AUA 2020 Annual Meeting

Abstracts

Airway Management

Airway Management-1 Mask and Direct Laryngoscopy Grade Characteristics of Difficult Airway Letters at a Single Institution from 2015-2019: A Retrospective Observational Study

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Introduction: The American Society of Anesthesiologists (ASA) defines a 'difficult airway' as the clinical situation in which a conventionally trained anesthesiologist experiences difficulty with facemask ventilation, tracheal intubation, or both.[1] Of characteristics able to help a health care provider anticipate a difficult airway, a history of difficult intubation has the best predictive value for subsequent difficult intubation, identifying up to 30% of these patients.[2] The ASA also recommends that a difficult airway letter (DAL) is provided to these patients if indicated. However, little research has evaluated if consensus exists amongst anesthesia providers regarding the clinical characteristics that merit a DAL. Our own departmental guidelines allow for attending anesthesiologist discretion as to which clinical characteristics merit a DAL, and these may include but are not limited to difficult mask ventilation, difficulty with direct or video laryngoscopy, difficult tube passage, and other pathologic airway features. However, the guidelines do recommend writing a DAL when encountering difficult mask ventilation combined with difficult direct laryngoscopy, defined as a grade 3 or 4 mask score (Han mask ventilation grading scale) combined with a grade 3 or 4 direct laryngoscopic view (Cormack Lehane).[3] Data previously analyzed within our own institution found that from 2004 to 2013 only 38% of patients with difficult mask ventilation combined with difficult direct laryngoscopy received a DAL.[4] The goal of this study was to evaluate the airway management characteristics associated with the primary composition of a difficult airway letter at a single academic medical center from 2015 to 2019. Our primary outcomes were characteristics associated with the primary composition of a difficult airway letter, including direct laryngoscopic grade view, mask ventilation grade, and the number of intubation attempts.

Methods: After obtaining institutional review board approval, we performed a retrospective observational study using the University of Michigan's electronic health record to define characteristics associated with writing DALs. We hypothesized that the frequency of a DAL would increase with worsening mask ventilation grade, worsening direct laryngoscopic view grade and increased number of intubation attempts. Also, we hypothesized that a significant number of patients with characteristics meeting departmental criteria for a DAL (combined grade 3 or 4 mask grade and grade 3 or 4 direct laryngoscopic view) would not have a DAL. Adults age ≥18 or older receiving general anesthesia, without a pre-existing airway at our institution from 1/1/2015 through 3/19/2019 were included. Patients with a documented prior difficult airway letter, ASA 6, those with pre-existing airways such as a tracheostomy or intubated patients, and patients whose primary intended procedure was a tracheostomy were excluded.

Results: In total, 121,349 patients met inclusion criteria, of these, 589 patients (0.5%) had a DAL recorded for the encounter. Of the 246 patients who had a combined grade 3 or worse mask grade and grade 3 or worse direct laryngoscopic view, 168 patients did not have a DAL and 78 did; i.e. only 32% of patients with combined difficult mask ventilation and direct laryngoscopic view had a difficult airway letter written in line with departmental recommendation ($p < 0.001$).[3]

Conclusion: Our data demonstrates that the frequency of a DAL increases with worsening mask ventilation grade, direct laryngoscopic view, and number of intubation attempts, and that a large portion of patients with combined difficult mask ventilation and direct laryngoscopic view continue not to receive a DAL. These results are consistent with previous work done in New Zealand which found that only 14% of patients with airway difficulty had a pertinent comment in their clinical record.[5] Further inquiry is merited into anesthesiologists' attitudes towards what represents a difficult airway, the barriers in place to providing a patient a DAL, and how to improve overall communication regarding difficult airways.

Reference(s):

1. Apfelbaum JL, Hagberg CA, Caplan RA, et al. Anesthesiology; 2013; 118: 251–70
2. Lundstrøm LH, Møller AM, Rosenstock C, et al. Anaesthesia; 2009; 64: 1081–8
3. Kheterpal S, Healy D, Aziz MF, et al. Anesthesiology 2013; 119: 1360–9
4. Cloyd BH, Healy D, Leis A, et al. (2019, November) Mask and Direct Laryngoscopy Grade Characteristics of Difficult Airway Letters. Poster session presented at the World Airway Management Meeting, Amsterdam, Netherlands.
5. Baker PA, Moore CL, Hopley L, et al. Anaesthesia and intensive care; 2013; 41(3), 334-341.

Table 1. Laryngoscopy and Mask Ventilation Characteristics by Difficult Airway Letter Status

		No Difficult Airway Letter (N = 120,760) n (%)	Difficult Airway Letter (N =589) n (%)	P-Value
Mask and DL grade view ≥ 3		168 (0.2)	78 (14.4)	<0.001
Laryngoscopy Grade View				<0.001
	1	84,262 (70.1)	122 (21.0)	
	2a	25,391 (21.1)	90 (15.5)	
	2b	8,678 (7.2)	67 (11.6)	
	3	1,872 (1.6)	273 (47.1)	
	4	57 (0.1)	28 (4.8)	
Mask Ventilation Grade				<0.001
	1	60,428 (54.1)	167 (30.3)	
	2	33,853 (30.3)	203 (36.8)	
	3	3,534 (3.2)	133 (24.1)	
	4	129 (0.1)	15 (2.7)	
Number of Attempts				<0.001
	1	115,065 (95.3)	371 (63.0)	
	2	4,947 (4.1)	110 (18.7)	
	3	680 (0.6)	83 (14.1)	
	4+	52 (0.0)	25 (4.2)	

Data are presented as frequency (percentage) of non-missing data. DL = Direct Laryngoscopy

Airway Management-2 Preoperative airway assessment: a prospective study to evaluate the association between voice parameters and Mallampati classification.

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Introduction: Difficult airway management still lacks an accurate predictor and subjective parameters such as the modified Mallampati test may hamper its prediction leading to misclassification [1,2]. Objective measurements, on the other hand, have been shown to enhance the accuracy of any test [1]. In this field, voice parameters have been proved to be associated with upper airway anatomy besides been deemed to predict difficult airway management [3-8]. This way, some voice parameters such as formant frequencies (Figure 1) are supposed to improve, as objective parameters, the preoperative airway assessment by better evaluating the upper airway anatomy. Therefore, we aimed at observing whether voice parameters would be associated with Mallampati classification so that they could improve the assessment of upper airway anatomy.

Methods: A prospective study with 453 patients scheduled for elective surgery under general anesthesia was performed. At transitional waiting hall before transport to the operating room, we collected data on sex, age, weight, height, ASA physical status, Body Mass Index, modified Mallampati test, and acoustic parameters from voice. Uni and multivariable analyses were conducted. Two logistic regression models and their predictive performances were determined.

Results: Of a total of 467 initially eligible patients, 453 were submitted to statistical analysis, with 14 being excluded because of missing data. The Mallampati I was present in 161 patients (35.5%), the II in 158 (34.9%), the III in 94 (20.7%), and the IV in 40 (8.9%). The main result was the association found between formant if5 (p=0.00) and modified Mallampati test. ASA physical status and age were also related to Mallampati classification. Obesity, sex, weight, height, and BMI did not show any association with the Mallampati test. The AUC for the regression model containing all formants together was 65.0%, whereas the AUC for the model containing only three formants (af2, af4, and if5) after a stepwise was 60.2%.

Conclusion: Voice formants are objective measurements associated with both upper airway anatomy and Mallampati classification. Such as, voice analysis may improve the upper airway assessment performed by the conventional modified Mallampati test.

Reference(s):

1. Assessment Before Airway Management. 2015; 33: 257–78.

2. Inter-observer reproducibility of 15 tests used for predicting difficult intubation. 2011; 155: 275–81.

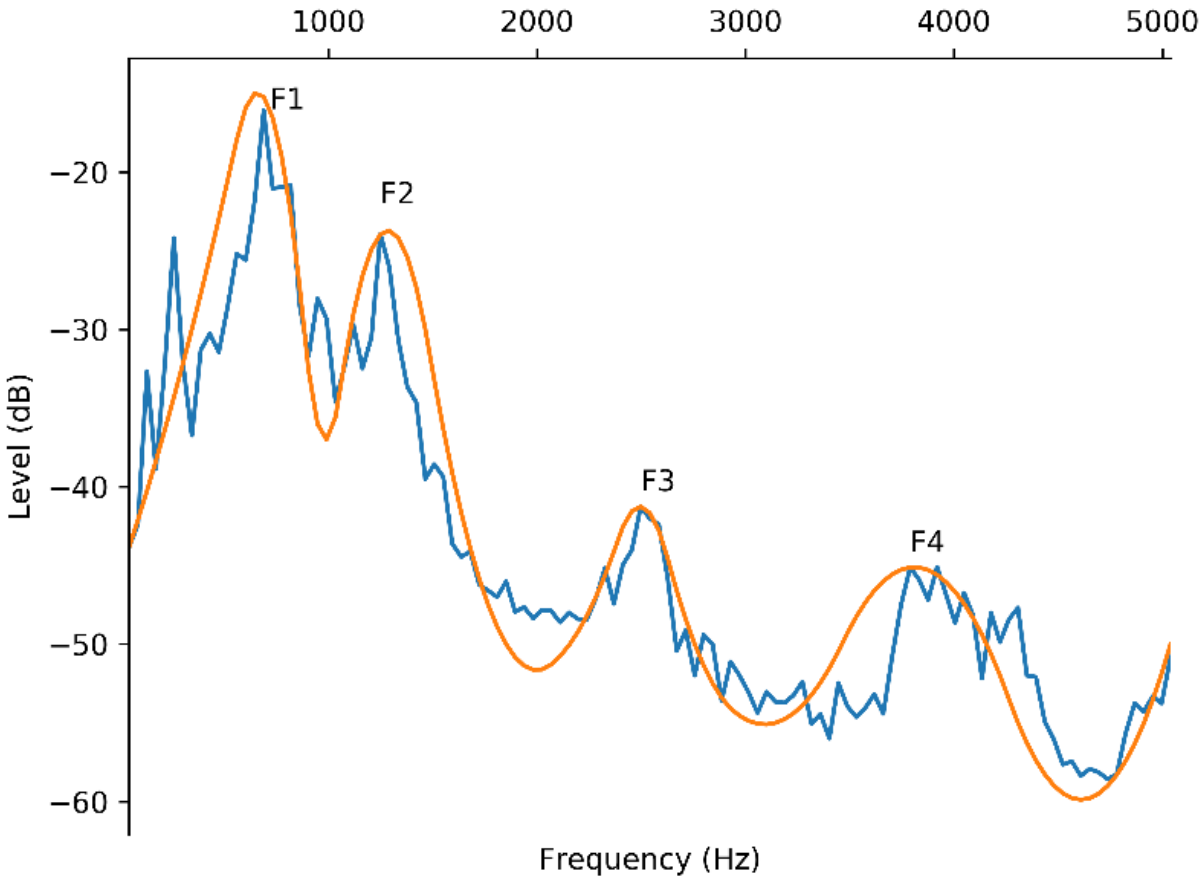
3. Pre-operative voice evaluation as a hypothetical predictor of difficult laryngoscopy. 2019; 74: 1147-52

4. A Formant Range Profile for Singers. 2017; 31: 382.e9-382.e13.

6. Acoustic pharyngometry measurement of minimal cross-sectional airway area is a significant independent predictor of moderate-to-severe obstructive sleep apnea. Acoustic pharyngometry and vowel formants. 2015; 138:833–45.

7. Influence of vocal tract geometry simplifications on the numerical simulation of vowel sounds. 2016;140:1707–18.

8. The singer's formant and the laryngeal adjustments used to realize it: a descriptive review. 2010; 21: 43-50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Airway Management-3 3D Cric Trainer and Silicone Skin: A Novel Approach to Emergency Airway Simulation.

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Introduction: Surgical cricothyrotomy is a life-saving skill with rare opportunities to improve competency given the low incidence (Ref 1). While a systematic review comparing needle versus surgical cricothyrotomy failed to demonstrate superiority of either approach (Ref 2), low-quality evidence suggests a simple technique for surgical cricothyrotomy may be advantageous. Simulation models in the literature include pig tracheas, cadavers, and mannequins - each with limitations. Pig tracheas are cheap and realistically simulate human anatomy (Ref 3 & 4) but the ethics have been called into question by animal advocacy groups, leading institutions to pursue alternatives. 3D printing offers a cheap sustainable alternative, but evidence is limited comparing efficacy for skills training. We hypothesized that the 3D Cric Trainer is not inferior to a pig trachea for improving competency and confidence levels in anesthesia trainees.

Methods: The publicly-available 3D Cric Trainer (Ref 5) was printed by our institutional engineering department (Pictures 1-3; NB: the green tape was omitted in this study). Pig trachea models were obtained from Hormel by our simulation center. To simulate the cricothyroid membrane, Hy-Tape (Picture 4, left side) was applied to the 3D model. Skin and fat was simulated using a silicone pad created by combining Smooth-On Ecoflex 00-20, Smooth-On Ecoflex Gel, power mesh fabric, and peach and yellow acrylic paints (Picture 4). After institutional IRB exemption (IRB #19-008949), a randomized prospective pilot study was performed. Participants were randomized into the pig trachea arm (control) or the 3D model arm (intervention). After a brief didactic, and instructor demonstration of the scalpel-finger-bougie technique (Ref 6) on both models, participants were assessed on time to cricothyrotomy completion by the instructor using a stopwatch. The instructor then ensured procedure success and quality. After this pre assessment, participants practiced five repetitions on their assigned model, followed by post assessment timing and a post-survey. Paired student's t-tests were performed to determine mean difference and confidence intervals between pre/post assessments between the individual control and intervention groups. A Wilcoxon ranked sums test was applied comparatively for the two groups to determine non-inferiority. Power calculation: 28 participants are necessary to achieve a β cutoff of 20% to detect the probability of type II error.

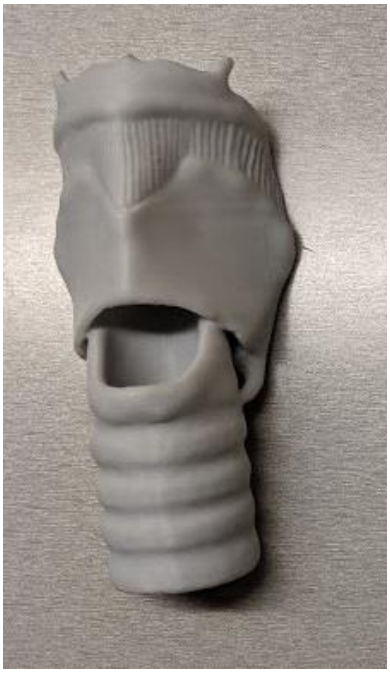
Results: Thirteen participants were included (Table 1). Six randomized to the 3D arm, and seven to the pig trachea arm. No participants had performed or witnessed a cricothyrotomy. At baseline, 23% (3/13) felt confident in performing the procedure, while 15.4% (2/13) strongly doubted their ability. After training, 92.3% (12/13) agreed or strongly agreed they would be confident in performing the procedure. 100% felt this training contributed to their education and should continue as part of a formal curriculum. Technique was satisfactory during 100% of the assessments. For the 3D Cric Trainer arm, the mean time pre-training was 36.33 seconds and post-training was 28 seconds (mean diff 8.33, CI, 1.8-14.86), p= 0.01). For the pig trachea arm, the mean time pre-training was 38.14 seconds and post-training was 32.29 seconds (mean diff 5.86, CI -8.51 - 20.23, p = 0.18). Comparing the two groups with a Wilcoxon Ranked Test given unequal variances, the mean time pre-training was 37.24 seconds, post-training 30.15 seconds (mean diff 7.09, CI -8.67 - 22.85, p = 0.99). See Table 1 for complete data.

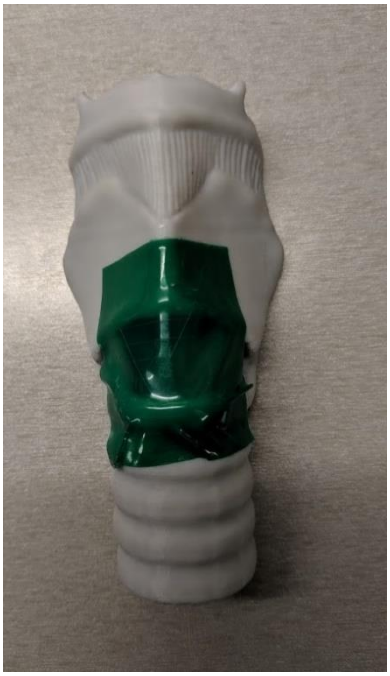
Conclusion: The 3D Cric Trainer is cheap, reusable, and does not involve either animal or human components. We were successfully able to show the use of the 3D Cric Trainer for emergency airway simulation of a surgical cricothyrotomy was not inferior to a pig trachea model. We found significant pre-to-post improvement within the 3D-printed group, and observed no significant change in the control group. Confidence levels significantly improved among participants, with unanimous satisfaction among participants. Limitations include the small sample size, which will be addressed by enrolling additional participants over two repeat sessions to achieve the expected power to complete this pilot study. This work provides a foundation for future modifications to simulate and practice on challenging airway anatomy. It provides a framework for simulation training of other care providers involved in airway management.

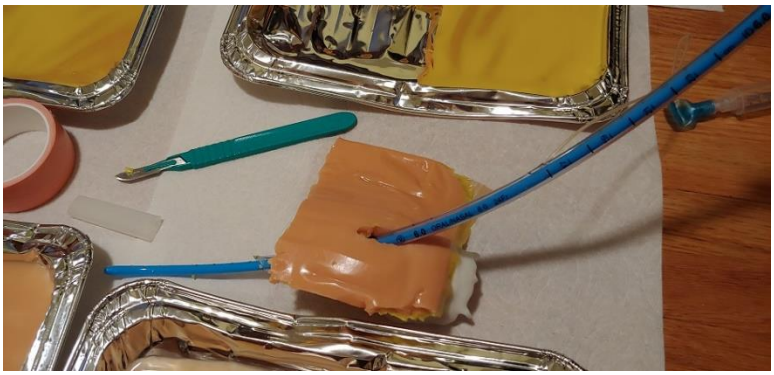
Reference(s): Ref 1: Br J Anaesth. 2011 May;106(5):617-31. Ref 2: Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 2013, 21:43. Ref 3: Emerg Med J. 2008 Nov;25(11):732-4. Ref 4: Rev Col Bras Cir. 2015 Jun;42(3):193-6. Ref 5: Can J Anesth/J Can Anesth (2017) 64:1079–1081. http://www.airwaycollaboration.org/3d-cric-trainer-1 Ref 6: EMCrit Podcast 131 - Cricothyrotomy - Cut to Air: Emergency Surgical Airway.

Table 1: 3D Model Arm Compared to Pig Model Arm for Pre and Post-training Completion Times.

3D Model Arm				
	Pre-Time (sec)	*Post-Time (sec)*	*Descriptive Statistics*	
n	6	6	Mean Diff	8.33
Mean	36.33	28	Std Dev	6.22
Variance	99.87	63.2	CI (95.0%)	6.53
P(T<=t) one-tail	0.01			
t Critical one-tail	2.02			
Pig Model Arm				
	Pre-Time (sec)	*Post-Time (sec)*	*Descriptive Statistics*	
n	7	7	Mean Diff	5.86
Mean	38.14	32.29	Std Dev	15.54
Variance	125.14	231.90	CI (95.0%)	14.37
P(T<=t) one-tail	0.18			
t Critical one-tail	1.94			
Wilcoxon Ranked Test	0.99			







Airway Management-4 Correlation between voice parameters and number of intubation attempts: a prospective study

Clístenes C de Carvalho[1], Danielle M da Silva[2]

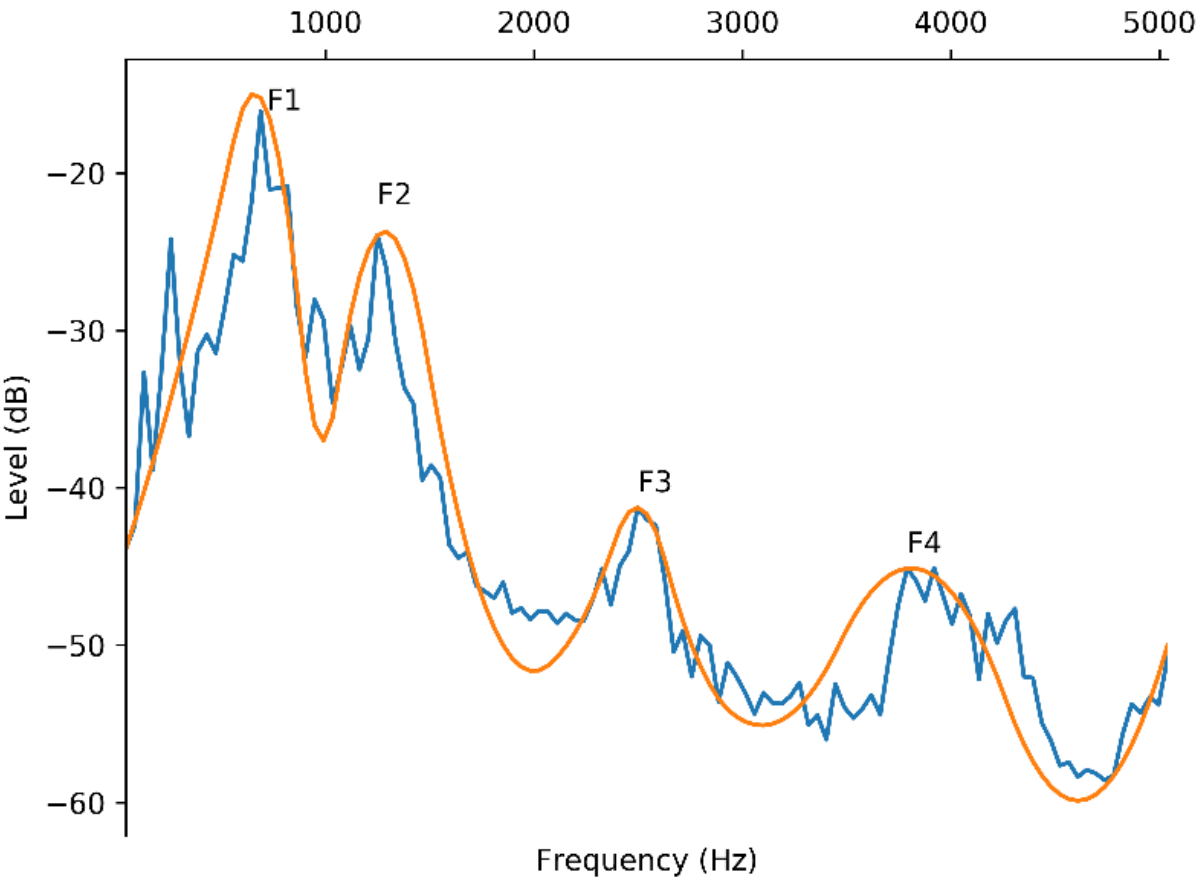
[1]Universidade Federal de Campina Grande, Campina Grande, Paraíba, [2]Hospital da Clínicas da UFPE, Recife, Pernambuco

Introduction: Predicting difficult airway management remains challenging so far. All predictors available to the present moment feature just a poor performance to anticipate problems over the airway manipulation. In this field, voice parameters have been proved to be associated with upper airway anatomy besides being deemed to predict difficult airway management. These conceptions led us to investigate the correlation between the formant frequencies (Figure 1) and the number of intubations attempts.

Methods: We performed a prospective study involving 453 patients who underwent elective surgeries under general anaesthesia with tracheal intubation. Before transporting the patients to the operating room, we collected their data on sex, age, weight, height, ASA physical status, Body Mass Index (BMI), and acoustic parameters from five phonemes (/a/, /e/, /i/, /o/, /u/). In the operating room, during the airway management maneuvers, the number of attempts to successfully allocate the orotracheal tube was noted. The Spearman correlation test was performed among the quantitative variables.

Results: The number of intubation attempts were correlated to the formants ef2 (r=-0.123, p=0.016); of2 (r=0.097, p=0.037); and of4 (r=0.114, p=0.014). Age, weight, height, and BMI did not show any correlation to the number of intubations attempts.

Conclusion: Voice formants were correlated to number of intubations attempts and may constitute an alternative tool for preoperative upper airway assessment.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Airway Management-5 Predictive value of combined Mallampati and Sternomental distance for difficult laryngoscopy: a prospective study.

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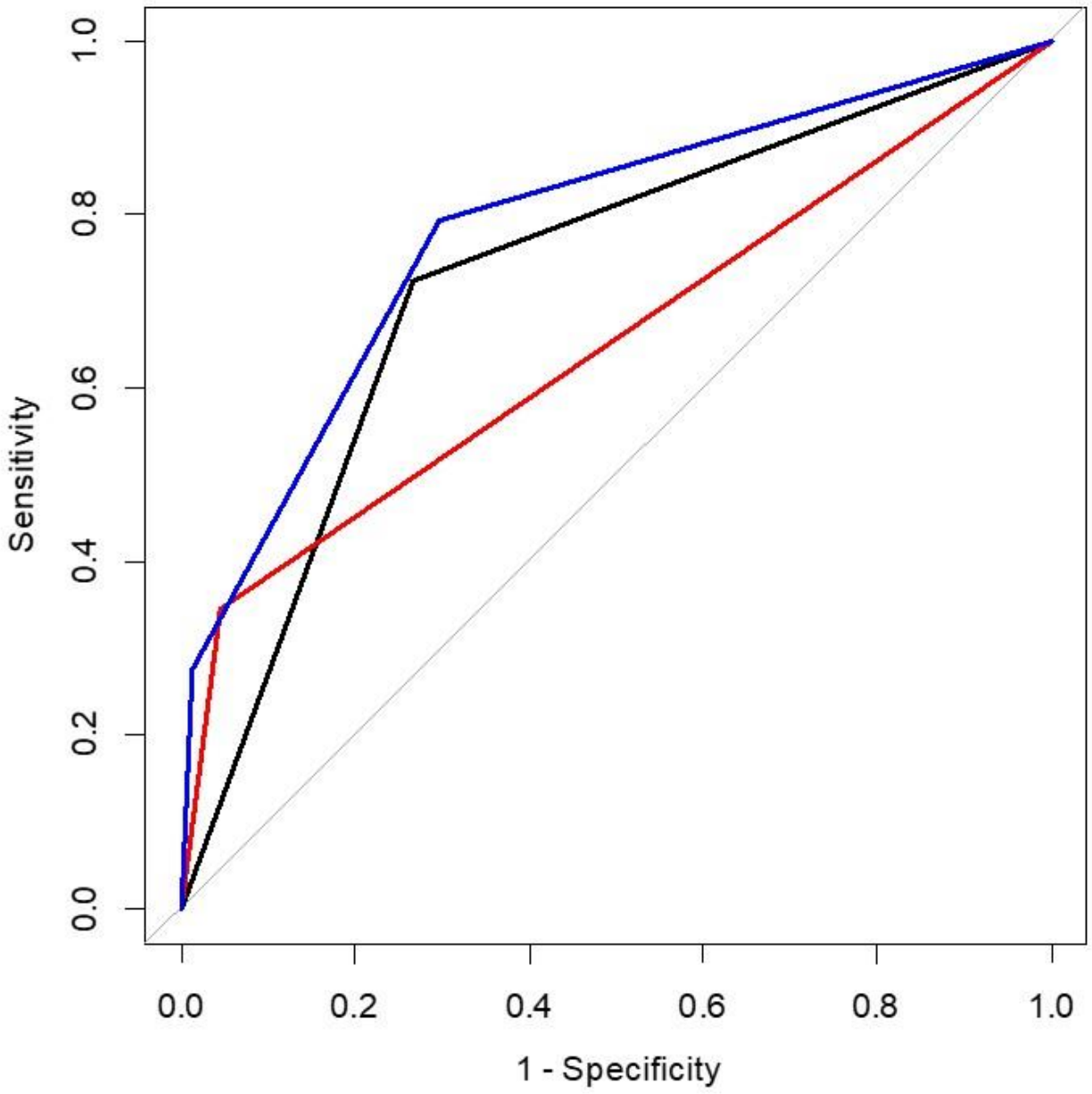
[1]Instituto de Medicina Integral Professor Fernando Figueira, Recife, Pernambuco, [2]Hospital da Clínicas da UFPE, Recife, Pernambuco

Introduction: Difficult airway prediction remains a challenging task as none of the predictors reported so far has featured satisfactory accuracy. Much of this poor accuracy may be due to the inability of predictors to assess the diverse anatomic structures involved in difficult airway management. This led us to investigate whether the Mallampati test, a parameter that assesses the upper region of the airway, along with the sternomental distance, a parameter which evaluates the lower region of the airway, would improve the preoperative airway assessment when bound together.

Methods: A prospective study with 453 patients scheduled for elective surgery under general anesthesia was performed. At transitional waiting hall before transport to the operating room, we collected data on sex, age, weight, height, ASA physical status, Body Mass Index, modified Mallampati test, and sternomental distance. In the operating room, after the induction of the anesthesia, direct laryngoscopies were performed by the assistant anesthesiologists who take note of the Cormack-Lahane classification. Uni and multivariable analyses were conducted and three logistic regression models were obtained.

Results: Of a total of 467 initially eligible patients, 453 were submitted to statistical analysis, with 14 being excluded because of missing data. Difficult laryngoscopy was present in 29 patients (6.4%). Mallampati classification (OR=7.17; p=0.000) and sternomental distance (SMD) (OR=11.08; p=0.000) were both associated with difficult laryngoscopy. The OR was 25.95 (p=0.000) when both Mallampati and SMD were indicative of difficult intubation. Three logistic regression models were evaluated (Figure 1) and their AUC defined as follows: Mallampati alone 72.88%; SMD alone 65.0%; Mallampati and SMD together 78.51%.

Conclusion: Mallampati test and sternomental distance have better predictive performance when evaluated together. Additionally, the chances of facing a real difficult airway are highly increased when both are indicative of difficulty.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Ambulatory Anesthesia

Ambulatory Anesthesia-1 A pragmatic randomized controlled trial comparing nasal positive airway pressure to usual care in endoscopy to reduce hypoxia

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Introduction: Hypoxia during propofol administration by anesthesia providers during upper endoscopic procedures has been to range from 8 to 62%.1,2 Use of nasal positive airway pressure has been shown to improve oxygenation in patients undergoing sedation in the operating room, in the endoscopy suite during colonoscopies, and is used by patients with obstructive sleep apnea during normal sleep at home.3,4 We hypothesized that the use of nasal positive airway pressure (NPAP) with a nasal anesthesia mask (SuperN02VAtm) could decrease the incidence of desaturation events compared with usual care with a nasal cannula (NC) in patients considered to be at increased risk for such events.

Methods: We performed a pragmatic randomized controlled trial at a single hospital. Patients with OSA and/or BMI > 30 were randomized to nasal positive airway pressure or usual care with nasal cannula during anesthesia with propofol sedation while undergoing upper endoscopic procedures with or without additional procedures. Patients randomized to NPAP received oxygen at 10 lpm via the anesthesia circuit with the pop-off valve set at 10 mmH2O while the control group received usual care with nasal cannula set. The primary endpoint was the incidence of oxygen desaturation < 90% for 15 seconds, and the primary endpoint was assessed by Chi-Square analysis.

Results: One hundred eleven patients were randomized to NC (N=58) or NPAP (N=53). The hypoxia rate in the NC group was 27.6% and the NPAP group was 5.7%, a statistically significant difference (p = 0.002). Excluding seven patients in NC (N=3) and NPAP (N=4) for enrollment failure (No OSA/BMI >30, or colonoscopy without upper endoscopy), the remaining 104 patients with OSA and/or BMI >30 with a procedure that included upper endoscopy the hypoxia rate remained similar with NC 29% (N=55), and NPAP 6% (N=49), still a significant difference (p=0.002).

Conclusion: NPAP was associated with a statistically significant decrease in the hypoxia rate in patients undergoing endoscopic procedures with propofol-based sedation from approximately 28% to 6%.

Reference(s):

1. Mehta PP, Kochhar G, Albeldawi M, et al. Capnographic Monitoring in Routine EGD and Colonoscopy With Moderate Sedation: A Prospective, Randomized, Controlled Trial. Am J Gastroenterol. 2016;111(3):395-404.
2. McVay T, Fang JC, Taylor L, et al. Safety Analysis of Bariatric Patients Undergoing Outpatient Upper Endoscopy with Non-Anesthesia Administered Propofol Sedation. Obes Surg. 2017;27(6):1501-1507.
3. Nozaki-Taguchi N, Isono S, Nishino T, Numai T, Taguchi N. Upper airway obstruction during midazolam sedation: modification by nasal CPAP. Can J Anaesth. 1995;42(8):685-690.

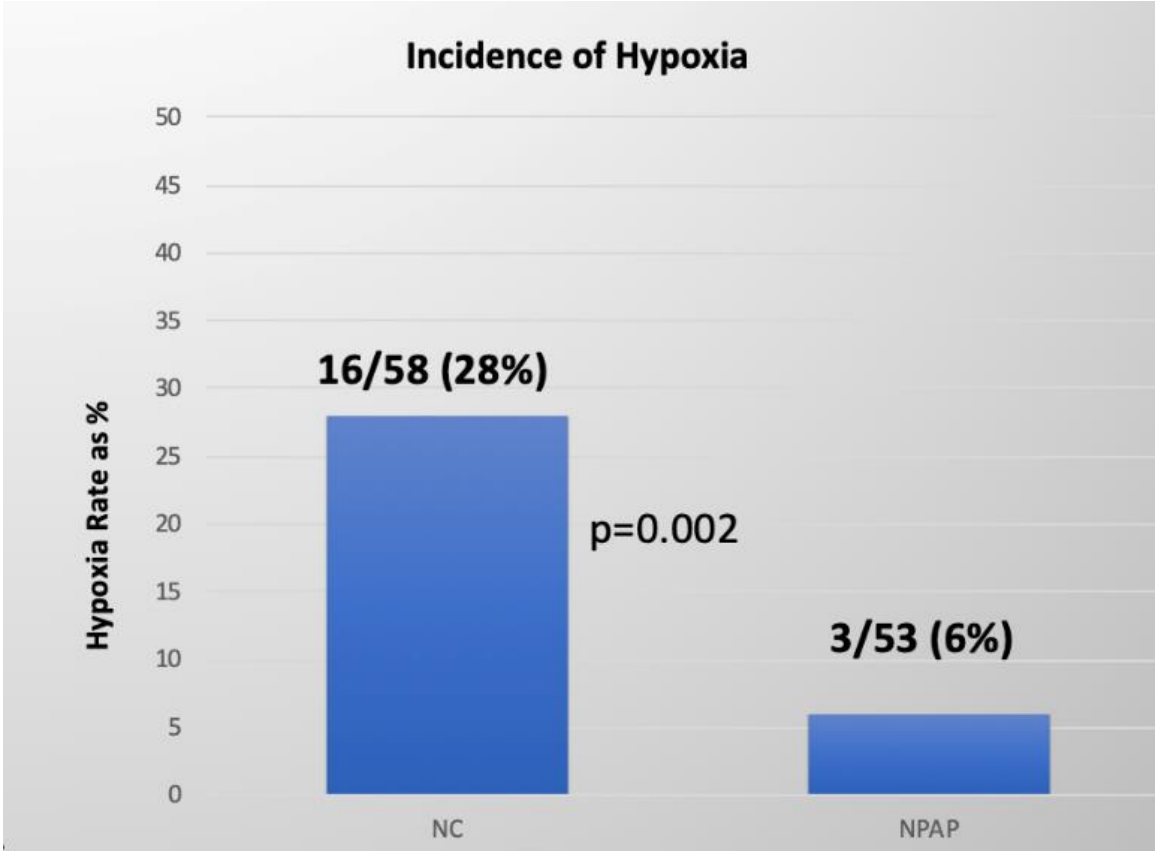

Table I	Control Group (n=58)	Treatment Group (n=53)	P value
Age	57.07±13.17	61.16±12.49	0.15
Gender	29 (50.8%)	24 (45.3%)	0.69
BMI	34.70±5.33	33.55±4.68	0.22
Outpatient	50 (87.7%)	51 (96%)	0.20
ASA	2.58±0.56	2.49±0.57	0.36
Obesity	50 (87.7%)	44 (83%)	0.66
OSA	25 (43.9%)	25 (47%)	0.87

Ambulatory Anesthesia-2 Incidence of Malignant hyperthermia during ambulatory surgery procedures. A national ambulatory surgery database 2016 study

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[1]University of Chicago, Chicago, United States of America, [2]The University of Chicago Medicine, Chicago, IL, [3]University of Chicago Medical Center, Chicago, IL

Introduction: While the incidence of malignant hyperthermia has been estimated to be from 10.2 to 13.3 per million of hospital discharges in national databases (1), the national incidence of malignant hyperthermia in ambulatory surgery setting is unknown. We analyzed Nationwide ambulatory surgery (NASS) database for year 2016 (published in 2019) to estimate this incidence. NASS is the largest all-payer calendar-year, encounter-level database in the US of hospital owned ambulatory surgery centers. It is constructed from State Ambulatory Surgery and Services Databases (SASD) of 34 geographically dispersed states. These States account for 83 percent of the total U.S. resident population, an estimated 59 percent sample of the universe of hospital-owned facilities, and an estimated 69 percent sample of the universe of ambulatory surgery encounters. The NASS contains clinical and resource-use information that is included in a typical hospital-owned facility record, including patient characteristics, clinical diagnostic and surgical procedure codes, disposition of patients, total charges, expected source of payment, and facility characteristics. Major ambulatory surgeries are identified through Current Procedural Terminology (CPT) codes. These major ambulatory surgeries are selected invasive therapeutic surgical procedures that typically require the use of an operating room and regional anesthesia, general anesthesia, or sedation. Procedures intended primarily for diagnostic purposes are excluded. Unweighted, the NASS contains approximately 7.3 million major ambulatory surgery encounters in 2016, corresponding to approximately 9.4 million major ambulatory surgeries (some encounters have more than one major ambulatory surgery). Weighted, it estimates approximately 10.5 million major ambulatory surgery encounters and 13.6 million major ambulatory surgeries in the United States.

Methods: We used SAS 9.4 program for analysis. continuous variables were compared using a test while categorical variables were compared using a chi square test. We identified presence of ICD 10 diagnosis code 'T883XXA' on any of the 15 diagnosis slots on each record to identify malignant hyperthermia occurrence during initial encounter and ICD 10 code 'T883XXD' to identify occurrence of malignant hyperthermia during subsequent encounter. Procedures were identified by presence of up to 30 Current procedural terminology (CPT) on the records. Death status was determined by variable value of dispuniform =1 to identify alive discharge and dispuniform = 20 to determine death at discharge. Mean age was compared using t-test. sex was compared using chi-square test.

Results: Of 10536618 weighted records in NASS, Malignant hyperthermia occurred in 37 records. The incidence was 3.5 per million. None of these patients had reported a previous history of malignant hyperthermia. All patients survived. In the entire database 56.87% (5989532) were females and 43.13% were males (4542109). Sex information was missing in 4940 subjects (0.046%). In MH cohort had more males 54.92% (20) than females 45.08% (17) p-value 0.03. Patients with MH were younger (mean age =38 years, median age 38.4; SEM 4.29 years) vs. non-MH patients (Mean age 50.2 years SEM 0.25 median age 38.4) p-value 0.004. We did not find preponderance of any particular procedure in patients with malignant hyperthermia. 17 records had H/o Malignant hyperthermia. Disposition status was missing in 1 record. All other patients survived at discharge. The age was similar in those with a history of malignant hyperthermia (53.4 SE 6.6 Median 57) vs. those without.(mean 50.2, SE 0.25, median 57.03). p-value 0.62. We could not compare sex in records with history of malignant hyperthermia due to low numbers.

Conclusion: Our study on national ambulatory surgery database from 2016 found much lower incidence of malignant hyperthermia than previously reported from national inpatient sample. It may be due to different population in two databases. It may also be due to different diagnosis codes (NASS used ICD-10 vs. NIS which used ICD-9). Further studies are needed to confirm this finding.

Reference(s): Trends and Outcomes of Malignant Hyperthermia in the United States, 2000 to 2005. Anesthesiology 2009;110(1):89-94. doi: https://doi.org/10.1097/ALN.0b013e318190bb08

Anesthetic Pharmacology

Anesthetic Pharmacology-1 Female rats are more sensitive to dexmedetomidine hypnosis than males

Risako Kato[1], Edlyn R Zhang[1], Olivia Moody[2], Ken Solt[3]

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Introduction: It has been reported in humans that females are more sensitive than males to the sedative effects of zolpidem, due to a combination of pharmacokinetic and pharmacodynamic factors.[1] However, it is not known whether gender differences exist for sensitivity to dexmedetomidine (DEX). We recently found that dextroamphetamine (d-AMPH) reverses DEX-induced loss of consciousness (LOC) in male rats.[2] In this study, we tested the sensitivity of female rats for DEX-induced LOC and reversal by d-AMPH.

Methods: All studies were approved by our Institutional Animal Care and Use Committee. Eight male and eight female Sprague-Dawley rats (13-15 weeks old) were housed on a standard day-night cycle (lights on from 7 am to 7 pm). All experiments were conducted between 9 am and 5 pm. A tail vein IV catheter was placed under brief isoflurane anesthesia. After full recovery from isoflurane (> 45 min), rats received DEX (50 µg/kg IV over 10 min), followed by saline (control) or d-AMPH (3 mg/kg IV over 2 min). A heating pad set to 37°C was used to maintain normothermia. LOC and return of consciousness (ROC) were defined by loss and recovery of the righting reflex, respectively. The time to ROC was defined as the time from initiation of the saline or d-AMPH infusion to return of righting. A randomized, blinded, crossover design was used, and a minimum of 3 days of rest was provided between experiments. Welch's t-test was used to test for gender differences in time to ROR, and a paired t-test was used to test for differences between saline and d-AMPH in time to ROR.

Results: When saline was administered after DEX, the mean time to ROC was significantly longer in females (138.4 ± 33.7 min) than males (87.2 ± 12.3 min, $P < 0.01$). When d-AMPH was administered after DEX, the difference in mean time to ROC was 1.7 ± 0.7 min in males, and 1.9 ± 0.5 min in females. The large decrease in time to ROR with d-AMPH was statistically significant for both genders ($P < 0.001$).

Conclusion: At the same dose of DEX, the duration of LOC was 59% longer in female rats compared to males. This finding may be due to pharmacokinetic or pharmacodynamic factors, and encourages future work to test whether gender differences in sensitivity to DEX also exist in humans. Reversal of DEX-induced LOC with d-AMPH was equally efficacious in female and male rats, suggesting that d-AMPH may be a clinically useful reversal agent for DEX.

Reference(s):

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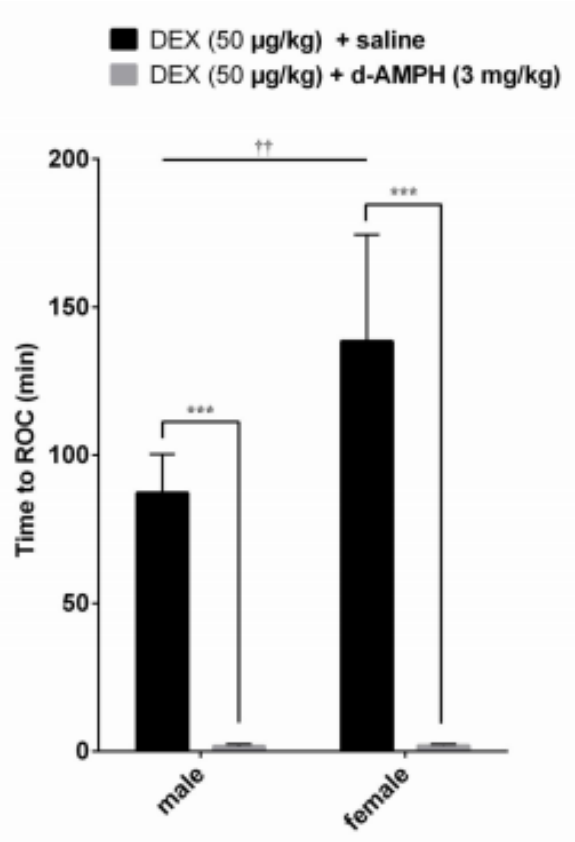
2 AUA/IARS 2019 (Abstract A65/F106)



The mean time to ROC in male and female rats that received DEX (50 µg/kg IV over 10 min) and saline were 87.2 ± 12.3 min and 138.4 ± 33.7 min, respectively. The difference was statistically significant (††: $P < 0.01$; Welch's t-test). The mean times to ROC after d-AMPH (3 mg/kg IV over 2 min) in males and females were 1.7 ± 0.7 min and 1.9 ± 0.5 min, respectively. The d-AMPH arousal effects in both sexes were statistically significant (***: $P < 0.001$; paired t-test).

Anesthetic Pharmacology-2 Propofol Toxicity in Cardiomyocyte Mitochondria of Developing Mice: A Novel Mechanism of Pediatric Propofol Infusion Syndrome?

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Introduction: Propofol infusion syndrome (PRIS) is a life-threatening condition characterized by metabolic acidosis, arrhythmias, cardiac failure, lactatemia, and fever.[1] Risk factors include young age and high cumulative doses. Prior studies suggest that propofol interferes with various components of the electron transport chain (ETC), including complexes I and IV and coenzyme Q (CoQ).[2] However, the exact mechanism of toxicity remains unknown. In addition, little is known regarding age-dependent vulnerability and few studies have assessed appropriate tissues of interest. Thus, we aimed to identify the mechanism of propofol toxicity within developing cardiomyocyte mitochondria in mice. We hypothesized that propofol would induce discrete defects within immature mitochondria.

Methods: 10-day old male C57BL6 mice were utilized to model a timepoint in human infancy. Ventricular myocardium was harvested and mitochondria isolated via differential centrifugation. Rates of oxygen consumption were measured polarographically prior to and following in vitro exposure to propofol. ETC enzyme kinetics were assessed via spectrophotometry. Substrate oxidation, ATP turnover, and proton leak were quantified relative to membrane potential. The source of proton leak was determined using specific inhibitors. 3-5 animals were evaluated per cohort. Data were analyzed using ANOVA and Tukey's post hoc analysis. Significance was set at $P < 0.05$.

Results: Propofol had minimal effect on state 3 respiration, however, caused significant dose-dependent increases in state 4 and oligomycin-induced state 4 respiration (proton leak). (Fig.1) ETC inhibition was only seen at Complex I with the highest concentration of propofol. (Fig 2.) Propofol-mediated excessive leak was cyclosporin (CsA) sensitive, indicating the mitochondrial permeability transition pore (mPTP) as a major source of pathological leak. (Fig 3.) As such, CsA abrogated the inefficient futile proton leak caused by propofol and fully repolarized the mitochondrial membrane potential. (Fig 4.)

Conclusion: Propofol uncouples immature cardiac mitochondria in a dose-dependent manner leading to excessive proton leak via the mPTP. Uncontrolled opening of the mPTP causes mitochondrial inefficiency, dissipates the mitochondrial membrane potential, and leads to apoptosis or necrosis. Such a novel mechanism could underlie the toxicity of propofol and may highlight a previously unknown therapeutic target; the mPTP. Future work will, therefore, focus on developing novel agents to prevent pediatric PRIS.

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Figure 1

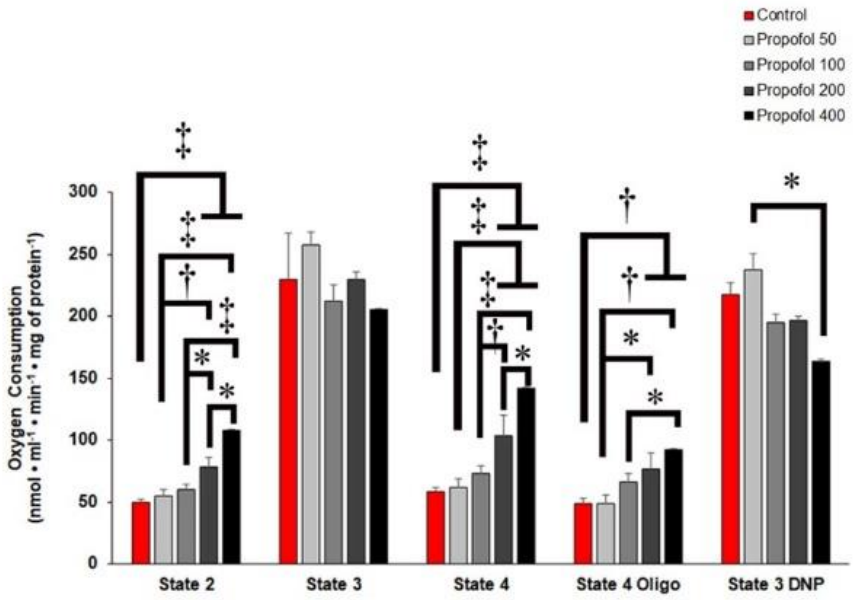


Figure 2

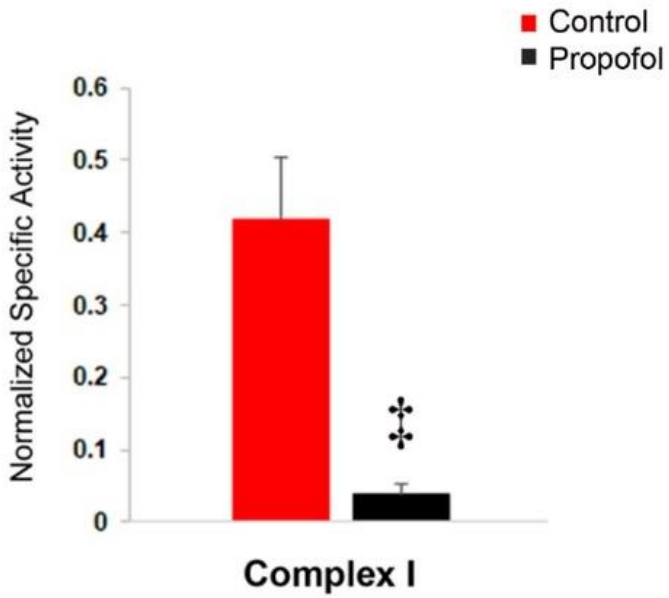


Figure 3

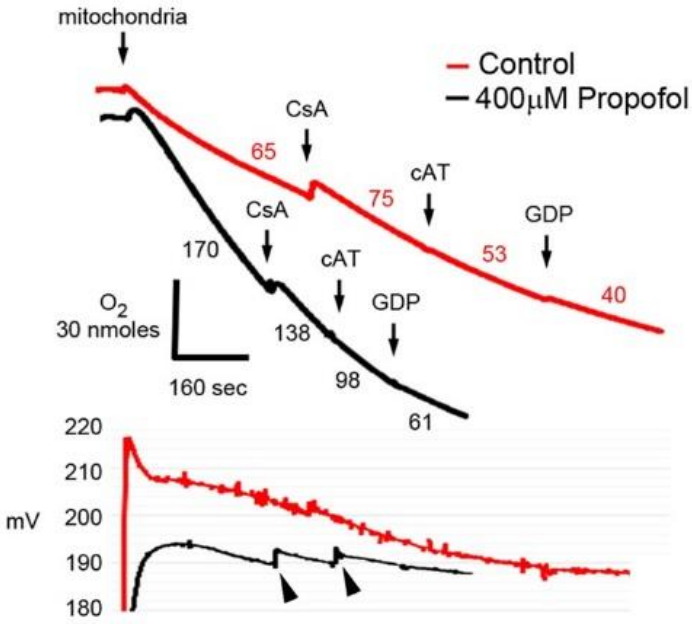
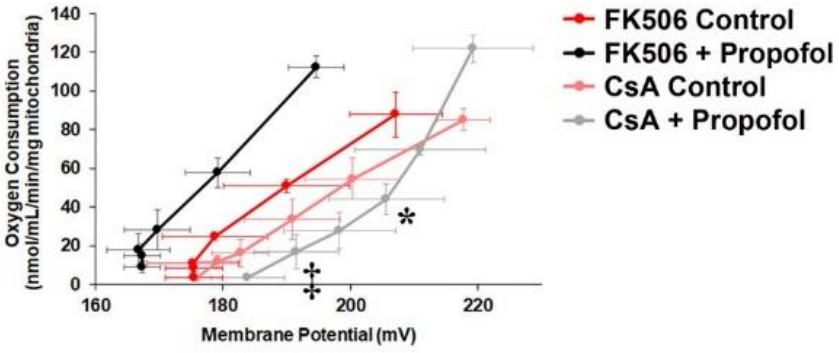


Figure 4



Anesthetic Pharmacology-3 Ketamine and metabolites bind to opioid receptors without significant activation

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Introduction: Part of the World Health Organization Model List of Essential Medicines, ketamine is administered primarily for its sedative and analgesic properties. One of its primary advantages in clinical anesthesia is hemodynamic stability compared to other common anesthetics such as propofol. It is also increasingly used as a rapidly acting antidepressant, for which the molecular mechanism is not yet clearly elucidated. Ketamine is thought to act as an N-methyl-D-aspartate (NMDA) receptor antagonist, binds ligand-gated ion channels [1, 2] and binds and/or results in activation of various G-protein coupled receptors (GPCRs) including opioid and olfactory receptors, as demonstrated by various experiments [3–8]. In mice, opioid receptor antagonists were shown to inhibit ketamine's effect on the tail flick test [9], suggesting an opiate-receptor-dependent functional role. In humans, pretreatment with naltrexone was shown to attenuate the antidepressant effect of ketamine [10], suggesting a clinically significant interaction of ketamine or its metabolites with mu and/or kappa opioid receptor. In a mouse model, there appeared to be an effect of enantiomer on ketamine's antidepressant activity [11]. These GPCR-related effects might occur directly, through the binding of ketamine or its metabolites to GPCRs themselves, or indirectly, through stimulation of endogenous opiate peptides. To evaluate which of these possibilities is most likely, we: 1) predict an atomic-level description, including calculated binding affinities, of protonation-state-dependent ketamine binding to horse spleen apoferritin (HSAF) and three GPCRs (mu and kappa opioid receptors and serotonin-2B receptor), with results consistent with previous experiments, and 2) conduct experiments quantifying ketamine-dependent G-protein and β-arrestin recruitment of mu and kappa receptors.

Methods: These GPCR-related effects might occur directly, through the binding of ketamine or its metabolites to GPCRs themselves, or indirectly, through stimulation of endogenous opiate peptides. To evaluate which of these possibilities is most likely, we: 1) predict an atomic-level description, including calculated binding affinities, of protonation-state-dependent ketamine (and metabolite) binding to horse spleen apoferritin (HSAF) and three GPCRs (mu and kappa opioid receptors and serotonin-2B receptor), with results consistent with previous experiments, and 2) conduct experiments quantifying ketamine-dependent G-protein and β-arrestin recruitment of mu and kappa receptors. Binding site prediction and refinement is done using computational molecular dynamics (MD) and free energy perturbation (FEP) methods. We evaluate ketamine as well as its metabolites norketamine and (2R,6R)-hydroxynorketamine. We included R- and S- enantiomers for ketamine and norketamine, and protonated states when they would be expected to exist in significant quantities at physiological pH.

Results: Atomic descriptions of ligand binding modes for ketamine, norketamine, and (2R,6R)-hydroxynorketamine were predicted using molecular dynamics (MD) simulations. For ketamine, and norketamine, both R and S enantiomers were included, and for ketamine, the protonated version was included as well. Binding affinities to opioid receptors were calculated using free energy perturbation MD. Ketamine and its metabolites were predicted to bind to both mu and kappa opioid receptors. Ketamine binding affinity to the tested GPCRs is heavily dependent on its protonation state, where the charged ketamine binds much more avidly. However, just because a ligand binds to a receptor does not mean it causes activation of downstream pathways. This was tested using GTP-gamma-S G-protein recruitment assay. Neither ketamine nor its metabolites, regardless of enantiomer, mediated significant G-protein activation.

Conclusion: We predicted binding modes of ketamine and its metabolites to opioid receptors, and showed that despite this binding, the resulting G-protein recruitment is unlikely to be significant in magnitude. Our data suggest that if the antidepressant effects of ketamine or its metabolites - which are clinically attenuated by naltrexone - are mediated by the opioid system, it is most likely that this is the result of an indirect effect, rather than direct binding of opioid receptors.

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Anesthetic Pharmacology-4 Oral dexmedetomidine is systemically available and promotes non-rapid eye movement sleep in healthy volunteers

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Introduction: The administration of dexmedetomidine is limited to highly monitored care settings largely because it is only available as an intravenous medication. An oral formulation of dexmedetomidine may broaden its use and benefits (e.g., delirium sparing, sedation)[1-3] to all care settings. Therefore, we investigated whether a capsule-based oral dosage formulation of dexmedetomidine is systemically available in a phase I dose-finding study. We also investigated the effect of a capsule-based oral dosage formulation of dexmedetomidine on polysomnography sleep quality and motor memory consolidation in a phase II study.

Methods: These studies were conducted under a Food and Drug Administration investigator-initiated Investigational New Drug Application and was registered on clinicaltrials.gov. First, we performed a single-site, open-label, phase I dose-escalating study of a solid oral dosage formulation of dexmedetomidine in healthy volunteers (n = 5, 300 mcg; followed by n = 5, 500 mcg; followed by n = 5, 700 mcg). The primary outcome for the Phase I study was hemodynamic stability. Mean arterial pressure and heart rate data were analyzed with polynomial mixed-effects models using time as a fixed predictor and subjects as random predictors. Plasma dexmedetomidine concentrations were determined by liquid chromatograph-tandem mass spectrometry. Next, we performed a single-site, placebo-controlled randomized, cross-over, double-blind phase II nighttime sleep study of oral dexmedetomidine (700 mcg) in healthy volunteers (n = 15). The primary outcome for the Phase II study was polysomnography sleep quality. Polysomnography data were recorded using the Somté PSG (Compumedics, Charlotte, NC) and scored using a validated automated sleep scoring software.[4] The motor sequence task and sleep questionnaires were also administered.

Results: In the Phase I study, we found that oral dexmedetomidine was systemically available and was associated with decreased heart rate and mean arterial pressure. However, these decreases did not meet our threshold for hemodynamic instability. The calculated elimination half-lives for the 300 mcg, 500 mcg, and 700 mcg groups were 2.7 hours, 2.5 hours, and 3.1 hours, respectively (Fig. 1). In the Phase II study, we found that oral dexmedetomidine increased the duration of non-rapid eye movement (non-REM) stage 2 sleep by 63 [95% CI: 19, 107] minutes (p = 0.010) (Fig. 2) and decreased the duration of REM sleep by 42 [5, 78] minutes (p = 0.031) (Table 1). We did not find any significant differences in measures of sleep latency, sleep stage switching, or subjective sleep quality (Table 2). Overnight motor memory consolidation improved after placebo sleep (7.9%, p = 0.003) but not after oral dexmedetomidine-induced sleep (-0.8%, p = 0.900) (Fig. 3).

Conclusion: We conclude that an oral capsule-based formulation of dexmedetomidine is systemically available in humans. Further, this formulation of dexmedetomidine promoted non-REM 2 sleep. The clinical significance of our motor memory consolidation findings are unclear. Overall, our results demonstrate the feasibility of developing oral dexmedetomidine as a non-REM sleep-promoting medication.

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Table 1. Sleep metrics derived from polysomnography

	Placebo (STD)	Dexmedetomidine (STD)	Diff (95% CI)	P value
Total dark time (mins)	600 (0.3)	600 (0.4)	0.1 (-0.5, 0.2)	0.422
Total sleep time (mins)	523 (40)	544 (33)	-16 (-43, 11)	0.207
Sleep Efficiency (%)	87 (7)	91 (5)	-3 (-7, 2)	0.211
WASO (mins)	53 (39)	42 (29)	5 (-19, 29)	0.639
Wake duration (min)	77 (40)	56 (33)	16 (-11, 43)	0.212
N1 (mins)	24 (13)	24 (19)	0.3 (-10, 11)	0.953
N2 (mins)	256 (46)	326 (69)	-63 (-107, -19)	0.010
N3 (mins)	122 (32)	108 (34)	5 (-7, 18)	0.362
REM (mins)	120 (27)	86 (53)	42 (5, 78)	0.031
N1 TST (%)	5 (3)	5 (4)	0.2 (-2, 2)	0.881
N2 TST (%)	49 (6)	60 (11)	-10 (-16, -4)	0.005
N3 TST (%)	24 (6)	20 (6)	2 (-0.2, 4)	0.071
REM TST (%)	23 (6)	16 (11)	8 (1, 15)	0.026

WASO, wake after sleep onset; N1, non-rapid eye movement stage 1; N2, non-rapid eye movement stage 2; N3, non-rapid eye movement stage 3; REM, rapid eye movement stage; TST, total sleep time. Diff, differences in the mean of the groups.

Fig. 1

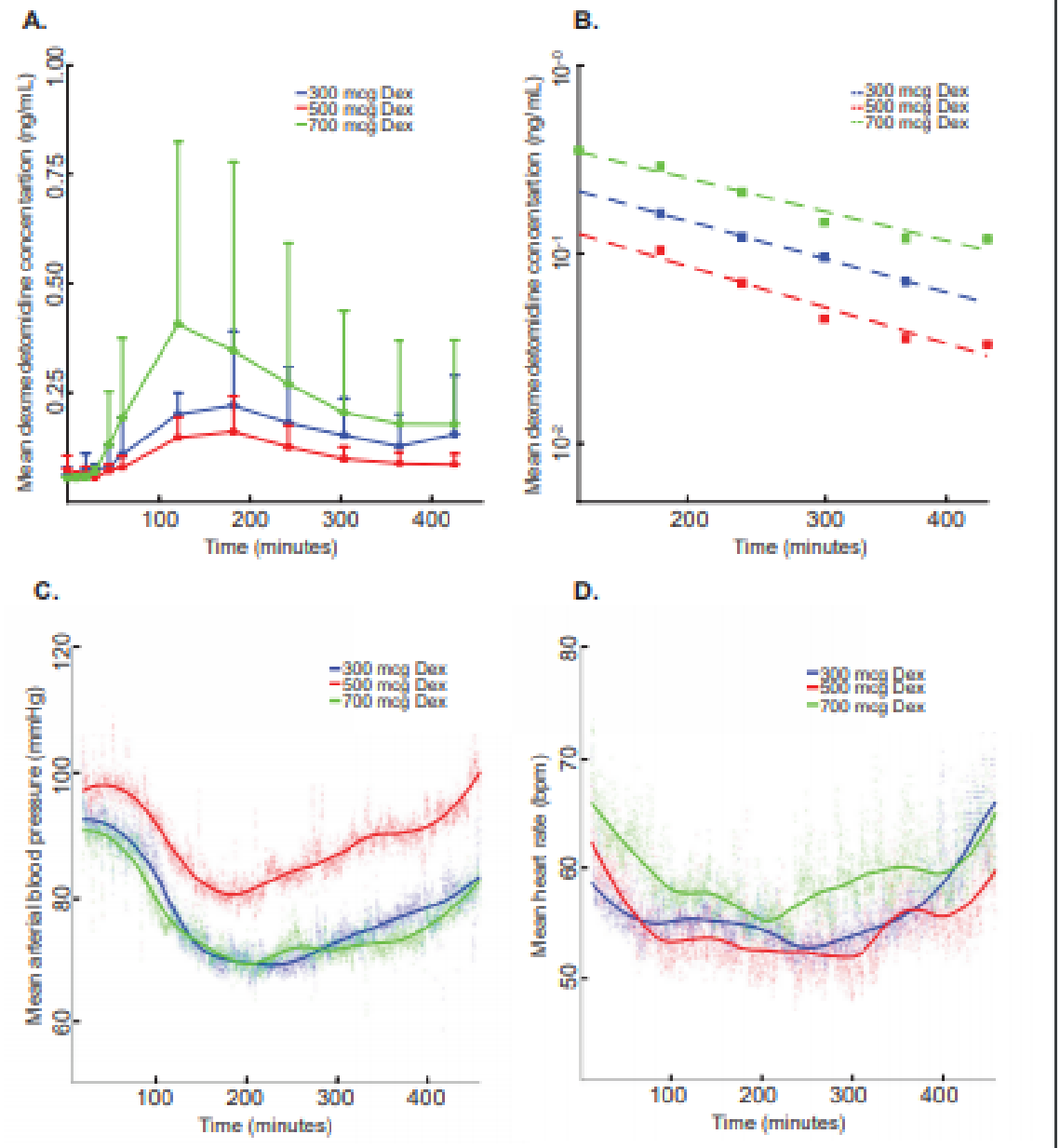

Fig. 1. Dexmedetomidine plasma concentration, mean arterial blood pressure, and heart rate. (A) Mean dexmedetomidine plasma concentration measured by liquid chromatograph-tandem mass spectrometry. The mean plasma concentration for the 500 mcg group was lower than the 300 mcg and 700 mcg groups at all time points beginning 30 minutes after drug administration. Vertical error bars represent the standard deviation. (B) We fit a line to the concentration (logarithmic) versus time (linear) starting at the peak plasma concentration. The slopes of the fitted lines were used to calculate the half-lives. (C) Group level mean arterial blood pressure. The line represents a smoothed best fit line to the data. Shaded colored bubbles represent the mean of arterial pressure over each group. (D) Group level mean heart rate. The line represents a smoothed best-fit line to the data. Shaded colored bubbles represent the mean of heart rate over each group. Blue color represents the 300 mcg group (n = 5), red color represents the 500 mcg group (n = 5), and the green color represents the 700 mcg (n = 5).

Table 2. Sleep latencies, fragmentation and administered sleep questionnaires

Sleep latencies derived from polysomnography

	Placebo (STD)	Dexmedetomidine (STD)	Diff (95% CI)	P value
Sleep latency (mins)	23.8 (18.4)	12.6 (7.5)	11.1 (-2.6, 24.7)	0.101
Wake duration (min)	77.0 (40.2)	55.6 (32.5)	16 (-10.9, 42.9)	0.212
Sleep latency to N1 (mins)	24.8 (18.6)	13.0 (7.4)	10.6 (-3.2, 24.4)	0.117
Sleep latency to N2 (mins)	28.3 (18.4)	21.0 (12.8)	5.5 (-8.4, 19.4)	0.395
Sleep latency to N3 (mins)	49.5 (27.0)	34.8 (21.4)	-10.7 (-2, 23.4)	0.089
Sleep latency to REM (mins)	70.6 (56.6)	74.3 (88.4)	-7.4 (-96.1, 81.2)	0.837
Switch	173.9 (44.7)	170.2 (64.0)	5.8 (-26.3, 38)	0.690
Switch index (per min)	0.3 (0.1)	0.3 (0.1)	0.02 (-0.03, 0.1)	0.404
Sleep fragmentation	59.1 (15.5)	58.7 (20.4)	1.9 (-10.7, 14.5)	0.746
Sleep fragmentation index (per min)	0.1 (0.01)	0.1 (0.04)	0.0 (-0.02, 0.03)	0.588

N1, non-rapid eye movement stage 1; N2, non-rapid eye movement stage 2; N3, non-rapid eye movement stage 3; REM, rapid eye movement stage; switch, number of stage shifts; sleep fragmentation, number of shifts to a lighter stage; Diff, differences in the mean of the groups.

Sleep metrics derived from questionnaire

	Placebo (STD)	Dexmedetomidine (STD)	Diff (95% CI)	P value
Total sleep (mins)	521.3 (62.2)	531.6 (59.5)	-16.9 (-44.2, 10.5)	0.203
Sleep latency (mins)	36.3 (27.3)	33 (24.4)	5.9 (-10.3, 22.2)	0.435
Times awakened (n)	3.7 (3)	3.2 (2.6)	0.9 (-1.1, 3.1)	0.315
Total time awake (mins)	23 (21.3)	24 (21)	-2.5 (-12.1, 17.1)	0.719
Overall sleepiness (1-Awake, 7-Not Awake)	2.6 (1.1)	2.6 (1.2)	-0.1 (-0.8, 1)	0.826
Quality of sleep (1-Bad, 4-Excellent)	2.5 (0.8)	2.6 (0.6)	-0.3 (-0.8, 0.2)	0.230

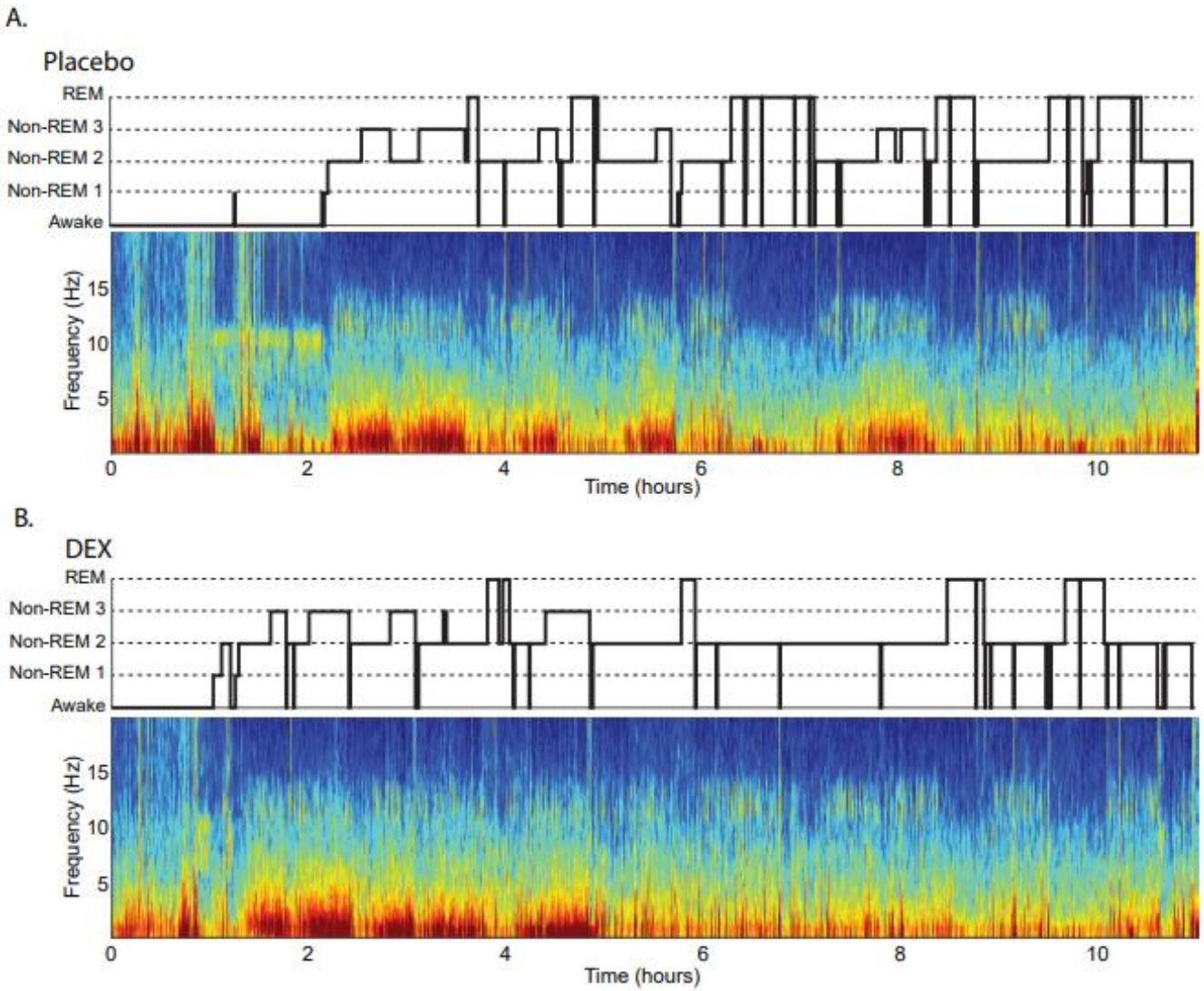

Fig. 2. Overnight sleep-wake profile of an illustrative subject during (A) Placebo visit and (B) 700 mcg oral-dexmedetomidine visit. Oral-dexmedetomidine administration is associated with an increased non-REM stage 2 sleep as compared to placebo visit.

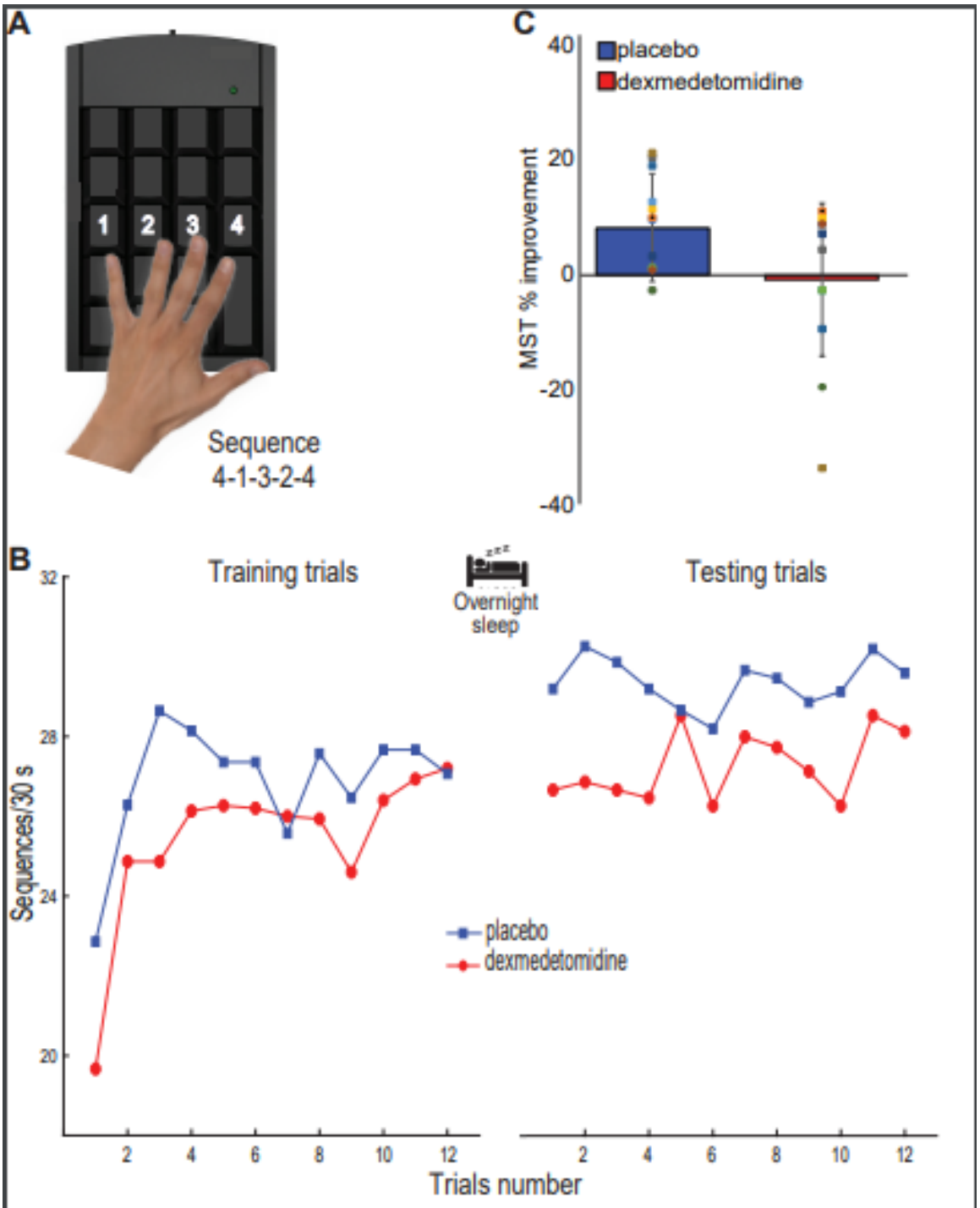

Fig. 3. MST performance. (A) The Motor Sequence Task (MST) involves typing a 5-digit sequence (4-1-3-2-4) as quickly and correctly as possible for 12 rounds of 30 second intervals. (B) MST performance during both the placebo and dexmedetomidine study visits. Placebo visits showed visibly improved overnight performance (average of first three testing sequences - average of last three training sequences), whereas oral dexmedetomidine immediate performance appeared similar between training and testing sessions. (C) Improvement in MST performance (%) met our threshold for statistical significance for the placebo (7.9%, p=0.003) but not for the dexmedetomidine (-0.8%, p=0.900) study visits. There were no statistically significant differences in immediate (p = 0.078) performance between groups.

Anesthetic Pharmacology-5 Site-specific effects of neurosteroids on $GABA_A$ receptor activation and desensitization

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Introduction: Neurosteroids (NS) are endogenous modulators of neuronal activity and behavior that have been therapeutically applied as anesthetics and anti-depressants (1-4). The principal target of NS is the γ-aminobutyric acid type A receptor ($GABA_AR$) (1-4) and NS analogues can be either positive (PAM-NS) or negative allosteric modulators (NAM-NS) of $GABA_AR$ function (4-6). We have previously shown that there are three PAM-NS binding sites on $\alpha_1\beta_3$ $GABA_ARs$, two of which mediate channel activation (7). In the current study, we explored the binding sites for NAM-NS with variable stereochemistry and substituents at the 3-carbon, and examined how site- and state-specific binding to these sites contributes to NS allosteric modulation of $GABA_ARs$.

Methods: In this study, we used direct photolabeling with NAM-NS analogues, KK148 and KK150, in which a diazirine replaced the C3-hydroxyl group to identify NAM-NS binding sites (8). We also measured the ability of NAM- and PAM-NS analogues to competitively prevent labeling by PAM-NS analogue photolabeling reagents. We then examined the effect of NS occupancy of each of the identified sites using site-directed mutagenesis coupled with electrophysiological and orthosteric ligand binding (3Hmuscimol) assays of $GABA_AsubR$ function.

Results: We found that the PAM-NS 3α5αP, but not the NAM-NS 3β5αP, binds to the $\beta_3(+)$–$\alpha_1(-)$ intersubunit site that mediates receptor activation by NS (Figures A-B), explaining the absence of 3β5αP PAM activity. In contrast, both 3α5αP and 3β5αP bind to an intrasubunit site in the β_3 subunit, promoting receptor desensitization. Interestingly, both 3α5αP and 3β5αP also bind to an intrasubunit site in the α_1 subunit. Occupancy of this site by 3α5αP promotes activation, whereas occupancy by 3β5αP promotes desensitization (Figures A-B). Binding to the intrasubunit sites provides a mechanistic explanation for the NAM effects of 3β5αP (6). The two NS analogues with 3-diazirine substituents (KK148 and KK150) bind to all three sites, but do not potentiate $GABA_AR$ currents. KK148 is an efficacious desensitizing agent, acting through the α_1 and β_3 intrasubunit sites (Figure C). KK150, the 17α-epimer of KK148, is devoid of allosteric activity (Figure D). These compounds provide potential chemical scaffolds for site-specific and general NS antagonists.

