing codes or both, to improve data capture[10]. Descriptive statistics were performed for the entire cohort and stratified by procedure type, elective vs. non-elective surgeries and cardiac vs. non-cardiac surgeries. Patients were also grouped by number of organ failures. Trends in prevalence were calculated. Only codes present on admission (POA designation) were considered to determine organ dysfunction at time of presentation. P-values less than 0.05 were considered significant. This study was approved by the Duke University Health System IRB.

RESULTS: There were nearly 21,000,000 adult patients who underwent inpatient surgery from 2008-2018. Patients were predominantly female (60%), White (72.4%) and non-Hispanic (59.0%). Median age was 59.0 years (IQR 40-71) and patients with 1, 2 or 3+ organs were generally older. While most patients in the entire cohort underwent elective procedures, patients with cumulative organ failures were more likely to present for emergent surgery. Comorbidity as calculated by vanWalraven (vW) scores[11] are correlated to organ failure present on admission and vW scores rise as number of organ failures rise. We show an upward trend in all pre-defined organ failures at time of admission across surgical patients. In 2018 alone, nearly ~15% of patients presenting for emergency surgery across the United States had preoperative acute renal failure. Upward deflections in trends are seen consistently in 2016, which likely correspond to the change from ICD-9 to ICD-10 codes. Nonetheless, the proportion of patient with MODS undergoing inpatient surgery has increased 2008-2018. The association remained consistent among our pre-defined surgical subgroups.

CONCLUSION: In a large dataset of adults undergoing inpatient surgery, we show that the proportion of patients with MODS has increased over the prior decade. Despite stratifying for acuity of procedures and specific types of procedures, these upward trends remain present. These suggest that progressively sicker patients are undergoing surgical procedures. Our study has a number of strengths including the cohort size, the use of billing and ICD codes when appropriate, to improve data capture and rigorous secondary analyses to determine if subsets of surgical patients are driving the majority of trends. Limitations of this study include inability to validate codes at the hospital- or granular patient-level, possible improved coding practices explaining rise in prevalence and the overall retrospective nature of our study.

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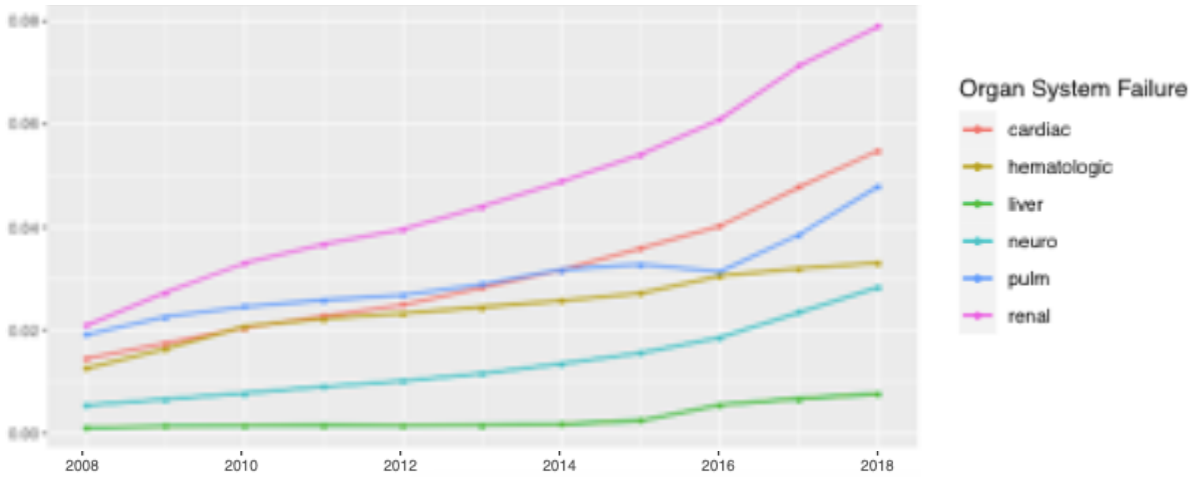
Cardiac/shock	**Pulmonary**	**Renal**	**Heme**	**Liver**	**Neuro**
ICD9—785.5, 785.50, 785.51, 785.52, 785.59, 427.5, 998.00, 669.1, 276.2, 995.92, 998.01, 998.02, 998.09 **ICD10 –**R57.0, R57.1, R57.2, R57.8, R57.9, R65.21, T81.10, T81.11, T81.12, T81.19, T79.4, A48.3, I46.2, I46.8, I46.9, E87.2,)75.1	**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,	**ICD9** – 287.4, 287.41, 287.49, 287.5, 286.9, 286.6 **ICD10** –D69.5, D69.59, D69.6, D65, D69.3, D688, D689	**ICD9** – 570, 573.4, 573.3, 572.2 **ICD10** – K72.0, K72.00, K72.01, K72.9, K72.90, K72.91, K76.3	**ICD9** –293.82, 293.83, 293.84, 293.89, 293.9, 348.1, 348.3, 293, 293.0, 293.1, 293.8, 293.81, 780.01, 780.09 **ICD10 –**F05, F05.0, F05.1, F05.8, F05.9, G93.1, G93.4, G93.41, G93.49, R41.82, R40.0, R40.1, R40.20, R40.211, R40.212, R40.222, R40.223, R40.224, R40.231, R40.232, R40.233, R40.234, R40.235, R40.242, R40.243, R40.244, R40.3, R40.4, F06.0, F06.30, F06.1, F06.8, F53, G93.40, F06.2

Table 1-Acute organ dysfunction categories and ICD9 and ICD10 codes. These were adapted from multiple definitions from the literature (Crit Care Med. 2001 Jul;29(7):1303-10; Crit Care Med 2003.Sep;31(9):2316-23; Crit Care Med.2007 Aug;35(8):1928-36; Crit Care Med. 2007 May;35(5):1244-50; NEJM. 2003 Apr 17;348(16):1546-54; Crit Care Med. 2020 Dec;48(12):1881-4) and then agreed upon by expert consensus.

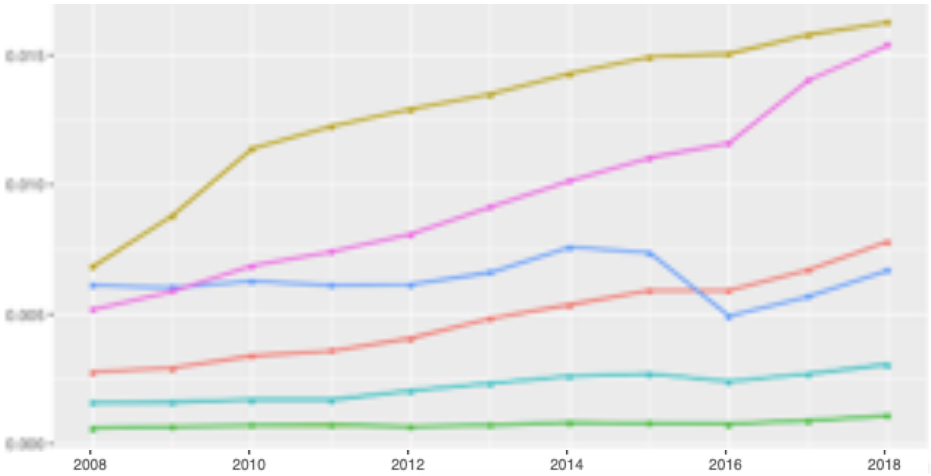
	0 (N=17030872)	1 (N=2412761)	2 (N=852105)	3+ (N=666585)	Total (N=21E6)	p value
GENDER						<0.0001
Female	10764551 (63.2	1146400 (47.5	376430 (44.2	281929 (42.3	12569310 (60.0	
Male	6263875 (36.8%)	1265776 (52.5	475446 (55.8	384492 (57.7	8389589 (40.0%)	
AGE						<0.0001
N	17030872	2412761	852105	666585	20962323	
Median	57.0	67.0	68.0	67.0	59.0	
Q1, Q3	37.0, 69.0	55.0, 77.0	57.0, 78.0	57.0, 77.0	40.0, 71.0	
RACE						<0.0001
Black	1830614 (10.7%)	331987 (13.8%)	118669 (13.9	97285 (14.6%)	2378555 (11.3%)	
Hispanic	204596 (1.2%)	22858 (0.9%)	7003 (0.8%)	4589 (0.7%)	239046 (1.1%)	
Other	2467380 (14.5%)	316167 (13.1%)	110445 (13.0	86853 (13.0%)	2980845 (14.2%)	
White	12364887 (72.6	1722894 (71.4	608336 (71.4	470263 (70.5	15166380 (72.4	
HISPANIC						<0.0001
Non-Hispanic	9939857 (58.4%)	1469107 (60.9	532207 (62.5	426519 (64.0	12367690 (59.0	
Unknown	5856185 (34.4%)	797069 (33.0%)	269112 (31.6	201444 (30.2	7123810 (34.0%)	
Hispanic	1234830 (7.3%)	146585 (6.1%)	50786 (6.0%)	38622 (5.8%)	1470823 (7.0%)	
INSURANCE						<0.0001
Medicaid	1379514 (8.1%)	115349 (4.8%)	40000 (4.7%)	35108 (5.3%)	1569971 (7.5%)	
Medicare	7473208 (43.9%)	1605014 (66.5	597821 (70.2	466420 (70.0	10142463 (48.4	
Other	2792269 (16.4%)	281848 (11.7%)	94605 (11.1%)	74058 (11.1%)	3242780 (15.5%)	
Private	5385881 (31.6%)	410550 (17.0%)	119679 (14.0	90999 (13.7%)	6007109 (28.7%)	
ADMISSION SOURCE						<0.0001
CLINIC	2500287 (14.7%)	245136 (10.2%)	67325 (7.9%)	43718 (6.6%)	2856466 (13.6%)	
EMERGENCY ROOM	662142 (3.9%)	160522 (6.7%)	59338 (7.0%)	41906 (6.3%)	923908 (4.4%)	
XFER FROM A HOSPITAL (DIFF FACILI	599400 (3.5%)	186339 (7.7%)	90196 (10.6%)	91485 (13.7%)	967420 (4.6%)	
TYPE OF SURGERY						<0.0001
ELECTIVE	9807629 (57.6%)	755582 (31.3%)	178351 (20.9	102137 (15.3	10843699 (51.7	
EMERGENCY	4392857 (25.8%)	1217744 (50.5	507033 (59.5	428010 (64.2	6545644 (31.2%)	
TRAUMA CENTER	128921 (0.8%)	40754 (1.7%)	19466 (2.3%)	12694 (1.9%)	201835 (1.0%)	
URGENT	2529380 (14.9%)	379968 (15.7%)	140975 (16.5	118633 (17.8	3168956 (15.1%)	
VANWALRAVEN SCORE						<0.0001
N	17030872	2412761	852105	666585	20962323	
Median	0.0	4.0	6.0	9.0	0.0	
Q1, Q3	0.0, 2.0	0.0, 9.0	2.0, 12.0	4.0, 15.0	0.0, 3.0	
HOSPITAL REGION						<0.0001
MIDWEST	3311581 (19.4%)	500894 (20.8%)	176996 (20.8	139510 (20.9	4128981 (19.7%)	
NORTHEAST	2821389 (16.6%)	372462 (15.4%)	127578 (15.0	96855 (14.5%)	3418284 (16.3%)	
SOUTH	7844521 (46.1%)	1140863 (47.3	405188 (47.6	313127 (47.0	9703699 (46.3%)	
WEST	3053381 (17.9%)	398542 (16.5%)	142343 (16.7	117093 (17.6	3711359 (17.7%)	
HOSPITAL URBAN STATUS						<0.0001
RURAL	1636411 (9.6%)	210734 (8.7%)	71629 (8.4%)	52442 (7.9%)	1971216 (9.4%)	
URBAN	15394461 (90.4	2202027 (91.3	780476 (91.6	614143 (92.1	18991107 (90.6	
TEACHING HOSPITAL						<0.0001
NO	9028855 (53.0%)	1206638 (50.0	408059 (47.9	305252 (45.8	10948804 (52.2	
YES	8002017 (47.0%)	1206123 (50.0	444046 (52.1	361333 (54.2	10013519 (47.8	
HOSPITAL BED VOLUME						<0.0001
000-099	636321 (3.7%)	60280 (2.5%)	16655 (2.0%)	10379 (1.6%)	723635 (3.5%)	
100-199	1978650 (11.6%)	236105 (9.8%)	75253 (8.8%)	56029 (8.4%)	2346037 (11.2%)	
200-299	2715391 (15.9%)	360417 (14.9%)	121961 (14.3	90817 (13.6%)	3288586 (15.7%)	
300-399	3007330 (17.7%)	416227 (17.3%)	142907 (16.8	109836 (16.5	3676300 (17.5%)	
400-499	2465447 (14.5%)	370066 (15.3%)	132154 (15.5	104082 (15.6	3071749 (14.7%)	
500+	6227733 (36.6%)	969666 (40.2%)	363175 (42.6	295442 (44.3	7856016 (37.5%)	

Table 2-Hospital and patient characteristics by number of organ dysfunctions present on admission. Missing or unknown data are not shown

Prevalence of organ failure present on admission in all inpatient surgeries



Prevalence of organ failure present on admission in elective surgeries



Prevalence of organ failure present on admission in non-elective surgeries

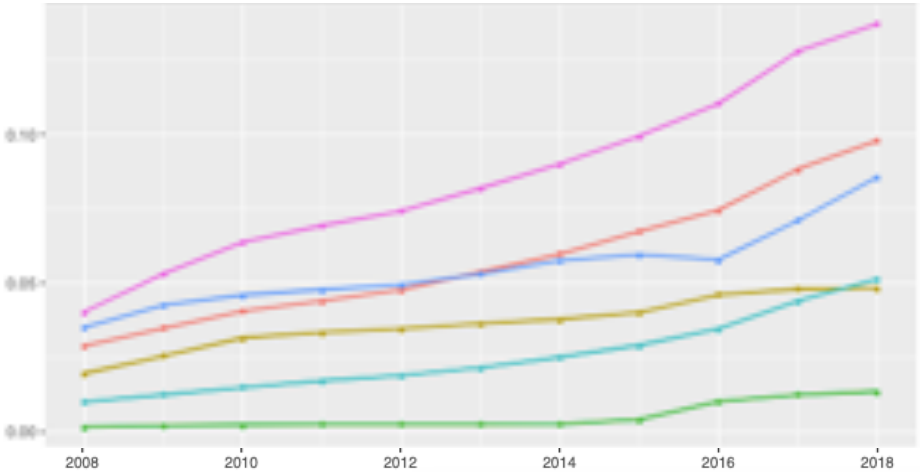


Figure 1 Trends in Prevalence of organ failure present at admission in (a) all inpatient surgeries; (b) emergent surgeries; and (c) elective surgeries

CRITICAL CARE 30

The Epidemiology of Multiorgan Dysfunction in United States Surgical ICU Patients from 2008-2018

Julien Cobert[1], Zachary Frere[2], Matthew Fuller[3], Yi-Ju Li[4], Galen Royce-Nagel[4], Krista L Haines[5], Raquel R Bartz[2], Vijay Krishnamoorthy[2], Karthik Raghunathan[6]

[1]University of California, San Francisco, San Francisco, CA, [2]Duke University, Durham, NC, [3]Duke University Hospital, Durham, United States of America, [4]Duke University Medical Center, Durham, NC, [5]Duke University, Durham, United States of America, [6]Duke University School of Medicine, Durham, NC

INTRODUCTION: Multiorgan dysfunction syndrome (MODS) remains a fundamental predictor of mortality in the intensive care unit (ICU)[1, 2]. It is used in a number of predictive scoring systems, such as Acute Physiology And Chronic Health Evaluation and Sequential Organ Failure Assessment. Regardless of the scoring system used, numbers of failing organs correlate with mortality[3]. Population-based estimates of MODS rely on claims-based medical codes, specifically International Classification of Diseases (ICD) codes primarily created to determine the prevalence of sepsis and septic shock. While the rise in incidence of sepsis has increased over time, mortality for this disorder has improved substantially. However, the prevalence and trends of perioperative MODS remain largely unknown. The burden of organ failure in ICU patients carries important clinical and economic implications in perioperative medicine. Given the correlation with morbidity and mortality after surgery[4], early recognition of organ failure and cumulative organ failure may be important triggers for goals-of-care conversations and greater than or equal to 3 failures of an organ has been proposed as a screening-criteria for specialized palliative care interventions in the ICU[5]. In this study, we sought to determine the prevalence and trends of organ in surgical ICU patients.

METHODS: Multiple definitions for organ dysfunction exist[6-8] for septic shock, based on ICD-9. However, few studies have developed definitions based on ICD-10 codes. Here, we aggregated previously used definitions using ICD-9 codes and cross-referenced them with ICD-10 using source data from the Centers for Medicare and Medicaid Services General Equivalence Mapping[9]. A final administrative claims definition for MODS was developed by expert consensus built around ICD-9/10 codes. Only acute organ dysfunction codes were used. We collected patient- and hospital-level data from the Premier Healthcare database (Premier Inc., Charlotte, NC, USA). This database includes a large, geographically diverse dataset that uses ICD-based diagnosis and procedure codes and charge codes. In this retrospective cohort study, we collated organ failure codes across all adult patients who had a surgery and an ICU stay of at least 24 hours from 2008-2018. We further stratified by procedure type, elective vs. non-elective status and cardiac vs. non-cardiac surgery.

RESULTS: From 2008 to 2018, there has been an increasing trend in pulmonary, renal and cardiac failure across postoperative ICU patients (Figure 1(a)-(c)). Trends in pulmonary failure (including any type of respiratory failure) increased predominantly in ICU patients who underwent emergency surgery but were relatively stable in patients undergoing elective surgeries. Cardiac failure and shock rose in elective and emergent patient groups while liver, neurologic and hematologic organ dysfunction remained relatively stable. The year 2016 represents a change from ICD-9 to ICD-10 coding dictionaries and changes or slopes at or from this year likely represent this coding system change. Figure 2 shows trends in 3 organ failures over the study period. Consistently across any combination of organ failures, trends suggest increasing prevalence. These are conserved before and after ICD-9 to ICD-10 coding changes. Three organ failure containing cardiac and renal failure demonstrated the largest increases over the time period

CONCLUSION: Using a large dataset of adult ICU patients who underwent surgery, cumulative organ failure not present admission has been increasing between 2008-2018. Three-organ failure increased from ~2% of ICU patients to ~10%. Rates of cardiac failure (which encompasses shock, acidosis and cardiac arrest) increased in all surgical groups. It remains unclear if these represent increasing rates of patients carrying comorbidities (i.e. higher risk) prior to their operations or if patients presenting to the ICU are sicker and evolving. The strengths of our study include the size of our cohort, the broad range of hospitals included in Premier and the ICD-10 codes used in our definition of organ failure. Limitations include the inability to obtain granular patient-level data and the lack of validation of ICD codes at the individual hospital level. It is possible that coding has improved over time. Finally, the retrospective nature of our study introduces biases and inability to control for all confounders common with this methodology.

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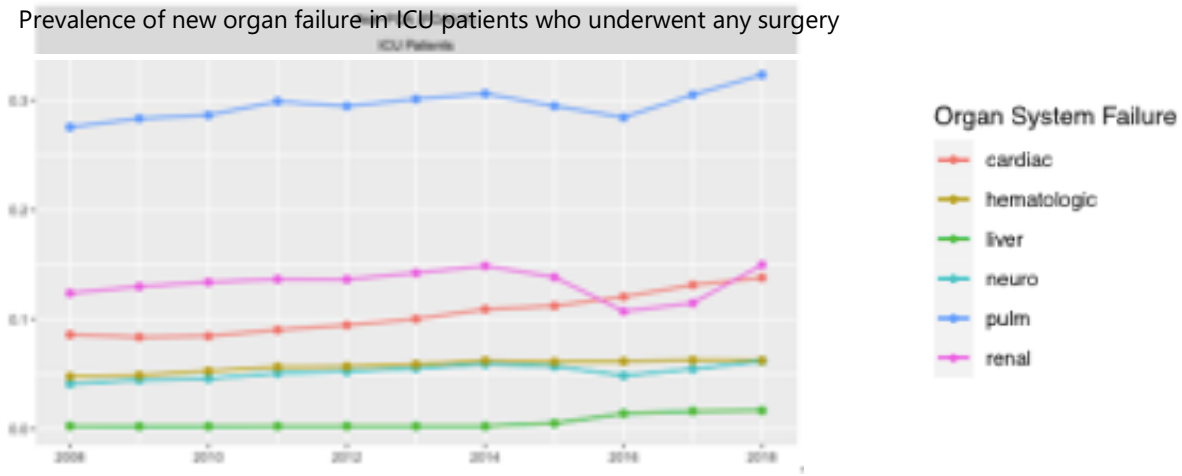
8. N Engl J Med. Apr 2003;348(16):1546-54.
9. J AHIMA. Jan 2016;87(1):48-53.

Cardiac/shock	Pulmonary	Renal	Heme	Liver	Neuro
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,)75.1	**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,	**ICD9** – 287.4, 287.41, 287.49, 287.5, 286.9, 286.6 **ICD10** –D69.5, D69.59, D69.6, D65, D69.3, D688, D689	**ICD9** – 570, 573.4, 573.3, 572.2 **ICD10** – K72.0, K72.00, K72.01, K72.9, K72.90, K72.91, K76.3	**ICD9** –293.82, 293.83, 293.84, 293.89, 293.9, 348.1, 348.3, 293, 293.0, 293.1, 293.8, 293.81, 780.01, 780.09 **ICD10 –**F05, F05.0, F05.1, F05.8, F05.9, G93.1, G93.4, G93.41, G93.49, R41.82, R40.0, R40.1, R40.20, R40.211, R40.212, R40.222, R40.223, R40.224, R40.231, R40.232, R40.233, R40.234, R40.235, R40.242, R40.243, R40.244, R40.3, R40.4, F06.0, F06.30, F06.1, F06.8, F53, G93.40, F06.2

Table 1-Acute organ dysfunction categories and ICD9 and ICD10 codes. These were adapted from multiple definitions from the literature (Crit Care Med. 2001 Jul;29(7):1303-10; Crit Care Med 2003.Sep;31(9):2316-23; Crit Care Med.2007 Aug;35(8):1928-36; Crit Care Med. 2007 May;35(5):1244-50; NEJM. 2003 Apr 17;348(16):1546-54; Crit Care Med. 2020 Dec;48(12):1881-4) and then agreed upon by expert consensus.

Prevalence of new organ failure in ICU patients who underwent any surgery



Prevalence of new organ failure in ICU patients who underwent emergency surgery

Prevalence of new organ failure in ICU patients who underwent elective surgery

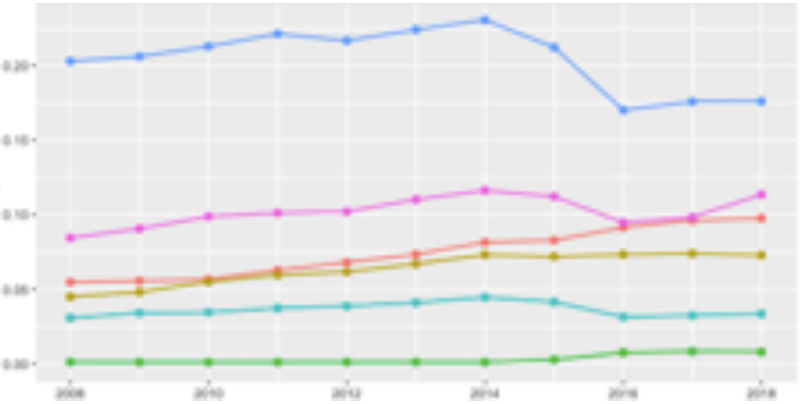


Figure 1-Trends in Prevalence of new organ failure not present at admission in (a) all inpatient surgeries; (b) emergent surgeries; and (c) elective surgeries.

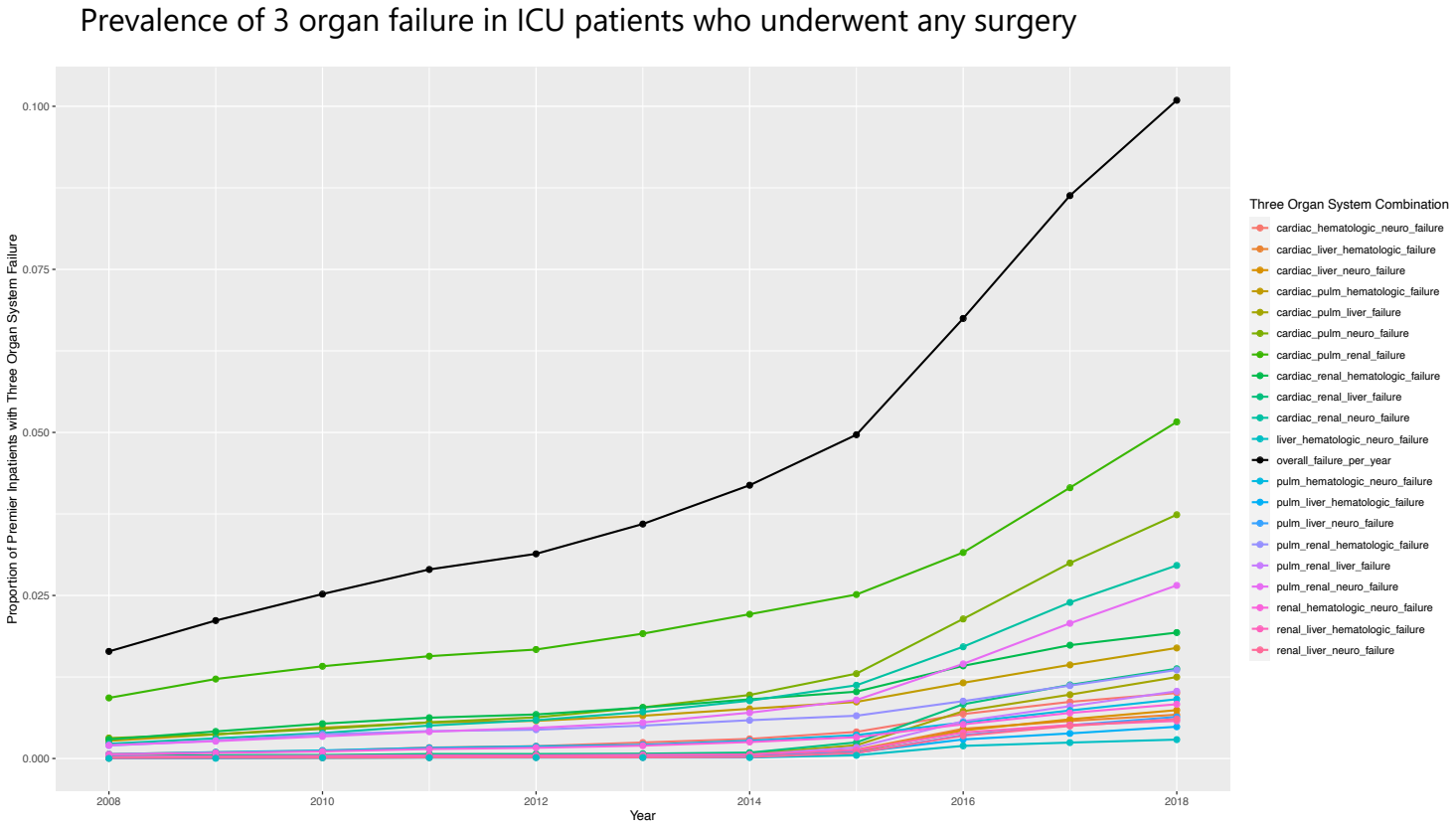


Figure 2: Prevalence of cumulative 3 organ failures in perioperative patients. 2016 represents the change from ICD-9 to ICD-10 coding system

CRITICAL CARE 31

Effects of Bacteriophage Therapy on Acute Lung Injury Caused by Pseudomonas Aeruginosa Pneumonia

Junya Ohara[1], Jumpei Fujiki[2], Toshihito Mihara[1], Keita Inoue[3], Mao Kinoshita[4], Masaru Shimizu[5], Hidetomo Iwano[2], Teiji Sawa[4]

[1]Kyoto Prefectural University of Medicine, Kyoto, Japan, [2]Rakuno Gakuen University, Ebetsu Hokkaido, Japan, [3]Kyoto Prefectural University of Medicine, Kyoto city, Kyoto prefecture, [4]Kyoto Prefectural University of medicine, Kyoto city, Kyoto prefecture, [5]Uji-Tokushukai Medical, Kyoto city, Kyoto prefecture

INTRODUCTION: Pseudomonas aeruginosa is a major opportunistic pathogen that causes acute and chronic infections. Recently, infections caused by multidrug-resistant P. aeruginosa(MDRP) have increased, and the emergence of pandrug-resistant P. aeruginosa has become a serious concern in hospitals worldwide. Bacteriophage therapy is expected to be an alternative choice of antimicrobial chemicals against multidrug-resistant bacteria. In this study, we examined the effects of bacteriophage therapy on acute lung injury caused by P. aeruginosa pneumonia.

METHODS: Design: a prospective randomized and controlled animal study Setting: University laboratory Subjects: Male ICR mice This study was carried out under the Guidelines for Proper Conduct of Animal Experiments, Science Council of Japan. The protocol was approved by the Committee on the Ethics of Animal Experiments of Kyoto Prefectural University of Medicine. A bacteriophage ϕÜR18, which demonstrates the bactericidal activity against P. aeruginosa PA103, was isolated from sewage treatment plants at Hokkaido in Japan in advance, as reported previously A lethal dose(1.0×106CFU) of P. aeruginosa PA103 was intratracheally administered to the lungs of mice. Then, 5 minutes later, the solution(90ml) containing bacteriophage(treated group)(40×106PFU) or the saline alone(non-treated control group) was intratracheally administered. Body temperature, activity, and survival of mice were monitored for 24 hours. To measure the activity of mice, we measured the distance moved in the cage for 10 seconds 8 hours after infection.

RESULTS: Regardless of the treated or non-treated, all mice once became severely hypothermic within 4 hours. However, after 8 hours, mice received bacteriophage recovered from hypothermia(32.3±1.1℃) while mice received saline remained hypothermic(29.2±0.8℃) ($p<0.05$). After 12hours, the body temperature of the treated group was 34.5±1.5℃ while that of the control group was 29.1±0.8℃($p<0.05$). About the activity of mice, the average moving distance of the treated group was 26.5±12.0cm, while that of the saline group was 11.9±6.9cm($p<0.05$). Finally, 5 of 11 mice that received the bacteriophage survived for 24 hours. All mice(n=12) received saline died in 24 hours($p<0.05$).

CONCLUSION: The bacteriophage therapy improved the survival of mice intratracheally received a lethal dose of P. aeruginosa. The bacteriophage therapy in our animal model demonstrated its potential in the protection of acute lung injury caused by P. aeruginosa pneumonia.

CRITICAL CARE 32

Endothelial Glycocalyx Degradation and Postoperative Acute Kidney Injury in Cardiac Surgery Patients

Austin C DeBeaux[1], Jing Zhou[1], Tracie Baker[1], Derwin D Campbell[1], Frederic (Josh) Billings[2], Marcos Lopez[1]

[1]Vanderbilt University Medical Center, Nashville, TN, [2]Vanderbilt University Medical Center, Nashville, Tennessee

INTRODUCTION: Acute kidney injury (AKI) occurs in an estimated 30% of cardiac surgery patients and is associated with increased mortality.[1,2] Intraoperative hyperoxia may promote the formation of reactive oxygen species (ROS) which have deleterious effects on renal permeability through oxidative stress.[1,3] The glomerular endothelial glycocalyx is a critical regulator of renal permeability and is composed of glycosaminoglycans, proteoglycans, and other glycoproteins including syndecan-1, a heparan sulfate proteoglycan.[4] Surgery, cardiopulmonary bypass, and oxidative stress induce shedding of soluble syndecan-1, and plasma syndecan-1 concentrations reflect glycocalyx degradation.[3,5] We tested the hypotheses that increased endothelial glycocalyx damage is associated with AKI following cardiac surgery and that intraoperative normoxia decreases glycocalyx damage compared to hyperoxia.

METHODS: We tested these hypotheses in a cohort of cardiac surgery patients enrolled in a randomized clinical trial of intraoperative normoxia (lowest fraction of inspired oxygen [FIO2] to maintain an arterial hemoglobin saturation of 95-97%) vs. hyperoxia (FIO2 =1).[6] Plasma concentrations of syndecan-1 were measured using an enzyme-linked immunosorbent assay (Abcam, Cambridge, MA) before surgery, immediately following cardiopulmonary bypass, and 6 hours after surgery. AKI was defined using KDIGO creatinine criteria. We measured the association between the area under the curve (AUC) of plasma syndecan-1 concentrations following CPB and 6 hours postoperatively and AKI using logistic regression adjusted for baseline syndecan-1 concentration, age, baseline estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula), and use of cardiopulmonary bypass. We measured the effect of intraoperative oxygen treatment on syndecan-1 concentration using the Mann-Whitney U test.

RESULTS: One hundred thirty patients comprised the cohort. The median (10th, 90th percentile) participant age was 66 (50, 76) years, 33 (25%) were female, median baseline eGFR was 74 (43, 96) mL/min/1.73m2. Twenty-five participants (19%) developed AKI. Seventeen participants (13%) developed stage I AKI), 5 (4%) stage 2 AKI, and 3 (2%) stage 3 AKI. Median syndecan-1 concentrations were 155.6 ng/mL (69.6, 601.6) at baseline, increased to 333.4 (138.1, 798.7) ng/ml after CPB and decreased to 273.1 ng/mL (109.1, 934.1) 6 hours postoperatively. A 50 ng/ml increase of plasma syndecan-1 concentration AUC was independently associated with an 10% increase in the odds of AKI (OR 1.10; 95% CI: 1.00 to 1.20; P=0.04). Median (10th, 90th percentile) syndecan-1 AUCs were 330.5 ng/ml (137.8, 701.2) and 314.6 ng/ml (138.5, 1038.2) in patients receiving normoxia vs. hyperoxia, respectively (P=0.92).

CONCLUSION: Increased perioperative plasma concentrations of syndecan-1 were independently associated with postoperative AKI in patients undergoing cardiac surgery. Intraoperative normoxia vs. hyperoxia did not affect perioperative plasma concentrations of syndecan-1. Future investigations will test therapeutic interventions to decrease glycocalyx degradation and reduce postoperative AKI.

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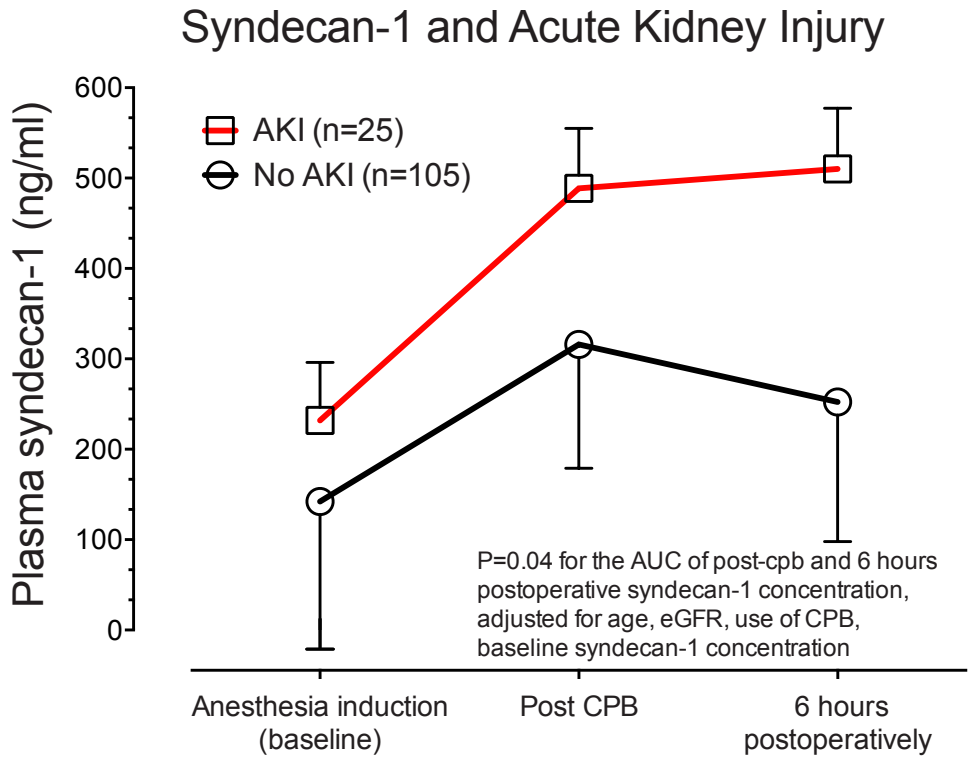

CRITICAL CARE 33

ICU Staff's Perception of Where (False) Alarms Originate: A Mixed Methods Study

Maximilian M Wunderlich[1], Akira Poncette[1], Claudia Spies[1], Patrick Heeren[1], Gerald Vorderwülbecke[1], Eduardo Salgado[1], Marc Kastrup[1], Markus Feufel[2], Felix Balzer[1]

[1]Charité – Universitätsmedizin Berlin, Berlin, Germany, [2]Technische Universität Berlin, Berlin, Germany

INTRODUCTION: Staff members of intensive care units (ICUs) monitor patients' vital parameters via medical devices, which issue an alarm if one such parameter deviates from a predefined range. Large numbers of alarms can make staff 'alarm fatigued', especially when the majority of alarms appear to be false[1]. Alarm fatigue creates a stressful working environment, which may result in a threat to patients' lives[2,3]. Alarm management interventions can help to reduce the overall number of alarms and should be based on the analyses of the alarm log data[4,5]. However, alarm logs neither contain information on whether an alarm was false nor on the individuals' capacity of dealing with alarms. Hence, we surveyed ICU staff's subjective idea of which medical devices are issuing most (false) alarms and compared their perceptions to alarm log data.

METHODS: IRB approval was obtained (EA1/127/18). No patient or staff identifying information was collected. Staff members of all ICUs of a german university hospital received a questionnaire containing three items (Q1-3) asking them to estimate the overall percentage of false alarms (Q1) and to indicate the top three medical devices in terms of their total number of issued (false) alarms (Q3 and Q2, respectively). For Q2 and Q3 respondents could choose from six medical devices: (non) invasive blood pressure (N)IBP, ventilator, electrocardiogram (ECG), pulse oximetry (SpO2) and temperature (Temp.). To compare ICU staff's estimates of the overall number of alarms, we collected 90 days of alarm log data from a representative 21-bed-ICU in 2019. To analyze the respondents' ranking of the medical devices in terms of the perceived (false) alarm rates, we calculated a weighted sum by multiplying the number of respondents who voted for a device's rank by either 3 (for rank 1), 2 (for rank 2) or 1 (for rank 3). E.g. if ten voted ECG for rank 1 of false alarms, seven for rank 2 and two for rank 3, the sum would be 10*3+7*2+2*1 = 46. Next, we calculated the percentage that each device's weighted sum has of the total weighted sum. The device with the highest percentage was perceived as having the most (false) alarms, the device with the lowest percentage was perceived as having the fewest.

RESULTS: In total, 85 ICU staff members completed the questionnaire. On average, respondents perceived the rate of false alarms to be 56% (SD 22%, median 60%, range 5-92%). Figure 1 shows a histogram of the respondents' estimated percentages of false alarms. Figure 2 shows that SpO2 was the device perceived as having the most alarms, holding 31% of the weighted ranking sums, closely followed by IBP (30%). ECG was on the third and the ventilator on the fourth place (23% and 12 %, respectively). When asked about the source of most false alarms, the vast majority of respondents agreed on SpO2 (43% of the weighted ranking sums) followed by ECG (22%), IBP (20%), ventilator (8%), Temp. (5%) and NIBP (3%). The subjective estimation of the number of alarms per medical device contrasts the results of the log data analysis (Figure 3), where the ventilator is the most frequent source of alarms. In the belief of ICU staff, SpO2 overtakes IBP as the most frequent alarm, while the log data shows IBP as the second most frequent one followed by ECG. Each of both sensors caused almost four times as many alarms as SpO2. Temperature and NIBP were ranked as having the least number of alarms of all sensor groups, which is in line with the results shown in Figure 3.

CONCLUSION: ICU staff's perception regarding SpO2 as the source of most false alarms is in line with the results published by Graham and Cvach[6], who found that SpO2 is the largest contributor of false alarms. The results of this study suggest that ICU staff's subjective notion of which medical device generates most alarms can differ from the actual situation as measured by the alarm log data. This contrast highlights the importance of inviting ICU staff to join in reviewing their unit's alarm log data and to design alarm management interventions (e.g. SOPs), as recently suggested by Poncette and colleagues[7]. Interventions might find broader acceptance if ICU staff knows why an intervention primarily targets one particular device instead of another.

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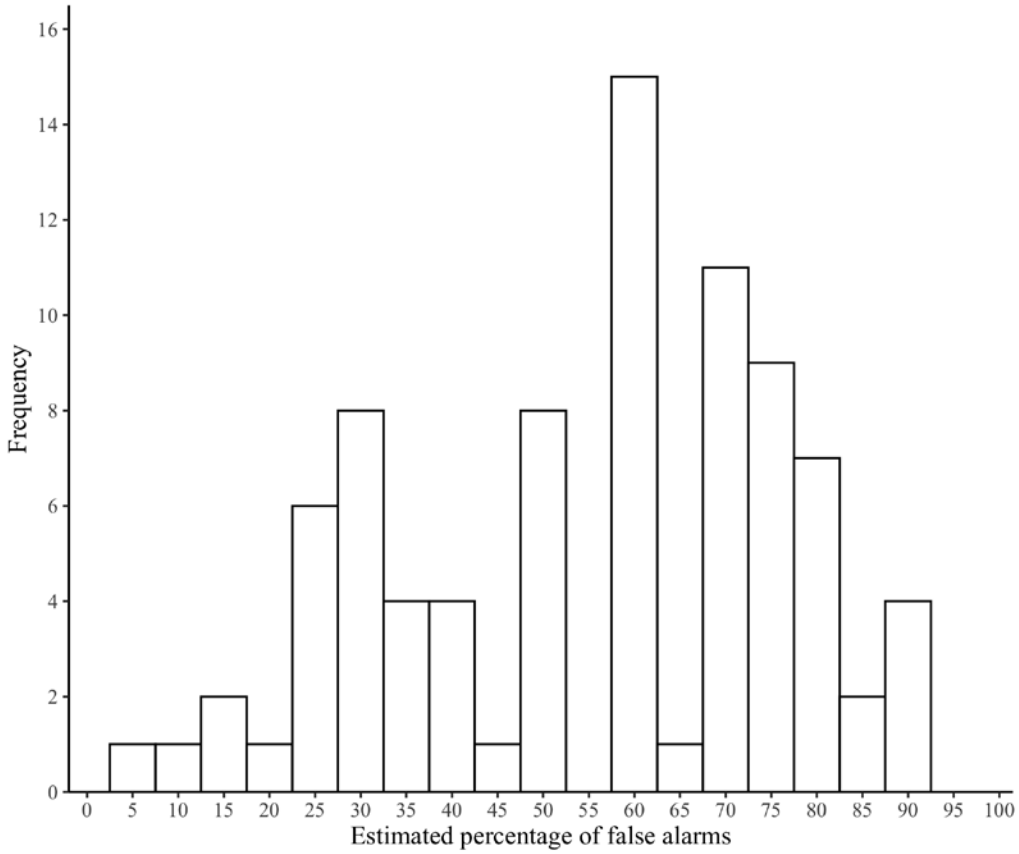

Fig. 1

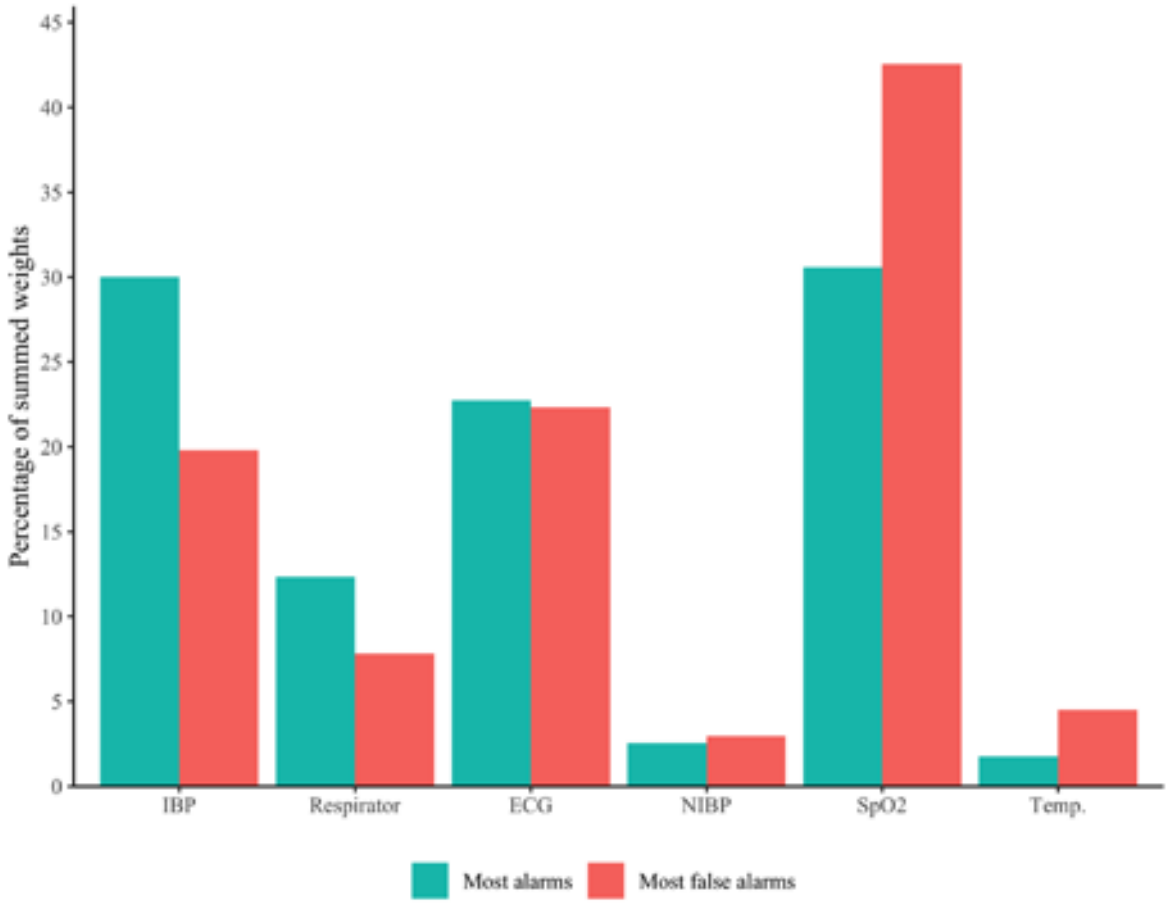

Fig. 2

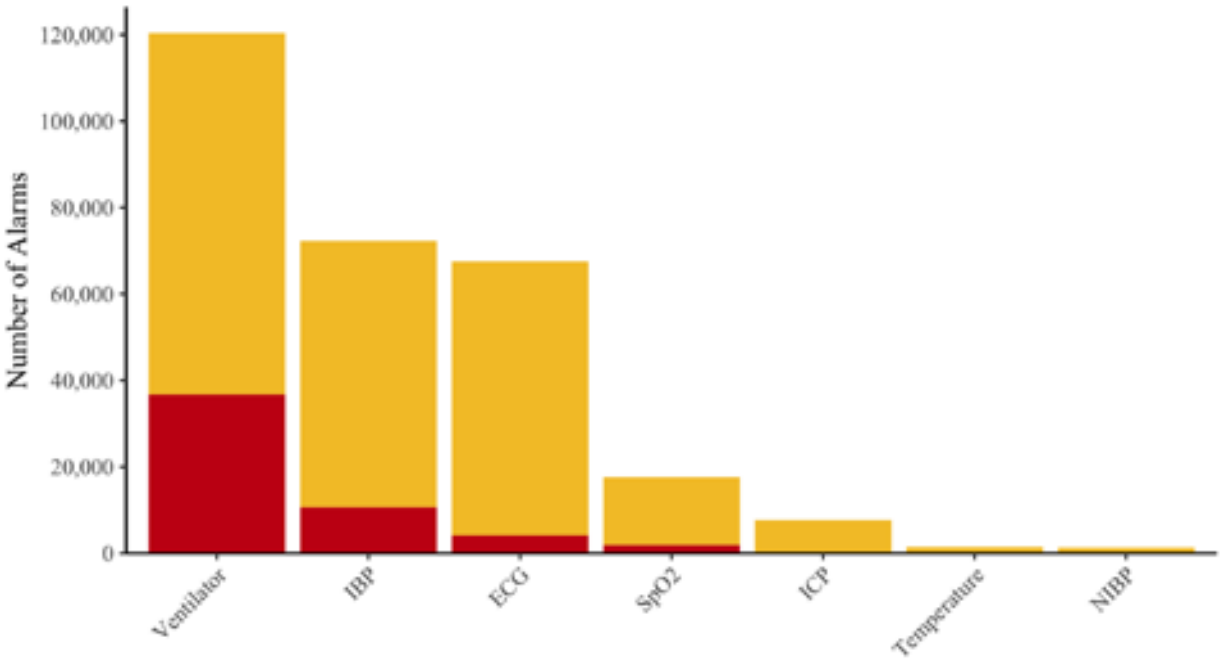

Fig. 3

CRITICAL CARE 34

Does Preventing Intubation in COVID-19 Save Lives? A CRUSH-COVID Multi-Center Study of the Outcomes of Advanced Respiratory Support Escalation in COVD-19

Ayal Z Pierce[1], Chris Payette[2], Benjamin Delprete[2], Ivy Benjenk[3], Wayne Woo[4], David Yamane[2], Jonathan H Chow[5]

[1]George Washington University Hospital, Washignton, DC, [2]George Washington University Hospital, Washington, DC, [3]The George Washington University School of Medicine & Health Sciences, Washington, DC, [4]George Washington University School of Medicine and Health Sciences, Washington, DC, [5]University of Maryland School of Medicine, Baltimore, MD

INTRODUCTION: The COVID-19 disease caused by the SARS-CoV-2 virus has become an important illness since its identification. Intubation with mechanical ventilation is widely recognized as a necessary intervention for patients suffering from respiratory failure. Critically ill COVID-19 patients often present with severe hypoxia, prompting the need respiratory support. In the early months of the COVID-19 pandemic, hypoxic patients were intubated early in their course of disease to decrease aerosolization of the virus from non-invasive ventilation (NIV) measures[1]. However, early reports revealed a high rate of mortality among intubated patients and ranged widely, reaching as high as 86%[2,3,4]. Both High Flow Nasal Cannula (HFNC) and Non-Invasive Positive Pressure Ventilation (NIPPV) are proven modalities in non-COVID-19 pathologies. Data remains mixed on the aerosolizing risk of SARS-Cov-2 virus with these noninvasive strategies[5,6]. Despite differing recommendations, the utility of NIV in COVID-19 remains unstudied. The literature currently lacks description of the outcomes between patients who were intubated immediately for respiratory failure due to COVID-19 versus intubating only after failing NIV methods.
Some have argued that patients should be placed on mechanical ventilation early to prevent lung injury[7] while others argued against this[8]. Our study aimed to describe the characteristics of patients who were intubated 'early,' defined as being intubated without NIV attempts, versus 'delayed', defined as intubated after failed initial NIV use. Our secondary aim was to characterize the use of NIV in COVID-19 to prevent intubation

METHODS: We performed a multi-center retrospective cohort study to investigate the differences between those patients who were intubated early and those in which intubation was delayed by a trial of NIV. Patients were abstracted from a multicenter registry of hospitalized patients admitted between March 2020 and June 2020. Four tertiary care centers, University of Maryland Medical Center, Wake Forest Baptist Medical Center, Northeast Georgia Health System, and George Washington University Hospital contributed data to the registry contributed. Patients were divided into three cohorts, early intubation, delayed intubation, and non-invasive ventilation (NIV) methods only. An 'early' intubation was defined as intubation without demonstrated NIV failure, and delayed were those intubations that occurred after failed NIV. NIV methods included HFNC and NIPPV. Patients who were 18 years or older, had confirmed COVID-19 test, were admitted to the hospital, and required advanced respiratory support (HFNC, NIPPV, or intubated during their hospitalization) were included in the study.

RESULTS: A total of 338 patients were collected on August 10, 2020 that met inclusion criteria. 127 patients were intubated early, without a trial of NIV prior to intubation, 101 intubated after failed NIV, and 110 who had NIV measures only. Pearson chi squared tests did not show any statistical demographic difference for age, race, BMI, and sex between the two groups. Mortality rates were significantly lower in the early group versus the delayed group, 37.8% vs 65.3% respectively. Crude odds ratio was 0.322 [0.187 – 0.556] ($p < 0.0001$), indicating the delayed intubated group had less odds of survival compared to the early. Stepwise logistic regression showed that age, gender, and institution were significant variables for adjustment. After controlling for these, the adjusted odds ratio 0.386 [0.204 – 0.721] ($p < 0.0001$), further indicating that even when controlled for age, gender, and institution, delayed intubation had less odds of survival. Secondary analysis showed that there were 92 patients who received HFNC alone, 5 NIPPV alone, and 13 received both. None of these 110 patients received mechanical ventilation during their hospital stay.

CONCLUSION: Our study suggests that HFNC and NIPPV may be useful modalities in the treatment of hypoxemia secondary to COVID-19 to prevent intubation. However, the likelihood of survival may decrease in those who fail these measures. Given the findings of our study, the authors believe a trial of NIV prior to intubation is reasonable, especially given the high mortality rates of intubation. Further randomized control trials are needed to not only evaluate the efficacy of NIV in COVID-19, but also quantify the risk of aerosolization to properly weigh the risks and benefits of this measure.

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CRITICAL CARE 35

Protease Activity Profiling as a Fast Tool for ARDS Risk Assessment and Monitoring

Catharina Conrad[1], Simon Cleary[1], Daniela Yildiz[2], Andreas Margraf[3], Lena Cook[4], Uwe Schlomann[4], Bernd Schmeck[4], Alexander Zarbock[3], Mark Looney[1], Joerg-Walter Bartsch[4]

[1]University of California, San Francisco, San Francisco, CA, [2]Saarland University, Homburg, Germany, [3]University Hospital Münster, Münster, Germany, [4]Philipps University Marburg, Marburg, Germany

INTRODUCTION: Acute respiratory distress syndrome (ARDS) represents a stereotypic response to various direct or indirect pulmonary insults and is characterized by excessive lung inflammation and respiratory failure. Although advances in supportive care and lung-protective mechanical ventilation have improved outcomes[1], the death rate remains unacceptably high and ranges from 27-46%[2]. A major reason for the high mortality is that no targeted therapies currently exist. The key to overcome the lack of success of pharmacological treatments may be developing personalized therapies based on molecular ARDS phenotypes[3, 4]. Despite advances in defining ARDS subtypes[4], no molecular tools are available that can be used as bedside tests to predict the outcome or risk for ARDS development. In ARDS progression, different classes of proteases can degrade microbes, extracellular matrix components and process signaling molecules and are readily activated upon pulmonary insults[5]. Their catalytic activities change during the course of ARDS and reflect cellular responses to lung damage[5]. Detection of ARDS-associated proteases under optimized in vitro conditions could be a sensitive and quick method to allow stratification of ARDS patients. Thus, we hypothesized that tracking proteolytic activities by using fluorescent reporter peptides in lung fluids of ARDS patients may provide a simple approach to monitor disease severity and responsiveness to therapy. Ultimately, improved knowledge of the contribution of specific proteases to ARDS pathology is instrumental to discover novel druggable targets for personalized therapeutic interventions.

METHODS: By using fluorescent reporter systems, we determined proteolytic activities in lung fluids from both patients with ARDS from pneumonia and patients with ARDS due to primary graft dysfunction after lung transplantation. In this approach, short polypeptides with amino acid sequence is based on those from natural protease substrates are flanked by Foerster resonance energy transfer (FRET) paired fluorophores. Cleavage of these reporter peptides by proteases in the lung fluid can be measured by real-time changes of fluorescence[6]. The function of a protease identified as being upregulated in ARDS lungs was further investigated through genetic and pharmacological inhibition in mouse pneumonia models. Two-photon intravital microscopy of inflamed mouse lungs[7] and in vitro migration assays were performed to evaluate immune cell responses in the absence of target protein function.

RESULTS: Protease profiling revealed increased levels of the metalloprotease-disintegrin 8 (ADAM8) in lung fluids of ARDS patients that correlated with disease severity. Detection of proteolytic activities was rapid (obvious quantitative differences within 20-30 min), sensitive and simpler than e.g. ELISA, suggesting its clinical utility for fast and reliable ARDS risk assessment and monitoring. Genetic knockout of Adam8 in mice affected the migration of immune cells during Pseudomonas aeruginosa infection and reduced disease severity and morbidity. Similarly, pharmacological ADAM8 inhibition in LPS-induced lung inflammation attenuated pulmonary injury. Adam8 deficiency had a significant impact on cell motility, but left microbe-clearing capacities of immune cells relatively unaffected. The favorable effect of blocking ADAM8 without compromising bacterial containment validates ADAM8 as a therapeutic target for ARDS.

CONCLUSION: Our study provides proof-of-concept data for the clinical use of tracking protease activities in lung fluids to monitor ARDS. Beyond proteolytic activities being indicators of ARDS progression, our analysis revealed for the first time that ADAM8 is mechanistically involved in ARDS pathology. Our data suggest that ADAM8 inhibition attenuated immune-mediated pulmonary injury while maintaining microbial control, which has important therapeutic implications. Thus, we conclude that ADAM8 is a promising target to improve ARDS management. With our studies, we hope to make important contributions to advance clinical trial design for ARDS prevention and treatment.

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CRITICAL CARE 36

Optoacoustic Measurement of Central Venous Oxygen Saturation During Simulated Hemorrhage

Tris M Miller[1], Donald Prough[2], Irene Petrov[3], Yuriy Petrov[2], Michael Kinsky[4], Sean Funston[3], Deepinder Mann[2], Beth M Teegarden[5]

[1]University of Texas Medical Branch, Texas City, TX, [2]University of Texas Medical Branch, Galveston, TX, [3]University of Texas Medical Branch, Galveston, United States of America, [4]The University of Texas Medical Branch (UTMB), Galveston, TX, [5]The University of Texas Medical Branch at Galveston, Galveston, TX

INTRODUCTION: Early identification and treatment of hemorrhagic shock is critical to reduce mortality. The development of noninvasive monitors to identify hemorrhage and monitor resuscitation is an area of ongoing research. The purpose of this study was to use lower body negative pressure (LBNP) to simulate hemorrhage in healthy volunteers to 1) observe its impact on central venous oxygen saturation (ScvO2) and 2) observe the correlation between ScvO2 measured by hemoximetric and optoacoustic (OA) measurement of oxygen saturation in the left innominate vein (LIV), which joins the right innominate vein to form the superior vena cava. Previous studies have demonstrated good correlations between in vivo oximetric measurements and concurrent hemoximetric measurements in blood samples from the pulmonary artery (bias and precision -1.12±3.29%)[1] and superior vena cava (-0.3±6.4%)[2].

METHODS: In a protocol approved by the institutional review board, arterial and central venous catheters were placed in six healthy volunteers. Volunteers' lower abdomen and lower extremities were placed in the LBNP box. Ultrasound guidance was used for OA probe placement in the sternal notch. Hemoximetric and OA measurements were collected at -20, -40, -60, and -80 mmHg. If the patient became symptomatic or hemodynamically unstable, the negative pressure in the LBNP box was immediately released. Data were analyzed as recommended by Bland and Altman[3].

RESULTS: The hemoximetric and OA measurements correlated well within six volunteers (bias and precision 2.45±6.45) (Figure).

CONCLUSION: Optoacoustic measurement of LIV oxygen saturation correlates well with hemoximetric measurements. In most volunteers, hemodynamic compensation prevented LBNP-induced hypotension until a critical level was reached, at which time blood pressure decreased too rapidly to reliably reduce venous oxygen saturation for an interval sufficiently long to permit measurements. Performance of this prototype OA system was similar to that of in vivo oximetry.

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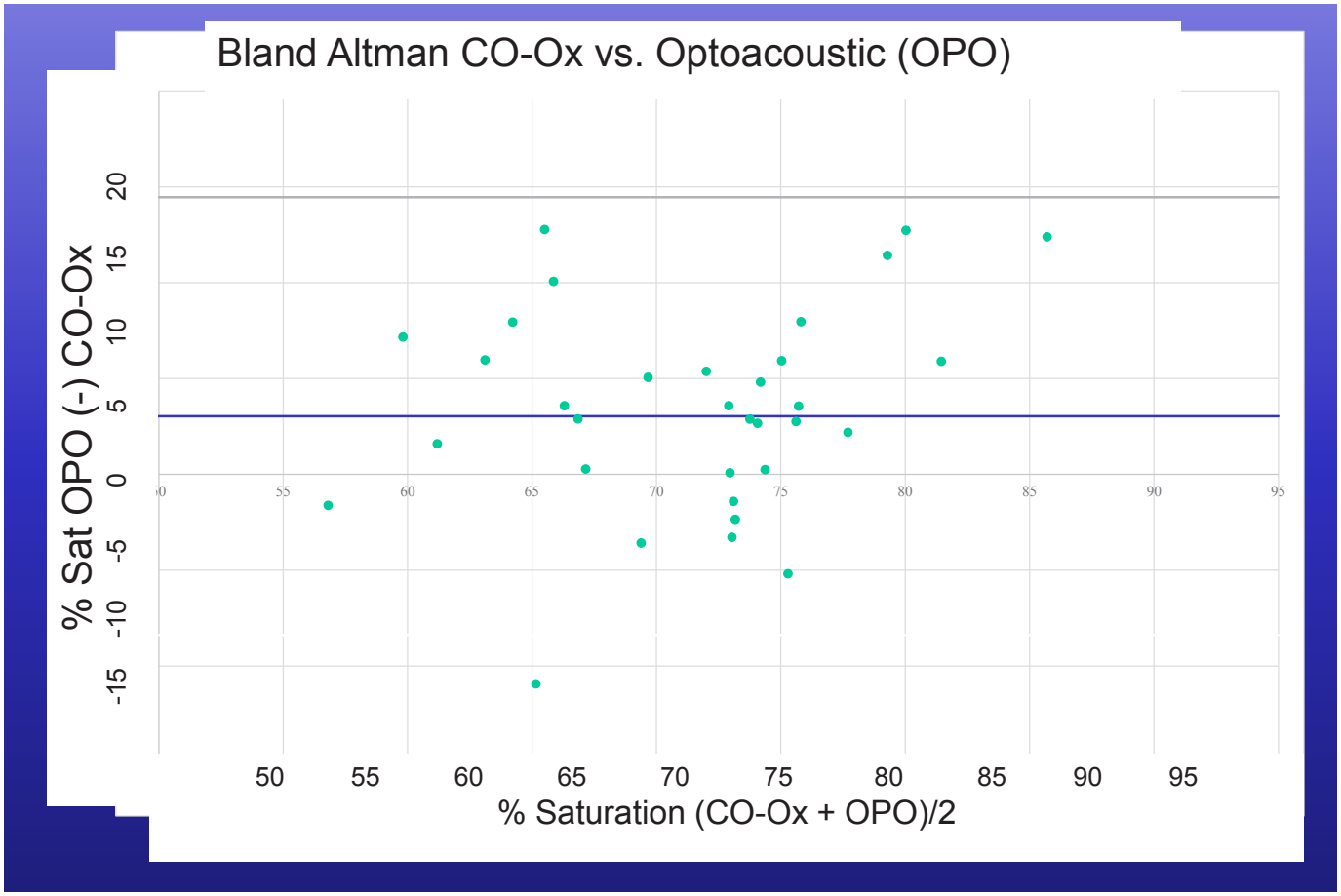

CRITICAL CARE 37

Propofol Sose is not Associated with English Language Proficiency in the ICU

Thanh-Giang Vu[1], Elizabeth L Whitlock[2], Aaron W Scheffler[3], Romain Pirracchio[3]

[1]University of California, San Francisco, San Francisco, CA, [2]University of California, San Francisco School of Medicine, San Francisco, CA, [3]UCSF, San Francisco, CA

INTRODUCTION: Language contributes to disparities in health care. Patients of limited English proficiency (LEP) experience, for example, limited primary care access, poorer maternal health outcomes, and delays in CPR initiation[1,2,3,4]. However, in critical care, LEP is associated with decreased mortality independent of race[5]. Because sedation practices affect critical care outcomes,[6] we tested the hypothesis that LEP status may affect sedation (propofol) use in a single-center retrospective cohort study of patients on mechanical ventilation.

METHODS: We studied 1650 adult patients (18 years and older) who were intubated and mechanically ventilated at our tertiary academic center between June 1, 2015 and June 1, 2018 (assessing first intubation for the hospitalization only). We excluded patients with neurologic deficits/diagnoses (n=465), DNR/DNI status (n=190), and those who were receiving dexmedetomidine (n=343), neuromuscular blockade (n=309), high-dose benzodiazepines (n=14), or high-dose opioids (n=30). The primary predictor was English language proficiency, as documented in our electronic medical record (EMR) by patient-identified language preference. The primary outcome was propofol dosage (mean mcg/kg/min for each day of ventilation) for up to 7 days after initial intubation. We modeled propofol dose using linear mixed effects regression adjusting for sex, race, age, BMI, SOFA score, insurance status, relationship status, post-operative status, and oral morphine equivalents (OMEs).

RESULTS: Of all patients, 13.3% (225/1695) comprised the LEP cohort. LEP status had no effect on average hourly propofol dosage (-0.91 mcg/kg/min, 95% confidence interval -2.7 to 0.89, P=0.32), nor did race. Age per decade (-1.2 mcg/kg/min, 95% confidence interval -1.7 to -0.77, P=0.00) had a decreasing effect on sedation given. Propofol dosage also was impacted by opioid use (1.16 mcg/kg/min per additional 30 OME, 95% confidence interval 0.82 to 1.49, P=0.00). Patients who arrived intubated after surgery had significantly lower propofol administration (-3.9 mcg/kg/min, 95% confidence interval -5.5 to -2.4, P=0.00).

CONCLUSION: We found no significant association between propofol dosage and LEP status at our institution. Our analysis was limited by inclusion of a medically heterogeneous cohort, a relatively small proportion of LEP patients, and the relatively large number of bilingual providers employed at our hospital, which may bias the effect towards the null. However, the effect size estimate for propofol by LEP was relatively narrow, and large differences in propofol administration based on English proficiency are unlikely.

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CRITICAL CARE 38

High Prevalence of Intra-Abdominal Hypertension in Cardiac Surgery Patients Detected by a Continuous Monitoring System- A Descriptive Observational Study

Vanessa Moll[1], Katherine Egan[2], Kelly Stanton[3], Brent Keeling[2], Daniel R Burnett[4], Amit Prabhakar[5]

[1]University Hospital Zurich, Zurich, Switzerland, [2]Emory University School of Medicine, Atlanta, GA, [3]Potrero Medical, Hayward, United States of America, [4]Theranova, San Fransisco, United States of America, [5]Emory School of Medicine, Atlanta, GA

INTRODUCTION: Increased intra-abdominal pressure (IAP) frequently occurs in critically ill patients and is independently linked with multiorgan dysfunction such as acute kidney injury and mortality[1,2]. In cardiac surgery patients, intra-abdominal hypertension ((IAP)≥12 mmHg) (IAH) occurs in approximately33-46%[3,4]. Cardiac surgery patients are already at an increased risk for postoperative kidney dysfunction which might be triggered or aggravated by IAH. Abdominal Perfusion Pressure (APP = MAP-IAP) is also strongly correlated with coronary arterial perfusion pressure. HenceIAP may inform coronary perfusion status and the response to pharmacologic optimization of cardiac function. In this report, we describe the course of IAP and associated UOP in the first 4 postoperative days.

METHODS: In this prospective observational registry study, we enrolled 41 (37% female) cardiac surgery patients of which 39 had complete data to be analyzed. All patients received the Accuryn monitoring system. This system automatically tracked urine output, intra-abdominal pressures, and core temperature. Preprocessing: These data were collected continuously (at 100hz). For analysis, urine production was interpolated between Active Drain Line Clearance events, and urine output (UO) was calculated as the derivative of urine production averaged over 15 min buckets and normalized by the patients' weights(ml/hour/kg). IAP was calculated as the end-expiratory pressure i.e. the minimum over 30s of continuous pressure measured inside the bladder. A rolling median of 10 mins is then applied to the end-expiratory pressures and it is resampled to 15 min buckets. Age, weight, and height were etrieved from medical records. Analysis: For each patient the mean values of UO and IAP were calculated for the following periods: pre-operative (insertion of bladder catheter until surgery end), 0-24hrs, 24-48hrs, 48-72hrs and 72-96hrs post-operative. Additional summary statistics were reported for IAP and UO using python with the pandas and numpy packages.

RESULTS: 38 out of 39 patients displayed IAH for at least 6 hours in the first 24hrs post cardiac surgery. Demographics are shown in Table 1. IAH persisted during the study period which ended with the removal of the foley catheter. Even on POD 3, IAP mean remained high at 15.5 mmHg. IAP values measured were: baseline (preoperative to surgery end) mean values of 9.1 (STD +/-2.4), postoperative day 0 (POD) 17.8 (STD +/-2.9), POD 1 17.5(STD +/-3.5) and POD 2 17.8 (STD +/-3.3) and POD 3 15.5 (STD +/-5.2) (see Table 2 and Figure 1). The UO curve correlated to the IAP curve is shown in Figure 2.

CONCLUSION: IAH is underreported in cardiac surgery patients. IAP persistently remained elevated for three days postoperative. With the continuous automatic measurement of IAP, IAH is identified in a majority of patients. The early identification of IAH might aid in the management and prevention of organ dysfunction and failure (such as acute kidney injury) and in future studies should be correlated with cardiac function.

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Table 1

	Mean	**SD**	**Range**
Age (years)	63.8	10.4	36 – 80
Height (cm)*	172.8	10.0	151.9 – 192.0
Weight (kg)	84.1	17.2	51.9 – 126.2
BMI*	28.3	4.2	18.2 – 36.9

Table 1: Demographics. * excludes two patients, no height recorded. BMI, body mass index

Table 2

POD	**-1**	**0**	**1**	**2**	**3**
N (Patients)	38	39	29	13	5
IAP Mean [mmHg]	9.1	17.8	17.5	17.8	15.5
STD	2.4	2.9	3.5	3.3	5.2
Min	3.4	12.1	8.9	10.9	10.0
25%	7.9	16.3	17.0	17.3	12.2
50%	8.6	17.7	17.9	18.3	15.1
75%	11.1	19.0	19.2	19.6	18.4
Max	15.4	27.1	23.5	21.8	21.9

Table 2: All intra-abdominal pressures (IAP) shown as a 24 hrs Mean. Only POD 0 is shown as the pre-incision baseline (from bladder catheter insertion to surgery end). POD, postoperative day. POD -1, time from foley catheter insertion to surgery end; POD 0, 0-24hrs; POD 1, 24-48hrs, POD 2, 48-72hrs,; POD 3, 72-96hrs.

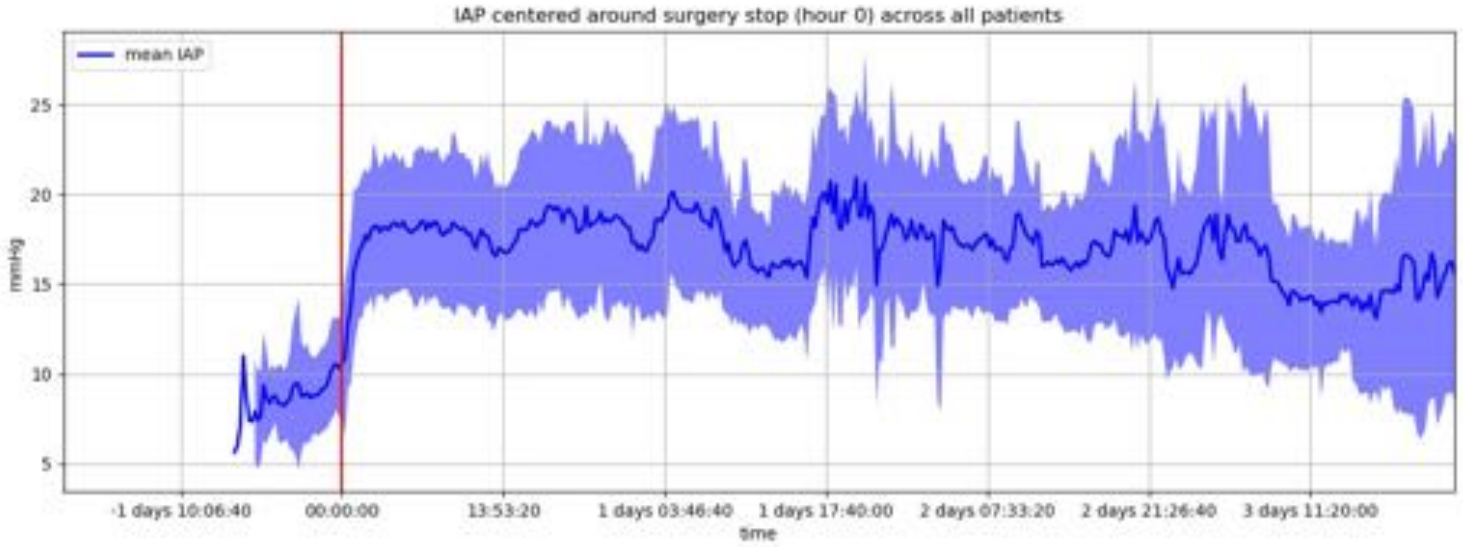

Fig. 1

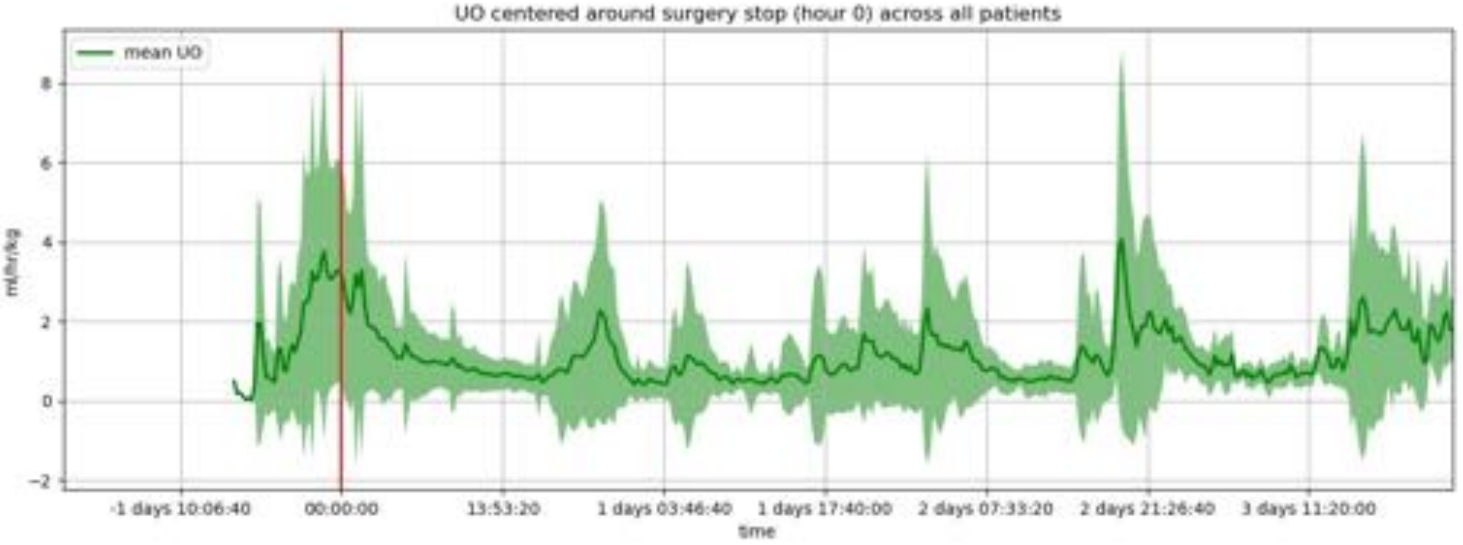

Fig. 2

CRITICAL CARE 39

Natural Killer Lymphocytes as Drivers of Kidney Fibrosis After Acute Cardiac Dysfunction

Kevin Burfeind[1], Yoshio Funahashi[2], Michael Hutchens[3]

[1]Oregon Health & Science University, Portland, OR, [2]Oregon Health & Science University, Portland, OR, [3]OHSU, Portland, OR

INTRODUCTION: Acute kidney injury (AKI) is a common sequela of perioperative critical illness, and is a cause of chronic kidney disease (CKD). The AKI to CKD transition presents an opportunity for early intervention to prevent CKD, for which there are currently no effective treatments. Our lab developed a novel model of critical illness-induced AKI, cardiac arrest and cardiopulmonary resuscitation (CA/CPR), in which all animals recover from AKI but nonetheless develop CKD at 7 weeks[1,2] (Fig. 1). We previously demonstrated that kidney inflammation occurs after CA/CPR[3]. The purpose of this study was to identify potential immune drivers of critical illness-induced CKD.

METHODS: Experiments were approved by the Portland Veterans Affairs Medical Center Institutional Animal Care and Use Committee. Mice were anesthetized with isoflurane, then intubated. Cardiac arrest was induced by potassium chloride. After 7.5 minutes, chest compressions were initiated at a rate of 550 per minute, then intravenous epinephrine was administered. Chest compressions were discontinued after spontaneous electrocardiographic activity. Sham treated mice received 15 minutes of isoflurane anesthesia. To profile the immune landscape of the kidney after CA/CPR, we performed 11-color flow cytometry analysis at 1 day, 3 days, 7 days, and 49 days post cardiac arrest. PDGFRB expression was assessed to identify myofibroblasts, expansion of which signals the AKI to CKD transition[4]. Flow cytometry data were analyzed with FlowJo software. To identify potential NK cell-derived mediators of fibrosis, data from two previously published single cell RNA sequencing studies[5,6] were combined and analyzed using Seurat[7] in Rstudio.

RESULTS: 77% of animals subjected to CA/CPR survived to the pre-designated endpoint. Mean (±S.D.) resuscitation time was 2.07±0.60 min, and mean epinephrine dose was 0.58±0.08 mg/g. Seven distinct immune cell populations were identified in the kidney after CA/CPR (Fig. 2). While there was no increase in kidney T-cells or B-cells after CA/CPR, neutrophils increased starting at 1 day (878±676 neutrophils per million total cells in sham kidney vs. 44,636±31,893 per million in CACPR), peaked at 3 days (53,654±54,172 cells/million), then returned to baseline at 7 days. Monocytes peaked at 1 day (4,069±4,011 cells/million in sham vs. 23,284±20,185 cells/million in CA/CPR), then decreased to near baseline levels by 49 days (8,232±6,864 cells/million). Macrophages increased starting at 7 days (34,909±7,380 cells/million in sham vs. 97,502±8,057 cells/million in CA/CPR), and decreased at 49 days, but remained above baseline (49,381±31,803 cells/million). Natural killer (NK) cells were the only cell type that continually increased, starting at 1 day (4,688±4,738 cells/million in sham vs. 13,777±6,312 cells/million in CA/CPR), and remained elevated at 49 days (17,399±11,428 cells/million) (Fig. 3). PDGFRB+ cells increased starting at 7 days (12,778±7,695 cells/million in sham vs. 26,122±2,554 cells/million in CA/CPR) and remained elevated at 49 days (30,008±14,923 cells/million) (Fig. 4A and B). *Gzmb* (which codes for granzyme B), *Gzma* (granzyme A), *Prf1* (perforin 1), and *Ifng* (interferon gamma) were identified as potential NK cell-expressed mediators of myofibroblast expansion and fibrosis[8-10] (Fig. 4C and D).

CONCLUSION: CA/CPR induces acute and lasting renal inflammation. NK cells remain persistently elevated throughout the AKI to CKD transition, implicating these cells as potential drivers of kidney damage and fibrosis after acute cardiac dysfunction. Continuing experiments will investigate potential NK cell-derived mediators of myofibroblast expansion, such as granzyme B and interferon gamma.

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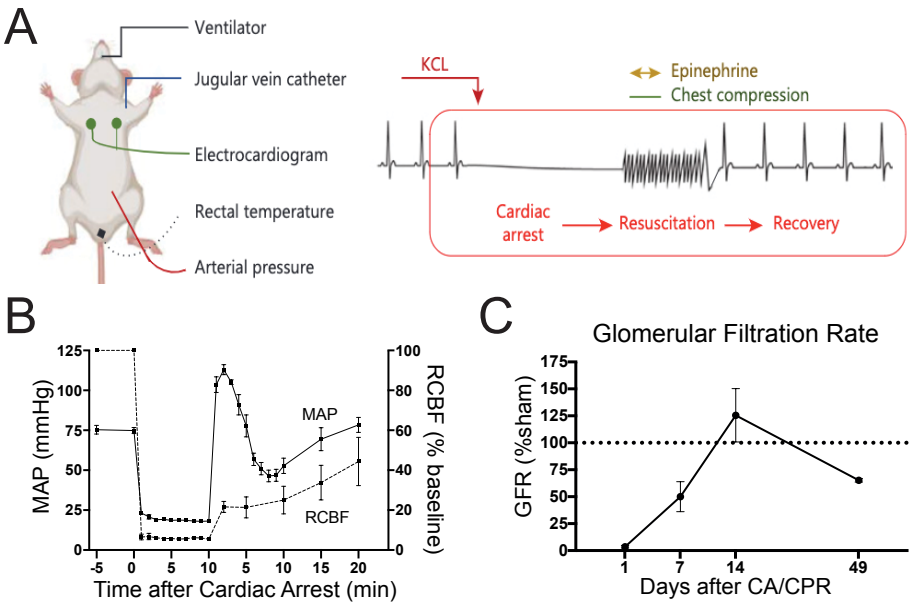

Figure 1. A mouse model of cardiac arrest and cardiopulmonary resuscitation. A) Schematic of CA/CPR experimental procedure. Adapted from ref. 1. B) Mean arterial pressure (MAP, solid lines, scale on left axis) and renal cortical blood flow (RCBF, dotted lines, scale on right Y axis) measurements after CA/CPR procedure. Return of spontaneous circulation was followed by relative hypertension then a gradual return to baseline. RCBF, in contrast, remained low after cardiac arrest and did not return to baseline within the 20-min follow-up period. *n*=5-6/group. Figure adapted from ref. 2. C) Glomerular filtration rate time course after CA/CPR, relative to sham. Results consist of data from ref. 2 and additional experiments combined. *n*=4-9/group. Error bars depict mean ± s.e.m.

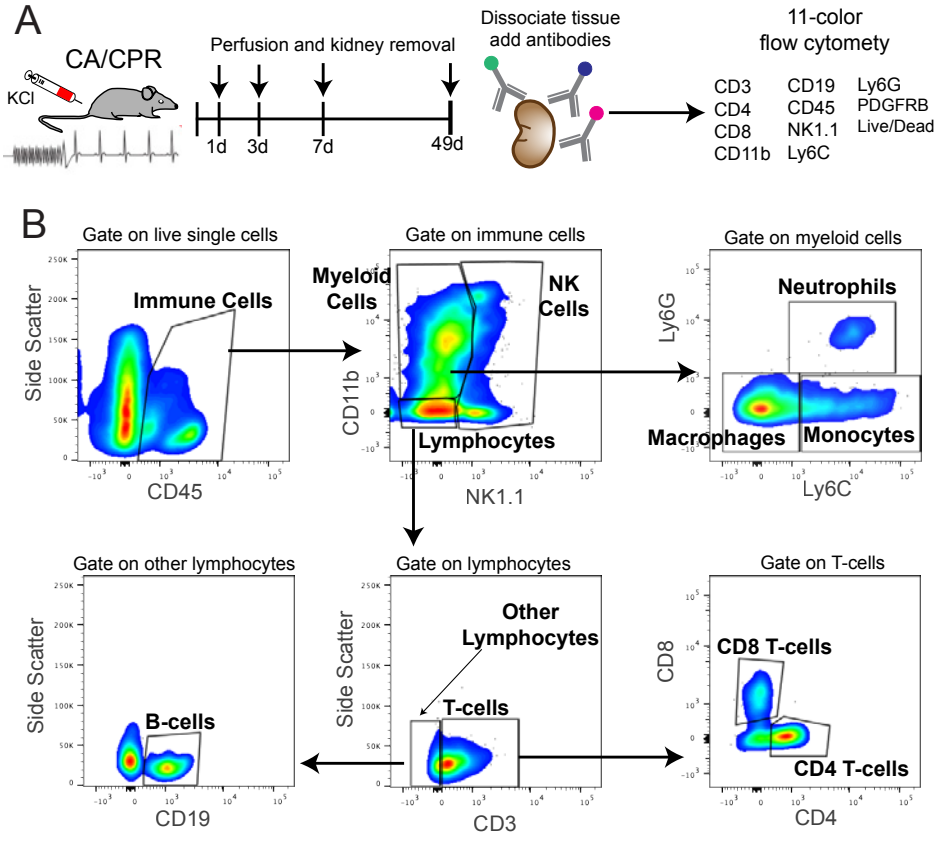

Figure 2. Flow cytometry analysis of kidneys after CA/CPR. A) Diagram of workflow for flow cytometry analysis. Mice were euthanized at 1 day, 3 days, 7 days, and 49 days after CA/CPR, then blood vessels were perfused with saline. Kidneys were immediately removed and dissociated. 11 different fluorescently conjugated antibodies were added, and flow cytometry was performed. B) Representative smoothed pseudocolor plots depicting gating strategy to identify different cell populations.

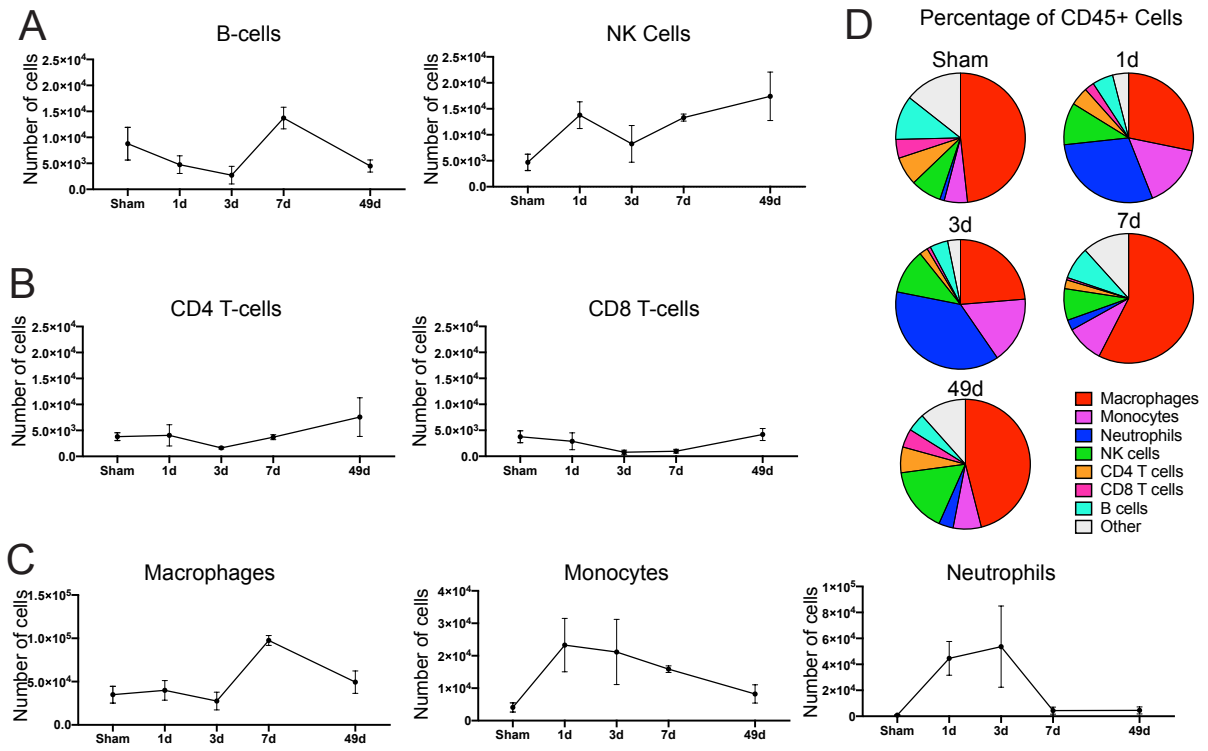

Figure 3. Immune cells infiltrate the kidney after CA/CPR. Time course quantification of different immune cell populations in the kidney, as identified by gating strategy depicted in Fig. 2. Number of cells = number of cells per one million live, single cells. Graphs depict lymphocytes (A), T-cells (B), myeloid cells (C). *n*=2-6/group. D) Relative number of cells as a percentage of total CD45+ cells in the kidney. Error bars depict mean ± s.e.m.

ICU Patients (n=14745)	ICU LOS (days) mean SD, median [IQR 25 - 75]	In-hospital Mortality, n (%)
All ICU Patients (n=14745)	8.2 ±8.9 5 [2, 11]	
Race		
Asian (n=511; 3.5%)	9.0 ±9.1 6 [2, 13]	195 (38.2%)
Black (n=3421; 23.2%)	8.0 ±8.3 5 [2, 11]	1260 (36.8%)
Other (n=3043; 20.6%)	9.1 ±9.7 6 [2, 12]	1176 (38.6%)
Unknown (n=862; 5.8%)	9.4 ±9.9 6 [3, 13]	373 (43.3%)
White (n=6908; 46.8%)	7.7 ±8.6 5 [2, 10]	2445 (35.4%)

Fig. 4

CRITICAL CARE 40

Evaluation of COVID-19 Treatments and Outcomes by Ethnicity and Race

Selby Johnson[1], Kathryn Pearson[1], Eric A JohnBull[2], Daryl Kerr[3], Galen Royce-Nagel[4], Matthew Fuller[5], Tetsu Ohnuma[6], Zachary Frere[6], Yi-Ju Li[7], Vijay Krishnamoorthy[6], Karthik Raghunathan[1], Raquel R Bartz[6]

[1]Duke University School of Medicine, Durham, NC, [2]Veterans Affairs Hospital, Durham, NC, [3]Rush University Medical Center, Chicago, IL, [4]Duke University Hospital, Durham, NC, [5]Duke University Hospital, Durham, United States of America, [6]Duke University, Durham, NC, [7]Duke University Medical Center, Durham, NC

INTRODUCTION: As COVID-19 has infected large portions of the American population, several states and studies have found that different ethnic and racial groups have different outcomes. Several hypotheses exist as to why these outcomes differ including structural racism, socioeconomic status, adverse housing conditions, decreased access to healthcare, increased exposure to air pollution, treatment differences, and increased baseline co-morbidities. However, few studies have considered whether hospital treatments differ between racial and ethnic groups. We examined racial and ethnic differences in treatment and outcomes in critically ill patients with COVID-19.

METHODS: Using the nationwide all-payer Premier Healthcare database (Premier Inc., USA) between April 1, 2020 and June 30, 2020, we examined the treatments and outcomes in 14,745 adult patients hospitalized with a diagnosis of COVID-19 (ICD-10 code U07.1) and with a hospital charge for intensive care across 438 hospitals in the United States. Patients less than 18 years of age were excluded. Our primary exposures were race and ethnicity while outcomes examined included in-hospital pharmacological treatments such as remdesivir, azithromycin, hydroxychloroquine, convalescent plasma, dexamethasone, and need for mechanical ventilation, and renal replacement. We also examined intensive care unit length of stay and in-hospital mortality. Descriptive statistics were used to examine the treatments and outcomes, stratified by race and ethnicity.

RESULTS: Within the cohort, the overall use of hydroxychloroquine and azithromycin as therapy were high compared to remdesivir, convalescent plasma, and dexamethasone. Utilization of these drugs were statistically different. Hydroxychloroquine (p=0.084) and remdesivir (p=0.271) however, showed no difference in use within ethnic and racial groups, respectively. Additionally, there was no difference between use of noninvasive or invasive ventilation and renal replacement therapy (Table 1, 2, 3). We did not find differences in ICU length of stay, hospital length of stay or mortality by ethnicity or race.

CONCLUSION: Although differences in various treatments across race are statistically significant, the absolute difference in the use of these treatments are clinically minor. However, these analyses are unadjusted for severity of illness due to COVID-19. On the other hand, there are clinically and statistically meaningful differences by ethnicity. Hispanic patients were more likely to receive all therapies of interest minus hydroxychloroquine. However, these analyses are unadjusted for severity of illness due to COVID-19 or additional confounders. Additionally, differences within dexamethasone, convalescent plasma, and azithromycin therapies may be due to rapidly evolving data early in the pandemic, suggesting dissimilar treatment protocols across types of hospital institutions or geography. There was no difference in invasive mechanical ventilation nor in in-hospital mortality to explain prior data reported in previous studies. Lastly, based on previous data, a large proportion of patients with unknown ethnicity are uninsured. In our study, many of these patients who did not receive more costly therapies such as convalescent plasma, remdesivir, and tocilizumab, which likely skews the data.

Table 1: Treatment by Ethnicity

Patient Group	Ethnicity			P Values
COVID patients in ICU	Hispanic	Non-Hispanic	Unknown	
(n=14745)	(n=2906; 19.7%)	(n=8409; 57.0)	(3430; 23.3%)	p-value
Dexamethasone for at least 5 days	234 (8.1%)	383 (4.6%)	180 (5.3%)	<0.001
*Remdesivir	241 (8.3%)	440 (5.2%)	71 (2.1%)	<0.001
*Convalescent plasma	167 (5.8%)	314 (3.7%)	65 (1.9%)	<0.001
Hydroxychloroquine	1069 (36.8%)	1547 (17.4%)	1209 (35.3%)	0.084
Azithromycin	1638 (56.4%)	3994 (47.5%)	1776 (51.8%)	<0.001
†Tocilizumab	757 (26.1%)	1617 (19.2%)	490 (14.3%)	<0.001
IMV	1633 (56.2%)	4548 (54.1%)	2177 (63.5%)	<0.001
NIV	695 (23.9%)	1921 (22.8%)	971 (28.3%)	<0.001
CRRT	11 (0.4%)	37 (0.4%)	11 (0.3%)	0.634
Dialysis	453 (15.6%)	1302 (15.5%)	579 (16.9%)	0.155

Data Represented as n(%)

Table 2: Treatments by Race

Patient Group	Race			P Values
COVID patients in ICU	Black/African American	White	Other	
(n=14745)	(n=3421; 23.2%)	(n=6908; 46.9%)	(4416; 30.0%)	p-value
Dexamethasone for at least 5 days	202 (5.9%)	332 (4.8%)	263 (6.0%)	0.010
Remdesivir	159 (4.7%)	352 (5.1%)	241 (5.5%)	0.271
Convalescent plasma	107 (3.1%)	288 (4.2%)	151 (3.4%)	0.015
Hydroxychloroquine	1314 (38.4%)	2323 (33.6%)	1788 (40.5%)	<0.001
Azithromycin	1689 (49.4%)	3420 (49.5%)	2299 (52.1%)	0.015
Tocilizumab	679 (19.9%)	1277 (18.5%)	908 (20.6%)	0.019
IMV	1976 (57.8%)	3547 (51.4%)	2835 (64.2%)	<0.001
NIV	810 (23.7%)	1667 (24.1%)	1110 (25.1%)	0.287
CRRT	20 (0.6%)	34 (0.5%)	5 (0.1%)	0.001
Dialysis	740 (21.6%)	821 (11.9%)	773 (17.5%)	<0.001

Data Represented as n(%)

Ethnicity Outcomes

ICU Patients (n=14745)	ICU LOS (days) mean SD, median [IQR 25 - 75]	In-hospital Mortality, n (%)
Ethnicity		
Hispanic (n=2906; 19.7%)	9.7 ± 10.1 6 [3, 13]	935 (32.2%)
Non-Hispanic (n=8409; 57.0%)	7.9 ± 8.5 5 [2, 10]	3097 (36.8%)
Unknown (n=3430; 23.3%)	7.8 ± 8.7 5 [2, 10]	1417 (41.3%)

Race Outcomes

ICU Patients (n=14745)	ICU LOS (days) mean SD, median [IQR 25 - 75]	In-hospital Mortality, n (%)
All ICU Patients (n=14745)	8.2 ± 8.9 5 [2, 11]	
Race		
Asian (n=511; 3.5%)	9.0 ± 9.1 6 [2, 13]	195 (38.2%)
Black (n=3421; 23.2%)	8.0 ± 8.3 5 [2, 11]	1260 (36.8%)
Other (n=3043; 20.6%)	9.1 ± 9.7 6 [2, 12]	1176 (38.6%)
Unknown (n=862; 5.8%)	9.4 ± 9.9 6 [3, 13]	373 (43.3%)
White (n=6908; 46.8%)	7.7 ± 8.6 5 [2, 10]	2445 (35.4%)

CRITICAL CARE 41

Is Pulmonary Microthrombosis the Main Pathology In COVID-19 Severity? – A Systematic Review of the Postmortem Pathological Findings

Omar H Fahmy[1], Farah M Daas[1], Vidyulata Salunkhe[2], Jessica L Petrey[1], Ediz F Cosar[3], Julio Ramirez[4], Ozan Akca[5]

[1]University of Louisville, Louisville, KY, [2]Medicine, Louisville, United States of America, [3]University of Massachusetts Medical School, Worcester, MA, [4]University of Louisville School of Medicine, Louisville, KY, [5]University of Louisville Hospital, Louisville-, KY

INTRODUCTION: COVID-19 mainly presents as pneumonia. Within the hospitalized patients, 20% develops critical pneumonia similar to ARDS. Severe lung disease manifestation of COVID-19 -whether true pneumonia, ARDS, or a distinct pneumonitis- has been the main cause of morbidity and mortality. Diffuse alveolar damage and thrombosis disease processes appear to contribute to the mortality of severe COVID-19. In this systematic review, we aimed to report the postmortem findings of deceased COVID-19 patients. Specific emphasis was given to pulmonary microthrombosis and widespread thrombotic manifestations in hospitalized COVID-19 patients.

METHODS: In this systematic review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Between December 1, 2019 and August 26, 2020, literature searches were conducted in PubMed, Cochrane and Embase. A total of 549 references were retrieved. After duplicates were extracted, 360 unique records remained for screening. Of the 360 distinct references identified through database searching, 58 studies were eligible for inclusion. Seven additional studies were identified through hand search, for a total of 65 studies included in the evidence synthesis. These studies were appraised for bias, methodological quality, and significance of results, but were not excluded based on their individual limitations. The heterogeneous nature of published literature did not allow for a full meta-analysis. Investigators independently abstracted all available data including study design, participant demographics, key histopathological findings, disease severity markers, duration of hospital stay, and cause of death.

RESULTS: From the 65 eligible studies, 691 total completed autopsies were included in evidence synthesis. Histopathological evaluation of the lungs revealed presence of diffuse alveolar damage in 323 out of 443 patients, and pulmonary microthrombi in 242 out of 326 patients. Deep venous thrombosis and pulmonary embolism were found in 41% and ~15%, respectively, of the cadavers examined for thromboembolic events. D-dimer levels were generally higher in patients with severe clinical course of COVID-19. Plasma levels of ferritin, LDH, IL-6 and CRP were higher in non-survivors when compared to survivors. Overall, microthrombi and extensive angiogenesis of lung vasculature were the most common pathological findings in the lungs.

CONCLUSION: Diffuse alveolar damage was the most predominant feature in the lungs of COVID-19 patients who underwent postmortem assessment. Widespread pulmonary microthrombosis and extensive pulmonary angiogenesis, in addition to frequent pulmonary and extrapulmonary microthrombotic and thromboembolic findings in patients with COVID-19, appear to be consistent with the disease-specific hypercoagulability. Further discovery efforts in assessing the link between COVID-19, hypercoagulable state, and immunothrombosis are warranted. In the interim, increased attention to anticoagulant treatment approaches in COVID-19 patients is needed.

Table. Summary of Postmortem Findings in the Lung Tissue

Eligible Studies Reporting Postmortem Outcomes - n	65
Total Number of Autopsies Reported - n	691
CRP Range – mg/L	[18 – 379]
IL-6 Range – pg/mL	[34 – 3,181]
D-dimer Range – ng/mL	[249 – 64,533]
Histopathology of the Lungs - n	443
Diffuse Alveolar Damage / Hyaline Membrane – n (%)	323/375 (73%)
Pulmonary Microthrombi – n (%)	242/326 (74%)
Pulmonary Emboli – n (%)	39/257 (15%)

CRITICAL CARE 42

CLABSI in COVID 19 in NYC Area Early 2020

Sofia Gilels[1], Shabaaz Baig[2], Carmine Gianatiempo[3], Jean D Eloy[4]

[1]Rutgers New Jersey Medical School, Fort Lee, NJ, [2]Rutgers New Jersey Medical School, Newark, United States of America, [3]Englewood Hospital Medical Center, Englewood, United States of America, [4]Rutgers New Jersey Medical School, Sparta, NJ

INTRODUCTION: Central line associated bloodstream infections (CLABSI) are a significant cause of morbidity and mortality worldwide. Classified as a type of healthcare associated infection, CLABSI is defined as an infection of the bloodstream that develops within 48 hours of central line placement and is not related to another source of infection. Bloodstream infection is confirmed through laboratory analysis, with some of the most common pathogens noted as staph species, enterococci, and candida. Based on data from the years 2001 and 2009, the CDC estimated that CLABSI was noted in 43,000 cases in 2001 and 18,000 cases in 2009. This represented a 58% decrease. This reduction in the incidence of CLABSI is surmised to be due to the effort to advance the best practice evidence based guidelines for central line placement and maintenance. The mortality rate was estimated to be between 12-25%. The CDC also stated that 'Assuming that each CLABSI carries excess health-care costs of $16,550 and mortality of up to 25%, and that CLABSI reductions were steady during 2001–2009, the cumulative excess health-care costs of all CLABSIs prevented in ICUs could approach $1.8 billion, and the number of lives saved could be as high as 27,000[3].' The Agency for Healthcare and Research Quality conducted a systematic review and reported that their estimate for CLABSI associated costs were even higher, with an average from the literature of $70, 696. With an estimated mortality rate of 12-25%, their healthcare associated cost savings were calculated to be $97,756,628–$244,270,620[4]. In 2019, several patients in China were hospitalized with pneumonia like symptoms due to an unknown cause. The cause of these symptoms was discovered to be the novel coronavirus, Sars-CoV-2. The virus spread, covering the globe and beginning the COVID-19 pandemic. During the COVID-19 pandemic, the ICUs in the United States were overwhelmed with patients. At Englewood hospital, virtually all patients admitted to the ICU received central lines. However, while COVID-19 was not considered a causative factor for CLABSI, the number of CLABSI noted during the height of the pandemic skyrocketed. In this report we discuss the factors behind this drastic increase in CLABSI and what strategies we can implement to prevent this from occurring at other hospitals and to prepare for future pandemics.

METHODS: Data was pulled on every patient identified with CLABSI between January 2020 and August 2020 at Englewood hospital in northern New Jersey. Variables identified included gender, age, admission date and reason, culture date, organism identified, and central line characteristics. Chart notes, provider comments, and COVID status were also noted.

RESULTS: 26 total CLABSI events were noted, with 69% occurring in April alone. The months of March, April, and May, regarded as the height of the pandemic, accounted for 88% of the infections. Zero events were recorded in January and February.The three ICUs accounted for 92% of CLABSI. The most common infected line type was quad lumen with 69% followed by triple lumen at 19%. The most commonly infected placement was the right internal jugular with 73%. Group D enterococci (faecalis) was the most commonly seen organism with 69%. Males accounted for 77% of CLABSI. The significant increase in CLABSI during the height of the COVID pandemic raised concern for increased mortality and morbidity rates. Though guidelines documenting the best evidence-based practice for central line placement have been in place for many years, we found that the pandemic introduced new variables to consider and difficulties that now would require reevaluation of strategies that previously proved to be successful. Based on the Practice Guidelines for Central Venous Access 2020 by the American Society of Anesthesiologists (ASA) some of the best practices included usage of aseptic techniques, selection of catheter insertion site, usage of dressings, and catheter maintenance.

CONCLUSION: Innovation to decrease provider exposure using of pumps outside patient rooms with tubing extending via the ground. This led to concern as a source of infection. Enterococcus Faecalis as the majority bug identified in our data makes this unlikely. CLABSI increased mortality, particularly those in the ICU during the pandemic. Adherence to evidence-based guidelines is imperative. However, in the setting of new challenges, it is important to reevaluate protocols and reestablish guidelines such that they are sustainable.

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CRITICAL CARE 43

Addition of Standardized Focused Critical Care Echocardiography (FCCE) Learning into Existing Critical Care Fellowship Training Programs: A Multi-Center Prospective Study of Blended Learning

Nibras Bughrara[1], Whitney Tse[1], Oliver Panzer[2], Tim Tran[3], Habib Srour[4], Andrew Gold[5], Sumit Singh[6], Ranjit Deshpande[7], Ashar Ata[1], Lorna Workman[1], Aliaksei Pustavoitau[8]

[1]Albany Medical College, Albany, NY, [2]Columbia University Medical Center; New York-Presbyterian Hospital, New York, NY, [3]University of Colorado - Anschutz, Aurora, CO, [4]University of Kentucky, Lexington, KY, [5]University of Pennsylvania, Philadelphia, PA, [6]UCLA, La, CA, [7]Yale School of Medicine, New Haven, CT, [8]Johns Hopkins University, Baltimore, MD

INTRODUCTION: Focused Critical Care Echocardiography (FCCE) is a time-sensitive examination performed by a non-cardiologist to evaluate cardiocirculatory or respiratory failure which can be performed serially to evaluate the impact of therapy. 'Non-traditional' users including intensivists have been using FCCE for over 20 years now. However, standardized FCCE training in anesthesiology critical care fellowship programs does not exist as there is a paucity of both evidence-based curricula and faculty proficient in this modality. Our goal is to examine the impact of a standardized 5-day curriculum of blended FCCE learning into existing Critical Care Medicine Fellowship training programs. Blended learning, or mixed-mode classes incorporates a portion of an educational process from web-based sources into an educational initiative.

METHODS: Our methodology is an adapted version from a study originally performed by Bughrara et al[1]. After IRB approval, 36 critical care fellows at seven large academic medical centers participated in the study during 2019-2020 academic year. Educational activities followed outline of 4-days fundamental Critical Care Ultrasound course and 1-day advanced course developed by SCCM (Appendix 1). Standardized 30 MCQs knowledge tests created by the SCCM were the main assessment tool. All participating fellows received a pre-test at the beginning of the academic year, a post-test immediately after the course, and retention test during the last month of the academic year. Tested items included identification and acquisition of standard transthoracic views, recognition of cardiac structures and interpretation of images from presented clinical cases.Test scores were recorded and ranged from 1 to 30. Departing 10 fellows (academic year 2018-2019) from 3 institutions completed the retention at the end of their academic year, and their test scores were compared with the retention test scores of the 16 fellows at the same 3 institutions who took the 5-day course in the following academic year. Additionally, the pre-test scores and post-test scores for the 36 fellows who did the 5-day course were compared for improvement. Both parametric (Student's T, Paired T, Fisher's Exact) and non-parametric (Mann-Whitney, Wilcoxon signed-rank) tests were used as appropriate.

RESULTS: 36 fellows in 7 institutions completed the 5-day standardized training course. Mean (SD) scores were available for 27 fellows who took pretest (18.0 (4.6)), 35 fellows who took post-test (24.8 (3.1)) and 33 fellows who completed retention test (25.2 (2.4)). Missing test data is related to pending IRB approval to use pretest scores (n=9) and off-cycle fellowship participation (n=3). Based on the passing score of 21/30 (70%) on the standardized test validated by SCCM, the passing rates for pre, post and retention tests were 29.6%, 88.6% and 97.0% respectively. The pre- and post-test scores were available for 26 fellows with a mean improvement of 6.5 (95% CI: 5.1 to 7.8, $p<0.001$). Among those who completed the course post and retention test scores were available for 32 fellows with a non-significant change in scores of 0.06 (95% CI: 0.7 to -0.8, $p<0.568$). The mean test scores of the 10 fellows that did not participate in the 5-day course was 22.2 and was lower by 2.9 units compared to the mean retention scores of 16 fellows from the same 3 institutions who completed the course which was 25. The corresponding pass rates among those not participating in the course was 60% and was significantly lower as compared to 93.8% among those who participated.

CONCLUSION: A 5-day course of blended FCCE learning in critical care fellowship programs results in rapid acquisition and retention of knowledge and improves FCCE knowledge test scores compared to alternative educational modalities. In addition, we were able to overcome other major obstacles to implement FCCE training like the paucity of trained faculty and lack of standardized curriculum. Implementation of the described course across medical centers will result in sustained passing score FCCE knowledge acquisition among critical care fellows.

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FCCE Curriculum

Dear fellows,

Welcome to our Comprehensive Critical Care Echocardiography Hands-On training program, please find the Agenda below. You will be relieved of any clinical duties from 8:00 AM to 4:00 PM on the course days.

Agenda:

Monday September 7th:

8-11:30 am	Basic Physics and Knobology, Fundamental Windows and Views, Lung ultrasound
12:15 – 1 pm	Lunch and Clinical cases 1, Introduction to perceptual Adaptive learning Modules (PALMs)
1- 4 pm	SICU 1:1 Scanning with report generation for each patient scanned

Tuesday *September* 8th:

8-12 am	Assessment of Left ventricular systolic function, Intra Vascular Volume Assessment, point of care ultrasound in cardiac arrest
12- 1pm	Lunch and Clinical Cases 2
1-4 pm	PACU/SICU 1-1 Scanning

Monday *September* 15th:

8-12 am	Basic evaluation of RV, Pulmonary Embolism, Vascular Ultrasound, Pericardial tamponade
12-1 pm	Lunch and Clinical Cases 3
1-4 pm	SICU 1-1 Scanning

Tuesday November 16th:

8-12 am	Echo approach to shock, EASy- FAST, CC Echo limitation, CCE Board Certification
12- 1pm	Lunch and Clinical cases 4
1- 4 pm	SICU 1-1 Scanning

Friday January 21st

8-4 pm	Advanced hemodynamic measurements, advanced evaluation of left and right ventricular function, focus transesophageal echocardiography, focus echocardiograph evaluation in life support, the Histology in the ICU, valvular assessment in the critically ill.

- *By the end of October, a portfolio of at least 20 supervised CCE studies (performed with report generation) must be achieved by the trainee.*

CRITICAL CARE 44

Respiratory non-Invasive Venous waveform Analysis (RIVA) for Assessment of Respiratory Distress in COVID-19 Patients: An Observational Study

Bret Alvis[1], Lexie Vaughn[1], Jeffrey Schmeckpeper[1], Jessica Huston[2], Marisa Case[1], Matthew Semler[1], JoAnn Lindenfeld[1], Colleen Brophy[3], Kyle Hocking[4]

[1]Vanderbilt University Medical Center, Nashville, TN, [2]University of Pittsburg Medical Center, Pittsburgh, PA, [3]Vanderbilt University Hospital, Nashville, United States of America, [4]Vanderbilt University Hospital, Nashville, TN

INTRODUCTION: In well under a year, the coronavirus 2 (SARS-CoV-2) has spread globally leading to a global pandemic that has crippled both economies and healthcare.[1,2] Evaluation and management of COVID-19 depends on the severity of the disease.[2] Unfortunately, knowing whose symptoms will remain mild and who will acutely progress to severe respiratory failure have proven very difficult and, often, requires observation in a hospital setting.[2] This sudden deterioration of patients with COVID-19 into critical illness is a major concern.[3] Rapid and effective triage is critical for early treatment and effective allocation of hospital resources.[3] This observational study describes a post-hoc discovery of the novel respiratory signal (RIVA) that has not been described to date. We report the relationship of the relative amplitude of the venous waveform to COVID-19 and the potential triage ability it holds for screening patients need for oxygen support therapy.

METHODS: This is a post-hoc analysis of respiratory data from a single institution observational study of non-invasive venous waveform analysis (NIVA). Peripheral venous waveforms were recorded (Figure 1) from admission to discharge in enrolled COVID-19+ patients and healthy age-matched controls. Data were analyzed in LabChart 8 to transform venous waveforms to the frequency domain using Fast Fourier Transforms (FFT; Figure 2 &3). The peak respiratory frequency was normalized to the peak cardiac frequency to generate respiratory non-invasive venous analysis respiratory indexes (RIVA-RI). Paired Fisher's exact tests were used to compare RIVA-RI on admission and discharge. A nonparametric one-way ANOVA was used for multiple comparisons between groups for RIVA-RI, respiratory rate, and SpO2.

RESULTS: In total, 50 COVID-19+ patients admitted to Vanderbilt University Medical Center from April-September 2020 were enrolled. Forty-five patient's venous waveforms were blindly analyzed and compared against 34 age-matched healthy controls. The RIVA RI for COVID-19+ patients requiring oxygen support during hospitalization (median = 0.27, IQR 0.11 – 1.28, n = 34) was significantly higher ($p < 0.01$; 95% CI 0.4008 – 2.037) than the RIVA RI for COVID-19 negative controls (median = 0.06, IQR 0.03 – 0.14, n = 34 and the RIVA RI for those same patients at time of discharge ($p = 0.02$, 95% CI 0.1023 – 1.939; median = 0.12, IQR 0.05 – 0.56, n = 24; Figure 4). RIVA RI of 0.64 demonstrated an AUC of 0.64 (sensitivity=92%, specificity=47%; Figure 5) as a predictor for requiring supplemental oxygen therapy during hospitalization. Positive predictive value was 93%. There was no significant difference ($p = 0.13$, 95% CI -0.7309 – 8.28) in the respiratory rate between COVID-19+ patients that required oxygen support during hospitalization (median= 20, IQR 19 - 25, n = 34) and those that did not require oxygen support during hospitalization (median=17, IQR 16 - 18, n =10) or between COVID-19+ patients on admission to the hospital (median= 20, IQR 19 - 25, n = 34) and at discharge (median=19, IQR 17 - 20, n = 27; $p = 0.66$, 95% CI -1.944 – 4.974). COVID-19+ patients that required oxygen support during hospitalization had a significantly lower oxygen saturation (SpO2) on admission (median= 93%, IQR 91 – 95%, n = 34; $p < 0.01$, 95% CI 2.536 – 8.727) and at discharge (median=93, IQR 92 – 95%, n = 27; $p < 0.01$, 95% CI 0.8066 – 7.426) than COVID-19 positive patients that did not require oxygen support during hospitalization (median=96, IQR 94 - 98, n = 10).

CONCLUSION: The peripheral venous waveform signal is able to be captured non-invasively in hospitalized COVID-19 patients. RIVA RI is a novel physiological measurement with a promising ability to predict the need for oxygen support therapy in COVID-19 patients. With the exploding need for efficient and correct triage, RIVA monitoring could aid clinicians in caring for patients both at home and at the hospital and potentially prevent unnecessary hospitalizations.

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Figure 1. Picture representation of NIVA device used to capture the venous waveforms that contain the cardiac and respiratory harmonics in COVID-19 and control subjects.

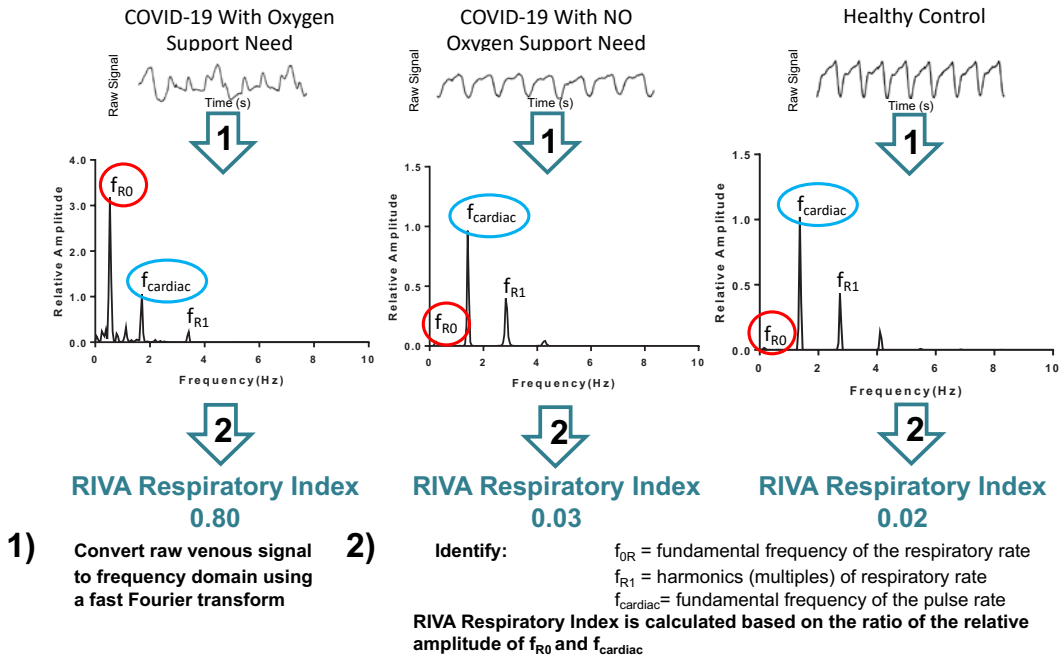


Figure 2. Representative RIVA respiratory signals from subjects with high to low risk of O_2 support need (left to right). Raw signals are transformed from the time domain (top) to the frequency domain (bottom) (1). The relative amplitude of the respiratory rate (f_{RO}, fundamental frequency) compared to the relative amplitude of the pulse rate ($f_{cardiac}$) is used to calculate a RIVA Respiratory Index.

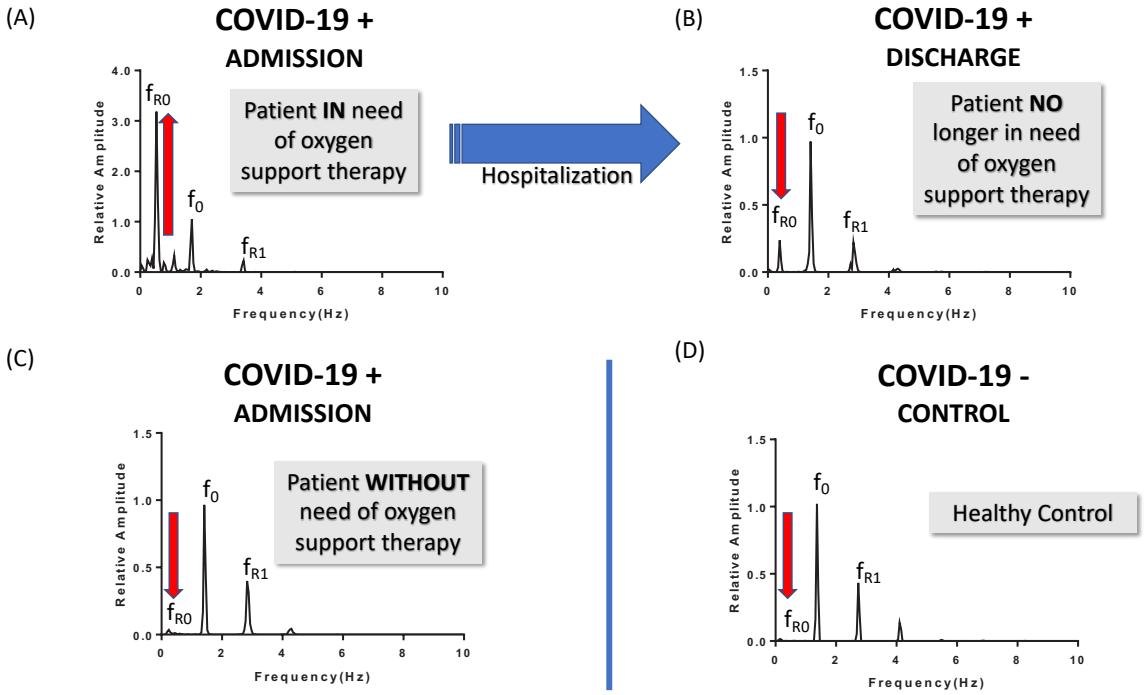


Figure 3. Representative examples of f_{R0} amplitude changes in the frequency domain recorded in COVID-19+ subjects. The fast fourier transform (FFT) of venous waveform recorded using non-invasive venous waveform analysis (NIVA) in COVID-19+ subjects admitted requiring oxygen support therapy (A) and at time of discharge when oxygen support was no longer required (B). A representative FFT of a COVID-19+ subject that did not require any oxygen support therapy and, for comparison, the FFT of a COVID-19 – healthy control subject (D). Abbreviations: COVID 19+ = positive for the SARS-CoV-2 virus; COVID-19- = negative for the SARS-CoV-2 virus.

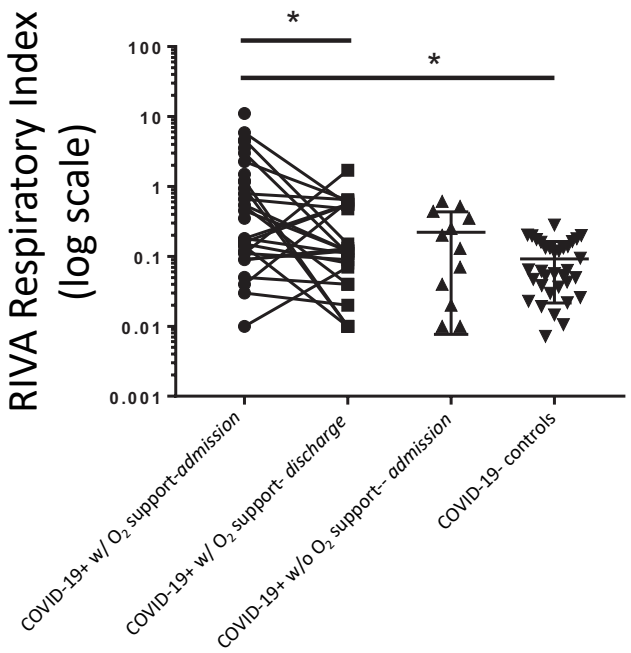


Figure 4. RIVA Respiratory Index (RIVA RI) for COVID-19 positive patients and COVID-19 negative controls. Venous waveforms were obtained using the RIVA device for patients admitted to Vanderbilt University Medical Center (VUMC) with COVID-19 from April - September 2020. The amplitude of the respiratory signal relative to the amplitude of the cardiac signal was derived from the venous waveforms after fast Fourier transformation and this ratio represents the RIVA RI. The RIVA RI for COVID-19 positive patients (COVID-19+) admitted to the hospital and requiring oxygen support during hospitalization (median = 0.27, n = 34) was significantly higher ($p < 0.01$, 95% CI 0.4008 – 2.037) than the RIVA RI for COVID-19 negative controls (median = 0.06, n = 34). The RIVA RI for COVID-19 + patients that required oxygen support was also significantly higher ($p = 0.02$, 95% CI 0.1023 – 1.939) than the RIVA RI for those same patients at time of discharge (median = 0.12, n = 24). The RIVA RI was not significantly different ($p = 0.09$, 95% CI -0.1242 – 2.265) for COVID-19+ patients that required oxygen support during hospitalization and those COVID-19+ patients that never required oxygen support during hospitalization (median = 0.2, n = 11). Statistical analysis was completed using ANOVA with multiple comparisons between groups. Horizontal bars with star (*) demonstrate statistical significance.

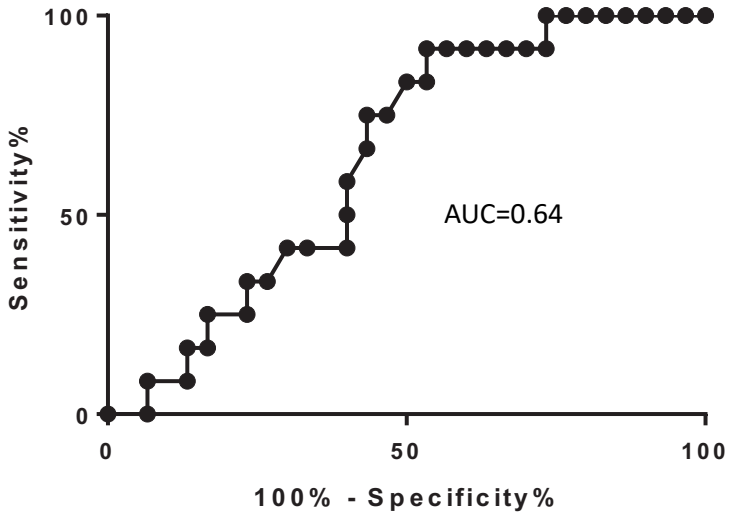


Figure 5. AUC for predicting oxygen requirement with RIVA RI. A RIVA RI of ≥ 0.6 demonstrates 92% sensitivity (95% CI, 61.52% to 99.79%) and 47% specificity (95% CI, 28.34% to 65.67%) for predicting need for oxygen support during admission for COVID-19 positive patients with an area under the ROC curve of 0.6431.

CRITICAL CARE 45

Perceptions of Anesthesiology Critical Care Medicine Physicians on Anxiety, Depression, Lack of Diversity and Bias in Critical Care Medicine - a follow-

Shahla Siddiqui[1]

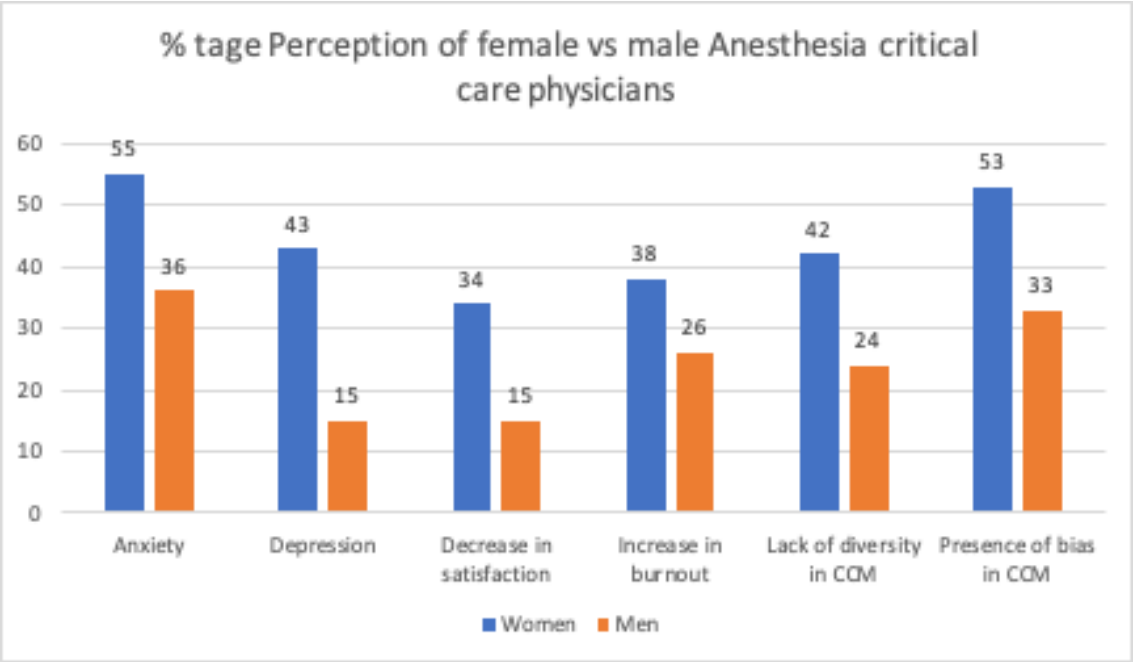
[1]*Beth Israel Deaconess Lahey Medical Center, Boston, MA*

INTRODUCTION: Recent studies have shown the immense psychological burden of the COVID 19 burden on healthcare. Studies have cited upto 50% frontline staff suffering from burnout, anxiety or depressive symptoms. These findings are especially seen in ICU staff and mostly nurses. Specific causes of these symptoms have been identified, however, previous studies have not focused on the presence of psychological effects in Anesthesiologist intensivists and the demographic distribution of these effects in this cohort. No previous study has evaluated the recent awareness of bias and the lack of diversity in CCM as well.

METHODS: After approval and waiver of written informed consent by the Beth Israel Deaconess Medical Center Institutional Review Board, an anonymous online survey was sent to all members of the American Society of Anesthesiologists (ASA) who self-identified as being CCM trained or practicing critical care and had given permission to be contacted for survey participation between September and October 2020. This same tool was sent to members of the Society of Critical Care Anesthesiologists (SOCCA) as well as the Anesthesiology section of the Society of Critical Care Medicine (SCCM). This was a mixed methods observational study using a validated survey tool, the Generalised Anxiety and Depression scale as well as open ended questions on presence of bias and diversity in CCM.

RESULTS: This survey reveals some important insights into the practice of critical care by Anesthesiologists, especially during the pandemic. 42% of the respondents felt symptoms of excessive anxiety and depression; 75% did not find the institutional wellness resources offered useful in mitigating these symptoms. More than half of the respondents did not find that these symptoms interfered in their abilities to concentrate. However, when these data were analyzed by gender and age, it was found that women and younger respondents felt more anxiety and depressive symptoms. Also, there was strong evidence to suggest that women and younger physicians felt emphatically that bias and lack of diversity were present in CCM. This study provides new and telling information about the disparity of perception of anxiety, depression, diversity and bias within CCM by different demographics. This information can be used to address these issues of systemic bias and provide personalized avenues of burnout mitigation.

CONCLUSION: In conclusion, this study reveals important challenges facing medicine and especially Critical Care currently. It is clear that bias and lack of diversity are more recognized by women and younger intensivists. The pandemic highlighted these disparities in much greater detail. Although overall there was satisfaction with the sense of respect and recognition, and low levels of stress and anxiety, there were differences between these perceptions by age and gender. Suggestions for reducing these disparities included diversity training of leadership, accountability for diversity and dealing with bias, and peer support. Other ideas include incorporating education about structural biases into curricula to raise both recognition and awareness of how perceptions of our own co-workers might be shaped by bias – for example, the failure to recognize or inertia around the effects of the demands around child or family care. Also, our results provide an important aspect for further study in this field.



Pic. 1

Pic. 2

Pic. 3

CRITICAL CARE 46

Fluid Loading Increases the Risk of Developing Delayed Cerebral Ischemia in Subarachnoid Hemorrhage

Matthew W Ison[1]

[1]*University of Tennessee Health Science Center, Graduate School of Medicine, Knoxville, TN*

INTRODUCTION: Delayed cerebral ischemia(DCI) occurs in 30% of patients who suffer a subarachnoid hemorrhage(SAH)[1]. It is a major contributor towards morbidity and mortality among these patients. Currently, the evidence for treatment and preventive measures for DCI are poor. Hypervolemia, hypertension, and hemodilution, so called triple H therapy, was the mainstay of prevention and treatment of DCI over the last two decades[2]. While fluid balance goals are not as aggressive today, SAH patients often receive large amounts of fluid in order to maintain an even to slightly positive volume status. The etiology of DCI remains elusive. The literature does not support a causal link between vasospasm and DCI. In the CONSCIOUS-2 trial, clazosentan an endothelin antagonist and vasodilator, reduced vasospasm but had no effect on DCI or functional outcome[3]. It has been proposed that DCI is a phenomenon of the microcirculation. Blood flow within the microcirculation becomes heterogeneous in during volume loading in euvolemic subjects. Similarly, the endothelial glycocalyx is shed and becomes dysfunctional in volume loading[4]. The glycocalyx shields adhesion molecules from components of the coagulation system and prevents their interaction with the vascular wall in states of health. During inflammation these interactions occur without regulation and result in microthrombi[5]. SAH induces a state of inflammation accompanied by signs of systemic inflammatory response[6]. Hypervolemia might then compound the effects of inflammation at the level of the microcirculation and contribute to worse clinical outcomes.

METHODS: 413 SAH patients were identified among the nearly 60,000 patient admissions in the MIMIC-III database[8]. These records were analyzed for the diagnosis of DCI, which was made according to the 2010 definition guidelines[6]. After excluding records without full input and output data and fewer than 7 days of ICU admission, 188 patient's records were analyzed for the study. Kendall's tau was used to find associations between non-normally distributed continuous variables and the occurrence of DCI. For the categorical variables, chi-square test was used to find significant associations. Fluid inputs and balances were calculated for mean daily, first 3 days, first 7 days and total admission. Kendall's tau was used to find the associations between the variables and the occurrence of DCI. Finally, multiple logistic regression was employed to explore the influence of the fluid variables on DCI while controlling for the influence of those factors that were found to have statistically significant associations with DCI in the univariate analyses. The data was compiled and analyses carried out with pandas, scipy, numpy, scikit-learn, and statsmodels[9-13].

RESULTS: Four factors were found to have statistically significant differences among those with and without DCI in the univariate analyses. They are age, modified Fisher scale, Hunt and Hess grade, and presence of an aneurysm. All fluid variables were statistically significant between the DCI + and DCI - groups in the unadjusted analyses. After controlling for these factors in a multiple logistic regression model, fluid inputs remained significantly associated with the diagnosis of DCI except for the daily mean fluid input. However, the fluid balance variables were not statistically significant after controlling for confounding variables. The total inputs for the admission had the strongest influence on the occurrence of DCI with an odds ratio of 2.39, $p = 0.004$.

CONCLUSION: DCI is an enigmatic phenomenon in SAH patients. The microcirculation and the endothelium play a vital role in maintaining the integrity and health of cerebral blood flow. Fluid resuscitation, a cornerstone of SAH management, has consequences that not only affect the cardiopulmonary system but affect the brain as well. In this study of SAH patients, larger degrees of fluid loading conferred a higher risk of having DCI. From the perspective of the endothelial glycocalyx and hence the microcirculation, fluid loading has destructive consequences. It is not a stretch to hypothesize that any dysfunction of the cerebral glycocalyx, be it from inflammation or from overly aggressive fluid resuscitation, can lead to DCI. The findings of this study support this hypothesis. Fluid overload is therefore something to avoid in patients with SAH.

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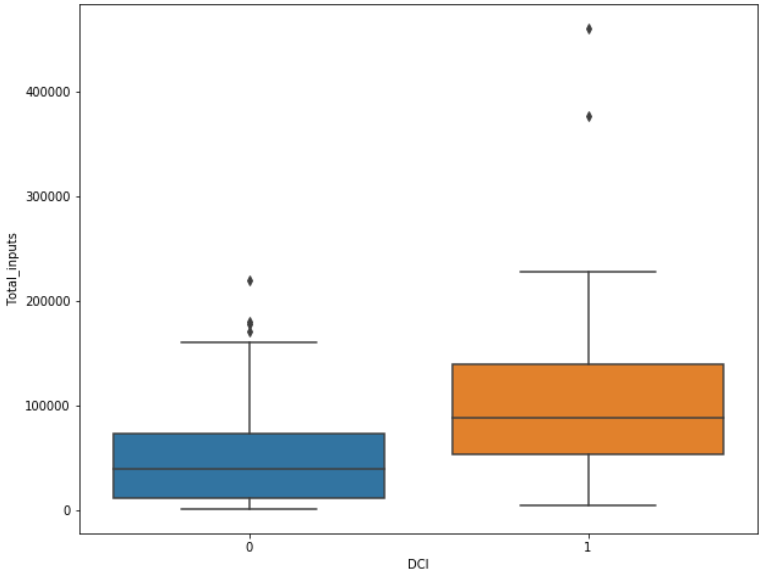
Inputs Log Reg Odds Ratios

	OR	p-value	95% CI
Mean Daily Inputs	1.59	0.087	0.94-2.70
First 3 Days Inputs	1.80	0.015	1.12-2.89
First 7 Days Inputs	2.03	0.02	1.12-3.69
Total Inputs	2.39	0.004	1.32-4.31

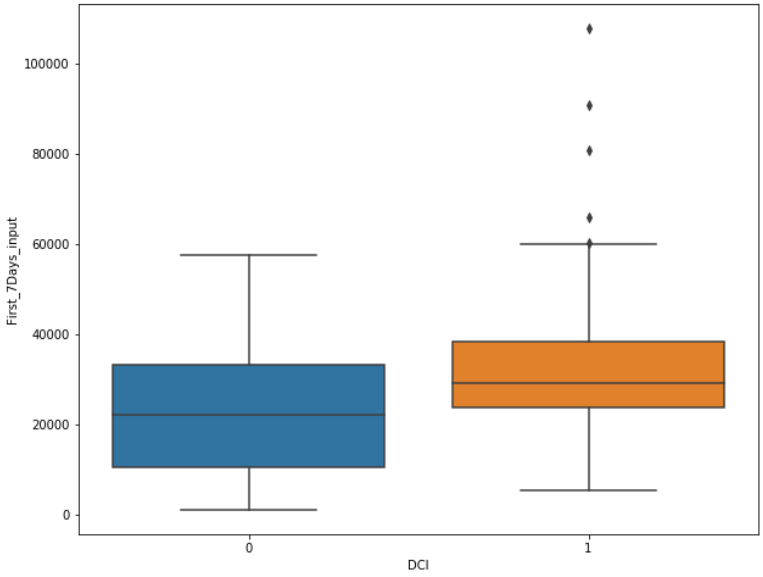
Cohort Characterstics Data Table

	-DCI (% of -DCI patients)	+DCI (% of +DCI patients)	p-value
Number of SAH patients	121(64%)	66(35%)	--
Number with No Aneursym Found	37(31%)	6(9%)	<0.05
Number with Aneursym	84(69%)	60(91%)	<0.05
Anterior Location of Aneurysm	51(61%)	40(67%)	NS
Posterior Location of Aneurysm	31(37%)	20(33%)	NS
Coiling	56(67%)	41(68%)	NS
Clipping	27(32%)	19(32%)	NS
Female	69(57%)	41(62%)	NS
Died	21(17%)	24(36%)	<0.05
Mean Age	54	60	<0.05
Mean Hunt and Hess Score	2.4	3.2	<0.05
Mean modified Fisher Scale	1.98	3.2	<0.05

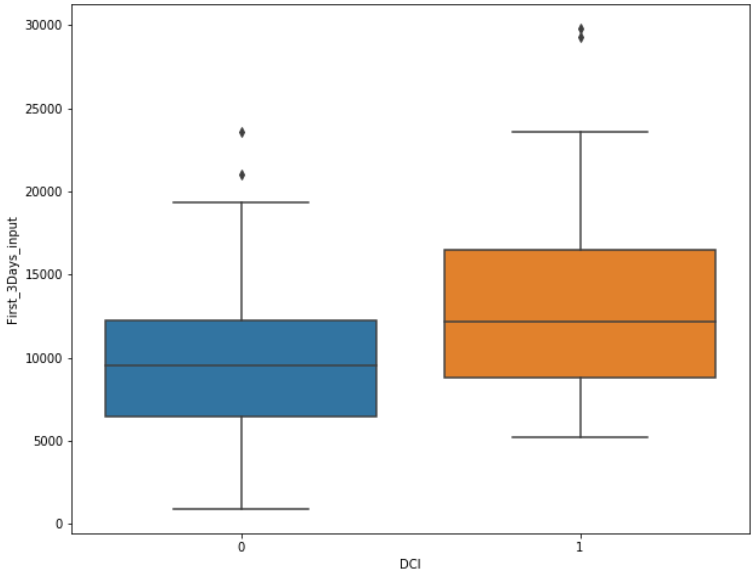
Total Inputs vs DCI



First 7 Days Input vs DCI



First 3 Days Input vs DCI



CRITICAL CARE 47

A Unique Low-density Pro-Inflammatory Neutrophil Population Correlates with Hypercoagulation and Disease Severity in Hospitalized COVID-19 Patients

Jiapeng Huang[1], Jun Yan[2]

[1]University of Louisville, Louisville, KY, [2]University of Louisville, Louisville , KY

INTRODUCTION: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel viral pathogen that causes a clinical disease called coronavirus disease 2019 (COVID-19). Approximately 20% of infected patients experience a severe manifestation of the disease, most commonly bilateral pneumonia and acute respiratory distress syndrome. Severe COVID-19 patients also have a pronounced coagulopathy with approximately 30% of patients experiencing thromboembolic complications. However, the cellular etiology driving the coagulopathy remains unknown.

METHODS: The Institutional Review Board at University of Louisville approved the present study and written informed consent was obtained from either subjects or their legal authorized representatives. COVID-19 patients enrolled in this study were diagnosed with a 2019-CoV detection kit using real-time reverse transcriptase–polymerase chain reaction performed at the University of Louisville Hospital Laboratory from nasal pharyngeal swab samples obtained from patients. The grouping of COVID-19 patients into Moderate Group vs. Severe Group is based on the initial clinical presentation at the time of enrollment. Severe Group participants were COVID-19 confirmed patients who required mechanical ventilation and this group had blood draw daily along with their standard laboratory work. Moderate Group participants were COVID-19 confirmed patients who were hospitalized without mechanical ventilation and had blood draw every two to three days along with their standard laboratory work. All COVID-19 patients were followed by the research team daily and the clinical team was blinded to findings of the research analysis to avoid potential bias. Peripheral blood (moderate and severe) and bronchial lavage fluid (severe) samples were collected from patients and mass flow cytometry was performed. Phagocytosis, NET formation and neutrophil-platelet aggregates were carried out with standard protocols. The two-tailed, unpaired Student t-test was used to determine the significance of differences between two groups. One-way ANOVA was used to determine differences between multiple groups. Since we have varied number of observations for each patient, we applied linear mixed effect models along with the Wald test statistics to compare the group differences (Fitzmaurice GM LN, 2012), where group was considered as fixed effects, and patients were considered random effects. To examine association between two variables, we estimated the marginal Pearson correlation coefficient and tested its significance. The marginal Pearson correlation coefficient captures the association between two variables at the population level. The analyses were carried out in the Statistical software R (https://www.r-project.org/) and Prism version 10. A statistical test was claimed significant if $p< 0.05$.

RESULTS: We found the emergence of a low-density inflammatory neutrophil (LDN) population that expresses intermediate levels of CD16 (CD16Int) in COVID-19 patients. These cells demonstrate proinflammatory gene signatures, activate platelets, spontaneously form neutrophil extracellular traps (NET), and exhibit enhanced phagocytic capacity and cytokine production. Strikingly, CD16Int neutrophils are also the major immune cells within the bronchoalveolar lavage fluid, exhibiting increased CXCR3, but loss of CD44 and CD38 expression. The percent of circulating CD16Int LDN is associated with D-dimer, ferritin, and systemic IL-6 and TNF-α levels and changes over time with altered disease status. We conclude that the CD16Int LDN subset contributes to COVID-19-associated coagulopathy (CAC) and systemic inflammation and could be used as an adjunct clinical marker to monitor disease status and progression.

CONCLUSION: We conclude that the CD16Int LDN subset contributes to COVID-19-associated coagulopathy (CAC) and systemic inflammation and could be used as an adjunct clinical marker to monitor disease status and progression.

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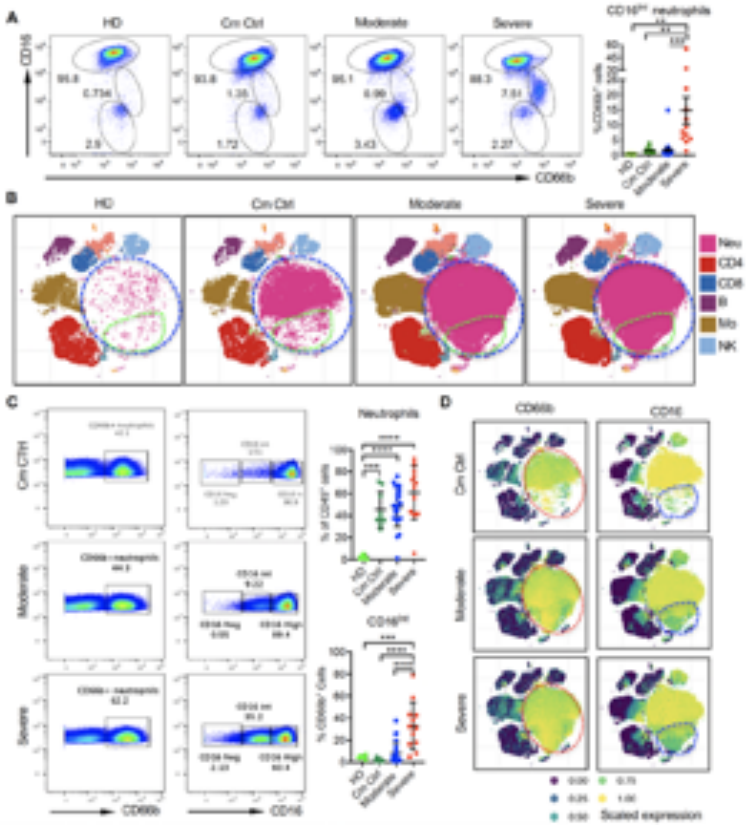

Figure 1. The identification of a CD16 intermediate low-density neutrophil population in COVID-19 patients. (A) The averaged percent of CD16 negative ($CD16^{neg}$), CD16 intermediate ($CD16^{int}$), and CD16 high ($CD16^{high}$) neutrophils from serially drawn whole blood samples among healthy donors (HD, n=6), comorbid control patients (Cm Ctrl, n=9), moderate (n=24), and severe (n=12) COVID-19 patients. Cells were gated on the $CD45^{+}CD66b^{+}$ population. Summarized data and representative dot plots are shown. **(B)** Cluster maps for moderate and severe COVID-19 patients as compared to HD and Cm Ctrl. The data was generated from CyTOF based analysis of $CD45^{+}$ PBMCs isolated from peripheral blood. **(C)** Representative dot plots (left) and summarized data (right) showing the overall percent of $CD66b^{+}$ neutrophils (gated on viable, $CD45^{+}$) and the $CD16^{int}$ subset as found in Ficoll isolated PBMCs analyzed using CyTOF mass cytometry in HD, Cm Ctrl, moderate and severe COVID-19 patients. **(D)** Representative viSNE cluster plots show the CD66b (left) and CD16 (right) expression within the $CD45^{+}$ PBMC populations in Cm Ctrl, and patients with moderate and severe COVID-19. Red circles indicate the location of the neutrophil population while blue circles indicate the $CD16^{int}$ neutrophil population. Data are presented as Mean±SD. p values were determined using a one-way ANOVA with multiple comparisons. $^{**}p< 0.01$, $^{***}p<0.001$, $^{****}p < 0.0001$.

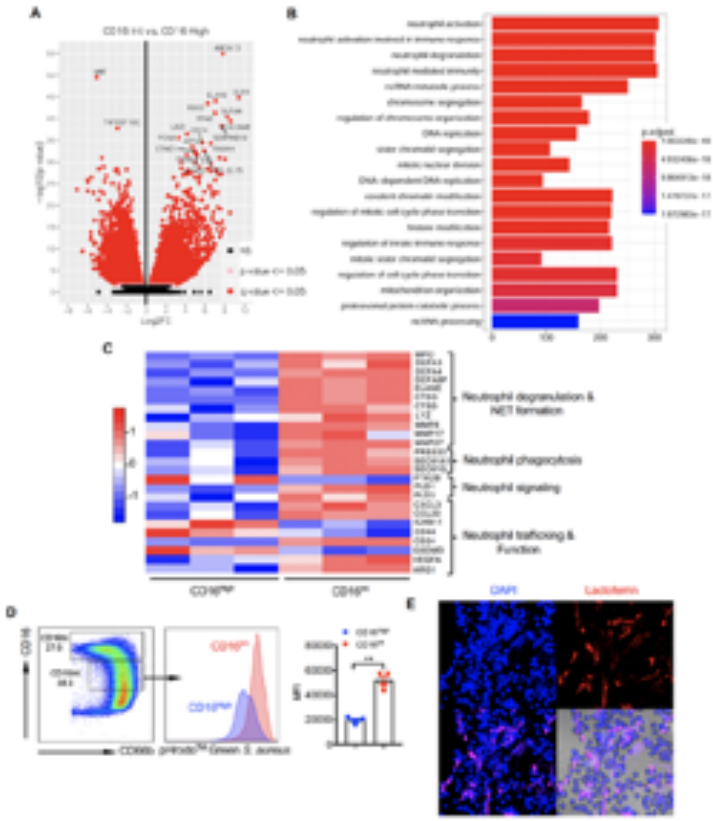

Figure 2. $CD16^{int}$ LDN exhibit proinflammatory gene signatures with functionally active phenotype. (A) Volcano plot shows differentially expressed genes (DEGs) between $CD16^{int}$ and $CD16^{high}$ LDN. **(B)** Top 20 enriched GO:BP categories for $CD16^{int}$ versus $CD16^{high}$ LDN from severe COVID-19 patients. **(C)** The heatmap shows DEGs related to neutrophil degranulation and NET formation, neutrophil phagocytosis, neutrophil signaling, and neutrophil trafficking and function between $CD16^{high}$ and $CD16^{int}$ LDN. **(D)** The phagocytic capacity of $CD16^{high}$ and $CD16^{int}$ neutrophils from whole blood in severe COVID-19 patients (n=4) was assessed using a pHrodo™ Green S. aureus BioParticles™ phagocytosis assay. Gating strategy, representative histogram, and summarized mean fluorescent intensity (MFI) data are shown. $^{**}p<0.01$ (student's t-test). **(E)** Representative confocal image of spontaneous NET formation from sorted $CD16^{int}$ LDN. Anti-human lactoferrin (shown in red) and neutrophil DNA stained with DAPI (shown in blue), merge image shows NETs characteristic structures.

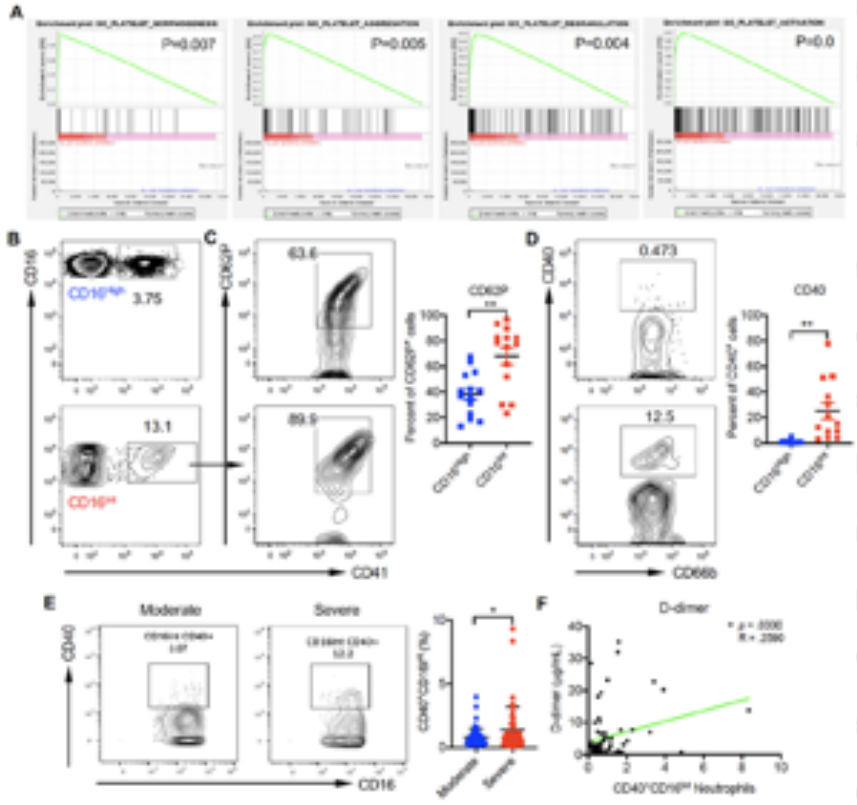

Figure 3. Enhanced cytokine production by CD16^{hi} LDN in severe COVID-19 patients. (A) Plasma concentrations of IL-6 and TNF-α in a single draw from HDs (n=6) and Cm Ctrl (n=9), and the average value during study enrollment for moderate (n=24), and severe (n=12) COVID-19 patients. **(B, C)** IL-6 and TNF-α levels in serial patient draws were then correlated with both the percent of total neutrophils (**B**) and the percent of CD16^{hi} neutrophils (**C**) in the corresponding sample as measured by CyTOF. Pearson correlations were used to indicate statistical significance in all correlations, where ns= p ≥.05, * p< 0.05, **** p < 0.0001. **(D)** Representative dot plots of TNF-α (top) and IL-6 (bottom) production from LPS stimulated neutrophils cultured from whole blood samples of Cm Ctrl (n=8), moderate (n=3) and severe patients (n=2), with accompanying summarized data. p values were determined using an one-way ANOVA with multiple comparisons **p<0.01, ***p<0.001, ****p < 0.0001. **(E)** Pie charts show the relative contribution of neutrophils to the total TNF-α and IL-6 ex vivo pool as compared to all other immune cells in Cm Ctrl patients and severe COVID-19 patients.

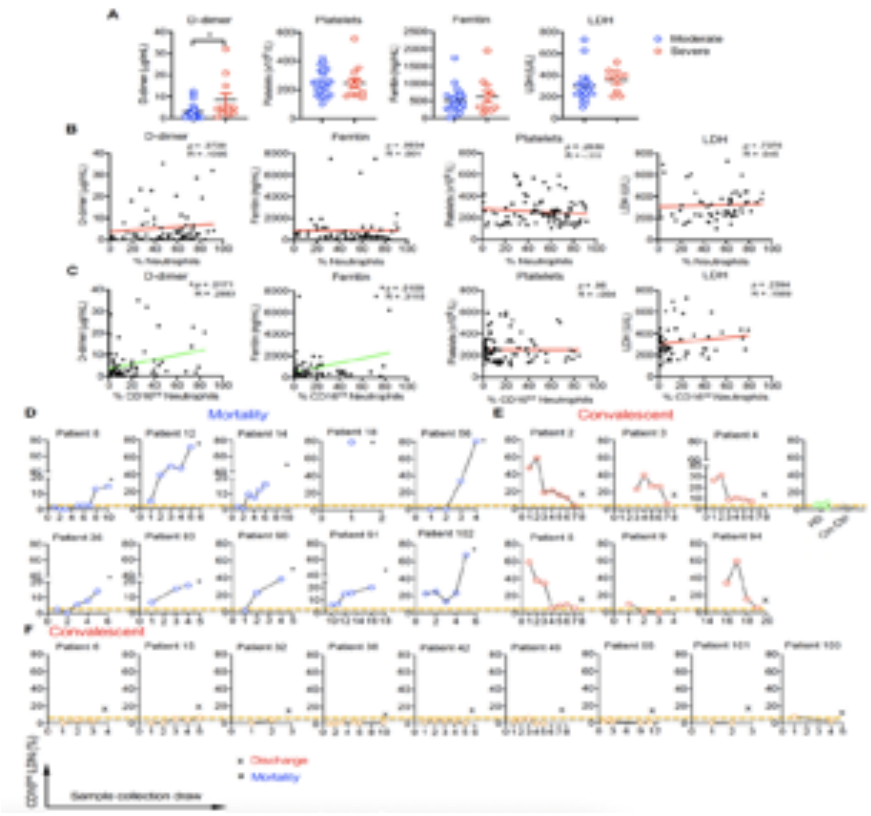

Figure 4. Correlations of clinical coagulation and systemic inflammation indicators and disease outcomes with CD16^{hi} LDN. (A) For severe and moderate patients, the clinical values of D-dimer, ferritin, platelets and LDH were acquired from patient charts. The average value of serial blood draws from patients were used. An unpaired student's t-test was used to determine significance. *p<.05 **(B, C)** The D-dimer, ferritin, platelet number and LDH levels for all COVID-19 patient samples were correlated with the total CD66b$^+$ neutrophil percentage (**B**) or CD16^{hi} (**C**) neutrophils in the PBMCs. For all correlation data, a line of best fit is shown to visually examine correlation, with a green line representing a statistically significant correlation and a red line representing a non-significant correlation. Pearson correlations were used to determine statistical significance in all correlations, where *p<0.05. **(D-F)** Longitudinal, serial blood draws from our patient cohort (25 patients) enables us to track the CD16^{hi} LDN population percentage in Ficoll isolated PBMCs over the course of patient hospitalization and correlate it with patient clinical outcomes. **(D)** COVID-19 patients (n=10) with mortality show increased CD16^{hi} LDN trend over time. **(E)** COVID-19 patients (n=6) with convalescent show decreased CD16^{hi} LDN trend over time and the frequency of CD16^{hi} LDN in the blood draw before discharge is similar to the level in healthy donors (HD, n=6) or comorbidity control patients (Cm Ctrl, n=9). **(F)** COVID-19 patients (n=6) with convalescent show low levels of CD16^{hi} LDN similar to those from HD over time. Dotted line represents the average level of CD16^{hi} LDN in PBMC from HD (n=6).

CRITICAL CARE 48

Profiling the Immunological Patterns Linked to the History of Smoking in Patients with COVID-19

Krzysztof Laudanski[1], Katalin Susztak[2]

[1]University of Pennsylvania, Philadlephia, PA, [2]University of Pennsylvania, Philadelphia, PA

INTRODUCTION: COVID-19 triggers a severe inflammatory response that is determinant to its clinical trajectory. Smoking modulates several aspects of the immune system and is linked to less favorable COVID-19 outcomes in individuals[1-3]. Smoking is a risk factor for the deterioration of lung tissue, but it can significantly modulate immune system response[4]. Here, we hypothesize that smoking history will deteriorate longitudinal immunological response, leading to less favorable clinical outcomes

METHODS: A total of 36 patients were enrolled in the study. The cohort is representative of subjects previously reported requiring hospitalization due to COVID-19. The subjects had serum collected upon admission (t1), 48 hours (t2), and seven days (t3) later. The preselected serum immunological profile was assessed using Olink proteomics[5]. We selected the specific kit based on the preliminary data[3, 6-11]. Clinical, demographics, and therapeutic information were retrieved from electronic medical records.

RESULTS: Smoking showed an association with abnormal serum levels of IL-6 (data not shown), MCP-1, MCP-4, TNFRS14, CCL3, and LAG3 (Figure 1A-D). Interestingly, a different protein pattern was seen in patients needing intubations. Chemokines (CXCL13, MCP-1, MCP-3, CCL20, CCL23), cytokine (IL15), immunological receptors (CD4, CD27, CD83, LAMP3, PD1-L1, PD1-L2, PDCD1), TNFα receptor superfamily members (TNFRSF12A, TNFRSF4), and VEGFR1 were elevated in patients needing intubation (Figure 1E). Concomitantly, levels of ANGPT1, CCL17, CD244, EGF, FAS-L were markedly lower (Figure 1E).

CONCLUSION: The presented profile suggests smoking being a covariable triggering several cytokines with potentially lytic effect on the lung. This smoking profile was only partially seen in intubated patients.

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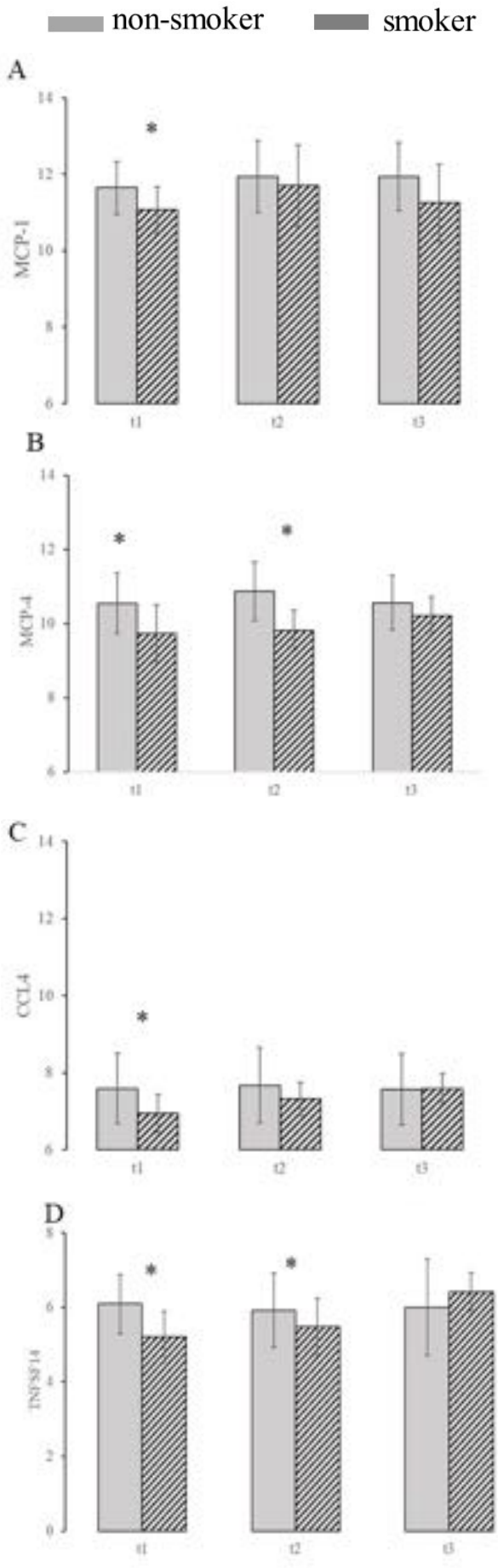

E.

Intubation	p≤0.05	p≤0.01
Lower as compared to Not Intubated		
Higher as compared to Not Intubated		
	t1	t2	t3 *
ADA	0.018		0.004
ADA2		0.030	0.018
ARG1	0.049		
CADM1			0.019
CCL17			0.048
CCL20	0.018	0.030	
CCL23	0.001	0.022	
CD244	0.028		
CD27	0.029	0.043	0.016
CD4	0.031		0.021
CD83	0.018		0.017
CXCL10			0.029
CXCL11		0.036	
CXCL13	0.001		0.001
CXCL5			0.027
CXCL9		0.034	
EGF			0.011
FASLG			0.015
Gal-9	0.001		
HGF	0.001		0.001
IDO-1	0.010		0.001
IFN-gamma			0.001
IL-8	0.029		
IL-10			0.001
IL-12			0.030
IL12RB1			0.043
IL-13	0.001	0.030	
IL-18	0.043		0.043
KIR3DL1		0.017	
KLRD1	0.031		
LAMP3	0.031		
MCP-1	0.001	0.001	0.001
MCP-3	0.001	0.030	0.025
MUC-16	0.001	0.001	0.001
NCR1	0.001	0.016	0.011
PD-L1	0.012		
PDCD1	0.022	0.001	
PGF	0.014		0.028
TNF			0.038
TNFRSF12A	0.001	0.001	0.017
TNFRSF21			0.047
TNFRSF4	0.012	0.001	0.024
VEGFA-2	0.034		0.042

CRITICAL CARE 49

Computational Endotypes of Sepsis and Septic Shock Derived from Time Series Data

Jason Guo[1], Han Kim[1], Robert D Stevens[2]

[1]Johns Hopkins University, Baltimore, MD, [2]The Johns Hopkins University School of Medicine, Baltimore, MD

INTRODUCTION: Sepsis is a life-threatening syndrome characterized by organ dysfunction and dysregulated host response to infection. Each year, sepsis is estimated to be responsible for 20% of deaths worldwide and $20 billion of healthcare costs in the US. Sepsis and septic shock, a more severe subset, are identified using sepsis-3 consensus criteria, but the few clinical and physiological variables of the criteria do not capture the complexity of sepsis, which is characterized by a constellation of different clinical presentations, biological mechanisms, pathophysiological patterns, and outcomes. The intrinsic heterogeneity in sepsis could be the most significant barrier to developing effective therapies and predicting the onset, severity, time course, and outcomes for patients. The aim of this research is to identify novel endotypes of sepsis and septic shock by leveraging granular time-series data available in electronic health records (EHRs).

METHODS: To identify adult patients in the Philips multi-center eICU database who meet sepsis-3 criteria, Sequential Organ Failure Assessment (SOFA) scores were calculated for each patient and infection status was determined by diagnosis and/or positive culture. With the granularity of time-series data, features could be calculated every 5 minutes. Patients were categorized into four data-driven cohorts, or 'statuses' (No Sepsis, Suspected Sepsis [only organ dysfunction], Sepsis, or Septic Shock), depending on the sepsis-3 criteria met at a given timepoint. We extracted 24 clinical and physiological variables from 24 to 48 h after ICU admission, and scaled features were used for unsupervised dimensionality reduction and clustering algorithms, accounting for mixed data types. Due to the large size of time-series data, analysis was performed on a subsample of the full dataset, which equalized the number of samples in each status to 80% of the number of the smallest status group. Endotypes from clustering were characterized by ICU length of stay and hospital discharge outcomes.

RESULTS: Initial clustering analysis identified four groups (Fig. 1), each associated with a unique pattern of statuses and outcomes. Cluster 1 contained a large proportion of septic shock patients and was also associated with longer ICU stay and lower likelihood of survival (Figs. 2,3). Clusters 3 and 4 contained mostly non-septic patients and did not have a significantly different length of stay (LOS). Interestingly, cluster 3 had a much higher likelihood of mortality than cluster 4, possibly representing non-septic patients with more severe conditions (Figs. 2,3). Cluster 2 contained mostly septic and suspected septic patients with a significantly higher LOS than patients in clusters 3 and 4 but a significantly lower LOS than patients in cluster 1 (Figs. 2,3). A summary table for cluster patient demographics and outliers is shown in Table 1.

CONCLUSION: We identified four candidate endotypes for sepsis and septic shock using only time-series data as a new paradigm for understanding and categorizing patients with sepsis. These endotypes identified groups of patients with distinct outcomes that generally coincided with sepsis-3 status identification, with Cluster 1 as the most severe 'septic shock' cluster and Cluster 3 as the least severe 'no sepsis' cluster. With a broader range of clinical and physiological features, these time-series-derived endotype approaches may help unlock the heterogeneity of sepsis, characterizing the evolution of its progression and yielding greater precision in detection, prediction, and therapy. Endotypes with a mix of status proportions (such as that in Cluster 1) may represent instances of misidentification of a patient's status using sepsis-3 criteria, thus offering a method for refinement of sepsis categorization. Ongoing research will further analyze identified endotypes in patient characteristics, outcomes, and response to specific treatments, as well as explore other machine learning algorithms and externally validate with other EHR data sources.

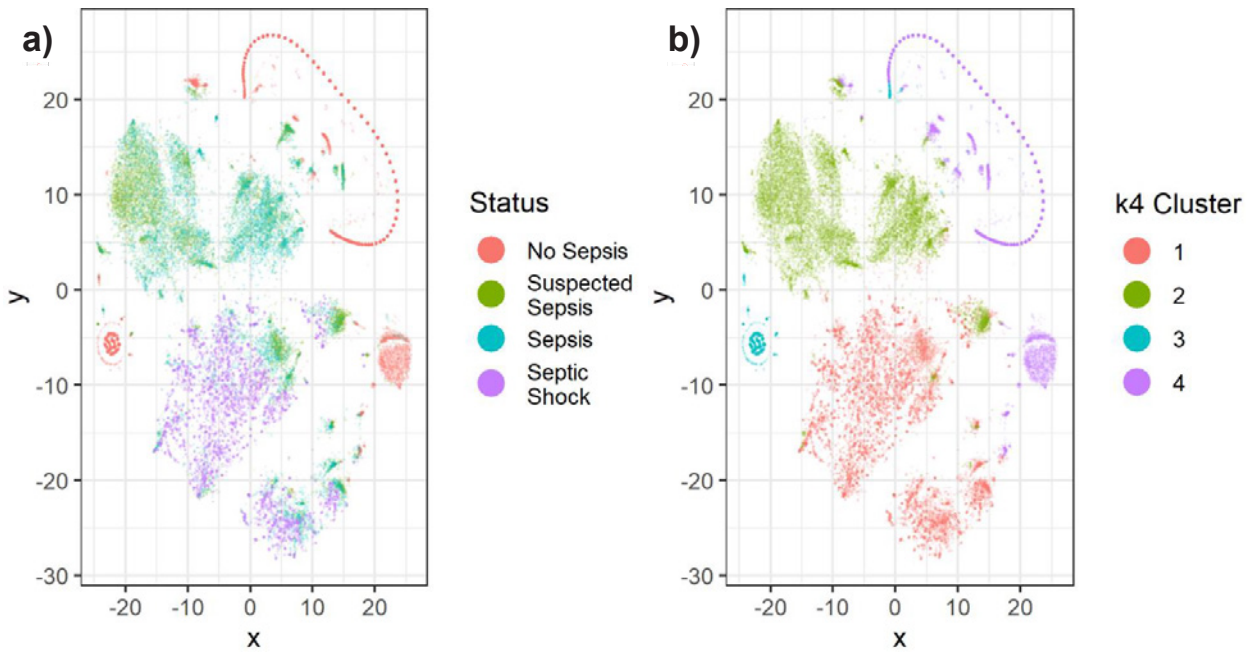

Figure 1. Identification of Computational Endotypes. **a)** Visualization of patient cohorts, or "statuses," with t-Distributed Stochastic Neighbor Embedding (tSNE). The scaled dataset containing 24 clinical and physiological variables was visualized with tSNE, a dimensionality reduction algorithm that probabilistically maps complex high-dimensional data (i.e. 24-dimensional data) to lower dimensions and identifies similar points. Each point represents one 5 min timepoint sample for each patient from 24-48h after ICU admission. 13,487 timepoints (80% of septic shock timepoints) were randomly sampled for each status. **b)** Visualization of clusters from K-Means (k4) on scaled data overlapped on previous tSNE plot.

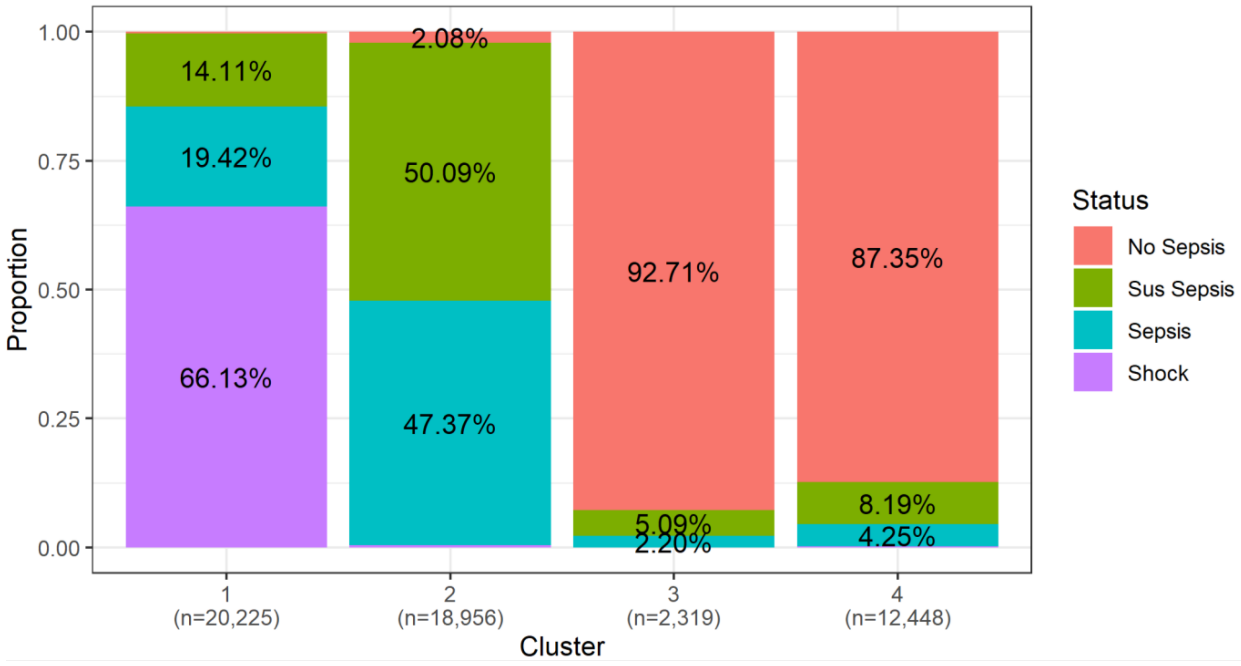

Figure 2. Cohort Characterization of Clusters. The proportion of samples in each status was calculated for every cluster. The number of samples in each cluster is given on the x-axis and only proportions larger than 0.5% are labelled. "Sus sepsis" = suspected sepsis; "Shock" = septic shock

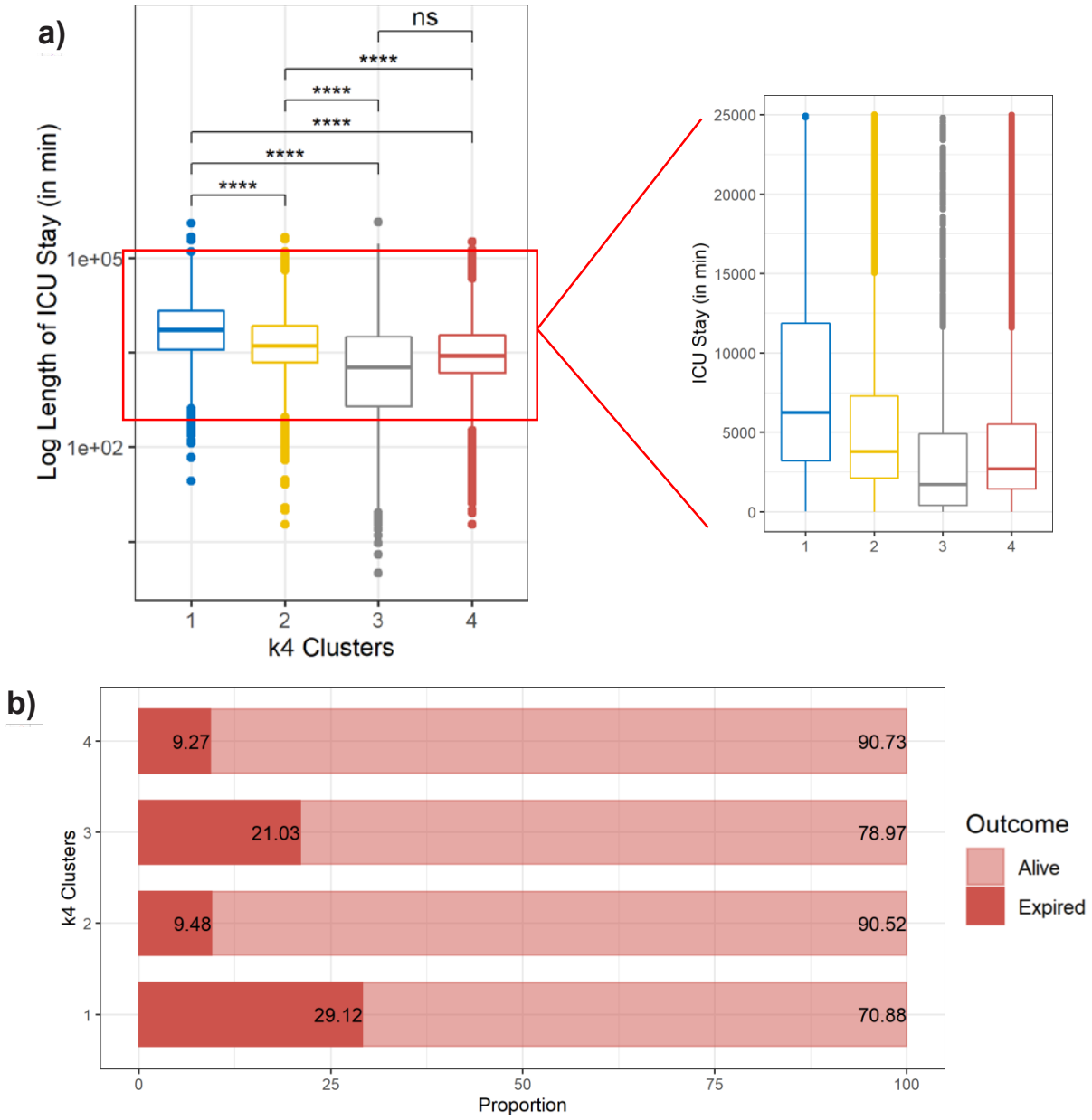

Figure 3. Clinical Characterization of Clusters. **a)** For each unique patient ID in a cluster, the ICU length of stay (LOS) was calculated, and the distribution of log LOS for each cluster is shown (left panel). A portion of the raw data from the red box is shown in the original linear scale (right panel). Log transformation of LOS was done only for y-axis visualization and after hypothesis testing. $p \leq 0.0001$, ****; $p \leq 0.001$, ***; $p \leq 0.01$, **; $p \leq 0.05$, *; $p > 0.05$, ns. **b)** For each unique patient ID in a cluster, the hospital discharge status was determined, and the proportion of outcomes for each cluster is shown.

Variable	k4 Cluster			
	1, N = 19,726[†]	**2**, N = 18,509[†]	**3**, N = 2,208[†]	**4**, N = 12,119[†]
age	65 (54, 75)	67 (54, 77)	64 (52, 76)	63 (51, 75)
sex				
Female	9,410 (48%)	8,885 (48%)	1,042 (47%)	5,586 (46%)
Male	10,316 (52%)	9,624 (52%)	1,166 (53%)	6,533 (54%)
race				
African American	1,831 (9.3%)	1,893 (10%)	333 (15%)	1,700 (14%)
Asian	266 (1.3%)	245 (1.3%)	30 (1.4%)	147 (1.2%)
Caucasian	15,547 (79%)	14,028 (76%)	1,697 (77%)	9,570 (79%)
Hispanic	780 (4.0%)	1,274 (6.9%)	53 (2.4%)	208 (1.7%)
Native American	379 (1.9%)	194 (1.0%)	12 (0.5%)	60 (0.5%)
Other/Unknown	923 (4.7%)	875 (4.7%)	83 (3.8%)	434 (3.6%)
los	7,153 (3,522, 14,565)	4,014 (2,223, 8,515)	1,796 (404, 5,610)	2,847 (1,504, 6,086)
mortality				
Alive	13,968 (71%)	16,743 (90%)	1,737 (79%)	10,983 (91%)
Expired	5,758 (29%)	1,766 (9.5%)	471 (21%)	1,136 (9.4%)

[†] Median (IQR) or Frequency (%)

Table 1. K-Means Clustering Characteristics and Demographics. For each cluster, summary statistics are given for the variables listed in bold, either as median/IQR or frequency/in % within cluster. Age, sex, and race are demographic variables while length of stay (los, in min) and mortality (at hospital discharge) are outcome variables.

CRITICAL CARE 50

Computational Subphenotype Discovery and Validation of ICU Stratum Traumatic Brain Injury Patients

Han Kim[1], Robert D Stevens[2]

[1]Johns Hopkins University, Baltimore, MD, [2]The Johns Hopkins University School of Medicine, Baltimore, MD

INTRODUCTION: Heterogeneity within Traumatic Brain Injury (TBI) populations is recognized as a major barrier in efforts to find effective treatments and improve outcomes. Existing classification paradigms do not capture the complexity of TBI which encompasses a broad array of clinical and biological features. We hypothesize that combinations of these features extracted from clinical electronic health records (EHR) and from physiological time series (PTS) monitoring data can be segregated using machine learning, enabling discovery of latent subphenotypes that have distinct likelihoods of clinical outcomes.

METHODS: Adult TBI patients (N=4,450) were identified in a multi-center ICU database (eICU) and clinical, laboratory and PTS data were extracted. Statistical PTS features were derived from heart rate, SaO2, blood pressure, and respiratory rate time series data. Unsupervised clustering algorithms were applied accounting for mixed data types. The discovered clusters were then characterized according to outcomes at discharge, and differences in physiology, then externally validated on TBI patients in the independent MIMIC III dataset.

RESULTS: We identified four TBI clusters (a, b, c, d) each with a distinct outcome probability distribution, and each associated with a unique, clinically relevant pattern of PTS and laboratory features. Subphenotype (a) captures TBI patients whose physiological features are associated with the highest likelihood of survival and favorable neurological outcome, while subphenotype (d) captured patients whose physiological features are associated with the highest risk of death and unfavorable neurological outcome, while subphenotypes (b) and (c) had intermediate outcome probabilities. Both the physiologic and outcome differences between clusters were reproduced in the MIMIC III cohort when eICU clusters were assigned using a multi-class classification. The mortality and neurological outcome proportions per subphenotype for the eICU cohort and assigned MIMIC III cohort can be seen in Figure 1 and an example of feature comparison between subphenotypes (a) and (d) are in Figure 2. A heatmap visualizing the differences between all four identified subphenotypes can be found in Figure 3.

CONCLUSION: Using unsupervised machine learning applied to electronic health records and PTS data of TBI patents admitted to the ICU, we identified four distinct and clinically meaningful clusters. Patients assigned to specific clusters had distinct outcome probabilities and unique laboratory/PTS signatures which suggesting that they are plausible candidate subphenotypes. Results indicate a novel approach to categorizing ICU stratum TBI patients based on numerical patient physiological and metabolic data. Ongoing research will explore other characteristics of these TBI subphenotypes and in particular their differential response to specific treatments and interventions.

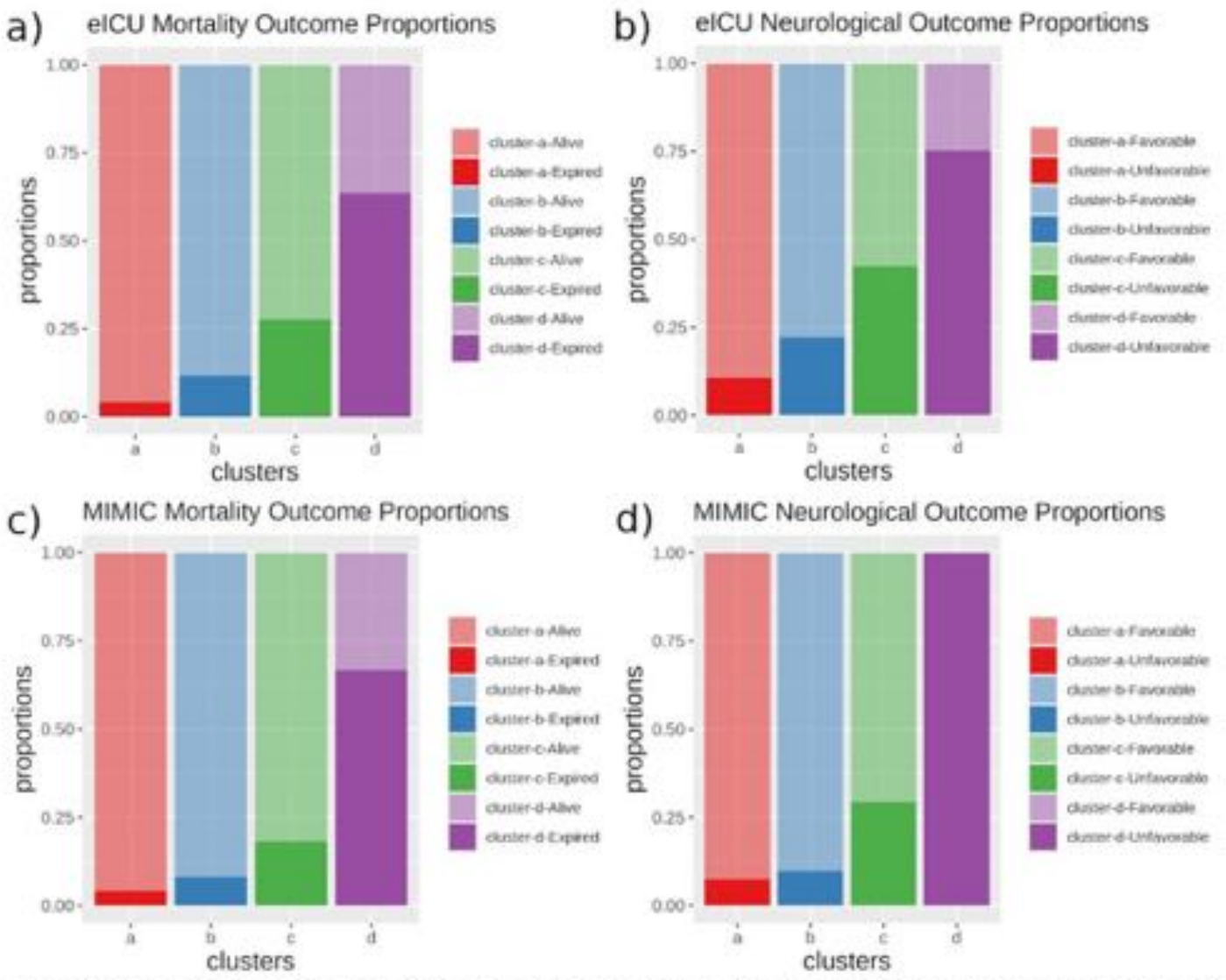

Figure 1. Mortality and Neurological Outcome Proportions corresponding to subphenotypes discovered in eICU (a, b) and externally validated in MIMIC III (c, d)

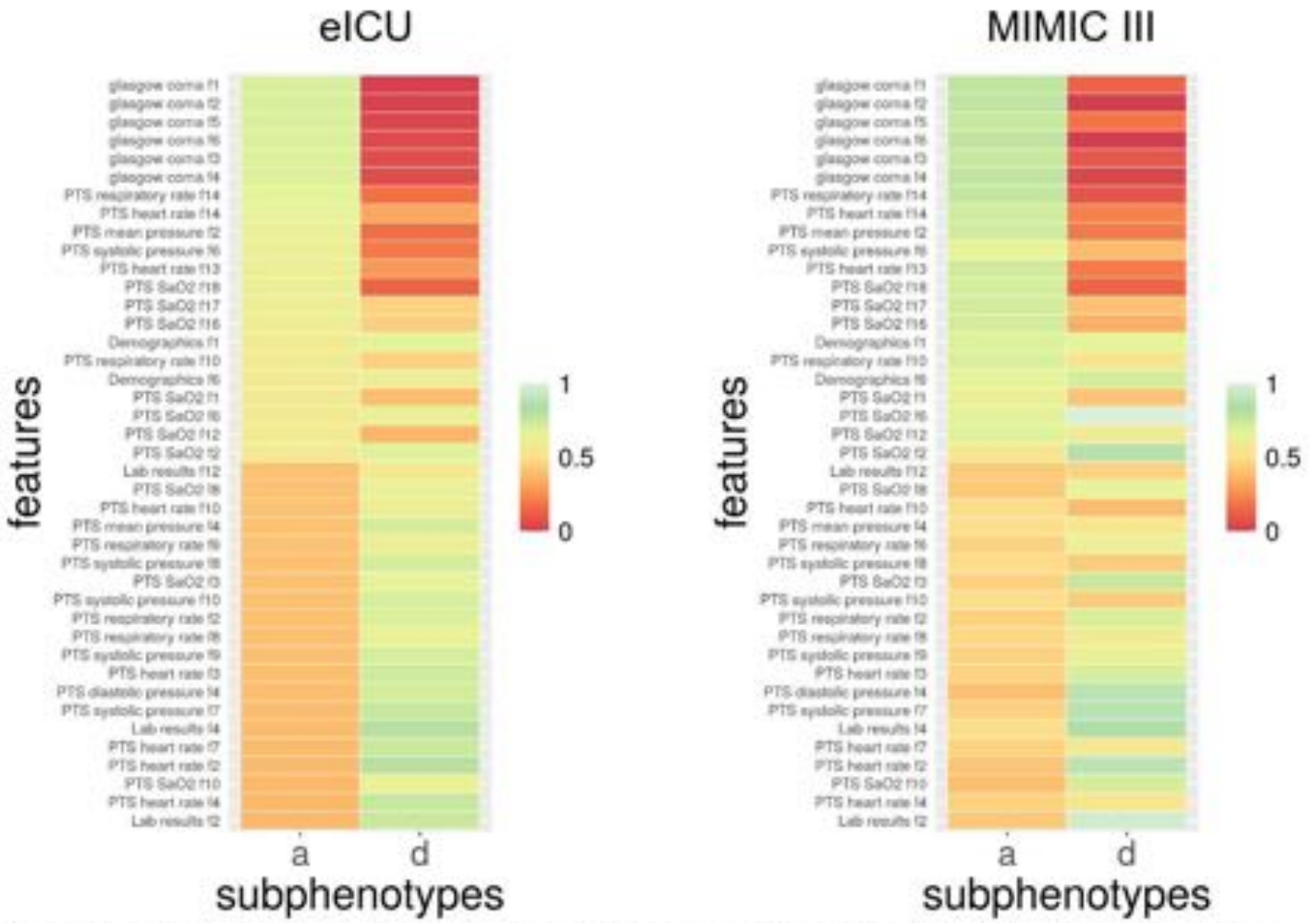

Figure 2. Standardized mean differences (SMD) of the top 40 discriminative features represented as heatmaps comparing subphenotype a and d as they correspond in Figure 1. (left) eICU SMD showing differences in individual variables and the standardized degree to which subphenotypes a and d differ. (right) MIMIC III SMD between subphenotypes a and d resulting from assigning MIMIC III TBI cohort to eICU identified subphenotypes.

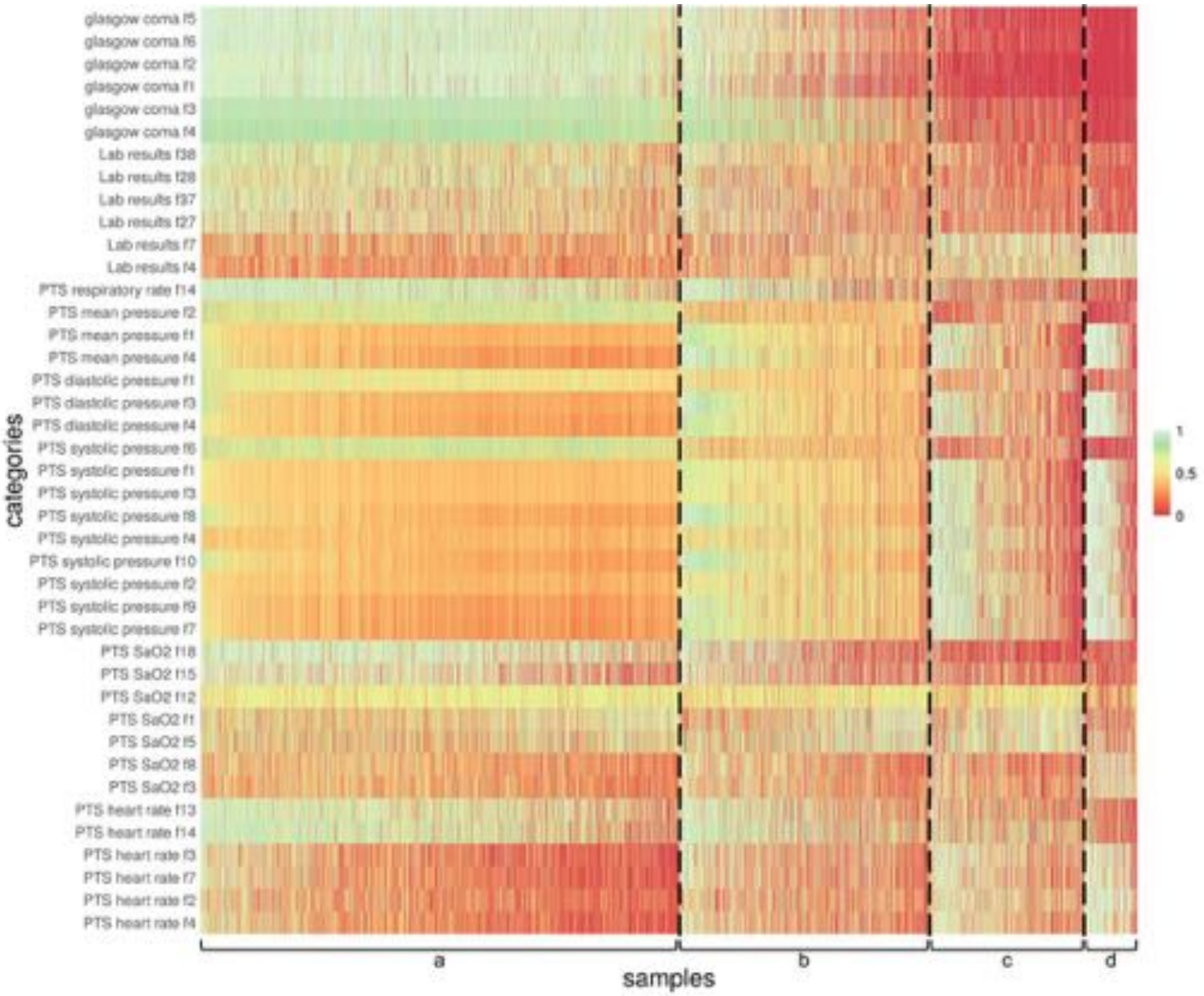

Figure 3. Heatmap of the normalized top 40 discriminative feature values for all four subphenotypes (a, b, c, and d) the eICU TBI cohort. The difference between the four subphenotypes can be visually seen in the heatmap with each subphenotype characterized by a range of physiologic value that defines as we see in figure 1 a specific illness severity and probability of clinical outcome.

CRITICAL CARE 51

Photothrombotic Stroke: A Novel Model to Study Immunodepression Following CNS injury in a Mouse Model

Bashir Bietar[1], Christian Lehmann[2]

[1]Dalhousie University, Halifax, Nova Scotia, [2]Department of Anesthesia, Halifax, NS

INTRODUCTION: Patients that suffer stroke, traumatic brain injury or other forms of central nervous system (CNS) injuries are at an increased risk to nosocomial infections. It is believed that CNS injury affects the patient's systemic immune response: Immediately after CNS injury, local inflammation is observed in the brain. A disproportional release of neurotransmitters and inflammatory mediators can transform the compensatory brain- protective downregulation of inflammation to systemic immunodepression (CNS injury- induced immunodepression syndrome, CIDS). This state of immunodepression puts patients of CNS-injury at an increased risk of acquiring infections. Various methods exist to model CNS injury, ranging from models of spinal cord injuries to TBI to stroke, including endothelin-1 vasoconstriction-induced stroke, hypoxia-ischemia and middle cerebral artery occlusion. Photothrombotic stroke (PTS) is a simple, non-intrusive and reproducible model of CNS injury employable in studying CIDS.

METHODS: Experimental animals (C57BL/6 mice) were injected with a photoreactive dye (Rose Bengal) that causes blood clots in an area of the brain that gets illuminated (i.e., PTS). Systemic immune response was evaluated by intravital microscopy of leukocyte activation as well as capillary perfusion within the peripheral (intestinal) microcirculation 6 and 24 hours following PTS.

RESULTS: PTS caused a significant reduction in the numbers of activated leukocytes in the intestinal microcirculation of mice challenged with LPS. We also observed decreased mucosal capillary perfusion following PTS.

CONCLUSION: Our results suggest that PTS can cause CNS injury-induced immunodepression. Therefore, PTS represents a viable experimental model to study novel treatments for patients with CIDS.

CRITICAL CARE 52

Development and Validation of a Physiology-Driven Machine Learning Model for Post-Cardiac Arrest Outcome Prediction Using a Large Multi-Center Database

Han Kim[1], Qingchu Jin[2], Hieu Nguyen[1], Christian Storm[3], Jose Suarez[1], Robert D Stevens[4]

[1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins University, Baltimore, United States of America, [3]Charité-Universitätsmedizin Berlin, Berlin, Germany, [4]The Johns Hopkins University School of Medicine, Baltimore, MD

INTRODUCTION: Survivors of cardiac arrest (CA) face a significant risk of neurological disability, however there is a lack of accurate and reliable methods to predict post-CA outcomes. The aim of this study is to build novel machine learning models to predict post-CA outcome by leveraging high-dimensional data available early after admission to the intensive care unit (ICU). We hypothesized that performance of clinical models using only electronic health record (EHR) data could be enhanced by integrating physiological time series (PTS) data obtained from ICU bedside monitoring devices.

METHODS: Analysis was performed using the eICU dataset, which includes 208 hospitals and 200,859 ICU admissions. We isolated 2,216 CA patients and considered only data obtained in the first 24 hours after ICU admission. We exhaustively extracted derived PTS and electronic health record (EHR) features and performed feature down-selection using collinearity analysis and nested Random Forest. We then combined various machine learning algorithms (GLM, Random Forest, Gradient Boosting, Neural Networks) and optimization techniques (hyperparameter tuning, model stacking) to maximize the prediction of mortality and neurological outcome. Model performance was evaluated using the area under the receiver operating characteristic curve (AUROC), sensitivity, and specificity; and clinical model interpretability was assessed using feature rankings utilizing random forest tree depth ranking and GLM beta coefficients (Fig 2, 3). Models trained on the eICU CA cohort were then externally validated on an analogous sample of CA patients in the independent MIMIC III dataset.

RESULTS: Three prediction models for mortality and neurological outcome were created using EHR and PTS features combined, EHR features alone, and PTS features alone (Fig 1). The best-performing neurological outcome prediction model achieved a higher sensitivity (0.81), specificity (0.76), and AUROC (0.87±0.01) compared to the APACHE IV baseline model (AUROC: 0.75±0.01, sensitivity: 0.76, specificity: 0.63). Additionally, our highest performing mortality prediction model (AUROC: 0.83±0.01, sensitivity: 0.79, specificity: 0.71) significantly outperformed the APACHE IV baseline model (AUROC: 0.74±0.01, sensitivity: 0.72, specificity: 0.63). A model comprised of PTS features derived from 5 signals (heart rate, SpO2, respiratory rate, diastolic and systolic blood pressure) provided discrimination (AUROC: mortality = 0.79, neurological outcome: 0.79) which was comparable to a model with EHR features alone (AUROC: mortality = 0.81, neurological outcome: 0.85). The models were interpretable, indicating several known as well as previously unreported predictive features and indicates the predictive importance of PTS derived features (Fig 2, 3). Our validation results, considering the limited sample size of our MIMIC III external validation cohort, show model generalizability (AUROC: mortality = 0.76, neurological outcome: 0.84).

CONCLUSION: These results demonstrate that machine learning models trained with clinical and PTS features extracted from data collected in the first 24 after ICU admission can effectively predict CA outcomes at ICU discharge. Ongoing work will explore the significance of a wider range of PTS features collected over different observation windows and compare them with current EEG- and neuroimaging-based prognostic models.

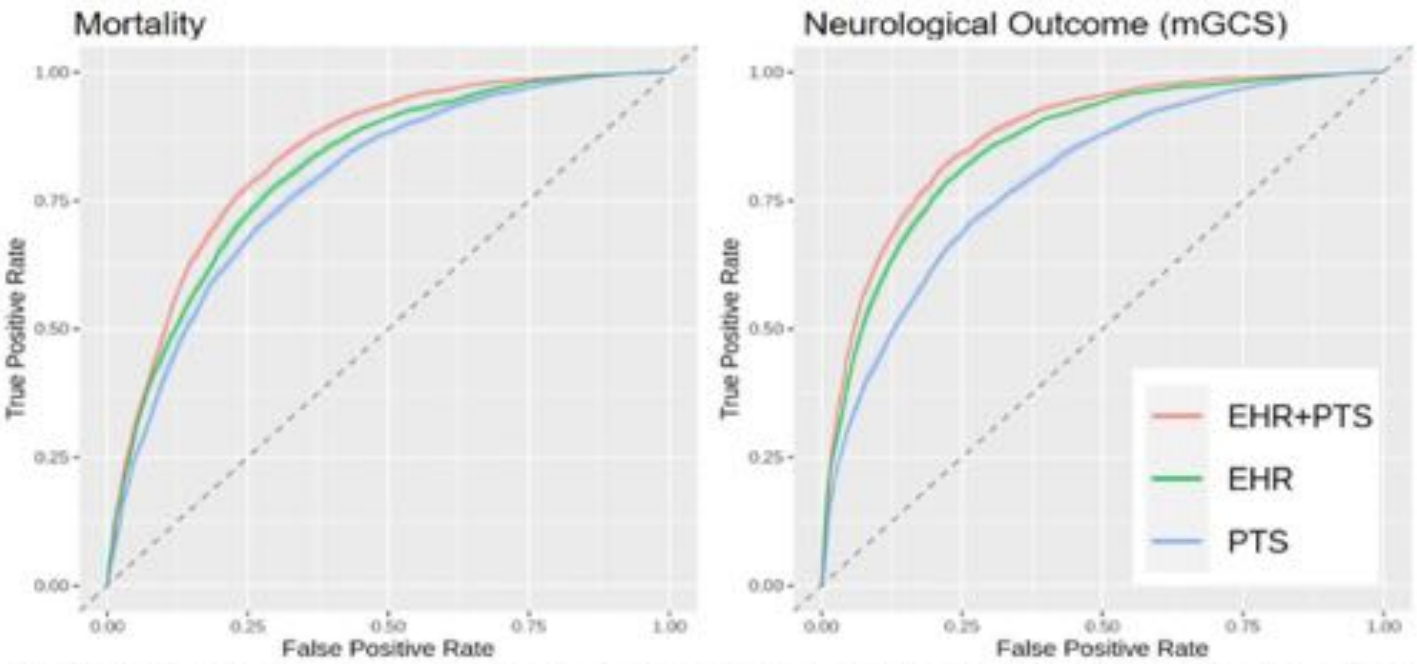

Fig.1. Median receiver operating curves of the best performing model using different feature subsets.

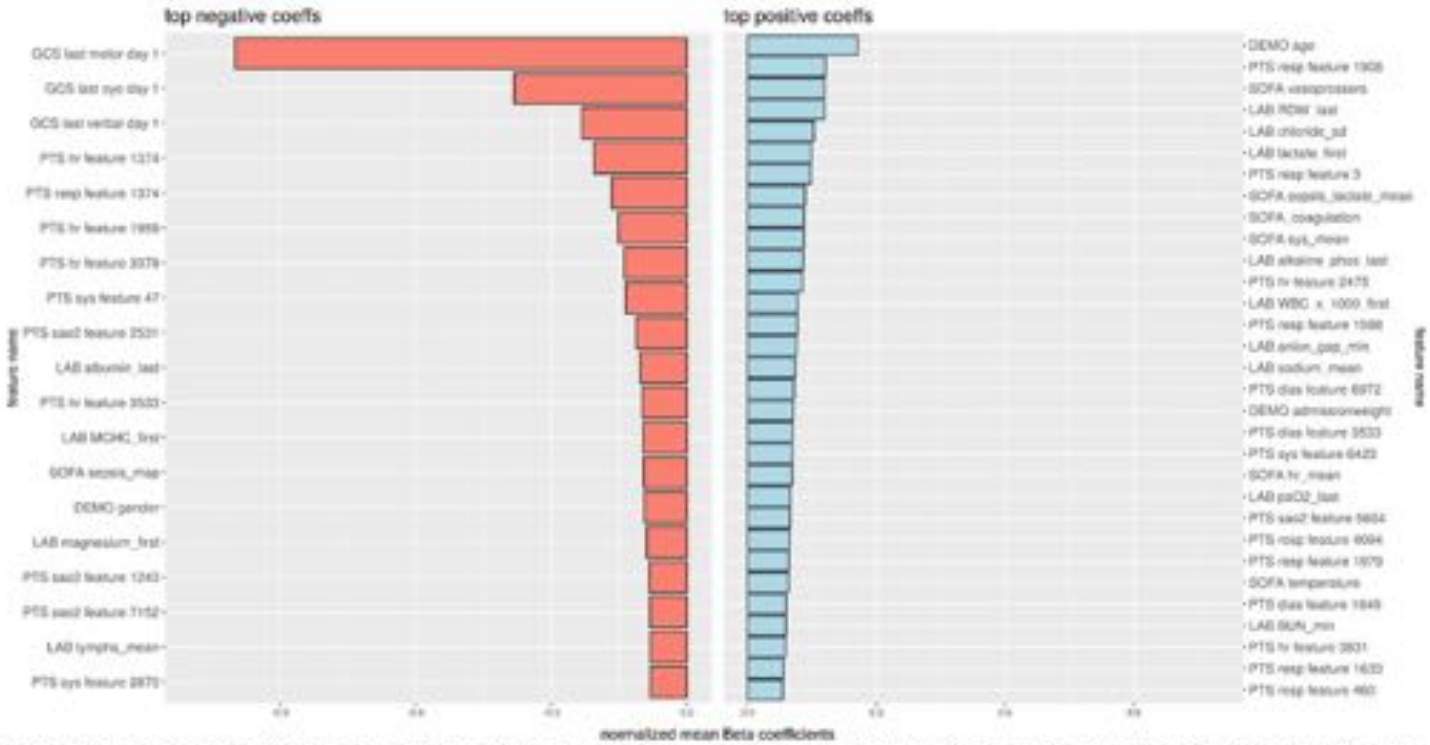

Fig.2. Normalized GLM beta coefficients of the top 50 features for mortality prediction with simplified PTS derived feature names for visualization purposes.

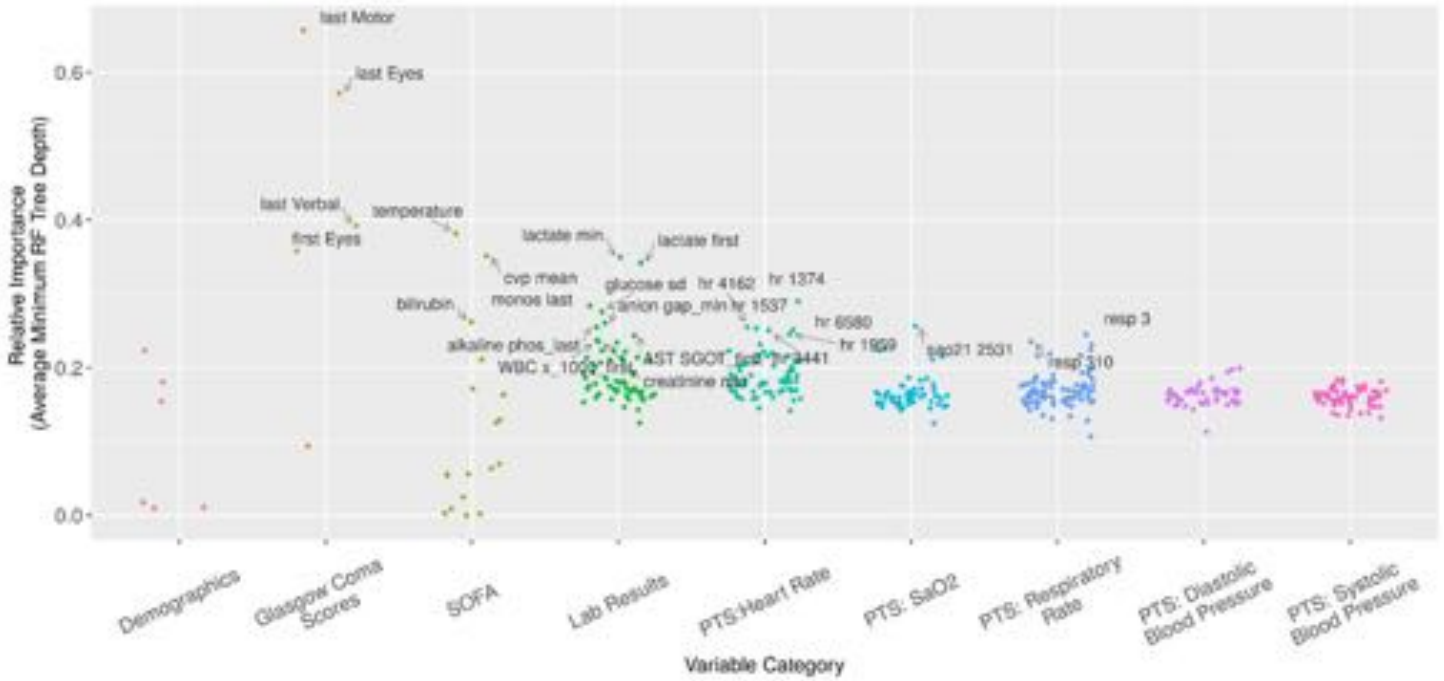

Fig.3. Feature importance visualized for the 410 mortality outcome features using Random forest relative importance visualized using feature categories with the top 25 features labeled.

CRITICAL CARE 53

A Physiology-Driven Machine Learning Model for Traumatic Brain Injury Outcome Prediction Using a Large Multi-Center Database

Han Kim[1], Robert D Stevens[2]

[1]Johns Hopkins University, Baltimore, MD, [2]The Johns Hopkins University School of Medicine, Baltimore, MD

INTRODUCTION: Traumatic Brain Injury (TBI) is a major health concern worldwide that not only is a leading cause of death but also results in life-long disability in many survivors. TBI outcome prediction models, which include the widely validated International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomization After Significant Head injury (CRASH) models, may not sufficiently capture available clinical and physiologic information to accurately determine the severity and outcome of TBI. This aim of this study was to identify physiologic signatures in TBI patients recorded in the first 24 hours of ICU admission, testing the hypothesis that these signatures are associated with short term clinical outcomes.

METHODS: In a multisite clinical database of 208 institutions in the US (eICU), we identified patients admitted to the ICU with a diagnosis of TBI (n=4450). Predictive features of interest were clinical variables, laboratory results, and physiologic time series data (PTS, i.e., high frequency monitoring data including heart rate, SaO2, respiratory rate, and blood pressure). Three different machine learning (ML) algorithms generalized linear models (GLM), random forest (RF), and gradient boosting (XGboost), were trained on a statistically pruned feature space of 147 derived variables using mortality and neurological outcome (motor subscore of the Glasgow Coma Scale) at hospital discharge as outcome labels. The resulting model was then externally validated on an analogous TBI sample in an independent single-center ICU database (MIMIC-III). ML model performance was determined by sensitivity, specificity, area under the receiver operating characteristic (AUROC) curve analysis and compared with adapted versions of the IMPACT core and CRASH core logistic regression models.

RESULTS: ML models performed well for neurological outcome prediction (mean±SD values for GLM, RF, and XGboost: AUROC 0.923±0.02, sensitivity: 0.866±0.048, specificity: 0.866±0.02) and for mortality prediction (AUROC: 0.900±0.03, sensitivity: 0.796±0.06, specificity: 0.835±0.03) (Fig 1). ML model performance was significantly higher than IMPACT and CRASH for neurological outcome (AUROC respectively 0.779±0.01 and 0.776±0.02) and mortality at discharge (AUROC 0.879±0.01 and 0.867±0.01 respectively). External validation utilizing MIMIC III corroborated the results from eICU for both neurological outcome (AUROC: 0.924±0.01, sensitivity: 0.844±0.04, specificity: 0.849±0.03) and mortality (AUROC: 0.931±0.01, sensitivity: 0.88±0.04, specificity: 0.841±0.06). Model performance measures are summarized in Table 1.

CONCLUSION: Results demonstrate that physiology-driven ML approaches outperform reference IMPACT and CRASH logistic regression models for both neurological outcome and mortality prediction after TBI. These models, established using a multi-center cohort, underwent successful external validation in an independent single center TBI cohorts. Results suggest that a data-driven approach incorporating PTS features captures prognostically relevant information on TBI patients which may be overlooked in existing TBI prediction systems.

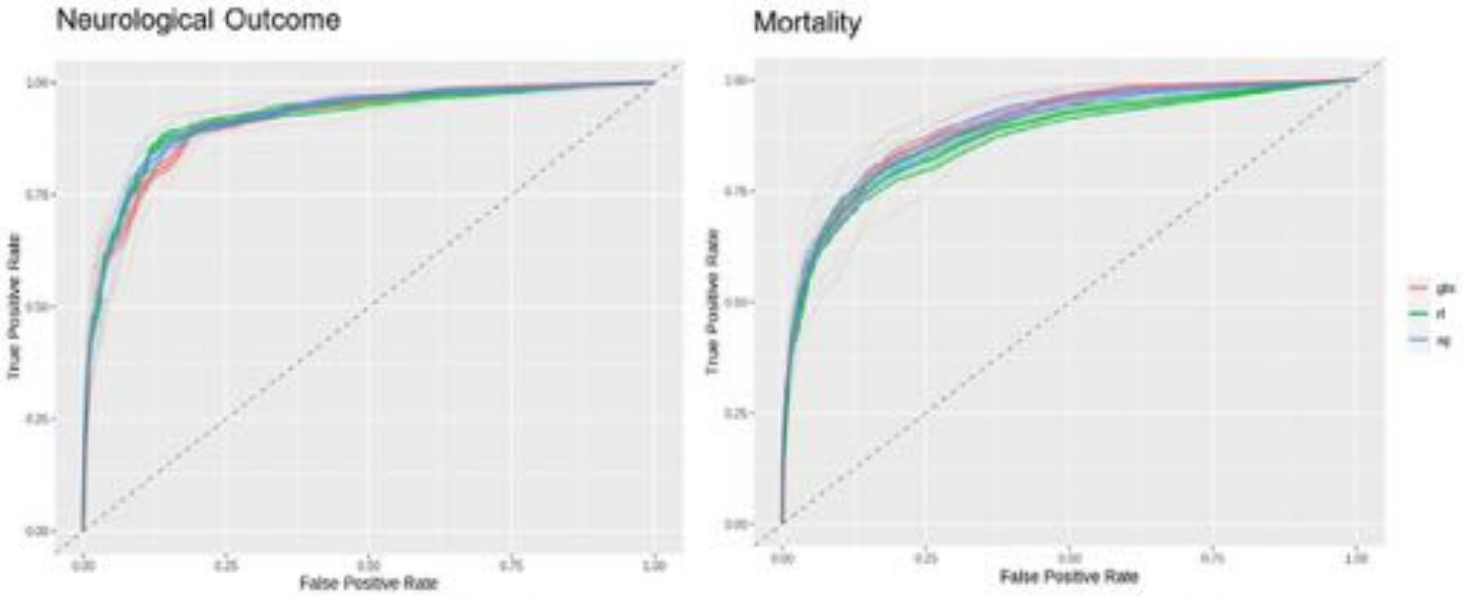

Figure 1. Receiver operating curves with confidence intervals for GLM, random forest, and XGBoost models to predict neurological outcome (left) and mortality (right) at discharge for the eICU TBI cohort.

Table 1. Summarized eICU TBI cohort results on test set in predicting neurological

Short-term Neurological Outcome			***Reference Models***	
	eICU model	**MIMIC III validation**	**IMPACT**	**CRASH**
AUROC	0.923 ± 0.015	0.924 ± 0.005	0.790	0.776
Sensitivity	0.866 ± 0.048	0.844 ± 0.044	0.773	0.790
Specificity	0.866 ± 0.017	0.849 ± 0.027	0.646	0.613
Short-term Mortality Outcome			***Reference Models***	
	eICU model	**MIMIC III validation**	**IMPACT**	**CRASH**
AUROC	0.900 ± 0.027	0.931 ± 0.011	0.879	0.867
Sensitivity	0.796 ± 0.058	0.880 ± 0.040	0.852	0.810
Specificity	0.835 ± 0.034	0.841 ± 0.062	0.727	0.755

CRITICAL CARE 54

Detection of Acute Right Heart Failure through Intravenous Waveform Analysis in an in vivo Rat Model

Matthew Barajas[1], Karl D Hillenbrand[1], Matthias L Riess[2], Franz Baudenbacher[3], Matthew J Hampton[1], Zhu Li[1], Susan Eagle[1]

[1]Vanderbilt University Medical Center, Nashville, TN, [2]TVHS VA Medical Center & Vanderbilt University Medical Center, Nashville, TN, [3]Vanderbilt University, Nashville, TN

INTRODUCTION: Differentiation of the etiology of shock is challenging in the perioperative period, and diagnosis can have large effects on management choices. While intraoperative echocardiography can provide substantial insight into the cause of undifferentiated shock, its utility may be limited by feasibility. Intravenous waveform analysis (IVA) has been previously shown in humans and pigs to be a sensitive indicator of volume status leveraging the nonlinear pressure volume relationship of the right heart and venous system.[1,2] Pulmonary air embolism often presents with hypotension and tachycardia which can be mistaken for hypovolemia in the operating room. We hypothesized that IVA would be able to discern the degree of obstructive shock from pulmonary air embolism of stepwise cumulative size.

METHODS: Nine Sprague Dawley rats were anesthetized with isoflurane, intubated, and mechanically ventilated. Following a hemorrhage and resuscitation protocol mimicking the perioperative period, 0.1 mL of air was injected via femoral vein twice, ten minutes apart. Arterial pressure was monitored via a femoral arterial catheter and central venous pressure was monitored via a right internal jugular catheter. Intravenous waveform was transduced via 22G IV catheter in the femoral vein. Transthoracic echocardiography was used to measure right ventricular base diameter (RVd) and cardiac output (CO) at 1, 5 and 10 minutes following injection of air. Fast Fourier transformation was performed on the femoral venous waveform, and the amplitude of the primary frequency F1, which corresponded with heart rate, was analyzed. Data was analyzed as percent change from baseline. Shapiro-Wilk test was used to assess the normality of data. Non-parametric analysis with Kruskal-Wallis Rank test followed by Dunn's tests with pairwise comparison was performed and significance adjusted using Bonferroni correction. Alpha set at p=0.05 (two-tailed).

RESULTS: CO was the most sensitive indicator of embolism and was able to discern between baseline and 0.1 ml and baseline and 0.2 ml cumulative air emboli, but not between 0.1 ml and 0.2 ml levels, p= 0.002, 0.0001 and 1.0, respectively. Mean arterial pressure was also able to discern between baseline and 0.1 and 0.2 ml air embolus, p=0.01 and 0.0002, respectively. Both F1 and RVd increased and were able to detect 0.2 ml air, p=0.0005 and 0.01 respectively, but not 0.1 ml air, p=0.36 and 0.56, respectively. No significant change in CVP occurred.

CONCLUSION: IVA is a novel minimally invasive technique to assess right-sided pressure-volume relationships. IVA has been shown to decrease nonlinearly in hemorrhage. Here we demonstrated increases in F1 corresponding to right heart failure from obstructive shock related to air embolus. This technique may aid in the diagnosis of undifferentiated shock.

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CRITICAL CARE 55

A Computational Model to Predict Successful Extubation from Mechanical Ventilation in ICU Patients

Alexandra Szewc[1], Han Kim[1], Robert D Stevens[2]

[1]Johns Hopkins University, Baltimore, MD, [2]The Johns Hopkins University School of Medicine, Baltimore, MD

INTRODUCTION: A model that accurately predicts extubation success could serve as a decision support tool to identify the ideal duration of mechanical ventilation for each patient and to decrease the risk of complications. The aim of this study is to create computational models that predict the likelihood of successful extubation from mechanical ventilation and describe features that are associated with extubation failure-operationally defined as need for reintubation within 72 hours of extubation.

METHODS: The data used in this study was from the Philips eICU clinical research database which contains >200,000 ICU admissions from 208 institutions across the United States[1]. We searched for patients admitted to the ICU who were extubated after receiving mechanical ventilation (MV). Patient MV occurrences were then separated into two classes: reintubated (n=8104) and non-reintubated (n=30659). Features were extracted from the entirety of a patient's first MV with the task of learning physiology to predict whether the patient extubated would require reintubation. Exposure variables of interest included age, gender, laboratory results, MV duration, severity of respiratory failure, congestive heart failure, neurologic state, motor strength, sepsis/septic shock, fluid balance, medications, standard pulmonary variables, procedures, prior diagnoses, and physiology-derived data. The observation window included data from the 6 hours preceding extubation from each patient's first MV occurrence. The prediction window was 72 hours following extubation. Three different machine learning (ML) algorithms, GLM, random forest (RF), and gradient boosting (XGboost), were evaluated on a preliminary set of a limited amount of the variables described.

RESULTS: Out of all the unique mechanically ventilated patients in the eICU database (n=38,769), the outcome class of non-reintubation (n=30,659) represented the majority of patients where the reintubation class (n=7,999) represented the remainder, excluding those who were reintubated following a time interval that exceeds 72 hours. Utilizing a total of 1310 demographics, laboratory results, and MV setting derived features, our preliminary model to predict the probability of reintubation showed promising results. XGBoost was the best performing model with AUROC: 0.79±0.01, sensitivity: 0.76±0.03, and specificity: 0.67±0.02.

CONCLUSION: Our results demonstrate the potential for clinical data-driven ML approaches to significantly outperform current clinical practices for the prevention of the reintubation outcome following mechanical ventilation in the intensive care unit.

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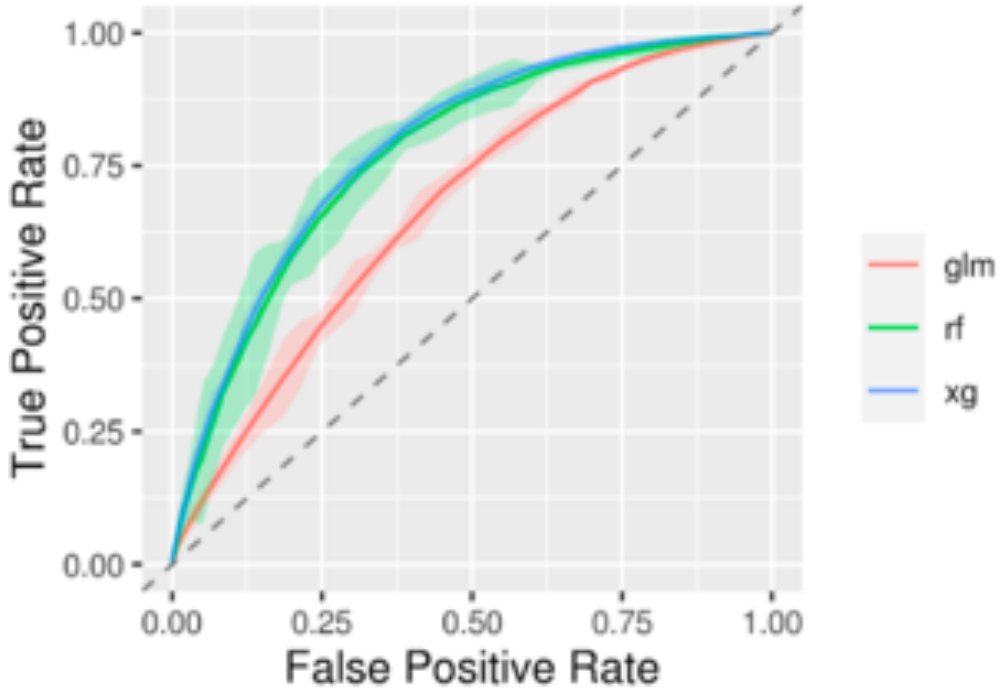

Figure 1. Receiver operating characteristic curve and 95% confidence interval of generalized linear model (GLM), random forest (RF), and XGBoost (XG) models. GLM models can be seen to struggle slightly due to increased dimensionality of the feature space. XGboost and Random forest models perform similarly with an average AUROC of 0.79.

CRITICAL CARE 56

Cardiac Output Estimation by Multi-Beat Analysis of Arterial Blood Pressure Waveform versus Continuous Pulmonary Artery Thermodilution in Post Cardiac Surgery Intensive Care Unit Patients

Ashish K Khanna[1], Lauren E Sands[2], Lillian M Nosow[3], Amit Saha[4], Bryan E Marchant[5]

[1]Wake Forest University School of Medicine, Winston-Salem, NC, [2]Wake Forest School of Medicine, Wake Forest Baptist Health, Winston-Salem, NC, [3]Wake Forest School of Medicine, Wake Forest Baptist Health, Winston-Salem , NC, [4]Wake Forest School of Medicine, WINSTON-SALEM, NC, [5]Wake Forest Baptist Hospital, Winston Salem, NC

INTRODUCTION: Cardiac output estimation is a critical component of monitoring critically ill patients after cardiac surgery. We sought to access the correlation between cardiac output estimation using a novel multi-beat analysis of arterial blood pressure waveform versus a traditional continuous pulmonary artery catheter guided thermodilution method.

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 retrieved from the electronic medical records (EMR) at a resolution of one measurement every 15 minutes. The arterial blood pressure waveform was fed into the Argos CO monitor (Retia Medical; Valhalla, NY, USA) via a reusable cable connected to the bedside patient monitor. The Argos monitor analyzes the arterial line blood pressure waveform using multi-beat analysis (MBA) and provides CO estimates (CO-MBA) once every 5 seconds. For every available CO-CTD measurement, CO-MBA was averaged over the preceding 30 minutes, in order to obtain paired CO-CTD and CO-MBA measurements. Correlation between CO-CTD and CO-MBA was computed within subjects, taking repeated observations into account and removing the between subject variability. Agreement between CO-CTD and CO-MBA was assessed via Bland-Altman analysis, accounting for multiple observations within patients. Specifically, the difference between CO-MBA and CO-CTD was modeled as $D_{ij}=\mu+b_i+\epsilon_{ij}$ where D_{ij} is the difference between CO-MBA and CO-CTD, μ is the bias, b_i is the intercept specific to the ith subjects, and ϵ_{ij} is the residual for the jth measurement in the ith subject. The overall variance of D_{ij} is given by the sum of the variances of b_i and ϵ_{ij}.

RESULTS: Out of the 26 eligible patients, 1 was rejected due to unavailability of continuous thermodilution CO measurements (CO-CTD) from the PAC. One patient was further excluded due to underdamped arterial BP waveforms evident in square wave tests performed throughout the recording. Median length of monitoring where measurement of CO-CTD overlapped with CO-MBA was 14 hours and 15 minutes. A total of 1012 paired measurements across 24 patients was available for final analysis.Mean CO-CTD was 5.12 L/min and mean CO-MBA was 5.54 L/min. Paired observations showed a moderate correlation ($r= 0.62$, $p<0.001$) across a range of values of CO-CTD and CO-MBA. (Figure 1) Bland-Altman plot of the difference between CO-MBA and CO-CTD, plotted against their mean, for all paired measurements showed a mean of differences (bias) of 0.43 L/min +- 1.08 L/min, 95% limits of agreement -1.69 to 2.55 L/min, and a percentage error of 39.4 %. (Figure 2)

CONCLUSION: Cardiac output measurements using a novel multi-beat analysis of radial artery pressure waveform are moderately correlated with the traditional more-invasive pulmonary artery thermodilution guided cardiac output measurements. Our results agree with a previous validation of the MBA method in 31 post-cardiac surgery patients in the ICU, where a percentage error of 40.7% was reported. Pending larger datasets, 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.

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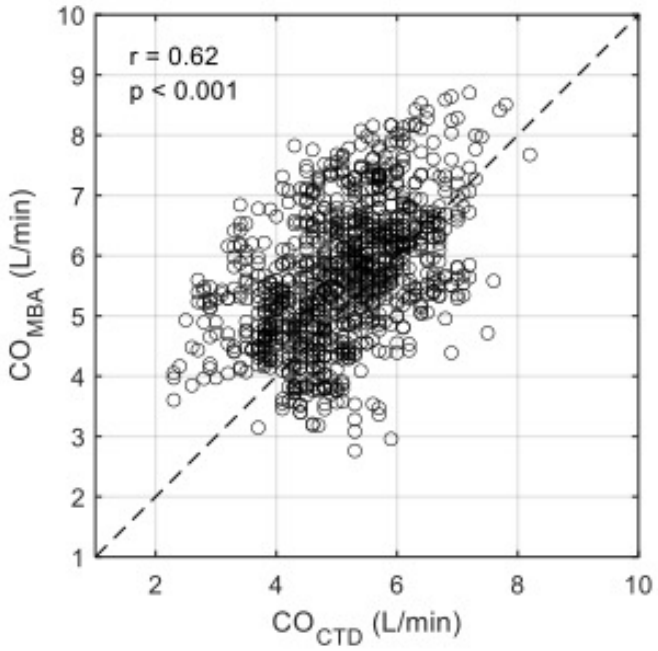

Figure 1

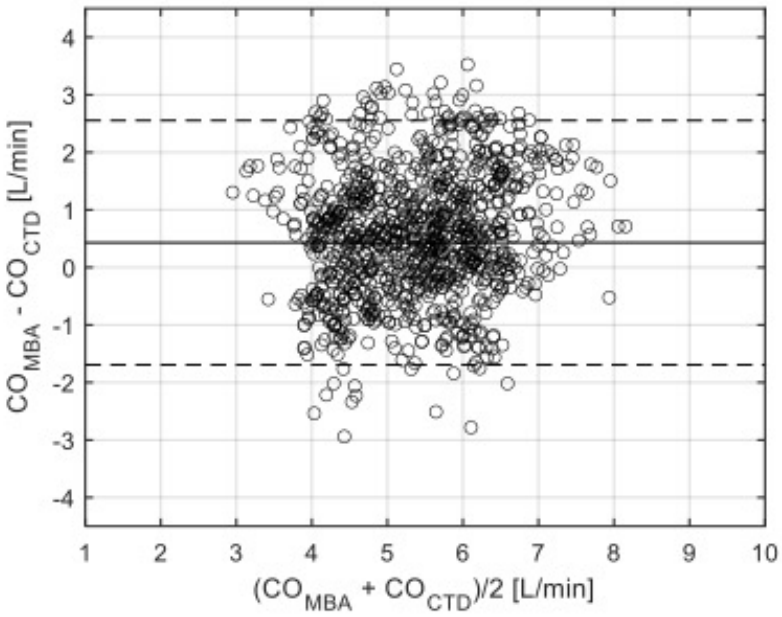

Figure 2

CRITICAL CARE 57

Procalcitonin and Duration of Mechanical Ventilation in COVID-19 Patients

Kevin Kim[1], Martin Krause[1], David Douin[1], Tim Tran[1], Ana Fernandez-Bustamante[1], Karsten Bartels[1]

[1]University of Colorado, Aurora, CO

INTRODUCTION: Patients diagnosed with COVID-19 frequently require mechanical ventilation.[1-4] Knowledge of laboratory tests associated with the prolonged need for mechanical ventilation may guide resource allocation. Procalcitonin is currently used to predict treatment failure and mortality in lower respiratory infections.[5] We hypothesized that an elevated plasma procalcitonin level (>0.1 ng/ml) would be associated with the duration of invasive mechanical ventilation.

METHODS: This is an observational cohort study using automated data collection and manual chart review from the Electronic Health Record from the Colorado University COVID-19 database. Patients diagnosed with COVID-19, who required invasive mechanical ventilation, were enrolled. The primary outcome was the duration of mechanical ventilation assessed within 28 days of admission. Patients' demographics, comorbidities, SOFA scores on admission, and initial procalcitonin levels were obtained. Multiple linear regression was fitted to assess the association between plasma procalcitonin levels and the duration of mechanical ventilation.

RESULTS: We included 93 mechanically ventilated patients, of which 18 died (19.4%) within 28 days of the initial admission. After adjusted analysis using multivariable linear regression, the duration of mechanical ventilation was, on average, 5.6 (p=0.016) days longer in patients with an initial procalcitonin level >0.1 ng/ml. In addition, older age (p=0.001) and higher BMI (p=0.033) were associated with a longer duration of mechanical ventilation.[6]

CONCLUSION: In this cohort of mechanically ventilated COVID-19 patients, we found an association between plasma procalcitonin levels >0.1 ng/ml on admission and prolonged mechanical ventilation. Our findings may help to identify patients at risk for prolonged mechanical ventilation upon admission.[6]

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CRITICAL CARE 58

Noninvasive Oxygenation Strategies for Obese Patients with Acute Hypoxemic Respiratory Failure: A Survey of Critical Care Anesthesiologists

Timothy G Gaulton[1], Meghan Lane-Fall[1], Lorenzo Berra[2], Maurizio Cereda[1]

[1]University of Pennsylvania, Philadelphia, PA, [2]Massachusetts General Hospital, Boston, MA

INTRODUCTION: Obesity is a major risk factor for acute hypoxemic respiratory failure (AHRF) and its complications[1]. In the Coronavirus Disease 2019 (COVID-19) pandemic, half of critically ill patients are obese[2]. Compared to standard oxygen therapy, noninvasive oxygenation strategies such as noninvasive ventilation and high flow nasal cannula (HFNC) can prevent endotracheal intubation and mortality in AHRF[3]. Yet, obese patients have distinct respiratory mechanics[4] and the efficacy and application of respiratory support might have significant variation in this population. We therefore sought to understand the use of noninvasive oxygenation strategies and criteria for tracheal intubation in obese patients who present with AHRF utilizing a survey of critical care anesthesia fellowship directors in the United States (US).

METHODS: We sent out a survey by electronic mail to all fellowship directors of certified US critical care anesthesia fellowship programs. In the survey, we defined obesity using conventional standards (body mass index (BMI) ≥ 30 kg/m2). We collected respondent information on the total years of clinical experience as an attending physician and the types of intensive care units (ICU) in which they spend clinical time (surgical, medical, mixed). We presented a hypothetical scenario of an obese patient with viral pneumonia who was on 6 liters per minute of standard nasal cannula and now requires noninvasive oxygenation support. We asked respondents to select their 1st line choice from the following options: HFNC, Bilevel positive airway pressure (BiPAP), continuous positive airway pressure (CPAP), standard face-mask oxygen therapy (e.g. venturi mask, non-rebreather) or avoiding noninvasive therapy and intubating. We further asked if obese patients with AHRF require different types of noninvasive oxygenation strategies than non-obese patients, if obesity modifies tracheal intubation criteria for AHRF and if so, how, and what measures respondents typically use to define obesity in clinical practice. Responses were summarized with medians and interquartile ranges (IQR) for continuous variables and number and proportions for categorical variables.

RESULTS: Of the 57 certified critical care anesthesia fellowships in the US, 29 (50.9%) fellowship directors responded. The median number of years of clinical experience as an attending anesthesiologist was 11 (IQR 7, 13). The majority of respondents (89.7%) had clinical time in surgical ICUs and 12 (41.4%) also had clinical time in mixed (medical/surgical) units. As shown in Figure 1, 18 (62.1%) respondents stated they would routinely use HFNC as their 1st choice for noninvasive oxygenation therapy compared to 7 (24.1%) respondents who selected BiPAP and 3 (10.3%) of respondents who selected CPAP. No respondents selected standard face-mask oxygen or avoiding noninvasive strategies entirely. 75.9% of respondents agreed that obese patients with AHRF require different noninvasive oxygenation strategies compared to non-obese patients (Figure 2). Respondents stated they were more likely to use support that delivered positive end expiratory pressure and ventilation. A history of obstructive sleep apnea and/or home use of BiPAP/CPAP were also listed as reasons why obesity would alter strategy selection. 34.5% of respondents stated that obesity modifies their intubation criteria for AHRF. Respondents were "less tolerant of time on NIV" and "more likely to intubate" due to both "lower reserve due to decreased FRC" and "avoiding developing a physiologically difficult intubation". Respondents universally used measured BMI to define obesity. 22 (75.9%) respondents also used their visual assessment.

CONCLUSION: In a survey of US critical care anesthesia fellowship directors, we found notable variability in the selection of noninvasive oxygenation strategies for obese patients with AHRF. The majority of respondents agreed that obese patients require different types of noninvasive oxygenation strategies compared to non-obese patients. Abdominal adiposity decreases transpulmonary pressure and increases alveolar collapse[4], leading to a strong physiologic rationale for why obesity would cause differential responses to noninvasive oxygenation. Future trials assessing noninvasive oxygenation strategies for AHRF, particularly those related to COVID-19, need to consider targeted enrollment and analyses by obesity and consider appropriate intubation criteria for this population.

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Figure 1: Initial Selection of Noninvasive Oyxgenation Support for Obese Patients with AHRF

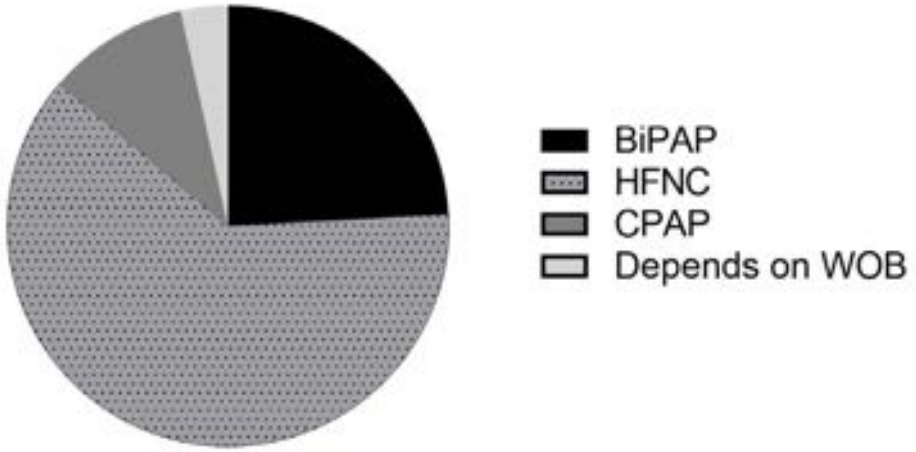
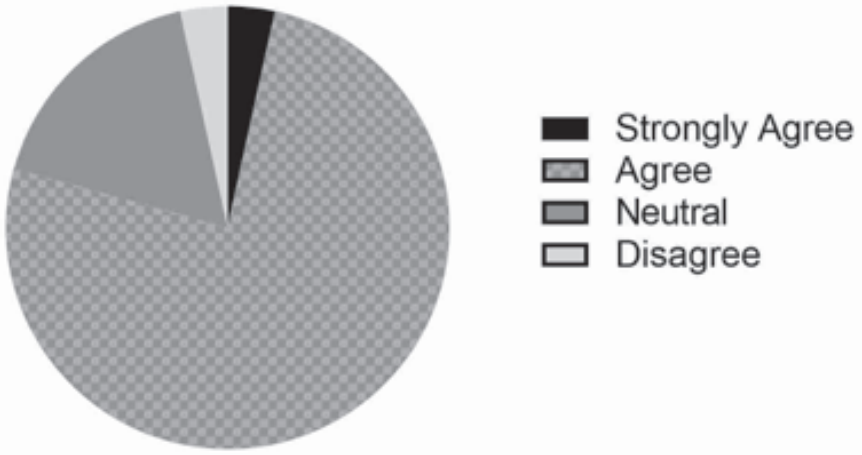


Figure 2: Obese patients with AHRF require different types of noninvasive oxygenation support compared to non-obese patients



CRITICAL CARE 59

A Novel Communications Approach for Covid-19 ICU Patients

Michael Urban[1], Mary Chisholm[2], Mary Kelly[2]

[1]N/A, United States of America, [2]Hospital for Special Surgery, New York, NY

INTRODUCTION: The Covid-19 pandemic has created an unprecedented influx of critically ill patients into ICUs; often exceeding the ability of hospitals to provide adequate care and necessitating the transfer of these patients to distant ICUs. In addition, in order to protect the patient's relatives, families have been prohibited from any direct interaction. This separation of critically ill patients from their families has disrupted the usual interaction between intensivists and families: impeding discussions with regard to management, procedures, and the withdrawal of life support. During this crisis we developed a team to address the required daily communication between intensivists and the families of ICU patients.

METHODS: In late March of 2020, elective surgical procedures in New York were suspended and in a surgical hospital the ambulatory operating rooms and post-anesthesia care unit was converted into an ICU designed specifically for Covid-19 patients. These patients were transferred into this unit from an affiliated tertiary care hospital that had become inundated with patients. In an effort to support the intensivists of this new unit, a family medical communications team (FMCT) was developed.

RESULTS: The FMCT was composed of an intensivist, physician volunteers not providing direct patient care, palliative care physicians and a service excellence liaison (SEL). Once a patient arrived in the unit, the SEL contacted the family for emotional support, determined the appropriate surrogate decision-maker and explained that a designated physician (DP) would contact the family daily or more often if required. Each morning the intensivist on the FMCT team communicated with the ICU team after rounds with regard to the patient's medical status, the management plans for the day and whether additional input was required from the family (DNR order, permission for a tracheostomy, enrollment in a medication study or withdrawal of support). This information was then conveyed electronically or by phone to the DP, who also had access to the patient's electronic record. Difficult end of life decisions were often handled through a conference call which included the family, the DP and a palliative care physician. When possible patient Face-Time sessions were scheduled with the family.

CONCLUSION: The FMCT consisted of more than 30 physicians, nurses, SELs and administrators who provided a link between the critically ill Covid-19 patient and their family. Family members expressed their frustration with the lack of contact with the medical team during the hospitalization before transfer to our facility and expressed gratitude for this new experience. The ICU physicians caring for the patients were able to make timely important decisions with regard to treatments and management via this communication with family decision makers. Although the FMCT was dissolved in the spring of 2020 as the pandemic subsided in New York, it may serve as a model for this winter and the future during circumstances where families and critical care patients are separated.

CRITICAL CARE 60

Combined Use of ECMO, Prone Positioning, and APRV in the Management of Severe COVID-19 Patients

Stephanie Ong[1], Hossam Tantawy[2], Roland Assi[2], Astha Chichra[2], Miriam Treggiari[2]

[1]University of Toledo, Toledo, OH, [2]Yale University, New Haven, CT

INTRODUCTION: The ongoing COVID-19 pandemic has resulted in an overwhelming number of ICU admissions, posing a significant challenge for the ICU community. Acute Respiratory Distress Syndrome (ARDS) is one complication of severe COVID-19 infection and may lead to rapid clinical deterioration, warranting extracorporeal membrane oxygenation (ECMO) in the most critical cases. A recently conducted literature review reported that the mortality rates for patients with COVID-19 admitted to the ICU is 40%, and 45% for those with associated ARDS.[1] In the context of the current pandemic, there have been reports of small series regarding the role of ECMO on patient outcomes. One retrospective cohort study reported a 57% mortality rate in COVID-19 ARDS patients on ECMO compared to 63% in those only mechanically ventilated, but this difference was not significant.[2] Another retrospective cohort study of COVID-19 patients with ARDS who received ECMO found a 60-day mortality of 31% and a 90-day mortality of 36%.[3] During the COVID-19 pandemic, we have employed an unconventional mix of therapeutic modalities while managing COVID-19 patients with severe, refractory ARDS, including prone positioning while on ECMO. We designed a study to evaluate the safety, physiologic changes in oxygenation and hemodynamic profile, and complications observed during ECMO, prone positioning, and APRV in a cohort of patients who received veno-venous (VV) ECMO support for COVID-19-associated ARDS.

METHODS: This retrospective cohort study included adult patients with COVID-19-associated ARDS who required VV-ECMO. Three intervention groups were defined: patients who received ECMO support (ECMO only), and patients who underwent prone positioning prior to or after ECMO (prone only) and while on ECMO (ECMO + prone). In addition to demographics of the entire cohort, we collected physiologic variables and ventilation settings at four time points for each modality: pre (prior to intervention), 1h-post (within one hour after intervention), 6h-post (six hours after intervention), and 24h-post (24 hours after intervention). Patients were placed in the prone position by a dedicated prone team consisting of three nurses, who regularly proned patients throughout the hospital, a respiratory therapist, a perfusionist, and the patient's bedside nurse. Patients were ventilated with either assist-control or airway pressure release ventilation (APRV). Patient tolerance of the intervention(s) was evaluated through changes in vital signs, ventilation settings, and pressor requirements before and after intervention initiation. We also documented the frequency of intervention-related complications, such as deep tissue injury and cannula damage. Post-intervention (1h-, 6h-, and 24h-post) continuous variables were compared with baseline (pre) using one-sample paired t-tests. We used Bonferroni correction to account for multiple comparisons. A two-sided alpha level of 0.05 was required for statistical significance.

RESULTS: We included 14 patients (mean age 48.1 [SD 9.3] years, male [100%]) who received VV-ECMO support, with ten undergoing prone positioning while not on ECMO, and seven while on ECMO (Table 1). Thirteen patients were ventilated using APRV while on ECMO. Patients on ECMO had an improvement in oxygen saturation, PaO_2/FiO_2 ratio, and minute ventilation up to 24 hours post intervention (Table 3). Vasopressor requirements increased with ECMO support at 1h- and 24h-post time points. Prone positioning, while on and not on ECMO, was not associated with clinically significant hemodynamic or respiratory changes. All patients sustained deep tissue injuries, but only those on the face or chest were related to prone positioning. One patient required cannula replacement due to cannula damage. The overall in-hospital mortality was 43%.

CONCLUSION: The use of VV-ECMO, prone positioning, and APRV in a select population of patients with COVID-19 ARDS was generally overall well-tolerated, however, the physiologic improvements observed were marginal. Patients sustained deep tissue injuries that resolved without further complications and were not entirely related to prone positioning. Cannula complications were rare (one patient), and the patient would have likely required cannula exchange regardless of prone positioning. Given the impact of these complications on patient care, it is critical for clinicians to be aware of these risks and be prepared to address them should they arise.

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Table 1. Patients' demographics and baseline characteristics at hospital admission.

Variable	N (%)	Mean (SD)
Age (y)	14 (100)	48.1 (9.3)
Gender		
Male	14 (100)	
Race		
White or Caucasian	6 (43)	
Black or African American	2 (14)	
Other / Not Listed	6 (43)	
BMI (kg/cm^2)	14 (100)	36.5 (6.2)
SOFA Score (0 - 24)		
ECMO	12 (86)	12.6 (1.2)
Prone	13 (93)	11.9 (1.3)
APRV	9 (64)	11.6 (4.5)
WHO Illness Severity Score	14 (100)	5.9 (1.4)
4 Hospitalized, O_2 mask or nasal cannula	4 (29)	
5 Non-invasive ventilation or high-flow O_2	1 (7)	
6 Intubation and mechanical ventilation	1 (7)	
7 Ventilation + additional organ support	8 (57)	
ECMO duration (days)	14 (100)	22.2 (7.5)
Prone Only	10 (66.7)	
Duration (hours)		14.6 (3.8)
Sessions		2.1 (1.4)
Prone + ECMO	7 (46.7)	
Duration (hours)		16.2 (2.9)
Sessions		4 (3.6)

Table 2. Patients' characteristics at hospital discharge.

Variable	N (%)	Mean (SD)
ICU stay (days)	14 (100)	37.4 (13.8)
Hospital stay (days)	14 (100)	41.7 (18.2)
WHO Illness Severity Score	14 (100)	5.6 (2.3)
2 Limitation of activity	1 (7)	
3 Hospitalized, no O_2 therapy	1 (7)	
4 Hospitalized, O_2 mask or nasal cannula	5 (36)	
6 Intubation and mechanical ventilation	1 (7)	
8 Death	6 (43)	

Table 3. Changes in Vital Signs and Ventilator/ECMO Settings Before and After the Intervention. Data are expressed as mean (SD).

Variable	Pre	1 h-post	6 h-post	24 h-post	p-values*
ECMO					
Temperature (°C)	37.2 (2.2)	36.9 (0.61)	36.4 (0.7)	36.6 (0.17)	> 0.99; 0.784; > 0.99
HR (beats/min)	113.2 (13.8)	97.2 (12.6)	87.4 (20.0)	93.6 (19.9)	0.001; 0.0004; 0.117
RR (breaths/min)	30.9 (4.3)	17.9 (10.5)	16.7 (9.1)	11.6 (6.4)	0.230; 0.023; 0.075
Systolic BP (mmHg)	113.8 (16.6)	116.3 (19.5)	109.4 (12.0)	117.8 (21.7)	> 0.99; 0.837; > 0.99
O_2 Saturation (%)	90 (5.3)	98.5 (2.5)	97.9 (2.2)	96.4 (2.9)	0.009; 0.009; 0.021
ECMO Sweep (L/min)	NA	5.2 (1.9)	4.6 (1.4)	5.7 (1.4)	
PaO_2/FiO_2 Ratio (mmHg)	93.4 (35.4)	213.4 (126.1)	210.4 (94.3)	222.3 (67.0)	0.027; 0.039; 0.002
Tidal Volume (mL/kg)	370.7 (68.5)	329.9 (123.6)	228.1 (115.8)	181 (123.7)	0.515; 0.0002; 0.001
Total RR (breaths/min)	29.2 (5.1)	17.7 (10.6)	14.8 (6.8)	11.6 (5.7)	0.047; 0.0004; 0.0007
Minute Ventilation (L/min)	10.7 (2.0)	5.7 (3.9)	3.0 (2.1)	2.1 (1.4)	0.034; 0.00001; 0.000002
PEEP (cmH_2O)	16 (3.3)	16.3 (3.1)	15.6 (3.0)	14.5 (2.8)	> 0.99; > 0.99; > 0.99
Plateau Pressure (cmH_2O)	34.9 (5.2)	34.7 (5.0)	31.3 (4.2)	26.8 (6.1)	> 0.99; 0.449; 0.130
Prone Positioning while Not on ECMO					
Temperature (°C)	37.7 (1.5)	38.1 (1.5)	38.4 (1.1)	37.4 (1.9)	0.223; 0.532; > 0.99
HR (beats/min)	98.9 (18.1)	98.5 (17.1)	107.1 (18.4)	106.2 (19.8)	> 0.99; 0.496; > 0.99
RR (breaths/min)	27.6 (5.3)	24.6 (7.5)	28.3 (4.6)	32.5 (2.7)	> 0.99; > 0.99; > 0.99
Systolic BP (mmHg)	119.3 (11.2)	129.2 (25.3)	113 (14.0)	120.2 (13.0)	0.844; 0.366; > 0.99
O_2 Saturation (%)	91.4 (4.5)	93.5 (3.9)	94 (3.3)	92.9 (5.0)	0.361; 0.206; 0.713
PaO_2/FiO_2 Ratio (mmHg)	98.5 (32.8)	124.3 (53.2)	123.2 (41.5)	118.2 (46.3)	0.170; 0.087; 0.396
Tidal Volume (mL/kg)	387.3 (48.7)	376.2 (33.7)	364 (42.9)	374.7 (69.7)	> 0.99; 0.512; > 0.99
Total RR (breaths/min)	26.7 (4.5)	28.8 (3.5)	28.9 (3.8)	28.6 (3.8)	0.220; 0.080; 0.282
Minute Ventilation (L/min)	10.4 (2.3)	10.9 (1.8)	10.6 (2.1)	10.8 (2.8)	0.955; > 0.99; > 0.99
PEEP (cmH_2O)	15.3 (1.7)	15.8 (2.7)	15.2 (2.5)	14.8 (2.2)	1; 0.585; 0.507
Plateau Pressure (cmH_2O)	35.3 (5.2)	34.8 (4.5)	33.7 (3.3)	32.5 (2.7)	0.960; 0.740; 0.107
Prone Positioning while on ECMO					
Temperature (°C)	36.7 (0.36)	36.6 (0.18)	36.7 (0.15)	36.6 (0.11)	> 0.99; > 0.99; 0.891
HR (beats/min)	102.3 (26.3)	100.6 (23.6)	91.3 (17.2)	95.9 (22.9)	> 0.99; 0.436; > 0.99
RR (breaths/min)	9.8 (3.5)	13.2 (4.3)	11.8 (10.3)	13 (9.1)	0.187; > 0.99; 0.799
Systolic BP (mmHg)	133.3 (20.8)	131.4 (20.3)	126.1 (16.2)	109.4 (10.5)	> 0.99; > 0.99; 0.038
O_2 Saturation (%)	92.1 (3.4)	94.9 (3.6)	95.4 (3.3)	95.7 (2.9)	0.307; 0.223; 0.145
ECMO Sweep (L/min)	6.1 (2.4)	6.1 (2.4)	6.8 (1.8)	6.5 (2.1)	
PaO_2/FiO_2 Ratio (mmHg)	76.6 (10.0)	90.5 (30.4)	94.3 (28.4)	81.7 (31.9)	0.605; 0.397; > 0.99
Tidal Volume (mL/kg)	244.1 (148.4)	190.7 (147.0)	192.1 (145.1)	241.6 (140.0)	0.752; 0.838; > 0.99
Total RR (breaths/min)	10.7 (5.9)	16.1 (13.8)	13 (10.0)	13.3 (11.6)	0.796; > 0.99; > 0.99
Minute Ventilation (L/min)	2.1 (1.2)	2.3 (1.9)	2.1 (1.8)	2.5 (1.4)	> 0.99; > 0.99; > 0.99
PEEP (cmH_2O)	13.7 (3.7)	13.7 (3.7)	13.7 (3.7)	13.7 (3.7)	NA; NA; NA
Plateau Pressure (cmH_2O)	28.9 (5.5)	28.9 (5.5)	28.9 (5.5)	28.9 (5.5)	NA; NA; NA

HR heart rate, *RR* respiratory rate, *BP* blood pressure, *ECMO* extracorporeal membrane oxygenation, *PaO2* partial pressure of oxygen in arterial blood, FiO_2 fraction of inspired oxygen, *PEEP* positive end-expiratory pressure.

* p-values comparing pre *versus* the post-intervention time points; 1 h (1^{st} p-value), 6 h (2^{nd} p-value), 24 h (3^{rd} p-value). P-values are adjusted for multiple comparisons using Bonferroni corrections.

CRITICAL CARE 61

Critical Care Outcomes of the COVID-19 patients at MHealth Fairview

Monica I Lupei[1], Alexander M Kaizer[2], Michael Wall[3], Simon Yang[4], Christopher J Tignanelli[4], Nicholas E Ingraham[4], Jeffrey G Chipman[4], Michael Todd[4]

[1]University of Minnesota, Saint Paul, MN, [2]Alexander Mark Kaizer, PhD, University of Colorado-Anschutz Medical Campus, Denver, CO, [3]University of Minnesota Medical School, Minneaoplis, MN, [4]University of Minnesota, Minneapolis, MN

INTRODUCTION: Understanding the COVID-19 disease outcomes is essential for patient safety and resource utilization during the pandemic[1,2]. Our study's goal was to assess the patients' critical care outcomes and associated risk factors.

METHODS: We performed a retrospective review of all adult patients with positive PCR COVID-19 test during the index admission admitted in our 12 hospital medical system between March 21 and November 5, 2020. Patients' variables were obtained during the first four days of admission. The outcomes measured included all-cause mortality at any time, need for mechanical ventilation, intensive care unit (ICU) admission. Two-sample independent t-tests (two groups) or linear regression (for more than two groups) were used for continuous variables and chi-square for categorical variables comparison. All analyses were conducted using R v3.6.3.

RESULTS: A total of 1060 patients were admitted with COVID-19 diagnosis confirmed during admission. The mortality and ventilation requirement decreased over time from 24% and 25% respectively (March to May) to 16 and 20% (June to August), and 10% and 15% (September to November). The ICU admission remained constant (~60%). The patients with the composite outcome (died, required mechanical ventilation or ICU) had a higher proportion of males (54% vs. 47%) and were older (65.2 ± 18 vs. 62.5 ± 19 years) when compared to the patients without it ($p<0.05$). The C-reactive protein (CRP) (107 ± 83 vs. 69 ± 66 mg/L) , lactic dehydrogenase (LDH) (392 ± 215 vs. 283 ± 104 U/L), D-dimers (2.5 ± 3.9 vs. 1.7 ± 2.3 ug/mL), neutrophils (77.5 % vs. 73.6 %), creatinine (1.44 ± 1.31 vs. 1.14 ± 0.91 mg/dL), respiratory rate (29 ± 15 vs. 24 ± 9 bmp) were significantly higher in the patients with the composite outcome versus the ones without it ($p<0.001$). The hemoglobin (10.4 ± 3.1 vs. 11 ± 2.7 g/dL), albumin (2.77 ± 0.62 vs. 2.92 ± 0.59 g/dL), and oxygen saturation (85 ± 10 vs. 90 ± 8 %) were significantly lower in the patients with the composite outcome versus those without it ($p<0.05$). The patients who died while on ventilation were significantly older, and had significantly higher CRP, D-dimers, LDH, and neutrophils than those who survived on the ventilation ($p<0.001$).

CONCLUSION: The survival and the ventilation rate of patients' admitted across our medical system improved over time, while the need for ICU remained constant. The composite outcome was associated with older age, higher CRP, LDH, D-dimers, neutrophils, and creatinine; those values were the highest in the patients who died while on mechanical ventilation.

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CRITICAL CARE 62

Intubation Timing vs Non-Intubation Management on the Outcomes of Patients with Respiratory Distress Secondary to COVID-19 Pneumonia

Mohamed Fayed[1], Abhishek Saluja[1], Katherine Nowak[2], Xiaoxia Han[3], ANOOP CHHINA[1]

[1]Henry Ford hospital, Detroit, MI, [2]Henry Ford Health System, Detroit, MI, [3]Henry Ford Hospital, Detroit, MI

INTRODUCTION: As COVID-19 is a novel virus, there is very limited information available about the impact of different clinical treatment approaches on patient outcomes. The Chinese Society of Anesthesiology Task Force on Airway Management's initial recommendation was to proceed with endotracheal intubation[1-2]. Most experts with experience managing COVID-19 patients suggest early intubation. There is also limited evidence that late intubation has been associated with increased mortality in patients with adult respiratory distress syndrome[3]. The rationale for early intubation in patients with COVID-19 is that these patients can deteriorate rapidly to life threatening hypoxemia with limited time to deal with the logistical complexity of intubation, and disease progression may limit the ability to be effectively pre-oxygenate the patient. On the other hand, one could argue that patients with COVID-19 are at risk of ventilator-induced lung injury and that intubation should be avoided if at all possible. Mechanical ventilation increases the risk of many complications for example muscle weakness, delirium, ventilator associated pneumonia or even mortality. The purpose of this retrospective chart review is to evaluate whether the timing of intubation (early vs late), as well as use of intubation vs no intubation, leads to differences in outcomes in patients with severe ARDS secondary to COVID-19.

METHODS: - Subject Population: All patients admitted to our facility between March 12th 2020 and December 15th 2020 with COVID-19 pneumonia that developed severe respiratory distress. - Enrollment and/or Screening: This is a retrospective chart review study. Participants were identified by searching in the EPIC electronic medical record database for a COVID-19 pneumonia diagnosis upon admission. - Inclusion Criteria: COVID-19 pneumonia with bilateral infiltrates on chest x-ray, with at least one of the following: Respiratory rate > 30 for 2 hours, and/or oxygen saturation <93% for 2 hours. - Exclusion Criteria: Patients with a "do not intubate" order. - Patients were be divided into 3 groups: • Early intubation group: Patients that were intubated within 24 hours of meeting inclusion criteria. • Late intubation group: Patients that were intubated after 24 hours of meeting inclusion criteria. • Non-intubated group: Patient that met inclusion criteria but were not intubated during hospital admission. - Number of patients enrolled in the study: 339. - Data measured: • Primary outcome: mortality. • Secondary outcome: ventilation days, ICU Days, hospital days, discharge disposition. • Age and SOFA (Sequential organ failure assessment) score. - Statistical method: Numeric variables were summarized with mean and standard deviation (SD) or median and interquartile range (IQR) and compared using ANOVA or Kruskal–Wallis test. Categorical variables were summarized with frequencies and proportions and compared using Chi-square test or fisher exact test. Post-hoc comparison will be conducted when appropriate. Adjusted p-values were reported for post-hoc multiple comparison. All tests will be two-sided. A p-value < 0.05 is considered statistically significant.

RESULTS: On analysis of the results in 3 groups (table 1), there is statistically significant difference in mortality where non intubated patients had 9% mortality, compared to 43% in early intubation and 52% in late intubation (p value <0.001). Non intubated patient stayed in hospital for shorted duration (7 days, IQR 5, 11) compared to early intubation (18 days, IQR 10.5, 29.5) and late intubation (19 days IQR 14, 28.5) (p value < 0.001). Non intubated patients are more likely to be discharged home under self care (61%) compared to early (1.8 %) and late intubation (5%) (p value < 0.001). Subhoc analysis in early vs late intubation groups, there is statistical significant difference in SOFA score, but no statistical significant difference in mortality, ventilation days, ICU or hospital length of stay.

CONCLUSION: Based on our results, we conclude that avoiding intubation in patients with COVID-19 pneumonia with respiratory distress without other organ involvement is associated with decreased overall mortality, hospital length of stay and patients were more likely to go home under self-care. In the patients who were intubated due to COVID-19 pneumonia, there was no statistical significant difference in outcomes regarding timing of intubation.

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VARIABLES	ALL (N=339)	EARLY INTUBATED (N=55)	LATE INTUBATED (N=55)	NON INTUBATED (N=229)	P VALUE
AGE, MEAN (SD)	62.2 (15.7)	64.29 (12.69)	63.47 (15.46)	61.43 (16.43)	0.392
SOFA SCORE:	3 (1, 5)	6 (4, 8)	4 (1, 6)	2 (1, 4)	<0.001
PRIMARY OUTCOME:					
MORTALITY, N (%)	75 (22.1)	24 (43.6)	29 (52.7)	22 (9.6)	<0.001
SECONDARY OUTCOMES:					
VENTILATION DAYS, MEDIAN (IQR)	12.5 (7, 21.8)	14 (10, 22.5)	10 (4.5, 20.5)	NA	0.352
TOTAL ICU DAYS, MEDIAN (IQR)	4 (0, 12)	17 (10.5, 26)	15 (10.5, 27)	0 (0, 5)	<0.001
HOSPITAL LENGTH OF STAY, MEDIAN (IQR)	10 (5.5, 16.5)	18 (10.5, 29.5)	19 (14, 28.5)	7 (5, 11)	<0.001
DISCHARGE DISPOSITION, N (%)					<0.001
• HOME OR SELF CARE (ROUTINE DISCHARGE)	145 (42.8)	1 (1.8)	3 (5.5)	141 (61.6)	
• HOME UNDER CARE OF ORGANIZED HOME HEALTH SERVICE ORG	48 (14.2)	8 (14.5)	8 (14.5)	32 (14)	
• MEDICARE CERTIFIED LONG TERM CARE HOSPITAL (LTCH)	12 (3.5)	5 (9.1)	6 (10.9)	1 (0.4)	
• SKILLED NURSING FACILITY (SNF) WITH MEDICARE CERTIFICATION	47 (13.9)	13 (23.6)	9 (16.4)	25 (10.9)	
• OTHER	12 (3.6)	4 (7.2)	0 (0)	8 (2.9)	

Table 1: Primary and secondary outcomes results in 3 groups.

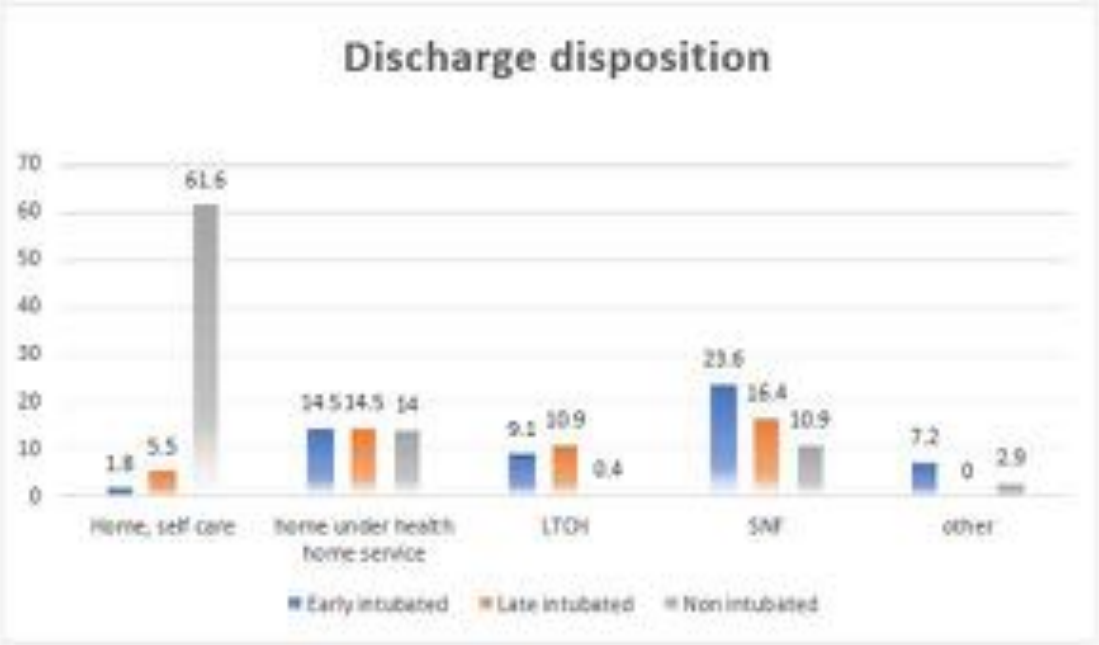

Figure 2 Discharge disposition in 3 groups.

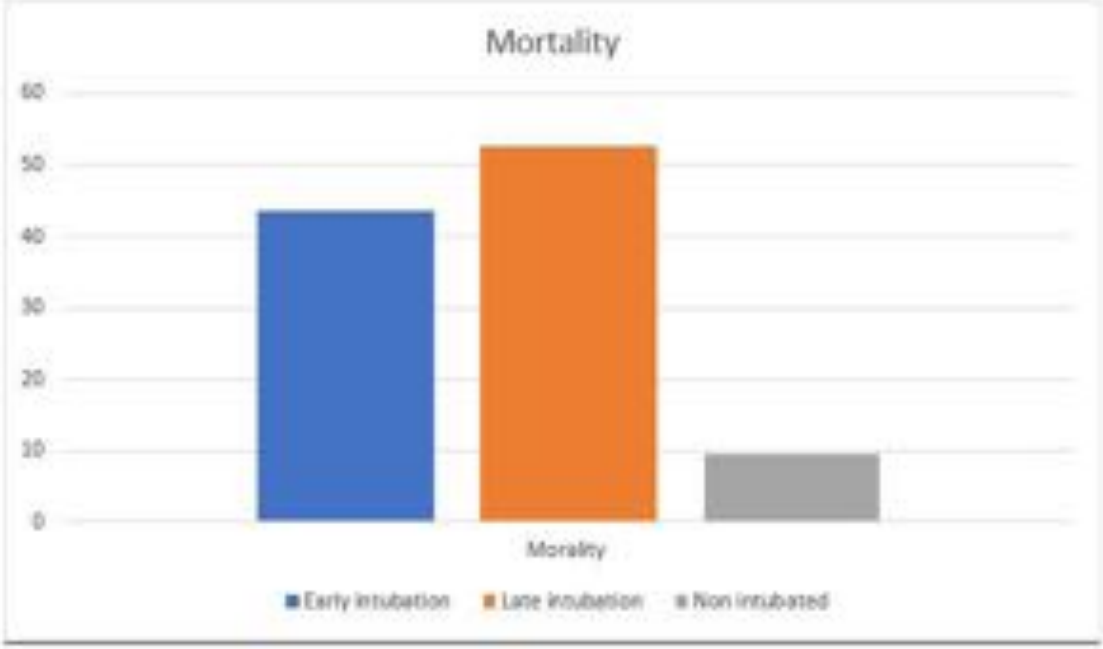

Figure 1: Mortality difference in 3 groups.

CRITICAL CARE 63

The Efficacy of Transfusion After Placement of an Automated Blood Bank Storage System in the Intensive Care Unit

Raksha Bangalore[1], Philip Sommer[2], Germaine Cuff[3], Yan Zhang[1], Binhuan Wang[1], Mark Nunnally[4]

[1]NYU Langone Medical Center, New York, NY, [2]NYU Langone Health, New York, NY, [3]NYU School of Medicine, New York, NY, [4]New York University Langone Medical Center, New York, NY

INTRODUCTION: Massive transfusion protocol (MTP) initially utilized for traumatic bleeding has been expanded for use in other hospital settings including the intensive care unit (ICU) to treat patients with uncontrolled bleeding[1, 3]. The implementation of such protocols has allowed for efficient release of blood bank products, decreased delays in transfusion and lower mortality[2, 4]. BloodTrack Haemobank (HB), an automated blood product storage system that housed 45 units of packed red blood cells (pRBC) was placed in the Surgical and Cardiothoracic ICU in October 2019. Our goal was to examine if the introduction of the HB reduced the time to transfusion of blood products to patients in the ICU.

METHODS: A retrospective chart review of 50 non-trauma patients that required MTP while admitted to the cardiovascular and surgical intensive care units between October 2018 and October 2020 was done. Patients who were admitted with a primary diagnosis of COVID-19 were excluded from this study. Of the 50 patients, 15 patients had MTP orders discontinued prior to any transfusions. An additional 9 patients with active MTP orders had incomplete documentation or had improved clinical status not requiring transfusion of any blood products. The time difference from MTP order placement to the first blood product administered was calculated for each of the patients. The median time of transfusion for each type of blood product was calculated. Additionally, the location of origin of all products during all the transfusions was noted.

RESULTS: The median time to transfusion from the placement of MTP order for pRBC is 23 minutes prior to and 14.5 minutes after the institution of HB. The median time to transfusion of fresh frozen plasma (FFP) is 33.5 minutes before HB and 19 minutes after HB. For transfusion of cryoprecipitate (Cryo), the median time before HB is 33 minutes and after HB is 7 minutes. The median times of transfusion of platelets (Plt) before HB is 28.5 minutes and after HB is 16.5 minutes. Fresh frozen plasma, cryoprecipitate and platelets originated from the blood bank before and after placement of HB. In all transfusions after the placement of HB, packed red blood cells were obtained from HB.

CONCLUSION: Our data suggest that there was a decrease in median time to transfusion after MTP orders were placed for all products after the implementation of HB in the ICU. The decrease in time to transfusion of packed red cells is an expected outcome given that they were obtained from the HB. However, it is noteworthy that a decreasing trend in the median time of transfusion was seen with all the other blood products which were obtained from the blood bank possibly due to change in workflow offered by the HB. Further analysis is required to study the efficacy of this practice and the financial implications related to this strategy.

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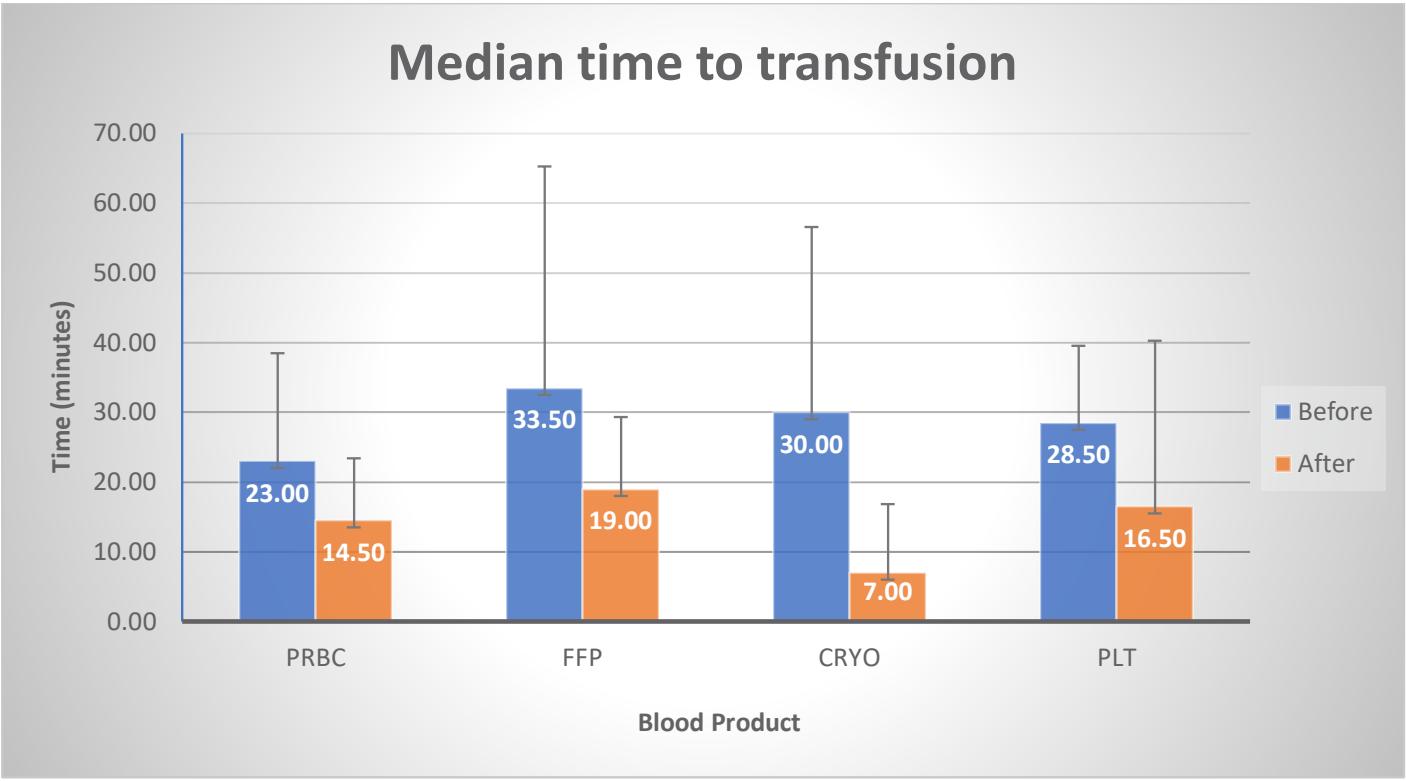

CRITICAL CARE 64

A Recipe for Success Using ECMO for COVID-19

Patrick Henthorn[1], Hans Tregear[1], Andrew Hennigan[1], Sarah Alber[1], Meghan Prin[1], Tim Tran[1], Martin Krause[1], Karsten Bartels[1], Maung Hlaing[1], Samuel Gilliland[1], Scott Wolf[1], Breandan Sullivan[1]

[1]University of Colorado School of Medicine, Aurora, CO

INTRODUCTION: Extracorporeal membrane oxygenation (ECMO) has traditionally been used to treat varying forms of respiratory or circulatory crises, including acute respiratory distress syndrome (ARDS). A subset of patients with COVID-19 develop severe ARDS and progress to requiring the intensive care unit. Since the inception of COVID-19, many different treatment modalities have been utilized including various pharmacologic agents, supplemental oxygen, mechanical ventilation and, most recently, vaccination. At some institutions, ECMO has been utilized in patients with COVID-19 disease that is refractory to the aforementioned treatment options. Much of the data available regarding ECMO use in patients with COVID-19 is derived from the first global surge of the disease from approximately January 2020 to May 2020. In this unique situation where real-time outcomes around the world were dictating constantly changing treatment plans, the lack of standardized protocols early in the pandemic has resulted in inconsistent ECMO outcomes among COVID-19 patients. University of Colorado results from a yet unpublished case series this year revealed excellent efficacy among 15 total patients receiving ECMO treatment from March 2020 to May 2020 with 87% of patients decannulated from ECMO and 73% of patients surviving to hospital discharge[1]. These results are largely attributed to strict selection parameters for ECMO treatment in patients with COVID-19. During a time in which healthcare resources are unprecedentedly limited, it is important to allocate resources as efficiently as possible to provide the best possible outcomes to the greatest number of patients.

METHODS: A comprehensive literature review of both domestic and international, small and large studies was performed to provide a basis of comparison against the data and patient outcomes for ECMO treatment of patients with COVID-19 at the University of Colorado Hospital.

RESULTS: Given the variable type and size of studies included for this comparison, it is difficult to compile the data in such a way that is uniform and standardized. However, Table 1 offers an opportunity to review and appreciate the differences in efficacy of ECMO treatment based on patient inclusion and exclusion characteristics at various institutions. The report from Mustafa et al. listed in Table 1 indicates that their inclusion and exclusion criteria were similar to the EOLIA trial group which was conducted by Combes et al in 2018[7].

CONCLUSION: Based on existing data from the first global COVID-19 pandemic surge, it is evident that strict selection criteria for ECMO candidates improves outcomes. This limited resource can be a life-saving tool if implemented under the appropriate circumstances. We believe that institutions should create a standardized protocol for patient selection in the use of ECMO for treatment of refractory ARDS in patients with COVID-19. Appropriate patient selection not only optimizes use of limited resources but also ensures that those with the greatest likelihood of survival with ECMO can receive it.

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AUTHORS	Barbaro, MacLaren et al.	Falcoz, Monnier et al.	Henningan et al.	Jacobs et al.	Li et al.	Mustafa et al.
TITLE	"Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal LIfe Support Organization registry"	"Extracorporeal Membrane Oxygenation for Critically Ill Patients with COVID-19-related Acute Respiratory Distress Syndrome: Worth the Effort?"	"Extracorporeal membranous oxygenation for the support of patient with COVID-19 respiratory failure"	"Extracorporeal Membrane Oxygenation in the Treatment of Severe Pulmonary and Cardiac Compromise in Coronavirus Disease 2019: Experience with 32 Patients"	"Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019 in Shanghai, China"	"Extracorporeal Membrane Oxygenation for Patients With Covid-19 in Severe Respiratory Failure"
INSTITUTION	Multicenter (213 hospitals), International (36 countries)	Strasbourg University Hospital	University of Colorado Hospital	Multicenter, United States (9 hospitals)	Shanghai Public Health Clinical Center	Advocate Christ Medical Center, Rush University Medical Center (Chicago, Illinois)
STUDY DATES	January 2020 – May 2020	March 2020 – April 2020	March 2020 – May 2020	March 2020 – April 2020	January 2020 – March 2020	March 2020 – July 2020
PATIENT SELECTION CRITERIA - INCLUSION	Patients aged 16 years or older with confirmed COVID-19 who had ECMO support initiated between Jan 16 and May 1, 2020	Inclusion - refractory ARDS with PaO2/FiO2 < 80 mmHg, pH <7.25, PaCO2 > 60 mmHg for more than 6 hours with a FIO2 > 80% despite low-pressure ventilation strategies and no participation of fluid overload	In order to reserve this resource only for those patients most likely to benefit, our multidisciplinary ICU team, which includes critical care anesthesiologists and cardiothoracic surgeons, created criteria for the initiation of ECMO in COVID-19 patients: ARDS with increasing hypoxemia and/or hypercarbia not managed by mechanical ventilation and suspected or proven COVID-19.	Entry criteria for placement on ECMO was determined by the individual patient care team at each of the nine hospitals submitting data; all patients were placed on ECMO with severe respiratory failure felt to be refractory to conventional management.	PaO2/FiO2 < 100 mmHg or PaCO2 > 60 mmHg for more than 6 hours despite optimal mechanical ventilation; ECMO should be immediately established if the following crieria are met after failure of aggressive ventilation management: PaO2/FiO2 < 50 mmHg for more than 1 hour, PaO2/FiO2 < 80 mmHg for more than 2 hours, existence of uncompensated respiratory acidosis with pH < 7.2 for more than 1 hour	"Similar to those of the EOLIA trial group"; ARDS, intubation < 7 days, AND one of the following disease-severity criteria despite optimisation of mechanical ventilation and despite potential use of various usual adjunctive therapies; PaO2/FiO2 < 50 mmHg for > 3 hours, PaO2/FiO2 < 80 mmHg for > 6 hours, arterial blood pH< 7.25 with a PaCO2 > 60 mmHg for > 6 hours
PATIENT SELECTION CRITERIA - EXCLUSION	None Indicated	Age > 70 years; severe comorbidities including severe chronic respiratory failure, severe cardiac failure and Child Pugh C cirrhosis; mechanical ventilation > 7 days	Multi-system organ failure, ARDS with unstable hemodynamics requiring multiple or high-dose vasopressors or inotropes, inability to tolerate systemic anti-coagulation, advanced age or multiple co-morbidities, and patient or family designation of do not resuscitate.	None Indicated	None Indicated	"Similar to those of the EOLIA trial group"; age < 18 years, mechanical ventilation > 7 days, pregnancy, BMI > 45, long-term chronic respiratory insufficiency with supplemental O2, cardiac failure requiring VA ECMO, cancer with life expectancy < 5 years, moribund condition, irreversible neurologic injury
NUMBER OF PATIENTS	1035	17	15	32	8	40
MEDIAN PAO2/FIO2	72	71	83.1	Not Available	66.5	66
INTERVENTIONS	*978x VV ECMO, 44x VA-ECMO*	*16x VV-ECMO, 1x VA-ECMO*	*15x VV-ECMO*	*27x VV-ECMO, 5x VA-ECMO*	*7x VV-ECMO, 1x VA-ECMO*	*40x VV-ECMO*
ECMO DURATION	*13.9 days (median)*	*9 days (median)*	*10 days (median, range 7-14.5 days)*	*6 days (median)*	*30 days (median, range 18-47 days)*	*30 days (mean)*
MORTALITY	*380 patients died (37%)*	*6 patients died (35.3%)*	*2 patients died (13%)*	*10 patients died (31%)*	*4 patients died (50%)*	*6 patients died (15%)*
OTHER OUTCOMES	*67 patients (6%) remained hospitalized, 311 (30%) discharged home or to acute rehab, 101 (10%) discharged to long-term acute care center, 176 (17%) discharged to another hospital*	*1 patient (5.9%) remained mechanically ventilated, 10 (59%) weaned from mechanical ventilation and discharged from ICU (of which 7 (41.1%) discharged fom hospital)*	*13 patients (87%) patients were decannulated, 12 (80%) survived to ICU discharge, 11 (73%) survived to hospital discharge with one pending discharge*	*17 patients (53%) remained on ECMO, 5 (15%) decannulated and extubated, 1 (3%) discharged from the hospital*	*3 patients (37.5%) weaned off ECMO but remain on mechanical ventilation, 1 (12.5%) remains on ECMO*	*40 patients (100%) extubated, 32 (80%) no longer on ECMO , 29 (73%) discharged from hospital*

CRITICAL CARE 65

Anesthetic predictors of Post-operative Respiratory Failure in patients with SARS-COVID 19 infection

Nitish Gupta[1], Michael E Kiyatkin[1]

[1]Montefiore Medical Center, Bronx, NY

INTRODUCTION: Postoperative respiratory failure (PORF) is a serious adverse event that is of particular concern for patients with SARS-CoV-2 infection. Given the frequent occurrence of viral pneumonia and respiratory failure with COVID-19, it is not surprising that the incidence of PORF, which before the pandemic occurred in 1-4% of non-cardiac surgeries[1-4], has been reported as high as 15-30% in patients with SARS-CoV-2 infection[5]. General anesthesia (GA) has long been associated with a higher incidence of PORF than non-GA techniques, especially in patients with respiratory comorbidities[6,7]. The aim of our study was to compare the incidence of PORF and major other surgical adverse events in SARS-CoV-2-infected patients who underwent surgery that could have been performed with either GA or non-GA techniques.

METHODS: This was a single-center retrospective cohort study performed in three urban, academic hospitals in New York City from March 14th to October 31st, 2020. Inclusion criteria were surgery that could have been performed with either GA or non-GA and a documented positive SARS-CoV-2 nasopharyngeal PCR test result within 30 days before or 7 days after surgery. Exclusion criteria were pre-operative respiratory failure, age <18-years-old, and obstetric procedures. The primary outcome, PORF, was a composite of inability to extubate for >24-hours after surgery, and re-intubation or use of high-flow nasal cannula or non-invasive ventilation for non-surgical, non-sleep apnea reasons within 30 days of surgery. The exposure of interest was anesthetic technique, either GA or non-GA (neuraxial, regional anesthesia or monitored anesthesia care, MAC). Other exposures included vasopressor use, fluid balance and type, blood transfusion within 48-hours of surgery, and use of rapid sequence intubation. Other data collected included demographic details, patient comorbidities and risk factors, and pre-operative vital sign parameters. Data were obtained via manual chart review. Continuous data were tested for normality, reported as either mean +/- SD or median (IQR), and compared with Student's t- or Mann-Whitney rank-sum tests. Categorical data were presented as proportions and compared with Chi-square or Fisher's exact tests.

RESULTS: A total of 195 SARS-CoV-2 infected patients had surgical procedures that could have been performed with either anesthetic technique. Of these, 72 met all inclusion and exclusion criteria, with 43 patients undergoing GA (~ 60%), 24 neuraxial (~30%), 1 regional anesthesia (~1%) and 3 patients had MAC (~4%). Comparing patients who had GA with those who had non-GA surgeries, there were no statistically significant differences in age, race or ethnicity. There were also no differences in comorbidity burden as evaluated by the Charleston Comorbidity Index (median 5 vs. 4), pre-operative vital signs, or peri-operative risk scores including ASA-PS (9% vs. 17% ASA 1-2, 74% vs. 66% ASA 3, and 16% vs. 21% ASA 4-5) and the Surgical Mortality Probability Model index (median 5 in both groups). There were also no differences in instances of symptomatic COVID-19 (42% vs. 31%). However, GA was more frequent in patients having vascular surgery compared with non-GA more frequent in orthopedic surgeries (67% vs. 35% vascular and 21% vs. 59% orthopedic in GA compared with non-GA patients, P=0.003). With regard to outcomes, there was a 15% incidence of PORF in our study cohort and this was significantly more common in patients who had GA (26% incidence in patients who had GA vs. no instances in non-GA patients, P=0.002). GA was also associated with greater mortality (19% in GA vs. none in non-GA, P=0.014) and incidence of ICU admission (33% vs. 3%, P=0.01)

CONCLUSION: In patients with recent SARS-CoV-2 infection undergoing surgery, GA was associated with a higher incidence of PORF when compared with non-GA techniques such as regional, neuraxial or MAC. Importantly, peri-operative risk indices were similar between patients who had surgery with and without GA, arguing that this is not merely a reflection of GA being more common in sicker patients but rather GA itself facilitating respiratory failure and/or exacerbating COVID-19 via immunomodulatory, mechanical or other means. If confirmed, this work warrants especially careful consideration of anesthetic technique and surgical approach in SARS-CoV-2 infected surgical patients.

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CRITICAL CARE 66

Ideal Approach to Higher Level Oxygenation in COVID-19: Early vs. Late Intubation

Emma Nash[1], Justin Birge[1], James Sullivan[2]

[1]University of Nebraska Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE

INTRODUCTION: As the critical care community sees larger volumes of refractory hypoxia in COVID-19 patients, the ideal method of respiratory support remains unclear. Traditionally there were limited options outside of endotracheal intubation for patients with respiratory failure, but over the last 20 years noninvasive respiratory support, including positive pressure ventilation masks and high flow nasal cannula systems, have been increasingly utilized for an expanding number of indications[1]. There are many disadvantages to invasive ventilation, but one advantage is controlling the factors that worsen lung damage in traditional ARDS pathology by adjusting tidal volumes, FiO2 and PEEP, and optimizing driving pressures[2]. Nearly half of COVID-19 patients that get admitted to the ICU end up on the ventilator, so it is imperative to know how best to manage this group[3]. The purpose of this particular study is to provide information to help guide clinical decision making regarding respiratory support for COVID19 patients, specifically regarding time to intubation and associated mortality.

METHODS: This is a retrospective cohort study of patients at one quaternary care hospital between March 1 and November 30. We identified 375 patients that met inclusion criteria defined as confirmed COVID-19 infection, age ≥18 years, and admitted to ICU. Outcomes included rates of mortality broken down by time from admission to intubation and were analyzed by chi-squared test. Time to intubation was also stratified by month.

RESULTS: The number of patients in each group is outlined in figure 1.The average time from admission to intubation for those that survived was 2.48 days, while average days to intubation of those that died was 5.2 days. Mortality was also analyzed by days from ICU admission to intubation, where the average time to ventilation of those that survived vs died was 1.56 and 4.03 days, respectively. Most notably, patients intubated between days 1-3 of hospital stay had a mortality rate of only 35%, vs the overall mortality of ICU patients which was 33% (n=123) Those that ended up on a ventilator had a 50% mortality rate, (n=89) with mortality rates increasing in a linear fashion as time to intubation increased (Fig. 2,3). The difference in mortality in early vs late (≥4 days) intubation, when measured from either initial admission or ICU admission, was statistically significant ($p<0.01$). When these rates were stratified by month, this data showed a relationship between the percentage of late intubations (≥7 days from admission) and overall ICU mortality rate (Fig. 4), as well as an inverse relationship between overall percent of patients intubated and ICU mortality (Fig. 5). The sample sizes of these was small and therefore statistical analysis was not performed.

CONCLUSION: Patients with COVID19 that require intubation have a statistically significant lower rate of mortality rate than those intubated later. Noninvasive support remains an invaluable tool, and this preliminary study does not clarify which patients requiring this will ultimately need to be intubated. However, the sharp increase in mortality rate would suggest that there may be a point at which the benefit of intubation outweighs the risk of allowing the patient to self regulate with only noninvasive assistance. Practice patterns regarding intubation have evolved as the pandemic has progressed. While only observational, this data suggests a relationship between ICU mortality and the practice delaying or avoiding intubation altogether (Figs 3–4). The ultimate goal is to better predict which patients will benefit from endotracheal intubation so they can be identified earlier. This data set leaves many confounding variables unaddressed, as limited documentation can be reliably gathered from the de identified data set. Subsequent projects will allow for gathering data points including duration and intensity of noninvasive support prior to intubation and of those that avoid it, ICU length of stay, biomarker trends, as well as patient specific characteristics, with the goal of will help guide the respiratory support for critically ill COVID19 patients.

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Figure 1:

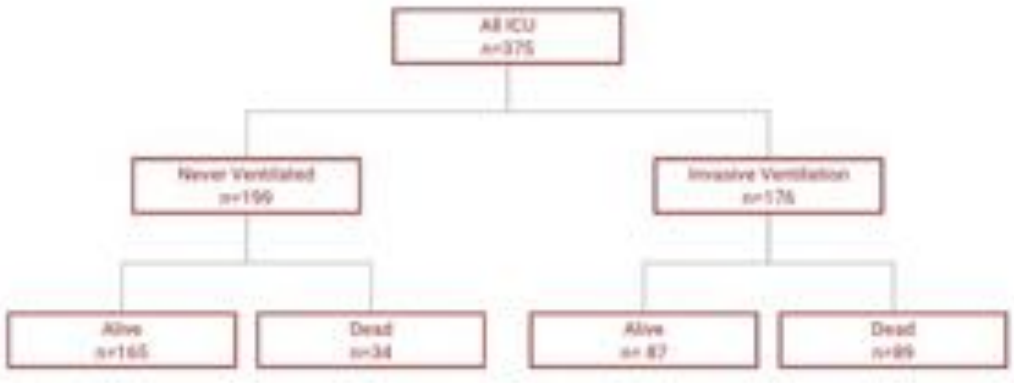


Figure 2: Mortality vs. Days from Hospital Admission to Intubation

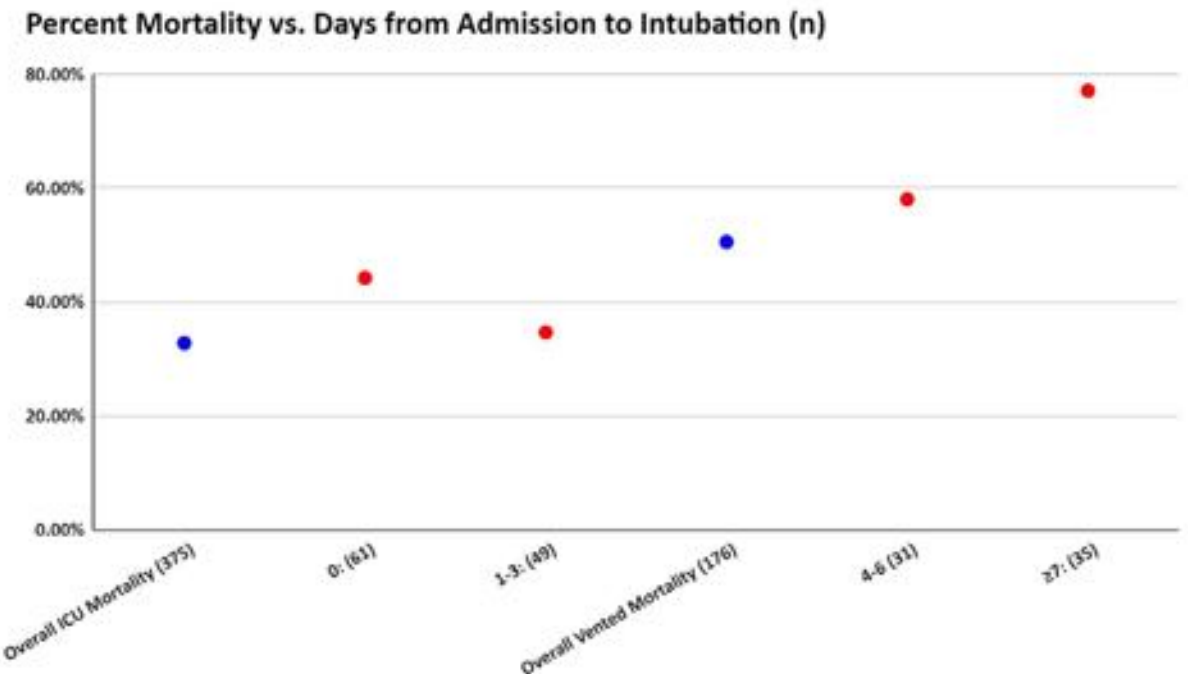


Figure 3

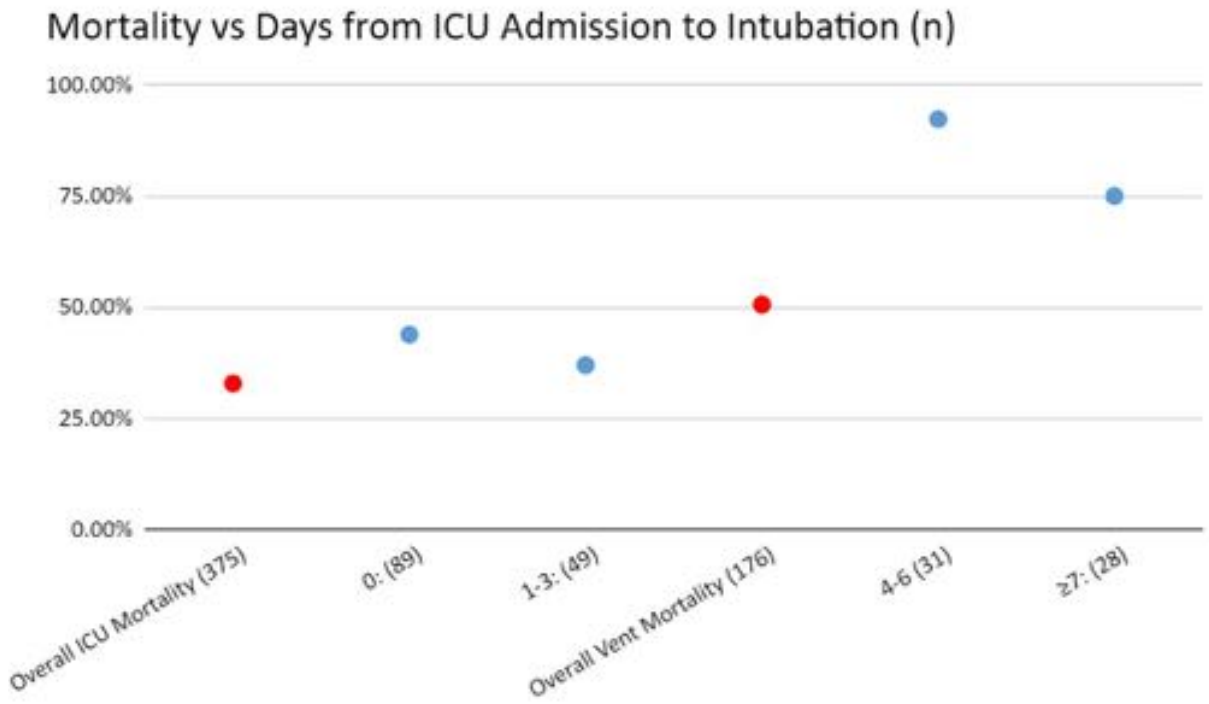


Table 1: Patient Distribution by Mortality and Time to Intubation (Chi-Square Table)
Difference in mortality of patients intubated early (1-3 days) vs. late (≥4 days) in their hospital course (a) and ICU course (b) (p<.01).

(a)

From Hospital Admission:	**Alive**	**Deceased**	
Intubated at day 1-3	32	17	49
Intubated day 4+	21	45	66
	53	62	115 (Grand Total)

(b)

From ICU Admission	**Alive**	**Deceased**	
Intubated at day 1-3	29	17	46
Intubated day 4+	8	33	41
	37	50	87 (Grand Total)

Figure 4

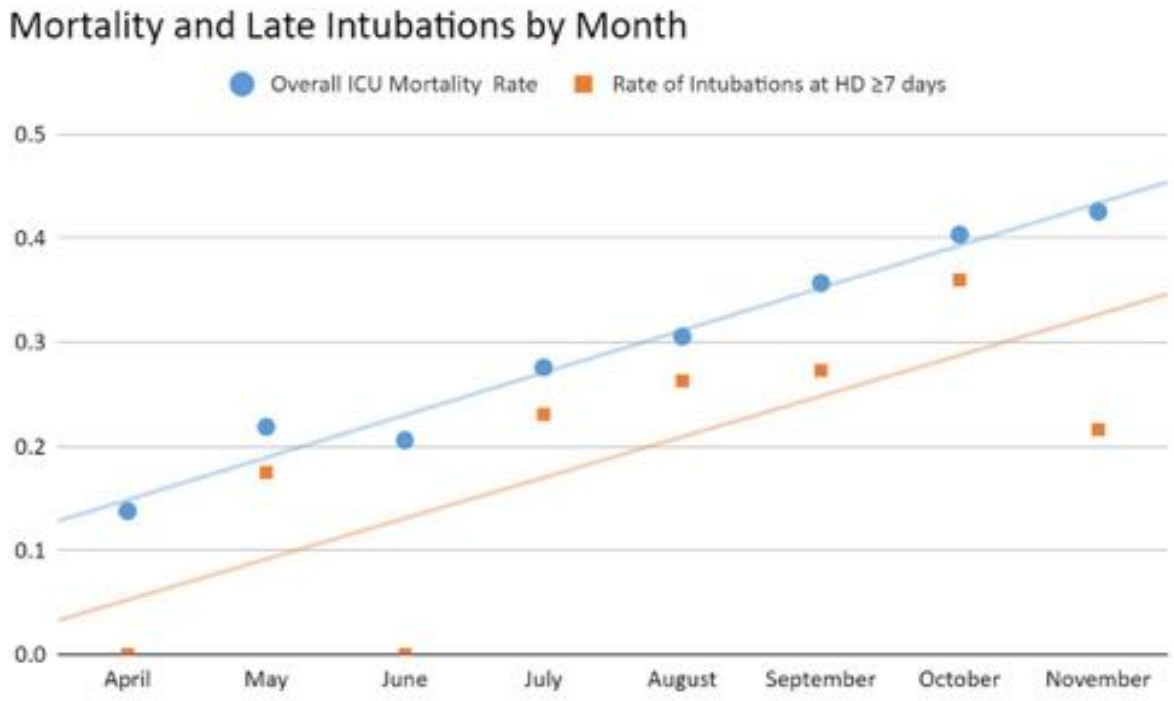
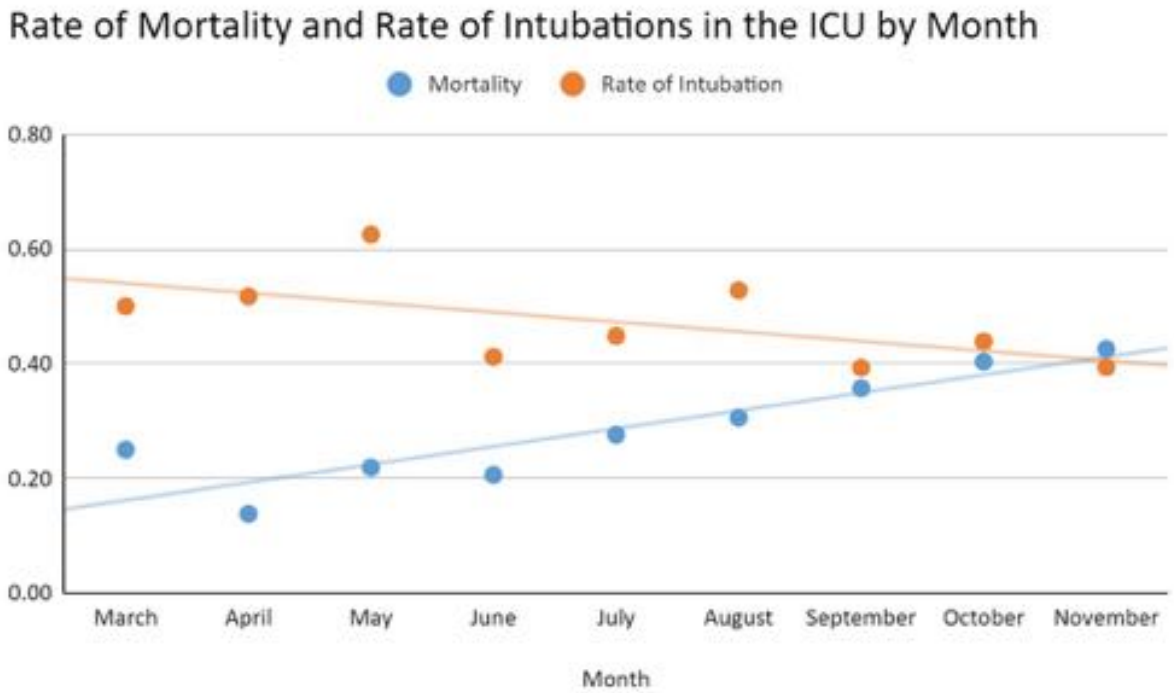


Figure 5



CRITICAL CARE 67

Assessment of Autonomic Nervous System Through High Frequency Variability Index In Covid-19 Patients: A Prediction Mortality Tool

Cristian Aragon-Benedi[1], Pablo Oliver-Forniés[2], Mario Fajardo-Perez[1]

[1]Mostoles General University Hospital, Madrid, Spain, [2]Clinical Hospital Lozano Blesa, Zaragoza, Spain

INTRODUCTION: A balance between the autonomic nervous system and the immune system against SARS-COV-2 is critical in the resolution of its severe macrophage proinflammatory activation[1,2]. We hypothesized that a low total power of an autonomic nervous system and a high level of the high frequency component of heart rate variability might be related to the number of proinflammatory cytokines and could have a predictive value in terms of severity and mortality in critically ill patients suffering from COVID-19. The main objective of this study is to demonstrate that most severely ill COVID-19 patients will show a depletion of the sympathetic nervous system and a predominance of parasympathetic tone reflecting the remaining compensatory anti-inflammatory response.

METHODS: A single-centre, prospective, observational was conducted including COVID-19 patients in mechanical ventilation admitted to the Surgical Intensive Care Unit. High frequency component of heart rate variability and total power of the autonomic nervous system (energy) were recorded using high frequency variability index monitor. To estimate the severity and mortality we used the SOFA score, and the date of discharge or date of death within 30 days. Spearman's Rho correlation test was used to detect the bivariate relationship between variables, and to find a threshold value to attempt to predict the risk of mortality the ROC curves were analyzed for both the mean high frequency variability index value and the energy value.

RESULTS: A total of fourteen patients were finally included in the study. High-frequency component of heart rate variability were higher in the non-survivor group ($p = 0.003$) and were correlated with higher IL-6 levels ($p = 0.002$). The total power of the autonomic nervous system (energy) was inversely correlated with SOFA ($p = 0.029$). A limit value at 80 of mean high frequency variability index value, predicted mortalities with the sensitivity of 100% and the specificity of 85.7%. In the case of energy, a limit value of 0.41 predicted mortality with all predictive values of 71.4%.

CONCLUSION: The different components of the spectral analysis of heart rate variability allow us to infer the association between the autonomic nervous system and critically ill patient's immune system. This autonomic dysregulation likely represents the cause and effect of the different stages of SARS-COV-2 disease, the severe inflammatory system response syndrome, and its compensatory anti-inflammatory response[3,4]. A low autonomic nervous system activity and a predominance of the parasympathetic system due to the sympathetic depletion in COVID-19 patients are associated with a worse prognosis, higher mortality and higher IL-6 levels.

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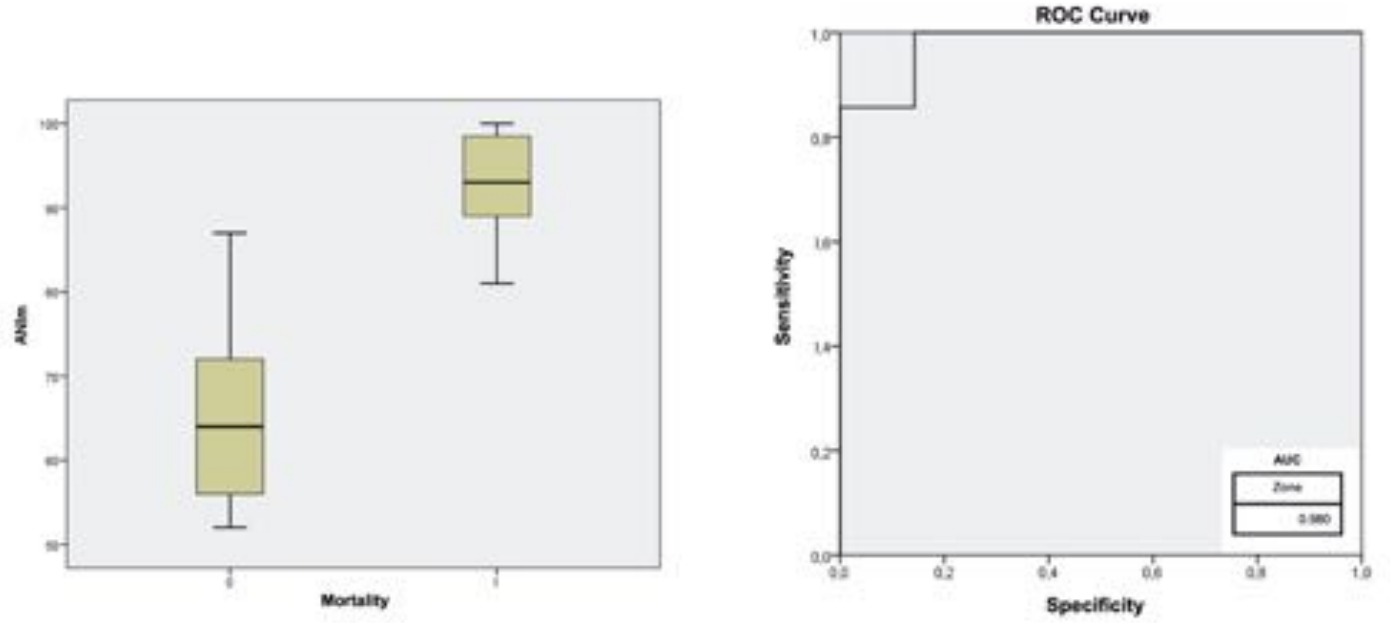

Figure 1

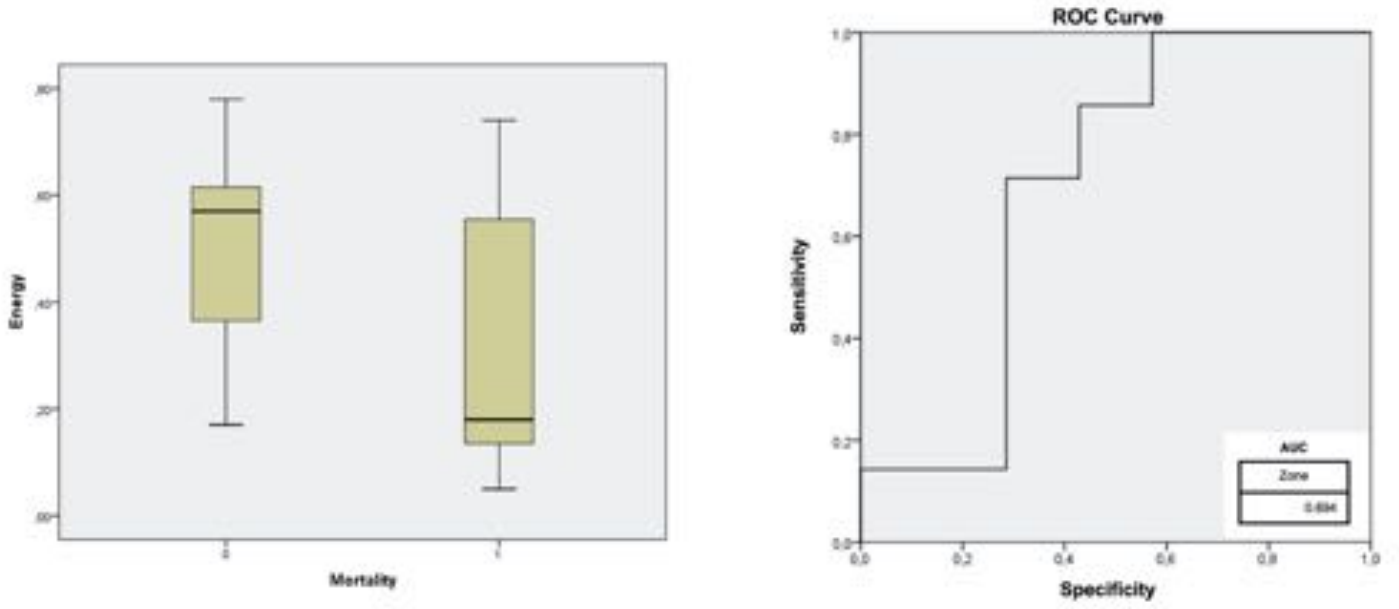

Figure 2

CRITICAL CARE 68

Brain Tissue Oxygenation Monitor Utilization Trends and Outcomes in Severe TBI. A Retrospective Cohort Study utilizing the NTDB

Jonathan Curley[1], Vijay Krishnamoorthy[2], Jordan M Komisarow[3]

[1]Duke University Medical Center, Chapel Hill, NC, [2]Duke University, Durham, NC, [3]Duke University, Durham, United States of America

INTRODUCTION: Brain tissue oxygenation (BtO2) monitoring devices are a relatively new clinical tool with utilization trends that are not well described. In addition, there is a paucity of data on the clinical outcomes associated with their utilization. In this project we seek to describe both US national utilization trends and clinical outcomes associated with utilizing this monitor device. TBIs are a significant public health concern as they are comprise near a half of all acute trauma deaths and have lasting impact on survivors chronicity of disease and healthcare costs[1,2]. TBI treatment centers on limiting primary injury and minimizing secondary injury. Traditionally prevention of secondary injury has involved monitoring and treating ICP[3]. However, numerous observational studies demonstrate decreases in brain tissue oxygenation occur before elevations in ICP[4,5]. Further, numerous observational studies suggest improved outcomes when low brain tissue oxygenation readings are avoided[5-8]. Recently the BOOST-II trial effectively demonstrated the feasibility of a neuro-critical care protocol to improve brain tissue oxygenation, but also demonstrated a trend toward improved mortality and outcomes in the BtO2 monitored population[9].