Conclusion: These results shed new light on the mechanisms of NS allosteric modulation of channel function, and demonstrate a novel pharmacology in which differential occupancy and efficacy at three discrete NS binding sites determine whether a NS has potentiating, inhibitory, or competitive antagonist activity on $GABA_ARs$.

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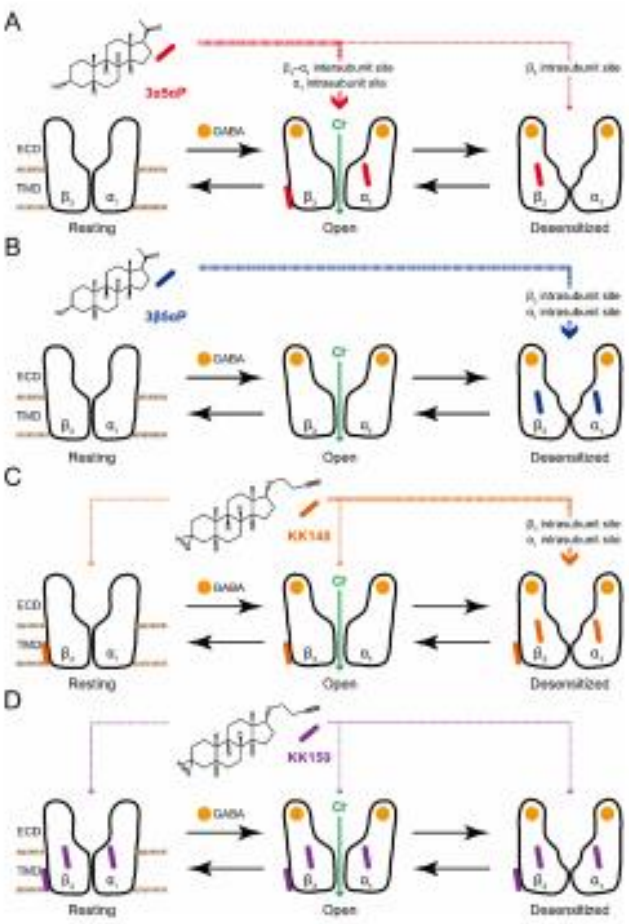

FIGURE: **Neurosteroids preferentially stabilize $GABA_AR$ in different states.** (A) Model showing three fundamental conformational states that depict the channel function in the $GABA_AR$: a resting state; an open state; and a desensitized state. Agonist (GABA: ●) binding shifts the equilibrium towards high-affinity states (open and desensitized). Allopregnanolone (3α5αP: ⬬) allosterically stabilizes the high-affinity states (an open state through the β_2–α_1 intersubunit and the α_1 intrasubunit sites; a desensitized state through the β_3 intrasubunit site). The width of red arrows indicates relative affinities of 3α5αP for the open or desensitized state of the receptor. (B) Same as (A) for epi-allopregnanolone (3β5αP: ⬬). 3β5αP stabilizes a desensitized state through the β_3 and α_1 intrasubunit sites. (C) Same as (A) for KK148 (⬬). KK148 allosterically stabilizes a desensitized state through the β_3 and α_1 intrasubunit sites, and equally stabilizes all three states of the receptor through the β_2–α_1 intersubunit site. The width of orange arrows indicates relative affinities of KK148 for each state of the receptor. (D) Same as (A) for KK150 (⬬). KK150 equally stabilizes all three states of the receptor through the β_3 and α_1 intrasubunit sites, and the β_2–α_1 intersubunit site.

Anesthetic Pharmacology-6

Dexmedetomidine use in awake fiber optic intubation improves patient satisfaction

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Introduction: Dexmedetomidine, an α2 adrenergic receptor agonist, is a sedative which has shown promise in its use in awake fiber optic intubation (AFOI) in combination with traditional sedatives. It has been shown to act as an antisialogogue, anxiolytic, and analgesic, all of which lend to its usefulness in sedation for AFOI. Importantly, it doesn't cause respiratory depression as seen with benzodiazepines and opioids. In this study, we were interested in learning whether its effectiveness as a sedative would translate to improved patient satisfaction.

Methods: Following IRB approval and informed consent, 77 narcotic-naïve patients undergoing elective surgical procedures requiring AFOI were enrolled in this double-blind RCT. Following consent, patients were started on an infusion of either placebo (normal saline) or dexmedetomidine (0.7 μg/kg/hr IV), midazolam (1-2 mg IV), and fentanyl (1 μg/kg, rounded to the nearest 25 μg IV). Patients with an RSS < 2 were titrated additional boluses of fentanyl to reach proper sedation. Once the patient was properly sedated the AFOI was commenced. We recorded the quantity of fentanyl required to reach proper sedation as a proxy for the efficacy of the dexmedetomidine as a sedative, and compared groups with an independent samples t test. Within 24 hours of the surgery, we identified any complications, inquired about recall and evaluated patient satisfaction with their sedation regimen on a 10-point scale (0=worst, 10=best). The satisfaction data presented herein were analyzed using the Wilcoxen-Mann-Whitney test.

Results: In the analysis of patient satisfaction, we only included patients who received infusions >21 minutes (n=41), as this was determined to be the threshold at which patients receiving dexmedetomidine required less rescue fentanyl (M=1.43 μg/kg) compared to the placebo group (M=1.97 μg/kg, $p<0.05$), thus demonstrating that dexmedetomidine had reached a therapeutic level. Patients in the dexmedetomidine group reported higher satisfaction (M=9.5) compared to patients who received placebo (M=8.1) ($p<0.05$). Within the placebo group, the patients who remembered the procedure accounted for most of the lower mean satisfaction. Comparing the two groups, those who didn't recall their AFOI were similarly satisfied, whether they received placebo (M=9.4) or dexmedetomidine (M=9.5). However, of those who did recall, the placebo group was significantly less satisfied (M=5.9) compared to the dexmedetomidine group (M=9.3) ($p<0.05$).

Conclusion: This study found that patients receiving dexmedetomidine infusions greater than 21 minutes were more satisfied with their AFOI sedation regimen, regardless of whether they recalled the event or not.

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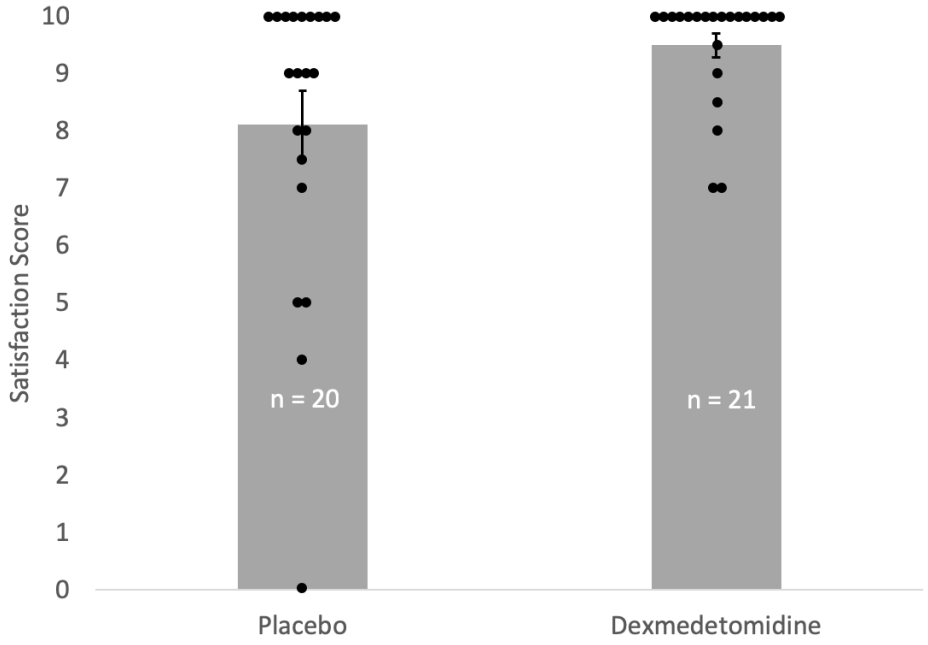

Figure 1. **Patient Satisfaction: Placebo vs. Dexmedetomidine.** Patients who received infusions of dexmedetomidine for >21 minutes reported higher satisfaction (M=9.5) compared to patients who received placebo (M=8.1) ($p<0.05$). Satisfaction was measured via survey and patients were asked to score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

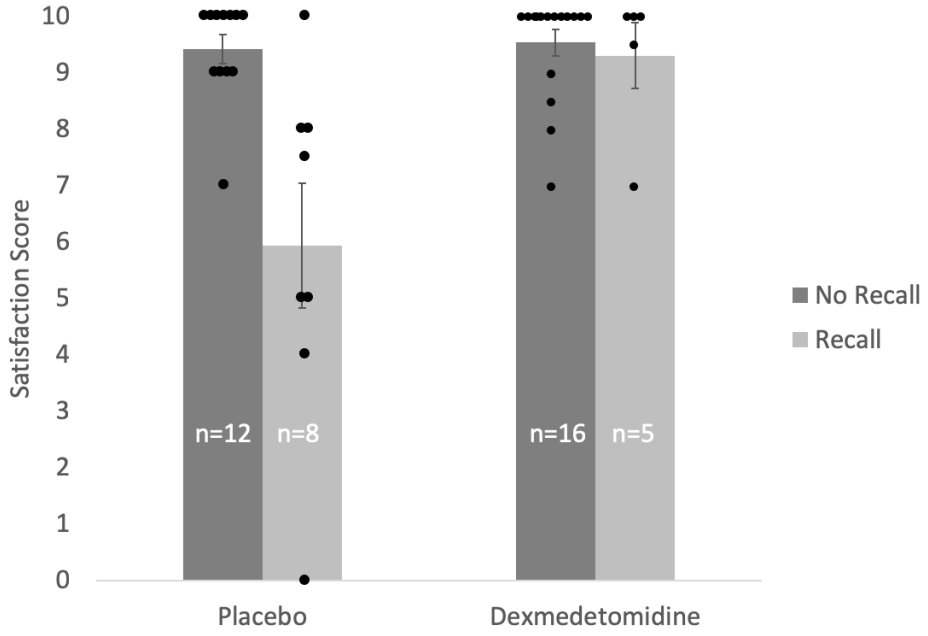

Figure 2. **Patient Satisfaction and Recall: Placebo vs. Dexmedetomidine.** Patients who didn't recall their AFOI were similarly satisfied, whether they received placebo (M=9.4) or dexmedetomidine (M=9.5). However, of those who did recall, the placebo group was significantly less satisfied (M=5.9) compared to the dexmedetomidine group (M=9.3) ($p<0.05$).

Anesthetic Pharmacology-7 Pathway- and cell type-specific effects of isoflurane on evoked responses in interneurons of non-primary mouse neocortex.

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Introduction: While their behavioral effects are well-characterized, the mechanisms by which anesthetics induce loss of consciousness are largely unknown. Anesthetics may ultimately influence both the level and contents of consciousness via actions on corticothalamic circuits, disrupting integration of information throughout the cortical hierarchy[1-5]. Recent studies have shown that isoflurane diminishes synaptic responses in a pathway-specific manner[6,7]. However, the degree to which the synaptic effects of isoflurane are cell-type specific has yet to be explored. Here, we evaluate the effects of isoflurane on evoked post-synaptic potentials (PSPs) in two inhibitory interneuron populations to thalamocortical (TC) and corticocortical (CC) layer 1 inputs in non-primary mouse neocortex.

Methods: To isolate TC or CC projections, adeno-associated virus containing channelrhodopsin (ChR2) and a fluorescent (eYFP) reporter was injected into either posterior thalamus (Po) or cingulate cortex (Cg) of mice expressing tdTomato in either somatostatin-(SOM+) or parvalbumin-positive (PV+) interneurons. Ex vivo brain slices were collected from a non-primary sensory association area in cortex. Whole cell patch-clamp recordings were obtained from layer 2/3 SOM+ and PV+ interneurons to evaluate post-synaptic responses to optogenetic activation of either TC or CC inputs to layer 1. PSPs with latency jitter <1 msec were considered putatively monosynaptic. The magnitude and paired pulse ratio (PPR) of PSPs were compared during control, isoflurane (0.24 mM), and recovery conditions for each cell type for each pathway. To evaluate the effect of isoflurane on EPSP magnitude and PPR, data were fit to a linear mixed-effects model, with fixed effects of drug condition and synapse combination, and random effect of slice experiment.

Results: CC afferents to cortical layer 1 evoked monosynaptic PSPs in both SOM+ and PV+ interneurons; TC afferents evoked monosynaptic PSPs in PV+, but not SOM+, interneurons. CC inputs to SOM+ cells displayed mild paired pulse depression (PPR=0.93±0.11, n=6), as did both TC (PPR=0.67±0.10, n=9) and CC (PPR=0.79±0.08, n=10) inputs to PV+ cells. Isoflurane increased PPR for CC inputs to SOM+ cells ($\Delta PPR_{control\_iso}$=0.30±0.10, p=0.005), but inputs to PV+ cells were unaffected for TC ($\Delta PPR_{control\_iso}$=-0.03±0.08, p=0.71) and CC ($\Delta PPR_{control\_iso}$=-0.01±0.08, p=0.87) inputs. Isoflurane suppressed CC-evoked PSPs in SOM+ interneurons ($\Delta PSP_{control\_iso}$=-31.4%±8.2%, p<0.001), enhanced TC PSPs in PV+ cells ($\Delta PSP_{control\_iso}$=33.9%±8.3%, p<0.001), but had no effect on CC inputs to PV+ cells ($\Delta PSP_{control\_iso}$=7.4%±6.3%, p=0.25).

Conclusion: Here, we demonstrate pathway- and cell type-specific effects of isoflurane on evoked responses in interneurons of non-primary neocortex. We show that feedback cortical inputs to SOM+ cells are suppressed during isoflurane. PPR was also enhanced at CC-SOM synapses, implicating pre-synaptic actions of isoflurane. SOM+ cells play a role in modulating inputs to pyramidal cells during sensory processing8; thus, anesthetic-induced changes in SOM+ cell activity may disrupt integration of sensory signals. Isoflurane amplified PV+ cell responses to TC inputs. PV+ cells restrict integration windows of pyramidal cells9 and regulate pyramidal cell spike timing in the context of network activity10. The amplification of PV+ cell activity by isoflurane may constrain spike outputs from local pyramidal cells, and therefore disrupt the computational power of the network.

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Anesthetic Pharmacology-8 Selective impairment of interaction of ADP and ATP synthase by anesthetics

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Introduction: Isoflurane, sevoflurane and desflurane have different neurotoxic effects 1. However, the underlying mechanisms remain unknown. Isoflurane, sevoflurane and desflurane can differently induce mitochondrial dysfunction 2-3 and ATP synthase is the critical component of mitochondrial function 4. We, therefore, set out to test a hypothesis that anesthetics selectively impair the interaction of ADP and ATP synthase.

Methods: The human H4-APP cells were treated with 2% isoflurane, 4% sevoflurane or 12% desflurane for 6 hours. The mitochondrial function was measured by using a Seahorse XFp Extracellular Flux Analyzer. Next, we used a nanobeam technology-based single molecular study 5 to determine the interaction of ADP and ATP synthase. The resonance shift, detected by a nanosensor, corresponded to such interaction. Finally, the single molecular dynamics simulation 5 identified the binding site between ATP synthase and isoflurane, sevoflurane or desflurane.

Results: The Seahorse XFp Extracellular Flux Analyzer demonstrated that isoflurane (Figure 1A), but not sevoflurane (Figure 1B) nor desflurane (Figure 1C), induced mitochondrial dysfunction in the H4-APP cells. Isoflurane significantly impaired the interaction of ADP and ATP synthase as evidenced by the decreased number of resonance shift (Figure 2A), longer duration between the resonance shifts (Figure 2B versus 2C) and decreased disassociation constant (Figure 2D). Neither sevoflurane (Figure 3) nor desflurane (Figure 4) impaired such interaction. Mechanistically, there were 7, 1 and 3 binding sites between isoflurane, sevoflurane and desflurane with ATP synthase alpha-subunit, respectively (Figure 5).

Conclusion: These findings suggest that isoflurane has more binding sites with ATP synthase than sevoflurane or desflurane, which accounts for the selective impairment of ADP and ATP synthase interaction following the treatment of isoflurane but not sevoflurane or desflurane. Consequently, isoflurane, but not sevoflurane and desflurane, causes the observed mitochondrial dysfunction and neurotoxicity.

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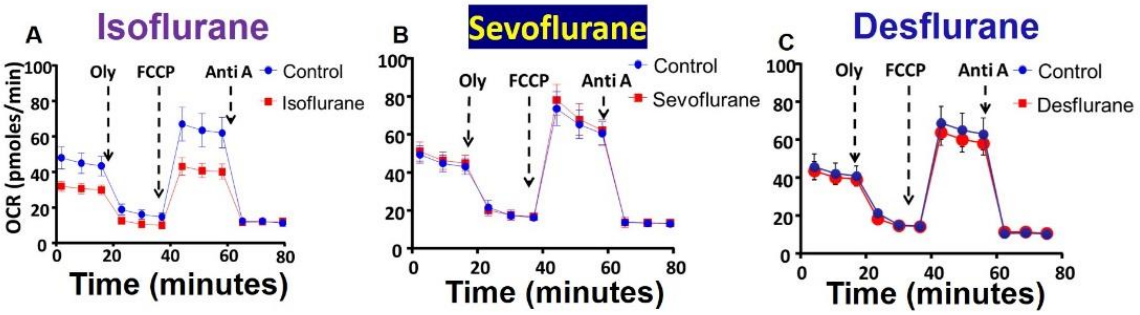

Figure 1: **Anesthetics and mitochondrial function:** The mitochondrial function in H4-APP cells following the treatment with isoflurane (**A**), sevoflurane (**B**) and desflurane (**C**).

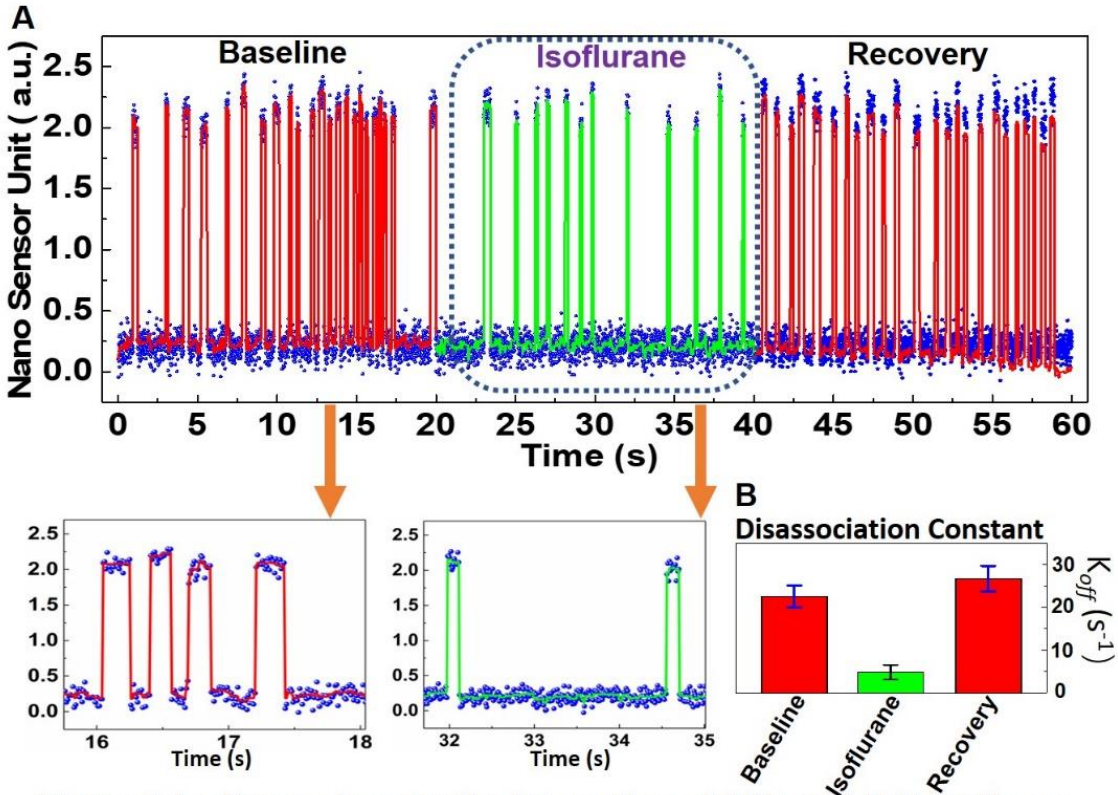

Figure 2: **Isoflurane impairs the interaction of ADP and ATP synthase**: Real-time binding dynamics of the ADP and ATP synthase in the standard binding buffer following the isoflurane treatment (**A**). **B**. The binding kinetics are fitted from the event as described in previous studies [5].

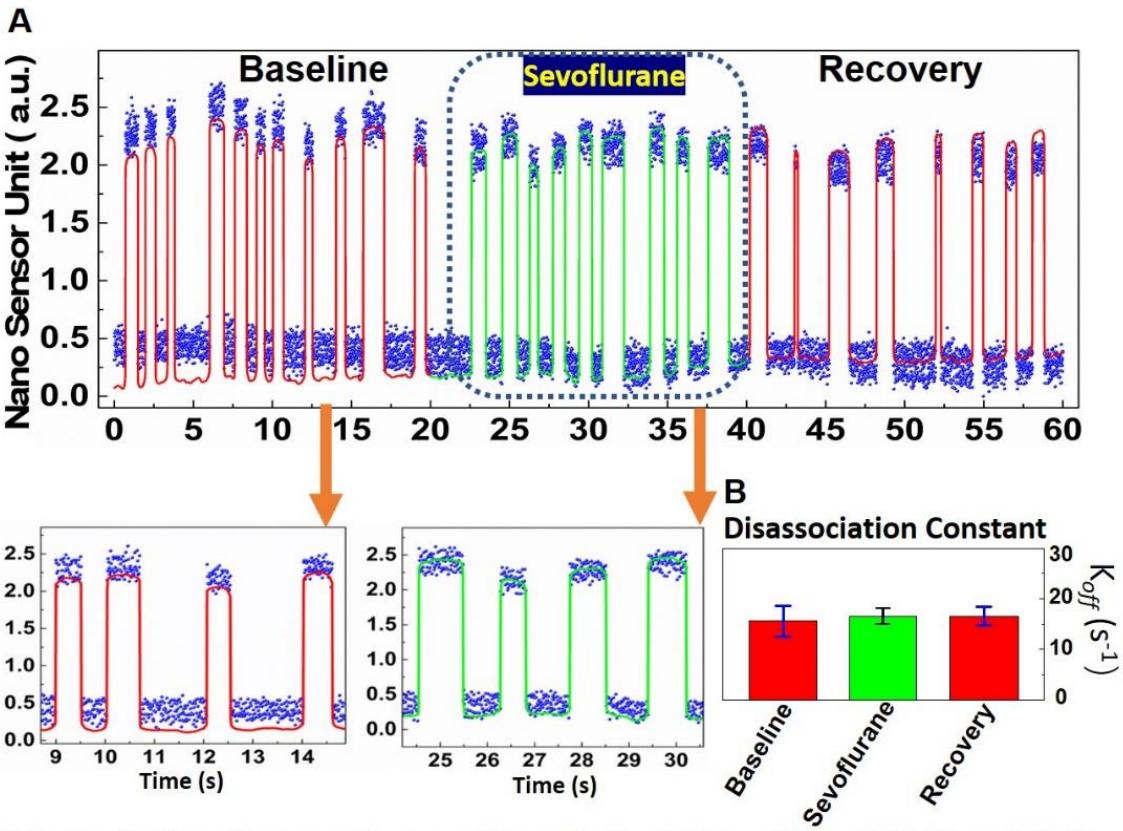

Figure 3: **Sevoflurane does not impair the interaction of ADP and ATP synthase**: Real-time binding dynamics of the ADP and ATP synthase in the standard binding buffer following sevoflurane treatment (**A**). **B**. The binding kinetics are fitted from the event as described in previous studies [5].

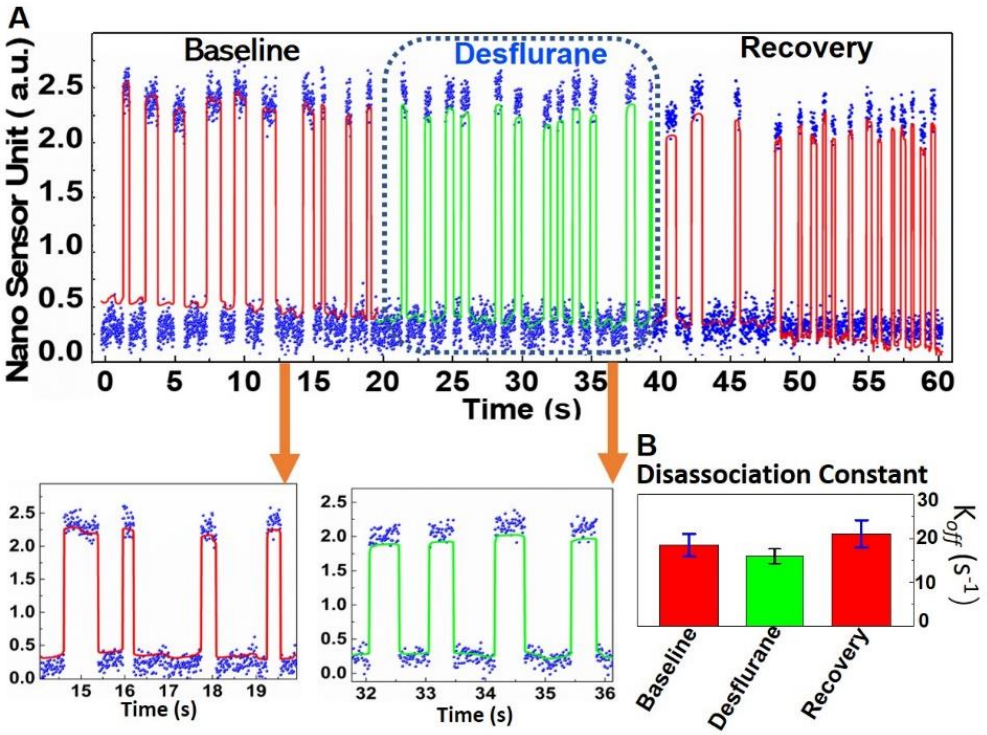

Figure 4: **Desflurane does not impair the interaction of ADP and ATP synthase**: Real-time binding dynamics of the ADP and ATP synthase in the standard binding buffer following desflurane treatment (**A**). **B**. The binding kinetics are fitted from the event as described in previous studies [5].

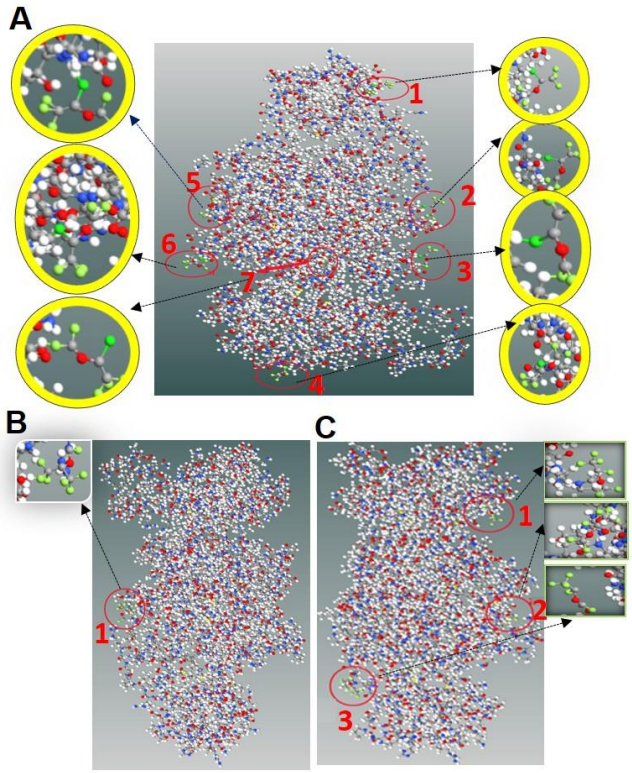

Figure 5: **Binding sites of anesthetics with ATP synthase:** The binding sites of ATP synthase with isoflurane (**A**), sevoflurane (**B**), and desflurane (**C**).

Anesthetic Pharmacology-9 Consistent 5-95% Recovery Intervals Shown by the NMBA CW 002 (RP 1000) in Humans Over the Clinical Dose Range May Enable Prediction of the Timing of Recovery After Any Dosing Regimen

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Introduction: In a Phase I study of the intermediate-duration NMBA CW 002 in volunteers under sevoflurane/N2O anesthesia, the 5-95% (and 25-75%) recovery times of the first twitch (T1 of TOF) did not differ following doses of ~ 1.0 to 1.8 times the ED95 (1). In the present study, this consistent recovery pattern has been reevaluated. The potential application of this property to clinical practice would be the ability to accurately predict the time required for recovery from deep neuromuscular blockade (5% twitch height), to twitch height 95% of baseline and to TOF ratio (TOFR) 0.90.

Methods: Healthy volunteers (n=34) aged 18 to 55 of either gender gave informed consent to an IRB-approved Phase I protocol. NMB was measured by mechanomyography during sevoflurane (0.5 MAC)/N2O (70%) anesthesia. Each volunteer received a single IV bolus of CW 002. At doses below 0.08 mg/kg, (n=18) 100% twitch inhibition occurred in NONE of the volunteers. 12 of 14 volunteers, however, who were given doses of 0.08, 0.10, or 0.14 mg/kg, developed 100% block: (n=2 of 6 at 0.08, 6 of 6 at at 0.10, and 4 of 4 at 0.14 mg/kg). During spontaneous recovery from 100% block, in all volunteers,TOF stimulation was applied to the ulnar nerve every 20 sec and the response of the thumb was monitored continuously until T1 of TOF had recovered to 95% of baseline and TOFR had reached 0.90. The total duration of block was calculated from injection to recovery of T1 to 95 percent of baseline and to recovery of TOFR to 0.90. The 5-95% recovery intervals during recovery from 100% block were measured. Following the completion of data acquisition for all dosage groups, a comparison was made by ANOVA of the 5-95% recovery times resulting after doses of 0.08, 0.10 and 0.14 mg/kg. Recovery data in the 12 volunteers who developed 100% block were then combined to show a single composite recovery pattern. ANOVA was again done to compare the recovery data (5-95% intervals) for the composite group to the corresponding intervals for the separate dosage groups of 0.08, 0.10, and 0.14 mg/kg. The recovery data for the composite group of twelve was then analyzed by linear regression. The regression essentially comprised data for 5-95% recovery time. The slope of the composite regression line was calculated.

Results: Results are summarized in Figs 1 and 2 and in Table 1. Fig 1 shows apparent parallelism of all recovery curves: for groups 0.08, 0.10, and 0.14 mg/kg, and for the composite group. Both comparisons where ANOVA was applied twice and showed no significant differences among the groups 0.08, 0.10, and 0.14 mg/kg; when comparison of the composite group was added, differences remained nonsignificant: P= 0.58 and P= 0.76 respectively. Fig 2 shows the regression of the composite recovery line from 5% twitch height to 25, 50, 75, and 95% twitch height, versus time for the twelve individuals who developed 100% block of twitch. The relation is significant (P= 0.002). The slope of the line is 2.518.

Conclusion: The pharmacology in humans of CW 002, an intermediate-duration nondepolarizing NMBA, has been reported. Pharmacokinetic measurements included in that report show an elimination half-life of 25-26 minutes in all dosage groups. This kinetic pattern is consistent with the pharmacodynamics of this drug and is likely due to the compound's degradation in a chemical reaction, cysteine adduction (1). The clinical pharmacology of CW 002 shows indications that recovery intervals following doses that caused 100% block of twitch do not differ in the three escalating dosage groups of 0.08, 0.10, and 0.14 mg/kg in the first study in humans (1). Combination of data from these three groups, to yield a composite group of twelve who developed 100% block, as done in the present study, results in a 5-95% recovery interval which does not differ from data which had been derived from any of the separate dosage groups (P= 0.58 by ANOVA) (Fig1). In the composite group, a comparison of recovery of NMB from 5% twitch height to several levels of function, i.e. recovery time of twitch (T1of TOF) from 5% to 25, 50, 75, and 95% of baseline, resulted in a regression where the linear relationship is significant. These results suggest that, using the slope of that regression line, the recovery time from 5% twitch height (which is a readily identifiable level of deep NM blockade) to any level of recovery of function, in the case of CW 002, may easily be calculated and forecasted in humans.

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	Doses (mg/kg)			
	0.08	**0.1**	**0.14**	**Composite**
5-95% recovery interval (min)	34.8 ± 12.5	39.4 ± 6.5	35.6 ± 3.1	37.4 ± 6.4
25-75% recovery interval (min)	15.7 ± 8.4	15.1 ± 2.0	14.2 ± 0.9	14.9 ± 3.0

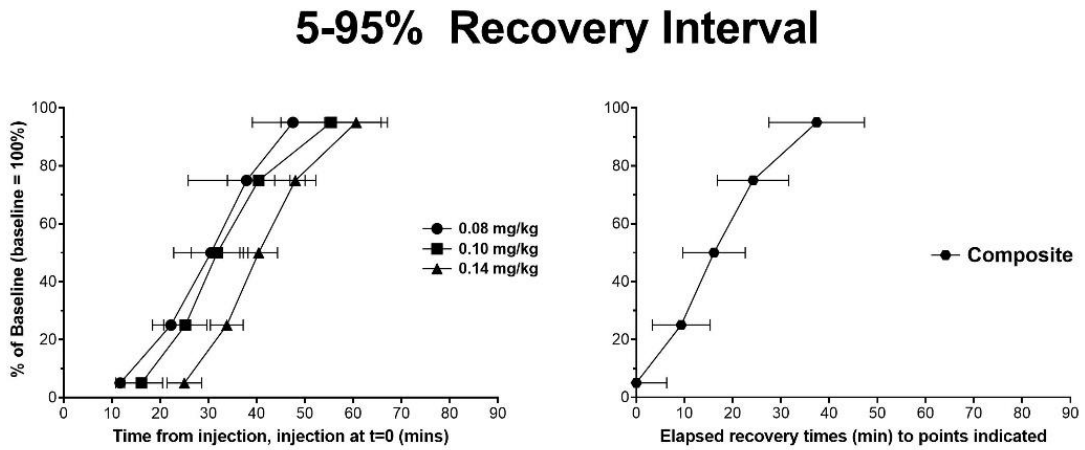

Fig 1. Recovery curves of CW 002 in healthy adult volunteers under sevoflurane/N2O anesthesia. The curves illustrate spontaneous recover after 100 percent block, from 5% T1 to 95% of baseline T1.

Left to right: Groups 0.08 mg/kg (n=2); 0.10 mg/kg (n=6); and 0.14 mg/kg (n= 4). These doses are ~ 1.0, 1.4 and 1.8 x ED95. Fourth curve to the right is the composite of all three groups (composite curve, n= 12). There are no significant differences among the groups in comparisons done by ANOVA of the 5-95% recovery intervals.

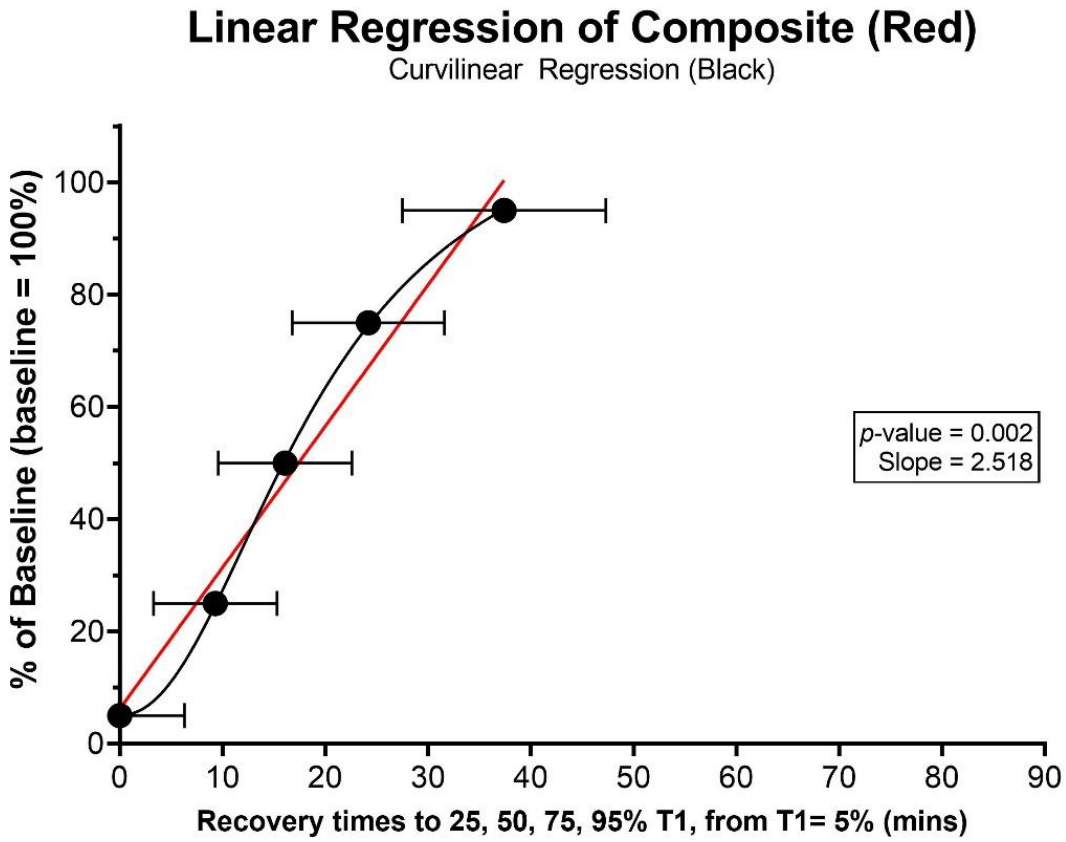

Fig 2. Linear regression for the composite group (n= 12). Times for recovery of T1 from 5% to T1 of 25%, 50%, 75%, and 95% of baseline. The linear relationship is significant (P= 0.002). This suggests that rather precise prediction of time required for recovery from CW 002- induced NMB may be done in humans.

Anesthetic Pharmacology-10 Effect of propofol on GABA(A) receptor deactivation kinetics determined using an automated high-precision electrophysiology rig

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Introduction: Our understanding of the molecular mechanisms of general anesthesia has been transformed over the last 30 years with the introduction of the high-resolution electrophysiology patch-clamp method. The technique has demonstrated that general anesthetics act directly on ion channels, changing the kinetics of how channels open and close. However, the inefficient technique remains low-throughput and requires prolonged training to attain proficiency and as a result the cost per data point remains high. The technique is commonly used in discovery-based physiology and pharmacology departments, where expert researchers can use the technique on a daily basis, but is less accessible in most anesthesia departments where it is difficult to fund the significant labor cost. If the technique could be simplified and automated, the need for specialist users would be reduced and automation would allow for increased perioperative insight from anesthesia providers, not just research scientists. Here we demonstrate the utility of a new automated system that incorporates electrode cleaning and re-use, manipulation of heterologous cells (whole cell and outside out patches) and control of submillisecond solution exchange to mimic the speed at which neurotransmitters are released and removed from the synaptic cleft, where they activate ligand-gated ionotropic receptors. The system can perform typical ligand-gated ionotropic receptors experimentation protocols autonomously that allows for a high experiment completion success rates and can reduce the operator's effort substantially. The system allows for the ability to conduct complex and comprehensive experimentation that yield datasets not normally within reach of conventional systems that rely on constant user control.

Methods: Starting with a conventional inverted microscope-based manual patch-clamp system equipped with rapid solution exchange, we added a camera and engineered pressure control systems and motor-driven adaptors for the micromanipulator systems. All system components were integrated via a National Instruments digital-analog converter and driven by bespoke control software written in Labview. The stable cell line was generated with human/humanized α1, β2 and ɣ2L2L GABA(A) receptor cDNAs in HEK293 cells. Data are reported as mean ± SEM.

Results: We used the automated electrophysiology system to determine the effect of 1 µM - 50 µM propofol on the kinetics of human GABA(A) receptors expressed in a stable cell line. In automated mode, the time between starting each patching protocol was 2 minutes. The 28 datasets collected in this study were gathered during 9.07 hours of operation in automated recording mode. The recording required only 2.49 hours of human effort. In contrast, 28 excised patches would take 1-2 weeks of effort using conventional manual methods. The receptors were successfully activated by synaptic concentrations of GABA in outside patches. In the clinical range (< 5 µM), propofol increased the time-constants for receptor deactivation and receptor desensitization. This effect continued beyond the clinical range.

Conclusion: Our data collected on human receptors in a stable cell line supports previous findings in transient and rodent systems that propofol increases synaptic inhibition by preventing channel closure via 2 different mechanisms. By utilizing the automated system, we were able to reduce labor time by 96% and increase real time throughput by more than 6 fold.

Anesthetic Pharmacology-11 Ketamine produces a long-lasting enhancement of excitatory synaptic transmission

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[2]Stanford, Stanford, CA

Introduction: Ketamine has recently been shown to improve major depressive disorder (MDD) in patients that 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, often for several weeks. Current evidence suggests that the mechanism for this effect does not involve 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 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 by electrically stimulating Shaffer-collateral axons while recording evoked responses from CA1 pyramidal neurons and GABA inhibitory interneurons using a paired-pulse paradigm.

Results: Concentration dependent effects were observed over clinical ranges (from 1.0 µM; antidepressant, to 350 µM; anesthetic). Ketamine produced three effects: 1) an acute depression of population spike amplitudes, 2) an enhancement of GABA-A fast and/or tonic inhibition, and 3) a long-lasting increase in population spike amplitude. The long-lasting increase in amplitude was observed following drug washout and lasted for at least 8 hours (longest duration of recording). This effect was unlike other anesthetics that also produce an acute depression of population spike amplitudes, but do not produce long-lasting effects following washout. These effects were mimicked by the primary ketamine metabolites. A long-lasting effect was not observed on EPSP responses, indicating a postsynaptic site for ketamine's action.

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 the brain slice. We suggest this long-lasting effect could be related to the long-lasting antidepressant effects produced by ketamine and its metabolites.

Blood Management

Blood Management-1 FEIBA administration reduces blood transfusions in pediatric patients with refractory bleeding after cardiopulmonary bypass surgery

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Introduction: Pediatric patients undergoing cardiac surgery are at risk for bleeding and large transfusions due to cardiopulmonary bypass (CPB) effects, immature coagulation systems, and surgical complexity (1-3). Blood transfusions are often needed to restore post-CPB hemostasis, but some patients have refractory bleeding despite maximal standard hemostatic therapy. Prothrombin Complex Concentrates (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). While one prospective study evaluates the prophylactic administration of a non-activated 4F-PCC (Confidex®; CSL Behring, Milan, Italy), there are no published data on the off-label use of the activated 4F-PCC FEIBA as rescue therapy for children undergoing cardiac surgery (6). We report our initial experience with FEIBA as rescue therapy in pediatric patients with refractory bleeding after CPB.

Methods: After IRB approval, we queried our institutional database between January 1, 2017 - June 5, 2019 for pediatric patients undergoing cardiac surgery with CPB who received FEIBA intraoperatively and performed a retrospective chart review. Our primary outcome was blood products given before and after FEIBA administration. Secondary outcomes included FEIBA dose, intubation time, ICU and hospital length of stay (LOS), and adverse events (AE). The Wilcoxon paired test was used to compare transfusions before and after FEIBA administration.

Results: Thirty-two patients (32/1287) received FEIBA® as rescue treatment for bleeding: median age 7.2 years [0.33-13.4]; median weight 23.05 kg [5.15-51.18]; 81% had a STAT score of ≥3; mortality score of 1.60 [1.40-2.40] (Table 1). The median dose of FEIBA was 12.98 units/kg [10-21.86]. Platelet (12.50 ml/kg [6.12-25.24] vs. 0.73 ml/kg [0.00-14.51]; p<0.001) and cryoprecipitate (4.76 ml/kg [2.72-10.18] vs. 0.00 ml/kg [0.00-1.56]; p<0.001) administration decreased significantly after FEIBA administration. There were no significant difference in PRBCs or FFP transfusion after FEIBA administration (Table 2). Intubation time was 42.50 hours [23.81-139.09], ICU LOS of 5 days [2-16] and hospital LOS of 14 days [6-33]. AE included thrombosis (6.3%), repeat surgery within seven days (18.8%), chest exploration (21.9%), infection (9.4%), stroke (6.3%), and ECMO within 24h (6.3%). Overall mortality was 9.4% (3/32) (Table 3).

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 pediatric patients who received FEIBA for refractory bleeding received significantly less platelets and cryoprecipitate after FEIBA administration. This study demonstrates that low dose FEIBA administration used as a rescue therapy significantly reduced blood utilization in high risk pediatric patients with refractory bleeding after CPB. While more studies are required, FEIBA may be a safe and effective hemostatic agent for rescue therapy in patients with refractory bleeding after CPB.

Reference(s):

1. Anesth Analg 1999; 89:57-64.
2. Ann Thorac Surg 1992; 54(3):541-6.
3. Anesth Analg 2015;120 (2): 405-410.
4. J Card Surg 2008;23: 614-621.
5. J Cardiothorac Vasc Anesth 2014;28:1221–66.
6. Pediatr Cardiol 2014; 35: 208-214.

Table 1. Patient Demographics and Intraoperative data

	n	N=32
Gender+	32	
Male		22 (68.8%)
Female		10 (31.3%)
Weight (kg)*	32	23.05 (5.15 – 51.18)
Height (cm)*	32	122.00 (59.75 – 160.00)
Age (months)*	32	86.69 (3.95 – 160.11)
Prematurity (yes) +	32	0 (0%)
≥1 Prior Sternotomy (yes) +	32	13 (40.63%)
Preoperative Hemoglobin (gm/dL)*	32	12.80 (11.05 – 14.40)
Preoperative oxygen saturation (%)*	32	99.00 (94.75 – 100.00)
STAT Score+	32	
1		0 (0%)
2		6 (18.75%)
3		4 (12.50%)
4		19 (59.37%)
5		3 (9.38%)
Mortality Score*	32	1.60 (1.40 – 2.40)
Anesthesia Time (min)*	32	686.00 (592.25 – 787.50)
Surgery Time (min)*	32	501.00 (440.50 – 628.50)
CBP Time (min)*	32	262.50 (198.50 – 336.50)
Aortic Cross Clamp Time (min)*	29	160.00 (74.00 – 219.00)
Regional Perfusion Time (min)*	7	30.00 (25.50 – 54.50)
DHCA Time (min)*	6	4.50 (4.00 – 8.00)
Lowest Temperature (˚C)*	32	28.00 (20.75 – 32.00)
Total FEIBA® dose (units/kg)	32	12.98 (10.00 – 21.86)

+percentage; *Median (Interquartile Range)

Table 2: Median patient blood products before and after FEIBA (compared using Mann-Whitney test, $p<0.05$ is considered significant)

Post Bypass Blood Products	n	Before FEIBA®	After FEIBA®	p-value
PRBCS (ml/kg)	32	3.54 (0.00 – 13.66)	0.00 (0.00 – 3.35)	0.223
FFP (ml/kg)	27	3.31 (0.00 – 7.22)	0.00 (0.00 – 3.17)	0.295
Platelets (ml/kg)	32	12.50 (6.12 – 25.24)	0.73 (0.00 – 14.51)	<0.001
Cryo (ml/kg)	31	4.76 (2.72 – 10.18)	0.00 (0.00 – 1.56)	<0.001

Table 3. Patient Outcomes

Outcomes	**n**	**FEIBA® N=32, %**
End CPB to FEIBA® Time (min)*	32	67.00 (50.25 – 96.00)
FEIBA® to End Anesthesia Time (min)*	32	113.50 (74.74 – 140.50)
Chest Tube Output (ml/kg)*	30	9.67 (6.48 – 23.17)
Intubation Time (min)*	32	43.50 (23.81 – 139.09)
ICU LOS (days)*	31	5.00 (2.00 – 16.00)
Hospital LOS (days)*	31	14 (6.00 – 33.00)
Adverse Outcomes+		
Thrombosis	32	2 (6.3%)
ECMO within 24h	32	2 (6.3%)
Repeat Surgery within 7 days	32	6 (18.8%)
Chest Exploration	32	7 (21.9%)
Arrhythmia requiring treatment	32	11 (34.4%)
Infection (positive blood culture)	32	3 (9.4%)
Stroke	32	2 (6.3%)
Death	32	3 (9.4%)
Death within 24h	3	0 (0%)
Death within 30 days	3	2(66.6%)

+percentage; *Median (Interquartile Range); LOS = Length of Stay

Blood Management-2 Ex Vivo Effect of Fibrinogen Concentrate on the Fibrin Network Structure in Neonates after Cardiopulmonary Bypass

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Introduction: Bleeding is a serious complication of cardiopulmonary bypass (CPB) in neonates and is associated with morbidity and mortality (1). To restore hemostasis, transfusion is often necessary. Given the risks associated with blood product transfusion, neonates would benefit from safe and effective alternatives to augment hemostasis after CPB. The use of fibrinogen concentrate (FC; RiaSTAP®, CSL Behring, Marburg, Germany) is increasing. However, it has not been studied in pediatric patients and the limited experience in adult cardiac patients may not be relevant to pediatric practice. Our recent studies demonstrate that adult and neonatal fibrinogen are structurally distinct and may not integrate seamlessly after transfusion (2). In this study we characterize the effect of FC on the structure of fibrin clots when added ex vivo to neonatal plasma obtained before and after CPB.

Methods: After IRB approval and parental consent, blood samples were collected from neonates undergoing cardiac surgery at baseline, after CPB, and after the transfusion of cryoprecipitate. All samples were centrifuged to yield platelet poor plasma for ex vivo fibrin clot formation. Clots were formed ex vivo from patient plasma 1) at baseline, 2) post-CPB, 3) post-transfusion, 4) post-CPB + 0.5mg/ml FC, and 5) post-CPB + 0.9mg/ml FC. The clinical dose of FC results in approximately 0.9mg/ml of FC. Fibrin clot structure was analyzed using confocal microscopy and scanning electron microscopy for fiber density (FD) and fiber alignment (AI). Tuckey's multiple comparisons test was used to compare mean difference between groups.

Results: Clots formed post-CPB had a significantly lower FD than any other condition. The average FD of clots formed post-CPB + 0.5mg/ml FC did not significantly differ from post-transfusion clots. However, FD of clots formed post-CPB + 0.9mg/ml FC was significantly more dense than post-transfusion clots ($p<0.001$)(Figure 1, Table 1A). Baseline clots showed the highest AI, and were significantly more aligned than fibrin clots formed post-transfusion (Table 1B). Additionally, baseline clots displayed significantly greater alignment than those formed post-CPB + 0.9mg/ml FC.

Conclusion: Our results show that clots formed with clinically relevant doses of FC (0.9mg/ml) displayed greater fiber density and less alignment than the in vivo transfusion of cryoprecipitate. While structurally dense clots may provide better post-CPB hemostasis, further analyses to examine strength and degradation kinetics are important to assess the risk of postoperative thrombosis.

Reference(s):

1. A&A 2015;120:405
2. Anesthesiology 2016;124:1021

Table 1A: Mean Difference of Fiber Density Comparisons

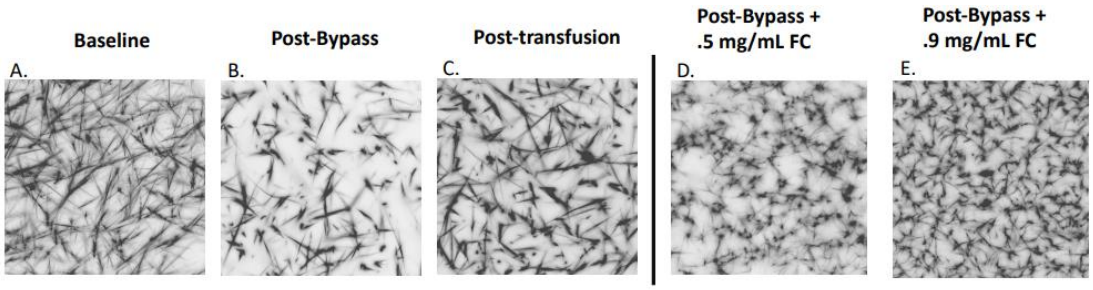
	Mean Difference (95% CI)	Adjusted p-value*
Baseline vs. Post-Bypass	0.176 (0.0599 to 0.292)	0.002
Baseline vs. Post-Transfusion	-0.136 (-0.252 to -0.0196)	0.02
Baseline vs. Post-Bypass + .5 mg/mL FC	-0.139 (-0.255 to -0.0228)	0.02
Baseline vs. Post-Bypass + .9 mg/mL FC	-0.327 (-0.443 to -0.211)	<0.0001
Post-Bypass vs. Post Transfusion	-0.312 (-0.428 to -0.196)	<0.0001
Post-Bypass vs. Post-Bypass + .5 mg/mL FC	-0.315 (-0.431 to -0.198)	<0.0001
Post-Bypass vs. Post-Bypass + .9 mg/mL FC	(-0.503) (-0.619 to -0.387)	<0.0001
Post Transfusion vs. Post-Bypass + .5 mg/mL FC	-0.003 (-0.119 to 0.113)	>0.99
Post Transfusion vs. Post-Bypass + .9 mg/mL FC	-0.191 (-0.307 to -0.0752)	0.001
Post-Bypass + .5 mg/mL FC vs. Post-Bypass + .9 mg/mL FC	-0.188 (-0.304 to -0.0721)	0.001

*Tukey's multiple comparisons test
FC = fibrinogen concentrate

Table 1B: Mean Difference of Fiber Alignment Comparisons

	Mean Difference (95% CI)	Adjusted p-value*
Baseline vs. Post-Bypass	0.026 (-0.027 to 0.078)	0.57
Baseline vs. Post-Transfusion	0.054 (0.002 to 0.106)	0.04
Baseline vs. Post-Bypass + .5 mg/mL FC	0.047 (-0.005 to 0.099)	0.09
Baseline vs. Post-Bypass + .9 mg/mL FC	0.058 (0.005 to 0.11)	0.03
Post-Bypass vs. Post Transfusion	0.02821 (-0.024 to 0.084)	0.48
Post-Bypass vs. Post-Bypass + .5 mg/mL FC	0.021 (-0.031 to 0.074)	0.72
Post-Bypass vs. Post-Bypass + .9 mg/mL FC	0.032 (-0.020 to 0.084)	0.36
Post Transfusion vs. Post-Bypass + .5 mg/mL FC	-0.007 (-0.059 to 0.045)	0.99
Post Transfusion vs. Post-Bypass + .9 mg/mL FC	0.004 (-0.048 to 0.056)	0.99
Post-Bypass + .5 mg/mL FC vs. Post-Bypass + .9 mg/mL FC	0.011 (-0.042 to 0.063)	0.97

*Tukey's multiple comparisons test
FC = fibrinogen concentrate



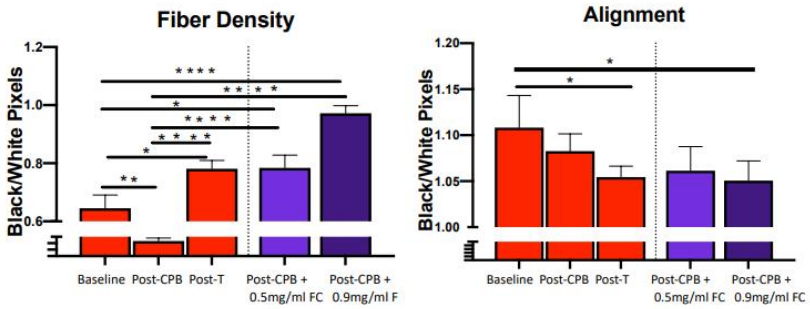


Figure 1. Sample confocal microscopy analysis of clots formed ex vivo from patients samples at baseline (A), post-bypass (B), post-transfusion of cryoprecipitate and platelets (C), post-CPB + 0.5mg/ml FC (D) and (E) post-CPB + 1mg/ml FC. Tuckey's multiple comparisons test was used to compare mean difference between groups. (N=4) FC = Fibrinogen Concentrate

Blood Management-3 Effect of preoperative ferric carboxymaltose injection on perioperative transfusion in patients undergoing total hip arthroplasty: A retrospective, propensity-score matched study

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Introduction: Despite ongoing efforts to reduce perioperative transfusion, there is still a high chance of transfusion in total hip arthroplasty (THA). We investigated the requirement and incidence of red blood cell (RBC) transfusion according to the administration of preoperative ferric carboxymaltose (FCM), which is one of the intravenous irons, in patients undergoing THA.

Methods: This retrospective study examined medical records of the patients who received FCM (FCM group) or did not (non-FCM group) in unilateral THA at a single tertiary care academic hospital from November 2014 to July 2018. To balance the two groups for analysis, a propensity-score matching method was used. The primary endpoint was the difference in the amounts of RBC transfused between the two groups. The secondary endpoints were the association between the FCM use and the requirement and incidence of RBC transfusion in the perioperative period.

Results: This study included 1032 cases of THA for final analysis, and the cases were divided into the FCM group (n = 568) and non-FCM group (n = 464). Propensity matching produced 389 patients in each group. In the FCM group showed significant lower amount (0.4 vs. 0.6 units) and incidence (21% vs. 31%) of RBC transfusion compared with non-FCM group (P = 0.035 and P = 0.003, respectively). Also, FCM administration was associated with lower requirement (coefficient -0.145, 95% CI -0.253 to -0.036, P = 0.009) and lower incidence (OR 0.492, 95% CI 0.317–0.765, P = 0.002) of RBC transfusion.

Conclusion: Preoperative intravenous iron administration may reduce the needs of RBC transfusion in patients undergoing THA.

Blood Management-4 Ideal Blood Component Transfusion Ratios for High and Ultra High-dose Cell Salvage Cases

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Introduction: Patients undergoing open reconstructive surgery for abdominal aortic aneurysms (AAA) and thoracoabdominal aortic aneurysms (TAAA) are ideal candidates for cell salvage due to the high blood loss nature of the surgery. It is common belief, however that transfusion of salvaged blood in sufficient quantities poses a risk for dilutional coagulopathy. In this study we tested the hypothesis that transfusion of large amounts of salvaged blood does not result in coagulopathy if delivered in a balanced ratio with plasma (FFP), platelets (PLTS) and cryoprecipitate (CRYO).

Methods: After IRB approval, 38 patients were chosen for a retrospective analysis of transfusion practices in AAA and TAAA surgeries where at least 1000 mL of salvaged blood was transfused between years 2016-2019. Patients were divided into two cohorts: those receiving 1000 to 2000 mL of salvaged blood (High Dose cohort) (n=20); and those receiving > 2000 mL (Ultra-high Dose cohort) (n=18). We assessed salvaged RBC volume transfused, the ratio of allogeneic RBC to FFP+PLTS+CRYO, and the same ratio adjusted to include both allogeneic and salvaged RBCs. Coagulation was assessed by the international normalized ratio (INR), thromboelastography (TEG) R time and MA values, and fibrinogen, all measured at the end of surgery. Students t tests, Mann-Whitney U, and Chi-squared tests were used to compare the two cohorts. $P < 0.05$ (two-tailed) defined significance.

Results: The two cohorts were similar for age and sex, and there were more TAAA cases in the Ultra-high Dose cohort (Table). The Ultra-high dose cohort received 4 times more salvaged blood and greater amounts of all allogeneic blood components compared to the High Dose cohort. The mean adjusted ratios of RBCs (including allogeneic and salvaged RBCs) to FFP+PLTS+CRYO was 1.64 in the High Dose and 1.21 in the Ultra-high Dose cohorts, whereas the unadjusted ratios were much lower (between 0.3 - 0.4). Both the High and Ultra-high Dose cohorts had no evidence for coagulopathy based on laboratory testing (Table).

Conclusion: Our study demonstrates that when High or Ultra-high dose salvaged blood is given, transfusion of extra non-RBC blood components (by 2 to 3-fold the typical amount used for massive transfusion) is associated with normalization of coagulation parameters. When providing care for cases that received large quantities of salvaged blood, good communication with transfusion medicine is helpful to obtain the extra non-RBC components needed to rebalance the ratio and avoid coagulopathy.

	High Dose Cell Salvage (n=20)	Ultra-High Dose Cell Salvage (n=18)	*P*-value
Age, years, mean±SD	65 ± 14	66 ± 15	0.75
Male sex, n (%)	15 (75.0)	12 (66.7)	0.57
TAAA/AAA, n	4/16	11/7	0.02
Estimated blood loss, mean±SD	2528 ± 1559	7153 ± 9791	0.063
Salvaged RBCs transfused (mL) mean±SD	1,240 ± 279	5,550 ± 3,801	0.0002
Salvaged RBCs transfused (mL) median (IQR)	1,143 (1,000-1,500)	4,253 (2,638-7,310)	<0.0001
Salvaged RBCs transfused (mL) range	1,000-1,879	2,025-15,000	--
RBC units (allogeneic), mean±SD	1.3 ± 3.0	11.0 ± 10.5	0.0011
Plasma units, mean±SD	3.2 ± 4.4	25.3 ± 20.1	0.0002
Platelet units, mean±SD	0.5 ± 1.0	3.9 ± 2.6	<0.0001
Cryo units, mean±SD	0.3 ± 1.0	1.1 ± 1.3	0.040
Unadjusted ratio (allogeneic-only RBC:FFP+PLTS+CRYO), mean±SD	0.36 ± 0.61	0.33 ± 0.33	0.88
Adjusted ratio (allogeneic and salvaged RBC:FFP+PLTS+CRYO), mean±SD	1.64 ± 1.35	1.21 ± 0.56	0.31
End surgery INR, median (IQR)	1.25 (1.1-1.3)	1.15 (1.1-1.2)	0.49
End surgery TEG R time, median (IQR)	5.2 (4-6.8)	4.7 (3.6-5.8)	0.59
End surgery TEG MA value, median (IQR)	59.6 (52.8-64.1)	56.55 (54.6-60.9)	0.49
End surgery Fibrinogen (mg/dL), median (IQR)	217 (140-246)	208 (169-256)	0.87

TAAA – thoracoabdominal aortic aneurysm, AAA – abdominal aortic aneurysm, RBC – red blood cell, FFP-fresh frozen plasma, PLT-platelets, CRYO – cryoprecipitate, INR – international normalized ratio, TEG – thromboelastography

Cardiovascular Anesthesiology

Cardiovascular Anesthesiology-1 Non-invasive Assessment of Cerebral Blood Flow and Oxygen Metabolism in Adults during Cardiac Surgeries with Circulatory Arrest

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Introduction: Cardiac surgeons rely on a technique called Deep Hypothermic Circulatory Arrest (DHCA) during surgeries such as aortic arch repair or replacement [1]. Over the years, it has become standard practice to add antegrade or retrograde cerebral blood perfusion (ACP and RCP, respectively) for extra brain protection during DHCAs [2]. Near infrared spectroscopy (NIRS) is often used to monitor cerebral blood perfusion during surgery because it can provide regional saturation of oxygen (rSO2) in the brain [3]. Changes in rSO2 often correlates with cerebral blood perfusion but is not a direct measure of cerebral blood flow, which is especially of interest during DHCA [4]. Measuring the blood flow to the brain can potentially guide the surgeon to deliver appropriate amounts of blood during cerebral perfusion. Diffuse correlation spectroscopy (DCS) is a novel optical technology used to monitor cerebral blood flow. We use a hybrid device employing frequency domain (FD) NIRS in conjunction with DCS to simultaneously characterize cerebral oxygenation and blood flow. Thus far, we have collected data on 11 patients undergoing DHCA. Initial results strongly suggest that this combination of non-invasive optical techniques can be used to provide timely and accurate insight into the efficacy of brain protection.

Methods: There are three groups in the study: DHCA only (n=4), DHCA with RCP (n=2) and DHCA with ACP (n=5). In patients with RCP, the brain gets the blood through superior vena cava. Blood is perfused through right axillary artery for ACP. We used a combined DCS and FD-NIRS system [4] that employs an 850-nm laser and 8 photon counting detectors for DCS and 8 sequentially illuminated lasers (670 to 830 nm) with 4 photomultiplier detectors for FD-NIRS, respectively. A DCS detector fiber is located at 5 mm from the source to detect skin blood flow. The remaining DCS detector fibers are located at 25 and 30 mm from the source. The 4 FD-NIRS detector fibers are located at separations of 20, 25, 30, and 35 mm from the source, and a multi-distance method is used to calculate optical properties [5]. The probe is secured against the right side of the patient's forehead. Standard clinical data including cerebral oximetry and other vital signs are acquired from electronic medical records (EPIC) during the measurement.

Results: Inclusion criteria for this study were patients scheduled for cardiac surgery with deep hypothermic circulatory arrest. Exclusion criteria were patients who could not consent in English. Figure 1 shows the data from our device (middle and top panels) and the standard hospital oximeter (bottom panel) during a double DHCA procedure with no cerebral perfusion. Our device responds to both DHCA's, showing immediate drops to zero in blood flow at the start of the procedure, and rapid overshoots when blood flow resumes. Our measurements of oxygen saturation show the expected consistent decrease in oxygenation throughout the DHCAs. The drop in hemoglobin concentration suggests hemodiluted blood in the brain during circulatory arrest. The addition of relative oxygen saturation from the hospital oximeter in this graph offers a useful comparison with our oximeter and gives bilateral readings. In all subjects, we found that DCS short and long separation signals were distinct, suggesting that longer separations are sensitive to cerebral flow rather than solely to skin flow. The FD-NIRS agreed with the hospital NIRS oximeter in every measurement. In terms of perfusion validation, our preliminary results show very low rates of perfusion and levels of oxygen delivery to the brain with RCP. These results also include a measurement in which the data suggests that ACP may not always provide adequate bilateral blood flow.

Conclusion: Our initial results suggest that DCS could be a crucial addition at the bedside during cardiac surgeries. Moving forward, we will plot the correlation trends between physiological parameters with cerebral blood flow to see how flow correlations change during different stages of the surgery. We will also quantify the magnitude of the CBF drops in blood flow signal at DHCA onsets to demonstrate signal responsiveness. Ultimately, demonstrating the ability to accurately and simultaneously measure oxygenation and cerebral blood flow during surgery will lead to new approaches to reduce neurological injury and the overall morbidity and mortality associated with anesthesia in general, and aortic arch replacement surgeries in particular.

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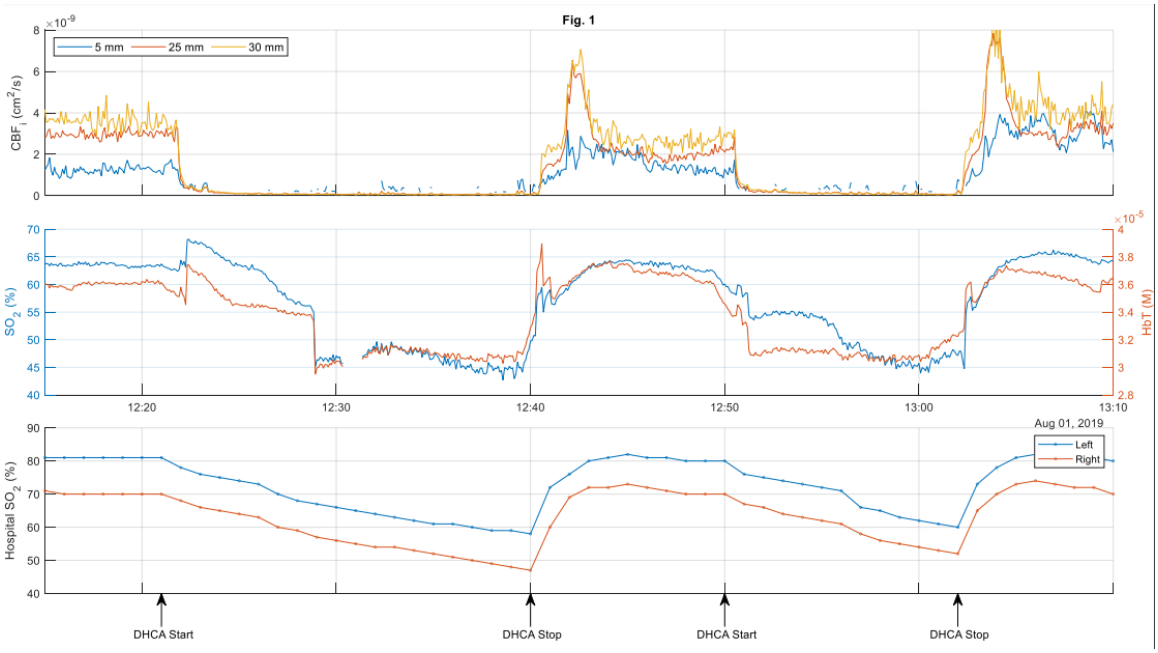
Fig. 1
5 mm
25 mm
30 mm
CBF_I (cm²/s)
SO2 (%)
HbT (M)
12:20
12:30
12:40
12:50
13:00
13:10
Aug 01, 2019
Left
Right
Hospital SO2 (%)
DHCA Start
DHCA Stop
DHCA Start
DHCA Stop

Cardiovascular Anesthesiology-2

Regulation of Cardiac Inflammation and Remodeling after Myocardial Infarction by Family with sequence similarity 3D (FAM3D)

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Introduction: Advances in the management of acute myocardial infarction (MI), such as timely reperfusion strategies, have greatly improved mortality. However, the risk for developing heart failure (HF) is close to 50% in those that survive acute MI. Although large infarct size and impaired function at the time of MI are strong predictors of eventual HF, a significant number of patients with initially preserved function experience late adverse remodeling in the heart that leads to a decline in left ventricular (LV) function and failure(1). The structural adaptations the heart undergoes after injury are termed 'cardiac remodeling' and involve cardiomyocytes as well as non-cardiomyocytes. Mechanistically, while neurohormonal activation plays an integral role in 'adverse' remodeling, many studies have highlighted the important role of inflammation(1-3). Favorable remodeling of the myocardium after injury involves appropriate sequential activation and inactivation of an immune program involving different subtypes of leukocytes. Indeed, recent clinical trials point to the benefits of anti-inflammatory therapy in preventing major cardiovascular events after MI(4). We used an aptamer-based proteomics platform to examine differences in plasma proteins between patients matched for clinical characteristics, infarct size, and initial post-MI LV function, who then went on to experience either recovery ('reverse' remodelers) or worsening (adverse remodelers) of function. Interestingly, FAM3D (chemokine Family with sequence similarity 3D) was highly elevated in the patients who did better after MI. Although FAM3D has no known role in cardiac biology, in other settings, this secreted factor binds to formyl-peptide receptors (FPR), expressed predominantly on neutrophils and monocytes, and regulates inflammation(5). In an animal model of ischemia-reperfusion injury (IRI), we found that FAM3D secretion, likely from the spleen, is dynamically regulated after IRI, and correlates with myocardial injury as reflected in plasma troponin. Importantly, overexpression of FAM3D dramatically reduces infarct size and myocardial inflammation after IRI. Our data suggest splenic FAM3D is secreted as an endogenous protective measure against ischemic injury and adverse remodeling by modulating cardiac inflammation and leukocyte trafficking.

Methods: In a discovery cohort, 374 patients underwent extensive cardiac phenotyping 4 weeks and 6 months after presentation for an acute coronary symptom. Cardiac MRI imaging with late gadolinium enhancement measured volumes, mass, function, and infarct. Patients were classified as 'Good' remodelers or 'Poor' remodelers based on a decrease or an increase, respectively, of > 20% in left ventricular end systolic volume index (LVESVI) at their 6-month followup. Importantly, the Good and Poor remodelers we profiled were matched on initial infarct size, and shared similar distributions for age, gender, BMI, risk factors (e.g., smoking), co-morbidities (e.g.,T2DM, hypertension, hyperlipidemia), and medication regimens (ACE inhibitors, ARBs, aspirin, statins, beta-blockers). We then used SOMAscan to quantify over 1300 human proteins in blood samples from 10 Good and 11 Poor remodelers that had been collected at 4 weeks post-MI. Statistical analysis of the results employed an empirical Bayesian analysis (LIMMA) that accounted for distribution of global protein expression, outliers, and likely false positives. Fig 1A is a volcano plot showing the 14 candidate molecules (green dots) whose difference in abundance between the Good and Poor groups satisfied threshold values for significance ($p<0.05$) and fold-change ($FC>1.4$).

Results: 1. FAM3D is highly elevated in Good remodelers by both SOMAscan and traditional ELISA (Fig 1). 2. FAM3D is dynamically upregulated after ischemia-reperfusion injury (IRI) in proportion to troponin-I levels (Fig 2). 3. FAM3D mRNA and protein in the spleen increase after myocardial IRI (Fig 3). 4. Exogenous FAM3D reduces infarct size in the heart after IRI (Fig 4). 5. Exogenous FAM3D reduces cardiac inflammation measured by flow cytometry after IRI (Fig 5).

Conclusion:

1. FAM3D is elevated in 'Good' Remodelers as measured by multiple detection methods.

2. FAM3D secretion is dynamically regulated after IRI in mice and is a biomarker for the extent of myocardial injury.

3. FAM3D may be a signal within the cardio-splenic axis.

4. Exogenous FAM3D dramatically reduces infarct size and inflammation after IRI.

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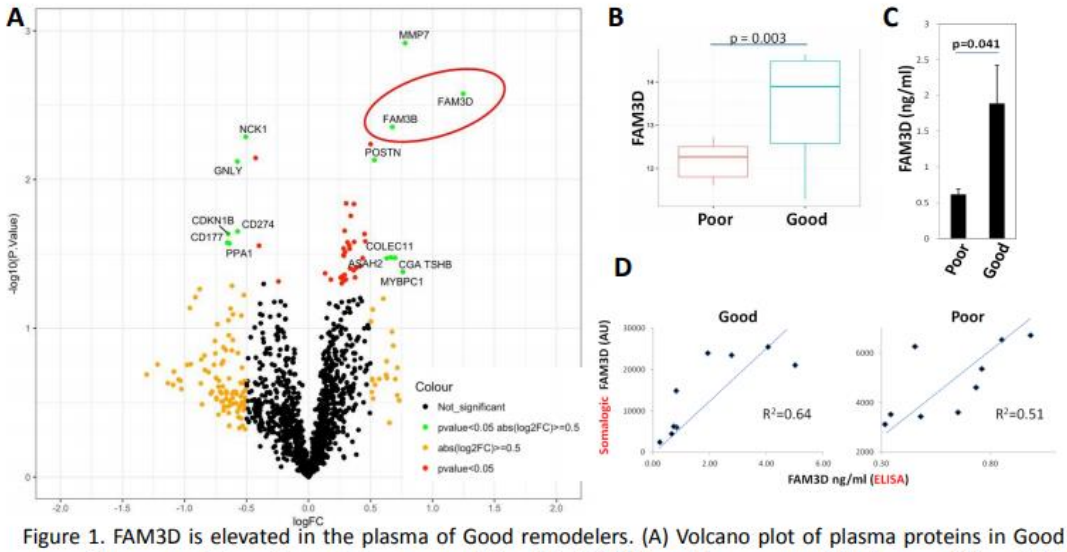

Figure 1. FAM3D is elevated in the plasma of Good remodelers. (A) Volcano plot of plasma proteins in Good versus Poor remodelers. Green dots represent the 14 of 1310 proteins surveyed that were differentially expressed in the Good versus Poor groups, with p-value < 0.05 and fold change(FC) > 1.4. (B) Relative quantification (AU) of plasma FAM3D measured by SOMAscan in Good and Poor remodelers. (C) Absolute quantification of FAM3D in the two groups as measured by traditional ELISA. Error bars represent SEM; p-value=two-tailed Student's t-test. (D) Correlation between individual measurements of FAM3D by SOMAscan versus ELISA.

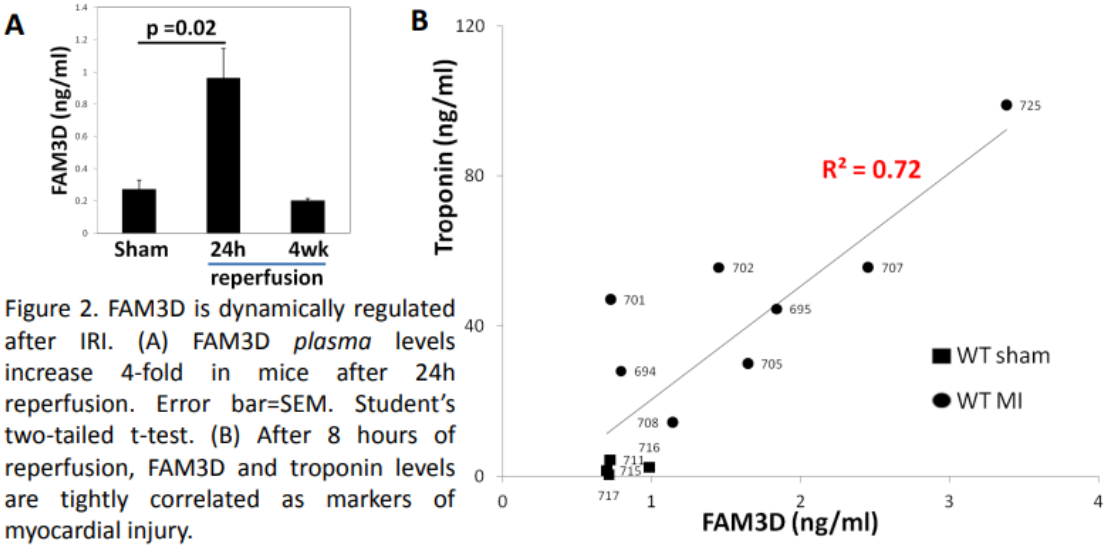

Figure 2. FAM3D is dynamically regulated after IRI. (A) FAM3D *plasma* levels increase 4-fold in mice after 24h reperfusion. Error bar=SEM. Student's two-tailed t-test. (B) After 8 hours of reperfusion, FAM3D and troponin levels are tightly correlated as markers of myocardial injury.

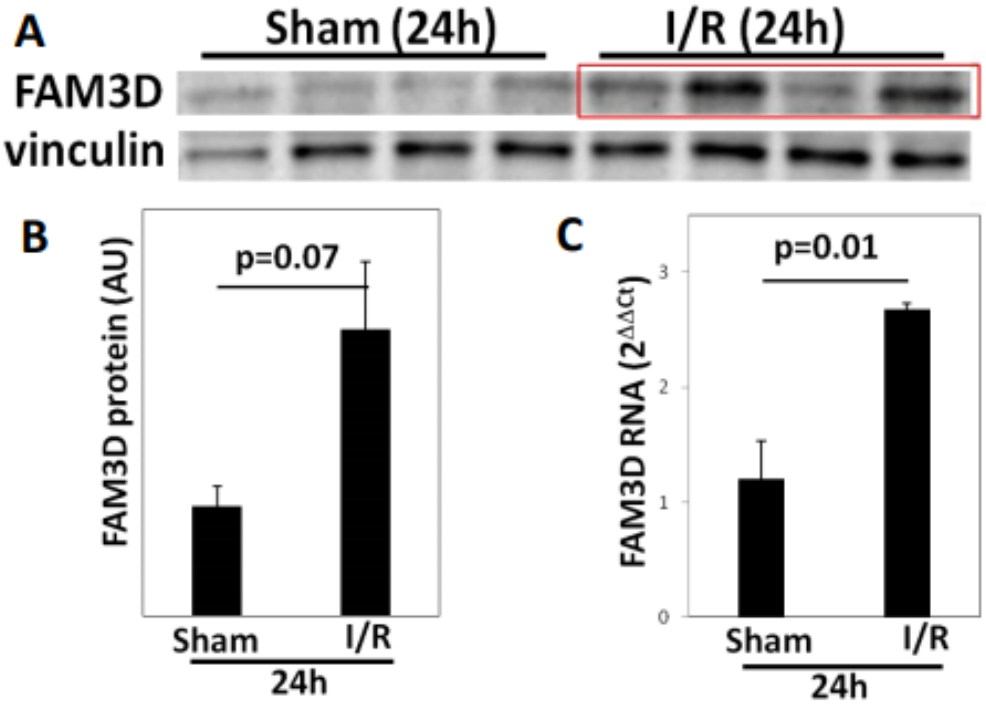

Figure 3. FAM3D protein and RNA increase in the spleen after myocardial injury. (A) Western blot of splenic FAM3D after 24h of myocardial reperfusion. (B) Quantification of FAM3D protein expression normalized to vinculin loading control (Image Lab Software, Biorad). (C) RNA level of splenic FAM3D after 24h of myocardial reperfusion. Error bars=SEM. p-value=two-tailed Student's t-test.

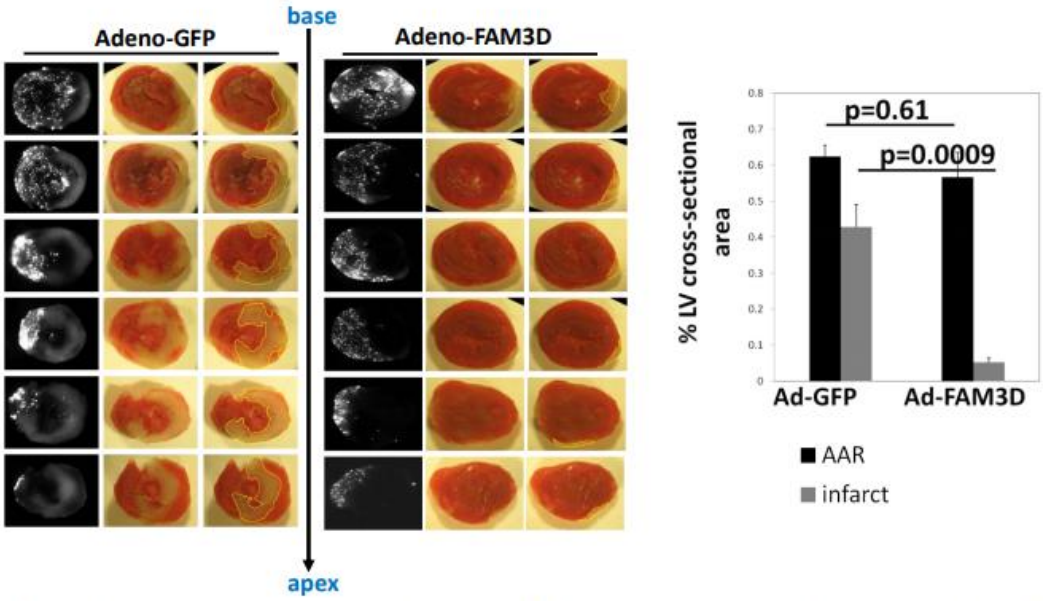

Figure 4. Mice injected with adenoviral FAM3D have dramatically reduced 24h infarct size. Mice were i.p. injected with either ad-GFP or ad-FAM3D 5&7 days prior to IRI. Hearts were collected after 24h of reperfusion, sectioned, and quantified for areas of underperfusion (area-at-risk, AAR, represented by black&white images) and infarct areas (red TTC stained images). One representative mouse from each group shown on the left. Quantification of AAR and infarcts from both groups above. Error bars represent SEM. p-value = two-tailed Student's t-test.

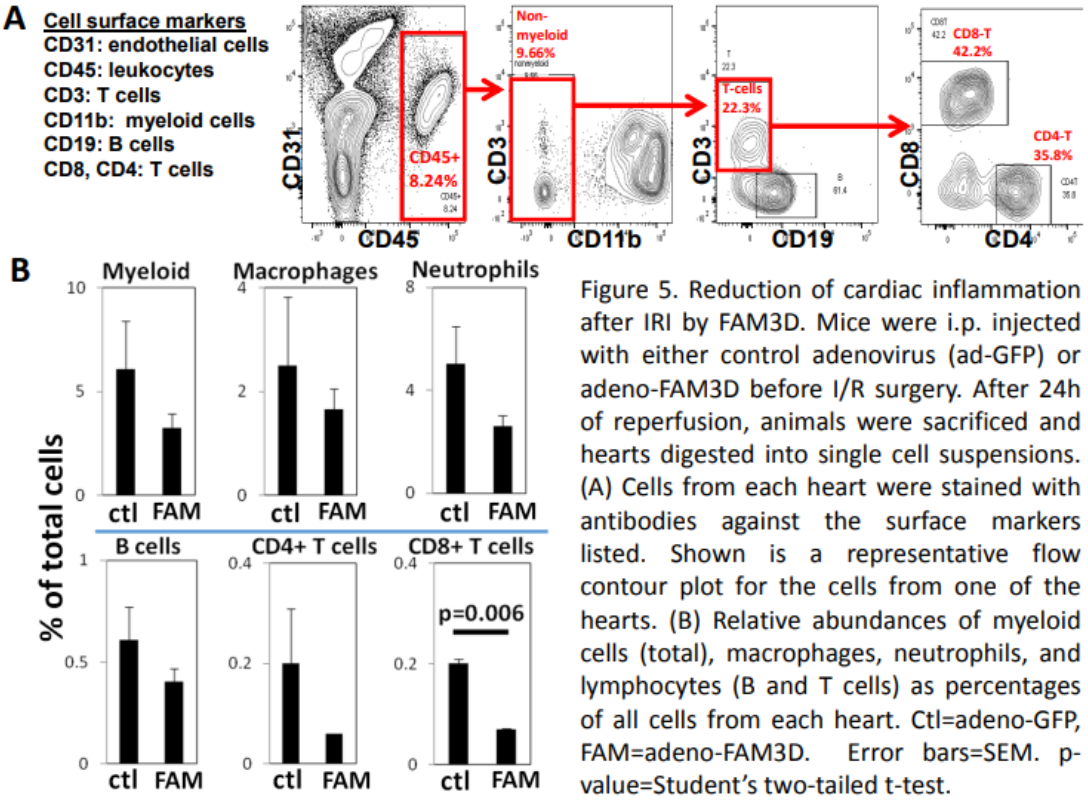

Figure 5. Reduction of cardiac inflammation after IRI by FAM3D. Mice were i.p. injected with either control adenovirus (ad-GFP) or adeno-FAM3D before I/R surgery. After 24h of reperfusion, animals were sacrificed and hearts digested into single cell suspensions. (A) Cells from each heart were stained with antibodies against the surface markers listed. Shown is a representative flow contour plot for the cells from one of the hearts. (B) Relative abundances of myeloid cells (total), macrophages, neutrophils, and lymphocytes (B and T cells) as percentages of all cells from each heart. Ctl=adeno-GFP, FAM=adeno-FAM3D. Error bars=SEM. p-value=Student's two-tailed t-test.

Cardiovascular Anesthesiology-3 Effects of Low dose Hydroxyethyl Starch 13//0.4 on FVIII and vWF in Cardiac Surgery

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Introduction: The FDA warns that use of hydroxyethyl starch (HES) for plasma volume replacement in patients undergoing open heart surgery increases risk of bleeding(1), although other investigations suggest that third-generation hydroxyethyl starch (HES) solutions, such as 6% HES 130/0.4 cause less coagulopathy than earlier solutions(2). We recently reported that a postoperative measure of coagulation, specifically clot initiation, was prolonged in cardiac surgical patients who received intraoperative plasma volume replacement with a third-generation HES versus those who received human albumin 5%. The purpose of this investigation was thus to examine the effect of HES on coagulation factors, specifically Factor VIII and von Willebrand's factor (vWF), which may contribute to prolonged clot initiation in cardiac surgical patients.

Methods: This sub study of a larger prospective, double-blind clinical trial randomized patients having aortic valve replacement with or without coronary artery bypass grafting to HES versus 5% human albumin at the Cleveland Clinic. Institutional Review Board approval and written informed consent was obtained. Exclusion criteria included renal failure, anticipation of deep hypothermic circulatory arrest, pre-existing coagulation disorders, patients in whom anticoagulant other than heparin was used. Coagulation tests including PT, INR, aPTT were performed at baseline following anesthetic induction before surgical incision, 1 hour and 24 hours after patient arrived in ICU. Components of thromboelastography including reaction time (R), kinetics time (K), maximum amplitude (MA), slope between R and K (alpha angle), amplitude reduction at 30 minutes after MA (lysis LY 30) and clotting indices were compared and evaluated at the same intervals. In twenty patients randomly selected from 141 patients enrolled in original study, we compared Factor VIII and von Willebrand factor concentrations. The non-inferiority between HES and albumin was assessed for each outcome at the 0.025 level. We could claim non inferiority of HES to albumin if non-inferiority was shown on all of the variables in this set. Therefore no adjustment for multiple testing was done (i.e. intersection-union test).

Results: 149 patients were randomized and 141 were included in the final analysis. (HES = 69, albumin=72). Demographics, medical comorbidities and surgical types were comparable between the two groups. Volume of HES used was 611±278 and albumin 674±275 (P=0.18) and were comparable . HES was found not comparable to albumin in initiation of coagulation after surgery (R at 1 hour sample (5.7±3.9 vs 5.1±2.0 in HES vs albumin groups (P=0.030), but HES performed non-inferior to that of albumin in other measures of coagulation such as INR, clotting time, APTT, K value, MA and alpha angles. In the subsequent factor analysis (N=20), HES was found to be non-inferior to that of albumin in the vWF --170 ± 46 HES vs174 ± 53 Albumin, P=0.84) and FVIII (149 ± 38 vs164 ± 59 HES vs Albumin, P= 0.34) assays. HES and albumin groups were comparable in terms of 24 hour chest drain median 590 (SD 460-810) mL HES and median 600 (SD 410-826) mL albumin) No difference in red blood cell transfusion was seen (19% HES versus14% albumin; P=0.13)

Conclusion: Although clot initiation was slightly longer in patients who received HES as assessed by TEG, other coagulation tests and Factor VIII and von Willebrand factor concentrations were comparable between groups. We conclude that HES had minimal effect on coagulation in patients having cardiac surgery

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Comparison of Non-Inferiority in Coagulation parameters between HES 130/0.4 and Albumin

Outcomes	HES (N=69)	Albumin (N=72)	Treatment Effect (95% CI)	Non-Inferiority	P Value
PT *Baseline*	10.9	11.1	0.98	1.15	<0.001
PT *Postop 1 hour*	13.2	13.3			
APTT *Baseline*	28	28	0.2	5.2	<0.001
APTT *Postop 1 hour*	35	34			
R Value *Baseline*	4.3±2.6	4.0±1.8	0.37	0.91	0.030
R value *Postop 1 hour*	5.7±3.9	5.1±2.0			
K value *Baseline*	1.2	1.2	1.04	1.15	0.011
K value *Postop 1 hour*	2.1	1.8			
MA (min) *Baseline*	63±6	65±6	-0.6	-8.3	<0.001
MA (min) *Postop 1 hour*	54±7	57±6			
Alpha angle *Baseline*	70±7	71±5	-1.5	-9.3	<0.001
Alpha *Postop 1 hour*	60±10	63±9			
LY-30 *Baseline*	1.17±1.76	1.21±1.80	-0.3	0.14	0.012
LY-30 *Postop 1 hour*	0.76±1.69	1.15±2.15			
CI *Baseline*	1.9±3	2.5±2			
CI *Postop 1 hour*	-0.9±3.5	-0.2±2.4			
CI *24 hour*	1.9±1.3	1.8±1.1			

Cardiovascular Anesthesiology-4 Feasibility of Perioperative Endothelial Glycocalyx Monitoring during Mechanical Circulatory Support

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Introduction: The endothelial glycocalyx serves a critical role in maintaining vascular integrity and may be compromised during the perioperative period potentially leading to worse patient outcomes (1). Currently, clinicians do not monitor the glycocalyx because a suitable method has not been established. The purpose of this study was to demonstrate the feasibility of perioperative glycocalyx monitoring and identify barriers to clinical implementation of the technique.

Methods: We performed the research in accordance with the guidelines stated in the Declaration of Helsinki. With a case series design, 7 subjects participated in the study at the University of Colorado Hospital (2 healthy controls, 3 patients undergoing cardiac surgery with cardiopulmonary bypass, and 2 patients with venous-arterial extracorporeal membrane oxygenation support). The primary outcome variable was glyocalyx thickness measured by non-invasive side stream dark field microscopy (Microvision Medical, Amsterdam, the Netherlands) using a method reported previously in healthy controls (2) and adapted for perioperative use. In brief, the sublingual microscope system was placed under the tongue and held securely with a custom mount attached to an IV pole. A powered USB extension connected the microscope to a dedicated workstation in the operating room or intensive care unit. We acquired a video with 300 frames of sublingual microcirculatory blood flow and imported the file into ImageJ software. We identified the passage of white blood cells through the microcirculation and measured the vessel thickness before and immediately after the passage of a white blood cell to measure the glycocalyx thickness with the following formula: Post-WBC vessel thickness - Pre-WBC vessel thickness = Glycocalyx thickness We collected 55 measurements from 6 subjects (healthy controls, 26 measurements and patients, 29 measurements). We performed the statistical analysis using JMP Pro 15 software (SAS institute, Cary, NC, USA) We compared the two groups using a Welch's t test. We also used a mixed effects linear regression model controlling for inter-individual variability and subject group. We considered a p-value less than 0.05 to be significant.

Results: Patients receiving mechanical circulatory support had significantly thinner glycocalyx compared to healthy controls (Figure 1 and Table 1). This result did not change when controlling for subject variability and exposure to mechanical circulatory support (Table 2). Figure 2 presents a schematic and representative image demonstrating the method for measuring glyocalyx thickness.

Conclusion: Perioperative glycocalyx monitoring is feasible with existing technology. Current barriers to implementing routine glycocalyx monitoring is a lack of automated software for image processing and reliable image acquisition. Further clinical research is necessary to determine whether glycocalyx monitoring is beneficial in the perioperative environment.

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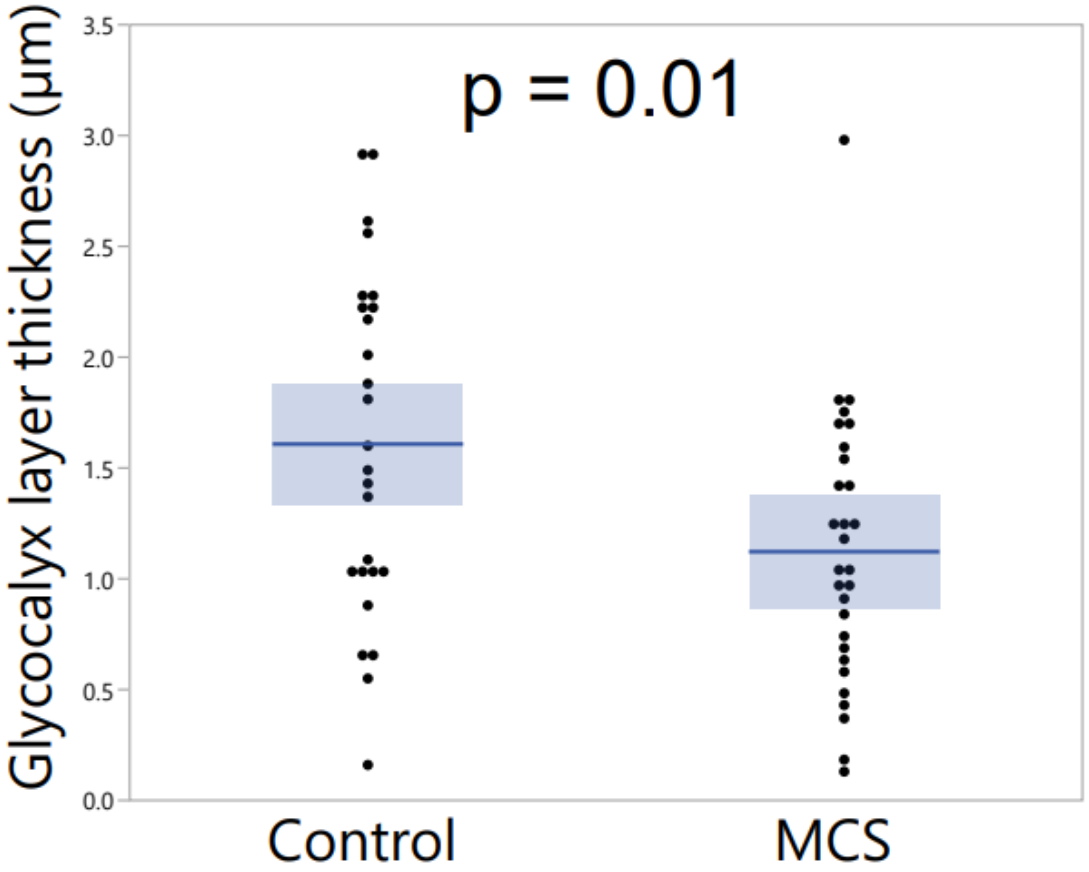

Figure 1. The glycocalyx is significantly thinner in the mechanical circulatory support (MCS) group than the control group.

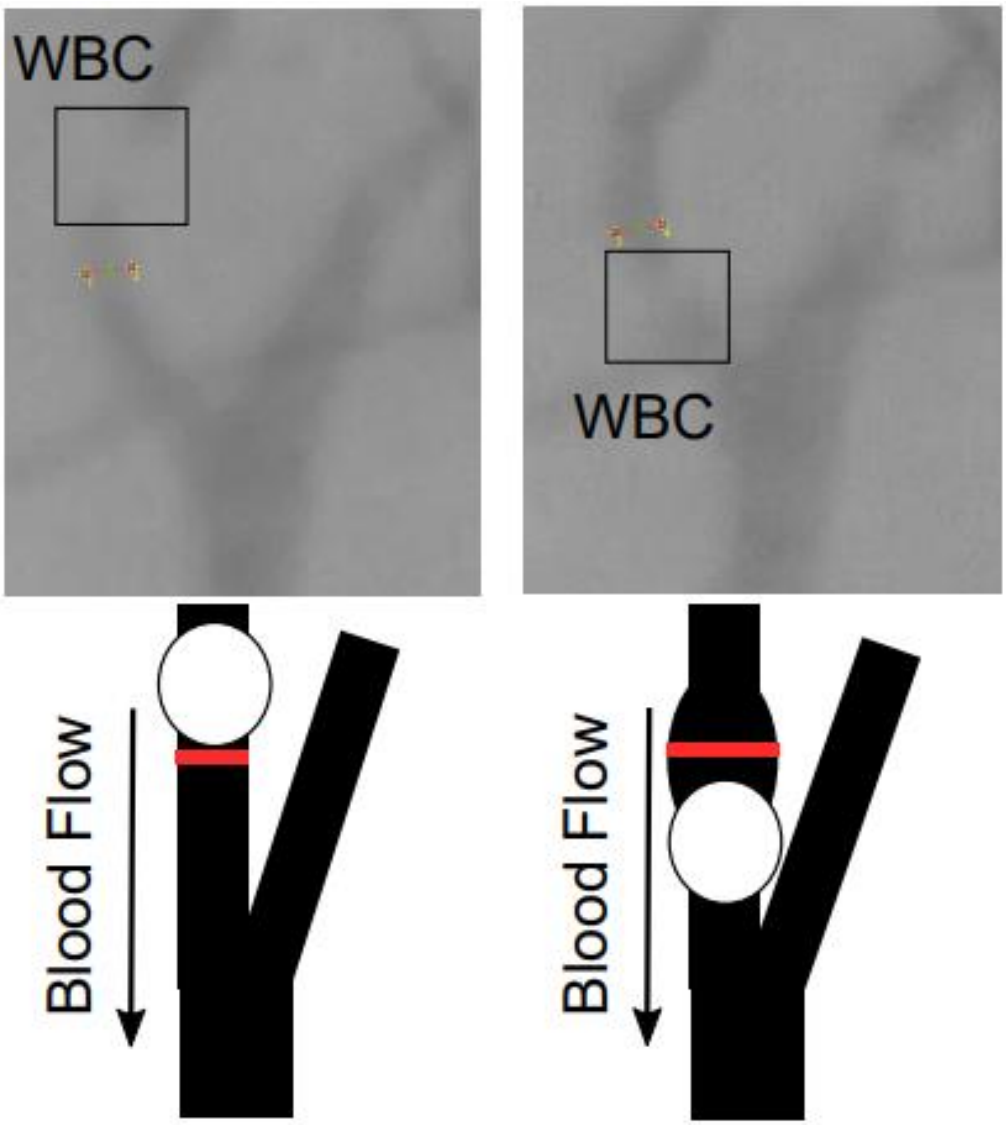

Figure 1. Representative images of the microcirculation and a schematic of how the glycocalyx is measured. The red line indicates the measured distance of the vessel diameter before and after white blood cell (WBC) passage.

Table 1. Data Summary. Cardiopulmonary bypass (CPB) Extracorporeal membrane oxygenation (ECMO)

Subject	Measurement Number	Capillary diameter (μM, Post-WBC)	Capillary diameter (μM, Pre-WBC)	Glycocalyx thickness (μM)
All (n = 6)	n = 55	13.40 (2.47)	12.06 (2.57)	1.35 (0.73)
Control 1	n = 19	13.51 (1.43)	11.91 (1.63)	1.67 (0.82)
Control 2	n = 7	15.77 (1.84)	14.35 (2.28)	1.45 (0.62)
CPB 1	n = 8	12.87 (4.18)	11.77 (4.13)	1.12 (0.36)
CPB 2	n = 2	11.08 (0.54)	9.35 (0.24)	0.95 (0.33)
ECMO 1	n = 10	12.70 (2.12)	11.62 (2.18)	1.13 (0.77)
ECMO 2	n = 9	13.61 (2.95)	12.42 (3.39)	1.18 (0.57)

Table 2. Mixed model linear regression results. Controlling for inter-individual variability, the control group had a glycocalyx 0.28 uM thicker than the patient group ($p < 0.0001$).

Term	Estimate	Std Error	95% CI	Prob>|t|
Subject variance	-0.024	0.0045	-.033 – -0.015	<0.0001
Fixed effect				
Intercept	1.39	0.056	1.28 – 1.50	<0.0001
Control group	0.28	0.056	0.17– 0.39	<0.0001

Cardiovascular Anesthesiology-5 Molecular changes in the Spinal Cord during Modulation of Myocardial Ischemia-Induced Ventricular Arrhythmias by Spinal Cord Stimulation in a Porcine Model

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Introduction: Myocardial ischemia (MI) induces changes in cardiospinal neural networks leading to ventricular tachyarrhythmias (VTs) and sudden cardiac death. We have shown that neuromodulation with spinal cord stimulation (SCS) decreases cardiac sympathoexcitation and VTs1,2. However, there is incomplete understanding of the molecular mechanisms through which SCS modulates cardiospinal neural pathways. We aimed to characterize the changes in anatomical distribution of activated neural cells in the spinal cord during MI - with and without SCS - by comparing changes seen at different spinal levels and in spinal segment laterality. We hypothesized that during MI, SCS modulates cardiospinal networks via GABA mediated neural signaling and that the anti-arrhythmic effects of SCS will be diminished in the presence of GABA receptor antagonists.

Methods: After approval by the animal research committee, Yorkshire pigs (n=50) were randomized to 1)Control(n=5), 2)MI (n=14), 3)MI+SCS (n=15), 4) MI+SCS+GABAA antagonist (Bicuculline, n=8), or 5) MI+SCS+GABAB antagonist (CGP55845, n=8). 4-pole lead was placed in T1-T4 epidural space for SCS (50 Hz, 200 μsec duration, 90% of motor threshold) 30 min prior to MI. After sternotomy, high-resolution cardiac electrophysiological mapping with measurement of Composite Arrhythmia Score was performed at; baseline, after SCS, and during MI from 30 min ligation of left anterior descending coronary artery. IHC was performed on thoracic (T1-T4) and lumbar spinal sections to map cardiospinal network cells activated with MI and SCS (C-fos) and identify cell types-neurons, microglia, and astrocytes (NeuN, IBA-1, GFAP).

Results: SCS significantly reduced MI induced VTs (10.5±4.3 vs. 6.9±4.3, $p<0.05$, Fig 1). Intrathecal GABA blockade during SCS therapy with GABAA and GABAB receptor antagonists abolished the SCS protection of VTs (6.9±4.3 vs 11.9±3.4 &. 12.7±1.3, $p<0.01$). IHC demonstrated that during MI there is an increase in spinal cord C-fos expression that is localized to T1-T4, with no change in lumbar segments (Fig 2A). Importantly, the greatest C-fos expression during MI was at T3 with no difference in right or left spinal segments. With MI+SCS there was an even greater increase C-fos expression, but no difference in expression by thoracic level or side. An increase in C-fos+/NeuN+ cells were observed with SCS, however, there was also an increase in C-fos+/NeuN- cells. Glial subtype analysis demonstrated an increase in microglial cells with SCS and a reduction in reactive astrocytosis (Fig 2B-C).

Conclusion: SCS during MI is associated with a reduction in VTs and an increase in activated neurons and microglia in both the left and right dorsal horns of T1-T4 spinal cord segments. The anti-arrhythmic effects of SCS during MI were strongly inhibited by GABA receptor antagonists. Thus, the results of this study emphasize the potential role of neuronal-glial interactions and GABA signaling pathways in neuromodulation by SCS.

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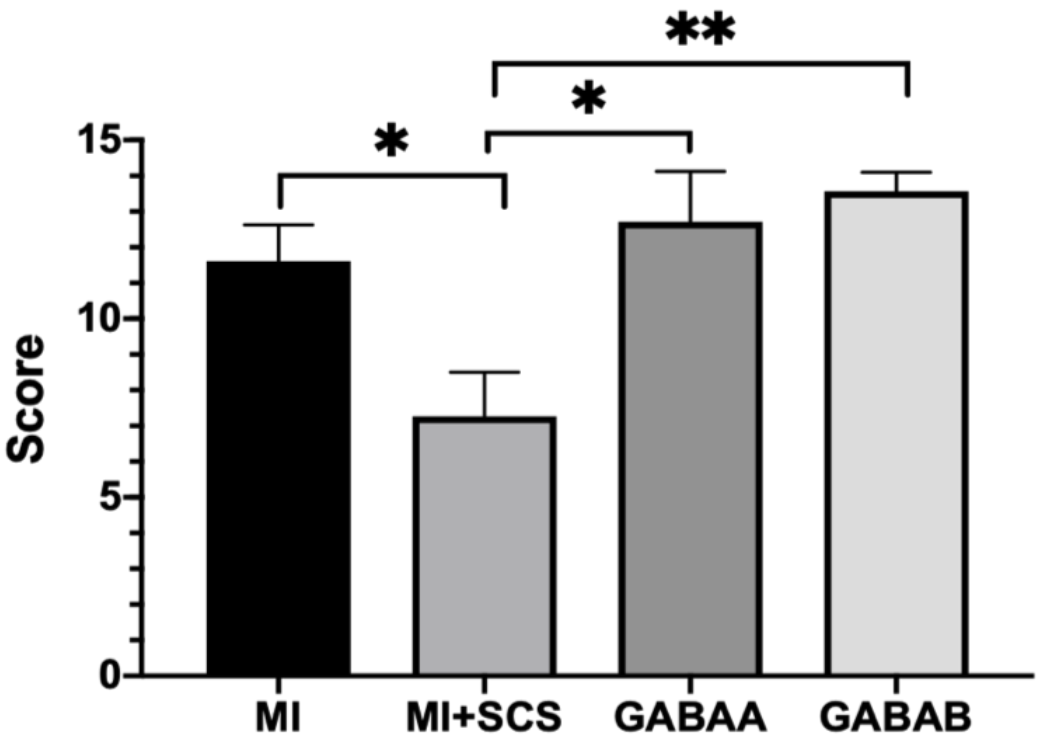

Figure 1. **Composite Arrhythmia Score-** increased incidence of cardiac arrhythmias with acute MI which was decreased with SCS during MI. Intrathecal GABA blockade reversed SCS arrhythmia reduction. MI=acute myocardial ischemia, MI+SCS = myocardial ischemia with spinal cord stimulation, GABA A = myocardial ischemia with spinal cord stimulation and $GABA_A$ antagonist (Bicuculline), GABA B = acute acute myocardial ischemia with spinal cord stimulation and $GABA_A$ antagonist (CGP55845). *=$p<0.05$, **=$p<0.01$

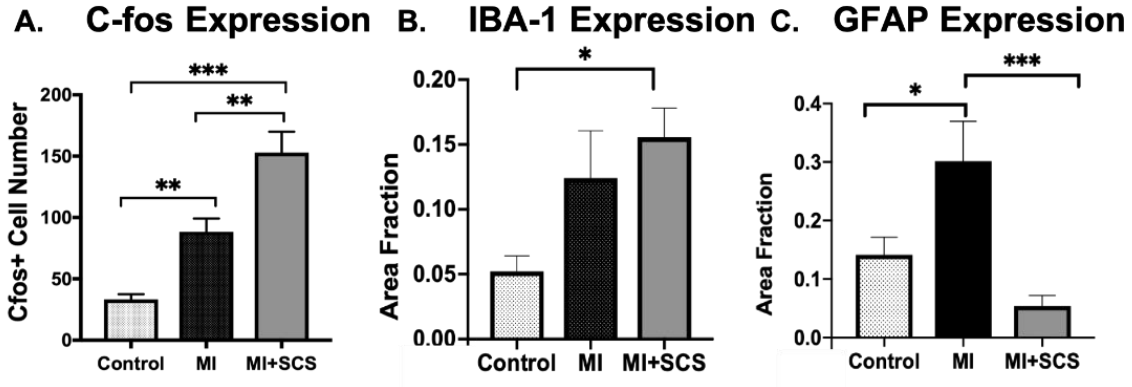

Figure 2. Thoracic Spinal Cord Immunohistochemistry – results represent averaged values from 3 sections per thoracic level, analysis performed blinded to animal, experimental group, spinal level, and side. **A)** Cfos expression characterizes activated neuronal cells, increased Cfos expression in MI and even greater increase in MI+SCS. **B)** IBA-1 expression demonstrates increase in microglia with SCS. **C)** GFAP expression show an increase in reactive astrocytosis with ischemia and a decrease with SCS during ischemia. Control = surgical prep and time control, MI=acute myocardial ischemia, MI+SCS = myocardial ischemia with spinal cord stimulation. *=p<0.05, **=p<0.01, ***=p< 0.001

Cardiovascular Anesthesiology-6 Snail Knockdown is a Novel Therapeutic Strategy for Inhibiting Endothelial-to-Mesenchymal Transition in Right Ventricular Failure Secondary to Pulmonary Hypertension

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Introduction: Right ventricular failure (RVF), the main cause of death in pulmonary hypertension (PH) patients, is associated with distinct structural remodeling which is poorly understood [1,2]. We performed transcriptome analysis of RV remodeling in two clinically relevant rat models of PH using RNASeq and investigated the role of transcription factor Snail in mediating Endothelial-to-Mesenchymal Transition (EndMT) [3-6] in rats and explanted human RV tissue. We also performed in vivo knockdown of Snail as a therapeutic strategy for RVF.

Methods: Adult male Sprague Dawley rats (250-300g) received either a single s.c. injection of Monocrotaline (MCT, 60mg/kg, n=4; followed for 30-days) or Sugen (SU5416 20mg/kg, n=4; 10% O2 hypoxia for 3-weeks followed by normoxia for 2-weeks) or PBS (CTRL, n=4). For in vivo Snail knockdown, MCT-rats either received Snail-siRNA (n=6; 5nM/injection every 3-4 days; 4-injections) or scramble (n=7) through tail vein from day 14-30 after MCT. Echocardiography and RV-catheterization were performed terminally. RVs were stained with Trichrome and EndMT markers. RNASeq was performed on rat RV tissue. Differential expression analysis was conducted. Gene expression was assessed by RT-PCR. Human RV sections (CTRL n=3; PAH n=7) were stained with Trichrome and Snail antibody. ANOVA and Student's t-test were used for statistical analysis. Values are mean±SEM.

Results: PH was confirmed by increased RVSP (mmHg) in MCT (97.6±6.6) and Su/Hx (85.26±15.6) vs CTRL (37.1±1.3; $p<0.05$). RV hypertrophy index was significantly increased in MCT (0.82±0.07) and Su/Hx (0.61±0.1) vs CTRL (0.27±0.01; $p<0.05$). MCT and Su/Hx had significant RV dilatation vs CTRL (RVID diastolic: MCT 3.5±0.3mm, SuHx 2.5±0.2 vs CTRL 1.3±0.1; $p<0.05$). PH patients had significantly elevated RVSP (80.7±9.9 mmHg) and reduced RV-function. MCT, Su/Hx rats and PH patients had increased RV-fibrosis. Double immunolabeling of RVs demonstrated colocalization of endothelial and smooth muscle markers, illustrating EndMT in RVs of MCT, Su/Hx and humans. RNASeq demonstrated EndMT as the top upregulated pathway in both MCT and Su/Hx RVs. Snail was significantly increased (~2-fold) in MCT and Su/Hx ($p<0.05$) and demonstrated increased nuclear immunolabeling (activation) in humans. Other known EndMT-transcription factors Snai2, Twist1, and Zeb1 were unchanged. Based on RNASeq, we propose that increased TGFβ (~2-fold), CDKN2B (~3-fold) and PRSS23 (~2-fold) upregulate Snail that recruits LOXL2 (~2-3-fold increase), causing HistoneH3 oxidation (~1.5-fold decrease) and CBX5 (~1.5-fold decrease) release leading to chromatin reorganization resulting in EndMT. Finally, MCT-rats treated with Snail-siRNA demonstrated decreased Snail expression (~3-fold), RVSP (45±1.6 vs 60±3.9 in scramble; $p<0.05$) and RV hypertrophy index (0.41±.01 vs 0.81±.06; $p<0.05$).

Conclusion: Pre-clinical and clinical PH-induced RVF is associated with EndMT mediated via Snail. Targeting Snail is a novel therapeutic strategy for PH-associated RVF.

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Cardiovascular Anesthesiology-7 Deletion of miR-155 in motor neurons protects from aortic cross clamping-induced paralysis in mice

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Introduction: Spinal cord (SC) injury after aortic aneurysm repair surgery is one of the most feared and devastating complication post-surgery, with 5-15% of patients experiencing paraparesis or paraplegia (1). Using our mouse model of paralysis induced by transient aortic cross-clamping (ACC) we had found that microRNA miR-155 is up-regulated in the SC after ischemia-reperfusion, in two compartments of the neurovascular unit, endothelial cells (ECs) and motor neurons (MNs). We had also found that mice with global miR-155 deletion present with reduced central cord edema and gray matter damage, and suffer roughly 35% less paralysis than wild-type mice. The aims of this study were: (1) to investigate the roles of miR-155 in these two compartments of the SC; and (2) to identify key miR-155-target genes in ECs and MNs.

Methods: To investigate the cell specific contribution of miR-155 in MN and EC in SC injury after ACC, we developed four strains of mice: Two knock-out (KO) strains: Mice that specifically lack miR-155 expression either in MNs (MN-miR-155-KO) or in ECs (EC-miR-155-KO); and two knock-in (KI) strains: Mice that over-express miR-155 specifically in MNs (MN-miR-155-KI) or in ECs (EC-miR-155-KI). The KO and KI strains were respectively produced by mating miR-155 fl/fl mice (that allow miR-155 deletion upon CRE expression) or Rosa-26-lox-stop-lox-miR-155-KI mice (where miR-155 expression is induced after the stop codon is eliminated upon CRE expression) to either ChAT-Cre transgenic mice (that express Cre in MNs) or Tie-Cre transgenic mice (that express Cre in ECs). The effects of ACC surgery on mice of these four strains were then compared to those on WT mice by recording the rate of paralysis and by measuring the volume of central cord edema using MRI. Additionally, we used Affymetrix MTA-Mouse total transcriptome profiling arrays to compare gene expression in SCs from WT mice and SCs from both MN-miR-155-KI and EC-miR-155-KI mice.

Results: We found that miR-155 activity in MNs is instrumental in the initiation of molecular malfunctions leading to paralysis in our mouse ACC model. Namely, specifically deleting miR-155 in MNs provided a level of protection against paralysis that is very similar to the level of protection provided by the global deletion of the miR-155 gene. In agreement with this result, MN-miR-155-KI developed more paralysis than the WT mice. Our finding suggests the urgency to focus on analyzing miR-155 intrinsic effects on neuron homeostasis and survival, at least in the context of our ACC model and thoracic-abdominal aneurism repair by open surgery. Interestingly, although EC-miR-155-KO mice developed less central cord edema than WT mice, that did not translate in protection from paralysis after ACC.

Conclusion: The deletion of miR-155 in MNs but not in ECs reduces the initial response to ischemia, thus limiting the spreading of inflammation and reducing the intensity of secondary SC damage.

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Cardiovascular Anesthesiology-8

Echocardiographic Assessment of Left Ventricle Function During Ex Vivo Heart Perfusion using Pump Supported and Passive Afterload Working Mode prior to transplant.

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Introduction: Heart transplant remains the gold standard for the treatment of end stage heart failure but it is limited by an increasing gap between available donor organs and recipients. As a result, many centers are introducing donation after circulatory death (DCD) to increase the donor pool. Ex vivo heart perfusion (EVHP) was created to decrease cold ischemia time and allow metabolic and functional assessment of donor hearts prior to transplantation. However, current clinical platforms do not allow functional evaluation of hearts. Echocardiography is a validated non-invasive imaging modality to assess heart function. We developed an EVHP system to allow functional donor heart evaluation in 2 working modes: Pump Supported (PSWM) and Passive Afterload Working Mode (PAWM). PSWM enables an antegrade flow to the left atrium, and a retrograde flow into the aorta. In systole, the LV must overcomes the aortic backpressure that in diastole provides retrograde coronary perfusion. PAWM is an alternative to PSWM to closer simulate systemic vascular resistances. In PAWM the ascending aorta is connected to a Windkessel-based afterload module. In this report, we performed echocardiographic evaluation of LV function during this two different working modes.

Methods: After approval of local ethics board, 4 Yorkshire male pigs underwent general anesthesia for heart harvesting. The hearts were procured after injection of cardioplegia solution and subsequent cardiac arrest. They were put in cold storage for 15 minutes to allow cannulation and were then mounted on our custom EVHP circuit. The reperfusion protocol consisted of Langherdorf mode (LM) for 30m, PSWM for 1h, PAWM for 4h, and PSWM for 1h. LV function was assessed using echocardiography in vivo, during PSWM1, PAWM and PSWM2. Echocardiography included the main standard LV views to quantify LV function according to current guidelines. We measured: EF, fractional shorting (FS), fractional area change (FAC), global longitudinal strain (GLS), global circumferential strain (GCS) and radial strain (RAD).

Results: During EVHP, our 3D custom setup was able to provide good quality images comparable to standard transthoracic and transesophageal views which allowed for measurements of functional cardiac assessment (Figure 1). The global systolic function of the LV (represented by EF, FAC, FS) was reduced over the course of the experiment (Figure 2). In addition, GLS and GCS increased while RAD strain decreased over the course of the experiment (Figure 3)

Conclusion: Heart transplantation after DCD is a viable option to increase the number of viable available organs, however DCD hearts are invariably exposed to warm ischemia that leads to a variable degree of LV dysfunction. It is of critical importance to assess DCD heart function to determine organ suitability before transplantation. Epicardial echocardiography assessment during EVHP in bi-PSWM and bi-PAWM was feasible with our system and provides high quality images to assess the cardiac function as per current guidelines. Echocardiography may be included as a diagnostic modality during the working mode in EVHP. Further experiments of transplant after PSWM and PAWM are needed to compare both preservation modalities.

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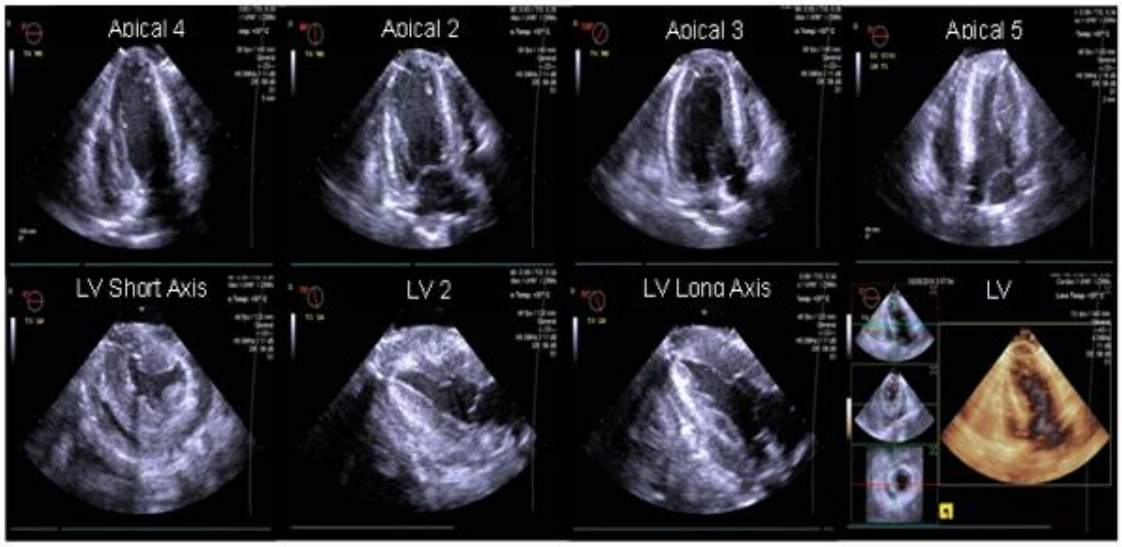

Figure 1: Modified epicardial echocardiography views acquired with a 3 D custom made setup
LV: left ventricle.

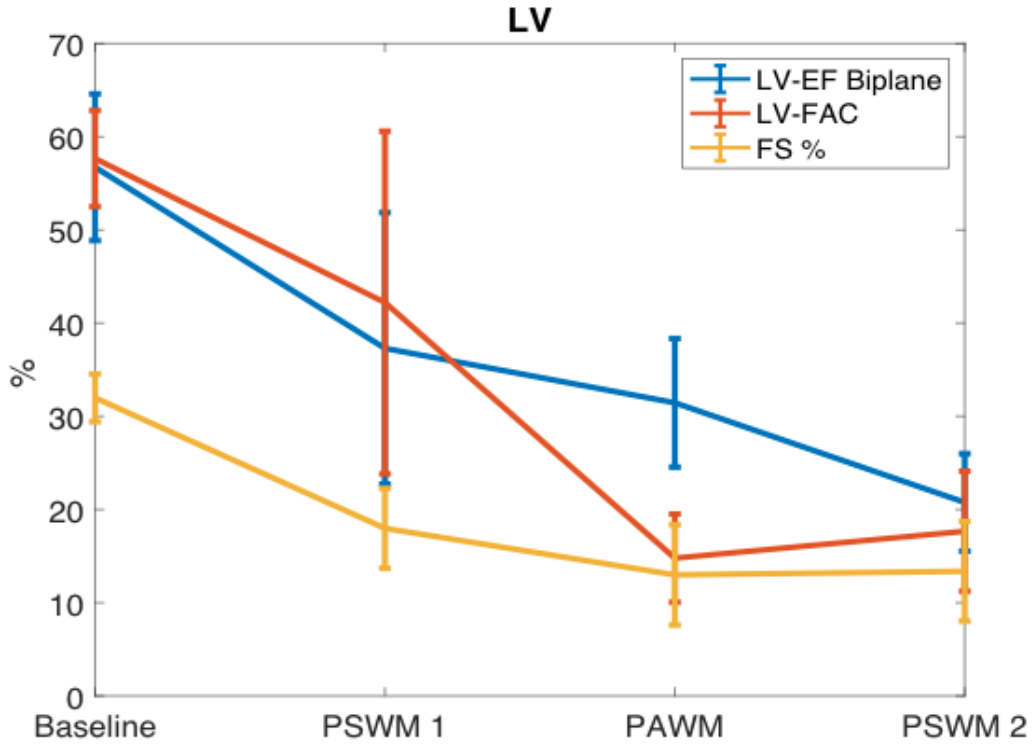

Figure 2: Trend of EF, FAC, FS during the experiment
PSWM: Pump Supported Working mode. PAWM Passive Afterload Working Mode EF: ejection fraction. FAC: fractional area change. FS: fractional shorting GCS: global circumferential strain. GLS: global longitudinal strain. LV: left ventricle.

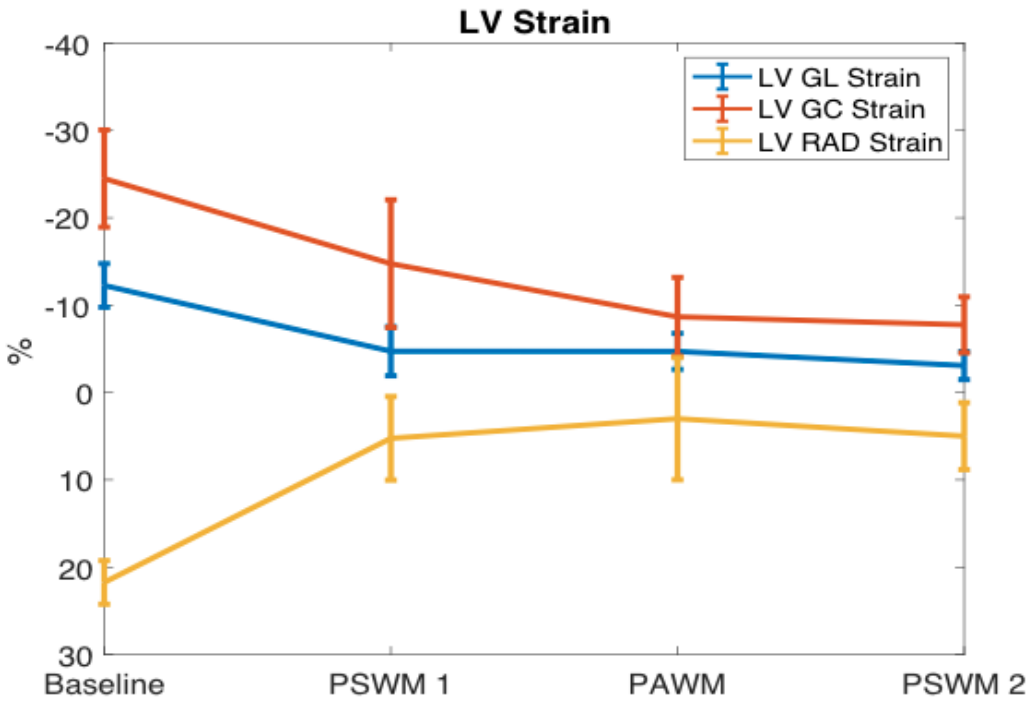

Figure 3: Trend of GLS, GCS, RAD during the experiment
PSWM: Pump Supported Working mode PAWM Passive Afterload Working Mode GCS: global circumferential strain. GLS: global longitudinal strain. RAD: radial LV: left ventricle.

Cardiovascular Anesthesiology-9

Perioperative multimodal general Anesthesia Focusing on specific CNS targets in patients undergoing cardiac surgeries: The PATHFINDER study

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Introduction: The current practice of balanced anesthesia generally uses intravenous propofol to induce and inhaled ethers to sustain unconsciousness, midazolam for amnesia, muscle relaxants for immobility and opioids for antinociception (1,2). However, recent advances in the understanding of specific neural circuits involved in antinociceptive and arousal pathways have made it possible to use medications synergistically to achieve proper levels of antinociception and unconsciousness. Evidence suggests that the selection of multiple classes of intravenous medications allows for a reduction in overall dosing requirement when compared to dosing each medication individually (3). Multimodal general anesthesia (MMGA) is a strategy designed to utilize known central and peripheral neurophysiology in designing a rational and explicit mechanism to control levels of unconsciousness and antinociception during anesthetic practice. MMGA uses a combination of multiple agents with specific central nervous system targets at low doses to maximize therapeutic benefit while minimizing the potential side effects of each agent. MMGA improves on the practice of balanced anesthesia by using multiple antinociceptive agents which act at different parts of the nociceptive system. These medications also contribute to unconsciousness by decreasing arousal and limit the amount of opioids necessary to manage nociception intraoperatively and pain postoperatively (4).

Methods: In the PATHFINDER pilot study, a rational strategy of multimodal general anesthesia with EEG-based neuromonitoring was employed in a group of 18 elderly patients undergoing cardiac surgery, a high risk population for hemodynamic instability, delirium, and post-operative cognitive dysfunction (5, 6 ,7). Antinociception was achieved by a combination of remifentanil, ketamine, dexmedetomidine, bupivacaine, and magnesium. The state of unconsciousness was achieved primarily by propofol; however, the chosen antinociceptive agents have secondary effects in decreasing levels of arousal (2). Image/ Chart Captions: Table 1: Demographics of study cohort. Table 2: Flowchart of multimodal general analgesia protocol.

Results: Quantitative data was collected (data collection ongoing) with a primary outcome of postoperative delirium and secondary outcomes of intraoperative hemodynamic stability (via area under the curve of hypotension and blood pressure coefficient of variation) and post-operative analgesic requirements. Qualitative observations include a) smooth wake-ups in the ICU (per nursing); b) stable hemodynamics in the operating rooms (per anesthesiologists); and c) a comprehensive use of the raw EEG waveforms, density spectral array, and patient state index to ensure adequate levels of unconsciousness states. Image/ Chart Captions: Figure 1: Incidence of burst-suppression in EEG of patients. Burst-suppression is an EEG waveform seen during medically induced coma that is undesirable during surgical unconsciousness. (A, B) Computed EEG spectrograms for a selected control and experimental group patient during cardiac surgery with labeled timepoints of surgical incision (S), sternotomy (ST), heparin bolus (H), bypass begin (BB), bypass end (BE), and sternal closure (CS) before ICU transfer. Suppression epochs are visible in the multitaper spectrograms and, suppressions were identified computationally as 2s epochs with EEG amplitude >5uV. Identified suppression epochs are plotted below each spectrogram. (C) Selected raw EEG samples comparing waveforms during general anesthesia versus a waveform of burst suppression. (D) Fraction of time spent in burst suppression from induction to closing of the sternum during cardiac surgery under multimodal anesthesia. Figure 2: Graphical representation of the area under the curve (AUC) of mean arterial pressure < 65 using trapezoidal rule (median = 911.03), time-weighted average of AUC adjusted to the length of surgery (TWA, median = 3.47), and mean arterial pressure coefficient of variation (CV, median = 0.345) during cases under the multimodel anesthesia paradigm.

Conclusion: By using multiple medications with specific CNS targets at low doses, it is possible to operationalize a strategy in cardiac anesthesia to optimize therapeutic benefit and minimize potential side effects of each agent.

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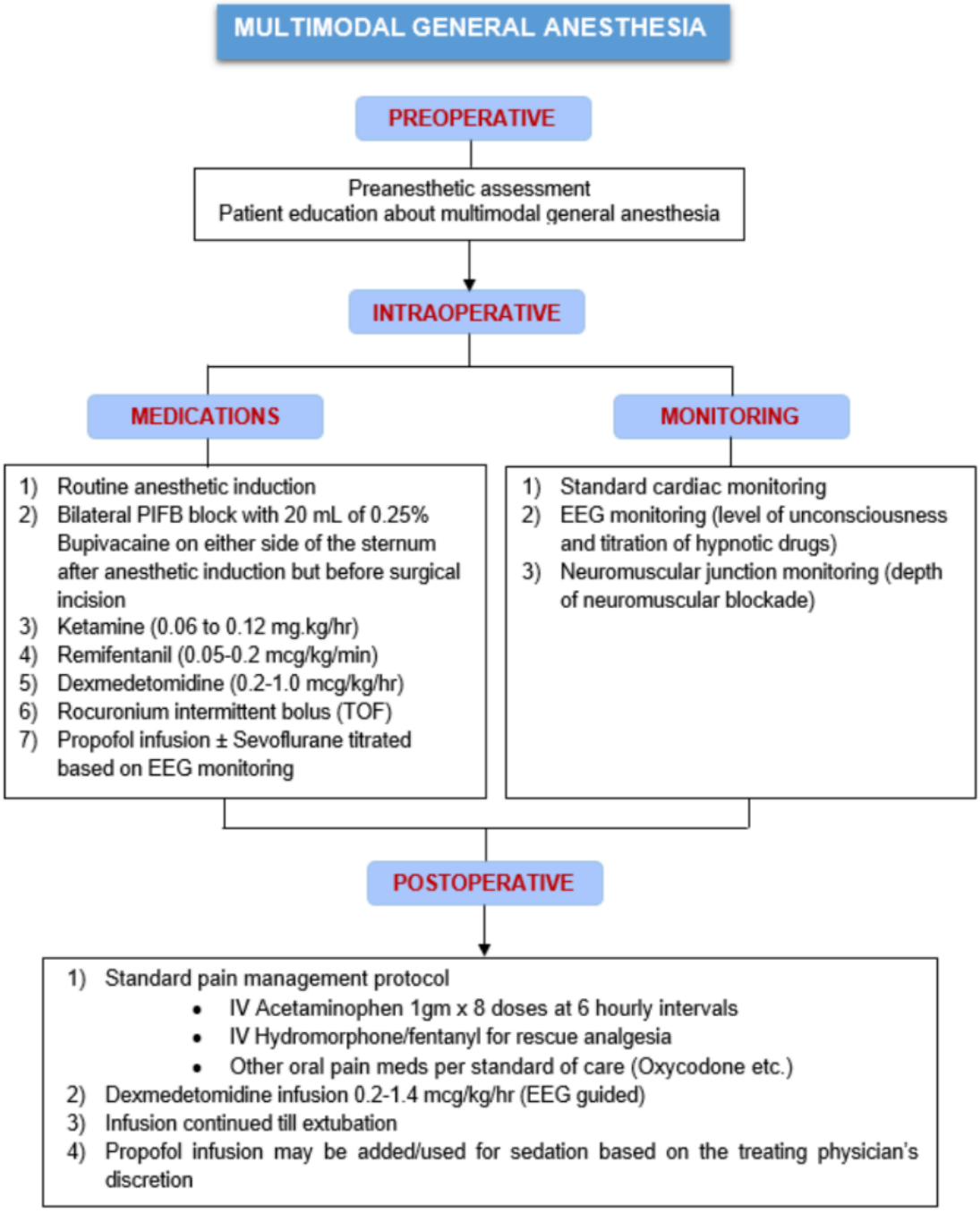
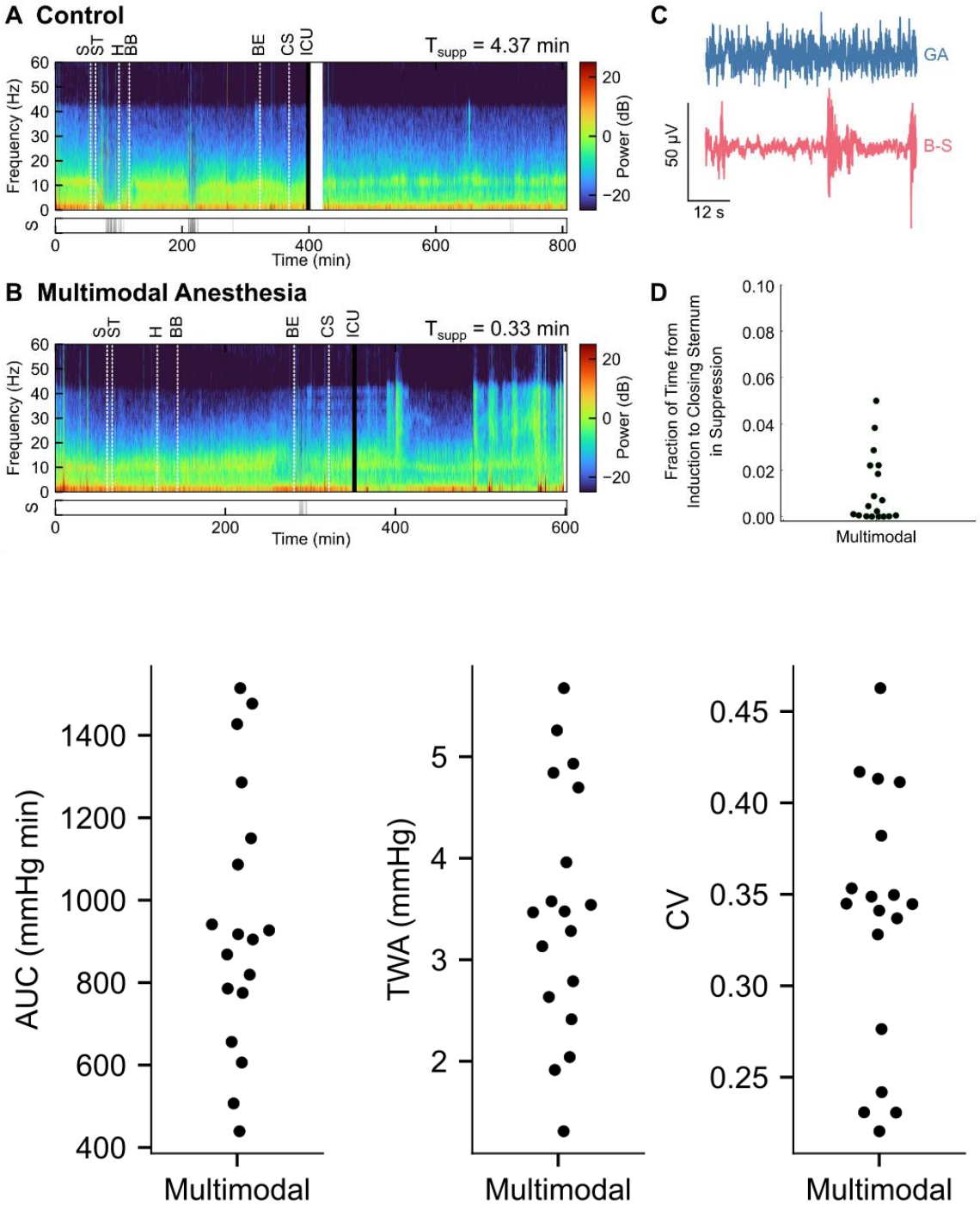
Table 1: Baseline Characteristics of Study Participants

Demographics:	Control (n=2)	Experimental (n=18)
Sex, no (%)		
Male	1 (50)	13 (72.2)
Female	1 (50)	5 (27.7)
Age, mean (SD)	67 (9.9)	72.7 (5.2)
Weight, mean (SD), kg	88.4 (0.3)	82.1 (17.6)
Height, mean (SD), cm	166.4 (1.8)	170.7 (9)
ASA status, no (%)		
3	1 (50)	9 (50)
4	1 (50)	9 (50)
Length of Surgery, mean (SD), min	338.5 (123.7)	346.5 (100.4)
Type of Surgery, no (%)		
Isolated CABG	1 (50)	8 (44.4)
Isolated valve	1 (50)	4 (22.2)
CABG + valve		5 (27.8)
Other		1 (5.6)


MULTIMODAL GENERAL ANESTHESIA
PREOPERATIVE
Preanesthetic assessment
Patient education about multimodal general anesthesia
INTRAOPERATIVE
MEDICATIONS
1) Routine anesthetic induction
2) Bilateral PIFB block with 20 mL of 0.25% Bupivacaine on either side of the sternum after anesthetic induction but before surgical incision
3) Ketamine (0.06 to 0.12 mg.kg/hr)
4) Remifentanil (0.05-0.2 mcg/kg/min)
5) Dexmedetomidine (0.2-1.0 mcg/kg/hr)
6) Rocuronium intermittent bolus (TOF)
7) Propofol infusion ± Sevoflurane titrated based on EEG monitoring
MONITORING
1) Standard cardiac monitoring
2) EEG monitoring (level of unconsciousness and titration of hypnotic drugs)
3) Neuromuscular junction monitoring (depth of neuromuscular blockade)
POSTOPERATIVE
1) Standard pain management protocol
• IV Acetaminophen 1gm x 8 doses at 6 hourly intervals
• IV Hydromorphone/fentanyl for rescue analgesia
• Other oral pain meds per standard of care (Oxycodone etc.)
2) Dexmedetomidine infusion 0.2-1.4 mcg/kg/hr (EEG guided)
3) Infusion continued till extubation
4) Propofol infusion may be added/used for sedation based on the treating physician's discretion


A Control
S
ST
H
BB
BE
CS
ICU
T_{supp} = 4.37 min
Frequency (Hz)
Power (dB)
Time (min)
B Multimodal Anesthesia
T_{supp} = 0.33 min
C
GA
B-S
50 μV
12 s
D
Fraction of Time from Induction to Closing Sternum in Suppression
Multimodal
AUC (mmHg min)
TWA (mmHg)
CV
Multimodal
Multimodal
Multimodal

Cardiovascular Anesthesiology-10 A Human Model of Whole-Body Ischemia-Reperfusion: Changes in Extracellular Vesicle microRNA Expression

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Introduction: In-depth knowledge of individual patients' physiology impacts perioperative management as well as efficacy and safety of surgical procedures. Extracellular vesicles (EVs), also named exosomes or microvesicles, are a new paradigm in cellular communication, cell stress, and biomarker development. EVs are secreted by all cells, carry biologically active microRNAs, proteins, lipids, and other molecules. The role of exosomes in the surgical population is not well known and may have major impact on perioperative care and monitoring. Deep hypothermic circulatory arrest (DHCA) is a profound perioperative stress event involving arrest of the circulation to major organ systems and whole body ischemia-reperfusion (IR). DHCA is used for surgical repair of the great vessels including pulmonary thromboendarterectomy (PTE). Our study tests the novel hypothesis that surgically induced DHCA alters exosome content and changes the ability of exosomes to affect cellular metabolism and function.

Methods: Plasma was obtained from 12 patients undergoing DHCA immediately after induction of anesthesia and after completion of the procedure following chest closure. Extracellular vesicles were isolated using membrane affinity spin columns and total RNA was extracted from the EV pellet. EV miRNAs were profiled with Next-Generation Sequencing (NGS). Differentially expressed miRNA pre- and post-DHCA were identified. Only miRNAs meeting stringent cut-off values of log2fold change (FC)≥

Results: NGS identified 10 differentially expressed EV miRNAs, all of which matched previously identified EV miRNAs on ExoCarta, an online exosome database. These miRNAs include miR-99a-5p (FC=+3.16, Padj=1.57E-04), which may target NOX4, a gene upregulated in response to IR, and associated with IR induced acute lung injury and myocardial injury; miR-25-3p (FC=+2.89, Padj=7.13E-03), shown to target mRNAs involved apoptosis, oxidative stress, inflammation and play important roles in pathogenesis of cerebral IR injury, acute myocardial infarction and left ventricular hypertrophy; and miR-191-5p (FC=-2.5, Padj=3.03E-04) which is increased in pulmonary hypertension, abnormally expressed in type 2 diabetes, and regulates cellular processes such as cell proliferation, apoptosis and migration.

Conclusion: miRNAs from isolated circulating EVs are potential biomarkers for IR and its effects on organs in the perioperative setting. Further studies can provide new information in intercellular communication and physiological or pathological pathways involved in IR in a human model. Furthering our understanding of the roles of EV miRNAs in cellular processes may also lead to development of novel therapeutics for IR.

Cardiovascular Anesthesiology-11

Comparative Analysis of Right Ventricular Transcriptome in Pulmonary Arterial Hypertension Animal Models

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Introduction: Right ventricular (RV) dysfunction is a significant prognostic determinant of morbidity and mortality in pulmonary arterial hypertension (PH). However, the underlying molecular mechanism of RV dysfunction secondary to PH remains unclear. To better understand its pathobiological characteristics, PH animal models have been used to study human PH. Here, we compare the RV transcriptome of two clinically relevant PH rat models with maladaptive RV remodeling.

Methods: Adults male Sprague Dawley rats received either a single subcutaneous injection of pulmonary endothelial toxin Monocrotaline (MCT group, 60mg/kg, n=7, followed 30-days), VEGF-receptor antagonist Sugen with 3-weeks of hypoxia (10% oxygen), followed by 2-weeks of normoxia (SU5416, 20mg/kg, SuHx group, n=7), or PBS for control (Ctrl, n=7). PH and RV failure were confirmed by echocardiography and RV-catheterization. RNA sequencing was performed on rat RV tissue, followed by differential expression and pathway analysis using a threshold of 0.05 for statistical significance (p-value). The p-value was corrected for multiple comparisons using false discovery rate and Bonferroni. Pathway analysis was done with hallmark gene sets. Real-time quantitative polymerase chain reaction (qRT-PCR) was used to confirm the RNA sequencing results.

Results: Both MCT and SuHx rats had severe PH, RV hypertrophy and RV dilation compared to Ctrl. RNA sequencing revealed 7,842 and 3,146 differentially expressed genes (DEG) in RV from MCT and SuHx groups compared to control, respectively, with significant overlap. The overlapping DEGs in RV exhibited a strong correlation between both animal groups. In addition, pathway enrichment analysis of DEGs in the RV from MCT and SuHx groups according to hallmark gene sets revealed 32 and 30 significant pathways, respectively, and 25 overlapping pathways. More specifically, both groups showed similar significant up-regulation of epithelial mesenchymal transition and TNFα signaling pathways, and down-regulation of fatty acid oxidation and oxidative phosphorylation pathways. We validated the RNA-sequencing with qRT-PCR by selecting several key dysregulated genes from epithelial mesenchymal transition (SPP1, CCN2), TNFA signaling (IL7R), oxidative phosphorylation (ACAT1, COX7B), fatty acid metabolism (DECR1, HSP90A), inflammation (C5AR1), and angiogenesis (S100A4). The qRT-PCR findings from RV tissue of independent MCT and SuHx groups (n= ≥6 rats per group) were consistent with sequencing results.

Conclusion: Our RV transcriptomic analysis of MCT and SuHx animal models identified similar patterns of gene expression changes. Targeting specific molecular mechanisms responsible for RV failure in both MCT and SuHx animal models may identify novel therapeutic strategies for PAH-associated RV failure.

Cardiovascular Anesthesiology-12

MicroRNA10b-5p Inhibition Rescues Severe Pulmonary Hypertensive Rats

Michael Zargari[1], Varina R Clark[2], Emma Said[2], Darnell Bagsik[2], Jacqueline Agopian[2], Asif Razee[1], Mansoureh Eghbali[3], Soban Umar[1]

[1]University of California Los Angeles, Los Angeles, CA, [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, [3]University of California, Los Angeles David Geffen School of Medicine, Los Angeles, CA

Introduction: Pulmonary hypertension (PH) is a fatal disease associated with pulmonary vascular remodeling that leads to right ventricular (RV) failure and death. While mir-10b-5p exerts pro-proliferative effects in various cancers via inhibition of its targets Cell Adhesion Molecule-1(CADM1) and Apoptotic Peptidase Activating Factor-1(APAF1), its role in PH is yet to be elucidated. We hypothesize that PH in rats is associated with upregulation of lung miR10b-5p and downregulation of its targets CADM1 and APAF1. Furthermore, inhibition of miR10b-5p may rescue pre-existing PH.

Methods: PH was induced in adult male Sprague Dawley rats (150-200 g) by either monocrotaline (MCT; 60 mg/kg single subcutaneous injection; n=4; followed for 30-days) or Sugen/Hypoxia (SU5416; 20 mg/kg single subcutaneous injection and 10% O2 hypoxia for 3-weeks followed by normoxia for 2-weeks; n=3). In vivo inhibition of miR10b-5p was performed from day 14-30 after MCT (5 intratracheal injections of miR10b-5p antagomir every 3-4 days; 5nM per injection; n=3). PBS treated MCT rats served as controls (n=5). Rats were followed via echocardiography. RV catheterization was performed terminally and RV hypertrophy index was calculated. MicroRNA microarray was performed to assess miR10b-5p levels in MCT rat lungs. Lungs were stained with trichrome to quantify pulmonary vascular remodeling. RT-PCR was performed to assess gene expression. Data is expressed as mean ± SEM. ANOVA was used to compare groups. P<0.05 was considered statistically significant.

Results: As expected, MCT and SU/Hx rats developed severe PH. MiRNA microarray data demonstrated a 3-fold increase in miR10b-5p levels in MCT rat lungs. RT-PCR demonstrated an increase in miR10b-5p in SU/Hx and MCT rat lungs. Furthermore, there was significant downregulation of miR10b-5p targets CADM1 (MCT 1.64-fold; Su/Hx 1.48-fold) and APAF1 (MCT 1.23-fold; Su/Hx 1.21-fold) in rat lungs. In vivo knockdown of miR10b-5p resulted in rescue of PH in MCT rats (RVSP: 50.7 ± 4.42 in antagomir vs. 95.81 ± 3.70 mmHg in placebo; p-value <0.005; RV hypertrophy index: 0.52 ± 0.02 in antagomir vs. 0.80 ± 0.07; p<0.05; RVID: diastolic 2.44 ± 0.68 in antagomir vs. 4.55 ± 0.42 mm; p<0.05). RT-PCR of lungs demonstrated 30% decrease in miR10b-5p expression of antagomir-treated rats. Histological analysis revealed that miR10b-5p antagomir treatment resulted in significantly decreased pulmonary arteriolar wall thickness (32.72 ± 1.12 in antagomir vs. 42.24 ± 3.26 % in placebo, p<0.005).

Conclusion: Pre-clinical PH is associated with an increase in miR10b-5p expression and decrease in its targets CADM1 and APAF1. MiR10b-5p inhibition rescues experimental PH and may serve as a novel therapeutic target.

Critical Care

Critical Care-1 Optimal Timing for Vasopressor Initiation in Septic Shock : Revisiting the Surviving Sepsis Campaign guidelines using Machine Learning

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Introduction: The Surviving Sepsis Campaign [1] recommends to administer 30 ml/kg of fluid within 3 hours following the onset of hypotension, before introducing vasopressors. However, evidence supporting this recommendation is lacking.

Methods: We used the data from the MIMIC II dataset. [2] To be included, patients had to present an acute hypotensive episode of septic origin and a lactate level > 2 mmol/l. The primary outcome measure was hospital mortality. We used a machine learning approach accounting for time-varying confounders called longitudinal targeted maximum likelihood estimation. [3]

Results: 933 patients were included: SOFA 7; arterial lactate 3.3 mmol/L, average hospital mortality rate 11.5%. Hospital Mortality was significantly minimized when vasopressors were introduced by hour 3 following the onset of hypotension. When compared to 30 ml/kg, switching to vasopressors after 5 or 10 ml/kg was associated with reduced mortality (Fig. 1).

Conclusion: In septic shock, administering 5-10 ml / kg within 3 hours after the onset of hypotension appears to maximize the chance of survival.

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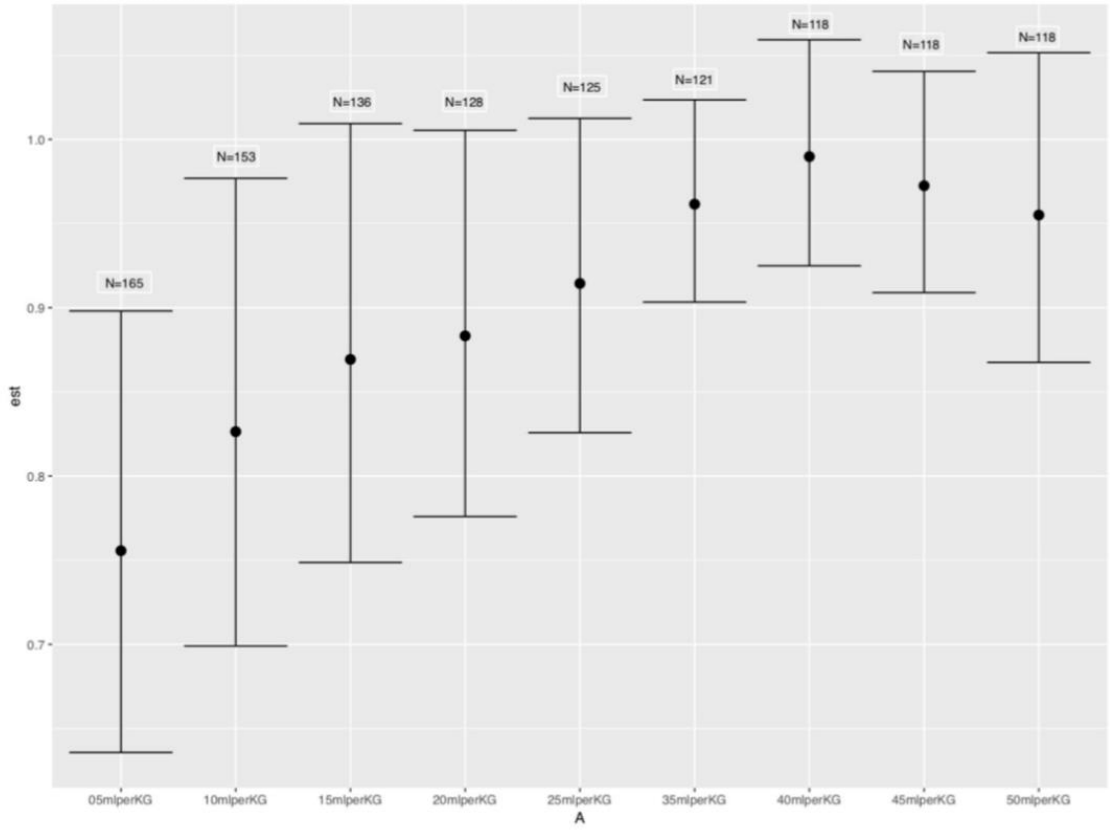
Relative Risk of Mortality amongst ICU patients by Dynamic Treatment vs Current Protocol



Critical Care-2 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[3], 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

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 mice1)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”²-ATC GAC TCT CGA GCG TTC TC-3”², 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 500μg, n=3, (2) PcrV 500μg + CpG-ODN 500μg, n=3, (3) CpG-ODN alone 500μg, 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 mice1)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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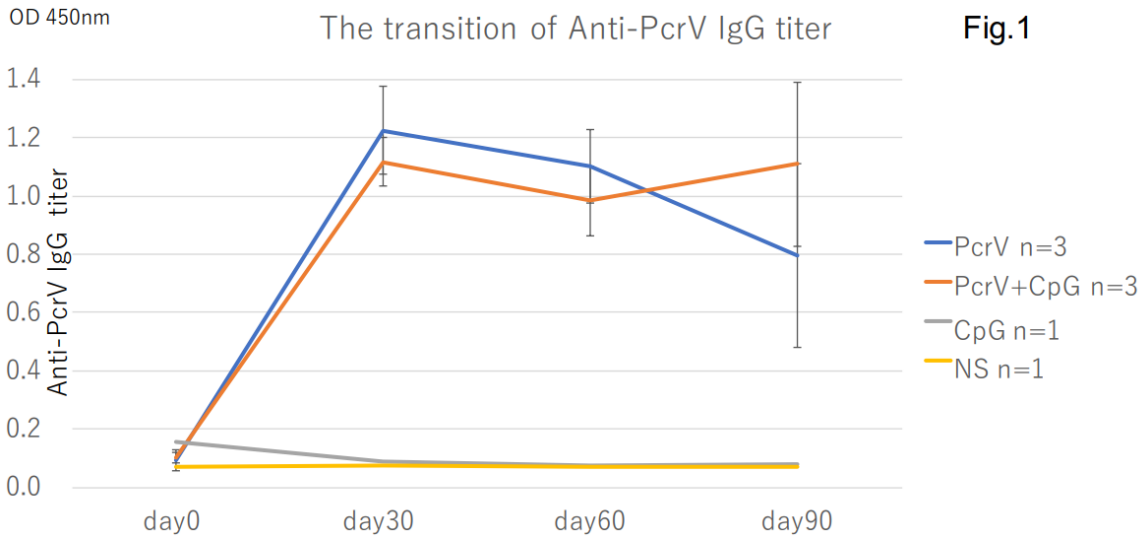
Fig.1


OD 450nm
The transition of Anti-PcrV IgG titer
Anti-PcrV IgG titer
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
day0
day30
day60
day90
PcrV n=3
PcrV+CpG n=3
CpG n=1
NS n=1

Critical Care-3 Mechanical ventilation with moderate tidal volume aggravates extrapulmonary sepsis-induced lung injury via IL33-WISP1 signaling pathway

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Introduction: Mechanical ventilation (MV) is a common requisite component of intraoperative care for adequate gas exchange and the delivery of anesthetics in patients with sepsis, whereas sepsis is the most common predisposing factor for ALI/ARDS. We previously showed that both interleukin (IL)-33 and WNT1-inducible signaling pathway protein 1 (WISP1) played important roles in a two-hit lung injury model that combined cecal ligation and puncture (CLP)-induced sepsis and MV with moderate tidal volume (MTV). However, the relationship between IL-33 and WISP1 is still unclear in the two-hit lung injury model.

Methods: Wildtype, IL-33 KO and ST2 KO mice underwent cecal ligation and puncture (CLP) followed by MV with moderate tidal volume (MTV) (10 ml/kg; 4 h), a two-hit model. A separate cohort of wildtype mice pretreated with intratracheal neutralizing antibodies to WISP1 or IgG as control were also performed in the two-hit model. RAW264.7 cell line in vitro was used to identify the specific components involved in the IL33-WISP1 signaling pathway.