METHODS: In this study the National Trauma Databank was utilized to retrospectively collect data, between the years of 2008-2016, on severe traumatic brain injury patients as defined by an admission GCS score less than 8 requiring an intracranial pressure monitoring device as ascertained via ICD-9 and ICD-10 procedural codes. In creating this cohort for retrospective analysis, exclusion criteria included age under 18, death within 24 hours of admission, death within the emergency department, discharge from ED with no admission, no data on GCS, or patients with missing hospital disposition data. At completion this cohort included 35,501 patients. Within this cohort, the utilization of BtO2 monitoring devise was determined by ICD-9 and ICD-10 procedure codes. Multivariable joinpoint regression was utilized to analyze utilization trends. Mixed Effects logistic regression analysis was utilized to describe utilization characteristics according to below listed covariates. Hospitals were modeled as a random effect in order to calculate a model ICC. Propensity-matching, nearest neighbor, with a caliper width of 0.01 was utilized to investigate the association of BtO2 with clinical outcomes. The covariates utilized in analysis included age, gender, insurance status, injury severity score, GCS, co-morbidities, mechanism of injury, mechanical ventilation, admission heart rate, admission blood pressure, region, hospital size, hospital teaching status, and hospital trauma level status. The primary outcome chosen for propensity matched analysis was in hospital mortality. Secondary outcomes chosen for propensity matched analysis included hospital length of stay, ICU length of stay, ventilator days, and the development of ARDS. Finally, sensitivity analysis was performed with propensity weighting with IPTW.

RESULTS: Descriptive (figures 1 & 2): Brain tissue oxygenation monitoring devises were used in 1,346 patients or 3.8%. Increasing age decreased the probability of BtO2 utilization while increased injury severity increased this. Medical comorbidities did not serve as predictor of BtO2 usage in our review save for a trend of decreased utilization in the DNR population. Geographically, it was found that the southern region of the United States utilized BtO2 monitors less frequently than other regions. Nationally usage peaked in the year 2011 and decreased thereafter. Finally, in our review we found large variation of utilization, 71%, at the hospital level Outcomes (figure 3): The primary outcome of mortality was found to be significantly decreased in the BtO2 with a risk difference of -0.05 (95% CI -0.09 to -0.02). In the BtO2 monitored patients had longer ICU LOS, hospital LOS, and ventilator days.). There was not a significant difference in the development of ARDS.

CONCLUSION: In conclusion we present utilization patterns of brain tissue oxygenation monitors in the US. We found decreased mortality in BtO2 monitored patients but also found markers of increased hospital utilization. We did not find a difference in the development of ARDS which served as a potential marker of lung injury given that treatments directed at low BtO2 readings may be deleterious to lungs (liberal transfusions and high FiO2).

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Table 1. Factors Associated with BtO2 utilization

Factor	Odds Ratio	95% CI	p
age	0.99	0.98-0.99	0.0001
male gender	1.06	0.88-1.27	0.56
Race: white	1	reference	
Race: Asian	0.93	0.58-0.1.5	0.77
Race: African American	0.8	0.61-1.05	0.11
Race: Latino	0.8	0.63-1.05	0.07
year: 2009	1.45	0.99-2.12	0.06
year: 2010	2.07	1.42-3.0	0.001
year: 2011	2.98	2.09-4.22	0.001
year: 2012	2.34	1.62-3.36	0.001
year: 2013	2.19	1.50-3.18	0.001
year: 2014	1.39	0.93-2.06	0.11
year: 2015	1.94	1.33-2.84	0.001
year: 2016	1.25	0.85-1.82	0.25
Region Northeast	1	reference	
region Midwest	0.46	0.12-1.2	0.18
region west	1.19	0.73-3.44	0.73
region south	0.12	0.04-0.34	0.001
level 1	1.78	1.19-2.65	0.005
bed number	2.82	1.32-5.99	0.007
teaching/university hospital	0.44	0.24-0.80	0.008
ISSAIS	1.01	1.0-1.02	0.01
hypotension	0.88	0.66-1.19	0.42
HR	0.73	0.55-0.97	0.03
HR	0.93	0.80-1.1	0.39
Chronic respiratory disease	0.9	0.60-1.34	0.6
Diabetes	0.97	0.69-1.36	0.84
DNR status	0.38	0.15-1.01	0.05
coagulopathy	0.65	0.38-1.13	0.13

Model ICC 0.71 (95% CI 0.63 – 0.77)

Figure 1

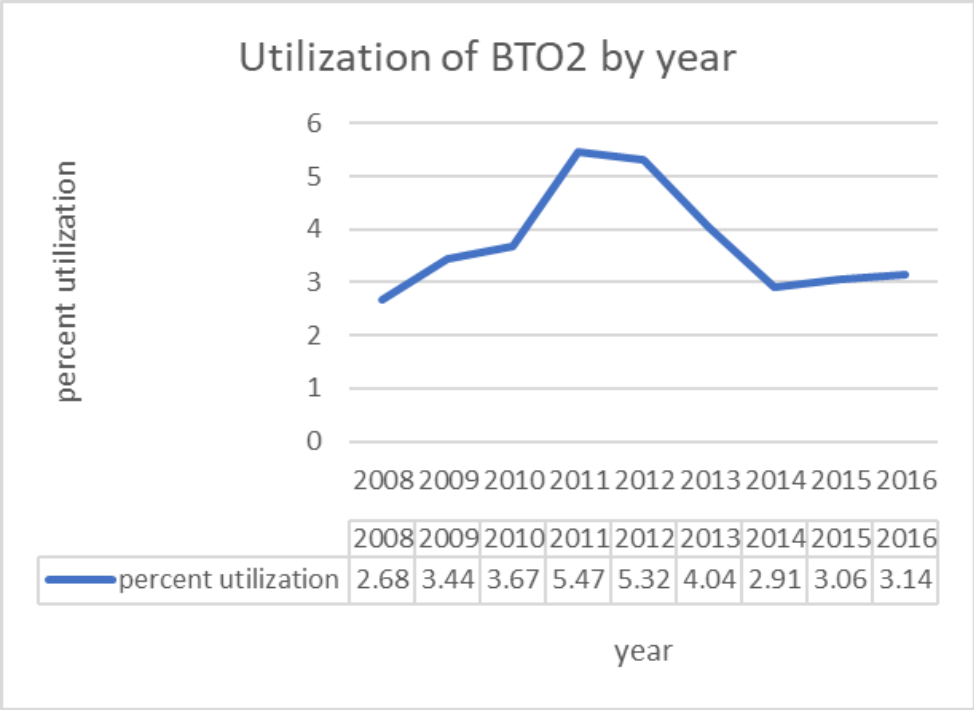

Figure 2

Table 3. Propensity matched sample characteristics

Event	**Risk Difference**	**95% CI**	**p**
Mortality or discharge to hospice	-0.05	(-) 0.09- 0.02	0.002
ARDS	-0.02	-0.04-0.001	0.06
Event	**Mean Difference**	**95% CI**	**p**
ICU length of stay	3.09	2.3-4.05	0.0001
Hospital length of stay	3.26	1.55-4.97	0.0001
Ventilator days	2.51	1.56-3.46	0.0001

Figure 3

Table 4. Crude data BtO2 plus ICP monitor vs ICP monitor only

Descriptive Patient Variables	ICP monitor	BtO2 plus ICP monitor
Number (%)	34155 (96.2%)	1346 (3.8%)
Age in years (SD)	40.3 (SD 17.2)	38.7 (SD 16.4)
Male	26,297 (77.0%)	1,049 (77.9%)
Female	7,853 (23.0%)	297 (22.1%)
Race/ethnicity		
White	22,394 (65.6%)	851 (63.2%)
Asian	581 (1.7%)	44 (3.3%)
African American	3,915 (11.5%)	109 (8.1%)
Hispanic	4,684 (13.7 %)	187 (13.9%)
Other	1683 (4.9%)	99 (7.4%)
Payor		
Private/commercial	9,509 (27.8%)	348 (25.9%)
Medicare	3,426 (10.0 %)	110 (8.2%)
Medicaid	5,943 (17.4%)	(220 (16.3%)
Other	14,022 (41%)	547 (40.6%)
Descriptive Clinical Variables		
Injury Mechanism (a)		
Motor vehicle trauma (motorcyclist, cyclist, pedestrian, other)	17,015 (49.8%)	699 (51.9%)
Fall	6,454 (18.9%)	311 (23.1%)
Firearm	1,430 (4.2%)	37 (2.8%)
Pedal cyclist, pedestrian, other transport	2,444 (7.2%)	100 (7.4%)
Struck	1,604 (4.7%)	63 (4.7%)
Others	5,208 (15.3%)	136 (10.1%)
Emergency Department GCS	3.95 (SD 1.6)	4.03 (SD 1.7)
Injury Severity Score	29.30 (SD 11.4)	30.56 (SD 11.6)
ED Systolic Blood Pressure	136.60 (SD 35.0)	136.75 (SD 34.2)
ED Heart Rate	96.3 (SD 28.2)	95.9 (SD 27.2)
Comorbidities		
Prior CVA / neurologic deficits	517 (1.5%)	19 (1.4%)
Respiratory disease	1,112 (3.3%)	63 (4.7%)
Hypertension	5,038 (14.8%)	174 (12.9%)
Diabetes	2,302 (6.7%)	68 (5.1%)
DNR status	458 (1.3%)	7 (0.5%)
Bleeding disorder	1,117 (3.3%)	32 (2.4%)
Disseminated cancer / active chemotherapy	87 (0.3%)	4 (0.3%)
Facility Characteristics		
Region		
Northeast	5273 (15.4%)	303 (22.5%)
Midwest	7487 21.9%)	245 (18.2%)
West	7946 (23.3%)	480 (35.7%)
South	12852 (37.6%)	287 (21.3%)
Bed size		
<=200	1,244 3.6%)	3 (0.2%)
201-400	7,333 (21.5%)	270 (20.1%)
401-600	10,515 (30.8%)	695 (51.6%)
>600	15,063 (44.1%)	378 (28.1%)
Teaching status		
Community and non-teaching hospitals	13,884 (40.65%)	681 (50.6%)
University hospitals	20,271 (59.4%)	665 (49.4%)
Crude Outcomes		
In-hospital mortality or discharge to hospice	11,456 (33.5%)	418 (31.1%)
In-hospital mortality	10,837 (31.7%)	406 (30.2%)
ICU length of stay	14.5 (SD 11.3)	16.5 (SD 11.7)
ICU length of stay (among survivors)	17.6 (SD 11.3)	20.0 (SD 11.3)
Hospital length of stay	22.6 (21.3)	24.2 (20.4)
Hospital length of stay (among survivors)	29.1 (22.0)	30.6 (20.4)
Development of ARDS	3,346 (9.8%)	124 (9.2%)
Development of ARDS (among survivors)	2,301 (9.9%)	89 (9.5%)
Mechanical ventilation duration - days*	11.9 (SD 10.2)	13.9 (SD 10.6)
Mechanical ventilation duration (among survivors)	13.9 (SD 10.6)	16.1 (SD 10.8)

Figure 4

CRITICAL CARE 69

Validation of the Tele-Critical Care Risk Stratification Model (TRISM)

Chiedozie Udeh[1], Christina Canfield[1]

[1]Cleveland Clinic, Cleveland, OH

INTRODUCTION: In contrast to bedside practice, tele-critical care (TCC) covers several ICUs. As per the American Telemedicine Association guidelines, a TCC intensivist can monitor up to 250 patients depending on program setup and operations[1]. In this context, good situational awareness helps triage clinician time and attention as necessary, to patients at higher risk of mortality[2]. The Tele-Critical Care Risk Stratification Model (TRISM) is a heuristic score developed to aid situational awareness across TCC patients. It uses only 15 common variables - certain vital signs, lab tests, vasopressor needs, and modes of oxygen delivery. They reflect cardiopulmonary changes, because other derangements result from, or will manifest in these 2 systems. The TRISM yields a score with a cut off of ≥8, selected by the developers as being higher risk. This study aims to retrospectively validate TRISM as a stratification tool for patients' relative risk of mortality.

METHODS: Retrospective cohort study of 27,380 adult patients admitted over 2 years to 8 mixed community and tertiary ICUs with TCC service. TRISM was analyzed as stratification tool for risk of in-hospital mortality, as a binary variable, and a multinomial categorical variable, using the 25th, 50th, and 75th percentiles. Analysis was via chi square test, hazard ratios and concordance index of Cox Regression Frailty models.

RESULTS: 2,247,865 hourly TRISM scores were recorded during the study period. 1,392 (5.08%) of the patients died in hospital. There were 1,310,108 (58.3%) high (≥8) and 937,757 (41.7%) low TRISM scores. Median (IQR) score was 10 (5, 15). The patients who died had significantly more high scores, 1287 (66.9%) than low scores 637 (33.1%). P <0.001. The hazard ratio for mortality in the binary analysis for scores ≥8 was 1.44 (1.31 – 1.58, p<0.001). The Concordance index was 0.79, indicating very good discrimination between high and low risk patients. Analysis by quartiles of hourly TRISM scores found that relative to the top quartile (scores >15), the patients with scores below 15 have lower risk of mortality (all p-values <0.001). Patients with scores 10-15 had half the hazard of those with score > 15 (HR=0.5 (0.44 – 0.57)). Similarly, patients with scores 0-5 and 5-10 had about 3/5ths the hazard of those with scores over 15 with hazard ratios of 0.58 (0.62 – 0.65) and 0.59 (0.53 – 0.66). The concordance index, measuring the score's ability to discriminate/rank high and low risk patients is 0.68, indicating good discrimination.

CONCLUSION: The results demonstrate that TRISM yields an expected distribution of increased risk of mortality with higher scores. The hazard ratios and the concordance indices of 0.79 (as a binary variable) and 0.68 (as rank ordered quartiles of TRISM scores) indicate that the TRISM score accurately ranks patients and discriminates well between higher and lower risk patients. This supports the use of the TRISM as a tool to provide situational awareness for tele-ICU clinicians.

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CRITICAL CARE 70

Transesophageal Atrial Pacing For Shock After Cardiac Surgery

Brendon Hart[1], Michael Lyaker[1], Kyle Ferguson[1]

[1]Ohio State University, Columbus, OH

INTRODUCTION: Transesophageal atrial pacing (TAP) can been used to increase the heart rate of patients who have an intact atrioventricular (AV) node. This modality has several advantages over other forms of pacing; however, there is very little literature describing its use in the critical care setting. Cardiogenic shock after cardiopulmonary bypass (CPB) is a strong predictor of morbidity and mortality[1]. Management is supportive with fluids, vasopressors, inotropic medications and sometimes epicardial pacing. The most common site of epicardial pacing wire placement is the right ventricle (RV). Epicardial ventricular pacing is inefficient due to the non-anatomic path of depolarization and the absence of atrial contraction[2]. We describe the use of TAP as a rescue modality for patients with cardiogenic shock after CPB. We were able to apply it in the setting of intact AV conduction and in combination with epicardial RV pacing for a patient with complete AV block.

METHODS: We present a series of four patients at an academic medical center admitted to the cardiovascular surgery intensive care unit (ICU) with cardiogenic shock surgery with CPB. Cardiogenic shock was defined as hypotension with low cardiac output, elevated lactic acid and inadequate response to fluid boluses. Each patient had epicardial RV pacing wires placed during surgery but no atrial pacing wires. A bipolar esophageal pacing electrode was inserted into the esophagus to the depth of atrial capture with the lowest threshold. The electrode was connected to an external pacing device from the manufacturer. Capture thresholds were between 10 and 20 milliamps using a 10 millisecond pulse duration. Since the fourth patient had AV block, the TAP pacer was triggered by a second external pacer which was connected to it and to the RV epicardial wires. Blood pressure was measured with an arterial line, cardiac output was measured by pulmonary artery catheter thermo-dilution.

RESULTS:

Patient 1: Descending thoracic dissection repair with CPB
- Initial: NSR 60 bpm; MAP 85 mmHg; CO 4.9 L/min
- TAP: 80 bpm; MAP 95 mmHg; CO 5.8 L/min

Patient 2: MVR and Maze; IABP in place
- Initial: Junctional rhythm 65 bpm; MAP of 63 mmHg; CO 4.6 L/min
- TAP: 95 bpm; MAP 75 mmHg; CO to 5.2 L

Patient 3: Coronary artery bypass and MVR; junctional bradycardia 30 bpm (MAP 45 mmHg)
- Initial: epicardial RV pacing 90 bpm; MAP 55 mmHg, CO 2.1 L/min
- TAP: 90 bpm, MAP 74 mmHg; CO 2.6 L/min

Patient 4: Repeat MVR; asystole with complete heart block
- Initial: epicardial RV pacing 90 bpm; MAP 63 mmHg; CO 4.7 L/min
- TAP & synchronized epicardial RV pacing 90 bpm; MAP 69 mmHg CO 5.4 L/min

(NSR = Normal Sinus Rhythm; bpm = beats per minute; CO = cardiac output; MAP = mean arterial pressure; IABP = intra-aortic balloon pump; MVR = mitral valve replacement)

CONCLUSION: In our small series TAP increased both MAP (by 6 to 19 mmHg) and CI (by 13 to 24%) in patients with cardiogenic shock after CPB. The increases in cardiac output resulted from increases in heart rate and the addition of atrial contraction. In the first three patients much of the increase was likely due to the increase in heart rate; however, in the fourth patient, the combined use of TAP and epicardial RV pacing increased MAP and CO compared to RV pacing alone at the same rate. TAP is a minimally invasive and highly reliable modality that can be rapidly deployed in the emergent setting. Successful pacing can be achieved in the vast majority of patients who have an intact AV node. Other forms of emergency pacing in the ICU have significant disadvantages in this setting. Transcutaneous pacing is painful and may cause skin injury. Temporary trans-venous pacing is more invasive and requires considerably more time, skill and specialized equipment to place. Furthermore, other modalities only provide ventricular pacing which lacks the benefit of atrial contraction that is especially important in patients with decreased contractility or RV failure. Prolonged use of TAP, especially with higher currents and heart rates can potentially cause esophageal injury, but severe complications requiring intervention were not identified in the literature[3].

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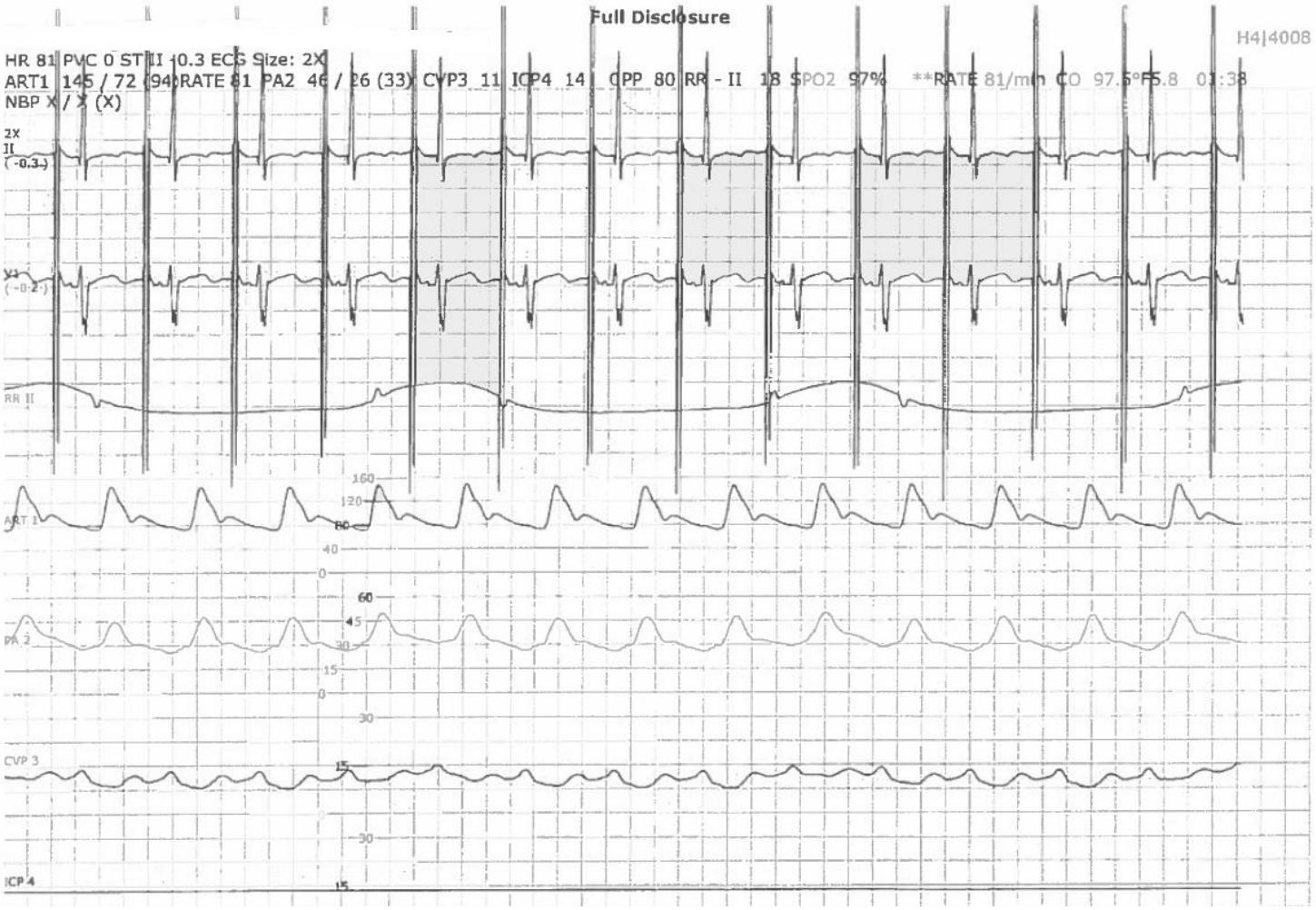
TAP



TAP and Epicardial

TAP and Epicardial Monitor

CRITICAL CARE 71

Intraoperative Phenylephrine Use Is Associated With An Increased Risk Of Acute Kidney Injury After Non-Cardiac Surgery: A Propensity Matched Cohort Analysis

Ashish K Khanna[1], Amit Saha[2], Scott Segal[3]

[1]Wake Forest University School of Medicine, Winston-Salem, NC, [2]Wake Forest School of Medicine, WINSTON-SALEM, NC, [3]Wake Forest University Health Sciences, Winston-Salem, NC

INTRODUCTION: Of the many multifactorial insults that may compromise intraoperative renal perfusion, and contribute to post-operative kidney injury, hypotension including even brief periods of low blood pressures are a major culprit.Intraoperative hypotension is often treated with vasopressors, phenylephrine being by far the most common one. This agent, a direct acting alpha-1 agonist works by increasing systemic vascular resistance and is used both as an intermittent bolus or as a continuous infusion.Much of intraoperative hypotension could also be attributed to excessive depth of anesthesia or an under-resuscitated volume depleted patient, both of which often go under-recognized. While phenylephrine is commonly used to manage intra-operative hypotension, there is conflicting evidence of the association of this agent with renal injury. We tested the hypothesis that the use of intra-operative phenylephrine during non-cardiac surgery is associated with post-operative AKI.

METHODS: A retrospective cohort analysis was performed that included 23,891 adults undergoing non-cardiac surgery with general anesthesia of at least 60 minutes and who received phenylephrine as an intravenous infusion of any duration or as 3 or more bolus doses between July 2016 and December 2019 at the Wake Forest University Health Sciences. A multivariable logistic regression was performed on 5,524 propensity matched patients with a group of non-phenylephrine controls. The probability of getting intra-operative phenylephrine was used as one of the covariates and other intraoperative confounders including total amounts of fluids and urinary output, estimated intraoperative blood loss , and duration of hypotensive minutes (MAP < 65mmHg) prior to initiation of phenylephrine were used as an independent variables for adjustment in the logistic regression. Our primary outcome was the association of the use of phenylephrine with the risk of post-operative AKI defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria. Secondarily, we evaluated the risk of different doses and durations of phenylephrine in varying combinations expressed as quintiles of totals and an exploratory analysis tested the association of the type of delivery of phenylephrine (infusion, bolus or both) with the outcome of renal injury.Statistical analysis was performed in R v3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) using RStudio environment v1.1.456 (RStudio, Boston, MA, USA). Data are summarized as mean and standard deviation or as numbers or percentages.

RESULTS: Our final cohort included 23,891 surgical cases of whom 13,893 (58%) had received phenylephrine infusion or three or greater phenylephrine bolus doses (phenylephrine group) administered during surgery with an 8.9% incident rate of postoperative AKI. Using propensity score matching we were able to match 5,524 (55%) of cases from the phenylephrine group with equivalent number of controls from non-phenylephrine group. A multivariate logistic regression analysis of propensity matched data showed a significant relative risk of 1.19 (95% CI: 1.03 - 1.38; p= 0.02) for developing AKI in patients who received either phenylephrine infusion or at least three boluses or more of phenylephrine after adjustment for crystalloids, colloids, urine output, estimated intraoperative blood loss and hypotensive minutes (MAP <65 mmHg) prior to initiation of phenylephrine in the logistic regression.Amount and duration of phenylephrine use also showed a significantly increased risk of AKI, at quintile 4 and 5 using dose times duration in microgram-minutes, total infusion dose in micrograms, and cumulative dose in micrograms and quintiles 3,4 and 5 of infusion duration in minutes. The risk of AKI progressively increased when phenylephrine was used as only infusion; RR 1.22(95% CI: 1.07-1.38; P=0.002), only bolus doses (3 or more); RR 1.34(95% CI: 1.18-1.51; P<0.001) and both (phenylephrine infusion and 3 or more boluses); RR 1.37(95% CI 1.21- 1.55; P<0.001) (Figure1)

CONCLUSION: The use of intra-operative phenylephrine is associated with an increased risk of post-operative renal injury. Anesthesiologists must consider a balanced approach to the correction of hypotension under anesthesia, including judicious fluids and an appropriate adjustment of the plane of anesthesia.

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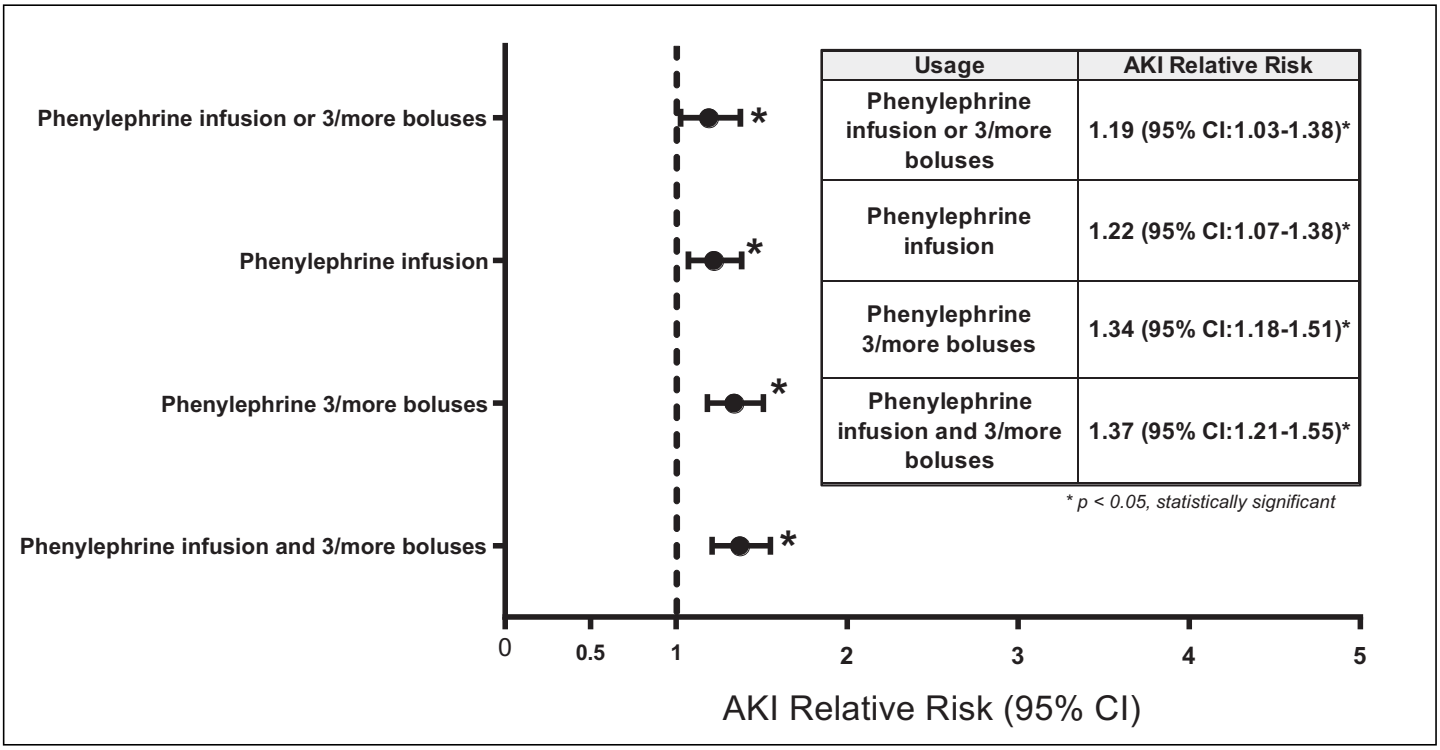

Usage	AKI Relative Risk
Phenylephrine infusion or 3/more boluses	1.19 (95% CI:1.03-1.38)*
Phenylephrine infusion	1.22 (95% CI:1.07-1.38)*
Phenylephrine 3/more boluses	1.34 (95% CI:1.18-1.51)*
Phenylephrine infusion and 3/more boluses	1.37 (95% CI:1.21-1.55)*

** p < 0.05, statistically significant*

Figure 1

CRITICAL CARE 72

Provider-Family Communication in the COVID-Era ICU, Improvements and Barriers: A Quality Improvement Project

Catherine Chiu[1], Rebecca Martinez[2], Dylan Masters[2], Kevin Thornton[3]

[1]University of California, San Francisco, San Francisco, United States of America, [2]UCSF, San Francisco, CA, [3]University of California, San Francisco School of Medicine, San Francisco, CA

INTRODUCTION: Direct family-to-physician communication is a key component of critical care.[1, 2] With the SARS-CoV2 pandemic in full force, hospitals have instituted strict family visitation policies that have made it difficult to track and confirm daily conversations with families about critical clinical updates. Some have attempted to improve communications in novel ways, such as with use of medical students; few have described interventions to improve communication from the existing team members and resources at hand.[3,4,5] This Quality Improvement project has two primary aims. First, to promote improved daily clinical updates for family members via incorporation of the family update status during rounds and in our electronic medical record. Second, to identify population-based disparities that could hinder successful family updates, such as language discordance.[6]

METHODS: Promotion of the project began in August 2020 and was formally audited in September 2020. We limited the scope of this project to our ICUs with a majority of residents on the rounding team, as well as to patients taken care of only by the ICU team (i.e. closed ICU patients). We incorporated use of a free-text box available in our electronic medical record (Epic) and accessible to all providers to track family updates each day. We encouraged residents to mention the last documented family update during their presentations. We also encouraged bedside nurses to discuss any family-related concerns during rounds. We tracked the successful documentation of provider-family updates for each patient day in the ICU. Demographic data, including patients' age, sex, preferred language, family member's preferred languages, and indication for ICU admission were aggregated and analyzed retrospectively. Qualitative analysis of the free-text was also performed.

RESULTS: One month after promotion of this project, the monthly average of successfully-tracked family updates increased from 47% to 75%. Our medical ICU tended to perform better than our surgical ICU by 15%. Race, sex, and patient's primary language did not affect the frequency of family updates with the ICU team. However, language discordance between family and ICU providers did affect the frequency of health communication. Families also received fewer updates on weekends and holidays.

CONCLUSION: As the SARS-CoV2 pandemic continues to affect patients and hospitals, it is important that the families do not get left behind. Our project shows that it is possible to continue aiming for 100% family updates. Language discordance continues to affect communication for both patients and their families. During days when there is less staffing, such as weekends and holidays, documented communication with families decreases. Future steps will include identifying any systems-based changes that may improve successful family updates regardless of language discordance.

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CRITICAL CARE 73

Modifiable Risk Factors In Postoperative Dysphagia for Transplant Patients

Jonathan Schirripa[1], Philip Sommer[2]

[1]New York University, New York, NY, [2]NYU Langone Health, New York, NY

INTRODUCTION: Postoperative dysphagia is a significant event that is associated with poor postoperative outcomes including increased hospital length of stay, increased mortality, and decreased quality of life[1,2]. In regards to post-cardiac surgery patients, Werle et al. described "the most prevalent factors found in the studies assessed were advanced age, use of cardiopulmonary bypass (CPB) and transesophageal echocardiography (TEE) during the surgical procedure, and associated comorbidities (neurological, metabolic, development of postoperative sepsis, and previous heart conditions)"[3]. Many different populations have been studied in regards to postoperative dysphagia, but cardiac and lung transplant patients are at particular risk due to a number of reasons including proximity of the vagus and recurrent laryngeal nerves to surgery. The purpose of this study was to investigate modifiable risk factors in patients undergoing heart and lung transplantation.

METHODS: In this retrospective study, patients were included if they underwent heart, heart-kidney, heart-lung, bilateral lung, and single lung transplant patients at New York University Langone Health from January 2018 to October 2020. A total of 204 patients were identified as having the previous procedures. Patients who had a preexisting diagnosis of dysphagia, esophageal disorders (reflux, hiatal hernia etc.), neurological disorders (stroke, etc.) were excluded. 18 patients were excluded for incomplete documentation, 1 excluded for perioperative death, and 44 excluded for the above pre-existing conditions. In total, 141 patients were included in the final analysis. Patients were then categorized by endotracheal tube (ETT) size (ranging from 7.5mm to 8.5mm). A chart review was then performed, and the presence or absence of postoperative dysphagia was recorded. Diagnosis of dysphagia was made via bedside swallow evaluation, and/or fluoroscopic endoscopic evaluation of swallowing (FEES) with a penetration aspiration score (PAS). A PAS ≥ 2 was considered a positive diagnosis of dysphagia. The presence or absence of dysphagia within each ETT size category was then calculated. P-value was calculated by fisher exact test.

RESULTS: Of the 141 patients selected, 61 were diagnosed with postoperative dysphagia. No patients received an 7.0mm ETT. Of the 7 patients who received an ETT size of 7.5mm, 2 patients were diagnosed with dysphagia. Of the 108 patients received an ETT size 8.0mm, and 42 were diagnosed with dysphagia. Of the 26 patients who received ETT size 8.5mm, 17 were diagnosed with dysphagia. This data demonstrated a statistically significant relationship between ETT size, and postoperative dysphagia with a p-value of 0.036.

CONCLUSION: The results of this study show that in this population of heart and heart-lung transplant patients, ETT size had a statistically significant relationship with postoperative dysphagia. Clinicians often cite reasons of decreased airway resistance and ease of bronchoscopy for using a larger ETT. This study suggests that more scrutiny should be given to those reasons when choosing an ETT in order to prevent dysphagia. While there are limitations to this study, it offers insight into future prospective studies on how to reduce dysphagia in this population.

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ETT Size (mm)	(-) Dysphagia	(+) Dysphagia	Sum
7.5	5	2	7
8.0	66	42	108
8.5	9	17	26
Sum	80	61	141

P-value = 0.036 based on Fisher Exact Test

CRITICAL CARE 74

Duration of Deep Sedation During Mechanical Ventilation in the Intensive Care Unit Predicts Delirium Risk After Extubation

Omid Azimaraghi[1], Karuna Wongtangman[2], Luca J Wachtendorf[3], Peter Santer[2], Bijan Teja[4], Balachundhar Subramaniam[2], Matthias Eikermann[5]

[1]Beths Israel Deaconess Medical Center, Harvard Medical School, Boston, United States of America, [2]Beth Israel Deaconess Medical Center, Boston, MA, [3]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [4]University of Toronto, Toronto, Ontario, [5]Beth Israel Deaconess Medical Center, Boston, United States of America

INTRODUCTION: Critically ill, mechanically ventilated patients are typically required to receive balanced sedation to ensure patient comfort, minimize anxiety and facilitate mechanical ventilation. However, sedation is closely linked to patient-centered outcomes such as delirium and immobility. Delirium is associated with increased in-hospital mortality, functional disability and accelerated cognitive decline[1]. Clinical practice guidelines raise concerns that interactions between sedative agents and depth of sedation are insufficiently understood[2]. It is unclear if a specific sedation level and/or specific sedative compound should be preferably used during mechanical ventilation, in order to minimize the risk of delirium after extubation. In this study, we sought to evaluate the association between the duration of deep sedation that patients receive while mechanically ventilated, on delirium-free days after extubation. Conditional on this association, we investigated to what degree this may be mediated by the type of sedative regimens and the underlying illness.

METHODS: 10,517 medical and surgical intensive care unit patients aged ≥18, mechanically ventilated >24 hours admitted to nine intensive care units (ICUs) from 2008 to 2019 were included in this hospital registry study. Proportion of deep sedation during mechanical ventilation was defined as percentage of days with deep sedation during mechanical ventilation. Level of consciousness was recorded at least every 4 hours. Deep sedation was defined as mean Richmond Agitation and Sedation Scale (RASS) ≤−3. Delirium-free days were defined as number of days within the first 14 days after extubation during which patient was alive, without delirium (Confusion Assessment Method negative) and not in coma (RASS>-3)[3]. For better comparison between an individual's cumulative burden from sedative and analgesic medications during mechanical ventilation, we calculated the Sedation Burden Index (SBI). To calculate the SBI, the cumulative drug dose administered to each individual was divided by the drug dose administered plus the minimum recommended daily dose during mechanical ventilation[4]. The primary sedative agent was defined as drug used with highest daily average effective dose during mechanical ventilation. Analyses were adjusted using a priori defined confounders relative to the outcome.

RESULTS: Approximately half of the patients were delirium-free during the first two weeks after extubation (54.5%, 5,740/10,517). The mean number of delirium-free days was 9.9±5.8 (mean ± standard deviation). On average, patients spent one-third of their mechanical ventilation period (28.2±32.0%) deeply sedated. Benzodiazepine and propofol-based sedation were used in 43.6% and 39.0% of patients, respectively. Negative binomial regression analysis revealed that higher proportion of days during mechanical ventilation with deep sedation was associated with lower delirium-free days after extubation (adjusted absolute difference -3.1 days, 95% CI -2.7,-3.5; p<0.001; figure 1).Association between proportion of days with deep sedation during mechanical ventilation and delirium-free days after extubation was modified by two conditions; sedative choice (p-for-interaction=0.001) and presence of organ failure (renal and/or liver failure, p-for-interaction<0.001). Propofol-based sedation was beneficial and associated with increased delirium-free-days compared to benzodiazepine-based sedation (adjusted absolute difference 2.92 days, 95% CI 3.34, 2.50; p<0.001). Organ failure was associated with decreased delirium-free days (adjusted absolute difference -2.99 days, 95% CI -3.33, -2.57; p<0.001), and magnified the association of sedative agent used and delirium-free days (adjusted absolute difference -3.8 days, 95% CI -4.8,-2.8; p<0.001).

CONCLUSION: Clinical guidelines suggest using light sedation in mechanically ventilated patients when possible[2]. However, deep sedation may be necessary in patients with ventilator-patient dyssynchrony, and/or in patients with neuromuscular blockade[5,6]. Our data indicate that duration of deep sedation during mechanical ventilation is a predictor of delirium after extubation. Considerations regarding type of sedative agents used and effect of organ failure on risk of delirium are particularly important when patients are deeply sedated for a lengthy period.

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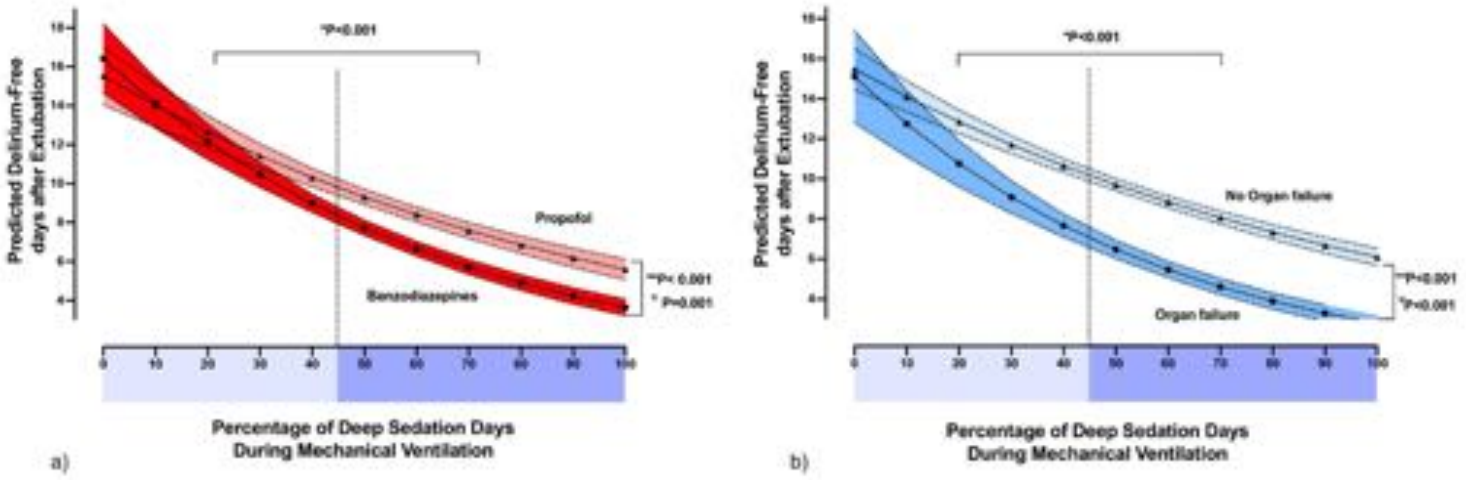

Figure 1: Effects of duration of deep sedation days during mechanical ventilation on post-extubation delirium expressed as delirium-free days.

Higher percentage of days with deep sedation during mechanical ventilation increased the odds of delirium after extubation (lower number of delirium-free days).
Subgroup analysis revealed that (a) benzodiazepine-based sedation, and (b) the presence of organ failure (hepatic or renal failure) magnify the effects of deep sedation on decreasing delirium-free days.
Delirium-free days were defined as the number of days in the first 14 days *after* extubation without evidence of delirium (CAM negative and not in coma: RASS>-3).

*P<0.001 for lower predicted number of delirium-free days in patients with high versus low proportion of deep sedation.

**P<0.001 for an effect modification. Lower odds of delirium-free days in patients a) receiving benzodiazepines versus propofol and b) with hepatic or renal failure.

¥ P for interaction between a) sedative agent choice and b) organ failure with percentage of days with deep sedation during mechanical ventilation.

ICU; Intensive Care Unit, CAM; Confusion Assessment Method, RASS; Richmond Agitation and Sedation Scale

CRITICAL CARE 75

ICU Bedside Timeout Process for Effective Perioperative Communication

Scott A Blaine[1], Jonathan McCollester[1], Omar Malas[1], Margaret A Murray[1], Melissa J Perkins[1], Katherine Kozarek[1], Gozde Demiralp[1]

[1]University of Wisconsin, Madison, WI

INTRODUCTION: Perioperative multidisciplinary communication is a crucial component in avoiding human error and its associated adverse events. Numerous studies have demonstrated that standardized handoff processes reduce lost or omitted information[1,2]. In 2013, the American Heart Association released a scientific statement on cardiac surgery patients stating that handoff failures were a significant source of error[3]. We developed a standardized timeout checklist and a mandatory process for the transfer of patients from the OR to the Cardiothoracic ICU (CTICU). We anticipate that the exchange of information will improve the clinical outcomes and lead to improved provider satisfaction.

METHODS: Utilizing input from critical care, anesthesia, surgical, and nursing team members, a 1-page timeout checklist was developed with intended use for patients undergoing any cardiac or thoracic surgery anticipated to require CTICU admission post-operatively (Image 1). Checklists were printed, laminated and distributed for use in the ICU and cardiothoracic ORs. The OR team was asked to bring the timeout sheets to the ICU with them and provide the completed document to the ICU RN at the end of the timeout. An electronic survey was distributed 6 weeks post-implementation to all participating teams. The goal was to assess perceived importance of the timeout process, staff satisfaction, and the need to include or remove information from the timeout process. A Likert scale from "strongly disagree" to "strongly agree" was used with an opportunity for staff to provide additional comments and feedback. Our institution utilizes a Patient Safety Net (PSN) event reporting system. For this particular study, we aim to examine PSN reports specifically related to CTICU patients six months prior to the timeout implementation, with the intention of comparing them to data six months post-implementation. We are using the system to collect data on medication errors, invasive line safety concerns, rate of reoperation, and other patient safety concerns.

RESULTS: 90 respondents completed the survey including 29 anesthesia attendings, residents, and fellows; 20 critical care attendings, fellows, and nurse practitioners; 20 critical care nurses; and 21 surgical attendings, fellows, and nurse practitioners. Overall, 74% of participants agreed or strongly agreed that the timeout process improved the quality of information transfer, 74% reported that it improved their understanding of the patient's immediate post-operative goals, and 85% reported that it helped them understand the intraoperative factors that may affect the patient's recovery. However, only 60% of respondents agreed or strongly agreed that they were satisfied with the timeout process with 22% responding neutrally and 18% responding negatively. From March 3 through September 27, 2020, 225 primary cases requiring CTICU admission were performed with 43 reoperations. From September 28 through December 31, 2020, 132 primary cases were performed with 17 reoperations. Data from the PSN system was collected from January 1 through March 27, 2020, prior to implementation of the ICU timeout, and reported 10 medication, 12 communication, and 4 equipment issues. Preliminary data collected post-implementation spans from November 7 to December 30, 2020, and reports 14 medication, 3 communication, and 8 equipment issues. Data collection is ongoing and will continue to provide information about the effect of the timeout process on extubation times and reoperation rates.

CONCLUSION: Our survey data suggests that the timeout process improves the quality of information transfer and aids the ICU team in their management of patients post-operatively. The PSN data, although incomplete, seems to suggest a decrease in communication related errors with no difference in overall patient errors pre- and post-timeout process initiation. With data collection ongoing, we anticipate this study will give us a better understanding of the patient safety issues mitigated by an organized OR to ICU handoff.

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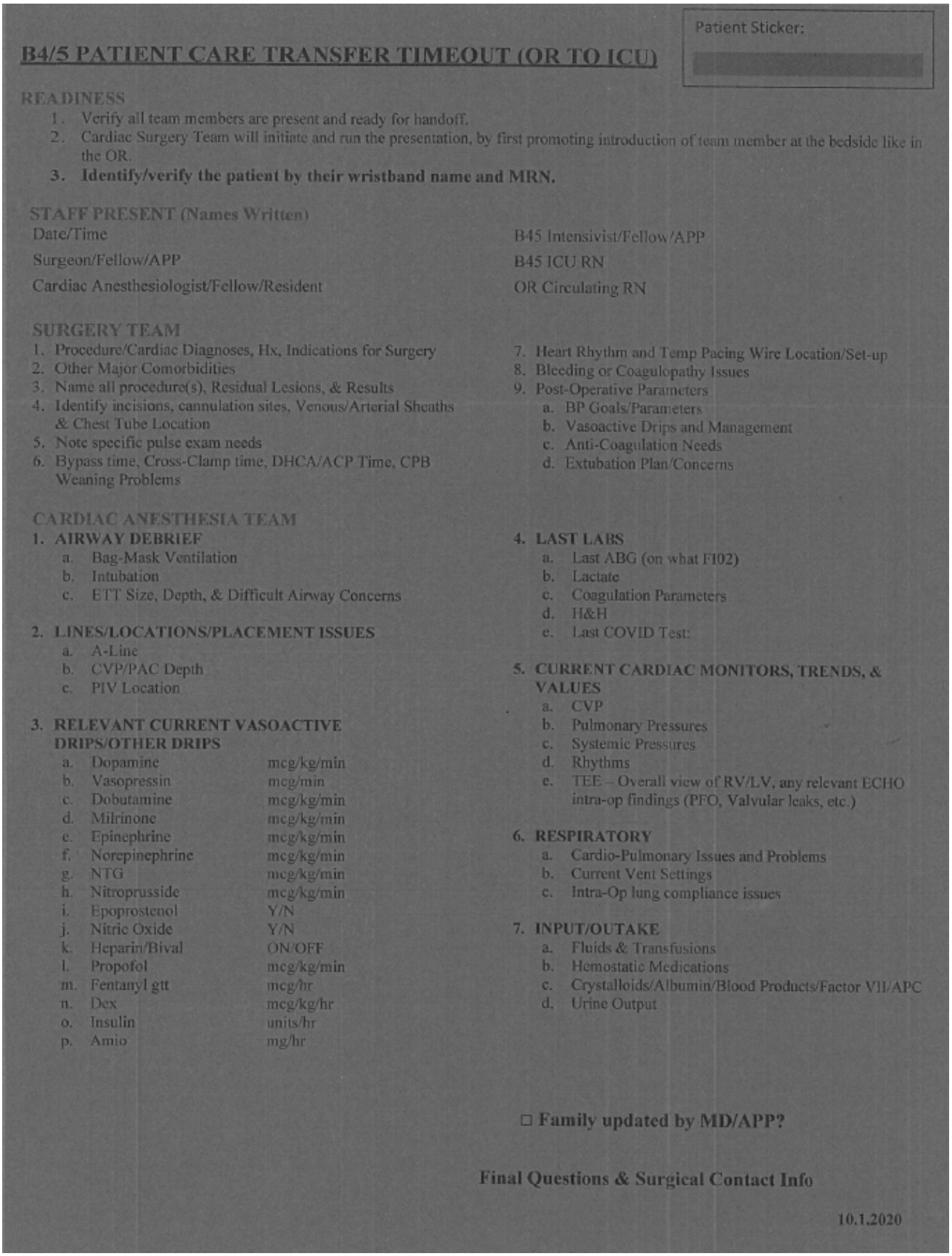

Patient Sticker:

B4/5 PATIENT CARE TRANSFER TIMEOUT (OR TO ICU)

READINESS

1. Verify all team members are present and ready for handoff.
2. Cardiac Surgery Team will initiate and run the presentation, by first promoting introduction of team member at the bedside like in the OR.
3. **Identify/verify the patient by their wristband name and MRN.**

STAFF PRESENT (Names Written)

Date/Time

Surgeon/Fellow/APP

Cardiac Anesthesiologist/Fellow/Resident

B45 Intensivist/Fellow/APP

B45 ICU RN

OR Circulating RN

SURGERY TEAM

1. Procedure/Cardiac Diagnoses, Hx, Indications for Surgery
2. Other Major Comorbidities
3. Name all procedure(s), Residual Lesions, & Results
4. Identify incisions, cannulation sites, Venous/Arterial Sheaths & Chest Tube Location
5. Note specific pulse exam needs
6. Bypass time, Cross-Clamp time, DHCA/ACP Time, CPB Weaning Problems
7. Heart Rhythm and Temp Pacing Wire Location/Set-up
8. Bleeding or Coagulopathy Issues
9. Post-Operative Parameters
   a. BP Goals/Parameters
   b. Vasoactive Drips and Management
   c. Anti-Coagulation Needs
   d. Extubation Plan/Concerns

CARDIAC ANESTHESIA TEAM

1. AIRWAY DEBRIEF
   a. Bag-Mask Ventilation
   b. Intubation
   c. ETT Size, Depth, & Difficult Airway Concerns

2. LINES/LOCATIONS/PLACEMENT ISSUES
   a. A-Line
   b. CVP/PAC Depth
   c. PIV Location

3. RELEVANT CURRENT VASOACTIVE DRIPS/OTHER DRIPS

a.	Dopamine	mcg/kg/min
b.	Vasopressin	mcg/min
c.	Dobutamine	mcg/kg/min
d.	Milrinone	mcg/kg/min
e.	Epinephrine	mcg/kg/min
f.	Norepinephrine	mcg/kg/min
g.	NTG	mcg/kg/min
h.	Nitroprusside	mcg/kg/min
i.	Epoprostenol	Y/N
j.	Nitric Oxide	Y/N
k.	Heparin/Bival	ON/OFF
l.	Propofol	mcg/kg/min
m.	Fentanyl gtt	mcg/hr
n.	Dex	mcg/kg/hr
o.	Insulin	units/hr
p.	Amio	mg/hr

4. LAST LABS
   a. Last ABG (on what FI02)
   b. Lactate
   c. Coagulation Parameters
   d. H&H
   e. Last COVID Test:

5. CURRENT CARDIAC MONITORS, TRENDS, & VALUES
   a. CVP
   b. Pulmonary Pressures
   c. Systemic Pressures
   d. Rhythms
   e. TEE – Overall view of RV/LV, any relevant ECHO intra-op findings (PFO, Valvular leaks, etc.)

6. RESPIRATORY
   a. Cardio-Pulmonary Issues and Problems
   b. Current Vent Settings
   c. Intra-Op lung compliance issues

7. INPUT/OUTAKE
   a. Fluids & Transfusions
   b. Hemostatic Medications
   c. Crystalloids/Albumin/Blood Products/Factor VII/APC
   d. Urine Output

□ Family updated by MD/APP?

Final Questions & Surgical Contact Info

10.1.2020

Image 1

CRITICAL CARE 76

Difference in Survivability of Rats with Cecal Ligation and Puncture Due to Prolonged Exposure to Propofol or Isoflurane

Keita Ikeda[1], Hari Prasad Osuru[1], Robert H Thiele[2]

[1]University of Virginia, Charlottesville, VA, [2]University of Virginia Health System, Charlottesville, VA

INTRODUCTION: Several studies have been conducted on the protective effects of volatile anesthetic agent (VAA) preconditioning improving the outcome of sepsis[1-6]. Several studies have also shown that VAA affects the proinflammatory pathways such as the cytokine response[7-9]. In contrast, Propofol has been shown having no protective effect on sepsis in murine and rat models[10,11]. The aim of this study was to investigate the efficacy of extended exposure to anesthetics, isoflurane and propofol.

METHODS: This study was approved by our Institutional Animal Care and Use Committee. All surgeries were done with a nose cone with 100% oxygen and spontaneous breathing. A 22 gauge intravenous catheter was introduced into the jugular vein for administering propofol and intralipid. Sepsis was induced in the rats by performing cecal ligation and puncture (CLP) through a paramedian incision into the abdominal cavity, with 33% ligation and two punctures with a 16-gauge needle. A rectal temperature probe was used to monitor keep the rats' core temperature and modulate the heating pad in a closed loop control at 37 + 0.5 C. A total of 72 Sprague Dawley rats, 36 male and 36 female, were randomized into four groups – Isoflurane during surgery followed by three days of 0.8% isoflurane, propofol during surgery and 314 ug/kg/hr propofol for three days, isoflurane during surgery and intralipid for three days, and propofol during surgery and intralipid for three days. After the three days, the rats were allowed to roam free in a properly vented, temperature and humidity controlled cage with food and water ad libitum. The surgical concentration of isoflurane was kept at 2%, propofol was maintained at 800 ug/kg/hr maintenance. We chose post op propofol dosing at 314 ug/kg/hr as the minimum amount of anesthetics that would prevent reaction from a toe pinch stimulus for the post op propofol group. Survival data was summarized using Kaplan-Meier curve with Log-Rank (LR) test to determine significance.

RESULTS: LR test for post op anesthetic agent groups showed rats that received isoflurane for three days survived longer than the propofol group (P = 0.0002, Figure 1). Within the post op no anesthetic agent (control) group, the group that received isoflurane during surgery survived longer than the propofol group (P = 0.0081, Figure 2). Within the control group, the male rats did not perform well with propofol against isoflurane (P = 0.2599).

CONCLUSION: There were significant difference in survivability of rats exposured to Propofol or isoflurane, for both control and post op anesthetics group. Though the statistical significance of the 1 MAC treatment group was greater than the controls, the controls group lived longer on average. Rats exposed to isoflurane during the 30-minute CLP surgery improved survivability, which supports the findings of Hermann et al 6. Osuru et al characterized the differences in the response to sepsis while under isoflurane and propofol and found that isoflurane and inflammation may lead to over expression of mRNA involved in the pro-inflammatory MAPK pathway[12]. Also, increased hypoxia-inducible factor-1a expression, despite a lack of hypoxia, increased oxidative stress in the brain, and increased serum lactate (unlike propofol)[13]. These differences between VAA and propofol may indicate that the inflammatory response induced by the VAA, in the absence of infection, is protective as it prepares the body for a future infection[14]. Further work needed to quantify optimum dosage and explain why there might be a gender difference in the effect of VAAs.

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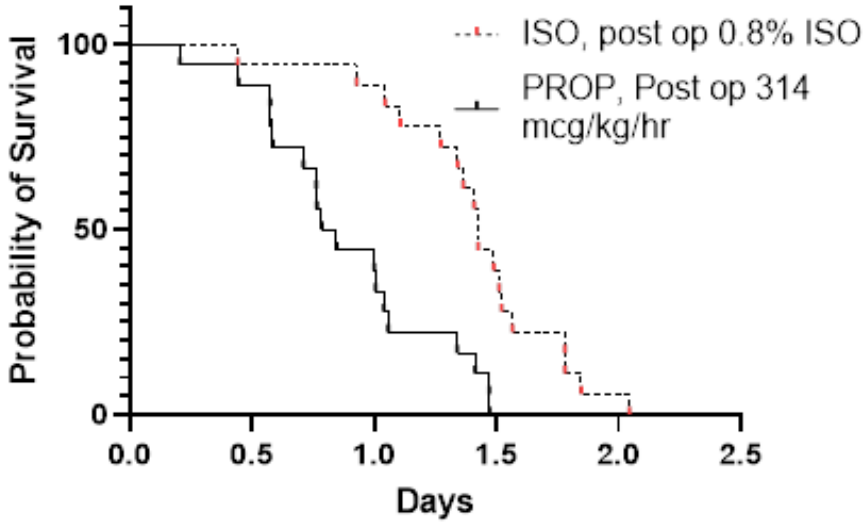

Figure 1

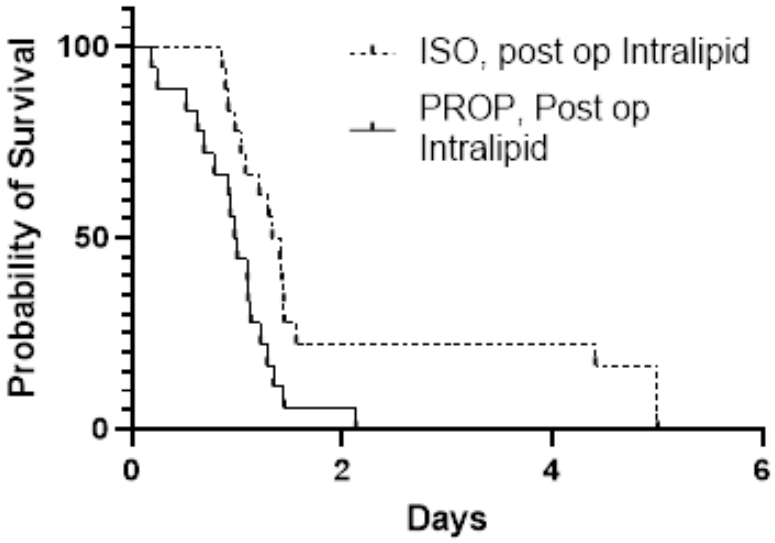

Figure 2

CRITICAL CARE 77

Association of Sedation, Coma, and In-Hospital Mortality in Mechanically Ventilated Patients with COVID-19 Related Acute Respiratory Distress Syndrome

Karuna Wongtangman[1], Peter Santer[1], Luca J Wachtendorf[2], Omid Azimaraghi[3], Elias N Baedorf-Kassis[4], Bijan Teja[5], Kadhiresan R Murugappan[1], shahla siddiqui[6], Matthias Eikermann[7]

[1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [3]Beths Israel Deaconess Medical Center, Harvard Medical School, Boston, United States of America, [4]Beth Israel Deaconess Medical Center, boston, MA, [5]University of Toronto, Toronto, Ontario, [6]Beth Israel Deaconess Lahey Medical Center, boston, MA, [7]Beth Israel Deaconess Medical Center, Boston, United States of America

INTRODUCTION: In patients with coronavirus disease 2019 (COVID-19) associated acute respiratory distress syndrome (ARDS), sedatives and opioids are commonly administered which may lead to an increased vulnerability to neurological dysfunction. We tested the hypothesis that patients with COVID-19 associated ARDS are at higher risk of in-hospital mortality due to prolonged coma compared with other patients with ARDS matched for disease severity.

METHODS: All mechanically ventilated COVID-19 patients from March to May 2020 were identified and matched with patients with ARDS of other etiology. Coma was identified using the Richmond Agitation Sedation Scale (RASS ≤-3). Logistic regression and mediation analyses were used to assess the percentage of comatose days, sedative medications used and the association between COVID-19 and in-hospital mortality.

RESULTS: Using clinical data obtained from a hospital network registry, we matched 114 COVID-19 patients to 228 non-COVID ARDS patients based on baseline disease severity. In-hospital mortality (48.3% versus 31.6%, adjusted odds ratio (aOR) 2.15, 95%CI 1.34-3.44; p=0.002), the percentage of comatose days (66.0±31.3% versus 36.0±36.9%, adjusted difference 29.35, 95%CI 21.45-37.24; p<0.001), and the hypnotic agent dose (51.3% versus 17.1% of maximum hypnotic agent dose given in the cohort, p<0.001), were higher among patients with COVID-19. Brain imaging did not show a higher frequency of structural brain lesions in patients with COVID-19 (6.1% versus 7.0%; p=0.76). Hypnotic agent dose was associated with coma (aCoef 0.61; 95%CI 0.45-0.78; p<0.001), and mediated (p=0.001) coma. Coma was associated with in-hospital mortality (aOR 5.84, 95%CI 3.58-9.58, p<0.001), and mediated 59% in-hospital mortality (p<0.001).

CONCLUSION: Patients with COVID-19 experienced a higher proportion of coma due to higher hypnotic agent doses during mechanical ventilation, which was associated with increased in-hospital mortality. Clinical practices focusing on safely minimizing analgesic and sedative doses and duration of administration should be applied.

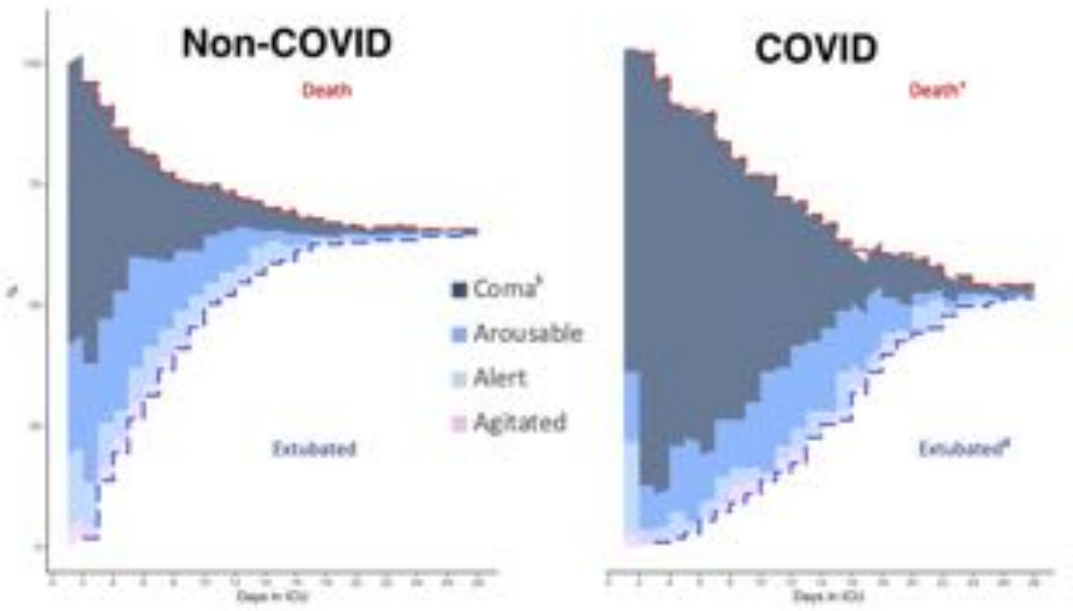

Figure 1. Cumulative incidence of survival and extubation, and patients' cognitive function during mechanical ventilation in patients with ARDS with and without COVID-19.

The cumulative proportion of subjects who died (red line) and those who were successfully extubated (blue line) are shown over time. Death (red line) substantially differed between patients with and without COVID-19 related ARDS. The shaded areas between the red and blue lines represent the Richmond Agitation Sedation Score; Coma (dark blue, Richmond Agitation Sedation Score; RASS ≤-3), arousable (blue, -3< RASS ≤-1), alert (light blue, -1 < RASS ≤ +1), and agitated (pink, RASS >+1) stage. Patients with COVID-19 were more likely to be in a comatose state and had a higher in-hospital mortality.

* p<0.05 for higher in-hospital mortality

# p<0.05 for lower ventilator-free days

$ p<0.05 for higher percentage of coma during the first 10 days of mechanical ventilation

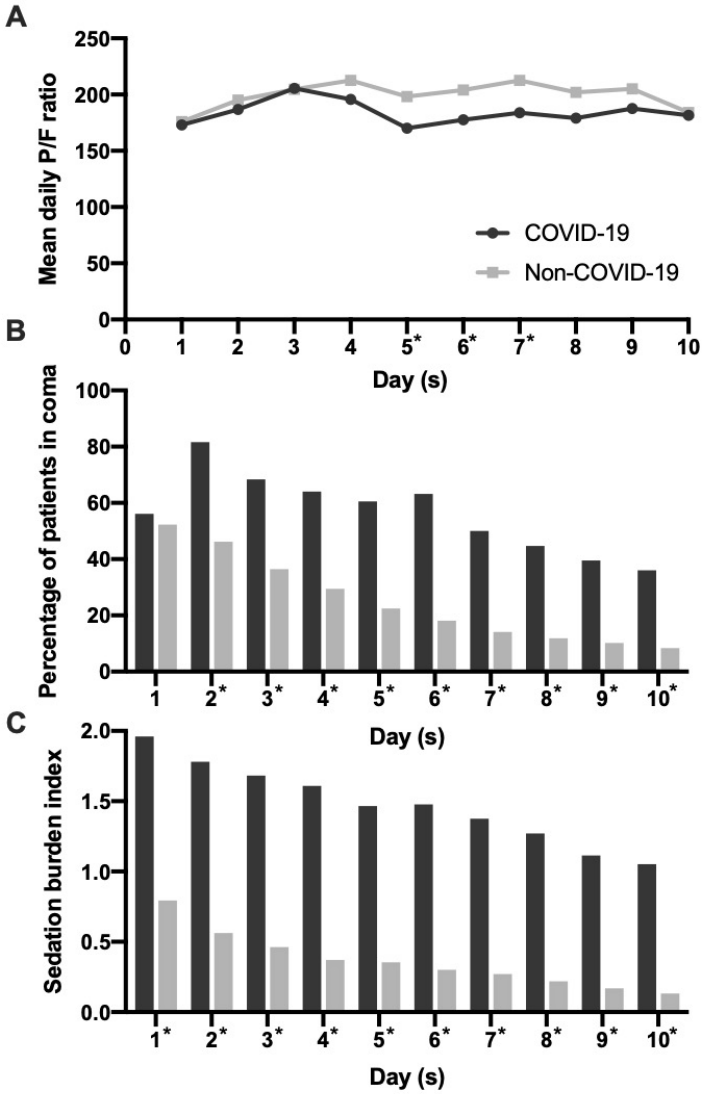

Figure 2. Daily mean P/F ratio, percentage of patients in coma and the Sedation Burden Index.

Daily mean P/F ratio.

Daily percentage of patients in a comatose state.

Daily percentage of patients in a comatose state defined as Richmond Agitation Sedation Score ≤ -3

Daily drug burden index. Sedation Burden Index (SBI) was calculated for an individual by summing the burdens from every sedative medication used on that day, using the equation: SBI=∑Dd+D-, where *D* is the drug dose taken, and *d* is the minimum recommended daily dose.

*p<0.05

CRITICAL CARE 78

The Role of an Amyloid Beta–TRPM2 Interaction in Causing Post-Stroke Cognitive Impairment and Synaptic Dysfunction

Jacob Basak[1], James E Orfila[1], Macy Falk[1], Robert M Dietz[1], Amelia Burch[1], Danae Mitchell[1], Benjamin Wassermann[1], Paco S Herson[1], Nidia Quillinan[1]

[1]The University of Colorado School of Medicine, Denver, CO

INTRODUCTION: Despite the increasing use of thrombolytics and mechanical thrombectomy in acute stroke management, cognitive impairments and memory loss remain a chronic problem afflicting stroke survivors. It is increasingly clear that in addition to neuronal injury following cerebral ischemia, impaired functional networks contribute to long-term deficits in learning, memory, and executive function. The mechanisms underlying these changes are poorly defined, but may involve perturbations in pathways involved in both neurodegeneration and oxidative stress. In this study, we used both behavioral paradigms and electrophysiological assessment of synaptic potentiation in mice subjected to a large-vessel ischemic stroke to evaluate the role of amyloid beta and the ion channel TRPM2 in mediating hippocampal dysfunction after a stroke.

METHODS: Extracellular field recordings of CA1 neurons were performed in acute hippocampal slices prepared 30 days after recovery from transient middle cerebral artery occlusion (MCAo, 45 min) in adult (6-8 week) mice. Long-term potentiation (LTP) was then assessed to evaluate for synaptic plasticity. A behavioral fear conditioning paradigm was used to evaluate contextual memory 30 days after MCAo. An ELISA assay was used to quantify soluble Aβ40 and 42 from the hippocampus of MCAo and sham mice. To evaluate if Aβ42 impairment of LTP is dependent on TRPM2, a calcium-permeable ion channel that regulates neuronal damage during ischemia, slices were treated with Aβ42 oligomers with and without our newly developed peptide inhibitor of TRPM2 (tatM2NX) and LTP was measured. Finally, the ability of TRPM2 to alter cognitive impairments after a stroke were assessed by treating MCAo mice with a tatM2NX inhibitor 29 days following the stroke and performing behavioral analysis.

RESULTS: Recordings obtained in brain slices 30 days after MCAO exhibited near complete loss of LTP (161±9%, n=6 in sham compared to 115±4%, n=7 30 days after MCAO) in the ipsilateral hippocampus. Similar deficits in LTP were observed in the contralateral hippocampus. Impairments in memory function, measured using contextual fear conditioning, were consistent with our LTP findings. MCAO decreased freezing behavior, indicating lack of memory (65±7% in sham mice (n=6) and 37±7% in MCAO mice, n=7). We observed a 61% increase in Aβ40 and a 48% increase in Aβ42 in the hippocampus 30 days after MCAo. Consistent with previous studies, we observed that addition of Aβ42 oligomers (500 nM) impaired LTP (160±9%, n=5 in control compared to 104±6%, n=3 Aβ42). This impaired LTP was prevented with co-application of the TRPM2 channel inhibitor tatM2NX (145±13%, n=3), demonstrating that TRPM2 is a downstream target of Aβ. MCAO mice treated with tatM2NX (20 mg/kg iv injection 24 hr before testing) on day 29 post MCA demonstrated increasing freezing to 72±5% (n=9), suggesting improved contextual memory and highlighting the role of role of TRPM2 channels in post-stroke cognitive impairment.

CONCLUSION: These data indicate that MCAo causes hippocampal dysfunction consistent with post-stroke cognitive impairment. Our data implicates increased levels of soluble Aβ42 in the hippocampus following stroke, resulting in activation of TRPM2 channels and impaired synaptic plasticity. Therefore, reducing soluble Aβ42 and/or inhibition of TRPM2 channels at chronic time points following ischemia may represent a novel strategy to improve functional recovery following stroke.

Subspecialty Abstracts

ECONOMICS, EDUCATION AND POLICY

ECONOMICS, EDUCATION AND POLICY 1

Implementation of a Diversity, Equity, and Inclusion (DEI) Curriculum to Residents: Workshops Targeted at Enhancing Performance Regarding Unconscious Bias, Allyship, and Microaggression

Odinakachukwu Ehie[1], Janette Tang[1], Rebecca Chen[1], John Turnbull[2], LaMisha Hill[1]

[1]University of California, San Francisco, San Francisco, CA, [2]University of California, San Francisco, San Francisco, United States of America

INTRODUCTION: The rate of burnout seems to be more prevalent among women, trainees, and perioperative specialties, particularly general surgery. In 2018, a cross-sectional national survey of general surgery residents (n=7409) demonstrated that 31.9% reported discrimination based on their self-identified gender and 16.6% reported racial discrimination. Furthermore, patients and their families were the highest source for racial discrimination as reported by 47.4% of residents and gender discrimination as reported by 43.6% of residents. There is unfortunately not much guidance for physicians and hospitals to navigate ways of effectively balancing medical personnel's employment rights, patients' interests, and the duty to treat. 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: 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. A needs assessment survey was administered at the end of an introductory session, which highlighted national data regarding mistreatment and discrimination of residents and each workshop session's goals and objectives. The diversity curriculum is being administered in a virtual format to all first-year clinical anesthesia residents and senior general surgery resident (PGY-4 and PGY-5) at UCSF from August 2020 to April 2021. The remaining anesthesia and surgery residents will be surveyed as a control group in April 2021. A post-curriculum survey will be administered after each 2-hour workshop and 6 months later after the fourth 2-hour (DEI) workshop to the participating residents. The anesthesia residents have didactic protected non-clinical time composed of lectures, workshops, and simulations every two weeks where half of the class is expected to attend. This recurring two-hour block was used to coordinate the availability of the senior surgery residents. The University of California San Francisco Institution Review Board deemed this study exempt from review (5/14/20). The survey items were adapted from previously published and validated instruments. Pretest cognitive interviews were conducted with 2 anesthesia fellows to assess the overall clarity, coherence, and balance of each survey question. The surveys were then iteratively revised and retested in a larger sample of 10 second-year and 6 fourth-year medical students prior to administration of the surveys to the resident participants.

RESULTS: We used a previously published assessment tool that consists of 5 Likert-scaled items to assess the concepts around unconscious bias, allyship, and frequency of conflict resolutions around microaggression. Participants provided demographic data including race, gender, sexual orientation, specialty, and previous experience with formal training for conflict resolution. The needs assessment surveys included questions about the curriculum's relevance to their future workplace career, the effectiveness of the facilitation, and whether they would recommend it to other peer colleagues. Lastly, the survey allowed residents to leave comments about what they thought were the most effective portions of the introductory DEI session and suggestions on how to improve the workshop. Twenty-four residents attended the introductory DEI session and completed the needs assessment online survey, giving us a response rate of 100% from twenty first-year clinical anesthesia residents and four senior surgery residents. Of those who responded, 87.5% felt that the workshop demonstrated the importance of the DEI curriculum to their training, that the workshop was relevant to their workplace, and that they would recommend the workshop to their peers (Table 1).

CONCLUSION: While primary care specialties have addressed educational tools for DEI, perioperative specialties have done little to address this gap among trainees within graduate medical education programs demonstrating the need for this curriculum.

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Implementation of a Diversity Curriculum

Table 1. Resident Evaluations of Introductory DEI Workshop (N = 24)

Statement	Strongly disagree	Somewhat disagree	Neutral	Somewhat agree	Strongly agree
This introductory workshop showed me that a DEI curriculum is important to my training.	0.00%	4.17%	8.33%	37.50%	50.00%
I believe this workshop is relevant to my workplace.	0.00%	0.00%	12.50%	20.83%	66.67%
I would recommend this workshop to my peers.	0.00%	0.00%	12.50%	41.67%	45.83%

ECONOMICS, EDUCATION AND POLICY 2

Estimating Preventable COVID-19 Infections Related to Elective Outpatient Surgery: A Quantitative Model

Yuemei Zhang[1], Sheng-Ru Cheng[2]

[1]University of Washington, Seattle, WA, [2]University of Illinois at Urbana-Champaign, Urbana, United States of America

INTRODUCTION: As the number of suspected and confirmed COVID-19 cases in the US continues to rise, the US surgeon general, Centers for Disease Control and Prevention, and several specialty societies have issued recommendations to consider canceling elective surgeries. However, these recommendations have also faced controversy and opposition.

METHODS: Using previously published information and publicly available data on COVID-19 infections, we calculated a transmission rate and generated a mathematical model to predict a lower bound for the number of healthcare-acquired COVID-19 infections that could be prevented by canceling or postponing elective outpatient surgeries. Since Washington (WA) was affected early on by the COVID-19 pandemic in the US and has relatively reliable data on COVID-19 infections compared to other US states, we used WA as a test case for our model.

RESULTS: Our model predicts that over the course of 30 days, at least 75.9 preventable patient infections and at least 69.3 preventable healthcare worker (HCW) infections would occur in WA state alone if elective outpatient procedures were to continue as usual.

CONCLUSION: In the absence of COVID-19 testing, canceling elective outpatient surgeries during the COVID-19 pandemic could prevent a large number of patient and healthcare worker infections. With appropriate data, our model can also provide predictions for different regions and time ranges, and thus may be a useful policy tool.

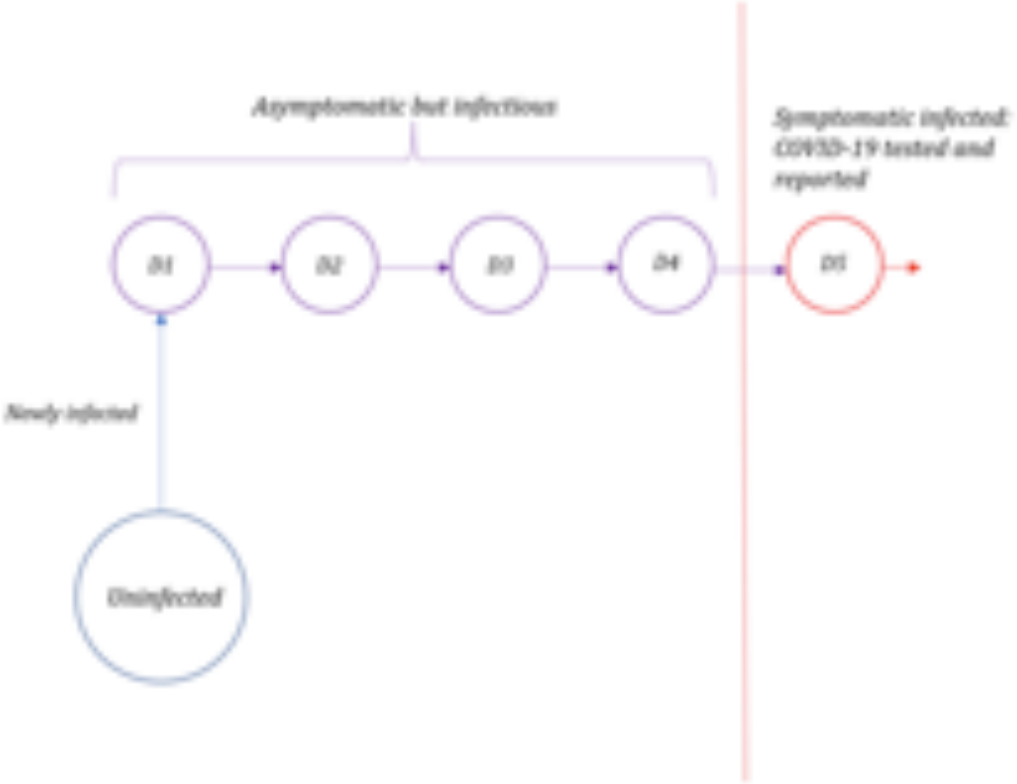

Figure 1. Timeline of Infection for Confirmed COVID19 Cases. After infection, the individual can transmit the infection to others but does not become symptomatic until day 5, at which point they become eligible for COVID19 testing and their infection is discovered and reported.

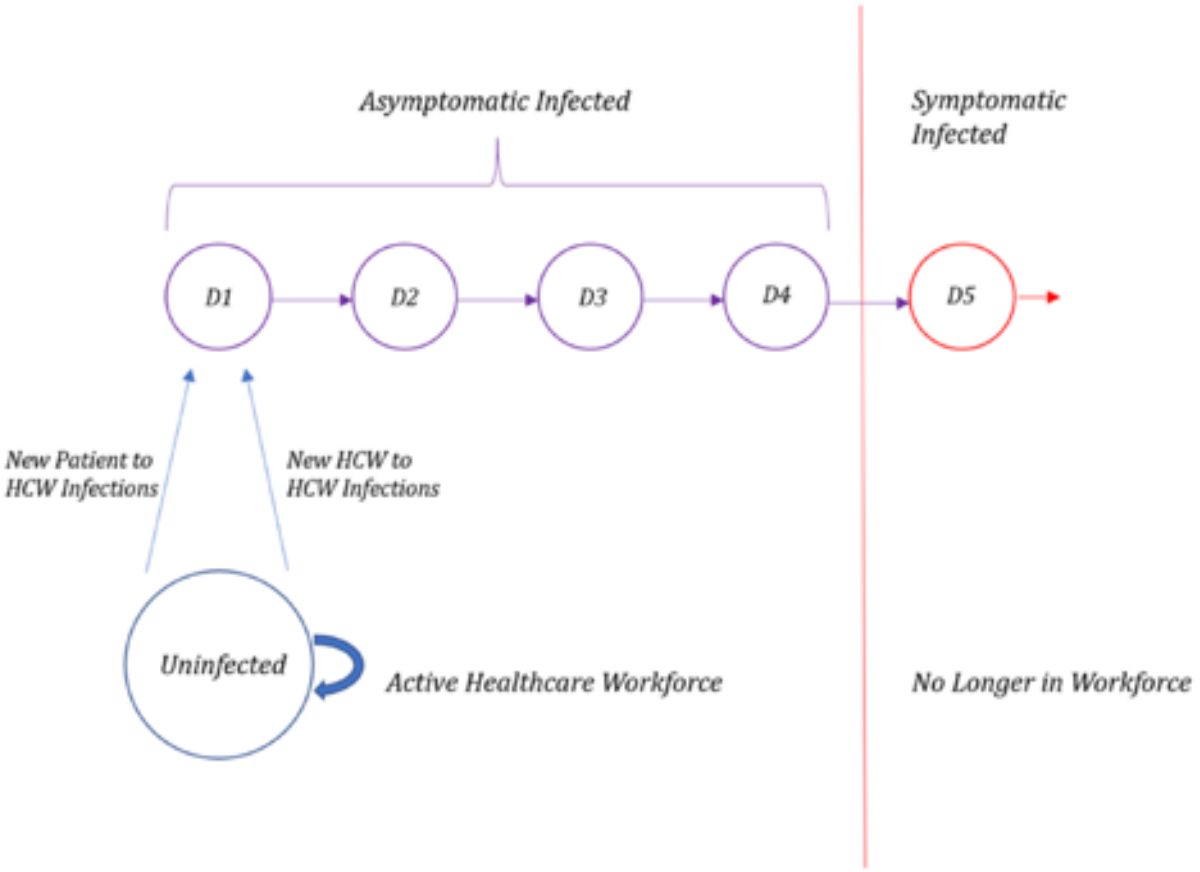

Figure 2. Markov Chain for Healthcare Workers. Healthcare workers (HCW) who are uninfected on any given day can either stay uninfected or become newly infected, at which point they would proceed to day 1 of infection the next day. Individuals who are infected will proceed to the next day of infection with each passing day. On days 1-4 of infection, infected HCW are asymptomatic and therefore continue to fully participate in the workforce, exposing other individuals to the risk of COVID19 infection. On day 5 of infection, infected individuals begin showing symptoms, at which point they may no longer participate in the perioperative workforce.

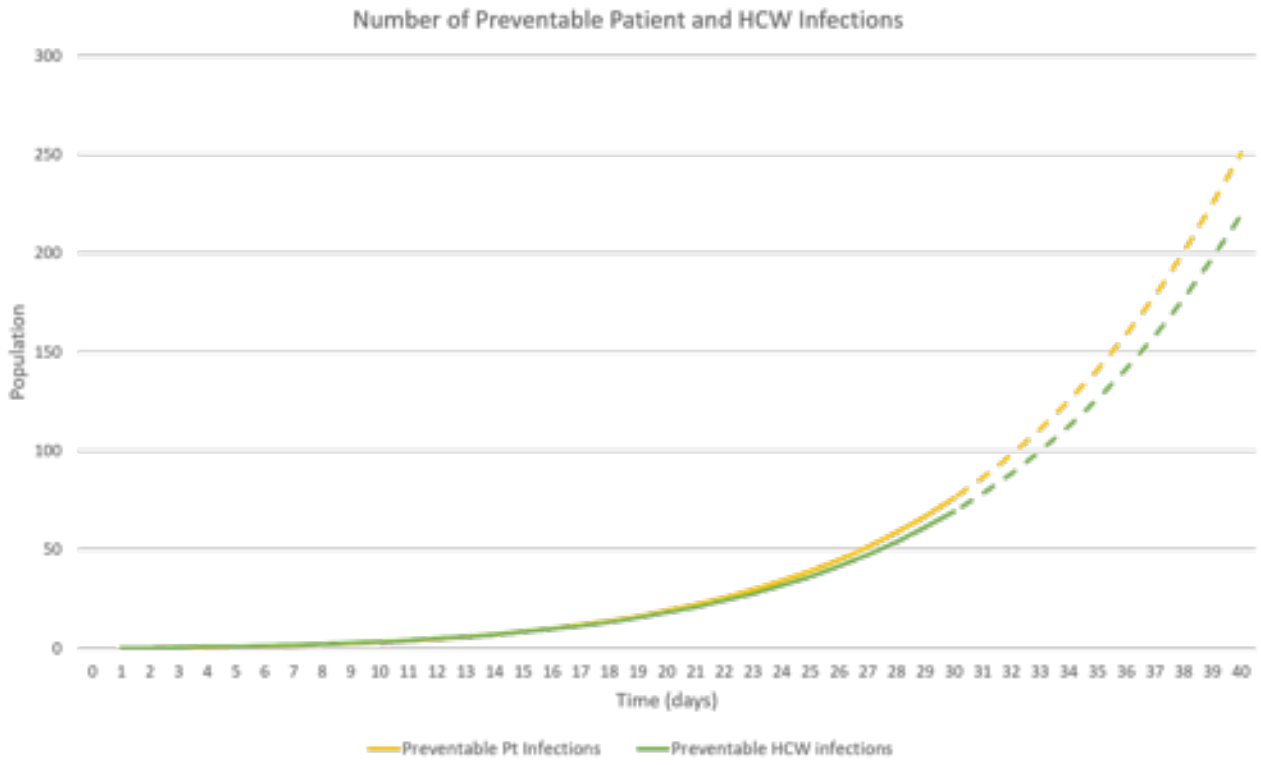

Figure 3. Number of Preventable Patient and HCW Infections. In the early phase of the pandemic, preventable patient infections (yellow line) and preventable HCW infections (green line) exhibit exponential growth, reaching a cumulative number of 75.9 preventable patient infections and 69.3 preventable HCW infections attributed to outpatient elective surgery. The dashed lines represent projections if the same surgical volume were to continue, but that is unlikely to happen given that HCW staffing would become an issue and start to limit case volume.

ECONOMICS, EDUCATION AND POLICY 3

Effects of stress on learning cardiopulmonary resuscitation

Ksenia Vinnikova[1], Frank Herbstreit[2], Cynthia Szalai[3]

[1]Universitätsklinikum Essen, Essen, North Rhine-Wesphalia, [2]University Medical Center Essen, Essen, VT, [3]Universität Duisburg-Essen, Dean's Office, Essen, Germany

INTRODUCTION: Cardiopulmonary resuscitation is a crucial skillset which can be taught using high-fidelity simulation. Simulation is a recognised method for teaching procedural skills[1]. Stress may have crucial impact on the learning process[2,3,4]. The influence of stress and cognitive load on the learning process is not entirely known[5]. Over one semester, we investigated the possible influence of context sensitive stress on the learning Cardiopulmonary resuscitation teaching sessions in a view to assess the possible effects of stress and changes in cognitive load on student performance.

METHODS: Using an experimental approach, 107 students performed baseline and second CPR simulations before and after their teaching sessions. Baseline and second simulations were recorded and graded. Teaching sessions were randomised into two groups. The control group received the traditional CPR training, the intervention group was taught with various stress factors. Students then repeated the simulation at the end of the semester. All simulations were graded using the standard checklist. Stressors mimicked typical emergency resuscitation factors such as anxious relatives and inexperienced colleagues. The cognitive load and perceived stress were quantified using validated questionnaires and scoring scales respectively to assess cognitive load and stress: baseline before the CPR course, before and after all simulations. Data sets were considered incomplete if students did not participate in all simulations. 93 participants submitted a baseline stress questionnaire before the study.107 students enrolled in the simulations, 21 did not participate in baseline performance and 18 were excluded due to protocol violations. 83 students attempted the stress scoring scales, 6 of which were not completed, 15 were excluded from analysis due to protocol violations. 72 participants attempted the cognitive load questionnaire, 19 of which were not completed and 6 were excluded due to protocol violations. A Mann-Whitney-U-Test was used to analyse checklist performances and the unpaired Student's t-test to quantify group differences and questionnaire results.

RESULTS: Identifying characteristics showed a female preponderance, 64,9 %. Thirteen percent of students reported previous medical experience such as nursing or paramedic experience. The mean age was 25 years ranging from 21 to 37. During the baseline simulation we found no differences in performance scores between the intervention group (MRank=31,51) and control group (MRank=37,49), U=476.500, Z=-1.262, p=.207. In the second simulation the scores for the intervention group were (MRank=25,48) and control group (MRank=30,61), U=307.500, Z=-1.214, P=.225. Final simulation results showed for the the intervention group (MRank=31,21), control group (MRank=33,87), U=469.000, Z=-.600, p=.549. The baseline stress score prior to study begin for the intervention group was (M=18.973 SD=7.057), control group (M=16.676 SD=7.972), t(72)=1.312, p=.194. The stress scores before and after the three simulations did not show any differences between the intervention and control group. The stress test score before the final simulation performance was (M=10.094 SD=2.632) and control (M=10.300 SD=2.336),t(60)=-.325, p=.746. After the intervention the score for the stress group was (M=32.875 SD=5.852) and the control (M=31.759 SD=5.069), t(59)=.793, p=.431. Cognitive load scores showed significant differences between the two groups reflecting an increased cognitive load by the intervention group (M=40.23 SD=7.274) and the control (M=33.17 SD=5.393), t(42)=3.503, p=0.001, d=6.578.

CONCLUSION: Results indicate that addition of a stressor to the learning environment does not significantly influence learner's performance in the cardiopulmonary resuscitation during a high-fidelity simulation training as evidenced by the unchanged p values throughout the tests. However, the perceived cognitive load was increased. As medical professionals often face stressful environments, the study shows stress may not negatively affect the learning process[6]. Further research would be required to investigate if various forms of stress could be beneficial[7]. Stress and increased cognitive load may not have any negative impacts on learning.

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ECONOMICS, EDUCATION AND POLICY 4

Implementation of a Clinical Practice Measure to Promote Cost-Conscious Use of Sugammadex

Megan Anders[1], Jennifer S Albrecht[1], Miranda Gibbons[2], Peter Rock[1]

[1]University of Maryland School of Medicine, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, United States of America

INTRODUCTION: Sugammadex (SUG) is a unique cyclodextrin drug indicated for the reversal of neuromuscular blockade induced by rocuronium and vecuronium. In contrast to acetylcholinesterase inhibitors such as neostigmine, which require some spontaneous recovery of neuromuscular function prior to use, SUG can be used to reverse blockade of any depth by administering higher per-kilogram doses. While there is increasing evidence that SUG use is associated with fewer postoperative complications, containment of the associated pharmaceutical cost remains an active topic in anesthesiology.[1,2] The authors hypothesized that implementation of a clinical practice measure designed to promote safe and cost-conscious use would result in lower per-kilogram dosing of SUG.

METHODS: Implementation: After 42 months of unrestricted SUG use, a large academic medical center introduced a clinical practice measure promoting the lower per-kilogram (i.e., 2mg/kg instead of 4mg/kg or higher) SUG dose. Specifically, and in recognition of the fixed cost of the smallest available (200mg) single-use vial, the measure promoted a reduction in doses that were both >200mg and >3mg/kg of SUG. Associated messaging encouraged clinicians to dose neuromuscular blocking drugs to allow use of this dose as often as safely possible. Clinicians received group and individual performance feedback via a web-based dashboard. Analysis: Data on medication administration as documented in the electronic anesthesia medical record were obtained from an IRB-approved anesthesiology perioperative data warehouse. Adult patients undergoing cardiac, head and neck, obstetric, and general surgery were included; characteristics of the patients, surgeries, and anesthetics in each time period were compared with chi square test for proportions and one-way ANOVA or Krushal-Willis test for means as appropriate based on distribution. The primary outcome was SUG dose (mg/kg) among patients who received SUG. The effect of the intervention on average SUG dose was estimated using segmented linear regression. Secondary outcomes focused on rocuronium dosing and selection of reversal medication and were analyzed across three time periods: 12 months prior to SUG introduction on formulary in 5/2016, unrestricted SUG use (pre-intervention), and after clinical practice measure implementation in 12/2019 (post-intervention). The effects of the introduction of SUG and subsequent implementation of the clinical practice measure on average rocuronium re-dose were estimated using segmented linear regression.

RESULTS: Records from 44,124 adult patients undergoing general anesthesia with rocuronium administration were included in analysis of the primary outcome (Table 1). SUG was administered to the majority of patients receiving rocuronium who were extubated in the operating room after introduction to formulary and more frequently after measure introduction (71.3% vs 89.2%; p<0.001; Table 2 and Figure 1). Among patients who received SUG, the mean dose decreased after the clinical practice measure intervention (2.74 mg/kg [SD 1.08] vs 2.53 mg/kg [SD 0.81]; Figure 2). Controlling for the time trend, the intervention resulted in a significant decrease in average SUG dose (-0.43 mg/kg; 95% CI –0.47, -0.39). Figure 3 demonstrates that the use of the lower per-kilogram dose (<3mg/kg), as a proportion of all SUG doses, increased after the intervention. Among patients who received rocuronium and were extubated in the operating room, the introduction of SUG to formulary was associated with a significant increase in average rocuronium redose from 18.4mg to 22.2mg (1.49; 95% CI 0.98, 2.01). The intervention significantly reduced average rocuronium redose from 22.2mg to 21.7mg (-1.11; 95% CI –1.96, -0.26).

CONCLUSION: Implementation of a clinical practice measure of SUG dosing was associated with increased use of lower per-kilogram SUG dose in a single academic medical center with frequent use of the drug before and after the intervention. Pragmatic estimation of cost savings is difficult to derive from electronic medical records as the cost of the drug does not increase linearly per milligram administered; cost is ultimately determined by the size and number of vials used to compound the dose. Further study is required to evaluate safety of the intervention as well as comprehensive pharmacoeconomic impact of low-dose promotion.

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Table 1 – Characteristics of adult patients undergoing general anesthesia with rocuronium blockade since addition of sugammadex to formulary (5/2016-10/2020)

	Pre-implementation, n=35,308	Post-implementation, n=8,816	P- value
Age in years (mean, SD)	55.8 (15.7)	56.5 (15.9)	<0.001
Sex (female)	17,617 (49.9)	4,289 (48.7)	0.10
Case Length in minutes (mean, SD)	207.0 (142.7)	204.5 (139.3)	0.38
Extubated in OR	24,141 (68.4)	6,095 (69.1)	0.60
Service			0.02
Gen surgery	17,451 (49.4)	4,255 (48.3)	
ENT	3,576 (10.1)	962 (10.9)	
Cardiac	4,448 (12.6)	1,083 (12.3)	
Out of OR	1,868 (5.3)	432 (4.9)	
Neurosurgery	4,512 (12.8)	1,203 (13.7)	
Obstetrics	236 (<1)	74 (<1)	
Orthopedics	3,198 (9.1)	805 (9.1)	

Table 2. Trends in reversal practices among adult patients who were extubated in the operating room before sugammadex introduction, after introduction but prior to measure implementation, and post-implementation (2012-2020, n=59,112)

	Prior to SUG introduction	Unrestricted SUG use (pre-intervention)	After measure implementation (post-intervention)	P-value
Reversal with SUG	n/a	18,111 (71.3)	5,564 (89.2)	<0.001
Reversal with neostigmine	22,829 (83.1)	4,505 (17.7)	215 (3.5)	<0.001
Reversal with both SUG and neostigmine	n/a	110 (0.5)	12 (0.2)	<0.001
No reversal administered	4,637 (16.9)	2,903 (11.4)	470 (7.5)	<0.001

Figure 1. Administration of neuromuscular blockade reversal medications to patients extubated in the operating room since the introduction of sugammadex to formulary.

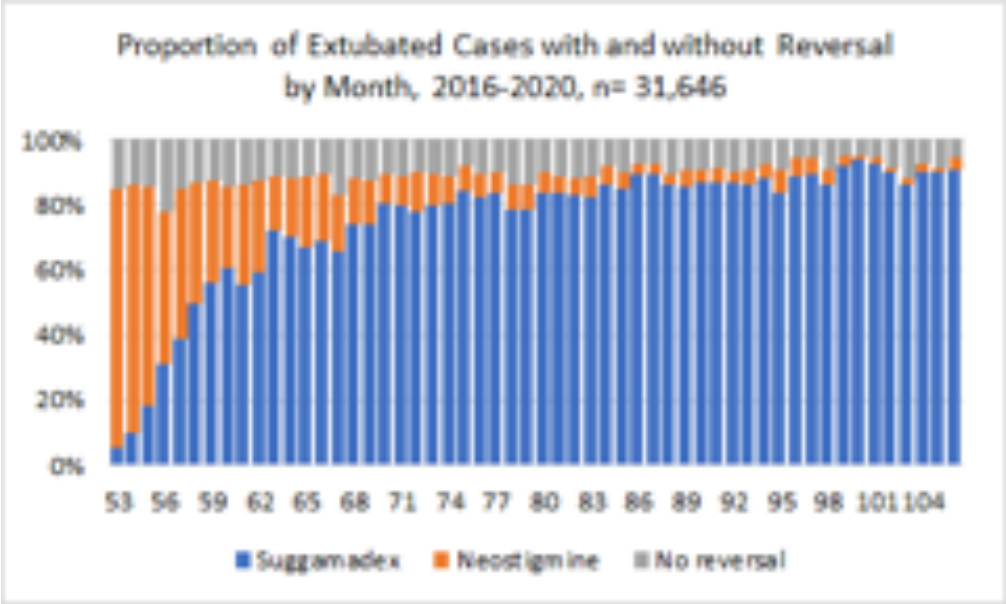


Figure 2. Trend in mean sugammadex dose administered to adult patients with rocuronium-induced neuromuscular blockade before and after the implementation of a clinical practice measure designed to promote lower per-kilogram dosing in late 2019.

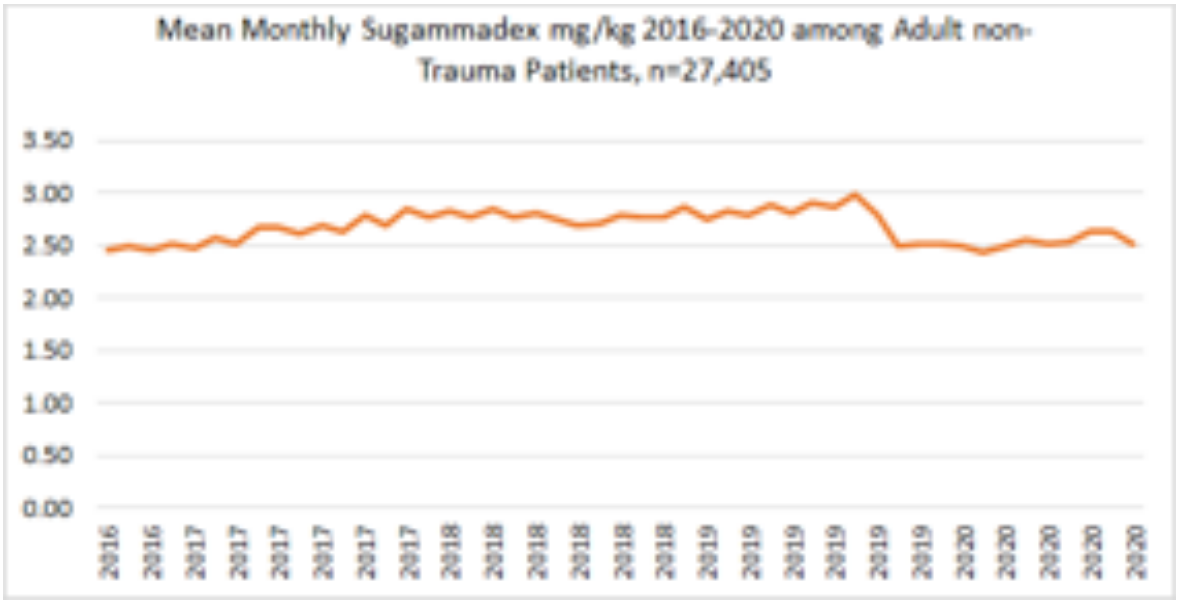
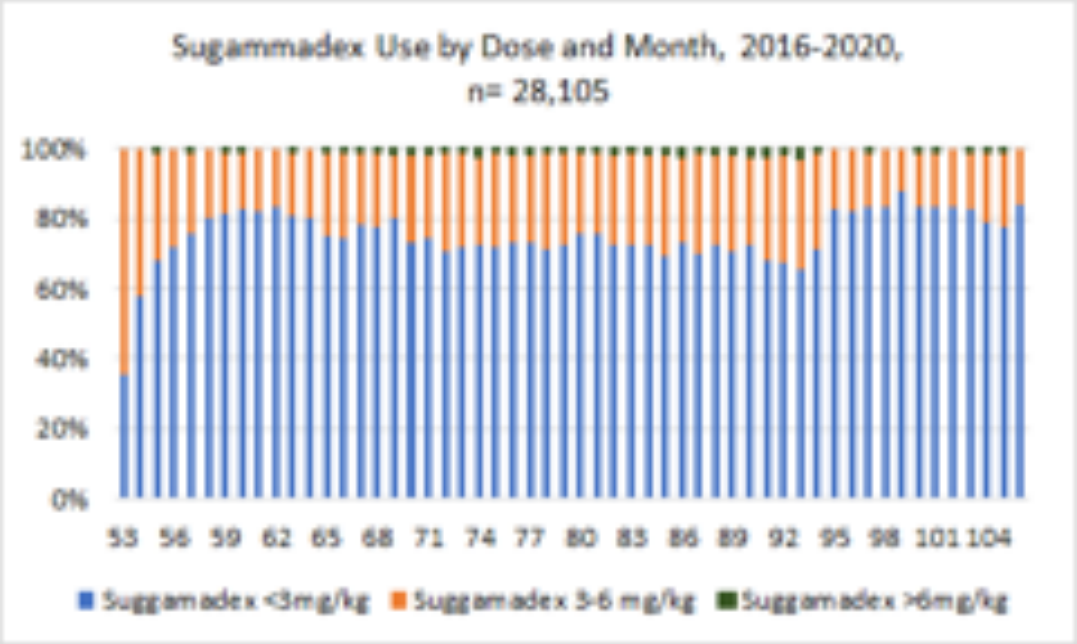


Figure 3. Trends in size of sugammadex dose among adult patients who received sugammadex since introduction to formulary in 2016.



ECONOMICS, EDUCATION AND POLICY 5

How Anesthesiologists Conceptualize and Experience Crisis: A Qualitative Analysis

Lukas Matern[1], Rebecca D Minehart[2], Roxane Gardner[3], Jenny Rudolph[4], Robert L Nadelberg[5]

[1]Massachusetts General Hospital, Boston, MA, [2]Harvard Medical School; Massachusetts General Hospital, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Massachusetts General Hospital, Boston, United States of America, [5]Center for Medical Simulation, Boston, MA

INTRODUCTION: By tacit convention, the term 'crisis' is often used by medical professionals with reference to a 'turning point' characterized by 'a distinct possibility of a highly undesirable outcome.' However, though the anesthesia crisis resource management (ACRM) model is now widely taught and implemented in perioperative emergencies, it is not understood precisely how anesthesiologists conceptualize and recognize crises and thus apply ACRM principles in practice. To address this gap in knowledge, we conducted a prospective and exploratory qualitative analysis aiming to pinpoint themes underlying the definition and features of the concept of 'crisis' in the field of anesthesiology.

METHODS: This prospective observational study was IRB-approved and integrated into a mandatory, recurring ACRM course at a freestanding simulation center. Over a 15-month period, a total of 91 attending anesthesiologists who were enrolled in the ACRM curriculum participated in 20 structured focus groups addressing the questions (1) 'How do you define a crisis?' and (2) 'How do you know when you are in a crisis?' Focus groups were video-recorded and facilitated by the investigators, who performed real-time transcription and coding with member-checking of participant dialogue. A separate researcher then viewed a random sampling of 10 video recordings to verify the accuracy and quality of the coding process. Two investigators next developed and assigned categories to coded material, after which an additional round of analysis was performed to derive themes inductively with constant comparison to the data. Finally, three separate researchers reviewed all themes and categories to ensure validity.

RESULTS: Attending anesthesiologists with a diverse array of professional experiences and backgrounds from across the United States were enrolled in the study (Table 1). Four central themes emerged from 16 categories applied methodically to coded focus group dialogue (Figure 1). According to these themes, the concept of a 'crisis' is characterized or understood by anesthesiologists as: (1) a scenario involving imminent or refractory patient deterioration requiring time-sensitive resource mobilization, (2) a situation evoking negative emotions in the clinician with congruent affective or physiologic responses, (3) a context influenced by or deviating from safety culture, and (4) pronounced changes in a provider-specific sense of situational control.

CONCLUSION: Apart from the conventional understanding of a 'crisis' as a critical event marked by an increased potential for patient harm, anesthesiologists also define and recognize crises as situations that provoke powerful psychological and physiological responses in the provider, that alter the clinician's perception of control, and that hinge upon the principles of safety culture. From these findings, several hypotheses emerge that may guide future research in the realms of patient safety and ACRM-focused education. Namely, for a crisis to be recognized and managed effectively, it is possible that (1) institutions need to cultivate robust cultures of safety, (2) educators should teach ACRM principles with careful attention to clinicians' past experiences and individual skill sets, and (3) anesthesiologists may be best served by acknowledging and normalizing the emotional reactions that inevitably arise in perioperative emergencies.

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Table 1. General participant and focus group characteristics. Focus groups consisted of board-certified/board-eligible U.S. attending anesthesiologists with representation from all recognized subspecialties.

Genders	30 (33%) female, 61 (67%) male
Time from Medical School Graduation	Median: 16 years (range: 4-43)
Regional Affiliations	65 (71%) from local academic centers, 26 (29%) from outside of the greater Boston area
Focus Group Size	Median: 4 participants (range: 2-7)

Figure 1. Themes surrounding the characteristics of perioperative crisis grouped with corresponding categories, definitions, and representative quotes. Dialogue elements were coded in real time with member-checking by investigators. Quotes were obtained from review of video footage.

Theme	Category	Definition of Category	Sample Quote
Crisis is a rare or time-sensitive situation marked by objective clinical deterioration, often refractory to initial treatments, in which help is needed to enact interventions necessary to mitigate the potential for patient harm.	**DNGR**	There is an increased potential for decompensation or serious harm to the patient.	*"For the patient, it means they're decompensating. I mean, that's a crisis."*
	FAIL	A clinician's treatments or interventions fail to produce meaningful effects.	*"Patient's condition [is] worsening despite interventions expected to produce results."*
	HELP	A clinician (1) needs additional help or (2) experiences a mismatch between required and available resources.	*"The resources I have are outstripped by the demands."*
	RARE	The scenario is objectively uncommon or improbable.	*"Beyond the normal scope of practice—nonroutine."*
	REAC	The clinician cannot stand by and must actively respond to a situation.	*"Needs urgent action to turn things around."*
	TIME	The clinician (1) needs to act immediately or urgently or (2) develops a sense that time is running out.	*"I can't do things fast enough."*
	TRIG	Contextual triggers or clinical signs suggest that the patient's status is changing adversely.	*"You've reached that cusp where it can deteriorate very quickly."*
Crisis is a powerful emotional event that may feature physiological responses and negative self-referential thinking that affect the clinician's actions.	**FEEL**	The clinician (1) feels overwhelmed, distressed, or panicked, or (2) otherwise negatively emotionally responds to an event.	*"I'm cursing in my head [and] feel overwhelmed."*
	GRAV	The situation instills a self-referential sense of gravity, personal risk, guilt, or vulnerability in the provider.	*"I'm asking myself: how would I explain this to the family?"*
	PHYS	The clinician experiences (1) signs of sympathetic arousal or (2) impaired cognition as a result of an autonomic response.	*"My heart rate goes up…my ST changes are worse than the patient's."*
Crisis is caused by activation or disturbance of a team's shared sense of safety culture, which may influence the clinician's ability to act.	**TEAM**	Dysfunctional team dynamics or communication errors increase the potential for a poor outcome.	*"[There are] two different event managers arguing back and forth."*
	VOIC	A sense of safety culture is either reinforced or violated by verbal or nonverbal interactions with other providers.	*"It's just not the fault of the anesthesiologist all the time."*
Crisis is marked by a change in a clinician's individual sense of control over a situation, which may be influenced by task load, lack of information, or an inability to determine next steps in management.	**INFO**	The clinician lacks or is unable to access necessary data to manage an event.	*"Is there something else I'm missing?"*
	LOAD	An objective increase in cognitive or physical task load arises.	*"[The] amount of mental energy needed to think of steps gets in the way of treatment."*
	LOSS	The clinician (1) experiences a loss of control, great uncertainty, or chaos or (2) cannot anticipate future events.	*"I don't have a Plan A, B, C, D..."*
	PROV	The clinician's unique prior experiences, specialty training, or individual perspectives drive a change in management.	*"Crisis is in the eye of the beholder."*

ECONOMICS, EDUCATION AND POLICY 6

Publication misrepresentation amongst pediatric anesthesiology fellowship applicants: A retrospective single center cohort study

Ashin Mehta[1], Palak V Patel[2], Thomas Caruso[3], Thomas A Anderson[3]

[1]Medical College of Wisconsin, Wauwatosa, WI, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]Stanford University School of Medicine, Stanford, CA

INTRODUCTION: Introduction: Many medical specialties have found publication misrepresentation in residency and fellowship applications, but pediatric anesthesia fellowship application data is lacking[1-4]. We sought to determine the prevalence of publication misrepresentation among pediatric anesthesia fellowship applications.

METHODS: In this retrospective cohort study, fellowship applications to Stanford University's pediatric anesthesiology fellowship program from 2009 to 2019 were reviewed. Only peer-reviewed journal articles listed as accepted or published were included. Nine additional variables were collected: applicant age, gender, citizenship status, American vs. international medical school, public vs. private medical school, allopathic doctor versus osteopathic doctor, number of years between college and medical school, additional degrees, and application year. The primary outcome was the rate of publication misrepresentation, defined as peer-reviewed journal citations listed on the application that could not be verified or on which the applicant was not listed as an author. Secondary outcomes were the associations between publication misrepresentation and the additional collected variables.

RESULTS: 1293 peer-reviewed journal publications from 880 applicants were reviewed. 3.6% of all citations listed as peer-reviewed journal articles were misrepresented and 9.2% of all applicants with at least 1 publication had ≥ 1 misrepresented publications. 27.7% of publications labelled 'misrepresented' were located in our search of databases but did not have the applicant as an author, and 72.3% could not be located using the search databases. None of the 9 collected variables were significantly associated with publication misrepresentation.

CONCLUSION: Publication misrepresentation exists in pediatric anesthesiology fellowship applications, and admission committees should be cognizant of the issue. While rates were low compared to those found in other studies, we found that one in 11 applications with at least one publication had PM. We hope these, and previously published, findings encourage ERAS and fellowship admissions committees to consider methods to improve application publication accuracy and to discourage PM.

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Figure 1. Publication misrepresentation among applicants to a single pediatric anesthesiology fellowship.

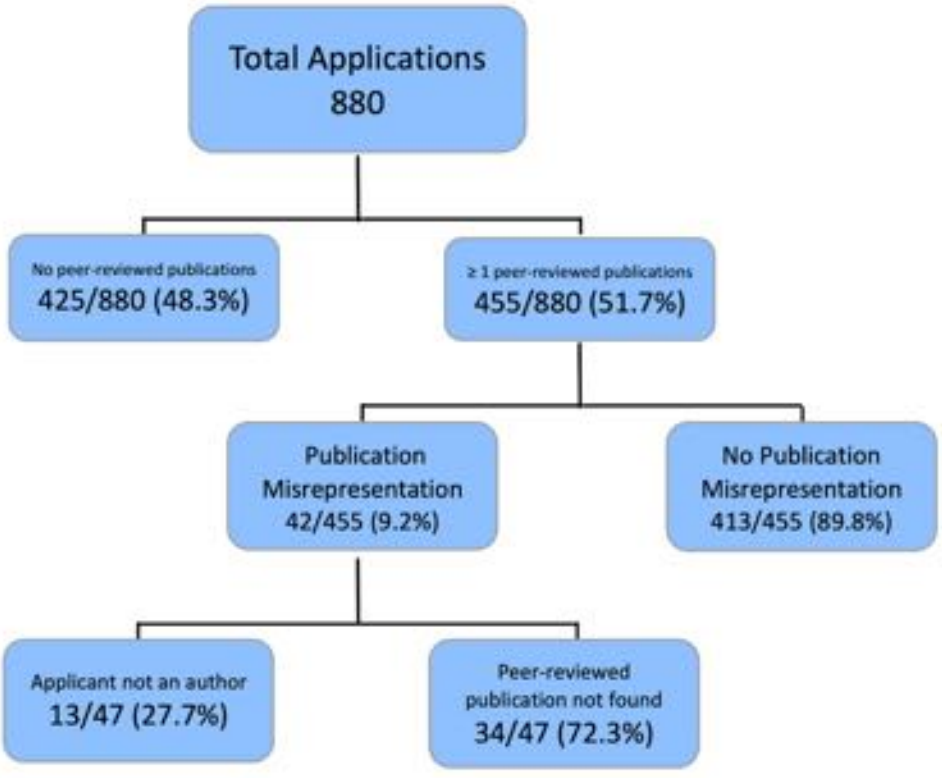
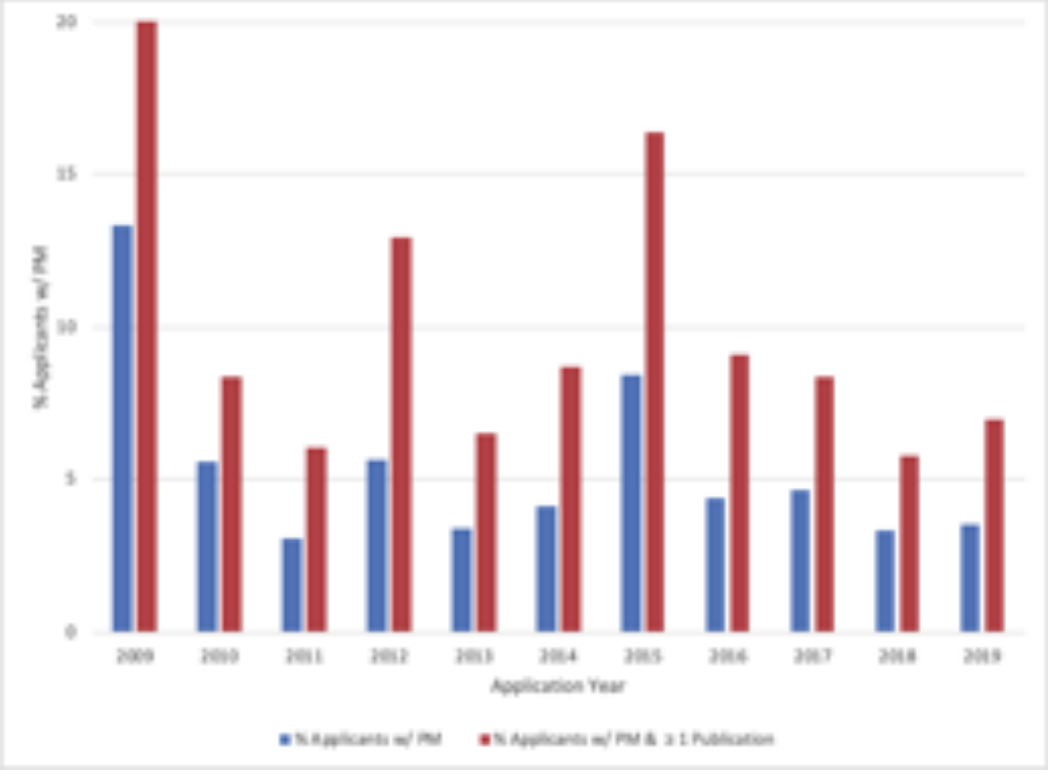


Figure 2. Percentage of PM for all applicants (blue), and percentage of PM for applicants with ≥ 1 listed publication (red) by year.



PM, publication misrepresentation

ECONOMICS, EDUCATION AND POLICY 7

Low health numeracy predicts postoperative complications and increased length of stay

Ryan R Hayter[1], Aaron S Hess[2]

[1]University of Wisconsin School of Medicine and Public Health, Madison, WI, [2]Department of Anesthesiology, University of Wisconsin, Madison, WI

INTRODUCTION: Treatment risks are usually expressed in numbers, and the ability to understand numbers and risks in the health domain is called 'health numeracy'.[1,2] Low health numeracy is independent from health literacy,[1] and is associated with poor health and comorbidities,[3,4] delays in making health decisions,[4] poor comprehension of health risks when making decisions,[5] difficulty in coping with chronic conditions,[6,7] and lower rates of maintaining medical treatments.[8] Low health numeracy jeopardizes patient autonomy, equity, and informed consent, principles essential for the practice of patient-centered medicine.[9] Patients who cannot comprehend health information as presented may make decisions incongruous with their preferences and suffer unanticipated complications or costs.[9] Previously, we found that patients scheduled to undergo surgery under general anesthesia had poor health numeracy and risk comprehension.[10] These patients also overestimated their own health numeracy, suggesting a lack of awareness. A critical unanswered question is whether low health numeracy influences perioperative decision making and outcomes. Our aim was to determine whether these potential associations were detectable among a cohort of patients scheduled for surgery under general anesthesia. Our hypothesis was that poor health numeracy and risk comprehension would be associated with a longer length of stay and a greater rate of perioperative complications.

METHODS: We conducted a prospective cohort study of patients who previously participated in a cross-sectional study of health numeracy prior to surgery under general anesthesia. The study was approved by the University of Wisconsin Hospital and Clinics Institutional Review Board, and all subjects provided written, informed consent to participate. The recruitment of the study cohort and baseline results have been described elsewhere.10 After enrollment, participants were followed for 365 days from the actual date of surgery, or 365 days after the originally scheduled date if the procedure was canceled. Data were collected on the patient, initial hospital stay, and surgical outcomes. We defined a composite outcome of major postoperative complications as any patient who had unplanned ICU admission, readmission within 30 days, reoperation within 30 days, discharge to skilled nursing facility or long-term care facility, or inpatient death.

RESULTS: Of the 213 participants, 199 (93%) had their scheduled surgery. Of those, 120 (60%) were anticipated to require postoperative hospitalization, and 94 (47%) stayed for at least one night. Median American Society of Anesthesiologists (ASA) Physical Status at time of surgery was 2 (interquartile range [IQR] 2-3). Major postoperative complications were associated with a lower health numeracy score (median [IQR] 3 [2-4] vs. 4 [3-5], $p = 0.028$, Figure 1) and higher ASA Physical Status (median [IQR] 2 [2-3] vs. 3 [2-3], $p = 0.037$). In a multivariable logistic regression model, only health numeracy score was significantly associated with major postoperative complications (odds ratio [OR] per 1-unit decrease = 1.46, 95% confidence interval [CI] = 1.02 – 2.09, $p = 0.037$). Length of stay among participants anticipated to require postoperative hospitalization (n=120) was correlated with ASA Physical Status ($\rho = -0.314$, $p = 0.003$) and inversely correlated with health numeracy score ($\rho = -0.268$, $p = 0.004$, Figure 2) highest level of educational achievement ($\rho = -0.216$, $p = 0.023$), and income ($\rho = -0.278$, $p = 0.003$). In a multivariable Cox proportional hazards model, length of stay was associated with ASA Physical Status (hazard ratio [HR] per 1-unit increase = 1.63, 95% CI = 1.19 – 2.23, $p = 0.002$) and health numeracy (HR per 1-unit decrease = 0.78, 95% CI = 0.67 – 0.91, $p = 0.002$).

CONCLUSION: In a prospective cohort of 199 patients who had surgery under general anesthesia, preoperative health numeracy scores were independently predictive of increased postoperative length of stay and major complications. Low comprehension of numbers in a health context may be a risk factor for poor surgical outcomes, excess health utilization, and undesired costs. More research is urgently needed to explore the relationships between health numeracy, patient desires, and perioperative decision making. Preoperative health numeracy screening could potentially identify patients at risk for poor comprehension and preventable complications.

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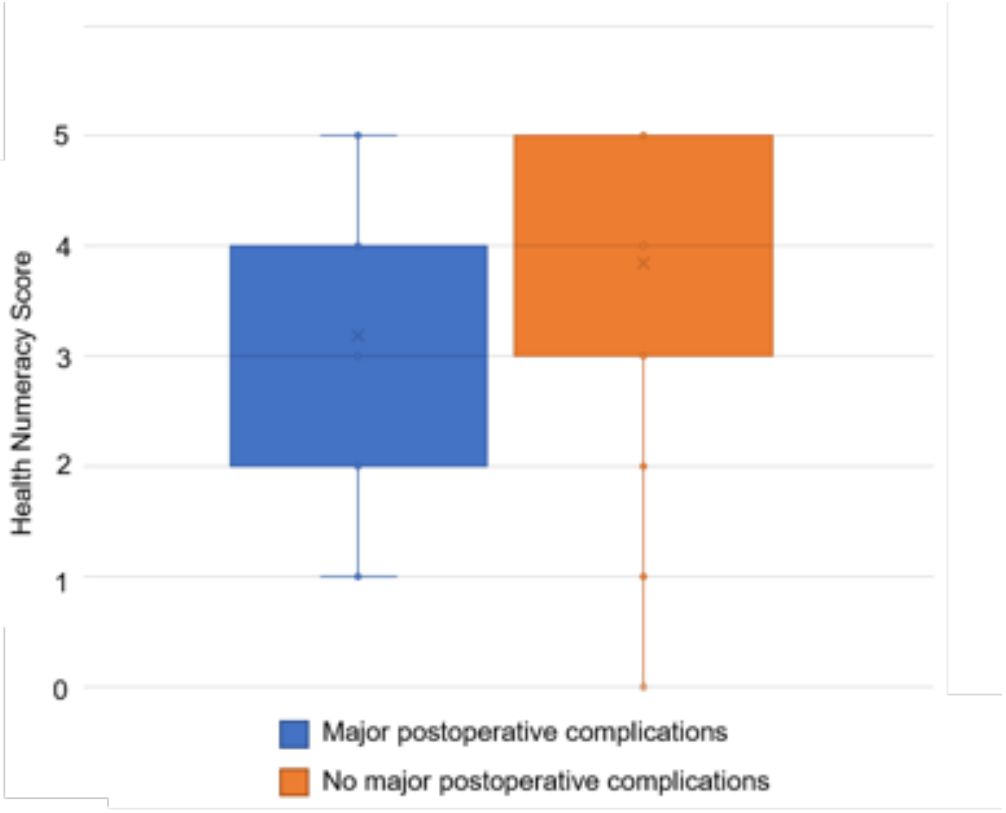

Figure 1: Preoperative health numeracy score among cohort patients who had their scheduled surgery (*n* = 199) and did (blue) or did not (orange) suffer major postoperative complications, defined as unplanned ICU admission, readmission within 30 days, reoperation within 30 days, discharge to skilled nursing facility or long-term care facility, or inpatient death.

ECONOMICS, EDUCATION AND POLICY 8

The Anesthetic Room Adjacent to the Operating Room— Mandatory or Outdated?

Hendrik Booke[1], Rolf D Nordmeier[2], Stefan Schad[3]

[1]Kliniken Frankfurt-Main-Taunus, Frankfurt, Germany, [2]Main Taunus Kliniken GmbH Bad Soden, Bad Soden, Hessen, [3]Kliniken Frankfurt-Main-Taunus, Bad Soden, Germany

INTRODUCTION: Nowadays, operation wings are planed with anesthetic rooms adjacent to each operating room. This allows for induction of anesthesia, while in the operating room the scrub nurses and surgeons get prepared for the operation. Having these perioperative procedures paralleled is supposed to save time, thus improving workflow, allowing for a decrease in turn-over-time, and improved OR-efficacy, thus guaranteeing more cases per time[1]. In the here presented study, we challenge the economic advantage of anesthetic procedure rooms, since the anesthetic processes can easily be paralleled within the operating room itself. This saves the invest of building extra anesthetic rooms including its expensive equipment.

METHODS: We moved our Department of Gynecology from an operating room with adjacent anesthetic procedure rooms for induction of and emergence from anesthesia to an operating room without such anesthetic rooms. No other changes were made. We compared work flow and turnover times for 3 months in each setting. For statistical analysis, we used an unpaired Student's t-test. Significance was defined as $p<0.05$.

RESULTS: The results are summarized in Table 1. There was no significant difference in turn-over-time, nor was the operating room itself significantly less occupied with adjacent anesthetic rooms. The OR efficacy, calculated as the ratio of the patients operating time over the related OR-occupancy, did not differ.

CONCLUSION: In the field of gynecology with the majority of cases requiring a general anesthesia, extra anesthetic rooms have no advantage. Kinetics of modern anesthetics allow for fast induction and emergence of anesthesia[2]. Our data show, that adjacent anesthetic rooms do not serve to improve the ORs efficacy. Since technically equipped anesthetic rooms adjacent to the OR are expensive, a return on invest in terms of a higher throughput cannot be achieved. In future, operating wings can be planned without adjacent anesthetic rooms.

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Table 1	operating time (Min)	OR occupany (Min)	turn-over-time (Min)	OR-efficacy (%)
OR with adjacent anesthetic rooms (N=236)	47.5 +/- 47.3	74.7 +/- 57.4	47.6 +/- 18.6	57.4 +/- 40.5
stand-alone OR (N= 254)	50.4 +/- 56.1	75.7 +/- 66.0	41.6 +/- 17.0	58.6 +/- 40.5

ECONOMICS, EDUCATION AND POLICY 9

Representation of women as editors in anesthesiology journals

Kaley McMullen[1], Monica Harbell[2], Molly B Kraus[2]

[1]Mayo Clinic Alix School of Medicine, Scottsdale, AZ, [2]Mayo Clinic, Scottsdale, AZ

INTRODUCTION: Although there has been a considerable increase in female representation in medicine, a gender gap still exists with regards to leadership positions. This gender discrepancy has been identified in the field of anesthesiology, in terms of first and senior authorship, as well as in general composition of editorial boards in Anesthesiology and Anesthesia and Analgesia. The goal of this study is to examine the representation of women in the top high impact anesthesia journals with respect to the hierarchy of different editorial positions.

METHODS: A comprehensive search was performed for anesthesiology journals indexed in the Scimago Journal and Country Rank in May 2020, and the top 20 journals were analyzed. Editorial board members were ranked on a scale of 1-5 depending on their title, with 1 being the highest ranking (editor-in-chief) and 5 being the lowest (associate/assistant editors) (Table 1). Female representation within each category was calculated.

RESULTS: Overall, women occupied 19% of editorial board positions. All editor-in-chiefs (rank 1) and assistant/associate/deputy editor-in-chiefs (rank 2) were males. Females consisted of 17.1% of executive/section/senior editors (rank 3), 17.9% of editors (rank 4), and 20.6% of associate/assistant editors (rank 5) (Figure 1).

CONCLUSION: These findings suggest that, in anesthesiology journals, women are underrepresented at all editorial levels, especially at levels of higher ranking.

Table 1
Editorial title classification and ranking

Numerical Ranking	Editorial Titles
1	Editor-in-chief
2	Associate editor–in-chief Assistant editor-in-chief Deputy editor-in-chief
3	Executive editors Senior editors Section editors Executive section editors
4	Editors Editorial board/international editorial board Editorial office Other editors: Social media editors, Statistical editors, Social media editor, CME editor, Infographic editor, Language editor, Proof editor, Managing editor, Editorial coordinator, Laboratory investigations editor, education editor, review articles editor, update editor, guest editor
5	Associate editors Associate editorial board Assistant editors Guest editors

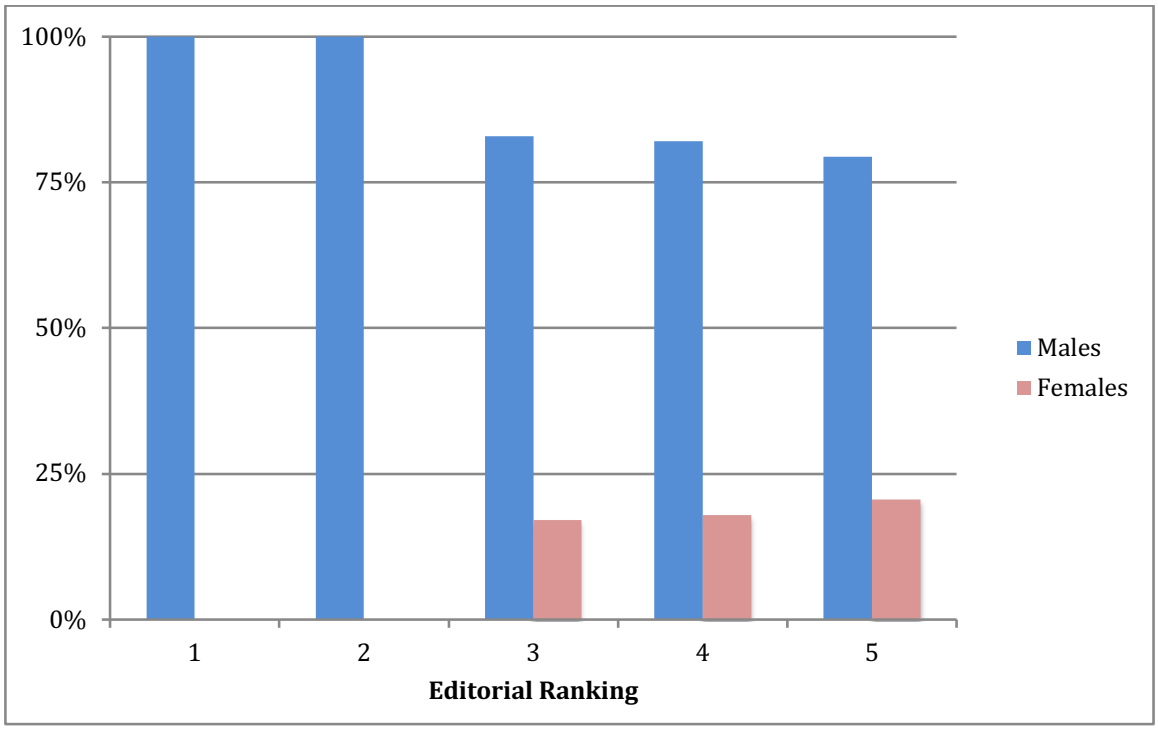

Figure 1. Percentage of men and women in various editorial roles divided into 5 hierarchical categories, with 1 being the highest journal position and 5 being the lowest.

ECONOMICS, EDUCATION AND POLICY 10

Impact of Near-Miss Pediatric Intraoperative Adverse Events on Anesthesiology Residents

James D Taylor[1], Zoe Brown[2], Theresa Newlove[1], Andrew Poznikoff[3]

[1]University of British Columbia, Vancouver, British Columbia, [2]British Columbia Children's Hospital, Vancouver, British Columbia, [3]The University of British Columbia, Vancouver, BC

INTRODUCTION: Pediatric anesthesiology residents, by nature of their training, will be involved in near-miss intraoperative events. The psychological and physical consequences of being involved in these near-miss events is not described in the literature and may not be recognized as significant by their supervising physicians. In comparison, the concept of the 'second victim' and the impact of catastrophic events on physician wellness has previously been well documented.[1] Near-miss intraoperative adverse events have the potential to elicit similar emotional responses to intraoperative death,[2] yet residency programs typically fail to proactively address aftermath management of these events.[3] The purpose of this study was to characterize the impact of near-miss pediatric intraoperative adverse events on anesthesiology residents and determine desirable support and wellness initiatives.

METHODS: Following ethics board approval, a survey administered via REDCap was e-mailed to all second to fifth year anesthesiology residents, as well as 2019 and 2020 graduates of the residency program. The survey was an adaptation of the previously validated Second Victim Experience and Support Tool.[2] This tool asks participants to evaluate their experiences with adverse patient safety events and rank their desirable support options on a five-point Likert scale. When completing the survey, respondents were asked to specifically reflect on any near-miss pediatric intraoperative adverse events. Scores of four or higher represented a negative second victim effect of these experiences or a desirable support option. Descriptive statistics were used for analysis.

RESULTS: Participants by year of residency training are outlined in Table 1. 35 of 66 eligible participants responded to the survey and 30 surveys were fully complete. This corresponds to a response rate of 45%. 27 of 30 respondents indicated at least one second victim response. On average respondents indicated a second victim response to 5 of the survey's 29 questions. Questions with the highest second victim response included fear of future occurrences, fear of patient care inadequacy, and embarrassment. The most desirable forms of support were peer support and a discussion with the residency site director to discuss the event.

CONCLUSION: The majority of anesthesiology residents in this particular program reported a range of both physical and psychological consequences following a near-miss pediatric intraoperative adverse event. Responses reaching threshold for 'second victimization' were related to fears about current and future patient care, as well as personal embarrassment. In addition to intraoperative death, residency programs must acknowledge near-miss intraoperative adverse events as significant and provide necessary support.

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Table 1. Participants by year of residency training

Residency year	n (%)
Second	4 (13%)
Third	8 (27%)
Fourth	7 (23%)
Fifth	6 (20%)
Graduated (2019 or 2020)	5 (17%)
Total Complete Responses	30 (100%)

ECONOMICS, EDUCATION AND POLICY 11

Creation of Simulation Based Curriculum of Perioperative Emergencies for Residents in Anesthesiology

Michael R Kazior[1], Jonathan Nguyen[1], Stefan A Ianchulev[1], Michael Czekajlo[1], Paras Shah[1]

[1]Central Virginia VA Health Care System, Richmond, VA

INTRODUCTION: The use of simulation-based training in graduate medical training programs has become widespread over the last decade[1,2]. An anesthesiology residency program that offers simulation, in combination with a traditional curriculum involving didactic lectures and clinical time, can better prepare trainees to be independent once they have graduated and comfortable managing any perioperative scenario. This has been supported by the Accreditation Council for Graduate Medical Education (ACGME) by including simulation education as part of their milestones project for assessing anesthesiology residents and by the American Board of Anesthesiology (ABA) adding the Objective Structured Clinical Examination (OSCE) to board certification[3]. The Central Virginia Veterans Affairs Health Care System (VA) is located in Richmond, VA and is an affiliate site for the training of residents in anesthesiology from Virginia Commonwealth University (VCU) and every four week block hosts three PGY-2 residents, one PGY-3, and one PGY-4. In the Fall of 2018, the need for simulation in the educational experience at VCU was identified. To address this educational need we proposed a simulation-based curriculum for the management of perioperative emergencies for all levels of anesthesiology learners. We aim to describe the process of curriculum development, content, and early outcomes of implementation.

METHODS: The goals for this project were to create a novel educational experience for the residency program, be relevant to the residents at their specific level of training, and to provide a non-judgmental environment to discuss participant behavior to further learning and inform real time behavior in the future. The first decision made pertained to the content of the simulations to ensure a novel experience. Using simulation to teach perioperative emergencies is the perfect environment for the residents to learn without the threat of real patient harm. This also meets several ACGME anesthesiology milestones in the sphere of Patient Care (PC). After deciding that the simulations would revolve around perioperative emergencies, the content had relevant for the residents in each level of training. Scenarios for the PGY-2 residents included anaphylaxis, malignant hyperthermia, and myocardial infarction. Scenarios for the upper level residents (PGY-3 and 4) included venous air embolism, local anesthetic toxicity, and obstetric hemorrhage. Each simulation scenario would be directly followed by a formal debriefing with the simulation faculty and all participating residents. This was done at the discretion of each faculty member but the Debriefing with Good Judgement model[4] was encouraged. This debriefing session allowed faculty to assess the ACGME resident milestones of Practice Based Learning and Improvement, Interprofessional and Team Communication, and Medical Knowledge. Simulations were scheduled on the first day of each rotation block and organized so the residents were broken up into two groups. A morning session would have two PGY-2s and a PGY-3 or 4 and the afternoon session would have a PGY-2 and the upper-level resident who did not go in the morning. Each resident would be given their own simulation scenario and would enter the simulated environment while the other residents watched from the debriefing room. One to two faculty members would help run the simulation and debriefing, a simulation operations specialist operated the SimMan, and two volunteers played simulated actors (nurse, surgeon, etc). At the end of the simulation session each resident filled out a survey to give feedback on the new curriculum on a 5-point Likert scale.

RESULTS: From September 2019 through October 2020 we completed nineteen simulation sessions involving seventy-nine residents for a total of three-hundred fifty-nine resident training hours. Several survey responses recorded an average Likert scale of 5.00 and included 'the instructor was well-prepared to teach this course', 'this training experience will be useful in my line of work', and 'the instructor provoked in depth discussions that led me to reflect on my performance.' The response that received the lowest Likert score was 'the objectives of the training session were clearly defined' with 4.79.

CONCLUSION: Preliminary data shows our simulation-based curriculum around perioperative emergencies is a novel experience that is relevant to anesthesia residents of all levels of training in an educational environment conducive to learning.

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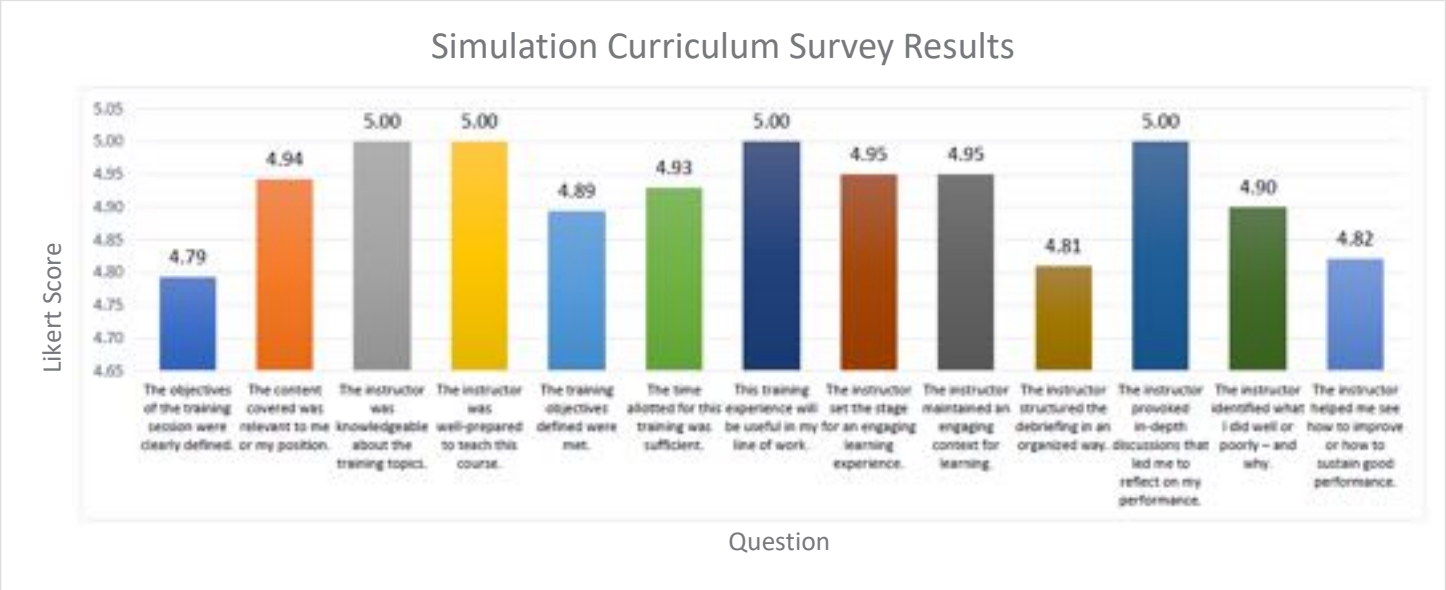

Figure 1: Simulation curriculum survey results. The above questions were present on a post-simulation survey the residents were asked to fill out. A five point 5-point Likert scale (1= strongly disagree, 2= disagree, 3= neutral, 4= agree, 5- strongly agree) was used to score the feedback. Average response values are seen above each bar.

Table 1

Additional Comments Provided on Surveys
It was a good learning environment, low pressure and educational.
The simulation experiences, both low and high fidelity, were realistic, timely, and relevant to anesthesia bootcamp. Instructors were encouraging and approachable, and stress was minimal, which all promoted learning.
It was very fun and good learning. High fidelity. We should do more.
Frantic at times. Slightly confused about a different ventilator than I am used to. Overall comfortable with the simulation.
I felt comfortable throughout. I did not feel like I being judged. It was a safe space to discuss the cases. These scenarios will help me be more comfortable in the OR.
I was able to learn and further tune my knowledge base and skills which at the end of the day had a positive impact on my confidence.
very educational experience good team building, motivated and challenged.
It was a great experience. Very fun and useful for providing how to work through problems in the OR as well as the educational debriefings.
I thought the simulation was appropriate for our current level of training and allowed us to trouble shoot the problems in a safe and educational environment.
Encouraged to keep learning.
Great facility, excellent learning opportunities.
Beneficial debriefing and not only going over the medicine aspects of the sim, but what steps should be taken to stablize the patient / grabbing help sooner.

ECONOMICS, EDUCATION AND POLICY 12

Assessing Interrater Reliability of a Faculty-Provided Feedback Rating System

John D Mitchell[1], Michael J Chen[1], Sara Neves[1], Lauren Buhl[1], Daniel Walsh[1]

[1]Beth Israel Deaconess Medical Center, Boston, MA

INTRODUCTION: Feedback is pivotal to promoting resident growth and development; therefore, it is crucial to assess the quality and utility of feedback being provided.[1] Having an accurate, reliable feedback rating system can help programs ensure accurate, reliable assessments of feedback, enabling them to assess the impacts of educational interventions aiming to improve the quality and utility of feedback. Our research group previously created a seven-item feedback rating system to accomplish this.[2] However, to this point we have only utilized it as a group where all raters must come to a consensus on ratings. In order to evaluate the scale for use by independent raters, we sought to explore the inter-rater reliability (IRR) of this rating system with faculty educators newly trained on said rating system.

METHODS: [2]Our research group previously created a seven-item feedback rating system developed by three anesthesiologists, each with over 5 years of educational experience.[2] We recruited three anesthesiology faculty volunteers from an academic medical center, including the residency program director and two associate residency program directors. Participants were trained on the seven-item feedback rating system in which the presence or absence of six predefined feedback traits are assessed on a binary scale and the overall utility of feedback with regards to devising a resident performance improvement plan is assessed on an ordinal scale from 1 to 5 (Table 1). Participants were trained as a group by a creator of the rating system via a series of three sixty-minute teleconference workshops and three independent rating exercises using deidentified feedback examples which were previously rated by consensus of the creators of the rating system (Figure 1).[2] During workshops, the trainer polled participants on their ratings and encouraged discussion when ratings differed between members to assess rationale. Each workshop covered 20 feedback comments randomly pulled from the pool of 1,925 previously rated examples and was constructed to have an equal distribution of utility scores (four for each score). The IRR was measured after each independent rating exercise, with results used to identify areas to focus on in subsequent training sessions. The IRR for feedback trait categories was measured using R[3,4] to calculate Gwet's first-order agreement coefficient (Gwet's AC1)[5] and interpreted using Landis & Koch's rule of thumb.[6] Unlike Cohen's Kappa,[7] Gwet's AC1 allows for chance-correlated agreement calculations between more than two raters and is robust against a 'Kappa paradox,' which can occur in datasets where one classification is observed substantially more than the other possible classification(s).8 The IRR for utility scores was measured using R[3,9] to calculate intraclass correlation (ICC - two-way random effects, consistency, multiple raters/measurements),[10] and interpreted using Koo & Li's guidelines.[11]

RESULTS: On the final rating exercise, participants achieved near-perfect IRR on two feedback traits (Gwet's AC1 ≥ 0.81: Actionable - 0.88, Professionalism / Communication - 0.83), substantial IRR on three feedback traits (Gwet's AC1 of 0.61 - 0.80: Behavior Focused - 0.80, Detailed - 0.74, Specific - 0.67), and moderate IRR for Negative Feedback (Gwet's AC1 of 0.41 - 0.6: 0.54). For utility score, IRR on the final exercise was on the cusp of excellent with an ICC of 0.90 (95% CI of 0.80 - 0.96). IRR for each feedback trait and utility score are reported in detail for each rating exercise and for all combined rating exercises in Tables 2 and 3.

CONCLUSION: At the end of a series of training sessions and rating exercises, participants achieved high IRR on six of seven rating categories and moderate IRR on the remaining category. Therefore, when this instrument is utilized by trained, expert educators, reliable assessments of faculty-provided feedback can be made, enabling programs to assess the quality and utility of their feedback and the impact of any educational interventions designed to improve feedback.

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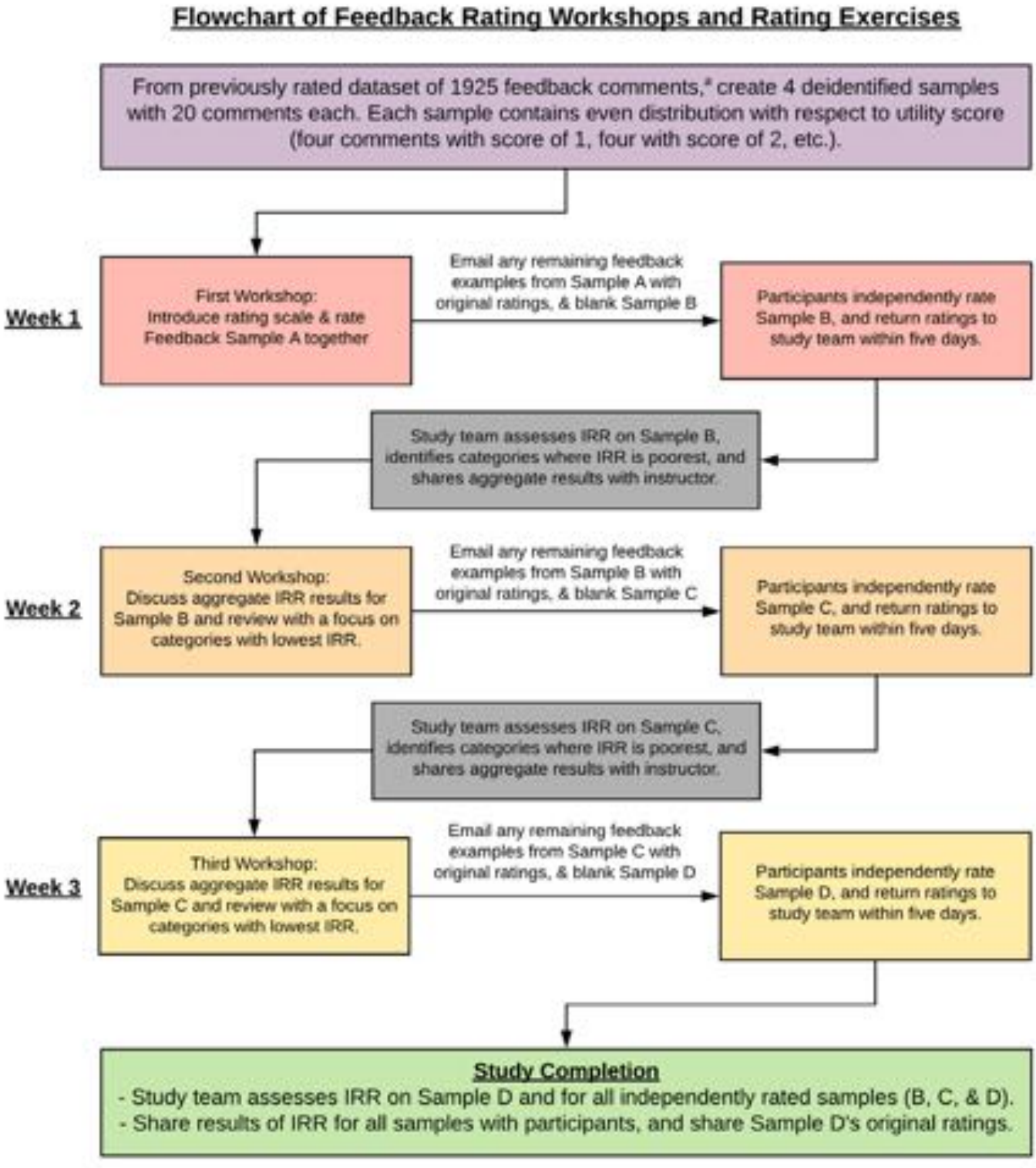
Table 1. Definitions for utility and the six feedback traits with emblematic examples.[a]

Term	Definition	Example[b]
Actionable	Identifies areas for residents to work on improving.	"Consider thinking out loud when going through your difficult airway algorithm."
Behavior Focused	Notes something done by the resident as modifiable or changeable. Raters differentiated the definition of a behavior from a characteristic, or personality attribute of the resident.	Behavior: "The resident placed lines with enthusiasm." Characteristic: "The resident was enthusiastic."
Detailed	Provides ample information describing observed cases or actions which occurred, but not necessarily how a resident performed.	"There were many difficult airway patients today, including a cervical spine injury case."
Negative Feedback	Notes areas the resident could improve on. Does not necessarily have to be hurtful or personal.	"The resident had trouble identifying areas of bronchial anatomy with the bronchoscope."
Professionalism / Communication	Notes an exceptional level of planning, preparation, and/or communication--or a lack of such.	"The resident was prepared with a McGrath and a difficult airway cart in case DL failed, and discussed their intubation approach plan with the OR team ahead of time." "The resident did not have a readily accessible bailout option in case of DL failure."
Specific	Provides information related to the resident's actions.	"The resident used manual inline stabilization when intubating the cervical spine injury patient.
Utility	Assessment of whether feedback can help devise a performance improvement plan for the resident.	High-Utility Example: "Did a great job, just needs to work on thinking and doing things quickly on their feet. For example, after we put in the LMA in our converted MAC, the patient was coughing and not tolerating the LMA. Rather than use their drawn up syringe of propofol and giving a bolus dose, they used the pump to try and deliver a bolus dose which took slightly longer. I think with time in their training, they will naturally continue to improve in this area."

[a]Adapted from table in *Using Machine Learning to Evaluate Attending Feedback on Resident Performance* by Neves SE, Chen MJ, et. al in *Anesth Analg (online ahead of print, 2020)*.
[b]Examples provided for Actionable, Behavior Focused, Detailed, Negative Feedback, Professionalism / Communication, and Specific are synthetic examples created to exemplify statements containing their respective feedback traits. The example for utility is a genuine, deidentified feedback comment left by faculty on a resident's performance which achieved the maximum utility score (5 out of 5); this example was also edited to use gender neutral pronouns.

Figure 1. Flowchart of feedback rating workshops and rating exercises.



[a]Previously rated dataset of 1925 feedback comments was collected during a prior study, where all three raters would come to a consensus on ratings.[2]

Table 2. Table of inter-rater reliability and percent agreement for feedback trait ratings.

	Sample B (n=20)		Sample C (n=20)		Sample D (n=20)		Combined Samples B,C, & D (n=60)	
	Gwet's AC1[a]	Percent Agreement[b]	Gwet's AC1[a]	Percent Agreement[b]	Gwet's AC1[a]	Percent Agreement[b]	Gwet's AC1[a]	Percent Agreement[b]
Actionable	0.68 (Substantial)	83%	0.56 (Moderate)	0.73%	**0.88** (Almost Perfect)	93%	0.70 (Substantial)	83%
Behavior	**0.83** (Almost Perfect)	87%	0.8 (Substantial)	0.83%	0.80 (Substantial)	83%	**0.81** (Almost Perfect)	84%
Detailed	0.54 (Moderate)	77%	**0.81** (Almost Perfect)	0.90%	0.74 (Substantial)	87%	0.69 (Substantial)	84%
Negative Feedback	0.68 (Substantial)	83%	0.47 (Moderate)	0.73%	0.54 (Moderate)	77%	0.56 (Moderate)	78%
ProfComm[c]	0.29 (Fair)	63%	0.55 (Moderate)	0.77%	**0.83** (Almost Perfect)	87%	0.57 (Moderate)	76%
Specific	0.2 (Slight)	60%	0.35 (Fair)	0.67%	0.67 (Substantial)	83%	0.40 (Fair)	70%

[a]Gwet's AC1: Gwet's first-order agreement coefficient.[5] Gwet's AC1 was calculated using R.[3,4] Results for Gwet's AC1 are reported with the value followed by interpretation in parentheses per Landis & Koch's interpretations for kappa values and strength of agreement,[6] and are likewise color-coded as follows:
< 0.00 is poor (unused), 0.00 to 0.20 is slight agreement (red), 0.21 to 0.40 is fair (orange), 0.41 to 0.60 is moderate (yellow), 0.61 to 0.80 is substantial (blue), and 0.81 to 1.00 is almost perfect (green and bold font).
[b]Percent Agreement represents the percent of feedback examples on which all three participants unanimously agreed on whether the feedback trait was present in an example or not.
[c]ProfComm: Abbreviation for Professionalism / Communication trait.

Table 3. Table of intraclass correlation and agreement rates for utility score ratings.

	ICC[a]	Adjacent Agreement[b]
Sample B (n=20)	0.95 (Excellent), 95% C.I. [0.88 - 0.98]	95%
Sample C (n=20)	0.75 (Good) 95% C.I. [0.88 - 0.98]	55%
Sample D (n=20)	0.90 (Good), 95% C.I. [0.88 - 0.98]	95%
Combined Samples B, C, & D (n=60)	0.87 (Good) 95% C.I. [0.88 - 0.98]	82%

[a]ICC: Intraclass correlation - Two-way random effects, consistency, multiple raters/measurements.[10] Reported as the calculated ICC value with interpretation in parentheses followed by the 95% confidence interval. Interpretations for ICC values taken from Koo & Li's guidelines, where values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively.[11] Calculations performed using R.[3,9]

[b]Adjacent Agreement represents the percent of examples on which all three participants' utility score ratings had a range of one or less (ex: scores of 3/4/3, 2/2/2, and 5/5/4).

ECONOMICS, EDUCATION AND POLICY 13

Development of an Educational Template for the Assessment of Vaping Practices by Anesthesiologists

Jane Xu[1], Susanne Tanski[2], Melissa Schwedhelm[2], Dean Jarvis[2], Humnah Khudayar[2], Yvon F Bryan[2]

[1]Geisel School of Medicine at Dartmouth, Hanover, NH, [2]Dartmouth-Hitchcock Medical Center, Lebanon, NH

INTRODUCTION: In the last five years, e-cigarettes have gained widespread popularity as smoking cessation tools and as recreational devices. During this time, reports have found that e-cigarette use, commonly known as vaping, is associated with harmful pulmonary and cardiovascular risks[1]. There has been an increase in hospitalizations and recurrent ICU admissions for E-cigarette and Vaping-associated Lung Injury (EVALI)[2,3]. Despite the health risks associated with e-cigarettes, it may be challenging for anesthesiologists and clinicians to understand and screen for vaping, given rapid changes in e-cigarette technology and patterns of use. We present our development of an educational template on vaping practices and patterns for anesthesiologists to understand the type of vaping devices, vaping-associated pulmonary risks in surgical settings, and assessment of peri-operative concerns related to vaping.

METHODS: This educational template was developed by a group that consisted of an anesthesiologist, neonatologist, pulmonologist, pediatrician, medical student, and research assistant to determine the main aspects of vaping and its health risks in current medical research on e-cigarettes. It was based on medical literature, CDC information, presentations at medical conferences, newspaper releases, and Zoom discussions.

RESULTS: The vaping educational template summarizes the main aspects of vaping (see Figure 1). All vaping devices contain an atomizer, a cartridge with e-liquid, and a battery. The battery powers the atomizer to heat the e-liquid in the cartridge to form an aerosol containing vaping particles, which may lead to respiratory symptoms when inhaled. Popular vaping devices have evolved and vary in their disposability/refill-ability, battery power (wattage), cartridge size, and type of e-liquid used. See Table 1 for an overview of popular vaping devices and their characteristics. See Table 2 for a summary of the reported pulmonary effects of vaping on different human cell types. See Table 3 for an overview of the assessment of perioperative concerns regarding vaping, such as the management of nicotine use disorder and cardiovascular complications.

CONCLUSION: We developed an educational template for teaching anesthesiologists and clinicians the basics of vaping and its effects on pulmonary and cardiovascular health to assist in perioperative assessment. Rates of vaping has accelerated, especially among young people, and the combination of poor indoor ventilation and the current COVID-19 pandemic may worsen the effects of vaping. E-cigarette use has been found to be associated with an increased risk of respiratory symptoms such as chronic bronchitis and asthma that may lead to peri-operative respiratory adverse events, indicating the need for anesthesiologists and residents to be educated on vaping[1,3]. After the first case was reported in April 2019, the American Center for Disease Control and Prevention (CDC) reported more than 2800 cases of EVALI (E-Cigarette Associated Lung Injury) by February 2020[2]. However, there are limited reports of EVALI in anesthesiology. Further studies are needed to determine the effectiveness of the template as a teaching tool for the assessment of vaping. Our goal was to utilize the template to develop better assessment tools in anesthesiology.

REFERENCE(S):

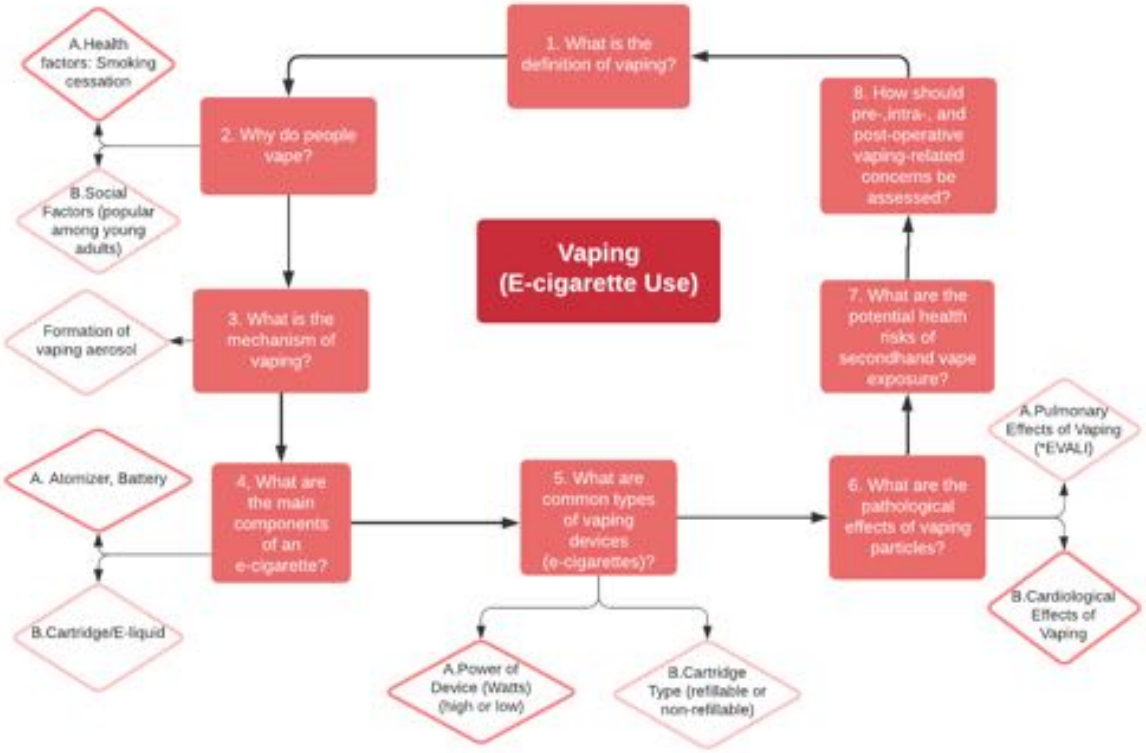
1. BMJ 2019; 366: l5275.
2. CDC. (2020, November 27). Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products. Retrieved December 28, 2020, from https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
3. APSF Newsletter 2020; 35(1):4.
4. Canadian Journal of Anesthesia/Journal Canadien Danesthésie 2020; 67(9): 1124-1129.

Table 1: Vaping Devices

Type of Vaping System	Popular Vaping Device	Power of device (Watts-W)	Amount of E-liquid (mL per pod/cartridge)	Type of E-Liquid Used	Estimated Nicotine Content (mg per pod/cartridge)
Disposable Pods: Requires replacement of cartridge (Pod)	JUUL™	8	0.7	Nicotine Salt E-Liquid	~20-42
	Riptide Ripstick™	10	1.4	Free-base Nicotine E-liquid	~70
Refillable: Requires refill with E-liquid	Suorin Drop™	13	2	Nicotine Salt, Free-Base Nicotine, or Non-nicotine E-liquid	~20-50
	Smok Alien™ (Adjustable Box Mod)	6-220	3	Free-Base Nicotine or Non-nicotine E-Liquid	~0-72
Disposable: requires replacement of apparatus	PUFF Bar™	7	1.3	Nicotine Salt E-liquid	~26-65
	Stig ™	Unknown	1.2	Nicotine Salt E-liquid	~72

References:
https://www.juul.com/, https://stigpods.com, https://puffbar.com/, https://www.smokstore.com/Smok-Alien-220W-Vape-Kit, https://www.suorinusa.com/collections/suorin-drop, https://www.vaperiptide.com/

Figure 1: Vaping Education Logical Flowchart



*E-Cigarette and Vaping-Associated Lung Injury

Table 2: Pulmonary Effects of Vaping on Different Human Cell Types (1)

Cell Type	Effect(s) of Vaping
Nasal Epithelia	Decreased immunity and cilia motility
Bronchial Epithelia	Cellular toxicity, decreased cilia motility, airway, dehydration, increased cytokine and MUC5ac mucin secretion
Bronchial Endothelia	Inhibited vasoconstriction and increased stiffness
Alveoli Endothelia	Impaired macrophages (lipid-laden) and gas exchange
Sputum	Impaired macrophage function, increased proteases and MUC5ac mucin

Table 3: Assessment of Perioperative Vaping Concerns (4)

Time of Management	Vaping-Associated Concerns	Assessment Questions for Patients
Pre-operative	• Chronic health issues associated with smoking prior to vaping • Nicotine dependence/nicotine use disorder can lead to withdrawal symptoms • Unknown if quitting vaping preoperatively decreases intra-operative risk of complications • Unknown if transitioning from smoking to vaping affects intra-operative risk of complications	• Do you vape? • Did you smoke before you began to vape? • What device do you use? • Do you use nicotine e-liquids? What concentration? • Do you vape every day? • How much e-liquid do you use on a typical day? • Do you use cannabis (THC) e-liquids?
Intra-operative	• Cardiovascular risks of nicotine-use in dual users • Respiratory risks unknown in vapers (not smokers)	• Since you started vaping, have you had any procedures/operations? • Have you had any previous negative health experiences associated with smoking and/or vaping?
Post-operative	• Nicotine replacement therapy for patients with nicotine use disorder • Smoking cessation clinic for smokers/vapers who want to quit	• Do you want to be placed on nicotine replacement therapy while recovering in the hospital after your operation? • Do you want to quit smoking/vaping?

ECONOMICS, EDUCATION AND POLICY 14

Curriculum Innovation: Introduction to Hospice and Palliative Medicine during the Clinical Base Year

Michael Wadle[1], Annette Rebel[1], Robert Weaver[1], Jessica McFarlin[1]

[1]University of Kentucky, Lexington, KY

INTRODUCTION: Even before the American Board of Anesthesiology recognized hospice and palliative medicine (HPM) as a subspecialty in 2006, this field of medicine has emerged as integral to the practice of anesthesiology. Anesthesiologists comprise only a small fraction of HPM physicians, but the clinical skills and practical knowledge required to care for such patients complements anesthesiology training. Despite this, few residency programs provide formal rotations in this discipline, probable due to limited ability to offer dedicated rotations in this field. We explored if a short exposure (2 days) in palliative care medicine during the PGY-1 year would be sufficient to relate the essential components of HPM to anesthesiology residents, increasing their understanding and ability to integrate HPM knowledge/procedures into patient care.

METHODS: As a curriculum innovation, we created a novel HPM course, incorporated into a preexisting chronic pain medicine rotation during the clinical base year of the anesthesiology residency. The PGY-1 residents spent 2 days with the institutional in-patient palliative care service, receiving on-line and in-person education and joining the team for rounds and patient care. After completion of the rotation, the participating residents were surveyed on the merits and contributions of added course into the Chronic pain rotation. The survey form is shown in Figure 1.

RESULTS: The Hospice and Palliative Medicine course was implemented in 7/2018, with the first PGY-1 residents participating in September 2018. Eleven (of twenty eight) residents completed the post experience survey (n=8 for 2018-2019; n=3 for 2019-2020). The survey responses were de-identified pre-analysis. Figure 2 demonstrates results pertaining to residents' prior exposure to palliative care. 73% of total residents surveyed had completed an ICU rotation prior to this palliative care experience: 63% of PGY-1 residents during the 2018-2019 year and 100% of residents during the 2019-2020 year. 45% of total residents surveyed reported previous exposure to palliative medicine prior to this palliative care experience: 38% of PGY-1 residents during the 2018-2019 year and 67% during the 2019-2020 year. Figure 3 demonstrates the results pertaining to residents' impressions of palliative medicine after the rotation. 100% of responders indicated they agreed or strongly agreed the rotation helped them understand the ASA guidelines regarding code status preference in the setting of procedure risk. 100% of responders agreed or strongly agreed the HPM rotation helped them understand how palliative care can modify plans and contribute to the care of seriously ill patients. 100% of responders indicated they agreed or strongly agreed the palliative care experience improved their anesthesiology training.

CONCLUSION: Our findings affirm that a short exposure to HPM is supportive and efficient in introducing HPM principles into the formal anesthesiology residency curriculum. Further studies will be needed to explore if the short-term exposure has impact on dependent anesthesiology care areas (perioperative medicine, critical care medicine) and if residents consider additional training time in HPM for elective rotations at a later stage of their residency.

Figure 1

Preview Form

Printed on Jan 14, 2021

Resident Evaluation of Palliative Care Consult Experience

Insufficient contact to evaluate (delete evaluation)

Dear Resident, we are evaluating the Palliative Care Consult component during the Chronic Pain rotation and would like to ask for your input about your experience. As this is a new component of the rotation, we are working to make it the best experience possible, and are very interested in all of your feedback. Thank you!

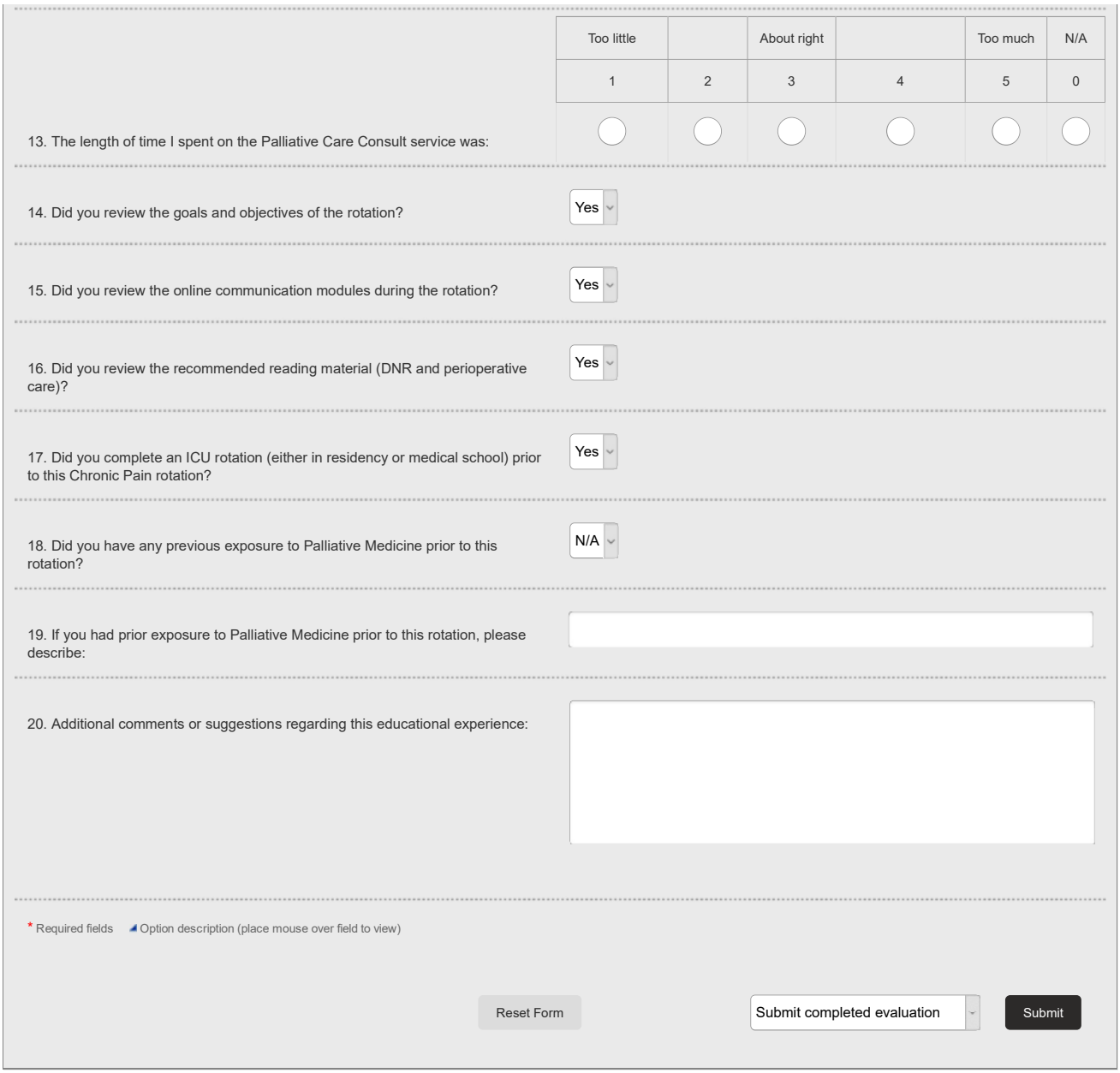
1. Please reflect and describe one thing you learned or experienced during your time on Palliative Medicine that was the most valuable to you. *

	Strongly Agree	Agree	Disagree	Strongly Disagree	N/A
2. This educational experience met the goals and objectives.	○	○	○	○	○
3. I was provided with adequate time for education/discussion with faculty on service.	○	○	○	○	○
4. This experience helped raise my awareness of how Palliative Medicine contributes to the care of my patients.	○	○	○	○	○
5. After the palliative care experience, I recognize the framework for a goals-of-care discussion with a patient with a serious illness.	○	○	○	○	○
6. The palliative care experience helped me to develop an understanding how palliative care involvement can modify the care plan for a patient with a serious illness.	○	○	○	○	○
7. After the palliative care experience, I understand the ASA guidelines for confirmation, suspension and modification of code status preferences in the context of procedural risk.	○	○	○	○	○
8. The palliative care experience improved my anesthesiology training.	○	○	○	○	○
9. The course material was sufficient and supplemented the learning experience.	○	○	○	○	○
10. I was satisfied with the overall learning experience on palliative care.	○	○	○	○	○
11. I would recommend this educational experience to other learners.	○	○	○	○	○

12. How many days did you spend in palliative care during your chronic pain rotation?

(e.g., 0, 1, 2, 3, more than 3)

Figure 1 (continued)



	Too little		About right		Too much	N/A
	1	2	3	4	5	0
13. The length of time I spent on the Palliative Care Consult service was:	○	○	○	○	○	○

14. Did you review the goals and objectives of the rotation? Yes

15. Did you review the online communication modules during the rotation? Yes

16. Did you review the recommended reading material (DNR and perioperative care)? Yes

17. Did you complete an ICU rotation (either in residency or medical school) prior to this Chronic Pain rotation? Yes

18. Did you have any previous exposure to Palliative Medicine prior to this rotation? N/A

19. If you had prior exposure to Palliative Medicine prior to this rotation, please describe:

20. Additional comments or suggestions regarding this educational experience:

* Required fields Option description (place mouse over field to view)

Reset Form Submit completed evaluation Submit

Figure 2: Resident Surveyr Response Regarding Prior Palliative Care Exposure

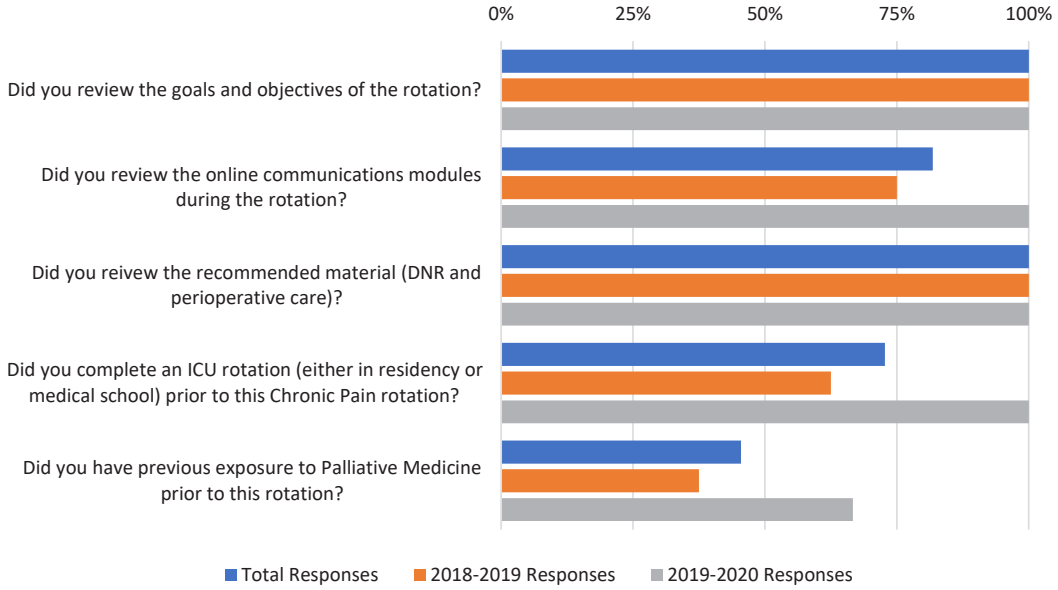
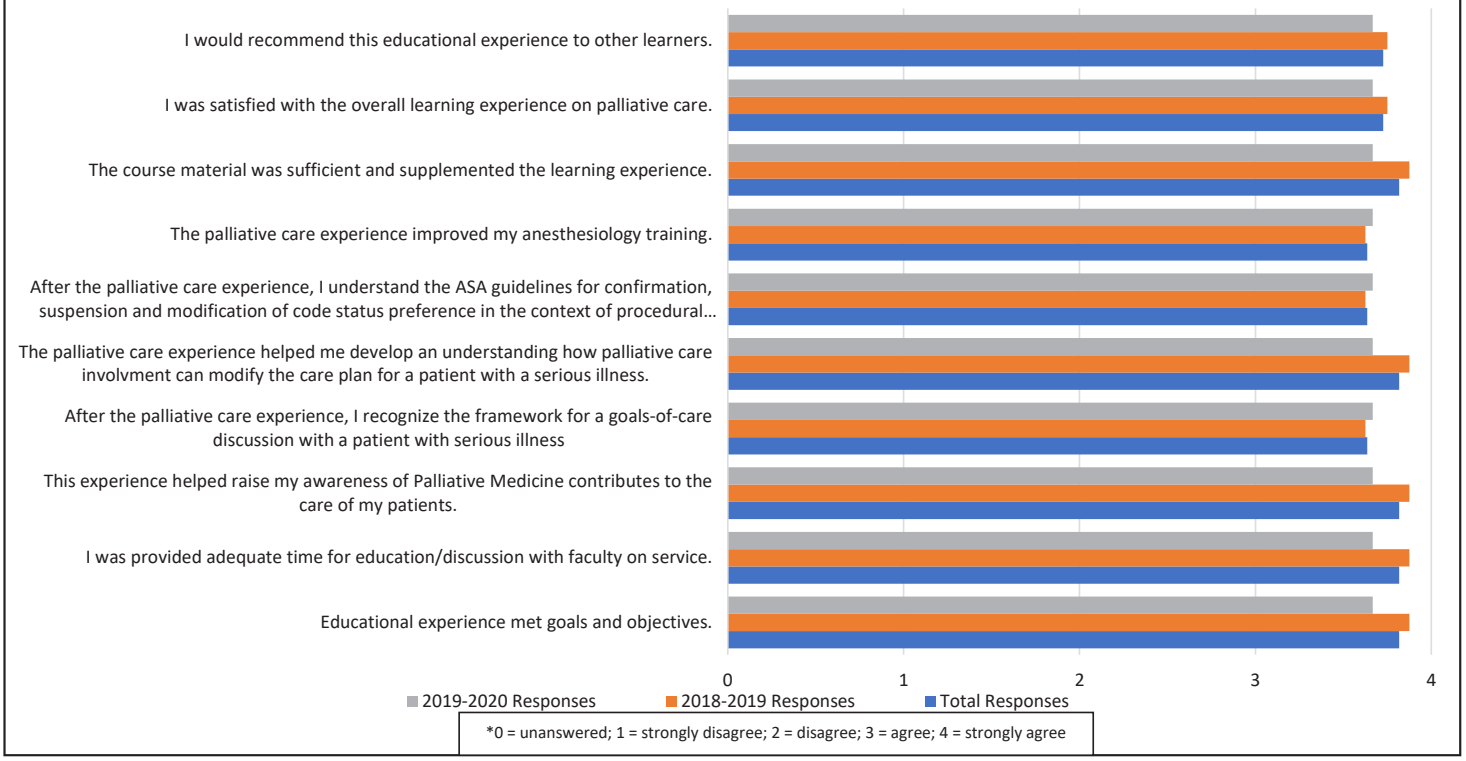


Figure 3: Resident Survey Response Regarding Rotation Experience*



ECONOMICS, EDUCATION AND POLICY 15

Development of Survey to Assess Vaping Knowledge and Screening Practices of Clinicians in an Academic Anesthesiology Practice

Jane Xu[1], Melissa Schwedhelm[2], Dean Jarvis[2], Humnah Khudayar[2], Susanne Tanski[2], Yvon F Bryan[2]

[1]Geisel School of Medicine at Dartmouth, Hanover, NH, [2]Dartmouth-Hitchcock Medical Center, Lebanon, NH

INTRODUCTION: The popularity of electronic nicotine delivery systems (ENDS), also known as e-cigarettes or vaping devices, has grown immensely with sales that are expected to surpass traditional tobacco sales by 2023[1]. In clinical studies, the inhalation of the vaping aerosol produced by ENDS has been found to be associated with many respiratory conditions, such as asthma, COPD, and E-cigarette and Vaping-Associated Lung Injury (EVALI)[2]. These findings suggest that chemical toxicities of e-cigarettes may cause respiratory complications in patients under anesthesia. Screening for ENDS may be challenging for anesthesiology clinicians, as there may be a lack of knowledge among clinicians about vaping. We present our development and findings of a vaping survey for anesthesiologists, residents, and certified nurse anesthetists to examine knowledge and screening practices for e-cigarette use.

METHODS: The electronic survey was developed by a group consisting of an anesthesiologist, neonatologist, pulmonologist, pediatrician, medical student, and research assistant. After IRB approval and waiver of consent, the survey was generated via DHMC Synergy REDCap and distributed to all members of the Dartmouth-Hitchcock Medical Center (DHMC) anesthesia team consisting of anesthesiology attendings and residents, and certified nurse anesthetists and student nurse anesthetists. The survey consisted of 18 questions with each question fitting into one of three categories (see Figure 1): a) ENDS screening, b) ENDS knowledge, c) ENDS education. These questions were based on current medical literature, CDC, medical conferences, lay press, and Zoom discussions.

RESULTS: 41/164(25%) of the clinicians had participated in the survey at the time of the abstract deadline. 28/41(68%) of the survey participants indicated that they did not screen for e-cigarette use. In addition, 3/41(7%) of participants reported being involved in a case with vaping complications, and all were respiratory complications. See Figure 2 for the demographics of the participants (role, sex, age, years since graduation, and educational background on vaping in CRNA or medical school). See Table 1 for the responses to questions regarding vaping screening. See Figure 3 for responses concerning ENDS education and knowledge.

CONCLUSION: Our survey found limited knowledge of vaping practices and lack of screening was noted amongst members of a clinical anesthesiology department. A recent study examined knowledge of ENDS among primary care clinicians but not screening practices, and current vaping screening practices by anesthesia providers remains unknown[3]. A nationwide EVALI epidemic in 2019 emphasized the significant pulmonary effects of ENDS use[4]. E-cigarette use may worsen respiratory risks in anesthetized patients, especially when respiratory function might already be compromised in the current COVID-19 pandemic. Clinical research has focused on vaping and its health risks, but studies on screening practices for e-cigarette use are limited. Our survey provided information on these practices, but it was limited to one institution, and other institutions may have different practices. Our goals of the survey were to educate anesthesia clinicians about vaping and ENDS screening and fill in the gap in knowledge between ENDS screening and prevention of peri-operative respiratory complications.

REFERENCE(S):

1. Am J Physiol. 2017; 313(2):L193-L206.
2. BMJ 2019; 366: l5275.
3. Heal Serv Res Manag Epidemiol. 2016; 3:233339281667849.
4. CDC. (2020, November 27). Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products. Retrieved December 28, 2020, from https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html

Figure 1

This is an 18-item survey that will be used to determine provider knowledge and beliefs regarding vaping and E-cigarette usage. All answers are anonymous and will be used to identify knowledge gaps to improve education and screening practices among providers.

1. Are your currently screening for tobacco use in patients?
    a. Yes
    b. No
2. Vaping is inhaling any heated aerosol from a vape device containing nicotine, THC, CBD oil, butane hash oil, any other psychoactive substance or just flavoring. Are you currently screening for vaping or e-cigarette use in patients?
    a. Yes, I ask if a patient vapes nicotine, THC or CBD oil
    b. Yes, I ask if a patient vapes nicotine only
    c. Yes, I ask if a patient vapes THC only
    d. No, I do not currently screen
3. Are you aware of how to quantify vaping or E-cigarette use in patients?
    a. Yes
    b. No
4. Do you ask about the type of E-cigarettes or vaping devices used?
    a. Yes
    b. No
5. What are the most important factors that would make you want to screen for vaping or E-cigarette use in patients?
    a. Patient age
    b. Current smoker
    c. History of substance use
    d. Positive drug test
    e. Male patient
6. From what sources do you retrieve information regarding E-cigarettes or vaping?
    a. Peers
    b. Youtube
    c. Twitter
    d. Internet newsfeed
    e. Professional organizations
    f. Scientific literature
    g. Medical or CRNA school
7. Have you ever been involved in a case with a vaping complication?
    a. Yes
    b. No
8. If so, what complication occurred?
    a. Cardiovascular
    b. Respiratory
    c. Inhalational burn
    d. N/A
9. What is the most important challenge to screening for vaping or E-cigarette use?
    a. Lack of time
    b. Lack of knowledge
    c. Lack of formal training on E-cigarettes
    d. Lack of questions included in anesthesia pre-screening questionnaire
    e. Discomfort with subject

Figure 1 (continued)

10. Do you want to learn more about E-cigarettes and vaping?
    a. Yes
    b. No
11. Given the current vaping trend, do you know someone who vapes?
    a. Yes, nicotine
    b. Yes, THC or CBD oil
    c. Yes, flavoring only
    d. Yes, combination of substances
    e. No
12. What would you like to learn about vaping or E-cigarette use?
    a. Device types
    b. Risks of vaping
    c. How to screen
    d. Anesthesia or other medical complications
    e. Other
13. How would you like to learn about vaping or E-cigarette use?
    a. Lecture
    b. Flipped classroom
    c. Module
    d. Lecture with hands-on teaching
14. What is your current role?
    a. Resident
    b. Fellow
    c. sCRNA
    d. CRNA
    e. Attending
15. When did you graduate from your respective CRNA or medical school?
    a. 0 to 5 years
    b. 6 to 10 years
    c. 11 to 20 years
    d. 21 years or greater
16. What is your gender?
    a. Female
    b. Male
17. What is your age?
    a. < 30
    b. 40-49
    c. 50-59
    d. 60+

Figure 2: Demographics of Participants

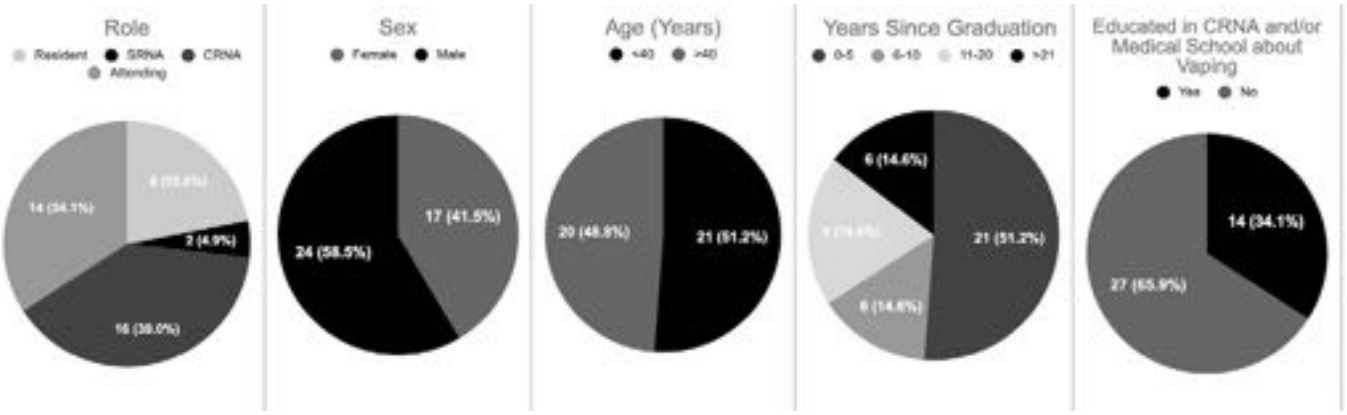
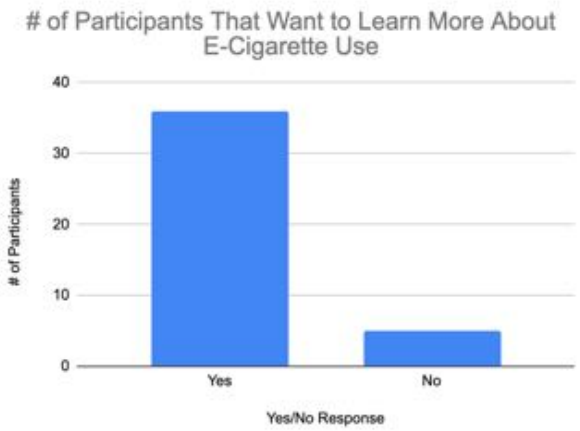
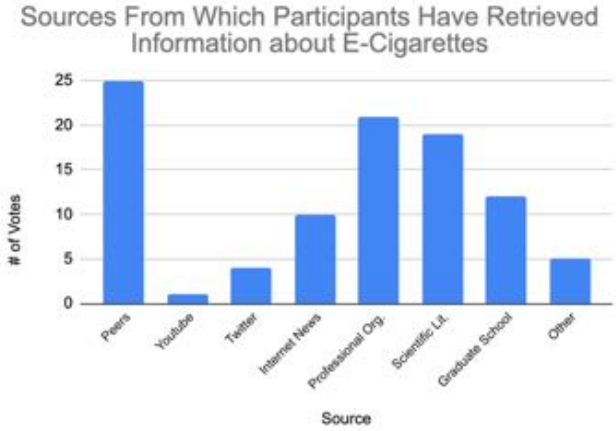


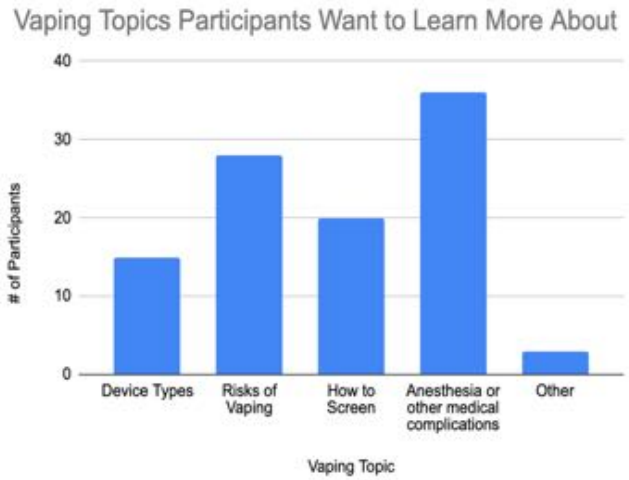
Table 1: Responses of Vaping Screening Questions

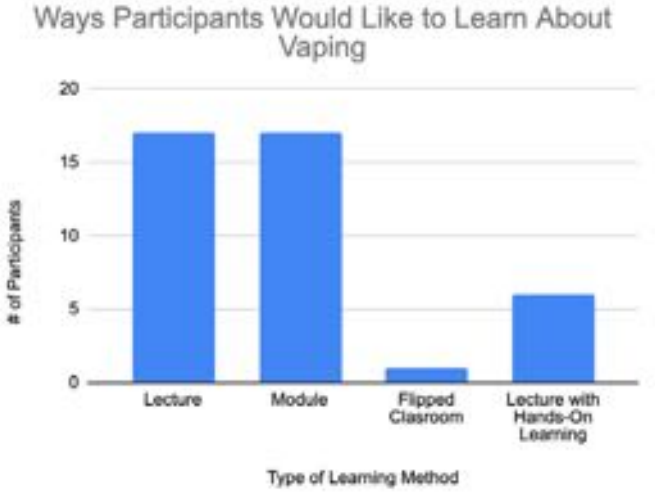
Demographics	Screens for Tobacco Use	Doesn't Screen for Tobacco Use	Screens for Vaping	Doesn't Screen for Vaping	Knows how to quantify vaping	Doesn't know how to quantify vaping	Asks about Type of E-Cigarettes	Doesn't ask about type of E-Cigarettes
Overall (n=41)	39 (95%)	2 (5%)	13 (32%)	28 (68%)	3 (8%)	38 (92%)	5 (12%)	36 (88%)
Sex								
Female (n=17)	17 (100%)	0 (0%)	5 (29%)	12 (71%)	2 (12%)	15 (88%)	2 (12%)	15 (88%)
Male (n=24)	22 (92%)	2 (8%)	8 (33%)	16 (67%)	1 (4%)	23 (96%)	3 (13%)	21 (87%)
Age								
<40 (n=21)	20 (95%)	1 (5%)	6 (29%)	15 (71%)	2 (10%)	19 (90%)	1 (5%)	20 (95%)
>40 (n=20)	19 (95%)	1 (5%)	7 (35%)	13 (65%)	1 (5%)	19 (95%)	4 (20%)	16 (80%)
Role								
Resident (n=9)	8 (89%)	1 (11%)	0 (0%)	9 (100%)	1 (11%)	8 (89%)	0 (0%)	9 (100%)
SRNA (n=2)	2 (100%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)
CRNA (n=16)	16 (100%)	0 (0%)	9 (56%)	7 (44%)	1 (6%)	15 (94%)	2 (13%)	14 (87%)
Attending(n=14)	13 (92%)	1 (8%)	3 (21%)	11 (79%)	1 (8%)	13 (92%)	3 (21%)	11 (79%)
Years since Graduation								
0 - 5 (n=21)	20 (95%)	1 (5%)	7 (33%)	14 (67%)	2 (95%)	19 (5%)	2 (5%)	19 (95%)
6 - 10 (n=6)	6 (100%)	0 (0%)	1 (17%)	5 (83%)	0 (0%)	6 (100%)	0 (0%)	6 (100%)
11 - 20 (n=8)	8 (100%)	0 (0%)	3 (38%)	5 (62%)	0 (0%)	8 (100%)	1 (13%)	7 (87%)
>20 (n=6)	5 (83%)	1 (17%)	2 (33%)	4 (67%)	1 (83%)	5 (17%)	2 (33%)	4 (67%)
Educated about Vaping in CRNA and/or Medical School								
Yes (n=14)	14 (100%)	0 (0%)	4 (29%)	10 (71%)	2 (14%)	12 (86%)	1 (7%)	13 (93%)
No (n=27)	25 (93%)	2 (7%)	9 (33%)	18 (67%)	1 (4%)	26 (96%)	4 (15%)	23 (85%)

Figure 3: Responses to Vaping Education Questions









ECONOMICS, EDUCATION AND POLICY 16

Effect of the Covid-19 Pandemic on Attitudes of Health Care Sector Employees on Resource Conservation, Healthcare Pollution and Environmental Sustainability

Shikha Shukla[1], Melia Bernal[2], Bianca Castro[2], Jodi Sherman[2]

[1]New York Presbyterian Hospital, New York City, NY, [2]Yale University, New Haven, CT

INTRODUCTION: Climate change has negative impacts on human health and is a growing public health crisis.[1, 2] In turn, the health care sector is a significant contributor to greenhouse gas and other environmental emissions. Energy consumption by facilities, pharmaceutical and equipment manufacturing, and biomedical waste management have sizeable environmental impacts. The United States health care sector contributes 8-9% of the nation's greenhouse gas emissions.[3, 4] Globally, the sector also contributes to air, water and soil pollution.[5] Resource conservation is one approach to reducing health care-related environmental harm. The need for resource conservation applies to both pandemic and climate change related disasters. The covid-19 pandemic created an unparalleled demand for intensive care unit beds, personal protective equipment, sedation medications, ventilators and other resources. The surge in demand and the supply chain interruption due to illness and economic shutdown, together, resulted in dramatic supply shortages leading many institutions to ration resources. The objective of this survey was to understand knowledge, beliefs and attitudes towards climate change and resource conservation in the context of the Covid-19 pandemic.

METHODS: From May to September 2020, we e-mailed a link to an optional, anonymous 10 question survey to all 29,000 employees at a 2,500 bed health care system within the United States. As the survey met institutional requirements for quality improvement projects, no IRB approval was required. Informed consent from the participants was obtained at the start of the survey. At the time of initial survey distribution, the health system had just passed the peak of the first wave of Covid-19 admissions. The survey was adopted from a prior survey of health professional student knowledge, attitudes and beliefs about climate change, pollution, and resource conservation in health care.[6] Descriptive statistics were used for data analysis.

RESULTS: Of the nearly 29,000 employees, 3,204 employees participated in the survey (approximately 11% overall). Participants included: 2,389 clinical/support staff (74.56%) and 815 administrative staff (17.34%). A majority (85.26%) of clinical/support staff respondents agreed or strongly agreed that healthcare workers are responsible for conserving resources and preventing healthcare pollution within their professional practice. Most clinical/support staff respondents (93.1%) and administrative staff respondents (92.54%) agreed or strongly agreed that they use resources according to hospital policy. As a result of the Covid-19 pandemic, 74.51% of clinical/support staff respondents agreed or strongly agreed with efforts to limit unnecessary orders or use of clinical supplies, medications, and tests. 76.60% further supported extending these efforts beyond the Covid-19 pandemic. Amongst the administrative staff, 77.89% agreed or strongly agreed with efforts to limit unnecessary orders or use of supplies and 83.38% supported continuing these efforts into the future. Only 16.33% of clinical/support staff and 13.90% of administrative respondents agreed or strongly agreed that they will go back to the usual way of ordering and using supplies and devices once Covid-19 related shortages are no longer of concern.

CONCLUSION: Health care sector employees, clinical and non-clinical, agree that they have a responsibility towards judicious use of resources and to decrease healthcare pollution. There is an interest in continuing the resource conservation policies and practices that started in the Covid-19 pandemic. Hospital policies heavily influence employee behavior, thus there is a need to amend system level policies to encourage and enforce environmentally sustainable practices. The lessons learned during this global pandemic likely need directed action to reinforce resource conservation behaviors, to better manage future pandemics, weather-related disasters, and prevent pollution.

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ECONOMICS, EDUCATION AND POLICY 17

The Role of Medical Students during Difficult Airway Management: Education and Contribution Beyond Intubation

Isabelle T Yang[1], Kelsey Flores[2], Jungbin A Choi[3], Yvon F Bryan[4]

[1]Geisel School of Medicine at Dartmouth, Hanover, NH, [2]Wake Forest University, Winston-Salem, NC, [3]Wake Forest School of Medicine, Winston-Salem, NC, [4]Dartmouth-Hitchcock Medical Center, Lebanon, NH

INTRODUCTION: Medical students may participate actively in patient care during their anesthesia clerkship, including airway management[1]. In high-intensity situations, such as difficult airway management, it may be difficult for medical students to find a contributory role. However, students lose educational opportunities if they only observe without participating actively[2]. We examined cases in which medical students actively participated and played a role in difficult airway management.

METHODS: Approval and waiver of consent was obtained. Patients with expected difficult airways were recruited. Patients met at least one of four inclusion criteria for the study: 1) one or more abnormal airway index(es); 2) expected challenges with intubation, ventilation or oxygenation by clinician judgement; 3) patient history or comorbidities suggesting difficult airway management; 4) planned use of specialized device for intubation and ventilation. For inclusion in this subanalysis, the procedure had a medical student who actively participated as a member of the clinical anesthesia team. Trained research assistants, who were not part of the clinical team, observed airway management and recorded events in real-time. Data analysis was conducted in Microsoft Excel and Stata/MP 15.0.

RESULTS: Of 1355 total cases in the study, 34 cases (2.5%) were included in our subanalysis as medical students played an active role in airway management (see Table 1 for demographics). Patients underwent the following procedures: 18 gastrectomy/gastric bypass; 6 thyroidectomy/parathyroidectomy; 3 orthopedic; 2 urology; 5 others, including ENT and general surgery. 5 (15%) patients required three or more attempts to visualize vocal cords and 3 (9%) patients required three or more attempts to place the endotracheal tube. 27 (79%) patients required maneuvers during intubation; 20 required lip retraction and 17 required anterior laryngeal pressure. 7 (21%) patients required three or more maneuvers during bag mask ventilation (BMV). All medical students assisted with intubation and/or ventilation. Medical students assisted with maneuvers required during ventilation, such as adjusting the adjustable pressure-limiting valve. In 17 cases (50%), the medical student successfully performed laryngoscopy and endotracheal tube placement with clinician guidance. In the other 17 (50%) cases, students played a supportive role in intubation, such as attempted laryngoscopy and/or ETT placement, placed ETT while clinician performed laryngoscopy, or performed maneuvers such as lip retraction or anterior laryngeal pressure with clinician direction. Medical students also observed patients for complications related to physiologic changes, oxygenation, ventilation, aspiration, and debriefed the case with the attending and research assistants (see Figure 1).

CONCLUSION: In high-intensity situations such as difficult airway management, we found that medical students assisted with multiple facets including patient assessment, preparation, induction, intubation, and ventilation. These cases demonstrate the situational and educational benefits of having students assist in complex cases and participate in subsequent debriefing. Having additional personnel to perform maneuvers and monitor hemodynamic changes was helpful for the clinical team. Even though medical students did not always have the opportunity to intubate or reintubate after an unsuccessful attempt, they developed a holistic understanding of clinical decision-making in difficult airway management, which is more valuable than simply knowing how to intubate. Through real-time challenges, students learned to identify relevant comorbidities, prepare an anesthetic-airway plan, and anticipate complications. Practical experience with difficult airway management may augment learning and performance in other disciplines such as surgery and critical care, and during situations such as emergency codes.

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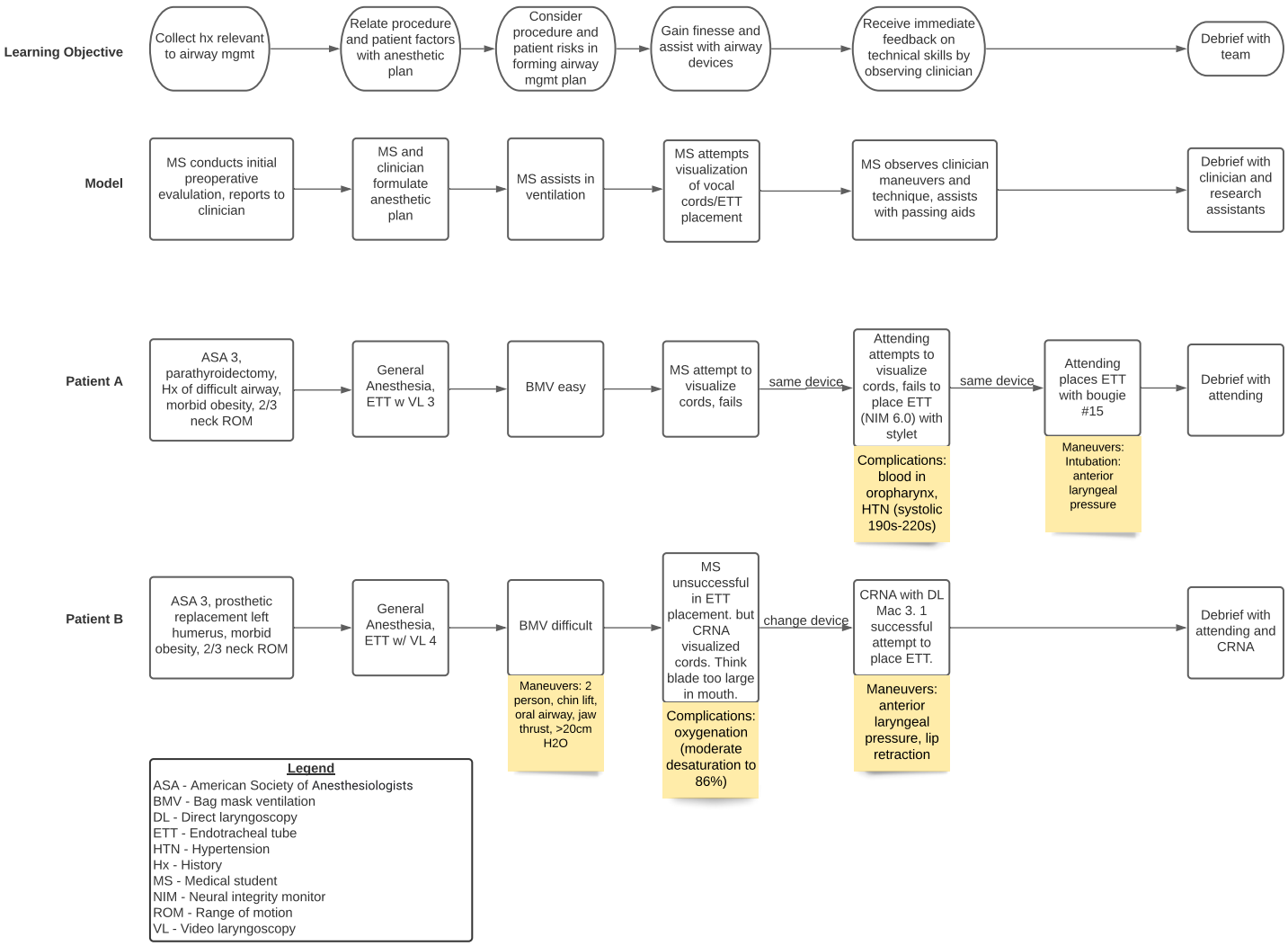
Table 1. Demographics

Patient Characteristics	
Characteristic	**All patients (N=34)**
Age (y) (median, IQR)	47 [42-57]
Weight (kg) (median, IQR)	117.5 [93.0-135.9]
Height (cm) (median, IQR)	165 [160.0-173.3]
BMI (kg/m^2) (median, IQR)	41.9 [36.3-47.7]
Sex (n, %)	Female: 24 (69%) Male: 10 (31%)
ASA classification (n, %)	
I/II	10 (29%)
III/IV	25 (71%)
Expected Difficult Airway* (n, %)	32 (94%)
Number (%) with at least 1 abnormal airway index	16 (46%)
1 abnormal	9 (26%)
2 abnormal	4 (12%)
3 abnormal	3 (9%)
Medical Students (N=34)	
MS2 (n, %)	5 (15%)
MS3 (n, %)	7 (21%)
MS4 (n, %)	19 (56%)
Not stated (n, %)	3 (8%)

*determined by patient history on chart, patient or family statement of previous history of difficult airway, and physical exam

Figure 1. Medical Student Role in Difficult Airway Management



ECONOMICS, EDUCATION AND POLICY 18

The value of just-in-time in-situ simulation training as a preparedness measure for the perioperative care of COVID-19 patients.

Liana Zucco[1], Michael J Chen[1], Nadav Levy[1], Allison Hyatt[1], Jeffrey R Keane[1], Richard pollard[1], John D Mitchell[1], Satya Krishna Ramachandran[1]

[1]Beth Israel Deaconess Medical Center, Boston, MA

INTRODUCTION: In anticipation of a surge of COVID-19 patients and the associated risks posed to healthcare workers involved in aerosol-generating procedures such as tracheal intubation, the rapid redesign of workflow processes was required to prepare staff to safely care for COVID-19 patients within the perioperative setting.[1] In March 2020, simulations were rapidly developed, and delivered through just-in-time (JIT) training, an educational technique known for its efficacy and ability to promote confidence in performing specific tasks.[2-5] Simulations were conducted in-situ in operating rooms (OR) to identify site-specific latent hazards and opportunities for improvement.[6,7]

METHODS: Based on available evidence, the Anesthesia Quality, Safety and Innovation group created new standard operating procedures (SOP's), cognitive aids (i.e.: single-page checklists) and established a core development group to facilitate training efforts (Figure 1). Four training simulations were developed with a focus on minimizing viral exposure and transmission risk in the perioperative setting (Figure 2; A: pre-op huddle & OR set up for COVID-19 case; B: donning & doffing PPE; C: transfer of a COVID-19 patient from the ICU to the OR; and D: airway management with enhanced infection control measures. Over 3 weeks, JIT in-situ training sessions were delivered up to twelve times per day to a total of 428 perioperative staff within a healthcare network which provides care in a metropolitan area containing nearly 5 million people. Comprehensive evaluation of this training method was performed using a post-simulation survey, which collected Likert scale assessments and free text responses from 110 participants. Post-simulation feedback helped facilitate iterative changes to training and organizational SOP's. Compliance with COVID precautions in the OR was retrospectively reviewed over 6 months (March-August 2020) after JIT in-situ training was initially delivered.

RESULTS: Survey responses (n=110) for each of the four simulations reported increased knowledge of and comfort in adopting new workflows post-sim (all p-values < 0.00001; Figure 3), and >90% of respondents agreed or strongly agreed that this training would impact their future practice (Figure 4). Free text responses were notable for identifying areas to improve upon, expressing appreciation of the timeliness of this training, and praising the 'hands-on' nature of in-situ simulation and inter-professional collaboration (Figure 5). Compliance with COVID precautions in practice was found to be 95% (121 out of 127 cases) and associated with lower than expected healthcare worker infection rates within the network during this same time period (<1%).

CONCLUSION: The JIT in-situ training method as a preparedness measure for perioperative care of COVID-19 patients demonstrates this approach is a notable training method during a crisis. Participants highly regarded the content and delivery of training and were themselves integral to improving organizational SOP's and further training materials. We encourage institutions to consider this approach for any refresher training on subsequent COVID-19 surges or other crises that require timely, effective training.

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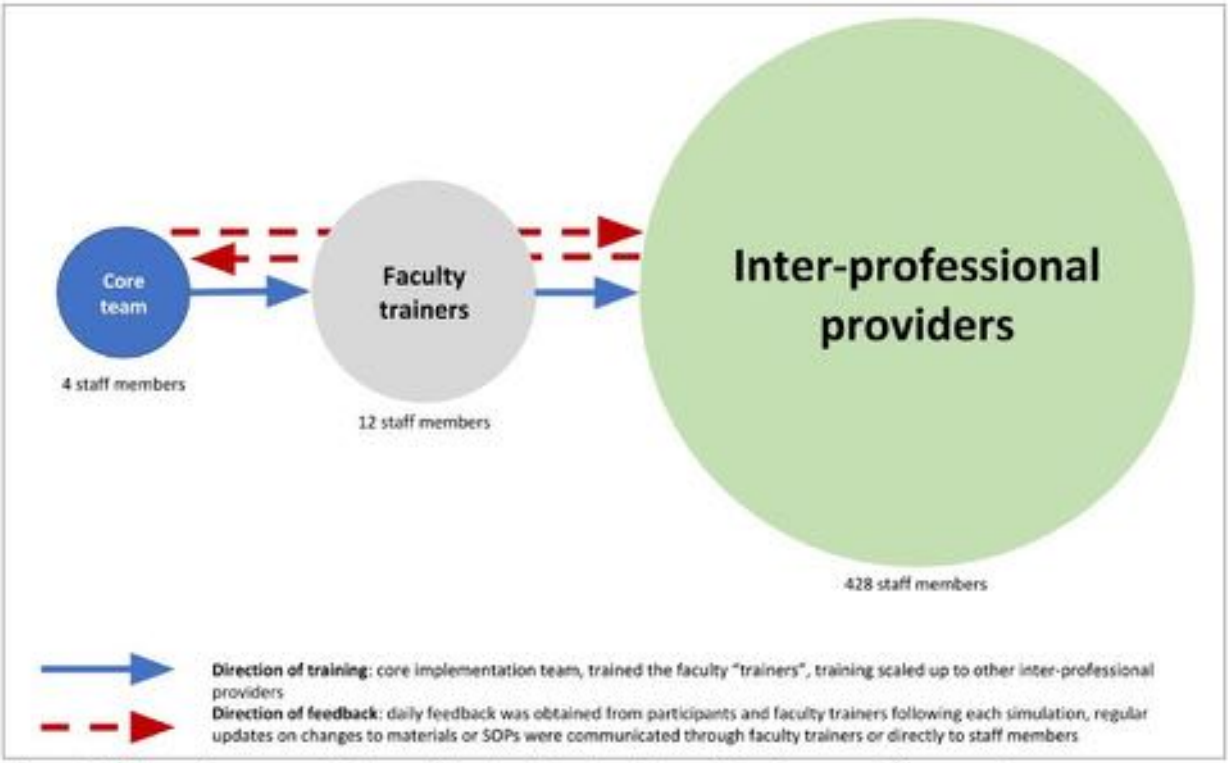

Figure 1. Schematic representation of the simulation implementation team and framework.

Figure 2. JIT in-situ simulation training stations. A: Pre-op huddle & OR set up for COVID-19 case. B: Donning & doffing PPE. C: Transfer of a COVID-19 patient from the ICU to the OR. D: Airway management with enhanced infection control measures

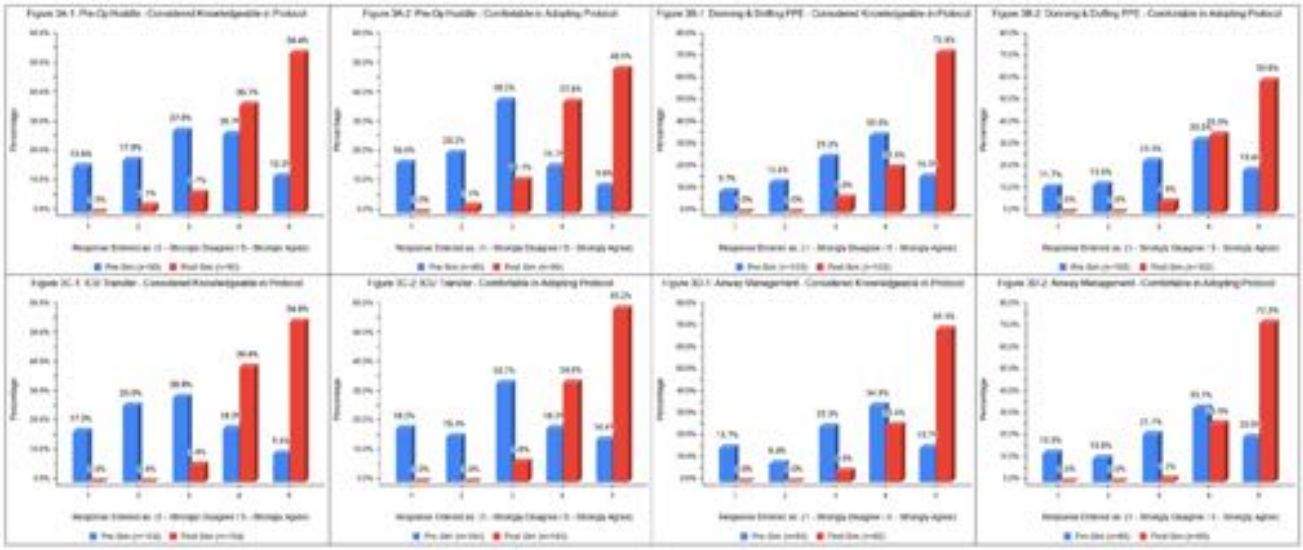

Figure 3. Pre-post simulation training survey results for all 4 simulation stations. Results for each simulation station (labeled A-D) on knowledge of protocols (labeled "...-1") and comfort in adapting protocols (labeled "...-2") are expressed as percentage of responses. Pre-simulation responses are noted in blue; post-simulation responses are in red. X-axes represents 5-point Likert scale (1=strongly disagree, 5=strongly agree).

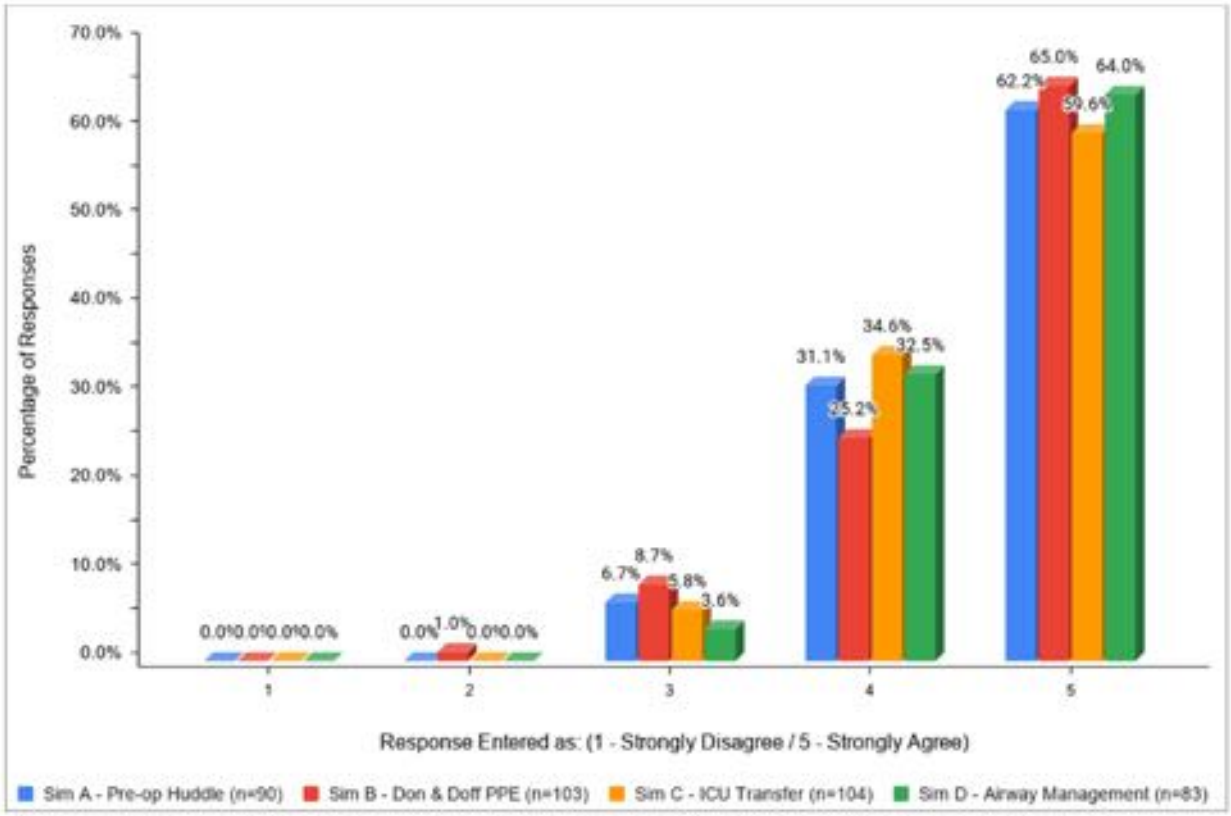

Figure 4. Survey results for perceived impact of JIT simulation training on clinical practice. Results are expressed as percentage of responses for each simulation drill. Simulations are labeled to aid interpretation as follows: sim A – pre-operative huddle (blue), sim B – donning & doffing PPE (red), sim C – intensive care unit (ICU) transfer (orange) and sim D – airway management using enhanced infection control measures (green). X-axis represents a 5-point Likert scale (1=strongly disagree, 5=strongly agree). Mean scores for sim A: 4.6 (SD=0.6), sim B: 4.5 (SD=0.7), sim C: 4.5 (SD=0.6) and sim D: 4.6 (SD=0.5).

Summary of Themes	Quotes
Simulation content and materials: Preference for greater number of clinical scenarios, use of visual materials to aid in learning and clarification of minor points in our protocols.	"Scenarios chosen were very clear, practical and common situations" "Content could have included emergency situations (stat calls, traumas, combative patients, extreme respiratory depression) … videos or pictures would also have been helpful."
Relevance to practical skills: Appreciation of the ability to practice a clinical skill not often performed and be "hands-on" in the process	"Donning and doffing was important to practice, as its not done regularly enough." "The hands-on nature of the ICU transfer was useful to me … it gave me the opportunity to test my abilities and be familiar with the process"
Relevance to clinical experience: Recognition of training as an opportunity to discuss upcoming or unanticipated hazards/safety issues	"Simulation got you thinking about the issues in dealing with a COVID-19 patient, and helped you learn from others' trial and errors." "I'm grateful to have had the training since none has been done at my facility. I had to lead a team for a suspected COVID-19 case today and I'm not sure how I could have done this without having had the training"
Perceived benefits of training: Increased awareness of new protocols, as well as comfort in adopting new protocols. Training method provided a forum to review protocols step-by-step, engage in teamwork, hear from others' experiences, and offer feedback. Contribution in alleviating anxieties about personal HCW safety in the workplace.	"It really helps the nursing staff in preparing to care for these patients and increases communication between the disciplines" "The simulations provided an opportunity to hear about the most up-to-date protocol/policy changes, and also about complaints" "This help[ed] prepare me to manage a COVID-19 case, I felt much more confident and comfortable following these simulations"
Perceived failures of training: Challenging to extrapolate lessons simulation into real life. Difficulty in keeping up to date due to frequent changes in hospital policy/guidelines.	"The knowledge that the content might be changing daily, impacted my learning" "The protocol changed after I did the simulation, but I wasn't aware of this change"
Inter-professionalism/Collaboration: Appreciation noted when groups contained multiple disciplines, and seen as a missed opportunity when logistical barriers & COVID-19 precautions occasionally resulted in groups where all disciplines were not equally represented.	"I found it most useful when there was nursing and anesthesia collaborating in the sim. There was a great discussion between the two disciplines on different ways to troubleshoot issues that were uncovered" "Assigned groups could have been better organized, fewer anesthesia providers, etc"
Leadership: Perception of leadership support within the organization	"Getting a feel for how thoughtful leadership was taking the situation"

Figure 5. Qualitative analysis of free text responses.
[a]COVID-19: Coronavirus disease 2019; HCW: healthcare worker; ICU: intensive care unit; JIT: just-in-time.

ECONOMICS, EDUCATION AND POLICY 19

Impact of COVID-19 on Free-standing Pediatric Ambulatory Centers

Vidya Raman[1], senthil krishna[2], Lyndi Forsythe[2], Joseph D Tobias[2]

[1]Ohio State University Wexner Medical Center, Columbus, OH, [2]Nationwide Children's Hospital, Columbus, OH

INTRODUCTION: Cost containment remains an important driving force in healthcare. In children, this has become vital as the healthcare landscape remains unpredictable without specific healthcare mandates and no firm re-authorization of the Children's Health Insurance Program (CHIP). Additionally, increasing bed shortages during seasonal periods make it imperative to develop strategies to deal with variations in surgical volumes and healthcare resources. The COVID pandemic has made this environment even more uncertain. As this pandemic is a novel and new situation, no one knows its true effect on work flow efficiency, cost, and patient flow. Also, what is the cost of social distancing and sanitization measures? Are these costs being configured into the charges or is that the cost of doing business? With these decreasing margins, will ambulatory centers function and thrive pre-COVID. There have been necessary changes to the workflow due to precautions taken for COVID 19. Although various societal task forces have given roadmaps for reopening (ASA), it is up to individual institution to outline their re-opening strategy.

We integrated our EMR/financial data to look at cost during period of 3/2019-9/2019 versus 3/2020-9/2020 for otolaryngology cases.

METHODS: We obtained IRB. Integrated Hospital EMR and financial data.

RESULTS: See table.

CONCLUSION: In the age of cost containment and decreasing resources, measures for safety comes at a price. During the COVID pandemic months, we had also limited testing availability and could only use screening questions which increased our costs in terms of personal equipment, social distancing, and sanitizing. Our freestanding ambulatory care center not only experienced decreased volume (56%) but increasing cost of business. More research needs to be done in viability of maintaining a free standing ambulatory center during a pandemic.

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Results

	2019	2020
Total Case count	2984	1673
Demographics		
Male	639	331
Female	542	295
Race		
African American	52	117
Asian	16	29
Multi-racial	25	0
Payors		
Medicaid	37%	41%
Medicaid/private	6%	8%
Private	55%	50%
Self-pay	8%	6%
Average Cost per Case		
	$11.47	$30.02

ECONOMICS, EDUCATION AND POLICY 20

Practical experience of residents in a Colombian anesthesiology program compared to the Accreditation Council for Graduate Medical Education (ACGME) and the Johns Hopkins Hospital suggested standards

German A Franco Gruntorad[1], María P Giraldo[2], Juan S Montoya[3], Félix R Montes[4], Manuela Téllez[4]

[1]Fundacion Cardioinfantil-Instituto de Cardiología, Bogota, FL, [2]Fundación Cardioinfantil-Instituto de Cardiología. Universidad del Rosario, Bogotá , Cundinamarca, [3]Fundación Cardioinfantil-Instituto de Cardiología. Universidad del Rosario, Bogotá, Cundinamarca, [4]Fundación Cardioinfantil-Instituto de Cardiología, Bogotá, Cundinamarca

INTRODUCTION: Assuring quality in medical education, is a universal goal that must be achieved by every single residency program in anesthesiology. They should be able to provide theoretical basics and practical scenarios, that allows the student to apply their knowledge to real life situations, and to develop all the required skills to become a qualified physician[1]. Many countries in cooperation with formal institutions, like the Accreditation Council for graduate medical education (ACGME), have established competencies and minimal caseloads, to achieve this goal[2,3]. Unfortunately, in Colombia, since there are no regulatory organizations in charge of this issue and there is no precise knowledge about the real exposure of residents during their training, the adequate number of cases has not been yet standardized. The aim of this study is to describe and compare the practical experience of residents in an anesthesiology program in Colombia, with the minimum standards established by the ACGME and the Johns Hopkins Hospital.

METHODS: This was a cross-sectional study, conducted in a hospital, linked to an anesthesiology program in Bogotá, Colombia. All cases in which 10 residents participated during their years of training (between 2015 and 2020) were included. As established by the teaching program, each resident had to register all the data related to the procedures they were involved, in a mobile Software (HanDBase v4.9.079. DDH Software.) Outcome variables were the number of cases performed by each resident, patients baseline features, ASA classification and type of procedure. Anesthetic techniques were described to characterize the procedures and its complexity, that each resident had to encounter during their training period. After a descriptive analysis of the values, all the caseloads were organized and compared with the minimum standard procedures, listed by the two selected organizations.

RESULTS: From 11711 cases of 10 eligible residents, 1652 were excluded, due to inconsistent and incomplete data. A total of 10059 cases were included (51.3% female patients and 70.1% adults). On average, each resident participated in 1006±122 cases during their training period (Table 1). The number of cases per resident, according to age range and ASA physical status classification, are shown in Table 2 and 3. Residents were mainly involved in procedures from general surgery (n=1836,18.3%), orthopedics (n=1679,16.7%) and obstetrics (n=1087, 10.8%). The total average procedures of our residents exceeded in most of the categories, the standards suggested by ACGME (n=400). In comparison with the standards of Johns Hopkins Hospital (n=1416.1), there is a considerable difference of 410.1 procedures (Table 4)

CONCLUSION: To our knowledge, this is the first time that the caseload of residents has been described for an anesthesiology program in Colombia. There was a high number of cases that were excluded due to incomplete data, an issue that needs to be addressed for future studies of this type. Regardless, this study aims to establish a starting point, to formulate the minimum number of cases in a realistic manner, and to assess the optimization of quality standards in our setting. This 3-year program ensures an extensive clinical experience for the residents during their training period, comparable to American standards.

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Table 1. Number of cases per resident

Resident	10059	
1	850	8%
2	999	10%
3	1078	11%
4	942	9%
5	956	10%
6	1191	12%
7	944	9%
8	1120	11%
9	837	8%
10	1142	11%
Average	1005,9	

Table 2. Number of cases per resident according to age range

Anesthesia according to age range	Resident 1 n=850	Resident 2 n=992	Resident 3 n=1075	Resident 4 n=935	Resident 5 n=945	Resident 6 n=1190	Resident 7 n=942	Resident 8 n=1119	Resident 9 n=822	Resident 10 n=1142	n=10012	Average
Anesthesia for children under 3 years of age	14	20	11	8	12	25	8	15	4	20	137	14
Anesthesia for children between 3 months to 3 years	59	85	54	58	94	83	66	86	60	82	727	73
Anesthesia for children between 3 to 12 years	87	149	116	122	119	156	123	146	123	145	1286	129
Anesthesia for people older over 12 years old	690	738	894	747	720	926	745	872	635	895	7862	786

Table 3. Number of cases per resident according to ASA physical status classification

ASA	Resident 1 n=850	Resident 2 n=999	Resident 3 n=1078	Resident 4 n=942	Resident 5 n=956	Resident 6 n=1191	Resident 7 n=944	Resident 8 n=1120	Resident 9 n=837	Resident 10 n=1142	n=10059	Average
I	212	296	299	302	249	341	215	304	226	309	2753	275
II	370	396	500	330	383	449	409	437	338	374	3986	399
III	253	276	232	276	308	366	255	314	240	337	2857	286
IV	14	30	43	32	16	28	45	47	27	113	395	40
V	1	1	1	2	0	0	17	12	0	9	43	4
VI	0	0	3	0	0	7	3	6	6	0	25	3

ASA: American Society of Anesthesiologists.

Table 4. Comparison with ACGME and the Johns Hopkins Hospital minimum standards (4)

Medical specialty	ACGME standards n=400	The Johns Hopkins Hospital average n=1416.1	Anesthesiology program in Colombia average n=1006
Anesthesia for Vaginal Delivery including High-Risk OB	40	118.9	40
Anesthesia for Cesarean Section	20	59.8	117
Anesthesia for Children 3-12 YO	75	237.1	129
Anesthesia for Children 3 months-3YO	20	89.8	73
Anesthesia for Children <3 months old	5	65	14
Anesthesia for Cardiac Surgery including CPB	20	41	25
Anesthesia for Major Vascular Surgery	20	36.4	17
Anesthesia for Non-Cardiac Intrathoracic Surgery	20	56	35
Anesthesia for Intracranial Surgery	20	162.1	44
Patients Undergoing Anesthesia in which Epidural Analgesia/Anesthesia is Used	40	192.7	78
New Acute or Chronic Pain Patien Evaluation	20	105.7	20
Anesthesia for Patients with Complex, Life-Threatening Injuries (Trauma)	20	48.8	0*
Patients Undergoing Anesthesia in which Spinal Anesthesia is Used	40	101.3	97
Peripheral Nerve Blocks	40	101.5	73

ACGME: Accreditation Council for Graduate Medical Education; OB: obstetrics; YO: years old; CPB: cardiopulmonary bypass.

*This item was not available for inclusion in the third group

ECONOMICS, EDUCATION AND POLICY 21

Investigating Gender Disparities in Case Assignments in an Academic Anesthesiology Department: Implications for Pay and Productivity

Ariana Stuart[1], Mark Muenchrath[1], Brandon M Togioka[1], Leila Zuo[1]

[1]Oregon Health & Science University, Portland, OR

INTRODUCTION: Gender bias has been described in anesthesiology.[1,2] Inequalities in compensation and career advancement have been reported.[3,4] Gender-based assumptions, such as the perception of women as less agentic (associated with stereotypically masculine qualities such as independence and ambition) and more communal (associated with stereotypically feminine qualities such as gentleness and dependence), are a possible explanation for these gender-based discrepancies.[5] Case scheduling within academic anesthesia departments consists of assigning attending anesthesiologists (attendings) to supervise up to four Certified Registered Nurse Anesthetists (CRNAs) or up to two resident physicians (residents). By supervising CRNAs, the attending has the potential to oversee more cases and may have a greater opportunity to earn American Society of Anesthesiologists (ASA) units and Relative Value Units (RVUs). We hypothesized that female anesthesia attendings are assigned at increased frequency to residents and produce less ASA units and less RVUs, compared to male colleagues.

METHODS: This retrospective cohort study qualified for IRB exemption. We reviewed attending assignments within our high-risk operating suite. Inclusion criteria were generalist attendings who worked a minimum of ten days in the high-risk operating suite in a supervisor role between January 1, 2020 and May 15, 2020. Attending assignments are determined by a rotating group of schedulers. Past assignments with respect to CRNA versus resident supervision is generally not considered by schedulers. Pediatric and cardiac attendings who were more likely to receive low ratio resident assignments were excluded. Primary endpoints were type of assignment (CRNA versus resident), ASA unit production, and RVU production. The analysis was by intention-to-treat. Data were analyzed using R Project version 4.0.3. We tested for treatment differences using Welch's t-test for mean comparisons of quantitative data and the chi-squared test for binary characteristics.

RESULTS: Thirteen male and seven female attendings met eligibility criteria. Attendings assigned CRNAs completed a mean of 16 cases per day whereas those assigned residents completed a mean of 6 cases per day. Male attendings were more likely to be Caucasian than female attendings (Table 1). Female attendings generated more RVUs working with residents compared with CRNAs (5.3 RVUs vs. 3.1 RVUs, $p<0.01$). Male attendings generated more RVUs working with residents compared with CRNAs (4.0 RVUs vs 2.8 RVUs, $P=0.07$) (Table 2). Male and female attendings were equally assigned to residents (60.8% vs. 55.7%) ($p=0.75$) (Table 3). Overall, there was a trend towards greater RVU production in female attendings (4.3 vs. 3.6, $p=0.21$), but there was no difference in ASA unit production (99.8 vs. 99.3, $p = 0.94$) (Table 3).

CONCLUSION: Our hypothesis was incorrect. Male and female attendings were equally assigned to residents. While we did not measure implicit bias in schedulers, our results suggest a lack of gender-based implicit bias with regards to frequency of CRNA assignments. Interestingly, we found that there is greater opportunity to earn RVUs working with residents, compared with CRNAs. This may be due to a preferential assignment of complex cases to residents, which often require more RVU generating procedures, such as invasive monitors. The trend of greater RVU production in female attendings suggests that female attendings may be assigned higher complexity cases. This study is limited to our anesthesia department and may not be generalizable to institutions with different scheduling practices and case mixes. It has been suggested that gender-based pay discrepancy can be corrected with the implementation of a compensation plan that includes objective evaluation measures.[6] A multi-centered study is suggested to determine if gender-based differences in anesthesia attending assignments may help explain the gender pay gap.

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Table 1: Subject Baseline Attending Characteristics Stratified by Sex

	Female (n = 7)	Male (n = 13)
Caucasian race, n (%)	3 (42%)	12 (92%)
Attending experience (years), mean	8	7
Fellowship trained, n (%)	4 (57%)	8 (61%)

Table 2. Average RVUs by Sex and Whether Worked with Residents

	Average Units Generated		
	Male	Female	Total
Worked with CRNAs	2.8	3.1	2.9
Worked with Residents	4.0	5.3	4.4
Student T-Test	-1.8	-2.9	-3
p-value	0.07	<.01	<.01
n	100	53	153

Table 3: Trial Endpoints Stratified by Sex

	Female (n = 7)	Male (n = 13)	p value
Assignment to Residents, %	55.7	60.8	0.75
ASA units, mean	99.8	99.3	0.94
RVUs (all cases), mean	4.3	3.6	0.21

ECONOMICS, EDUCATION AND POLICY 22

Robust Scholarly Activity from a New Online Elective in Anesthesia Medical Education Research: A Response to the UME Call for Virtual Learning Opportunities During Covid-19 Pandemic

Tanna J Boyer[1], Sally A Mitchell[2]

[1]IU Health, Zionsville, IN, [2]Indiana University School of Medicine, Indianapolis, IN

INTRODUCTION: The ability to conduct high-quality medical education research is a needed and coveted skill among academic physician faculty. However, this skill is not routinely taught in current UME and GME programs. In fact, medical students most likely equate future careers in research with bench research, clinical research, and NIH grant funding, and are unaware of this inspiring and fulfilling career path. The medical education community needs to attract, engage, and support medical students and physician trainees as medical education researchers to advance the profession, revise curricula, and guide future training. We report how a 100% online course of 2- or 4-week elective in medical education research in the field of anesthesiology garnered interest among medical students and delivered robust academic output. The aim of this elective was to explore opportunities in medical education research in anesthesiology, outline the process for conducting research, and support medical student projects. Our hypothesis was that by developing a research plan and supporting a specific scholarly activity deliverable, medical students would be able to produce appropriately written and methodologically sound research, which would be published in various venues and subsequently add scholarly activity to their ERAS portfolios.

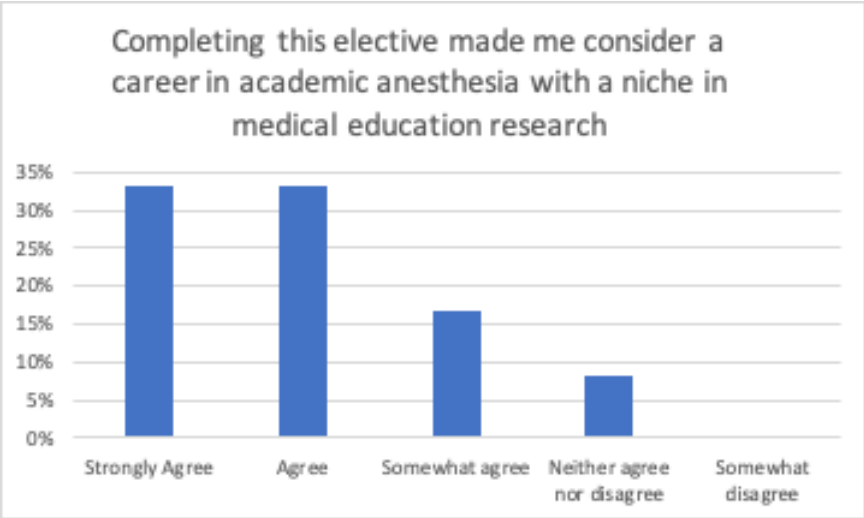
METHODS: Students were invited to read a half-page summary about the course faculty and reply with a half-page summary about themselves and their interests. They were given a list of 10-20 ongoing projects in anesthesia medical education research and asked to rank their top three. Faculty then matched students' needs and interests with a project. Student researchers were given directives, resources, support, and feedback as they worked independently or in pairs toward their deliverable. Communication was via email, document sharing, and occasionally phone calls.

RESULTS: Since the first offering in July 2020, 22 students have completed the course. Students chose to register for a 4-week elective (n=3) or a 2-week elective (n=19), 3 of whom chose to register for a second 2-week rotation. Thus, 22 students completed a total of 56 weeks of instruction and produced 34 scholarly activity deliverables:

- 12 follow-up sim surveys in Qualtrics
- 1 survey for BIPOC students' interest in anesthesia as a career
- 2 Just in Time Training videos for on-demand tutorials of how-to-use task trainers
- 6 posters presented to Indiana Society of Anesthesiologists annual meeting
- 1 poster presented to Society of Hospital Medicine meeting
- 1 podcast accepted to Anesthesia Toolbox
- 8 MedEdPORTAL write-ups in progress
- 2 Journal of Education in Perioperative Medicine write-ups in progress
- 1 Academic Medicine write up in progress

The post-rotation survey was completed by 15 (68%) of 22 students. All students intend to match into anesthesiology residency, 6 (40%) intend to go into private practice, and 9 (60%) intend to join academic anesthesia. Students reported that they spent just the right amount of time on their project (11, 73%) or that they spent too little time on their project (4, 27%). None answered that the elective requirements were too difficult or took too much time. While 14 (93%) agreed that the autonomy given for my project was just right, 11 (73%) were either passive or detractors to the statement the feedback I received on my project was timely. All students agreed or strongly agreed with the statement I learned more about anesthesiology medical education research by completing this elective. Graph 1 shows how this elective has the potential to impact future career plans. One student added a free-text comment: 'Such a great opportunity. It's incredible what can be accomplished in 2 short weeks. The potential for this elective is incredible.'

CONCLUSION: Creation of an elective in medical education research in anesthesiology has been a big success as measured by the 34 deliverables from 22 students. It was run completely online in both 2- and 4-week versions, and produced a substantial amount of high-quality, disseminated scholarly activity. We gave students elective credit for research, provided resources and support, and they proved motivated and capable of producing publishable deliverables. This elective could be replicated for medical education research in other disciplines as well as selective projects in clinical, informatics, and QI research.



ECONOMICS, EDUCATION AND POLICY 23

Financial Impact of Replacing a Daily Emergency Anesthesia Set-up with a Mobile Emergency Case Cart

Deirdre C Kelleher[1], Jimmy Y Lin[2], Erin M Adams[2], Jason E Crowther[2], Patricia F Mack[1]

[1]Weill Cornell Medicine, New York, NY, [2]NY-Presbyterian Hospital - Weill Cornell Medicine, New York, NY

INTRODUCTION: Advanced preparation for emergencies is a cornerstone of quality anesthetic practice. However, the desire to be ready for anything can lead to over-preparation and waste.[1] Furthermore, the safety of advanced set-ups has been brought into question, as they often violate The Joint Commission (TJC) guidelines (e.g., the USP 797 'one-hour' rule).[2] Previously, our institutional practice was to have a full anesthetic set-up prepared every evening and weekend for any emergent cases that may occur. As part of a quality improvement initiative to reduce operating room (OR) waste, it was discovered that most residents and faculty reported never using the emergency set-up. Additionally, our Clinical Practice Committee (CPC) wanted to revise the emergency preparedness practices to better align with TJC recommendations. Therefore in an effort to reduce waste and become more compliant with best practice guidelines, the emergency set-up was replaced with a mobile emergency supply cart containing all the necessary items to start an emergency anesthetic. Additionally, a 'virtual' trauma medication kit was created in order to quickly access emergency medications from the anesthesia work station (AWS). In this project, we sought to quantify the cost savings from eliminating the practice of daily emergency set-ups.

METHODS: A list of all supplies and medications involved in the daily emergency set-up was compiled. Supplies were categorized as either 'disposable,' defined as an item that would have to be thrown out because it was opened (e.g., intravenous tubing and fluid bags), or 'reusable', defined as an item that would not be opened unless needed (e.g., central line kit) or could be used for the first case the next day (e.g., anesthesia machine circuit). Similarly, pharmacy medications were categorized as 'opened' (and thereby must be thrown out if unused) versus 'unopened' (and thereby returnable to the pharmacy). The cost of all supplies and medications were obtained from materials management and pharmacy. Using de-identified operational data for 2019, the total number of emergency cases in each OR were identified. Emergency cases were defined as cases documented as emergent in the anesthesia record and performed by Trauma, Burn, and Critical Care surgeons on patients categorized as ASA Physical Classification System 4 or 5, thereby excluding any routine urgent procedures (e.g., appendectomy). Obstetrical, transplant, and cardiac emergencies were also excluded through this algorithm. The emergency set-up was identified as being used if the case was performed in the designated emergency OR. If the case was performed in any other room or there were no emergency cases in a 24-hour period, the set-up was considered to be wasted.

RESULTS: From January 1 to December 31, 2019, 51 emergency cases (as defined above) were performed at our institution (Figure 1). Of those, only 8 (15.7%) were performed in the designated emergency OR, indicating 357 (97.8%) wasted emergency set-ups in 2019. The full cost of emergency supplies was estimated at $418 plus $163 in medication costs (total: $581, Figure 2). Of those costs, $116 were disposable supplies and $25 were opened medications (total: $141). The estimated annual cost of unused emergency set-ups if only disposable supplies and opened medications were wasted is $50,337. If all supplies and medications were wasted, the cost would increase to $207,417. Currently, an additional $15,708 would be wasted annually, since COVID-19 precautions require a viral filter and plastic anesthesia machine cover (cost: $44).

CONCLUSION: The introduction of a mobile emergency case cart and elimination of a daily emergency set-up has the potential to save our department between $50,000 and $223,000 annually. Beyond cost savings, the change improves compliance with TJC guidelines (including USP 797) and makes emergency equipment readily available for any OR receiving an emergency case, thereby improving both overall safety and preparedness. Eliminating unnecessary set-ups also conserves resources including both the manpower required to prepare the set-up and the supplies that are wasted. Investigations into the frequency and ease of mobile emergency cart use are needed before expanding the cart to other areas of the hospital, such as the interventional neuroradiology and radiology suites.

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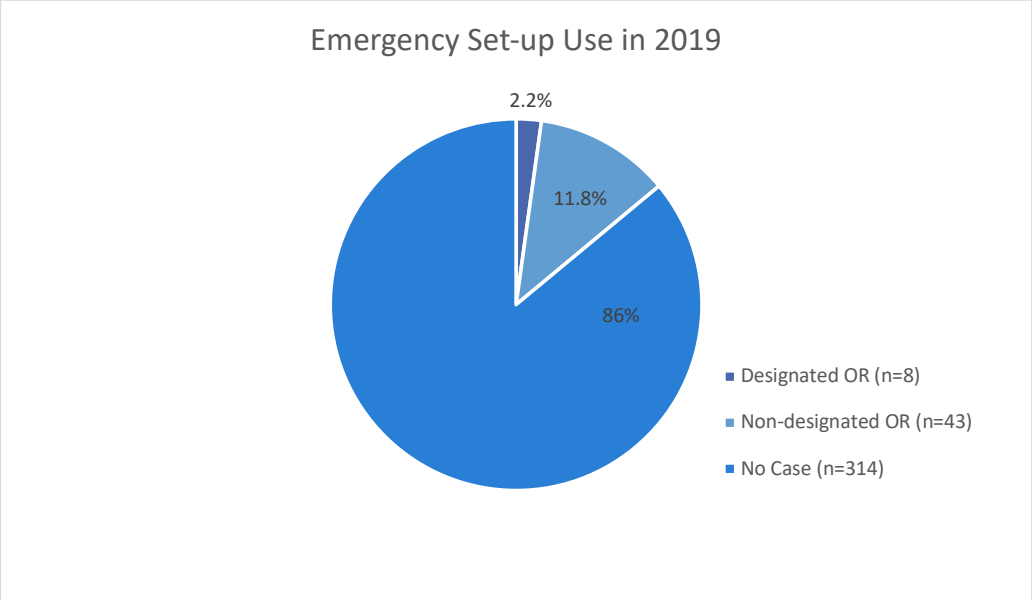

Figure 1. Emergency set-up use in 2019. The set-up was considered used only if an emergency case was performed in the designated emergency operating room (OR). Set-ups were considered wasted if emergency cases went to any other OR or if there were no emergency cases in a 24-hour period.

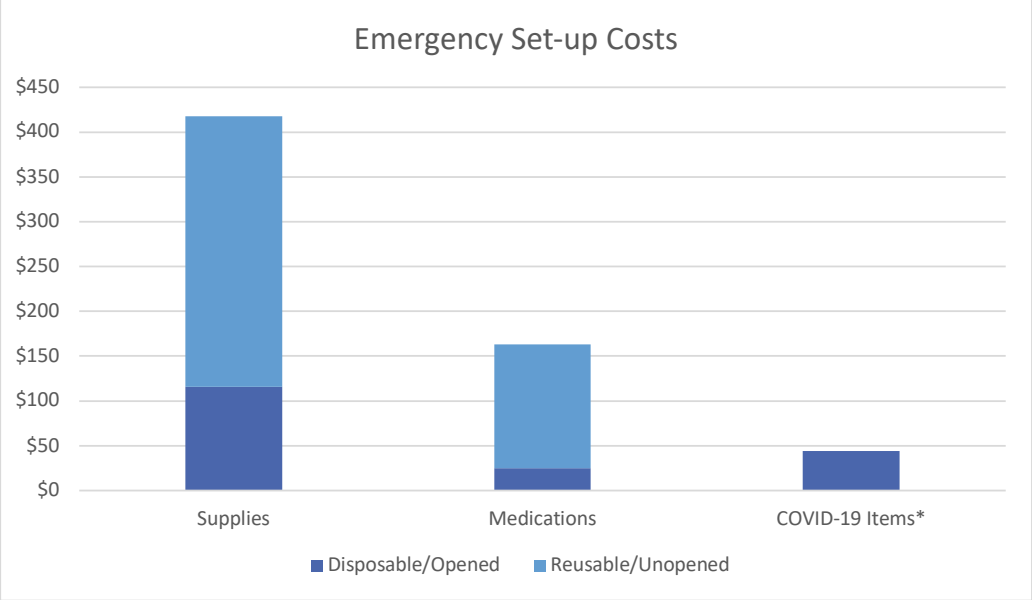

Figure 2. Cost of supplies and medications used in the emergency set-up. “Disposable” items or opened medications must be discarded if not used for an emergency case. “Reusable” items or unopened medications are returnable to the supply cabinet or pharmacy and less likely to be wasted. *Covid-19 items (viral filter and anesthesia machine cover) were a required part of the set-up at the time of the practice change, but were not part of the set-up in 2019.

ECONOMICS, EDUCATION AND POLICY 24

The Development of a Template for Learning Anesthetic and Airway Management: the Medical Student Perspective

Isabelle T Yang[1], Yvon F Bryan[2]

[1]Geisel School of Medicine at Dartmouth, Hanover, NH, [2]Dartmouth-Hitchcock Medical Center, Lebanon, NH

INTRODUCTION: Medical students learn about anesthesiology through independent reading, observation, teaching from clinicians, and active participation. New learners must develop skills to assess and prepare patients, choose anesthetic techniques and airway devices, and understand when and how to use aids and maneuvers for intubation and ventilation. Medical students tend to focus on intubations during their clinical rotation in anesthesia, and most studies on medical students learning anesthesiology have studied best practices for teaching intubations to medical students[1-5]. Though intubation is an important clinical skill in airway management, redirecting learners to appreciate the multiple dimensions of anesthetic and airway management may be more comprehensive. We present a learning guide for medical students to understand the phases of anesthetic and airway management to optimize their learning potential and utilize their skill sets.

METHODS: We divided anesthetic and airway management into seven phases: patient chart review, preoperative evaluation, preparation/premedication, induction, intubation, maintenance, and extubation. For each phase, we separated the clinical course into tasks (interventions and actions by the anesthesia team) and events (complications).

RESULTS: The template was developed by anesthesiologists and medical students. It was used to introduce medical students on a clinical anesthesia elective clerkship to anesthetic and airway management (Figure 1). During procedures, from the preoperative evaluation to the patient exiting the operating room, medical students referenced the guide with consideration to patient risk factors. Medical students were encouraged to record clinical events in relation to interventions employed by the anesthesiologist (see Figure 2 and Figure 3).

CONCLUSION: Our template encouraged medical students to participate in every phase while they maintained a high-level understanding of goals in anesthetic and airway management. A recent survey showed that clinical anesthesia teaching for U.S. medical students occurred in the operating room during the clinical years, and 68% of responding clinician teachers reported that they had no formal training for faculty teachers[6]. This report highlights the need for structure not only in anesthesia teaching, but also in student-driven learning in clinical environments. Our proposed template would be easy to bring to the operating room and reference throughout a procedure. Further work on best practices for teaching and learning in anesthesia would optimize clinical learning for medical students.

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Figure 1. Learning Template for Anesthetic and Airway Management

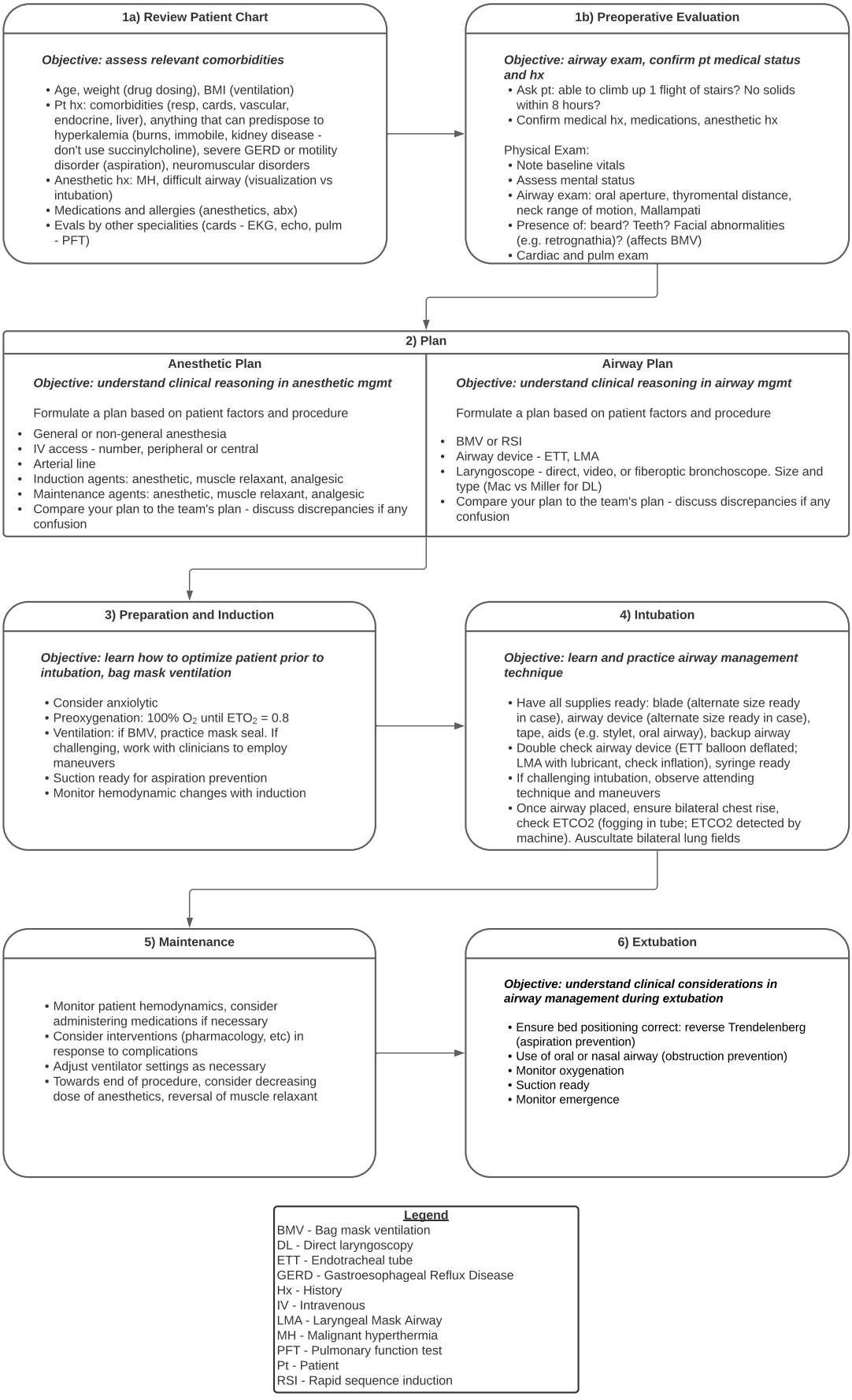

Figure 2. Learning Worksheet for Anesthetic and Airway Management

			CLINICIAN TASK		EVENTS*				
		Medical Student Assisting Task	Intervention	Intubation	Ventilation	Physiologic	Oxygenation	Aspiration	Other
1	Pre-operative Evaluation								
2	Preparation/ Premedication								
3	Induction								
4	Intubation								
5	Maintenance								
6	Extubation								

*For events, record complications experienced. Ventilation includes increases in end-tidal CO2 or periods of apnea. Physiologic changes include large variations in blood pressure or heart rate. Oxygenation includes desaturations. Aspiration includes aspirations risks such as vomiting or dislodging endotracheal tube.

Figure 3. Example of Completed Learning Worksheet for Anesthetic and Airway Management

			CLINICIAN TASK		EVENTS*				
		Medical Student Assisting Task	Intervention	Intubation	Ventilation	Physiologic	Oxygenation	Aspiration	Other
1	Pre-operative Evaluation	40yo male w stable angina, morbid obesity, OSA, GERD, Mallampati 3, beard undergoing femoral bypass graft, cardiac workup normal. No solids for 8h. Baseline vitals 142/96, HR 90, SpO2 99%							
2	Preparation/ Premedication	Help transport pt to OR. My anesthetic plan: general anesthesia, BMV (Trendelenberg for aspiration prevention), 7.5mm ETT with VL #4 due to Mallampati 3. Start A-line due to obesity (BP cuff likely inaccurate) and two peripheral IVs. NG tube? Compare to team.	administered 5mg midazolam. Ordered beside EKG			tachycardic and hypertensive			sweating, anxious
3	Induction	Suction ready. Ask team if I can perform BMV. Expect to be challenging due to beard, so oral airway ready. My induction plan: lidocaine + propofol + rocuronium. Compare to team	Clinician demonstrated jaw thrust, inserted oral airway, rotated patient head to right, squeezed bag		Laborious. Required two-hand BMV. Max detected ETCO2 54mmHg.		99%		
4	Intubation	Ask team if I can perform intubation. Supplies ready. Once tube placed, check for ETT fogging, bilateral chest rise, ETCO2 detected. Ask clinician for ventilation settings. Ask clinician if I can place peripheral IV.	Guided my left hand to performing laryngoscopy, provided cricoid pressure. Administered fentanyl in response to physiologic changes. Administered A-line	Vocal cords difficult to visualize, required few attempts		BP 182/126, HR 101, went back down after fentanyl	Dropped to 94%		
5	Maintenance	My maintenance plan: sevofluorane + propofol, rocuronium (vascular procedure, don't want patient to move) fentanyl if needed. Monitor hemodynamics.	Administered phenylephrine (drip), norepinephrine, fentanyl, adjusted propofol and sevofluorane in response to hemodynamic changes		ETCO2 35-45mmHg	BP 174/116 HR 98 after first incision	97-99%		
6	Extubation	Trendelenberg, oral and nasal airway ready. Suction ready.	Decreased anesthetic dosing 15-30 minutes before end of procedure. Suction NG tube. Twitch monitor showing residual paralysis, administered suggamadex				dropped to 93% during extubation	Some fluid in NG tube, suctioned	

*For events, record complications experienced. Ventilation includes increases in end-tidal CO2 or periods of apnea. Physiologic changes include large variations in blood pressure or heart rate. Oxygenation includes desaturations. Aspiration includes aspirations risks such as vomiting or dislodging endotracheal tube.

ECONOMICS, EDUCATION AND POLICY 25

Promoting perioperative neuroscience exchange and excellence: Neuroanesthesia Program Relations (NPR) committee for International Council on Perioperative Neuroscience Training (ICPNT)

Chanhung Lee[1], Shobana Rajan[2], Val Luoma[3], John Bebawy[4], william a kofke[5]

[1]University of California, San Francisco, San Francisco, CA, [2]Allegheny Health Network, Pittsburgh, PA, [3]UCL, London, United Kingdom, [4]Northwestern University Feinberg School of Medicine, Chicago, IL, [5]University of Pennsylvania, philadelphia, PA

INTRODUCTION: International council on perioperative neuroscience training (ICPNT) is the first international and non-ACGME accreditation council for an anesthesia subspecialty fellowship training. The ICPNT was created in 2019, given increasing interest internationally for standardization and accreditation of neuroanesthesia fellowship programs. One of the unique services that ICPNT offers is a collaborative sharing of educational, scientific, and professional resources between programs. With this mission in mind, the Neuroanesthesia Program Relations (NPR) committee was created. In this abstract, we seek to present the launching of collaborative activities of NPR committee in an effort to promote and connect neuroanesthesia education and training in fellowship programs around the world.

METHODS: A number of activities were designed as part of this effort to be a center for education in neuroanesthesia. NPR organized its first patient safety session on 'Crisis management in neuroanesthesia' at the 2020 annual meeting of Society of Neuroscience for Anesthesiology and Critical Care (SNACC). The other goal is to offer the 'ICPNT rounds' regularly, similar to grand rounds. The aim is to enable fellows in the ICPNT accredited fellowship programs to present at journal clubs, to facilitate case-based discussions and to organize academic seminars using online video communication platforms. The online platform has greatly facilitated the international programs to participate the virtual NPR activities, despite the time zone laps. Up to date, ICPNT has conducted three webinars. The first, a seminar with timely discussion on 'Neurological Manifestations of COVID-19 ' after the initial surge of the pandemic (June 2020). More recently, a journal club was conducted to discuss three recent articles in areas of perioperative management of neurological surgical patients (November 2020). Participant feedback was collected after the journal club. It was followed by a case based reasoning webinar: ' When the Going Gets Tough - The Tough Get Going!' (January 2021).

RESULTS: Our first NPR/ICPNT webinar on case-based discussions welcomed 98 registrants, including neuroanesthesia faculty, fellows, and residents. They represent medical institutions located at continents around the globe: Africa, Asia, Europe, North America, Oceania, and South America. (Figure 1) The first NPR/ICPNT journal club was also well-attended by 100 registrants from around the world. Our post-event survey demonstrated that 81.8% of respondents rated it as excellent and 18.2% as good, respectively (n=26). (Figure 2)

CONCLUSION: The Neuroanesthesia Program Relations committee (NPR) for ICPNT creates an international collaborative platform for the accredited programs which may wary widely in their neuroanesthesia practices, to share academic resources and to learn from each other's experiences. This program represents an opportunity for fellows and faculty to gain worldwide exposure of educational presentations. We believe this is one of the first such innovative educational efforts in sub-specialty education.

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ICPNT Webinar Registrants Map

Fig. 1

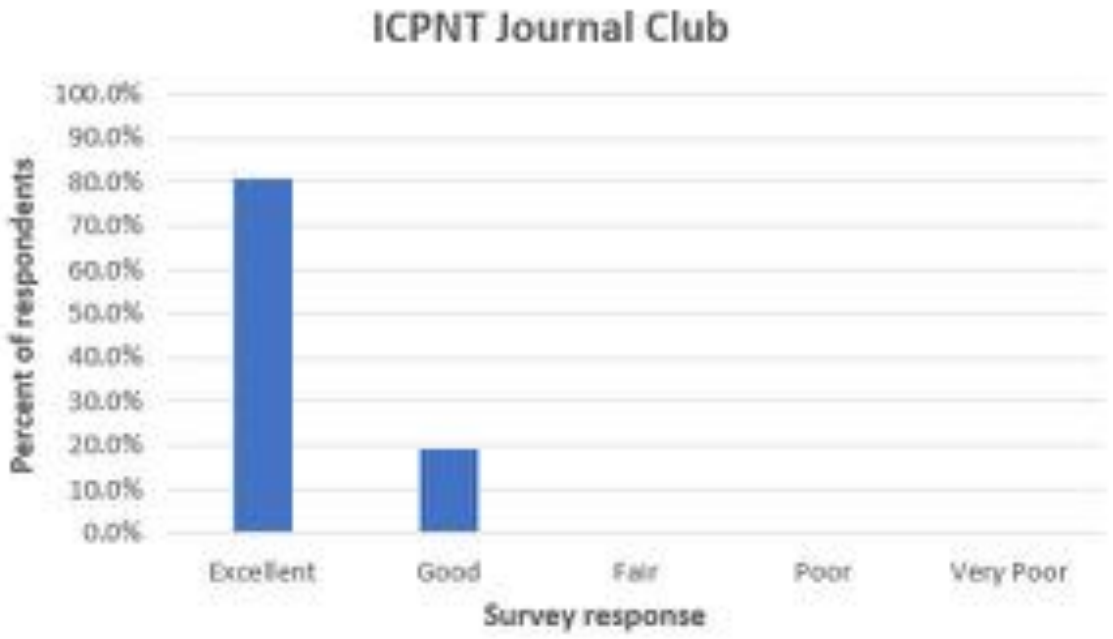

Fig. 2

ECONOMICS, EDUCATION AND POLICY 26

Assessing the Quality and Impact of Randomized Control Trials in Predatory Journals

Ajit S Rai[1], Nikesh Chander[2], Ahmed Al Khalil[1], Kelly Cobey[2], Gregory L Bryson[3], Daniel I McIsaac[1], Manoj M Lalu[3]

[1]University of Ottawa Faculty of Medicine, Ottawa, Ontario, [2]University of Ottawa, Ottawa, Canada, [3]The Ottawa Hospital, Ottawa, Ontario

INTRODUCTION: Predatory journals are entities that prioritize self-interest at the expense of scholarship[1]. They lack transparency, and/or use aggressive and indiscriminate solicitation practices, while often publishing articles with virtually no peer reviewing, editing or quality control. This can lead to dissemination of false or misleading information. Randomized controlled trials (RCTs) serve as one of the highest denominations in guiding decisions that affect healthcare and policy. If a poor quality RCT is published in a predatory journal but is identified by a clinician, literature reviews, policy makers, or other sources, it could impact treatment decisions. We investigated the prevalence, characteristics and impact of RCTs published in predatory anesthesia journals.

METHODS: We identified potential predatory anesthesia journals using Beall's list and a previous study characterizing these journals[2]. All articles from these journals were screened independently and in duplicate to identify RCTs. Included journals were assessed for predatory characteristics using a 10-item list. We assessed articles by using three categories; false or misleading information, deviation from best practice, and lack of transparency. Basic study characteristics, completeness of reporting (selected CONSORT items), and the risk of bias (Cochrane risk of bias tool) were assessed in duplicate by two independent reviewers. A citation analysis was conducted using four independent databases (Google Scholar, Web of Science, Dimensions, and Microsoft Academic) to determine the impact of these articles on the legitimate literature. Citation in policy documents was assessed using the OVERTON database.

RESULTS: 5646 articles were screened from 66 journals and 1265 reports of RCTs were identified (67% published since 2015). These RCTs were conducted in 63 countries (India n=543, Iran n=230, and Egypt n=153, were most frequent, Figure 1), with a total of 106,934 participants and a median sample size of 69 (range: 12-800). Journals had a median of 2 (range: 1-5) predatory characteristics. Overall, reporting of key methodological criteria was poor, with less than 50% of studies reporting a sample size calculation and less than 20% reporting a participant flow diagram. Only one trial was found to be at a low risk of bias across all assessed domains, while 1,125 trials were determined to be at a high or unclear risk of bias across the majority of domains (≥4 out of 7). 1,146 studies reported research ethics board approval, 194 were registered in a clinical trials database (35 were registered a priori or within 21 days of trial initiation, as per best practices). 172 studies reported a source of funding including academic (144 studies), industry (13 studies), government (6 studies), and foundations (5 studies). Articles were cited a total of 5523 (range: 0-112) times on Google Scholar, 1574 (0-30) times on Web of Science, 2557 (0-45) times on Dimensions, and 2346 (0-113) times on Microsoft Academic. Of note, 29 RCTs were cited by Cochrane Reviews, with 13 included in quantitative syntheses. 33 RCTs were cited by 21 different policy documents from the United Kingdom (n=11), Canada (n=6), the United States (n=5), and Germany (n=1).

CONCLUSION: A large number of RCTs in the field of anesthesia have been published in predatory journals. The majority of these trials were at an unclear risk of bias due to poor methodological reporting. Despite the potential poor quality of data, these articles have permeated the legitimate scientific literature including influential systematic reviews and policy documents.

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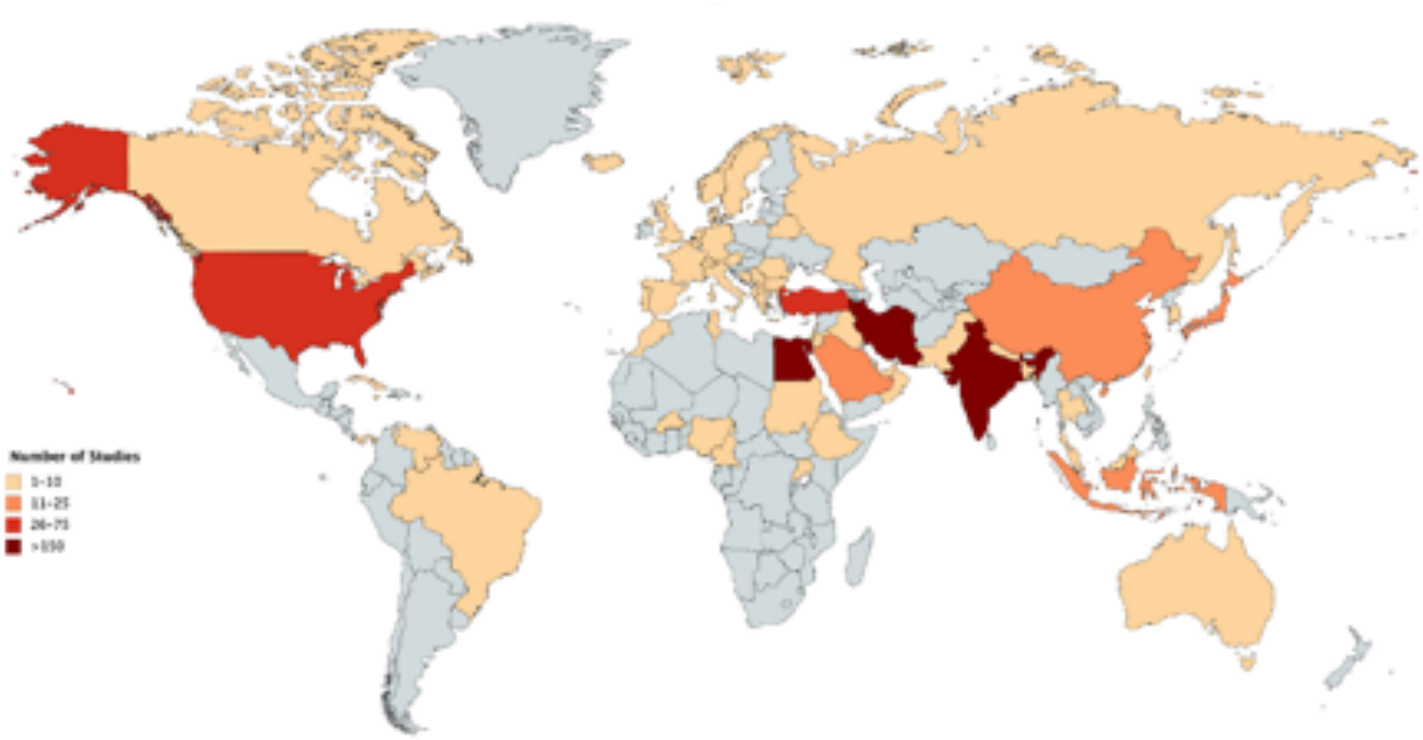

Fig. 1

Subspecialty Abstracts

GERIATRIC ANESTHESIA

GERIATRIC ANESTHESIA 1

Documentation of Perioperative Neurocognitive Disorder Risk led to Change in Perioperative Anesthetic Management

Justyne Decker[1], Arash Motamed[1], Jeniffer Kim[2], Hojean Yoon[2], Tatyana Gurvich[3], Carolyn L Kaloostian[4], Carol J Peden[5], John Margetis[2]

[1]Keck School of Medicine, University of Southern California, Los Angeles, CA, [2]University of Southern California, Los Angeles, CA, [3]USC School of Pharmacy, Los Angeles, CA, [4]Keck School of Medicine of USC, Los Angeles, CA, [5]Keck Medicine of USC, Los Angeles, CA

INTRODUCTION: The most common perioperative complication to affect older adults is the development of a perioperative neurocognitive disorders (NCD) with the biggest risk factor being the presence of preoperative cognitive impairment[1,2] American College of Surgeons, American Geriatric Society and American Society of Anesthesiologists recommend routine preoperative cognitive screening in the geriatric surgical population.[2,3] In response to recommendations, the Pre-Operative Clinic at Keck Medical Center of USC implemented routine cognitive screening to identify older surgical patients at risk for perioperative NCD. Our aim is to determine whether documentation of preoperative cognitive screening status leads to a change in perioperative anesthetic management.

METHODS: This retrospective study seeks to determine whether knowledge of preoperative cognitive status influences perioperative anesthetic management. All patients age >65 years presenting for preoperative evaluation prior to elective surgery are routinely screened with Mini-Cog; a score <2 was a positive screen consistent with preoperative cognitive impairment [1]. This score was documented in the preoperative consultation note without a direct perioperative recommendation for day-of-surgery anesthesiology team.A sample was taken during the time of transition into EMR documentation, meaning that the preoperative cognitive status was known to the study but may have not been included in the EMR. A departmental grand rounds was delivered on perioperative brain health, which contained suggested action items, such as, discussion of perioperative cognitive risk during informed consent, encouraging low risk medications, BIS monitoring and age adjusted MAC, and avoidance of high risk medications with suggested alternatives[1]. A chart review was performed to detect change in perioperative management. Variables considered were use of multimodal analgesia, administration and dose of high-risk medications, such as benzodiazepines and anticholinergic medications, administration of low-risk medications, such as acetaminophen, use of BIS to monitor depth of anesthesia and age adjusted MAC.

RESULTS: We retrospectively reviewed 250 patients who had Mini-Cog screens performed, of which 125 had no documentation of Mini-Cog and 125 did. We excluded patients with pre-existing dementia, emergency surgery, and preoperative inpatient status. The demographics of the two groups were not statistically, significantly different (Table 1). Patients with documented Mini-Cog scores received significantly lower rates and amounts of benzodiazepine premedication, Odds Ratio (OR) 3.6, $p<0.001$ (Table 2). This was regardless of Mini-Cog result, but benzodiazepine use was more markedly reduced in patients with documentation of a poor Mini-Cog score. Documentation of preoperative cognitive status led to decrease in other high-risk medications with anticholinergic properties (OR 3.4, $p=0.04$), such as scopolamine, meperidine, diphenhydramine (Table 2). In addition, low-risk medications, such as acetaminophen, and multimodal analgesia techniques were more frequently utilized (OR 8.0, $p<0.001$; OR 3.4, $p<0.001$ respectively) (Table 2). Lastly, the use of BIS was more likely in patients, who had preoperative cognitive status reported (OR 3.4, $p<0.001$) (Table 2).

CONCLUSION: We screened all patients at risk for preoperative cognitive impairment and observed a change in anesthetic practice when there was documentation of preoperative cognitive status in the EMR, as evidenced by reduced high-risk medication administration (benzodiazepines, anticholinergics), increased administration of low-risk medication (acetaminophen), increased multimodal analgesics and increased use of BIS monitoring and age adjusted MAC. Future studies will assess whether these changes led to differences in PACU ready times or incidence of emergence and/or postoperative delirium.

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Table 1: Patient Demographics

	All Patients (N=250)		POC Note (n=125)		No POC Note (n=125)		
	mean (SD)	range	mean (SD)	range	mean (SD)	range	
Age (years)	74.7 (6.3)	65.3-95.0	75.2 (6.7)	65.3-95.0	74.1 (5.8)	65.3-90.4	
Sex	n	%	n	%	n	%	p-value
Male	168	67.2	88	70.4	80	64.0	0.3
Female	82	32.8	37	29.6	45	36.0	
Race							
Asian	15	6.0	8	6.4	7	5.6	0.7
Black or African Am.	15	6.0	7	5.6	8	6.6	
Native Hawaiian/PI	1	0.4	1	0.8			
White	180	72.0	89	71.2	91	72.8	
Other	37	14.8	18	14.4	19	15.2	
Refuses/Don't Know	2	0.8	2	1.6			
Ethnicity							
Hispanic or Latino	35	14.0	18	14.4	17	13.6	0.8
Non Hispanic or Latino	207	82.8	104	83.2	103	82.4	
Refuses/Don't Know	7	2.8	3	2.4	4	3.2	
Unknown	1	0.4			1	0.8	
Service							
CRS	4	1.6	3	2.4	1	0.8	0.06
Cardiac	6	2.4			6	4.8	
ENT	6	2.4	3	2.4	3	2.4	
GYN	1	0.4			1	0.8	
General	13	5.2	8	6.4	5	4	
HBS	2	0.8	1	0.8	1	0.8	
Ortho	31	12.4	16	12.8	15	12	
Spine	17	6.8	9	7.2	8	6.4	
Thoracic	5	2.0	1	0.8	4	3.2	
Urology	149	59.6	81	64.8	68	54.4	
Vascular	16	6.4	3	2.4	13	10.4	
Mini Cog Score							
5	53	21.2	25	20	28	22.4	0.6
4	54	21.6	27	21.6	27	21.6	
3	68	27.2	39	31.2	29	23.2	
2	43	17.2	17	13.6	26	20.8	
1	20	8.0	11	8.8	9	7.2	
0	12	4.8	6	4.8	6	4.8	

Table 2: Anesthetic Management

	All Patients* (N=250)			Documentation (n=125)		No Documentation (n=125)			
	n	%		n	%	n	%	p-value	Odds Ratio
Anticholinergics									
Yes	16	6.4		4	3.2	12	9.6	**0.04**	**3.2**
No	234	93.6		121	96.8	113	90.4		
Multimodal									
Yes	173	69.2		102	81.6	71	56.8	**<0.001**	**3.4**
No	77	30.8		23	18.4	54	43.2		
Tylenol									
Yes	113	45.2		86	68.8	27	21.6	**<0.001**	**8.0**
No	137	54.8		39	31.2	98	78.4		
Benzo									
Amount (mg) [mean, SD, range]	0.78	0.9	0-4	0.4	0.7	1.2	1.0		
Yes	119	47.6		40	32.0	79	63.2	**<0.001**	**3.6**
No	131	52.4		85	68.0	46	36.8		
BIS (n=110)									
Amount [mean, SD]	49	7.1	29.0-60.0	52.6	4.4	41.8	6.3		
Yes	110	44.0		73	58.4	37	29.6	**<0.001**	**3.4**
No	140	56.0		52	41.6	88	70.4		

GERIATRIC ANESTHESIA 2

Effects of Comprehensive Geriatric Care Models on Postoperative Outcomes in Geriatric Surgical Patients: A Systematic Review and Meta-analysis

Aparna Saripella[1], Sara Wasef[1], Mahesh Nagappa[2], Sheila Riazi[1], Marina Englesakis[3], Jean Wong[4], Frances F Chung[1]

[1]Toronto Western Hospital; University Health Network; University of Toronto, Toronto, Ontario, Canada, [2]London Health Sciences Centre and St. Joseph Health Care; Western University, London, Ontario, Canada, [3]Toronto General Hospital; University Health Network, Toronto, Ontario, Canada, [4]Toronto Western Hospital; University Health Network; Women's College Hospital; University of Toronto, Toronto, Ontario, Canada

INTRODUCTION: Surgery on the elderly results in greater complications, prolonged length of hospital stay (LOS), increase in emergency department visits, readmission rates, post-discharge care requirements, and health care costs. It is not clear whether comprehensive geriatric care models are effective in reducing adverse events. The objective of this systematic review and meta-analysis is to determine whether the comprehensive geriatric care models improved clinical outcomes, particularly in decreasing the prevalence of delirium and length of hospital stay (LOS) in elderly surgical patients.

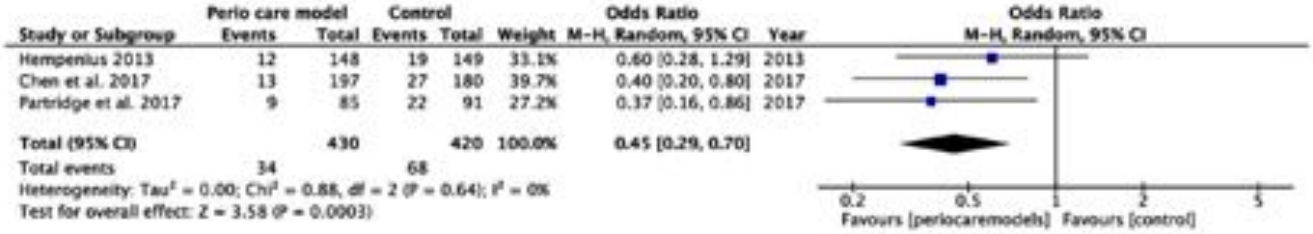
METHODS: We searched Medline, PubMed, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Emcare Nursing, Web of Science, Scopus, CINAHL, ClinicalTrials.Gov, and ICTRP between 2009 to January 23, 2020. We included studies on geriatric care models in elderly patients (≥60 years) undergoing elective, non-cardiac high-risk surgery. The included studies were randomized controlled trials (RCTs) and observational studies (including cohort and cross-sectional). Two reviewers (AS, SW) screened literature studies (using Rayyan), assessed the risk of bias, collected data, and analyzed independently. All conflicts were resolved by consensus and a third reviewer (FC). The risk of bias was assessed using the Cochrane Risk of Bias Tool (RCTs) and Newcastle-Ottawa scale (observational studies). The outcomes were the prevalence of delirium, LOS, rates of 30-days readmission, and 30-days mortality. Random effect meta-analysis was conducted using the Cochrane Review Manager Version 5.3. We assessed the quality of the evidence by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

RESULTS: Eleven studies were included with 2,672 patients; RCTs: 4;Observational studies (non-RCTS): 7. Data pooled from three RCTs showed that there was a significant difference in the prevalence of delirium between the intervention and control groups: 7.9% vs. 16% (odds ratio: 0.45; 95% CI: 0.29, 0.7; I2: 0%; p=0.0003) with an absolute risk reduction of 8%; and number needed to treat of 13. For both RCTs and non-RCTs, there were no significant differences in the LOS (non-RCT: p=0.90), (Figure A, B) rates of 30-day readmission (RCT: p=0.25; non-RCT: p=0.96), and 30-day mortality (RCT: p=0.11; non-RCT: p=0.86). All geriatric care models contained CGA, which is an established multi-domain assessment addressing patients' physiological, social, psychological, and functional state before surgery. Using the Cochrane tool, the four RCTs had low bias on most of the domains. According to the Newcastle Ottawa scale scoring system, the quality of the six non-RCTs ranked from 7 to 9 indicated a low risk of bias. The quality of evidence was low to very low.

CONCLUSION: The geriatric care models involved pre-operative comprehensive geriatric assessment, and intervention tools to address cognition, frailty, and functional status. In non-cardiac high-risk surgeries, these care models decrease the prevalence of delirium in geriatric patients. We found no differences in the LOS, rates of 30-days readmission, and mortality. Further RCTs are warranted to evaluate these models on the postoperative outcomes. PROSPERO registration number - CRD42020181779.

Figure A - Delirium

Randomized Controlled Trials



Non-Rondomized Controlled Trials

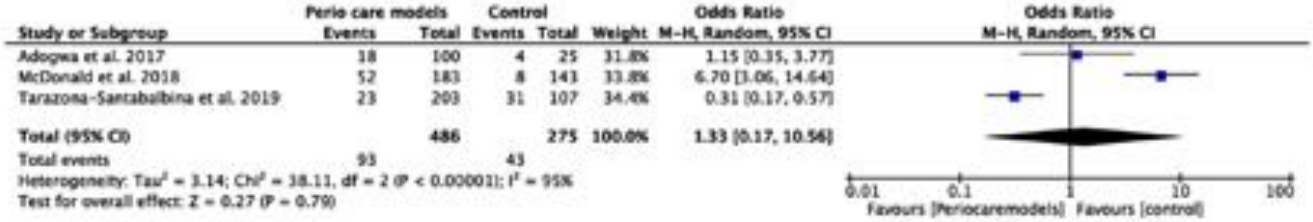
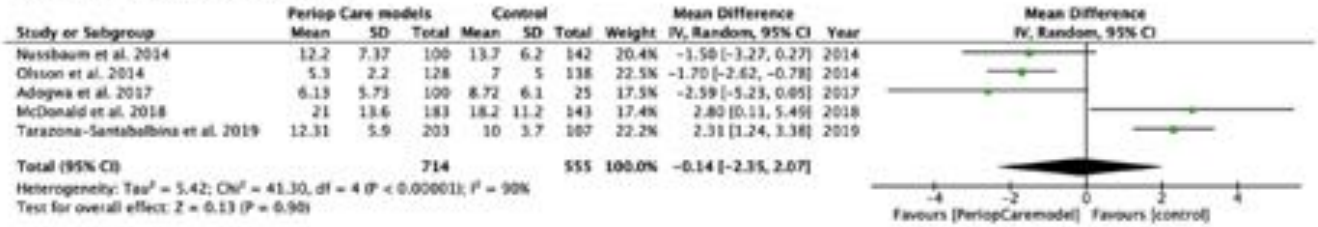


Figure B - Length of Hospital Stay

Non-Randomized Controlled Trial



GERIATRIC ANESTHESIA 3

Association between sleep duration on the night before surgery and postoperative cognitive function: a prospective cohort study

Masakazu Kotoda[1], Ayasa Takamino[1], Yosuke Nakadate[1], Sohei Hishiyama[1], Kazuha Mitsui[1], Tetsuya Iijima[1], Takashi Matsukawa[1]

[1]University of Yamanashi, Chuo, Japan

INTRODUCTION: Postoperative cognitive dysfunction (POCD) is a growing health care problem and a serious complication after anesthesia and surgery, especially among elderly populations.[1] Despite cumulative efforts, the precise underlying mechanisms and risk factors of POCD are not fully understood. A growing body of evidence suggests an association between cognitive function and sleep duration, showing that both short and long sleep durations are associated with impaired cognitive function.[2,3] However, the impact of preoperative sleep duration on postoperative cognitive function is unclear. Therefore, this study aimed to test the hypothesis that extreme sleep duration on the night before surgery negatively affects the postoperative cognitive function and increases the incidence of POCD.

METHODS: After acquiring Institutional Review Board approval, this prospective cohort study enrolled 321 patients aged ≥65 years who underwent elective non-cardiac and non-cranial surgery under general anesthesia. Mini-Mental State Examination (MMSE) was conducted to assess preexisting cognitive impairment. Sleep duration was measured using a wearable sleep tracker on the night before surgery, and the patients were categorized into following four groups according to the sleep duration: <5 h, 5–7 h, 7–9 h, and >9 h. Perioperative cognitive function was monitored using a cognitive test battery (Rey auditory verbal learning test, trail making test, letter fluency test, and category fluency test) prior to surgery (baseline) and 1 week, 1 month, 3 months, and 6 months after surgery. Patients were considered to have POCD if their postoperative scores decreased by >1 standard deviation of all the included patients' baselines scores on at least two tests.4 The incidence of POCD at 6 months after surgery was analyzed using the multiple logistic regression analysis. The group with 7–9 h sleep duration served as a reference group. Additionally, each cognitive test result over 6 months was analyzed using two-way repeated measures analysis of variance. $P < 0.05$ was considered statistically significant.

RESULTS: A total of 195 patients (mean age: 72.9 years, 48 % female) was included in the analysis, and 126 patients were excluded due to preexisting cognitive impairment (MMSE score < 24), dropout/withdrawal, or missing sleep duration data. The group with a sleep duration of 7–9 h exhibited the lowest incidence of POCD at 6 months after surgery (13.5%) [Figure]. Extremely short sleep duration (<5 h) was associated with a significantly higher incidence of POCD than a sleep duration of 7–9 h (adjusted odds ratio 5.53, 95% confidence interval 1.64–18.7, $P < 0.01$). Compared with the reference group (7–9 h), the extremely short (<5 h) and long (>9 h) sleep duration groups had significantly worse scores in all four cognitive tests over 6 months.

CONCLUSION: Both short and long sleep durations on the night before surgery were associated with worse postoperative cognitive function, and sleep duration <5 h was associated with a higher incidence of POCD.

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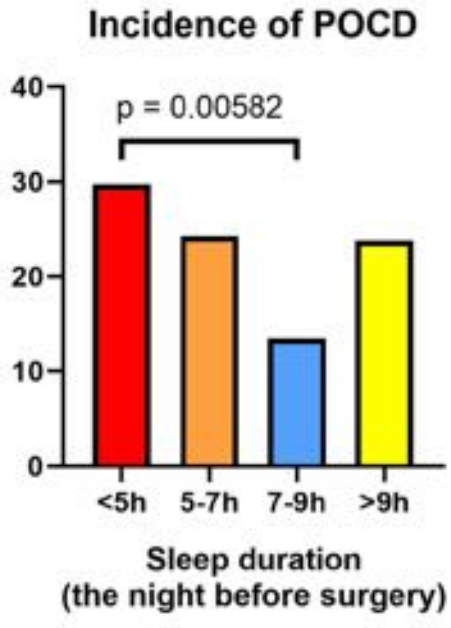

GERIATRIC ANESTHESIA 4

Preoperative cognitive impairment and frailty are risk factors for adverse postoperative outcomes after perioperative potentially inappropriate medication administration

Kevin Burfeind[1], Praveen Tekkali[2], Joseph Quinn[3], Katie J Schenning[1]

[1]Oregon Health & Science University, Portland, OR, [2]Oregon Health and Science University, Portland, OR, [3]Oregon Health & Science University, Portland, United States of America

INTRODUCTION: The American Geriatrics Society maintains a list of potentially inappropriate medications (PIMs) best avoided in adults ≥65 years[1]. Recent best-practice guidelines recommend avoiding perioperative administration of these medications in all geriatric surgical patients[2,3]. However, it is unclear whether PIM administration increases the incidence of poor postoperative outcomes in at-risk older adults. We investigated whether preoperative frailty or cognitive impairment increases the risk for poor postoperative outcomes after perioperative PIM administration.

METHODS: We performed a retrospective study of patients ≥65 years that underwent elective inpatient surgery at a large academic medical center from February 2018 to January 2020. Edmonton Frail Scale and Mini-Cog screening tools were administered to all patients at their preoperative clinic visit. A Mini-Cog score 0-2 was considered cognitive impairment, and frailty was defined by an Edmonton Frail Scale score≥ 8. The effects of preoperative frailty, cognitive impairment, and perioperative PIM administration on length of hospital stay and discharge disposition were assessed. One-way ANOVA or t-test was used to compare average length of hospital stay or discharge disposition. Linear regression analysis was used to determine relationships between frailty status, cognitive status, PIM administration, and length of stay.

RESULTS: 1,627 patients (mean age 73.7±6.3 years, 49.1% male) were included (Table 1). 72% of frail patients and 71% of patients with Mini-Cog 0-2 received at least one PIM (Table 2). Perioperative administration of at least one PIM was associated with longer hospital stay after surgery (3.00±4.83 days vs. 4.84±5.65 days, P<0.001). Linear regression analysis demonstrated an association between Edmonton Frail Scale score and length of stay (R^2=0.009, F=14.2, P<0.001), as well as number of PIMs and length of stay (R^2=0.004, F=7.2, P=0.007) (Fig. 1). Frail patients that received PIMs had a longer length of stay than non-frail patients who received PIMs (4.67±5.63 days vs. 6.26±6.00 days, P=0.009) (Table 3). While PIMs had no effect on discharge disposition for cognitively intact and nonfrail patients, cognitively impaired patients that received at least one PIM were more likely to discharge to a care facility than cognitively intact patients that received at least one PIM (36% vs. 30%, P=0.02). In addition, frail patients that received at least one PIM were more likely to discharge to a care facility than frail patients that did not receive any PIMs (41% vs 60%, P<0.001) (Table 4).

CONCLUSION: PIM administration to cognitively impaired and frail older adults is common in the perioperative period, and associated with increased length of hospital stay. Preoperative frailty and cognitive impairment increase the detrimental effects of perioperative PIMs, and should be screened for preoperatively to guide perioperative medication administration.

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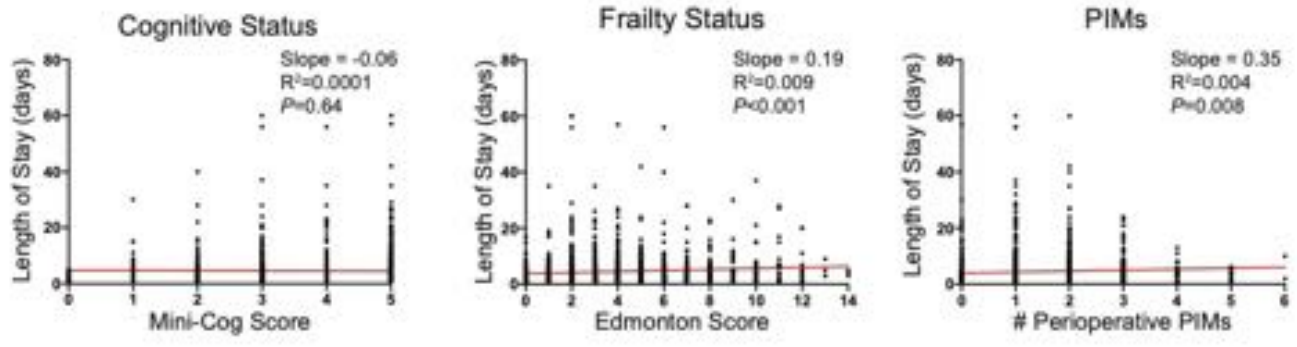

Fig. 1

Patient Characteristics	
Age, yr (SD)	73.7 (6.3)
Male Sex, n (%)	800 (49.1)
ASA Class, n (%)	
I	7 (0.4)
II	450 (27.7)
III	948 (58.4)
IV	219 (13.5)
Procedure Department, n (%)	
Orthopedic	569 (35.0)
Cardiac	261 (16.1)
General	220 (13.5)
Neurosurgery	161 (9.9)
Otolaryngology	98 (6.0)
Vascular	92 (5.7)
Urlogy	82 (5.0)
Gynecology	17 (1.0)
Other	124 (7.6)
Type of Anesthesia, n (%)	
General	1168 (71.7)
MAC	299 (18.3)
Nerve Block	68 (4.2)
Spnal	48 (2.9)
Epidural	45 (2.8)
Cogntivie Status, n (%)	
Mini-Cog 3-5	1450 (89.1)
Mini-Cog 0-2	177 (10.9)
Frailty Status, n (%)	
Edmonton 0-7	1428 (87.8)
Edmonton 8+	199 (12.2)

Table 1

Number of PIMs	Mini-Cog 3-5 (n=1450)	Mini-Cog 0-2 (n=177)	Edmonton 0-7 (n=1428)	Edmonton 8+ (n=199)
0	268	50	269	49
1	505	58	496	67
2	460	54	454	60
3	172	13	166	19
4	31	2	30	3
5	12	0	11	1
6	2	0	2	0

Table 2

Group	n	Mean±SD	Comparison	P-value	Comparison	P-value
Mini-Cog 3-5	1450					
PIM (-)	268	2.93±4.85	Mini-Cog 3-5	**<0.001**	Mini-Cog 3-5 PIM (-)	>0.99
PIM (+)	1182	4.85±5.71	PIM (-) vs. PIM (+)		Mini-Cog 0-2 PIM (-)	
Mini-Cog 0-2	177					
PIM (-)	50	3.36±4.75	Mini-Cog 0-2	0.18	Mini-Cog 3-5 PIM (+)	>0.99
PIM (+)	127	4.92±5.11	PIM (-) vs. PIM (+)		Mini-Cog 0-2 PIM (+)	
Edmonton 0-7	1428					
PIM (-)	269	2.79±4.70	Edmonton 0-7	**<0.001**	Edmonton 0-7 PIM (-)	>0.99
PIM (+)	1159	4.67±5.63	PIM (-) vs. PIM (+)		Edmonton 8+ PIM (-)	
Edmonton 8+	199					
PIM (-)	49	3.21±4.53	Edmonton 8+	0.05	Edmonton 0-7 (+)	**0.009**
PIM (+)	150	6.26±6.00	PIM (-) vs. PIM (+)		Edmonton 8+ (+)	

Table 3

Group	n	Discharge Home	Discharge to CF	Percentage CF	Comparison	P-value	Comparison	P-value
Mini-Cog 3-5	1446							
PIM (-)	265	198	67	25%	Mini-Cog 3-5	0.82	Mini-Cog 3-5 PIM (-)	0.48
PIM (+)	1181	869	312	26%	PIM (-) vs. PIM (+)		Mini-Cog 0-2 PIM (-)	
Mini-Cog 0-2	177							
PIM (-)	50	35	15	30%	Mini-Cog 0-2	0.48	Mini-Cog 3-5 PIM (+)	**0.02**
PIM (+)	127	81	46	36%	PIM (-) vs. PIM (+)		Mini-Cog 0-2 PIM (+)	
Edmonton 0-7	1428							
PIM (-)	269	207	62	23%	Edmonton 0-7	>0.99	Edmonton 0-7 PIM (-)	**0.01**
PIM (+)	1159	893	266	23%	PIM (-) vs. PIM (+)		Edmonton 8+ PIM (-)	
Edmonton 8+	199							
PIM (-)	49	29	20	41%	Edmonton 8+	**0.02**	Edmonton 0-7 (+)	**<0.001**
PIM (+)	150	60	90	60%	PIM (-) vs. PIM (+)		Edmonton 8+ (+)	

Table 4

GERIATRIC ANESTHESIA 5

Smartphone based walking cadence to assess functional status in older adults

Daniel S Rubin[1], Sylvia Ranjeva[2], Megan Huisingh-Scheetz[3], Jacek Urbanek[4]

[1]University of Chicago, Chicago, IL, [2]Massachusetts General Hospital, Boston, United States of America, [3]University of Chicago, Chicago, United States of America, [4]Johns Hopkins, Baltimore, United States of America

INTRODUCTION: Functional status is an important predictor of perioperative morbidity and mortality. A 6-minute walk test (6MWT) predicts perioperative morbidity and mortality using a distance cutoff; however, this may underestimate functional status in older adults as stride length decreases in older age.[1,2] Walking cadence is an easy to use metric with 100 steps/min equivalent to moderate intensity physical activity.[3] Further, accelerometers embedded in smartphones may make an easily accessible platform to measure walking cadence and perform a 6MWT prior to a preoperative clinic visit. We hypothesized that walking cadence during a 6MWT may provide a better estimate of the ability to perform moderate intensity activity.

METHODS: We conducted a cohort study using a smartphone application developed to administer and measure a 6MWT and DASI survey for patients in the Successful Aging and Frailty Evaluation (SAFE) Clinic at the University of Chicago. The SAFE clinic was chosen as older adults have decreased overall activity and less likely to engage in moderate activity. The application recorded accelerations of the participants at a sampling rate of 30Hz during the 6MWT. A smartphone was placed on a hip holster or front pants pocket for each walk. Data was sent to a secure server and analyzed using an adaptive empirical pattern transformation (ADEPT) application for stride segmentation to estimate walking cadence.[4] Cadence was determined at each minute and overall for the entire 6-minutes. Informed consent was obtained for all participants.

RESULTS: We enrolled 30 patients into our cohort from the SAFE clinic. The median(IQR) age was 71(69-73) years, 24(80%) were female and 15 (50%) were pre-frail according to Fried's frailty phenotype. The median DASI score was 41 (33-51) and mean 6MWT distance 350(112) meters, with only 7 (23%) participants walking greater than 437m. Of the 30 6MWT performed using the smartphone application 3 were excluded, 1 could not complete the walk, 1 fell because he was not using his walker and 1 because walking strides could not be identified by the ADEPT program. The raw accelerometer output and vector mean counts and aligned and segmented strides from the walks, can be seen in Figure 1. The median cadence for all walks (strides/min) was 109(100-116). 7 patients did not reach the threshold of 100 steps/min during the 6MWT and 6 (86%) walked less than 437 meters.

CONCLUSION: Cadence rates for older adults reached a threshold considered moderate activity despite only 26% of them reaching the distance threshold. We identified that older adults can reach a moderate activity threshold (100 steps/min) and are commonly classified as having a poor functional status that may require additional preoperative workup. The 6MWT may be prone to misclassify older adults and further research is required to further clarify functional status estimate in older adults. Smartphones offer a novel platform to measure functional status and may be leveraged for walking interventions prior to major non-cardiac surgery.

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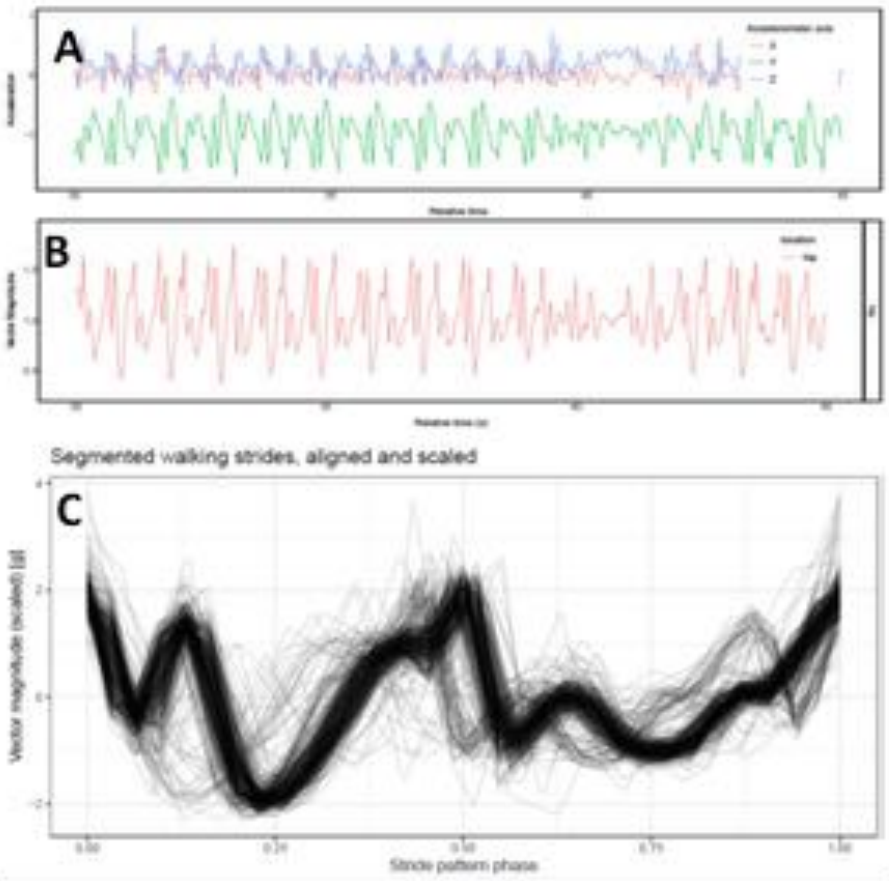

Figure 1: **A**: 15 second sample of raw triaxial accelerometer output from 6MWT. X-axis is time in seconds and y axis is amplitude in gravitational units
B: Accelerometer output converted to vector mean counts
C: Segmented, aligned and smoothed stride pattern used to estimate walking cadence (steps/min).

GERIATRIC ANESTHESIA 6

Mini-Cog as a supplemental preoperative cognitive screening tool for the Risk Analysis Index

Sara M Safiullah[1], Stephen A Esper[2], Daniel Hall[1], James W Ibinson[1]

[1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh Medical Center, Pittsburgh, PA

INTRODUCTION: The Risk Analysis Index (RAI) is a 14-item pre-operative screening questionnaire, designed to assess surgical frailty.[1] Recent work has explored the use of a prospective tool (RAI-C), suggesting it is effective but further efforts to identify the optimal components is needed.[1] The questionnaire includes one yes/no question concerning a self-identified decline in cognitive health (specifically, remembering 'things' or organizing thoughts) over the past 3 months, representing one area for potential improvement. The Mini-Cog (https://mini-cog.com/) is a brief, two-part preoperative screening test that uses a word recall exercise and a clock drawing test to assess cognitive health in older adults.[2] Multiple studies have used Mini-Cog to predict post-operative mortality in elderly patients.[3] The aim of our study was to determine if Mini-Cog test scores correlated with self-identified pre-operative cognitive deterioration for elderly patients as indicated by the response to the RAI cognitive decline question.

METHODS: This study is an examination of de-identified QI data gathered by our Center for Perioperative Care. Data acquisition and analysis was approved by the UPMC Quality Review Committee as a quality improvement initiative, not constituting research. The preliminary data set consisted of 864 patients above the age of 65, of which 140 had Mini-Cog test scores and a RAI response. A Mini-Cog score for <3 was used to identify cognitive impairment (coded as yes/no). This was correlated with RAI responses in a two-by-two table (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY) in order to investigate the Mini-Cog correspondence with the 'yes' response for self-identified impairment for the RAI. The individual components of the Mini-Cog test, the clock score and word score, were then individually cross examined with RAI responses to determine if one identified more 'missed' self-assessment responses.

RESULTS: Of the 140 patients, 93 (66%) passed both neurocognitive screenings, leaving 47 (33%) that failed either one or both the RAI self-identification and the Mini-Cog. Only 6 (4%) failed both; the other 41 (29%) would have been missed if only 1 of the 2 brief screens was used. Breaking this down further, 12 of the 41 (29%) self-identified no cognitive deterioration on the RAI, but failed the Mini-Cog test. The other 29 of the 41 self-identified some cognitive deterioration on the RAI but passed the Mini-Cog. A total of 18 (13%) patients failed Mini-Cog screening; 13 (72%) patients had a clock score of 0.

CONCLUSION: A significant portion of our population showed some evidence of cognitive decline, and a substantial fraction (9%) may be missed by the traditional RAI score alone. If choosing tools to keep the assessment as brief as possible, self-identification should be selected first, followed by the clock drawing task, and then word recall if the goal was to maximize the number of those with potential cognitive issues. Future work will examine if the RAI's predicative ability can be enhanced by the addition of the Mini-Cog screen.

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GERIATRIC ANESTHESIA 7

Cognitive trajectory before and after elective total joint arthroplasty in a population-based cohort of older adults

Elizabeth L Whitlock[1], L G Diaz-Ramirez[1], Alexander K Smith[1], Derek Ward[1], W J Boscardin[1], M. M Glymour[1]

[1]University of California, San Francisco, San Francisco, CA

INTRODUCTION: Following total joint arthroplasty (TJA) of the hip or knee, 10-15% of older adults experience a decrement in neuropsychiatric test performance lasting 3 months or longer. However, it is not known whether this decrement represents a change in longitudinal rate of cognitive decline compared with pre-TJA cognitive trajectory.

METHODS: We studied Health and Retirement Study (HRS) participants, a longitudinal population-based cohort of Americans, linked to Medicare fee-for-service billing records. Participants underwent TJA between 1998 and 2016 at age 65 or older. We compared TJA recipients to laparoscopic cholecystectomy (LC) recipients, who undergo surgery and a hospital stay of comparable duration. We modeled covariate-adjusted 'memory score,' a Z-scored summary measure of biennial HRS cognitive test scores and proxy cognition reports,[1] using multivariable linear mixed effects models with linear splines (a priori: knots at -2, 0, 0.5, 2y, and a discontinuity at time=0). The a priori primary outcome was change in rate of memory decline in the interval [2 to 0 years before surgery], versus [0.5 to 2 years after surgery], chosen to align with time to clinical benefit from TJA and exclude the 0-6 month period of initial recovery from surgery.

RESULTS: 1,575 participants underwent TJA (474 hip, 1,101 knee) and 296 underwent LC. After TJA, participants' memory score declined 0.006 [-0.022 to 0.034] units/year more slowly (p=0.67), and LC recipients declined 0.003 [-0.098 to 0.092] units/year more quickly (p=0.95), compared to their own preoperative rate of cognitive change. The change was not significantly different between TJA and LC recipients (difference-in-differences, -0.009 [-0.11 to 0.092] units/year, p=0.86). In both groups, the change in cognitive slope represents a difference of fewer than 2 months of cognitive aging, which is unlikely to be clinically significant.

CONCLUSION: On average, older adults who undergo TJA do not experience a clinically or statistically significant change in longitudinal cognitive prognosis following surgery, compared to preoperative trajectory or to older adults who undergo LC.

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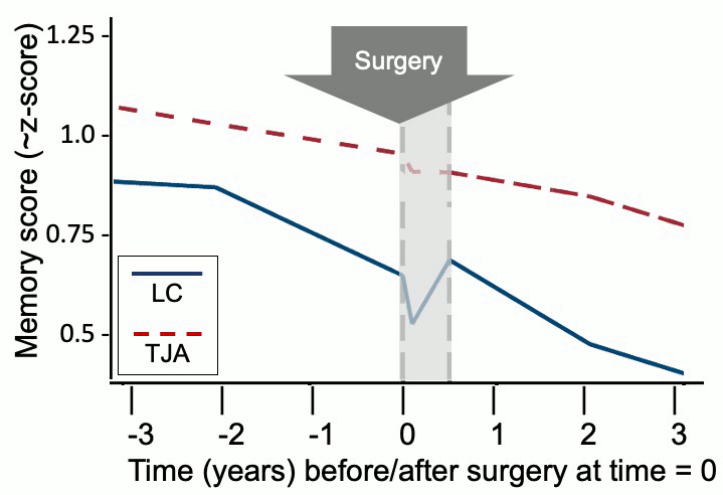

Figure 1

GERIATRIC ANESTHESIA 8

Postoperative Delirium in non-ICU High Risk Geriatric Patients

Frederick Sieber[1], Susan Gearhart[2], Dianne Bettick[3], Nae-Yuh Wang[4]

[1]Johns Hopkins Medical Institutions, Baltimore, MD, [2]Bayview Medical Center, Baltimore, MD, [3]Johns Hopkins Bayview, Baltimore, MD, [4]Johns Hopkins Medical Institutions, Baltimore, MD

INTRODUCTION: The American college of surgeons defines high risk geriatric patients as those who are frail or age ≥ 85 years (HRGP). Frailty and age are associated with higher postoperative complications, including postoperative delirium (POD). Most associations between HRGP and POD have been determined in surgical populations requiring post-operative icu admission. However, it is not clear whether being a HRGP is a strong risk factor for POD in surgery not requiring ICU admission. Our aim was to determine the association between HRGP and POD in surgical patients recovering in the PACU.

METHODS: Patients undergoing surgery at a single institution from 1/1/2018-3/1/2020 were studied. The Edmonton frailty score was used to assess for frailty, with a score ≥ 6 defined as frail. CAM-ICU and 4AT were used to assess for POD with possible POD defined as CAM-ICU positive or 4AT score ≥4, and possible cognitive impairment defined as 4AT score 1-3, at any time on the surgical ward postoperatively. Eligibility criteria included age ≥ 65 years undergoing non-ICU surgery, with documented preoperative Edmonton frailty score assessment and POD evaluations. Groups were divided into HRGP and non-HRGP and compared. Multivariate modelling incorporating age, sex, race, anesthesia technique (spinal/epidural vs regional vs MAC vs general), surgical service, and surgical urgency (elective vs urgent vs emergency surgery) was used to determine relationships of HRGP with possible POD, length of stay, discharge disposition, and mortality.

RESULTS: 410 patients were included with 129 HRGP. Incidence of POD and possible cognitive impairment were 15.5% vs 3.6% and 8.5% vs 2.5% comparing HRGP vs non-HRGP; Fishers exact p<0.0001. Length of stay (6.0 ± 6.9 days vs 4.2 ± 4.6 days; p=0.0098) was increased, but PACU length of stay (5.7 ± 3.5 h vs 5.5 ± 2.7 h; p=0.6) and mortality (7.7% vs 5.3%; p=0.3) were similar comparing HRGP vs non-HRGP. Comparing HRGP vs non-HRGP, 55% vs 88% (p<0.0001) were discharged to home. Neither gender nor race were associated with POD. In comparison to general surgery, neurosurgical procedures had an increased risk of POD (OR 3.8 [1.3-11.1]; p=0.009). In multivariate modelling frailty (OR 3.4 [1.8-6.4]; p=0.0002), age (OR 1.1 [1.0-1.1]; p=0.04), and ASA status (OR 2.6 [1.4-5.0]; p=0.003) were risk factors for POD; however, surgical urgency (OR 1.7 [0.2-16.7]; p=0.6) and anesthetic technique (spinal vs general: OR 0.8 [0.2-3.8]; p=0.9) were not.

CONCLUSION: HRGP undergoing surgery with PACU recovery have a higher incidence of POD and are less likely to be discharged home. Frailty, age, and ASA status are strong risk factors for POD in this population, but gender, surgical urgency, and anesthetic technique are not. These results emphasize the importance of preoperative frailty assessment in determining risk of postoperative geriatric syndromes in patients undergoing non-ICU procedures.

GERIATRIC ANESTHESIA 9

Lumosity Gameplay as a Quantitative Cognitive Reserve Measure in Older Adults: A Secondary Analysis of the Neurobics Trial

Michelle Humeidan[1], Joshua-Paolo Reyes[1], Ana Mavarez Martinez[2], Cory Roeth[3], Alix Zuleta-Alarcon[1], Mahmoud Abdel-Rasoul[4]

[1]The Ohio State University Wexner Medical Center, Columbus, OH, [2]Stony Brook University, Stony Brook, United States of America, [3]Wright State University Boonshoft School of Medicine, Dayton, OH, [4]The Ohio State University College of Medicine, Columbus, OH

INTRODUCTION: It is estimated that roughly a quarter of patients 65 years of age or older presenting for elective surgery may have cognitive impairment leading to poorer postoperative outcomes, including an increased risk of delirium.[1] Identifying these at-risk patients before surgery could lead to targeted interventions to minimize postoperative neurocognitive disorders. Though it has been shown that implementation of a routine cognitive screening assessment like the Mini-Cog is feasible in preoperative clinics,[2] this type of evaluation is not widespread at this time, despite current best practice recommendations.[3] A self-administered cognitive assessment that could identify patients at-risk for postoperative delirium could expand identification of these patients with minimal operational investment. Here we report a secondary, observational analysis of the Neurobics Randomized Clinical Trial (NCT02230605) examining preoperative cognitive exercise participation and performance among intervention patients grouped by postoperative delirium incidence.

METHODS: Details of Neurobics Trial enrollment and primary analysis have been previously reported.[4] Briefly, patients 60 and above undergoing major, noncardiac surgery under general anesthesia were eligible for trial inclusion. Patients were excluded for preexisting cognitive dysfunction as determined by the Mini Mental Status Exam (MMSE) and active depression. Patients randomized to the intervention group were asked to play 10 hours of cognitive exercise games before surgery targeting memory, speed, attention, flexibility, and problem-solving functions using an electronic tablet application (Lumosity, Lumos Labs Inc.). All patients were evaluated for postoperative delirium. We completed a follow-up secondary analysis of intervention patients grouped by delirium status (No Delirium versus Delirium). Gameplay data including total number of games, time played, and median gameplay percentile (performance-based measure from compiled Lumosity user data) was collected and summarized overall and by functional category. Summary statistics were reported as medians [interquartile range] for continuous variables and compared between No Delirium and Delirium groups using Wilcoxon rank-sum tests. Categorical variables were summarized as frequency (percentage) and compared between groups using chi-square tests. Hypothesis testing was conducted at a 5% type 1 error level (alpha = 0.05). Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS: Of the 134 patients randomized to the cognitive exercise intervention, 9 were subsequently excluded and 125 patients were included in this analysis. Study groups were unequal as most intervention patients did not develop delirium (No Delirium (N = 107); Delirium (N = 18)). A total of 121 of 125 patients (96.8%) completed some brain exercise (median [IQR], 4.6 [1.3-7.4] hours), where 4 patients did not play any games (No Delirium (N = 2); Delirium (N = 2)).4 Baseline characteristics were similar between the No Delirium and Delirium groups, including age (Overall median [IQR]; 67 [64-70] years, P = 0.097), education level (14 [12-16] years, P = 0.054), MMSE score (29 [28-30], P = 0.744), and Charlson Comorbidity Index (2 [1-3], P = 0.885). There was no statistically significant difference between the groups in total games played (No Delirium, 154 [45-224]; Delirium, 102.5 [25-185]; P = 0.2081) and total time played (No Delirium, 319.1 [78.6-448.3] minutes; Delirium, 197.7 [50.1-442.6] minutes; P = 0.243). Likewise, no differences were found across the functional domains. The median per patient gameplay percentile was lower in the Delirium group (6 [4.5-14.5]) when compared to the No Delirium group (16 [10-27]; P = 0.002).

CONCLUSION: Preoperative patient performance on cognitive exercises may be an effective measure of quantitative cognitive reserve to predict postoperative delirium risk. Further analysis is needed to determine which gameplay domains better predict postoperative delirium risk.

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Subspecialty Abstracts

GLOBAL HEALTH

GLOBAL HEALTH 1

Impact of the COVID-19 Pandemic on Surgical Care and Outcomes at Two Tertiary Hospitals in Ethiopia

Amany Alshibli[1], Masresha G Teklehaimanot[2], Rahel Seyoum[3], Gebrehiwot A Tegu[3], Haftom B Desta[2], Gosa Tesfaye[3], Agenchew N Tsegaw[3], Abraha Y Abay[2], Naod B Etanaa[2], Mulat Mossie[3], Kore M Binwe[2], Fantahun Tarekegn[3], Hagos G Gebremedhin[2], Mark Newton[1], Bantayehu Sileshi[1]

[1]Vanderbilt University Medical Center, Nashville, TN, [2]Mekelle University, Mekelle, Ethiopia, [3]Bahir Dar University, Bahir Dar, Ethiopia

INTRODUCTION: Disruption to routine healthcare services during the COVID-19 pandemic has been multi-faceted, with an estimated 72% cancellation rate of non-urgent surgeries worldwide.[1] Beyond the obvious impact of COVID-19 infection, experts fear the 'collateral damage' as a result of delaying care for unrelated conditions.[2–4] There is little known about how the pandemic has and will continue to affect the provision of surgical care in a low-resource setting. We set out to determine the impact of the COVID-19 pandemic on surgical care and outcomes at two tertiary hospitals in Ethiopia using perioperative data collected with a previously validated electronic tool.[5]

METHODS: We conducted a retrospective cohort study comparing surgeries performed during the pandemic to a year prior at Ayder Comprehensive Specialized Hospital in Mekelle (ACSH) and Tibebe Ghion Specialized Hospital in Bahir Dar (TGSH). We defined 'surgical cases' as procedures performed in an operating room with an anesthesia provider present. The exposure is the COVID-19 pandemic pre-defined as three phases. 'Phase 0' is defined as cases performed August-September 2019. 'Phase 1' is the time period when hospitals cancelled elective surgeries: April 1– June 10 and July 8-August 3, 2020 at ACSH and April 17– July 1, 2020 at TGSH. 'Phase 2' is when elective surgery activity was resumed until the end of the study on August 31, 2020. Primary outcome is 28-day perioperative mortality. Secondary outcomes are case volume and referral patterns. Perioperative data was collected via a REDCap form.[5] Missing data was collected retrospectively. P values were calculated using Pearson's chi-squared and Fisher's exact tests for categorical variables, two-sample t-test for continuous variables, and Kruskal-Wallis test for case volume. Case volume was estimated by dividing daily case frequency in REDCap by monthly percent of total cases recorded. Impact of the exposure on 28-day mortality was determined with a logistic regression controlling for age, ASA status, urgency, procedure type, surgery length, and anesthesia type.

RESULTS: Data from 3449 surgical cases were captured in the REDCap database during the study period (Table 1). We observed a reduction in estimated daily case volume during phase 1 and phase 2 of the pandemic at TGSH (14 vs. 5 vs. 10 daily cases in phase 0, 1, and 2 respectively; $p<0.001$) and at ACSH (18 vs. 6 vs. 8 daily cases during phase 0, 1, and 2; $p<0.001$) (Figure 1). After restrictions were lifted in phase 2, hospitals continued operating at reduced surgical volume (44% of baseline at ACSH and 71% at TGSH). At ACSH there was an increase in proportion of patients from outside Mekelle during phase 1 and 2 compared to phase 0 ($p<0.001$ and $p=0.001$ respectively). Contrarily, at TGSH there was a decrease in proportion of patients from outside the district during phase 2 compared to phase 0 ($p=0.01$) (Table 2). 28-day mortality did not differ significantly between phases 0, 1, and 2 (2.1% vs. 3.0% vs. 2.8% respectively, $p=0.265$). Odds ratios of 28-day mortality were not significantly increased for cases performed during phase 1 (OR 1.19 [95% CI 0.57-2.43]) and phase 2 (1.33 [95% CI 0.77-2.35]) compared to phase 0 when accounting for age, ASA status, urgency, procedure type, surgery length, and anesthesia type. ASA status 3 or more, emergency status, surgery length, and subspecialty surgeries were associated with increased mortality, consistent with previous literature[5–7] (Figure 2).

CONCLUSION: Daily surgical case volume was significantly reduced during and after the lockdown. The proportion of patients from outside the district undergoing surgery differed during the pandemic for each hospital, suggesting a possible shift in provision of surgical care at surrounding hospitals in both regions. These findings suggest that during the pandemic patients may experience delays in seeking or obtaining surgical care. However for patients who underwent surgery, perioperative mortality did not differ between pre-and post-pandemic care when accounting for confounders. Differences between phase 0 and phase 2 suggest that the pandemic continued to affect surgical volume and referral patterns even after restrictive policies were lifted. Our results describe the impact of the pandemic and lockdown period on surgical care and outcomes at two low-resource referral hospitals which may assist in the development of surgical plans during future public health crisis.

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		Phase 0	Phase 1	Phase 2	P-value
Number of cases (N)		1402	558	1489	
Age		30.14 (19.55)	31.04 (17.87)	31.84 (19.05)	0.057
Gender					0.512
	Female	619 (46.5)	262 (49.4)	704 (47.4)	
	Male	713 (53.5)	268 (50.6)	781 (52.6)	
Urgency					<0.001
	Elective	739 (54.3)	126 (22.7)	690 (46.7)	
	Emergency	621 (45.7)	429 (77.3)	786 (53.3)	
Trauma		290 (21.4)	154 (27.8)	342 (23.1)	0.011
ASA Status					<0.001
	ASA1	805 (58.3)	125 (22.6)	756 (50.9)	
	ASA2	478 (34.6)	364 (65.8)	640 (43.1)	
	ASA3+	98 (7.1)	64 (11.6)	88 (5.9)	
Comorbidity					0.002
	Anemia	33 (2.4)	10 (1.8)	40 (2.7)	
	Diabetes	19 (1.4)	6 (1.1)	13 (0.9)	
	HIV	29 (2.1)	4 (0.7)	15 (1.0)	
	Hypertension	48 (3.5)	24 (4.3)	95 (6.4)	
	Other	99 (7.1)	16 (2.9)	175 (11.8)	
	None	1160 (83.6)	497 (89.2)	1144 (77.2)	
Time of surgery					0.042
	Daytime	940 (69.3)	379 (69.0)	1074 (72.8)	
	Nighttime	371 (27.4)	155 (28.2)	375 (25.4)	
	Weekend	45 (3.3)	15 (2.7)	26 (1.8)	
Procedure group					<0.001
	C-Section	184 (13.4)	106 (19.0)	238 (16.0)	
	General Surgery	289 (21.0)	114 (20.5)	414 (27.9)	
	Orthopedic	357 (25.9)	125 (22.4)	334 (22.5)	
	Other*	548 (39.8)	212 (38.1)	498 (33.6)	
Surgery length in minutes		85.10 (61.70)	82.78 (47.81)	90.59 (66.97)	0.013
Anesthesia type					0.006
	General	694 (50.7)	285 (51.4)	778 (52.6)	
	Regional	620 (45.3)	262 (47.3)	634 (42.8)	
	Other	56 (4.1)	7 (1.3)	68 (4.6)	
Safe surgery checklist used?					<0.001
	Yes	1295 (94.3)	535 (96.1)	1480 (99.7)	
	No	78 (5.7)	22 (3.9)	4 (0.3)	

Table 1. Demographics of patients undergoing surgery during three phases. Data are presented as absolute counts (%) for categorical and mean (SD) for continuous variables age and surgery length. P value was calculated using Fisher's Exact test for comorbidity and safe surgery checklist, Pearson's chi-square test for remaining categorical variables, and t-test for age and surgery length.
Phase 0 = unexposed, Phase 1 = lockdown, Phase 2 = post-lockdown.
*"Other" procedure group includes subspecialty surgeries: ENT, neurosurgery, cardiothoracic, urology, ophthalmology.

** p=0.001

*** p<0.001

	Patient origin	Phase 0	Phase 1	Phase 2	P-value
Ayder Hospital	N	727	508	211	
	Mekelle (local zone of hospital)	356 (50.2)	257 (50.9)	94 (45.0)	<0.001
	Outside zone within Tigray region	277 (39.1)	237 (46.9)	106 (50.7)	
	Outside region	76 (10.7)	11 (2.2)	9 (4.3)	
Tibebe Ghion Hospital	N	675	50	1278	
	West Gojjam (local zone of hospital)	411 (61.5)	39 (78.0)	865 (67.7)	0.02
	Outside zone within Amhara region	243 (36.4)	11 (22.0)	396 (31.0)	
	Outside region	14 (2.1)	0 (0.0)	16 (1.3)	

* p = 0.01

Table 2. Region or district of origin of patient undergoing surgery at each hospital, presented as absolute count (%). ACSH is located in Mekelle in the Tigray region, and TGSH is located in Bahir Dar in the West Gojjam zone of the Amhara region. P value calculated using Pearson's Chi-squared for ACSH and Fisher's exact test for comparisons involving phase 1 at TGSH. Pairwise P values are only displayed if significant at p<0.05.
P value * < 0.05, ** < 0.01, *** < 0.001

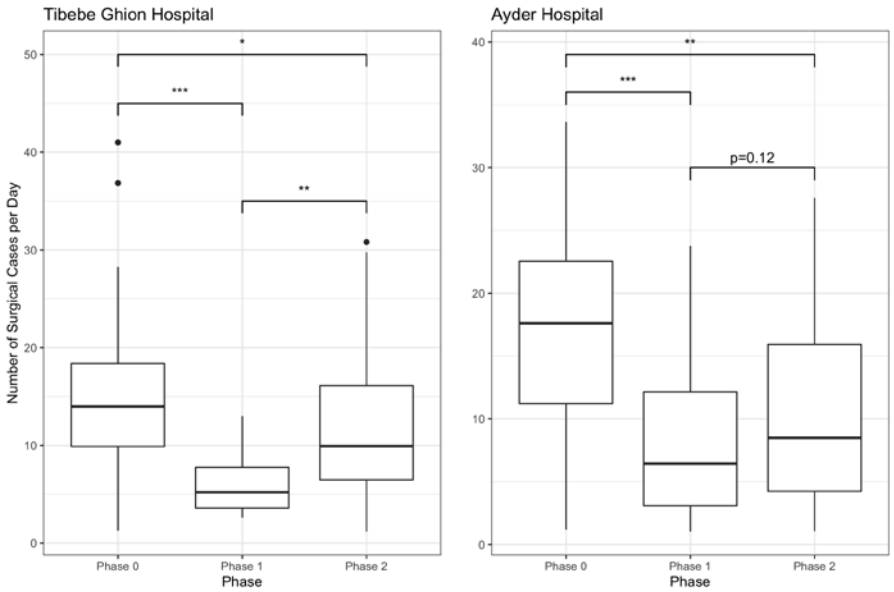

Figure 1. Estimated daily case volume. Estimates were obtained by adjusting the daily case totals in the REDCap database by the monthly proportion of logbook cases recorded in the database. Difference in medians was evaluated with Kruskal-Wallis test. P-value ***<0.001, **<0.01, *< 0.05

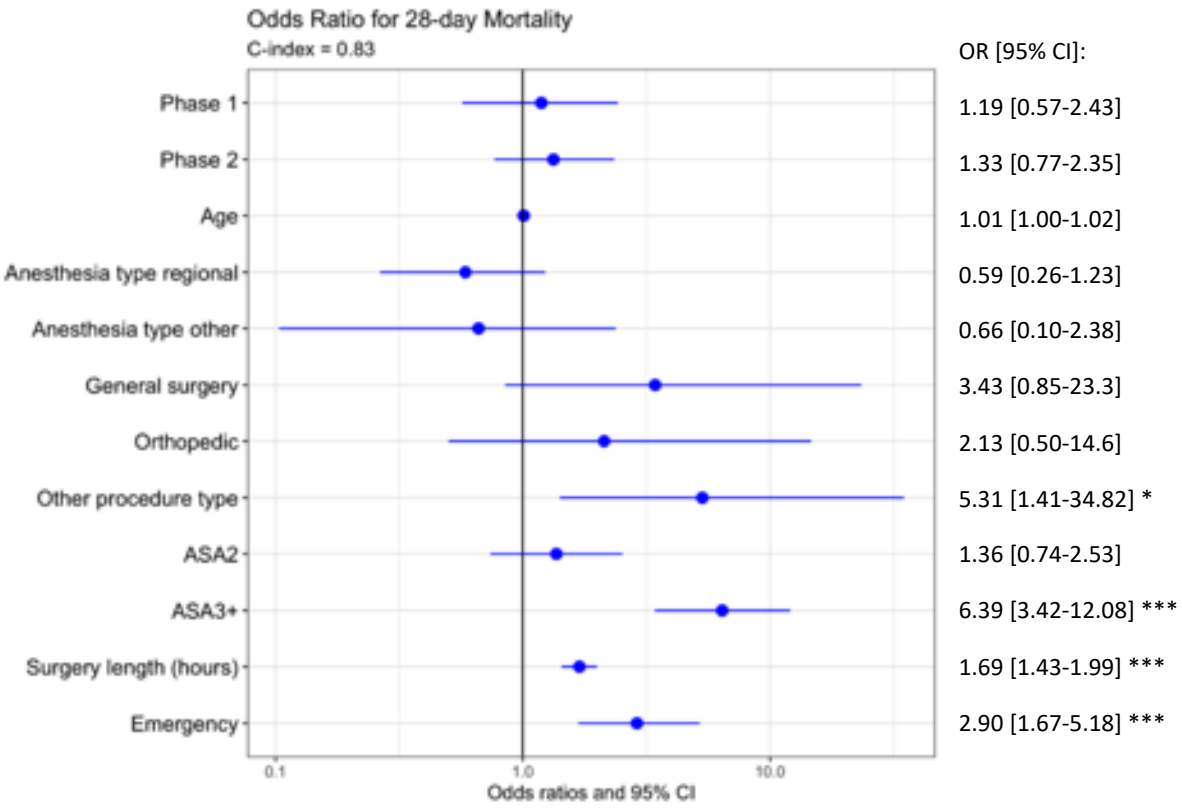

Figure 2. Multivariable logistic regression of 28-day perioperative mortality outcome adjusting for potential confounders. Phase 1 and Phase 2 surgeries were not significantly associated with increased mortality when controlling for confounders. Variables associated with mortality include ASA status 3 or more, emergency status, subspecialty surgery, and surgery length. 'Other procedure type' includes subspecialty surgeries: ENT, neurosurgery, cardiothoracic, urology, ophthalmology.
P-value ***<0.001, **<0.01, *< 0.05

GLOBAL HEALTH 2

Assessing participant satisfaction and knowledge acquisition after implementation of a hybrid simulation course among maternal and neonatal healthcare providers in Ethiopia

Claire Spradling[1], Naod B Etanaa[2], Gebrehiwot A Tegu[3], Haftom B Desta[2], Claire Posey[1], Getulio R De Oliveira Filho[4], Amanuel S Endeshaw[3], Gosa Tesfaye[3], Kore M Binwe[2], Hagos G Gebremedhin[2], Fantahun Tarekegn[3], Mulat Mossie[3], Hibist Z Mekbib[3], Abraha Y Abay[2], Agenchew N Tsegaw[3], Mark Newton[5], Bantayehu Sileshi[1]

[1]Vanderbilt University Medical Center, Nashville, TN, [2]Mekelle University, Mekelle, Ethiopia, [3]Bahir Dar University, Bahir Dar, Ethiopia, [4]Federal University Of Santa Catarina, FLorianopolis, SC, [5]Kijabe AIC Hospital, Kijabe, Kijabe

INTRODUCTION: Reducing peripartum maternal and neonatal mortality in low- and middle-income countries (LMICs) is a topic of growing interest in the global health community due to a maternal death rate in excess of 800 per day.[1] To address the lack of skilled providers as a contributing factor of mortality,[2] the Mobile Obstetric Simulation Training (MOST) program, a hybrid simulation course involving low-fidelity mannequins integrated with tablet-based vital sign monitors, was implemented at several hospitals in Ethiopia to strengthen the entire obstetrical team in the management of maternal and neonatal crises.

METHODS: This study is a retrospective data analysis assessing efficacy, as measured by participant satisfaction, knowledge acquisition, and trainer observation, of a simulation training course held at eight hospitals in one low-income country over a 3-month period. Hospital staff were selected to participate in MOST by hospital administrators based on their involvement in maternal and neonatal peripartum care. MOST incorporated didactics on obstetrical emergencies, teamwork concepts of crisis resource management, and simulation training for the most prevalent peripartum emergencies. Low-fidelity, high-durability Laerdal C-section simulators, combined with tablet-based vital sign monitors, were utilized to create a flexible and impactful hybrid simulation environment during which monitors were manipulated by trainers to demonstrate a wide-variety of scenarios. Monitoring and evaluation of MOST included a post-course Likert scale-based participant survey and a 20-question pre- and post-training knowledge exam. Analysis of the surveys was done to assess frequency of answer per question while a Mann-Whitney W test was used to compare the overall score difference between pre- and post-course tests. Additionally, trainers completed a qualitative post-training survey and participated in a series of focus group interviews to assess trainer experience and implementation.

RESULTS: Thirteen trainers from two regional academic hospitals in Ethiopia, who previously underwent intensive training in high- and low-fidelity medical simulation and teaching methodology, were involved in facilitating MOST. 222 providers, including obstetricians, generalists, pediatricians, midwives, and anesthetists from eight hospitals in Ethiopia participated in the training. Likert scale-based surveys, to assess Kirkpatrick's 1st level of evaluation, found that of 200 participants who completed surveys, 75 (37.5%) had never participated in simulation training; 188 (95.9%) found the course and 182 (96.3%) found the instructors to be very or somewhat effective; 162 (82.7%) participants found it very or somewhat easy to attend training; and 188 (97.9%) respondents said they would choose to participate in further simulation training if offered at their institution (Fig 1). On the 20-question knowledge assessment exam, the average score improved from 46% (range 30-65%, median 45%) to 64% (range 45-85%, median 65%) after the course ($p < 0.001$). Seven out of eight hospitals experienced significant improvements between participant pre- and post- test scores (range $p < 0.001$-0.045), with the largest improvement being a 35% improvement (45% baseline, 80% post-test, $p < 0.001$) (Fig 2). A qualitative post-training survey and series of focus group interviews among 12 trainers identified key lessons learned during implementation of the hybrid simulation course. Common themes highlighted by the trainers included: the practicality of portable and uncomplicated equipment for simulation training in rural settings; the adaptability of the hybrid model to overcome various cultural barriers and resource constraints; the importance of prior training in high-fidelity medical simulation for trainers; optimization of various training components and duration; and the importance of communication and buy-in from hospital leadership.

CONCLUSION: A new low-cost, mobile, hybrid simulation training program focused on management of maternal and neonatal emergencies was well received by trainers and participants, and demonstrated improved knowledge acquisition in one East African country. Limitations of this study include potential for

misinterpretation of questions and answers on the knowledge based exam due to wording or language barriers. Follow up studies need to be conducted to assess long-term retention of knowledge and impact on clinical outcomes, which are currently in progress.

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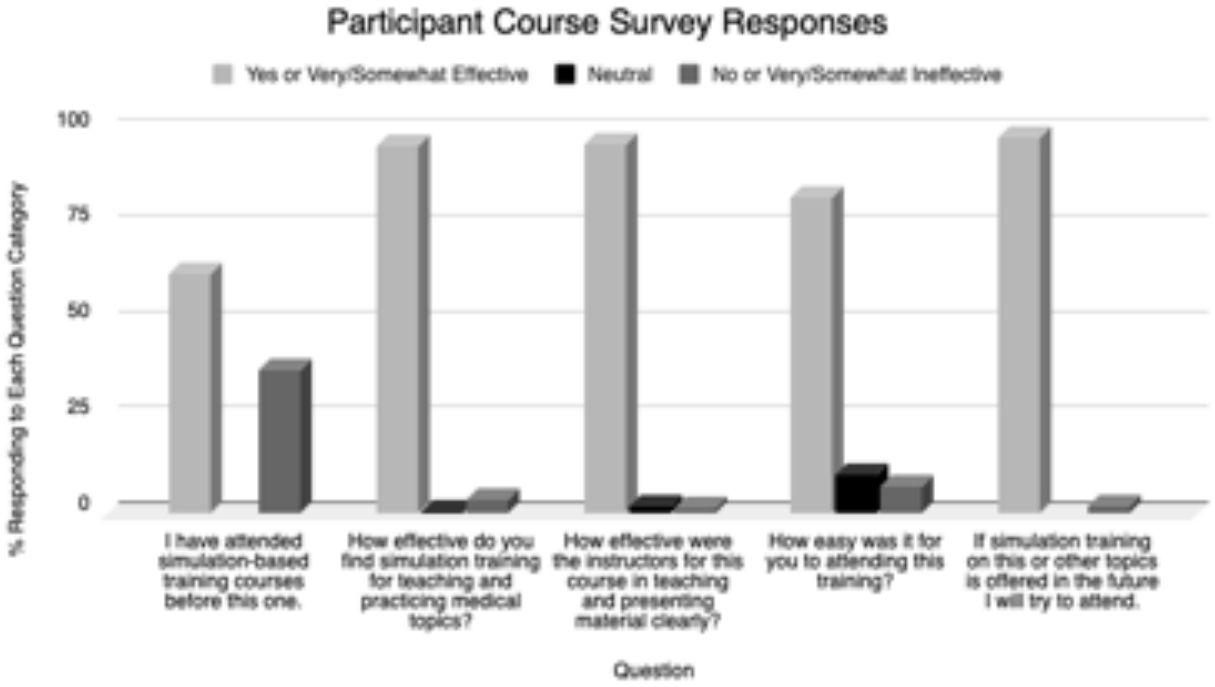

Figure 1

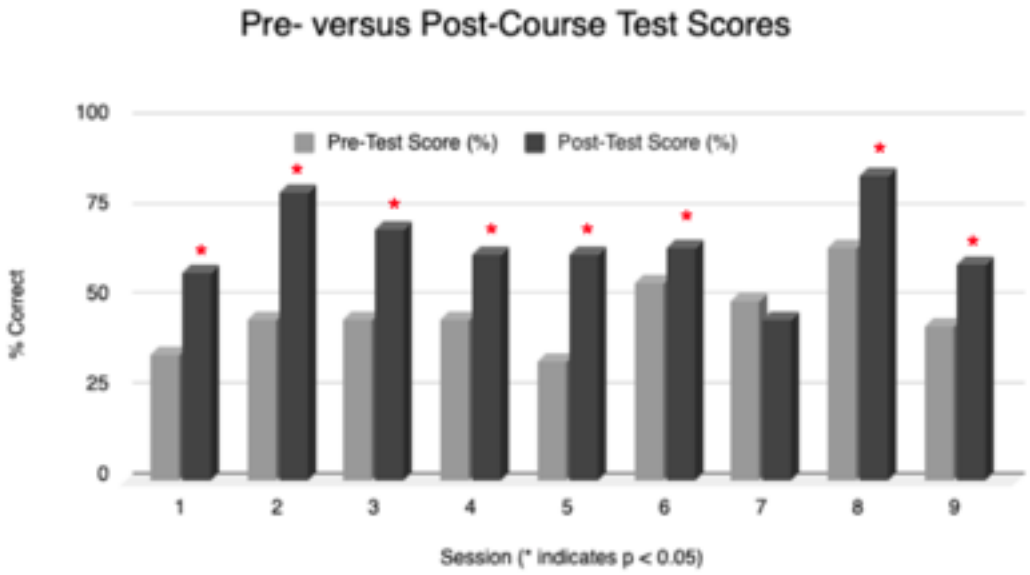

Figure 2

GLOBAL HEALTH 3

Influence of Pandemic on Self-Protection Simulation Performance

Matthew Holt[1], Catherine D Tobin[1], Lacey Menkin-Smith[1], Dulaney A Wilson[2], Ken Catchpole[1], Lydia Zeiler[1], Fletcher Brian[1], J.G. Reves[1]

[1]Medical University of South Carolina, Charleston, SC, [2]Medical University of South Carolina, Charleston , SC

INTRODUCTION: SARS-CoV-2 (COVID) is a pandemic unlike any seen in over a century. Highly infectious pathogens pose a significant threat to healthcare workers around the world, especially for those who come in direct contact with infected patients. Despite only accounting for approximately 3% of the global population, healthcare workers constitute roughly 14% of COVID infections.[1] This demonstrates the need to improve self-protection and infection control strategies. Simulation training is an effective educational approach in training.[2,3] However, it is unclear how training in the midst of an active pandemic impacts healthcare worker learning. The purpose of this study was to compare performance of novice trainees instructed by newly trained trainers in simulation courses for either Ebola virus disease (EVD) or COVID. We hypothesized that performance would be superior in the COVID group due to the ongoing pandemic.

METHODS: The EVD and COVID groups both consisted of 4 trainers and 8 trainees who volunteered to participate in this study. Trainees completed a demographic and confidence survey prior to beginning a two-part training course for EVD or COVID. Part 1 included online knowledge-based training with pre- and post-tests. Part 2 consisted of simulation tasks using procedural and team-based checklists. Trainee team performance was evaluated by trainers in real-time using a performance assessment tool. Trainers took a train the trainer (TTT) course for EVD or COVID prior to training trainees. The TTT course included both on-line and in-person practice. Simulation tasks and checklists were developed using evidence based safe practice guidelines for common tasks performed when caring for EVD or COVID patients. The tasks were designed for teams of 3 individuals ('supervisor', 'provider', and 'buddy'). The structure of the training for this course was mastery-based learning in which steps were repeated until performed correctly. Errors were defined as any action that led to risk of infection or contamination. The primary outcome was trainee performance, measured by the number of steps required to complete each task. Performance was further dichotomized into those who repeated at least one step and those who did not. Secondary outcomes included time to complete each task and pre- vs. post- training confidence. Demographic and performance data were compared across the two groups with Chi-square tests of homogeneity for categorical data; continuous data were evaluated with t-tests of means and Wilcoxon rank-sums tests of medians, as appropriate.

RESULTS: There was no significant difference in demographic characteristics or pre- vs. post-test knowledge scores between the two groups [Table 1]. Performance was described as the number of participants that repeated at least one step for each task [Table 2]. Participants in the COVID group performed better than the EVD group on the 'Doffing Gown with N95' task (P=0.02). Overall, the COVID group had fewer repeated steps; however, difference in performance between the two groups for the other tasks was not statistically significant. The COVID group took less time on average to complete all tasks [Table 3], however, only the 'Doffing Gown with N95' was completed significantly faster in the COVID group compared to the EVD group (P=0.04). There was no statistically significant change in confidence levels for either the EVD or COVID group [Table 4].

CONCLUSION: We found that the COVID group significantly differed in one training scenario and tended to perform better than the EVD group. These findings suggest that training for a real pandemic enhances learning of self-protection skills to a greater degree than training for a seemingly hypothetical threat, such as EVD. This study provides insight into the education, performance, and preparedness of healthcare workers to protect themselves while caring for patients with highly contagious pathogens.

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Table 1. Demographic characteristics of trainee cohorts

	EVD trainees N=8		COVID trainees N=8		
	n	(%)	n	(%)	p-value
Gender					
Female	7	(87.5)	5	(62.5)	0.25
Male	1	(12.5)	3	(37.5)	
Education					
Baccalaureate	7	(87.5)	7	(87.5)	1.00
Masters	1	(12.5)	1	(12.5)	
MD	0	(0.0)	0	(0.0)	
Other	0	(0.0)	0	(0.0)	
Specialized Education					
Medical Fellowship	0	(0.0)	0	(0.0)	0.52
Medical Residency	0	(0.0)	0	(0.0)	
Nursing Specialty Training	1	(12.5)	2	(25.0)	
Other	7	(87.5)	6	(75.0)	
None	0	(0.0)	0	(0.0)	
Current Employment					
Hospital Staff	1	(12.5)	0	(0.0)	0.30
Medical Staff	0	(0.0)	0	(0.0)	
Resident	0	(0.0)	0	(0.0)	
Student	7	(87.5)	8	(100.0)	
Score on didactic					
Pre-test	18.0	±2.3	15.8	±3.6	0.18
Post-test	24.1	±1.1	23.3	±2.7	0.41
pre/post test change	6.1	±2.6	7.4	±5.1	0.54

Table 2. Providers with at least one repeated step

	EVD		COVID		
Task	# providers	>1 repeated step	# providers	>1 repeated step	chi^2 p-value
Donning Gown with N95	7	0	5	1	0.26
Doffing Gown with N95	7	4	7	0	0.02
Don Coverall with N95	6	1	6	0	0.34
Doff coverall with N95	8	4	7	1	0.14
Spill Cleanup	8	2	5	0	0.22

Table 3. Average time (min) to complete task

Task	EVD mean ±Std	COVID mean ±Std	P-value
Donning Gown with N95	13.6 ±3.3	10.8 ±2.5	0.14
Doffing Gown with N95	11.0 ±3.8	7.1 ±2.1	0.04
Don Coverall with N95	13.6 ±3.0	12.7 ±2.3	0.56
Doff coverall with N95	14.6 ±2.9	10.3 ±1.1	0.27
Spill Cleanup	11.0 ±2.8	10.0 ±2.3	0.64

Table 4. Change in confidence score indicating self-assessed readiness to care for patients.

		EVD N=8 Median (IQR)	COVID N=8 Median (IQR)	Rank-Sum Test P-value
Total Score		1.7 (1.3-2.0)	1.4 (1.0-1.5)	0.22
Q1	Confidence in ability to care for patient with Ebola	3.0 (1.0-3.0)	2.0 (1.0-2.5)	0.37
Q2	The level of protective equipment used during care is adequate to prevent contamination	0.5 (0.0-1.0)	0.0 (0.0-1.0)	0.56
Q3	While working in an Ebola Clinical unit, my team is confident	2.0 (0.5-2.5)	2.0 (1.0-2.5)	0.87
Q4	If I care for a patient with Ebola, my loved ones, coworkers, and patients are at risk for contracting disease from me	1.5 (1.0-2.0)	2.0 (1.0-2.0)	0.91
Q5	Trust our team of coworkers to practice 100% accountability for their own actions and for our own teammates actions	0.5 (0.0-1.5)	1.0 (0.5-1.5)	0.41
Q6	My new background knowledge of Ebola has improved my ability to care for someone with the disease	1.0 (1.0-2.5)	1.0 (1.0-1.5)	0.68
Q7	I believe my infection control techniques will help reduce my risk of exposure to Ebola	2.0 (0.5-3.0)	1.0 (0.0-1.0)	0.08
Q8	Confident in my ability to recognize signs and symptoms of heat stress in myself and my team members	1.0 (0.0-1.0)	1.0 (0.5-1.5)	0.49
Q9	I feel proficient in donning and doffing PPE	3.0 (1.5-3.0)	2.0 (1.0-3.0)	0.44
Q10	I feel competent to perform my duties in PPE	2.0 (1.0-3.0)	1.0 (1.0-2.0)	0.35

GLOBAL HEALTH 4

Quantitative fit-testing of a locally produced, reusable, valved half-face respirator during COVID-19 pandemic

Arnaud Romeo Mbadjeu Hondjeu[1], William C. K. Ng[2], Vahid Anwari[3], ZiXuan Xiao[4], Kate Kazlovich[2], Andy Afemu[5], Azad Mashari[6]

[1]Toronto General Hospital, Toronto, Ontario, [2]University Health Network, Toronto, Ontario, Canada, Toronto, Canada, [3]University Health Network, Toronto, ON, Canada, Toronto, Canada, [4]University of Alberta, Toronto, Canada, [5]University of Toronto, Toronto, Ontario, Canada, Toronto, Canada, [6]University Health Network, Toronto, ON, Canada, Toronto, Canada

INTRODUCTION: The COVID-19 pandemic continues to stimulate demands for respiratory protective equipment, hence increased interest in developing reusable respirators.[1] Validation of such devices is challenging. We present the development of a reusable, silicone, valved respirator combined with pleated-membrane filters (Duo). To validate its performance, we quantitatively fit-tested (QNFT) and compared Duo with disposable N95 respirators.

METHODS: A multidisciplinary team used 3D-printing and silicone casting to develop the Duo. A prospective observational cohort study was then conducted on 41 healthcare workers (HCWs). Users were tested on Duo and disposables by QNFT according to industry standards. Lastly, volunteers scored the comfort and breathability of Duo.

RESULTS: Duo was designed, modified, and produced locally using 3D printing and silicone molding techniques.Figure 1 depicts a fully assembled Duo respirator. HCW characteristics are detailed in Table 1. Table 2 depicts the distribution of participant demographics, anthropometric characteristics, and types of 3M N95 respirators. Passing rates in Duo and disposable N95 respirators by QNFT were 100% and 58.5%. Heat maps illustrating individual participant success rates across seven different maneuvers are depicted in Figures 2. Median QNFT overall scores were 2947 and 77.2 respectively. The median scores for stationary and dynamic maneuvers of the Duo were 3179 and 2794 and of the disposable respirator was 84 and 73 ($p < 0.0001$). Visualization of pairwise comparison of log10 adjusted overall fit-factors for 41 participants are shown in Figure 3. Average comfort and breathability scores of the Duo were 3.9/5 and 4.2/5. Estimated unit cost for a production run of 1000 are $25-CAD in materials and 35 minutes of labor.

CONCLUSION: We present a locally-manufactured valved respirator that can match the filtration efficiency of commercial N95s and may be used in case of disruption of the supply chain. Effective protection and comfort may increase the compliance and safety of HCW during extended wear.

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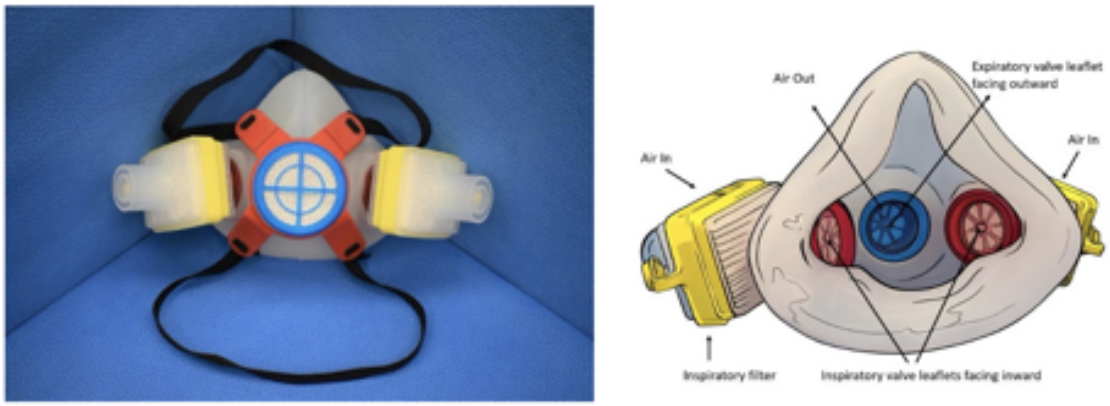

Figure 1. A fully assembled Duo respirator ready for testing (left) with unidirectional air flow through inspiratory valve leaflets (Air in) and through expiratory valve leaflet (Air Out) on the right

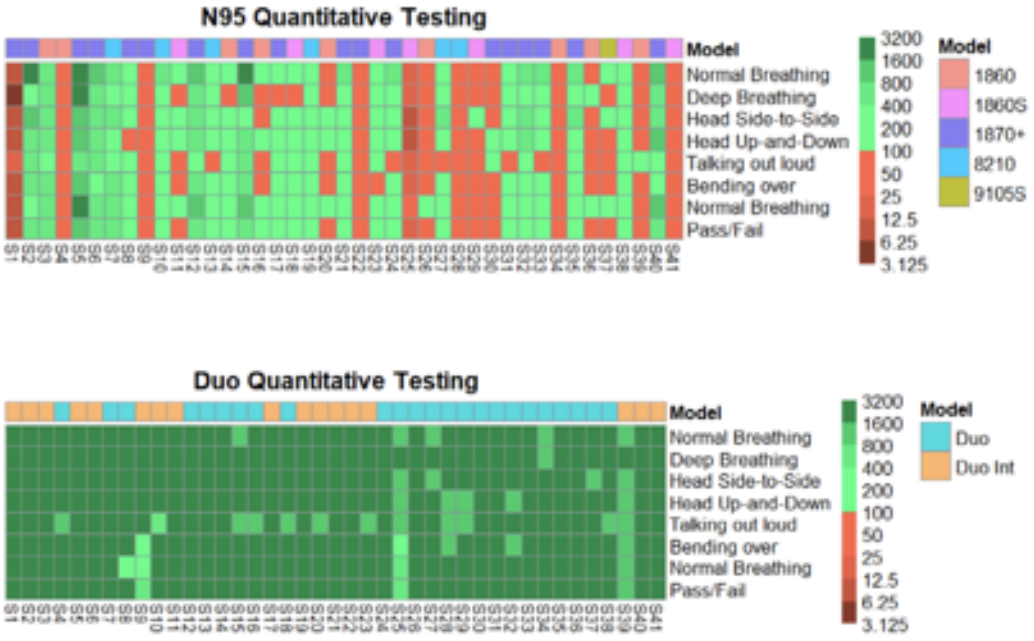

Figure 2. Representation of success rate of disposable N95 and Duo respirator throughout the 7 runs of test on 41 participants. Green indicates pass (fit-factor of 100 or greater) and red indicates fail (fit-factor less than 100).

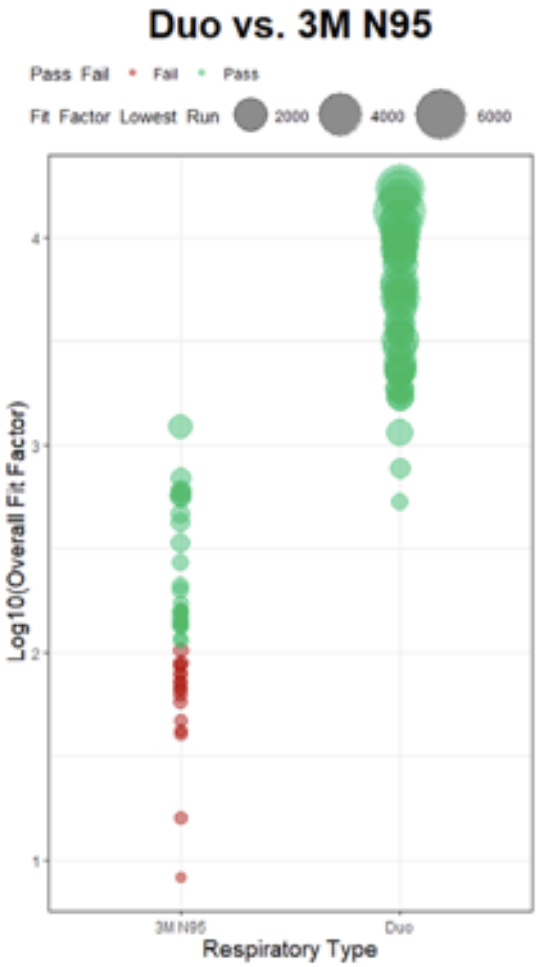

Figure 3. Log10 group comparison between disposable N95 and Duo overall fit factors for 41 participants. The overall fit-factor was defined as the harmonic mean of the seven individual run fit-factors.

Participant Demographics	**N = 41**
Age, mean (SD), y	36.1 (7.0)
Female – no./total (%)	20/41 (48.8%)
Body Mass Index, categorical no./total (%)	
Under-weight (BMI<18.5 kg/m2)	0/41 (0.0%)
Normal weight BMI (18.5 - 25 kg/m2)	33/41 (80.5%)
Overweight BMI (25-30 kg/m2)	6/41 (14.6%)
Obese BMI (>30 kg/m2)	2/41 (4.9%)
Body Mass Index, mean (SD), kg/m^2	22.90 (3.3)
Anthropometric	
Face Width mean (SD), mm	133.15 (11.6)
Face Length mean (SD), mm	120.10 (9.3)
Menton-sellion distances mean (SD), mm	103.79 (8.7)
NIOSH panel	
1 no./total (%)	2/41 (4.9%)
2 no./total (%)	0/41 (0.0%)
3 no./total (%)	7/41 (17.1%)
4 no./total (%)	4/41 (9.8%)
5 no./total (%)	3/41 (7.3%)
6 no./total (%)	5/41 (12.2%)
7 no./total (%)	8/41 (19.5%)
8 no./total (%)	1/41 (2.4%)
9 no./total (%)	2/41 (4.9%)
10 no./total (%)	2/41 (4.9%)
NA no./total (%)	7/41 (17.1%)
Disposable N95 Model	
1860 no./total (%)	9/41 (21.9%)
1860S no./total (%)	7/41 (17.1%)
1870+ no./total (%)	18/41 (43.9%)
8210 no./total (%)	6/41 (14.6%)
9105S no./total (%)	1/41 (2.4%)

Table 1. Demographics, Anthropometric Characteristics, and Qualitatively Fitted disposable N95 Model.

	Disposable N95 Test		P-Value
	Pass no./total (%) 24/41 (58.5%)	Fail no./total (%) 17/41 (41.5%)	
Demographic			
Age mean (SD), y	35.7 (7.1)	36.6 (7.0)	P = 0.681
Female sex – no./total (%)	11/24 (45.8%)	9/17 (52.9%)	P = 0.654
BMI, mean (SD), kg/m²	22.84 (3.5)	22.94 (3.3)	P = 0.979
BMI			
Normal weight no./total (%)	21/24 (87.5%)	12/17 (70.6%)	P = 0.047
Overweight no./total (%)	1/24 (4.2%)	5/17 (29.4%)	
Obese no./total (%)	2/24 (8.3%)	0/17 (0.00%)	
Anthropometric			
Face width mean (SD), mm	132.21 (9.1)	134.47 (14.7)	P = 0.3399
Face length mean (SD), mm	119.79 (7.4)	120.53 (11.6)	P = 0.7707
Menton-sellion distance mean (SD), mm	102.38 (7.6)	105.79 (10.0)	P = 0.1978
NIOSH panel			
1 no./total (%)	2/24 (8.3%)	0/17 (0.0%)	P = 0.210
2 no./total (%)	0/24 (0.00%)	0/17 (0.0%)	
3 no./total (%)	5/24 (20.8%)	2/17 (11.8%)	
4 no./total (%)	2/24 (8.3%)	2/17 (11.8%)	
5 no./total (%)	2/24 (8.3%)	1/17 (5.9%)	
6 no./total (%)	5/24 (20.8%)	0/17 (0.00%)	
7 no./total (%)	4/24 (16.7%)	4/17 (23.5%)	
8 no./total (%)	1/24 (4.2%)	0/17 (0.00%)	
9 no./total (%)	1/24 (4.2%)	1/17 (5.9%)	
10 no./total (%)	0/24 (0.00%)	2/17 (11.8%)	
NA no./total (%)	2/24 (8.3%)	5/17 (29.4%)	
Disposable N95 model (3M)			
1860 no./total (%)	2/24 (8.3%)	7/17 (41.2%)	P = 0.016
1860S no./total (%)	3/24 (12.5%)	4/17 (23.5%)	
1870+ no./total (%)	14/24 (58.3%)	4/17 (23.5%)	
8210 no./total (%)	5/24 (20.8%)	1/17 (5.9%)	
9105S no./total (%)	0/24 (0.00%)	1/17 (5.9%)	

Table 2. Demographic Anthropometric Characteristics and disposable N95 Model Distribution Based on Success of disposable N95 Fit Test.

GLOBAL HEALTH 5

In-hospital and 30-day Postoperative Mortality in an Upper Middle-Income Country

Javier H Eslava-Schmalbach[1], Nathaly Garzon-Orjuela[2], Cesar Bustillo-Torres[2], Giancarlo Buitrago[2], Eric Rosero[3]

[1]Universidad Nacional de Colombia, Bogota, D.C., [2]Universidad Nacional de Colombia, Bogota, Colombia, [3]UT Southwestern Medical Center, Dallas, TX

INTRODUCTION: Global surgery mortality has been selected as an indicator to monitor health systems and providers performance around the globe.[1] Assessment of variability in perioperative mortality among countries may be helpful to identify gaps between healthcare systems of nations with different income levels.[2,3] However, reports on global mortality after surgery in low- and middle-income countries are scarce. The aim of the study was to describe in-hospital and 30-day postoperative mortality in Colombia, a middle-income country.

METHODS: Data on nationwide surgical procedures were extracted from the 2015 administrative database of third payer payments to hospitals within the contributory health care system of Colombia. The database was anonymously linked to death certificates within the same study period. Surgical procedures were extracted according to the list of Colombian Surgical Procedures Codes (CUPS), which are similar to CPT codes used in the US. A total of 25 surgical groups were structured based on CUPS. Patient sex, age, and hospital length of stay were extracted directly form the database. The Charlson comorbidity index (CCI) was estimated for each patient using ICD-10 codes of services provided within 3 months prior to the surgery. Crude in-hospital and 30-day mortality rates for each surgical group were calculated as the number of patients who died within each time frame divided by the total number of patients having the respective surgical group procedures. The mortality risk excess of 30-day compared to in-hospital mortality was calculated as the difference between 30-day mortality rate and in-hospital mortality rate divided by the 30-day mortality rate. SAS 9.4 software was used for the analyses.

RESULTS: Table 1 describes patient characteristics (sex and age), length of stay, postoperative in-hospital and 30-day mortality rates, and excess mortality risk by group of surgical procedures. Operations associated with the highest in-hospital mortality rates were Heart transplantation, thoracic surgery, major digestive surgery and cardiac surgery. 30-day mortality was highest for thoracic surgery, heart transplantation, interventional neuroradiology, major digestive surgery and cardiac surgery. Liver transplantation, major liver surgery, urologic surgery, multiple trauma-related surgery were associated with highest mortality risk excess at 30 days.

CONCLUSION: The in-hospital and 30-day postoperative mortality rates described for Colombia, a middle-income country, can be used as a benchmark for comparison with other low-, middle-, or high-income countries. These data could be used to direct quality improvement efforts aimed at decreasing postoperative adverse outcomes in surgical groups with the highest mortality rates.

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Table 1. In-hospital and 30-day Postsurgical Mortality Rates by Type of Procedure

Type of Surgery	Female n (%)	Age X (SD)	CCI>=1 n (%)	LOS Median (IQR)	In-hospital mortality n (%)	30-day mortality n (%)	Risk excess mortality
Thoracic surgery (n=9005)	3451 (38.32)	53.0 (23.3)	3913 (43.45)	6 (1-15)	954 (10.59)	1197 (13.29)	20%
Heart transplantation (n=59)	18 (30.51)	51.8 (12.3)	51 (86.44)	3 (3-25)	6 (10.17)	6 (10.17)	0%
Major digestive surgery (n=11274)	6823 (60.52)	50.4 (21.0)	2960 (26.25)	3 (0-8)	509 (4.51)	659 (5.85)	23%
Cardiac surgery (n= 5208)	2005 (38.5)	50.7 (25.0)	2011 (38.61)	8 (1-15)	213 (4.09)	301 (5.78)	29%
Interventional Neuroradiology (n=3862)	1912 (49.51)	57.7 (19.5)	1597 (41.3)	2 (0-9)	143 (3.7)	245 (6.34)	42%
Neurosurgery (n=12116)	4941 (49.03)	50.8 (21.7)	3530 (29.13)	3 (1-9)	341 (2.81)	522 (4.31)	35%
Trauma related Orthopedic surgery (n=6743)	3643 (54.03)	56.5 (28.0)	1801 (36.44)	3 (0-7)	119 (1.76)	237 (3.51)	50%
Multiple trauma related surgery (n=5707)	3047 (53.39)	56.4 (30.2)	1443 (25.28)	4 (1-7)	80 (1.4)	184 (3.22)	57%
interventional cardiorhythmology (n= 5647)	2702 (47.8)	65.3 (18.8)	2574 (45.5)	1 (0-7)	59 (1.04)	101 (1.79)	42%
Major liver surgery (n=105)	59 (56.19)	56.9 (19.1)	75 (71.42)	4(1-11)	1 (0.95)	3 (2.86)	67%
General surgery (n=269642)	150347 (55.76)	47.6 (20.5)	51939 (19.26)	0 (0-1)	2506 (0.93)	4137 (1.53)	39%
Major vascular surgery (n=13457)	9399 (69.84)	55.7 (14.42)	2289 (17.0)	0 (0-1)	91 (0.68)	128 (0.95)	28%
Liver surgery biliary tract) (n=38968)	27551 (70.70)	50.3 (17.3)	6426 (16.49)	1 (0-4)	260 (0.67)	494 (1.27)	47%
Major urologic surgery (n=13664)	5445 (39.85)	51.7 (18.7)	3887 (28.44)	1 (0-3)	79 (0.58)	178 (1.3)	55%
Arthroplasty and spine surgery (n=19382)	11346 (58.54)	57.8 (20.3)	4142 (21.3)	1 (0-5)	96 (0.50)	180 (0.93)	46%
Endoscopy (n=412862)	276943 (67.08)	50.7 (18.6)	86869 (21.04)	0 (0-0)	2004 (0.49)	3630 (0.88)	44%
Minor vascular surgery (n=16999)	11862 (69.7)	54.2 (13.6)	3076 (18.09)	0 (0-1)	70 (0.41)	120 (0.71)	42%
Plastic reconstructive surgery (n=113506)	61299 (54.01)	46.5 (20.7)	19659 (17.31)	0 (0-1)	283 (0.25)	472 (0.42)	40%

Ear, nose, throat, Maxillofacial surgery (n=997291)	546820 (54.83)	38.0 (21.6)	114678 (11.49)	0 (0-0)	2379 (0.24)	3892 (0.39)	38%
Orthopedic surgery (n=87847)	45899 (52.25)	46.3 (19.9)	12343 (14.05)	0 (0-1)	176 (0.20)	291 (0.33)	39%
Minor urologic surgery (n=125440)	26901 (21.45)	46.9 (23.1)	21898 (17.4)	0 (0-1)	110 (0.09)	271 (0.22)	59%
Ophthalmologic surgery (n=134859)	76271 (56.56)	60.7 (18.2)	35653 (26.43)	0 (0-1)	115 (0.09)	257 (0.19)	53%
Liver transplantation (n=75)	39 (52)	48.3 (21.5)	64 (85.33)	1 (1-6)	0 (0)	2 (2.67)	100%
Renal transplantation (n=1568)	616 (39.29)	45.8 (14.5)	1476 (94.13)	0 (0-3)	0 (0)	0 (0)	0%

X, mean; SD, standard deviation; CCI, Charlson comorbidity index; LOS, length of hospital stay; IQR=Interquartile range.

GLOBAL HEALTH 6

A Randomized Comparison of Educational Booster Strategies on Team-based Clinical Performance During C-Section in Kenya

J Matthew Kynes[1], Steve Muchai[2], Joash Kiptanui[2], Phyllis Ngure[2], Mark Newton[3], Matthew D McEvoy[1]

[1]Vanderbilt University Medical Center, Nashville, TN, [2]AIC Kijabe Hospital, Kijabe, Kenya, [3]Kijabe AIC Hospital, Kijabe, Kijabe

INTRODUCTION: Large deficiencies in the quantity of healthcare workers in low-resource settings contributes to poor anesthesia-related outcomes including maternal mortality. Educational interventions to improve training and care are often limited by access and cost. High-fidelity simulation improves individual and team clinical performance in a variety of settings but gains often decay over time and methods to extend the efficacy of such training remain uncertain. Advances in short message service (SMS) technology and increased cellular accessibility may provide a means to supplement in-person training courses (Butler 2015), although data on the use of such technology for medical education in low- and middle-income countries (LMICs) is limited (Gomez 2018). This study seeks to evaluate SMS quizzing compared to additional in-person simulation sessions for improving long-term retention of skills for obstetric care during C-section in a low-resource setting.

METHODS: Multidisciplinary high-fidelity simulation training in obstetric management was provided on-site to multiple hospitals in Kenya through the Mobile Obstetric Simulation Training (MOST) course. Hospitals were randomized for course participants to receive booster education to reinforce initial training through either quizzes distributed via SMS two to three times per week over a period of 8 months, or an in-person refresher course conducted four months after the initial training utilizing small group discussion and low-fidelity simulation. SMS quizzing was conducted with the application QuizTime which allows for tracking of individual participant performance over time. The primary outcome was team performance during actual C-Section cases. Assessment was performed using the 'Safe C-Section Team Checklist' (Alexander 2019) as assessed by blinded observers. Performance was measured during two-week intervals at baseline, and immediately, eight and twelve months after the MOST course (Figure 1). Performance was evaluated using two-tailed, unpaired or paired Student's t-test, as appropriate. Patient demographics and additional measures of team performance including duration of surgery, maternal deaths, and neonatal deaths or stillbirths were collected, as well.

RESULTS: MOST training was conducted at three sites, two of which were assigned to SMS booster and one to in-person booster. Out of 42 users registered to participate in SMS quizzing, 76% responded to multiple quiz questions during the study period. Baseline clinical performance was comparable between SMS and in-person groups (16.4 vs 16.2 out of 18 checklist items, $p=0.72$). Both groups improved in performance following the course. By month 8 the in-person follow-up group returned to baseline performance, and at 12-months was performing below baseline (14.9 vs. 16.2 checklist items, $p<0.001$). In contrast, performance of the SMS group remained elevated until month 12 and had higher measured performance at 8 and 12 months than the in-person group (Figure 2). A high percentage of C-sections were urgent or emergent in both groups (Table 1).

CONCLUSION: Educational interventions that demonstrate reliable improvement in clinical performance and outcomes are critical for environments with fewer material and human resources commonly encountered in LMICs. This study demonstrates the feasibility of SMS-based quizzing as an educational tool to supplement in-person training among medical providers in Kenya. SMS-based quizzing was also associated with prolonged performance improvement following in-person simulation training compared to an in-person refresher course. Given the costs associated with training courses in these settings, use of a low-cost automated quizzing system may be particularly advantageous. Funding for this study has been provided by the Foundation for Anesthesia Education and Research (FAER).

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Alexander LA, Newton MW, et al. Development and Pilot Testing of a Context-Relevant Safe Anesthesia Checklist for Cesarean Delivery in East Africa. Anesth Analg. 2019 May;128(5):993-998.

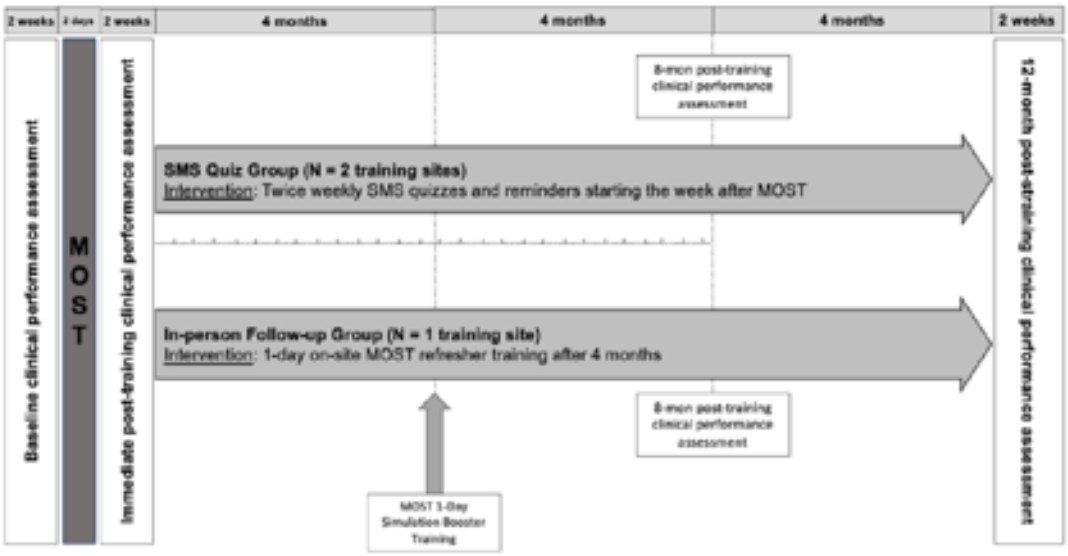

Figure 1. Study design demonstrating collection of clinical performance data for SMS Quiz and In-person Booster groups at four time points.

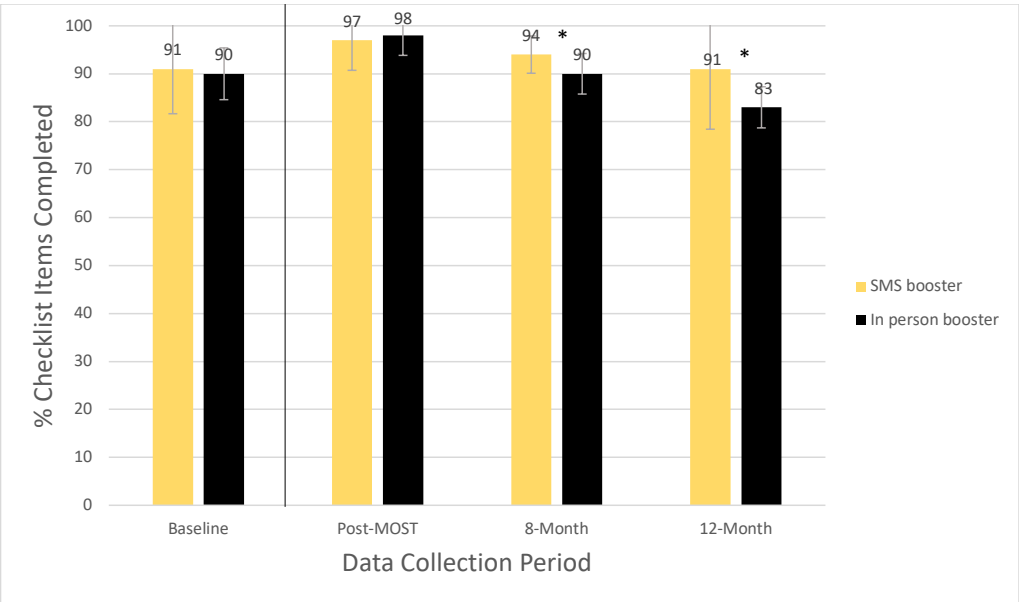

Figure 2. The percentage of Safe C-Section Team Checklist items completed for routine C-sections for the SMS and in-person booster groups at baseline and immediately, 8-months and 12-months following Mobile Obstetric Simulation Training (MOST). Error bars indicate 1 standard deviation above and below mean performance. Mean performance compared between groups at each time point using unpaired, two-tailed Student's t-test. *p<0.01.

Table 1. Comparison of clinical performance and outcomes for SMS booster and in-person booster groups at timepoints before and after Mobile Obstetric Simulation Training (MOST) course. Mean checklist performance was compared between groups using unpaired, two-tailed Student's T-test. *p<0.01

	SMS Booster Group	In-person Booster Group
Safe C-Section Checklist Items (out of 18)		
Baseline	16.4	16.2
Post-MOST	17.5 (1.12)	17.7
8-month	16.9*	16.2
12-month	16.4*	14.9
Surgery Duration (minutes)		
Baseline	34	33
12-month	36	48
Clinical Outcomes		
Observations	171	89
Maternal deaths	0	0
Neonatal deaths/stillbirths	7 (4.1%)	3 (3.4%)
Urgent/emergent	149 (87%)	56 (63%)

GLOBAL HEALTH 7

Risk factors and protective measures for healthcare worker infection during highly infectious viral respiratory epidemics: a systematic review and meta-analysis

Chenchen Tian[1], Olivia Lovrics[2], Alon Vaisman[3], Ki Jinn Chin[4], George Tomlinson[1], Yung Lee[2], Marina Englesakis[3], Matteo Parotto[1], Mandeep Singh[4]

[1]University of Toronto, Toronto, Canada, [2]McMaster University, Hamilton, Canada, [3]University Health Network, Toronto, Ontario, [4]University of Toronto, Toronto, Ontario

INTRODUCTION: Healthcare workers (HCWs) are highly susceptible to emerging infectious diseases. Factors believed to contribute to the rapid spread among healthcare workers include suboptimal infection control practices, performance of aerosol generating medical procedures, and failure to continue adequate mask use in break rooms[1,2]. The prevalence of infected HCWs also differs by hospital units, being highest in medical intensive care units and emergency departments[3]. This systematic review and meta-analysis investigated risk factors for HCW infection in viral respiratory pandemics (SARS-CoV-2, MERS, SARS CoV-1, influenza A H1N1, influenza H5N1) to improve understanding of HCW risk management amidst the COVID-19 pandemic.

METHODS: MEDLINE, EMBASE, CINAHL, and Cochrane CENTRAL databases were searched from conception until July 2020 for studies comparing infected HCWs (cases) and non-infected HCWs (controls) and risk factors for infection. Outcomes included HCW types, infection prevention practices, and medical procedures. Pooled effect estimates stratified meta-analysis and inverse variance meta-regression analysis were completed. Evidence was evaluated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. The study was registered on PROSPERO (CRD42020176232) on 6 April 2020.

RESULTS: Fifty-four comparative studies were included (n=191,004 HCWs). Infectious agents evaluated included COVID-19 (17 studies, n=152,019), H1N1 (18 studies, n=26,349), SARS (15 studies, n=6360), MERS (three studies, n=5750), and H5N1 (one study, n=526). No eligible RCTs were identified. The vast majority of studies (90%; 49/54) used WHO-defined criteria for confirmation of cases. Compared to non-frontline HCWs, frontline HCWs were at increased infection risk (OR 1.66 95%CI 1.24 to 2.22; figure 1) and greater for HCWs involved in endotracheal intubations (OR 4.72 95%CI 2.71-8.24, p<0.001; risk difference [95%CI]: 35.2% [21.4 to 47.9]; figure 2; table 1). Use of gloves, gown, surgical mask, N95 respirator, face protection, and infection training were strongly protective against infection (table 1). Summary odds ratios for meta-analysed risk factors are reported in figure 3. Meta-regression showed reduced infection risk in frontline HCWs working in facilities with infection designated wards (OR -1.04, 95%CI -1.53 to -0.33, p=0.004) and performing aerosol-generating medical procedures in designated centres (OR -1.30 95%CI -2.52 to -0.08; p=0.037).

CONCLUSION: There was a paucity of higher quality evidence from randomised trials to better evaluate these interventions. Despite the limitations, our findings draw attention to salient risk factors associated with HCW infection and provide direction for future research to better protect frontline HCWs in the midst of the COVID-19 pandemic. During highly infectious respiratory pandemics, widely available protective measures such as use of gloves, gowns, and face masks are strongly protective against infection and should be instituted, preferably in dedicated settings, to protect frontline HCW during waves of respiratory virus pandemics.

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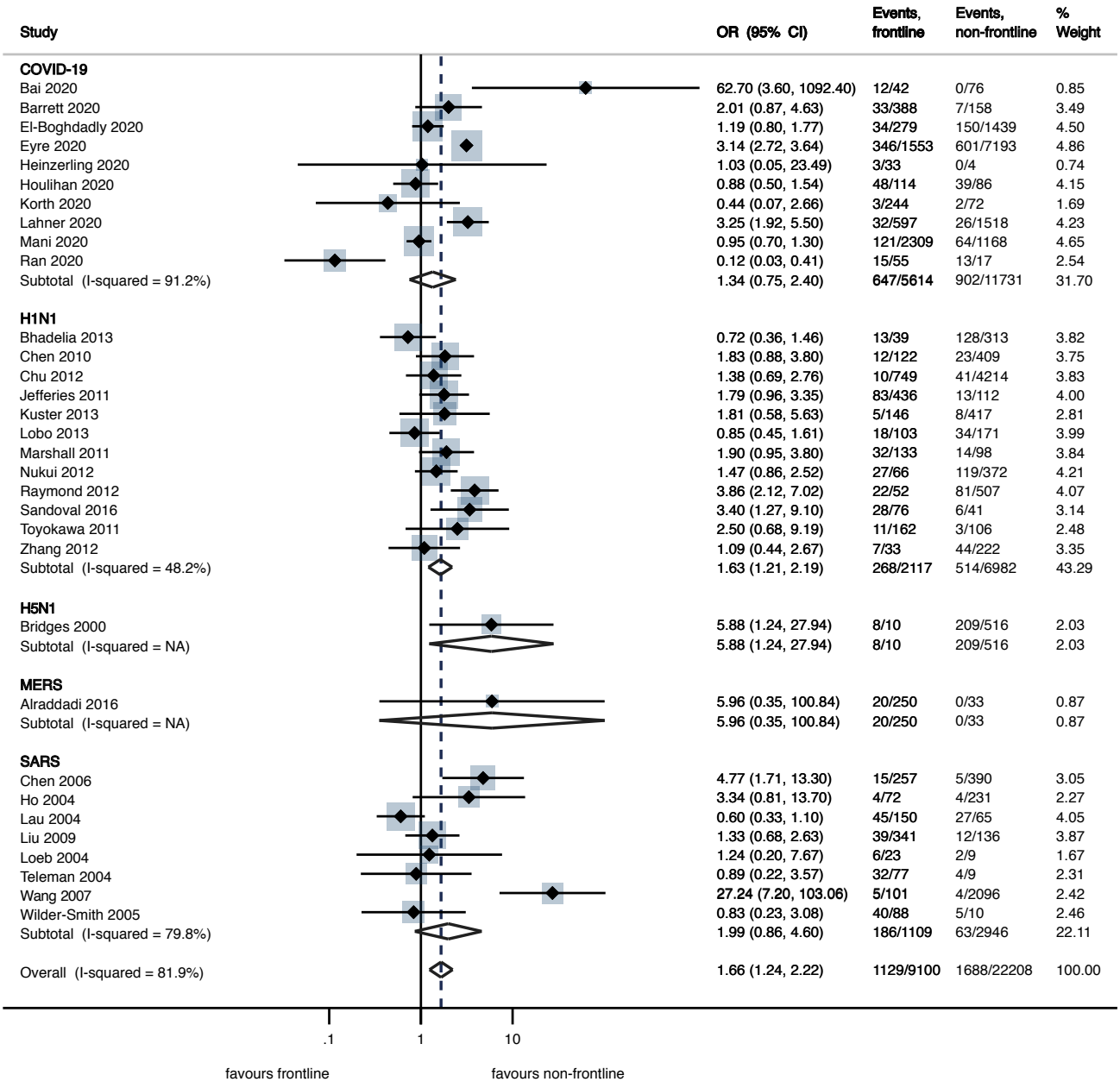
Table 1. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) of meta-analyzed outcomes by Knowledge Questions: **A)** Which types of HCW are at increased risk of infection? **B)** Which infection prevention and control practice are associated with protective effects for infection in HCW? **C)** What is the association of AGMPs with infection in HCW?

Certainty assessment							Summary of findings			
No. of studies (total participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations†	Overall certainty of evidence	Anticipated absolute risk i.e. chance of viral infection (95% CI)		Risk difference (95% CI)	Anticipated effects
							Control risk	Intervention risk		
A) Knowledge Question #1: Which types of HCW are at increased risk of infection?										
Frontline vs. non-frontline HCW										
32 (31,308)	not serious[1]	not serious[2]	not serious[5]	not serious	none	⨁⨁◯◯ LOW	7.6%	12.0% (9.3 to 15.4)	4.4% (1.7 to 7.8)	Frontline HCW may be at considerable increased risk of infection compared to non-frontline HCW.
Physicians (reference group) vs. nurses										
29 (131,794)	not serious[1]	not serious[2]	not serious[5]	not serious	none	⨁⨁◯◯ LOW	3.1%	2.9% (2.4 to 3.5)	-0.2% (-0.7 to 0.4)	There may be little to no difference in rate of infection between physicians and nurses.
B) Knowledge Question #2: Which infection prevention and control practice are associated with protective effects for infection in HCW?										
Gloves										
16 (4,498)	not serious[1]	not serious[2]	not serious[5]	not serious	strong association[7]	⨁⨁⨁◯ MODERATE	25.7%	14.3% (9.7 to 20.6)	-11.5% (-16.0 to -5.1)	The use of gloves probably results in a large reduction of infection risk.
Gown										
8 (3,048)	not serious[1]	not serious[2]	not serious[5]	not serious	strong association[7]	⨁⨁⨁◯ MODERATE	30.6%	16.9% (9.9 to 16.0)	-13.7% (-20.7 to -3.3)	Gown use probably result in a large reduction of infection risk.
Surgical mask										
12 (1,960)	not serious[1]	not serious[2,3]	not serious[5]	not serious	strong association[7]	⨁⨁⨁◯ MODERATE	20.6%	8.8% (4.9 to 14.6%)	-11.9% (-15.7 to -6.0)	Surgical mask use probably results in a large reduction in infection risk.
N95 mask										
15 (9,178)	not serious[1]	not serious[2]	not serious[5]	not serious	strong association[7]; publication bias[8]	⨁⨁⨁◯ MODERATE	6.6%	2.2% (1.3 to 3.5)	-4.4% (-5.2 to -3.0)	N95 use probably results in a large reduction of infection.
Face protection										
11 (5,116)	not serious[1]	not serious[2]	not serious[5]	not serious	strong association[7]; publication bias[8]	⨁⨁⨁◯ MODERATE	19.9%	9.2% (6.3 to 13.3)	-10.6% (-13.6 to -6.5)	Wearing goggles or face shields probably results in a large reduction of infection.
Hand hygiene										
13 (3,499)	not serious[1]	not serious[4]	not serious[5]	not serious	publication bias[8]	⨁⨁◯◯ LOW	14.6%	8.5% (5.5 to 13.0)	-6.1% (-9.1 to -1.6)	Hand hygiene may result in considerable reduction in infection risk.
Infection control and prevention training										
6 (2,589)	not serious[1]	not serious[2]	not serious[5]	not serious	strong association[7]	⨁⨁⨁◯ MODERATE	24.4%	7.2% (4.3 to 12.0)	-17.1% (-20.1 to -12.4)	Infection control training probably results in a large reduction in infection risk.
H1N1 vaccine (during H1N1 pandemic)*										
3 (1,527)	not serious[1]	not serious[3]	not serious[5]	not serious	strong association[7]	⨁⨁⨁◯ MODERATE	3.6%	0.4% (0.2 to 0.8)	-3.2% (-3.5 to -2.8)	Receiving H1N1 vaccine probably reduces rate of H1N1 infection during an outbreak.
C) Knowledge Question #3: What is the association of AGMPs with infection in HCW?										
Participation in intubation procedure										
8 (3,208)	not serious[1]	not serious[2]	not serious[5]	not serious	strong association[7]	⨁⨁⨁◯ MODERATE	22.1%	57.3% (43.5 to 70.1)	35.2% (21.4 to 47.9)	Involvement in intubation procedures probably causes large increases in risk of infection.
Participation in aerosol generating medical procedures, including intubation										
19 (6,897)	not serious[1]	not serious[2]	not serious[5]	not serious	strong association[7]	⨁⨁⨁◯ MODERATE	22.7%	41.5% (31.0 to 52.9)	18.8% (8.3 to 30.2)	Performance of aerosol generating medical procedures probably results in a considerable increase in rate of infection.

1. All studies were non-randomised and evaluated using the Newcastle-Ottawa Scale (NOS). The majority of the studies were at a lower risk of bias (NOS ≥7 stars). Furthermore, sensitivity analysis excluding studies with higher risk of bias did not yield any important difference in effect. Therefore, risk of bias was not downgraded.
2. While there was a high I2 value, there was a large amount of overlapping of confidence intervals and low variation of effect estimates across studies. Thus, inconsistency was not downgraded.
3. Low heterogeneity was detected with overall I2 <50% or some heterogeneity was explained through subgroup analysis demonstrating lower I2 value(s) <50%.
4. Clinical heterogeneity associated with variable definitions of hand hygiene was probably introduced and inconsistency was downgraded.
5. All studies included reported risk factors for health care workers infection of a highly infectious respiratory virus (SARS, H1N1, MERS, or H5N1) with a valid non-infected comparator group. Each disease-causing pathogen have caused epidemics with sufficient similarity in severity and transmission patterns. All outcomes (i.e. infected cases) were 'confirmed' or 'probable' based on World Health Organization case definition criteria. Therefore, we did not rate down for indirectness of population, exposure, comparator, or outcomes.
6. Downgraded one point because of large confidence intervals that overlaps both little to no effect, as well as appreciable benefit or appreciable harm of the intervention/exposure. This suggests that more studies with larger sample sizes are needed to calculate precise effect estimate.
7. Magnitude of effect is large considering the thresholds set by GRADE (RR >2 or <0.5) with consistent evidence from at least 2 studies. Effect size assumes that the odds ratios translate into similar magnitudes of relative risk estimates.
8. Although publication bias was suggested through Egger's test, visual inspection of funnel plots was largely symmetrical and thus, we did not downgrade for strongly suspected publication bias.

*No other virus-specific immunizations were identified in the literature

Figure 2. Forest plot of random effect meta-analysis of the risk of infection in frontline HCWs* by virus type.



* Frontline HCWs were defined as those with high occurrence of patient face-to-face contact, including ER staff, ICU, staff, and HCWs who responded affirmatively to having direct exposure with patients.

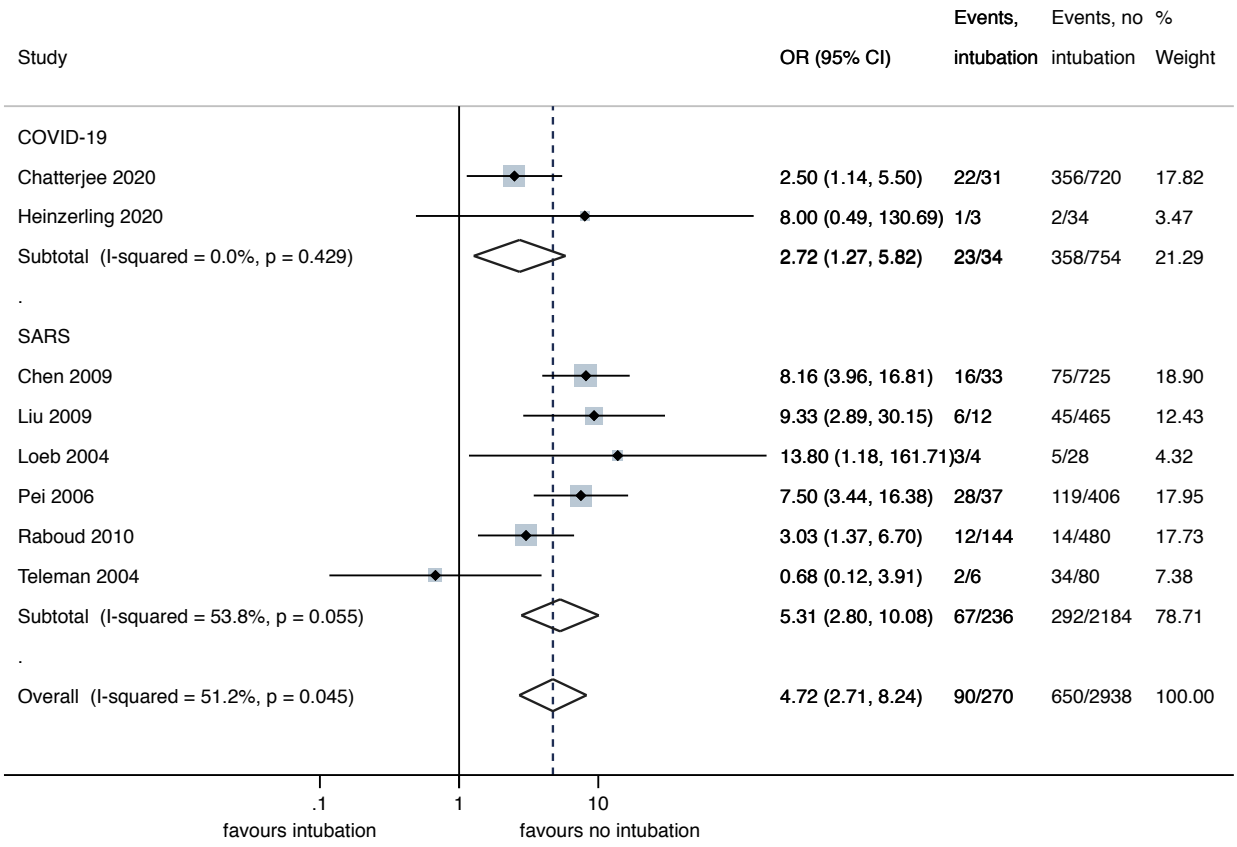
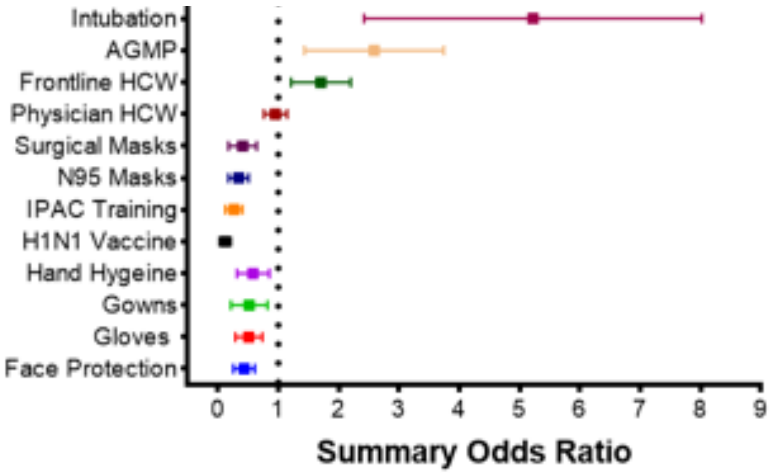


Figure 3

Figure 4. Forest plot of all the summary odds ratios for meta-analysed risk factors.*



* Comparator groups: intubation vs no intubation; AGMP vs no AGMP; frontline HCW vs non-frontline HCW; physician vs nurse; surgical mask vs no surgical mask; N95 mask vs no N95 mask; IPAC training vs no IPAC training; hand hygiene vs no hand hygiene; gowns vs no gowns; gloves vs no gloves; face protection vs no face protection.

Subspecialty Abstracts

LIVER

LIVER 1

A Retrospective Cohort Study of Pediatric Patients Undergoing Early Extubation After a Staged Laparotomy

Mitchell Phillips[1], Heather A Ballard[1], Nicholas Volpe[2], Eric Cheon[1]

[1]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL

INTRODUCTION: Congenital portosystemic shunts, otherwise known as Abernethy malformations, are a condition in which splanchnic blood bypasses the liver and drains directly into the systemic circulation. The approximate incidence of this malformation is 1:30,000 births with less than 300 cases reported in the literature.[1] Currently, these patients undergo temporary portosystemic shunt ligation and remain intubated in the intensive care unit (ICU) for approximately 5 days before returning to the operating room for permanent ligation.[2] However, there is substantial evidence that prolonged mechanical ventilation after surgery leads to higher costs, longer ICU and hospital length of stay (LOS), and higher mortality.[3, 4] In contrast, early extubation in pediatric patients undergoing liver transplantation and congenital cardiac surgery experienced shorter ICU admission, hospital LOS, and decreased cost.[5, 6, 7] However, there is a paucity of data regarding the effect of early extubation in pediatric patients undergoing staged laparotomy. Therefore, we designed this retrospective cohort study to (1) examine whether early extubation between the two stages of an Abernethy shunt ligation had an effect on ICU and total hospital LOS, and (2) determine if there was a difference in duration of scheduled opioids and benzodiazepine administration in patients who were extubated early.

METHODS: A retrospective cohort study was performed to examine all patients who underwent a two-stage ligation of a portosystemic shunt at Ann & Robert H. Lurie Children's Hospital of Chicago from January 2016 to August 2020. Patients who were electively extubated between the two operations were considered to be in the early extubation cohort and were compared to a cohort of patients that were not extubated between stages. The primary outcome was total ICU LOS. Secondary outcomes of interest were total hospital LOS, duration of scheduled opioid administration, duration of scheduled benzodiazepine administration, methadone prescribed on discharge, need for adjuvant sedatives (ketamine, dexmedetomidine, clonidine), and in-hospital cardiac arrest. We report descriptive summaries of collected data as medians with interquartile ranges (IQRs) for continuous data and counts and frequencies (%) for categorical data. The paired Wilcoxon signed-rank test was used to evaluate differences for continuous variables, while the Fisher's exact test was used to evaluate categorical variables. Outcome data were analyzed using logistic regression with calculation of odds ratios, 95% confidence intervals (CI), and P-values.

RESULTS: Thirteen patients with type 2 congenital portosystemic shunts were identified, 6 of whom were extubated early. Among the study participants, the median age was 5 years old (IQR 2.8-16). Patients in the early extubated group were significantly older than those who were not extubated. There were no differences in preoperative laboratory test results, preoperative shunt occlusion pressures, and American Society of Anesthesiologists (ASA) physical status classification between the two cohort groups. Patients who were in the early extubation cohort had significantly shorter ICU LOS (8 days, IQR 6-9) and total hospital LOS (13.5, IQR 11-14) than that of the non-extubated cohort ($p<0.01$). The total duration of mechanical ventilation was also significantly shorter in the extubated group, 1 (IQR 0-2) day versus 11 (IQR 9-17) days respectively. Patients who were extubated early received significantly fewer days of scheduled opioids (6.5 days vs. 27 days) and fewer days of scheduled benzodiazepines (0 days vs. 14 days). Significantly more patients in the non-extubated group (5 versus 0 patients) required methadone at discharge ($P=0.03$). No patients in either cohort needed to be reintubated in the ICU.

CONCLUSION: This study showed that an early extubation approach among patients who are undergoing a staged surgical procedure is associated with improved outcomes. Patients who were extubated early not only consumed less benzodiazepines and opioids, but also had significantly shorter ICU and hospital LOS. We believe that early extubation among patients undergoing staged portosystemic shunt ligation is safe and beneficial. While this study consisted solely of patients undergoing Abernethy ligations, this proof of concept could have greater implications for all pediatric patients undergoing staged operations.

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Table 1. Univariable Analysis of Patients Undergoing Portosystemic Ligation

Baseline Characteristic	All Patients, n = 13 (100%)	Extubation Median, IQR/n (%)		*P*-value
		Extubated, n = 6 (46.2%)	Not Extubated, n = 7 (53.8%)	
Gender, n (%)				
Male	4 (30.8)	1 (16.7)	3 (42.9)	
Female	9 (69.2)	5 (83.3)	4 (57.1)	0.55
Age at surgery, years	5, 2.8-16	16, 4-16	2.8, 1.3-12	0.03
Preoperative Lab				
Hemoglobin	12.6, 11.7-13.8	12.9, 11.7-13.8	12.6, 11.2-14.1	0.94
Platelet	220, 200-270	248, 206-303	210, 194-223	0.15
INR	1.1, 1.0-1.3	1.1, 1.0-1.1	1.2, 1.0-1.3	0.23
Preoperative Pressures				
Nonoccluded Shunt Pressure	9, 6-11	9, 6-9	10, 6-11	0.57
Occluded Shunt Pressure	24, 16-29	24, 19-27	23.5, 16-29	0.74
ASA Physical Status Classification, n (%)				
2	3 (23.1)	2 (33.3)	1 (14.3)	0.55
3	10 (76.9)	4 (66.7)	6 (85.7)	
Weight	16.0, 12.2-71.6	59.8, 16.0-71.6	12.2, 10.9-75.8	0.11
BMI	18.0, 15.1-22.2	20.0, 14.9-23.5	16.6, 15.1-22.2	0.66
Shunt Type				
2a	1 (7.7)	1 (16.7)	0	0.01
2b	6 (46.2)	0	6 (85.7)	
2c	6 (46.2)	5 (83.3)	1 (14.3)	
History of Pulmonary Disease	3 (23.1)	0	3 (42.9)	0.19

ASA, American Society of Anesthesiologists; BMI, body mass index; INR, international normalized ratio; IQR, interquartile range

Table 4. Univariable Analysis of Patients Undergoing Portosystemic Ligation

Baseline Characteristic	All Patients, n = 13 (100%)	Extubation Median, IQR/n (%)		OR (95% CI)	*P*-value
		Extubated, n = 6 (46.2%)	Not Extubated, n = 7 (53.8%)		
Total Days Scheduled Opioid	14, 7-27	6.5, 6-9	27, 15-33	0.67 (0-0.91)	<0.01
Total Days Scheduled Benzodiazepine	9, 0-14	0, 0-8	14, 9-26	0.60 (0.08-0.95)	0.01
Adjuvants					
Ketamine	4 (30.8)	2 (33.3)	2 (28.6)	1.25 (0.12-13.24)	0.85
Clonidine	4 (30.8)	1 (16.7)	3 (42.9)	0.27 (0.019-3.65)	0.32
Dexmedetomidine	9 (69.2)	3 (50.0)	6 (85.7)	0.17 (0.01-2.36)	0.18
Discharged on Methadone	5 (38.4)	0	5 (71.4)	0.82 (0-0.83)	0.03
Total Length of Mechanical Ventilation, days	8, 1-11	1, 0-2	11, 9-17	0.64 (0-0.88)	<0.01
Cardiac Arrest	1 (7.7)	0	1 (14.3)	1.17 (0-45.5)	0.35
Total ICU Stay, days	10, 8-20	8, 6-9	20, 13-20	0.52 (0-0.88)	<0.01
Total Hospital Stay, days	19, 14-28	13.5, 11-14	28, 19-33	0.59 (0.20-0.93)	<0.01

OR, odds ratio

LIVER 2

An Analysis of Postoperative Strokes following Introduction of Goal-Directed Coagulation Management Guidelines during Liver Transplantation

Daniel Arango[1], Bobby D Nossaman[2], Joseph Koveleskie[3], Joseph Queen[4]

[1]Ochsner Medical Center, New Orleans, LA, [2]Ochsner Clinic Foundation, New Orleans , LA, [3]University of Queensland-Ochsner Clinical School, New Orleans, LA, [4]University of Queensland, New Orleans, LA

INTRODUCTION: Early liver transplantation (LT) was frequently associated with significant hemorrhagic diathesis due to surgical technique and to end-stage liver disease (ESLD) coagulopathy.[1] Although advances in control of surgical hemorrhagic diathesis have occurred, the underlying coagulation abnormalities observed in ESLD patients continue to be problematic.[2] In 2018, the International Liver Transplant Society proposed coagulation management guidelines to assist LT centers.[3] The purpose of this study was to measure our version of these recommendations on a prospective cohort on the incidences of stroke following LT.[4]

METHODS: Following IRB approval, all adult (≥18 years of age) patients with ESLD undergoing LT were entered into this study. Categorical variables were presented as counts and percentages. Risk differences with CI were calculated for the probabilities of postoperative stroke following introduction of goal-directed coagulation management guidelines during hepatic LT.[5]

RESULTS: The incidences of postoperative strokes following LT are shown in Tables 1 and 2. The incidence of postoperative ischemic stroke was not clinically different following introduction of the goal-directed coagulation management guidelines (Table 1). However in Table 2, no postoperative hemorrhagic strokes were observed in patients following LT following introduction of goal-directed coagulation management guidelines (Table 2).

CONCLUSION: The results from this preliminary study cautiously suggest an improvement in postoperative hemorrhagic stroke rates but not in postoperative ischemic stroke rates following the introduction of the goal-directed coagulation management guidelines.

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Table 1: The Incidence of Postoperative Ischemic Stroke following Introduction of Intraoperative Goal-Directed Coagulation Management Guidelines (GDCMG)

		Postoperative Ischemic Stroke		
	Patients n(%)	Yes	No	Totals
Intervention	GDCMG	2 (2.7)	72 (97.3)	74
	Control	19 (1.7)	1121 (98.3)	1140
	Totals	21	1193	1214

n (%): number and percentage of patients. Risk Differences: -0.01 [-0.5 to 0.2]

Table 2: The Incidence of Postoperative Hemorrhagic Stroke following Introduction of Intraoperative Goal-Directed Coagulation Management Guidelines (GDCMG)

		Postoperative Hemorrhagic Stroke		
	Patients n(%)	Yes	No	Totals
Intervention	GDCMG	0 (0)	74 (100)	74
	Control	14 (1.2)	1126 (98.8)	1140
	Totals	14	1200	1214

n (%): number and percentage of patients. Risk Differences due to Intervention: 0.01 [-0.02 to 0.02]

LIVER 3

Preoperative left ventricular diastolic dysfunction: outcomes after orthotopic liver transplantation

Marianne C Chen[1], Michael Tien[2], hendrikus lemmens[3]

[1]Stanford University, Stanford, CA, [2]Stanford Healthcare, Stanford, CA, [3]Stanford, Stanford, CA

INTRODUCTION: Left ventricular diastolic dysfunction (LVDD) is common in patients with end-stage liver disease.[1] It has been reported to be an independent predictor of systolic heart failure and all-cause mortality after orthotopic liver transplantation (OLT).[2,3] However, its effect on intraoperative management and postoperative outcomes is still unclear in patients undergoing OLT especially in cases with veno-venous bypass (VVB). The objective of this study was to determine whether or not preoperative LVDD was associated with intraoperative and postoperative inotropic requirement, development of postoperative systolic heart failure, and one-year survival in patients undergoing OLT.

METHODS: After obtaining Institutional Review Board approval, we retrospectively reviewed the medical records of all patients undergoing OLT from January 2015 to December 2017 at a single, tertiary-care, academic hospital. Data were collected on baseline patient characteristics such as age, sex, body mass index (BMI), Model for End-Stage Liver Disease (MELD) scores, and continuous renal replacement therapy (CRRT) requirement. Surgical records were reviewed for ischemia times, VVB times, transfusion requirements, and intraoperative and/or postoperative inotropic requirement. Preoperative transthoracic echocardiograms (TTEs) were reviewed for presence of LVDD. Postoperative TTEs were reviewed for systolic heart failure, defined as new ejection fraction (EF) <50% measured within one year after transplant. Patients were grouped based on the presence or absence of preoperative LVDD and comparisons were made using two-sample t-test, Chi-squared test, or Fisher's exact test as appropriate.

RESULTS: 196 patients underwent OLT with VVB over the 3-year period. Of these, 186 patients had preoperative TTE performed and were included for analysis. All patients had preoperative EF >50% and 83 patients were diagnosed with LVDD. Patient data and outcomes are reported in Table 1. Patients with LVDD were older, but other baseline characteristics such as sex, BMI, MELD score, and CRRT requirements were comparable. Surgical parameters such as ischemia times, VVB times, and blood products transfused were not significantly different between patients with and without LVDD. There was no difference in intraoperative and postoperative inotropic requirement, development of postoperative heart failure, and one-year survival.

CONCLUSION: In our patient population, preoperative LVDD was not associated with intraoperative or postoperative inotropic requirement, development of postoperative heart failure, or one-year survival. This finding is inconsistent with previous studies which report worse cardiovascular outcomes and mortality in patients with preoperative LVDD.

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2. Sharma S, Karamchandani K, Wilson R, Baskin S, Bezinover D. Acute heart failure after Orthotopic liver transplantation: a case series from one center. BMC Anesthesiol 2018;18:102.
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Table 1. Baseline patient characteristics, intraoperative and postoperative data and outcomes.

	Left Ventricular Diastolic Dysfunction	
	Yes (n=83)	No (n=103)
Age (years)*	61 ± 9	55 ± 12
Sex		
Male	53 (63.9%)	73 (70.9%)
Female	30 (36.1%)	30 (29.1%)
BMI (kg/m^2)	28 ± 5	27 ± 5
MELD score	33 ± 6	34 ± 6
CRRT	47 (56.6%)	55 (53.4%)
Cold ischemia time (min)	452 ± 105	447 ± 102
Warm ischemia time (min)	50 ± 12	49 ± 11
Veno-venous bypass time (min)	108 ± 35	109 ± 32
PRBC (units)	13 ± 21	9 ± 12
FFP (units)	11 ± 17	9 ±9
Platelets (units)	2 ± 4	2 ± 2
Cryoprecipitate (units)	2 ± 2	2 ± 1
Intraoperative inotropes	38 (45.8%)	39 (37.9%)
Postoperative inotropes	17 (20.5%)	16 (15.5%)
Postoperative heart failure	4 (4.8%)	6 (5.8%)
One-year survival	76 (91.6%)	92 (89.3%)

Data are reported as mean ± SD or n (%). Abbreviations as follows: BMI = body mass index, MELD = Model for End-Stage Liver Disease, CRRT = continuous renal replacement therapy, PRBC = packed red blood cells, FFP = fresh frozen plasma. *p<0.01 between groups.

LIVER 4

Mild Hypothermia and Acute Kidney Injury in Liver Transplantation: Second update on a randomized controlled trial

Michael P Bokoch[1], Brooke C Clemmensen[2], Dieter Adelmann[3], Rishi P Kothari[1], Scott A Lindberg[4], Ana Fernandez-Bustamante[5], Trevor Nydam[5], Claus U. Niemann[6]

[1]University of California, San Francisco, San Francisco, CA, [2]University of Nevada, Reno School of Medicine, Reno, NV, [3]University of California, San Francisco School of Medicine, San Francisco, CA, [4]Houston Methodist Hospital, Houston, United States of America, [5]University of Colorado School of Medicine, Aurora, CO, [6]University of California, San Francisco, San Francisco, United States of America

INTRODUCTION: Patients undergoing liver transplantation (LT) are at high risk of postoperative acute kidney injury (AKI). In LT patients, AKI predicts negative outcomes such as progression to chronic kidney disease, graft loss, and mortality.[1-3] Mild hypothermia (MHT, 34-35 °C) has been shown to protect against AKI in rodent models of renal ischemia and to reduce delayed graft function after kidney transplant from deceased donors.[4] Based on these results, we are conducting a single-blinded, multi-center randomized controlled trial (NCT03534141) of MHT during LT, with the hypothesis that MHT will reduce the incidence of AKI after LT.

METHODS: The study was approved by the local institutional review boards (IRB) and is overseen by a data safety monitoring board. Written informed consent was obtained from all subjects and surrogate consent was obtained for patients with hepatic encephalopathy. Patients were randomized to MHT or normothermia at the time of LT. Patients on pre-op renal replacement therapy, those undergoing simultaneous liver/kidney transplant or transplant from a donor after cardiac death were excluded. Temperature was maintained with standard measures (forced air, fluid, table, and circuit warmers) plus an esophageal temperature management device.[5] In the MHT arm, systemic cooling was initiated after induction of anesthesia and maintained through portal vein reperfusion (Fig. 1). To enhance local cooling, ice was placed over the right kidney during the anhepatic phase. In the control arm, normothermia was maintained. The primary outcome remains blinded and is the incidence of AKI within 72 h of the end of LT. Safety endpoints were defined as estimated blood loss, units of blood products transfused, and severity of acidosis. Statistical analysis was performed in R 4.0.2 and GraphPad Prism 7.0e. Numerical variables were compared between the two study arms with t-tests if normally distributed and Mann-Whitney U-tests otherwise. Categorical variables were compared with Fisher's exact or chi-squared tests as appropriate.

RESULTS: To-date, 131 of a planned 202 patients have completed the study. The study database currently holds data for 112 (85%) of those patients (MHT, n=56; normothermia, n=56). Of these, 56% were enrolled at coordinating site #1 and the remainder enrolled at site #2. At all time points, the temperature was lower in the MHT arm (Figure 2). With the exception of sex, the two study arms were well balanced in baseline characteristics including comorbidities, etiology of liver disease, and MELD scores (Table 1). With the exception of a slightly higher base deficit in the MHT arm, case data were not different between arms (Table 2). Notably, there was no difference in estimated blood loss, number of blood products transfused, peak INR, or nadir platelet count between the two arms.

CONCLUSION: Preliminary data indicate that mild therapeutic hypothermia is safe in liver transplantation and the temperature management protocol of the trial is effective. No clinical evidence for exacerbated coagulopathy or increased bleeding due to MHT was detected.

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Fig. 1 – Scheme of temperature management protocol

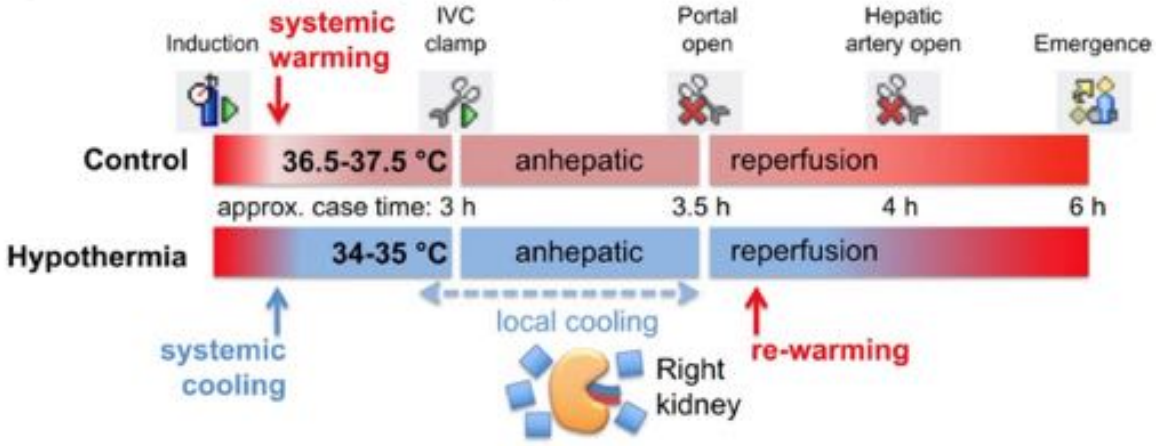

Figure 2: Patient nasopharyngeal temperatures at key case times
(Mean +/- SD)

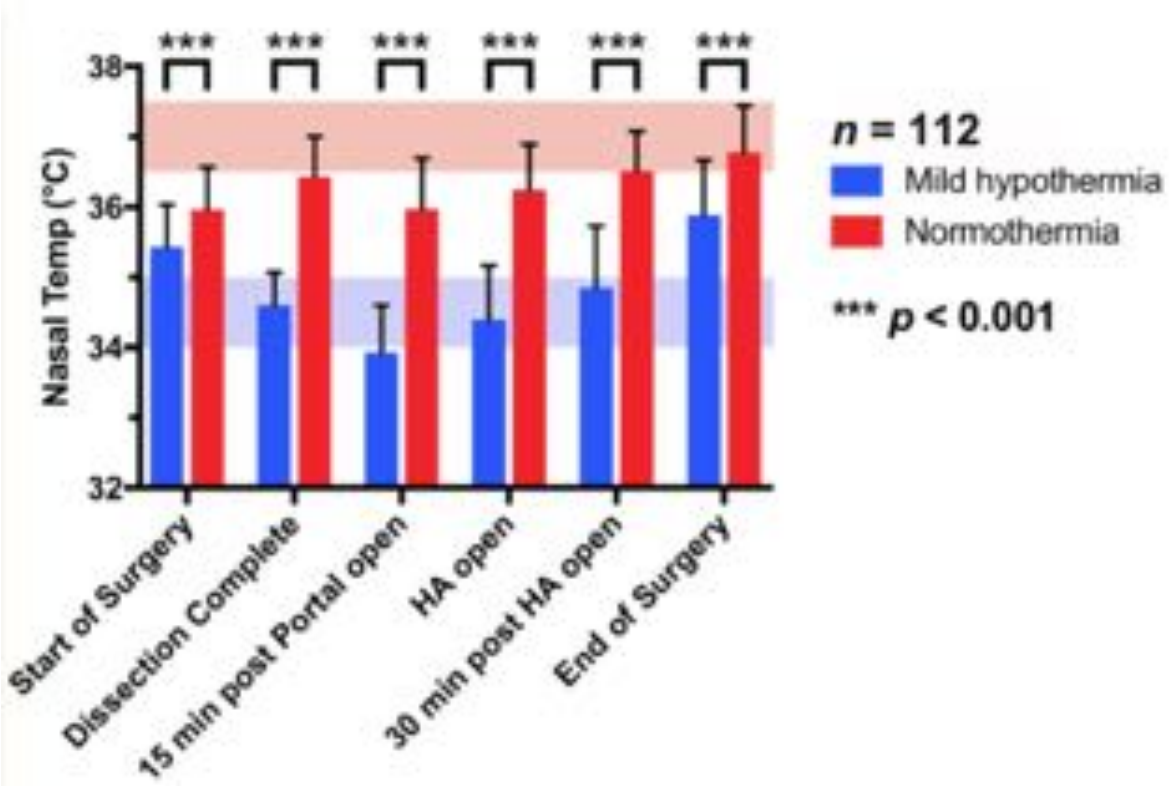

Table 1: Baseline characteristics

Characteristic	N	Normothermia, N = 56[1]	Mild hypothermia, N = 56[1]	p-value[2]
Study site	112			>0.99
1		31 (55%)	32 (57%)	
2		25 (45%)	24 (43%)	
Female (%)	112	15 (27%)	27 (48%)	**0.032**
BMI (kg/m^2)	112	27.1 (24.2, 30.3)	28.9 (25.7, 32.8)	0.13
Hypertension	112	26 (46%)	20 (36%)	0.34
Diabetes mellitus	112	24 (43%)	16 (29%)	0.17
Chronic kidney disease	112	4 (7.1%)	5 (8.9%)	>0.99
Etiology of liver disease	112			0.21
Hepatitis C		9 (16%)	13 (23%)	
Hepatitis B		2 (3.6%)	3 (5.4%)	
Alcoholic		21 (38%)	13 (23%)	
NASH		11 (20%)	15 (27%)	
Cryptogenic		7 (12%)	2 (3.6%)	
Other		6 (11%)	10 (18%)	
Hepatocellular carcinoma	110	23 (43%)	24 (43%)	>0.99
MELD Score	107	19 (13, 25)	18 (11, 25)	0.73
MELD-Na Score	107	22 (16, 27)	20 (14, 29)	0.78
Creatinine, preop (mg/dL)	112	0.90 (0.71, 1.16)	0.84 (0.76, 1.16)	0.91
Bilirubin, preop (mg/dL)	108	3.2 (1.5, 7.3)	3.0 (1.5, 8.2)	0.72
INR, preop	110	1.7 (1.3, 2.5)	1.6 (1.3, 2.5)	0.78
Serum Sodium, preop (mEq/L)	112	136 (133, 139)	136 (132, 138)	0.82
Hematocrit, preop (%)	112	33 (27, 38)	33 (26, 37)	0.78
Fibrinogen, preop (mg/dL)*	62	274 (171, 342)	261 (156, 330)	0.66
Platelets, preop (x10^3 cells/uL)	111	80 (49, 112)	68 (46, 98)	0.20
Albumin, preop (g/dL)*	63	3.1 (2.5, 3.5)	3.0 (2.6, 3.4)	0.64

[1] Statistics presented: n (%); Median (IQR)

[2] Statistical tests performed: chi-square test of independence; Wilcoxon rank-sum test; Fisher's exact test

*Data only reported by coordinating site #1 currently

Table 2: Case data and safety results

Characteristic	**N**	**Normothermia**, N = 56[1]	**Mild hypothermia**, N = 56[1]	**p-value**[2]
Case duration (min)*	63	511 (444, 584)	537 (479, 582)	0.35
Cold ischemia time (h)*	51	7.6 (6.0, 9.8)	8.1 (6.8, 9.3)	0.58
Warm ischemia time (min)*	61	31 (30, 36)	34 (30, 36)	0.28
Piggyback clamp (%)*	63	30 (97%)	27 (84%)	0.20
Caval replacement (%)*	63	1 (3.2%)	5 (16%)	0.20
Crystalloid (mL)*	63	1,000 (950, 1,750)	1,300 (1,000, 2,000)	0.35
Albumin 5% (mL)	111	1,000 (0, 1,500)	500 (0, 1,500)	0.46
Red blood cells (units)	109	6 (2, 10)	4 (2, 7)	0.54
Fresh frozen plasma (units)	109	11 (4, 20)	9 (6, 16)	0.57
Platelet concentrates (units)	106	2 (0, 3)	2 (1, 3)	0.97
Cell Saver blood returned (mL)	112	900 (288, 2,862)	725 (395, 2,044)	0.75
Urine output (mL)	111	1,100 (612, 1,950)	910 (589, 1,725)	0.38
Estimated Blood Loss (mL)	109	4,000 (1,562, 8,000)	3,929 (2,000, 6,450)	0.93
Base excess, lowest (mEq/L)	105	-8.1 (-11.0, -5.4)	-9.7 (-12.9, -7.3)	**0.025**
Lactate, maximum (mmol/L)*	61	4.7 (3.8, 5.4)	4.6 (3.8, 8.0)	0.39
INR, maximum	109	2.15 (1.90, 2.77)	2.40 (2.10, 2.80)	0.19
Platelets, minimum (x10^3 cells/uL)	111	64 (44, 88)	57 (42, 74)	0.24
Mechanically ventilated post-op (%)*	63	6 (19%)	10 (31%)	0.43
Model for Early Allograft Function (MEAF) score*	63	4.66 (3.58, 5.97)	4.46 (3.09, 5.74)	0.56

[1] Statistics presented: Median (IQR); n (%)

[2] Statistical tests performed: Wilcoxon rank-sum test; Fisher's exact test; chi-square test of independence

*Data only reported by coordinating site #1 currently

LIVER 5

Central Venous Pressure Monitoring during Living Donor Hepatectomies

Laura Ramírez[1], Andrés G Beltrán[1], German A Franco Gruntorad[2], Yimy A Santana[3], Manuela Téllez[3], Félix R Montes[3]

[1]Fundación Cardioinfantil-Instituto de Cardiología. Universidad del Rosario, Bogotá, Cundinamarca, [2]Fundacion Cardioinfantil-Instituto de Cardiología, Bogota, FL, [3]Fundación Cardioinfantil-Instituto de Cardiología, Bogotá, Cundinamarca

INTRODUCTION: Low central venous pressure (CVP) has been recommended during liver resection to reduce blood loss and transfusion requirements. Consequently, CVP monitoring is considered an integral part of the anesthetic management of major liver surgery, including living donor hepatectomy. However, the routine implementation of this monitoring remains controversial and it may not be the best option concerning the living donor's safety.[1,2] The objective of this study was to evaluate the impact of CVP monitoring on intraoperative bleeding, procedural and in-hospital outcomes, in patients undergoing living donor hepatectomy.

METHODS: Following approval from the institutional review board, all patients who underwent living donor hepatectomy from January 2014 to December 2019 at our institution were reviewed. Patients were divided into two groups, according to whether they were monitored intraoperatively with CVP or without CVP. The primary endpoint was the estimated blood loss and secondary endpoints were procedural and in-hospital outcomes. In addition, the central venous catheter features and complications were recorded. Data were analyzed by t-test, Fisher's exact test, or Chi-square as appropriate. $P < 0.05$ was considered statistically significant.

RESULTS: 122 subjects were initially selected for our study. From this group 2 patients were excluded, as they were simultaneously liver and kidney donors. A total of 120 individuals underwent hepatectomy monitored with CVP (n=53) and without CVP (n=67). There were no differences between the two groups in baseline characteristics (Table 1). Likewise, no significant difference was found between the groups, regarding the estimated blood loss (295.1 ± 203.8 ml vs 238.5 ± 140.4 ml, p=0.075). The use of CVP was associated with a longer procedure time (362.0 ± 79.4 min vs 317.8 ± 49.7 min, p<0.001) and an extended hospital stay (5.1 ± 2.1 days vs 4.0 ± 1.8 days, p=0.03) (Table 2). No other variables associated with the surgical procedure were significantly different. In the group monitored with CVP, most of the catheters were placed in the internal jugular vein and very few were positioned with ultrasound guidance (n=5, 9.4%). Complications were present in 11.3% (n=6) of the cases (Table 3).

CONCLUSION: The use of CVP as an intraoperative monitoring strategy to decrease blood loss in living donors during hepatectomy may not be necessary. It can lead to unwanted outcomes, which are normally not expected in this population composed mainly of healthy individuals.

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Table 1. Baseline characteristics

	CVP n = 53	No CVP n = 67	P value
Age (years), mean±SD	28 ± 7.0	28±8.0	0.65
Sex			
Female n (%)	22 (41.5)	31 (46.3)	0.6
Male n (%)	31 (58.5)	36 (53.7)	
BMI (kg/m^2), mean±SD	23.0±3.7	22.8±2.5	0.76
ASA physical status classification			
I n (%)	51 (96.2)	62 (92.5)	0.39
II n (%)	2 (3.8)	5 (7.6)	

CVP: central venous pressure; BMI: body mass index; ASA: American Society of Anesthesiologists.

Table 2. Procedural and in-hospital outcomes

	CVP n = 53	No CVP n = 67	P value
Surgical procedure			
Left hepatectomy n (%)	42 (79.3)	58(86.6)	
Right hepatectomy n (%)	7 (13.2)	1 (1.5)	0.8
Segmental hepatectomy n (%)	4 (7.5)	8 (11.9)	
Procedure time (min), mean±SD	362.0±79.4	317.8±49.7	<0.001
Urine output (mL/kg/h), mean±SD	1.0±0.7	0.8±0.5	0.12
Final lactate measurement (mmol/L), mean±SD	2.1±1.0	2.3±1.0	0.39
Estimated blood loss (mL), mean±SD	295.1±203.8	238.5±140.4	0.075
Crystalloid load administration (mL), mean±SD	2,290±1,017	2,056±838	0.17
Δ Creatinine mean±SD	0.08±0.11	0.07±0.08	0.7
Δ BUN mean±SD	2.7±2.3	3.8±3.8	0.11
Hospital stay (days), mean±SD	5.1±2.1	4.0±1.8	0.003

CVP: central venous pressure; BUN: blood urea nitrogen.

Table 3. CVC placement features

	n	%
Anatomical approaches		
Internal jugular vein	46	86.8
External jugular vein	3	5.7
Peripheral insertion	4	7.5
Ultrasound-guided	5	9.4
Guided by anatomical landmarks	48	90.6
Complications		
Pneumothorax	0	0.0
Infection	2	3.8
Hematoma	4	7.5

CVC: central venous catheter.

LIVER 6

Postoperative testing in low MELD liver transplant recipients

Tom Salih[1], Rishi P Kothari[2], Garrett R Roll[2], Seema Gandhi[3]

[1]UCSF, San Francisco, United States of America, [2]University of California, San Francisco, San Francisco, CA, [3]University of California San Francisco, San Francisco, CA

INTRODUCTION: Laboratory testing is important after liver transplantation (LTX) to monitor of graft function and detect complications.[1–3] However unnecessary repetition of tests is wasteful, low yield,[4] and causes patient harm.[5] Consensus guidelines about laboratory frequency in low-risk LTX recipients do not exist. Our institution has a post op order set specifying timing of postoperative tests (Table 1) however this is not used consistently. Our aim is to describe typical patterns of lab testing after LTX in patients at low risk of complications (identified as pre-transplant MELD<20), and the incidence of abnormal results. Our hypothesis is that patients have frequent lab testing despite clinical stability, and that groups of repetitive tests of low utility can be identified.

METHODS: Retrospective observational study using EHR and non-EHR data from the prospective Transplant Outcomes in Anesthesia Database (IRB #15-18341). Data extracted included patient and surgical characteristics, the results of common laboratory tests and their reference ranges. Inclusion criteria were adult patients with Model for End-Stage Liver Disease (MELD) score < 20 receiving a LTX. Re-transplants and multiorgan transplants were excluded. We performed descriptive analysis of characteristics of postoperative testing. Results were defined as normal or abnormal based on local laboratory reference ranges. For repeated tests we calculated deviation from previous recorded value.

RESULTS: 657 patients with a MELD score less than 20 received a primary LTX, 214 (33%) were female and the mean age was 60 years. The median length of stay was 8 days and patients had a median 13 blood sample collections per admission. Patients had a median of 4 blood sample collections (range 2 to 12) in the postoperative 24 hours and this reduced to a median of 1 sample daily from day 3 until discharge. Temporal patterns of lab testing are shown in Figure 1 and Figure 2. We observed significant inter-patient variation in these patterns and explored their association with other perioperative variables. We examined the value of test results (using laboratory reference ranges and clinically significant reference ranges) and change between tests to estimate the information yield from new results. Surprisingly, 46% of results were within the laboratory reference range. The median change between repetitive tests for common test components is shown in Figure 3. We identified high and low yield tests based on predicted change between repetitive tests.

CONCLUSION: We describe patterns of postoperative testing in a cohort of patients at relatively low risk of complications. We identified two main targets for intervention: 1) Defining and standardizing the optimal frequency of testing in the immediate postoperative period after low risk LTX, and 2) increasing the time interval between testing that is low yield. We plan to expand this analysis to a multicenter study to identify multilevel variation in practice.

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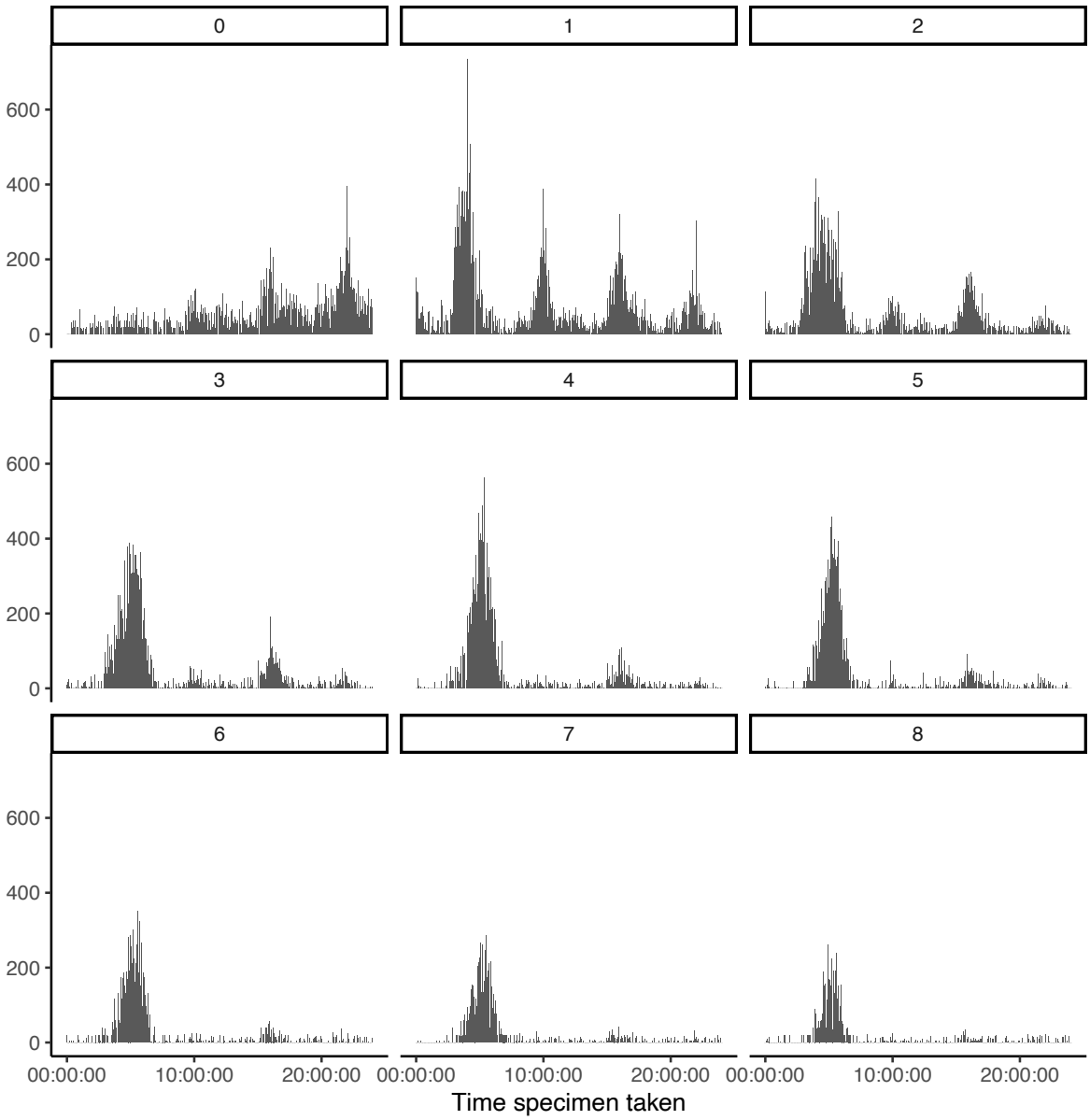

Figure 1

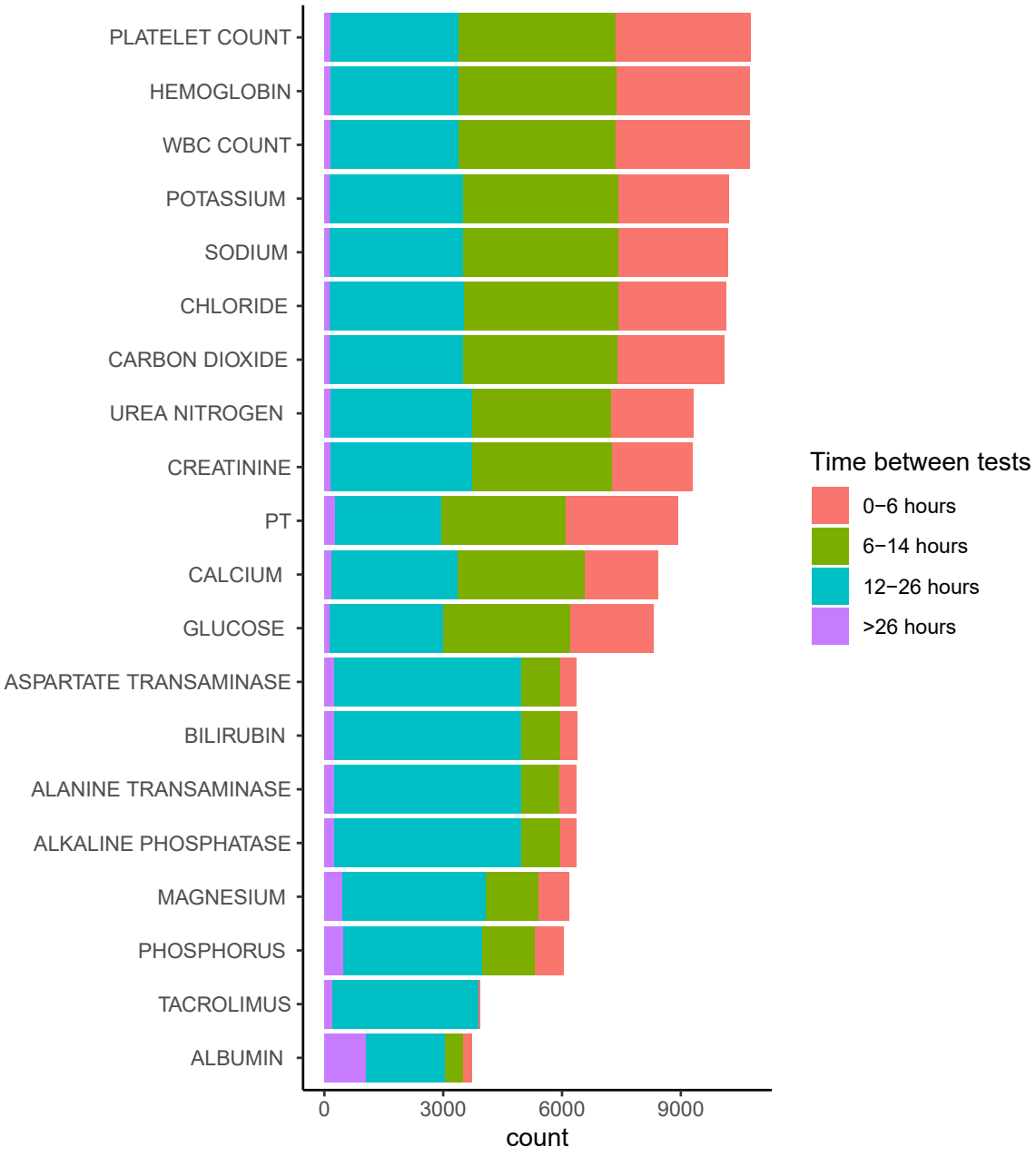

Figure 2

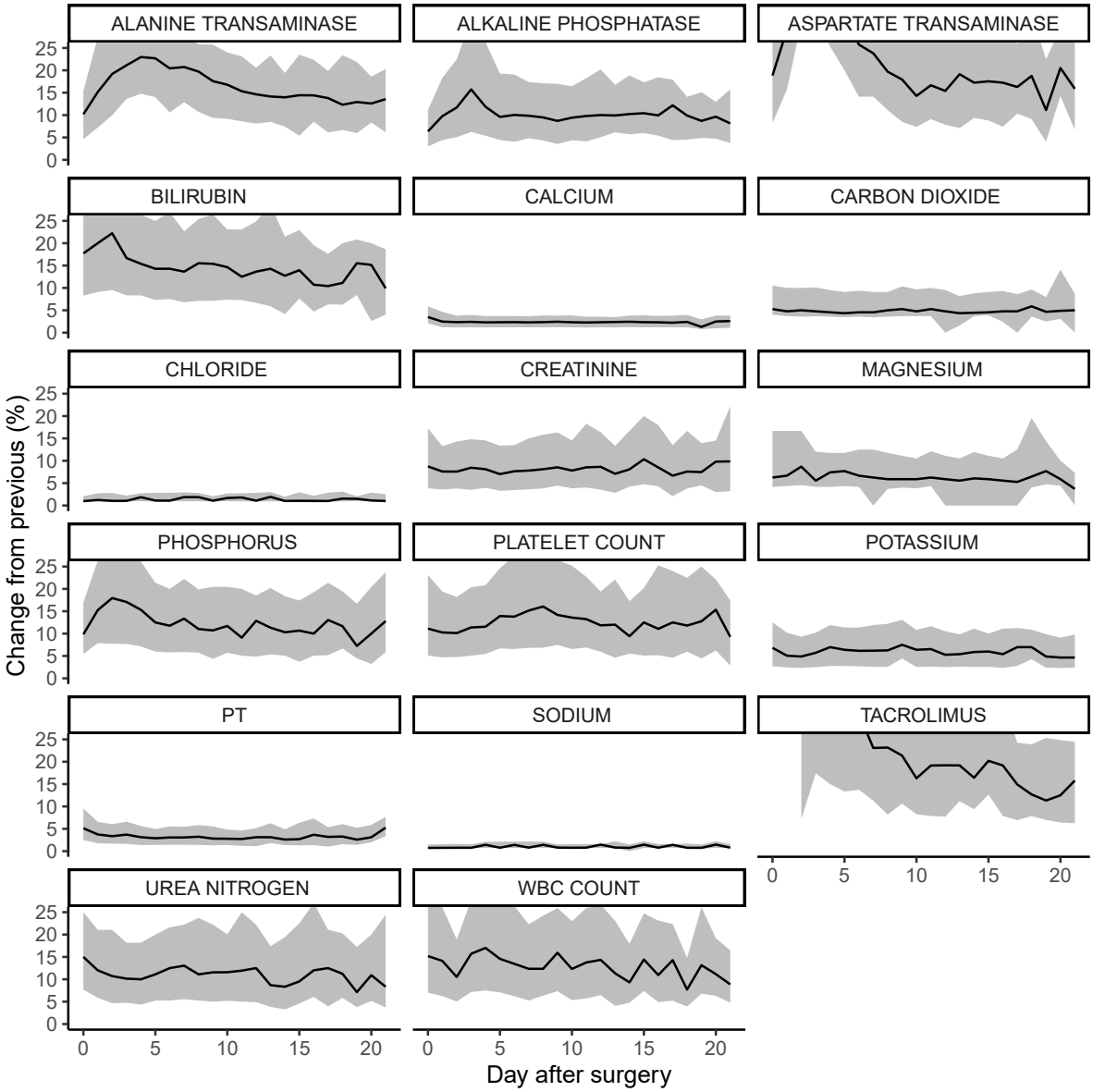

Figure 3

Complete blood count (includes platelet count)	STAT, Every 6 hours until specified
Basic metabolic panel (Na, K, Cl, CO2, BUN, Cr, Glu, Ca	STAT, QAM until specified
Aspartate transaminase	STAT, QAM until specified
Alanine Transaminase	STAT, QAM until specified
Bilirubin, total	STAT, QAM until specified
Alkaline Phosphatase	STAT, QAM until specified
Calcium, total	STAT, QAM until specified
Magnesium	STAT, QAM until specified
Phosphorus	STAT, QAM until specified
Prothrombin time	STAT, Every 6 hours until specified
Albumin	Monday, Wednesday, Friday
Tacrolimus level	QAM
Cyclosporine A level	QAM

Table 1

Subspecialty Abstracts

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 1

A Machine Learning Approach for Predicting Real Time Risk of Intraoperative Hypotension in Traumatic Brain Injury

Shara Feld[1], Daniel S Hippe[2], Nirnaya Miljacic[3], Nayak L Polissar[2], Shu-Fang Newman[2], Bala G Nair[4], Monica S Vavilala[5]

[1]University of Washington, Seattle, WA, [2]University of Washington, Seattle, United States of America, [3]Mountain Whisper Light, Seattle, United States of America, [4]University of Washington, Seattle, Washington, [5]University of Washington Medicine, Seattle, WA

INTRODUCTION: Traumatic brain injury (TBI) is a major cause of death, disability and health care utilization[1,2]. Episodes of hypotension after TBI are associated with worse outcomes[3,4]. Studies have shown preoperative risk factors for intraoperative hypotension[5]. Our aim was to build a model to predict the real- time risk of intraoperative hypotension in TBI patients, identify the features that may contribute to intraoperative hypotension and understand the advantage of using machine learning methods (which are less interpretable, but better capture non-linear structure and interactions between variables) over traditional statistical methods in this model.

METHODS: This was a retrospective and prognostic study that analyzed TBI patients undergoing neurosurgical procedures for 1005 patients at Harborview Medical Center (an academic level 1 trauma center caring for patients from the Pacific Northwest) between 2008 and 2017. The patients were divided into a training dataset used for model development and a testing data set used for estimating model performance; there was no overlap in patients between the two data sets. The clinical event was intraoperative hypotension, defined as mean arterial pressure (MAP) < 65 mmHg for five or more consecutive minutes (Figure). We developed two types of models: one based on preoperative patient-level predictors and one based on intraoperative predictors that were available minute by minute. For each of these models, we took two approaches to predict the occurrence of an event: a logistic regression model and a gradient boosting tree model. Model performances were evaluated with area under the ROC curve (ROC-AUC) and under the precision-recall curve (PR-AUC); we present results from the test set. The contribution of predictor variables were evaluated.

RESULTS: 45.7% of the patients in the training set and 43.4% of patients in the test set had at least one episode of hypotension. Model performance based on preoperative predictors was poor, with an ROC-AUC of 0.55 logistic regression models and ROC–AUC of 0.47 for the gradient boosting model. The ROC-AUC for the intraoperative logistic regression model was 0.80 (95% CI: 0.78–0.83), and for the gradient boosting model was 0.83 (95% CI: 0.81–0.85). The PR-AUC for the intraoperative logistic regression model was 0.16 (95% CI: 0.12-0.20), and for the gradient boosting model was 0.19 (95% CI: 0.14-0.24). By both ROC- and PR-AUC metrics, the XGBoost intraoperative model had higher predictive performance than the logistic intraoperative model (ΔROC-AUC: 0.03, 95% CI: 0.01-0.04, $p<0.001$; ΔPR-ROC: 0.03, 95% CI: 0.00-0.06, $p=0.023$). Features related to MAP (current MAP, recent averages and recent variance) emerged as most predictive in both the logistic regression and gradient boosting models.

CONCLUSION: This study developed a model for real-time prediction of intraoperative hypotension in patients with TBI, and demonstrated that machine learning techniques achieve better performance than traditional statistical techniques. ML allows the analysis of a large set of features with more complex interactions through efficient computing techniques[6]. Features representing the temporal trend of MAP are key for predicting future hypotension, while preoperative risk factors are poor predictors for intraoperative hypotension. The combination of computationally efficient models with a streamlined set of key features lays the groundwork for developing real-time intraoperative decision support in TBI.

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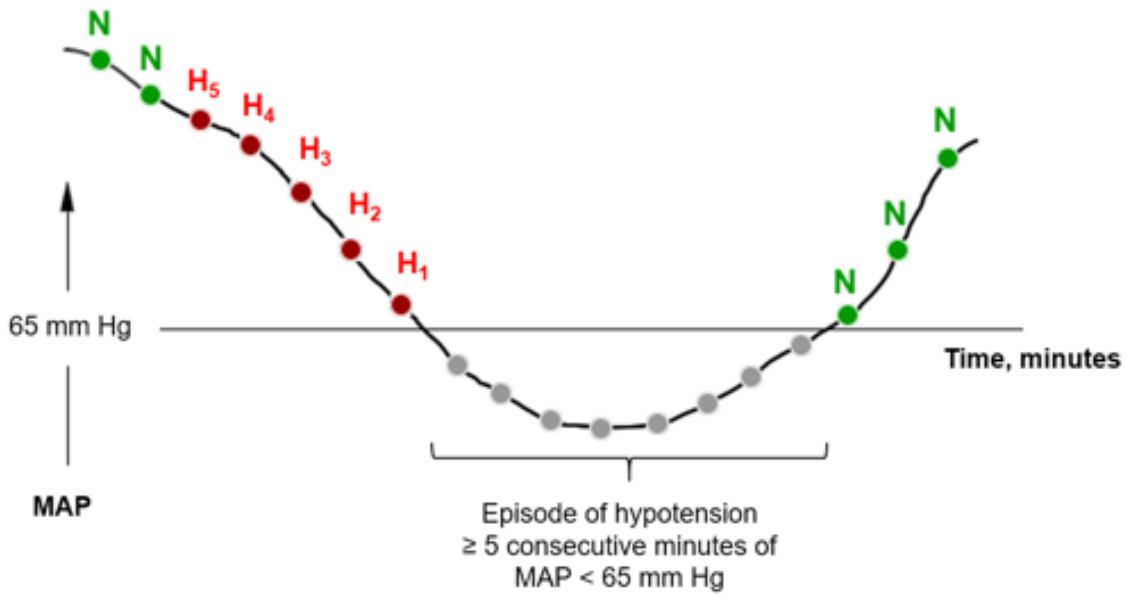
FIGURE. Use of timing in definition of intraoperative hypotension.



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 2

Ketamine dissociation triggers a universal switch in neuronal activity across neocortex

Joseph Cichon[1], Max B Kelz[2], Alexander Proekt[2], Andrzej Wasilczuk[1]

[1]University of Pennsylvania, Philadelphia, PA, [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

INTRODUCTION: Since antiquity indigenous cultures have used plant-derived medicines to create a state of internally generated experiences divorced from reality for medicinal and religious purposes. Recently, clinical trials revealed that a single dose of dissociative agents produces robust and durable improvements in diverse, treatment-resistant psychiatric disorders, and that the dissociative experience itself is a powerful predictor of clinical response[1–7]. The neuronal and circuit mechanisms underlying the dissociative experience, however, remain unknown.

METHODS: Two-photon microscopy in living cortex.

RESULTS: Here, using in vivo calcium imaging, we found that ketamine-induced dissociative state is accompanied by a switch in cortical network activity – active neurons become suppressed while previously silent neurons become activated. All the while the net cortical activity is preserved. Ketamine-induced switch in network activity is universal across excitatory neurons in all cortical layers and regions, and all major genetically-defined interneuron subtypes. Cortical application of ketamine or combined pharmacologic blockade of cortical NMDA receptors and HCN1 channels was sufficient to recapitulate the activity switch and impaired sensorimotor processing.

CONCLUSION: These experiments reveal that the neocortex contains two largely non-overlapping distributed neuronal populations: one engaged in processing sensory stimuli, the other giving rise to the dissociative state. Identification of this dissociative circuit lays the groundwork for mechanistic understanding of the therapeutic efficacy of dissociative agents.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 3

State decoupling of the C. elegans neural system under anesthesia and during emergence

Christopher W Connor[1], Greg Wirak[2], Andrew S Chang[2], Christopher V Gabel[3]

[1]Brigham and Women's Hospital, Boston, MA, [2]Boston University, Boston, MA, [3]Boston University School of Medicine, Boston, MA

INTRODUCTION: Essentially all multicellular organisms are susceptible to exposure to volatile anesthetic agents[1,2]. In mammals, EEG is the usual method for detecting resultant changes in neural function. Many EEG patterns have been empirically characterized in the anesthetized brain[3,4], but the causal relationship is unclear. This limitation can be overcome by functional fluorescent imaging in the nematode C. elegans, a well-established model for anesthetics, allowing the activity of individual neurons to be captured simultaneously across the majority of the nervous system[5].

METHODS: The predominant hypothesis is that anesthesia results from a disruption in coordinated neural activity, causing dissociation between stimuli and behavior[6]. Thus, metrics based on information theory have been explored such as mutual information (MI)[7], which measures the entropy shared between two sources, and transfer entropy (TE)[8], which measures the future entropy of a source that can be predicted from another source but not from itself. The application of MI and TE directly to EEG data has an unclear neuronal basis, whereas functional imaging in C. elegans can identify the activity state of individual neurons and their temporal relation. C. elegans data were obtained in a total of 10 specimens progressively equilibrated to atmospheres of 4% and 8% isoflurane (1.3 and 2.6 MAC) with volumetric fluorescent imaging performed with a diSPIM microscope, using 5mW 488nm and 561nm lasers to excite cytoplasmic GCaMP6s and nuclear RFP fluorophores respectively. For each animal, N=120 neurons were tracked in the head region using the fixed RFP, and their activity extracted using fluctuations in GCaMP6s fluorescence. Data were quantized to 4 levels[9], producing a 2-bit value for each neuron at each imaging timestep. For each neuron pair in each animal ($X,Y \in N, X \neq Y$), joint entropies were calculated for the past and future states of X and Y (Xp,Yp,Xf,Yf). These entropies can be recombined to produce the metrics of MI and TE (Fig 1), but also to derive arbitrarily any other information metric[10]. We arrive at a novel metric, state decoupling, that quantifies the degree of independent information unique to individual neurons across time. To evaluate state decoupling over time, C. elegans were anesthetized with 4% isoflurane and then exchanged to fresh buffer to achieve a gradual emergence over 2 hours with continuous imaging.

RESULTS: Figure 2 shows the collection of the entropy regions for MI (Fig 2A1) for C. elegans when under 0%, 4% and 8% isoflurane (Fig 2A2). Figures 2B1 and 2B2 show these results for TE. No statistically significant differences were detected between any pair of conditions. However, the entropy collection shown in Figure 2C1 indicates the extent to which the state of each source is informationally decoupled from any of the others, and we therefore give this novel metric the name of state decoupling. The 4% isoflurane group is statistically significantly different from both the 0% isoflurane group ($P < 0.00001$) and the 8% isoflurane group ($P < 0.0001$), as shown in Figure 2C2. During emergence from isoflurane 4%, state decoupling progressively resolves from the level seen in these anesthetized animals to the level seen in an unexposed control group. Figure 3 shows the recovery of state decoupling for the emerging anesthetized specimens, versus state decoupling in control specimens. Black lines show time-smoothed averages, though individual anesthetized specimens show significant cyclical non-smooth recovery. Controls evince a slow downward drift in state decoupling, most likely an artifact of slow, progressive photobleaching of the fluorophores under prolonged imaging producing a gradual artifactual suppression of the apparent activity.

CONCLUSION: State decoupling has a straightforward biological interpretation that parallels its mathematical definition: it quantifies individual neurons becoming decoupled from their previous state and the state of surrounding neurons. Under moderate anesthesia (1.3 MAC), increased state decoupling represents induced disorder of the usual functioning of the neuronal system. Under profound anesthesia (2.6 MAC), C. elegans evinces episodes of quiescence in which individual neurons are stuck in either an inactive or active state. This simplification decreases state decoupling as the neural state appears more predictable, but actually represents a diminished repertoire of states and transitions that the system can enact.

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Figure 1

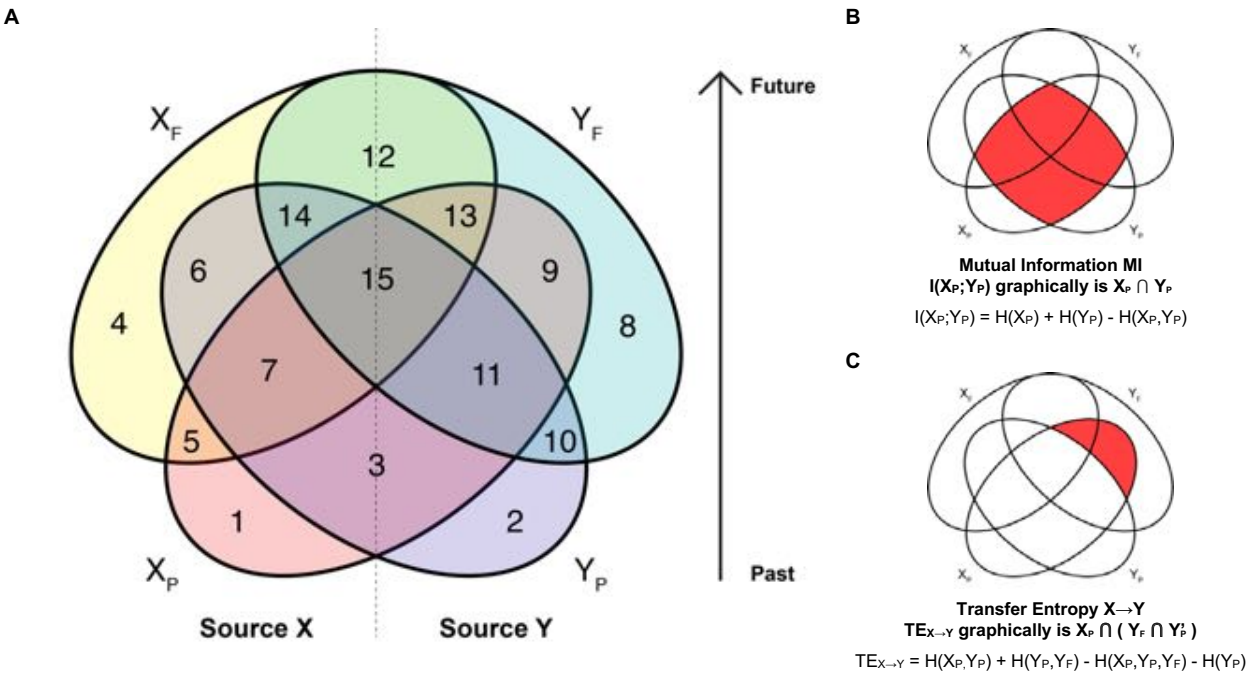


Figure 2

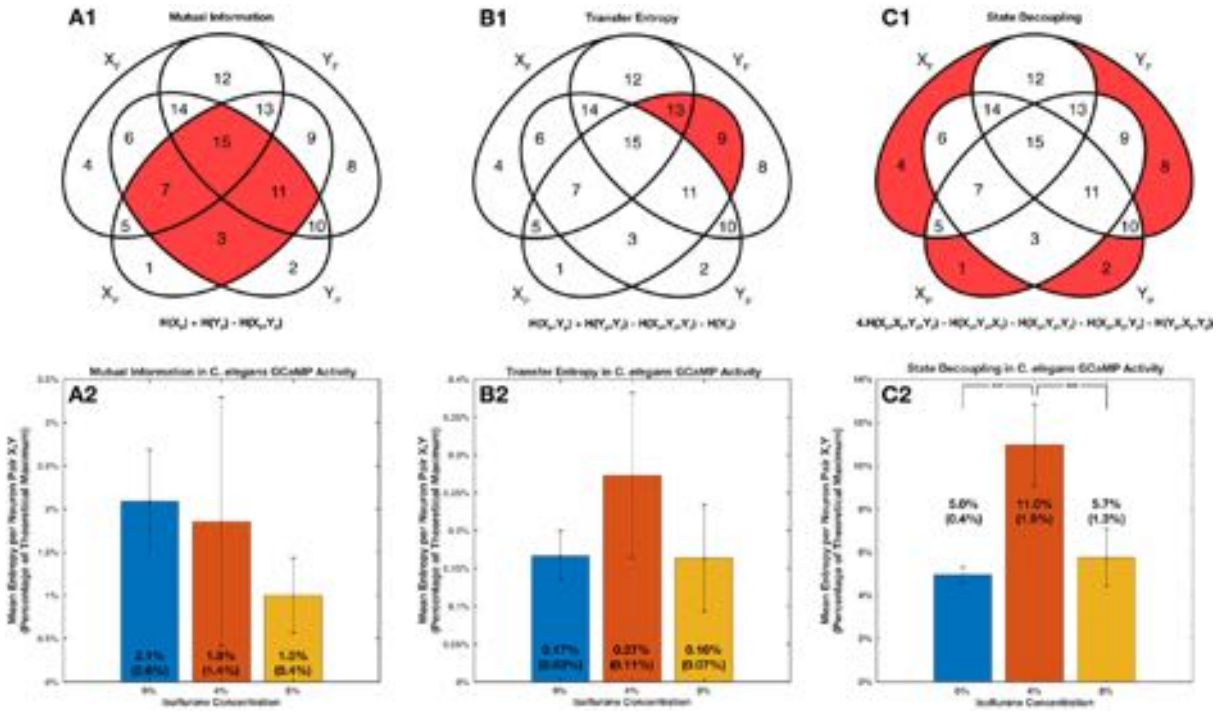
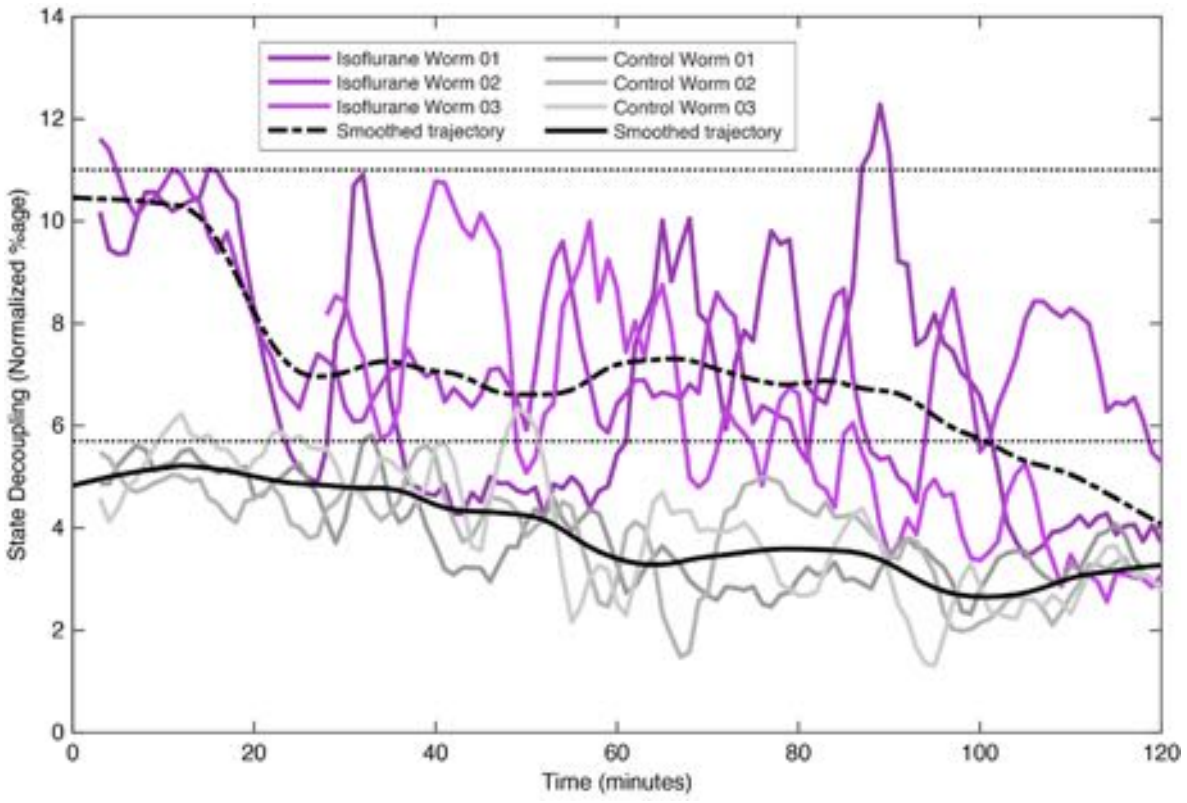


Figure 3



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 4

Whole-brain network connectivity changes with midazolam sedation during task performance and periodic pain: A functional MRI study in healthy young adults

Keith M Vogt[1], Christopher T Smith[2], James W Ibinson[1], Julie Fiez[1]

[1]University of Pittsburgh, Pittsburgh, PA, [2]Northwestern University, Chicago, IL

INTRODUCTION: Despite the widespread use and well-known pharmacology of midazolam, the brain network correlates of its action, especially during pain, are less well characterized. Though converging evidence suggests that decreases in long range Functional Connectivity (FC) is a feature of anesthetic-induced unconsciousness[1], FC under conscious sedation is more varied. Previous studies of fMRI-based FC under midazolam have employed independent component analysis (a data-driven approach) to organize brain areas into large resting-state networks. The first of these found increased FC in the mid-cingulate and decreased FC in the posterior cingulate, with the component they identified as default-mode network[2]. A subsequent study showed mixed non-robust results, with both increased and decreased FC throughout the brain[3]. A recent study in older adults showed midazolam-associated increases in FC between networks labelled default-mode (predominantly posterior cingulate and medial prefrontal areas) and salience (notably including insula and dorsal anterior cingulate)[4]. This is a focused secondary analysis of data from a within-subject crossover imaging study comparing midazolam and ketamine on multiple behavioral and imaging endpoints. We used background FC as a dynamic measure of midazolam's effect on neural communication, during a novel experimental paradigm of memory encoding during the periodic aversive experience of acute pain. Our previous FC analysis focused on anatomical seed regions with known roles in memory, fear, and pain processing. From these seed regions, we found predominantly increased FC to targets throughout the brain[5]. In this current expanded network-level whole-brain analysis, we anticipated widespread increased FC under midazolam, compared to saline.

METHODS: Data is from 16 healthy volunteers (age 25.7 ± 5.3 years, 11 male), who underwent fMRI (3 T BOLD, TR=1 s, 2.3 mm isotropic) under saline, followed by a target-controlled infusion of midazolam (effect-site concentration 10 ng/ml). Light sedation was achieved, with all subjects able to respond to voice. Under both saline and midazolam conditions, subjects performed a memory encoding task[6] with 270 auditory word items. One-third of these were immediately followed by painful (subjective rating 7/10) electric nerve stimulation to their left index finger. FMRI data were processed and analyzed using Conn Toolbox[7]; motion parameters, CSF signal, and task-event timing were removed by regression. The Saline > Midazolam contrast (looking for drug-induced differences in FC) was calculated using 30 standard network regions of interest (defined from resting-state data from the Human Connectome Project; cerebellum and brain stem excluded). Fig. 1 shows anatomic locations of selected networks used as seed and target regions of interest in the analysis. Significant FC changes were adjusted for an analysis-level false detection rate of $p < 0.05$ (correcting for multiple comparisons).

RESULTS: Fig. 2 shows FC differences between networks for saline versus midazolam conditions. Increased (blue hue) FC under midazolam was found between 29/30 networks investigated. The majority of changes were localized to nodes in the parietal, posterior temporal, and occipital lobes. The identified FC changes crossed functional network labels, including between nodes within the default-mode, visual, language, and sensorimotor networks. Fig. 3 graphically displays the network FC changes overlaid anatomically on the brain. This allows visualization of the overall pattern of increased FC from posterior network nodes to nearby targets, as well as to a sparser array of more anterior target nodes centered in the prefrontal cortex and anterior temporal lobes.

CONCLUSION: These findings add to the previous resting-state (pain-free) studies of midazolam, which overall show mixed results for direction, magnitude, and locations of connectivity change under the drug. In this clinically relevant paradigm of a memory task **during periodic painful stimulation, light sedation with midazolam caused robust increases in background network connectivity throughout the brain**, with predominance of posterior FC changes. These findings support that behavioral context, including pain, may influence anesthetic effects on brain networks. Further, we found increases in FC during conscious sedation, which differ from broad decreases seen under general anesthesia.

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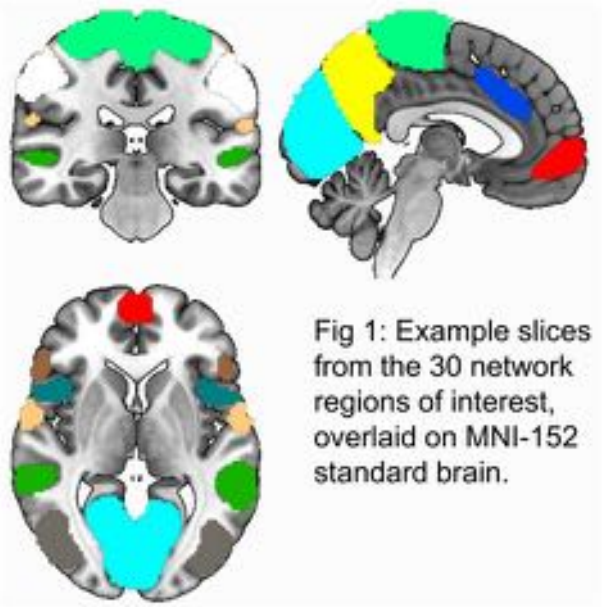
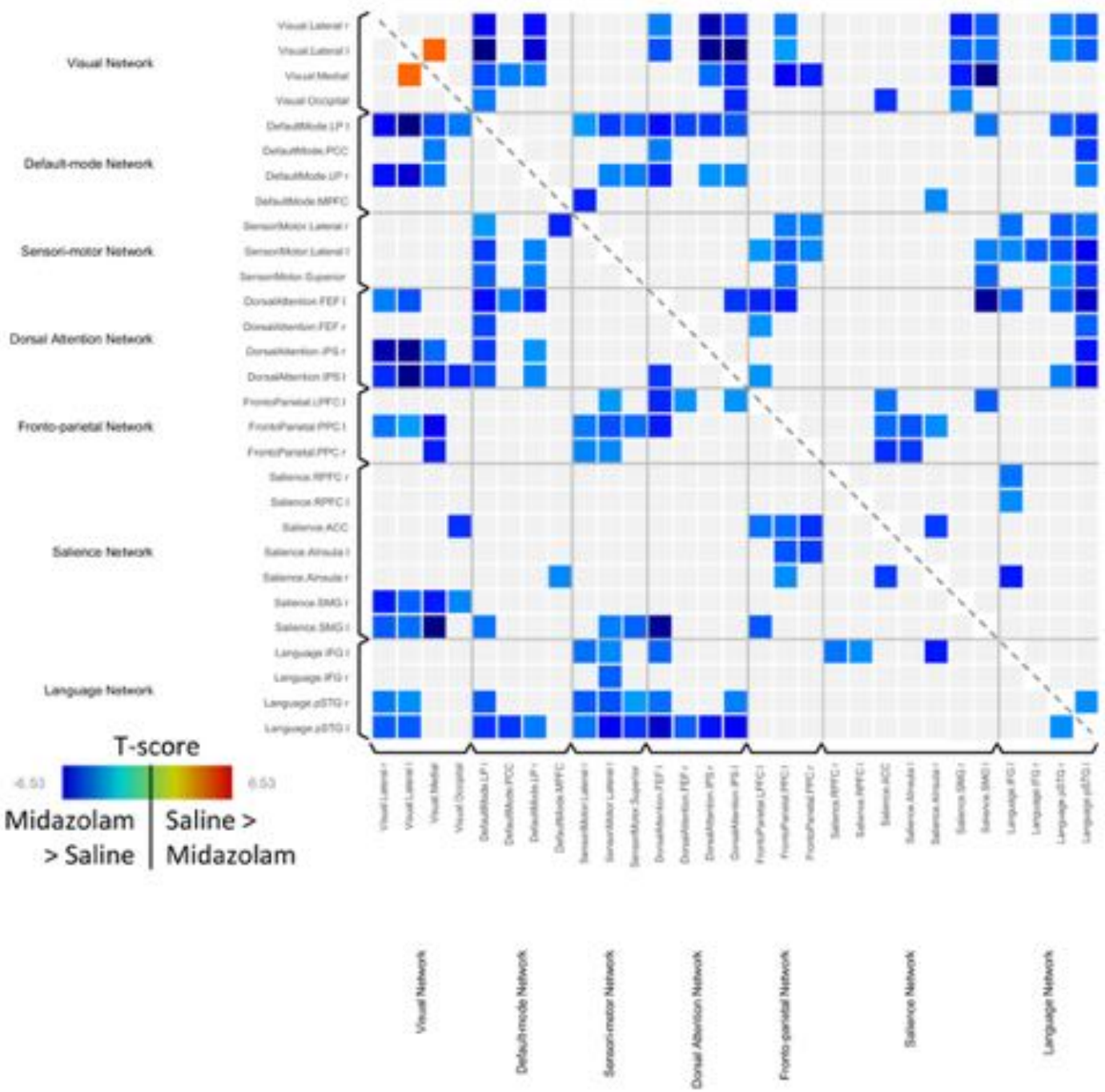


Fig 1: Example slices from the 30 network regions of interest, overlaid on MNI-152 standard brain.



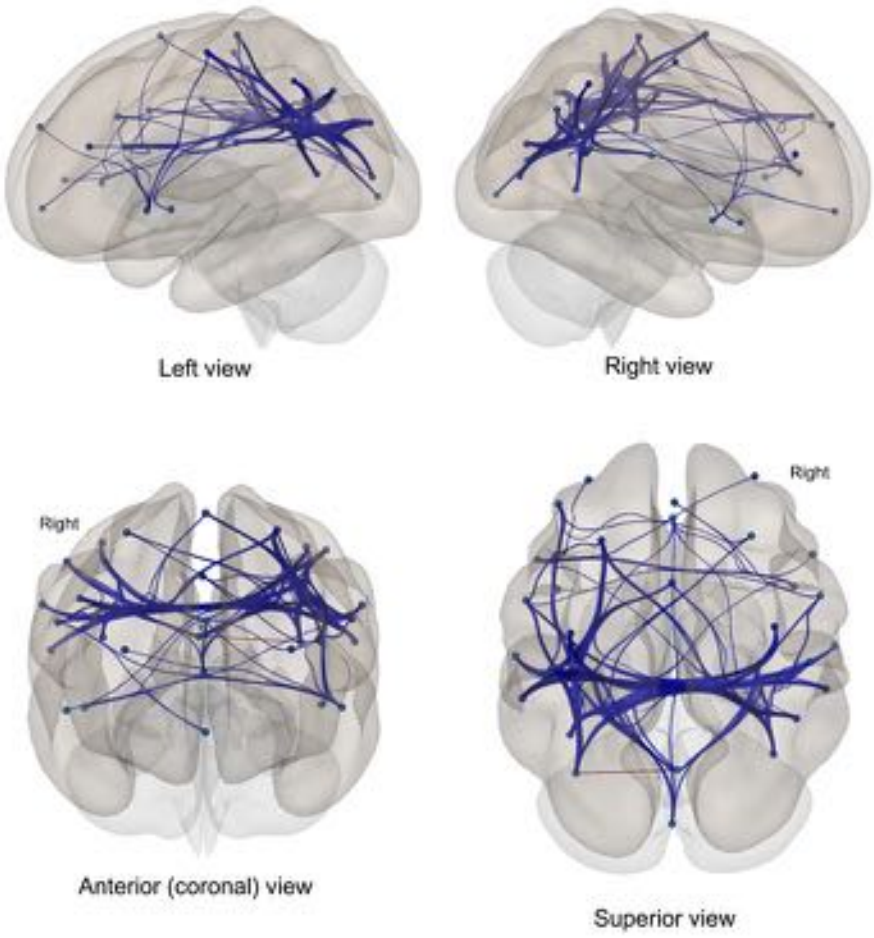


Fig 3: Anatomical visualization of between-network changes in functional connectivity comparing, saline to midazolam conditions. Views are slightly oblique from four labelled perspectives.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 5

Using the 5-choice serial reaction time task to measure cognitive recovery in rats following anesthetic emergence

Kathleen Vincent[1], Edlyn R Zhang[1], Risako Kato[1], Angel Cho[1], Olivia Moody[1], Ken Solt[2]

[1]Massachusetts General Hospital, Charlestown, MA, [2]Harvard Medical School; Massachusetts General Hospital, Boston, MA

INTRODUCTION: While healthy adults recover cognitive function rapidly following anesthesia, cognitive complications such as post-operative delirium become more prevalent as we get older[1]. As the proportion of elderly continues to increase globally, understanding how the brain restores neurocognition following anesthetic-induced breaks in consciousness becomes a more clinically and neurophysiologically important question to address. In rodents, levels of consciousness are traditionally captured by physiological responses such as the return of righting reflex (RORR) and electroencephalographic recordings; however, the return of cognitive function is more difficult to assess. The advent of touchscreen operant chambers with programmable tasks has vastly improved our ability to measure more complex cognitive features in animals, though their usage in anesthesia research has been limited. The 5-choice serial reaction time task (5-CSRTT), an analog to human continuous performance tasks, measures aspects of working memory, sustained attention, and inhibitory control using a fully automated system[2]. Previous work has demonstrated that exposure to isoflurane anesthesia produces no long-term consequences in rat 5-CSRTT performance, but how quickly performance recovers has not been established[3]. Here we use the 5-CSRTT to capture cognitive recovery trajectories in rats immediately following emergence from both inhaled and intravenous anesthetic regimens. By assessing the recovery trajectories of cognitive function in young, healthy rats we establish a foundation for which future models of post-anesthetic cognitive impairment may be compared.

METHODS: Sprague Dawley rats (4 males and 4 females) were trained to perform the 5-CSRTT (Fig. 1). In a 5-CSRTT trial, the rat attends a 5-windowed screen for the appearance of a white square in 1 of 5 locations. The rat must recall and select the correct location via nose poke within 5s to receive a food reward. Selecting the wrong tile (incorrect responses) or not responding (omissions) are punished with a time-out. Primary outcome measures were accuracy (% correct responses) and omissions (% of trials with no response). Rats were trained until they could perform the 5-CSRTT with >80% accuracy and <20% omissions, after which they were tested once per week following anesthesia. The following anesthetic regimens were tested: 2% isoflurane for 1h (ISO), 3% sevoflurane for 20 min (SEVO), 10mg/kg I.V. propofol (PROP), 35 µg/kg and 20 µg/kg IV dexmedetomidine over 10 min (high and low DEX), and 50 mg/kg I.V. ketamine over 10 min (KET). Rats recovered from anesthesia in the 5-CSRTT testing chamber where they could initiate trials ad libitum during a 2-3h period. Recovery of low omission rate is the time from RORR to when a response is made in ≥4 out of 5 consecutive trials and is a metric of sustained attention. Recovery of accuracy performance is the time from RORR to when ≥4 out of 5 consecutively responded trials are correct and is a metric of working memory. Recovery trajectories were analyzed by survival curve comparison using a Mantel-Cox test.

RESULTS: The time to recover accuracy performance ($\chi2 = 21.37$, $p = 0.0007$) and low omission rates ($\chi2 = 27.95$, $p < 0.0001$) on the 5-CSRTT following RORR varied among anesthetic regimens. Recovery of accuracy performance, a measure of working memory, was achieved in 87% of rats following SEVO, in 75% of rats following PROP, in 62% of rats following ISO and KET, and 37% and 25% of rats following either low or high doses of DEX (Fig. 2). Recovery of low omission rates, a measure of sustained attention, was achieved in 87% of rats following ISO, SEVO, and PROP, in 37% of rats following KET, in 12% of rats following low dose of DEX, and no rats recovered a low omission rate following high doses of DEX. RORR was unrelated to cognitive recovery (Table 1).

CONCLUSION: Using the 5-CSRTT, we found that metrics of working memory and sustained attention follow anesthetic-specific trajectories. The return of cognitive function is most delayed following dexmedetomidine and is most rapidly recovered following sevoflurane anesthesia. Importantly, RORR – which is widely used to measure the return of consciousness in animals models – is not predictive of how quickly cognitive function returns. Overall, we demonstrate that the 5-CSRTT can be exploited to track real-time cognitive recovery in trained rats following anesthetic emergence to capture clinically relevant neurocognitive function.

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Figure 1

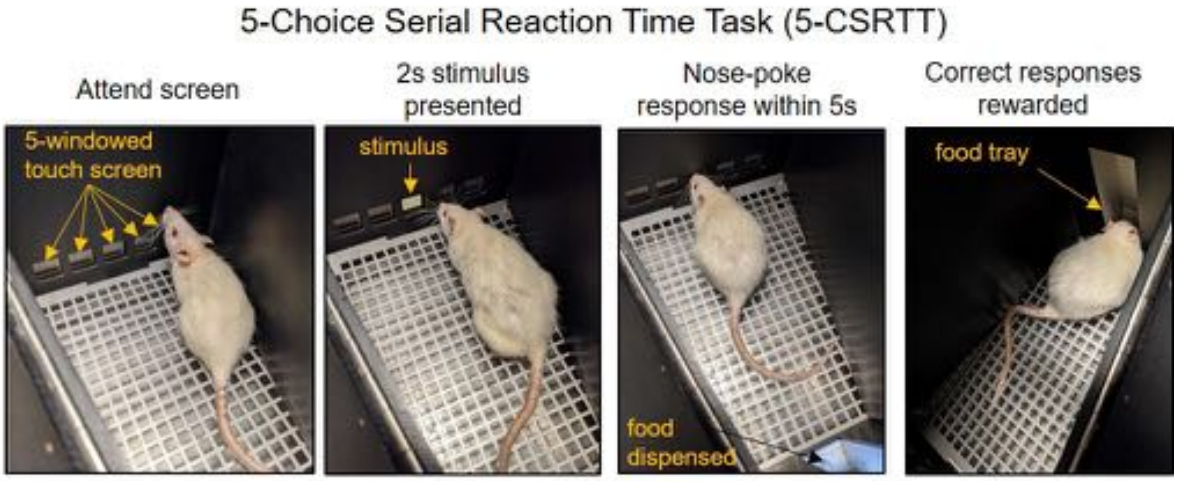

Figure 2

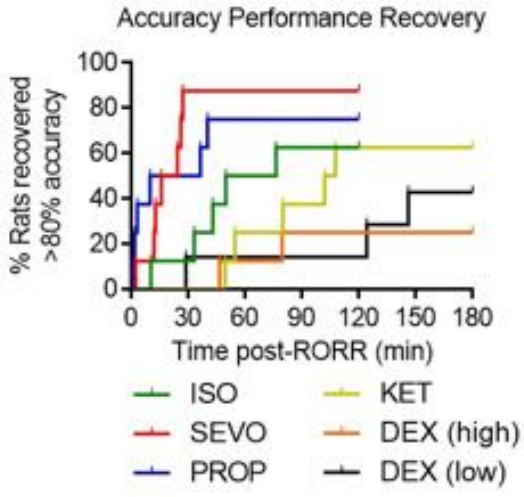

Figure 3

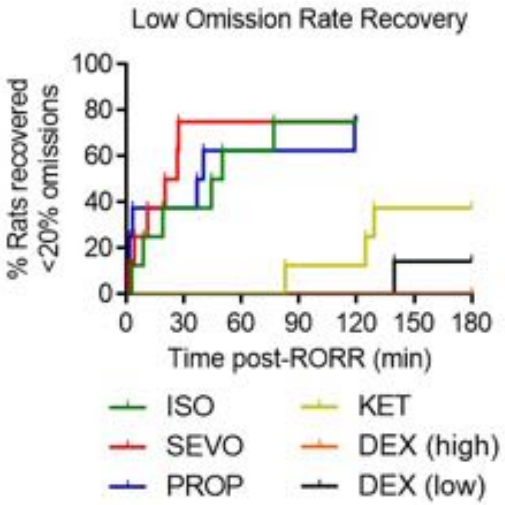

Table 1

	RORR (min)		Median recovery time (min post-RORR)	
	Mean	S.D.	Accuracy performance	Omission performance
ISO	10.2	5.4	63.1195	47.1631
SEVO	7.5	2.5	20.16	23.4503
PROP	12.9	2.4	23.27	38.475
KET	75.0	20.8	104.886	Undefined
DEX (high)	35.4	10.6	Undefined	Undefined
DEX (low)	49.8	20.2	Undefined	Undefined

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 6

Modulation of Resistance to State Transitions is Dose Independent Across Volatile Anesthetics

Andrzej Wasilczuk[1], Cole Rinehart[1], Andrew McKinstry-Wu[1], Max B Kelz[1], Alexander Proekt[1]

[1]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

INTRODUCTION: Recent studies have begun to investigate the relationship between population-based and individual-based anesthetic pharmacology[1-3]. At steady state concentrations, population level measures of anesthetic potency are constant, yet they mask spontaneous fluctuations in behavioral arousal observed between the responsive and unresponsive states within individuals[2]. These changes in behavioral arousal demonstrate resistance to state transitions (RST), a tendency to remain in the same arousal state upon repeated behavioral assessment. Volatile anesthetics differentially modulate RST at equipotent concentrations[3]. However, it remains unclear whether this observation is dose dependent. Furthermore, the relationship between RST and transition probability have not been fully explored. We hypothesize that RST is a novel feature of state transitions independent of drug dosing or potency.

METHODS: Adult (14-24 weeks old) C57Bl/6 mice (n=140 in total) were exposed to steady state concentrations of isoflurane (0.3%, 0.4%,0.6%, 0.7% atm), sevoflurane (0.5%, 1.0% atm), or halothane (0.4%, 0.5% atm). After a 2-hour equilibration period, righting reflex assessments were performed every 3 minutes for 2 hours on 4 separate occasions. Results were used to determine transition probability matrices for each individual. Response probability, transition probability, and RST were computed from the transition probability matrices. A 2x2 transition probability matrix can be fully described by 2 parameters (a and b), where a corresponds to the probability of staying responsive on two consecutive righting reflex assessments, and b corresponds to the probability of staying unresponsive on two consecutive righting reflex assessments. Response probability, transition probability, and RST can be analytically be derived using a and b. Equations for said features are found below. TPM=[a 1-a;1-b b] Response Probability=(1-a)/(2-a-b) Transition Probability=2(1-a)(1-b)/(2-a-b) RST=(a+b)/2 A linear regression was used to compare predicted and experimental transition probabilities. Analyses were performed in Matlab 2020b.

RESULTS: At steady state concentrations, a 2x2 transition probability matrix is sufficient to describe experimental transition probabilities, regardless of anesthetic choice or dose. There is a unique relationship between response probability, transition probability, RST, and the defining parameters of the transition matrix. Transition probability and RST are distinct measures of state transition characterization, explaining differences between RST and measures of transition likelihood based on stochastic switching between a 2-well energy landscape[1,3].

CONCLUSION: RST is a novel means of characterizing state transitions. While unique to the anesthetic choice, RST does not depend on anesthetic dose, and is distinct from more traditional measures of anesthetic potency. In combination with seemingly random fluctuations in arousal, assessment of RST offers additional insights for precision-based practice.

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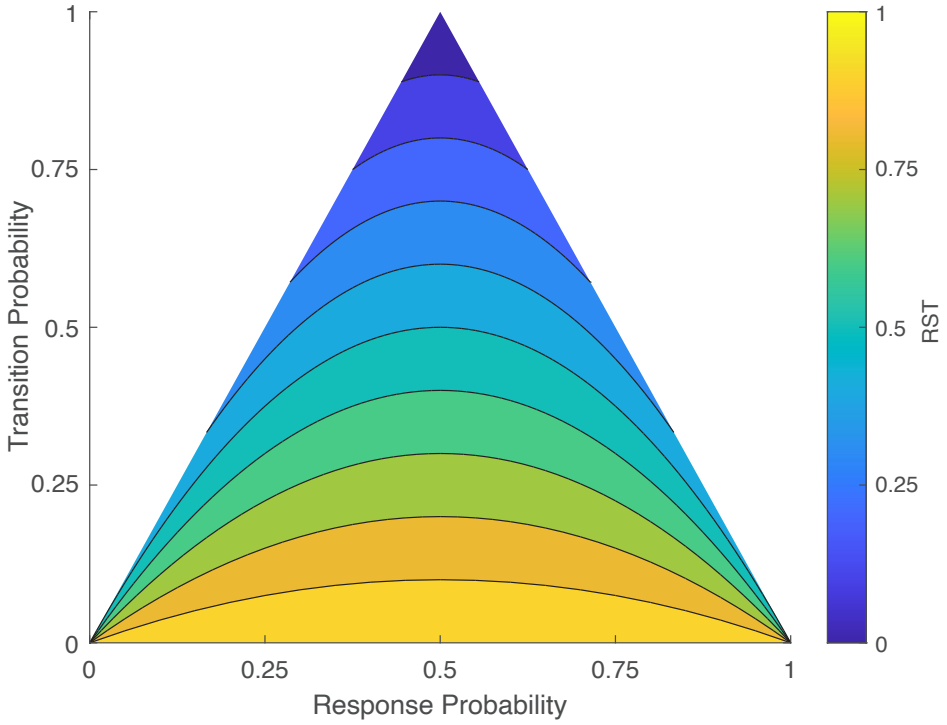

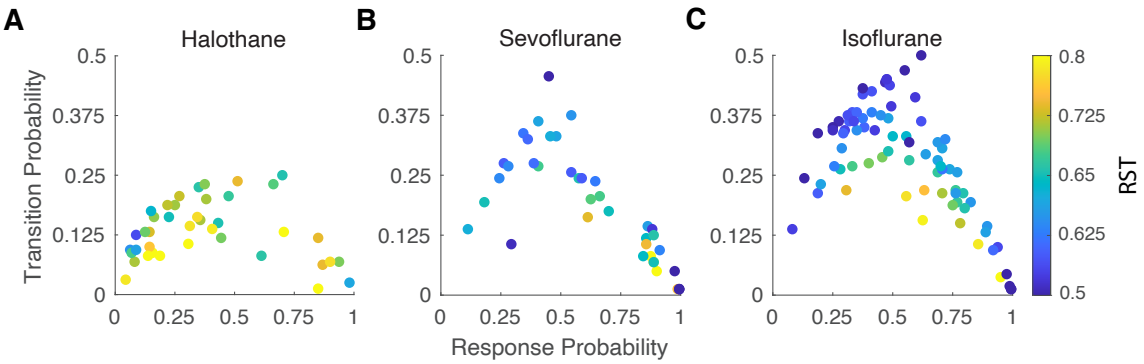

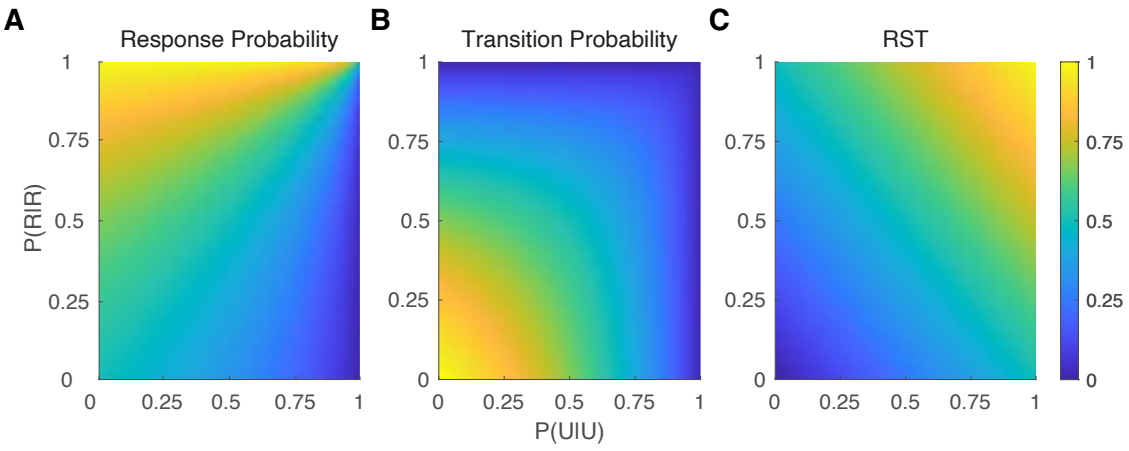

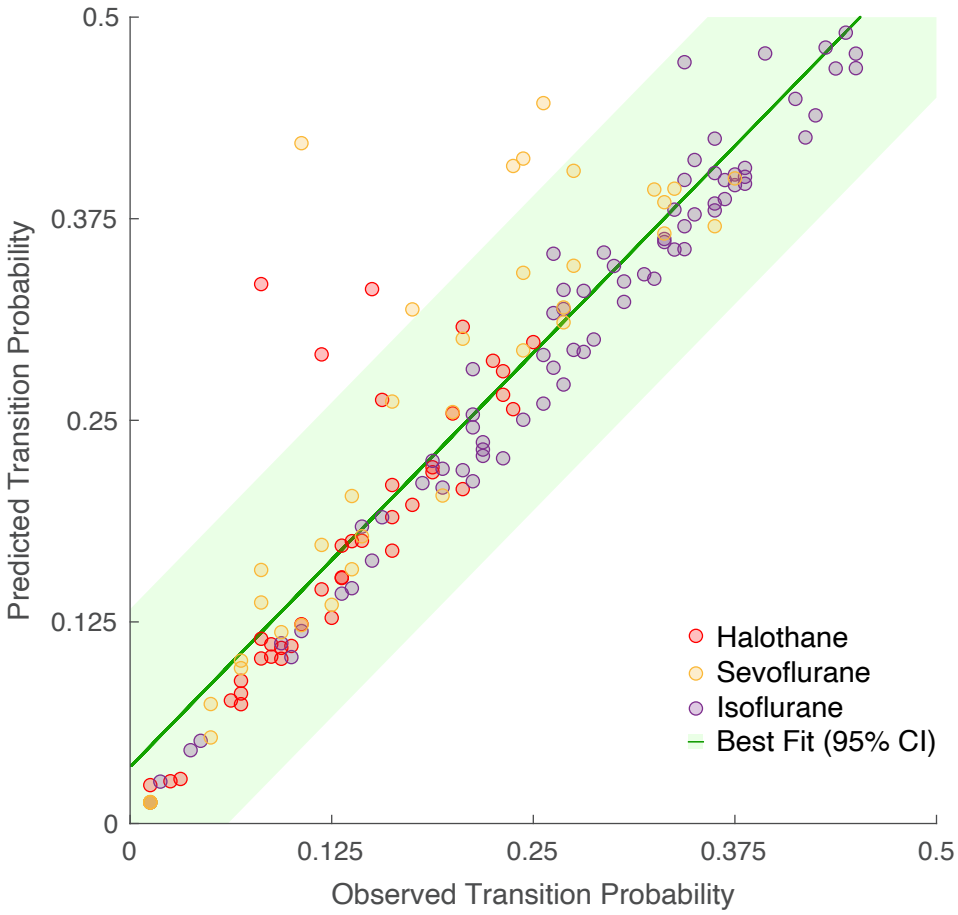

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 7

Effect of Oral Versus Intravenous Methadone on Postoperative Pain and Opioid Use after Major Spine Surgery

William Tennant[1], Lawrence Jones[1], Bhiken Naik[1], Lauren K Dunn[1]

[1]University of Virginia, Charlottesville, VA

INTRODUCTION: Perioperative pain management is challenging after major spine surgery. Opioids are frequently used for perioperative analgesia and part of a total intravenous anesthetic to facilitate neuromonitoring. Methadone has previously been shown to reduce postoperative pain scores and opioid requirements after spine surgery with no difference in adverse effects.[1,2] With development of enhanced recovery protocols utilizing preoperative oral analgesics, our institutional practice has shifted from use of intravenous (IV) to oral methadone administered preoperatively for patients undergoing spine surgery. The two formulations have different pharmacokinetic profiles and bioavailability that may contribute to different analgesic efficacy. Our aim was to compare the efficacy of oral versus IV methadone in spine surgery patients. We hypothesized that there would be no difference between oral or IV methadone for postoperative pain or opioid requirement.

METHODS: We performed a single-center, retrospective review of electronic medical record data from patients undergoing >3 level spine surgery from January 2017 to May 2020 who received either oral or intravenous methadone. Primary outcome was differences postoperative opioid use in oral morphine equivalents (OME) and verbal response scale (VRS) pain scores. Secondary outcomes were time to extubation and adverse effects (respiratory depression, reintubation, myocardial infarction, and QTc prolongation). Categorical data were analyzed using the Chi-square test, unless the expected number of events under the null hypotheses decreased below 5 for any combination of the two drug regimen and outcome; in these cases, Fisher exact test was used. Continuous data were analyzed using the Wilcoxon rank sum test (equivalent to the Mann-Whitney U test), which is robust to the skewness exhibited in many of the continuous variables. Total opioid use over the three postoperative days were combined and log transformed due to the skewness of the data. A generalized linear model, modeling log transformed total opioid use and exploratory variables was created. Values for continuous variables are expressed as mean ± SD or median [25th-75th quartile]. $P<0.05$ was considered significant. All statistical analyses were conducted in RStudio(Version 1.3.1093) R (version 4.0.3).

RESULTS: Of 1005 patients reviewed, 688 received oral methadone and 317 received IV. There was no difference in baseline patient demographics including age or sex. Median dose of methadone administered was significantly greater in the IV group compared to the oral group when comparing IV equivalent dosing (10 mg [10, 10] IV compared to 5 mg [5, 10] oral, $p<0.0001$). Postoperative opioid requirements did not differ on postoperative days 0, 1, and 2 (Figure 1), but were significantly lower in the oral compared to IV group on day 3 (15.2 mg [5.0-30.0] vs 20.0 mg [10.0-30.4], $p<0.005$). Median pain score was significantly lower in the oral compared to IV group on Day 0 (7 [5-8] vs 7 [5-9], $p=0.018$), but did not differ on postoperative days 1-3. There was no difference in maximum pain score. There were no significant differences in postoperative complications examined.

CONCLUSION: There were no observable differences in postoperative opioid requirements, pain scores or adverse events in patients who received oral methadone compared to intravenous methadone for major spine surgery. The cost of oral methadone is overall less than the intravenous form, thus this may represent a cost-effective analgesic substitute for use during major spine surgery.

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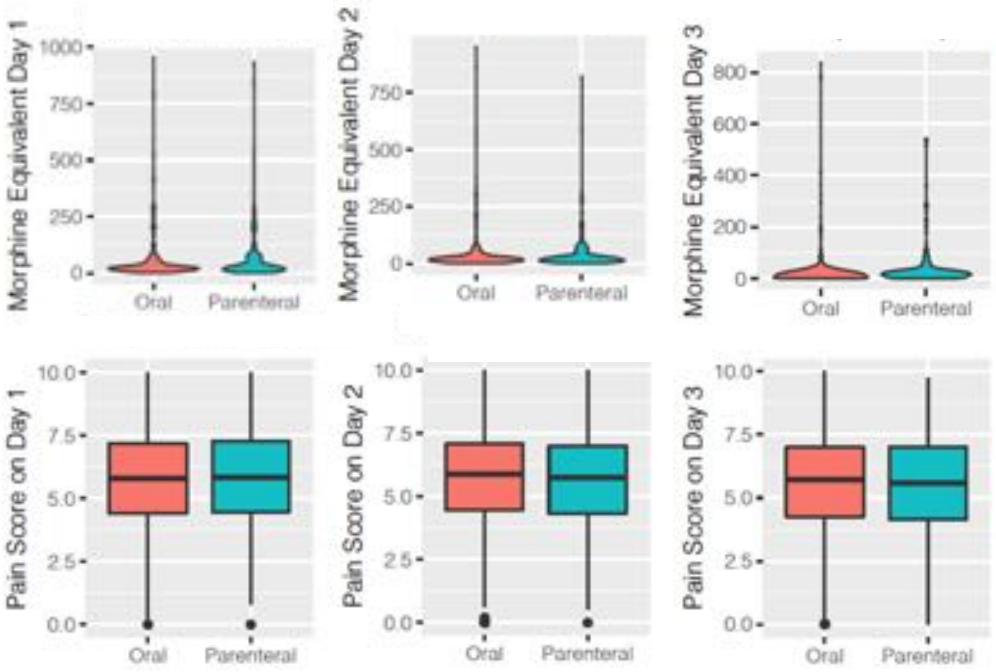

Figure 1: Violin plots for opioid use and boxplots for pain scores for days 1-3.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 8

EEG-Derived State Dynamics At EC50 Isoflurane in Mice

Andrew McKinstry-Wu[1], Andrzej Wasilczuk[2]

[1]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA

INTRODUCTION: Spontaneous shifts among distinct neurophysiologic states occur at steady-state anesthesia, even in the absence of significant external stimulation[1,2]. Spontaneous arousals only occur from certain states, and a behavioral correlate of spontaneous state switching occurs near population anesthetic EC50[1,3]. Previous studies of anesthetic-induced neurophysiologic states and arousals either terminated with arousal or altered anesthetic concentration before the full range of state dynamics could be assessed. Here, we examine mouse electroencephalographic states at population EC50 for isoflurane in order to examine the relationship between neurophysiologic state dynamics and patterns of spontaneous arousal at the intersection of aroused and anesthetized behavioral states.

METHODS: Male C57/B6 mice (n=6) were chronically implanted with 25 lead EEG and 4 EMG as previously described[1]. After a 2 week recovery, they were exposed to 0.6% isoflurane unrestrained in open chambers with continuous acquisition of EEG and EMG. Analyses were performed on 4 contiguous hours of acquisition with minimal artifacts beginning at least 90 minutes after the start of exposure. EEG was band pass filtered from 1 to 100 Hz, and EMG high pass filtered at 15 Hz, with root mean squared of 4 second windows of EMG used for analysis. EEG signals were mean rereferenced and multitaper spectral analysis with 4 second non-overlapping windows performed in Matlab. Spectral states were determined using optimized kmeans clustering (silhouette method) of the first 10 principle components spectra of the 12 EEG leads of the right hemisphere across animals, base on methods used by Hudson et al.[2] All analyses were performed using Matlab with the Chronux toolbox and PRISM. Alpha of 0.05 (corrected for multiple comparisons where appropriate) was used for all statistical tests.

RESULTS: At steady-state isoflurane, we found 4 clusters in the EEG data representing 3 EEG states with distinct spectral signatures and EMG tone and 1 cluster associated with movement artifact (Fig 1A,B). While spontaneous movement (and consequent movement artifact) occurred subsequent to each of the three states, it was vastly more likely to occur following state 3 (Fig 1C.) Dwell time distributions for states under isoflurane, as in rats, are consistent with those expected from a Markov process, but the observed distribution in mice were markedly shorter than those observed in rats (Fig 2, Ref 1:Fig S7.) We thus modelled EEG-derived state transitions as a Markov chain, estimating transition probability matrices for each animal and across animals. Transitions among all states occurred, though transition between states 1 and 3 occurred at a lower probability, and did not occur in all animals (Fig 3). State transitions showed significant autocorrelation, suggesting a cyclic process, with all mice displaying period lengths between 93 and 227 seconds (Fig 4.) The total amount of time spent in spontaneous arousal/movement in a given individual, which could be considered an individual's anesthetic sensitivity, best tracks with lower values of a measure of systemic state stability derived from the estimated Markov matrix, the mixing time (Fig 5).

CONCLUSION: We have found that at steady-state isoflurane, mice spontaneously fluctuate through a limited set of EEG-derived states. These states, though similar to those described in rats, are shorter in duration. Spontaneous arousals occur predominantly from a single state. State stability, as measured by mixing time, is a better predictor of aroused/spontaneously moving time than any single state prevalence. Unlike previous characterizations of such states, the states we observe are oscillatory. Whether the combined oscillatory nature of state transitions and the state-specificity of spontaneous arousals/movement has implications for times to emergence from anesthesia is an open question, as are means of manipulation of state stability or oscillatory period.

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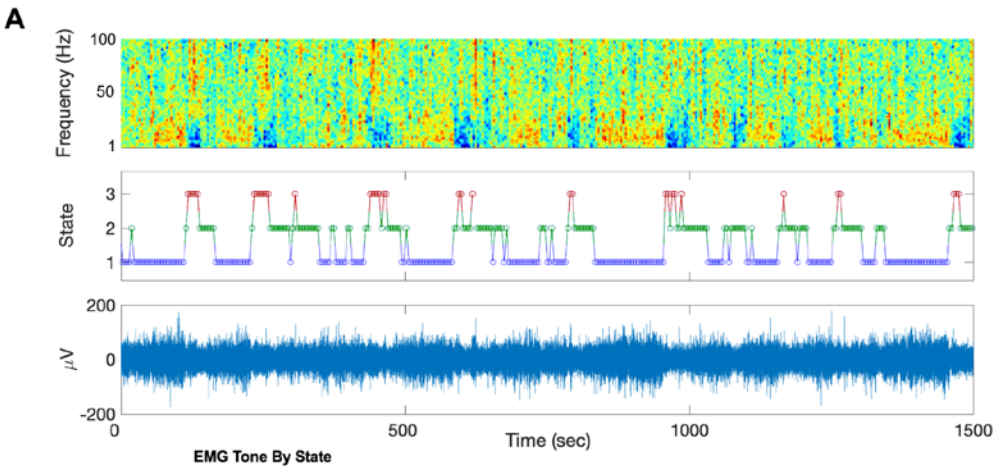

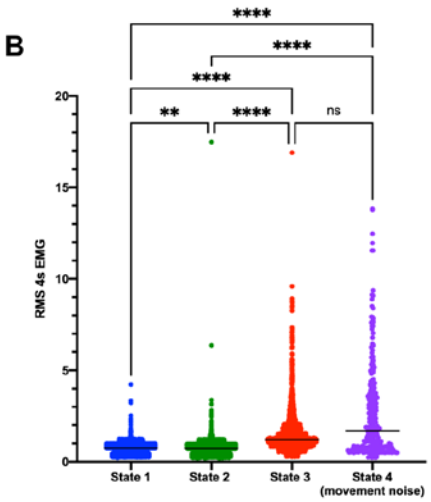

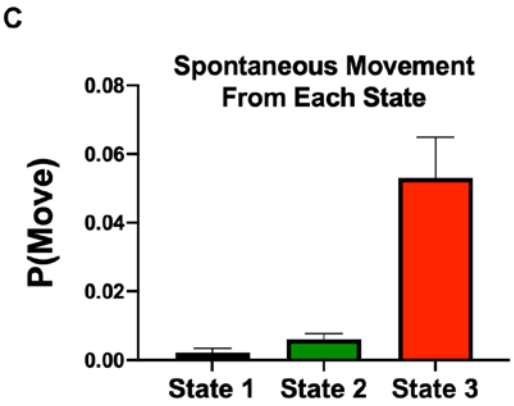

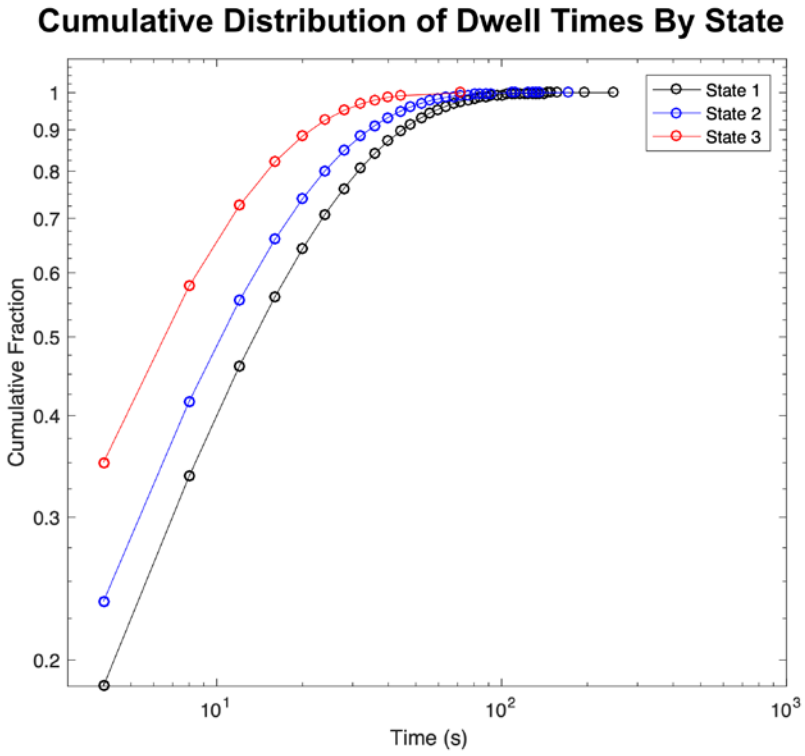

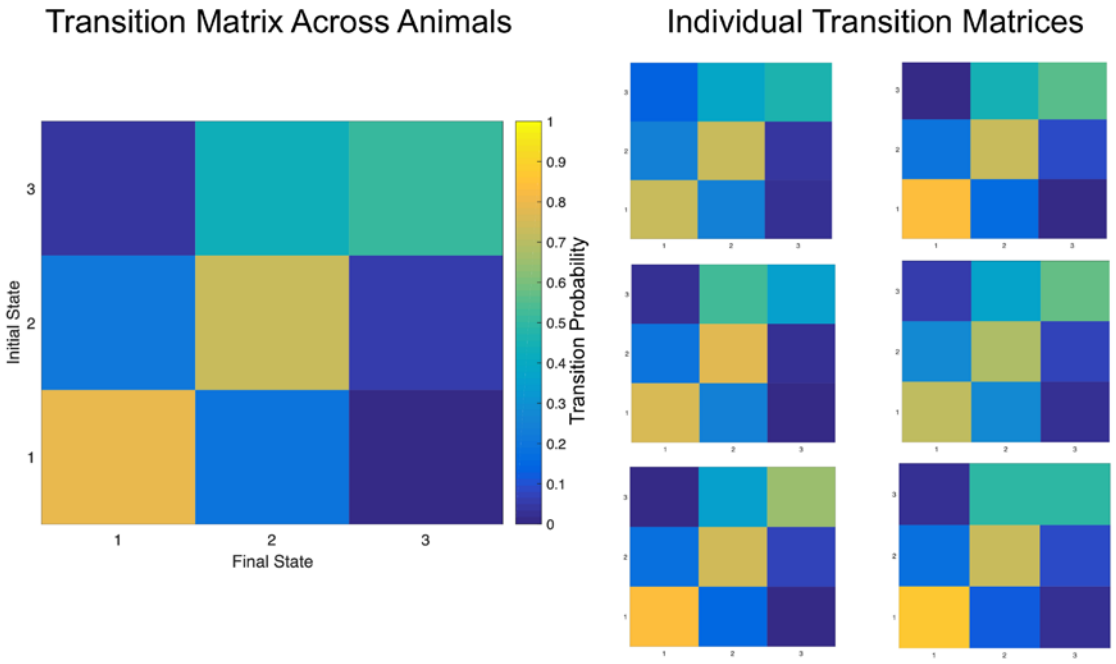

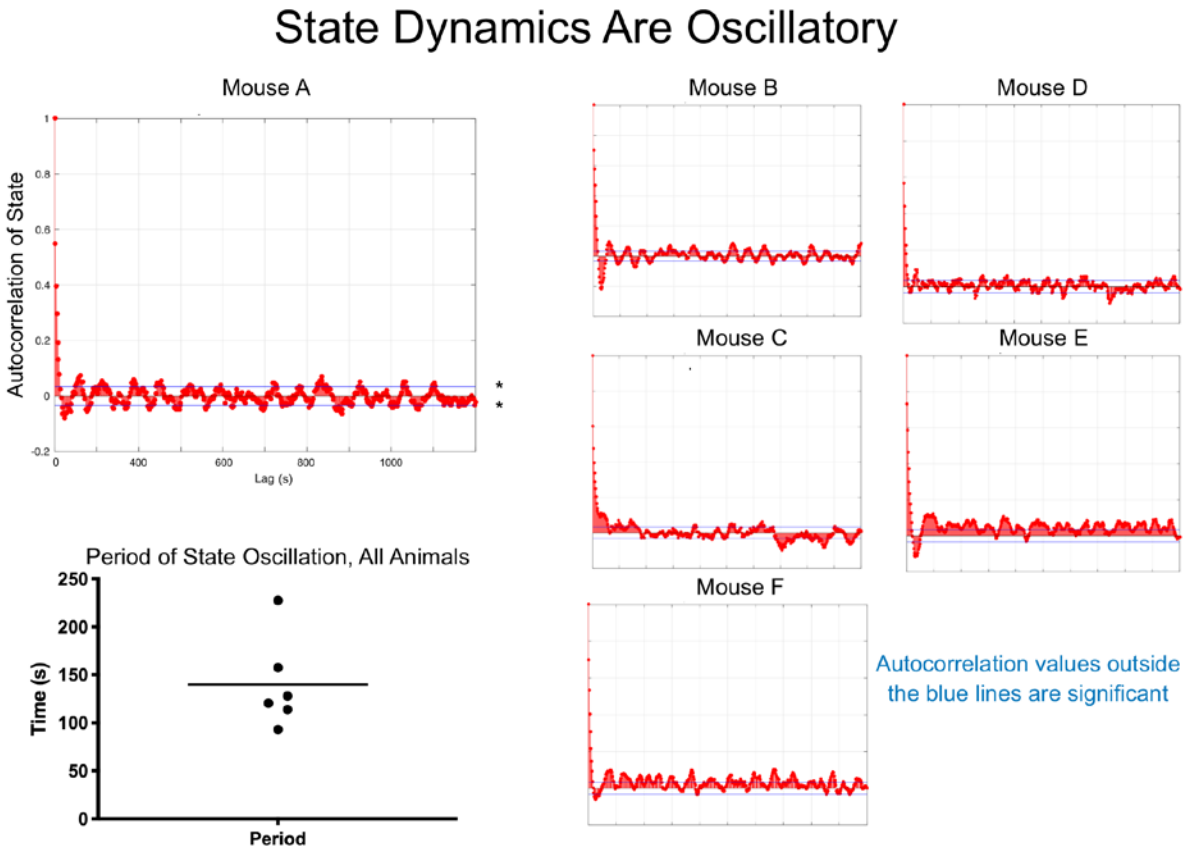

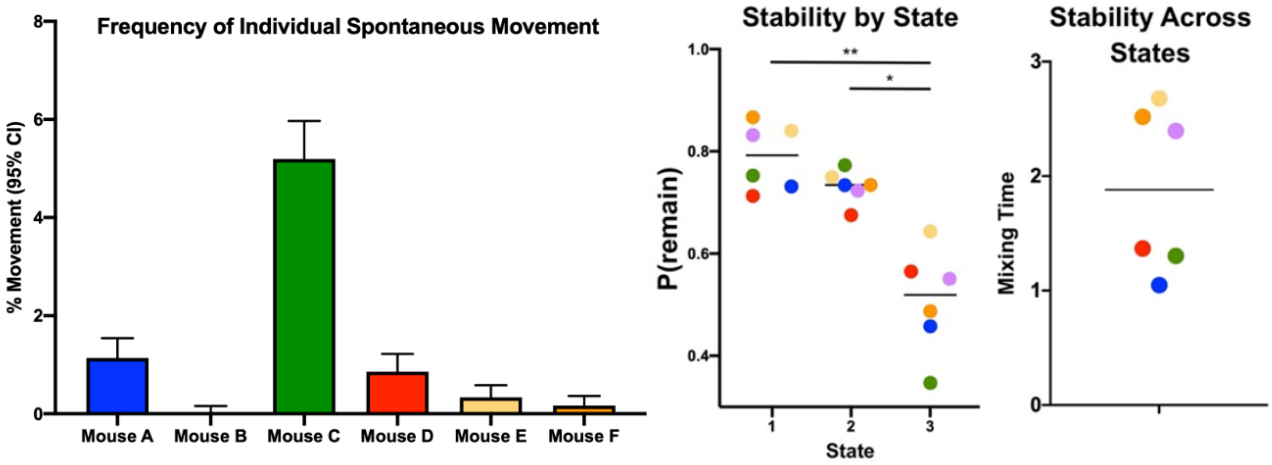

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 9

Modulation Of Microvascular Blood Flow And Stroke Outcome Via GPR39 in Mice

Yifan Xu[1], Wenri Zhang[2], Lev Fedorov[1], Anthony P Barnes[1], Ruikang Wang[3], Nabil Alkayed[4]

[1]Oregon Health and Sciences University, Portland, OR, [2]Oregon Health & Science University, Portland, OR, [3]University of Washington, Seattle, Seattle, WA, [4]Oregon Health & Science University, Portland, United States of America

INTRODUCTION: Ischemic stroke is a leading cause of morbidity and mortality. Efficacy of current thrombolytic and endovascular therapies are not uniform in all patients, and depends on age, stroke severity and diabetic status. This is in part due to impaired microvascular reperfusion, which limits the benefit from large-vessel recanalization[1]. Microvascular blood flow is regulated by a number of molecules including P450 eicosanoids whose levels are known to be altered in stroke[2,3]. We have recently identified GPR39 as a dual sensor for two vasoactive P450 eicosanoids: the vasodilator and neuroprotective 14,15-epoxyeicosatrienoate (14,15-EET) and vasoconstrictor and neurotoxic 15-hydroxyeicosatetranoate (15-HETE) (4). GPR39 is expressed in arteriolar vascular smooth muscle cells and peri-capillary pericytes. Thus, GPR39 is uniquely positioned to sense the balance of vasoactive eicosanoids and modulate microvascular blood flow during and following stroke. To investigate the role of GPR39 in stroke, we have generated a global GPR39 knock-out (KO) mouse via CRISPR/Cas9 deletion of the receptor's first exon, eliminating expression of GPR39. We tested the hypothesis that GPR39 KO mice sustain larger infarcts, associated with lower microvascular reperfusion after transient focal cerebral ischemia compared to wild-type (WT) littermates with intact GPR39.

METHODS: A 60-min middle cerebral artery occlusion (MCAO) was induced in 3-month old male and female mice using a silicone coated filament introduced through an external carotid stump under isoflurane anesthesia. A total of 26 KO (14 males, 12 females) and 18 WT (9 males and 9 females) mice were used for the study. Brains were harvested at 24 hours of reperfusion, sliced coronally in 2-mm segments, sections and stained with triphenyltetrazolium chloride (TTC) for measurement of infarcted areas after accounting for edema. Optical microangiography (OMAG) imaging was used to measure microvascular perfusion over the ischemic penumbra at baseline and 24 hours after MCAO in separate groups of 10 WT and 8 KO male mice.

RESULTS: Striatal infarct size was 69.3% ± 3.51% in male GPR39 KO mice compared to 47.15% ± 3.19% in WT male littermates (mean ± sem, $p<0.0005$). In females, infarct size was 50.9% ± 7.24% in GPR39 KO mice compared to 48.3% ± 6.35% in WT littermates ($p = 0.81$). Two-way ANOVA demonstrated significant difference between male GPR39 KO and WT hemispheric and striatal infarct size (P=0.038). OMAG demonstrates decreased red blood cell flux in deeper cortical layers after MCAO, with GPR39 KO mice showing decreased microvascular reperfusion in deeper cortical layers compared to WT.

CONCLUSION: Our results suggest that GPR39 plays a sexually-dimorphic protective role in ischemic stroke, and that GPR39 may serve as a potential therapeutic target in stroke.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 10

General Anesthesia Suppresses Mismatch Negativity During Surgery

Richard E Kolesar[1], Adianes Herrera-Diaz[1], Rober Boshra[1], John F Connolly[1]

[1]McMaster University, Hamilton, ON

INTRODUCTION: In order to explore the nature of anesthesia-induced unconsciousness and its relationship to nociception, investigators attempted to determine whether the mismatch negativity (MMN) could be detected during general anesthesia and surgery. The MMN is a late-latency auditory evoked potential elicited in the electroencephalogram to infrequent deviant stimuli imbedded amongst frequent standard stimuli that signifies extensive cortical processing of sensory input[1,2]. Presence of the MMN is associated with consciousness[3]. Previous studies failed to identify the MMN during single agent anesthesia when no surgery was performed[4,5]. The current study investigates whether this response could be elicited under more pragmatic conditions of balanced general anesthesia and surgical stimulation.

METHODS: After local REB approval, ten patients undergoing surgeries of four hours or longer consented to participate in this study. The protocol consisted of 64 channel EEG recordings during which an 'oddball' auditory paradigm designed to elicit the MMN was presented via earphones. The paradigm presented 2400 tones among which 1968 standard tones were randomly dispersed with 432 deviant tones (of three different types)[6]. An EEG recording during presentation of all 2400 tones was labeled one block and typically lasted 35 minutes. Recordings of two blocks were obtained in five of the ten patients in the 'awake' state a few days before the scheduled surgery. During these sessions patients were instructed to not attend to the tones. During surgery as many blocks were recorded as possible following induction of general anesthesia and prior to emergence. Anesthesiologists were asked to provide standard care adapted to the patients' needs and were only required to provide a minimum of 0.7 MAC (minimum alveolar concentration) of inhaled agent of choice. Raw EEG recordings were preprocessed using EEGLAB[7]. ERP analysis was performed on cleaned blocks using MNE-Python. Analyses included a variety of approaches aimed at detecting responses displaying negative polarity in 150-300 ms time range. These included: visual inspection, targeted t-tests, cluster-based permutation tests[8], and multivariate pattern analysis (MVPA)[9]. Methods focused specifically on detecting statistical differences between the standard and duration deviant evoked responses. Responses of interest were identified primarily using time-sensor cluster tests and MVPA, thereby managing both the low signal to noise ratio and the multiple comparison problem. A response was labelled an MMN response if it displayed typical topography and latency—maximum amplitude in front-central electrodes occurring 150-250 ms post-stimulus. All analyses were performed at the single block level.

RESULTS: A total of 10 'awake' blocks obtained from 5 patients and 35 general anesthesia or 'GA' blocks obtained from 9 patients (range: 2 – 7 per patient) were suitable for further analysis. Maximal response to the duration deviant was uniformly observed, so subsequent analysis excluded other deviants. The average number of standards per block was 1541 (Interquartile range or IQR: 1386 – 1702); the average number of (duration) deviants was 111 (IQR: 99 – 127). Electrocautery was the most common cause of data loss. In all 10 'awake' blocks time-sensor cluster tests and MVPA could reliably distinguish standards from deviants. In the 35 'GA' blocks no time-sensor clusters were identified and the MVPA classifier could not distinguish standards from deviants.

CONCLUSION: The present study utilized a dense EEG setup in the operating room during surgery with sufficient data quality for robust ERP analyses. Results show that balanced general anesthesia which incorporates 0.7 MAC of an inhaled agent suppresses the MMN response. This finding is consistent with past studies[4,5], recent studies of auditory processing during general anesthesia[2,10], current theories of anesthesia-induced unconsciousness[11], and clinical studies addressing intra-operative awareness[12]. Clinicians have additional neuroscientific evidence that delivery of 0.7 MAC anesthesia substantially disrupts cortical processing.

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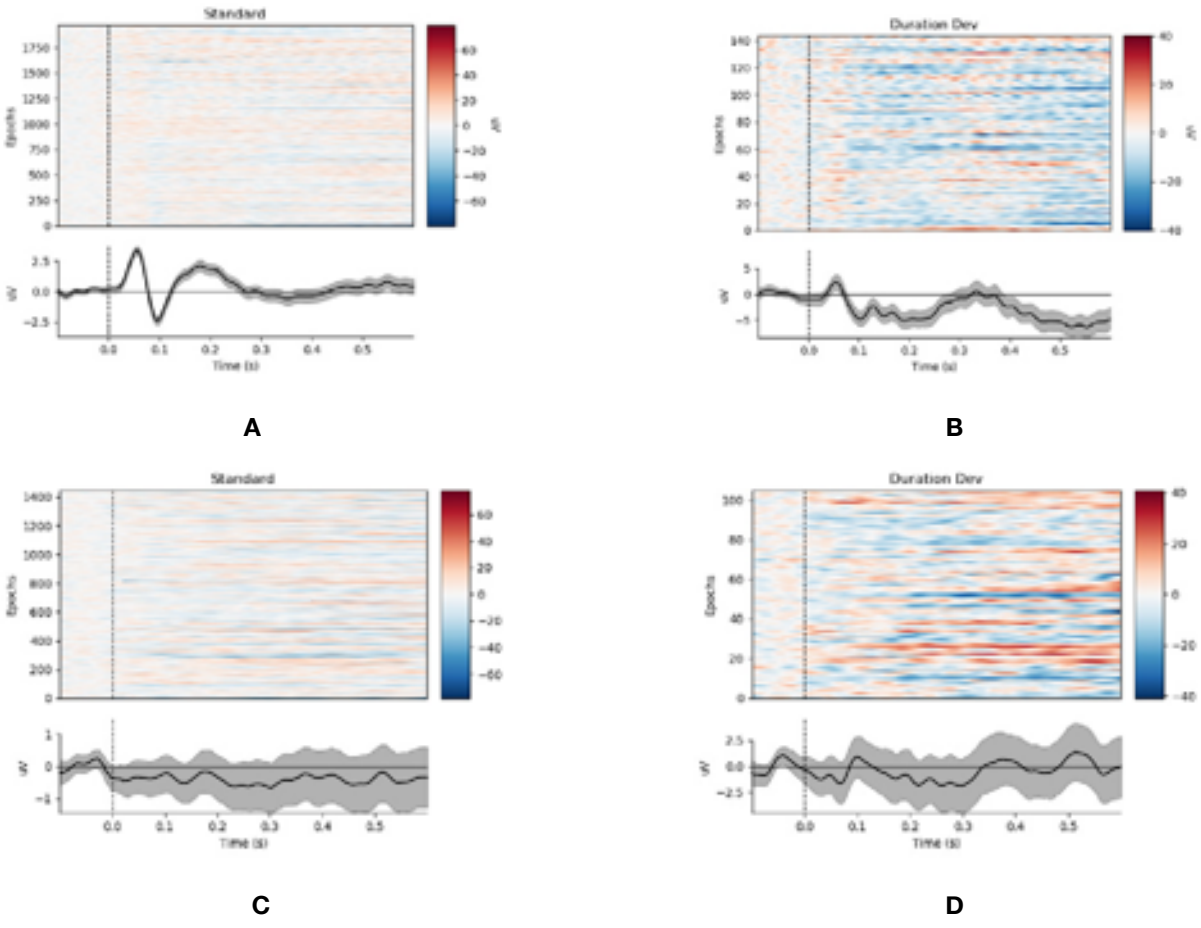

Figure 1: Example ERP images: A. standard epochs in an awake patient; B. deviant epochs in an awake patient; C. standard epochs in a GA patient; D. deviant epochs in a GA patient. Mean amplitudes with 95% confidence interval are shown below each image. Images in the awake patient demonstrate typical ERP responses including a classic MMN around 200 ms. Responses in the GA patient are not statistically different from zero microvolts.

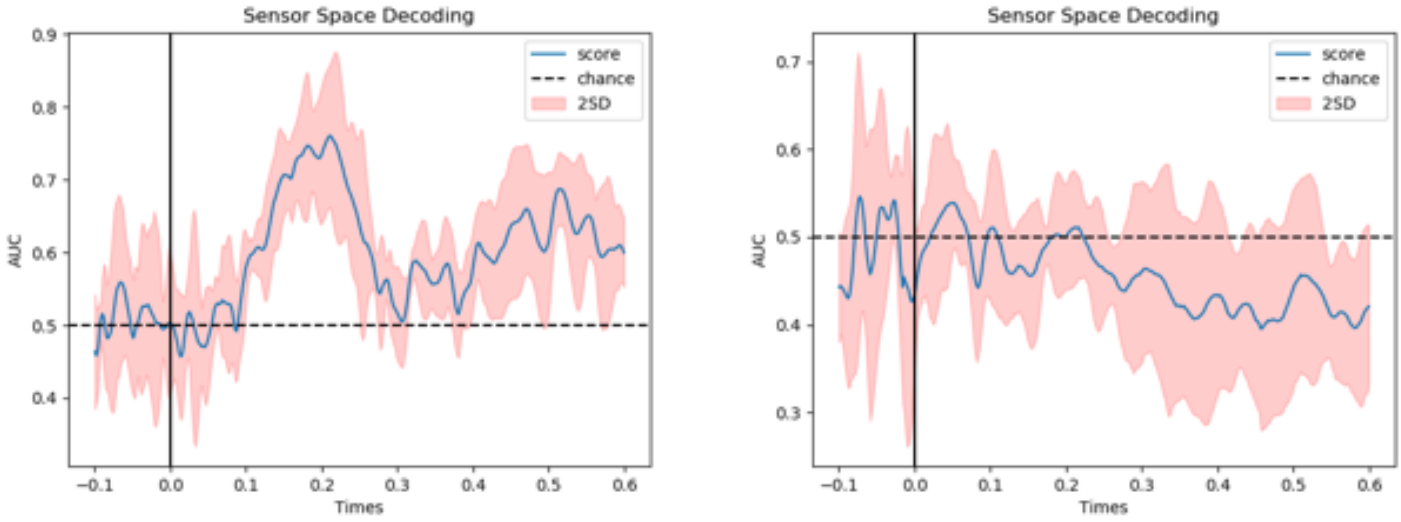

Figure 2: Example of accuracy of MVPA classifier in differentiating standard from deviant in awake and GA states: A. the accuracy of the classifier is statistically different from chance (AUC of 0.5) around 200 ms; B. the accuracy of the classifier is not statistically different from chance (AUC of 0.5).

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 11

Imaging Cortical Circuitry during General Anesthesia-Induced Analgesia

Jarret Weinrich[1], Christopher R Andolina[1], Mollie Bernstein[1], Cindy D Liu[1], Allan Basbaum[1]

[1]University of California San Francisco, San Francisco, CA

INTRODUCTION: General anesthetics work in a concentration-dependent manner on the central nervous system (CNS) to induce loss of consciousness and block the experience of pain. Interestingly, however, with nitrous oxide anesthesia and during the initial stages of diethyl ether anesthesia, analgesia can be produced independently of loss of consciousness. In contrast, isoflurane and sevoflurane, which are halogenated ethers, unquestionably produce unconsciousness, but produce little to no pain relief at subanesthetic doses. As the effects of general anesthetics on pain processing circuits in the brain are largely unexplored, the mechanisms that underlie the analgesic actions of certain general anesthetics are unknown. In the present studies in the mouse, we investigated the influence of non-analgesic (isoflurane) and analgesic (nitrous oxide) anesthetics on the anterior cingulate cortex (ACC), a brain region that encodes affective/emotional, but not sensory/discriminative, features of the pain experience. We continuously monitored, over time, the in vivo activity of hundreds of individual ACC neurons during the induction to, and emergence from, isoflurane or nitrous oxide anesthesia. Our objective is to uncover the mechanisms through which general anesthetics alter the perception of pain.

METHODS: In adult mice, we continuously monitored the spontaneous activity of neurons in the ACC before, during, and after the inhalation of (1) isoflurane or (2) nitrous oxide anesthesia. Concentrations of anesthetic gases were monitored using a Datex Ohmeda S/5 patient monitor. Virally delivered, genetically encoded fluorescent reporters of neural activity were expressed ubiquitously across neuronal subtypes (AAV1-Synapsin-GCaMP6f). To capture GCaMP6f fluorescence, we implanted a gradient index (GRIN) lens into the ACC and monitored fluorescence changes with an Inscopix nVista (v3) head-mounted miniscope. Imaging data were recorded and processed with Inscopix nVista (v1.1.0) and Inscopix Data Analysis (v1.1.1) software, respectively and with custom-written MATLAB (R2017b) code. As individual fluorescence changes produced by an active neuron do not necessarily correspond to a single action potential, we classified these as events.

RESULTS: Consistent with previous studies demonstrating that the global activity of the cerebral cortex is decreased during general anesthesia, we find that the rate of spontaneous neural activity decreases with increasing concentrations of isoflurane. Interestingly, isoflurane-induced alterations of ACC activity have two clear phases, a transient increase in ACC activity (1.2-1.4 fold increase from baseline) at low concentrations (>0 – 0.4% isoflurane), followed by a steep decline, and then cessation, as the concentration increased (>1% isoflurane). Surprisingly, and in sharp contrast, during the inhalation of nitrous oxide, we observed a significant increase in spontaneous activity of ACC neurons. Furthermore, we found that nitrous oxide also increases the activity of ACC neurons in two waves, with modest increases below 30% (1.5-2 fold increase from baseline) and greater increases above 30% (3-4 fold increase from baseline).

CONCLUSION: We conclude that non-analgesic and analgesic general anesthetics differentially alter neural activity in the ACC, a region of the brain that is a major contributor to the pain percept. In both patients and animals, decreases in ACC activity are generally associated with analgesia. Therefore, our finding that nitrous oxide, an analgesic, increased ACC activity, and that isoflurane, which is non-analgesic, decreases ACC activity, was unexpected. Of particular interest, nitrous oxide concentrations above 20-30%, which are considered analgesic in patients, are comparable to the concentrations that produced dramatic increases in neural activity in the mouse ACC. Additionally, preliminary data from our lab dissecting the effects of general anesthetics on functionally distinct neurons within the ACC (i.e., excitatory vs subtypes of inhibitory), suggest that the analgesic potential of a general anesthetic results from the preferential modulation of the activity of particular subtypes of neurons. Our findings indicate that selectively modulating the activity of subtypes of ACC neurons, thereby disrupting pain processing by specific ACC circuits, provide an advantageous target to guide the development of novel classes of general anesthetics that exhibit increased analgesic potency.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 12

Testosterone is sufficient to impart susceptibility to isoflurane neurotoxicity in female neonatal rats

Gregory A Chinn[1], Katrina Duong[1], Tal Horovitz[1], Jeffrey Sall[2]

[1]UC San Francisco, San Francisco, CA, [2]University of California, San Francisco School of Medicine, San Francisco, CA

INTRODUCTION: Early life volatile anesthetic exposure is associated with life-long neurotoxic effects in animals as varied as rodents to non-human primates[1,2]. This toxicity is characterized by persistent learning and memory deficits. We have previously found that susceptibility to this deficit is dependent on sex, age of exposure, androgen receptor function and the function of the chloride transporter NKCC13–5. Manipulation of these variables has led to consistent findings which support our hypothesis that volatile anesthetic, through its GABAergic action is altering brain development to cause this deficit through GABAA receptor excitation(caused by high levels of NKCC1, inward chloride transporter, relative to KCC2, outward chloride transporter). Here we explore the effects of exogenous testosterone on the susceptibility of female rats to isoflurane exposure on postnatal day 7.

METHODS: Female rats were injected with exogenous testosterone (100ug), subcutaneously on postnatal day 1-6. Control female rats were injected with equal volume of vehicle (sesame oil). On postnatal day 7, animals were exposed to 6hrs. of 1 MAC of isoflurane or sham (control)[(3,5)]. This combination of interventions gave 4 groups- Test/Iso (n=15), Veh/Iso (n=15), Test/Con (n=15) and Veh/Con(n=15). After return of righting reflex, animals were returned to dams. On postnatal day 41, animals began training on the Barnes Maze with 1 trial per day over 5 days with latency to goal recorded[3,5]. One week after the final training day, the probe trial was completed which consisted of the escape box removed and a continuous tracking of the animals movements for 4 minutes. The amount of time exploring holes around the maze was recorded. Times exploring holes equidistant relative to the goal were averaged. A Dunnet's multiple comparison test compared the time spent at the goal vs the equidistant positions around the maze. A curve fit of the distribution of exploration of positions was applied and an F test asked whether the curve was likely a one-phase decay vs a straight line. To study the effects of exogenous testosterone on the chloride transporters NKCC1 and KCC2, animals were again exposed to vehicle or testosterone (100ug) on days 1-6, sacrificed on post-natal day 7, and frontal cortex was removed to create protein lysates. Western blots for NKCC1 and KCC2 with normalization to GAPDH were performed[(3,5)]. Blood from these animals was also collected at the time of sacrifice and used to measure serum testosterone levels by ELISA.

RESULTS: In the learning phase of the Barnes maze, all groups successfully learned the position of the escape box (Figure 1). In the probe trial, Veh/Con, Test/Con and Veh/Iso all differentiated the goal position from many other positions around the maze. This contrasts to the Test/Iso group which had no difference in exploration of the goal vs any other equidistant position. The curve fit analysis confirmed that the Veh/Con, Test/Con and Veh/Iso all favored a one-phase decay while the Test/Iso group favored a straight line. Western blot analysis found differences in NKCC1 expression by Tukey's multiple comparison test of Female+Vehicle vs Female+Testosterone ($p<0.0001$) and Male+Vehicle vs Female+Testosterone ($p=0.0005$) (Figure 2). For KCC2, Tukey's showed differences between Female+Vehicle vs Female+Testosterone ($p=0.003$) and Male+Vehicle vs Female+Vehicle ($p=0.01$). Both external genitalia changes and serum testosterone levels were substantially altered with the given dose of exogenous testosterone (Figure 3). The testosterone ELISA found the exogenous testosterone treated animals had significantly higher serum testosterone than vehicle treated females which were below the level of detection.

CONCLUSION: These results support our hypothesis that anesthetic neonatal neurotoxicity is mediated by excitatory GABAergic activation in rats. We found that female rats, which are normally not susceptible to spatial memory deficits (Barnes Maze), developed a lasting deficit after exogenous testosterone followed by isoflurane exposure. We also found that exogenous testosterone alters the protein levels of specific chloride transporters thought to dictate the function of the GABAA receptor; specifically, NKCC1 was increased after testosterone, and KCC2 was reduced. Testosterone may be an important regulator of these proteins which potentially determine susceptibility to neonatal anesthetic neurotoxicity.

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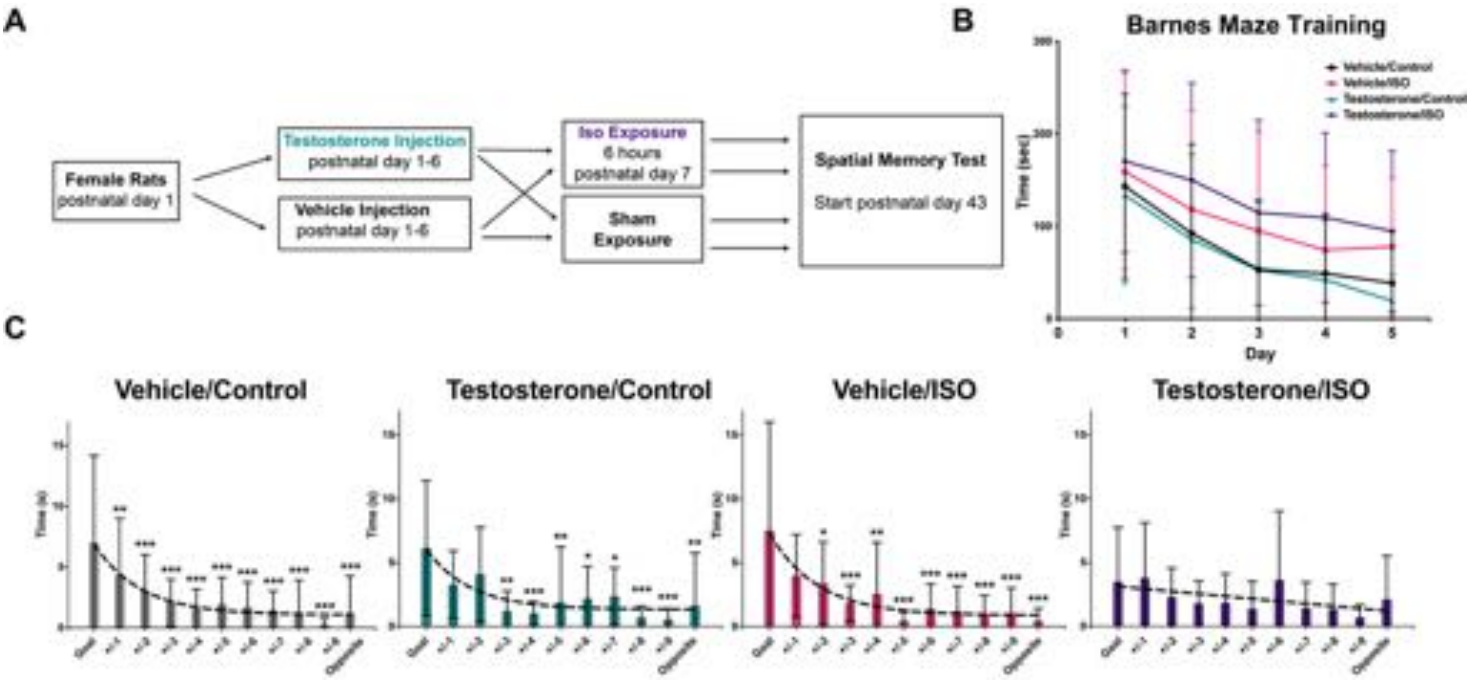

Fig. 1

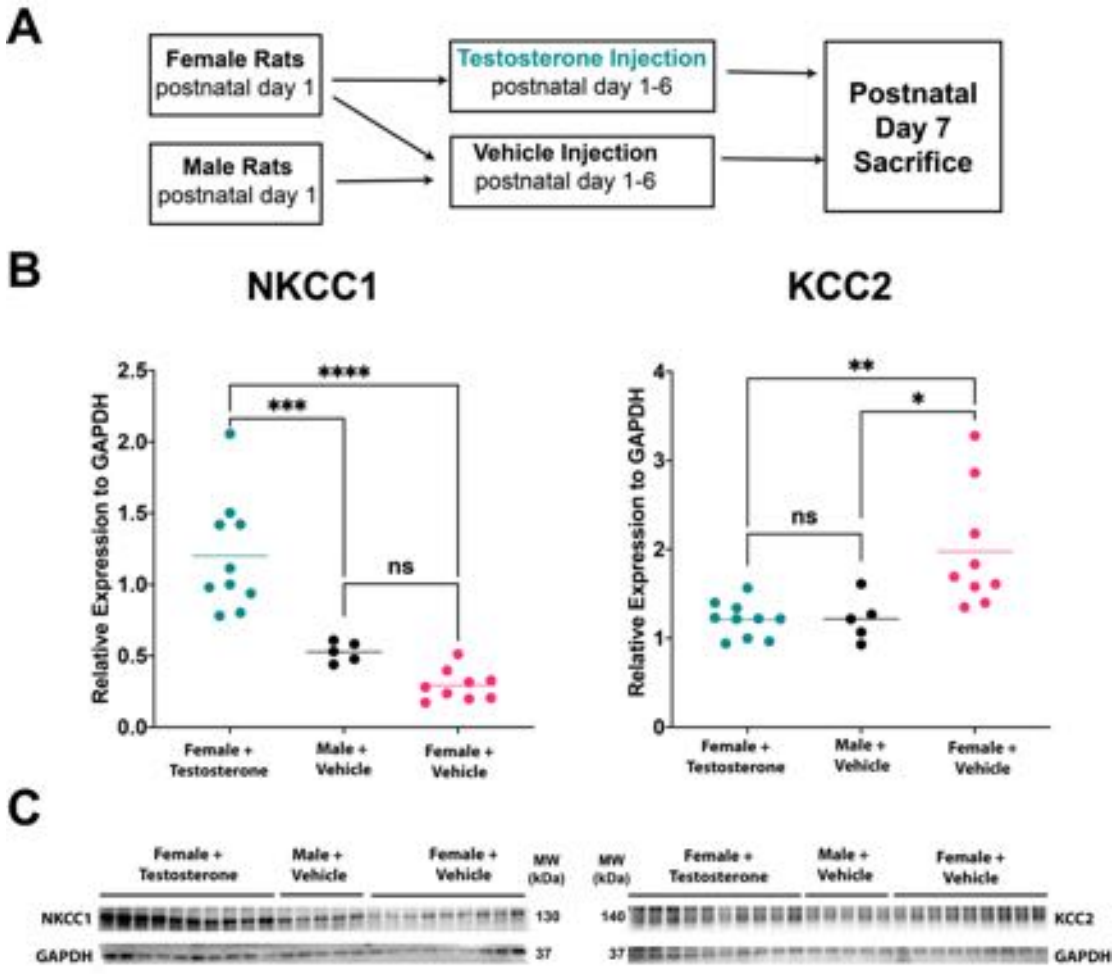

Fig. 2

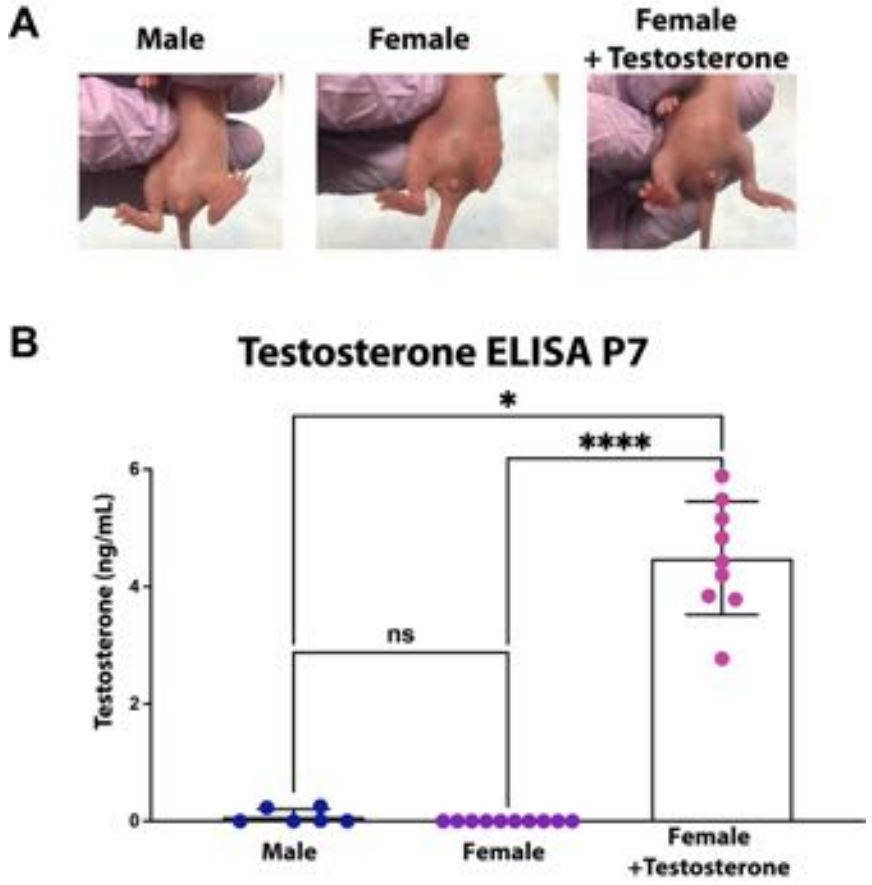

Fig. 3

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 13

Perioperative neurocognitive and neuroimaging trajectories in older APOE4 carriers vs non-carriers: A prospective cohort study

Rosa O Yang[1], Jeffrey N Browndyke[2], Mary Cooter[2], Miles Berger[2]

[1]Duke University School of Medicine, Durham, NC, [2]Duke University Medical Center, Durham, NC

INTRODUCTION: Neurocognitive disorder postoperative is a cognitive deficit of >1 or >2 SDs that occurs 1-12 months after surgery when accompanied by a subjective cognitive complaint.[1] A smaller group of neurocognitively vulnerable patients may have more significant postoperative cognitive decline than these objective thresholds, perhaps related to genetic polymorphisms associated with increased dementia risk.[1] Thus, we examined the effect of *APOE4*, the most common genetic variant associated with late-onset Alzheimer's disease (AD), on perioperative neurocognition in older patients.

METHODS: The observational cohort study Markers of Alzheimer's Disease and neuroCognitive Outcomes after Perioperative Care (MADCO-PC) enrolled English-speaking patients ≥ 60 years (N=140) scheduled for non-neurologic, non-cardiac surgery under general anesthesia with a planned hospital stay.[2] Cognitive testing was completed before and six weeks after surgery using our established cognitive assessment battery.[3] Assessments were categorized into four cognitive domains by factor analysis. These four domains were averaged together to create the continuous cognitive index (CCI); a positive score indicates cognitive improvement and vice versa. CSF samples were collected before, 24 hours and six weeks after surgery via lumbar punctures. CSF amyloid beta1-42, t-tau, and p-tau181p levels were measured per Alzheimer's Disease Neuroimaging Initiative study methods.[4] Patients were PCR genotyped for *APOE4* as described.[5] Patients underwent resting state functional magnetic resonance imaging (rs-fMRI) before and 6 weeks after surgery; data processing and analyses were performed as described.[6]

RESULTS: Complete assessments were available for 52 patients (Fig 1). No significant differences in baseline CSF AD biomarker concentrations were seen between *APOE4*-positive and -negative groups except for baseline Aβ levels, which were higher in *APOE4*-negative patients compared with *APOE4*-positive patients (p=0.0011) in accord with prior studies.[4] After multiple comparison corrections, there were no significant *APOE4*-related differences for Aβ, pTau, Tau, pTau/Aβ, and Tau/Aβ over time (p > 0.05 for all). There were no significant *APOE4*-related differences in CCI change from before to 6-weeks after surgery (p=0.8273), nor in the percentage of *APOE4* carriers vs non-carriers who had a ≥1 SD drop in ≥1 cognitive domain from before to 6 weeks after surgery (p=0.7478) (Fig 2). *APOE4* carriers (vs non-carriers) had significant greater rs-fMRI functional connectivity differences between left posterior cingulate and left angular/supramarginal gyrus region and between right entorhinal cortex and left inferior frontal lobe region before surgery, and this connectivity pattern decreased to a greater extent following surgery in *APOE4* carriers vs non-carriers, resulting in a postoperative "normalization" of functional connectivity between these brain regions in *APOE4* carriers (Fig 3).

CONCLUSION: In older surgery patients, there was no *APOE4*-related difference in post-operative changes in cognition or CSF AD biomarkers, though *APOE4* carriers (vs non-carriers) had a greater post-operative drop in rs-fMRI connectivity between specific brain regions. Since increased functional brain connectivity has previously been suggested to act as a compensatory mechanism to maintain normal cognition in *APOE4* carriers[7], the loss of this increased functional connectivity pattern following surgery in *APOE4* carriers may later contribute to the interaction effect previously observed between *APOE4* and surgery exposure for cognitive decline.[1] Future studies should thus examine 1-year and 5-year postoperative cognitive follow-up data to determine if this 6-week postoperative decrease in functional hyperconnectivity between specific brain regions in *APOE4* carriers is associated with worsened long-term cognitive trajectories. Lastly, these findings represent the first evidence for a genetic variant associated with altered brain functional connectivity patterns weeks after surgery/anesthesia.

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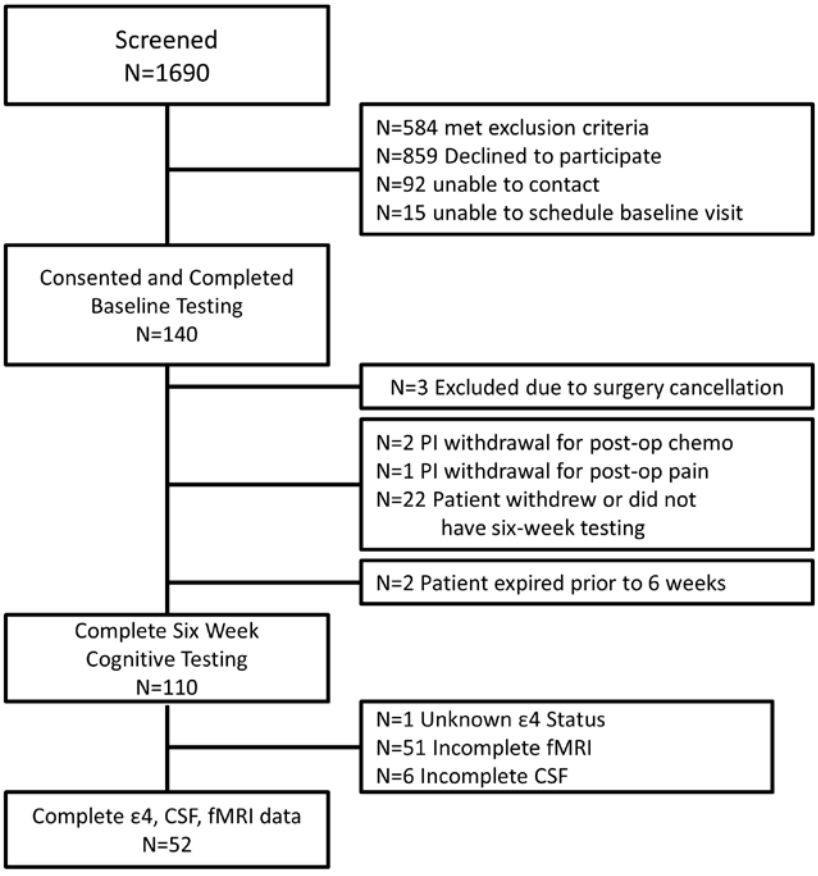
Figure 1: MADCO-PC surgical patients consort diagram



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 14

Study Anesthesia Mechanism in Mouse through the Projections to Basal Forebrain by Hypothalamic Orexin Neurons

Wei Zhou[1], Xuaner Xiang[2]

[1]University of California San Francisco, San Francisco, CA, [2]University of California San Francisco, San Francisco, United States of America

INTRODUCTION: Intricate networks of neural circuits regulate arousal, analgesia, and mobility – the three essential components of anesthesia, but how anesthetics interact with neural network remains poorly understood[1–4]. In the past few years, we focused on studying the mechanism of anesthesia, in particular, the role of hypothalamic orexin (Ox) circuit[5]. Ox neurons are considered as a master regulator controlling sleep and wakefulness[6,7]. Lack of Ox activity is associated with narcolepsy and cataplexy, characterized as fragmentation of wakefulness/sleep structure and sudden loss of muscle tone, respectively[8–13]. As a major step to understand the Ox system, we have mapped the three-dimensional Ox projections in detail in the mouse brain with light-sheet and confocal microscopy. Building upon these findings, we focused on the Ox projections to the BF. BF, a brain region affected early in Alzheimer's disease, is known for its role in cortical activation[14,15]. Therefore, we used an optogenetic approach to investigate the specific contributions of the Ox projections to BF in anesthesia. Ultimately, we hope to further our understanding of the key neural components for anesthesia and analgesia, which will help the development of new therapeutic tools for better anesthetic management.

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 gene. After validation of the expression, we started with selecting the optimal frequency to activate Ox neurons on acute brain slices with 473 nm blue light. To stimulate the mice through the Ox projections, we implanted the optical fiber into the BF and stimulated the fiber while the animal was under isoflurane anesthesia. We also implanted EEG onto the animal's head and analyzed the EEG spectrum during the test.

RESULTS: We found distinctive patterns in the Ox neuronal projections to the basal forebrain (BF), lateral habenula (LHb), periaqueductal gray (PAG), and many other regions in the brain. Patch-clamp recording showed Ox neurons can be activated by 473nm blue light and 5-20 Hz stimulation can induce reliable neuronal activation. Our EEG data and behavior test results indicated that activation of orexin neuron projections in the BF region through optical stimulation facilitates the emergence from isoflurane anesthesia.

CONCLUSION: 1. The Ox neurons from the hypothalamus project broadly in the brain. 2. Activation of the BF neurons by optical stimulation of Ox projections can significantly accelerate the emergence from anesthesia.

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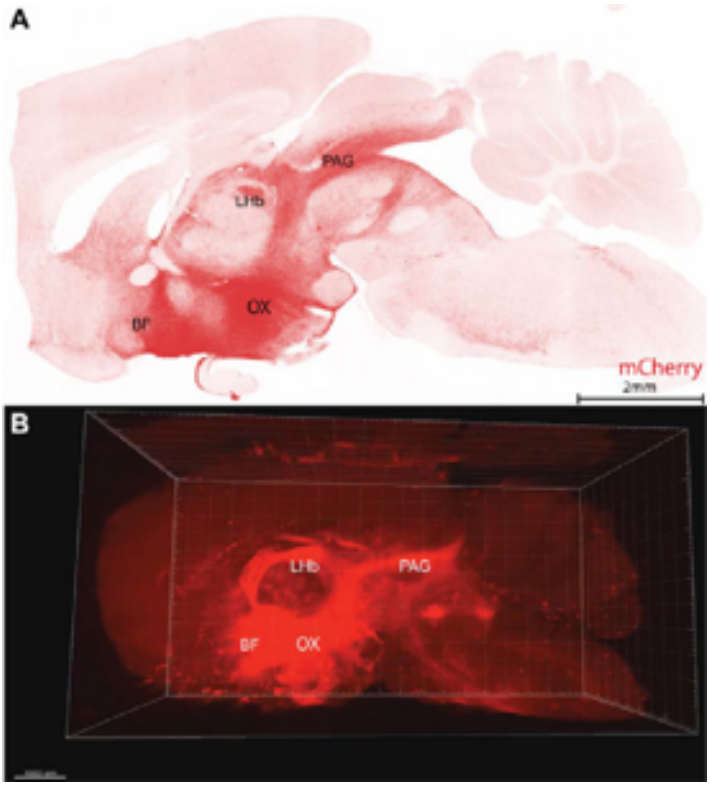

Fig. 1 | Broad projections of orexin (Ox) circuit with mCherry staining shown by confocal image (A) and lightsheet image (B). The 3D lightsheet rendering is visualized with Imaris program. BF, basal forebrain; LHb, lateral habenula; PAG, periaqueductal gray.

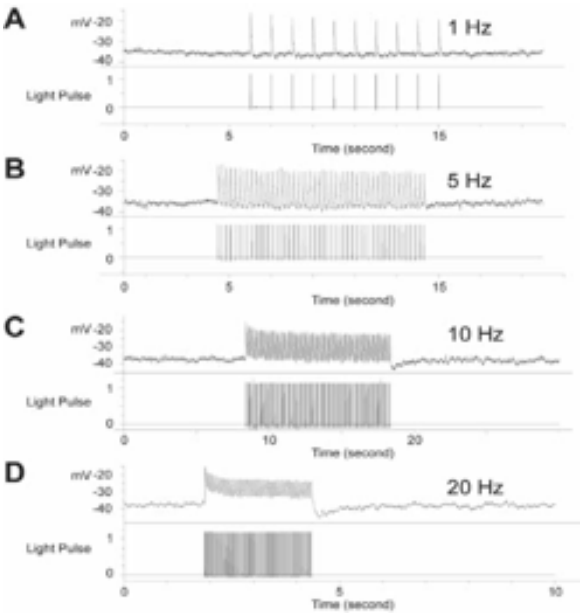

Fig. 2. | Patch-clamp recordings show that Ox neurons expressing ChR2(H134R) can be reliably excited by blue light (473 nm) at different frequencies.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 15

Anesthesia disrupts long range visual evoked gamma waves present in the awake mouse brain

Adeeti Aggarwal[1], Connor Brennen[1], Diego Contreras[1], Max B Kelz[2], Alexander Proekt[2]

[1]University of Pennsylvania, Philadelphia, PA, [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

INTRODUCTION: How general anesthetics block sensory perception remains a mystery. It was previously thought that anesthetics impede information flow from the thalamus into the cortex[1]. However, even under surgical anesthesia, evoked responses are readily recorded from primary sensory cortices[2,3]. This suggests that anesthetics block perception by disrupting the interactions among primary and higher order cortical networks. Evidence of these interactions can be observed in the complex electrical signals that outlast the stimulus and propagate across the cortex[4–6]. Here, we investigated two interrelated questions: 1) How do anesthetics affect these long range interactions in the cortex? and 2) Are these long range interactions involved in processing sensory stimuli? To answer these questions, we recorded responses to visual stimuli in mice using high density electrocorticography that densely samples electrical activity from large areas of the cortex. We also developed four criteria that must be fulfilled for such long range visual evoked responses to be significant for processing stimuli into sensory perception. We then characterized the features of these long range sensory responses to determine whether these four criteria are fulfilled exclusively in the awake state by quantifying long range interactions in the awake state and under anesthesia induced with mechanistically distinct agents.

METHODS: We performed high density electrocorticography recordings in head-fixed mice that were awake (n=9) and under isoflurane (n=18), propofol (n=7) and ketamine (n=6) anesthesia. We recorded spontaneous and evoked local field potentials and visual responses evoked with a 10 ms LED. Spectral analysis of single trial data was performed using wavelet decomposition. Spatiotemporal activity patterns were identified using complex singular value decomposition.

RESULTS: We find that there is much trial-to-trial and animal-to-animal variability in visual evoked potentials (VEPs). However, one consistent feature of VEPs across trials, animals and anesthetics, is an early (<250 msec) visual-evoked gamma band oscillation (20-60Hz). This coherent gamma oscillation organizes into standing, traveling and rotational waves that cover large swaths of cortical surface. If these visual evoked gamma waves are integral for visual stimulus processing into conscious perception, we would expect that these waves are 1) detectable in primary visual cortex (V1) and higher order cortices, 2) reliably elicited from trial to trial, 3) have high signal to noise ratio and 4) have a consistent pattern of cortical activation from trial to trial. Under propofol, the spatial propagation and coherence of long range gamma oscillations is greatly attenuated, consistent with the notion that anesthetics disrupt long range interactions. Remarkably, under both isoflurane and ketamine anesthesia, this was not the case, and visually evoked gamma oscillations were present in secondary visual areas, and association areas. Moreover, visually evoked coherent gamma oscillations spread over even larger areas of the cortex when the same animals were awake. Thus, anesthetics do not universally disrupt long range interactions in the brain. While under isoflurane and in the awake state, visual stimulus reliably evokes coherent gamma waves in the majority of trials, under ketamine and propofol, the number of trials without visual evoked gamma waves increases. Furthermore, in the awake state or under isoflurane, visual evoked gamma waves have higher signal to noise ratio, relative to ketamine and propofol. Lastly, the variability of the spatial pattern of visual evoked gamma waves from trial to trial is decreased in the awake state compared to all three anesthetics studied, isoflurane, propofol, and ketamine.

CONCLUSION: Our results show that long range coordinated visual evoked gamma waves are not universally disrupted by anesthetics, suggesting that under both ketamine and isoflurane anesthesia, there is organized intercortical processing of visual stimuli in higher order cortical areas. However, only when animals are awake and therefore have the ability to perceive the stimulus, do visual evoked gamma waves meet all four criteria necessary for these responses to be important for processing visual stimuli into visual perception.

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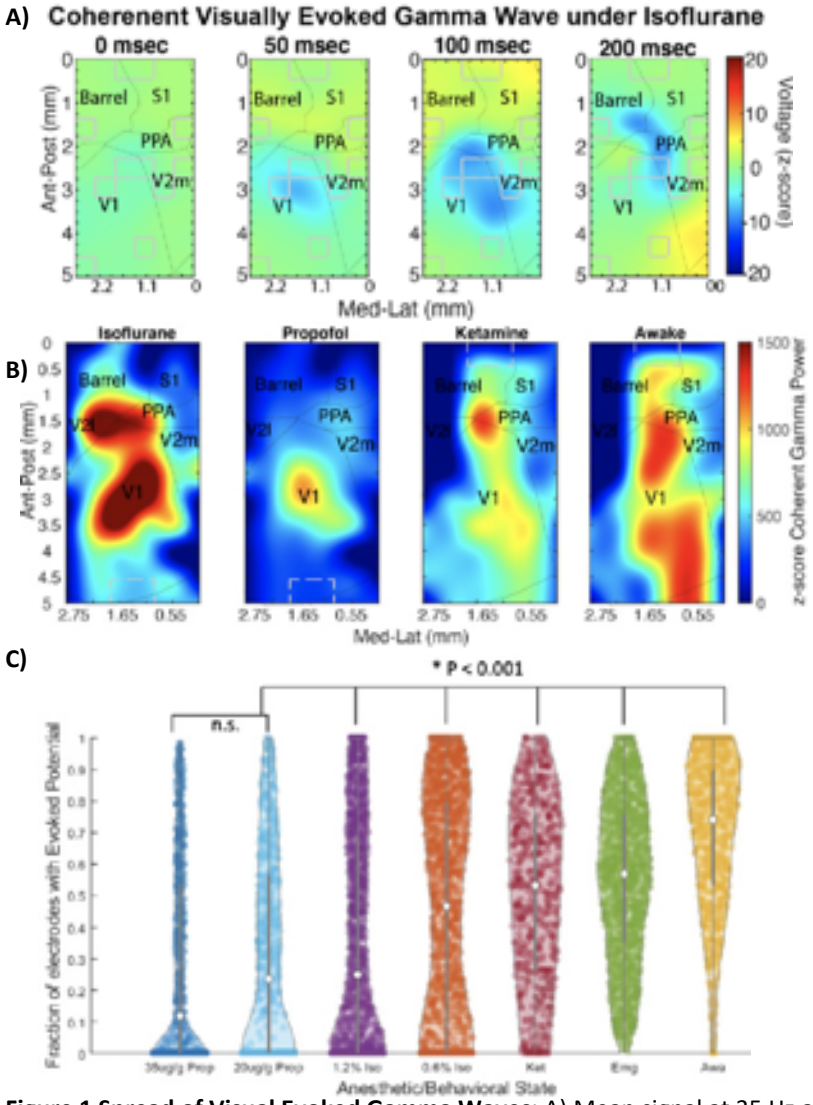

Figure 1 Spread of Visual Evoked Gamma Waves: A) Mean signal at 35 Hz at each of the 64 electrodes on top of the mouse's left hemisphere under 0.6% isoflurane. The LED is flashed at 0 ms. The x and y axis are in distance covered by the grid. The color axis is in baseline normalized power at 35 Hz. Gray squares indicate interpolated signal over electrodes with excess noise. V1 = primary visual, V2m= secondary medial visual, PPA = posterior parietal association, Barrel = whisker barrel, S1 = primary corporeal somatosensory. B) Heat plot of average integrated coherent visual evoked gamma activity of an example mouse under isoflurane, propofol, ketamine and awake. C) Violin plot showing the spread of VEP by measuring the proportion of electrodes in which the evoked gamma power exceeds 5 standard deviations of the baseline gamma power as a function of anesthetic state (where emergence is from isoflurane).

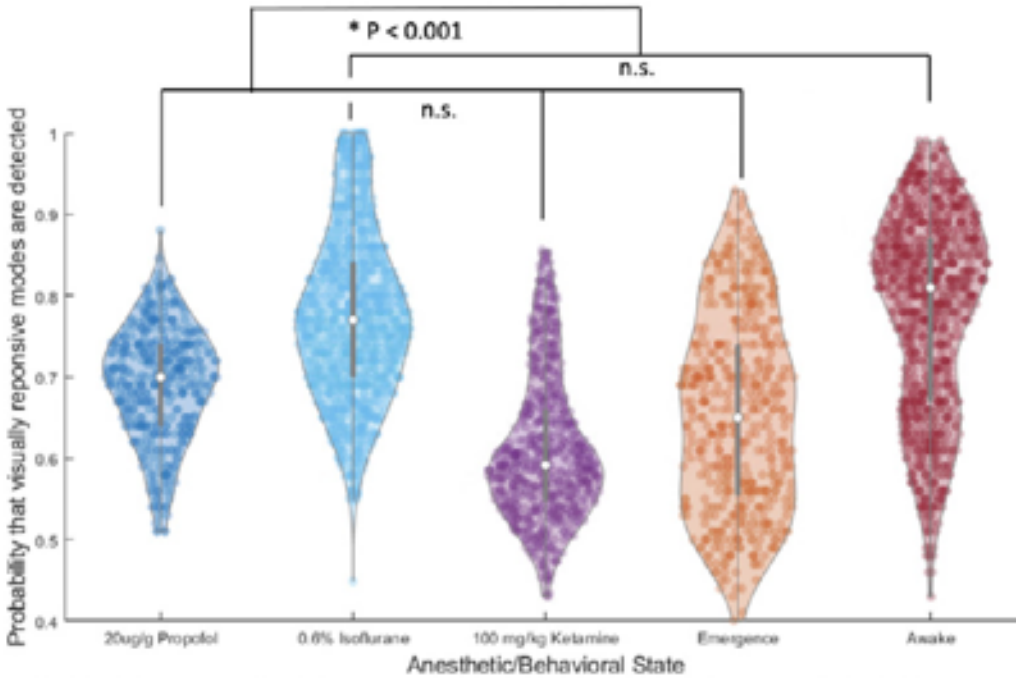

Figure 2 Reliability of Visual Evoked Gamma Waves: Single trial data filtered at gamma was subjected to singular value decomposition in order to identify coherent gamma waves (modes) under each anesthetic condition. The x-axis plots the probability that a randomly chosen single trial would have at least one mode that is visually responsive (a mode that increases in amplitude after the stimulus is presented), in first ten modes identified. The y axis signifies anesthetic state (where emergence is from isoflurane).

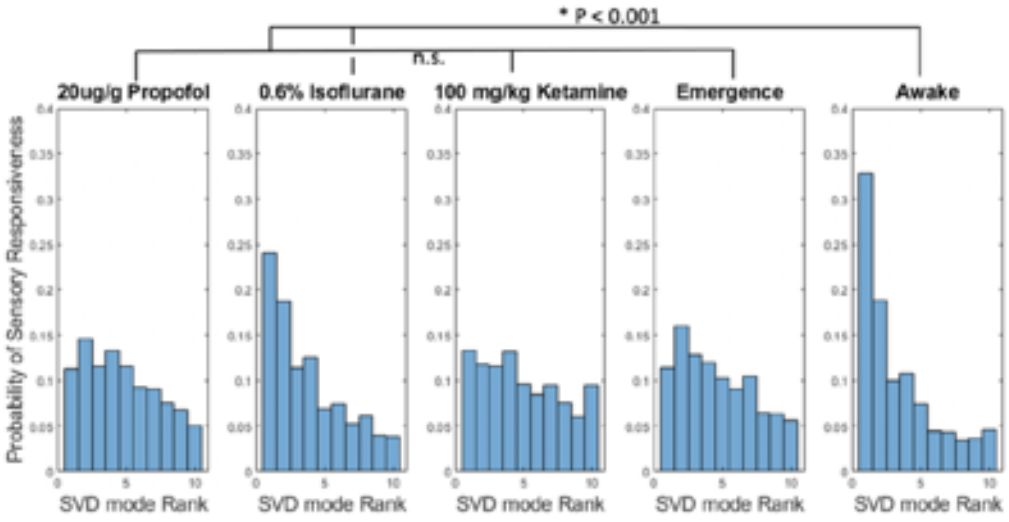

Figure 3 Signal to Noise of Visual Evoked Gamma Waves: The x-axis in each subplot orders the modes from highest amount of variance explained in the data (mode 1) to lowest variance explained (mode 10). The y-axis denotes the probability that each mode is the most sensory responsive mode, as determined by the largest increase in activity after stimulus presentation, when compared to baseline. Each subplot signifies the anesthetic state of the animal (where emergence is from isoflurane).

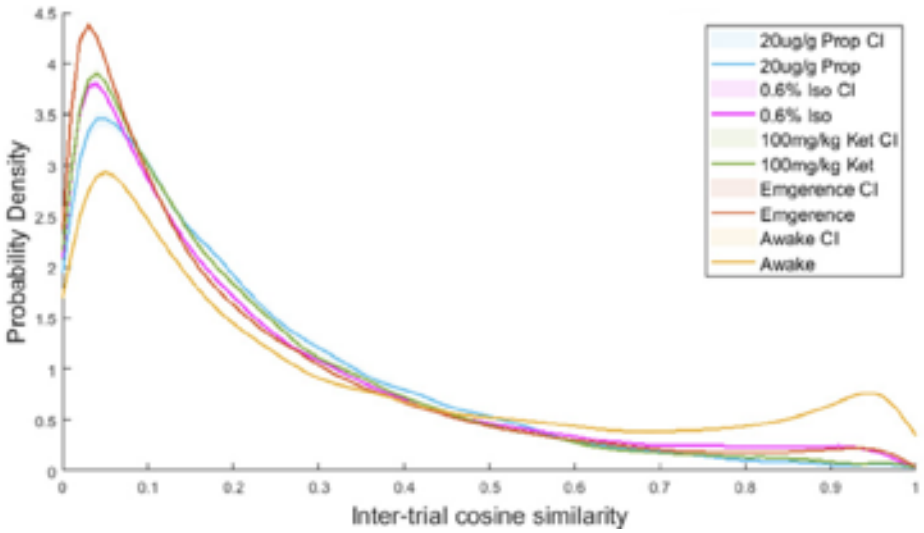

Figure 4 Consistency of Visual Evoked Gamma Waves Activation Pattern: To determine the similarity of visual evoked gamma waves on a single trial basis, the cosine distance was calculated between of the spatial loadings of the most sensory responsive mode iteratively across pairs of single trials. The x-axis shows the cosine distance between trials, with the highest value, 1, as most similar. The y-axis denotes the probability density of the cosine distances between the spatial modes in all pairs of trials. The colors indicate the anesthetic state: cyan =20 ug/g propofol, and magenta = 0.6% Isoflurane, green = 100mg/kg ketamine, orange = emergence from isoflurane, gold = awake, which shading corresponding to their respective 95% confidence intervals., Notably, the awake state (red) has an increase in very similar modes, compared to the anesthetic states.

	Propofol	Isoflurane	Ketamine	Awake
Spread	X	Present	Present	Present
Reliably elicited	X	Present	X	Present
High Signal to Noise	X	X	X	Present
Consistent activation pattern	X	X	X	Present

Figure 5 Summary table of four criteria necessary for visual evoked gamma waves to be important for processing visual stimuli into perception: The four criteria include: 1) detectable in primary visual cortex (V1) and higher order cortices, i.e., have a large spread, 2) reliably elicited from trial to trial, 3) have high signal to noise ratio and 4) have a consistent pattern of cortical activation from trial to trial. Only when animals are awake do visual evoked gamma waves meet all four of these criteria.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 16

The effect on cerebral oxygen saturation of vasopressors administered to treat intraoperative hypotension: a Bayesian network meta-analysis

Anna Maria Bombardieri[1], Narinder P Singh[2], Ban Tsui[3], Umeshkumar Athiraman[4], Preet M Singh[5]

[1]Stanford University School of Medicine, Palo Alto, CA, [2]MMIMSR, MM (DU), Mullana-Ambala, India, [3]Stanford University, Stanford, CA, [4]Washington University in Saint Louis, St.Louis, MO, [5]Washington University in Saint Louis, Saint Louis, MO

INTRODUCTION: The optimal choice of vasopressor for managing hypotension during surgery is unclear. One of the main concerns in the setting of intraoperative hypotension is cerebral perfusion. Cerebral blood flow (CBF) is tightly regulated by a set of powerful mechanisms that include cerebral autoregulation, neurovascular coupling and carbon dioxide reactivity[1]. CBF decreases passively if mean arterial pressure (MAP) falls below the lower limit of cerebral autoregulation, exposing the patient to possible cerebral hypoperfusion which has been associated with worst postoperative outcomes, such as delirium and postoperative cognitive dysfunction[2]. The mainstay of management of intraoperative hypotension is the use of vasopressors. Different vasopressors have different pharmacological effects on cerebral hemodynamics[3] and there is no consensus on the best agent to use in each situation. We therefore performed a network meta-analysis (NMA) to pool and analyze data comparing various vasopressors used for the treatment of intraoperative hypotension.

METHODS: Randomized control trials were searched in Embase, Ovid Medline, Scopus, Cochrane Central Register of Controlled Trials, and Web of Science until April 14, 2020. We included studies that enrolled adult patients (at least 18 years old) undergoing surgery under spinal/general anesthesia, that compared at least two vasopressors for the treatment of hypotension. The primary outcome assessed was the change in cerebral oxygen saturation (ScO2) as measured by cerebral oximetry following the administration of vasopressors.

RESULTS: Of the 51 full-text manuscripts we reviewed, 9 were deemed eligible for our final network analysis. We included a total of 399 patients. The network geometry across outcomes revealed a majority of studies comparing phenylephrine with ephedrine, relative to other intervention comparisons, as shown in Figure 1. Our Bayesian network meta-analysis showed the likelihood that dopamine, ephedrine, and norepinephrine had the lowest probability of adversely affecting ScO2 as measured by cerebral oximetry. The suggested rank order from our analysis was Dopamine<Ephedrine<Norepinephrine<Phenylephrine, as shown in Figure 2. Because of the inherent imprecision when collecting direct/indirect comparisons, the rank orders suggested are possibilities rather than absolute ranks.

CONCLUSION: The results of our NMA suggest the possibility that dopamine and ephedrine are the vasopressors that better preserve ScO2, followed by norepinephrine. When compared to any of the other vasopressors, phenylephrine resulted to decrease ScO2. More research into these agents and preferably multi-drug trials are required to improve the strength of the evidence and to inform clinical practice. From the studies included in this NMA, it appears that the role of cardiac output needs to be taken into account when evaluating the effect of a vasopressor treatment on CBF/ScO2.

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Fig. 1. Network Plot

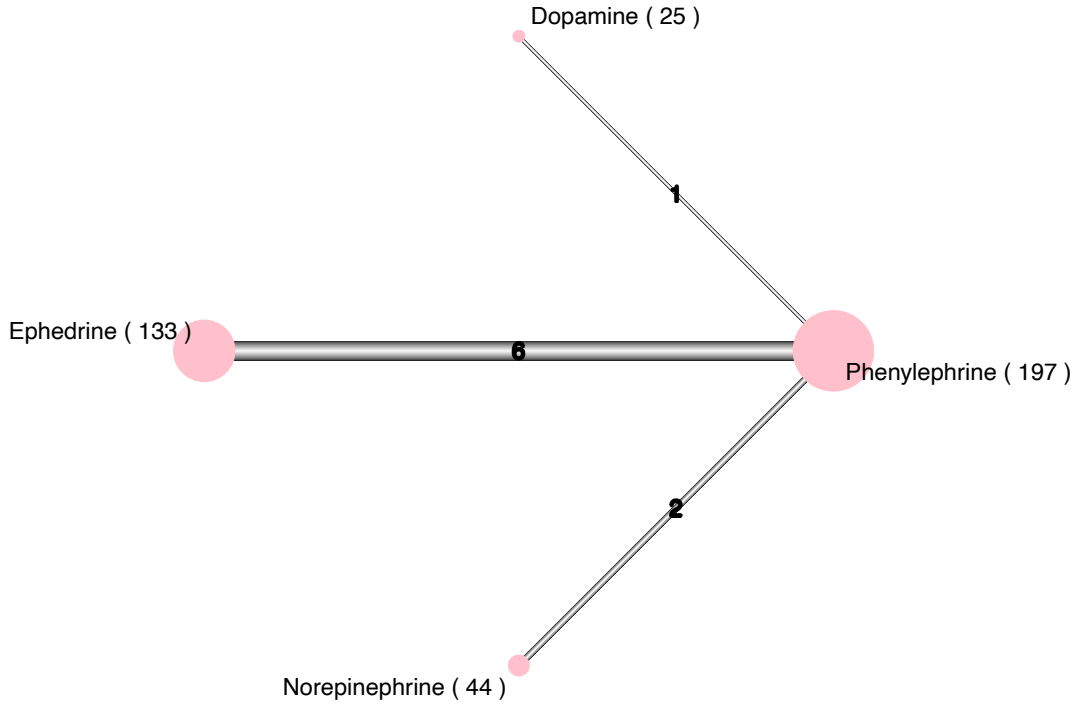
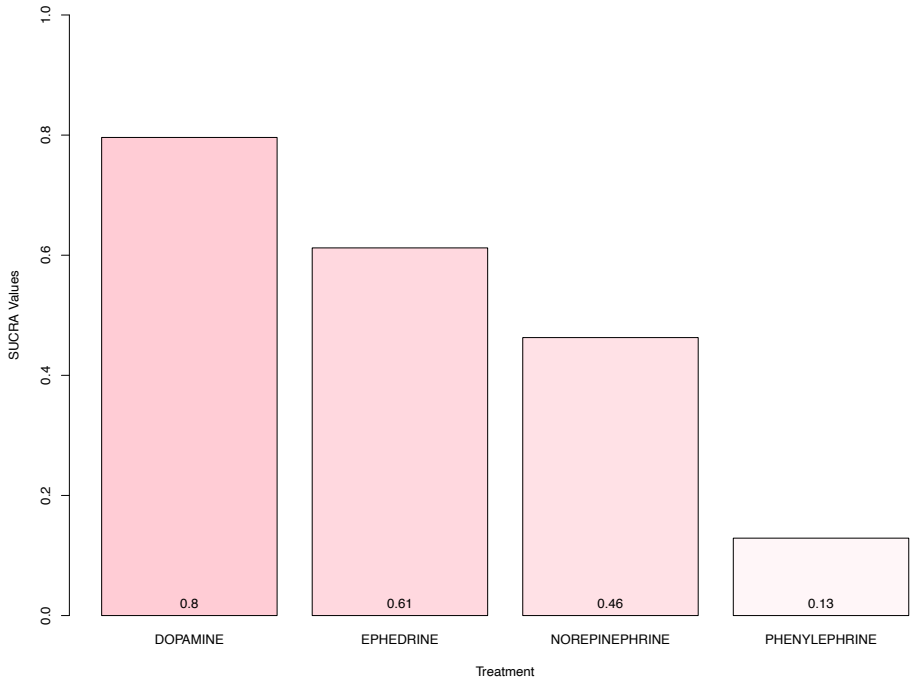


Figure 2. Surface Under the Cumulative Ranking (SUCRA) plot



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 17

Spectral electroencephalographic features of a slow sevoflurane induction in the mouse

David P Obert[1], Marie Engl[1], Fabian Novak[1], Gerhard Schneider[1], Matthias Kreuzer[1], Thomas Fenzl[1]

[1]Technical University of Munich, School of Medicine, Munich, Germany

INTRODUCTION: General anesthetics are used every day a million times[1], highlighting the relevance of these agents. Despite enormous research efforts and a history of more than 150 years[2] the exact mechanisms of how anesthetics induce unconsciousness are still not fully understood. Much of the present knowledge comes from murine studies. Due to low maintenance costs, practicability and ease of genetic modification the mouse became one of the most intensively studied organisms in neuroscience[3]. Even though there are physiological and genetic similarities it remains unknown to what extent findings from the mouse can be transferred to humans[4]. A large body of literature on the influence of sevoflurane on the human electroencephalogram (EEG) exists[5,6], but we have only scarce knowledge of its effects on the mouse brain. In the present study we performed an experimental bed-to-bench approach to evaluate the spectral EEG changes during slow induction of sevoflurane anesthesia.

METHODS: We included data of 10 male, adult mice (C57BL6). Experimental procedures were approved by the Com. on Animal Health and Care of the State of Upper Bavaria. We implanted 9 epidural electrodes (isoflurane anesthesia). One electrode pair each was placed on the frontal association, the primary somatosensory, the primary motor, and the primary visual cortex; one electrode placed frontally on the right hemisphere served as ground/reference. After 10 days recovery, we placed the mice in an acrylic glass chamber and increased the sevoflurane concentration every 2 min by 0.2 Vol.-% (inspiratory oxygen fraction 0.5; 3 l/min fresh gas flow) until we observed an EEG suppression phase of 30 s. For EEG recording each channel was individually amplified, band-pass filtered (hardware filter: 0.1–100 Hz for EEG/gain: 1000x), and sampled with 250 Hz. We calculated the relative and absolute delta (0.7–4.2 Hz), theta (4.2–7.7 Hz), alpha (7.7–12.5 Hz), and beta band (12.5–25.1 Hz) power. As the mice were freely moving in the chamber there were large movement artefacts which we removed (artifact subspace reconstruction). Observation periods were split into (i) start sevoflurane to loss of righting reflex (LORR) with a moving mouse and the risk of EMG contamination and (ii) from LORR to burst suppression (normalized these to correct for different durations). We used descriptive statistics (median [interquartile range]) to present the time to LORR and the gas concentration at LORR and the paired Wilcoxon test to test for changes in the EEG band power during induction.

RESULTS: During induction mice showed a homogeneous behavior as they lost righting reflex approximately 1080 [960; 1080] s after start of anesthesia and at an inspiratory sevoflurane concentration of 1.6 [1.5; 1.6] Vol.-%. We found distinct EEG changes until LORR (Figure 1) as well as from LORR to BSUPP (Figure 2). Topographic plots in these figures highlight the changes in different cortices. We also found a significant increase in the relative beta power before LORR in the prefrontal ($p=0.039$) and the motor cortex ($p=0.049$) (Figure 3). After LORR the absolute delta power increased significantly in the posterior cortical areas (Figure 3), reflecting a slowing of the EEG before the emergence of burst suppression (indicating extensively deep levels of anesthesia). Additionally, we found a significant increase of the alpha band power in the primary motor cortex ($p=0.004$) after the LORR (Figure 3).

CONCLUSION: Our results showed significant changes in the spectral electroencephalographic features during induction of sevoflurane anesthesia. These changes are partially in line with observations in humans. Before LORR, the relative beta power increased, which may be similar to the reported paradoxical excitation (7). We observed a general slowing of the EEG (reflected by an increasing delta power), which has also been found in humans. We did not see the described increase in frontal alpha power during induction of general anesthesia (6), but we rather found a centralization of the alpha power after LORR. Our pilot analyses demonstrate the strengths but also limitations of a mouse model. However, as certain questions regarding complex neuroscientific process during anesthesia can only be answered by animal models, our work provides a basis for improved face validity and constructive validity.

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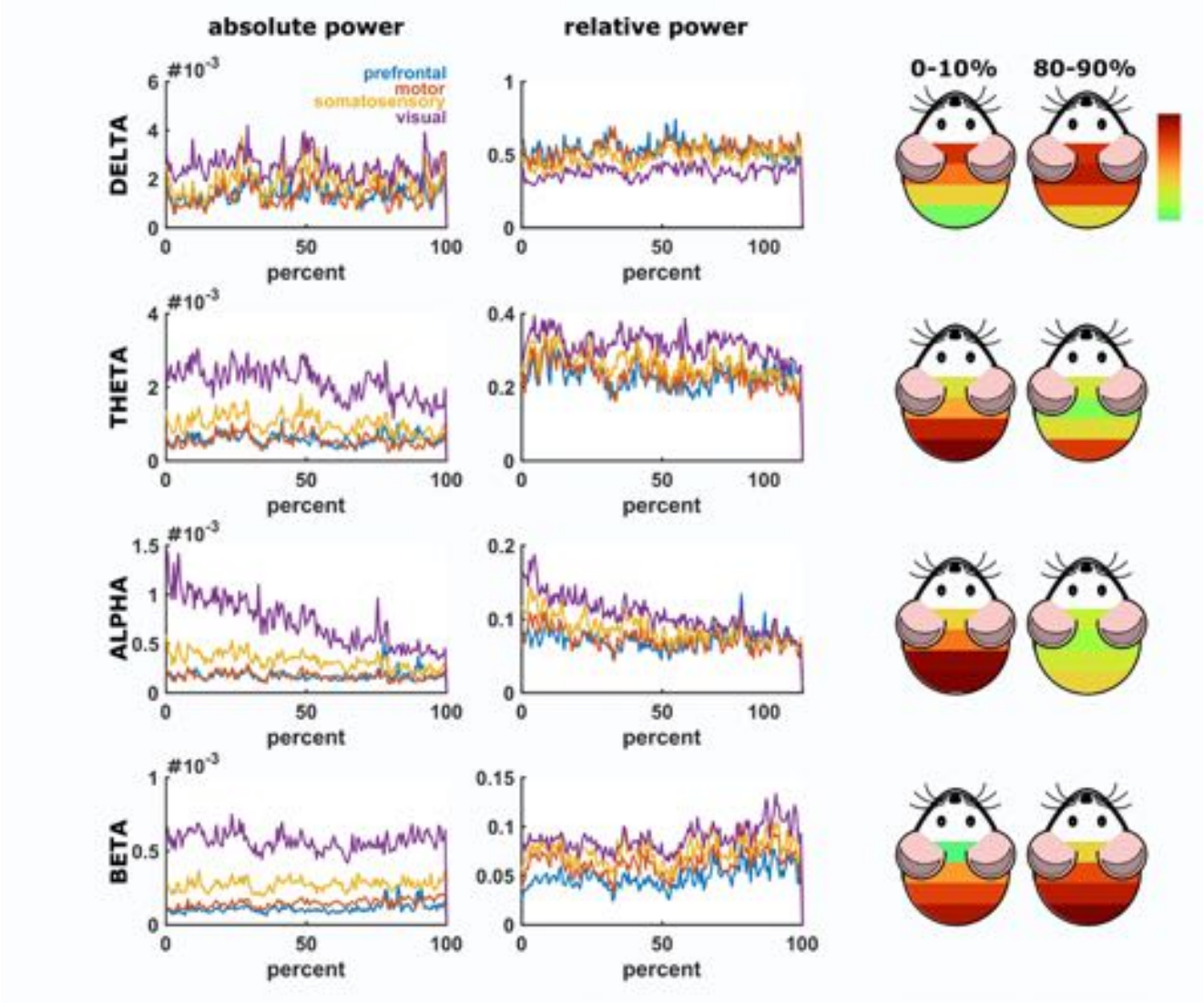

Fig. 1

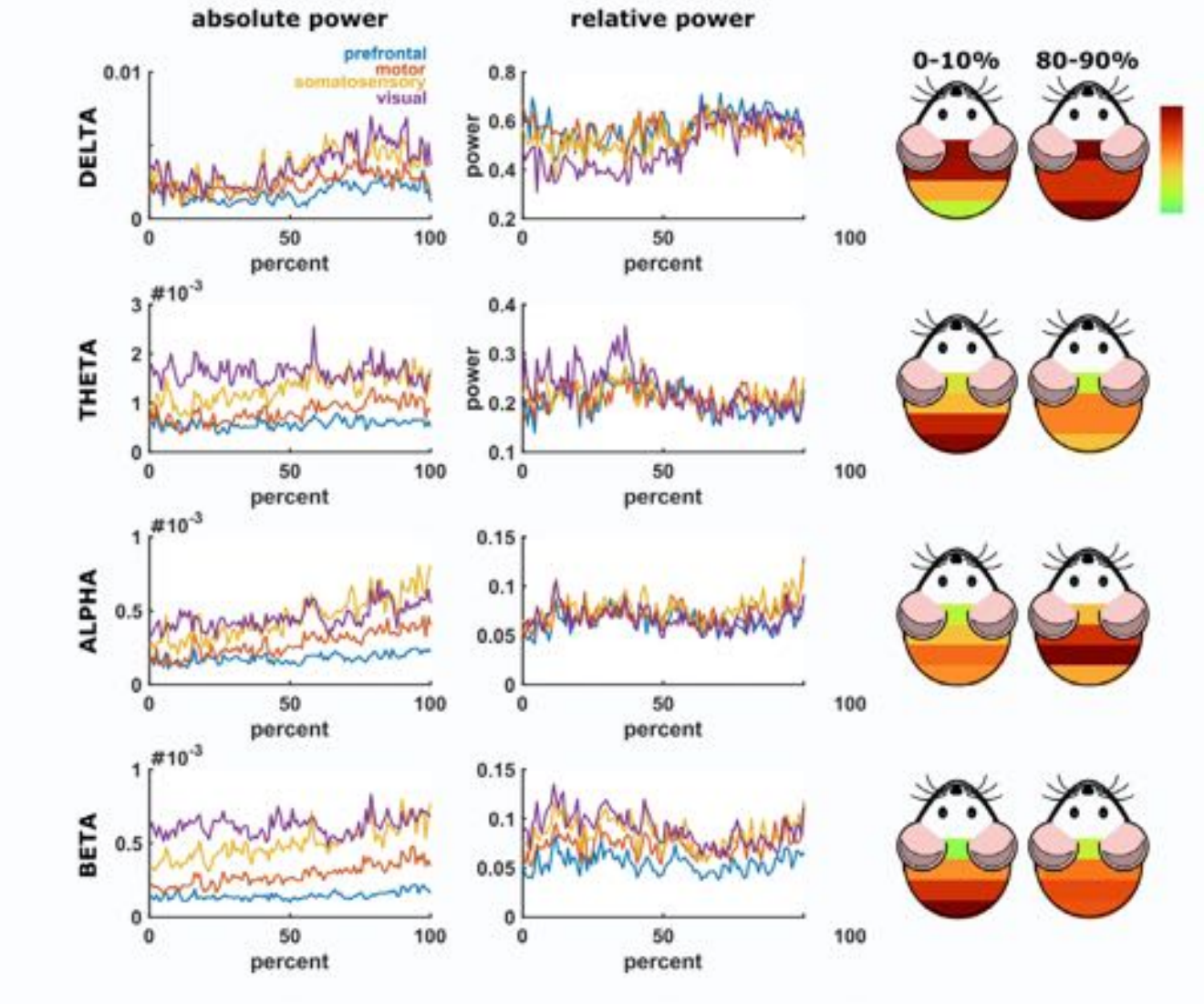

Fig. 2

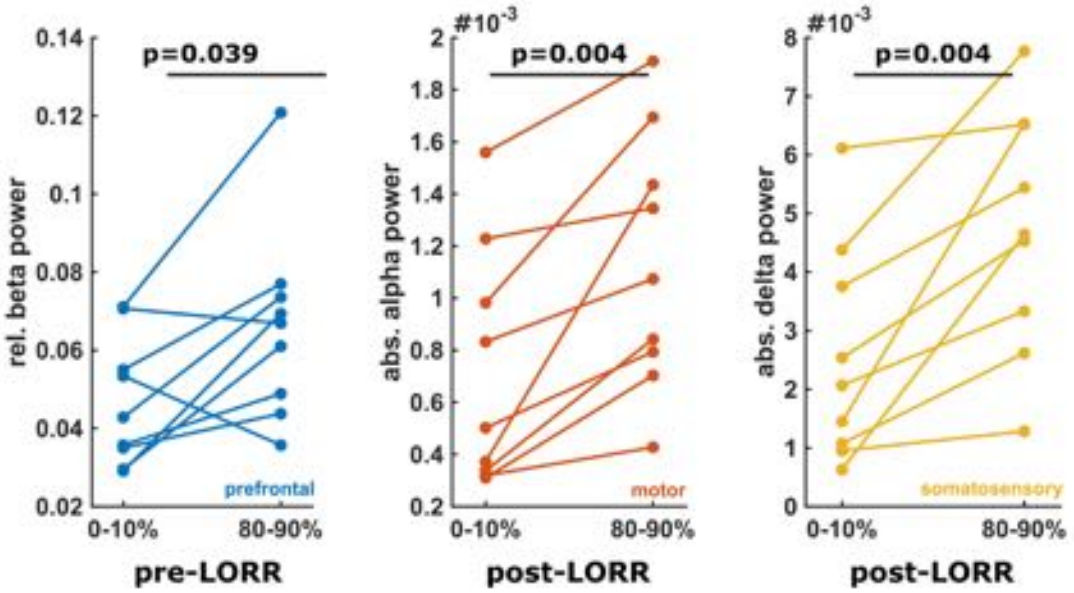

Fig. 3

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 18

Neuron-glia crosstalk plays a major role in the neurotoxic effects of ketamine via extracellular vesicles

Donald H Penning[1], Simona Cazacu[1], Vesna Jevtovic-Todorovic[2], Steve Kalkanis[1], Michael C Lewis[1], Chaya Brodie[1]

[1]Henry Ford Health System, Detroit, MI, [2]University of Colorado School of Medicine, Aurora, CO

INTRODUCTION: There is overwhelming evidence from animal studies that general anesthetics (GA) lead to neurodevelopmental abnormalities including cell death, cognitive and behavioral changes.[1] Human studies have not been conclusive and are challenging since they must account for numerous confounding factors. There is now powerful evidence for non-cell autonomous mechanisms[2] in almost every pathological condition in the brain, especially relevant to glial cells[3], mainly astrocytes and microglia, that exhibit structural and functional contacts with neurons. These interactions were recently reported to occur via the secretion of extracellular vesicles (EVs) that play important roles in both physiological and pathological pathways[4]. EVs carry a specific cargo consisting of RNA molecules, proteins and lipids. Dysregulated EV-related cargo and communication have been implicated in a variety of pathological conditions[5], including stroke, brain injury and neurodevelopmental disorders. Here, we employed primary human neural cells to analyze ketamine effects, focusing on the functions of glial cells and their polarization/differentiation state. We also explored the roles of extracellular vesicles (EVs) and different components of the BDNF pathway.

METHODS: Ketamine effects on neuronal and glial cell death were analyzed using live/dead assay, caspase 3 activity and PARP-1 cleavage. Astrocytic (A1 vs. A2) and microglial (M1 vs. M2) cell differentiation were determined using RT-PCR and phagocytosis assays. The impact of the neuron-glial cell interactions in the neurotoxic effects of ketamine was analyzed using transwell cultures. The roles of the brain-derived neurotrophic factor (BDNF) pathway, including levels of BDNF, pro-BDNF, the lncRNA BDNF-AS and the receptors p75 and TrkB were analyzed using RT-PCR, ELISA western blot and gene silencing. EVs secreted by ketamine-treated cells were isolated, characterized and analyzed for their effects in neuron-glia cell interactions. The results are presented as the mean values ± SE. Data were analyzed using analysis of variance or a Student's t test with correction for data sets with unequal variances.

RESULTS: Ketamine induced neuronal and oligodendrocytic cell apoptosis and promoted the expression of pro-inflammatory astrocytes (A1) and microglia (M1) phenotypes. Astrocytes and microglia enhanced the neurotoxic effects of ketamine on neuronal cells, whereas neurons increased oligodendrocyte cell death. Ketamine modulated different components in the BDNF pathway: decreasing BDNF secretion in neurons and astrocytes while increasing the expression of p75 in neurons and oligodendrocytes. In addition, ketamine treatment increased the lncRNA BDNF-AS levels and the secretion of pro-BDNF secretion in both neurons and astrocytes. We found an important role of EVs secreted by ketamine-treated astrocytes in neuronal cell death. Using knockdown experiments, we demonstrated that EVs secreted from ketamine-treated astrocytes expressed high levels of BDNF-AS and that silencing of the expression of this lncRNA in astrocytes abrogated the increased ketamine toxicity in neuron-astrocytes co-cultures, indicating a role for EV-associated BDNF-AS in this effect.

CONCLUSION: Ketamine exerted a complex neurotoxic effect on neural cells by impacting both neuronal and glial cells, therefore indicating that ketamine neurotoxicity involves both autonomous and non-cell autonomous mechanisms. We identified the role of different components of the BDNF pathway expressed by neurons and glial cells as major regulators of ketamine effects. Finally, we demonstrated for the first time a role of EVs as important mediators of ketamine effects by the delivery of specific non-coding RNAs between cells. These results may contribute to a better understanding of cellular and molecular mechanisms underlying ketamine neurotoxic effects in humans and to the development of potential approaches to decrease its neurodevelopmental impact.

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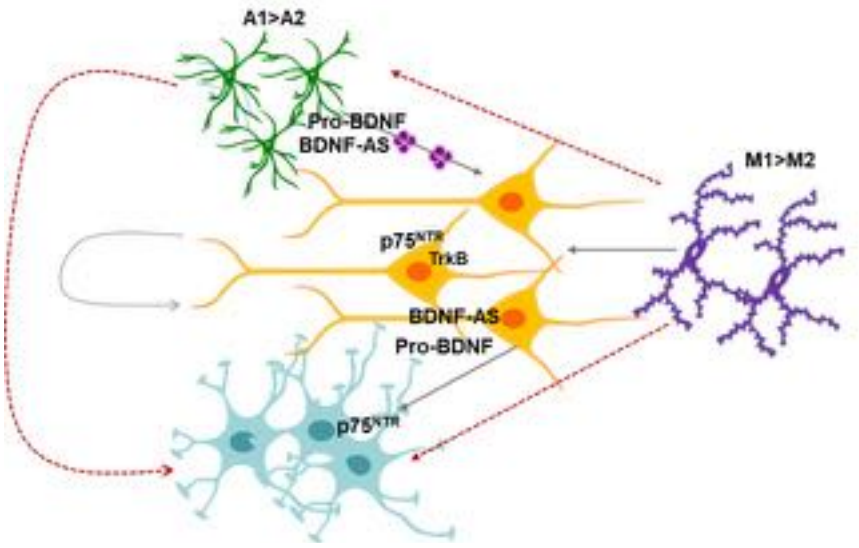

A diagram summarizing the roles of neuron-glia interactions, the BDNF pathway and extracellular vesicles in ketamine's effects. The effects of ketamine on various components of the BDNF pathway, the interactions of neuron and glial cells and the role of EVs as mediators of these interactions are depicted in this diagram.

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 19

Three distinct low-frequency (<4Hz) traveling wave types in volunteer propofol anaesthesia revealed by empirical mode decomposition

Marco S Fabus[1], Andrew Quinn[1], Mark Woolrich[1], Katie Warnaby[1]

[1]Wellcome Centre for Integrative Neuroimaging (WIN), University of Oxford, Oxford, United Kingdom

INTRODUCTION: The human electroencephalogram (EEG) during propofol anaesthesia shows high delta-band (<4Hz) activity accompanied by traveling slow waves (~1Hz)[1]. Slow-wave saturation (SWAS) has been proposed as an individualised endpoint for perception loss in anaesthesia[2,3]. In NREM sleep, slow-waves have been proposed to be of two types with separate thalamocortical and cortico-cortical generators[4,5]. Much remains unclear about the dynamics of anaesthetic slow-waves and their role in perception loss. In this advanced secondary analysis, we used a novel data-driven signal decomposition technique called iterated masked empirical mode decomposition (EMD)[6–8] to analyse dose-dependent behaviour of low-frequency waves.

METHODS: Data for this analysis came from an ultra-slow target-controlled intravenous infusion of propofol up to 4 µg/ml in 16 healthy volunteers (8 female, age 28.6±7 years) described in 2. EEG was acquired using a 32-channel cap sampled at 5kHz referenced to FCz. Here data was re-referenced to linked earlobes, downsampled to 500Hz, and filtered with an 8th-order zero-phase 0.1-30Hz filter. Masked EMD was performed using an open-source Python EMD toolbox (https://emd.readthedocs.io) on 46 one-minute segments of data from induction of each subject. EMD was iterated 10 times, starting with an initial mask of [14,7,2.5,0.5,0.2]Hz. The mask was updated each iteration as the amplitude-weighted mean of instantaneous frequency. The decomposition was robust to changes in the initial mask and number of modes. Cycles were found from jumps in instantaneous phase calculated by the Hilbert transform. Cycles from intrinsic mode functions (IMFs) falling in 0.5-4Hz band were analysed further. Those with negative duration 0.125-1.5s, amplitude in the upper 50th percentile, and appearing on at least 5 channels within ±200ms of an arbitrary reference channel were accepted as traveling waves. Their wave density (waves detected per minute), frequency, globality (% of channels involved in slow wave), peak-to-peak amplitude, speed, and origin were calculated[9]. Subject-averaged properties were compared using one-way ANOVA with Bonferroni correction for multiple comparisons. Significance was set at $P<0.05$.

RESULTS: All 16 subjects were included in the analysis. EMD decomposed EEG into five IMFs. IMF-1 corresponded to alpha spindles (f=11.9±0.5Hz, mean±standard deviation across subjects). The next three modes captured low-frequency (<4Hz) activity (Figure 1). They had significantly different frequencies ($P<10^{-15}$) and are referred to as *high delta* (IMF-2, f=3.44±0.2Hz), *low delta* (IMF-3, f=1.44±0.1Hz) and *slow* (IMF-4, f=0.74±0.1Hz). IMF-5 captured residual EEG drifts and was discarded. Waves from low-frequency modes had consistent between-subject morphological and topographical properties (Figures 2,3). Slow waves were fronto-central, decreased in globality with propofol concentration, had diffuse origins, and became saturated in wavenumber and amplitude. Low-delta waves also saturated in amplitude and wavenumber but increased in globality with anaesthetic concentration, had mostly lateral origins, and were faster (v=7.9±0.9m/s vs v=4.6±0.4m/s for slow waves, $P<10^{-11}$). High-delta waves were identified at high concentrations past SWAS. They had low globality, frontal origins, and were fastest (v=14±1m/s). All wave types decreased in frequency with increasing propofol concentration.

CONCLUSION: We identified three distinct types of low-frequency traveling waves in propofol anaesthesia using a novel data-driven signal processing technique. High delta, low delta, and slow waves were found in all subjects and with increasing dose they had significant differences in their frequency, globality, origin, and speed. Our results show some similarities with Type I/II wave distinction proposed for sleep slow waves[4,5]. Type II waves (local, small amplitude) behave similarly to high delta, but Type I (global, large amplitude) is comprised of two distinct types of waves, faster frontal low-delta and slower fronto-central slow waves. Similarly, SWAS results from an interplay between the low delta and slow modes as typically defined[3].The physiological origin of these types of waves remains to be investigated. We hypothesise these may reflect cortico-cortical and thalamocortical processes. The three wave types might thus have different functional significance and implications for optimal anaesthetic induction and maintenance.

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Figure 1: (A) Example iterated masked EMD signal decomposition in 20 seconds of deep propofol anaesthesia EEG and (B) frequency of waves from IMFs in all 16 subjects. The **** marks significant differences at corrected $P<10^{-15}$.

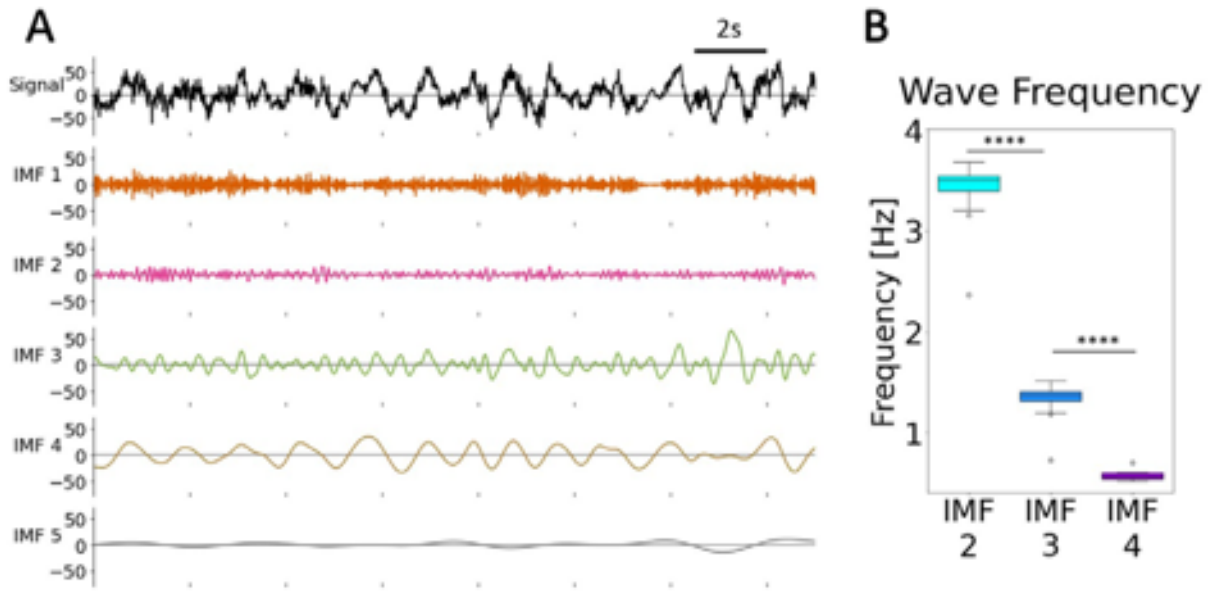


Figure 2: Changes observed with increasing propofol concentration in grand mean across subjects of the A) globality, B) wave density, C) frequency, and D) amplitude for the 3 low-frequency (<4Hz) wave types.

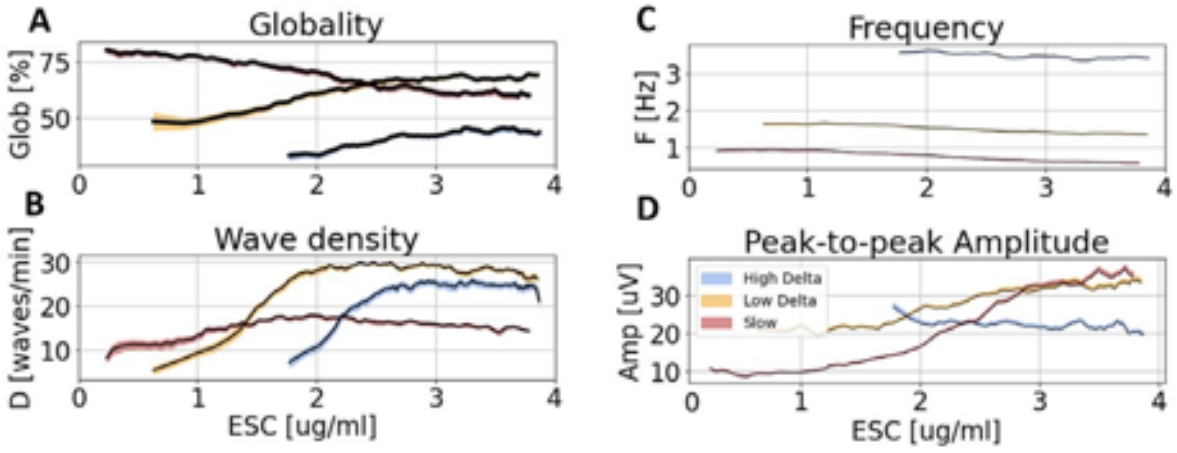
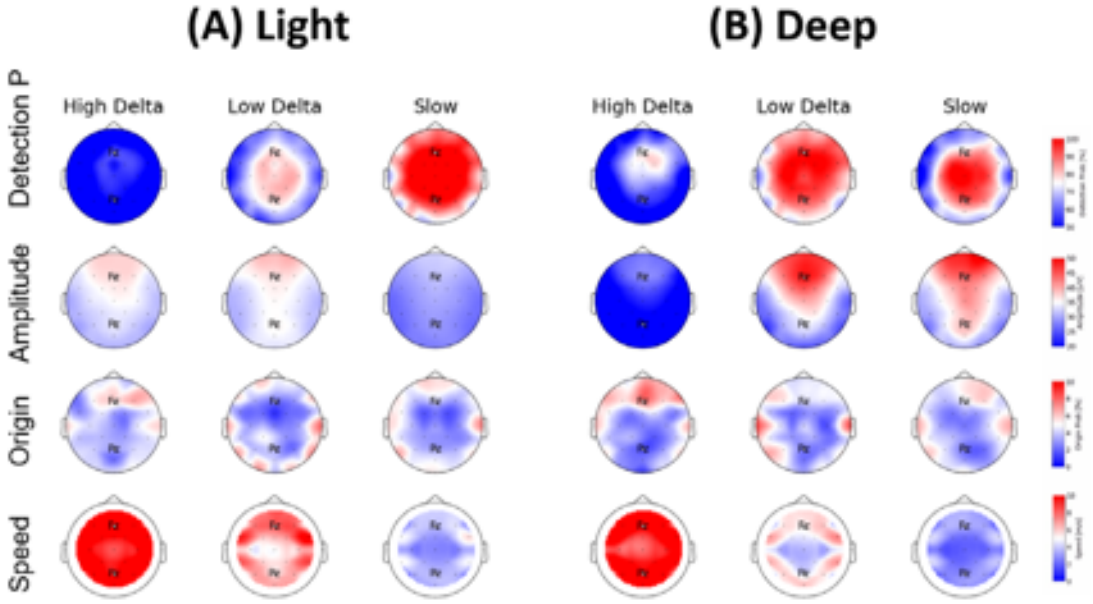


Figure 3: Changing topography of wave properties with increasing propofol concentration. (A) low concentrations near loss of behavioural response. (B) high concentrations near end of induction.



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 20

A double hit of inflammation and sevoflurane persistently increases tonic inhibition in mouse hippocampal neurons

Shahin Khodaei[1], Woosuk Chung[2], Dian-Shi Wang[1], Beverley A Orser[1]

[1]University of Toronto, Toronto, Canada, [2]Chungnam National University Hospital, Daejeon, Republic of Korea

INTRODUCTION: Perioperative neurocognitive disorders (PND), which include postoperative delirium and postoperative cognitive dysfunction, are associated with poor long-term outcomes, increased healthcare costs, and increased mortality[1]. Emerging evidence suggests that both inflammation and anesthetic drugs are contributing factors to the development of PNDs[2,3]. In fact, a "double hit" of these two factors may be critical – preliminary findings from our lab show that a double hit of inflammation and anesthesia causes persistent cognitive impairments in mice that are not observed with either factor alone.
The underlying mechanisms for the cognitive deficits after a double hit in mice are currently not well understood. Dysregulation of inhibitory neurotransmission in the brain is a potential underlying mechanism. Both inflammation and anesthetic drugs have been shown to independently increase tonic inhibition mediated by γ-aminobutyric acid type A ($GABA_A$) receptors in the hippocampus, which can impair cognition[4–6]. Based on this convergence, here we addressed the hypothesis that there is a greater increase in tonic inhibition after a double hit of inflammation and anesthesia, compared to the increase caused by each factor alone.

METHODS: All experiments were approved by the institutional animal care committee. Male C57BL/6 mice, aged 6-7 weeks, were first injected with lipopolysaccharide (LPS) intraperitoneally (i.p; 1 mg/kg) to induce inflammation, or injected with saline alone as vehicle. Twenty-four hours later, mice were anesthetized with sevoflurane (2.3%, delivered in 30% O2) for 2 hours; vehicle-treated animals were exposed to 30% O_2 for 20 minutes. Forty-eight hours after anesthesia, hippocampal brain slices were prepared, and whole-cell voltage-clamp recordings were performed in CA1 pyramidal neurons to study tonic inhibition. Also, miniature inhibitory postsynaptic currents (mIPSCs) were recorded to study phasic inhibition. Data are presented as means ± SEM. Groups were compared using ordinary two-way ANOVA followed by Tukey's multiple comparisons test.

RESULTS: LPS did not increase the tonic inhibitory current (control: 17.6 ± 3.2 pA, n = 9, LPS: 17.1 ± 1.4 pA, n = 14; effect of LPS: P = 0.84). In contrast, sevoflurane led to a marked increase in tonic inhibitory current 48 hours after exposure (sevoflurane: 29.9 ± 4.0 pA, n = 12; effect of sevoflurane: P = 0.0008). The tonic current was not further increased in mice treated with the double hit of LPS and sevoflurane (LPS + sevoflurane: 31.9 ± 5.5 pA, n = 11, effect of interaction: P = 0.74). With regard to phasic inhibitory transmission, there were no differences between groups in the frequency, amplitude, rise-time, area, or decay of mIPSCs (P > 0.05 for all).

CONCLUSION: A brief exposure to sevoflurane triggered a sustained increase in tonic inhibition in hippocampal CA1 pyramidal neurons; there was no further increase in a double hit of LPS and sevoflurane. These results suggest that mechanisms other than a further increase in tonic inhibition contribute to the cognitive deficits after a double hit of inflammation and anesthesia. Exploring such alternative mechanisms are the focus of ongoing studies.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 21

Altered Brown Adipose Mitochondrial Respiration in Fragile X Syndrome Mice

Yash Somnay[1], Aili Wang[1], Keren K Griffiths[1], Richard J Levy[1]

[1]Department of Anesthesiology, Columbia University Irving Medical Center, New York, NY

INTRODUCTION: Mitochondrial proton leak is a physiological process that is integral to thermoregulation and metabolic homeostasis[1]. Brown adipose tissue (BAT) mitochondria primarily generate heat via uncoupled respiration due to the excessive proton leak mediated by uncoupling proteins (UCPs)[2]. We have previously reported coenzyme Q (CoQ) deficiency in the forebrain mitochondria of newborn Fragile X Syndrome (FXS) mice (Fmr1 KO) that lack fragile X mental retardation protein (FMRP)[3]. This defect resulted in inefficient thermogenic mitochondrial respiration and hyperthermia due to a pathologically open mitochondrial permeability transition pore. Because the phenotype of these uncoupled forebrain mitochondria was highly reminiscent of the metabolic features of BAT mitochondria[4], and that FMRP is ubiquitously expressed, we hypothesized that Fmr1 KO BAT mitochondria would demonstrate discrete defects. Using a top down approach, we aimed to characterize the effect of FMRP deficiency on BAT mitochondria in newborn FXS mice.

METHODS: Interscapular BAT mitochondria from ten-day-old male Fmr1 KO and FVB control mice were isolated and tested. Immunoblot analysis for UCP-1 was performed and electron transport chain (ETC) complex activities and oxidative phosphorylation were assessed using spectrophotometry and polarography, respectively. Mitochondrial CoQ levels were quantified and source of proton leak was determined using specific inhibitors. We evaluated 5-6 animals per cohort per assay. Significance was assessed with non-parametric Kruskal-Wallis test and post hoc Bonferroni correction set at $p < 0.05$.

RESULTS: Immunoblot analysis demonstrated no significant difference in steady-state BAT UCP-1 expression in Fmr1 KOs relative to controls. Fmr1 KO BAT mitochondria demonstrated significantly slower state 3, dinitrophenol (DNP)-induced state 3, and oligomycin-induced state 4 oxygen consumption rates and lower membrane potentials for all substrates assessed. There was no significant difference in steady-state ETC complex kinetic activities between strains for the majority of enzymes. However, the linked kinetic activities of complexes I+III and II+III were significantly decreased in Fmr1 KOs, suggesting CoQ deficiency. Spectrophotometric quantification of mitochondrial CoQ content confirmed significantly decreased CoQ levels in Fmr1 KOs. Modular kinetics analyses revealed impaired substrate oxidation in Fmr1 mutants and pathologically increased proton conductance relative to controls, albeit at relatively low oxygen consumption rates. Grossly, Fmr1 KO BAT fat pads were visibly smaller than controls and weighed significantly less as a fraction of total body weight.

CONCLUSION: Our findings suggest defective BAT mitochondrial respiration in the setting of FMRP deficiency. Specifically, we identified CoQ deficiency, impaired substrate oxidation, and relatively lower membrane potentials in BAT mitochondria from newborn Fmr1 KO mice. Although our data provide further evidence of a link between FMRP and CoQ biosynthesis, the results highlight the importance of CoQ in developing tissues and suggest tissue-specific differences in the effects of CoQ deficiency. Because BAT mitochondria are primarily responsible for regulating core body temperature, the defects we describe in Fmr1 KOs could manifest as an adaptive downregulated response to hyperthermia or could result from FMRP deficiency directly. Given that anesthetic agents can interfere with the ETC[5] and induce hypothermia[6], future work will focus on mechanisms of anesthetic-induced thermodysregulation with a specific focus on BAT mitochondria and CoQ.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 22

Differences in Response to Commands Among Tonal Language Speakers and Non-Tonal Language Speakers During Emergence from Anesthesia

Elise Hall[1], Spencer J Satz[2], Ryan Hoang[3], Tracy Dinh[4]

[1]Villanova University, Villanova, PA, United States of America, [2]Tel Aviv University Sackler School of Medicine, Tel Aviv, Israel, [3]University of Chicago, Chicago, IL, [4]University of Chicago Pritzker School of Medicine, Chicago, IL

INTRODUCTION: It has been observed in recent studies (Ge et al.) that while different language groups reliably use the same typical brain regions in speech (i.e. Broca's and Wernicke's areas) some unique dynamics may occur between these cortical regions among different language groups, namely tonal languages (such as mandarin) and non-tonal languages. This study evaluates whether these subtle differences may appear more pronounced in a post-anesthesia setting, as brain regions are sequentially reactivated from sleep. Bilingual patients were given commands (for example, 'wiggle your toes') in English followed by their first language, and these commands were repeated in an alternating fashion until the patient responded. It was recorded how many times the commands were repeated before the patient responded in each language. In the absence of a detailed mapping of cortical interactions specific to these language groups is yet unknown, this study provides further evidence that the tonal languages may make use of altered language processing, setting them apart from non-tonal languages.

METHODS: Data was collected from 202 bilingual patients undergoing anesthesia for a variety of procedures. The first language of the patients was recorded as well as their proficiency in English and their first language, where the patients were from, where they learned English, in what language they dream, as well as other various relevant information about their language experience. As these patients were waking up from anesthesia, they were given the commands 'Open your eyes,' 'Wiggle your fingers,' and 'wiggle your toes,' sequentially, and alternating between English and the patients' first language. It was recorded how many repetitions of each command were necessary before the patient responded for each language.

RESULTS: From these data, response frequencies of patients whose first language was tonal (n=19) were compared with patients whose first language was non-tonal (n=152). Both of these groups were also compared with response frequencies of the group as a whole. Small differences were found in the patterns of recognition to commands between the tonal languages and the non-tonal languages. For example, tonal language speakers were less likely to never respond to the commands in both languages than were non-tonal language speakers. Furthermore, tonal language speakers were much more responsive to commands in their first language than non-tonal language speakers. Tonal language speakers were more likely to respond on the first try of the foreign language command and less likely to never respond to the foreign commands than non-tonal language speakers. The figures attached show the percentage of patients who responded first to the foreign language, first to English, to both languages equally or to neither language.

CONCLUSION: According to Merriam-Webster's dictionary, a tonal language is 'a language in which variations in tone distinguish words or phrases of different meaning that otherwise would sound alike.' While the variation in these languages is at the surface purely linguistic, they may provide a lens by which to understand how cognitive processing of language can differ among language categories. The data from this study suggests that such differences may be exaggerated post-anesthesia.