Results: MTV itself did not change the levels of WISP1 and IL-33 in the lung of septic mice, however, MTV significantly up-regulated both WISP1 and IL-33 in the two-hit lung injury model. Consistent with it, MTV alone did not cause lung injury and inflammation, but MTV increased lung injury score, W/D weight ratio, alveolar-capillary permeability and cytokines (IL-6 and TNF-α in plasma and BALF) in mice that previously underwent CLP. Whereas IL-33 or ST2 deletion as well as WISP1 blockade partially inhibited the two-hit phenotype. Furthermore, IL-33 or ST2 deletion decreased WISP1 expression in vivo. In vitro, IL-33 induced WISP1 production by activating AKT-GSK-β-catenin and ERK-GSK-β-catenin signaling pathway via ST2 in macrophage, which is mediating by the interaction of β-catenin/TCF/CBP/P300 in nucleus.

Conclusion: We first demonstrated that IL-33/ST2-WISP1 pathway plays an important role in mediating exacerbations of acute lung injury caused by systemic sepsis under MV with MTV. The results will guide the potential development of new therapeutic strategies for patients with extrapulmonary sepsis under mechanical ventilation in critical care units.

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Critical Care-4 Proximal Tubule Megalin Inhibition Prevents Acute Kidney Injury Due To Rhabdomyolysis in Mice

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Introduction: Destruction of skeletal muscle by crush, blast, burn, or exertion releases myoglobin into the systemic circulation. Rhabdomyolysis-induced acute kidney injury (rhAKI) ensues and can be lethal due to hyperkalemia. Supportive management aims to reduce myoglobin toxicity by increasing and alkalinizing urine flow with protocol-based therapy (1). As rhAKI commonly occurs in austere environments such as earthquakes and armed conflict, such therapy may be challenging or impossible. Therefore specific therapy to ameliorate AKI would be a significant advance. Myoglobin is taken into proximal tubular cells (PTECs) via the renal cortex-specific endocytic transporter megalin (2). We therefore hypothesized that interfering with megalin would ameliorate rhAKI.

Methods: Animal studies were approved by the OHSU IACUC. We bred inducible, proximal tubule-specific megalin knockout mice (LRP2 fl/fl, Ndrg1CreERT2, iMegKO). These mice are phenotypically normal until induction of cre recombinase with tamoxifen. GFR was measured by transcutaneous decay of injected fluorescent sinistrin at baseline and 24 hours and urine was collected for 24 hours before and after experiments. Male mice, 8-12 weeks old, received 8mL/kg 50% glycerol solution into the vastus medialis muscle (3). 24 hours later, GFR was measured and mice were killed. Plasma and urine myoglobin, and myoglobin clearance were quantified. Kidney sections were evaluated for pathology, injury markers (KIM-1 and cleaved caspase-3), and for megalin and myoglobin by specific stains. In a second protocol, C57BL/6 mice received cilastatin, a pharmacologic megalin inhibitor, or vehicle at the time of glycerol injection, and were evaluated in the same manner. Statistical analysis (t-test and repeated measures ANOVA) was conducted in Prism 7.0 and data expressed as mean±SEM.

Results: Upon treatment with tamoxifen, the renal cortex of iMegKO mice demonstrated absence of proximal tubular megalin while that of tamoxifen-treated cre-negative littermates (controls) demonstrated intact proximal tubular megalin. Glycerol injection caused elevated plasma myoglobin. 24h after glycerol injection, iMegKO mice exhibited normal GFR (92.8 ± 5.9 % of baseline) and normal 24h urine output (5.3±0.9 mL/24h), with very attenuated histologic renal injury and primarily medullary distribution of myoglobin, while littermate controls demonstrated severe loss of GFR (22.4± 0.3 %baseline $p<0.001$ compared with iMegKO, n=4-5), oliguria (mean urine output 2.4±0.9 mL/24, $p=0.008$ compared with iMegKO, n=4-5), severe histologic injury and primarily cortical distribution of myoglobin. When glycerol injection was conducted in wild type mice, cilastatin also preserved GFR (526±125 vs.67±31 µl/min/100g, $p=0.03$, n=4/gr), urine output (.8 ±0.3 vs. 0.4±0.1, $p=0.01$, n=4/gr), and histologic architecture compared with vehicle. KIM-1 and cleaved caspase-3 were reduced by megalin interference and cilastatin treatment and in both iMegKO mice and cilastatin-treated mice, clearance of plasma myoglobin was greatly increased (5-16x) compared with respective controls.

Conclusion: Proximal tubule-specific megalin deletion ameliorates rhAKI by increasing plasma clearance of myoglobin and shifting intrarenal distribution of myoglobin away from cortical PTECs. The pharmacologic inhibitor cilastatin, ameliorates rhAKI similarly to megalin interference. Given the lack of specific therapy for rhAKI and the burden of supportive therapy in austere environments, further mechanistic and translational study is warranted.

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Critical Care-5 Return of Spontaneous Circulation and Survival After In-Hospital Cardiac Arrest in Patients With and Without Right Ventricular Dysfunction

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Introduction: In 2012, the rate of hospital discharge after in-hospital cardiac arrest (CA) was reported as 17%.(1) In 2016, the American Heart Association reported survival rate in adults after in-hospital CA was 24.8%.(2) When re-establishment of a stable heart rhythm does not result in physiologic blood pressure during advanced cardiac life support (ACLS) one possible cause might be pre-existing right ventricular dysfunction (RVD) that might impair filling of the left ventricle. Theoretically, patients with RVD might have improved outcome after CA if, in addition to epinephrine, dobutamine and/or inodilators were administered during ACLS as these pharmacologic agents might increase flow through the pulmonary circuit. The goal of this study is to learn whether pre-existing RVD is in fact associated with lower rates of successful resuscitation after in-hospital CA, as compared to patients without pre-existing right ventricular dysfunction.

Methods: With IRB approval and waiver of informed consent, the EMR was searched and a list of all patients, ages 18 - 90, who suffered in-hospital CA at our medical center from January 2010 - September 2018 was created. Subjects were excluded if the record indicated hemorrhage within six hours prior to CA. To be included, RV function had to have been assessed with echo within six months prior to CA. Data recorded included age, gender, LV Ejection Fraction (LVEF %), moderate or severe aortic or mitral valve disease, diagnosis of HTN, DM, CAD, prior coronary artery stenting, prior CABG, COPD, presence or absence of RVD (and severity of RVD categorized as mild, moderate or severe), and mg of epinephrine administered during ACLS. Outcomes included initial return of spontaneous circulation (ROSC), and survival. Outcomes were compared between subjects with, and without RVD. (Some data not documented in medical records resulted in less than 476 subjects in some analyses). Categorical variables were analyzed using Chi-square test. Continuous variables were analyzed using Mann-Whitney U-test. p-value <0.05 was considered statistically significant.

Results: 1,044 Charts were reviewed. 476 subjects met inclusion criteria. There were no differences in demographics between survivors and non-survivors (see table 1). Initial ROSC was achieved in 85/146 (58.2%) of subjects with RVD (of any grade of severity) vs. 170/302 (56.3%) subjects without RVD ($p = 0.699$). Among patients with RVD of any grade (mild, moderate, or severe), 124/153 (81%) died vs. 243/318 (76.4%) of patients without RVD, $p = 0.25$. Significantly more epinephrine was administered in the group that died, $p < 0.01$. Future analyses will compare survival between subjects with different grades of severity of RVD, and as compared with subjects with no RVD.

Conclusion: By echo criteria, RVD has been reported present in 88% of patients after CA.(3) Furthermore, RVD after CA predicts poor outcome, independent of LV function.(4) In a swine model, post-CA RVD was successfully treated with dobutamine 10 mcg/kg/min, as compared to controls(5) and, in swine treated with dobutamine, RV ejection fraction (RVEF) returned to baseline (normal) two hours post-CA, while RVEF remained depressed in controls five hours post-CA.(5) This work influenced us to undertake this pilot study, although it is noted that post-CA RV dysfunction is a different entity than RV dysfunction that precedes CA. The results of this pilot study indicate that rates of initial ROSC, and survival, are not different in patients with pre-existing RVD as compared with patients without pre-existing RVD. Current analyses grouped together all subjects with RVD. Future work will compared rates of ROSC and survival across three grades of RVD as graded by echo (mild, moderate and severe), as compared with subjects without RVD. The fact that more epinephrine was administered in the group that died could perhaps be explained by prolonged and aggressive attempts to resuscitate in the group that died.

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5. Vimal Ramjee, et al. Resuscitation 96:2015, 186–191

Table 1. Demographics Between Survivors and Non-Survivors

	Death (366)	Survived (106)	P value
Age	69 (59-80)	69 (58-77)	0.34
Gender (F)	50.10%	46.20%	0.47
LVEF (%)	60 (40-65)	56 (40-65)	0.52
Moderate or severe Aortic valve disease (yes)	19.80%	19.10%	0.85
Moderate or severe mitral valve disease (yes)	29.60%	21%	0.12
Diagnosis of hypertension	86.60%	87.00%	0.77
CAD	48.20%	50%	0.748
Prior stenting	20.30%	17.90%	0.58
Prior CABG	12.40%	16%	0.33
DM	53.40%	57%	0.44
COPD	22.20%	19.80%	0.6
Epinephrine (mg)	2 (1-3)	1 (1-2)	<0.01

Data presented as median (25^{th} and 75^{th} percentile) and in percentages.

Critical Care-6 Ischemia Reperfusion Injury Induces IL-1β Secretion via NLRP3 Inflammasome in Alveolar Macrophages

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Introduction: Lung ischemia reperfusion (IR) injury is a sterile inflammatory process that is commonly associated with diverse clinical situations such as hemorrhage followed by resuscitation and pulmonary embolism (PE). We previously reported that these inflammatory responses require toll-like receptor (TLR) 4 and the presence of alveolar macrophages (AMs)[1]. Whether TLR4 expression on AMs mediates lung IR injury, however, is still unknown. TLR4 receptor engagement activates the intracellular signaling pathway via nuclear factor-ÎºB (NFÎºB) and increases the transcription of the Il1b gene encoding pro-IL-1β and thus intracellular levels of this pro-cytokine. Subsequent protein processing by the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome, a complex that includes NLRP3 and caspase-1, cleaves pro-IL-1β to the mature protein. We therefore explored whether IR enhances expression of Il1b mRNA and NLRP3 inflammasome in vitro by using mouse AMs.

Methods: A mouse AM cell line (MH-S) was subjected to in vitro nutritional IR. The condition of in vitro nutritional ischemia was established by replacing medium with PBS (as the IR group). We did not include hypoxic conditions for this period because in PE alveolar macrophage cells are not subjected to hypoxia. After the period of in vitro 'ischemia,' medium was added for the 'reperfusion' phase. Cells and supernatants were collected for qRT-PCR analysis to evaluate Il1b mRNA expression and for ELISA to measure IL-1β. In addition, MH-S were treated with MCC950 (selective NLRP3 inhibitor) or VX-765 (Caspase-1 specific inhibitor) to determine how IR induces IL-1β in AMs. After IR stimulation, the supernatants were collected, and we measured the level of IL-1β by ELISA. Data are shown as mean ± SD and the groups were compared using two-tailed unpaired t-test or One-Way ANOVA with Tukey post-hoc test. $P < 0.05$ was considered as statistically significant.

Results: IR group had significantly up-regulated expression of Il1b mRNA compared with control group (1.0 ± 0.2 [Control] vs 2.1 ± 0.3 [IR], $P = 0.019$) and secreted significantly more IL-1β than control group (15.1 ± 1.9 [Control] vs 54.4 ± 9.1 [IR] pg/mL, $P < 0.0001$) (Figure 1). Both MCC950 and VX-765 significantly attenuated IL-1β secretion (88.3 ± 5.4 [IR] vs 67.2 ± 3.1 [IR + MCC950] pg/mL, $P = 0.0005$ and 67.8 ± 1.5 [IR] vs 22.6 ± 0.7 [IR + VX-765] pg/mL, $P < 0.0001$) (Figure 2).

Conclusion: Our results suggest that nutritional IR stimulation 1) significantly increased Il1b mRNA expression in AMs and 2) induced IL-1β secretion in NLRP3 inflammasome-dependent manner.

Reference(s):

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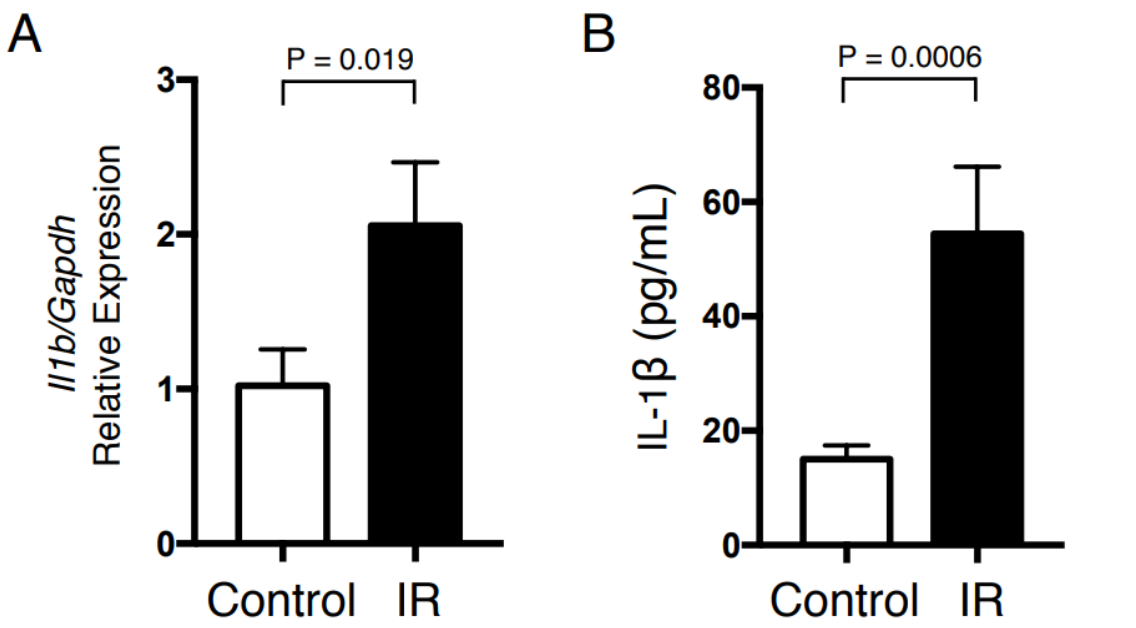

Figure 1. Nutritional IR induces IL-1β mRNA expression **(A)** and IL-1β secretion **(B)**.

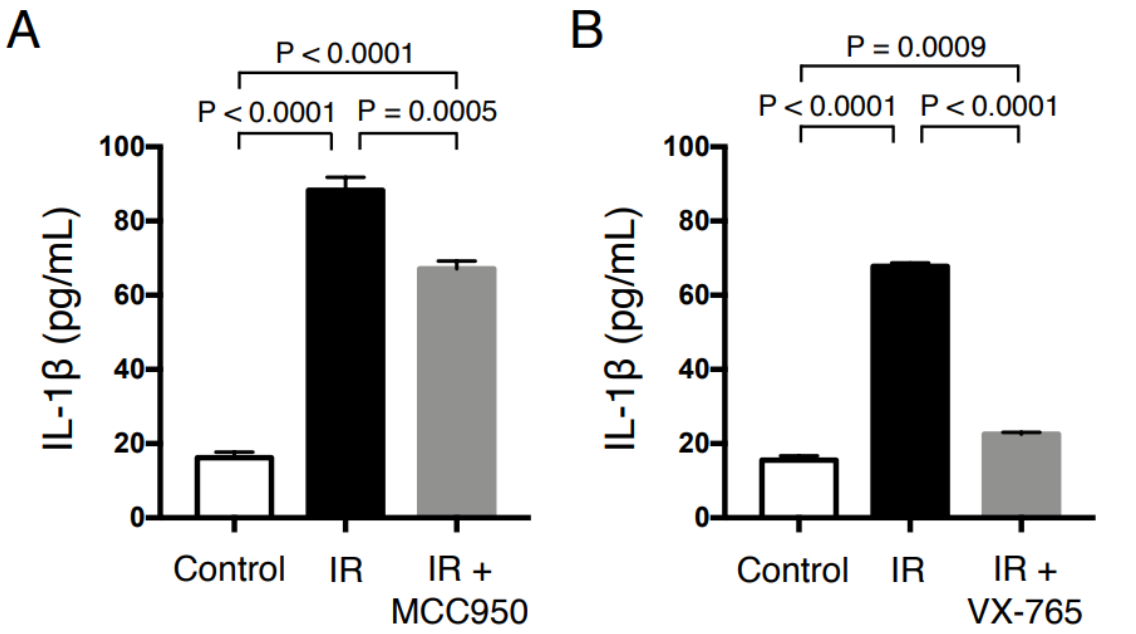

Figure 2. Nutritional IR induces IL-1β in an NLRP3- and caspase-1-dependant manner.

Critical Care-7 Novel Machine Learning Model to Predict Intensive Care Unit Readmission or Mortality After Cardiothoracic Surgery

George A Cortina[1], Shujin Zhong[2], Michael Gao[2], William Ratliff[2], William S Knechtle[2], Suresh Balu[2], Kelly Kester[2], Mary Lindsay[2], Jill R Engel[2], Jacob N Schroder[2], Mark Sendak[2], Mihai V Podgoreanu[2]

[1]Duke University; University of Virginia School of Medicine, Durham, NC, [2]Duke University, Durham, NC

Introduction: Patients readmitted to the intensive care unit (ICU) after transfer to a lower acuity care unit demonstrate increased mortality, length of stay, and healthcare expenditures compared to those never readmitted.(1,2) In high acuity specialized units, such as the cardiothoracic ICU (CTICU), identifying patients at highest risk of readmission and subsequent complications is challenging. Traditional rule-based risk tools overpredict complications, illustrating the need for dynamic means of prediction.(3) Machine learning models have demonstrated improved success at identifying patients at risk for ICU readmission.(4) However, these models use datasets from a variety of different ICU types (e.g. surgical vs. medical), which limits specificity. We hypothesized that machine learning-based models will accurately discriminate cardiothoracic surgical patients at high risk for CTICU readmission or death within two weeks of discharge.

Methods: A dataset was curated to include 5559 encounters of patients between August 2015 and October 2018 who underwent cardiothoracic surgery then survived to initial CTICU discharge. Input features included both patient derived data such as past hospitalizations, and laboratory values along with provider actions such as orders and procedures performed (Table 1). The primary outcome was a composite of ICU readmission or mortality within 14 days of initial discharge from the CTICU (Figure 1). The model was trained using LightGBM (a gradient boosting method using tree-based learning algorithms) and compared to a logistic regression (LR) using sk-learn. Model performance was evaluated using 500 iterations of bootstrapping on a test split of 30% to calculate a 95% CI, and compared across three metrics: area under the receiver-operating characteristic curve (AUC), area under the precision-recall operating curve (AUPRC), and positive predictive value (PPV) at a fixed sensitivity of 20%.

Results: Of the 5559 encounters, 564 (10%) demonstrated decompensation or death within 14-days of discharge from the CTICU. The LightGBM model performed best compared to logistic regression (LR) across precision-recall and positive predictive value performance measures. AUCs were 0.834 ± 0.001 for LightGBM and 0.851 ± 0.001 for LR. The AUPRC was 0.400 ± 0.004 for LightGBM and 0.360 ± 0.003 for LR. Finally, the PPV at a fixed sensitivity of 20% was 0.568 ± 0.007 for LightGBM, compared to 0.405 ± 0.003 for LR.

Conclusion: A novel machine learning model achieves good discrimination in identifying post-cardiothoracic surgical patients at risk of ICU readmission or mortality. Compared to methods using only snapshot measurements, this model strengthens its predictions by integrating grouped trends data from multiple source domains - both related to patient-specific disease processes along with interventions (medication profiles, treatments, actions and orders) performed by the clinical team. Accurate prediction of unplanned readmission could be used in decision support tools to inform ICU discharge readiness and target resources for step-down unit care (increased patient surveillance), especially for high-risk patients requiring complex discharge planning.

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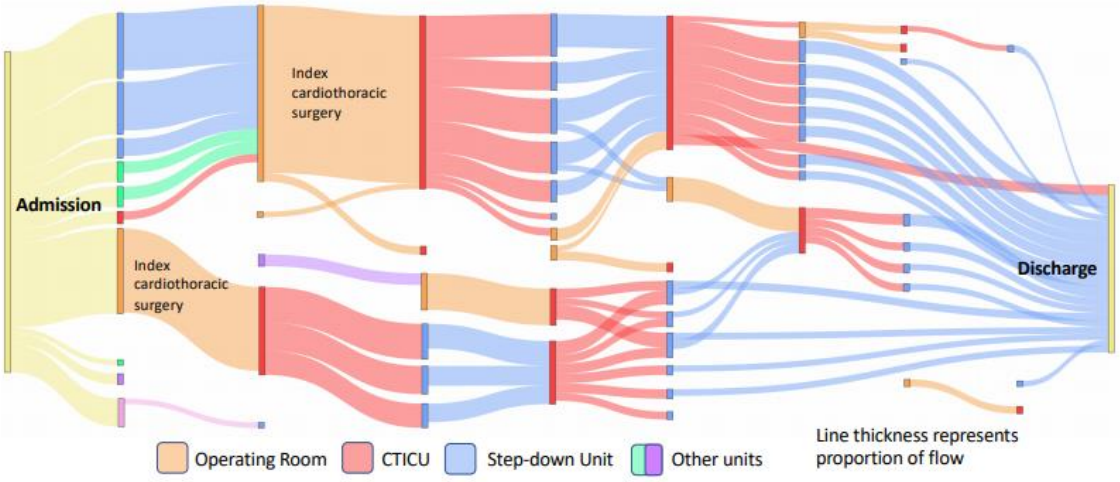

Figure 1. CTICU readmission phenotype: flow of encounters readmitted to the CTICU during index hospitalization. Readmission to the CTICU complicates hospital stay and often results in several transitions of care between the CTICU (red) and step-down units (blue). Avoiding these cycles through the identification of patients at risk (both by refining ICU discharge readiness and increase surveillance in step-down unit) could reduce the length of stay, complications, and improve patient mortality and failure to rescue rates.

Table 1. Multiple domain input features for ML model of patient decompensation (CTICU readmission or mortality)

Features (number of data elements)	**Variables**
I. Patient-specific disease processes, grouped trends	
Demographics (2)	Age, Gender
Encounter Info (10)	(12 and 3 month) Count of General Admissions, ED Visits and CTICU Admissions; Length of Stay in CTICU and/or Hospital Admission
Comorbidities (282)	Clinical Classification Software of ICD-10 Codes*
Laboratory Values† (25)	Albumin, ALT, Ammonia, Anion Gap, Arterial Bicarbonate, Arterial PCO_2, Arterial pH, AST, Bands, BUN, Creatinine, CRP, ESR, Fibrinogen, Glucose, Hematocrit, Hemoglobin A1c, INR, Lactate, LDH, Magnesium, OR Arterial PO_2, Platelets, Potassium, Sodium, Venous PCO_2
Physiologic Measures† (11)	Blood Pressure, BMI, Cardiac Index, Cardiac Output, Height, Level of Consciousness, Pulse, Pulse Oximetry, Respiratory Rate, Urine Output, Weight
Patient status‡ (4)	Delirium, Dyspnea, Hypothermia, Length of Stay, Stroke Work-up
II. Clinical interventions (medication profiles, treatments, actions and orders), grouped trends	
End Organ Support‡ (9)	Bilevel Positive Airway Pressure, Continuous Positive Airway Pressure, Continuous Renal Replacement Therapy, Extracorporeal Membrane Oxygenation, Impella, Intra-aortic Balloon Pump, Mechanical Ventilation, Ventricular Assist Device (VAD) (durable), VAD (temporary)
Orders for labs‡ (8)	Arterial Blood Gas, Blood Typing, Coagulation Panel, Cytomegalovirus, Human Papilloma Virus, JC virus, PT, INR, Toxoplasmosis, Sputum Culture
Orders of procedures/status changes‡ (12)	Arterial Line Insertion, Arterial line Removal, Chest Tube Placement, Intubation, NPO, Peripherally Inserted Central Catheter (PICC) insertion, PICC Removal, Stroke Workup, Tracheostomy Placement, Transfusion (Fresh frozen plasma/Platelet/RBC/Cryoprecipitate), VAD Placement, Wound Care
Orders for imaging/monitoring‡ (6)	Chest Radiograph, ECG, Echocardiogram, Kidneys Urine Bladder Radiograph, Telemetry, Ultrasound (any)

*-Classification categories listed at:
https://www.hcup-us.ahrq.gov/toolssoftware/ccs10/CCSCategoryNames(FullLabels).pdf

†-numeric data summarized over encounter using: max, min, mean, standard deviation, 1st quartile, 3rd quartile number of entries, time of first order, time of last order

‡-boolean event data summarized over encounter using: any event occurred, number of events, time of first event, time of last event

Critical Care-8 Echocardiographic Assessment Using Subcostal-Only View in Advanced Life Support (EASy-ALS): Feasibility of and Obstacles to Implementation in the In-Hospital Setting

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Introduction: Traditionally, echocardiography is performed by a technician and later interpreted by a cardiologist. Focused cardiac ultrasound (FOCUS) is different because it allows physicians in fields including anesthesiology to immediately assess and manage critically-ill patients [1]. High-quality cardiopulmonary resuscitation (CPR) is the backbone of resuscitation, but the American Heart Association [2] suggests FOCUS can be used to identify potentially reversible causes of cardiac arrest in patients with pulseless electrical activity (PEA). In the out-of-hospital setting, application of FOCUS to ALS was found effective in distinguishing true PEA (without wall motion) from pseudo-PEA (with wall motion); it also allowed identification of treatable conditions such as hypovolemia and pericardial effusion [3]. We applied ALS-compliant FOCUS to the in-hospital setting as echocardiographic assessment using subcostal-only view in ALS (EASy-ALS). We trained anesthesiology attendings and residents in FOCUS and EASy-ALS with a modified previously-described curriculum [4-6], allowing us to integrate FOCUS into peri-resuscitative management while exploring the feasibility of its performance after limited training and identifying obstacles to its routine implementation.

Methods: We explored the feasibility of anesthesiology attendings and residents performing FOCUS and EASy-ALS. A total of 29 patients were examined from December 2016 to December 2019. Patients were evaluated in the peri-resuscitative period, defined as a period of profound hypotension, cardiac arrest, or return of spontaneous circulation (ROSC). Patients for whom FOCUS could not be safely performed were excluded. Providers performed EASy-ALS exams after completion of a course consisting of didactics, hands-on practice, and simulation. EASy-ALS protocol is as follows. A provider is contacted by call from the primary service or overhead Code Blue page. On arrival, the provider places the ultrasound probe on the chest without obstructing chest compressions. The exam is performed during the pulse/rhythm check, never exceeding 10 seconds. After resumption of chest compressions, the provider interprets images and relays findings. Afterwards, the provider completes a report documenting indication for exam, initial cardiac rhythm, FOCUS findings, and immediate patient outcome. Descriptive statistics were used to summarize EASy-ALS exam findings. Cases in which diagnostic quality images were obtained, as determined by a FOCUS-credentialed attending anesthesiologist, were presented as a proportion.

Results: Data were collected for 29 patients. Indications for EASy-ALS included PEA (48%), post-ROSC (24%), pre-arrest (14%), asystole (7%), and pulseless ventricular tachycardia (7%). Image quality was good in 72% of cases and adequate in the rest. Major findings included absence of cardiac causes of event (45%), right ventricular syndrome (17%), severe hypovolemia (17%), cardiac standstill (7%), dilated left ventricle (3%), biventricular dysfunction (3%), pericardial effusion (3%), and systolic anterior motion of the mitral valve (3%). Pleural effusion was an additional finding in 2 cases. Of the 18 patients evaluated during cardiac arrest, 12 achieved ROSC.

Conclusion: It is feasible for trained providers to perform EASy-ALS in the in-hospital peri-resuscitation period, expanding the role of anesthesiologists in acute patient care. Providers consistently obtained diagnostic images and identified cardiac motion and causes of instability. Several system-wide obstacles, including a limited number of trained providers and a lack of readily-available ultrasound machines, hinder regular use of EASy-ALS. Use of handheld ultrasound devices and expanding training can help address these issues and allow routine implementation of EASy-ALS.

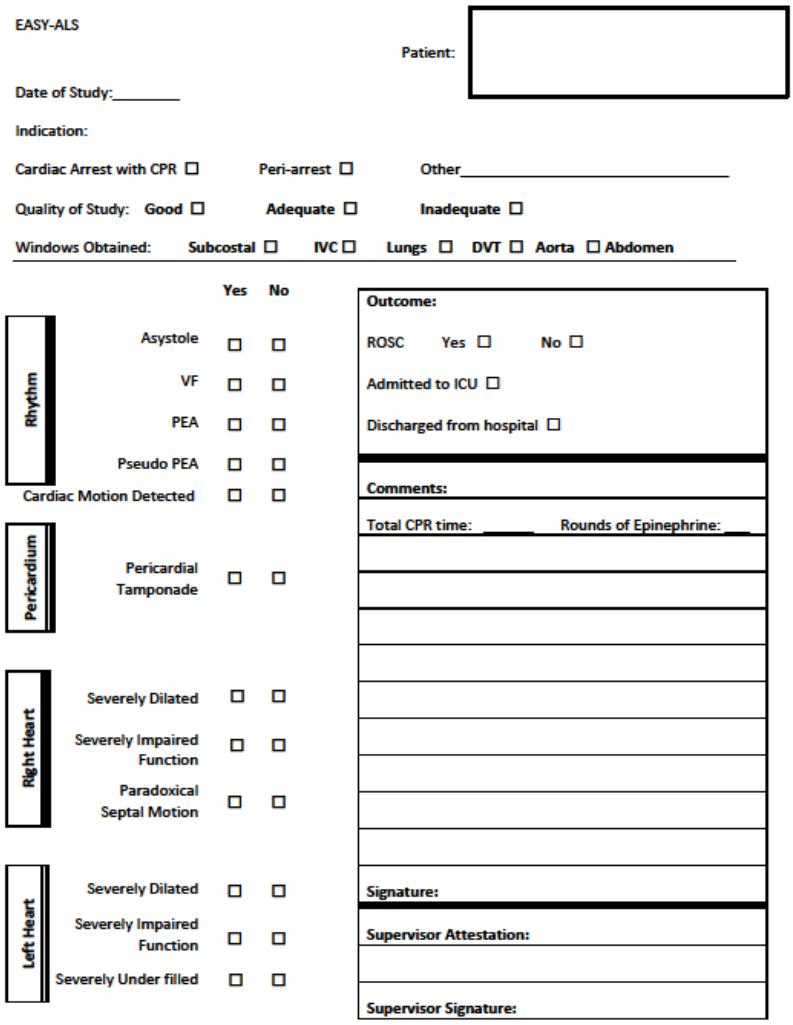
Reference(s):

1. Curr Opin Crit Care. 2010 Jun;16(3):211-5.
2. Circulation. 2010 Nov 2;122(18 Suppl 3):S729-67.
3. Resuscitation. 2010 Nov;81(11):1527-33.
4. Minerva Anestesiol. 2009 May;75(5):285-92.
5. Resuscitation. 2005 Oct;67(1):81-7.
6. Simul Healthc. 2015 Aug;10(4):193-9; quiz 199-201.

Table 1: Protocol for echocardiographic assessment using subcostal-only view in advanced life support (EASy-ALS Protocol)

Timing	Tasks
Prior to pulse/rhythm check	1. Wait until 2 minutes of chest compressions have been completed. 2. Remove barriers to ultrasound such as clothing or surgical dressing. 3. Place probe on patient to prepare to obtain subcostal 4-chamber view.
During pulse/rhythm check	4. Perform subcostal 4-chamber view and record images. • Do NOT delay resumption of chest compressions • Wipe ultrasound gel from skin
After pulse/rhythm check	5. Interpret recorded images. 6. Communicate findings to code leader. 7. Determine if patient would benefit from further FOCUS or lung ultrasound during subsequent pulse/ rhythm checks.

Figure 1: Standardized report completed after echocardiographic assessment using subcostal-only view in advanced life support (EASy-ALS) exam.



EASY-ALS

Patient:

Date of Study:_____

Indication:

Cardiac Arrest with CPR ☐ Peri-arrest ☐ Other_____

Quality of Study: Good ☐ Adequate ☐ Inadequate ☐

Windows Obtained: Subcostal ☐ IVC ☐ Lungs ☐ DVT ☐ Aorta ☐ Abdomen

		Yes	No
Rhythm	Asystole	☐	☐
	VF	☐	☐
	PEA	☐	☐
	Pseudo PEA	☐	☐
	Cardiac Motion Detected	☐	☐
Pericardium	Pericardial Tamponade	☐	☐
Right Heart	Severely Dilated	☐	☐
	Severely Impaired Function	☐	☐
	Paradoxical Septal Motion	☐	☐
Left Heart	Severely Dilated	☐	☐
	Severely Impaired Function	☐	☐
	Severely Under filled	☐	☐

Outcome:

ROSC Yes ☐ No ☐

Admitted to ICU ☐

Discharged from hospital ☐

Comments:

Total CPR time: _____ Rounds of Epinephrine: ___

Signature:

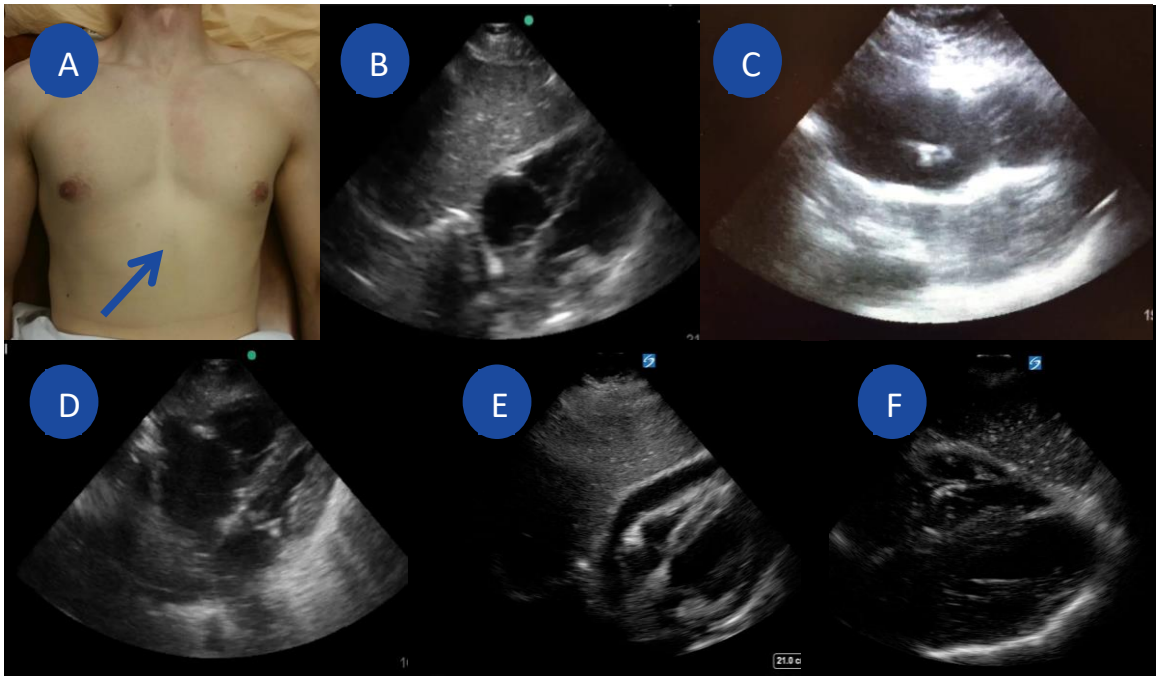
Supervisor Attestation:

Supervisor Signature:

Table 2: Results of focused cardiac ultrasound (FOCUS) evaluations

Case Number	Indication	Image Quality	Cardiac Motion	Assessment	ROSC Achieved
1	PEA	Adequate	Yes	Hypovolemia, pleural effusion	Yes
2	PEA	Adequate	Yes	Ruled-out cardiac causes of event	Yes
3	PEA	Good	Yes	Ruled-out cardiac causes of event	Yes
4	Asystole	Good	No	Cardiac standstill	No
5	Post-ROSC	Good	Yes	Ruled-out cardiac causes of event	Yes
6	Post-ROSC	Adequate	Yes	Biventricular dysfunction	Yes
7	Post-ROSC	Adequate	Yes	Ruled-out cardiac causes of event	Yes
8	Post-ROSC	Good	Yes	RV syndrome, pleural effusion	Yes
9	Asystole	Good	Yes	Hypovolemia	Yes
10	PEA	Good	Yes	Ruled-out cardiac causes of event	Yes
11	PEA	Good	Yes	Ruled-out cardiac causes of event	No
12	PEA	Good	Yes	Hypovolemia	Yes
13	Post-ROSC	Good	Yes	Pericardial effusion	Yes
14	Post-ROSC	Adequate	Yes	Ruled-out cardiac causes of event	Yes
15	Post-ROSC	Good	Yes	Ruled-out cardiac causes of event	Yes
16	PEA	Good	No	Cardiac standstill	No
17	Pre-Arrest	Good	Yes	RV syndrome	Not Applicable
18	PEA	Good	Yes	RV syndrome	Yes
19	Pre-Arrest	Good	Yes	SAM	Not Applicable
20	Pulseless ventricular tachycardia	Good	Yes	LV dysfunction	Yes
21	Pre-Arrest	Adequate	Yes	Ruled-out cardiac causes of event	Not Applicable
22	PEA	Good	Yes	Ruled-out cardiac causes of event	Yes
23	Pulseless ventricular tachycardia	Adequate	Yes	Ruled-out cardiac causes of event	No
24	PEA	Good	Yes	Ruled-out cardiac causes of event	No
25	Pre-Arrest	Good	Yes	Ruled-out cardiac causes of event	Not Applicable
26	PEA	Adequate	Yes	RV syndrome	Yes
27	PEA	Good	Yes	Hypovolemia	Yes
28	PEA	Good	Yes	RV syndrome	No
29	PEA	Good	Yes	Hypovolemia, ASD	Yes

Figure 2: Selection of resident-obtained subcostal echocardiogram images; (A) probe location (arrow), (B) normal heart, (C) clot in right atrium, (D) right ventricular syndrome, (E) pericardial effusion, (F) left ventricular failure



Critical Care-9 Association of Skeletal Muscle Mass and Quality with Long-Term Functional Outcomes in Survivors of Critical Illness

Kimberly Rengel[1], Jo Ellen Wilson[1], Heidi J Silver[2], Christopher Hughes[1], Brummel E Nathan[3]

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Introduction: Low muscle mass and density prior to hospitalization are associated with higher morbidity and mortality during critical illness. (1,2) Their association with long-term disability and physical function, however, is unclear. We hypothesized that lower pre-critical illness muscle mass and density would be associated with worse disability and physical function at 3 and 12 months after discharge.

Methods: We conducted a nested study within the BRAIN-ICU prospective cohort study of patients admitted to the medical or surgical intensive care unit (ICU) for respiratory failure and/or shock. We included only those patients who had abdominal CT imaging in the 6 months prior to admission and who survived and participated in follow-up assessments. We quantified the cross-sectional area of all skeletal muscle present in axial images at the L3 vertebrae using an automated version of Slice-O-Matic software (TomoVision, Magog, Quebec) and indexed this value by dividing by height (m2) to give the skeletal muscle mass index (SMI). We assessed muscle density based on Houndsfield units. At 3 and 12 months after hospital discharge, we assessed for functional disability in Basic Activities of Daily Living (BADLs) using the Katz ADL and Instrumental Activities of Daily Living (IADLs) using the Functional Activities Questionnaire (FAQ). We used multivariable regression to describe the association between skeletal muscle mass and density and functional outcomes, adjusting for baseline and in-hospital covariates including age, sex, baseline functional disability, and severity of illness.

Results: We included 133 patients who had abdominal CT imaging available for analysis and who participated in follow-up assessments. Patients were a median [IQR] of 56 [47-64] years old, 63 (47%) were female, median BMI was 29 [25-35], and 121 (91%) required mechanical ventilation. The SMI prior to ICU admission was 51.9 [42.3-64.9]. Using predetermined sex-specific cutoffs (3), 54 (40%) of patients met criteria for low muscle mass (Figure 1). At 3 and 12 months, baseline SMI was not associated with greater odds of new or worsened disability in BADLs (OR 1.0 [0.9-1.0] and 1.0 [0.9-1.0], respectively) or IADLs (OR 1.0 [0.9-1.0] and 1.0 [0.9-1.0], respectively). Similarly, muscle density was not associated with disability in BADLs (OR 1.0 [0.9-1.0] and 1.0 [0.9-1.1], respectively) or IADLs (OR 1.0 [0.9-1.0] and 1.0 [0.9-1.0], respectively).

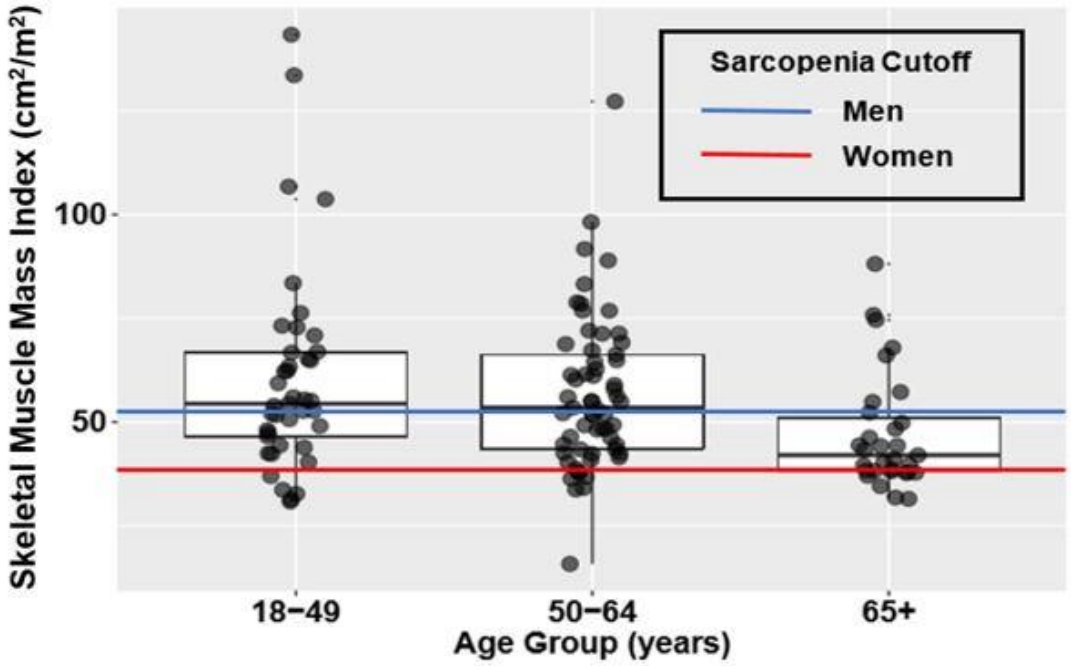
Conclusion: In this nested cohort of survivors of critical illness, low skeletal muscle mass was present in 40% of patients despite 95% of the cohort presenting with a normal BMI. We did not find an association between skeletal muscle mass or density and long-term disability or physical function. Larger cohort studies are needed to better characterize the role of skeletal muscle in long-term recovery after critical illness.

Reference(s):

1. JAMA Surgery 2013; 17: R206

2. Crit Care 2016; 20: 3863. Lancet Oncol 2008; 9: 629

Figure 1. Sarcopenia in Critical Illness



Critical Care-10 Risk Factors and Complications associated with Post-lung Transplantation Vocal Cord Paralysis

Natan Hekmatjah[1], Mariana Gomez[2], Michael Zargari[3], Varina R Clark[4], Ashwini Y Prasad[1], Sumit Singh[1]

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Introduction: Lung transplantation (LTx) has improved the quality of life and longevity of patients with end-stage lung diseases, including cystic fibrosis, interstitial lung disease, and pulmonary hypertension. These patients are particularly vulnerable to increased morbidity and mortality due to complications such as vocal cord paralysis (VCP), a result of recurrent laryngeal nerve injury. Although often overlooked postoperatively, VCP may present clinically as hoarseness of voice or impaired cough reflexes, often leading to aspiration pneumonia.[1] Despite a doubling of LTx in the past 15 years,[2] the risk factors associated with VCP in the setting of LTx are understudied. In this study, we assessed the risk factors and complications associated with VCP in unilateral and bilateral LTx recipients who developed dysphonia.

Methods: A retrospective chart review was conducted on patients who underwent unilateral or bilateral LTx between May 2013 and June 2018. Participants were identified as adult patients (≥18 years old) who presented to the ICU and subsequently developed hoarseness of voice post-LTx. Patients with a history of stroke, paralysis, and current state of coma were excluded from the study. Patients who met criteria and presented with dysphonia were referred to speech pathology for assessment of voice quality, impaired cough reflex, and VCP. Outcome variables measured included aspiration pneumonia, pneumonia, incidence of reintubation, length of intubation, incidence of arrhythmias (atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, and ventricular fibrillation), vocal cord paralysis, and incidence of vocal cord injections. Values are frequency (%) or mean (SD) and compared between groups using the chi-squared test or t-test.

Results: We screened 142 patients that underwent a unilateral or bilateral LTx, of which 141 were included for analysis. Of those patients, 87 (62%) were diagnosed with VCP. Bilateral LTx had VCP incidence of 65.7%, left LTx 56.0%, and right LTx of 47.1% ($p<0.281$) (Table 1). Outcomes comparing VCP vs. no VCP found that those with VCP had an increased incidence of aspiration pneumonia (11.5% vs 3.7%; $p<0.107$) and pneumonia (33.3% vs 20.4%; $p<0.097$). Patients without VCP had a higher reintubation rate vs those with VCP (16.7% vs 8.0%; $p<0.117$). Incidence of arrhythmias (Afib, SVT, Vtach, and Vfib) were higher in the VCP group vs no-VCP (32.2% vs 22.2%; $p<0.202$). Subgroup analysis found no statistical significance between VCP and atrial fibrillation. However, when comparing bilateral vs left vs right LTx patients separately, we found a statistically significant reduction of atrial fibrillation (18.2% vs 44.0% vs 47.1%; $p<0.004$). In sum, our results demonstrate trends in adverse outcomes in our patients who developed VCP after LTx, despite not reaching statistical significance.

Conclusion: Preliminary data analysis shows an increased incidence of VCP in bilateral vs unilateral LTx recipients. Such a higher rate may be expected, as surgical manipulation within bilateral thoracic compartments predisposes the patient to mechanical recurrent laryngeal injury. The increased diameter of a double-lumen tube, utilized for LTx, can be a significant risk factor contributing to laryngeal nerve injury as a result of compressive trauma. Additionally, our data demonstrates a higher incidence of VCP in left vs right LTx patients. While not certain, a possible reason for this finding is most likely due to a higher probability of mechanical injury from surgical manipulation given the long thoracic course of the left recurrent laryngeal nerve. Patients with VCP were at higher risk of aspiration pneumonia, which may in part be due to isolated VCP or a combination of VCP and impaired reflexes. Despite the fact that the exact mechanism is unknown, we found a significant reduction in atrial fibrillation in bilateral vs. unilateral lung transplant patients. Although there were no significant differences in outcomes in patients with vs without VCP, the lack of significance can, in part, be attributed to a limited sample size. VCP in patients undergoing LTx is associated with increased morbidity and mortality. Routine and comprehensive postoperative evaluation of VCP, especially in the presence of associated clinical symptoms such as dysphonia, may allow for timely treatment and decreased perioperative morbidity.

Reference(s):

1. Meszarich Z, Patel N, Reed A, et al. Incidence of Vocal Cord Palsy and Aspiration Status in the Lung Transplant Population A Multi-Centre Study on the Effects of Iyengar Yoga on Health Related Quality of Life in Patients with Pulmonary Arterial Hypertension Lung Transplantation Does Not Impact on Daily Physical Activity Despite Substantial Improvements in Respiratory Function and Exercise Capacity. Vol 35.; 2016. doi:10.1016/j.healun.2016.01.138
2. National Data - OPTN. https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#. Accessed December 18, 2019.

Table 1: Incidence of Vocal Cord Paralysis by Lung Transplantation Type

Right (n= 17)	**Left** (n= 25)	**Bilateral** (n= 99)
8 (47.1%)	14 (56.0%)	65 (65.7%)

Critical Care-11 The Role of Extracorporeal Membrane Oxygenation in Lung Transplantation: a Single Institution Retrospective Review

Lida Shaygan[1], Jayanta Mukherji[2]

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Introduction: Extracorporeal membrane oxygenation (ECMO) is a closed circuit that provides days to weeks of cardiopulmonary and/or pulmonary support in critically ill patients with severe respiratory and/or cardiac failure (unresponsive to conventional treatment). (1) Based on the UNOS database from 2005 to 2011, prior to lung transplantation roughly 1% of critically ill patients required ECMO support as a bridge to lung transplantation. (2) The numbers have continued to grow since then as an increasing number of single-center studies have demonstrated the utility and successful outcomes associated with ECMO as a bridging strategy to lung transplantation. (3) However, few studies have examined the indications, impact, and related outcomes of ECMO pre-lung transplant, during lung transplant, and post-lung transplant. (3,4,5)

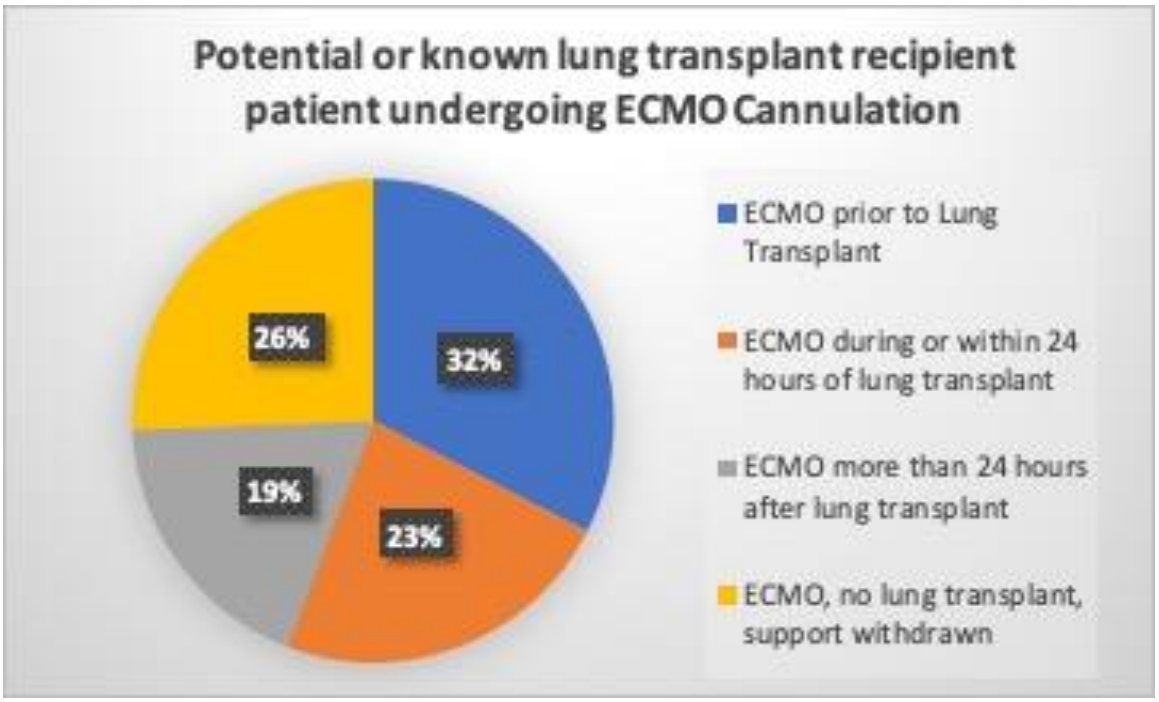
Methods: We performed a retrospective chart review of 43 patients who received ECMO support prior to lung transplant, during or after lung transplant, or as a bridge to lung transplantation and deceased. Patients were selected over 7 years (from 2013 to 2019) at Loyola University Medical Center and were divided into 4 groups: ECMO prior to lung transplantation, ECMO within 24 hours of lung transplantation, ECMO more than 24 hours after lung transplantation, and ECMO as a bridge to lung transplantation (with no lung transplantation) and support withdrawn. Exclusion criteria included patients who receive ECMO cannulation, but without an indication for a lung transplant. Patient age ranged from 15 to 70 years. Outcome variables examined in the retrospective review for all groups included patient demographics, medical history, co-morbidities, mortality rate, type of ECMO, whether conversion from VV to VA ECMO was performed, the duration of ECMO, and whether the patient was extubated on ECMO. In patients who received ECMO cannulation prior to lung transplantation, we looked at the number of days on ECMO prior to lung transplantation. In patients who received a lung transplant, we looked at 30 day survival, indications for the lung transplant, single versus bilateral lung transplant, whether intraoperative cardiopulmonary bypass was used (planned versus unanticipated), ventilation requirements prior to lung transplant, and ECMO complications. In patients who received ECMO cannulation as a bridge to lung transplantation and then had support withdrawn, we looked at the number of days on ECMO prior to patient deceased. Statistical analysis of our data was performed using the software of research data capture (REDCap).

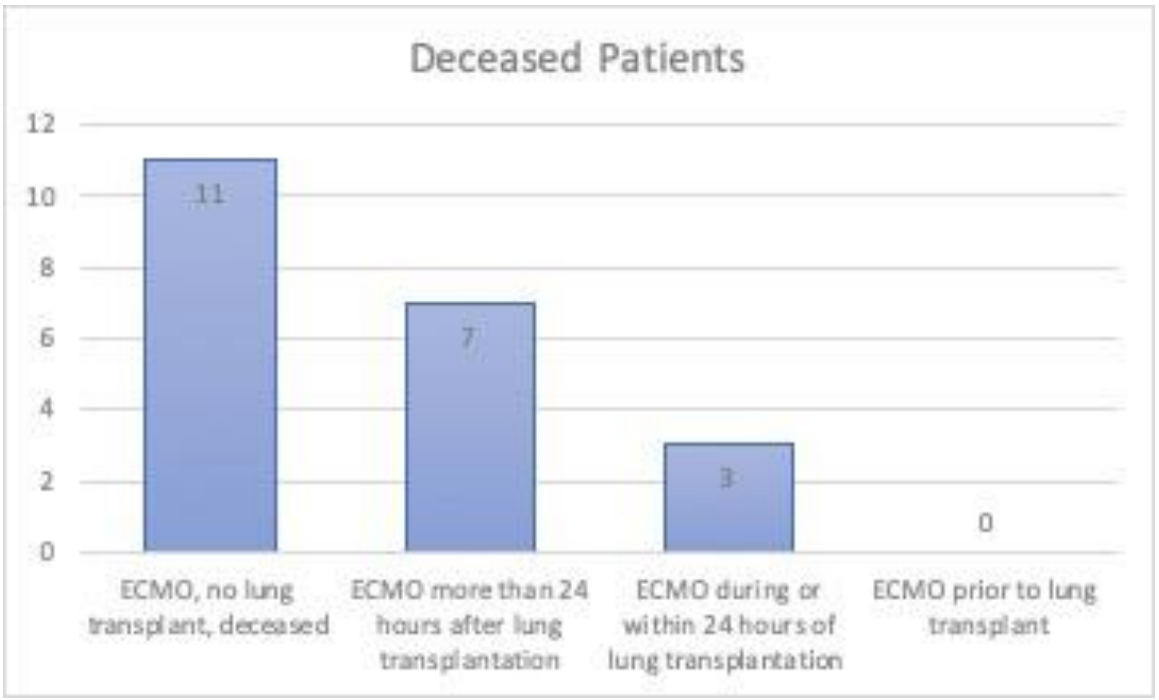
Results: Of the 43 patients in our study population, 33% (14 of 43 patients) received ECMO prior to lung transplantation, 23% (10 of 43 patients) had ECMO cannulation during or within 24 hours of lung transplant, 19% (8 of 43 patients) received ECMO more than 24 hours after lung transplantation, and 26% (11 of 43 patients) received ECMO and then support was withdrawn with no lung transplantation (Chart 1). The combined mortality rate for the 43 patients studied was 49% (21/43). Of the total 21 deceased patients, 52% (11/21) were on ECMO as bridge to transplant and never received transplant, 33% (7/21) received ECMO cannulation more than 24 hours after lung transplantation, 14% (3/21) received ECMO cannulation during or within 24 hours of lung transplantation, and no patients were deceased in the population that received ECMO prior to lung transplantation (Chart 2). In addition, the mortality rate from all groups decreased from the year 2014 (100%) to the year 2019 (42%).

Conclusion: Preliminary analysis of our data reveals that ECMO cannulation prior to lung transplantion leads to the lowest post-transplant mortality rate in our study population. Survival rates in patients, who receive ECMO cannulation during or within the first 24 hours after a lung transplantation, are much higher than in patients who undergo ECMO cannulation more than 24 hours after a lung transplant. The overall decrease in mortality rate from 2013 to 2019 may be correlated to the increase in the number of ECMO cannulations pre-lung transplantation, improvements in critical care team experience, or surgeon experience in managing ECMO patients. While our preliminary data reveals key findings from a retrospective review at one institution, further statistical analysis must be completed to confirm the significance of variables examined as predictors of adverse outcomes and survival in potential and/or known lung transplant recipients undergoing ECMO cannulation.

Reference(s):

1. Squiers JJ, Lima B, DiMaio JM. Contemporary extracorporeal membrane oxygenation therapy in adults: Fundamental principles and systematic review of the evidence. J ThoracCardiovasc Surg. 2016;152:20-32.
2. George TJ, Beaty CA, Kilic A, et al. Outcomes and temporal trends among high-risk patients after lung transplantation in the United States. J Heart Lung Transplant 2012;31:1182-91.
3. Gulack BC, Hirji SA, Hartwig MG. Bridge to lung transplantation and rescue post-transplant: the expanding role of extracorporeal membrane oxygenation. J Thorac Dis. 2014;6(8):1070-9.
4. Boffini M, Simonato E, Ricci D, et al. Extracorporeal membrane oxygenation after lung transplantation: risk factors and outcomes analysis. Ann Cardiothorac Surg. 2019;8(1):54–61.
5. Mulvihill, Michael S., et al. “Extracorporeal Membrane Oxygenation Following Lung Transplantation: Indications and Survival.” The Journal of Heart and Lung Transplantation, vol. 37, no. 2, 2018, pp. 259-267


Potential or known lung transplant recipient patient undergoing ECMO Cannulation
26%
32%
19%
23%
ECMO prior to Lung Transplant
ECMO during or within 24 hours of lung transplant
ECMO more than 24 hours after lung transplant
ECMO, no lung transplant, support withdrawn


Deceased Patients
12
10
8
6
4
2
0
11
7
3
0
ECMO, no lung transplant, deceased
ECMO more than 24 hours after lung transplantation
ECMO during or within 24 hours of lung transplantation
ECMO prior to lung transplant

Critical Care-12 When intensivists pay heed to patient wills: impact on mortality and economics

Hendrik Booke[1], Rolf D Nordmeier[2]

[1]Kliniken des MTK, Frankfurt, Germany, [2]Main Taunus Kliniken GmbH Bad Soden, Bad Soden, Hessen

Introduction: More and more patients have a written patient's decree to make sure that doctors follow their end-of-life decisions even in cases of unconsciousness or inability to enforce their final will personally. We investigated, why patients died on an 18-bed Intensive Care Unit (ICU) in a teaching hospital of the Johann Wolfgang Goethe University of Frankfurt.

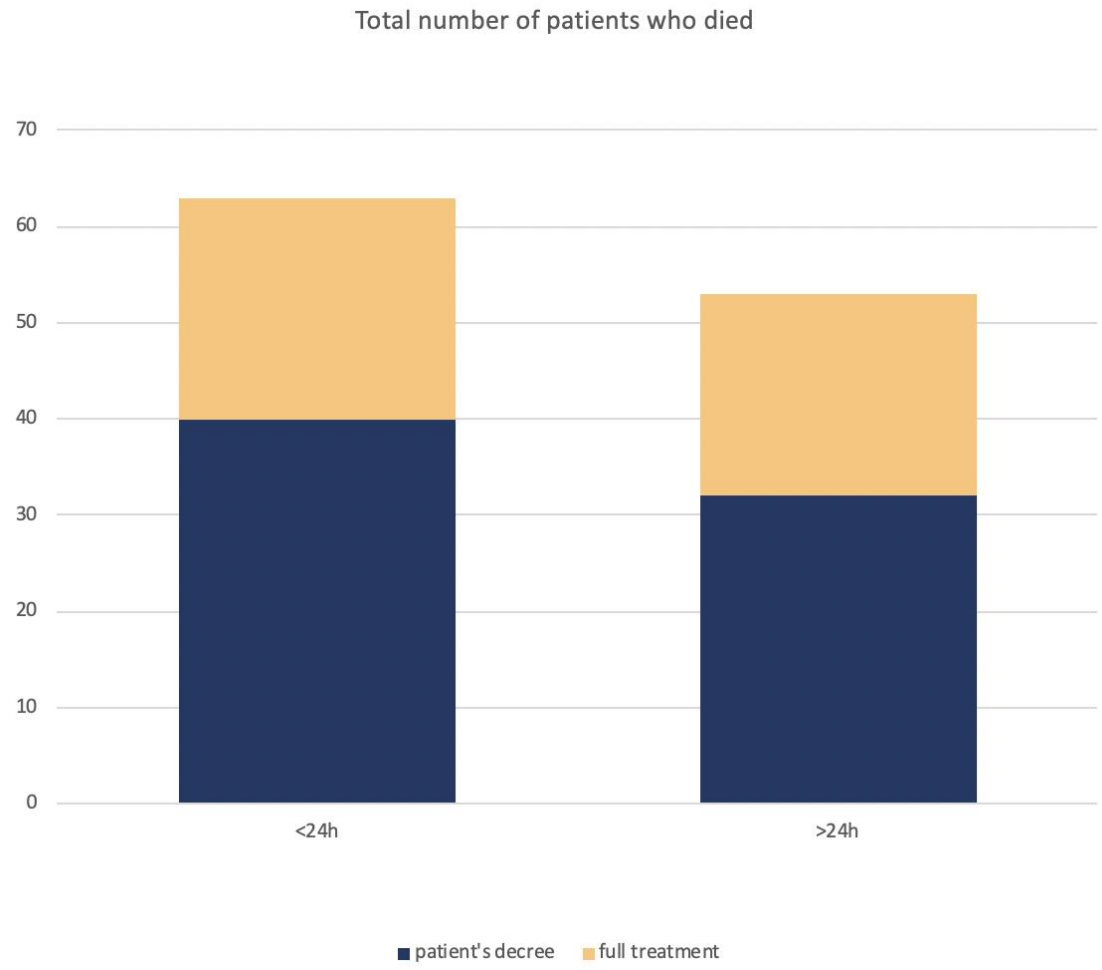
Methods: We included all patients admitted to the ICU in 2018. The patients were then divided into two groups depending on whether they stayed on the ICU for more than 24 hours or less than 24 hours.

Results: A total of 801 patients were admitted to the ICU, from whom 116 died (mortality rate 14,5 %). Out of these 116 patients, 72 died based upon a patient's decree or when relatives assumed that full treatment was not wished by the patient. 44 patients died despite full treatment (mortality rate 5,5 %). Out of 63 patients who deceased within 24 hours after being admitted to the ICU, in 63,5% (40 out of 63 patients, Fig. 1) therapy was withheld because of a written patient's decree. 53 of those 116 patients who have died, had been on the ICU for more than 24h. In 60,3% of these patients therapy was terminated because of a patient's decree. They passed away after an average of 8,2 days on ICU.

Conclusion: Our overall mortality rate of 14,5% is in line with the mortality rate reported by Galloways Meta-Analysis published in 2018: 18,2% of 902,551 patients (1). Just a decade ago, mortality on ICU was primarily associated with the degree and severity of (multi) organ failure and the quality of the consecutive therapeutic regimen. Nowadays, more and more patients or their relatives present written patient's wills, limiting doctors in their ability to treat the underlying disease. As a result, more than two thirds of our patients died based upon a patient's decree, which, according to German law, is mandatory to be heeded by. Consecutively, the mortality rate is on the increase (14,5% versus 5,5%). Our data, showing that nearly two thirds of our ICU-patients refuse (ongoing) therapy, support the idea of the Improving Palliative Care in the ICU (IPAL-ICU) Advisory Board to increase the involvement of palliative care specialists for critically ill patients on ICU (2). Further, while ICU beds are rare, this resource is wasted when costly treatment is initiated in patients, who in the end refuse to be treated. ICU-beds are one of the most expensive resource in every hospital, especially on the day of admission (day 1), when new therapies are initiated in emergency cases. Reimbursement of cases staying only one or two days on ICU is inadequate, since the high costs are not adequately refunded. Subsequently, patients admitted to ICU despite an existing patient's decree, which is not on file right away, is an economic and ethical burden. We therefore suggest, that case managers have the patient's decree scanned before a patient is admitted to ICU or the Medical Emergency Team is called for. This would help to utilize our costly staff, equipment and knowledge for patients who really need it and want to be treated, leading to a significant improvement of ICU-efficiency and ICU-economics.

Reference(s):

1. The effect of ICU out-of-hours admission on mortality: a systematic review and Meta-Analysis. Crit Care Med 2018, 46: 290-299
2. Choosing and using screening criteria for palliative care consultation in the ICU: a report from the Improving Palliative Cae in the ICU (IPAL-ICU) Advisory Board. Crit Care Med 2013, 41: 2318-2327


Total number of patients who died
70
60
50
40
30
20
10
0
<24h
>24h
patient's decree
full treatment

Critical Care-13 Risk Factors for Increased Opioid Use in the Intensive Care Unit after Surgery

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[1]Duke University, Durham, NC, [2]University of Michigan, Ann Arbor, MI, [3]University of Michigan Health System, Ann Arbor, Michigan

Introduction: With improved survival from the intensive care unit (ICU) (1), many patients are being discharged with impaired quality of life, and 30% have chronic pain attributed to the ICU stay (2). However, no studies to our knowledge have identified risk factors for increased opioid use during the ICU course. The purpose of this study is to describe the use of opioids during an ICU course after surgery and identify risk factors of increased opioid use.

Methods: Data for this single center prospective observational cohort was collected between 2012 and 2017 for the Michigan Genomics Initiative (MGI). Inclusion criteria were: 1) Adults (age > 18 years), 2) Had a procedure done at a University of Michigan site, 3) Experienced an ICU admission within 24 hours after surgery. Exclusion criteria were: 1) Language barrier, 2) Cognitive impairment, 3) Current pregnancy, or 4) Death during the ICU course. The database included baseline sociodemographic, pain, mental and physical health characteristics from a questionnaire completed prior to surgery. Moderate anxiety and depression were defined as scores ≥8 on PROMIS and HADS questionnaires. Preoperative opioid use and oral morphine equivalents (OME) administered in the ICU were collected from the electronic medical record. The primary outcome variable was average daily OME use in the ICU. Univariable and multivariable linear regressions were performed to examine associations of baseline risk factors with average daily OME in the ICU. Statistical analysis was conducted with SPSS.

Results: A total of 2135 participants were included. Mean (SD) age was 56 (15.2) years, 1097 (51%) were male, and 1023 (48%) were ASA Class III. The mean (SD) ICU length of stay was 2.5 (3.6) days. The most common type of surgery was neurosurgical followed by cardiac and abdominal surgery. Preoperative opioid use was noted in 25% of patients, and 26% and 47% had preoperative depression and anxiety, respectively. During the ICU stay, average OME use per day was 56 mg, and 66% of participants received opioids each ICU day (Graph 1). Some of the strongest univariate predictors of increased opioid use in the ICU were pre-surgery self-reported current tobacco use (B=29.6, 95% CI 18.1-41.1, p<0.001), current/past alcohol use (B=14.1, 95% CI 2.7-25.4, p=0.015), and current/past illicit drug use (B=29.5, 95% CI 12.6-46.5, p=0.001). Other significant univariate associations with increased ICU opioid use were preoperative opioid use, major surgery, lower age, increased anesthesia duration, depression, low life satisfaction, overall pain, and centralized pain (Table 1). By multivariable linear regression, preoperative opioid use, major surgery, age, and anesthesia duration remained significantly associated with opioid use in the ICU (Table 2).

Conclusion: Patient factors such as pre-existing tobacco use, substance use, opioid use, and depression could help predict, in addition to surgical factors, those who will be most at risk for increased opioid use in the intensive care unit.

Reference(s):

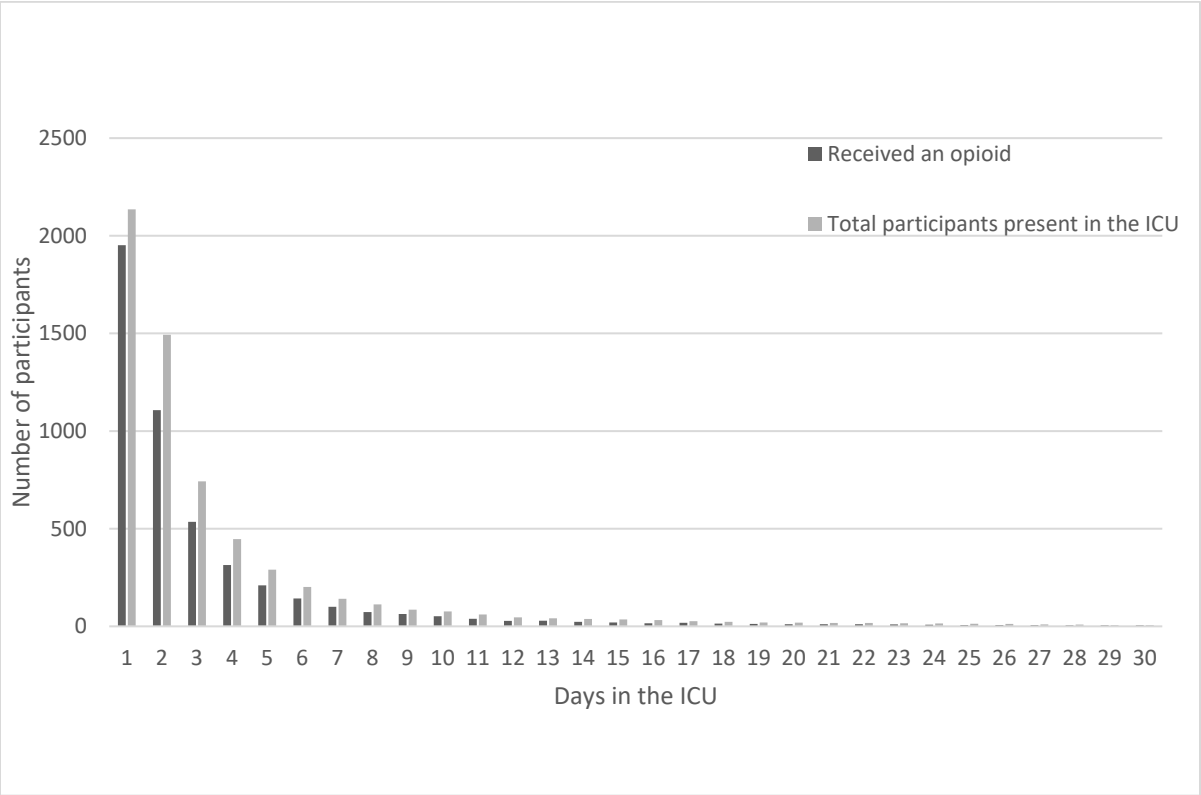
1. Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. Critical care. Apr 27 2013;17(2):R81.
2. Baumbach P, Gotz T, Gunther A, Weiss T, Meissner W. Prevalence and Characteristics of Chronic Intensive Care-Related Pain: The Role of Severe Sepsis and Septic Shock. Critical care medicine. Jun 2016;44(6):1129-1137.

	n (%) unless otherwise noted N=2135	Coefficient	p-value	95% Confidence Interval		R^2
Male sex	1097 (51.4)	1.46	0.74	-7.18	10.10	0.007
Age in years (standard deviation)	56.44 (15.22)	-0.99	**<0.001**	-1.27	-0.71	-0.15
Race						
Caucasian *(reference)*	1966 (92.1)					
African American	98 (4.6)	0.001	1.00	-20.64	20.65	0.001
Other	71 (3.3)	-18.42	0.13	-42.51	5.68	-0.03
Insurance						
Medicaid / Medicare *(reference)*	740 (34.7)					
Private or other	948 (44.4)	1.41	0.78	-8.37	11.19	-0.01
Uninsured or unknown	740 (34.7)	11.00	0.07	-0.94	22.94	0.04
WHO Obesity Class*						
Class 1 BMI <18.5 (*reference)*	27 (1.3)					
Class 2 BMI 18.5-24.9	413 (19.3)	-31.60	0.14	-73.42	10.22	-0.03
Class 3 BMI 25.0-29.9	591 (27.7)	-20.30	0.34	-61.73	21.14	0.03
Class 4 BMI 30.0-34.9	441 (20.7)	-29.40	0.17	-71.14	12.34	-0.02
Class 5 BMI 35.0-39.9	213 (10.0)	-22.04	0.32	-55.05	20.97	0.01
Class 6 BMI >40.0	175 (8.2)	-28.55	-0.20	-72.08	14.98	-0.009
ASA Classification*						
ASA I *(reference)*	23 (1.1)					
ASA II	525 (24.6)	-5.71	0.80	-50.15	38.73	0.07
ASA III	1023 (47.9)	-19.45	0.39	-63.44	24.53	-0.03
ASA IV	324 (15.2)	-28.51	0.21	-73.52	16.51	-0.05
Major Surgery*	1602 (75.04)	26.84	**<0.001**	13.74	39.94	0.09
Surgical Service*						
Neurosurgical *(reference)*	616 (28.85)					
Cardiac surgery	349 (16.35)	-7.00	0.31	-20.42	6.41	-0.07
Abdominal/Colorectal	262 (12.27)	-9.42	0.21	-24.19	5.35	-0.07
Otolaryngology/Oral Maxillofacial	214 (10.02)	41.84	**<0.001**	25.95	57.73	0.11
Spine Surgery	175 (8.20)	91.88	**<0.001**	74.73	109.03	0.25
Plastic surgery	73 (3.42)	-9.80	0.44	-34.58	14.99	-0.04
Thoracic	47 (2.20)	3.23	0.83	-27.07	33.54	-0.008
Other	165 (7.73)	-16.34	0.07	-33.90	1.21	-0.07
ICU length of stay in days (Standard deviation)	2.51 (3.63)	1.11	0.07	-0.08	2.30	0.04
Anesthesia Duration in minutes (Standard deviation)	432.72 (180.93)	0.09	**<0.001**	0.06	0.11	0.14
Tobacco						
Never *(reference)*	863 (40.4)					
Current	463 (21.7)	29.60	**<0.001**	18.14	41.06	0.12
Former	789 (37.0)	0.04	0.99	-9.76	9.840	-0.05
Current or past Alcohol use¥	1234 (57.8)	14.07	**0.015**	2.73	25.40	0.06
Current or past Illicit Drug Use	147 (6.9)	29.53	**0.001**	12.59	46.46	0.08
Preoperative opioid use	537 (25.2)	55.35	**<0.001**	45.25	65.44	0.24

Preoperative Survey questionnaire						
Moderate Anxiety[¥]	790 (37.0)	9.62	0.067	-0.66	19.89	0.05
Moderate Depression[¥]	427 (20.0)	25.84	**<0.001**	14.09	37.58	0.11
Life Satisfaction Scale[¥] (0 least to 10 most satisfied)	6.64 (2.68)	-2.98	**0.002**	-4.86	-1.11	-0.08
Fibromayalgia Survey Score[¥] (range 0-28)	6.04 (4.76)	2.81	**<0.001**	1.75	3.88	0.13
Brief Pain Inventory[§] (average of two overall body pain items, 0 no pain to 10 worst pain)	3.02 (2.96)	8.31	**<0.001**	6.70	9.92	0.23
Pain Detect Neuropathic Pain Scale[¤] (range -1 to 34)	6.50 (7.50)	1.75	**<0.001**	1.24	2.26	0.20

Bold test denotes statistical significance of at least p < 0.05
**10-15% of data missing*
[§]15-20% of data missing
[¥] 20-25% of data missing
[¤]45-50% of data missing

Table 1: Univariate associations of sociodemographic and surgical factors with increased average daily oral morphine equivalent use in the intensive care unit. The r-squared for each predictor is also displayed.



Graph 1: Opioid administration over time in the ICU. Dark grey bars indicate number of participants who received an opioid. Light grey bars indicate the total number of participants in the ICU.

	Coefficient	p-value	95.0% Confidence		R^2
Age	-0.412	**0.030**	-0.78	-0.04	-0.08
Major Surgery*	18.94	**0.014**	3.90	33.98	0.15
Current smoker (vs never)	13.77	0.064	-0.80	28.34	0.15
Former smoker (vs never)	7.02	0.28	-5.69	19.72	-0.05
Alcohol use¥	4.63	0.46	-7.62	16.875	0.06
History of Illicit drug use	2.01	0.85	-19.14	23.15	0.06
Anesthesia Duration	0.043	**0.006**	0.013	0.074	0.17
Preoperative opioid use	20.17	**0.005**	6.12	34.22	0.19
Moderate Depression¥	5.03	0.50	-9.63	19.70	0.12
Moderate Anxiety¥	4.31	0.49	-7.90	16.52	0.10
Life Satisfaction Scale¥	-0.55	0.62	-2.76	1.65	-0.10
Fibromayalgia Survey Score¥	-0.78	0.37	-2.48	0.92	0.10
Brief Pain Inventory§	2.46	0.077	-2.534	5.18	0.15
Pain Detect Neuropathic Pain Scale¤	0.004	0.99	-0.97	0.97	0.12

Bold test denotes statistical significance of at least p < 0.05
**10-15% of data missing*
§*15-20% of data missing*
¥ *20-25% of data missing*
¤*45-50% of data missing*

Table 2: Multivariate associations of sociodemographic and surgical factors with increased average daily oral morphine equivalent use in the intensive care unit. The r-squared for each predictor is also displayed.

Critical Care-14 Selective nanoparticle-mediated targeting of renal tubular TLR9 attenuates ischemic acute kidney injury in mice

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Introduction: Acute kidney injury (AKI) continues to be a major clinical problem with health care costs of more than $10 billion per year in the US (1). AKI due to renal ischemia and reperfusion (IR) is a major cause of clinical AKI (2). Unfortunately, there is no effective preventive therapy for AKI (2,3). We previously showed that deletion of renal proximal tubular TLR9 protects against renal IR injury in mice demonstrating a critical role for renal proximal tubular TLR9 in generating ischemic AKI (4). However, global delivery of TLR9 antagonist will target renal as well as extrarenal cells and may have non-specific effects and systemic side effects. One way to circumvent the confounding effects of multiple organ targeting of drugs and less-than-effective dosing problems is to devise a strategy to selectively deliver or concentrate drugs in the kidney by renal-specific delivery methods. Utilizing mesoscale nanoparticle (MNP) technology, we developed an innovative and effective therapy for ischemic AKI by selective kidney-targeted delivery of specific TLR9 antagonist in mice subjected to renal IR injury.

Methods: Herein, we used ~300-400 nm polymer-based mesoscale nanoparticles (MNP) that localize to the renal tubules with >30-fold kidney selectivity after intravenous injection over other organs (liver, heart, lung and spleen, Figure A) (5,6). In our previous studies, we determined that peak MNP delivery to the kidney occurs 3-6 hr after intravenous injection (5,6). After Columbia University Institutional Animal Care and Use Committee approval, C57BL/6 mice weighing 20-25g were subjected to sham surgery or to 30 min renal ischemia and 24 hr reperfusion. Some mice received intravenous MNPs encapsulating control oligodeoxynucleotides (ODN) or MNPs encapsulating 3.25 or 6.5 μg/kg ODN2088 (a selective TLR9 antagonist) 6 hr before renal ischemia. To test the renal protective effects of delivering MNP ODN2088 after renal ischemia, separate cohorts of mice were injected with 6.5 μg/kg MNP-ODN2088 at the time of reperfusion or 1.5 hr after reperfusion. Some mice received 5 mg/kg ODN2088 without MNP (naked ODN2088) 6 hr before renal ischemia to test the effects of global TLR9 antagonism against ischemic AKI. Data were analyzed with Student's t-test, one-way ANOVA plus Tukey's post hoc multiple comparison test or Mann–Whitney nonparametric U test to analyze renal injury scores. All data are expressed as means ± SEM.

Results: Mice treated with 3.25-6.5 μg/kg MNP-encapsulated TLR9 antagonist ODN2088 either 6 hr before renal ischemia, at the time of reperfusion or 1.5 hr after reperfusion were protected against ischemic AKI (Figure B). However, 5 mg/kg naked ODN2088 failed to protect against ischemic AKI. ODN2088-encapsulated MNP attenuated renal tubular necrosis (Renal injury score of 3.5±0.13, N=6 for MNP encapsulating control ODN vs. 1.5±0.22, N=6 for MNP encapsulating 6.5 μg/kg ODN2088 given 6 hr before renal ischemia and 1.75±0.11, N=6 for MNP encapsulating 6.5 μg/kg ODN2088 given 1.5 hr after reperfusion, $P<0.05$), inflammation (decreased synthesis of pro-inflammatory cytokines KC, IL-6, MCP-1, MIP-2 and TNF-α) and apoptosis (decreased DNA fragmentation, caspase 3 and caspase 8 activation) when compared to negative control ODN MNP treated mice.

Conclusion: Taken together, we demonstrate in this study a novel and innovative method to treat ischemic AKI using MNPs. We show that selective renal tubular delivery of TLR9 antagonist via MNP protects against ischemic AKI in mice. In contrast, systemic administration of ~1000-fold higher dose of naked ODN2088 failed to protect against ischemic AKI. Our study suggests that kidney targeted MNP-mediated selective drug delivery is an exciting method to treat AKI with improved therapeutic specificity and potentially reduced systemic toxicity by allowing lower drug dosage and reduced systemic side effects.

Reference(s):

1. J Am Soc Nephrol 2005; 16: 3365-3370.
2. Anesthesiology 2015; 123: 1301-1311.
3. Br J Anaesth 2015; 114: 919-926.
4. J Immunol 2018; 201(3):1073-1085
5. Hypertension 2018; 71: 87-94.
6. Kidney Int 2016; 90: 740-745

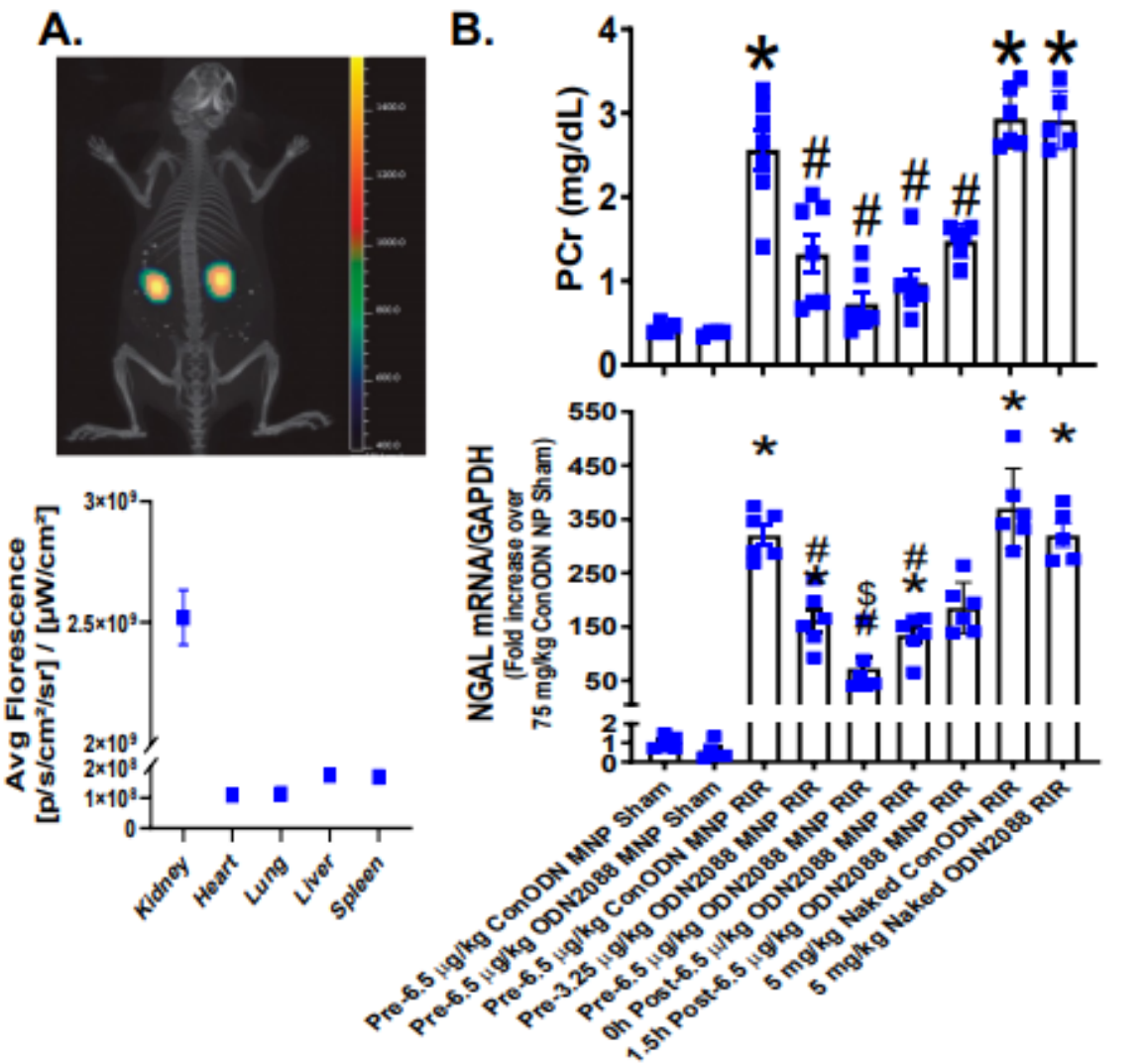

Figure. Mesoscale nanoparticle (MNP) encapsulated ODN-2088 selectively localizes to kidneys and attenuates ischemic renal IR (RIR) injury. A. In vivo biodistribution of MNPs. (top) Fluorescence plus CT transaxial section of a mouse treated with Flororescent MNPs showing bright fluorescence throughout the kidneys. (bottom) Quantification of fluorescence efficiency in each organ demonstrating ~30-fold selective delivery of MNP to the kidneys compared to other organs (N=3). Data are background subtracted and represent mean ± SEM. **B**. C57BL/6 mice were injected with control MNP-ODN or with ODN2088 encapsulated in MNPs (MNP-ODN2088) and subjected to sham-surgery (N=3) or to 30 min renal ischemia and 24 hr reperfusion (IR, N=4-7). Some mice were injected with MNP-ODN2088 6 hr before renal ischemia. A separate cohort of mice was injected with MNP-ODN2088 at the time of reperfusion or 1.5 hr after reperfusion. MNP-ODN-2088 treatment given before or after renal ischemia protected against RIR injury evaluated by plasma creatinine and neutrophil gelatinase-associated lipocalin (NGAL) mRNA. *P<0.05 vs. control MNP injected mice subjected to sham surgery. #P<0.05 vs. control ODN mice subjected to renal IR. Error bars represent 1 SEM.

Critical Care-15 Machine learning in the septic surgical patient: a systematic review of postoperative sepsis diagnosis and prediction machine learning algorithms

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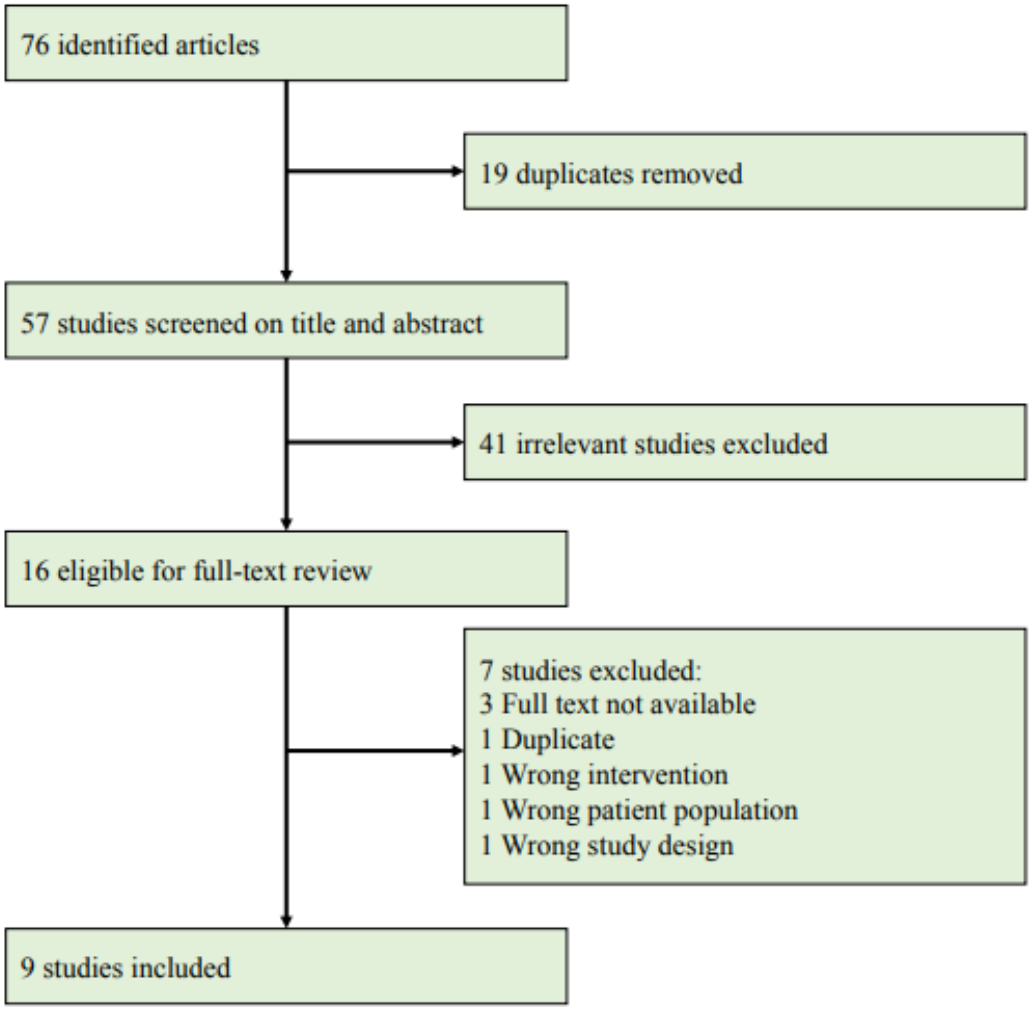
Introduction: Sepsis is one of the leading causes of morbidity and mortality in surgical patients with estimated mortality rates for sepsis and septic shock of 5.4% and 33.7%, respectively. Early diagnosis and treatment of sepsis with appropriate antibiotic coverage and source control is critical to improving outcomes and reducing end-organ damage. Unfortunately, sepsis has a wide range of clinical presentations and nonspecific signs and symptoms, making the early diagnosis of sepsis and detection of sepsis progression challenging. SIRS (systemic inflammatory response syndrome) and qSOFA (quick sepsis-related organ failure assessment) scores have poor sensitivity for diagnosing organ dysfunction, ranging 39-88% and 10-54%, respectively, in a 2018 review (Serafilm, Chest 2018). Early evidence suggests that machine learning can improve perioperative medicine and management of high-risk surgical patients through development of algorithms capable of identifying septic surgical patients prior to clinical decompensation. The aim of this systematic review is to evaluate the performance of machine learning models for perioperative sepsis, severe sepsis and septic shock.

Methods: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for Diagnostic Test Accuracy Studies extension statement (McInnes, JAMA 2018). PubMed, MEDLINE and Embase databases were broadly searched for English-language literature until October 1, 2019. Studies meeting all eligibility criteria were included in the qualitative and quantitative data analyses. Data extracted from eligible studies included study population, sample size, sepsis definition, predicted outcomes (sepsis, severe sepsis or septic shock), machine learning model type, validation method, input features and model performance (AUROC, sensitivity, specificity, accuracy and contingency tables).

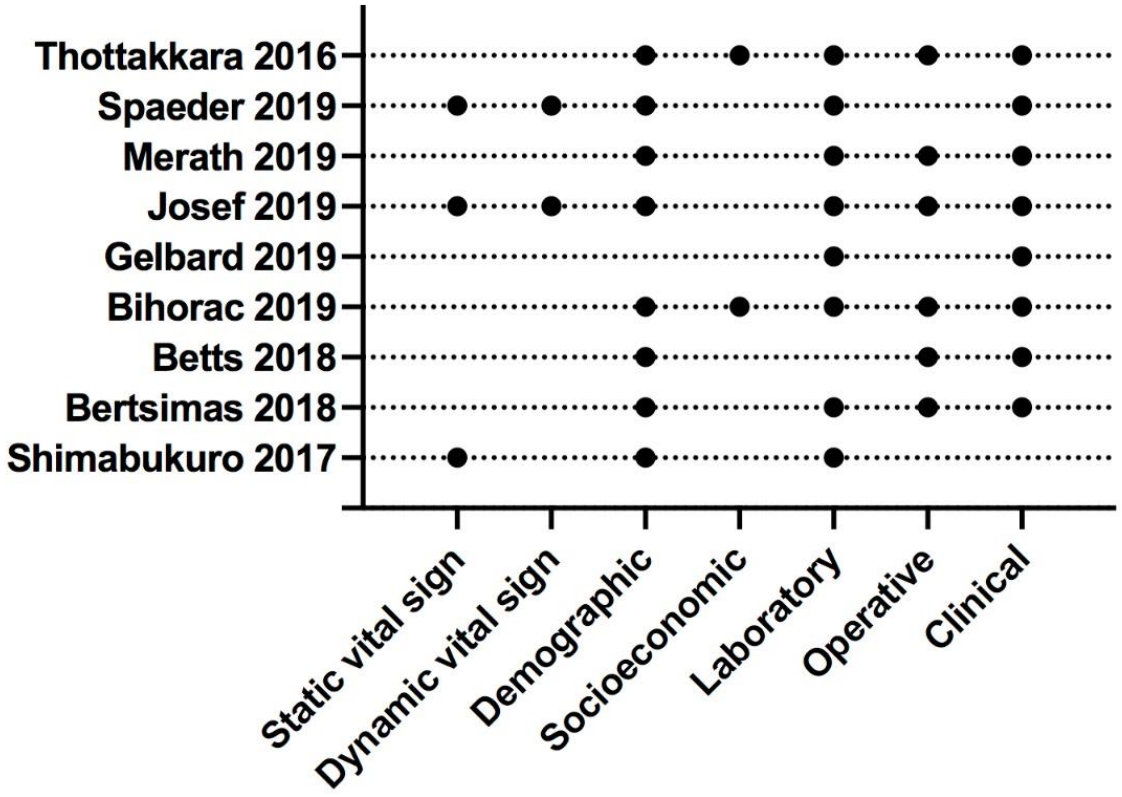
Results: A total of 57 studies were identified by the combined search queries following removal of 19 duplicates (Fig. 1). After title and abstract screening, 41 irrelevant studies were excluded and 16 full-text studies were assessed for inclusion. Nine studies met the inclusion criteria for data extraction (Fig. 2). Eligible studies evaluated machine learning algorithms for prediction of sepsis (n=6), severe sepsis (n=3) and septic shock (n=2) in surgical and mixed medical-surgical patient populations. Studies evaluated patients that underwent any inpatient surgical procedure (n=3), adult critical care (n=2), pediatric critical care (n=1), exploratory laparotomy (n=1), labor and delivery (n=1) and hepaticopancreatic and colorectal surgery (n=1). Input features of the studied algorithms included age, sex, socioeconomic factors, BMI, coexisting diseases, medications, ASA status, functional status, surgical history, prior ICU admissions and length of admissions, laboratory results, surgical procedures, anesthetic types, vital signs and other patient variables (Fig. 3). All studies evaluated predictive model accuracy using AUROC (area under the receiver operating characteristic curve). AUROC for each individual machine learning model ranged from 0.66 to 0.95. Mean AUROC for studies grouped by machine learning methodology (Fig. 4a) and severity of sepsis (Fig. 4b) were calculated and no statistically significant differences were found. However, mean AUROC for prediction of septic shock was 0.13 (15.6%) greater than the mean AUROC for prediction of sepsis, and this finding approached significance (p=0.037). As only two studies evaluated machine learning algorithms for prediction of septic shock, additional studies are needed to assess performance.

Conclusion: In this systematic review, machine learning algorithms appeared to outperform historical SIRS and qSOFA scores in the prediction of postoperative sepsis, severe sepsis and septic shock with all except one studied algorithm having acceptable discrimination, as defined by AUROC greater than 0.7. The accuracy of machine learning algorithms in predicting sepsis was consistent across all surgical populations, machine learning methodologies and illness severities, except for the study by Betts et al of an XGBoost algorithm for the prediction of postpartum sepsis.

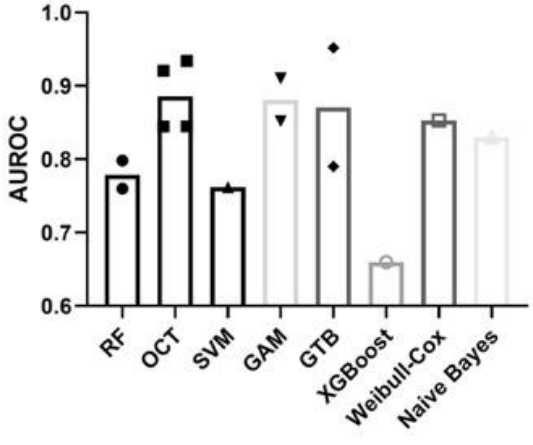
Reference(s): A Comparison of the Quick-SOFA and Systemic Inflammatory Response Syndrome Criteria for the Diagnosis of Sepsis and Prediction of Mortality: A Systematic Review and Meta-Analysis. Chest, 153(3), 646–655.
Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA, 319(4), 388–396.



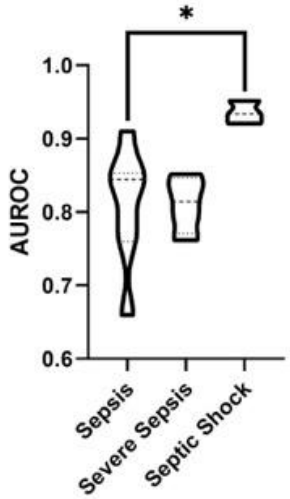
Study	Study type	Test population	Training Population	Operation type	Relevant Output(s)	Machine Learning Model	Training Set Size	Validation Method	Performance (AUROC/Sens/Spec)
Shimabukuro et al, 2017	Single center RCT of existing model	Medical-surgical intensive care units	MIMIC II (MICU)	n/a	Severe Sepsis	Proprietary (Insight)	1394	4-FCV	0.952/0.9/0.9
Bertsimas et al, 2018	Retrospective	ACS-NSQIP (2014)	ACS-NSQIP (2007-2013)	all surgical procedures	1) Sepsis 2) Septic Shock	OCT, Optimal Impute	382,960	Bootstrapping	1) 0.844 2) 0.92
Betts et al, 2018	Retrospective	PDC/QHAPDC (n=61177)	PDC/QHAPDC (n=361332)	cesarean section, vaginal delivery	Sepsis	XGBOOST	361332	5-FCV	0.66
Bihorac et al, 2019	Retrospective	Single site EHR (n=10291)	Single site EHR (n=41166)	all inpatient surgical procedures requiring at least 24 hour hospital stay	Sepsis	GAM, SVM	41166	5-FCV on 50 bootstrap samples	0.91/0.82/0.86
Gelbard et al, 2019	Retrospective	Single site EHR (n=15)	Single site EHR (n=117)	exploratory laparotomy for abdominal trauma	Severe Sepsis	RF	117	LOOCV	0.798/0.797/0.74
Josef et al, 2019* (abstract only)	Retrospective	Multi-site EHR (ICUs)	Multisite EHR (ICUs)	SICU (all surgical patients)	Sepsis	Proprietary (AISE)	15223	10-FCV (80%/20%)	0.853/0.85/0.683
Merath et al, 2019	Retrospective	ACS-NSQIP (2014-2016)	ACS-NSQIP (2014-2016)	Hepatic, pancreatic and colorectal surgery	1) Sepsis 2) Septic Shock	Decision Tree	15657	Bootstrapping (50%)	1) 0.79 2) 0.87
Spaeder et al, 2019	Retrospective	Single site EHR (PICU)	Single site EHR (PICU)	Mixed medical-surgical PICU (pediatric surgeries)	Sepsis (24h prior)	RF	1425	LOOCV	0.762
Thottakkara et al, 2016	Retrospective	Single site EHR	Single site EHR	all inpatient surgical procedures requiring at least 24 hour hospital stay	Severe Sepsis	1) GAMs 2) SVM 3) Naive Bayes	50318	CV (70%/30%)	1) 0.852 2) 0.762 3) 0.83


Thottakkara 2016
Spaeder 2019
Merath 2019
Josef 2019
Gelbard 2019
Bihorac 2019
Betts 2018
Bertsimas 2018
Shimabukuro 2017
Static vital sign
Dynamic vital sign
Demographic
Socioeconomic
Laboratory
Operative
Clinical

A.


AUROC
1.0
0.9
0.8
0.7
0.6
RF
OCT
SVM
GAM
GTB
XGBoost
Weibull-Cox
Naive Bayes

B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AUROC
1.0
0.9
0.8
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0.6
Sepsis
Severe Sepsis
Septic Shock

Critical Care-16 USE OF EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION FOR INTRAOPERATIVE CARDIAC ARREST AT AN ACADEMIC MEDICAL CENTER

Kerri Lydon[1], Quintin J Quinones[2], JOSE M DEL RIO[1]

[1]Duke University School of Medicine / Duke University Medical Center, Durham, NC, [2]Duke University Medical Center, Durham, NC

Introduction: Intraoperative cardiac arrest has distinctive characteristics that differentiate it from other in-hospital and out-of-hospital cardiac arrest. It occurs in a highly monitored and controlled environment and it is typically managed by surgeons, nurses, and anesthesiologists using advanced cardiac life support techniques. Extracorporeal Cardiopulmonary Resuscitation (ECPR) in patients with refractory cardiac arrest represents a unique approach in the intraoperative setting. The ultimate aim of this study is to determine patient and procedural barriers to ECPR as well ECPR utilization rates during cardiac and non-cardiac surgery. Our hypothesis is that decision-making regarding ECPR is a complex process integrating multiple procedural factors. ECPR may not be utilized in some instances because of an overall lack of familiarity with the process and eligibility criteria. We aim to compare rates of ECPR in cardiac and non-cardiac surgery and to identify barriers to deployment of ECPR that could serve as opportunities for education.

Methods: We queried the department of anesthesiology quality improvement and patient safety database at Duke University Hospital (from July 2013 until November 2018) for intraoperative cardiac arrest and other similar events. The search yield 297 patients suspected to have suffered intraoperative cardiac arrest. After retrospective chart review, we confirmed 112 intraoperative cardiac arrest events. Of those patients, 83 arrested during non-cardiac surgery and 29 had cardiothoracic surgical procedures. Confirmed cardiac arrests were then crosschecked with our ECMO database by using name and medical record number. We determined the rate of intraoperative ECPR utilization and also compared patient and procedural characteristics.

Results: During the study period, 112 patients had confirmed intraoperative cardiac arrest in all operating rooms. The overall rate of ECPR utilization was 12.5% (14 total, 8 non-cardiac). Cardiac patients suffered 25.9% of all arrest events. Of the 29 cardiac surgical patients with intraoperative cardiac arrest, 6 received ECPR (20.7%). In 5 out of 6 cardiac surgery ECPR patients, it was VF/VT cardiac arrest occurring during or shortly after induction and PEA arrest in 1 patient secondary to hypoxemia during lung transplantation. In the non-cardiac patients ECPR was used for 9.6% of cardiac arrests. For these patients the etiology was unexpected surgical complications in 3, hemorrhage/hypovolemia in 2, amniotic fluid embolism in 1, and VF/VT arrest in 1 patient.

Conclusion: At our institution, ECPR utilization is higher in cardiac surgery patients. It is possible that familiarity with ECPR initiation techniques play a role. We plan to identify discrete knowledge gaps that may exist preventing appropriate utilization of ECPR outside of the cardiac OR. We hope that with further education this potentially lifesaving technique could be employed in a higher percentage of appropriate patients.

Reference(s): Anesth Analg 2015;120(2):364-70 J Cardiothorac Vasc Anesth 2016;30(2):338-344

Critical Care-17 Baseline serum albumin concentration is associated with length of stay and 90-day mortality in patients after transcatheter aortic valve replacement

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[1]Tufts Medical Center, Boston, MA, [2]Tufts Medical Center, Tufts University School of Medicine, Boston, MA

Introduction: Transcatheter aortic valve replacement (TAVR) is an increasingly popular intervention for high-risk patients with severe aortic stenosis. Although it is considered minimally invasive, in-hospital costs of TAVR are comparable to surgical aortic valve replacement. TAVR candidates have significantly greater comorbidities compared to their surgical counterparts and 90-day mortality ranges from 6-13%. Given that it is an expensive therapy, with relatively high mortality, patient selection may help to improve outcomes. Emerging data suggests that frailty plays an important role in recovery after TAVR. However, to data there is no universally accepted scoring system or biomarker to assess frailty in TAVR patients. Serum albumin concentrations have been used to assess for frailty in various disease states; preliminary data suggest that it may be useful for short (30-day) or long-term (1-year) risk-stratification in TAVR patients. Our goal was to investigate whether baseline serum albumin concentrations are associated with outcomes within a clinically meaningful period (90-days) after TAVR.

Methods: We conducted a retrospective analysis of data from patients who presented for TAVR at the Tufts Medical Center (Boston, MA). We only included patients who had serum albumin concentrations measured between one and four weeks before TAVR. We also excluded all patients who had been hospitalized within 4 weeks before the procedure. We constructed a locally weighted scatterplot smoothing (LOWESS) curve to graphically represent the relationship between serum albumin concentration and 90-day mortality. Kaplan-Meir curves were constructed and compared using long-rank tests for intensive care unit (ICU) as well as hospital length of stay (LOS), stratified by albumin concentration. A Cox Proportional-Hazards model was used to investigate the relationship between albumin concentration and ICU as well as hospital LOS, controlling for potential confounders. Logistic regression, adjusting for potential confounders, was used to investigate the association of albumin concentration with 90-day mortality.

Results: 245 patients comprised the analytic cohort and 90-day mortality was 8%. Characteristics of the cohort are shown in Table 1. LOWESS curve (Figure 1) analysis demonstrated a notable flattening of the risk between albumin concentrations of 3 g/dL and 4 g/dL. As such, we assumed that the 'normal' population serum albumin concentration threshold of 3.5 g/dL may be applicable to TAVR patients as well. Kaplan-Meir curves comparing TAVR patients with baseline serum albumin concentrations of <3.5 g/dL to those with concentration >3.5 g/dL, and who survived to hospital discharge, demonstrated a significant difference between groups for ICU (Figure 2) as well as hospital LOS (Figure 3). Cox-proportional hazards analysis demonstrated that when controlling for Society of Thoracic Surgeons (STS) score and New York Heart Association (NYHA) classification, patients with albumin concentrations <3.5 g/dL were 70% more likely to have prolonged ICU LOS compared to their counterparts with albumin concentrations >3.5 g/dL (HR 1.70;95%CI 1.04-2.46, p=0.03). Similarly, when controlling for ICU LOS and NYHA classification, patients with albumin concentrations <3.5 g/dL were greater than 50% more likely to have prolonged hospital LOS compared to their counterparts with albumin concentrations >3.5 g/dL (1.56; 95%CI 1.01-2.42, p=0.04). Logistic regression analysis, controlling for STS score and NYHA classification, demonstrated that patients with albumin concentrations <3.5 g/dL were almost 4 times more likely to not survive to 90-days post-TAVR compared to their counterparts with albumin concentrations >3.5 g/dL (OR 3.79; 1.13-12.64, p=0.03).

Conclusion: Our data suggests that TAVR patients with low baseline serum albumin concentrations are at an increased risk for prolonged hospitalization and have a greater likelihood of not surviving to 90-days post-procedure when compared to their counterparts with 'normal' albumin concentrations. Further studies are needed to validate our findings and to determine whether baseline serum albumin concentrations can be used as a biomarker of frailty to better risk-stratify and improve patient selection for TAVR.

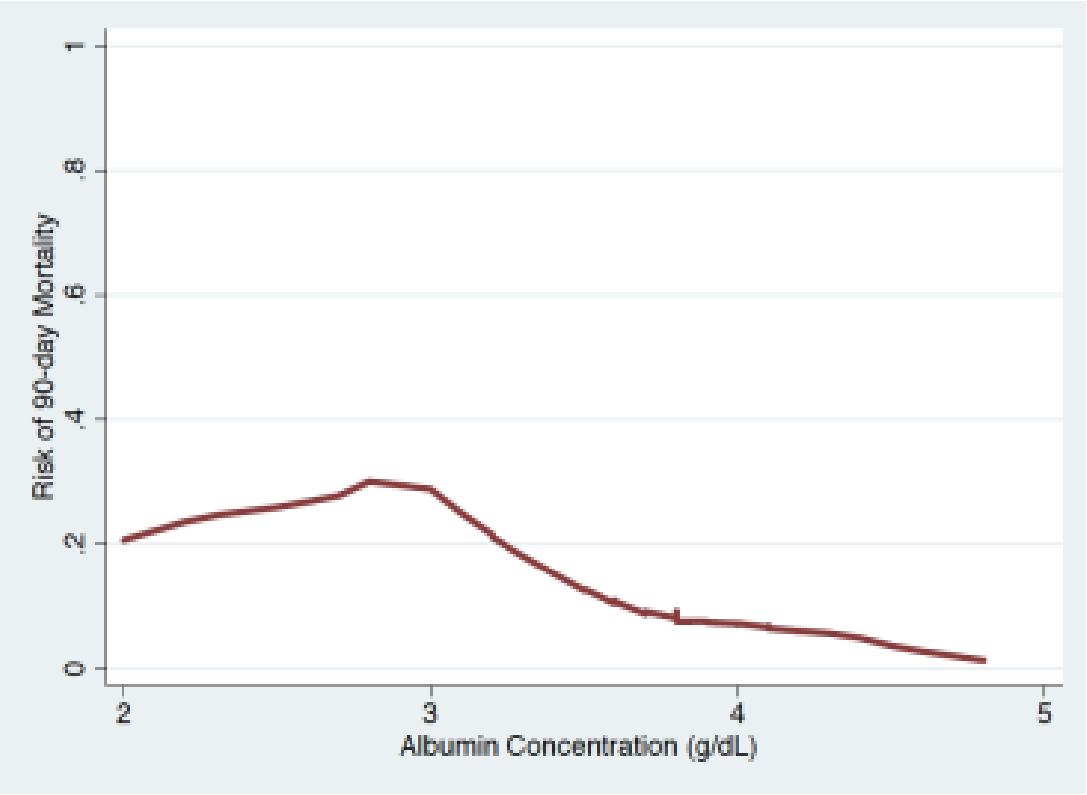
Reference(s): Comparison of U.S. Hospital Costs Between Transcatheter Aortic Valve Replacement (TAVR) and Surgical Aortic Valve Replacement (SAVR) 20(9), A579-A580 (2017,) Utility of 90-day mortality vs 30-day mortality as a quality metric for transcatheter and surgical aortic valve replacement outcomes (2019,) Habitual Physical Activity in Older Adults Undergoing TAVR Insights From the FRAILTY-AVR Study 12(8), 781-789 (2019,) Albumin Is Predictive of 1-YearMortality After Transcatheter AorticValve Replacement 106(5), 1302-1307 (2018)

Table 1. Characteristics of the study cohort (n=245).

	90-days - Deceased (n=19)	**90-days - Alive (n=226)**	**P-value**
Age (years)	81 ± 7	80 ± 9	0.57
Sex (%)			0.78
Female	53	51	
Male	47	49	
BMI (kg/m^2)	26 ± 5	28 ± 6	0.12
BSA (m^2)	1.8 ± 0.2	1.8 ± 0.3	-
Major comorbidities	3 ± 1	3 ± 1	-
STS Risk Score	3 ± 1	10 ± 8	**<0.001**
6-minute walk test (%)			**0.03**
No	47	32	
Yes	53	68	
KCCQ12	51 ± 24	92 ± 18	**<0.001**
NYHA Classification (%)			**0.02**
Class I	0	3	
Class II	16	13	
Class III	53	70	
Class IV	0	1	
Class V	32	13	
Class VI	0	0	
LVEF (%)	48 ± 17	53 ± 13	0.23
AVA (cm^2)	0.71 ± 0.18	0.74 ± 0.20	0.50
AMG (mmHg)	44 ± 14	39 ± 15	0.15
Albumin (g/dL)	3.7 ± 0.5	4.0 ± 0.4	**0.02**
ICU LOS (hours)	74 (55-135)	46 (27-75)	**0.04**
Hospital LOS (days)	5 (2-8)	4 (3-6)	**0.01**

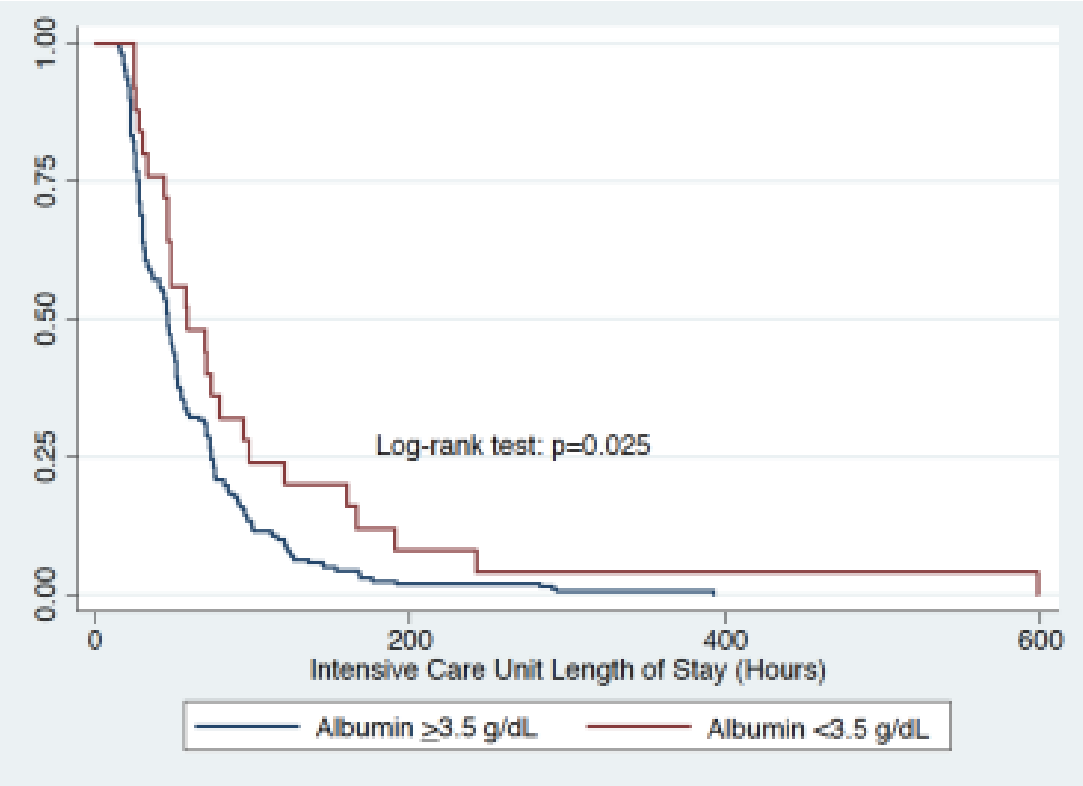
Data are shown as mean ± standard deviation, medial (interquartile range), or proportions and compared using t-tests, log-rank tests, and chi-square tests, respectively. Statistically significant p-values are shown in bold. BMI = body mass index; BSA = body surface area; STS = Society of Thoracic Surgeons; KCCQ12 = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; AVA = aortic valve area; AMG = aortic valve mean gradient; ICU = intensive care unit; LOS = length of stay.

Figure 1. Graphical representation of the relationship between baseline serum albumin concentration and risk of 90-day mortality (n=245).



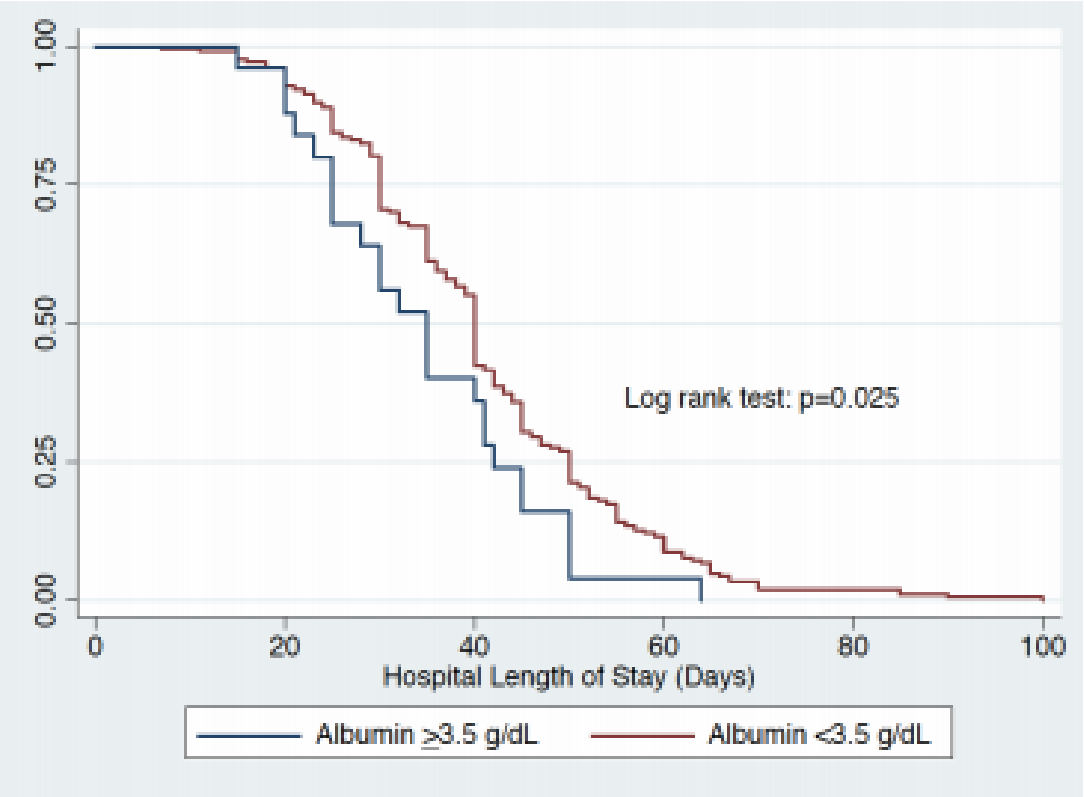
Locally weighted scatterplot smoothing demonstrates significant flattening of the risk curve between albumin concentrations of 3 d/dL and 4 g/dL.

Figure 2. Intensive care unit length of stay stratified by albumin concentration (n=238).



Kaplan-Meir curves demonstrate that intensive care unit length of stay (in hours) is significantly longer in patients with albumin concentration <3.5 g/dL compared to patients with concentrations ≥3.5 g/dL. All patients survived to hospital discharge.

Figure 3. Hospital length of stay stratified by albumin concentration (n=238).



Kaplan-Meir curves demonstrate that hospital length of stay (in days) is significantly longer in patients with albumin concentration <3.5 g/dL compared to patients with concentrations ≥3.5 g/dL. All patients survived to hospital discharge.

Critical Care-18 Intraoperative Narcotic Use and Its Effect on Extubation Time After Cardiac Surgery

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[1]NYU Langone Health, New York, NY, [2]NYU Langone Health, New York City, NY

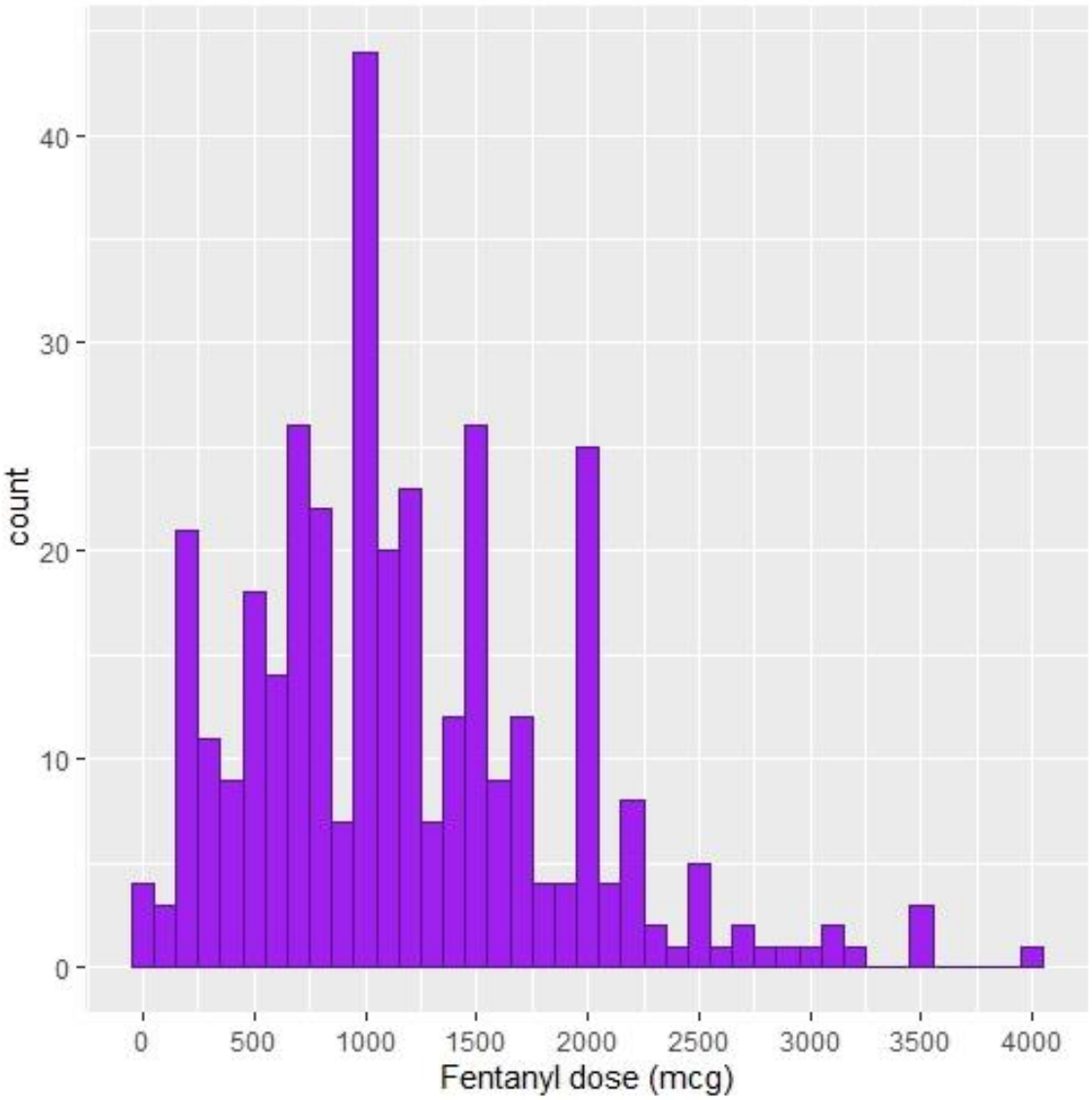
Introduction: The Society of Thoracic Surgeons (STS) has been promoting the use of early extubation after cardiac surgery, as defined by extubation within 6 hours, as a quality of care benchmark[1]. Institutions are implementing fast-track cardiac recovery programs that try and focus on decreasing costs, reducing length of stay in the hospital and intensive care unit (ICU), and improving clinical outcomes for patients[2]. One initiative has been to promote the use of a 'balanced anesthetic' to reduce the amount of narcotics and benzodiazepines that could contribute to increased time on the ventilator[3]. With this study, we looked to see if there was a correlation in our anesthesia practices with the amount of narcotic given in the operating room (OR) and the time to extubation in the ICU. Our hypothesis was that the more narcotic given in the OR, the longer the patients remained intubated in the ICU and missed the 6 hour extubation mark. The goal of this study is to try and change clinical practice in the operating room and create a fast track program that identifies patients who could be optimized prior to ICU admission to decrease ICU LOS.

Methods: This study was a retrospective chart review looking at cardiac cases done between November 1, 2018 and October 31, 2019. Data was gathered from electronic health records with patients age, ASA status, type or surgery, surgery time, and time of extubation. The total dose of fentanyl was gathered from the intraoperative record as fentanyl is the sole narcotic used in the cardiac ORs. The data was compared and validated against the STS data that is collected in the hospital. A cutoff of 8 hours from the time frame to extubation was used as those who were intubated longer than 8 hours had more significant clinical confounders relating to prolonged intubation. We plotted the data comparing the dose of fentanyl with extubation times controlling for length of operation, the type of procedure, and the ASA score.

Results: Using an 8 hour extubation as a cut off, there were a total of 398 patients included in the analysis. All patients undergoing cardiac surgery were included in the study except patients who were take backs to the OR as indicated by two procedures in the same day. When controlling for length of case, type of surgery, and ASA score, beta value being 0.00031 and the p-value was 0.075.

Conclusion: In this study, we attempted to show a correlation between the amount of intraoperative fentanyl being used and the effect it has on the time to extubation in the ICU. When controlling for the length of the case, type of surgery, and ASA score, a trend that was not statistically significant was seen with increased fentanyl dose. While not statistically significant, this information will help guide our anesthesia teams to adopt a more balanced anesthetic approach to pain control in the operating room by using other adjuncts that do not affect extubation times. Using this data will be one part of a more comprehensive fast track cardiac surgery program that will be implemented with the aim to decrease ICU and hospital LOS.

Reference(s): STS Quality Webinar Series: Prolonged Ventilation. Available at: https://www.sts.org/sites/default/files/documents/pdf/ProlongedVentilarWebinarSlides_120414.pdf Pro: Early Extubation after cardiac surgery decreased intensive care unit stay and cost. J Cardiothoracic Vasc Anesth 1995;9:460-4 Current evidence on fast track cardiac recovery management. Eur Heart J Suppl 2017;19;A3-7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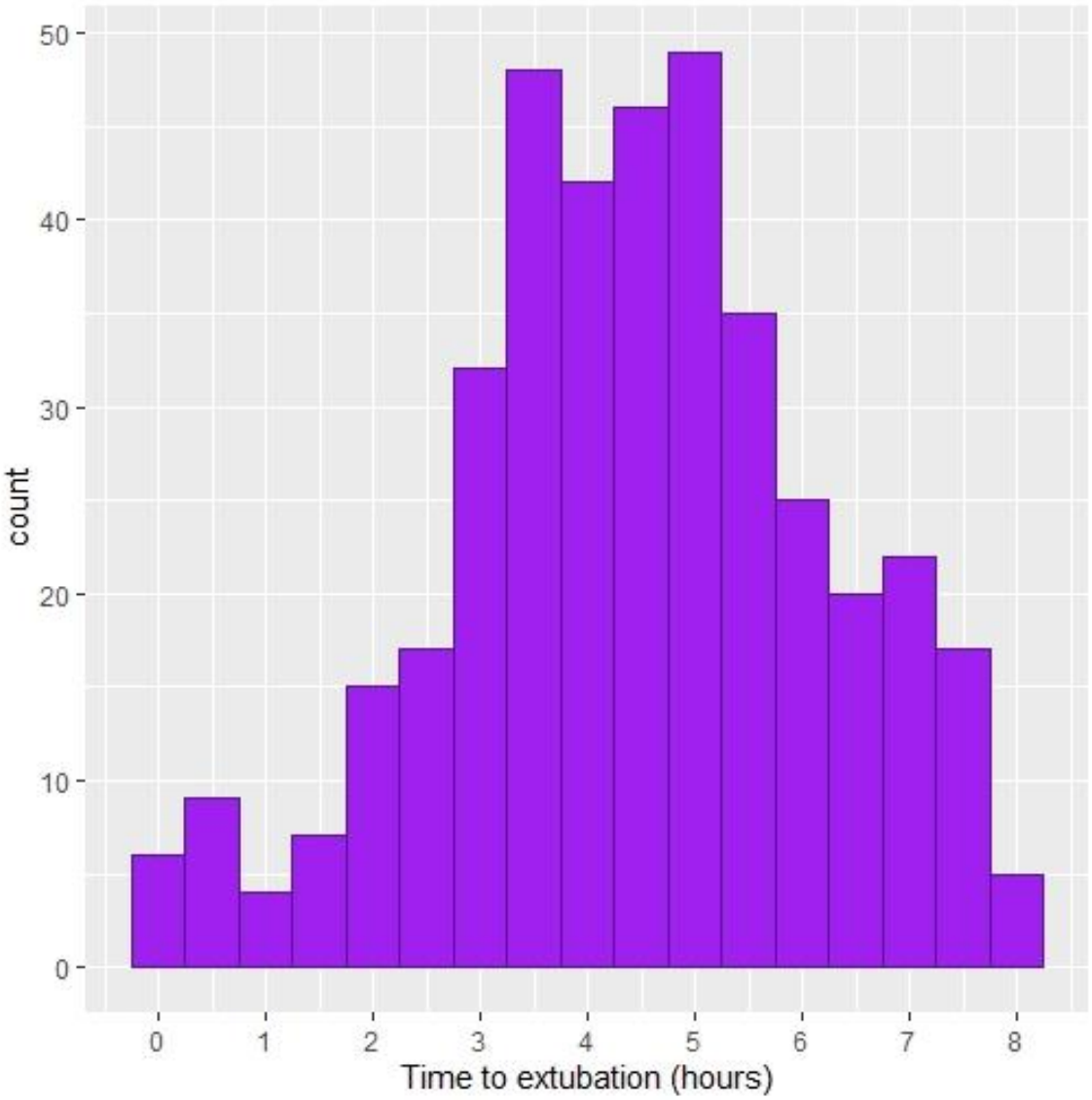
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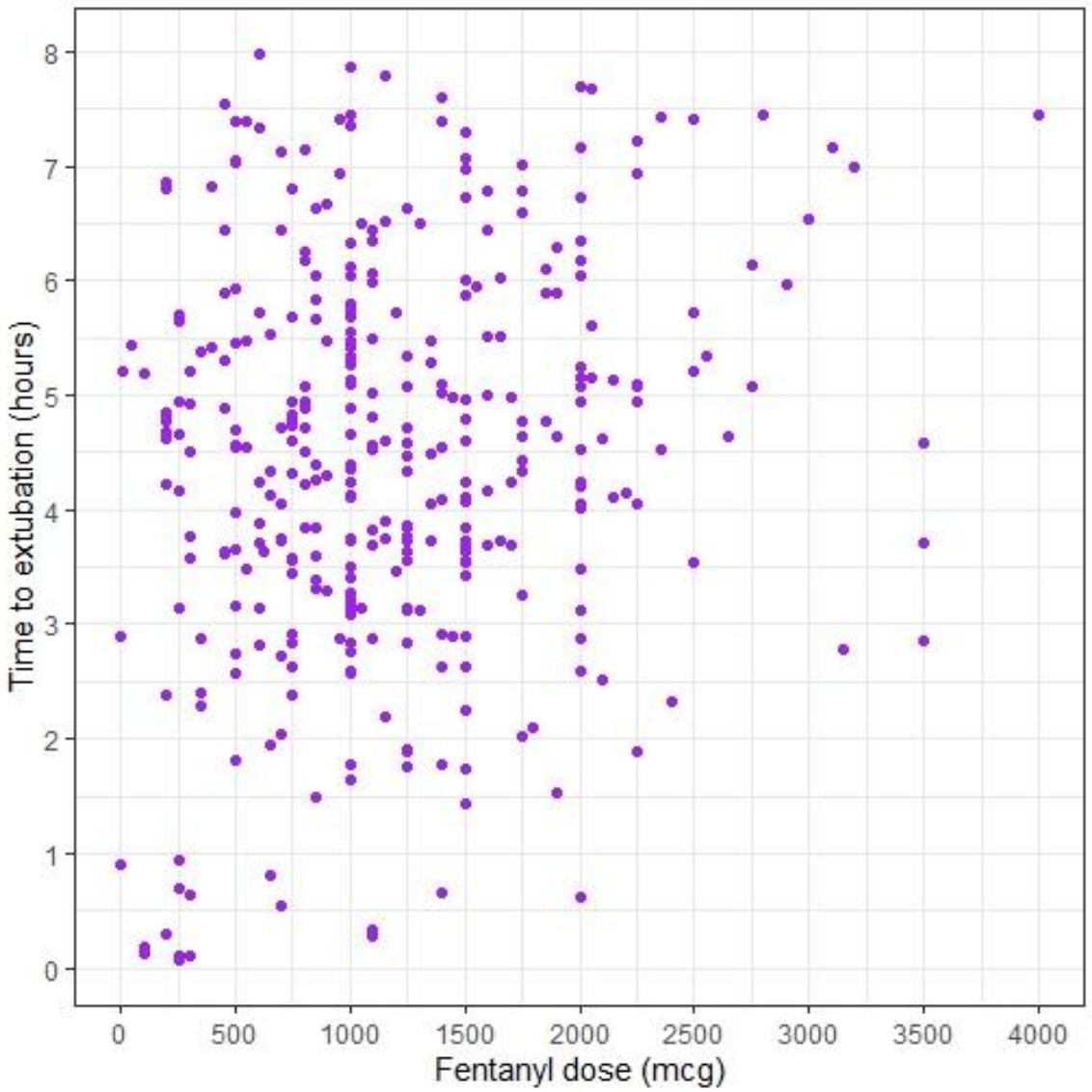
Time to extubation (hours)


Time to extubation (hours)
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Fentanyl dose (mcg)

Critical Care-19 Robotically assisted Transcranial Doppler with Artificial Intelligence for Assessment of Cerebral Vasospasm after Subarachnoid Hemorrhage

Shooka Esmaeeli[1], Courtney Mcvey[1], Andres Brenes Bastos[1], Jeffrey Wang[1], Santiago Gomez-Paz[1], Khalid Hanafy[1], Lioutas Vasileios-Arsenios[1], Christopher S Ogilvy[1], Shahzad Shaefi[2], Corey Fehnel[1], Ala Nozari[3]

[1]Beth Israel Deaconess medical center, Harvard Medical School, Boston, United States of America, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [3]Beth Israel Deaconess medical center, Boston, United States of America

Introduction: Transcranial Doppler Ultrasound (TCD) is an important tool for detection of cerebral vasospasm after subarachnoid hemorrhage (SAH), but is limited by availability of skilled operators. We examined the clinical feasibility and concordance of a robotically assisted TCD system with artificial intelligence with routine handheld TCD after SAH.

Methods: We evaluated TCD velocities in the anterior (ACA) and middle cerebral arteries (MCA) of two patients with high-grade SAH and angiographic evidence of vasospasm. A single channel TCD device with a handheld diagnostic probe as well as a robotically assisted TCD device were used, the relationship of the two tests was evaluated using the Concordance correlation coefficient paired with a Pearson's correlation analysis, followed by a Bland-Altman plot.

Results: Patient 1 developed angiographic and TCD evidence of vasospasm in the proximal right MCA, but except for periods of disorientation remained neurologically intact. Angiographic, TCD and clinical evidence of ACA spasm occurred six days after ictus in patient 2. Robotically measured mean flow velocities were comparable to manual TCDs in the MCAs (concordance correlation coefficient = 0.83 (95% COI = 0.52 - 0.95), P = 0.001) but not in the ACAs (concordance correlation coefficient = 0.32 (95% COI = -0.15 - 0.68), P = 0.15).

Conclusion: Robotically assisted TCD system with artificial intelligence provides an alternative to manual TCD for assessment of MCA velocities in patients with SAH, expanding the availability of TCD to settings in which specialized clinicians are not available. Further studies for validation of this technology are warranted.

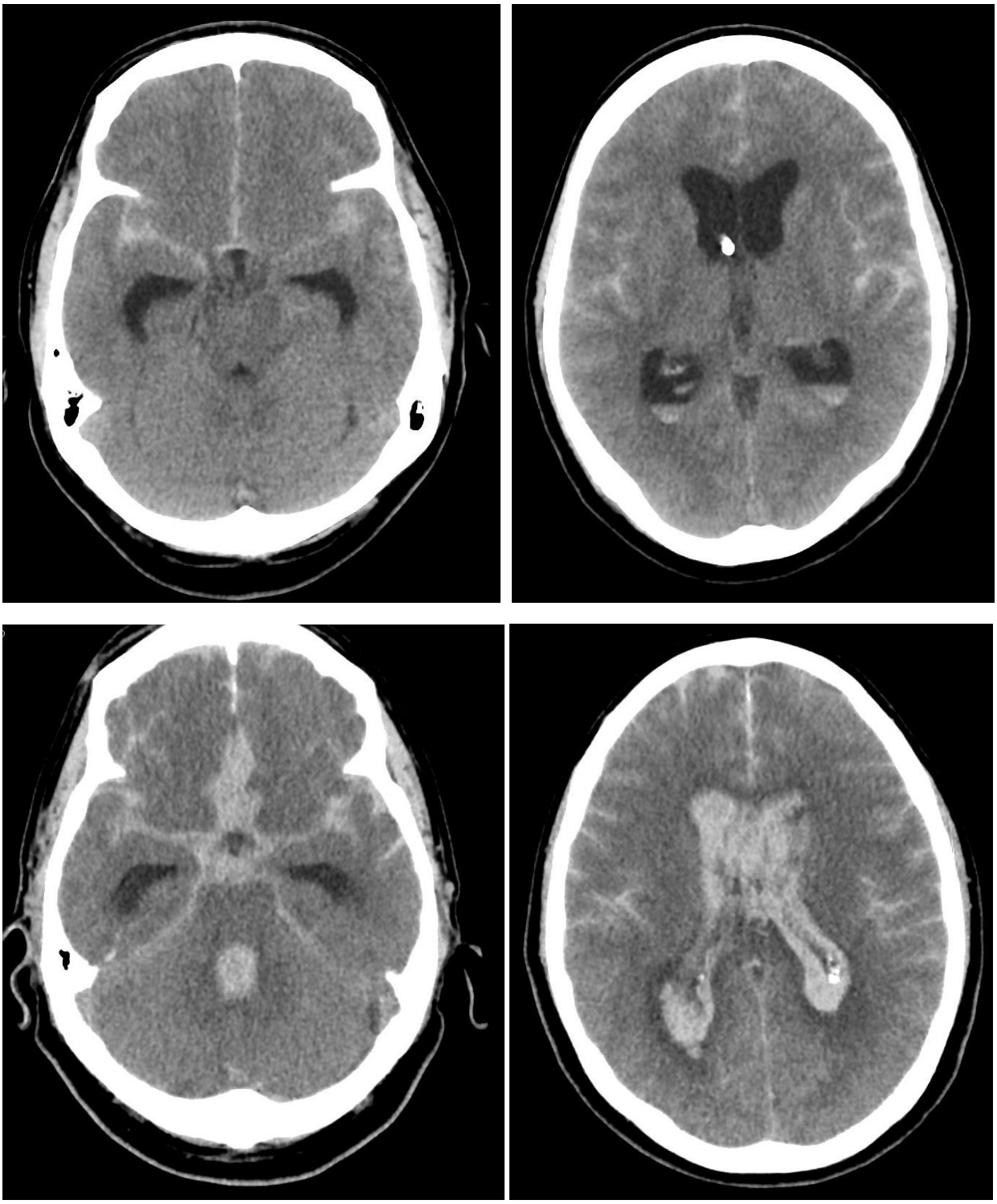


Figure 1. Computer tomography imaging of patient 1 (above) and 2 (below) showing diffuse thick subarachnoid hemorrhage with intraventricular blood.

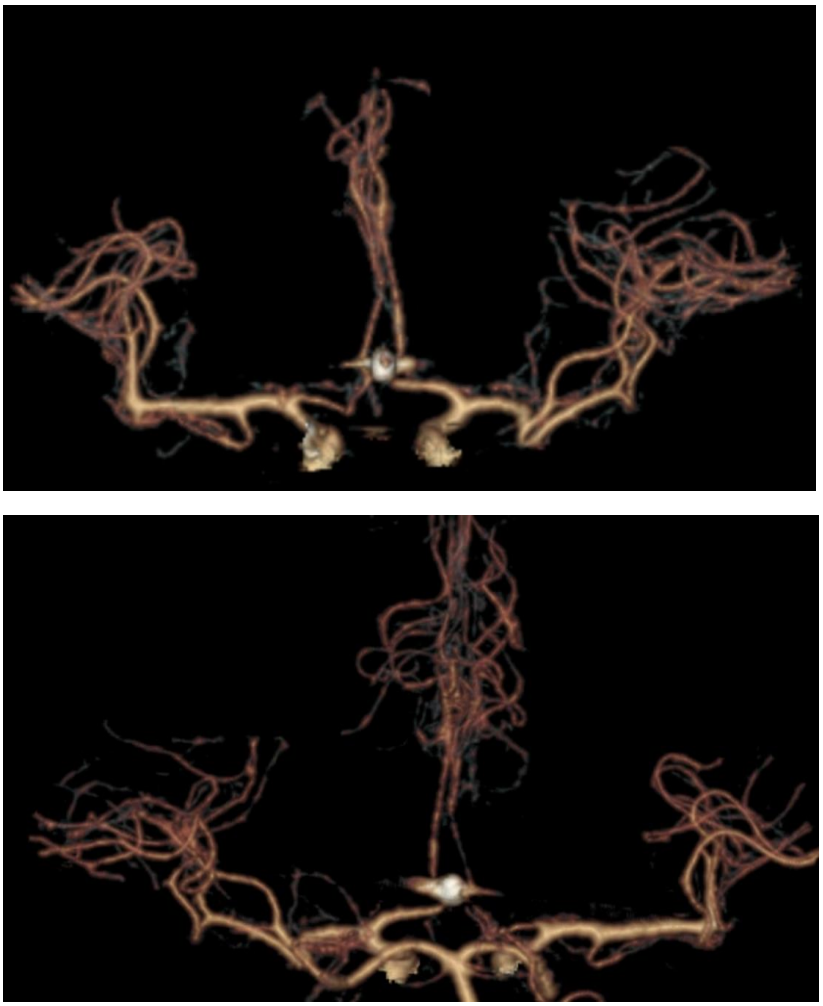
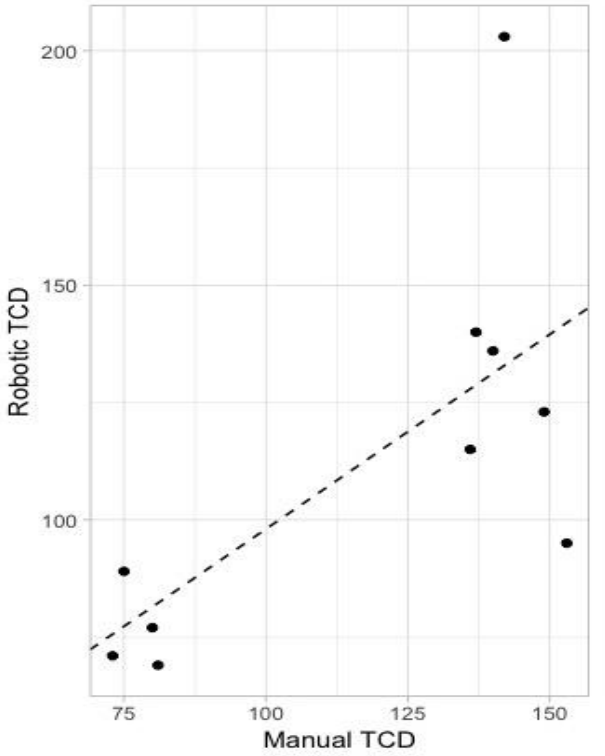


Figure 2. Angiographic findings in patient 2, initially demonstrating normal calibers in alll cerebral vessels but significant vasospasm in bilateral ACAs 6 days after ictus.

A



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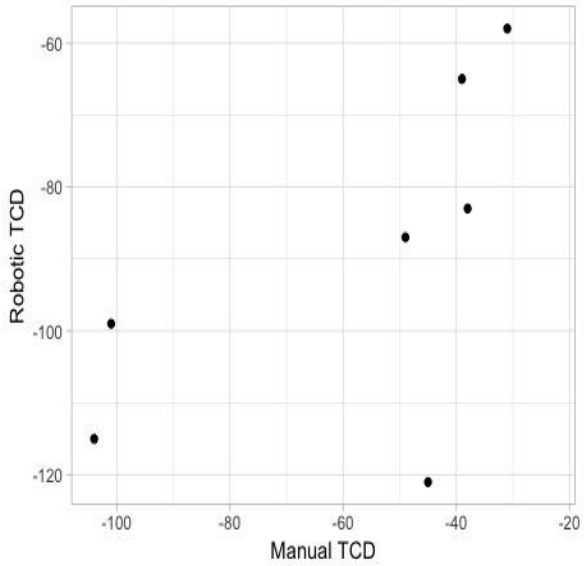
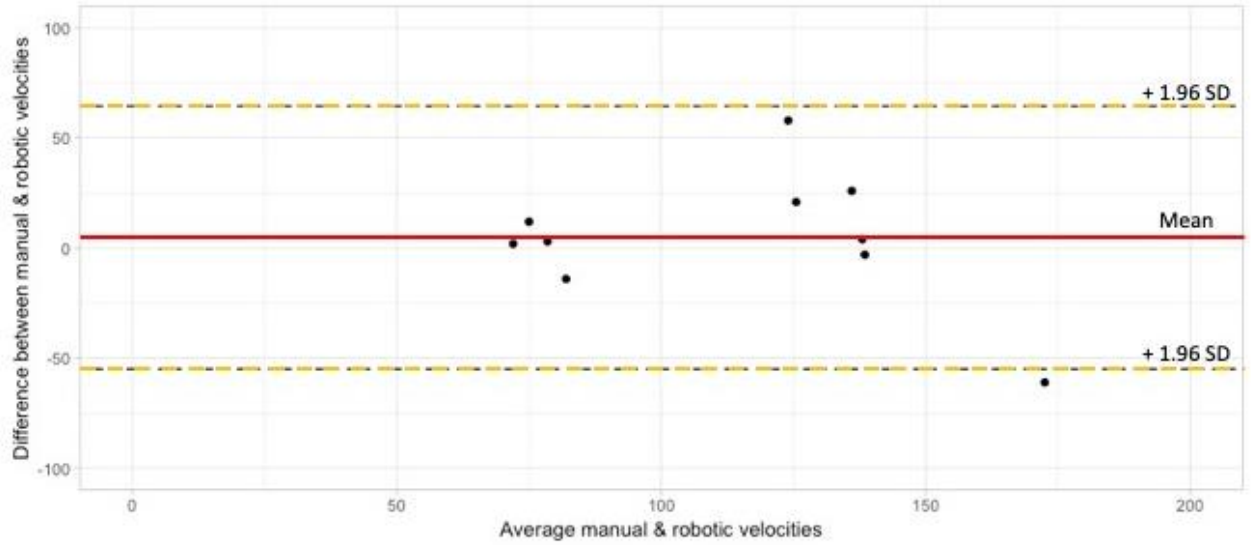


Figure 3. A) Moderate agreement between Trans cranial doppler (TCD) findings using robotic technique and TCD findings using manual technique for the middle cerebral artery (concordance correlation coefficient = 0.83 (95% COI = 0.52 - 0.95)) B) Poor agreement between Trans cranial doppler (TCD) findings using robotic technique and TCD findings using manual technique for the anterior cerebral artery (concordance correlation coefficient = 0.32 (95% COI = -0.15 - 0.68)

A



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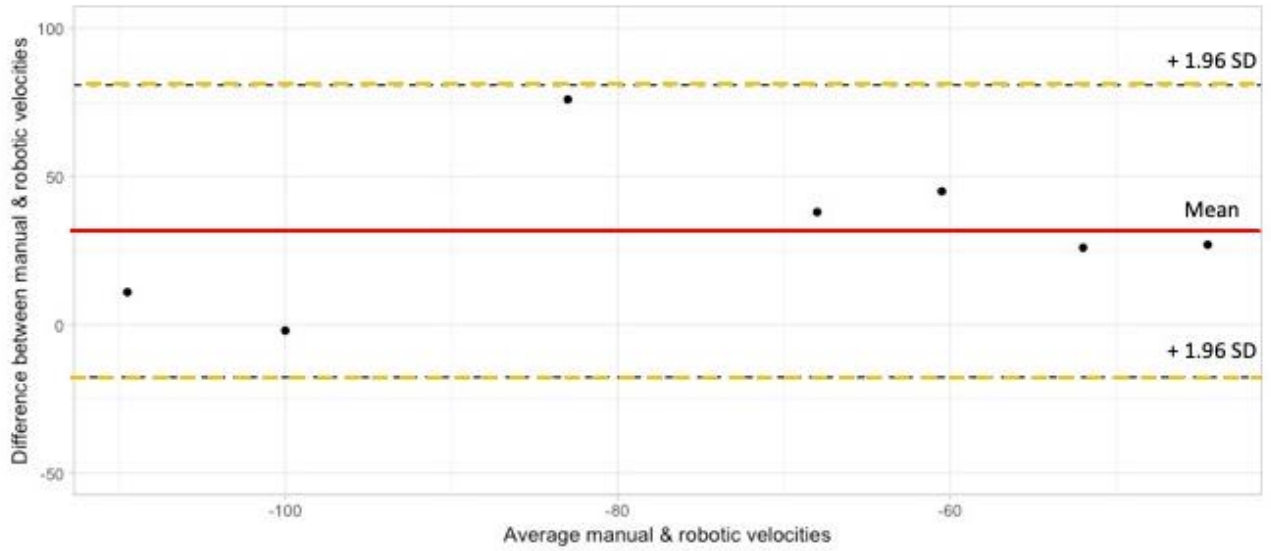

Figure 4. Bland-Altman plot shows no proportional bias, indicating agreement between the two methods for the middle cerebral artery (A) and anterior cerebral artry (B).

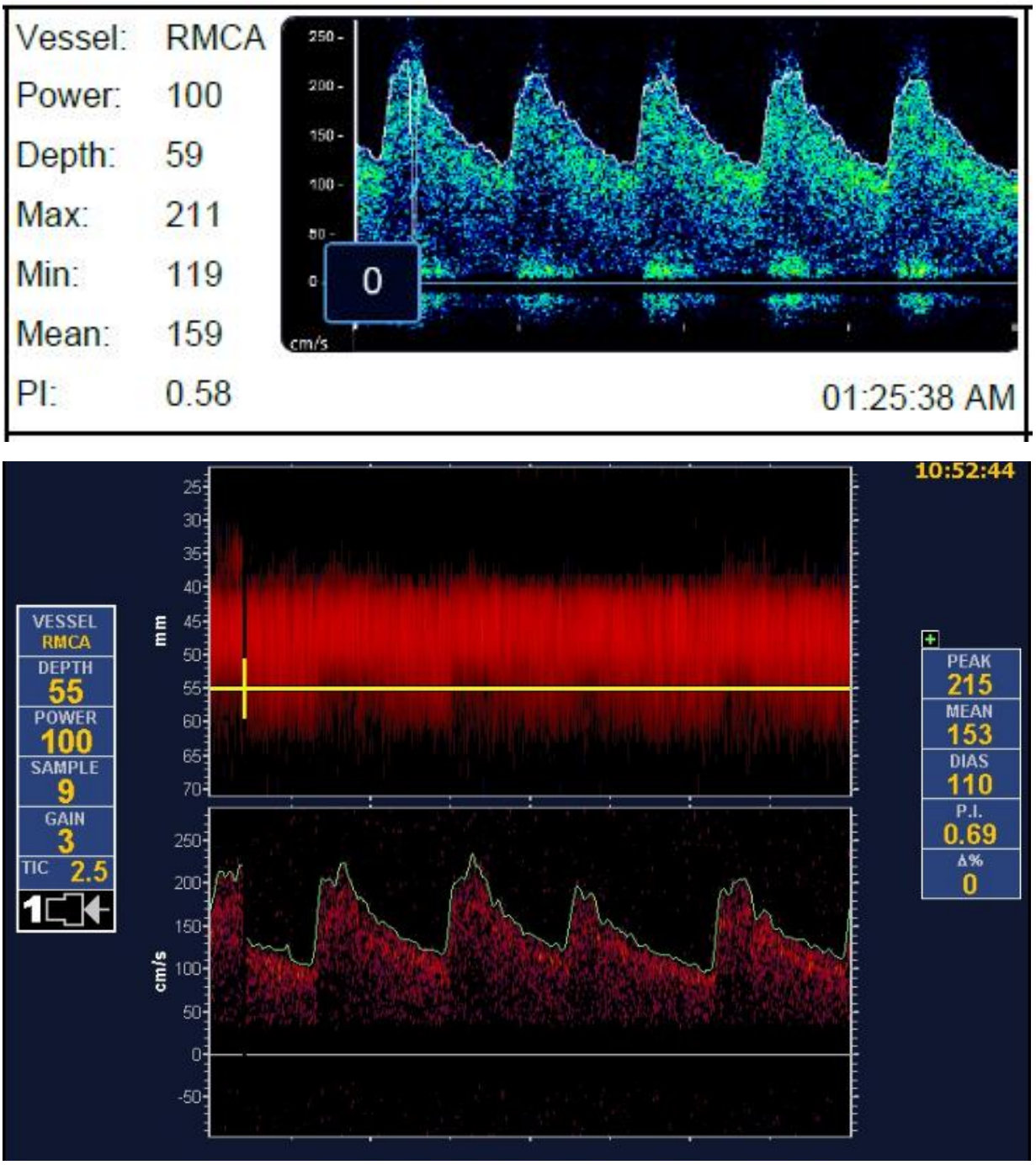

Figure 5. Robotic (above) and Manual (below) TCD waveform of the right MCA of Patient 1 on post-ictus day 10 demonstrating elevated right MCA mean flow velocity, consistent with vasospasm in both techniques.

Critical Care-20 A Physiology-Driven Machine Learning Model for Post-Cardiac Arrest Outcome Prediction Using a Large Multi-Center Database

Robert D Stevens[1], Han Kim[2]

[1]The Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD

Introduction: Cardiac arrest (CA) poses a significant risk of neurological disability, however there remains a large unmet need for accurate and reliable methods to predict post-CA neurological outcomes and mortality. 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). Additionally, we hypothesize that model performance could be enhanced by integrating physiological time series (PTS) data obtained from ICU bedside monitoring devices.

Methods: We utilized the critical care Philips eICU database, which spans 208 hospitals and 200,859 ICU admissions. Our pipeline incorporated data of CA patients within 24 hours of ICU admission. We first exhaustively extracted statistical PTS and electronic health record (EHR) features and performed feature selection using nested Random Forest. We then combined various machine learning algorithms (GLM, Random Forest, Gradient Boosting, Neural Networks) and optimization techniques (hyperparameter tuning, model stacking, and transfer learning) to maximize the prediction of mortality and neurological outcome.

Results: We built a neurological outcome prediction model combining EHR and PTS features. Our best-performing neurological outcome prediction model achieved a higher sensitivity (0.78), specificity (0.88), and AUC (0.87±0.01) compared to the APACHE III baseline model (AUC: 0.74±0.01, sensitivity: 0.77, specificity: 0.63). Additionally, our highest performing mortality prediction model (AUC: 0.85±0.01, sensitivity: 0.80, specificity: 0.75) also significantly outperforms the APACHE III baseline model (AUC: 0.75±0.01, sensitivity: 0.86, specificity: 0.56). The incorporation of PTS was observed to increase mean AUC by 3.7% for neurological outcome and 4.5% for mortality.

Conclusion: Results attest to the effectiveness of machine learning models for post-CA predictive modeling, and suggest that PTS recorded in very early phase after resuscitation encode short-term outcome probabilities following CA.