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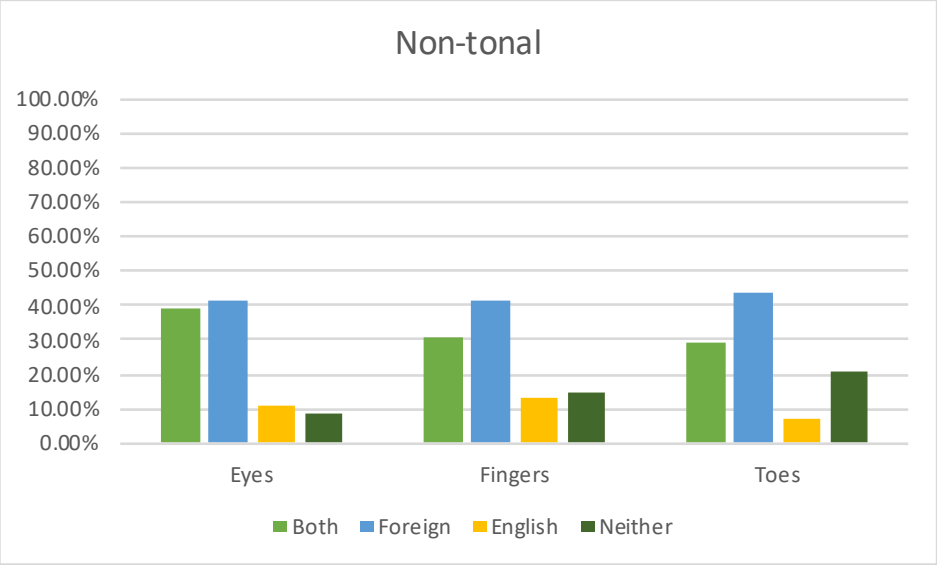

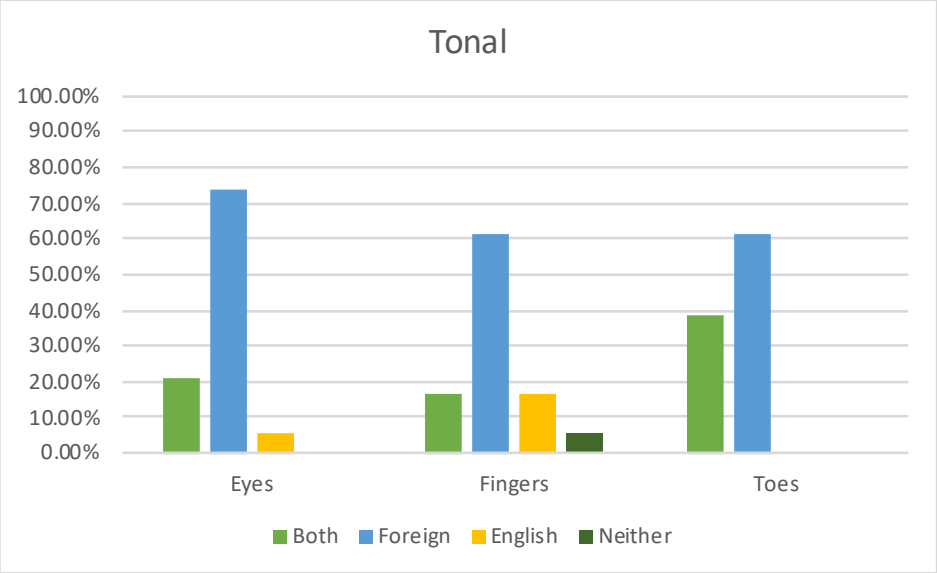

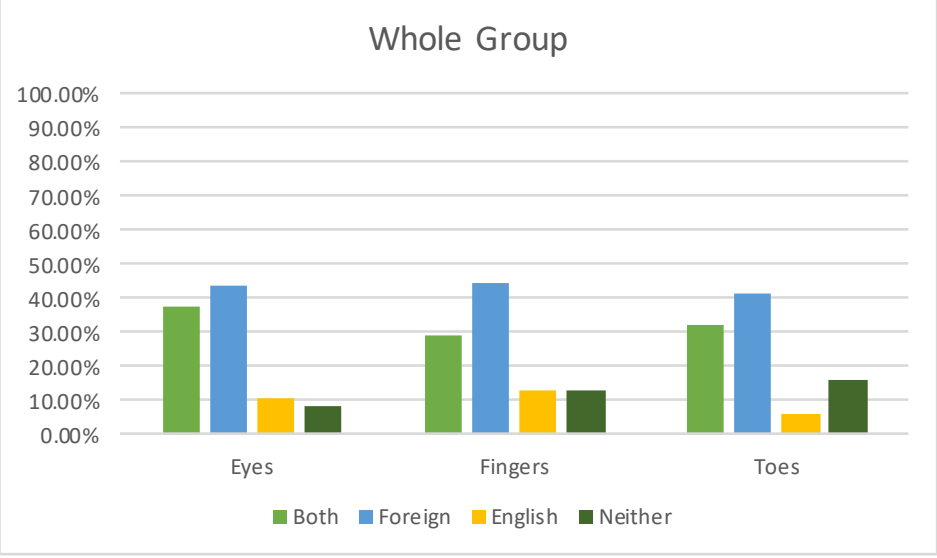

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 23

Anesthetic activation of GABAA receptors in astrocytes triggers a persistent increase in cell-surface expression of α5GABAA receptors in neurons via IL-1β in mice

Arsene Pinguelo[1], Kirusanthy Kaneshwaran[1], Allison Chown[1], Sina Kiani[1], Dian-Shi Wang[1], Beverley A Orser[2]

[1]University of Toronto, Toronto, Ontario, [2]University of Toronto Faculty of Medicine, Toronto, Ontario

INTRODUCTION: Many patients develop delirium and cognitive deficits in the postoperative period, which is associated with poor long-term outcomes[1,2]. Preclinical studies have shown that even a brief exposure to commonly used general anesthetic drugs triggers a sustained increase in inhibitory tonic current generated by α5 subunit–containing $GABA_A$ receptors ($\alpha5GABA_ARs$) in mouse hippocampal neurons[3]. The resulting increase in inhibition causes subtle, yet sustained postanesthetic cognitive deficits. Interestingly, astrocytes are necessary for this effect and express anesthetic sensitive $GABA_A$ receptors. Furthermore, the proinflammatory cytokine IL-1β also increases tonic current in neurons via a p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway[4]. Additionally, inhibiting the IL-1 receptor or p38 MAPK function in neurons prevents the anesthetic-induced increase in tonic current[5]. However, how the release of IL-1β is stimulated, the cellular source of IL-1β, and if this promotes the persistent phosphorylation of p38 MAPK, are currently unknown. Synthesizing these observations, we hypothesize that anesthetic drugs activate $GABA_ARs$ in astrocytes to trigger the release of IL-1β which acts on neurons through p38 MAPK to induce an increase in the cell-surface expression of $\alpha5GABA_ARs$.

METHODS: Studies were approved by the local animal ethics committee. Cortical astrocytes and hippocampal neurons were isolated from fetal CD1 mice and grown in cell cultures. Astrocyte cultures were treated with etomidate (1 μM) +/- the $GABA_A$ receptor antagonist bicuculline (20 μM) plus etomidate for 1 hour, then the drug was washed out and the cultures were incubated for further 2 hours. The conditioned medium was then transferred to hippocampal neuronal cultures, and 24 hours later the cell-surface expression of $\alpha5GABA_ARs$ was assessed via biotinylation and Western blot. The protein levels of IL-1β and p38 MAPK were measured with Western blot in etomidate-treated astrocytes and conditioned medium-treated neurons. Furthermore, the protein levels of IL-1β in the treated conditioned media was measured via ELISA. The detected IL-1β concentration was then used to treat neurons, and 24 h later tonic current was recorded with voltage clamp techniques.

RESULTS: Treating astrocytes with etomidate induced a significant increase in neuronal $\alpha5GABA_AR$ cell-surface expression. Furthermore, cotreating the astrocytes with bicuculline prevented the etomidate-induced persistent increase in $\alpha5GABA_AR$ surface expression in neurons. Following etomidate treatment, mature IL-1β protein was increased in astrocytes and the phosphorylation of p38MAPK was increased in neurons. A significant increase in IL-1β protein was also detected in etomidate-treated astrocyte conditioned media. The detected concentration of IL-1β was sufficient to drive a persistent increase in tonic current in neurons.

CONCLUSION: These results suggest that anesthetic activation of $GABA_ARs$ in astrocytes triggers the maturation and release of IL-1β from astrocytes. The released IL-1β then acts on neurons through the phosphorylation of p38 MAPK, driving an increase in $\alpha5GABA_AR$ surface expression and function. Our results identify a novel cross-talk mechanism between astrocytic $GABA_ARs$ and neuronal $GABA_ARs$ that might be targeted to mitigate postanesthetic cognitive deficits.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 24

Machine Learning to Identify Acute Pain Signals from EEG Recordings

Deborah Ok[1], Lisa Doan[1], Zhe S Chen[1], Jing Wang[1]

[1]New York University School of Medicine, New York, NY

INTRODUCTION: The CDC reports an estimated 20.4% (50.0 million) of U.S. adults have chronic pain[1], with low back pain being one of the most common chronic pain syndromes[2-4]. Neuroimaging has been used to better understand structural and functional changes in the brain in subjects with chronic pain[5]. EEG directly measure neuronal activity with high temporal resolution and is ideal to study the functional changes in pain. In particular, EEG can be obtained non-invasively to provide high temporal resolution neural signals. However, more information on the EEG signals present at the precise onset of pain needs to be further investigated. Identifying these signals from distributed cortical circuits may reveal important information on the mechanisms of pain, and in the future could guide the optimization of neuromodulation therapies for pain.

METHODS: This is a prospective, observational study. A 64 channel EEG system in addition to pinpricks of varying pain intensities were utilized. During the EEG recordings the pinpricks were administered in a random order to both the lower back and the back of the hand to subjects with chronic low back pain and pain-free controls. The subjects' eyes remained opened while covered, limiting subject anticipation of the pinpricks. Enrollment is ongoing, with 27 subjects enrolled thus far from a single, urban academic institution. We developed an unsupervised machine learning method for sequential detection of acute pain signals based on EEG recordings. Specifically, signals from regions of interests (ROIs) were first estimated with EEG source localization, followed by a state-space model (SSM) to identify the onset of pain signal. Additionally, we also ran a supervised learning analysis based on a support vector machine (SVM) classifier to compare their detection accuracy. We used nonparametric statistical tests to assess the statistical significance based on the significance level of $p<0.05$. All data analyses reported were conducted in Python or MATLAB.

RESULTS: Our preliminary results suggest that SSM-based detection method was successful in two human EEG datasets including one public EEG recording of 50 subjects. Though the detection accuracy of the onset of pain varied between subjects and modality, it was feasible to predict the detection of acute pain signals. Additionally, our preliminary results also demonstrated good generalization ability, and showed the feasibility in cross-subject and cross-modal detection. The proposed unsupervised learning method requires fewer training trials while achieving similar or improved detection performance than the supervised learning methods.

CONCLUSION: We developed an unsupervised SSM-based method in conjunction with EEG source localization to detect the onset of acute pain signals in human subjects, and our approach showed a good performance in detection accuracy and generalization ability.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 25

Isoflurane exposure disrupts metabolic fluxes in neonatal brain

Kevin N Su[1], Rebecca L Bornstein[1], John Snell[2], Philip Morgan[1], Margaret Sedensky[1], Simon Johnson[1]

[1]University of Washington, Seattle, WA, [2]Seattle Children's Research Institute, Seattle, WA

INTRODUCTION: Volatile anesthetics are widely utilized in modern medicine, yet their precise targets and underlying molecular mechanisms remain poorly defined. While these anesthetic agents are considered safe in healthy individuals, there is evidence of anesthetic sensitivity and toxicity in select clinical populations, including children with mitochondrial disease[1]. Recent animal studies have also demonstrated that neonatal mammals and developing invertebrates are susceptible to CNS damage following extended exposure to volatile anesthetics[2]. Together, these data suggest that the toxic effects of volatile anesthetics may be mediated by molecular mechanisms that are unique to neonates. We have recently uncovered that volatile anesthetic exposure results in significant reductions of circulating ketone and glucose levels in neonatal mice. Here, we have elucidated a novel molecular mechanism that underlies the potent metabolic effects of volatile anesthetic exposure specific to neonates.

METHODS: All rodent experiments were approved by the Institutional Animal Care and Use Committee of Seattle Children's Research Institute. Blood ß-hydroxybutyrate and glucose levels were measured using point-of-care ketone/glucose meters. To investigate the dynamic metabolic changes with isoflurane exposure, we developed a novel ex vivo metabolomic assay that utilizes stable isotope tracing with 13C-glucose. Statistical analyses were performed using GraphPad Prism.

RESULTS: Isoflurane exposure led to a rapid and sustained depletion of circulating levels of ß-hydroxybutyrate in neonatal mice at postnatal day 7 (P7). The disruption in ketogenesis was observed at varying concentrations of isoflurane, even those well below the anesthetizing dose of 1.5%. However, in adolescent animals at P30, isoflurane had no impact on blood ketone levels. Isoflurane exposure also resulted in profound hypoglycemia, which was attenuated by ß-hydroxybutyrate, but not glucose, injections. Given that both ß-hydroxybutyrate and glucose are key metabolic substrates for the brain, we developed a novel metabolomic assay to examine the effects of isoflurane on dynamic metabolic fluxes in neonatal cortex ex vivo. Isoflurane exposure led to striking TCA cycle perturbations. Percentage of 13C-labeled citrate was increased by threefold in the 1.5% isoflurane exposed group as early as 2 minutes (6.50% vs. 2.21%, $p<0.05$). There was also a significant elevation of labeled isocitrate that persisted up to 30 minutes (24.80% vs. 18.21%, $p<0.05$). While pyruvate levels did not differ between groups, isoflurane exposure caused a nearly threefold increase in labeled lactate and alanine levels at 5 minutes (all $p<0.001$). A concomitant treatment of ß-hydroxybutyrate attenuated the increase in labeled citrate and isocitrate in the isoflurane exposed group but had no effects on lactate or alanine.

CONCLUSION: We developed a targeted metabolomic approach to study dynamic metabolic flux through glycolysis and TCA cycle in neonatal brain. Our data demonstrate that short-term exposure to volatile anesthetics results in substantial disruptions in cerebral metabolism, including a striking accumulation of citrate and isocitrate. Our results uncover a novel molecular mechanism that underlies the physiologic effects of volatile anesthetics on neonatal metabolism. These mechanistic links reveal potential therapeutic targets for the prevention of volatile anesthetic induced neurotoxicity in vulnerable populations.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 26

Isoflurane specifically inhibits endocytosis due to acute ATP depletion in mouse neurons: a mechanism of action for volatile anesthetics

Phil Morgan[1], Margaret Sedensky[1], Pavel Zimin[2], Sangwook Jung[1], Christian Woods[2], Jan-Marino Ramirez[2]

[1]University of Washington, Seattle, WA, [2]Seattle Children's Research Institute, Seattle, WA

INTRODUCTION: Volatile anesthetics (VAs) selectively inhibit mitochondrial complex I of the electron transport chain; defects in complex I cause VA hypersensitivity in nematodes, flies, mice and humans[1-4]. Spontaneous excitatory presynaptic frequencies are decreased by VAs[5]. The pattern of presynaptic inhibition in hippocampal CA1 neurons is consistent with failure of neurotransmitter cycling and is seen at lower VA concentrations in the mitochondrial mutant, Ndufs4(KO), than in wildtype. In order to identify which synaptic functions are most sensitive to VA inhibition, we investigated synaptic vesicle cycling during exposure to isoflurane (ISO) in hippocampal cultures from Ndufs4(KO) and wild type mice. We also investigated the relationship between intracellular ATP and vesicle dynamics in this system.

METHODS: All studies were approved by the local IACUC committee. Cells from the hippocampus of P0-P1 Ndufs4 floxed mice were grown in culture for 7-10 days. Cells were transfected with a construct containing a FRET sensor to measure relative ATP concentrations, VGLUT1-pHluorin to measure synaptic vesicle cycling and an mCherry-synaptophysin (to identify synaptic boutons)[6]. To generate Ndufs4(KO) cells, Cre-recombinase was also transfected into cells from Ndufs4 floxed mice. Increases in pHluorin fluorescence were recorded upon high frequency stimulation (HFS) with and without ISO. Cells were supplemented with pyruvate to support mitochondrial function while glucose was varied to restrict or support glycolysis. Extracellular acidification was used to measure reuptake of synaptic vesicles into the presynaptic cell.

RESULTS: At baseline, mitochondrial respiration is similar in control and Ndufs4(KO) hippocampal cultures indicating similar baseline energy stores (Fig 1). At physiologic concentrations of glucose, in both genotypes high frequency stimulation (HFS) increased VGLUT1-pHluorin fluorescence (synaptic vesicle exocytosis) followed by rapid return to baseline (endocytosis) (Fig 2A). Endocytosis, but not exocytosis, was delayed in both wildtype and KO cultures exposed to ISO at their behavioral EC95 (WT, 1.8% isoflurane, 0.74mM; KO, 0.6% isoflurane, 0.25mM) (Fig 2B). Exposure to high concentrations of glucose to artificially support glycolysis and with pyruvate to support mitochondrial respiration led to improved endocytosis in ISO (Fig 2C). Decreased extracellular glucose greatly increased the endocytosis blockade by ISO (Fig 2D). HFS did not prolong decreases in ATP concentrations in boutons of either genotype when not exposed to ISO (Fig 3A). HFS of cells superfused with ISO at their EC95s and glucose/pyruvate as in Figure 2, reduced ATP concentrations to similar degrees in both genotypes, matching their whole animal behaviors (Fig 3B-C). Extracellular acidification caused a return of pHluorin fluorescence to baseline (Fig 4) indicating that the block in endocytosis, associated with decreased ATP levels, occurred at reuptake of synaptic vesicles into the presynaptic cell (Fig 5). Legends. Fig 1. Oxygen uptake from control and KO cells shows similar baseline and stimulated rates when neurons are quiescent, indicated similar ATP production. Fig 2.A Exocytosis (upslope of fluorescence) and endocytosis (downslope) during HFS stimulation (blue bars) are rapid in absence of ISO for WT and KO cells. B-C. Endocytosis shows an increasing defect in presence of ISO as glucose is restricted. Fig 3.A. ATP levels decrease during HFS stimulation but recover rapidly in absence of ISO. B-C. ATP levels show an increasing deficit as glucose is restricted in the presence of ISO. Fig 4. Fluorescence rapidly decreases when acidic buffer (MES, pH 5.5) is superfused showing that pHluorin is on the cell surface. Fig 5. The resulting model for the action of ISO at the presynapse to inhibit neurotransmission.

CONCLUSION: The data indicate that clinical concentrations of isoflurane inhibit mitochondrial ATP production with resulting failure of presynaptic endocytosis. Endocytosis is blocked at the step of reuptake of synaptic vesicles from the presynaptic cell surface. Inhibition of presynaptic mitochondrial complex I occupies a central role in the mode of action of VAs, the failure of synaptic transmission.

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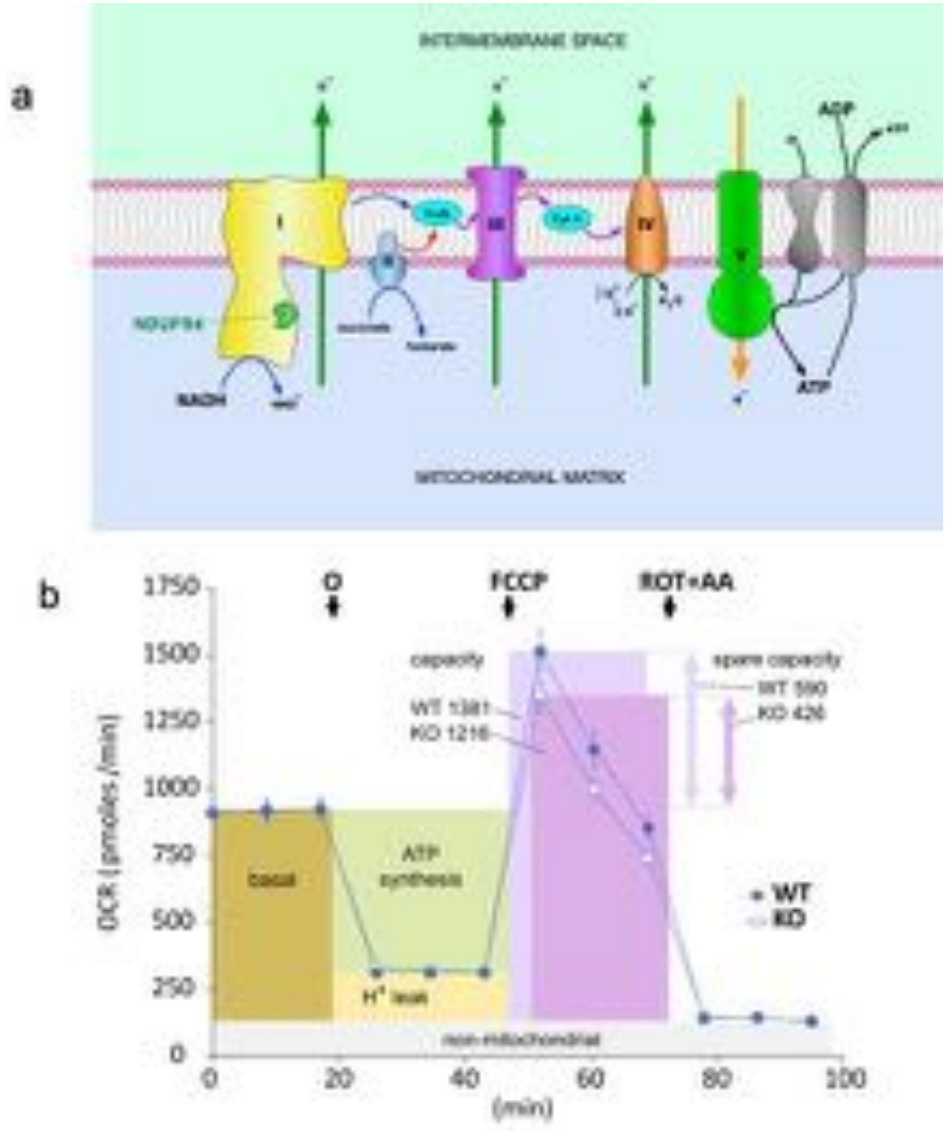

Fig. 1

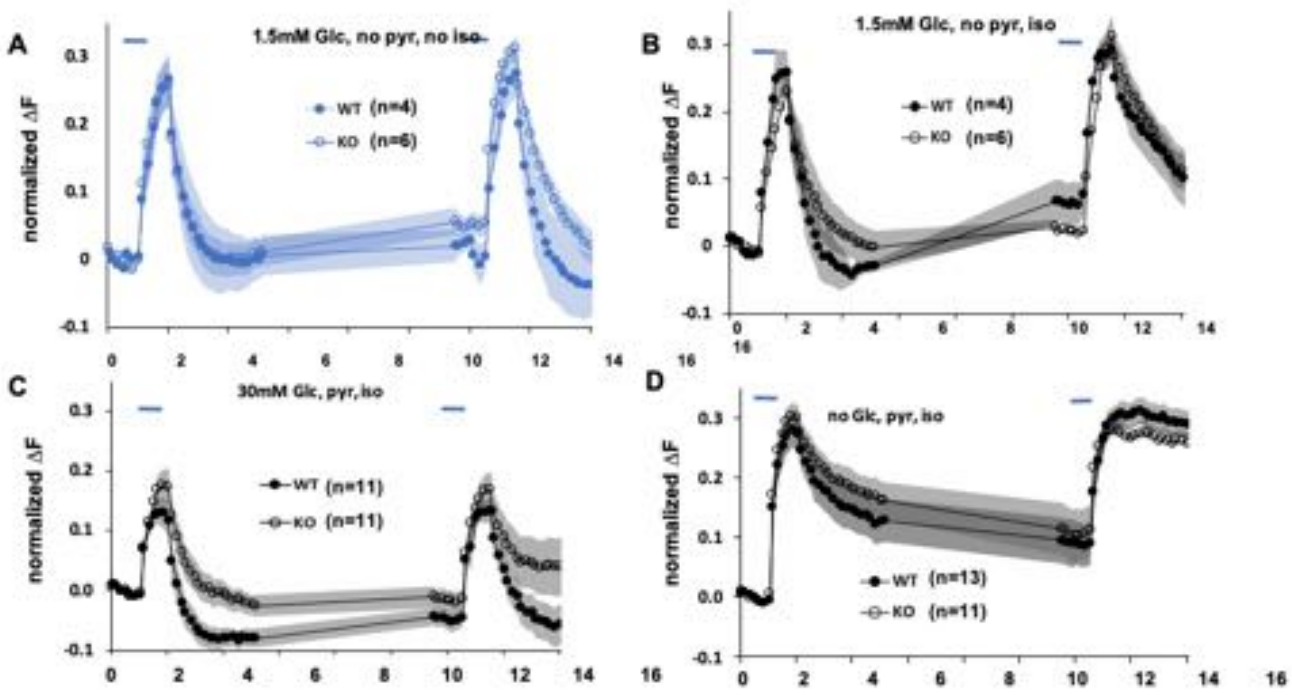

Fig. 2

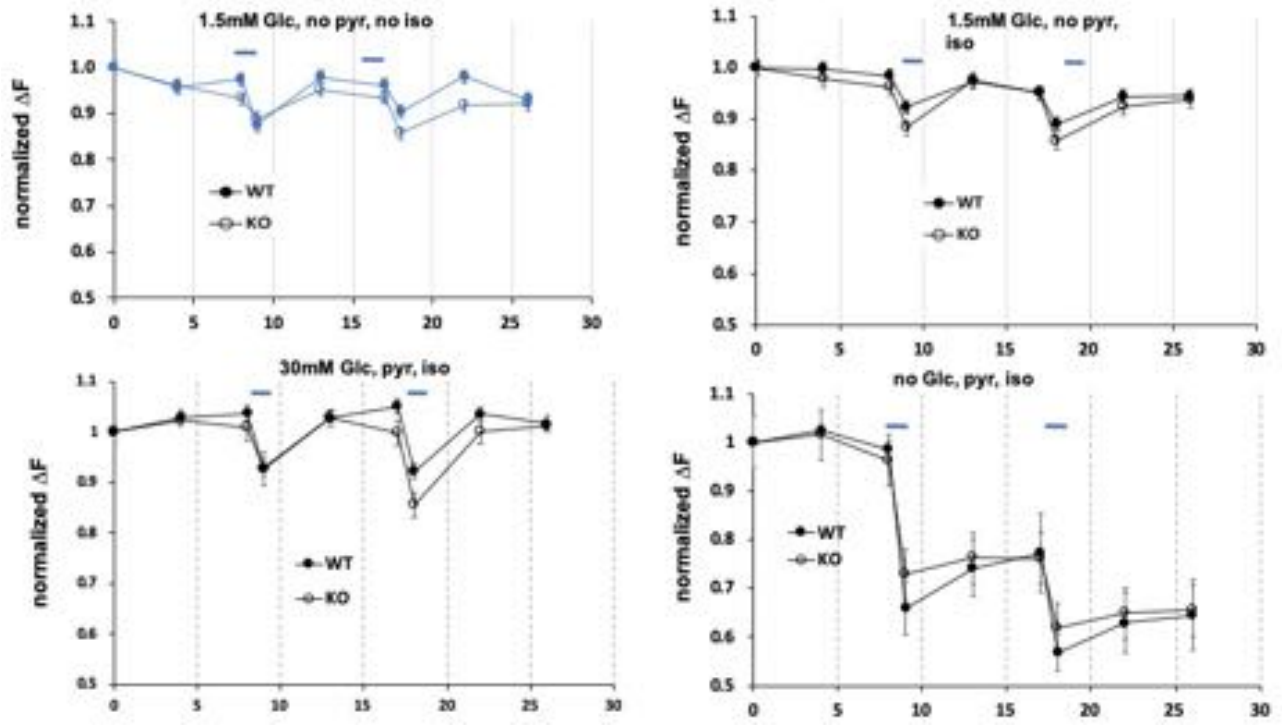

Fig. 3

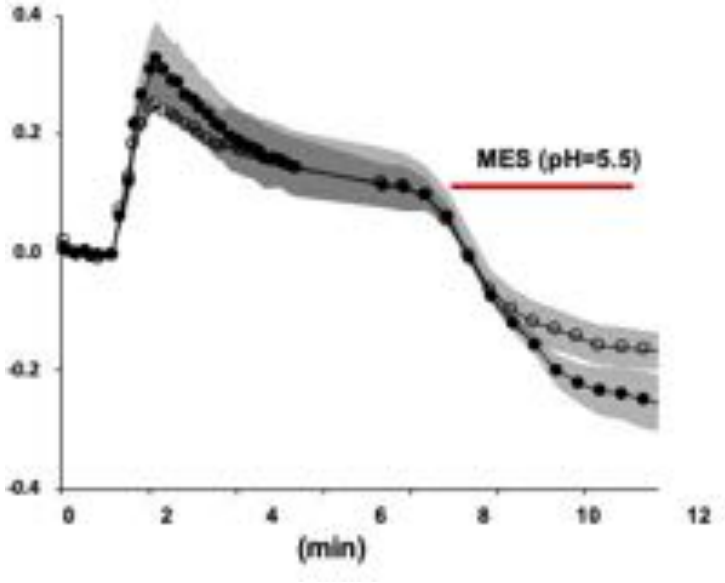

Fig. 4

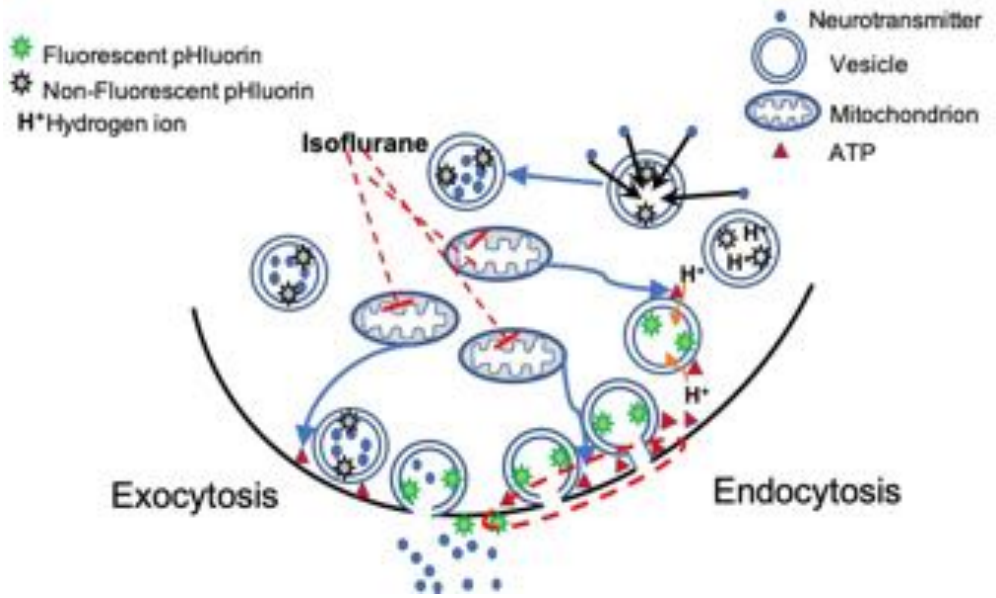

Fig. 5

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 27

Anesthesia and Clock Drawing Performance as Predictors of Length of Stay in Older Adults Undergoing Total Knee Arthroplasty

Catherine Dion[1], Jared J Tanner[1], Margaret Wiggins[1], Shawna Amini[1], David J Libon[2], Hari K Parvataneni[1], Chancellor F Gray[1], Hernan Prieto[1], Patrick J Tighe[1], Catherine Price[1]

[1]University of Florida, Gainesville, FL, [2]Rowan University, Glassboro, NJ

INTRODUCTION: Older adults are increasingly electing surgical procedures such as total knee arthroplasty (TKA) where anesthesiology teams choose between anesthetic approaches; spinal (SA) vs. general (GA) anesthesia. Although anesthesiologists are increasingly considering preoperative cognition when choosing anesthesia approach for these patients, little is known scientifically regarding how preoperative cognition interacts with anesthesia approach thereby producing different outcomes. Although some studies suggest TKA under GA leads to increased length of stay (LOS) (Wilson et al., 2019), it is unknown if this finding is partially attributed to preoperative cognitive status. Objective: Using a convenience sample from a federally funded investigation, we retrospectively examined the interaction between anesthesia approach (SA/GA) and preoperative cognitive screening metrics on LOS for adults age 65+ electing TKA. Cognitive screening was completed with digitally acquired clock drawing to command and copy conditions. Research from our team has shown that the copy condition (Amini et al., 2019) and specific latency and graphomotor metrics from this condition (Wiggins et al., in press) are important for predicting LOS across different surgical samples, and have neurobiological and neuropsychological validity (Dion et al., 2020; Formanski et al., 2021). The interaction of these clock variables with anesthesia approach in TKA, however, has not been examined. We therefore explored the interaction between anesthesia approach and copy clock drawing performance on LOS.

METHODS: Data were acquired from a NIH funded investigation examining digital clock drawing performance in adults age 65+ completing clock drawing throughout a tertiary care hospital prior to all elective surgeries. Data were acquired through honest broker and IRB approved methods from data from January 2018 to December 2019 for TKA only. Digital clock variables of interest: Latency: 1) total completion time in seconds (TCT), 2) time prior to setting the first hand in seconds (pre-first hand latency; PFHL), 3) seconds after placing the clock face to next pen stroke (post-clock face latency; PCFL); Graphomotor: 1) hour hand distance from center, and 2) digit misplacement (sum of each digit's degree of absolute deviation from ideal placement). Outcome: LOS (hours).

RESULTS: Final sample (GA, n=202; SA, n=78) did not statistically differ in age, education years, comorbidity, or ASA score (p= .063 - .974). Separate analysis of variance (ANOVA) showed significant main effects of Group [$F(1,278)= 11.076$, $p< .001$, $\eta^2= .039$; general > spinal], Copy PFHL [$F(1,278)= 4.926$, $p= .027$, $\eta^2= .018$]. Interactions were significant for Group x Copy PFHL [$F(1,278)= 3.964$, $p= .047$, $\eta^2= .014$] such that only individuals with slower time to first hand placement and who received SA experienced longer LOS, and Group x Copy hour hand distance from center [$F(1,276)= 5.505$, $p= .020$, $\eta^2= .020$] such that GA individuals with greater hour hand distance from center had longer LOS.

CONCLUSION: These retrospective data of demographically similar groups receiving TKA under GA or SA suggest further research is needed to understand baseline cognitive characteristics and choices for GA vs. SA. Clock drawing latency variables and graphomotor variables show unique neurobiological contributions and may prove useful for anesthesiologist consideration regarding anesthesia approach. Data argue for conducting prospective anesthesia randomized studies with a) participants representing a range of cognitive profiles and b) digital metrics sensitive to behavioral nuances. Grant Funding: R01AG055337 (CP/PT).

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 28

Electroencephalographic Characteristics Associated with the Use of Dexmedetomidine During Supratentorial Craniotomies

Shilpa Rao[1], Cinira Diogo[2], Brooke Callahan[2], Miriam Treggiari[3]

[1]Yale University/Yale School of Medicine, Wallingford, CT, [2]Nuvasive Clinical Services, New Haven, CT, [3]Yale University, New Haven, CT

INTRODUCTION: Neurosurgical procedures involving eloquent cortex and critical neurovascular structures require extensive multimodal neuromonitoring to allow the assessment of different anatomical brain structures. The most common neuromonitoring modalities employed during supratentorial brain surgeries are electroencephalography (EEG), motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP). It is particularly challenging to optimize the anesthesia approach for the simultaneous acquisition of EEG and MEPs. To allow reliable simultaneous neuromonitoring of EEGs and MEPs, the neuroanesthesiology team at Yale New Haven Hospital has successfully introduced the use of dexmedetomidine in combination with reduced MAC of sevoflurane and opioids, as a balanced protocol for multimodal neuromonitoring during supratentorial brain surgeries. Currently there are limited data available regarding the characteristics of intraoperative EEG changes associated with the use of dexmedetomidine in adult patients undergoing neurosurgical procedures. We designed a retrospective observational study to determine differences in intra operative EEG signals resulting from the use of dexmedetomidine, compared with a balanced general anesthesia using propofol without dexmedetomidine.

METHODS: This retrospective cohort study was approved by the Yale IRB with a waiver of informed consent. Eligible patients were adults older than 18 years of age, who underwent elective supratentorial brain tumor resections or carotid endarterectomy, with intraoperative use of continuous EEG monitoring, and a surgical duration >2 hours. EEG and Data Processing Intraoperative EEG was recorded using an 8 channel Cadwell Intraoperative Monitoring System.For each patient, a total of 9 high quality EEG recordings (free from noise and artifacts) were collected on a 3-3-3 basis corresponding to beginning-mid-end of procedure, during which infusions of propofol and/or dexmedetomidine were stable. Conversion of the raw EEG file to the European Data format was performed by data extraction software commercialized by Cadwell. The unprocessed electroencephalogram and its spectrogram were used to characterize the EEG signature.[3,4] The EEG data was merged with demographics, anesthesia, medications and physiology data abstracted from the Electronic Health Record. During the EEG intervals, the following data were recorded: Rate and dose of propofol or dexmedetomidine infusions, MAC of sevoflurane, vitals including blood pressure, end tidal CO2, temperature, respiratory rate and any medication bolus. We categorized patients into 2 groups: 1. Utilization of propofol infusion as part of intra operative anesthesia without dexmedetomidine (Prop group); and 2. Utilization of dexmedetomidine infusion (without propofol) as part of intra operative anesthesia (Dex group). We compared patients' characteristics between the two groups using two-sample Student's t-test for continuous variables or chi-square test for categorical variables. A two-sided alpha level less than 0.05 was required for statistical significance. In this report, we present preliminary data for the first 27 patients included.

RESULTS: 16 patients were in the Dex group and 11 in the Prop group. Mean surgery duration was 224 (SD 114) min in the Dex group and 187 (SD 93) min in the Prop group. Average infusion rate of dexm was 0.62 mcg/kg/hour and average infusion rate of prop was 80 (SD 24) mcg/kg/min. Average infusion rate of remifentanil was 0.2 (SD 0.06) mcg/kg/min in the Dex group and 0.18 (SD 0.04) mcg/kg/min in the Prop group. Sevoflurane MAC was 0.89 (SD .26) in the Dex group and 0.46 (SD 0.39) in the Prop group ($p<0.01$). Hemodynamic profiles were comparable between the two groups. Fig 1 and 2 show a representative spectrogram of two patients that received either propofol or dexmedetomidine. Patterns suggest higher global suppression & greater power in theta range for the prop group. There was greater power in the alpha range with spindles in the 12-15 Hz range for the dex group. Both groups showed the greatest power in the delta range.

CONCLUSION: We found higher global suppression and greater power in theta range for the propofol group, while there was greater power in the alpha range with spindles in the 12-15 Hz range for the dexmedetomidine group.This is important to correctly interpret EEG signals and choose the optimal combination of anesthetic techniques during supratentorial craniotomies in which EEG monitoring is utilized.

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Figure 1.

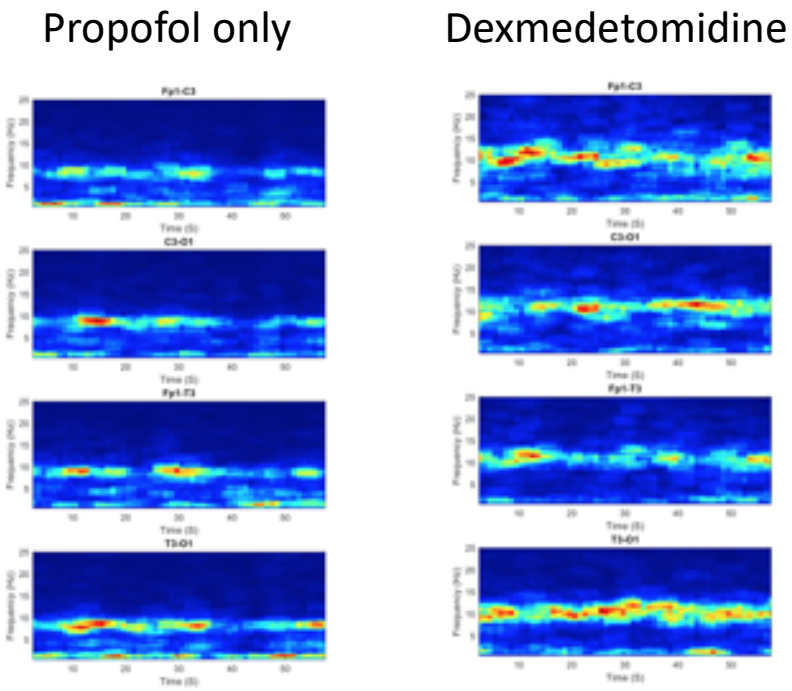
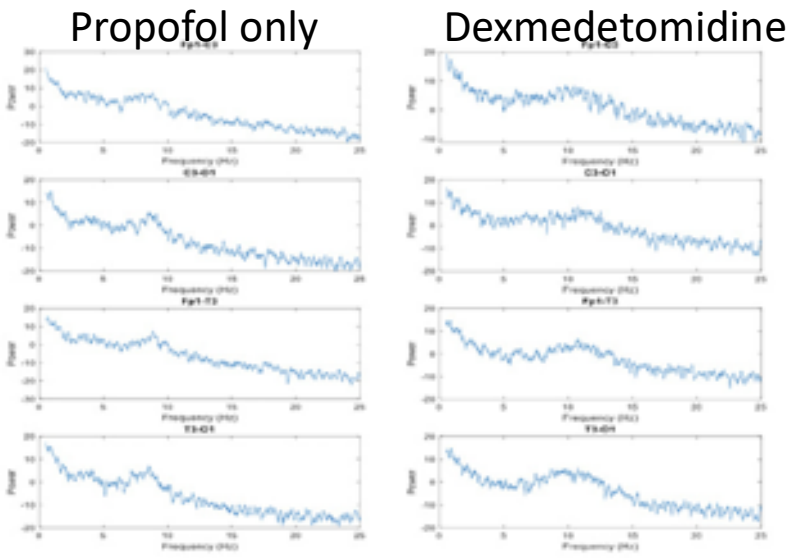


Figure 2.



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 29

Effect of Spaced Learning on Acquisition of Factual Knowledge of Monitoring and Dosing of NMB and Reversal Agents and its Impact on Clinical Practice

Robert Gregory[1], Sheila Blogg[1], David Eberle[2], Harvey Woehlck[1], Cynthia A Lien[1]

[1]Medical College of Wisconsin, Milwaukee, WI, [2]Froedtert Hospital, Milwaukee, WI

INTRODUCTION: Neuromuscular blockade (NMB) is an integral part of perioperative care and in spite of many chapters, publications and presentations, practices in terms of monitoring depth of NMB and dosing of neuromuscular blocking agents (NMBA) and reversal agents remain variable and postoperative complications resulting from residual NMB are not rare. A single report of education and close follow up by departmental administration documented the ability to increase routing quantitative monitoring, decrease residual NMB and eliminate the need for reintubation following surgery because of respiratory failure secondary to inadequate recovery of neuromuscular function. We hypothesized that with spaced learning, retention of information regarding NMB monitoring and dosing of NMBAs would be improved and that this would result in increased quantitative monitoring of depth of NMB and more correct dosing of NMBAs and reversal agents.

METHODS: This study was done as a quality improvement project and determined to be exempt from IRB approval. A 20-question pretest was distributed to all members of the department of anesthesiology (faculty, residents and advanced practice professionals) in March of 2019, one week before a Grand Rounds Presentation on NMB and reversal agents, risks of residual NMB, quantitative monitoring of depth of NMB, and costs of NMB and reversal agents. Assessment of retention of knowledge was performed by distributing the identical test two weeks and then 10 months after the presentation. Percent correct answers on each of the pre-and post-tests were compared using paired t-tests. Additionally, questions were grouped into target areas and the % or correct answers were determined. The anesthetic records of all patients receiving a non-depolarizing NMBA during the two months preceding the Grand Rounds presentation, the two months immediately following, and the two months preceding the 10-month assessment were collected. Each anesthetic record was assessed for use of a monitor of depth of NMB and dosing of reversal agents.

RESULTS: 166 anesthesiologists and CRNAs participated in the pre-test, 81 completed the post-test at two weeks, and 71 completed the post-test 10 months later. 59 completed the pre-test and post-test at two weeks while 53 completed the pre-test and post-test at 10 months. Only 20 individuals completed all three tests. One question was excluded from analysis due to multiple correct answers. With the exception of test questions related to the adequacy of neuromuscular function, the % of correct answers increased from the pre-test and that continued through to the 10-month post-test (Figure 1). The average pre-test scores among all test-takers was 67.5%, 73.8% at two-weeks, and 76.6% at 10 months. Among test takers who completed the pre-test and post-test at two weeks there was a statistically significant increase in percent questions correct ($p = 0.0024$). Among test takers who completed the pre-test and post-test at 10 months there was also a statistically significant increase in percent questions correct ($p = 0.000235$). There was no statistically significant difference between post-test at two weeks and at 10 months (77% vs. 78.7%, p-value=0.632). Data from chart reviews is still being collected.

CONCLUSION: Neuromuscular blockade and reversal are often misunderstood among members of the anesthesia care team and are among the factors leading to variable dosing and monitoring practices. Understanding of dosing of NMB and reversal agents and proper monitoring of depth of NMB was variable among anesthesiology faculty, staff and residents. There was a small but statistically significant increase in scores among those who participated in the pre- and post-test at two weeks and the pre- and post-test at 10 months, showing that knowledge was gained from the Grand Rounds presentation. There was no evidence of degradation of knowledge at 10 months, supporting that spaced learning assists in knowledge retention. Current in-process investigations of chart analysis to identify use of monitoring of depth of NMB and dosing of reversal agents are underway to determine if the documented changes in knowledge impacted monitoring and dosing practices.

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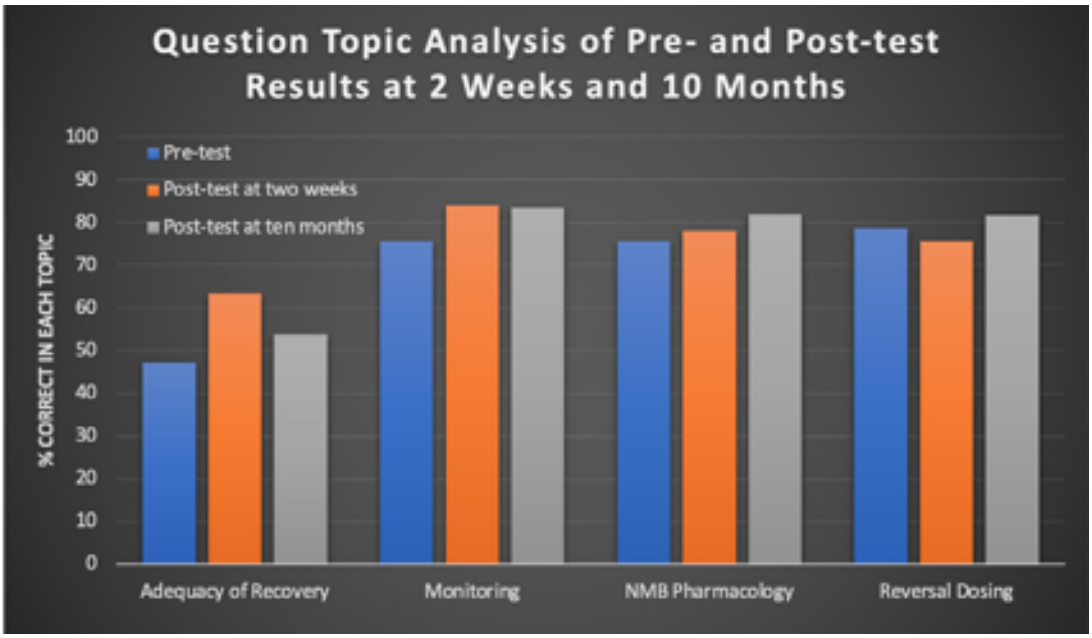
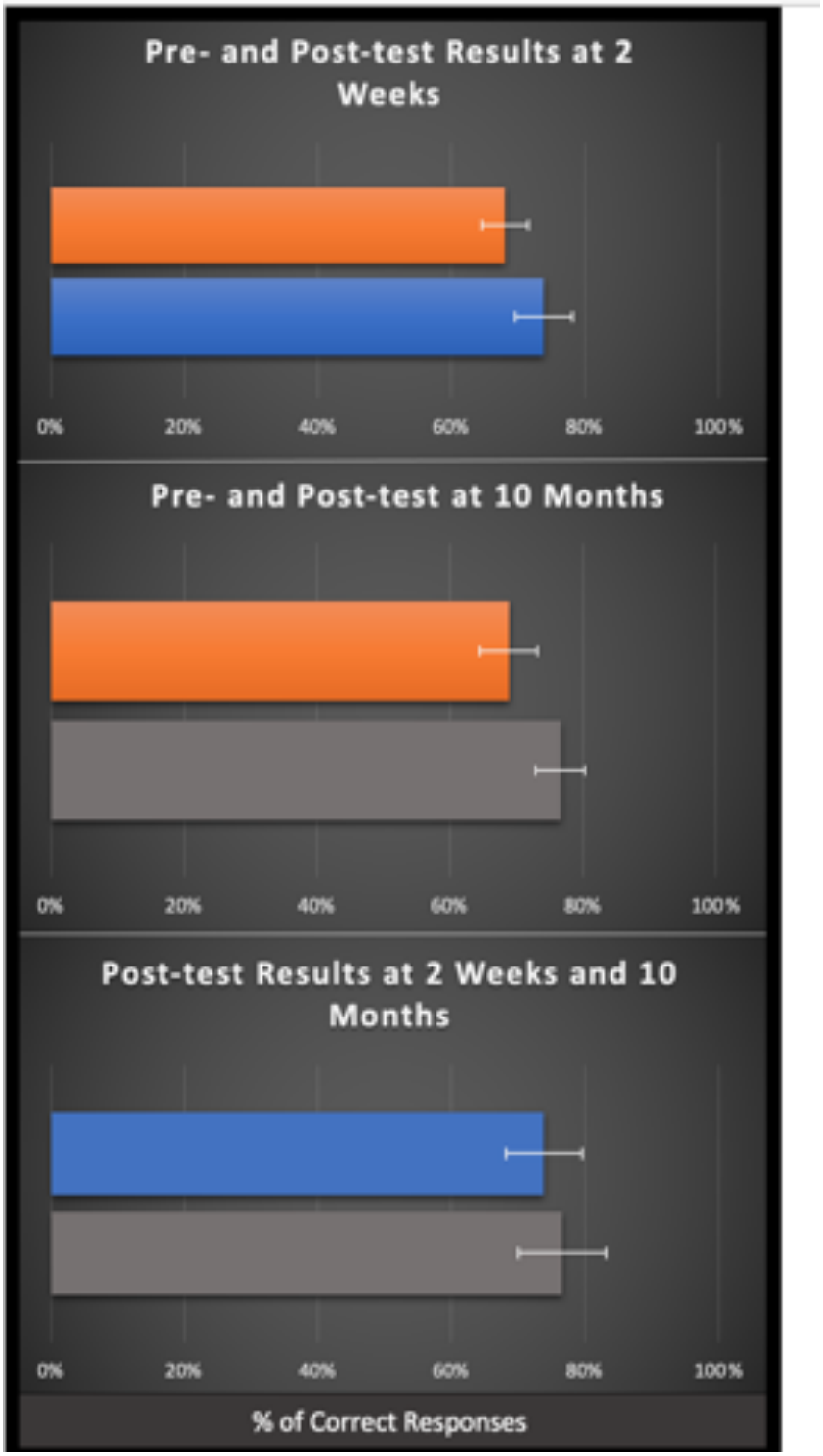


Fig. 1

Figure 2: (Pre-Test, Post-Test at 2 Weeks, Post -Test at 10 Months)



NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 30

Electroencephalogram signatures of ketamine general anesthesia induced dissociation

Isabella Turco[1], Katherine Adelsberger[1], Katia Colon[1], Shubham Chamadia[1], Oluwaseun Johnson-Akeju[2]

[1]Massachusetts General Hospital, Boston, MA, [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA

INTRODUCTION: Dissociation is an altered behavioral state accompanied by reduced self-awareness, emotional detachment, and distorted perception of reality[1]. Dissociation can be an undesired side-effect of anesthetic drugs such as ketamine, a phencyclidine analog that is commonly administered as part of general anesthesia. In this study, we aimed to characterize the electroencephalogram (EEG) correlates of ketamine-induced dissociation.

METHODS: The Partners Institutional Review Board approved this human research study (2018P000417) registered on www.ClinicalTrials.gov (NCT03553758). Details of our subject recruitment and study design have previously been reported[2]. Briefly, we administered and allowed recovery from ketamine general anesthesia (2 mg/kg) in 15 healthy subjects. 2 mg of midazolam was administered post ketamine-recovery to attenuate dissociation. We recorded high-density EEG and longitudinally assessed subject-reported dissociation using the Clinician-Administered Dissociative States Scale (CADSS)[3]. Figure 1a illustrates schematic of the study design. The EEG data was down-sampled to 250 Hz and remontaged using nearest neighbor Laplacian referencing scheme. Data from three channels was averaged to approximate both frontal (Fz) and occipital (Pz) channel location. Five 2-min EEG epochs of interest were extracted: baseline (2 minutes prior to ketamine administration), ketamine (2 minutes post ketamine administration), pre-midazolam (3 minutes prior to midazolam administration), post-midazolam (3 minutes post midazolam administration) and emergence (2 minutes post last CADSS assessment). We computed multitaper spectral estimates using MATLAB toolbox. Measures of global coherence were estimated using methods previously described[4].

RESULTS: No serious adverse events were reported during this study. Mean longitudinal CADSS score have been reported in table 1[2]. Group-average frontal spectrogram (Fig. 1b), occipital spectrogram (Fig. 1c), baseline-normalized frontal spectra (Fig. 1d), baseline-normalized occipital spectra (Fig. 1e), and baseline-normalized spatial head plots (Fig. 1f) are presented. Compared to baseline, ketamine administration was associated with an increased slow-delta, theta, and frontally dominant beta-gamma oscillation power. Strikingly, midazolam administration was associated with an increase in frontally dominant beta oscillation power and decreased dissociation as measured by CADDS. However, none of the oscillatory dynamics we elicited on the surface EEG correlated with dissociation.

CONCLUSION: While commonly used as an anesthetic adjunct for its analgesic properties, ketamine's undesirable dissociative properties are not well understood. Previous studies have suggested that gamma oscillations are fundamental to ketamine associated dissociation. In contrast, our current study supports recent findings that suggest dissociation-associated rhythms are located in deep brain regions that are not reflected on the surface EEG[5]. Future intracranial studies of ketamine in humans may advance our knowledge of neural circuits underlying dissociation.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 31

Brain-wide unbiased mapping of neuronal activity pinpoints ketamine's interaction with the opioid system in mice

Daniel Ryskamp[1], Tuuli Hietamies[2], Sofia Schlozman[2], Pierre Llorach[2], Juliana S Salgado[2], Daniel A Barbosa[3], Boris D Heifets[4]

[1]Stanford University, Stanford, CA, [2]Stanford University, Stanford, United States of America, [3]Stanford University School of Medicine, Stanford, United States of America, [4]Stanford University School of Medicine, Palo Alto, CA

INTRODUCTION: A diagnosis of depression strongly predicts poor postoperative outcomes, including chronic pain and opioid use disorder. Perioperative interventions for depression are largely absent because available treatments have limited efficacy and are difficult to implement on a perioperative timetable. Considerable evidence now shows that ketamine (KET) has a rapid-onset, large effect size for the treatment of depression. Developing safer, better KET-like drugs requires a clear understanding of KET's mechanism of action. KET's mechanism involves NMDA receptor (NMDAR) antagonism, but other NMDAR antagonists fail to mimic the diversity of KET's clinical effects. We recently found that the antidepressant effect of KET is blocked by the opioid receptor antagonist naltrexone (NAL) in humans[1]. This finding adds to evidence for a complex interaction between KET and the opioid system, as KET can also markedly potentiate opioid analgesia and prevent opioid-induced hyperalgesia. We hypothesize that a discrete set of neuronal circuits exist that are activated by KET, but not by KET + NAL. Here, we use an unbiased, whole-brain approach to identify brain regions in which neuronal activity is selectively modulated by KET in an opioid receptor-dependent manner.

METHODS: All mouse experiments were approved by the Stanford IACUC. Mice were injected with either KET (10 mg/kg i.p.) with or without pre-injection of an opioid receptor antagonist, naltrexone (NAL; 5 mg/kg i.p.) 30 min prior. Mice were perfused 90 min after injection of ketamine with 4% PFA, brains were bisected, made optically transparent with the iDISCO+ protocol, and immunolabeled for cFos to fluorescently label neurons that were active during KET exposure. Light sheet microscopy was used to acquire Z-stacks spanning each hemisphere. Using open-source software (MIRAcL[2] and Ilastik[3]), we registered images to the Allen brain atlas5, detected active cells based on sparse user input and machine learning, and quantified voxelized regional cell counts.

RESULTS: The total number of cFos+ (active) neurons was similar in KET (114322 ± 9912 cells; N = 10) and NAL/KET hemispheres (123174 ± 11471 cells; N = 7). Counts from 486 grey matter regions were normalized to total counts. We found that NAL significantly decreased the number of cFos+ cells in layer 5 of the lateral agranular retrosplenial cortex (KET = 0.005071 ± 0.00037 vs. KET + NAL = 0.003902 ± 0.000358 cells/total brain cells; p = 0.0453) and of the ventral retrosplenial cortex (KET = 0.006853 ± 0.000421 vs. KET + NAL = 0.005622 ± 0.000303 cells/total brain cells; p = 0.0461). NAL, also suppressed activity in the adjacent posteromedial visual area (layer 5) and anteromedial visual area (layer 6a) in addition to a number of subcortical regions such as the inferior colliculus, substantia nigra pars reticulata, arcuate hypothalamic nucleus, superior olivary complex (periolivary region), pontine reticular nucleus medial vestibular nucleus, and facial motor nucleus. NAL also enhanced activity in several regions including the temporal association areas, primary somatosensory areas, intercalated amydalar nucleus, and pre/parasubthalamic nucleus.

CONCLUSION: Through unbiased whole-brain mapping of neurons differentially activated by SAL/KET vs NAL/KET, we identified a novel network of brain regions that may mediate some of KET's opioid receptor-dependent clinical effects. Recent data suggests that a 1-3-Hz rhythm in layer 5 neurons of the retrosplenial cortex is associated with dissociation from drugs or certain seizures[4]. Ketamine injection drives cFos expression in layer 5 neurons of the retrosplenial cortex[4] in an opioid-receptor dependent manner, suggesting a role for dissociation and opioid receptor activation in the antidepressant effect of KET. Future work will test for causal links between these structures' activity and ketamine's efficacy in animal models of pain and depression.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 32

Brain wide mapping of neuronal activity evoked by MDMA, a rapid-acting therapy for post-traumatic stress disorder

Daniel Ryskamp[1], Pierre Llorach[2], Sofia Schlozman[2], Zahra Rastegar[2], Juliana S Salgado[2], Tuuli Hietamies[2], Daniel A Barbosa[2], Daniel Cardozo Pinto[2], Peter Neuman[2], Michel Hell[3], Kevin Beier[2], Robert C Malenka[2], Boris D Heifets[4]

[1]Stanford University School of Medicine, Stanford, CA, [2]Stanford University School of Medicine, Stanford, United States of America, [3]Federal University of Juiz de Fora, Juiz de Fora, Brazil, [4]Stanford University School of Medicine, Palo Alto, CA

INTRODUCTION: Psychiatric diagnoses, including depression and post-traumatic stress disorder (PTSD), strongly predict poor postoperative outcomes, including chronic pain and opioid use disorder. Perioperative interventions for psychiatric risk are largely absent because available treatments have limited efficacy and are difficult to implement on a perioperative timetable. Recent evidence supports the efficacy of rapid-acting therapies in treating psychiatric diseases, with notable results from pharmacotherapy with drugs like ketamine, a well-known anesthetic, and MDMA, a substituted amphetamine. We focus here on MDMA, the recreational drug known as 'ecstasy', which has a large effect size for the treatment of PTSD. For patients with PTSD in therapy, MDMA fosters strong feelings of social connection, empathy and trust. However, MDMA has abuse potential, and long-term heavy use is associated with a host of neurological, psychiatric and cardiovascular complications. Improving on MDMA to develop a safe, rapid treatment for patients with PTSD requires an understanding of the neural circuit mechanism underlying MDMA's therapeutic effects. We have shown that a mouse model recapitulates the prosocial effects of MDMA, key to MDMA's therapeutic effect in humans. We now use an unbiased, whole-brain approach to identify brain regions in which neuronal activity is modulated by MDMA in non-social and social contexts in mice.

METHODS: All mouse experiments were approved by the Stanford IACUC. Brain-wide activity, indexed by the immediate early gene Fos, was imaged for two distinct behavioral states (social and nonsocial) in each mouse by sequential use of the TRAP2 activity reporting and conventional cFos staining. TRAP2 mice (Targeted Recombination in Active Populations 2)[1] contain a genetic construct that allows the neuron firing-dependent Fos promoter to drive expression of CreER, a recombinase sensitive to 4-hydroxytamoxifen (4-OHT). TRAP2 mice were crossed to a Cre-dependent reporter line (Ai14). 4-OHT transiently enables CreER to trigger permanent expression of the fluorophore tdTomato (encoded by Ai14). To map MDMA effects in a non-social environment, TRAP2;Ai14 mice were singly housed and i.p. injected with saline or MDMA (7.5 mg/kg), along with 4-OHT (50 mg/kg). 1 day later mice were regrouped with littermates. To map prosocial effects of MDMA in the same mice, after 2 weeks mice were again injected with saline or MDMA (7.5 mg/kg). 90 minutes later mice were perfused with 4% PFA to capture expression of Fos, analogous to the tdTomato label generated by the TRAP2 technique. Brains were bisected, made optically transparent with the iDISCO+ protocol, and immunolabeled. Light sheet microscopy was used to acquire Z-stacks spanning each hemisphere. Using open source software[2,3], we registered images to the Allen brain atlas[4], detected active cells based on sparse user input and machine learning, and quantified voxelized regional cell counts. Activity maps were compared for MDMA and saline in each behavioral context (social and nonsocial).

RESULTS: Counts from 486 grey matter regions (MDMA, N=7; saline, N=6) were normalized to total counts. MDMA significantly enhanced neuronal activity relative to saline in several pre-frontal cortical regions in both social and non-social contexts, including the prelimbic area, agranular insular areas, infralimbic area, dorsal anterior cingulate area, and orbital areas. In the social context only, MDMA enhanced activity in several areas including the nucleus accumbens, lateral amygdalar nucleus, taenia tecta, rhomboid nucleus, and intermediodorsal nucleus of the thalamus. In the non-social context only, MDMA selectively decreased activity in several regions including the pre/post subiculum, superior colliculus, red nucleus and posterior pretectal nucleus.

CONCLUSION: Through unbiased whole-brain mapping of neurons differentially activated by saline vs MDMA in social and non-social contexts we identified a novel network of regions that may mediate some of MDMA's prosocial effects. Future work will test for causal links between these structures' activity and MDMA's effects on mouse sociability and relief from traumatic

experiences. Characterizing circuits that are selectively modulated by MDMA in a social context may yield novel targets for noninvasive brain stimulation therapy and safe, rapid treatment for PTSD.

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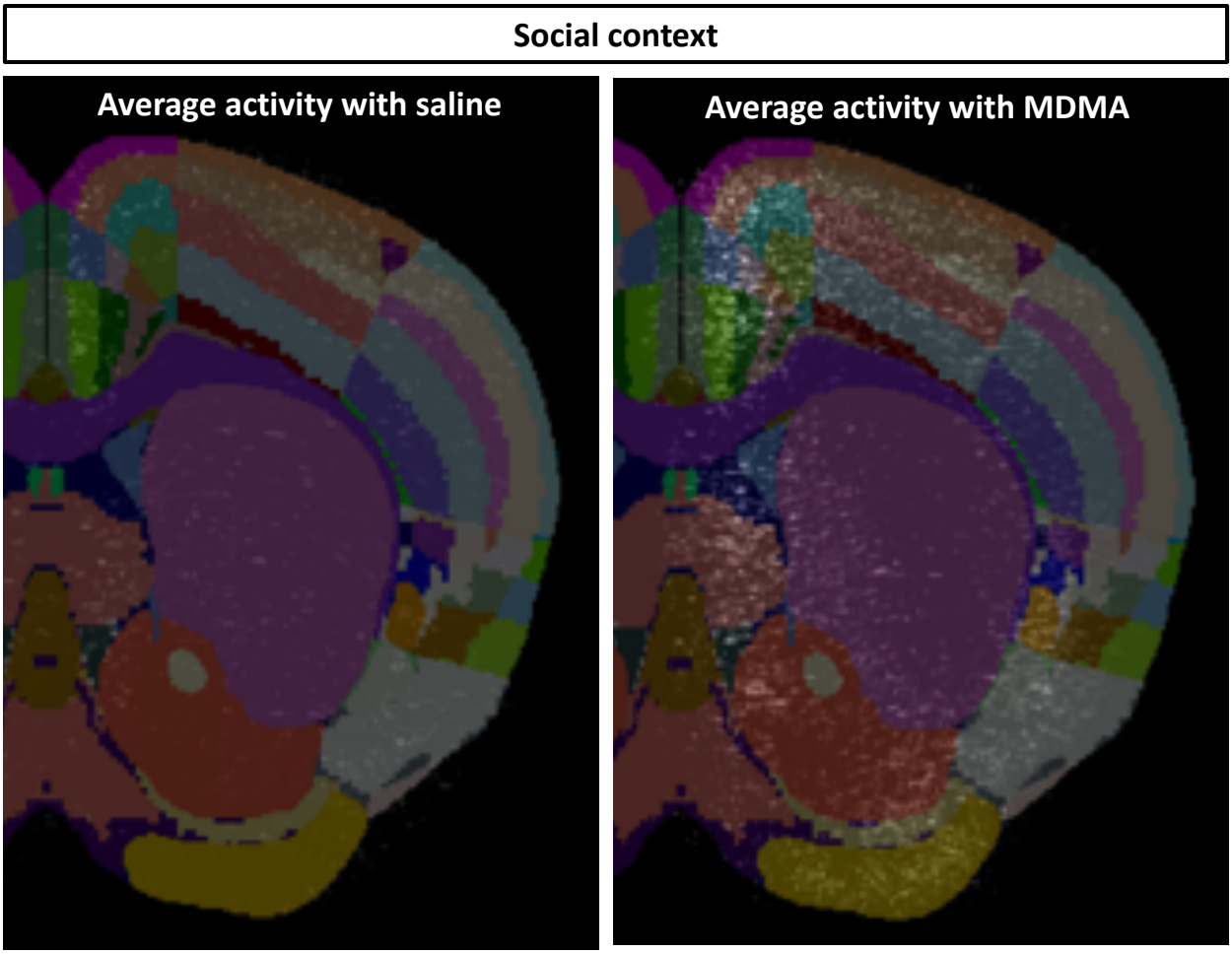

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 33

Processing of auditory and pain stimulation is severely disrupted at slow wave activity saturation under general anaesthesia

Jostein Holmgren[1], Lara Prisco[1], Mark Chiew[1], Saad Jbabdi[1], Myles Allen[1], Jamie Sleigh[2], Irene Tracey[1], Katie Warnaby[1]

[1]University of Oxford, Oxford, United Kingdom, [2]Waikato Hospital, Hamilton, Waikato

INTRODUCTION: Slow wave activity (≈1Hz) dominates the electroencephalogram (EEG) under deep general anaesthesia for most anaesthetic agents. We have previously shown that slow wave activity increases to saturation prior to peak dosing[1,2]. Concurrent functional magnetic resonance imaging (FMRI) indicated that the individuals' thalamocortical system became isolated from external sensory stimuli at propofol concentrations at or in excess of slow wave activity saturation (SWAS;1). This suggested that SWAS may represent a state of perception loss and could provide a useful individualised brain-based target for anaesthesia titration. In the present study, we aimed to further validate SWAS as a state of perception loss. We titrated anaesthesia according to each individual's brain activity to achieve SWAS using concurrent EEG and identified changes in the behavioural responsiveness and brain activity.

METHODS: 23 healthy adults were administered sevoflurane using real-time EEG feedback in a 3T Siemens MRI scanner. SWAS was identified as the 97.5% plateau of slow wave power as a function of end-tidal sevoflurane concentration using a real-time Bayesian model. The concentration for loss of responsiveness (LOR) to auditory beeps was also determined during titration. Additionally, SWAS was modelled post hoc on the complete datasets. A series of MRI acquisitions were performed when the volunteers were awake (breathing 100% O2) and at SWAS (sevoflurane and 100% O2 mix), and in a baseline recording (normoxia) on the previous evening. Changes in brain activity to both heat pain stimuli and auditory command to perform a modified isolated forearm test (IFT) were assessed using a novel EEG-compatible multiband FMRI sequence (2x2x2mm voxels). A novel EEG-compatible pulsed arterial spin labelling (PASL) sequence (3.5x3.5x6mm voxels) was used to collect whole-brain perfusion data for the same conditions. Group-level FMRI mixed effects analyses were used to identify the mean brain activity to pain and auditory stimulation when awake (hyperoxia) and at SWAS, and assess any changes between conditions (preliminary N=12). Individual grey matter (GM) perfusion for each condition was included as a confound regressor, after the PASL images were preprocessed and quantified in accordance with standard techniques[3]. Group-level paired T-tests for each PASL contrast were run using permutation testing (preliminary N=10) to identify changes in perfusion associated with each condition. Finally, we performed a region of interest (ROI) analysis in the primary somatosensory cortex (S1), primary auditory cortex (PAC) and anterior insula (AI) to demonstrate BOLD signal changes in these key sensory regions.

RESULTS: 18 of 23 participants completed the full session. Of these, 16 participants had sufficient EEG and anaesthesia data quality to model and identify SWAS post hoc (Fig 1A). LOR was reached at sevoflurane ET (%) of M±SD 1.09±0.31 and SWAS at 2.38±0.44 (Fig 1B). Fig 1C shows a Bland-Altman plot of agreement between C_{SWAS} and the concentration during the FMRI scan. No participants were responsive to IFT prompts when held at SWAS. Stereotypical brain activation to pain (incl. S1, AI and cingulate cortex) and auditory stimuli (incl. PAC and AI) was evident when awake, but not at SWAS (Fig 2). An awake > SWAS contrast confirmed that activation in these regions was significantly reduced at SWAS compared to awake (Fig 3). The ROI analysis revealed no evoked BOLD response in either S1, PAC or AI at SWAS (Fig 4). Median GM perfusion was significantly higher at SWAS (M±SD 72.7±14.7 ml/100g/min) compared to both hyperoxia (40.5±13.8 ml/100g/min) and normoxia (53.2±10.3 ml/100g/min; Fig 5).

CONCLUSION: These preliminary results provide further evidence that SWAS is a state of perception loss to the outside world. The absence of pain and auditory evoked responses at SWAS compared to wakefulness is indicative of severe disruption of external sensory processing. Importantly, no participants were responsive to IFT prompts at SWAS. This further supports SWAS as a potential clinically target for titration of anaesthesia. Moreover, our perfusion data showed that cerebral brain perfusion was significantly increased with sevoflurane when compared to awake. To our knowledge, this is the first time this has been shown using brain imaging. This novel PASL sequence is compatible with EEG and can be incorporated to most standard MRI studies of anaesthesia to control for altered cerebral cardiovasculature.

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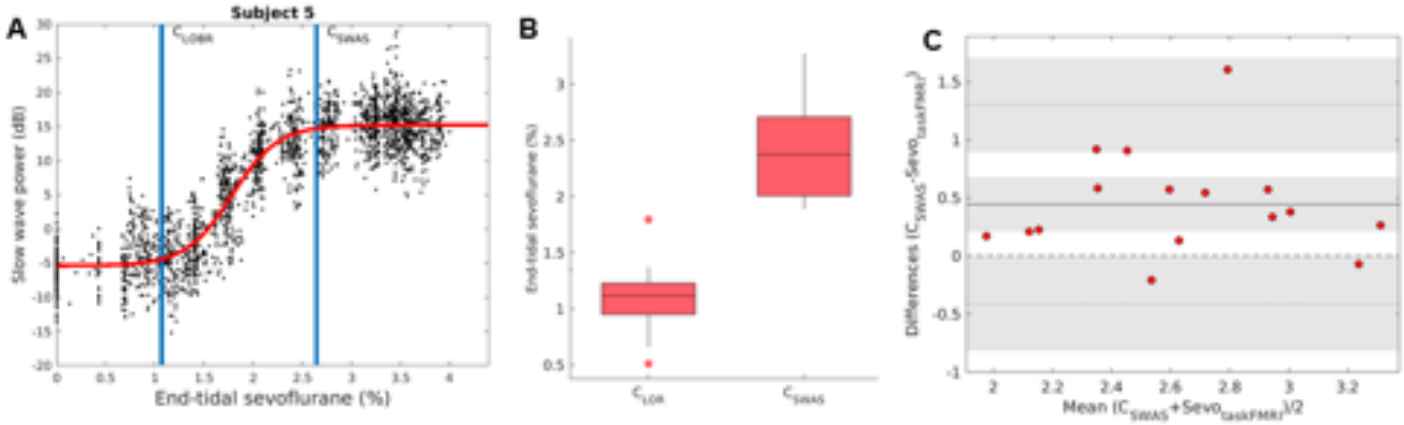

Fig. 1: A) Post hoc SWAS model fit for one example subject. The anaesthetic concentration at SWAS (C_{SWAS}) was defined as the concentration that contains 97.5% of the posterior distribution around SWAS. B) Boxplots showing sevoflurane concentrations at loss of responsiveness (C_{LOR}) and at SWAS (C_{SWAS}). C) Bland-Altman plot showing the concentration that each participant was held at during the FMRI acquisition ($Sevo_{targetFMRI}$) compared C_{SWAS} for that individual.

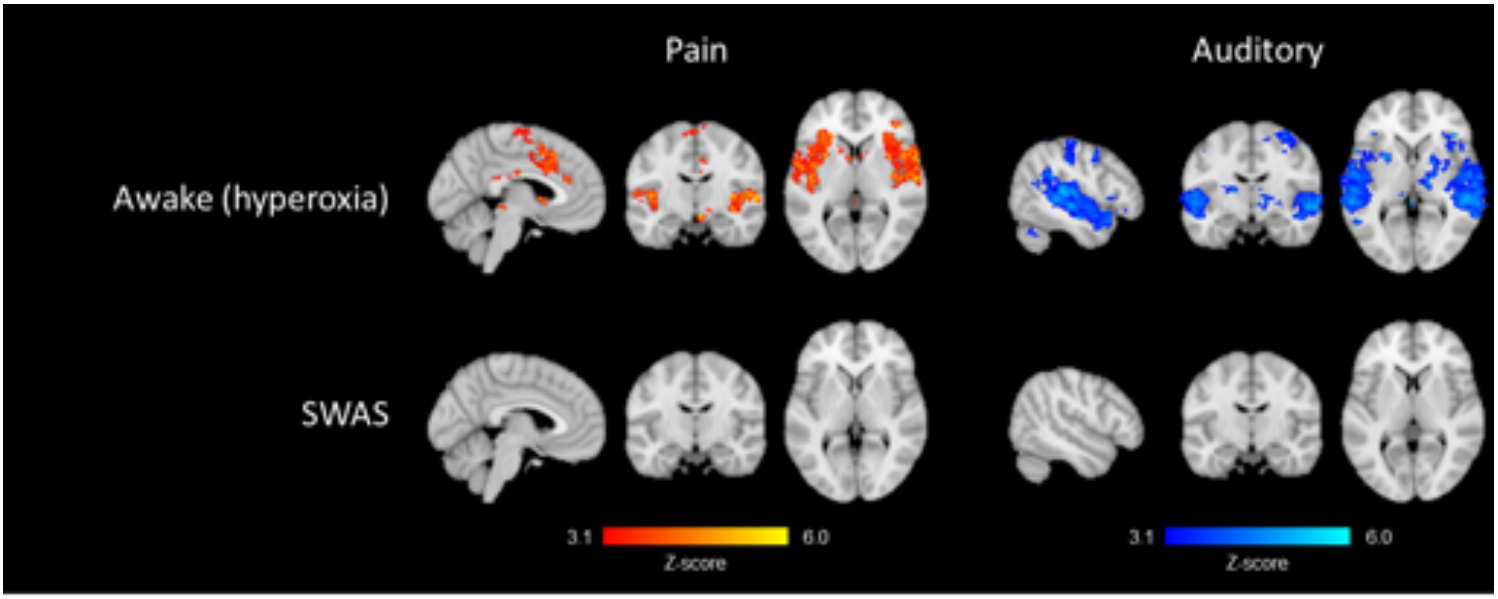

Fig. 2: Mean brain activation in response to pain (left) and auditory (right) stimulation when awake (top) and at SWAS (bottom; Z>3.1, p<0.05).

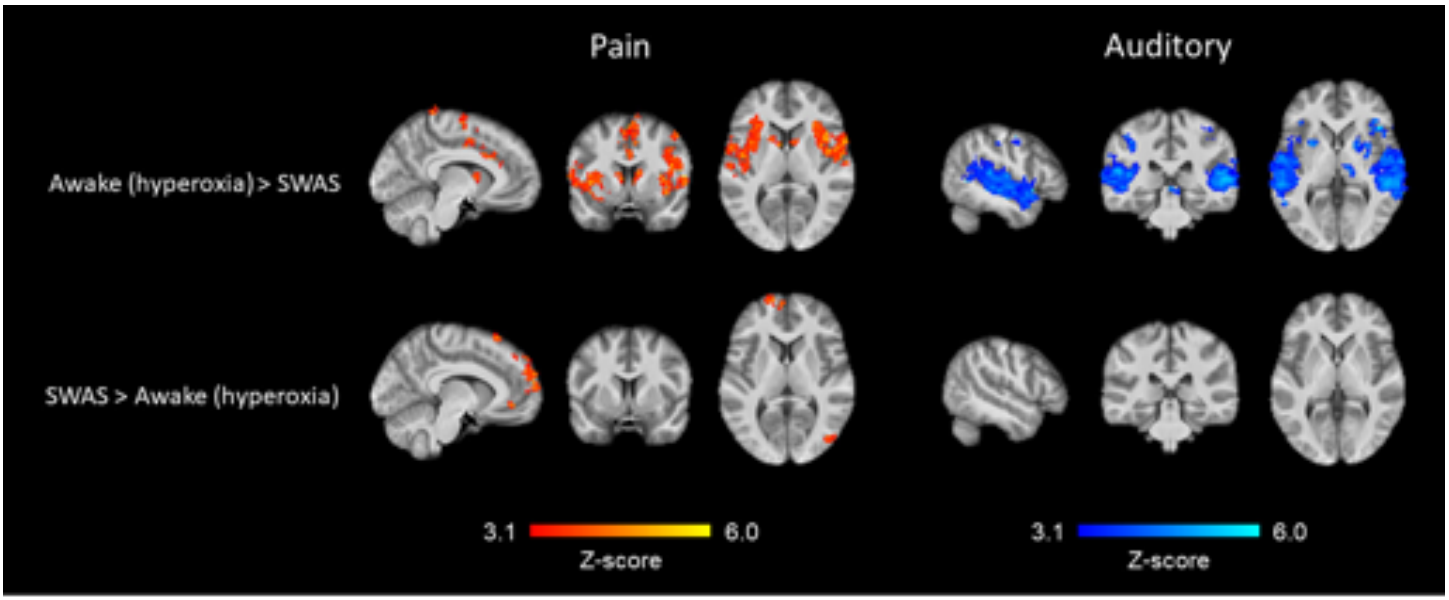

Fig. 3: Evoked BOLD responses to pain (left) and auditory (right) stimulation that was significantly greater when awake (hyperoxia) compared to SWAS (top) and vice versa (bottom). Paired T-tests, Z>3.1, p<0.05.

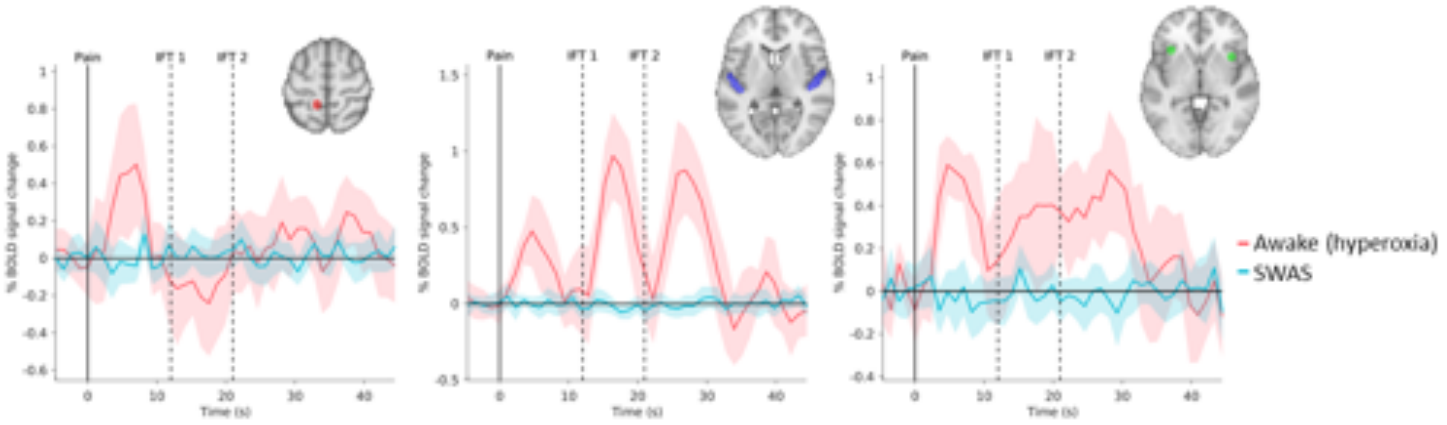

Fig. 4: Stimulus-locked BOLD signal averaged within left primary somatosensory cortex (left), bilateral primary auditory cortex (middle), and bilateral anterior insula (right). The shaded area indicates the standard deviation around the group mean percent BOLD signal change.

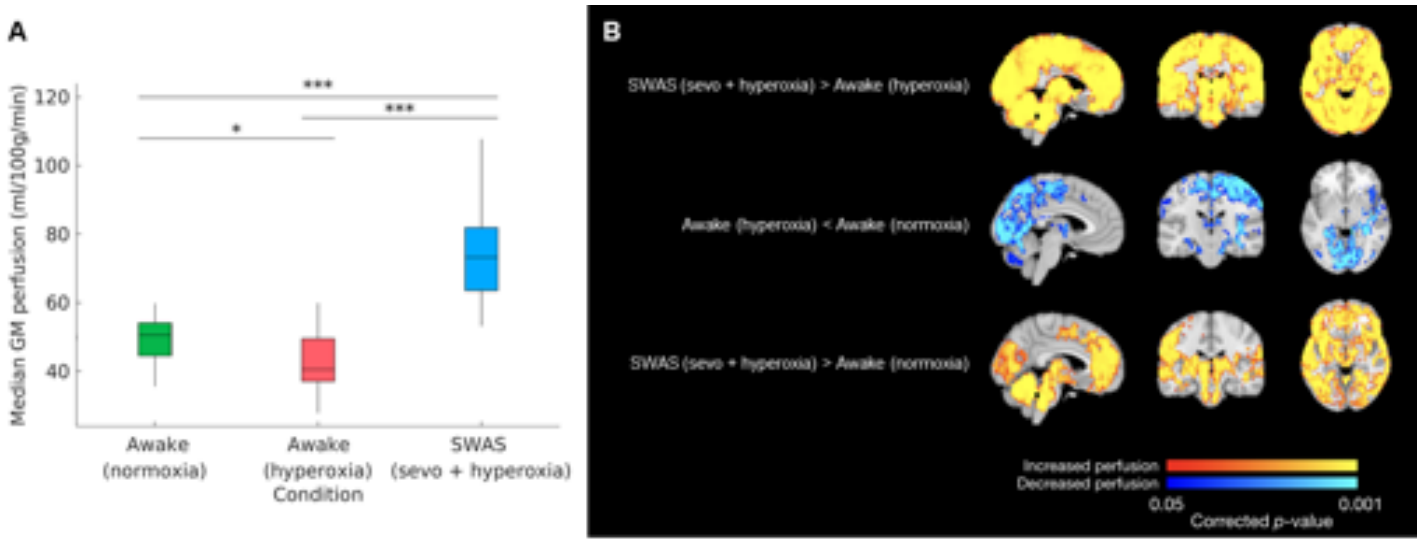

*Fig. 5: A) Between-subject median grey matter perfusion corrected for partial volume effects. Individual grey matter perfusion means were calculated from pure grey matter voxels (>80% grey matter). *** indicates p<0.001 and * indicates p<0.05. B) Statistical maps of significant (p<0.05) increases changes in cerebral blood perfusion. No other contrasts had any significant changes.*

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 34

Adolescent rhesus monkeys repeatedly exposed to sevoflurane in infancy show regional alterations in synaptic ultrastructure related to synapse target and complexity

Tristan Fehr[1], William G Janssen[1], Mark G Baxter[1]

[1]Icahn School of Medicine at Mount Sinai, New York, NY

INTRODUCTION: Several human epidemiological studies show an increased risk for socioemotional changes and learning disability after multiple, early-life (age <4) general anesthesia exposures[1-4]. Animal studies show early-life anesthetic exposures cause widespread neuron and glia death, as well as synapse loss and mitochondria damage[5-8]. In rhesus monkeys repeatedly exposed to sevoflurane anesthesia as infants, we found elevated anxiety and impaired visual recognition memory later in life[9-11]. We also found early-life anesthesia altered synaptic ultrastructure, including an interaction with sex in the largest 5% of synapses in CA1 of the hippocampus, and a reduction in synapse size in the largest 5% of synapses in dorsolateral prefrontal cortex (dlPFC). In the present study, we used electron microscopy with unbiased stereological sampling to further investigate synapse structure across four synaptic subtypes related to synaptic target and complexity. The study was performed in hippocampal region CA1 and dorsolateral prefrontal cortex (dlPFC) in monkeys repeatedly exposed to sevoflurane in infancy, and matched controls, at the age of ~4 years (approximating ~12 years in humans).

METHODS: Female and male rhesus macaques received four-hour exposures to sevoflurane, or brief maternal separation as a control, on postnatal days ~7, 21, and 35. Monkeys were tested in socioemotional and cognitive tasks from 6-48 months of age. We performed electron microscopy targeted to area CA1 of the hippocampus and dorsolateral prefrontal cortex (dlPFC). We measured synapse area and number for synapses targeting dendritic spines (spinous synapses) or dendritic shafts (dendritic synapses) that we also classified by their perforated or nonperforated morphology. Ultrastructural measures were collected by an experimenter blind to anesthetic condition. Data were analyzed by ANOVA for point measures or linear mixed models for nested data, as appropriate.

RESULTS: In CA1, perforated dendritic synapses in CA1 increased by 180% (X^2 (1, N = 18) = 6.11, p = 0.01), and nonperforated dendritic synapses increased by 63% (X^2 (1, N = 18) = 6.02, p = 0.01) in anesthesia monkeys. By contrast, in dlPFC there was no effect of anesthesia on numbers of perforated dendritic synapses (X^2 (1, N = 18) = 0.21, p = 0.64), or nonperforated dendritic synapses (X^2 (1, N = 18) = 1.13, p = 0.29). There was no significant effect of anesthesia on numbers of spinous synapses in CA1 or dlPFC. Conversely, anesthesia caused perforated spinous synapse areas to be reduced by 7.6% in CA1 ($F(1,11.80) = 5.19$, p = 0.04), but not in dlPFC ($F(1, 15.73) = 0.02$, p = 0.90). Nonperforated spinous synapse areas were not affected in CA1 ($F(1, 14.07) = 0.24$, p = 0.63), but were reduced in anesthesia monkeys by 9.7% in the dlPFC ($F(1, 14.89) = 6.66$, p = 0.02). No anesthesia effects on synapse area were observed for any dendritic synapses in CA1 or dlPFC.

CONCLUSION: Repeated anesthesia exposures during infancy can differentially impact the synaptic ultrastructure of distinct synapse classes in area CA1 of the hippocampus and in dorsolateral prefrontal cortex up to (at least) four years after exposure. The type-specific changes in number and area of synapses appear to exhibit regional specificity. These ultrastructural changes may be related to the persistent changes in socioemotional behavior and cognition seen after repeated anesthesia exposures during infancy.

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NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 35

Postoperative Delirium in Patients Undergoing Radical Cystectomy

Alberto A Uribe[1], Nicoleta Stoicea[2], Ana Mavarez Martinez[3], Juan Fiorda-Diaz[1], Alicia Gonzalez-Zacarias[1], Ahmad Shabsigh[1], Marilly Palettas[2], Sergio D Bergese[3]

[1]The Ohio State University Wexner Medical Center, Columbus, OH, [2]The Ohio State University, Columbus, OH, [3]Stony Brook Medical Center, Stony Brook, NY

INTRODUCTION: Postoperative delirium (PD) is characterized by a sudden, fluctuating, and reversible impairment of cognitive status during the post-anesthesia recovery phase, and up to 7 post-operative days. Based on DSM V criteria, the impairment in brain function is different from the baseline normal cognitive status.

METHODS: A prospective clinical trial was conducted at The Ohio State University Wexner Medical Center between January 2018 and May 2019. Adult patients (≥18 years old) undergoing elective radical cystectomy were enrolled. Baseline cognitive function was assessed preoperatively by using Self Assessed Cognitive Evaluation (SAGE) and Memorial Delirium Assessment Scale (MDAS). Emergence delirium was diagnosed using the Confusion Assessment Method (CAM) combined with Richmond Agitation-Sedation Scale (RASS). On postoperative Day 1 and 2, each patient was interviewed and assessed using MDAS. A MDAS score >13 (out of a maximum of 30) was indicative of delirium. Opioid consumption (morphine equivalents dose) was also documented.

RESULTS: The data of 44 enrolled subjects was analyzed. The incidence of POD was 15.9% (7/37). Moreover, duration of anesthesia in patients who developed POD was 783.0 [606, 834] minutes compared to 549.1 [473, 616) minutes in the non-POD group. The PACU length of stay was higher in the POD group when compared with the non-POD group (636 [516. 783] vs. 483 [424, 553], p= 0.018). Total opioid consumption on Day 1 and 2 was significantly higher in the POD group than the non-POD group (Day 1= 20 [10, 53] vs 7.5 [3, 15.8], p= 0.021 and Day 2 = 17 [10, 26] vs. 5 [0, 12.5], p= 0.010).

CONCLUSION: The incidence of POD in patients undergoing radical cystectomy for our study population was 15.9%. The occurrence of POD might be related to a longer length of anesthesia/surgery and a higher postoperative opioid consumption. Future research should assess POD in a larger surgical patient population considering the interplay between the preexisting chronic diseases, the length of surgery and anesthesia, and the perioperative opioid consumption

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 36

Machine Learning for Intensive Care Delirium Prediction

Kirby D Gong[1], Ryan Lu[1], Teya Bergamaschi[1], Akaash Sanyal[1], Joanna Guo[1], Han Kim[1], Robert D Stevens[2]

[1]Johns Hopkins University, Baltimore, MD, [2]The Johns Hopkins University School of Medicine, Baltimore, MD

INTRODUCTION: ICU delirium is frequent, associated with unfavorable outcomes, increased health expenditures, and may be largely preventable. Accurate prediction models are needed to allow early intervention strategies in patients most at risk of becoming delirious. The aim of this study was to leverage machine learning applied to early physiological and clinical data to predict delirium in an ICU stay.

METHODS: Data from the first 24 hours of ICU admission were extracted from the multi-center eICU database with a special emphasis on features derived from physiologic time series signals. A statistically pruned feature space of 116 derived variables was established and three different machine learning (ML) algorithms were evaluated (logistic regression [LR], random forest [RF], and gradient boosting [CatBoost]). A separate dynamic model was built that predicts delirium from 1 to 12 hours in advance, using a similar initial feature space and algorithms. Model performance was evaluated using nested cross-validation and area under the receiver operating characteristic curve (AUROC) analysis, and compared with the PRE-DELIRIC score which has been previously validated for prediction of delirium in the ICU. The models were also evaluated with precision-recall and calibration metrics. Top features of models were analyzed using LASSO for logistic regression, random forest, or Shapley values for CatBoost.

RESULTS: 27,939 patient stays that had delirium scoring were identified. For the first 24-hour predictive model, best mean AUROC on an expanded feature space was 0.791 (95% confidence interval: [0.768, 0.814]), obtained using the Catboost algorithm. For comparison, AUROC of the PRE-DELIRIC model trained on the same dataset was 0.732 (95% confidence interval: [0.703 , 0.760]). AUROC of the novel model is significantly better than the PRE-DELIRIC model, $t(6) = 4.93$, $p = .003$. The top ten predictive features according to the LR model included mean verbal GCS score, mean eyes GCS score, APACHE IV score, age, coma, and minimum mean corpuscular volume. The dynamic model performed best with shorter prediction lead times, but an association between observation window duration and performance was not observed. At 1 hour lead time, the best AUROC was 0.889 (95% confidence interval: [0.878, 0.901]), best precision-recall was 0.652 (95% confidence interval: [0.613, 0.690]), and best Brier score was 0.095 (95% confidence interval: [0.088, 0.103]). Based on Shapley values, the most important features included current length of stay, GCS, RASS, APACHE scores, age, and serum chloride concentrations. Of note, physiological time series data did not increase prediction performance of either model beyond a 95% confidence interval.

CONCLUSION: Machine learning applied to features from the first 24h after admission predicted ICU delirium onset with higher accuracy than the reference PRE-DELIRIC score. Results suggest that high-resolution data contain predictive information on delirium risk in the ICU which is overlooked in current prediction systems. Machine learning applied to features from observation windows hours before the onset of delirium had even greater predictive performance. Results warrant prospective validation and additional studies integrating other data modalities such as brain-specific molecular biomarkers, neurophysiology, and neuroimaging.

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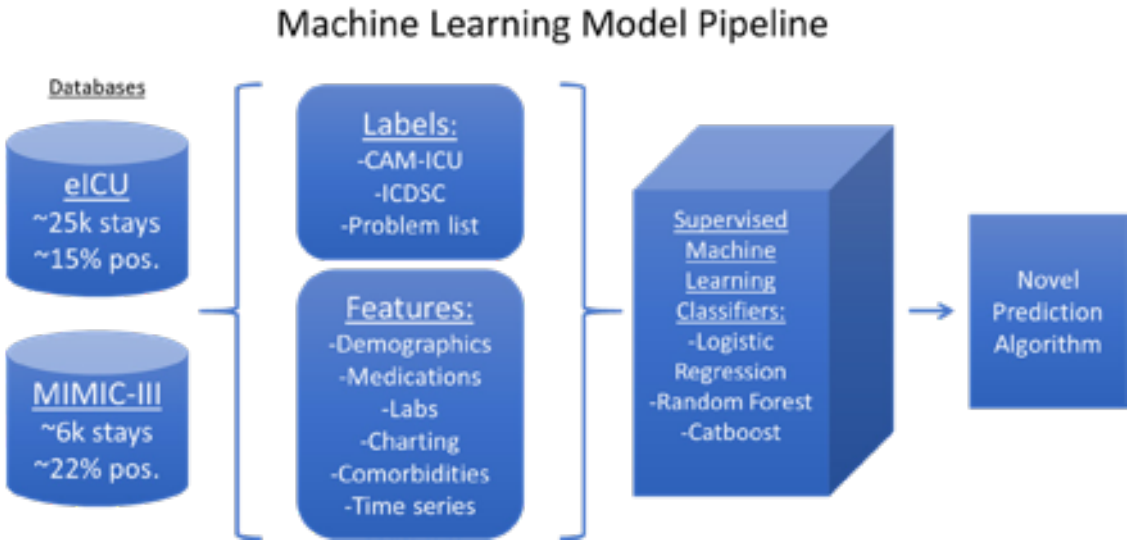

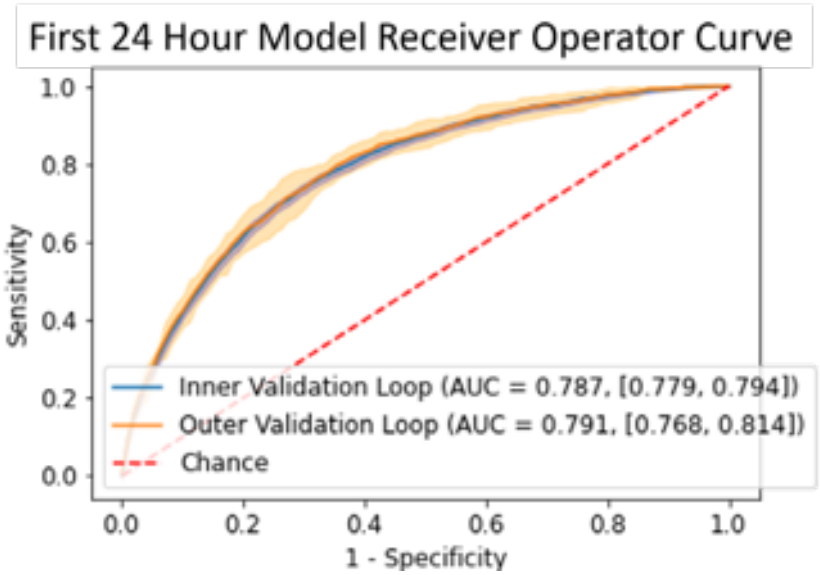

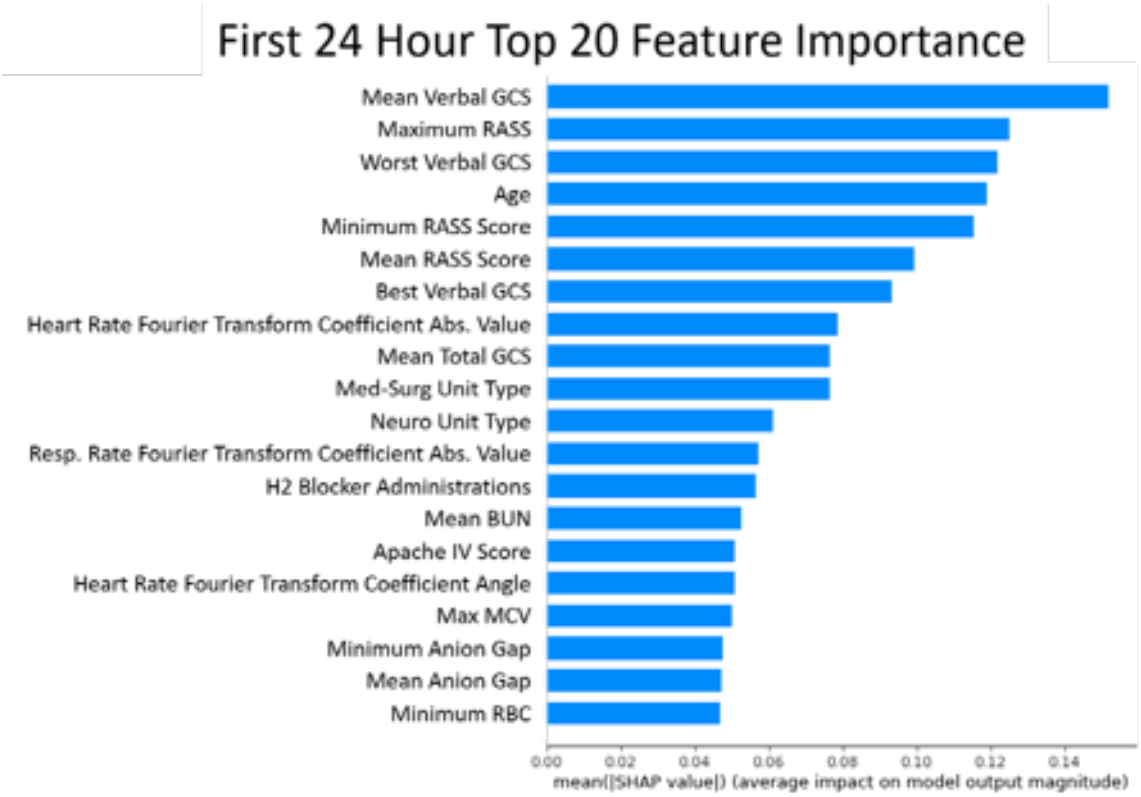

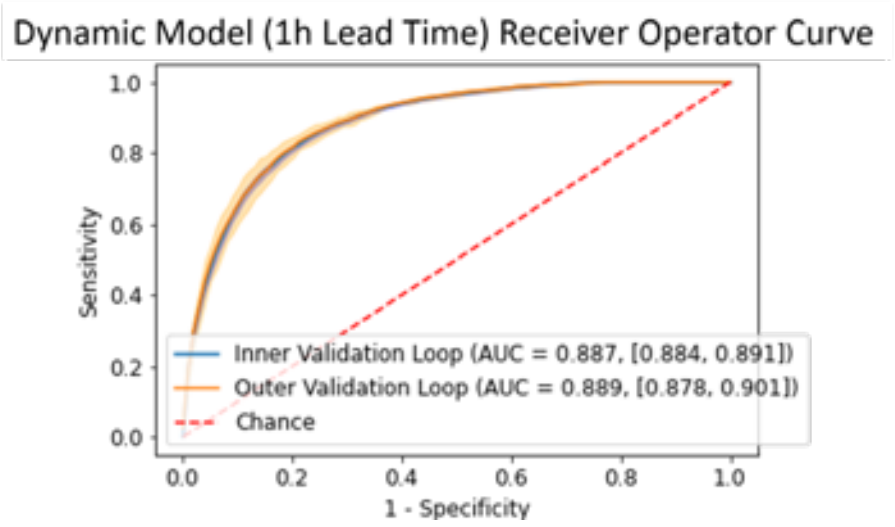

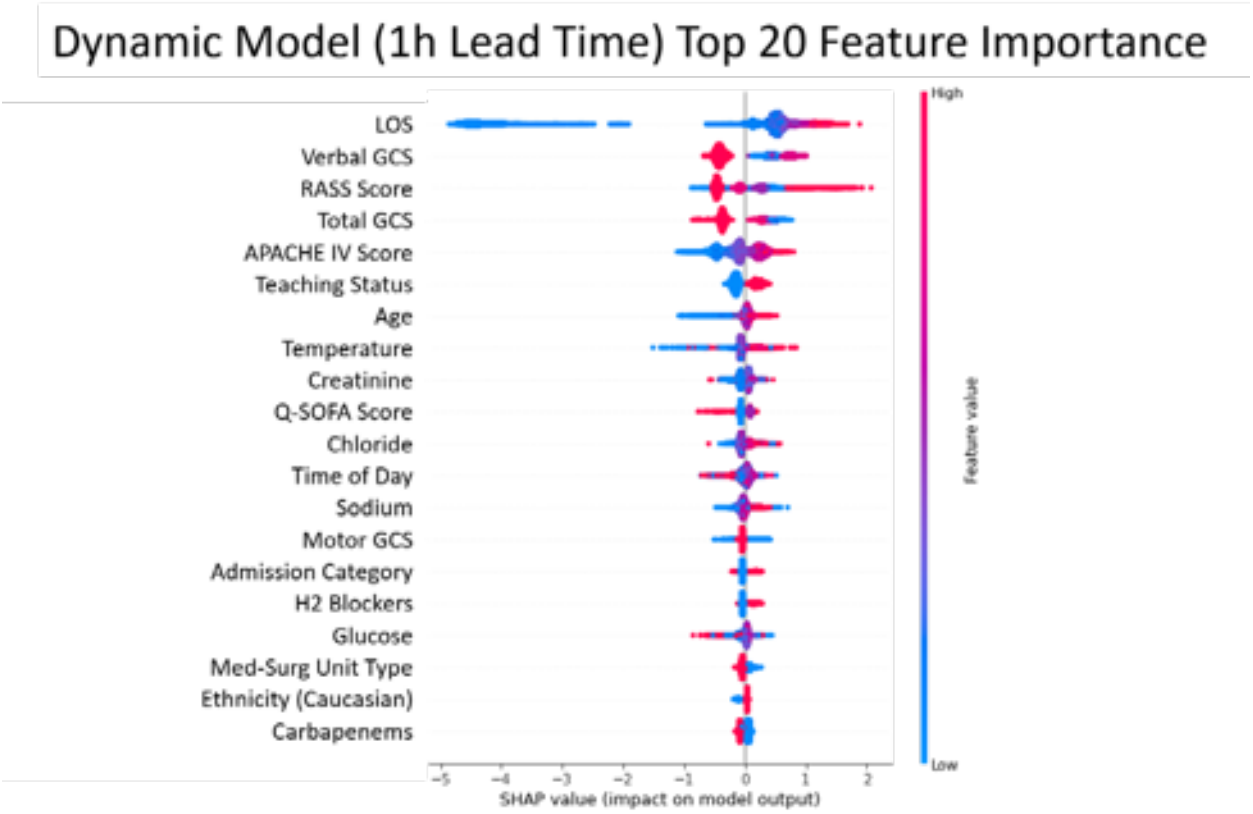

NEUROSCIENCE IN ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE 37

Fatigue-Induced Decrease in Motoneuron Excitability: Role of Repetitive Activation and Group III/IV Muscle Afferent Feedback

Vincent P Georgescu[1], Joshua C Weavil[1], Taylor S Thurston[1], Nate Birgenheier[1], Scott Junkins[1], Markus Amann[1]

[1]University of Utah Health Care, Salt Lake City, UT

INTRODUCTION: Although fatiguing exercise is recognized to decrease motoneuronal excitability, the underlying mechanisms responsible for this impact remain unclear. The purpose of this study was to investigate the roles of repetitive motoneuron activation and group III/IV muscle afferent feedback in determining the decrease in motoneuronal excitability as a result of fatiguing exercise.

METHODS: On 3 separate days, 7 healthy young subjects (25 ± 5 yrs) performed intermittent isometric knee extensions (at 20% of maximal voluntary quadriceps torque): 1) voluntarily (VOL; i.e. requiring repetitive motoneuron activation), 2) electrically-evoked (EVO, femoral motor nerve stimulation at 40 Hz; no motoneuron activation), 3) electrically-evoked with group III/IV muscle afferent feedback attenuated via lumbar (L3-L4) intrathecal fentanyl (EVO+FENT, no motoneuron activation and attenuated neural feedback from the lower limbs). Exercise consisted of 50-s quadriceps contractions followed by 10-s breaks during which potentiated quadriceps twitches (Qtw) were assessed to monitor the development of peripheral fatigue during each trial. Exercise continued until the goal of achieving a similar reduction in Qtw (ΔQtw ~40%) was reached in each trial. Before and immediately after exercise, a transcranial magnetic stimulation was followed by a cervicomedullary stimulation with a 100 ms inter-stimulus interval to elicit conditioned cervicomedullary motor-evoked potentials (cond.CMEP). All cond.CMEPs were normalized to M-waves (maximal compound muscle action potentials) and evoked during a constant electromyographic (EMG) activity corresponding to 20% of the EMG obtained during pre-exercise maximal voluntary contractions. A priori planned comparisons of cond.CMEPs were made between VOL and EVO via Student's t-test to assess the influence of repetitive activation, and between EVO and EVO+FENT to assess the influence of group III/IV muscle afferent feedback on motoneuron excitability.

RESULTS: Per study design, ΔQtw was not different between all 3 trials (-45±1%). During VOL, cond.CMEP fell by 79±6% from pre to post fatiguing quadriceps contractions ($p < 0.01$). Although the exercise-induced decrease in cond.CMEP was also significant during EVO (-51±10%), the reduction was substantially smaller compared to VOL. The exercise-induced decrease in cond.CMEP during EVO+FENT (-42±10%) was not different compared with that observed during EVO ($p = 0.5$).

CONCLUSION: Voluntary fatiguing muscle contractions compromise motoneuron excitability. While repetitive motoneuron activation accounts for part of the decrease, group III/IV muscle afferent feedback does not contribute to this depression. Importantly, the observation that the fall in motoneuron excitability is still significant during fatiguing muscle contractions performed without repetitive motoneuron activation suggests that other factors, such as extrasynaptic serotonin spillover and afterhyperpolarization, may play a role in the fatigue-related decrease in motoneuron excitability.

Subspecialty Abstracts

OBSTETRIC ANESTHESIOLOGY

OBSTETRIC ANESTHESIOLOGY 1

Attenuating Spinal-Induced Hypotension with Ondansetron in Parturients Undergoing Casarean Section

Johnson Ogah[1], Ajibola U Otegbeye[2]

[1]University College Hospital, Ibadan, Nigeria, [2]university college hospital, Ibadan, FM

INTRODUCTION: Hypotension is the commonest side effect following spinal anaesthesia. This is even more pronounced in parturients as over fifty percent of them who have spinal anaesthesia will develop hypotension. The prevention and treatment of hypotension have traditionally involved the use of fluids and vasopressors with variable outcomes hence the search for better outcomes using other drugs with other mechanisms of action.

METHODS: With the approval of the University of Ibadan/University College Hospital Ethics Committee, 128 patients who were American Society of Anesthesiologists (ASA) Physical Status I and II, aged 18 to 45 years, scheduled for elective caesarean section at the University College Hospital were studied. The patients were randomized into groups O and P each comprising of 64 patients. Group O received 8 mg intravenous ondansetron diluted to 10 ml with isotonic sodium chloride, while group P received 10 ml of isotonic sodium chloride. These were administered 5 minutes before spinal anaesthesia for caesarean delivery. All patients were premedicated with 10mg metoclopramide and 150mg ranitidine orally the night before surgery. Through a size 16 or 18 IV cannula, all patients were preloaded with crystalloids (0.9% saline) 15mls per kilogram body weight over 20 minutes before establishing the subarachnoid block with 2.5mls of 0.5% heavy bupivacaine at L3/L4 or L4/L5 interspace. Baseline values of Non-Invasive Blood Pressure (NIBP), Heart Rate and oxygen saturation (SpO2), were recorded and repeated at 2 minute intervals initially for 20 minutes then at 5 minute intervals until the end of surgery. Intraoperative hypotension was treated with ephedrine.

RESULTS: The two groups were comparable with respect to demographic characteristics, and peri-operative variables. Baseline blood pressures and heart rates were also comparable.

Thirty patients (47.6%) in group P and seventeen patients (28.8%) in group O had hypotension [P=0.033]. The mean dose of ephedrine used in Groups O and P were 13.41±9.13 mg and 16.60±8.59 mg respectively (P>0.05).

Mean heart rates were lower in group P 88.83 ±16.35beats/min vs group O 95.45 ±17.37 beats/ min. [P=0.033]. Four patients (6.3%) in group P and three patients (5.1%) in group O required atropine for bradycardia. (P=0.764)

In Group P 6.3% had nausea while no patient in Group O had nausea (P=0.120). Two patients (3.2%) in Group P vomited while no patient in Group O did (P=0.496). The incidence of chest heaviness was 3.4% and 7.9% among Patients in Groups O and P respectively (P=0.441), while shivering occurred in 8.5% of patients in group O and in 7.9% of patients in group P.

CONCLUSION: It was found from this study that intravenous ondansetron attenuates the decreases in blood pressure seen after spinal anaesthesia. It may therefore be of value in obstetrics for parturients going for elective cesarean section.

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OBSTETRIC ANESTHESIOLOGY 2

Retrospective chart review of patients undergoing cesarean section under spinal anesthesia

Christopher Busack[1], Dev Vyas[1], Joseph Thornhill[1]

[1]Tulane University School of Medicine, New Orleans, LA

INTRODUCTION: Spinal anesthesia with hyperbaric bupivacaine is the most commonly utilized anesthetic for cesarean section. Studies have identified statistically significant increases in hypotension and nausea with increasing doses of bupivacaine, yet it is unclear if these differences are clinically relevant[1-3]. Although hemodynamic consequences of spinal blockade are worrisome, intraoperative pain or a failed spinal anesthetic may represent a worse outcome for patients than manageable hypotension or nausea.

METHODS: A retrospective review was performed including 206 patients who underwent cesarean section under spinal anesthesia from 6/30/2019 to 12/31/2019 at an academically affiliated 121-bed community hospital. The primary outcome was inadequate analgesia. Secondary outcomes included failed spinal blockade, postoperative nausea, intraoperative nausea, intraoperative vasopressor requirements, neonatal Apgar score at 5 minutes, and postoperative pain. Data was extracted from the electronic medical record including total administered amounts of intraoperative antiemetic, intraoperative vasopressor, postoperative antiemetic, and postoperative opioid. Inadequate analgesia was recorded as present if additional intravenous opioid or epidural local anesthetic was given within 90 minutes of incision. The need to convert to general anesthesia was considered a failed spinal. Total intraoperative administration of antiemetics represented a quantitative measurement of intraoperative nausea. Total postoperative antiemetic administration within the first 24 hours represented a quantitative measurement of postoperative nausea. Total opioid administration for the first 24 hours represented a quantitative measurement of postoperative pain. Patients were divided into two groups. Doses above 0.08mg/cm were considered the high bupivacaine group and doses below 0.08mg/cm were considered the normal bupivacaine group. A sample size of 190 patients was required to achieve 80% power to detect a 30% difference in rate of inadequate analgesia.

RESULTS: 206 patients were included for analysis. Mean height for patients in this series was 161.4cm, and mean bupivacaine dose was 12mg. Mean bupivacaine dose per cm was 0.074mg/cm. Mean intraoperative vasopressor use was 8.7mg of ephedrine and 345mcg of phenylephrine. Intraoperatively, 29% of patients exhibited inadequate analgesia, and 13% of patients exhibited nausea. Mean 24 hour postoperative opioid use was 22mg oral morphine equivalents. Mean 5 minute Apgar score was 8.7. No statistical differences were found in any of the analyzed outcomes (Table 1). In our cohort, inadequate analgesia rates were similar between the two groups (27 vs. 30%, P= 0.79). The overall rate of conversion to general anesthesia was 1.4% (3 cases of 206). No failed spinals were noted in the high dose bupivacaine group (n=15).

CONCLUSION: Failed spinal blockade was found at a rate (1.4%) similar to previously reported rates of 1-5%[4]. Although inadequately powered to detect a statistical difference between the two groups, the lack of any failed spinals in the high dose group may suggest improved surgical anesthesia at higher doses. Lack of significant differences in hypotension and nausea parameters is congruent with a previous retrospective review of over 3,000 patients where the amount of plain bupivacaine was not found to be a significant predictor of hypotension[5]. Although blood pressure was not evaluated in our study, the total amount of vasopressors used was recorded as a surrogate for the degree of hypotension. Although a trend towards higher phenylephrine requirements was observed in the high dose group (426.7mcg versus 344.8 mcg), this was not statistically significant and, even if so, likely not clinically relevant. Limitations of this study include its small sample size and its retrospective nature. Many variables represent possible confounders including patient, surgical, and environmental factors. Although the high dose bupivacaine group only had 15 patients, this group closely resembles a prospectively selected cohort. Most of these patients received 15mg of hyperbaric bupivacaine as per routine practice of one anesthesiologist at our institution. This study's inability to show a definitive benefit for different bupivacaine doses in and of itself demonstrates viability of different doses and supports differences in clinical judgment.

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	High Dose Group (n=15)	Standard Deviation	Normal Dose Group (n=191)	Standard Deviation	P-Value
Failed Spinal Blockade (%)	0.00	0.00	1.57	12.5	P = 0.53
Inadequate Analgesia (%)	26.6	45.8	29.8	45.9	P = 0.79
5 minute Apgar Score	8.93	0.26	8.69	0.91	P = 0.30
Intraoperative Phenylephrine Use (mcg)	426.7	443.2	344.8	326.5	P = 0.36
Intraoperative Ephedrine Use (mg)	4.67	6.11	9.21	12.18	P = 0.15
Intraoperative Nausea or Vomiting (%)	13.3	35.2	12.6	33.2	P = 0.93
24 Hour Oxycodone Use (mg)	17.00	9.78	11.91	12.57	P = 0.13
24 Hour Ondansetron Use (mg)	0.80	1.66	1.38	2.52	P = 0.38

Table 1

OBSTETRIC ANESTHESIOLOGY 3

The effect of ERAS on opioid use and opioid prescribing behaviors for opioid naive patients undergoing cesarean section

Erica Langnas[1], Zachary Matthay[1], Andrew Lin[1], Rosa Rodriguez-Monguio[1], Catherine Chen[1]

[1]UCSF, San Francisco, CA

INTRODUCTION: Cesarean sections are the most common inpatient surgical procedure performed in the United States, with approximately 1.3 million cases performed annually[1]. Almost all women undergoing cesarean section are exposed to opioids during their inpatient stay[2]. Between 1 in 300 to up to 1 in 45 women who received an opioid prescription after cesarean section develop new persistent opioid use[2,3]. Furthermore, 83% of women undergoing cesarean section report having leftover prescription opioids, potentially contributing to non-medical use of these products by others[4]. Enhanced Recovery after Surgery (ERAS) has emerged as a promising tool to reduce opioid use after surgery[5-9]. However, implementation of such protocols can have unintended effects on provider prescribing patterns, but these effects have not been described in the literature for ERAS implementation in patients undergoing cesarean section. To better understand the impact of ERAS implementation on provider opioid and non-opioid pain medication prescribing behavior, we performed a single center interrupted time series analysis comparing provider opioid prescription behavior pre and post ERAS adoption for cesarean sections.

METHODS: We conducted a retrospective observational cohort study of adult opioid-naïve patients undergoing cesarean section from 2/1/2015 through 12/31/2019 at the University of California San Francisco Medical Center. Data were summarized using descriptive statistics and chi-squared tests were used to compare patient characteristics pre and post ERAS implementation. An interrupted time-series analysis (ITSA) was used to model the changes in pain medication prescribing associated with the implementation of ERAS to account for pre-existing temporal trends. All ITSAs were performed using the ordinary least squares method with Newey-West standard errors. A Cumby-Huizinga test was used to assess for temporal autocorrelation, and standard error adjustments were incorporated for up to a 12-month lag in our models. As a sensitivity analysis, we examined whether patient characteristics or prescribing provider type impacted the models when included as covariates. None of these significantly altered the association of ERAs with the pain medication outcome variables and were therefore not included in the final models. All data analyses were performed in Stata (Version 15, Stata Corps).

RESULTS: In total, 2249 opioid naïve patients underwent cesarean section. In our pre-ERAS group, 21.01% were opioid free in the 24 hours prior to discharge compared to 49.76% in our post-ERAS group ($p < 0.01$) and pre-ERAS 95.35% were discharged with an opioid prescription compared to 80.72% of the post-ERAS group ($p<0.01$). Post-ERAS, we observed an increase in the percent of discharge prescriptions with a total daily OME of 90 or more (11.35% vs 61.35%, $p < 0.01$) and a reduction of discharge prescriptions with a total daily OME of less than 50 (79.86% vs 25.85%, $p<0.01$). Prior to ERAS, both the strength (daily OMEs) and total OMEs prescribed at discharge were decreasing (daily OMEs by -0.50/month and total OMEs by 2.3/month, both $p<0.01$). However, there was a sharp increase in the strength of discharge opioid prescriptions associated with ERAS implementation (level shift up in daily OMEs by 35, $p<0.01$), followed by a month to month decrease in daily OMEs of 1.4/month (figure 1, $p<0.01$). Total OMEs showed both an immediate decrease (level shift down) in total OMEs by 50/month ($p<0.01$), and a post eras trend of 3.8 fewer OMEs/month. Pre-ERAS, there was no significant trend in the percent of patients receiving opioid refills within 90 days. Rates of 90-day opioid refills decreased by 4.96% ($p=0.04$) immediately following ERAS implementation, and this rate remained stable during the post-ERAS period.

CONCLUSION: This is the first study to report an unintended consequence on provider opioid prescribing patterns in the immediate post-ERAS period for patients undergoing cesarean section. While ERAS led to an increase in opioid free pain control prior to discharge, we observed an increase in discharge prescription daily OMEs. Most notably, more patients received >90 daily OMEs on their discharge prescription, a dose that is associated with increased risk of misuse and overdose. Although this finding did not lead to increases opioid refills, this study highlights the importance of early and continued evaluation after new pain medication prescribing interventions.

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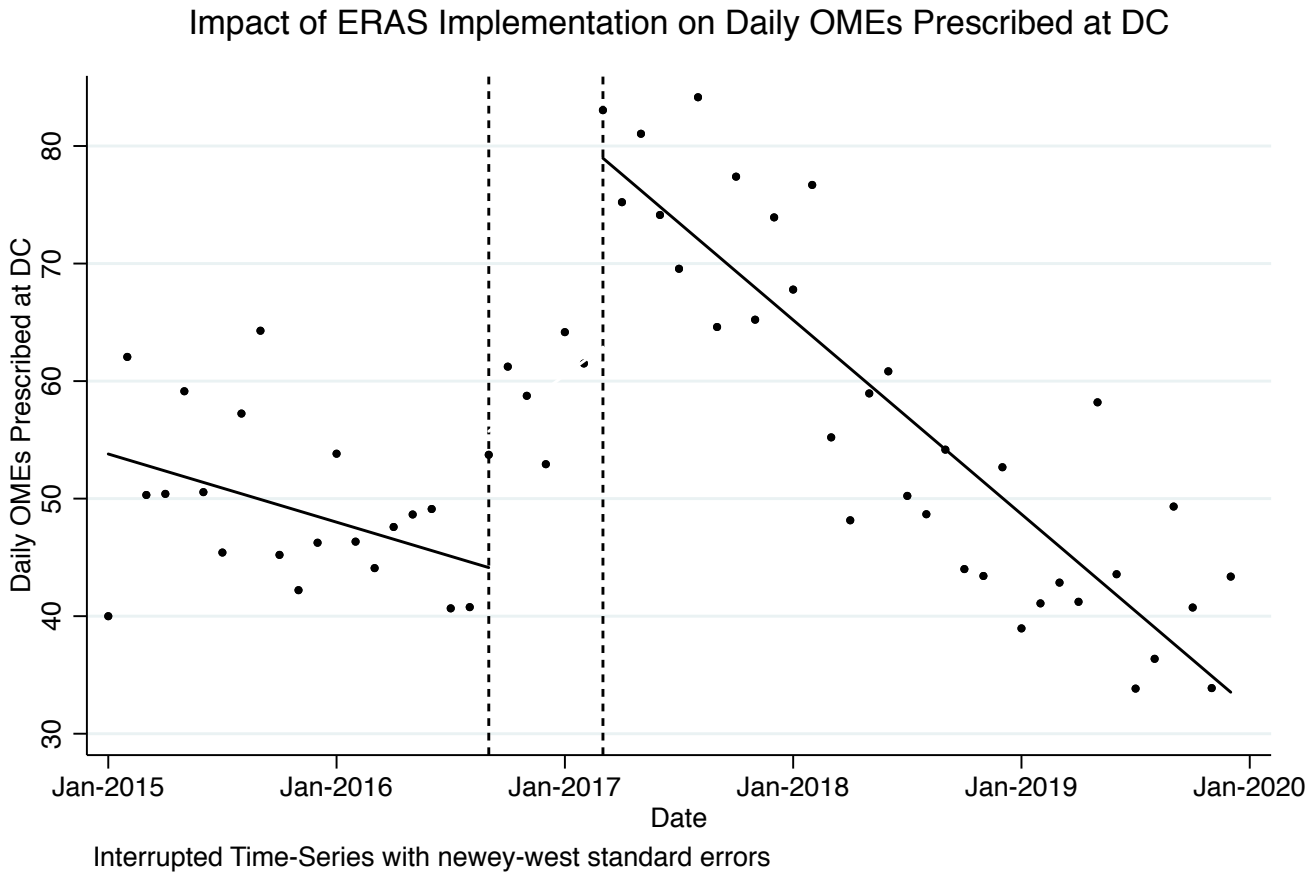

OBSTETRIC ANESTHESIOLOGY 4

Can the Gender of the Neonate Affect Intra-cesarean Nausea and Vomiting?

Danielle Levin[1], Rohan Shah[2], Kate Balbi[2], Shaul Cohen[2]

[1]St. Elizabeth's Medical Center, Brighton, MA, [2]Rutgers - Robert Wood Johnson Medical School, New Brunswick, NJ

INTRODUCTION: 73-80% of parturients who undergo cesarean section under regional anesthesia experience intraoperative nausea.[1-2] Not only is nausea an unpleasant physical condition, but intraoperative vomiting can cause additional challenges, such as inadvertent surgical trauma, increased risk of bleeding, and aspiration pneumonitis.[3-4] Various prophylactic antiemetic medications exist, but they are not entirely effective and may have multiple adverse effects. Knowing which parturients are at a higher risk of experiencing intraoperative nausea and vomiting could help anesthesiologists provide appropriate prophylactic antiemetic management. Semizet al.[5] suggested that parturients who have a female neonate have a significantly higher rate of intraoperative nausea and vomiting than parturients who have a male neonate. To our knowledge, no other study has yet validated these findings. The goal of our retrospective study was to compare the rate of nausea and vomiting experienced by parturients undergoing cesarean section under combined spinal-epidural anesthesia who had female neonates with those that had male neonates.

METHODS: Following IRB approval, 195 parturients who underwent elective cesarean section under combined spinal-epidural anesthesia between 09/2016 and 06/2019 were analyzed. Group I (n = 99) had male neonates, and Group II (n = 96) had female neonates. The rate of nausea and vomiting were compared between the two groups. Excel version 2013 was used for Chi-squared test and Student T-test analysis of our data.

RESULTS: Baseline characteristics were similar between the two groups (Table 1). The rate of intraoperative nausea was similar between the two groups (Group I - 52.5%, Group II - 46.9%, P = 0.43). The rate of intraoperative vomiting was also similar between the two groups (Group I - 32.3%, Group II - 30.2%, P = 0.75) (Figure 1).

CONCLUSION: In our cohort of parturients, the gender of the neonate did not appear to have a significant effect on whether a parturient experienced intra-cesarean nausea or vomiting. Based on our findings, we were unable to validate Semizet al.'s5 results. We will continue to explore other risk factors that may contribute to intra-cesarean nausea and vomiting to further improve parturient satisfaction and safety during delivery.

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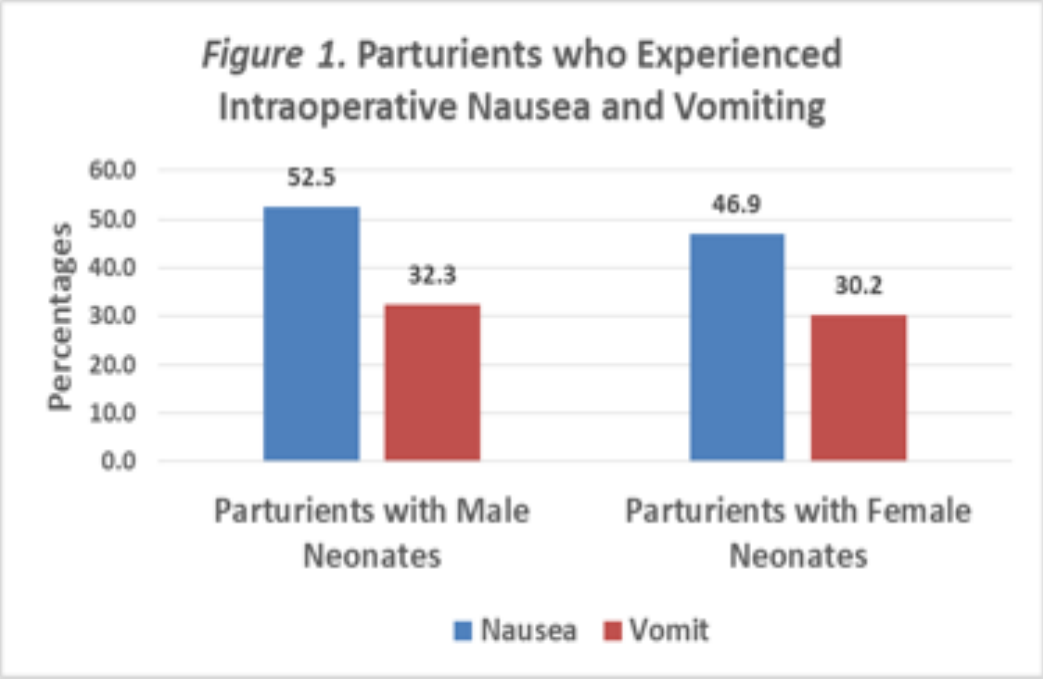
Table I. ***Patient and procedural characteristics***			
Characteristics	**Male Neonate (n=99)**	**Female neonate (n=96)**	**P-value**
Age (years)	31.8 ±6.0	31.8± 5.3	0.98
BMI	31.5± 6.5	31± 6.5	0.55
Gestational age (wks)	38.7± 1.0	38.5± 1.8	0.25
Hypotension, n (%)	48 (49%)	43 (45%)	0.61
Hypoxia, n(%)	0	0	1
Blood loss (mL)	776.0± 123.7	807.0± 199.0	0.19
Surgery duration (min)	62.6± 17.4	63.9± 16.8	0.61
Continuous variables were expressed as mean ± standard deviation, and P values were calculated using the Student T-test. Categorical variables were expressed as number (percentage), and P values were calculated using the chi-square test. P<0.05 were considered statistically significant. ‡Hypotension was defined as an SBP <90 mm Hg at any point.[6]			



OBSTETRIC ANESTHESIOLOGY 5

Does the Timing of P6 stimulation Affect Intra-cesarean Nausea and Vomiting? A Retrospective Study

Danielle Levin[1], Rohan Shah[2], Kate Balbi[2], Shaul Cohen[2]

[1]St. Elizabeth's Medical Center, Brighton, MA, [2]Rutgers - Robert Wood Johnson Medical School, New Brunswick, NJ

INTRODUCTION: Approximately 80% of parturients experience nausea and vomiting during cesarean section[1] when no prophylactic antiemetic treatment is given. While intravenous antiemetic medications have been advocated to prevent intraoperative nausea and vomiting during cesarean section, they are not entirely effective and may carry multiple adverse effects, including the development of gastrointestinal, renal, neurological, cardiovascular, and allergic reactions.[2-7] In our recent randomized clinical trial, we found that a non-pharmacological method, P6 stimulation, reduces intraoperative nausea and vomiting, without any side effects. We conducted a 3.5 year retrospective review to evaluate whether a 1-hour pre-treatment with P6 stimulation prior to the initiation of combined spinal epidural anesthesia (CSE) could further reduce the rate of intraoperative nausea and vomiting.

METHODS: Following IRB approval, a chart review from June 2015 to December 2018 was conducted: Group I (n=67) began receiving transcutaneous point P6 stimulation on the right wrist 1 hour prior to induction of CSE and continued receiving it throughout the cesarean section (Figure 1). Group II (n=45) began receiving P6 stimulation immediately prior to CSE administration and continued receiving it throughout the cesarean section. Group III (n=60) did not receive P6 stimulation. The P6 stimulator output current was adjustable from 0-70mA by a control dial that had ten different knob settings. The device was turned on gradually to the highest level of intensity tolerated by the patient. Evidence of N&V was collected intraoperatively. Excel and IBM SPSS Statistics V22.0 were utilized for Chi-squared test, T-test, and ANOVA analyses.

RESULTS: Baseline characteristics were similar between the three groups (Table 1). Markedly fewer patients experienced intraoperative vomiting in the Immediate P6 group (18.2%) than in the 1-hour P6 pretreatment group (31.4%, P=0.04). Interestingly, patients in the Immediate P6 group tolerated a significantly lower level of P6 stimulation (36.9±11.5mA) than in the 1-hour P6 pretreatment group (42.7±9.6mA, P<0.005). Furthermore, fewer patients experienced intraoperative nausea and vomiting in each of the treatment groups than in the control group (P<0.05).

CONCLUSION: Higher P6 stimulation for longer period of time before the induction of CSE did not further reduce the incidence of nausea and vomiting in our patients undergoing cesarean section. We suspect that P6 stimulation overtime increases patient tolerance and makes it less effective. P6 stimulation continues to be a simple, non-invasive, effective prophylactic alternative antiemetic treatment that could be of great interest to patients and obstetric anesthesiologists who prefer less invasive care with fewer side effects for cesarean section performed under CSE. We recommend applying prophylactic antiemetic P6 right before initiation of CSE for cesarean section.

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***Table I.* Patient and procedural characteristics**

Characteristics	P6 stimulation applied 1 hour before CSE administration (n = 67)	P6 stimulation applied right before CSE administration (n = 45)	Control Group (no P6 stimulation) (n = 60)	*P*-value
Age (years)	31.3 ± 5.1	31.8 ± 4.7	30.8 ± 4.8	0.59
Gestational age (weeks)	38.6 ± 1.4	38.3 ± 1.5	38.2 ± 2.4	0.44
BMI (kg/m^2)	30.5 ± 5.9	34.0 ± 9.2	31.6 ± 7.0	0.05
Hypertension, n (%)	45 (67.2)	23 (53.5)	32 (53.3)	0.16
Hypotension, n (%)	32 (47.8)	26 (59.1)	31 (53.4)	0.58
Hypoxia, n (%)	0 (0)	0 (0)	0 (0)	1
Surgery duration (min)	60.8 ± 17.5	65.4 ± 24.3	63.5 ± 21.4	0.52
P6 stimulation level	6.1 ± 1.4	5.3 ± 1.6	N/A	0.005
CSE induction position				
• Right lateral, n (%)	24 (35.8)	16 (36.4)	13 (21.7)	0.15
• Sitting, n (%)	43 (64.2)	28 (63.6)	47 (78.3)	0.15

Continuous variables were expressed as mean ± standard deviation, and P values were calculated using the one-way ANOVA test. Categorical variables were expressed as number (percentage), and P values were calculated using the chi-square test. P<0.05 were considered statistically significant.

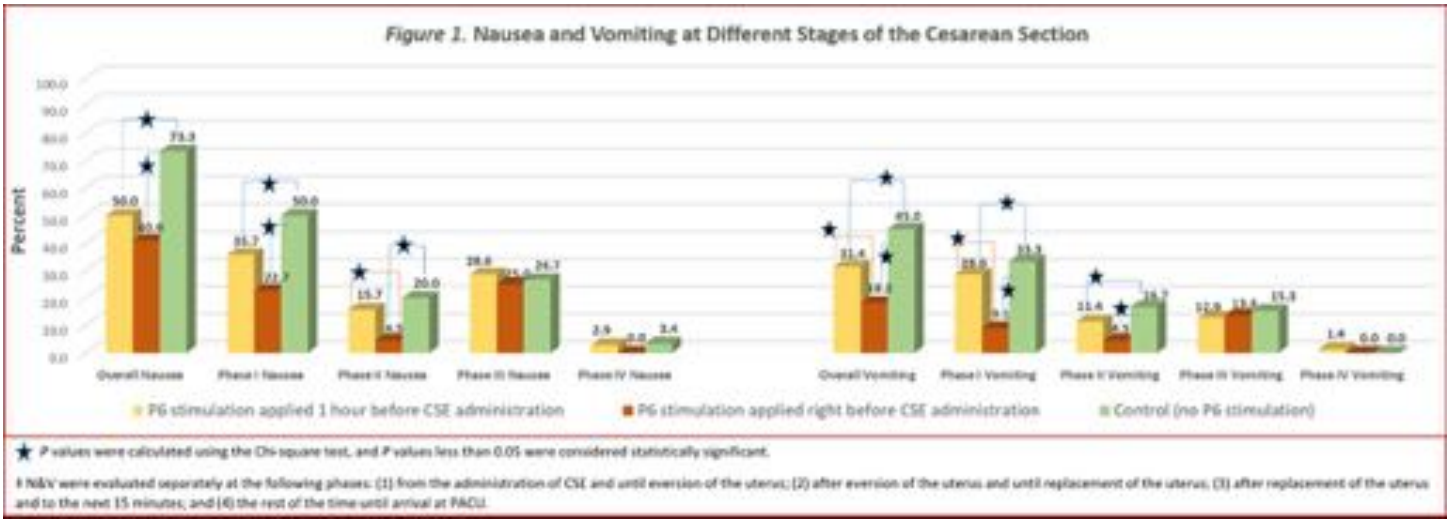

Figure 1. Nausea and Vomiting at Different Stages of the Cesarean Section

★ *P* values were calculated using the Chi-square test, and *P* values less than 0.05 were considered statistically significant.

† N&V were evaluated separately at the following phases: (1) from the administration of CSE and until eversion of the uterus; (2) after eversion of the uterus and until replacement of the uterus; (3) after replacement of the uterus and to the next 15 minutes; and (4) the rest of the time until arrival at PACU.

OBSTETRIC ANESTHESIOLOGY 6

Labour pain relief information: what women get, what they want, and how it influences their decisions and satisfaction

Milena Kovacevic[1], Rachel M Cheung[2], Michelle R Mozel[1], Susan M Lee[1]

[1]University of British Columbia, Vancouver, British Columbia, Canada, [2]University of British Columbia, Vancouver, Canada

INTRODUCTION: It is important for pregnant women to have adequate information about their labour pain relief options in order to make informed decisions, as it leads to higher childbirth satisfaction[1,2,3]. Unfortunately, many women feel that they lack adequate knowledge about pain relief before labour and delivery[3] and that they are not in a position to make a decision about their pain management prior to labour[4]. The purpose of this study was to better understand how women intending to deliver at a tertiary care obstetric center in Canada sought and used information about labour pain relief, what influenced their pain management decisions, and how prenatal information contributed to birth satisfaction.

METHODS: Institutional REB was obtained and participants recruited through prenatal hospital tours and hospital/clinic posters provided written and verbal informed consent. A qualitative approach was used involving 30 minute semi-structured telephone interviews until thematic saturation was reached. Interviews were recorded and transcribed verbatim. Data were analyzed using thematic analysis[5]. Two investigators independently generated codes which were discussed and applied to the data to identify themes. The themes generated were then used to create a comprehensive thematic map, outlining the relationships between the themes and codes.

RESULTS: Thematic saturation was reached after 13 patients, 9 postpartum and 4 antepartum ranging from 30 weeks gestational age to 15 weeks post-partum. Five themes emerged from the data. 1. 'Trustworthiness of various information sources.' There was a hierarchy of trustworthiness of the various information sources. Anecdotal sources, such as social media, the Internet, friends and family were perceived to be less trustworthy compared to objective sources, such as healthcare professionals and prenatal classes. 2. 'Role of information in labour anxiety.' Labour pain relief information and sources also played a role in increasing and decreasing anxiety. Anecdotal information sources, such as social media, fear of pain, ineffective pain management, uncertainty of labour and the pain experience, and inadequate knowledge about labour pain relief increased anxiety, while being prepared and seeking information about pain relief options helped to reduce labour anxiety. 3. 'Using information to prepare for labour.' It was important for women to have sufficient knowledge and to use the information they learned prior to labour to prepare for the uncertainty of labour and to make informed decisions for their labour pain management and birth plan. A variety of approaches, including both independent and collaborative decision-making, were used to prepare for labour. 4. 'Internal vs external influences on pain relief decision-making.' Both internal values and external factors were identified and found to influence patients' labour pain decision-making. 5. 'Managing the labour pain experience.' Most women preferred to have flexible birth plans, knowing that labour pain could be difficult to cope with, and methods to manage their pain could change in the moment. Effective pain management and meeting pain management expectations was found to lead to birth satisfaction.

CONCLUSION: Women seek information from a variety of sources, though most find information from hospital institutions, their healthcare providers, and prenatal classes more trustworthy. Having accurate information can lead to lower anxiety and better coping with labour pain, including better alignment of internal values with their labour pain management experience, and may lead to improved birth satisfaction. Therefore, it is important for healthcare providers to ensure that women have adequate and timely access to pain relief information prior to labour. Future research can focus on addressing gaps and barriers to obtaining knowledge.

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OBSTETRIC ANESTHESIOLOGY 7

Maternal Hypotension Requiring Pharmacologic Intervention: Is There a Clinically Significant Difference With the Various Modalities of Labor Epidural?

Eugenia Pugach[1], Bethany Wolf[2], Ashley Williams[3], Melissa Mahajan[3], Latha Hebbar[2]

[1]Medical University of South Carolina, Charleston, SC, [2]Medical University of South Carolina, Charleston, SC, [3]Medical University of South Carolina, Charleston, SC

INTRODUCTION: Dural puncture epidural (DPE) has gained popularity for labor analgesia due to early onset of action and better sacral spread compared to traditional labor epidural (LE), and lack of fetal bradycardia associated with combined spinal epidural (CSE)[1,2]. Past studies did not report increased incidence of maternal hypotension with DPE/CSE compared to LE, however the sample size of these studies was limited[3]. Therefore, the primary goal of this study was to compare incidence of maternal hypotension by labor epidural placement modality in a large cohort of laboring patients. With the plethora of definitions for hypotension, we chose physician directed pharmacological intervention as the surrogate for clinically significant hypotension.

METHODS: A retrospective cohort chart review (N=1752) examined rates of hypotension by epidural placement modality in laboring patients admitted between January and December of 2019 at one tertiary academic medical center. Maternal hypotension was defined as documentation of any of the following events in the patient electronic medical record within 2 hours of epidural catheter placement: a) administration of vasopressors (phenylephrine or ephedrine); or b) administration of IV fluid boluses. Analysis of the hypotension rates by epidural modality was performed using a Fisher's exact test approach. For the primary comparison, patients who had an incidental dural puncture (IDP) were included in the group of patients who received an LE as this was the planned modality. However, a secondary comparison was conducted excluding these patients. All analyses were conducted in SAS v. 9.4 (SAS Institute, Cary, NC).

RESULTS: The percentages of patients that experienced hypotension requiring pharmacologic intervention by labor epidural approach are shown in Table 1. There were no statistically significant differences in the rates of maternal hypotension between the different labor epidural modalities in the primary ($p = 0.591$) and secondary ($p = 0.58$) analyses.

CONCLUSION: In this retrospective chart review of a large cohort of laboring patients, there was no difference in the incidence of maternal hypotension requiring pharmacologic intervention between LE, DPE and CSE. The main limitation of this study was the retrospective nature of the analysis, including utilization of data physically entered into the electronic medical records by medical staff. Failure to document the surrogates for hypotension could have resulted in underreporting of maternal hypotension requiring medical intervention.

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Table 1: Incidence of hypotension requiring intervention by modality

Neuraxial Modality	N	N (%) with Hypotension
Epidural	1135	64 (5.6%)
DPE	511	35 (6.9%)
CSE	103	5 (4.9%)
Total	1752	104 (5.9%)

OBSTETRIC ANESTHESIOLOGY 8

Oxycodone Utilization following Cesarean Section in Women Receiving Continuous Epidural Infusion versus Single Dose Neuraxial Morphine

Daniel H Hart[1], Madina Gerasimov[2], Greg Palleschi[2], Judith Aronsohn[3]

[1]Northwell Health, Queens, NY, [2]Zucker School of Medicine at Hofstra/Northwell, Manhasset, NY, [3]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Manhasset, NY

INTRODUCTION: Cesarean section is the most common surgical procedure in the United States. There are two existing paradigms of pain control for patients undergoing cesarean section at our major healthcare centers. One is a single-dose neuraxial morphine (SDNM) technique while the other is patient-controlled epidural analgesia (PCEA). We compared the two paradigms with the goal of improving patient care through decreased postoperative opioid consumption and improving cost effectiveness. We sought to determine how total opioid consumption (in morphine milligram equivalents, MME) and patient satisfaction after cesarean section is affected by the mode of post-operative analgesia.

METHODS: A retrospective cohort study was performed of all cesarean sections within North Shore University and Long Island Jewish Hospitals from 2016 to 2018 comparing the total milligrams of oxycodone use in patients who received a combined spinal-epidural (CSE) followed by a PCEA using fentanyl/bupivacaine solutions versus SDNM. The study population consisted of 10,058 patients with 4,556 and 5,502 in the PCEA and SDNM groups, respectively. Both populations utilized the same multimodal pain protocol. The primary outcome was postoperative oxycodone use. Secondary outcome included patient satisfaction score. For continuous parametric outcomes, data was presented as means with 95% confidence intervals and groups were compared using the student t-test. If necessary, log transformation was applied to continuous outcome variables in order to meet the required assumptions for validity of a t-test. If no suitable transformation was available, the Wilcoxon rank sum test was used, and data was presented as medians with interquartile ranges. Categorical data was presented as percentages and frequencies and was analyzed using the chi-square test. Multiple linear regression analysis was used to assess the effect of postoperative anesthesia protocol (SDNM vs. PCEA) on oxycodone use (milligrams) in the first two postoperative days while controlling for other potential risk factors. Statistical power for this study was estimated using the outcome oxycodone requirement in mg.

RESULTS: The study population consisted of 10,058 patients between 16 and 55 years of age, with a mean age of 33 years. Patient baseline characteristics are presented in table 1. While 8% (n=372) of patients in the PCEA group required oxycodone on the first postoperative day, 28.4% (n=1,563) of SDNM patients received oxycodone rescue ($p<0.0001$). On the second postoperative day, 47.2% (n=2,148) of PCEA and 52.7% (n=2,899) of SDNM patients required oxycodone ($p<0.0001$). The median number of oxycodone doses administered over the first two postoperative days were 0 (0-10) for the PCEA group and 5 (0-20) for the SDNM group ($P<0.0001$). Additional patient recovery characteristics are presented in table 2. Results of a multiple regression analysis where other patient factors (age, height, weight, ethnicity, race and previous opioid use) were included alongside site/protocol demonstrated that for the PCEA group the predicted amount of oxycodone used was 3.3 mg (95% CI: -3.9 to -2.7, $p<0.0001$) less than SDNM holding all other variables constant. Interestingly, the predicted oxycodone use was 2.7 mg higher in previous opioid users (95% CI: 1.01-4.46, $P=0.02$) adjusting for all other variables including site/protocol. With respect to overall patient satisfaction with anesthesia using a 5-point Likert scale, median satisfaction scores were 5 or 'very satisfied' (IQR: 4-5 or 'somewhat to very satisfied', n=879) and 5 (IQR: 5-5, n=691) for SDNM and PCEA protocols, respectively ($p=0.0007$).

CONCLUSION: We observed that use of PCEA after cesarean section reduces inpatient oxycodone use during the first two postoperative days compared to SDNM. Although PCEA use was associated with less oral oxycodone use than the SDNM group, when accounting for total neuraxial opioid use, the PCEA group used 240 MMEs per day versus the SDNM use of 45 MME on Day1. There was no difference in pain scores or overall satisfaction with pain relief between groups. The SDNM modality does not involve continuous infusion and therefore requires fewer nursing assessments, compared to the PCEA group, lessening the cost burden of post-operative analgesia. The SDNM method is not only more cost-effective, but also appears to be relatively opioid-sparing without affecting patient satisfaction or comfort compared to PCEA after cesarean section.

Table 1: Patient baseline characteristics.

	SDNM (n=5,502)	PCEA (n=4,556)	P value
Age (years)	32.1 (31.9-32.2)	33.7 (33.6-33.8)	<0.0001
Weight (kg)	83.7 (83.3-84.2)	81.4 (80.9-81.8)	<0.0001
Height (cm)	161.4 (161.2-161.6)	161.8 (161.5-163.0)	0.02
Hispanic ethnicity	782 (14.2)	464 (10.2)	<0.0001
African-American race	1,304 (23.7)	364 (8.0)	<0.0001
History of opioid use	94 (1.7)	176 (3.9)	<0.0001

Data are provided as n (percentage) or median (interquartile range)

Table 2: Oxycodone use during postoperative days 1 and 2.

	SDNM (n=5,502)	PCEA (n=4,456)	P value
Total oxycodone received (mg)	11.60 (11.19-11.99)	8.23 (7.86-8.60)	<0.0001
Median oxycodone doses	5 (0-20)	0 (0-10)	<0.0001
Patients who received oxycodone	3,142 (57.1)	2,169 (47.6)	<0.0001

Data are provided as n (percentage) or median (interquartile range)

OBSTETRIC ANESTHESIOLOGY 9

Institutional Readiness for COVID-19 Parturient and the Ethical Trilemma of healthcare staff safety versus maternal and fetal safety

Vandana Vaishnav[1], Michelle Morais[2], Annemaria De Tina[2], Kara Gibson[2]

[1]McMaster University, Hamilton, Ontario, [2]Hamilton Health Sciences, Hamilton, Ontario

INTRODUCTION: The UK National Institute for Health and Care Excellence (NICE) guidelines recommends decision-to-delivery interval of 30 min for category 1 emergency cesarean section[1]. The time pressure demands a seamless coordination among obstetrician, anesthesiologist, neonatologist, respiratory therapist and operating room (OR) staff to execute this task. Spinal anesthesia is more common mode of anesthesia as compared to general anesthesia and considered as a safer option for cesarian section[2,3]. When there is a need to deliver the baby immediately, fetal safety overrides mom's safety and general anesthesia is provided to facilitate rapid onset of unconsciousness and muscle relaxation. The corona virus disease -19 (COVID-19) pandemic has woven another layer of complexity. For a COVID-19 patient, the OR team needs to don personal protective equipment (PPE) prior to the procedure which causes delay. This study highlights key steps undertaken at our institute in planning, implementation and evaluation of new COVID workflow at Labour & Delivery (L & D) unit (Figure 1). It assesses operational readiness of L & D unit for emergency cesarean section of a COVID-19 parturient using in situ simulation as a tool, and addresses the ethical trilemma of healthcare staff versus maternal and fetal safety.

METHODS: This is a qualitative study and was exempted from institutional ethics board review for quality improvement initiative. Planning At the outset of COVID-19 pandemic, we reviewed literature for information regarding COVID-19 microbiology and pathophysiology and the latest guidelines[2-4]. We also reviewed the institutional policies and algorithms for management of parturients at risk of COVID-19 infection (Figure 2). Implementation We used evidence-based tools like checklists and simulation-based training to prepare anesthesiologists and other staff. We designated one OR at L & D unit for COVID (suspected or confirmed) patients. Institutional COVID policies and algorithms were circulated to all acute care areas. Evaluation We gathered interdisciplinary team involving anesthesiology and obstetrics and gynecology, along with clinical educators and nurse managers from L & D to conduct an unannounced in situ simulation to assess systems integration and workflow with new COVID-19 specific clinical pathways. There were two instructors from anesthesiology, one instructor from obstetrics and gynecology, and two clinical educators from L & D staff who recorded the observations. The assessment included response from the nurse at the L & D reception on arrival of patient, immediate response of the team to fetal distress, patient transfer to the OR, interdisciplinary interaction before cesarean section, donning and doffing of team members, COVID safe airway management, Neonatal Intensive Care Unit (NICU) team response to neonatal bradycardia and overall conduct of the procedure. At the end of the simulation, we organized a debrief to gain feedback from participants and for short interval education opportunity.

RESULTS: In situ simulation facilitated recording of active failures and latent safety issues5. Active failures were errors related to non-technical skills like leadership, situational awareness, decision-making, communication, teamwork or breach in COVID protocol. Latent safety issues were in-built flaws in the system related to environment, equipment, drugs, personnel or policy. We identified 7 instances of active failures and 5 latent safety issues during in situ simulation (Table 1). First unanticipated error was patient not being screened over phone by the reception staff for COVID symptoms. A significant error observed during simulation was failure to inform the anesthesiologists and NICU team of the COVID status of patient. Equally significant concern was the ethical trilemma of team weighing the pros and cons of providing general anesthesia versus spinal anesthesia for prompt delivery of the baby and wasting extra time for appropriate donning of PPE. Appropriate recommendations were circulated to staff.

CONCLUSION: Our assessment of new COVID policy and workflow in L & D unit raised an important ethical trilemma of prioritizing healthcare staff safety versus maternal or fetal safety. In situ simulation helped identify gaps in current practice and areas for systemic improvement. Further training and implementation of recommended changes were required to upgrade the institutional policies and documents.

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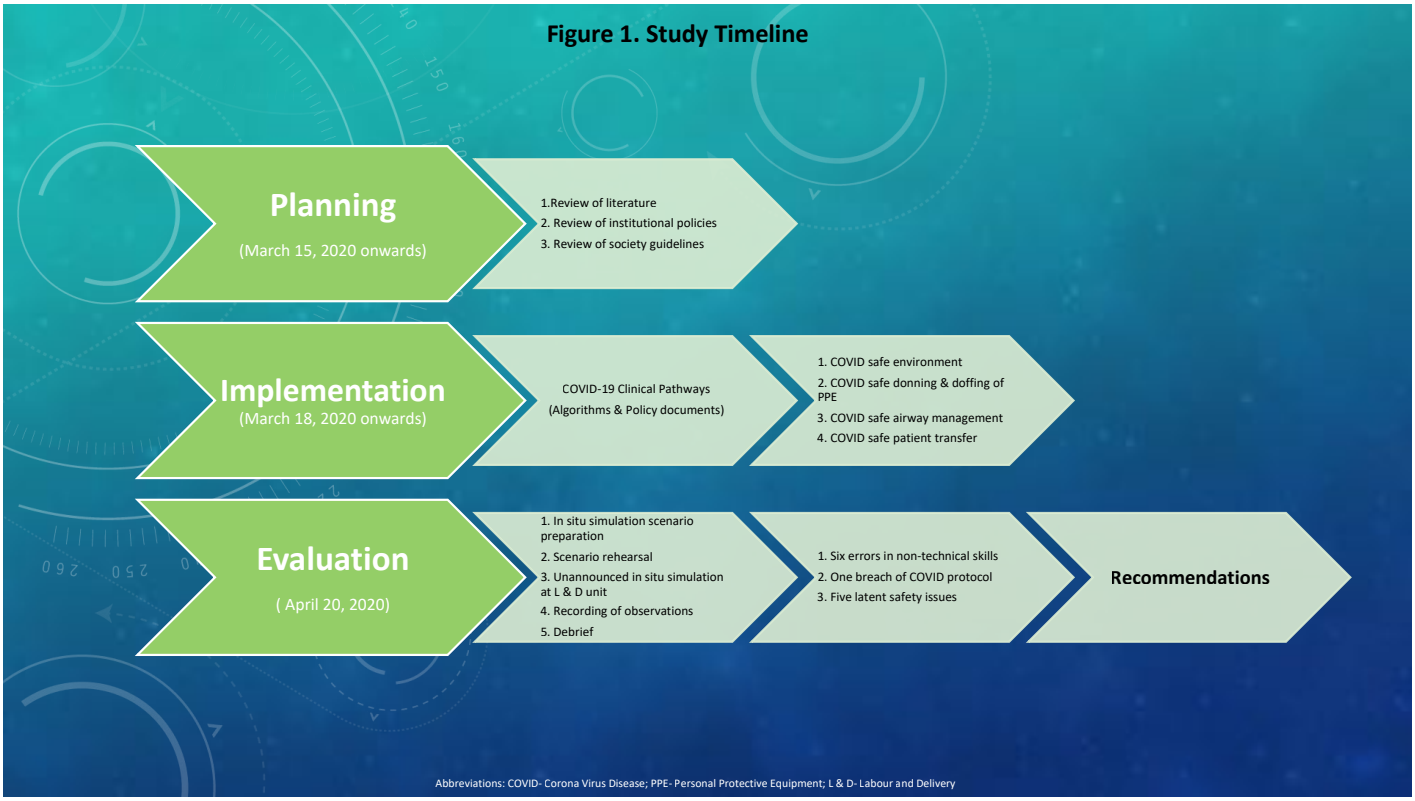
Table 1: In-Situ Simulation Observations & Recommendations

ACTIVE FAILURES	OBSERVATIONS	RECOMMENDATIONS
Leadership	Anesthesiologist and NICU team not informed of patient's COVID-19 status	Providing COVID status information to all involved teams about infection precautions facilitates timely donning and doffing of PPE.
Situatonal Awareness	Patient was not screened over phone and she arrived to L & D without a mask.	If patient is not screened at the hospital entrance, then screening should be done on the phone before entering L&D. A mask should be provided at the entrance and the phone should be wiped with ant-viral agent.
Decision Making	An emergency cesarian section announcement required all team members to don PPE before entering OR in anticipation of general anesthesia and AGMP. With limited space in donning area, a lot of time was consumed in donning.	Careful consideration of general anesthesia (GA) versus spinal anesthesia (SA) should be given by Obstetrician and Anesthesiologist. Trying to save time by doing GA is counterproductive with extra time required for donning of PPE.
Communication	NICU team transferred baby outside of the crowded OR without informing the team.	NICU team should pause the team for baby transfer. Closed loop communication is helpful.
Team Work	There was only one clean team member available outside the OR to obtain and provide fresh supplies.	One clean team member inside and one outside of OR door should coordinate to get supplies.
COVID Precautions	Patient's temperature measured with an oral thermometer on arrival	An infrared temperature monitor should be used to measure forehead skin temperature and maintain safe distance.
	In the absence of an anteroom, the doffing area is within OR and in the exit path of OR.	The doffing area should be marked with a colored tape, to avoid traffic around it.
LATENT SAFETY ISSUES		
Environment	Two baby supply carts were stored in the OR. It occupies space in an already crowded room and prevent smooth movement of OR staff and NICU team. There is potential contamination of the unused cart as well.	The second baby supply cart should be stored outside and only brought inside when needed.
Equipment	Glidescope cart was full of extra supplies.	The cart should store one blade of size 3 and 4 each to avoid contamination of multiple blades.
Drugs	Obtaining individual opioid ampoules and vial dispensing is time consuming from the drug cart.	A pre-prepared opioid kit would save time.
Personnel	OR was crowded with multidisciplinary staff at the time of AGMP.	Minimal staff presence at intubation and extubation.
Policy/Procedures	Intubation checklist, equipment/drugs checklist not available in OR.	Checklists help in planning all essential tasks and supplies. Checklists should be laminated and either attached to the anesthesia machine or pasted on walls. Checklists should be wiped clean after each case.

Notes: COVID-19: Corona Virus Disease-19; L & D: Labour & Delivery; PPE: Personal Protective Equipment; AGMP: Aerosol Generating Medical Procedure; OR: Operating Room; NICU: Neonatal Intensive Care Unit.



Cesarian Section for Suspected or Positive COVID-19 Patient

Surgical mask for patient on transfer to OR

PPE for all staff
Limited OR staff in attendance, no students
Airborne/ droplet precautions signage on door

Regional anesthesia preferred
GA only for fetal or maternal emergencies

Anticipate significant hypotension with regional anesthesia.
Not very responsive to lateral tilt, fluid boluses or vasopressors.
(*may consider invasive BP monitoring and/or Levophed infusion)

Baby resuscitation in OR only
(maternal contact as per OB/Peds)

Maternal recovery in her own /negative pressure room and not in PACU
Maternal Monitoring for vital signs and respiratory deterioration

Chen et al. Safety and efficacy of different anesthetic regimens for parturients with COVID-19 undergoing cesarian deliveries: a case series of 17 patients. CJA;MAR 2020

*** as per institutional policy**

Sept 3, 2020 HHS Labour and Delivery algorithm for management of COVID Risk Patients

Labour and Delivery algorithm for management of COVID RISK patients

We recommend all pregnant women with COVID RISK (confirmed[1]/suspected[2] COVID) be followed by the obstetrical service, as possible.

- Pregnant women with COVID RISK will be asked to call before coming to hospital where possible, so L&D can be prepared for arrival
  - All patients presenting to L&D should be screened for COVID symptoms/ exposures
  - If MRP determines patient "COVID Risk" follow below algorithm (for antepartum/intrapartum/postpartum management)

COVID-19 Risk patient presents to labour & delivery
Inform site specific ICP[3] and MRP as soon as feasible (if unsure of history – can clarify risk factors with ICP – call 36443, infection control on call)

- RN or delegate to provide surgical mask to patient, patient to be masked if not in private room (e.g.: transport between rooms), ensure hand hygiene, wipe phone
- RN dons PPE and triages patient, moves patient to designated isolation area
- Isolate in DROPLET CONTACT[4] precautions
- Limit staff involved in the care as possible
- Send single NPS at the direction of ICP or MRP

For management of support person in labour/postpartum, refer to visiting guideline.

Well women

Unwell women

Not in labour/Post partum
- Continue follow up as required

If Admitted: Transfer to appropriate level of care
If Discharged: Provide education for self-isolation, inform public health[4]

In labour (see Labour and Delivery below)
Initiate continuous fetal monitoring
Assessment to decide appropriate level of care
Consider type and location of delivery
Anesthesia consult early, inform NICU as appropriate

Not in labour/Post Partum
Fetal assessment as appropriate
Assessment to decide appropriate level of care

Requiring medical care
- Admission to Ward
- Isolate in single room, DROPLET CONTACT precautions

If Discharged: Provide education for self-isolation, inform public health[4]

Requiring intensive care
- Admission to womens' ICU
- Isolate in single room, DROPLET CONTACT precautions
- AGMP treatment in Progress[5] if AGMP[6] to be done
- Transfer to Ward if not needing ICU care

If Discharged: Provide education for self-isolation, inform public health[4]

Labour and Delivery procedure:
Droplet contact precautions during delivery (minimize staff in the room)
- Wipe secretions off infant ASAP, early bath as possible (for infant procedures see page 2)

Vaginal Delivery
- DROPLET/CONTACT PPE for all obstetrical staff involved directly in the delivery due to body fluid contact exposure

Caesarean Section Delivery
- Place surgical mask on patient prior to transfer, advise hand hygiene.
  - Mask on patient for transfer to OR, mask removed in OR
- Minimize staff in the room as much as possible (eg: NICU staff, learners)
- N95 mask/eye protection/gown/gloves if unable to leave the room for AGMP
- For regional anesthetic, droplet/contact precautions

Status of mother post delivery
COVID-19 status is not relevant when making this decision

Stable mom:
- Deferred Cord Clamping as per routine guideline
- Can do skin to skin once mom's chest /neck washed with soap and water, mom to wear surgical mask when within 2m of infant
- Cord blood storage – outside of the room if planned

- Reassess need for isolation with ICP once NPS results available
- mom and infant, if well, can be transferred to Ward
- If mom is within 14d of COVID exposure (eg. travel OR contact with confirmed COVID+ person), mom to remain in DROPLET CONTACT isolation for that duration (infant as well if with mom for any duration post partum)

If Discharged: Provide education for self-isolation, inform public health

Unstable mom (unable to care for infant):
- Early Cord Clamping
- Separation of infant and mother
  - Transfer infant to designated potential COVID space
  - Keep infant in single room with DROPLET CONTACT PRECAUTIONS pending maternal swab result
- Admit mom to womens' ICU or womens' SD
- DROPLET CONTACT PRECAUTIONS for mom unless requiring AGMP
- AGMP – N95, eye protection, gown and gloves
- Cord blood storage – outside of the room if planned

[1] **Confirmed COVID-19**: someone who has tested positive for COVID-19 in the last 14days, or is still requiring additional precautions for COVID
[2] **Suspected COVID-19**: someone who has had direct contact with someone confirmed to have COVID-19 (COVID exposed), OR who has travelled internationally IN THE PAST 14DAYS, or has symptoms of COVID-19 and is pending testing
- If no symptoms but have the above exposures, they would be on HOME ISOLATION as per public health/ Infection Control guidelines.
- All suspected COVID-19 patients symptomatic or not should be kept in DROPLET CONTACT PRECAUTIONS for the 14DAYS from their LAST EXPOSURE TO COVID-19 or date of return from international travel)

[3] **ICP**: Infection Control Practitioner on call (24/7)
[4] **Droplet Contact precautions**: surgical mask with visor, face shield or goggles, gloves and gown (for delivery staff)
[5] **AGMP treatment in Progress** – N95 respirator with face shield/goggles/visor, gown and gloves
[6] **Aerosol-Generating Medical Procedures (AGMP)**, refer to guidance on AGMP and Oxygen Therapy document. For AGMP through closed incubator, no need for N95 if greater than 2m from closed incubator.
Procedures NOT considered to be AGMP: collection of a Nasopharyngeal swab

OBSTETRIC ANESTHESIOLOGY 10

Assessment of left ventricular diastolic function by analyzing intraventricular pressure difference during third trimester of pregnancy

Yurie Obata[1], Koichi Akiyama[1], Yu Hirase[1], Teiji Sawa[2]

[1]Yodogawa Christian Hospital, Osaka, Japan, [2]Kyoto Prefectural University of medicine, Kyoto, Japan

INTRODUCTION: Physiologic and hemodynamic changes during pregnancy have been well investigated[1]. However, changes in left ventricular (LV) diastolic function associated with pregnancy is not fully understood[2]. Recently, the intraventricular pressure difference (IVPD) which is the driving force of the LV suction is drawing attention as a crucial parameter of diastolic function[3]. The purpose of the present study was to investigate LV diastolic function during the third trimester of pregnancy assessed using conventional echocardiographic parameters and IVPD.

METHODS: This is a prospective observational study. We performed transthoracic echocardiography in healthy pregnant women in the third trimester and non-pregnant controls, and assessed left ventricular diastolic function using the following parameters: end diastolic and end systolic diameter of LV (Dd, Ds); mitral inflow peak velocities in early diastole (E wave) and late diastole (A wave); E/A ratio; tissue Doppler-derived peak velocities in early diastole at lateral and septal basal regions (lateral e' and septal e'); and IVPD. We stored color M-mode Doppler images of the mitral inflow and estimated IVPD using an in-house MATLAB code (MathWorks, MA, USA). Wilcoxon rank-sum test was used to compare the parameters in pregnant and non-pregnant groups. A p-value less than 0.05 was considered statistically significant.

RESULTS: We included 20 pregnant women and 19 non-pregnant controls. Dd was not significantly different between the two groups whereas Ds was significantly higher in pregnant group than non- pregnant group (Ds: 28.15 mm [24.85 to 30.05] vs 25.6 mm [22.5 to 27.4], $p<0.05$). E wave was not significantly different between the two groups, whereas A wave was higher and E/A was lower in pregnant women compared to those in non-pregnant controls (A wave: 50.6 cm/sec [45.93 to 62.73] vs 38.5 cm/sec [35.1 to 42.1], $p<0.0005$, E/A: 1.33 [1.17 to 1.54] vs 1.73 [1.52 to 1.94], $p<0.0005$). Also, lateral e' and septal e' were significantly lower in pregnant women. (lateral e': 12.77 cm/sec [10.73 to 14.94] vs 16.31 cm/sec [13.25 to 19.92], $p<0.005$, septal e': 10.41 cm/sec [8.32 to 11.80] vs 13.93 cm/sec [12.03 to15.24], $p<0.0001$). There was no significant difference in IVPD (total IVPD: 3.43 mmHg [2.70 to 4.33] vs 4.32 mmHg [2.92 to 5.36] $p=0.18$; apical IVPD: 1.94 mmHg [1.55 to 2.69] vs 2.21 mmHg [1.82 to 2.86]), $p=0.48$).

CONCLUSION: We found that IVPD doesn't change during the third trimester of pregnancy although conventional parameters of LV diastolic function are altered. Our results suggest that the heart adapts to meet the significant increase in total blood volume during pregnancy by increasing atrial contraction and maintaining the ventricular sucking force.

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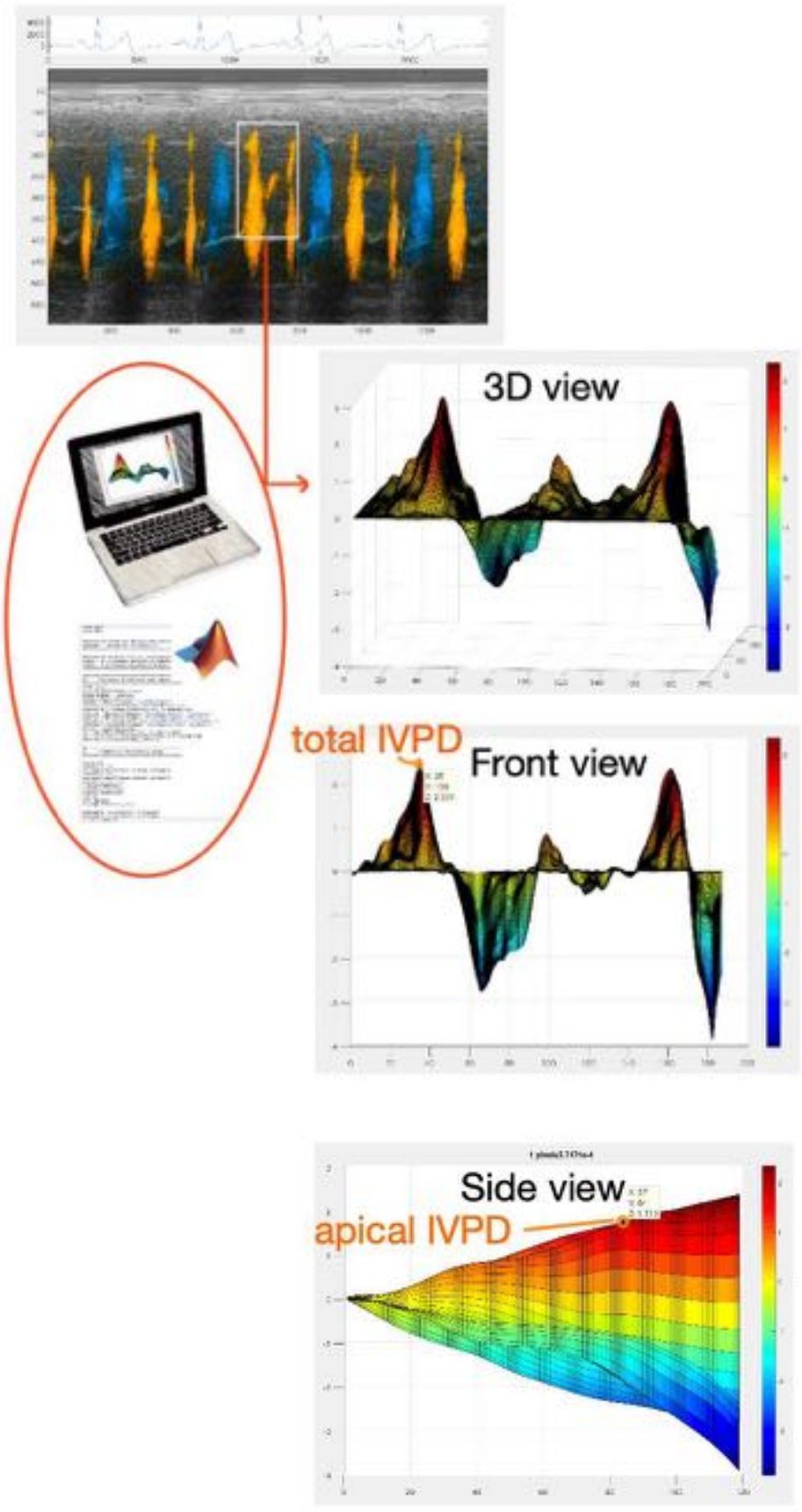

OBSTETRIC ANESTHESIOLOGY 11

Genome-wide Association Study of patients with Post-partum Hemorrhage

Shubhangi Singh[1], Melissa E Bauer[2], Thomas T Klumpner[1], Anita Pandit[1], Vesela Kovacheva[3,4]

[1]University of Michigan, Ann Arbor, MI, [2]Duke University School of Medicine, Durham, NC, [3]Brigham and Women's Hospital , Boston, MA, [4] Harvard Medical School, N/A

INTRODUCTION: Postpartum hemorrhage (PPH) is one of the leading causes of maternal morbidity and mortality world-wide and in the United States[1]. Although there are a number of clinical risk factors for PPH such as multiple gestation, polyhydramnios, prolonged labor, chorioamnionitis, pre-eclampsia, some women develop PPH with no known risk factors. Epidemiological studies[2] have suggested that a portion of the PPH risk may be heritable. We undertook a genome wide association study (GWAS) to investigate the genetic risk factors that may be associated with PPH.

METHODS: Study participants were obtained from the Michigan Genomics Initiative (MGI) which is a collaborative research effort among physicians, researchers, and patients at the University of Michigan funded through Precision Health with the goal of harmonizing patient electronic health records with genetic data to gain novel biomedical insights. We identified 250 PPH cases (by ICD 9/10 codes 666/O72 or a blood loss of >1000 mL at the time of delivery) and 714 controls of European ancestry. The control patients had at least one live birth, no PPH and age >18 yrs. Standard quality control was performed at the sample and SNP level. Genetic ancestry was determined by principal component (PC) analysis. Data analysis was performed using the additive logistic mixed model implemented in SAIGE v0.43.3, adjusted for age, 10 PCs and genotyping chip version. SAIGE adjusts for relatedness and also performs a saddlepoint approximation adjustment that accounts for case-control imbalance.

RESULTS: This maternal PPH GWAS did not identify any genetic loci at genome wide significance level (< 5x10^-8). The three top genes of suggestive significance were CRAMP1 (p= 1.30x10^-7), which is a transcriptional factor associated with blood pressure, body height, erythrocyte count and self-reported educational attainment, ZNF556 (p= 1.59x10^-7), which is a transcriptional factor associated with variants for cholesterol and triglycerides, risk for, AML, chronotype measurement, CSF biomarkers and HTR2C (p= 4.03x10^-7), which codes for a G-protein coupled receptor for 5-hydroxytryptamine.

CONCLUSION: We did not identify any genes that reached genome-wide significance in this GWAS study. This could be due to the sample size, confounding factors or small effect size. A gene coding for 5-hydroxytryptamine or serotonin receptor was among the top 3 genes of suggestive significance. Serotonin promotes hemostasis by inducing vasoconstriction of injured vessels as well as enhancing platelet aggregation[3], making this one of the plausible physiological pathways for genetic factors influencing PPH. In fact, use of selective serotonin reuptake inhibitors during pregnancy has been associated with increased risk of PPH[4,5]. Larger GWAS studies are needed to investigate the role of genetic factors in the risk for PPH. Further research is also needed to elucidate biological mechanisms underlying this association.

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Subspecialty Abstracts

PAIN MECHANISMS

PAIN MECHANISMS 1

A two-insult model of temporomandibular disorder produces painful gnawing dysfunction in rats

Anthony Phero[1], Luiz F Ferrari[1], Norman E Taylor[1]

[1]University of Utah, Salt Lake City, UT

INTRODUCTION: Temporomandibular disorders (TMD) are a cluster of painful orofacial conditions that are characterized by pain in the temporomandibular joint (TMJ) and surrounding muscles/tissues. Studies show TMJ stress during medical procedures such as endotracheal intubation can trigger TMD, and a predisposition seems to play a role in this condition. In this study, we characterize a two-insult rat model of TMD that mimics this clinical pathophysiology.

METHODS: This study was approved by the authors' IRB for animal research. Male Sprague Dawley rats had their jaws opened with a 3.5N force for one hour daily, for 7 days (Panel A) to recapitulate the initiation and progression of TMD. This protocol was combined with either a local injection of the inflammatory agent carrageenan (CARR, 125 µg/TMJ) or a 14-day sustained 15mg/kg/day dose of the catechol-O-methyltransferase (COMT) inhibitor OR486. The 'ratgnawmeter' was used as the behavioral endpoint, which uses time taken to chew through a resin dowel as a surrogate for painful TMD. Tests in the ratgnawmeter were performed on days 1 to 8, 10, and 13 for all groups.

RESULTS: Daily overloading the temporomandibular system with a 3.5N force for 7 days did not significantly alter pain behavior in the ratgnawmeter (Panel B). However, previous inflammation produced by CARR (Panel C) or sustained inhibition of COMT by OR486 (Panel D), significantly increased the time taken to complete the assay during the ongoing jaw extension period ($p < 0.001$), i.e., the 'acute phase'. Interestingly, after the end of this protocol (day 7), chewing time remained elevated above baseline ($p < 0.05$) in the OR486-treated group, suggesting that COMT plays a role in the progression to persistent pain during masticatory function.

CONCLUSION: These results are consistent with clinical findings that TMJ stress alone does not trigger TMD, and describes how a two-insult model of TMD is able to induce painful masticatory dysfunction during both the jaw loading and post-jaw loading periods.

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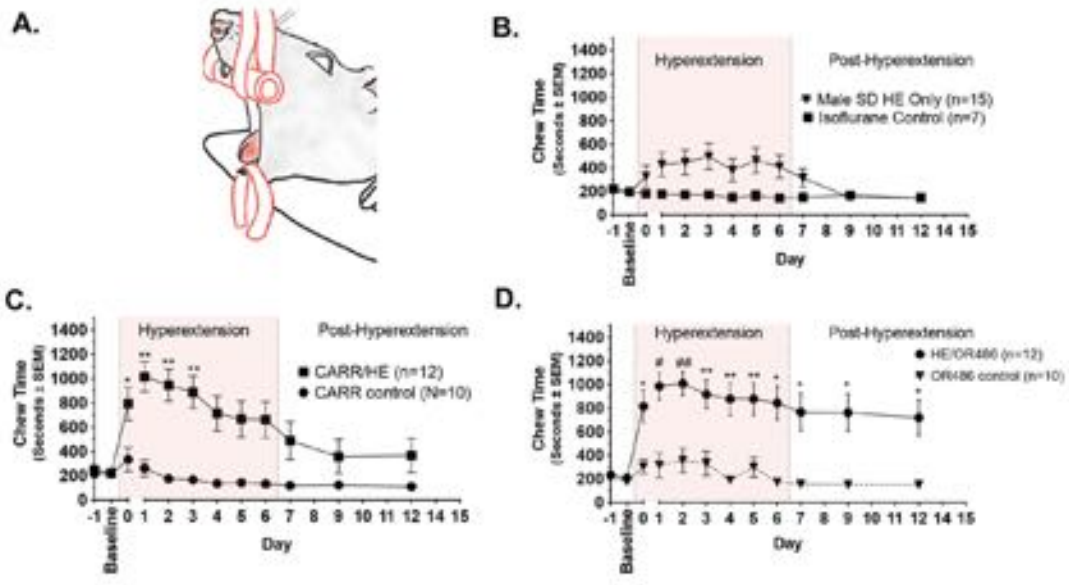

Figure 1: (A) Mechanical jaw overloading method. (B) Sprague Dawley male rats subjected to a 7-day 3.5N mechanical jaw hyperextension (HE) did not exhibit any significant increases in painful gnawing dysfunction, and returned back to baseline following the cessation of loading. (C) Rats pretreated with carrageenan showed a significant increase in chewing time that peaked 24 hours post injection and gradually resolved over time. (D) The sustained inhibition of COMT using OR486 in conjunction with a repeated hyperextension disposes rats to develop painful gnawing dysfunction during the 7 day loading period, and persisted 7 days after the jaw loading period.
##P < 0.0001, #P < 0.001, **P < 0.01, *P < 0.05 versus respective controls.

PAIN MECHANISMS 2

What Predicts the Outcome of Postsurgical Neuropathic Pain rather than Numbness? A Prospective, Longitudinal Assessment of Chronic Postmastectomy Sensory Disturbances out to 1 year Postop

Kristin L Schreiber[1], Kelsey Mikayla Flowers[2], Natt Zinboonyahgoon[2], Yun-Yun K Chen[2], Robert R Edwards[2]

[1]Brigham and Women's Hospital; Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA

INTRODUCTION: Both painful (e.g.,burning, stabbing, and allodynia) and non-painful (numbness) sensory disturbances may arise after surgical injury of peripheral nerves, and may significantly impact patients' lives if persistent. Most questionnaire-based measures of neuropathic pain combine painful neuropathic symptoms together with the more benign, and arguably adaptive, symptom of numbness, in a single score. The purpose of this prospective longitudinal study was to investigate the overlap and divergence of surgical, psychosocial and psychophysical predictors of painful neuropathy vs numbness throughout the first year after breast surgery.

METHODS: Patients (n=259) undergoing lumpectomy or mastectomy completed the Breast Cancer Pain Questionnaire(BCPQ) preoperatively and postoperatively at 2 weeks, 3, 6 and 12 months, including a question about numbness and a validated subscale assessing the presence of painful neuropathic symptoms (NeuPPS), including pins and needles, electric shock, heat/burning, allodynia, and pain from cold temperatures. Additional validated psychosocial questionnaires and psychophysical testing (bedside QST) were also completed at baseline.

RESULTS: Numbness was the most frequently reported sensory disturbance, present in approximately 50% of patients, and stable across time. NeuPPS was highest at 2 weeks, decreasing over time ($F(1,124)=37.71$, $p<.001$). Both NeuPPS and numbness were closely associated with greater clinical pain severity and impact, as well as associated with younger age, axillary surgery, and psychosocial factors including anxiety and catastrophizing. Interestingly, many surgical and treatment factors, including greater surgical extent, bilateral surgery, surgical duration, and chemotherapy were associated with greater numbness, but not NeuPPS. Conversely, other chronic pain, lower activity level, larger perioperative opioid requirement, higher temporal summation of pain, and lower pressure pain threshold and tolerance were associated with NeuPPS, but not numbness.

CONCLUSION: Identifying factors that uniquely predict numbness compared to those that uniquely predict painful neuropathic symptoms may offer insight into the pathophysiologic plasticity underlying persistent postsurgical pain in those patients that develop this outcome.

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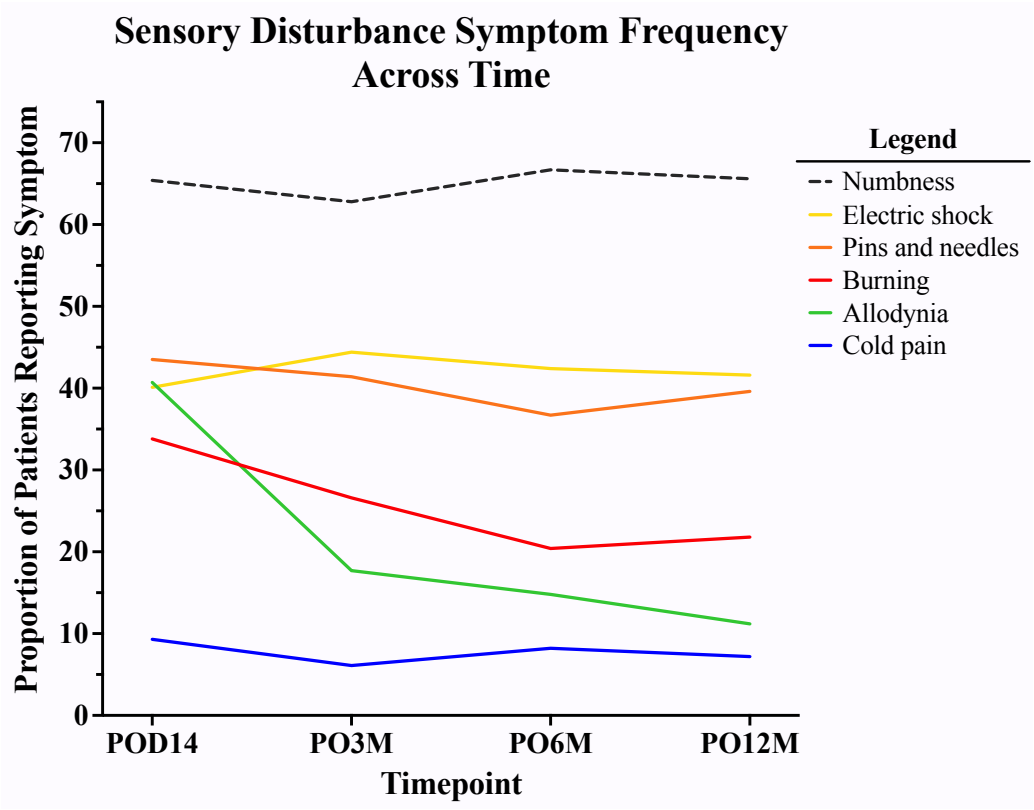

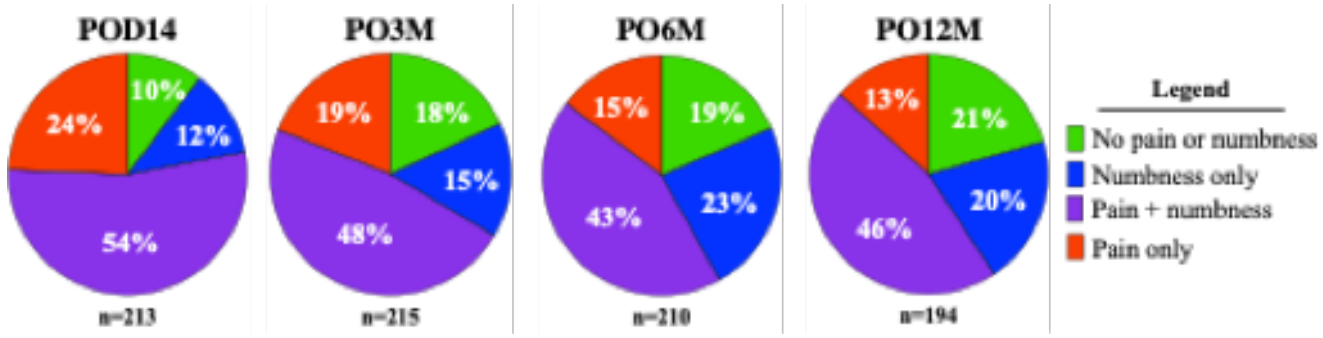

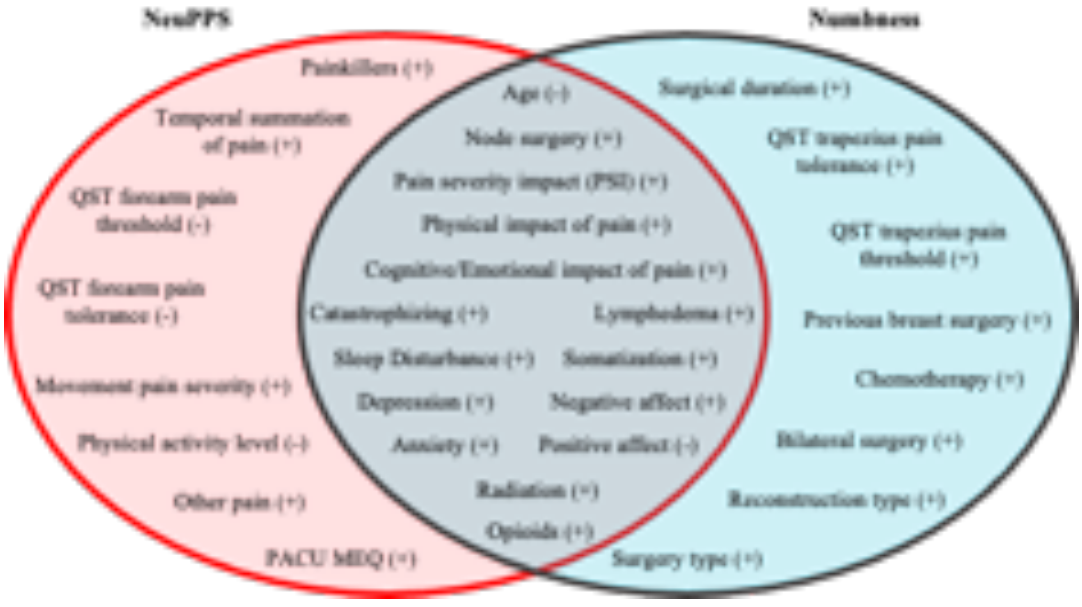

PAIN MECHANISMS 3

Leveraging TRPV1 genetic divergence between avian and mammalian species to develop a TRPV1^{K710N} knock-in mouse and a novel analgesic

Shufang He[1], Vanessa Zambelli[2], Yang Bian[3], Freeborn Rwere[4], Eric R Gross[5]

[1]The Second Hospital of Anhui Medical University; Stanford University, Hefei, China, [2]Stanford University; Laboratory of Pain and Signaling, Butantan Institute, Palo Alto, United States of America, [3]Stanford University, Palo alto, United States of America, [4]Stanford University, Palo Alto, United States of America, [5]Stanford University, Stanford, CA

INTRODUCTION: Pain afflicts ~1 in 5 individuals worldwide and treatment for pain, such as opioids, can lead to secondary health problems including abuse, addiction, and overdose. Therefore, there is an unmet need to understand the molecular mechanism of pain and in doing so, develop novel analgesics. One target is the transient receptor potential vanilloid 1 channel (TRPV1), a cation channel triggering calcium influx in the presence of noxious stimuli[1]. Interestingly avian species, unlike mammalian species, have a limited response to capsaicin; accredited to the genetic divergence of the TRPV1[2]. Here, we questioned whether introducing a genetically divergent avian TRPV1 sequence by CRISPR/Cas9 to rodents limits pain responses without exacerbating cellular injury.

METHODS: To identify genetically divergent TRPV1 residues between avian and mammalian species, multiple sequence alignment was performed. These identified variants were analyzed using Chimera using the rat TRPV1 crystal structure (PDB ID: 3J5P)[3]. Next, a TRPV1^{K701N} knock-in mouse was created by CRISPR/Cas9 gene-editing. To evaluate behavioral differences in response to noxious stimuli, wild type TRPV1 and TRPV1^{K701N} mice were exposed to capsaicin-laced bird food, intraplantar capsaicin, or intraplantar Brp lysophosphatidic acid (Brp-LPA, an analogue of LPA that directly targets TRPV1 at K710)[4]. Primary dorsal root ganglion (DRG) neurons were also isolated from wild type TRPV1 and TRPV1^{K701N} mice and capsaicin-induced calcium influx was measured. Further, a cell-permeable peptide (V1-Cal, 701RAITILDTEKS711+TAT) targeting the K710 TRPV1 region was injected in the paw to evaluate the capsaicin-induced nociception in wild type TRPV1 and TRPV1^{K701N} mice. Finally, cardiomyocytes were isolated from the wild type TRPV1 and TRPV1K701N mice and subjected to cellular injury (hydrogen peroxide (H2O2) or hypoxia/reoxygenation). Data were analyzed using ANOVA followed by Tukey's post hoc analysis. Significance was set at $P < 0.05$.

RESULTS: NWe identified ~60 non-conserved amino acids when comparing avian with mammalian TRPV1 by multiple sequence alignment. Among these residues, we focused on the C-terminus TRP domain (687-711), which is critical for TRPV1 channel gating[3,5]. Unlike mammals having K710, birds have N710 in the TRP domain (Figure 1a). Substitution of K710 to N710 changes the structure of the TRP domain α-helix (Figure 1 b, c). CRISPR/Cas9 gene-edited TRPV1^{K701N} knock-in mice were generated and verified by sequencing (Figure 1 d, e). When exposed to the bird food containing capsaicin, behavioral response was markedly decreased for TRPV1^{K701N} mice relative to wild type TRPV1 mice (Figure1 f, g, 15±6 vs. 50±6 instances of paw withdrawal/10 min, n=10, P<0.0001). Moreover, paw-licking time after capsaicin or Brp-LPA injection was reduced in TRPV1^{K701N} mice relative to wild type TRPV1 mice (Figure 1h, Capsaicin: 27±4 sec vs. 57±6 sec, respectively, n=10, P=0.0001; Figure 1i, Brp-LPA: 50±6 sec vs. 80±5 sec, respectively, n=8, P<0.0001). The peak intracellular calcium influx (Δ ratio 340/380) was also lower in TRPV1^{K701N} DRG cells (n=13) than wild type TRPV1 DRG cells (n=14) (0.07±0.01 vs. 0.12±0.02, ratio of 340/380, respectively, P=0.030 from 3 biological replicates). When subjecting wild type TRPV1 mice to acute capsaicin, V1-cal peptide substantially reduced the nociceptive response to capsaicin relative to the vehicle peptide (TAT) -treated rodents (Figure 1j, 32.8±4.4 vs. 86.0±6.9 sec, respectively, n=8, P<0.001). TRPV1^{K701N} mice treated with V1-cal had similar behavioral responses relative to TAT-treated mice. In addition, following H_2O_2 treatment or hypoxia/reoxygenation, TRPV1^{K701N} cardiomyocytes had more calcein-AM stained viable cells and less PI stained dead cells, as well as slightly increased cell viability measured by MTT compared to the wild type cardiomyocytes.

CONCLUSION: We generated a novel TRPV1^{K701N} mouse based upon avian and mammalian genetic differences. Introducing this avian variant into rodents mitigates TRPV1-mediated response to noxious stimuli with an added benefit of reducing cellular injury. Together, these data unlock a crucial genetic difference between avian and mammalian species regulating TRPV1-mediated pain responses that was leveraged to develop a novel analgesic.

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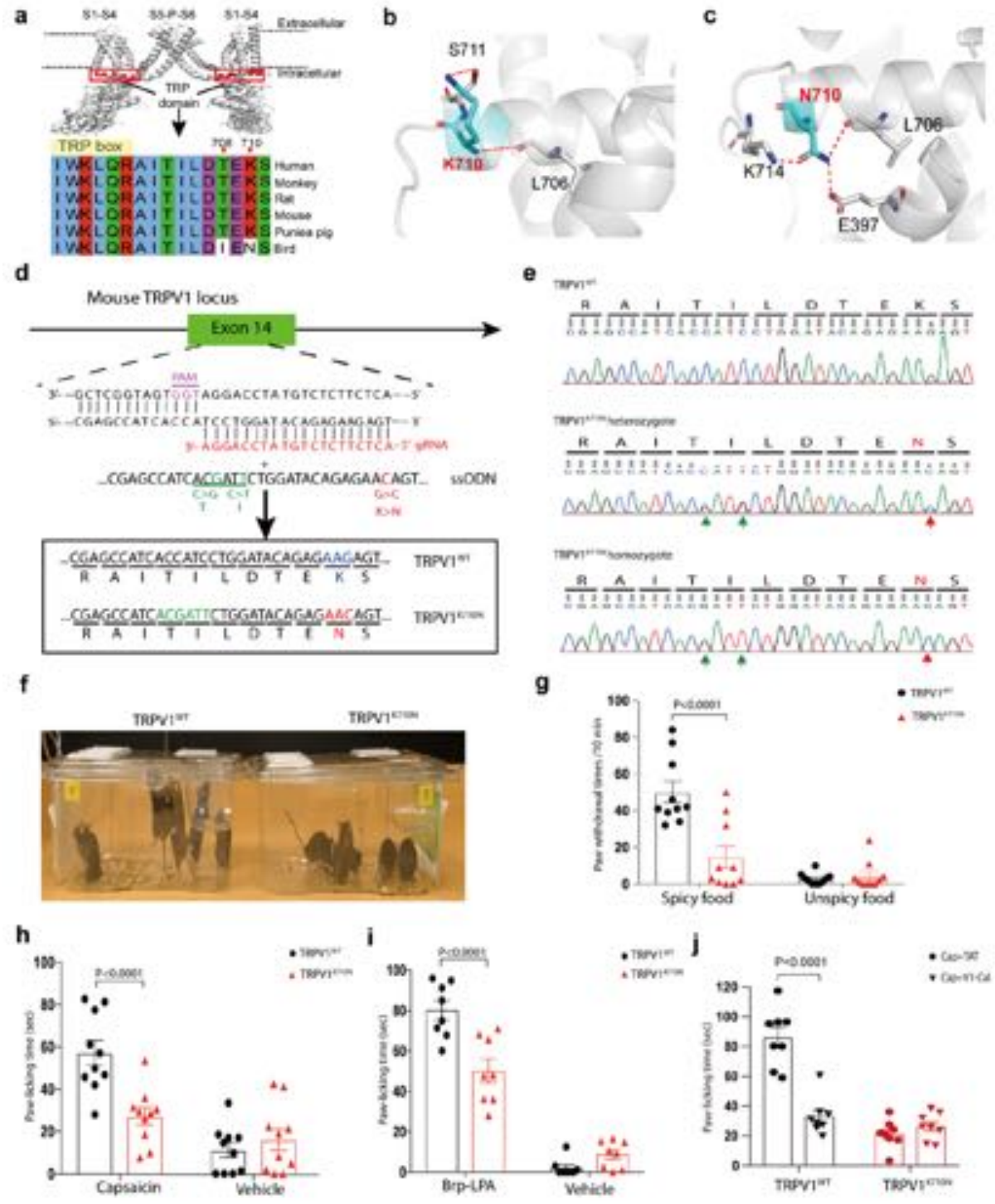

Figure 1 **(a)** Sequence alignment of the C-terminus TRP domain for mammalian and avian TRPV1. The zoom-in view of 3D structure of **(b)** wild type rat TRPV1, **(c)** K710N, based on the closed-state rat TRPV1 molecular model (PDB ID: 3J5P). **(d)** Design of gRNA, ssODNs lead to the K710N mutation (red) and two silent mutations (green) in the protospacer adjacent motif (PAM, purple). **(e)** Representative DNA sequencing data for wild type (WT) TRPV1, TRPV1^{K710N} heterozygotes (double peaks), or TRPV1^{K710N} homozygotes (single peak). **(f)** Representative image showing the difference in response to capsaicin-laced food for wild type TRPV1 and TRPV1^{K710N} mice. **(g)** Paw withdrawal behavior for wild type TRPV1 and TRPV1^{K710N} mice exposed to capsaicin-laced bird food or regular bird food. **(h)** Pain behavior induced by paw-injection of capsaicin or vehicle for wild type TRPV1 and TRPV1^{K710N} mice. **(i)** Pain behavior induced by paw-injection of Brp-LPA or vehicle in wild type TRPV1 and TRPV1^{K710N} mice. **(j)** Pain behavior induced by paw-injection of capsaicin after V1-cal or TAT in wild type TRPV1 and TRPV1^{K710N} mice.

PAIN MECHANISMS 4

Role of generalized inflammation and oxidative stress in a rodent model of fibromyalgia

Charles Rey[1], Luiz F Ferrari[1], Norman E Taylor[1]

[1]University of Utah, Salt Lake City, UT

INTRODUCTION: Fibromyalgia (FM) is a chronic widespread pain syndrome that affects 2-4% of the general population.[1] Research showing increased levels of nociceptive cytokines in FM patients suggests a possible role for inflammation in FM pain.[2] The nucleotide binding oligomerization domain (NOD)-like receptor 3 (NLRP3) has been identified as a key regulator of inflammation and hyperalgesia in FM patients.[3] Activation of NLRP3 requires a priming step triggered by Toll-like receptor 4 (TLR4) signaling, combined with an activating step, initiated by reactive oxygen species (ROS) (Fig 1)[4,5] which leads to nociceptive cytokine maturation and nociceptor sensitization. We have identified a novel rat model of FM, the Dahl salt-sensitive rat (SS), which exhibits spontaneous mechanical hyperalgesia and systemic inflammation, key FM phenotypes. We previously showed that systemic corticosteroid treatment increases the mechanical nociceptive threshold in SS rats (Fig 2), indicating a role for generalized inflammation in SS hyperalgesia. In this study, we hypothesized that (1) NLRP3 is responsible for the increased nociceptive cytokine production, (2) elevated ROS is a key reason for increased NLRP3 activity and (3) inhibiting NLRP3 or scavenging ROS would increase the nociceptive threshold in SS rats.

METHODS: This study was approved by the authors' IRB for animal research. Male SS Dahl and Brown Norway (BN) rats were used in this study. Hind paw nociceptive thresholds were determined by the Randall Selitto paw-withdrawal test. The pharmacological agents used were: Dexamethasone (1mg/kg) administered subcutaneously (s.c.) in the nape of the neck, the NLRP3 inhibitor MCC995 (10mg/kg) administered intraperitoneally (i.p.), and the chemical superoxide dismutase mimetic, TEMPOL (10mM) administered via drinking water. Relative ROS levels were quantified by measuring 8-isoprostanes levels in urine.

RESULTS: Systemic treatment with the NLRP3 inhibitor MCC950 for five days increased the nociceptive threshold of SS rats ($p<0.0001$, $n=6$, significant difference of hind paw withdraw threshold between MCC950 and control treatment) (Fig 3), suggesting that the nociceptive cytokines IL-1β and IL-18 significantly contribute to the hyperalgesia of this strain. We then measured 8-isoprostanes, a marker of oxidative stress, in the urine and found that they were higher in SS rats compared to Brown Norway rats ($p<0.05$, $n=13$, significant difference between 8-isoprostanes levels in SS and Brown Norway rats) (Fig 4). The importance of this elevation in ROS on hyperalgesia was demonstrated by the administration of the superoxide scavenger TEMPOL. TEMPOL significantly attenuated hyperalgesia in SS rats ($p<0.0001$, $n=7$, significant difference of hind paw withdraw threshold between tempol treatment and baseline) (Fig 5). β

CONCLUSION: The results indicate that systemic inflammation is at least in part mediated by increased NLRP3 activity in SS rats and increased levels of cytokines, natural features of the SS strain, are the underlying cause of the 'hyperalgesic phenotype' observed. We also conclude that increased ROS significantly contribute to hyperalgesia. Future studies are needed to determine whether ROS are the cause of increased NLRP3 inflammasome activity in this strain. These findings support the use of the SS rat as a tool to investigate mechanisms by which systemic inflammation contribute to persistent pain syndromes.

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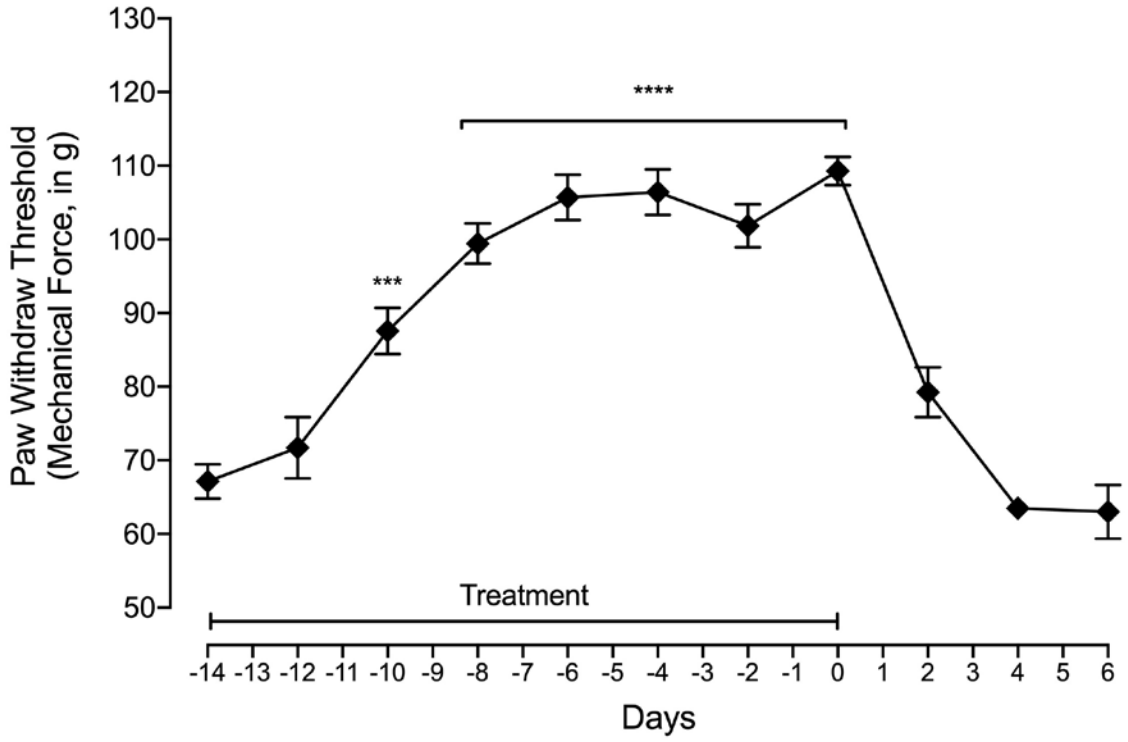

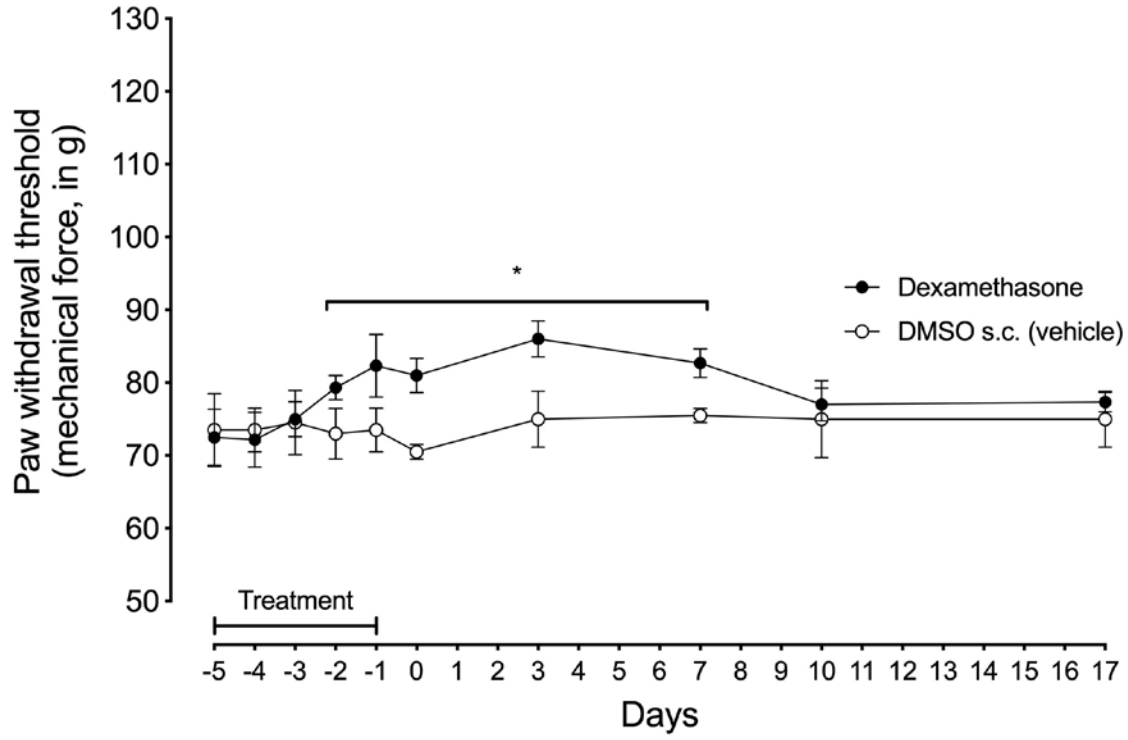

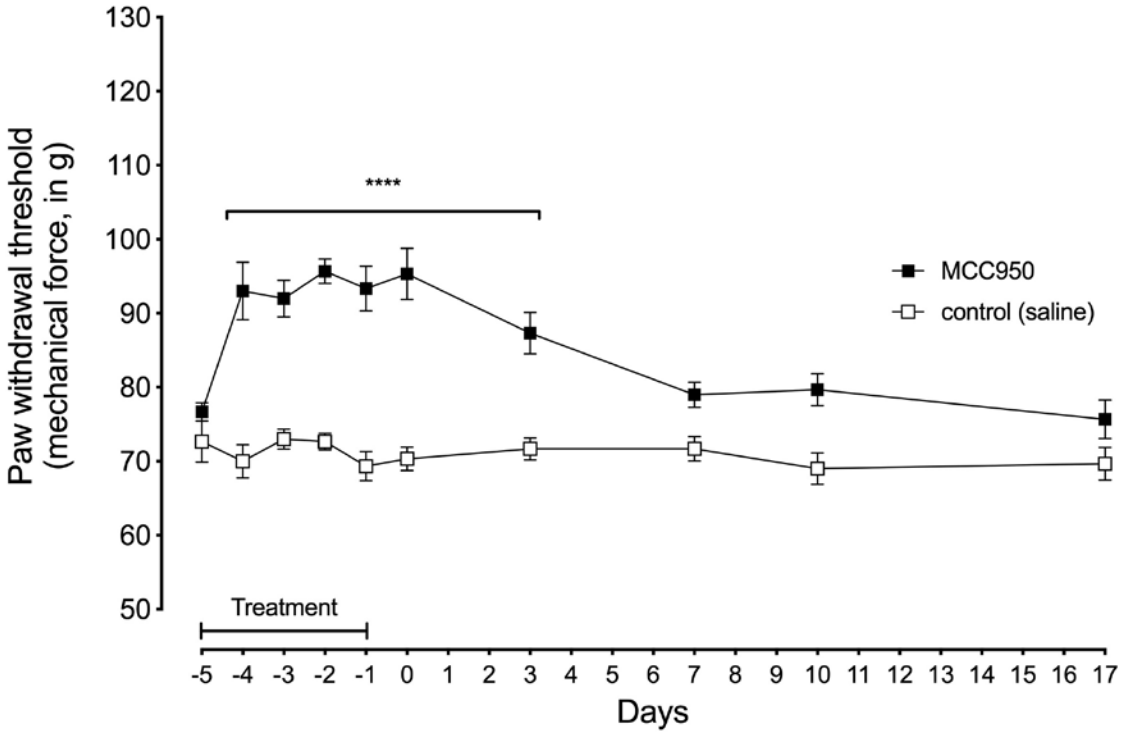

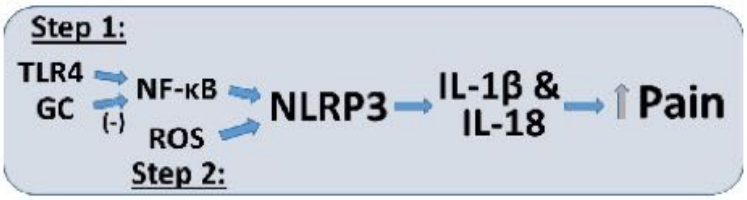

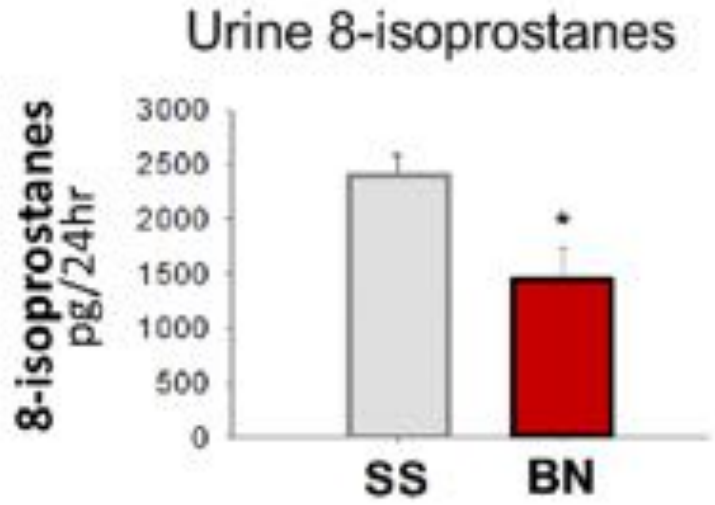

PAIN MECHANISMS 5

Morphine Tolerance and Reward is Regulated by Aldehyde Dehydrogenase-2 in Mice

Vanessa Zambelli[1], Juliana S Salgado[2], Boris D Heifets[3], Vivianne Tawfik[4], Eric R Gross[5]

[1]Stanford University, Palo Alto, CA, [2]Stanford University, Stanford, Palo Alta, CA, [3]Stanford University School of Medicine, Palo Alto, CA, [4]Stanford University School of Medicine, Stanford, California, [5]Stanford University, Stanford, CA

INTRODUCTION: Aldehyde dehydrogenase-2 (ALDH2) plays a key role in controlling toxic aldehydes involved in inflammatory and neuropathic pain development. This enzyme also converts aldehyde metabolites of amine neurotransmitters, including dopamine, norepinephrine, and serotonin, to less reactive forms[1]. An aldehyde dehydrogenase 2 (ALDH2) genetic variant, ALDH2E487K or ALDH2*2, is present in 540 million people world-wide, mostly of East Asian descent, which has impaired enzymatic activity (~ 60-90% versus wild type). Genomic studies revealed that opioid-dependence in Asians is higher than in population controls[2]. However, whether this genetic variant contributes to opioid-induced side effects including tolerance and addiction is unclear. Therefore, our aim was to investigate whether ALDH2 modulates opioid-induced tolerance and opioid reward in wild-type (WT) and ALDH2*2 mice. Further, we determined whether Alda-1, a small molecule activator of ALDH2, reverses these effects.

METHODS: ALDH2*2 mice were generated as previously described[3] with the specific inactivating point mutation in ALDH2 that occurs in the East Asian population. Male and female WT C57BL/6J and ALDH2*2 mice (10-12 weeks) received morphine 10 mg/kg (s.c.), once daily for 10 days (Fig. 1a). A subset of these mice also received the ALDH2*2 activator Alda-1 (16 mg/kg/day, s.c. by osmotic pump) for the duration of morphine treatments. To measure morphine analgesia, the hot plate and tail flick tests were conducted on days 1, 3, 5, 8 and 10, thirty minutes after morphine administration. To investigate reward-related behavior with morphine, an unbiased conditioned place preference (CPP) paradigm was performed. In addition, respiratory function was monitored by whole body plethysmography (Fig. 1a). All procedures were approved by the Administrative Panel on Laboratory Animal Care at Stanford University. Data were analyzed by t-test (CPP experiments) or two-way ANOVA with post-hoc Bonferroni correction (hot plate, tail immersion and respiratory function studies). Statistical significance was indicated by *$p<0.05$.

RESULTS: Morphine was analgesic in ALDH2*2 or WT mice on day 1 of treatment as evidenced by increased latency to withdrawal in the hot plate and tail flick assays. This analgesic effect was decreased in ALDH2*2 mice at day 5, compared to WT mice in the hotplate (21.5±4% vs 72.9±5.8% of analgesia, respectively, *$p<0.05$, n=8/group, Fig. 1b) and tail flick (32±5% vs 89±8.2% of analgesia, respectively, *$p<0.05$, n=8/group, Fig. 1c) assays, suggestive of analgesic tolerance. Alda-1 partially reversed this morphine tolerance in ALDH2*2 mice, compared to vehicle-treated controls at day 5 (48±4% vs 20% of analgesia, respectively, *$p<0.05$, n=8/group). No differences were detected in the sensitivity to hot plate or tail immersion tests in saline-treated control animals. ALDH2*2 mice presented increased preference for the morphine-paired compartment compared to WT (Δ pre- and post-morphine): 3.11±0.7s, vs 1.09±0.7s, respectively, n=12/group, (Fig. 1 d, f) suggesting that these mice may develop morphine-induced reward despite being tolerant to the analgesic effect. Alda-1 prevented morphine-induced reward effects in both WT and ALDH2*2 mice (Fig. 1 e, g). Importantly, ALDH2*2 mice also displayed increased respiratory depression at day 5 compared to WT mice (32±2% vs 16.5±6%, respectively, n=8/group, Fig. j), however, no differences were detected at day 10 (12.2±4% and 14.5±4%, respectively, n=8/group).

CONCLUSION: Our findings indicate that ALDH2 regulates morphine analgesic tolerance and reward. Further, East Asians with the ALDH2*2 genetic variant (ALDH2E487K) may experience enhanced tolerance to the analgesic effect of opioids, however, may still remain susceptible to respiratory depression (Fig. 1k). Patients with an ALDH2*2 genetic variant may therefore be at greater risk of respiratory depression as opioid dose escalation to mitigate analgesic tolerance may be more common and should be carefully monitored.

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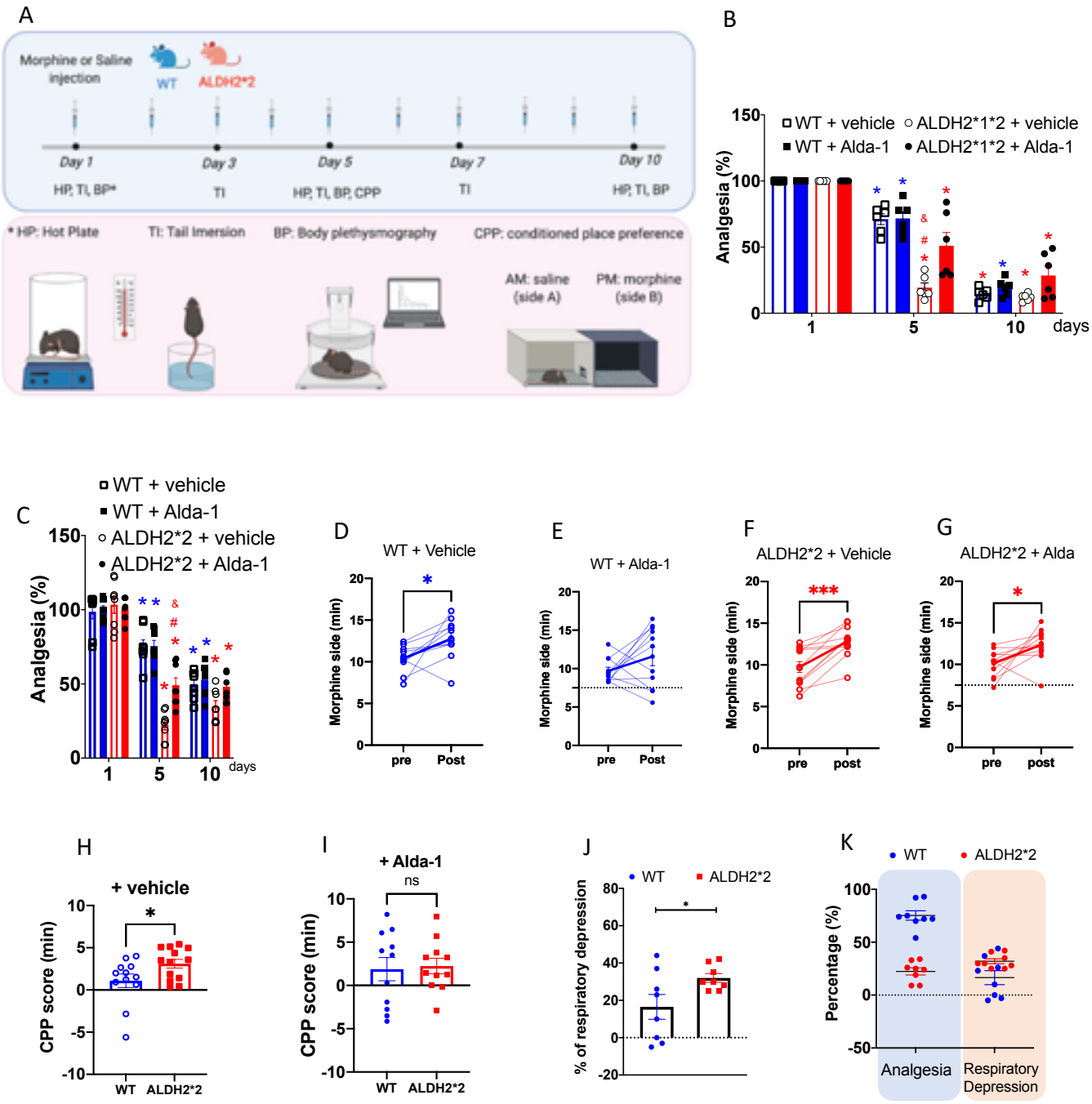

Fig. 1

PAIN MECHANISMS 6

A sexually dimorphic role of gasdermin D in nucleus pulposus-induced nociceptive behaviour in mice

Jazlyn P Borges[1], Milind Mulley[1], Amy Tu[1], Michael Salter[1], Benjamin Steinberg[1]

[1]The Hospital for Sick Children, Toronto, Canada

INTRODUCTION: Lumbar radiculopathy is one of the leading causes of disability around the world. While the resulting pain often stems from nerve injury due to nerve compression, a subset of patients shows no signs of compression and yet experiences persistent severe pain. Such non-compressive disc herniation pain is poorly understood but is thought to involve a neuroimmune mechanism whereby leaked intervertebral nucleus pulposus material triggers a local inflammatory response, such as through the release of pro-inflammatory cytokine interleukin (IL)-1β, that yields a pain state. Neuroimmune interactions are well-established in their contribution to the development and maintenance of many neuropathic chronic pain states in a sexually dimorphic way. IL-1β in particular can promote hyperalgesia and allodynia. Recently, the pore-forming protein gasdermin D (GSDMD) has been shown to be important for the release of this algogenic cytokine through a programmed cell death pathway termed pyroptosis. However, the role of GSDMD in pain has not been investigated to date, and thus, the therapeutic potential of GSDMD pharmacologic modulation in pain remains unknown. We hypothesize that pyroptosis-mediated cytokine secretion through GSDMD from immune cells, such as macrophages, drives sensitivity in nucleus pulposus-induced nociceptive behaviour in a sexually dimorphic fashion, and that GSDMD blockade will improve pathological pain states.

METHODS: All animal procedures were approved by the Animal Care Committee at the Hospital for Sick Children and were performed in accordance with regulations and standards from the Animals for Research Act of Ontario and the Canadian Council on Animal Care. To induce nociceptive behavior, nucleus pulposus tissue from wildtype donor mice was placed on the sciatic nerve in GSDMD knockout and littermate control mice of both sexes. Nociceptive behavior was measured using von Frey algesiometry to evaluate mechanical allodynia. Experimenters were blinded to genotype and data disaggregated by sex for analysis. To evaluate mechanism, we use ATP, a known pain mediator, to activate pyroptosis in wildtype and GSDMD knockout macrophages in vitro. We assess in vitro cytokine secretion and cellular cytotoxicity by western blot and LDH release, respectively.

RESULTS: Using the nucleus pulposus approach, mechanical allodynia is fully established by post-operative day 1 and persists until approximately day 5 in both genotypes and sexes, at which point animals begin to recover. Male GSDMD knockout animals (n=10) recover from mechanical allodynia more rapidly than their wildtype counterparts (n=8) at post-operative day 5 ($p < 0.05$). In contrast, female knockout (n=4) and wildtype (n=6) animals have similar recovery dynamics. In vitro, genetic knockout of GSDMD blocks IL-1β release from macrophages and cell death in response to extracellular ATP.

CONCLUSION: Our work is the first to demonstrate a role for GSDMD in a preclinical pain model. GSDMD appears to be important for the maintenance of nucleus pulposus-induced nociceptive behaviour in male but not female mice. Understanding the mechanisms of pain and sex differences in such mechanisms is critical to identify new therapeutic targets and improve treatment options for chronic pain patients with non-compressive disc herniation pain.

Subspecialty Abstracts

PAIN MEDICINE

PAIN MEDICINE 1

Impact of Pecto-intercostal Fascial Block on Opioid Consumption and ICU length of Stay in Patients Undergoing Sternotomy for Open Heart Surgery

Ankit Bhatia[1], Andres Missair[2], Julio Benitez Lopez[3], Joshua J Livingstone[2], Ricardo Martinez-Ruiz[4]

[1]University of Miami/ Jackson Memorial Hospital, Miami, FL, [2]University of Miami, Miami, FL, [3]Univeristy of Miami, Miami, FL, [4]Jackson Memorial Hospital, Miami, FL

INTRODUCTION: Open heart surgery with median sternotomy is associated with significant postoperative pain. Inadequate pain control is associated with activation of the sympathetic nervous system and a heightened stress response which may contribute to various postoperative complications. The risk of postoperative myocardial ischemia, pulmonary complications such as atelectasis and pneumonia, thromboembolic events, wound infection, and length of ICU stay is increased when postoperative pain is poorly controlled. Local anesthetic infiltration, pharmacologic agents such as opioids and NSAID's, thoracic epidural's, and nerve blocks are currently used to manage postoperative pain in this patient population. Pecto-intercostal fascial plane blocks are a relatively new minimally invasive regional block technique that targets the anterior intercostal nerves in the fascial plane between the pectoral and intercostal muscles and have been shown to decrease analgesic requirements and improve pain scores in noncardiac and thoracic procedures when administered in the perioperative period. Clinical evidence regarding the use of of pecto-intercostal fascial plane blocks for pain management in cardiac surgery remains sparse and warrants further investigation. The aim of this study was to determine the effect of pecto-intercostal fascial plane blocks on postoperative opioid consumption and ICU length of stay in patient's undergoing median sternotomy for cardiac surgery in the VA population.

METHODS: A retrospective analysis of open heart surgeries between 2017 and 2019 at a single institution was performed. Utilizing CPT codes for midline sternotomy, a total of 226 patient records were identified and screened. Adult patients (>18 y) undergoing cardiac surgery with midline sternotomy, such as coronary artery bypass grafting (CABG), CABG with or without valve replacement, and isolated valve surgeries, were included in the study. Chart reviews were then conducted to identify those patients who received pecto-intercostal fascial plane blocks postoperatively (study group) versus those only receiving opioid analgesics (control group). At our institution, the standard practice for open-heart pecto-intercostal fascial block placement requires a bilateral intraoperative block upon sternotomy wound closure (POD 0) and a subsequent block by 9:00am on POD 1. Patients who did not meet this block criteria or underwent minimally invasive surgery were excluded. Postoperative opioid consumption and length of ICU stay were the primary and secondary outcome variables measured respectively. Postoperative opioid consumption per patient was calculated as morphine milliequivalents (MME) and reported as daily averages for postoperative day 0 through 5. Length of ICU stay was defined as the total hours from the time of ICU admission on POD 0 until the patient floor transfer order was placed. Statistical analysis was performed using SPSS. Continuous and categorical variables were analyzed utilizing independent t-test, Mann-Withney test, and chi square respectively. A 2-sided p value of <0.05 was considered statistically significant.

RESULTS: A total of 226 patient records were identified and screened utilizing the cpt codes for midline sternotomy. 48 patients were excluded from the study on the basis of incomplete data and not meeting inclusion criteria. The remaining 178 patient records were further stratified into the study group receiving pecto-intercostal fascial plane blocks (n= 132) and the control group who were managed without nerve blocks (n= 46). Daily opioid MME requirements and average ICU length of stay were the primary and secondary outcomes measured. Daily opioid MME requirements were significantly reduced ($p<0.01$) in the study group compared to the control group on POD 1 through 5 with a reduction in opioid use between 26% and 71% respectively. Average ICU length of stay was also significantly reduced ($p<0.05$) by 39.35 hours in the study group compared to the control group.

CONCLUSION: Open heart surgery patients with median sternotomy receiving pecto-intercostal fascial plane blocks on POD 0 and 1 showed a statistical significant decline in average daily opioid requirements and average ICU length of stay compared to patients not receiving nerve blocks in the perioperative period. Pecto-intercostal fascial plane blocks are a quick, minimally invasive technique that can be utilized to hasten recovery and decrease opioid requirements in the cardiothoracic surgery patient.

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PAIN MEDICINE 2

Social Isolation-Induced Worsening of Chronic Pain: The Protective Effect of Introversion

Kristin L Schreiber[1], Kelsey Mikayla Flowers[2], Carin A Colebaugh[2], Robert R Edwards[2], Valerie Hruschak[2]

[1]Brigham and Women's Hospital; Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA

INTRODUCTION: The COVID-19 pandemic social distancing mandates have increased levels of social isolation, a change which appears to have impacted some chronic pain patients more than others. Previous research suggests that feelings of loneliness and sleep disturbance may importantly modulate pain. In the present study, we examined whether the personality trait of introversion served as a protective factor against worsening pain interference during conditions of social isolation, and whether this was related to differences in sleep disturbance and loneliness.

METHODS: Chronic pain patients in Massachusetts (n=150) completed electronic questionnaires 4-8 weeks after the state-wide social distancing mandate. Validated questionnaires included the Brief Pain Inventory (BPI), Myers-Briggs introversion/extroversion subscale (1-10), UCLA Loneliness and PROMIS Sleep Disturbance short forms. Change scores were calculated by subtracting recalled scores from current scores. Linear regression was used to assess association between factors, and mediation analyses were used to assess the degree to which other factors mediated the relationship between introversion and change in pain interference.

RESULTS: Introversion scores were inversely related to increased pain interference since social distancing (Rho=-0.194, p=0.017), such that patients with higher introversion scores showed little to no change in pain interference, compared to more extroverted patients. Higher introversion was also associated with lower increases in sleep disturbance (Rho=-0.163, p=0.046) and loneliness (Rho=-0.279, p=0.001) since social distancing. Multiple simple mediation analyses revealed that the relationship between introversion and change in pain interference was partially mediated by differential changes in sleep disturbance and loneliness.

CONCLUSION: Chronic pain patients experience varying degrees of worsening of pain interference with social distancing, which may be partially explained by their degree of introversion/extroversion. In particular, more introverted patients appeared to be partially protected, experiencing less of an increase in loneliness and sleep disturbance and, in turn, less of an increase in pain interference.

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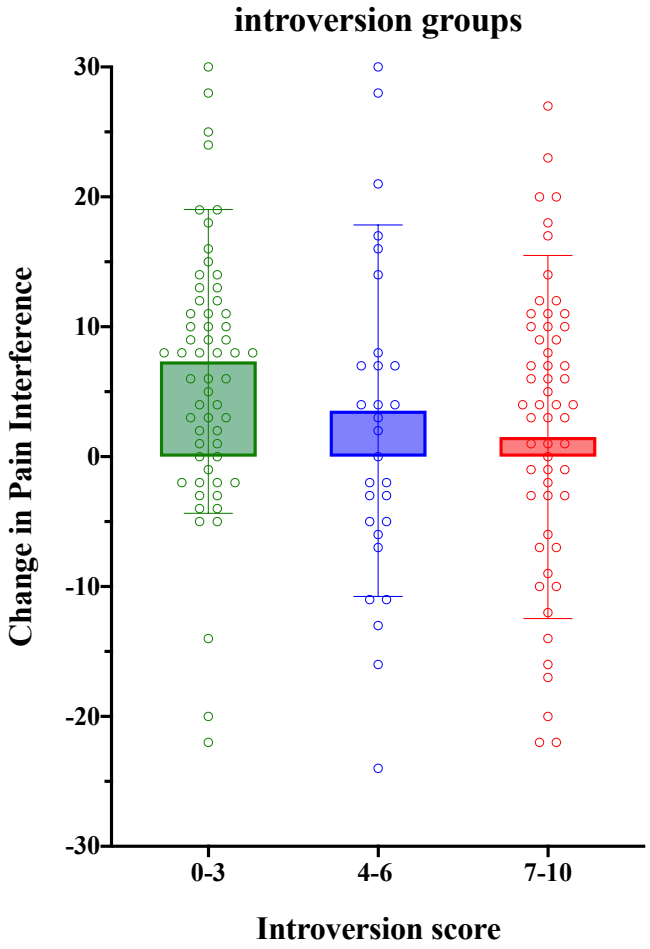

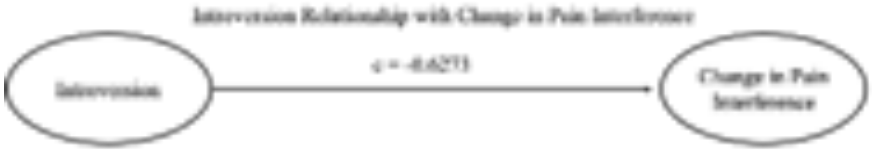

PAIN MEDICINE 3

Association of Postoperative Opioid Misuse with Prolonged Postoperative Pain, Opioid Use, and Delayed Recovery

Chinwe Nwaneshiudu[1], Eric Cramer[2], Sean Mackey[3], Ian Carroll[4], Jennifer Hah[5]

[1]Stanford University School of Medicine, Redwood City, CA, [2]Stanford University School of Medicine, Palo Alto, CA, [3]Stanford University School of Medicine, Palo Alto, CA, [4]Stanford University, Palo Alto, CA, [5]Stanford University, Stanford, CA

INTRODUCTION: Opioid exposure during surgical recovery is associated with risks such as the development of new persistent postoperative opioid use. With prolonged postoperative opioid exposure, little is also known about the resulting risks for developing opioid misuse. Currently, available measures of opioid misuse have not been validated among surgical patients, and the link between postoperative opioid misuse and postoperative pain, opioid use, and recovery long after hospital discharge has not been examined.

METHODS: A secondary analysis of the Stanford Accelerated Recovery Trial, a randomized, double-blinded trial was conducted at a single-center of 422 participants in a mixed surgical cohort between May 25, 2010, and July 25, 2014. Of the 422 patients enrolled, 381 patients on post-operative opioids with 7.6 % missing data were included in the analysis. After discharge from surgery, a modified Brief Pain Inventory was administered over the phone to assess pain related to the surgical site using the Numeric Pain Rating Scale, opioid medication use, and recovery. Calls occurred daily for the first 3 months, weekly thereafter up to 6 months, and monthly thereafter until patients reached pain cessation, opioid cessation, and full recovery up to 2 years after surgery, amounting to 19,511 distinct postoperative calls. The presence of opioid misuse behavior was defined as any use of opioid medication for sleep or using more opioid than prescribed. Multivariate Cox proportional hazards regression was conducted for time to opioid cessation (defined as the first of 5 consecutive days of no opioid use), pain cessation (defined as the first of 5 consecutive days of 0 out of 10 pain on the NRS) and surgical recovery (defined as a 'yes' response to the question of complete surgical recovery). Data-mining algorithms were applied using the R programming language, version 3.3 (R Foundation), and subsequent statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc).

RESULTS: Postoperative opioid misuse was significantly associated with an increased time to pain resolution (hazard ratio [HR], 0.52; $P < 0.001$), delayed opioid cessation (HR, 0.44; $P < 0.001$) and prolonged surgical recovery (HR, 0.67; $P < 0.001$).

CONCLUSION: These findings suggest the presence of postoperative opioid misuse is associated with worse postoperative outcomes including prolonged pain, opioid use, and delayed recovery. Future studies are needed to replicate these findings, and to validate postoperative opioid misuse assessments.

PAIN MEDICINE 4

Best pre-discharge time intervals of opioid intake as predictor of post-discharge opioid use after surgery to inform opioid prescribing

Benjamin Schenkel[1], Susan Mikulich-Gilbertson[2], Martin Krause[2], Ana Fernandez-Bustamante[3], Marisa Wiktor[3], Jean Kutner[2], Karsten Bartels[4]

[1]University of Colorado School of Medicine, Denver, CO, [2]University of Colorado, Aurora, CO, [3]University of Colorado School of Medicine, Aurora, CO, [4]University of Nebraska Medical Center, Omaha, NE

INTRODUCTION: Following inpatient surgery, opioids are often prescribed using a one-size-fits-all regimen rather than a patient-centered approach.[1] To reduce the quantity of unnecessary opioids prescribed post-discharge, it has previously been demonstrated that pre-discharge opioid use is the most reliable and practical predictor of post-discharge opioid intake following surgery.[2-4] However, the most appropriate pre-discharge time frame to be used for the prediction of post-discharge opioid use is not known. While longer time frames before discharge could yield more comprehensive information on analgesic requirements, they would more likely include the immediate post-operative period during which analgesic requirements could be lower (e.g., from residual local anesthetic effect) or higher (e.g., from the more recent response to tissue damage). Conversely, shorter (<24h) time frames closer to discharge may be unevenly impacted by diurnal/nocturnal variations in activity. This study investigated the strength of the association between the quantity of opioids taken during four pre-discharge time frames (48h, 24h, 12h, and 6h) and self-reported opioid intake over four weeks post-discharge after three categories of inpatient surgery (Cesarean section, thoracic surgery, and gastrointestinal surgery). We hypothesized that the 24h pre-discharge time frame would show the strongest correlation with post-discharge use.

METHODS: The local institutional review board approved this study prior to enrollment of the first patient. Written informed consent was obtained from all subjects or their legal surrogates. This study was prospectively registered at clinicaltrials.gov, NCT03034278. We conducted a secondary analysis of outcomes reported in three prospective cohort studies in 587 adult patients undergoing Cesarean section, thoracic, and gastrointestinal surgery.[3-5] These patients were followed with four weekly surveys that yielded >80% response rates. [3-5] For this study, pre-discharge opioid use during four pre-discharge time frames: 48h, 24h, 12h, and 6h was assessed by individual chart review of the electronic medication administration records. These quantities were converted to oral milligram morphine equivalents (MME) for comparison.[6-7] Since these records listed medication administration hourly, discharge times were rounded to the nearest hour. Data for patients with hospital stays less than 48 hours were excluded. Spearman rank correlation coefficients were calculated to estimate the association between the quantity of opioids taken pre-discharge with self-reported cumulative opioid use during the first four weeks following discharge.

RESULTS: We found the strongest association with post-discharge opioid use for the 24h window (ρ=0.59, $p < 0.01$). The weakest correlations were with the 48h and 6h windows (ρ=0.55, $p < 0.01$, ρ=0.49, $p < 0.01$), Table 1. Our hypothesis that the 24h window provides the most useful pre-discharge opioid intake information for predicting opioid use following discharge was confirmed.

CONCLUSION: When comparing different time frames of pre-discharge opioid intake in 587 patients who underwent inpatient surgery, we found that 24h pre-discharge opioid use yields the strongest association with four-week post-discharge opioid use. Consistent with our findings, guidelines for post-discharge prescriptions after surgery recommend a tiered approach toward determining the total quantity of opioids to be prescribed.[8] The feasibility and effectiveness of using 24h pre-discharge opioid intake to appropriately inform post-discharge analgesic prescriptions deserves further study.

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Pre-discharge time frames	Spearman rank correlation ρ	P value
6 hours	0.49	<0.01
12 hours	0.56	<0.01
24 hours	0.59	<0.01
48 hours	0.55	<0.01

Table 1: Correlations of opioid intake during different pre-discharge time frames with post-discharge opioid use in surgical patients.

PAIN MEDICINE 5

The Effect of Covid-19 on the Opioid Epidemic

David Kim[1], Shantha Ganesan[2]

[1]SUNY Downstate Medical Center, Brooklyn, NY, [2]NYC Health + Hospitals/Kings County, Brooklyn, NY

INTRODUCTION: The opioid epidemic is a serious national crisis that has detrimental impacts on both public health, and social and economic welfare. Therefore, any efforts to combat the opioid epidemic, including minimizing or weaning opioid prescriptions, and using other modes of analgesia when possible are undeniably necessary in this day and age. With the onset of Covid-19 pandemic, healthcare providers abruptly changed their care delivery. In-person clinic visits were changed to telemedicine, and elective cases were cancelled. Due to a growing concern that chronic pain patients may have limited resources from this unprecedented time of social and economic shutdown, organizations such as American Medical Association and Drug Enforcement Administration have supported implementing measures to ensure these patients achieve adequate pain control by increasing access to pain medications, but at the cost of reducing barriers and restrictions to controlled substances. Some of these policies include allowing all 'authorized practitioners' to prescribe controlled substances via telemedicine without first conducting an in-person examination, and removing existing barriers for patients, which includes dose, quantity, refill restrictions on controlled substances. Given the cancellation of elective interventional pain management procedures and relaxed regulations on controlled substances during the Covid-19 pandemic, it is reasonable to suspect a dramatic increase in opioid prescription during this time. However, to my understanding, there are no reports measuring the rate of opioid prescriptions during the pandemic although there has been numerous reports of increased rates of opioid-overdose related cases when compared to previous years. Our study focused on the change in opioid consumption in chronic pain patients who were unable to undergo their interventional pain procedure during the Covid-19 pandemic. By demonstrating whether or not there has been a significant increase in opioid consumption in this patient population, we can justify the efficacy and necessity of these procedures. A significant increase can also support the importance of creating protocols that allow for elective interventional pain procedures to continue during the next pandemic.

METHODS: Our study took place at King's County Hospital Center. It is a retrospective chart review study that looked at chronic pain patients who were scheduled for an interventional pain procedure from the months of March 1st to May 30th, 2020 using EPIC and QuadraMed. Study has been approved to be IRB exempt. Subjects were classified into groups based on their cancelled interventional pain procedure, including ESI, SI joint injections, and intra-articular facet joint injections. For each patient, the frequency and dose of each opioid prior to and after notification of their cancelled procedure were recorded. The change in opioid consumption was calculated by measuring the change in morphine milligram equivalents per day (MME/day).

RESULTS: A total of 22 subjects were included in the study. 91% were female and 9% were male. The mean change in opioid consumption (MME/day) in all subjects showed a statistically significant increase of +14.96 (95% CI [2.04, 27.87], p = 0.02). The mean change in opioid consumption was determined for subjects categorized based on procedure scheduled. The mean changes in opioid consumption (MME/day) in subjects scheduled for lumbar ESI (7 subjects), SI joint injection (4 subjects), intra-articular facet joint injection (6 subjects), both intra-articular facet joint injection and SI joint injection (5 subjects) were +9.64 (95% CI [-5.72, 25.01], p = 0.17), +1.13 (95% CI [-2.45, 4.71], p = 0.39), +26.92 (95% CI [-23.49, 77.32], p = 0.23), and +19.1 (95% CI [-13.20, 51.40], p = 0.17). Subjects were also stratified based on whether or not they received the same procedure in the past. Subjects who received the same procedure in the past (8 subjects) showed a mean change in opioid consumption of +31.44 (95% CI [-3.86, 66.73], p = 0.07), while subjects who were scheduled to receive the procedure for the first time (14 subjects) showed a mean change in opioid consumption of +5.54 (95% CI [-1.50, 12.57], p = 0.11).

CONCLUSION: The mean change in opioid consumption (MME/day) in all subjects showed a statistically significant increase (+14.96 MME/day, p-value = 0.02). This may justify the need for a protocol that allows for elective interventional pain procedures to continue in a future pandemic.

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	Total number of subjec	Mean change in opioid consumption (MME/day)	p-value
Lumbar ESI	7	9.64 CI(-5.72, 25.01)	0.17
SI joint injection	4	1.13 CI(-2.45,4.71)	0.39
intra-articular facet joint injection	6	26.92 CI(-23.49,77.32)	0.23
intra-articular facet join injection + SI joint injection	5	19.1 CI(-13.20,51.40)	0.17
Patients who received procedure in the past	8	31.44 CI(-3.86,66.73)	0.07
Patients receiving procedure for the first time	14	5.54 CI(-1.50,12.57)	0.11

Total change in opioid consumption (MME/day) in all subjects

Subject	Sex	Opioid consumption prior to cancelled procedure (MME/day)	Opioid consumption after cancelled procedure (MME/day)	Change in MME/day
1	F	0	15	15
2	F	0	4.5	4.5
3	F	0	0	0
4	F	0	0	0
5	F	60	75	15
6	F	18	78	60
7	F	0	30	30
8	F	0	0	0
9	F	210	334	124
10	F	15	15	0
11	F	15	15	0
12	F	4.5	10	5.5
13	F	0	0	0
14	F	45	45	0
15	F	0	15	15
16	F	0	0	0
17	F	75	75	0
18	F	0	0	0
19	F	15	22.5	7.5
20	M	15	60	45
21	F	7.5	15	7.5
22	M	15	15	0
Mean				**14.96 CI(2.04,27.87)**
p value				**0.02**

PAIN MEDICINE 6

Effects of methylprednisolone on early postoperative pain and recovery in patients undergoing thoracoscopic lung surgery: a randomized controlled trial

Hai Yu[1], Wei Shi[1]

[1]West China Hospital, Sichuan University, Chengdu, China

INTRODUCTION: Postoperative acute pain, one chanllenge in postoperative managnement of thoracic surgery, induced unsatisfaction of patients and delayed postoperative recoevery. Emerging evidence has found that methylprednisolone plays a critical role in postoperative analgesia. However, the effectiveness of methylprednisolone with regards to postoperative acute pain and recovery is unclear in thoracoscopic lung surgery. The aim of this study was to evaluate the effects of methylprednisolone on acute pain and quality of recovery after thoracoscopic lung surgery.

METHODS: In this single-center, patient-and-evaluator-blinded, superiority randomized trial, 180 patients scheduled for elective thoracoscopic lung surgery were randomly assigned to receive 40 mg methylprednisolone, 120 mg methylprednisolone or placebo. The primary outcome was the proportion of moderate-to-severe pain (numerical rating scale, NRS≥ 4) on the first day postoperatively. The pain scores, postoperative quality of recovery-15 (QoR-15) and other secondary outcomes were also recorded. All data were checked for normal distribution with inspection of Kolmogorov-Smirnov. Continuous data were presented as mean with standard deviation (SD) or confidence interval (CI) for normally distributed variables and medians with CI for nonnormally distributed data. Categorical variables were summarized using proportion with CI. Continuous variables were analyzed using Student's t test or Mann-Whitney U test. Categorical variables were compared using the Pearson's X^2 test or Fisher's exact test as appropriate. Specifically, generalized estimating equations (GEE) with robust standard error estimates were used to account for repeated measures of pain scores and QoR-15 scores. To investigate for a linear trend between the dosage of methylprednisolone and the proportion of patients with moderate-to-severe pain, a CochranArmitage test of trend was used. Secondary analyses for the primary outcome were adjusted analyses (for sex, age, body mass index (BMI), duration of surgery, anesthesia regimens and surgical procedures) by logistic regression. The pairwise comparisons among three groups were considered as an exploratory analysis. The level of significance and CI were 0.05 and 95% for primary and secondary outcomes compared the combined methylprednisolone groups with the placebo group, 0.017 and 98.3% for the exploratory outcomes (3 pairwise comparisons).

RESULTS: A total of 173 patients were included in the primary analysis. There was no difference in the proportion of moderate-to-severe pain between patients in the combined methylprednisolone groups and the placebo group (51.7% vs 64.9%; absolute difference, 13.2%; 95% CI, -2.1 to 29.3; P= 0.10). Patients in the combined methylprednisolone groups had lower pain scores at rest and coughing on the first day after surgery compared with the placebo group, with mean difference of 0.6 and 0.8, respectively (P< 0.01). QoR-15 scores were higher in the combined methylprednisolone groups on the first (mean difference, 6.9; P< 0.001) and second days after surgery (mean difference, 7.2; P< 0.001) than the placebo group. Patients in the 120 mg methylprednisolone group had lower pain scores at rest than the 40 mg methylprednisolone group (mean difference, 0.8; 95% CI, 0.3 to 1.3; P< 0.001) and the placebo group (mean difference, 1.0; 95% CI, 0.5 to 1.4; P< 0.001), respectively. Patients in both methylprednisolone groups had higher QoR-15 scores than the placebo group and patients in the 120 mg methylprednisolone group had higher QoR-15 scores in contrast with the 40 mg methylprednisolone group on the first and second days after surgery. No side-effects were observed.

CONCLUSION: A single dose of methylprednisolone did not reduce the proportion of moderate-to-severe pain. However, it could decrease postoperative pain scores and improve quality of recovery without increasing adverse events in thoracoscopic lung surgery.

PAIN MEDICINE 7

Naloxone Dispensing in Patients at Risk for Opioid Overdose after Total Knee Arthroplasty within the Veterans Health Administration

Mary Jarzebowski[1], Sam Lahidji[2], Elizabeth Oliva[3], Seshadri Mudumbai[4], Tamar Lake[5], Vijay Krishnamoorthy[6], Karthik Raghunathan[7], William E Bryan[8]

[1]VA Ann Arbor Healthcare System, Ann Arbor, MI, [2]Veterans Administration, Ann Arbor, MI, [3]VA Palo Alto, Palo Alto, CA, [4]Stanford University School of Medicine, Stanford, CA, [5]University of Michigan, Ann Arbor, MI, [6]Duke University, Durham, NC, [7]Duke University School of Medicine, Durham, NC, [8]Durham VA Medical Center, Durham, NC

INTRODUCTION: Naloxone prescribing among patients undergoing surgery is not well understood. This cohort study was designed to examine patients' risk factors for opioid overdose and their association with naloxone prescribing among Veterans undergoing total knee arthroplasty (TKA) after a system-wide Overdose Education and Naloxone Distribution (OEND) initiative.

METHODS: A retrospective analysis of Veterans Health Administration (VHA) records was performed. The study cohort consisted of 38,011 Veterans undergoing primary TKA from 2013 to 2016. Patient overdose risk was determined using a validated risk index for overdose or serious opioid-induced respiratory depression (RIOSORD) based on patient diagnoses, healthcare utilization, and prescription drug use. Patients were then categorized to low, moderate, or high-risk RIOSORD groups. Naloxone dispensing was examined within the year before surgery until 7 days after discharge. These rates were examined the year prior to implementation of a national OEND initiative (2013), the year of implementation (2014) and two years following implementation (2015-2016).

RESULTS: Veterans presenting for TKA had significant risk factors for opioid overdose. From 2013 to 2016, of 38,011 patients, lung disease was present in 9,170 (24.1%), sleep apnea in 6,630 (17.4%), chronic kidney disease in 4,036 (10.6%), liver disease in 2,822 (7.4%), bipolar disorder in 1,748 (4.6%), opioid use disorder in 1,213 (3.2%), and schizophrenia in 618 (1.6%). Regarding prescription drug use related factors, in 2013, 63.1% of patients presenting for surgery were actively prescribed opioids (Figure 1). By 2016 this decreased to 50.5%. Benzodiazepine use decreased from 13.2% to 8.8% and long acting opioid use decreased from 8.5% to 5.8% over the same time period. Patients on ≥50 MEDD decreased from 8.0% to 5.3% and patients on ≥100 MEDD decreased from 3.3% to 2.2%. From 2013 to 2016, the prevalence of patients in the moderate risk group decreased from 2.5% to 1.6% (Figure 2). During this period the prevalence of patients in the high-risk group decreased from 0.8% to 0.6%. Cumulatively, the prevalence of patients presenting with either moderate or high risk of overdose from 2013 to 2016 decreased from 3.3% to 2.2%. In 2013, 3.3% of patients presenting for TKA had moderate or high risk for overdose and none were prescribed naloxone. By 2016, after implementation of an OEND initiative, 2.2% of patients presenting for TKA had moderate or high risk for overdose, but 10.9% of the moderate risk and 12.7% of the high-risk patients were prescribed naloxone (Figure 3).

CONCLUSION: Patients presenting for TKA routinely have risk factors for opioid overdose and significant proportions are at moderate or high risk for overdose. Despite this, most patients at moderate and high risk do not receive a perioperative naloxone prescription. Risk mitigation strategies using validated tools such as RIOSORD may help identify surgical patients who may be at greatest risk for opioid overdose and could benefit from OEND.

Figure 1

Prescription risk factors in Veterans undergoing TKA between January 2013 and December 2016 within the VHA

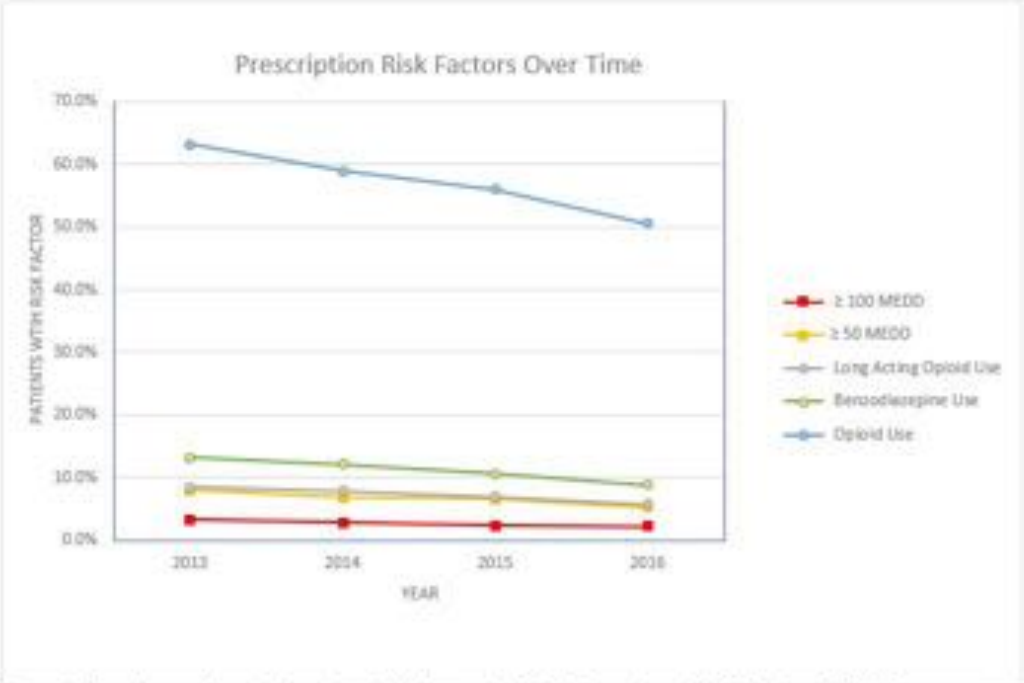
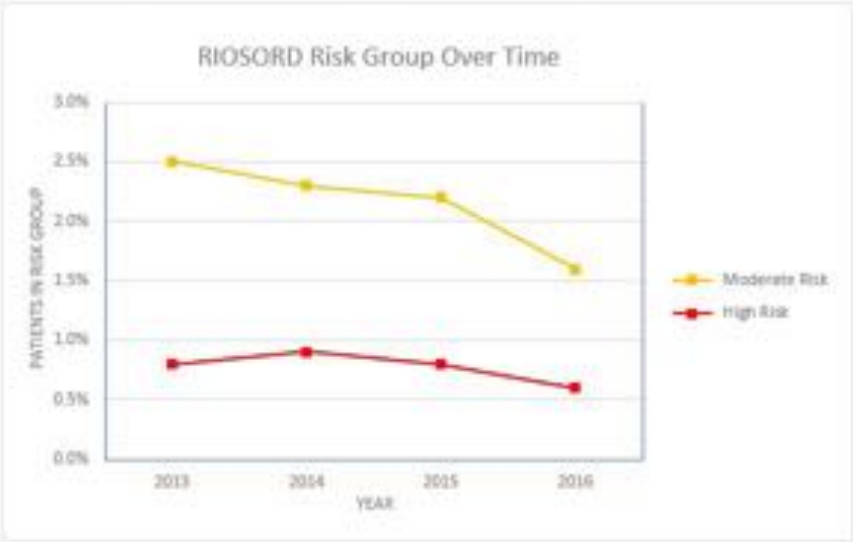


Figure 1: Prevalence of prescription-related risk factors for OSORD over time. 100 MEDD and 50 MEDD represents Veterans taking greater than or equal to 100 or 50 MEDD at the time of surgery. Long acting opioid use, benzodiazepine use indicate use at time of surgery. "Opioid use" indicates any active opioid prescription at the time of surgery.

Figure 2

RIOSORD risk group in Veterans undergoing TKA between January 2013 and December 2016 within the VHA



The yellow line shows the percentage of patients within the RIOSORD moderate risk group (classes 5-7). The red line shows the percentage of patients within the RIOSORD high risk group (classes 8-10).

Figure 3

Naloxone dispensing among RIOSORD low, moderate and high risk Veterans undergoing TKA between January 2013 and December 2016 within the VHA

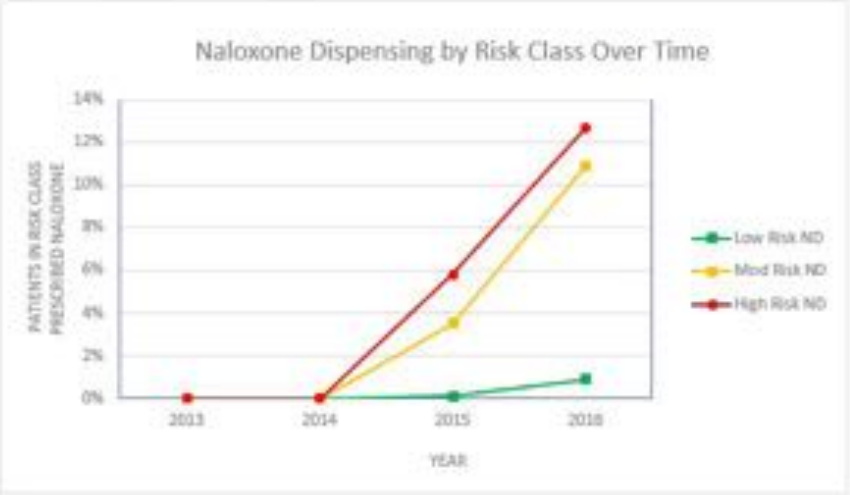


Figure 3: Naloxone dispensing represents naloxone dispensed within the year before surgery until 7 days after postoperative discharge to estimate patients likely to have naloxone at home after surgery. The green line shows the rate of naloxone dispensing for Veterans within the RIOSORD low risk group (classes 1-4).

PAIN MEDICINE 8

Association between the Number of Prescribers of Concurrent Opioid and Benzodiazepine Medications and the Risk of Overdose: A Retrospective Analysis

Chris A Rishel[1], Soleil Shah[1], Yuting Zhang[2], Beth Darnall[3], Eric Sun[4]

[1]Stanford University, Stanford, CA, [2]University of Melbourne, Melbourne, Australia, [3]Stanford University, Palo Alto, CA, [4]Stanford University School of Medicine, Stanford, CA

INTRODUCTION: Previous work has shown that having a greater number of providers involved in prescribing opioids is associated with an increased risk of an emergency room visit or inpatient admission for overdose.[1] Furthermore, concurrent prescriptions of opioids and benzodiazepines have been associated with an increased risk of overdose compared to prescriptions for either drug class alone.[2,3] However, it remains unknown if there is a relationship between the number of providers responsible for prescribing concurrent opioids and benzodiazepines and the risk of overdose. This study used a large national database of health insurance claims to examine this question.

METHODS: The data consist of administrative health claims provided by the Optum©'s Clinformatics® Data Mart. The final sample included 2,000,529 patients aged 18-89 with no history of cancer and any concurrent benzodiazepine and opioid prescriptions between January 1, 2003 and June 30, 2019. The primary outcome was whether a patient had an emergency room visit or inpatient admission for overdose which occurred within 30 days of being prescribed both a benzodiazepine and an opioid. Using previously described methods,[4,5] we defined overdose to be an admission or visit with ICD-9 or ICD-10 codes indicating poisoning by benzodiazepine-based tranquilizers, opioids, sedatives, or hypnotics. Our independent variable of interest was the number of unique providers responsible for prescribing benzodiazepines and opioids for each patient based upon the National Provider Identifier (NPI) associated with each prescription. We analyzed the distribution of demographic and comorbidity data using descriptive statistics including means and 95% confidence intervals. We then estimated the association between the number of prescribers and the risk of overdose by using multivariable proportional hazard regression modeling, which included adjustments for potential confounders including age, sex, patient comorbidities, as well as the average daily doses of benzodiazepines and opioids in diazepam milligram equivalents (DME) and morphine milligram equivalents (MME) respectively. The model aggregated data in 30-day intervals of continuous concurrency of benzodiazepine and opioid prescriptions for each patient. Gaps in concurrency less than 30 days were considered continuous, while gaps greater than 30 days were treated as separate events in the model. The number of prescribers was measured using the NPI associated with each prescription and was modeled based upon whether the patient had one, two, three, or four or more prescribers of benzodiazepines or opioids during each 30-day period. Hazard ratios were then calculated comparing the risk of overdose for patients with two, three, and four or more providers compared to having one provider.

RESULTS: The average age of was 51 years (SD 16 years), with 1,301,038 (64.8%) female patients. The average duration of concurrency was 129 days (SD 248 days), and the average number of providers was 2.0 (SD 0.5 providers). 11,838 (0.6%) patients had an overdose event. Prior to adjustment, the risk of overdose was higher for increasing number of providers compared to 1 provider prescribing concurrent benzodiazepine and opioid medications (2 providers: hazard ratio 1.24, 95% CI 1.17 to 1.31, $p<0.001$; 3 providers: hazard ratio 2.24, 95% CI 2.10 to 2.40, $p<0.001$; 4+ providers: hazard ratio 4.45, 95% CI 4.11 to 4.82, $p<0.001$). After adjusting for potential confounders, the risk of overdose remained higher when a greater number of providers were responsible for prescribing concurrent benzodiazepine and opioid therapy compared to 1 (2 providers: hazard ratio 1.08, 95% CI 1.02 to 1.15, $p=0.008$; 3 providers: hazard ratio 1.42, 95% CI 1.33 to 1.52, $p<0.001$; 4+ providers: hazard ratio 2.10, 95% CI 1.93 to 2.28, $p<0.001$) (Table 1, Figure 1).

CONCLUSION: In this retrospective analysis of 2,000,529 patients with concurrent prescriptions for benzodiazepines and opioids, an increased number of providers responsible for prescribing these medications was associated with an increased risk of an emergency room visit or inpatient admission for overdose. This increased risk was also observed after adjusting for patient demographics, comorbidities, and the doses of opioid and benzodiazepine being prescribed. These results provide support for policies which encourage the fewest possible number of providers to manage prescriptions for medications associated with a potentially synergistic risk of overdose.

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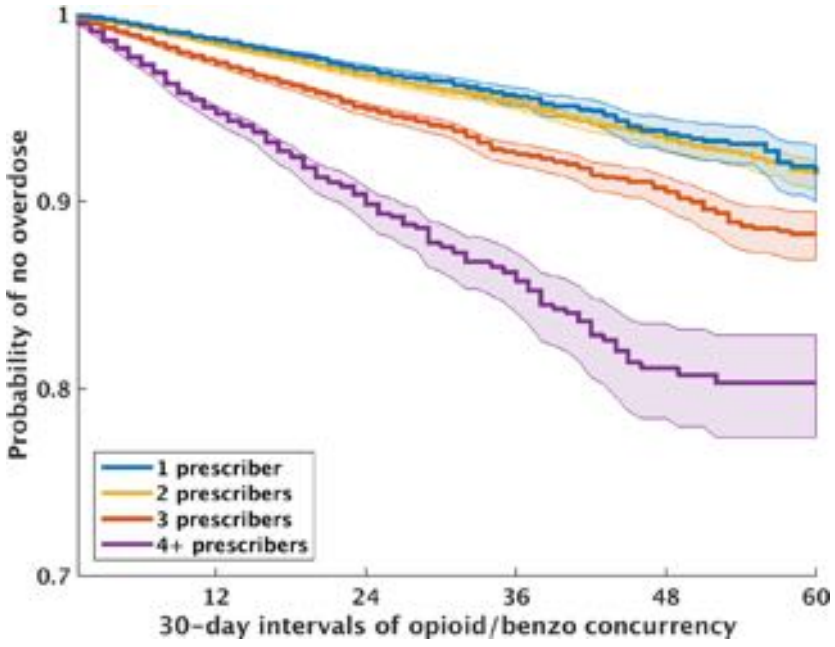
Table 1. Primary outcomes

Number of prescribers	Unadjusted		Adjusted	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-Value
2 prescribers	1.24 (1.17 to 1.31)	P<0.001	1.08 (1.02 to 1.15)	P=0.008
3 prescribers	2.24 (2.10 to 2.40)	P<0.001	1.42 (1.33 to 1.52)	P<0.001
4+ prescribers	4.45 (4.11 to 4.82)	P<0.001	2.10 (1.93 to 2.28)	P<0.001

The unadjusted and adjusted results of the hazard analysis show an association between having a greater number of prescribers for concurrent opioids and benzodiazepines and increased risk of having an emergency room visit or inpatient admission for overdose.

Figure 1: Kaplan-Meier survival curve for the probability of overdose



The Kaplan-Meier curve for the probability of overdose is shown. A greater number of providers was associated with increased risk of overdose.

PAIN MEDICINE 9

Randomised control trial to compare ultrasound (USG) guided TRANS ABDOMINAL PLANE (TAP) BLOCK & QUADRATUS LUMBORUM (QL) BLOCK to evaluate post-caesarean section analgesia after spinal anaesthesia

Dhaval H Shastri[1], Ila Patel[1], KAJAL A BHATT[2]

[1]GMERS Medical College And Civil Hospital Sola, Ahmedabad, Gujarat, [2]GMERS Medical College and Civil Hospital, Sola, Ahmedabad, Gujarat

INTRODUCTION: Substantial pain & discomfort is anticipated after caesarean delivery. Post-operative effective & safe analgesia helps early amelioration, expedites breastfeeding, early ambulation: avoiding various complications like venous thromboembolism, respiratory complications & prolonged hospital stay[1,2]. TAP block is given in the fascial plane between internal oblique & transverse abdominis muscle containing thoracolumbar nerves (T10toL1): providing somatic analgesia[3]. QL block is given at lateral border of QL muscle, anterior to the aponeurosis of the transverse abdominal muscle & within the anterior thoracolumbar fascia involving nerves (T7toL2): providing visceral & somatic analgesia[5]. We hypothesised that post operative analgesia with 0.25%ropivacaine in two different USG-guided blocks will show comparison b/w their effects on:time taken for first dose (rescue) analgesia, reduction in total requirement of analgesics in first 48h & their effect & adequacy for pain reduction (VAS Score)[2,3]. Also hemodynamics changes are compared.

METHODS: Ethical approval was taken from the college ethical committee before starting the study. Oral & written consent was taken from all participants & they were informed that they can leave the study at any time during the study & also assured that it won't affect their further treatment. In randomized controlled trial study, 40 ASA (American Society of Anesthesiology)[2] physical status, Age 20-40 years, Weight 50-70 kg, scheduled & emergency caesarean sections undergoing spinal anesthesia were selected between June-September 2020 (120 days)[2,5]. Sample size: 40 patients as per hospital statistics as >120 patients are undergoing caesarean section.We considered that a clinically important reduction in 48h tramadol consumption would be 25% absolute reduction[2]. This was a conservative assumption based on our reference data. We calculated that 20 patients per group would be required for an experimental design incorporating two equal-sized groups, using 0.05 and 0.2 alpha and beta errors. The allocation sequence was generated by a random number table. The patients, anesthesiologists & staff were blinded to the allotment. Thorough history and examination were done of all patients. All investigations including complete blood count, ECG, routine vitals were done for all patients. Demographic characteristics, post operative vitals in monitor, VAS scoring & clinical examination were used to study. In the operating room, patients received all standard anesthetic monitors & all baseline parameters including heart rate,blood pressure & oxygen saturation were recorded. All patients received spinal anesthesia with 0.5% hyperbaric bupivacaine 10mg. Group I(n=20) received USG-guided TAP block, Group II (n=20) received USG-guided QL block With 0.25% Ropivacaine 15 ml on either side after skin closure with the guidance of a linear array transducer probe(6-13 MHz)[6]. Pain severity was assessed by a blinded investigator in post-operative recovery room every 2, 4, 6, 12, 24, 36 & 48h. It was measured using visual analogue score (VAS) (0=no pain & 10=worst possible pain). Rescue analgesia was given to patients on demand or when VAS was (>4) in the form of[4] tramadol 2 mg/kg. The parameters studied & compared in both the groups are time to first request for analgesia, total tramadol requirement in 48h and VAS at 2, 4, 6, 12, 24, 36 & 48h. Also pulse, blood pressure and oxygen saturation is also measured at all interval mentioned[6,7]. SPSS version 25 software was used. Demographic data were analysed using student t-test & other parameters using paired t-test.

RESULTS: Under USG-guidance QL block in comparison with TAP block shows; Time for rescue analgesic (first dose) was prolonged (mean±SD: 38±2.236h vs.9.5±1.27h) (P=.017), Mean requirement of tramadol in 48h is reduced from 262mg to 144mg (P=0.029),Reduction in post operative VAS at rest & movement at 48h (P=0.014). No significant difference was found in hemodynamic profile.

CONCLUSION: After caesarean section,total analgesic requirement in first 48h is reduced,time for rescue analgesia is prolonged & VAS scoring is improved with QL block compared to TAP block under USG-guidance. USG guidance assures definite administration of local anesthesia-significant effect of local anesthetic[8]. Due to reduction in post-operative analgesia like opioids,tramadol, NSAIDs helps in reduction of their complications like constipation, vomiting, gastric bleeding,thromboembolism,renal & respiratory complications[9,10]. No alterations in hemodynamics.

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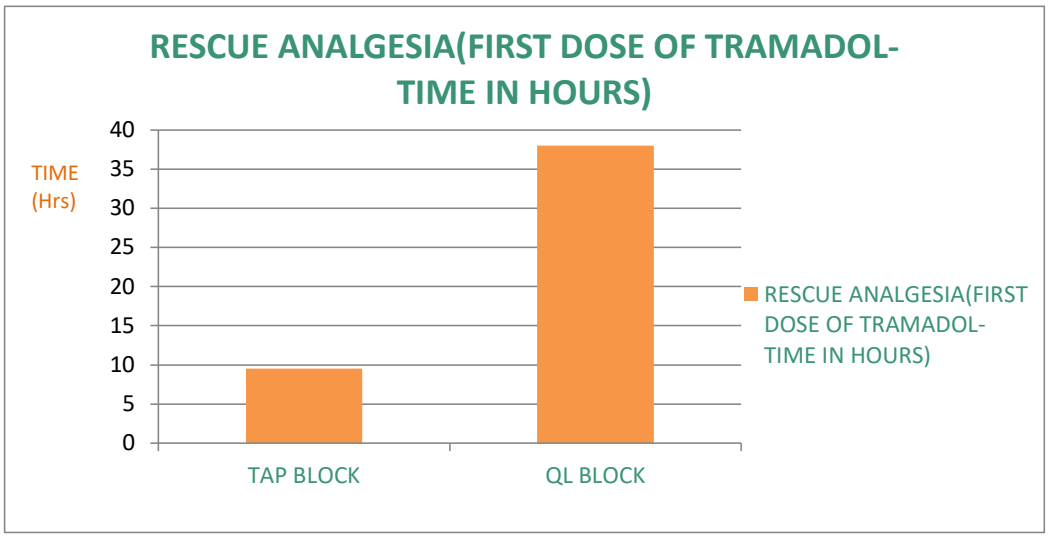
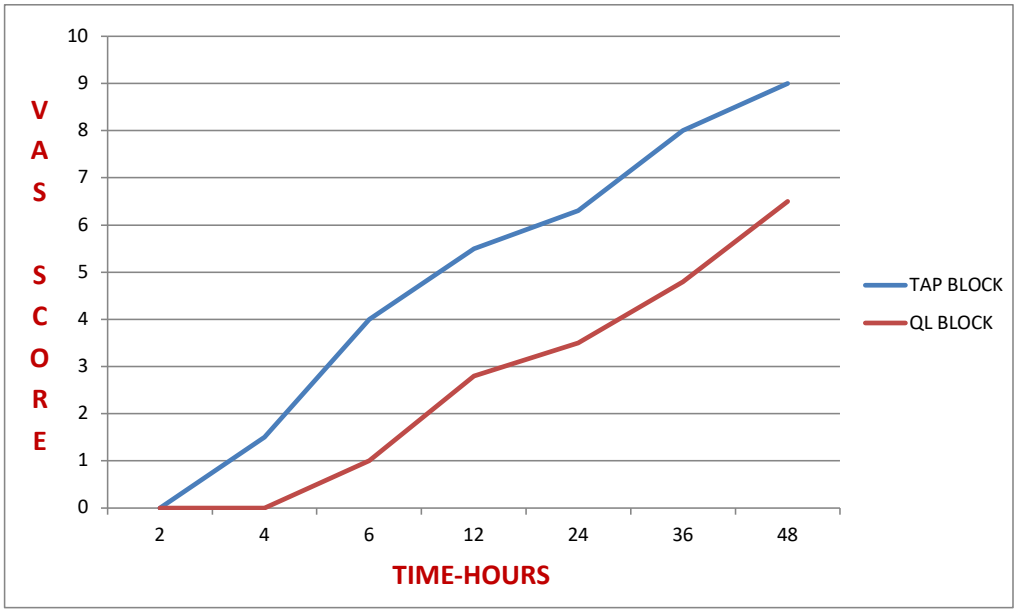
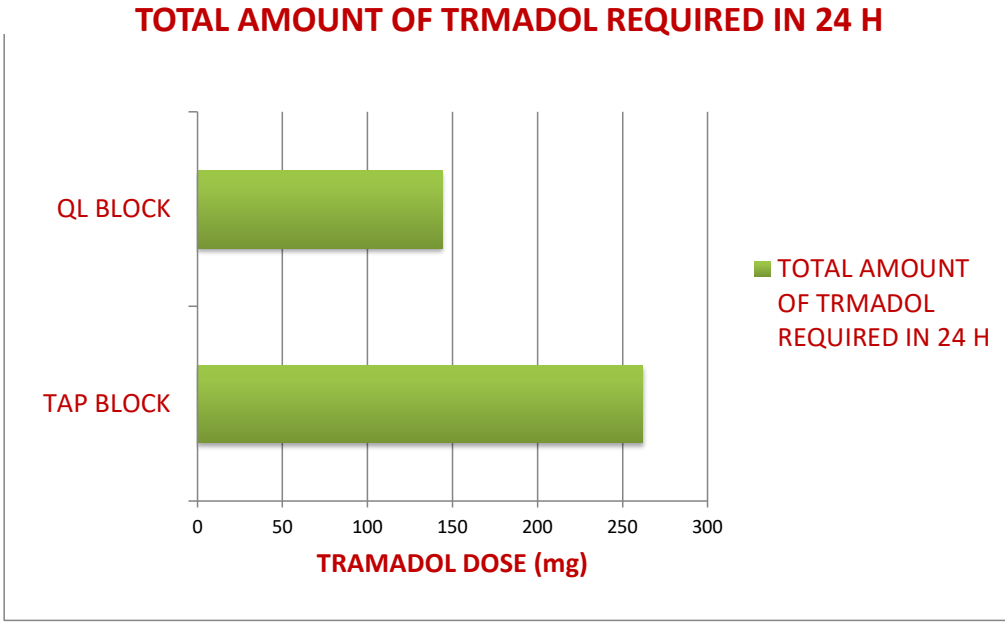
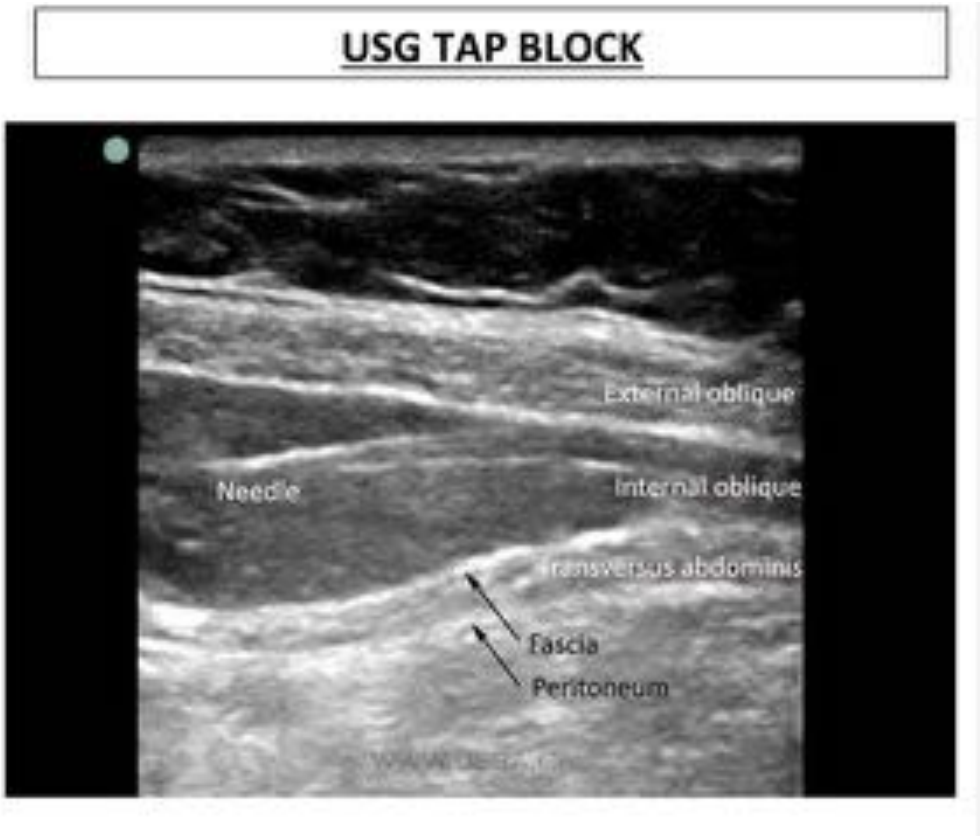
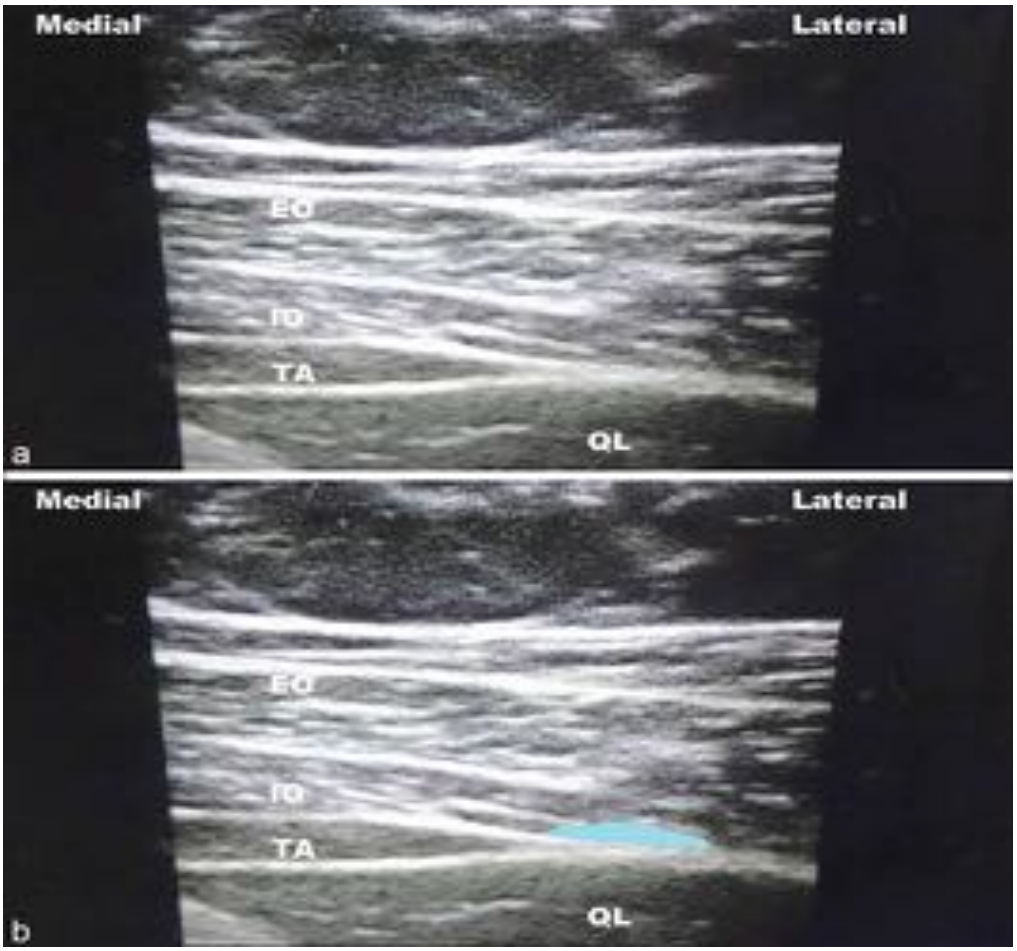








USG-guided QL Block



PAIN MEDICINE 10

Positive airway pressure therapy for chronic pain in patients with obstructive sleep apnea: a systematic review

Kristian McCarthy[1], Aparna Saripella[2], Janannii Selvanathan[2], Mahesh Nagappa[3], Marina Englesakis[2], David Wang[4], Philip Peng[2], Frances F Chung[2]

[1]University of Toronto Faculty of Medicine, Toronto, Ontario, [2]Toronto Western Hospital, Toronto, Ontario, [3]Western University, London, Ontario, [4]Royal Prince Alfred Hospital, Sydney, Australia

INTRODUCTION: Patients with chronic pain often have sleep-disordered breathing (SDB), which includes obstructive sleep apnea (OSA)[1]. Evidence has demonstrated that individuals with chronic pain who report higher pain intensity also experience greater sleep impairment and vice versa[2]. The standard management of OSA is positive airway pressure therapy (PAP). Although there is robust evidence supporting PAP's use in improving the Apnea-Hypopnea Index of OSA, its use in improving pain is mostly unknown. Our goal was to evaluate whether PAP for OSA in the chronic pain population improves pain outcomes, including pain intensity, tolerance, and threshold.

METHODS: We performed a systematic search for studies published after 1990, utilizing Medline, Medline In-Process/ePubs, Embase, Cochrane CENTRAL, and the Cochrane Database of Systematic Reviews. Blocks of search terms included 'chronic pain,' 'sleep disorders,' and 'positive airway pressure.' Two reviewers independently performed the abstract and full-text screening, data extraction, and study quality appraisal.

RESULTS: Of 1,982 initial results, ten studies met the inclusion criteria. These studies included 323 chronic pain patients with OSA who underwent PAP and 64 chronic pain patients with OSA who were not adherent to PAP. The average age was 52 ± 12 years, and 80% were male. Six studies investigated chronic headaches. One study investigated chronic non-headache pain. Three studies focused on patients' pain tolerance or threshold (surrogate markers of pain outcomes). Of the six studies examining headaches, five demonstrated improved pain outcomes at follow-up, ranging from one-day to 42 months. In one study, PAP resulted in a decreased morning headache prevalence; but, the result was non-significant ($p = 0.065$). The study examining PAP's effect on non-headache pain found that PAP didn't significantly decrease pain intensity ($p > 0.05$). Out of three studies measuring pain tolerance or threshold, PAP significantly improved these outcomes in two studies ($p = 0.03$ and $p = 0.01$). Conversely, in another cohort study, PAP for one month resulted in a decreased pain threshold ($p = 0.027$).

CONCLUSION: In chronic pain patients with OSA, we found that PAP decreased chronic headaches. Our results also support the idea that PAP may increase pain threshold and tolerance. However, a gap in the literature exists regarding PAP's effectiveness in improving chronic non-headache pain. One study found a lack of pain intensity improvement, which may be due to patients with more psychiatric comorbidities and more neuropathic pain. Another study also found a lack of PAP effectiveness, which may be due to unfamiliarity with PAP, causing muscle tension and lower pain thresholds. The advancement of this understanding would help inform the promotion of OSA screening in patients with chronic pain, pain management in OSA patients, and PAP's potential use as an adjunct/alternative therapy to current analgesics.

Table 1. Study outcomes

Study	Study Design; Population (n)	Pain classification	PAP therapy duration	Outcome Measure	Conclusion	Effect of PAP
Chronic pain						
Poceta, 1995	Pre-post cohort; 14	Headache-type: • Cluster: 1 • Migraine: 5 • Tension: 3 • Mixed: 5	CPAP: range, 4–36 months	Morning headache questionnaire: *Frequency of waking up with a headache: 'never', 'rarely', 'weekly', or 'nightly'. 'Weekly' or 'nightly' considered symptomatic.*	CPAP: 50% overall showed headache improvement: • Cluster: 1/1 • Migraine: 3/5 • Tension: 0/3 • Mixed: 3/5	Positive
Loh, 1999[a]	Retrospective pre-post cohort; 25	Headache-type: • Headache AM: 23 • Tension: 12 • Migraine: 6 • Cervicogenic: 5 • Cluster: 1 • Other: 12	CPAP: duration NR	Telephone interview: *Numerical rating scale of headache improvement: 0-100% (in increments of 10%), lowest to highest*	Headache AM or cluster: CPAP: average of 80% headache improvement Tension, migraine, or cervicogenic: CPAP: minimal improvement	Positive
Goksan, 2009	Retrospective pre-post cohort; 76	Headache AM: 76	CPAP: follow up, 1 day, 1 week, and 1 month	Morning headache questionnaire: *Presence of morning headache (yes/no)*	1 day, 1 week, 1 month headache improvement: 72.4%, 84.2%, 92.1% showed headache improvement	Positive
Kallweit, 2011	Pre-post cohort; 11	Migraine: 11	CPAP: 12 months	Migraine disability assessment scale	Attack frequency post-CPAP vs. baseline: 0.1 ± 0.3 vs. 5.8 ± 7.8 attacks per month ($p < 0.05$) Attack duration post-CPAP vs. baseline: 0.5 ± 0.7 vs. 6.4 ± 11.9 hours ($p < 0.05$) Intensity of attacks (VAS) post-CPAP vs. baseline: 2.1 ± 3.2 vs. 7.4 ± 1.7 ($p < 0.001$) Workdays lost post-CPAP vs. baseline: 0.2 ± 0.3 vs. 1.8 ± 2.2 days/month ($p < 0.05$) Acute antimigraine medication post-CPAP vs. baseline: 0 vs. 6.5 ± 8.0 units/month ($p < 0.05$)	Positive

Cruz, 2012	Pre-post cohort; 97	Headache AM: 10	APAP: 6 months	Sleep Disorder Questionnaire: *Presence of morning headache: 5-point Likert scale, '4' or '5' considered symptomatic*	Post-APAP vs. baseline: 3.0% vs. 10.0% considered symptomatic (p = 0.065)	Negative
Johnson, 2013[b]	Retrospective cohort; CPAP adherent: 27 CPAP non-adherent: 6	Headache-type: • Migraine • Tension • Post-traumatic • Medication overuse • Total: 27	CPAP: range, 18–42 months	Telephone interview: *Headache improvement definition: ≥50% reduction in headache severity and frequency*	CPAP adherent vs. CPAP non-adherent or no CPAP: 78% vs. 33% or 42% showed headache improvement (p = 0.045)	Positive
Jaoude, 2016	Retrospective cohort; CPAP adherent: 35 CPAP non-adherent: 58	Non-malignant pain	CPAP: 12 months	Numerical Categorical Scale *Pain intensity scored from 0-10, lowest-highest*	CPAP adherent at 12 months vs. baseline: 1.9 ± 1.5 vs. 2.1 ± 1.4 (p > 0.05) CPAP non-adherent at 12 months vs baseline: 2.6 ± 1.5 vs. 2.7 ± 1.4 (p > 0.05)	Negative
Pain tolerance or threshold						
Onen, 2010[c]	Randomized blinded crossover; 11	Pain tolerance	CPAP: 3 days[d]	Pain Matcher *Pain tolerance scored from 0-99, lowest-highest*	Mean tolerance post-high CPAP Rx vs baseline: 28.4 ± 16.0 vs. 21.2 ± 10.9 (p = 0.03) Mean tolerance post-low CPAP Rx vs. baseline: 23.8 ± 12.4 vs. 21.2 ± 10.9 (p = 0.44)	Positive
Khalid, 2011	Pre-post cohort; 12	Pain threshold	CPAP: follow up, 2 nights, and 6–8 weeks	Finger Withdrawal Latency Testing *Time until finger was withdrawn from heat source, in seconds*	Post-CPAP (2 nights) vs. baseline: 13.7 ± 5.1 vs. 9.8 ± 1.3 sec. (p = 0.01) Post-CPAP (6-8 weeks) vs. CPAP discontinuation: 21.1 ± 16.2 vs. 11.5 ± 5.9 sec. (p = 0.03)	Positive
Jitsuparat, 2018	Pre-post cohort; 15	Pain threshold	CPAP: 1 month	Digital Electronic Algometer (in kg/m^2)	Post-CPAP therapy vs. baseline: 1.51 vs. 2.02 (p = 0.027)[e]	Negative

[a]Headache-types were not mutually exclusive.
[b]Distribution of headache-types not stated.
[c]Subjects randomized to 2 consecutive 3-day sequences, either beginning with low CPAP or high CPAP.
[d]Low CPAP: 4 cm H_2O; High CPAP: 5 to 10 cm H_2O auto-adjusted-CPAP.
[e]All ten muscles analyzed displayed similar significant decreases in pain threshold.

PAIN MEDICINE 11

The Efficacy of PECs Block in Addition to Multimodal Analgesia in Reducing Perioperative Opioid Consumption among Patients Undergoing Elective Breast Surgery: A Retrospective Study

Alberto A Uribe[1], Luis Periel[1], Joshua Pasek[1], Marco Echeverria-Villalobos[1], Juan Fiorda-Diaz[1], Roman J Skoracki[2], Stephen J Poteet[3], Marilly Palettas[4], Sanjay Mohan[3], Tristan Weaver[1], Jarrett A Heard[3]

[1]The Ohio State University, Wexner Medical Center, Columbus, OH, [2]The Ohio State University, Wexner Medical Center, Columbus, United States of America, [3]The Ohio State University, Wexner Medical Center, Columbus, OH, [4]The Ohio State University, Columbus, OH

INTRODUCTION: Thoracic epidural block has been widely used for postoperative pain management in patients undergoing breast surgery. However, due to its potential associated complications, it has been recently substituted by pectoral nerves (PECs) block. There are two types of PECs blocks; the PECs I is an interfacial plane block administered between the pectoralis major and the pectoralis minor muscles, at the level of the third rib and the PECs II block, a combination of PECs I block plus a second injection block administered above the serratus anterior muscle. PECs block has been linked with satisfactory pain management and perioperative opioid consumption. In addition, there have been an increased interest on different multi-modal analgesia (MMA) approaches, particularly as part of enhanced recovery after surgery (ERAS) protocols. Various agents have shown efficacy in reducing perioperative opioid consumption, particularly in breast cancer surgery. For instance, reduced pain scores and opioid consumption have been reported when a combination of gabapentin and acetaminophen alone or in conjunction with regional anesthesia are used. Considering the limited reported evidence on perioperative pain management in this surgical population, we conducted a retrospective chart review in order to assess perioperative opioid consumption (oral morphine mg equivalent [OME]) between patients undergoing elective breast surgery that received MMA with or without PECs block.

METHODS: A retrospective chart review was conducted to assess the efficacy of preoperative PECs block in addition to MMA (oral administration of acetaminophen and/or gabapentin) in reducing perioperative opioid requirement in adult patients undergoing elective breast surgery at The Ohio State Wexner Medical Center between July 1, 2015 and June 26, 2020. Medical records were reviewed and subjects were assigned to either of the following groups: Control (MMA only) and PECs (MMA + PECs block) groups. Demographics, clinical/surgical variables and perioperative opioid consumption (intraoperative and Post-Anesthesia Care Unit [PACU]) were collected. The project described was supported by Award Number UL1TR002733 from the National Center for Advancing Translational Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

RESULTS: Two hundred and twenty eight subjects (n=228) were enrolled in the study. Subjects were allocated into one of the two groups, 174 subjects in the control group and 54 subjects in the PECS block group. The average age was 48 ± 15.1 years old. Around 98% of subjects received acetaminophen, around 84% of the subjects received gabapentin, and 82% of the subjects received a combination of acetaminophen and gabapentin. Most of the subjects in the PECs group (90.7%) received bilateral PECs block, with PECs II being the most used block (79.6%). Breast reduction and mastectomy/lumpectomy surgeries were the most common performed procedures (48% and 28% respectively). Opioid consumption during surgery in the control and PECs groups were 27 [19, 38] and 28.5 [22, 38] ($p = 0.21$) OME, respectively. PACU opioid requirements were 14.3 [7, 24.5] OME for the control group and 17 [8, 23] OME ($p = 0.732$) for the PECs group.

CONCLUSION: Our results suggest that there are not significant differences in intraoperative and/or PACU opioid requirements in patients undergoing elective breast surgery that received MMA with or without PECs block. Therefore, both approaches could be effective regimens for perioperative pain management. Future randomized prospective trials testing the combination of MMA with or without PECs blocks and assessing opioid consumption and postoperative pain during the first 24-48 hours should be performed. This would allow anesthesia providers to elucidate better techniques for pain management without increasing the risk of perioperative complications in this surgical population.

The Efficacy of PECs Block in Addition to Multimodal Analgesia in Reducing Perioperative Opioid Consumption among Patients Undergoing Elective Breast Surgery

Tables:

Table 1. Demographic and surgical variables

1. Demographics and surgical characteristics

Variables	Control (N= 174)	PECS Block (N= 54)	Total (N= 228)	P-value
Age, years, mean (SD)	50.4 (14.2%)	40.3 (15.7%)	48 (15.1%)	**<0.001**
Weight, kg, mean (SD)	80.2 (17.5%)	80.2 (15%)	80.2 (16.9%)	0.996
Height, meters, mean (SD)	1.6 (0.1%)	1.6 (0.1%)	1.6 (0.1%)	0.219
BMI, units, mean (SD)	29.9 (6.5%)	30.3 (5.4%)	30 (6.2%)	0.652
ASA I/II/III, N	25/101/48	18/31/5	43/132/53	**0.001**
History of PONV or motion sickness, N (%)	42 (24%)	9 (17%)	51 (22%)	0.25
MMA pre-op with gabapentin, N (%)	143 (82%)	49 (91%)	192 (84%)	0.132
MMA pre-op with acetaminophen, N (%)	171 (98%)	53 (98%)	224 (98%)	0.95
MMA pre-op gabapentin + acetaminophen, N (%)	140 (80%)	48 (89%)	188 (82%)	0.155
MMA pre-op gabapentin dose, mg, median (IQR)	600 [300, 900]	600 [300, 900]	600 [300, 900]	**0.002**
MMA pre-op acetaminophen dose, mg, median (IQR)	650 [650, 975]	975 [650, 975]	975 [650, 97]	**0.002**
Intraoperative medication				
Dexamethasone, N (%)	153 (88%)	53 (98%)	206 (90%)	**0.032**
Dexamethasone, mg, median (IQR)	8 (4, 8%)	53 (98%)	206 (90%)	0.859
Ondansetron, N (%)	166 (95%)	53 (98%)	219 (96%)	0.69
Ondansetron, mg, median (IQR)	4 (4, 4%)	4 (4, 4%)	4 (4, 4%)	0.599
Ketamine, N (%)	18 (10%)	7 (13%)	25 (11%)	0.56
Ketamine, mg, median (IQR)	30 [30, 50]	50 [30, 50]	40 [30, 50]	0.824
Fentanyl, N (%)	170 (98%)	53 (98%)	223 (98%)	0.341
Fentanyl, mcg, median (IQR)	125 [100, 200]	150 [100, 200]	125 [100, 200]	0.341
Hydromorphone, N (%)	66 (38%)	27 (50%)	93 (41%)	0.115
Hydromorphone, mg, median (IQR)	1 [1, 2]	1 [1, 2]	1 [1, 2]	0.202
Ketorolac, N (%)	14 (8%)	10 (19%)	24 (11%)	**0.029**
Ketorolac, mg, median (IQR)	30 [30, 30]	30 [30, 30]	30 [30, 30]	0.074
Pectoral nerves (PECS) block type				
Bilateral blocks	NA	49 (90.7%)		
PECS I	NA	5 (9.3%)		
PECS II	NA	43 (79.6%)		
PECS Unknown	NA	6 (11.1%)		
Length of surgery, minutes, mean (SD)	125 [77, 168]	153 [128, 182]	132 [93, 174.5]	**0.001**
Length of anesthesia, minutes, mean (SD)	163 [110, 211]	190 [164, 231]	175 [127, 221.5]	**0.004**
Length of PACU stay, minutes, mean (SD)	146 [125, 186]	141 [122, 168]	144 [124, 184.5]	0.501
Type of surgery				
Breast reduction, N (%)	67 (39%)	42 (78%)	109 (48%)	**< 0.001**
Mastectomy/lumpectomy, N (%)	60 (34%)	3 (6%)	63 (28%)	
Masteopexy, N (%)	14 (8%)	5 (9%)	19 (8%)	
Breast augmentation, N (%)	16 (9%)	2 (4%)	18 (8%)	
Breast reconstruction, N (%)	17 (10%)	2 (4%)	19 (8%)	
PONV				
PONV incidence, N (%)	30 (17%)	12 (22%)	42 (18%)	0.41
PONV rescue medication, N (%)	30 (17%)	12 (22%)	42 (18%)	0.41
Rescue with Promethazine, N (%)	1 (1%)	0 (0%)	1 (0%)	0.577
Rescue with Ondansetron, N (%)	28 (16%)	4 (7%)	32 (14%)	0.109
Ondansetron dose, mg, Median (IQR)	4 [4, 4]	4 [4, 4]	4 [4, 4]	0.712
Rescue with Haloperidol, N (%)	3 (2%)	8 (15%)	11 (5%)	**< 0.001**
Haloperidol dose, mg, median (IQR)	1 [1, 1]	1 [1, 1]	1 [1, 1]	0.999
Postoperative complication (30 Days)				
Wound infection, N (%)	0 (0%)	2 (100%)	2 (29%)	0.2
Wound dehiscence, N (%)	1 (20%)	0 (0%)	1 (14%)	
Hematoma, N (%)	2 (40%)	0 (0%)	2 (29%)	

Table 2. Perioperative opioid consumption

Variables	Control (N= 174)	PECS Block (N= 54)	Total (N= 228)	P-value
Intraoperative opioid consumption, oral morphine mg, mean (SD)	27 [19, 38]	28.5 [22, 38]	27 [19, 38]	0.21
PACU opioid consumption, oral morphine mg, mean (SD)	14.3 [7, 24.5]	17 [8, 23]	15 [8, 23.8]	0.732
Overall opioid consumption, oral morphine mg, mean (SD)	43.5 [31, 61]	45.5 [38, 58.3]	45.5 [33, 60.5]	0.284

PAIN MEDICINE 12

12 Pain prevalence audit in the Oncohematologic and Surgical Departments of an Italian Third Level Pediatric Hospital: preliminary results

Alessandro Vittori[1], Giuliano Marchetti[2], Elisa Francia[2], Ilaria Mascilini[2], Sergio G Picardo[2]

[1]Ospedale Pediatrico Bambino Gesù, Rome, Italy., Rome, Italy, [2]Ospedale Pediatrico Bambino Gesù, Rome, Rome

INTRODUCTION: Although there is evidence that pain prolongs hospitalization, it is also well known that it is still undertreated in both adults and children. This study aimed to assess the prevalence of pain in the Oncohematologic and Surgical Departments, 5 years after the previous audit in an Italian Third Level Pediatric Hospital that joined the project 'Pain Free Hospital'.

METHODS: On February 2019, during a single day work, four committees administered a questionnaire to patients or to the parents to assess the prevalence of pain, the adherence to the hospital internal protocols and to the 'Pain Free Hospital' project. The four commissions were made up of two health workers chosen among anestetists, surgeons, oncohematologists and nurses who did not work in the department to be studied. The study was approved by the local Ethic Committee.

RESULTS: 63 patients were enrolled in the study (an age ranging from 4 months to 17 years, with an average of 8.3 years), 21 from the Oncohematologic Department and 42 from the Surgical Department. FLACC or NRS pain scales were used to assess pain. During hospitalization 33 patients experienced pain (52.8%): 9 of the 21 (43%) patients from the Oncohematologic Departement had pain, while 24 of the 42 with pain (57%) were hospitalized in the Surgical Department. 30 children (47.62%) had no pain.. Mild pain score (up to 3) was present in 2 patients, moderate pain score (4 to 7) was present in 14 patients, severe pain score (8 to 10) was present in 13 patients. In no case were there any linguistic or cultural barriers such as to prevent correct communication between health professionals, patients and care givers.

CONCLUSION: Prevalence of pain is still high in both the department but especially in the Surgical one. More worryingly, pain is mostly moderate or severe. Although we are now analyzing all the variables of this study we can say that possible causes include: prescription of intermittent rather than around-the-clock therapies, failure both in communicating information about pain therapy to patients and caregivers and translating the actual knowledge on pain therapy into clinical practice.

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PAIN MEDICINE 13

Microglia proliferation after peripheral nerve injury in mice involves two distinct phases

Paul Su[1], Wulin Tan[2], Jacqueline Leff[3], Zhonghui Guan[4]

[1]University of California San Francisco, San Francisco, CA, [2]First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China, [3]University of California, San Francisco, San Francisco, United States of America, [4]University of California San Francisco, San Francisco, United States of America

INTRODUCTION: Adult microglia proliferate to self-renew at baseline, and to expand their population upon stimulation. Microglia proliferation is hallmark to a myriad of neurological disorders, including nerve injury; more importantly, inhibition of microglia proliferation attenuates the development of neuropathic pain, indicating the critical contribution of microglia proliferation in the pathogenesis. However, the underlying mechanism is largely unknown.

METHODS: All animal research protocols were approved by the institutional animal care and use committee. We crossed Cx3cr1-yfp-CreER mice with Mycfl or Tnfaip3fl mice to genetically delete the respective genes from microglia. Sciatic nerve transection was used as the model for peripheral nerve injury. Single cell RNA sequencing (scRNA-Seq): Single microglia cells from lumbar spinal cord were isolated by fluorescence-activated cell sorting (FACS) and processed for single cell RNA sequencing using 10X Genomics platform. Flow cytometry: Dissociated single cells from spinal cord were stained for cell viability, specific microglia marker (CX3CR1), and Ki67 and analyzed by a flow cytometer. Gene Expression is evaluated by quantitative RT-PCR (qRT-PCR) of RNA isolated from FACS sorted microglia.

RESULTS: Our scRNA-Seq reveals that the time course of microglia proliferation can be divided into early and late phases, corresponding to our qRT-PCR results of early and transient Myc upregulation and prolonged Tnfaip3 downregulation in spinal lumbar cord microglia after nerve injury. Our flow cytometry results demonstrate that deletion of Myc specifically abolished the early microglia proliferation 2 days after nerve injury. On the other hand, downregulation of Tnfaip3 regulates late phase of proliferation day 3 and beyond after nerve injury; and our scRNA-Seq shows that Tnfaip3 deletion in naïve animals resulted in transcriptomic signature similar to late phase nerve injured animals with increased baseline microglia proliferation. In addition, Myc and Tnfaip3 expression returned to baseline at the termination of microglia proliferation, and over-expression of Myc or deletion of Tnfaip3 prevented the cessation of microglia proliferation.

CONCLUSION: Microglia proliferation after nerve injury consists of an Myc upregulation-mediated early and a Tnfaip3 downregulation-mediated late phase; and termination of microglia proliferation requires the normalization of Myc and Tnfaip3 expression.

PAIN MEDICINE 14

Opioid Sparing Effects of Light Induced Analgesia for Chronic Pain in Fibromyalgia Patients

Amanda Nelli[1], Padma Gulur[2]

[1]Duke University Heath System, Durham, NC, [2]Duke University School of Medicine, Durham, NC

INTRODUCTION: The opioid epidemic has resulted in exploration in opioid sparing and non-opioid analgesics strategies. One promising non-opioid analgesic is the manipulation of the visual light spectrum resulting in narrow spectrum colored light. The preclinical studies using green wavelengths of light offer potential for the clinical use of green light for patients with pain[1]. We hypothesize that patients exposed to green light therapy will have greater pain reduction and lower opioid use when compared to patients exposed to other spectrums of light.

METHODS: Patients with fibromyalgia, on opioids were consented and randomized to one of three groups: blue, clear or green. Patients were recruited from August 2019 to December 2020 and instructed to wear their study glasses for a minimum of 4 hours per day for the 2 weeks they are in enrolled in the study. They were also asked to record their glasses use and daily opioid use in a diary. At the consenting visit, one week and two weeks, patients completed the PROMIS-57 survey. Patients were called to complete the week one survey and the week two survey was completed either over the phone or in clinic.

RESULTS: A total of 34 patients completed the study: 10 blue, 12 clear and 12 green. Opioid use, recorded as average oral morphine equivalents, OME, for each group was analyzed and compared to average pain scores for each group. Patients randomized to the blue group displayed a 13% decrease in opioid use and 9% decrease in pain scores. The clear group demonstrated a decrease of 0.1% of opioid use and 8% decrease in pain scores. The green group displayed a decrease of 13% in opioid use and a 15% reduction in pain scores.

CONCLUSION: Exposure to blue light showed some benefit to patient's pain as seen in the decrease in both opioid use and pain scores. Full spectrum light exposure, as seen in the clear group, proved less beneficial with no decrease in opioid use with a slight decrease in pain scores. Green light exposure demonstrated benefit to patients in both decrease in opioid use and pain scores. The significant decrease of the pain and opioid use in this group supports our hypothesis of efficacy and provides exciting potential for this novel pain therapy.

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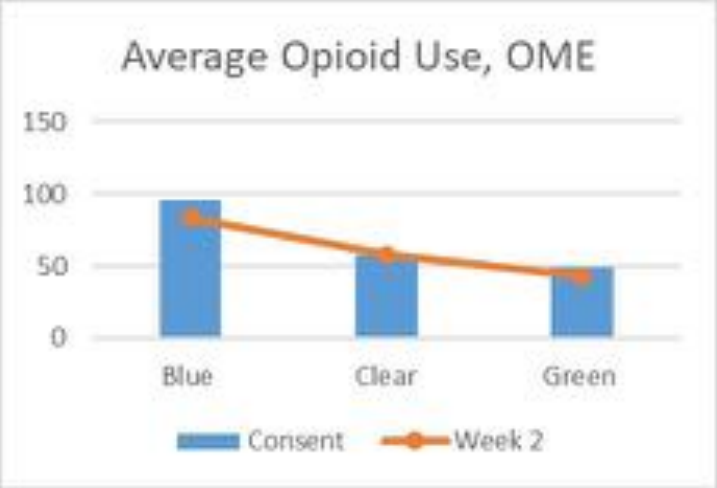

PAIN MEDICINE 15

Storage and Disposal Practices of Prescribed Opioids in the Postoperative Patient

Amanda Nelli[1], Padma Gulur[2], Nancy Pahwa[1]

[1]Duke University, Durham, NC, [2]Duke University School of Medicine, Durham, NC

INTRODUCTION: Opioid prescriptions for acute, postoperative pain have been linked to the opioid misuse and abuse[1-2]. Patients who do not use all of their opioid prescription may store their extra medication for late use for themselves or others. While this is not recommended, it may, in part, be due to lack of patient education of proper storage and disposal of opioid medications. The objective of this study is to assess at home opioid utilization, storage, and disposal practices of patients postoperatively prescribed an opioid analgesic.

METHODS: After obtaining IRB approval, patients from three surgical specialties at Duke University Health System (DUHS) were postoperatively contacted to determine opioid utilization and handling practices from January 2017-July 2018. Patients who were prescribed opioids after Urology, Cesarean-Section, and Neurosurgery procedures completed a telephone survey regarding opioid usage, storage, and handling practices.

RESULTS: A total of 247 patients were evaluated between the three surgical specialties. We determined that only 37% of patients used their full opioid prescription and 30% of patients used none of their opioid prescription. The remaining patients used an average of 54% of their prescribed dose. There were 145 patients (59%) who were able to recall how they disposed of their left over opioid prescription. Only 16% of patients properly disposed of the drug (either returned to a take back site or flushing down the toilet). The remaining 86% of patients stored the prescription drug in various unsecured locations around the home such as the bedroom or bathroom, with 49 patients being unaware of where the medication was stored.

CONCLUSION: Our study demonstrates that physicians may be overprescribing the discharge opioid(s), leaving patients with excess medication in the home. We also observed the majority of patients retaining left over opioids did so in a casual manner, increasing the risk for misuse or abuse. C-section patients had the highest rate non-opioid use; however, this group was the least likely to properly dispose of the opioid medication. Education for both patients and providers on safe handling and disposal practices is essential in decreasing the misuse and abuse potential of prescribed opioids.

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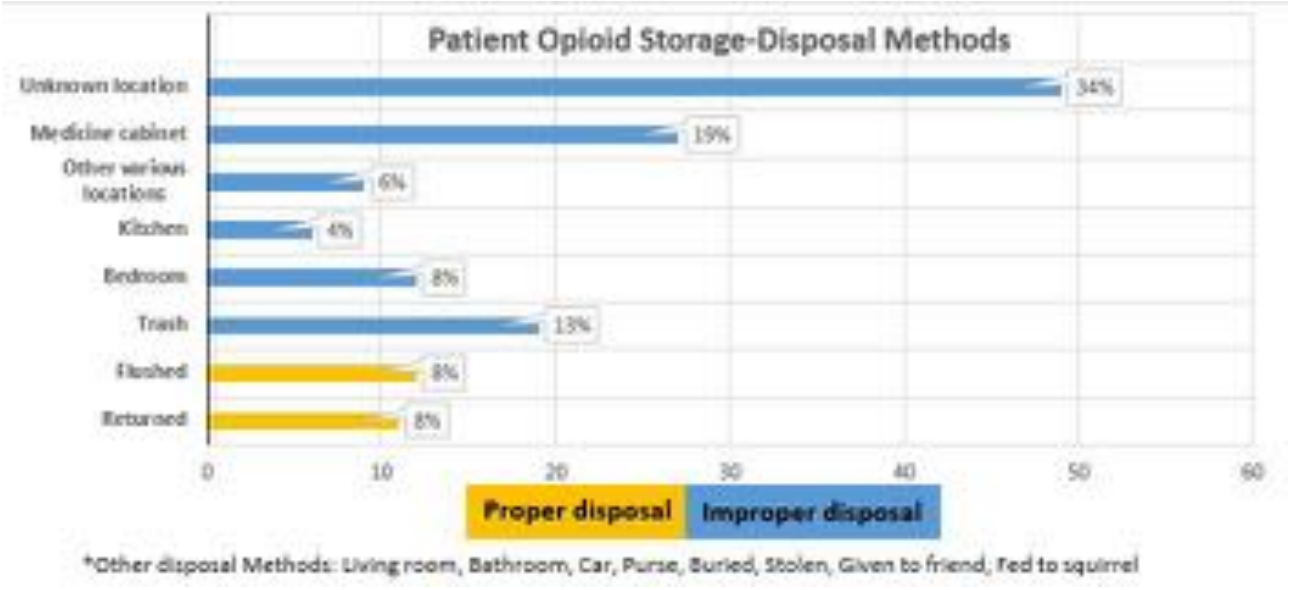

PAIN MEDICINE 16

Pain management in bilateral versus unilateral total knee arthroplasty

Gozde Gursoy Cirkinoglu[1], Fikret Maltepe[2], Vasfi Karatosun[2], Sule Ozbilgin[2], Bayram Unver[3], Ayten Deniz[4]

[1]Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey, [2]Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [3]Dokuz Eylul University, School of Physical Therapy and Rehabilitation, Izmir, Turkey, [4]Dokuz Eylul University, Faculty of Nursing, Izmir, Turkey

INTRODUCTION: Total knee arthroplasty can be performed in the form of a one-stage bilateral procedure or a unilateral procedure. Adequate analgesia decreases complications and increases functional recovery. The aim of this study is to investigate whether patients undergoing one-stage bilateral total knee arthroplasty and those undergoing unilateral total knee arthroplasty differed in their responses to a standard intravenous patient-controlled analgesia protocol.

METHODS: Data from patients with the physiological status I-III according to American Society of Anesthesiologists, aged 18-99 years, undergoing one-stage bilateral or unilateral total knee arthroplasty (TKA) under spinal anesthesia in Dokuz Eylul University Hospital between January 2014 and December 2017 and offered a standard intravenous patient-controlled analgesia with morphine were retrospectively reviewed. Demographic data, Visual Analogue Scale scores and postoperative complications were examined. The total dose of analgesics consumed, analgesia demands, doses delivered and the ratio of delivered doses to demands in 0-24 hours and 24-48 hours after surgery available in the patient-controlled analgesia (PCA) pump monitoring forms were recorded. Patients planned to have TKA in the hospital where this study was conducted are firstly recommended spinal anesthesia. Following the standard monitoring, the patients are administered spinal anesthesia through vertebral spaces L2-3 or L3-4 when seated. To achieve spinal anesthesia, bupivacaine heavy 2,5 - 3ml (12,5-15mg) and morphine (0.1 - 0.2mg) are administered intrathecally. Intravenous PCA is utilized after surgery. PCA is achieved by an intravenous 1mg bolus of morphine with a lockout interval of 20 min.