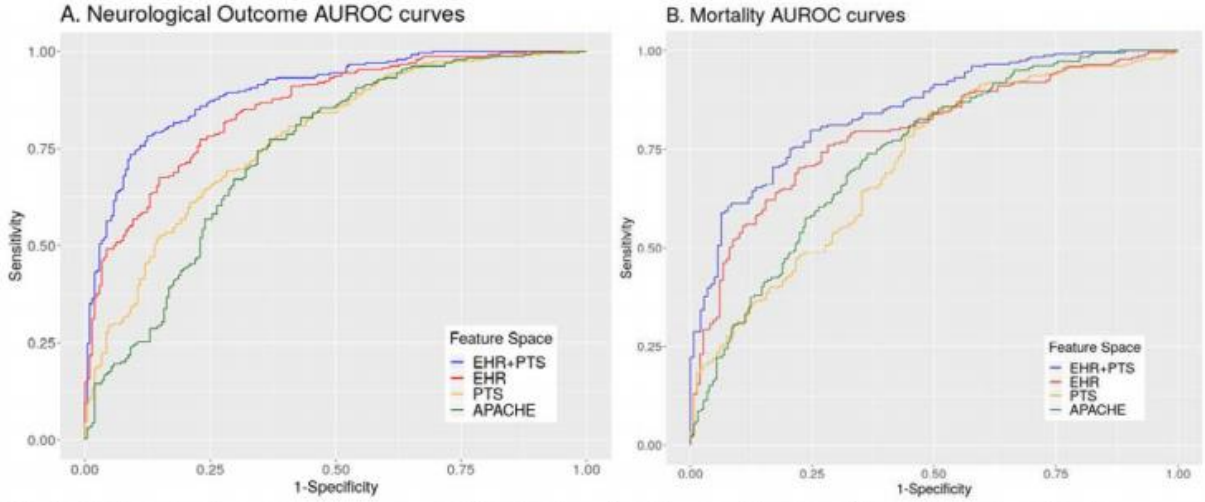

Fig.1. Median receiver operating curves of the best performing model using different feature subsets

Critical Care-21 Postoperative delirium in veterans undergoing cardiac surgery: an analysis of predisposing and precipitating factors

Carolyn Pinkerton[1], Matthew D Russell[1], Katherine Sherman[2], Thomas Ebert[1], Paul Pagel[3]

[1]Medical College of Wisconsin, Milwaukee, WI, [2]Clement J Zablocki VA Medical Center, Milwaukee, WI, [3]Zablocki Veterans Affairs Medical Center, -, United States of America

Introduction: Patients treated at Veterans Affairs (VA) facilities are in poorer health, suffer from more medical and psychiatric conditions, and make greater use of medical resources than patients in the general population. We examined our recent experience at a large VA Medical Center to determine the incidence and risk factors associated with the development of postoperative delirium (POD) in VA patients after cardiac surgery and hypothesized that the risk factors for POD after cardiac surgery are different between VA and non-VA patients.

Methods: After IRB approval, 250 consecutive patients undergoing cardiac surgery from July 2014 to March 2016 were retrospectively studied. Patients undergoing deep hypothermic circulatory arrest were excluded. Demographics, coexisting diseases, medications, the type and duration of the procedure, and the duration of bypass were recorded from the medical record. Intraoperative crystalloid, colloid, cell saver, and blood product volumes were compiled. Progress notes and ICM-10 codes were searched for documentation of POD. A stepwise logistic regression analysis was performed to determine the association between predisposing and precipitating factors and POD. Descriptive and univariate statistics were performed, and odds ratios were computed.

Results: Thirty-eight patients (15.2%) developed POD. Congestive heart failure (2.223 [1.046-4.722]; odds ratio [95% confidence interval], P=0.0377), preexisting cognitive impairment (5.147 [1.994-13.28], P=0.0007) and the presence of a neuropsychiatric disorder (2.015 [1.004-4.043], P=0.0487) were predisposing factors associated with higher odds of POD. The duration of surgery (1.236 [1.003-1.524], P=0.0469), transfusion of blood products (1.190 [1.038-1.364], P=0.0125), the durations of mechanical ventilation (1.254 [1.109-1.419], P=0.0003) and conscious sedation (e.g., propofol: 1.736 [1.301-2.317], P=0.0002), and the length of intensive care unit (ICU) stay (1.649 [1.368-1.988], P<0.0001) were precipitating factors associated with higher odds of POD.

Conclusion: Congestive heart failure, preexisting cognitive impairment, and the presence of a neuropsychiatric disorder are predisposing risk factors for POD after cardiac surgery in VA patients, whereas the duration of surgery, transfusion of blood products, the durations of mechanical ventilation and conscious sedation, and the length of ICU stay were precipitating factors for POD. These findings in VA patients are generally similar to those observed in the civilian population despite the well-known differences between these cohorts.

Economics, Education and Policy

Economics, Education and Policy-1

National Patterns and Process of Milestones Assessment in Anesthesiology: Survey Data from Program Directors and Clinical Competency Chairpersons

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Introduction: Anesthesiology programs report Milestones (1) performance assessments for each of the 25 subcompetencies every six months for every resident. Residency program directors utilize resident evaluations and a Clinical Competency Committee to make these assessments and assign specific Milestones ratings. The percentage of Straightlining (SL), defined as 'a string of identical Milestones ratings for a learner across all subcompetencies within that specialty', is especially high in Anesthesiology compared to other specialties (2). In collaboration with the Accreditation Council for Graduate Medical Education (ACGME) and as part of an ongoing mixed-methods study, the authors used a national survey to investigate the patterns and process of Milestones assessments in Anesthesiology.

Methods: With IRB exemption, Anesthesiology Program Directors (PD) and Clinical Competency Committee Chairpersons (CCC-C) were asked to voluntarily complete a short (5-10 minute) on-line questionaire (Summer 2019) assessing the utility and early impact of the Next Accreditation System (NAS) Milestones in the evaluation of trainees in Anesthesiology. E-mail reminders were utilized. An opportunity to select 'all that apply' was provided when appropriate and when 'other' was a response option selected, the respondent was prompted to explain their response. The opportunity for 'additional comments' at the end of the survey was provided. Data was analyzed in aggregate and the frequency and range of responses noted.

Results: The survey response rate was 53% for PD and 40% for CCC-C. Select PD Survey Responses: 51.7% (n=45) served 4 years or longer as PD at the program where they were currently located and 29 were also Vice Chair. 'Reviewed the ACGME common and specific training requirements' was the most frequent response to the kind of training they received in role of PD. Direct observation and In-Training examination performance were the most common assessment tools to help inform Milestones. The majority of PDs 'never' or 'rarely' (one or two times ever) change a Milestone report from the recommendations of the CCC. 'Difficult to gather specific data for some Milestones' and 'Too many Milestones areas to rate', were identified as the most frequent barriers to accurately characterize resident performance in Milestones ratings. Select CCC-C Survey Responses: 38.8% (n=26) have served 1-3 years as CCC-C and 34.3% (n=23) for >5 years. The CCC size ranges from 4-30 members. 60.5% (n=49) CCC-C are core faculty members as their singular role in the residency program and report 'Reviewed the ACGME CCC Guidebook' as the most common mode of training for role. Most utilize multiple faculty to examine each resident's performance prior to the formal Milestones meeting while 19.6% (n=11) reported only one reviewer. Most programs did not utilize CCC subcommittees (Range 0-12 subcommittees/program) to review resident assessment data prior to the formal CCC Milestones meeting which ranged in duration from 1-4 hours. The most common elements in the CCC Milestone assessment process were 'Resident's performance is pre-screened before the meeting by PD and/or CCC chair' (14.95, n=32), 'All resident 'files' reviewed by CCC members' (14.1%, n=35), and 'Specific Milestone levels are assigned by PD and/or CCC chair' (13.3%, n=33). 'Difficult to gather specific data for some Milestones' and 'Too many Milestones to rate' were identified as the most frequent barriers to the CCC being able to accurately assign Milestones.

Conclusion: This national survey of PD and CCC-C helps inform an understanding of the current pattern and process of Milestones assessment in Anesthesiology residency training programs. Being able to detect appropriate Milestone variation from level of training would theoretically be useful for designing and delivering specific feedback to each learner. PD and CCC-C identify similar barriers to being able to accurately characterize resident performance in semi-annual Milestones submission.

Reference(s):

(1) https://www.acgme.org/What-We-Do/Accreditation/Milestones/Overview

(2) https://www.acgme.org/Portals/0/PDFs/Milestones/2019MilestonesNationalReportFinal.pdf?ver=2019-09-30-110837-587

Economics, Education and Policy-2

National Patterns of Straightlining and Variability in Milestones Assessments in Anesthesiology

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Introduction: Anesthesiology programs report Milestones (1) performance assessments for each of the 25 subcompetencies every six months for every resident. In the Milestones National Report 2019 (2), straightlining (SL) was defined as 'a string of identical Milestones ratings for a learner across all subcompetencies within that specialty'. The percentage of SL for Anesthesiology residents was especially high compared to other specialties (Anesthesiology residents n=6525; PGY1[38.1%], PGY2[25.0%], PGY3[28.2%], PGY4[32.6%]) and was greater in 2019 than in 2018. In collaboration with the Accreditation Council for Graduate Medical Education (ACGME), the authors investigated national patterns and variability in Milestones assessment in Anesthesiology as part of an ongoing mixed-methods study of SL in Anesthesiology.

Methods: Milestones data gathered by the population of ACGME accredited Anesthesiology residency training programs in the United States for the January-June 2019 reporting period were evaluated with IRB exemption and in collaboration with the ACGME. We examined the relationship of specific program attributes, including size (number of residents), length (Categorical [4-year] or Advanced [3-year]), geographic location using the four US census regions, and Milestones assignments for each of the subcompetencies by postgraduate year (i.e. specifically 'post-graduate year [PGY] consistent rating' defined as % residents with Milestone level assigned for subcompetency = same as PGY), on rates of straightlining. Odds ratios, logistic regression, means, and ranges were calculated (SAS Enterprise Guide 7.15, Cary, NC) with $p<0.05$ considered significant.

Results: Categorical programs (127, n=5816 residents) that may offer both categorical and advanced positions and Advanced programs (24, n=708) that offer only advanced positions were included in this analysis. No difference in percent of SL was observed between Categorical and Advanced programs. From the Milestones National Report 2019, the highest percentage of SL was in PGY1 (38.1%) residents. As the size of program increases, the rate of residents with SL rating increases in both Categorical ($p<0.0001$) and Advanced ($p<0.0001$) programs. We used Categorical programs to determine the correlation between geographic location and SL. The Western region showed a higher rate of SL than the South (47.1 vs 31.9%, $p<0.0001$). There was no difference between the Southern and Midwestern regions (31.9 vs 28.8%, $p=0.0534$). The Midwest region showed a higher SL rate than the Northeast (28.8 vs 22.5%, $p<0.0001$). Program size did not explain the observed geographic variation. We also used Categorical program data to compare each postgraduate year (PGY1;1284, PGY2;1572, PGY3;1519, PGY4;1441) against each of the 25 Milestones subcompetencies and calculated the % 'PGY-consistent rating', mean and range: PGY1; 53.9% (47.2%[Prof3]-59.8%[PBLI4]), PGY2; 48.9% (45.2%[Prof2]-56.7%[PC3]), PGY3; 49.2% (44.5%[Prof3]-54.2%[SBP1]), PGY4; 60.3% (56.2%[PC2]-65.5% [PBLI1]).

Conclusion: Straightlining in Milestones performance assessment is common in Anesthesiology and greater than in many other specialties (2). Within Anesthesiology, there is an association of increased SL with larger programs and geographic location of the program. There appears to be an association of increased SL and PGY-consistent rating for individual subcompetencies at the beginning (PGY1) and end (PGY4) of training. The subcompetency of Professionalism had the lowest % PGY-consistent rating for PGY1, PGY2, and PGY3. Being able to detect appropriate Milestone variation from level of training would theoretically be useful for designing and delivering specific feedback to each learner. It is unknown whether the observed SL effect represents actual lack of variation in competence, or if clinical competency committees are providing similar ratings across competencies for other reasons.

Reference(s):

(1) https://www.acgme.org/What-We-Do/Accreditation/Milestones/Overview

(2) https://www.acgme.org/Portals/0/PDFs/Milestones/2019MilestonesNationalReportFinal.pdf?ver=2019-09-30-110837-587

Economics, Education and Policy-3

Operating Room Efficiency: Addressing Issues in an Academic Institution GI Suite

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Introduction: The Digestive Disease Center (DDC) at the University of Cincinnati is part of a large, Academic hospital complex. It serves acute and specialized patients that other satellite locations cannot; it must also participate in the larger peri-operative service system of the Hospital, provides a catch-all for indigent care, serves a central teaching function for GI, and has many process 'traditions.' So intertwined, the DDC has been a known source of frustration for providers and patients alike, and a source of concern for the system, particularly in the setting of increasing demand and budgetary limitations[1]. Many working there cited failed reform attempts because of the academic setting noted above[2], or things like time-and-motion studies are too advanced to begin with in a complex setting[3]. Our process improvement strategy focused on problems that, oftentimes, all staff 'know' about but no one has addressed. We hypothesized that fixing 'known' things would have a practical impact, such as by creating an earlier first procedure start time.

Methods: Our 'known' intervention strategy started at the end of 2014 and ran through the end of 2016, and included the following components: 1. We made a team including nursing, GI, Anesthesia, and Support Staff that met weekly and spent time on the 'front lines' i.e. actually working in the DDC. 2. We interviewed providers and support staff such as cleaning and transportation. 3. We noted issues from our own regular work experiences there. 4. We gathered data from the EMR to corroborate information. We took the information gathered, expressed the 'known' issues, and then addressed them: 1. Addressed tardiness directly using data with staff and their leadership. 2. Aligned all staff to report for duty at the same time each day. 3. Removed excess equipment, fixed broken/faulty equipment, supplied missing equipment. 4. Renumbered bed spaces to reduce confusion. 5. Recruited recovery nurses help with intake before the first start. 6. Made sure each computer had EMR access. We used Student's T-Test to compare the independent means of the first start times before and after our intervention.

Results: Because first start time impacts the rest of the day, patient/provider experience, and costs, we hoped to find that our first start times improved in comparison to before our interventions began. We compared January 2014 to the first month our interventions were complete (January 2017). Holding the month the same reduced fluctuations due to time of year, provider skillset, etc. We included only rooms using nursing, GI, and anesthesia staff, which are the most complex to start from a staffing, equipment, and patient care standpoint. Average first start time was 9:10am (95%CI: 8:56 to 9:24) in January 2014 for 105 first cases, while by 2017 it had improved to 8:29am (95%CI: 8:18-8:40) in the 95 first start cases (p=0.0000109). Assuming an 8:56am start time for 2014, and the 8:40 start time for 2017, the DDC starts a minimum of 16 minutes earlier per room, per day.

Conclusion: There are many ways to address issues in a system, but often they can seem, or get, very complicated--and as a result, have little impact. After just addressing the 'known' issues staff experience daily we start on average 41 minutes earlier, and at least 16 minutes earlier--enough time at minimum to do an additional EGD. This additional efficiency can create even more process improvement, reduce costs further based on procedural room costs4, or just get patients and staff home on time for the day for once and improve their experience! Impactful system improvement does not have to be overwhelming; it can be achieved just creating a team to express and address what staff members 'know' need to be done.

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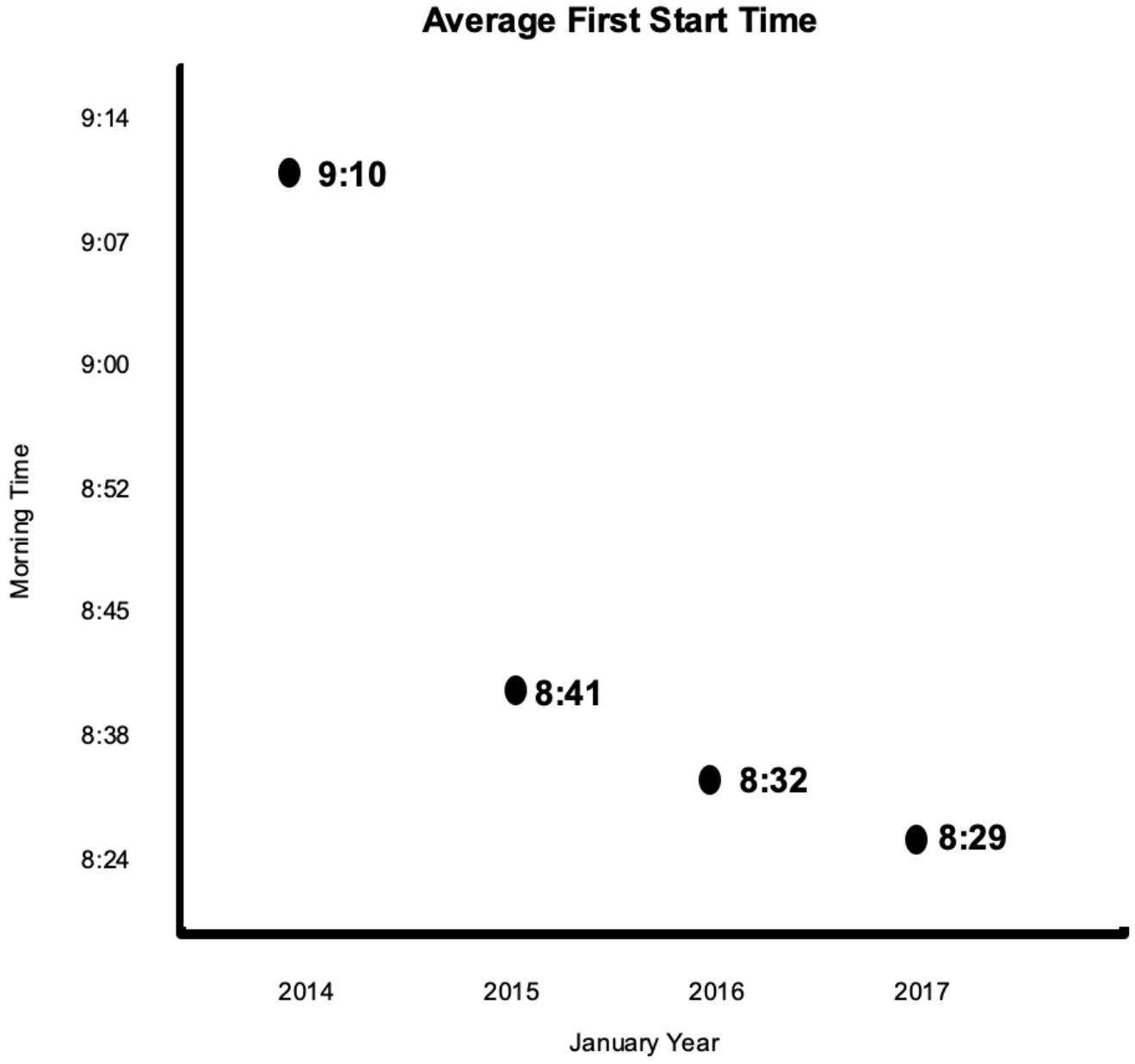
"PTU-081"…Enhancing efficiency in endoscopy unit using the "˜time and motion' model." Gut 68: A231-A232; 2019.
"Efficiency of an endoscopy suite in a teaching hospital: delays, prolonged procedures, and hospital waiting times." Gastrointestinal Endoscopy 64: 760–764; 2006.
"Understanding Costs of Care in the Operating Room." JAMA Surg 153(4):e176233; 2018.


Average First Start Time
9:14
9:07
9:00
8:52
8:45
8:38
8:24
Morning Time
9:10
8:41
8:32
8:29
2014
2015
2016
2017
January Year

Economics, Education and Policy-4 Gender differences in the authorship of contemporary anesthesia and surgery literature

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Introduction: The number of women in medicine has steadily increased over the past five decades, representing 36% of all practicing physicians in the United States in 2019. (1) A gender gap exists, however, and women remain underrepresented in leadership roles and academic journals.(2–4)A 2014 American Association of Medical Colleges analysis of female rank within academic medicine found that women comprised only 20% of full professors. This number was lower within anesthesiology (18%) and surgery (9%). (5) This trend holds true when looking at departmental and national leadership positions.(6) At most academic institutions, key criteria for tenure and promotion is research productivity as measured by publication in peer-reviewed journals. Studies have shown that while the proportion of women as first and senior authors in major academic journals has increased decade by decade, a gender gap remains and women represent only 29.3% of first and 19.3% of last authors.(4) In this study, we examined the prevalence of women first and last authors in original research articles published from 2008 to 2018 in the five anesthesia and five surgery journals with the highest impact factor. We sought to quantify the eventual gender gap, examine changes over time, and identify factors associated with woman authorship.

Methods: The five highest impact journals for anesthesia and general surgery were identified from Thomson Reuters-Clarivate Analytics. Anesthesia journals included Anesthesiology, British Journal of Anaesthesia, Anaesthesia, European Journal of Anaesthesiology, and Anesthesia and Analgesia. Surgery journals included Annals of Surgery, British Journal of Surgery, Journal of the American College of Surgeons, JAMA-Surgery, and Surgery (Table 1). For each journal, all original research articles, systematic reviews, and meta-analyses published in 2008, 2010, 2012, 2014, 2016, and 2018 were selected. Case reports, conference presentations, editorials, review articles not classified as a systematic review, and expert opinions were excluded. This study was prospectively registered with the International Prospective Register of Systematic Reviews (registration number 151092). Articles with either a first or last woman author were classified as 'woman-authored'. All others were classified as 'man-authored'.

Results: 10,836 articles authored by 76,587 authors were analyzed: 4720 anesthesia and 6116 surgery articles. (Table 1) A total of 4181 (38.6%) articles were woman-authored, with 22.3% woman first authors and 9.4% woman last authors, and 1872 (39.6%) in anesthesia and 2309 (37.8%) in surgery. (Table 2) Woman-authored studies constituted 34.2% of overall articles in 2008, compared to 45.1% in 2018, with similar trends for anesthesia (37.3% to 45.7%) and surgery (30.9% to 44.5%) (p for trend <0.001). (Figures 1,2) Compared to articles originating from North America, articles from Europe (odds ratio [OR}: 1.18, 95% confidence interval [CI]: 1.01-1.38, p=0.04) and Asia (OR: 1.31, 95% CI: 1.03-1.65, p=0.02) were more likely to be woman-authored (Table 1)

Conclusion: To conclude, the woman in authorship in anesthesia and surgery has increased significantly over the last decade, with number of woman first authors in the current anesthesia and surgery literature consistent with the percentage of practicing women in the two fields. We found that woman first and last authors are more likely to hold a PhD or non-medical academic degree compared to man authors and significant geographic variations exist. While this is encouraging, woman last authorship has increased minimally in 10 years, and the proportion of woman last authors is significantly less than their representation in the fields of anesthesiology and surgery. Our data suggest that resources should be invested in the junior women investigators to allow rise up in the ranks to become senior authors. Further studies should be focused on barriers to women becoming last author.

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4. Jagsi R et al. The “gender gap” in authorship of academic medical literature--a 35-year perspective. N Engl J Med. 2006;355(3):281-287. doi:10.1056/NEJMsa053910
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6. Burden M et al. Gender disparities in leadership and scholarly productivity of academic hospitalists. J Hosp Med. 2015;10(8):481-485. doi:10.1002/jhm.23

Table 1. Summary of the articles analyzed by gender (percentages are per row, not per column).

	Overall	Woman-authored study	Man-authored study	P-value
Total	10836	4181 (38.6)	6655 (61.4)	-
Anesthesia articles (%)	4720 (43.6)	1872 (39.7)	2848 (60.3)	-
Surgery articles (%)	6116 (56.4)	2309 (37.7)	3807 (62.3)	-
Woman first author	2425 (22.3)	2425 (100.0)	NA	-
Woman last author	1019 (9.4)	1019 (100.0)	NA	-
Woman first and last author	737 (6.8)	737 (100.0)	NA	-
Median year of publication	2014 [2010, 2016]	2014 [2010, 2016]	2012 [2010, 2016]	<0.001*
Number by year (%)				<0.001*
• *2008*	1871 (17.3)	639 (34.2)	1232 (65.8)	-
• *2010*	1678 (15.5)	565 (33.7)	1113 (66.3)	-
• *2012*	1818 (16.8)	655 (36.0)	1163 (64.0)	-
• *2014*	1749 (16.1)	691 (39.5)	1058 (60.5)	-
• *2016*	1760 (16.2)	748 (42.5)	1012 (57.5)	-
• *2018*	1960 (18.1)	883 (45.1)	1077 (55.0)	-
Median number of co-authors per study	6 [5, 8]	6 [5, 8]	7 [5, 9]	<0.001*
Median number of man co-authors per study	5 [3, 6]	4 [2, 5]	5 [4, 7]	<0.001*
Median number of Woman co-authors per study	1 [1, 3]	2 [1, 3]	1 [0, 2]	<0.001*
Retrospective study (%)	4408 (40.7)	1698 (38.5)	2710 (61.5)	0.92
Prospective study (%)	6413 (59.2)	2478 (38.6)	3935 (61.4)	0.90
Single center study (%)	6390 (59.0)	2440 (38.2)	3950 (61.8)	0.31
Academic hospital (%)	3557 (32.8)	1386 (39.0)	2171 (61.0)	0.58
Study origin				<0.001*
• *Africa*	53 (0.5)	19 (35.9)	34 (64.2)	0.79
• *Asia*	1258 (11.6)	373 (29.7)	885 (70.4)	<0.001*
• *Australia*	272 (2.5)	100 (36.8)	172 (63.2)	0.58
• *Europe*	3740 (34.5)	1402 (37.5)	2338 (62.5)	0.09
• *North America*	4892 (45.1)	2096 (42.9)	2796 (57.2)	<0.001*
• *South America*	86 (0.8)	38 (44.2)	48 (55.8)	0.34

• *Multi-continental*	535 (4.9)	153 (28.60)	382 (71.40)	<0.001
Academic degrees of first authors (%)				<0.001*
• *MD*	5380 (49.6)	1998 (37.1)	3382 (62.9)	<0.01*
• *MD and others*	2476 (22.8)	815 (32.9)	1661 (67.1)	<0.001*
• *PhD*	679 (6.3)	367 (54.1)	312 (46.0)	<0.001*
• *Others*	675 (6.2)	366 (54.2)	309 (45.8)	<0.001*
• *Not reported*	1626 (15.0)	635 (39.1)	991 (61.0)	0.69
Academic degrees of last authors (%)				<0.001*
• *MD*	4164 (38.4)	1503 (36.1)	2661 (63.9)	<0.001*
• *MD and others*	4005 (37.0)	1544 (38.6)	2461 (61.5)	0.97
• *PhD*	949 (8.8)	454 (47.8)	495 (52.2)	<0.001*
• *Others*	163 (1.5)	99 (60.7)	64 (39.3)	<0.001*
• *Not reported*	1555 (14.3)	581 (37.4)	974 (62.6)	0.29
Median number of author departmental affiliations	3 [2, 4]	3 [2, 4]	3 [2, 4]	0.33
Funding				
• *Internal (%)*	2154 (19.9)	893 (41.5)	1261 (58.5)	0.72
• *Public (%)*	3252 (30.0)	1384 (42.6)	1868 (57.4)	0.19
• *Industrial (%)*	616 (5.7)	224 (36.4)	392 (63.6)	<0.01*
• *Private (%)*	1666 (15.4)	771 (46.3)	895 (53.7)	<0.001*
Journal (%)				<0.001*
• *Anaesthesia*	608 (5.6)	242 (39.8)	366 (60.2)	0.55
• *Anesthesia & Analgesia*	1661 (15.3)	723 (43.5)	938 (56.5)	<0.001*
• *Anesthesiology*	1056 (9.7)	345 (32.7)	711 (67.3)	<0.001*
• *British Journal of Anaesthesia*	933 (8.6)	365 (39.1)	568 (60.9)	0.75
• *European Journal of Anaesthesiology*	462 (4.3)	197 (42.6)	265 (57.4)	0.07
• *Annals of Surgery*	1567 (14.5)	515 (32.9)	1052 (67.1)	<0.001*
• *British journal of Surgery*	1053 (9.7)	391 (37.1)	662 (62.9)	0.32
• *Journal of the American College of Surgeons*	1180 (10.9)	458 (38.8)	722 (61.2)	0.88
• *JAMA Surgery*	702 (6.5)	301 (42.9)	401 (57.1)	0.01*
• *Surgery*	1614 (14.9)	644 (39.9)	970 (60.1)	0.25

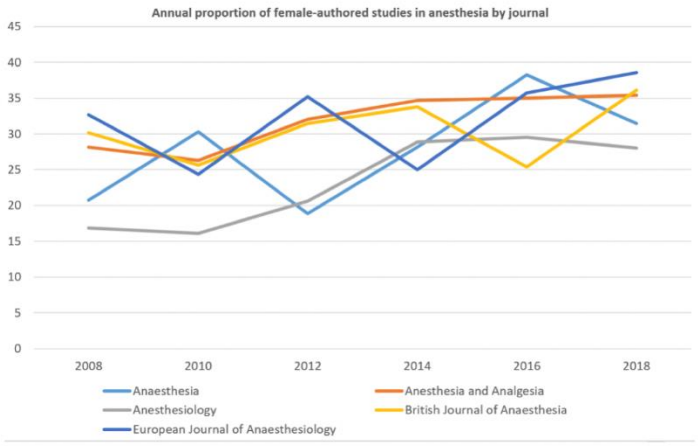
Table 2. Summary of studies authored by woman physicians by year (First author and Last author)

	Overall	Man-authored study	Woman-authored study	Women first author	Women last author	Woman first and last authors	P-value
Total	10836	6655	4181	2425	1019	737	
Number by year (%)							<0.001*
2008	1871 (17.3)	1232 (65.8)	639 (34.2)	360(19.24)	176(9.41)	103(5.51)	
2010	1678 (15.5)	1113 (66.3)	565 (33.7)	320(19.07)	154(9.18)	91(5.42)	
2012	1818 (16.8)	1163 (64.0)	655 (36.0)	390(21.45)	150(8.25)	115(6.33)	
2014	1749 (16.1)	1058 (60.5)	691 (39.5)	425(24.30)	150(8.58)	116(6.63)	
2016	1760 (16.2)	1012 (57.5)	748 (42.5)	416(23.64)	181(10.28)	151(8.58)	
2018	1960 (18.1)	1077 (55.0)	883 (45.1)	514(26.22)	208(10.61)	161(8.21)	

¶ Percentages calculated of the overall number

*For Man-authored study vs Woman-authored study

Annual proportion of female-authored studies in anesthesia by journal



Annual proportion of female-authored studies in surgery by journal

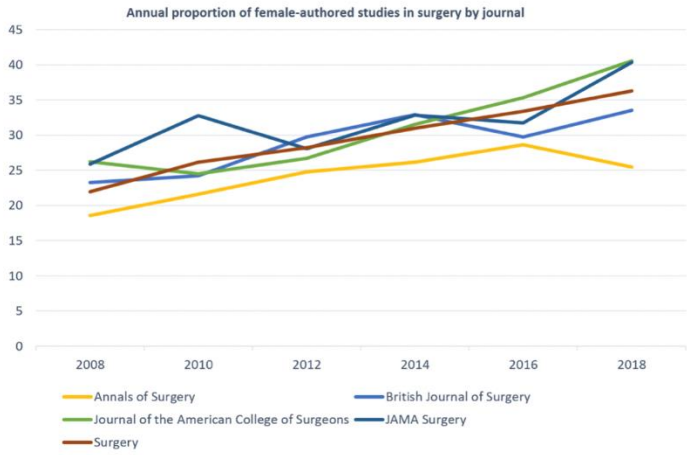
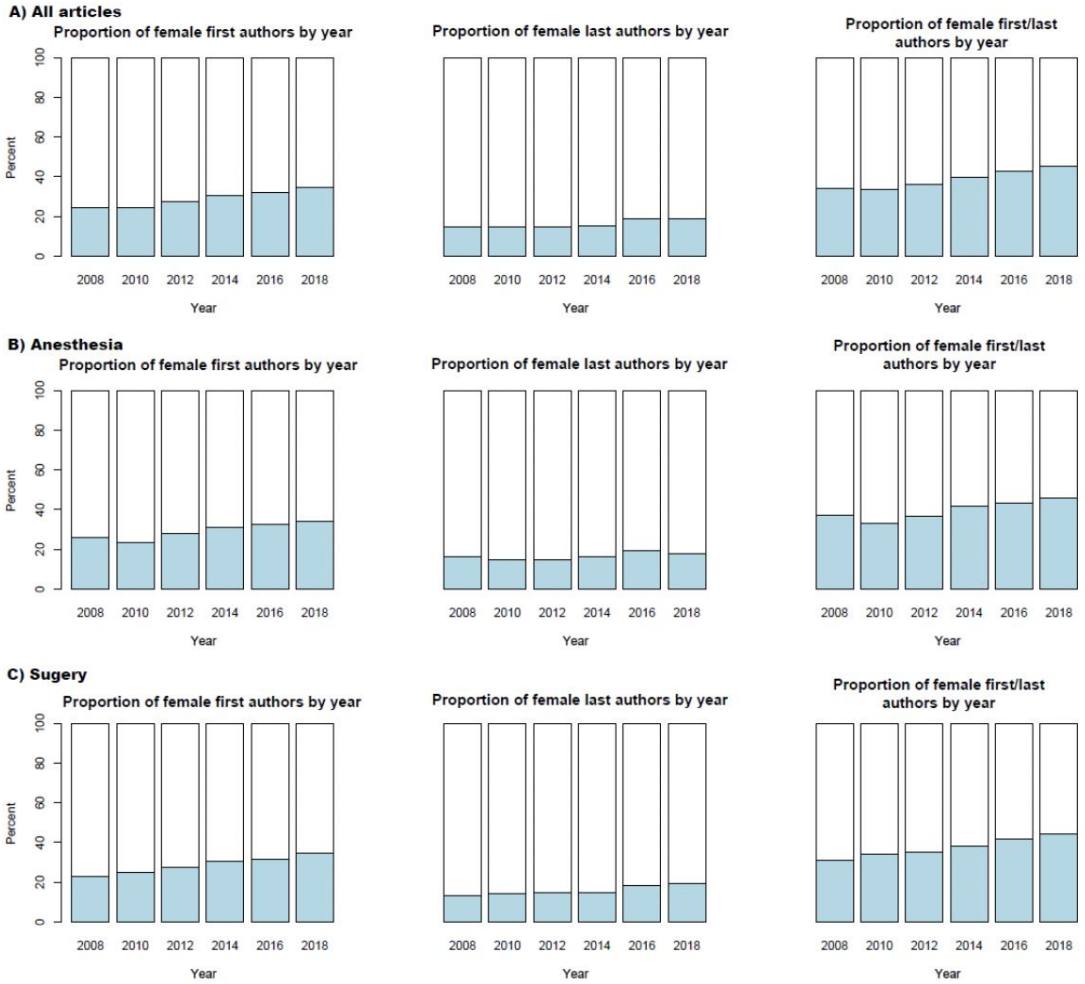


Figure: Proportion of female first, last and female first and last authors by year 2008-2018



Economics, Education and Policy-5

Geospatial Variations and Neighborhood Deprivation in Drug-Related Admissions and Overdoses

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Introduction: The use of geospatial analysis to target high risk areas of drug overdose has allowed for a more nuanced understanding of the socioeconomic and demographic factors associated with overdose. Studies suggest that usual classifications of geographic areas (e.g. urban vs. rural) may not be adequate when describing the changes in geographical distributions of drug overdoses [1]. The Area Deprivation Index (ADI) is a socioeconomic index of variables from the United States Census and American Community Survey that is tabulated at the census block group level and may serve as an alternative classification [2]. ADI has recently been used as a predictor for medical outcomes, including 30-day rehospitalization [3]. In order to develop a better understanding of socioeconomic indicators contributing to drug abuse, overdose and death, we hypothesized that ADI may correlate to drug overdose and drug-related hospitalization. Given that ADI is a neighborhood level index, it is linked and thus, dependent on geospatial context. In this retrospective study, we seek to determine whether neighborhood socioeconomic disadvantage as captured by ADI, could be a useful metric to determine drug-related hospital admissions. We also seek to characterize the spatial distribution of patients admitted to a large urban academic medical center in Durham county, NC for drug-related admissions and overdoses.

Methods: We searched within the Duke University Health System electronic health records to identify patients admitted for any conditions related to opioid, amphetamine or psychostimulants and further stratified patients who were admitted for drug overdoses. ADI was used to evaluate the influence of neighborhood socioeconomic disadvantage on drug admissions and overdoses [3-4]. The objectives were to (1) examine the association between spatial characteristics and drug-related admissions; (2) examine the association between ADI and drug-related admissions; and (3) to adjust spatial distributions for ADI to determine if spatial heterogeneity could be abolished by considering ADI alone. Nonspatial statistics were used including chi-square, t-tests as appropriate. For spatial analysis, we fit hierarchical Bayesian spatial models using the statistical programming language R and the package INLA. Primary outcome variables were (1) number of drug-related admissions per census block group, and (2) the number of drug overdoses per census block group. Models were conditional autoregressive models using a Besag-York-Mollie spatial correlation structure [5].

Results: Using ICD diagnoses for patients with a drug-related diagnosis and those with an overdose-related diagnosis (Tables S1 and S2), we identified 10,352 and 859 patients, respectively, who were included in the initial analysis. Of those, 3,314 patients had geocoded addresses and an address in Durham County. Of the drug overdose cohort, 387 patients had geocoded addresses in Durham County and were included in geospatial modeling. Patient characteristics are shown in Table 1. Overdoses and admissions were closely correlated (Figure 1). Higher ADI (greater neighborhood disadvantage) was associated with both more drug admissions (probability of a positive effect was 99.8% for admissions and 97.0% for overdoses) (Figure 2). Both drug-related admissions and overdoses were geographically variable (Figures 3 and 4). As a proportion of total Duke patients, the prevalence of drug-related admissions was between 0.4% and 8.3% within the block groups of Durham County. Drug overdoses ranged from 0.05% to 0.95%. In both cases, the highest prevalence was in the city of Durham in the center of Durham County, a higher population density urban area with a large minority population.

Conclusion: We found geospatial clustering of substance use-related admissions and overdoses compared to the general population. ADI is associated with an increased risk of admissions but does not correct for spatial variability suggesting unmeasured socioeconomic indicators. Alternatively, because ADI does not correct the spatial heterogeneity, the socioeconomic patterns of drug use may be changing such that socioeconomically-affluent and impoverished areas may be similarly affected. We also demonstrate that ICD codes can be coupled with local coordinates via EMR for studying drug epidemics. These may have important policy implications regarding isolation of high risk geographic locations and for future studies on how drug use, misuse and overdoses change with temporally.

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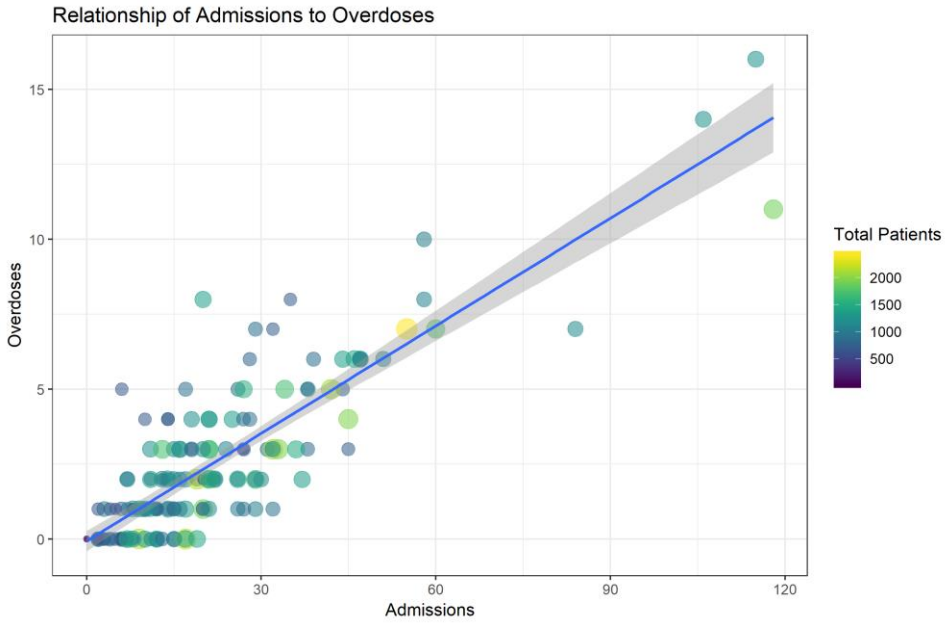

Figure 1 – Scatterplot of drug-related admissions vs overdoses with point size and color mapped to the total number of patients

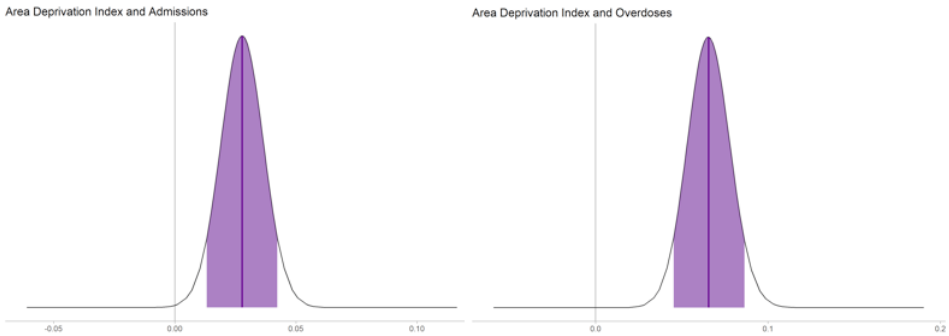

Figure 2 – Posterior fixed effects plot looking at ADI associated with drug-related admissions and overdoses. ADI is scaled such that 1 represents a 20%ile change in ADI. Note that the distributions do not cover 0 and thus would be extremely improbable that there is no effect of ADI on admissions for drug-related issues or overdoses.

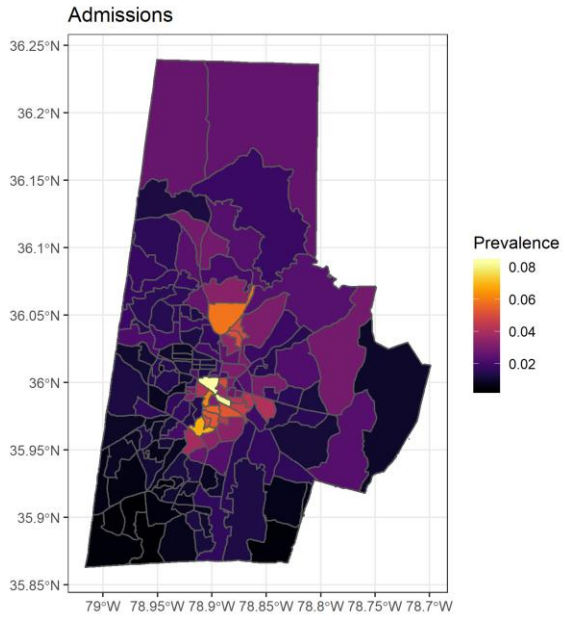

Figure 3 - Bayesian Spatial Regression of drug-related admissions adjusted for ADI – color scale represents the rate ratio based on number of Duke patients per census block group

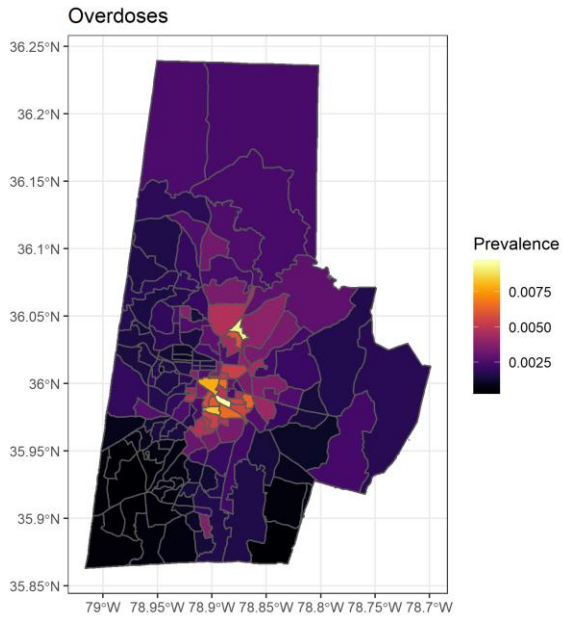

Figure 4 - Bayesian Spatial Regression of drug-related overdoses adjusted for ADI – color scale represents the rate ratio based on number of Duke patients per census block group

Characteristics	All Drug-related Admissions n=10352	% or IQR	Overdoses n=859	% or IQR
Age	49 years	(IQR 36,59)	48 years	(IQR 40,57)
Male	5228	50.5	461	53.7
Unknown gender	1	0.0	0	0.0
Female	5123	49.5	398	46.3
Dead	2542	24.6	204	23.7
Alive	7810	75.4	655	76.3
Black or African American	3984	38.5	370	43.1
Caucasian/White	5733	55.4	446	51.9
Multiracial	155	1.5	14	1.6
Hispanic	232	2.2	17	2.0
Asian	42	0.4	3	0.3
American Indian	80	0.8	2	0.2
Unknown race/ethnicity	126	1.2	7	0.8

Table 1 – Characteristics of patients across drug-related admission and overdose cohorts

Economics, Education and Policy-6 CVC Coaching, a Multimodal Approach to Central Venous Catheter Training

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Introduction: Research evaluating central venous catheter (CVC) adverse events, has revealed statistically significant increases in patient morbidity, mortality, and cost to American healthcare1. This consequently negatively impacts the profession of all health care workers and, most importantly the health of our patients. Quality improvement (QI) initiatives through education have been shown to decrease CVC complication rates2. Previous studies have concluded that medical professionals learn more effectively if material was taught using a combination of visual, auditory, and kinesthetic instruction3 (VAK). These studies suggested revising medical curriculum to incorporate a combination of VAK resources for more efficacious teaching. To address CVC complication rates and this instruction gap, we developed a multimodal curriculum based on these aforementioned educational principles. This was done in order to provide a more effective CVC curriculum for medical students, residents, and attendings. During this first phase of our program, we aim to show that CVC placement knowledge and confidence is improved with the VAK based training program we developed.

Methods: 23 subjects consisting of University of Texas Medical Branch Anesthesiology residents consented and participated in our multi-stage approach. Participants first watched our online video. Instructors then lectured and demonstrated these skills, in person, on a CVC training mannequin. Subsequently, subjects practiced what they had been taught on the CVC training mannequin (figure 1). Our instructional videos and training via our CVC mannequin were supplemented by checklists. Our approach also used principles based on Mayer's cognitive theory of multimedia learning. Aspects of this theory include teaching using two modes of representation rather than only using one. By design, our approach to CVC instruction targeted the three aspects of VAK learning. Our CVC curriculum incorporated online training videos, checklists, in-person instructor training, participant kinesthetic practice with CVC mannequins, and assessments. Another principle of Mayer's cognitive theory emphasizes explaining a principle while the corresponding material is illustrated. For example, lecturing on central line placement while illustrating the procedure at the same time.

Results: Pre and post-training questionnaire data was compared using paired t-tests, with significance set to $\alpha = .05$. This revealed a statistically significant mean increase in objective CVC knowledge and confidence post-training. This increase was found in all parameters described in figure 2.

Conclusion: Our CVC curriculum incorporated online training videos, checklists, hands-on training with CVC mannequins, and assessments. By design, it targeted all three aspects of VAK learning. We attribute the effectiveness of the program to this multimodal approach. We are currently using this preliminary data and participant feedback to further improve our program. We are working on an affordable CVC trainer prototype of our own design to make the visual/kinesthetic aspect of our initiative more affordable and ubiquitously available to medical professionals. We hope to expand our comprehensive CVC training program, state and nationwide. The statistically significant results are most likely due, in part, to this multimodal approach with applied Mayer's cognitive theory of multimedia learning.

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Economics, Education and Policy-7 Year-End Variation in Adult Surgical Caseload at a Large Private U.S. Anesthesia Practice

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Introduction: Anesthesia staffing models often rely on minimal seasonal variation in surgical caseload.1-3 An analysis of a 1994-1996 national database found no relationship between month of the year and ambulatory surgical volume.[4] However, recent shifts in insurance coverage in the U.S. raise the possibility that patients may be more likely to seek high-cost surgical care at the end of the year when deductibles have been met.[5] We hypothesized that daily caseload in December would be higher than during other months of the year. To assess this possibility, we reviewed 2018 case data from a large multi-state U.S. anesthesia practice.

Methods: This study was deemed exempt by the Institutional Review Board. We retrospectively reviewed case data from 2018 at a large private U.S. anesthesia practice located primarily in Florida and Texas. Cases involving patients with missing age, under 18 years old, over 100 years old, and cases from anesthesia groups acquired by the practice during the year were excluded. The remaining anesthesia cases were used to generate monthly case counts, which were then divided by the number of working days in each month to generate average daily case counts (ADCC).6 Negative binomial regression models were used to determine the overall effect of the month of the year on anesthesia caseload and to assess the difference in caseload between December and other months, overall and for two age subgroups (18-65 years old and over 65 years old), controlling for practice location (Florida or Central, Southern, or Northern Texas). Data analyses were performed in R 3.5.3.

Results: A total of 1,273,891 surgical procedures were performed in 2018. Of those, 1,199,439 adult surgical cases were included in the study (Figure 1). The overall ADCCs are shown in Figure 2. After controlling for practice location, ADCCs increased on average by 1.1% from one month to the next (Incidence Rate Ratio (IRR) 1.011 (1.007-1.016), p<0.001). When patients were stratified by age, ADCC for patients 18-65 years old increased by 1.9% per month (IRR 1.019 (1.016-1.024), p<0.001). However, for patients >65 years old, ADCC did not vary significantly by month of the year (p=0.352). After controlling for practice location, overall ADCC in December was not significantly different from ADCC during other months (p=0.31). However, ADCC was 12.7% higher in December for patients 18-65 years old (IRR 1.127 (1.040-1.222), p=0.004) than during the January-November period. For patients >65 years old, ADCC was 12.1% lower in December than during the January-November period (IRR 0.879 (0.826-0.936), p=0.005).

Conclusion: In this large retrospective study, we observed that for patients 18-65 years old, the December daily caseload was higher than during other months. In contrast, for patients >65 years old, caseload did not differ by month and was not higher in December. One possible mechanism for this difference may be higher deductibles, causing younger patients more likely to be on private insurance to delay high-cost surgical care until later in the year when deductibles have been paid. Further work is needed to understand the mechanism for this observation and to verify whether these results are generalizable to other practices.

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Figure 1. Flowchart Detailing Exclusion Criteria from the Study.

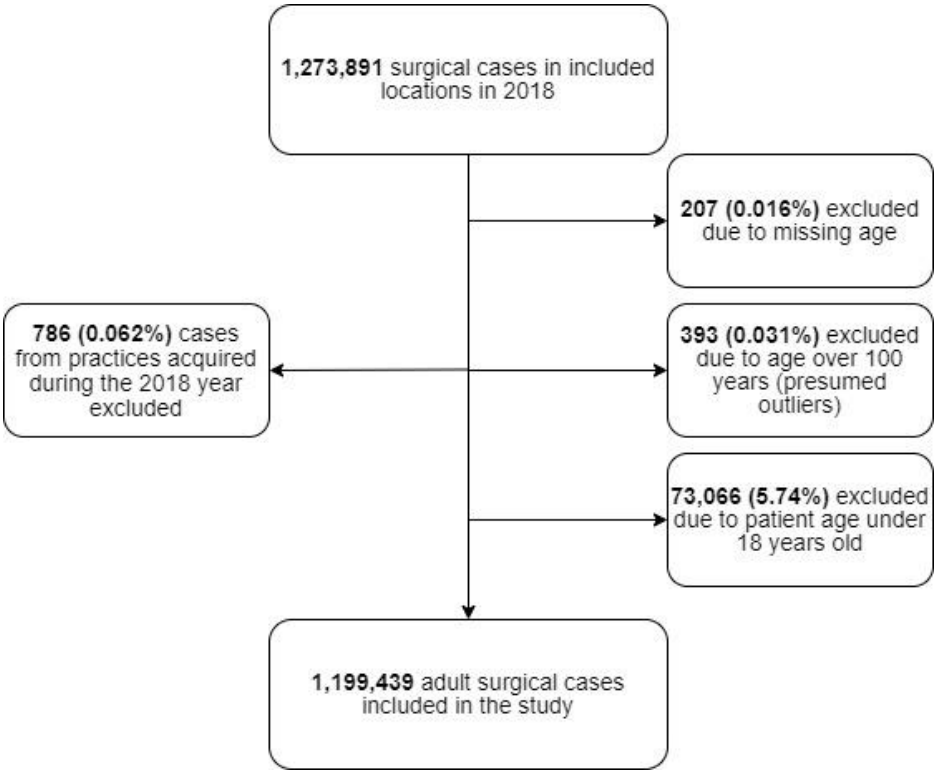
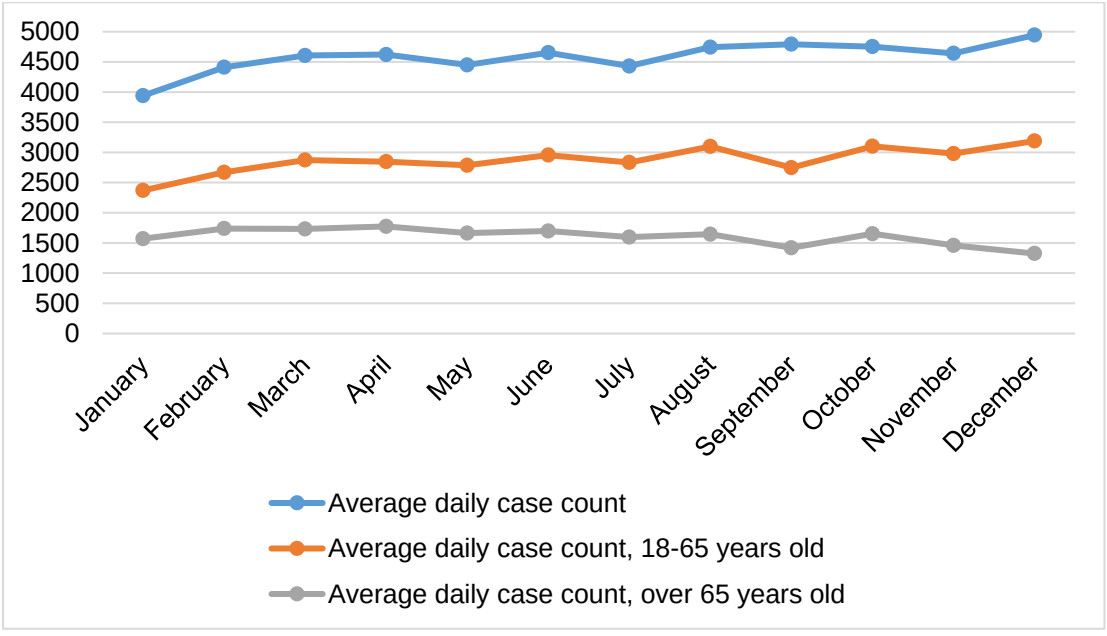


Figure 2. Average Daily Case Counts for Each Month During the 2018 Calendar Year.



Economics, Education and Policy-8 OR's for Future - Reducing Anesthesia's CO_2 Footprint: The End of Desflurane?!

Hendrik Booke[1], Rolf D Nordmeier[1]

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Introduction: While global warming and its reasons are still discussed politically, scientists agree upon global warming as such and on the significant impact of global CO2-production (1). While the public discussion focusses on coal-fired power plants, energy-driven industries, general air traffic and road traffic, the impact of our health care system has been neglected so far. Anesthetic gases are either chlorofluorocarbons (CFCs, e.g. isoflurane, nitrous oxide) or hydrofluorocarbons (HFCs, e.g. sevoflurane, desflurane), all being very potent green house gases (GHG): A gas in the atmosphere becomes a GHG by absorbing and/or reflecting infrared radiation from earth that would otherwise escape into space (2). We here analyse the contribution of a community hospital to global warming by using desflurane and/or sevoflurane and put it into an easier to understand perspective.

Methods: Using a mathematical bottom-up model, we calculated the impact of maintaining general anesthesia at low-flow ventilator settings using desflurane or sevoflurane on global warming. To proportion these results, we translated desflurane's and sevoflurane's CO2-footprint into kilometers driven by car. We further asked each anesthesiologist in the OR, how many kilometers he or she is driven in 2019.

Results: Our community hospital runs 11 ORs, in which we provided 16.348 hours of general anesthesia in 2019. The calculated driving equivalence for maintaining anesthesia for one hour using desflurane is 561 km, versus 112 km when sevoflurane is used (1 MAC, 0,5 l/min fresh gas flow) (2). Using solely desflurane would sum up to a driving equivalence of 9.171.228 km., while using solely sevoflurane sums up to a driving equivalence of 1.830.976 km. Anesthesiology's CO2-footprint is somewhere in between, depending on the percentage of desflurane use. This is between 10,8 times (only sevoflurane) and 54,1 times (only desflurane) more when compared to 169.400 km driven by all of our attending anesthesiologists in 2019.

Conclusion: In 2030, desflurane will be banned by the Kyoto protocol, signed in 1997 and entered into force in 2005 (3). Desflurane has the largest global warming impact when compared to isoflurane and sevoflurane, and it has the longest atmospheric half-life, so that desflurane released nowadays still has an impact in 2030 (4). In 2014, 3.1 Million tons of CO2-equivalent were released into the atmosphere via anesthetic gases, with around 80% stemming from desflurane (5). A community hospital like ours using desflurane signs responsible for a CO2-footprint which is comparable to approximately 9,2 million kilometers driven by car. Using solely sevoflurane reduces the CO2-footprint by 80% to a calculated equivalence of 1,8 million kilometers. Nonetheless, both numbers are far higher than the amount of driven kilometers of all anesthesiologists in our department. This comparison may put the use of desflurane into a new perspective for anesthesiologists.

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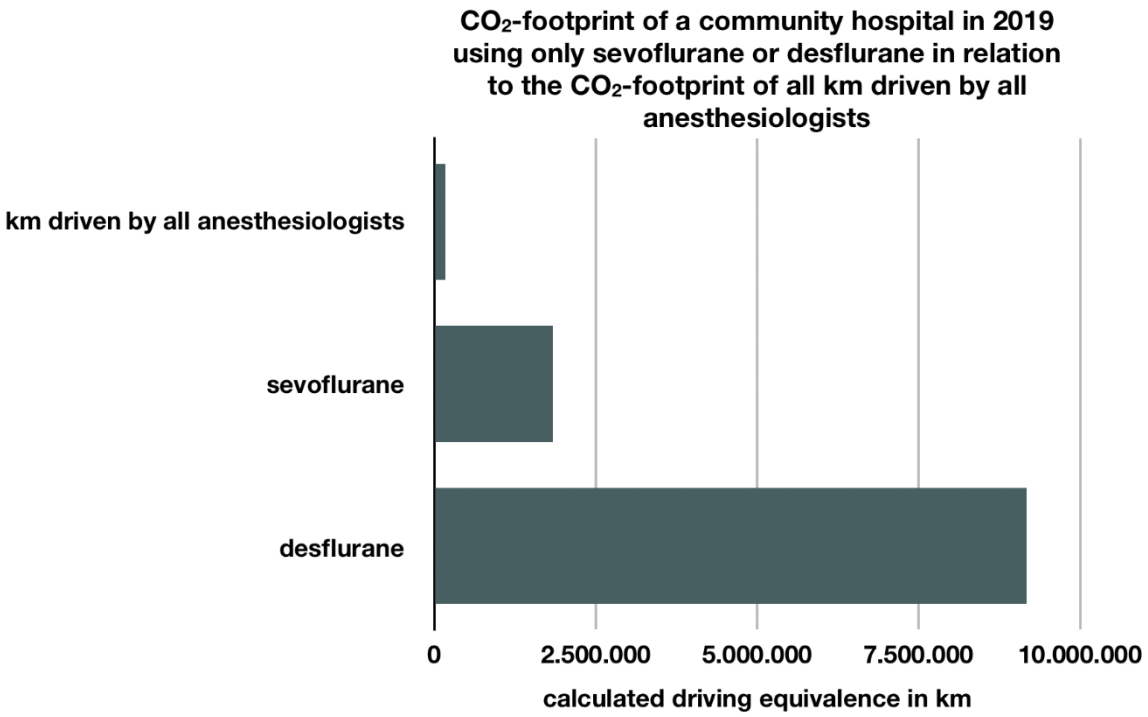
CO_2-footprint of a community hospital in 2019 using only sevoflurane or desflurane in relation to the CO_2-footprint of all km driven by all anesthesiologists
km driven by all anesthesiologists
sevoflurane
desflurane
0
2.500.000
5.000.000
7.500.000
10.000.000
calculated driving equivalence in km

Economics, Education and Policy-9 Years Since Primary Anesthesia Training as a Predictor to Identify Cohorts for Focused Neuromuscular Blockade Reversal Continuing Medical Education

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[1]Brooke Army Medical Center, San Antonio, TX, [2]Defense & Veterans Center for Integrative Pain Management, San Antonio, TX

Introduction: Clinically effective reversal of neuromuscular blockade remains an important component of safe anesthetic care. Multiple studies have demonstrated a significant residual paresis hours after initial dosing of neuromuscular blocking drugs in the absence of reversal.[1,2] A blanket approach of mandatory education for all members of a given department is both inefficient and difficult. A more preferred approach would be to find the population within the group that is most likely to deviate from accepted best practices and focus continuing education efforts on these providers. In this investigation, the association between the cumulative number of years since completion of primary anesthesia training and the choice of neostigmine reversal dose in the context of a clinical vignette was investigated.

Methods: This investigation was developed under the auspices of Quality Improvement with review by our Human Research Protections Office determining an Institutional Review Board Research Application was not required. A case vignette focused on neuromuscular blockade reversal was appended to a survey distributed to staff anesthesia providers in a single large academic anesthesia department. Appendix 1. A survey investigation was chosen after a review of department clinical activity revealed a very low rate of neostigmine utilization versus sugammadex for neuromuscular blockade reversal, so much so that a retrospective cohort would be insufficient to reliably assess clinical neostigmine administration. Our null hypothesis was there would be no association between the cumulative number of years since completion of primary anesthesia training and neostigmine reversal administration dose. The alternative hypothesis was that a non-zero linear relationship would exist between cumulative years and dose of neostigmine. Univariate analysis was conducted using simple linear regression for variables years since graduation, age, and training program type. Variables with $p<0.1$ would be included in multiple linear regression analysis. A priori power analysis using G*Power[3], for a large effect size, Cohen's $f2 = 0.35$, with $\alpha = 0.05$ and $\beta = 0.20$ yielded a total sample size of 25. Statistical analysis were performed with jamovi.[4]

Results: A total of fifty-eight staff providers provided responses to the survey. Descriptors of responses are displayed in Table 1. Linear regression results for Years since Graduation yielded a predictor coefficient of 0.000059 (95% CI -0.000676, 0.000796), $p = 0.870$, which was not significant. Variables of age, $p = 0.792$, and primary anesthesia training program type, $p = 0.752$, were also not significant.

Conclusion: Based on survey responses from staff anesthesia providers in a single large academic anesthesia department, there was no evidence supporting a large association between years since graduation from primary anesthesia training and neostigmine dose administration for neuromuscular agent reversal. Limitations include lack of existing survey measurement(s) with documented validity for our construct and a limited sampling frame of a single institution. There may be smaller degrees of association between years since graduation from primary anesthesia training and neostigmine dose administration detectable with a larger sample size, however, assuming multiple factors are associated with neostigmine dose administration, using years since graduation from primary anesthesia training alone to develop cohorts for neuromuscular agent reversal education is likely to be ineffective.

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Table 1: Descriptives

	Age	Provider (1=CRNA, 2=MD/DO)	Years Since Graduation	Primary Anesthesia Training Program (0=Civ, 1=Mil)	Neostigmine Dose
N	56	57	40	55	58
Missing	2	1	18	3	0
Mean	43.8				
Median			8.00		0.0400
Mode		2		1	
Standard deviation	8.82				
Minimum			1		0
Maximum			39		0.0670
Shapiro-Wilk p	0.268		< .001		< .001
25th percentile			4.00		0.0285
75th percentile			15.0		0.0423

Frequencies of Primary Anesthesia Training Program

Levels	Counts	% of Total	Cumulative %
Civilian	16	29.1 %	29.1 %
Military	39	70.9 %	100.0 %

Frequencies of Anesthesia Provider

Levels	Counts	% of Total	Cumulative %
CRNA	22	38.6 %	38.6 %
MD/DO	35	61.4 %	100.0 %

Appendix 1: Survey Clinical Vignette

Please read the following vignette.

You are taking over an anesthetic case from a colleague; a 53yo female ASA 2 undergoing gynecologic diagnostic laparoscopy. She weighs 75kg and is 168.5cm tall. She underwent uneventful general endotracheal anesthesia after 2mg Midazolam, 1.5mg/kg propofol, 50mg lidocaine, 100mcg fentanyl and 25mg of rocuronium for intubation, with no further neuromuscular blockade given. Anesthesia was maintained with sevoflurane titrated between 1-3% to maintain bispectral index at 40-60 and as needed intravenous fentanyl. Total fluids for the case include 1300mL isotonic crystalloid and an estimated blood loss of 30mL. Total opioid received for the case is 150mcg of fentanyl. It has been 90 minutes since intubation, and the surgeon has finished laparoscopy moving on to suturing the laparoscopic port incisions and applying dressings. She received 8mg dexamethasone at induction and 4mg ondansetron approximately 10 minutes ago for nausea/vomiting prophylaxis. Her vital signs have been stable within 20% of her baseline, core temperature is 36.1 degrees centigrade, and she has resumed spontaneous ventilation. TOF monitoring at the ulnar nerve reveals 4 out of 4 twitches without fade. (Quantitative neuromuscular monitoring is unavailable) You proceed with a decision on whether to administer neostigmine to reverse neuromuscular blockade at that moment. (sugammadex, edrophonium, and physostigmine are not available).

The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Uniformed Services University, the Department of the Army, the Department of Defense, or the U.S. Government.

Economics, Education and Policy-10

Institutional Practices for Albumin Utiltization for Intraoperative Fluid Resuscitation. A Data Review from 2018-2019

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Introduction: Despite the abundance of research in this area, the topic of crystalloid versus colloid fluid resuscitation is still very controversial. Adding in the current trend of more restrictive perioperative intravenous fluid management with the desire to keep patients normovolemic without concrete or objective criteria to define normovolemia, the overall perioperative fluid management paradigm may be shifting to more timed fluid administration 1,2. Colloids (5% Human Albumin [HA]) may be preferred as a faster and more titratable option over crystalloid, leading to a trend in increased HA administration 3,4. Our institution changed the HA access system to improve process efficiency without limiting access to HA. This study investigated the use of HA before and after the system change. The hypothesis was that the patient specific HA access may facilitate a more evidence-based HA utilization.

Methods: We selected 3 months as a random and representative sample to reflect patterns of intraoperative albumin administration (November 2018, August 2019 and November 2019.Institutional data were collected by retrospective review of the Operating Room business records during the selected observation periods for surgical procedure frequency and OR pharmacy charges for HA (250ml). The surgical procedures included abdominal, major plastics and ENT, orthopedic, neuro-spine, vascular and thoracic procedures. Cardiac procedures and transplant surgeries were excluded from the data collection. In April 2019, the institution changed the albumin access from a combination system (Resuscitation Box, containing 6 HA units) to a more specific dispensation system (Pyxis, provider has to order a specific albumin unit number). Therefore, November 2018 reflects albumin use before the system change; August and November 2019 reflects the albumin use after the change to Pyxis.

Results: In November 2018, 119 out of 1549 surgical procedures received HA (7.8%). A total of 254 HA units were intraoperatively infused. If the primary anesthesia provider was a CRNA, an average of 2 HA were given during the procedure; resident as anesthesia provider gave an average of 2.4 HA units. After the access change (August and November 2019) we noticed an increase in HA frequency and quantity. In August 2019, 161 out of 1701 surgical procedures received HA (9.5%). A total of 426 HA units were infused perioperatively. If HA was given, an average of 2.6 HA units were given (CRNA 2.68 and resident 2.6). The percentage of surgical case receiving albumin increased further in November 2019 (197 out of 1614 cases; 12.2%; total of 503 HA units). CRNA gave an average of 2.45 HA units, residents gave an average of 2.69 HA units per case.

Conclusion: The data show that the change in albumin access from a liberal to patient specific system has not reduced the HA consumption. The perioperative HA consumption moved in the opposite direction and increased. This observation is worrisome as it results in a significant economic impact. The pharmacy charges for HA are $364 per unit compared to approximate $10 for 1000ml crystalloid fluid. It is unclear if the increase in perioperative HA use has been caused by the access change or by the shift in intravenous fluid management. In addition to monitoring the HA consumption and collect more data about overall perioperative fluid management (crystalloids / blood component therapy), more education and guidelines may be needed to facilitate appropriate perioperative fluid management.

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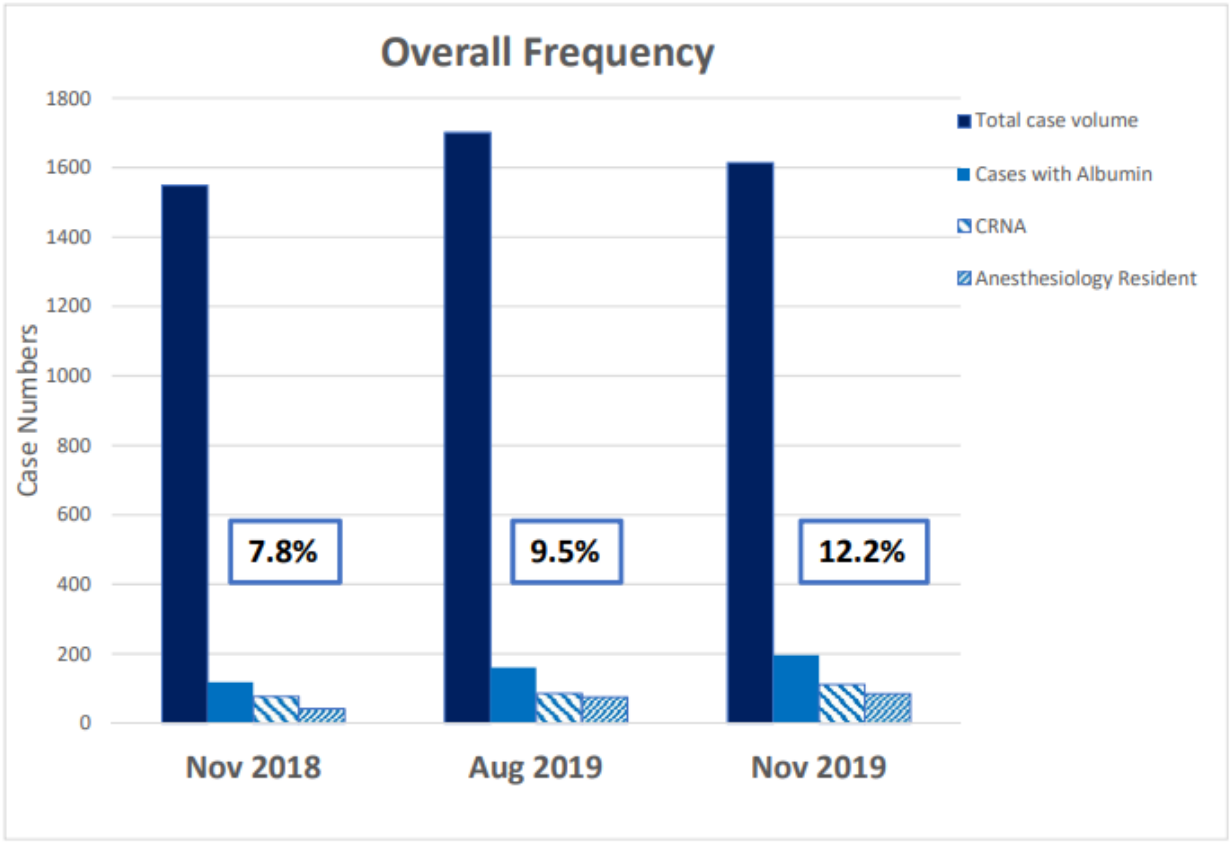
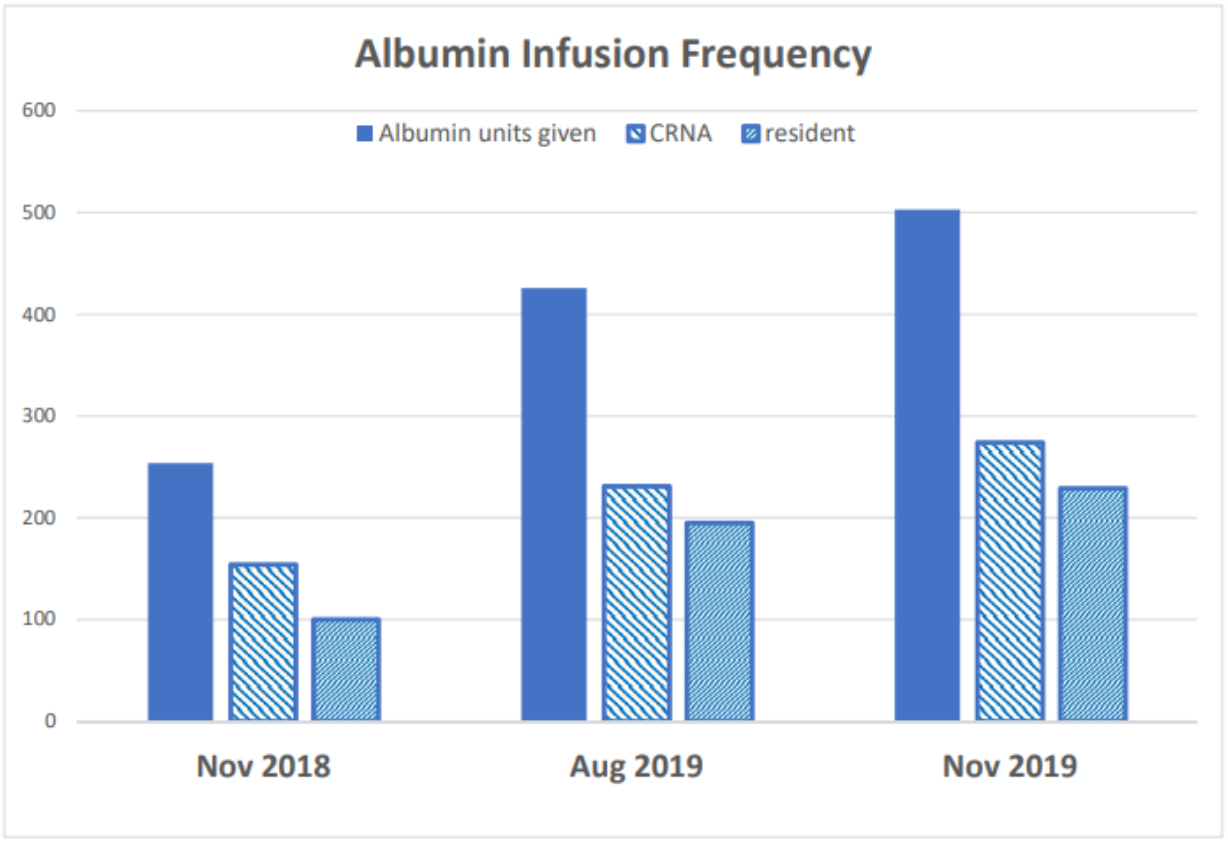

Overall Frequency
1800
1600
1400
1200
1000
800
600
400
200
0
Case Numbers
Total case volume
Cases with Albumin
CRNA
Anesthesiology Resident
7.8%
9.5%
12.2%
Nov 2018
Aug 2019
Nov 2019


Albumin Infusion Frequency
600
500
400
300
200
100
0
Albumin units given
CRNA
resident
Nov 2018
Aug 2019
Nov 2019

Economics, Education and Policy-11

Defining Entrustable Professional Activities for United States Anesthesiology Residency Training

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Introduction: Modern competency-based medical education promotes a learner-centered approach that requires a granular framework for competency assessment across the spectrum of practice.(1) Through the delineation of specific core competencies and milestones, the Accreditation Council for Graduate Medical Education (ACGME) provides a descriptive framework of competency but does not provide standardized instruments to tools to assess, document, and track trainee competency over time.(2) Entrustable professional activities (EPAs) utilize a set of common tasks that each inform multiple competencies, and which can be assessed by supervisors who document the level of trust that they perceive in the trainee's performance of the task.(3,4) EPAs represent a practical mechanism to repeatedly assess competency at the point-of-care, yet no consensus set of EPAs have been described for Anesthesiology training programs in the United States (US).(5-10)

Methods: After IRB approval and informed consent, experts in education and competency assessment were recruited to participate in a six-step process to develop a consensus list of EPAs for US Anesthesiology Residency Training. For step 1, a modified Delphi method was used with multiple iterative rounds until consensus was reached on a final list of EPAs. Step 2 was to collectively define an entrustment scale. The final list of EPAs was then divided amongst the group to create detailed EPA definitions (step 3) and map entrustment levels for each EPA to ACGME Anesthesiology Milestones (step 4). Four project leaders (AM, GW, RM, PT) reviewed the final results and provided minor edits to step 3 EPA definitions for consistency between individual EPAs. Step 5 used a modified Delphi method to create graduation targets for each EPA. Participants were asked to report the level of entrustment that a graduating resident would be expected to achieve for each item on the 1 to 5 scale developed in step 2. Scores were averaged, rounded to an integer and re-sent to participants until consensus was reached. Finally, step 6 used a modified Delphi method to create a consensus list of specific procedural skills to include for competency assessment.

Results: Participants included 18 education experts from 11 different institutions. For step 1, three Delphi rounds produced a final list of 20 EPAs, each differentiated as simple or complex (Table 1). Step 2 resulted in consensus definition of an entrustment scale incorporating elements of multiple published scales (Table 2). Steps 3 and 4 were completed as described above. In step 5, averaged and rounded scores from a first round of graduation target votes were agreed upon with consensus in round 2 (Tables 3 and 4). Finally, Step 6 utilized two Delphi rounds to develop a consensus list of 159 anesthesiology procedures.

Conclusion: While the ACGME, via core Competencies and Milestones, provides a conceptual framework for assessment of competency in anesthesiology training, they do not provide specific tools to assess each trainee on the competency continuum. EPAs can provide a practical mechanism to assess competency at the point-of-care and a list of 20 core anesthesiology EPAs has now been developed using rigorous methodology and consensus amongst education experts. These EPAs are now being piloted across multiple US anesthesiology programs to evaluate the feasibility of implementation using a mobile app, and the utility for competency and milestone assessment.