RESULTS: Patient records about 927 cases were enrolled and data about 192 patients fulfilling the inclusion criteria were retrospectively analyzed. Records about 68 patients who had one-stage bilateral total knee arthroplasty and 124 patients who had unilateral total knee arthroplasty were accessed. The rate of the gender female was higher in both groups of the patients. The preoperative hospital stay and the total hospital stay were longer in the unilateral total knee arthroplasty group. The patient-machine interaction in patient-controlled analgesia gives hints at many issues. Examination of demands and delivered doses recorded by the machine can help to evaluate patient adherence to the analgesia offered. The total number of pressing the button refers to the number of demands and shows needs for analgesics and the severity of anxiety[1]. At intervals when the machine is not locked, the successful administration of analgesia demanded by the patient refers to the amount of delivered analgesics and shows the severity of pain[2]. The ratio of delivery to demand is the indicator of the compatibility between the patients and PCA machine. Increased ratios show that the programmed dose and lockout interval have been well adjusted with the patient needs while decreased ratios show that the patient needed to press the pump button more frequently during lockout intervals. This can be attributed to patient anxiety, failure to offer adequate information to the patient about the machine, insufficient doses of analgesics and long lockout intervals[3]. The analgesia demands and analgesic doses delivered and utilized by the patients with one-stage bilateral total knee arthroplasty were significantly higher in 0-24 hours and 24-48 hours after surgery. The ratio of delivery to demand was not significantly different between the groups Side-effects of the analgesia were similar in both groups. Visual Analogue Scale scores in 24-48 hours after surgery were higher in the patients with unilateral total knee arthroplasty.

CONCLUSION: To conclude, the patients with bilateral TKA had higher analgesic consumptions after surgery. However, their VAS scores were lower possibly due to their higher analgesic consumptions, and VAS scores were acceptable in both patient groups. When the lack of a significant difference in side-effects due to morphine consumptions and the ratio of delivery to demand are considered, the analgesic agent used in the PCA protocol, its dose and lockout interval can be considered to provide safe and effective analgesia in both groups.

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Tables

Table 1. Demographic Features of the Patients

	Bilateral TKA n (%) or mean (±SD)	**Unilateral TKA n (%) or mean (±SD)**	**p**
Age (years)	64.51 (±8.04)	67.34 (±10.63)	0.055
Gender			
Female	58 (%85.3)	90 (%72.6)	**0.045***
Male	10 (%14.7)	34 (27.4)	
Weight (kg)	80.85 (±11.00)	81.09 (±13.76)	0.203
Height (cm)	163 (±6.8)	162 (±7.77)	0.143
Body Mass Index (cm^2/kg)	30.43 (±3.97)	31.81 (±4.68)	0.054
ASA scores			
ASA I	6 (%8.8)	7 (%5.6)	0.079
ASA II	51 (%75.0)	79 (%63.7)	
ASA III	11 (%16.2)	38 (%30.6))	
Smoking status (Yes/No)	17/51 (%25.0/%75.0)	20/104 (%16.1/%83.9)	0.136
Comorbidities			
Cardiovascular	43 (%63.3)	84 (%67.7)	0.528
Respiratory System	7 (%10.3)	23 (%18.5)	0.132
Endocrine System	23 (33.8)	42 (%33.9)	0.995
Neurological System	1 (%1.5)	7 (%5.6)	0.264
Chronic Renal Failure	1 (%1.5)	3 (%)	1.000
Obesity	37 (%54.4)	84 (%67.7)	0.067
Obstructive Sleep Apnea Syndrome	0	4 (%3.2)	0.299
***p<0.05: significant difference**			
SD: standard deviation			

Table 2. Preoperative Hospital Stay and Total Hospital Stay

	Bilateral TKA n (%) or Mean (±SD)	Unilateral TKA n (%) or Mean (±SD)	p
Preoperative hospital Stay (days)	2.55 (±1.88)	4.08 (±3.50)	**0.003***
Total Hospital Stay (days)	9.17 (±2.98)	12.95 (±6.91)	**<0.001***
***p<0.05: statistically significant difference** **SD: Standard Deviation**			

Table 3. Information about PCA Uses

	Bilateral TKA Mean (±SD)	Unilateral TKA Mean (±SD)	p
24 hours			
Delivery	10.16 (±7.02)	7.53 (±5.52)	**<0.001***
Demand	27.22 (±60.58)	13.00 (±15.88)	**<0.001***
Ratio of Delivery to Demand	0.61 (±0.64)	0.68 (±0.25)	0.059
Total Morphine Consumption (mg)	8.92 (±7.04)	6.01 (±5.15)	**0.001**
24-48 hours			
Delivery	8.17 (±5.16)	6.13 (±4.43)	**0.010***
Demand	14.05 (±12.18)	9.13 (±6.77)	**0.007***
Ratio of Delivery to Demand	0.67 (±0.23)	0.73 (±0.23)	0.099
Total Morphine Consumption (mg	7.07 (±5.44)	4.79 (±3.83)	**0.004***
Total			
Delivery	18.20 (±8.61)	13.63 (±8.28)	**<0.001***
Demand	39.95 (±60.70)	22.10 (±19.49)	**<0.001***
Ratio of Delivery to Demand	0.65 (±0.29)	0.60 (±0.21)	0.137
Total Morphine Consumption (mg	15.75 (±8.79)	10.80 (±7.59)	**<0.001***
***p<0.05: statistically significant difference** **SD: standard deviation**			

Table 4. VAS Scores of the Patients

	Bilateral TKA Mean (±SD)	Unilateral TKA Mean (±SD)	p
Maximum VAS score in the recovery room	0.85 (±1.24)	1.02 (±1.26)	0.311
VAS score at rest in 0-24 hours	4.05 (±2.06)	4.00 (±1.81)	0.849
VAS score at rest in 24-48 hours	2.52 (±2.32)	3.29 (±2.17)	**0.030***
***p<0.05: statistically significant difference SD: standard deviation**			

PAIN MEDICINE 17

Clinical outcomes of combined dorsal root and medial/lateral branch radiofrequency ablation for sacroiliac joint-related pain

Jordan Sam[1], Ognjen Visnjevac[2]

[1]St. Michael's Hospital, Toronto, Canada, [2]McMaster Faculty of Health Sciences, Dept. of Anesthesiology, Toronto, Ontario

INTRODUCTION: Chronic lower back and leg pain (LBP/ LP) in America has a prevalence of 13.1% and it is the most commonly reported anatomical site of pain among Canadian adults with chronic pain[1,2]. A common cause for LBP and LP arises from dysfunction in the sacroiliac joint (SIJ) complex. When conventional medical management or rehabilitative efforts for SIJ-related LBP and LP fail to provide analgesia, pulsed radiofrequency (PRF) and/or radiofrequency ablation (RFA) can also be suitable means for treatment. Both PRF and RFA are interventional techniques that utilize heat/energy to ablate or attenuate transmission of painful signals, where the former is neuromodulating nerves and the latter is ablative. We aimed to explore the clinical outcomes of combined PRF and RF treatments on the SIJ complex to treat patients experiencing LBP and LP.

METHODS: Following institutional review board approval, we performed a retrospective chart review from June 2018 to February 2021 of chronic LBP and LP patients that underwent combined PRF and RF treatments for a diagnosis of SIJ complex pain at an interventional pain clinic in Toronto, Canada, and assessed for the primary outcomes of >/= 50% analgesia at last follow-up, with secondary outcomes assessing duration of effect, degree of analgesia, patients' functional improvements, and changes in medication use patterns. Both qualitative and quantitative measures were investigated.

RESULTS: We reviewed data from 145 patients, all of whom presented with chronic LBP or LP. There were 57 men and 87 women, and the mean age was 59 years. RF and PRF procedures were guided by patient anatomy and sensory stimulation to have the patient identify the anatomic branches involved in transmission of their pain, which included dorsal roots and/or branches (lumbar medial and sacral lateral) from L4-S5 of the vertebra. A total of 193 SIJs were ablated over the period of data collection amongst the 145 patients and 85.0% (n=163) of procedures were considered a success for the primary outcome. Of these 163 successful outcomes, 78 patients reported on-going analgesia (mean 75.3% pain relief, SD +/- 22.1) on the last date of follow up (mean 43.5 days, SD +/- 28.0). For those procedures after which complete data for duration of analgesia with recurrence of pain was available, the mean amount of analgesia was reported to be 85.5% with an average duration of 90.5 days. Among all treatments, 4.8% (n=10) provided no analgesic effect. Among the patients that reported an analgesic benefit following PRF/RF procedures, 56.6% (n=82) reported increased activity/mobility, 25.5% (n=37) reported improved sleep, 46.9% (n=68) reported improved mood, and 9% (n=13) reported decreased medication usage. Six patients have reported complications following the procedure. The complications arising from our sample include transient soreness, bruising, and two mild vagal responses.

CONCLUSION: Our chart review suggests combined PRF and RF as a suitable intervention to treat SIJ-related LBP and/or LP. Although there was a lack of comparison to conventional treatment options, a large proportion of our cases were successful and the majority of patients report lasting analgesic effects with minimal complications following their combined RF-PRF procedures.

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Subspecialty Abstracts

PATIENT SAFETY

PATIENT SAFETY 1

A systematic review of provider and patient reported cases of awareness under general anesthesia: Analysis of data from a multi-hospital academic health system

Amanda Deis[1], Keith M Vogt[2]

[1]University of Pittsburgh Medical Center, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA

INTRODUCTION: The purpose of this retrospective study was to identify cases of awareness with recall (AWR) under general anesthesia and determine associated factors within a large multi-hospital health system. While AWR is fortunately rare, it can have devastating psychological sequalae in a subset of those affected.[1] We wanted to identify correlated patient and anesthetic factors, particularity in the era of enhanced recovery, which commonly calls for avoidance of volatile anesthetics. Using structures in place for centralized event reporting, we identified cases of AWR and sought to determine common themes that might lead to updated strategies to reduce risk.

METHODS: This study was approved by the local IRB. Because AWR is a rare phenomenon, we pursued two routes to identify cases as inclusively as possible. First, cases of AWR were identified through the electronic anesthesia record shared across our large multi-hospital health system, with a mix of tertiary/academic centers and suburban hospitals.[2] This query for all available electronic anesthesia records, spanned approximately eight years. Patients with AWR were identified by an adverse event flag ('Intraoperative Recall') selected by any anesthesia provider prior to finalizing the anesthesia record. Additionally, our system-wide quality improvement committee had received patient AWR complaints. For all of these identified cases, records were manually reviewed for factors that might contribute to awareness. We limited the subsequent analysis to cases done under general anesthesia. Depth of consciousness monitoring at our institution is available for all anesthetics, using the Bispectral Index (BIS) monitor system.

RESULTS: Fourteen cases of awareness were identified, 7 from the electronic anesthesia record flags and 7 from patient reporting. The table below provides specifics for each case. In 2 cases, depth of anesthesia was limited by hypotension and neuromuscular blockade was used. Four cases utilized low-dose anesthesia, but were not accompanied by hypotension. In 3 cases, awareness was attributed to IV infiltration with total intravenous anesthesia. In 3 cases, a clear reason for AWR could not be identified. Six cases had elevated BIS values, that did not trigger additional anesthetic administration. Two cases utilized total intravenous anesthesia and had reassuring BIS values < 60. Two cases had recall during emergence, prior to reversal being given.

CONCLUSION: Consistent with non-prospective studies,[3] our case identification from quality improvement data identified a lower incidence of AWR than prospective studies.[4] Thus the cases identified in this retrospective study likely underestimate the true incidence of AWR and may be biased in severity. We first conclude that many cases of intraoperative awareness are likely undetected by provider or patient reported adverse event data. Several themes were identified among these cases, including classic risk factors: low anesthesia concentrations and use of neuromuscular blockade. Notably, we did find AWR occurrence despite midazolam premedication in a majority of identified cases. Total intravenous anesthesia has recently emerged as an AWR risk-factor,[5] and was employed in several of the cases we identified. Identification of cases with IV infiltration was not surprising; there were also several cases in which high BIS values were apparently ignored. This pattern of high BIS overlapped with ketamine use, suggesting confirmation bias for high BIS when non-GABAergic anesthetics are used. Tachycardia and hypertension were not seen in any cases, demonstrating the unreliability of clinical signs for detecting awareness and the importance of depth of consciousness monitoring during. We also identified cases with adequate anesthetic delivery, reassuring BIS, and no clear etiology for AWR. This supports the notion that a small minority of patients may be prone to awareness without clear explanation [6]. In summary, modern anesthesia providers should continue to maintain vigilance in monitoring the depth and dose of anesthesia to prevent AWR.

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Table 1. Case characteristics and awareness associations

(NMB= neuromuscular blocking agent, TIVA= low total intravenous anesthesia dosing, ETAG= low end-tidal gas concentration)

	Case Description	Premed	Potential Associations	Maintenance Anesthetics	BIS use
Low-dose anesthesia, hemodynamic instability	20 M, ASA 4, laparoscopic procedure	No	Low ETAG NMB **hypotension**	Isoflurane @ 0.2 - 0.4%, MAC 0.3-0.4, no adjuncts	No
	30 F, ASA 4E, on V-V ECMO; tracheostomy	Midazolam	e**mergency**, **hypotension** TIVA NMB	Propofol @ 50 mcg/kg/min of propofol on V-V ECMO Intermittent boluses of fentanyl	50 -71
Low-dose anesthesia, without hemodynamic instability	70 F, ASA 2, Laparoscopic procedure	Midazolam	Low ETAG NMB	Sevoflurane @ 0.4-0.5%, MAC 0.3 Ketamine infusion at 0.4 mg/kg/hr	No
	47 M, ASA 4E, Vascular bypass	Midazolam	**emergency,** low ETAG, high BIS NMB	Isoflurane. MAC 0.2 -0.7, with most of case at 0.6 MAC;	50-72
	60 F, ASA 3, Orthopedic surgery	Midazolam	Low ETAG NMB	Sevoflurane @ 1.3%, < 0.5 MAC,	< 60
	61 F, ASA 2, Breast surgery	Midazolam	TIVA NMB, high BIS, Delayed propofol infusion	TIVA: Remifentanil 0.2 mcg/kg/min, Dexmedetomidine 0.2 to 0.7 mcg/kg/hr; Propofol 50 – 75 mcg/kg/min	> 60
TIVA, IV infiltrate, High BIS	48 F, ASA 3, Laparoscopic procedure	Midazolam	TIVA high BIS, NMB, arms tucked IV infiltrated	Propofol at 150 mcg/kg/min, ketamine boluses	majority of case >74
	73 F, ASA 3, Cervical spine surgery	No	TIVA, high BIS, NMB, arms tucked IV infiltrated	TIVA: Propofol at 150 mcg/kg/min, remifentanil at 0.02-0.05 mcg/kg/min	majority of case >70
	29 F, ASA 2, Plastic surgery	Midazolam	IV infiltration TIVA NMB	TIVA: propofol 75 mcg/kg/min, dexmedetomidine at 0.6 mcg/kg/hour and intermittent boluses of midazolam	majority of case >70
Unclear	55 F, ASA2, ENT procedure	Midazolam	TIVA NMB	TIVA: propofol at 150 mcg/kg/min	44-61
	55 F, ASA 3, Lymph node dissection	Midazolam	TIVA NMB	TIVA: propofol at 100-150 mcg/kg/min, dexmedetomidine at 0.2 mcg/kg/hr and ketamine at 0.2 mg/kg/hr	< 47
	75 M, ASA 3, ENT procedure	Midazolam	NMB	Sevoflurane, MAC 0.9	No
Other	39 M, ASA 2, Posterior spinal surgery	Midazolam	NMB, Early discontinuation of anesthesia, while prone	Sevoflurane, MAC 0.9, remifentanil 0.2 mcg/kg/min	No
	33 F, ASA 3, Open abdominal surgery	No	TIVA NMB, Awareness prior to extubation	TIVA: propofol at 100-150 mcg/kg/min, dexmedetomidine at 0.4 mcg/kg/hr and ketamine at 0.2 mg/kg/hr ; additional midazolam bolus during maintenance	> 65

PATIENT SAFETY 2

Implementation of an electronic medical record-based handoff system in the intensive care unit

Jianzhou Xiao[1], Stephen Estime[2]

[1]University of Chicago Medical Center, Chicago, IL, [2]University of Chicago Medicine, Chicago, IL

INTRODUCTION: Effective care hand-offs are a critical component of safe patient care, particularly in the complex and demanding milieu of the intensive care unit. Hand-off systems vary significantly by hospital system and, in some cases, even by unit within the same facility. An ideal hand-off system is not only comprehensive in terms of patient information but also efficient and facile to use for the provider. Unfortunately, hand-offs have frequently been identified as a source of potential patient harm[1,2]. A major factor impeding effective hand-off is a lack of standardization[2,3]. With the increasing prevalence of electronic medical record (EMR) systems, it is now possible to rapidly create hand-off instruments with automatic pre-population of clinical data. We created one such EMR-based hand-off system for pilot use, and we present survey results from providers comparing impressions of the EMR-based hand-off system (EHOS) to the previous non-automatic, manual hand-off system (MHOS).

METHODS: From July 1, 2019 to December 31, 2019, we piloted the use of a semi-automated, EMR-based, hand-off system in the surgical intensive care unit (SICU). The prior hand-off methodology utilized in the SICU was a shared Microsoft Word document (Redmond, WA) that was manually updated with all patient information during the twice-daily formal handoffs of care that occurred in the unit. Compared to the shared Microsoft Word document hand-off system, the EMR-based hand-off system was housed entirely within EPIC (Verona, WI) and featured multiple auto-populated fields, including demographics, vital signs, medications, and ins/outs. The only components of the EMR-based hand-off system that required manual updating were patient events and comments. After six of using the novel EHOS, a survey (SurveyMonkey; San Mateo, CA) was sent to all providers in the SICU who used both the old and new hand-off systems. This 10-item survey included items assessing providers' perceptions of the relative ease of use, efficiency, and advantages/disadvantages of the old and new hand-off systems.

RESULTS: There were 21 total respondents to the survey (Figure 1). The majority (13 persons; 62%) of respondents were resident physicians. Nineteen respondents (90%) stated that the EMR-based hand-off system saved time in the daily workflow (Figure 2), with a slight majority (6 respondents; 29%) reporting 1-2 hours of time saved per day. Eighteen respondents (86%) reported improvements in sign-out errors (Figure 3), including those associated with laboratory values, active medications, and allergies. Nineteen respondents (90%) reported improvements in various workflow factors (Figure 4), including fatigue, burnout, work-hours, and time available for direct patient care. Overall, 17 respondents (85%) deemed the EHOS an improvement over the MHOS, and nineteen respondents (90%) stated that they preferred using the EHOS over the MHOS.

CONCLUSION: We piloted the use of a semi-automated, EMR-based hand-off system in an intensive care unit setting and sought to determine provider perceptions of the EMR-based hand-off system compared to a manual, computer document-based hand-off system. To this end, a 10-item survey was sent to providers who had experience using both the novel EHOS and the older MHOS. A clear majority of end-users (85%) perceived the EHOS as an overall improvement over the MHOS, and a majority (90%) of end-users preferred using the EHOS over the MHOS in an ICU setting. Notably, the EHOS was perceived to be more time-efficient and less error-prone by 86% and 90% of respondents, respectively. There is a notable dearth of data regarding novel hand-off methodologies, particularly in ICU settings [4]. We conclude that a semi-automated, EMR-based hand-off system was perceived by a majority of end-users to be more efficient, more accurate, and overall preferred over a manual, computer document-based hand-off system. With increasing patient complexity and clinician workload, a semi-automated and EMR-integrated hand-off system may reduce work burden and errors. Further study is needed to determine if these positive user perceptions of an EHOS indeed lead to improved patient outcomes.

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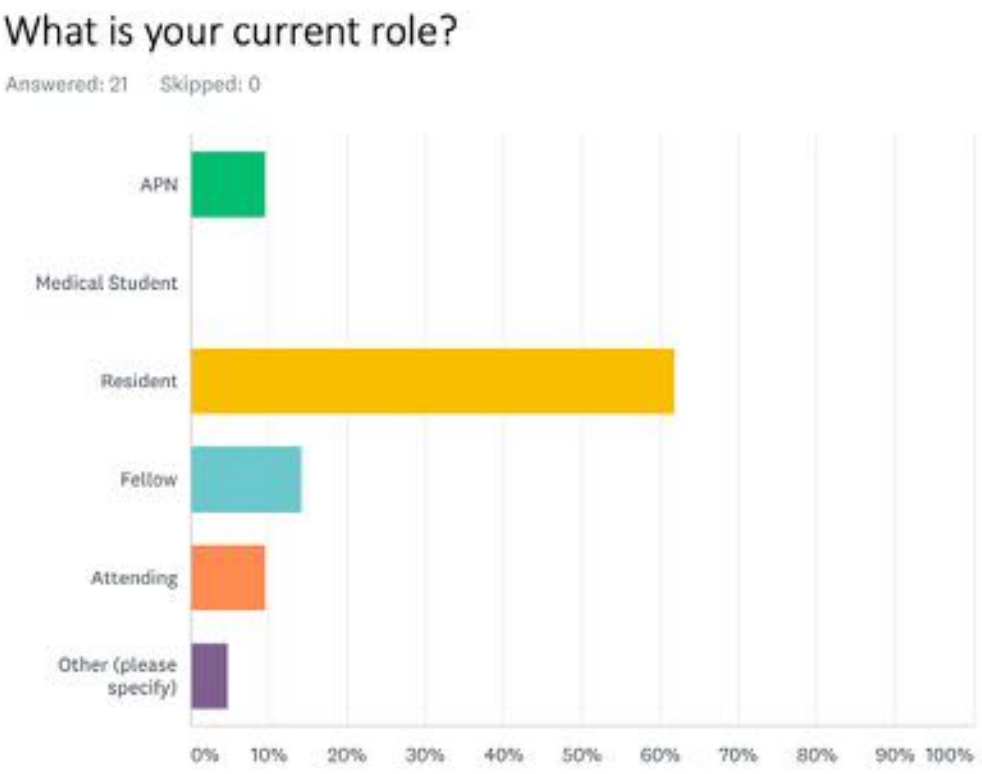
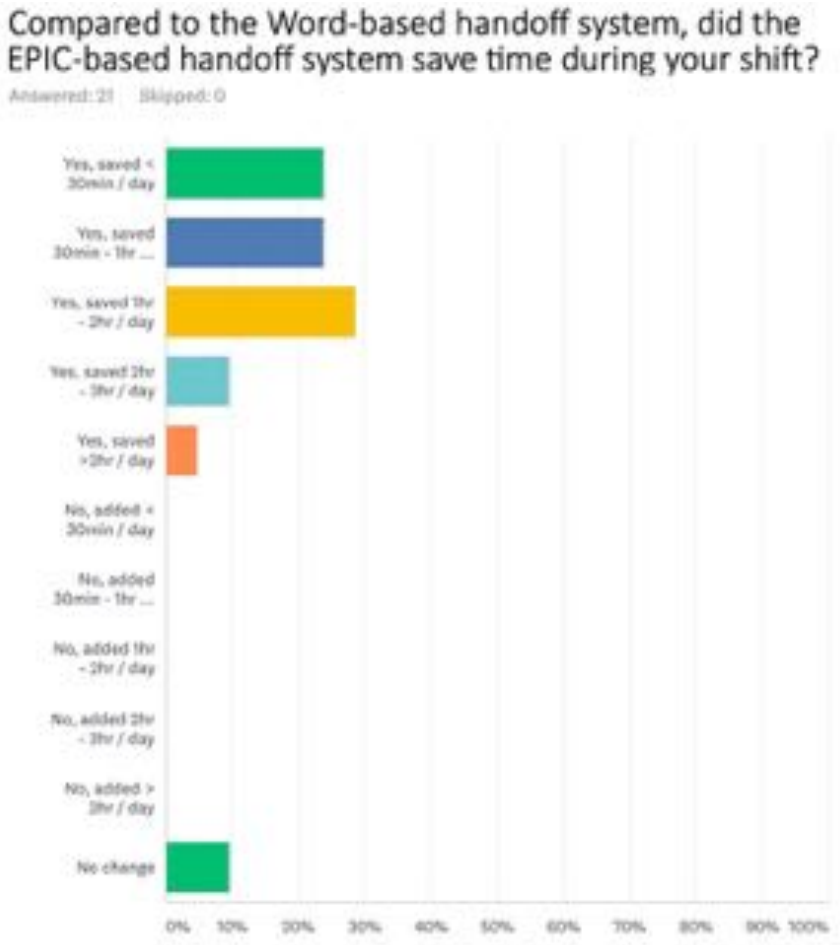


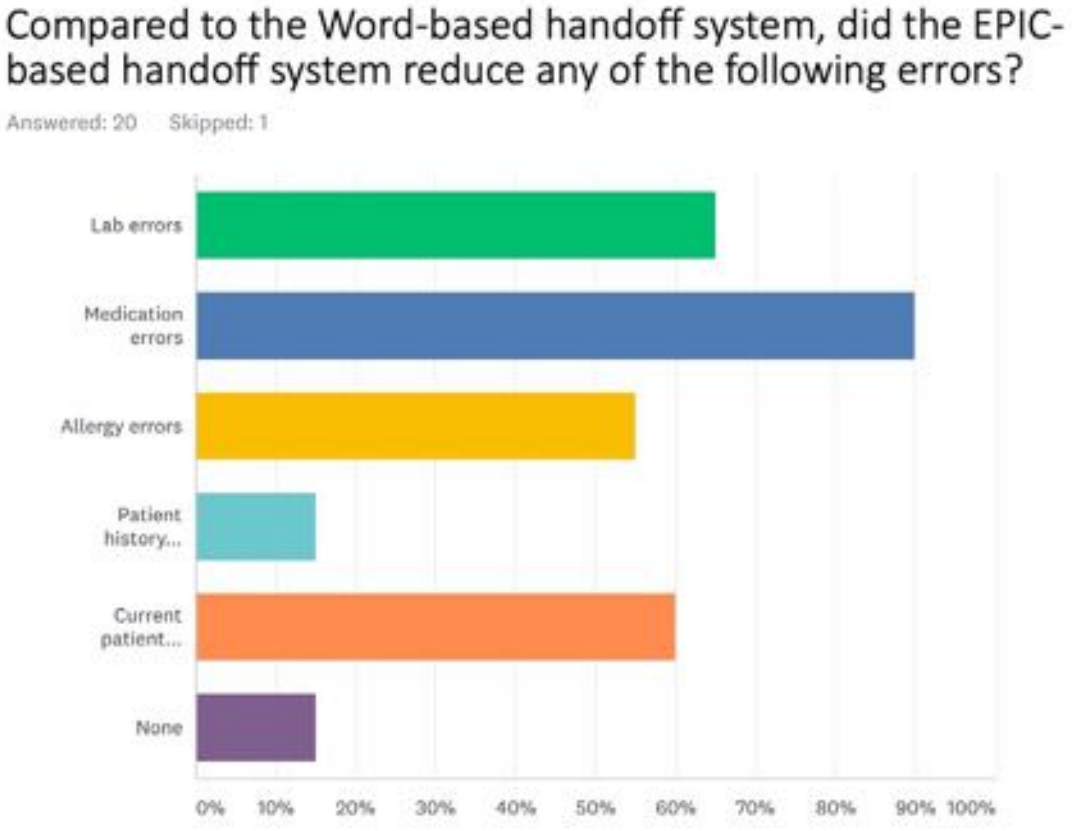
ANSWER CHOICES		RESPONSES	
APN		9.52%	2
Medical Student		0.00%	0
Resident		61.90%	13
Fellow		14.29%	3
Attending		9.52%	2
Other (please specify)	Responses	4.76%	1
TOTAL			21

Figure 1



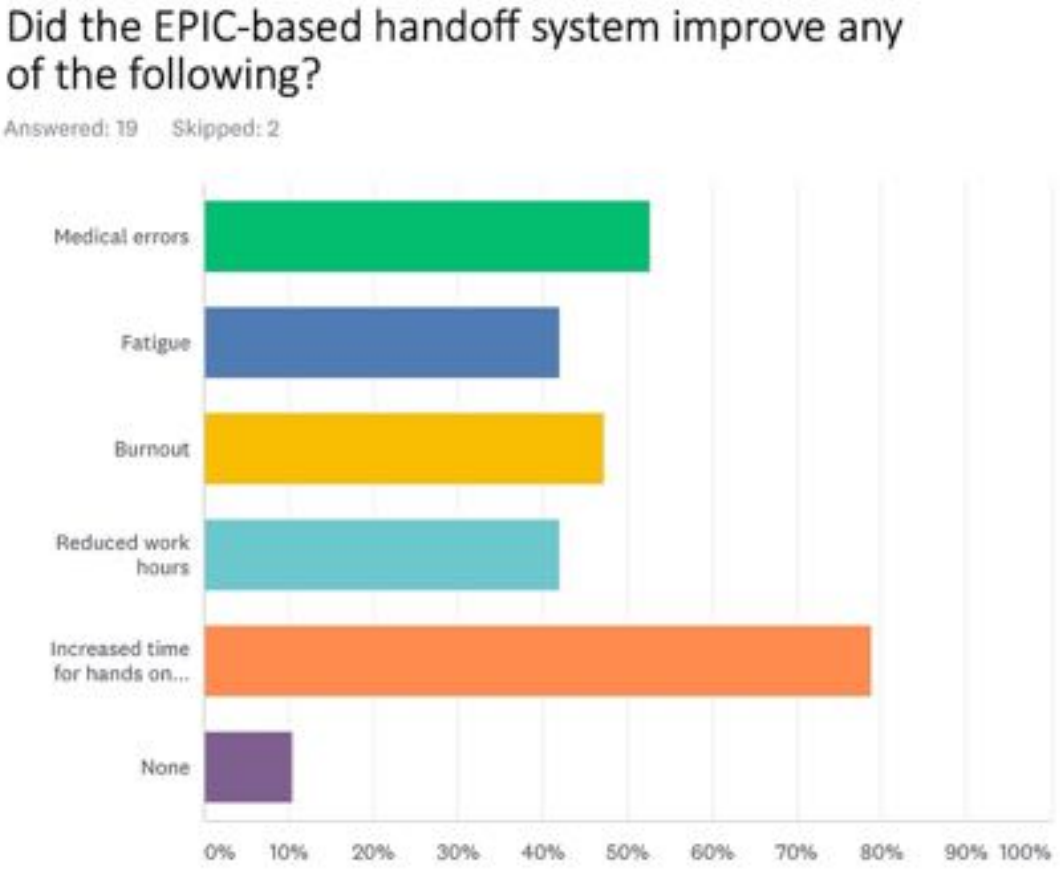
ANSWER CHOICES	RESPONSES	
Yes, saved < 30min / day	23.81%	5
Yes, saved 30min - 1hr / day	23.81%	5
Yes, saved 1hr - 2hr / day	38.57%	8
Yes, saved 2hr - 3hr / day	9.52%	2
Yes, saved >3hr / day	4.76%	1
No, added < 30min / day	0.00%	0
No, added 30min - 1hr / day	0.00%	0
No, added 1hr - 2hr / day	0.00%	0
No, added 2hr - 3hr / day	0.00%	0
No, added > 3hr / day	0.00%	0
No change	9.52%	2
TOTAL		21

Figure 2



ANSWER CHOICES	RESPONSES	
Lab errors	65.00%	13
Medication errors	90.00%	18
Allergy errors	55.00%	11
Patient history (including hisory and hospital course)	15.00%	3
Current patient location	60.00%	12
None	15.00%	3
Total Respondents: 20		

Figure 3



ANSWER CHOICES	RESPONSES	
Medical errors	52.63%	10
Fatigue	42.11%	8
Burnout	47.37%	9
Reduced work hours	42.11%	8
Increased time for hands on clinical work	78.95%	15
None	10.53%	2
Total Respondents: 19		

Figure 4

PATIENT SAFETY 3

Team factors influence emotions and stress in a non-operating room anesthetizing location. A Qualitative interview study among anesthesia clinicians

Hedwig Schroeck[1], June Dong[2], Sophia Jacobi[2], Andreas Taenzer[3], Karen Schifferdecker[2]

[1]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [2]Dartmouth College, Hanover, NH, [3]Dartmouth-Hitchcock Medical Center, Hanover, NH

INTRODUCTION: Care for patients in non-operating room anesthesia (NORA) locations is associated with multiple challenges, including working with unfamiliar teams and equipment in a location distant from the resources the standard operating room (OR) offers.[1-3] Anesthesia clinicians generally consider working in the NORA environment demanding which may contribute to feelings of stress and burnout among anesthesia clinicians.[4] To date, no qualitative studies exist to describe the impact of those challenges on anesthesia clinicians. In addition, the difference in type and invasiveness of procedures in NORA and OR settings often complicates direct comparisons. Our institution is uniquely positioned to examine the impact of the NORA environment in our hybrid magnetic resonance imaging OR suite (MRI-OR) which is several minutes walking distance from the regular OR. Comparable craniotomy and spine surgery cases are performed in both locations, which allows to isolate the effect of the environment on anesthesia clinicians' perceptions of stress. This study utilizes qualitative interviews to characterize the workload, emotions, and stress experienced by anesthesia clinicians during similar cases in the two different environments.

METHODS: Synthesizing literature about human factors and challenges in NORA locations, we developed an open-ended interview guide to explore the following key areas that may influence experiences in providing anesthesia care: environment, equipment, people, processes, and culture.[1-3,5,6] The study population consisted of anesthesia clinicians at a single institution who were involved in patient care in both the regular OR and a specific NORA location (the MRI-OR). Sampling was purposive to include 8-12 nurse anesthetists, anesthesiology residents, and attendings. Interviews were recorded and transcribed, then coded and analyzed using a qualitative data analysis program. The analytic strategy was developed using a mixed deductive and inductive approach with some codes being pre-determined based on literature-derived challenges and other additional codes being identified based on iterative review of the data. Member-checking was performed to validate the results.[7]

RESULTS: Saturation of major themes was achieved after ten interviews with 2 residents, 4 attending anesthesiologists, and 4 nurse anesthetists. Table 1 displays the emerging themes (remoteness, team factors, culture, unfamiliarity, and safety protocols) with representative quotes. Every interviewee mentioned the remoteness of MRI-OR (for a total of 35 excerpts), but team factors were discussed most frequently (54 excerpts from 9 interviews). Higher workload, anxiety, and stress in the MRI-OR were identified uniformly by the interviewees (Table 2). Asked about the main determinant of emotions and stress, five of ten interviewees named team factors – both within the anesthesia care team and between the anesthesia and OR – as the most important determinant, while remoteness and unfamiliarity were less frequently reported (2 interviewees for each).

CONCLUSION: Our findings corroborate that known challenges of the NORA environment increase the workload, anxiety, and stress for anesthesia clinicians (Figure 1). Some of the identified challenges, for instance the physical location within the healthcare institution, are hardly modifiable, but the large emphasis on team factors in our study is notable and points towards team training initiatives as opportunities to alleviate the stress experienced by clinicians in the NORA environment. For other healthcare settings, clinician stress has been linked to provider burnout and medical errors.[8] Conversely, physician well-being has been postulated as a quality indicator.[9] While a large retrospective study finds that most adverse events were less frequently reported for the NORA environment compared to the OR, the mortality rate for some NORA locations including radiology and cardiology was actually higher.[1] Given the rising incidence of NORA procedures – which already comprise more than 30% of anesthesia cases – , it is critical for optimal patient safety to improve workload and stress for the clinicians working in these environments. Future investigations are needed to examine the effect of multi-disciplinary team training on both provider stress and patient safety in NORA locations.

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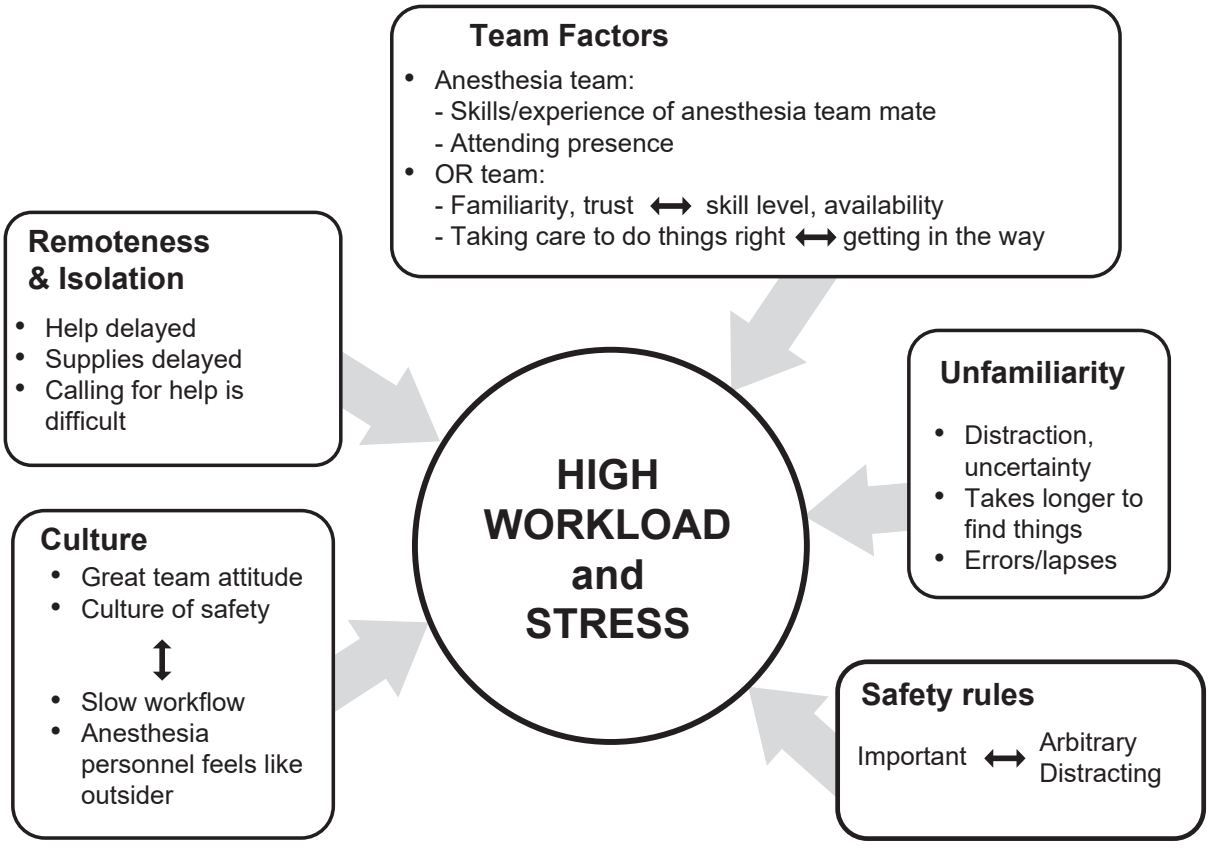

Table 1: The most salient themes affecting anesthesia clinicians in the non-operating room environment, a MRI-hybrid operating room ("CSI"), compared to the regular operating room (" main OR").

Theme	**N (interviews, *excerpts)***	**Representative quotes**
REMOTENESS/ISOLATION Due to its location distant from the regular OR, help or supplies arrive later to CSI. Communicating to/from CSI is hard because use of personal devices and pagers is restricted in CSI.	10, *36*	"You're further from help, should something kind of go wrong" (A, CRNA) "In the main OR, we have access to multiple phones […] in CSI sometimes, that's a little bit more challenging. We don't have our beepers. We don't have cellphones." (C, resident)
TEAM FACTORS The CSI-relevant skills and availability of the anesthesia team members and the OR personnel, familiarity with the surgeon, and quality of teamwork influence the work day of anesthesia clinicians.	9, *54*	"So the circulating nurse may not be paying attention quite as much to what I'm doing […] in CSI because they're focused on their own part" (C, resident) "it just raises the stress level of the room if there are people who aren't comfortable being there" (G, CRNA).
CULTURE The CSI OR team is generally perceived as helpful with a great attitude, yet some interviewees describe a sense of being an "outsider" to that team. The workflow is slow with extra attention given to safety protocols.	9, *38*	"I'm always a visitor to that team, […]. There's not a feeling of exclusion, but I'm clearly a visitor down there" (B, attending) "You know, the main OR is slow. CSI is even slower." (F, CRNA)
UNFAMILIARITY WITH ENVIRONMENT AND EQUIPMENT The differences in equipment and environment and the presence of environment-specific rules/restrictions creates a sense of unfamiliarity and distraction.	8, *36*	"People operating […] in an environment that they're not 100% comfortable I think poses a risk to the patient in general." (H, CRNA) "with the MRI cases we can't use the syringe pumps so […] you have to sort of adjust how you're […] running your infusion." (G, CRNA)
SAFETY PROTOCOLS/PROCESSES Safety rules and protocols in CSI, such as ferromagnetic item counts and restricted use of non-MRI-compatible equipment, are viewed as important for safety, but also as difficult, distracting, or arbitrary.	8, *24*	"Well, you have the steps that are required because you are working in with an MRI and I think those are reasonable […] given the fact we've got a big magnet sitting there" (J, attending) "So there certainly is a very sort of stringent adherence to some regulations that don't always make a lot of sense to me." (I, resident)

Table 2: Workload and emotions in the non-operating room environment, a MRI-hybrid operating room ("CSI"), compared to the regular operating room (" main OR").

Theme/Sentiment	**N (interviews, *excerpts)***	**Representative quotes**
WORKLOAD IN CSI Workload in CSI is described as higher, in part due to the need to follow protocols and to plan ahead for any additional needs.	10, *20*	"I think overall the workload of the entire team is quite a bit more. Positioning, making sure there's no metal […]" (H, CRNA) "Of having to be, again, extra mindful of having sort of every piece of equipment and every medication that one could forseeably need. I think it's objectively more... requires more preparation up front." (I, resident)
EMOTIONS IN CSI Working in CSI is associated with feelings of stress, anxiety, and frustration, despite positive feelings about some aspects.	10, *39*	"The mental work we've already gone over, and so the mental work is much higher, and that's where the stress comes from." (B, attending) "I think when I'm working in CSI, my guard is a little bit higher. My threshold to call for help is a little bit lower. I think my adrenaline sympathetic system is a little bit more in overdrive." (C, resident) "I love working in the CSI. The reasons for that are the people that we work with down there tend to be very helpful in facilitating the care of the patient […]." (D, attending)

PATIENT SAFETY 4

Absence of venous thromboembolism in transgender male to female patients following the gender-affirming procedure of facial feminization: a retrospective study of 236 patients using hormone therapy

Ryan K Price[1], Deen Debryn[1], Shivali Mukerji[1], Lina Nurhussien[1], Eugene Kim[1]

[1]Boston University School of Medicine, Boston, MA

INTRODUCTION: Estrogen-containing hormone therapy is associated with an increased risk of venous thromboembolism (VTE) when used for both contraceptive purposes and postmenopausal symptom relief.[1] Estrogen therapy is also a mainstay of treatment for male to female transgender patients, individuals who experience incongruence between their biological sex and self-identified gender. Estrogen therapy is meant to feminize these patients to more appropriately align their physical characteristics with their gender identity.[2] To further this aim, gender-affirming surgical procedures are typically the final step in the treatment algorithm. Considering the World Professional Association of Transgender Health insists upon 12 months of hormone therapy prior to genital-altering procedures,[3] a large proportion of male to female transgender patients have a history of using estrogen therapy prior to undergoing surgery- a well-known risk factor for VTE in itself. Recent literature has illustrated that transgender females receiving feminizing hormone therapy have a similar VTE risk factor profile to cisgender females undergoing hormone replacement therapy,[4] and that there is little to no evidence to support the discontinuation of hormone therapy in transgender patients prior to gender-affirming surgery.[5] This study seeks to contribute to the growing fund of knowledge regarding the transgender patient population, by evaluating for the perioperative risk of VTE in male to female transgender patients undergoing the gender-affirming procedure of facial feminization.

METHODS: A retrospective chart review was performed of all patients who underwent facial reconstruction with a specific surgeon at an urban academic institution from 2014- 2020. Inclusion criteria included those patients receiving facial feminization procedures who were 18-60 years old at the time of chart review, totaling 282 patients. Patient characteristics including age, ethnicity, body mass index, comorbidities, ASA classification, history of prior VTE, use of VTE chemoprophylaxis, presence of hormone therapy, and perioperative hormone therapy management were reviewed (Figure 1). The incidence of VTE during perioperative hospital stay and within 1 week and 1 month of the surgical procedure was examined by reviewing the patients' perioperative hospital course, future care at the institution, and outpatient follow up.

RESULTS: From a total of 434 facial reconstruction cases, there were 296 facial feminization procedures performed on 282 patients between 2014 and 2020. These patients were predominantly young (mean age 33.75) with a lack of significant comorbidities (97.2% ASA 1 or 2), and no patients received VTE chemoprophylaxis during their perioperative stay. There were 0 VTE incidents noted during patients' hospital course or within 1 week and 1 month postoperatively. 236 (83.6%) patients had been prescribed hormone therapy, 160 (67.8%) of the patients who were prescribed hormone therapy held these medications prior to the procedure, and 125 (78.1%) of the patients who held hormone therapy discontinued these medications between 2-4 weeks.

CONCLUSION: There was a VTE incidence of 0% among 236 patients using hormone therapy who did not receive VTE chemoprophylaxis prior to undergoing facial feminization, with the majority of these patients holding these medications for 2-4 weeks prior to the procedure. A recent study of patients undergoing rhinoplasty noted an incidence of VTE of 0% across 412 cisgender patients, of which 51% were female, 17% were taking estrogen-containing hormone therapy, and none of whom received VTE chemoprophylaxis.[6] Our findings support that male to female transgender patients who use estrogen-containing hormone therapy are at a similarly minimal risk to experience VTE compared to their cisgender counterparts when undergoing facial plastic surgical procedures. This minimal risk supports the notion that providers should take into account the individual patient risk factors and the nature of the surgical procedure when discussing perioperative hormone management and the use VTE prophylaxis in the transgender population. Future directions include analyzing the risk of VTE in the gender-affirming procedures of neovaginoplasty and orchiectomy at our institution.

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Table 1: Baseline characteristics for all patients (N=282) included in the study

Baseline Characteristics	Mean/N
Age at date of surgery (years)	33.75 ± 12.93
Height (m)	4.23 ± 20.74
Weight (kg)	72.43 ± 15.08
BMI (kg/m^2)	
Less than 30	255
Greater than or equal to 30	27
Race	
Asian	10
Native American/Alaska Native	1
Black/African American	8
White	154
Unknown	109
Hispanic or Latino	
Yes	21
No	252
Unknown	9
Marital Status	
Single	185
Married	27
Unknown	66
Other	4
Preferred Pronouns	
She/Her/Hers	254
He/Him/His	4
They/Them/Theirs	2
Unknown	22
ASA Status	
1	157
2	117
3	8
Hormone Therapy	
Yes	236
No	46
Was hormone therapy held?	
Yes	160
No	28
Unknown	48
Duration of withholding prior to surgery	
2 weeks or less	21
2-4 weeks	125
4 weeks	10
Unknown	4

PATIENT SAFETY 5

Transcranial Motor Evoked Potential Monitoring During Scoliosis Surgery in Children with Cerebral Palsy: Is it Feasible?

Sabina Dicindio[1], Katherine Kenny[1], MARY C THEROUX[1], Suken Shah[1], Kenneth Rogers[1], Alier Franco[2], Anthony Dinardo[2], Michael W Shrader[1]

[1]Nemours Alfred I duPont Hospital for Children, Wilmington, DE, [2]Specialty Care, Nashville, TN

INTRODUCTION: Routine use of intraoperative neuromonitoring (IONM) in children with spastic quadriplegic cerebral palsy (CP) and neuromuscular scoliosis is both challenging and controversial. Previous reports suggest low success rates in using motor evoked potentials in the setting of CP, and it is unclear whether repetitive high-voltage transcranial electric stimulation for motor evoked potential (TcMEP) monitoring is contraindicated in the presence of active seizure disorder. The specific aims of this study was to determine:

1) Can TcMEP be appropriately elicited in patients with CP in order to adequately monitor their spinal cord integrity during spine surgery?

2) Does eliciting TcMEP cause an increase in seizure activity in a patient with CP who has an active seizure disorder?

METHODS: This was an Institutional Review Board approved retrospective cohort study that observed 304 patients with CP undergoing posterior spinal fusion (PSF) during the years 2011 to 2020. Preoperative data points including seizure history, medical history, and gross motor function classification system (GMFCS) levels were recorded from their medical records. Perioperative data points included anesthesia (blood pressure, heart rate, and anesthetic administered) and IONM data. Patients were followed for 3 months after PSF to determine any increase in seizure activity.

RESULTS: Of the 304 patients that were observed, IONM was attempted in 231, Group I (GI). Seventy-three patients, Group II (GII), did not have any attempt at IONM due to surgeon preference and this group was used as an 'internal control' group to compare the rate of increased seizure activity postoperatively. Within GI, one hundred seventy nine of the 231 (77.4%) patients were successfully monitored with TcMEPs, 48 (20.8%) patients were unable to be monitored because they lacked baseline signals from the extremities, and 4 (1.7%) patients had some monitoring but not motors. (Figure 1) Twenty-six patients had a temporary intraoperative loss of signals; none of those patients had permanent change in their neurological function. At the time of surgery, seizures were present in 168 (72.7%) GI and 54 (73.9%) GII patients. Postoperatively, five patients had an increase in the number of seizures, 1.2% in Group I and 2.7% in Group II. (Table 1) All 5 patients had return to baseline seizure activity by the first postoperative visit.

CONCLUSION: At our institution, 77.4% patients with CP, who had IONM attempted, were successfully monitored with TcMEPs. This differs from what has previously been published. Furthermore, the fear of increased seizure activity after TcMEPs was not supported by the data from this cohort. Successful IONM of these patients often requires higher stimulation intensity with slower stimulation frequency

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Group (n)	IONM	Number of Patients (%)	Number of Patients with Seizures at time of Surgery (%)	Number of Patients with Increase in Seizures Postoperatively
GI (231)	TcMEP, SSEP and EEG	179 (77.4)	126 (70.4)	2
	No Baseline	48 (20.8)	41 (85.4)	1
	NO TcMEP	4 (1.7)	1 (25)	0
GII (73)	NO MONITORING	73 (100)	54 (73.9)	2

IONM, Intraoperative neuromonitoring; TcMEP, transcranial motor evoked potential; SSEP, somatosensory evoked potential; EEG, electroencephalogram

Table 1

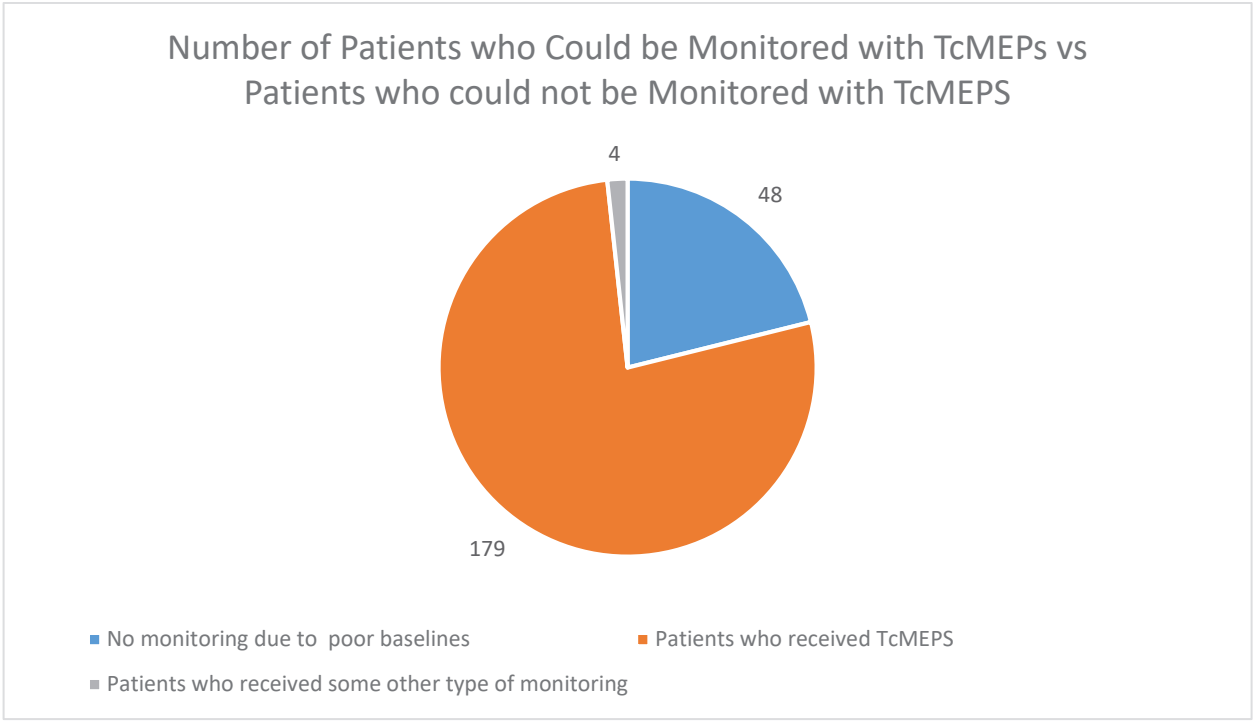

Figure 1

PATIENT SAFETY 6

Four-fold increase in case capture after implementation of an electronic anesthesia reporting system compared to paper reporting

Cori Van Gorkom[1], Scott Kolesky[1], Thomas M Austin[1]

[1]Emory University School of Medicine, Atlanta, GA

INTRODUCTION: True quality assurance and process improvement requires accurate outcomes data measurement as well as non-punitive reporting.[1] Underreporting exists in a voluntary and non-anonymous incident reporting system.[2] Minor incidents may be underreported compared to major incidents. To improve peri-anesthesia event capture, providers were transitioned from paper reporting to an electronic capture system with a prompted quality improvement (QI) reporting response. This retrospective observational study compares the incidence of encounters with adverse events during two consecutive 42 month periods. Laryngospasm and cardiopulmonary resuscitation (CPR) events were utilized as surrogates for minor and major events, respectively.[3]

METHODS: The incidence of voluntarily reported events was calculated from 1/2014 - 6/2017 (paper) and 7/2017 - 9/2020 (electronic). Differences in reported case rates were determined using Student's t-test univariately. In order to adjust for background trends, an interrupted time series analysis was performed with the interruption occurring when the electronic QI reporting system was implemented (7/2017 or study month 43). Due to lack of linearity in the QI case rate before and after implementation, the time variables were represented as B splines in the statistical model. Lastly, the standard errors were modeled as being temporally correlated with an autoregressive 1 correlation structure. All analyses were performed with R 4.0.2.

RESULTS: QI cases for a total of 81 months were included in this analysis ranging from a case report rate of 0.6-22.9 per 1000 anesthetics (Figure 1). Univariately, there was an increase in case report rate with electronic reporting (9.75 more captured cases per 1000 anesthetics per month, 95% CI 8.3-11.2, P-value < 0.001). On the interrupted time series analysis, this difference in captured cases per month increased to 13.7 cases per 1000 anesthetics (95% CI 8.3-19.1, P-value < 0.001), representing a four-fold increase in captured QI cases with the implementation of electronic reporting. There was not an increase in CPR events with electronic reporting (P-value = 0.84), but laryngospasm reports increased three-fold (P-value = 0.001).

CONCLUSION: Implementation of an electronic QI case reporting system improved peri-anesthesia adverse event capture by a four-fold increase. The lack of increase in CPR events suggests that the increase in total reported cases is not simply due to more overall events, but to more efficient capture of all events, particularly minor events. More accurate adverse event data collection should help in identifying common system risk factors and lead to targeted QI initiatives.

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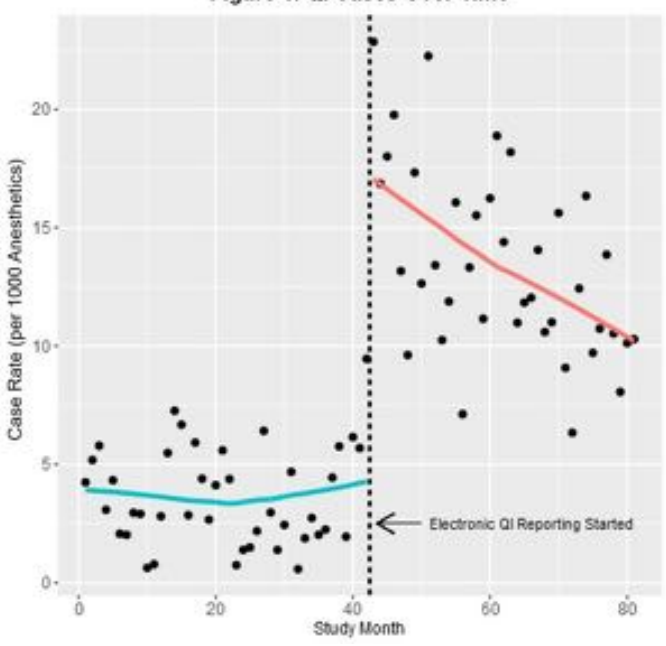
Figure 1. QI Cases Over Time



PATIENT SAFETY 7

Increased incidence of PONV in transgender patients following facial feminization surgery

Shivali Mukerji[1], Deen Debryn[1], Ryan K Price[1], Eugene Kim[1]

[1]Boston University School of Medicine, Boston, MA

INTRODUCTION: Postoperative nausea and vomiting (or PONV) are some of the most undesirable self-reported patient outcomes. Not only does it cause significant discomfort, but can also prolong recovery time and hospital length of stay, which has significant administrative and financial implications with one study reporting a 20-minute delay in hospital discharge per PONV episode.[1] While effective treatment options, such as Zofran (ondansetron) and other anti-emetics are readily available and risk factors such as age, sex, BMI, and type of anesthetic, etc.[1] are well known, the prevalence of PONV in the vulnerable population of transgender patients is not as well understood. An established risk factor for PONV is female sex and previous studies have shown a higher incidence of PONV among women in the periovulatory phase of their menstrual cycle than in the perimenstrual phase.[3] This phenomenon has been linked to the presence of the hormone estrogen.[4] Considering the prevalence of hormone therapy among transgendered patients, and the relative paucity of perioperative data with regards to gender-affirming surgeries, this study aims to evaluate the perioperative risk of PONV for transgender patients undergoing facial feminization surgery.

METHODS: This study was approved by the Institutional Review Board at our institution. A non-experimental retrospective chart review was conducted and all transgender patients who underwent any facial feminization 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, and history of PONV. PONV was defined as any episode of nausea and/or vomiting in the PACU. Anesthesia record for the surgery was reviewed and PACU notes were assessed for any indication of PONV. If PONV was indicated, antiemetics administration and overnight hospital stay due to PONV were also recorded. Mild PONV was defined as the administration of one antiemetic in PACU and no overnight admission whereas moderate PONV required the admission of 2-3 antiemetics in PACU along with no overnight admission for PONV. Finally, severe PONV was defined as the administration of 2 or moreantiemetics in the PACU AND overnight admission due to PONV. The effect of previously studied risk factors such as age, volatile anesthetic use, duration of anesthesia, BMI, and previous opioid/tobacco use was independently assessed as well as in conjunction with hormone therapy.

RESULTS: 434 facial feminization surgeries were performed between 2014- 2020. 282 unique transgender patients, representing 296 separate surgical procedures were identified (Table 1). 104 patients experienced PONV, leading to a PONV rate of 38% in this population of transgender patients undergoing facial feminization procedures, which is higher than has been previously reported. Further stratification revealed that the majority of patients, 272 (90.67%) experienced none to mild PONV, 6 patients (2%) experienced moderate PONV, and 22 (7.3%) experienced severe PONV. The incidence of PONV was not significantly associated with any risk factors. Hormone use also did not affect the incidence of PONV in this patient population (Figure 1).

CONCLUSION: Previous studies have reported a PONV rate of anywhere between 20-30% for all surgeries, and a rate of 25% specifically for oral and maxillofacial surgery (OMFS) (2). Our study reports a PONV rate of 38% in a population of transgender patients undergoing facial feminization surgery, which is higher than has been previously reported. The majority of these patients were relatively young and healthy and held hormonal therapy for 2 weeks prior to the procedure. Prior hormone therapy was not associated with a greater risk of PONV and neither were any previously known risk factors such as age, BMI, type of anesthetic, and tobacco use. Given the lack of literature studied in this population of patients and due to the limitations imposed by the small sample size, further studies with a larger sample size are needed for conclusive results.

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Baseline Characteristics	Mean/N
Age at date of surgery	33.75 ± 12.93
Patient's Height (m)	4.23 ± 20.74
Patients Weight (kg)	72.43 ± 15.08
Patients BMI	
Less than 30	255
Equal to or more than 30	27
Race	
Asian	10
Native American/ Alaska Native	1
Black/ African American	8
White	154
Unknown	109
Hispanic or Latino?	
Yes	21
No	252
Unknown	9
Marital Status	
Single	185
Married	27
Unknown	70
Other	4
Preferred Pronouns	
She/Her/Hers	254
He/Him/His	4
They/Them/Theirs	2
Unknown	21
Missing	1
ASA Status	
1	157
2	117
3	8
Hormone Therapy	
Yes	236
No	46
Was hormone therapy held?	
Yes	160
No	28
Unknown	48
Duration of withholding prior to surgery	
2 weeks or less	21
2-4 weeks	125
4 weeks	10
Unknown	4

Figure 1: Baseline characteristics for all patients (N=282) enrolled in study.

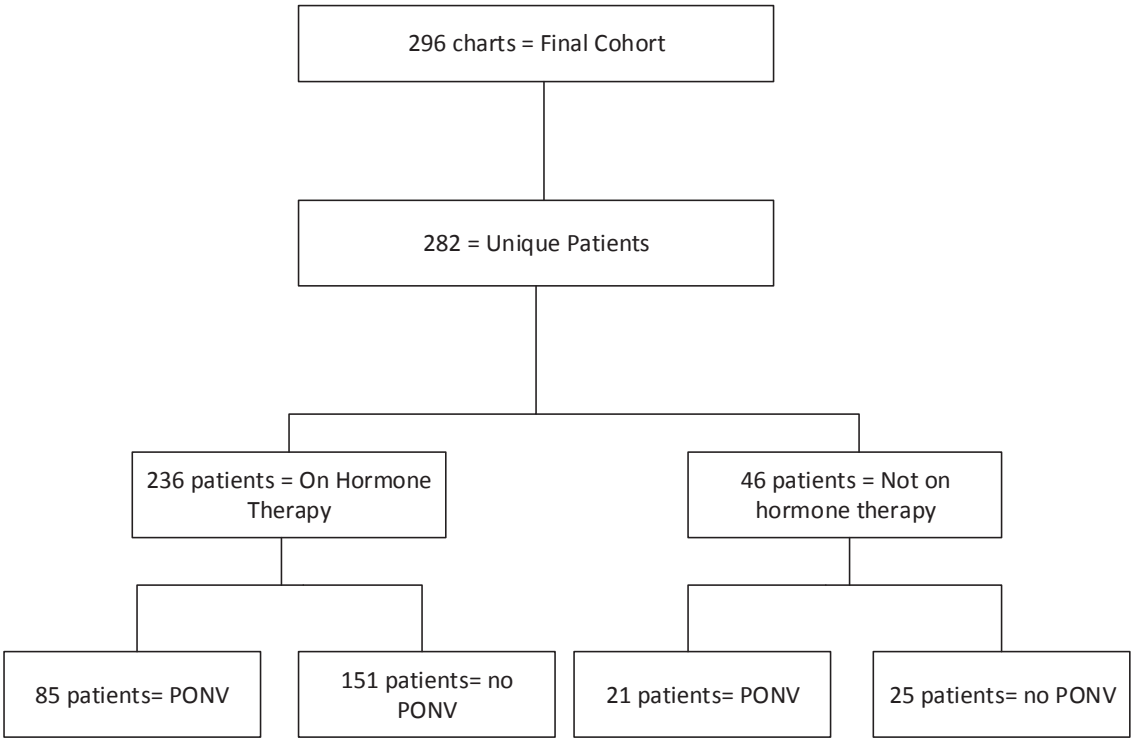


Figure 1: Consort Diagram showing patients who experienced PONV as a subset of the total population.

PATIENT SAFETY 8

Intraoperative Reading Policies: A National Survey of Residency Program Directors

Steven Char[1], Michal Gajewski[1], Rotem Naftalovich[1], James Schiffenhaus[1]

[1]Rutgers New Jersey Medical School, Newark, NJ

INTRODUCTION: Distractions in the operating room are categorized as either externally imposed (e.g. operating room noise, music, case-irrelevant conversation) or internally motivated (e.g. personal-electronic-devices [PED] and reading). These distractions may pose a threat to anesthesiologists if they disrupt focus while the physician delivers care. Data is limited on whether perioperative distractions directly relate to adverse patient outcomes, and data looking specifically at PED use affecting patient care is even scarcer.[1,2] As our dependency on PEDs has increased over the last two decades, we felt it was important to investigate whether the use of this technology has an adverse effect on patient care.

METHODS: We conducted a ten-question survey that was sent to 148 Accreditation Council for Graduate Medical Education (ACGME) accredited anesthesiology residency programs. A total of 23 survey responses were received over the span of two months (Table 1). The aim of the survey was to gain further understanding on whether institutions have intraoperative reading policies and whether PED use among anesthesia providers has beneficial, detrimental, or no effect on patient care.

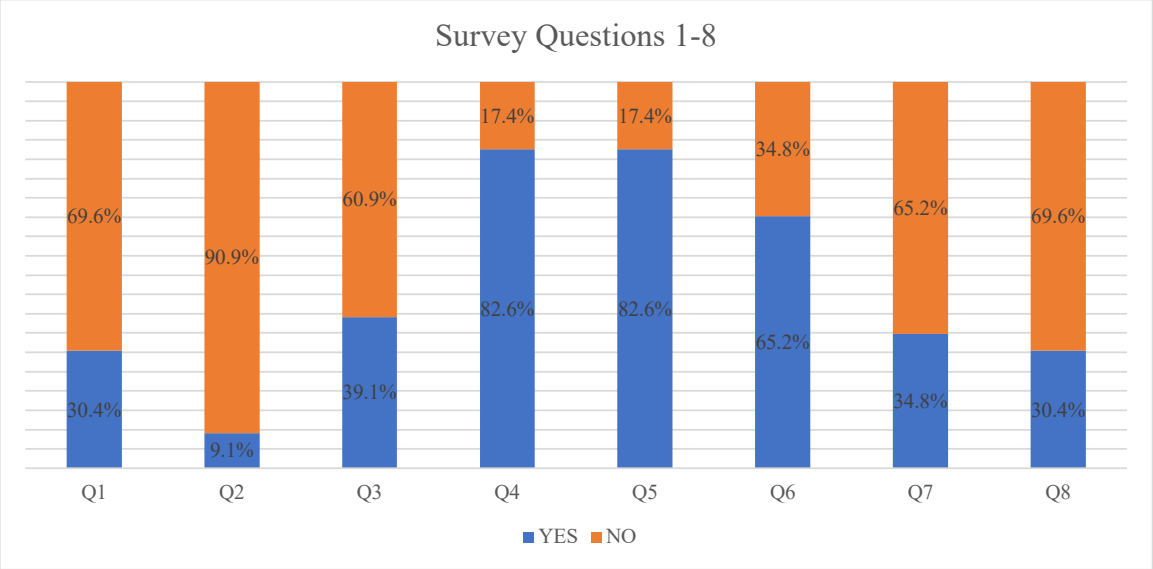
RESULTS: Overall, 35% of programs have an intraoperative reading policy (8/23), and 70% (16/23) did not have an intraoperative policy specifically directed towards the use of PEDs. 30% (7/23) of programs have encountered issues regarding noncompliance with intraoperative reading policies. 65% (15/23) believe intraoperative reading promotes a negative public image of anesthesia providers. 83% of programs (19/23) educate residents on proper use of PEDs around patient care and 9% of programs (2/23) reported an adverse patient outcome as a direct result of PED use (Figure 1). Of the institutions that reported an adverse event, only one of them reported having an intraoperative policy on PED use.

CONCLUSION: With the increased daily use of PEDs, the need to investigate their effects on patient care during the intraoperative setting is crucial. Results from our survey support the perspective that, although not a common occurrence, PEDs have the potential of causing adverse patient outcomes. This begets the question: should all residency programs have policies directed towards PED use and if so, what is the best way to enforce them?

Table 1. Anesthesiology Residency Programs Surveyed

Name of Institution
Albany Medical Center
Beth Israel Deaconess Medical Center
Emory University
Johns Hopkins University
John H. Stroger Cook County
Mayo Clinic - Rochester
Michigan State University
Mount Sinai West/Morningside
Naval Medical Center San Diego
New York Medical College
New York Presbyterian – Brooklyn Methodist Hospital
New York Presbyterian – Weill Cornell Medical Center
Rutgers - New Jersey Medical School
Rutgers - Robert Wood Johnson
Saint Barnabas Medical Center
Stony Brook University
Tulane University
University of Chicago
University of Florida
University of Kentucky
University of Rochester
University of Virginia
University of Wisconsin

Figure 1. Survey Questions 1 through 8



Q1: Does your hospital have an intraoperative policy on mobile devices or personal-electronic-devices (PEDs)
Q2: Have there been any adverse patient outcomes as a direct result of PED use?
Q3: Does your program reimburse residents for purchasing electronic media devices?
Q4: Do you educate your residents on proper use of PEDs around patient care?
Q5: Does your program pay for online question banks for residents?
Q6: Do you think intraoperative reading promotes a negative public image of anesthesia providers?
Q7: Does your department have an intraoperative reading policy?
Q8: Have you encountered issues with noncompliance?

Figure 2. Question 9

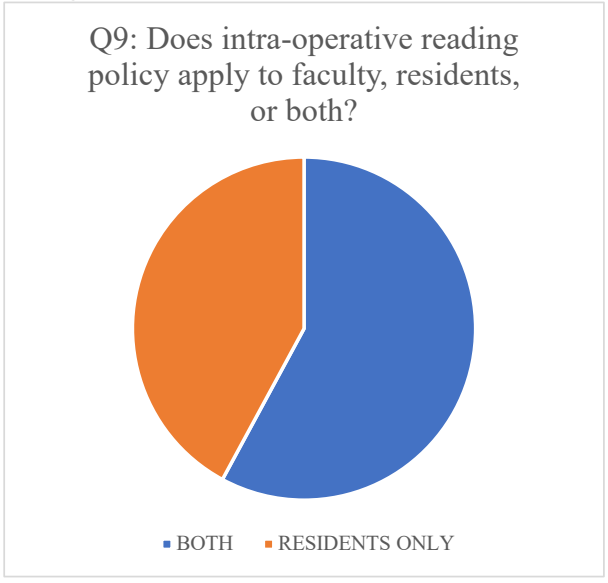
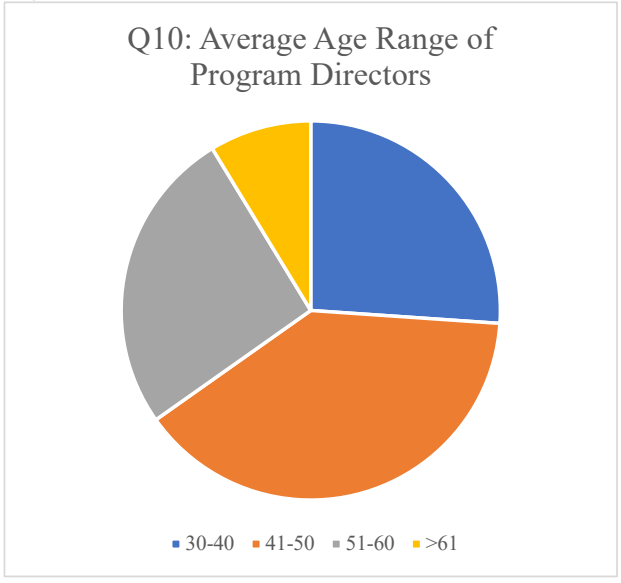


Figure 3. Question 10



PATIENT SAFETY 9

Delabeling of antibiotic allergy history in an anesthesia preop-clinic by a simple checklist

Sebastian Schulz-Stübner[1], Franz Kehl[2], Mathias Schreiner[3]

[1]Deutsches Beratungszentrum für Hygiene (German Consulting Center for Infection Control and Prevention), Freiburg, Germany, [2]Städtisches Klinikum Karlsruhe, Karlsruhe, Germany, [3]Städtisches Klinikum Kalrsruhe, Karlsruhe, Germany

INTRODUCTION: Approximately 10% of the US population is reported to be allergic to the β-lactam agent penicillin, with higher rates reported by older and hospitalized patients. Although many patients report that they are allergic to penicillin, clinically significant IgE-mediated or T lymphocyte–mediated penicillin hypersensitivity is uncommon (<5%), according to a recent review in JAMA.[1] As part of a quality assurance project we introduced a simple checklist to verify the history of antibiotic allergy during the pre-op visit in an anesthesia clinic of a tertiary care hospital in Germany in order to delabel unsubstantiated allergy histories and optimize preoperative antibiotic prophylaxis.

METHODS: The checklist has 7 items and comprises the type of antibiotic, time of the presumed reaction, typical symptoms to differentiate between anaphylactic and non-anaphylactic reactions,[2] time between antibiotic administration and onset of symptoms, medical treatment, diagnostic allergy testing and whether an allergy passport was issued.

RESULTS: 2005 patients were screened with the checklist in 2020. 238 (12%) reported an allergy to antibiotics. Penicillin being the culprit in 62% of cases, followed by amoxicilline in 13%, chinolones in 4%, cephalosporines and macrolides in 3% and all others in less of 2% of cases. More than 10 years had passed after the reaction in 47% of patients. Time of onset of symptoms was less than 1 hour in 18% of cases. Specific symptoms indicative of anaphylaxis were reported by 28% of patients. Diagnostic allergy tests were reported in 16 % but 28% had an allergy passport. Medical treatment was reported in 30% of cases. Checklists were screened and evaluated by an independent expert reviewer. Anaphylaxis could be ruled out in 61% of the 238 cases with reported allergy, confirmed in 25% of cases and classified as likely, needing specific allergy test evaluation, in 14%.

CONCLUSION: Our quality assurance project found a history of antibiotic allergy in 12% of all screened patients which is in accordance with the literature (1). 61% of those patients could be delabeled. Specific symptoms, time of onset and an issued allergy passport were indicative of anaphylactic reaction, whereas allergy testing was often not remembered and did not correspond to the rate of allergy passports as well as medical treatment. Exact time of symptom onset was often not remembered and did not correspond with otherwise confirmed anaphylaxis, making this theoretically highly indicative item in this real life observation unreliable. Based on our preliminary results the checklist can be optimized and the anesthesia pre-op-visit seems to be a great opportunity to verify the antibiotic allergy history.[3] This could reduce the use of second line antibiotics for the prevention of surgical site infections[4,5] and potentially reducing the increased mortality of patients wrongfully labeld as allergic to antibiotics.[6]

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PATIENT SAFETY 10

The Impact of Volatile Anesthetic Selection on Response to Emergence Commands in Patients with a First Language Other than English

Spencer J Satz[1], Ryan Hoang[2], Elise Hall[3], Tracy Dinh[4], David Glick[2]

[1]Tel Aviv University Sackler School of Medicine, Tel Aviv, Israel, [2]University of Chicago, Chicago, IL, [3]Villanova University, Villanova, PA, United States of America, [4]University of Chicago Pritzker School of Medicine, Chicago, IL

INTRODUCTION: Several existing studies have shown that language barriers between providers and patients negatively impact the delivery of quality care.[1] Our group has previously demonstrated that patients with a native language other than English may preferentially respond to verbal commands in their native language during the anesthesia emergence process. They may also report greater satisfaction with the anesthesia care they receive. Selection of volatile anesthetics desflurane or sevoflurane affects both the rate and safety of the emergence process,[2,3] however its impact on patient response to native language or English is not currently known. The purpose of our study was to investigate response to emergence commands in patients' native languages and English in those receiving desflurane or sevoflurane. Potential implications include increased patient satisfaction and comfort with anesthesia.

METHODS: Patients with a native language other than English and varying levels of English proficiency in a multi-center urban hospital system were identified and consented in the pre-operative area. Following completion of a general anesthetic course including either desflurane or sevoflurane, patients were given three verbal commands, first in English by the researcher followed by their native language on an iPad using either pre-recordings from family members or a translation application (Google Translate) while still in the operating room. The specific commands were 'open your eyes', 'squeeze my finger', and 'wiggle your toes.' Response to the command was defined as compliance on either the first or second delivery of the command. Patients were then divided in to two groups: those who responded to a command in their native language only and those who responded to commands in both English and their native language. The rate of response to each language was calculated. The group that responded only to foreign language for any of the commands was analyzed, as this is the relevant group for potential intervention, using a Fisher's exact T-test.

RESULTS: A total of 38 patients with a first language other than English were enrolled in the study and received the verbal commands during emergence. 6 patients received a combination of both desflurane and sevoflurane and were thus excluded from the study. The desflurane group consisted of 14 patients and the sevoflurane group consisted of 18 patients. In the desflurane group, 8 patients responded to only their native language for one or more of the commands and 6 patients in the sevoflurane group responded similarly. When desflurane was administered, subjects responded to 88.2% of commands in their native language and 17.6% of commands in English. When sevoflurane was administered, subjects responded to 83.3% of commands in the native language and 20.0% of commands in English (Figure 1). Fisher's exact T-test conducted with SPSS 26 software revealed no significant difference ($p>0.05$) in patient response between the desflurane or sevoflurane groups to both the native language and English.

CONCLUSION: There was no observed difference in response to native language or English between the use of sevoflurane and desflurane. Therefore, the selection of either anesthetic is appropriate for patients with a native language other than English. Future studies should include a more geographically diverse sample for a large-scale extrapolation of our findings. In addition, commonly used isoflurane should be included.

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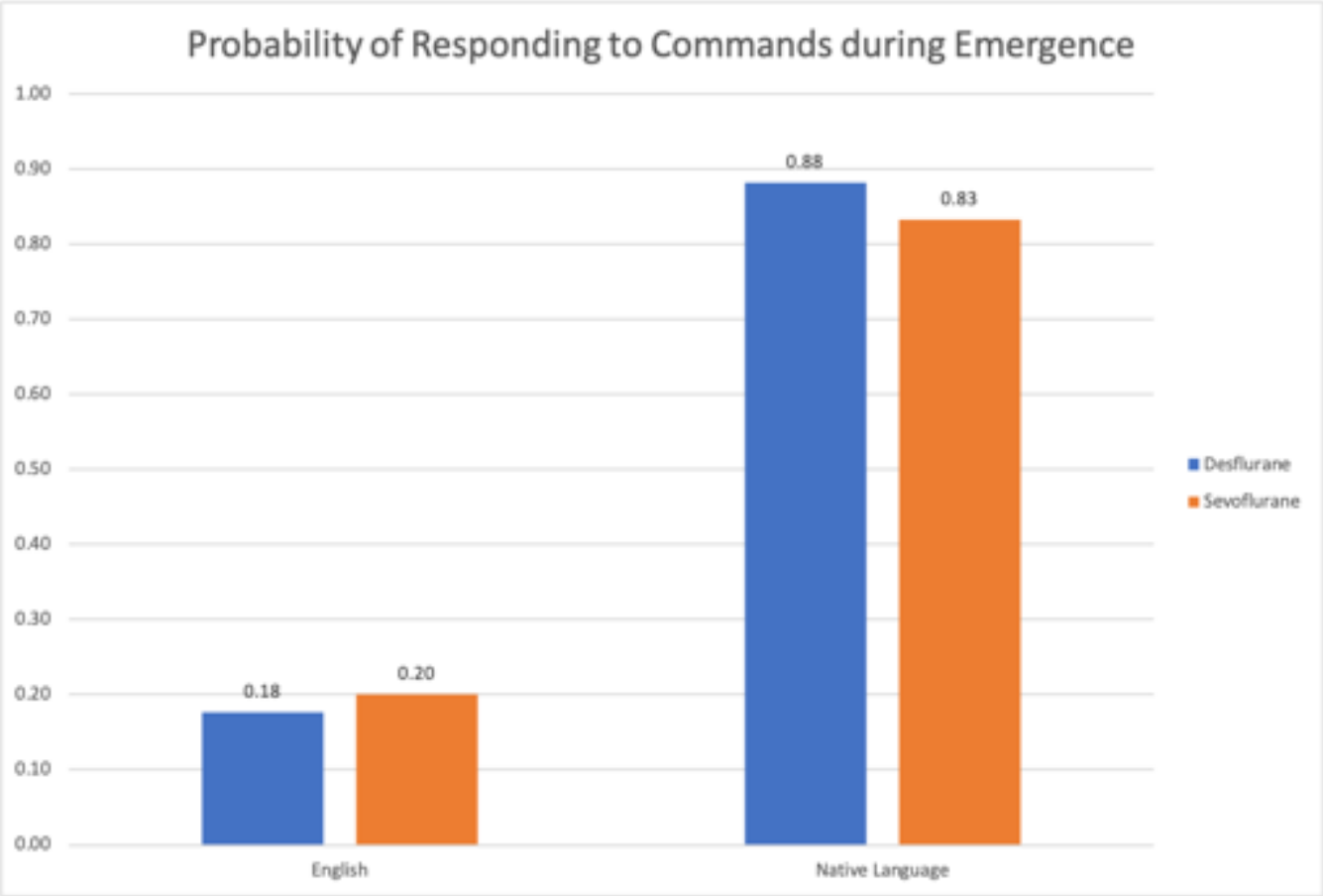

Figure 1

PATIENT SAFETY 11

Intravenous Amisulpride: Pharmacokinetics and Cardiac Safety when Administered with and without Ondansetron at Doses Effective in Postoperative Nausea & Vomiting

Andrew Wahlert[1], Gabriel Fox[2]

[1]Acacia Pharma, Indianapolis, IN, [2]Acacia Pharma, Cambridge, United Kingdom

INTRODUCTION: Drug-induced prolongation of the QT interval may result in serious and potentially fatal cardiac dysrhythmias, such as torsades de pointes. The International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use established a threshold of concern for QT interval prolongation of 10 milliseconds (msec). Prolongation significantly above that level has led to regulatory warnings and even product withdrawals. For example, the clinical use of droperidol for postoperative nausea and vomiting (PONV) has significantly declined due to evidence of substantial, dose-dependent QT prolongation[1] and reports of cardiac fatalities, leading to the imposition of a boxed warning by the United States Food and Drug Administration.[2] Intravenous (IV) amisulpride, a selective dopamine D2/D3 antagonist, was demonstrated to be effective for the management of PONV in multiple, randomized, placebo-controlled studies.[3-6] Here we report a study evaluating the effect of IV amisulpride, administered with or without ondansetron, on cardiac conduction.

METHODS: A phase I, randomized, double-blind, placebo-controlled, crossover study was conducted in 30 healthy adults to evaluate the effect of IV amisulpride, with or without concomitant ondansetron, on cardiac conduction. The study consisted of 3 treatment periods (with a washout of ≥2 days between each), each involving 2 IV infusions 2 hours apart, as follows: (A) 10 mg amisulpride (therapeutic dose for treatment of established PONV) followed by 10 mg amisulpride; (B) 10 mg amisulpride co-administered with 4 mg ondansetron, followed by placebo; and (C) placebo followed by placebo. Each subject was scheduled to go through each period, in a randomly assigned order. Electrocardiogram (ECG) recordings and blood samples for pharmacokinetic (PK) analysis were taken at multiple timepoints up to 6 hours post-dosing.

RESULTS: Thirty subjects were enrolled, of whom all received treatments B and C, and 29 received treatment A. One subject, randomized to the sequence BCA, withdrew due to infusion-site pain after receiving the placebo treatment.

For a 10 mg dose of amisulpride, infused over 1 minute (min), the largest mean time-matched placebo-corrected change from baseline in QTcF (ΔΔQTcF) was 5.2 msec (90% Confidence Interval [CI]: 3.53, 6.96), which occurred at 10 minutes after the start of dosing. After a second 10 mg dose, ΔΔQTcF peaked at 8.0 msec (90% CI: 5.49, 10.58), again at 10 minutes post-dosing. When amisulpride and ondansetron were co-administered, ΔΔQTcF peaked at 7.3 msec (90% CI: 5.48, 9.16), at 5 minutes post-dose. There were no QTcF outliers (no absolute values ≥480 msec; no change from baseline >30 msec) in any treatment group.

By-timepoint analysis of ΔΔQTcF is shown in Figure 1.

Plasma levels of amisulpride were highly consistent across the subjects at all time points, with or without co-administration of ondansetron. Peak plasma concentration (Cmax) occurred at the end of infusion; mean Cmax was 451 ng/mL after a first infusion of 10 mg amisulpride and 516 ng/mL after a second 2 hours later; after a 10 mg dose given with ondansetron, it was 463 ng/mL. A significant relationship was evident between amisulpride concentration and ΔΔQTcF, with an estimated population slope of 0.006 msec per ng/mL (90% CI: 0.0020 to 0.0098).

Joint plots of ΔΔQTcF and amisulpride plasma concentration over time are shown in Figure 2.

CONCLUSION: Amisulpride PK parameters showed little inter-subject variability after a 10 mg IV dose, with or without concomitant IV ondansetron. Amisulpride at 10 mg did not have a clinically significant effect on QT interval, even when co-administered with 4 mg ondansetron.

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Figure 1: Placebo-Corrected Change from Baseline QTcF (ΔΔQTcF) Across Time Points

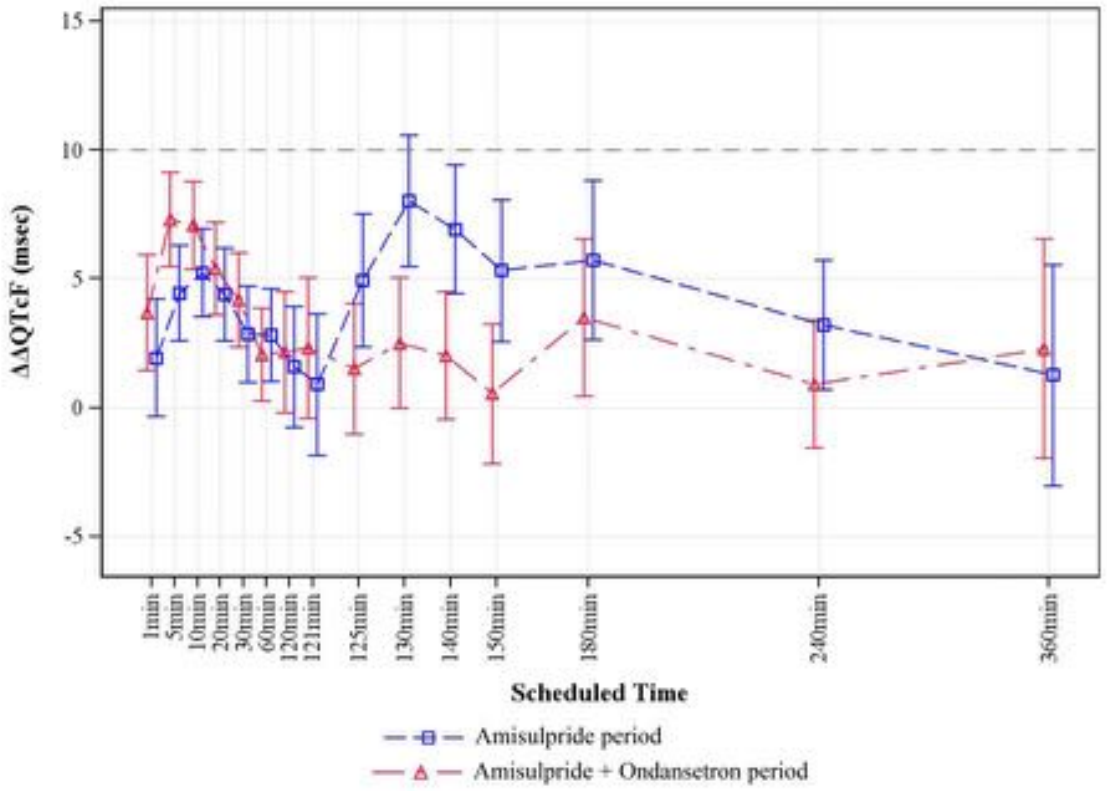


Figure 2: Plasma Concentrations and Placebo-Corrected Change from Baseline QTcF (ΔΔQTcF) Across Time Points

A. 10 mg Amisulpride

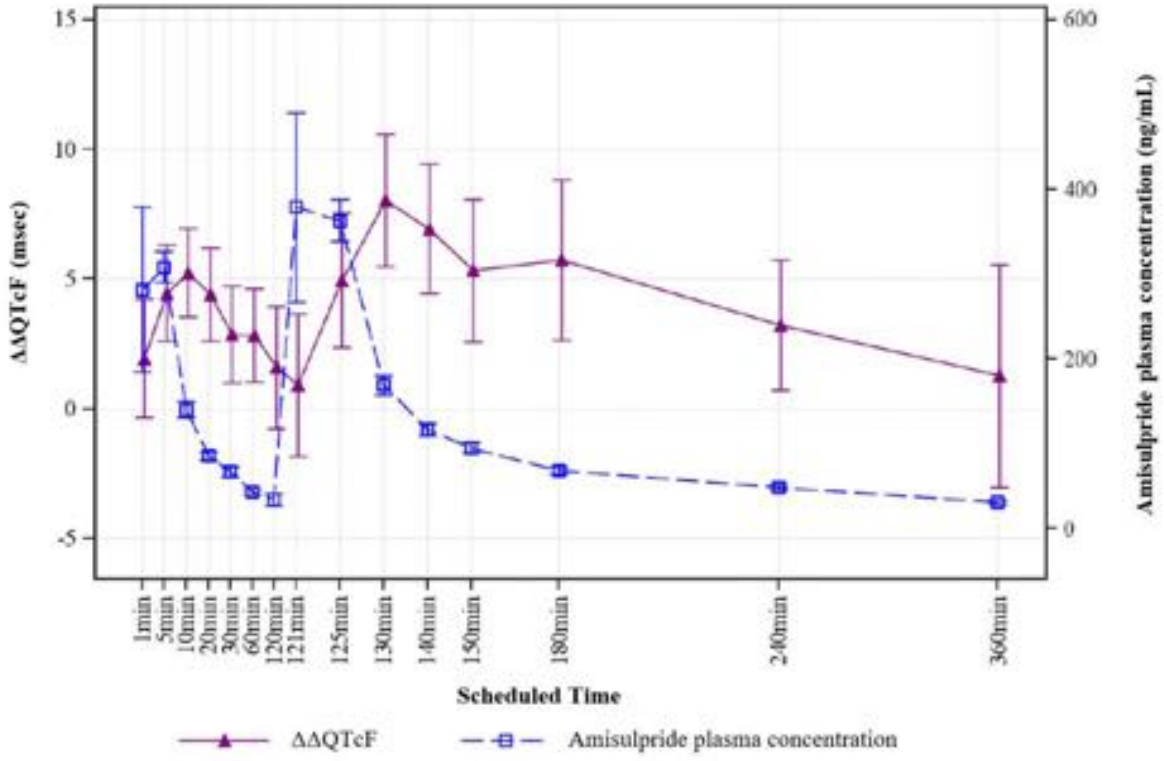
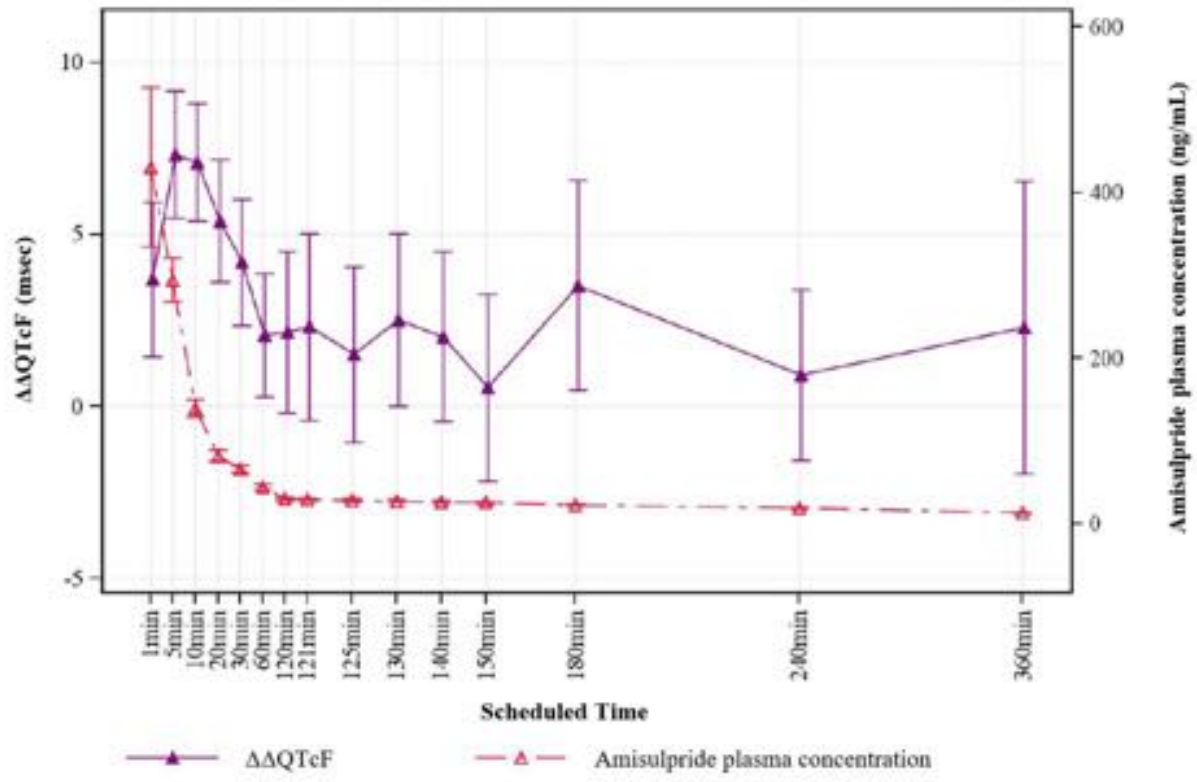


Figure 2: Plasma Concentrations and Placebo-Corrected Change from Baseline QTcF (ΔΔQTcF) Across Time Points

B. 10 mg Amisulpride + 4 mg Ondansetron



PATIENT SAFETY 12

Impact of PPE Type and Healthcare Worker Characteristics on Perioperative Communication

Onassis Naim[1], Michael Aguad[2], Stephanie Hernandez[2], Xiwen Zheng[1], Maria Frosth[3], Walter Diaz[3], Cameron Howard[4], George Semien[5], Benjamin Houseman[6]

[1]Memorial Hospital West, Pembroke Pines, FL, [2]Herbert Wertheim College of Medicine, Miami, FL, [3]Envision Physician Servies, Pembroke Pines, FL, [4]Envision Physician Services, Pembroke Pines , FL, [5]Envision Healthcare Services, Hollywood, FL, [6]Envision Physician Services, Pembroke Pines, FL

INTRODUCTION: The use of extensive PPE during for the care of patients with SARS-CoV-2 has significantly impacted the ability of healthcare providers to communicate with each other and with their patients. Challenges in communication represent a risk to patient safety and have motivated the use of written signs, call backs, and other techniques.[1-5] However, it is unclear whether certain types of PPE or certain characteristics of healthcare providers impact their ability to communicate effectively. This study examines how specific types of PPE as well as specific healthcare worker characteristics impair communication in the perioperative setting. We also examine the ability of an Iasus GP-3 throat microphone to improve communication between providers wearing PPE.

METHODS: QUALITATIVE ASSESSMENT: 75 healthcare workers at Memorial Hospital West completed a 19 item survey (Figure 1) to qualitatively assess the impact of gender, age, healthcare role (preop nursing, recovery nursing, OR nursing, surgeon, surgery assistant, anesthesia), native language (English, other), respirator type (N95, P100) and eye protection type (face shield, goggles) on employee perception of communication. Data analyzed using Microsoft Power BI and are presented in Figure 2. QUANTITATIVE ASSESSMENT: The Bamford-Kowal-Bench(BKB) sentence list, a benchmarked tool for evaluating comprehension of verbal communication, was utilized to analyze communication between healthcare workers wearing varying PPE. Variables in the quantitative analysis included distance between workers (3 versus 6 feet), phone versus in person communication, and ambient noise level (60 dB, 90dB). An Iasus GP3-R throat microphone was utilized for speakers to assess its efficacy as an intervention. Data were analyzed using Microsoft Power BI and results are presented in Figures 3, 4, and 5.

RESULTS: QUALITATIVE SURVEY Responses from a standard survey (Figure 1) were compiled and analzyed using microscft power BI. Responses were not statistically different between male and female workers, nor were they statistically different between native English speakers and non-native English speakers. However, as shown in Figure 2, results were statistically different between younger cohorts (21-30, 31-40 year old) and more mature workers (41-50, 51-60 year old). These differences appeared in both speaker and listener roles. In this survey there was a non-statistically significant difference between individuals who routinely wore P100 respirators and those who wore N95 ($p=0.12$). QUANTITATIVE ASSESSMENT Comprehension of a standard set of BKB phrases were studied under several standard conditions (distance apart, phone versus in person, background noise 60 dB versus 90 dB). For consistency, we utilized a set of 4 speakers between 41-50 year old (male native English, female native English, male native Spanish, female native Spanish). Figure 3 demonstrates that non-native speakers wearing P100 respirators were more poorly understood under most conditions. Gender of speaker did not influence these results. While the combination of face shield + P100 appeared worse than goggles + p100, the difference was not statistically significant. Figure 4 demonstrates the effect of an Iasus GP-3 throat microphone on in person BKB phrase comprehension. Participants were kept 6 feet apart with a background noise level of 90 dB for this portion of the work because the baseline comprehension scores were lowest. The throat microphone produced an impressive improvement in comprehension of all speakers, but failed to statistically improve the comprehension of non-native speakers wearing P100 respirators. Figure 5 demonstrates the impact of the Iasus GP-3 throat microphone on comprehension via phone using 90 dB background noise for both listener and speaker. Again, the throat microphone produced an impressive improvement in comprehension, but not statistically so in the case of non-native speakers wearing P100 respirators.

CONCLUSION: This study demonstrates that multiple factors influence the quality of comprehension when wearing PPE. These include speaker respirator type, native language, and the age of both the listener and speaker. The use of Iasus GP3-R throat microphone improved comprehension except in the case of non-native speakers wearing a P100 respirator. Limitations include sample size, the use of only two respirator types, and the simulated setting, which may not reflect clinical practice.

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Figure 1. Qualitative survey of healthcare worker perception of communication when wearing PPE.

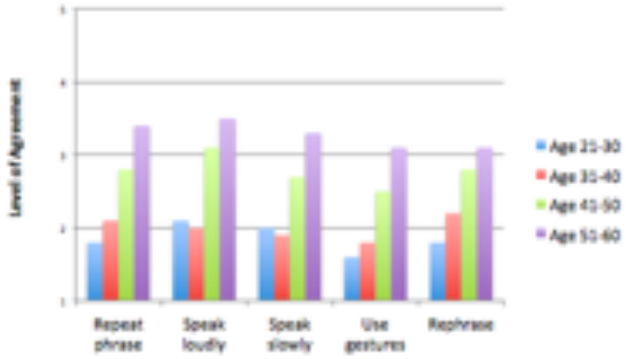

Figure 2. Data from qualitative survey regarding communication when wearing PPE. . In chart, 1 = never and 5 = always. Responses between male/female and native/non-native speakers were not statistically different but there was a statistically significant difference between 21-30 /31-40 and 50-61 year old participants (p<0.05).

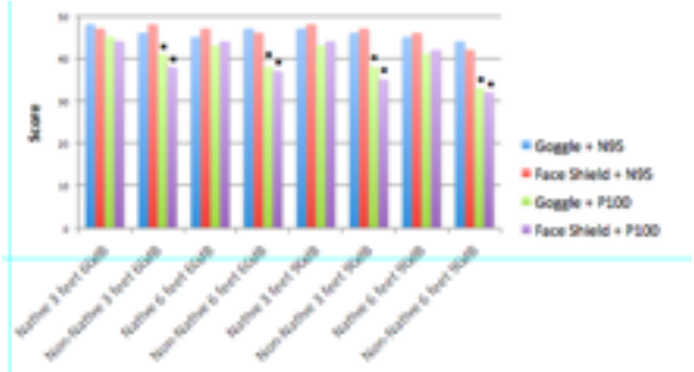

Figure 3. Evaluation of in person standardized phrase comprehension under standard conditions. Male and Female speakers between ages 41-50 recited standard phrases from the Bamford-Kowal-Bench (BKB) to listeners under the conditions shown. Compared to speakers with N95, scores with speakers wearing P100 respirators were consistently lower, particularly with non-native speakers (* = p < 0.05).

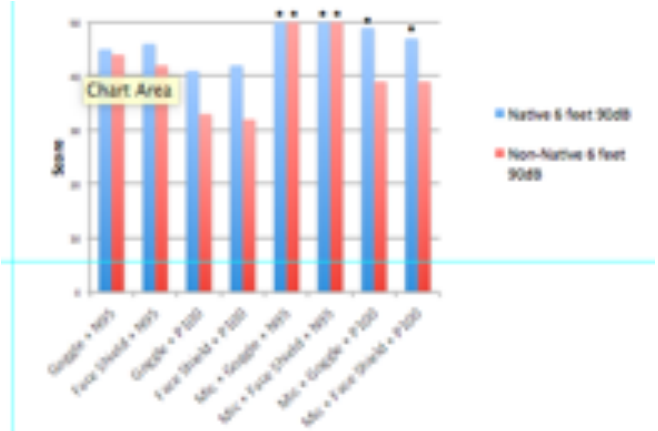

Figure 4. Impact of Iasus Throat Microphone on BKB Phrase comprehension under standard conditions. The throat microphone improved comprehension in all groups, but improvement with non-native speakers wearing P100 respirator was not statistically significant.

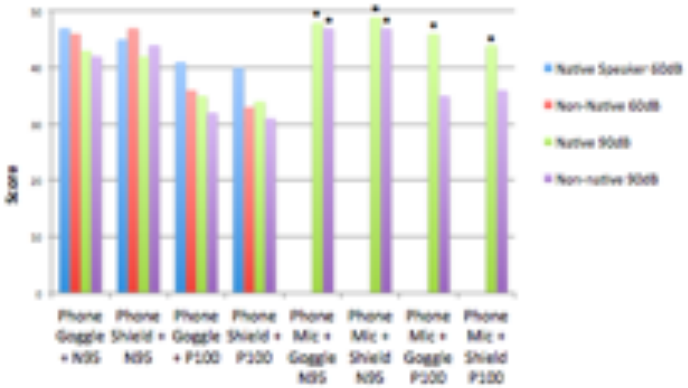

Figure 5. Evaluation of BKB phrase comprehension via phone call under standardized conditions. An Iasus GP3-R throat microphone showed a statistically significant improvement in comprehension in all groups except non-native speakers wearing P100 respirators (* p<0.05).

PATIENT SAFETY 13

Non-Operating Room Anesthesia Care and Crisis Management in a Hybrid Magnetic Resonance Imaging-Operating Room: A Human Factors-based Assessment

Stefana Voicu[1], Sarah K Stark[1], Janelle V Pickering[1], Michaela A Whitty[2], Barbara K Burian[3], Hedwig Schroeck[4]

[1]Geisel School of Medicine at Dartmouth, Hanover, NH, [2]Dartmouth Hitchcock Medical Center, Lebanon, NH, [3]NASA Ames Research Center, Moffett Field, CA, [4]Dartmouth-Hitchcock Medical Center, Lebanon, NH

INTRODUCTION: Human factors and ergonomics (HFE) research in healthcare focuses on the interactions of humans with the complex and dynamic systems in which they provide patient care. This discipline has informed process improvement, patient safety, and provider well-being initiatives in many clinical work settings, including the perioperative environment.[1-3] More than 30% of anesthetic cases take place in non-operating room anesthesia (NORA) environments,[4] which are challenging for anesthesia clinicians to navigate.[5] Operating in this stressful environment may have detrimental effects on physician well-being, performance, and patient safety, making this fertile ground for HFE research.[6,7] At our institution, several near misses in a specific NORA site – a hybrid MRI-OR – prompted this investigation. Our objective was to generate an inventory of clinically relevant differences between this MRI-OR and the standard operating room (OR), describe these differences within an HFE framework, and determine how these differences might affect the ability of anesthesia clinicians to respond to a crisis.

METHODS: In an iterative process, three anesthesia clinicians and an operating room manager with expertise in both MRI-OR and OR created an inventory of differences between the typical steps and tasks required for patient care in the two settings during a hypothetical brain tumor resection. Next, we determined how these differences may affect clinician task load using the domains of the NASA Task Load Index (NASA-TLX). This instrument was originally developed for pilots and military personnel and has been extensively studied and validated in many different environments, including medicine and specifically anesthesiology. It considers 6 domains – mental demand, physical demand, temporal demand, performance, effort, frustration.[8] Coding of the identified task differences continued until a consensus was reached. Finally, we identified in a similar fashion aspects of crisis management which are likely to be affected by these differences in task load.

RESULTS: Multiple differences in anesthesia-care related tasks were identified, spanning the entire continuum from preoperative case preparation to postoperative transport. Table 1 displays illustrative examples. The differences were most likely to increase the temporal and mental demand and effort for anesthesia clinicians working in the MRI-OR compared to the OR. Similarly, multiple important steps in crisis management were found to be different in the MRI-OR environment – involving more personnel and increased effort and temporal demand (Table 2).

CONCLUSION: An HFE framework allows for a systematic assessment of the dynamic and interdependent components of a work system that influence clinician well-being and patient outcomes. Our analysis outlined important differences in the MRI-OR and OR settings and their implications for crisis management. This approach highlights concrete elements in the work environment that can be effectively targeted by guided interventions aimed to ease clinician mental and temporal load and enhance crisis management. For the MRI-OR in the present study, possible interventions include (1) simplification and standardization of equipment and processes; (2) formalized education about the differences that cannot be eliminated; (3) development of physical barriers to prohibit errors associated with some of these differences, and (4) standardization of roles and tasks during a crisis. Finally, creation of standardized location-specific cognitive aids to make this information available at the point of care is likely to decrease the workload for clinicians, particularly during a crisis. This systematic, HFE-informed approach can be used as a template for other NORA environments, thereby enhancing both clinician well-being and patient safety in our growing and heterogenous NORA landscape.

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Table 1: Illustrative examples of anesthesia-relevant task differences for a routine brain tumor resection in the MRI-OR vs OR, NASA-TLX domains affected, and implications for anesthesia clinicians

Phase/Step	Task differences for MRI-OR vs OR	NASA -TLX[1]	Implications for anesthesia clinicians
Preparation			
Exposure	• Exposure to MRI-OR environment and case type may be more infrequent.	**M E**	• Less familiarity with environment leads to higher cognitive load and effortful processing rather than relying on "muscle memory" during case preparation and plan execution.
Case set up on day of procedure	• MRI-OR suite requires badge access. • Prior to OR entry, ferromagnetic personal items have to be removed/stored.	**M T E F**	• Extra processes are required to access this environment • May correspond with increase in the temporal and mental demand and effort domains.
Operating Room Set-up			
Safety check	• MRI-OR safety equipment check includes additional equipment (e.g., code drug box, airway grab bag).	**M T E**	• Although the additional time needed to check for these items is small, the mental demand to remember, and the effort required to do it increase the workload.
Ferrous item count	• A two-person ferromagnetic object count is required in MRI-OR before patient enters room to avoid accidents in the magnetic field of the MRI scanner. • Count repeated at pre-defined time-points intraoperatively.	**M T F**	• Process is time-consuming and may disrupt regular workflow of these two independent clinicians.
Supplies planning	• Planning for medication/supplies unavailable in the regular anesthesia cart is more important in MRI-OR due to the time-inefficient process of having items delivered as needed. • Any ferromagnetic piece of equipment must be added to the object count sheet.	**Ph M T F**	• Clinicians need to anticipate which non-routine items might be needed and how urgently these items might be needed. • Clinicians must either (1) physically retrieve the items from the OR area themselves or (2) ask a colleague to do this for them. • Clinicians need to be aware of ferromagnetic concerns and regulations in the MRI-OR.
Case Execution			
Induction	• Patient/airway is typically located far from anesthesia machine due to the size and layout of MRI-OR.	**M T E**	• Extra person with anesthesia expertise is required to perform routine ventilation from anesthesia machine during induction sequence.
Positioning	• Patient in MRI-OR is typically positioned with arms tucked in by their side. • Loops in IV tubing or monitor cables have to be avoided to prevent radiofrequency-induced heat/burn injury during MRI scan. • Skin-to-skin and skin-to-tubing/cable points of contact must be padded with gauze to prevent moisture build-up and burn injury during MRI scan.	**Ph M T E**	• This time- and labor-intense process is performed by MRI-OR nurse and tech team in parallel with anesthesia team. • May result in "competing workflow" as the anesthesia team may still need to acquire more intravascular access sites or connect infusions and monitor cables. This leads to a high workload and the need for "multitasking" for the anesthesia team.

Table 2: Illustrative examples of anesthesia-relevant task differences for non-routine anesthesia care in the MRI-OR vs OR

Equipment or Process	Task differences for MRI-OR vs OR	NASA-TLX[1]	Implications for anesthesia clinicians in times of crisis
Code cart	• Code cart and defibrillator prohibited in the MRI-OR while magnet is in the room due to ferromagnetic properties.	**M T E**	• Clinicians recall that the normal code cart is unavailable while the MRI magnet is in the room. • Deviation from usual crisis management can increase mental demand by forcing effortful processing.
Airway management	• Access to patient's airway in the MRI-OR is often complicated by the patient's position, turned 180 degrees away and far from the anesthesia machine. • Patient inaccessible due to being fully wrapped in multiple layers of drapes during MRI scans.	**Ph M T**	• Physically impossible for a single clinician to assess the airway while controlling the anesthesia machine/adjust ventilation. • Clinicians need to be aware of the "airway grab bag", which allows a single person to provide positive pressure ventilation without simultaneously controlling the anesthesia machine. • Clinicians must rely on help from other MRI-OR team members to obtain access to the patient under the surgical drapes.
Availability of help	• The MRI-OR is located several minutes walking distance from the ORs.	**M E P**	• Arrival of additional personnel or equipment to MRI-OR is delayed due to its remote location two levels below the standard ORs. • Imparts a sense of vulnerability and isolation on the clinician.
Cognitive Aids/2-way communication	• Personal devices are restricted in MRI-OR, limiting access to the internet and digital cognitive aids. • Phone lines and internet are disabled during MRI scanning.	**M T E F**	• Limits (1) communication between anesthesia care team members, (2) access to the internet and digital cognitive aids. • Additional time and effort are required to access information needed for diagnosis and management of a crisis.

*1: The North American Space Association (NASA) has developed a task load index tool (NASA-TLX) to grade tasks using 6 different domains which contribute to task load. The TLX domains are Physical demand (**Ph**), Mental demand (**M**), Temporal demand (**T**), Effort (**E**), Performance (**P**), Frustration (**F**). Abbreviations: **OR**: Operating Room; **MRI-OR**: Magnetic resonance imaging operating room, a specific operating room remote from other ORs.*

PATIENT SAFETY 14

A Quality Improvement Project to Improve Medication Administration by Anesthesia Providers during Non-OR Airway Emergencies

Abraar M Muneem[1], Tonya King[1], Kunal Karamchandani[2]

[1]Penn State College of Medicine, Hershey, PA, [2]Penn State Health Milton S. Hershey Medical Center, Hershey, PA

INTRODUCTION: Inconsistent medication administration during airway emergencies outside of operating rooms (ORs) can impact patient safety.[1-2] Untimely and inappropriate documentation of medications administered during these emergencies can interfere with anesthesia providers' ability to distinguish between deterioration in patient condition due to hemodynamic effects of the medication or due to worsening of medical condition.[3] Recognizing this challenge interferes with optimal decision-making, treatment, and continuum of care,[3] a quality improvement project was instituted to reduce lapses in medication documentation administered during non-OR airway emergencies by anesthesia providers. The goal was to standardize documentation of medications administered during non-OR airway emergencies in the electronic health record (EHR).

METHODS: Prior process: Upon activation of an out-of-OR airway emergency, the assigned anesthesia response team including a senior resident and an attending anesthesiologist responded to the emergency. The airway team carried the 'emergency airway drug kit' (figure 1) and 'airway box' (supplies) to the emergency location. During each airway emergency, anesthesia providers were expected to document the drug administration details in the airway intubation note. In the case that additional or controlled medications were needed during this process, nursing staff dispensed those medications with an override of the 'pyxis' machine i.e., medications were removed in the absence of an order. During a review of this process, providers discovered that used and unused/wasted medications were not documented consistently in the EHR and used medications were not charged to the patient. Intervention: In January 2018, members from the Department of Anesthesiology and Perioperative Medicine Quality Improvement Committee (AQIC) along with representatives from the Department of Pharmacy and Nursing worked with Information Technology (IT) to develop a physician order set in the EHR, called Powerplan (Cerner) that would help document the medications administered during a non-OR airway emergency. The EHR linked the order set to a universal 'Intubation Note' that all anesthesia providers were asked to use during each emergency airway procedure. The order set contained built-in details of medications administered, including the drug name and dose. Figures 2-3 outline the physician order set. Administered medications, now visible real time in the EHR, were officially considered to be 'tasked off' by an anesthesia provider. This allowed for nurses to chart any excess or unused medications. To overcome inaccurate billing, disposal, and drug waste, as well as to standardize the availability of required medications, the pharmacy provided and replenished the 'emergency airway kit' after each use. So, each time the emergency airway kit was used, providers returned the kit to the pharmacy with the patient's identification label and obtained a new kit. In order to check adherence with the process and identify the opportunities for improvement, a monthly report was compiled of all non-OR emergency airways managed by the anesthesia providers. The monthly adherence rate was calculated as the number of correctly documented intubation notes out of the total number of non-OR airway emergencies performed. After plotting the results over time, the QI team fit a regression line and evaluated whether a significant trend existed over time.

RESULTS: From January 2018 to November 2020, anesthesia providers managed a total of 1505 out-of-OR emergent airways, an average of 43 per month. As seen in figure 4, adherence rates ranged from 69% (March, 2018) to as high as 100% in four different months. The regression line (figure 5) showed a significant upward trend in the adherence rates over time ($p<0.001$).

CONCLUSION: The multidisciplinary QI initiative significantly improved the documentation of medication administered during out-of-OR emergent airways by anesthesia providers. Appropriate documentation during similar high-risk procedures ensures accurate and timely recording in the EHR and ultimately improves patient safety. Additionally, appropriate medication documentation allows providers to track wastage and dispose of excess controlled medications, minimizing concerns related to charge capture and controlled substance misuse.

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Emergency Drug Kit consists of:

Ephedrine 25 mg/5 ml syringe #1
Epinephrine 100 mcg/10 ml syringe # 2
Etomidate 20 mg/10 ml vial #1
Phenylephrine 1000 mcg/10 ml #2
Propofol 200 mg/20 ml vial #2
Rocuronium 50 mg/5 ml syringe #2
Succinylcholine 200 mg/10ml syringe #2
Sugammadex #8 (2 ml)
Sodium chloride 0.9% syringe #2
10 ml syringes #2
18 g needles #2
Alcohol packets

Figure 1

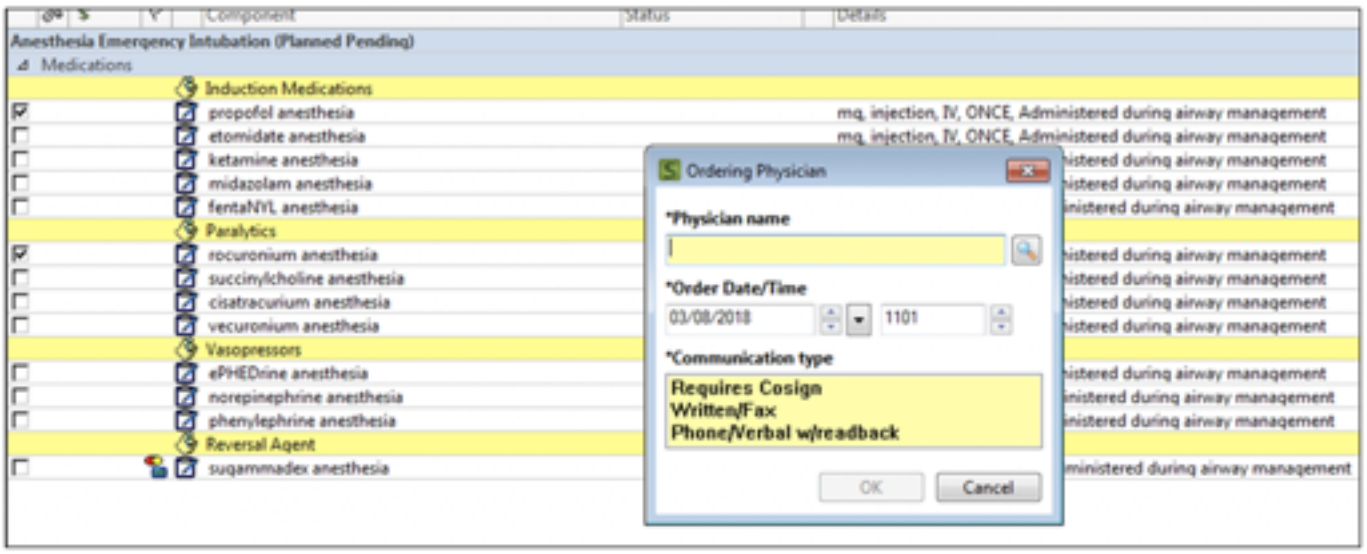

Figure 2

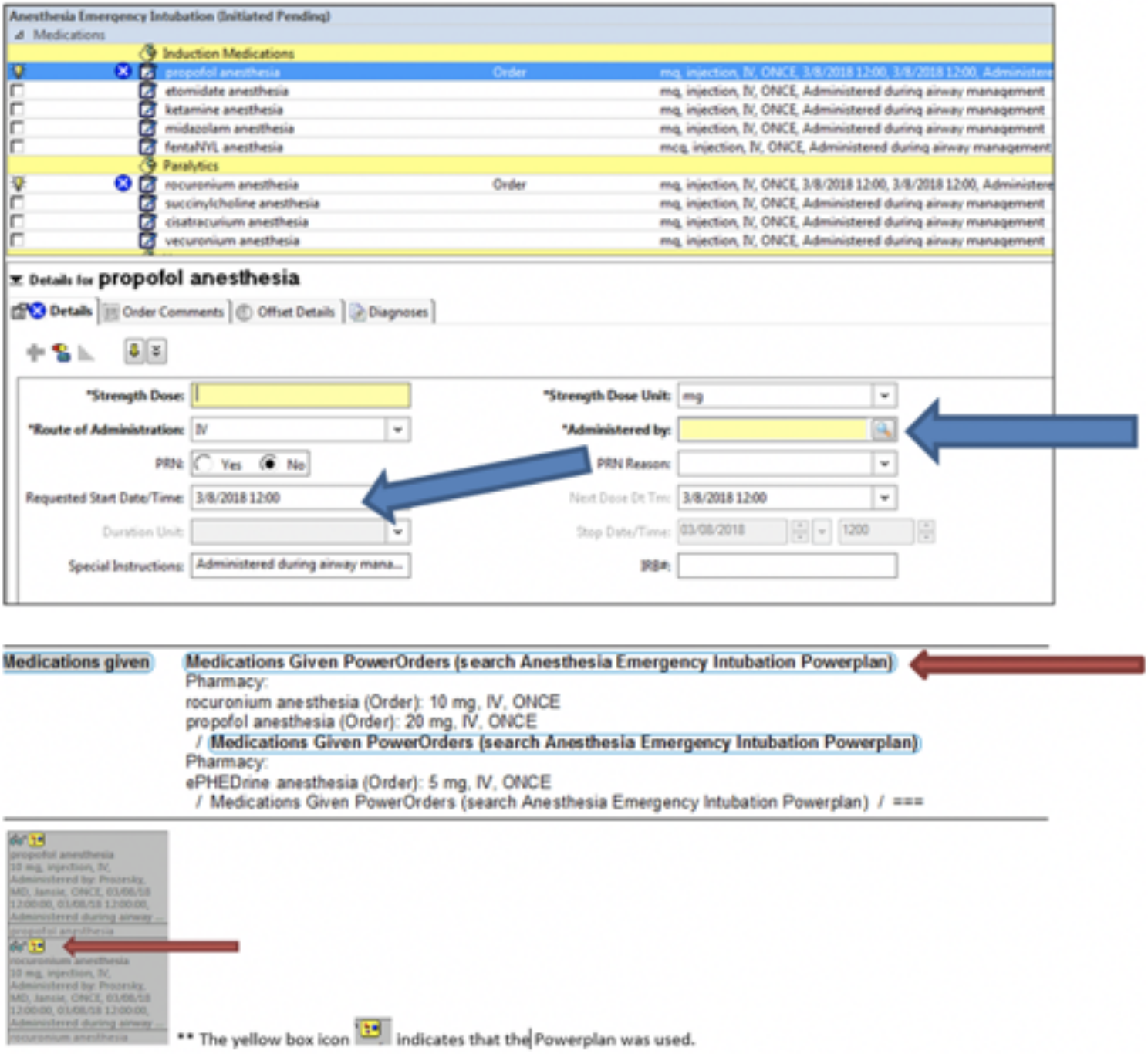

Figure 3

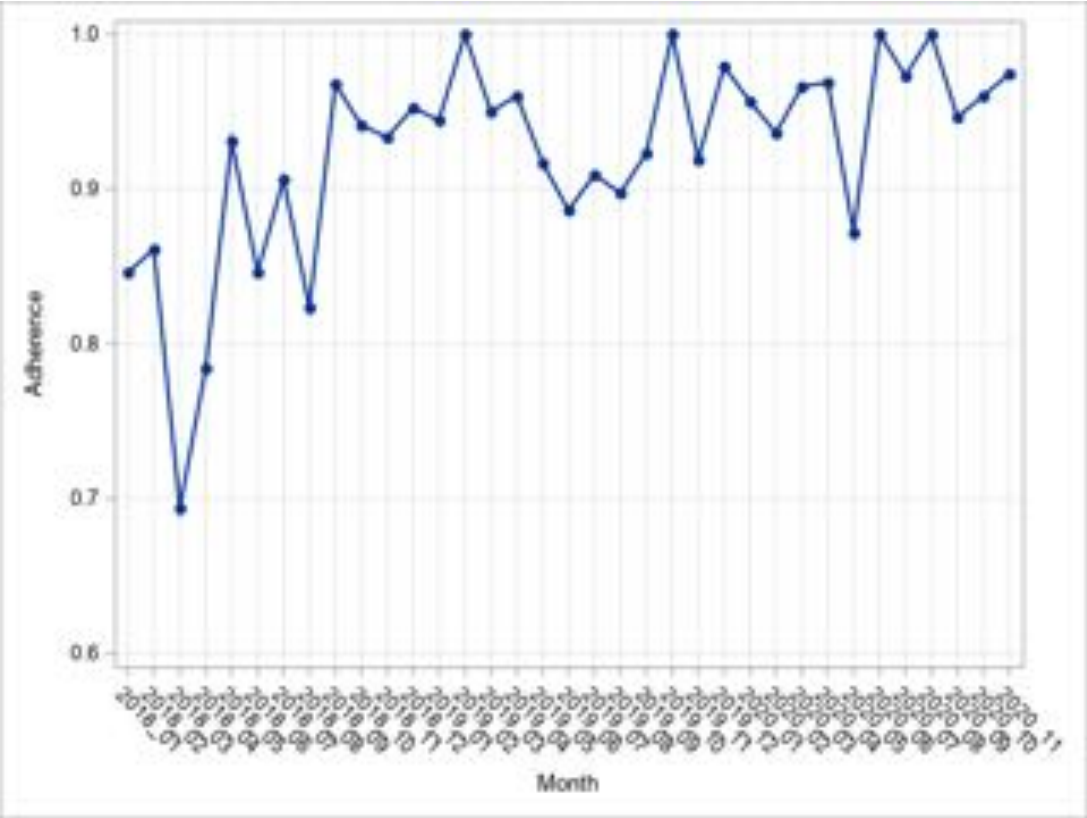

Figure 4

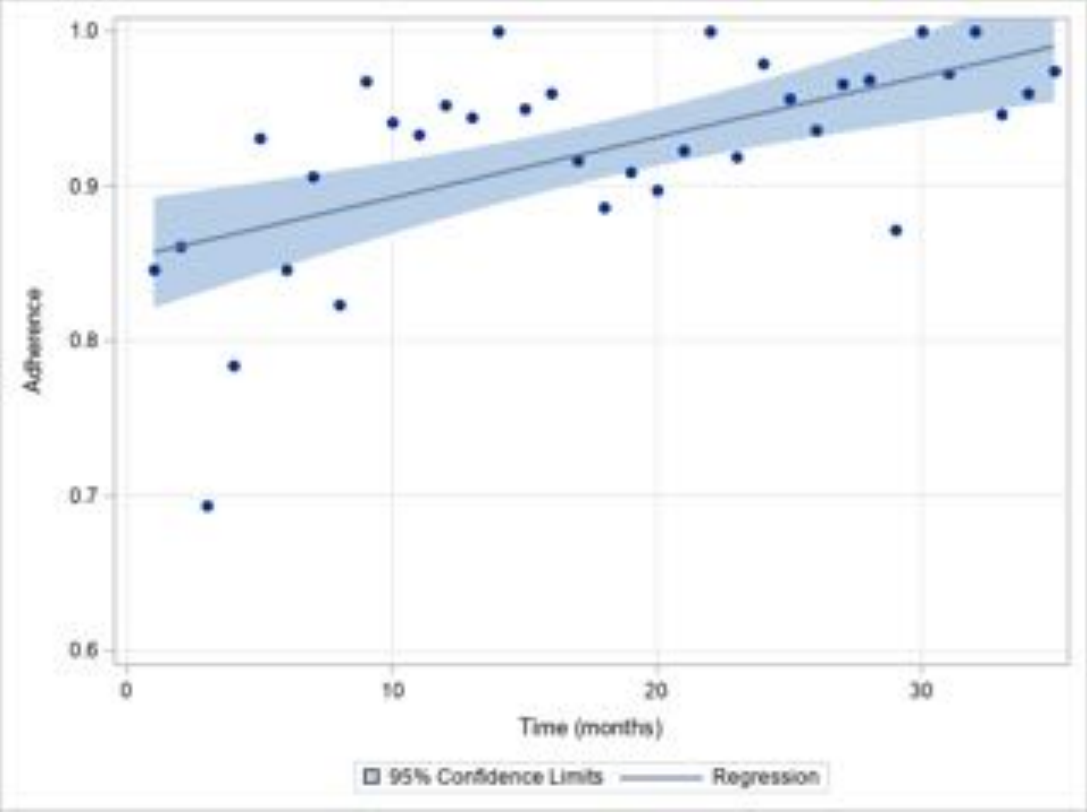

Figure 5

PATIENT SAFETY 15

Level of sedation in Monitored Anesthesia Care (MAC) cases: an observational pilot examination of processed EEG output

Priscilla Nelson[1], Robert White[2], Sarah Wu[1], Patricia F Mack[3]

[1]New York Presbyterian / Weill Cornell Medical College, New York, NY, [2]New York Presbyterian Weill Cornell, New York, NY, [3]Weill Cornell Medicine, New York, NY

INTRODUCTION: Closed claims analyses continue to demonstrate challenges with monitored anesthesia care (MAC) and sedation.[1,2] Oversedation resulting in respiratory depression has been a major source of injuries in MAC cases. An understanding of true depth of sedation is lacking. Available evidence from three studies in gastroenterology using propofol suggest that depth of sedation approach general anesthetic (GA) levels,[3,4,5] yet these findings have not been generalized in wider populations. Processed EEG enables real time depth of anesthesia monitoring. The purpose of this pilot study was to examine depth of anesthesia in a cohort of patient over 50 years of age undergoing MAC procedures to determine the incidence of sedation consistent with levels of GA. We hypothesized that many patients undergoing MAC would reach sedation levels consistent with GA.

METHODS: This pilot study, reviewed by our IRB, was an observational examination of 50 patients over the age of 50 who underwent MAC at a single urban academic center over a 2-month period of time in both operating room and non-operating room settings. The SedLine Sedation monitor was applied to all patients at the start of anesthesia care. Data obtained in two second intervals was collected from the anesthesia start to anesthesia end. The primary outcomes of interest were the level of sedation determined by the Patient Sedation Index (PSI) and the Suppression Ratio (SR). PSI quantifies anesthetic depth using the electroencephalogram (EEG) with a proprietary algorithm. SR is a measure of the degree of burst suppression as a function of time. Sedation consistent with GA is defined as a PSI value <50. Deep sedation is defined as a PSI value <25. Total case time was utilized to determine the percentage of case procedure under GA level sedation. Patients with burst suppression were compared to those without suppression to determine risk factors for deep sedation.

RESULTS: Overall, 50 patients were prospectively evaluated with full chart reviews. These cases ranged across 12 specialties (Table 1) which included proceduralists from surgery, medicine and radiology. The average patient age was 69 years, and 50% of patients demonstrated more than two comorbidities. Median case length was 34.5 minutes, ranging from 7 to 204 minutes (Table 2). Propofol was administered in 94% of procedures, with propofol as the only pharmacologic agent in 32% of procedures. No patients underwent conversion to invasive airway. The median PSI across all patients and timepoints was 43.5 (8.5), with 94% of patients demonstrating PSI values <50. The median percentage of case time with a PSI <50 was 80.4%. Overall, 44% patients had PSI values<25, and 46% demonstrated some degree of burst suppression. The average PSI decreased in early timepoints of a procedure then increased with length of procedure duration (figure 1). Hypotension was common, with 32% of patients requiring vasopressors for blood pressure augmentation. No significant differences were noted in demographics, procedure or anesthetic characteristics of patients who experienced burst suppression ($p>0.05$). No adverse anesthetic events were noted in the 50 patients observed.

CONCLUSION: Most patients over 50 years of age undergoing MAC procedures in this observational heterogenous case examination experienced sedation levels consistent with GA. Nearly half of patients reached levels of deep sedation and experienced burst suppression. No specific risk factors were identified. No patient required placement of endotracheal tube or supraglottic airway and there were no adverse anesthetic events in the population. This data confirms previous reports in specific populations that patients scheduled as MAC spend a significant portion of procedure time under general anesthesia. If confirmed in broader practices and populations, this has implications for clinician and patient education as well as informed consent in procedures in which MAC is requested.

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Figure 1

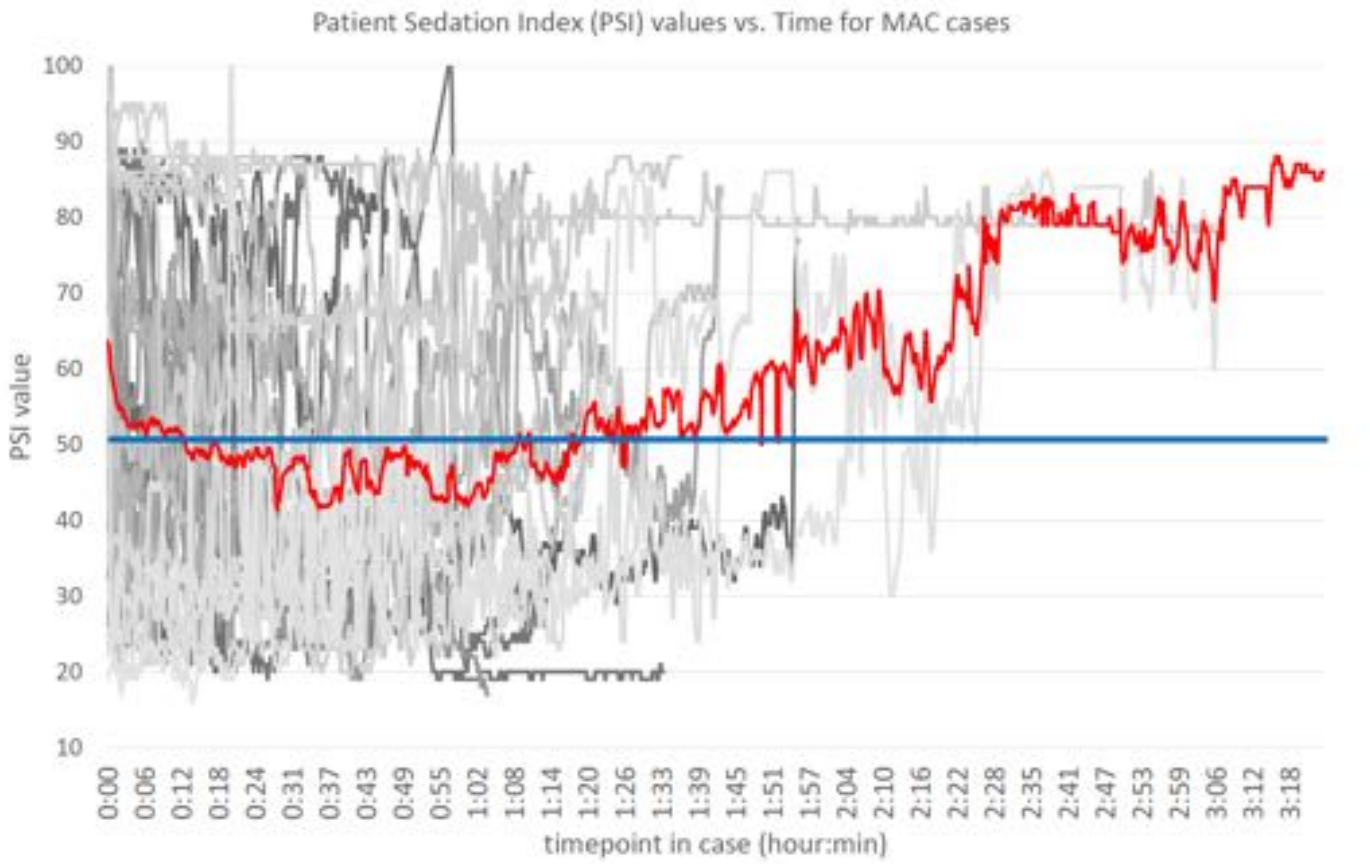

Table 1

Variable	Value	%
Age	68.98 (11.25)	
ASA	2.34 (0.63)	
ASA Median	2	
Baseline HR	74.0 (12.6)	
Wt in KG (mean, SD)	70.4 (19.6)	
BMI	25.6 (7.0)	
Past Medical History		
Stroke/TIA	4	8%
Chronic Kidney Disease	7	14%
Obstructive Sleep Apnea	4	8%
COPD	1	2%
Hypertension	22	44%
Hyperlipidemia	19	38%
Coronary Artery Disease	5	10%
Peripheral Vascular Disease	1	2%
Cardiac Arrythmias	5	10%
Diabetes	6	12%
Asthma	2	4%
GERD	15	30%
Chronic Infectious Disease	5	10%
Rheumatologic Disorder	6	12%
Psychiatric Diagnosis	11	22%
Cancer	20	40%
History of >2 comorbidities	25	50%
Type of Case		
Breast Surgery	1	2%
Electrophysiology	1	2%
Gastroenterology	9	18%
Gynecology	4	8%
General Surgery	14	28%
Interventional Neuroradiology	1	2%
Interventional Radiology	8	16%
Neurosurgery	1	2%
Orthopedics	5	10%
Cardiact Surgery (TAVR)	2	4%
Urology	2	4%
Vascular	2	4%

Table 2

Variable	Value	%
General Case and Pharmacology variables		
Total Case length (mean (SD)) (minute)	54.0 (44.6)	
Total Case length (median IQR) (minute)	34.5, IQR 55	
Case Max, Min	204, 7	
Extra Room time (Mean (SD) (minute)	40.2 (21.3)	
Any propofol administered	47	94%
propofol bolus mean (mg) (SD)	56.0 (64.7)	
propofol gtt highest (mg/kg/min) (SD)	111.9 (38.8)	
propofol gtt lowest (mg/kg/min) (SD)	73.6 (37.5)	
Processed EEG variables		
Mean PSI (SD)	48.1 (11.2)	
Median PSI (IQR)	43.5 (8.5)	
Any PSI <50	47	94%
% of case time PSI <50 median;IQR*	80.4%;52.4%	
Any PSI <25	22	44%
% of case time PSI <25median;IQR**	13.7%;40%	
Any Suppression Ratio (SR)	23	46%
% of case time in SR (mean(sd, median;IQR))***	6.2%;23.7%	
Sedation and Blood pressure variables		
mOAAS score overall, Median (max, min)	2 (3, 0)	
Any MAP <55	7	14%
Time MAP <55 (seconds (SD))	87.3 (331.33)	
Any SBP<85mmHg	10	20%
Time SBP<85 (seconds (SD))	142.5 (376.0)	
Phenylephrine Boluses	16	32%

*in any case noting PSI<50; **of any case noting PSI<25; ***in any case noting a SR

PATIENT SAFETY 16

Effect of intraoperative arterial hypotension on the risk of perioperative stroke after non-cardiac surgery: A retrospective multicenter cohort study

Karuna Wongtangman[1], Luca J Wachtendorf[2], Michael Blank[3], Stephanie Grabitz[1], Felix C Linhardt[3], Omid Azimaraghi[4], Dana Raub[1], Stephanie Pham[3], Samir Kendale[5], Ying Hui Low[6], Timothy Houle[7], Matthias Eikermann[8], Richard pollard[9]

[1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [3]Harvard Medical School, Boston, MA, [4]Beths Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [5]NYU School of Medicine, New York, NY, [6]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [7]Massachusetts General Hospital, Boston, MA, [8]Beth Israel Deaconess Medical Center, Boston, MA, [9]Beth Israel Deaconess medical center, Boston, MA

INTRODUCTION: About one percent of patients undergoing non-cardiac surgery develop ischemic stroke. Perioperative stroke is an underdiagnosed disease – some patients with significant perioperative hypoperfusion of the brain may be diagnosed as perioperative neurocognitive disorder (dPND). We hypothesized that intraoperative hypotension is associated with an increased risk of perioperative ischemic stroke and dPND within 7 days after surgery.

METHODS: Adult, non-cardiac surgical patients undergoing general anesthesia at Beth Israel Deaconess Medical Center and Massachusetts General Hospital between 2005 and 2017 were included in this retrospective cohort study. The exposure was intraoperative hypotension (IOH) defined as mean arterial pressure below 55 mmHg and categorized as none, short (1-15 minutes, median [interquartile range, IQR] 2 [1, 5] minutes) and prolonged (>15 minutes, median [IQR] 21 [17,31] minutes) duration. The primary and key secondary outcomes were early perioperative stroke and dPND within 7 days after surgery. Analyses were adjusted for the preoperative STRoke After Surgery (STRAS) prediction score, work relative value units and duration of surgery.

RESULTS: Among 358,391 included patients, a total of 1,553 (0.4%) experienced an early ischemic stroke and 2,502 (0.7%) dPND. In adjusted analysis, no association of IOH and early perioperative stroke was found (short-duration: adjusted odds ratio [ORadj] 0.95, 95%CI 0.85–1.07, p=0.417; prolonged-duration: ORadj 1.18, 95%CI 0.91–1.55, p=0.220). By contrast, IOH was associated with a duration-dependent increase in the odds of dPND (ORadj 1.46; 95% CI 1.34-1.58; p<0.001 and 1.84; 95% CI 1.53-2.21; p<0.001 for short and long duration of IOH, respectively; p-for-trend<0.001).

CONCLUSION: In patients undergoing non-cardiac surgery, intraoperative hypotension within the range studied did not independently predict early perioperative stroke within 7 days after surgery but was associated with a higher risk of perioperative neurological disorder. Our data indicate that even short durations of mean arterial blood pressure of lower than 55 mm Hg are associated with adverse perioperative neurological outcomes.

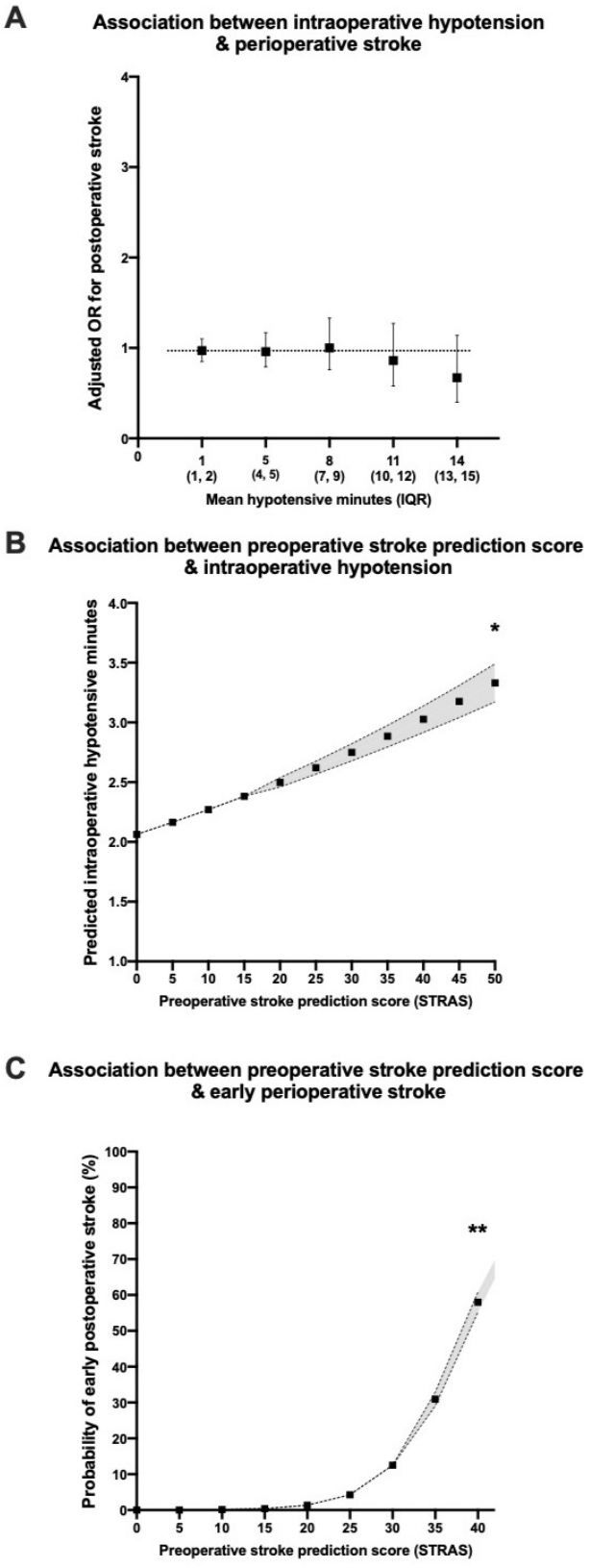

Figure 1. Association between intraoperative hypotension, perioperative stroke and preoperative STRoke After Surgery prediction score (STRAS)

Panel A: Odds of perioperative stroke as a function of the duration of intraoperative hypotension defined as a mean arterial blood pressure (MAP) less than 55 mmHg; squares: adjusted odd ratio (OR), error bars: 95% confidence interval.

Panel B: Duration of intraoperative hypotension (MAP < 55 mmHg) as a function of the preoperatively calculated stroke risk. A higher preoperative stroke prediction score (STRAS) value was associated with higher intraoperative duration of hypotension (*p<0.001). The grey area indicates the 95% confidence interval.

Panel C: Odds of perioperative stroke as a function of the preoperatively calculated stroke risk in per cent. A higher preoperative stroke prediction score was associated with higher probability of stroke (**p<0.001).

PATIENT SAFETY 17

Comparison of ToFscan and TetraGraph during Recovery of Neuromuscular Function in the Post Anesthesia Care Unit

Vivian Hernandez[1], Johnathan R Renew[2], Ilana Logvinov[3], Reka Nemes[4], Zhuo Li[5], Glenn S Murphy[6], Liah Watt[7]

[1]Mayo Clinic, Jacksonville, FL, [2]Mayo Clinic Florida, Jacksonville , FL, [3]Mayo Clinic Florida, Jacksonville, FL, [4]Mayo Clinic, Jacksonville, FL, [5]Mayo Clinic, Jacksonville, United States of America, [6]NorthShore University HealthSystem, Evanston, IL, [7]NorthShore University, Chicago, United States of America

INTRODUCTION: Residual neuromuscular blockade (RNMB) is common in the post-anesthesia care unit (PACU) when neuromuscular blocking agents (NMBAs) are used intraoperatively.[1-3] The use of quantitative neuromuscular monitors can reduce the number of patients with RNMB and its associated complications.[4-6] The ToFscan (Drager, Germany) is a standalone acceleromyography (AMG)-based quantitative monitor; the TetraGraph (Senzime, Sweden) is a standalone electromyography (EMG)-based quantitative monitor. The aim of this randomized, multi-center trial is to compare the performance of the two quantitative monitors throughout various stages of neuromuscular recovery with assessments obtained subjectively by using a peripheral nerve stimulator (PNS). The secondary aim was to determine the overall incidence of postoperative residual weakness and identify whether subjective evaluation provides a reliable indication of adequate neuromuscular function recovery.

METHODS: After IRB approval, consenting adult patients scheduled for elective surgery requiring neuromuscular blockade were enrolled. Intraoperative NMBA management and reversal were at the discretion of the anesthesiologist. Upon arrival to PACU, the ToFscan (TS) and TetraGraph (TG) were placed on opposite arms (dominant and non-dominant hand), based on randomization. Train-of four (TOF) stimulation was performed twice at 50 mA every 15 sec at three time intervals: upon arrival to the PACU (t = 0), and 5 min (t = + 5 min), and 10 min (t = + 10 min) after PACU arrival. RNMB was defined as a mean ratio (TOFR) < 0.9 obtained by either device. A paired t-test compared the mean score for a device in the 3 time periods. Bland-Altman plots expressed the agreement between the two devices. The association between the type of antagonism and RNMB incidence was tested using Fisher's exact test and Wilcoxon rank sum test.

RESULTS: Patients (n=120) from three institutions were enrolled. Five were excluded due to technical issues. TOFRs were higher at all time intervals in the TG compared with TS group. There was no significant difference in the mean TOFRs obtained with the TG and TS at t = 0, and t = + 5. At (t = + 10), there was a statistically significant difference in mean TOFRs obtained with the TG and TS, (0.99 ± 0.14 vs 0.94 ± 0.12, P < 0.001, respectively). The bias between the two devices at t = 0 was 0.03 (95% CI, -0.29 to 0.35, P=0.26; Fig 1a). The bias between the two devices at t = + 5 min was 0.02 (95% CI, -0.36 to 0.40, P=0.54; Fig 1b), and at t = + 10 min it was 0.05 (95% CI, -0.25 to 0.36, P=0.77). The use of a peripheral nerve stimulator (vs. quantitative neuromuscular monitor) was associated with higher incidence of RNMB (75.0% vs 25.0%, p=0.012, respectively). The use of neostigmine (vs. sugammadex) was associated with a higher incidence of RNMB (56.2% vs 43.8%, p < 0.001, respectively) when measured at extubation.

CONCLUSION: This multi-center study demonstrates that the TS and the TG devices provide similar quantitative neuromuscular measurements and they can be used interchangeably in the clinical setting. These measurements differed after the first 10 PACU minutes, as the variability of the TS-obtained measurements increased. This decreased consistency of the AMG-based TS monitor data may be due to the awakening of PACU patients who exhibited involuntary and voluntary withdrawal movements following neurostimulation, thus affecting the consistency of AMG (but not EMG) data. The results suggest that the two technologies yield comparable neuromuscular recovery data, but the TS is more prone to unreliable data in awakening PACU patients. As reported previously, subjective evaluation of neuromuscular responses to PNS is unreliable and results in postoperative neuromuscular weakness.

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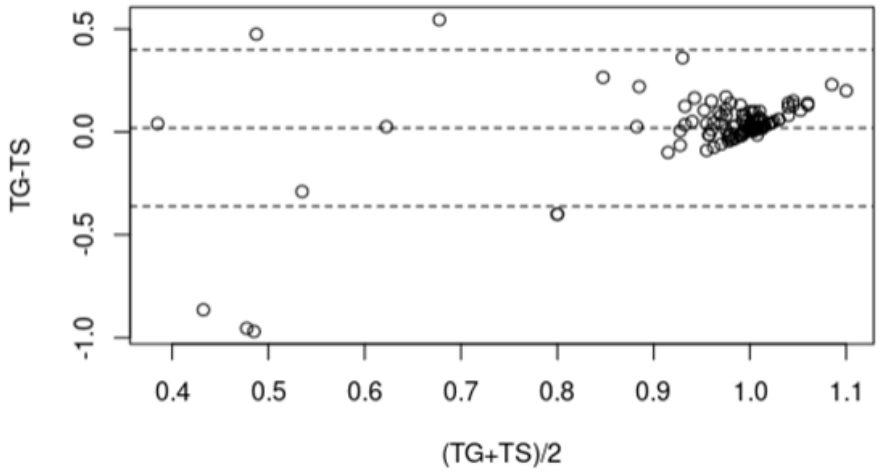

Figure 1

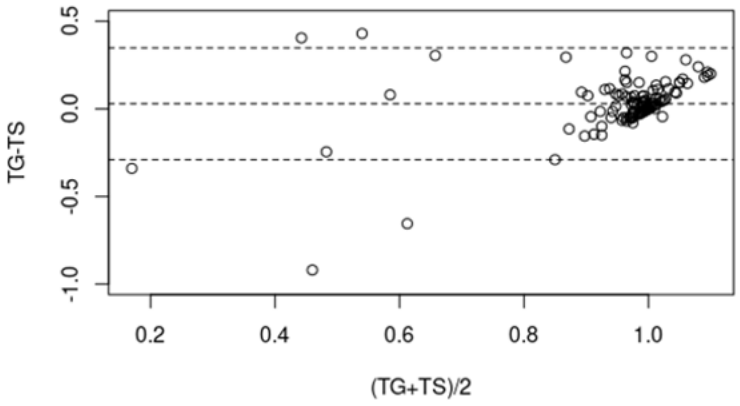

Figure 1b

PATIENT SAFETY 18

Intralesional bleomycin injection and skin hyperpigmentation: A retrospective review of a single centers' experience with a standardized skin-protective protocol

Jacob Heninger[1], Daniel Thompson[2]

[1]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [2]Ann & Robert H Lurie Children's Hospital, Chicago , IL

INTRODUCTION: Bleomycin is a cytotoxic antibiotic that can be used to treat vascular anomalies given its sclerosing effect on vascular endothelium. With systemic use, bleomycin is known to cause flagellate hyperpigmentation; however, there is evidence that even the smaller doses used for more targeted, localized injections can precipitate skin hyperpigmentation. Given the use of bleomycin to treat vascular malformations has increased in recent years, we implemented a skin protective protocol aiming to mitigate this preventable side effect. Of particular concern is the development of hyperpigmentation in areas of skin micro-trauma, such as on the face from taping endotracheal tube and eyes, and on the chest from sticky ECG leads. The shearing force from tape removal or the pressure from monitor cords and gown folds can cause the drug to leak into the interstitial space, where it is unable to deactivated due to the lack of bleomycin hydrolase, leading to darkening of the skin. The exact incidence of this complication is unknown but thought to be underreported. We conducted a retrospective chart review of patients who underwent intralesional bleomycin injection since implementation of our skin protective protocol to evaluate its impact on hyperpigmentation.

METHODS: Cases performed from November 2019 to December 2020 were obtained for chart review. Age, bleomycin dose, anatomic location of lesion, type of lesion, adherence to protocol, side-effects and length of follow up were recorded. The charts were reviewed for adherence to skin precaution protocol and all post procedure notes were reviewed for documentation of skin hyperpigmentation. The protocol emphasizes avoidance of adhesives and minimizing pressure points to the patient. All gowns are removed to prevent the folds from creating pressure points, and the patient lies on a smooth flat surface, typically the flat side of egg create foam. Intravenous lines are secured with cotton roll and self-adherent elastic wrap with 2 transparent dressings stuck to each other to create a viewing window. Endotracheal tubes are secured with padded ties and the eyes are lubricated with ointment as opposed to tape. The adhesive of ECG leads is removed and immersed in jelly on the chest. The SpO2 probe adhesive sticker is removed and bare probe is secured around a finger with self-adherent elastic wrap. Prior to implementation, anesthesiology, interventional radiology, and nursing staff were educated via grand rounds, department emails and a written protocol. All necessary supplies are stocked and stored in a bucket near the interventional radiology suite.

RESULTS: Since the implementation of the skin protective protocol in November 2019, 12 patients received a total of 35 injections of bleomycin (5-10mg per injection) for various vascular malformations. Skin protective precautions were employed in all cases. Only 1 patient was lost to follow up. 2 patients scratched around the vascular access site in the PACU and developed hyperpigmentation both of which resolved. 1 patient developed a rash at the IV site (antecubital fossa) which was evaluated by dermatology and deemed to be a viral exanthem. Ages, anatomic location, number of injections per patient and length of follow up are presented in table 1.

CONCLUSION: Since the implementation of a skin protective protocol, no cases of skin hyperpigmentation attributable to adhesive or pressure points were discovered on retrospective chart review. The protocol was followed 100% of the time with no identifiable barriers to implementation. There are numerous limitations of this single center retrospective review. The small sample size limits generalizability. Follow up was limited and patients were not formally assed for hyperpigmentation. Documented adherence to the protocol does not ensure that such measures were actually taken. Post procedure documentation may be inaccurate. Given the ethical concerns of conducting a trial where skin protection measures are forgone, this retrospective review aims to inform and present our results regarding skin hyperpigmentation after intralesional bleomycin injections. Given that the only cases of hyperpigmentation were due to patients scratching themselves post procedurally, administering an antihistamine intraoperatively may decrease incidence of scratching. Future studies are needed to further evaluate the true incidence of hyperpigmentation following intralesional bleomycin injection and efficacy of skin protective measures.

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PATIENT SAFETY 19

The addition of a PACU transfer to the flow of ICU-bound postoperative patients is not associated with increased complication rates

Gina C Russell[1], Athena Christakos[2], Alexandra M Mapp[3], LeRoi S Hicks[3], Meghan Lane-Fall[2]

[1]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA, [3]Christiana Care Health System, Newark, DE

INTRODUCTION: Perioperative handovers are a potential source of patient harm. Standardization of handoffs from the operating room (OR) to the intensive care unit (ICU) has been demonstrated to improve communication and outcomes, but prior studies have not included patients admitted to the ICU via the post anesthesia care unit (PACU). The purpose of this study was to determine whether a PACU transfer prior to ICU admission (i.e., an additional handoff) is associated with patient outcomes for ICU-bound postoperative patients.

METHODS: This IRB-approved, retrospective observational cohort study was conducted at a large tertiary care independent academic medical center. This project was part of a research study to standardize OR-to-ICU handoffs. Electronic medical record patient-level data from calendar year 2017 were combined with outcome data from Vizient. All patients transmitted from the OR to the ICU (with or without an intervening PACU stop) were deemed eligible. Patients with missing data on preoperative location were excluded. The primary outcome was a composite rate of major postoperative complications, including in-hospital stroke, myocardial infarction, aspiration pneumonia, and postoperative infection. We used bivariate statistical testing to compare cohort demographics and tested the association of a PACU stop with postoperative complications using a negative binomial model that adjusted for patient age, gender, comorbidities, and surgery type.

RESULTS: Of all eligible patients (n=915), 567 underwent direct OR-to-ICU handovers and 348 included an additional PACU transfer (OR-to-PACU-to-ICU). Group demographics differed based on gender and age, with direct OR-to-ICU transfers including more male (64.5% vs. 50.0%, $p<0.001$) and older (66.7 vs. 63.3 years, $p=0.004$) patients. Cardiac surgery patients comprised a majority direct OR-to-ICU observations (74.6%), while neurosurgery patients were most represented among OR-to-PACU-to-ICU observations (39.4%). After multivariable adjustment, there was no statistically significant difference in the rate of postoperative complications between the two groups (10.0% vs 14.4% for OR-to-ICU and OR-to-PACU-to-ICU flows, respectively, $p>0.05$).

CONCLUSION: The addition of a PACU transfer was not associated with greater rates of postoperative complications among patients requiring postoperative ICU-level care. Additional research is needed to determine how to measure the effects of patient flow on outcomes, including ways to adjust for confounding by indication.

PATIENT SAFETY 20

Intraoperative Handoffs' Impact on Surgeon-Anesthesiologist Relations

Aubrey L Samost-Williams[1], Allison Doney[1], May Pian-Smith[2]

[1]Massachusetts General Hospital, Boston, MA, [2]Harvard Medical school, Boston, MA

INTRODUCTION: Intraoperative handoffs are a high-risk time in a patient's perioperative care, yet there remains no standard approach for information to be passed along. Retrospective studies have shown that the number of anesthesia providers in a case was correlated with incidence of surgical complications.[1,2] Even beyond this, intraoperative handoffs when done well can facilitate communication in the surgeon-anesthesiologist dyad[3]. In this study, we sought to understand the content of intraoperative handoffs and the role that the anesthesia handoff plays in promoting multi-disciplinary communication.

METHODS: This was an observational study using a convenience sample of operating room cases at a large academic medical center. Handoffs were observed by members of the research team as well as by trained anesthesia clinicians receiving handoffs. Subjects giving handoff were unaware of the observations. Data were analyzed first with descriptive statistics. Paired t tests and ANOVA was used to assess for differences between role groups, surgery type, break time, and anesthesia versus multidisciplinary surgical information. All statistics were done with Microsoft Excel. This quality improvement initiative was IRB exempt.

RESULTS: 45 lunch break handoffs and 35 end-of-day handoffs were observed. The most common elements of the intraoperative handoffs were surgical procedure (95.1%) and past medical history (88.9%) with the leas common being surgery specific medications (28.4%) and tasks to do (37.1%). 5.7% of handoffs included an introduction of the new anesthesia provider to the surgical team. Handoffs were broken down first by role group – anesthesiologist, nurse anesthetist, or trainee. These role groups included significantly different information in their handoffs ($p<0.001$). Figure 1 shows the elements included by role group. Handoff elements were then classified as multidisciplinary or anesthesia specific. Multidisciplinary elements were overall passed along in 42.9% of handoffs versus anesthesia specific elements in 61.0% of handoffs observed ($p=0.2$) with no significant differences by role group, shown in Figure 2.

CONCLUSION: Handoffs are an opportunity to share information amongst anesthesiologists and anesthetists and an opportunity to deliberately reinforce information sharing and alignment with surgical colleagues. When we start cases at our institution we have a multidisciplinary huddle where the surgeon-anesthesiologist dyad communicates about the patient and the procedure as well as sharing names to facilitate communication throughout the case. When we hand over the case to a new anesthesia team, we have lost that direct multidisciplinary communication, and key surgical information, such as surgery specific conditions, are not passed along more than half the time. Additionally, without introducing new team members to the surgical team we have raised the barrier to communication across the drapes that we had sought to lower by sharing names during the pre-operative huddles. Intraoperative handoffs have real impacts on quality of care, and based on our data, we argue that some of that impact comes from disruption to the surgeon-anesthesiologist dyad function.

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Figure 1: Percentage of handoffs including each listed element broken down by provider role group.

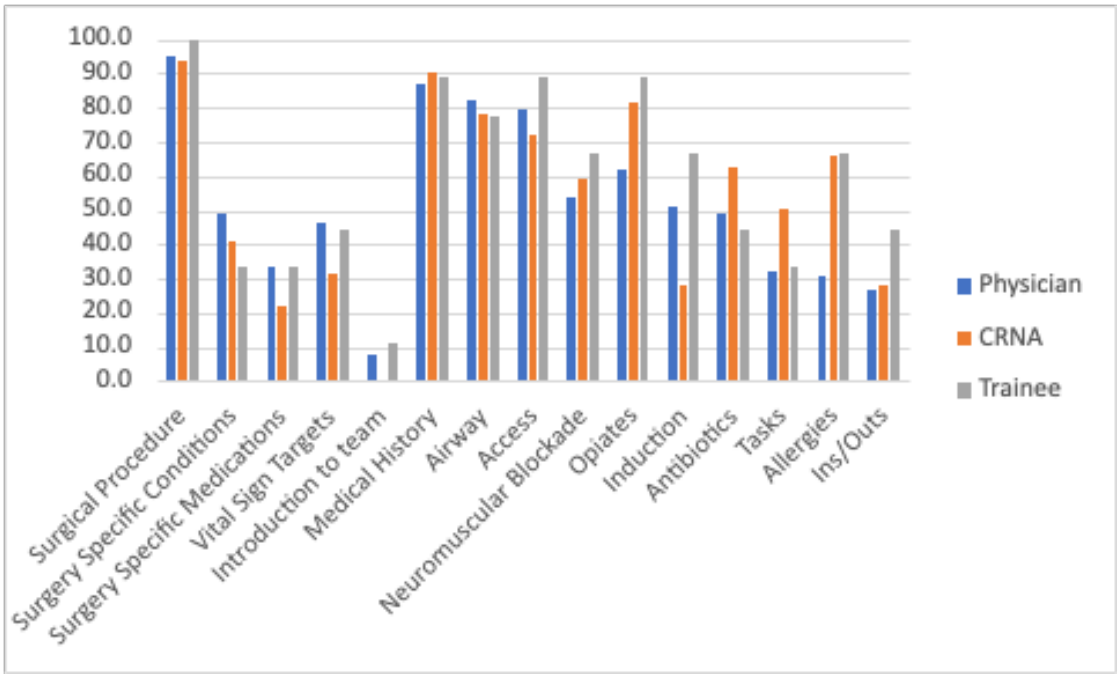
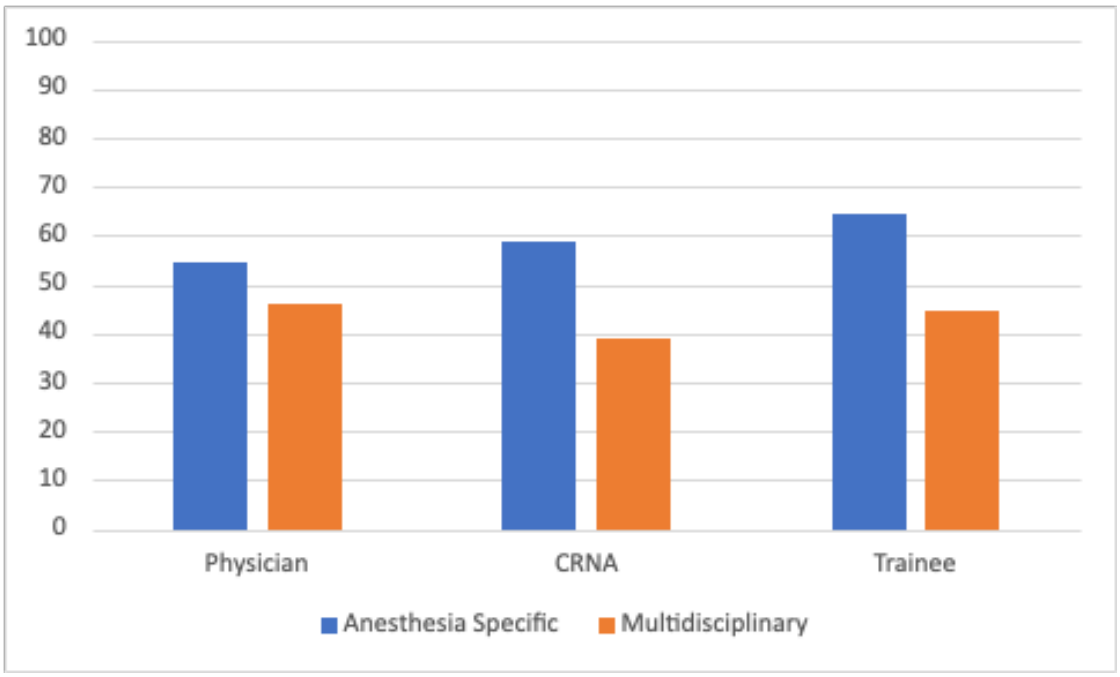


Figure 2: Percentage of handoffs including anesthesia specific elements versus multidisciplinary elements broken down by role group



PATIENT SAFETY 21

IARS Late-Breaking Abstract Submission - 1365

Azin Kheirandish[1], JD Williams[2], Colby Simmons[1], Jason Brainard[3]

[1]University of Colorado School of Medicine, Aurora, CO, [2]University of Colorado Hospital, Aurora, CO, [3]University of Colorado, Aurora, CO

INTRODUCTION: Peripheral intravenous (PIV) catheter placement is the most common invasive procedure in hospitalized patients. Complications associated with PIVs can limit longevity of a peripheral line and result in repeated unnecessary procedures.[1,2] The majority of PIV complications are related to degree of catheter stabilization, provided by the dressing.[3,4] Literature review demonstrates a paucity of cost-effective dressings that provide appropriatestability.[5] Appropriate choice of PIV dressing, along with proper training, can significantly reduce complication rates, lower costs, and improve patient comfort and nursing satisfaction.

METHODS: A quality assurance project was implemented comparing a new PIV dressing (SorbaView ShieldTM, a dressing and stabilization device in one) to the standard of care device (StatlockTM, a stabilization device) at the University of Colorado Hospital (UCH). This project was approved as quality assurance work per institutional policies. Surgical patients (n =174) in the pre-operative care unit undergoing spine, joint, neurosurgical or open abdominal procedures, were initially randomized to either SorbaviewTM (n=101) or StatlockTM (n=73), but additional patients with longer anticipated length-of-stay were added in the trial group to assess for complications with longer indwell times. Pre-operative Registered Nurses (RN), who received education on the new dressing prior to project initiation, placed both styles of PIV dressings prior to surgery. Nursing staff was surveyed at time of dressing placement for ease of use and satisfaction. Patients were then followed daily during their inpatient admission to monitor for possible PIV complications, including: skin irritation, phlebitis, dislodgment, infiltration, and occlusion. Patient comfort and nursing satisfaction was also assessed by a daily survey on each consecutive post-operative day. Survey results were analyzed with descriptive statistics and Student's t-Test (unpaired, two-tailed). Significance was set at a p-value of < 0.05 for all analyses. Qualitative summary comments were compiled. Financial analysis was also performed by UCH Values Analysis, using PIV data from prior years and comparing per unit cost of each device.

RESULTS: All consecutive patients who were selected were included in the study and analysis. Of the 174 total PIV dressings placed, 73 were StatlockTM (standard of care) with a total catheter indwell time of 170 days and average indwell time of 2.3 days. A total of 101 patients were included in the SorbaViewTM group (new dressing), with a total catheter indwell time of 289 days and average indwell time of 2.9 days. StatlockTM had a higher incidence of overall complications (35.6%, n=26), compared to SorbaviewTM (12.9%, n=13) dressing (Table 1). Survey of pre-operative RNs at time of dressing application showed statistically-significant higher satisfaction for the SorbaviewTM dressing when assessing for adhesive ($p = 0.02$), stability ($p = 0.009$), efficiency ($p = 0.02$), and overall satisfaction ($p = 0.008$, Figure 1). Ease of application was also higher for the SorbaviewTM at time of placement, although it was not statistically significant (p=0.07). Follow-up survey during each consecutive post-operative day showed statistically-significant higher rating for SorbaviewTM across all categories including: stability (p=0.0004), adhesive (p=0.002) and overall satisfaction (p=0.0002, Figure 2). Patient comfort was also significantly higher with SorbaviewTM both at time of PIV placement (p=0.00009) and in daily follow up surveys (p=0.0001, Figure 3). Cost comparison of the two dressings, assuming a similar volume of PIVs and system-wide change, estimated a total system savings of $544,108 per year.

CONCLUSION: At project completion, SorbaView ShieldTM showed statistically significant higher ratings across all categories: stability, adhesive quality, and overall satisfaction. In addition, overall cost of SorbaViewTM provided annual cost savings of ~$500,000. In conclusion, the SorbaView ShieldTM PIV dressing can provide better stability for PIV securement, with lower rates of complications, higher patient and nursing satisfaction, and lower cost to the health system.

Table 1. Peripheral IV Complications

Complication Type	Statlock (control)	Sorbaview Shield (trial)
Phlebitis	0	0
Dislodgement	2	2
Occlusion	5	1
Infiltration	11	9
Skin irritation	3	1
Removal Problems	5†	0
Other complications	2x insertion failures‡	None
Premature dressing replacement (no complication, IV functional)	3	0

†Statlock adhesive difficult to remove, *resulted in multiple skin tears*
‡Unable to place Statlock near knuckles

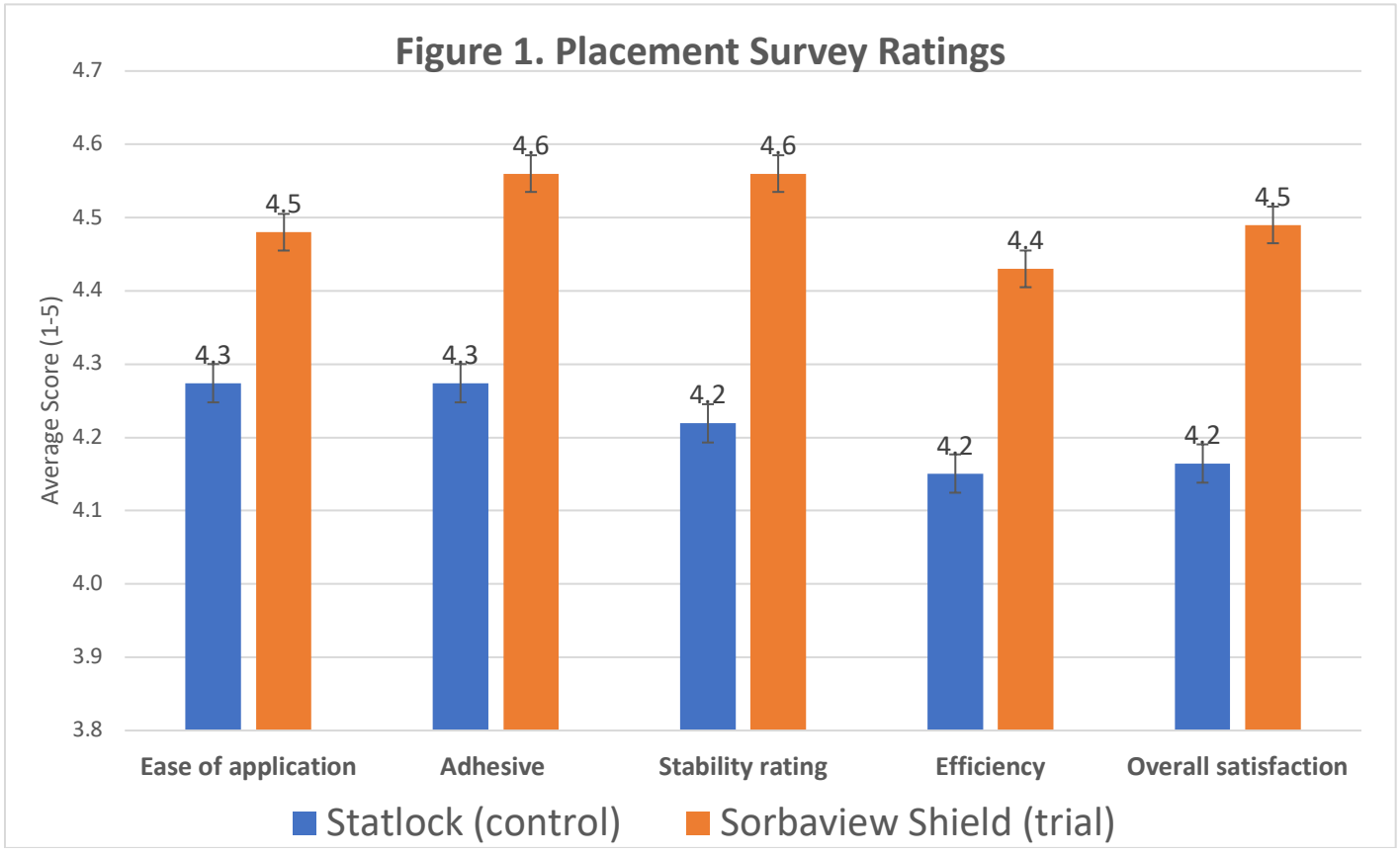


Figure 2. Maintenance Survey

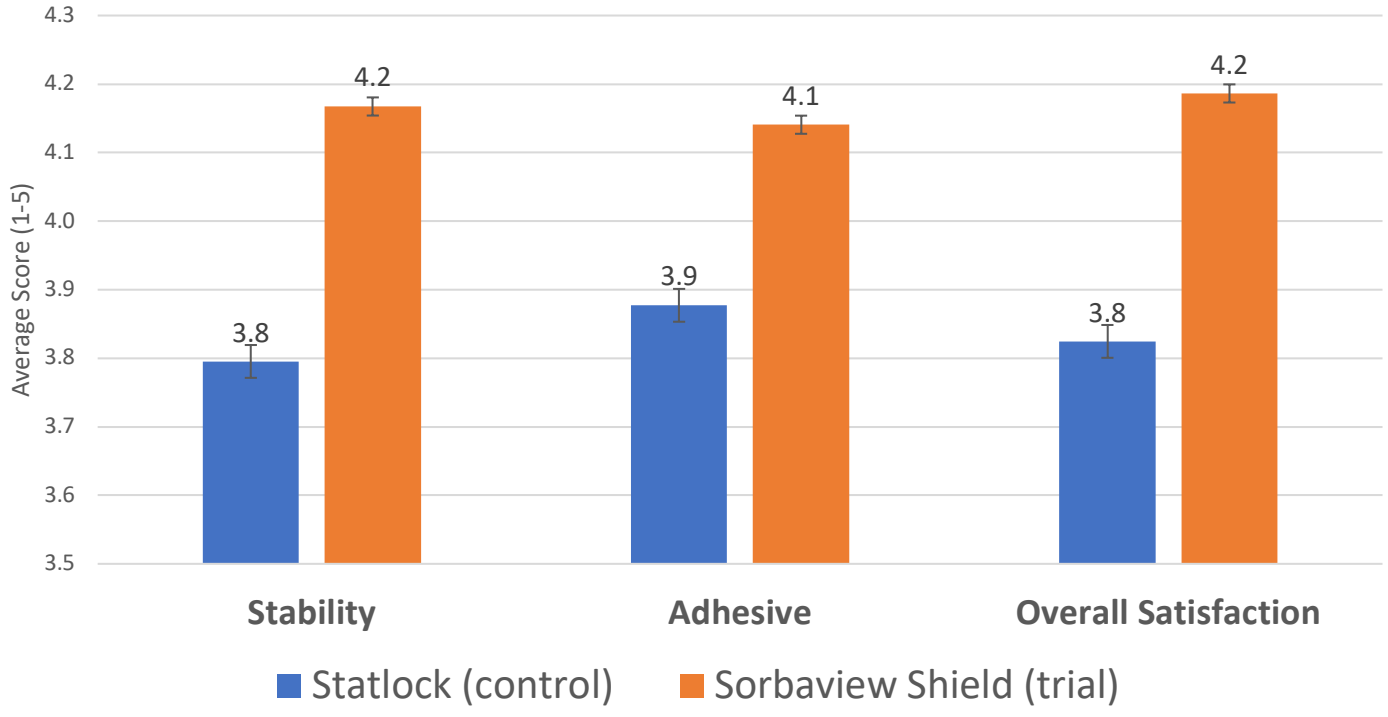
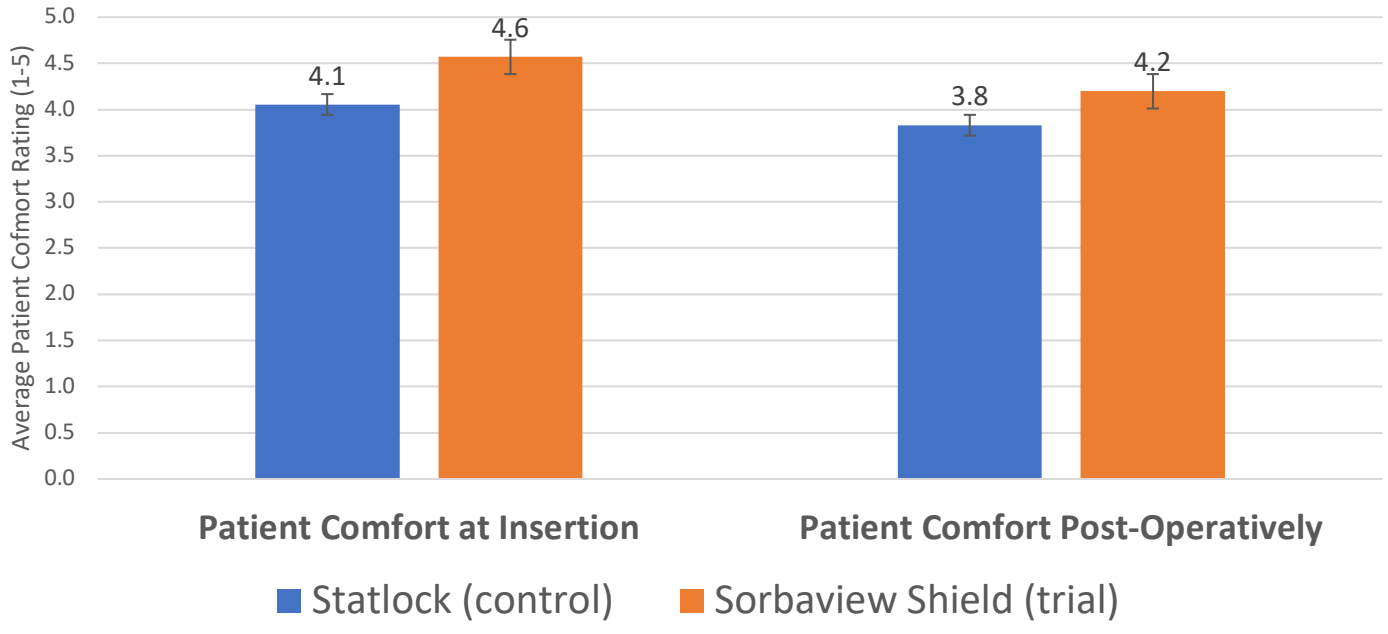


Figure 3. Patient Comfort



PATIENT SAFETY 22

Reducing Opioid Induced Respiratory Depression in Post-Operative Arthroplasty Patients

Anoop Chhina[1], William T Peruzzi[2], Gary Loyd[2], Donald H Penning[2], Jie X Tang[2], Peter Boateng[2]

[1]Henry Ford hospital, Detroit, MI, [2]Henry Ford Health System, Detroit, MI

INTRODUCTION: Pain management in post-operative hospitalized patients often involves the use of opioids and other potential sedating medications. However, with an aging population accompanied by increasing co-morbidities, there is growing concern for opioid induced respiratory depression (OIRD). In hospitalized patients, OIRD is cited as a major cause of preventable adverse events. There is lack of consensus on how to identify patients at risk and which monitoring modalities are most effective at reducing this risk. Several tools have been suggested for identification of patients at high risk of developing OIRD, including Michigan Opioid Safety Score (MOSS) and Opioid Predictive Risk Assessment Tool (OPRAT), PRODIGY score. Based on our own Henry Ford Health System (HFHS) data as well as literature review, we modified the existing OPRAT into the HFHS OPRAT tool which we believe is more clinically applicable. Our study aimed to compare two clinical tools on their efficacy in predicting opioid induced respiratory depression (OIRD), as well as to determine whether our remote monitoring strategy reduces naloxone usage which serves as a marker for OIRD.

METHODS: Masimo SafetyNet system was implemented in October 2018 for post operative arthroplasty patients. Post-operative arthroplasty 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 total joint arthroplasty patients at HFH 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 are subjected to continuous pulse oximetry with either acoustic respiratory rate monitor or end-tidal carbon dioxide monitor. Data was collected from Masimo SafetyNet monitoring system and analyzed to see the predictability of 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. We also compared the rates of naloxone usage on arthroplasty patients with remote monitoring in place to a historical cohort (2017).

RESULTS: There was significant reduction in naloxone use over one year study period when compared to historical cohort. Retrospective data analysis from Masimo SafetyNet monitoring system shows that the HFHS OPRAT score when compared with MOSS score has higher predictability of recognizing Opioid Induced Respiratory Depression.

CONCLUSION: Upon analysis of data from naloxone administration after implementation of the Masimo Safety Net System, it is evident that remote monitoring system can help with early detection of OIRD, and it can be effective in other inpatient areas, and especially for post operative patients. HFHS OPRAT score has higher predictability of recognizing OIRD as compared to MOSS score. Further data analysis is in progress which includes, but not limited to the frequency of OIRD, types of alerts captured during the admission and prior to naloxone administration. Upon validation of HFHS OPRAT tool in other inpatient populations, goal is to utilize it for identifying high risk patients who can benefit for more intensive monitoring in the post operative period.

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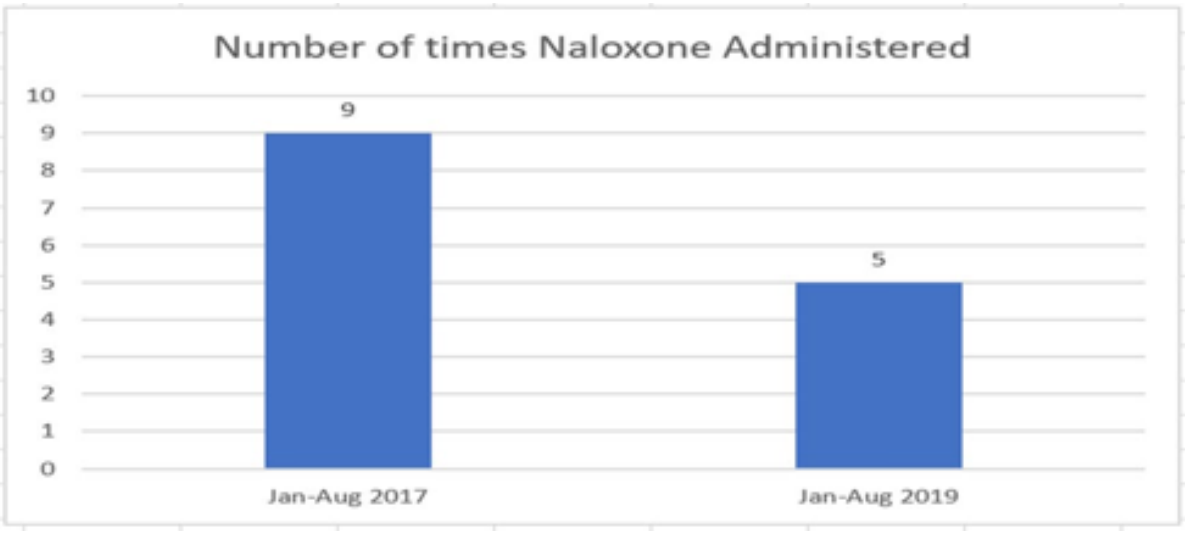
Naloxone administration compared from January – December 2017 & January – December 2019.



OPRAT vs MOSS

	AUC		Fitted Model (all data)	
Predictor	Training	Test	OR (95% CI)	p-value
MOSS Score	0.967	0.696	1.01 (0.49, 2.05)	0.977
OPRAT Points	0.967	0.831	1.13 (1.03, 1.25)	0.0125

PATIENT SAFETY 23

Limitations of Colorimetric $etCO_2$ Detection during Cardiopulmonary Resuscitation

William J Cleveland[1], Alyssa K Streff[1], Matthew Barajas[1], Matthew J Hampton[1], Zhu Li[1], Matthias L Riess[2]

[1]Vanderbilt University Medical Center, Nashville, TN, [2]TVHS VA Medical Center & Vanderbilt University Medical Center, Nashville, TN

INTRODUCTION: During cardiopulmonary resuscitation (CPR), display of end tidal carbon dioxide ($etCO_2$) is critical for two reasons: 1) to determine proper placement of the endotracheal tube, and 2) to assess cardiac output during CPR and/or return of spontaneous circulation (ROSC). Colorimetric $etCO_2$ detectors allow for rapid and instant visual feedback of the $etCO_2$. However, these devices rely on optically differentiating a gradient between two different colors. We investigated how well colorimetric $etCO_2$ detection is able to differentiate between different CO_2 concentrations between 0 and 10% (0 and 76 mmHg) and, thus, would be suitable for use in confirming proper endotracheal tube placement vs assessing cardiac output.

METHODS: A tank of 100% CO_2 and a tank of 100% O_2 were connected to an electronically controlled gas mixer (GSM-4, CWE Inc) that allows for precise control of the gas composition. Its output was connected in line with a colorimetric $etCO_2$ (Easy Cap II CO_2 Detector, Nellcor) and an electronic capnograph (Capnogard $ETCO_2$ Monitor 1265, Novametrix) to verify the chosen percentage of CO_2. The percentage of CO_2 was then increased from 0% up to 10% in increments of 1% and back down to 0% to ensure the color change was reversible. A video camera was used to monitor the color change in the detector and shots from the video were analyzed using color analysis software to determine the Red/Green/Blue (RGB) color values of the detector.

RESULTS: Changes in the color of the $etCO_2$ detector as well as their respective RGB values are displayed for each CO_2% level (Fig 1). The largest change occurred between 1% and 2% CO_2 when the color changed from purple to yellow with corresponding RGB values changing from 184/135/179 to 225/186/168, respectively. Otherwise, all further changes in RGB values were relatively small with equally small changes in the color of the detector.

CONCLUSION: Based on the unexpectedly limited visual changes in the colorimetric $etCO_2$ detector, it is possible to use it to determine the proper placement of an endotracheal tube, providing the $etCO_2$ is 2% or higher. Meaningful changes in $etCO_2$ beyond 2%, however, cannot be discriminated so that colorimetric $etCO_2$ detection is not useful during CPR to assess the quality of chest compressions or ROSC. Instead, if available, quantitative capnography should be used during CPR.

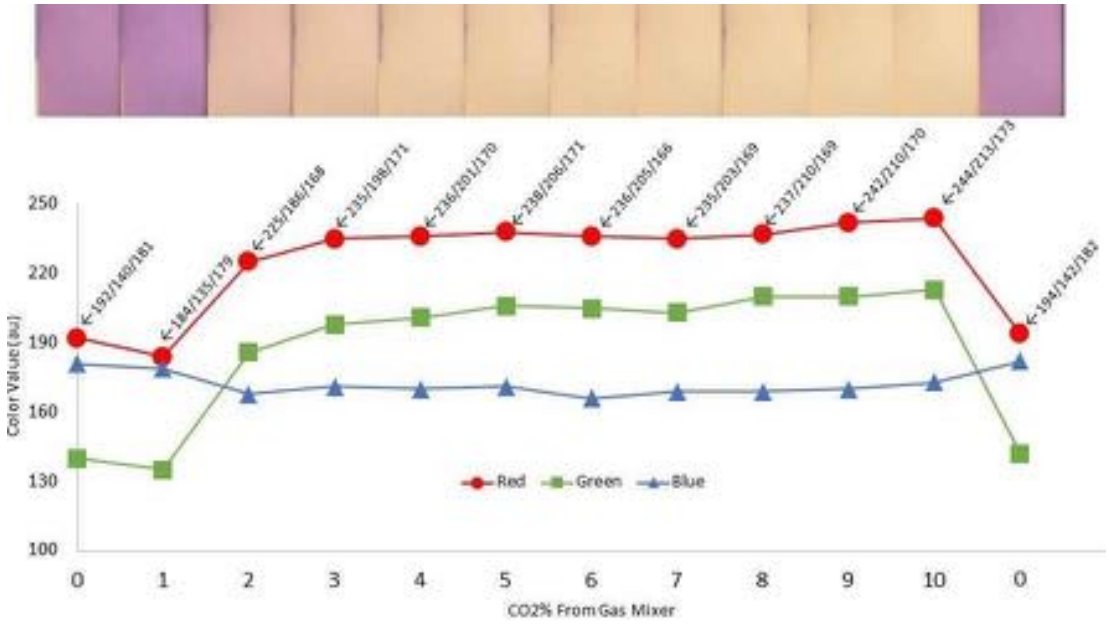


Figure 1

Subspecialty Abstracts

PEDIATRIC ANESTHESIOLOGY

PEDIATRIC ANESTHESIOLOGY 1

Epidural analgesia for Kasai portoenterostomy

Evelyn E Bae[1], Arjunan Ganesh[2], Harshad Gurnaney[1]

[1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]The Children's Hospital of Philadelphia, PHiladelphia, PA

INTRODUCTION: Biliary atresia is a rare obstructive cholangiopathy that presents in young infants. A Kasai portoenterostomy is the main intervention shown to improve survival with the native liver, with infants typically undergoing surgical correction within the first year of life. Options for postoperative analgesia for a Kasai portoenterostomy include systemic opioids (intravenous and enteral) and epidural analgesia. Systemic opioids in young infants can be associated with a higher risk of side effects such as respiratory depression, sedation, hypotension, vomiting, and constipation. In this study, we aimed to compare postoperative outcomes of patients who received continuous epidural analgesia to those that did not have an epidural for analgesia following a Kasai procedure. We hypothesized that those receiving epidurals would have lower pain scores, lower opioid requirements, and shorter length of stays postoperatively.

METHODS: We conducted a retrospective cohort study of 91 infants with biliary atresia undergoing a Kasai portoenterostomy between January 1, 2009 and September 1, 2019 at the Children's Hospital of Philadelphia. Our primary outcome of interest was total postoperative opioid consumption, in morphine equivalents, on postoperative days 0 through 3. Secondary outcomes were median pain scores on postoperative days 0 through 3 using the FLACC scale, median hospital length of stay, number of ICU admissions, and postoperative oxygen requirement in the two groups. Descriptive statistics was used to characterize these measures. For the primary outcome of total postoperative opioid consumption, means and 95% confidence intervals values were tabulated for both groups and compared using a T-test. In order to characterize the quality of analgesia between the two groups, postoperative pain scores during the first 72 hours were compared between the 2 groups using the Wilcoxon rank sum test.

RESULTS: Of the 91 patients who underwent Kasai portoenterostomy for biliary atresia, 69% (n = 63) received intraoperative continuous epidural catheters for postoperative analgesia while 31% of patients did not (n = 28) (Table 1). Patients who received epidurals had significantly lower total opioid requirements postoperatively (0.52, 95% CI [0.38-0.67]) compared to the non-epidural group (1.15, 95% CI [0.8, 1.48], $p < 0.01$). (Table 2). Median pain scores were also significantly lower in the epidural group on postoperative day 0 (0, [0,1]) compared to the non-epidural group (2, [0,3]) (Table 3). Median length of stay in the epidural group was 8.4 (6.4, 10) days compared to 11.7 (6.4, 17.1) days in the non-epidural group. Patients without epidurals had significantly higher rates of unplanned ICU admissions (36% epidural group vs. 3.3% non-epidural group, $p < 0.01$) and also had higher rates of postoperative oxygen requirements (32.1% vs. 11.3%) though the latter did not reach statistical significance (Table 2). The average duration of the caudally threaded epidural catheter was 45.8 (43.1, 48.8) hours. In 2 patients, FFP was administered prior to the removal of the epidural catheter secondary to an elevated INR postoperatively.

CONCLUSION: The use of continuous thoracic epidural analgesia significantly decreased total postoperative opioid consumption and median pain scores on postoperative day 0 in infants undergoing open Kasai portoenterostomy. Epidural analgesia may be an effective method to decrease opioid requirements, while improving early postoperative pain control following Kasai portoenterostomy.

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Table 1.

	Epidural (63)	No Epidural (28)
Age (days) (mean (sd))	67 (37)	70 (36)
Weight	4.6 (1)	4.3 (0.8)
ASA	3 (2-4)	3 (2-4)

Table 2.

Morphine equivalents Mean (CI)	Epidural	No Epidural	p value
POD #0	0.1 (0.08, 0.13)	0.34 (0.24, 0.44)	<0.01
POD#1	0.18 (0.14, 0.23)	0.41 (0.31, 0.51)	<0.01
POD#2	0.13 (0.09, 0.16)	0.26 (0.15, 0.37)	<0.01
POD#3	0.11 (0, 0.21)	0.15 (0.05, 0.24)	0.63
Total	0.52 (0.38, 0.67)	1.15 (0.8, 1.48)	<0.01
Median Length of stay	8.3 (6.4, 10.2)	12.1 (6.4, 17.9)	0.1
ICU admission (Y/N)	2/58 (3.3%)	9/16 (36 %)	<0.01
Post-op oxygen requirement (Y/N)	7/55 (11.3%)	9/19 (32.1%)	0.02

Table 3.

Median Pain Scores (Median(IQR))	Epidural	No Epidural	P value
Pain POD#0	0 (0, 1)	2 (0, 3)	<0.01
Pain POD#1	0 (0, 2)	1 (0, 3)	0.1
Pain POD#2	0 (0, 0)	0 (0, 1)	0.19
Pain POD#3	0 (0, 0)	0 (0, 0)	0.1

PEDIATRIC ANESTHESIOLOGY 2

Enhanced Recovery after Pediatric Congenital Heart Repair with Erector Spinae Plane Blockade: An Ongoing Prospective, Randomized Controlled Trial

Charles K Lee[1], Thomas Caruso[2], Kiley Lawrence[1], Ahtziri Fonseca[2], Gail Boltz[2], Zoel Quinonez[2], Katsuhide Maeda[2], Ban Tsui[2]

[1]Stanford University School of Medicine, Stanford, CA, [2]Lucile Packard Children's Hospital Stanford, Stanford, CA

INTRODUCTION: Children who undergo congenital heart repair are at high risk for morbidity. Prolonged postoperative intubation is associated with high mortality, long ICU stays, and long hospital stays. While intubated, children are typically sedated with opioids, which are associated with increased risks of pneumonia. Bilateral ESPB catheters have been described as effective regional anesthesia during cardiac surgery.[1] Unlike paravertebral blocks, the ESPB is superficial with a lower risk of pneumothorax. Given the potential opioid-sparing benefits of ESPB catheters, we report the preliminary findings of an ongoing prospective, randomized controlled trial examining bilateral ESPB compared to standard of care (SOC). The primary aim was to determine whether lidocaine ESPB reduces CVICU length of stay (LOS) compared to SOC. Secondary aims examined time to extubation and total opioid consumption.

METHODS: After IRB approval, patients were randomized to SOC control or treatment (ESPB). Patients in the treatment group received bilateral T7 ESPB catheters, with lidocaine 0.25% 1.5 mg/kg (max 20mL) through each catheter prior to surgery, followed by alternating-side lidocaine boluses every 2 hours postoperatively. Both groups received a standardized postoperative pain management regimen: acetaminophen 15 mg/kg every 6 hours, ketorolac 0.5 mg/kg every 6 hours for 6 doses, and as needed parenteral morphine, oral ibuprofen, and oral oxycodone. Inclusion criteria were patients age 0-21 years old undergoing these congenital heart surgeries: atrial septal defect repair, ventricular septal defect repair, anomalous aortic origin of a coronary artery repair, and left ventricular or right ventricular outflow repairs. Exclusion criteria were patients weighing <5kg, patients who were clinically unstable or requiring emergent surgery, and patients with pre-existing kidney or liver insufficiency.

RESULTS: At the time of submission, 28 patients, ages 2 months to 19 years were enrolled. 14 patients were randomized to control and 14 to ESPB . Compared to SOC patients, ESPB patients had a lower mean total opioid consumption, measured in morphine equivalents per weight in kg (2.607 ± 1.440 vs. 6.367 ± 9.585, p =0.1922, Figure 1) and a shorter mean time to Extubation (15.86 ± 7.049hrs vs. 22.24 ± 32.14hrs, p=0.4750, Figure 2) but a longer CVICU LOS (55.71 ± 37.72hrs vs. 34.86 ± 19.28hrs, p=0.0769, Figure 3), though all the differences were not yet statistically significant. No adverse events were recorded in either group. Data collection is ongoing; final presentation will include aggregate results from patients collected to date.

CONCLUSION: Given the increasing use of regional during cardiac surgery,[1] this study may yield important findings to help guide clinical indications for ESPB during pediatric heart repair.

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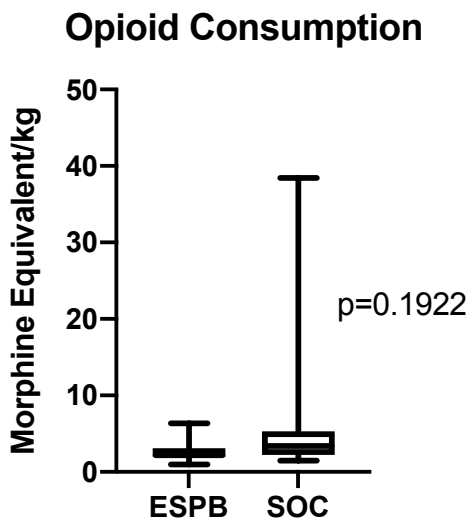

Figure 1. Total opioid consumption (in morphine equivalents per weight in kg) of ESPB and SOC patients. ESPB patients had a lower mean total opioid consumption than SOC patients, though not statistically significant (2.607 ± 1.440 vs. 6.367 ± 9.585, p =0.1922).

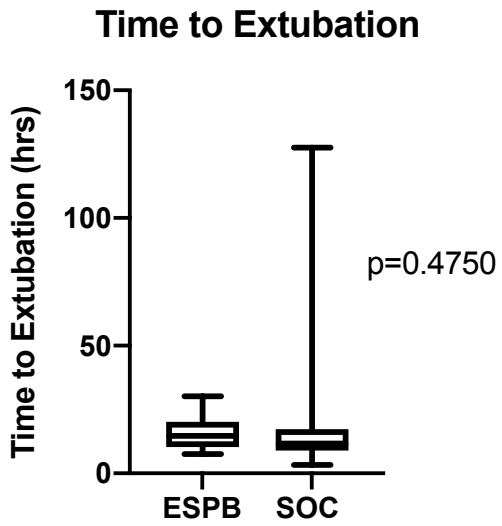

Figure 2. Time to Extubation of ESPB and SOC patients. ESPB patients had a shorter mean time to Extubation compared to SOC patients, though not statistically significant (15.86 ± 7.049 vs. 22.24 ± 32.14, p=0.4750).

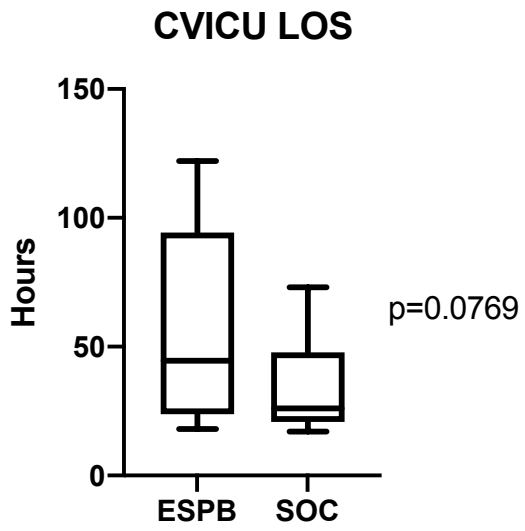

Figure 3. CVICU Length of Stay (in hours) of ESPB and SOC patients. SOC patients had a shorter mean CVICU LOS compared to ESPB patients, though not statistically significant (34.86 ± 19.28 vs. 55.71 ± 37.72, p=0.0769).

PEDIATRIC ANESTHESIOLOGY 3

A Single Center Retrospective Matched Cohort Study Comparing Efficacy of Liposomal Bupivacaine and Bupivacaine for Pre-Incision Scalp Block in Children Undergoing Craniofacial Surgery

Jed Kinnick[1], Thejovathi Edala[2], Anita Akbar Ali[3], Sagar Mehta[4], Arundathi Reddy[4]

[1]University of Arkansas for Medical Sciences, Little Rock, AR, [2]University of Arkansas of Medical sciences, Little Rock, AR, [3]1 Children's Way, Slot # 203, Little Rock, AR, [4]University of Arkansas Medical Sciences, Little Rock, AR

INTRODUCTION: Liposomal bupivacaine is a long-acting local anesthetic reported to provide up to 96 hours of pain relief and was approved by the U.S Food and Drug Administration for local infiltration and interscalene blocks in adults.[1] There are numerous case reports and studies demonstrating the safety of liposomal bupivacaine as an agent for local infiltration in patients 0-16 years of age.[2,3] Its efficacy has also been studied for local infiltration in pediatric patients undergoing spine surgery and palatoplasty;[4,5] however, its potential role in the postoperative course of pediatric patients undergoing craniofacial surgeries is unexplored. The authors demonstrate the first safe use of liposomal bupivacaine in pediatric patients with improved pain control and decreased length of stay following craniofacial surgery.

METHODS: This is a retrospective, single center & surgeon, matched cohort study of pediatric surgical patients undergoing cranial vault remodeling or cranioplasty surgery who received pre-incision scalp block with either liposomal bupivacaine (LB) or bupivacaine (BU) at Arkansas Children's Hospital between July 2019 and October 2020. A total of 67 patients met inclusion criteria. Outcome measures included total opioid requirements in weight-based IV morphine milligram equivalents (MME), incidence of postoperative nausea and vomiting from antiemetic dosing requirements, hospital length of stay and documented complications of local anesthetic toxicity. Subjects were matched 1:1 using propensity score optimal matching for age. Postoperative opioid requirements and hospital length of stay were compared between those who received LB and BU using t-test. Postoperative incidence of nausea & vomiting and antiemetic dosing requirements were compared using signed-rank test.

RESULTS: A total of 67 surgical cases met inclusion criteria, and 58 were included in the final analysis after matching (29 LB and 29 BU cases). No subjects enrolled had documentation suggesting evidence of local anesthetic toxicity. There was no significant difference in number of emesis between LB and BU groups. For each of the first three postoperative days, the LB group had lower opioid requirements than the BU group: POD1: LB 0.0184 vs BU 0.1742mg/Kg IV MME; $P < 0.0001$ POD2: LB 0.0012 vs BU 0.1331mg/Kg IV MME; $P = 0.0002$ POD3: LB 0.026 vs BU 0.0675 mg/Kg IV MME; $P = 0.0321$ The LB group were also discharged 1.2 days ($P = 0.0108$) earlier than the BU group.

CONCLUSION: This study showed that single dose of pre-incision scalp block with liposomal bupivacaine appears to be safe and associated with decreased opioid requirements following craniofacial surgeries. More adequately powered trial with optimal matching to correct for confounding factors, and measurements of more outcome variables such as plasma bupivacaine levels, pain scores, timing to first oral intake, median days of opioids prescribed postoperatively in the outpatient setting is underway. These results suggest that liposomal bupivacaine could be considered as a safe and effective part of multimodal pain therapy in pediatric patients undergoing craniofacial surgeries.

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Outcomes	N per group	Difference (LB - BU)	P-value	Test
MME POD 1 Difference (Mean(Std))	29	-0.1558 (0.1742)	<.0001	T-test
MME POD 2 Difference (Mean(Std))	21	-0.1319 (0.1331)	0.0002	T-test
MME POD 3 Difference (Mean(Std))	15	-0.0415 (0.0675)	0.0321	T-test
Total Emesis (Mean (Std))	29	-0.9655 (3.1223)	0.1070	T-test
Emesis Average	29	-0.1429 (-1, 0.3333)	0.3639	Signed Rank
Length of Stay	29	-1.2069 (2.3812)	0.0108	T-test

Table 1: Differences between Liposomal Bupivacaine and Bupivacaine Groups

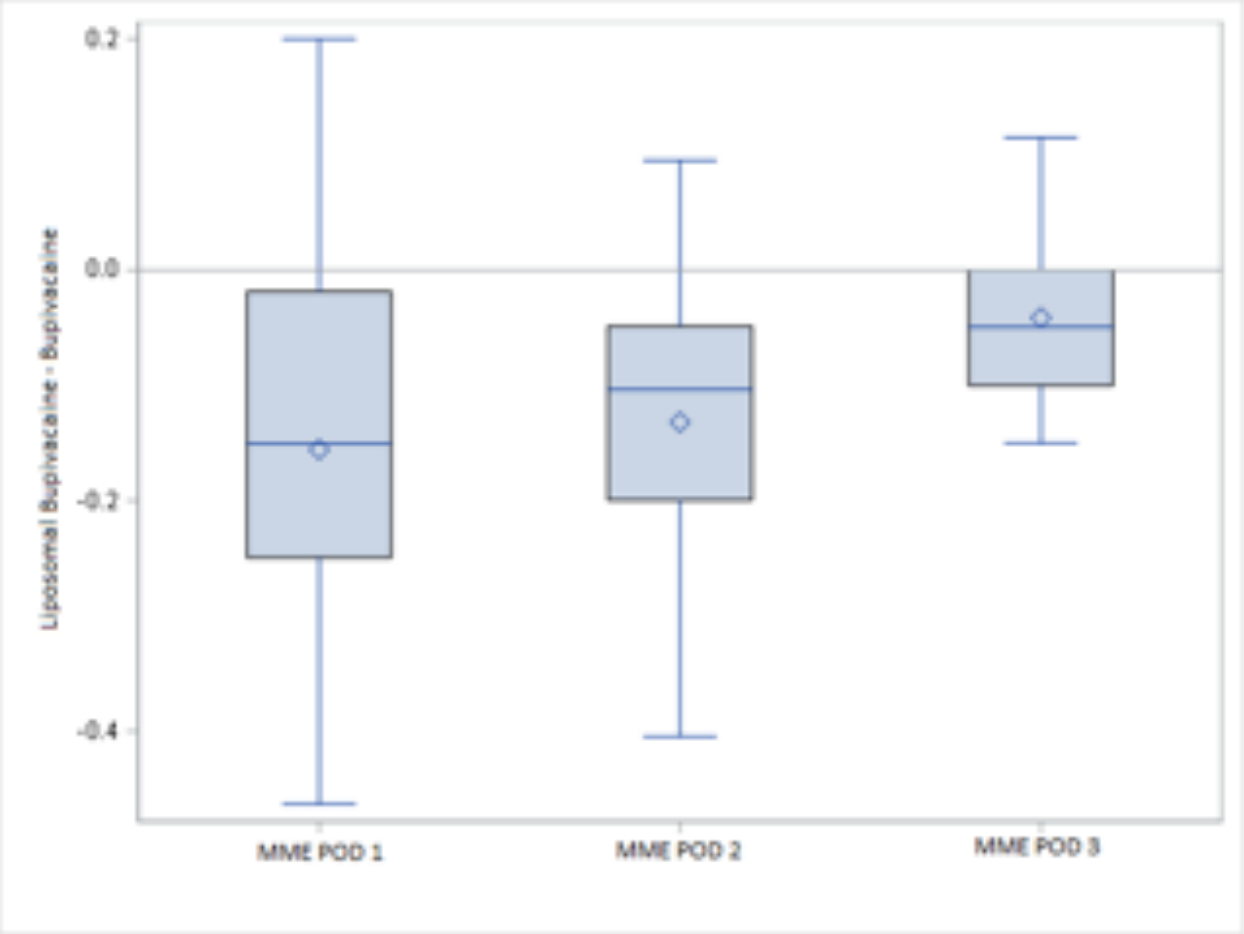

Figure 1: Box plot demonstrating differences in IV morphine milligram-equivalents (in mg/kg) between liposomal bupivacaine and bupivacaine groups for the first three post-operative days.

PEDIATRIC ANESTHESIOLOGY 4

Intramuscular Ketorolac vs. Intranasal Fentanyl for Postoperative Pain Reduction and Decreased Emergence Delirium in Pediatric Patients Undergoing Myringotomy and Tube Placement

Kimpreet Kaur[1], Angela D McElrath[1], Michael Patzkowski[1], Ryan J Schutter[1], Katherine M Slogic[1]

[1]Brooke Army Medical Center, San Antonio, TX

INTRODUCTION: Bilateral myringotomy and tubes (BMT) is one of the most common ambulatory pediatric surgeries in the United States. BMT is usually performed with an inhaled anesthetic without intravenous access due to the brevity of surgery. Common anesthetic concerns include postoperative pain control and emergence delirium (ED). Up to 70% of pediatric patients undergoing a routine otolaryngology procedure will experience emergence delirium when receiving sevoflurane.[1] Although BMT placement is a common surgery, there is no consensus for an optimized regimen to decrease postoperative pain and emergence delirium. Our null hypothesis is that there is no difference between intramuscular (IM) ketorolac and intranasal (IN) fentanyl in the setting of rectal acetaminophen for BMT in postoperative pain and ED.

METHODS: This was a retrospective study that analyzed already practiced anesthetic regiments performed by individual pediatric anesthesiologists at the home institution and was approved by our local institutional review board. Data was collected from our Pediatric Sedation Unit over the course of 10 months from January 1st, 2018 to October 1st, 2018. Inclusion criteria included healthy children classified as ASA 1 or 2, ages 1-8 years of age, and meeting criteria for unilateral or bilateral myringotomy. The Cravero scale was used to measure ED and scores were recorded by nursing staff at time of arrival to the PACU, at 15 minutes, and 30 minutes. Pain was assessed by nursing staff using the Face, Legs, Activity, Cry, and Consolability (FLACC) scale upon arrival to the recovery suite, at 15 minutes, and 30 minutes. All these data points, including time to discharge could be found in individual electronic records. Categorical factors were summarized using frequencies and percentages. Quantitative covariates were summarized as means and standard deviations or medians and inter-quartile ranges. Repeated measures would be analyzed with analysis of variance (ANOVA). Factors that are significantly associated with each dependent variable may be combined in a multiple regression analysis if the cohorts of different treatment modalities are deemed to be heterogeneous. We anticipate approximately 120 patients meeting inclusion criteria, and based on this we can expect to see significance with 80% power for any factor with an effect size (Cohen's d) of 0.5 with alpha set at 0.05.

RESULTS: 145 patients were captured, 2 patients did not have intervention arm data and were excluded. Summary statistics of each group are presented in table one. Given heterogeneity of groups in age and weight, multiple regressions (generalized linear and mixed models) were performed to assess for associations between predictor variables and outcomes while controlling for these unbalanced factors. For the FLACC outcome, pairwise comparisons revealed a statistically significant difference in favor of fentanyl at 15 minutes (-1.064 [95%CI -2.124, -0.005], $p = 0.049$) and 30 minutes (-1.358 [95%CI -2.227, -0.488], $p < 0.002$), while there was no difference upon arrival ($p = 0.85$). For the Cravero outcome, there was no significant differences between groups at wake-up and 15 minutes afterwards ($p = 0.51$ and 0.22 respectively). Discharge time was also not significantly different between groups ($p = 0.76$).

CONCLUSION: In this retrospective cohort study, there was a statistically significant, but not clinically meaningful, reduction in pain score using the FLACC scale in favor of fentanyl at 15 and 30 minutes. Upon review of existing literature, a minimal clinically important difference (MCID) has not been established for the FLACC scale, however, for a similar pain scale, the 100mm Visual Analog Scale, there is evidence supporting a MCID of 17mm.[2] Further support for the lack of clinical significance for our FLACC differences was that patients given ketorolac were discharged at the same time as those administered fentanyl. IM ketorolac may be a better first line analgesic agent given its lack of effect on the respiratory system. This study supports the growing body of literature emphasizing the appropriate use of non-opioids analgesics in order to minimize the need for opioids.

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Descriptives

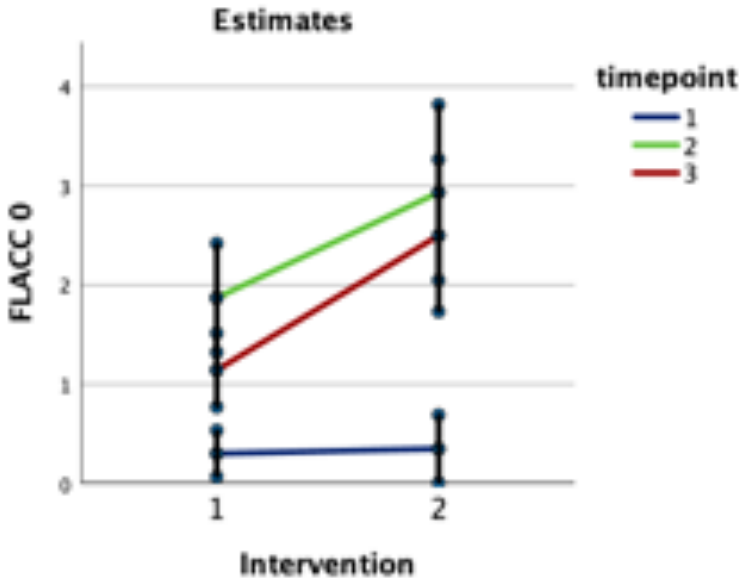
Descriptives

	Intervention	Age (yrs)	Weight (kg)
N	Fentanyl	96	96
	Ketorolac	47	47
Median	Fentanyl	1.85	12.1
	Ketorolac	1.80	12.0
Minimum	Fentanyl	0.600	8.00
	Ketorolac	0.750	8.50
Maximum	Fentanyl	8.00	29.0
	Ketorolac	11.0	40.0
Shapiro-Wilk p	Fentanyl	< .001	< .001
	Ketorolac	< .001	< .001
25th percentile	Fentanyl	1.40	10.4
	Ketorolac	1.45	10.9
50th percentile	Fentanyl	1.85	12.1
	Ketorolac	1.80	12.0
75th percentile	Fentanyl	2.10	14.1
	Ketorolac	2.50	15.8

Frequencies

Frequencies of Gender

	Intervention	
Gender	Fentanyl	Ketorolac
Male	64	30
Female	32	17



Continuous predictors are fixed at the following values: Age = 2.3486453201970500, weightkg = 13.2996551724138000

PEDIATRIC ANESTHESIOLOGY 5

Ultrasound assessment of gastric volume after ingestion of clear liquid up to 1 hr prior to induction of anesthesia in pediatric patients

Chris S McLaughlin[1], Joelle Karlik[2], Thomas M Austin[3], Laura Gilbertson[2], Humphrey Lam[2], Soumya Nyshadham[2]

[1]Children's Healthcare of Atlanta (Emory University School of Medicine), Atlanta, GA, [2]Emory University, Atlanta, GA, [3]Emory University School of Medicine, Atlanta, GA

INTRODUCTION: Nil per os (NPO) guidelines are developed to minimize the risk of pulmonary aspiration. Several European and Canadian pediatric anesthesia societies have recently published guidelines allowing clear liquids up to one hour prior elective anesthesia.[1] The aim of this study was to use gastric ultrasound to determine if the ingestion of clear liquids up to one hour prior to an elective procedure in pediatric patients requiring general anesthesia is associated with a full stomach (or > 1.5 ml/kg of gastric fluid). Our hypothesis is that patients who ingested clear liquid 60-119 minutes prior to an ambulatory surgical procedure would not have evidence of full stomach defined as less than 1.5 mL/kg based on gastric antral ultrasound assessment.[2,3]

METHODS: This is a prospective cohort study that included ASA 1 or 2 pediatric patients ages 1-18 who presented for ambulatory surgery. Exclusion criteria included comorbidities that affected gastric emptying or positive pressure ventilation >20 mL of H2O during induction. After patients were identified and consent was obtained, they were provided with 5 mL/kg (maximum of 240 mL) of clear liquid to drink approximately 1 hour prior to induction. After induction of general anesthesia, gastric ultrasound was performed in the supine and right lateral decubitus positions to determine gastric volume in mL/kg.[4] Presence of solid contents, vomiting, and/or aspiration were recorded.

RESULTS: 11 patients were consented for this pilot study with enrollment ongoing. Average PO volume ingested was 170.2 mL (range 55-240 mL) of an average of 4.1 mL/kg (range 2.6-5.3 mL/kg). Average time from ingestion to anesthesia induction was 99 minutes (range 64-232 minutes). Two patients had ingestion-induction time over 120 minutes. One patient vomited on induction and was not scanned as a result. In the remaining 10 patients, average mL/kg on measurement was 0.68 mL/kg (range 0.32-1.34 mL/kg). 1 patient had solid matter on ultrasound examination.

CONCLUSION: Our pilot study suggests that 5 mL/kg up to 240 mL of clear liquids ingested between 60-119 minutes prior to anesthesia induction results in gastric antral measurements less than 1.5 mL/kg. While these initial results are overall reassuring, two high risk findings raise safety concerns and should be investigated further. One patient in our pilot study experienced vomiting during induction that was expeditiously managed and did not experience aspiration. Vomiting during induction is a known anesthesia complication however the high incidence (9%) in our pilot study warrants further study. In addition, one patient had potential solid particles on ultrasound examination. This pilot study suggests that 5 mL/kg of clear liquids to a maximum of 240 mL one hour prior to anesthesia induction results in low risk ultrasound antral measurements but requires further study to determine safety.

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PEDIATRIC ANESTHESIOLOGY 6

Association Between Intra-Operative Ketorolac Administration During Pediatric Adenotonsillectomy and Reduced Post-Operative Pain After Discharge

Laura Gilbertson[1], Humphrey Lam[1], Joelle Karlik[1], Soumya Nyshadham[1], Stephanie Tran[1], Kasia Maziar[1], Julie Schuman[1], Matthew Cucino[1], Nikhila Raol[1], Thomas M Austin[1]

[1]Emory University, Atlanta, GA

INTRODUCTION: Adenotonsillectomy (T+A) is one of the most common pediatric surgical procedures performed in the United States. Sleep disordered breathing and obstructive sleep apnea (OSA) as the indication for T+A has increased significantly over the past ten years and is now the most common indication for this procedure in children.[1] Opioids continue to be the primary pain medication for these procedures, however studies have shown that patients with OSA have significantly increased sensitivity to opioids which result in post-operative respiratory depression and apnea when administered at standard opioid dosing protocols.[1-3] Unfortunately, poor pain control and subsequent dehydration continues to be a main factor in post-operative Emergency Department (ED) visits and hospital readmissions. The most recent data estimates the overall ED return rate at 13.3% for all children who underwent T+A (4). Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) that possesses similar efficacy to morphine without the side effects of respiratory depression, nausea and vomiting (5). Importantly, ketorolac has a synergistic effect when combined with opioids resulting in a lower dose of opioid required to achieve the same level of analgesia. In this study, we aim to determine if there is a significant correlation between intra-operative administration of ketorolac in pediatric T+A and the rate of post-operative pain after discharge resulting in post-operative phone calls, emergency room visits and readmission to the hospital.

METHODS: After IRB approval, information was collected from pediatric patients who underwent tonsillectomy at either a free-standing pediatric hospital or a pediatric outpatient surgical center over a 5-year period by two pediatric otolaryngologists. The primary outcome of this analysis was significant postoperative pain after leaving the hospital/surgical center. This was defined as a phone call to the surgeon regarding post-surgical pain, an ED visit due to post-surgical pain, and/or a hospital admission due to post-surgical pain. In addition, the lone secondary outcome was significant postoperative bleeding defined as an ED visit for post-surgical bleeding, a hospital admission due to post-surgical bleeding, and/or returning to the operating room for post-surgical bleeding. Logistic mixed effects regression models were used to determine significant predictors for the outcomes. Variables accounted for included age, ASA classification, surgical location, inpatient vs outpatient, intraoperative steroid use, intraoperative dexmedetomidine use, perioperative morphine equivalents, surgical time, and surgeon. All analyses were performed with R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS: 878 patients were included with a median [IQR] age of 6 [4, 9] years. 39.2% of patients in this sample received intraoperative ketorolac. Significant postoperative pain at home and significant postoperative bleeding occurred in 157 (17.9%) and 21 (2.4%) patients, respectively. Intraoperative ketorolac was associated with a decreased incidence of significant postoperative pain (adjusted odds ratio [aOR] 0.65, 95%CI 0.44 to 0.95, P-value = 0.027, Table 1) without an apparent increase in significant postoperative bleeding (adjusted odds ratio [aOR] 0.96, 95%CI 0.35 to 2.44, P-value = 0.932, Table 1). However, this latter analysis is underpowered due to a low event rate.

CONCLUSION: OSA predisposes children to respiratory depression and apnea after opioid administration, prompting providers to minimize the amount of narcotics these patients recieve. Therefore, patients undergoing T+A often experience significant post-operative pain resulting in frequent phone calls, ED visits and readmissions after discharge. These incidences are not only unpleasant for the patient and caregiver, but they place significant burden on the hospital system. This study demonstrates that intraoperative ketorolac administration during T+A reduces post-operative pain and the incidence of these untoward events. It also appears that ketorolac does not increase the adverse event of post-operative bleeding, although a larger cohort is needed to further delineate this outcome.

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Table 1. Association between intraoperative ketorolac use and outcomes

Outcomes	Levels	§Unadjusted			¥Adjusted		
		Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Significant Postoperative Pain	Intraoperative Ketorolac vs None (Referent)	0.61	0.41 to 0.90	0.009	0.65	0.44 to 0.95	0.027
Significant Postoperative Bleeding	Intraoperative Ketorolac vs None (Referent)	0.77	0.26 to 2.07	0.656	0.96	0.35 to 2.44	0.932

CI = Confidence Interval.

§Based on Fisher's Exact Test. P-values <0.05 considered statistically significant.

¥Based on mixed effects logistic regression models after control of various patient, surgical, and analgesic variables. Variables accounted for included age, ASA classification, surgical location, inpatient vs outpatient, intraoperative steroid use, intraoperative dexmedetomidine use, perioperative morphine equivalents, surgical time, and surgeon. P-values <0.05 considered statistically significant.

PEDIATRIC ANESTHESIOLOGY 7

The Influence of Postanesthesia Care Unit Nurses on Recovery Times in Pediatric Patients

Annie Song[1], Soumya Nyshadham[1], Joelle Karlik[1], Laura Gilbertson[1], Humphrey Lam[1], Justin B Long[1], Thomas M Austin[1]

[1]Emory University, Atlanta, GA

INTRODUCTION: Many factors contribute to length of stay (LOS) for pediatric patients in the postanesthesia care unit (PACU). LOS is often used as a measure of the efficacy of anesthetic care. Prolonged PACU recovery may also compromise patient care, create inconvenience for families, and increase costs for patients and hospitals. We designed this retrospective study to identify the association between Phase I PACU duration and the assigned PACU nurse while adjusting for patient-, anesthetic-, and surgical-related factors that may affect PACU LOS.

METHODS: After IRB approval, we included pediatric patients who underwent laparoscopic appendectomies, adenoidectomies, supracondylar fracture percutaneous pinning, inguinal hernia repairs, and umbilical hernia repairs at two free standing pediatric hospitals over a five-year period. Factors included in this analysis were patient gender, age, race/ethnicity, ASA classification, previous surgery, preop midazolam, preop opioids, preop gabapentin, off-hours surgery, surgery type, intraop morphine equivalents, intraop ketorolac, intraop local anesthetic, intraop dexmedetomidine, deep extubation, time admitted to PACU, PACU dexmedetomidine, PACU opioid doses, PACU nurse, anesthesiologist, and hospital. A linear mixed effects regression model was used to determine significant predictors for Phase I PACU duration while variable importance was found by calculating the likelihood ratio chi-squared statistic minus the degrees of freedom (d.f.) for each variable. All analyses were performed with R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS: 12334 patients were included in this analysis with a median [IQR] Phase I PACU duration of 29 [21, 40] minutes. Out of the variables that were added to the regression model, the PACU nurse who was assigned to the patient was the second-most important predictor of Phase I PACU duration by a large margin (Figure 1). The difference in average adjusted PACU duration from the nurse with the least time to the one with the most was approximately 30 minutes (Figure 2). This is in contrast to the anesthesiologist who cared for the patient where this difference in the extremes averaged a mere 2 minutes.

CONCLUSION: Individual PACU nurse is shown to be a leading determinant of Phase I PACU LOS in pediatric patients, second only to PACU opioid administration. This effect greatly surpasses effects of other factors such as patient demographics, surgical variables and common preop or intraop medications. Although the important role of PACU nursing care has been observed previously in adults [1], our study has been the first to determine this in children. Moreover, we demonstrated that the potential difference in recovery duration associated with Phase I nurses is clinically significant, ranging up to 30 minutes, comparable to the average total LOS in PACU. These findings serve to guide further strategies to improve nursing efficiency and reduce delays in PACU recovery, benefiting both patients and the healthcare system.

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Figure 1. Variable Importance on PACU Duration

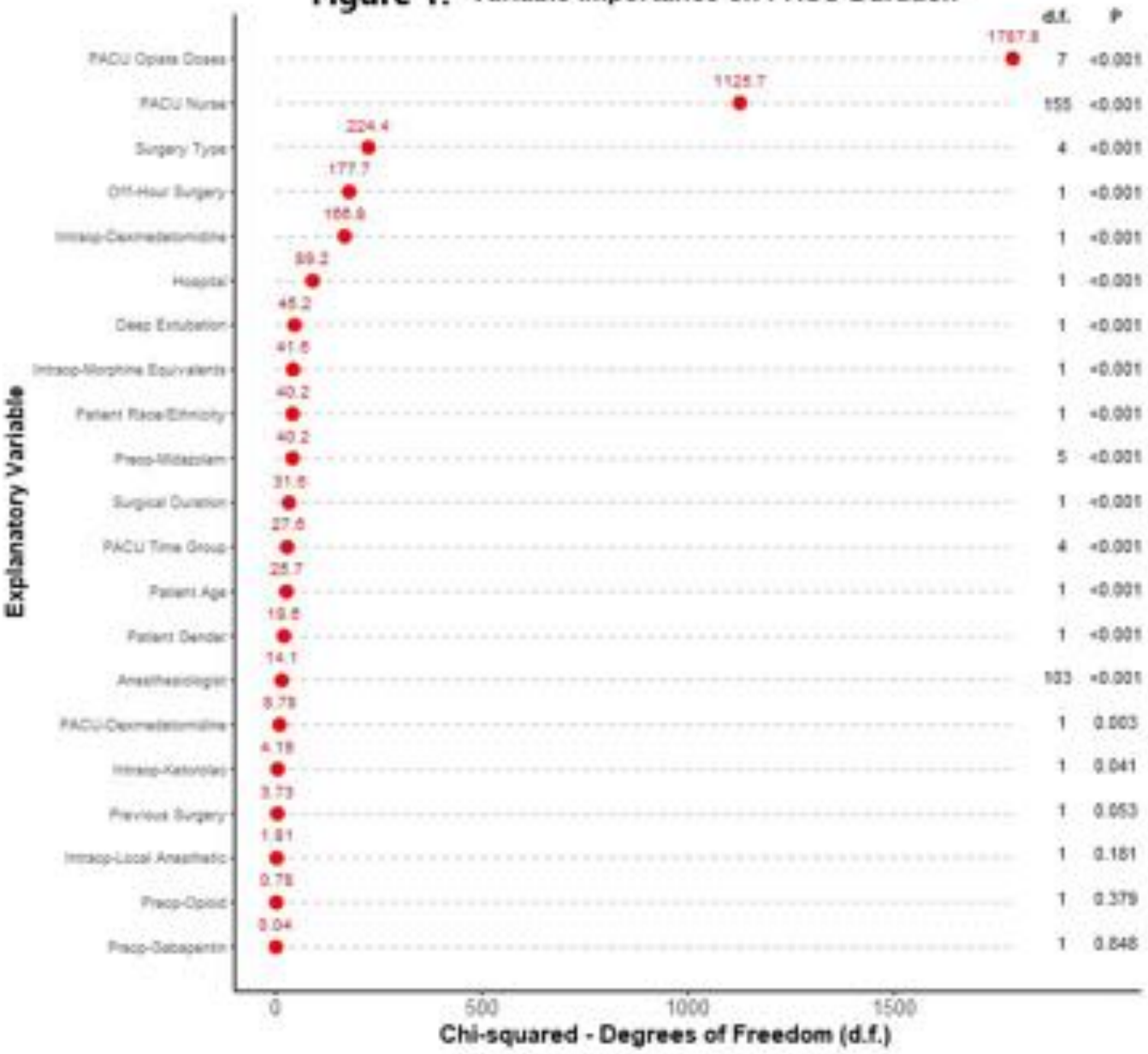
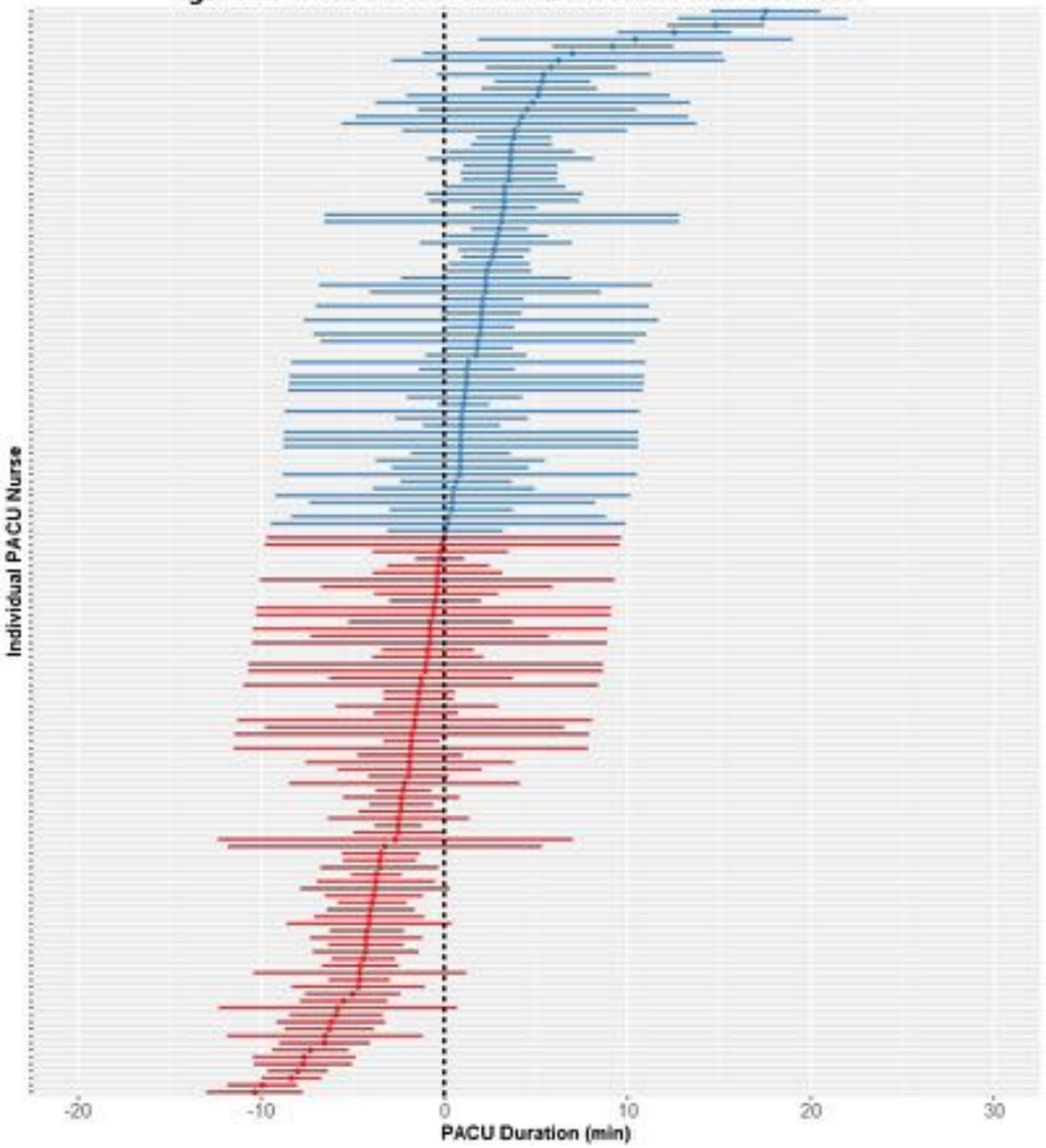


Figure 2. PACU Duration Variability Associated with PACU Nurse



PEDIATRIC ANESTHESIOLOGY 8

A novel simplified technique for carbon dioxide titration in anesthetized patients undergoing cerebral vascular reactivity BOLD-fMRI studies

Kunal Kolhatkar[1], Nomazulu Dlamini[2], Benjamin Steinberg[2], David Levin[2], Asad Siddiqui[2], Amanda Robertson[2]

[1]University of Toronto, Toronto, Canada, [2]SickKids Hospital, Toronto, Canada

INTRODUCTION: Cerebrovascular reactivity (CVR), the response of blood vessels in the brain to vasodilatory stimuli, is a useful tool for monitoring ischemic risk and prognosis of patients with cerebrovascular diseases like moyamoya disease and neurofibromatosis type 1.[1,2] Blood oxygenation level dependent (BOLD) imaging can be used in functional magnetic resonance imaging (fMRI) to visualize and quantify CVR, and CVR can be induced in patients by increasing their arterial partial pressure of CO2 (PaCO2). While this PaCO2 elevation is achieved through a series of breath holds in cooperative patients, the process in young children or children with behavioural or cognitive challenges involves inducing general anesthesia, endotracheal intubation, neuromuscular blockade, and controlled ventilation to mimic breath holds. Unfortunately, this is fraught with risks for the patient and does not allow for a predictable and reliable in PaCO2, limiting its use as a diagnostic tool. We therefore propose a novel technique that simplifies PaCO2 manipulation and improves reliability in the pediatric population. The technique involves inducing anesthesia intravenously or via a mask such that the patient can breathe spontaneously, placing a laryngeal mask airway to keep the patient's airway open, and modifying the anesthetic circuit to allow the patient to re-breath expired air. This is accomplished by removing the CO2 absorbent from the circuit and reducing fresh gas flows until the desired PaCO2 level is reached, at which point the circuit is flushed by opening fresh gas flows. Although this method is a departure from usual practice and requires vigilance on the anesthesiologist's part, we believe that it represents a practical physiology-based approach that greatly simplifies the imaging process and reduces the risk for adverse effects in a high-risk patient population.

METHODS: Our updated technique is to induce anesthesia via mask or IV with the goal of maintaining the patient's capacity for spontaneous ventilation, introduce a laryngeal mask airway (LMA), and facilitate an increase in PaCO2 by removing the CO2 absorbent from the canister in the anesthesia machine circuit before reducing fresh gas flows to allow intentional rebreathing. Once the ETCO2 reaches the desired peak, the fresh gas is increased to flush the circuit and allow return of PaCO2 to baseline. In this technique, the depth of anesthesia is increased only enough to allow introduction of an LMA, and then maintained on a minimum dose of propofol infusion to prevent patient movement and maintain spontaneous ventilation on the LMA. The LMA position is carefully assessed to ensure there in no circuit leak before moving from the induction area to the MRI suite. The anesthesia circuit must be primed with a high fraction of oxygen to avoid hypoxemia during rebreathing. The reservoir bag remains partially inflated when flows are lowered to protect against negative pressure pulmonary edema or entrainment of room air through the negative pressure escape valve. Aside from the manipulation in fresh gas flows, this technique closely approximates the usual routine around induction, maintenance, and recovery often used for anesthesia for routine pediatric MRI. Furthermore, if the patient receives intravenous access pre-induction, the entire anesthetic can be achieved with a single drug, propofol, which has minimal effect on CVR.[3]

RESULTS: The attachment shows the vital signs monitor for a pediatric patient undergoing anesthesia using this technique (Attachment 1).

CONCLUSION: There are no previous reports of anesthetic techniques to facilitate CVR under general anesthesia. On balance, we believe this is a safer anesthetic that achieves the goal of tight, accurate, and reproducible CO2 titration more effectively than GA with ETT using a time-based apnea. Moreover, it is easily reproducible in most MRI settings equipped with an anesthesia machine (or even with a simple T-piece and spare corrugated tubing).

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Figure 1: Sample calculations to approximate the times needed to see a rise in the ETCO2 from baseline and to achieve a specific ETCO2 target value.

Definition of Terms:

- Total CO2 in circuit at baseline (when flows exceed minute ventilation; **mL**) = 0
- Target ETCO2 (**mmHg**) = 45
- Atmospheric pressure (**mmHg**) = 760
- Circuit volume (**mL**) = Y
- Patient weight (**kg**) = wt
- Tidal volume (**mL/(kg x breath)**) = 7[1]
- Minute ventilation (**mL/(kg x min)**) = Tidal volume x Respiratory Rate (RR; **breaths/min**)
- Average CO2 production (**mL/(kg x min)**) = 6.3[2]

Time until a rise in CO2 baseline is evident on the monitors (min)
= Circuit volume (mL) / [Minute ventilation (mL/(kg x min)) x Patient weight]
= Y / (7 x RR x wt)
Total CO2 in circuit at target ETtCO2 (mL)
= (Target EtCO2 (mmHg)/ Atmospheric Pressure (mmHg)) x Circuit volume (mL)
= (45 / 760) x Y
= 0.059 x Y
Time needed to reach CO2 peak once flows are shut off (min)
= [Total CO2 in circuit at target (mL) - Total CO2 in circuit at baseline (mL)] / CO2 production (mL/(kg x min))
= [(0.059 x Y) – 0] / (6.3 x wt)
= (0.059 x Y) / (6.3 x wt)
= (0.0094 x Y) / wt

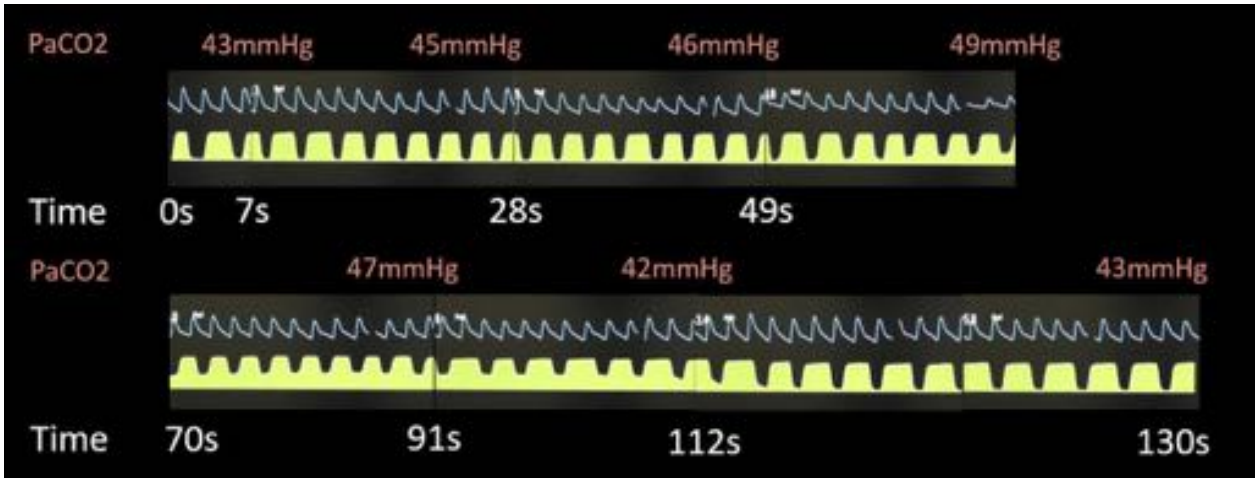

Figure 2

PEDIATRIC ANESTHESIOLOGY 9

Temperature Management for Paediatric Patients undergoing outpatient (OP) Magnetic Resonance Imaging (MRI) scans under General Anaesthetics (GA)

Guanmei Luo[1], S Bew[2]

[1]Leeds Teaching Hospitals, Leeds, United Kingdom, [2]Leeds Children's Hospital, Leeds, United Kingdom

INTRODUCTION: MRI is increasingly used for diagnosis and disease monitoring in the paediatric population. However, some, especially those with neurodevelopmental conditions, require a GA to tolerate the scans. Radiofrequency waves tend to increase body temperature, whilst MRI suites are usually kept cool and GA results in a general body temperature reduction. Research studies looking at temperature changes in paediatric patients (Ppts) undergoing MRI scans have shown mixed results.[1,2] The aim of the project is to assess temperature changes in Ppts undergoing OP MRI scans under GA and evaluate adequacy of current departmental practices in temperature management due to anecdotal concerns for hyperthermia.

METHODS: Data prospectively collected over four month period across two MRI suites;1.5T and 3T. Data collected included basic demographics (age, gender, indications for scan), temperature pre- and post-scan using tympanic temperature probes. Other factors that may influence temperature changes also assessed include scan duration, ambient temperature and humidity and temperature management adopted (clothing choice, heating/cooling methods) during GA and in PACU. Data analysed using Excel™ and statistical significance calculated using two tailed paired T test.

RESULTS: Fifty Ppts were included, 21 females and 29 males at mean age 4.24 years (95% CI 3.49 - 4.99) and mean weight 17.25kg (95%CI 15.13 - 19.38). 74% (37/50) scans were indicated for neuro-oncology or neurodevelopmental reasons. 68% (34/50) patients were scanned in 3T suite. Mean scan duration was 58.98 mins (95% CI 52.09 - 65.87), with mean scan room temperature 19.39°C and humidity 50.34%. Mean pre-scan temperature was 36.62°C (95% CI 36.50 - 36.75) dropping to mean post-scan temperature 36.43°C (95% CI 36.29 - 36.57; p=0.028). The mean temperature change was a decrease of 0.15°C (95% CI -0.33 - + 0.03). 14 % (7/50) patients were hypothermic (<36°C) post scan (mean 35.61, 95% CI 35.22 - 35.90), 4 in 1.5T group and 3 in 3T group. 92% (46/50) patients were covered with a blanket during the scan, whilst the rest were not covered. 22% (11/50) required additional blankets in PACU. No patients were hyperthermic (>37.5°C) and there was no delay discharge in any of the patients.

CONCLUSION: Our study has shown a statistically significant decrease in temperature for Ppts undergoing MRI with 14% hypothermic post scan, although this does not translate into a clinical significance. We did not observe a correlation between temperature change in relation to strength of magnet, duration of scan or patient weight. This is likely to reflect the complex physiological interactions at play. It is recommended extra vigilance is taken with the temperature management of these patients.

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PEDIATRIC ANESTHESIOLOGY 10

Protocols in Pediatric Ambulatory Surgeries Do Not Decrease Disparities: A Single-Center Retrospective Study

Anjali Dixit[1], Katherine Gentry[1], Nathalia Jimenez[1], Amber Yun[1], Vikas O'Reilly-Shah[1]

[1]Seattle Children's Hospital; University of Washington, Seattle, WA

INTRODUCTION: Racial/ethnic disparities exist in the perioperative care of children. Non-Hispanic Black (NHB) children have higher perioperative morbidity and mortality compared to their non-Hispanic White (NHW) counterparts.[1] Minority children receive opioids in the post-anesthesia care unit at different rates than NHW children,[2,3] and racial/ethnic differences in administration of regional anesthetics in children may also exist.[4] Enhanced recovery after surgery (ERAS) protocols aim to standardize care and are associated with decreased racial/ethnic disparities in adults.[5] While pediatric ERAS protocols are less common, it has been hypothesized that they may also ameliorate disparities.[6] We examined the effect of protocolized pediatric anesthetic care on reducing intraoperative racial/ethnic disparities for three well-established markers of quality of care: administration of antiemetics, non-opioid analgesic adjuvants, and regional anesthetics. We hypothesized protocol-driven approaches would decrease disparities by supporting objective intraoperative decision-making and decreasing provider-related variation.

METHODS: Study design: retrospective cohort study using a level 1 pediatric hospital's medical record data for: 1) knee, foot, and ankle (KFA) orthopedic surgery (patients ≤18 years old), or 2) circumcision (patients ≤3 years old) from 2014-2019. Exposure: protocol (intraoperative administration of ≥1 antiemetic, ≥1 non-opioid analgesic, and a regional anesthetic). Exposure was determined by surgical location (the protocol was implemented at our ambulatory center but not our main campus). Primary outcomes: administration of 1) an antiemetic (ondansetron/dexamethasone), 2) a non-opioid analgesic (acetaminophen/ketorolac), and 3) a regional anesthetic (caudal/pudendal block for circumcision, and lower extremity block for KFA surgery). Statistical analysis: we calculated the rate of each outcome, stratified by exposure and racial/ethnic subgroup (Hispanic, NHW, NHB, Non-Hispanic Asian [NHA], and Other) and estimated the Wald binomial confidence interval for each.

RESULTS: 4,185 patients were included in our study (Table 1). 1,904 (45.5%) were treated at our ambulatory center and received protocolized care. A majority (71.0%) were male. Surgical distribution varied, with a higher proportion of circumcisions done at the ambulatory center and a higher proportion of KFA surgeries at our main campus. There were no differences in location of surgery by race/ethnicity. Among patients who underwent KFA surgery and received protocolized care, NHW patients were more likely than all other racial/ethnic subgroups to receive: 1) an antiemetic (97.2%, 95% CI 95.6-98.8), with Hispanic patients significantly less likely (88.4%, 82.8-93.9) and 2) a regional block (80.1%, 76.1-84.0), with NHB patients least likely (70.0%, 58.4-81.6). NHW (83.1%, 79.4-86.8) and Other (88.4%, 83.2-93.6) patients were also most likely to receive a non-opioid analgesic, while Hispanic patients were least likely (76.0%, 68.6-83.3) (Figures 1, 2, and 3). In patients who underwent circumcision, all racial/ethnic subgroups were more likely to receive a regional block if they underwent protocolized care. However, differences between groups persisted, and NHB patients continued to be least likely to receive a regional block (86.1%, 79.4-92.9), while NHA patients were almost ten percent more likely (95.8%, 92.7-98.8). Overall protocol adherence to administer prophylactic antiemetics and non-opioid analgesics was low. Patients in the protocolized care group were less likely than those in the non-protocolized group to receive antiemetic and non-opioid analgesic medications.

CONCLUSION: We found persistence of racial/ethnic disparities with protocolized care. While protocols were associated with improved care for most NHW patients – particularly in KFA surgery and with the provision of a regional block – this was not the case for other racial/ethnic groups. Specifically, NHB and/or Hispanic patients were identified repeatedly as less likely to receive antiemetics, non-opioid analgesics, and/or regional anesthetics. Our findings suggest that implicit biases persist despite the implementation of protocolized anesthetic care.

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Table 1: Characteristics of the Study Population

	Overall	Ambulatory Center (Protocol)	Main Campus (No Protocol)
N (%)	4185	1904 (45.5)	2281 (54.5)
Demographic Characteristics			
Sex (Male) (%)	2971 (71.0)	1486 (78.0)	1485 (65.1)
Race/Ethnicity (%)			
NHW	2145 (51.3)	961 (50.5)	1184 (51.9)
NHB	354 (8.5)	161 (8.5)	193 (8.5)
Hispanic	549 (13.1)	230 (12.1)	319 (14.0)
NHA	461 (11.0)	250 (13.1)	211 (9.3)
Other (Non-Hispanic)	676 (16.2)	302 (15.9)	374 (16.4)
Age in years (%)			
0-3	1824 (43.6)	1173 (61.6)	651 (28.5)
>3-10 (only KFA subgroup)	657 (15.7)	138 (7.2)	519 (22.8)
>10-18 (only KFA subgroup)	1704 (40.7)	593 (31.1)	1111 (48.7)
Surgery Type			
Circumcision	1513 (36.2)	1089 (57.2)	424 (18.6)
Knee/Foot/Ankle	2672 (63.8)	815 (42.8)	1857 (81.4)
Outcomes			
Received Antiemetic (%)	2954 (70.6)	1116 (58.6)	1838 (80.6)
Received Non-opioid Analgesic (%)	2445 (58.4)	773 (40.6)	1672 (73.3)
Received Regional Block (%)	3058 (73.1)	1615 (84.8)	1443 (63.3)

Figure 1

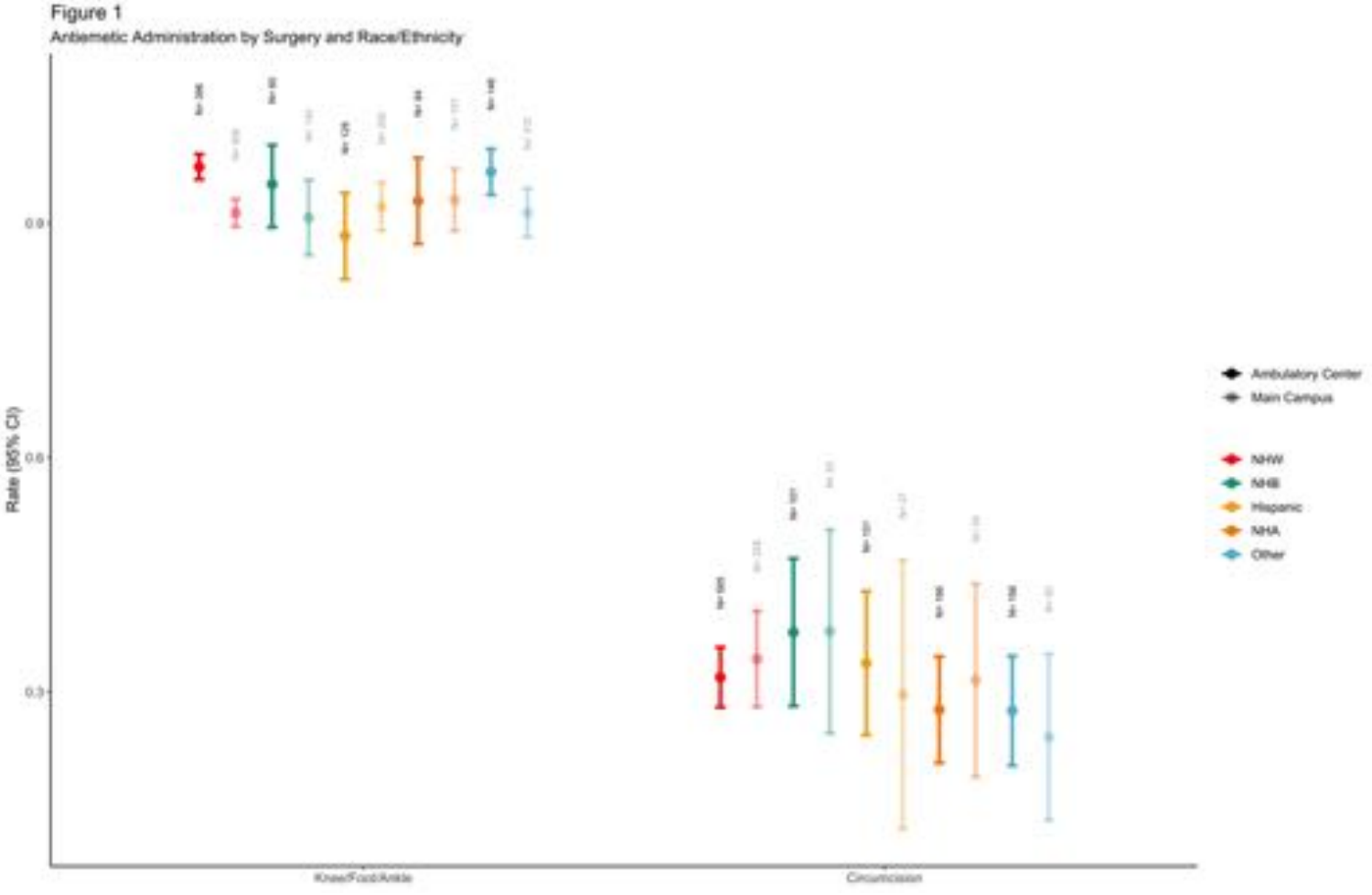


Figure 2

Analgesic Administration by Surgery and Race/Ethnicity

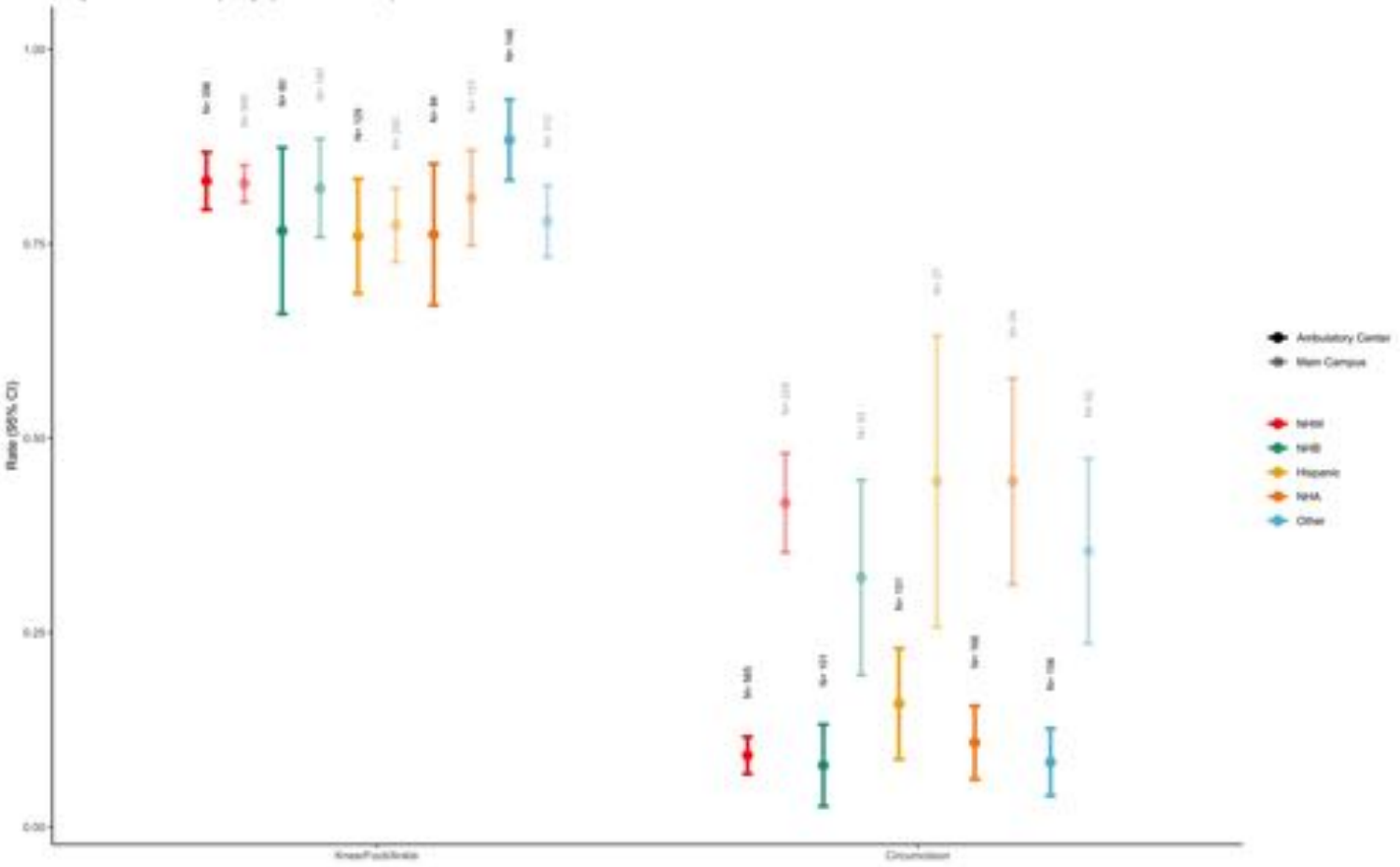
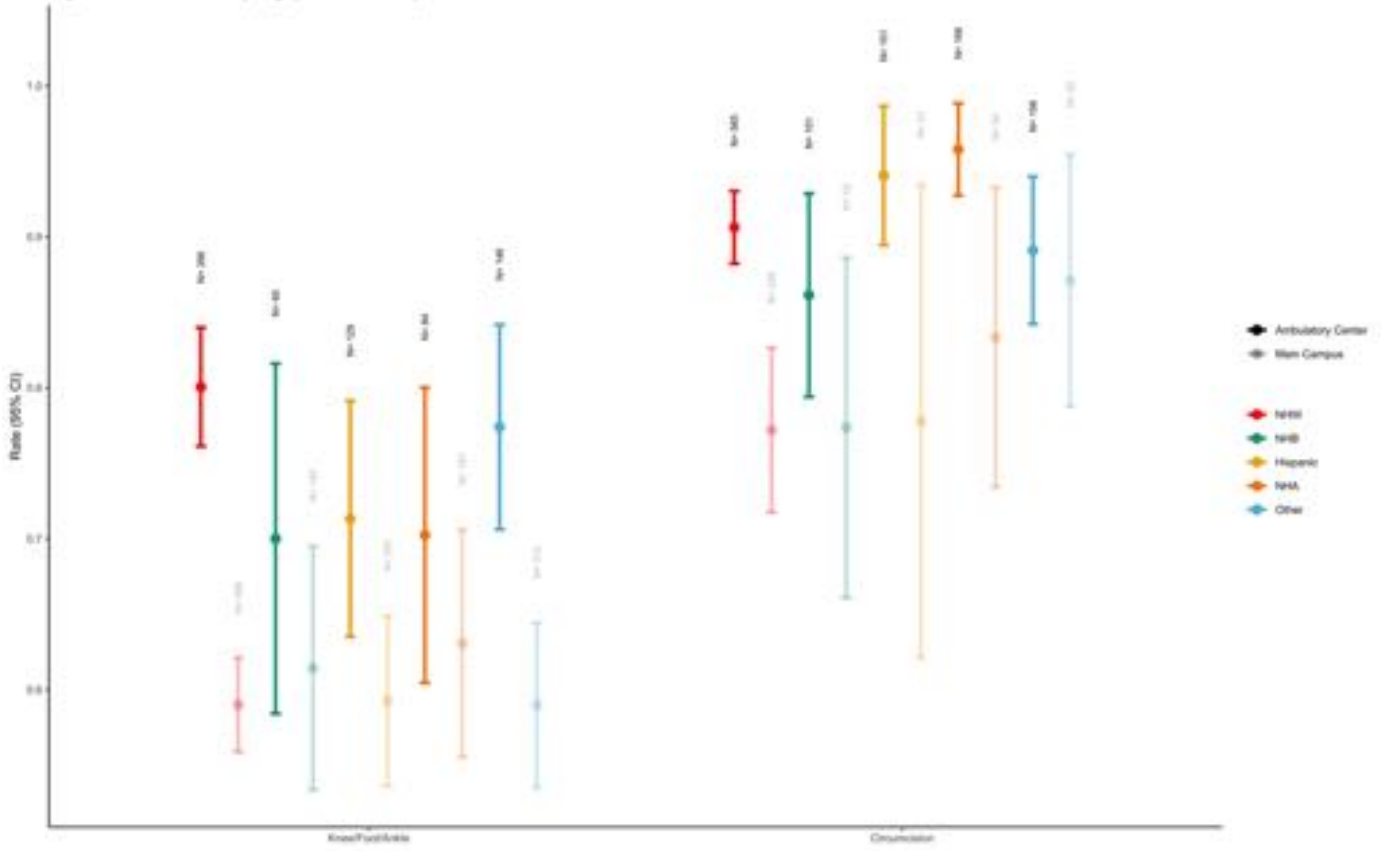


Figure 3

Regional Block Administration by Surgery and Race/Ethnicity



PEDIATRIC ANESTHESIOLOGY 11

Implementation of Telemedicine in a Pediatric Preoperative Anesthesia Clinic During COVID-19: Evaluating Patient Satisfaction

Richa Taneja[1], Ana Campos[2], Chaitanya Challa[1], Jessica Cronin[3], Caroll Vazquez-Colon[1], Anjna Melwani[1], Sohel Rana[1], Giuliana Geng-Ramos[1]

[1]Children's National Hospital, Washington, DC, [2]The George Washington University, Washington, DC, [3]Children's National Health System, Washington D.C., DC

INTRODUCTION: The COVID-19 pandemic has presented an unprecedented challenge in delivering healthcare to patients around the world. Telemedicine was increasingly adopted as a way to deliver healthcare during this pandemic while reducing staff exposure to potentially ill patients, preserving PPE, and minimizing the crowding of patients in waiting rooms. Our institution's pediatric Anesthesiology Preoperative Care Clinic was presented with the opportunity to implement telehealth in order to assess patients' risks prior to surgery. This is the first examination of patient satisfaction of telemedicine use in pediatric preoperative clinics since the start of the COVID-19 pandemic. This study explores patient satisfaction with video-based telemedicine visits utilizing telemedicine satisfaction survey in pediatric patients and their guardians presenting to an anesthesiology preoperative clinic.

METHODS: A retrospective chart review of telemedicine outpatient encounters by anesthesiologists from September 1, 2020 to December 15, 2020 was conducted. Only patients who were seen via video-based encounter were included, while patients who received telephone consults or in-person visits were excluded. If the patient was over the age of 18 and able to make medical decisions, they participated in the survey. Non-English-speaking patients were contacted with an interpreter. Demographic data and survey responses were collected anonymously. Data was stored in a REDCap database. Following the telemedicine visit, the patient and/or guardian was contacted by a research assistant to voluntarily complete the anonymous patient satisfaction survey. Verbal consent to participate was obtained. The survey included questions regarding interaction quality, ease of use, privacy considerations, comparison to in-person visits, and overall satisfaction. The survey tool allowed responses using the Likert scale to range over a spectrum from 1-strongly disagree' to 5-strongly agree. This project was submitted to the Institutional Review Board (IRB) and was determined to be a Quality Improvement Initiative that was exempt from further IRB review.

RESULTS: Between September 1, 2020 and December 15, 2020, a total of 325 patients received clinic-based preoperative consultations, of which 204 encounters were conducted using a video-based telemedicine platform. Survey responses were obtained from 101 of the 204 encounters, for a response rate of 49.5%. Patient demographic characteristics are presented in Table 1. The majority of participants preferred English as their primary language (88%). Most participants conducted the telemedicine visit via a smartphone (52%), followed by a laptop (37%). The majority of participants (>93%) either agreed or strongly agreed with statements regarding the benefits of the preoperative visit, concerns being addressed, clarity of the video, ability to talk easily and understand recommendations, maintenance of patient privacy, saving traveling time, overall satisfaction with the visit and participating in telemedicine again. Fewer participants (84% agree or strongly agree) felt the technology was easy to use. The lowest mean score was with effectiveness of a telemedicine visits being as good as an in-person visit (4.2), still a clear majority had positive responses with 84% who agreed or strongly agreed the telemedicine visit was as effective as an in-person visit. The results of satisfaction survey can be seen in Table 2.

CONCLUSION: The utilization of telehealth in Anesthesiology preoperative clinic has allowed healthcare practices to mitigate spread of COVID-19 in addition to other illnesses while also preserving PPE. While only a limited physical exam can be ascertained from a telehealth visit, anesthesiologists in preoperative clinic are otherwise able to obtain a comprehensive history over protected video-based visits. Specifically in a pediatric preoperative clinic setting, patients and guardians overwhelmingly had positive experiences with telemedicine visits. Most respondents agreed that telemedicine visits were as effective as in-person visits. However, follow-up with participants regarding limitations of virtual visits and potential difficulties with technology use could lead to further improvements with telehealth visits. Moving forward, given the positive feedback regarding telemedicine in Anesthesiology preoperative clinic, telemedicine can continue to be an effective tool to provide increased healthcare access to patients.

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Table 1: Patient demographics (N= 101)

Patient demographics	N= 101
Age (years), mean (SD)	9.1 (6.4)
Sex, n (%)	
Male	55 (54.5)
Female	46 (45.5)
Race, n (%)	
White	30 (33.3)
Black	43 (47.8)
Asian	3 (3.3)
American Indian or Alaska Native	1 (1.1)
Other	13 (14.4)
Ethnicity, n (%)	
Hispanic or Latino	19 (19.6)
Not Hispanic or Latino	78 (80.4)
Insurance status, n (%)	
Uninsured	1 (1.0)
Private insurance	57 (57.0)
Medicaid	40 (40.0)
Medicare	2 (2.0)
Preferred language, n (%)	
English	88 (88.0)
Spanish	11 (11.0)
Pashto	1 (1.0)
Procedure, n (%)	
Orthopedic	37 (37.0)
General Surgery	9 (9.0)
Otolaryngology	27 (27.0)
Plastic Surgery	3 (3.0)
Ophthalmology	1 (1.0)
Dental	4 (4.0)
Radiology	1 (1.0)
Urology	9 (9.0)
Other, Multiple Surgeons	9 (9.0)
Device used, n (%)	
Smartphone	52 (51.5)
Tablet	8 (7.9)
Laptop	37 (36.6)
Desktop	4 (4.0)
Educational attainment, n (%)	
Did not complete high school	5 (5.3)
Completed high school	18 (18.9)
Some college	24 (25.3)
Bachelor's degree	33 (34.7)
Post-graduate degree	15 (15.8)

Table 2: Likert scale score data (N=101)

Likert Scale Score	n (%)					Mean score (SD)	Median score (Range)
	Strongly Disagree (1)	Disagree (2)	Neutral (3)	Agree (4)	Strongly Agree (5)		
My concerns were addressed during this visit	0 (0%)	0 (0%)	1 (1.0)	34 (33.7)	66 (65.3)	4.6 (0.5)	5.0 [3.0, 5.0]
Preoperative anesthesia instructions were given during this visit	1 (1.0)	3 (3.0)	3 (3.0)	35 (35.0)	58 (58.0)	4.5 (0.8)	5.0 [1.0, 5.0]
I feel this preoperative consultation was beneficial to my child's care	0 (0%)	0 (0%)	0 (0%)	37 (37.0)	63 (63.0)	4.6 (0.5)	5.0 [4.0, 5.0]
The technology to set up the telemedicine visit was easy to use	1 (1.0)	5 (5.0)	10 (9.9)	36 (35.6)	49 (48.5)	4.3 (0.9)	4.0 [1.0, 5.0]
I was able to talk comfortably with the providers on the video screen	0 (0%)	2 (2.0)	2 (2.0)	32 (31.7)	65 (64.4)	4.6 (0.6)	5.0 [2.0, 5.0]
I was able to understand the provider's recommendations for my child	0 (0%)	1 (1.0)	1 (1.0)	30 (29.7)	69 (68.3)	4.7 (0.6)	5.0 [2.0, 5.0]
I was able to see the providers easily during the telemedicine visit	0 (0%)	1 (1.0)	2 (2.0)	31 (30.7)	67 (66.3)	4.6 (0.6)	5.0 [2.0, 5.0]
I feel confident my child's privacy was respected during the telemedicine visit	0 (0%)	0 (0%)	2 (2.0)	34 (33.7)	65 (64.4)	4.6 (0.5)	5.0 [3.0, 5.0]
Overall, I am very satisfied with this preoperative anesthesia visit	0 (0%)	0 (0%)	0 (0%)	38 (37.6)	63 (62.4)	4.6 (0.5)	5.0 [4.0, 5.0]
The telemedicine pre-operative anesthesia visit was as good as a regular in-person visit	3 (3.0)	5 (5.0)	8 (7.9)	39 (38.6)	46 (45.5)	4.2 (1.0)	4.0 [1.0, 5.0]
Telemedicine saved me time traveling to a hospital or clinic	1 (1.0)	1 (1.0)	2 (2.0)	27 (26.7)	70 (69.3)	4.6 (0.7)	5.0 [1.0, 5.0]
The visit provided over the telemedicine system is as effective as in-person visits	2 (2.0)	7 (6.9)	7 (6.9)	30 (29.7)	55 (54.5)	4.3 (1.0)	5.0 [1.0, 5.0]
I would use telemedicine services again	2 (2.0)	1 (1.0)	2 (2.0)	33 (33.0)	62 (62.0)	4.5 (0.8)	5.0 [1.0, 5.0]
Overall, I am satisfied with this telemedicine system	0 (0%)	1 (1.0)	1 (1.0)	39 (38.6)	60 (59.4)	4.6 (0.6)	5.0 [2.0, 5.0]

PEDIATRIC ANESTHESIOLOGY 12

Anesthesia and Neurotoxicity Study Design, Execution, and Reporting in the Nonhuman Primate: a Deep Dive

Feng Gao[1], Joseph A Wahl[2], Thomas F Floyd[3]

[1]Baylor College of Medicine, Dallas, TX, [2]Texas Tech University, Lubbock, United States of America, [3]University of Texas Soutwestern, Dallas, TX

INTRODUCTION: Concern for role of anesthesia in developmental delay in children primarily originated from neonatal rodent and non-human primate (NHP) studies, yet prospective clinical trials, including Pediatric Anesthesia Neuro Development Assessment (PANDA) and General Anesthesia versus Spinal Anesthesia (GAS), have largely not supported this concern[1-2]. Largely relying on these neonatal animal studies, the FDA issued the 2016 'Drug Safety Communication' warning on general anesthetics as potentially neurotoxic agents to young children[3]. Lately, the legitimacy of the rodent data has been called into concern by recent studies on confounding factors of hypoxia and hypercarbia during experiments[4-6]. However, the validity NHP data has not been reviewed in a systematic fashion. Herein, we present an objective and quantitative assessment of published NHP study rigor in experimental design, conduct, and reporting of outcomes.

METHODS: We conducted a systematic MEDLINE search from 2005 to November 2019 focusing on animals between postnatal age 0 to 40 days who underwent anesthetic exposure (Figure 1). Article screening and data extraction were conducted by 2 independent reviewers, with all conflicts reviewed and resolved by the principal investigator. A total of eighteen manuscripts were included (Table 1). We extracted anesthetic, route, dose, frequency and duration of exposures, age at exposure, ventilation, mortality, sample size, vitals, blood gases, anesthesia monitoring, behavioral and neuroapoptosis outcomes. We also assessed adherence to the ASA (American Society of Anesthesiologist) monitoring and ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. Data were summarized as median (25th-75th percentile) and mean (SD).

RESULTS: Important deficits in study design, execution, and reporting were identified in neonatal NHP studies. Critical issues identified in study design included (Table 2): lack of blinding in data acquisition (56%) and analysis (100%), supratherapeutic (4-12 fold) maintenance dosing in 28% of studies, lack of sample size justification (89%) resulting in a mean (SD) sample size of 6 (3) animals per group. Critical items identified in the conduct and reporting of studies included (Table 3): documentation of anesthesia provider (0%), electrocardiogram monitoring (40%), arterial monitoring (5%), spontaneous ventilation employed (40%), failed intubations resulting in commingling ventilated and unventilated animals in data analysis, inaccurate reporting of failed intubation, and only 50% reporting on survival. Inconsistencies were also noted in drug related induction of neuroapoptosis and region of occurrence. Further, 66-100% of behavior outcomes were not significantly different from controls (Figure 2).

CONCLUSION: Important deficits in study design, execution, and reporting were identified in neonatal NHP studies. These results raise concern for the validity and reliability of these studies and may explain in part the divergence from results obtained in human neonates.

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Table 1. Nonhuman primate study characteristics

Year	Citation	Species	Age	Anesthetic	Dose/Route	Duration	Outcome
2007	Slikker *et al.*[31]	Macaca mulatta	G122	Ket	20-50 mg kg^{-1} h^{-1} (i.v.)	24h	Neuroapoptosis
			P5-6	Ket	20-50 mg kg^{-1} h^{-1} (i.v.)	24h	Neuroapoptosis
			P35-37	Ket	20-50 mg kg^{-1} h^{-1} (i.v.)	24h	Neuroapoptosis
			P5	Ket	20-50 mg kg^{-1} h^{-1} (i.v.)	3h	Neuroapoptosis
2009	Zou *et al.*[21]	Macaca mulatta	P5	Ket	20-50 mg kg^{-1} h^{-1} (i.v.)	3h	Neuroapoptosis
			P5-6	Ket	20-50 mg kg^{-1} h^{-1} (i.v.)	9h	Neuroapoptosis
			P5-6	Ket	20-50 mg kg^{-1} h^{-1} (i.v.)	24h	Neuroapoptosis
2010	Brambrink *et al.*[28]	Macaca mulatta	P6	Iso	0.7-1.5% (I)	5h	Neuroapoptosis
2011	Paule *et al.*[33]	Macaca mulatta	P5-6	Ket	20-50 mg kg^{-1} h^{-1} (i.v.)	24h	Behavior
2011	Zou *et al.*[29]	Macaca mulatta	P5-6	N2O	70% (I)	8h	Neuroapoptosis
			P5-6	Iso	1% (I)	8h	Neuroapoptosis
			P5-6	N2O+Iso	70% N2O + 1% Iso (I)	8h	Neuroapoptosis
2012	Brambrink *et al.*[27]	Macaca mulatta	G120	Ket	48.1-86.5 mg kg^{-1} h^{-1} (i.v.)	5h	Neuroapoptosis
			P6	Ket	18.4 - 56.0 mg kg^{-1} h^{-1} (i.v.)	5h	Neuroapoptosis
2012	Brambrink *et al.*[26]	Macaca mulatta	P6	Iso	0.7-1.5% (I)	5h	Neuroapoptosis
2012	Zhang *et al.*[23]	Macaca mulatta	P5-6	N20 + Iso	70% N20 + 1% Iso (I)	8h	18F-FEPPA uptake by PET/CT
2013	Creeley *et al.*[25]	Macaca mulatta	G120	Pro	350-450 mcg kg^{-1} min^{-1} (i.v.)	5h	Neuroapoptosis
			P6	Pro	300-400 mcg kg^{-1} min^{-1} (i.v.)	5h	Neuroapoptosis
2015	Zhou *et al.*[30]	Macaca fascicularis	P6	Sev	2.0-2.6% (I)	5h	Behavior, Protein Expression
2015	Liu *et al.*[24]	Macaca mulatta	P5-6	Sev	2.5% (I)	9h	Neuroapoptosis, Lipid Metabolism
2015	Raper *et al.*[15]	Macaca mulatta	P6-10, 14d later, 28d later	Sev	2% (I)	4h (3x)	Behavior
2016	Zhang *et al.*[35]	Macaca mulatta	P5-6	Sev	2.5% (I)	8h	18F-FEPPA uptake by PET/CT, Neuroapoptosis
2017	Schenning *et al.*[32]	Macaca mulatta	P20	Iso	1.3-2.5% (I)	5h	Neuroapoptosis
			P40	Iso	1.3-2.5% (I)	5h	Neuroapoptosis
2017	Coleman *et al.*[36]	Macaca mulatta	P6, P9, P12	Iso	0.7-1.5% (I)	5h (3x)	Behavior
			P6	Iso	0.7-1.5% (I)	5h	Behavior
2017	Alvarado *et al.*[34]	Macaca mulatta	P6-10, 14d later, 28d later	Sev	2% (I)	4h (3x)	Vision impairment
2017	Noguchi *et al.*[37]	Macaca mulatta	P6	Iso	0.7-1.5% (I)	3h	Neuroapoptosis
2018	Raper *et al.*[22]	Macaca mulatta	P6-10, 14d later, 28d later	Sev	2% (8% max with 100% O2) (I)	4h (3x)	Behavior

i.v.: intravenous; I: inhaled; G: gestational; P: postnatal; Ket: ketamine; Iso: isoflurane; N2O: nitrous oxide; Pro: propofol; Sev: sevoflurane; 14d: 14 days; 28d: 28 days; 18F-FEPPA: 18F-labeled fluoroethoxybenzyl-N-(4-phenoxypyridin-3-yl) acetamide; PET-CT: positron emission tomography–computed tomography.

Table 2. Characteristics of included studies

Characteristics	Exposed (n=18 studies)	Unexposed (n=18 studies)
Animal species, No. (%)		
Macaca mulatta	17 (94)	17 (94)
Macaca fascicularis	1 (6)	1 (6)
Age at first exposure, PND, No. (%)		
5-10	17 (94)	17 (94)
20	1 (6)	1 (6)
35-37	1 (6)	1 (6)
40	1 (6)	1 (6)
Anesthetics, No. (%)		
Isoflurane	7 (39)	
Sevoflurane	6 (33)	
Ketamine	4 (22)	
Propofol	1 (6)	
Isoflurane + Nitrous Oxide	2 (11)	
Exposure frequency, No. (%)		
Single	14 (78)	
Triple	4 (22)	
Duration maternal separation, min, No (%)		
0		5 (28)
30		3 (17)
Unspecified		1 (4)
Duration of behavior follow up, yr, No. (%)		
< 1	2 (11)	2 (11)
1-2	2 (11)	2 (11)
2-3	1 (6)	1 (6)
3-4	1 (6)	1 (6)
Primary study outcome, No. (%)		
Apoptosis	10 (56)	10 (56)
Behavior	6 (33)	6 (33)
PET-CT	2 (11)	2 (11)
Sample size, mean (SD)	6 (3)	6 (3)
Apoptosis studies	4 (1)	4 (1)
Behavior studies	8 (2)	9 (2)
PET-CT	5 (1)	4 (0)
Study design, No. (%)		
Randomization	17 (94)	17 (94)
Blinding data collecting	8 (44)	8 (44)
Blinding data analysis	0 (0)	0 (0)
Sample size calculation	2 (11)	2 (11)

PND: postnatal day.

Table 3. Summary of anesthesia monitoring

Characteristics	Exposed (n=18 studies)	Unexposed (n=18 studies)
Overall mortality, No. (%)	1 (4)	0 (0)
Perioperative mortality, No. (%)		
Reported all animals survived	9 (50)	
Did not mention survival or mortality	9 (50)	
Ventilation, No. (%)		
Controlled	11 (61)	
Spontaneous	4 (22)	
Not specified	3 (17)	
Fraction of inspired oxygen, No. (%), %		
Not specified	13 (72)	
30	4 (22)	
100	1 (6)	
Recovery after anesthesia, No. (%)		
Room air	17 (94)	
Not specified	1 (6)	
ASA Monitoring, No. (%)		
Presence of anesthesia personnel	0 (0)	0 (0)
Pulse oximetry	17 (94)	6 (33)
Heart rate	17 (94)	6 (33)
Capnography	17 (94)	5 (28)
NIBP	16 (89)	6 (33)
Temperature	16 (89)	11 (61)
FIO2	10 (83)[a]	0 (0)
Electrocardiogram	7 (39)	0 (0)
Intubation Reporting, No. (%)		
Pre-oxygenation	0 (0)	
Skill level of personnel intubating	0 (0)	
Number of attempts	0 (0)	
MAP, median [25th-75th], mmHg		
Nadir MAP (n = 5 exposed, 2 unexposed)	38 [35-42]	66 [62-69]
Venous blood gases, median [25th-75th], mmHg		
Nadir pH (n = 3)	7.31 [7.28-7.31]	7.30 [7.30-7.30]
Peak PCO2 (n = 3)	40 [39-44]	43 [43-43]
Peak *P*CO2 (n = 1)	49	
Nadir *P*O2 (n = 1)	211	
Monitoring frequency, median [25th-75th], hr		
Blood pressure (n = 14 exposed, 6 unexposed)	0.25 [0.25-0.50]	2 [1.8-3]
Heart rate (n = 15 exposed, 6 unexposed)	Cont [Cont-0.08]	1.5 [1.5-1.8]
End-tidal CO2 (n = 15 exposed, 5 unexposed)	Cont [Cont-0.08]	1.5 [1.5-1.5]
Pulse oximetry (n = 15 exposed, 6 unexposed)	0.25 [0.08-1]	1.5 [1.5-1.8]
Temperature (n = 14 exposed, 11 unexposed)	1 [0.25-2]	1 [twice[b]-1.5]
Blood gases (n = 14 exposed, 9 unexposed)	2 [1.5-2]	twice [twice-2]
Blood gas monitoring, No. (%)		
VBG	11 (61)	9 (50)
ABG	1 (6)	0 (0)

NIBP: Non-invasive blood pressure; MAP: Mean arterial pressure; FIO2: Fraction inspired oxygen; Cont: Continuous; VBG: Venous blood gas; ABG: Arterial blood gas; *P*O2: partial pressure of oxygen; *P*CO2: partial pressure of carbon dioxide. [a]Only 12 studies were mechanically ventilated where FIO2 was measurable. [b]At baseline and after recovery.

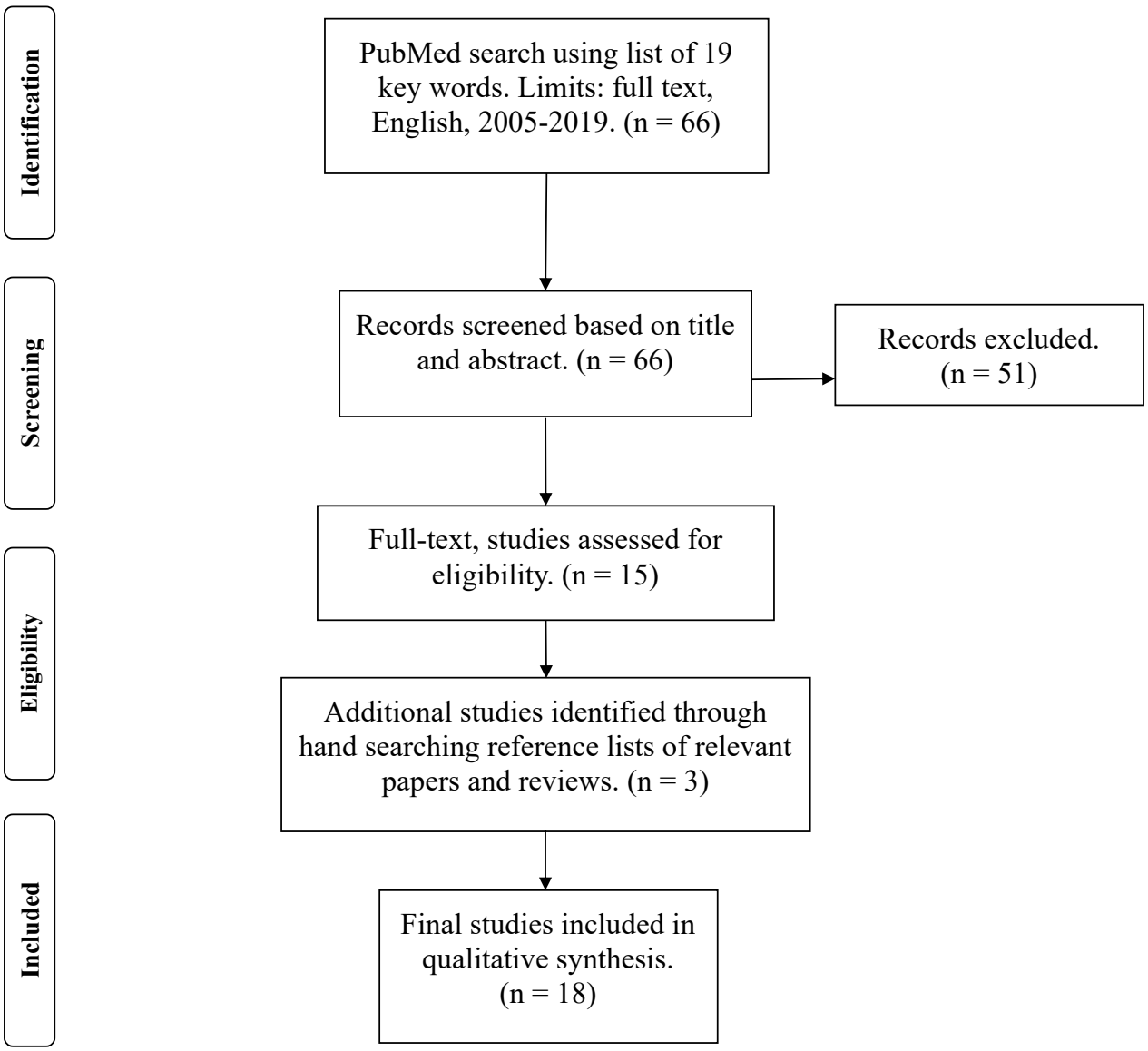

Figure 1. PRISMA flow chart: methodology applied and results.

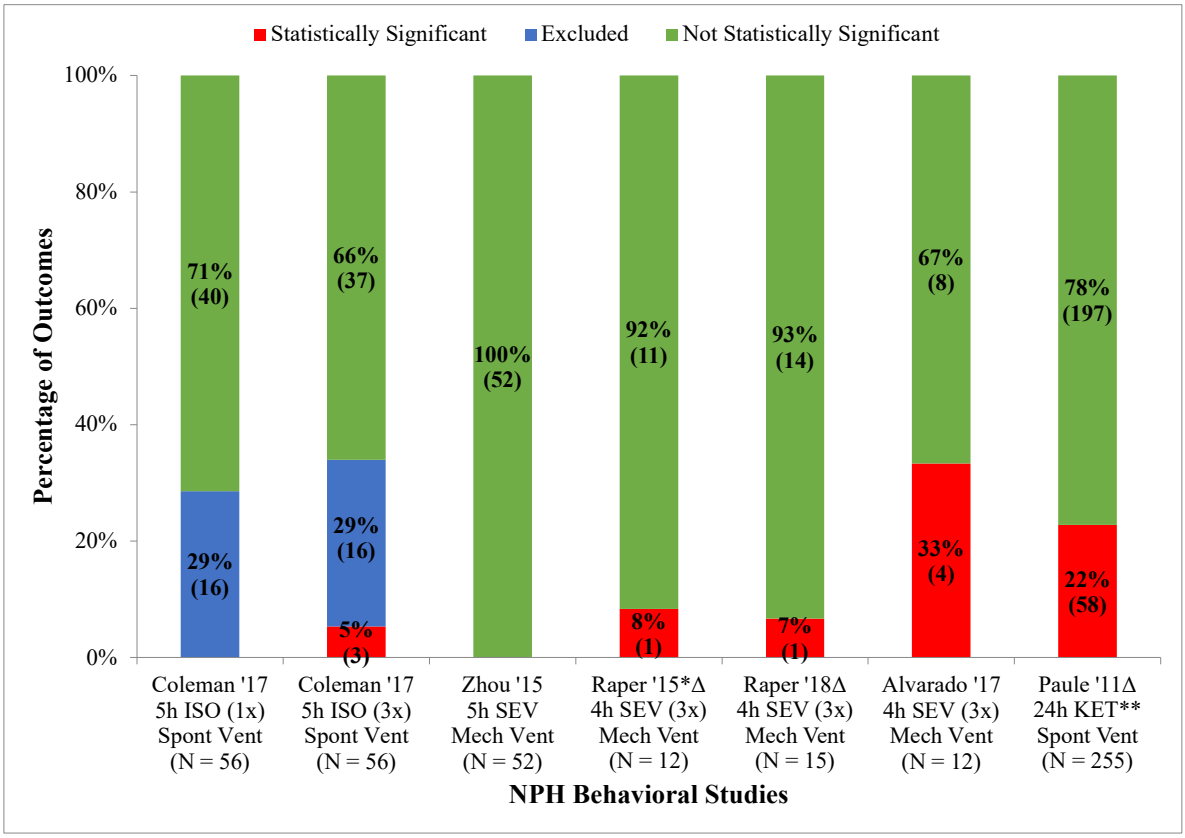

Figure 2. Behavioral study outcome breakdown. ISO: isoflurane; SEV: sevoflurane; KET: ketamine; Mech Vent: mechanical ventilation; Spont Vent: spontaneous ventilation. *Same test no longer statistically significant at 2-year follow up in Raper 2018. **Anesthetic Overdose by 4 to 11-fold. Δ: Rater not blinded.

PEDIATRIC ANESTHESIOLOGY 13

Development and Validation of an Efficient Pediatric Affect Scale

Kristin M Kennedy[1], Michael Khoury[2], Madison Kist[2], Ellen Wang[1], Sam Rodriguez[1], Christian Jackson[3], Justin C Yuan[1], Thomas Caruso[1]

[1]Stanford University School of Medicine, Stanford, CA, [2]Lucile Packard Children's Hospital, Palo Alto, CA, [3]Stanford University, Stanford, CA

INTRODUCTION: Pediatric anesthesiologists must be able to rapidly assess and treat perioperative distress (PMID: 18633018). Behavioral assessments require reliable scales that can be efficiently completed (PMID: 3430286). We investigated an internally developed scale that can be utilized for preprocedural affect during peripheral intravenous (PIV) placement and mask induction of anesthesia. The primary aim was to report the correlation between our scale and previously validated scales. The secondary aims were to report inter and intra rater reliability.

METHODS: The HRAD+/- scale was developed after survey to 10 pediatric anesthesiologists from institutions in the United States. HRAD+/- stands for Happy, Relaxed, Anxious, Distressed, equally scaled from 0 to 3, with a dichotomous answer to cooperativity, yes or no. Preoperative pediatric nurses and pediatric anesthesiology faculty were recruited from April 2020 to November 2020 for participation. Using 24 previously collected videos of children 4-7 years old undergoing preoperative PIV placement and mask induction, participants rated the videos with the new scale, called HRAD+/-. Participants repeated the video scoring process 3 months after their initial assessment. The Observation Scale of Behavioral Distress (OSBD) was the reference scale for preoperative PIV affect, the Yale Preoperative Anxiety Scale (mYPAS) was the reference scale for mask induction anxiety, and the induction compliance checklist (ICC) was the cooperativity reference. Two trained research advisors provided mYPAS, OSBD, and ICC scores for each video. Correlations between HRAD+/- and each of the reference scales were analyzed using R. Inter- and intra-rater reliability was assessed using Light's kappa and Cohen's kappa, respectively.

RESULTS: 21 anesthesiologists and 21 preoperative nurses independently rated each video twice. HRAD+/- scores had strong correlation with OSBD and mYPAS (0.723 and 0.846, respectively). The cooperativity scores had strong correlation with ICC scores in the preoperative PIV and mask inductions groups (-0.869 and -0.715, respectively). Inter-rater reliability for HRAD+/- was mild for the preoperative PIV and moderate for mask induction assessments (0.378, $p < 0.0001$ and 0.414, $p < 0.0001$, respectively). Inter-rater reliability for cooperativity were moderate for both the preoperative PIV and mask induction assessments (0.683, $p < 0.0001$ and 0.797, $p < 0.0001$, respectively). Intra-rater reliability for HRAD+/- were moderate for the preoperative PIV and mask induction assessments (0.678 and 0.675, respectively). Intra-rater reliability for cooperativity were strong for the preoperative PIV and mask induction assessments (0.765 and 0.894, respectively).

CONCLUSION: HRAD+/- is an efficient and reliable evaluation scale that serves as a practical alternative for measuring pediatric affect during preoperative PIV placement and during mask induction. The results demonstrate strong correlation against well-known more complex affect scales.

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Elliott CH, Jay SM, Woody P. An observation scale for measuring children's distress during medical procedures. J Pediatr Psychol. 1987 Dec;12(4):543-51. doi: 10.1093/jpepsy/12.4.543. PMID: 3430286.

Figure 1: Correlation between OSBD and HRAD+/- scores, (r=0.723)

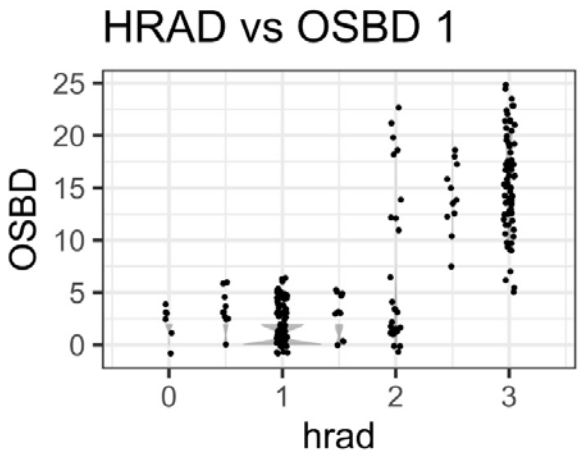
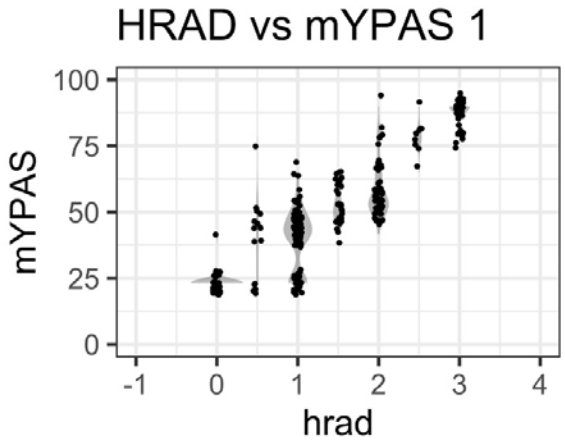


Figure 2: Correlation between mYPAS and HRAD+/- scores, (r=0.846)



PEDIATRIC ANESTHESIOLOGY 14

Anesthetic Outcomes in Pediatric Patients with COVID-19: A Matched Cohort Study

Jessica Cronin[1], Jonathon H Nelson[1], Ian Farquhar[2], Barbara Braffett[3], Ionut Bebu[4], Sophie Pestieau[5], Giuliana Geng-Ramos[6], Eugenie Heitmiller[5], Nina Deutsch[7]

[1]Childrens National, Washington, DC, [2]George Washington School of Medicine, Washington, DC, [3]George Washington University, Washington, DC, [4]George Washington University, Washington, DC, [5]Children's National Health System, Washington, DC, [6]Children's National Hospital, Washington, DC, [7]Children's National Medical Center, Washington DC, DC

INTRODUCTION: Severe acute respiratory syndrome coronavirus 2 (SARS-Co-V-2) is now widespread in most countries. As evidence regarding the clinical implications of SARS-Co-V-2 continues to evolve, such data is crucial to inform decision making in healthcare. Pediatric patients with viral infections are known to be vulnerable to perioperative complications, often respiratory in nature. Although the SARS-Co-V-2 pandemic has been raging for over a year, limited information is available regarding the perioperative and anesthetic risks associated with concurrent SARS-CO-V-2 infection, particularly in children. Several studies have demonstrated that postoperative pulmonary complications occur frequently in adult patients with perioperative SARS-CoV-2, however comparable data is not available for pediatric patients. This observational study compared anesthetic outcomes in pediatric patients with and without confirmed SARS-CoV-2 infection, undergoing general anesthesia. We hypothesized that among children with SARS-CoV-2, an association exists between the presence of symptoms and post- anesthesia complications.

METHODS: We completed a single-center, retrospective, case-control study of 35 pediatric patients with confirmed SARS-CoV-2 infection who underwent anesthesia for a surgical procedure or diagnostic study and 70 non-SARS-CoV-2 control patients, matched 1:2 by age and type of procedure, occurring between 1/3/2020 and 9/24/2020. The co-primary outcomes of the study were 30-day mortality and hospital length of stay (LOS). Secondary outcomes included intraoperative and post-anesthesia complications within 30 days of the procedure or diagnostic study under anesthesia. This study was approved by the institutional review board. Conditional logistic regression models were used to evaluate the relationship between cases and controls and prognostic factors.

RESULTS: There was no significant difference in age, weight, or gender between cases and controls (Table 1). SARS-CoV-2 cases were more likely to exhibit preoperative upper respiratory infection symptoms than controls. There were no deaths within 30 days of procedure. While there was no statistically significant difference in hospital LOS between the two groups, there was a trend toward a longer LOS among SARS-CoV-2 cases. There were no intraoperative complications in either group. Twenty-six percent of SARS-CoV-2 cases had post-anesthesia complications compared to 1% of controls (OR=18.00, 95% CI 2.49,788.96, p=0.0007). This included a diagnosis of Systemic Inflammatory Response Syndrome, the need for prolonged invasive or non-invasive respiratory support, vasopressor requirement, clinically significant stridor, and a small pericardial effusion. Comparing SARS-CoV-2 patients that were symptomatic (n=13) to those that were asymptomatic (n=22), there was no difference in the incidence of post-anesthesia complications (4 cases among the symptomatic patients vs. 5 cases among the asymptomatic patients, p=0.8869) or in LOS (11.3 days among the symptomatic patients vs. 10.5 days among the asymptomatic patients, p=0.8733). In the adult literature, SARS-CoV-2 positive surgical patients are at higher risk of serious adverse events than their SARS-CoV-2 negative counterparts, even when they are asymptomatic at the time of the procedure. Our study suggests that a similar pattern may be present in SARS-CoV-2 positive pediatric patients as well. An increased need for respiratory support in the post-anesthesia period, even for patients who are asymptomatic, suggests that elective procedures and exams under anesthesia should be postponed in SARS-CoV-2 positive patients. In line with this, current guidelines recommend postponing elective surgery until the patient is no longer infectious and has demonstrated recovery from SARS-CoV-2. Importantly, while adult studies have demonstrated increased mortality, our study population had no 30-day mortality. However, our analysis is limited by the small number of patients in this study. As the pandemic continues, the number of SARS-CoV-2 positive pediatric patients will only continue to grow, warranting further studies to continue to guide best practice.

CONCLUSION: SARS-CoV-2 positive pediatric patients undergoing surgical procedures or exams under anesthesia may be at higher risk for immediate post-anesthesia complications than their SARS-CoV-2 negative counterparts. SARS-CoV-2 status is important to discern in evaluating risk for post-anesthesia complications in this patient population.

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Table 1. Demographic Characteristics and Anesthesia Outcomes

	SARS-CoV-2 Diagnosis			
	Not Detected (n=70)	**Detected (n=35)**	**OR (95% CI)**	**p-value***
Race, n (%)				
Asian	8 (11)	2 (6)		
Black or African American	20 (29)	13 (37)		
White	17 (24)	1 (3)		
Unknown / Not Reported	25 (36)	19 (54)		
Ethnicity, n (%)				
Hispanic or Latino	20 (29)	17 (49)		
Not Hispanic or Latino	50 (71)	18 (51)		
ASA, n (%)				
1-2	50 (71)	14 (40)		
3-5	20 (29)	21 (60)		
Age, median, years	3.6 (0.9-6.5)	3.7 (0.9-6.3)	0.84 (0.48,1.48)	0.5477
Sex, n (%)				
Female	35 (50)	16 (46)	1.0	
Male	35 (50)	19 (54)	1.17 (0.50,2.74)	0.8421
Number of chronic conditions, n (%)†				
None	50 (71)	20 (57)	1.0	
One	15 (21)	11 (31)	3.94 (0.89,23.94)	0.0769
Two or more	5 (7)	4 (11)	7.06 (0.57,129.72)	0.1641
Weight, median, kg	16.2 (9.9-25.9)	16.0 (9.4-28.0)	1.00 (0.96,1.05)	0.8270
Any URI symptoms at time of anesthetic, n (%)~				
Absent	65 (93)	22 (63)	1.0	
Present	5 (7)	13 (37)	21.07 (3.06,907.48)	**0.0001**
Post-anesthesia complications, n (%)				
Systemic Inflammatory Response Syndrome	0	2 (6)		
Respiratory support	1 (1)	7 (20)		
Vasopressors	0	2 (6)		
Ventilation ≥24 hours	0	4 (11)		
Other pulmonary	0	4 (11)		
Thrombotic	0	0		
Hemorrhagic	0	0		
Cardiac	0	1 (3)		
Any post-anesthesia complications, n (%)	1 (1)	9 (26)	18.00 (2.49,788.96)	**0.0007**
Hospital length of stay, mean ± sd, days	6.8 ± 15.9	10.8 ± 18.2	1.03 (0.99,1.07)	0.1515

*P-value from stratified exact logistic regression models.

†P-value=0.0546 with the number of chronic conditions as a quantitative variable defined as 0=no chronic conditions, 1=one chronic condition, and 2=two or more chronic conditions. Chronic conditions included: asthma, congenital heart disease, cancer, history of prematurity, diagnosed congenital syndrome with multiple comorbidities, or other. Other conditions included: hepatoblastoma, seizures, sickle cell anemia, history of necrotizing enterocolitis with dependence on total parental nutrition.

~ URI=upper respiratory infection. Symptoms include cough, fever, rhinorrhea, diarrhea, cervical lymphadenopathy, sore throat, or acute respiratory failure.

PEDIATRIC ANESTHESIOLOGY 15

The Impact of Routine Hemoglobin Screening in Young Infants Undergoing General Anesthesia

Alison L Robles[1], Anthony Tantoco[1], Kristen Rao[2], John Hajduk[1], Karen Rychlik[3], Hubert Benzon[1], Eric Cheon[1]

[1]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, United States of America, [3]Biostatistics Research Core, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

INTRODUCTION: Use of routine, preoperative hemoglobin testing in pediatric patients has long been debated. A nadir occurs in term infants at 8–12 weeks and in preterm infants at 3–6 weeks, making this population at risk for clinically significant anemia.[1] Identifying these patients allows for case postponement for treatment of anemia and intraoperative caffeine administration to mitigate risk for apnea imparted by anemia. However, preoperative testing is costly and unpleasant for the patient, and may not alter management in certain contexts.[2] We sought to determine the value of hemoglobin screening in infants undergoing anesthesia.

METHODS: This study was approved by our Institutional Review Board (IRB 2019-2313). Patients ≤6 months who underwent procedures at our institution January 1, 2015-December 31, 2017, were included in this study. Cases excluded were those with non-elective case type, missing covariate data, an American Society of Anesthesiologists (ASA) classification of ≥3, or another indication for hemoglobin testing. The authors' institutional policy dictates preanesthetic screening hemoglobin for term infants ≤3 months and preterm infants ≤6 months. The primary outcome was case postponement while the secondary outcome was caffeine administration. Associations between baseline variables of interest and 1) hemoglobin testing and 2) caffeine administration were evaluated using univariable generalized linear mixed models. To identify adjusted associations between preoperative hemoglobin testing and caffeine administration, a multivariable generalized linear mixed model was generated.

RESULTS: 533 patients were included in this analysis. 147 patients (27.6%) had a hemoglobin drawn prior to their anesthetic. The mean hemoglobin value was 11.92 g/dL (SD + 2.19) with 18 (12.24%) qualifying as anemic. Hemoglobins were drawn a mean of 6.41 days (SD + 8.34) prior to anesthesia. No case cancellations were attributed to anemia. One patient who was identified as anemic was started on iron supplementation and proceeded with anesthesia as planned less than 1 week later. ASA 2 classification, preterm birth, and operative procedure type were associated with intraoperative caffeine administration on multivariable analysis.

CONCLUSION: In our analysis, neither case cancellation nor caffeine administration were altered by hemoglobin screening. One patient found to be anemic was started on iron supplementation but underwent anesthesia as originally scheduled, prior to when supplementation would have taken effect. Our findings demonstrate routine hemoglobin screening does not alter clinical management, even in this cohort of young infants, who are at risk for anemia.

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Table A. Cohort Characteristics

Baseline Characteristic	Total Sample, n = 533
Gender, n (%)	
Male	359 (67.35)
Female	174 (32.65)
Race, n (%)	
White	262 (49.16)
Black/African American	72 (13.51)
Asian	37 (6.94)
Multiple Races	33 (6.19)
Other	129 (24.2)
Ethnicity, n (%)	
Not Hispanic	400 (75.05)
Hispanic	126 (23.64)
Unknown/Declined	7 (1.31)
ASA Physical Status Classification, n (%)	
1	232 (43.53)
2	301 (56.47)
Premature birth, n (%)	186 (34.9)
Procedure type	
Nonoperative	114 (21.39)
Operative	419 (78.61)
Age at visit, years	0.2 (± 0.10)

ASA, American Society of Anesthesiologists

Table B. Univariable Analysis of Patients Undergoing Hemoglobin Screening

Baseline Characteristic	Screening Hemoglobin Mean ± SD/n (%)		OR (95% CI)	*P*-value
	Drawn, n = 147 (27.58%)	Not Drawn, n = 386 (72.42%)		
Gender, n (%)				
Male	106 (72.1)	253 (65.5)	[ref]	
Female	41 (27.9)	133 (34.5)	0.74 (0.47 - 1.15)	0.168
Race, n (%)				
White	75 (51.0)	187 (48.5)	[ref]	
Black/African American	16 (10.9)	56 (14.5)	0.71 (0.37 - 1.38)	0.297
Asian	12 (8.2)	25 (6.5)	1.20 (0.54 - 2.65)	0.643
Multiple Races	10 (6.8)	23 (6.0)	1.08 (0.46 - 2.54)	0.845
Other	34 (23.1)	95 (24.6)	0.89 (0.54 - 1.49)	0.645
Ethnicity, n (%)				
Not Hispanic	106 (73.6)	294 (77.0)	[ref]	
Hispanic	38 (26.4)	88 (69.8)	1.20 (0.74 - 1.93)	0.438
ASA Physical Status Classification, n (%)				
1	62 (42.2)	170 (44.0)	[ref]	
2	85 (57.8)	216 (56.0)	1.08 (0.71 - 1.63)	0.705
Premature birth, n (%)	49 (33.3)	137 (35.5)	0.91 (0.59 - 1.40)	0.647
Procedure type, n (%)				
Nonoperative	18 (12.2)	96 (24.9)	[ref]	
Operative	129 (87.8)	290 (75.1)	2.38 (1.33 - 4.28)	0.006
Age at visit, years	0.18 (± 0.09)	.21 (± 0.10)	0.035 (0.004 - 0.319)	0.005

SD, standard deviation; ASA, American Society of Anesthesiologists; OR, odds ratio

Table C. Multivariable Generalized Linear Mixed Models for Intraoperative Caffeine Administration

Independent Variables	OR (95% CI)	*P*-value
ASA Physical Status Classification		
1	[ref]	
2	4.14 (1.74 - 9.87)	0.003
Preterm Birth	8.47 (3.98 - 18.06)	<.0001
Procedure Type		
Nonoperative	[ref]	
Operative	3.41 (1.17 - 9.93)	0.027

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

PEDIATRIC ANESTHESIOLOGY 16

Applying Machine Learning to Identify Pediatric Patients at Risk of Critical Perioperative Adverse Events: using the APRICOT Dataset

Hannah Lonsdale[1], Geoffrey M Gray[2], Hannah Yates[3], Luis Ahumada[4], Mohamed Rehman[5], Anna Varughese[5], Jim Fackler[6], Walid Habre[7], Nicola Disma[8]

[1]Johns Hopkins University, St Petersburg, FL, [2]Johns Hopkins All Children's Hospital, St Petersburg, FL, [3]Johns Hopkins All Children's Hospital, St Petersburg, FL, [4]Johns Hopkins All Children's Hospital, St Petersburg, United States of America, [5]Johns Hopkins All Children's Hospital, St. Petersburg, FL, [6]Johns Hopkins, Baltimore , United States of America, [7]University Hospitals of Geneva, Geneva, Switzerland, [8]Istituto Giannina Gaslini, Genova, Italy

INTRODUCTION: Literature on pediatric anesthesia focuses on clinical audits of morbidity and mortality from a single institution or country, which were not sufficiently powered to study rare, severe complications or mortality. The APRICOT (Anesthesia PRactice In Children Observational Trial) study aimed to identify the incidence, nature, and outcome of serious perioperative adverse events (PAEs) in children undergoing anesthesia, and the associated potential risk factors, using traditional statistical methodology. Anesthesia risk is currently calculated on a population 'one size fits all' basis, perhaps modified by the presence of certain known risk factors. However, each child presents a unique clinical picture and to incorporate this into individualized risk prediction is not yet possible. Experienced clinicians will recognize risk factors, especially for children who are ASA III or higher. The availability of a precision medicine approach to risk calculation for children generally considered 'low risk' enables anesthesia teams to better prepare the appropriate level of care for these children. Here we present a high performance machine learning model for classification of patients as high or low risk for a PAE as a secondary use of the APRICOT dataset.

METHODS: APRICOT studied the primary endpoint of incidence of perioperative severe critical events in 30 874 children undergoing anesthetic procedures across 33 European countries. Severe critical events defined by APRICOT were laryngospasm, bronchospasm, pulmonary aspiration, drug error, anaphylaxis, cardiovascular instability, neurological damage, peri-anesthetic cardiac arrest and post-anesthetic stridor. The critical event rate was 4.7%. We identified 27 425 patients (88% of the registry) categorized as ASA I or II, presenting for their first procedure and whose PAE was not caused by drug error. This subset experienced 1087 PAEs, for a rate of 4%. We handled missing fields using multiple imputation for continuous variables and random draw for discrete variables. A 25:1 class imbalance existed in the original dataset. Several sampling techniques were tested, of which under-sampling of the majority class produced the most effective results. Data was split in a stratified fashion 17:1 between training and testing. K-fold stratified cross validation was used for training (k=5). Models were built using random forest, extreme gradient boosting (XGB), XGB with histograms, Naïve-Bayes, k-nearest neighbor, AdaBooster, multi-level perceptron neural networks and support vector machines. A stacked classifier composed of random forest, XGB and XGB with histograms was also built. Model performance was evaluated using accuracy, AUROC, positive predictive value and negative predictive value. This study was classified as IRB exempt.

RESULTS: The top performing single model was extreme gradient boosting and achieved an accuracy between 0.7 and 0.8, an AUROC of 0.6-0.7, a maximum positive predictive value (PPV) of 0.13 and a negative predictive value (NPV) greater than 0.9. The stacked classifier models had an accuracy in excess of 0.8, AUROC of 0.7-0.8, a maximum PPV of 0.15 and a NPV in excess of 0.97. Our results show that airway interface, in-patient status and history of influenza are the most substantial predictive factors for severe PAEs. This study demonstrates the application of machine learning to classify risk in healthy children undergoing anesthesia. Our models show an AUROC that is considered acceptable when using a highly imbalanced dataset. However, even our best performing stacked model demonstrates a low PPV- as do many other models trained on clinical data, where class imbalance is common. This suggests that the most clinical utility may lie in using the high NPV as a screening tool to identify patients at low risk for PAE.

CONCLUSION: Individually identifying patients at low risk of severe critical PAE has clinical utility through helping clinicians to identify cases that have a low likelihood of care escalation to greater than routine levels. This may help in stratifying patients to receive care at satellite sites, or in informing the managing clinician's decisions in teaching and levels of supervision. We will continue to develop our work with providers to increase clinical confidence in the model, including the development of interpretability. We aim to produce a calculator and intuitive user interface using visual analytics methods so that front line clinical staff can use the models in real-time.

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PEDIATRIC ANESTHESIOLOGY 17

The Conundrum of Opioid Use in the Neonatal Intensive Care Unit (NICU): Providing Comfort or Aggravating Development?

Kunal Sualy[1], Sneh Koul[2], Jordan Hernandez[2], Victoria Schaal[2], Ann Anderson-Berry[1], Somwmya Yelamanchili[2], Steven J Lisco[2], Mohanad Shukry[1], Sneham Tiwari[2], Gurudutt Pendyala[2]

[1]University of Nebraska Medical Center/Children's Hospital & Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE

INTRODUCTION: Newborns in intensive care unit (ICU) settings post-surgery are often treated for prolonged periods with sedative medications, including opioids. Whilst developmental neurotoxicity associated with anesthetic agents has received attention from anesthesiologists for decades, it is still common practice to expose infants or toddlers to such agents during pediatric surgery. Studies suggest almost all general anesthetics could potentially induce structural and functional changes in the brain of neonatal animals.[1] Moreover, large-scale clinical studies also indicated learning disabilities and behavioral disturbances in some children are correlated with surgery under anesthesia before 4 years of age, especially in children undergoing multiple surgeries under general anesthesia.[2] Evidence from studies conducted in animal models, including rodent[3] and non-human primates,[4] suggest the possibility early developmental exposure to general anesthesia (GA) has harmful consequences for brain development. Although nearly all the evidence in human studies and animal models relates to GA as practiced in operating room (OR) settings, the FDA has issued a warning regarding the of risks associated with medications described as 'sedation drugs' used during surgery and other procedures.[5] The current proposal focuses on fentanyl, a mu opioid-receptor agonist, which is used commonly as part of GA, as well as to promote sedation in the neonatal intensive care unit (NICU). Of note, the duration of exposure may be the most critical difference between ICU sedation and OR GA, as NICU sedation can continue for days or even weeks. This leaves open an important question with potentially substantial public health ramifications: Does sedation for infants and young children as practiced in ICU settings have the potential to cause harm to the developing brain? Based on these factors, and the absence of any clear and comprehensive literature on long-term exposure of analgesics/sedatives, there is a compelling rationale and pressing need to study the effects of ICU-type sedation on the developing brain. Accordingly, our proposed studies will focus on testing the outcomes associated with long-term exposure of fentanyl in pre-term infants (23-36 week gestation) vs term infants (37-40 week gestation) on synaptogenesis – a key process of formation of synapses during brain development and subsequent impairment of behavioral outcomes at a later stage of life.

METHODS: The current study focused on rat pups at postnatal (P) 3 and 7 that mimic the pre-term and term infants equivalent in humans, respectively. Pups were injected with subcutaneous fentanyl at doses similar to seen in the NICU population for 11 and 7 days for the two groups. At P14 (represents peak synaptogenesis in rodents), body weights, lengths and head size circumference were measured, along with isolation of brains and blood plasma. The remainder of the pups underwent behavioral testing at P45 and P90.

RESULTS: Our preliminary results demonstrated that P3 animals had a marked reduction in the physical attributes compared to the control and P7 animals. Currently, molecular and behavioral studies are in progress and will be discussed in further detail at the conference.

CONCLUSION: The studies proposed are timely, novel and importantly help delineate the long-term exposure of Fentanyl in pre-term vs term infants on synaptogenesis and subsequent impairment of behavioral outcomes at a later stage of life. The outcomes will then help the pediatric clinical community to help decipher the conundrum of the safety of opioids use in neonates.

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PEDIATRIC ANESTHESIOLOGY 18

Risk factors for pediatric emergence delirium: a systematic review

Lieven F Ameye[1], Machiko Furuta[2], Marina Englesakis[3], Maria Alexandra Petre[4], Nan Gai[5], bibek saha[6], arie peliowski[7], Kazuyoshi Aoyama[8]

[1]Sick Kids Hospital Toronto, Toronto, Ontario, [2]National Center for Child Health and Development, Tokyo, Japan, [3]University Health Network, Toronto, Ontario, [4]Montreal Children's Hospital, Montreal, Quebec, [5]Hospital for Sick Children Toronto, Toronto, Canada, [6]John A. Burns School of Medicine of Hawaii at Manoa, Manoa, United States of America, [7]Sick Kids Hospital Toronto, Toronto, Canada, [8]SickKids Hospital, Toronto, Canada

INTRODUCTION: Emergence delirium (ED) is a transient abnormal mental state occurring in the immediate post-anesthesia period characterized by symptoms such as confusion, disorientation, irritability, inconsolable crying, and thrashing.[1] ED impacts approximately 25% of pediatric general anesthetics[2] and has substantial adverse effects such as injury to the patient and personnel, and increased nursing requirements, placing a significant burden on the healthcare system.[3] In order to reduce the incidence of ED and associated morbidities, patients at risk must be identified allowing the implementation of prophylactic care. However, our previous systematic review revealed that there is no useful risk prediction model or score for predicting ED in children(4). Hence, our objective is to conduct a systematic review to determine which risk factors are the most well established and have the best supporting evidence in pediatric patients undergoing general anesthesia.

METHODS: Data sources: We conducted a systematic literature search through 8 databases including Medline, Pubmed, Embase, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, PsycINFO, Scopus and Web of Science starting from their inception until December 2020, containing sets of terms reflecting our topic of interest, including general anesthesia, emergence delirium, risk factor, and children. Eligibility criteria for selecting studies and data extraction: According to PRISMA guidelines two reviewers independently reviewed titles, abstracts, and full texts; extracted data; and assessed study quality(5). Inclusion criteria included randomized controlled trials (RCTs) and prospective observational studies that investigated pre- and intra-operative risk factors of ED in pediatric patients undergoing general anesthesia. We excluded studies that investigated prognostic or diagnostic models for ED, and studies investigating interventions of ED. Retrospective observational studies, case-reports and -series, reviews, editorials, conference proceedings, comments, and animal studies were excluded. Primary outcome was an adjusted risk factor of ED through multi-variable regressions. The degree of each identified risk factor was assessed based on the adjusted risk ratios (RRs) or Odds ratios (ORs) with 95% confidence intervals. The protocol was registered at PROSPERO [CRD42020192221].

RESULTS: Out of 8721 abstracts we searched, the systematic review identified 37 eligible prospective observational studies (See the PRISMA flow). There were no eligible RCTs. The Pediatric Anesthesia Emergence Delirium (PAED) scale was used to determine ED in 18 studies, whereas 19 studies used another scale such as 3-point scale, 4-point scales with Aono or Watcha modifications, Cole 5-point scale. In the studies that used the PAED-scale, 12 studies (64,7%) used multi-variable regressions to identify risk factors for ED, while only 4 studies (21%) used multi-variable regressions in the studies that used another scale. Statistically significant risk factors of ED in children, identified in more than one study among 16 studies employed multi-variable regressions, are following: 1) younger than 6-years old; 2) otorhino-laryngological surgical procedures; 3) preoperative anxiety; and 4) fast emergence from general anesthesia.

CONCLUSION: Our systematic review has elucidated 4 adjusted risk factors of ED in children. These risk factors can be used in clinical setting to identify children at risk for ED. Furthermore, when conducting clinical research of ED in children, these risk factors should be employed for risk adjustment or stratification in the analyses.

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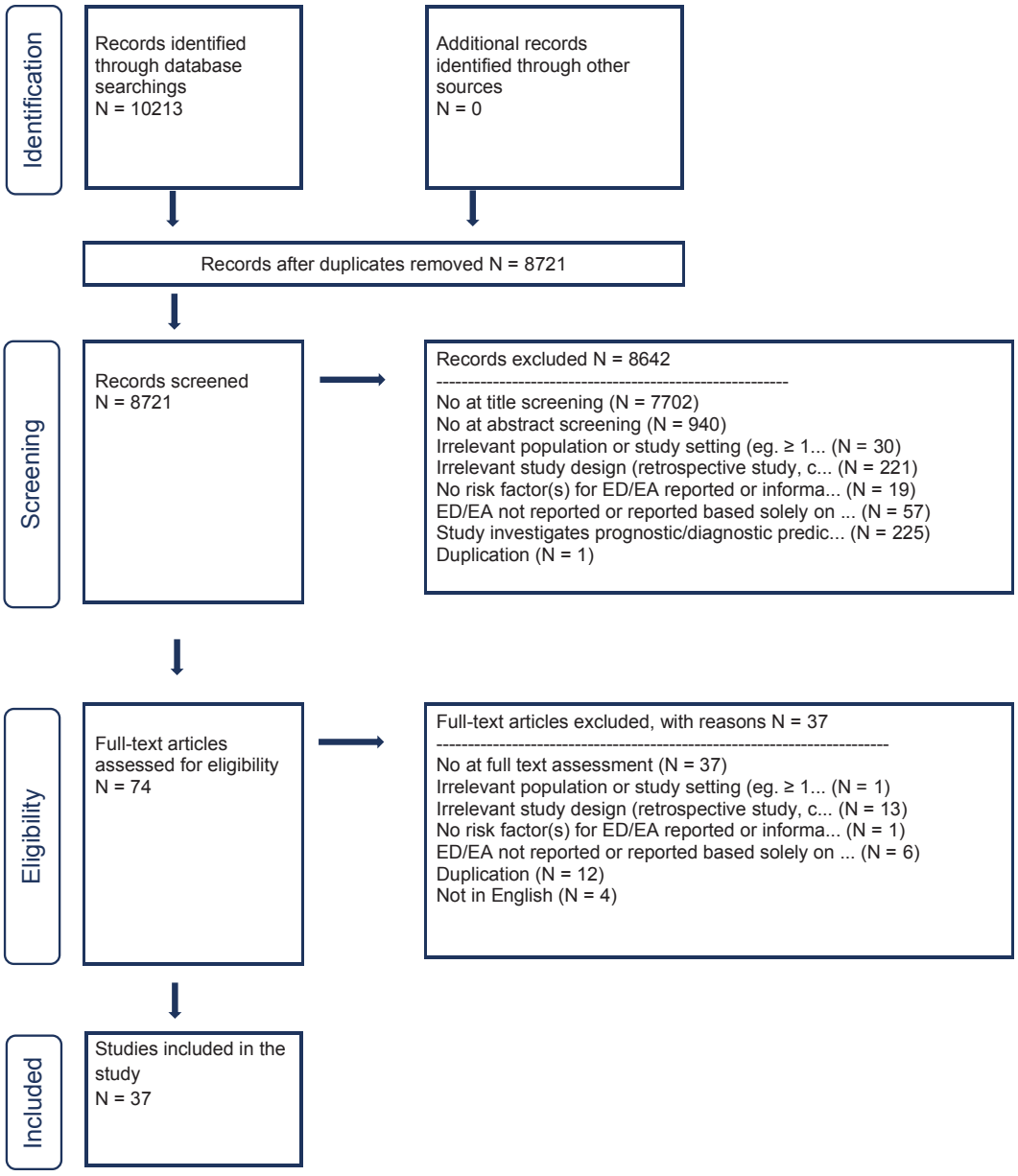
PRISMA WITH DETAILS



PEDIATRIC ANESTHESIOLOGY 19

Investigation of the DNA methylation profile in children presenting emergence delirium

Vinicius Quintao[1], Leslie Kulikowski[1], Maria Carmona[1]

[1]Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil

INTRODUCTION: Among cognitive changes related to anesthesia, emergence delirium is frequent in children and could be observed in up to 30% of cases. The occurrence of delirium may be related to postoperative cognitive and behavioral changes. Recent studies demonstrated the involvement of epigenetic processes in the behavioral changes related to anesthesia. Thus, performing the DNA methylation profiles is an important tool for studying the role of epigenetic factors in these events.

METHODS: After IRB approval, children between 1 and 12 years old, submitted to general anesthesia for endoscopic procedures, were recruited. Emergence delirium was considered as Pediatric Anesthesia Emergence Delirium Scale score ≥ 10. DNA from blood lymphocytes were extracted by QIAamp DNA BloodMidi Kit (QIAGEN®). The genomic array was performed using iScan (Illumina®) with HumanCytoSNP850K and Infinium MethylationEPIC BeadChips. Arrays data were treated and analyzed using Bluefuse®, GenomeStudio®, and specific packages in R environment. The methods are summarized in the Methods Flow Diagram.

RESULTS: We included 53 patients. Twenty-three children (43.4%) presented emergence delirium. Eight children with emergence delirium and eight controls (after age and gender matching) were selected for methylation profile evaluation. Copy number variation analysis demonstrated no presence of pathogenic deletions or duplications. Analysis of methylation raw data showed a difference in the average beta value between cases and controls in selected chromosomes. Bioinformatics analysis demonstrated that children with emergence delirium presented hypomethylation of the genes SLC22A23 and GNA12 compared to children that did present emergence delirium, in which those genes were hypermethylated.

CONCLUSION: Our results suggest that DNA methylation profiles may present significant differences between children with emergence delirium and controls, including specific genomic regions. The gene SLC22A23, a Brain Organic Cation Transporter family, expresses proteins that function as uniporters, symporters, and antiporters to transport organic ions across cell membranes. The gene GNA12 is involved in the G protein-coupled receptors recognizing diverse messengers such as light, small molecules, and neurotransmitters. Lactic acid concentrations and other metabolites after sevoflurane anesthesia measured by functional MRI are related to emergence delirium. Those metabolites could be involved in the emergence delirium physiopathology through specific genes. Therefore, we emphasize the importance of investigating and identifying epigenetic alterations to understand this relevant clinical adverse event.

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Figure 1

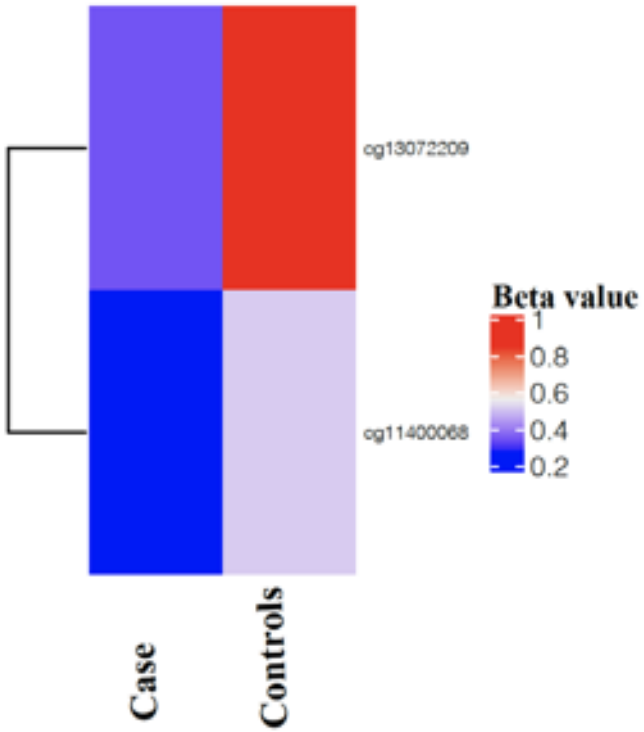


Figure 2

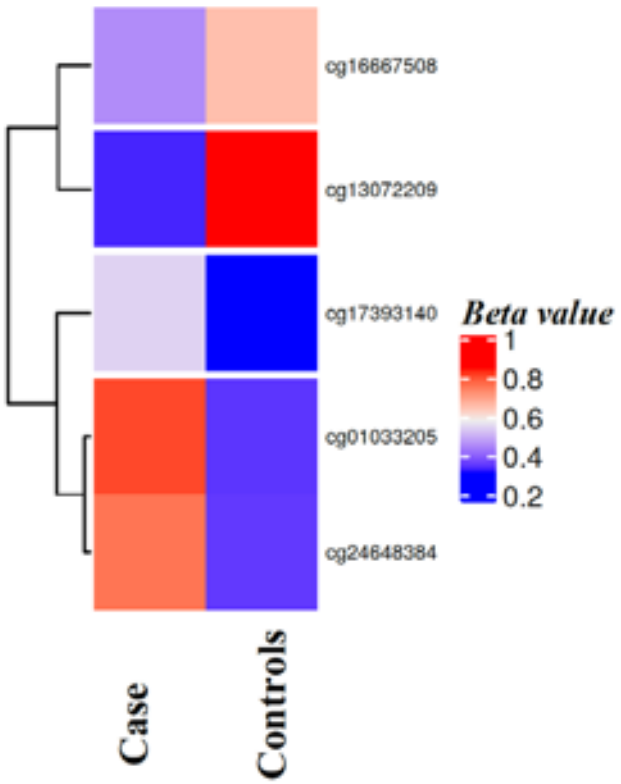
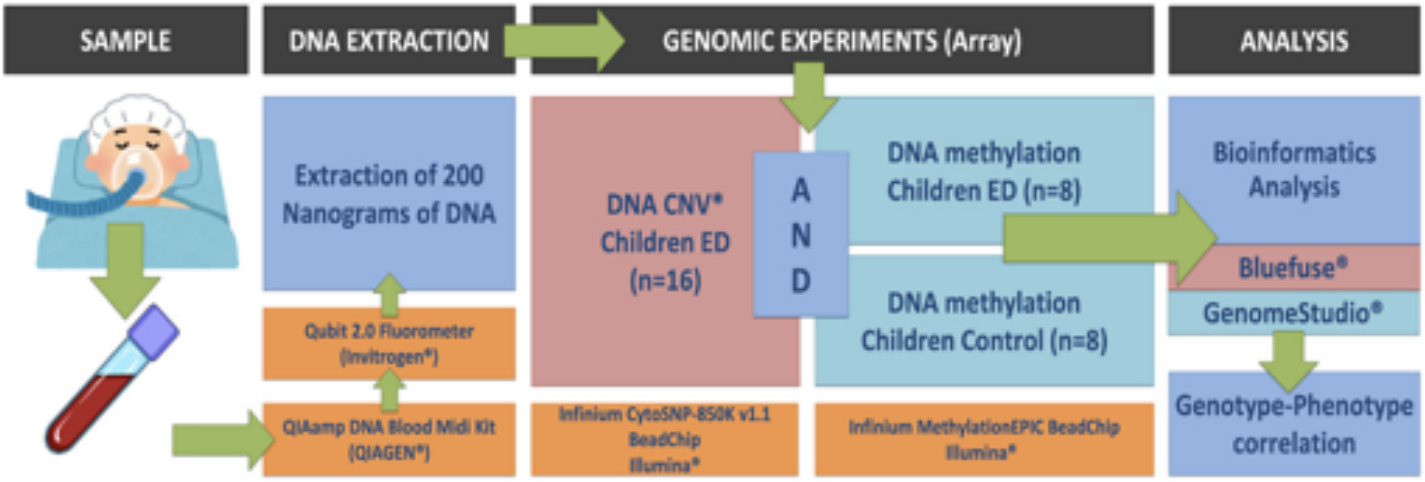


Figure 3



PEDIATRIC ANESTHESIOLOGY 20

Association Between S100β, NSE and BDNF Levels and Different Exposure Time of General Anesthetics in Pediatric Patients Undergoing Non-Cardiac Surgeries

Tarun Pant[1], Richard J Berens[2], Amy Henry[3], Susan P Taylor[4], Hershel Raff[5], Zeljko Bosnjak[4]

[1]Medical College Of Wisconsin, Milwaukee, WI, [2]Medical College of Wisconsin, Wauwatosa, WI, [3]Anex SC, Elm Grove, WI, [4]Medical College of Wisconsin, Milwaukee, WI, [5]Medical College of Wisconsin, Miluaukee, WI

INTRODUCTION: Compelling evidence from preclinical studies using neonatal rodent models has demonstrated detrimental effects of general anesthetics on the developing brain after prolonged exposure. Some of these clinical studies suggest that children may develop cognitive and behavioral impairment if exposed to more than one surgery with anesthesia before the age of 4 yr. However, the lack of studies evaluating long-term anesthesia exposure and its impact on the developing human brain has limited diagnostic and therapeutic options. The present study investigated the effect of general anesthetics on serum brain-derived neurotrophic factor (BDNF), calcium-binding protein β (S100β) and neuron specific enolase (NSE) protein concentrations in pediatric patients aged <4 yr and 4-17 yr undergoing long (>3 hr) vs. short duration (<1 hr) non-cardiac surgeries. We hypothesized that prolonged anesthesia and surgery will reduce a known neurotrophic agent that attenuates neuroinflammation (BDNF) and increase the biomarkers known to be elevated due to the neuronal cell damage (S100β and NSE).

METHODS: To investigate the effect of general anesthetics and surgery on serum concentration of S100β, NSE, BDNF in pediatric patients aged (<4 yr and 4-17 yr) (n=10/group), we collected blood samples before and after surgery. We determined the protein levels by ELISA on 3 pooled samples per group due to the limited amount of serum. Data analysis was performed using Graph Pad Prism software ($P<0.05$).

RESULTS: Patients aged <4 yr undergoing lengthy surgeries (>3 hr) had statistically significant differences (*$P<0.05$, **$P<0.01$) in the serum protein concentration of S100β, NSE, and BDNF, before vs. after the surgery, as compared to patients with short surgery durations (<1 hr) (Figures A-B). In addition, the pediatric population aged 4-17 yr showed smaller (S100β) or no differences (BDNF) in biomarker levels as a function of duration of surgery (Figures C-D).

CONCLUSION: These preliminary results suggest that the serum concentration level of S100β, NSE, and BDNF correlate with the duration of surgery for patient aged <4 yr. These effects might point to a greater detrimental effect of surgery and anesthesia in younger children that may contribute to developmental neurotoxicity.

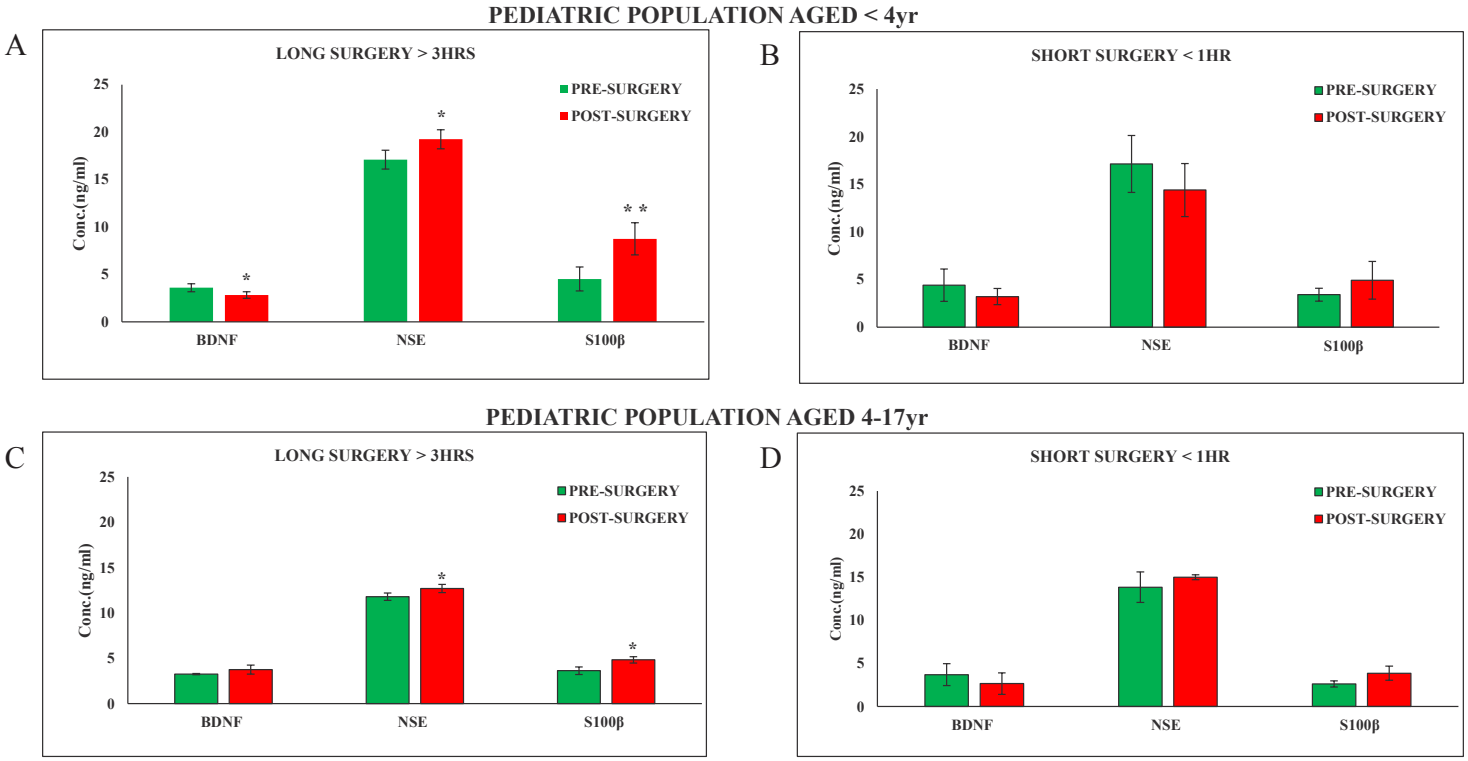


Figure: The serum concentration of BDNF, NSE and S100β in non-cardiac pre and post operative surgery were measured by sandwich ELISA (A) >3hrs & age <4 yr (B) <1hr & age <4 yr (C) >3hrs & age 4-17 yr. (D) <1hr & age 4-17 yr The protein expression of BDNF, NSE and S100β are shown in ng/mL. Data represent mean ± SD (n = 3). *P < 0.05, **P < 0.01 by Student's t-test.

PEDIATRIC ANESTHESIOLOGY 21

A Survey of the Global Impact of COVID-19 on the Practice of Pediatric Anesthesia: a study from the PEACOC group

Victoria Bradford[1], Codruta Soneru[2], Allison M Fernandez[3], Steven Staffa[4], Vidya Raman[5], Joseph Cravero[6], David Zurakowski[6], Petra M Meier[6]

[1]University of Kentucky, Lexington, KY, [2]University of New Mexico, Albuquerque , NM, [3]Johns Hopkins All Children's Hospital, St. Petersburg, FL, [4]Children's Hospital Boston, Boston , MA, [5]Ohio State University Wexner Medical Center, Columbus, OH, [6]Boston Children's Hospital, Boston, MA

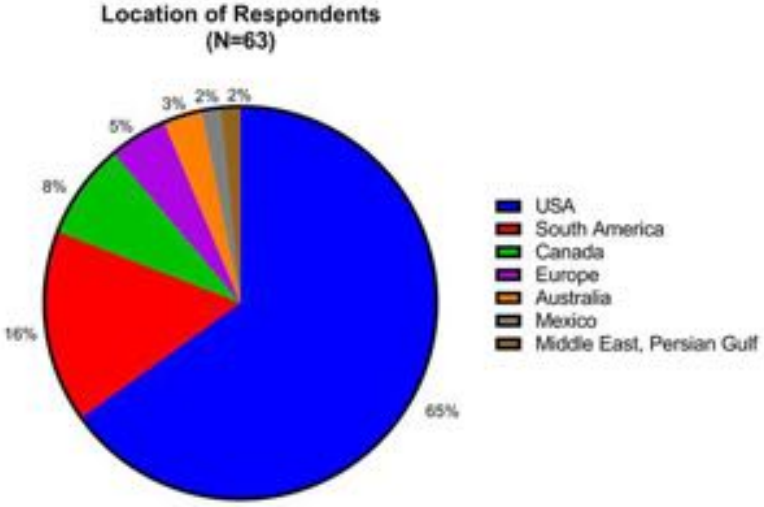
INTRODUCTION: The COVID-19 global pandemic has upended traditional hospital policies regarding preoperative testing, personal protective equipment, staffing, and visitation. No data exist on how the pediatric perioperative experience has changed for patients and providers due to the pandemic. With this study, we sought to survey pediatric centers and highlight how COVID-19 has altered the delivery of care by pediatric anesthesiologists, the practice of pediatric anesthesia, and its economic impact. Responses showed COVID-19 has strained healthcare resources, and drastically changed the environment in which pediatric anesthesiologists practice.

METHODS: Institutional Review Board (IRB) exemption was obtained from Boston Children's Hospital. A prospective survey questionnaire concerning four major domains (testing, safety, clinical management/policy, economics) was developed. It was pilot tested for clarity and content by members of the Pediatric Anesthesia COVID-19 Collaborative (PEACOC). The survey was administered by email to all PEACOC members on September 1, 2020. There were no exclusion criteria. Respondents had 6 weeks to complete the survey and were instructed to answer the questions based on their institution's practice during September 1 - October 13, 2020. If an institution had several anesthesiologists as members of PEACOC, they were instructed to select a representative to respond. Respondents were instructed to answer the questions based on the current situation at their institutions during the study period September 1-October 13, 2020. Individual institution data were fully de-identified, so study authors knew only that a member from the corresponding institution had completed the survey. Descriptive statistical analysis was performed by statisticians at Boston Children's Hospital.

RESULTS: 63 institutions (100% response rate) participated in the COVID-19 Pediatric Anesthesia Survey. 41 hospitals (65%) were from the United States, and 35% included other countries. N95 masks were available to anesthesia teams at 91% of institutions (95% CI: 80%-96%). The most common PPE worn by anesthesiologists while caring for an untested, patient under investigation (PUI), or COVID-19 positive patient were N95 masks (89%), face shields or goggles (86%), hat/bonnet (79%), and gloves (71%). In the event of a shortage of PPE, 51% of institutions allowed anesthesiologists to use their own equipment. Patient PCR testing for COVID-19 was required for elective surgery in 65% of hospitals and for urgent surgery in 56% of hospitals. Thirteen percent of respondents (n=8) reported that PCR testing was not used at their institution. Perioperative screening questionnaires were used at 92% of institutions. COVID-19 testing criteria of anesthesia staff and guidelines to return to work varied by institution. Seventy-one percent of hospitals have airway barrier methods utilized when intubating a PUI or COVID-19 positive patient. In 38 institutions of the 45, it was at the discretion of the anesthesiologist in which age group airway barriers were utilized. During the care of a COVID-19 positive patient or PUI 65% of institutions had a designated spotter available for donning and doffing of PPE, however during the off hours this safety feature was only available in 35% of institutions. Structured simulation training aimed at improving COVID-19 safety and patient care occurred at 62% of institutions. Pediatric anesthesiologists were economically affected by losses of incentive pay, retirement matching, vacation time and restriction of personal travel. Incentive pay was negatively impacted at 46% of institutions (95% CI: 33% - 59%) during the pandemic, vacation time was reduced at 27% of hospitals (95% CI: 17% - 40%), and personal travel restrictions were implemented at 62% (95% CI: 49% - 74%). Sixty-eight percent (95% CI: 55% - 79%) of respondents indicated that staff are not given the choice regarding working with COVID-19 positive patients.

CONCLUSION: Our data indicate that the COVID-19 pandemic has impacted the testing, safety, clinical management, and economics of pediatric anesthesia practice. Lessons learned from the operational challenges posed by COVID-19 should be used to inform preparation for similar challenges in the future. Further investigation into the long-term consequences for the specialty are indicated.

Figure 1. Description of Respondent Characteristics



Demographics and Respondent Characteristics	
Variable	n (%)
Primary Practice Setting	
Public (government supported)	16 (27%)
Private (non-government supported)	15 (24%)
Academic	41 (65%)
Other	0 (0%)
Number of Hospital Beds Dedicated to Pediatric Population	
0 – 50	4 (6%)
50 – 100	9 (14%)
100 – 250	21 (33%)
250 – 500	22 (35%)
> 500	7 (11%)
Primary Site of Practice	
Free standing pediatric hospital	36 (57%)
Pediatric hospital within an adult hospital	20 (32%)
Adult hospital	7 (11%)

Figure 2. COVID-19 Testing of Pediatric Anesthesia Staff

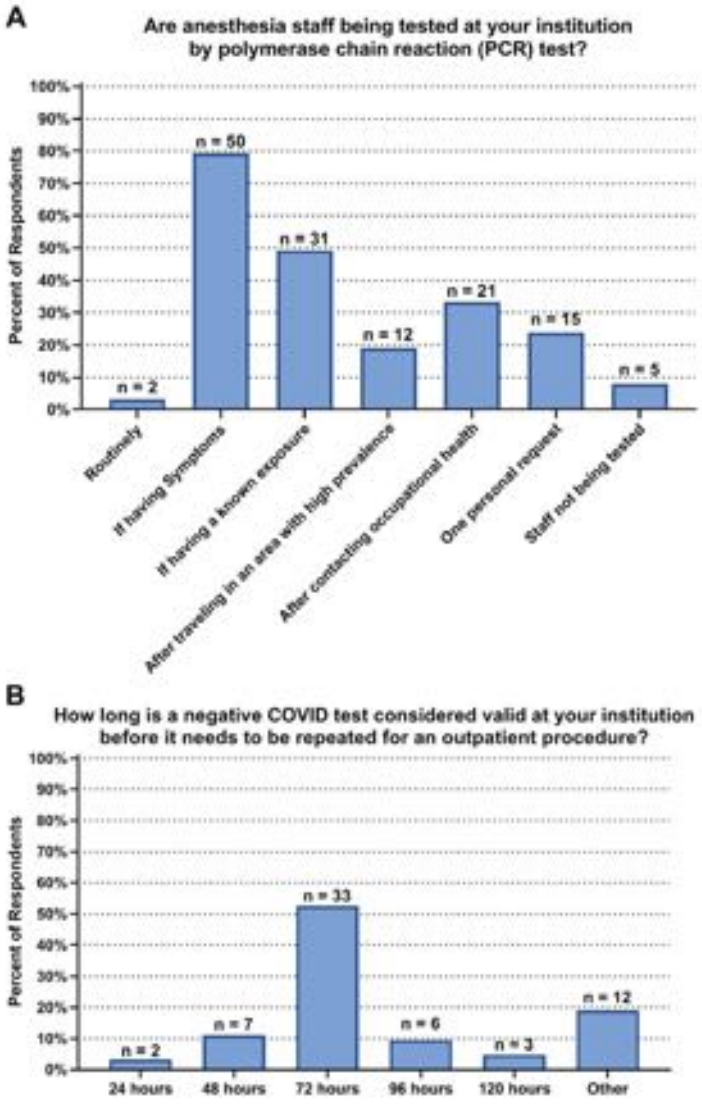
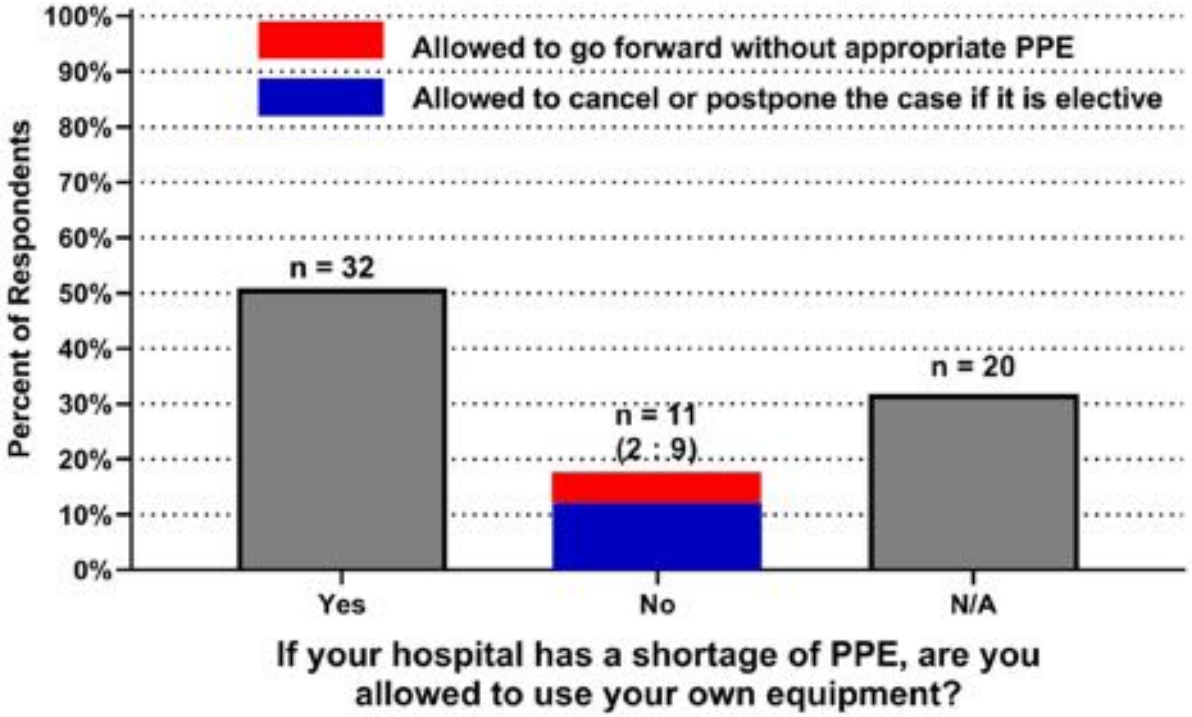


Figure 3. PPE during a Shortage



PEDIATRIC ANESTHESIOLOGY 22

Frequency of Emergence Delirium in Pediatric patients undergoing Hemato-oncological Procedures under General Anesthesia: A Single Center Study

María P Gómez[1], German A Franco Gruntorad[2], Manuela Téllez[3], Vera Winograd[3], Félix R Montes[3]

[1]Fundación Cardioinfantil-Instituto de Cardiología. Universidad del Rosario, Bogotá, Cundinamarca, [2]Fundacion Cardioinfantil-Instituto de Cardiología, Bogota, Cundinamarca, [3]Fundación Cardioinfantil-Instituto de Cardiología, Bogotá, Cundinamarca

INTRODUCTION: Emergence Delirium (ED) is defined as an alteration in the level of consciousness and mental status, often encompassing disruptive behaviors observed during the immediate post-anesthesia period. ED takes place particularly in pediatric patients, with an incidence of 10-80%[1]. Its occurrence is associated with the use of sevoflurane for anesthetic induction and maintenance. Likewise, ophthalmological and otorhinolaryngological surgeries are risk factors for the development of ED[2]. However, not much literature can be found related to hemato-oncological procedures, even though this population is at high risk of ED, due to their critical illness, repeatedly submission to procedures, frequently hospitalizations and family high anxiety levels[3]. The aim of the present study is to establish the frequency of ED in pediatric patients undergoing hemato-oncological procedures at our institution.

METHODS: We performed a single-center, prospective, observational study from September to November 2019. We included all patients aged 1-18 years old undergoing general anesthesia for a hemato-oncological procedure (e.g., bone marrow biopsy, intrathecal chemotherapy, and/or lumbar puncture). Anesthetic techniques were divided into balanced anesthesia (fentanyl/propofol/sevoflurane), inhaled anesthesia (sevoflurane only), and intravenous anesthesia (fentanyl/propofol). Upon arrival in the post-anesthesia care unit, the Pediatric Anesthesia Emergence Delirium (PAED) scores were assessed every 5 minutes for the first 15 minutes and then every 15 minutes until discharged. A PAED score of 10 or higher was defined as an ED episode.

RESULTS: A total of 101 subjects were studied (mean age 10±7.3 years, 63.4% men). Demographic variables and procedure type are showed in Table 1. The anesthetic techniques used were balanced anaesthesia (n = 73, 72.3%), inhaled anesthesia (n = 13, 12.9%) and intravenous anesthesia (n = 15, 14.9%). 21 patients (20.8%) developed ED during the immediate postoperative care. Incidence of ED was higher with inhaled anesthesia (n = 5; 38.5%), followed by balanced anesthesia (n = 16; 21.9%) and intravenous anesthesia (n = 0; 0%).

CONCLUSION: The frequency of ED in paediatric patients who underwent hemato-oncological procedures at our institution is significant. The use of intravenous anesthesia seems to protect against the appearance of ED. We are conducting a properly prospective designed study to corroborate this finding

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Table 1. Demographic variables, procedure type and frequency of Emergence Delirium

	n =101
Age (years) mean±SD	10±7.3
Sex	
Male n (%)	64 (63.4)
Female n (%)	37 (36.6)
ASA physical status classification	
I n (%)	7 (6.9)
II n (%)	11 (10.9)
III n (%)	83 (82.2)
Intrathecal chemotherapy/lumbar puncture n (%)	49 (48.5)
Intrathecal chemotherapy/bone marrow biopsy n (%)	19 (18.8)
Bone marrow biopsy n (%)	33 (32.7)
Emergence Delirium n (%)	21 (20.8)

SD: standard deviation; ASA: American Society of Anesthesiologists

PEDIATRIC ANESTHESIOLOGY 23

Ultrasound-Guided Occipital Nerve Blocks as Part of Multi-Modal Perioperative Analgesia in Pediatric Posterior Craniotomies: A Retrospective Review of Initial 24-Hour Pain Management in 44 Patients

Andrew Gu[1], John Hajduk[2], Angelica A Vargas[2], David Krodel[2], Ravi Shah[2], Hubert Benzon[3], Michael King[2]

[1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [3]Lurie Children's Hospital of Chicago, Chicago, IL

INTRODUCTION: Greater occipital nerve blocks have been described in a variety of headache conditions in pediatric patients. Their use in the perioperative setting, however, is limited to published case reports in neurosurgical procedures such as ventricular shunt placements and revisions[1,2]. We describe our institutional experience with greater occipital nerve blocks in pediatric posterior fossa decompressions and posterior craniotomies, and present postoperative pain scores and analgesic use as primary and secondary endpoints, respectively, to evaluate adequacy of perioperative pain control in this population.

METHODS: Following IRB approval, we reviewed the medical records of 44 patients who received bilateral greater occipital nerve blocks for posterior fossa decompression or craniotomies between January 2016 and October 2019. Blocks were performed prior to incision with ultrasound-guidance under general anesthesia. We evaluated postoperative pain scores, obtained as FACES, verbal/NRS, or rFLACC, and opioid and non-opioid analgesic use in the first 24 hours postoperatively.

RESULTS: Patient and perioperative details are presented in Table 1. Blocks were performed 215 [161-262] minutes prior to emergence, with 0.18 [0.13-0.26] mL/kg of 0.2% ropivacaine under USG with no related untoward events at any point. In the PACU, pain was rated as zero or well-controlled in 77% of patients, and with 43% receiving IV or demand PCA opioid in the earliest period. Seventy-five percent of median pain scores remained zero through the 12th post-op hour (Figure 1). Opioid administration, standardized as morphine equivalents, was similar between the initial and second 12-hour periods (0.06 vs 0.07 mg/kg) as non-opioid analgesic usage was initiated.

CONCLUSION: We present the largest cohort report of occipital nerve blocks in pediatric posterior craniotomies and posterior fossa decompressions to date. A large portion of patients had excellent pain control in the immediate and initial period after surgery, with pain scores rising thereafter. We postulate occipital nerve blocks aided to this efficacy, with wearing effect from clearance of ropivacaine from the greater occipital nerve block over time. Future prospective and controlled studies are needed to better characterize the clinical benefit of occipital nerve blocks. Our data identifies an opportunity to reevaluate and improve analgesia in the later 12 hours following anesthesia.

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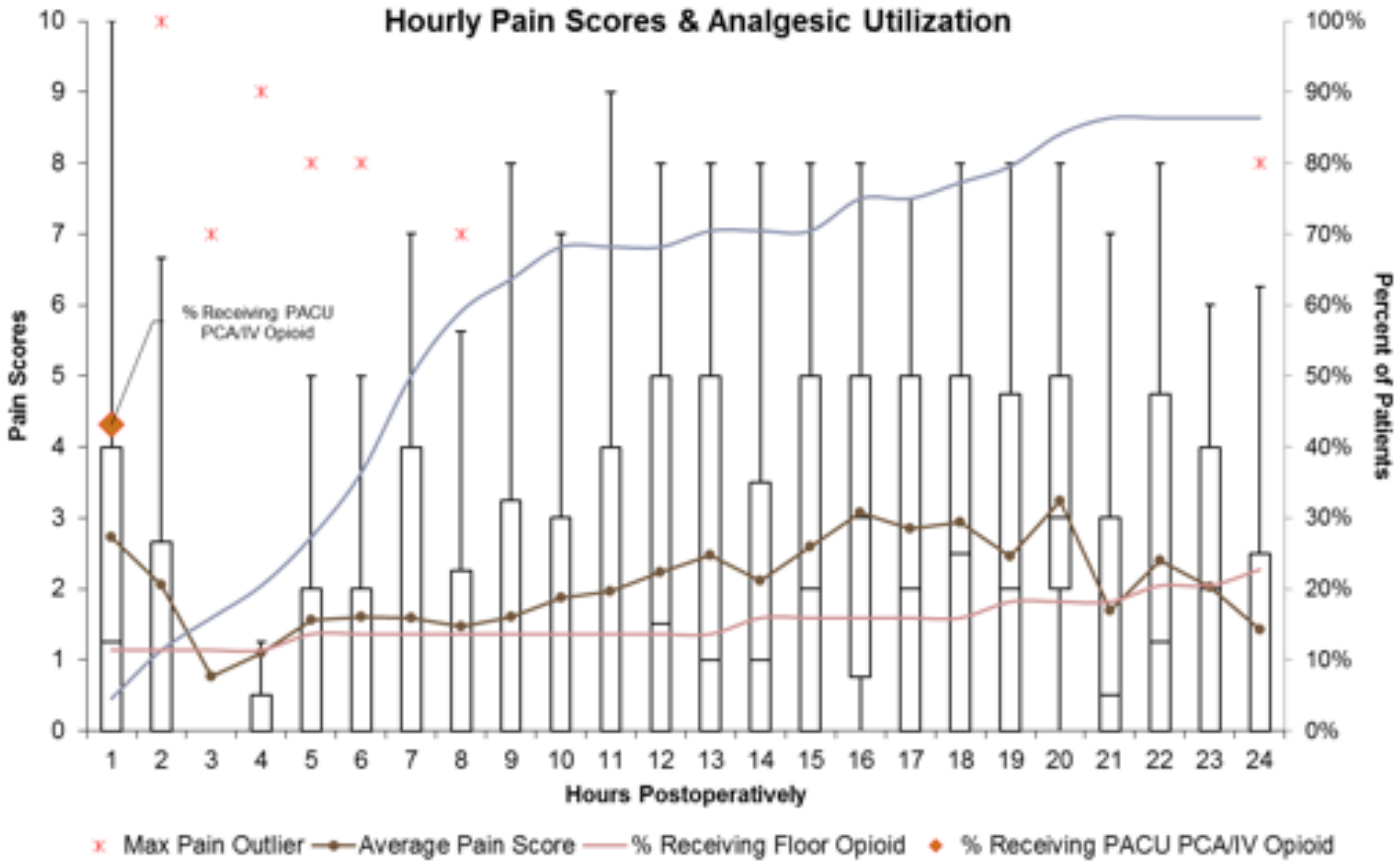
Table 1: Patient/Procedure Characteristics and Analgesia Outcomes

Patient Demographics	
Gender, male	18 (41%)
Age, yrs	12 [4 – 15]
Weight, kg	35.2 [17.2 – 52.8]
ASA	
2	25 (57%)
3	19 (43%)
Intraoperative Characteristics	
Anesthesia Duration, min	266 [202 – 304]
Block to Case End Duration, min	215 [161 – 262]
Surgeon Local Anesthetic, yes	44 (100%)
Intraoperative Medications	N (% Receiving); Dose mg/kg
Fentanyl	44 (100%); 3.2 [2.0 – 4.3]
Dexamethasone	38 (86.4%); 0.16 [0.09 – 0.28]
Acetaminophen	26 (59.1%); 12.8 [12.5 – 15.0]
Dexmedetomidine	14 (31.8%); 7.5 [12.6 – 24.6]
Remifentanil	5 (11%)
Block Details*	
Total Bilateral Volume, mL	6 [4 – 9]
Total Bilateral Volume, mL/kg	0.18 [0.13 – 0.26]
Postoperative Course	
PACU Pain Scores	
No Pain (0/10)	30 (68%)
Well Controlled (1-3)	4 (9%)
Poorly Controlled (4-7)	7 (16%)
Uncontrolled (8-10)	3 (7%)
Pts. Requiring PACU Opioid	19 (43%)
PACU Morphine Equivalents, mg	0 [0 – 0.025]
PONV	6 (13.4%)
1st 12-Hour Floor Morph. Equiv.	0.06 [0.04 – 0.13] mg/kg
2nd 12-Hour Floor Morph. Equiv.	0.07 [0.03 – 0.16] mg/kg
PCA Discontinuation	
≤ 1 Day	30 (73%)
≥ 1 Day	11 (27%)
Time to Discharge, Days	3 [2 – 4]

*Ropivacaine, 0.2%, Ultrasound-Guided

Figure 1: Hourly Pain Scores and Analgesic Utilization



PEDIATRIC ANESTHESIOLOGY 24

Trends in Obesity Among a Pediatric Anesthesia Population in a Children's Hospital, 2004-2020

Michael Henry[1], Patrick Ross[1], Jonathan M Tan[2]

[1]Children's Hospital of Los Angeles, Los Angeles, CA, [2]Childrens Hospital Los Angeles, Los Angeles, CA

INTRODUCTION: In 2019, the World Health Organization (WHO) found that 5.6% (38.3 million) of children under five were overweight or obese, an increase of 8 million when compared to 2000.[1] In the United States, 18.5% of children between the age of 2 and 19 were considered obese. Perioperatively, obesity increases anesthetic risks related to airway management, ventilation and can make intravenous access and safe positioning more challenging. While the prevalence of obesity has increased in the general pediatric population, limited data exists on whether obesity prevalence has also increased in a pediatric anesthesia population. Our objective was to describe the trends in obesity among a pediatric anesthesia population through examining Body Mass Index (BMI) trends of pediatric patients presenting for surgery at a children's hospital with regional and national data.

METHODS: Following institutional review board approval, we conducted a retrospective study using clinical, demographic and anthropometric data from the electronic health record of pediatric patients who had surgery at an academic children's hospital from 2004 to 2020. Descriptive statistical analysis and comparison of trends were conducted using Microsoft Excel and Stata. Patient's age, gender, weight, and height were used to calculate BMI for age using WHO growth curves for children < 2 years and Centers for Disease Control and Prevention (CDC) data for children > 2 years. Patients were grouped by age and categorized by Z-Score BMI by age and gender.

RESULTS: Our study included 223,398 anesthetics over 16 years. There was no statistically significant difference in the BMI for age and gender Z-Score groups at any age range, and for the entire study population (Figure 1). When comparing American Society of Anesthesiologists (ASA) classification with BMI for age and gender Z-Score groups, the distribution of ASA classification was evenly distributed among the BMI Z-Score groups (Figure 2).

CONCLUSION: In our study population, the BMI of children presenting for surgery and anesthesia services did not change significantly from 2004 to 2020. While the general pediatric population in the United States experienced increases in the prevalence of obesity from the 1970's to 2000, and subsequent slower increases in obesity in 12–19-year-olds, the pediatric anesthesia population in our study did not experience the same changes. Similar trends in our anesthesia population were observed in studies of obesity prevalence in the Los Angeles Unified School District from 2001-2013, and in other school districts in New York City and Philadelphia.6 Furthermore, our research suggests that obese patients were not more likely to be categorized with a higher ASA score.

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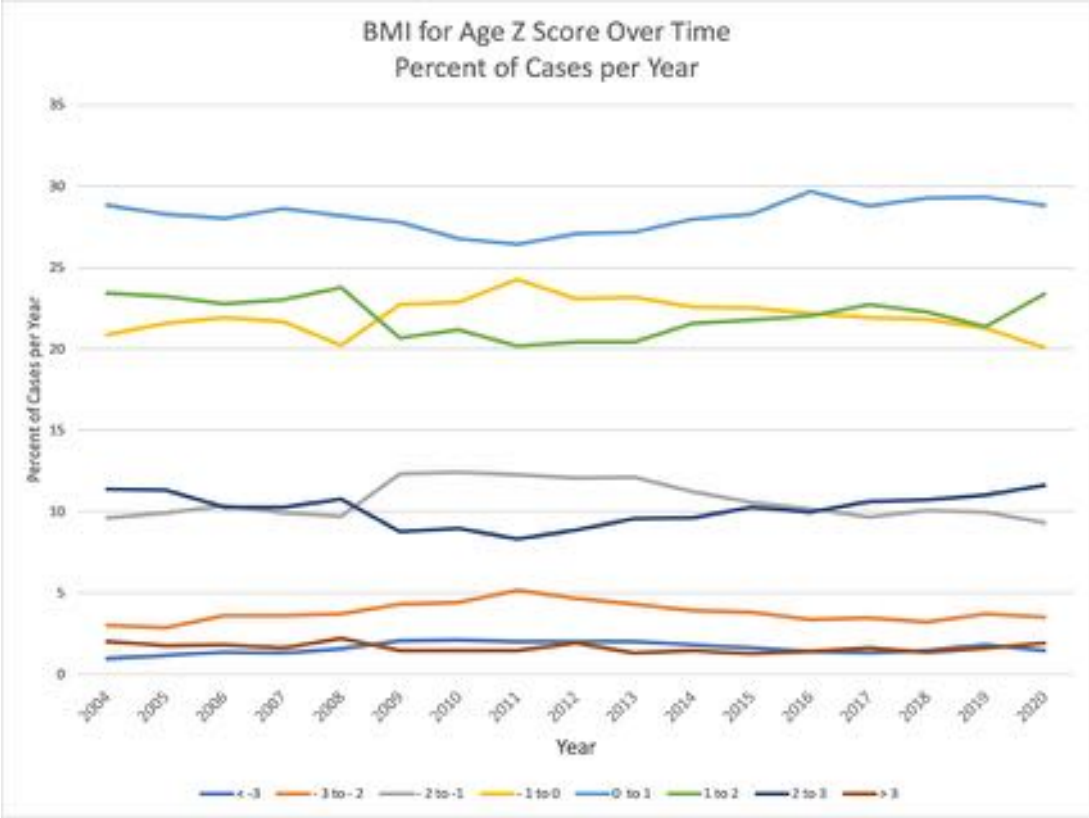

Figure 1. Percent of Cases per year by BMI for Age Z Score for years 2004 to 2020

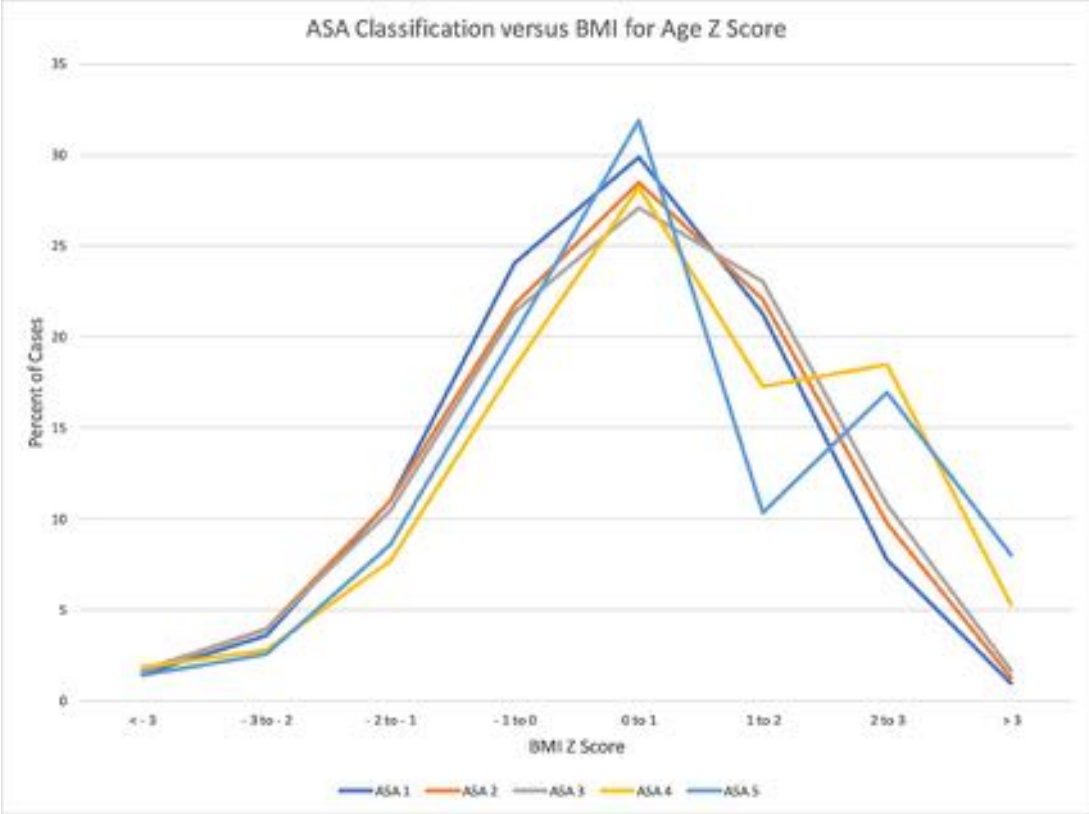

Figure 2. ASA Classification by BMI for Age Z Scores

PEDIATRIC ANESTHESIOLOGY 25

Anesthetic Considerations for Creation of Potts Shunt in Children with End-Stage Pulmonary Hypertension

Teresa Murray-Torres[1], Anshuman Sharma[2]

[1]Washington University School of Medicine, St Louis, MO, [2]Washington University School of Medicine, St Louis , MO

INTRODUCTION: Pulmonary hypertension (PH) is a rare disorder in infants and children that is associated with a high morbidity and mortality. Despite improvements in survival rates[1-3], a subset of children will ultimately develop medically-refractory PH[4]. Historically, palliative interventions have been limited to atrial septostomy or more invasive lung transplantation. Recently, creation of a Pott's shunt, an anastomosis between the left pulmonary artery and descending aorta (Figure 1), has been evaluated as a method to decompress the right ventricle, thereby preserving right ventricular function and potentially offering survival benefits[5-7]. We describe the anesthetic care of four pediatric patients who have undergone this procedure at our institution.

METHODS: This was a retrospective chart review of the cases performed at our institute between Jan 2018 and May 2019.

RESULTS: All patients had severe disease with suprasystemic RV pressures and were on triple drug medical therapy, including continuous prostacyclin derivative infusions (Table 1). Patients underwent IV induction (Table 2) and invasive monitoring including arterial and central venous pressure monitoring. Regional anesthetic catheters were placed prior to incision, and continued in the postoperative period for 1 to 4 days. Single lung ventilation was achieved to facilitate the left posterior thoracotomy surgical approach. Use of SLV was associated with hypoxemia, particularly during the time of partial aortic cross clamp (Figure 2). Three patients were preemptively initiated on vasopressin infusion prior to induction; severe hemodynamic instability in one patient, associated with the release of the aortic and pulmonary cross clamps (Figure 3), was treated with intermittent boluses of epinephrine. All procedures were successfully completed without the use of cardiopulmonary bypass or ECMO. Creation of shunt successfully decompressed the right ventricle as evidence by lower extremity SpO2 values 5-15% lower than upper extremity SpO2 values. Three patients were successfully extubated in the operating room. One patient had severe pulmonary hemorrhage and required prolonged postoperative ventilation (18 days).

CONCLUSION: Perioperative care for children with irreversible PH is a complex, high-risk endeavor and requires extensive preparation with a multidisciplinary team collaboration. This small study demonstrates the feasibility of creating Potts shunt without the use of cardiopulmonary bypass support. Preoperative preserved RV function, use of vasopressin and regional techniques to achieve adequate postoperative pain control appear to assist with successful extubation in the operating room

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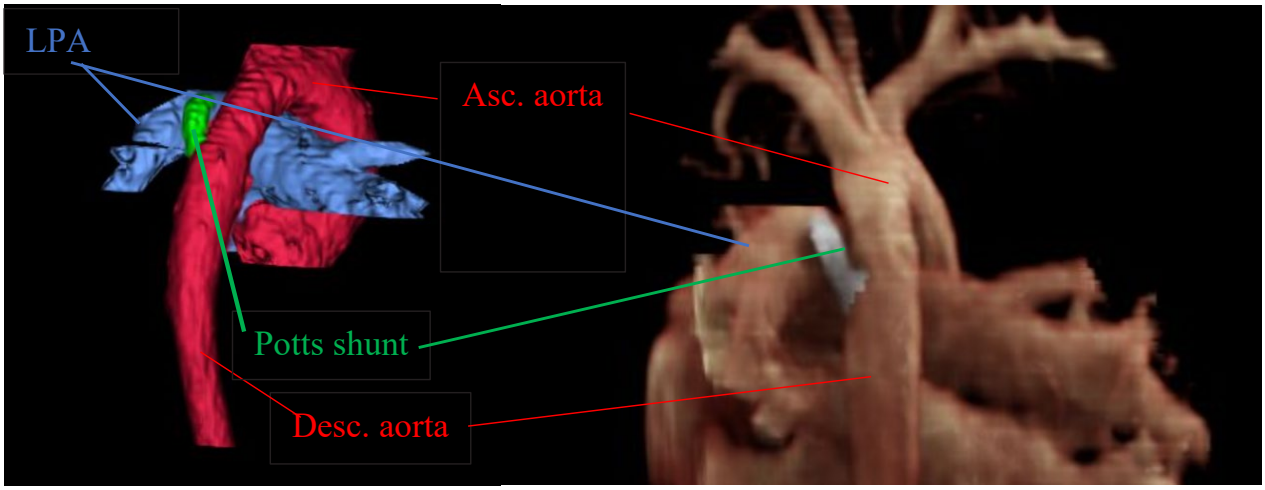

Figure 1. MR reconstructions showing Potts shunt from a posterior view. The connection between the descending aorta and the left pulmonary artery (LPA) offloads the right ventricle and the pulmonary arterial system at the expense of desaturation of blood in the descending aorta. These shunts are placed through a left posterolateral thoracotomy with one-lung ventilation to facilitate exposure.

Table 1. Preoperative clinical characteristics

Case	Age	Years since diagnosis	Sex	Weight, kg	PRVi, WU/m^2	BNP, pg/ml	Transthoracic echo Estimated RV pressure mmHg	RV function
1	14.4	7.6	female	49.6	7.4	18	100	Normal
2	10.7	5.3	female	27.2	16.0	21	121	Normal
3	14.4	3	male	66.4	24.0	399	100	Mildly decreased
4	9.2	2.7	female	21.6	9.9	1202	100	Mildly decreased

PRVi - indexed Pulmonary Vascular Resistance; WU - Woods units; BNP – Brain Natriuretic Peptide

Table 2. Anesthetic variables

	Duration anesthesia	Lung isolation method/duration	Regional technique	Induction agents	Site extubation	ICU LOS days	Vasoactive infusions During clamp	Vasoactive infusions ICU transfer
1	6.4 h	Univent™/1.8 h	ESP	M, K, F	OR	5	V	None
2	7.1 h	DLT/0.7 h	epidural	Inhalation	OR	4	None	None
3	6.5 h	Univent™/2.7 h	ESP	P, F	OR	4	V, NE, E	NI, E
4	6.4 h	Univent™/2.3 h	ESP	M, Me, K	ICU	31	V	NE, V

h – hours; ESP – Erector Spinae Plane; M – midazolam; K – ketamine; F – fentanyl; P – propofol; Me – methadone; ICU – intensive care unit; LOS – length of stay; V – vasopressin; NE – norepinephrine; E – epinephrine; NI – Sodium nitroprusside

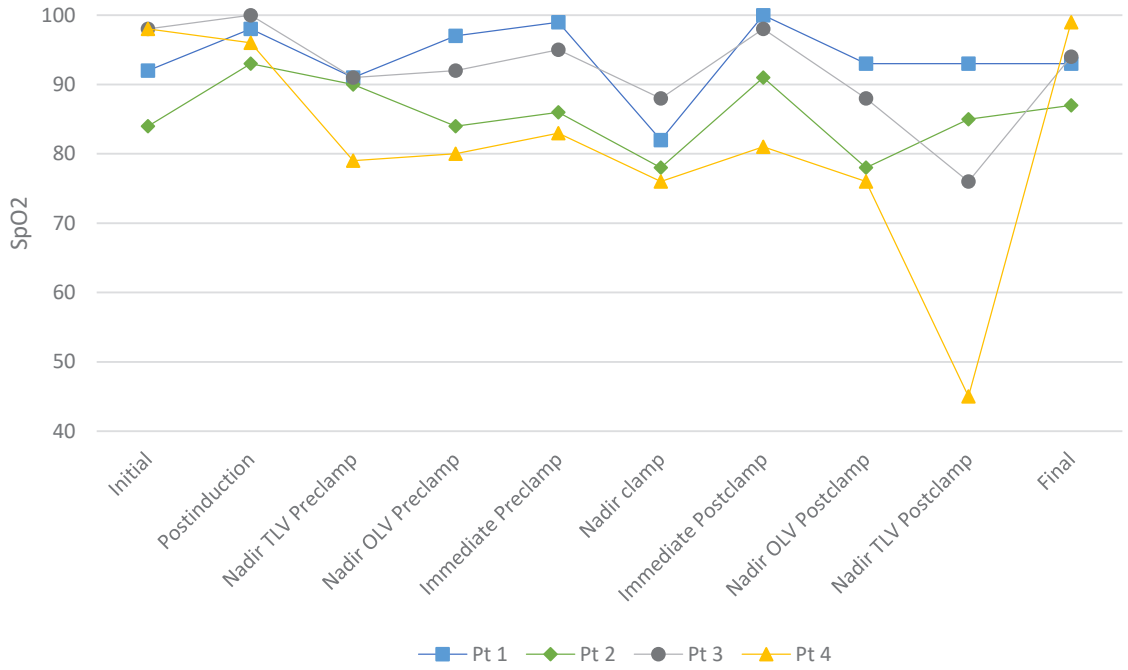

Figure 2. Pulse oximetry readings during specific intraoperative time periods. Values are both from specific time points and also nadir readings preceding, during, and following partial aortic cross clamp. TLV - two lung ventilation OLV - one lung ventilation

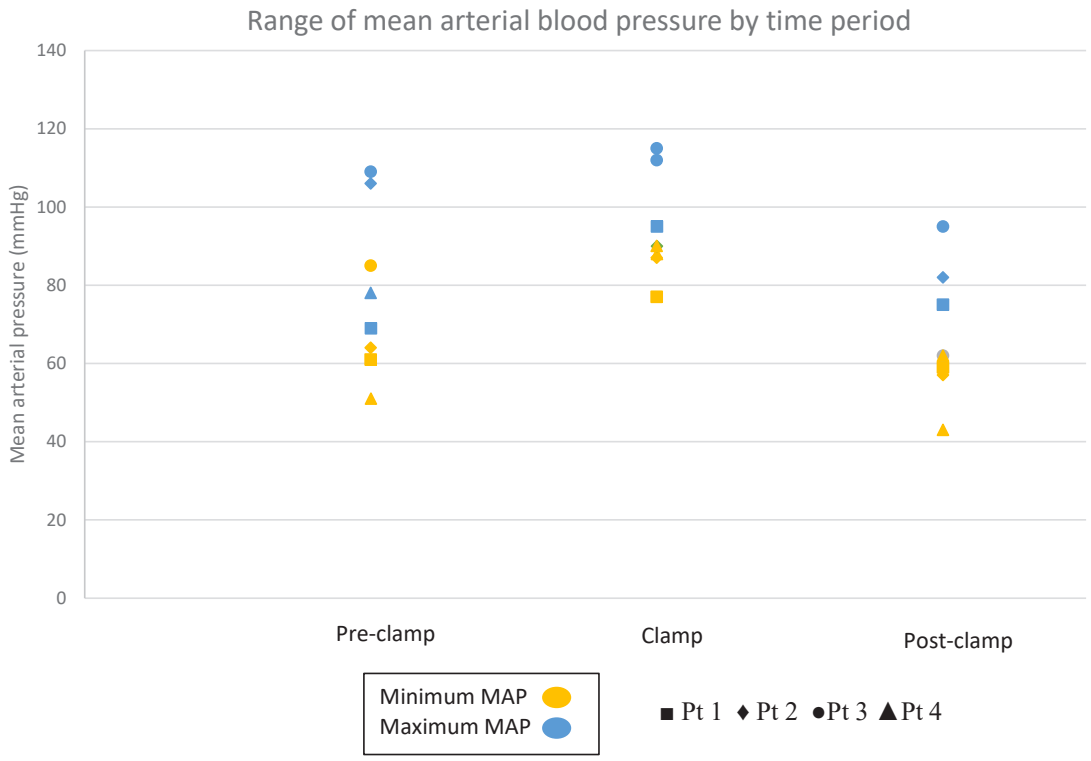

Figure 3. Minimum and maximum mean arterial blood pressure recorded for each patient in the time preceding, during, and following partial cross-clamp of the left pulmonary artery and the descending aorta.

PEDIATRIC ANESTHESIOLOGY 26

Anesthestic Management for Posterior Tracheopexy and Descending Aortopexy for Repair of Complex Tracheobronchomalacia: A Single Institutional Experience

Jue T Wang[1], Steven Staffa[2], Dusica Bajic[1], Carlos Munoz[1], Walid Alrayashi[3], Russell W Jennings[1], Michael Hernandez[3]

[1]Boston Children's Hospital, Boston, MA, [2]Children's Hospital Boston, Boston , MA, [3]Boston Children's Hospital, Boston, United States of America

INTRODUCTION: Tracheobronchomalacia (TBM) refers to a process wherein the trachea is abnormally weak and collapses, even completely obstructing the trachea, when pressure is applied[1,2]. The incidence of congenital TBM is 1:2,100 children, but is likely underdiagnosed due to non-specific symptoms[3]. Clinical symptoms include: brassy cough, stridor, respiratory distress, cyanosis, frequent respiratory infections, and apneic spells[4]. The disease can be self-limited with symptom resolution by age 2, but some patients will need surgery[5,6]. The Esophageal and Airway Treatment (EAT) Center at Boston Children's Hospital is a multidisciplinary team. Together we pioneered a surgical treatment for patients with moderate to severe TBM. Previous studies have shown that posterior tracheopexy and descending aortopexy is effective at alleviating airway collapse from TBM[7,8,9]. Surgery must be done under continuous intra-operative bronchoscopy with direct visualization of each suture placed in the airway. The EAT anesthesiologists developed a method to provide continuous bronchoscopy by using a bronchoscope swivel adaptor with a fiberoptic bronchoscope inserted through a 14 French nasal trumpet (Figure 1). This allows for adequate oxygenation and ventilation while providing uninterrupted views of the trachea to guide surgical repair. Our report describes the intra-operative anesthetic management for this novel surgery and examines initial clinical outcomes from our institution.

METHODS: We retrospectively reviewed patients who underwent posterior tracheopexy with or without descending aortopexy via thoracotomy from January 2017 through March 2020 (institutional IRB-P00034976). Patient demographics, associated syndromes, anesthetic complication such as 1. unintended intraoperative extubation, 2. rate of post-operative extubation, 3. ICU length of stay (LOS), and 4. hospital LOS were collected via electronic medical records. A statistician performed statistical analysis. All categorical data are described using frequencies and percentages. Continuous data are presented as medians and interquartile ranges. Multivariable logistic regression analysis was utilized to determine adjusted associations between predictors and extubation rate, with results presented as odds ratios with corresponding 95% confidence intervals and P values. All statistical analyses were performed using Stata (version 16.0, StataCorp LLC., College Station, Texas). A two-tailed $P<0.05$ was considered as statistically significant.

RESULTS: There were 199 patients with median age 1.6 years, median weight 10.8kg; 69 (34.7%) female and 130 (65.3%) male patients. Furthermore, 34 patients (17.1%) were ASA II, 142 (71.4%) ASA III, 22 (11.1%) ASA IV, and 1 (0.5%) ASA V. Total of 141 patients (70.8%) had tracheoesophageal fistula, esophageal atresia, or both, and 58 (29.2%) did not. In addition, 65 (32.7%) patients had syndromes; 19/65 patients (29%) had syndromes with congenital cardiac disease. Median ICU length of stay (LOS) was 4 days (IQR1-11), median hospital LOS was 15 days (IQR 6-36). Finally, 76 (38.2%) of patients were extubated in the operating room (OR), while 123 (61.8%) remained intubated. Extubation rates increased by year from 14/65 (21%) in 2017 to 30/66 (45.5%) in 2019. Patients with syndromes were extubated at lower rates 29.2% compared with patients without syndromes (42.5%) or patients with syndromes and congenital heart disease (31.65%). Patients with isolated congenital heart disease had the lowest rate of extubation with 0%. There were also 9 cases (4.5%) of unplanned extubation in the OR from airway manipulation. The complexity of these patients requires prolonged ICU LOS (median of 4 days) and hospital course (with a median of 15 days).

CONCLUSION: We pioneered a novel treatment for TBM using posterior tracheopexy and descending aortopexy. Our retrospective analysis shows TBM is often associated with other airway diseases and syndromes[10]. Under general anesthesia, continuous intraoperative bronchoscopy allows for efficient surgical repair with minimal risk except rare unplanned extubations (9; 4.5%) during airway manipulations. As our experience grew from year to year, extubations increased between 2017 to 2019 from 21.5% to 45.5%. Future studies are needed to identify patient risk factors for anesthesia and improve intraoperative management to decrease overall ICU and hospital LOS.

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Table 1.
Demographics and Patient Characteristics

Variable	n (%)	Median	IQR	Range
Age (years)	199	1.6	(0.5, 4.3)	0.01-23.6
Weight (kg)	199	10.8	(6.1, 16.1)	2-104.2
ASA Classification				
I	0 (**0%**)			
II	34 (17.1**%**)			
III	142 (71.4**%**)			
IV	22 (11.1**%**)			
V	1 (0.5**%**)			
Sex				
Female	69 (34.7%)			
Male	130 (65.3%)			
Prematurity / GA (weeks)	101 (50.8**%**)	34	(32, 35)	23-36
28-36 weeks GA	95/101 (94.1%)			
<28 weeks GA	6/101 (5.9%)			
Underlying Diagnosis				
TEF only	6 (3%)			
EA only	21 (10.6%)			
TEF and EA	114 (57.3%)			
No TEF or EA	58 (29.2%)			
Syndromes	65 (32.7%)			
With Congenital Heart Disease	19/65 (29.2%)			
Without Congenital Heart Disease	46/65(70.8%)			
Length of Stay (days)				
Hospital LOS	199	15	(6, 36)	2-273
ICU LOS	199	4	(1, 11)	0-48

Table 1 Legend. Demographic data and patient characteristics. Data presented as percent (%) from the total number of subjects in the cohort (n=199). Median length of stay in the intensive care unit (ICU) and the median hospital length of stay (LOS) are shown in days. *Abbreviations*: **ASA** Classification, American Society of Anesthesiologists physical status classification; **EA**, esophageal atresia; **GA**, gestational age; **IQR**, interquartile range; **kg**, kilogram; **TEF**, tracheoesophageal fistula.

Table 2.
Rate of Successful Extubation in the Operating Room

Variable	n	%
Planned Extubation		
Extubated in Operating Room (OR)	76/199	38.2%
Intubated to Intensive Care Unit (ICU)	123/199	61.8%
Unplanned Extubation in OR	9/199	4.5%
Incidence of Planned Extubation in OR by Year		
2017	14/65	21.5%
2018	26/60	43.3%
2019	30/66	45.5%
2020	6/8	75%
Incidence of Planned Extubation in OR by Disease Association		
No Syndromes	57/134	42.5%
No Syndromes with Congenital Heart Disease	0/3	0%
Syndromes	19/65	29.2%
Syndromes with Congenital Heart Disease	6/19	31.6%

Table 2 Legend. Rate of successful planned extubations. Extubation rate was calculated based on total subjects in the cohort (n=199), per individual years (2017-2020), related to specific disease association. Odds ratio for extubation by year (while adjusting for age ASA, prematurity, and syndromes) is 1.79 (95% CI: 1.24, 2.58; P=0.002). The rate of extubation is increasing by year. Syndromes refer to all patients with syndromic associations either with or without congenital heart disease.
Abbreviations: **ICU**: intensive care unit; **OR**: operating room.

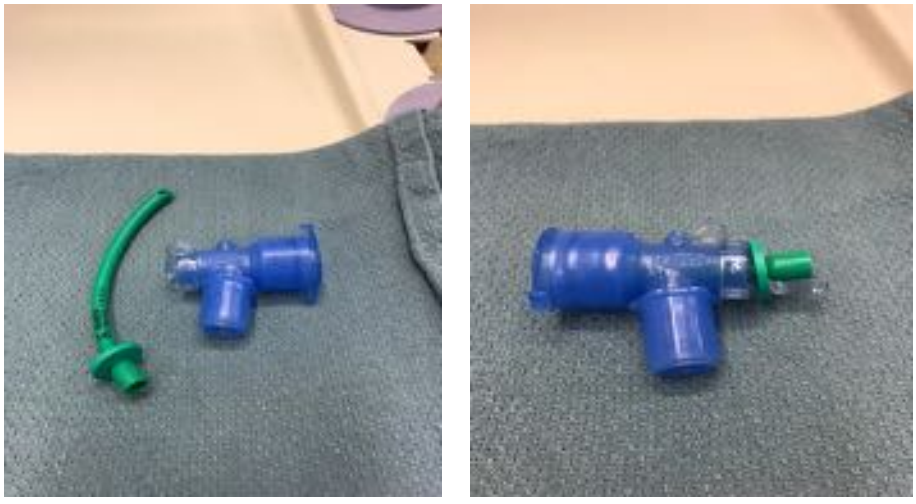

Figure 1. Use of bronchoscopy swivel adaptor (blue) with 14 French nasal trumpet (green) to facilitate continuous intra-operative bronchoscopy (left panel). The pediatric fiberoptic bronchoscope (not shown) inserts into the nasal trumpet which seals the leak between the bronchoscope and facilitates oxygenation and ventilation (right panel). This adaptation facilitates effective oxygenation and ventilation during hours of real-time intra-operative bronchoscopy to guide surgical suture placement.

PEDIATRIC ANESTHESIOLOGY 27

Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) Use During Microdirect Laryngoscopy and Bronchoscopy: Initial Data from a Randomized, Prospective, Multi-Collaborative Trial

Alex Swanger[1], Romy Yun[1], Vanessa Olbrecht[2], Vera Winograd[3], Michael A Evans[4], Mary Stein[5], Niroop Ravula[6], Maria Menendez[1], Ellen Wang[7], Douglas Sidell[7], Thomas Caruso[7]

[1]Lucile Packard Children's Hospital, Palo Alto, CA, [2]Cincinnati Children's Hospital, Cincinnati, OH, [3]Fundación Cardioinfantil-Instituto de Cardiología, Bogotá, Cundinamarca, [4]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [5]Boston Children's Hospital, Boston, MA, [6]University of California, Davis Medical Center, Sacramento, CA, [7]Stanford University School of Medicine, Stanford, CA

INTRODUCTION: Pediatric patients undergoing microdirect laryngoscopy and bronchoscopy (MDLB) pose anesthetic challenges of maintaining adequate oxygenation and ventilation while providing a motionless surgical field without an endotracheal tube. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) may increase apnea time while providing up to 7 cm H2O positive end-expiratory pressure to help prevent alveolar collapse and atelectasis[1]. It is not known if the use of THRIVE in pediatric patients undergoing MDLB reduces oxygen desaturation events and surgical interruptions in these patients without an increased risk of adverse events.

METHODS: This multicenter, randomized, prospective pragmatic study seeks to evaluate the effectiveness of high flow nasal cannula (HFNC) versus standard of care (SOC) without HFNC as part of an anesthetic plan in individuals undergoing MDLB at Lucile Packard Children's Hospital, Cincinnati Children's Hospital, Lurie Children's Hospital, University of California Davis Health Center, and Boston Children's Hospital. Patients are randomized in a 1:1 ratio (HFNC or SOC) using REDCap-generated randomization. Target enrollment will be 120 patients per site, for a total of 600 patients. Physiological data (oxygen saturation, heart rate) is captured real-time using the Masimo Rad-97 Pulse Co-Oximeter (Masimo Corporation, Irvine, CA, USA) and HFNC is provided to the intervention arm using the Optiflow THRIVE system (Fisher & Paykel Healthcare, Irvine, CA, USA). Surgical interruptions are recorded by a trained research observer. The primary aim is to determine if HFNC during MDLB reduces oxygenation desaturations as measured by oxygen desaturation index (ODI, a 4% decrease in SpO2 from a 120-sec rolling mean for > 10 secs) compared to SOC. Secondary aims include number of desaturations below 90% lasting > 2 sec as a function of overall case duration and the number of surgical interruptions as defined by any time the procedure is temporarily halted due to suboptimal airway conditions. Power calculation done by simulation using pilot data from a prior study indicates a sample size of 600 (300 per group) will yield 82% power.

RESULTS: Twenty-two patients have been enrolled in the study. Nine patients (41%) have been randomized to THRIVE while 13 (59%) have been randomized to SOC. Patients have a mean age of 5.96 years, with a mean of 8.08 years and 4.50 years in the THRIVE and SOC groups, respectively. On average, THRIVE patients have fewer desaturations below 90% (0.22 vs. 1.00). THRIVE patients also have fewer interruptions than their control group counterparts (0.33 vs. 0.41). Overall, mean number of adverse events are lower in the control patients when compared with THRIVE patients (0.08 vs. 0.22) (Table 1). Of the three total adverse events reported, nausea was reported twice (1 in SOC vs. 1 in THRIVE), and headache was reported once (THRIVE).

CONCLUSION: Pediatric patients undergoing MDLB pose anesthetic challenges. THRIVE has been shown to deliver humidified oxygen and provide adequate ventilation as an alternative to invasive airways in several populations[2,3]. We introduce THRIVE as a method for airway management in pediatric patients undergoing MDLB and propose a prospective, multi-site, randomized controlled trial to evaluate HFNC in pediatric patients undergoing MDLB. Early data have been collected and further enrollment continues.

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	All Patients		Standard of Care			THRIVE		
	Number or Mean	% or SE	Number or Mean	% or SE	Row %	Number or Mean	% or SE	Row %
	22	100%	13		59%	9		41%
Patient Characteristics								
Age (mean years)	5.96	1.16	4.50	1.37		8.08	1.91	
Gender								
Male	12	55%	3	23%	25%	9	100%	75%
Female	10	45%	10	77%	100%	0	0%	0%
Race								
American Indian/Alaska Native	0	0%	0	0%	0%	0	0%	0%
Asian	2	9%	2	15%	100%	0	0%	0%
Native Hawaiian or Other Pacific Islander	0	0%	0	0%	0%	0	0%	0%
Black or African American	0	0%	0	0%	0%	0	0%	0%
White	14	64%	9	69%	64%	5	56%	36%
More Than One Race	0	0%	0	0%	0%	0	0%	0%
Other	6	27%	2	15%	33%	4	44%	67%
ASA Class								
1	2	9%	1	8%	50%	1	11%	50%
2	11	50%	7	54%	64%	4	44%	36%
3	9	41%	5	38%	56%	4	44%	44%
4	0	0%	0	0%	0%	0	0%	0%
Outcomes								
Surgical Interruptions (mean)	0.41	0.20	0.46	0.31		0.33	0.24	
Number of Desaturations <90% (mean)	0.68	0.35	1.00	0.58		0.22	0.15	
Adverse Events (mean)	0.14	0.07	0.08	0.08		0.22	0.15	
Nausea	2	67%	1	8%	50%	1	11%	50%
Headache	1	33%	0	0%	0%	1	11%	100%

PEDIATRIC ANESTHESIOLOGY 28

A Systematic Review of Evidence Synthesis Studies Investigating Interventions that Reduce the Incidence of Post-Operative Nausea and Vomiting in Children

Jessica Nghiem[1], Alfonso E Albornoz[1], Maria Alexandra Petre[2], Evelina Pankiv[3], Marina Englesakis[4], Conor McDonnell[1], Kazuyoshi Aoyama[5]

[1]The Hospital for Sick Children, Toronto, Ontario, [2]Montreal Children's Hospital, Montreal, Quebec, [3]University of Toronto, Toronto, Ontario, [4]University Health Network, Toronto, Ontario, [5]SickKids Hospital, Toronto, Canada

INTRODUCTION: Postoperative nausea and vomiting (PONV) is the most common adverse reaction following general anesthesia. The incidence of PONV in pediatric anesthesia is approximately two times higher than in adults, ranging from 33% to 82%, depending on patient risk factors[1]. PONV has significant impacts on perioperative care, being the leading cause of unplanned admissions, prolonging hospital stays, and increasing healthcare costs[2]. The purpose of this systematic review is to summarize existing evidence of interventions that reduce the incidence of PONV in children. As such, the current study can identify knowledge gaps and areas on which future clinical research of PONV in children should focus.

METHODS: The current study followed PRISMA guidelines[3]. Two reviewers independently reviewed titles, abstracts, and full texts. Data sources: A systematic search of current literature from 10 databases (MEDLINE, PubMed, EMBASE, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, Scopus(Elsevier), Web of Science, ClinicalTrials.gov, International Clinical Trials Registry Platform, and International Standard Randomized Controlled Trial Number Registry), from their inception to March 2020, was performed to identify evidence synthesis studies that investigated either pharmacologic or non-pharmacologic interventions with any comparator for prophylaxis of PONV in pediatric patients undergoing general anesthesia. Inclusion criteria were followings: 1) study population was <18 years of age; 2) study design was evidence synthesis (i.e., systematic review, meta-analysis, and clinical practice guideline); 3) study included only randomized controlled trials of interventions to prevent PONV; and 4) study was published in English. Risk of bias was assessed using the Risk Of Bias In Systematic reviews (ROBIS) tool[4].

RESULTS: The database search identified 6,305 studies and after removing duplicate studies, 3207 studies were screened. Following title and abstract screening, 79 evidence synthesis studies (1 clinical practice guideline, 18 systematic reviews, 57 meta-analyses, and 3 network meta-analyses) were identified and assessed for further eligibility. Out of 79 studies, only 22 studies (5 systematic reviews, 16 meta-analyses, and 1 network meta-analysis[NMA]) met the above inclusion criteria. While 16 eligible studies investigated various pharmacologic interventions, all of the rest investigated acupuncture of non-pharmacologic interventions. Sixteen studies (72.3%) investigated PONV as primary outcome. The target cohort of the eligible studies were a general surgical population (63.6%), tonsillectomy (22.7%), and ophthalmology (13.7%). There were only 2 meta-analyses in 6 studies investigating acupuncture, which confirmed that compared to placebo, acupuncture at PC6 significantly prevented pediatric PONV in a general surgical population (Relative Risks[RR] 0.69: 95% Confidence Intervals[CIs] 0.59-0.80) and a cohort undergoing tonsillectomy (RR 0.77: 95%CIs 0.63-0.94), respectively. In 16 studies investigating pharmacologic interventions, there were 13 meta-analyses and 1 NMA. Out of 13 meta-analyses, 3 studies (23.1%) concluded that compared to placebo, dexamethasone, 5-HT3 antagonist, and clonidine were effective in preventing PONV in pediatric ophthalmology. Five studies (38.5%) concluded that compared to placebo, dexamethasone, 5-HT3 antagonist, and metoclopramide significantly prevented PONV in pediatric tonsillectomy. Other 5 studies' cohort (38.5%) was a general pediatric surgical population, and these studies concluded that total intravenous anesthesia, supplemental intravenous crystalloid, dexamethasone, and 5-HT3 antagonist were effective in preventing PONV. The NMA explored 6 different single medications and 5 different combined medications as prophylaxis of pediatric PONV in various surgical population, and concluded that compared to placebo, a combination of 5-HT3 antagonist plus dexamethasone showed the lowest RR 0.17 (95% CIs: 0.14-0.21) among total 11 prophylactic strategies. However, eligible cohorts of this NMA seemed very heterogeneous although heterogeneity across eligible cohorts was not properly assessed.

CONCLUSION: The current study warrants future NMAs that explore the relative efficacy of effective pharmacologic and non-pharmacologic prophylaxes for PONV in pediatric tonsillectomy and ophthalmology, as well as a general pediatric surgical population.

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PEDIATRIC ANESTHESIOLOGY 29

Short Term Mortality After Anesthesia for Non-Surgical Indications Among Children with Complex Chronic Conditions in the United States

Sydney Brown[1], Matt Hall[2], Chris Feudtner[3]

[1]The University of Michigan, Ann Arbor, MI, [2]Children's Hospital Association, Lenexa, KS, [3]Children's Hospital of Philadelphia, Philadelphia, PA

INTRODUCTION: Children with complex chronic conditions (CCCs) often require anesthesia for non-surgical indications, such as diagnostic imaging, and minimally invasive cardiac or interventional radiology procedures. Children with CCCs are more likely to suffer adverse events after even low risk anesthetics, however little data regarding outcomes after non-surgical anesthetics currently exists. We hypothesized that non-surgical anesthetics would be followed by death within three days at a rate comparable to low-risk non-cardiac surgery.

METHODS: Using the Pediatric Health Inpatient Sample database 4/1/2016 to 10/31/2018, we measured the incidence of death following non-surgical and surgical anesthetics in neonates, infants, and children with CCCs, including cardiac procedures, imaging, interventional radiology, endoscopy, and oncology procedures. We examined first anesthetics of last hospitalizations each year, and used multivariable logistic regression to calculate incidence of death after each procedure type.

RESULTS: Fifty-nine percent of patients received a non-surgical anesthetic during the study period. 51,170 (38%) were performed for non-surgical indications (11% cardiac procedures, 30% diagnostic imaging, 40% interventional radiology, 18% endoscopy, and 17% oncology procedures); 134,564 were performed for surgery. Death within three days of the anesthetic occurred in 0.8% (319/38,546) of children, 1.6% (104/6,480) of infants, and 5.2% (322/6,236) of neonates. Table 1 shows the incidence of death within three days of anesthesia performed in children during elective hospitalizations. Non-surgical cardiac procedures had a higher incidence of death than cardiac surgery (one in 278 vs. one in 769). The incidence of death after imaging (one in 667), interventional radiology (one in 588), and endoscopy (one in 1,429) was similar to high-risk non-cardiac surgery (one in 1,111). For urgent/emergent hospitalizations (Table 2), in children the incidence of death after non-surgical cardiac procedures was comparable to cardiac surgery (one in 36). The incidence of death after imaging and interventional radiology procedures was comparable to high-risk non-cardiac surgery (one in 78). Similar results were seen among infants and neonates, except that non-surgical cardiac procedures were more than 10x as likely to be followed by death within three days than cardiac surgery.

CONCLUSION: Over one third of the anesthetics in this population are for non-surgical indications; almost 1% of children with a CCC die a short duration after, with higher incidence among infants and neonates. Mortality after imaging and interventional radiology procedures was comparable to high-risk non-cardiac surgery in children, and twice as high as high-risk non-cardiac surgery among infants and neonates. Future research should examine whether anesthesia staffing or technique contribute to these outcomes.

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Table 1. Indicence of Mortality within Three Days of Anesthesia for Children > 1 Year Presenting for Anesthesia for Surgery and Non-Surgical Indications During Elective Hospitalizations

	Marginal Probability % (95%CI)	Number Needed to See Effect
Surgery		
Cardiac Surgery	0.13 (0.08, 0.18)	769
High Risk Non-Cardiac Surgery	0.09 (0.07, 0.12)	1111
Low Risk Non-Cardiac Surgery	0.02 (0.01, 0.03)	5000
Non-Surgical Indication		
Cardiac Procedures	0.36 (0.23, 0.48)	278
Imaging	0.15 (0.1, 0.21)	667
Interventional Radiology	0.17 (0.11, 0.22)	588
Endoscopy	0.07 (0.04, 0.09)	1,429
Oncology	0.04 (0.02, 0.06)	2,500

Table 2. Incidence of Mortality within Three Days of Anesthesia for Patients Presenting for Anesthesia for Surgery and Non-Surgical Indications During Urgent / Emergent Hospitalizations

	Marginal Probability % (95%CI)	Number Needed to See Effect
Neonates		
Surgery		
Cardiac Surgery	1.35 (0.94, 1.75)	74
High Risk Non-Cardiac Surgery	3.45 (3.01, 3.9)	29
Low Risk Non-Cardiac Surgery	1.31 (0.99, 1.63)	76
Non-Surgical Indication		
Cardiac Procedures	15.68 (13.07, 18.29)	6
Imaging	4.34 (3.18, 5.5)	23
Interventional Radiology	8.2 (7.19, 9.22)	12
Endoscopy	5.15 (4.01, 6.29)	19
Oncology	3.84 (2.09, 5.6)	26
Infants		
Surgery		
Cardiac Surgery	0.18 (0.07, 0.29)	556
High Risk Non-Cardiac Surgery	0.74 (0.59, 0.9)	135
Low Risk Non-Cardiac Surgery	0.17 (0.1, 0.23)	588
Non-Surgical Indication		
Cardiac Procedures	3.32 (2.37, 4.27)	30
Imaging	2.07 (1.58, 2.55)	48
Interventional Radiology	2.07 (1.61, 2.53)	48
Endoscopy	0.66 (0.32, 1.01)	152
Oncology	0.7 (0.25, 1.15)	143
Children		
Surgery		
Cardiac Surgery	2.81 (2, 3.61)	36
High Risk Non-Cardiac Surgery	1.29 (1.11, 1.46)	78
Low Risk Non-Cardiac Surgery	0.19 (0.14, 0.24)	526
Non-Surgical Indication		
Cardiac Procedures	2.82 (2.32, 3.31)	35
Imaging	1.41 (1.22, 1.61)	71
Interventional Radiology	1.33 (1.15, 1.51)	75
Endoscopy	0.52 (0.39, 0.66)	192
Oncology	0.47 (0.34, 0.61)	213

PEDIATRIC ANESTHESIOLOGY 30

Impact of Smoke Exposure from the Northern California Wildfires on Pediatric Perioperative Respiratory Outcomes

Benjamin J Marsh[1], David Robinowitz[1], Marla Ferschl[1]

[1]University of California, San Francisco, San Francisco, CA

INTRODUCTION: Wildfire activity has increased over the past two decades in the United States. This increase has been attributed to climate changes including warmer temperatures, earlier snowmelts, and less rainfall. Studies have demonstrated a link between wildfire smoke and emergency department visits for respiratory symptoms in pediatric age groups. In the perioperative setting, exposure to tobacco smoke has been identified as a strong risk factor of laryngospasm in children and infants undergoing general anesthesia, but the association between poor air quality and anesthesia-related adverse respiratory events is not known. We hypothesize that wildfire smoke and its associated poor air quality, as measured by an air quality index (AQI) >100, may increase the risk of perioperative respiratory complications in pediatric populations undergoing anesthesia.

METHODS: Following IRB approval, a retrospective double-cohort pilot study was conducted at a single US tertiary care hospital. Perioperative records of all ambulatory pediatric patients (<18 years old) were reviewed from two two-week periods in August and September 2020 before and during wildfire smoke exposure, corresponding to AQI 100, respectively. Exclusion criteria included inpatients, emergency cases, and congenital heart disease. Preoperative variables included procedure type, age, weight, ASA status, pre-existing medical conditions including respiratory disease and history of prematurity, known tobacco exposure, and use of pulmonary medications. Adverse respiratory outcomes were defined as intraoperative use of inhaled albuterol or intravenous epinephrine, bronchospasm, laryngospasm, SpO2 < 90%, use of propofol boluses in the recovery area, and reintubation.

RESULTS: 662 patients were identified in the August and September time periods, and 203 patients were excluded. A composite incidence of adverse respiratory outcomes was found to be 2.8% in the August group and 1.6% in the September group.

CONCLUSION: Further research on the effects of poor air quality and exposure to particulate matter on cardiopulmonary health is needed. While no significant difference between groups was found in this small pilot study, this lack of effect may be due low power given the rarity of serious respiratory complications in pediatric anesthesia for outpatient procedures. In addition, brief respiratory events with rapid improvement after treatment may not always generate documentation given their relative infrequency. Additional data from wildfires in November 2018 is being investigated. Wildfires are a growing problem in many areas of the United States, and future steps would include a multi-institutional study to increase statistical power along with a data quality initiative to encourage documentation of all respiratory events. Wildfire smoke exposure may have a negative effect on perioperative respiratory outcomes in pediatric age groups, and further research is warranted in pediatric populations.

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PEDIATRIC ANESTHESIOLOGY 31

CYP2B6 and POR Polymorphisms Influence Metabolism and Clinical Outcomes of Perioperative Methadone in Children

Senthil Packiasabapathy[1], Blessed Aruldhas[1], Pengyue Zhang[1], Senthilkumar Sadhasivam[1]

[1]Indiana University School of Medicine, Indianapolis, IN

INTRODUCTION: Methadone is a long-acting opioid agonist, with actions on NMDA and SNRI pathways. It is being increasingly used for perioperative analgesia in both adults and children, due to minimal abuse potential and beneficial effects in terms of minimal opioid induced hyperalgesia, opioid sensitization and chronic pain prevention. CYP2B6 is the most significant enzyme that mediates de-methylation and elimination of methadone[1-5]. CYP enzymes (3A4, 3A5 and 3A7) require electron transfer through the P450 oxidoreductase (POR)[6]. Polymorphisms in the CYP2B6 as well as POR genes can potentially influence the individual variability in clinical response to methadone. Studies have associated CYP2B6 and POR polymorphisms with methadone response and dose requirements[1-6]. But these are adult studies in the setting of methadone maintenance therapy (MMT) for opioid use disorders (OUD). The current study is focused on assessing the influence of CYP2B6 and POR genetic variants on pharmacokinetics (PK) and clinical outcomes of perioperative methadone therapy in children.

METHODS: Adolescents undergoing posterior spinal fusion (PSF) for idiopathic scoliosis or pectus excavatum (PE) repair were included in this prospective observational study. They received methadone intraoperatively (0.1 mg/kg IV, maximum 5 mg) and postoperatively every 12 h for 3-5 doses (0.1 mg/kg PO, maximum 5 mg) as part of multimodal analgesic protocol. Blood samples were collected up to 72 hours post-operatively for measurement of plasma levels of R- and S-methadone and primary metabolite: 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) chiral assay; Metabolite to parent ratios of R-, S- and total methadone were calculated. Genotyping was also performed using Whole genome sequencing (WSG) analysis at 40x coverage (mapped to hg19). Aldy, a high-throughput sequencing data analysis tool was used to identify the genotypes of relevant, highly polymorphic genes from the mapped data. Outcomes: The primary PK outcome measure was metabolite to parent drug ratios for R- and S-methadone. The primary clinical outcome measure was analgesia: described by pain scores and opioid consumption (other than methadone). The secondary clinical outcomes included adverse events like postoperative nausea and vomiting (PONV), respiratory depression (RD) and heart-rate corrected QT (QTc) interval prolongation. The effect of genotypes on outcomes like maximum and median pain score, morphine equivalent dose and PONV were analyzed using univariate regression and multiple regression analyses (adjusted for BMI, age and the type of surgery).

RESULTS: A total of 50 children were enrolled in the study. Adolescents that were poor metabolizers (*6/*6) had >2-fold lower metabolite/drug ratios, compared with normal (*1/*1) or rapid metabolizers (*1/*22) (Fig.1). Beside PK variability, we identified novel associations between methadone induced PONV (increased risk) and CYP2B6 SNPs, rs1038376 (P=.005), rs10853744 (P=.024), rs7250601 and rs7250991 (P=.022), as well as maximum post-surgical pain (rs11882424, P=.007). Also, POR rs1057868 TT and CT genotypes (with anticipated higher CYP3A4 activity, higher methadone inactivation and higher requirements of non-methadone opioids) was associated with higher incidence of PONV than the wild type, CC (P=.026); the higher total opioid use in those with PONV (P = .005, R2 = 0.21) supports this association (Fig.2).

CONCLUSION: Along with the CYP2B6 genotype mediated metabolic variability, this study demonstrates positive associations of CYP2B6 polymorphisms with methadone induced PONV and maximal pain scores. We also found POR polymorphisms that are associated with an increased risk of PONV, secondary to increased opioid requirements. Genetic polymorphisms could explain variable clinical responses to perioperative methadone. More, well-powered studies are required to establish robust associations and also to examine other genes influencing pharmacokinetics and pharmacodynamics of methadone, to enable development of a multi-gene predictive model. Genotyping might hold the key to personalize perioperative methadone use in children, to ensure efficacy and safety.

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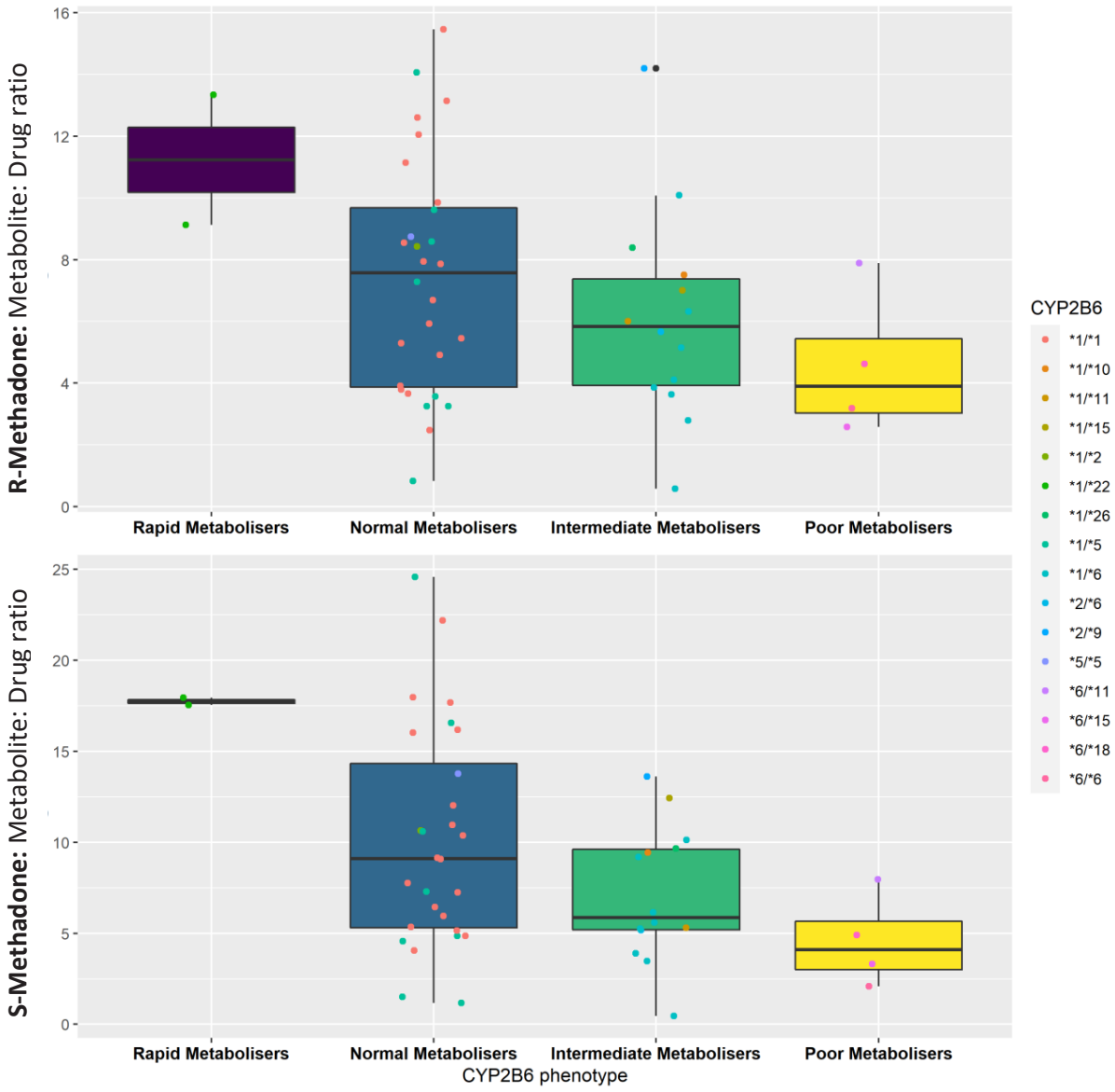

Fig. 1

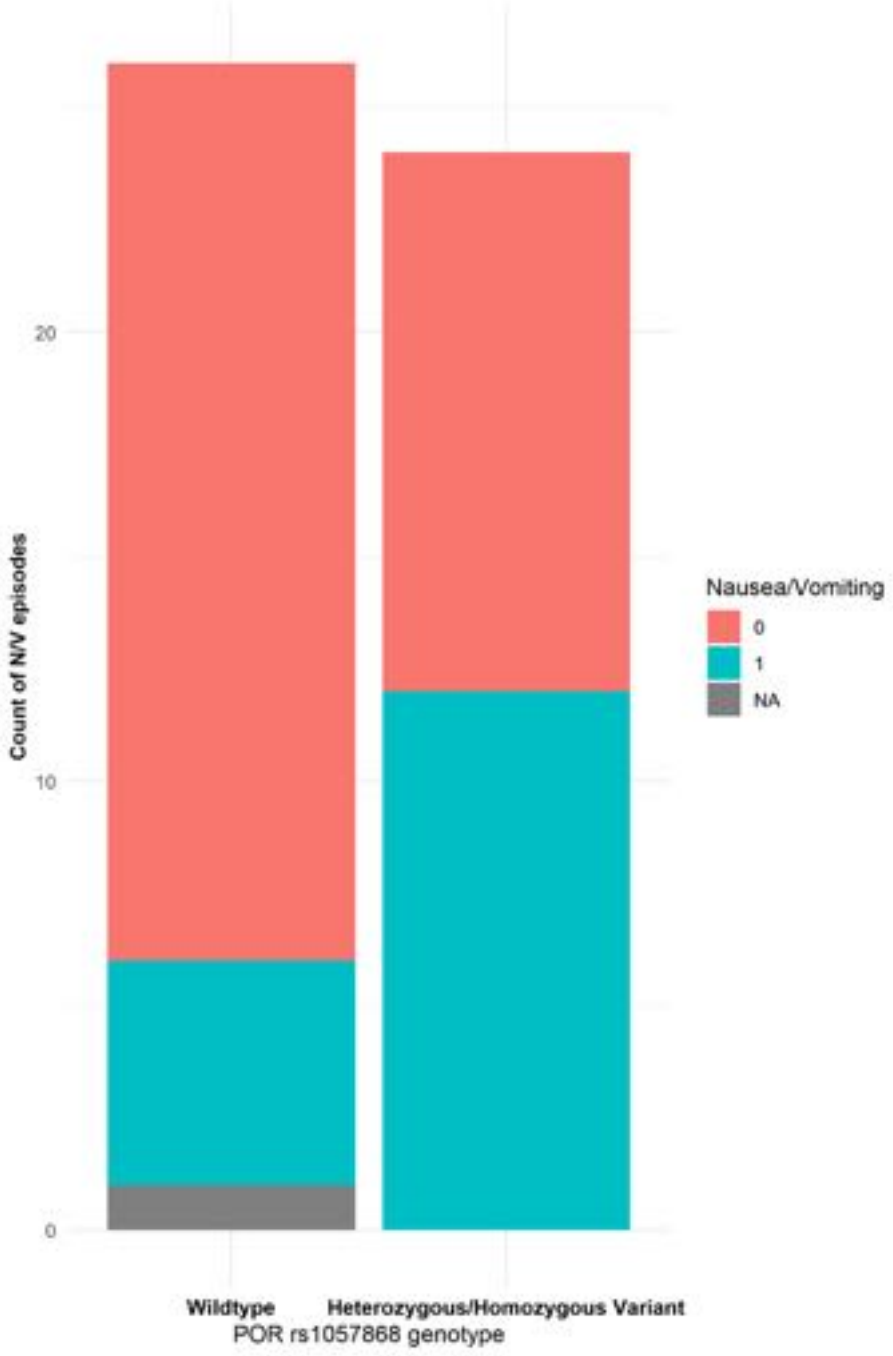

Fig. 2

PEDIATRIC ANESTHESIOLOGY 32

Present Anesthesiology Practices in the Context of Patent Foramen Ovale: PFO Anesthesiology Survey

Huynh Nguyen[1], Ricardo Falcon[2], Tim Petersen[2], Codruta Soneru[3]

[1]University of Southern California, Los Angeles, United States of America, [2]University of New Mexico, Albuquerque, United States of America, [3]University of New Mexico, Albuquerque, NM

INTRODUCTION: Many institutions have no stated standard of care for perioperative management of spine surgery patients with PFO. Patients who undergo posterior spinal fusion are at risk for pulmonary air embolism[1,2,3]. However, patients with PFO are at risk of paradoxical air embolism, in which air passes from the right atrium to the left and then systemic circulation possibly causing stroke, myocardial or other organ infarction, cardiovascular collapse, or mortality. We conducted a survey to learn whether standards are arising surrounding: 1) routine preoperative echocardiography for spinal fusion patients, and 2) any PFO defect closure prior to spinal surgery.

METHODS: We surveyed 350 pediatric anesthesiologists in multiple states to identify perioperative anesthesia practice patterns related to posterior spinal fusion patients.

RESULTS: There were 49 respondents, of whom 46 completed the survey. Most respondents' practice involved OR care for surgical patients (81%) and spine surgery patients (92%). Our respondents were generally experienced; 63% had been practicing anesthesia for >10 years, and 88% had completed a fellowship in pediatric anesthesia. A minority of anesthesiologists (6%) would routinely perform or order echocardiograms on surgery patients with idiopathic scoliosis, but 35% would for those patients with neuromuscular scoliosis. For patients with known PFO, most respondents (61%) would not advise/require device closure prior to spinal fusion, consistent with most of them not having ever experienced a spinal fusion surgery complicated by a significant air embolism (82%) or paradoxical air embolism (86%).

CONCLUSION: Consistent with previous studies, we found that most anesthesiologists would perform echocardiograms in at least some patients presenting for spine surgery; however, most would not do so if the patient was otherwise healthy with idiopathic scoliosis despite a 3.6% risk of undiagnosed heart defect[4]. Most respondents would not advise/require device closure of the defect prior to spinal fusion, contrary to a study suggesting that patients with PFO should undergo closure of the defect prior to procedures with air embolism risk[5]. Our response rate was somewhat low, so we cannot definitely determine whether preoperative echocardiogram is becoming standard of care for all spinal fusion patients. However, we can say that many anesthesiologists would not routinely require PFO closure prior to spinal fusion. Given the risk of fatal events from paradoxical air embolism after spinal fusion, this is an area that requires further research.

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PEDIATRIC ANESTHESIOLOGY 33

Modeling Intraoperative Opioid Administration Variation: A Single-Center Retrospective Cohort Study of Children

Conrad Safranek[1], Sarah Poole[2], Beth De Souza[2], Tracey Hong[2], Ellen Wang[2], David Scheinker[1], Thomas A Anderson[2]

[1]Stanford University, Stanford, CA, [2]Stanford University School of Medicine, Stanford, CA

INTRODUCTION: Determining the appropriate intraoperative opioid dose requires anesthesiologists to analyze and integrate numerous patient and healthcare details to effectively manage nociception and analgesia while minimizing risk of opioid-related adverse health outcomes.[1] Guidelines informing intraoperative analgesic administration are not clearly delineated for different patient populations or types of surgery. However, administration of too little or too much opioid has negative consequences.[2,3] Comprehensive investigation of anesthesia providers' opioid administration patterns and patient and healthcare contributions to intraoperative administration practices may inform practice and improve patient outcomes. We sought to determine variables associated with variance in the intraoperative opioid dose administered to children.

METHODS: Patient, surgery, and anesthesia details were extracted for all surgeries at a single pediatric center from May 2014 to August 2019. Variables expected to impact intraoperative opioid dose administration were selected. Filtration criteria, including exclusion of the highest 0.5% of weight-normalized opioid doses, were applied to obtain a final case cohort for primary analyses: univariable modeling determined the association of each variable with intraoperative opioid dose; parameters for multivariable machine learning models were optimized on ‚Öì of the final case cohort; the model best able to predict intraoperative opioid dose was trained and tested with 30-fold cross-validation to determine a coefficient of determination (R^2) for the final case cohort. Secondary analyses with the best performing model were conducted to understand the impact of varying the threshold of weight-normalized outlier exclusion, and to determine model performance for select surgery types.

RESULTS: The final cohort included 33,631 surgical cases. Univariable modeling identified variables with the greatest impact on intraoperative opioid dose: patient weight (R^2 24.84%), patient age (R^2 23.68%), surgery type (R^2 19.64%) (Table 1). Multivariable model optimization identified gradient boosting as the most predictive model. With the final case cohort, this model achieved an R^2 of 58.6% (interval 46.4% to 69.2%). Varying the stringency of the weight-normalized-dose outlier threshold from 0 to 1% of cases resulted in R^2 varying from 42.3% to 59.2% (Figure 1). The mean R^2 for the five selected common surgeries ranged from 39.6% to 48.7%.

CONCLUSION: Multivariable modeling explains a modest proportion of variation in intraoperative opioid dose delivered to children; however, greater than 40% of variation is not explained by the captured features. Additional healthcare and patient features, including innate differences in patient nociception and opioid sensitivity (as indicated by physiological parameters), likely play significant roles in intraoperative opioid dose delivery variation. Future efforts to optimize intraoperative analgesia delivery must acknowledge and account for this unexplained variation.

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Table 1. Results of univariable regression models relating each feature of interest to the total amount of oral morphine equivalent units (MEU) of opioids utilized intraoperatively.

Feature	Number of categories	Median [interquartile range]	R^2
Weight (kilograms)	NA	22.2 [13.4-43.0]	**24.84%**
Age (years)	NA	6.6 [2.7-11.9]	**23.68%**
Surgery type	224	NA	**19.64%**
Primary surgeon	122	NA	**12.48%**
Anesthesia duration (hours)	NA	1.6 [1.1-2.5]	**11.71%**
Procedure duration (hours)	NA	0.7 [0.3-1.3]	**11.66%**
Surgical service	26	NA	**7.97%**
Sum RVUs	NA	8.8 [4.3-16.5]	**6.64%**
Case complexity classification (based on RVUs)	3	NA	**4.68%**
Primary anesthesiologist	68	NA	**3.60%**
Patient class (inpatient, outpatient, surgery admit)	3	NA	**3.10%**
Weight percentile for age (0 - 100%)	NA	0.6 [0.3-0.9]	**1.56%**
Overweight (weight percentile > 85)	2	NA	**1.41%**
History of chronic pain	2	NA	**1.00%**
Postoperative disposition (PACU, ICU)	2	NA	**0.47%**
Intraoperative non-opioid analgesics (0, ≥1)	2	NA	**0.47%**
Presence of anesthesia trainee (resident, fellow)	2	NA	**0.29%**
History of mood disorder	2	NA	**0.26%**
Race	8	NA	**0.22%**
Case year (2014 - 2019)	6	NA	**0.20%**
History of obstructive sleep apnea	2	NA	**0.08%**
ASA class (I - VI)	6	NA	**0.06%**
Ethnicity	5	NA	**0.04%**
Gender	2	NA	**0.02%**
History of substance use disorder	2	NA	**0.02%**
Intraoperative remifentanil	2	NA	**0.01%**
History of personality disorder	2	NA	**0.01%**

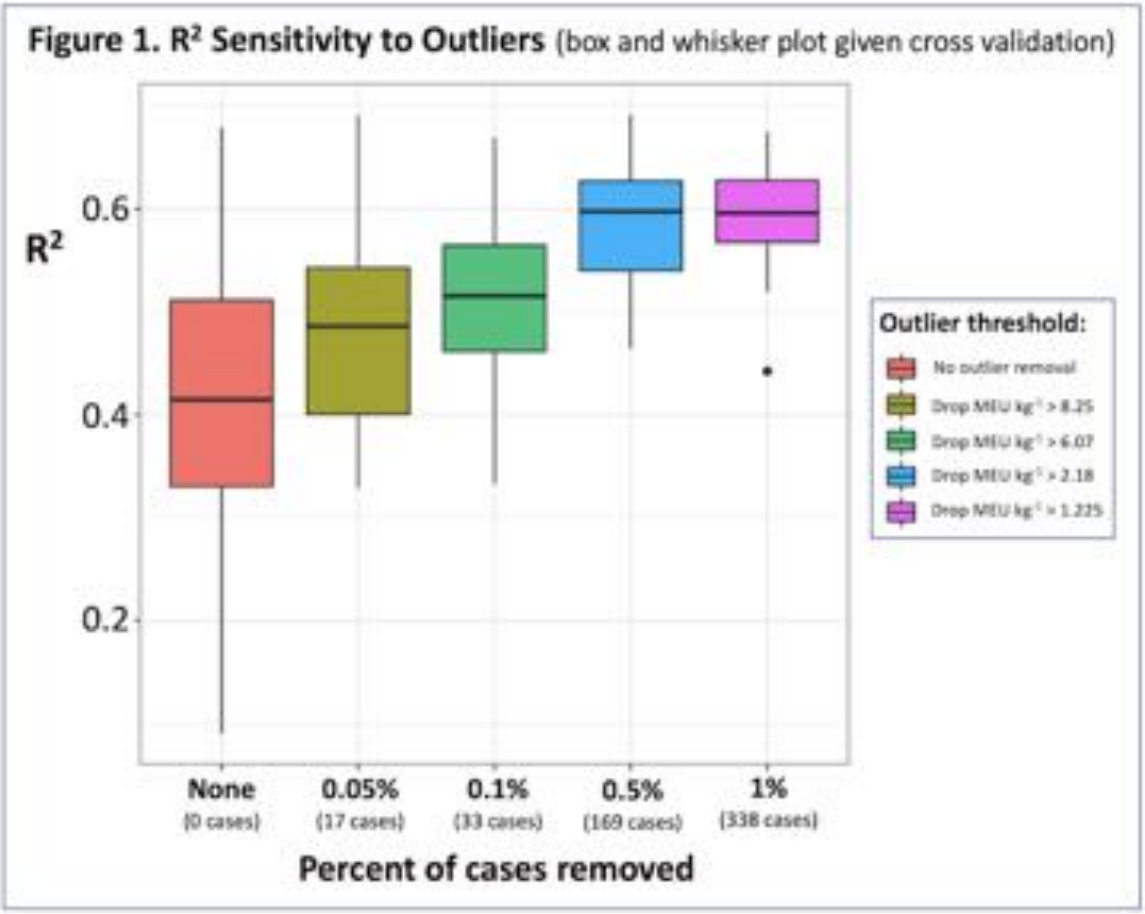

Figure 1. R^2 Sensitivity to Outliers (box and whisker plot given cross validation)

PEDIATRIC ANESTHESIOLOGY 34

A Novel Method to Detect Changes in Mitochondrial Permeability Transition Pore Voltage Gating in Isolated Mouse Heart Mitochondria

Keren K Griffiths[1], Aili Wang[2], Yash Somnay[3], Richard J Levy[2]

[1]Columbia University Medical Center, New York, NY, [2]Columbia University, New York, NY, [3]Columbia University, New York City, NY

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 disease processes, from diabetes to ischemia-reperfusion injury[2,3]. Regulation of mPTP opening is also essential for normal cellular development and homeostasis[4]. Thus, detecting mPTP opening within mitochondria is key when considering specific pathophysiological mechanisms. Typically, in order to determine the threshold for pore opening, calcium is used to trigger the permeability transition, leading to collapse of the membrane potential, rapid uncoupling of oxidative phosphorylation, and swelling[5]. We aimed to develop a method to detect mPTP opening without inducing it to open, per se. We hypothesized that we could determine the threshold for opening by monitoring sensitivity to the inhibitor cyclosporine A (CsA) relative to the mitochondrial membrane potential. We describe a novel method to assess for voltage threshold for mPTP opening in isolated mitochondria using polarography and a TPP+ selective electrode. We hypothesized that using this approach, we could identify differences in voltage gating in cardiac mitochondria from Fragile X Syndrome (FXS) mice which were previously found to have excess CoQ and increased closed probability of the mPTP.

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. Oxygen consumption and mitochondrial membrane potential were measured simultaneously using polarography and a TPP+ selective electrode. Complex II-dependent proton leak respiration was initiated using succinate, rotenone and oligomycin. In separate experiments, CsA was added at three specific TPP+ voltage levels (low, intermediate and high) relative the TPP+ standard as the proton motive force declined in order to determine open or closed mPTP probability. We evaluated up to 11 mice per group. Significance was assessed via chi-squared test with set $p < 0.05$.

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 significant differences between strains, with open mPTP probability in 89% of FVB controls and only 45% in Fmr1 KOs.

CONCLUSION: Here we describe a new technique to assess the voltage threshold for mPTP opening in isolated mitochondria by monitoring sensitivity to CsA over a range of mitochondrial membrane potentials during oligomycin-induced state 4 respiration. Using our novel technique, we were able to identify differences in voltage gating of the mPTP between Fmr1 KO and FVB controls. This technique will permit assessment of both physiological and pathological regulation of the mPTP without the need to induce the pore to open. Thus, it will have utility when investigating the role of the mPTP in health and disease.

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PEDIATRIC ANESTHESIOLOGY 35

Evaluation of Opioid Usage in the Early Postoperative Period for Pediatric Patients with Scoliosis Following Surgical Correction

Esteban Esquivel[1], William Johnson[1], Elizabeth Rossmann Beel[1], Nihar Patel[1], Kim-Phuong Nyguyen[1], Michael Zelisko[1], Eduardo Medellin[1], Andrew Lee[1], THIEN-DUY TRAN[1], HILLARY CLOYD[1], ANGELA MEDELLIN[1], Chris D Glover[1]

[1]Baylor College of Medicine, Houston, TX

INTRODUCTION: Scoliosis is a multidimensional deformity of the thoracolumbar spine that may require surgical correction as the severity of symptoms worsens with disease progression. Postoperative management includes the use of opioid-based patient-controlled analgesia (PCA) and adjuncts without a consensus on optimal perioperative management. This lack of consensus combined with current societal concerns around opioid abuse and dependency led us to evaluate the perioperative opioid use characteristics of our scoliosis population while in the hospital and at follow up.

METHODS: This retrospective comparative study included pediatric patients from December 2014 to March 2017 who underwent posterior spinal instrumentation and fusion for repair of idiopathic, neuromuscular, or congenital scoliosis. 130 patients met inclusion criteria. The primary outcome was long-term opioid use noted by active use of an opioid agent at the first postoperative follow up. The doses and amounts of opioids and adjuvants given in the early postoperative period (postop day 0 to postop day 5) were analyzed. Opioids were converted to morphine milligram equivalents (MME). The data are presented as Mean ± SD. Continuous variables were examined for normality and the data were analyzed using independent t-tests or Whitney U-tests.

RESULTS: In our cohort, 42.3% (N=55) required opioid medications at their first follow up visit. The total amounts for both opioid PCA and PRN opioids during the early postoperative time period were not significant when looking at patients on and off opioid therapy at follow up. Patients on opioids at follow up received larger amounts of diazepam (On opioids: 26.3±23.3 mg; Not on opioids: 16.8±16.6 mg; $p<0.05$). Patients not on opioids at follow up received larger amounts of acetaminophen (On opioids: 2818.6±986.4 mg; Not on opioids: 3341.3±1536.1 mg; $p<0.05$). When stratified by types of scoliosis, the idiopathic scoliosis group that required opioids at follow up received higher amounts of PRN opioids and diazepam while those not requiring opioids received higher amounts of acetaminophen. Additionally, the idiopathic scoliosis patients who underwent surgical repair of ≥ 13 levels and were requiring opioids at follow up received higher amounts of PRN opioids (complete subgroup analysis shown in Table 1). None of the patients were given epidural analgesia or ketamine.

CONCLUSION: Providing sufficient analgesia during the immediate time period after surgery remains a critical aspect of the recovery for these patients undergoing scoliosis repair. There is not an obvious link between opioid usage during the early postoperative period and at postoperative follow up. In our cohort, those requiring more diazepam and PRN opioids specifically in the idiopathic scoliosis population were requiring opioid medications at their follow up while those not requiring opioids received more acetaminophen. Additional studies that include data from multiple institutions can be used to create a best practice guideline.

Mean Cumulative Amount of Medication Administered (POD0-POD5)

	Opioid PCA		*Opioids*		*Diazepam*		*Ketorolac*		*Ibuprofen*		*Acetaminophen*		*Gabapentin*	
	OF (SD)	**NF (SD)**	**OF (SD)**	**NF (SD)**	**OF (SD)**	**NF (SD)**	**OF (SD)**	**NF (SD)**	**OF (SD)**	**NF (SD)**	**OF (SD)**	**NF (SD)**	**OF (SD)**	**NF (SD)**
Congenital	66.6 (29.0)	58.6 (27.4)	84.0 (51.7)	87.2 (43.4)	29.2 (18.4)[a]	11.9 (5.1)[a]	248.0 (194.2)	137.3 (99.3)	N/A[b]	N/A[b]	3097.5 (1262.5)	3530.1 (1833.2)	N/A[b]	137.5 (388.9)
7-12 Levels	72.7 (0)	52.5 (25.4)	127.5 (0)	86.6 (64.4)	55.0 (0)[a]	12.7 (6.4)[a]	510.0 (0)[a]	122.3 (76.3)[a]	N/A[b]	N/A[b]	2800 (0)	3270.3 (2223.0)	N/A[b]	N/A[b]
≥ 13 Levels	64.6 (35.2)	62.4 (30.7)	69.5 (52.4)	87.6 (35.0)	20.6 (8.1)[a]	11.5 (4.8)[a]	160.7 (103.9)	146.2 (118.5)	N/A[b]	N/A[b]	3196.7 (1527.1)	3686.0 (1824.5)	N/A[b]	220.0 (491.9)
Idiopathic	82.5 (41.0)	93.4 (127.7)	112.8 (53.0)[a]	84.4 (44.2)[a]	27.8 (23.8)[a]	18.8 (16.8)[a]	214.1 (136.0)	176.9 (142.4)	19.51 (74.9)	109.8 (395.0)	2719.9 (734.2)[a]	3233.4 (1283.1)[a]	212.2 (697.9)	349.0 (1012.0)
7-12 Levels	77.5 (35.7)	98.5 (157.4)	107.3 (47.6)	84.8 (49.4)	24.3 (20.5)	17.7 (17.1)	208.6 (154.7)	178.1 (157.0)	7.4 (38.4)	131.3 (470.0)	2586.9 (732.3)[a]	3129.5 (1147.0)[a]	111.1 (408.9)	275.0 (1012.2)
≥ 13 Levels	92.2 (49.6)	84.9 (50.2)	123.5 (62.5)[a]	83.7 (34.9)[a]	34.5 (28.7)	20.8 (16.5)	224.6 (94.2)	174.9 (117.5)	42.9 (115.8)	73.7 (223.2)	2976.4 (691.7)	3408.4 (1501.9)	407.1 (1049.9)	473.7 (1026.8)
Neuromuscular	49.4 (31.9)	37.1 (34.8)	112.4 (100.5)	266.2 (634.1)	19.3 (24.0)	12.9 (19.3)	102.5 (106.2)	65.8 (130.0)	250.0 (790.6)	87.5 (241.9)	3112.0 (1654.2)	3590.9 (2111.8)	N/A[b]	262.5 (725.6)
7-12 Levels	N/A[b]	28.7 (0)	N/A[b]	115.0 (0)	N/A[b]	2.0 (0)	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	2280 (0)	N/A[b]	N/A[b]
≥ 13 Levels	49.4 (31.9)	37.7 (35.9)	112.4 (100.5)	276.2 (655.1)	19.3 (24.0)	13.6 (19.8)	102.5 (106.2)	70.1 (133.4)	250.0 (790.6)	93.3 (249.2)	3112.0 (1654.2)	3678.3 (2155.7)	N/A[b]	280.0 (747.6)

Abbreviation: POD, postoperative day; OF, group receiving opioids on follow up; NF, group not receiving opioids on follow up; SD, standard deviation
Units: Opioid reported in morphine milligram equivalents (MME); Diazepam, ketorolac, ibuprofen, acetaminophen, gabapentin reported in milligrams
[a]Statistically significant with independent t-test (P<0.05)
[b]Drug not administered

PEDIATRIC ANESTHESIOLOGY 36

Demographic Information on Surgical Patients At A Tertiary Children's Hospital in New York City During the COVID19 Pandemic

Albert Y Lin[1], Gracie Almeida-Chen[2], Laura Siedman-Albanese[3], Jennifer J Lee[4], Jerri C Price[5], Steven Stylianos[5], Lena Sun[6]

[1]Columbia University, New York, NY, [2]Columbia Presbyterian Hospital - Morgan Stanley Children's Hospital, New York, NY, [3]Columbia University Medical Center, New York, United States of America, [4]Columbia University Medical Center, New York, NY, [5]Columbia University Irving Medical Center, New York, NY, [6]Columbia University College of Physicians and Surgeons, New York, NY

INTRODUCTION: During the period when New York state enacted an elective surgery ban starting from 3/23/2020 through 6/7/2020, only emergent and urgent surgical and non-surgical procedures were performed. We report the patient characteristics of those who received anesthetic care at our tertiary children's hospital during the initial peak at the epicenter in New York City, which can serve as a basis for comparison for the ongoing pandemic at other parts of the United States.

METHODS: After Institutional Review Board approval, data of each anesthetic performed at our facility from 3/23/2020 through 6/7/2020 were reviewed and entered into a secure spreadsheet by a member of the study team. Demographic information included date of procedure, case description, procedure specialty, COVID19 status, procedure location, ASA physical status, airway management, and if a negative pressure environment was used. Data was organized and analyzed using Microsoft Excel.

RESULTS: A total of 940 cases was performed during the study period, with 27 cases that were COVID19 positive or indeterminate and assumed to be positive. Of the 27 cases of COVID19 positive or assume to be positive, there were 18 patients who had single procedures, 3 patients who had two procedures, and 2 patients who had 3 or more procedures. There were 3 cases after universal testing had started and presented with pending COVID19 tests, and full COVID19 PPE precautions were used. The surgical services are shown in tables 1 and 2. In 40% (11/27) of cases, a negative pressure procedure room/OR was used. The type of airway management used is shown in Table 3.

CONCLUSION: During the elective surgery ban period, 3% (27/940) cases were performed on COVID19 positive patients plus an additional 3 cases where the patient was under investigation status. In all except one case using an LMA, airway management was either via natural airway to minimize viral particle aerosolization or using a cuffed endotracheal tube to filter viral particles through the breathing circuit. While 16/27 cases were surgical procedures, of the remaining non-surgical procedures, the most common involved interventional radiology procedures . As the COVID19 pandemic continues to worsen, this information may be useful for comparative purposes for the current pandemic surge, and better inform allocation of surgical resources.

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Table 1: Patients with COVID19 negative or no testing status	
Subspecialty Service	Number of cases
Pediatric Surgery	183
Interventional Radiology	104
Cardiac Surgery	98
Cardiology	80
Orthopedic Surgery	69
Oncology	62
Radiology Imaging	62
Gastroenterology	47
Otolaryngology	38
Radiation Therapy	25
Other Surgical Services (Urology, Neurosurgery, Plastic Surgery, Liver Transplant, Oral maxillofacial Surgery, Thoracic Surgery, Ophthalmology, Gynecology	103
Other Nonsurgical Services (Neurology, Rehabilitation, Pulmonology, Dental)	39

Table 2: For patients with COVID19 positive or PUI status	
Subspecialty Service	Number of Cases
Interventional Radiology	8
Pediatric Surgery	4
Orthopedic Surgery	4
Otolaryngology	3
Thoracic Surgery	3
Oncology	3
Cardiac Surgery	2
Radiology Imaging	1
Cardiology	1
Gynecology	1

Table 3: Type of Airway Used		
	COVID19+/PUI	All Cases
Natural airway/mask	13	296
Tracheostomy	0	18
CPAP/BiPAP	0	1
LMA	1	46
ETT uncuffed	0	10
ETT cuffed	16	568

PEDIATRIC ANESTHESIOLOGY 37

Neurocognitive Outcomes following Dexmedetomidine Sedation versus General Anaesthesia for Inguinal Hernia Surgery in Infants: A Randomized Controlled Trial (DEGA Study)

Choon L Bong[1], Yew N Siow[2], john C allen[3], Josephine Tan[4], Serene S Lim[2], Michael Meaney[5], Anne Rifkin-Graboi[6]

[1]KK Women's and Children's Hospital Singapore, Singapore, Singapore, [2]KK Women's and Children's Hospital, Singapore, Singapore, [3]Duke-NUS Medical School Singapore, Star, ID, [4]KK Women's and Children's Hospital, Singapore , Singapore, [5]Singapore Institute for Clinical Sciences, Singapore, AK, [6]National Institute of Education, Singapore, Singapore, Singapore

INTRODUCTION: The effects of general anesthesia (GA) on infants' neurodevelopment has been a subject of recent concern.[1] Dexmedetomidine has been shown to be neuroprotective in preclinical studies[2] but the neurocognitive outcomes in infants following dexmedetomidine sedation relative to GA is unknown. We conducted a randomized controlled trial comparing outcomes of infants who underwent inguinal hernia surgery with dexmedetomidine sedation with caudal block versus GA with caudal block and previously reported that dexmedetomidine sedation was associated with significant benefits during the peri-operative period.[3] We also aimed to compare the neurocognitive outcomes of these infants at 6 months and 2 years of age.

METHODS: This prospective randomized controlled trial was conducted in a single tertiary children's hospital in Singapore. Institutional ethics approval was granted and written informed consent was obtained from parents of all patients. 104 infants up to 3 months old undergoing inguinal hernia surgery were randomized to dexmedetomidine sedation with caudal block or GA with caudal block in a 1:1 ratio. 51 infants eventually received DEX and 48 received GA and were followed up for the study. Figure 1 shows the study outline and recruitment profile. Neurocognitive assessments were conducted when infants were at 6 months of age, which included tests of memory (deferred imitation and habituation) as well as attention (visual expectation and event related potential [ERP]). Assessments at 2 years of age include deferred imitation, Bayley Scales of Infant Development version III (BSID-III) and the Child Behaviour Checklist (CBCL).

RESULTS: 42 infants who received DEX and 45 infants who received GA attended for neurocognitive assessments at 6 months, 33 who received DEX and 30 who received GA attended at 24 months. Table 1 shows the demographic characteristics of each group. Usable and complete data were used for analysis for each task. Table 2 shows the results of the various assessments. There were no statistically significant differences in deferred imitation, habituation, visual expectation or ERP scores between infants who received DEX and those who received GA groups at 6 months of age, or in BSID-III and CBCL scores at 2 years of age.

CONCLUSION: We found no significant differences in neurocognitive outcomes at 6 months and 2 years of age between infants who received dexmedetomidine sedation and those who received GA for inguinal hernia surgery before 3 months of age. Dexmedetomidine does not appear to confer neurodevelopmental benefits compared to GA at 6 months or 2 years of age.

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Table 1: Demographic Data

	DEX (n=42)	GA (n=45)	Mean difference	95% CI	P value
Gestational Age (days)	232.6 (50.6)	231 (28.1)	1.5	-14.8, 18.0	0.850
Post-menstrual Age (days)	286.6 (48.7)	287.2 (34.9)	-0.6	-17.5, 16.3	0.946
Birthweight (kg)	1.88 (0.86)	1.86 (0.90)	-0.02	-0.76, 1.03	0.918
Weight at surgery (kg)	3.58 (1.36)	3.43 (1.62)	0.15	-0.44, 0.74	0.613
Male gender (n, %)	27(64.2%)	24 (53.3%)	-		0.300
Race Chinese Malay Indian Others	 27 (64.2) 7 (16.7) 6 (14.2) 2 (4.8)	 33 (73.3) 8 (17.8) 1 (2.2) 3 (6.7)			0.227
Prematurity (n, %)	39 (73.6%)	36 (75%)	-	-	0.871
Antenatal Steriods	33 (62.3)	31 (68.9)		-	0.705
Chorioamnionitis	4 (7.7)	5 (11.4)			0.394
Pre-eclampsia	8 (15.4)	13 (29.5)			0.077
Antenatal sepsis	1 (1.9)	2 (4.5)			0.437
Maternal gestational diabetes	5 (10)	10 (22.7)			0.081
Mode of Delivery NVD Instrumental Cesarean section	 22 (41.5) 1 (1.9) 31 (58.5)	 15 (31.3) 0 33 (68.8)			 0.308 1.000 0.308
Perinatal anesthestic exposure GA Cesarean section Spinal Epidural	 8 (15.1) 3 (5.7) 19 (35.8)	 6 (13) 8 (16.7) 20 (41.7)			 0.779 0.110 0.346
Previous intubation	17 (32.1)	12 (25.5)			0.514
Previous CPAP	30 (56.6)	27 (56.3)			0.971
Previous oxygen therapy	29 (54.7)	27 (56.3)			0.877
Oxygen therapy at time of surgery	3 (5.7)	0			0.245
Maternal university education	24 (57.1)	27 (60.0)			0.630
Paternal university education	23 (54.7)	24 (53.3)			0.427
Public housing	37 (88.1)	34 (75.6)			0.205

Table 2: Neurocognitive Outcomes at 6 Months and 2 Years of Age

Category	Outcome	DEX	GA	Difference (95% CI)	p-value
6 Months					
Memory					
Deferred Imitation[1]	DF2 [3]	0.55±0.70 (n=32)	0.60±0.70 (n=31)	0.05 (-0.28, 0.39)	0.758
Habituation	Proportion Total Look	0.53±0.18 (n=17)	0.52±0.16 (n=24)	0.008 (-0.10, 0.11)	0.874
	Longest look time (ms)	14.3±8.6 (n=31)	15.1±13.7 (n=33)	-0.80 (-6.49, 4.89)	0.780
Attention					
Visual Expectation[2]	Reaction	346.4±51.8 (n=26)	331.8±51.8 (n=36)	14.6 (-12.4, 41.6)	0.284
	Anticipation	4.61±4.17 (n=34)	3.03±4.17 (n=40)	1.58 (-0.36, 3.52)	0.109
Event Related Potential [1]	n	29	27		
	N1 amplitude Oddball	-2.07±1.16	-2.25±1.43	0.18 (-0.51, 0.88)	0.589
	N1 amplitude Standard	-1.75±0.99	-1.97±0.86	0.22 (-0.27, 0.72)	0.378
	EP amplitude Oddball	3.57±1.79	4.21±1.53	-0.63 (-1.53, 0.26)	0.161
	EP amplitude Standard	3.38±1.45	3.31±1.43	0.08 (-0.69, 0.859)	0.840
	N1 latency Oddball	141.4±42.7	132.5±46.5	8.8 (-15.0, 32.7)	0.459
	N1 latency Standard	143.5±61.5	138.9±53.1	4.6 (-26.3, 35.4)	0.766
	EP latency Oddball	453.9±63.8	436.4±83.7	17.5 (-22.2, 57.2)	0.380
	EP latency Standard	441.4±73.0	444.1±80.3	-2.70 (-43.7, 38.4)	0.896
2 years					
Bayley Scales of infant Development _III	n	35	32		
	Cognitive Composite	102.8±10.3	105.3±12.3	-2.56 (-8.4, 3.3)	0.387
	Language Composite	95.1±14.5	98.4±11.5	-3.37 (-10.5, 3.8)	0.350
	Motor Composite	103.3±14.7	104.9±12.7	-1.59 (-9.1, 5.9)	0.672
	SE Composite	96.2±16.4	101.7±14.6	-5.51 (-13.5, 2.3)	0.170
	GAC Composite	98.3±19.2	101.6 ± 15.2	-3.34 (-12.3, 5.6)	0.459
Child Behaviour Checklist (T-Score)	n	33	30		
	Internal Problems	48.2±11.7	49.3±11.7	-0.91 (-6.8, 5.0)	0.759
	External Problems	49.8±12.5	48.4±9.1	1.39 (-4.2, 7.0)	0.620
	Total Problems	49.4±12.6	49.0±10.6	0.39 (-5.5, 6.3)	0.894

[1] Mean ± SD

[2] LSM, Least Squares Mean; RMSE, Root Mean Squared Error

[3] Responses adjusted for Control

PEDIATRIC ANESTHESIOLOGY 38

Reduction of Preoperative Anxiety Using Virtual Reality vs Midazolam: A Randomized Controlled Trial

Anthony Koo[1], Sanjana Khanna[2]

[1]Phoenix Childrens Hospital, Scottsdale, AZ, [2]Phoenix Children's Hospital, Scottsdale, AZ

INTRODUCTION: More than 50% of pediatric patients experience significant stress and anxiety prior to surgery[1]. High anxiety can result in increased postoperative pain, increased analgesic consumption and delayed recovery[2]. In order to reduce this preoperative anxiety, multiple therapeutic modalities have been developed, including the use of distraction, such as playing video games, watching movies, and listening to music. In severe cases of anxiety, anxiolytic and sedative medications like midazolam are used. However, given the acknowledged drawbacks of medications, including the risk of paradoxical reactions to the drug, alternatives to medication for reducing preoperative anxiety in patients may be useful. Our study compares the use of Virtual Reality (VR) to midazolam in reducing preoperative anxiety in surgical patients, and assesses differences in induction compliance, emergence delirium, pain scores, and opioid use in VR vs midazolam-treated patients.

METHODS: 28 first-time surgical patients between the ages of 5-11 undergoing tonsillectomy or tonsillectomy and adenoidectomy procedures were randomly assigned to either receive midazolam (0.5mg/kg up to 25mg) or play an interactive underwater-themed immersion game using VR. The Modified Yale Preoperative Anxiety Scale (mYPAS) was administered by a single child life specialist preoperatively, and only patients who reached a threshold of >40 on mYPAS scoring were enrolled (scale range: 23-100). Additional anxiety measurement was tested using the adult and child State-Trait Anxiety Inventory (STAI). Midazolam or VR was administered prior to transport to the OR, and mYPAS was scored again at the time of separation from family. The Induction Compliance Checklist (ICC) was utilized for further data collection and assessment of patients at the time of anesthesia induction. VR-treated patients continued use of the VR headset up to and through mask induction. A standardized anesthesia induction protocol was used for all patients. The Pediatric Anesthesia Emergence Delirium scale (PAED) was administered at emergence, post-operatively. Postoperative nurses scored pain and administered IV pain medication as needed. Group means and standard deviations were reported and compared with 2-sided t tests.

RESULTS: Interim results showed that 57% of first-time surgery patients scored with mYPAS had scores >40, indicating anxiety. The mYPAS anxiety scores dropped 21.6 ±12.5 points following midazolam treatment ($p<0.001$) and dropped 28.4 ±9.8 points following VR treatment ($p<0.001$). There was no significant difference in mYPAS scores between groups following treatment (midazolam= 32.0±5.2; VR= 25.4±4.9; $p= 0.12$). There were no significant differences between midazolam and VR-treated groups in the Induction Compliance Checklist (ICC), emergence delirium (PAED), peak postoperative pain scores, and medication use for pain control, post-operatively. This study is currently ongoing.

CONCLUSION: Based on these results, VR appears to provide an equivalent alternative to midazolam in reducing preoperative anxiety. Distraction and immersion with VR can help minimize preoperative anxiety during peak stress events, including separation from parents, arrival in the OR, and anesthetic induction. VR was equivalent to midazolam in preoperative induction compliance, and, postoperatively, patients in both groups had similar emergence delirium, pain scoring, and pain medication use. The patient population for this study was limited and additional studies will be necessary to confirm if the conclusions formed are generalizable to the entire pediatric population, including patients with developmental delays and previous surgical experience undergoing a variety of procedures.

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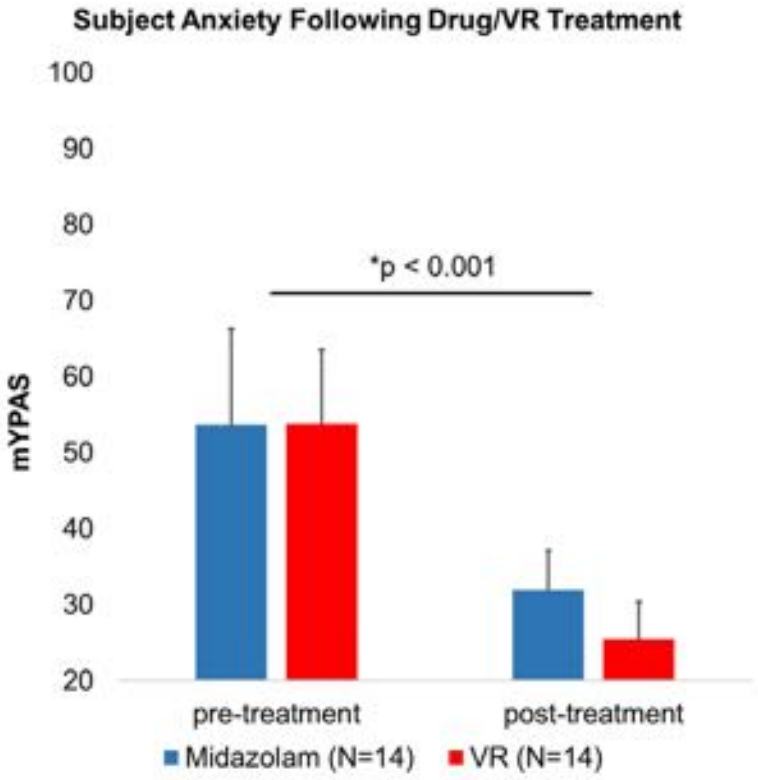

PEDIATRIC ANESTHESIOLOGY 39

Applying the Pareto Principle to Pediatric Post-Surgical Mortality

Christian Mpody[1], Joseph D Tobias[1], Olubukola Nafiu[1]

[1]Nationwide Children's Hospital, Columbus, OH

INTRODUCTION: Serious postoperative complications and mortality are almost inexorably linked. In addition, postoperative complications are also linked to a variety of heterogeneous perioperative factors, making targeted preventive measures quite challenging. In economics and increasingly in clinical care, where risk mitigation is prioritized, the Pareto principle (the law of the vital few and trivial many), has been used as a tool to identify problems that offer the greatest potential for improvement.[1] In this study, we applied the Pareto principle to identify the small subset (20%) of patients responsible for the majority (80%) of pediatric post-surgical mortality.

METHODS: We used the National Surgical Quality Improvement Program database (2012-2018), to identify children who developed major complications following inpatient surgery. We first categorized children into decile risk groups, of equal size, according to the risk of developing serious post-surgical complications. We then tested the Pareto principle by estimating the fraction of mortality, which is accounted for by the top 20% of high-risk subjects.

RESULTS: We identified 55,702 children who developed one or more serious postoperative complications, of whom 1280 (2.4%) died within 30 days of surgery. We found that 20% of children (top surgical risk) accounted for 78% of non-survivors, who typically died within the first week of surgery (median survival: 5 days vs 10 days, P-value < 0.001). In these children, who accounted for 78% of non-survivors, pulmonary complications were the most common adverse events (21.8% of cases), and mostly initiated the cascade of complications leading to mortality (typically occurring within 4 days following surgery: 4 days vs 8 days, P-value <0.001).

CONCLUSION: The distribution of pediatric post-surgical mortality was highly aggregated, 20% of children with identifiable preoperative risk profiles contribute to approximately 80% of postoperative mortality, an indication of the Pareto principle. This suggests that targeted preventive efforts should be directed at the small subset of high-risk children in order to have the greatest effect on reducing pediatric postoperative mortality.

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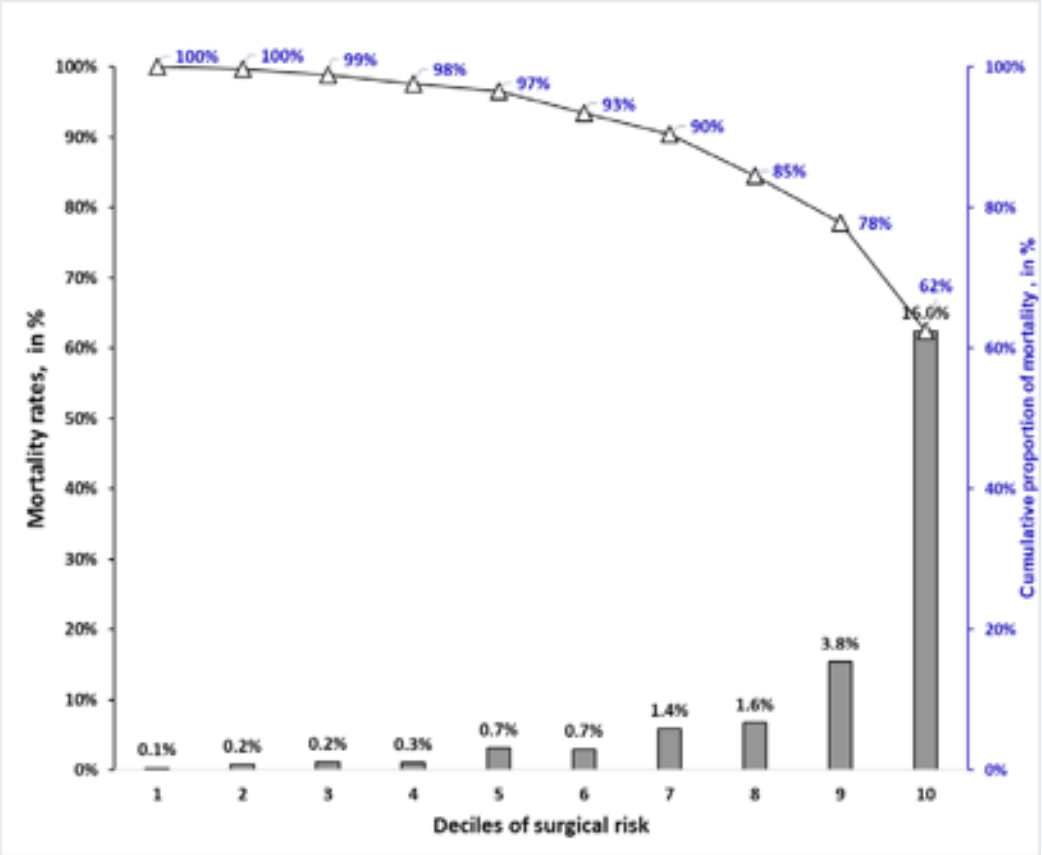

Fig. 1

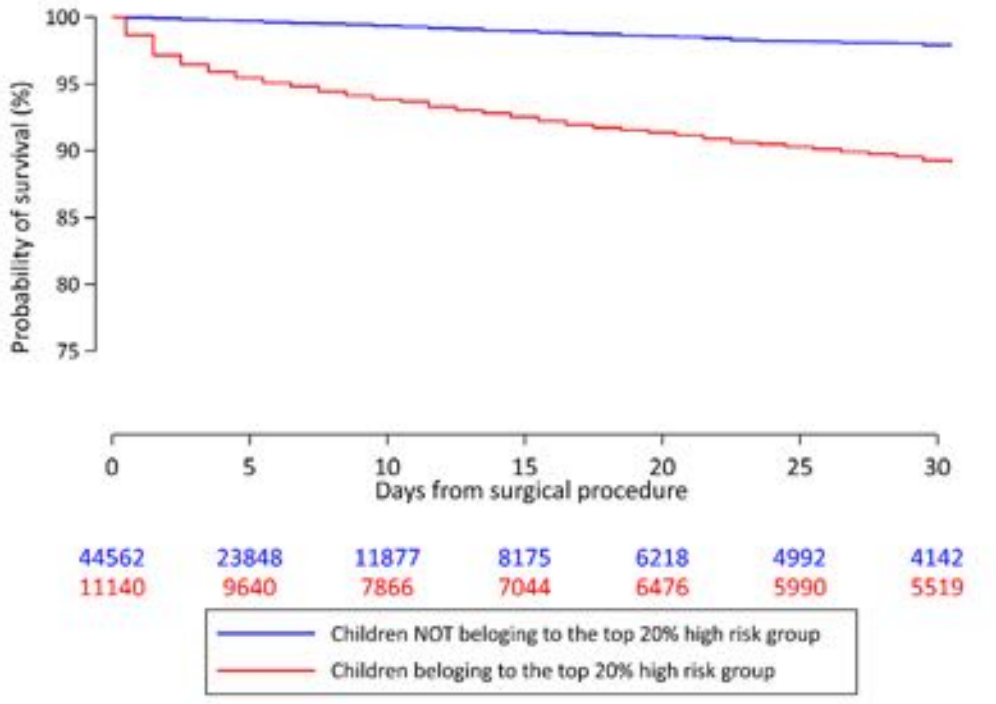

Fig. 2

PEDIATRIC ANESTHESIOLOGY 40

Economic Burden of the Racial Disparities in Pediatric Surgical Outcomes in the United States

Christian Mpody[1], Joseph D Tobias[1], Olubukola Nafiu[1]

[1]Nationwide Children's Hospital, Columbus, OH

INTRODUCTION: That African American (AA) children have poorer post-surgical outcomes compared to their White counterparts has been previously demonstrated. What is not known is if there are financial implications of these disparities, and what their impact is on our healthcare system. The objective of this study was to evaluate the economic burden of the racial disparities in pediatric surgical outcomes in the United States (U.S.).

METHODS: In this retrospective cohort study, we performed a ratio-of-cost-to-charges (RCC) based analysis of inpatient pediatric surgical care over a period of 12 years (2007-2019), across 49 U.S. tertiary hospitals participating in the Pediatric Health Information System. Costs were calculated from Consumer Price Index adjusted charges based on annual hospital specific RCCs. We estimated the cost ratios (CRs) and their 95% confidence intervals (CIs), comparing AA to White patients, using general estimating equations with log link and gamma distribution, while accounting for within-hospital clustering. We also estimated the costs attributable to the excess risk of resource utilization in AA children, relative to their White peers.

RESULTS: We identified 756,737 children who underwent inpatient surgery between 2007 and 2019, of whom 19.4% were AA and 80.6% were White. AA children were at higher risk of surgical complications (23.3% vs 19.6%, P<0.001) and ICU admissions (34.8% vs 32.9%, P<0.001). These differences resulted in a higher cost for the care of AA children, compared to their White peers ($10,849 higher geometric mean cost in AA; CR: 1.30; 95%CI: 1.28, 1.32, P-value <0.001). Surgical care on the respiratory system incurred the greatest difference in costs ($36,475 higher geometric mean cost in AA; CR: 1.69; 95%CI: 1.54, 1.86, P-value <0.001) – Table 1. Overall, other services (including operating room and anesthesia services) were the driver of costs (50 to 64% of cost, depending on race); followed by clinical services (10 to 15% of cost, depending on race) - Fig. 1. We estimated that the costs associated with the higher rates of ICU admission among AA children over the 12-year study period was about $561 million.

CONCLUSION: Racial disparities in pediatric surgical outcomes imposes serious financial burden on the healthcare system. Implementing effective interventions that improve the racial disparities in pediatric postoperative complications has the potential to reduce this massive economic burden.

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Procedural group	No. of children(%)	Cost, $ (geometric mean)		Cost difference, $	Cost Ratio (95% confidence interval)	*P*-value
		White	AA	AA vs White		
Overall	756,737(100)	90,626	101,475	10,849	1.30(1.28,1.32)	<0.001
Orthopedics	113,264(15)	67,765	68,621	856	1.03(1.01,1.05)	<0.001
Cardiovascular	75,853(10)	224,389	225,017	628	1.05(1.02,1.08)	<0.001
Neurology	87,537(12)	94,591	96,762	2,170	1.19(1.15,1.23)	<0.001
Neonatology	56,628(7)	579,577	685,936	106,359	1.24(1.20,1.27)	<0.001
Other surgical	228,759(30)	59,647	64,312	4,665	1.43(1.38,1.48)	<0.001
Digestive	139,152(18)	52,616	68,390	15,774	1.67(1.60,1.74)	<0.001
Respiratory	20,483(3)	101,089	137,563	36,475	1.69(1.54,1.86)	<0.001

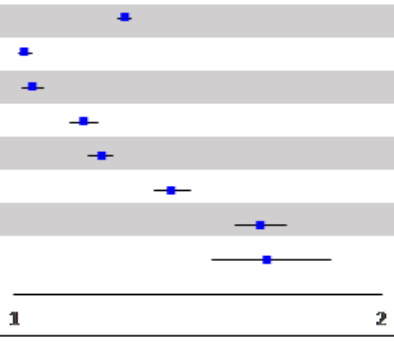

Figure 1. Comparison of RCC-based adjusted cost of pediatric surgical care between African American and White children, over the period of 12 years, across 49 US hospitals (Pediatric Health Information System 2007-2019).
Abbreviations: AA, African American, RCC: ratio-of-cost-to-charges.

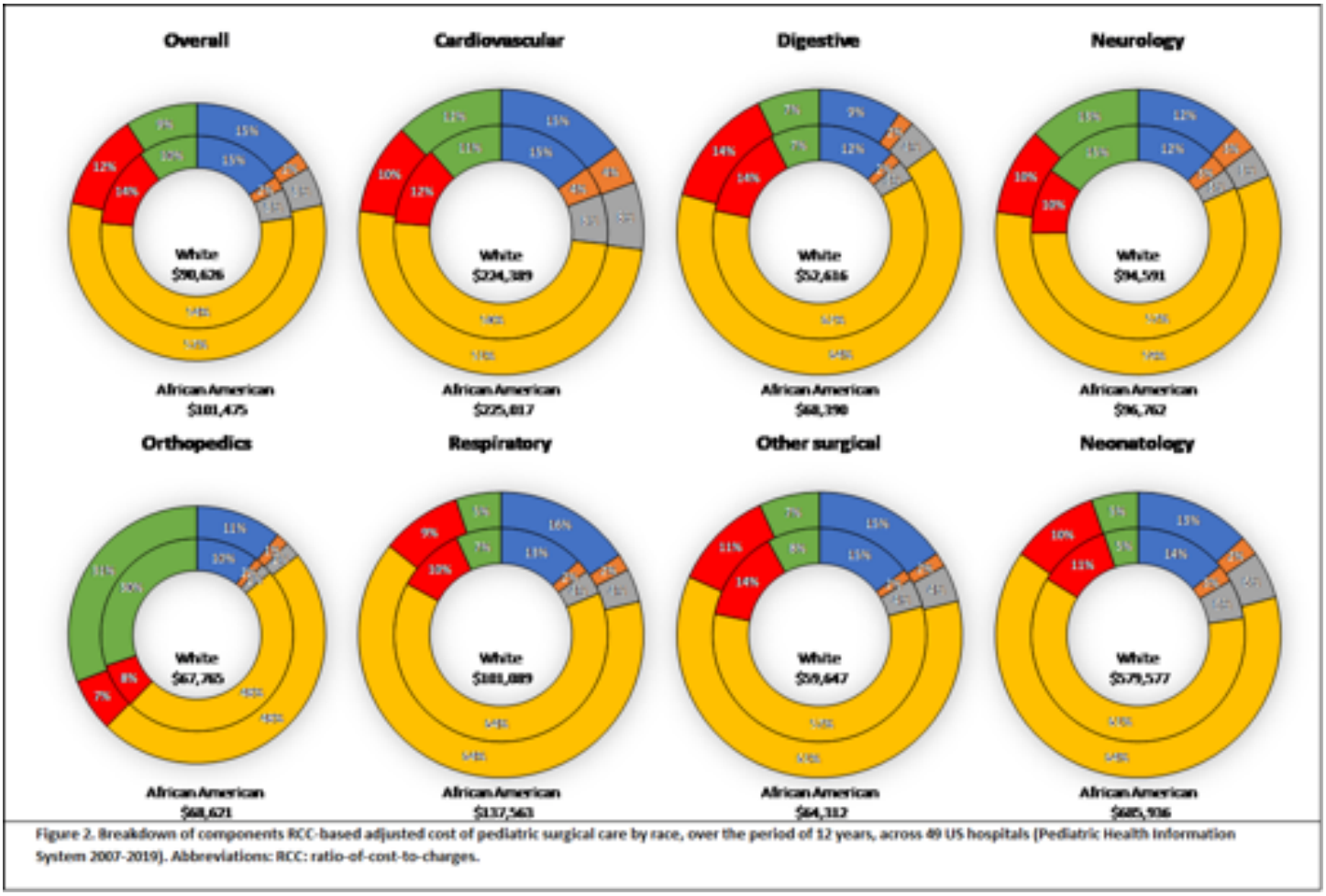

Figure 2. Breakdown of components RCC-based adjusted cost of pediatric surgical care by race, over the period of 12 years, across 49 US hospitals (Pediatric Health Information System 2007-2019). Abbreviations: RCC: ratio-of-cost-to-charges.

PEDIATRIC ANESTHESIOLOGY 41

Covid-19 Elective Surgery Restrictions and Social Distancing Coincided with a Significant Reduction in Laparoscopic Pyloromyotomy Procedures Performed at Our Institution

Sarah Hall[1], Audra Stacy[1]

[1]University of Kentucky, Lexington, KY

INTRODUCTION: Due to the rapid early spread of Covid-19, Kentucky hospitals and surgical centers followed the U.S. Surgeon General and Kentucky Governor's recommendations to stop performing elective surgical procedures on March 19, 2020. Phased reopening allowed some elective procedures to resume May 6, 2020, although statewide social distancing and safety measures remained in effect. Certain procedures considered non-elective that were allowed to proceed uninterrupted at our institution included pyloromyotomy for treatment of hypertrophic pyloric stenosis. Therefore, the number of infants presenting with and needing surgical treatment for hypertrophic pyloric stenosis would not be expected to change despite Covid-19 restrictions.

METHODS: A retrospective review of surgical billing codes was used to collect de-identified data on the number of laparoscopic and open pyloromyotomies performed at the University of Kentucky in the 6 months following March 19, 2020 compared to the preceding 12 months. A paired t-test was used to determine whether the number of pyloromyotomies performed each month was significantly different from the monthly average before March 19, 2020.

RESULTS: In the 12 months preceding the March 19, 2020 restriction on elective surgeries, our institution performed 46 laparoscopic pyloromyotomies (monthly average 3.83 ± 2.44). In the 6 months following March 19, 2020, our institution performed 10 laparoscopic pyloromyotomies (monthly average 1.67 ± 0.51). There was a statistically significant reduction in number of laparoscopic pyloromyotomies performed in the 6 months following March 19, 2020 compared to the 12 months prior ($P < 0.01$). No open pyloromyotomies were performed during the time frames reviewed.

DISCUSSION: This hypothesis-generating inquiry highlights a puzzling trend in a non-elective procedure that was performed significantly less often at our institution after the temporary interruption of elective surgical procedures and continuation of social distancing measures during the Covid-19 outbreak. Potential contributors to this observation include: 1. natural fluctuation in birth rates or disease incidence, however limited report of seasonal variation in pyloric stenosis previously showed higher incidence in summer months[1] 2. change in pediatric hospital referral patterns due to Covid-19 travel concerns 3. change in pre-hospital management of less severe cases of hypertrophic pyloric stenosis due to Covid-19 concerns 4. other unknown factors in disease progression and presentation of hypertrophic pyloric stenosis affected by social distancing or restrictions

CONCLUSION: Our institution performed significantly fewer operations for pyloric stenosis after introduction of Covid-19 restrictions, despite this being a non-elective procedure. A larger multi-center analysis is needed to explore this observation further.

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PEDIATRIC ANESTHESIOLOGY 42

An International Study of Isoelectric EEG Events in Infants During Surgery

Adam Richter[1], Camille van Hoorn[2], Ting Xu[3], ZhenZhen Gao[4], Mengmeng Ding[5], Abhusani Bhuju[6], Ian Yuan[7]

[1]University of Pennsylvania, Philadelphia, PA, [2]Erasmus MC Sophia Children's Hospital, Rotterdam, Netherlands, [3]Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, China, [4]Beijing Children's Hospital, Beijing, China, [5]Shengjing Hospital of China Medical University, Shenyang, China, [6]West China Hospital, Chengdu, China, [7]The Children's Hospital of Philadelphia, Philadelphia, PA

INTRODUCTION: Current anesthetic dosing is based on population pharmacokinetic models and hemodynamic monitoring, which does not reflect individual brain responses to anesthetics. Electroencephalography (EEG) provides a non-invasive method to assess depth of hypnosis, allowing the titration of anesthetic drugs to the individual patient. Isoelectric EEG, indicating an electrically inactive brain from excess anesthesia is common (52-63%) in infants undergoing routine surgery.[1,2] In adults, patients with isoelectric EEG were more likely to experience post-operative delirium.[3] In children, the outcome of isoelectric EEG is unclear but has been associated with younger age, higher American Society of Anesthesiologists (ASA) physical status, propofol bolus, endotracheal tube use, and lower arterial pressure during surgical phase.[1,2] Given the difference in anesthesia practice worldwide, a multicenter study was initiated by the BRain Anesthesia Infant Network (BRAIN), an international consortium of pediatric hospitals, to determine the incidence of isoelectric EEG and its associated perioperative factors.[4]

METHODS: This prospective observational study included 15 international pediatric hospitals. Inclusion criteria: ≤ 36mo, gestational age > 36weeks, maintenance with sevoflurane or propofol infusion (TIVA), airway management with a Laryngeal Mask Airway (LMA) or tracheal tube (ETT). Exclusion criteria: ASA> 3, severe neurological abnormality, cardiac, brain, or emergency surgery. Each of the 15 sites aimed to enroll 50 evaluable patients evenly divided into 10 subgroups in table 1 (5 patient per subgroup). Masimo Sedline was used for EEG recording that started with anesthesia induction and ended after extubation. Isoelectric EEG was defined as amplitude <±10uV for ≥ 2 secs simultaneously across all four channels. Visual analysis was done on 20% of patients and custom Matlab program processed all EEG files to calculate: isoelectric EEG occurrence(Y/N), total duration(sec), average duration for each occurrence(sec), and percent of time in isoelectric EEG. EEG with amplitude > 200uV were excluded as artifact. Demographic data was presented with descriptive statistics. Association of isoelectric EEG with categorical perioperative factors were tested using Chi-square test. Statistical significance was set at p 0.05.

RESULTS: 653 patients (out of 708) were included for final analysis (Table 1). The median age and interquartile range (IQR) was 340 [156-547] days. Isoelectric EEG occurred in 32% of patients (209/653) with a range of 9-78% (Table 2). In patients with isoelectric events, the median and IQR number of events was 16 [4-63] and percent of time in isoelectric EEG was 1.3 [0.3-5.2%] (Table 3). Occurrence of isoelectric EEG was associated with use of ETT (p 0.002) and muscle relaxant (p 0.046) (Table 4).

CONCLUSION: Compared to single center studies, this multicenter study showed a lower incidence of isoelectric EEG (32% vs 52-63%) in infants undergoing routine general anesthesia.[1,2] However, wide variations exist (9-78%) reflecting differences in anesthetic practice worldwide. The perioperative factors associated with occurrence of isoelectric EEG, likely reflected a deeper state of anesthesia required for ETT placement when muscle relaxant was not used. Future analyses will focus on association of isoelectric EEG with other perioperative factors (age, anesthetic dose, physiological signs, and temporal factors) and two outcome variables (emergence behavior and change in quality-of-life score after surgery).

BYLINE: Abstract submitted on behalf of the BRAIN collaborative investigators. Author affiliations based on institution listed in Table 2. 1-M Menezes, J Skowno; 2-L Slevin, BS von Ungern-Sternbert; 3-S Sheppard, AJ Davidson; 4-Z Gao, J Zhang; 5-D Lei, X Song; 6-J Zheng, M Zhang; 7-M Ding, P Zhao; 8-T Xu, P Chen; 9-A Bhuju, B Du, Y Zuo; 10-Y Jiang, H Liu, Q Lian; 11-C van Hoorn, JC De Graaff J; 12-L Vutskits; 13-A Richter, I Yuan, CD Kurth; 14-VA Olbrecht; 15-P Szmuk.

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Table 1

	N	Sevoflurane	Propofol TIVA	Male
All ages	653	359 (55%)	294 (45%)	500 (77%)
0-3 months	124	70	54	77
4-6 months	118	70	48	83
7-12 months	133	74	59	113
13-18 months	126	68	58	106
19-36 months	152	77	75	121

Table 2

	N	Yes Isoelectric	% Isoelectric
All Sites	652	209	32.1
AUSTRALIA			
Children's Hospital at Westmead-Sydney[1]	57	22	38.6
Perth Children's Hospital[2]	38	10	26.3
Royal Children's Hospital-Melbourne[3]	9	7	77.8
CHINA			
Beijing Children's Hospital[4]	55	13	23.6
Guangzhou Women and Children's Medical Center[5]	54	25	46.3
Shanghai Children's Medical Center[6]	46	11	23.9
Shengjing Hospital of China Medical University[7]	53	6	11.3
Sichuan Provincial People's Hospital[8]	54	17	31.5
West China Hospital-Sichuan[9]	52	13	25.0
Yuying Children's Hospital of Wenzhou Medical University[10]	51	22	43.1
EUROPE			
Erasmus MC Sophia Children's Hospital[11]	23	2	8.7
University Hospitals of Geneva[12]	38	14	36.8
USA			
Children's Hospital of Philadelphia[13]	51	22	43.1
Cincinnati Children's Medical Center[14]	22	8	36.4
UTSW-Children's Medical Center Dallas[15]	49	17	34.7

Table 3

All Sites	Median (50%)	Q1 (25%)	Q3 (75%)
Number of Iso Events	16.0	4.0	63.0
Total Iso Duration (s)	84.0	14.8	312.7
Avg Iso Duration Per Event (s)	3.6	2.8	5.5
Percent Time Iso Over Total Time (%)	1.3	0.3	5.2

Table 4

	All Patients	Yes Iso	No Iso	p value
ASA I & II	601	195 (32%)	406 (68%)	0.58
ASA III	39	11 (28%)	28 (72%)	
Yes Propofol Bolus	296	87 (29%)	209 (71%)	0.19
No Propofol Bolus	357	122 (34%)	235 (66%)	
Yes Relaxant	429	126 (29%)	303 (71%)	0.046*
No Relaxant	224	83 (37%)	141 (63%)	
ETT	457	162 (35%)	295 (65%)	0.002*
LMA	193	45 (23%)	148 (77%)	
Sevoflurane	567	123 (22%)	444 (78%)	0.17
Propofol TIVA	294	86 (29%)	208 (71%)	

PEDIATRIC ANESTHESIOLOGY 43

Risk Factors Associated with Hospitalization in Pediatric Patients with COVID-19 Infection

Jerry Y Chao[1], Ariel Sugarman[2], Atsumi Kimura[3], Steven Flamer[3], Tina Jing[3], Danielle Fernandes[4], Michael Cabana[4]

[1]Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, [2]Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, United States of America, [3]Albert Einstein College of Medicine, Bronx, NY, [4]Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, NY

INTRODUCTION: Research to date has described clinical characteristics of patients with COVID-19 with fewer studies of pediatric patients[1]. In this study, we asked the focused clinical question 'Among pediatric patients with SARS-CoV-2 RT-PCR-confirmed infection, who requires hospitalization and what are the associated risk factors?' We hypothesized that asthma, obesity, diabetes, and lower socioeconomic status (SES) are associated with increased risk of hospitalization.

METHODS: Patients less than 23 years of age with PCR-confirmed SARS-CoV-2 were identified from March to October 2020. We performed double chart-extraction using a custom-designed REDCap instrument (Nashville, TN) for: (1) index positive test, (2) demographic data, (3) obesity (BMI greater than the 95th percentile)[2], (4) SES z-score3, (5) temporally associated Emergency Department (ED) visit(s) or admission(s), (6) past medical history, (7) clinical symptomatology, (8) ED vitals, and (9) supplemental oxygen and/or modality. Two pediatricians independently assessed the association of each patient's hospital admission with index positive test. Agreement was measured by a Kappa score. Discordant assessments were adjudicated by a third clinician until consensus. Admissions were categorized as 'definitely not related' when there was a defined, independent clinical cause. Admissions were categorized as 'probably related' in cases of an underlying condition with acute exacerbation that could have plausibly been triggered by SARS-CoV-2 based on existing evidence. Admissions were categorized as 'definitely related' if there was a known pathophysiologic link to COVID-19 infection. Statistical Analyses: After assessing underlying assumptions, we used the 2-sample student t-test or Wilcoxon rank-sum test vs. Pearson Chi-square or Fisher's Exact test using Stata 13.1 (StataCorp, College Station, TX). Power analysis: Assuming a sample size of n=375, 150 admissions:225 non-admissions, and a 20% prevalence of pediatric asthma and obesity, our sample would have 0.89 power, with 0.05 alpha to detect a difference of 15% in the prevalence of asthma and obesity. With a 2% prevalence of pediatric diabetes (type 1 and 2), we would have a 0.89 power, with 0.05 alpha to detect a difference of 8% in the prevalence of diabetes.

RESULTS: We compared hospitalizations definitely or probably related to COVID-19 infection (Kappa=0.69) to non-hospitalizations (Table 1). Admitted children tended to be younger and non-admitted children older, p <0.001. There were no differences in sex, race/ethnicity, or SES z-score. There was a greater proportion of obese (27, 40.30% vs. 25, 14.71%, p <0.001) and diabetic (5, 5.21% vs. 0, 0%, p =0.003) children. There was no difference in pregnancy or asthma. Fever, fussiness, a history of fatigue or decreased energy level were significantly more prevalent, as well as shortness of breath and multiple gastrointestinal symptoms: abdominal pain, nausea and vomiting, and diarrhea. Decreased urination, conjunctivitis, and rash were also more prevalent. Unrelated admission (Supplemental Table 1) test results returned 2.72 SD (8.21) days after the admission compared to -013 SD [1.99] days for related admissions. The most common admitting unrelated diagnoses were obstetric, psychiatric, gastrointestinal, and preoperative testing (Figure 1). We describe narratively 12 patients in whom there was an ED visit within 14 days prior to index positive test (Figure 2).

CONCLUSION: Our rate of hospitalization (25.9%) is in line with previous studies (6.7-62.7%)[4-6]. More hospitalized children were obese and diabetic, consistent with the plausible pathophysiologic mechanism of SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2) receptors expressed in key metabolic organs and tissues including pancreatic beta cells, adipose tissue, small intestine, and kidneys[7]. Decreased expression of ACE2 receptors that may occur in the lungs of atopic children could explain the lack of association with asthma[8]. Gastrointestinal involvement sometimes manifested as surgical emergencies and may be related to altered patient behaviors during the pandemic leading to delayed presentation[9]. Inclusion of unrelated cases could have introduced error, but may have more pragmatically reflected clinical decision-making before the complete breadth of COVID-19 pathophysiology was yet known. Targeting children with obesity and diabetes with telehealth initiatives, masking, and prioritization of vaccination may reduce morbidity.

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Table 1. Demographics and clinical characteristics of patients who tested positive on SARS-CoV-2 RT-PCR from 3/14/20 to 10/2/20 and their hospitalization status (admission "definitely" or "possibly" related to COVID-19 infection) (n=324)

	Overall (n=324)	Hospitalized (n=97)	Not hospitalized (n=227)	p value*
Overall age (years)	17.97 (9.78, 21.20)	15.01 (3.50, 20.26)	18.89 (11.49, 21.43)	0.0005
Age categories				
Age <1	28 (8.64)	19 (19.59)	9 (3.95)	<0.001
Age <2	38 (11.73)	23 (23.7)	15 (6.61)	<0.001
2 < Age < 11				<0.001
<2	38 (11.73)	23 (23.71)	15 (6.61)	
2 – 11	55 (16.98)	14 (14.43)	41 (18.06)	
>11	231 (71.30)	60 (61.86)	171 (75.33)	
Age >11	231 (71.30)	60 (61.86)	171 (75.33)	0.01
Sex				0.13
Female	161 (49.69)	42 (43.30)	119 (52.42)	
Ethnicity				0.72
Hispanic	176 (54.32)	56 (57.73)	120 (52.86)	
Non-Hispanic	94 (29.01)	26 (26.80)	68 (29.96)	
Unknown	54 (16.67)	15 (15.46)	39 (17.18)	
Race				0.83
White	13 (4.01)	3 (3.09)	10 (4.41)	
Black or AA	59 (18.21)	17 (17.53)	42 (18.50)	
Asian	8 (2.47)	2 (2.06)	6 (2.64)	
American Indian	1 (0.31)	0 (0)	1 (0.44)	
Multiple/other	168 (51.85)	56 (57.73)	112 (49.34)	
Unknown	75 (23.15)	19 (19.59)	56 (24.67)	
SES z-score	-4.23 (2.75)	-4.06 (2.64)	-4.28 (2.80)	0.62
BMI	23.20 (19.06, 30.45)	22.59 (17.36, 32.30)	23.5 (20.15, 29.87)	0.81
BMI over 95%-tile for age				<0.001
No	125 (52.74)	38 (56.72)	87 (51.18)	
Yes	52 (21.94)	27 (40.30)	25 (14.71)	
Unknown	60 (25.32)	2 (2.99)	58 (34.12)	
Pregnant	12 (8.76)	3 (8.11)	9 (9.00)	<0.99
Asthma	68 (20.99)	19 (19.59)	49 (21.59)	0.46
Exacerb. (<1 yr)	8 (11.76)	2 (10.52)	6 (12.24)	<0.99
Exacerb. ever	14 (20.59)	5 (26.32)	9 (18.37)	<0.99

*Comparison of hospitalized vs. non-hospitalized patients
Two sample student's t-test for comparison of means
Wilcoxon Rank-Sum Test for comparison of medians
Pearson Chi-Square for comparison of proportions
Fisher's Exact Test for comparison of proportions if any cell <5

Table 1. Continued

	Overall (n=324)	Hospitalized (n=97)	Not hospitalized (n=227)	p value*
Diabetes	5 (1.63)	5 (5.21)	0 (0)	0.003
Diagnosis				-
T2 w/o comps	1 (20.00)	1 (20.00)	-	
T2 w/ hypergly	4 (80.00)	4 (80.00)	-	
Known COVID sick contacts				<0.001
No	134 (42.95)	60 (62.50)	74 (32.60)	
Yes	65 (20.83)	18 (18.75)	47 (20.70)	
Unknown	113 (36.22)	18 (18.75)	95 (41.85)	
Symptoms				
Asymptomatic	31 (9.57)	1 (1.03)	30 (13.22)	<0.001
Fever	148 (45.68)	69 (71.13)	79 (34.80)	<0.001
Chills	36 (11.11)	9 (9.28)	27 (11.89)	0.49
Short of breath	60 (18.52)	32 (32.99)	28 (12.33)	<0.001
Chest tightness	12 (3.70)	5 (5.15)	7 (3.08)	0.35
Chest pain	26 (8.02)	10 (10.31)	16 (7.05)	0.32
Rhinorrhea	36 (11.11)	14 (14.43)	22 (9.69)	0.21
Congestion	45 (13.89)	17 (17.53)	28 (12.33)	0.22
Sore throat/pain	25 (7.72)	3 (1.10)	22 (9.69)	0.04
Fussiness	9 (2.78)	6 (6.19)	3 (1.32)	0.02
Fatigue	48 (13.37)	30 (30.93)	18 (7.93)	<0.001
Taste decr	13 (4.01)	5 (5.15)	8 (3.52)	0.54
Smell decr	13 (4.01)	4 (4.12)	9 (3.97)	<0.99
Headache	41 (12.65)	13 (13.40)	28 (12.33)	0.79
Abdominal pain	38 (11.73)	20 (20.62)	18 (7.93)	0.001
Nausea/vomiting	73 (22.53)	41 (42.27)	32 (14.10)	<0.001
Diarrhea	30 (9.26)	18 (18.56)	12 (5.29)	<0.001
Constipation	4 (1.23)	1 (1.03)	3 (1.32)	<0.99
Dysuria/pain	2 (0.62)	2 (2.06)	0 (0)	0.09
Urination decr	6 (1.85)	5 (5.15)	1 (0.44)	0.01
Eye conjunct.	9 (2.78)	6 (6.19)	3 (1.32)	0.02
Rash	16 (4.94)	10 (10.31)	6 (2.64)	0.004
Hand desquam	2 (0.62)	0 (0)	2 (0.88)	<0.99
Oral ulcers/sore	3 (0.93)	2 (2.06)	1 (0.44)	0.21
Lip erythema	1 (0.31)	0 (0)	1 (0.44)	<0.99
Lymphaden.	1 (0.31)	0 (0)	1 (0.44)	<0.99
Joint pain	4 (1.23)	1 (1.03)	3 (1.32)	<0.99
Joint swelling	0 (0)	0 (0)	0 (0)	-
Other	118 (34.22)	31 (31.96)	87 (38.33)	0.28

*Comparison of hospitalized vs. non-hospitalized patients
Two sample student's t-test for comparison of means
Wilcoxon Rank-Sum Test for comparison of medians
Pearson Chi-Square for comparison of proportions
Fisher's Exact Test for comparison of proportions if any cell <5

Table 1. Continued

	Overall (n=324)	Hospitalized (n=97)	Not hospitalized (n=227)	p value*
Fever (days)	2 (1, 4)	3 (1, 5)	2 (1, 3)	0.48
Tmax (F)	101.5 (100.6, 102.8)	101.8 (100.6, 103)	101.3 (100.4, 102)	0.30
Antipyretic use	79 (36.92)	30 (40.54)	49 (35.00)	0.42
Vital signs in ED				
Temp (F)	99.62 (1.78)	100.16 (2.11)	99.27 (1.43)	<0.001
SpO2 (%)	99 (97, 100)	98 (96, 100)	99 (98, 100)	0.002
SpO2 worst (%)	98 (97, 99)	97 (94, 98)	99 (97, 99.5)	<0.001
Oxygen suppl in ED				
Yes	34 (10.90)	32 (33.68)	2 (0.92)	<0.001
FiO2 (%) in ED	60 (40, 100)	60 (40, 100)	-	-
Suppl. O2 modality in ED				
Nasal cannula	23 (7.10)	21 (21.65)	2 (0.88)	<0.001
Facemask	7 (2.16)	7 (7.22)	0 (0)	<0.001
HFNC	9 (2.78)	9 (9.28)	0 (0)	<0.001
Endotracheal Intubation	9 (2.78)	9 (9.28)	0 (0)	<0.001
Other**	1 (0.31)	1 (1.03)	0 (0)	0.30
Proning in ED	12 (3.88)	12 (13.04)	0 (0)	<0.001

*Comparison of hospitalized vs. non-hospitalized patients
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**one patient on BiPAP

Figure 1. Diagnoses of children with positive SARS-CoV-2 RT-PCR admission for reasons unrelated to COVID-19 infection (n=50)

Diagnosis	Number
Obstetric/pregnancy	18 (36%)
Psychiatric admission	9 (18%)
Bacterial infections	9 (18%)
Abscess	3 (6%)
Cellulitis	1 (2%)
Pelvic pain/PID	1 (2%)
UTI, dehydration	1 (2%)
Nephrolithiasis/urosepsis	1 (2%)
Osteomyelitis (Sickle Cell)	1 (2%)
VP shunt infection (bacterial)	1 (2%)
Gastrointestinal	4 (8%)
Emesis (pyloric stenosis)	1 (2%)
Foreign body ingestion	1 (2%)
Gastroparesis (chronic)	1 (2%)
Crohn's Disease for initiation of IV treatment	1 (2%)
Preoperative testing	3 (6%)
Well baby with SARS-CoV-2 Positive mother	2 (4%)
Neurologic	4 (8%)
Headache	1 (2%)
Seizures	1 (2%)
Spasticity, worsening (in-situ baclofen pump)	1 (2%)
Leg pain (chronic known Neuropathy history)	1 (2%)
Opthalmologic (new onset esotropia)	1 (2%)

Table 1. Demographics and clinical characteristics of patients who tested positive on SARS-CoV-2 RT-PCR from 3/14/20 to 10/2/20 and their hospitalization status (admission "definitely" or "possibly" related to COVID-19 infection) (n=324)

	Overall (n=324)	Hospitalized (n=97)	Not hospitalized (n=227)	p value*
Overall age (years)	17.97 (9.78, 21.20)	15.01 (3.50, 20.26)	18.89 (11.49, 21.43)	0.0005
Age categories				
Age <1	28 (8.64)	19 (19.59)	9 (3.95)	<0.001
Age <2	38 (11.73)	23 (23.7)	15 (6.61)	<0.001
2 < Age < 11				<0.001
<2	38 (11.73)	23 (23.71)	15 (6.61)	
2 – 11	55 (16.98)	14 (14.43)	41 (18.06)	
>11	231 (71.30)	60 (61.86)	171 (75.33)	
Age >11	231 (71.30)	60 (61.86)	171 (75.33)	0.01
Sex				0.13
Female	161 (49.69)	42 (43.30)	119 (52.42)	
Ethnicity				0.72
Hispanic	176 (54.32)	56 (57.73)	120 (52.86)	
Non-Hispanic	94 (29.01)	26 (26.80)	68 (29.96)	
Unknown	54 (16.67)	15 (15.46)	39 (17.18)	
Race				0.83
White	13 (4.01)	3 (3.09)	10 (4.41)	
Black or AA	59 (18.21)	17 (17.53)	42 (18.50)	
Asian	8 (2.47)	2 (2.06)	6 (2.64)	
American Indian	1 (0.31)	0 (0)	1 (0.44)	
Multiple/other	168 (51.85)	56 (57.73)	112 (49.34)	
Unknown	75 (23.15)	19 (19.59)	56 (24.67)	
SES z-score	-4.23 (2.75)	-4.06 (2.64)	-4.28 (2.80)	0.62
BMI	23.20 (19.06, 30.45)	22.59 (17.36, 32.30)	23.5 (20.15, 29.87)	0.81
BMI over 95%-tile for age				<0.001
No	125 (52.74)	38 (56.72)	87 (51.18)	
Yes	52 (21.94)	27 (40.30)	25 (14.71)	
Unknown	60 (25.32)	2 (2.99)	58 (34.12)	
Pregnant	12 (8.76)	3 (8.11)	9 (9.00)	<0.99
Asthma	68 (20.99)	19 (19.59)	49 (21.59)	0.46
Exacerb. (<1 yr)	8 (11.76)	2 (10.52)	6 (12.24)	<0.99
Exacerb. ever	14 (20.59)	5 (26.32)	9 (18.37)	<0.99

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Table 1. Continued

	Overall (n=324)	Hospitalized (n=97)	Not hospitalized (n=227)	p value*
Diabetes	5 (1.63)	5 (5.21)	0 (0)	0.003
Diagnosis				-
T2 w/o comps	1 (20.00)	1 (20.00)	-	
T2 w/ hypergly	4 (80.00)	4 (80.00)	-	
Known COVID sick contacts				<0.001
No	134 (42.95)	60 (62.50)	74 (32.60)	
Yes	65 (20.83)	18 (18.75)	47 (20.70)	
Unknown	113 (36.22)	18 (18.75)	95 (41.85)	
Symptoms				
Asymptomatic	31 (9.57)	1 (1.03)	30 (13.22)	<0.001
Fever	148 (45.68)	69 (71.13)	79 (34.80)	<0.001
Chills	36 (11.11)	9 (9.28)	27 (11.89)	0.49
Short of breath	60 (18.52)	32 (32.99)	28 (12.33)	<0.001
Chest tightness	12 (3.70)	5 (5.15)	7 (3.08)	0.35
Chest pain	26 (8.02)	10 (10.31)	16 (7.05)	0.32
Rhinorrhea	36 (11.11)	14 (14.43)	22 (9.69)	0.21
Congestion	45 (13.89)	17 (17.53)	28 (12.33)	0.22
Sore throat/pain	25 (7.72)	3 (1.10)	22 (9.69)	0.04
Fussiness	9 (2.78)	6 (6.19)	3 (1.32)	0.02
Fatigue	48 (13.37)	30 (30.93)	18 (7.93)	<0.001
Taste decr	13 (4.01)	5 (5.15)	8 (3.52)	0.54
Smell decr	13 (4.01)	4 (4.12)	9 (3.97)	<0.99
Headache	41 (12.65)	13 (13.40)	28 (12.33)	0.79
Abdominal pain	38 (11.73)	20 (20.62)	18 (7.93)	0.001
Nausea/vomiting	73 (22.53)	41 (42.27)	32 (14.10)	<0.001
Diarrhea	30 (9.26)	18 (18.56)	12 (5.29)	<0.001
Constipation	4 (1.23)	1 (1.03)	3 (1.32)	<0.99
Dysuria/pain	2 (0.62)	2 (2.06)	0 (0)	0.09
Urination decr	6 (1.85)	5 (5.15)	1 (0.44)	0.01
Eye conjunct.	9 (2.78)	6 (6.19)	3 (1.32)	0.02
Rash	16 (4.94)	10 (10.31)	6 (2.64)	0.004
Hand desquam	2 (0.62)	0 (0)	2 (0.88)	<0.99
Oral ulcers/sore	3 (0.93)	2 (2.06)	1 (0.44)	0.21
Lip erythema	1 (0.31)	0 (0)	1 (0.44)	<0.99
Lymphaden.	1 (0.31)	0 (0)	1 (0.44)	<0.99
Joint pain	4 (1.23)	1 (1.03)	3 (1.32)	<0.99
Joint swelling	0 (0)	0 (0)	0 (0)	-
Other	118 (34.22)	31 (31.96)	87 (38.33)	0.28

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Fisher's Exact Test for comparison of proportions if any cell <5

Table 1. Continued

	Overall (n=324)	Hospitalized (n=97)	Not hospitalized (n=227)	p value*
Fever (days)	2 (1, 4)	3 (1, 5)	2 (1, 3)	0.48
Tmax (F)	101.5 (100.6, 102.8)	101.8 (100.6, 103)	101.3 (100.4, 102)	0.30
Antipyretic use	79 (36.92)	30 (40.54)	49 (35.00)	0.42
Vital signs in ED				
Temp (F)	99.62 (1.78)	100.16 (2.11)	99.27 (1.43)	<0.001
SpO2 (%)	99 (97, 100)	98 (96, 100)	99 (98, 100)	0.002
SpO2 worst (%)	98 (97, 99)	97 (94, 98)	99 (97, 99.5)	<0.001
Oxygen suppl in ED				
Yes	34 (10.90)	32 (33.68)	2 (0.92)	<0.001
FiO2 (%) in ED	60 (40, 100)	60 (40, 100)	-	-
Suppl. O2 modality in ED				
Nasal cannula	23 (7.10)	21 (21.65)	2 (0.88)	<0.001
Facemask	7 (2.16)	7 (7.22)	0 (0)	<0.001
HFNC	9 (2.78)	9 (9.28)	0 (0)	<0.001
Endotracheal Intubation	9 (2.78)	9 (9.28)	0 (0)	<0.001
Other**	1 (0.31)	1 (1.03)	0 (0)	0.30
Proning in ED	12 (3.88)	12 (13.04)	0 (0)	<0.001

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**one patient on BiPAP

Supplemental Figure 1. Narrative description of patients with a prior Emergency Department visit who later re-presented, tested positive for SARS-CoV-2, and were admitted for COVID-19 infection (n=12)

1) 20 year old obese female with a past medical history of asthma with 9 day history of fevers, cough, shortness of breath, visited the Emergency Department 3 days prior to index positive SARS-CoV-2 test, diagnosed with bacterial infection and prescribed azithromycin and discharged, returned again with worsening shortness of breath, pneumonia found on chest radiograph and admitted for COVID-19 infection.
2) 21 year old male with a complicated past medical history of Dandy Walker Syndrome, autism, speech delay, seizure disorder, and recurrent UTIs presented 8 days prior to index positive SARS-CoV-2 test, diagnosed with altered mental statusi and UTI, returned to ED with seizures, admitted for COVID-19 encephalitis.
3) 20 month old male seen 2 days prior to index positive SARS-CoV-2 test presenting with periorbital edema and facial edema, was otherwise well appearing the ED, mother with a history of COVID positivity 3 months ago. The patient re-presented with continued fever, increased fussiness, poor feeding, nausea, vomiting, diarrhea, decreased urination, rash admitted for dehydration.
4) 21 year old male presenting to outside ED 8 days prior to index positive SARS-CoV-2 result with fever, shortness of breath, and cough and was discharged home at that time, returned to same outside ED in respiratory distress, intubated, and transferred to tertiatry care hospital; died within 24 hours after admission.
5) 19 year old male with past medical history of asthma seen in ED 2 days prior to index positive SARS-CoV-2 result for cough and pneumonia on chest radiograph, was not in respiratory distress and otherwise reassuring exam, diagnosed with bacterial pneumonia and discharged home with antibiotics and steroids, re-presented with fever, worsening cough, chest tightness, and required HFNC, later intubated.
6) 13 year old female seen in ED 2 days prior to index positive SARS-CoV-2 result for fever, diagnosed with UTI and discharged with prescription for antibiotics, returned with worsening symptoms.
7) 5 year old male seen in ED 3 days prior to index positive SARS-CoV-2 result for 4-5 day history of fever, generalized abdominal pain, headache, urinalysis and urine culture sent which were negative, discharged with diagnosis of viral illness, returned with worsening symptoms and admitted, diagnosed with atypical Kawasaki vs. MIS-C.
8) 21 year old male presented to ED 9 days prior to index SARS-CoV-2 result for unresolving chest pain in the past couple of weeks, recent shortness of breath, facial flushing, afebrile, negative workup for PE, elevated hemoglobin, diagnosed with polycythemia vera, re-presented with worsening chest pain shortness of breath, cough, and subjective fever.
9) 8 year old male seen in ED 3 days prior to index positive SARS-CoV-2 result with 3 day history of fever and abdominal pain, no sick contacts, ruled out for appendicitis, SARS-CoV-2 test negative at that time, diagnosed with viral gastroenteritis vs. UTI and discharged home, returned to ED with worsening symptoms, required HFNC, eventually intubated, on pressors, diagnosed with atypical KD, improved after IVIG and steroids.
10) 21 year old male with a past medical history of Sickle Cell Disease, acute chest syndrome, and avascular necrosis seen in ED 10 days prior to index positive SARS-CoV-2 result with pain crisis but without fever, URI symptoms, chest pain, or abdominal pain without sick contacts, stable to be discharged from ED after pain control, returned admitted for sickly cell crisis, no significant pulmonary symptoms.
11) 10 year old female seen in ED 3 days prior to index positive SARS-CoV-2 result with 4 day history of fever, headache, 3 day history of non-bloody non-bilious vomiting, and one day on non-bloody diarrhea, with 1 day history of rash on arms, trunks, and legs, patient was stable and discharged with diagnosis of viral syndrome, SaRS-CoV-2 swab was done at urgent care and not reswabbed in ED, returned, and admitted.
12) 16 year old male presented with lower abdominal pain, nausea, and diarrhea 2 days prior to index positive SARS-CoV-2 result without fever or URI symptoms, no sick contacts, CT scan results positive for early appendicitis, patient otherwise well and discharged home after surgical consult with diagnosis of early appendicitis, returned with continued emesis and abdominal pain and admitted, underwent laparoscopic appendectomy.

PEDIATRIC ANESTHESIOLOGY 44

Perioperative Management of Pediatric Patients on the Ketogenic Diet for Drug Resistant Epilepsy

Jue T Wang[1], Scellig Stone[1], Steven Staffa[2], Ann M Bergin[1], sulpicio T Soriano[1], Craig T McClain[1]

[1]Boston Children's Hospital, Boston, MA, [2]Children's Hospital Boston, Boston , MA

INTRODUCTION: Ketogenic diets are an increasingly popular treatment for pediatric patients with refractory epilepsy. Patients who are on ketogenic diets frequently require general anesthesia (GA) for minor procedures and major surgery. Preparation for anesthesia, including prolonged NPO time, conflict with ketogenic diet requirements; which could cause significant complications in the perioperative period[1]. Due to the relative rarity of the treatment, management of patients on ketogenic diet undergoing GA is well not described in the literature[2,3]. We're conducting this study to assess for risk factor and outcomes in this patient population to improve perioperative management.

METHODS: This is a retrospective study of pediatric patients with intractable epilepsy on ketogenic diet treatment (n=46) that received Institutional Ethical approval (IRB-P00035169). Over 13 years, patients in our cohort received 127 general anesthetics. Information was gathered from the electronic medical record (Powerchart, Metavision AIMS). Key outcome measures include: time of surgery, rate of hypoglycemia (blood glucose <40mg/dL), change in seizure patterns, use of lactate and glucose containing intravenous fluids, use of intravenous Acetaminophen, and incidence of unplanned hospital or ICU stay.

RESULTS: A total of 46 patients with a median age of 8 years (IQR 5-15 yrs.) and median weight of 27.2kg (IQR 18.1-38.7kg) were included in the study. Gender was evenly distributed with 63 female and 64 male encounters. There was a variety of ASA status classifications with 1 ASA I, 26 ASA II, 91 ASA III, and 9 ASA IV patients with only 3 emergency cases. The median length of the anesthetic cases was 86 minutes (IQR 44-139 min). Out of 126 cases 67 (52.3%) were first start cases while 24/59 (40.7%) non-first start cases started after 12:00PM. There were 103/127 cases with documented NPO time for solids with a median time of 11 hours (IQR 8.5-12.7hrs). A total of 107/127 patients had documented NPO time for liquids with a median time of 4.5 hours (IQR 3/1-9.5hrs). Patient on a ketogenic diet need to avoid glucose and lactate in meds and IV fluids. In our cohort 58/127 (45.7%) of patients received LR while 56/127 (44.1%) received NS. Another 5/127 (4.7%) received both NS and LR, 6/127 (4.7%) of patient received no fluids, 1/127 (0.8%) received dextrose, and 1/127 (0.8%) pt. received a special ICU fluid. IV Acetaminophen contains mannitol which interfere with glucose monitoring and is contra-indicated in patients on ketogenic diets, but 10/127 (7.9%) of patients received IV Acetaminophen. Out of the 127 pts none had changes from baseline seizure activity after GA. Despite the complexity of these patients 65/127 (51.2%) were discharged home (DSU) post-op, 12/127 (9.5%) were planned overnight admits, 47/127 (37.8%) were inpatients, and 1/127 (0.8%) was planned for ICU admit post-op but was discharged home. There were no unplanned hospital or ICU admits, and 2/127 (1.6%) patients were downgraded from admit to DSU.

CONCLUSION: Our study represents the largest cohort of pediatric patients with intractable epilepsy on ketogenic diet with respect to (1) perioperative management and (2) outcomes. Our retrospective analyses show that patients on the ketogenic diet can tolerate standard NPO times with little risk of hypoglycemia. There were no changes in the baseline seizure patterns and patients can be successfully discharged home after general anesthesia. Based on our data we created a novel triage flow diagram for the perioperative management of patients on the ketogenic diet (Figure 1). Areas of improvement include reducing the use of (1) Lactate containing IV fluids and (2) IV Acetaminophen, both of which are contra-indicated but were used frequently. Future goals should be directed towards development of clear perioperative practice guidelines to standardize anesthesia care of pediatric patients with intractable epilepsy on the ketogenic diet.

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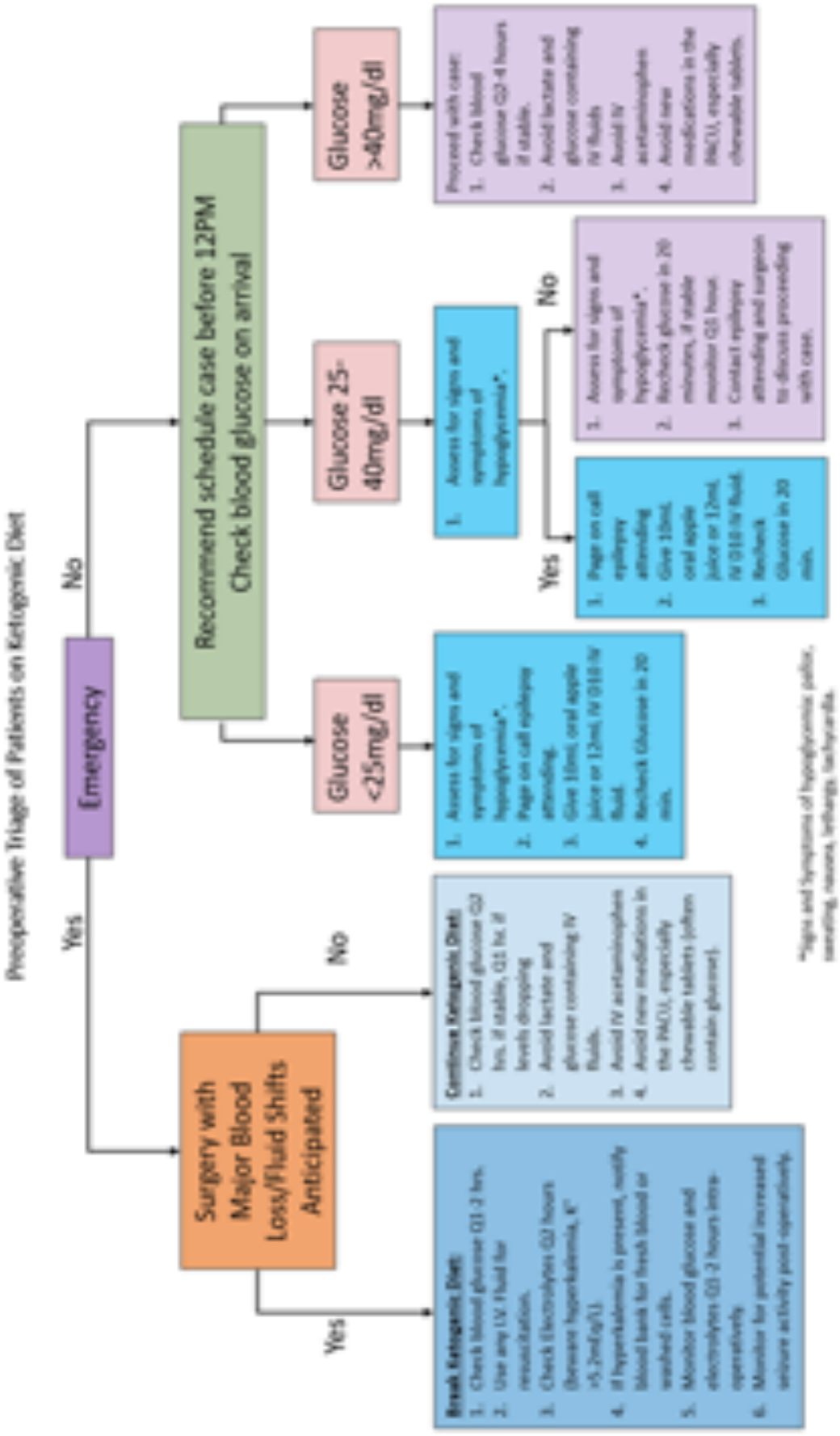

Figure 1. Novel Flow Diagram for Preoperative Triage of Patients on the Ketogenic Diet.

PEDIATRIC ANESTHESIOLOGY 45

Monitoring Depth of Anesthesia in Pediatrics Using the qCON and qNOX Indices

Joana Cañellas[1], Umberto Melia[2], Carmen González[2], Erik W Jensen[2]

[1]Universitat Politècnica de Catalunya (UPC), Barcelona, Spain, [2]Quantium Medical, Barcelona, Spain

INTRODUCTION: Maintaining an adequate level of general anesthesia during surgical interventions has been proved to be of great importance. Insufficient anesthesia can lead to awareness with recall during the surgeries and anesthetic overdose may be translated into longer recoveries and adverse events[1]. The increasing concern about controlling anesthetic dosages has led to the development of devices able to monitor the clinical state of the patients in real time by capturing and processing the electroencephalogram (EEG) signal to obtain an indicator of the patient's level of consciousness. Even though these devices have already proven to be affective with adult subjects, there is less information available about their use in pediatric patients. The pediatric EEG is known to have different characteristics than the adult one, hence it is important to study if these characteristics affect the normal functioning of these devices. In this study, it is evaluated the performance of a depth of anesthesia monitor, Conox, in surgeries with pediatric patients.

METHODS: After approval from the Ethical Committee of Hospital Universitario La Paz de Madrid with protocol number HULP: PI-3871 and written informed consent, data was recorded from 17 patients between 3 and 17 years of age scheduled for general anesthesia with a combination of propofol, sevoflurane and fentanyl. The patient demographics are summarized in Table 1. The EEG signals, qCON and qNOX (Conox, Fresenius Kabi, Bad Homburg, Germany) and the BIS (Medtronic, Boulder, CO, USA) were recorded simultaneously throughout the complete procedure. The data from the Conox monitor were stored in a personal computer with proprietary software, ConoxView (Quantium Medical), while the data from the Bispectral Index were recorded with Rugloop (Demed, Temse, Belgium). The BIS was taken into account in order to have a reference for the validation of the qCON, since it was already validated to be used with pediatric patients[2,3]. The recorded data was divided in different surgical states based on the annotations of clinical events recorded during the procedures: Pre-anesthesia, Anesthesia and Recovery. Acquired data with either high burst suppression ratio (BSR>10) or low signal quality index (SQI<50) were rejected. The values of the qCON and qNOX indices were evaluated during the three clinical states and a Mann-Whitney U test with a significance level of 0.05 was applied to evaluate the presence of significant differences between states. The Prediction probability index (Pk) was used to measure the performance of the indices differentiating between awake and asleep states. A Pearson correlation and the Pk between the qCON and the BIS indices were calculated to assess the performance of the Conox monitor. The qCON and BIS were also contrasted using the Bland-Altman and the density plots. To assess the performance of the nociception index (qNOX), the pediatric patient's movement response to a series of nociceptive stimuli given was compared with the qNOX values.

RESULTS: The indices qCON, qNOX and BIS showed higher values during Pre-anesthesia and Recovery and lower ones during Anesthesia (Mann-Whitney U test, p-value<0.05) (Figure 1). The Pk (SE) values of qCON, qNOX and BIS for predicting awake versus anesthetized states were 0.847 (0.002), 0.858 (0.001) and 0.655 (0.002) respectively, the patients are administered hypnotic and analgesic agents at the same time, hence the three indices discriminate between awake and anesthetized states. Regarding the hypnotic effect indices, the Bland Altman and the density plot (Figure 2) showed that the most common values between qCON and BIS are close to 50, corresponding to an adequate unconsciousness state. The qCON and the BIS indices showed a correlation of 0.829 and a Pk (SE) of 0.928 (0.001). The probability of the qNOX to predict response to noxious stimulation was Pk (SE) = 0.804 (0.008), showing that higher values of the qNOX indicate a higher probability of movement (Figure 3).

CONCLUSION: The qCON and qNOX indices have proven to be good indicators of the subject's clinical state in pediatric surgeries under general anesthesia. The level of consciousness index qCON outperformed the BIS index, and the nociception index (qNOX) has correctly identified the children's probability of response to a noxious stimulation.

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	Pediatric population
Number of patients	17
Female/Male (%)	41.2% / 58.8%
Age, years	11.08 (4.47)
Height, cm	144.12 (26.12)
Weight, kg	44.15 (22.77)

Table 1

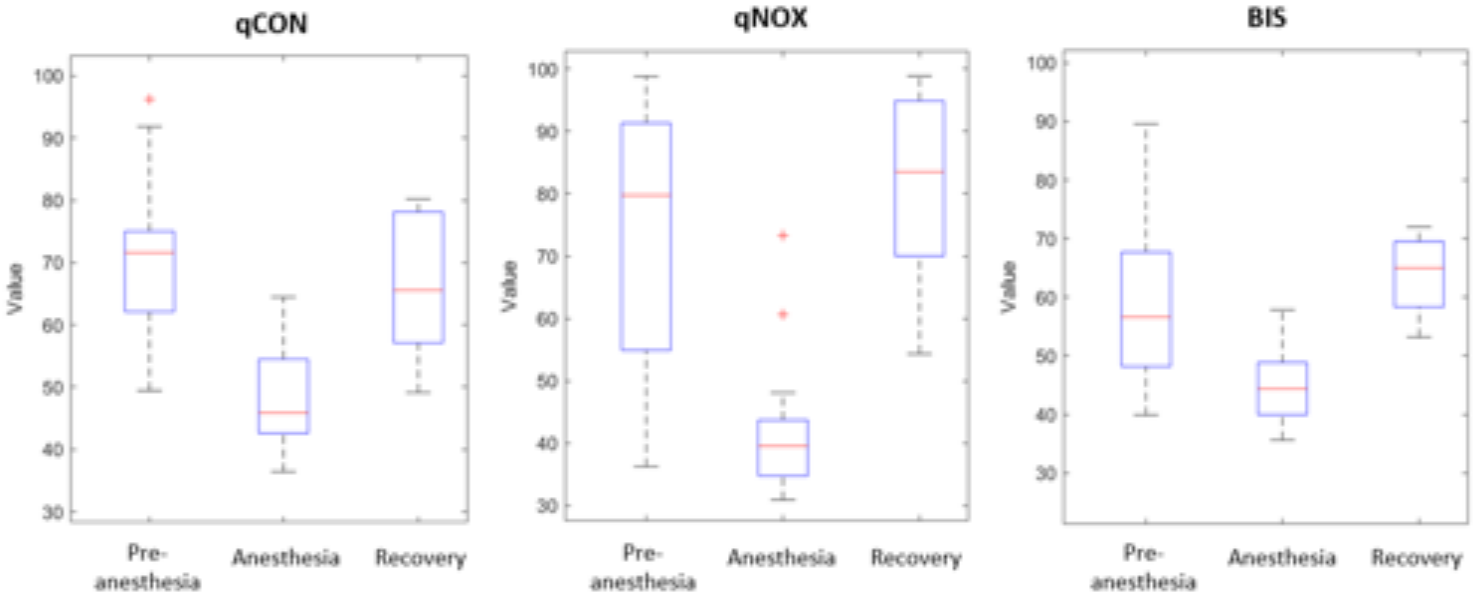

Fig. 1

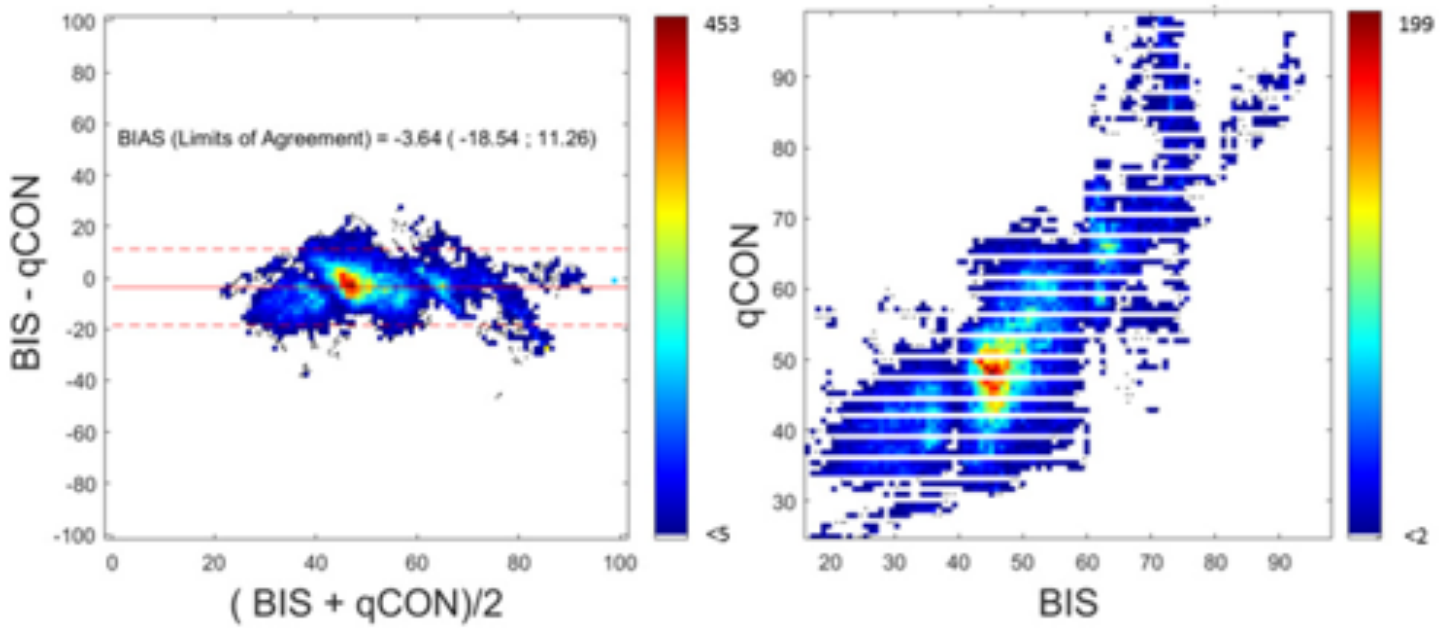

Fig. 2

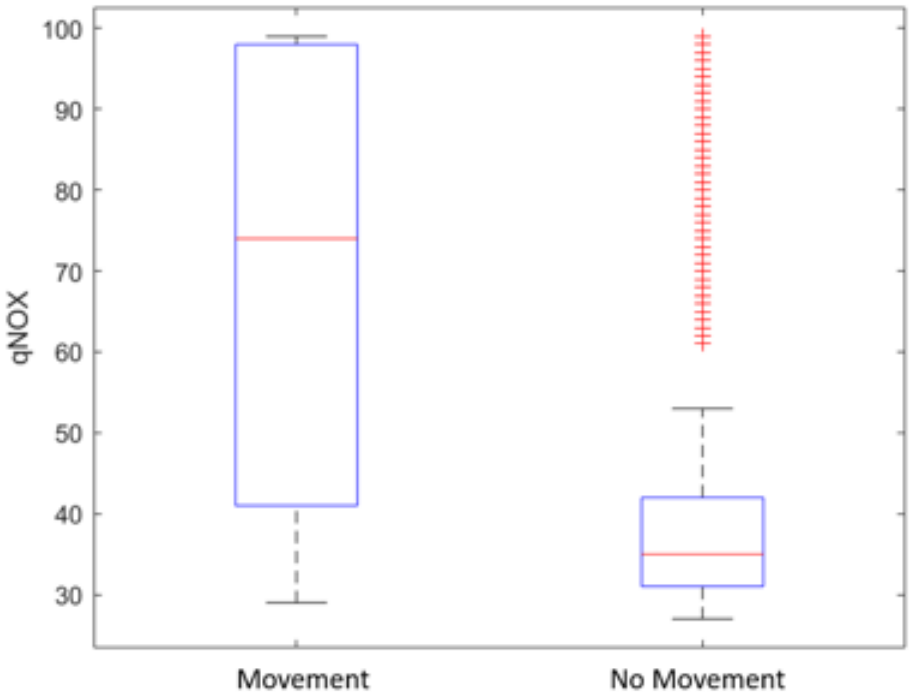

Fig. 3

PEDIATRIC ANESTHESIOLOGY 46

Association Between General Anesthesia Exposure Before 4 Years of Age and Attention Deficit/Hyperactivity Disorder in Pediatric Patients: A Nationwide Retrospective Cohort Study

Si Ra Bang[1]

[1]*Inje University Seoul Paik Hospital, Seoul, Korea*

INTRODUCTION: It has been reported that multiple anesthesia exposure was associated with later development of attention deficit/hyperactivity disorder (ADHD)[1]. ADHD can affect a wide range of psychological domains, such as cognition, interpersonal, school, and family functioning, which might increase not only the familial but also the social financial burden[1]. However, a retrospective matched-cohort study in Taiwan found that exposure to general anesthesia before 3 years of age was not associated with ADHD[2]. In this study, we used a nationwide database to evaluate the association of general anesthesia with ADHD in pediatric patients who underwent health care checkups. The primary outcome was the development of ADHD before school age.

METHODS: In Korea, all newborn babies have an opportunity to undergo infant medical checkup without charge. The medical checkup service includes seven checkups between the ages of 4 and 71 months (1st at 4–6; 2nd at 9–12; 3rd at 18–24; 4th at 30–36; 5th at 42–48; 6th at 54–60; and 7th at 66–71 months). The database includes infants who underwent at least one of the first or second medical checkup, and 5% of the sample is extracted for each birth year between 2008 and 2012. The collected data include social and economic variables (including age, location, type of subscription, income rank, disability, death, etc.), medical resource utilization status (consultations and medical checkups), and clinic status (status, facility, equipment, and personnel data of the clinics by type, establishment, and location [city and state]). Group G included pediatric patients who had been exposed to general anesthesia at least once before 4 years of age. Group O included a control matched cohort. The primary outcome was the prevalence of ADHD, which was diagnosed based on the ICD-10 code 'F90.'

RESULTS: We identified 17,485 pediatric participants who were born in 2008 and 2009 with available data from the seventh medical health checkup. Of these, 34 who had missing data were excluded. Among the 17,451 participants, 315 (1.8%) had a history of exposure to general anesthesia. Group O included 1,259 patients. Among all 1,574 participants, 17 (1.08%) were diagnosed with ADHD, with no significant difference between the two groups (P=0.33).

CONCLUSION: In this study, we evaluated the association of general anesthesia with development of ADHD in pediatric patients based on a nationwide database. Our results indicated that exposure to general anesthesia before the age of 4 years was not associated with an increased risk of ADHD before school age.

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Subspecialty Abstracts

PERIOPERATIVE ANESTHESIA

PERIOPERATIVE ANESTHESIA 1

Effects of end-tidal carbon dioxide on postoperative nausea and vomiting

Austin Eells[1], Skye Buckner Petty[2], Molly B Kraus[3]

[1]Mayo Clinic Alix School of Medicine, Scottsdale, AZ, [2]Mayo Clinic Arizona, Scottsdale, AZ, [3]Mayo Clinic, Scottsdale, AZ

INTRODUCTION: Postoperative nausea and vomiting (PONV) is one of the most common post-surgical complications. Proposed mechanisms of action include compression of gastrointestinal mucosa and hypoperfusion of emetic centers which may be improved by hypercapnia induced vasodilation. Mild hypercapnia has been shown to increase perfusion, leading to improved cardiac index, hemodynamics, oxygenation, and reduced emergence time.[1] The relationship between carbon dioxide levels and PONV is unclear and studies have found conflicting results. One randomized controlled trial showed a fivefold decrease in PONV with hypercapnia while another showed no difference.[2,3] This study will examine the relationship between end-tidal carbon dioxide (EtCO2) levels and PONV in surgical patients.

METHODS: 474 patients who underwent total knee arthroplasty under general anesthesia between October 2018 and July 2019 at the Mayo Clinic in Phoenix, Arizona were identified for a retrospective analysis. Patient records were reviewed for risk factors of PONV including age, gender, smoking history, PONV history, preoperative antiemetic administration, and inhaled anesthetic administration. Patients receiving total intravenous anesthetic (TIVA) or regional anesthesia were excluded. 343 patient records had intraoperative EtCO2 data. Median EtCO2 levels for the duration of the anesthetic (OEtCO2), last 30 minutes prior to extubation (30EtCO2), and final 10 minutes prior to extubation (10EtCO2) were calculated. Administration of a postoperative antiemetic in the recovery room was used as proxy for PONV. Hypocapnic (mmHg<36) and hypercapnic (≥36) groups were identified. Logistic regression was used for each group as well as dichotomous groups (<36 or ≥36).

RESULTS: The incidence of PONV as measured by antiemetic administration was 12.2% (42/343). Patients who were administered an antiemetic were more likely to be female (69% vs 48%, p-value 0.01). However, other risk factors such as smoking history, age, a history of PONV were not significant. Median (Q1, Q3) EtCO2 for the OEtCO2, 30EtCO2, and 10EtCO2 groups were 34.3 (32.7, 36.0), 38.1 (35.1, 41.4), 38.9(35.1, 43.4). Rates of antiemetic administration are reported in Table 1. No statistical relationship is seen within or across groups. Logistic regression of continuous EtCO2 levels showed odds ratios and p-value of OEtCO2 1.03 (0.586), 30EtCO2 1.01 (0.683), and 10EtCO2 0.98 (0.576). EtCO2 levels evaluated as dichotomous groups (<36, ≥36), likewise, did not show a significant relationship with odds ratios (p-values) of OEtCO2 1.215 (0.631), 30EtCO2 1.253 (0.538), and 10EtCO2 1.114 (0.767).

CONCLUSION: The results of this study do not show any relationship between intraoperative EtCO2 levels and PONV rates in the PACU. There is controversy in the literature regarding this relationship with recent randomized controlled trials finding both significant and insignificant results.2,3 This study contributes to the body of knowledge available and indicates that a relationship may not exist. However, this study is limited by relatively few data points greater than 40 mmHg EtCO2. Large randomized controlled prospective trials are needed to more effectively determine the existence of a relationship between EtCO2 and PONV.

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Table 1: $EtCO_2$ separated by duration of anesthesia			
	Number of patients receiving PACU Antiemetic / total patients (%)		
$EtCO_2$, mmHg	**<36**	**≥36**	**OR (p-value)**
$EtCO_2$ full duration of anesthesia	32/257 (12.5%)	10/86 (11.6%)	1.215 (0.631)
$EtCO_2$ 30 min prior to extubation	14/113 (12.4%)	28/230 (12.2%)	1.253 (0.538)
$EtCO_2$ 10 min prior to extubation	13/104 (12.5%)	29/239 (12.1%)	1.114 (0.767)

PERIOPERATIVE ANESTHESIA 2

Changes in analgesic strategies for lobectomy from 2009 to 2018

Theresa Lo[1], Robin Schiller[1], Karthik Raghunathan[1], Vijay Krishnamoorthy[2], Michelle McGauvran[1], Selby Johnson[1], Oliver Jawitz[1], Srinivas Pyati[2], Thomas J Van de Ven[2], Raquel R Bartz[2], Annemarie Thompson[1], Tetsu Ohnuma[2]

[1]Duke University School of Medicine, Durham, NC, [2]Duke University, Durham, NC

INTRODUCTION: Thoracic surgery is associated with significant postoperative pain. Inadequate pain control can exacerbate pulmonary complications by worsening lung restriction, decreasing ventilation, reducing clearance of secretions, and increasing atelectasis in the perioperative period.[1] Moreover, poorly controlled postoperative thoracic pain may also lead to the development of chronic pain.[2] Since pain is a major modifiable factor affecting patient perioperative morbidity and mortality following thoracic surgery,[3] this provides an opportunity for the healthcare team to optimize patient outcomes with a strategic pain management.[4] There are many ways to manage postoperative pain in thoracic surgery. For thoracic surgery, there is currently no multicenter study that characterizes the recent usage in neuraxial techniques and multimodal analgesia in the U.S. The objective of this study was to depict changes over time in the usage of epidural analgesia and nonopioid analgesics and to examine whether there was any change in opioid administration for open and video-assisted lobectomy.

METHODS: We conducted a retrospective study by querying the Premier Healthcare database for adult patients undergoing open or video assisted thoracic surgery (VATS) lobectomy from 2009 to 2018. The outcome of interest was changes in the receipt of epidural analgesia and nonopioid and opioid analgesics as measured by charges on the day of surgery. We also evaluated postoperative average daily opioid use. We used multivariable logistic and linear regression models to examine the association between utilization of each analgesic modality and year.

RESULTS: We identified 81,380 patients undergoing lobectomy: 36,775 (45.12%) patients had open lobectomy and 44,605 (54.81%) patients had VATS lobectomy. Median age for both cohorts was 65 years. Fifty percent of open cohort and 45% of VATS cohort were male. Predicted probabilities and values of use of analgesic techniques, medications, and opioid consumption by year using that were estimated using multivariable logistic and linear regression models. Epidural analgesia use decreased from 29.6% in 2009 to 14.7% in 2018 for open lobectomy ($P < 0.0001$), and from 14.2% in 2009 to 4% in 2018 for VATS lobectomy ($P < 0.0001$). Nonopioid local and systemic analgesics, including liposomal bupivacaine, oral and intravenous acetaminophen, gabapentinoids, ketamine, dexmedetomidine, COX-2 inhibitors, and dexamethasone increased over time for both open and VATS lobectomy. On the contrary, the use of intravenous nonsteroidal anti-inflammatory drugs declined over time. Use of patient-controlled analgesia decreased, while opioid consumption on the day of surgery increased and postoperative opioid consumption remained relatively stable over time.

CONCLUSION: In this large sample of patients undergoing open and VATS lobectomy, utilization of epidural analgesia declined, use of non-opioid analgesics increased, opioid consumption on day of surgery increased, and postoperative daily opioid consumption initially declined but slowly increased back to its level in 2009. This suggests that the analgesics chosen to replace epidurals for lobectomy patients might not be as effective at reducing opioid use. Further research will be required to examine the association of these changes with outcomes.

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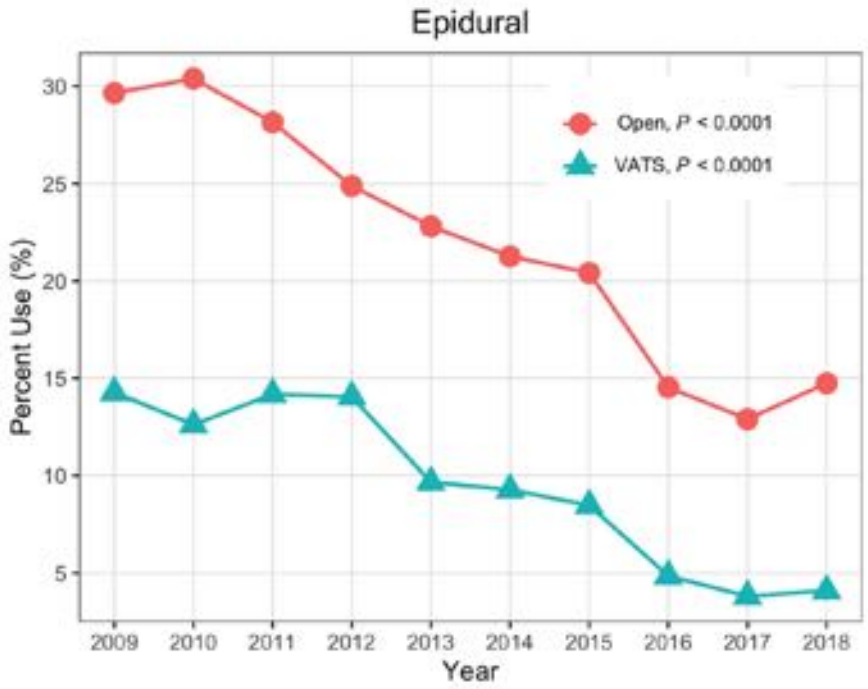
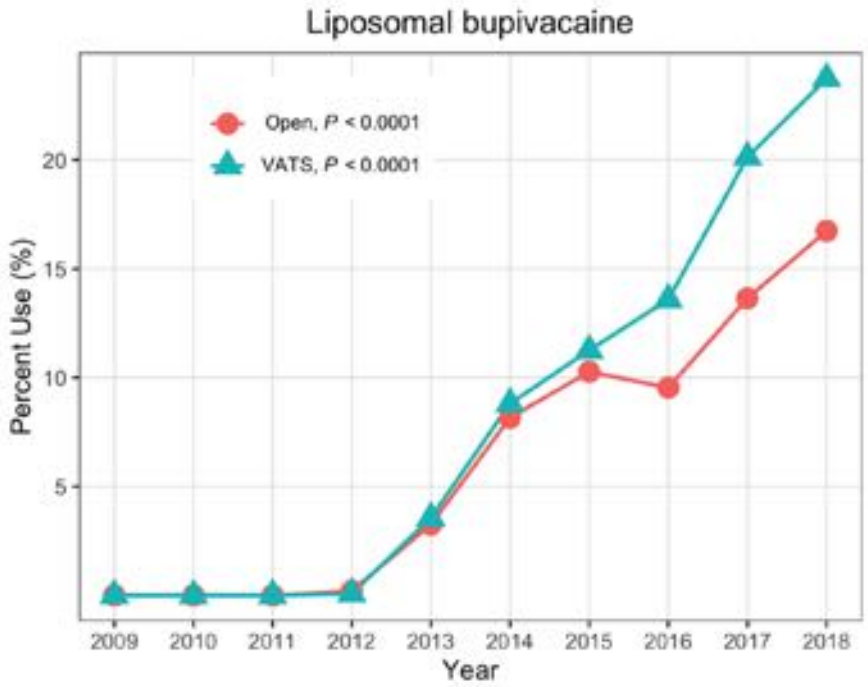
Table 1. Patient baseline characteristics and comorbidities and hospital-related characteristics

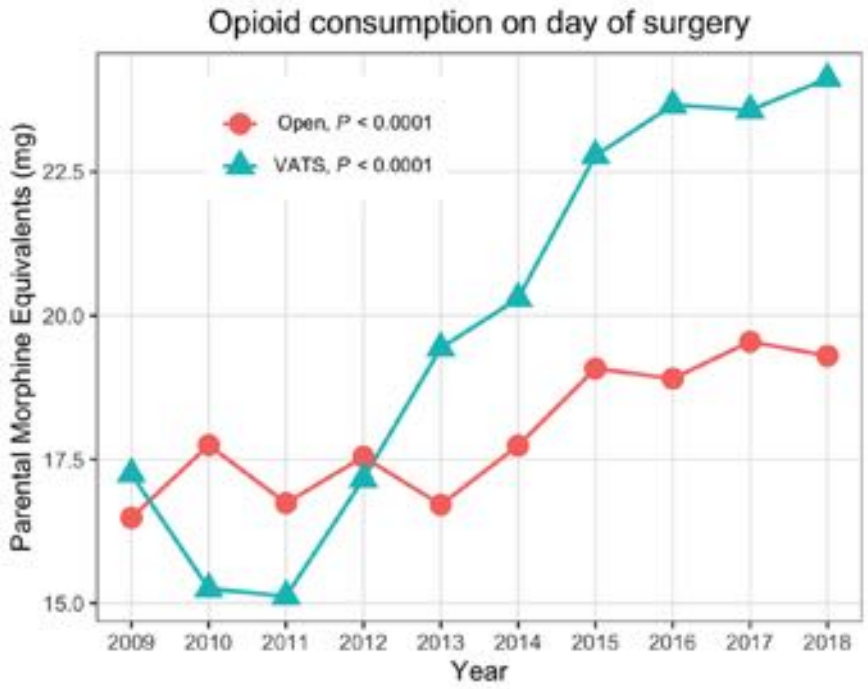
	Open Lobectomy (n = 36,775)	VATS Lobectomy (n = 44,605)
Age, ± SD (years)	65.5 ± 12.2	65.1 ± 12.9
Male [no. (%)]	18325 (49.8)	20145 (45.2)
Race [no. (%)]		
African Americans	2739 (7.4)	3473 (7.8)
Caucasians	29898 (81.3)	36706 (82.3)
Other	4138 (11.3)	4426 (9.9)
Payor [no. (%)]		
Managed care organization	8069 (21.9)	10643 (23.9)
Medicaid	2469 (6.7)	3097 (6.9)
Medicare	22729 (61.8)	26671 (59.8)
Other	3508 (9.5)	4194 (9.4)
Comorbidity		
Congestive heart failure	1621 (4.4)	1716 (3.8)
Valvular disease	1328 (3.6)	1517 (3.4)
Pulmonary circulation disease	430 (1.2)	261 (0.6)
Peripheral vascular disease	3271 (8.9)	3069 (6.9)
Paralysis	58 (0.2)	59 (0.1)
Other neurological disorders	1438 (3.9)	1584 (3.6)
Chronic pulmonary disease	18606 (50.6)	19203 (43.1)
Diabetes without chronic complications	6296 (17.1)	6973 (15.6)
Diabetes with chronic complications	1350 (3.7)	1888 (4.2)
Hypothyroidism	4410 (12)	5557 (12.5)
Renal failure	2393 (6.5)	2623 (5.9)
Liver disease	616 (1.7)	850 (1.9)
Peptic ulcer Disease excluding bleeding	72 (0.2)	104 (0.2)
Acquired immune deficiency syndrome	38 (0.1)	60 (0.1)
Lymphoma	303 (0.8)	395(0.9)
Metastatic cancer	5499 (15)	4176 (9.4)
Solid tumor without metastasis	4865 (13.2)	4996 (11.2)
Rheumatoid arthritis/collagen vascular disease	1301 (3.5)	1677 (3.8)
Coagulopathy	578 (1.6)	663 (1.5)
Obesity	4233 (11.5)	5236 (11.7)
Weight loss	1337 (3.6)	994 (2.2)
Fluid and electrolyte disorders	1953 (5.3)	1626 (3.6)

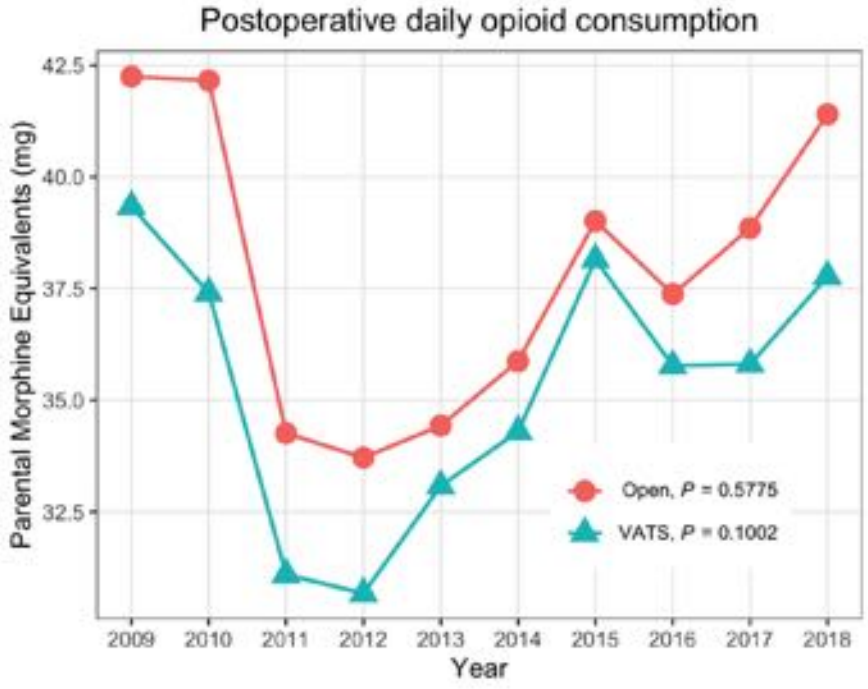
Table 1 (continued)

Chronic blood loss anemia	124 (0.3)	98 (0.2)
Deficiency Anemias	3077 (8.4)	2593 (5.8)
Alcohol abuse	1047 (2.8)	967 (2.2)
Drug abuse	425 (1.2)	442 (1)
Psychoses	719 (2)	850 (1.9)
Depression	4153 (11.3)	4964 (11.1)
Hypertension	23057 (62.7)	26401 (59.2)
Teaching hospital	18530 (50.4)	27146 (60.9)
Rural hospital	3275 (8.9)	3327 (7.5)
Hospital number of beds [no. (%)]		
0-99	344 (0.9)	310 (0.7)
100-199	2003 (5.4)	2022 (4.5)
200-299	4749 (12.9)	4851 (10.9)
300-399	6957 (18.9)	6843 (15.3)
400-499	7372 (20)	6679 (15)
500+	15350 (41.7)	23900 (53.6)
Fiscal year [no. (%)]		
2009	2486 (6.8)	1212 (2.7)
2010	2922 (7.9)	1807 (4.1)
2011	3460 (9.4)	2405 (5.4)
2012	3404 (9.3)	2541 (5.7)
2013	3591 (9.8)	2865 (6.4)
2014	3602 (9.8)	2975 (6.7)
2015	3653 (9.9)	3350 (7.5)
2016	5380 (14.6)	9484 (21.3)
2017	4968 (13.5)	10497 (23.5)
2018	3309 (9)	7469 (16.7)









PERIOPERATIVE ANESTHESIA 3

Factors Associated with Failure to Rescue after Postoperative Respiratory Failure in Patients Undergoing Non-cardiac Surgery: An Analysis of the NSQIP Database

Kunal Karamchandani[1], Brittany McDowell[2], Sarah M Khorsand[3], Zyad J Carr[4]

[1]Penn State Health Milton S. Hershey Medical Center, Hershey, PA, [2]Penn State University - Milton S. Hershey Medical Center, Hershey, PA, [3]University of Texas Southwestern, -, TX, [4]Yale School of Medicine, Hershey, PA

INTRODUCTION: Despite significant advances in medical care, postoperative mortality after non cardiac surgery remains high. Many deaths after surgery can be attributed to 'failure to rescue'(FTR), defined as death after suffering a postoperative complication. It has been proposed that failure to rescue might be a better surgical quality indicator than just the occurrence of a complication. FTR after postoperative respiratory failure is not well defined and the aim of this study is to identify the incidence of FTR after postoperative respiratory failure in patients undergoing non-cardiac surgery.

METHODS: We conducted a retrospective cohort study using patient-level data from all hospitals participating in the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) from 2012 to 2018 inclusive. Data was obtained from the ACS NSQIP Participant Use File. All adult patients that underwent non cardiac surgery during this time period were included. Patients who had outpatient surgery and those requiring ventilator support prior to surgery were excluded. Patients who developed postoperative respiratory failure, defined as, 'undergoing an unplanned intubation in the postoperative period and requiring mechanical ventilation for longer than 48 hours' were identified. The primary outcome was 'Failure to rescue', (defined as death within the first 30 days after surgery) in patients who developed postoperative respiratory failure.

RESULTS: A total of 5,881,881 patients who underwent non cardiac surgery were identified, of which 3,429,950 met the inclusion criteria. Amongst the patients included in the analysis, 20,561(0.6%) developed postoperative respiratory failure, of which 5494 (26.7%) died within 30 days of surgery. Table 1 depicts the incidence of postoperative respiratory failure as well as failure rescue over the years.

CONCLUSION: Amongst a cohort of patients identified from the ACS NSQIP database who underwent non cardiac surgery from the years 2012-2018, and developed postoperative respiratory failure, the incidence off failure to rescue was significantly high. Identification of underlying risk factors that can predict failure to rescue after postoperative respiratory failure may help devise interventions that can prevent the mortality associated with this common post-surgical complication.

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Table 1. Year wise incidence of postoperative respiratory failure and failure to rescue

Year	Patients undergoing non-cardiac surgery (n)	Patients meeting inclusion criteria (n)	Patients who developed postoperative respiratory failure (n)	Patients who died within 30 days of surgery (n)	Failure to rescue (%)
2012	543885	339942	2449	590	24.09
2013	651940	399134	2862	664	23.2
2014	750937	447261	2919	765	26.2
2015	885502	517394	3180	856	26.9
2016	1000393	575883	3111	888	28.5
2017	1028713	583416	3142	911	29
2018	1020511	566920	2898	820	28.2

PERIOPERATIVE ANESTHESIA 4

Unintended consequences of the 2016 CDC opioid prescribing guidelines on opioid dispensing after surgery

Tori Sutherland[1], Hannah M Wunsch[2], Ruxandra Pinto[3], Craig Newcomb[4], Colleen Brensinger[4], Lakisha Gaskins[4], Brian Bateman[5], Mark D Neuman[6]

[1]Children's Hospital of Philadelphia/University of Pennsylvania, Philadelphia, PA, [2]University of Toronto Faculty of Medicine, Toronto, Ontario, [3]Sunnybrook Health Sciences Centre, Toronto, Ontario, [4]University of Pennsylvania Perelman School of Medicine, Philadelphia, United States of America, [5]Brigham and Women's Hospital, Boston, MA, [6]University of Pennsylvania, Philadelphia, PA

INTRODUCTION: Opioids are frequently overprescribed after common surgeries.[1,2] Excess supply leads to increased community availability and subsequent risk of diversion,[3,4] and may contribute to adverse outcomes, including new long-term use.[5,6] In 2016, the US Centers for Disease Control (CDC) released guidelines on opioid prescribing for pain management, including a recommendation for acute pain management. While the guideline was not intended to address postoperative pain management, observers have noted potential unintended impacts of this guideline on opioid prescribing after surgery. We hypothesize that the guideline release did affect opioid dispensing after surgery.

METHODS: We performed a retrospective interrupted time series analysis involving 361,556 privately insured opioid-naïve patients undergoing 8 general and orthopedic surgeries between 2014 and 2018. The primary outcome was the total amount of opioids dispensed in the first prescription filled within 7 days after surgery in morphine milligram equivalents (MME); secondary outcomes included the total amount of opioids prescribed within 30 days after surgery and the incidence of any opioid refill within 30 days. To characterize absolute levels of opioid dispensing, we compared the amount dispensed in initial prescriptions with available procedure-specific recommendations based on anticipated pain severity.

RESULTS: The total amount of opioids dispensed in the first prescription after surgery decreased over the 2 years following the CDC guideline release, compared to an increasing trend over the 2 years prior (pre-release trend: 1.43 MME/month (95% Confidence Interval (CI): 0.62, 2.24, P=0.001); post-release trend: -2.18 MME/month (95% CI: -3.01, -1.35, P<0.001); trend change: -3.61 MME/month (95% CI -4.87, -2.35, P<0.001)). Changes in initial dispensing amount trends were greatest for patients undergoing hip or knee replacement (-8.64 MME/month (95% CI -11.68, -5.60, P<0.001)). Minimal changes were observed in rates of refills over time (net change: 0.14%/month (95% CI 0.06, 0.23, P=0.001)). Absolute amounts prescribed remained high throughout the period, with 47.7% of patients treated in the post-guideline period receiving at least twice the initial opioid dose anticipated to treat postoperative pain based on available procedure-specific recommendations.

CONCLUSION: Opioid dispensing after surgery decreased markedly after the 2016 CDC guideline release, compared to an increasing trend over the two years prior, suggesting unintended impacts of the guideline on postoperative pain management. Absolute amounts prescribed for surgery remained high over the study period, supporting further efforts to improve postoperative pain management.

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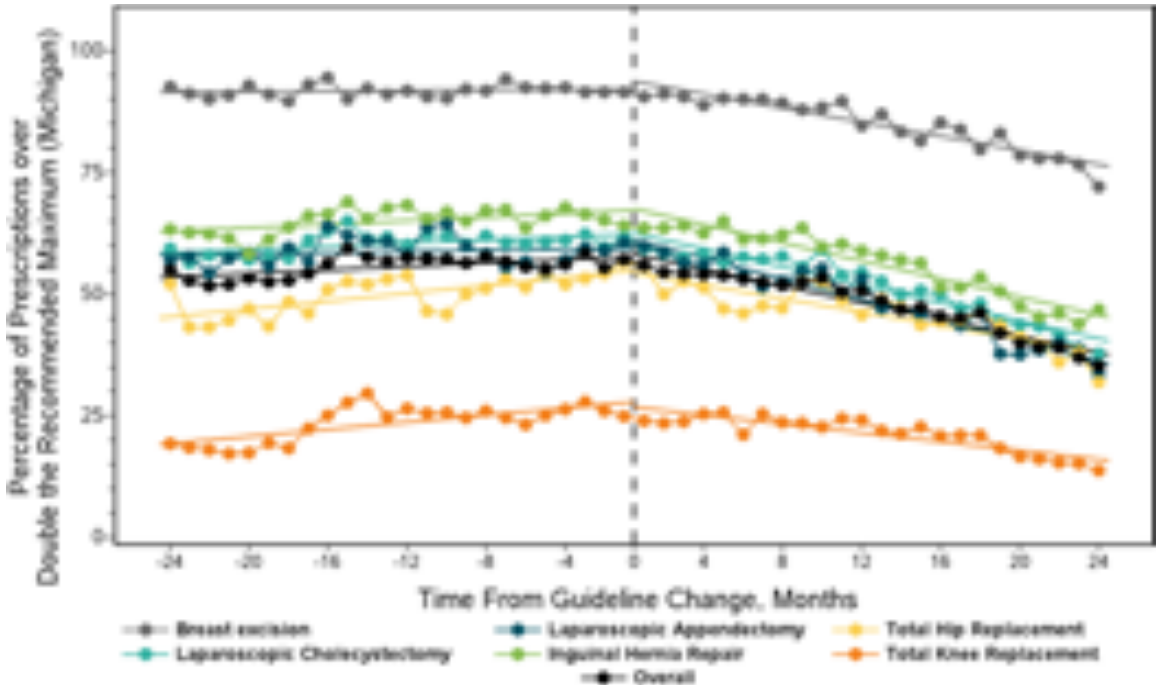

PERIOPERATIVE ANESTHESIA 5

Effect of β2-receptor blockers on mortality and cancer recurrence in patients undergoing cancer surgery: a retrospective cohort study

Lynn A Miggelbrink[1], Teus Kappen[1], Rhodee Bijlsma[1], Wilton van Klei[1], Judith van Waes[1]

[1]University Medical Center Utrecht, Utrecht, Netherlands

INTRODUCTION: β-Blockers are used as treatment of cardiovascular disease and have an antagonist effect on β-adrenergic receptors.[1–4] In addition, β-blockers may have an effect on cancer cells. In laboratory research, an association was found between β-receptors and metastasis.[5] Inhibition of the β2-receptor, but not the β1-receptor, decreased migratory activity and increased apoptosis of cancer cells for multiple cancer types.[6–12] Based on previous studies investigating the effect of β-blockers on cancerous tumors, we hypothesized that selective β2-receptor blockade may reduce the risk of postoperative cancer recurrence and metastasis.[13–19] Therefore this study aimed to assess the effect of β2-receptor blockade on cancer recurrence in patients undergoing surgical treatment.

METHODS: This retrospective cohort included patients ≥60 years old undergoing surgery as primary treatment of cancer. Patients with multiple primary tumors, or with tumors that are not primarily treated with surgical intervention, were excluded. The Institutional Review Board waived the need for informed consent, and only routinely collected data were used.

As β-blockers have different selectivity for β1- and β2-receptors, patients were divided into groups based on β-blocker selectivity. Most selective β1-blockers have low affinity with β2-receptors, and vice versa. Metoprolol was categorized in a separate group, as it is most commonly used and mostly selective for the β1-receptor, but to a lesser extent.[4]

Outcome was all-cause mortality or cancer recurrence within 5 years. The outcome was censored at the last known contact before loss to follow-up, or if follow-up had not yet been completed.

Statistical analysis

Baseline characteristics were compared. Because cancer recurrence and death could both occur in one patient, and this cannot be modulated in regular time-to-event models, a multi-state model was used to determine the effect of β-blockers on multiple transitions (Figure 1). A patient could develop cancer recurrence after surgery (transition 1), could die without recurrence (transition 2), or could die after cancer recurrence (transition 3). These multiple states were added to a Cox regression model in order to determine the effect of β-blocker subtypes on each transition.

RESULTS: 5,652 patients underwent cancer surgery, of which 830 were included (Figure 2). Of these 830 patients, 240 (29%) used a β-blocker (Table 1). In comparison to patients using selective β2-blockers, patients using selective β1-blockers more frequently had preexistent hypertension and less frequently had either ischemic heart disease or chronic heart failure. A total of 420 patients (51%) died within 5 years after surgery, while 326 (39%) patients had cancer recurrence within that period: 40% in patients without β-blockers, 44% in patients using β1-selective blockers, 36% using metoprolol and 30% in patients using β2-selective blockers. Figure 3a and 3b show the survival curve for cancer recurrence and mortality as competing risks: patients using β2-receptors had the lowest probability of cancer recurrence, although this analysis was not adjusted for confounding. Cox regression analysis including a multi-state model showed the following (Figure 1, Table 2):

For cancer recurrence (transition 1), patients using selective β2-blockers had the lowest risk (adjusted HR 0.8, 95%-CI 0.4-1.5) when compared to the group without β-blockers. For death, the risk was highest for patients using selective β2-blockers (adjusted HR 2.5, 95%-CI 1.4-4.6), whilst the risk was lowest for patients using selective β1-blockers (adjusted HR 1.3, 95%-CI 0.6-2.9). For death after cancer recurrence, the β2-receptor blocker group had the highest (adjusted HR 1.38), and patients using selective β1-blockers the lowest risk (adjusted HR 0.87).

CONCLUSION: The results of our study suggest a protective effect of β2 selective β-blockers on cancer recurrence. Although the sample size was too limited to achieve statistical significance, the observed signal illustrates the necessity to differentiate in β-blocker selectivity. In our opinion, this hypothesis has sufficient merit to warrant further research on the role of β2-receptor blockers on cancer recurrence.

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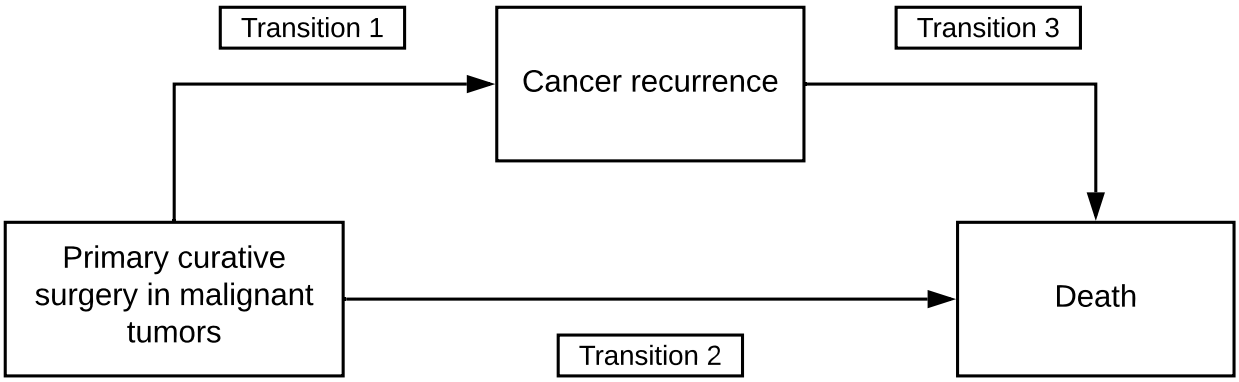

Fig. 1

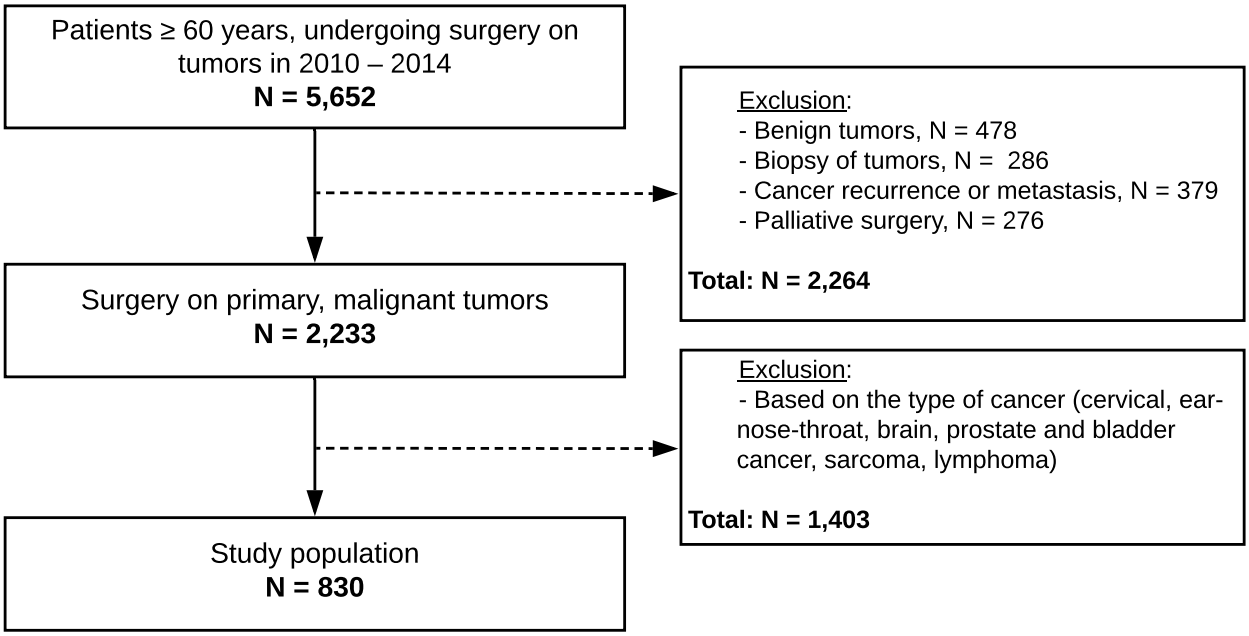

Fig. 2

Figure 3a

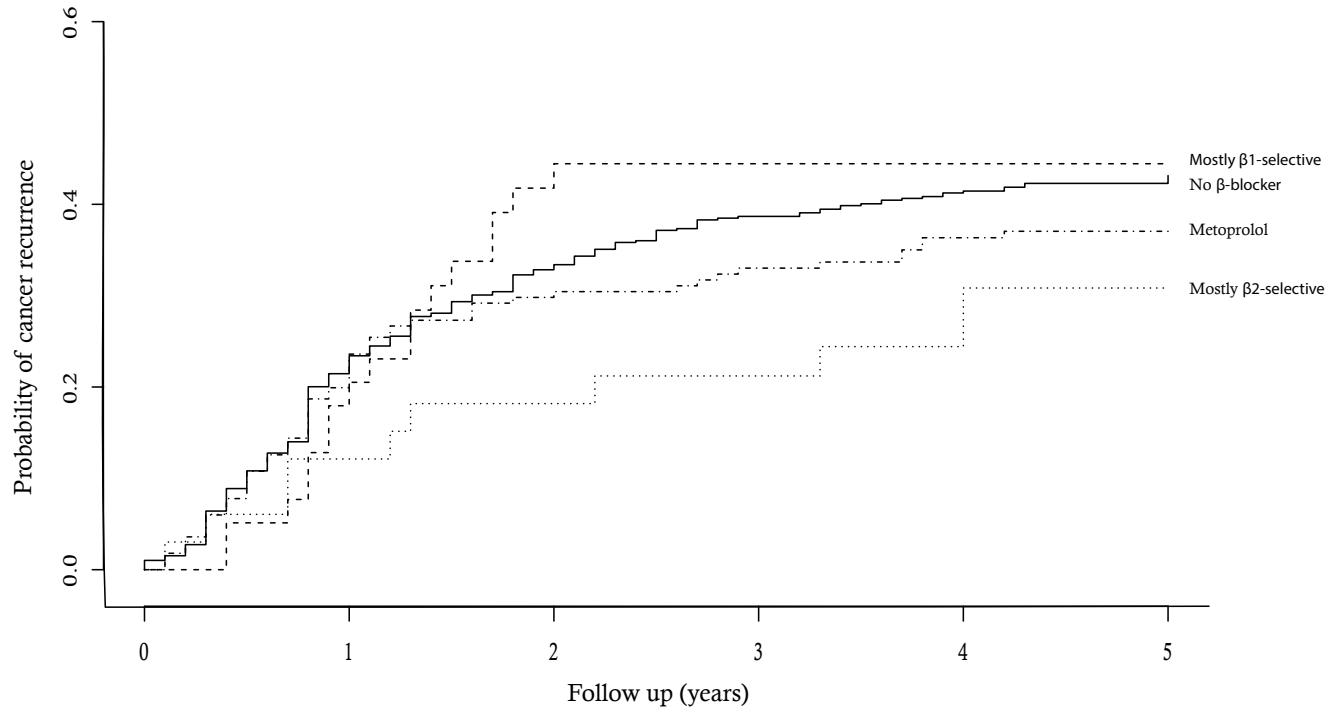

Figure 3b

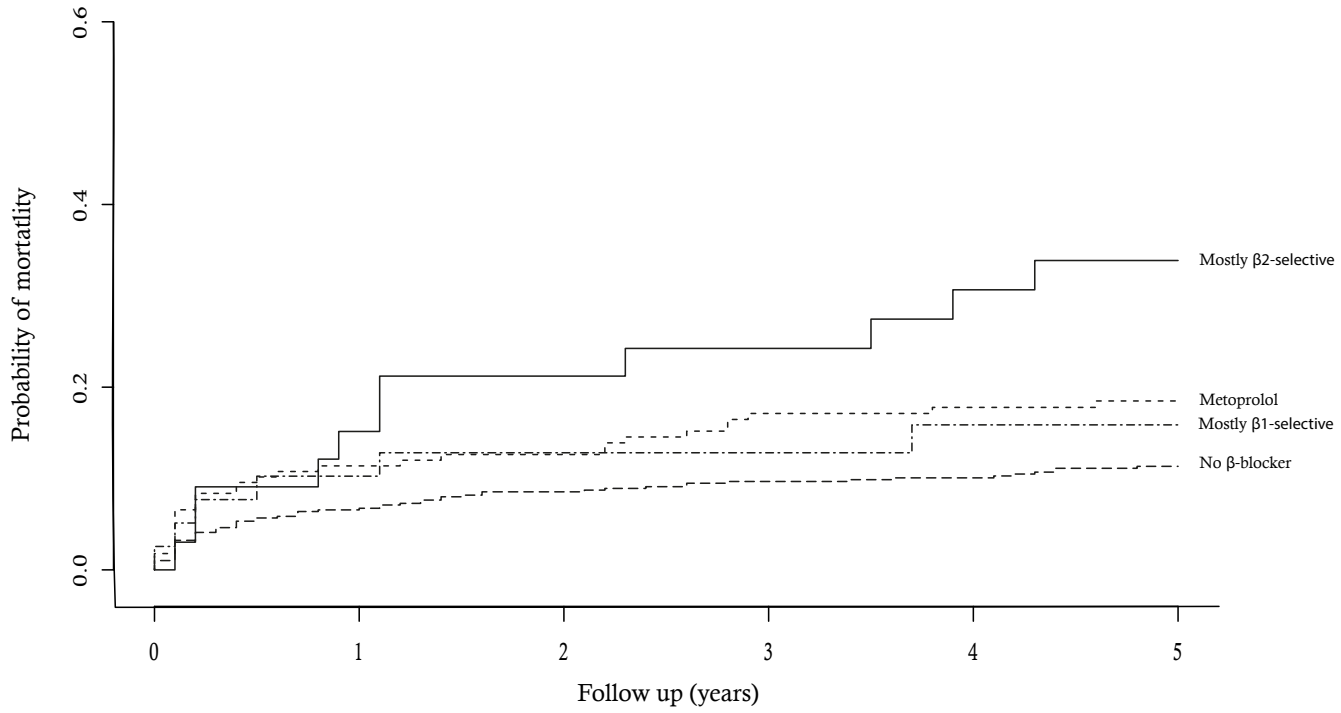

Table 1 Baseline characteristics for patients with and without chronic use of different β-blocker types.

		No β-blocker N = 590	**Mostly selective for β1-receptor** N = 39	**Metoprolol** N = 168	**Mostly selective for β2-receptor** N = 33	**Missing**, N (%)
Age, years (IQR)		69 (64 – 74)	71 (67 – 77)	71 (65 – 75)	71 (66 – 79)	0 (0)
Male gender, N (%)		253 (42.9)	17 (43.6)	68 (40.5)	13 (39.4)	0 (0)
ASA classification, N (%)	1	141 (23.9)	0 (0)	0 (0)	0 (0)	0 (0)
	2	358 (60.7)	29 (74.4)	116 (69.0)	20 (60.1)	
	3 and 4	91 (15.4)	10 (25.6)	52 (31.0)	13 (39.4)	
BMI, kg/m^2 (IQR)		24.7 (22.5 – 27.6)	28.2 (24.6 – 30.5)	26.9 (24.2 – 30.1)	25.9 (23.6 – 29.2)	1 (0.1)
Medical history, N (%)	Hypertension	207 (35.1)	38 (97.4)	149 (88.7)	21 (63.6)	0 (0)
	Diabetes mellitus	95 (16.1)	11 (28.2)	42 (25.0)	10 (30.3)	0 (0)
	Ischemic heart disease	37 (6.3)	6 (15.4)	45 (26.8)	7 (21.2)	0 (0)
	Chronic heart failure	3 (0.5)	1 (2.6)	8 (4.8)	5 (15.2)	0 (0)
	Atrial fibrillation	27 (4.6)	4 (10.3)	24 (14.3)	10 (30.3)	0 (0)
	Cerebrovascular disease	58 (9.8)	5 (12.8)	24 (14.3)	4 (12.1)	0 (0)
	COPD	36 (6.1)	4 (10.3)	10 (5.9)	6 (18.2)	0 (0)
	Renal failure	36 (6.1)	8 (20.5)	24 (14.3)	4 (12.1)	0 (0)
	Peripheral vascular disease	22 (3.7)	1 (2.6)	18 (10.7)	1 (3.0)	0 (0)
History of smoking, N (%)	Never	320 (54.2)	22 (56.4)	97 (57.7)	19 (57.6)	0 (0)
	Quit	184 (31.2)	15 (38.5)	42 (25.0)	10 (30.3)	
	Current	85 (14.4)	2 (5.1)	29 (17.3)	4 (2.4)	
Type of cancer, N (%)	Gastro-intestinal tract [a]	107 (18.1)	2 (5.1)	22 (13.1)	2 (6.1)	0 (0)
	Upper Gastro-intestinal [b]	140 (23.7)	11 (28.2)	45 (26.8)	8 (24.2)	
	Gynaecological [c]	135 (22.9)	8 (20.5)	33 (19.6)	7 (21.2)	
	Colorectal	93 (15.8)	8 (20.5)	33 (19.6)	7 (21.2)	
	Other [d]	115 (19.5)	10 (25.6)	35 (20.8)	9 (22.3)	
Type of beta blocker, N (%)	None	590 (100)	NA	NA	NA	0 (0)
	Atenolol	NA	22 (56.4)	NA	NA	
	Bisoprolol	NA	16 (40.0)	NA	NA	
	Nebivolol	NA	1 (2.6)	NA	NA	
	Metoprolol	NA	NA	168 (100)	NA	
	Pindolol	NA	NA	NA	1 (3.0)	
	Propranolol	NA	NA	NA	3 (9.1)	
	Sotalol	NA	NA	NA	22 (66.7)	
	Carvedilol	NA	NA	NA	6 (18.2)	
	Labetalol	NA	NA	NA	1 (3.0)	

a liver, bile ducts, gall bladder, pancreas; b esophagus, stomach; c ovarium, endometrium, vulva; d kidney, thyroid, mamma

Table 2 Multi-state Cox Proportional Hazard model showing the effect of different β-blocker on multiple transitions

	Unadjusted				Adjusted		
	HR	**P-value**	**95%-CI**		**HR**	**P-value**	**95%-CI**
Type of β-blocker							
None	Ref				Ref		
Mostly selective for β1 receptor							
Post-surgery to cancer recurrence	1.14	0.61	0.69 – 1.86		1.51	0.58	0.70 – 1.91
Post-surgery to mortality	1.31	0.49	0.61 – 2.83		1.33	0.48	0.61 – 2.89
Cancer recurrence to death	0.88	0.64	0.51 – 1.51		0.87	0.63	0.50 – 1.52
Metoprolol							
Post-surgery to cancer recurrence	0.93	0.61	0.70 – 123		1.00	1.00	0.74 – 1.35
Post-surgery to mortality	1.42	0.087	0.95 – 2.11		1.53	0.044	1.01 – 2.30
Cancer recurrence to death	0.84	0.26	0.61 – 1.14		0.89	0.48	0.64 – 1.24
Mostly selective for β2 receptor							
Post-surgery to cancer recurrence	0.73	0.33	0.39 – 1.38		0.76	0.41	0.40 – 1.45
Post-surgery to mortality	2.40	0.0045	1.31 – 4.40		2.50	0.0036	1.35 – 4.62
Cancer recurrence to death	1.36	0.43	0.64 – 2.91		1.38	0.44	0.61 – 3.16
Overall hazard mortality after cancer recurrence	19.38	< 0.001	14.82 – 25.35		18.91	< 0.001	14.45 – 24.76
Age, per year	N.A.	N.A.	N.A.		1.02	0.00036	1.01 – 1.03
Gender female	N.A.	N.A.	N.A.		0.77	0.00050	0.66 – 0.89
Hypertension	N.A.	N.A.	N.A.		0.98	0.86	0.83 – 1.17
Ischemic heart disease	N.A.	N.A.	N.A.		0.68	0.0071	0.52 – 0.90
Chronic heart failure	N.A.	N.A.	N.A.		0.94	0.84	0.50 – 1.74
Atrial fibrillation	N.A.	N.A.	N.A.		1.02	0.91	0.76 – 1.35
Diabetes mellitus	N.A.	N.A.	N.A.		0.98	0.84	0.80 – 1.20

CI, confidence interval ; HR, hazard ratio ; N.A., not applicable

PERIOPERATIVE ANESTHESIA 6

Association between Preoperative Systemic Inflammation and Major Adverse Cardiovascular Events after Noncardiac Surgery: A Multicenter Prospective Cohort Study

Sebastian Roth[1], Giovanna Lurati Buse[1], Christian Puelacher[2], Danielle Gualandro[2], Christian Mueller[2]

[1]University Hospital Duesseldorf, Duesseldorf, Germany, [2]University Hospital Basel, Basel, Switzerland

INTRODUCTION: Each year more than 200 million people worldwide undergo noncardiac surgery of whom about 5% will develop cardiovascular complications.[1] Therefore, prevention and early recognition of major adverse cardiovascular events (MACE) is crucial. Recent studies demonstrated the important role of systematic inflammation in the development of MACE.[2] Neutrophil-lymphocyte ratio (NLR) is a low cost and widely available marker of systemic inflammation that may be associated with cardiovascular disease as well. While there are some promising data on its predictive value for myocardial injury,[3] the use of NLR to enhance preoperative risk assessment for MACE remains underexplored. The aim of this study was to answer the question if an elevated preoperative NLR (defined as NLR>4) is independently associated with MACE at 30 days after noncardiac surgery.

METHODS: This study reports prospectively collected data of a multicentre cohort study (NCT02573532) that included patients undergoing major noncardiac surgery aged ≥ 65 years OR ≥ 45 years in presence of a history of coronary artery disease, peripheral arterial disease or stroke. NLR was assessed within 7 days prior to surgery. The primary endpoint was MACE at 30 days after surgery. Secondary outcomes included MACE at 1 year, all-cause mortality at 30 days and 1 year and the occurrence of perioperative myocardial injury (PMI) defined as an increase in hsTNT ≥ 14 ng/l within the first 3 postoperative days. The discrimination of NLR for the events of interest was quantified using the area under the receiver operating characteristics curve (AUC). The independent association between NLR and MACE was calculated using multivariable Cox regression with predefined covariables.

RESULTS: Among 4828 patients (55% male, mean age 74±8 years), we registered 312 MACE at 30 days and 577 at 1 year. The AUC for 30-day and 1-year MACE was 0.65 [95% confidence interval (CI) 0.62-0.68] and 0.62 [95% CI 0.60-0.65], respectively (see figure 1). The adjusted hazard ratios for preoperative NRL>4 were 1.99 [95% CI 1.53-2.6] for 30-day and 1.57 [95% CI 1.31-1.89] for 1-year MACE (see figure 2). All-cause mortality was 3.1% at 30 days and 12.5% at 1 year. The AUC of NLR for 30-day and 1-year all-cause mortality was 0.73 [95% CI 0.69-0.78] and 0.66 [95% CI 0.63-0.68], respectively. The AUC for PMI was 0.59 [95% CI 0.57-0.61] and the adjusted odds ratio was 1.53 [95% CI 1.26-1.98].

CONCLUSION: Preoperative systemic inflammation as defined by NLR > 4 was independently associated with MACE at 30 days and 1 year after noncardiac surgery. Our findings support the potential value of NLR as a low-cost approach to enhance preoperative risk stratification in noncardiac surgery patients.

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Figure 1:

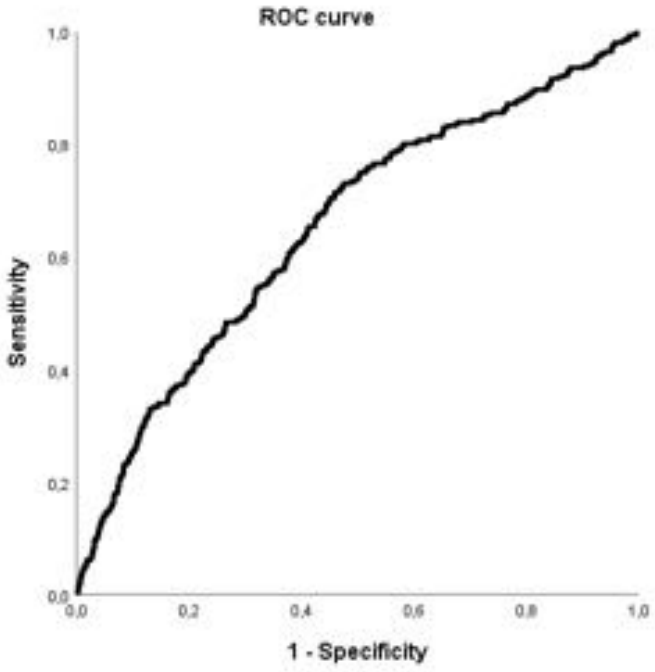
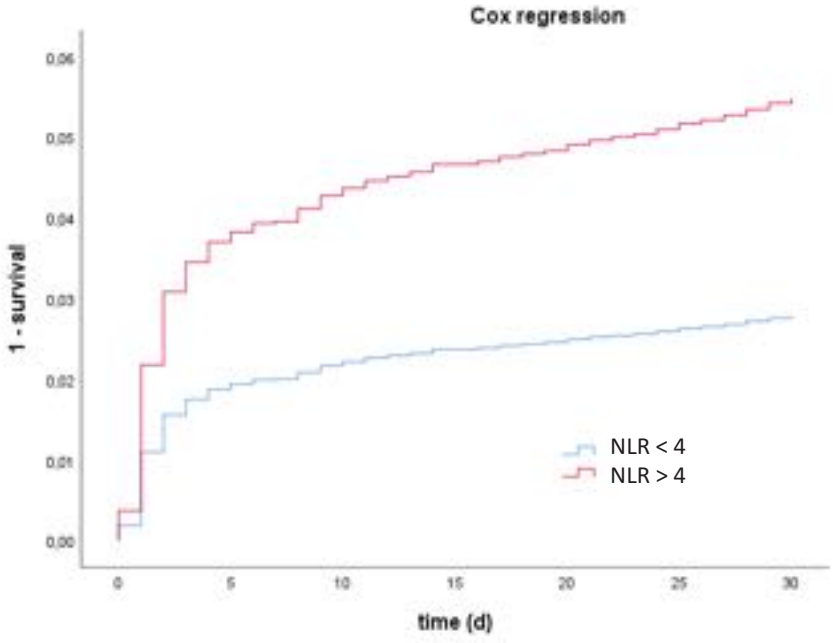


Figure 2:



PERIOPERATIVE ANESTHESIA 7

Pre-treatment with Lignocaine, Dexmedetomidine or Ketamine to relieve Propofol Injection Pain and Withdrawal movements during Anesthetic Induction

Karishma Batra[1], Pavan Nayar[1]

[1]VMMC & Safdarjung Hospital, New Delhi, New Delhi

INTRODUCTION: Propofol is one of the most widely used anesthetic induction agents, world over. A common problem encountered with the injection of Propofol is severe injection site pain, with reported incidence as high as 28-90%. It activates the kinin-kallikrein system, which through vasodilatation and hyperpermeability, increases the contact between aqueous phase propofol and free nerve endings.[1-3] Various studies using Lignocaine, Ketamine and Dexmedetomidine have shown promising results in ameliorating this pain. We aimed to compare these three drugs as a pretreatment, to alleviate Propofol injection pain and reduce withdrawal movements, during anesthetic induction. We also aimed to study the hemodynamic stability of these interventions.

METHODS: A single-center, prospective, interventional, randomized, controlled trial was conducted. We enrolled 135 patients, aged 18-65 years, with a BMI<= 30kg/m^2, ASA Physical Status I & II undergoing elective surgery under general anesthesia with endotracheal intubation. The patients were randomly allocated into three groups of 45 each, using Block Randomization with sealed envelope system with three arms of intravenous pre-treatment: 40mg of Lignocaine, 0.5mcg/kg Dexmedetomidine and 0.2mg/kg of Ketamine. The intervention drug was administered intravenously as a 2ml solution over 10 seconds, along with manual occlusion of the forearm for one minute, followed immediately by 2mg/kg of 1% concentration of Propofol, injected over the next 30 seconds. Every 5 seconds, a doctor blinded to the intervention asked the patient to grade any pain felt using a score from 0-3 Verbal Rating Scale by McCrirrick and Hunter[4]; the overall highest pain score and visible withdrawal reactions were recorded. Hemodynamics were recorded until 7 minutes post intubation. Statistical tests used were Independent t test/Mann-Whitney Test, ANOVA/ Kruskal Wallis test, Chi-Square test.

RESULTS: The incidence of pain relief, defined as a score of 0 on the Verbal Rating Scale, was 75.56% with Lignocaine, 51.11% with Dexmedetomidine and 37.78% with Ketamine. Pain was significantly reduced in patients receiving Lignocaine, compared to Dexmedetomidine (P=.02) and Ketamine (P=.0005), although there was no significant difference found in the latter two groups (P=0.427). Only 7.4% of patients (4 in the Dexmedetomidine group and 6 in the Ketamine group) had moderate pain (pain score of 2), and none reported severe pain (pain score of 3). No withdrawal reactions were noted in any of the groups.

CONCLUSION: Pretreatment with Lignocaine was proven superior compared to Dexmedetomidine and Ketamine in providing relief from Propofol injection pain, while maintaining hemodynamic stability. Since pain during Propofol injection is one of the most common side effects of anesthetic induction, this study could help standardize the use of Lignocaine as pretreatment in ameliorating this common but low morbidity problem.

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PERIOPERATIVE ANESTHESIA 8

Comparative analysis between general and neuraxial anesthesia for outpatient total hip and knee arthroplasty: a cohort study

Edward N Yap[1], Julia Wei[2], Kevin Ng[3], Matthias Behrends[4], Christopher Webb[1]

[1]The Permanente Medical Group, South San Francisco, CA, [2]Kaiser Permanente Division of Research, Oakland, CA, [3]The Permanente Medical Group, Walnut Creek, CA, [4]UCSF, San Francisco, CA

INTRODUCTION: Total hip and knee arthroplasties are elective orthopedic surgeries that dramatically improve the quality of life for patients with end stage osteoarthritis. The recent shift from multiday hospitalization to outpatient total joint arthroplasty has gained traction throughout the United States. Although one of the main drivers for this change is the creation of bundled payments from insurance reimbursement, improved surgical and anesthesia care, and enhanced perioperative and rehabilitation programs are what has made this new practice feasible[1]. Anesthetic management for lower extremity total joint arthroplasty has been extensively studied, and most studies have shown that neuraxial anesthesia compared to general anesthesia is associated with a reduction in morbidity and mortality[2,3]. However, there are limited studies examining if these findings hold true in the outpatient total joint arthroplasty population. Patients selected for outpatient arthroplasty are typically healthier, and with improvements in general anesthetic techniques, there may be an argument to prefer general anesthesia over neuraxial techniques[4]. Our study's goal was to determine if there were significant differences in outcomes between patients who received general anesthesia versus neuraxial anesthesia for outpatient primary total hip and knee arthroplasties.

METHODS: A retrospective cohort study of 13,019 patients who underwent same day discharge unilateral primary total hip or knee arthroplasty from 2017- 2019 at our hospitals was conducted, comparing patients who received general anesthesia to those who received neuraxial anesthesia. Our primary outcome examined 30-day composite outcome comprising of the following events: mortality, readmission, urinary tract infection, major adverse coronary event, stroke, deep venous thromboembolism, pulmonary embolism, acute renal failure, surgical site infection, and pneumonia. Secondary outcomes include intraoperative and post-anesthesia care unit (PACU) opioid use, PACU pain scores, PACU nausea and vomiting, and length of stay. Chi-square test, t-test, and Wilcoxon rank sum test were used to compare outcomes between general anesthesia patients to neuraxial anesthesia patients and logistic regression was used to calculate unadjusted odds ratios.

RESULTS: Of the 13,019 surgeries (11,199 Knee, 1820 Hip), 1,679 (12.9%) received a general anesthetic and 11,340 (87.1%) received a neuraxial anesthetic (Table 1). Composite outcome for neuraxial anesthesia (6.6%) compared to general anesthesia (5.6%) was not statistically significant (OR 0.84, 95% CI 0.68 - 1.04, p = 0.1). Of the individual outcomes, neuraxial anesthesia had a statistically significant decrease rate and OR for major adverse coronary event (0.2% vs 0.6%, OR 0.4, 95% CI 0.19-0.82, p = 0.01) and acute renal failure (0.6% vs 1%, OR 0.58, 95% CI 0.34-0.99, p = 0.04) (Table 2). Neuraxial anesthesia showed a significant reduction in intraoperative and PACU administered opioid, PACU pain scores, nausea and vomiting, and an increase in PACU length of stay (Table 3).

CONCLUSION: Although our primary end point of composite outcomes was not significant, our study shows that neuraxial anesthesia for patients undergoing outpatient unilateral primary total hip or knee arthroplasty was associated with a reduction in 30-day postoperative major adverse coronary events and acute renal failure. Furthermore, neuraxial anesthesia when compared to general anesthesia was associated with a reduction in administered opioids on the day of surgery, lower postoperative pain scores and postoperative nausea and vomiting in the PACU. Our study adds to the existing literature of the benefits and positive modifying effects of neuraxial anesthesia compared to general anesthesia for the same day discharge total joint arthroplasty patient population. Despite a longer recovery room time, the clinical benefits of neuraxial anesthesia are better than general anesthesia for this patient population. Even with the selection of healthier patients and improvements using multimodal analgesia and anesthesia, neuraxial anesthesia showed clinically significant decrease in worse outcomes. These findings highlight the benefits of neuraxial anesthetics in providing preventive analgesia[5] and may play a role in the reduction in cardiovascular and renal injury by decreasing the sympathetic neuroendocrine response following surgical stimuli and pain associated with surgery[6].

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Table 1. Patient demographics

Characteristic		**Anesthesia Type**	
	Overall	**General**	**Neuraxial**
	N = 13019 (100%)	**N = 1679 (12.9%)**	**N = 11340 (87.1%)**
	N (%)	**N (%)**	**N (%)**
Age (Mean, SD)	68.0 (8.8)	67.3 (9.1)	68.1 (8.8)
Sex			
Male	5192 (39.9%)	670 (12.9%)	4522 (87.1%)
Female	7827 (60.1%)	1009 (12.9%)	6818 (87.1%)
Race/Ethnicity			
Non-Hispanic White	8858 (68.0%)	1120 (12.6%)	7738 (87.4%)
Asian	1042 (8.0%)	73 (7.0%)	969 (93.0%)
Black	821 (6.3%)	157 (19.1%)	664 (80.9%)
Hispanic	1717 (13.2%)	258 (15.0%)	1459 (85.0%)
Other	581 (4.5%)	71 (12.2%)	510 (87.8%)
BMI			
Normal	1917 (14.7%)	191 (10.0%)	1726 (90.0%)
Overweight	4421 (34.0%)	525 (11.9%)	3896 (88.1%)
Obese	6680 (51.3%)	963 (14.4%)	5717 (85.6%)
ASA			
I	188 (1.4%)	8 (4.3%)	180 (95.7%)
II	7751 (59.5%)	762 (9.8%)	6989 (90.2%)
III	4986 (38.3%)	871 (17.5%)	4115 (82.5%)
IV	94 (0.7%)	38 (40.4%)	56 (59.6%)
Type			
Knee	11199 (86.0%)	1370 (12.2%)	309 (17.0%)
Hip	1820 (14.0%)	9829 (87.8%)	1511 (83.0%)
Laterality			
Left	6223 (47.8%)	804 (12.9%)	5419 (87.1%)
Right	6796 (52.2%)	875 (12.9%)	5921 (87.1%)

Table 2. 30-day post-operative outcomes. (*) statistically significant

Postoperative Outcome	Anesthesia Type					
	General		Neuraxial			
	N = 1679 (12.9%)		N = 11340 (87.1%)			
	N	%	N	%	OR (95% CI)	p-value
Mortality	3	0.2	16	0.1	0.79 (0.23-2.71)	0.71
Readmission	50	3.0	265	2.3	0.78 (0.57-1.06)	0.11
Surgical Site Infection	26	1.6	155	1.4	0.88 (0.58-1.34)	0.55
Pneumonia	10	0.6	49	0.4	0.72 (0.37-1.43)	0.35
Urinary Tract Infection	31	1.9	182	1.6	0.87 (0.59-1.27)	0.47
Major Coronary Event	10	0.6	27	0.2	0.40 (0.19-0.82)	0.01*
DVT/PE	17	1.0	100	0.9	0.87 (0.52-1.46)	0.6
Cerebrovascular Event	1	0.1	17	0.2	2.52 (0.33-18.92)	0.37
Acute Renal Failure (stage 1)	17	1.0	67	0.6	0.58 (0.34-0.99)	0.04*
Composite Outcome	111	6.6	637	5.6	0.84 (0.68-1.04)	0.10

Table 3. Intraoperative and Recovery Room Outcomes

Postoperative Outcome	Anesthesia Type				p-value
	General		Neuraxial		
	N = 1679 (12.9%)		N = 11340 (87.1%)		
	N	%	N	%	
Intraoperative Opioid (Morphine Equivalence in mg), Median (Q1-Q3)	50	30-75	30	15-30	<0.01
Length of PACU Stay	135	89-221	189	112-277	<0.01
PACU Nausea and Vomiting	72	4.3	337	3.0	0.01
PACU Pain Scores (Maximum on NRS 0-10), Median (Q1-Q3)	7	5-8	5	2-7	<0.01
PACU Pain Scores (Minimum on NRS 0-10), Median (Q1-Q3)	0	0-0	0	0-0	<0.01
PACU Pain Scores (Average on NRS 0-10), Median (Q1-Q3)	2.5	1.8-3.2	1.6	1.1-2.4	<0.01
PACU Opioid Usage (Morphine Equivalence in mg), Median (Q1-Q3)	38	19.3-65.0	15	7.5-41.3	<0.01

PERIOPERATIVE ANESTHESIA 9

Postoperative Complications Associated with Differing Neuromuscular Blockade Reversal

Selby Johnson[1], Michael L Kent[2], Tetsu Ohnuma[3], Vijay Krishnamoorthy[3], Karthik Raghunathan[1]

[1]Duke University School of Medicine, Durham, NC, [2]Duke University Medical Center, Durham, NC, [3]Duke University, Durham, NC

INTRODUCTION: Residual neuromuscular blockade remains a significant risk factor for postoperative complications.[1] Recently, a large observational matched-cohort study of inpatient surgeries demonstrated that use of Sugammadex resulted in a significant decrease in postoperative pulmonary complications.[2] However, there is little evidence regarding the use of Sugammadex in outpatient surgery. Therefore, we sought to examine the association between utilization of Sugammadex (versus Neostigmine) for NMBA reversal and Discharge Disposition (discharge to home: primary outcome) and Complications (anaphylaxis and postoperative pulmonary complications: secondary outcome) after laparoscopic cholecystectomy.

METHODS: In this retrospective observational cohort study, the US nationwide all-payer Premier Healthcare database (Premier Inc., USA) from 2016 to 2018 was queried for the International Classification of Diseases, Ninth Revision (ICD-9) and tenth (ICD-10) procedure codes for laparascopic cholecystectomy. Inclusion criteria consisted of patients undergoing laparascopic cholecystectomy with a same day surgery designation, receipt of rocuronium or vecuronium, reversal with either neostigmine or Sugammadex. Patients less than 18 years of ages were excluded along with hospitals without Sugammadex charges, and patients that received both neostigmine and Sugammadex. We examined patterns of use of Sugammadex use over time and Institutional variation in use (Figures 1 and 2). We compared baseline characteristics as well as outcomes in patients who had received either neostigmine vs Sugammadex. Statistical significance was determined using Chi Square or Kruskall Wallis tests as appropriate.

RESULTS: Our study cohort consisted of 32,789 adults who had undergone laparoscopic cholecystectomy with a 'same day surgery' designation between 2016 and 2018, and who were admitted from home, receiving either rocuronium or vecuronium, and receiving either Sugammadex (n=6736) or Neostigmine (n=26,503). The use of Sugammadex increased markedly over the study period and by Q1 2018, Sugammadex was utilized by 40% of institutions. 99.7% of patients receiving Sugammadex vs 98.6% receiving neostigmine were discharged to home ($p< 0.0001$). The need for postoperative mechanical ventilation was significantly great in the neostigmine group ($p=0.035$) but no differences were observed for non invasive ventilation and anaphylaxis.

CONCLUSION: In 32,789 patients undergoing Lap Chole in a Same Day Surgery setting, utilization of Sugammadex increased significantly reaching 40% of institutions in 2018. Patients who received Sugammadex had higher rates of discharge to home versus Patients who received Neostigmine. There were no differences in PPCs or readmissions. Given the baseline differences between the two groups, risk-adjusted studies are needed to draw further inferences regarding the impact of type of NMBA reversal on important outcomes after Same Day Surgery.

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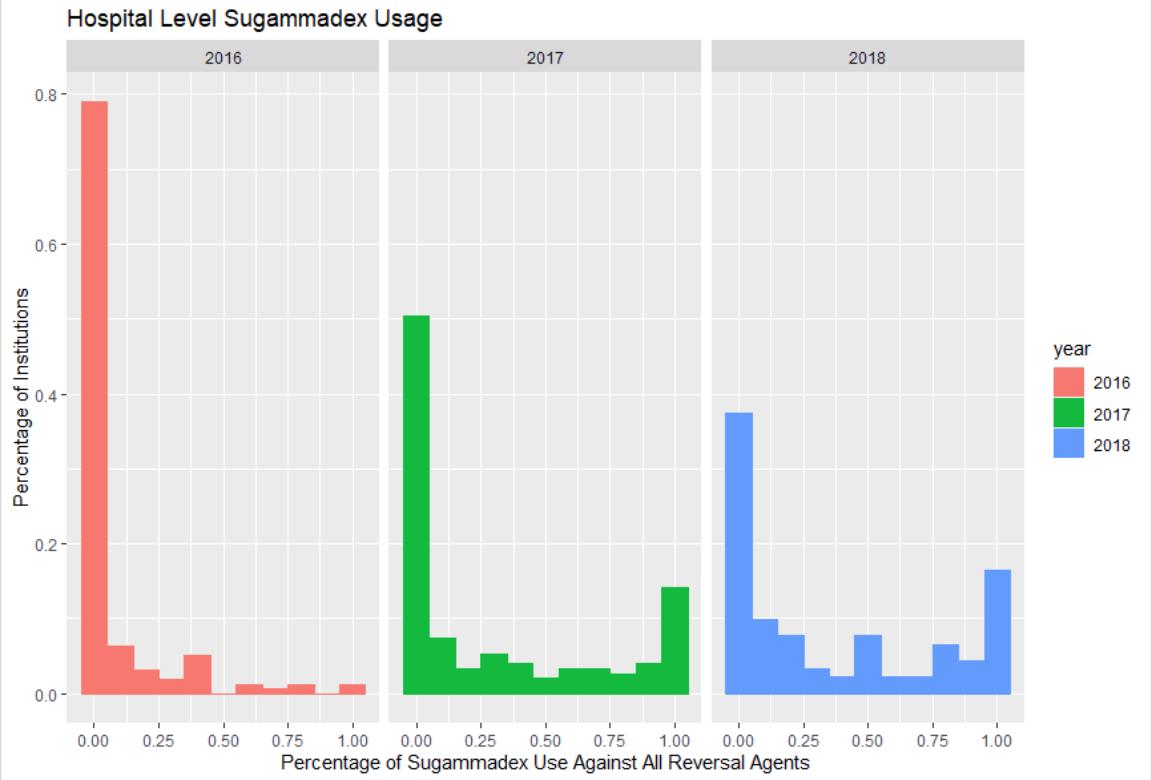

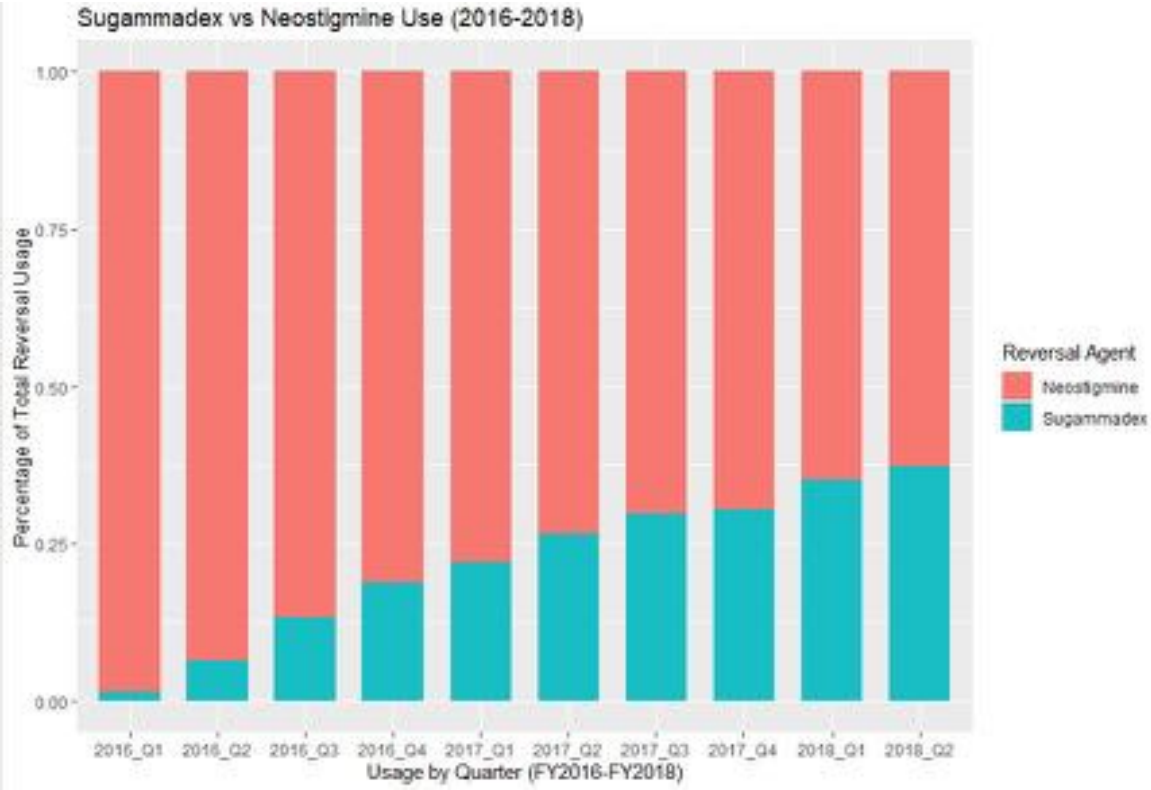

PERIOPERATIVE ANESTHESIA 10

Intraoperative hypotension before critical care admission is common but not associated with in hospital mortality in non-cardiac surgery

Rishi Patel[1], Natasha Palamuttam[2], YoungGeun Choi[3], Michael Diamreyan[1], Simon Liu[1], Seong Jae Park[1], Sebastian Salazar[1], Lee Goeddel[4]

[1]Johns Hopkins, Baltimore, United States of America, [2]Johns Hopkins School of Medicine, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD, [4]Johns Hopkins Hospital, Baltimore, MD

INTRODUCTION: At the time of ICU admission after non cardiac surgery, it is not always possible to predict which patients will further decompensate. Since intraoperative hypotension has been associated with acute kidney injury, myocardial injury and 30 day mortality, many advocate looking at intraoperative hypotension at time of ICU admission to project future clinical course. Previous analysis has quantified intraoperative hypotension by time weighted average under different blood pressure thresholds and absolute time under certain thresholds. No study has evaluated a population of exclusively ICU patients. We sought to first quantify the magnitude and time below different blood thresholds in patients requiring critical care after non cardiac surgery and then explore the association between these data and in-hospital mortality.

METHODS: We identified a retrospective cohort of 10,014 elevated risk non cardiac surgery patients cared for at Johns Hopkins hospital from July 2016 to October 2018 (Table 1). All patients that had an ICU stay after their surgery were included. Exclusion criteria included availability of discharge date, more than one surgery, insufficient data recorded for blood pressure measurements taken from the arterial line, and ASA physical status V (Figure 1). 3991 intraoperative records were included in analysis. Derived feature calculation: Area under and over time-weighted average curve of MAP were calculated for each patient episode. In particular, total area of the curve and the area between the set baseline and the curve were calculated. Example time-weighted average curves of MAP are shown in Figure 2. Main outcome: In hospital mortality. Statistical Analysis: Mann Whitney analysis comparing the mean values for Area under MAP threshold and time weighted area under MAP threshold between the alive versus deceased group. Data analysis and representation were performed using Python Libraries of Pandas, Numpy, and Scipy.

RESULTS: Intraoperative hypotension ranging from MAP 45 to 65 mmHg and hypertension ranging from MAP 70 to 90 mmHg for multiple cumulative duration in minutes was common. There was no association with intraoperative hypotension or hypertension with in-hospital mortality (Figures 3 and 4).

CONCLUSION: Despite previous literature associating periods of hypotension below MAP thresholds of 50 to 65 mmHg and kidney and myocardial injury, we saw no association with in-hospital mortality in a population of surgical patients requiring post-operative critical care. Upon ICU admission, looking at the time below target threshold and magnitude below threshold likely does not reveal clinically useful information about the risk of in-hospital mortality. Our next steps are to examine other pertinent patient centered outcomes such as length of stay and cardiac and renal injury as they relate to intraoperative blood pressure management. One of our study's strengths is exploring multiple MAP thresholds instead of one single cut-off threshold to define intraoperative hypotension/hypertension. Both additional severity (area under MAP threshold) and averaged (time- weighted average under MAP threshold) characterizations were comparable with our main characterization of duration below the threshold. Several limitations were present in this study. First, the data was measured in one university hospital limiting generalizability. Second, some blood pressure recordings were accepted by clinical judgment. Third, we did not account for intravenous fluids, volatile anesthesia, inotropes, and vasopressors, which have a substantial contribution to intraoperative hypotension, though this is dependent on the institution's protocols and anesthetists' preferences. These variables may have been sources of confounding.

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Intraoperative blood pressure variability predicts postoperative mortality in non-cardiac surgery—A prospective observational cohort study.International Journal of Environmental Research and Public Health,16(22). https://doi.org/10.3390/ijerph16224380

Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: A retrospective cohort analysis. Anesthesiology 2017; 126:47–65.

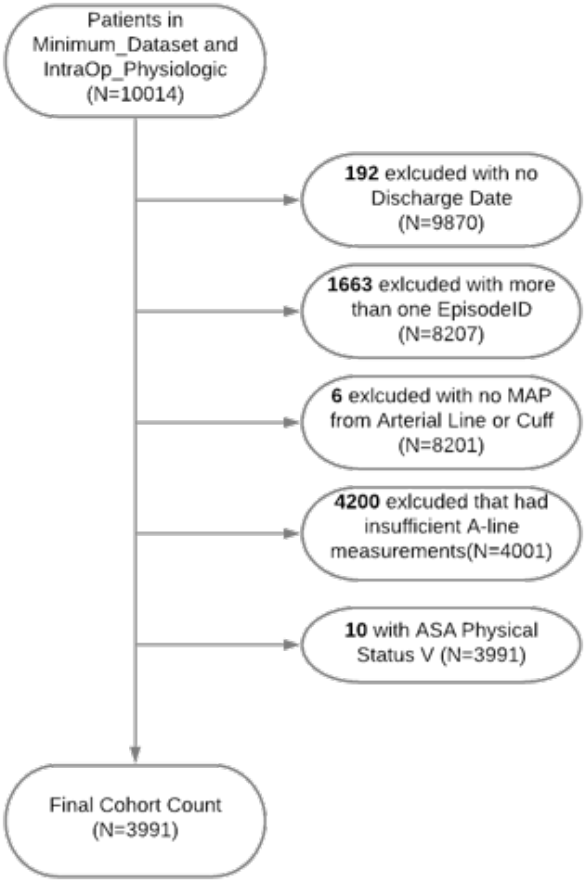

Figure 1. Data Preprocessing – Application of Exclusion Criteria

		Missing	Overall	Alive	Deceased	P-Value	Grouped by Status Test
n			8201	7758	367		
Age, mean (SD)		0	58.3 (15.6)	58.1 (15.7)	62.6 (14.8)	<0.001	Two Sample T-test
Gender, n (%)	F	0	2961 (48.3)	2771 (48.6)	155 (42.2)	0.020	Chi-squared
	M		4240 (51.7)	3987 (51.4)	212 (57.8)		
FirstRace, n (%)	Declined to Answer	0	6 (0.1)	5 (0.1)	1 (0.3)	<0.001	Chi-squared (warning: expected count < 5)
	Non-White		2476 (30.2)	2332 (30.1)	120 (32.7)		
	Unknown		42 (0.5)	32 (0.4)	10 (2.7)		
	White or Caucasian		5677 (69.2)	5389 (69.5)	236 (64.3)		
BMI, mean (SD)		71	29.0 (7.4)	29.0 (7.5)	27.6 (6.4)	<0.001	Two Sample T-test
LOS, mean (SD)		0	7.6 (8.4)	7.4 (7.1)	12.3 (22.4)	<0.001	Two Sample T-test
ASA_PhysicalStatus, n (%)	I	0	71 (0.9)	69 (0.9)	2 (0.5)	<0.001	Chi-squared (warning: expected count < 5)
	II		1964 (23.9)	1915 (24.7)	33 (9.0)		
	III		4882 (59.5)	4638 (59.8)	191 (52.0)		
	IV		1167 (14.2)	1051 (13.5)	109 (29.7)		
	Unknown		75 (0.9)	69 (0.9)	6 (1.6)		
	V		32 (0.4)	16 (0.2)	16 (4.4)		
	VI		10 (0.1)		10 (2.7)		
SmokingStatus, n (%)	Never Smoker	0	4315 (52.6)	4113 (53.0)	163 (44.4)	<0.001	Chi-squared (warning: expected count < 5)
	Smoker		3797 (46.3)	3589 (46.3)	171 (46.6)		
	Unknown		89 (1.1)	56 (0.7)	33 (9.0)		

Table 1. Characteristics of Study Population

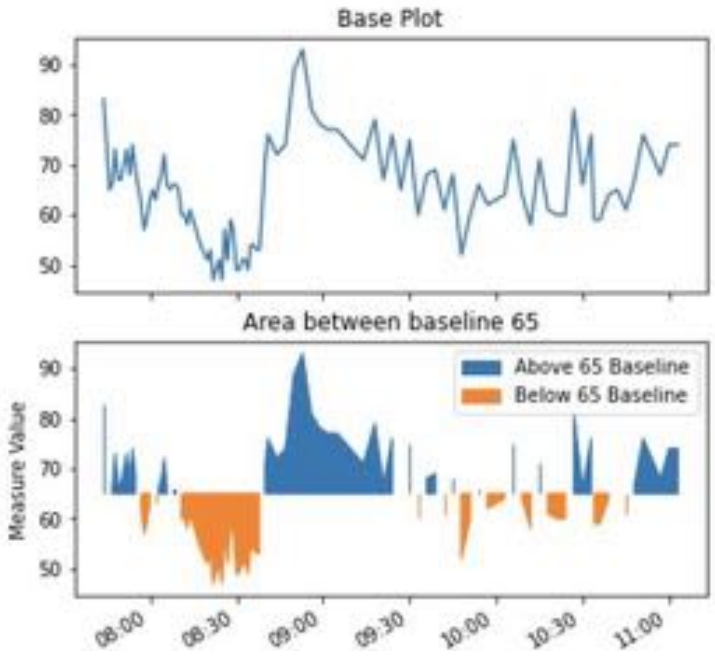

Figure 2. Sample time-weighted average curve of MAP from a single episode. Base plot shows a regular time-weighted average curve, and the second graph shows the curve separated by 65mmHg 'normal' line.

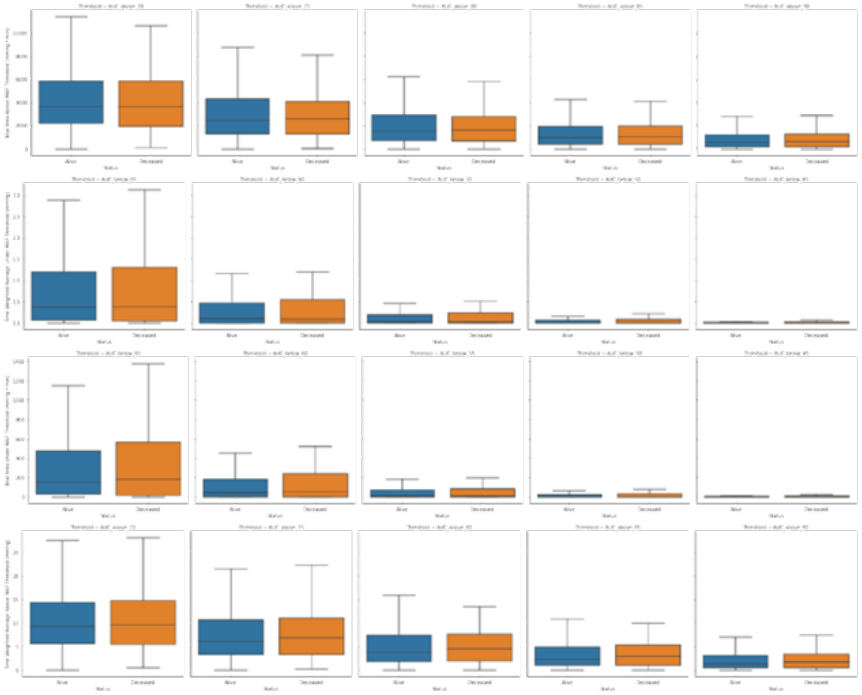

Figure 3. Association of Intraoperative Hypotension and Hypertension, as Total Area and TWA-MAP Under/Above multiple MAP Thresholds, and In-hospital Mortality

Threshold	Status	median_TWA-MAP	P-value	mean_TWA-MAP	P-value	median_Total Area	P-value	mean_Total Area	P-value
AUC_below_45	Alive	0	0.290494526	0.133832869	0.145258806	0	0.289110743	53.85461863	0.144566878
AUC_below_45	Deceased	0		0.271495987		0		72.26610644	
AUC_below_50	Alive	0	0.884654592	0.172135876	0.442345408	0	0.864264872	69.22159091	0.432150474
AUC_below_50	Deceased	0		0.340939428		0		95.86554622	
AUC_below_55	Alive	0.017857499	0.533592277	0.255072891	0.266809932	7.333333333	0.450355909	102.5815685	0.225190548
AUC_below_55	Deceased	0.014984227		0.463305472		7.333333333		141.7654062	
AUC_below_60	Alive	0.09829946	0.654508326	0.435896714	0.327268895	41.25	0.545220713	176.2959496	0.272623917
AUC_below_60	Deceased	0.092032967		0.699212271		54		236.67507	
AUC_below_65	Alive	0.363169046	0.80270397	0.86768939	0.401367621	150.9166667	0.712600995	355.7773545	0.356315571
AUC_below_65	Deceased	0.380487805		1.171243892		180.8333333		438.2044818	
AUC_above_70	Alive	9.234127471	0.621338935	10.58400863	0.310683729	3659.416667	0.645552734	4412.686682	0.322790861
AUC_above_70	Deceased	9.657330567		11.07202664		3648.333333		4125.144258	
AUC_above_75	Alive	6.148689884	0.508439009	7.658800205	0.254232452	2464.416667	0.837101826	3174.231233	0.418566687
AUC_above_75	Deceased	6.854090354		8.152991082		2605.333333		2977.07493	
AUC_above_80	Alive	3.838341397	0.389985713	5.329021514	0.195003991	1558.666667	0.933601036	2193.380811	0.466816574
AUC_above_80	Deceased	4.546747967		5.792715839		1624.666667		2072.654762	
AUC_above_85	Alive	2.312651563	0.326293386	3.616160951	0.163156645	957.3333333	0.760404182	1478.589704	0.38021747
AUC_above_85	Deceased	2.942879499		4.011173009		1048.333333		1408.238095	
AUC_above_90	Alive	1.327669388	0.28442603	2.377060626	0.1422221	542.6666667	0.645287238	966.784629	0.322658111
AUC_above_90	Deceased	1.662170841		2.710213506		655.3333333		933.2815126	

Table 2. Association of Mean and Median Intraoperative Hypotension and Hypertension, as Total Area and TWA-MAP Under/Above multiple MAP Thresholds, and In-hospital Mortality

PERIOPERATIVE ANESTHESIA 11

Mortality and costs associated with postoperative acute kidney injury in elective, non-cardiac surgery

William B French[1], Pranav Shah[1], Yahya Fatani[1], Megan Rashid[1], Spencer Liebman[1], Brian Cocchiola[1], Kenneth Potter[1], Salem Rustom[1], Michael Scott[1]

[1]Virginia Commonwealth University, Richmond, VA

INTRODUCTION: Acute Kidney Injury (AKI) is a common postoperative complication and is associated with increased mortality and costs[1]. Perioperative hemodynamic management is under the control of the anesthesiologist. As fluid resuscitation and perioperative hypotension are associated with the development of postoperative AKI, the anesthesia provider plays a critical role in efforts to reduce its incidence[2,3]. Studies have suggested that AKI may be associated with long-term mortality and renal dysfunction in certain surgical populations[4–6]. However there is little published data on the long-term effects of smaller changes in perioperative renal function, which meet the definition of lower stages of AKI. Older studies are limited by variable patient populations, lack of long-term outcomes, and varying definitions of AKI. To better understand the significance of postoperative AKI, at our institution we evaluated the effect of AKI by stage on postoperative length of stay (LOS), costs, in-hospital mortality, and 1-year mortality in elective, non-cardiac surgical patients.

METHODS: This study was a retrospective analysis of patients undergoing elective, non-cardiac surgery at our institution from January 2015 to May 2020 with a postoperative LOS of at least 24 hours. Patient data was extracted electronically from medical and surgical records at our institution. Urological procedures, nephrectomies, organ transplants, and patients with preoperative end stage renal disease were excluded. Postoperative AKI was staged using the Kidney Disease Improving Global Outcomes (KDIGO) definitions[7]. Baseline creatinine was defined as the preoperative creatinine closest to the time of surgery that was also within 30 days of surgery. Creatinine values through postoperative day 7 were used for AKI analysis. Data on in-hospital mortality, postoperative LOS, and total costs of the surgical hospitalization were collected for each patient using hospital records. To determine 1-year mortality, we utilized data from the United States Social Security Administration's death master file and the Virginia Department of Health in addition to our institutional records. Patients were excluded from 1-year mortality analysis if they underwent surgery after June 1st, 2019 to align with our most recent mortality data update. Linear and logistic regression models were created to determine the independent effect of the stage of postoperative AKI on patient outcomes.

RESULTS: We identified 8887 patients for analysis. Of these 6729 patients met criteria for 1-year mortality analysis based on their date of surgery. Of all patients, 648 (7.29%) had postoperative AKI. All stages of AKI were associated with a severity-dependent increase in LOS, cost of the surgical admission, in-hospital mortality, and 1-year mortality (Table 1). Mean total costs of the surgical hospitalization were $23,896 (SD $23,736) for patients without AKI compared to $33,042 (SD $27,115), $39,133 (SD $34,006), and $73,216 ($82,290) for patients with stage 1, 2, and 3 AKI, respectively ($p<0.001$). Patients with AKI had rates of in-hospital mortality of 2.0%, 3.8%, and 12.5% for stage 1, 2, and 3 AKI compared to 0.3% for patients without AKI ($p<0.001$). AKI patients also had 1-year mortality rates of 13.9%, 19.4%, and 22.7% compared to 5.2% for patients without AKI ($p<0.001$). Similar patterns were identified after adjusting for confounding variables in multivariate analysis (Table 2). In these models, stage 1 AKI patients still had a higher probability of 1-year mortality (OR 1.88, 95% CI 1.323-2.627, $p<0.001$) in addition to $4391 of additional costs when compared to patients without AKI (95% CI 2497.98-6285.09, $p<0.001$).

CONCLUSION: In this retrospective study of 8887 patients undergoing elective, non-cardiac surgery, all stages of postoperative AKI were associated with longer LOS, higher costs, and higher rates of in-hospital and 1-year mortality. These findings showed that patients with even a lower-grade, stage 1 AKI had a long-term reduction in survival. Efforts at perioperative quality improvement and cost reduction should likely target surgical populations with a high prevalence of postoperative AKI.