Reference(s):

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2. Nasca T et al. NEJM. 2012;366(11):1051–56.
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8. Shaughnessy AF et al. J Grad Med Educ. 2013;5(1):112-8.
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Table 1. Final List of Entrustable Professional Activities for US Anesthesiology Residency Training

Category	**EPA Title**
Foundational	Preoperative Assessment and Optimization
	Perioperative Care of a General Operating Room Case
	Airway Management
	PACU Management
	Transfer of Care
Obstetric	Labor Analgesia
	Perioperative Care for Cesarean Section
	Perioperative Care of a Pregnant Patient Undergoing Non-Obstetric Surgery
Pediatric	Perioperative Care of a Pediatric Patient Presenting for Anesthesia
	Perioperative Care of Neonatal Patient Presenting for Anesthesia
Cardiothoracic	Perioperative Care for Cardiac Surgery
	Perioperative Care for Thoracic Surgery
Critical Care	Critical Care of Non-OR Patients (ICU Management)
RAPM	Management of Acute Pain Out of the OR
	Perioperative Care of a Patient Managed with Regional Anesthesia
Chronic Pain	Management of a Non-OR Patient with Chronic Pain
Other Special Cases	Perioperative Care for Intracranial Procedures
	Perioperative Care for Major Trauma
	Perioperative Care for Abdominal Aortic Surgery
	Perioperative Care of an Out-of-OR Case

Abbreviation: RAPM, regional anesthesia and acute pain management

Table 2. Entrustment / Supervision Scale

Entrustment Level	Explanation
1: I did it	Supervisor did the activity, trainee observed or assisted
2: Direct supervision	Supervisor talked trainee through activity (constant or near constant supervision, requires physical presence of the supervisor)
3: Reactive supervision	Supervisor directed trainee from time to time (supervisor does not need to be constantly observing, trainee often requires consultation)
4: Available if needed	Supervisor was available just in case (trainee requires infrequent consultation)
5: Independent practice	Trainee ready for independent practice

Table 3. Target Levels of Entrustment for Graduation using US Anesthesiology Residency Training EPAs

Simple EPAs	Mean[a]	STD	Score[b]
Preoperative Assessment and Optimization	4.93	0.3	5
Perioperative Care of a General Operating Room Case	4.80	0.4	5
Airway Management	4.93	0.3	5
PACU Management	4.87	0.4	5
Transfer of Care	4.87	0.4	5
Labor Analgesia	4.80	0.4	5
Perioperative Care for Cesarean Section	4.80	0.4	5
Perioperative Care of a Pregnant Patient Undergoing Non-Obstetric Surgery	4.53	0.5	5
Perioperative Care of a Pediatric Patient Presenting for Anesthesia	4.53	0.5	5
Perioperative Care of Neonatal Patient Presenting for Anesthesia	3.40	1.1	3
Perioperative Care for Cardiac Surgery	3.67	1.0	4
Perioperative Care for Thoracic Surgery	3.93	1.1	4
Critical Care of Non-OR Patients (ICU Management)	3.80	1.0	4
Management of Acute Pain Out of the OR	4.60	0.9	5
Perioperative Care of a Patient Managed with Regional Anesthesia	4.07	0.8	4
Management of a Non-OR Patient with Chronic Pain	3.87	1.1	4
Perioperative Care for Intracranial Procedures	4.53	0.7	5
Perioperative Care for Major Trauma	4.33	0.8	4
Perioperative Care for Abdominal Aortic Surgery	4.40	0.8	4
Perioperative Care of an Out-of-OR Case	4.87	0.4	5

[a]Average of ratings given in modified Delphi round one (on the 1-5 Entrustment Scale in Table 2)

[b]Whole-number rounding of the mean: 0.49 round down; 0.5 round up.

Table 4. Target Levels of Entrustment for Graduation using US Anesthesiology Residency Training EPAs

Complex EPAs	**Mean[a]**	**STD**	**Score[b]**
Preoperative Assessment and Optimization	4.53	0.5	5
Perioperative Care of a General Operating Room Case	4.60	0.5	5
Airway Management	4.67	0.5	5
PACU Management	4.67	0.5	5
Transfer of Care	4.67	0.5	5
Labor Analgesia	4.40	0.5	4
Perioperative Care for Cesarean Section	4.47	0.5	4
Perioperative Care of a Pregnant Patient Undergoing Non-Obstetric Surgery	4.13	0.7	4
Perioperative Care of a Pediatric Patient Presenting for Anesthesia	3.47	0.9	3
Perioperative Care of Neonatal Patient Presenting for Anesthesia	2.73	1.0	3
Perioperative Care for Cardiac Surgery	2.73	1.0	3
Perioperative Care for Thoracic Surgery	3.33	1.2	3
Critical Care of Non-OR Patients (ICU Management)	3.13	1.0	3
Management of Acute Pain Out of the OR	3.93	1.0	4
Perioperative Care of a Patient Managed with Regional Anesthesia	3.67	0.9	4
Management of a Non-OR Patient with Chronic Pain	3.07	1.0	3
Perioperative Care for Intracranial Procedures	3.53	1.0	4
Perioperative Care for Major Trauma	3.80	1.1	4
Perioperative Care for Abdominal Aortic Surgery	3.53	0.9	4
Perioperative Care of an Out-of-OR Case	4.60	0.5	5

[a]Average of ratings given in modified Delphi round one (on the 1-5 Entrustment Scale in Table 2)

[b]Whole-number rounding of the mean: 0.49 round down; 0.5 round up.

Economics, Education and Policy-12 A New Accreditation Process for Neuroanesthesiology Fellowships: International Council for Perioperative Neuroscience Training (ICPNT)

Chanhung Lee[1], Rafi Avitsian[2], Leslie Jameson[3], John Bebawy[4], lara Ferrario[5], Shobana Rajan[6], Alana Flexman[7], Maria Bustillo[8], Ricard Valero[9], Stewart Hinckley[10], william a kofke[11]

[1]University of California, San Francisco, San Francisco, CA, [2]Cleveland Clinic Foundation, -, United States of America, [3]University of Colorado School of Medicine, Aurora, CO, [4]Northwestern University Feinberg School of Medicine, Chicago, IL, [5]University of Texas, Houston, Houston, United States of America, [6]Allegheny health Network, Pittsburgh, PA, [7]Vancouver general Hospital. The Universit of British Columbia, Vancouver, Canada, [8]Cornell University, New York, United States of America, [9]Universiyt Barcelona, Barcelona, Spain, [10]International Council for Perioperative Neuroscience Training, Richmond, VA, [11]university of pennsylvania, philadelphia, PA

Introduction: Neuroanesthesia fellowships has been a topic of great interest since the early years of the Society of Neuroscience in Anesthesiology and Critical Care (SNACC).(1,2) The importance of a standardized guideline and an international network to improve training for perioperative neuroscience were strongly endorsed by neuroanesthesiologists internationally.(3,4,5,6) (Figure 1) However, to align with SNACC's international inclusive strategy, the accreditation and certification process for the neuroanesthesiology fellowship programs had encountered hurdles with existing accreditation bodies.

Methods: "The SNACC Executive Council committed to develop a SNACC-based international neuroanesthesiology fellowship accreditation service, the 'International Council for Perioperative Neuroscience Training (ICPNT)'. (Figure 2) This arrangement allowed ICPNT to function under the regulatory umbrella of SNACC. A writing committee was created which was tasked with creating the foundational documents for this organization. The program requirements are written to facilitate international differences in regional training culture and regulations, and to allow for different methods of funding.(icpnt.net) Unique features: 1. A novel inclusive approach is introduced to review the application for ICPNT accreditation. Each application has two stages; the first is a formative submission by which reviewers provide constructive feedback to enable improvement of the applying program, then followed by a summative evaluation by which final accreditation is provided.(Figure 3) 2. Promote and support the development of an international network of Neuroanesthesiology fellowship programs to enhance education, quality improvement and research.(Figure 4) The Neuroanesthesia Program Relations (NPR) Committee has been initiated to foster academic and professional relations and networking among ICPNT accredited programs. 3. Fellows can be junior faculty; eliminating dependence on federal funding. 4. Enfolded fellowship during residency."

Results: Two cycles of total seven programs were invited to be pilot programs in 2019, and have been reviewed and granted accreditation since May 30th, 2019. Nine additional invited pilot programs encompassing North America, Oceania, Europe, Asia, and South America have applications in preparation to be reviewed in April 2020.(Figure 5) As the network grows, international educational, research, and clinical quality improvement activities are anticipated.

Conclusion: ICPNT is the first international and non-ACGME accreditation council for an anesthesia subspecialty fellowship training. It has drawn widespread interest across nations in the world. To meet the challenge at its early development stage, ICPNT has conducted three rounds of pilot program reviews and accreditation to strengthen the program requirements, governing procedures, and application and review process, despite regional variations in different parts of the world.

Reference(s):

1. Journal of Neurosurgical Anesthesiology. 9(4):296-307. 1997.
2. Journal of Neurosurgical Anesthesiology. 24(4):260-80. 2012.
3. Journal of Neurosurgical Anesthesiology. 22(3):252-5. 2010.
4. Journal of Neurosurgical Anesthesiology. 25(1):1-7. 2013.
5. Rev Esp Anestesiol Reanim. 59:1-2. 2012
6. European Journal of Anaesthesiology. 34(2):51-3. 2017.

Figure 1. A web-based survey was distributed and filled out by 339 US based SNACC members.(3) A majority of respondents endorsed the development of an accreditation process for Neuroanesthesiology fellowships.

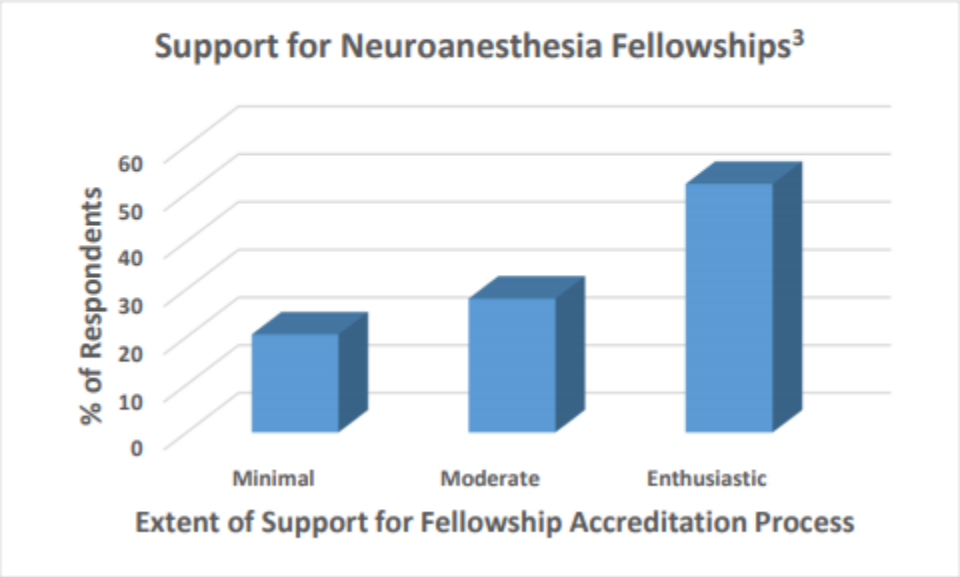

Figure2. Logo for the "International Council for Perioperative Neuroscience Training (ICPNT)".

Figure 3. The accreditation process for an ICPNT application to demonstrate an inclusion vision rather than exclusion, with the emphasis on helping programs to get accredited rather than "policing". Note the two-stage process of formative followed by summative evaluation. The not acceptable category includes constructive advice to subsequently resubmit an application which will be acceptable.

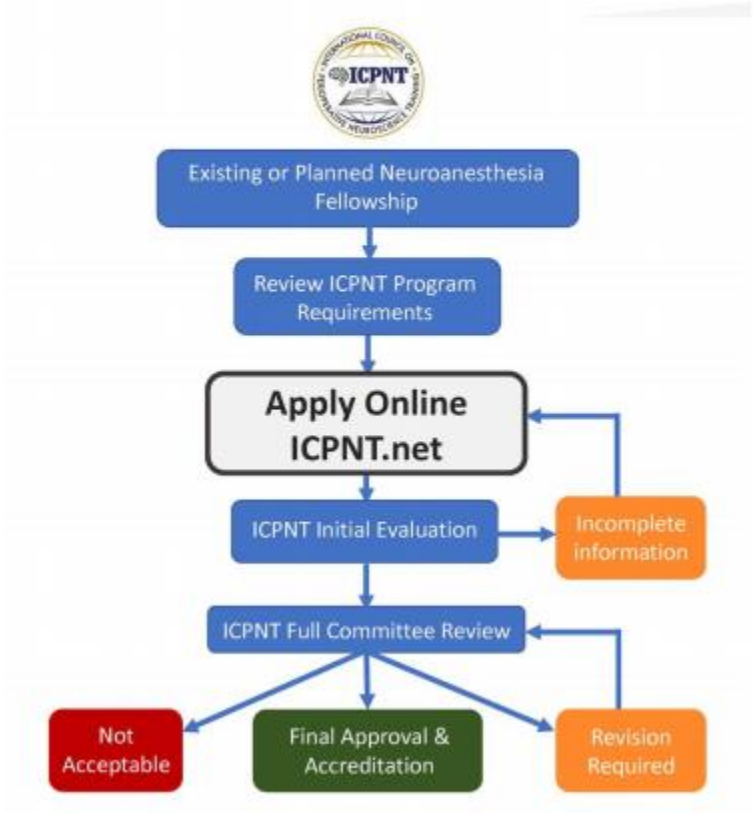

Figure 4. a. Traditional relationship of accreditation agents to programs. Programs do not work with each other. This approach is rejected by ICPNT.
b. ICPNT will communicate with programs, but also support development of an inter-fellowship program network to facilitate quality improvement, education, research, and evaluation of fellowship training outcomes.

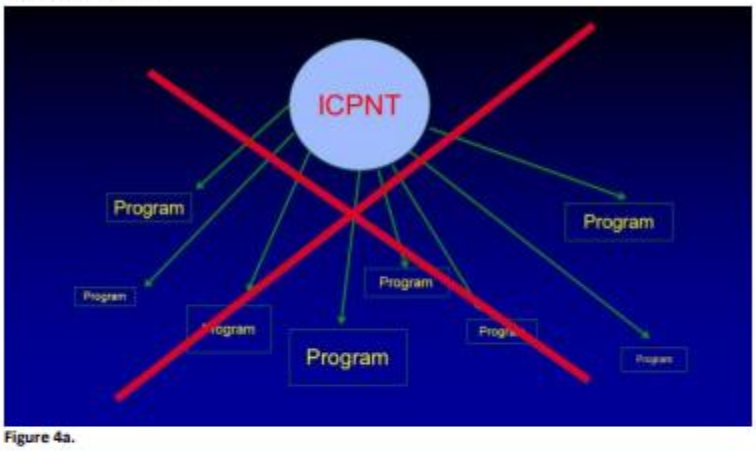

Figure 4a.

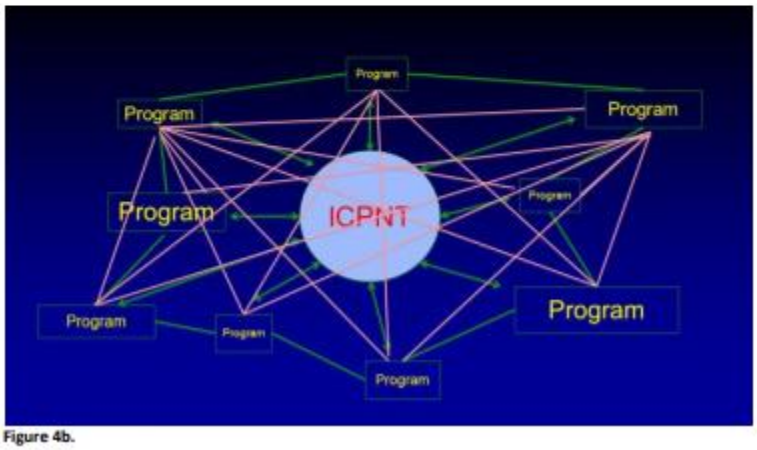

Figure 4b.

Figure 5. Worldwide distribution of 3 cycles of sixteen ICPNT pilot programs.

Economics, Education and Policy-13

Survey of Program Directors Regarding Resident Training in Anesthesiology

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Introduction: Introduction: The third clinical anesthesia (CA-3) year was added in 1989. From 1989 to 2018, 25 topics and skills were added to Accreditation Council on Graduate Medical Education (ACGME) requirements, with no increase in training. 2018 ACGME requirements were 40 pages long; 1989's were 4-1/2 pages. (1) Despite 25 required topics and skills added to ACGME requirements from 1989 to 2018, there was no increased length of training. Objective Structured Clinical Examination (OSCE) already requires interpretation of transesophageal echocardiography (TEE), and ACGME has indicated transthoracic echocardiography (TTE) will be added. Learning echo requires several months, at minimum. Patients with cardiac assist devices present for outpatient procedures, and care of a few patients with such devices or ECMO during cardiac anesthesia rotations may not be sufficient to train the general anesthesiologist to care for such patients. New disruptive technologies that have improved survival of critically ill patients, combined with the increasing age of the population, results in general anesthesiologists caring for increasingly older and sicker patients. Increasing educational requirements and the need for residents to learn to use new disruptive technologies in practice might require additional length of training, or at least modification of the current residency curriculum. We performed a survey to learn Anesthesiology Program Directors (PDs) opinions' regarding whether to institute a CA-4 year, and additional questions to assess residency training in general.

Methods: With IRB exemption a 16-question anonymous survey (Survey Monkey) of U.S. PDs was performed. Questions sought opinions regarding need for a CA-4 year, whether residents are ready to be consultant anesthesiologists after the CA-3 year, how much improvement would be seen in graduates if a CA-4 year is added, and assessment of the knowledge base and clinical skills residents must master now vs. residents who graduated in 1989 when the CA-3 year was added. Additional questions focused on opinions regarding value of the Clinical Base Year, and whether achievement of milestones should result in early graduation.

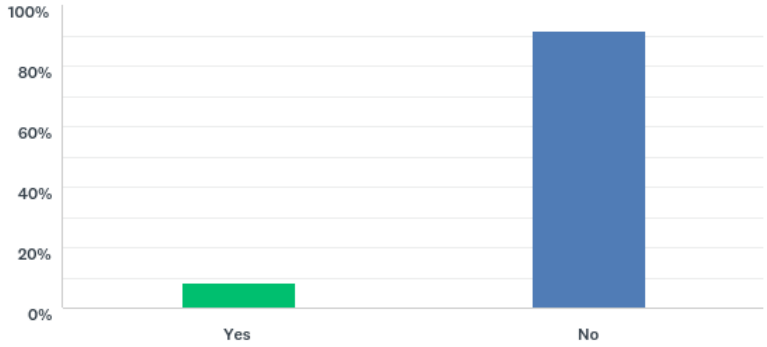
Results: 71/156 (45.5%) of PDs completed the survey. [Q# refers to a corresponding image]. 23.9% indicated that adding a CA-4 year would significantly improve the quality of residents at graduation; 76.6% of PDs indicated it would not. PDs indicated that 30% of residents would be significantly better prepared for independent practice after a CA-4 year. Regarding current knowledge base and clinical skills, 57.8% reported 2019 residents needed to learn significantly more vs.1989 graduates; 29.6% responded 2019 residents needed to learn somewhat more, 8.5% responded 2019 residents needed to learn the same amount and 4.2% indicated 2019 residents needed to learn somewhat less than 1989 graduates.[Q14] 65/71(91.6%) PDs reported that achievement of the ACGME milestones should not result in early graduation.[Q7] 5/6 (83.3%) responders who served on the ACGME milestones committee indicated that completion of ACGME milestones should not result in early graduation. 80% of PDs reported that residents are better prepared to begin a Clinical Anesthesiology Residency after a Clinical Base Year (Internship) than if they did not complete a Clinical Base Year.[Q10] PDs reported that if achievement of milestones could result in graduation prior to completion of the CA-3 year, the likelihood it would impact patient safety due to a staffing shortage was 64%. (Only some questions reported due to abstract size limitations).

Conclusion: 76.6% of PDs indicated addition of a CA-4 year would not improve quality of residents. Some of these negative responses might be due to concern over increased workload for themselves, but the survey cannot determine if this is so. 23.9% Of PDs indicated a CA-4 year would significantly improve quality of graduating residents. This indicates some PDs see room for improvement in the current curriculum. It is indisputable that educational requirements have increased greatly since addition of the CA-3 year, and that older and sicker patients are presenting for anesthesia care. Anesthesiology educators should continually assess increasing educational requirements and adoption of new technologies anesthesiologists need to learn to use, and remain sensitive to the possibility of adding a CA-4 year at some time in the future.

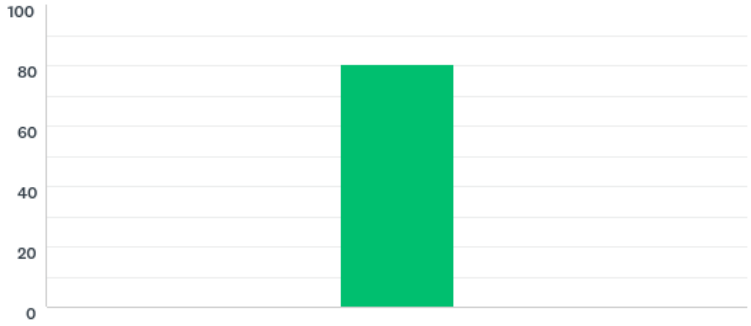
Reference(s):

1.https://www.acgme.org/Portals/0/PFAssets/ProgramRequirements/040Anesthesiology2018.pdf?ver=2018-06-14-142529-527

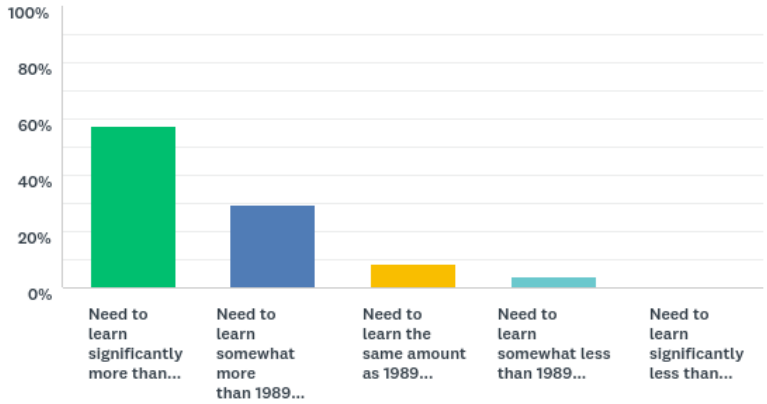
Q7 Do you believe that once a resident completes ACGME Milestones , he should be graduated from Anesthesiology residency, even if prior to completion of CA-3 year ?



Q10 Do you think residents are better prepared to begin a Clinical Anesthesiology Residency after a Clinical Base Year(Internship) than if they did not complete a Clinical Base Year?



Q14 Comparing knowledge base and clinical skills, the graduating Anesthesiology residents of 2019 compared to the Anesthesiology residents of 1989



Economics, Education and Policy-14

Publication Trends and Levels of Evidence in Anesthesiology Literature

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Introduction: The purpose of publication of scholarly articles in any peer-reviewed journal is to present quality research which contributes to the scientific community. However, in the field of anesthesiology, research production in the United States has been on a decline sharply since the 1980s (Pagel and Hudetz, 2012). Previous studies have shed light on this trend but on a rather superficial level. This study was designed to assess the study design and quality of literature published in major anesthesiology journals in order to provide insight as to whether there has been improvement over the past two decades.

Methods: We performed a literature search through three anesthesiology journals: Anesthesiology: Journal of the American Society of Anesthesiologists (ASA), British Journal of Anaesthesia (BJA), and Anesthesia & Analgesia (A&A). We identified all original research articles from the month of January for over a twenty-year period in three-year increments and analyzed them for measures of quality and article type. Two different reviewers who were blinded to each other's assessments performed the data collection. The assessments were then analyzed for concordance using kappa which signifies agreement beyond chance.

Results: A total of 552 original research articles were assessed for publication trends and levels of evidence. Since 1997, there has been a 52%, 32%, and 29% decrease in publication quantity across the three journals ASA, BJA, and A&A, respectively. The proportion of studies that are randomized has stayed consistent over the past 20 years, as have the proportions of controlled and blinded studies. Investigations utilizing multi-center collaborations have increased (0% to 19.61%), but the proportion of research that is prospective has decreased considerably (92.5% to 58.82%). Studies addressing questions of therapy/prevention composed the largest portion, followed by etiology/harm, until 2012. Since 1997, the proportion of level I articles has remained fairly stagnate. However, the proportion of level II articles has decreased while the proportion of level IV articles has drastically increased. Within therapy/prevention, there is a higher proportion of high levels (I and II) compared to low levels (III and IV), and when comparing the three journals, ASA appears to publish greater proportions of high levels of evidence whereas BJA appears to have an indistinct spread. When analyzed, there is a larger proportion of publications with high levels of evidence in ASA (72.7%) compared to A&A (65.4%) and BJA (69.9%).

Conclusion: The results of this study may serve clinicians and researchers in understanding the climate of anesthesiology research. We recommend for investigators to assess the metrics of experimental design and rigor in order to produce studies of high levels of evidence; these studies can contribute to the adherence to EBM standards so that the gap in translation of academia to clinic is better bridged.

Reference(s): Recent trends in publication of basic science and clinical research by United States investigators in anesthesia journals. BMC Anesthesiology.12:5. 2012

Economics, Education and Policy-15

Correlations of Faculty Evaluations to ACGME Milestone Assessments in Anesthesia Critical Care Fellows

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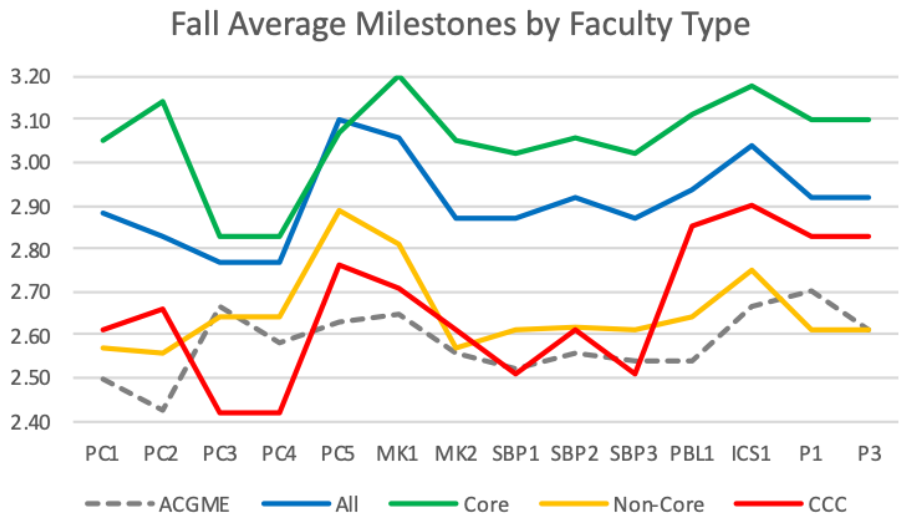
[1]Vanderbilt University Medical Center, Nashville, TN

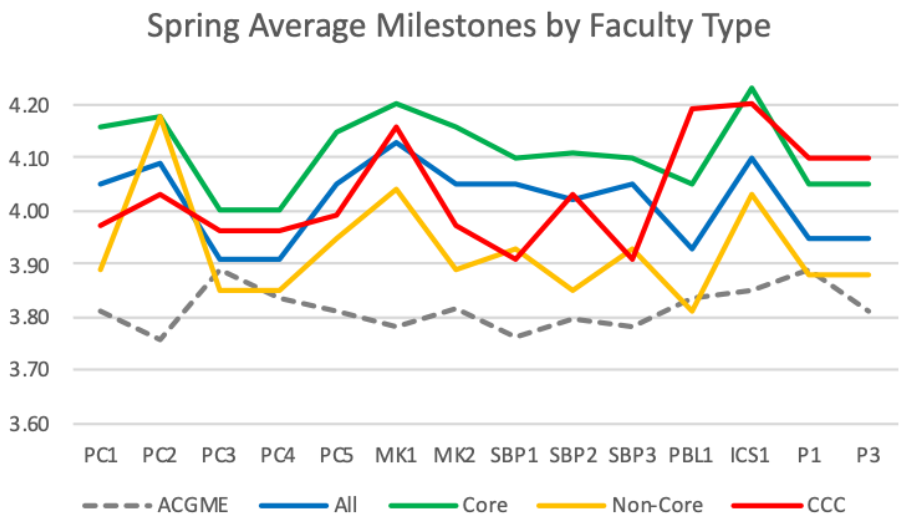
Introduction: Evaluation of fellow competency remains challenging due to its subjective nature and the 1-year duration of fellowships. The ACGME Milestone Project standardized competence evaluation of trainees and provided a framework for longitudinal evaluation. Program leadership and Clinical Competency Committees (CCC), however, rely on faculty evaluations to inform achievement of milestones. The correlation between CCC consensus milestone scoring and faculty evaluations in our institution has not yet been examined. We developed a system whereby questions on faculty clinical evaluations, including rotation-specific clinical performance, were mapped to relevant milestones. Using this system, we hypothesized that milestone mapping linked to rotation-based faculty evaluations correlates positively with the CCC-assigned milestone evaluation of Critical Care Fellows. We also hypothesized that individual CCC faculty evaluation scores would correlate most with CCC milestone scoring, followed by core teaching faculty, with non-core teaching faculty scores correlating least with CCC milestone scoring.

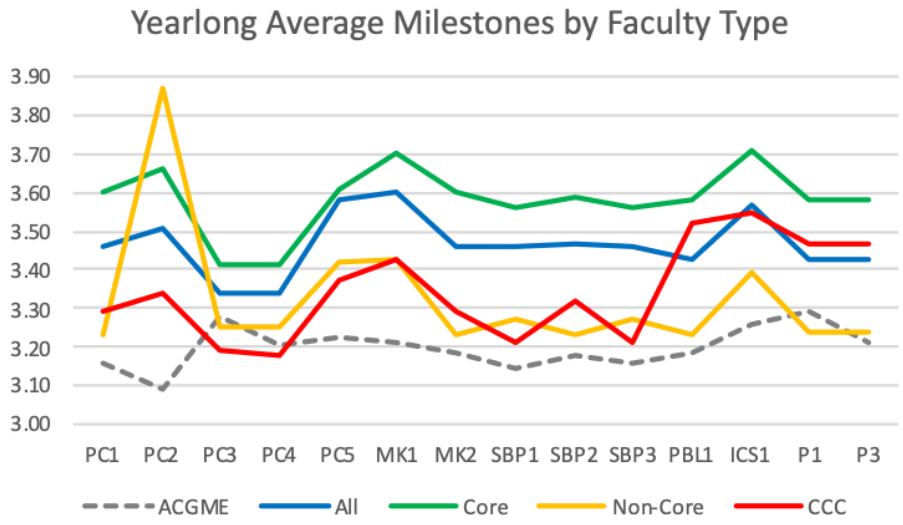
Methods: A retrospective cohort study was performed with all Anesthesiology Critical Care Medicine fellows from the preceding three years included (n=25). Faculty evaluations and CCC Milestone assignments, as reported to the ACGME, were deidentified by participant, rotation, and evaluator, and blinded milestone mapping was generated. Faculty attendings were classified as core education faculty (which included CCC members), non-core faculty, and CCC faculty members. Descriptive data and direct correlation analyses were performed to illustrate milestone scoring determined by milestone mapping and by the CCC, as well as for the faculty evaluation scores based on faculty type.

Results: Overall, faculty evaluations were, when averaged, generally within 0.5 points of the CCC determined ACGME reported milestones (Figure 1). Across all milestones, core teaching faculty reported the highest average milestone for fellows. In contrast, CCC members and non-core faculty evaluation-based milestones were most similar to the CCC reported milestones, with the all faculty average still higher than the CCC reported milestones. There was wider spread in reported milestones across faculty types in the fall than in the spring. The non-core faculty scores correlated most with ACGME reported milestones, followed by CCC faculty scores. The core faculty scores correlated least with ACGME reported milestones.

Conclusion: While often overestimating the ACGME reported milestones, there was positive correlation between milestone mapping linked to faculty evaluations with all faculty types. Because of this, milestone assignments can become more automated and objective by leveraging the milestone mapping system with faculty evaluations. Similarly, increased confidence can be placed on the quality of the evaluation questions and faculty understanding of milestones, including non-core teaching faculty. Thus, in our institution, we believe that all faculty should continue to evaluate fellows. Our study is limited by a lack of randomization and the use of only descriptive data and is unable to identify causes for the differences in evaluation scores between faculty types.


Fall Average Milestones by Faculty Type
3.20
3.10
3.00
2.90
2.80
2.70
2.60
2.50
2.40
PC1 PC2 PC3 PC4 PC5 MK1 MK2 SBP1 SBP2 SBP3 PBL1 ICS1 P1 P3
ACGME
All
Core
Non-Core
CCC


Spring Average Milestones by Faculty Type
4.20
4.10
4.00
3.90
3.80
3.70
3.60
PC1 PC2 PC3 PC4 PC5 MK1 MK2 SBP1 SBP2 SBP3 PBL1 ICS1 P1 P3
ACGME
All
Core
Non-Core
CCC


Yearlong Average Milestones by Faculty Type
3.90
3.80
3.70
3.60
3.50
3.40
3.30
3.20
3.10
3.00
PC1 PC2 PC3 PC4 PC5 MK1 MK2 SBP1 SBP2 SBP3 PBL1 ICS1 P1 P3
ACGME
All
Core
Non-Core
CCC

Economics, Education and Policy-16

Improving Resident and Faculty Satisfaction with Trainee Feedback and ACGME Milestone Assessment with Interpreted Professional Activities (IPAs) evaluations

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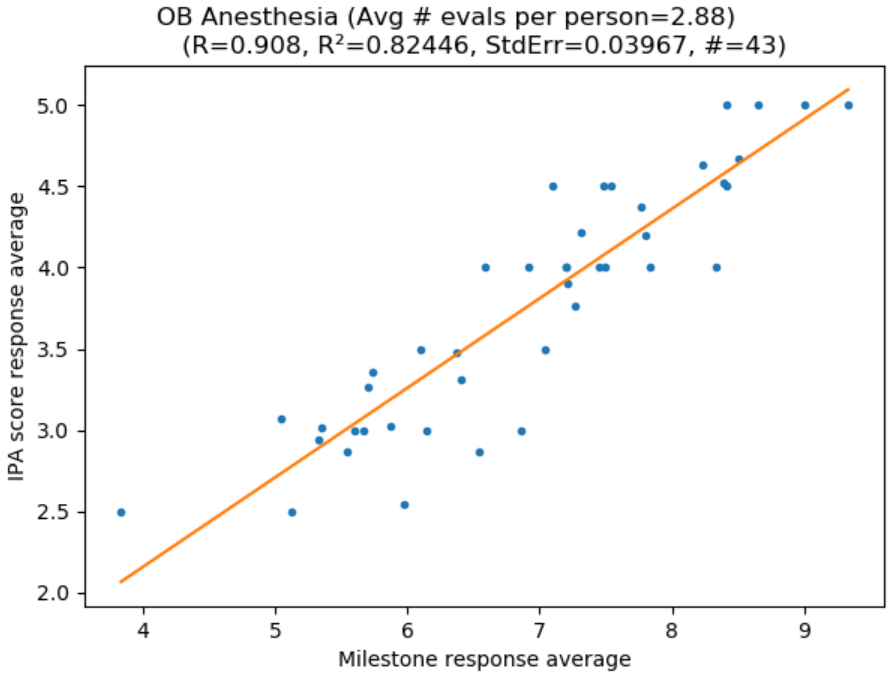
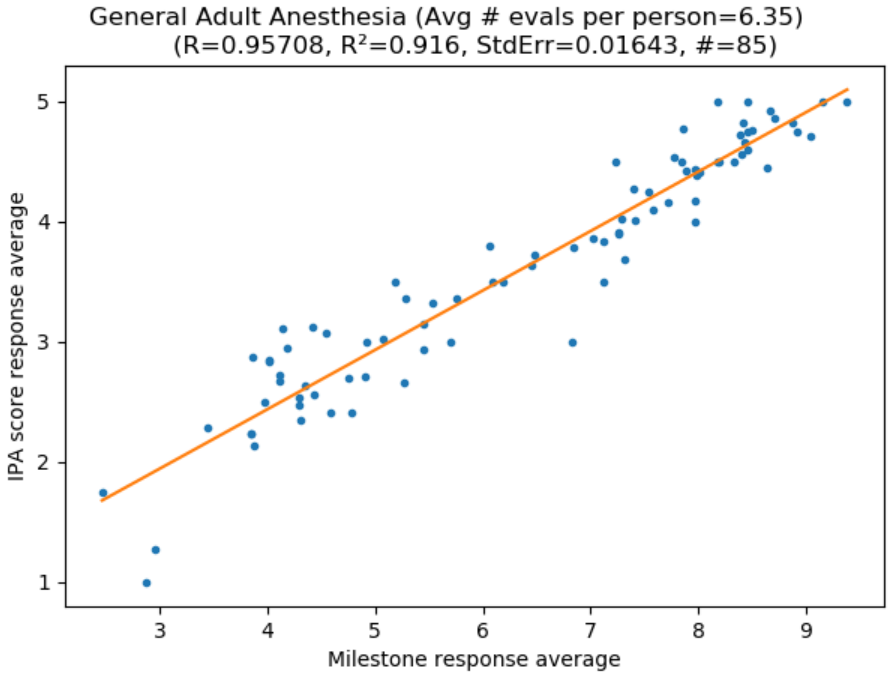
Introduction: Resident evaluations by faculty mentors are critical to identify strengths and areas for development in their educational progress. Current ACGME Milestone assessments require resource intensive judgment ratings and have the potential risk of becoming low-value 'checkboxes' aligned with level of training rather than attestation of clinical competency. We evaluated whether faculty entrustment ratings (IPAs) of anticipated resident supervision needs in managing standardized case scenarios would provide meaningful feedback to residents and positively correlate with ACGME Milestone assessments.

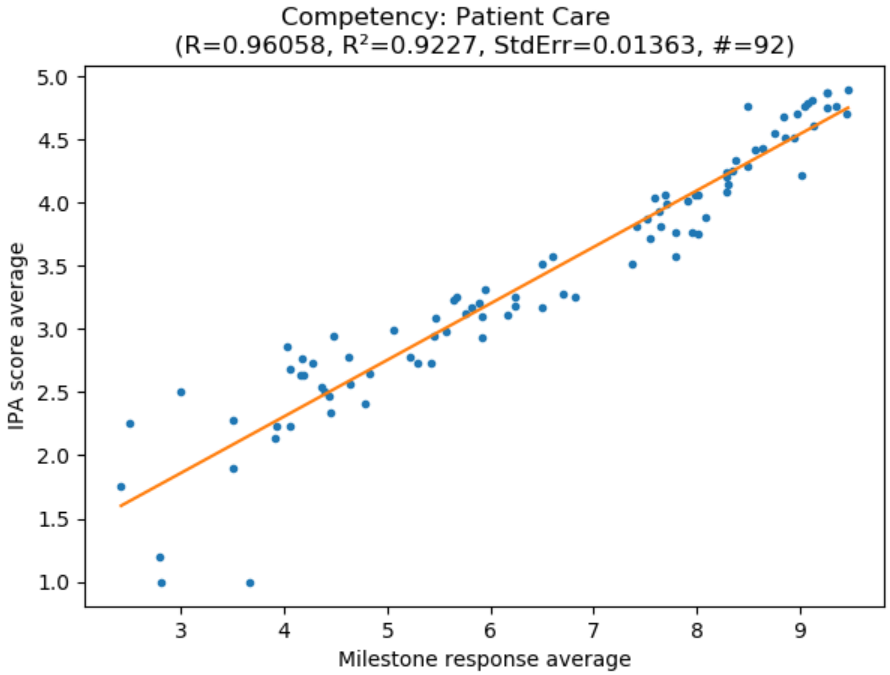
Methods: A modified Delphi method was used by expert faculty to develop specialty-specific, standardized case scenarios termed Interpreted Professional Activities (IPA) for a number of anesthesia subspecialties (general adult, pediatric, obstetric, trauma, regional neuro and critical care). End of rotation resident Milestone and IPAs evaluations were completed by faculty assessors. IPA entrustment ratings were subspecialty-specific and on a 5 point scale with the basic structure of '1= lacks knowledge/skill requiring constant supervision' to '5= can manage cases independently.' Residents were surveyed on the value of IPA entrustment scores to their development. Linear regression models were applied with standard error estimates to evaluate relationships between subspecialty entrustment scores and average Milestone scores. Core competency ratings from corresponding learner Milestone scores were derived and competency scores were correlated to entrustment ratings.

Results: Entrustment scores from general adult anesthesiology, obstetrics, neuro, trauma and pediatric anesthesiology IPAs were strongly correlated with average Milestone scores (R=0.96, .91, .89, .85, .84 respectively, Figures 1 and 2). Relationships were moderately positive for critical care (R=0.7) and was weakest for regional anesthesia (R=0.35). Entrustment scores related strongly (R=0.89 to 0.96) to core competencies with the strongest relationships for patient care and medical knowledge (Figures 3 and 4) . Forty seven % of residents rated ACGME Milestone assessments as adequate and meaningful to their development, while 76% of residents indicated entrustment scores on IPAs added meaning to their Milestone assessments.

Conclusion: These results suggest that IPAs may serve as a valid and useful tool for trainee evaluation. All subspecialty IPAs with exception to regional anesthesia had a moderate to strong positive correlation with the current ACGME Milestones. Trainees indicated that current Milestone evaluations may be insufficient, and that they may prefer IPA ratings in addition to or in place of traditional Milestone evaluations. Ultimately, the use of IPAs should continue to be developed and studied as they can provide more substantive resident assessment than Milestones alone.


OB Anesthesia (Avg # evals per person=2.88)
(R=0.908, R²=0.82446, StdErr=0.03967, #=43)
IPA score response average
Milestone response average
5.0
4.5
4.0
3.5
3.0
2.5
2.0
4
5
6
7
8
9


General Adult Anesthesia (Avg # evals per person=6.35)
(R=0.95708, R²=0.916, StdErr=0.01643, #=85)
IPA score response average
Milestone response average
5
4
3
2
1
3
4
5
6
7
8
9


Competency: Patient Care
(R=0.96058, R²=0.9227, StdErr=0.01363, #=92)
IPA score average
Milestone response average
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
3
4
5
6
7
8
9

Geriatric Anesthesia

Geriatric Anesthesia-1 Population-level cognitive trajectory before and after coronary revascularization in older adults

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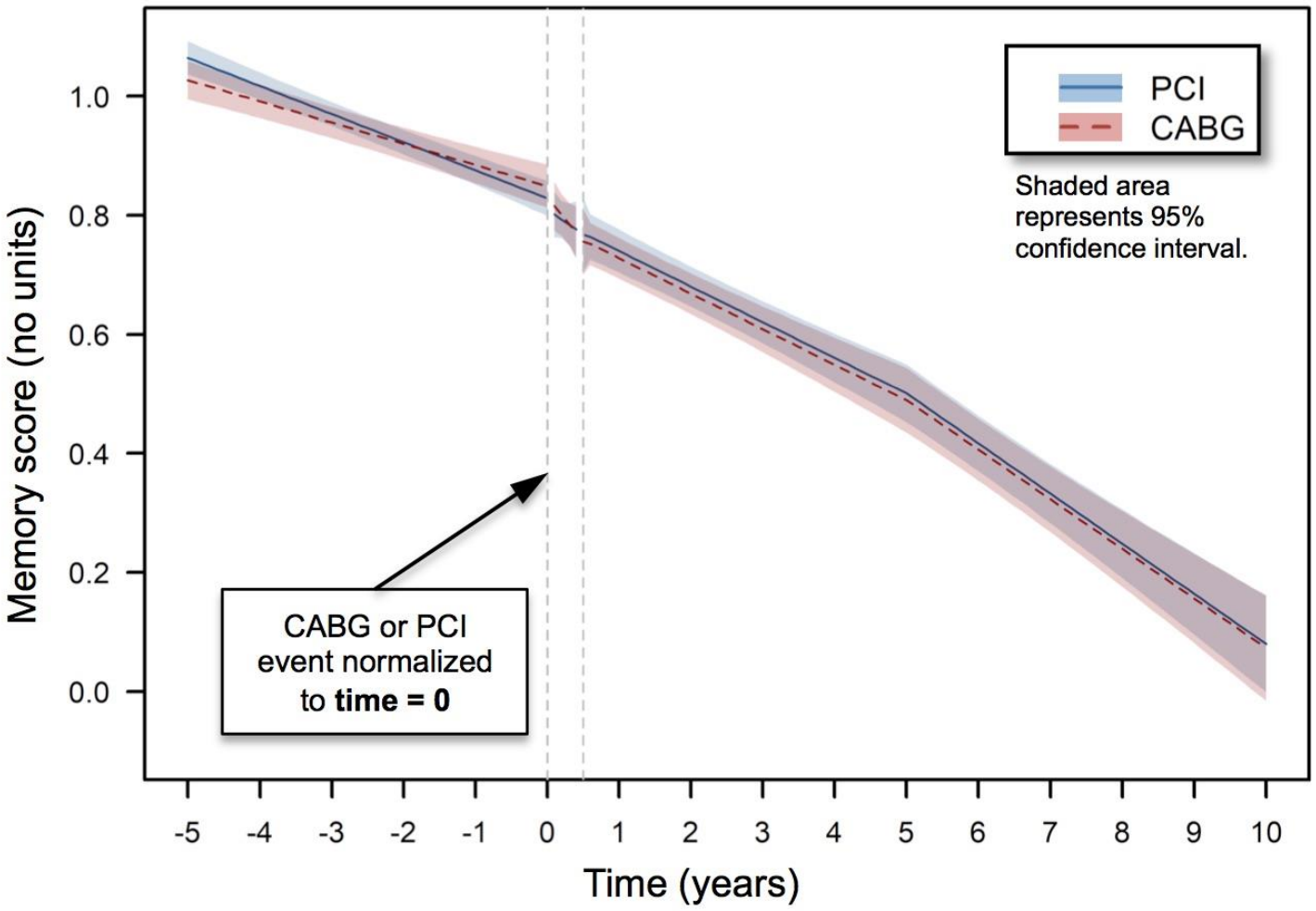
Introduction: Cognitive decline after coronary artery bypass grafting (CABG) is commonly reported and a major concern for patients, but it is unknown whether this represents an acute worsening of the rate of preoperative cognitive change, and whether the postoperative rate of cognitive change is similar to those undergoing nonsurgical coronary revascularization (i.e., percutaneous coronary intervention [PCI]).

Methods: We selected Health and Retirement Study (HRS) participants who underwent CABG (n=665) or PCI, (n=1,015) between 1998 and 2015 and were 65 or older. Date of CABG or PCI was ascertained from Medicare billing data. We modeled up to 15 years of memory score,(1) a biennially-assessed summary measure of memory-focused cognitive tests from the HRS battery including proxy cognition reports, using linear mixed-effects models with random slopes and intercepts. We incorporated discontinuities at the time of procedure and 6 months after, and a spline knot at 5 years. Trajectories were adjusted for demographic, health (including frailty), and other covariates at the time of the last pre-procedure interview.

Results: Prior to the procedure, the CABG group was declining 0.012 memory units per year more slowly than the PCI group (95% CI [0.0004-0.023], p=0.043). When compared to the rate of cognitive decline in the PCI group, the CABG group was declining 25% more slowly than the PCI group prior to the procedure (95% CI [7.9% to 48% more slowly]). After the procedure, the CABG group rate of memory change accelerated by 68% compared with the pre-procedure trajectory (additional 0.024 memory units per year decline; 95% CI [0.011-0.038], p=0.001). CABG and PCI cognitive trajectories were statistically indistinguishable after the procedure.

Conclusion: Compared with nonsurgical coronary revascularization, CABG is associated with an acceleration in rate of cognitive decline compared with pre-procedure cognitive trajectory; however, the post-procedure rate of cognitive change is indistinguishable from PCI recipients. The long-term post-procedure rate of cognitive change may reflect the cognitive impact of cardiovascular disease, which would be expected to be similar between the CABG and PCI groups.

Reference(s): (1) Wu Q et al. Combining direct and proxy assessments to reduce attrition bias in a longitudinal study. Alz Dis Assoc Disord 2013; 27(3):207-12.


PCI
CABG
Shaded area represents 95% confidence interval.
CABG or PCI event normalized to **time = 0**
Memory score (no units)
1.0
0.8
0.6
0.4
0.2
0.0
-5
-4
-3
-2
-1
0
1
2
3
4
5
6
7
8
9
10
Time (years)

Geriatric Anesthesia-2 Effect of a Multi-Component Safety Intervention on Falls after Major Surgery

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Introduction: Falls occur in many older patients after surgery. Polypharmacy is a known risk factor for falls among elderly outpatients [1], and certain classes of medications such as benzodiazepines and some anticholinergics have been specifically associated with falls. In addition, physical hazards that increase the risk of falls are present in nearly all homes [2]. The purpose of this study was to evaluate whether a safety intervention consisting of medication review by a geriatric psychiatrist and home safety evaluation by an occupational therapist could reduce the incidence of falls after major surgery.

Methods: This is a secondary outcome of the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) randomized trial. The population included patients age 60 or older undergoing surgery at a single academic medical center with anticipated hospital length of stay ≥ 2 days. All patients in the trial (both arms) received a multi-component safety intervention. A geriatric psychiatrist reviewed each patient's home medication list and sent a letter to the patient's primary physician describing any recommended changes to reduce the patient's risk for postdischarge falls. All patients received an informational packet about fall prevention. Patients with a recent history of falls who lived less than 45 miles from the hospital were offered a postdischarge occupational therapy home visit to identify hazards and discuss solutions. The primary outcome was self-reported falls in the first postoperative year. Patients enrolled in ENGAGES were compared to a matched cohort of patients who did not enroll. These matches were drawn from a prospective observational cohort of surgical patients at the same center age 60 or older with hospital length of stay of at least 2 days. The difference in self-reported fall incidence in the first postoperative year was determined.

Results: Of the 1232 patients randomized in the ENGAGES trial, all 1232 underwent medication review and 27 received a home visit from an occupational therapist. A total of 531 medication changes were recommended for 351 unique patients. Of the enrolled patients, 953 (77% of 1232) responded to the follow-up survey one year after surgery. The population of potential controls included 2413 patients. Of the ENGAGES patients who returned the one-year survey, 786 patients (82% of 953) were successfully matched to control patients. Falls were reported by 223 ENGAGES patients (28% of 786) and by 239 matched controls (30% of 786). There was no difference in fall incidence between the groups (difference -0.02, 95% confidence interval -0.07 to 0.03).

Conclusion: The safety intervention was not associated with a significant decrease in the incidence of postoperative falls. The lack of effect may be explained by inadequate implementation of recommended changes, performance of home visits in a limited number of patients, residual confounding, or inadequate power.

Reference(s):

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2. Age Ageing 2006; 35: ii55-ii59

Geriatric Anesthesia-3 Association between the 5-HT3 receptor antagonists and postoperative delirium in elderly patients undergoing orthopedic lower limb surgery: A retrospective study

heijin Lee[1], Hyun-Jung Shin[1]

[1]Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do

Introduction: Delirium is a major postoperative complication. We investigated the association between the selective 5-hydroxytryptamine (serotonin, 5-HT) receptor, 5-HT3, antagonists and the occurrence of postoperative delirium (POD).

Methods: We retrospectively reviewed the electronic medical records of patients (> 65 years) who underwent orthopedic lower limb surgeries at a single tertiary academic hospital between July 2012 and September 2015. POD incidence and patient-, surgery-, and anesthesia-related factors were evaluated. Multivariable logistic regression analysis was conducted to investigate an association between 5-HT3 receptor antagonists and the occurrence of POD.

Results: In total, 855 patients were included, and 710 (83%) were associated with 5-HT3 receptor antagonists use. POD was confirmed for 46 (5.4%) patients. In multivariable logistic regression analysis, 5-HT3 receptor antagonists reduced the POD incidence by 63% (odds ratio [OR] 0.37, 95% confidence interval [CI] 0.15”’0.94, P = 0.036). Moreover, the POD incidence was decreased by 72% (OR 0.28, 95% CI 0.10”’0.77, P = 0.014), when palonosetron was administered. Other identified risk factors of POD were older age, lower body mass index, emergency surgery, hip surgery, and intraoperative propofol sedation.

Conclusion: 5-HT3 receptor antagonists may be associated with a significantly lower risk of POD in elderly patients undergoing orthopedic lower limb surgeries; palonosetron was a more effective 5-HT3 receptor antagonist for POD prevention.

Global Health

Global Health-1 Using Peer and Near-Peer Assisted Learning (PAL) in Point of Care Ultrasound (POCUS): Piloting a Resident-Driven Training Program for Global Anesthetic Capacity Building

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Introduction: Surgical conditions comprise approximately one third of the global burden of disease. Yet still, access to quality surgical, obstetric, and anesthetic care in low- and middle-income countries (LMICs) is a harrowing global health disparity. Five billion people are unable to reach surgical services that are timely, safe, and affordable.1 To that end, Point of Care Ultrasound (POCUS) is a useful tool in clinical evaluation and management of patients in low resources settings. Short-stent training interventions are common global health initiatives that quickly enrich ultrasound skill and result in long-term skill retention.2-4 In centers across the US, POCUS is becoming increasingly utilized in preoperative regional anesthesia procedures, vascular access, diagnosis, and resuscitation5-6. Nonetheless, overstretched bandwidth for experienced clinical faculty is a near universal challenge in clinical academia, which restricts time for teaching.8-9 To fill that need, peer or near-peer assisted learning (PAL) is commonplace throughout residency training. Moreover, it is an evidence supported, effective instructional modality for focused knowledge and skill transfer with comparable outcomes for milestone progression to faculty lead teaching.9-13 In this abstract, we describe our institution's development of a collaborative, resident-driven Global Anesthesia Program between our institution and an anesthesiology residency program in Toluca, Mexico. Through international resident exchanges and reciprocal peer/near-peer assisted learning (PAL), our program aims to structure a short-stent, resident lead POCUS training program as a global anesthetic capacity building tool.

Methods: Our program is structured as a bi-directional, two to four week resident rotation for US residents to travel to Mexico and vice versa for Mexican residents to travel to the USA. The US based curriculum centers on a flipped classroom model for POCUS with online modules covering transthoracic and transesophageal echo, lung, airway, FAST, gastric, regional, vascular access, and foundations of ultrasound physics. Residents engage in peer/near-peer assisted experiential learning with task trainers, needle work phantoms, standardized patient simulations, and bedside scanning for patients in ambulatory, perioperative, critical care, and PACU settings. The Mexican curriculum continues and reinforces learned ultrasound knowledge and skill foundations through core content review and repetition, as well as augments POCUS training by incorporating pediatric and obstetric scanning for neuraxial anesthetics.

Results: Data will be gathered by near-peer instructor pre-series/post-series self-assessments that use Likert scales, Objective Structured Teaching Evaluations that use a checklist, and Likert scale learner satisfaction surveys along with learner Objective Structured Clinical Examinations that uses a checklist. Datasets will be gathered in both the US and at the clinical sites in Toluca, Mexico to examine validity and inter-rater reliability in different clinical environments/low resource settings.

Conclusion: Launched in 2018, our Anesthesia Global Health Outreach Program is a collaboration between our Department of Anesthesiology and an Obstetric Hospital in Mexico to provide medical education and training, working towards developing sustainable surgical systems. Our main objectives in this collaboration were to develop knowledge, skills, behaviors essential for effective anesthesia practice in less developed, international healthcare settings; broaden awareness of cultural diversity and international healthcare delivery systems; and teach and exchange knowledge and clinical skills regarding perioperative management and Point-of-Care Ultrasound. We hope to use our initial project as a pathway to enrich our international collaborations. Likewise, we believe a compact, Train-the-Trainer educational delivery framework is amenable to an array of clinical anesthesia content beyond our starting point of PoCUS. This specific project, if successful, and its underlying framework similarly could be transferrable to other international sites as a cornerstone of the larger vision for global, sustainable anesthetic and surgical capacity building.

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Global Health-2 Clonality analysis of clinical isolates of Pseudomonas aeruginosa: The outbreak of high-risk clone ST357

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Introduction: Multi-drug resistant Pseudomonas aeruginosa cause severe infections, especially in the elder and immunocompromised patients. It is critical to characterize the epidemiological trends of high-risk P. aeruginosa isolates by continuous monitoring in hospitals. In this study, we performed two genetic analyses, Multi-Locus Sequence Typing (MLST) and Multiple-Locus Variable-number tandem repeat Analysis (MLVA), to check the clonality of clinically isolated antimicrobial-resistant P. aeruginosa strains. Then, we investigated the association between the characteristics of the isolates and the patient background.

Methods: This study was approved by the Medicine Ethics Committee of Kyoto Prefectural University. We investigated the antimicrobial susceptibility profiles of clinically isolated drug-resistant P. aeruginosa and the medical records of drug-resistant infected. Then, we performed clonality tests, MLST and MLVA, for 53 antimicrobial-resistant strains out of 2,119 P. aeruginosa isolated in the hospital between the years 2005 and 2018. In MLST, the DNA sequences of seven housekeeping genes were analyzed to determine the sequence type (ST). In MLVA, 15 genomic regions possessing variable-number tandem repeats (VNTR) were analyzed to determine the MLVA type (MT).

Results: Among 53 isolates, 36 (67.9%) were genotyped as ST357 in MLST and identified to have the same clonality type in MLVA. The most of these ST357 isolates possessed two class one integrons associated resistance to β-lactams and aminoglycosides. All 53 isolates were fluoroquinolone-resistant, 39 isolates (73.6%) were gentamicin-resistant, and 18 isolates (34.0%) were carbapenem-resistant. None of the isolates satisfied the clinical criteria for MDR P. aeruginosa. Comparison of ST357 and other STs revealed that a significantly higher proportion of ST357 isolates was resistant to gentamicin (p = 0.006). Among 53 patients, 13 patients (24.5%) died during the period of hospitalization. The mortality rates of the patients who harbored with ST357 and other ST isolates were 19.4% (n = 7/36) and 35.3% (n = 6/17), respectively (not significant).

Conclusion: The outbreak of ST357 strains s characterized by two clonality tests, MLST and MLVA. ST357 is reported worldwide as a high-risk clone with cytotoxic phenotype and drug-resistance, and it is necessary to monitor drug-resistant P. aeruginosa continuously.

Liver

Liver-1 Intraoperative Cardiac Arrest during Adult Liver Transplantation: Incidence and Risk Factor Analysis from Seven Academic Centers in the United States

Natalie K Smith[1], Jeron Zerillo[2], Sang J Kim[3], Guy E Efune[4], Cynthia Wang[5], Sher-Lu Pai[6], Ryan Chadha[7], Todd Kor[8], David R Wetzel[9], Michael A Hall10</s

[1]The Mount Sinai Hospital, New York, NY, [2]The Mount Sinai Hospital, New York, United States of America, [3]Hospital for Special Surgery, New York, United States of America, [4]University of Texas Southwestern Medical Center, Dallas, United States of America, [5]Greater Los Angeles VA Healthcare System, Los Angeles, United States of America, [6]Mayo Clinic, Jacksonville, FL, [7]Mayo Clinic Jacksonville, Jacksonville, FL, [8]Mayo Clinic, Rochester, MN, [9]Mayo Clinic, Rochester, United States of America, [10]Christiana Care Health System, Newark, DE, 11Perelman School of Medicine University of Pennsylvania, Philadelphia, PA, 12University of Washington School of Medicine, Seattle, WA, 13University of Pittsburgh Medical Center, Pittsburgh, PA, 14The Ohio State University, Columbus, OH, 15New York Medical College, Valhala, NY, 16Icahn School of Medicine at Mount Sinai, New York City, NY, 17University of Texas Southwestern Medical Center, Dallas, TX, 18University of Kansas Medical Center, Kansas City, KS, 19University of Colorado, Aurora, CO

Introduction: Intraoperative cardiac arrest (ICA) has a reported frequency of 1 in 10,000 anesthetics but has a higher estimated incidence in orthotopic liver transplantation (OLT).[1-3] Single center studies of ICA in OLT are limited by small sample size which prohibits multivariate regression analysis of risks.[4-6] Utilizing data from seven academic medical centers, we performed a retrospective, observational study of adult patients experiencing ICA during OLT compared with those who did not experience ICA. We sought to identify the rate of ICA in OLT, the risk factors associated with the development of ICA, and outcomes following ICA.

Methods: 5,296 adult liver transplant recipients from 2000 to 2017 were retrospectively enrolled . Recipients under 18 and over 80 years old and recipients of multi-organ transplants were excluded. Patient characteristics and outcome groups were compared using chi-square or Fisher's exact test. To evaluate for independent risk factors for ICA, 30-day and 1-year mortality, the generalized linear mixed model for logistic regression was utilized.

Results: ICA occurred in 196 cases (3.7%) and mortality occurred in 62 patients (1.2%). The intraoperative mortality rate was 31.6% in patients with ICA. In a multivariate generalized linear mixed model, ICA was associated with body mass index (BMI) <20 (OR: 2.04, 95% CI 1.05 - 3.98; p=0.0386), BMI ≥ 40 (2.16 (1.12 - 4.19) p=0.022), Model for End-Stage Liver Disease (MELD) score: (MELD 30-39: 1.75 (1.09 - 2.79) p=0.02; MELD ≥ 40: 2.73 (1.53 - 4.85) p =0.001), post-reperfusion syndrome (PRS) (3.83 (2.75 - 5.34) p<0.001), living donors (2.13 (1.16-3.89) p=0.014), and reoperation (1.87 (1.13 - 3.11) p = 0.015) (Figure 1). Overall 30-day and one-year mortality were 4.18% and 11.0%, respectively. After ICA, 30-day and one-year mortality were 43.9% and 52%, respectively, compared to 2.6% and 9.3% without ICA. In a multivariate analysis, ICA was the most significant risk factor for both 30-day mortality (5.83 (3.37-10.07) p < 0.001) (Figure 2) and one-year mortality (2.81 (1.83-4.32) p < 0.001) (Figure 3). Figure 1-3: : Factors Associated with Intraoperative Cardiac Arrest (ICA), 30-day and 1-year Mortality Risk factors associated with (Figure 1) ICA, (Figure 2) 30-day Mortality and (Figure 3) One-year Mortality in a multivariable generalized linear mixed model with study sites as random effects. Risk factors (x-axis) are expressed as odds ratios and confidence intervals (CI) (y-axis).

Conclusion: We established a 3.7% prevalence of ICA and a 1.2% prevalence of intraoperative mortality in liver transplantation and confirmed previously identified risk factors for ICA including BMI, MELD score, PRS, and reoperation and identified new risk factors including living donor and length of surgery in this multicenter retrospective cohort. ICA, while rare, is associated with poor patient survival and future research must focus on therapy to reduce the incidence of ICA.

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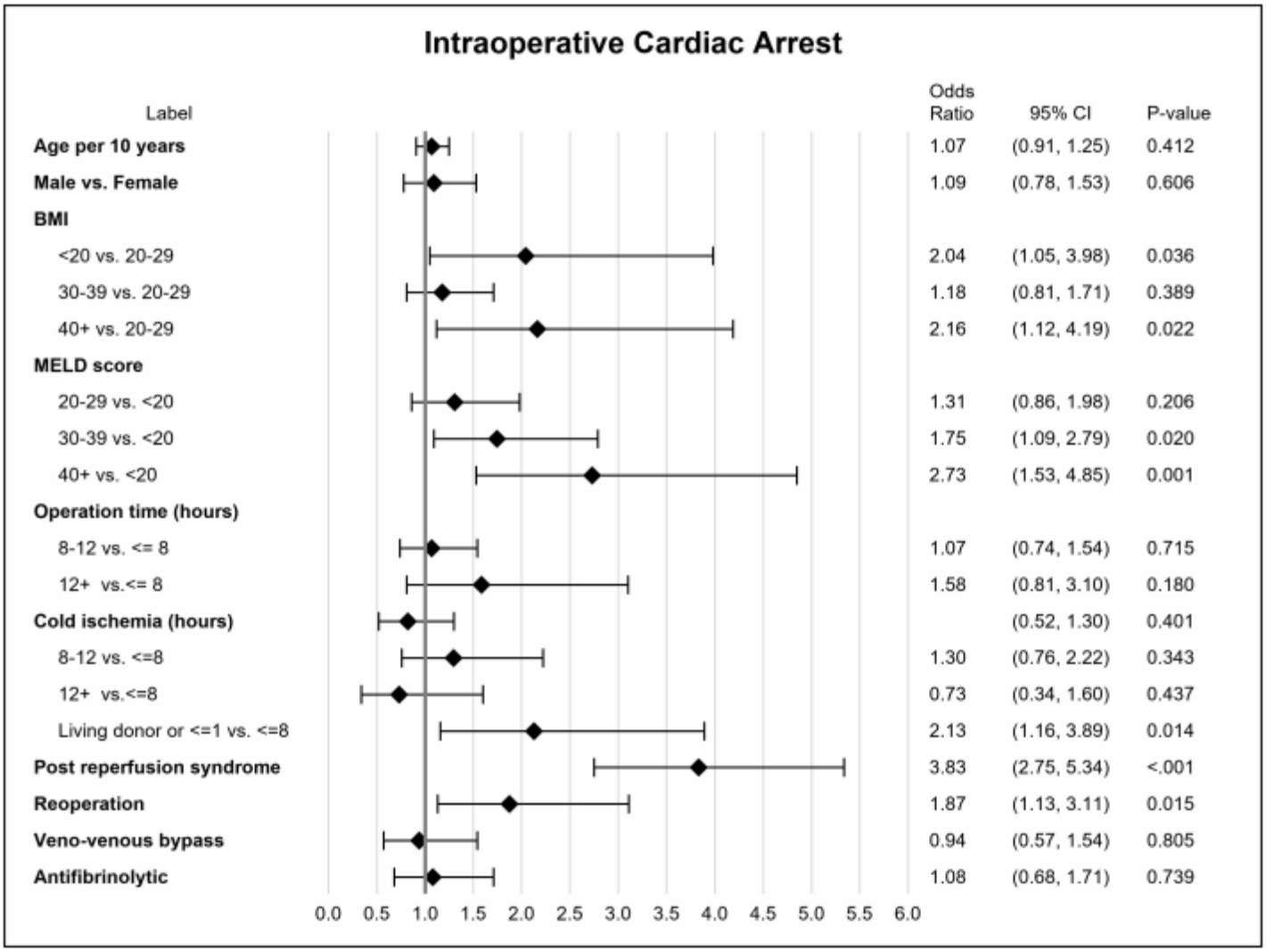
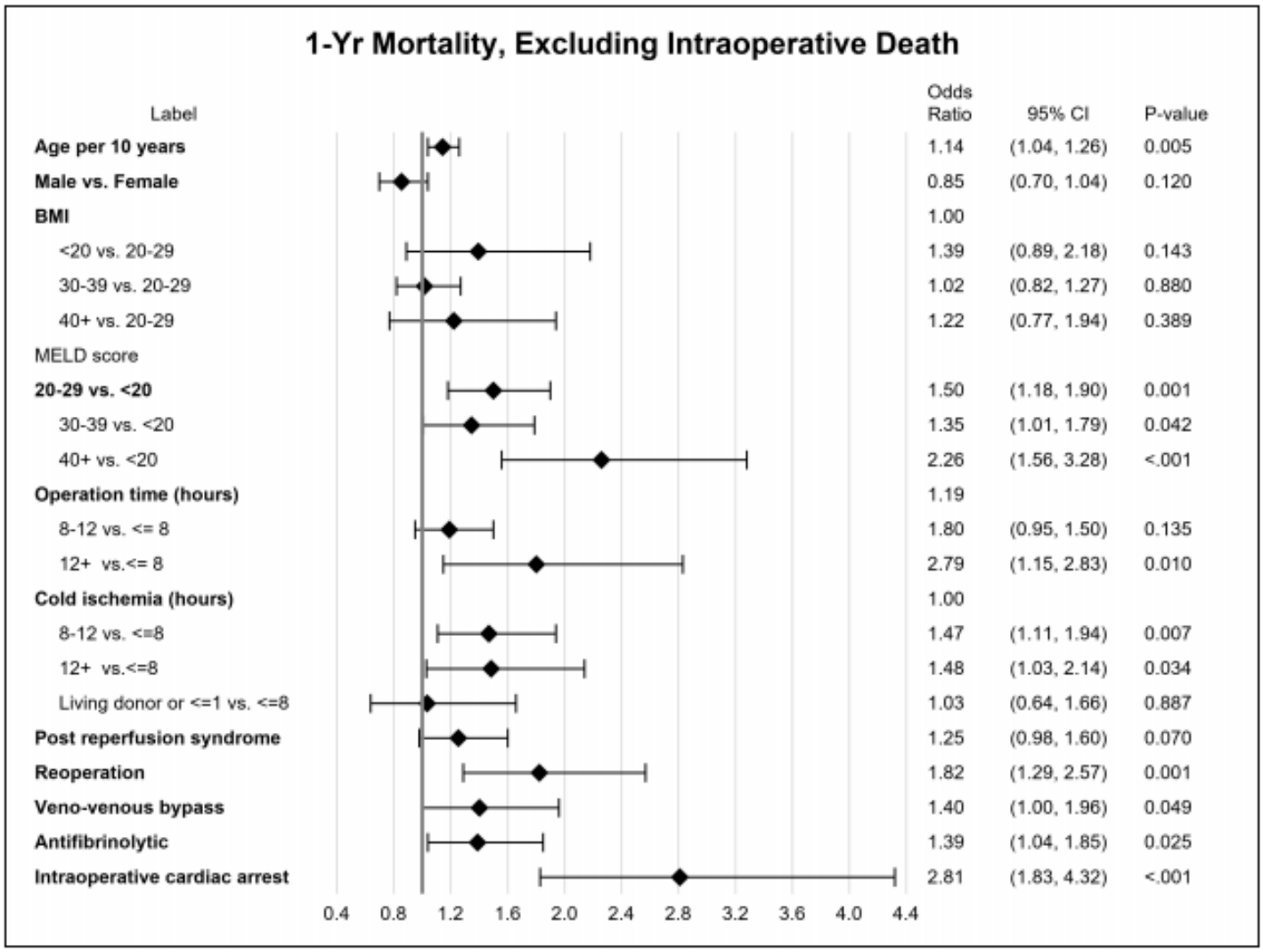
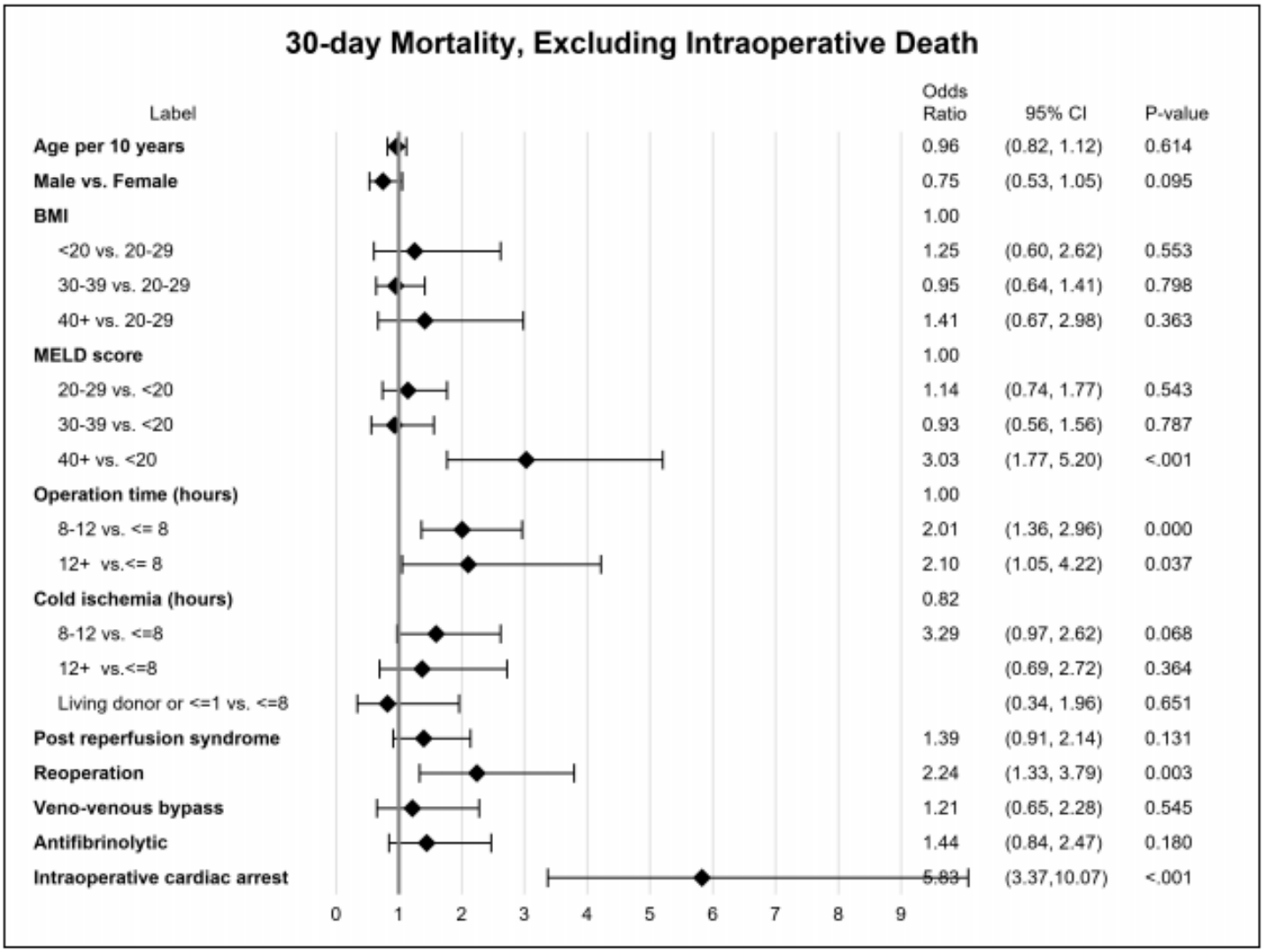

Intraoperative Cardiac Arrest
Label
Odds Ratio
95% CI
P-value
Age per 10 years
1.07
(0.91, 1.25)
0.412
Male vs. Female
1.09
(0.78, 1.53)
0.606
BMI
<20 vs. 20-29
2.04
(1.05, 3.98)
0.036
30-39 vs. 20-29
1.18
(0.81, 1.71)
0.389
40+ vs. 20-29
2.16
(1.12, 4.19)
0.022
MELD score
20-29 vs. <20
1.31
(0.86, 1.98)
0.206
30-39 vs. <20
1.75
(1.09, 2.79)
0.020
40+ vs. <20
2.73
(1.53, 4.85)
0.001
Operation time (hours)
8-12 vs. <= 8
1.07
(0.74, 1.54)
0.715
12+ vs.<= 8
1.58
(0.81, 3.10)
0.180
Cold ischemia (hours)
(0.52, 1.30)
0.401
8-12 vs. <=8
1.30
(0.76, 2.22)
0.343
12+ vs.<=8
0.73
(0.34, 1.60)
0.437
Living donor or <=1 vs. <=8
2.13
(1.16, 3.89)
0.014
Post reperfusion syndrome
3.83
(2.75, 5.34)
<.001
Reoperation
1.87
(1.13, 3.11)
0.015
Veno-venous bypass
0.94
(0.57, 1.54)
0.805
Antifibrinolytic
1.08
(0.68, 1.71)
0.739
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0


1-Yr Mortality, Excluding Intraoperative Death
Label
Odds Ratio
95% CI
P-value
Age per 10 years
1.14
(1.04, 1.26)
0.005
Male vs. Female
0.85
(0.70, 1.04)
0.120
BMI
1.00
<20 vs. 20-29
1.39
(0.89, 2.18)
0.143
30-39 vs. 20-29
1.02
(0.82, 1.27)
0.880
40+ vs. 20-29
1.22
(0.77, 1.94)
0.389
MELD score
20-29 vs. <20
1.50
(1.18, 1.90)
0.001
30-39 vs. <20
1.35
(1.01, 1.79)
0.042
40+ vs. <20
2.26
(1.56, 3.28)
<.001
Operation time (hours)
1.19
8-12 vs. <= 8
1.80
(0.95, 1.50)
0.135
12+ vs.<= 8
2.79
(1.15, 2.83)
0.010
Cold ischemia (hours)
1.00
8-12 vs. <=8
1.47
(1.11, 1.94)
0.007
12+ vs.<=8
1.48
(1.03, 2.14)
0.034
Living donor or <=1 vs. <=8
1.03
(0.64, 1.66)
0.887
Post reperfusion syndrome
1.25
(0.98, 1.60)
0.070
Reoperation
1.82
(1.29, 2.57)
0.001
Veno-venous bypass
1.40
(1.00, 1.96)
0.049
Antifibrinolytic
1.39
(1.04, 1.85)
0.025
Intraoperative cardiac arrest
2.81
(1.83, 4.32)
<.001
0.4
0.8
1.2
1.6
2.0
2.4
2.8
3.2
3.6
4.0
4.4


30-day Mortality, Excluding Intraoperative Death
Label
Odds Ratio
95% CI
P-value
Age per 10 years
0.96
(0.82, 1.12)
0.614
Male vs. Female
0.75
(0.53, 1.05)
0.095
BMI
1.00
<20 vs. 20-29
1.25
(0.60, 2.62)
0.553
30-39 vs. 20-29
0.95
(0.64, 1.41)
0.798
40+ vs. 20-29
1.41
(0.67, 2.98)
0.363
MELD score
1.00
20-29 vs. <20
1.14
(0.74, 1.77)
0.543
30-39 vs. <20
0.93
(0.56, 1.56)
0.787
40+ vs. <20
3.03
(1.77, 5.20)
<.001
Operation time (hours)
1.00
8-12 vs. <= 8
2.01
(1.36, 2.96)
0.000
12+ vs.<= 8
2.10
(1.05, 4.22)
0.037
Cold ischemia (hours)
0.82
8-12 vs. <=8
3.29
(0.97, 2.62)
0.068
12+ vs.<=8
(0.69, 2.72)
0.364
Living donor or <=1 vs. <=8
(0.34, 1.96)
0.651
Post reperfusion syndrome
1.39
(0.91, 2.14)
0.131
Reoperation
2.24
(1.33, 3.79)
0.003
Veno-venous bypass
1.21
(0.65, 2.28)
0.545
Antifibrinolytic
1.44
(0.84, 2.47)
0.180
Intraoperative cardiac arrest
5.83
(3.37,10.07)
<.001
0
1
2
3
4
5
6
7
8
9

Liver-2 ASSOCIATION BETWEEN HYPONATREMIA AND PERIOPERATIVE MORTALITY IN PEDIATRIC POPULATION UNDERGOING LIVER TRANSPLANTATION.