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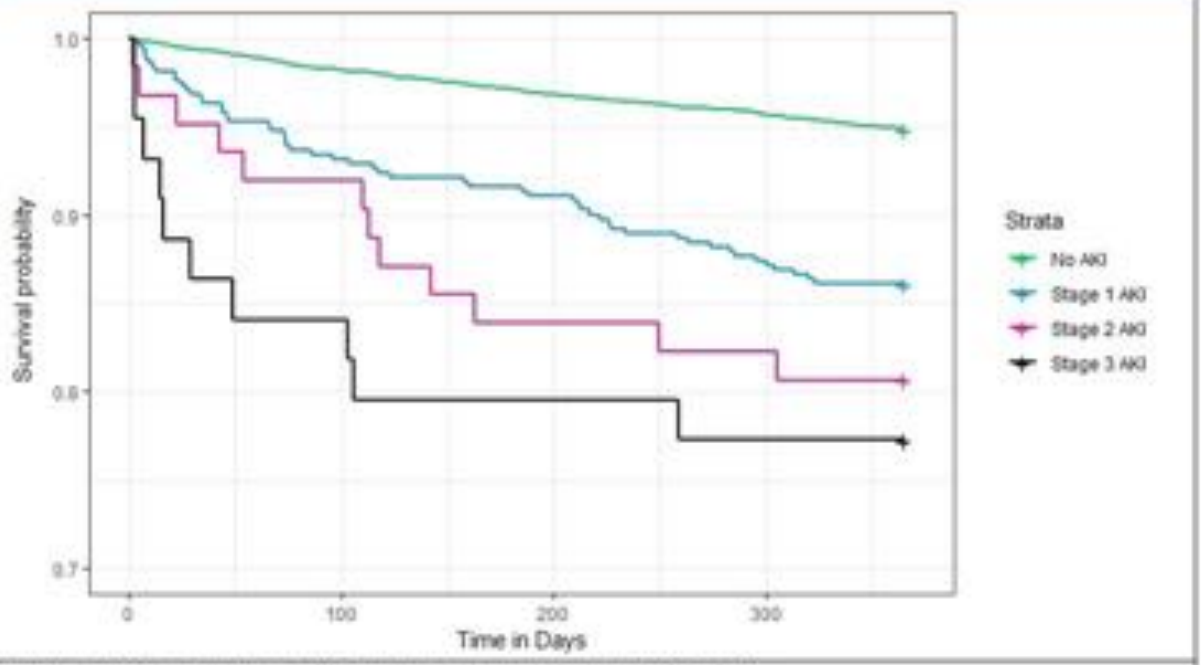
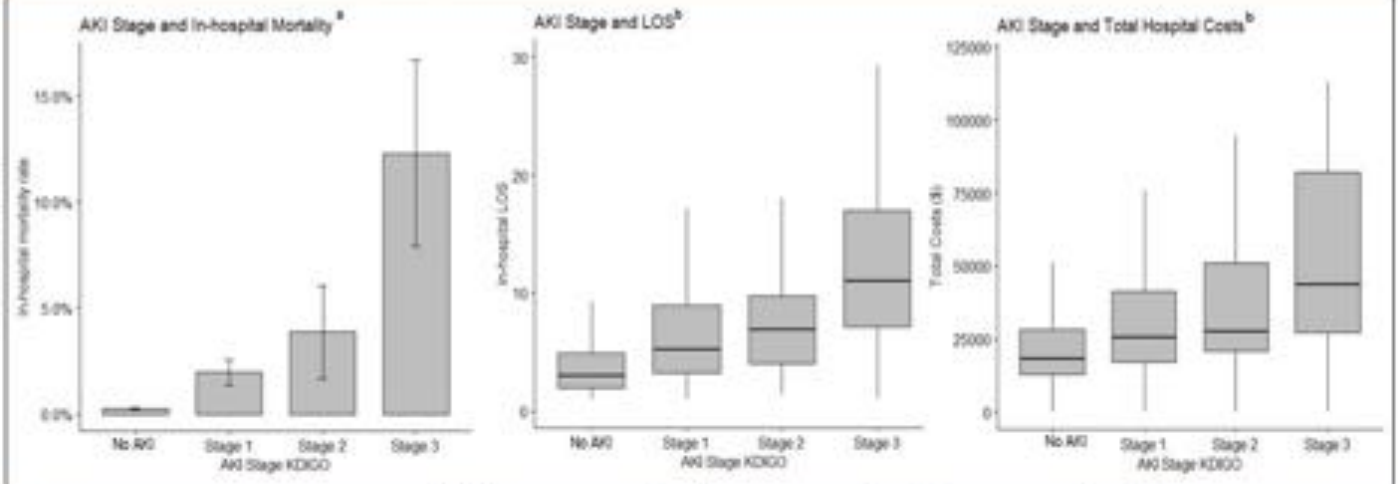
Figure 1. Unadjusted survival curve for 1-year mortality following surgery, displayed by severity of postoperative AKI



Includes 6729 patients undergoing elective non-cardiac surgery. Log rank P < 0.001.

Table 1. Severity of postoperative AKI and patient outcomes



Variable	No AKI [n=8239]	Stage 1 [n=513]	Stage 2 [n=78]	Stage 3 [n=57]	P value
Inpatient Mortality - no. (%)	24 (0.3)	11 (2.0)	3 (3.8)	8 (12.5)	<0.001
Median Postoperative LOS (IQR) - days	3.0 (2.0, 5.0)	5.2 (3.2, 8.9)	6.9 (3.2, 7.4)	11.0 (7.3, 17.2)	<0.001
Mean Total Costs (SD)	$23,896 ($23,736)	$33,042 ($27,115)	$39,133 ($34,006)	$73,216 ($82,290)	<0.001
Median Total Costs (IQR)	$18,174 ($12,780-$28,101)	$25,525 ($17072-$41,111)	$27,679 ($20,767-$50,811)	$43,428 ($27,165-$82,091)	<0.001
1-year Mortality - no. (%)[c]	325 (5.2)	53 (13.9)	12 (19.4)	10 (22.7)	<0.001

Abbreviations: AKI - Acute Kidney Injury, LOS - Length of Stay
[a]Bar plot displays in-hospital mortality rate with standard error.
[b]Box plots display median and IQR. Whiskers extend to 1.5 times the IQR from the 1st and 3rd quartiles.
[c]1-year mortality analysis performed for cases prior to June 1st, 2019, n = 6242, 381, 62, 44 for no AKI and stages 1, 2, and 3, respectively.

Table 2. Adjusted models for inpatient mortality, 1-year mortality, postoperative LOS, and total costs associated with severity of postoperative AKI

	Postoperative LOS[a]			Inpatient Mortality[b]			1-year Mortality[b]			Total Costs[a]		
	Additional days[c]	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	Additional costs[c]	95% CI	P value
Stage 1 AKI vs No AKI	2	(1.5, 2.5)	<0.0001	5.5	(2.3, 12.5)	0.0002	1.9	(1.3, 2.6)	0.0006	$4,391	($2,498, $6,285)	<0.0001
Stage 2 AKI vs No AKI	2.6	(1.5, 3.7)	<0.0001	10.9	(2.3, 36.2)	0.0048	2.4	(1.1, 4.7)	0.0218	$6,759	($2,054, $11,423)	0.0048
Stage 3 AKI vs No AKI	10.1	(8.8, 11.5)	<0.0001	13.9	(4.0, 42.8)	0.0001	2.3	(0.96, 5.1)	0.0607	$41,493	($36,004, $46,983)	<0.0001

[a] Adjusted linear regression models for LOS and Total costs.
[b] Adjusted logistic regression models for inpatient and 1-year mortality.
[c] Linear regression estimates, interpreted as the additional hospital days and dollar cost amount associated with the variable listed for the patient's hospitalization for surgery.

PERIOPERATIVE ANESTHESIA 12

A model to predict level of prehabilitation adherence in older adults with frailty having cancer surgery

Julia F Shaw[1], E Hladkowicz[1], Colin McCartney[2], Gregory L Bryson[3], Daniel I McIsaac[2]

[1]Ottawa Hospital Research Institute, Ottawa, Canada, [2]University of Ottawa, Ottawa, Ontario, [3]The Ottawa Hospital, Ottawa, Ontario

INTRODUCTION: Frailty is a well-established predictor of adverse postoperative outcomes in older surgical patients and is especially common in older people having cancer surgery.[1–4] Early evidence suggests exercise could improve postoperative outcomes for people with frailty,[5] however little is known about how to predict older people's engagement in exercise before surgery (i.e., prehabilitation) programs. Our objective was to derive and validate a model to predict prehabilitation adherence in older adults living with frailty before cancer surgery.

METHODS: This was a nested prospective cohort study of older adults with frailty having cancer surgery who participated in a randomized controlled trial of home-based prehabilitation. The trial compared a home-based exercise prehabilitation program to standard perioperative care in people living with frailty undergoing elective intra-abdominal and intrathoracic cancer surgery at The Ottawa Hospital. We constructed a multivariable ordinary least squares linear regression model using pre-specified, prospectively collected covariates to predict adherence (% prescribed exercise sessions attempted). Our covariates (collected at baseline) were selected a priori based on clinical expertise and systematic review; they included age, sex, health-related quality of life, disability, frailty, previous physical activity, depression, and neoadjuvant therapy. Assumptions of normality were checked. Collinearity was assessed using variance inflation factor. All continuous variables were standardized and assessed for best fit using fractional polynomials. Optimism was estimated through internal validation using bootstrap validation. A sensitivity analysis was performed using multiple imputation to account for missing data.

RESULTS: Two hundred four participants were enrolled and randomized into the trial. The 102 participants in the intervention arm were included in this study's nested cohort. Four participants were excluded, 1 died, and 2 had missing data, leaving 95 participants in the derivation set. Percent adherence ranged from 0% to 100%, with a mean of 60.9% (SD 34.0%). Previous physical activity and age were the only predictors significant at the 5% level (Table 1). The final model explained 26.8% of the variance in adherence, had a root mean square error (RMSE) of 31.3, and an optimism of 24.3%. Results of the multiply imputed model did not differ substantively.

CONCLUSION: A multivariable model based on evidence-based predictors helps to explain a moderate degree of variation in prehabilitation adherence in older people with frailty; however, only two postulated factors were strong predictors individually. This model is an important first step toward personalizing prehabilitation support, but future research is needed to better understand predictors of prehabilitation adherence in older people with frailty.

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Table 1. Regression Coefficients (β) for Final Model

Variable	β (95%CI)	P-value
Intercept	57.49	<0.001
Age		
Age^1	-17.62	0.012
Age^2	3.50	0.244
Age^3	6.69	0.007
Female	-11.00	0.132
HRQoL	11.7	0.063
Disability	-3.07	0.559
Frailty score 4	Reference	
CFS 5	19.12	0.07
CFS 6	28.14	0.241
Physical activity	9.73	0.012
Depression		
$Depression^1$	11.07	0.112
$Depression^2$	2.17	0.725
$Depression^3$	-1.51	0.622
Neoadjuvant therapy (vs none)	3.45	0.719

PERIOPERATIVE ANESTHESIA 13

Feasibility of Blood Flow Restriction Exercise Prehabilitation to Attenuate Postoperative Loss of Function after Total Knee Replacement: A Randomized Pilot Study

Rene Przkora[1], Kimberly Sibille[1], Sandra Victor[1], Matthew Meroney[1], Christiaan Leeuwenburgh[2], Anna Gardner[1], Terrie Vasilopoulos[1], Hari K Parvataneni[1]

[1]University of Florida, Gainesville, FL, [2]University of Florida, Gainesville , FL

INTRODUCTION: Prehabilitation is an expanding tool in Anesthesiology to improve postoperative outcomes of patients undergoing major surgeries such as total knee arthroplasty (TKA). TKA is associated with significant morbidity and mortality[1,2]. Up to 20% of patients have reported dissatisfaction with postoperative outcomes[3,4,5]. A meta-analysis of studies evaluating lower limb strength for up to 3 years after TKA revealed decreased strength in multiple leg muscle groups after TKA compared to controls, despite routine physical therapy/rehabilitation in the first months after surgery[5]. Because knee replacement surgery is an elective surgery, interventions applied during the preoperative period are feasible. However, the available studies show mixed results[6,7,8]. Based on this dilemma, blood flow restriction (BFR) exercise may provide an alternative. The BFR exercise entails the concurrent application of a tourniquet on a limb during exercise. The BFR exercise has been shown to improve muscle mass in a shorter period of time and at a lower exercise intensity and it appears to be an attractive alternative for patients who cannot undergo a lengthy exercise program secondary to pain and a limited time schedule[9,10]. Based on these findings, we tested the feasibility of a low-resistance exercise protocol with blood flow restriction (BFR) in the preoperative period for patients awaiting TKA.

METHODS: Our pilot randomized control study was approved by the Institutional Review Board and participants provided written informed consent. Ten patients were included to study the feasibility of BFR exercise in the preoperative period in older patients undergoing unilateral TKA. Patients were randomized to undergo the BFR exercise ('BFR' group) 4 weeks prior to TKA or standard of care (no exercise, 'Control' group). After random assignment to the BFR exercise group and determination of the 1RM, participants engaged 2 days per week with at least 2 days apart in a center-based exercise intervention for 4 weeks. We tested the following parameters 4 to 5 weeks preoperatively and 2 weeks postoperatively: the Short Physical Performance Battery (SPPB), the 6-Minute Walk Test (6MWT), leg strength of the operative leg (peak torque knee extension), and pain score (numerical rating scale). Anesthetic and postoperative management was similar among patients; all surgeries were performed under a spinal anesthetic and regional anesthesia including a femoral nerve catheter and sciatic nerve single-injection regional anesthetic. Measures were summarized as means and standard deviations (± SD) for continuous measures and counts for categorical measures. Differences scores between baseline and follow-up were reported as mean differences with 95% confidence intervals (95%CI). To compare difference between groups, linear regression analyses were run with follow-up measurement as dependent variable and group and baseline measures as independent variables. By including baseline measurement as an independent variable, a 'residual change score' across time points was created; thus, an effect of group assignment would then be interpreted as an effect on the change from baseline to follow-up. $P < 0.05$ was considered statistically significant. All analyses were conducted in JMP Pro 15.0.

RESULTS: Ten patients were included in this study (total n=10; n=6 BFR exercise group, n=4 No exercise group). Table 1 reports baseline patient demographics, for full sample and stratified by group. The average age of patients was 67.2 and average BMI was 31.2. The majority of the sample were women and non-Hispanic, white. There were significant group differences in change for SPPB ($p = 0.011$, Figure 1). The BFR group, on average, showed less decline in SPPB following surgery (-2.2, 95%CI:-4.4,0.1) compared to no exercise group (-4.8, 95%CI:-7.8,-1.7). Group differences for SMW ($p = 0.626$), leg strength ($p=0.852$), and pain ($p=0.713$), did not achieve statistical significance.

CONCLUSION: Findings show that BFR exercise was feasible preoperatively and, more importantly, it was associated with significantly less decline in physical function measured by the SPPB when compared to the control group without any complications in patients undergoing a TKA. Additionally, and as anticipated, our findings suggest across all measurements a clinically significant decline in physical function following elective TKA, indicating the need for prehabilitation.

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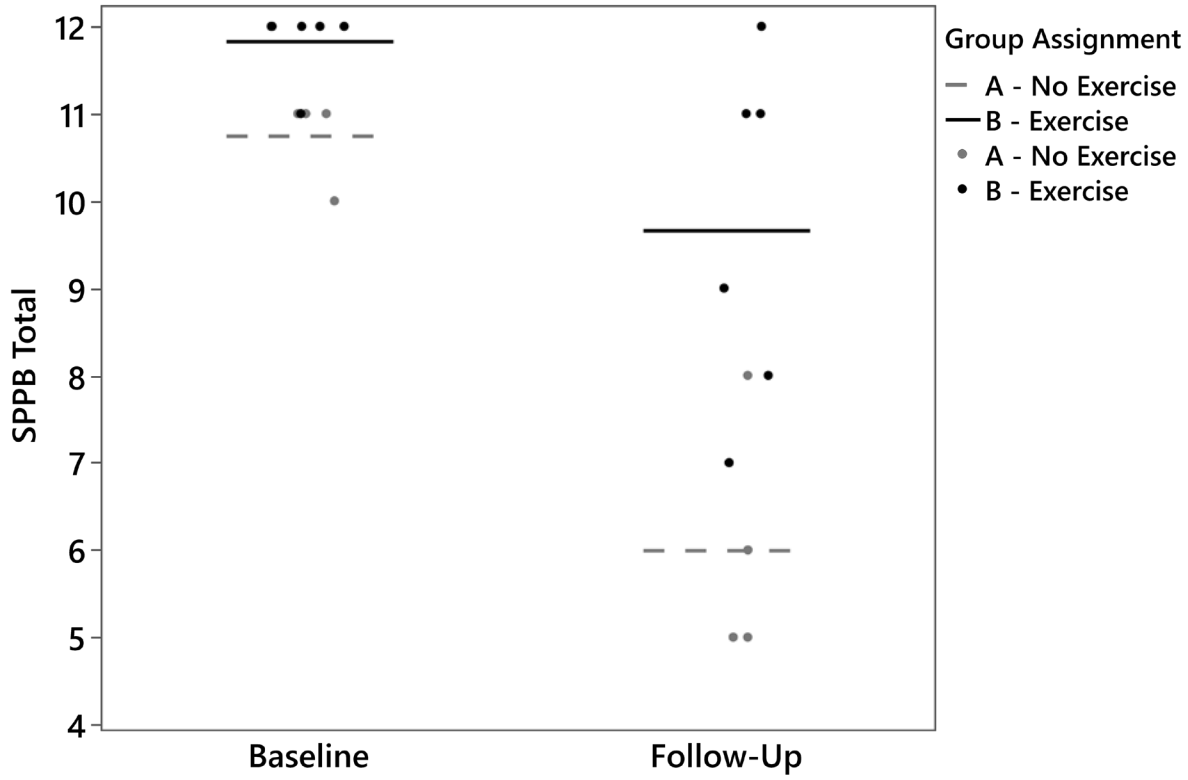

Figure 1. Short Physical Performance Battery (SPPB) scores at baseline to follow-up, stratified by group. Horizontal lines represent group means, dots represent individual patient values.

	Total Sample n=10	BFR Exercise n=6	No Exercise n=4
Age, mean year ± SD	67.2 ± 7.1	66.5 ± 9.0	68.3 ± 3.9
Gender, n for women	7/10	4/6	3/4
Ethnicity, n for non-Hispanic	9/10	6/6	3/4
Race, n for white	9/10	6/6	3/4
BMI, mean ± SD	31.2 ± 5.4	29.7 ± 4.7	33.3 ± 6.3

Table 1. Baseline patient demographics, for full sample and stratified by group.

PERIOPERATIVE ANESTHESIA 14

Natural Language Processing Predicts ASA Physical Status Classification from Pre-operative Note Text

Philip Chung[1], Christine T Fong[1], Vikas O'Reilly-Shah[2]

[1]University of Washington, Seattle, WA, [2]University of Washington, SEATTLE, WA

INTRODUCTION: Large studies have demonstrated the value of the American Society of Anesthesiologists Physical Status Classification System (ASA-PS) as an independent predictor of post-operative morbidity and mortality. Prediction of ASA-PS has value for a variety of reasons; prior approaches to this prediction task have used tabular data.[1,2] In the present work, we describe using neural natural language processing (NLP) to predict ASA-PS. Neural NLP combines linguistics, deep learning, and statistics in order to create numerical representations of text data, allowing for development of predictive models utilizing a sequence of words as input data. We hypothesized that text from the 'History of Present Illness' (HPI) section of the anesthesiology pre-operative evaluation note would predict the ASA-PS assigned by the anesthesiologist on day of surgery.

METHODS: Data was extracted from the electronic health record at the University of Washington Medical Center and affiliated hospitals and clinics. Inclusion criteria was all patients who had surgery from Jan 1, 2018 – Oct 31, 2019 who also had a pre-anesthesia preoperative evaluation note with a 'History of Present Illness' (HPI) section in the medical record prior to the surgery. We do not distinguish between emergent (presence of ASA-PS 'E' modifier) and non-emergent cases. The model was trained using transfer learning, starting with the Bio+Clinical BERT model and fine-tuned on our task by adding a linear classification layer to perform multi-class sequence classification.[3] Model performance was evaluated on validation and test sets by receiver operator characteristic (ROC) curve, area under ROC curve (AUC), precision-recall (PR) curve, and average precision for predicting each ASA-PS class as well as micro-average of all classes.

RESULTS: Our dataset is comprised of 28244 unique surgical procedurs, randomly split into a training set of 25392 samples (90%) and test set of 2852 samples (10%). The distribution of ASA-PS among patients is described in Figure 1. Given the rarity of ASA V and VI, these classes were merged with ASA IV forming a compound class 'ASA IV-VI'. To control for class imbalance, the training data was randomly resampled to boost minority classes and generate an augmented dataset with 12000 samples from each class (48000 total), which was again randomly split into training set of 38400 samples (80%) and validation set 9600 (20%). The model was trained for 150 epochs on the training set with batch size of 256, learning rate of 5 x 10-5 with AdamW optimizer, 10% dropout, and cross-entropy loss. Training and validation loss both decreased with number of training samples, suggesting that the model did not overfit on the training set. We achieve micro-averaged AUC of 0.96 on the validation set and 0.8 on the test set (Figure 2). Micro-averaged average precision is 0.90 on the validation set and 0.50 on the test set (Figure 3).

CONCLUSION: Our NLP model performs well on predicting ASA I & IV-VI with AUC 1.0 & 0.97 on the validation set and 0.9 & 0.81 on the test set, respectively. Model performance suffers particularly with patients assigned ASA II or ASA III, which suggests that the truncated HPI input may not always be descriptive enough to accurately categorize these patients. Additionally, ASA-PS has been shown to have moderate inter-rater reliability among anesthesiologists, and our NLP model may have difficulty accounting for inter-rater differences.[4] However, even when our model misclassifies ASA-PS, it typically only does so by one ASA-PS class (Figure 4). This suggests that the NLP model is able to correlate the presence of specific words and its contextual meaning in natural language to a patient's underlying perioperative risk. Additional investigation using explainable artificial intelligence techniques is needed to determine whether this is the case. Our results demonstrate that HPI text alone can predict ASA-PS well. We plan to include additional data in this prediction task as well to build on these results to predict additional elements of perioperative patient risk. The use of neural NLP for perioperative risk stratification based on naturally acquired medical language appears to be promising.

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ASA Physical Status	Training Set	Test Set
I	1992 (7.8%)	224 (7.8%)
II	7824 (30.8%)	884 (31.0%)
III	11438 (45.0%)	1288 (45.2%)
IV	3953 (15.6%)	446 (15.6%)
V	166 (0.7%)	10 (0.4%)
VI	19 (0.1%)	0 (0%)
Total	**25392**	**2852**

Figure 1: Distribution of ASA Classes in training and test dataset prior to data augmentation.

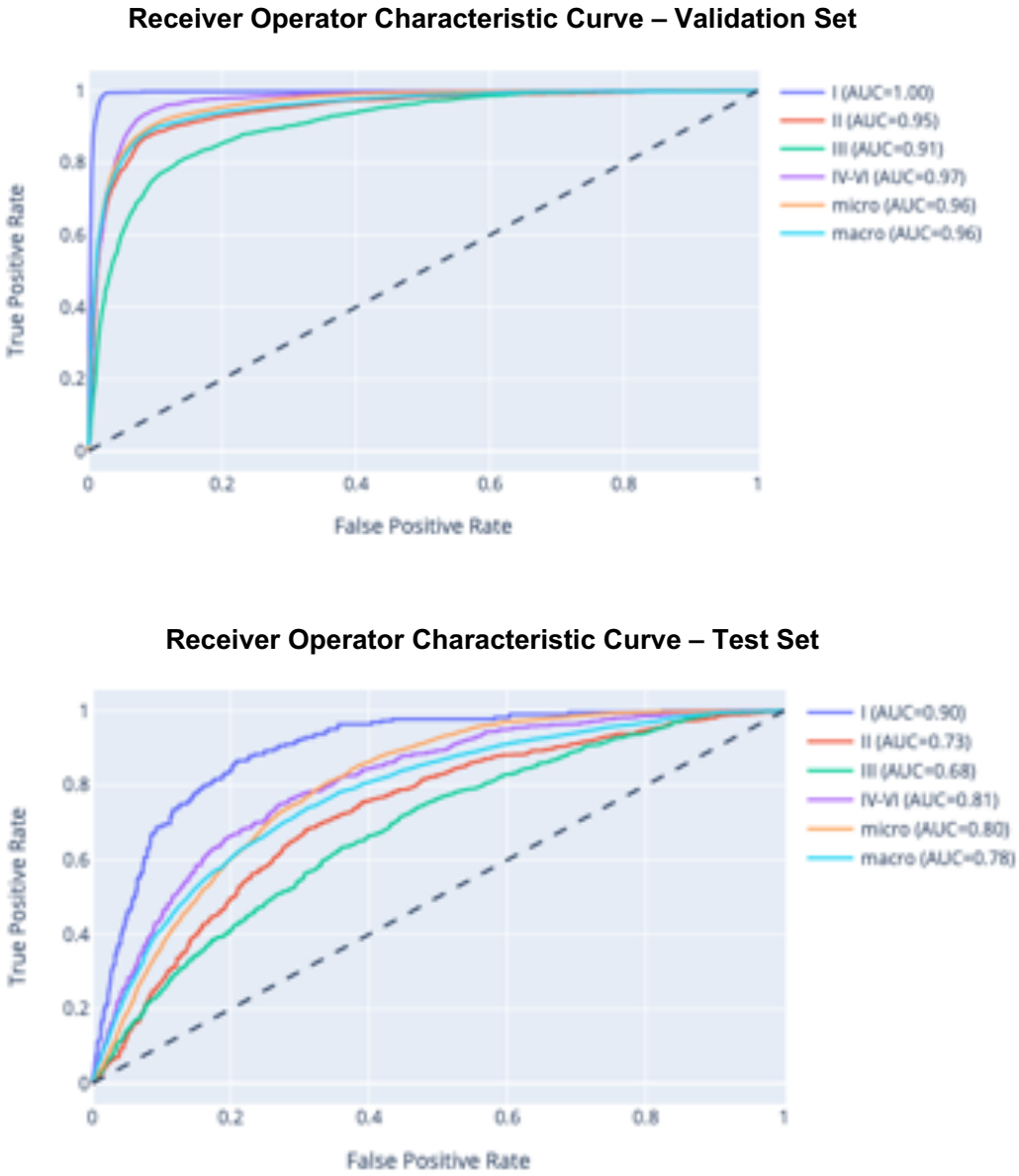
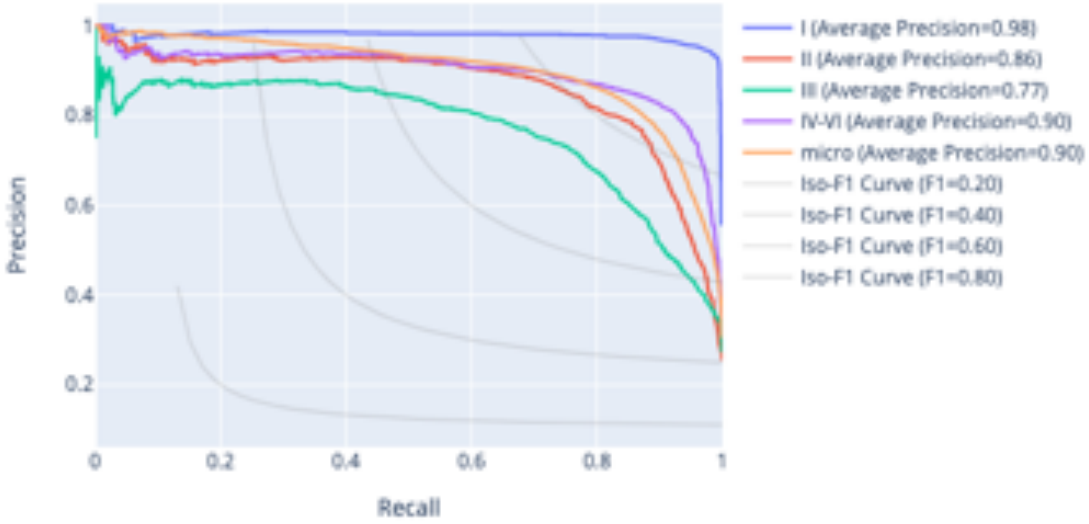


Figure 2: Receiver operator characteristic (ROC) curve for predicting each ASA-PS category in the validation set and test set. Also plotted is the micro-average and macro-average ROC across all classes. Area under ROC curve (AUC) is noted in the legend next to each class.

Precision-Recall Curve – Validation Set



Precision-Recall Curve – Test Set

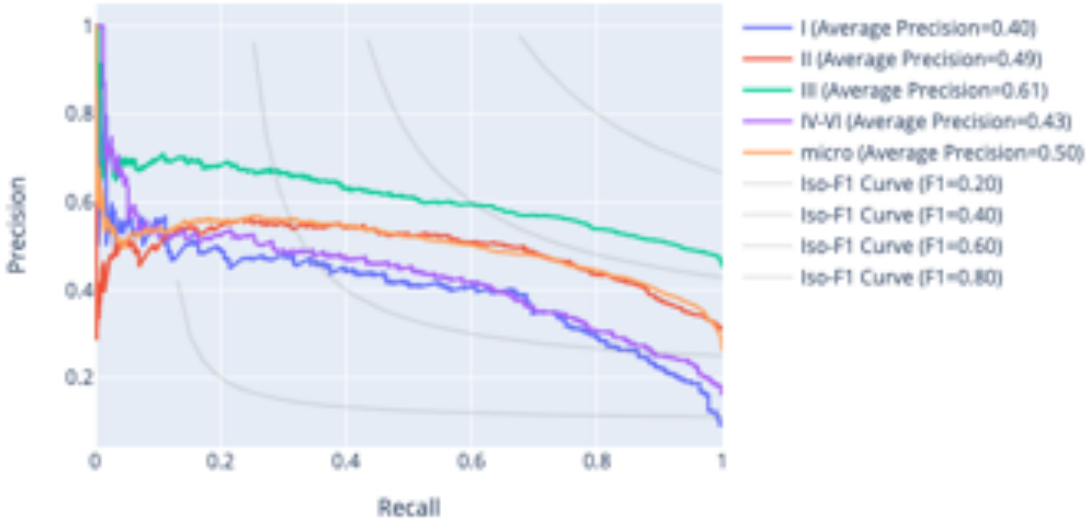


Figure 3: Precision-recall (PR) curve for predicting each ASA-PS category in the validation set and test set. Also plotted is the micro-average PR curve across all classes. Average precision is noted in the legend next to each class.

Confusion Matrix – Validation Set					
		True ASA-PS			
		I	**II**	**III**	**IV-VI**
Predicted ASA-PS	**I**	92.9%	0.6%	0.2%	0%
	II	6.1%	84.0%	15.7%	2.0%
	III	0.7%	13.6%	78.2%	18.8%
	IV-VI	0.3%	1.8%	5.9%	79.2%
	Total	*100%*	*100%*	*100%*	*100%*

Confusion Matrix – Test Set					
		True ASA-PS			
		I	**II**	**III**	**IV-VI**
Predicted ASA-PS	**I**	41.8%	12.1%	1.0%	0.3%
	II	48.7%	52.8%	24.4%	8.3%
	III	8.7%	32.0%	61.0%	50.7%
	IV-VI	0.8%	3.1%	13.6%	40.7%
	Total	*100%*	*100%*	*100%*	*100%*

Figure 4: Confusion Matrices for validation and test set with predicted ASA-PS normalized for each true ASA-PS class. Predictions are made by our fine-tuned model. Cells shaded in green represent correct predictions. Majority of incorrect classifications are a single ASA-PS class off from the true ASA-PS.

PERIOPERATIVE ANESTHESIA 15

Perioperative Factors Affecting Acute Kidney Injury Following Major Abdominal Surgery

Monica J Horvath[1], Simon J Davies[2]

[1]York Teaching Hospital NHS Foundation Trust, York, United Kingdom, [2]York Hospitals NHS Trust, York, Yorkshire

INTRODUCTION: Acute Kidney Injury (AKI) is a common postoperative complication[1]. It is associated with adverse postoperative outcomes including increased hospital length of stay, increased risk of developing chronic kidney disease and increased mortality[2]. We examined perioperative factors that may influence the occurrence of AKI, including comorbidities, types of surgery and volumes of fluid administered in the perioperative period.

METHODS: We conducted a retrospective analysis of prospectively acquired data on patients undergoing major abdominal surgery at York Teaching Hospital NHS Foundation Trust between October 2015 and March 2020. The primary outcome was AKI within the first seven days following surgery. The Kidney Disease: Improving Global Outcomes (KDIGO) AKI 2012 Guidelines were used to define AKI[3]. The association between patient parameters and occurrence of AKI within the seven-day postoperative period was examined using bivariate analysis and a model was constructed using logistic regression. AKI occurring within the 30 day postoperative period was also examined, as well as length of hospital stay and mortality at two years. York Teaching Hospital NHS Foundation Trust sponsored the study, which was approved by the UK Health Research Authority (IRAS 286488).

RESULTS: A total of 693 patients were included in the study. The primary outcome occurred in 95 patients (13.7%). Overall median hospital length of stay was 6 days (IQR 5 days). Overall two year mortality was 11.7%. Multivariate predictors for AKI within the seven-day postoperative period were male sex, history of valvular heart disease, obesity classes I and II, length of surgery ≥4 hours and open surgery compared to laparoscopic. Multivariate analysis also showed the same predictive factors for AKI in the first 30 days following surgery. The median length of hospital stay for patients with the primary outcome was 10 days (IQR 7-16 days), compared to 6 days (IQR 4-8 days) in patients who did not have the primary outcome. Mann-Whitney U test showed p value <0.001, see figure 1. The mortality rate for patients who had the primary outcome was 13.0%, compared to 11.5% in those who did not have the primary outcome (OR 1.15, 95% CI 0.56, 2.39).

CONCLUSION: Acute kidney injury is common in the seven days following major abdominal surgery. It can be predicted by male sex, history of valvular heart disease, obesity classes I and II, length of surgery of four hours or more and having open compared to laparoscopic surgery. Of these factors, obesity, open surgery and length of surgery are modifiable. This can be used to inform shared decision making in the perioperative period to optimise patient outcomes

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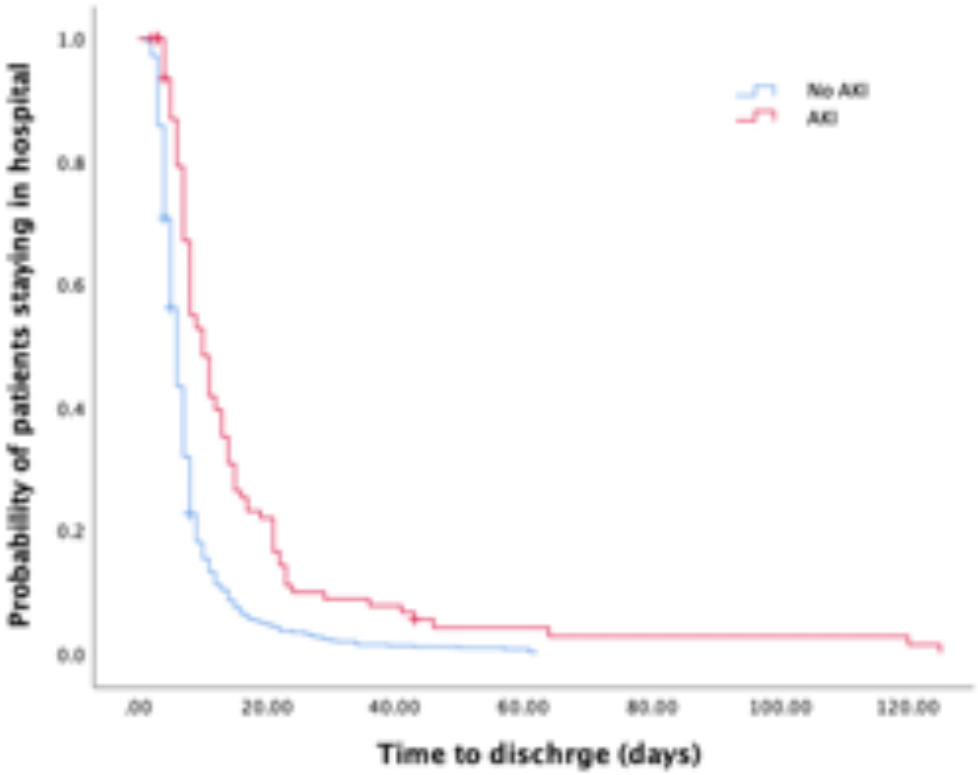

Figure 1: Kaplan Meier curve for hospital length of stay in patients with and without AKI in the seven days following surgery. Deaths censored.

PERIOPERATIVE ANESTHESIA 16

Antidepressant Effect of Intraoperative Ketamine in Patients with Major Depression Undergoing Surgery: An Open-Label Pilot Study

Theresa Lii[1], Robin Okada[1], Kayla Pfaff[2], Rasmus Thordstein[3], Lisa Cianfichi[4], Boris D Heifets[1]

[1]Stanford University School of Medicine, Palo Alto, CA, [2]Ohio University Heritage College of Osteopathic Medicine, Athens, OH, [3]Lund Univsersity, Lund, Sweden, [4]Stanford Healthcare, Palo Alto, CA

INTRODUCTION: Depression strongly predicts postoperative chronic pain[1], and optimizing this risk factor may improve outcomes. Ketamine is a well-investigated rapid-acting therapy for major depression[2], yet it is unclear whether ketamine is effective in reducing depressive symptoms when administered with other anesthetics during surgery. The purpose of this pilot study was to determine whether intravenous ketamine administered intraoperatively to clinically depressed patients undergoing joint replacement surgery is associated with reduced depressive symptoms postoperatively. We also explored whether intraoperative electroencephalogram (EEG) predicts ketamine response.

METHODS: IRB approval was obtained for this open-label pilot study conducted at a tertiary academic medical center. Five patients with moderate-to-severe depression were recruited from an orthopedic surgery clinic. Each participant received intravenous ketamine (0.5 mg/kg administered over 40 minutes) with routine anesthesia during total joint replacement surgery. Montgomery-Asberg Depression Rating Scale (MADRS) was used to rate depression severity before and after surgery. Mean and standard deviations are described at each assessment time point. Power spectral density analysis of EEG data obtained from a commercially-available EEG monitor was used to identify the alpha peak frequency (APF) of each patient before and after ketamine administration. The association between MADRS and APF was assessed with simple linear regression.

RESULTS: On average, there was a 40% decrease in MADRS scores from preoperative baseline to postoperative day 1 (mean=28.2 [SD=3.1] to mean=17.0 [SD=13.0]). This antidepressant effect was sustained at postoperative day 14 (52% decrease in MADRS, to mean=13.6 [SD=12.6]). Ketamine administration shifted the mean APF from 10.2 to 8.1 Hz. Individual shifts in APF predicted the decrease in MADRS scores.

CONCLUSION: Clinically depressed patients undergoing joint replacement surgery experienced reduced depressive symptoms after receiving ketamine intraoperatively, which correlated with EEG. This preliminary data from an uncontrolled open label study demonstrates feasibility for an appropriately powered randomized, placebo controlled trial.

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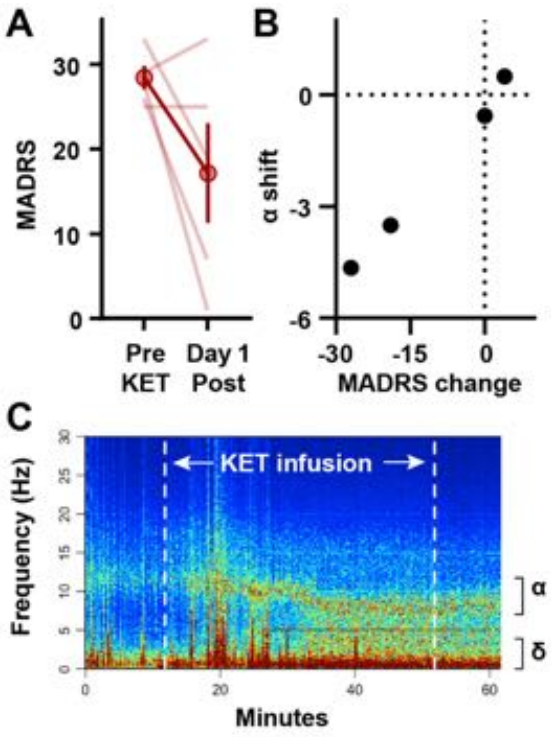

Fig. 1. A. Depression score (MADRS) pre and post ketamine. B. Shift in EEG alpha peak vs. MADRS change. C. Example density spectral array during ketamine + anesthesia

PERIOPERATIVE ANESTHESIA 17

A Mixed Methods Study of Patients' and Caregivers' Experiences After Same Day Discharge from Robotic-Assisted Laparoscopic Prostatectomy

Athena Christakos[1], Ayah El-Fahmawi[2], David I Lee[3], Mitchell Weinstein[2]

[1]Hospital of the University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA, [3]Penn Presbyterian Medical Center, Philadelphia, PA

INTRODUCTION: There has been a trend towards increasing the breadth of outpatient surgeries. Robotic-assisted laparoscopic prostatectomies (RALPs) are one of the most common major urologic surgeries. Though there have been series of patients undergoing same day discharge after RALP with favorable postoperative outcomes, patients' and caregivers' perspectives on satisfaction have not been captured[1,2]. The objectives were to capture elements of the perioperative experience and describe the unique challenges and perspectives of patients and caregivers during recovery after same day discharge using a qualitative research method. This will improve preoperative counseling to patients and decrease potential readmissions.

METHODS: The study was reviewed and accepted by the University of Pennsylvania's IRB committee. All RALPs were performed by a single surgeon from 3/2019-1/2020. Patients were evaluated by an anesthesiologist and the surgeon for possible same day discharge; patients were approached by phone before surgery. 27 patients were consented, and 17 interviews were completed. Within four weeks of surgery the subject and his caregiver (consented at the time of interview) underwent a recorded telephone interview. Recordings were uploaded to a secure HIPAA-compliant server for transcription. The transcripts were coded qualitatively for thematic and content analysis via Dedoose, a qualitative-research software program. Study-relevant information from each patient's electronic medical record was collected.

RESULTS: Patient characteristics are shown in Table 1. No patients required transfusion and no patients were readmitted; 3 presented to an emergency room. Over 1/3 of patients received an opioid in PACU; only 2 of 17 patients received additional ondansetron after the OR (Table 2). Analysis of interviews showed patient and family satisfaction with same day discharge and appreciation for discharge home. All found the preoperative reading material adequate. All subjects recommended same day discharge in the appropriate patient with an adequate support system. Management of the Foley catheter was biggest postoperative challenge with shoulder pain from insufflation as the second. No patients cited postoperative pain as a limitation for activity for more than one day. Caregivers' biggest challenge was watching a loved one go through distress after surgery.

CONCLUSION: Same day discharge after RALP continues to be shown as safe, especially in a high-volume center with strong advanced practice provider presence, now with clear evidence of patient satisfaction. Areas of improvement may be addressed through further preoperative and PACU education and counseling. This study not only showed feasibility, but also allowed patients and caregivers to provide their voices in a qualitative format.

REFERENCE(S):

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Table 1. Patient Characteristics

	Mean ± Standard Deviation
Age	61.4 ± 8.5 (45-77)
BMI	27.2 ± 2.7 (24.0-34.9)
EBL	< 200 mL
Operative time	108 ± 32.1 (76-201)
Interview length	25.1 ± 10.65 (9-44)

Table 2. Post-operative Readmissions and Medications Administered

	Percentage of participants
Readmissions	0% (0/17)
Presented to emergency department	17.6% (3/17)
Opioid given in PACU	35.2% (6/17)
Ondansetron given in PACU	11.8% (2/17)
Oxybutynin given in PACU	70.6% (12/17)
Opioid taken at home	64.7% (11/17)

PERIOPERATIVE ANESTHESIA 18

Retrograde Amnestic Effect of Midazolam on Post-Operative Word Recall

Eric Arellano[1], Kimberly Klafta[1], Yaman Kherallah[1], David Glick[2]

[1]University of Chicago Pritzker School of Medicine, Chicago, IL, [2]University of Chicago, Chicago, IL

INTRODUCTION: Benzodiazepines, like midazolam, are commonly used as sedatives and anxiolytics in the perioperative setting. They are known to cause anterograde amnesia, but they are not classically associated with retrograde amnesia. There is, however, some limited research suggesting a possible retrograde amnestic effect for benzodiazepines in animals, and there are scattered case reports of retrograde amnestic effects of midazolam in the clinical setting. The current study demonstrates a statistically and clinically significant occurrence of retrograde amnesia in a series of patients given midazolam preoperatively as part of a clinical research study.

METHODS: Following Institutional Review Board approval, a total of 363 patients undergoing general anesthesia for a surgical procedure consented to participate in this study. Each patient was given six equally memorable words preoperatively to remember. Words 1, 2, and 3 were given 5 minutes, 3 minutes, and 1 minute before administration of midazolam, respectively; word 4 was given during administration of midazolam; words 5 and 6 were given 1 minute and 3 minutes after the administration of midazolam, respectively. The words were given only once, and patients were asked to repeat each word to confirm that they heard it correctly. Following their operation, each patient was asked to recall the six words given to them before the operation. Which, if any, words each patient recalled post-operatively were recorded. Word recall rates for words 1, 2, and 3 (words given before administration of midazolam) were calculated and used for analysis in this study.

RESULTS: Figure 1 shows the post-operative recall rates of words 1, 2, and 3. The number of patients used in analysis for word recall is shown under each bar and the y-axis designates the recall rate. Although all three words were given before administration of midazolam, there is a markedly diminished recall rate for word 3 compared to words 1 and 2 (where the recall rates were nearly identical). The recall rates for word 1 and 2 were 80.2% and 81.5%, respectively, while the recall rate for word 3 was only 58.4%. The difference in proportion of correct recall between words 1 and 3, as well as words 2 and 3, were both found to be statistically significant ($p<0.0001$). The difference in proportion of correct recall between words 1 and 2 was not statistically significant ($p=0.6974$).

CONCLUSION: Midazolam is a benzodiazepine that is known to cause anterograde amnesia. Our results suggest it also has a significant retrograde amnestic effect. Although words 2 and 3 are given only two minutes apart, that two-minute difference is enough to show an approximate 20% reduction in overall recall rate for patients in our study. This retrograde amnestic effect in the preoperative area could lead to a failure to recall important instructions or the considerations discussed in the process of informed consent. More studies are needed to more clearly delineate the timing and character of this retrograde amnestic effect.

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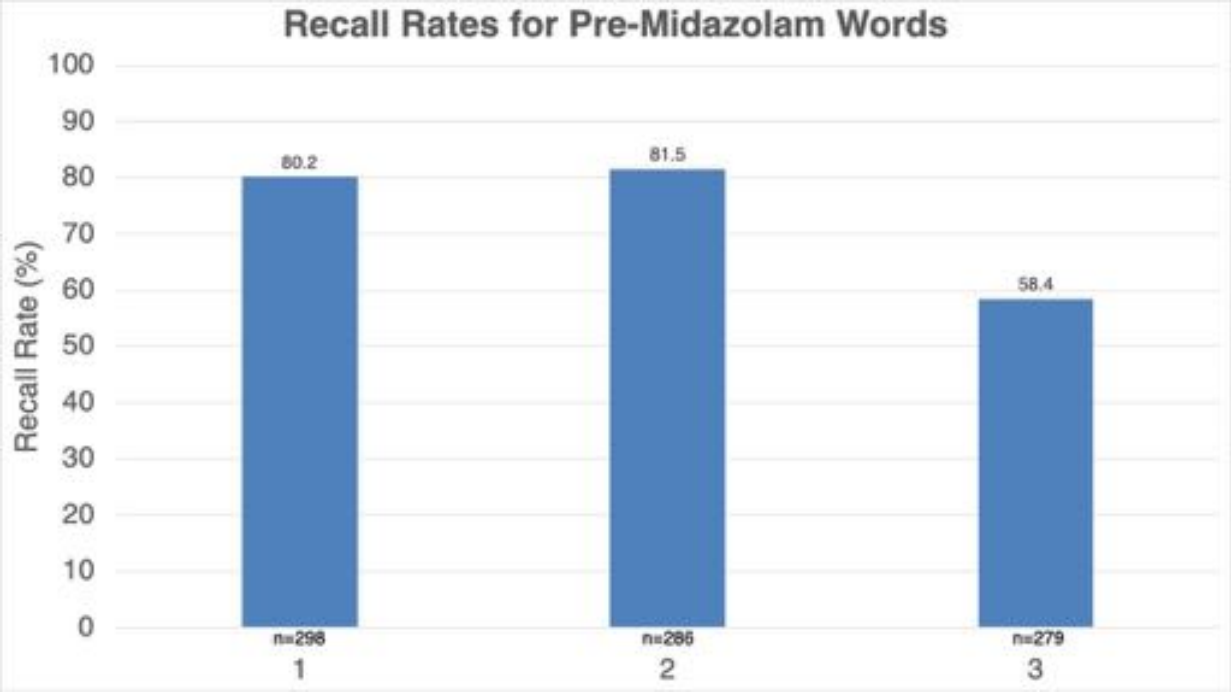

PERIOPERATIVE ANESTHESIA 19

Association of a FDA Warning on Hydroxyethyl Starch solutions with Bleeding After Major Spine Surgery: Differences between Hospitals That Did Versus Did Not Switch to Albumin

Sachin Mehta[1], Suhas Kochat[1], Alan Ellis[2], Tetsu Ohnuma[1], Vijay Krishnamoorthy[1], Karthik Raghunathan[1]

[1]Duke University School of Medicine, Durham, NC, [2]North Carolina State University, Raleigh, NC

INTRODUCTION: After the Food & Drug Administration (FDA) issued a 'black box' safety warning for the perioperative use of Hydroxyethyl Starch (HES) in June 2013, its usage in noncardiac surgery decreased in many US hospitals (Figure 1, top). Many hospitals that moved away from the use of HES switched to Albumin ('Albumin Switchers', AS), while others did not ('Crystalloid Switcher', CS) (Figure 1, bottom). Albumin usage has been associated with smaller transfusion volumes in sepsis. We tested the hypothesis that patients undergoing major spine surgery where significant blood loss can occur, transfusion and bleeding would be decreased in the AS hospitals more than in the CS hospitals.

METHODS: Approval was obtained from the IRB at Duke University Health System. The study population consisted of patients undergoing major spine surgeries between July 2012 and June 2014. Data was obtained from surgery (ICD9 Codes, 81.08, 81.07, 81.06, 81.02) in hospitals who contribute to Premier Healthcare Database (PHD), a de-identified administrative and financial dataset, between July 2012 and June 2014. Only hospitals who perform at least ≥ 50 such procedures every quarter were included. The exposures were treatment in either the year pre-warning or the year post-warning, within AS or within CS hospitals. The outcome was a composite of either bleeding (defined by ICD diagnosis codes 998.11 or 998.12) or transfusions (identified by ICD Procedure code 99.1 and by Charge Codes). Information on baseline covariates that were extracted from PHD included socio-demographics, comorbidities (defined using Elixhauser's ICD9 code-based algorithms), and various cotreatments. Standardized Mean Differences (SMDs in means or proportions) were computed for over 80 covariates between patients treated pre- versus post-warning within a) AS hospitals and b) within CS hospitals. Propensity scores were computed as the probability of treatment pre- versus post- warning (Standardized Mortality Ratio-weighting). SMDs were also computed between patients treated in AS versus in CS hospitals, and propensities computed as the probability of treatment in either type of hospital. Propensity density plots were examined (Figure 2). Using Segmented Regression of Interrupted Time Series analysis, we estimated risk-adjusted differences in outcomes pre- versus post-warning within AS (difference 1), and within CS (difference 2). The difference-in-differences (DiD) was calculated as difference 1 minus difference 2. This represents the change in outcomes attributable to the change in fluid choice after the FDA-warning, adjusted for differences in patient attributes and temporal trends.

RESULTS: Of the 79 'switcher' hospitals where 5,965 patients underwent major spine surgery between July 2012 and June 2014, 29 were AS hospitals where 3,937 patients were treated (1,426 pre-warning versus 2,511 post-warning), and 50 were CS hospitals where 2,028 patients were treated (1,313 pre-warning versus 715 post-warning). Based on average SMDs $<|0.1|$, and on common support (overlap) in propensity density plots (Figures 2 and 3), confounding was less likely when comparing patients treated pre- versus post-warning within AS and within CS hospitals, but not when comparing patients treated in AS versus CS hospitals as a whole. Focusing on pre- versus post-warning differences, in unadjusted analyses, we observed a decrease in the outcome within the AS hospitals versus an absolute reduction of 1.9% or 38% in relative terms regarding bleeding / transfusions (increase within CS hospitals, Table 1). In propensity adjusted segmented regression analysis, the DiD estimate corresponded to a 72% reduction (95%CI, 1%-92% reduction) in the risk of the outcome in AS hospitals, when compared to CS hospitals (relative risk 0.28, 95% CI 0.08 - 0.99, $p<0.05$).

CONCLUSION: A 2013 FDA warning on HES solutions was followed by a significant decrease in the perioperative use of HES on the day of major spine surgeries in 79 US hospitals. In risk-adjusted analyses, we observed a statistically significant decrease in the proportion of patients with either bleeding or need for transfusions in the 29 hospitals that had 'switched' from HES to Albumin, when compared to the 50 hospitals that had not. Further research is needed to understand how FDA warnings impact upon clinical practice and future patient outcomes.

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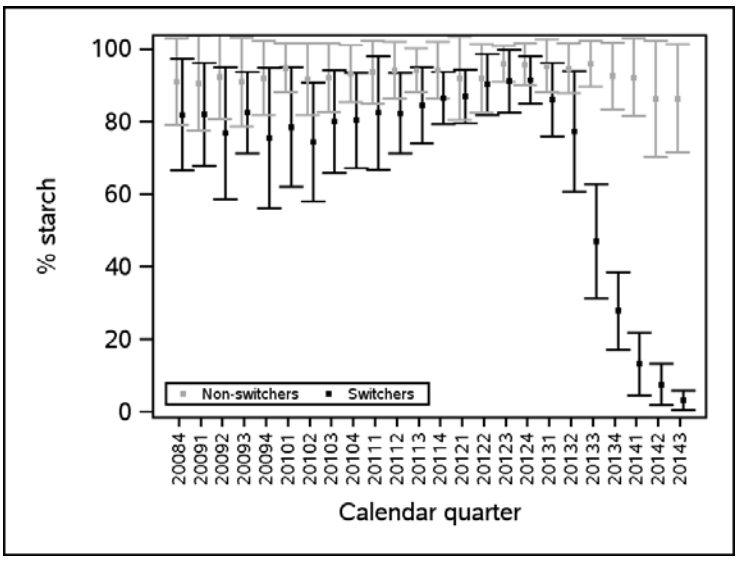
Figure 1: Perioperative Use of HES declined drastically after the FDA warning in 79 US hospitals conducting at least 50 major spine procedures every quarter between July 2012 and June 2014 (top panel). Among these 79 hospitals, the use of albumin increased rapidly in 29 AS hospitals (black bars) but not in 50 CS hospitals (grey bars), bottom panel.



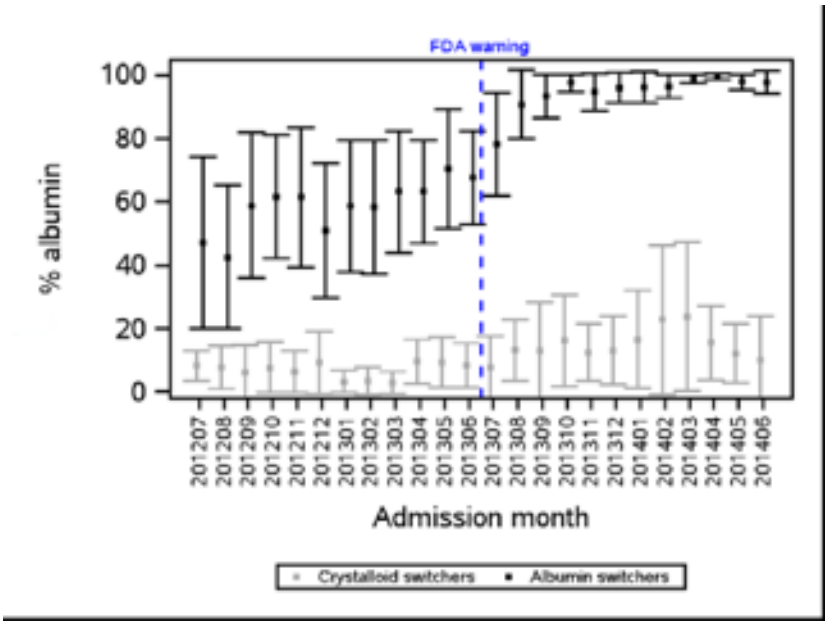
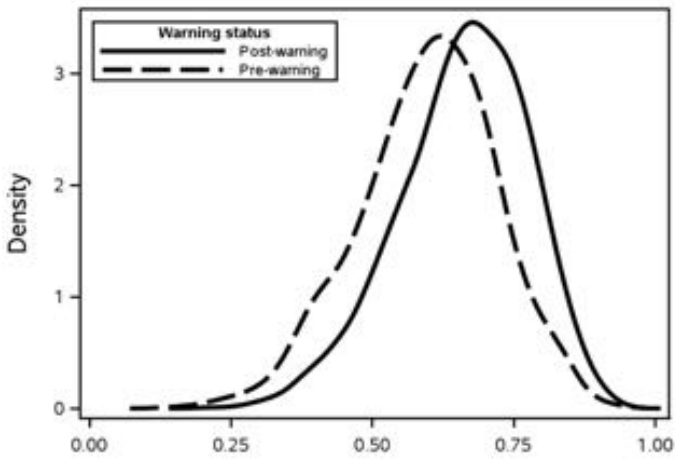
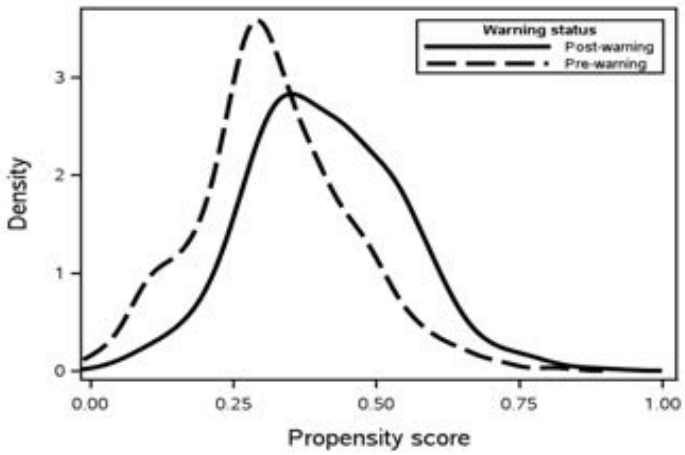


Figure 2: Propensity density plots. There is significant overlap (top panels) where the propensity is the probability of treatment pre- versus post-warning (AS hospitals top left and CS hospitals top right). This suggests that patients are, on average, comparable pre- versus post-warning within AS and CS hospitals. In contrast, in the bottom panel the propensity is the probability of treatment in AS versus CS hospitals. The figure suggests that patients are, on average, less comparable when contrasted across AS versus CS hospitals.





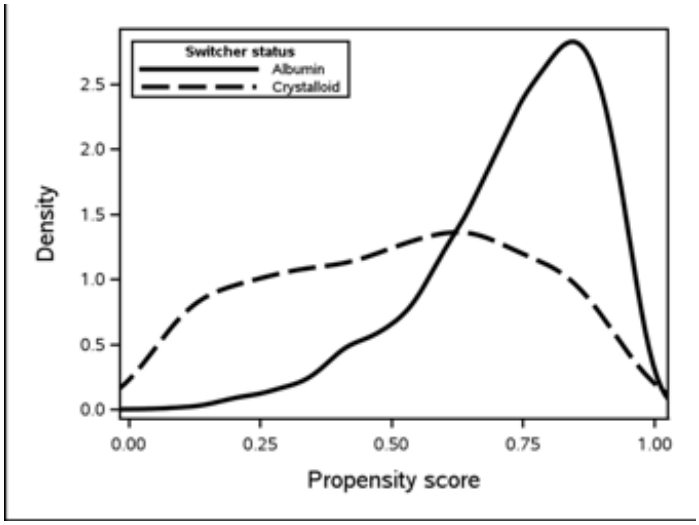
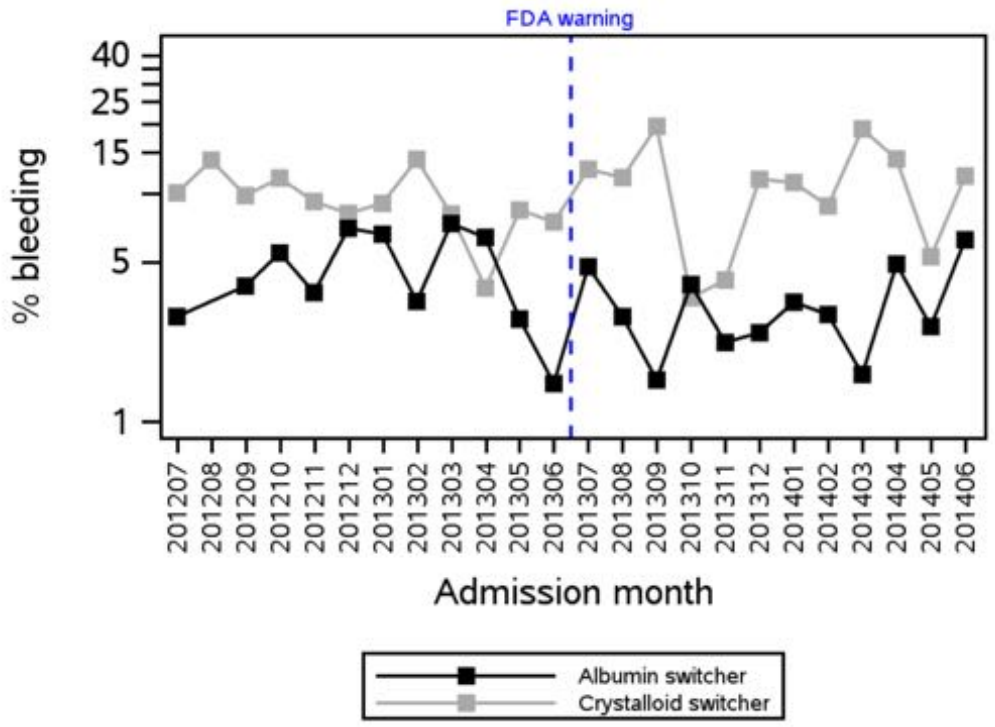


Figure 3: SMDs in Socio-demographics, Co-morbidities, and Co-treatment characteristics across: a) patients in AS pre- versus post- warning, unadjusted (open triangles) and propensity score adjusted (filled triangles) b) patients in CS pre- versus post- warning, unadjusted (open circles) and propensity score adjusted (filled circles), and c) patients treated in AS versus CS over the entire time period, unadjusted (open squares) and propensity score adjusted (filled squares)

Table 1: Number of patients - overall and bleeding - in AS and CS hospitals, Pre- and Post-Warning.

	Total Patients	Bleeding	Proportions	Differences	DinD
Albumin Pre	1426	60	4.2%	Difference 1 = Absolute Decrease in Bleeding of 0.9%	D2 minus D1 = 1.9% absolute difference in rate of bleeding (equivalent to a relative reduction of 38% in AS)
Albumin Post	2511	83	3.3%		
Crystalloid Pre	1313	126	9.6%	Difference 3 = Absolute increase in Bleeding of 1%	
Crystalloid Post	715	76	10.6%		

Figure 4: Changes over time in the proportion of patients with bleeding in AS and CS groups through the study period.



PERIOPERATIVE ANESTHESIA 20

Implementation of an Enhanced Recovery after Procedure (ERAP) Initiative to Improve Analgesia for Hepatic Microwave Ablation (MWA) in the Interventional Radiology (IR) Suite

Casey Hamilton[1], Rafael Vazquez[1]

[1]Massachusetts General Hospital, Boston, MA

INTRODUCTION: Advances in the interventional radiology (IR) field have resulted in expanded treatment options for a range of diseases, most notably in the area of interventional oncology (IO). IO procedures are increasingly utilized as minimally invasive treatment options for patients. Hepatic microwave ablation (MWA) for liver tumors is one of the most commonly performed IO procedures worldwide. Despite the percutaneous nature of IO procedures including hepatic MWA, these interventions can cause significant peri-procedural acute pain necessitating opioid rescue therapy, and the patient experience can be unpleasant[1]. There is ample evidence showing that pre-procedure multimodal analgesic interventions can be beneficial for peri-procedural acute pain related to hepatic MWA[2,3,4]. In clinical practice application of these evidence-based analgesic therapies is inconsistent. Currently, there is no formal pathway that implements evidence-based analgesic interventions for patients undergoing hepatic MWA. Many surgical specialties have adopted evidence-based protocolized Enhanced Recovery After Surgery (ERAS) pathways leading to improved patient outcomes including reduced opioid use[5]. Computerized physician/provider order entry (CPOE) sets are useful tools for incorporating evidence-based guidelines into pathways and can lead to increased utilization of such guidelines[6].

METHODS: As part of a quality improvement (QI) initiative, we designed an Enhanced Recovery After Procedure (ERAP) pathway which includes administration of pre-procedure analgesics and regional anesthesia blocks for patients undergoing hepatic MWA procedures (Figure 1). We developed a CPOE set which includes recommendations for peri-procedural analgesics, anti-inflammatories, and antiemetics. Multidisciplinary education sessions detailing peri-procedural acute pain management and the ERAP protocol were conducted with stakeholders from IR, anesthesia, and a dedicated regional anesthesia block team. Eligibility criteria for paravertebral blocks included INR < 1.4, platelets > 90,000/ microliter, and no antiplatelet or anticoagulant medication contraindications. The goal was to increase pre-procedure analgesic administration to 80% and eligible patients receiving regional blocks to 50%. Utilization of multimodal analgesics and compliance to and sustainability of the ERAP pathway were tracked in 316 consecutive patients from 2016 to 2020. Statistical process control P-charts were used to assess changes before implementation of the ERAP protocol (baseline data obtained from May 2016 through September 2017) and after ERAP implementation (October 2017 through March 2020).

RESULTS: Prior to implementation of ERAP there was rare and inconsistent administration of pre-procedure analgesics and paravertebral blocks, with baseline averages of 12% and 15% respectively. After implementation of the ERAP protocol there was a significant and sustained increased in the administration of pre-procedure analgesics (Figure 2; mean increased from 12% to 93%, special cause variation met with all subsequent data points above baseline mean and multiple data points above upper control limit). Similarly, there was a significant and sustained increased in the percentage of eligible patients who received paravertebral blocks (Figure 3; mean increased from 15% to 78%, special cause variation met with all subsequent data points above baseline mean and multiple data points above upper control limit). There was some minor month-to-month variation in the utilization of pre-procedure analgesics and more apparent variation in the percentage of eligible patients that received paravertebral blocks.

CONCLUSION: Analgesic administration and regional anesthesia with paravertebral blocks for patients undergoing hepatic MWA can be improved and sustained utilizing a formalized ERAP pathway with foundations on multidisciplinary education and CPOE. Ongoing education of new or rotating team members from IR, nursing, and anesthesia teams is an important part of sustaining such pathways. Implementation of ERAP pathways could have broad implications to improving patient care for a variety of other IR and other painful IO procedures. Further research into potential impacts on patient outcomes will be necessary as NORA needs increase with advances in percutaneous interventions.

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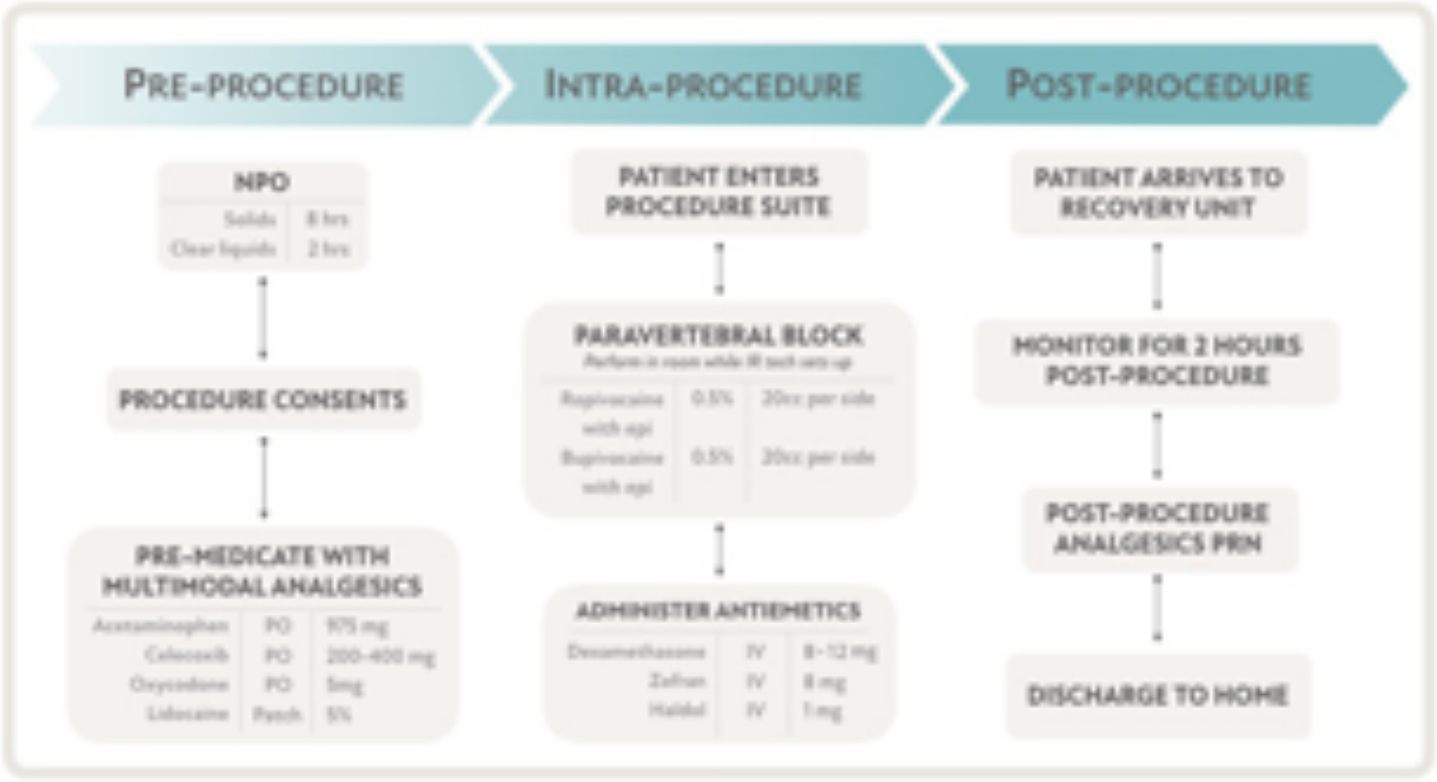

Fig. 1

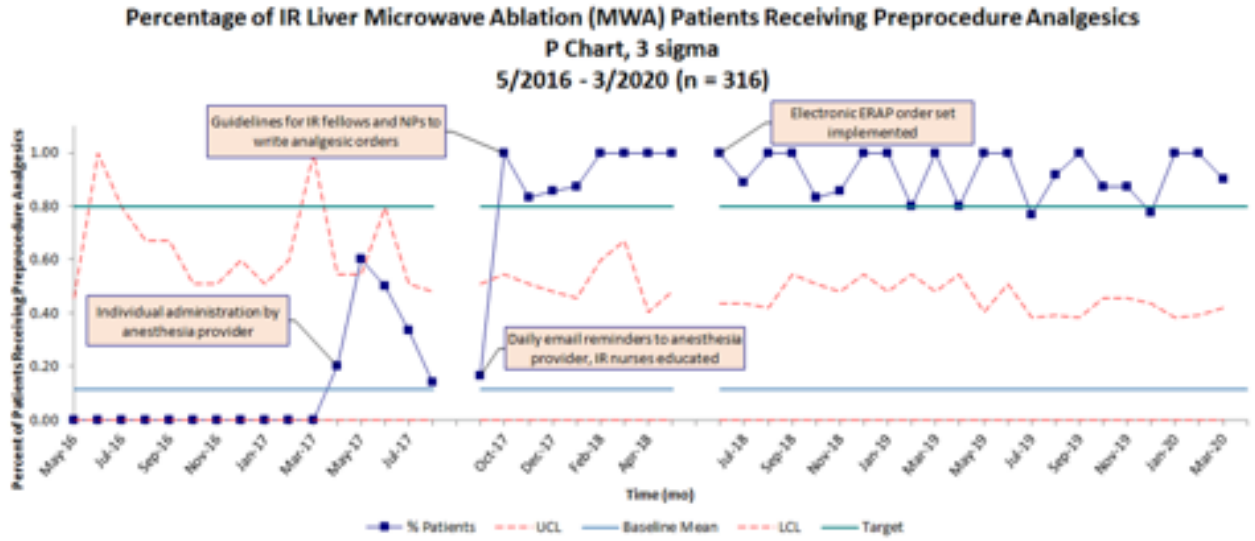

Figure 2. P-chart showing percentage of patients undergoing interventional radiology (IR) liver microwave ablation who received pre-procedure analgesics (PA: acetaminophen, celecoxib, and/or tramadol or oxycodone). Upper and lower control limits (UCL and LCL (0), respectively) 3 sigma, n = 316. Baseline mean of 12% calculated from data collected on patients from 5/2016 through 9/2016 prior to first intervention to implement ERAP protocols, with a target of 80%. Special cause variation criteria met after ERAP implementation, with all subsequent data points above baseline mean, multiple data points above 3 sigma UCL.

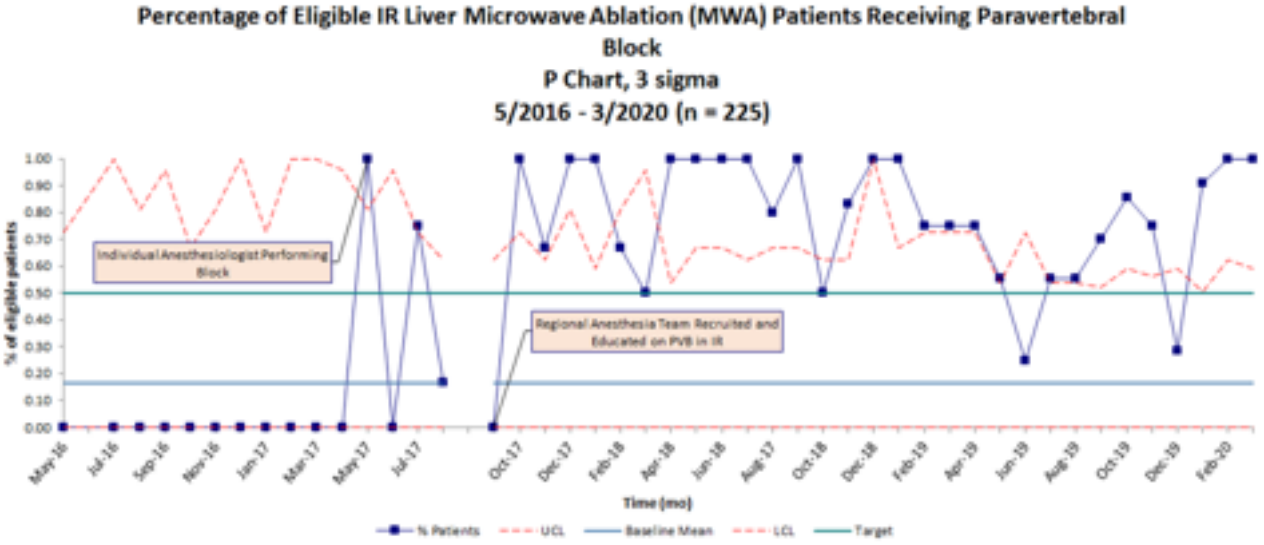

Figure 3. P-chart showing percentage of eligible patients based on PT and platelet levels undergoing IR liver microwave ablation who received a paravertebral block. Upper and lower control limits (UCL and LCL (0), respectively) 3 sigma, n = 215. Baseline mean of 15% calculated from data collected on patients from 5/2016 through 9/2016 prior to recruitment of a dedicated regional anesthesia team as part of ERAP protocol, with a target of 50%. Special cause variation criteria met with all subsequent data points above baseline mean, multiple data points above 3 sigma UCL.

PERIOPERATIVE ANESTHESIA 21

Evaluating Subjective Cognitive Complaint and Informant-Reported Questionnaires Used for Subjective Cognitive Decline Screening in Older Adults: A Systematic Review

Isabelle Laksono[1], Sara Wasef[2], Paras Kapoor[2], David F Tang-Wai[1], David Gold[2], Aparna Saripella[3], Sheila Riazi[1], Sazzadul Islam[3], Marina Englesakis[3], Jean Wong[1], Frances F Chung[1]

[1]University of Toronto Faculty of Medicine, Toronto, ON, Canada, [2]University of Toronto, Toronto, ON, Canada, [3]University Health Network, Toronto, ON, Canada

INTRODUCTION: A spectrum of cognitive impairment exists, starting with subjective cognitive decline (SCD), followed by mild cognitive impairment (MCI) and dementia.[1] SCD may represent at-risk persons progressing to MCI. Screening for SCD is advantageous due to easy administration and low cost.[2] The objective of this systematic review is to identify the most common subjective and informant-reported individual questions in subjective cognitive complaint and informant-reported questionnaires used to assess cognitive impairment of elderly patients that are also correlated with standardized tests.

METHODS: We searched Medline, PubMed, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database, Emcare Nursing, Web of Science, Scopus, CINAHL, ClinicalTrials.Gov, and ICTRP between January 1, 2010 to August 31, 2020. The search process followed the PRISMA guideline. We included studies that evaluated subjective cognitive complaints and informant-reported questions in patients aged 50 years old or more. Data on validation and prevalence were extracted for the SCC questionnaire as a whole as well as for each individual question. Questions are grouped under the six domains of cognitive function described by the Neurocognitive Work Group which include: complex attention, executive function, learning and memory, language, perceptual–motor function, and social cognition.

RESULTS: A total of 28,407 patients were included from 22 studies that assessed 21 subjective complaint questionnaires and nine informant-reported questionnaires. The most common subjective cognitive complaints were those assessing learning and memory, specifically, anterograde memory. This was closely followed by spatial orientation and executive function (Table 1). The most common informant-reported questions were those assessing executive function, temporal orientation, and learning and memory. Fifteen articles included questionnaires assessing learning and memory. Of these, seven showed a positive association between the subjective/informant-reported questions related to anterograde memory and cognitive measure tests.

CONCLUSION: Questions assessing learning and memory were most associated with results from standardized tests assessing cognitive impairment. Study results are consistent with the fact that Alzheimer's disease and amnestic MCI are defined by deficits in memory, and that these conditions make up the majority of dementia and MCI cases among elderly patients.[3] Therefore, assessing learning and memory plays a key role in evaluating SCD in elderly patients. Thus, the results from this review contribute to knowledge for perioperative healthcare professionals regarding the use of subjective cognitive complaints and informant-reported complaints for SCD screening in busy clinic settings.

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Table 1. Most Common Questions.

Neurocognitive Domain	**Learning and Memory**						**Perceptual-Motor Function**	**Executive Function**	**Language**	**Complex Attention**
Question Category	Anterograde memory (e.g. do you/does the patient have difficulty remembering things that have happened recently?)	Ability to remember and/or keep appointments (e.g. do you/does the patient have trouble remembering appointments?)	Forgetfulness of common objects (e.g. do you/does the patient lose objects more often that you did previously?)	Temporal orientation (e.g. do you/does the patient have trouble remembering the time/date?)	Comparing own memory to others of similar age (e.g. do you/does the patient think that your memory is poorer than that of other people your age?)	Remembering routine tasks (e.g. do you/does the patient have trouble remembering how to turn off the stove or lights?)	Spatial orientation (e.g. do you/does the patient have trouble finding your way around familiar streets?)	Executive function (e.g. do you/does the patient have trouble working household appliances?)	Language (e.g. do you/does the patient have trouble finding the right word to describe something you know well?)	Ability to follow a conversation (e.g. do you/does the patient have trouble following TV program or a book?)
Number of Studies (SCC)	11	9	7	5	4	4	9	7	6	6
Number of Studies (Informant-report questions)	4	2	0	5	0	0	1	6	2	3

PERIOPERATIVE ANESTHESIA 22

Neuromuscular Blockade Usage and Reversal Trends in U.S. Inpatients

Richard D Urman[1], Lori D Bash[2], Vladimir Turzhitsky[3], Wynona Black[3]

[1]Brigham and Women's Hospital; Harvard Medical School, Boston, MA, [2]Merck and Co., Inc., Kenilworth, NJ, [3]Merck & Co., Inc., Boston, MA

INTRODUCTION: As an important component of general anesthesia, whose use may vary by patient and procedural characteristics, neuromuscular blockade (NMB) utilization patterns have changed in recent years in the U.S. We sought to describe how clinical characteristics among those receiving NMB and NMB reversal agents have changed in the inpatient setting since the U.S. introduction of sugammadex (December 2015).

METHODS: A retrospective longitudinal analysis of a large all-payer national electronic healthcare database (Premier Healthcare Database, PHD) assessed U.S. adult inpatients who received rocuronium and/or vecuronium (without renal failure, myasthenia gravis or pyridostigmine therapy) between January 2014 and June 2019.

RESULTS: Approximately 4.3 million adults undergoing inpatient procedures received rocuronium or vecuronium (+/- succinylcholine) overall, the vast majority of whom were given rocuronium alone (86.0%), or in combination with succinylcholine (4.8%). Trends show modest increases in the use of rocuronium alone compared to decreases in combination with succinylcholine between 2016 and 2019 (Figure 1). Between 2014 and 2016, almost two-thirds of inpatients were reversed with neostigmine, and just over one-third were not actively pharmacologically reversed (ie. spontaneous reversal). Since then, both the use of neostigmine and spontaneous reversal have decreased over time, reaching lows of 38.3% and 27.6%, respectively, with NMB reversal with sugammadex reaching 34.2% by June 2019 (Figure 2). On average, patients were 58.2 years old, more often women (55.3%), the majority were white (78.4%), non-Hispanic (93%), and undergoing a musculoskeletal (37.2%) or digestive (29.1%) procedure. Overall, the proportion of elderly among the study population increased in later years; in concurrent years, those reversed with sugammadex tended to more often be older than the neostigmine population and younger than those spontaneously reversed (Figure 3). Over time, overall, and within each NMB reversal group, the proportion of patients with any comorbidities increased, as did most individual comorbidities (Figure 4). Generally, those spontaneously reversed and reversed with neostigmine tended to most, and least often have comorbidities, respectively.

CONCLUSION: In a large population of US adult inpatients administered NMBs, we observed an increase in age, number and frequency of comorbidities, and an increase in pharmacologic reversal compared to spontaneous reversal between 2014 and 2019. Additional research to understand how these NMB treatment patterns continue to change in light of the increasing efforts to expand capacity and shift patient care out of the inpatient hospital setting, accompanying the unprecedented burden on the US healthcare systems in 2020 is warranted.

Figure 1: *NMB with rocuronium alone rises, other combinations decline*

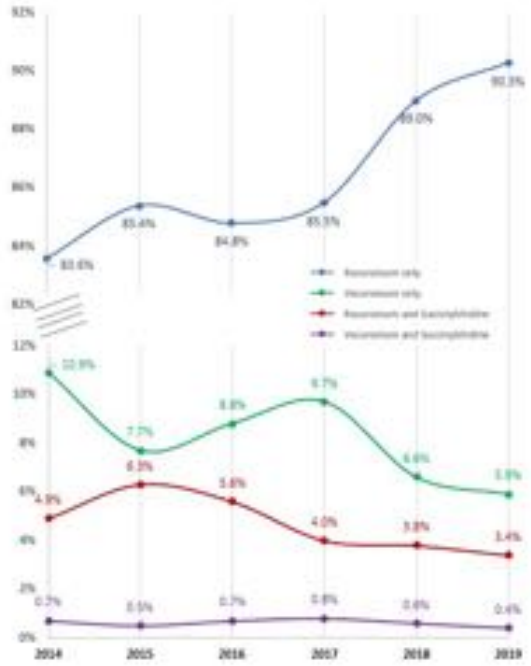


Figure 2: *Spontaneous NMB and Neostigmine Use Decline with Introduction of Sugammadex*

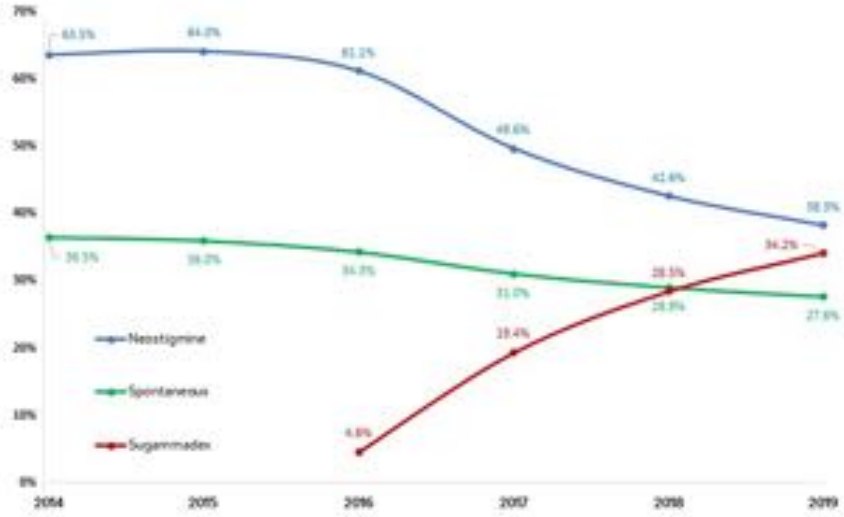


Figure 3: *Population Ages Over Time and Across All NMBRA Types*

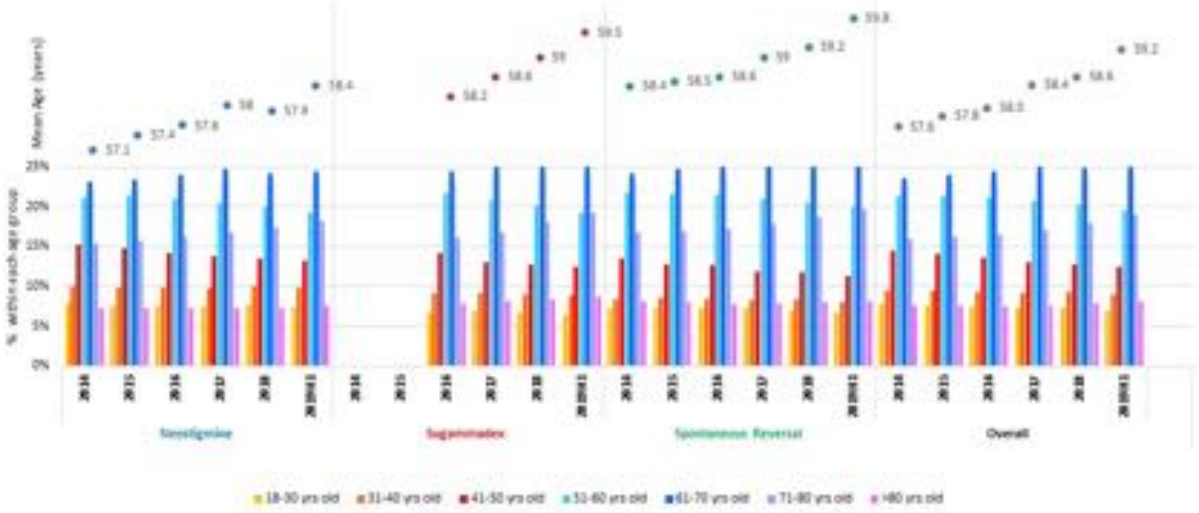
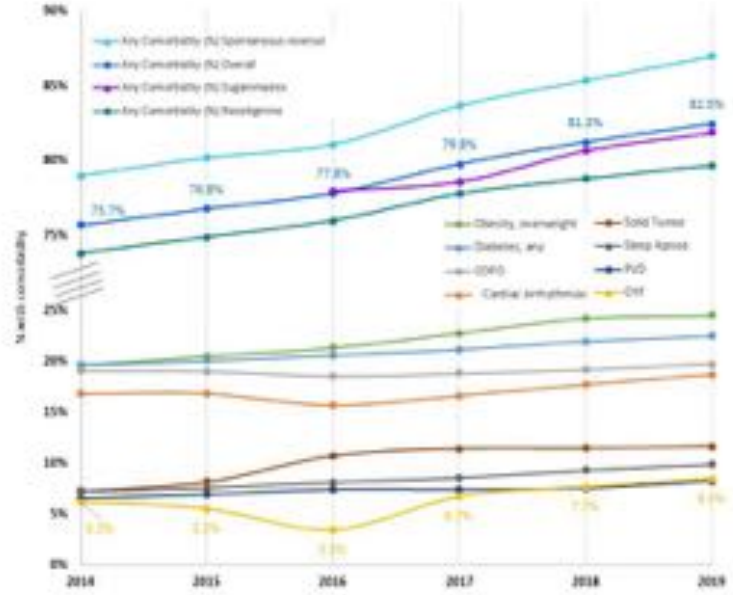


Figure 4: *Comorbidities Increase Over Time and Across All NMB Reversal Types*



PERIOPERATIVE ANESTHESIA 23

Patient and Procedural Characteristics Associated with Neuromuscular Blockade Reversal Choices in the U.S. Inpatient Setting

Richard D Urman[1], Lori D Bash[2], Vladimir Turzhitsky[3], Wynona Black[3]

[1]Brigham and Women's Hospital; Harvard Medical School, Boston, MA, [2]Merck and Co., Inc., Kenilworth, NJ, [3]Merck & Co., Inc., Boston, MA

INTRODUCTION: Patient, provider, and environmental factors impact patient care. As an important component of general anesthesia, whose use is also impacted by budgetary pressures, we sought to understand factors impacting the use of neuromuscular blockade (NMB) reversal agents in inpatients since the U.S. introduction of sugammadex (December 2015).

METHODS: A retrospective longitudinal analysis of a large all-payer national electronic healthcare database (Premier Healthcare Database, PHD) assessed U.S. adult inpatients using rocuronium and/or vecuronium (without renal failure, myasthenia gravis or pyridostigmine therapy) between January 2014 and June 2019. Multivariable logistic regression assessed the independent association of patient, site and procedural characteristics with NMB reversal choice (active vs. spontaneous 2014-2019, and neostigmine vs. sugammadex 2016-2019).

RESULTS: Approximately 4.3 million inpatients, across 909 sites, received rocuronium or vecuronium (+/- succinylcholine). Between 2014 and 2016, about two thirds were reversed with neostigmine and one third spontaneously reversed. Since then, the frequency of both have decreased, while the use of sugammadex increased to 34.2% and active reversals overall, reaching 73%, by June 2019. The most common types of procedures were musculoskeletal (35.9%), digestive (28.5%) and cardiovascular (12.2%). NMB reversal choice varied by procedure type with cardiovascular procedures being most often spontaneously reversed, and digestive procedures most often actively reversed (Figure 1). Patients with comorbidities were also actively reversed less frequently than the overall population; patients with cardiovascular comorbidities were actively reversed the least often (Figure 2). Multivariable analyses showed time to have a strong, positive independent association with patients' likelihood to be pharmacologically reversed between 2014 and 2019, as well as a patients' likelihood to be reversed with sugammadex compared to neostigmine among those actively reversed between 2016 and 2019. Several other patient, site and procedural characteristics were associated with NMB reversal choice independent of time, NMB agent, and each other. While the associations of patient and procedural characteristics including age and comorbidities were more pronounced when comparing choice of active vs. spontaneous reversal, the independent associations of time, race, ethnicity, and geographic region were more pronounced on choice of reversal agent (sugammadex vs. neostigmine) .

CONCLUSION: Among U.S. adult inpatients administered NMBs, we observed complex relationships between patient, site, regional, procedural characteristics and NMB management choices. Observations suggest that patient and procedural characteristics are important factors in NMB reversal choices in whether a patient is pharmacologically reversed, while external factors may be more influential in impacting choice of pharmacological reversal agent when a patient is actively reversed. Additional research to understand how these associations may continue to shift with increasing economic pressures on the U.S. healthcare system is warranted.

Figure 1: *NMB Reversal Choice Varies by Type of Procedure*

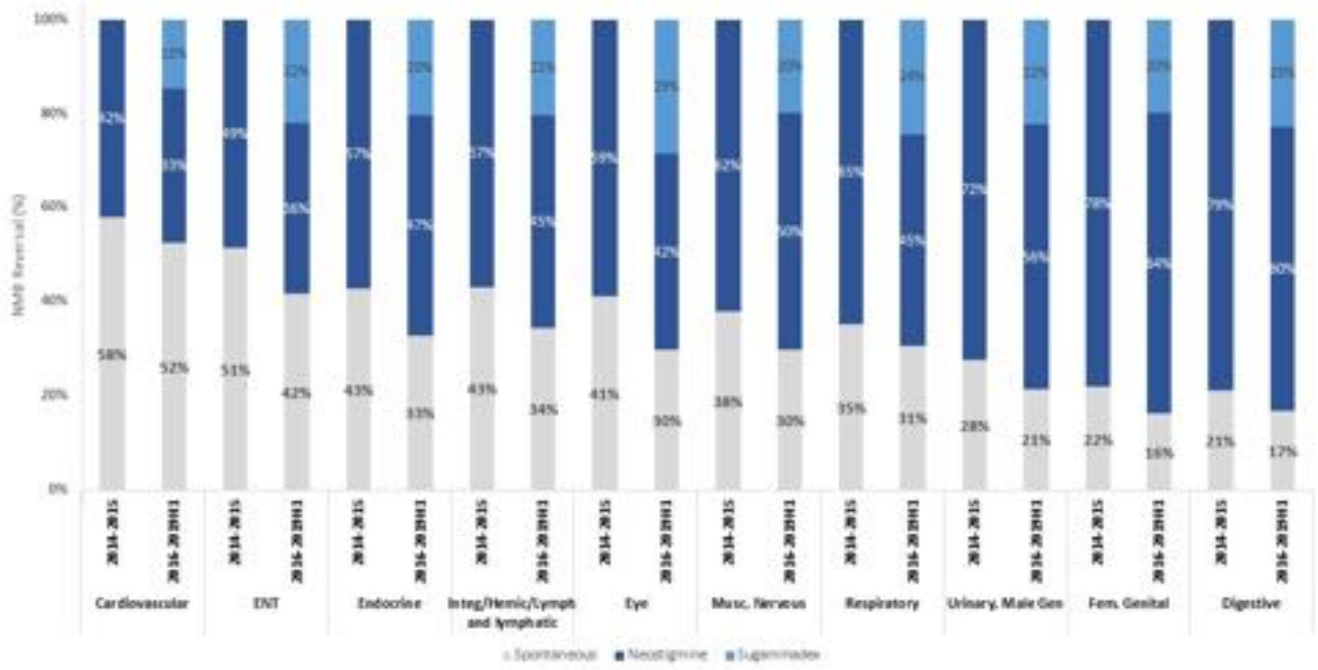
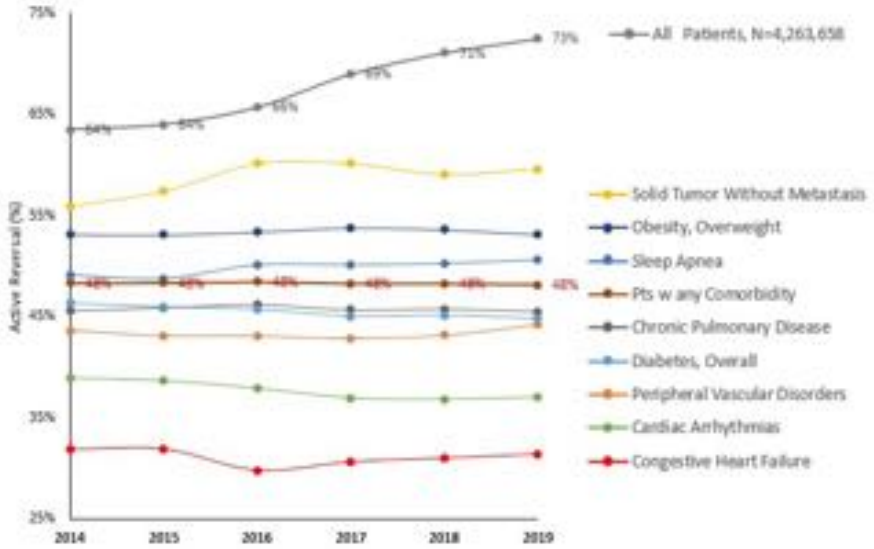


Figure 2: *Patients with Comorbidities are less often actively reversed*



PERIOPERATIVE ANESTHESIA 24

Multifactorial Preoperative Assessment of Frailty, Cognition and Nutrition in Orthopedic Surgical Patients: A Single-Academic Center Pilot Experience

Megan Schramski[1], Darrell Randle[1], Joyce A Wahr[2], Tjorvi Perry[1]

[1]University of Minnesota, Minneapolis, MN, [2]University of Minnesota Medical School, Minneapolis, MN

INTRODUCTION: Preoperative frailty, poor nutritional status and preexisting cognitive decline are associated with worse outcomes following orthopedic surgery.[1-4] However, little is known about immediate postoperative outcomes associated with these conditions. We hypothesize that orthopedic surgical spine patients who meet criteria for frailty will have longer hospital lengths of stay (HLOS) and will be less likely to be discharged home from their index hospitalization. Furthermore, we hypothesize that frail patients are more likely to be malnourished with preexisting cognitive decline.

METHODS: In this single-center, retrospective observational study, preoperative assessment of frailty, nutrition and cognition was performed on nineteen orthopedic surgical spine patients using the Edmonton Frail Scale (EFS), the Duke Activity Scale Index (DASI), the Pre-Operative Nutrition Screen (PONS), the Mini Cognitive Assessment (Mini-Cog), and the Fall Risk Screen (FRS). Demographic data and outcomes (HLOS and discharge disposition) were extracted from the Electronic Medical Record. Patients were divided into two groups: Frail (EFS 6-17) and Non-Frail (EFS less than 5). Data are described as means (± SD) and percentages. $P<0.05$ was considered statistically significant.

RESULTS: Between 06/10/20 and 10/28/20, nineteen patients were assessed in our preoperative anesthesia clinic prior to orthopedic spine surgery. Of these, 58% met criteria for frailty. Compared to non-frail patients, frail patients were younger and female (Table). There was no statistically significant difference in HLOS, however a clinically meaningful number of frail patients were not discharged to home following their index hospitalization. Although there were no meaningful differences in the DASI, PONS or Mini-Cog scores, the frail patients scored significantly lower on FRS.

CONCLUSION: In this small observational study, 58% of our orthopedic surgical patients met criteria for preoperative frailty. These patients were less likely to be discharged to home and were predisposed to having increased risk of falls. Future work will be directed at increasing our sample size and identifying modifiable risk factors for frailty where pre-habilitation efforts may be implemented.

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Table 1. Frailty Outcomes for Orthopedic Surgical Patients

	Frail N=11	Non-Frail N=8	P Value
Demographic Data			
Age (Years) (Mean ± SD)	50.9 ± 12.2	65.5 ± 7.2	0.005*
Female, N (%)	6 (54.6)	1 (12.5)	0.061
Race (White), N (%)	11 (100)	8 (100)	NA
BMI (Mean ± SD)	28.9 ± 9.5	31.0 ± 6.4	0.576
Frailty Testing Outcomes			
Frailty Score (Mean ± SD)	7.2 ± 1.1	3.1 ± 1.0	<0.001*
Nutrition Screen (% Positive)	27.3	0	0.108
DASI Score (Mean ± SD)	18.9 ± 11.9	32.9 ± 15.9	0.056
Fall Risk Screen (% Positive)	100	50.0	0.008*
Mini-Cog Test (Mean ± SD)	3.6 ± 1.4	4.3 ± 0.9	0.267
Clinical Outcomes			
HLOS (Days) (Mean ± SD)	4.4 ± 3.7	4.3 ± 2.7	0.939
Disposition (% Home)	63.6	100	0.055

Data are expressed as means ± standard deviation, or absolute numbers (n) and percent (%). *p<0.05.
Abbreviations: BMI: body mass index. SD: standard deviation. HLOS: hospital length of stay. DASI: Duke Activity Status Index.

PERIOPERATIVE ANESTHESIA 25

Feasibility of Recruiting Elective Spinal Surgery Patients in the Preoperative Anesthesia Clinic for a Tele-Health Behavioral Pain Management Intervention Study During the COVID-19 Pandemic

Maryam Hussain[1], Rosalie Macias[2], Gabrielle Santiago[2], Monica Lu[2], Margeaux Epner[2], Chase Plowman[2], Brett Dillon[2], Geanise Nguyen[2], Ahmed Zaafran[3], Jennifer Klljajic[4], Roohina Diwan[4], Jessica Stark[2], Albert Fenoy[2], Evan G Pivalizza[5]

[1]University of California - Merced, Merced, United States of America, [2]UTHealth McGovern Medical School, Houston, United States of America, [3]Stanford University School of Medicine, Palo Alto, United States of America, [4]Lucid Lane, Los Altos, United States of America, [5]UTHealth McGovern Medical School, Houston, TX

INTRODUCTION: In anticipation of a surge of SARS-CoV-2 (COVID-19) infections and demand for personal protective equipment, the American College of Surgeons recommended postponing or canceling elective procedures in March 2020[1]. As elective surgery restrictions changed, researchers had to adjust strategy on conducting perioperative trials[2]. Emerging literature suggested that study investigators consider ethical principles, local/national guidelines, local pandemic risk, limited study staffing, and participant exposure to COVID-19 to decide the best course of action[2,3]. The purpose of this report was to describe the feasibility of continuing with a study of a HIPAA-compliant telehealth behavioral pain management and opioid tapering program for post-surgical spine patients. We examined the process of recruiting patients, retention of consented patients for the 1st post-surgical telehealth intervention appointment and predictors of retention.

METHODS: The study is a prospective parallel arm study examining the effects of weekly telehealth behavioral therapy on opioid naive (no opioid exposure in the last 30 days) and opioid tolerant (taking an opioid at least once during the last 30 days) patients. Recruitment was planned in the preoperative anesthesia clinic of a large urban hospital that serves mixed socioeconomic communities. Due to local COVID-19 restrictions temporarily halting the in-person clinic for a period, recruitment was attempted on the morning of surgery until clinic activities slowly resumed. Within the bustle of preoperative preparation, recruitment on the day of surgery was challenging given limitation of adequate time for subjects to consider participation. Medical students on a clinical research rotation and an external investigator were available for recruitment as their schedule allowed so was unintentionally random. Inclusion criteria included adults (aged 18+ years) undergoing elective spine surgery with 4 identified surgeons who would be receiving postoperative opioids. Subjects needed access to a smartphone or computer with video capabilities and agreed to have therapy summaries shared with their surgical team. Outcomes of interest include number of patients consented and number of consented patients that successfully engaged in their 1st post-surgical telehealth appointment. Binary logistic regression was used to determine odds ratios for successful first appointment.

RESULTS: From August 2020, 72 patients scheduled for elective spine surgery were approached. 37 (51.4%) consented to participation of which, 15 (40.5%) successfully attended the 1st post-surgical intervention appointment to date (demographics shown in Table 1). The likelihood of attending the 1st appointment did not differ by prior opioid use, gender, ethnicity or age (Table 2).

CONCLUSION: In this preliminary report of a small cohort of an ongoing study of postsurgical telehealth interventions to assist patients with postoperative opioid weaning, we describe challenges with recruitment during the COVID-19 pandemic. Although elective surgery resumed, appropriate safety considerations for the preoperative clinic and increased use of virtual assessment likely impacted subject follow-up to the 1st post operative appointment. In a behavioral study, adequate time is necessary to perform baseline survey instruments, engage the subject and reinforce the potential mental health benefits of postoperative participation. We suggest that in the current pandemic, limited preoperative anesthesia clinic availability may not be ideal for recruitment for perioperative clinical studies. Given the expansion and success of telehealth platforms in the preoperative setting, use of a HIPAA-compliant telehealth platform for study recruitment would allow for adequate time to increase recruitment for a clinical study[2]. In the small cohort, there were no differences in likelihood of attending the1st post-surgical telehealth intervention. Further data on the impact of the intervention program on postoperative patient outcomes are awaited as enrollment continues to accrue.

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Table 1.

Demographics and length of opioid use on consented patients (*n* =37)

	n (%)
Opioid Use- Tolerant	12 (32.4)
Attended 1st Appointment	16 (43.2)
Ethnicity	
White	17 (45.9)
Black	10 (27.0)
Hispanic	10 (27.0)
Gender- Female	24 (64.9)
	M (SD)
Age (years)	55.3 (11.8)

Table 2.

Odds-ratios of attending 1st appointment

	OR	*95% CI* [LL, UL]
Opioid Use (Tolerant)	1.50	[.38, 6.00]
Ethnicity (White)	1.17	[.316, 4.32]
Gender (Female)	.74	[.187, 2.92]
Age	1.00	[.95, 1.06]

Note. *OR* = odds ratio; predictor reference value is noted in parentheses for categorical variables

PERIOPERATIVE ANESTHESIA 26

Anesthesia and the Gut Microbiome: Exploring the Effects of Isoflurane, Propofol, and Supplemental Oxygen in a Murine Model of General Anesthesia

Mara A Serbanescu[1], Reilley P Mathena[1], Jing Xu[2], Sivapriya Ramamoorthy[3], James White[4], Cyrus D Mintz[5]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins School of Medicine, baltimore, MD, [3]Metabolon, Inc, Durham, NC, [4]Resphera Biosciences, Baltimore, MD, [5]Johns Hopkins School of Medicine, Baltimore, MD

INTRODUCTION: Derangements in the composition and/or function of the intestinal microbiota, a state known as microbial dysbiosis, have been shown to alter local and systemic immune responses rendering the host more susceptible to infection. The gut microbiome provides crucial molecular cues directly through microbial surface antigens, and indirectly by regulation of biochemical pathways and the synthesis of metabolites which in turn influence innate and adaptive responses essential to host immunity. For example, gut-derived short chain fatty acids exert anti-inflammatory properties by strengthening gut mucosal integrity and promoting T-reg differentiation, and amino acids like arginine contribute to macrophage and T-cell activation[1]. Thus far, however, little is known about the effects of anesthetic practices on the gut microbiome and related metabolites, largely due to a paucity of investigations. We have shown in a previous study that after four hours of general anesthesia with isoflurane, the composition of the murine intestinal microbiome is altered up to seven days after exposure[2]. However, the contribution of inhaled oxygen to these alterations, and whether these findings extended to intravenous anesthetics, remains incompletely understood. Moreover, whether the effects of anesthetics on the gut microbiome also confer changes in microbial-mediated metabolites has been unexplored altogether. We hypothesized that practices commonly employed in the operating room – such as the administration of supplemental oxygen as well as inhaled and intravenous anesthetics – result in distinct changes in the gut microbial environment and are accompanied by derangements in microbial-mediated metabolites. To this end, we used a multi-omics approach including 16s rRNA sequencing and untargeted metabolomics in a mouse model to explore how brief exposure to 100% oxygen, isoflurane, and propofol separately affect the gut microbiota and associated metabolites.

METHODS: Briefly, 12-14 week-old C57/BL6 cagemates were exposed to one of four interventions (n=8 per group): 100% oxygen, 1.5% isoflurane in 100% oxygen, intravenous propofol infusion (equivalent to 200ug/kg/hr), and intravenous intralipid. Fecal samples were collected immediately prior to exposure, and at 3 and 7 days after. At each time point, samples from each mouse were divided and sent for both 16s rRNA sequencing to generate taxonomic profiles, and untargeted metabolomics by gas chromatography-mass spectrometry (GC-MS) for identification of fecal metabolites. We then analyzed the changes over time in taxonomic profiles to species-level resolution, and metabolic products, both within each exposure type and between groups. Finally, we used multivariate analyses to identify significant associations between microbial species and specific metabolites. Comparisons were made between exposure to isoflurane and oxygen, propofol and intralipid, and isoflurane and propofol.

RESULTS: We found that both exposure to oxygen and isoflurane resulted in specific, and sometimes opposing, alterations in the composition of the gut microbiota. Differences were particularly notable in the abundances of several species belonging to the genera Lachnospiraceae and Ruminococcaceae (Clostridiales order) which have been implicated in host immune responses and short-chain fatty acid production. While exposure to oxygen alone increased the abundance of these taxa in day 3 and day 7, these populations declined significantly in the isoflurane group. In contrast, propofol and intralipid yielded significantly different effects on other members of the Clostridiales order: taxa from the genera Peptococcus and Hespellia increased in abundance at day 7 after intralipid, but decreased after propofol. We also found that different exposures resulted in characteristic alterations in metabolic pathways. For example, exposure to isoflurane was associated with significant increases in the concentration of argininate and arginine when compared to oxygen and propofol. Finally, we discovered over 30 significant, microbiome-metabolite pairs in our multivariate analysis and identified distinct metabolic changes that are a result of both exposure-specific as well as microbiota-specific interactions.

CONCLUSION: The present study confirmed that multiple therapies routinely used during the provision of general anesthesia are associated with significant alterations in the gut microbiota and their metabolites, and have the potential to shape key immune responses.

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PERIOPERATIVE ANESTHESIA 27

Ketamine Prevents Sevoflurane-Induced Persistent Memory Deficits in Mice

Daheng Liu[1], Shahin Khodaei[1], Dian-Shi Wang[1], Beverley A Orser[2]

[1]University of Toronto, Toronto, Ontario, [2]University of Toronto Faculty of Medicine, Toronto, Ontario

INTRODUCTION: Many surgical patients experience persistent cognitive impairments in the postoperative period and general anesthetic drugs may be a contributing factor[1]. In preclinical studies, we showed that a brief exposure to a general anesthetic drug triggers a sustained increase in the activity of α5 subunit-containing GABAA receptors (α5GABAARs) and this increase is associated with sustained memory deficits in mice[2,3]. Several clinical studies have shown that a subanesthetic dose of ketamine attenuates postoperative cognitive deficits in surgical patients while other studies have shown no cognition-sparing effects[4,5]. Thus, the cognition-sparing properties of ketamine remains controversial[6]. Interestingly, our preliminary in vitro studies show that ketamine prevents the sustained increase in α5GABAAR activity triggered by sevoflurane in cultured hippocampal neurons. The goal of this in vivo study was to determine whether ketamine attenuates sevoflurane-induced sustained memory deficits in mice.

METHODS: Male C57BL/6 mice ranging from 8-15 weeks old were handled for 7 days. On day 7, they were anesthetized with 2.3% sevoflurane for 2 hours in a heated and oxygenated environment; control mice were exposed to 30% O2 for 20 minutes. To assess effects of ketamine, some mice were injected with a subanesthetic dose of ketamine (10 mg/kg, I.P.) while other mice were injected with a vehicle 30 minutes prior to sevoflurane exposure. Twenty-four and 48 hours after drug treatment, the mice underwent memory testing with the novel object recognition (NOR) assay, which assesses recognition memory, and the object location recognition (OLR) test, which assesses spatial memory, respectively. Behavior data were scored by an observer who was blinded to the treatment groups. Memory performance was quantified using the discrimination ratio, which was defined as the time spent interacting with the novel or displaced object divided by the total interaction time with all objects. For the NOR and OLR assays, the chance levels are 0.5 and 0.33, respectively; discrimination ratio values significantly greater than chance values were deemed to indicate preference for the novel or the displaced object. A one-sample t-test was used to compare discrimination ratios. Mice that spent less than 1 second interacting with any of the objects were excluded from analyses.

RESULTS: The discrimination ratio of control mice was greater than the chance level in the NOR assay (0.62 ± 0.14, n = 16, $P < 0.01$); in contrast, the discrimination ratio of sevoflurane-treated mice was not (0.54 ± 0.12, n = 17, P = 0.20). There was a trend towards significant difference between the two groups (P = 0.059). Similarly, the discrimination ratio of mice treated with sevoflurane and vehicle was similar to the chance value (0.49 ± 0.16, n = 18, P = 0.75). However, discrimination ratio of sevoflurane treated mice that were preinjected with ketamine was significantly higher than the chance level (0.58 ± 0.16, n = 18, P = 0.045). There was no significant difference in discrimination ratios between these two groups (P = 0.090). For the OLR assay, control mice demonstrated a significantly higher discrimination ratio than the chance level (0.48 ± 0.09, n = 17, $P < 0.0001$). In comparison, the ratio decreased to the chance level (0.35 ± 0.12, n = 17, P = 0.48) after sevoflurane treatment. There was a significant difference in the discrimination ratios between sevoflurane-treated and control mice ($P < 0.01$). As expected, mice treated with sevoflurane and vehicle had a ratio that was similar to the chance level (0.35 ± 0.10, n = 18, P = 0.41). The discrimination ratio was significantly higher than the chance level (0.41 ± 0.13, n = 18, P = 0.028) in mice treated with both sevoflurane and ketamine. No difference was detected between the ratios of the two groups (P = 0.17).

CONCLUSION: Sevoflurane caused persistent memory deficits in both the NOR and OLR assays, and these deficits were prevented by pretreatment with ketamine. There results are consistent with the cognitive-sparing properties of ketamine demonstrated in some clinical studies. Future studies will determine whether ketamine can similarly prevent persistent memory deficits induced by injectable anesthetics.

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PERIOPERATIVE ANESTHESIA 28

Use of Artificial Intelligence (AI) in Predicting the Length of Hospital Stay for Spinal Surgical Procedures

Zhaoyi Tang[1], Jun Tang[1], Benison Pang[2], Steve Sun[3], Stephan Yang[1]

[1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]Cedars Sinai Medical Center, Los Angeles, CA, [3]Cedars Sinai Medical Center, Los Angeles, United States of America

INTRODUCTION: Enhanced Recovery after Surgery (ERAS) protocols are multimodal and multidisciplinary perioperative care strategies, and have been demonstrated to be associated with facilitated functional recovery process, improved patient experience and outcomes, reduced cost and length of hospital stay (LOS)[1,2]. Recently, artificial intelligence (AI) devices (intelligent data analysis systems that possess the ability to store, process and utilize experiential knowledge) have been developed and successfully used in both the diagnosis of disease and prediction of outcomes[3]. However, there is no data related to AI programs on the recovery process after spine surgical procedures following the ERAS protocol. In this retrospective analysis, we evaluated the validity and feasibility of AI to predict the LOS in spinal surgeries with the implementation of ERAS protocol.

METHODS: The medical, surgical and anesthesia records of 3597 patients aged ≥ 18 yr and ASA 1-3 who had undergone elective spinal surgical procedures between 2017 and early 2020 in our institution were reviewed. All patients were enrolled in both the ERAS spine protocol and daily Progression of Care Rounds (POCR) program (multidisciplinary team members continuously provided patient care by addressing key points for each patient and taking necessary steps to improve the patient recovery process). To predict postoperative LOS, 76 features were used to form the training set for this study. The training data was used to train 20 different machine learning models in our institutional AI machine learning framework, which were then ranked and compared using root mean squared error (RMSE) as the optimization metric. The advantage of this AI device is its ability to consistently learn from simulations to identify the core impact factors for the LOS after spine surgeries. Furthermore, the best predictors can be modified and adjusted as data changes.

RESULTS: There were 76 different variables used in this AI study, including (1) pre-operative: age, gender, preexisting conditions, etc.; (2) intra-operative: duration of surgery, duration of anesthesia, type of surgery, etc.; (3) postoperative: pain scores, narcotic dosages, time spent in post-anethesia care, postoperative complications, ect. The most important predictors for LOS in this study were duration of surgery, patient age and procedure type. Interestingly, the best model, a Random Forest regressor, had an RMSE of 2.14 and Mean Absolute Error of 1.6 on the holdout data.

CONCLUSION: In this retrospective study, the results suggested that AI can become a viable predictor for LOS after spinal surgery especially with the implementation of ERAS protocol. Future studies are needed to (1) increase model transparency such that AI will gain a deeper understanding for individual variables, (2) improve prediction of LOS to less than 1 day, (3) realize the barriers for discharge by the AI and allow medical staff to act immediately, (4) predict the cost of care for hospital operations.

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PERIOPERATIVE ANESTHESIA 29

Predictive Analytics for Inpatient Postoperative Opioid Use in Patients Undergoing Mastectomy

Isabella Dolendo[1], Rodney Gabriel[2]

[1]University of California, San Diego, La Jolla, CA, [2]University of California, San Diego, La Jolla, United States of America

INTRODUCTION: The use of opioids in patients undergoing mastectomy is a particular challenge, having to balance the management of acute pain while minimizing risks of continuous opioid use postoperatively. The goal of this study is to identify risk factors and to develop machine-learning based models to predict patients who are at higher risk for acute postoperative opioid use after mastectomy. The ability to predict patients' postoperative pain could have significant impact on preoperative counseling and patient satisfaction. Additionally, the predictive ability may direct different pain management techniques perioperatively (i.e. intercostal cryoanalgesia or two-level paravertebral catheters)[1-3].

METHODS: In this retrospective cohort study, we collected data from all patients that underwent mastectomy procedure from either of two surgeons from 2019 to 2020. The primary outcome of interest was binary and defined as oxycodone milligram equivalents (OME) greater than or equal to the 75% of OME use on postoperative day 1. We included a number of surgical and patient characteristics as independent variables. We performed multivariable logistic regression, lasso, ridge regression, and elastic net regression to develop predictive models. Model performance (area under the receiver operating characteristics curve [AUC]) was calculated via 10-fold cross-validation. Odds ratio (OR) and 95% confidence intervals (CI) were reported for significant predictors.

RESULTS: There was a total of 148 patients that underwent mastectomy included in our final analysis. The medium [quartiles] postoperative day 1 opioid use was 5mg OME [0, 25mg OME] with a range from 0mg to 211.2mg OME. We separated the population into two cohorts, one with less than the third quartile of OME (25mg OME) and another with ≥ third quartile (n = 38). Table 1 lists the patient characteristics in both cohorts. On crude analysis, the only covariate that was statistically significantly different in both cohorts was whether patient was post-menopausal (42.7% vs. 21.1% in the lower versus higher opioid use cohorts, respectively, p = 0.03). We performed a multivariable logistic regression model with variable selection in order to identify specific covariates associated with opioid use and to develop a predictive model. From this model (Table 2), the most protective factors against higher opioid use was being post-menopausal (OR 0.13, 95% CI 0.03 – 0.61, p = 0.009) and cancer diagnosis (OR 0.19, 95% CI 0.05 – 0.73, p = 0.01). The predictive model had an AUC of 0.777 (95% CI 0.699 – 0.855) and the HL-test demonstrated adequate goodness-of-fit (p=0.59) (Figure 1). On 10-fold cross-validation, the average AUC was 0.725 (95% CI 0.572, 0.876). Compared to our reference model, there were no statistically significant differences between AUCs among each model: multivariable logistic regression including all variables (p=0.92), ridge regression (p=0.39), lasso (p=0.22), and elastic net regression (p=0.15).

CONCLUSION: We developed a predictive model to identify patients who are at high risk for higher acute opioid use after mastectomy. Using different machine learning approaches, we found that logistic regression performed just as well as other methodologies. The model had excellent discrimination and included predictors such as post-menopausal, age, race, bilateral surgery, mastectomy with tissue expander placement, cancer diagnosis, depression, substance abuse history, smoking, hypertension, and asthma. Post-menopausal woman and those with a cancer diagnosis had less odds for requiring higher amounts of opioids in the acute setting. While debated, some studies have shown that post-menopausal women have higher pain tolerance while others have shown lower sensitivity to analgesics[4-5]. Women who choose prophylactic mastectomy over breast conserving treatment have higher rates of psychological distress (anxiety, depression, and pain catastrophizing) which is associated with higher postoperative pain levels[6-7]. Cancer diagnosis as a protective factor may in part be due to higher rates of resilience among this group and the association between resilience and decreased risk of high intensity acute post-operative and chronic pain[6]. Additional research is necessary to determine an appropriate methodology to apply this model in clinical settings and determine the most effective preventative measures to reduce opioid use among high-risk patients.

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		OME <75% quartile		OME ≥75% quartile		
		n	%	n	%	p-value
Total		110		38		
Mastectomy Surgery						
Node Dissection Involvement		40	36.4	12	31.6	0.74
Tissue Expander Placement		21	19.1	9	23.7	0.71
Bilateral Surgery		58	52.7	22	57.9	0.72
Cancer Diagnosis		83	75.5	23	60.5	0.12
Age (years), mean [SD]		45.5 [17.1]		40.5 [13.1]		0.06
Male Sex		11	10.0	3	7.9	0.95
BMI ≥ 35kg/m2		11	10.0	2	5.3	0.58
White Race		61	55.5	26	68.4	0.23
Non-English speaker		21	19.1	4	10.5	0.34
Transgender		24	21.8	11	28.9	0.51
Post-menopausal		47	42.7	8	21.1	0.03
ASA Physical Status Score						0.25
	1	13	11.8	7	18.4	
	2	46	41.8	19	50.0	
	3	51	46.4	12	31.6	
Active Smoker		1	0.9	2	5.3	0.33
Active Alcohol Use		43	39.1	19	50.0	0.32
Chronic Opioid Use		0	0.0	2	5.3	0.11
Illicit Drug Use		1	0.9	1	2.6	0.99
Marijuana Use		6	5.5	5	13.2	0.23
Preoperative Vital Signs						
Systolic Blood Pressure		116.5 [17.3]		112.8 [14.1]		0.19
Heart Rate		77.1 [14.2]		73.5 [11.6]		0.13
Comorbidities						
Diabetes Mellitus		6	5.5	1	2.6	0.79
Chronic Kidney Disease		4	3.6	0	0.0	0.54
Obstructive Sleep Apnea		5	4.5	3	7.9	0.71
Depression		30	27.3	6	15.8	0.23
Anxiety		24	21.8	9	23.7	0.99
ADHD		3	2.7	3	7.9	0.36
Fibromyalgia		2	1.8	2	5.3	0.58
Hypertension		29	26.4	4	10.5	0.07
COPD		1	0.9	1	2.6	0.99
Asthma		16	14.5	2	5.3	0.22
Congestive Heart Failure		0	0.0	0	0.0	0.99
Coronary Artery Disease		1	0.9	0	0.0	0.99

Table 1. Patient characteristics of the two study cohorts. Abbrivations: ADHD = attention-deficity hyperactive disorder, OME = oxycodone milligram equivalents; SD = standard deviation

	OR (95% CI)	p-value
Post-menopausal	0.13 (0.03 - 0.61)	0.009
Age (years)	1.04 (0.99 - 1.09)	0.12
Mastectomy with Tissue Expander Placement	2.12 (0.73 - 6.17)	0.17
Bilateral Surgery	0.36 (0.11 - 1.17)	0.09
Cancer Diagnosis	0.19 (0.05 - 0.73)	0.01
White Race	2.95 (1.17 - 7.42)	0.02
Depression	0.31 (0.09 - 1.07)	0.06
Substance Abuse History	16.11 (0.66 - 391.8)	0.09
Active Smoker	30.99 (1.36 - 703.6)	0.03
Hypertension	0.28 (0.06 - 1.20)	0.09
Asthma	0.19 (0.03 - 1.09)	0.06

Table 2. Results of the multivariable logistic regression, in which the outcome was oxycodone equivalents ≥ 75% quartile on postoperative day 1. The final model was developed by a combination of forward selection and backwards elimination based on the Akaike Information Criterion. Only covariates with p<0.2 were allowed to stay in the final model. Abbreviations: CI= confidence interval, OR = odds ratio

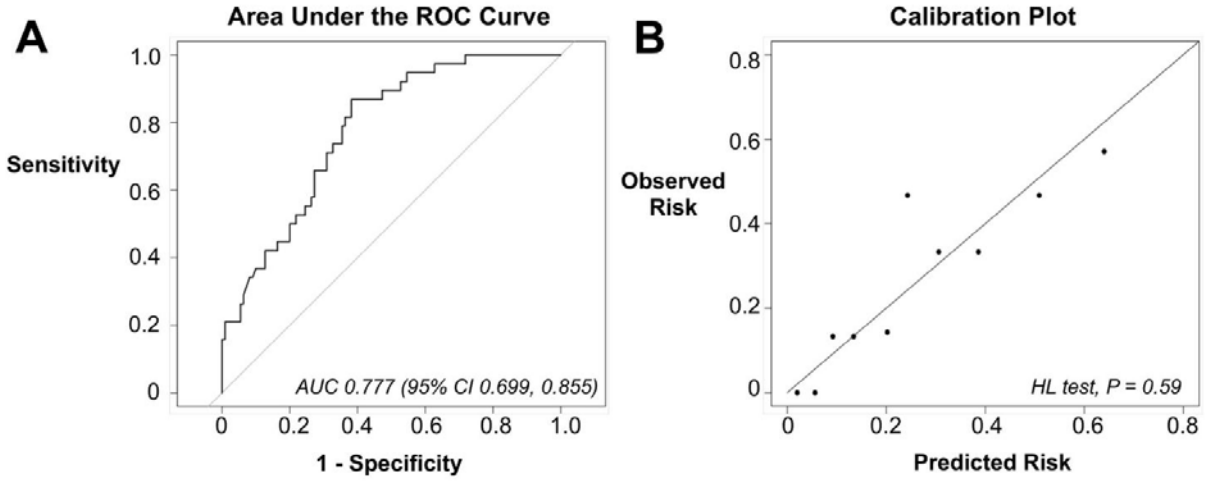

Figure 1. Performance of the multivariable logistic regression with variable selection predicting patients at risk for higher acute opioid use on postoperative day 1: A) area under the receiver operating characteristics curve and B) calibration plot illustration goodness-of-fit. Abbreviations: AUC = area under the receiver operating characteristics curve, CI = confidence interval, HL = Hosmer-Lemeshow, ROC = receiver operating characteristics.

PERIOPERATIVE ANESTHESIA 30

Comparison of Visual and Electromyography Assessments in Response to Train-of-Four Stimulation

Vivian Hernandez[1], Johnathan R Renew[2], Sorin J Brull[3], Richard Pence[4]

[1]Mayo Clinic, JACKSONVILLE, FL, [2]Mayo Clinic Florida, Jacksonville , FL, [3]Mayo Clinic Florida, Jacksonville, FL, [4]Mayo Clinic, Jacksonville, United States of America

INTRODUCTION: Neuromuscular blocking agents (NMBAs) are a class of medications routinely used during anesthesia to facilitate endotracheal intubation and optimize surgical conditions. However, these medications are also associated with respiratory complications in the early postoperative period due to residual neuromuscular blockade (RNMB) (1-3). Even when neuromuscular blockade is reversed in the operating room, postoperative RNMB continues to be a common problem in the post-anesthesia care unit (PACU), and a significant number of patients have objective evidence of muscle weakness. The use of quantitative monitoring was shown to reliably reduce the incidence of postoperative residual weakness and ensuing complications. Many clinicians default to the antiquated and unreliable practice of subjective monitoring, which includes visual or tactile evaluation of the train-of-four (TOF) in response to neurostimulation provided by peripheral nerve stimulation. The aim of this study is to correlate electromyographic responses of the adductor pollicis muscle obtained with the TetraGraph (Senzime AB, Uppsala, Sweden) monitor with visual (subjective) assessment of the thumb movement, throughout various stages of neuromuscular blockade.

METHODS: After IRB approval, 20 adult patients scheduled for elective surgery requiring neuromuscular blockade were screened and enrolled after giving written informed consent. Intraoperative NMBA management and antagonism was at the discretion of the anesthesiologist. Prior to induction of anesthesia, Tetragraph electrodes were placed over the ulnar nerve and the thumb randomly assigned to their dominant or non-dominant hand. Anesthesia providers were blinded to the TetraGraph values during the entire procedure. After every dose of NMBA administration, and before and after sugammadex antagonism, a set of EMG measurements was obtained, and the researcher asked the provider to give a subjective assessment of the TOF count based on the visual assessment following peripheral nerve stimulation of ulnar nerve with TetraGraph. A paired sample t-test was used to compare the mean score in the different time periods.

RESULTS: Twenty patients (aged 58 ± 14 yr) were enrolled in the study. One patient was excluded due to profuse sweating that precluded the electrodes of either monitor from adhering to the skin. Anesthesia providers were CRNAs in all cases. In the 19 patients, a total of 218 observation pairs were collected. Compared to TetraGraph, anesthesia providers subjectively assessed a higher TOF count in 114 (53%) observations and a lower count in 18 (8%) observations. Intraoperatively, providers assessed a higher TOF count especially during maintenance and before sugammadex. There was a significant difference obtained from measurements obtained just prior to maintenance dosing that maintained neuromuscular blockade, and before sugammadex (95% CI; -1.22 to 0.55, p <0.001) and (95% CI; -1.87 and -0.33, p 0.007) respectively. Medians were 0 for objective assessment and 1 for subjective. IQR was 1-0 and 4-2 respectively. The incidence of residual paralysis was 16% at the time of extubation.

CONCLUSION: This study demonstrated that anesthesia providers assessed a significantly higher TOF count using visual assessment than the quantitative data obtained from the TetraGraph. The subjective assessment of TOF count may affect clinical care, and lead to inappropriate administration of NMBAs and/or premature administration of the reversal agents. Subjective evaluation may provide inaccurate information and assessment of full recovery compared to objective evaluation placing the patients at increased risk of residual block and attendant complications.

PERIOPERATIVE ANESTHESIA 31

Prevalence and Associated Characteristics of Hospitalized Patients with DNAR Orders

Kelly Cheung[1], Ashton Engdahl[1], Jason Gassman[1], Deividas Gustainis[1], Alex Saffran[1], Perry Taylor[1], Sarah Hobgood[1], W. Paul Murphy[1]

[1]Virginia Commonwealth University School of Medicine, Richmond, United States of America

INTRODUCTION: Anesthesiologists face a unique challenge when caring for patients with 'do not attempt resuscitation' (DNAR) orders, as resuscitation is an integral part of anesthetic practice. The American Society of Anesthesiologists (ASA) guidelines suggest discussing DNAR orders preoperatively to ensure patients' goals of care are met and that relevant aspects of this communication are documented. If DNAR orders are suspended, definitive plans to reinstate pre-existing directives post-operatively must be determined. However, studies show that these discussions are often not held or inadequately documented. Examining the demographics and clinical characteristics of preoperative patients with DNAR orders may help facilitate conversations about goals of care. Previous studies have demonstrated higher prevalence of DNAR orders with increasing age, white race, acute settings, and emergent surgeries. Additionally, patients in the cardiac and medical intensive care units and internal medicine wards have a higher prevalence of DNAR orders in comparison to the surgical wards and emergency department. However, literature on additional factors affecting DNAR status remains limited, including involvement of geriatric and palliative care services and proper documentation and adjustment of DNAR orders. As part of a quality improvement initiative, the aims of this study were to 1) identify the prevalence of DNAR orders in hospitalized patients and 2) determine how this prevalence varies by preoperative characteristics.

METHODS: Data was collected from our electronic medical record on 560,031 DNAR orders placed from 1/1/2016 to 12/31/2020. 211,417 unique medical record numbers (MRNs) were identified during that period. DNAR orders that appeared under an MRN more than once were separated from unique DNAR orders. Descriptive statistics were used to summarize the prevalence of all DNAR orders over time and unique DNAR and non-DNAR orders by race, ASA class, surgery cases, emergent and elective surgeries, admitting service, admitting level of care, and geriatrics/palliative care services. Non-DNAR orders were patients with a full code or attempt resuscitation order. Pediatric patients (< 18-years-old) and pediatric services were excluded.

RESULTS: The prevalence of all DNAR orders from 2016-2020 appeared to remain stable over time or increase slightly in the latter years (Figure 1). 10,306 unique DNAR orders and 206,835 unique non-DNAR orders were identified. Patients aged 80 and up had the highest prevalence of DNAR orders, while patients aged 18-44 had the highest percentage of non-DNAR orders (Table 1, Figure 2). The percentage of DNARs in white, African-American, and Asian patients were 6%, 4%, and 3% (Table 1), respectively. Full results will be presented at the conference. We anticipate that the majority of patients receiving palliative or geriatric services during their visit will have more DNAR orders compared to all other patients not receiving these services. We also suspect that patients undergoing emergent surgeries will have a lower prevalence of DNAR orders and that patients classified as ASA 3 to 4 will have a higher number of DNARs. Finally, it is anticipated that DNAR orders will be highest at an intensive level of care and in the medical respiratory ICU, internal medicine unit and the cardiac ICU.

CONCLUSION: The present study found that older patients had a higher percentage of DNAR orders. Contrary to existing literature, however, this study found that African-American patients had a higher than expected number of DNAR orders. It is imperative to approach conversations about DNAR to ensure that patients' wishes are honored during surgery and anesthesia. Understanding the prevalence of DNAR orders and the associated characteristics of hospitalized patients with DNAR orders could better assist anesthesiologists in initiating these discussions. Future directions of research include assessing the quality of DNAR discussions, barriers to efficient documentation of DNAR orders, and determining risk factors that prevent DNAR orders from being fulfilled during the perioperative period.

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Table 1. Characteristics of DNAR Orders and non-DNAR orders

	DNAR	non-DNAR	%DNAR	%non-DNAR
Age				
18-44	732	102679	1%	99%
45-64	3426	69816	5%	95%
65-80	3974	32506	11%	89%
>80	2247	6584	25%	75%
Race				
American Indian-Alaskan	4	249	2%	98%
Asian	62	2181	3%	97%
Black or African American	4034	91877	4%	96%
Multiple	37	524	7%	93%
Native Hawaii/Other Pac Island	4	65	6%	94%
Other	318	15226	2%	98%
Unknown	297	3703	7%	93%
White	5550	93010	6%	94%

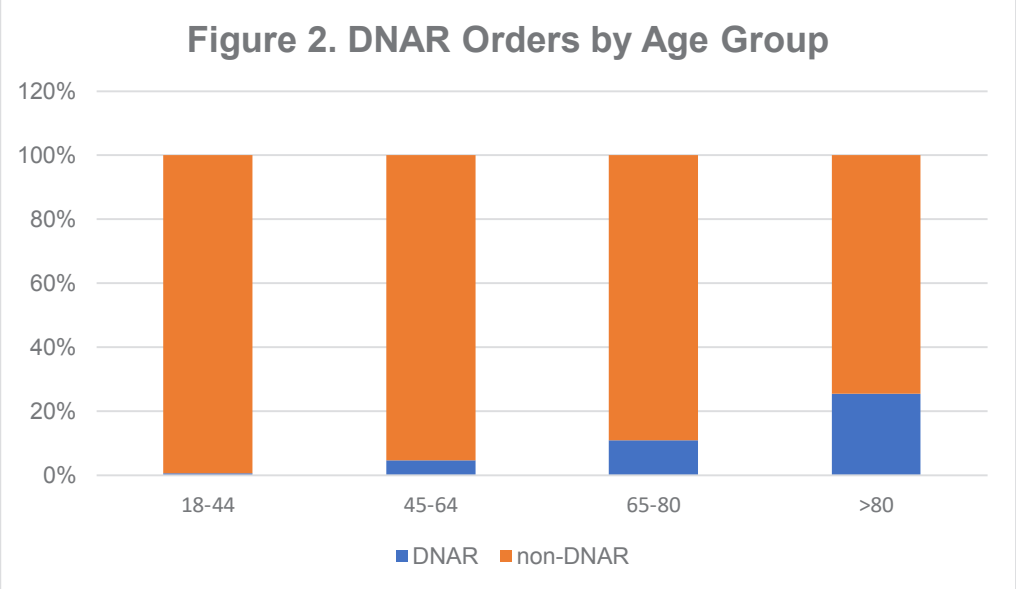
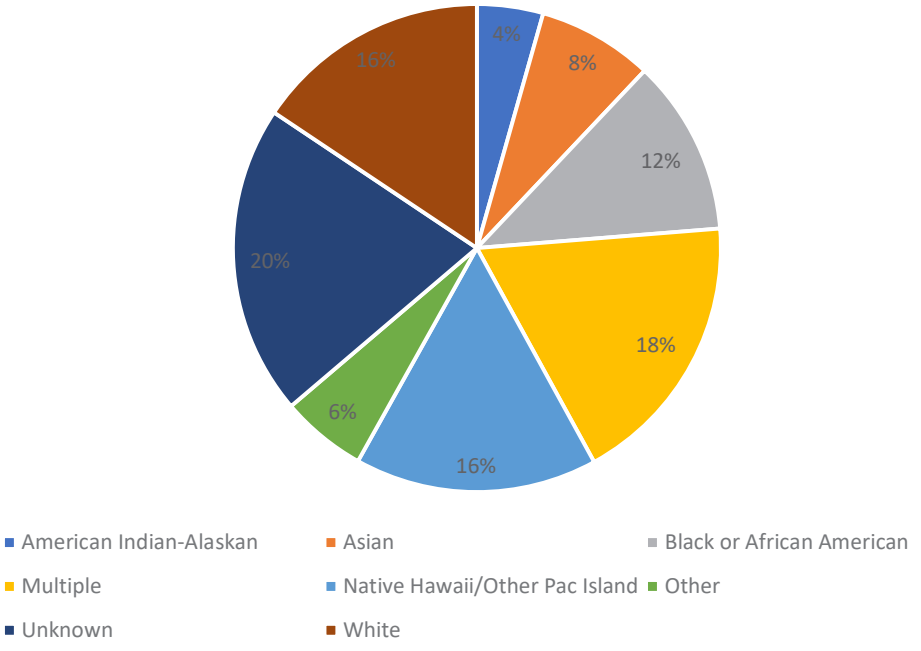
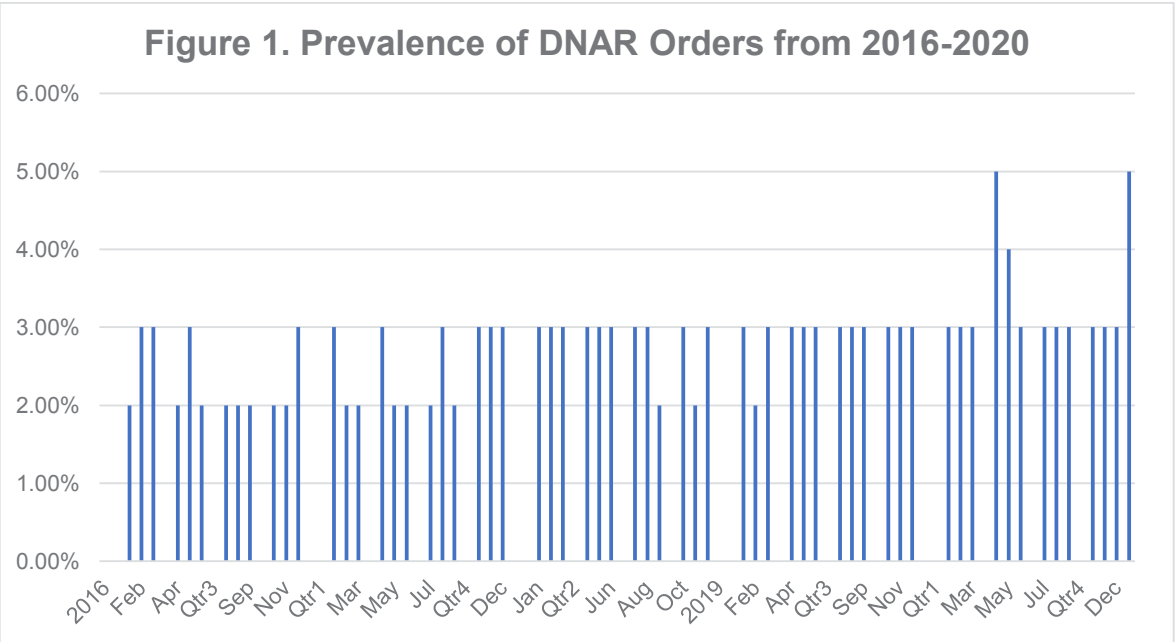


Figure 3. DNAR Orders by Race





PERIOPERATIVE ANESTHESIA 32

Reasons for Elective Surgery Case Cancelations-A Single-Center Retrospective Study

Atsumi Kimura[1], Agathe Streiff[2], Isabel Pesola[2], Samuel Herzig[2], Singh Nair[2], Curtis Choice[2]

[1]Albert Einstein College of Medicine, Bronx, NY, [2]Montefiore Medical Center, Bronx, NY

INTRODUCTION: Cancelations of elective procedures on the intended day of surgery constitute a substantial financial burden. Cancelations can also have significant psychological, social, and financial implications for patients and their families. The reported rate of operation room (OR) cancelations varies from as low as 0.21% to as high as 27% in the US. Common reasons for cancelations include acute changes in medical condition, inability to follow preoperative instructions, and patient-related non-medical issues. In this retrospective study, we evaluate reasons for cancelations of elective procedures on the day of surgery and assess whether some same-day cancelations were potentially avoidable.

METHODS: We included all same-day cancelations of elective procedures scheduled between September 1–October 27, 2020 across four medical centers associated with Montefiore Medical Center. Medical records were reviewed for the type of surgery, ASA status, documented reasons for OR cancelation, and record of pre-anesthetic testing (PAT) visit with Anesthesiology. Reasons for cancelations were divided into four categories: medical/preventable, medical/non-preventable, non-medical/preventable, non-medical/non-preventable. We used descriptive statistics to report our data.

RESULTS: There were 296 case cancelations (6.0%) out of 4939 cases that were scheduled during the study period. Figure 1 depicts the rate of case cancelation in the stand-alone ambulatory surgery center (ASC) and hospitals. The mean age of patients who had cancelations was 51 years, among whom 150 (50.7%) were male. The specialty associated with most cancelations on the day of surgery was orthopedics (54 cases; 18.2%), followed by general surgery (50 cases; 16.9%) and urology (50 cases; 16.9%). Among cancelations, 153 (51.7%) cases were classified as preventable, of which 53 were due to medical reasons and 100 due to non-medical reasons. Additionally, 120 (40.5%) cases were assessed to have a non-preventable reason. The reason for cancelation could not be identified in 23 cases. Among canceled cases, only 44 patients were seen in the PAT clinic; of these, 7 cases were medical/preventable, 23 cases were medical/non-preventable, 9 cases were non-medical/non-preventable, and five did not have a documented reason. Compared to 2017-2018, ASC cancelation rate decreased from 8.1% to 6.8% in the study period.

CONCLUSION: During our assessment, we found that an overwhelming number of cancelations were due to preventable causes. Improving proper communication between different OR services could potentially prevent case cancelations. The utilization of a checklist filled by responsible parties could make an impact in mitigating the issue. Additionally, cost-effective analysis of appointing a cancelation coordinator should be explored. The decrease in cancelation rate at the ASC may be partly explained by increased engagement between centers and patients following the first wave of the Covid-19 pandemic.

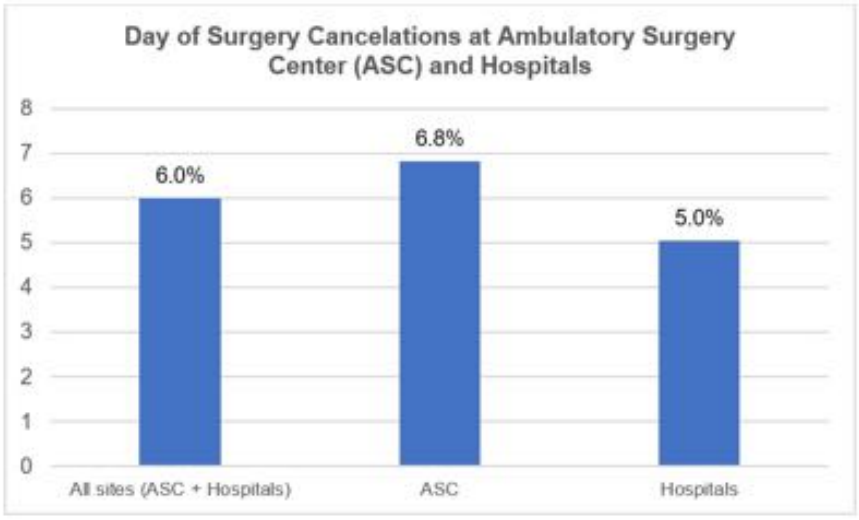


Fig.1 Comparison of case cancelations between ASC and hospitals

PERIOPERATIVE ANESTHESIA 33

Impact of Total Knee Arthroplasty on HbA1c levels in Patients with Diabetes Mellitus- A Single-Center Retrospective Study

Atsumi Kimura[1], Timothy Edmonds[2], Fadi Farah[3], Singh Nair[2], Naum Shaparin[2]

[1]Albert Einstein College of Medicine, Bronx, NY, [2]Montefiore Medical Center, Bronx, NY, [3]Montefiore Medical Center - Albert Einstein College of Medicine, Bronx, NY

INTRODUCTION: There is an increasing prevalence of multimorbidity in people undergoing joint replacements, one common condition being diabetes mellitus (DM). It has been established that regular exercise is an effective lifestyle modification for improvement in insulin sensitivity and glycemic control among DM patients. However, osteoarthritis can pose a significant barrier to mobility. Many patients with knee osteoarthritis experience increased physical function and decreased knee pain following total knee arthroplasties (TKA). An increase in mobility not only increases exercise capacity but can positively affect patients' moods and the ability to go to appointments and pharmacies. The impact of TKA on diabetes management, reflected by hemoglobin A1c (HbA1c) levels, remains unclear. In this study, we evaluate the trajectory of HbA1c values in DM patients during the period encompassing their TKA surgery.

METHODS: We identified DM patients who had a unilateral TKA between January 2015-May 2016 using a hospital proprietary software. We included patients who had HbA1c values measured closer to surgery and within two years after the surgery date. HbA1c levels were averaged in patients who had more than one pre-or postoperative HbA1c drawn. Patients were split into groups based on their preoperative HbA1c values: (<6.4, 6.5-7.4, 7.5-9.4, and >9.5). We calculated the absolute and percentage change from the baseline value. Additionally, we compared changes between the groups. We reported our results using descriptive statistics and used one-way ANOVA to compare changes between the groups. All tests are two-tailed, and a p-value of 0.05 was considered statistically significant.

RESULTS: Out of 1399 patients who had a unilateral TKA during the study period, 399 (28.5%) had a diagnosis of DM. A total of 220 patients (55%) had both pre- and postoperative HbA1c measurements. Within this cohort, 174 (79.1%) were female. Table 1 represents the median age, percentage of females, median pre-and postoperative HbA1c, and median pre-and postoperative BMI in the four groups. Additionally, Figure 1 depicts the percent change of HbA1c in each group. The median age of patients was similar across the groups. BMI was also comparable in the groups, with no significant changes before and after surgery in any group. The two groups with higher baseline HbA1c (i.e., 7.5-9.4 and >9.5) had negative percentage changes in their HbA1c levels following surgery, with a greater change seen in the >9.5 group. The other two groups (i.e., <6.4 and 6.5-7.4) had increased percentage changes in HbA1c after TKA. Additional data points will be presented at the conference.

CONCLUSION: Improvements in HbA1c levels following TKA were seen in patients who had preoperative HbA1c over 9.5 and to a lesser extent in patients with HbA1c values 7.5-9.4, while this was not observed in patients with baseline levels less than 7.5. This suggests that TKA confers benefits to glycemic control in patients with high preoperative HbA1c levels but not in those with normal or moderately controlled DM. Given minimal changes in BMI before and after surgery, it is possible that these benefits are independent of weight loss. Further studies are needed to investigate factors associated with improved HbA1c in DM patients following surgery.

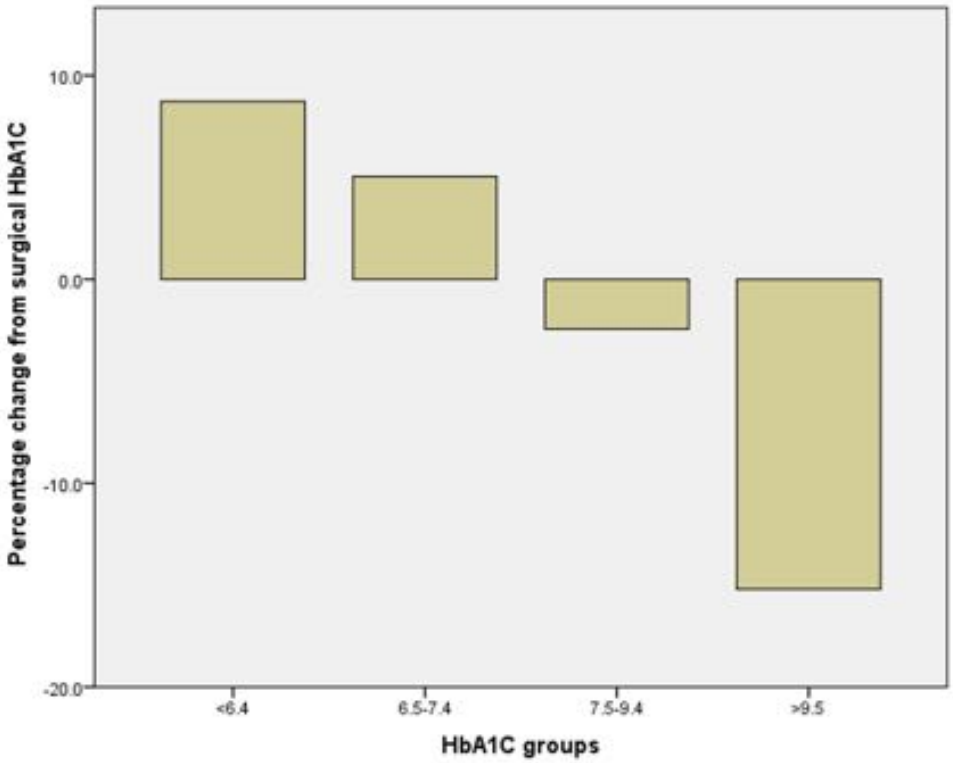


Fig.1 Percentage change in HbA1c values from baseline

Table 1: Demographics and pre- and post-surgical HbA1c values

	Baseline HbA1c <6.4	**Baseline HbA1c 6.5-7.4**	**Baseline HbA1c 7.5-9.4**	**Baseline HbA1c >9.5**	**p-value**
Age	66.0 (60.0-73.0)	66.0 (61.0-72.0)	68.0 (64.0-75.0)	70.0 (61.5-76.0)	0.477
% Female	80.2%	76.3%	80.4%	84.6%	0.862
Preoperative HbA1c	5.9 (5.6-6.1)	6.8 (6.7-7.1)	8.3 (7.8-8.8)	10.2 (9.7-11.4)	N/A
Postoperative HbA1c	6.2 (6-6.7)	7 (6.6-7.6)	8 (7.5-8.8)*	8.6 (7.8-9.5)*	0.001
Preoperative BMI	33.8 (30.4-38.9)	34.4 (30.3-42.2)	31.5 (29.2-37.1)	35.0 (32.2-40.3)	0.427
Postoperative BMI	33.6 (29.5-37.6)	34.7 (30.2-40.5)	31.8 (26.9-37.2)	34.5 (32.9-40.8)	0.051

*- not statistically significant

PERIOPERATIVE ANESTHESIA 34

An Evaluation on a Low Dose of Ketamine Preventing from Post-Induction Hypotension in General Anesthesia

Chaoxuan Dong[1], Xi Tan[1]

[1]Department of Anesthesiology, The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong

INTRODUCTION: Post-induction hypotension (PIH) is common in general anesthesia[1], directly resulting in intraoperative hypotension[2]. Although etomidate is widely employed to minimize blood pressure drop, PIH is still occurred often during the induction of general anesthesia[3]. Ketamine has a positive effect on hemodynamic changes, increasing heart work, heart rate, and blood pressure[4]. This study is to investigate whether PIH can be prevented by a low dose of ketamine administered in the induction of general anesthesia.

METHODS: In this randomized controlled clinical trial, sixty American Society of Anesthesiology (ASA) I and II patients aged 15-60 years scheduled for elective surgery under general anaesthesia were randomized into two groups: Ketamine group: received intravenous induction with midazolam (0.05mg/kg), fentanyl (4мg/kg), etomidate (0.4mg/kg) ketamine (0.25mg/kg) and cisatracurium (0.2mg/kg)intravenously; Control group: received introvenous induction with midazolam (0.05mg/kg), fentanyl (4мg/kg), etomidate (0.4mg/kg) and cisatracurium (0.2mg/kg). Patients with cardiovascular complications (hypertension, heart disease, arrhythmia), respiratory diseases (upper respiratory infection, airway stenosis), allergic to anesthesia, mental disease, epilepsy, a history of drug and alcohol abuse, diabetes, opiate-dependence were excluded. General anaesthesia was standardized in both groups. The patients and physicians administering anaesthesia were blinded to the study. Hemodynamic responses were evaluated by determining blood pressure. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at different times (pre-induction 5 min, induction, intubation, post-induction 5min, post-induction 10 min, surgery start), and the mean arterial pressure (MAP) was calculated via the formula: MAP=(SBP + 2×DBP)/3. Data were showed as mean ± standard error (M±SEM), analyzed using GraphPad Prism 5.01 statistical software. T-tests were used to compare the two groups. A satistical significance was set at $P<0.05$.

RESULTS: A low dose of ketamine during the induction did not critically increase MAP in the ketamine group compared with the control goup at different peri-induction time: Baseline ($P>0.05$), Induction ($P>0.05$), Post-Induction 5 minutes ($P>0.05$), Post-Induction 10 minutes ($P>0.05$), and Surgery Start ($P>0.05$). However, it can significantly reduce the increase of MAP during Intubation compare with the control group ($P=0.027$) (Figure 1). A limitation is that side effects of ketamine are not monitored in this study.

CONCLUSION: An induction of general anesthesia with a low dose of ketamine cannot show a significant advantage in stablizing MAP in the peri-induction. However, it prevents blood pressure from critically fluctuating in the process of intubation.

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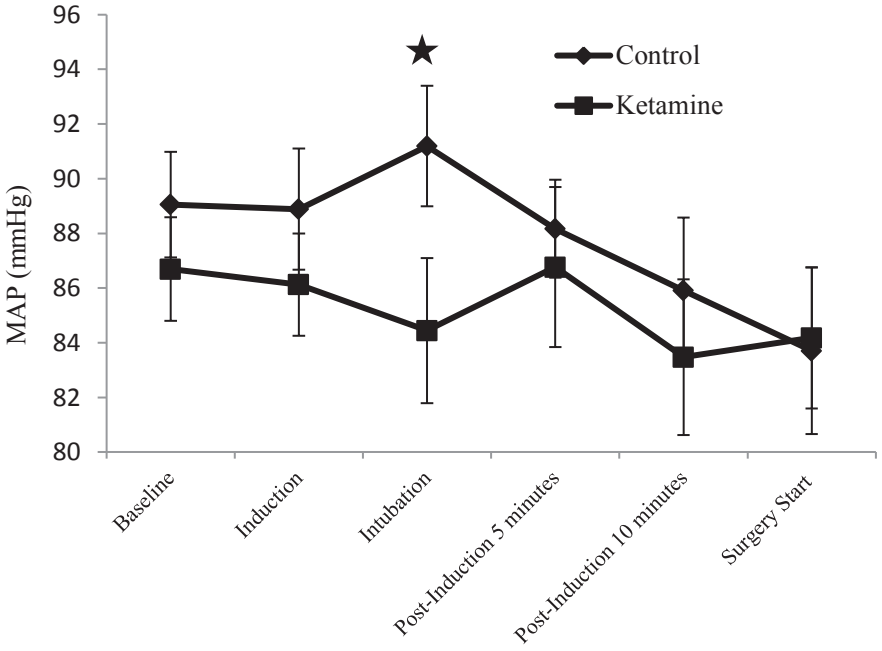
Figure 1 The effect of an induction with a low dose of ketamine on mean arterial pressure (MAP) in the peri-induction period.



PERIOPERATIVE ANESTHESIA 35

The Empathic Patient Centered Approach in the Anesthetic Preoperative Interview

Sofia Gilels[1], Dennis Grech[2], Alexa M Sangalang[3], Christine J Ha[3]

[1]Rutgers New Jersey Medical School, Fort Lee, NJ, [2]Rutgers New Jersey Medical School, newark, United States of America, [3]Rutgers New Jersey Medical School, Newark, United States of America

INTRODUCTION: Multiple studies in the primary care field have indicated the benefits of using a patient centered approach in communication with the patient; such interviewing methods have been shown to improve patient satisfaction and adherence. There is a scarcity of anesthetic literature regarding communication skills in the perioperative period. In addition, there is minimal literature on how anesthesia providers' communication skills compare to other providers in the medical field. The overall purpose of this study is to observe and grade the preoperative communication techniques used by anesthesia providers. The goal is to analyze to what extent empathic patient-centered communication methods are being used by anesthesia providers. Communication scores will be compared among providers, as well as to providers across several different subspecialties.

METHODS: This study is an observational descriptive study at a large tertiary care center, University Hospital in Newark, NJ. The observer and grader of the preoperative interviews is the medical student who is unaffiliated with the anesthesiology staff. The observer observes and grades patient interviews, scoring against established criteria using an adapted version of the Kalamazoo grading tool. The study period is 2 years (until 50 provider interviews are reached) and the subjects participate in the study for less than a half hour each. The goal of 50 provider interviews is met before participants are made aware of deception in this study. Participation is voluntary and written informed consent is obtained from anesthesia providers. Researcher is introduced as a student observer of the preoperative interview. The researcher observes and grades the preoperative interview using the adapted Kalamazoo scale. At the end of the observed encounter, the anesthesia providers are asked to fill out a brief form detailing their demographic history, details regarding the providers' length and type of clinical education and training, undergraduate education, previous communication training, number of years of practice, primary language, gender, and age will be obtained. The researcher repeats this process for 50 preoperative interviews.

RESULTS: Anesthesia providers included in the study were physician anesthesiologists, residents, and nurse anesthetists. Those with less than 6 months of experience were excluded. The average Kalamazoo score was 28.7 amongst all providers. Average scores across the 7 Kalamazoo criteria were 4.36, 4.03, 4.14, 3.86, 4.33, 3.83, and 4.14, respectively. Average physician, nurse, and resident scores were 27.5, 28.7, and 31.6 respectively. There was no significant effect of provider level on score at the $p < 0.05$ level for the three conditions [$F(2,33) = 2.192$, $p = 0.068$]. There was also no significant effect of provider level on length of encounter [$F(2,33) = 2.762$, $p = 0.077$].

CONCLUSION: The data revealed anesthesia providers provide patient-centered encounters with a mean score of 28.7, which is higher than the average for providers from multiple different specialties observed in Joyce, et al. study (mean score 25.25). This indicates anesthesia providers are implementing an empathic patient centered approach during the preoperative interview. On average, providers also scored at least 4/5 for 5 of the 7 Kalamazoo criteria. The subcategories 'Understanding patient's perspective' and 'reaches agreement' scored 3.86, and 3.83, respectively. This may indicate that anesthesia providers can improve on allowing the patient to communicate their understanding of anesthesia, as well as collecting information from the patient that can affect their anesthesia (i.e, severe nausea following previous anesthesia).The importance of continued training and enhancement in patient communication is critical to improve patient experience. Our research is intended to clarify the need for areas of improvement to better communicate with patients at the time of their preoperative evaluation. There was no significant difference in patient-centered communication among the various provider levels. There was also no significant difference in length of encounter among the various provider levels. This reveals the extent patients receive patient-centered care from anesthesia providers, regardless of provider level.

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PERIOPERATIVE ANESTHESIA 36

Combined General/Epidural Anesthesia vs General Anesthesia on the Postoperative Inflammation or Stress Response: a Systematic Review and Meta-Analysis

Zhaosheng Jin[1], Ru Li[1], Annie Wen[1], Jun Lin[1]

[1]Stony Brook Medicine, Stony Brook, NY

INTRODUCTION: Local and systemic inflammation is common after surgery and is associated with morbidity and mortality. The use of epidural analgesia is thought to improve postoperative outcomes through pain reduction and opioid sparing. The present study aimed to assess whether addition of epidural anesthesia or analgesia (EA) to general anesthesia (GA) was associated with altered inflammatory response after surgery.

METHODS: We systematically searched PubMed, Central, EMBASE, CINAHL, Google Scholar and Web of Science citation index, for clinical studies comparing the two techniques. We carried out a meta-analysis to evaluate the postoperative plasma levels of cytokines including Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α), IL-1β, IL-4, IL-8, IL-10, as well as C-Reactive Protein (CRP) and cortisol, after EA plus GA or GA alone.

RESULTS: The literature search was last updated on Oct 10th, 2020. We identified a total of 20 studies which compared postoperative inflammatory mediators with EA plus GA compared to EA alone. EA plus GA was associated with significantly lower serum levels of IL-6, TNF- α, CRP, as well as cortisol and other pro-inflammatory cytokines. In cancer surgery, EA plus GA was also associated with lower postoperative cytokines (Fig 1).

CONCLUSION: Our meta-analysis indicates that EA plus GA is associated with diminished postoperative inflammatory response. This offers an alternative explanation for the benefit of epidural analgesia on postoperative outcomes. Considering the link between postoperative inflammation and recurrence after cancer surgery, this is an area that warrants further research.

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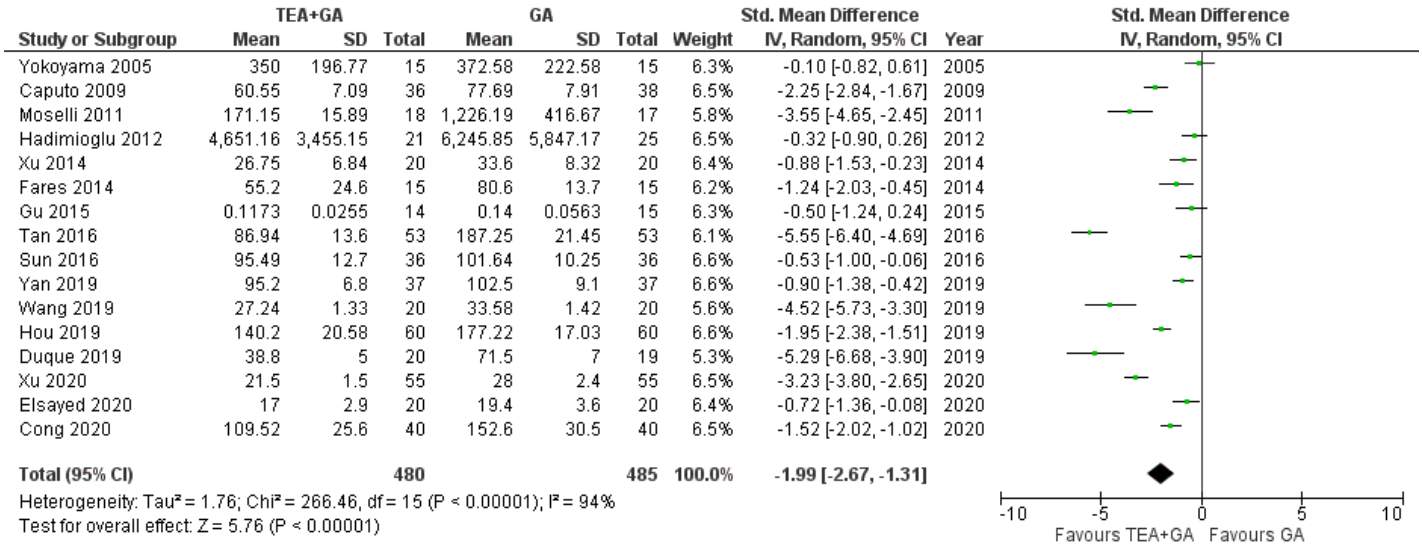

Study or Subgroup	TEA+GA Mean	TEA+GA SD	TEA+GA Total	GA Mean	GA SD	GA Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Yokoyama 2005	350	196.77	15	372.58	222.58	15	6.3%	-0.10 [-0.82, 0.61]	2005
Caputo 2009	60.55	7.09	36	77.69	7.91	38	6.5%	-2.25 [-2.84, -1.67]	2009
Moselli 2011	171.15	15.89	18	1,226.19	416.67	17	5.8%	-3.55 [-4.65, -2.45]	2011
Hadimioglu 2012	4,651.16	3,455.15	21	6,245.85	5,847.17	25	6.5%	-0.32 [-0.90, 0.26]	2012
Xu 2014	26.75	6.84	20	33.6	8.32	20	6.4%	-0.88 [-1.53, -0.23]	2014
Fares 2014	55.2	24.6	15	80.6	13.7	15	6.2%	-1.24 [-2.03, -0.45]	2014
Gu 2015	0.1173	0.0255	14	0.14	0.0563	15	6.3%	-0.50 [-1.24, 0.24]	2015
Tan 2016	86.94	13.6	53	187.25	21.45	53	6.1%	-5.55 [-6.40, -4.69]	2016
Sun 2016	95.49	12.7	36	101.64	10.25	36	6.6%	-0.53 [-1.00, -0.06]	2016
Yan 2019	95.2	6.8	37	102.5	9.1	37	6.6%	-0.90 [-1.38, -0.42]	2019
Wang 2019	27.24	1.33	20	33.58	1.42	20	5.6%	-4.52 [-5.73, -3.30]	2019
Hou 2019	140.2	20.58	60	177.22	17.03	60	6.6%	-1.95 [-2.38, -1.51]	2019
Duque 2019	38.8	5	20	71.5	7	19	5.3%	-5.29 [-6.68, -3.90]	2019
Xu 2020	21.5	1.5	55	28	2.4	55	6.5%	-3.23 [-3.80, -2.65]	2020
Elsayed 2020	17	2.9	20	19.4	3.6	20	6.4%	-0.72 [-1.36, -0.08]	2020
Cong 2020	109.52	25.6	40	152.6	30.5	40	6.5%	-1.52 [-2.02, -1.02]	2020
Total (95% CI)			**480**			**485**	**100.0%**	**-1.99 [-2.67, -1.31]**	

Heterogeneity: Tau² = 1.76; Chi² = 266.46, df = 15 (P < 0.00001); I² = 94%
Test for overall effect: Z = 5.76 (P < 0.00001)

PERIOPERATIVE ANESTHESIA 37

Quality Indicators in the Perioperative Period Specific to the Practice of Anesthesiology: An Umbrella Review

Frederic Nguyen[1], Gary Liao[2], Daniel I McIsaac[3], Manoj M Lalu[4], Christopher Pysyk[5], Gavin M Hamilton[5]

[1]The Ottawa Hospital, Ottawa, Canada, [2]University of Ottawa, Ottawa, Canada, [3]University of Ottawa Faculty of Medicine, Ottawa, Ontario, [4]The Ottawa Hospital, Ottawa, Ontario, [5]University of Ottawa, Ottawa, Ontario

INTRODUCTION: Improvement in health care delivery depends on the ability to measure outcomes that can direct changes in the system. Existing systematic reviews have examined specific aspects of perioperative quality indicators in different settings, but no study has clearly synthesized a concise overview of the important quality indicators specific to anesthesiology. This umbrella review was undertaken to provide an overview of evidence-based quality indicators specific to the perioperative period.

METHODS: An umbrella review was conducted according to Joanna Briggs Institute methodology[1] A systematic search was conducted in accordance with the Peer Review of Electronic Search Strategies (PRESS) checklist. We included systematic reviews examining perioperative indicators in patients greater than 18 years of age undergoing non-cardiac surgery. The primary outcome was any quality indicator specific to anesthesiology. Classification system (eg. Donabedian[2], Institute of Medicine), strength of evidence (eg. Oxford, GRADE), perioperative phase, and surgical subspecialty were collected. All indicators were classified into a Donabedian and Institute of Medicine (IOM) domain of quality and were then classified into a novel perioperative classification system we created. Risk of bias of each of the included studies was evaluated using AMSTAR2 (A MeaSurement Tool to Assess systematic Reviews).

RESULTS: Our initial systematic literature search returned 1216 studies. After duplicate removal, title and abstract screening and full text screening, twenty-three systematic reviews encompassing 3164 primary studies met our inclusion criteria. In total, 339 perioperative quality indicators were collected. Two hundred and fifty (250/339) indicators were classified according to a Donabedian domain in their original systematic review. After classification of remaining indicators, process indicators were most common (n=173), followed by outcome indicators (n=119), then structure indicators (n=47). When classifying quality indicators by our novel perioperative classification system, indicators for General Complications or Adverse Events (n=96) and Preoperative Management (n=70) occurred with highest frequency (Fig 1). Few identified quality indicators were supported by Oxford Level of Evidence (90/339=27%), with an even smaller portion supported by high level of evidence (46/339=14%). Indicators with the highest evidence included antibiotic prophylaxis (Oxford Level of Evidence: Ia), venous thromboembolism (VTE) prophylaxis (Ia), and post-op nausea/vomiting prophylaxis (Ib) Intraoperative management indicators focused on maintenance of normothermia (Ia) and goal-directed fluid therapy (Ib).

CONCLUSION: This review highlights the importance of utilizing high quality evidence to guide quality improvement but also emphasizes the scarcity of evidence that exists for perioperative quality indicators. By summarizing the existing quality indicators related to anesthesiology, we provide an overview of potential targets for future evidence-based quality improvement programs in anesthesiology.

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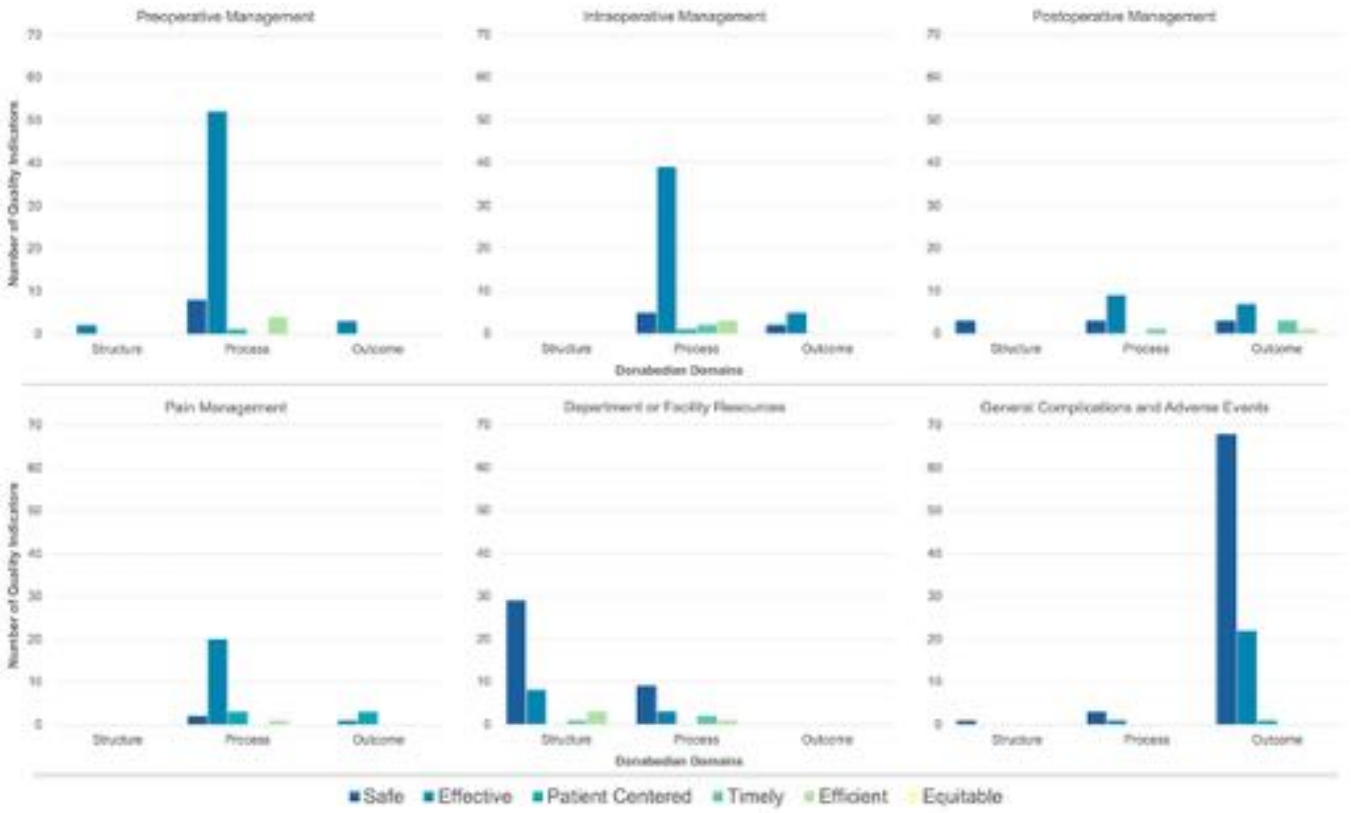

Figure 1. Quality indicator distribution by Institute of Medicine domains separated into Structure, Process, and Outcome indicators. Quality indicators are organized by perioperative domain.

PERIOPERATIVE ANESTHESIA 38

Influence of 3% Hypertonic Saline vs 0.9% Saline on Maintenance Fluid Requirements in Adult Patients Undergoing Major Abdominal Surgeries: Randomized Triple-Blind Trial

Satyajeet Misra[1], Sri Hari Priya Behera[1], Bikram K Behera[1]

[1]AIIMS Bhubaneswar, Bhubaneswar, Odisha

INTRODUCTION: The ideal strategy for intraoperative maintenance fluid requirements in major abdominal surgeries remains a challenge. Goal directed fluid therapy suffers from lack of universal acceptance of the goals. Liberal fluid strategy may result in postoperative weight gain and tissue edema. Net gain of 550 ml of intraoperative fluid has been shown to be associated with increased complications like tissue edema and poor wound healing[1].Conversely, restrictive fluid strategy may result in acute kidney injury[2]. 3% hypertonic saline (HTS) acts like an osmotic buffer in intravascular lumen and draws fluid from the extracellular space into the intravascular compartment[3,4]. The HYSLAR trial had shown that a fixed dose of HTS (1 ml/kg/hr) administered intra and postoperatively, allowed for a restrictive fluid regimen with reduced net fluid balance and postoperative complications[5]. However, in that study, intraoperative maintenance fluids were given in a fixed dose. Till date, no trials have investigated the role of HTS in reducing intraoperative maintenance fluid requirements. Therefore, we hypothesized that administration of HTS will reduce the intraoperative maintenance fluid requirement by at least 500 ml, which may lead to better postoperative outcomes.

METHODS: Study design was triple-blind and carried out in the operating theatres and intensive care unit of a tertiary teaching hospital. ASA 1& 2 adult patients, 18-65 years, undergoing elective major open abdominal surgery were randomized to receive infusions of either HTS or 0.9% saline (NS) at 1ml/kg/hr. Both HTS and NS were administered through large bore peripheral i.v cannulas or through a central venous catheter (if inserted) after induction of anesthesia. The drugs were prepared by anesthesia providers not involved in the case to maintain blinding. Intraoperative maintenance fluids were administered to maintain standard targets of mean arterial pressure (70-110 mmHg) and urine output (0.5-1ml/kg/hr). Where central venous catheters were used, the target central venous pressures were 8-10 cm H2O. Primary objective was to see the difference in maintenance fluid requirement. Secondary objectives were differences in 24 hr fluid requirements, postoperative serum sodium, serum creatine, arterial lactates, c-reactive protein, postoperative complications like sepsis or anastomotic leaks and incidence of any adverse events (hypernatremia, extravasation). The planned sample size including 10% dropout was 100 (50 in each group) to detect a net difference of 500 ml intraoperative maintenance fluid (standard deviation of 850 ml) with the study power at 80% and alpha error of 0.05 (2-tailed). Data for continuous outcomes were represented as mean (standard deviation) or median (interquartile range) depending on normality and tested accordingly with the independent t-test or the Mann Whitney U-test respectively. Dichotomous data were tested with the Pearson's chi-square test. SPSS (version 22) was used for data analysis.

RESULTS: Interim analysis of 81 patients are reported (39 in HTS group and 42 NS group). There was no difference in the primary outcome of intraoperative maintenance fluid requirement between the two groups (2115 + 930 ml in HTS group vs 1976 + 897 ml in NS group; P= 0.54). There was no difference in the 24 hours postoperative maintenance fluid requirement (1970 + 473 ml in HTS group vs 2038 + 391 ml in NS group; P= 0.49). The total perioperative fluid requirement was similar between the two groups (79 + 20 ml/kg in HTS vs 77 + 25 ml/kg in NS group; P = 0.60). Postoperative creatinine, lactates, C-reactive protein and incidence of sepsis and anastomotic leaks were comparable between the two groups. Though not clinically significant, compared to the NS group, patients in HTS group had statistically significant difference in serum sodium at postoperative 12 (137.4 vs 135.3; P= 0.03) and 24 hours (137.4 vs 135.5; P=0.02). No complications were reported due to administration of HTS through peripheral lines.

CONCLUSION: Administration of 3% hypertonic saline did not reduce perioperative maintenance fluid requirements in patients undergoing major open abdominal surgery. There was no incidence of adverse events related to the use of HTS.

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Subspecialty Abstracts

REGIONAL ANESTHESIA

REGIONAL ANESTHESIA 1

Peak Plasma Concentration of Total and Free Bupivacaine after Erector Spinae Plane and Pecto-Intercostal Fascial Plane Blocks

Sarah Maximos[1], Éric Vaillancourt-Jean[1], Samer Mouksassi[1], Alessandro De Cassai[2], Sophie Ayoub[1], Monique Ruel[1], Julie Desroches[1], Pierre-Oliver Hétu[1], Alex Moore[1], Stephan Williams[1]

[1]Université de Montréal, Montreal, Canada, [2]UOC Anesthesia and Intensiva Care Unit, Padova, Italy

INTRODUCTION: Erector spinae plane block (ESPB) and pecto-interfascial plane block (PIFB) are novel interfascial plane blocks for which the local anesthetic (LA) dose and concentration necessary to achieve optimal analgesia is not yet known. In clinical settings, increased LA doses and concentrations are associated with more profound blocks and longer lasting analgesia[1]. However, the potential for LA toxicity limits maximum doses to the lowest effective dose for each block. The goal of this prospective, observational study was therefore to provide timing (Tmax) and value (Cmax) of peak bupivacaine serum concentrations after both ESPB and PIFB.

METHODS: To study ESPB, 18 patients between 18 and 90 years of age undergoing mastectomy were recruited from July to October 2019. For the PIFB, 18 patients between 18 and 90 years of age undergoing elective coronary artery bypass graft surgery ± valve replacement were recruited from August to September 2019. Patients with inability to provide informed consent, allergy to LA, severe heart failure, severe liver disease, severe renal insufficiency, infection in the designated block area or who refused to participate were not recruited. Patients for whom the predetermined sampling regimen could not be observed or who required allogeneic blood transfusions during the sampling period were excluded. The ESPB was performed at the level of the 5th thoracic vertebra with a total dose of 2 mg/kg of ideal body weight bupivacaine 0.5% with epinephrine 5 µg/ml[2]. The PIFB was performed at the third and sixth intercostal spaces bilaterally with a total dose of 2 mg/kg of ideal body weight bupivacaine 0.25% with epinephrine 5 µg/ml divided equally between four injection sites[2]. For both blocks, LA was delivered, in 5 ml aliquots or less, with negative aspiration in between each injection. Blood samples were withdrawn at 10, 20, 30, 45, 60, 90, 120, 180 and 240 minutes after the last injection. Total and free bupivacaine plasma concentration were measured using liquid chromatography-mass spectroscopy tandem (LC-MS/MS). Primary outcomes were plasma Cmax and Tmax of total and free bupivacaine after PIFB and ESPB. A standard non-compartmental pharmacokinetic data analysis was performed with Phoenix® NLME. Individual Cmax and Tmax were identified. The slope of the terminal phase was computed when and the terminal half-life was reported as T1/2 = log (2)/terminal slope. The software R was used to generate model diagnostic figures and tables of descriptive statistics[3]. Data was verified for normality by Shapiro-Wilk test and presented as means ± standard deviation or medians with an interquartile range, as appropriate.

RESULTS: For ESPB, 44 patients were screened, 26 recruited, and 18 completed the protocol. The average dose and volume of bupivacaine injected was 108 ± 10 mg (22 ± 2 ml). Total bupivacaine Tmax median was 30 minutes (IQR 50 minutes). Free bupivacaine Tmax median was 30 minutes (IQR 20 minutes). Total bupivacaine Cmax ranged from 0.19 to 0.64 (mean: 0.37 ± 0.12 ug/mL). Free bupivacaine Cmax ranged from 0.003 to 0.067 (mean: 0.015 ± 0.017 ug/mL). No correlation was observed between pharmacokinetic and demographic parameters. For PIFB, 53 patients were screened, 34 eligible recruited and 18 completed the protocol. The PIFB was completed in 7 ± 2 minutes. The average dose and volume of bupivacaine injected was 127 ± 16 mg (51 ± 6 ml). Total bupivacaine Tmax median was 120 minutes (IQR 150 minutes). Free bupivacaine Tmax median was 180 minutes (IQR 120 minutes). Total bupivacaine Cmax ranged from 0.14 to 0.95 (mean: 0.32 ± 0.21 ug/mL). Free bupivacaine Cmax ranged from 0.005 to 0.048 (mean: 0.019 ± 0.010 ug/mL). Plasma concentrations did not show a clear peak for 60-240 minutes after PIFB.

CONCLUSION: Previous studies have shown that LA arterial toxic total plasma bupivacaine levels are 4 ± 1.4 µg/mL; whereas venous toxic total plasma bupivacaine levels are 2.1 ± 1.2 µg/mL;whereas venous toxic total plasma bupivacaine levels are 2.1 ± 1.2 µg/mL[4,5]. Total and free plasma bupivacaine levels observed after the ESPB and PIFB in this study are more than four to ten times lower than these toxic levels. Bupivacaine pharmacokinetics after ESPB and PIFB are compatible with the possibility of safe and prolonged analgesia after these blocks. Given the pharmacokinetic characteristics observed in the present study, adrenalized doses higher than 2 mg/kg of ideal body weight can be considered for both ESPB and PIFB if found to be necessary to optimise the clinical effect of the blocks.

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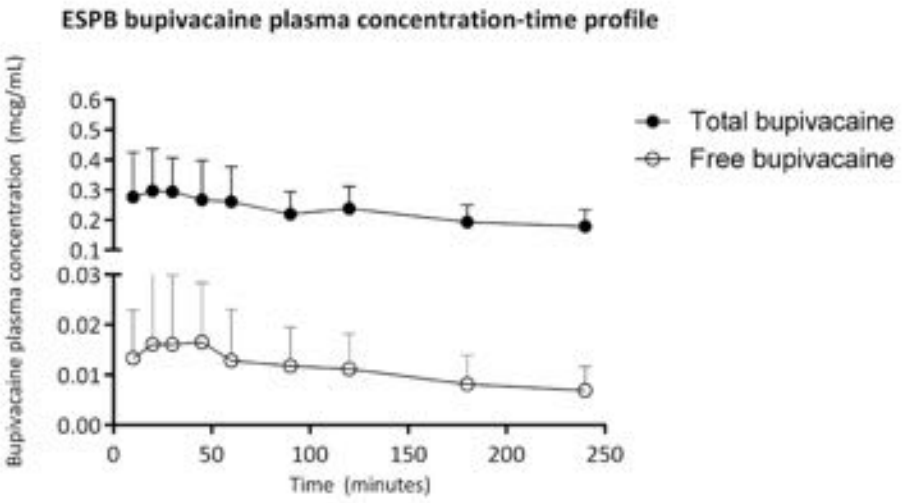

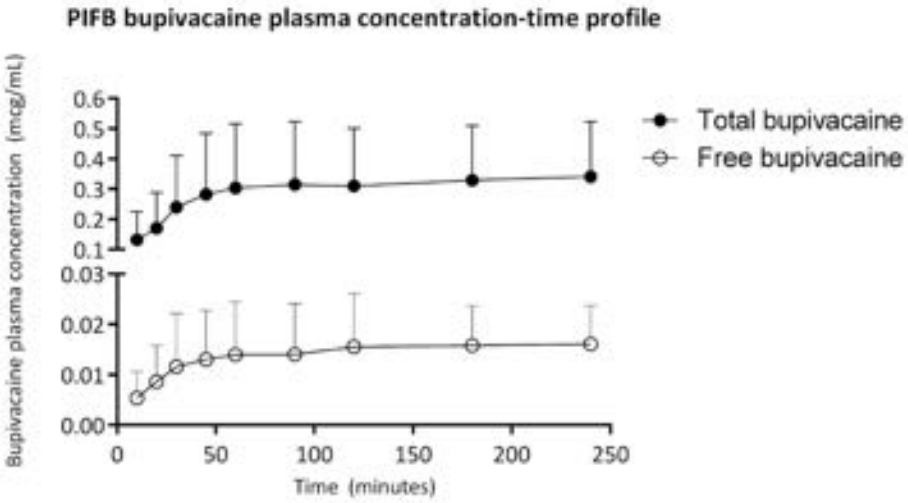

REGIONAL ANESTHESIA 2

Computer Assisted Instrument Guidance (CAIG) to Improve Adductor Canal Block Performance for Total Knee Arthroplasty: A Pilot Randomized Controlled Trial

Kiana D de Guzman[1], Noud van Helmond[1], Ronak G Desai[2], Kinjal M Patel[2]

[1]Cooper Medical School of Rowan University, Camden, NJ, [2]Cooper University Health Care, Camden, NJ

INTRODUCTION: Post-operative pain associated with total knee arthroplasties is routinely managed with ultrasound-guided adductor canal blocks (ACBs)[1]. Computer assisted instrument guidance (CAIG) systems supplement existing ultrasound machinery and block needles, allowing the operator to navigate the needle in real-time while displaying a projected trajectory of its path onto the ultrasound monitor (Figure 1)[2]. Previous studies have shown that CAIG systems reduce the time to target for needle insertions performed by training emergency residents[3] and student registered nurse anesthetists[4]. This study explored how ACBs done with CAIG compare to conventional ultrasound-only ACBs in terms of block efficiency, success and potential tissue damage for patients undergoing total knee arthroplasty.

METHODS: This randomized clinical trial was conducted in a New Jersey medical institution between October 2015 and May 2016. Potential subjects were screened for enrollment through the hospital's operating room schedule. Twenty-six patients undergoing total knee arthroplasty under spinal anesthesia with an ACB were randomized by a computer-generator to ACB utilizing conventional real-time ultrasound or to ACB utilizing real-time ultrasound supplemented with CAIG. The primary outcome measure was time to block completion. Secondary outcome measures included number of needle insertions, postoperative pain scores until postoperative day 3, postoperative muscle weakness, opioid requirements on postoperative day 0 converted to oral morphine equivalents, length of stay, and patient satisfaction with pain management. Primary and secondary outcomes in the CAIG and conventional ACB groups were compared using unpaired t-tests, Mann-Whitney U tests, or chi-squared tests.

RESULTS: All 26 patients enrolled were present until completion and included in data analysis for the study (Figure 2). The time required to complete the block (Figure 3) as well as the number of needle insertion attempts were similar between the CAIG and conventional ACB groups (Mann-Whitney U test $P = 0.76$) (Table 1). Postoperative outcomes such as pain scores up to postoperative day 3 (Figure 4), postoperative muscle weakness, opioid requirements on postoperative day 0, length of stay, and patient satisfaction with perioperative pain management were comparable between the CAIG and conventional ACB groups as well (Table 1).

CONCLUSION: CAIG does not reduce ACB performance times or patient outcomes when ACBs are performed by experienced anesthesiologists. Further studies exploring the use of CAIG systems in novice anesthesiologists might show its potential value in training physicians who are less experienced in the mechanical skills of nerve blocks.

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Table 1. Secondary adductor canal block and postoperative study outcomes in the computer assisted instrument guidance (CAIG) and conventional adductor canal block groups.

	CAIG Adductor canal block (n = 13)	Conventional adductor canal block (n = 13)	*P*-value
Adductor Canal Block Characteristics			
Needle insertion attempts mean (range)	1 (1-1)	1 (1-1)	1.0
Complications			
Muscle weakness, n (%)	2 (15)	1 (8)	0.54
Other, n (%)	0 (0)	0 (0)	1.0
Postoperative Characteristics			
Opioid requirements on postoperative D0 in mg oral morphine equivalents, median (IQR)	60 (50 – 130)	45 (29 – 131)	0.14
Length of stay in days, median (IQR)	4 (3 – 4)	4 (3 – 4)	0.66
Satisfaction with pain management on 0-10 scale, median (IQR)	9 (8 – 10)	10 (9.25 – 10)	0.16

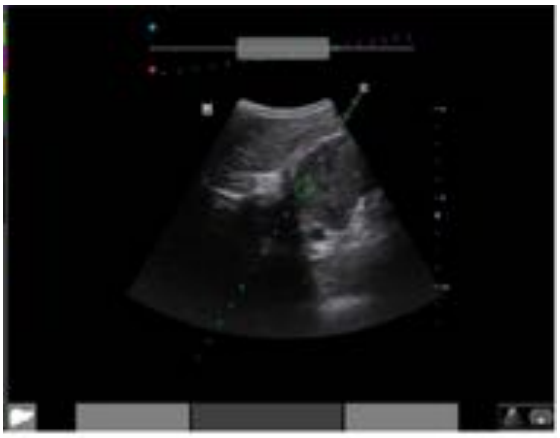

Figure 1. Exemplar ultrasound needle path projection with the Clear Guide system.

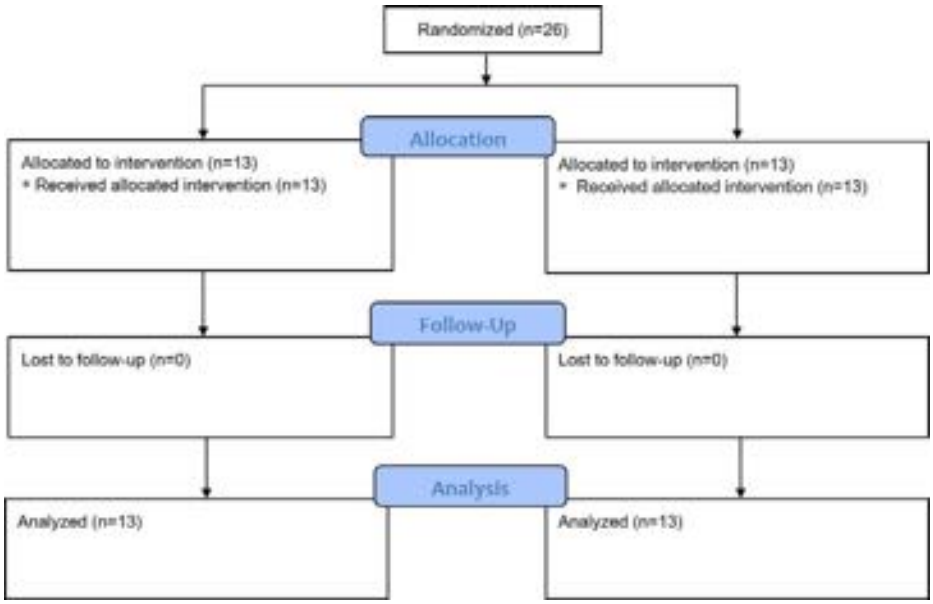

Figure 2. Trial flow diagram.

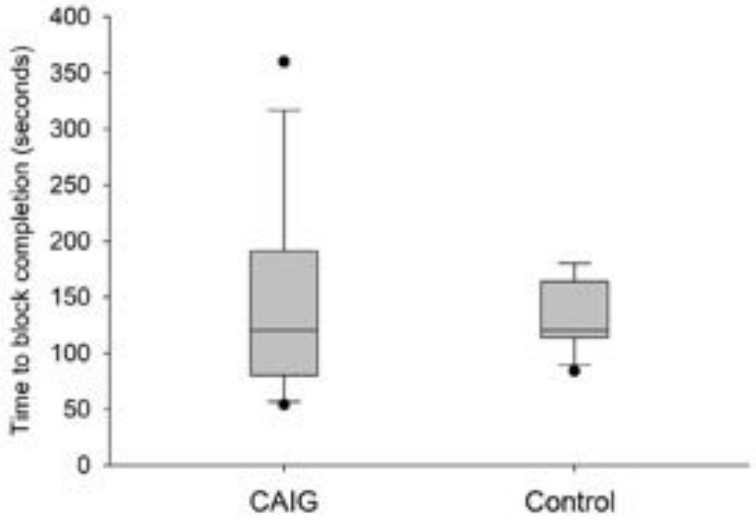

Figure 3. Duration of adductor canal block procedure in the computer assisted instrument guidance (CAIG) and conventional adductor canal block groups. Duration of adductor canal block procedure was not statistically different between the CAIG and conventional adductor canal block groups (Mann-Whitney U test P = 0.76). Normality Shapiro-Wilk test failed (P < 0.05).

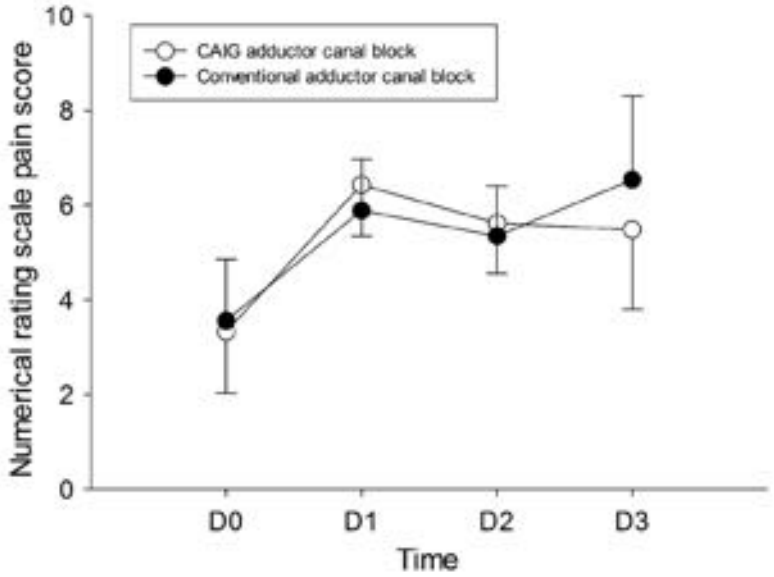

Figure 4. Pain up to postoperative day 3 in patients in the computer assisted instrument guidance (CAIG) and conventional adductor canal block groups. Pain scores were not statistically different between the CAIG and conventional adductor canal block groups. D0 = postoperative day 0; D1 = postoperative day 1; D2 = postoperative day 2; D3 = postoperative day 3.

REGIONAL ANESTHESIA 3

Multimodal opioid-sparing analgesia for posterior cervical spine fusion using erector spinae plane blocks: A Case Series

Theresa Bowling[1], Vlad Frenk[1], Robert Suriani[1], David Maduram[1]

[1]St. Vincent's Hospital, Bridgeport, CT

INTRODUCTION: Posterior cervical 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 of patients undergoing posterior cervical fusion in which 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 howthis multimodal regimen would impact postoperative pain and opioid requirements in patients undergoing posterior cervical fusion surgery. In addition, we looked at the length of hospital stay, as well as the safety profile of erector spinae blocks for cervical posterior spine surgery. This study was approved by the St Vincent's Medical Center Institutional Review Board (Bridgeport, CT). Written consent for publication of non-identifying medical information and Health Insurance Portability and Accountability Act authorization was obtained from the patients in this study.

METHODS: We reviewed medical records of five patients who underwent posterior cervical fusion surgery between August 1, 2020 to November 1, 2020 at St. Vincent's Medical Center. The demographic data of all patients in this sample were recorded. In the postoperative period, VAS scores on movement were measured at 6, 12, and 24 hours postoperatively. Postoperative morphine equivalent requirements were noted and recorded. All patients in this series received general anesthesia with an intraoperative cervical erector spinae block. As part of a multimodal regimen, all patients received intravenous methadone 0.1 mg/kg and ketamine 0.5 mg/kg at the beginning of the case. Anesthesia was maintained with intravenous propofol 100mg/kg/min and remifentanil 0.15 mcg/kg/min. After induction of general endotracheal anesthesia and preoperative positioning by the operating team, bilateral ultrasound-guided ESP blocks were performed at the T1 level. After wide chlorhexidine 4% prep, an ultrasound transducer probe (SonoSite PX, SonoSite Inc, Bothell, WA) was positioned in a longitudinal orientation to obtain a parasagittal view. The transverse process was identified as a hyperechoic structure with acoustic shadowing below it (Figure 1). A hyperechoic 22-gauge needle (B-Braun, Melsungen, Germany), was inserted in a caudal-to-cranial direction using the in-plane technique. When the needle tip came into contact with the transverse process, the correct tip position was confirmed by the visualization of linear fluid spreading in the myofascial plane between the erector spinae muscle and the transverse process (Figure 2 and 3). Further confirmation of both spinal level and needle position was obtained by fluoroscopy (Figure 4). After confirming needle tip position, a total of twenty milliliters of 0.25% bupivacaine with 5mg dexamethasone was injected in 5cc aliquots. This procedure was repeated on the opposite side for a total of 40ml of local anesthetic. No other local anesthetics were used by the surgical team. Intravenous acetaminophen 1000mg and ketorolac 30 mg were given at the end of the procedure. After completion of the surgery, all patients were taken to the postanesthesia care unit (PACU) and then to a dedicated orthopedic inpatient care unit. Post-operative pain was treated with scheduled oral acetaminophen, oral opioids as needed, and IV opioids for breakthrough pain as needed. Hospital record data from posterior cervical fusion patients were extracted and analyzed. Continuous data are expressed as medians (interquartile ranges), because of the non-normal distribution of this data set.

RESULTS: Five patients underwent posterior cervical fusion with multimodal analgesic regimen inclusive of bilateral erector spinae blocks. Patient data is shown in Table 1. The median 24h pain score was 4 [4-4.25]. The median 24h postoperative opioid consumption was 24 [24-33] mg of oral morphine milliequivalent units.

CONCLUSION: Our findings on efficacy and safety of erector spinae blocks for posterior cervical spine fusion are consistent with other studies of erector spinae blocks for posterior thoracolumbar surgery. The potential that this multimodal anesthetic approach may hold for significantly improving postoperative pain control following posterior cervical spinal fusion surgery warrants further investigation.

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Fig. 1

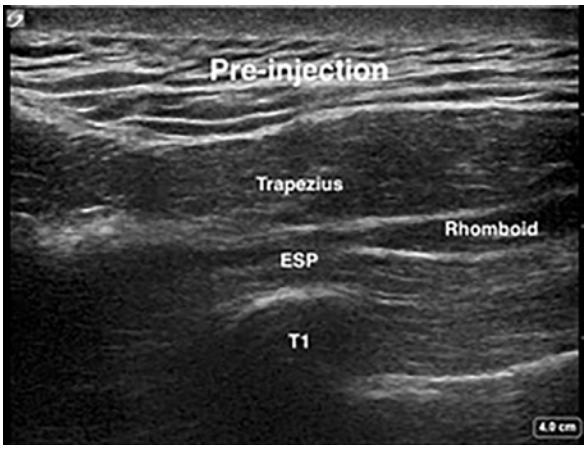

Fig. 2

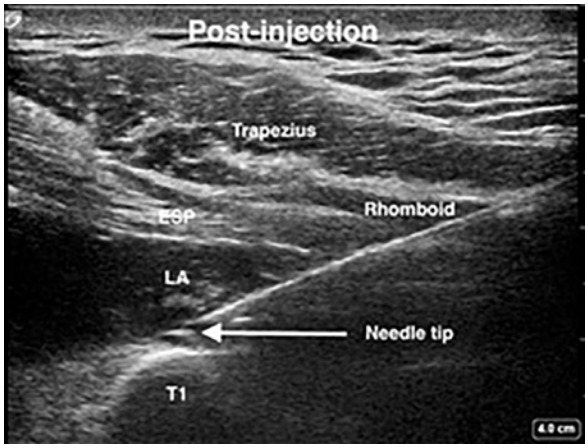

Fig. 3

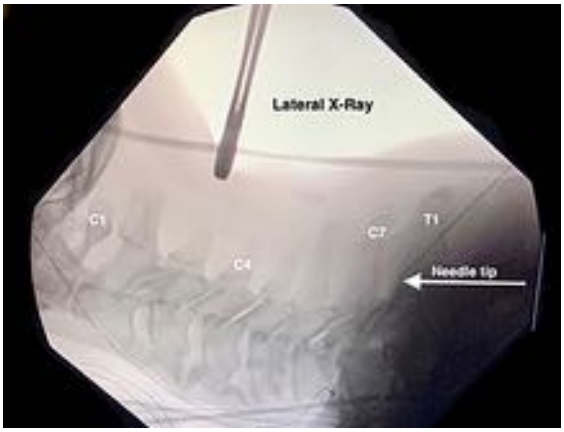

Fig. 4

Subject Number	Age (y)	Sex	LOS	Pain at 6h, 12h, 24h	24h Opioid Dose in MME
1	70	M	2.1	0,3,4	8
2	60	M	1.3	3.0,2	36
3	69	M	1.3	2,6,5	32
4	63	F	2.7	2,0,2	8
5	59	M	3.3	5,4,4	24

Table 1

REGIONAL ANESTHESIA 4

Interscalene single shot with plain bupivacaine versus liposomal bupivacaine for arthroscopic rotator cuff surgery

Paul Lee[1], Richard A Newhart[2], William Wang[2], Mohamed Eloustaz[1], Gligor Gucev[2]

[1]University of Southern California, Los Angeles, CA, [2]University of Southern California, Los Angeles, CA

INTRODUCTION: The current standard of care is to perform an interscalene peripheral nerve block for patients receiving arthroscopic shoulder surgery as it is an effective opioid-free alternative for post-operative pain control. While catheters have shown to have extended benefit throughout the perioperative period, most institutions do not have the staffing to provide follow-op for peripheral nerve catheters and therefore only perform single shot injections for analgesia. An ideal option for patients is a single shot injection that is able to provide prolonged analgesia. In a recent study comparing liposomal bupivacaine to placebo for interscalene nerve blocks, patients receiving liposomal bupivacaine had significantly lower pain scores over 48 hours and received less opioid over 72 hours. This study is assessing whether an interscalene nerve block with liposomal bupivacaine will provide superior analgesia and lower opioid requirement compared to plain bupivacaine.

METHODS: This is a double-blinded randomized controlled trial of patients undergoing outpatient arthroscopic rotator cuff surgery at Keck Hospital of University of Southern California. Currently, 40 of our goal of 80 patients have been enrolled and 37 have completed follow up with data collection. Each patient was randomized to receive a single-shot ultrasound-guided interscalene nerve block with either plain (19 patients) or liposomal bupivacaine (18 patients). Patients were then called on postoperative days (POD) 1, 2, 3, and 7 to collect data on visual analog scale (VAS) at rest and movement and morphine milligram equivalents (MME). This data was recorded and analyzed using a two-tailed t-test.

RESULTS: The two groups consisted of American Society of Anesthesiologists physical status I-III patients similar in demographics. Exclusion criteria were patients with a history of chronic opioid use, respiratory compromise, allergy to local anesthetics or opioids, and non-English speaking patients. Three patients were withdrawn due to the rotator cuff being found intact and subsequent change in procedure (2) and being lost to follow up (1). The difference in VAS and MMEs between the plain and liposomal bupivacaine groups was largely insignificant except for VAS score being higher with movement on postoperative day 1 for the plain bupivacaine group (5.9 vs. 3.4; $p = 0.03$). One patient from each group complained of shortness of breath which resolved by POD 3.

CONCLUSION: Neither group was associated with a consistent significant difference in morphine equivalents and pain scores postoperatively after arthroscopic rotator cuff surgery with an interscalene block. While much research has been done to show that an interscalene nerve block significantly improves postoperative analgesia, this sample size shows that the form of bupivacaine used in the nerve block does not have a significant effect on analgesia. A higher sample size will be collected and studied by the end of this study.

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Exparel Figures

Table 1.
Patient Demographics

Characteristic	Plain Bupivacaine	Liposomal Bupivacaine	*p* value
Gender			0.63
Male	11 (57.9)	9 (50)	
Female	8 (42.1)	9 (50)	
Age (years)	57.6 ± 11	60.3 ± 13.3	0.51
BMI (kg/m^2)	29.6 ± 5.9	29.0 ± 6.5	0.76
Race			0.73
Caucasian	12 (63.2)	13 (72.2)	
Hispanic	4 (21.1)	2 (11.1)	
Black	1 (5.3)	1 (5.6)	
Asian	1 (5.3)	0 (0)	
Other	1 (5.3)	2 (11.1)	

Data are mean ± SD or n (%).

Table 2.
Results

Outcome	Plain bupivacaine (n = 19)	Liposomal bupivacaine (n = 18)	*p* value
POD 1			
VAS worst	5.0 ± 3.2	3.1 ± 3.2	0.07
VAS with movement	5.9 ± 3.3	3.4 ± 3.5	0.03
POD 2			
VAS worst	5.4 ± 2.4	5.2 ± 3.3	0.78
VAS with movement	6.8 ± 2.9	5.3 ± 3.4	0.17
POD 3			
VAS worst	4.4 ± 2.5	4.5 ± 3.7	0.92
VAS with movement	6.2 ± 3.0	5.2 ± 3.7	0.41
POD 7			
VAS worst	3.5 ± 3.0	3.3 ± 2.4	0.89
VAS with movement	5.1 ± 3.5	4.6 ± 2.7	0.69
MMEs			
POD 1	26.9 ± 28.7	26.9 ± 20.7	1.0
POD 2	35.6 ± 32.0	27.1 ± 24.4	0.39
POD 3	15.5 ± 17.0	20.6 ± 17.8	0.41
POD 7	8.1 ± 9.6	8.8 ± 11.9	0.86

Data are mean ± SD.

REGIONAL ANESTHESIA 5

The effects of two spatially separate injections on the onset and duration of median and ulnar nerve blocks

Sam Van Boxstael[1], Ana Lopez[1], Angela Lucia Balocco[1], Catherine Vandepitte[1], Ingrid Meex[1], Maxine M Kuroda[1], Joris F Duerinckx[1], Dieter Mesotten[1], Admir Hadzic[1]

[1]Ziekenhuis Oost-Limburg, Genk, Belgium

INTRODUCTION: Injection of local anaesthetic at more than one spatial level alongside a peripheral nerve may increase exposure of the nerve to the injectate. We postulated that two spatially separate injections for median and ulnar nerve block at the forearm will shorten onset time and prolong the duration of neural blockade.

METHODS: This prospective, randomized, controlled trial with a factorial 2 by 2 design included subjects scheduled for primary unilateral carpal tunnel release surgery. 36 subjects(ASA I or II) were randomly assigned to receive either one or two injections for median and ulnar nerve blocks. Injections for both groups were made under ultrasound guidance at the level of the mid-forearm. Onset and duration of neural blockade was measured. In subjects receiving two injections, local anaesthetic was administered at two sites 10-15cm apart (distal-proximal) alongside the median and ulnar nerves, using two separate punctures. To assess any effect of local anaesthetic, subjects were also randomized to receive both blocks with either single or double injections of lidocaine 2% or bupivacaine 0.5%. The Ethics Committee at ZOL approved the study protocol in October 2017 (17/060U). The study was approved and registered by the European regulatory authorities (2017-003694-34, October 2nd, 2017). Written informed consent was obtained from all subjects.

RESULTS: With lidocaine, the sensory block onset was 9.4±2.5 and 8.9±4.3min in the single and two injection groups, respectively. With bupivacaine, the onset of the sensory block was 9.7±3.3 and 9.3±3.1min in the single and two injection groups, respectively. Sensory block duration with lidocaine was 7.3±2.3 and 9.5±5.3h in the single and double injection groups, respectively. With bupivacaine, the sensory block duration was 25.0±12.6 and 29.3±10.9h in the single and double injection groups, respectively.

CONCLUSION: Two spatially separate injections in median and ulnar blocks did not shorten onset time or lengthen duration of the blocks with either lidocaine or bupivacaine.

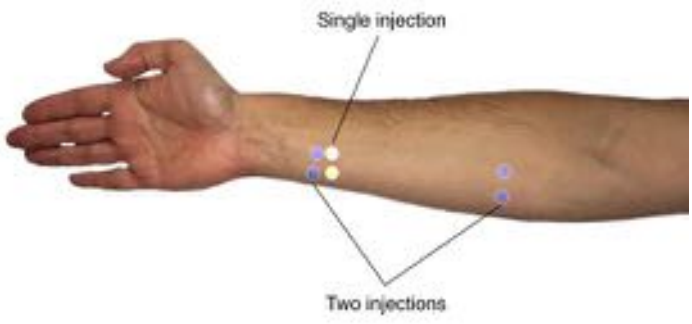

Fig. 2

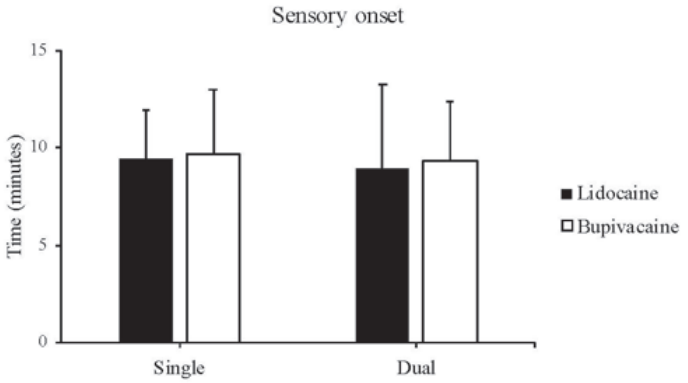

Fig. 3

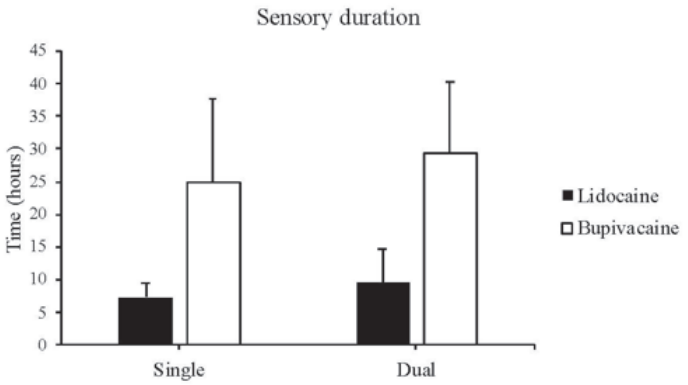

Fig. 4

REGIONAL ANESTHESIA 6

Association between regional anesthesia and analgesic outcomes: a single-center retrospective study of 2,761 pediatric regional anesthetics

James J Xie[1], Beth De Souza[2], Felipe D Perez[3], Maria V Suarez-Nieto[4], Ellen Wang[2], Thomas A Anderson[2]

[1]Stanford Universisty, Stanford, CA, [2]Stanford University School of Medicine, Stanford, CA, [3]Stanford University School of Medicine, Stanford, CA, [4]Stanford Unviersity, Stanford, CA

INTRODUCTION: Results from adult clinical trials show that perioperative regional anesthesia often improves analgesic outcomes.[1,2,3] Significantly fewer pediatric studies have been published. A 2018 systematic review of pediatric regional anesthesia outcomes included 40 randomized controlled trials with 2,408 patients (study arm size ranged from 5-73, the majority were 20-40) with most studies reporting a decrease in postoperative pain and opioid consumption. However some studies did not show an analgesic benefit of regional anesthesia for certain procedures.[4] As most pediatric studies are small trials conducted under idealized conditions, we sought to explore pediatric analgesic outcomes in a large pragmatic study. We hypothesized that children who received regional anesthesia (both single-shot and catheter-based) would have reduced perioperative opioid consumption and pain scores compared to patients without a regional anesthetic.

METHODS: Using our institution's electronic medical record, we identified patients ≤18 years of age who underwent surgery from May 2014 to August 2019. Inclusion criteria: surgeries with regional anesthesia performed in at least one of the included cases. Exclusion criteria: postoperative ICU admission, ASA class ≥4, ≥1 operation performed during the same anesthetic, and non-operative procedures. Regional anesthetics were categorized as catheter-based blocks and single-shot blocks. Primary outcome: PACU opioid exposure (any/none) and dose. Secondary outcomes: intraoperative and inpatient opioid exposure (any/none) and dose, procedure and anesthesia lengths, PACU length of stay, and mean postoperative pain scores (mild vs moderate/severe). Mild pain was defined as numeric rating scale 0-3, while moderate/severe was defined as 4-10. Linear and logistic regressions were used to estimate the association of exposure to regional anesthesia with outcomes; adjustments were made for possible confounders.

RESULTS: 13,526 eligible procedures met inclusion criteria; 2,761 (20.4%) regional anesthetics were performed. Cohort demographics are summarized in Table 1. Regional anesthesia was significantly associated with having an opioid-free intraoperative anesthetic (Table 2). For patients who did receive opioid intraoperatively, catheter-based regional anesthesia had an associated intraoperative reduction of 0.035 mg kg-1 oral morphine equivalents (MEUs) while single-shot blocks had a reduction of 0.038 mg kg-1 MEUs. Regional anesthesia had a weaker association with having an opioid-free PACU course. For patients who did receive opioid in the PACU, regional anesthesia was not associated with a significant difference in dose received. The difference in procedure length for patients who received single-shot blocks was +8 minutes and for patients who received regional catheters was +19 minutes. Odds of having moderate/severe PACU pain scores was slightly higher in catheter block patients whereas the single-shot block group had similar pain scores to patients who did not undergo regional anesthesia. Preliminary analysis of inpatient outcomes data showed a small decrease in probability of opioid exposure in the catheter block group, and no major difference in the probability of opioid exposure in the single-shot block group. At 12-24 hours, the single-shot group patients had a slightly higher probability of higher pain scores compared to no-block and catheter block patients.

CONCLUSION: While evidence from prospective trials under idealized conditions with stringent inclusion and exclusion criteria suggests regional anesthesia improves postoperative pain parameters, results from large pragmatic studies are lacking. In this retrospective review of children undergoing routine care in the perioperative setting, regional anesthesia was associated with a statistically significant decrease in intraoperative opioid exposure and administration. Furthermore, there was a significant difference in PACU opioid administration but no clinically significant difference in PACU pain severity, corroborating the opioid-sparing effect of single-shot blocks. Inpatient outcome results suggest a small decrease in opioid exposure in patients who receive a catheter-based block. Our results suggest that in real-world conditions, regional anesthesia may play an opioid-sparing role intraoperatively and in the PACU, but it is unclear if meaningful differences in analgesic outcomes occur beyond this.

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Table 1: Cohort Demographics

	Intraoperative Block Type							
	No Block		**Catheter Block**		**Single Shot Block**		**Total**	
	#	%	#	%	#	%	#	%
Female	4401	(40.88)	188	(42.25)	670	(28.93)	5259	(38.88)
Male	6364	(59.12)	257	(57.75)	1646	(71.07)	8267	(61.12)
Mean age (yrs), (sd)	8.04	(5.20)	11.68	(5.55)	7.35	(6.12)	8.05	(5.43)
ASA class								
1	4655	(43.24)	141	(31.69)	1336	(57.69)	6132	(45.33)
2	4603	(42.76)	186	(41.80)	763	(32.94)	5552	(41.05)
3	1507	(14.00)	118	(26.52)	217	(9.37)	1842	(13.62)
Disposition								
Hospital Outpatient Surgery	7669	(71.24)	103	(23.15)	1868	(80.66)	9640	(71.27)
Inpatient	956	(8.88)	29	(6.52)	62	(2.68)	1047	(7.74)
Surgery Admit	2140	(19.88)	313	(70.34)	386	(16.67)	2839	(20.99)
Intraop remifentanil								
No	10094	(93.77)	427	(95.96)	2283	(98.58)	12804	(94.66)
Yes	671	(6.23)	18	(4.04)	33	(1.42)	722	(5.34)
History of OSA								
No	10318	(95.85)	440	(98)	2278	(98.36)	13036	(96.38)
Yes	447	(4.15)	<10	(2)	38	(1.64)	490	(3.62)
History of chronic pain								
No	10289	(95.58)	372	(83.60)	2094	(90.41)	12755	(94.30)
Yes	476	(4.42)	73	(16.40)	222	(9.59)	771	(5.70)
Overweight								
No	6709	(62.32)	297	(66.74)	1545	(66.71)	8551	(63.22)
Yes	4037	(37.50)	148	(33.26)	771	(33.29)	4956	(36.64)
Unknown	19	(0.18)	0	(0.00)	0	(0.00)	19	(0.14)
History of mood disorder								
No	10651	(98.94)	438	(98)	2301	(99.35)	13390	(98.99)
Yes	114	(1.06)	<10	(2)	15	(0.65)	136	(1.01)

Table 2: Regression Analysis of Analgesic Outcomes

Association Evaluated	Regression Model	Confounders Adjusted	Regression Result
Opioid exposure intraoperative if receiving regional anesthesia	Logistic	Procedure, procedure length	OR for having intraoperative opioid exposure: *Catheter block*: 0.21 (95% CI: 0.13-0.32) *Single-shot block*: 0.13 (95%CI: 0.11-0.16)
Total intraoperative opioid dose for patients who did receive intraoperative opioid	Linear	Procedure, procedure length, use of intraoperative remifentanil	Total intraoperative opioid dose lower by mg/kg MEUs: *Catheter block*: 0.035 (95% CI: 0.055-0.014 decrease) *Single-shot block*: 0.038 (95% CI: 0.047-0.029 decrease)
Opioid exposure in PACU if receiving regional anesthesia	Logistic	Procedure, age	OR for having PACU opioid exposure: *Catheter block*: 0.58 (95% CI: 0.36-0.96) *Single-shot block*: 0.89 (95%CI: 0.78-1.02)
Total opioid dose in PACU for patients who did receive PACU opioid	Linear	Procedure, age	Total opioid dose lower by mg/kg MEUs: *Catheter block*: 0.002 (95%CI: -0.019-0.02) *Single-shot block*: -0.004 (95% CI: -0.009, 0.001)
Intraoperative time difference between patients who did and did not receive regional anesthesia	Linear	Procedure, age, anesthesiologist, surgeon, ASA class, case complexity	Intraoperative time difference in minutes: *Catheter block*: +20.4 (95% CI: 18.0-22.8-0.38) *Single-shot block*: +8.4 (95% CI: 7.8-9.6)
Mean PACU pain score (categorized as 0-3 for low pain or ≥4 for high pain)	Logistic	Procedure, sex, age, history of chronic pain or mood disorders.	OR for high pain: *Catheter block*: 1.79 (95% CI: 1.32-2.43) *Single-shot block*: 1.04 (95% CI: 0.83-1.30)

REGIONAL ANESTHESIA 7

Randomized, Double-Blinded Study to Evaluate the Analgesic Efficacy of IPACK (interspace between the Popliteal Artery and Capsule of the Knee) Block when Combined with Adductor Canal (Saphenous) Nerve

Dexter Gregg[1], Jonathan Hausman[1], Tony Chiang[1], Brian Mendelson[1], Shawn Coleman[1], Jun Tang[1], Andrew Spitzer[1], Titus Jackson[1]

[1]Cedars-Sinai Medical Center, Los Angeles, CA

INTRODUCTION: In order to provide excellent postoperative pain management and minimize opioid related side effects after total knee arthroplasty (TKA), various regional blocks have been implemented into multimodal analgesic strategy. The adductor canal block (ACB) (saphenous) is becoming popular in TKA because of its comparable anesthesia and analgesia without quadriceps muscle weakness rather than the traditional femoral nerve block. However, it does not adequately address the posterior aspect of the knee, which is innervated by the sciatic nerve. The recently introduced IPACK block (interspace between the popliteal artery and the capsule of the knee) has been alleged to be effective to provide significant posterior knee analgesia, however, its efficacy on postoperative pain control and knee function in TKA were controversial[1,2]. Therefore, we designed this prospective, randomized, and double-blinded study to assess our hypothesis that the combined ACB and IPACK would improve analgesic effects, decrease pain scores and opioid requirement, as well as facilitate early recovery and improve patient satisfaction with pain management in patient after TKA.

METHODS: This is a still ongoing study project. Following IRB approval, 31 consenting patients, aged between 18 and 80 years old, and ASA 1-3 undergoing primary, unilateral TKA were randomly assigned to one of two study groups: before the surgery, the study patient received ultrasound-guided ACB with 0.25% bupivacaine (with 1:200,000 epinephrine) 30 ml and ultrasound-guided IPACK with either normal saline 15 ml (Group 1, 16 patients) or 0.25% bupivacaine (with 1:200,000 epinephrine) 15 ml (Group 2, 15 patients). All of the study patients received spinal anesthesia, propofol infusion to maintain BIS 40-60 during TKA, and standard multimodal pain regimen postoperatively. The demographic characteristics, recovery profiles, pain scores, opioid dosages (intravenous morphine equivalence doses), side effects, and hospital length of stay (LOS) were recorded. Data were analyzed using Student's test, Mann-Whitney U-test, chi-square test or the Fisher exact test, with with p-values < 0.05 considered statistically significant.

RESULTS: Both study groups were similar with respect to their demographic characteristics, including age, weight, height, gender, and history of postoperative nausea and vomiting. There were also no differences in the durations of anesthesia, surgery, PACU, and hospital LOS. Interestingly, study patients who received ACB-IPACK showed significantly longer walking distance at the first postoperative day (114±75 feet vs 64±13 feet in ACB group). Although the postoperative opioid requirements and pain scores were similar between the two study groups at 0-12h, 12-24h, 24-48h intervals, respectively, the morphine equivalence doses were decreased about 20% in Group 2 (ACB-IPACK) during the first 12 hours postoperatively.

CONCLUSION: The combination of ultrasound guided ACB and IPACK blocks can facilitate knee function recovery after TKA procedure. Even though the IPACK block did not show significant benefits on the postoperative opioid requirements, pain scores and hospital LOS, IPACK did decrease opioid requirements by 20% at the earlier postoperative period when combined with ACB. The next step that is needed is to continue the enrollment for this ongoing study to assess the effects of IPACK while avoiding type II error.

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Table 1: Demographics and results for Group 1 (no IPACK) and Group 2 (IPACK)

	Group 1	Group 2
Age (yr)	68±10	70±6
Weight (kg)	86±16	91±19
Height (cm)	171±9	170±11
Anesthesia time (min)	156±22	165±46
Surgery time (min)	101±16	105±10
Duration of PACU (min)	142±98	144±77
Walking distance at first attempt, postop 24h (feet)	64±50	114±75*
Hospital LOS (days)	2.3±0.5	2.0±0.8
Narcotic requirement (Morphine equivalent in mg)		
-0h to postop 12 h	20±12	16±9
-postop 12h to 24 h	17±9	17±6
-postop 24h to 48 h	26±21	32±12

Values are mean ± SD or numbers
*p<0.05 vs Group 1

REGIONAL ANESTHESIA 8

Association of hospital safety-net burden with morbidity and mortality after elective total knee arthroplasty

Deirdre C Kelleher[1], Briana Lui[1], Xiaoyue Ma[2], Ryan Lippell[1], Roniel Weinberg[2], Tiffany Tedore[1], Robert White[3]

[1]NY-Presbyterian Hospital - Weill Cornell Medicine, New York, NY, [2]New York Presbyterian Cornell, new york, NY, [3]New York Presbyterian Weill Cornell, New York, NY

INTRODUCTION: Total knee arthroplasty (TKA) is among the most common surgical procedures performed annually in the United States and comprises an outsized proportion of Medicare procedural expenditures.[1] By 2030, primary TKA is projected to increase as much as 189% to 1.28 million procedures annually.[2] Previous work demonstrated an impact of higher safety-net burden hospitals, defined by their high proportion of Medicaid and uninsured patients, on morbidity and in-hospital mortality following total hip arthroplasty.[3] Here we examine the impact of safety-net burden on in-hospital mortality, postoperative complications, and length of stay (LOS) in patients who underwent elective TKA to further quantify hospital-level social determinants of health. By examining a purely elective procedure such as TKA we hoped to further control for any unmeasured confounding factors and better understand the role of safety-net burden on postsurgical outcomes.

METHODS: Using data from the Healthcare Cost and Utilization Project's (HCUP) State Inpatient Databases (SID), we retrospectively analyzed 1,141,587 patients aged ≥ 18 years who underwent isolated elective TKA (ICD-9-CM code 81.54) in Florida, Kentucky, Maryland, New York, and Washington from 2007 through 2018, comparing patient demographics, present-on-admission comorbidities, and hospital characteristics by hospital safety-net burden status. Using generalized estimating equation (GEE) models with exchangeable correlation structure, we assessed the association of hospital safety burden status (high, medium, or low) on in-hospital mortality (primary outcome), patient complications and LOS (secondary outcomes). We similarly analyzed type of anesthesia used by burden level for patients in New York, the only state for which this data was available. A post-hoc sensitivity analysis of the data by state was also performed to control for any state-level differences in reporting and outcomes. We report adjusted odds ratios (aOR), 95% Confidence Intervals (CI), and p-values.

RESULTS: In-hospital mortality for the cohort was low (n=642, 0.056%), however, patients undergoing TKA at medium safety-net burden hospitals were 40% more likely to die in-hospital when compared to patients at low safety-net burden hospitals (aOR: 1.40, 95% CI 1.09 to 1.79, p=0.008). Additionally, patients who underwent TKA at medium or high safety-net burden hospitals were more likely to experience intraoperative complications (medium aOR: 1.94, 95% CI 1.34 to 2.83, p <0.001; high aOR: 1.91, 95% CI 1.35 to 2.72, p <0.001). Only a non-significant trend towards increased mortality risk was observed when comparing high and low safety-net burden hospital outcomes (aOR: 1.35, 95% CI 0.99 to 1.86, p=0.06) and there were no statistically significant differences in likelihood of developing other postoperative complications or LOS between the levels of safety-net burden hospitals. New York state data analysis found that anesthesiologists at high safety-net burden hospitals were more likely to utilize general rather than regional anesthesia for TKA procedures (aOR: 4.04, 95% CI 1.05 to 15.5, p=0.042). Post-hoc analysis of mortality, complications, and LOS by state revealed that no single state was driving the combined results.

CONCLUSION: This analysis suggests that patients undergoing TKA at higher safety-net hospitals may be at higher odds of mortality when compared with patients undergoing TKA at lower safety-net hospitals. This increase in mortality may be related to the increased risk of intraoperative complications and use of general anesthesia found at higher safety-net burden hospitals. Further research is needed to determine the causes of these differences and ways to best mitigate the risk of complications after TKA at higher safety-net burden hospitals.

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REGIONAL ANESTHESIA 9

Efficacy for pain control and decreased opioid medication usage of erector spinae block for reduction mammoplasty surgery in an ambulatory setting: A retrospective study

Aryeh M Ginsburg[1], Brian Aviles[2], Galila Flatow[1], Ricardo Maturana[1], Fadi Farah[1], Singh Nair[3], Elilary Montilla Medrano[1]

[1]Montefiore Medical Center - Albert Einstein College of Medicine, Bronx, NY, [2]Montefiore Medical Center- Albert Einstein College of Medicine, Bronx, NY, [3]Montefiore Medical Center, Bronx, NY

INTRODUCTION: Perioperative pain control for breast reduction mammoplasty has traditionally centered on using parenteral opioid medications, and regional techniques including tumescent anesthesia, thoracic epidural anesthesia, and intercostal nerve blocks, and paravertebral nerve blocks[1-4]. The erector spinae plane block (ESB) has more recently been described as an effective and safe alternative. This study evaluates the efficacy of ESB, as well as paravertebral (PVB), pectoralis nerve (PEC), and other types of blocks in patients who underwent elective reduction mammoplasty based on decreased opioid medication usage and decreased pain scores in the perioperative period.

METHODS: All patients who underwent bilateral reduction mammoplasty, with or without a nerve block at a large urban ambulatory surgery center between January 2018 and October 2019, were identified, and data points were collected by reviewing medical charts. Patients were divided into two groups: those who did not receive a block, and those who received a block (ESB, PVB, both ESB and PVB, PEC, or any other type of block). We collected demographic information, the total amount of intra and postoperative opioids in morphine milligram equivalents (MME), preoperative use of medications, postoperative use of other pain medications, post-anesthesia care unit (PACU) pain scores at 30 minutes on arrival and at discharge, as well as discharge time, and the use of postoperative antiemetics. We used descriptive statistics to report our data; continuous variables were compared using non-parametric t-tests and categorical variables using chi-square analysis. All tests are two-tailed, and a p-value of 0.05 was considered statistically significant.

RESULTS: In total, 482 patients were included in the analysis. The mean (standard deviation) age was about 40 (40±12 for block, 41±14 for no block), and the majority of patients were ASA Class 2 (~75%) (Table 1). An average of 17±7.6 and 20±10 total intraoperative IV MME were given to patients who received an ESB and no block, respectively ($p < 0.05$). Total postoperative IV MME was 4±3.4 for ESB and 4±5 for no block (p=0.961). Average PACU pain scores at 30 minutes were 5±4 and 5±3.9 (p=0.954), and at discharge were 2±1.6 and 2±1.9 (p=0.430) for ESB versus no block (Table 3). Additional data will be presented at the conference.

CONCLUSION: There was a statistically significant difference in total intraoperative MME requirements between patients who received a block, and those who had no block. However, we did not find a significant difference in postoperative opioid usage and PACU pain scores. Our results are contradictory to what is reported in the randomized controlled studies. Non-standardized pain management in the PACU and the local anesthetics dose selection could be the reasons for conflicting results. Additionally, the study results should be interpreted cautiously due to the small sample size and retrospective design.

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Table 1.

	No Block (318)	Block (164)	P value
Age	41±14	40±12	0.217
Preop Medication (Yes)%	31	26	0.375
Preop Pregabalin (Yes)%	55	17	0.001
ASA 2 (%)	75	76	0.334

Table 2.

	No Block (318)	Block (164)	P value
Total Intraop IV MME	20±10	16±8	0.001
Total Postop IV MME	4±5	3.7±3	0.618
PACU Pain 30 min.	5±3.9	4±5	0.537
PACU Pain D/C	2±1.9	2±1.7	0.140

Table 3.

	No Block (318)	ESB (87)	PVB (60)	ESB+PVB (11)	PEC/other (6)	P value (ESB)
Total Intraop IV MME	20±10	17±7.6	17±9	14±5.7	10±11	0.02
Total Postop IV MME	4±5	4±3.4	4±2.7	4±2.9	3±4	0.961
PACU Pain 30 min	5±3.9	5±4	4±3.7	4±3.5	4±4.4	0.954
PACU Pain D/C	2±1.9	2±1.6	2±1.7	3±1	2±1.6	0.430

REGIONAL ANESTHESIA 10

Learning curves of brachial plexus blocks estimated by the risk-adjusted learning curve cumulative sum method (RA-LC-CUSUM)

Getulio R De Oliveira Filho[1], Adilto Mezzari[2], Giulia N Bianchi[2]

[1]Federal University Of Santa Catarina, FLorianopolis, SC, [2]Federal University of Santa Catarina, Florianópolis, SC

INTRODUCTION: Statistical sequential methods can identify the learning curves associated with gains in procedural skills.[1] Among them, the risk-adjusted learning-curve cumulative sum method (RA-LC-CUSUM) detects when the acquisition process of skill deviates from an unstable state (learning curve) to a stable state (proficiency), controlling for factors that influence the chances of failure in procedures.[2] Figure 1 illustrates learning curves constructed with the RA-LC-CUSUM method. Upper and lower horizontal lines represent the absorption barrier set at zero (H1) and the proficiency limit (H0), respectively. The learning curve starts at zero. For each success the curve shifts downwards, while failures shift the curve upwards. Proficiency is attained when the curve crosses H0. R1 represents the learning curve of a resident who had not yet reached proficiency after 17 consecutive blocks. R2 represents the learning curve of a resident who reached the proficiency limit (H0) after 18 blocks. This study aimed to estimate the number of procedures necessary for residents to achieve proficiency in brachial plexus blocks using the RA-LC-CUSUM method.

METHODS: With IRB approval and waived informed consent, the sequential records of brachial plexus blocks (BPB) performed by residents in a dedicated database were retrospectively extracted, anonymized, and analyzed. The number of months since the resident's admission on the date of the block, the number of attempts (skin punctures), the access route to the brachial plexus, the primary technique for identifying the nervous structures (neurostimulation or ultrasound), the quality of anatomical references (precise or inaccurate according to ease of identification of the anatomical landmarks), and the type of resident supervision (direct or distance), were extracted. The outcome variable was a success, defined as a complete sensitive block at terminal nerve territories, or a failure, defined as the need for supplementation with opioids, supplementary blocks, or general anesthesia. Univariate tests estimated the associations between the independent variables and the outcome variable. Variables with significant associations ($p < 0.2$) entered a logistic regression. Model fit was assessed by using the Hosmer & Lemeshow test and the ROC curve was constructed to assess the predictive ability of the model.Probabilities of failure were estimated for each procedure, using the logistic equation. Learning curves were constructed using the RA-LC-CUSUM method with acceptable and unacceptable failure rates set at 5% and 20%, respectively. The proficiency limit (H0) was estimated assuming $\alpha = 5\%$ and $1\text{-}\beta = 20\%$.[2] Residents who achieved failure rates equal to or less than the defined acceptable failure rate were considered proficient. The number of procedures performed in sequence until reaching proficiency was extracted from the learning curves.

RESULTS: 1,720 records of BPB performed by 36 residents (median = 37 ; 25th - 75th percentiles = 22 - 75 blocks per resident included 847 (49.2%) axillary, 507 (29.5%) interescalene, and 366 (21.3%) infraclavicular blocks. The overall success rate was 93.1% (87.6% - 96.3%).The direct supervision rate was 95.8%. The following were identified as predictive factors for failure by logistic regression: the number of months in training on the date of the blockade (OR = 0.97; 95% CI = 0.95 – 0.99; p = 0.01); the use of ultrasound relative to neurostimulation (OR = 0.26; 95% CI = 0.18 – 0.37; $p < 0.001$), the number of attempts (OR = 2.06; 95% CI = 1.60 – 2.65; p = < 0.001); inaccurate anatomical references (OR = 3.74; 95% CI = 2.32 – 6.05; $p < 0.001$), and inadequate patient positioning (OR = 2.34; 95% CI = 1.19 – 4.62; p = 0.013. Data fitted the model (χ^2 (8 d.f.) = 12.14; p = 0.14). The area under the ROC curve was 79% (95% CI = 75% - 83%; p <0.001). Twenty-five residents (69.4%) achieved proficiency after a median of 15 blocks (25th - 75th percentiles = 11 - 22).

CONCLUSION: The number of months of training and the use of ultrasound decrease, while the low quality of anatomical references, patient's inadequate positioning, and the number of attempts to perform the block increase the probabilities of failure in BPB. The learning curve adjusted for predictive factors of failure aiming at failure rates lesser than 20% requires a median experience of fifteen blocks during supervised training.

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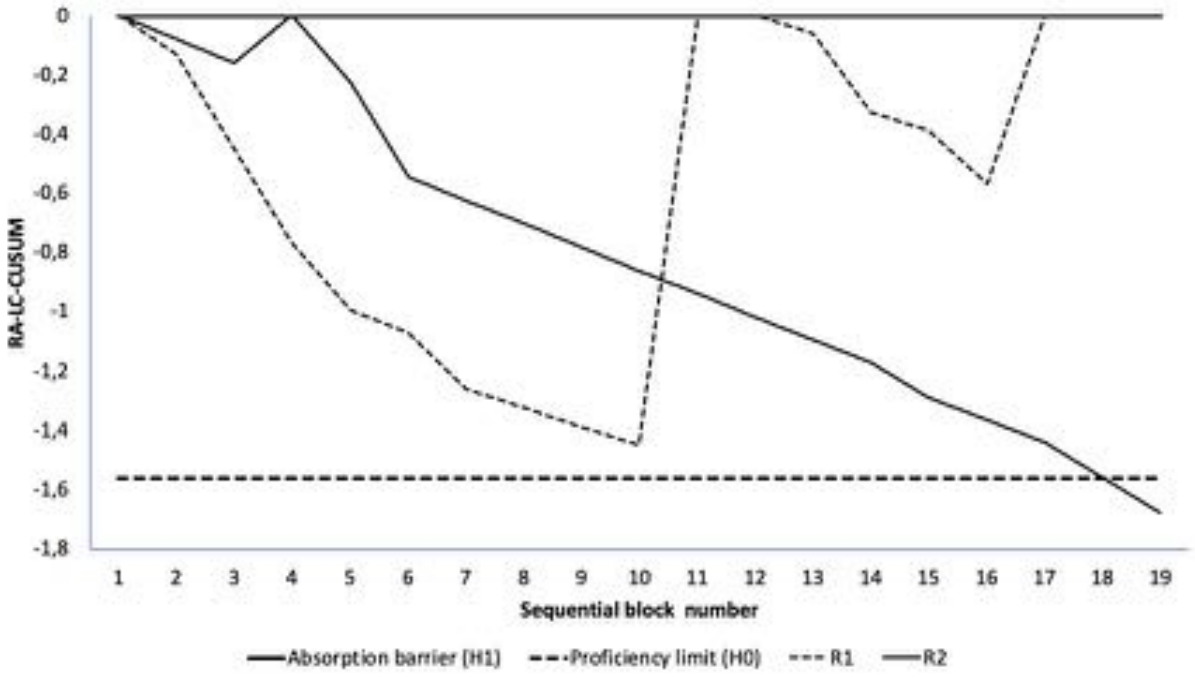

Fig. 1

REGIONAL ANESTHESIA 11

General versus neuraxial anesthesia for outpatient total knee arthroplasty: differences in patient demographics and outcomes

Kevin Ng[1], Edward N Yap[2], Julia Wei[3], Matthias Behrends[4], Christopher Webb[2]

[1]The Permanente Medical Group, Walnut Creek, CA, [2]The Permanente Medical Group, South San Francisco, CA, [3]Kaiser Permanente Division of Research, Oakland, CA, [4]UCSF, San Francisco, CA

INTRODUCTION: Total knee arthroplasty is an increasingly common surgery that provides pain relief and improved function in patients with severe osteoarthritis. Unlike major thoracic or abdominal surgery that require general anesthesia (GA), knee surgery can be performed successfully under neuraxial anesthesia (NA). While studied extensively, there is still controversy over whether GA or NA is associated with the best patient safety and satisfaction outcomes. We aimed to determine if there were significant differences in demographics and outcomes between patients who received GA versus NA for outpatient primary total knee arthroplasty.

METHODS: Our retrospective cohort study consisted of 11,199 same day discharge unilateral primary total knee arthroplasty patients between the years of 2017- 2019. Our primary exposure of interest was type of anesthesia, comparing GA to NA. Demographic data included age, sex, race, body mass index, American Society of Anesthesiologist (ASA) physical status classification, and Charlson Comorbidity Index (CCI). We examined 30-day composite outcome as our primary outcome. The composite outcome consisted of the following events: mortality, readmission, urinary tract infection, major adverse coronary event, stroke, deep venous thromboembolism, pulmonary embolism, acute renal failure, surgical site infection, and pneumonia. We also collected secondary outcomes which included intraoperative and post-anesthesia care unit (PACU) opioid use, PACU pain scores, PACU nausea and vomiting, and length of stay. We used the Chi-square test, t-test, and Wilcoxon rank sum test to compare demographics and outcomes between GA patients to NA patients. Additionally, we used logistic regression to calculate unadjusted odds ratios.

RESULTS: Of the 11,199 knee arthroplasty surgeries, 1370 (12.2%) received a general anesthetic and 9,829 (87.8%) received NA (Table 1). The composite outcome comparing NA (5.8%) to GA (6.7%) was not statistically significant ($p = 0.17$). Of the individual outcomes, NA had a statistically significant decreased rate for major adverse coronary events (OR 0.41, 95% CI 0.19-0.93, $p = 0.03$). NA showed a significant reduction in intraoperative and PACU administered opioid, PACU pain scores, and nausea and vomiting. NA showed a significant increase in PACU length of stay (Table 3). Older age ($p < 0.01$), higher BMI ($p < 0.01$), and patients with higher ASA classification ($p < 0.01$) and CCI ($p = 0.02$) were significantly associated with receiving a general anesthetic. Patients who identified their race as African Americans and Hispanics compared to Caucasians and Asians were more likely to receive a general anesthetic ($p < 0.01$). We found no difference in sex and laterality affecting the decision between anesthetic technique.

CONCLUSION: Our study shows that NA for patients undergoing outpatient unilateral primary total knee arthroplasty was associated with a reduction in 30-day postoperative major adverse coronary events. In addition, NA when compared to GA was associated with a reduction in administered opioids on the day of surgery, lower postoperative pain scores, and postoperative nausea and vomiting in the PACU. Being older, having a higher BMI, ASA classification, and CCI was associated with a higher chance of receiving GA. There were significant differences between the type of anesthesia administered to different ethnic groups. The choice of general anesthesia for patients with older age, higher BMI, ASA classification, and CCI is most likely multifactorial. One reason may include patient characteristics that can lead to clinician bias to choose general anesthesia, such as the higher disease burden and intolerability to a sympathectomy from NA. Patients with higher BMI may also pose a technical challenge for neuraxial technique or longer surgical duration, leading to more use of GA. Racial and ethnic disparities in healthcare has been an ongoing national discussion, and it is not entirely surprising to find these differences in our study. Although our study did not dive into the reason for these findings, we know that there are language and cultural barriers that could make communication difficult, potential racial differences in trust of healthcare providers, and even implicit racial biases by physician and healthcare providers. Further studies need to be conducted to fully assess the causes of these differences.

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Table 1. Sociodemographic and clinical characteristics of same-day discharge unilateral primary total knee replacement surgery patients, 2017-2019

Characteristic		Anesthesia Type		p-value
	Overall	General	Neuraxial	
	N = 11199 (100%)	N = 1370 (12.2%)	N = 9829 (87.8%)	
	N (%)	N (%)	N (%)	
Age (Mean, SD)	68.3 (8.7)	67.5 (8.8)	68.4 (8.6)	< 0.01
Sex				
Male	4419 (39.5%)	543 (12.3%)	3876 (87.7%)	0.89
Female	6780 (60.5%)	827 (12.2%)	5953 (87.8%)	
Race/Ethnicity				
Non-Hispanic White	7433 (66.4%)	892 (12.0%)	6541 (88.0%)	
Asian	968 (8.6%)	63 (6.5%)	905 (93.5%)	< 0.01
Black	682 (6.1%)	122 (17.9%)	560 (82.1%)	
Hispanic	1600 (14.3%)	229 (14.3%)	1371 (85.7%)	
Other	516 (4.6%)	64 (12.4%)	452 (87.6%)	
BMI				
Normal	1532 (13.7%)	135 (8.8%)	1397 (91.2%)	< 0.01
Overweight	3757 (33.6%)	423 (11.3%)	3334 (88.7%)	
Obese	5909 (52.8%)	812 (13.7%)	5097 (86.3%)	
ASA				
I	141 (1.3%)	4 (2.9%)	137 (97.2%)	
II	6616 (59.1%)	627 (9.5%)	5989 (90.5%)	< 0.01
III	4369 (39.0%)	712 (16.3%)	3657 (83.7%)	
IV	73 (0.7%)	27 (37.0%)	46 (63.0%)	
CCI				
0	3856 (37.4%)	428 (11.1%)	3428 (88.9%)	0.02
1-2	4398 (42.6%)	519 (11.8%)	3879 (88.2%)	
3+	2067 (20.0%)	281 (13.4%)	1786 (86.4%)	
Laterality				
Left	5413 (48.3%)	663 (12.3%)	4750 (87.8%)	0.96
Right	5786 (51.7%)	707 (12.2%)	5079 (87.8%)	

Table 2. 30-day post-operative outcomes of same-day discharge unilateral primary total knee replacement surgery patients, 2017-2019

Postoperative Outcome	Anesthesia Type				OR (95% CI)	p-value
	General		Neuraxial			
	N= 1370 (12.2%)		N = 9829 (87.8%)			
	N	%	N	%		
Mortality	2	0.2	15	0.2	1.04 (0.24-4.57)	0.95
Readmission	39	2.9	229	2.3	0.81 (0.58-1.15)	0.24
Surgical Site Infection	21	1.5	139	1.4	0.92 (0.58-1.46)	0.73
Pneumonia	9	0.7	43	0.4	0.66 (0.32-1.37)	0.27
Urinary Tract Infection	27	2	158	1.6	0.81 (0.54-1.23)	0.32
Major Coronary Event	8	0.6	24	0.2	0.41 (0.19-0.93)	0.03
Venous Thromboembolism/Pulmonary Embolism	15	1.1	96	1.0	0.89 (0.52-1.54)	0.68
Cerebrovascular Event	1	0.1	14	0.1	1.95 (0.25-14.86)	0.52
Acute Renal Failure (stage 1)	13	1	63	0.6	0.67 (0.37-1.23)	0.20
Composite Outcome	92	6.7	569	5.8	0.85 (0.68-1.07)	0.17

Table 3. Intraoperative and PACU outcomes of same-day discharge unilateral primary total knee replacement surgery patients, 2017-2019.

Postoperative Outcome	Anesthesia Type				p-value
	General		Neuraxial		
	N= 1370 (12.2%)		N = 9829 (87.8%)		
	N	%	N	%	
Tranexamic Acid Administered	1343	98.0	9462	96.3	<0.01
Intraoperative Opioid (Morphine Equivalence), Median (Q1-Q3)	50	30-75	30	15-30	<0.01
Length of PACU Stay	138	92-221	185	112-273	<0.01
PACU Nausea and Vomiting (PASS Emetic)	63	4.6	313	3.2	0.02
PACU Pain Scores (Maximum on NRS 0-10), Median (Q1-Q3)	7	5-8	5	2-7	<0.01
PACU Pain Scores (Minimum on NRS 0-10), Median (Q1-Q3)	0	0-0	0	0-0	<0.01
PACU Pain Scores (Average on NRS 0-10), Median (Q1-Q3)	2.5	1.7-3.2	1.5	1.1-2.3	<0.01
PACU Opioid Usage (Morphine Equivalence), Median (Q1-Q3)	38	18.8-63.0	15	7.5-39.0	<0.01

REGIONAL ANESTHESIA 12

Timing Effects of Ultrasound-Guided Paravertebral Block (PVB) in Patients Undergoing Robotic Mitral Valve Repair: A Retrospective Study

Manxu Zhao[1], Jonathan Hausman[2], Thomas J Wilson[1], Nicola D'Attellis[1], Alfredo Trento[1], Danny Ramzy[2]

[1]Cedars Sinai, Los Angeles, CA, [2]Cedars-Sinai Medical Center, Los Angeles, CA

INTRODUCTION: Robotic mitral valve repair (MVr), a minimally invasive cardiac surgery for select patients with mitral regurgitation, is becoming a standard approach with demonstrated benefits of shorter duration of post-operative ventilation, decreased length of intensive care unit (ICU) and hospital stay (LOS), and excellent surgical outcomes[1]. Regional nerve blocks serve an important role in multimodal analgesic regimens for robotic MVr. Although the efficacy of ultrasound-guided paravertebral block (PVB) for postoperative analgesia after robotic MVr has been demonstrated, the optimal timing of its administration (before versus after surgery) has not been established. Preoperative PVB is intriguing because it may provide intraoperative analgesia with a potential opioid-sparing effect and it avoids the issue of post-cardiopulmonary bypass coagulopathy. However, the efficacy of postoperative nerve block could potentially be limited if PVB was performed before surgery. Therefore, we designed this retrospective study to investigate the timing effects of ultrasound guided PVB administered before or after surgery with respect to pain scores, opioid requirements, and ICU and hospital LOS after robotic MVr.

METHODS: Medical records were queried for ASA 3-4 patients aged ≥ 18 years who underwent minimally invasive cardiac surgery at our institution between 01/2019 to 06/2020. 100 patients who underwent robotic MVR and received perioperative PVB (with 40 ml of 0.25% bupivacaine) were identified and assigned into one of two study groups based on timing of PVB. 50 patients with PVB performed before surgery in Group 1, and 50 patients in Group 2 with PVB performed after surgery. All study patients received institutional standard general anesthesia, multimodal pain regimen, and postoperative care. The demographic characteristics, recovery profiles, pain scores, opioid dosages (expressed in milligrams of intravenous morphine equivalents), side effects, and hospital LOS were recorded. Data were analyzed using Student's test, Mann-Whitney U-test, chi-square test or the Fisher exact test, with p-values < 0.05 considered statistically significant.

RESULTS: The two study groups were similar with respect to their demographic characteristics including age, weight, height, baseline biventricular function and severity of mitral regurgitation. The durations of anesthesia, surgery, cardiopulmonary bypass, aortic cross-clamp, and time to extubation after surgery were not significantly different between the study groups. Intraoperatively, patients in Group 1 (preop PVB) received significantly less midazolam and opioid than patients in Group 2 (postop PVB): midazolam 4.4 ± 2.4 mg vs 6.5 ± 3.0 mg and IV morphine equivalents 32 ± 17 mg vs 69 ± 29 mg. Percentage of patients requiring 'rescue' PVB re-block after surgery was similar despite timing (36% in Group 1 vs 32% in Group 2). Finally, the postoperative (0-72 hr) pain scores and opioid requirements, as well as durations of ICU and hospital LOS were similar between two study groups (Table).

CONCLUSION: In this retrospective review study, PVB administered before or after surgery produced similar postoperative analgesic effects with respect to pain scores, opioid requirements, and duration of ICU and hospital LOS. However, PVB performed before surgery could provide superior intraoperative analgesia, as suggested by lower doses of midazolam and opioids. Future studies in the form of prospective randomized, double-blinded, and controlled clinical studies are needed to evaluate the timing effects of PVB for robotic MVr.

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Table 1. Study group characteristics and outcomes. Patients receiving preoperative ultrasound-guided paravertebral block (PVB) assigned to Group 1. Postoperative PVB Group 2.

	Group 1	**Group 2**
Number (n)	50	50
Age (yr)	61±12	62±11
Gender (M/F) (n)	10/40	13/37
Weight (kg)	82±17	81±14
Height (cm)	176±9	174±9
Cross-clamp time (min)	76±15	79±23
Anesthesia time (min)	306±46	315±46
Extubation time (min)	274±86	243±108
Midazolam intraop (mg)	4.4±2.4	6.5±3.0*
IV Morphine equivalents intraop (mg)	32±17	69±29*
ICU LOS (d)	2.3±1.1	2.2±1.0
Hospital LOS (d)	5.4±1.4	5.4±1.2
Number receiving re-block (n,%)	18,32	16,34
IV Morphine equivalents (mg)		
-0 to postop 24 h	13±9	14±16
-postop 24 to 48 h	9±8	9±9
-postop 48 to 72 h	7±7	6±9

REGIONAL ANESTHESIA 13

Evaluation of postoperative analgesia of erector spinae plane block in elective laparoscopic cholecystectomy: a randomized control trial

Garima Garg[1], Divya Sethi[2]

[1]ESIC-PGIMSR, Basaidarapur, New Delhi, Delhi, India, [2]ESIC-PGIMSR, Basaidarapur, New Delhi, New Delhi, India

INTRODUCTION: Laparoscopic cholecystectomy is a minimally invasive and commonly performed surgical procedure. The pain of laparoscopic cholecystectomy has different components including somatic pain due to trochar insertion sites, visceral pain from gall bladder resection, parietal pain from peritoneal distention, and shoulder tip pain (referred visceral pain) due to diaphragm irritation from carbon dioxide insufflation. Commonly non-steroidal inflammatory agents, intravenous opioids, dexamethasone, gabapentin, local anesthetics infiltration at liver bed or port site, and regional anesthesia techniques such as epidural, transversus abdominis plane block, and paravertebral block have been used for postoperative pain management. Ultrasound-guided ESPB (Erector Spinae Plane block) is a regional anesthetic technique first described by Forero et al in 2016 for the treatment of thoracic neuropathic pain. In ESPB, the local anesthetic is administered in the inter-facial plane between the erector spinae muscle and the transverse process of the vertebrae. The drug spreads in a craniocaudal direction over multiple paravertebral spaces blocking both ventral and dorsal rami of spinal nerve roots. Since the initial description of ESPB, there have been several case reports and a few clinical trials demonstrating its analgesic efficacy in surgeries including thoracic, abdominal, breast, and spinal surgeries. We planned the present study to evaluate the analgesic benefits of ESPB in laparoscopic cholecystectomy.

METHODS: Seventy patients of ASA grade I / II, aged 18-60 years undergoing elective laparoscopic cholecystectomy were enrolled. They were randomized to group C or T using a computer-generated random numbers list. Patients in group C were given general anesthesia alone and patients in group T were given bilateral ultrasound-guided ESPB followed by general anesthesia. The primary objective was total 24hr postoperative analgesic consumption of tramadol and the secondary objective was need for rescue analgesia (fentanyl) and numeric pain rating scores (NRS) at rest and on movement (coughing). A linear high frequency (6-13 MHz) ultrasound probe (SonoSite, Bothell, WA, USA) was placed 3cm lateral to the T7 spinous process in longitudinal parasagittal orientation. The transverse process of the T7 vertebral and the three muscle layers above it including trapezius (uppermost), rhomboid major (middle), and erector spinae (lowermost) were identified using a linear high-frequency ultrasound probe, A 22-gauge 8-cm SonoTap needle was inserted in-plane in craniocaudal direction to place needle tip above the T7 transverse process and deep to the erector spinae muscle and 20 ml of 0.25% levobupivacaine was injected visualizing the lifting of the erector spinae muscle away from the transverse process bilaterally. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median (interquartile range). The normality of data was tested by the Kolmogorov-Smirnov test. If the normality was rejected then the non-parametric test was used. Normally distributed continuous variables (age, weight, times, the dose of tramadol, and fentanyl) were compared using the independent t-test, whereas non-normally distributed variables (NRS) were compared using the Mann-Whitney U test. Categorical variables were compared using the Chi-Square test. A P value of <0.05 was considered statistically significant.

RESULTS: Sixty-six patients were included for the final analysis. The total tramadol consumption in 24hr postoperative period for Group C was 178.12 ± 54.3 mg and for group T was 178.12 ± 54.3 mg, the difference was statistically highly significant (P = 0.0001). The need for rescue analgesia (fentanyl) was also statistically significantly lower in group T compared to group C (0.91 ± 5.22 mcg vs. 13.64 ± 23.82 mcg, P= 0.002). The postoperative NRS at ½, 2, 4, 6, 8 hr at rest and on movement (coughing) were statistically lower in group T than group C, although this difference was not of clinical significance.

CONCLUSION: In patients undergoing laparoscopic cholecystectomy, bilateral ultrasound-guided ESPB provided effective analgesia as it reduced the total tramadol consumption and the need for rescue analgesia (fentanyl) in 24hr postoperative period.

REGIONAL ANESTHESIA 14

Development and potential clinical application of a new long-lasting anesthetic

Yuan-Xiang Tao[1], Xue Tian[1], Xaioyang Xu[2]

[1]Rutgers New Jersey Medical School, Newark, NJ, [2]New Jersey Institute of Technology, Newark, NJ

INTRODUCTION: The management of persistent postsurgical pain and neuropathic pain remains a challenge in the clinic. Local anesthetics have been widely used as simple and effective treatment for these two disorders, but the duration of their analgesic effect is short. We here reported a new and injectable poly lactic-co-glycolic acid (PLGA)-coated ropivacaine that produced the long-lasting analgesic effect on postsurgical pain and neuropathic pain and no significant changes in motor function.

METHODS: Ropivacaine hydrochloride-loaded PLGA microparticles were first prepared and characterized. The amount of the PLGA-coated ropivacaine released into in vitro medium or in vivo blood plasma was quantified by HPLC analysis. Behavioral tests were carried out to examine the effect of the PLGA-coated ropivacaine on incisional pain and spared nerve injury (SNI)-induced neuropathic pain. Electron microscopy, TdT-mediated dUTP nick end labeling (TUNEL) and cresyl violet histochemical staining were used to examine whether the PLGA-coated ropivacaine let to neurotoxicity. Immunohistochemistry assay was performed to assess the expression of myelin basic protein (MBP, an important component of the myelin sheath) in the sciatic nerve and the expression of CD68 (a marker of microphages and monocytes) in adjacent muscles at the injected site. Western blot assay was carried out to examine the effect of the PLGA-coated ropivacaine on the SNI-induced increases in expression of phosphorylated extracellular signal-regulated kinase 1/2 (p-ERK1/2, a marker of neuronal hyperactivity) and glial fibrillary acidic protein (GFAP, a marker of astrocyte hyperactivity) in the dorsal horn.

RESULTS: PLGA-coated ropivacaine was continuously released in vitro for at least 6 days. Peri-sciatic nerve injection of the PLGA-coated ropivacaine attenuated paw incision-induced mechanical allodynia and heat hyperalgesia during the incisional pain period, and spared nerve injury-induced mechanical and cold allodynia for at least 7 days post-injection. This effect was dose-dependent. Peri-sciatic nerve injection of the PLGA-coated ropivacaine did not produce detectable inflammation, tissue irritation, or damage in the sciatic nerve and surrounding muscles at the injected site, dorsal root ganglion, spinal cord or brain cortex, although the scores for grasping reflex were mildly and transiently reduced in the higher dosage-treated groups.

CONCLUSION: Given that PLGA is an FDA-approved medical material, and that ropivacaine is used currently in clinical practice, the injectable PLGA-coated ropivacaine represents a new and highly promising avenue in the management of postsurgical pain and neuropathic pain.

Subspecialty Abstracts

RESPIRATION

RESPIRATION 1

Deterioration of Oxygenation Index and Oxygen Saturation Index after intubation predicts mortality in critically ill COVID-19 patients

Shivali Mukerji[1], Molly Vora[2], Ala Nozari[2], Robert Canelli[2], Rafael Ortega[3], Gerardo Rodriguez[4], Sadeq Quraishi[5], Alexander Nagrebetsky[6], Riccardo Pinciroli[7], Nicholas Flores[8], Alfonso Garcia[7], Alyssa Park[7]

[1]Boston University, Roxbury, MA, [2]Boston University School of Medicine, Boston, MA, [3]Boston University, Boston, MA, [4]Boston Medical Center, Boston, MA, [5]Tufts Medical Center, Boston, MA, [6]Harvard University, Boston, MA, [7]Boston University School of Medicine, Boston, MA, [8]Boston Medical Center, Boston, MA

INTRODUCTION: Acute hypoxemic respiratory failure is a major cause of death from Coronavirus disease 2019 (COVID-19). We examined if PaO2/FiO2, Oxygenation Index (OI), SpO2/FiO2 and Oxygen Saturation Index (OSI), used to assess the severity of respiratory failure in ARDS, predict mortality in intubated COVID-19 patients.

METHODS: In this single-centered retrospective cohort study we enrolled 68 critically ill adult patients with confirmed COVID-19 infection requiring mechanical ventilation. Respiratory and other physiological variables were recorded on the day of intubation (day 0), post-intubation days 3 and 7. The association between physiological parameters, PaO2/FiO2, OI, SpO2/FiO2 and OSI with mortality were analyzed using logistic and multivariate regression. The area under the receiver-operating characteristic curve (AUC) for mortality was calculated. Significant predictors of mortality were identified in bivariate analysis and were entered into multivariate analysis to identify independent predictors of in-hospital mortality.

RESULTS: The ARDS severity indices PaO2/FiO2, OI, SpO2/FiO2 and OSI were not statistically different in surviving versus non-surviving patients on the first day of intubation. Three days after intubation, however, they were significantly worse in the non-surviving patients. The ARDS severity indices continued to worsen in the non-survivors, but improved in survivors on day 7, resulting in an even greater group difference (PaO2/FiO2 106.3 [94.2] vs. 178.0 [69.3], $p<0.001$; OI 150.0 [118.4] vs. 61.5 [46.7], $p<0.001$; SpO2/FiO2 130 [90] vs. 230 [50] $p<0.001$; OSI 14.7 [13.2] vs. 6.5 [5.4], $p<0.001$, respectively). All measures were independently associated with hospital mortality, with significantly greater odds ratios (ORs) observed on day 7. The AUC for mortality prediction was greatest on intubation day 7 (AUC =0.775, 0.808, 0.830 and 0.828 for PaO2/FiO2, OI, SpO2/FiO2 and OSI, respectively) compared to days 0 and 3.

CONCLUSION: ARDS severity indices are not of prognostic value on the day of intubation but deteriorate within three days in non-surviving COVID-19 patients. Saturation based measurements are of similar prognostic value as measures that rely on invasive blood gas monitoring, and can reliably predict mortality in patients with acute hypoxemic respiratory failure due to SARS-CoV-2 infection.

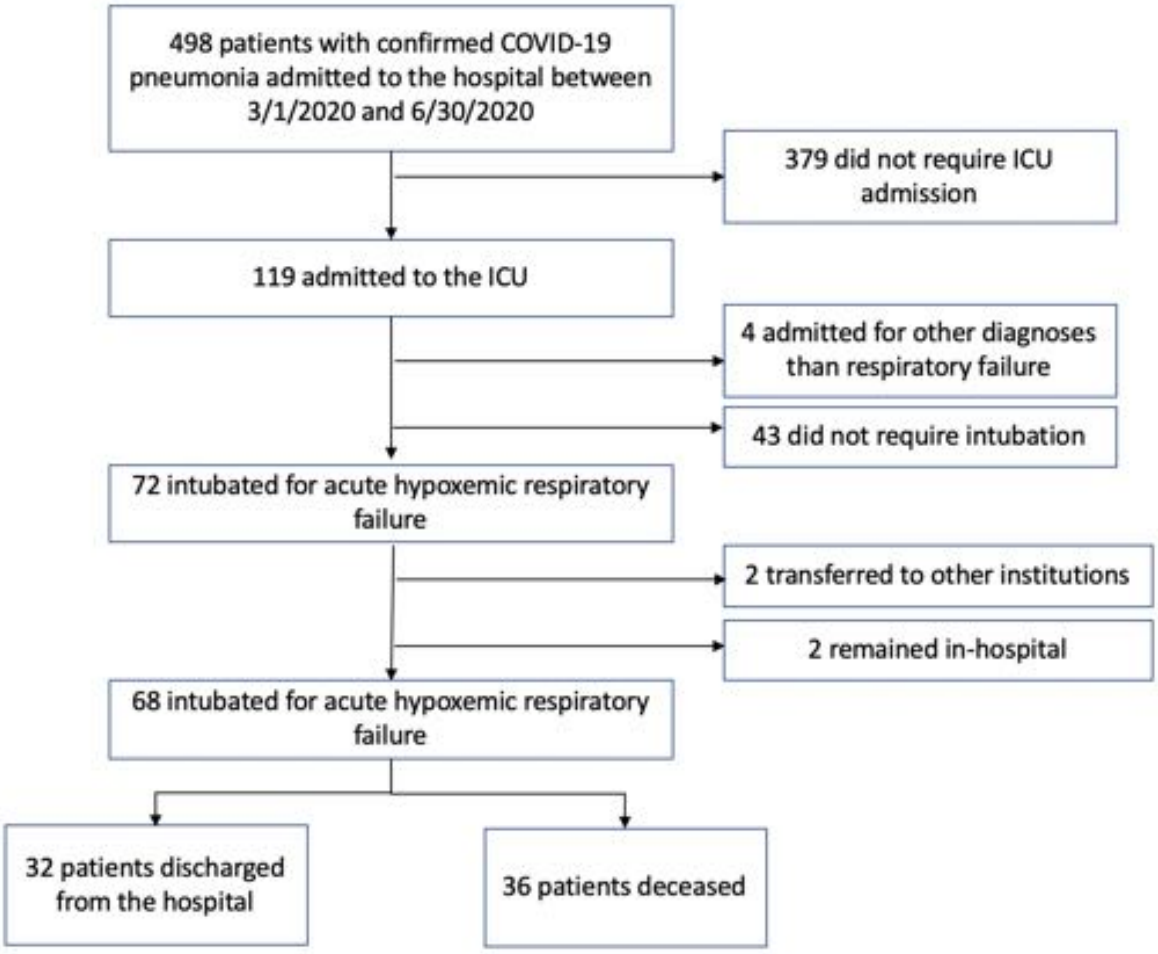

Fig. 1

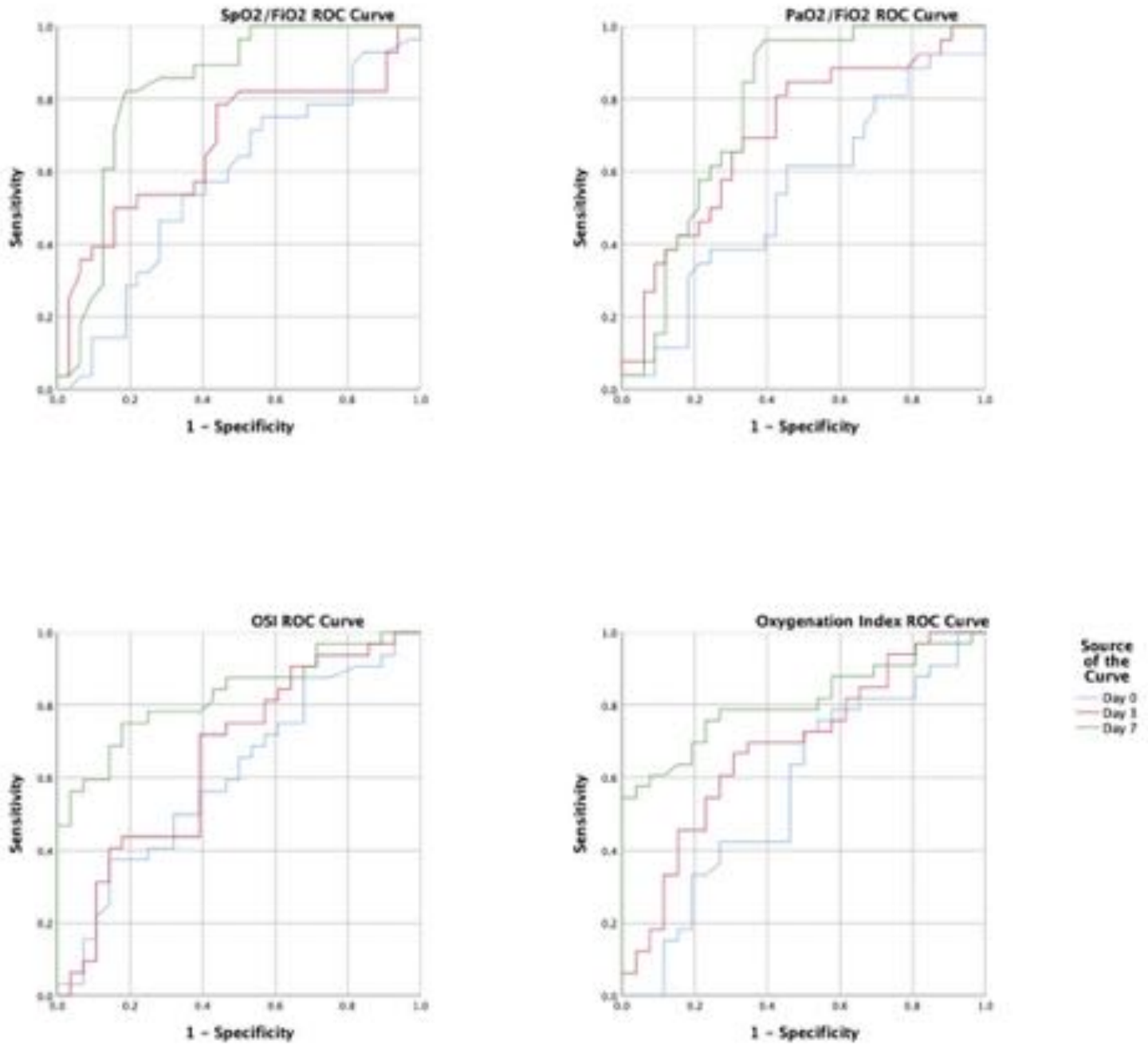

Fig. 2

Characteristic	Survivors	Non-survivors	p
Age in years (SD)	58.1 (16.3)	68.3 (10.8)	0.0036
Gender			
Female (n (%))	7 (21.21%)	15 (42.86%)	0.0565
Male (n (%))	26 (78.79%)	20 (57.14%)	0.0565
Race			
White (n (%))	9 (31.03%)	7 (20.59%)	0.6544
African American (n (%))	14 (48.28%)	18 (52.94%)	0.6544
Asian	0 (0%)	1 (2.94%)	0.6544
Other (n (%))	0 (0%)	1 (2.94%)	0.6544
Unknown	6 (20.69%)	7 (20.59%)	0.6544
Ethnicity			
Hispanic	14 (42.42%)	9 (25.71%)	0.1455
Non-hispanic	19 (57.58%)	26 (74.29%)	0.1455
BMI	31.89 (8.43)	33.48 (7.66)	0.4731
SOFA	8 (2.30)	9 (3.42)	0.4768
APACHE II	21.2 (6.8)	20.3 (10.5)	0.8314
Charlson Comorbidity Index	3.5 (2.9)	5.9 (2.2)	0.0004
Myocardial Infarction	1 (3.03%)	10 (28.57%)	0.0043
Congestive Heart Failure	4 (12.12%)	9 (25.71%)	0.1543
Peripheral Vascular Disease	3 (9.09%)	5 (14.29%)	0.5064
Cerebrovascular disease	5 (15.15%)	4 (11.43%)	0.6507
Chronic Obstructive Lung Disease	3 (9.09%)	6 (17.14%)	0.3275
Liver Disease	1 (3.03%)	0 (0%)	0.4821
Chronic Kidney Disease	2 (6.06%)	10 (28.57%)	0.0149
Diabetes Mellitus	13 (39.39%)	26 (74.29%)	0.0036
Laboratory Parameters			
C-reactive Protein (mg/dL)	119.4 (121.0)	113.8 (110.9)	0.8532
D-dimer (mcg/mL)	1.6 (2.4)	3.2 (6.8)	0.2059
Hemoglobin (mg/dL)	12.1 (2.2)	11.9 (1.7)	0.7908
Procalcitonin	1.2 (3.1)	3.0 (5.8)	0.1084
Creatinine (mg/dL)	1.2 (1.3)	1.9 (1.9)	0.0734
Respiratory paramaters			
PEEP (CmH2O))	10.2 (3.3)	11.8 (3.1)	0.045
FiO2 %	69.3 (21.7)	73.6 (21.1)	0.4113
MAP (cm H2O)	14.3 (3.5)	16.5 (3.7)	0.0183
Tidal Volume (ml)	446.3 (41.7)	420.5 (65.7)	0.0565
Days ventilated	13.9 (9.1)	14.7 (8.3)	0.7304
ICU legnth of stay (days)	13.7 (7.7)	15.8 (8.5)	0.3652
Hospital length of stay (days)	21.6 (10.2)	16.9 (8.7)	0.0859

Table 1. Clinical characteristics of the COVID-19 patients with acute hypoxic respiratory failure requiring intubation. Values are presented as mean (%), mean (SD) when normally distributed or median (IQR).

	Intubation day	Survivors	Non-survivors	P
Lung Compliance	Day 0	18.8 [IQR 18.5]	16.8 [IQR 7.8]	0.105
	Day 3	19.4 [IQR 22.4]	14.6 [IQR 7.2]	0.014
	Day 7	21.5 [25.3]	15.8 [IQR 9.9]	0.007
PaO2/FiO2 Ratio	Day 0	118.1 [IQR 103.3]	105.0 [IQR 78.1]	0.432
	Day 3	140.2 [IQR 109.6]	101.0 [IQR 61.4]	0.004
	Day 7	178.0 [IQR 69.3]	106.3 [IQR 94.2]	<0.001
Oxygenation Index	Day 0	82.9 [IQR 95.3]	116.0 [IQR 90.8]	0.165
	Day 3	84.8 [IQR 86.1]	135.0 [IQR 129.7]	0.003
	Day 7	61.5 [IQR 46.7]	150.0 [IQR 118.4]	<0.001
SpO2/FiO2 Ratio	Day 0	1.5 [IQR 0.8]	1.2 [IQR 0.7]	0.217
	Day 3	2.1[IQR 0.9]	1.3 [IQR 0.9]	0.003
	Day 7	2.3 [IQR 0.5]	1.3 [IQR 0.9]	<0.001
Oxygen Saturation Index	Day 0	10.9 [IQR 7.8]	12.2 [IQR 9.2]	0.052
	Day 3	8.0 [IQR 10.0]	12.0 [IQR 11.7]	0.006
	Day 7	6.5 [IQR 5.4]	14.7 [IQR 13.2]	<0.001

Table 2. ARDS severity indices for COVID-19 survivors and non-survivors on days 0, 3 and 7 after intubation; data presented as median [Interquartile Range].

Day 0	Unadjusted OR (95% CI)	Multivariate OR*(95% CI	P-val (unadj)	P-val (adj)
Crs (per 10 ml/cmH2O decrease)	1.644 (0.951, 2.839)	1.318 (0.960, 2.456)	0.0737	0.383
PaO2/FiO2 (per 10 mmHg decrease)	1.020 (0.951, 1.083)	1.010 (0.942, 1.083)	0.6193	0.8289
OI (per 10 cmH2O/mmHg increase)	1.041 (0.961, 1.116)	1.030 (0.942, 1.12)	0.3593	0.5039
SpO2/FiO2 (per 10 unit decrease)	1.051 (0.961, 1.161)	1.062 (0.961, 1.172)	0.3908	0.2285
OSI (per cmH2O increase)	1.107 (0.996, 1.230)	1.119 (0.996, 1.258)	0.0587	0.0588
Day 3	**Unadjusted OR (95% CI)**	**Multivariate OR*(95% CI**	**P-val (unadj)**	**P-val (adj)**
Crs (per 10 ml/cmH2O decrease)	1.930 (1.149, 3.219)	1.708 (1.00, 2.943)	0.0124	0.0512
PaO2/FiO2 (per 10 mmHg decrease)	1.104 (1.020, 1.207)	1.116 (1.020, 1.231)	0.0164	0.0229
OI (per 10 cmH2O/mmHg increase)	1.093 (1.020, 1.207)	1.0937 (1.010, 1.184)	0.0142	0.0242
SpO2/FiO2 (per 10 mmHg decrease)	1.138 (1.041, 1.243)	1.116 (1.020, 1.231)	0.0048	0.0235
OSI (per cmH2O increase)	1.092 (1.017, 1.173)	1.088 (1.007, 1.177)	0.0156	0.0333
Day 7	**Unadjusted OR (95% CI)**	**Multivariate OR*(95% CI**	**P-val (unadj)**	**P-val (adj)**
Crs (per 10 ml/cmH2O decrease)	2.119 (1.207, 3.772)	2.004 (1.072, 3.740)	0.0094	0.0282
PaO2/FiO2 (per 10 mmHg decrease)	1.149 (1.041, 1.268)	1.172 (1.051, 1.318)	0.0053	0.0045
OI (per 10 cmH2O/mmHg increase)	1.267 (1.105, 1.452)	1.357 (1.138, 1.613)	0.0006	0.0006
SpO2/FiO2 (per 10 unit decrease)	1.293 (1.138, 1.466)	1.344 (1.161, 1.568)	<0.0001	0.0001
OSI (per cmH2O increase)	1.275 (1.120, 1.451)	1.346 (1.146, 1.581)	0.0002	0.0003

Table 3. Unadjusted and multivariate adjusted odds ratio of death for Crs, PaO2/FiO2, OI, SpO2/FiO2, and OSI.

RESPIRATION 2

The association between preoperative forced expiratory volume and postoperative respiratory failure and/or death in patients undergoing non-pulmonary and non-cardiac surgeries

Toshiyuki Mizota[1], Miho Hamada[1], Akiko Hirotsu[1], Li Dong[1], Chikashi Takeda[1]

[1]Kyoto University Hospital, Kyoto, Japan

INTRODUCTION: Pulmonary function tests are used to perform a preoperative risk assessment prior to pulmonary resection[1], but it is inconclusive as to whether the results of pulmonary function tests predict the outcomes of patients undergoing non-pulmonary surgery. The forced expiratory volume in one second (FEV1), which is measured by pulmonary function tests, is a robust measure of the patient's pulmonary physiology and a strong predictor of mortality[2]. Therefore, we hypothesized that low FEV1 values are associated with adverse outcomes after non-pulmonary surgery. The purpose of this study was to determine the association between preoperative FEV1 values and the occurrence of postoperative respiratory failure and/or death in patients who underwent non-pulmonary and non-cardiac surgeries.

METHODS: The study was approved by the ethics committee of our institution and included 15,358 patients who met our inclusion criteria. The patients were the age of 18 years or older who underwent non-pulmonary and non-cardiac surgeries under general anesthesia at our institution from 2012 to 2018 and had pulmonary function tests within 6 months prior to surgery. The primary exposure was preoperative percent predicted FEV1 (%FEV1). The primary outcome was respiratory failure (invasive positive pressure ventilation for more than 24 hours after surgery or reintubation) and/or death within 30 days after surgery. Secondary outcomes were in-hospital mortality and 1-year mortality. Logistic regression models were used to adjust for known risk factors for postoperative pulmonary complications (age, congestive heart failure, chronic lung disease, anemia, hypoalbuminemia, functional dependence, type of surgery, and emergency surgery) and to examine the association between preoperative %FEV1 and the incidence of postoperative respiratory failure and/or death. Additionally, to facilitate interpretation, %FEV1 was classified with 3 cutoff values of 80%, 70%, and 60%, and the odds ratios for each category were calculated using %FEV1 ≥80% as the reference category. To evaluate the association between preoperative %FEV1 and 1-year mortality, Cox proportional hazards regression analysis was used.

RESULTS: Respiratory failure and/or death occurred within 30 days after surgery in 200 (1.3%) of the 15,358 patients studied. Low preoperative %FEV1 was significantly associated with postoperative respiratory failure and/or death, with an adjusted odds ratio of 1.19 (95% confidence interval: 1.11–1.28, P < 0.001) per 10% decrease in the %FEV1 (Figure 1). Compared with patients with a %FEV1 of ≥80%, the adjusted odds ratios for respiratory failure and/or death in patients with a %FEV1 of 70%–<80%, 60%–<70%, and <60% were 1.36 (95% confidence interval: 0.88–2.09, P = 0.169), 1.76 (95% confidence interval: 1.07–2.91, P = 0.026), and 2.34 (95% confidence interval: 1.47–3.74, P < 0.001), respectively. A low preoperative %FEV1 was also significantly associated with increased in-hospital mortality (adjusted odds ratio per 10% decrease: 1.19, 95% confidence interval: 1.09–1.31, P < 0.001) and increased 1-year mortality (adjusted hazard ratio per 10% decrease: 1.13, 95% confidence interval: 1.08–1.17, P < 0.001).

CONCLUSION: In patients undergoing non-pulmonary and non-cardiac surgeries, a low preoperative FEV1 is significantly associated with increased postoperative respiratory failure and/or death.

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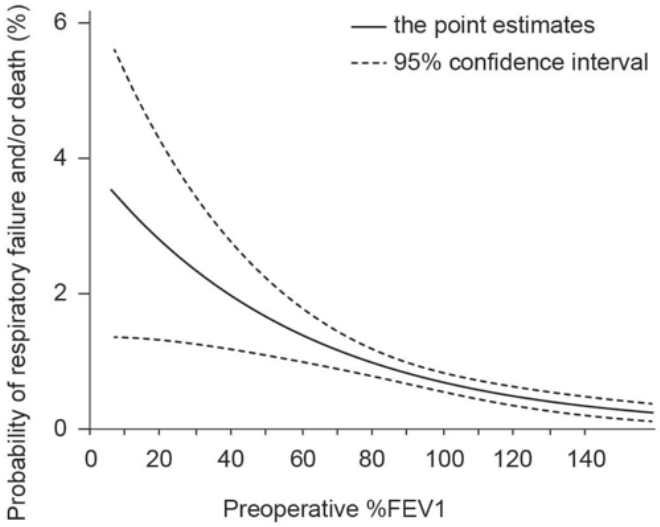
Figure 1. The Association between preoperative %FEV1 and the probability of postoperative respiratory failure and/or death.



RESPIRATION 3

The TMEM16A Antagonist Benzbromarone Decreases β2-Adrenergic Receptor Desensitization in Human Airway Smooth Muscle In Vitro

Amy Wu[1], Aisha Kuforiji[1], Charles W Emala[2], Jennifer Danielsson[2]

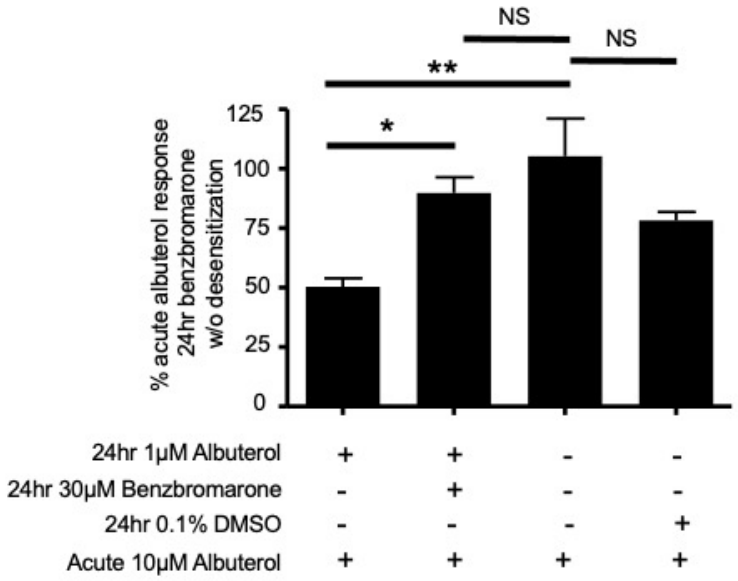
[1]Columbia University, New York, United States of America, [2]Columbia University, New York, NY

INTRODUCTION: We have previously shown that antagonism of the calcium-activated chloride channel, TMEM16A (also known as ANO1), exerts a pro-relaxant effect in airway smooth muscle (ASM). TMEM16A antagonism may thus serve as a novel therapeutic for bronchoconstrictive diseases such as asthma. We have previously demonstrated that TMEM16A antagonism-mediated relaxation is still effective after β-adrenoreceptor desensitization ex vivo and in vivo. In the current study, we hypothesized that concurrent treatment with the TMEM16A antagonist benzbromarone during desensitization with a β2-agonist would attenuate β2-adrenergic receptor (βAR) functional desensitization.

METHODS: Primary human bronchial ASM cells were purchased from Lonza and maintained in Lonza smooth muscle growth media in 95% air/5%CO2. Cells were desensitized with 1 μM albuterol with or without 30 μM benzbromarone for 24 hrs. Subsequently, to confirm functional desensitization, cells were treated with an acute dose of 10 μM albuterol. The measurement of cAMP levels was assayed via ELISA (Enzo) and values were normalized to protein levels (BCA assay) (Thermofisher). Data are expressed as mean±SEM and as a percent of the acute albuterol response after overnight benzbromarone treatment without β2-agonist-mediated desensitization. One-way ANOVA and Bonferroni post-hoc was performed with Prism 4 (Graphpad).

RESULTS: Human ASM cells treated for 24hr with 1 μM albuterol ("desensitizing albuterol") subsequently exhibited reduced cAMP production in response to 10 μM acute albuterol compared to cells not treated for 24hr with albuterol (50.4±4.19% vs.105 ±15.8% p<0.001, n=5-7). Co-incubation of 30 μM benzbromarone with desensitizing albuterol, increased the subsequent cAMP response to acute albuterol compared to desensitized cells without concurrent benzbromarone (89.8±7.75% vs. 50.4±4.19%, p<0.01, n=7). Co-incubation with benzbromarone during β2-agonist-mediated sensitization restored cAMP levels to the levels in non-desensitized controls (89.8±7.75%, n=7 vs.105±15.8%, n=5, respectively).

CONCLUSION: Concurrent treatment of TMEM16A antagonist benzbromarone and β2-agonist reduces percent β2AR functional desensitization, which suggests that treatment with the TMEM16A antagonist benzbromarone could help attenuate desensitization to β2-agonist.



RESPIRATION 4

Mechanical power during general anesthesia and postoperative respiratory complications: A hospital registry study

Peter Santer[1], Daniel S Talmor[1], Matthias Eikermann[2], Elias N Baedorf-Kassis[3], Maximilian S Schaefer[4]

[1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Beth Israel Deaconess Medical Center, Boston, United States of America, [3]Beth Israel Deaconess Medical Center, boston, MA, [4]Beth Isreal Deaconess Medical Center, Boston, MA

INTRODUCTION: Postoperative respiratory complications and respiratory failure occur in over 11 million patients each year and have been linked to the physico-mechanical parameters of mechanical ventilation, including stress from inspiratory pressure, strain from tidal volume, and cyclic repetition through the respiratory rate[1, 2]. Mechanical power is a concept that integrates these parameters and estimates the energy delivered to the respiratory system[3]. Although controversies exist with regards to its computation[4], mechanical power derived from a simplified calculation[5] has been associated with increased mortality in critically ill patients[6]. It remains unknown how intraoperative mechanical power during general anesthesia influences the occurrence of postoperative respiratory failure, and whether this integrative concept provides additional value compared to its individual components.

METHODS: In this retrospective cohort study, we investigated the association between mechanical power and postoperative respiratory failure requiring re-intubation in adult patients with American Society of Anesthesiologists status I-IV, undergoing non-cardiac surgery, between 2006 and 2018 at Beth Israel Deaconess Medical Center and Massachusetts General Hospital in Boston, MA. The median intraoperative mechanical power was estimated from median values of intraoperative tidal volume, respiratory rate and inspiratory pressures using a previously validated method[5]. The primary outcome was postoperative emergent re-intubation within seven days after surgery. The secondary outcome was post-extubation hypoxemia <90% hemoglobin oxygen saturation. We applied multivariable logistic regression analysis to adjust for potential confounding factors including patient demographics, comorbidities, procedural severity, and intraoperative factors. We compared the area under the receiver operating characteristics curve (ROC-AUC) for predicting postoperative reintubation solely based on mechanical power, respiratory rate, or tidal volume.

RESULTS: 241,107 out of 259,370 patients were included (Figure 1). Patient and perioperative characteristics are depicted in Table 1. The median intraoperative mechanical power was 6.7 [IQR 4.7; 9.2] J/min (Figure 2). Emergent postoperative reintubation occurred in 2,524 (1.1%) cases and post-extubation hypoxemia in 11,155 (4.6%) patient cases. Increased intraoperative mechanical power was associated with an increased risk of postoperative re-intubation (aOR 1.06 [95%CI 1.05; 1.08], per every J/min increase, p<0.001, Figure 3). This association was robust in high-risk patients after excluding ambulatory patients and surgeries less than 3 hours (n= 71,805, aOR 1.05 [1.04; 1.07], p<0.001). Increased intraoperative mechanical power was further associated with higher odds of post-extubation hypoxemia (aOR aOR 1.05, [1.05; 1.06], p<0.001). Finally, mechanical power predicted PRC better than tidal volume or respiratory rate alone (ROC-AUC 0.57, 0.49 and 0.51, respectively, p<0.001).

CONCLUSION: A high intraoperative mechanical power is associated with increased risk of emergent re-intubation after surgery and general anesthesia. Our findings suggest that this integrative concept adds additional information compared to established parameters such as tidal volume or respiratory rate. Adjustment of intraoperative tidal volume, inspiratory pressure and respiratory rate should aim at reducing mechanical power.

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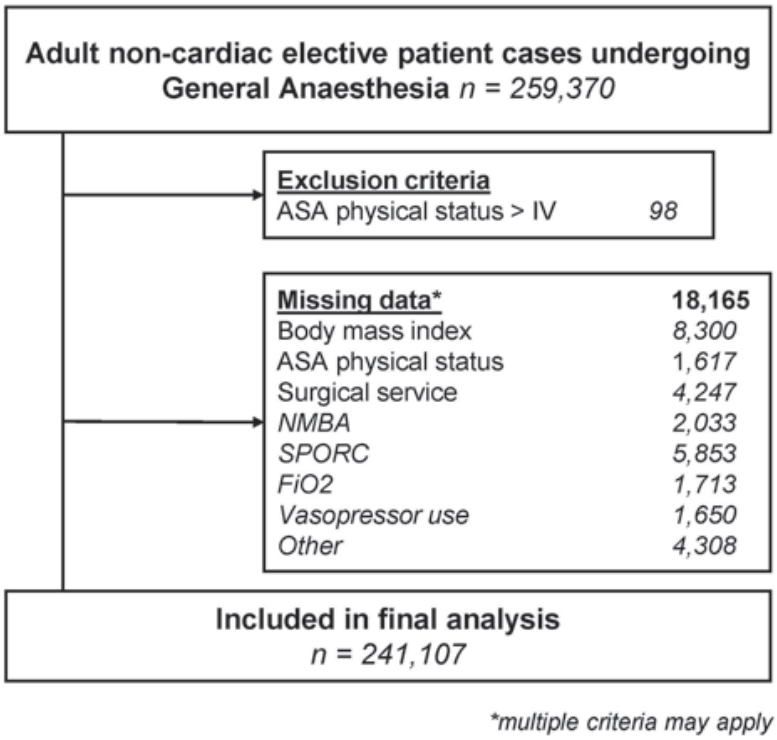

Fig. 1

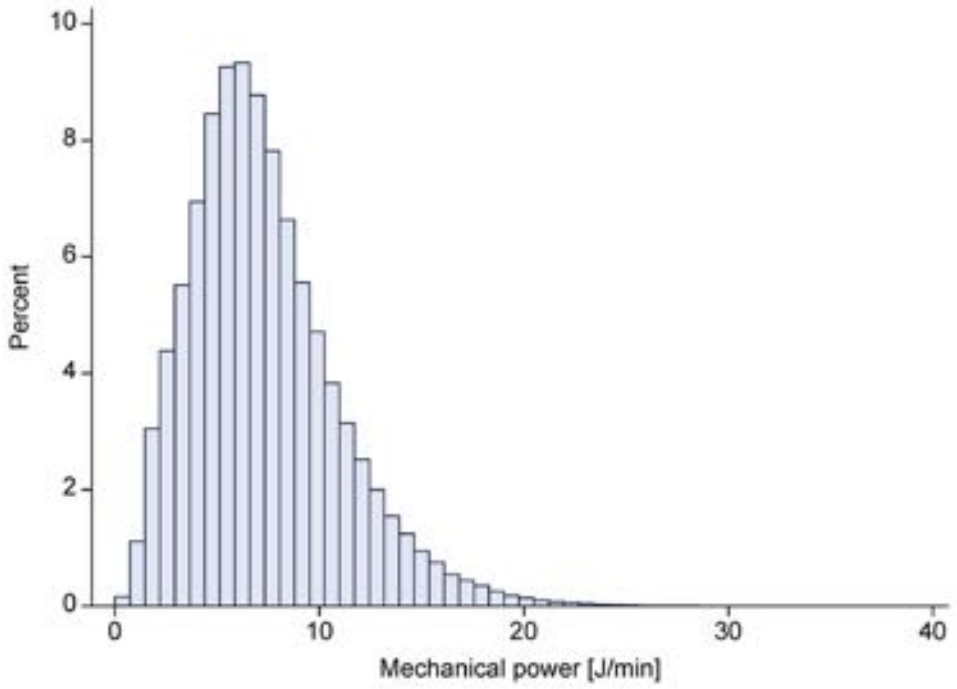

Fig. 2

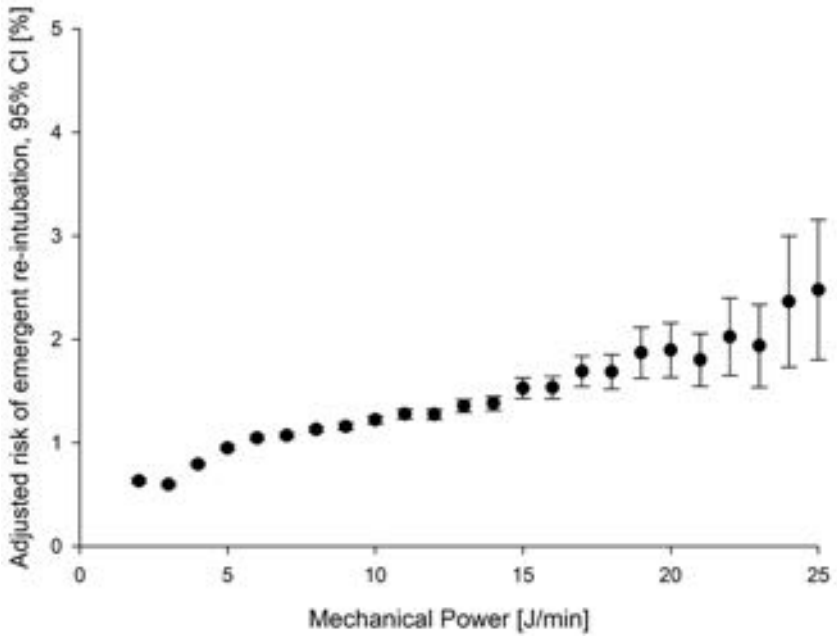

Fig. 3

Table 1

	No postoperative reintubation	Postoperative reintubation
N	238,583	2,524
Age, years	54.4 ± 16.2	62.3 ± 15.0
Female sex	134,645 (56.4%)	1,191 (47.2%)
Body mass index, kg/m^2	28.6 ± 6.9	28.5 ± 7.5
ASA status	2 (2, 3)	3 (3, 3)
ASA status ≥3	80,349 (33.7%)	1,917 (76.0%)
Charlson Comorbidity Index	1 (0, 3)	3 (1, 6)
SPORC	2 (0, 3)	5 (3, 6)
History of COPD	12,623 (5.3%)	383 (15.2%)
History of chronic heart failure	13,827 (5.8%)	555 (22.0%)
Smoking history	27,913 (11.7%)	371 (14.7%)
Type of surgery		
General	40,644 (17.0%)	292 (11.6%)
Gynecology	24,857 (10.4%)	63 (2.5%)
Neurosurgery	15,656 (6.6%)	301 (11.9%)
Orthopedic	50,614 (21.2%)	552 (21.9%)
Plastic	15,910 (6.7%)	55 (2.2%)
Oncological	11,610 (4.9%)	68 (2.7%)
Thoracic	15,739 (6.6%)	406 (16.1%)
Transplant	4,364 (1.8%)	89 (3.5%)
Urological	20,819 (8.7%)	74 (2.9%)
Vascular	9,188 (3.9%)	261 (10.3%)
Other	29,182 (12.2%)	363 (14.4%)
Duration of surgery, min	134 (86, 207)	203 (130, 319)
Work relative value units	13.2 (7.4, 19.9)	20.1 (12.3, 26.7)
Vasopressor requirement	129,942 (54.5%)	2,065 (81.8%)
Fluids, ml	1,000 (750, 1,800)	1,600 (1,000, 3,000)
Tidal volume, ml per kg IBW	8.3 ± 2.2	8.2 ± 2.1
Peak inspiratory pressure, cmH_2O	20.1 ± 6.5	22.6 ± 6.1
Positive end-expiratory pressure, cmH_2O	4.1 (2.0, 5.0)	5.0 (2.5, 5.1)
Respiratory rate, 1/min	12 (10, 13)	12 (10, 13)
Inspiratory oxygen fraction, %	55.8 ± 17.5	63.48 ± 19.8
Mechanical Power, J/min	7.3 ± 3.6	8.1 ± 3.7
30-day mortality	954 (0.4%)	251 (9.9%)
Hospital length of stay, days	2 (1, 5)	13 (8, 22)

Data are expressed as mean±SD, median (IQR), or frequency (percent).
ASA, American Society of Anesthesiologists; SPORC, Score for the Prediction of Postoperative Respiratory Complications

RESPIRATION 5

Pulmonary Mechanical Power and Energy are Increased by Body Habitus During Robotic Assisted Laparoscopic Surgery

Sydney Chatfield[1], Max Breidenstein[2], Serena Murphy[2], Alexander F Friend[3], S. Patrick Bender[2], Ryan Harned[1], William G Tharp[2]

[1]University of Vermont Larner College of Medicine, Burlington, VT, [2]University of Vermont Medical Center, Burlington, VT, [3]University of Vermont, Burlington, VT

INTRODUCTION: Pulmonary mechanical power, the cumulative energy delivered to the lung over time, is emerging as a potential predictor of ventilator-induced lung injury (VILI). Once sufficient mechanical energy has been delivered to the lung (theoretically ~2500 mJ/breath), molecular bonds in the extracellular matrix will begin to break leading to structural deformation and the development of inflammation[1]. Current intraoperative lung protective ventilation strategies attempt to prevent VILI by controlling tidal volumes, driving pressures, and end-expiratory pressures[2]. However, dynamic intraoperative conditions and patient comorbidities, like obesity, may exert enough additional stress to exceed the power threshold for lung injury. Currently, the damage threshold in humans and the relative contributions of body habitus or surgical positioning to the delivery of pulmonary mechanical power are unknown. Pulmonary mechanical power of 12–13 J/min was identified as the LD_{50} in studies of short-term ventilation using piglets[3]. We hypothesized that increasing body mass index (BMI) is associated with increased energy and mechanical power, which are further exacerbated by pneumoperitoneum and Trendelenburg positioning during robotic assisted laparoscopic abdominal surgery (RALS), even with lung protective ventilation settings.

METHODS: We conducted a secondary analysis of a previously published cross-sectional study of respiratory mechanics in 91 subjects with BMI ranging 18–60 kg/m^2 undergoing RALS. Intraoperative total respiratory system, chest wall, and lung mechanics were quantified at four different times: after intubation, with pneumoperitoneum, in steep Trendelenburg, and level without pneumoperitoneum prior to extubation. Subjects had follow-up after 30 days to assess for post-operative pulmonary complications. We calculated mechanical energy transmitted to the lungs as *Energy = Transpulmonary Driving Pressure^2 / Lung Elastance* and mechanical power defined as *Power = Energy × RR*. Differences in energy and power between BMI categories (<25, 25–29.9, 30–34.9, 35–39.9 and ≥40) and surgical positioning were analyzed by generalized estimating equations.

RESULTS: After intubation, lungs of subjects with BMI <25 experienced 142±74 mJ/breath and 1.9±1.1 J/min mechanical power. At this stage, energy and power increased with each BMI category (mean difference: 84±33 mJ/breath and 1.3±0.6 J/min, respectively; p≤0.001). Pneumoperitoneum increased pulmonary energy and mechanical power in all subjects compared to baseline (mean difference 124±49 mJ/breath and 2.0±0.8 J/min, respectively; p≤0.001). Subjects with BMI <30 had further increases in mechanical power with Trendelenburg compared to pneumoperitoneum only (mean difference 1.8±0.4 J/min; p≤0.001). Subjects with BMI ≥40 had pulmonary mechanical power of 11.9±2.8 J/min in Trendelenburg. After return to level and release of pneumoperitoneum, energy and power were similar to baseline, but differences among BMI were only significant between BMI <25 and ≥40 (3.6±2.7 vs 8.5±2.8 J/min, respectively; p≤0.001). Post-operative pulmonary complications were present in 2% of subjects 30 days after surgery.

CONCLUSION: Body habitus and surgical conditions incur large increases in the energy and power input to the lungs during intraoperative mechanical ventilation. While energy and power thresholds of ventilator induced lung injury are not known for humans, subjects with BMI ≥40 experienced pulmonary mechanical power near the LD_{50} identified for short-term ventilation of piglets[3]. Whether these patients have biotrauma without clinically significant pulmonary complication is unknown. Power thresholds associated with lung injury may help identify patients at risk for intraoperative VILI and PPC and further guide protective ventilation strategies.

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RESPIRATION 6

STIL-STRONGER: Association of Sugammadex Use with the Incidence of Postoperative Pulmonary Complications in a Population at Increased Risk

Douglas Colquhoun[1], Shelley Housey[2], Lori D Bash[3], Sachin Kheterpal[1]

[1]University of Michigan Medicine, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]Merck and Co., Inc., Kenilworth, NJ

INTRODUCTION: Sugammadex selectively reverses rocuronium and vecuronium induced neuromuscular blockade (NMB) and was introduced to the US in December 2015. The STRONGER Study demonstrated an association between sugammadex use and decreased odds of postoperative pulmonary complications (PPCs).[1] It is not known if this effect is present in patients thought to be at increased risk of PPCs.[2] We therefore evaluated the association of NMB reversal choice with incidence of PPCs in this subset of the STRONGER cohort.[1]

METHODS: After obtaining IRB approval, using data from the Multicenter Perioperative Outcomes Group Database,[3] we conducted a retrospective matched cohort study. Noncardiac, nonemergency adult (>18yrs) surgical inpatients were included if they had general anesthesia with an endotracheal intubation, received rocuronium and/or vecuronium, were reversed with neostigmine (27 to 77 mcg/kg) or sugammadex (1.8-4.4mg/kg) and were considered at increased risk of a PPC based on: [ASA Physical Status (PS) of 3 or 4]; AND [Age > 80 or Procedure Length > 2hrs]; AND [Intrathoracic or Abdominal Surgery]. As in STRONGER[1], cases were included if administered neostigmine between January 2014 and the date sugammadex was first used at that site, or administered sugammadex 6 months after first use of sugammadex at that site and August 31st 2018. Patients were excluded if they: were intubated prior to OR or transferred from the ICU, underwent liver or lung transplantation, received both sugammadex and neostigmine, were reversed to facilitate neuromuscular monitoring, had myasthenia gravis, were taking pyridostigmine chronically, had renal failure, lacked follow up or exposure data. The cases were matched 1:1 based on several patient and procedural characteristics (See Table 1). A conditional logistic regression model estimated the association between postoperative pulmonary complications (defined as ICD 9/10 coded diagnoses of Respiratory Failure or Pneumonia) and the choice of neuromuscular blockade reversal.

RESULTS: 16,042 cases from 12 institutions were eligible for matching and resulted in 3,817 matched pairs. The distribution of match characteristics of the matched and un-matched populations are presented in Table 1. Additional characteristics after matching are presented in Table 2. The primary outcome occurred in 5.9% (n=225) of patients reversed with neostigmine and 2.6% (n=99) of those reversed with sugammadex ($p < 0.01$) – Figure 1. After adjustment, the use of sugammadex was associated with a decreased odds of the occurrence of a PPC (OR: 0.44, 95% CI: 0.33-0.59 $p < 0.0001$, Figure 2), of respiratory failure (OR: 0.32 CI: 0.21-0.5 $p < 0.0001$) and of pneumonia (OR: 0.51, 0.36-0.72 $p < 0.0001$).

CONCLUSION: In a multicenter cohort of US patients at increased risk of postoperative pulmonary complications presenting for major surgery, the use of sugammadex was associated with decreased odds of subsequent occurrence of postoperative pulmonary complications compared to neostigmine.

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Figure 1 - Incidence of Primary Outcome and component parts in the Sugammadex vs Neostigmine Groups

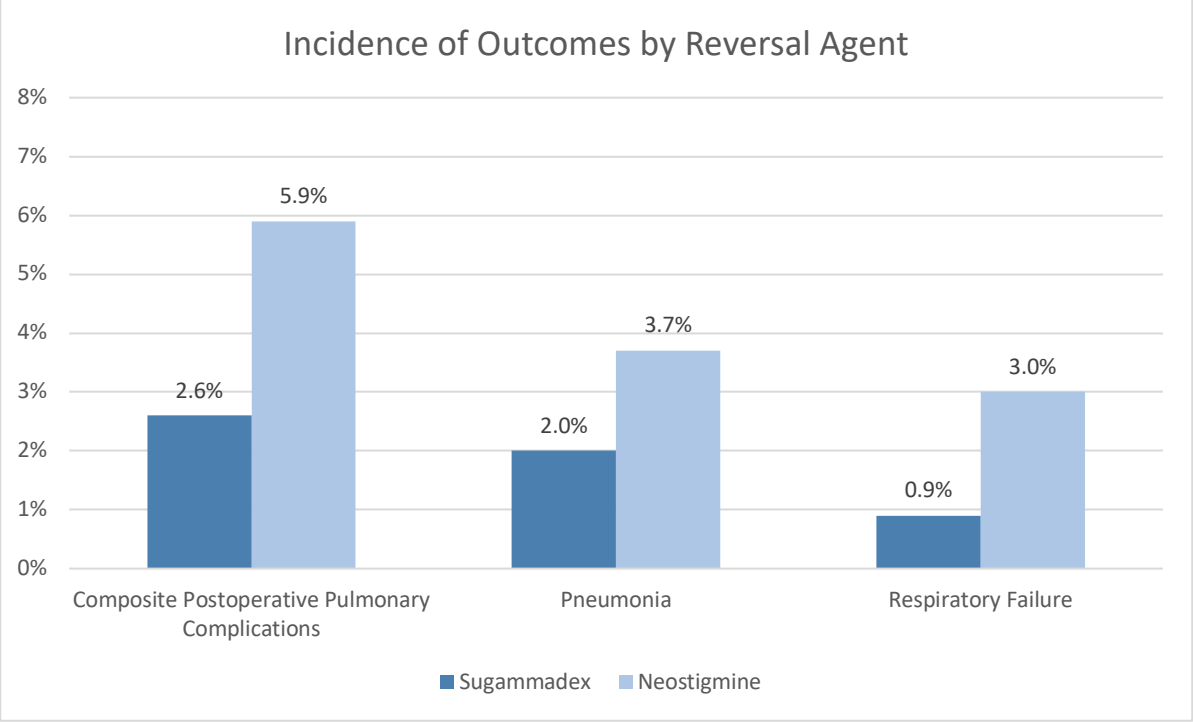

Figure 2 – OR Plot for Model Covariates for the Conditional Logistic Regression Model Examining the Association Between Neuromuscular Blockade Reversal Agent Selection and Development of Postoperative Pulmonary Complication.

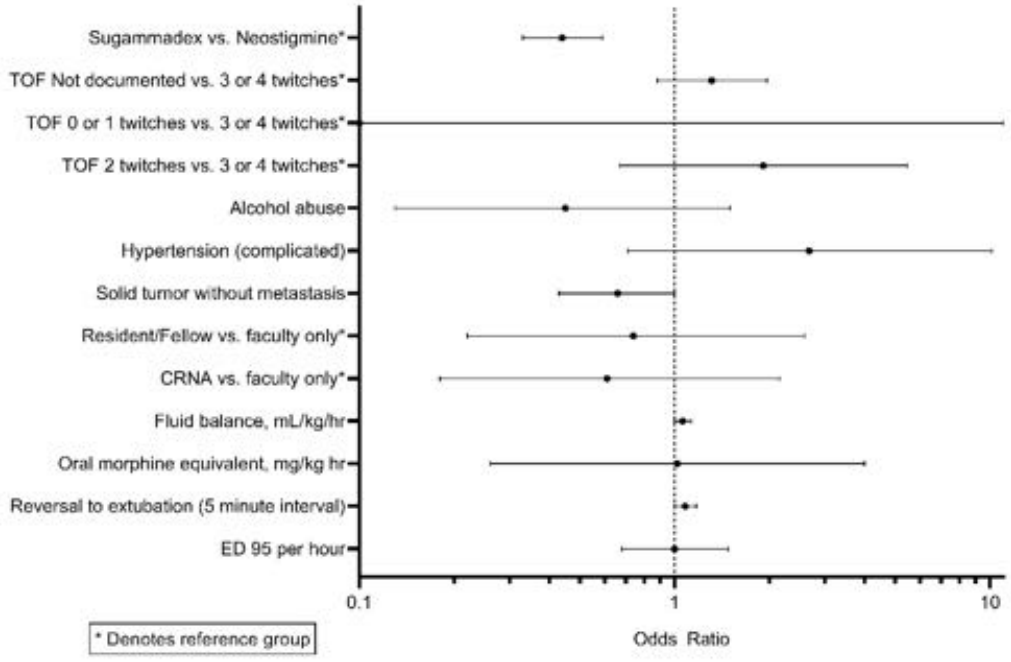

Table 1 – Patient demographics and case characteristics of matched and unmatched sugammadex cases and neostigmine cases.

Covariate Used for Matching:	Matched Cases		Unmatched Cases			
			Unmatched Sugammadex Cases		Unmatched Neostigmine Cases	
	N=3,817		N=1,689		N=6,719	
	N	Column %	N	Column %	N	Column %
Age*						
18-40 years	251	6.6%	196	11.6%	597	8.9%
41-50 years	408	10.7%	195	11.5%	817	12.2%
51-60 years	896	23.5%	341	20.2%	1,456	21.7%
61-70 years	1,251	32.8%	463	27.4%	2,099	31.2%
71-80 years	773	20.3%	345	20.4%	1,150	17.1%
81-90+ years	238	6.2%	149	8.8%	600	8.9%
Sex:						
Male	1,774	46.5%	799	47.3%	3,646	54.3%
Female	2,043	53.5%	887	52.5%	3,066	45.6%
ASA Status:						
3	3,784	99.1%	1,528	90.5%	6,383	95.0%
4	33	0.9%	161	9.5%	336	5.0%
WHO BMI:						
Underweight	22	0.6%	63	3.9%	160	2.6%
Normal	868	23.1%	379	23.2%	1,541	24.7%
Overweight	1,168	31.1%	414	25.4%	1,796	28.8%
Class I	771	20.5%	360	22.0%	1,285	20.6%
Class II	429	11.4%	211	12.9%	714	11.5%
Class III	501	13.3%	206	12.6%	738	11.8%
Select Elixhauser Comorbidities:						
Cardiac Arrhythmias	453	11.9%	578	34.2%	1,279	19.0%
Chronic Pulmonary Disease	579	15.2%	559	33.1%	1,621	24.1%
Congestive Heart Failure	50	1.3%	192	11.4%	423	6.3%
Liver Disease	140	3.7%	232	13.7%	625	9.3%
Paralysis	6	0.2%	46	2.7%	65	1.0%
Body Region/Type of Procedure:						
Intrathoracic Non-Cardiac	454	11.9%	432	25.6%	1,390	20.7%
Abdominal	3,363	88.1%	1,257	74.4%	5,329	79.3%
Type of neuromuscular blockade:						
Rocuronium only	2,849	74.6%	1,093	64.7%	5,239	78.0%
Vecuronium or (Rocuronium and Vecuronium)	968	25.4%	596	35.3%	1,480	22.0%

Table 2 - Patient demographics and case characteristics of non-matched covariates after matching sugammadex

	Sugammadex Cases N=3817		Neostigmine Cases N=3817		
	N	%	N	%	Absolute Standardized Difference
Last TOF documented within 30 minutes of extubation					0.32
Not documented	961	25.2%	1,426	37.4%	
0 or 1 twitches	175	4.6%	63	1.7%	
2 twitches	196	5.1%	100	2.6%	
3 or 4 twitches	2,485	65.1%	2,228	58.4%	
General Anesthesia Technique					0.09
GA yes, volatile yes	3,730	97.7%	3,774	98.9%	
GA yes, no volatile, no nitrous	80	2.1%	37	1.0%	
GA yes, nitrous yes	7	0.2%	6	0.2%	
Other Elixhauser comorbidities					
AIDS/HIV	8	0.2%	4	0.1%	0.03
Alcohol Abuse	10	0.3%	48	1.3%	0.12
Blood Loss Anemia	67	1.8%	40	1.0%	0.06
Coagulopathy	116	3.0%	100	2.6%	0.03
Deficiency Anemia	151	4.0%	105	2.8%	0.07
Depression	398	10.4%	500	13.1%	0.08
Diabetes (complicated)	53	1.4%	36	0.9%	0.04
Diabetes (uncomplicated)	709	18.6%	700	18.3%	0.01
Drug Abuse	62	1.6%	59	1.5%	0.01
Fluid/Electrolyte Disorders	414	10.8%	447	11.7%	0.03
Hypertension (complicated)	61	1.6%	21	0.6%	0.10
Hypertension (uncomplicated)	2,094	54.9%	2,112	55.3%	0.01
Hypothyroidism	442	11.6%	469	12.3%	0.02
Lymphoma	35	0.9%	44	1.2%	0.02
Metastatic Cancer	736	19.3%	699	18.3%	0.03
Other Neurological Disorders	93	2.4%	111	2.9%	0.03
Peptic Ulcer Disease, Excluding Bleeding	46	1.2%	48	1.3%	0.01
Peripheral Vascular Disorders	171	4.5%	172	4.5%	0.00
Psychoses	14	0.4%	26	0.7%	0.04
Pulmonary Circulation Disorders	92	2.4%	93	2.4%	0.00

Table 2 (continued)

Rheumatoid Arthritis Collagen Vascular Diseases	91	2.4%	89	2.3%	0.00
Solid Tumor Without Metastasis	2,198	57.6%	1,607	42.1%	0.31
Valvular Disease	118	3.1%	132	3.5%	0.02
Weight Loss	297	7.8%	329	8.6%	0.03
Primary In-Room Provider					0.11
Faculty Only	156	4.1%	101	2.6%	
Resident/Fellow	2,029	53.2%	2,199	57.6%	
CRNA	1,631	42.7%	1,516	39.7%	
Estimated Blood Loss					0.09
0-500 ml	3,429	89.8%	3,322	87.0%	
501-1000 ml	260	6.8%	330	8.6%	
>1000 ml	128	3.4%	165	4.3%	
Surgical Duration					0.02
>=2 hrs	3,710	97.2%	3,699	96.9%	
<2 hrs	107	2.8%	118	3.1%	
Sugammadex Dosing Range					
1.8 to 2.2 mg/kg	2,231	58.4%			
>2.2 AND < 3.6 mg/kg	1,108	29.0%			N/A
3.6 to 4.4 mg/kg	478	12.5%			
Neostigmine Dosing Range					
27 to <40 mcg/kg			1,296	34.0%	
=>40 AND =<60 mcg/kg	N/A		2,046	53.6%	N/A
>60 to 77 mcg/kg			475	12.4%	
	Median	**IQR**	**Median**	**IQR**	**Standardized Difference**
Surgical duration, hours	3.3	[2.5,4.5]	3.3	[2.5, 4.5]	0.01
Fluid balance, mL/kg/hr	3.1	[1.8, 4.6]	3.6	[2.2, 5.5]	0.21
Intraop PRBC Transfusions (Units)	0	[0,0]	0	[0,0]	0.02
Intaop FFP Transfusions (Units)	0	[0,0]	0	[0,0]	0.01
Oral Morphine Equivalent, mg/kg hr	0.23	[0.16, 0.31]	0.26	[0.19, 0.36]	0.26
Median ventilator driving pressure	16	[13, 21]	17	[13, 22]	0.06

Table 2 (continued)

Age (years)	64	[54, 71]	63	[54, 71]	0.02
Time from last NMB dose to first reversal (15 minute interval)	4	[2.8, 5.9]	4.1	[2.8, 5.8]	0.00
Time from first reversal to Extubation (5 minute interval)	2.6	[1.4, 4.2]	3.4	[2.2, 5.2]	0.34
Time from last NMB to extubation (15 minute interval)	5	[3.7, 7.0]	5.4	[4.0, 7.3]	0.09
ED 95 per hour	1.3	[1.1, 1.7]	1.2	[1.0, 1.6]	0.12

RESPIRATION 7

Impact of hyperoxia on renal tissue oxygenation, reactive oxygen species production, and oxidative damage in a murine ischemia reperfusion model

Melissa Kimlinger[1], Matthew Barajas[2], Raymond Harris[2], Ming-Zhi Zhang[2], Antonio Hernandez[2], Matthias L Riess[2], Frederic (Josh) Billings[2]

[1]Vanderbilt University School of Medicine, Nashville, TN, [2]Vanderbilt University Medical Center, Nashville, TN

INTRODUCTION: Acute kidney injury (AKI) affects 10% of patients following major surgery and is independently associated with extra-renal organ injury, increased duration of hospitalization, long-term development of chronic kidney disease and dialysis, and death. Perioperative renal ischemia and reperfusion (IR) is common and contributes to the development of AKI, in part, by increasing production of reactive oxygen species (ROS) and leading to oxidative damage. Patients are frequently given excess oxygen during surgery (hyperoxia) to reduce hypoxia, but hyperoxia constricts arterioles and may shunt blood away from some tissue beds. The impact of hyperoxia on tissue oxygenation, reactive oxygen species production, and oxidative damage during perioperative IR is unclear. We hypothesized that hyperoxia during renal IR affects kidney hypoxia, ROS production, and oxidative damage.

METHODS: We randomly assigned 8-week-old FVBN male mice (N=20) to receive hyperoxia (100% oxygen) or normoxia (room air) during dorsal unilateral nephrectomy with contralateral renal ischemia/reperfusion surgery as follows. Mice were anesthetized with intraperitoneal ketamine/xylazine, the dorsal flanks were shaved and prepped for surgery, and we administered the assigned oxygen treatment through a nose cone for the remainder of the experiment. We dissected the right kidney through a dorsal lateral incision and then ligated, removed, and discarded it. We then exposed the left kidney through a contralateral incision, dissected the renal hilum, and placed a clamp on the renal artery and vein. At 30 minutes of ischemia, the clamp was released. Following 30 minutes of reperfusion, the animals were sacrificed via terminal bleed, and the left kidney was harvested and bisected. Half the kidney was placed in formalin for fixation and pimonidazole and 4-hydroxy-2-nonenal (4-HNE) staining, and half the kidney was snap frozen in liquid nitrogen for F2-isoprostane quantification by gas chromatography/mass spectrometry. Pimonidazole forms adducts with thiol-containing peptides under hypoxic conditions and therefore serves as a tissue hypoxia marker. 4-HNE is a product of ROS-mediated oxidation of cellular polyunsaturated fatty acids, thus 4-HNE serves as a ROS marker. F2-isoprostanes are end products of non-enzymatic arachidonic acid peroxidation that quantify oxidative damage in vivo.

RESULTS: One mouse assigned hyperoxia died following anesthesia. The 19 remaining mice survived IR surgery and completed the study. Pimonidazole staining (hypoxia marker) was primarily located in the outer medulla (Panel A), consistent with corticomedullary ischemia, and was similar in mice treated with hyperoxia or normoxia. Renal 4-HNE staining (ROS marker) was increased in mice treated with hyperoxia. 4-HNE staining was primarily located in the outer medulla (Panel B). Renal F2-isoprostanes (oxidative damage markers) were 2.2 ± 0.4 pg/mg kidney in mice treated with hyperoxia and 2.1 ± 0.5 pg/mg kidney in mice treated with normoxia. (Panel C).

CONCLUSION: Hyperoxia during renal IR did not appear to affect the degree of hypoxia in the kidney, but medullary ROS production and renal F2-isoprostanes appeared to be increased in mice treated with hyperoxia, compared to mice treated with normoxia during renal IR. In subsequent studies we will determine if indeed hyperoxia during renal IR increases renal oxidative damage, if molecular markers of hypoxia and oxidative damage are associated with kidney injury, and if hyperoxia during renal IR affects kidney injury in mice and AKI in surgical patients.

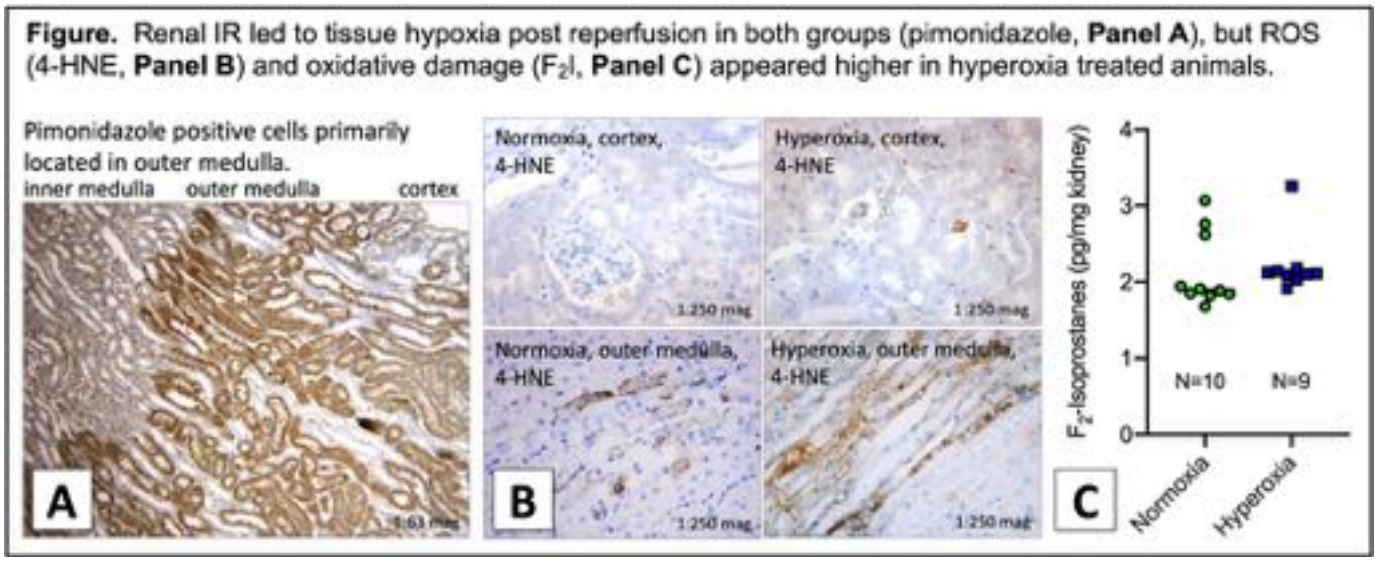

Figure. Renal IR led to tissue hypoxia post reperfusion in both groups (pimonidazole, **Panel A**), but ROS (4-HNE, **Panel B**) and oxidative damage (F_2I, **Panel C**) appeared higher in hyperoxia treated animals.

RESPIRATION 8

Mathematical Modeling of Impaired Pulmonary Mechanics during Robotic Assisted Laparoscopic Surgery

Ryan G Harned[1], Max Breidenstein[2], Serena Murphy[2], Sydney Chatfield[1], Alexander F Friend[3], S. Patrick Bender[2], Jason Bates[4], William G Tharp[2]

[1]University of Vermont Larner College of Medicine, Burlington, VT, [2]University of Vermont Medical Center, Burlington, VT, [3]University of Vermont, Burlington, VT, [4]University of Vermont College of Engineering and Mathematical Sciences, Burlington, VT

INTRODUCTION: Intraoperative mechanical ventilation induces complex changes in the mechanics and function of the respiratory system. Patient body habitus and surgical conditions exacerbate the derangement in pulmonary mechanics and increase the risk of postoperative complications and ventilator-induced lung injury. While a simple linear mathematical model is commonly employed to describe changes to pulmonary mechanics, this approach does not account for regional variations in alveolar distention or repetitive collapse, impairments that may be common during intraoperative ventilation. More complex nonlinear or two-compartment mathematical models may better describe these mechanics and help define the underlying impairments. Accordingly, we assessed the predictive ability of several equations of motion for pulmonary mechanics on intraoperative respiratory data from subjects with varying body mass index (BMI) undergoing robotic assisted laparoscopic surgery (RALS).

METHODS: We conducted a secondary analysis of a prior cross-sectional study that measured respiratory flow, airway pressures, and esophageal pressures in 91 subjects with BMI 18.3-60.6 kg/m2. Subjects received lung protective ventilation with an average tidal volume of 6.8±0.9 mL/kg IBW and PEEP ranging from 5 to 12 cmH2O. Pulmonary mechanics were quantified at four stages: supine and level after intubation (Baseline), level with Pneumoperitoneum, in Trendelenburg docked with the surgical robot, and level without pneumoperitoneum (Desufflated). Transpulmonary pressures were calculated as the difference between the airway and esophageal pressures. A linear single-compartment model (1C), nonlinear quadratic and cubic elastance models (E2 and E3), a nonlinear quadratic resistance model (R2), and a linear two-compartment model (2C) were fit to a 2-3 minute segment of the airway, esophageal, and transpulmonary pressure and flow data for all subjects at each surgical stage. Goodness-of-fit for each model was compared using the corrected Akaike information criterion with best fit defined by the lowest score. Subjects were stratified into five BMI categories: <25, 25-29.9, 30-34.9, 35-39.9, and ≥40 and percentages of best-fit models at each stage and category were compared.

RESULTS: The E3 and 2C models provided best fit for the total respiratory system (TRS, 61-100%), lung (54-100%), and chest wall (CW, 79-100%) data for all stages and BMI categories. The R2 model was the third most frequent best fit model. At Baseline, these two models best described TRS mechanics in 76-100% and lung mechanics in 71-80% of subjects depending on BMI category with almost equal frequency, and the 2C model best described CW mechanics in 71-90% of subjects. With Pneumoperitoneum, the 2C model best described TRS mechanics in 33-87% and lung mechanics in 33-67% of subjects depending on BMI category, whereas the E3 model best fit TRS data in 7-50% and lung data in 7-44% of subjects. At this stage, the 2C model provided the best fit in 73-93% of subjects' CW data. In Trendelenburg, the 2C model best described TRS mechanics in 23-70%, lung mechanics in 31-70%, and CW mechanics in 69-100% of subjects across BMI categories, while the E3 model best fit 6-38% of subjects' TRS and 16-31% of lung pressure data. After Desufflation, the 2C model provided the best fit in 33-70% of subjects' TRS, 17-70% of lung pressures, and 80-94% of CW pressure data over BMI categories, while the E3 model best described 20-67% of subjects' TRS and 20-67% of lung mechanics data.

CONCLUSION: A cubic elastance (E3) or linear two-compartment (2C) model best describes the majority of pulmonary mechanics data in subjects receiving lung-protective ventilation during RALS. Nonlinear elastic recoil may arise from derecruitment of lung tissue, and a 2C model can represent either two distinct regions of heterogeneous mechanics or a single region with viscoelastic (compound exponential) mechanics. In case of the chest wall data, the latter is most likely, but, for the total respiratory system and lung data, the interpretation is not clear. Despite this ambiguity, these data support the finding that intraoperative pulmonary mechanics during RALS exhibit mechanical heterogeneity, possibly from atelectasis and repetitive alveolar collapse, which may be a preventable source of intraoperative ventilator associated lung injury.

RESPIRATION 9

Inhibition of phospholipase C in human airway epithelial cells with ginger metabolite-inspired compounds

Elvedin Lukovic[1], Benjamin Redenti[1], Yingdong Zhu[2], Shengmin Sang[2], Charles W Emala[1]

[1]Columbia University, New York, NY, [2]North Carolina Agricultural and Technical State University, Kannapolis, NC

INTRODUCTION: Asthma causes pathological alterations in airway smooth muscle (ASM), and chronic inflammation and mucus production in airway epithelium (AE). Available therapies provide poor symptom management in ~40% of severe asthmatic patients, indicating the need for novel treatment alternatives. Our lab has demonstrated that 6-shogaol (6S), a primary constituent of ginger, its metabolites, and synthetic derivatives (Fig. 1A) relax ex vivo human ASM, and attenuate intracellular calcium ($[Ca^{2+}]_i$) increases and IP_3 synthesis, likely by inhibition of phospholipase C (PLC). These compounds may also affect airway epithelial PLC, which has been implicated in the expression and secretion of mucins and inflammatory cytokines that are upregulated in asthma. Thus, we hypothesize that ginger constituents, metabolites, and synthetic derivates will also inhibit airway epithelial PLC and prevent PLC-mediated $[Ca^{2+}]_i$ increases.

METHODS: Gingerols, shogaols, 6S metabolites, or synthetic derivatives (Fig. 1A) were assayed for their ability to inhibit bradykinin-induced increases in $[Ca^{2+}]_i$ in airway epithelial cells (NCI-H292 and BEAS-2B). Cells were loaded with a Ca^{2+}-specific ratiometric fluorophore Fura-2 AM (5 μM), pretreated with 6S derivatives (50 μM) and challenged with the Gq-coupled ligand bradykinin (10 μM) to measure $[Ca^{2+}]_i$ fluorescence. Statistical analysis included one-way ANOVA with Dunnett's post-test, and was performed using GraphPad Prism version 4.0 for Windows, GraphPad Software.

RESULTS: As prior studies suggested that ASM relaxation by ginger phytochemicals is caused by inhibition of ASM phospholipase C (PLC)-mediated increases in $[Ca^{2+}]_i$, we measured the effects of 6S metabolites and derivatives on $[Ca^{2+}]_i$ in human AE cells. Pretreatment of BEAS-2B cells with M9, a major 6S metabolite, and M14-4, a synthetic derivative of metabolite M14, significantly reduced bradykinin-induced increases in intracellular calcium compared to vehicle (49.7 ± 10%, $p < 0.001$, and 69.4 ± 5%, $p < 0.05$, respectively, n = 6-8) (Fig. 1B).

CONCLUSION: 6S metabolites and metabolite-based novel synthetic derivatives attenuate the rise of Gq-mediated $[Ca^{2+}]_i$. Since these Gq-coupled pathways regulate mucin and cytokine production in airway epithelial cells, these compounds offer promise as inhibitors of these pathologic contributions to airway asthmatic responses. This may be the first class of drugs, by targeting two key pulmonary cell types (ASM and AE), that could control both asthma progression and exacerbation.

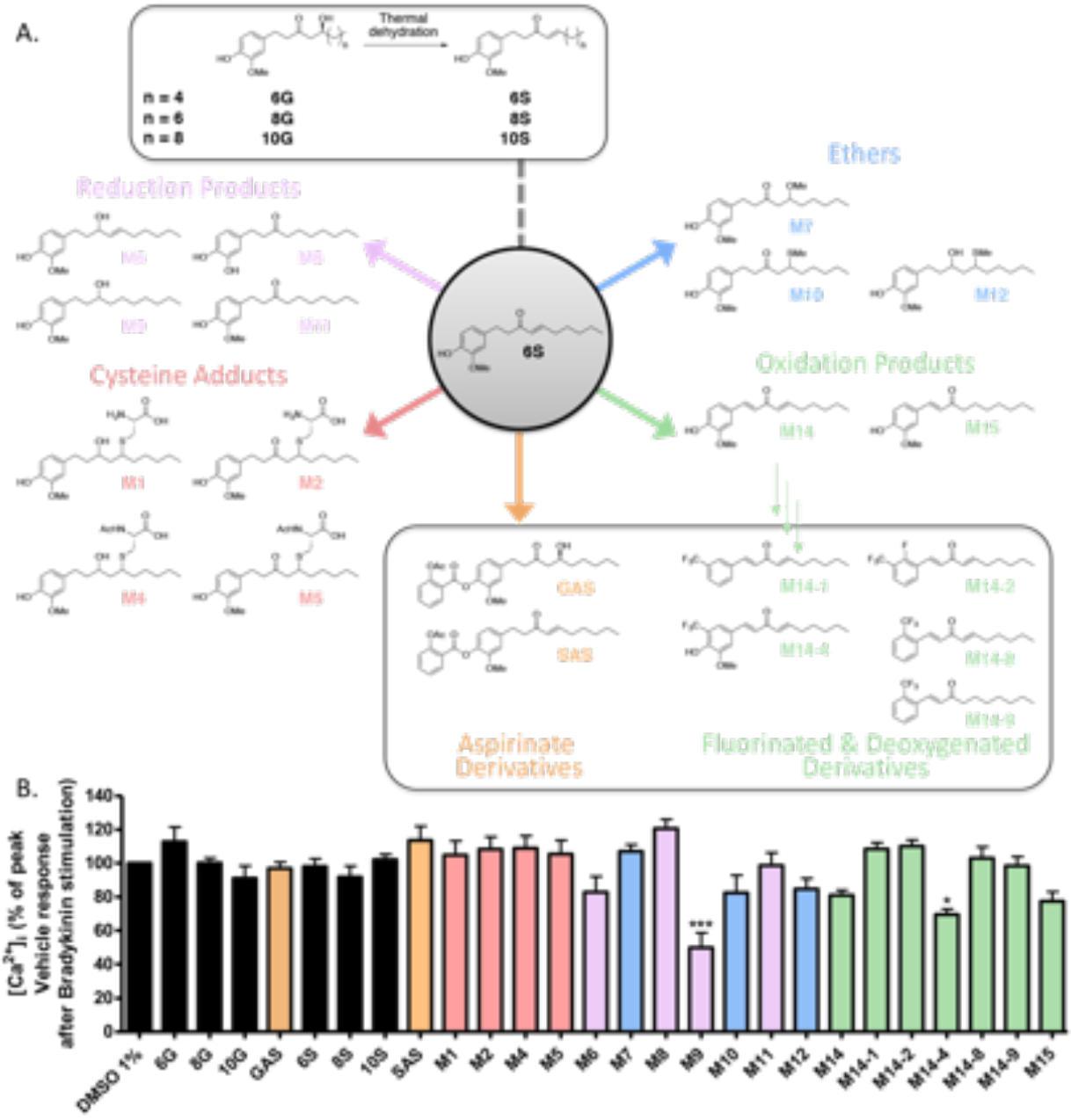

Fig 1. A natural ginger constituent 6-shogaol (6S), its human metabolites and synthetic derivatives as modulators of airway epithelial cell response to inflammatory stimuli. A. Structures of gingerols, shogaols, 6-shogaol (6S) human metabolites, and synthetic derivatives of 6S. B. Inhibition of increases in $[Ca^{2+}]_i$ in BEAS-2B human bronchial epithelial cells pretreated with either vehicle (1% DMSO), gingerols, shogaols, or shogaol derivatives (50 μM) stimulated by bradykinin (10 μM). * $p < 0.05$; *** $p < 0.001$ compared to vehicle, n = 6-8.

RESPIRATION 10

Group III/IV muscle afferents determine arterial oxygenation and gas exchange efficiency during prolonged locomotor exercise

Joshua Weavil[1], Vincent P Georgescu[1], Robert Jenkinson[1], Jen Chang[1], Scott Junkins[1], Markus Amann[1]

[1]University of Utah, Salt Lake City, UT

INTRODUCTION: Via their projections to the ventilatory control areas of the brain stem, feedback from mechano- and metabosensitive group III/IV skeletal muscle afferents has been identified as a key determinant of the ventilatory response during relatively short (~3 minutes) bouts of locomotor exercise executed at different intensities ranging from 30-100% of VO2max. However, the influence of these muscle afferents on arterial oxygenation during physical activities of longer duration (>15 minutes) is unknown. It was therefore the purpose of this study to evaluate the role of group III/IV muscle afferent feedback in determining arterial oxygenation and gas exchange efficiency during long duration leg cycling exercise.

METHODS: Five healthy males (24±6 yrs) performed an incremental maximal leg cycling test for the determination of peak power (Wpeak, 315±54 W). After a familiarization session, participants returned to the laboratory on two additional days. All subjects performed 20 minutes of leg cycling at 30% of Wpeak (92±19 W) immediately followed by 20 min at 50% of Wpeak (155±34 W) under a) control conditions (i.e. intact neural feedback from group III/IV muscle afferents from the legs; CTRL), and b) with lumbar intrathecal fentanyl (attenuated group III/IV muscle afferent feedback from the legs; FENT). Metabolic and ventilatory responses were continuously monitored throughout exercise. Blood samples were taken from a radial catheter to determine the partial pressure of arterial O2 and CO2 (PaO2 and PaCO2) at rest and every 5 min during the exercise. The alveolar PO2 was calculated (PAO2 = PiO2 - (PaCO2/RER)) and used to determine pulmonary gas exchange efficiency, i.e. the alveolar-to-arterial O2 difference (A-aDO2). Variables are presented as the average over the last 5 minutes of each of the two 20-min stages. A priori statistical comparisons were made between CTRL and FENT within each condition via Student's T-tests corrected for family-wise comparisons.

RESULTS: Fentanyl had no effect on A-aDO2, minute ventilation (VE), hemoglobin saturation, and pulmonary O2 uptake (VO2) and CO2 production (VCO2) at rest. While VCO2 was similar during the last 5 minutes of exercise (30% Wpeak: ~1.5±0.2 L/min; 50% Wpeak: ~2.5±0.4 L/min, P>0.11), VO2 was significantly higher during FENT (30% Wpeak: 1.8±0.3 vs 1.6±0.2 L/min; 50% Wpeak: 2.7±0.4 vs 2.5±0.3 L/min), and the ventilatory equivalent for O2 (VE/VO2) was significantly lower during FENT compared to CTRL (30% Wpeak: 25±2 vs 28±2; 50% Wpeak: 29±5 vs 31±5, P<0.05). Finally, without affecting PAO2 (30% Wpeak: ~84±5 mmHg; 50% Wpeak: ~92±1 mmHg), PaO2 (30% Wpeak:71±3 vs 80±4 mmHg; 50% Wpeak: 73±6 vs 80±5 mmHg, P<0.05) and hemoglobin O2 saturation (30% Wpeak: 94±1 vs 96±1%; 50% Wpeak: 94±1 vs 95±1% , P<0.05) were significantly lower, and the A-aDO2 significantly wider (30% Wpeak: 12±3 vs 6±1 mmHg; 50% Wpeak: 19±1 vs 12±2 mmHg, P<0.05) during FENT compared to CTRL.

CONCLUSION: In addition to their previously documented critical contribution to the cardiopulmonary response to the first few minutes of locomotor exercise, feedback from group III/IV muscle afferents remains an important determinant of arterial oxygenation during prolonged physical activities. The current data also emphasize the continuous significance of sensory feedback in matching the ventilatory response to the oxygen cost of prolonged human locomotion and in perpetually optimizing gas exchange efficiency during longer physical activity.

Subspecialty Abstracts

SLEEP MEDICINE

SLEEP MEDICINE 1

Sleep Medicine and Anesthesia Core Curriculum Topics for Anesthesia Residency – A Modified Delphi Technique Survey

Linor Berezin[1], Mahesh Nagappa[2], Jean Wong[3], Frances F Chung[4], Sleep Medicine Curriculum Group[1]

[1]University of Toronto, Toronto, Canada, [2]Western University, London, Ontario, [3]University of Toronto, Toronto, ONTARIO, [4]University of Toronto Faculty of Medicine, Toronto, Ontario

INTRODUCTION: Sleep disorders affect up to 25% of the general population and are prevalent in surgical patients. Patients with sleep-disordered breathing such as obstructive sleep apnea (OSA), central sleep apnea, and sleep-related hypoventilation are at an increased risk of adverse perioperative events. Despite the potential impact of sleep-disordered breathing to the practice of anesthesia, the key topics of sleep medicine that should be included in anesthesia residency curricula have not been well-defined. The objective of this study was to determine the high priority sleep medicine topics that should be included in the education of anesthesia residents based on the insight of experts in the fields of Anesthesia and Sleep Medicine.

METHODS: Two iterations of a prospective cross-sectional survey of 58 experts in the fields of Sleep Medicine and Anesthesia based on the Delphi technique were used to establish consensus on the sleep medicine topics that should be incorporated into anesthesia residency curricula. Experts were identified based on their publication record and include key opinion leaders, educational experts, and members of the Society of Anesthesia and Sleep Medicine (SASM). An initial topic list was generated by content experts based on well-known Sleep Medicine resources and guidelines from the SASM. The initial survey was a 17-item online questionnaire requesting feedback on the initial topic list through the use of 5-point Likert scale ratings, and open response questions inviting novel topic suggestions. The process was repeated in the second survey with the new topics identified in the initial iteration. The level of agreement used to define consensus for inclusion of a topic was over 80% of all experts selecting 'agree' or 'strongly agree' on the 5-point Likert Scale. Responses to the survey questions were analyzed with descriptive statistical methods and presented as percentages of participants selecting 'agree' and 'strongly agree'. A Mean Agreement Score (weighted average of ratings on the 5-point Likert scale) was determined to represent the distribution of ratings amongst participants. A weighted mean with standard deviations was calculated for the Mean Agreement Score.

RESULTS: A total of 33 (57%) invited experts responded to the initial survey, and 28 (48%) responded to the second round. Most of the participants were anesthesiologists (82%) and 18% were sleep medicine physicians. The majority of participants (42%) had 11-20 years in practice and most survey respondents were from the United States (70%). The topics that were found to have 100% 'strong agreement' amongst experts were 1) the influence of opioids and anesthetics on control of breathing and upper airway obstruction; 2) potential interactions of wake-promoting/hypnotic medications with anesthetic agents; 3) effects of sleep and anesthesia on upper airway patency; 4) anesthetic considerations of OSA; and 5) postoperative respiration monitoring strategies for sleep-disordered breathing. Other topics identified as high priority for inclusion into anesthesia residency curricula (Mean Agreement Score 4.8-4.99) were 1) the effects of anesthetic drugs on respiratory control [4.97 (0.17)]; 2) mechanism of action and pharmacologic effects of hypnotic medications [4.85 (0.36)]; 3) relationship between pain, analgesia, and sleep [4.85 (0.44)]; 4) sleep assessment questionnaires and scales [4.88 (0.33)]; 5) OSA definition, epidemiology, risk factors, and perioperative management [4.94 (0.24)]; and 6) obesity hypoventilation syndrome, central sleep apnea, and periodic breathing anesthetic considerations and perioperative management [4.82 (0.39-0.53)]. The topics which had less than 80% agreement amongst the expert panel included the anesthetic implications of other sleep disorders, future pathways in sleep medicine and anesthesia, indications and efficacy of various surgical airway modification options to treat OSA, anesthesia for the fiberoptic diagnosis of OSA, impact of sleep deprivation on the immune system and pulmonary muscle function, the effect of alcohol and other recreational drugs on sleep, and CPAP therapy compliance strategies.

CONCLUSION: We provide a framework of key sleep medicine topics that can be incorporated into future design of anesthesia residency training curricula. The results of our survey will be instrumental to program directors and specialty boards in defining specific topics of sleep medicine deemed most important for the practice of anesthesiology.

Table 1. Sleep Medicine topics and their level of agreement for inclusion in the Sleep Medicine and Anesthesia core curriculum for anesthesia residency (n=33)

Topic	Mean Agreement Score* (SD)	No. of participants in agreement** (%)	No. of participants who strongly agree (%)
Definition and physiology of sleep			
• Sleep stages and cycle	4.48 (0.76)	30 (91)	20 (61)
• Circadian rhythms	4.12 (1.02)	27 (82)	14 (43)
• Overview of functional neuroanatomy of sleep	4.24 (1.00)	27 (82)	17 (52)
• Cardiovascular and respiratory regulation during sleep	4.70 (0.53)	32 (97)	24 (73)
Pharmacology and sleep			
• Hypnotic medications: mechanisms of action and pharmacologic effects	4.85 (0.36)	33 (100)	28 (85)
• Wake-promoting medications: mechanisms, efficacy and adverse events	4.70 (0.47)	33 (100)	23 (70)
• Potential interactions with anesthetic agents	5.00	33 (100)	33 (100)
• Influence of opioids and anesthetics on control of breathing and upper airway obstruction	5.00	33 (100)	33 (100)
Sleep physiology and anesthesia			
• Similarities and differences between sleep, anesthesia, and coma	4.70 (0.53)	32 (97)	24 (73)
• EEG activity in sleep stages and anesthesia	4.36 (0.93)	28 (85)	19 (58)
• Effects of anesthetic drugs on respiratory control	4.97 (0.17)	33 (100)	32 (97)
• Effects of sleep and anesthesia on upper airway patency	5.00	33 (100)	33 (100)
• Sleep and circadian rhythm in the preoperative period	4.30 (0.77)	27 (82)	16 (49)
• Pain, analgesia, and sleep	4.85 (0.44)	32 (97)	29 (88)
• Effects of anesthesia and surgery on sleep and circadian rhythms	4.67 (0.54)	32 (97)	23 (70)
Effects of anesthesia and surgery on sleep and circadian rhythms			
• Acute and chronic sleep deprivation	4.45 (0.56)	32 (97)	16 (49)
• Interaction between sleep deprivation and anesthesia	4.64 (0.49)	33 (100)	21 (64)
Methods to assess sleep			
• Sleep-related history and physical examination	4.58 (0.56)	32 (97)	20 (61)
• Questionnaires and scales (STOP-BANG, the Berlin Questionnaire, Epworth sleepiness scale etc.)	4.88 (0.33)	33 (100)	29 (88)
• Actigraphy, Respiratory, Polygraphy, Polysomnography	4.27 (0.88)	29 (88)	15 (46)
• Potential methods to use in the perioperative setting	4.67 (0.54)	32 (97)	23 (70)
Obstructive sleep apnea (OSA)			
• Definition, epidemiology and risk factors	4.94 (0.24)	33 (100)	31 (94)
• Clinical presentation	4.79 (0.48)	32 (97)	27 (82)
• Anesthetic considerations	5.00	33 (100)	33 (100)

Table 1 (continued)

• OSA in children and pregnant patients	4.70 (0.59)	31 (94)	25 (76)
• Pathophysiology of upper airway collapse in OSA	4.79 (0.48)	32 (97)	27 (82)
• Co-morbidities and complications	4.76 (0.56)	31 (94)	27 (82)
• Treatment options (surgery, CPAP and oral appliances)	4.79 (0.48)	32 (97)	27 (82)
• Perioperative guidelines and management	4.94 (0.24)	33 (100)	31 (94)
Central sleep apnea and periodic breathing			
• Definition, epidemiology and risk factors	4.67 (0.54)	32 (97)	23 (70)
• Clinical presentation	4.55 (0.56)	32 (97)	19 (58)
• Anesthetic considerations	4.82 (0.46)	32 (97)	28 (85)
• Treatment	4.64 (0.60)	31 (94)	23 (70)
• Perioperative management	4.82 (0.39)	33 (100)	27 (82)
Obesity hypoventilation syndrome			
• Definition, epidemiology and risk factors	4.76 (0.56)	31 (94)	27 (82)
• Clinical presentation	4.67 (0.60)	31 (94)	24 (73)
• Anesthetic considerations	4.82 (0.53)	31 (94)	29 (88)
• Perioperative implications and management	4.82 (0.53)	31 (94)	29 (88)
Anesthetic implications of other sleep disorders			
• Overview and anesthetic implications of non-respiratory sleep disorders	4.19 (1.09)	25 (76)	17 (53)
• Central disorders of hypersomnolence: Narcolepsy	3.91 (0.96)	23 (70)	9 (28)
• Central disorders of hypersomnolence: Idiopathic hypersomnia	3.66 (1.15)	20 (61)	8 (25)
• Circadian rhythm sleep-wake disorders	3.72 (1.11)	20 (61)	9 (28)
• Parasomnias	3.56 (1.13)	18 (55)	7 (21)
• Restless legs syndrome	3.69 (1.15)	21 (64)	8 (25)
Sleep in the hospialized patient			
• Implications of sleep disturbances to patient health	4.34 (1.07)	28 (85)	19 (59)
• Sleep hygiene in perioperative and critical care setting	4.44 (0.95)	27 (82)	21 (66)
• Sleep and strategies to improve sleep in ICU	4.56 (0.84)	30 (91)	22 (69)
• Pain, analgesia, and disrupted sleep	4.78 (0.49)	31 (94)	26 (61)
Impact of sleep deprivation on physician wellness			
• Performance deficit during sleep deprivation	4.47 (0.72)	28 (85)	19 (59)
• Strategies for good sleep hygiene	4.50 (0.72)	28 (85)	20 (63)
• Sleep, stress, and burn out	4.53 (0.67)	29 (88)	20 (63)
• Effects of shift work on sleep	4.44 (0.67)	29 (88)	17 (53)
Obstructive sleep apnea			
• Differences between clinical presentation of pediatric vs. adult OSA	4.21 (0.96)	23 (82)	13 (46)
• When questionnaires (e.g. STOP-Bang, Berlin Questionnaire, Epworth sleepiness scale) are not applicable	4.54 (0.51)	28 (100)	15 (54)
• Indications and efficacy of various surgical airway modification options to treat OSA (e.g. drug induced sleep endoscopy and genioglossus stimulation)	4.11 (0.83)	22 (79)	10 (36)

Table 1 (continued)

• Anesthesia for the fiberoptic diagnosis of OSA and its anatomical location	4.11 (1.03)	20 (71)	13 (46)
• Role of oxygen therapy in patients at risk for OSA	4.54 (0.58)	27 (96)	16 (57)
Impact of sleep deprivation			
• Impact of sleep deprivation on immune system	4.00 (0.90)	21 (75)	9 (32)
• Impact of sleep deprivation on pulmonary muscle function	4.07 (0.90)	22 (79)	10 (36)
• Sleep deprivation and delirium	4.61 (0.69)	25 (89)	20 (71)
• Effect of alcohol and other recreational drugs on sleep	4.21 (0.83)	21 (75)	13 (46)
Non-invasive ventilation			
• Different non-invasive ventilation modalities and their indications in sleep-disordered breathing	4.79 (0.42)	28 (100)	22 (79)
• CPAP therapy compliance strategies	4.29 (0.85)	21 (75)	15 (54)
• Pressure considerations in sleep-disordered breathing	4.32 (0.77)	25 (89)	13 (46)
• Mask/interface options	4.25 (0.75)	25 (89)	11 (38)
• Advanced PAP therapies for complicated sleep-disordered breathing	4.07 (0.90)	22 (79)	10 (36)
Perioperative considerations in sleep-disordered breathing			
• Postoperative respiration monitoring strategies	5.00	28 (100)	28 (100)
• Preoperative considerations in sleep-disordered breathing	4.89 (0.42)	27 (96)	26 (93)
• Indications for and appropriate use of high care and intensive care facilities	4.75 (0.52)	27 (96)	22 (79)
• Indications for Sleep Medicine consultation	4.54 (0.69)	27 (96)	17 (61)
Future pathways in Sleep Medicine and Anesthesia			
• Sleep medicine and fellowship training	3.75 (1.00)	17 (61)	7 (25)
• Pathways to certification in Sleep Medicine	3.71 (1.08)	18 (64)	7 (25)
• What a Sleep Medicine practice could look like (e.g. in academic vs. private practice setting)	3.32 (1.22)	15 (54)	4 (14)

*Data are presented as means of ratings on a 5-point Likert scale, where 5 indicates strong agreement and 1 indicates strong disagreement.

**Percentage of participants who selected either “agree” or “strongly agree”

SLEEP MEDICINE 2

Validation of the STOP-Bang questionnaire as a screening tool for obstructive sleep apnea in patients with cardiovascular risk factors: a systematic review and meta-analysis

Mark Hwang[1], Kevin Zhang[2], Mahesh Nagappa[3], Aparna Saripella[4], Marina Englesakis[5], Frances F Chung[6]

[1]University of British Columbia, VANCOUVER, Canada, [2]University of Toronto, Toronto, Ontario, [3]Western University, London, Ontario, [4]Toronto Western Hospital, Toronto, Ontario, [5]University Health Network, Toronto, Ontario, [6]University of Toronto Faculty of Medicine, Toronto, Ontario

INTRODUCTION: Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder that has been associated with various forms of cardiovascular disease, including hypertension, stroke, heart failure, atrial fibrillation, and coronary artery disease. Accordingly, OSA is highly prevalent in patients with cardiovascular risk factors and is associated with increased morbidity and mortality.[1,2] However, up to 80% of patients remain undiagnosed, leading to poor quality of life, increased healthcare costs, and exacerbation of comorbid conditions.[3] The gold standard for diagnosis of OSA is polysomnography (PSG), which is costly and requires overnight observation. Given the high prevalence of OSA and limited resources for PSG, a valid and accessible screening tool is crucial to identify high-risk patients for diagnosis and treatment. The STOP-Bang questionnaire (SBQ) is an easy-to-administer OSA screening tool that has been validated in the sleep clinic and surgical populations. The purpose of this systematic review and meta-analysis is to evaluate whether the SBQ is a valid screening tool for OSA in patients with cardiovascular risk factors.

METHODS: We searched the following electronic databases: MEDLINE (Ovid), MEDLINE In-Process/ePubs, Embase, EmCare Nursing, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, PsycINFO, Web of Science, Scopus, CINAHL, and Journals@Ovid. All queries started from 2008 when the SBQ was first published and our search ended in March 2020. Continued literature surveillance was done through August 2020. The inclusion criteria were: 1) use of the SBQ to screen for OSA in adults (>18 years) with cardiovascular risk factors; 2) PSG or home sleep apnea testing (HSAT) performed as a reference standard; 3) OSA defined by either Apnea-Hypopnea Index (AHI) or Respiratory Disturbance Index (RDI); and 4) data on predictive parameters of the SBQ. We defined cardiovascular risk factors as diabetes mellitus, hypertension, hyperlipidemia, obesity, heart disease, cerebrovascular disease, and other disorders for which cardiovascular risk factors are part of the disease process. All study subjects had at least one of the above risk factors to be included. To address heterogeneity, a bivariate random-effects model was used to obtain the pooled predictive parameters (sensitivity, specificity, positive (PPV) and negative predictive value (NPV), and area under the curve (AUC) to assess the validity of the SBQ for different AHI cut-offs: AHI ≥ 5, ≥ 15, and ≥ 30 events per hour.

RESULTS: The literature search resulted in 3,888 articles, of which nine studies met the inclusion criteria, involving 1,894 patients. The average age of patients with cardiovascular risk factors was 58 ± 13 years with BMI of 30 ± 6 kg/m2, and 64% were male. The cardiovascular risk factors explored in the studies included diabetes mellitus (n=4), stroke (n=3), heart disease (n=3), hypertension (n=2), retinal vein occlusion (n=1), and non-alcoholic fatty liver disease (n=1). For validation purposes, four studies (44%) used PSG, while five (56%) used HSAT. The pooled predictive parameters of the SBQ are presented in Table 1. The SBQ has high pooled sensitivities of 89.1%, 90.7%, and 93.9% to screen for all (AHI ≥ 5), moderate-to-severe (AHI ≥ 15), and severe (AHI ≥ 30) OSA, respectively. The pooled specificities were relatively low at 32.3%, 22.5%, and 18.3 for all, moderate-to-severe, and severe OSA, respectively. The pooled PPV was highest at 80.7% to detect all OSA. With an NPV of 92.7%, the SBQ is most effective in ruling out severe OSA. The AUC was 0.86, 0.65, and 0.52 for all, moderate-to-severe, and severe OSA, respectively.

CONCLUSION: We found that the STOP-Bang questionnaire with a cut-off score ≥ 3 has excellent AUC at 0.86 in detecting OSA in patients with cardiovascular risk factors and is a valid screening tool for detecting OSA in this population. The high sensitivity and PPV of the STOP-Bang questionnaire enables risk stratification and early detection, facilitating the diagnosis and treatment of OSA.

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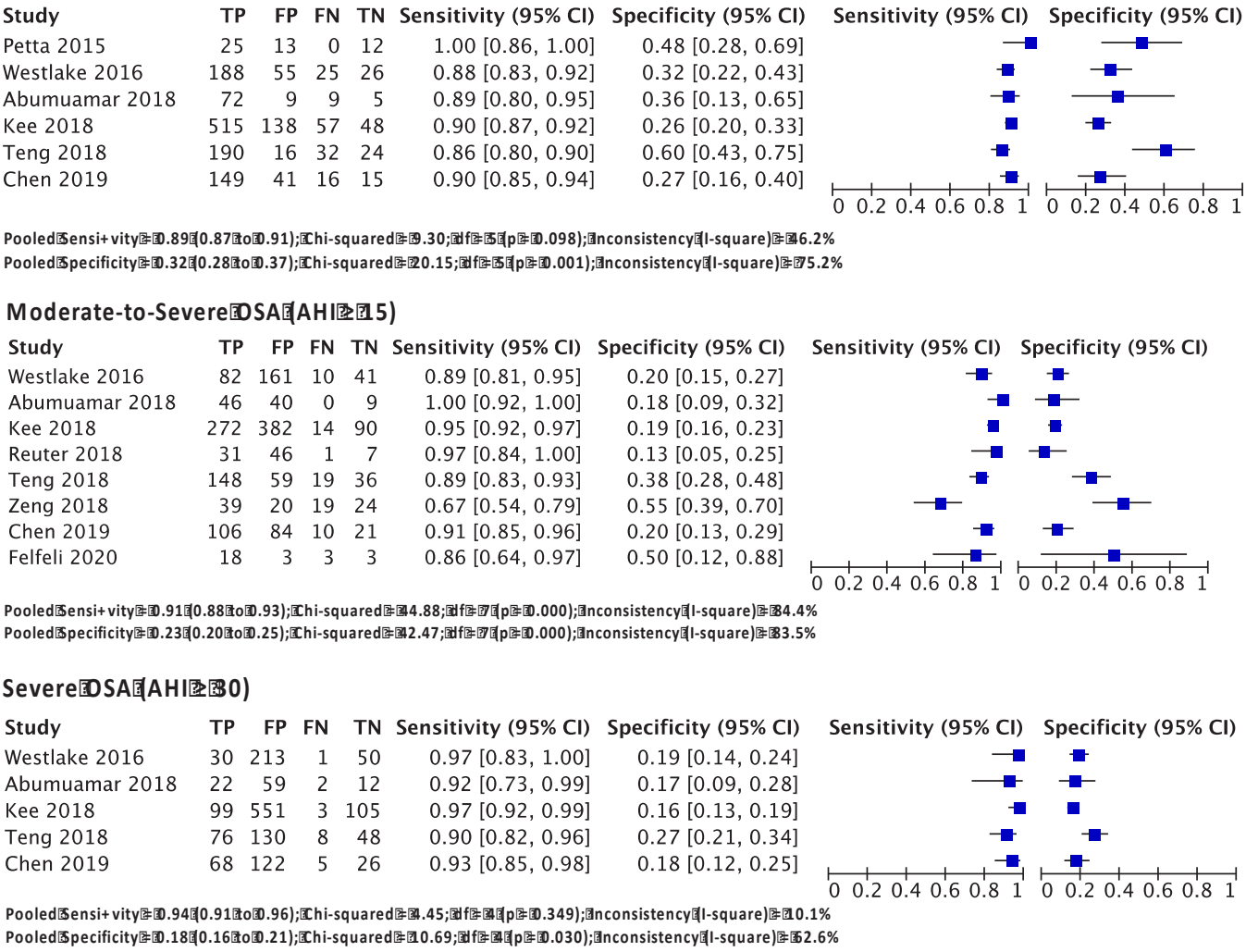
Figure 1. Forest plots for pooled sensitivity and specificity of STOP-Bang questionnaire for various OSA severities in patients with cardiovascular risk factors



Values are presented as means with 95% confidence interval in parentheses. Abbreviations: AHI, Apnoea hypopnea index; CI, confidence interval; df, degrees of freedom; OSA, obstructive sleep apnoea.

Table 1. Pooled predictive parameters of STOP-Bang score ≥ 3 to screen for OSA in patients with cardiovascular risk factors

Predictive parameters (95% CI)	All OSA AHI ≥ 5	Moderate-to-Severe OSA AHI ≥ 15	Severe OSA AHI ≥ 30
	(6 studies, n = 1680)	(8 studies, n = 1844)	(5 studies, n = 1630)
Prevalence	76.1 (73.9-78.1)	44.4 (42.1-46.7)	19.3 (17.4-21.3)
Sensitivity	89.1 (87.3-90.8)	90.7 (88.5-92.6)	93.9 (90.1-96.3)
Specificity	32.3 (27.8-37.2)	22.5 (20.0-25.2)	18.3 (16.3-20.5)
Positive predictive value	80.7 (78.5-82.7)	48.3 (45.8-50.8)	21.5 (19.4-23.8)
Negative predictive value	48.3 (42.2-54.5)	75.2 (70.0-79.9)	92.7 (88.6-95.4)
Diagnostic odds ratio	4.37 (2.83-6.75)	3.52 (2.60-4.77)	3.72 (2.25-6.15)
AUC	0.86 SE = 0.054	0.65 SE = 0.064	0.52 SE = 0.24

Data presented as means with 95% confidence interval in parentheses where appropriate. Abbreviations: AHI, Apnoea hypopnea index; AUC, area under the ROC curve; CI, confidence interval; OSA, obstructive sleep apnoea; SE, standard error.

SLEEP MEDICINE 3

Can the complete blood count be used as a reliable screening tool for obstructive sleep apnea?

Emer Cummins[1], Rida Waseem[1], Deween Piyasena[1], Chew Yin Wang[2], Colin Suen[1], Clodagh Ryan[1], Jean Wong[1], Meir Kryger[3], Frances F Chung[1]

[1]University of Toronto, Toronto, Ontario, [2]University of Malaya, Kuala Lumpur, Malaysia, [3]Yale School of Medicine, New Haven, CT

INTRODUCTION: Obstructive sleep apnea (OSA) is a common disorder, defined by nocturnal intermittent hypoxia. Hypoxia has been shown to cause increases in erythropoietin production and inflammation.[1,2] Thus, we hypothesized that the complete blood count (CBC) parameters would reflect the hypoxic burden in OSA, and may act as an inexpensive alternative clinical tool for the screening and assessment of OSA patients. The objective of this study was to evaluate whether nocturnal intermittent hypoxia and severity of OSA, as measured by the apnea-hypopnea index (AHI) and mean oxygen saturation (SpO2), affect hematological parameters as measured by the CBC.

METHODS: This post-hoc analysis included 941 surgical patients enrolled from 2007 to 2017 from two hospitals. Consented patients, aged ≥18 years, underwent a portable sleep apnea study (Embletta or ApneaLink Plus). Pre-operative CBC data was extracted from electronic medical records. Patients were stratified according to their AHI scores, into no OSA (AHI <5), mild (AHI ≥5 – <15), moderate (AHI ≥15 – <30), and severe (AHI ≥30) OSA groups. Patients on OSA therapy were excluded from this study. One-way analysis of variance or Kruskal-Wallis tests were conducted to examine the difference in severity of OSA for continuous variables, and chi-square tests were conducted for categorical variables. A Pearson correlation analysis was used to examine the association between mean SpO2, body mass index (BMI), age, and the different hematological parameters. Multivariable regression analysis was preformed to examine the predictors of intermittent hypoxia by considering confounding factors including age, BMI, sex, and hypertension.

RESULTS: There were 244 patients without OSA, 294 with mild, 223 with moderate, and 180 with severe OSA. Patients had a mean age 63(11) years, BMI 31(7) kg/m2, and 50% were male. There were significant differences among BMI, age, gender, hypertension, mean SpO2, hemoglobin, hematocrit and basophils for the different severity of OSA. Further, post hoc analysis showed a difference between the different severities of OSA for the significant variables. Compared to patients with no OSA, those with severe OSA had lower mean SpO2 (Figure 1A). Hemoglobin was significantly different between patients with moderate OSA vs no OSA, as well as severe OSA vs no OSA (Figure 1B). Hematocrit and basophils were significantly different between severe OSA vs no OSA. For mean SpO2, there were negative associations with body mass index (r= -0.287; P<0.001), age (r=-0.077; P=0.021), hemoglobin (r=-0.208; P<0.001), hematocrit (r=-0.220; P<0.001), red blood cells (r=-0.107; P=0.001), mean corpuscular volume (MCV) (r=-0.159; P<0.001), mean corpuscular hemoglobin (r=-0.142; P<0.001), and basophils (r=-0.091; P=0.007). All analyzed parameters remained within normal clinical range. Controlling for age, BMI, sex and hypertension, multivariable regression identified hemoglobin and MCV to be an independent predictor of hypoxia defined by mean SpO2.

CONCLUSION: This study demonstrated significant associations among hemoglobin, hematocrit, MCV, and basophils, with both SpO2 and AHI. Using mean SpO2, we identified hemoglobin and MCV as significant independent predictors of hypoxia in OSA patients. However, all of the CBC parameters were within normal clinical ranges. Thus, while we have found modest changes among the CBC to reflect the hypoxic burden seen in OSA, no single parameter can aid reliably in the prediction or assessment of OSA.

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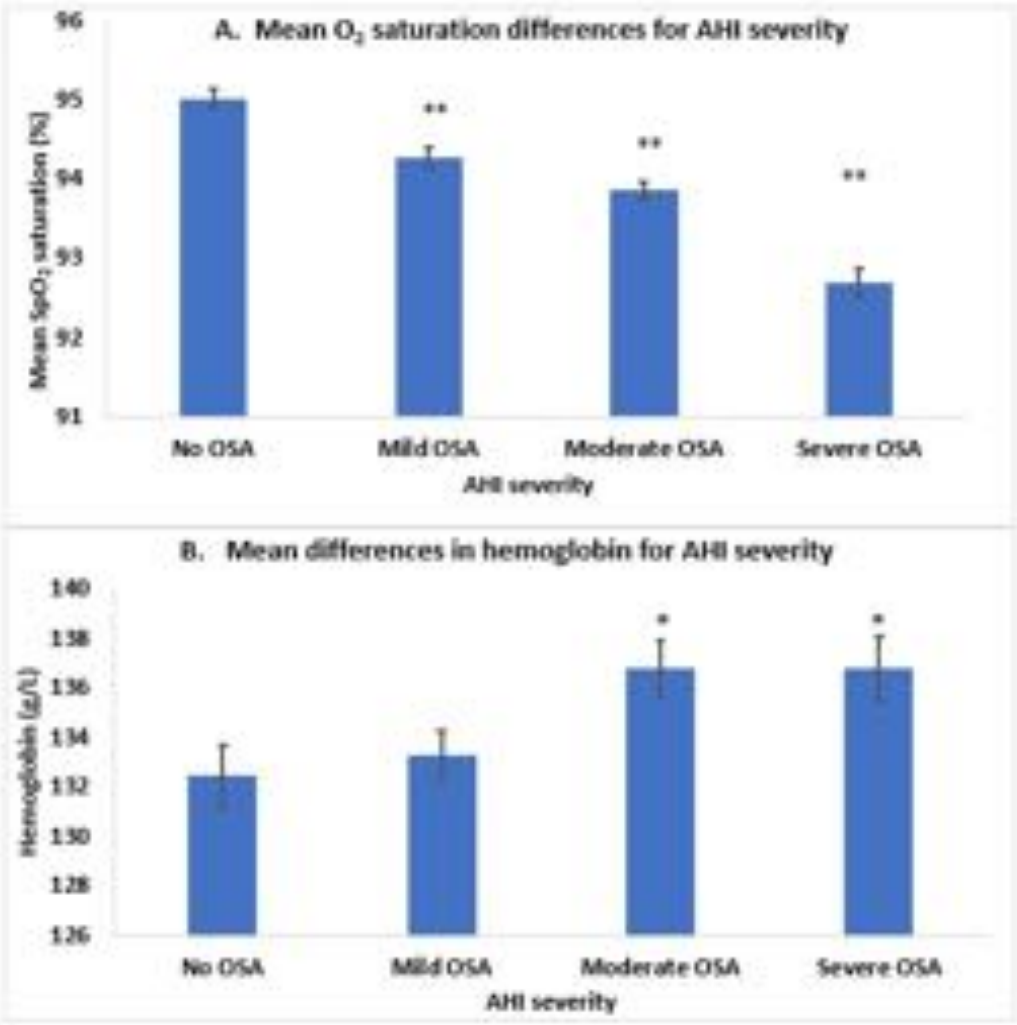
Figure

Figure 1. (A) shows that there was a significant difference in the severity of OSA for mean oxygen saturation. Further post-hoc analysis showed that there was a significant difference between no OSA and mild OSA (P<0.01), no OSA and moderate OSA (P<0.01), and no OSA and severe OSA (P<0.01).

Figure 1. (B) shows that there was a significant difference in the severity of OSA for hemoglobin. Further post-hoc analysis showed that there was a significant difference between no OSA and moderate OSA (P<0.05), no OSA and severe OSA (P<0.05).



*p<0.05, **p<0.01, Vertical lines on the bars represent standard error of the mean.
Abbreviation: AHI, Apnea hypopnea-index; OSA, Obstructive sleep apnea. SpO_2, Oxygen saturation

SLEEP MEDICINE 4

Prevention of delirium in elderly with obstructive sleep apnea (PODESA): A randomised controlled trial

Jean Wong[1], Helen R Doherty[2], Mandeep Singh[3], Stephen Choi[4], Naveed Siddiqui[3], David Lam[5], Frances F Chung[6]

[1]University of Toronto, Toronto, ONTARIO, [2]University Hospitals Network (UHN), Toronto, Ontario, [3]University of Toronto, Toronto, Ontario, [4]Sunnybrook Health Sciences Centre, Toronto, Ontario, [5]University Health Network, Toronto, Ontario, [6]University of Toronto Faculty of Medicine, Toronto, Ontario

INTRODUCTION: Delirium is a common problem that occurs in 5-50% of elderly individuals following surgery. Patients who develop delirium after surgery are at increased risk for longer hospital stay, and subsequent cognitive decline. Obstructive sleep apnea (OSA) is more prevalent in older individuals but may be under-reported because some of the symptoms may be attributed to normal aging. OSA is associated with neurocognitive impairment and treatment with continuous positive airway pressure (CPAP) improves cognition in the general population.[1] It is unclear whether OSA increases risk of postoperative delirium and whether treatment is protective. The objectives of this trial were to identify OSA preoperatively with a portable home sleep study and to determine whether auto-titrating continuous positive airway pressure (APAP) treatment would decrease post-operative delirium in older individuals undergoing elective hip or knee replacement surgery.

METHODS: This was a multi-centre, prospective, randomized controlled superiority trial that was conducted at three academic hospitals in Canada. Research ethics board approval was obtained from the participating sites and informed consent was obtained from all participants. A computer-generated randomization list for each participating site allocated participants 1:1 into either 1) intervention (APAP) or 2) control (usual care) group. Inclusion criteria were patients who were: 1) ≥60 years; 2) scheduled for elective hip or knee replacement surgery at least 4 working days after the preoperative clinic visit; 3) possessed the cognitive and physical capability necessary to comprehend and complete the study questionnaires; 4) proficient in English; 5) accessible for follow-up via telephone, or via the Internet; and 6) able to provide informed consent. Patients with a prior diagnosis of sleep-related breathing disorder who were compliant with CPAP/APAP treatment were excluded. Other exclusion criteria were patients with central sleep apnea, significant cardiac, lung, or psychiatric disease. Patients with a STOP-Bang score of 3 or higher had a portable home sleep study with ApneaLinkTM Air (ResMed, San Diego, California, USA) for one night. Patients were defined as having OSA if the apnea-hypopnea index (AHI) was ≥10/h. These patients were randomized to receive APAP or control (usual care) after surgery for 72 hours or until discharge if the hospital stay was <72 hours. The primary outcome was postoperative delirium based on assessing the Confusion Assessment Method (CAM) twice daily for 72 hours or until discharge if hospital stay >72 hours. The secondary outcome measures included length of stay, and perioperative complications occurring within 30 days after the surgical procedure. Differences in the primary and secondary outcomes were assessed using parametric and non-parametric tests where appropriate, and a P-value <0.05 was considered statistically significant.

RESULTS: There was no difference in baseline characteristics between the two groups. The mean age was 68.2 (6.2) years, 58.6% were male and the mean body mass index was 33.3 (6.3) kg/m2. Of the 549 patients who were assessed for eligibility, 474 with a STOP-Bang score ≥3 underwent a home sleep study with ApneaLink Air™. A total of 234 (49.4%) patients who completed the sleep study were identified as having OSA (Apnea hypopnea index ≥ 10/h) and were randomized in a 1:1 ratio to treatment (APAP) or control (usual care). Eight patients in the treatment group and 6 patients in the control group were lost to follow-up or discontinued participation in the study. Analysis was performed for a total of 220 patients, 107 patients in the treatment group and 113 patients in the control group. Five (4.4%) patients in the usual care group, and one patient (0.9%) in the treatment group who was not adherent with APAP developed postoperative delirium, P=0.24. The mean length of stay for the APAP vs. usual care group was 2.9 (2.9) days vs. 3.5 (4.5) days, P=0.24, respectively. There was no difference in intraoperative and postoperative complications between the two groups.

CONCLUSION: There was a high prevalence of unrecognized OSA in older patients undergoing elective hip and knee replacement. We did not find a higher incidence of postoperative delirium in the usual care group compared to the APAP group, however, as the incidence of delirium was lower than reported in previous literature, our study was underpowered to detect a difference.

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SLEEP MEDICINE 5

Sleep Health in young adults with chronic pain attending a multidisciplinary clinic: A retrospective observational cohort study

Shikha Bansal[1], Rachael Bosma[2], YEN SHUANG LAW[3], Mohamed Eissa[4], Tania Di Renna[5], Mary B McLoone[6], Mandeep Singh[2]

[1]Northern Ontario School of Medicine & Thunder Bay Regional Health Sciences Centre, Thunder Bay, Ontario, [2]University of Toronto, Toronto, Ontario, [3]Toronto Western Hospital, Johor Bahru, Johor, [4]Women's College Hospital and Toronto Western Hospital, Toronto, Canada, [5]University Health Network (UHN), Toronto, Ontario, [6]St Michael's Hospital, Toronto, Ontario

INTRODUCTION: Every fifth Canadian child has chronic pain and 5-8% of the adolescents have pain affecting their quality of life.[1] There are transition programs for graduating pediatric chronic pain patients to the adult healthcare system. The Toronto Academic Pain Medicine Institute (TAPMI) Young Adult Clinic (YAC) offers services to promote successful transition of clients aged 17-25 years with persistent pain to adult healthcare services. Sleep deficiency which is either a deficit in the quantity or quality of sleep obtained as opposed to the amount required for optimal health, performance and well-being has been reported in more than fifty percent of the youths with chronic pain.[2,3] Long-term sleep disruption has been associated with increased sensitivity to pain, prolonged pain duration, and predicts chronic pain. Also, the degree of pain relief can directly impact the quality and disruption of sleep. Hence, the program was expanded in January 2019 to include a sleep medicine specialist for systematic evaluation of sleep health. We hypothesize that poor sleep health is common in YAC population as well and share our initial clinical experience in this multi-disciplinary clinic for young adults with chronic pain.

METHODS: After approval from institutional review board, we retrospectively reviewed YAC patients medical charts from March 2018 to April 2019. Only patients attending the TAPMI YAC during the specified period were included in the study. Information extracted included demographics, data on chronic pain and sleep. Others measures collected include Pain Self Efficacy Questionnaire (PSEQ)[4], Patient Health Questionnaire (PHQ-9)[5,6] and, Pain Catastrophizing scale (PCS)[7]. Descriptive statistics were used, and reported as frequency (percentage) and mean ± standard deviation (SD).

RESULTS: Fifty-five medical charts were reviewed which included 40 females, 13 males, 2 non binary individuals, with a mean age of 20.3±2.4 years. Majority (53%) of the patients had chronic widespread pain. The mean duration of pain was 7±5 years. Most commonly used medications were anticonvulsants (60%), non-steroidal anti-inflammatory drugs (45.5%), and acetaminophen (40%). Eight five percent patients reported sleep health disruption, as evidenced by problems with sleep initiation, difficulty in maintaining sleep, both initiation & maintenance, frequent night awakenings due to pain, restless leg syndrome (RLS), suspected obstructive sleep apnea (OSA), diagnosed OSA or OSA on treatment, parasomnia behavior, circadian rhythm disorder such as delayed sleep phase disorder, etc. Mean sleep duration in our study group was 8±1.9 hours. Epworth sleepiness scale (ESS)[8] showed that 12.5% of the patients had mild, 12.5% had moderate and 3% had severe daytime sleepiness. As assessed by the PSEQ questionnaire, in which patients rated how confident they feel doing certain things despite the pain, 47% of the youths demonstrated a low self-efficacy score (PSEQ<30). PHQ-9 questionnaire was used to measure the severity of depression which showed that 6% 32.7% 20.4%, 16.3%, 24.5% of the YAC patients suffered from minimal, mild, moderate, moderately-severe and severe depression respectively. PCS suggested that 28%, 34% and 38% were at low, moderate and high risk respectively in having catastrophizing thoughts related to pain. There was no statistical difference in the means PSEQ, PHQ-9 and PCS scores of young adults with and without sleep problems.

CONCLUSION: This retrospective review showed notable sleep disturbances in YAC patients. Sleep disturbances may be an important modifiable risk factor for alleviating distress in young adults with chronic pain. There is a need for research to identify effective ways to jointly improve sleep quality and reduce pain in young people by including sleep specific management strategies. Owing to this, we have expanded our program by creating a multi-disciplinary program, integrating systematic evaluation of sleep health, identifying the specific domains of sleep health disruption, and targeting treatment strategies in a coordinated fashion between the chronic pain physician, sleep physician and the occupational therapist, with the goal to improve overall health, and quality of life this vulnerable patient population.

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SLEEP MEDICINE 6

The association between recent cannabis use and sleep duration in adults in the USA from 2005-2018

Calvin Diep[1], Chenchen Tian[1], Karim Ladha[1], Mandeep Singh[1]

[1]University of Toronto, Toronto, Canada

INTRODUCTION: Shifts in medicolegal attitudes towards cannabis, coupled with widespread decriminalization, have led to North America having the highest prevalence of cannabis use worldwide[1,2]. Amongst other known physiologic effects, regular cannabis use can cause changes to sleep duration and quality[3]. The purpose of this study was to examine the relationship between recent cannabis use and sleep duration using a nationally representative data set.

METHODS: A cross-sectional analysis of adults was undertaken using the National Health and Nutrition Examination Survey data from 2005–2018. Respondents were dichotomized as recent or non-recent users if they respectively had or had not used cannabis in the past 30 days. The primary outcome was inadequate nightly sleep duration (<6 hours) and secondary outcomes were related to self-reported issues with sleep. Multiple logistic regression was used to adjust for sociodemographic and health-related confounders and survey sample weights were considered in modelling.

RESULTS: Compared to those with no recent cannabis use (n=18,631), recent users (n=3,135) were more likely to report less than 6 hours of sleep per night (aOR 1.33 95% 1.13–1.57, p<0.001). Recent users were also more likely to report difficulty falling asleep, staying asleep, or sleeping too much in the past two weeks (aOR 1.21, 95% CI: 1.09–1.35, p<0.001), and having ever mentioned these issues to a physician (aOR 1.21, 95% CI: 1.07–1.37, p=0.003). Respondents using cannabis at least 20 of the past 30 days were characterized as heavy users, and were even more likely than moderate users to report insufficient sleep. These results did not significantly differ between years of survey administration.

CONCLUSION: Recent cannabis use was associated with inadequate nightly sleep duration in adults and demonstrated a dose-dependent relationship. Although this relationship is complex and our findings cannot suggest directionality, they highlight the need to further characterize the sleep health of regular cannabis users in the general population[4,5]. This is especially prudent as cannabinoids are becoming widely accepted for recreational use and increasingly prescribed as medical therapy.

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SLEEP MEDICINE 7

Perioperative Adherence to Continuous Positive Airway Pressure and its Effect on Postoperative Nocturnal Hypoxemia in Obstructive Sleep Apnea Patients: a Prospective Cohort Study

Colin Suen[1], Jean Wong[2], Kahiye Warsame[3], Yamini Subramani[4], Tony Panzarella[1], Rida Waseem[5], Dennis Auckley[6], Sazzadul Islam[7], Frances F Chung[8]

[1]University of Toronto, Toronto, Ontario, [2]University of Toronto, University Health Network, Toronto, Ontario, [3]University of Toronto, Toronto, ON, [4]Victoria Hospital, London, Ontario, [5]Toronto Western Hospital, Toronto, Canada, [6]MetroHealth Medical Center, Cleveland, OH, [7]University of Toronto, Toronto, Canada, [8]University of Toronto Faculty of Medicine, Toronto, Ontario

INTRODUCTION: Although continuous positive airway pressure (CPAP) is the first line treatment for obstructive sleep apnea (OSA) patients, the perioperative adherence rate is unclear. The objective of this study was to determine the perioperative adherence rate of patients with OSA with a CPAP prescription and the effect of adherence on nocturnal oxygen saturation.

METHODS: This prospective cohort study included adult surgical patients with a diagnosis of OSA with CPAP prescription undergoing elective non-cardiac surgery. Patients were divided into CPAP adherent and non-adherent groups based on duration of usage (≥ 4h/night). Overnight oximetry was performed preoperatively and on postoperative night 1 and 2 (N1, N2). The primary outcome was adherence rate and secondary outcomes were nocturnal oxygen saturation. A linear fixed effects model was used to test the relationship between CPAP adherence and oxygen saturation, adjusted for supplemental O2 therapy.

RESULTS: One hundred and thirty-two patients completed the study. CPAP adherence was 61% preoperatively, 58% on postoperative N1, and 59% on N2. Forty-nine percent were consistently CPAP adherent pre- and postoperatively. Using a linear fixed effects regression, oxygen desaturation index (ODI) was significantly improved by CPAP adherence ($p = 0.0011$). The interaction term CPAP x N1 was significant ($p = 0.0015$), suggesting that the effect of CPAP adherence varied on N1 vs preoperatively. There was no benefit of CPAP adherence on postoperative mean SpO2, minimum SpO2, and percentage of sleep duration with SpO2 <90%. Supplemental oxygen therapy was higher in the CPAP non-adherent group vs adherent group on N1 (47% vs 9.8%, $p < 0.001$).

CONCLUSION: Among patients with a preoperative CPAP prescription, approximately 50% were consistently adherent. CPAP adherence was associated with improved preoperative ODI and the benefit was maintained on N1 and improved pain control. These modest effects may be underestimated by a higher severity of OSA in the CPAP adherent group and a higher rate of oxygen supplementation in the non-adherent group.

Subspecialty Abstracts

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT & MONITORING

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 1

Evaluation of the efficacy and safety of a novel dermatotomy device for central venous cannulation

Worasak Keeyapaj[1], Albert T Cheung[2]

[1]Stanford University, Stanford, CA, [2]Stanford University, Redwood City, CA

INTRODUCTION: Central venous cannulation (CVC) is one of the most common procedures performed in the United States. More than 5 million CVC's are performed annually in the United States. Dermatotomy incision and dilation are important steps for CVC. A precise incision is necessary to ensure success, minimize bleeding, and avoid the need for a second dermatotomy. The Guideblade® is a novel wire-guided scalpel that utilizes the Seldinger's technique to facilitate the dermatotomy incision. The hypothesis that the Guideblade® is a safe and effective instrument for performing the dermatotomy for CVC was tested.

METHODS: In an IRB-approved protocol, cardiac surgical and major vascular patients who required CVC insertion were enrolled after written informed consent. CVC was performed according to the institutional protocol. The CVC catheter type, triple lumen catheter (ABG+ Multiple-Lumen Central Venous Catheterization, Arrow Inc®, Reading, PA), Introducer catheter (ARROWg+ard Blue PSI kit Cath-Gard, Arrow Inc®, Reading, PA), and Multi-lumen access catheter (MAC®, Arrow Inc®, Reading, PA) was chosen by the attending anesthesiologist. It was common practice to place two central lines (double sticks) for cardiac operations. The Guideblade®, was used to create the dermatotomy incision after guidewire insertion. The number of dermatotomies required, dilations required, catheter insertion attempts, wire kinking, or need for additional tools for CVC were recorded. The primary outcome was the rate of successful CVC without additional equipment. The secondary outcomes were bleeding at the insertion site at 30 min after CVC and immediately after operation.

RESULTS: 99 patients, 61 (61.6%) male and 38 (38.4%) female, participated in the study with 187 CVC procedures. The mean and standard deviation (mean+SD) of body weight (kg), height (cm) and BMI (kg/m2) were 85+22, 172+10 and 29+6. 89 (89%) patients received 2 central lines. 13% of patients had abnormal baseline coagulation defined as INR > 1.5 or aPTT >48 seconds. 98% of patients received heparin during the procedure with a mean maximum ACT value of 708+180 seconds. All CVC procedures were performed by anesthesiology residents or cardiothoracic anesthesiology fellows. CVC was successful without need for additional equipment in 100%. Only a single dermatotomy was required for CVC in 90% (89 out of 99 patients). There were no observations of of wire kinking or user injury. Bleeding at the insertion sites was classified as 'no bleeding' or 'minimal bleeding' at 30 min after insertion in 90% and 86% at the conclusion of surgery. Two patients required sutures at their CVC sites to stop bleeding. One patient required oxidized regenerated cellulose powder application at the CVC site.

CONCLUSION: The novel, wired-guided scalpel, Guideblade®, was safe and effective for performing the dermatotomy incision for CVC with a 100% success rate and a very high first attempt success rate with no report of user injuries. It may also help decrease bleeding at the insertion site by improving the precision of the dermatotomy and avoiding the need for multiple dermatotomy incisions for CVC.(Guideblade® used for the study were supplied by Ambitus Medical Supplies LLC).

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TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 2

High Fidelity CRISPR Libraries to Interrogate Anesthetic Coding and Non-Coding Genetic Susceptibilities

Alexendar R Perez[1], Joana A Vidigal[2]

[1]University of California, San Francisco, San Francisco, CA, [2]National Cancer Institute, NIH, Bethesda, MD

INTRODUCTION: High-throughput CRISPR screens accelerate the discovery of novel genetic susceptibilities pertinent to human health. Already CRISPR screens are being utilized to uncover gene susceptibilities relevant to cancer and neurodegenerative disease processes[1,2]. The ease and effectiveness of CRISPR screens derives from the technology's simplicity in needing 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 non-coding regulatory elements such as microRNAs. Many current genome-wide CRISPR libraries contain non-specific gRNAs that add substantial 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 both coding and non-coding elements in both the human and mouse genomes. We utilized our GuideScan and CSC softwares to design ultra-specific CRISPR gRNA libraries to interrogate all coding genes and all microRNAs in both the human and mouse genomes. Recent studies have highlighted the importance of genomics in suggesting new avenues of anesthetic discovery and therapeutic involvement[3]. We will use our high-fidelity CRISPR gRNA libraries to prospectively interrogate how anesthetic exposure affects human cell proliferation following coding gene or microRNA knockout. Overall, CRISPR screens, using high fidelity gRNA libraries, promise to accelerate the development of anesthetic genomics.

METHODS: Enumeration of Guide RNA (gRNA) Targets We constructed retrieval trees (tries) consisting of all possible 20mer Cas9 gRNA target sites in the mouse and human genomes as previously published[4]. Unlike the original tries reported in GuideScan[4], these were constructed without alternative chromosome data and thus produce a more accurate description of the off-target space of individual gRNAs. To determine the mismatch neighborhood for each gRNA in the library, we traversed each of their sequences through the 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[4] 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[5]. 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[5]. Guide RNA Library Design Guide RNA libraries were constructed for all coding genes and all microRNAs in the human and mouse genomes. Guide RNA specificity was determined by using the GuideScan software to select gRNAs that were maximally unique to their target feature. The target features of these libraries being human and mouse coding genes and microRNAs. After determining each feature's set of maximally unique gRNAs, we selected for the final library those gRNAs with the highest Rule Set 2 scores. In this manner we designed genome-wide libraries against human and mouse coding and non-coding features that are maximally specific and efficient at cutting their genomic targets. We will use these libraries to prospectively interrogate how anesthetic exposure affects human cell proliferation following coding gene or microRNA knockout.

RESULTS: CRISPR libraries containing non-specific gRNAs limit screen utility (Fig 1a-d) as non-specific gRNAs confound screen readout (Fig 1e). GuideScan libraries eliminate non-specific gRNAs and are designed to be maximally specific and efficient at cutting target loci.

CONCLUSION: GuideScan libraries contain maximally specific and efficient gRNAs capable of targeting all coding genes and microRNAs in human and mouse genomes. These libraries are prerequisite for anesthetic CRISPR screens.

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Figure 1

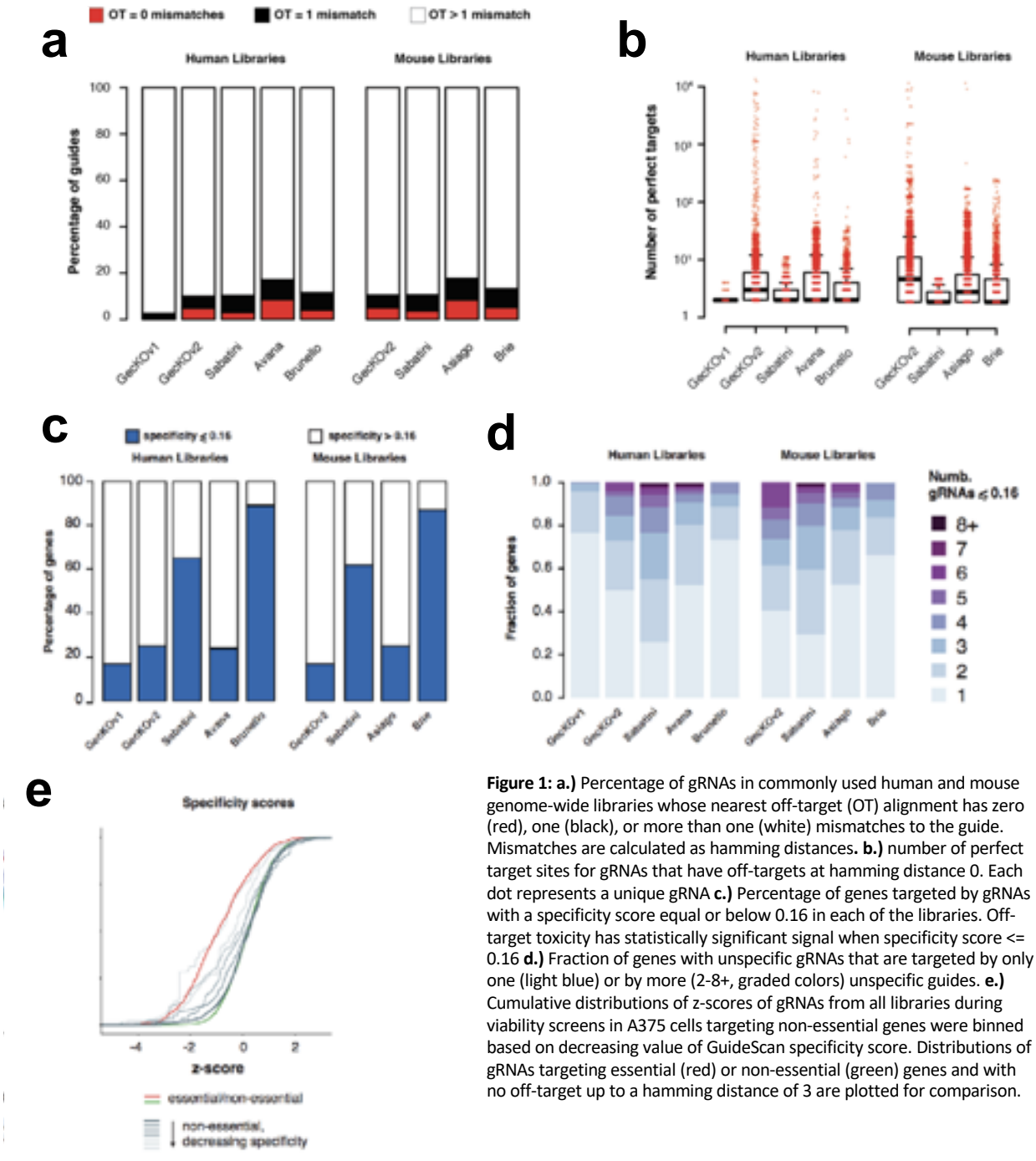

Figure 1: a.) Percentage of gRNAs in commonly used human and mouse genome-wide libraries whose nearest off-target (OT) alignment has zero (red), one (black), or more than one (white) mismatches to the guide. Mismatches are calculated as hamming distances**. b.)** number of perfect target sites for gRNAs that have off-targets at hamming distance 0. Each dot represents a unique gRNA **c.)** Percentage of genes targeted by gRNAs with a specificity score equal or below 0.16 in each of the libraries. Off-target toxicity has statistically significant signal when specificity score <= 0.16 **d.)** Fraction of genes with unspecific gRNAs that are targeted by only one (light blue) or by more (2-8+, graded colors) unspecific guides. **e.)** Cumulative distributions of z-scores of gRNAs from all libraries during viability screens in A375 cells targeting non-essential genes were binned based on decreasing value of GuideScan specificity score. Distributions of gRNAs targeting essential (red) or non-essential (green) genes and with no off-target up to a hamming distance of 3 are plotted for comparison.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 3

Towards a user-centered design of a display interface for machine learning predictions of postoperative complications

Bradley A Fritz[1], Christopher R King[1], Michael Avidan[1], Joanna Abraham[1]

[1]Washington University in St. Louis, St. Louis, MO

INTRODUCTION: Postoperative death and complications such as acute kidney injury are common[1-2]. Some of these adverse outcomes can be prevented through intraoperative risk mitigation, requiring early identification of at-risk patients. Telemedicine can augment risk stratification and provide guidance on mitigation strategies while bedside clinicians are occupied with other tasks. We have developed machine learning (ML) tools to assist in prediction of postoperative death and acute kidney injury during surgery[3-4]. To make such tools effective and user-friendly to clinicians, we need to understand the intraoperative clinician information workflow. Our aims in this study were (1) to characterize the content needs for an ML display interface to support intraoperative decision making and (2) to ascertain the optimal structural format for the content.

METHODS: Attending anesthesiologists, certified registered nurse anesthetists (CRNAs), and anesthesiology residents who work in the intraoperative telemedicine suite at our institution were recruited for focus group interviews. Focus groups were conducted by the first and senior authors using a semi-structured interview guide. Activities included (1) discussion of workflows for selecting patients to evaluate, conducting comprehensive patient case reviews, and estimating risk for postoperative complications; (2) a card sorting activity to classify information elements to include, to maybe include, or to not include in a display interface showing ML predictions for postoperative complications; and (3) discussion of preferences among display formats for each content element. Participants completed card sorts independently and then discussed the rationale behind their choices, attempting to reach consensus within each focus group. Focus groups were audio-recorded, transcribed, and qualitatively analyzed using thematic analysis. Two authors openly coded each transcript independently. Recurring patterns or combinations of codes that yielded sub-themes leading to overarching themes were identified and iteratively analyzed, until consensus was achieved. Card sort results were tallied for frequencies.

RESULTS: Twenty clinicians (8 attending anesthesiologists, 3 CRNAs, and 9 residents) participated in six focus groups. Three themes emerged during the qualitative analysis. First, clinicians wanted to identify patients for whom they can take action to prevent complications. They felt ML could assist by identifying patients with an elevated risk and a large portion of the risk driven by modifiable factors. Second, clinicians performed case reviews using a systematic approach, frequently starting with the pre-anesthesia clinic note and mirroring the approach they use when personally caring for patients in the operating room. An ideal ML tool would be accessible from within the existing case review workflow and might reduce time spent reviewing onerous parts of the medical record such as flowsheets. Finally, clinicians preferred display formats that minimize the energy and time spent interpreting complex data. They identified several strategies such as simplifying interface display layout, indicating risk level with color (e.g., red for high risk), hovering for details, and showing risk trends over time with graphs. Card sort results are shown in Table 1 (individual participant sorts) and Table 2 (consensus sorts from each focus group). All participants agreed on including the variables contributing to the risk prediction and the name of the scheduled surgery in the display. There was also strong interest in seeing the quantitative predicted risk and the change over time. They expressed mixed opinions about other elements, such as whether and how to convert numeric risk predictions to 'high risk' and 'low risk' categories.

CONCLUSION: The results suggest that telemedicine clinicians are more likely to accept ML-augmented interface displays if contents are simple to use, flag patients at elevated risk, and highlight actionable risks and potential mitigation strategies. Our finding that information and decision making workflows of telemedicine clinicians mirrored bedside practices can be leveraged in the design of clinical decision support tools for both telemedicine and bedside intraoperative care decision making processes. Insights from this study inform our ongoing and planned research including prototype development, prototype testing using simulated patient cases, and lastly a large-scale evaluation and implementation trial.

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Table 1. Clinician preferences for elements to include in the display interface.
Results from individual participant card sorts (N = 20)

Display Element	Yes – Definitely include in the display n (%)	Maybe – Maybe include in the display n (%)	No – Do not include in the display n (%)
Quantitative predicted risk (percentage)	16 (80%)	4 (20%)	0 (0%)
Confidence interval around quantitative predicted risk	5 (25%)	10 (50%)	5 (25%)
Qualitative predicted risk (high/average/low)	8 (40%)	7 (35%)	5 (25%)
Change in predicted risk in last 15 minutes	11 (55%)	6 (30%)	3 (15%)
Variables contributing to this patient's predicted risk	13 (65%)	6 (30%)	1 (5%)
Average risk for all patients at the hospital	1 (5%)	3 (15%)	16 (80%)
Average risk for patients undergoing the same surgery	5 (25%)	12 (60%)	3 (15%)
Average risk for patients of the same age	1 (5%)	14 (70%)	5 (25%)
Predicted risk from preoperative information only	9 (45%)	8 (40%)	3 (15%)
Patient identifiers	8 (40%)	7 (35%)	3 (15%)
Name of scheduled surgery	16 (80%)	4 (20%)	0 (0%)
Patient age	14 (70%)	5 (25%)	1 (5%)

Table 2. Clinician preferences for elements to include in the display interface.
Results from consensus card sorts within each focus group (N = 6)

Display Element	Yes – Definitely include in the display n (%)	Maybe – Maybe include in the display n (%)	No – Do not include in the display n (%)	Not sorted (consensus not achieved) n (%)
Quantitative predicted risk (percentage)	5 (83%)	1 (17%)	0 (0%)	0 (0%)
Confidence interval around quantitative predicted risk	1 (17%)	5 (83%)	0 (0%)	0 (0%)
Qualitative predicted risk (high/average/low)	2 (33%)	3 (50%)	1 (17%)	0 (0%)
Change in predicted risk in last 15 minutes	5 (83%)	1 (17%)	0 (0%)	0 (0%)
Variables contributing to this patient's predicted risk	6 (100%)	0 (0%)	0 (0%)	0 (0%)
Average risk for all patients at the hospital	0 (0%)	0 (0%)	6 (100%)	0 (0%)
Average risk for patients undergoing the same surgery	1 (17%)	5 (83%)	0 (0%)	0 (0%)
Average risk for patients of the same age	0 (0%)	5 (83%)	1 (17%)	0 (0%)
Predicted risk from preoperative information only	2 (33%)	3 (50%)	0 (0%)	1 (17%)
Patient identifiers	2 (33%)	1 (17%)	1 (17%)	2 (33%)
Name of scheduled surgery	6 (100%)	0 (0%)	0 (0%)	0 (0%)
Patient age	3 (50%)	3 (50%)	0 (0%)	0 (0%)

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 4

Early Detection of Postoperative Deterioration in Cardiac Surgery Patients using Electronic Health Record and Waveform Data: A Machine Learning Approach

Michael R Mathis[1], Milo Engoren[2], Sachin Kheterpal[1], Kyle Gunnerson[3], Aaron Williams[3], Benjamin Biesterveld[3], Alfred Croteau[4], Kevin Ward[3], Hasan Alam[5], Harm Derksen[6], Gang Liu[2], Renaid Kim[2], Neriman Tokcan[7], Kayvan Najarian[3], Jonathan Gryak[3]

[1]University of Michigan Medicine, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]Michigan Medicine, Ann Arbor, MI, [4]Hartford Healthcare, Hartford, CT, [5]Northwestern Medicine, Chicago, IL, [6]Northeastern University, Boston, MA, [7]Broad Institute of MIT and Harvard, Boston, MA

INTRODUCTION: Postoperative hemodynamic deterioration among cardiac surgical patients can indicate or lead to major complications, associated with increased healthcare costs and mortality.[1,2] Data science techniques, leveraging high-fidelity intensive care unit (ICU) data, may recognize subclinical digital signatures of deterioration prior to overt manifestations, and through improved early detection may enable more timely life-saving interventions.[3] We sought to evaluate the performance of machine-learning models for predicting postoperative deterioration after cardiac surgery using multiparameter electronic health record (EHR) and ICU waveform data.

METHODS: Postoperative ICU data following elective adult cardiac surgical procedures at an academic quaternary care center between 2013 and 2017 were reviewed. Features used for prediction modelling included discrete EHR features (patient demographics, comorbidities, lab values, medications, ventilator settings, nursing flowsheet vital signs) and processed physiologic waveform features from electrocardiogram, pulse plethysmography, and arterial catheter monitoring. Tensor decomposition was used for waveform feature reduction (Figure 1). Machine learning models (concave/convex kernels, support vector machines, random forest, and naive Bayes) were used to predict a postoperative deterioration event target output (Figure 2). Postoperative deterioration events were defined as a composite of low cardiac index (<2.0 L/min/m2), sustained hypotension (mean arterial pressure 120 minutes), new or escalated (>2-fold increase) inotrope or vasopressor infusion, epinephrine bolus (>10 mcg), or mortality, and were adjudicated by a panel of clinician experts. Prediction models analyzed data with a temporal gap of 8 hours prior to events (primary analysis) as well as gaps ranging from 1-12 hours (sensitivity analyses). Training, cross-validation, and testing datasets were used with parameter tuning. Discrimination was assessed using receiver operating characteristic area under the curve (AUC) on the test set, as well as precision (positive predictive value), recall (sensitivity), specificity, and F1 score (harmonic mean of sensitivity and positive predictive value).

RESULTS: Among 1,258 cases, 103 (8.2%) patients experienced 153 postoperative deterioration events (Table 1). Most common deterioration events were low cardiac index (52%), sustained hypotension (12%), and vasopressor infusion escalation (10%, Table 2). Feature extraction yielded 320 discrete EHR features and 5,150 waveform features. Via tensor decomposition, waveform features were reduced to 430 features on average. Following model training and hyperparameter tuning, the concave/convex kernels model yielded the highest 8-hour predictive performance for deterioration events on the test set (0.884, standard deviation 0.030), followed by random forest (0.875, 0.026), support vector machines (0.823, 0.044), and naive Bayes (0.738, 0.050), Table 3.

CONCLUSION: Machine learning-based approaches of complex ICU data to predict clinical deterioration following cardiac surgery are feasible and demonstrate clinically useful levels of performance. Future studies are needed to evaluate the generalizability of our findings to multiple centers, and the suitability for deployment directly into the electronic health record, available for clinician use at the point of care.[4]

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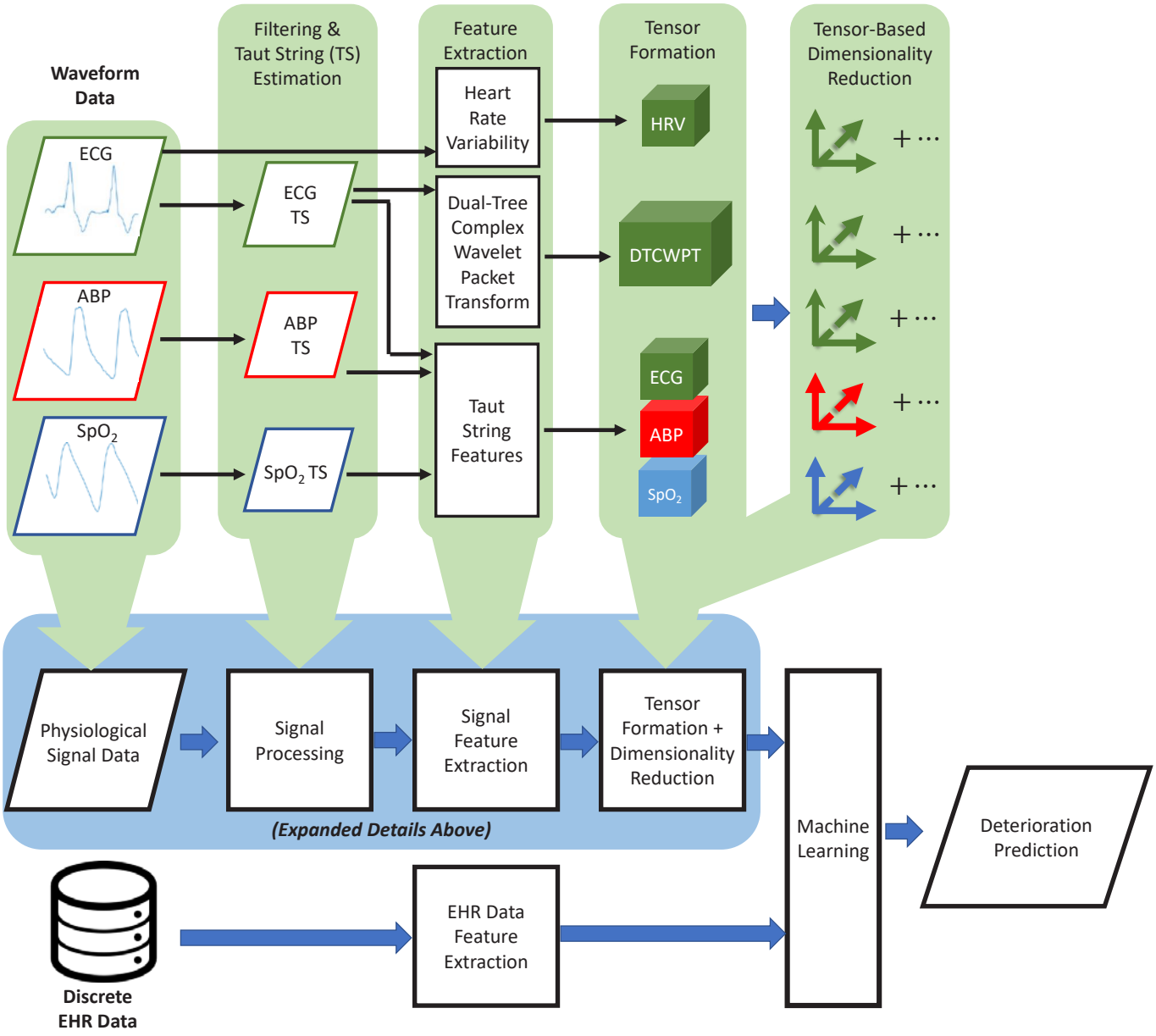

Figure 1 - Data Pipeline: Overview of waveform and discrete EHR data conditioning, featurization, and tensor decomposition

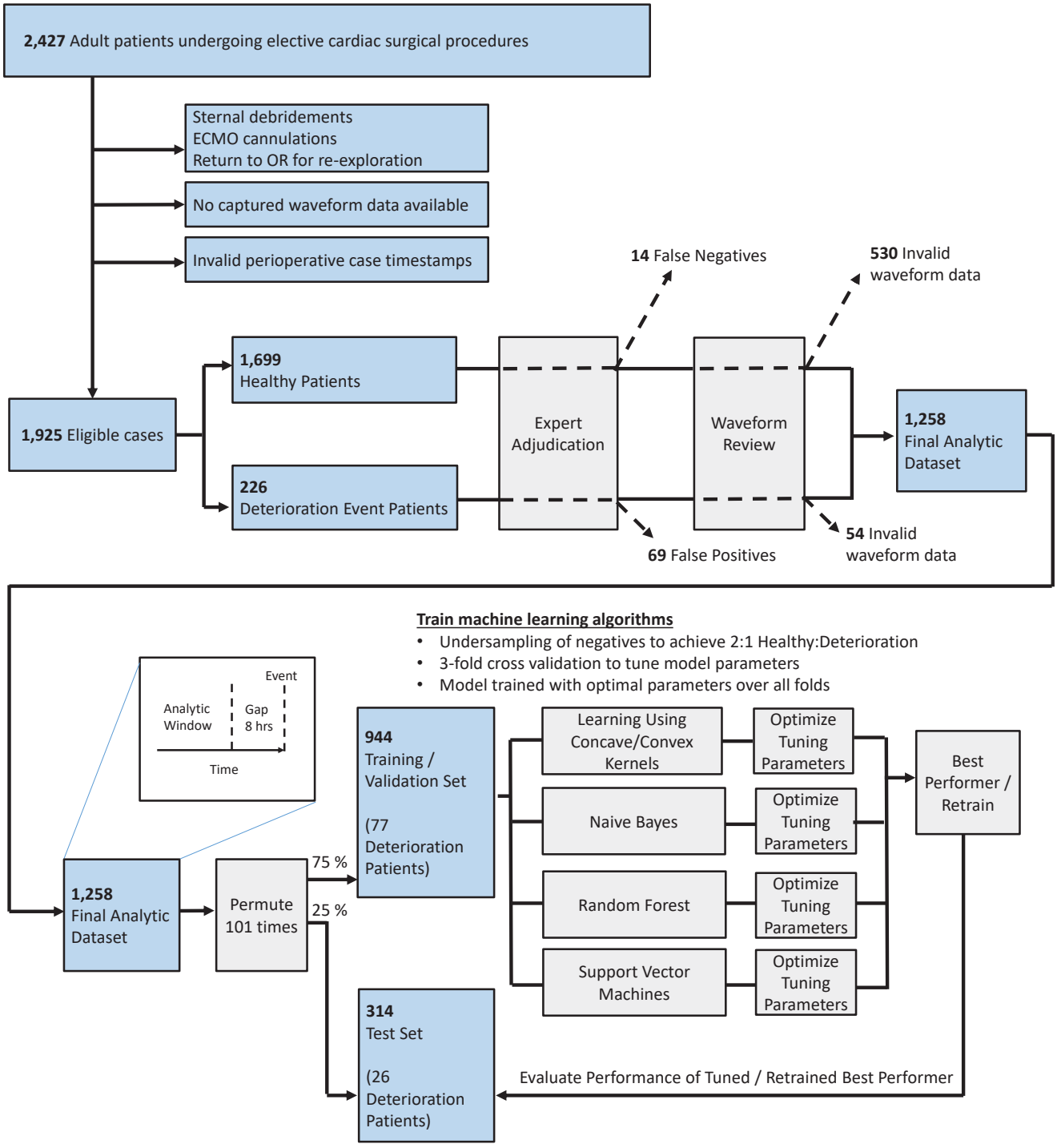

Figure 2: Study inclusion and exclusion criteria, expert adjudication, development of feature analysis time window / temporal gap, and machine learning model training/validation and testing

Table 1 - *Selected* Characteristics For Entire Cohort, Healthy Controls, and Deterioration Event Patients (Abbreviated Table)

Category	Feature	Entire Cohort N =1,258 n(%) or median (IQR)			
			Healthy Controls n = 1,155 n (%) or median (IQR)	Deterioration Event Patients, n = 103 n (%) or median (IQR)	p-Value
Demographic / Anthropometric Data	Age, years	67.0 [58.0 - 75.0]	67.0 [58.0 - 74.0]	69.0 [62.0 - 78.0]	0.230
	Male Gender	778 (61.8%)	665 (66.3%)	113 (44.3%)	<0.001
	Race Caucasian	1103 (87.7%)	885 (88.2%)	218 (85.5%)	0.350
	Other	18 (1.4%)	16 (1.6%)	2 (0.8%)	
	Unknown	19 (1.5%)	13 (1.3%)	6 (2.4%)	
	African American	85 (6.8%)	65 (6.5%)	20 (7.8%)	
	Asian	23 (1.8%)	16 (1.6%)	7 (2.7%)	
	Patient Refused	6 (0.5%)	6 (0.6%)	0 (0.0%)	
	American Indian / Alaskan Native	2 (0.2%)	2 (0.2%)	0 (0.0%)	
Patient Medical History	Congestive Heart Failure	472 (37.5%)	325 (32.4%)	147 (57.6%)	<0.001
	Cardiac Arrhythmias	643 (51.1%)	489 (48.8%)	154 (60.4%)	<0.001
	Valvular Disease	1119 (89.0%)	896 (89.3%)	223 (87.5%)	0.392
	Pulmonary Circulation Disorders	286 (22.7%)	180 (17.9%)	106 (41.6%)	<0.001
	Peripheral Vascular Disorders	611 (48.6%)	503 (50.1%)	108 (42.4%)	0.026
	Hypertension, Complicated	77 (6.1%)	50 (5.0%)	27 (10.6%)	<0.001
	Paralysis / Other Neurological Disorders	14 (1.1%)	8 (0.8%)	6 (2.4%)	0.035
	Chronic Pulmonary Disease	448 (35.6%)	319 (31.8%)	129 (50.6%)	<0.001
	Diabetes, Complicated	46 (3.7%)	42 (4.2%)	4 (1.6%)	0.047
	Liver Disease	116 (9.2%)	91 (9.1%)	25 (9.8%)	0.719
	Coagulopathy	164 (13.0%)	116 (11.6%)	48 (18.8%)	0.002
Selected Postoperative Data	SpO2, %	97.0 [95.0 - 99.0]	97.0 [95.0 - 99.0]	96.0 [95.0 - 98.0]	0.812
	Temperature, Celsius	36.9 [36.5 - 37.2]	36.9 [36.6 - 37.2]	36.9 [36.5 - 37.3]	0.393
	Median hourly urine output, mL	21.9 [0.0 - 50.0]	25.0 [0.0 - 60.0]	15.0 [0.0 - 40.0]	0.790
	Intubated at 24 hours	368 (29.3%)	250 (24.9%)	118 (46.3%)	<0.001
	FiO2 at 24 hours if intubated, %	21.0 [21.0 - 40.0]	21.0 [21.0 - 40.0]	30.0 [21.0 - 40.0]	0.520
	PEEP at 24 hours if intubated, cm H2O	0.0 [0.0 - 5.0]	0.0 [0.0 - 5.0]	5.0 [0.0 - 5.0]	0.340

Table 2 - Postoperative Deterioration Event Summary

	Deterioration Event Time				
	All Event Times, n (%)	24-48 hours postoperative, n (%)	48-96 hours postoperative, n (%)	96 hours - 7 days postoperative, n (X)	>7 days postoperative, n (%)
All Deterioration Events	**153 (100%)**	82 (100%)	34 (100%)	16 (100%)	21 (100%)
Mortality	4 (3%)	1 (1%)	0 (0%)	1 (6%)	2 (10%)
Cardiac Index <2.0 L/min/m^2	79 (52%)	58 (71%)	15 (44%)	6 (38%)	0 (0%)
Mean Arterial Pressure <55 mmHg for >120 minutes	18 (12%)	5 (6%)	6 (18%)	2 (13%)	5 (24%)
Epinephrine bolus >10 mcg	5 (3%)	2 (2%)	3 (9%)	0 (0%)	0 (0%)
Inotrope Infusion Initiated	14 (9%)	7 (9%)	3 (9%)	1 (6%)	3 (14%)
Inotrope Infusion Escalated ≥100%	9 (6%)	3 (4%)	1 (3%)	1 (6%)	4 (19%)
Vasopressor Infusion Initiated	9 (6%)	4 (5%)	2 (6%)	1 (6%)	2 (10%)
Vasopressor Infusion Escalated ≥100%	15 (10%)	2 (2%)	4 (12%)	4 (25%)	5 (24%)

Table 3 - Performance of Optimized Postoperative Deterioration Prediction Models Using 8-Hour Gap for Prediction Window, Test Set

Prediction Model	**AUC (±SD)**	**F1 Score (±SD)**	**Precision (±SD)**	**Recall (±SD)**	**Specificity (±SD)**
Learning Using Concave & Convex Kernels	0.884 ± 0.030	0.501 ± 0.072	0.518 ± 0.103	0.520 ± 0.103	0.959 ± 0.031
Random Forest	0.875 ± 0.026	0.487 ± 0.060	0.484 ± 0.101	0.522 ± 0.115	0.957 ± 0.023
Support Vector Machines	0.829 ± 0.044	0.425 ± 0.072	0.375 ± 0.101	0.530 ± 0.105	0.930 ± 0.038
Naive Bayes	0.738 ± 0.050	0.297 ± 0.049	0.205 ± 0.045	0.574 ± 0.096	0.834 ± 0.064

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 5

Efficacy of COVID-19 specific simulation training in improving intubator's experience during intubation of COVID-19 patients

Esther Lee[1], Reem Q Al Shabeeb[2], Muhammad El Shatanofy[2], Collin F Mulcahy[2], Ivy Benjenk[2], David Yamane[3], Eric Heinz[4], Marian Sherman[5]

[1]George Washington University Medical Faculty Associates, Washington, DC, [2]The George Washington University School of Medicine & Health Sciences, Washington, DC, [3]George Washington University Hospital, Washington, DC, [4]The George Washington University, Washington DC, United States of America, [5]The George Washington University Hospital, Washington, DC

INTRODUCTION: Since the start of the pandemic, approximately 3.2% of patients with COVID-19 required intubation and mechanical ventilation at some point during their treatment course[1]. Intubators are at particular risk of infection due to the aerosol-generating nature of the procedure. Simulation training (ST) offers an opportunity for trainees to enhance knowledge and skills in airway management[2,3] and has been used as a training tool to prepare health providers for airway management of COVID-19 patients. The purpose of this study is to explore the demographics of providers participating in COVID-19 specific ST and the efficacy of ST in improving provider experience during the intubation of COVID-19 patients.

METHODS: In this multicenter cross-sectional national study, electronic surveys were disseminated using a snowball sample approach to intubators from 32 hospitals between 9/2020 and 12/2020. Surveys were pilot tested for reliability. The survey assessed providers' comfort of intubating and fear of contracting COVID-19 during COVID-19 intubations using 1-10 scale. Various demographic and exposure factors were also collected. Simulation training group (ST) and no simulation training group (non-ST) were compared using the Mann-Whitney U test, Fisher's exact test, and Chi-square test of homogeneity. Statistical significance was declared at $p<0.05$.

RESULTS: A total of 186 surveys from 32 hospitals were analyzed after excluding surveys that reported no experiences with COVID-19 intubations. From 32 hospitals, 28 hospitals (87.5%) had providers participating in ST. Within those hospitals, the attendance of ST ranged from 44.4% to 100.0%. From 186 providers, 62 providers (33.3%) reported participating in a ST. Of those, 45 (72.6%) of them reported that the ST helped reduce their fear of intubating COVID-19 patients. More women participated in the ST compared to men (n=36, 58.1% vs. n= 26, 41.9%; p=0.049). There was no difference in the number of COVID-19 intubations and COVID-19 exposure factors between the two groups. Providers in the ST group reported a higher level of comfort level with intubating COVID-19 patients than providers in the non-ST group (median=9, IQR= 3-10 vs. 8, 1-10; p=0.021).

CONCLUSION: Our study demonstrated that COVID-19 specific intubation simulation training improved providers' comfort level during COVID-19 intubations. Moreover, the majority of providers reported reduction in fear of intubating COVID-19 patients after participating in a simulation training. Simulation training on intubation may be implemented as part of airway management training for health care providers during the COVID-19 pandemic as well as in novel pandemic situations to help providers' comfort and fear. Additional studies with a larger sample size from diverse institutions are recommended to explore the efficacy of the simulation training.

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TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 6

Utilization of wearable pedometer devices in the perioperative period: A systematic review

Zhaosheng Jin[1], Christopher Lee[1], Kalissa Zhang[1], Deborah C Richman[1]

[1]Stony Brook Medicine, Stony Brook, NY

INTRODUCTION: A pedometer is an electromechanical device used to count the number of steps taken in a given time. With the advances in mobile technology, pedometers are now integrated in a wide range of wearable devices. Daily step counts could be used to infer a patient's functional capacity, which is vital in the assessment of both perioperative risks and postoperative functional recovery. We therefore conducted this systematic review to summarize the clinical evidence on the perioperative use of wearable pedometer devices.

METHODS: We systematically searched PubMed, identifying clinical studies which evaluated the perioperative use of wearable pedometers. Prospective studies of patients who underwent surgery with general or regional anesthesia, with the use of wearable pedometer devices in the perioperative period (30 days prior to surgery to 30 days after surgery) were included. The primary outcome is feasibility of use in a clinical setting, the secondary outcome is whether step count data could be used to predict perioperative outcomes (such as complications or postoperative recovery).

RESULTS: We identified a total of 30 studies for inclusion, of which 21 studies used pedometer devices in the preoperative setting, and 24 studies used the pedometers in the postoperative setting. Studies were conducted in the setting of various orthopedic, abdominal and pelvic surgeries, including thirteen studies on patients undergoing cancer surgeries. Pedometer data was collected and transmitted reliably in the clinical setting with minimal data loss. Preoperative pedometer data has been used to estimate baseline functional capacity, and appear to correlate with VO2max through formal CPET testing[1]. Preoperative pedometer may be predictive of postoperative complications and hospital length of stay[2,3]. Postoperative pedometer data could be used to monitor functional recovery, predict risks of readmission and complications[4-7].

CONCLUSION: There is now extensive literature supporting the feasibility of wearable pedometer use in the perioperative setting. There is additional evidence suggesting that perioperative pedometer data could be used to predict postoperative outcomes. Objective data regarding preoperative functional capacity has been lacking. In the wake of the COVID-19 pandemic, healthcare infrastructure has undergone drastic changes in favor of virtual clinical interaction. This will further impact objective assessments of patients presenting for surgeries. A wearable pedometer device could be invaluable tool for increasing accuracy of the perioperative patient assessment.

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TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 7

Non-invasive assessment of the effect of noradrenalin continuous dosing on left ventricular end-systolic elastance, arterial elastance and end-diastolic volume, analyzing eight cases of bleeding

Takahiro Shiraishi[1], Yukiko Suzuki[2], Mitsuyo Hayabuchi[2], Yoshiaki Taniai[3], Satoshi Matsuoka[4], Kenji Shigemi[2]

[1]Fukui Saiseikai Hospital, Fukui, Japan, [2]University of Fukui Hospital, Fukui, Japan, [3]Department of Human and Artificial Intelligent Systems, University of Fukui, Fukui, Japan, [4]Department of Integrative and Systems Physiology, Faculty of Medical Sciences, University of Fukui, Fukui, Japan

INTRODUCTION: The changes in stroke volume (SV) and systemic vascular resistance (SVR) in response to vasopressors are well known. However, it is unclear that the effect of the vasopressors on left ventricular end-systolic elastance (Ees), atrial elastance (Ea), and left ventricular end-diastolic volume (Ved). The present study aimed to assess the changes in Ees, Ea, Ved associated with noradrenalin continuous dosing in several cases of bleeding.

METHODS: This is a pilot retrospective observational study. We enrolled patients who underwent non-cardiac surgeries with clinical indication of radial arterial blood pressure. We recorded electrocardiogram, radial arterial waveform, and phonocardiogram. Then we measured the pre-ejection period (PEP), ejection time (ET), end-systolic pressure (Pes), and diastolic pressure (Pd) using a computer-automated technique. We calculated the ventricular aortic coupling (Ees/Ea) using PEP, ET, Pes, and Pd as described previously[1]. Furthermore, we calculated Ees and Ea separately, and Ved with SV obtained from FloTrac sensor®(Edwards Lifesciences, CA, USA). We extracted those variables as well as heart rate (HR), and mean arterial pressure (MAP) at 2 points, 1 minute before increasing (or decreasing) noradrenalin continuous dosing and 5 minutes after the conversion. Noradrenalin dose was up to 0.5 Mg/kg/min. We used paired t-test to compare pre and post those variables as stated before. We standardized Ea, Ees, and Ved using body surface area(BSA). We calculated BSA with Du bois formula[2]. Statistical significance was set at $p<0.05$.

RESULTS: We analyzed 8 bleeding cases using noradrenalin for keeping the blood pressure. In 4 cases, which we increased the continuous dose of noradrenalin, MAP, and Ea×BSA increased significantly from 66±5.0 to 90±15 mmHg, $p<0.05$; from 2.3±0.3 to 2.9±0.3 mL×m^2/mmHg, $p<0.05$, respectively. On the other hand, we observed no significant changes in HR, Ees×BSA and Ved/BSA (from 83±10 to 85±8.0 bpm, $p=0.24$, 3.8±2.0 to 5.7±3.2 mL×m^2/mmHg, $p=0.11$; from 50±9.1 to 53±11 mL/m^2, $p=0.15$, respectively). In another 4 cases, which we decreased the continuous dose of noradrenalin, MAP, Ea×BSA, and Ees×BSA decreased significantly from 94±10 to 82±4.6 mmHg, $p<0.05$; from 2.4±0.5 to 2.0±0.4 mL×m^2/mmHg, $p<0.05$; from 4.4±1.1 to 2.6±0.6 mL×m^2/mmHg, $p<0.05$, respectively. Ved/BSA increased significantly from 65±7.3 to 74±6.1 mL/m^2, $p<0.05$. There were no significant changes in HR (from 82±6.5 to 79±7.0 bpm, $p=0.27$).

CONCLUSION: Our method enabled further assessment of the effects of continuous noradrenalin dosing. Noradrenalin elevates blood pressure by increasing left ventricular afterload. Our results are consistent with the action mechanism proposed previously.

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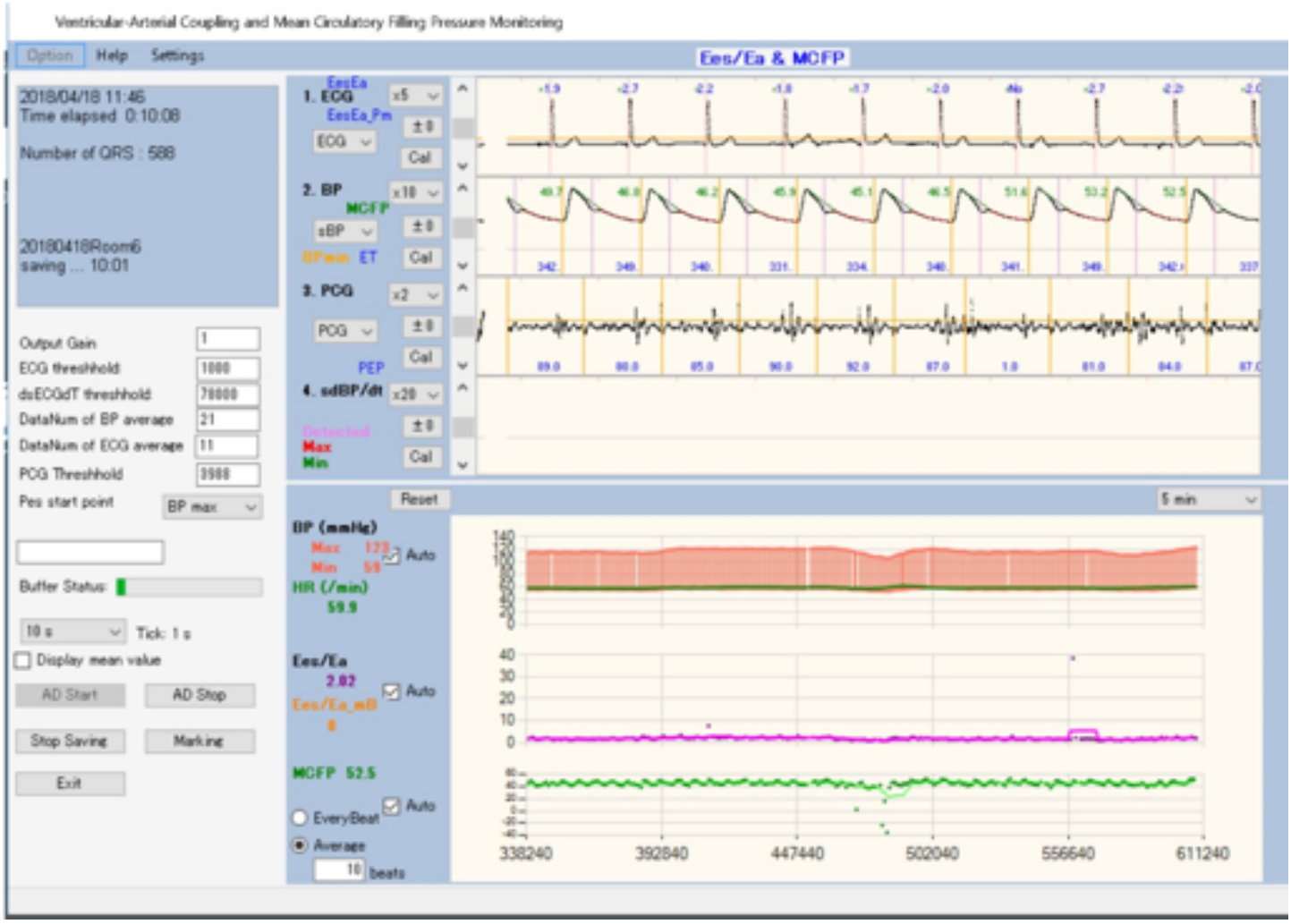

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 8

Comparison of Supervised Machine Learning Techniques for Prediction of Blood Products Transfusion after High Risk Cardiac Surgery

Ryan L Melvin[1], Luz A Padilla[1], Domagoj Mladinov[1], Dan Berkowitz[1]

[1]University of Alabama at Birmingham, Birmingham, AL

INTRODUCTION: Cardiac surgeries carry a significant risk for requiring allogeneic blood transfusion, which is associated with increased morbidity and mortality[1,2]. Application of machine learning and artificial intelligence (AI) to large clinical data sets may be of great clinical value in enhancing clinical prognostic and therapeutic abilities[3]. In this study we hypothesize that machine learning techniques can be used to identify risk factors and predict incidence of allogeneic blood transfusion based on preoperative and intraoperative data, in high-risk cardiac surgeries. Additionally, we compared the ability to predict blood transfusion among several supervised machine learning algorithms.

METHODS: A cross-sectional study with data from 313 patients who underwent high risk cardiac surgery (repeat sternotomies, thoracic aortic repairs, multiple valve repairs, coronary bypass grafts, either alone or in combination on cardiopulmonary bypass (CPB)) during 2019-2020 was created. Exclusion criteria were hemodynamic instability, severely reduced left ventricular function, and hematocrit <30%. The database contained demographic, medical history, transfusion, laboratory and surgical data. The five supervised learning techniques we used were logistic regression, support-vector machines (SVM), classification trees, random forests, and extreme gradient boosting (XGBoost). For logistic regression, two different variable selection techniques were assessed: (1) variables with $p<0.05$ in single-variable selection in a multi-variable regression model, and (2) a forward-backward stepwise regression model. Each machine learning model's hyperparameters were tuned using an exhaustive grid search with quality judged by the accuracy score (ACC) from leave-one-out cross-validation (LOO-CV) out-of-sample predictions. Final model forms were evaluated and compared on their ability to predict allogenic blood transfusion using accuracy (ACC), area under the receiver operating characteristic curve (AUC), and balanced F-score based on the out-of-sample predictions of each round of LOO-CV.

RESULTS: By both ACC (0.757) and F-score (0.797), the best-performing model for predicting allogeneic blood transfusion using preoperative and intraoperative data was an XGBoost model. Averaging feature importance across all rounds of LOO-CV for the XGBoost model indicates that the most important features for predicting the need for allogeneic blood transfusion were: patient's weight, EuroSCORE, INR after separation from CPB, need for circulatory arrest, and use of acute normovolemic hemodilution (ANH). By AUC (0.815) the best performing model was a multi-variable logistic regression using variables with $p<0.05$ in single-variable logistic regression models (Figure 1). The significant ($p<0.05$) variables in the final logistic regression model were: INR and platelet count after separation from CPB, need for circulatory arrest, and use of ANH (negative predictor).

CONCLUSION: Important risk factors for allogenic blood transfusion in patient who underwent high risk cardiac surgery, that were consistently present in the highest scoring models were INR after separation from CPB, need for circulatory arrest and utilization of ANH (negative predictor). Logistic regression and XGBoost held the best predictive ability across techniques, depending on the quality metric used. This study informs the selection of machine learning and statistical techniques for prediction of allogeneic blood utilization.

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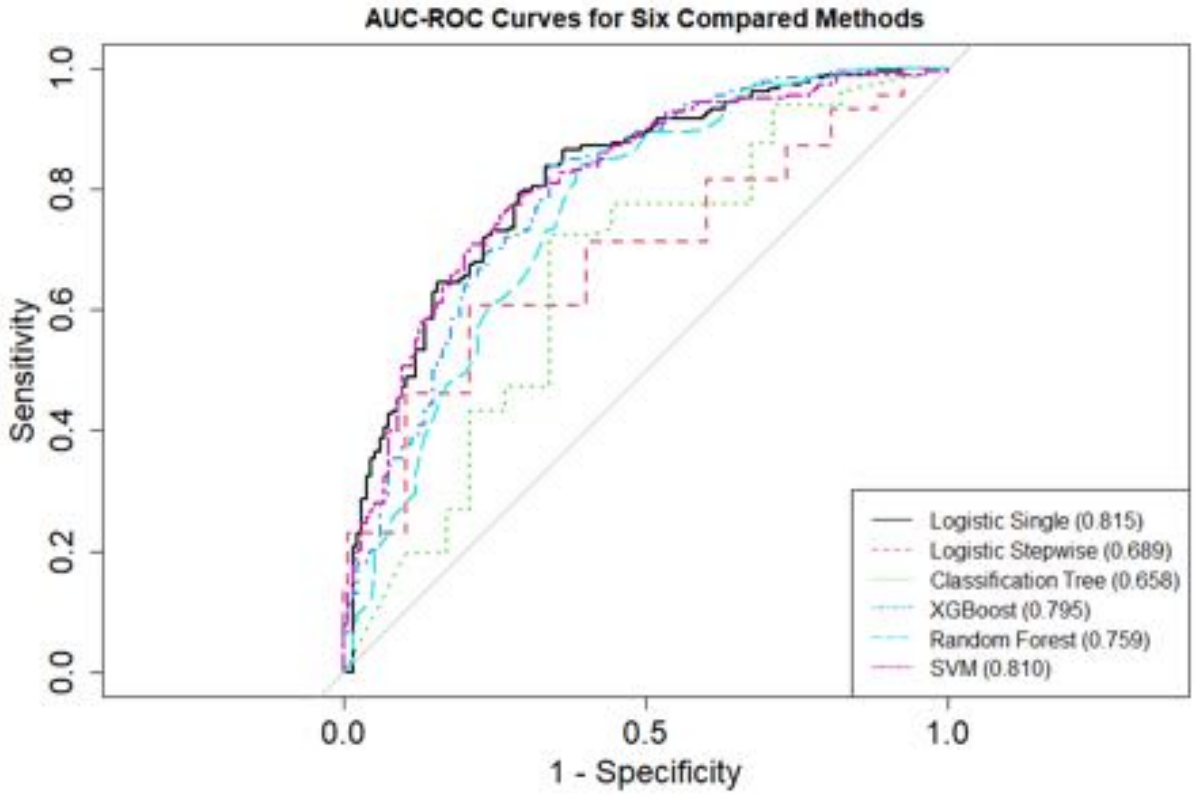

Figure 1: Receiver operating characteristic (ROC) curves are shown for the final model of each of the 6 assessed techniques and the corresponding areas under curve (AUCs) are presented in the figure legend. By AUC (0.815), the best performing model was a multi-variable logistic regression using variables with $p<0.05$ in single-variable logistic regression models.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 9

Remote Surveillance to Detect Early Physiologic Abnormalities Associated with Readmission to the Surgical ICU

Johanna Rajotte[1], Katarina Ruscic[1], Jeanine P Wiener-Kronish[1], Kyan C Safavi[1]

[1]Massachusetts General Hospital, Boston, MA

INTRODUCTION: For a patient to be transferred out of the SICU, both the surgery and critical care teams have assessed that it is of no medical harm to the patient to relocate to the general care unit. Though ICU-level monitoring has been deemed unnecessary, a subset of patients will be readmitted to the ICU. Recognition of patients starting to decompensate on the wards is a critical step towards intervening at the appropriate time to prevent readmission to the ICU. If early markers of decompensation were present in the electronic health record (EHR), they could be identified by a remote surveillance system to alert clinicians in real-time of declining patients warranting attention, thus potentially preventing an ICU readmission. We hypothesized that the presence of any of a predefined cadre of vital sign or laboratory abnormalities, such as tachycardia, desaturation, low hemoglobin, hypo or hyperglycemia, or hyperkalemia preceded readmission to the ICU.

METHODS: In this single-center prospective observational study conducted at a large academic hospital in Boston, a remote surveillance system was designed to extract patient data in real-time via their EHR. This study was performed over a period of 18 months between May 31, 2017 to December 26, 2018. There were 432 transfers out of the ICU with 350 unique patients and 363 unique surgical encounters followed in that time period. Alerts were predefined as any of the following: tachycardia (heart rate > 130 bpm), hypotension (systolic blood pressure < 80 mm Hg), hypoxemia (SpO2 < 88%), hyperkalemia (potassium > 6 mmol/L), hyperglycemia (glucose > 350 mg/dL), hypoglycemia (glucose < 60 mg/dL), anemia (hemoglobin < 7 g/dL or hematocrit < 21%). The primary outcome measured was readmission to the ICU. The data was analyzed (STATA, Version 13) to determine potential patterns of physiologic abnormalities within the population of patients that were transferred out of the SICU to the general care unit using descriptive statistics. Clopper-Pearson confidence intervals were used for sensitivity and specificity. Chart review was utilized to investigate the events surrounding readmission for cases not triggering alerts. In this pilot study, alerts were sent to an electronic database and were not paged out to clinicians for intervention.

RESULTS: Of 432 transfer events, 66 (15.3%) were readmitted to the ICU. Of the 66 readmitted transfers, 40 triggered alerts while on the floor. The sensitivity of triggering any alert for readmission was 60.6 [95% CI 47.8 – 72.4] %, while the specificity was 11.2 [95% CI 8.2 – 14.9] %. Individual alerts were relatively specific, but less sensitive. For example, tachycardia, the most prevalent type of alert in the dataset, was 71.9 [95% CI 67.0 – 76.4] % specific, but only 30.3 [95% CI 19.6 – 42.9] % sensitive for readmission. Surprisingly, hypoglycemia had zero sensitivity for readmission. The frequency, sensitivity and specificity of each alert is presented in Table 1. Figure 1 shows a scatter plot of the time an alert was triggered after transfer from the ICU, and readmission time. We repeated analysis on the subset of alerts that were within 24 hours of readmission, regardless of how long ago the patient initially left the ICU and found that tachycardia was again the most common abnormality captured by the alert system (42.1%). Detailed chart review of the 26 patients who failed to produce an alert prior to ICU readmission revealed abnormalities within several hours of readmission uncaptured by the alert system including rising creatinine (2 patients), rising white blood cell count (5 patients), positive urinalysis (2 patients), positive blood culture (2 patients), elevated respiratory rate >= 40 breaths/minute (2 patients), fever (6 patients) and combinations of alert abnormalities at sub-threshold values (7 patients). Several scenarios had no overt vital sign or laboratory abnormalities in the EHR despite acute events.

CONCLUSION: We chose predetermined vital sign and laboratory abnormalities that, based on clinical intuition, we believed would be harbingers of decompensation leading to readmission. Perhaps not surprisingly, trigger of any of these wide-ranging variables was not very specific for readmission, but was 60.6% sensitive. This hypothesis-generating work revealed that combinations of sub-threshold alert values, leukocytosis, acute kidney injury, positive urinalysis or positive blood culture should be explored as potential alerts for remote surveillance in a future study.

Table 1: Alert Frequency, Sensitivity and Specificity

Alert Type	Threshold	Frequency	Sensitivity (95% CI)	Specificity (95% CI)
Tachycardia	HR > 130 BPM	366 (38.6 %)	30.3 [19.6 - 42.9] %	71.9 [67.0 - 76.4] %
Hypotension	SBP < 80 mm Hg	60 (6.3 %)	15.2 [7.51 - 26.1] %	91.5 [88.2 - 94.2] %
Hypoxemia	SpO2 < 88%	111 (11.7 %)	15.2 [7.51 - 26.1] %	82.0 [77.6 - 85.8] %
Hyperkalemia	K > 6 mmol/L	46 (4.9 %)	4.55 [0.95 - 12.7] %	92.3 [89.1 - 94.9] %
Hyperglycemia	gluc > 350 mg/dL	73 (7.7 %)	15.2 [7.51 - 26.1] %	88.0 [84.2 - 91.1] %
Hypoglycemia	gluc < 60 mg/dL	10 (1.1 %)	0.00 [0.00 - 5.44] %	97.8 [95.7 - 99.1] %
Anemia: Hgb	Hgb < 7 g/dL	201 (21.2 %)	12.1 [5.38 - 22.5] %	73.0 [68.1 - 77.4] %
Hct	Hct < 21%	80 (8.4 %)	9.10 [3.41 - 18.7] %	88.8 [85.1 - 91.8] %

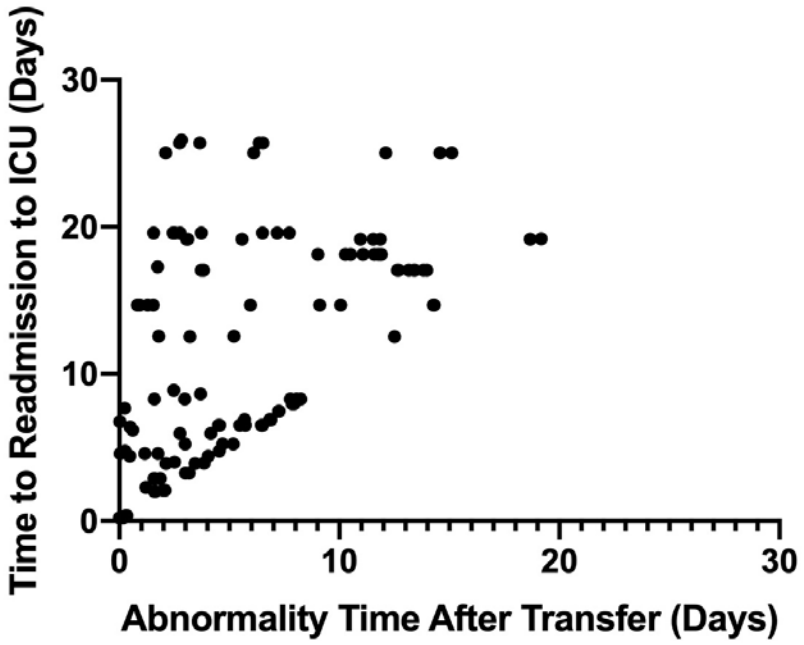

Fig. 1

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 10

A Prospective, Single Center Study of the Effects of Modulating Music in the Operating Room

Olivia Henry[1], Alexandra Bruder[2], Christy Crockett[3], Joseph Schlesinger[4], Joshua Shive[5]

[1]Vanderbilt University School of Medicine, Nashville, TN, [2]Vanderbilt University, Nashville, TN, [3]Vanderbilt University Medical Center, Nashville, TN, [4]Vanderbilt Univeristy Medical Center, Nashville, TN, [5]Tennessee State University, Nashville, TN

INTRODUCTION: Music is played in about 53-72% of surgical operations performed in the operating room (OR). Studies on music in the OR have resulted in mixed data on the potential benefits and harms (Weldon et al., 2015). While music is thought to have a calming effect in some cases, it can impair vital communication between staff members. Several studies have found music during procedures to be a cause of distraction and lowered performance, particularly in training (Miskovic et al., 2008). Weldon et al. analyzed video recordings of operating rooms and found that almost 2% of requests were repeated between the operating team when music was playing, in contrast to only 0.3% when music was absent. In a survey of 200 anesthesiologists, 51% felt music was distracting when a problem was encountered during the surgery, 25% felt that music reduced their vigilance and impaired their communication, and 11.5% felt the music might interfere with attention to alarms (Hawksworth et al., 1997). The effect of modulating music volume during critical times of surgery, however, has not been quantitatively researched as a possible opportunity to lessen the negative impact of music during surgery. We are testing a music volume controller that integrates operating room music with vital sign data from the anesthesia monitor. Using the CanaryBox (CB), background music volumes are reduced or silenced based on flexible algorithms for heart rate, oxygen saturation or blood pressure.

METHODS: This study examines whether clinician performance is improved with the reduction of music volume during critical alarm events. We are collecting data from 100 surgical cases: 50 intervention and 50 control. Data is collected throughout each case by having anesthesia providers press a button on a keypad each time they recognize an alarm as true or false. A study coordinator provides training for each anesthesia provider. In addition, the study coordinator, who is not involved in providing care, is present in the OR during the case and uses a laptop to record the approximate time that each alarm occurs, as well as the qualitative details about the alarm. Throughout the intervention case, the CB lowers music by one-half or shuts the music off depending on the patient's vitals. The CB also records exact time stamps of the alarm, which are compared with the anesthesia provider's button presses and the study coordinator's recordings of the alarm details using a script written in MATLAB. Anesthesia providers also complete post-procedure surveys designed to measure whether in-room anesthesia providers find the volume adjusting device to be useful and beneficial.

RESULTS: We qualitatively analyzed preliminary data to assess the impact of the CB. After implementing the music modulating device in 30 procedures, we surveyed anesthesiologists and operating room personnel and found that 29 of 30 participants would use the controller again, and 27 of 30 rated the device as working well. We expect to complete our quantitative data collection by March 2021. We hypothesize that anesthesia providers will be able to detect important alarms more quickly and accurately when the background music is reduced during critical events. Response time will be measured as the latency between when the vitals monitor triggers an alarm and when the anesthesia provider responds to the alarm, measured in milliseconds. The study coordinator response data allows us to see the difference is response time with reduced cognitive load. The effects of intervention on the average response time will be assessed using a t-test that compares mean response times of the intervention and exposure group. Random intercept indexed by study participant will be used to account for the fact that one provider may participate in the study up to three times. Intervention effects will be estimated with Wald-type 95% confidence interval and tested using a Wald-type test.

CONCLUSION: Information gathered in this study will advance our understanding of how music volume affects anesthesia provider reaction times, which may benefit both surgeons and anesthesia providers in the future. The survey will help the experimenters understand the potential quantitative and qualitative benefits and drawbacks to the utilization of the music volume reduction device. The study not only assesses whether or not response times are improved with music modulation but also creates a new paradigm for assessing reaction times of anesthesia providers in the OR setting.

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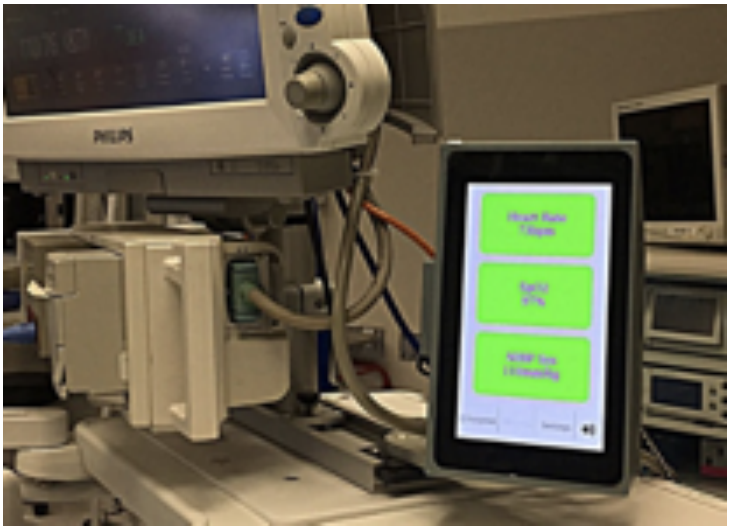
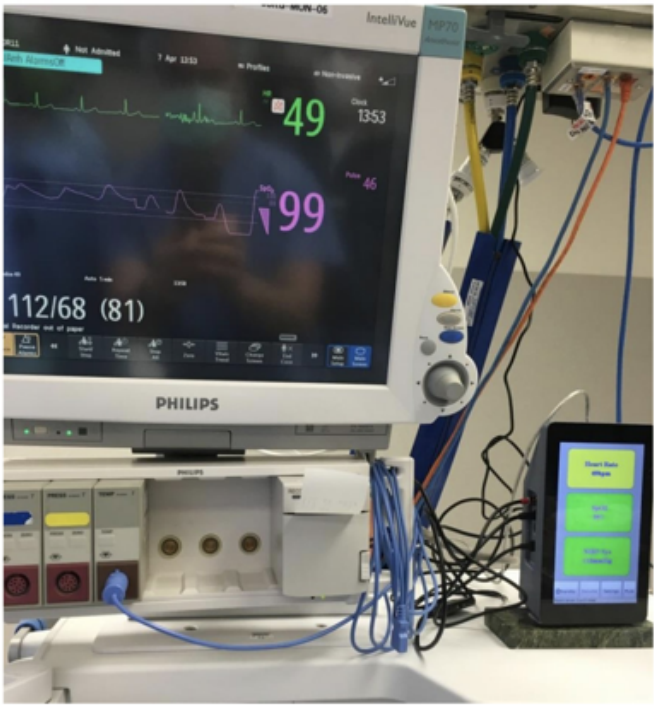


Pic. 1 – CanaryBox

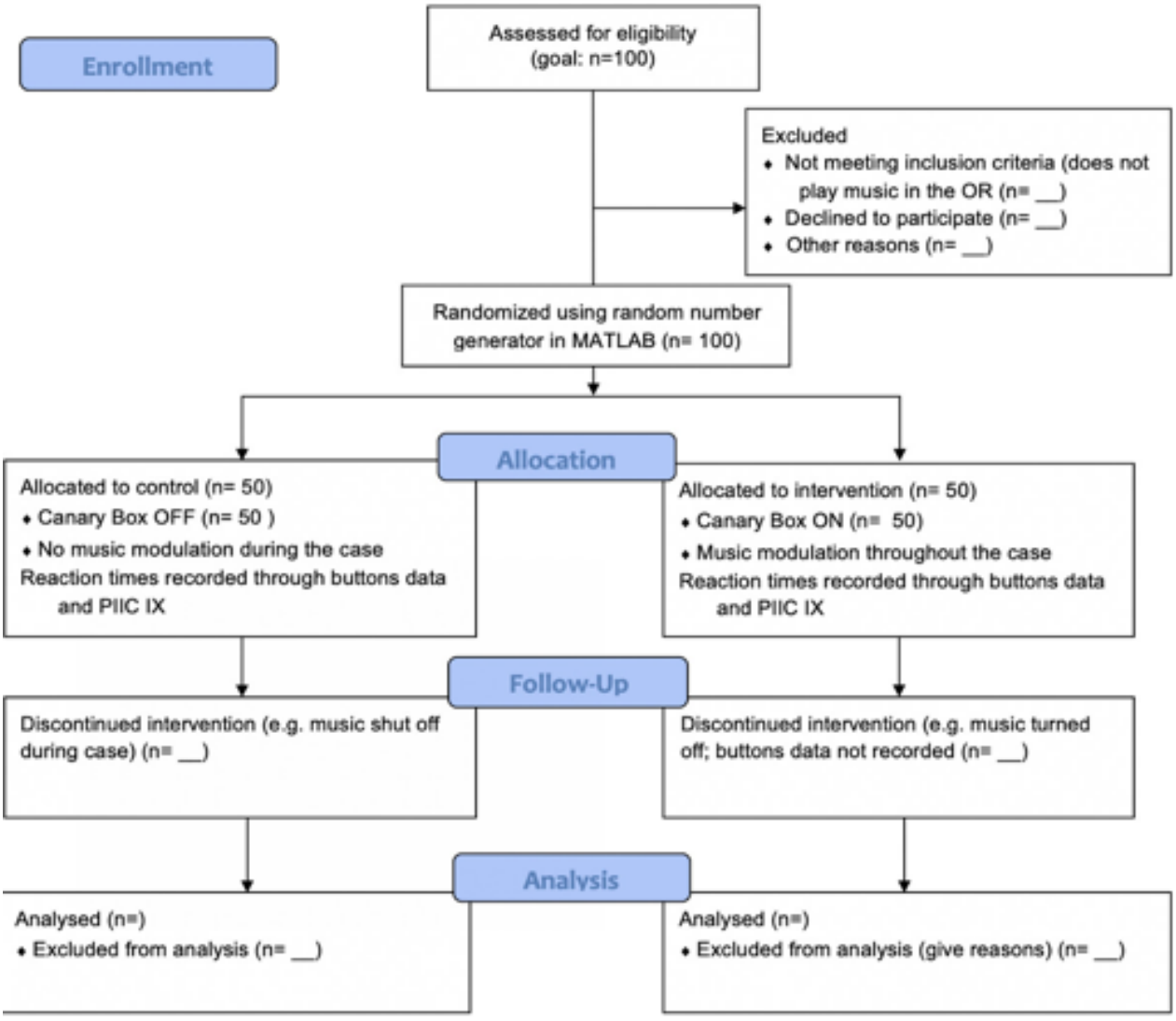


Pic. 2 – CanaryBox Setup Vitals

Example Settings

	Full volume	*Half volume*	*Music off*
Oxygen saturation (SpO_2) %	$90 \leq SpO_2$	$85 \leq SpO_2 < 90$	$SpO_2 < 85$
SpO_2 delay		20 seconds	10 seconds
Heart Rate (HR) bpm	$50 \leq HR \leq 130$	$40 \leq HR < 50$, or $130 < HR \leq 150$	$HR < 40$, or $HR > 150$
HR delay		20 seconds	10 seconds
Systolic Blood Pressure (SBP) mm Hg	$80 \leq SBP \leq 170$	$70 \leq SBP < 80$, or $170 < SBP \leq 190$	$SPB < 70$, or $SPB > 190$
SBP delay		60 seconds	30 seconds

Study Design



TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 11

Evaluation of machine learning models as decision aids for anesthesiologists

Mihir Velagapudi[1], Akira A Nair[2], Wyndam Strodtbeck[3], David N Flynn[4], Keith Howell[5], Justin S Liberman[3], Joseph D Strunk[3], Mayumi Horibe[6], Bala G Nair[7]

[1]University of California, Berkeley, CA, [2]Brown University, Providence, RI, [3]Virginia Mason Franciscan Health, Seattle, WA, [4]University of North Carolina - Chapel Hill, Chapel Hill, NC, [5]University of Florida, Gainesville, FL, [6]VA Puget Sound Health System, Seattle, United States of America, [7]University of Washington, Seattle, Washington

INTRODUCTION: The development of machine learning (ML) models to predict perioperative clinical events has become increasingly popular recently.[1] To realize clinical benefit, these models must serve as decision aids for anesthesia providers, facilitating proactive clinical planning. Yet, validation of these models has been limited thus far, with the focus primarily on performance assessment using electronic medical record data. It is unclear how effective these models are in providing decision support to anesthesia providers. We have previously developed and validated ML models for predicting peak glucose levels during surgery and postoperative opioid requirements in ambulatory surgery patients.[2,3] In this study, we evaluated whether these ML models can improve anesthesiologists' preoperative estimation of peak intraoperative glucose levels and postoperative opioid requirements. These models address two very different clinical needs, enabling us to evaluate their effectiveness as decision aids in a wider context.

METHODS: Six practicing anesthesiologists from four hospitals in different states and a range of clinical experience (2-30 years) participated in this study. For each ML model, two sets of 50 unique patients were randomly selected from the perioperative electronic medical record databases that were used to validate the ML models (hold out datasets that were not used for model development). A web-based evaluation tool was developed that presented the relevant patient and procedure specific data for each patient and recorded the responses of the anesthesiologists. The anesthesiologists were asked to review the clinical information and record their estimates of the peak intraoperative glucose level and postoperative opioid requirement. The peak glucose level was recorded as a numeric value while the opioid requirement was recorded as a categorical value (none, low, medium or high). For the initial set of 50 patients, the anesthesiologists made their estimates based on clinical and procedural information alone. For the second set, ML predictions were provided along with clinical and procedural information. The individual estimates made by each anesthesiologist were used to determine group estimates by taking the mean of peak glucose and the mode of the opioid estimates for each patient. The group estimates of the anesthesiologists were compared against the actual peak glucose levels and postoperative opioids with and without ML model predictions for reference. Estimation accuracies were compared using t-test for peak glucose and Fisher's exact test for postoperative opioid requirements.

RESULTS: For each ML model, the relevant patient and procedure factors for the two data sets used for evaluation were similar with no statistical difference (Chi-squared and Wilcoxon rank-sum tests, $p>0.05$). The accuracy of peak glucose level estimates increased from 76.1 ± 16.9% without ML assistance to 86.9 ± 8.6% ($p=0.0001$) when ML estimates were provided as reference. The individual anesthesiologist's estimation accuracies ranged from 66.0 ± 31.2% to 81.0 ± 16.1% without ML assistance and from 84.0 ± 15.3% to 92.5 ± 8.7% with ML assistance, with all anesthesiologists showing improvement. The ML model accuracies were similar between the two groups: 82.0 ± 15.9% for no ML assistance group and 85.6 ± 12.7% for ML assistance group ($p=0.21$). The accuracy of opioid requirement estimates increased from 10% without ML assistance to 42% ($p=0.0001$) when ML estimates were provided as reference. The individual anesthesiologist's estimation accuracies ranged from 4% to 26% without ML assistance and from 28% to 48% with ML assistance with 5 out 6 anesthesiologists showing improvement. The ML model accuracies were similar between the two groups: 56% for no ML assistance group and 60% for ML assistance group ($p=0.84$).

CONCLUSION: Machine learning models can act as decision aids to improve anesthesiologists' estimation of clinical events and requirements. Embedding these models into clinical workflow has the potential of enhancing perioperative care and outcome.

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TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 12

A Mobile App for the Precise Measurement of Healthcare Provider Activity Times to Support Time-Driven Activity Based Costing Studies

Brian Waldschmidt[1], Kyle Kellett[2], Ricardo B Cardoso[3], Ana P da Silva Etges[3], Tsai Mitchell[4]

[1]University of Vermont Medical Center, Burlington, VT, [2]Larner College of Medicine, University of Vermont, Burlington VT, Burlington, VT, [3]National Institute of Science and Technology for Health Technology Assessment (IATS)- CNPq/Brazil, Porto Alegre, Brazil, [4]University of Vermont Medial Center, Burlington, VT

INTRODUCTION: Time-Driven Activity-Based Costing (TDABC) is increasingly used for healthcare costing studies. The duration of activities performed by healthcare providers are key to this costing model (Kaplan, 2014). However, many existing studies lack precise time measurements—relying instead on time estimates or small numbers of observations. Accurate time measurements have been recommended to assess the costs of complex healthcare activities in order to avoid drawing erroneous conclusions (Keel, 2017). To address this implementation barrier of TDABC, this study examines the use of smartphone mobile application technology to record activity times. This study seeks to validate a novel use of smartphone app technology as follows: 1) for accuracy of the app compared to manual handwritten time recordings when used by an observer, and 2) for accuracy of the app when used by a healthcare provider to self-record activity times in real-time while also providing patient care. The app validated in this study, dTool Healthcare ('dTool'), is an open source mobile application developed by a private hospital in Porto Alegre, Brazil, and financed by the Brazilian Health Ministry though its national healthcare system improvement program (PROADI-SUS).

METHODS: In order to validate the app, we compared time entries made using dTool to a standard procedure of manually recording activity times using a pen, paper, and stopwatch. The study authors timed anesthesia providers in the operating rooms at an academic medical center hospital in the United States for the durations of 'Case Start' and 'Case End' activities (Boggs, 2018). One of the study authors (K.K.) measured these activity times while observing from outside the operating rooms. Two sets of time measurements were simultaneously recorded by the observer. One measurement used manual tools (pen, paper, stopwatch) and a second recording used dTool on a smartphone device. Additionally, to validate the use of dTool by a provider, self-recorded times were made by an anesthesia provider working inside the observed operating room. A total of four anesthesia providers were observed, and one provider made self-recorded time measurements. Differences between recording methods were evaluated using Student's t-test.

RESULTS: Total number of recordings in the observer protocol was n=72. Total number of recordings in the provider self-recorded protocol was n=21. The Case Start activity duration ranged from 1 to 32 minutes and Case End activity duration ranged from 1 to 25 minutes. In the observer protocol, the average difference between manual and dTool measurements was 0.05 minutes (SD 0.07 minutes). This difference did not reach statistical significance in the t-test (p value = 0.5076). In the provider self-recorded protocol, the average difference between provider and observer recorded times was 0.83 minutes. This difference did not reach statistical significance in the t-test (p value = 0.955).

CONCLUSION: This study validates the accuracy of time entries recorded using a mobile smartphone application (dTool) when used in the perioperative environment. Manually recorded times did not differ significantly from those made using this novel smartphone technology. Furthermore, self-recorded time measurements by a healthcare provider using dTool did not differ significantly from those made by an observer. By validating the accuracy of a novel smartphone technology in the hands of an observer, this study presents an exciting option for future TDABC costing research. Compared to traditional paper/pen recordings, taking measurements on a smartphone can be less conspicuous and less distracting, thereby minimizing the Hawthorne effect. Our study also suggests that a healthcare provider can reliably self-record activity times using dTool while providing patient care. This opens the possibility for future studies to obtain activity times in any location, in any department, at any time of the day. Given the importance of accurate activity times in TDABC, using smartphone technology to record valid time measurements opens up many exciting possibilities for future healthcare costing studies.

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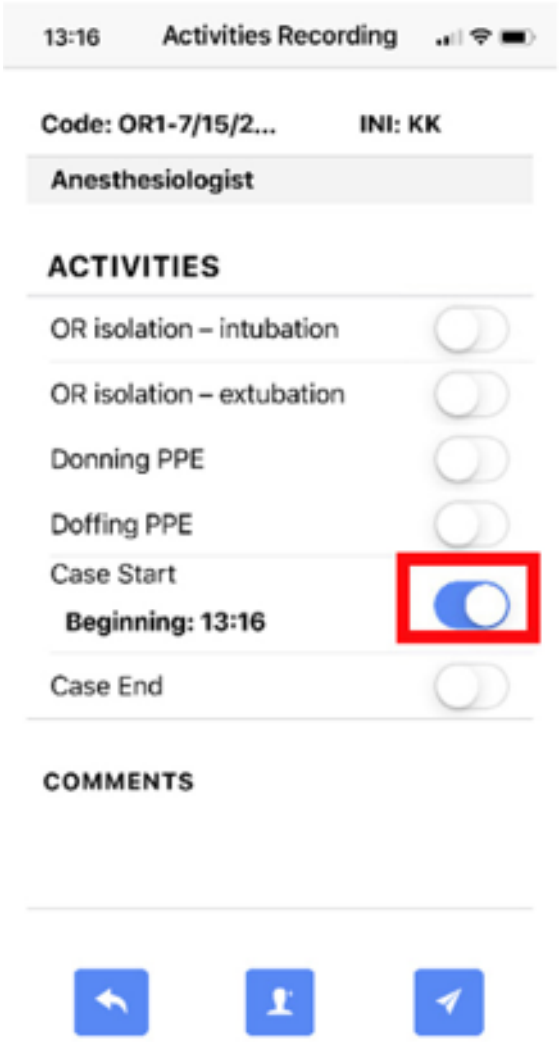

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 13

Device assessment for the application of computer vision to identification drug vials and syringes during anesthesia care

Kelly Michaelsen[1], T. Andrew Bowdle[1], Srdjan Jelacic[2], Shyamnath Gollakota[1], Ananditha araghu@cs.washington.edu[1]

[1]University of Washington, Seattle, United States of America, [2]University of Washington, Seattle, WA

INTRODUCTION: Real-time video data collection in the operating room (OR) coupled with computer vision algorithms to identify syringes, vials and drug administration events may improve patient safety and record keeping. In a study of anesthesia records, drugs were omitted from the electronic medical record in 15% of instances and the documented drug matched the administered drug name and dose 83% of the time[1]. Drug administration errors in anesthesia are common, can result in morbidity or mortality, and should be preventable. Numerous attempts to minimize drug errors and improve documentation have resulted in incremental improvement but these efforts generally require additional steps by providers[2–4]. This study assesses commercially available point of view (POV) cameras in terms of their ability to record syringes and detect text in an OR environment.

METHODS: Only devices that had battery and video recording capabilities of greater than one hour, and no restriction of the wearer's visual field (Microsoft Hololens, Google Glass Enterprise, Axon Body Flex 2 and GoPro Hero 8) were included in this study. Initial comparisons were performed with a single provider performing a series of vial to syringe drug transfers to determine if cameras could visualize the text and actions. Optical character recognition was performed after image cropping using an off-the-shelf online tool5. GoPro images at 1080p and 4K resolution were analyzed to assess the effects of distance and camera resolution on syringe label readability at four-inch intervals from the edge of the anesthesia cart to 30 inches away. Frame rate was compared using two GoPro cameras, one at 30 and one at 60 frames per second (FPS) for a low light simulation, as might be encountered in a darkened operating room with static and moving image targets to understand image blur. After Institutional Review Board exemption, the POV cameras were used in the OR to record case preparation and assess wearability and durability.

RESULTS: Initial testing looked at the field of view (FOV) of each camera and the effects on the wearer's visual field. Figure 1 shows each device being worn by the author and FOV when standing eight inches from an anesthesia cart. In simulation and OR, Microsoft Hololens and Google Enterprise frequently missed syringes and vials during manipulation by the anesthesia providers as these events were outside the FOV of the provider. The Axon Flex 2 and GoPro have much greater flexibility in angle and orientation and were able to record drug preparation events, especially when the GoPro was mounted vertically. Figure 2 shows cropped images from each device for a single syringe and the optical character recognition output for propofol (protamine results were unobtainable; this syringe was much further from the camera as it was at the back of the tray). Figure 3 illustrates the impact of resolution on optical character recognition. Propofol label text was unrecognizable at distance > 6 inches using 1080 image resolution while propofol label was partially recognizable up to 24 inches using 4K resolution. Figure 4 shows static and motion low light images of propofol syringe label obtained with the GoPro camera at 12 inches. Sixty FPS images were noisier than 30 FPS in a low light conditions, impacting optical character recognition, but had less image blur with motion.

CONCLUSION: POV camera recording can detect vial and syringe manipulations by anesthesiologists. Of the four cameras tested, the GoPro camera provided the greatest image quality, visualizing all drug preparation events during a case turnover in multiple FOV settings and allowed for optical character recognition of the majority of characters on the syringe label, even when the provider was standing more than a foot from the anesthesia cart.

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Figure 1: View of Anesthesia Cart from Left Top to Bottom-Google Enterprise, Microsoft Hololens, Axon Flex 2. Images on the Right are from GoPro with different fields of view and GoPro headmount design below.

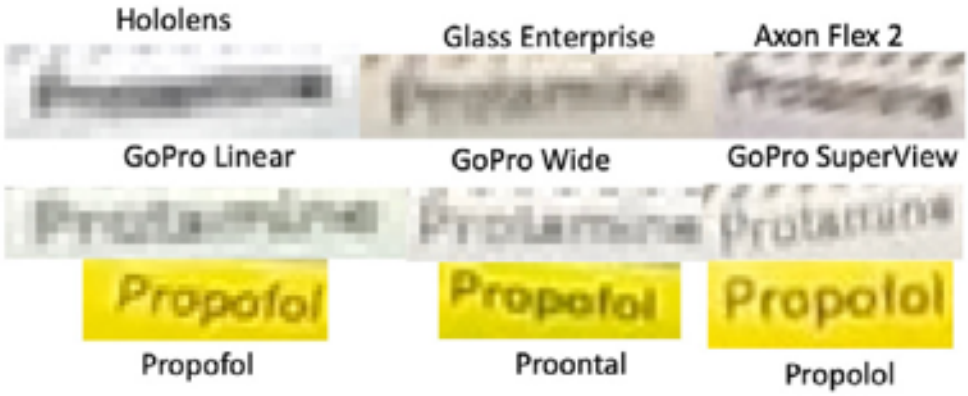

Figure 2: Zooming in on the labels for protamine (top two rows) and propofol (bottom two rows) for different cameras and three FOV settings for the GoPro. Character recognition results are shown for propofol only below those images (protamine was unrecognizable in all cases).

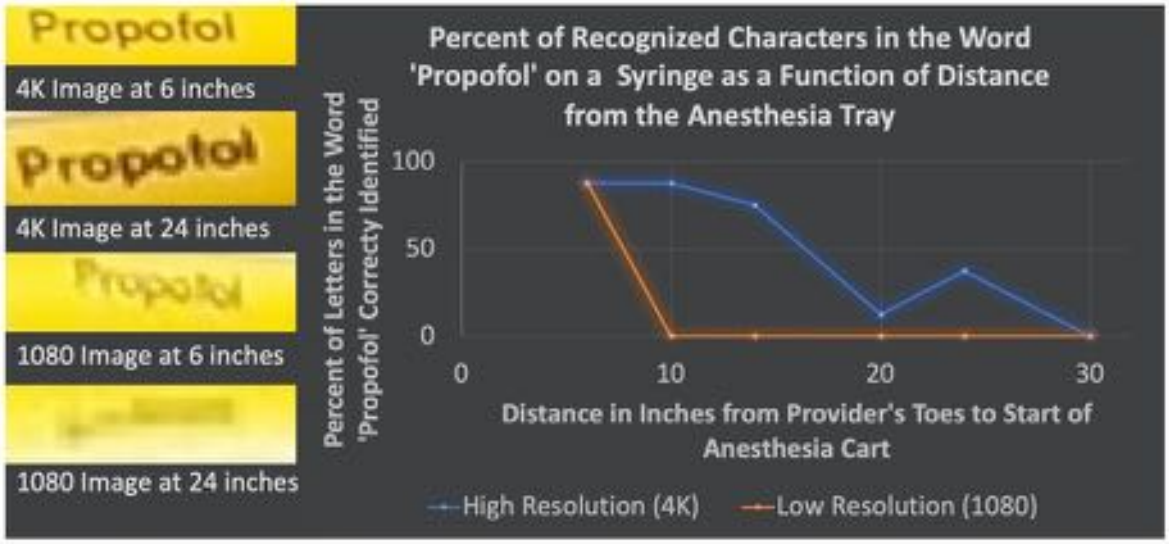

Figure 3: Higher resolution imaging improves optical character recognition of a syringe label

Figure 4: In dark rooms, lower frames per second (FPS) performs better at optical character recognition (OCR) in static conditions (left), but has more blur with movement (right)

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 14

Strength of association between five commercial depth of anesthesia monitors during emergence-like EEG patterns

Darren F Hight[1], Matthias Kreuzer[2], Peter Schuller[3], Heiko Kaiser[4]

[1]University Hospital of Bern, Bern , Other, [2]Klinikum rechts der Isar, Technical University of Munich, Munich, Germany, [3]Department of Anaesthesia & Intensive Care, Cairns, Australia, [4]Inselspital, Bern, BE

INTRODUCTION: In a recent publication[1] we observed electroencephalogram (EEG)-patterns similar to those seen during the emergence period occurring during ongoing cardiac surgery. This occurred in around 5% of our patients, with more than 80% of these patterns taking place during the transition from the heart-lung machine back to the ventilator. We recorded our (EEG) traces using the Narcotrend monitor, giving us access to the Narcotrend Index values. To date it is not known to what degree the responses of various commercial indexes correlate when responding to these EEG patterns visible in the spectrogram. As a preliminary analysis, we assessed the correlation strengths between five commercial depth of anesthesia index values, when all were exposed to the same emergence-like signals using an EEG playback method[2].

METHODS: In the original study[1], EEG recordings from 1002 patients in the EPOCAS trial (ClinicalTrials.gov identifier: NCT02976584) were analyzed. These were recorded with the Narcotrend® Monitor (2-channels, sampling frequency 125 Hz). Of the 55 patterns detected using power and frequency thresholds, we took 15 patterns with the starkest visual power difference in the spectrogram. These EEG sections were then rerun through the EEG player with four additional EEG-based anesthesia monitors and the index values recorded. Index correlation strengths were quantified using the Pearson correlation coefficient.

RESULTS: In the 15 example patients, correlations strengths ranged from r = – 0.64 to 0.92. Mean correlations were strongest between the BIS, Entropy and Sedline monitors (between 0.67 and 0.70), and were weakest between the Narcotrend and qCON monitors (at r = 0.36, see Figure 3). Figures 1 & 2 show two example patients with emergence-like EEG patterns, showing spectrograms and index values over time, with correlations. Figure Texts: Figure 1: First example patient data showing a spectrogram (upper panel) and five DOA index values over time (middle panel). The lower checkerboard panel shows index histograms and correlations between indexes. All p-values < 0.001. Figure 2: Second example patient data showing a spectrogram (upper panel) and five DOA index values over time (middle panel). The lower checkerboard panel shows index histograms and correlations between indexes. All p-values < 0.001. Figure 3: Mean Pearson correlation coefficients (r) for the 15 example patients. Mean correlations strengths displayed in black text.

CONCLUSION: One limitation of this study is that the referencing system and number of electrodes are not the same for each monitor, and may have played a minor role in limiting index accuracy. We conclude that correlation values between monitors were variable, and included negative correlations, indicating that the same EEG pattern can induce an increase in one commercial index and a decrease in another. The highest mean correlations were between the BIS, Entropy, and Sedline monitors, and lowest between the Narcotrend and qCON monitors.

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Figure 1

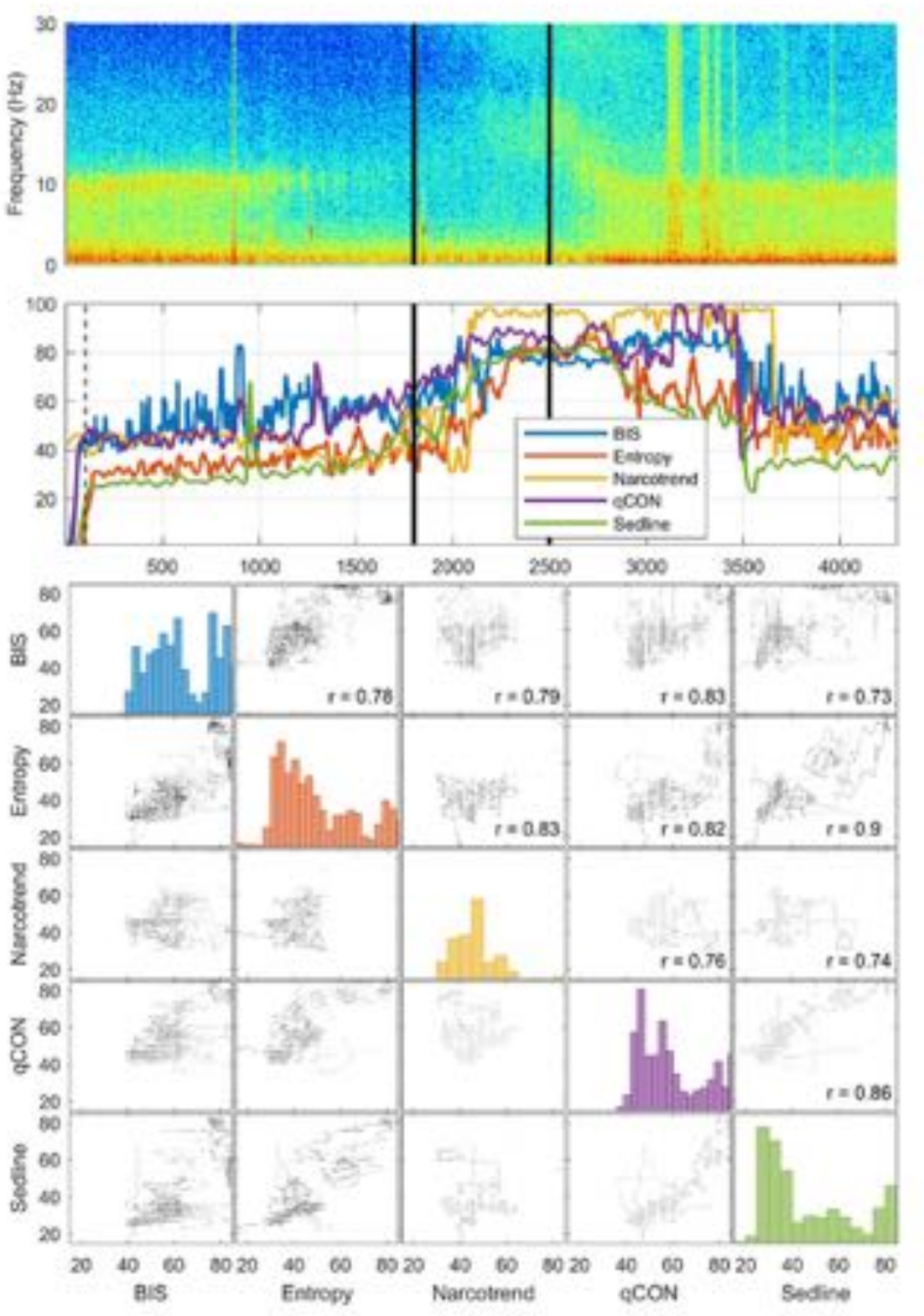


Figure 2

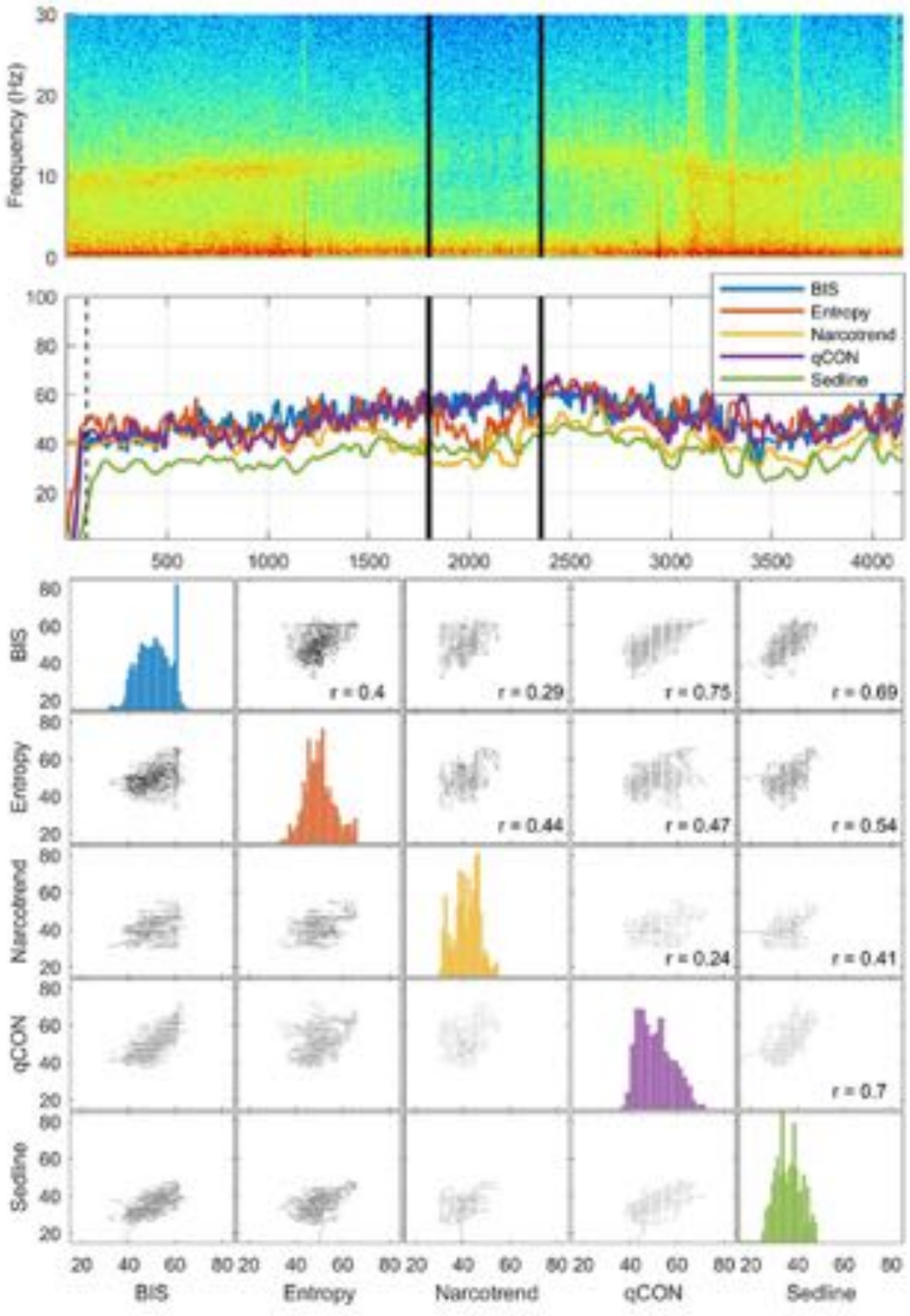
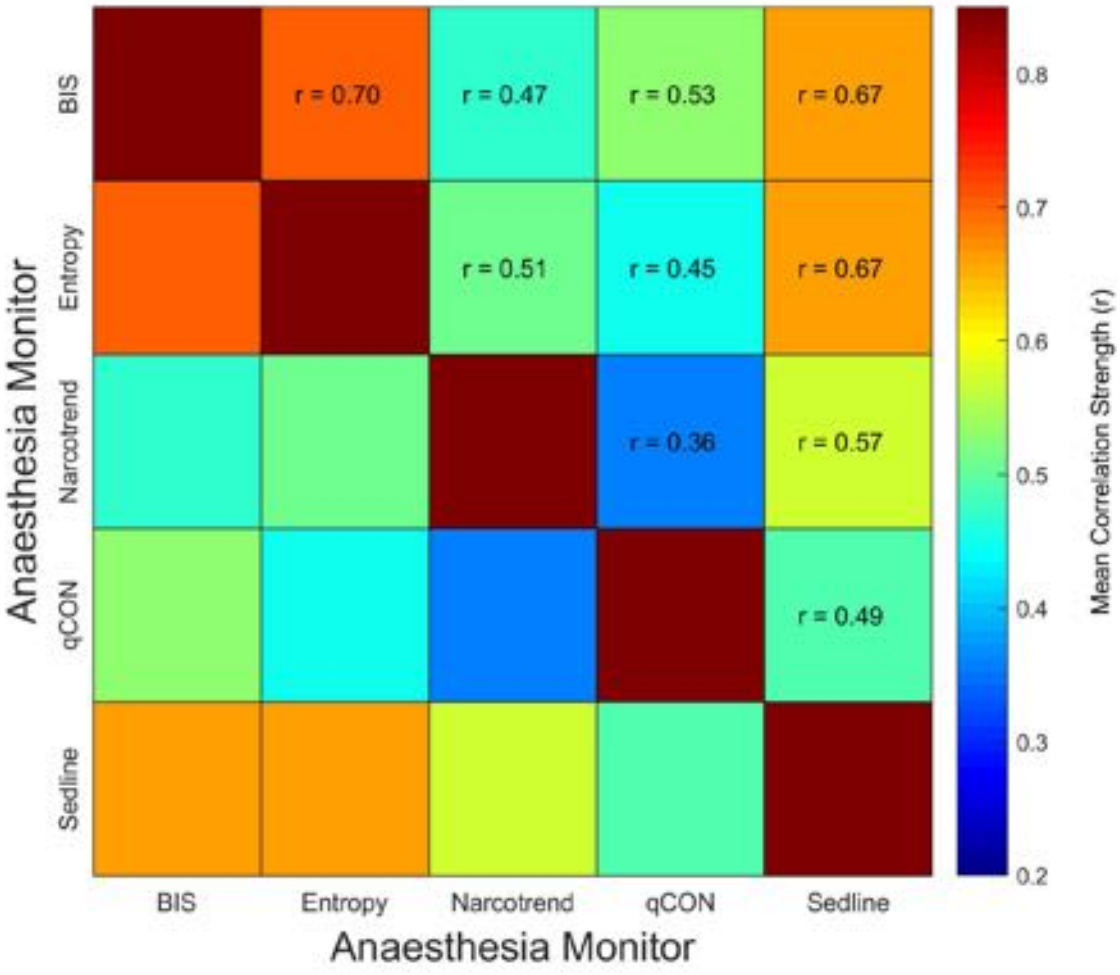


Figure 3



TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 15

Clevidipine infusion dose accuracy: How does pump-driven continuous delivery of a lipid emulsion compare to a saline solution in a laboratory model?

Anders Knudsen[1], David Arney[1], Nathaniel M Sims[1], Robert D Butterfield[2], Robert A Peterfreund[1]

[1]Massachusetts General Hospital, Boston, MA, [2]Becton-Dickinson, San Diego, CA

INTRODUCTION: Critically ill or anesthetized patients commonly receive treatment with potent, fast-acting medications delivered by pump-driven, continuous, intravenous infusion. Infusion rates are titrated stepwise up or down over short intervals, e.g. 5 minutes, according to physiologic responses. Depending on the clinical setting and drug formulation, initial flow rates may range from < 0.5 ml/hr to > 30 ml/hr. Most potent drugs are formulated for infusion in aqueous solutions, e.g. normal saline (NS). However, hydrophobic drugs may be formulated as lipid emulsions (LE). Clevidipine is a key example of a hydrophobic drug formulated in a LE and infused at low flow rates. Infusion pumps often exhibit inaccurate delivery of aqueous solutions at low flow rates thereby contributing to dose errors. Lipid emulsions and aqueous solutions have different physical and chemical properties. How will the characteristics of LE infusion delivery at low flow rates compare to an NS infusion? In a laboratory model of continuous intravenous infusion, where flow rates could be accurately measured, we asked whether pump-driven delivery of a 20% emulsion differs from delivery of NS.

METHODS: A representative clinical large volume pump (LVP) and a representative clinical syringe pump (SP) delivered continuous infusions of either a lipid emulsion, (LE, 20% w/v) or NaCl (NS, 0.9% w/v). New disposables were used for each experiment. A balance with a resolution of 0.1 mg measured delivery by weight over time. Weight/time data were converted to ml/hr. In the first protocol, each pump delivered the LE or the NS continuous infusions in steps of 5 minutes duration, exponentially ascending from 0.5 -32 ml/h and descending from 32 – 0.5 ml/hr. Delivery data for each 5 min step were compared to the expected delivery rate and then analyzed by mean flow rate error (%), averaged across 3 identical experiments. Data were compared using a Kruskal-Wallis test followed up by a Dunn's test for multiple comparisons corrections. In a second protocol, LE or NS infusions flowed continuously for 2 hours at a rate of 0.5 ml/hr. Data were compared by two-sample t-test or Mann Whitney U test depending on data distribution The results were represented graphically, and numerically, with the key outcome values being mean flow rate, mean flow rate % error and the duration of no flow periods.

RESULTS: Each pump delivered the LE and NS infusions similarly in both ascending and descending steps across the flow rate range of 0.5 to 32 ml/hr (Figure 1 A & B, Table 1 A & B). Only at 32 ml/hr were there statistically significant differences in flowrate between emulsion and aqueous solutions, however, the mean flowrates are comparable, the mean flowrate error is low, and at 32 ml/hr the difference is not clinically relevant. Each pump delivered the LE and NS infusions similarly at a continuous flow of 0.5 ml/hr over 2 hours for each interval epoch of 30 minutes duration (Figure 2 A & B, Table2 A & B). There were no statistically significant differences. Both pumps exhibited periods of no flow for both fluids, defined as flow 50% below the set rate (i.e. <0.25 ml/hr). The longest periods of no flow were at least one minute and, in some cases, longer than 2 minutes.

CONCLUSION: We show that clinical infusion pumps with different mechanisms of action, in this study a syringe pump and a large volume pump, delivery by continuous infusion of a lipid emulsion (20%) was similar to delivery of an aqueous solution (normal saline) under clinically relevant conditions, stepwise escalating doses, stepwise decreasing doses, and continuing infusion. Both pumps, for both fluids, exhibited periods of no flow. The relevance of this finding may depend on the drug's circulating half-life. For commonly used critical care medications that are potent, rapid acting, and frequently administered by pump-driven continuous effect-titrated infusion, we conclude that differences in the diluent formulation (aqueous vs. emulsion) will not detectably influence delivery to cause unusual or unexpected under- or over- dosing. Specialized management of clevidpine infusions is not required for accurate dosing in pump driven infusions.

Figure 1 A & B

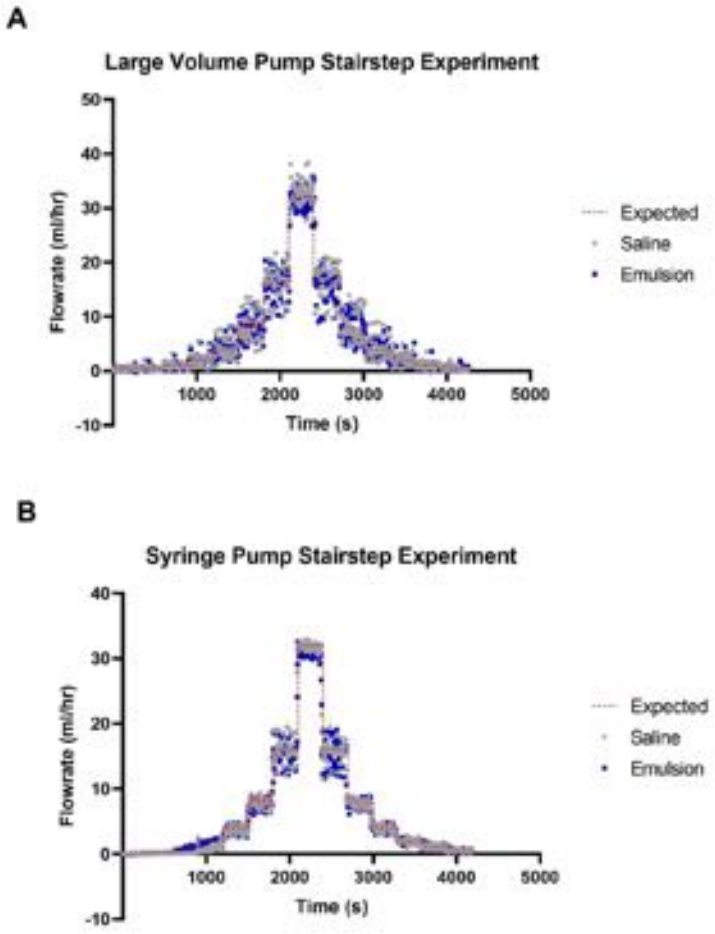


Figure 1.
Flowrate was calculated over 5 s windows with a 2 minute startup before data collection. Flowrate was set to 0.5 ml/hr and then doubled to 1 ml/hr after 10 minutes, and subsequently doubled every 5 minutes until reaching 32 ml/hr, after which it was halved every 5 minutes until reaching 0.5 ml/hr. Representative individual experiments

Figure 2 A & B

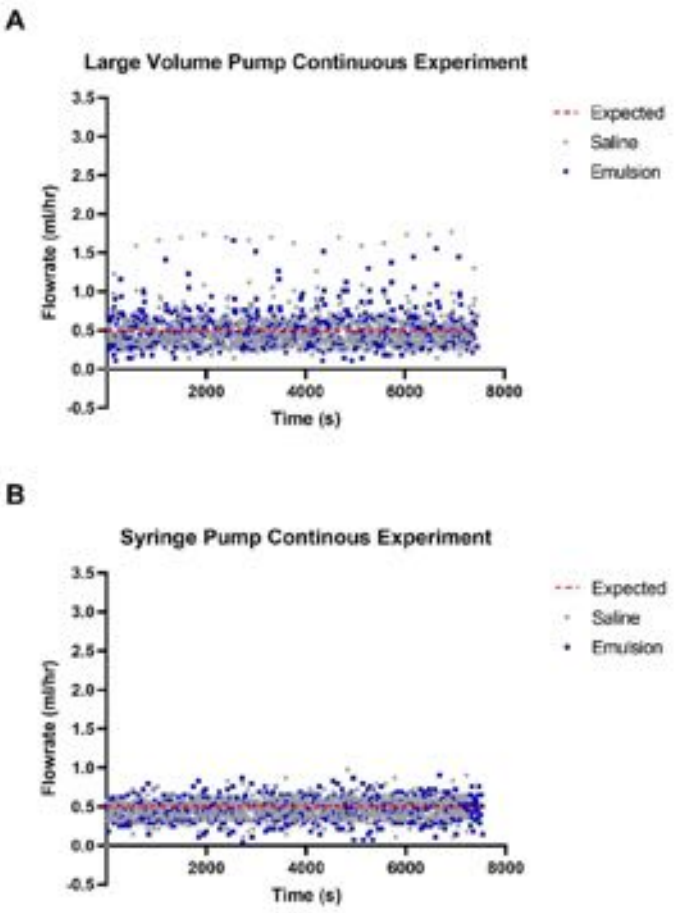


Figure 2.
Flowrate was calculated over 10 s windows and then graphed over a 2 hour period. Both pumps were primed and ran for sufficient time to prevent any startup delay in the flow. Representative individual experiments

Table 1 Stairstep

A

Large Volume	**Average Flowrate** (ml/hr)		Dunn's Test	Mean Flowrate Error (%)	
Expected Flowrate (ml/hr)	**Intralipid**	**Saline**	**Probability**	**Intralipid**	**Saline**
0.5	0.4314	0.3748	1	13.72	25.03
1	0.9734	0.9849	1	2.66	1.51
2	2.0312	2.0846	1	1.56	4.23
4	4.1802	4.2685	1	4.50	6.71
8	8.2368	8.4973	1	2.96	6.22
16	16.3852	16.9272	1	2.41	5.79
32	31.4242	32.6291	0.0049	1.80	1.97
16	15.8571	16.5262	1	0.89	3.29
8	7.9430	8.3441	1	0.71	4.30
4	3.9715	4.1576	1	0.71	3.94
2	2.0138	2.0724	1	0.69	3.62
1	0.9473	1.0288	1	5.27	2.88
0.5	0.5347	0.5256	1	6.95	5.13

B

Syringe	**Average Flowrate** (ml/hr)		Dunn's Test	Mean Flowrate Error (%)	
Expected Flowrate (ml/hr)	**Intralipid**	**Saline**	**Probability**	**Intralipid**	**Saline**
0.5	0.0119	0.0289	1	97.62	94.22
1	0.2054	0.2042	1	79.46	79.58
2	0.8095	1.2355	0.098	59.52	38.22
4	3.1457	3.6885	0.4774	21.36	7.79
8	7.4846	7.7929	0.8318	6.44	2.59
16	15.5716	15.9930	1	2.68	0.04
32	30.5231	31.4000	0.0009	4.62	1.88
16	15.0500	15.3167	1	5.94	4.27
8	7.5364	7.6663	1	5.79	4.17
4	3.7807	3.8302	1	5.48	4.25
2	1.9125	1.9081	1	4.37	4.59
1	0.9620	0.9549	1	3.80	4.51
0.5	0.5149	0.5078	1	2.97	1.57

Table 1

Mean Flowrate Error was calculated $Error\ (\%) = \left|\frac{Average\ Flowrate - Expected\ Flowrate}{Expected\ Flowrate}\right| * 100.$

Table 2 Continuous Flow

A

Large Volume	Average Flowrate (ml/hr)		P-value
Time Interval	**Emulsion**	**Saline**	**Mann-Whitney U test**
0-30min	0.4876	0.4994	0.131
30-60min	0.4951	0.5052	0.1247
60-90min	0.4943	0.5076	0.1993
90-120min	0.4969	0.5092	0.1514

Large Volume	Longest Period of No Flow (s)		Mean Flowrate Error (%)	
Time Interval	**Emulsion**	**Saline**	**Emulsion**	**Saline**
0-30min	13.33	13.33	2.474302351	0.125048477
30-60min	10	10	0.97769134	1.042326103
60-90min	10	13.33	1.14479827	1.517077721
90-120min	10	10	0.628093267	1.833861171

B

Syringe	Average Flowrate (ml/hr)		P-value
Time Interval	**Emulsion**	**Saline**	**Two-sample t-test**
0-30min	0.4517	0.4474	0.9331
30-60min	0.4671	0.4686	0.9491
60-90min	0.4733	0.4742	0.9611
90-120min	0.4750	0.4759	0.9636

Syringe	Longest Period of No Flow (s)		Mean Flowrate Error (%)	
Time Interval	**Emulsion**	**Saline**	**Emulsion**	**Saline**
0-30min	10	10	9.66254445	10.5240035
30-60min	10	6.67	6.587696823	6.285911588
60-90min	10	6.67	5.346432389	5.16193951
90-120min	10	6.67	5.00198883	4.828856639

Table 2 Mean flowrate, N=3, calculated by taking the mean of 10 s windows over a 30 min period. Mean flowrates were compared at each time interval using two-sample t-tests for the SP and Mann-Whitney U tests for the LVP. Period of no flow was determined as any flowrate below 50% of the set rate (<0.25 ml/hr). Mean Flowrate Error was calculated

$$Error\ (\%) = \left|\frac{Average\ Flowrate - Expected\ Flowrate}{Expected\ Flowrate}\right| * 100.$$

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 16

Leveraging the Human Digital Twin for Perioperative Monitoring of Pediatric Patients- An Early Case Study

Hannah Yates[1], Mohamed Rehman[2], Giovanni Cucchiaro[2], Anna Varughese[2], Luis Ahumada[3], Hannah Lonsdale[4]

[1]Johns Hopkins All Children's Hospital, St Petersburg, FL, [2]Johns Hopkins All Children's Hospital, St. Petersburg, FL, [3]Johns Hopkins All Children's Hospital, St Petersburg, FL, [4]Johns Hopkins University, St Petersburg, FL

INTRODUCTION: The Internet of Medical Things (IoMT) connects patient devices with healthcare systems such as the electronic medical record (EMR). Wearable tracking devices such as Fitbit can contribute data to the IoMT, giving clinicians more information about a patient's baseline physiological levels known as a human digital twin (HDT). This can then allow comparisons after an illness, treatment, or surgery and give a measure of how long it takes to restore the patient to a good level of daily physical function. It could lead to a precision medicine personalized post-operative recovery plan. A digital twin is an ultrahigh fidelity mathematical model of a system constructed from all available information. For medicine, the system is the human body. The available information might include fitness tracker metrics, EMR information, radiological imaging, genomics and exposomics- the non-genetic exposures that contribute to health, such as environmental pollution, weather, diet and psychosocial behaviors. This case study demonstrates an early use of the HDT to track a patient's recovery from major scoliosis surgery.

METHODS: The patient wore a Fitbit Charge 3 device for several weeks prior to his posterior spinal fusion procedure, and 5 months postoperatively. A Fitbit app account was created and anonymously linked to Fitabase, a data collection platform which de-identifies and collects data from the Fitbit app in near real-time. From the Fitabase server, the patient's heart rate (HR), step count, active minutes, and sleep data were available to the clinical team. This data was used to establish the patient's preoperative HDT, identify post-surgery variability, and determine when the patient regained or exceeded their HDT baseline.

RESULTS: The patient was an 18-year-old white, non-Hispanic male, who was otherwise well. He was compliant with both wearing the device and regularly syncing it to the Fitbit app. The measured baseline HDT and time for each metric to recover postoperatively are reported in table 1. Five months after surgery, he now exceeds his preoperative HDT by over 800 steps per day. Postoperative restless sleep was initially lower than baseline HDT but increased for several days when the acute prescriptions for diazepam and oxycodone were stopped.

CONCLUSION: This case study demonstrates an early use of wearable technology to create a HDT that was used to track trends in recovery after major surgery. The Fitbit is a relatively inexpensive wearable consumer grade device that has been demonstrated to be the most accurate of commercially available fitness trackers1 and therefore has potential clinical utility as a trend monitor. The measured elements of the patient's HDT varied considerably in their time to return to baseline- from 3 weeks for sleep to 19 weeks for resting heartrate. We can also measure the potential benefit of the surgery- the patient is now more active than his preoperative HDT as evidenced by an increased daily step count, perhaps as a result of increased FEV1 and improved mobility. The observations demonstrated in this single patient report reveal the start of the future potential of the HDT. With further study and the recording of many HDTs, it may be possible to use machine learning to discover new trends. We could predict delayed recovery or the early onset of postoperative complications, thereby allowing earlier intervention and improved patient outcomes.

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Metric	Baseline Human Digital Twin	Postoperative time to return to baseline
Mean daily step count	4471 steps	7 weeks
Resting heart rate	52 bpm	19 weeks
Daily moderate or very active movement	18 minutes	10 weeks
Mean nightly sleep duration	7 h 26 m	3 weeks
Nightly restless sleep	22 minutes	N/A

Table 1: Patient's baseline Human Digital Twin (HDT) and time taken to recover.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 17

Modulation of EEG alpha band activity differently influences parameters used for anesthesia monitoring

Stephan A Kratzer[1], Clara Weyer[2], Eva Prötzl[2], Cornelius Husemann[3], Hubert Hautmann[4], Gerhard Schneider[5], Matthias Kreuzer[6]

[1]Technical University Munich School of Medicine, Munich, BY, [2]Technical University Munich, München, Germany, [3]Technical University Munich, München, Deutschlan, [4]Technical University Munich, München, Deutschland, [5]Technical University Munich, Munich, na., [6]Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

INTRODUCTION: Intraoperative electroencephalographic (EEG) recordings can help the anesthesiologist to optimize anesthesia quality. Processed EEG parameters and indices translate complex EEG characteristics into a single number that should correlate with the level of anesthesia. Common parameters and indices estimate the anesthetic level by tracking the anesthetic-induced EEG changes from a low amplitude – high frequency signal during wakefulness towards a slow signal with high amplitudes under general anesthesia. Besides this slowing of the EEG, strong alpha oscillatory activity (~8-12 Hz) can develop in the frontal cortex. An intraoperative EEG with dominant alpha oscillatory activity seems to be associated with a good anesthetic level[1]. The way EEG parameters and indices react to changes in the alpha oscillatory activity are mostly unknown. Anier et al. reported an increase of the spectral entropy indicating a lower level of anesthesia and a decrease of approximate entropy indicative of a deeper level when the alpha oscillatory activity becomes stronger in patients under general anesthesia[2]. Here we investigated the impact of an artificial modulation of the alpha oscillations on parameters used in anesthesia research.

METHODS: We used EEG episodes from 20 patients who underwent a bronchoscopy under propofol sedation/anesthesia of 30 s length, extracted from a stable period with a clearly identifiable alpha peak in the density spectral array (DSA) and a state entropy around 50, indicative of adequate anesthesia, as calculated by the GE Entropy Module. We then extracted the alpha oscillatory activity from 8-12 Hz from the EEG episodes by using Butterworth filters. We subtracted and added the isolated alpha oscillations back to the EEG in 20% steps from -100% to +500% to simulate a weaker or stronger alpha oscillatory activity. For each original and simulated EEG, we calculated the beta ratio (as used in the BIS [3]), spectral edge frequency (SEF95)[3], spectral entropy (SpEn) as used in the Entropy Module[4], approximate entropy (ApEn), and permutation entropy (PeEn) with settings suggested for anesthesia monitoring[5]. Figure 1 presents the impact of alpha modulation on the signal and the power spectral density.

RESULTS: The different parameters reacted differently to the alpha modulation. The beta ratio and PeEn indicated an increase in the anesthetic level with increasing alpha amplitudes. The ApEn indicated a lighter anesthesia with increasing alpha. SEF95 and SpEn did not behave uniformly. The stronger alpha caused an increase in SEF95 in some and a decrease in other patients. The behavior depended on the SEF95 of the original EEG. If SEF95 was below the alpha band then SEF increased and if it was above the alpha band it decreased. The SpEn either increased (lighter anesthesia) with stronger alpha or showed an initial increase followed by a decrease. The increase occurs if the spectrum becomes more uniform, i.e., if the alpha amplification leads to a decrease of the dominant spectral peak in the slow frequencies. As soon as the alpha peak becomes dominant, the SpEn starts to decrease. Figure 2 presents the parameter trends for the single patients.

CONCLUSION: The strength of alpha oscillatory activity in the intraoperative EEG seems to present a marker for anesthesia quality. Changes in its strength causes different EEG parameters to react differently making it difficult to extract the strength of the alpha oscillation and hence of anesthesia quality from the respective parameter or to compare the parameters. Next generation monitoring systems should incorporate a component that focuses on alpha oscillations to the index.

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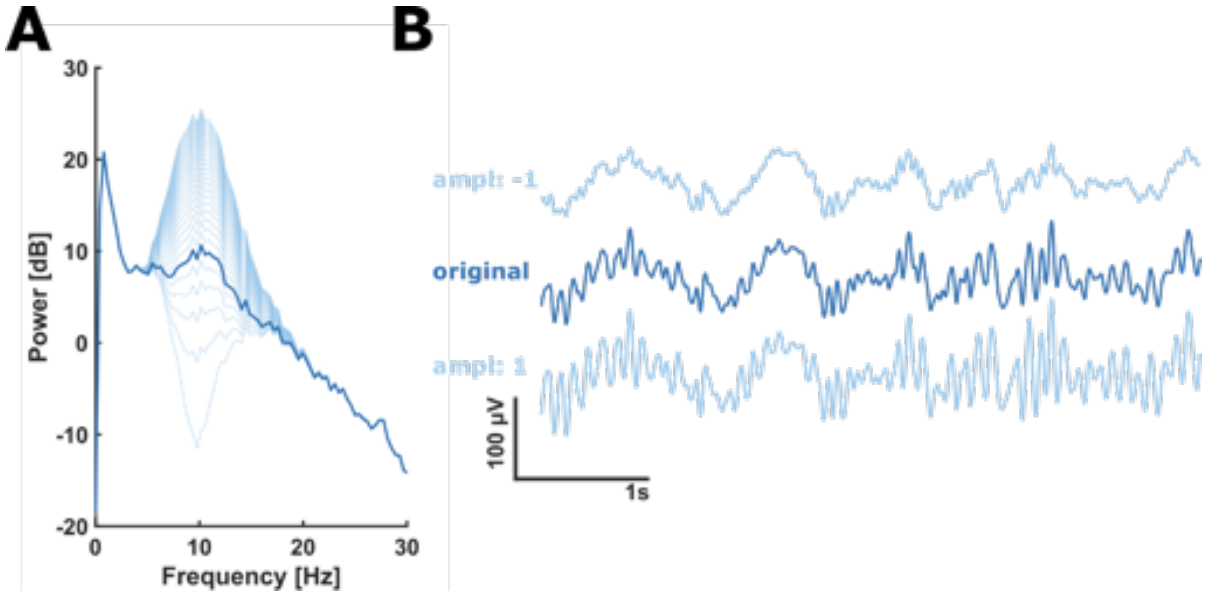

Figure 1: A) Power spectral density (PSD, median over all patients) for the different amplification steps. The thick line indicates the PSD from the original EEGs. B) Exemplary 5 s EEG episode of a patient without modification (center), after reducing the alpha band amplitudes (top) and after increasing the amplitude (bottom)

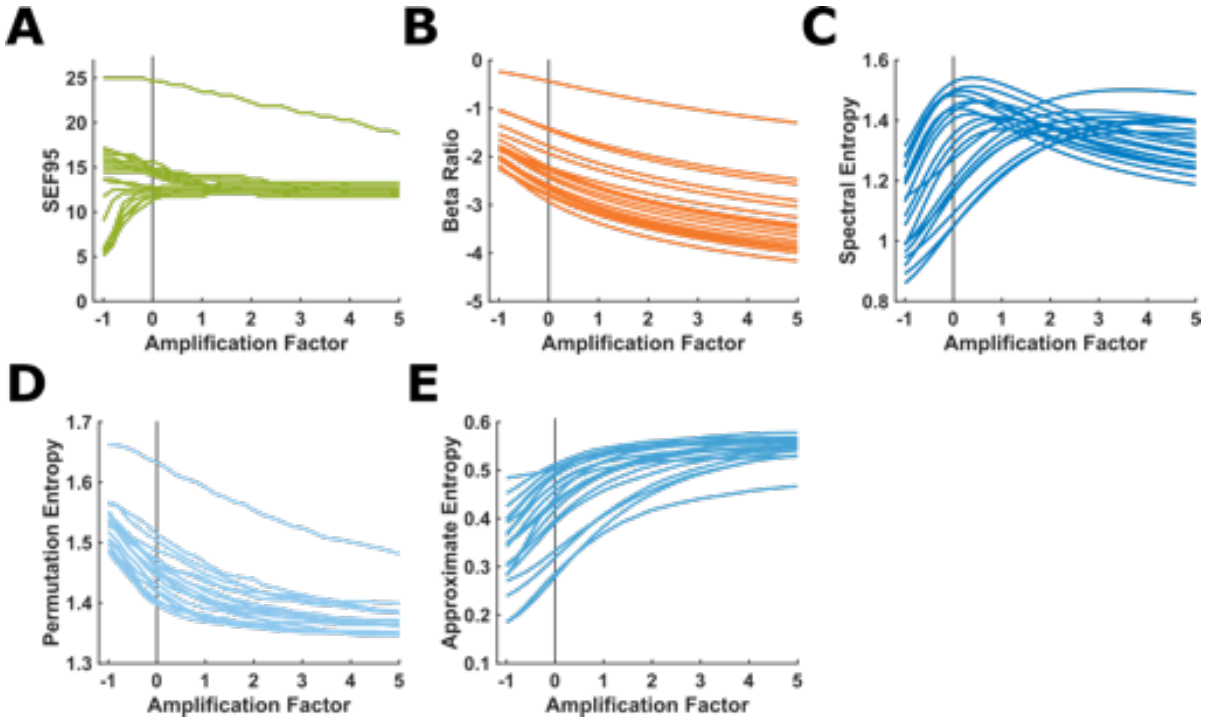

Figure 2: Parameter trends for the different amplification steps for A) SEF95, B) beta ratio, C) spectral entropy, D) Permutation entropy, and E) approximate entropy. The vertical line indicates the parameter values of the original -not modified- signal

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 18

The high-fidelity ORSIM® fiberoptic simulator is a superior training tool than the low-fidelity wooden block simulator among anesthesia and emergency medicine residents

Kong Eric You-Ten[1], Martina Melvin[1], Evan Wild[1], Matteo Parotto[2], Sev Perelman[1], Naveed Siddiqui[1]

[1]Mount Sinai Hospital, Toronto, Canada, [2]Toronto General Hospital, Toronto, Canada

INTRODUCTION: The omission of fiberoptic intubation(FOI) when indicated was a major contributor to airway morbidity and mortality according to the National Audit Project 4(NAP4)[1]. In this study we compared two different FOI teaching simulators; the low fidelity wooden block in which Naik et al. showed superiority compared to didactic teaching, and the high fidelity ORSIM® a virtual reality simulator (Airway Simulation Limited, Auckland, New Zealand)[2-4]. The purpose of the study is to compare these simulators as training tools and translation to clinical performance.

METHODS: Following REB approval and informed consent, 20 anesthesia and 4 emergency medicine residents(postgraduate year 1-3 and with <8 clinical FOI) completed this 2-arm observational study. Residents were randomised into two groups: High fidelity ORSIM®(ORSIM, n=12) and Low fidelity wooden-block(LFS, n=12).Each resident performed 20 consecutive FOI on their assigned simulator to generate an individual learning-curve and within 3 months each resident performed FOI clinically in the operating room on a healthy anaesthetised patient. A successful FOI is advancing the scope 1-2 cm above the carina. Residents who did not achieve this view, and/or who required more than 8 minutes (safe apnoea time post adequate oxygenation) were considered a failure.[5] Each clinical FOI was video-recorded and graded by two blinded, expert-raters, using validated checklist and global rating scale(GRS).[2,6] Primary outcome was (i) Learning-curve cumulative sum(CUSUM) chart with mean procedure time of each resident to perform 20 FOI plotted against a target time of 60 seconds to infer simulator competence, as it was previously shown by Smith and colleagues that after 18 FOIs, 70-80 % completed it in< 60 seconds.7 Secondary outcomes were(i) total simulator training time (s),(ii) GRS and checklist score. (iii) time(s) to pass scope 1-2 cm above the carina. The Analyze-it software was used to plot the CUSUM charts.

RESULTS: The ORSIM® group outperformed the wooden block group in terms of CUSUM analysis (Figure 1). The upward CUSUM for ORSIM was flat indicating that their performance met the specified standard unlike the wooden block which was outside the control limit until procedure number 19. The downward CUSUM for ORSIM showed a continuous downward trend from procedure number 4 onward crossing the lower control limit at procedure number 10 whereas the wooden block only showed a declining trend after procedure number 14. Mann-Whitney test revealed that the two groups were statistically significant in terms of the mean time(s) to perform 20 FOIs on their respective simulator with mean difference of -22.975 and p=0.007.These results suggest, it takes less time for residents using the ORSIM® as a training tool to learn the procedure than residents using the wooden block (Table 1). Mean training time to perform 20 simulated FOI was significantly less with the ORSIM than the wooden block (mean 899± 440 vs 1358 ± 405 s, 95% CI [100.46-818.54], p=0.01, Table 2).However, we found no difference in GRS and checklist score of clinical FOI performances.

CONCLUSION: Our findings are in congruence with prior studies which have shown no differences in clinical performance between high and low fidelity FOI simulators8.However, the high fidelity ORSIM is a superior training tool, compared to the low fidelity wooden block, with achieving simulator competence in fewer attempts, and significantly decreased learning and training time. These findings have important implications in establishing a FOI training programme. With clinical exposure to FOI reduced due to several issues such as time pressure in the operating room, various working time directives and the current pandemic, it is pertinent more than ever that training activities are time efficient. The information provided in this study should assist course directors when it comes to the investment and allocation of fiberoptic simulator resources for training.

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TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 19

Usability Evaluation of a Remote Patient Monitoring System for Intensive Care Medicine: A Human-Centered Design Approach

Lars Stablo[1], Lina Mosch[2], Akira-Sebastian Poncette[2], Maximilian M Wunderlich[2], Markus Feufel[1], Claudia Spies[2], Felix Balzer[2]

[1]Technische Universität Berlin, Berlin, Germany, [2]Charité – Universitätsmedizin Berlin, Berlin, Germany

INTRODUCTION: The efficacy of patient monitoring systems in intensive care is highly dependent on usability[1-4]. Healthcare interfaces that lack usability can hinder the implementation of medical devices, cause medical errors, and thus compromise patient safety[2-4]. A previous study of the barriers to implementing a remote patient monitoring system in an intensive care unit (ICU) showed a high potential for improvement in terms of usability[5]. In this study, we investigated the hypothesis that a human-centered design approach is feasible to evaluate the usability of a patient monitoring system in the intensive care context.

METHODS: Following IRB approval (EA1/031/18), we conducted a formative evaluation of the patient monitoring interface (Design A) as a first step. Simulated use tests with think-aloud protocols were conducted with ICU staff (n=5) to conceptualize informed design changes. In a second step, an improved prototype version of the monitoring interface was developed and tested based on the usability issues identified in the first step (Design B). To compare the two interfaces, we evaluated (a) subjectively perceived usability using the System Usability Scale (SUS), (b) performance efficiency using normative path deviation (NPD), and (c) effectiveness by measuring task completion rate. To test these measures for statistical significance, we used two-sample t test (a), Poisson regression with a generalized linear mixed-effects model (b), and the N-1 chi-square test (c). P values <.05 were considered significant.

RESULTS: In the first step, we found 37 individual usability problems that were specific to the remote patient monitoring system and could be subsumed under six categories: Comprehensibility of labeling of technical terms, usefulness of the system, clarity of user interface (UI) elements, navigation problems, responsiveness, and response time. Based on these usability problems, in the second step, the previous interface was revised by making the design more responsive and making changes regarding labeling and UI elements. Statistical analysis of the SUS showed that perceived usability improved significantly (Design A: mean 68.5, SD 11.26, n = 5, Design B: mean 89, SD 4.87, n = 5 ; p = .003), as did performance efficiency (NPD Design A: mean 8.8, SD 5. 26, n = 5, Design B: mean 3.2, SD 3.03, n = 5 ; p = .001), and effectiveness based on improved task completion rate (Design A: failed 7 times, passed 11 times; trials = 18; Design B: failed 0 times, passed 20 times; trials = 20; p = .002).

CONCLUSION: Usability testing is a feasible method for identifying usability problems of medical technologies as a basis for improving the usability of monitoring devices. The ICU is a particularly challenging work environment, given pervasive use of technology, severe conditions of patients, and high stress levels of staff. In such a work environment, difficult-to-use technology may result in detrimental outcomes for staff and patients. Thus, technical ICU devices should be designed to support efficient and effective work processes. Our results suggest that this can be achieved by applying use-centered design methods and principles. Especially, human-centered design in form of usability testing with think-aloud protocols proved to be an effective means of improving the usability of a remote patient monitoring system in an ICU setting. We believe that time and resources spent on developing user-centered labeling pays off when designing user-friendly medical interfaces.

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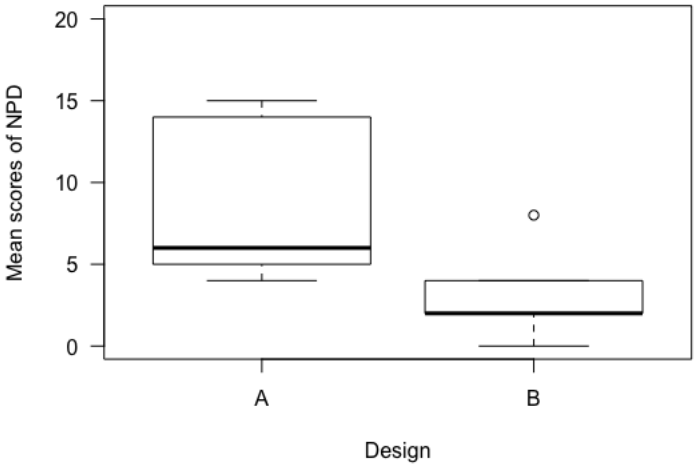

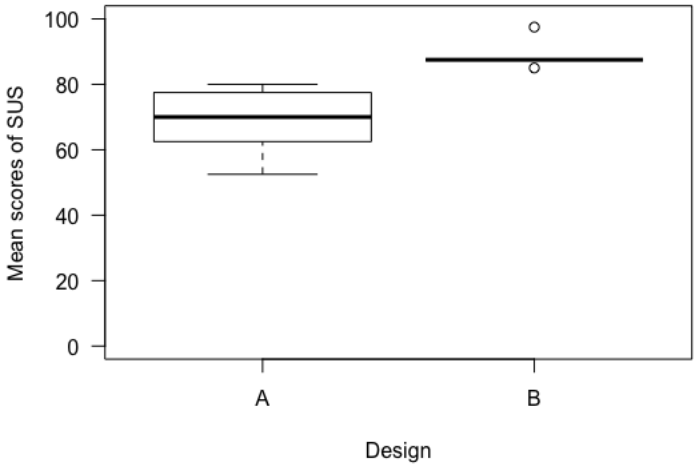

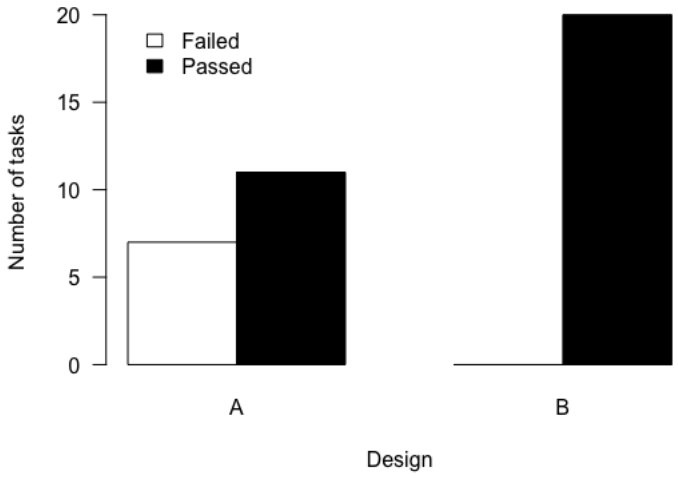

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 20

Negative Pressure Airway Chamber as a protective equipment for healthcare providers: measurement of aerosol particulate reduction efficiency of an isolation chamber

Alberto Baldelli[1], Kevin Heieis[2], Steven Rogak[2], Matthias Görges[3], Andrew Poznikoff[3], Robert Purdy[4]

[1]The University of British Columbia - BC Children's Hospital, Vancouver, BC, [2]The University of British Columbia, Vancouver, Canada, [3]The University of British Columbia, Vancouver, BC, [4]University of British Columbia, Vancouver, Canada

INTRODUCTION: Aerosol transmission, while controversial, is thought to contribute to the infectious pattern of transmission in the current COVID-19 pandemic[1,2]. There are several aerosol generating medical procedures (AGMP) that are a cause of concern for the health and safety of healthcare providers (HP) including high flow oxygen therapy, preoxygenation, non-invasive ventilation such as CPAP, bag mask ventilation, and intubation[3,4]. Isolation chambers have been proposed, providing a physical barrier between patient and operator to limit aerosol exposure, however concerns have been raised on the lack of evidence for the added protection of HP and the limitations placed on airway procedures that come with some designs [5]. Rigorous testing of these chambers in a simulated setting, with iterative design improvements to address shortcomings, is necessary before clinical implementation. We developed a Negative Pressure Airway Chamber (NPAC) to address many of these design concerns[5]. Preliminary results in the clinical usability of the chamber are promising and might allow for the safe use of some pre-intubation patient optimization strategies. The aim of this study was to quantify the aerosol particulate matter (PM) reduction efficiency of the NPAC.

METHODS: A Negative Pressure Airway Chamber (NPAC) was developed with a patient warmer adapted as a HEPA filtered vacuum pump. The pump had a suction velocity of 19.4 m/s through the 2.5' outlet. An intubating manikin was centered inside the chamber with a nebulizer, filled with saline, attached to one bronchi. Mass and size distribution of the resulting aerosols were measured both inside and outside the chamber using optical particle sensors, arranged as shown in Figure 1. The test matrix was carried out in both an operating room (OR) and a small patient room with minimal air flow. An ambient steady state baseline for each room was established by measuring PM over 15 min. A second steady state measurement with the aerosol generator freely releasing particles was also measured over 15 min. Four efficiency trials and three task trials were run. The efficiency trials matrix was set up as follows: a) each trial ran for 15 min, starting with the NPAC in place and aerosols being generated for the first 5 min. b) variable 1, removal time, the NPAC was removed either immediately after 5 min or at the 10 min mark. c) variable 2, passive/active NPAC, the NPAC was tested both with and without the vacuum pump. The task trials were set up as follows: a) each trial ran for 10 min with the aerosol generator running for the first 3 min. b) one task was completed on the manikin during the first 3 min, either bag mask ventilation, preoxygenation, or fitting of an N95 mask, with subsequent removal of arms from the chamber. Each task trial was completed both with and without the NPAC in the OR.

RESULTS: During the efficiency trials with the NAPC in place, the average levels of PM next to the position of the HP were reduced to levels below the aerosol steady state in both locations, with levels at ambient baseline when negative pressure is used (Figure 2). A spike in aerosol exposure was observed at the 5 min lift time only when negative pressure was off and the aerosols were allowed to build inside the chamber. Turning negative pressure on or leaving the NPAC in place for 10 min mitigated this effect. The use of negative pressure reduces the highest level of PM next to the HP by 99% and 95% in the OR and patient room respectively. During the task trials, the NPAC also reduced PM next to the HP by 99% to ambient baseline values (Table 1).

CONCLUSION: We designed, built, and characterized an isolation chamber with the purpose of enclosing and filtering the aerosols generated by a patient while performing typical airway-related procedures. The use of the NPAC with negative pressure was found to significantly reduce aerosolized particulate matter next to the position of the healthcare provider in both an OR (99%) and patient room (95%), using a saline aerosol model. Aerosol exposure was also reduced by 99% during bag mask ventilation, preoxygenation, and fitting an N95 mask on an aerosol generating manikin. These results add much needed data to the evidence for protecting healthcare providers using this particular type of design. Follow up simulation trials assessing clinical usability of this design are warranted.

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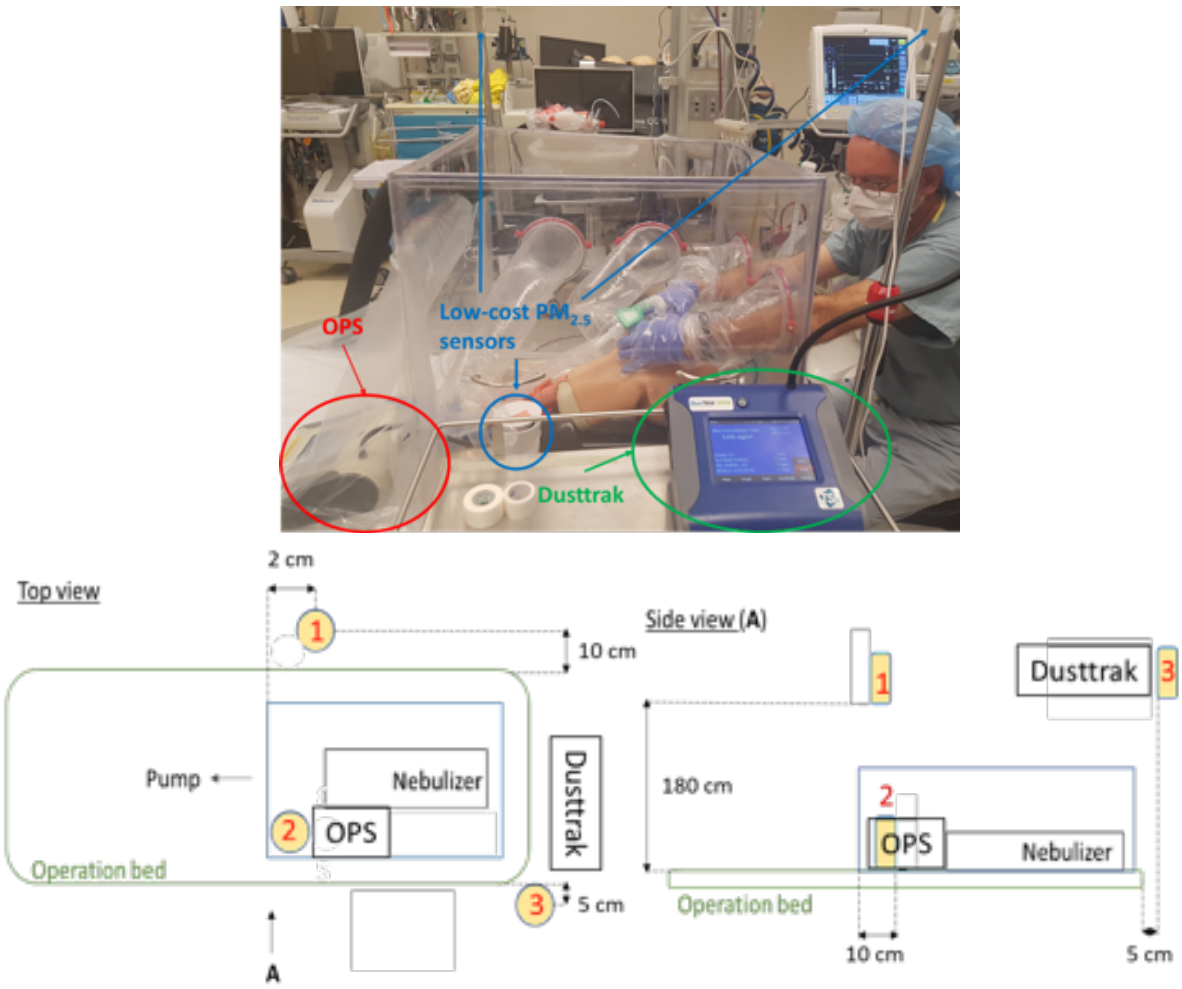

Figure 1. Positions of low-cost $PM_{2.5}$ sensors (numbered yellow circles/squares), OPS, and Dusttrak, with respect to the nebulizer, NPAC (blue square), and operation bed.

Operating Room **Patient Room**

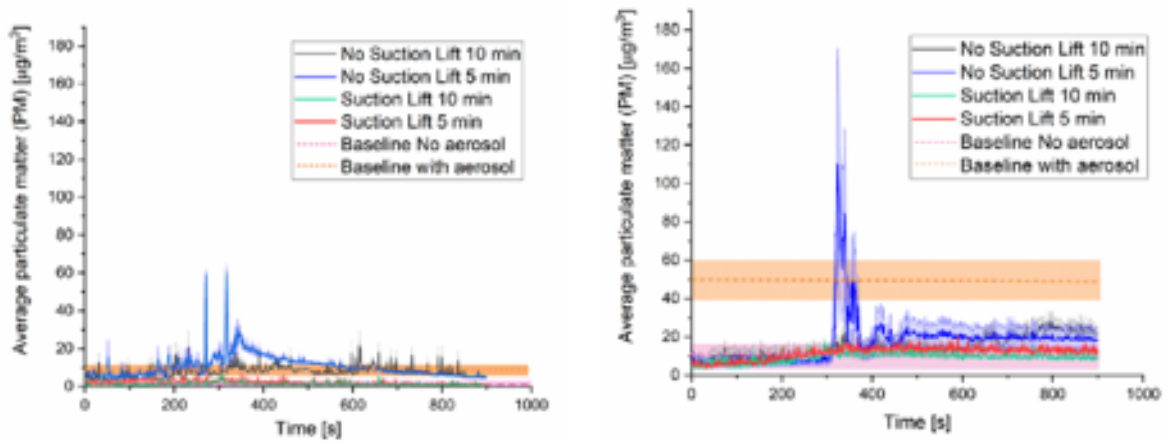

Figure 2. Average particulate matter trend over trial time next to the healthcare provider position, in two locations. Six trials were completed; ambient steady state baseline, steady state with aerosol generator on, two trials with the NPAC and negative pressure suction on (NPAC removed at 5 and 10 minutes), and two trials with the NPAC and negative pressure suction off (NPAC removed at 5 and 10 minutes). The aerosols were turned off after 300 second (5 min) from the beginning of each trial.

Table 1. Minimum, mean, and maximum values of average particulate matter measured next to the patient and healthcare provider (HP) during preoxygenation, bag mask ventilation, and fitting an N95 mask, both with and without the NPAC in place. The row called "difference" relates to the % decrease in minimum, mean, and maximum PM from the patient to HP positions. The difference at the HP position represents the decrease in PM when using the NPAC compared to no NPAC.

Task	**NPAC**	**Position**	**Particulate Matter Average ($\mu g/m^3$)**		
			Minimum	**Mean**	**Maximum**
Preoxygenation	N	Patient	35.2 ± 1.82	177 ± 57.1	879 ± 330
		HP	6.51 ± 0.51	13.1 ± 2.03	34.2 ± 10.9
		Difference [%]	81.1	92.3	96.4
	Y	Patient	59.8 ± 0.89	934 ± 54.8	1380 ± 167
		HP	2.08 ± 0.11	2.94 ± 0.36	5.41 ± 1.72
		Difference [%]	96.6	99.6	99.6
	Difference at HP [%]		68.8	77.5	84.1
Bag mask	N	Patient	23.9 ± 0.08	89.1 ± 20.4	760 ±214
		HP	4.51 ± 0.07	12.4 ± 2.23	53.1 ± 18.3
		Difference [%]	81.1	86.5	95.9
	Y	Patient	8.91 ± 2.69	712 ± 42.9	1052 ± 126
		HP	0.67 ± 0.03	1.59 ± 0.28	3.53 ± 1.22
		Difference [%]	93.2	99.7	99.7
	Difference at HP [%]		85.1	87.2	93.3
N95	N	Patient	41.9 ± 6.32	263 ± 89.2	1138 ± 427
		HP	6.11 ± 0.18	13.3 ± 3.02	35.9 ± 12.9
		Difference [%]	85.3	95.1	96.8
	Y	Patient	11.8 ± 1.11	479 ± 43.8	758 ± 119
		HP	0.67 ± 0.03	1.14 ± 0.12	3.33 ± 1.34
		Difference [%]	94.1	99.7	99.5
	Difference at HP [%]		89.9	91.4	92.2

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 21

Offline comparison of brain function monitors for geriatric anesthetic-induced electroencephalogram changes

Sarah Eagleman[1], Caitlin Drover[2], Xi (Emma) Li[1], Bruce Maciver[3], David Drover[3]

[1]Stanford University, Palo Alto, CA, [2]University of Washington, Seattle, WA, [3]Stanford University School of Medicine, Stanford, CA

INTRODUCTION: Several devices record and interpret patient brain activity via electroencephalography (EEG) to aid physician assessment of anesthetic depth. Few studies have compared brain function monitors on data from the same patient. Here we describe a setup to simultaneously compare the performance of three brain function monitors using prerecorded geriatric surgical EEGs.

METHODS: A playback system was designed to replay EEG signals into three different commercially available EEG monitors. This way, we could simultaneously calculate indices from the SedLine Root (PSI), bilateral BIS Vista (BIS), and Datex Ohmeda S/5 monitor with entropy module (Entropy). We tested each system's ability to distinguish activity before anesthesia administration (Pre-Med) and before and after loss of response (LOR), and to detect significant suppression incidences in EEGs recorded from geriatric surgical patients on beta-adrenergic blockade. We show examples of the output of brain function monitors tested on 29 geriatric cases.

RESULTS: All monitors showed significantly different indices and high effect sizes between comparisons Pre-Med to after LOR and before and after LOR. Both PSI and BIS showed the highest percentage of deeply anesthetized indices during periods with suppression ratios (SR) greater than 25%. We observed significant negative correlations between percentage of suppression and indices for all monitors (at SR > 5%). Receiver operating characteristic curves were generated to assess burst suppression performance. BIS-L and BIS-R had the highest performance followed closely by PSI. Entropy exhibited poor burst suppression performance.

CONCLUSION: All monitors significantly distinguished EEG changes before anesthesia was administered and around LOR. PSI and BIS best detected suppressed periods. Our results suggest PSI and BIS monitors should be recommended for geriatric patients with risk factors for intraoperative awareness or sensitivity to anesthesia.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 22

Smile for the Trail Cam: Capturing Just in Time Training Cart Usage at Three Hospitals: A Case Report of User Adoption of a New Educational Intervention

Tanna J Boyer[1], Johnny F Cartwright[1], Sally A Mitchell[1]

[1]Indiana University School of Medicine, Indianapolis, IN

INTRODUCTION: Just in Time Training (JiTT) refers to teaching and learning right at the point of need, for example, practicing a procedure on a task trainer immediately before performing the same procedure on a real patient, with feedback/coaching from an experienced instructor. JiTT is popular in the fields of emergency medicine and pediatrics. It has not yet been widely implemented in anesthesia departments across the US, despite readily available task trainers for most basic anesthesia skills taught in UME. We report successful implementation of JiTT in the Department of Anesthesia across hospitals for all anesthesia learners, including: M3s, M4s, SAAs, residents, and fellows. STUDY AIM Measuring the use of JiTT rooms is documented as difficult in both the literature and per verbal experience shared among our colleagues. We propose the measurement of JiTT rooms/carts by use of a trail camera that is intended for use by hunters following animals via motion activation. Our hypothesis is that the trail camera will accurately capture the number of JiTT uses by learners.

METHODS: We implemented JiTT carts at three hospitals: Riley Hospital for Children, IU Health University Hospital, and Eskenazi Hospital. The trail camera was installed and attached to each JiTT cart such that anyone in the vicinity of the cart would trigger the motion detector and the camera would snap pictures at regular intervals. Pictures were stored on a microSD chip and downloaded bi-weekly to a secure, password-protected storage drive. Pictures were examined for the number of learners and types of learners. All learner data was de-identified and did not affect grades or evaluations.

RESULTS: We measured over 2000 uses of JiTT among the three institutions over three months, thus supporting the hypothesis. University Hospital had the highest JiTT usage followed by Eskenazi Hospital and then Riley Hospital for Children. This aligns with the number of learners assigned to each institution. We also noted faculty champions who emerged at each institution and were instrumental to encouraging learners and other faculty to use the JiTT setup. Unsolicited praise and excitement have accompanied the implementation of our JiTT carts as well as increased faculty interest in simulation and education research.

CONCLUSION: JiTT in anesthesia education is feasible and measurable via trail cameras. Having equipment near the operating rooms has greatly increased access to task trainers and improved the learning environment for medical students, student anesthesiologist assistants (SAAs), residents, and fellows. Future projects will examine the use of JiTT on traveling carts throughout the perioperative area, organic adoption versus incentivized or required assignments, and constructs surrounding faculty champions.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 23

Central Lines in Virtual Reality, Procedural Training in the Era of COVID-19

Alexander Pop[1], Sal Salavat Yulaman[2], Raymond Powers[1], Richard Goldmann[1], Lionel Willams[1], Sanjay Thomas[1]

[1]Vassar Brothers Medical Center, Poughkeepsie, NY, [2]University of Texas Medical Branch, Houston, TX

INTRODUCTION: In excess of 5 million Central Venous Catheters (CVC) are placed annually in the United States. Unfortunately, this life-saving procedure also has many complications associated with its placement. Adverse events pertaining to CVC placement have been shown to significantly increase morbidity, mortality, and cost to American healthcare[1]. More ubiquitously available CVC training resources are needed to address this issue. Vassar Brothers Medical Center in Poughkeepsie, New York, does not currently have a formal training program regarding CVC placement. Furthermore, the coronavirus (COVID-19) pandemic has proven to be incredibly disruptive to this type of procedural medical education. Virtual Reality (VR) technology has seen a tremendous increase in investment, popularity, and in its applications. VR can be utilized in novel training programs to teach students and medical professionals. A scoping review of 21 papers found that 74% of these studies concluded more efficacious learning through the use of VR[2]. Furthermore, physicians that learned through VR modalities were found to have better accuracy in their respective medical practice[3]. A VR based curriculum would be especially useful when teaching procedures such as CVC placement. This technology would afford medical professionals 360-degree, immersive, procedural training. This firsthand experience would be from a skilled physician's eyes performing said procedure, while additional educational media (e.g., diagrams, checklists, narration) is interjected in the virtual world. Traditionally, such an educational experience could only be offered through direct observation of procedures being performed on patients. Direct observation/participation would not only put patients at a greater risk of procedural complications but could also increase transmission of diseases such as COVID-19. VR technology can now make firsthand accounts of procedures ubiquitously and remotely available, without risking patient or student health. Participants can determine and increase their competency regarding a specific procedure prior to performing on a patient. Through the use of our novel VR based CVC curriculum, we aim to increase the cumulative CVC knowledge and confidence of our participants.

METHODS: This preliminary phase of our VR CVC training program started in July 2020 and ended in October 2020. 14 participants consisting of Nuvance Health transitional year residents participated. Participants first took a pre-training questionnaire testing core CVC subjects. Participants then put on the VR headset and completed the instructional CVC VR program. Subsequently, participants took a post-training questionnaire testing core CVC subjects. These assessments consisted of 10 multiple choice questions testing core CVC parameters. The 10 parameters that were compared pre- and post-training are described in Figure 2. Participant knowledge and confidence were evaluated through questionnaires pre- and post-training. These assessments consisted of 10 multiple choice questions testing core CVC parameters. Pre- and post-training questionnaire data comparison was analyzed through paired t-tests, with significance set to $\alpha = .05$.

RESULTS: Paired t-tests were significant for a post-intervention increase in all tested parameters (figure 2). Correct patient positioning responses increased by a mean of 42.9 % (90% CI 18.5 - 67.2, $p < 0.05$). Correct steps regarding sterile technique increased by a mean of 71.4 % (90% CI 49.2 - 93.6, $p < 0.001$). Correct responses regarding vascular anatomy of the neck increased by a mean of 50.0 % (90% CI 25.4 - 74.6, $p < 0.05$). Femoral vascular anatomy correct responses increased by a mean of 42.9 % (90% CI 12.3 - 73.4, $p < 0.05$). Correct steps regarding inadvertent arterial access increased by a mean of 57.1 % (90% CI 32.8 - 81.4, $p < 0.001$).

CONCLUSION: We attribute much of this drastic improvement in all tested CVC knowledge and confidence parameters to the use of a virtual medium. The applications of VR technology in procedural medical education are innumerable. Our VR program affords medical professionals a full sensory, immersive experience of CVC placement without having to step foot in a hospital. As we expand this program, we aim to correlate Central Line-Associated Bloodstream Infection rates to the incorporation of our VR curriculum.

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Figure 1. Example of our VR Curriculum and Setup

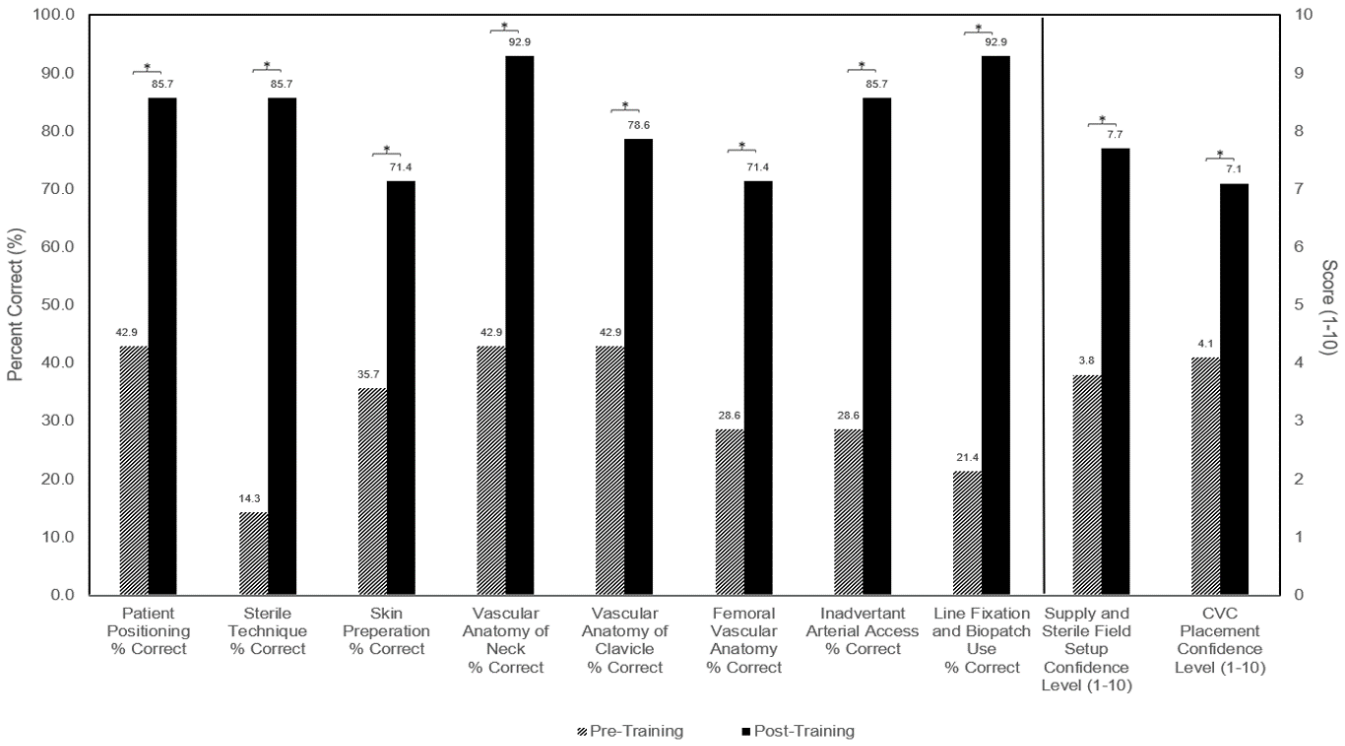
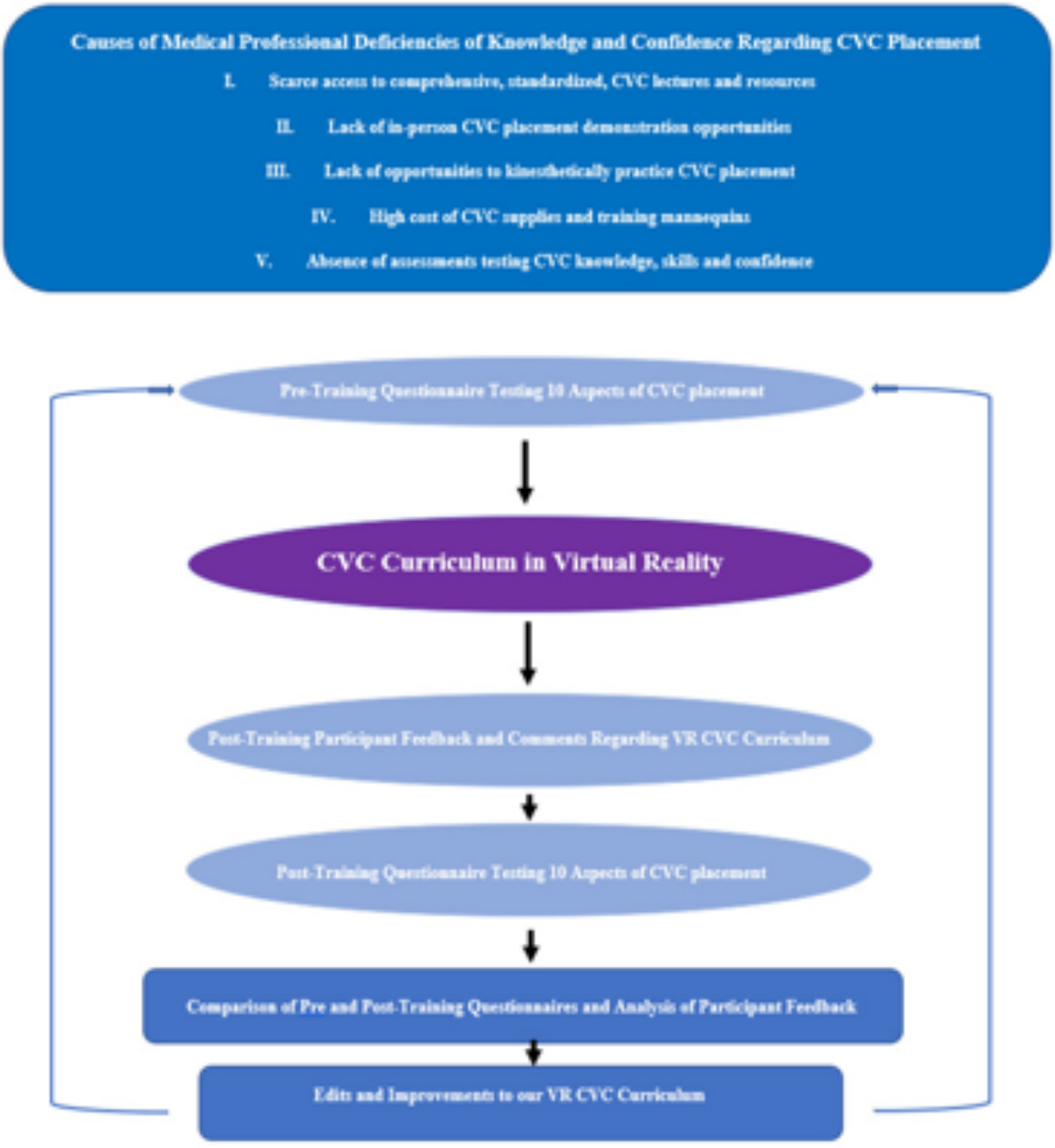


Figure 2. Comparison of Pre and Post Training CVC Questionnaires

Figure 3



TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 24

HoloSIM: Development and Usability Testing of a Mixed Reality Medical Crisis Telesimulation Platform

Julian Wiegelmann[1], Lilia Kaustov[2], Stephen Choi[3], Fahad Alam[3]

[1]University of Toronto, Toronto, Ontario, [2]University of Toronto, Toronto, Canada, [3]Sunnybrook Health Sciences Centre, Toronto, Ontario

INTRODUCTION: The current state-of-the-art in medical simulation and assessment is mannequin based and utilizes highly specialized personnel, equipment, and dedicated space. Costs are exorbitant[1] and therefore access is limited. The Microsoft Hololens[2] head-mounted display allows for mixed reality: spatially stable, interactable, and animated holograms inserted into a user's workspace. This permits the augmentation of existing operating rooms and training spaces with holographic (i.e. virtual) equipment and patients. In addition, ubiquitous resources such as CPR training mannequins may be extended to have animations, interactivity, and dynamic visual features as required. High-speed internet connections allow parameter monitoring and control from any distance (i.e. telesimulation).

METHODS: An iterative software design and prototyping process involving cycles of piloting and usability feedback occurred over a one-year period. Input from resident and staff anesthesiologists was incorporated following demonstration sessions. Usability and learner satisfaction were assessed via a questionnaire tailored to the desired final software features following a demonstration session with either staff or resident level Anesthesia department members.

RESULTS: The developed telesimulation platform, HoloSIM, allows a wide variety of medical emergencies involving a holographic patient to be initiated using laptop-based instructor software. Immersed in the mixed reality simulations, learners undertake the decision-making steps in managing the medical care for a patient with an acute medical crisis. They then navigate through the scenarios that-by instructor control-provide feedback depending on their actions in the form of either the patient's hemodynamic changes, verbal prompts from the holographic patient in the scenario, or a holographic medical team confederate. We have designed the HoloSIM 'student experience' for use with typical Hololens controls of intuitive hand gestures and directing visual gaze towards holographic areas of interest. A limited set of dialogue, facial expressions, animations, clothing, skin visual cues, auscultations, physical exam findings, holographic confederates, and patient monitor physiologic changes have been incorporated to date. However, the underlying prototype program structure has been designed to allow this catalogue to be rapidly and easily expanded, allowing the software to be used to simulate a practically limitless variety of crisis scenarios. See the attached images for examples of a learner interacting with a holographic patient with the HoloSIM software. Eight demonstration and usability testing sessions lasting approximately 15 minutes have occurred to date, six with residents and two with staff department members. All participants rated the software favourably regarding likeability/effectiveness, user interface, system outputs such as graphical quality, fidelity of crisis simulations, and immersion. No ergonomic issues with the Hololens 2 Headset were identified. All participants indicated they would participate in this type of simulation in the future.

CONCLUSION: This is the first report, to our knowledge, of a mixed reality telesimulation capable platform. These early results suggest mixed reality medical crisis simulation on the Microsoft Hololens 2 is feasible and usable. Mixed reality technology could potentially create infinite numbers of immersive clinical scenarios. This modality could provide a lower cost learning and assessment platform that can align with any context-specific clinical practice and professional development. Further work is needed to delineate the effect on user acquisition of technical and non-technical skills and the feasibility of mixed reality based telesimulation curricula.

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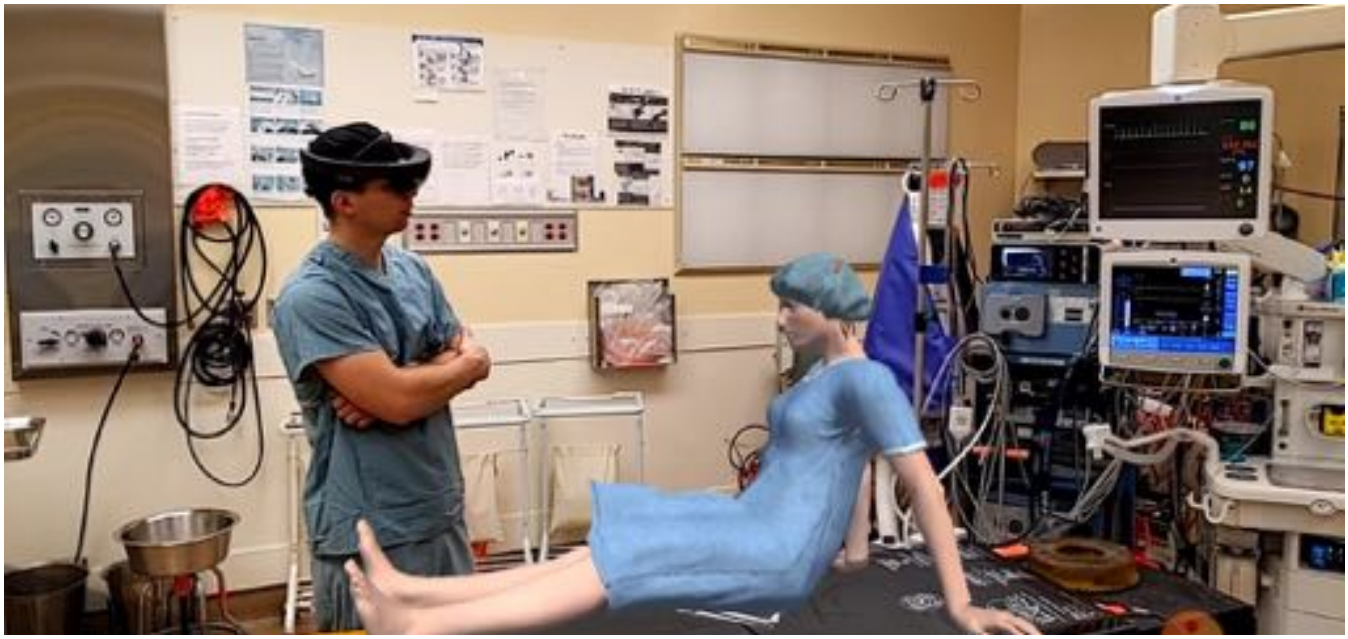

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 25

Photoplethysmography Dropout in COVID-19

Jacquelin Peck[1], Frederick Hasty[1], Guillermo Garcia[2], Hector Davila[3], S H Wittels[2]

[1]Mount Sinai Medical Center, Miami Beach, FL, [2]Mt. Sinai Medical Center, Florida, Miami, FL, [3]Mount Sinai Medical Center of Florida, Miami, FL

INTRODUCTION: Photoplethysmography is highly prevalent in modern medicine and is the science behind pulse oximetry monitoring. Photoplethysmography dropouts (waveform depressions more than one standard deviation below the moving mean waveform voltage) are waveform findings that rarely appear in healthy patients but have been noted in COVID-19 patients. The aim of this study is to compare rates of COVID-19 photoplethysmography dropout to healthy controls.

METHODS: This IRB-approved prospective, observational, cohort study compares photoplethysmography waveform dropouts and skew from 197 COVID-19 positive ICU patients to 300 healthy controls using a noninvasive armband monitor. COVID-19 disease status was confirmed using SARS-CoV-2 RT-PCR. Because D-dimer is an established marker for COVID-19, photoplethysmography dropouts for the 197 COVID-19 patients were also compared to serum D-dimer levels[1,2].

RESULTS: Results are displayed in Table 1. 100% of COVID-19 patients displayed photoplethysmography dropouts compared to only 2.3% of healthy controls. COVID-19 patients had significantly higher median photoplethysmography dropout rates than healthy controls (dropouts in 58% of heartbeats [IQR: 42% – 72%] vs 0% [IQR: 0% - 0%], p<<0.05). The maximum observed photoplethysmography dropout rate among healthy controls was 1%, which is significantly lower than the lowest recorded rate of photoplethysmography dropout among COVID patient (11%) and was likely caused by patient motion artifact. Sample photoplethysmography waveforms are shown in Figures 1 and 2. Median photoplethysmography skew, a measure of waveform symmetry, was more likely to be negative among COVID-19 patients than healthy controls (-0.43 [IQR: -0.70, -0.20] vs. 0.60 [IQR: 0.38, 0.87], p<<0.05). Photoplethysmography skew is plotted for all included patients in Figure 3. Photoplethysmography dropout showed strong correlation with serum D-dimer levels (Figure 4). This pattern was statistically significant following linear regression ($R2 = 0.919$ ($p < 0.05$)) (Figure 5).

CONCLUSION: Analysis of photoplethysmography showed significant differences between COVID-19 patients and healthy controls. Photoplethysmography findings may have clinical application for COVID-19 detection, however ongoing research is being conducted to determine the sensitivity and specificity of our findings for COVID-19 screening.

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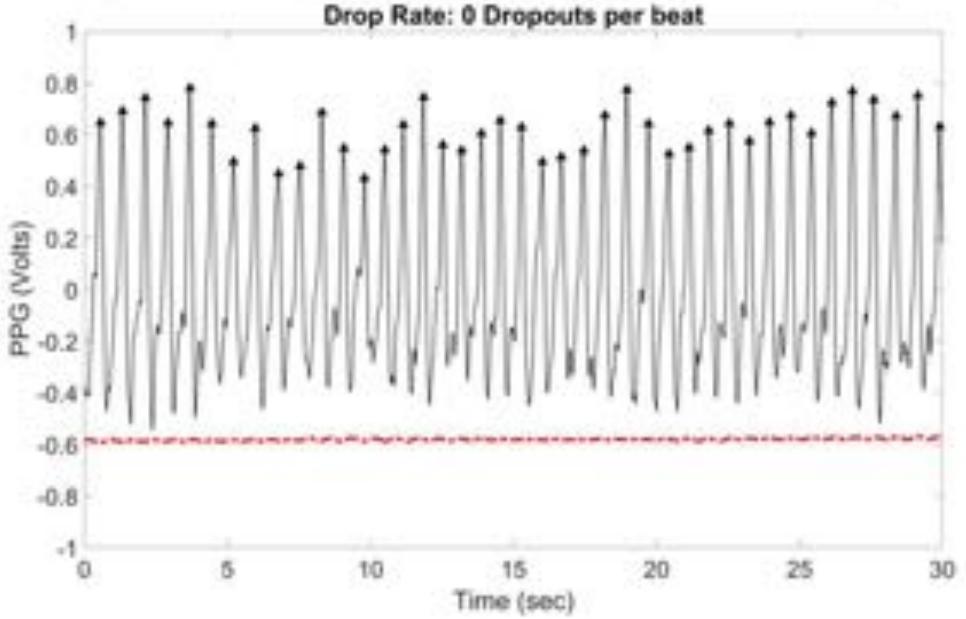
Table 1. Photoplethysmography Dropout Rates and Skew among COVID-19-Positive and COVID-19-Negative Patients

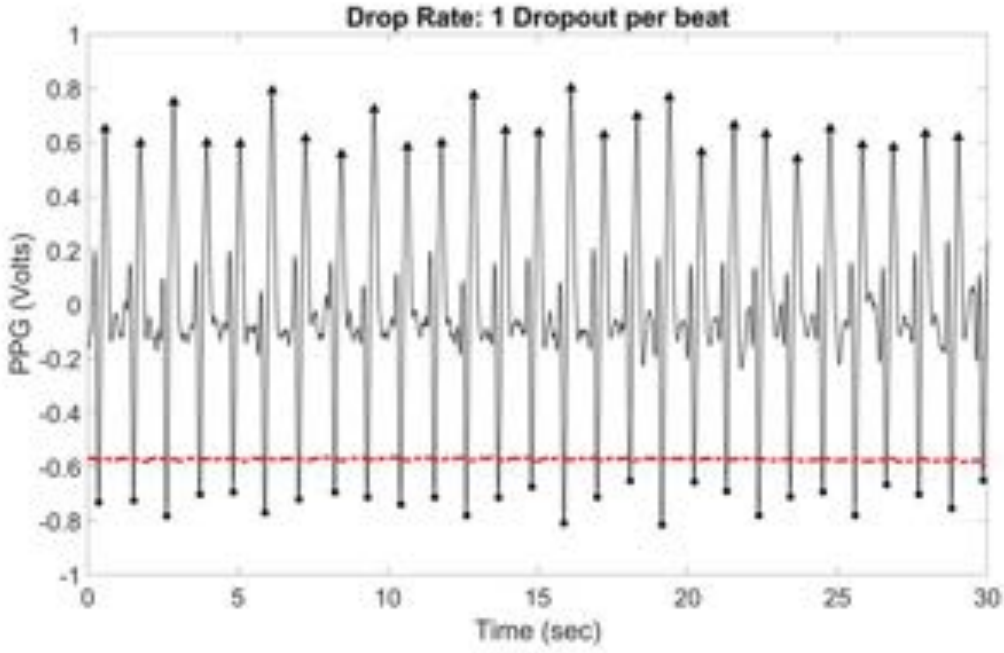
COVID-19 Status	COVID-19 Positive (n=197)	COVID-19 Negative (n=300)	p-value
Drop rate in dropouts/beat, median (IQR)	0.58 (0.42 – 0.72)	0.00 (0.00 – 0.00)	<< 0.05
Number with dropouts (%)	197/197 (100.0%)	7/300 (2.3%)	-
Max dropout rate	1.00	0.01	-
Min dropout rate	0.11	0.00	-
Skew, median (IQR)	-0.43 (-0.70, -0.20)	0.60 (0.38, 0.87)	<<0.05
Max Skew	0.3	1.25	-
Min Skew	-1.15	-0.02	-

Figure 1. Representative Photoplethysmography Tracing from a COVID-19 Negative Patient.



*The black solid line demonstrates a representative, PPG waveform taken from a NON-COVID subject. The bias was removed, and the PPG was normalized for clarity. Black triangles represent detected peaks utilized for calculating pulse rate. The red dot dash line marks PPG moving mean minus standard deviation. Since dropouts (excursions below the dotdash line) are not present here, the drop rate is zero.

Figure 2. Photoplethysmography tracing from a COVID-19 Positive patient.



*The black solid line demonstrates a representative, raw PPG waveform taken from a COVID subject. The bias was removed and the PPG was normalized for clarity. Black triangles represent detected peaks utilized for calculating pulse rate. The red dotdash line marks PPG moving mean minus standard deviation. Black circles denote dropouts or excursions below the red dotdash line. Since a dropout occurs for every beat the drop ratio is 1. Drop rate is the ratio of dropouts per minute and beats per minute.

Figure 3. PPG Skew scatter plot comparing skew for COVID-19 Negative and Positive subjects. The solid red line is set a zero. COVID-19 positive subjects typically have a negative skew and COVID-19 negative subjects typically have a positive skew.

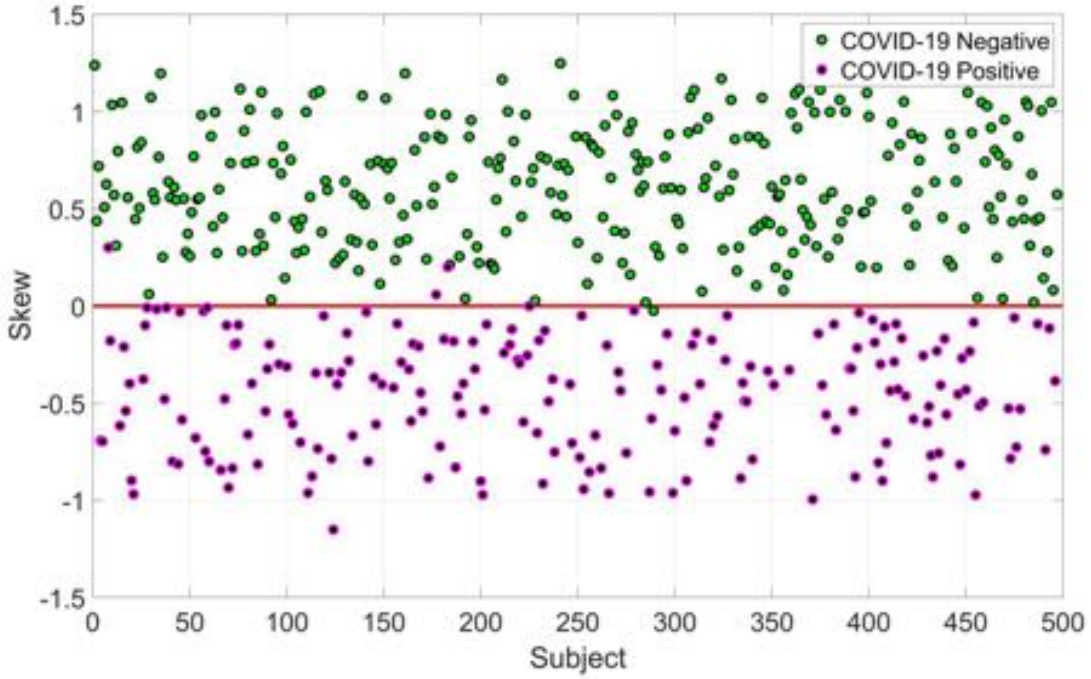


Figure 4. Sample D-Dimer Protein Level and PPG Drop Rate Plotted over Time

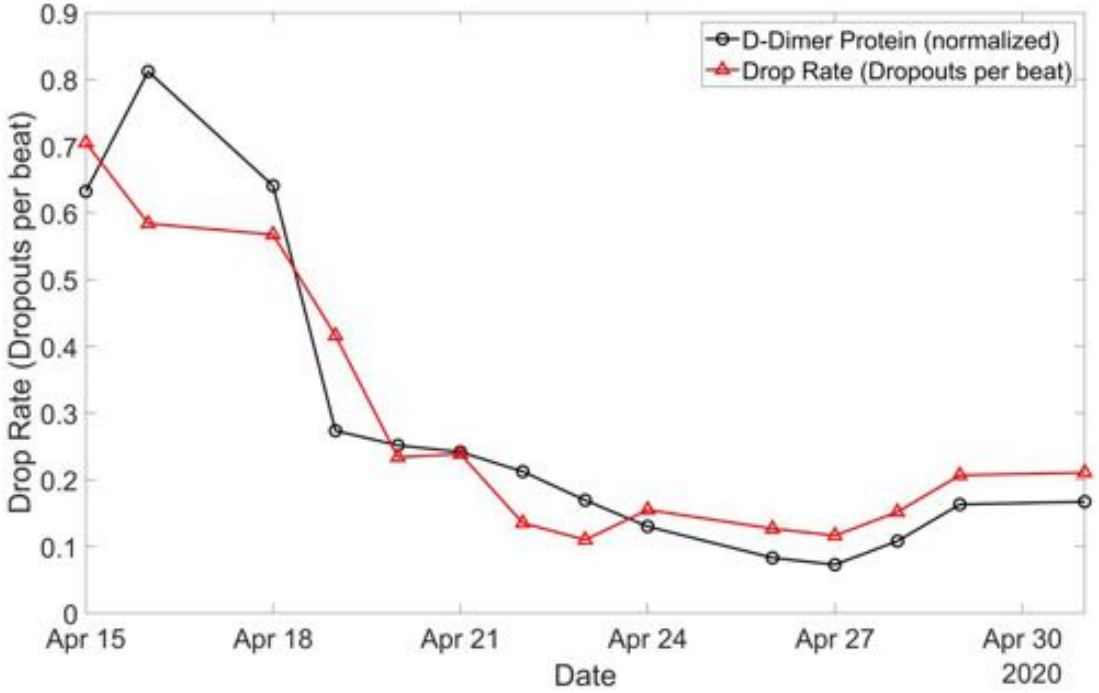
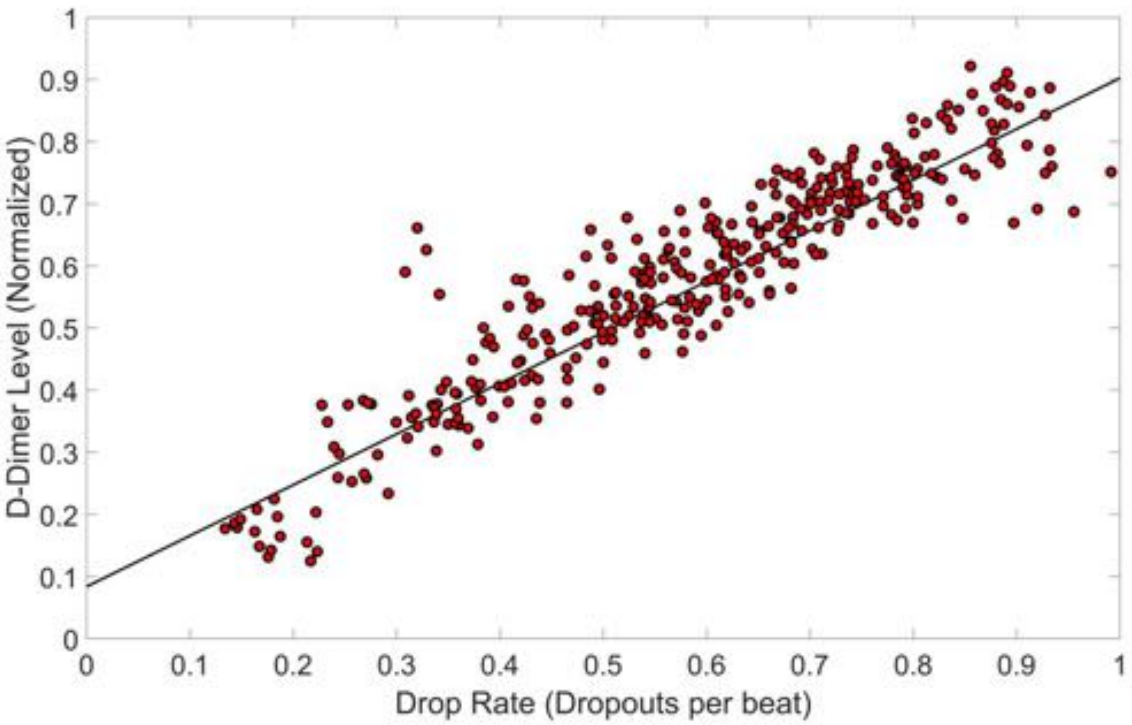


Figure 5. Plot of D-dimer vs. PPG Drop Rate following Linear Regression Analysis



TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 26

The neurological injury motion sensing (NIMS) project: quantifying, decoding, and validating accelerometry features in the neurocritical care setting

Shubhayu Bhattacharyay[1], Robert D Stevens[2]

[1]University of Cambridge, Cambridge, UK, [2]The Johns Hopkins University School of Medicine, Baltimore, MD

INTRODUCTION: Despite a consistent relationship observed between physical activity and functional outcomes in patients with severe neurological injury (SNI)[1-5], methods to objectively monitor patient motion in the critical care setting are limited. In this work, we implement and validate an automated system of ambient motion sensing in the neurosciences critical care unit (NCCU) through a wearable matrix of unobtrusive, tri-axial accelerometers. Our general hypothesis is that the quantitative analysis of time-series accelerometry can yield neuromechanical biomarkers that can automate motor evaluations and enhance the prediction of state transition in SNI patients.

METHODS: Six accelerometers (sample rate: 10 Hz, amplitude: ±16 g) were placed on each of the elbows, wrists, and ankles (Fig. 1) of SNI patients (n = 69). Across the total recording duration of each patient (median: 24.09 hours), we extracted the following six types of motion features from non-overlapping 5-second windows of filtered accelerometry: signal magnitude area (SMA)[6], a pair of high-frequency component and low-frequency component time-domain medians (HLF)[7], median frequency (MFR)[8], frequency-domain entropy (FDE)[9], band power between 0.3 and 3.5 Hz (BPW)[10], and level 2 – 6 detail coefficients of the 5th-order Daubechies wavelet transform (WVL)[11]. Missing feature values were replaced with stochastic multiple imputation (m = 9) and external movements were corrected from a sensor placed on the bed. Motion features across extremity sensors were binned by four different observation windows (0.5, 1, 3, and 6 hours) directly preceding Glasgow Coma Scale (GCS) evaluations which coincided with recordings (n = 653). Dimensionality reduction and relative importance assessment of the features was performed using linear optimal low-rank (LOL) projection with the motor sub-score of GCS (GCSm) as the outcome label. Reduced features then served as predictors for multiclass logistic regression models to detect GCSm on validation sets.

RESULTS: In spite of regular bedside interventions, interfering equipment, and frequent patient migrations for surgery, imaging, or interunit transfers, sensors successfully monitored extended periods of ambient, multi-segmental SNI motor activity with high fidelity (median: 1.56% median missingness per patient) and no inconvenience to clinical staff or patients (Fig. 2). SNI patients are largely inactive (median: 5.34% active extremity movement per patient) and percentages of daily activity were significantly ($\alpha = 0.05$) positively correlated with GCSm ($\rho = 0.25$) (Fig. 3). Upper extremity-based features were more important than ipsilateral lower extremity-based features ($p < 0.0001$) while right-side-based features are more important than contralateral left-side-based features ($p < 0.0001$). Frequency-domain entropy (FDE) and signal magnitude area (SMA), particularly of the right wrist, were the most important features in explaining the variance of GCSm (Fig. 4). Our results also suggest that a combination of both time-domain features and frequency-domain features is advisable for GCSm discrimination. Models discriminate GCSm: 1–4 excellently (AUROC > 0.80), GCSm: 6 acceptably (AUROC > 0.70), and GCSm: 5 poorly (AUROC > 0.60), and model performance and calibration improve significantly as observation window increases from 1 hour to 3 or 6 hours (Fig. 5). Our results suggest that the observation window of accelerometry should span at least 3 hours before prediction or detection of the event of interest.

CONCLUSION: We demonstrate the feasibility of an automated sensor-to-feature approach of quantifying motion in the NCCU using accelerometry. The motion features we extracted from accelerometers are validated against GCSm, though further exploration of machine learning methods is necessary for reliable, automatic classification. Results support the development and integration of automated motion capture in the NCCU in the hopes of delivering individualized treatment and prognosis for SNI patients.

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Figure 2

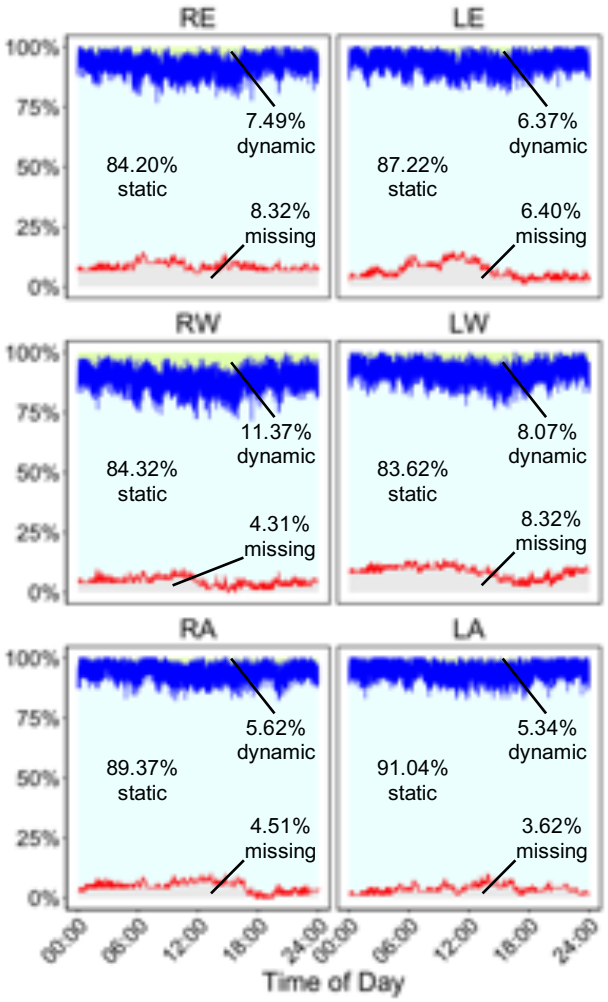

Fig. 2: Characterization of missing, static, and dynamic accelerometry data by time of day of recording and sensor placement (bed sensor excluded) across the entire study population. The red line represents the percentage of missing data per time of day and the blue line represents percentage of missing data plus the percentage of static activity (SMA < 0.135 g) per time of day. Thus, the light grey shaded area represents the percentage of total missing data, the light cyan shaded area represents the percentage of total static activity, and the light green shaded area (barely visible) represents the percentage of total dynamic activity.

TECHNOLOGY, COMPUTING AND SIMULATION, EQUIPMENT MONITORING 27

Using a Natural Language Processing Machine Learning Model to Classify Subarachnoid Hemorrhage Patients with Delayed Cerebral Ischemia

Matthew W Ison[1], Blake Moore[2]

[1]University of Tennessee Health Science Center, Graduate School of Medicine, Knoxville, TN, [2]UTHSC Graduate School of Medicine, Knoxville, TN

INTRODUCTION: Delayed cerebral ischemia (DCI) is a complication that occurs in 30% of all subarachnoid hemorrhage (SAH) patients. It is the leading cause of death and disability in those who survive the initial event[1]. It is notoriously difficult to define. In 2010, a consensus definition was published to create consistency for research[2]. The diagnosis of DCI is often never made. ICD-9 code 435.9 is used to signify DCI in SAH patients however, this code is rarely used. In fact, it was not used at all in any of the SAH patients within the MIMIC III database. MIMIC III v1.4 is a database containing information on almost 60,000 ICU admissions[3]. The database offers a large number of clinical variables that can be used to gain insights into disease and treatment. However, in the case of DCI, there is no way to easily define these patients for further study. Using natural language processing, a subset of machine learning, it is possible to classify patients using their unstructured clinical text documents.

METHODS: Among 58,361 hospital admissions in the MIMIC database, 413 had SAH. 19,950 documents from these SAH patients were available to be analyzed. First, the texts underwent a process of cleaning that consisted of removing numbers, punctuation, white space characters and symbols. Then stop words, common words that have little weight on the meaning of the text, such as 'the', 'it', 'and', etc, were removed. The text was then tokenized, which is a process of creating single word entities. Finally, the tokens were grouped into n-grams, groups of 2 or more tokens that occur next to each other within the text. The n-grams were vectorized using 'term frequency*inverse document frequency' or tfidf. This is a process of assigning a weight to each n-gram according to how frequently it occurs in the documents. N-grams that occur more frequently are less likely to influence the classification of the patient. All 413 SAH patients were manually classified as having had DCI or not. The models were trained using a 10-fold cross-validation. This is a process by which the model gets trained on 9/10ths of the data and gets tested on 1/10th, repeating this process until it has trained and tested on the entire set of data. At the completion of each cycle, the model "forgets" what it has learned in the previous fold. Finally, receiver operating characteristic curves were generated for 3 different machine learning models. Support vector machine classifier, random forest classifier, and decision tree classifier models were trained. The work was done using Python, Pandas, Numpy, and Sci-kit learn[4-6].

RESULTS: Two of the three models stood out as having good predictive ability for the task of classifying patients with DCI. The random forest classifier (RFC) and support vector classifier (SVC) were the best performers with AUC-ROC of 89 and 87%, respectively, while both had a standard deviation of 0.06. The decision tree classifier (DTC) had the poorest performance among the 3 models with an AUC-ROC 0.71 and a standard deviation of 0.07.

CONCLUSION: The diagnosis of DCI can be subjective and difficult to make with certainty. A machine learning model that can classify patients with DCI is a useful tool. Not only is the diagnosis often never made but, DCI is often confused with vasospasm. In this report, with the use of natural language processing tools and machine learning algorithms, DCI patients were classified with a good degree of recall or sensitivity. The aim of creating this model is to use it for further study of DCI patients within databases in which the diagnosis is not clear. The performance of the algorithm also raises the possibility that a tool like this could be used in the clinical setting to make the diagnosis from texts in the EMR.

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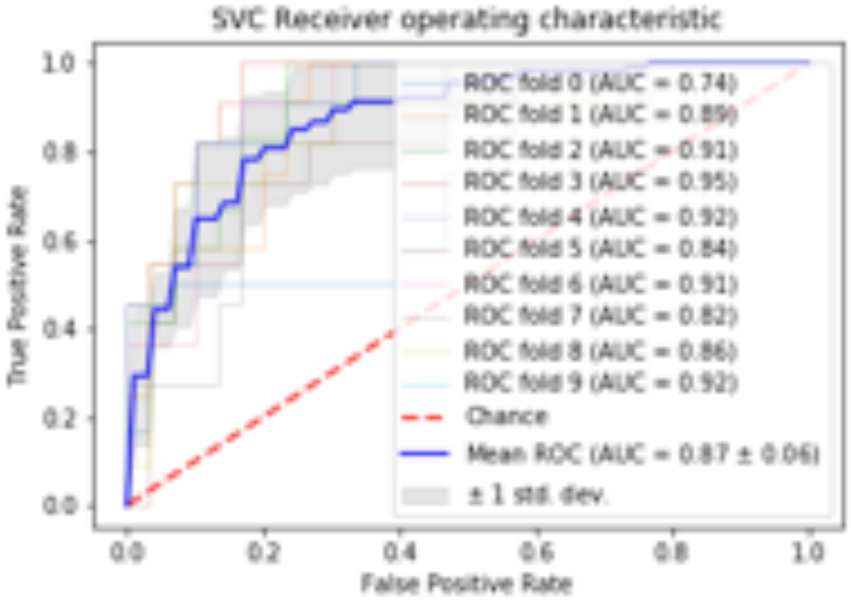

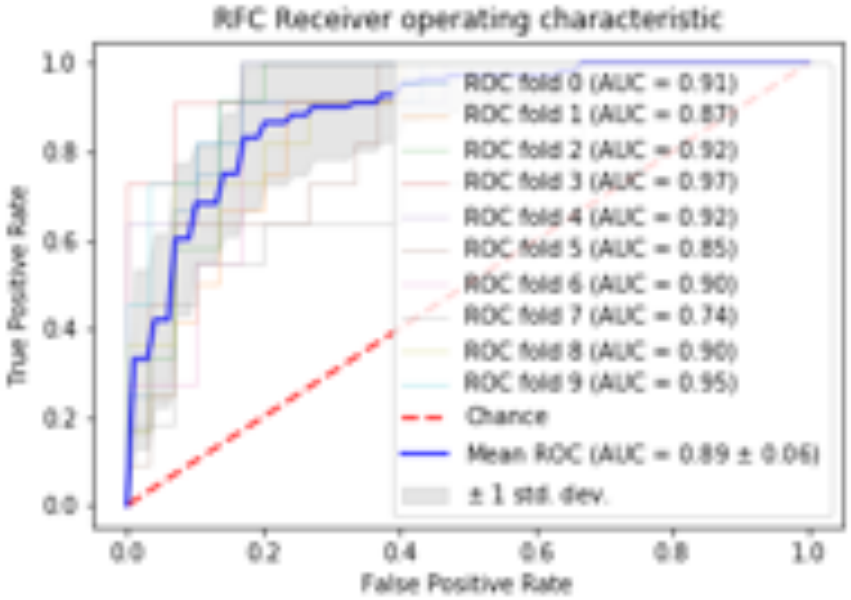

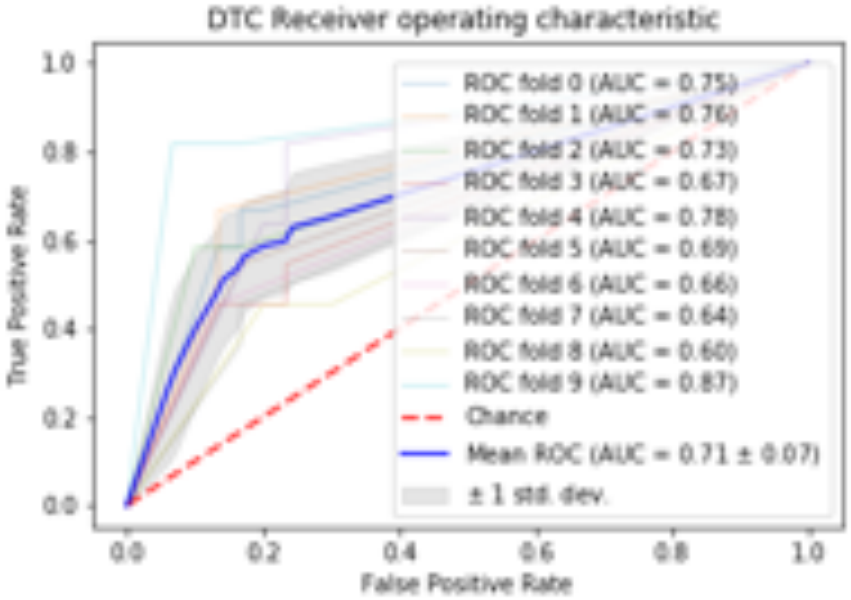

Subspecialty Abstracts

TRAUMA

TRAUMA 1

Impact of Trauma Resuscitation Guidelines on Blood Product Utilization

Brooke Calabrese[1], Nick Schiavoni[1], Laura Kirk[1], Lauren Mclaughlin[1], Stephanie Vega[1], Alexander M Kaizer[2], Fareedul Azam[1], Erik Nelson[3]

[1]University of Colorado, Aurora, CO, [2]Alexander Mark Kaizer, PhD (feel free to use M. or nothing for the middle name depending on what others are using) University of Colorado-Anschutz Medical Campus, Denver, CO, [3]University of Colorado, Denver, CO

INTRODUCTION: It has been established previously that organized teamwork training improves the care of trauma patients. The Anesthesia Quality Institute reported that 'Teamwork and Collaborations' have resulted in improved patient outcomes in trauma care. In the final phase of our Department of Anesthesiology's Trauma Anesthesiology Quality Improvement Project, we hypothesized that using standardized guidelines and continued education would show improved trauma patient blood product utilization and patient resuscitation indices.

METHODS: Trauma Anesthesiology Guidelines were drafted and released to the Department of Anesthesiology in 2014 based on a literature search of the most current trauma resuscitation practices and modified in 2017 after review by faculty and residents in the Departments of Anesthesiology and Surgery, Trauma and Acute Care Division. Data analysis was restricted to the University of Colorado Hospital. After IRB approval, pre-guideline and post-guideline data were collected on all operative trauma alerts/activations, from local and national prospective trauma registries with additional information extracted from manual chart review. Data was collected from 01/01/2015 to 12/31/2018 with 147 patients included. Time periods analyzed were based upon the following events: Grand Rounds presentation (GR, 09/2015), Quality Improvement Project update at Grand Rounds (QIP, 08/2016), and Version 2 of Trauma Guidelines (V2, 11/2017). In the analyses, these periods are referred to as Pre-GR, Post-GR, Post-QIP, and Post-Guidelines V2. The data were analyzed using linear and logistic regression modeling to compare changes over time in continuous and dichotomous outcomes, respectively. Outcomes measured were thromboelastography (TEG) utilization, blood product utilization, and laboratory values. Blood products analyzed were packed red blood cells (PRBC), fresh frozen plasma (FFP), platelets (plt), and cryoprecipitate (cryo). Laboratory values measured were starting and ending hemoglobin (Hgb), platelet count, pH, PaCO2, PaO2, SaO2, base excess, ionized calcium, INR, and TEG results including R-time, K-time, alpha-angle, maximum amplitude (MA), and lysis at 30 minutes (Ly30).

RESULTS: TEG utilization increased with time (OR 1.63 for one-year period, p 0.008) and each 10-unit increase in Injury Severity Score (ISS) (OR 1.59, p<0.001). In patients receiving TEG (vs. no TEG), adjusted for confounding factors, there was increased administration of units of FFP in the first 4 (8.1 vs 3.8, p 0.033) and 24 (10.3 vs 3.9, p 0.007) hours, units of plt in the first 4 (1.4 vs 0.5, p 0.010) and 24 (2.8 vs 0.5, p 0.014) hours, and an increased ratio of FFP/RBC (0.8 vs 0.4, p 0.047) and plt/RBC (0.2 vs 0.1, p 0.005) in the first 24 hours. No difference was seen in administration of RBC in the first 4 (9.7 vs 7.0, p 0.180) or 24 (12.0 vs 7.4, p 0.061) hours or cryo in the first 4 (8.7 vs 0.1, p 0.240) or 24 (8.7 vs 9.5, p 0.991) hours. No change was seen in Hgb (11.4 vs 10.5, p 0.098), platelet count (168.4 vs 179.5, p 0.447), pH (7.3 vs 7.3, p 0.360), or INR (1.4 vs 1.5, p 0.577) pre- and post-guidelines, adjusted for confounding factors. There was no difference in TEG values including R time (5.0 vs 5.2, p 0.869), K time (3.2 vs 1.8, p 0.451), alpha angle (59.4 vs 64.1, p 0.776), MA (51.9 vs 61.5, p 0.941), or Ly30 (0.2 vs 0.1, p 0.416), unadjusted due to small sample size.

CONCLUSION: Trauma Anesthesiology Guidelines and continued provider education showed improved utilization of blood product administration with the recommended massive transfusion protocol product ratio of 1:1:1, as well as TEG utilization. TEG utilization may have improved blood product choices during resuscitation, especially with respect to FFP/PRBC and plt/RBC ratios. Early cryoprecipitate usage was also improved, though the sample size was too small to detect a significant change. While there was no difference in laboratory values post-resuscitation, patient care was improved in choices in blood product utilization via TEG guidance. Our small sample size of patients receiving TEG pre-guidelines limits our analysis of changes in TEG values and a trend toward improved values was seen. During the study time period, the Department of Surgery changed their trauma resuscitation protocols which may have influenced the results. Future studies are needed to determine if changes in patient outcome, mortality, and morbidity are related to this specific trauma care quality improvement project.

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Table 1. Firth's penalized logistic regression models examining TEG utilization over time

Covariate	OR	95% CI	p-value
Model 1: Time in Periods			
Intercept	0.034	(0.000, 0.257)	<0.001
Post-Grand Rounds (vs. Pre-GR)	5.80	(0.552, 790.403)	0.163
Post-QIP (vs. Pre-GR)	12.43	(1.459, 1,630.217)	0.016
Post-Guidelines V2 (vs. Pre-GR)	15.49	(1.882, 2,018.769)	0.006
Model 1b: Time in Periods, Adjusted for ISS			
Intercept	0.013	(0.000, 0.118)	<0.001
Post-Grand Rounds (vs. Pre-GR)	6.07	(0.546, 841.304)	0.161
Post-QIP (vs. Pre-GR)	12.59	(1.385, 1,679.222)	0.020
Post-Guidelines V2 (vs. Pre-GR)	14.78	(1.685, 1,955.471)	0.010
Injury Severity Score (Increments of 10)	1.59	(1.218, 2.141)	<0.001
Model 2: Time as Continuous Measure			
Intercept	0.11	(0.035, 0.290)	<0.001
Time from Jan 2015 (Years)	1.63	(1.129, 2.420)	0.008
Model 2b: Time as Continuous Measure, Adjusted for ISS			
Intercept	0.04	(0.010, 0.143)	<0.001
Time from Jan 2015 (Years)	1.59	(1.080, 2.434)	0.018
Injury Severity Score (Increments of 10)	1.59	(1.22, 2.13)	<0.001

Table 2. Linear regression models comparing the amount of blood products for TEG vs. no TEG among those who received blood products

Outcome	TEG Mean (SD) [N]	No TEG Mean (SD) [N]	Unadj. Diff. (95% CI)	Unadj. p-value	Adj. Diff. (95% CI)	Adj. p-value
RBC First 4 Hours	9.7 (10.3) [29]	7.0 (11.0) [21]	2.7 (-3.2, 8.6)	0.371	3.6 (-1.7, 9.0)	0.180
RBC First 24 Hours	12.0 (12.4) [29]	7.4 (10.9) [21]	4.7 (-1.7, 11.0)	0.152	5.8 (-0.3, 11.8)	0.061
FFP First 4 Hours	8.1 (9.4) [29]	3.8 (9.1) [21]	4.3 (-0.8, 9.4)	0.101	4.9 (0.4, 9.4)	0.033
FFP First 24 Hours	10.3 (11.6) [29]	3.9 (9.1) [21]	6.4 (0.8, 12.0)	0.025	7.4 (2.0, 12.7)	0.007
FFP/RBC Ratio (First 24 Hours)	0.8 (0.3) [29]	0.4 (0.5) [21]	0.4 (0.1, 0.6)	0.006	0.3 (0.0, 0.6)	0.047
Platelets First 4 Hours	1.4 (1.7) [29]	0.5 (1.0) [21]	1.0 (0.2, 1.7)	0.010	1.2 (0.3, 2.1)	0.010
Platelets First 24 Hours	2.8 (5.9) [29]	0.5 (1.0) [21]	2.3 (0.2, 4.5)	0.035	2.8 (0.6, 5.1)	0.014
Plate/RBC Ratio (First 24 Hours)	0.2 (0.2) [29]	0.1 (0.1) [21]	0.1 (0.0, 0.2)	0.003	0.2 (0.0, 0.3)	0.005
Cryo First 4 Hours	8.7 (45.8) [29]	0.1 (0.4) [21]	8.6 (-7.8, 25.0)	0.304	10.0 (-6.7, 26.6)	0.240
Cryo First 24 Hours	8.7 (45.8) [29]	9.5 (43.6) [21]	-0.8 (-25.3, 23.7)	0.949	-0.2 (-26.7, 26.4)	0.991
Cryo/RBC Ratio (First 24 Hours)	0.2 (0.8) [29]	1.9 (8.7) [21]	-1.7 (-5.4, 1.9)	0.349	-1.9 (-5.8, 2.0)	0.345

TRAUMA 2

Reduction in Cerebral Blood Flow During Aeromedical Evacuation-Relevant Hypobaria Following Rat Traumatic Brain Injury

Gary Fiskum[1], Rao Gullapalli[1], Julie Proctor[1], su xu[1], Catriona H Miller[2]

[1]University of Maryland School of Medicine, Baltimore, MD, [2]Air Force Research Labs, Baltimore, MD

INTRODUCTION: Simulated aeromedical evacuation (AE), or hypobaria equal to 8000 ft cabin pressure, worsens neurologic and neuropathologic outcomes after traumatic brain injury (TBI) in several animal models and species[1-5]; however, the underlying mechanisms responsible for this form of secondary brain injury are unknown. This study tested the hypothesis that cerebral blood flow (CBF) is reduced following TBI in rats and is further reduced during exposure to AE- relevant hypobaria at 24 hr post-injury.

METHODS: All animal protocols were approved by the Univ. of Maryland, Baltimore Institutional Animal Care and Use Committee and by the US Air Force Research Oversight and Compliance Division (SGE-C). The animal TBI model consisted of controlled cortical impact with adult male rats. Shams underwent anesthesia and craniotomy but no impact. Naïve rats had no surgery. Magnetic resonance imaging (MRI) and spectroscopy (MRS) measurements were performed 1 week prior to Sham or CCI, 1 day after CCI, followed by during 6 hr AE, and at 14 days post- injury. For each 2 hr scan, isoflurane anesthetized rats were placed in an MRI-compatible, custom built hypobaric chamber and then positioned within the bore of the 7 Tesla magnet. MRI and MRS measurements during AE were made under a combination of normoxic (30-40% O2) or hyperoxic (100% O2) conditions and normobaric (sea level) or hypobaric (equivalent to 8000 ft) barometric pressures. Arterial spin labeling was used to measure brain region-specific blood flow.

RESULTS: Cerebral blood flow was reduced by 30 to 40% in the ipsilateral cortex and hippocampus at 24 hr post-CCI. Additional reductions in CBF were observed during exposure of CCI rats to normoxic or hyperoxic hypobaria in the ipsilateral and contralateral hippocampus and thalamus. This reduced CBF occurred under both normoxic and hyperoxic conditions. Moreover, blood flow in the thalamus was reduced by an additional 40% specifically in Shams exposed to hypobaria. Rats in the Sham group underwent a craniotomy, which results in mild inflammation and tissue damage. We therefore included an additional group of naïve rats to detect any effects of hypobaria on uninjured rats. Remarkably, there was a small, 10% reduction in CBF during exposure to hypobaria, relative to the flow rate present prior to hypobaric exposure. Lactate levels present in the ipsilateral cortex one day after CCI rose to 7 times greater than baseline. Lactate rose an additional 46% in rats under normobaric hyperoxia compared to levels present a 4 hr prior to exposures. There was a 45% increase in lactate when rats were exposed to normobaria under 100% O2. Lactate present in the cortex of all groups normalized by 14 days post-injury. There was also a 65% reduction in ipsilateral glutathione one day following CCI, followed by an additional 60% reduction during exposure to normobaria under 100% O2.

CONCLUSION: Exposure to AE-relevant hypobaria one day after moderate TBI or Sham surgery reduced CBF in the cerebral cortex and hippocampus. During flight, there was an increase in cortical lactate in rats exposed to normobaria under 100% O2 compared to rats exposed to hypobaria under 100% O2. Thus, being exposed to normobaria under 100% O2 creates more metabolic stress than hypobaria under high O2. Cortical glutathione levels fell after TBI and were exacerbated by exposure to normobaria under 100% O2. This finding indicates that there is more oxidative stress when exposed to normobaric hyperoxia compared to hyperbaric hyperoxia. When comparing the CBF and neurochemical outcomes across the animal groups, the CCI group that fared the best was the one with rats maintained under normobaric and normoxic conditions. These results support the recommendation that TBI patients should either wait at least several days before flying or fly at cabin pressures higher than those typically used. In addition, the use of unnecessarily high levels of supplemental O2 should be avoided during flights as hyperoxia can worsen oxidative stress and metabolic dysfunction.

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TRAUMA 3

Induction in Trauma Patients: Etomidate vs. Propofol on Mortality and Hemodynamics

Shay Huang[1], David Glick[2], Avery Tung[3]

[1]University of Chicago Pritzker School of Medicine, Chicago, IL, [2]University of Chicago, Chicago, IL, [3]The University of Chicago Medicine, Chicago, IL

INTRODUCTION: Traumatic injury is the leading cause of death for adults under age 45.[1] When trauma patients require emergent surgery, an ongoing question is whether anesthetic induction with etomidate is more hemodynamically stable and results in better long-term survival than propofol. [2] Because trauma victims are often hypovolemic due to hemorrhage, vasodilatory effects of propofol may cause or worsen hemodynamic instability. Conversely, although anesthetic induction with etomidate may be more hemodynamically stable, suppressive effects of etomidate on adrenal function may worsen long term outcomes after surgery.[3,4] To evaluate the impact of induction agent on peri-induction hemodynamic variables and postoperative outcome, we reviewed intra and postoperative outcomes in emergent trauma cases from an urban Level I trauma center.

METHODS: Because all data were deidentified, this study was exempt by the Institutional Review Board. We conducted a retrospective chart review of all patients who underwent emergent trauma surgery on the day of admission from an urban Level I trauma center from May 1 to November 9, 2020. Data collection included demographic information, ASA physical status score, method of injury, blood transfusion prior to induction, hemodynamic variables (systolic and diastolic blood pressure and heart rate), and time of intubation (night vs. day). Our primary outcomes included change in blood pressure and heart rate post induction, and mortality in the operating room or during the hospitalization. Data were analyzed between groups using t-test for continuous variables and chi-squared test for categorical variables.

RESULTS: During the study period, 183 patients underwent emergent surgery on the day of admission. The average age was 32.9 years (SD=13.1), and average weight was 82.0 kg (SD=23.4). The mechanism of injury was penetrating in 154 of 183 patients (84.2%). We excluded 47 patients who were intubated before the operating room or who received induction agents other than propofol or etomidate. Of the remaining 136 patients, 96 were induced with propofol (70.6%), and 40 with etomidate (29.4%). The average propofol dose was 1.61 mg/kg (SD=0.71) while etomidate was 0.22 mg/kg (SD=0.065). Demographic, time of induction, and baseline hemodynamic data did not differ between the propofol and etomidate groups (Table 1). More patients who were transfused prior to the operating room received etomidate (70.0% etomidate vs. 38.5% propofol; $p < 0.001$) (Table 1). Outcomes, including changes in hemodynamic variables post-induction (blood pressure and HR), mortality in the operating room, and mortality during the hospitalization did not differ between patients induced with propofol and those induced with etomidate (Table 2).

CONCLUSION: In this study of 136 trauma patients who underwent emergent surgery at an urban level 1 trauma center, we found that peri-induction changes in hemodynamic variables, operating room and overall mortality did not differ between patients induced with etomidate or propofol. Although most demographic data were similar between groups, patients who had been transfused prior to surgery were more likely to receive etomidate. Although limited by our retrospective study design, our findings suggest that propofol may be used safely in trauma patients. Further work is needed to clarify the role of induction agent in outcome after emergent trauma surgery.

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Table 1. Demographics and characteristics of trauma patients in the Propofol vs. Etomidate group

	Propofol (n=96)	Etomidate (n=40)	P value
Age (SD)	32.3 (12.3)	36.4 (15.9)	0.154
Weight in kg (SD)	81.5 (24.0)	83.6 (23.1)	0.631
SBP < 90*	3 (3.4%)	3 (9.4%)	0.219
MAP (SD)	101.4 (21.5)	102.6 (24.3)	0.800
PP (SD)	50.2 (19.9)	43.2 (17.8)	0.076
HR (SD)	94.3 (18.9)	96.0 (18.9)	0.664
ASA Score (SD)	2.5 (1.4)	2.85 (1.4)	0.163
Penetrating trauma	88 (91.7%)	31 (77.5%)	**0.023**
Blood transfusion pre-induction	37 (38.5%)	28 (70.0%)	**0.001**
6AM-6PM	36 (37.5%)	17 (42.5%)	0.586

*n=87 for propofol, n=32 for etomidate
SBP= systolic blood pressure, MAP= mean arterial pressure (mmHg), PP= pulse pressure (mmHg), HR= heart rate (beats per minute), ASA score = American Society of Anesthesiology physical status score

Table 2. Mortality & hemodynamic outcomes of trauma patients in the Propofol vs. Etomidate group

	Propofol (n=96)	Etomidate (n=40)	P value
Mortality in operating room	1 (1.1%)	1 (2.5%)	0.520
Mortality during hospitalization	4 (4.2%)	4 (10.0%)	0.188
SBP < 90*	16 (17.4%)	5 (12.8%)	0.514
MAP (SD)	90.4 (24.5)	95.4 (28.9)	0.316
PP (SD)	52.6 (21.6)	53.3 (19.8)	0.864
HR (SD)	104.1 (17.0)	106.1 (21.2)	0.606

*n=92 for propofol, n=39 for etomidate
SBP= systolic blood pressure, MAP= mean arterial pressure (mmHg), PP= pulse pressure (mmHg), HR= heart rate (beats per minute)

TRAUMA 4

Role of Microtubule Instability in Histone-Induced Endothelial Barrier Dysfunction

Kamoltip Promnares[1], Boyoung Cha[1], Junghyun Kim[2], Chenou Zhang[2], Kenichi Tanaka[1], Konstantin Birukov[1], Anna Birukova[2]

[1]Dept of Anesthesiology, University of Maryland School of Medicine, Baltimore, MD, [2]Dept of Medicine, University of Maryland School of Medicine, Baltimore, MD

INTRODUCTION: Histones are highly conserved, alkaline, positively charged proteins. They act as damage-associated molecular pattern molecules when released into the extracellular space. Extracellular histones are mediators of inflammation, tissue injury, and organ dysfunction. Elevation of circulating histones is associated with traumatic injuries and relevance to severity of condition. Among the various histones, histone H3 and H4 are known to be involved in endothelial barrier dysfunction. Disturbances in endothelial cell (EC) barrier regulation are critically dependent upon rearrangements of EC actin cytoskeleton and microtubule (MT) network. We investigated whether the EC barrier dysfunction after the histone H3 treatment is associated with MT disassembly at the cell periphery and MT growth rate.

METHODS: Human Pulmonary Artery Endothelial Cell (HPAEC) were used to study the effects of histone H3 on EC barrier function by determining transendothelial electrical resistance (TER) in electrical cell-substrate impedance sensor (ECIS) array and evaluation of EC monolayer permeability for FITC-avidin. Cytoskeletal remodeling and MT organization were monitored by immunofluorescence staining with Texas Red- phalloidin, and b-tubulin or VE-cadherin antibodies. MT growth rate was tracked in EGFP-EB1 transfected HPAEC using EVOS FL Auto 2 microscope and analyzed with ImageJ software.

RESULTS: Histone H3 induced EC barrier disruption in a dose and time-dependent manner with maximal decline by 6 hours with the H3 concentration ≥ 50 ug/ml. H3 caused significant stress fiber formation and development of intracellular gaps. In addition, H3 stimulation of EC suppressed peripheral microtubule growth and decreased the pool of acetylated MT. Moreover, H3 also inhibited MT growth rate.

CONCLUSION: Histone, H3 induced endothelial barrier dysfunction via disruption of adherens junctions and cytoskeleton derangement. Collectively, our data demonstrate, for the first time, a critical involvement of MT disassembly at the peripheral region of the EC and a decrease in MT growth rate in histone-induced endothelial barrier dysfunction.

TRAUMA 5

Comparison of Intravenous Waveform Analysis to Current Markers for Detection of Hemorrhage in a Rat Model

Matthew Barajas[1], Susan Eagle[1], Franz Baudenbacher[2], Matthew J Hampton[1], Zhu Li[1], Matthias L Riess[3]

[1]Vanderbilt University Medical Center, Nashville, TN, [2]Vanderbilt University, Nashville, TN, [3]Vanderbilt University, TVHS VA Medical Center, Nashville, TN

INTRODUCTION: Quantification of hemorrhage and assessment of volume status remain challenging, particularly in the perioperative period. Central venous pressure (CVP) poorly correlates with volume status. Dynamic measurements such a pulse pressure variation (PPV), stroke volume variation (SVV) and systolic pressure variation (SPV) are predictive of cardiac preload only within a narrow set of clinical parameters[1]. Obtaining serial measurements of left ventricular end diastolic area (LVEDA) is often impractical. Intravenous waveform analysis (IVA) is a novel method of volume status assessment which relies on spectral frequency analysis of amplitudes within the intravenous waveform. We hypothesized that IVA would be superior to current clinical markers in assessing intravascular volume during hemorrhage.

METHODS: Ten male Sprague Dawley rats were anesthetized, intubated, and mechanically ventilated. Intravascular volume was altered through stepwise hemorrhage totaling 20% of the estimated blood volume (EBV) over 50 min. 2% of the EBV was removed over 1 minute every 5 minutes for 10 repetitions. PPV and SPV were derived from femoral arterial pressure tracings. Right ventricular base diameter (RVd), LVEDA, SVV and cardiac output (CO) were measured via echocardiography. Fast Fourier transformation was performed on the femoral venous waveform and the amplitude of the primary frequency, F1, was analyzed. The F1 frequency corresponded with heart rate measured on ECG. Data was evaluated as percent change from baseline. Repeated measures ANOVA analysis with pairwise comparisons and Bonferroni correction was performed. If either interval of comparison was non-normally distributed Dunn's test was used. Significance was set at p=.05.

RESULTS: IVA amplitude F1 differed significantly from baseline with loss of 2% of the EBV, p=.0001 (95% CI -44% to -24%). CO also fell at loss of 2% EBV, p=.004 (95% CI -18% to -2%). Notably F1 continued to fall significantly over the first four intervals while cardiac output did not, Table 1. CVP was able to detect a loss of 6% EBV, p=.012 (95% CI -28% to -2%). All other markers required hemorrhage of ≥8% of the EBV to achieve statistical significance, Table 2. Heart rate and RVd did not change significantly at any interval.

CONCLUSION: In this study, IVA displayed a higher sensitivity to change in volume status than cardiac output and was able to estimate blood loss with higher precision. Additionally, it outperformed commonly used static, dynamic and echocardiographic markers of volume status including CVP, PPV, and LVEDA. Clinically the advantage of IVA stems from its practicality. IVA can be performed via a venous catheter, making this minimally invasive technique more available than invasive volume status assessment methods or repeat ultrasonography. Further work is required in assessing both its prediction of volume responsiveness in resuscitation and its applicability in varying clinical scenarios, e.g., spontaneously breathing, open chest, non-supine subjects.

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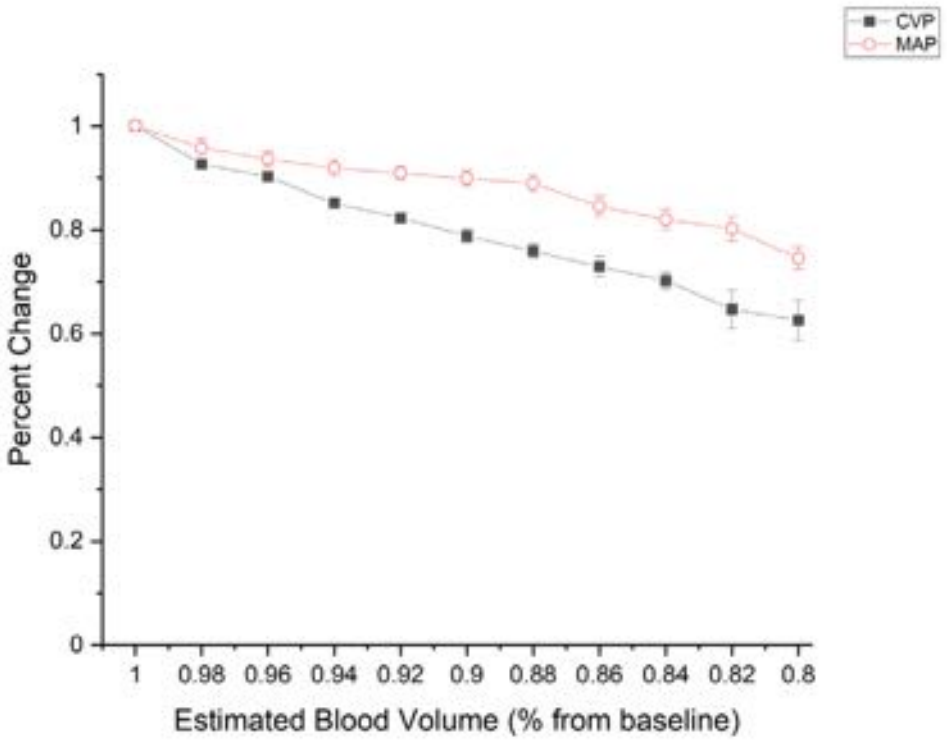

Figure 1. Mean value and standard error are displayed for central venous pressure and mean arterial pressure at each interval of the experimental protocol. Values are displayed as percent change from baseline measurements.

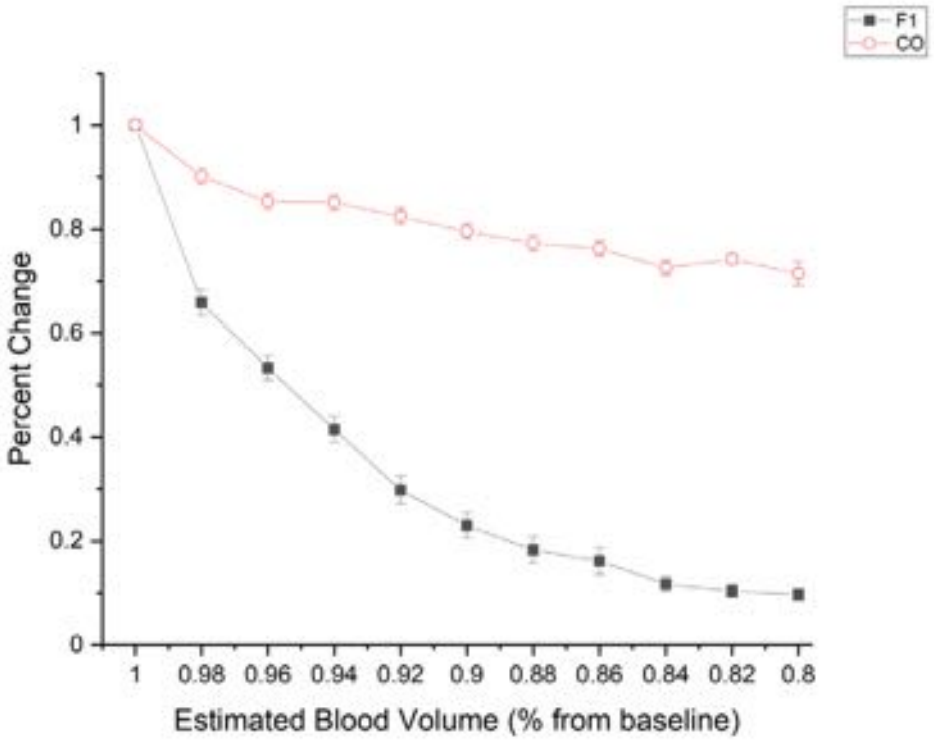

Figure 1. Mean value and standard error are displayed for the F1 amplitude derived from intravenous waveform analysis and cardiac output measured by transthoracic echocardiography at each interval of the experimental protocol. Values are displayed as percent change from baseline measurements.

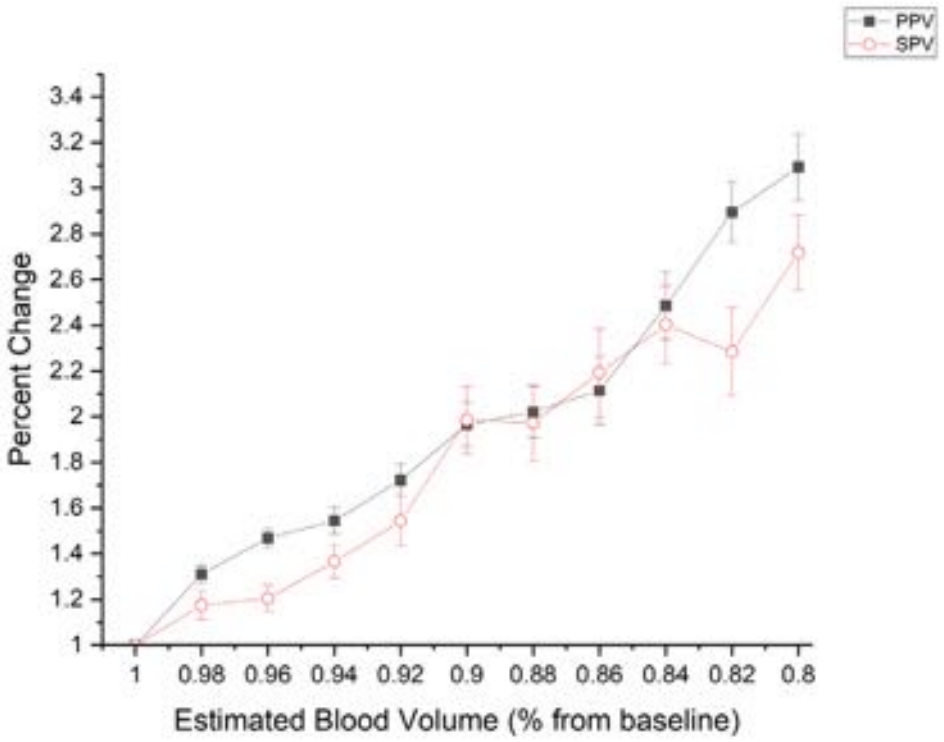

Figure 1. Mean value and standard error are displayed for the pulse pressure variation and the systolic pressure variation derived from femoral arterial line transduction at each interval of the experimental protocol. Values are displayed as percent change from baseline measurements.

Table 1.

	F1 amplitude		Cardiac Output	
Blood loss (experimental interval)	P value	95% Confidence interval as % change	P value	95% Confidence interval as % change
0% to 2% (1)	0.0001	-44% -24%	0.004	-18% -2%
2% to 4% (2)	0.0028	-22% -2%	1.000	-12% +3%
4% to 6% (3)	0.0068	-22% -2%	1.000	-8% +7%
6% to 8% (4)	0.0094	-22% -1%	1.000	-11% +4%
8% to 10% (5)	1.0000	-17% +3%	1.000	-10% +5%

Table 1. The P values and 95% Confidence Intervals are displayed for both the F1 amplitude derived from intravenous waveform analysis and the cardiac output measured on transthoracic echo. Values are displayed for evaluation amongst time points separated by one experimental interval. F1 was sensitive to early blood loss and was able to discern between loss of 0%, 2%, 4%, 6% and 8% of the estimated blood volume.

Table 2.

Variable	Blood Loss Required for Significant Change	P value	95% Confidence Intervals
F1	2%	0.0001	-44% -24%
CO	2%	0.004	-18% -2%
CVP	6%	0.012	-28% -2%
PPV	8%	0.005	+12% +132%
EDV	8%	0.017	-26% -1%
MAP	10%	0.017	-19% -1%
SPV	10%	0.001	+27% +170%
SVV	14%	0.002	+17% +146%
HR	N/A	1.000	-4% +5%
RVd	N/A	1.000	-15% +7%

Table 2. The smallest amount of blood loss required for statistically significant deviation from baseline for each parameter is displayed.

TRAUMA 6

Induction of Endothelial Barrier Dysfunction by Serum Factors of Traumatic Brain Injury in Rat

Yunbo Ke[1], Julie Proctor[1], Chenou Zhang[1], Juliana Medina[1], Catriona H Miller[2], Thomas E Grissom[3], Anna Birukova[4], Gary Fiskum[1], Konstantin Birukov[1]

[1]University of Maryland School of Medicine, Baltimore, MD, [2]Air Force Research Labs, Baltimore, MD, [3]University of Maryland School of Medicine, Baltimore, Maryland, [4]Dept of Medicine, University of Maryland School of Medicine, Baltimore, MD

INTRODUCTION: Mild to severe acute respiratory distress syndrome (ARDS) can be induced by traumatic brain injury (TBI)[1,2]. Furthermore, potential effects of hypobaria associated with air-evacuation of wounded personnel on severity of TBI-induced lung injury and breach of lung blood-gas barrier remain unknown, and no effective drug-based therapeutics are currently available. In order to gain knowledge on the potential mechanistic link between traumatic brain injury (TBI) and acute respiratory distress syndrome (ARDS), we have adopted a unique approach to characterize the endothelial barrier dysfunction, a key feature of ARDS, induced by serum factors of traumatic brain injury from model rats[3]. To gain insight into mechanisms linking traumatic brain injury (TBI) with development of acute respiratory distress syndrome (ARDS) and explore effects of hypobaric exposure. To achieve this goal, we characterized the endothelial barrier dysfunction, a key feature of ARDS, induced by serum factors released during traumatic brain injury in unique rodent model of polytrauma and exposure to hypobaric conditions.

METHODS: The adult male rat polytrauma model consisted of controlled cortical impact(CCI)–induced TBI followed by 30 minutes of hemorrhage shock (HS, mean arterial pressure, 35–40 mm Hg) 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. Then the animals were exposed to either hypo- or normobaric conditions. 48 hours after the CCI, blood was drawn from right ventricle and serum samples were obtained. Serum collected from the TBI or sham rats were used to treat endothelial cells in culture with a 50-200 fold dilution. The endothelial barrier dysfunction was assessed by a decrease of electrical resistance across endothelial cell monolayers which was measured with the electrical cell impedance sensor (ECIS) as previously described[4,5] and by Xpert which assesses and visualizes formation of gaps between endothelial cells. Polytrauma induced alteration in signal transduction was probed by Western blot analysis.

RESULTS: Pronounced barrier-disruptive effects were registered in sera of TBI animals exposed to both, hypo- and normobaric conditions. However, hypobaric conditions decreased survival compared to normobaric groups. Serum from TBI rats but not sham rats induced significant barrier dysfunction in human pulmonary artery endothelial cells. Compared to the sham, serum samples from the TBI rats induced a resistance decrease 3 hours after addition of serum from 23.6±17% to 35.5±4.9%. Further analysis indicated that thrombin was responsible for a transient early-phase barrier disruptive activity in TBI-serum because both thrombin inhibitor and thrombin receptor antagonist attenuated the TBI-serum-induced EC barrier dysfunction only during the early time, not in late stage. There were more sustained late-phase barrier disruptive activities following thrombin. It was found that both the early and late-phase barrier disruptive activities were inhibited by heparin, an anti-coagulant. In addition, the late phase barrier disruptive activities were depleted by heparin-sepharose. Cultured endothelial cells treated with serum from polytrauma rats for 3-4 hours have demonstrated significant reduction in expression of VE-Cadherin, an endothelial cell junctional protein. Moreover, AUY954, OxPAPC and 8CPT, the EC barrier protective agents, partially inhibited or reversed the barrier disruptive activities of the TBI-serum.

CONCLUSION: Serum from the polytrauma rats contain both early and late-phase barrier disruptive activities that are reversible by exogenous intervention and the early phase barrier disruptive activities were contributed by thrombin. The barrier disruptive serum factor(s) may function through down regulation of endothelial junctional protein VE-Cadherin. Studies in our group are underway to identify late phase disruptive factors activated by hypobaric conditions and define severity of injury and associated levels of vascular barrier dysfunction.

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