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Introduction: Hyponatremia is a frequent complication of end stage liver disease (ESLD) with an overall high prevalence. The general prevalence in the adult population with cirrhosis is almost 50% (1). Several studies have clearly demonstrated that hyponatremia is an independent predictive factor for liver transplantation (LT) waiting list mortality in the adult population (2). However, little data exists related to hyponatremia in the pediatric ESLD population. Therefore, in this analysis we attempted to evaluate an association between hyponatremia and both waiting list and postoperative survival for the pediatric population.

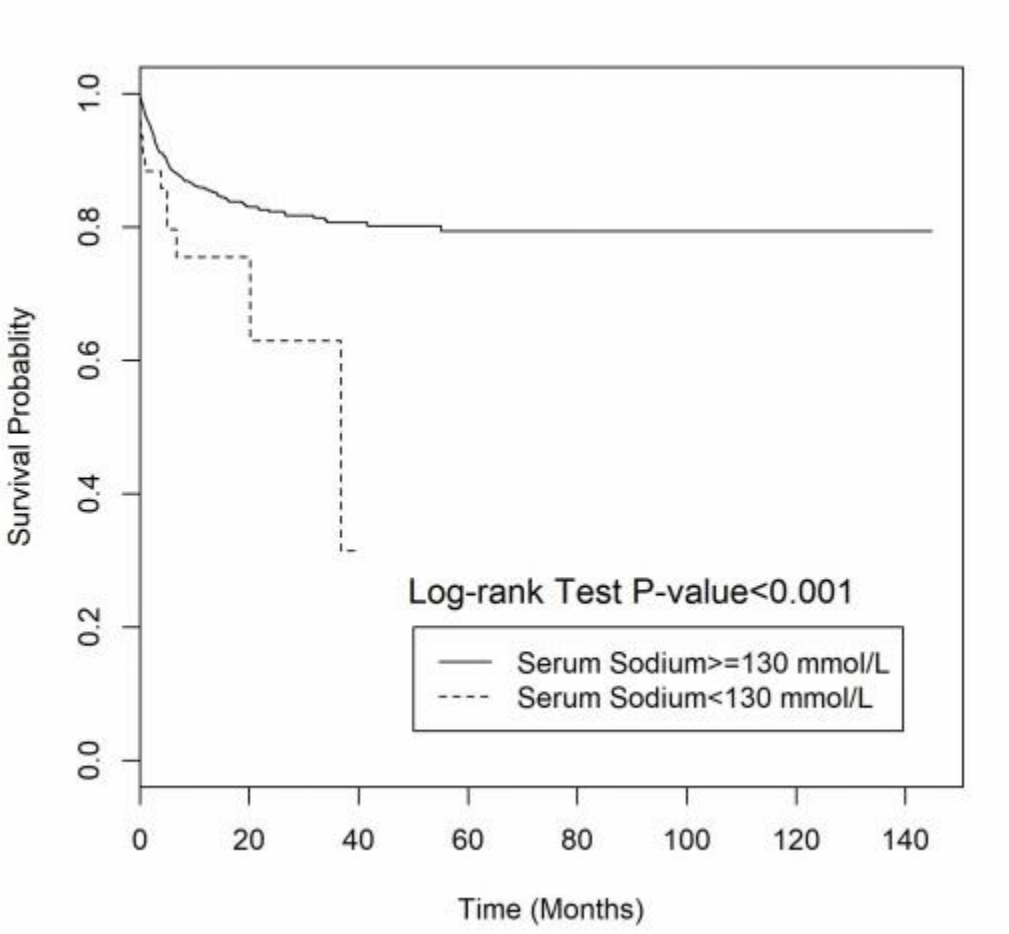
Methods: We conducted a retrospective analysis of the United Network for Organ Sharing (UNOS) database and enrolled pediatric patients listed for LT between 1988 and 2016. Hyponatremia was defined as a sodium concentration of 130 mEq/L or below. Subjects were divided in two groups by age: Group I (0-6 years old) and Group II (7-18 years old). Survival data from subjects before and after LT, as well as graft survival between groups with and without hyponatremia was evaluated. Multivariable cox proportional hazards models were constructed for perioperative mortality.

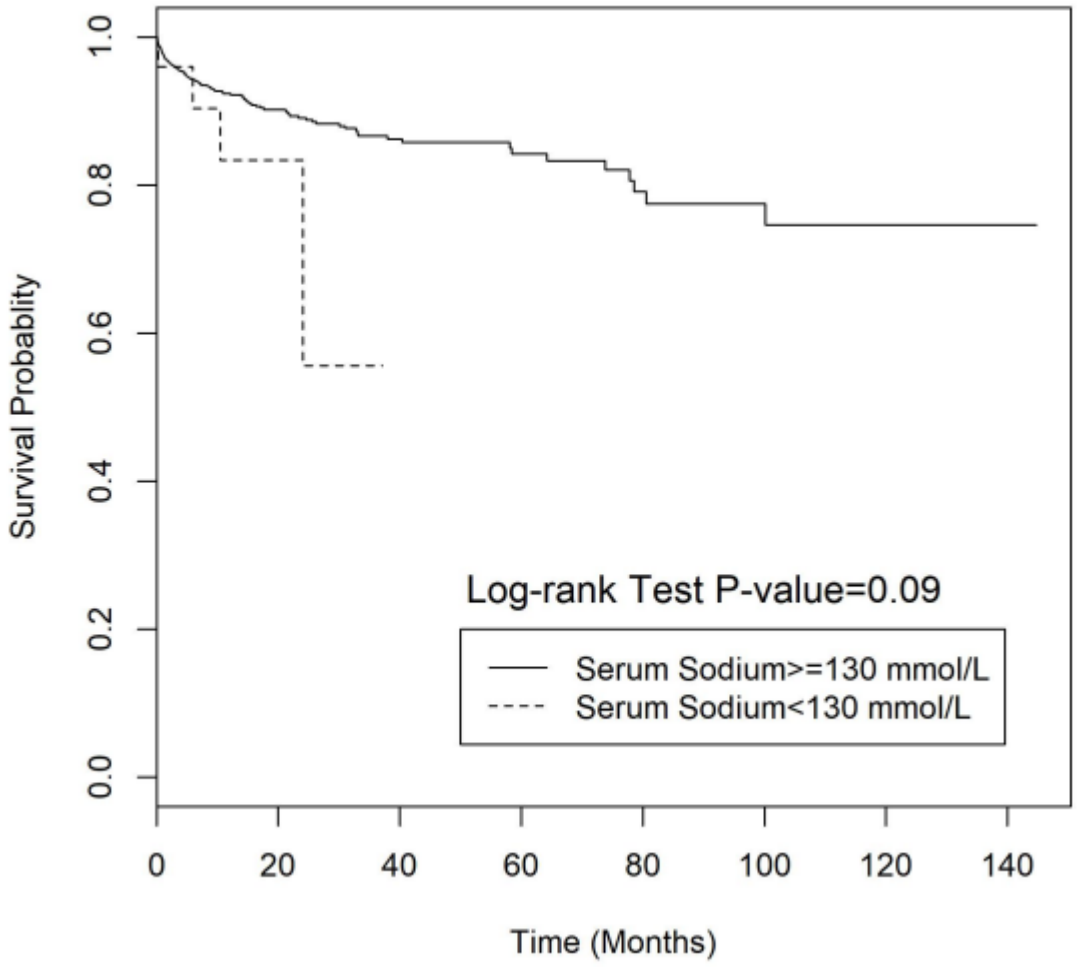
Results: Between June 6, 1988 and December 31, 2015, 10428 pediatric patients between 0 and 18 were register on the waiting list for LT. Data of 3822 (37%) patients was incomplete and couldn't be included in the analysis. Finally, data from 6606 children (4251 patients in Group I and 2355 patients in Group 2) were available for preoperative analysis and 4478 (2983 children in Group I and 1495 in Group II) for postoperative analysis. Observed overall preoperative mortality was 11%. Prevalence of hyponatremia while on the waiting list was 2.8% (3.1% and 2.3% in Groups I and II, respectively). Waiting list mortality in patients with hyponatremia was significantly higher in Group I ($p < 0.001$) (Figure 1) but not in Group II ($p=0.09$) (Figure 2). Other independent factors predictive of increased waiting list mortality included sodium level below 130 mEq/L (HR=1.7), younger age (Group I) (HR=2.0), and need for dialysis (HR=2.2) (Figure 3). There was no difference in overall postoperative patient or graft survival stratified by hyponatremia. Factors associated with increased postoperative mortality included younger age (Group I) (HR=2.2), African American race (HR=1.3), and the use of deceased-donor grafts (OR=1.7) (Figure 4).

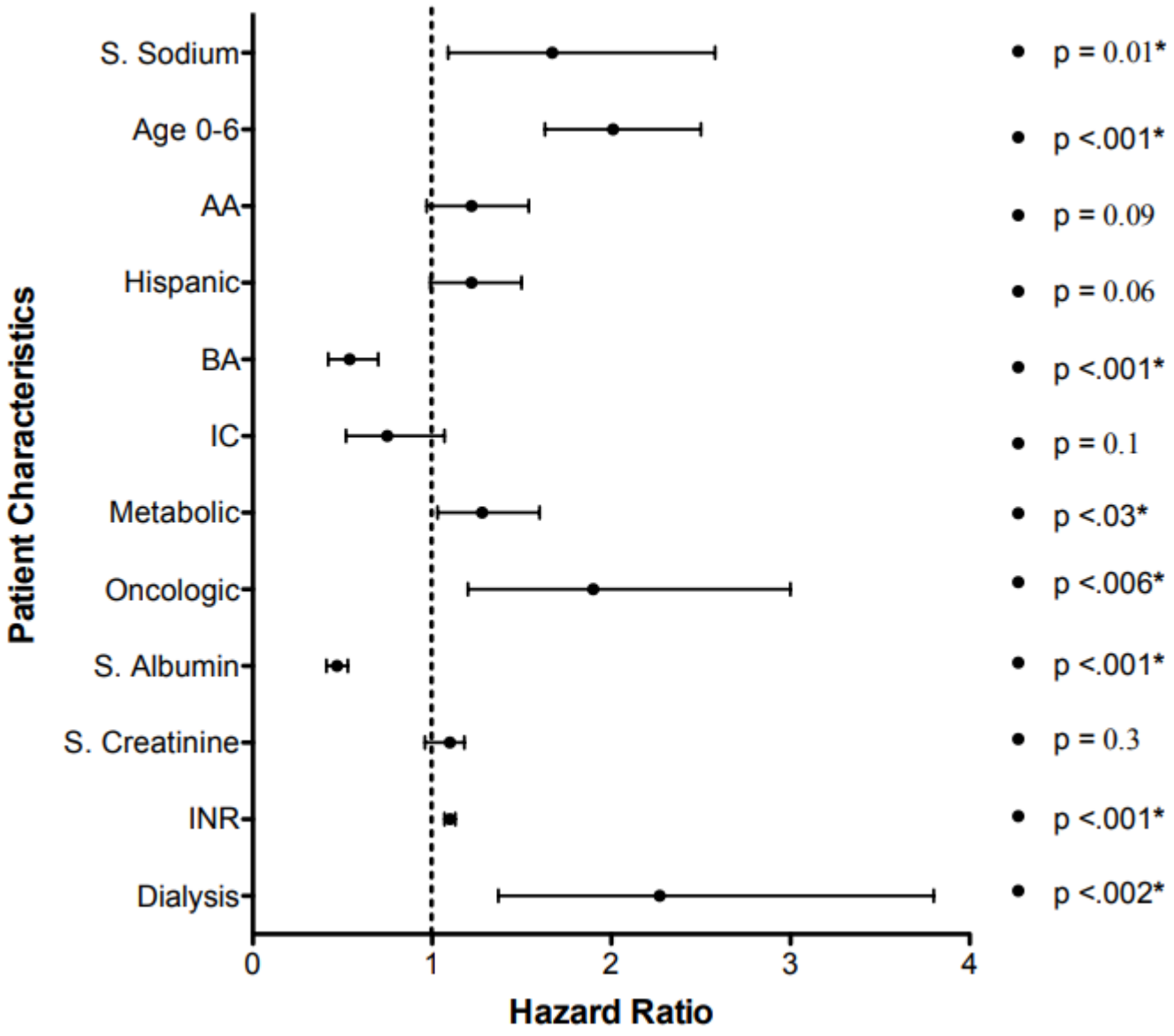
Conclusion: Our study has demonstrated an overall low prevalence of hyponatremia in children with ESLD in comparison to adult patients with liver failure. This most likely reflects shorter waiting times and earlier transplantation as well as the more aggressive management of hyponatremia in the pediatric population. Only in younger children (less than 7 years old) was hyponatremia associated with increased mortality while on the waiting list. Addition of sodium to the Pediatric End Stage Liver Didease (PELD) score for this subpopulation can be potentially beneficial for improvement in organ allocation.

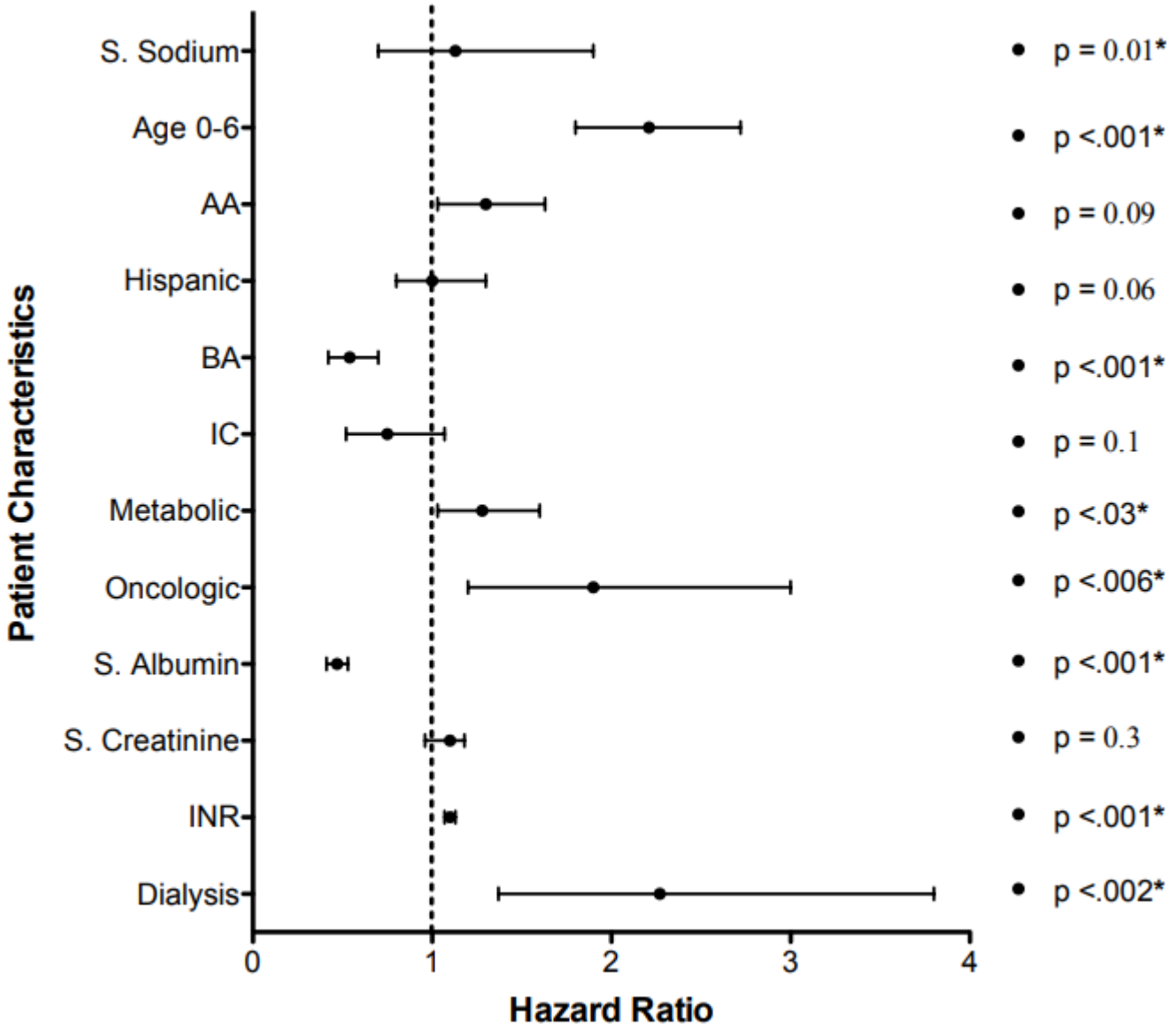
Reference(s):

1. Angeli P, Wong F, Watson H, Gines P, Investigators C. Hyponatremia in cirrhosis: Results of a patient population survey. Hepatology 2006;44:1535-42.
2. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. The New England journal of medicine 2008;359:1018-26.


Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
Time (Months)
Log-rank Test P-value<0.001
Serum Sodium>=130 mmol/L
Serum Sodium<130 mmol/L


Survival Probablity
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
Time (Months)
Log-rank Test P-value=0.09
Serum Sodium>=130 mmol/L
Serum Sodium<130 mmol/L


Patient Characteristics
S. Sodium
Age 0-6
AA
Hispanic
BA
IC
Metabolic
Oncologic
S. Albumin
S. Creatinine
INR
Dialysis
p = 0.01*
p <.001*
p = 0.09
p = 0.06
p <.001*
p = 0.1
p <.03*
p <.006*
p <.001*
p = 0.3
p <.001*
p <.002*
0
1
2
3
4
Hazard Ratio


Patient Characteristics
S. Sodium
Age 0-6
AA
Hispanic
BA
IC
Metabolic
Oncologic
S. Albumin
S. Creatinine
INR
Dialysis
0
1
2
3
4
Hazard Ratio
p = 0.01*
p <.001*
p = 0.09
p = 0.06
p <.001*
p = 0.1
p <.03*
p <.006*
p <.001*
p = 0.3
p <.001*
p <.002*

Neuroscience in Anesthesiology and Perioperative Medicine

Neuroscience in Anesthesiology and Perioperative Medicine-1 Postoperative Delirium after Spine Surgery: Does Time Under Anesthesia Matter?

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Introduction: Adults 65 years and older account for over one-third of all surgical patients. Evidence suggests that the geriatric population have the highest risk for deleterious postoperative neurocognitive outcomes, including postoperative delirium.1 Postoperative delirium is an acute disturbance of consciousness characterized by fluctuations in attention, cognition and perception.2 Delirium is associated with morbidity and mortality, but there is limited information surrounding modifiable factors that may help limit this occurrence.2 Our objective was to determine whether prolonged surgical times were associated with increased risk of postoperative delirium in geriatric patients undergoing elective spine surgery.

Methods: This prospective, observational study analyzed patients aged 65 and older undergoing elective spine surgery under general anesthesia. Patients scheduled for elective, inpatient spine surgery were contacted for study participation. Of the 100 participants contacted to be involved in the study, 68 participants consented and were enrolled. The primary outcome was a diagnosis of postoperative delirium during the hospitalization, and the exposure was surgical duration, measured as total time in the operating room in minutes. An unpaired t-test was performed to determine whether surgical duration was significantly associated with the occurrence of postoperative delirium prior to hospital discharge.

Results: In total, 68 patients aged 66-89 (mean 72.2 years) underwent spine surgery/general anesthesia ranging from 111 - 779 minutes duration. Of these, 62% were women. 13 participants developed postoperative delirium prior to hospital discharge. Participants who developed postoperative delirium had an increased surgical duration compared to participants who did not develop postoperative delirium (mean ± SEM, 453.5 ± 49.5 vs. 274.8± 17.1 minutes, $p<0.0001$)

Conclusion: Among geriatric patients undergoing elective, inpatient spine surgery, an increased duration of surgery/general anesthesia was associated with an increased risk of developing postoperative delirium prior to hospital discharge.

Reference(s):

1. Prog Neuro-Psychopharmacol Biol Psychiatry. 2013; 47:162-6

2. Ravi B, Pincus D, Choi S, Jenkinson R, Wasserstein DN, Redelmeier DA. Association of Duration of Surgery With Postoperative Delirium Among Patients Receiving Hip Fracture Repair. Jama Netw Open. 2019;2(2):e190111. doi:10.1001/jamanetworkopen.2019.0111

Neuroscience in Anesthesiology and Perioperative Medicine-2 Reactive oxygen species play role in P2X7 receptor-mediated IL-6 production in spinal astrocytes

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Introduction: Astrocytes mediate a remarkable variety of cellular functions, including gliotransmitter release. Under pathological conditions, high concentrations of the purinergic receptor agonist adenosine triphosphate (ATP) are released into the extracellular space activating the purinergic P2X7 receptor to initiate signaling cascades. It is well-established that reactive oxygen species (ROS) increase in macrophages and microglia following P2X7 receptor activation. However, direct evidence that activation of P2X7 receptor leads to ROS production in astrocytes is lacking to date. While it is known that P2X7R activation induces cytokine production, the mechanism involved in this process is unclear. The goal of this research was to investigate the mechanism involved.

Methods: Spinal cord astrocyte cultures were prepared from neonatal (P3 - P5) mice as described previousl. Astrocytes (1.5x103) were cultured in 14 mm glass bottom 35 mm petri dishes for 24 h, and then loaded with 5 µM CellROX (Life Technologies, Carlsbad, CA) at 37°C for 30 minutes in Tyrode's solution containing (in mM) 140 NaCl, 5 KCl, 1 MgCl2, 2 CaCl2, 10 HEPES, 5.6 glucose (pH 7.4) according to manufacturer's instructions. Calcium imaging was performed in cultured spinal cord astrocytes as we described previously [32,14]. IL-6 in the supernatant was then measured by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA). Treatment effects were statistically analyzed with a one-way analysis of variance (ANOVA). When ANOVA showed a significant difference, comparisons between means were performed by the post hoc Tukey's test. Error probabilities of $P < 0.05$ were considered statistically significant. The statistical software GraphPad Prism 7 was used to perform all statistical analyses.

Results: 1) Purinoreceptor activation induces ROS production through P2X7R in spinal astrocytes 2) The ROS scavenger PBN does not interfere P2X7R-induced calcium entry 3) NADPH oxidase contributes to P2X7R-mediated ROS production 4) P2X7R induces IL-6 release in spinal astrocytes 5) NADPH oxidase-induced ROS production contributes to P2X7R-mediated IL-6 release"

Conclusion: We demonstrated that P2X7 receptor activation induced ROS production in spinal astrocytes in a concentration dependent manner. We also found that P2X7R-mediated ROS production is at least partially through NADPH oxidase. In addition, our ELISA data show that P2X7R-induced IL-6 release was dependent on NADPH oxidase-mediated production of ROS. Collectively, these results reveal that activation of the P2X7 receptor on spinal astrocytes increases reactive oxygen species production through NADPH oxidase, subsequently leading to IL-6 release. Our results reveal a role of ROS in the P2X7 signaling pathway in mouse spinal cord astrocytes and may indicate a potential mechanism for the astrocytic P2X7 receptor in chronic pain.

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Neuroscience in Anesthesiology and Perioperative Medicine-3 Neural correlates of memory formation during periodic acute pain with low-dose midazolam and ketamine: A randomized within-subject crossover functional MRI study in healthy young adult subjects

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Introduction: Despite widespread clinical use of anesthetic drugs, there is much we do not know about the neural correlates of their actions, particularly in the setting of processing painful stimuli. For example, no published study has shown modulated functional MRI (fMRI) activation for inhibition of human memory encoding by midazolam - a commonly-induced clinical phenomenon. A better understanding of this neuropharmacology could improve clinical decision-making, as well as further elucidate the mechanisms of specific cognitive functions associated with consciousness. We used fMRI, dually analyzed for brain activity and functional connectivity (FC), to determine the neurosignature of two distinct anesthetics, midazolam and ketamine, in a novel combined experimental paradigm of memory encoding during the periodic aversive experience of acute pain. Previous ketamine fMRI studies have showed reduced activation in specific areas for memory [1] and pain [2] tasks. Task-free FC-MRI studies have demonstrated decreased long-range FC with midazolam [3] and that ketamine decreased FC between a large 'somatosensory' seed network (including the insula) to target regions in the amygdala and hippocampus [4]. Based on a previous analysis of our pilot data (presented at IARS 2018) assimilated with the literature above, we anticipated that both drugs would reduce fMRI activation in and the FC between the brain systems for memory encoding, threat response, and pain processing.

Methods: Healthy volunteers (n=23, 11 female, age 25.6 ± 4.9) underwent fMRI (3T BOLD, TR=1 s) in a randomized single-blind within-subject crossover trial comparing midazolam and ketamine at equisedative (light sedation) levels. Starting under saline control, subjects performed a memory encoding task [5] with 90 auditory word items (repeated 3 times), while receiving periodic painful (7/10) electric nerve stimulation to their left index finger. Task responses were indicated by right-hand button press. After a targeted drug infusion reached steady-state, the task was repeated with 90 different words. Recognition was assessed the next day using the Remember-Know memory test [6]. After at least 5 days, subjects returned and performed the experiment using the other drug. FMRI data timeseries were compared between saline and drug conditions for brain responses related to experimental events (using SPM12) and for background functional connectivity (using Conn Toolbox 18a), after task-related activity was removed by regression. Group average activation was calculated for whole-brain responses to items subsequently recognized as familiar. FC was examined from atlas-defined anatomical regions to all other voxels in the brain. Clusters were thresholded for significance at $p < 0.001$ and a minimum of 27 contiguous voxels.

Results: Memory was differentially impaired; recollection decreased 25% with ketamine and 60% with midazolam. Response rates and times were similar between drugs, indicating equal sedation. Annotated group average activation maps are shown in Figure 1. Task-related activation under saline is seen in specific areas within different functional networks. These include: the hippocampus, representative of the memory encoding network; the amygdala, representing the network for threat/fear responses; and the insula, a characteristic structure in the network for pain processing. Both drugs show broad comparative reductions in task activation. Table 1 lists the significant FC changes with midazolam, demonstrating increased FC between brain areas in the functionally-discrete networks listed. Table 2 lists FC changes with ketamine, showing predominantly decreased FC between component brain areas within the same functional networks.

Conclusion: In a clinically-relevant paradigm of memory formation with periodic pain, equisedative levels of both midazolam and ketamine globally disrupted task-related activity in brain areas subserving memory formation, threat response, and pain processing. In contrast, the two drugs caused diverging FC changes between the same brain areas. We thus demonstrate, for the first time, the neural underpinnings distinguishing the brain states achieved by these pharmacologically-different drugs. The overlapping inhibition of activation may explain the similar levels of sedation achieved, while the distinct FC neurosignatures may reflect the drugs' differing effects on memory and other neuropsychological behaviors.

Reference(s):

[1] Cereb Cortex, 2005. 15:749-59.

[2] Anesth Analg, 2006. 103:729-37.

[3] Hum Brain Mapp, 2015. 36:4247-61.

[4] Anesthesiology, 2012. 117:868-77.

[5] Exp Brain Res, 2019. 237:1615-1627.

[6] Conscious Cogn, 2012. 21:1435-55.

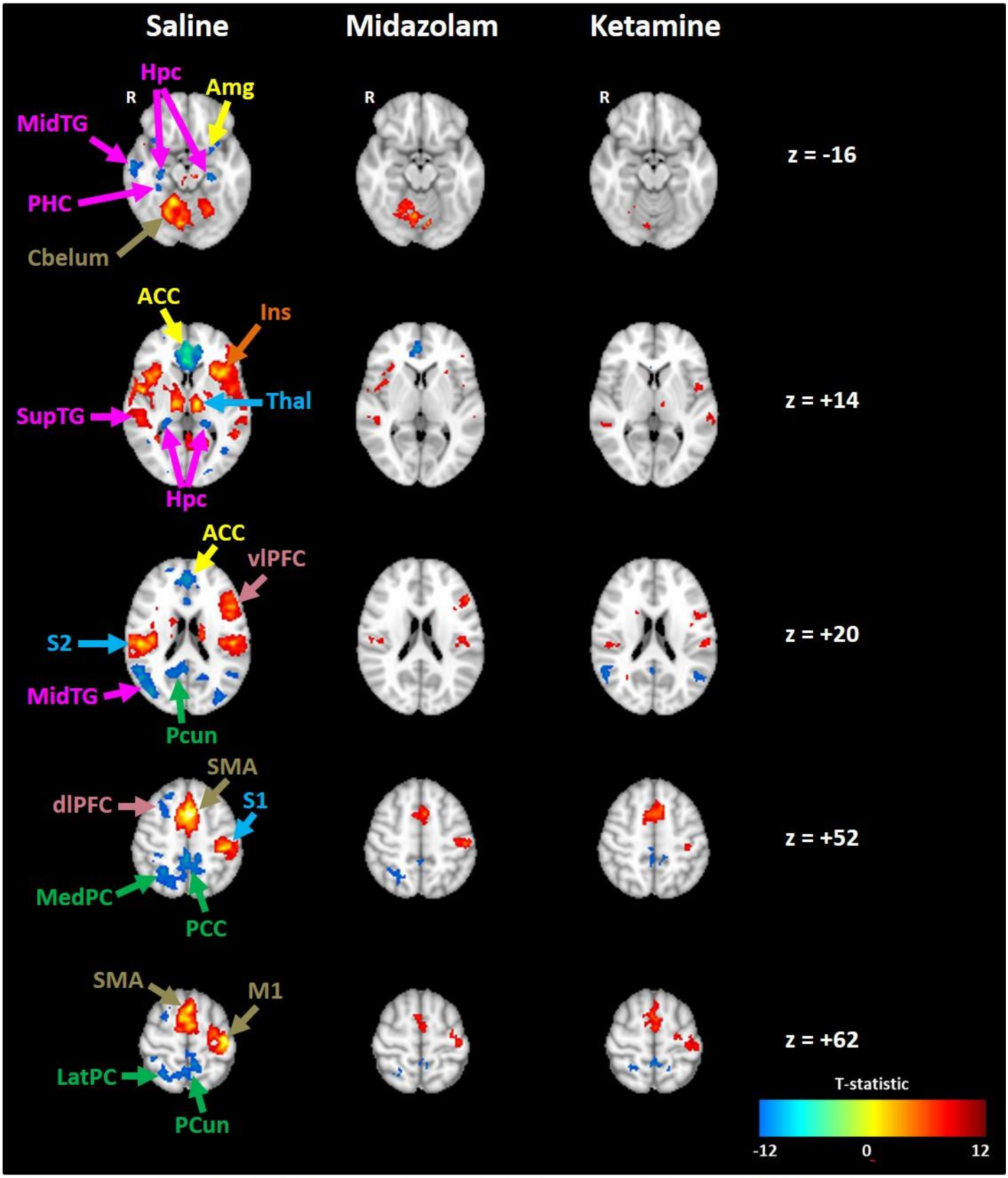

Figure 1: Group average activation for experimental items subsequently recognized as familiar under saline and drug conditions. Labels are color-coded based on functional organization: memory encoding in purple (Hpc= hippocampus, PHC= parahippocampus, MidTG= middle temporal gyrus, SupTG= superior temporal gyrus), threat response areas in yellow (Amg= amygdala, ACC= anterior cingulate cortex), sensory processing in blue (Thal= thalamus, S2 & S1 = secondary & primary (respectively) somatosensory cortices), parietal association in green (Pcun= precuneus, PCC= posterior cingulate cortex, MedPC= medial parietal cortex, LatPC= lateral parietal cortex), prefrontal cortex (PFC) in pink (vlPFC= ventrolateral PFC, dlPFC= dorsolateral PFC), and motor areas are in olive (M1= primary motor cortex, SMA= supplementary motor area).

Midazolam FC Changes

Seed Region		Target Identified		
Network	**Specific Area**	**Network**	**Specific Area**	**FC Change**
Default-mode	mPFC	Somatosensory	S1	Increased
Default-mode	mPFC	Pain processing	Insula	Increased
Default-mode	mPFC	Motor Response	M1	Increased
Default-mode	mPFC	Memory Encoding	Temporal pole/gyrus	Increased
Default-mode	Precuneus	Somatosensory	S1	Increased
Default-mode	Precuneus	Memory Encoding	vlPFC	Decreased
Default-mode	Precuneus	Association Cortices	Lateral Parietal lobe	Increased
Default-mode	Precuneus	Memory Encoding	Temporal pole/gyrus	Increased
Memory Encoding	Parahippocampus	Memory Encoding	Parahippocampus	Increased
Memory Encoding	Parahippocampus	Association Cortices	Lateral Parietal lobe	Increased
Memory Encoding	Parahippocampus	Memory Encoding	Temporal pole/gyrus	Increased
Pain processing	Insula	Threat response	ACC/Paracingulate	Increased
Pain processing	Insula	Somatosensory	S1	Increased
Pain processing	Insula	Working Memory	dlPFC	Increased
Pain processing	Insula	Default-mode	vmPFC	Increased
Pain processing	Insula	Motor Response	M1	Increased
Pain processing	Insula	Association Cortices	Lateral Parietal lobe	Increased
Pain processing	Insula	Memory Encoding	Temporal pole/gyrus	Increased
Somatosensory	S1	Association Cortices	Lateral Parietal lobe	Increased
Somatosensory	S1	Default-mode	Precuneus/PCC	Increased
Somatosensory	S1	Working Memory	dlPFC	Increased
Somatosensory	S1	Higher Cognition	dmPFC	Increased
Somatosensory	S1	Memory Encoding	vlPFC	Increased
Somatosensory	S1	Default-mode	vmPFC	Increased
Somatosensory	S1	Memory Encoding	Temporal pole/gyrus	Increased
Somatosensory	Thalamus	Somatosensory	Thalamus	Increased
Threat response	ACC	Memory Encoding	vlPFC	Increased

Table 1: Significant functional connectivity changes under midazolam, compared to saline. Seed anatomical regions were defined with a standard atlas and targets identified from signals throughout the brain. Target networks are described based on atlas anatomy and purported function of the region, relevant to the experimental framework.

Ketamine FC Changes

Seed Region		Target Identified		
Network	**Specific Area**	**Network**	**Specific Area**	**FC Change**
Default-mode	mPFC	Threat response	ACC/Paracingulate	Increased
Memory Encoding	Hippocampus	Motor Response	M1	Decreased
Memory Encoding	Hippocampus	Somatosensory	S1	Decreased
Memory Encoding	Parahippocampus	Motor Response	M1	Decreased
Memory Encoding	Parahippocampus	Somatosensory	S1	Decreased
Memory Encoding	Parahippocampus	Somatosensory	Thalamus	Increased
Somatosensory	S1	Association Cortices	Lateral Parietal lobe	Increased
Somatosensory	S1	Motor Response	M1	Decreased
Somatosensory	Thalamus	Memory Encoding	Temporal pole/gyrus	Increased
Threat response	Amygdala	Somatosensory	S1	Decreased
Threat response	Amygdala	Motor Response	M1	Decreased

Table 2: Significant functional connectivity changes under ketamine, compared to saline. Seed anatomical regions were defined with a standard atlas and targets identified from signals throughout the brain. Target networks are described based on atlas anatomy and purported function of the region, relevant to the experimental framework.

Neuroscience in Anesthesiology and Perioperative Medicine-4 Neuroprotective effects of 1-O-hexyl-2,3,5-trimethylhydroquinone on ischemia/reperfusion-induced neuronal injury by activating the Nrf2/HO-1 pathway

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Introduction: With the acceleration of the aging population and formation of unhealthy living habits, the incidence of stroke is increasing in the world yearly. Notably, stroke remains the second leading cause of death worldwide, and the second most common cause of disability adjusted life-years, yet its diseases burden has been under-recognized[1]. Clinical data showed that ischemic strokes account for over 80% of all stroke cases[2]. Accumulating evidence indicates that oxidative stress plays a pivotal role in cerebral ischemic/reperfusion (I/R) injury. Under conditions of oxidative stress, Nuclear factor-E2-related factor 2 (Nrf2) binds to the antioxidant response element (ARE) sequences and promotes the expression of antioxidant enzymes, including haemoxygenase-1(HO-1)[3]. Data from numerous studies indicated that Nrf2 plays an important role in the protection of brain from I/R injury[4]. 1-O-Hexyl-2,3,5-trimethylhydroquinone (HTHQ), a lipophilic phenolic agent, has potent antioxidant activity and reactive oxygen species (ROS) scavenging properties[5]. The recent research indicated that HTHQ can ameliorate dopaminergic neuronal cell death induced by oxidative stress in vitro[6]. However, the role of HTHQ on cerebral I/R injury and the underlying mechanisms remain unclear. In the present study, we provide evidence that HTHQ significantly ameliorate cerebral I/R injury in vivo and protect PC12 cells against hypoxia and reperfusion (H/R) injury in vitro via Nrf2-mediated antioxidant pathway.

Methods: Focal cerebral ischemia was induced by MCAO in mice. The mice were randomly assigned into: Sham, MCAO, HTHQ 100 and 200 group. The sham and MCAO groups received an equivalent volume of tween 80. The HTHQ 100 and 200 groups were orally administered with HTHQ (100 or 200 mg/kg) for three consecutive days before MCAO. The operation was performed after 30min the last administration. The neurological deficits were assessed using a previously described neurologic scoring system[7]. TTC staining was used to detect the infarct volume. Brain water content was also calculated. SOD, CAT, GSH activities and MDA contents were measured by commercially available kits. The number and percentage of positive cells in the region were detected by staining with TUNEL kit and calculated to evaluate the extent of cell apoptosis. Protein expression were detected by Western blot. The intensity of the blots was normalized to that of β-actin. si-Nrf2 were designed and manufactured according to the previous literature to knockdown the genes. For hypoxic treatment, the PC12 cells were cultured in preconditioned hypoxic medium under 5% CO2 and 95% N2 in a humidified chamber for 6 h, and then re-oxygenation 18 h under normal growth conditions. Meanwhile, the cells were exposed to HTHQ for 3 h before H/R injury. The cell apoptosis was detected by Annexin V-APC/7-AAD apoptosis detection kit. Flow cytometer was used to detect the percentage of apoptotic cells. Data were analyzed by GraphPad Prism 6.0 by using Student's t-test or one-way ANOVA followed by Tukey's Post-Hoc test. Values were considered statistically significant when $P < 0.05$. Data are presented as the mean ± SD unless stated otherwise.

Results: HTHQ treatment significantly decreased the infarct volume ratio and neurologic scores dose dependently, and also significantly ameliorated brain water content; restored SOD, CAT and GSH activities and decreased MDA contents; decreased neuronal apoptosis following I/R; increased the expression of Nrf2 and HO-1; in addition, increased the expression levels of Nrf2 in the nucleus, while decreasing its expression in the cytoplasm compared with MCAO group; restored SOD, CAT, GSH activities and decreased MDA contents compared with H/R group; decreased neuronal cell death following H/R. PC12 cells were more vulnerable to H/R-induced oxidative stress after si-Nrf2 transfection. Meanwhile, the HTHQ mediated protection was lost in PC12 cells transfected with siNrf2. Knockdown of Nrf2 accordingly increased the apoptosis ratio after H/R, and HTHQ treatment did not affect neuronal apoptotic in PC12 cells transfected with siNrf2.

Conclusion: The present study indicates that HTHQ can significantly ameliorate cerebral I/R injury in vivo and protect PC12 cells against H/R injury in vitro via Nrf2/HO-1 pathway. These findings suggest that potential of HTHQ for prevention or treatment of stroke.

Reference(s):

[1] Lancet Neurol, 2019, 18(5): 417-418.

[2] Oxid Med Cell Longev, 2018, 2018(8678267.

[3] Free Radic Biol Med, 2014, 66(36-44.

[4] Front Pharmacol, 2019, 10(153.

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[6] Molecules, 2019, 24(5):

[7] Stroke, 1989, 20(1): 84-91.

Neuroscience in Anesthesiology and Perioperative Medicine-5 Imaging the neuronal response to nociceptive pain and opioids in *C. elegans*

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Introduction: While the traditional understanding of pain has focused on feed-forward processing from sensory neurons to the brain, it is increasingly evident that sensory processing embeds a complex integration of pain signaling into wider neurological dynamics (e.g. descending feedback onto nociceptive circuits). Fundamentally lacking is an understanding of how pain sensation is integrated into, and modulated by, broader brain activity. The complexity of higher organisms presents a major hurdle to disambiguating these effects. However, C. elegans is clearly capable of nociceptive sensation that triggers aversive behavioral responses, despite its obvious lack of complex high-end and emotional behaviors. Moreover, the emerging capabilities for pan-neuronal imaging in C. elegans permit the definition of system-wide integrated sensory processing that is not possible in other animals.

Methods: Intense blue and UV light triggers an avoidance response in C. elegans and is transduced by amphid neurons including ASJ [1,2]. Previously [3], we measured the ASJ response to intense blue light, i.e. 480nm, >10mW. QW1217 C. elegans, expressing pan-neuronal nuclear RFP and somatic GCaMP6s, a calcium-sensitive fluorophore (Figure 1), were encapsulated in a permeable hydrogel and immersed in a 50ml solution of S-basal buffer for three-dimensional imaging in a dual inverted Selective Plane Illumination (diSPIM, or light-sheet) microscope. Imaging was acquired at 2 volumes/second. The location of 120 discrete neurons in the worm head were tracked over time in three dimensions and their activity extracted using custom supercomputer algorithms. At 5- and 10-minutes elapsed imaging time, the worms were exposed to a 2 second flash of bright blue light. At 15 minutes, morphine sulfate 5mg was instilled into the buffer solution to produce a concentration of 320 μM [4]. Under continuous imaging, the worms were equilibrated to this morphine concentration. At 45- and 50-minutes elapsed time respectively, a further flash of bright light of two seconds duration was applied.

Results: Comparison of neuron activity identified 9 neurons with the largest response to the blue light stimulus (by change in fluorescence), thus identifying both the primary sensory neuron and the pattern of downstream activity that defines the nociceptive response (Figure 2). Using PCA, the neural activity of the worms was reduced to a manifold in 3D space. Nociceptive processing of the stimulus clearly pushes the system out of its baseline manifold and into a distinct region of activity space (Figure 3). Morphine sulfate also realigns the neural activity manifold, and the nociceptive response are comparatively suppressed (Figure 4).

Conclusion: These experiments provide evidence of a distinct nociceptive response as a form of highly-integrated sensory processing in even the simplest of nervous systems, and preliminarily establish C. elegans as a novel model for functional neuronal imaging in nociception.

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2. Cell 2016;167(5):1252-1263
3. PNAS 2016;113(20):E2852-60
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Figure 1

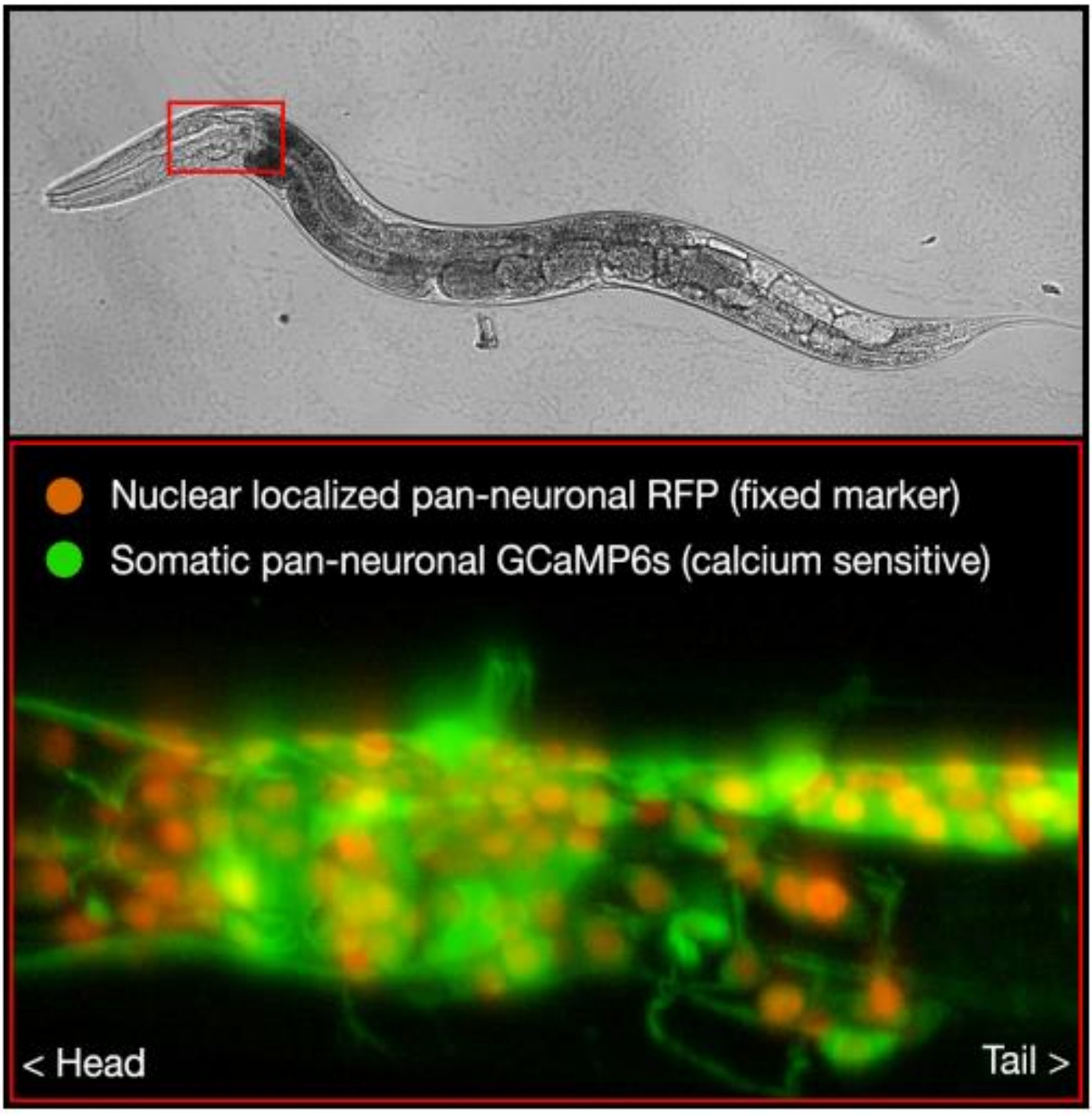

Nuclear localized pan-neuronal RFP (fixed marker)
Somatic pan-neuronal GCaMP6s (calcium sensitive)
< Head
Tail >

Figure 2

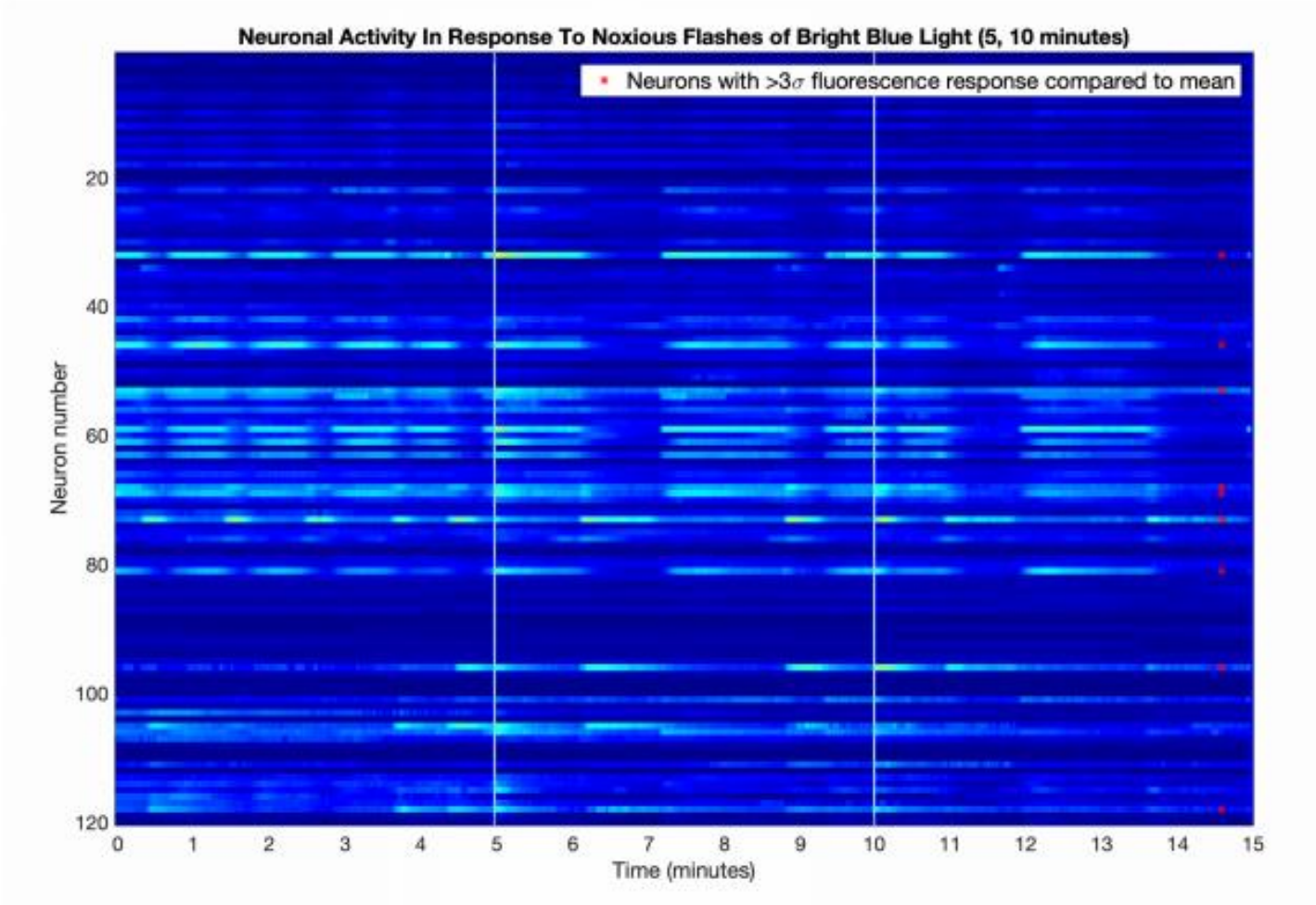

Neuronal Activity In Response To Noxious Flashes of Bright Blue Light (5, 10 minutes)
Neurons with >3σ fluorescence response compared to mean
Neuron number
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Time (minutes)

Figure 3

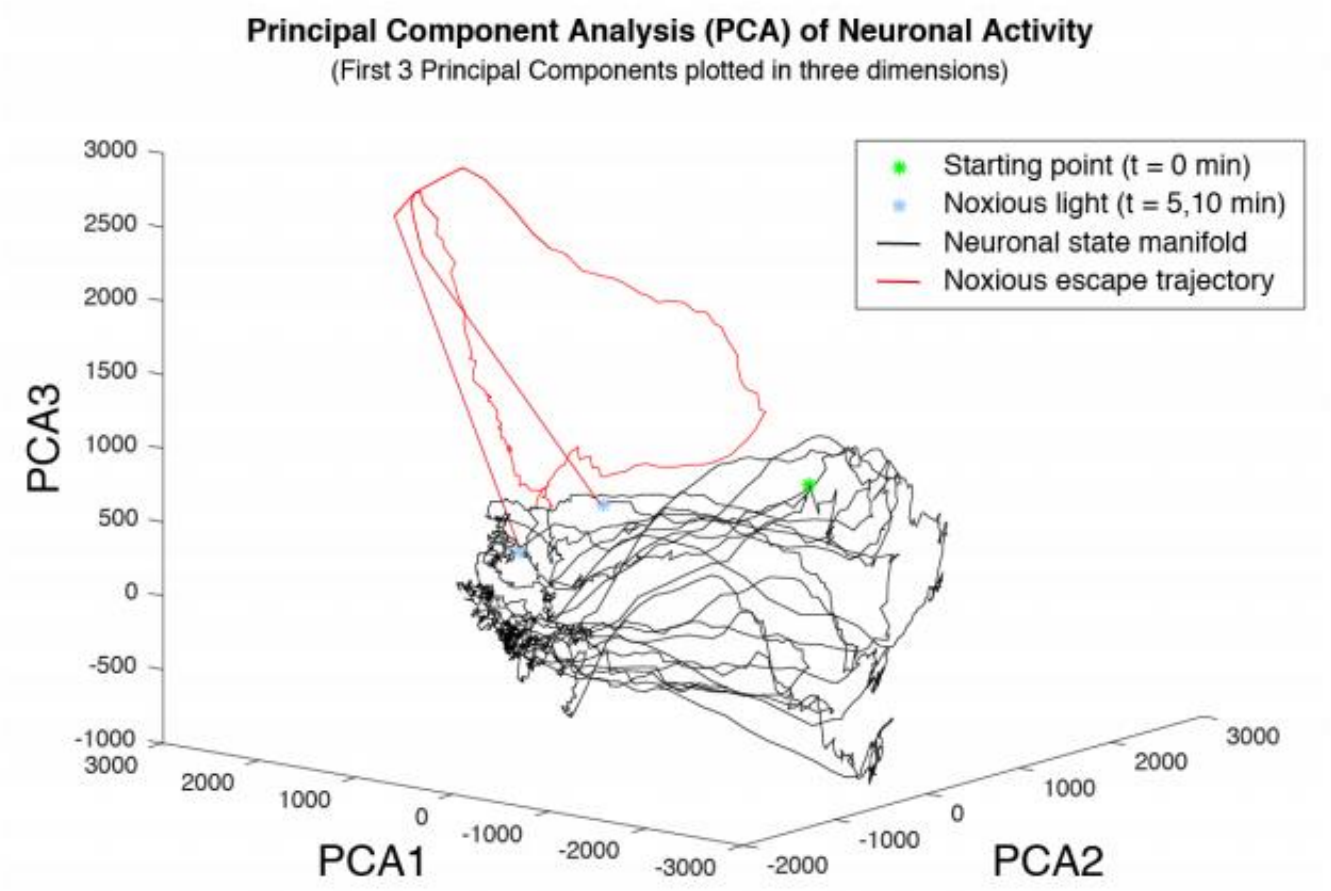
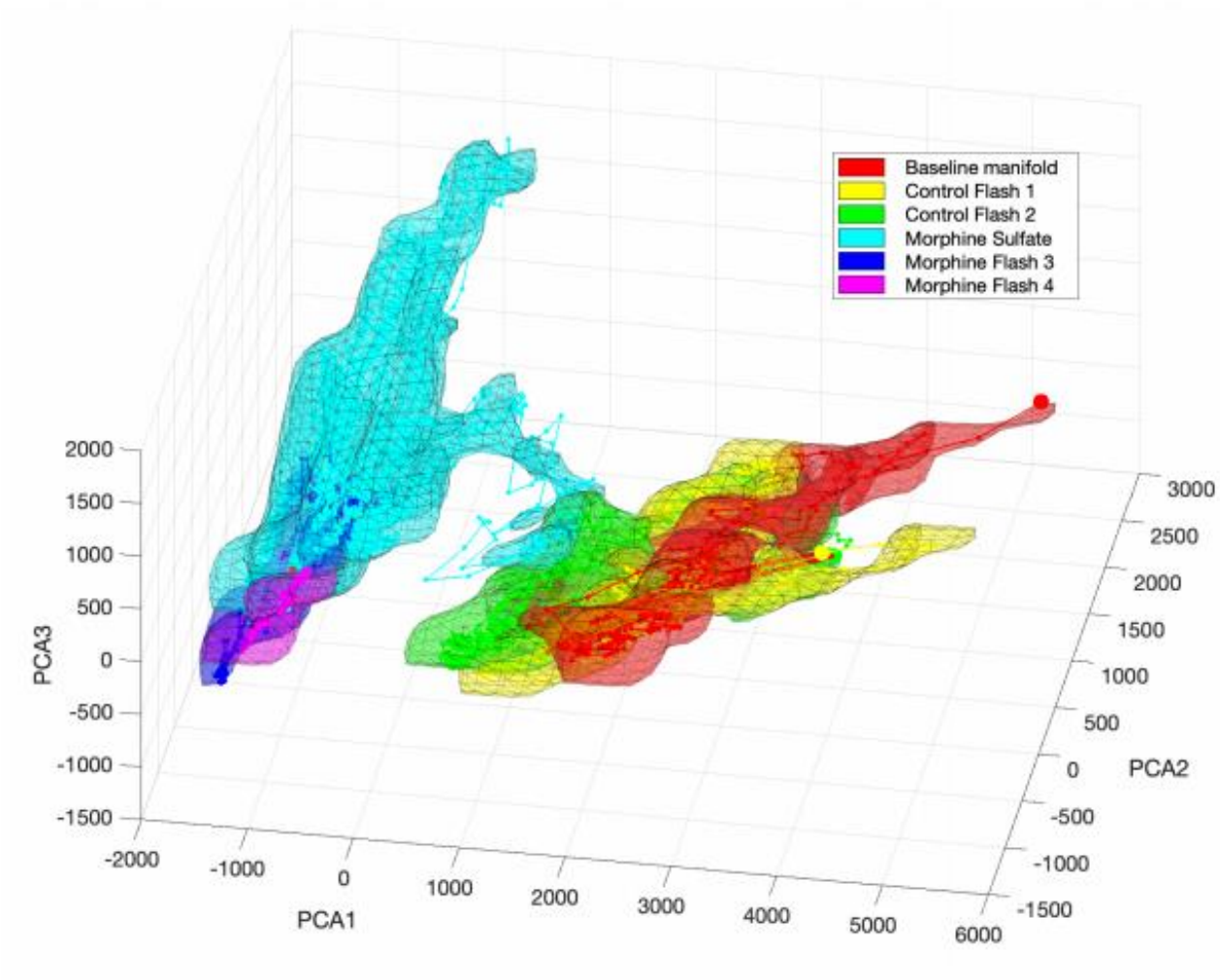

Principal Component Analysis (PCA) of Neuronal Activity
(First 3 Principal Components plotted in three dimensions)
Starting point (t = 0 min)
Noxious light (t = 5,10 min)
Neuronal state manifold
Noxious escape trajectory
PCA3
PCA1
PCA2
3000
2500
2000
1500
1000
500
0
-500
-1000
2000
1000
0
-1000
-2000
-3000

Figure 4


Baseline manifold
Control Flash 1
Control Flash 2
Morphine Sulfate
Morphine Flash 3
Morphine Flash 4
PCA1
PCA2
PCA3
2000
1500
1000
500
0
-500
-1000
-1500
-2000
-1000
0
1000
2000
3000
4000
5000
6000
3000
2500
2000
1500
1000
500
0
-500
-1000
-1500

Neuroscience in Anesthesiology and Perioperative Medicine-6 Brain-wide unbiased mapping of neuronal activity pinpoints ketamine's interaction with the opioid system in mice

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Introduction: Ketamine (KET) and the opioid system have a complex, poorly understood relationship. KET is considered to be a non-opioid analgesic, yet can markedly potentiate opioid analgesia, prevent opioid-induced hyperalgesia, and rapidly relieve depression in an opioid-receptor dependent manner[1]. KET's mechanism involves NMDA receptor (NMDAR) antagonism, but other NMDAR antagonists fail to mimic the diversity of KET's clinical effects. Developing KET-like drugs requires a refined understanding of KET's mechanism of action, looking beyond the NMDAR. We used an unbiased, whole-brain approach to identify brain regions mediating KET's interaction with the endogenous opioid system.

Methods: To image brain-wide neuronal activity, TRAP2 mice (Targeted Recombination in Active Populations 2)2, in which the neuron firing-dependent Fos promoter drives expression of CreER, were crossed to a reporter line (Ai14). In effect, 4-hydroxytamoxifen transiently enables CreER to trigger permanent expression of the fluorophore tdTomato. TRAP2;Ai14 mice were injected with either saline (SAL) and KET (10 mg/kg i.p.) or an opioid receptor antagonist, naltrexone (NAL; 5 mg/kg i.p.), and KET. Mice were perfused 7 days later with PFA, 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 (MIRAcL3 and Ilastik4), 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. Hierarchical groupings of related brain subregions were analyzed by two-way ANOVAs and Holm-Sidak comparisons of SAL/KET vs. NAL/KET.

Results: The total number of tdTomato+ (active) neurons was similar in KET (270072 ± 63987 cells; N = 8) and NAL/KET hemispheres (227923 ± 47892 cells; N = 10). Counts from 491 grey matter regions were normalized to total counts. NAL significantly decreased the number of tdTomato+ cells in the intermediodorsal nucleus of the thalamus (KET = 0.00108 ± 0.000156 vs. KET + NAL = 0.000543 ± 0.0000869 cells/total brain cells; multiplicity adjusted p = 0.0354). NAL non-significantly suppressed activity in the neighboring anteroventral nucleus of the thalamus, medial pretectal area, nucleus of the posterior commissure, and ventral lateral septal nucleus. These nuclei were visualized in 3D using Brain Explorer6 and opioid receptor expression data was overlaid. Remarkably, the NAL-sensitive regions formed a 'shell' of nuclei encasing a region of high-density mu opioid receptor expression.

Conclusion: Through unbiased whole-brain mapping of neurons differentially activated by SAL/KET vs NAL/KET, we identified a novel network of nuclei that may mediate some of KET's opioid receptor-dependent clinical effects. Future work will test for causal links between these structures' activity and ketamine's efficacy in animal models of pain and depression.

Reference(s):

1. Am J Psychiatry, 175 (12), 1205-1215, 2018
2. Science, 357 (6356), 1149-1155, 2017
3. https://github.com/mgoubran/MIRACL
4. https://github.com/ilastik
5. https://mouse.brain-map.org/
6. mouse.brain-map.org/static/brainexplorer

Neuroscience in Anesthesiology and Perioperative Medicine-7 A high throughput screen for inhibitors of Anesthetic-induced Developmental Neurotoxicity in C. elegans

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Introduction: Early developmental exposure to volatile anesthetics leads to anesthetic induced neurotoxicity (AIN) in nematodes, rodents, and humans (1-3). However, the precise mechanisms by which anesthetics cause neurotoxicity are unknown. Using a genetic approach in C. elegans, we identified ER-stress as a marker for AIN and showed that inhibition of the metabolic switch mTOR by rapamycin alleviated ER-stress and AIN (4). Here, we undertook a high throughput screen for other drugs that could be used to alleviate both the induction of ER-stress and the adult behavioral defect in chemotaxis induced by larval exposure to isoflurane.

Methods: Drugs. All drugs screened were reagent quality and dissolved in 100% DMSO. For exposure of nematodes, the drugs were diluted 1:100 in double distilled water for a final DMSO concentration of 1%. For all studies, 1% DMSO was used as a control. ER-Stress Induction. Larval VA exposure produces a profound activation of ER stress. Using a green fluorescent protein (Phsp-4::GFP) that reports on ER-stress, we screened C. elegans for inhibitors of UPRER induction by isoflurane. An RFP marker (Prab-3::RFP) was used to normalize for of numbers of worms. The EC50s for inhibition of GFP induction by each drug were determined and used to guide drug concentrations used to measure effects on chemotaxis. Chemotaxis. C. elegans L1 larvae were age synchronized and exposed to isoflurane at their EC95s from hours 4-8 after hatching. Larvae were removed from the anesthetic, and grown to adulthood. Chemotaxis on day one of adulthood was used as a measure of integrated neuronal function (1).

Results: Examples of a negative (left panel, induction of GFP fluorescence from isoflurane exposure, no inhibition by drug) and positive (right panel, inhibition of induction) drug effect on ER-stress are shown in Figure 1A. We then screened a phosphorylase/kinase library for drugs that inhibit isoflurane induced ER stress, and identified nine (of the 1300 drugs tested) inhibitors. Two drugs, trehalose and tetraethylammonium, were effective in alleviating the adult chemotaxis defects caused by larval exposure to isoflurane (Figure 1B).

Conclusion: Prior data in C. elegans suggest that highly conserved pathways, including mitochondrial dysfunction and the ER unfolded protein response (UPR) are key regulators of AIN. Our results indicate that inhibition of ER-stress alone is not sufficient to alleviate the behavioral effects of isoflurane on development of C. elegans. The two drugs that did alleviate behavioral AIN, trehalose and tetraethylammonium, have been shown to alleviate other neurodegenerative disorders (5,6) and are current strong candidates to test for inhibition of AIN in mice.

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1. Anesth Analg 116; 185, 2013.
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3. Pediatrics 128; 1053, 2011.
4. Neurotoxicol Teratol 60; 40, 2017.
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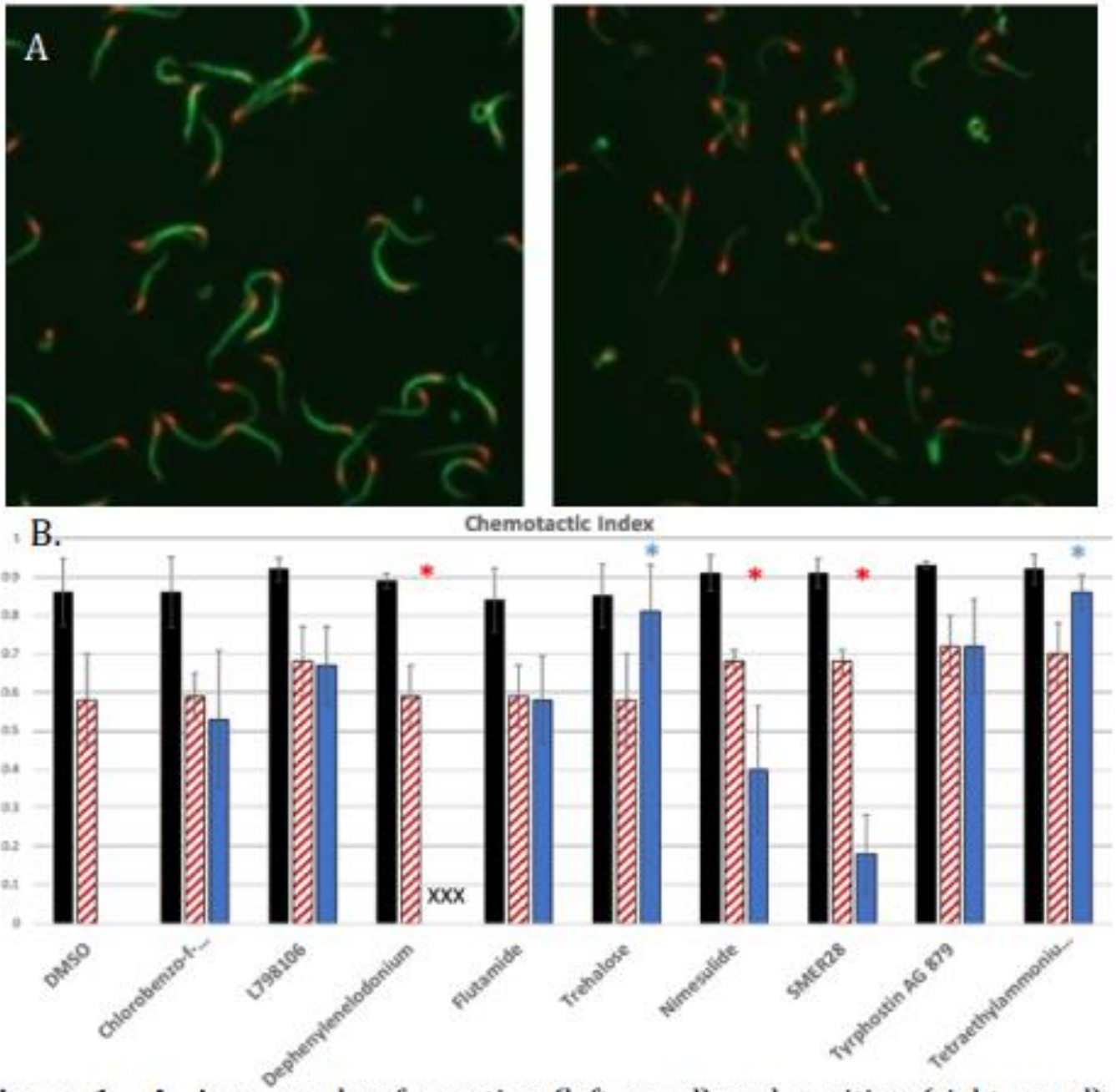


Figure 1. **A.** An example of negative (left panel) and positive (right panel) inhibition of isoflurane induction of the ER stress. We identified 9 positive inhibitors of ER-stress that identify potential for protection from AIN that were further studied using chemotaxis. **B**. Chemotaxis rates (Y axis) in adult *C. elegans* exposed to isoflurane as larva. Black bars show date for naïve animals, no isoflurane (X-axis labels). Crosshatched shows results after isoflurane exposure. Blue bars show response in the presence of isoflurane and drug. For each experiment, N=8 cultures of > 50 animals. Red asterisks (*) indicate a significant worsening of AIN. Blue asterisks (*) indicate alleviation of AIN.

Neuroscience in Anesthesiology and Perioperative Medicine-8 The MARBLE Study: Modulating ApoE signaling to Reduce Brain inflammation, deLirium, and postopErative Cognitive Dysfunction

Keith W VanDusen[1], Sarada Eleswarpu[2], Eugene Moretti[3], Michael Devinney[3], Ken Roberts[4], Mary Cooter[3], Daniel T Laskowitz[1], Frank W Rockhold[4], Miles Berger[3]

[1]Duke University School of Medicine, Durham, NC, [2]Duke University Medical Center, Nashville, TN, [3]Duke University Medical Center, Durham, NC, [4]Duke University, Durham, NC

Introduction: Perioperative neurocognitive disorders (PND) are common postoperative complications in older adults associated with increased 1-year mortality and long-term cognitive decline [1]. One risk factor for worsened long term postoperative cognitive trajectory is the Alzheimer's Disease (AD) genetic risk factor APOE4. Its product, apolipoprotein E4 (apoE4), is thought to elevate AD risk partly by increasing neuroinflammation, which is also a theorized mechanism for PND [2]. Yet, it is unclear whether modulating apoE4 signaling in older surgical patients would reduce postoperative neuroinflammation or PND risk/severity.

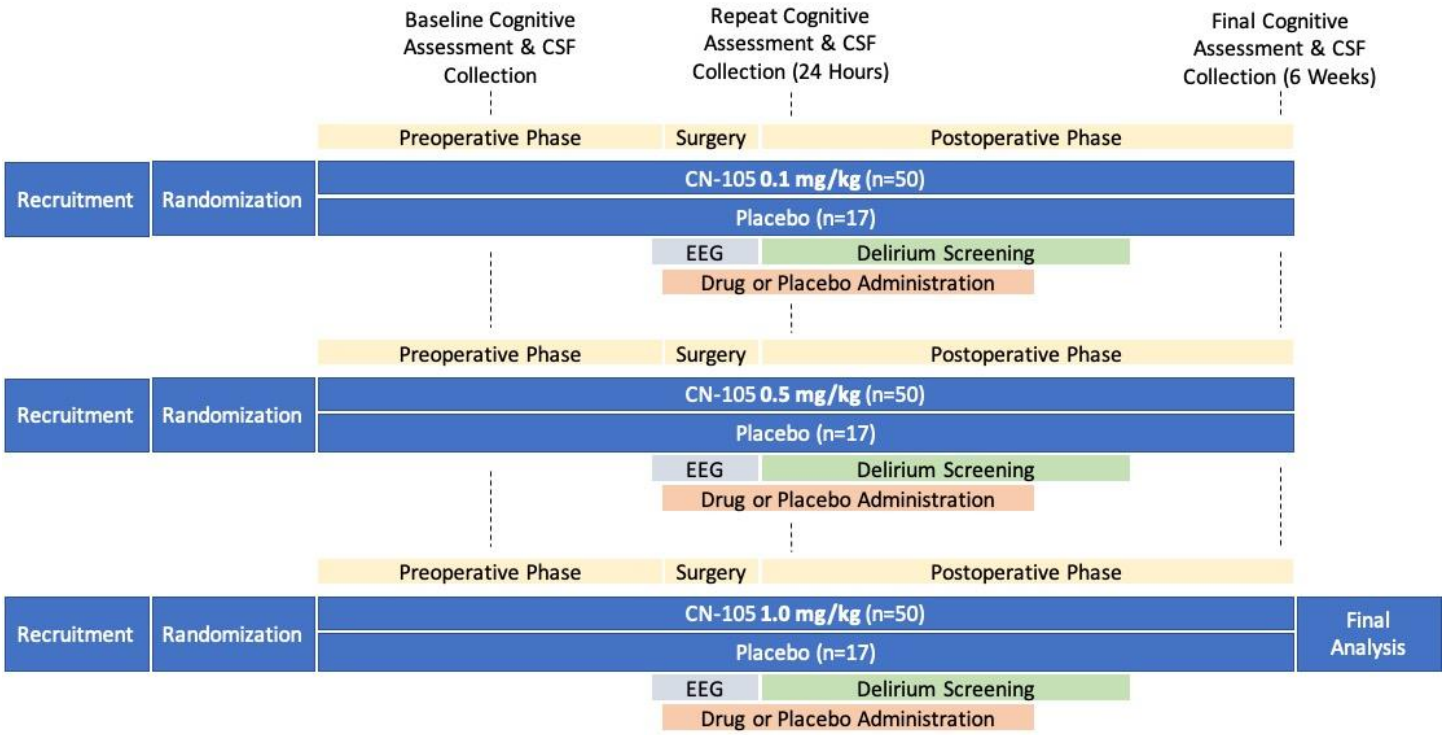
Methods: MARBLE is a randomized, blinded, placebo-controlled phase II sequential dose escalation trial designed to evaluate perioperative administration of an apoE mimetic peptide drug, CN-105, in older surgical patients. 201 patients age 60+ undergoing non-cardiac, non-neurological surgery of ≥2 hours duration are randomized to control or CN-105 treatment groups. The primary aim is safety, measured by adverse event (AE) rates in CN-105 versus placebo-treated patients. Secondary aims include assessing the feasibility of perioperative CN-105 administration and its efficacy for reducing postoperative neuroinflammation and PND risk and severity. CSF and blood samples are obtained before, 24 hours after and 6 weeks after surgery for measurements of cytokines, amyloid beta, and tau, as well as APOE genotyping. Cognitive testing is performed before and 6 weeks after surgery, delirium screening is performed twice daily while patients are hospitalized, and intraoperative 32 channel EEG recordings are completed. Patients receive either intravenous CN-105 at 0.1, 0.5, or 1.0 mg/kg or placebo immediately before and q6 hours after surgery, for up to three days or 13 doses maximum.

Results: MARBLE has enrolled 35 patients, of which 40% are female and 60% are male. 94.3% of the patients have completed or are completing all trial procedures. Case types represented included 31.4% orthopaedic surgery, 22.9% urologic surgery, 8.6% gynecologic surgery, 11.4% plastic surgery, and 25.7% other surgery types. CN-105 efficacy will be assessed upon trial completion by comparing cognitive test results, delirium rates, and blood/CSF markers of neuroinflammation between the drug and placebo groups. Analysis will be stratified by CN-105 dose and by patient APOE genotype to account for pharmacogenomic effects.

Conclusion: MARBLE is a transdisciplinary Phase II clinical trial designed to measure the safety and efficacy of CN-105 for preventing PND in older surgical patients and to provide insight into the pathogenesis of these geriatric syndromes.

Reference(s):

1. Berger et al., Anesthesiol Clin 33, 517-550.
2. Berger et al., Frontiers in Immunology 8, 1528.


Baseline Cognitive Assessment & CSF Collection
Repeat Cognitive Assessment & CSF Collection (24 Hours)
Final Cognitive Assessment & CSF Collection (6 Weeks)
Preoperative Phase
Surgery
Postoperative Phase
Recruitment
Randomization
CN-105 0.1 mg/kg (n=50)
Placebo (n=17)
EEG
Delirium Screening
Drug or Placebo Administration
Preoperative Phase
Surgery
Postoperative Phase
Recruitment
Randomization
CN-105 0.5 mg/kg (n=50)
Placebo (n=17)
EEG
Delirium Screening
Drug or Placebo Administration
Preoperative Phase
Surgery
Postoperative Phase
Recruitment
Randomization
CN-105 1.0 mg/kg (n=50)
Placebo (n=17)
EEG
Delirium Screening
Drug or Placebo Administration
Final Analysis

Neuroscience in Anesthesiology and Perioperative Medicine-9 Synaptic Vesicle Endocytosis is Inhibited in Mouse Neurons by Isoflurane or Ndufs4 Knockdown

Philip Morgan[1], Pavel Zimin[2], Jan-Marino Ramirez[2], Margaret Sedensky[1]

[1]University of Washington, Seattle, WA, [2]Seattle Children's Research Institute, Seattle, WA

Introduction: The mechanisms of action of volatile anesthetics (VAs) remain unknown. VAs selectively inhibit mitochondrial complex I; mutations in complex I cause anesthetic hypersensitivity in nematodes, flies, mice and humans (1-4). The mouse complex I mutant, Ndufs4(KO), is hypersensitive to VAs, but resistant to ketamine (3). Excitatory presynaptic function of hippocampal CA1 neurons in Ndufs4(KO), but not controls, is selectively depressed by VAs (5). Here we investigated the effect of isoflurane on synaptic vesicle exocytosis and endocytosis.

Methods: All studies were approved by the SCRI IACUC committee. Neurons were isolated from the hippocampus of 0-1 days old mice Ndufs4 floxed mice. Cells were transfected with the following constructs: AT1.03YEMK fluorescence resonance energy transfer (FRET) sensor (for measuring ATP concentrations), VGLUT1-pHluorin (synaptic vesicle cycling), mCherry-synaptophysin (mCs) (to identify synaptic boutons) or Cre recombinase (to generate Ndufs4(KO) cells). For VGLUT1-pHluorin imaging synaptic boutons were identified by co-localization with the mCs fluorescence. Increases in pHluorin fluorescence were recorded upon high frequency stimulation (HFS) with and without isoflurane.

Results: HFS increased the pHluorin signal (synaptic vesicle exocytosis) followed by return to baseline (endocytosis) (Figure 1A-C). During HFS without isoflurane, Ndufs4(KO) neurons show normal upstroke and slower downstroke when compared to controls. Application of 0.6% isoflurane to KO cells or 1.8% isoflurane to control cells (their respective EC95s) led to a profound decrease in downstroke (endocytosis) in the pHluorin signal when compared to Ndufs4(KO) or to control cells exposed to air-equilibrated pyruvate solution (Figure 1D,E). To more closely approximate the physiologic state, which limits glycolysis, we removed glucose and added pyruvate as a mitochondrial substrate with resulting increased failure of endocytosis (not shown). Measurements of ATP concentrations using FRET construct (Figure 1F) revealed that HFS did not cause changes in ATP concentration in boutons of either genotype when exposed to an air-equilibrated solution (Figure 1G,H). HFS of the Ndufs4(KO) cells superfused with 0.6% (EC95 for Ndufs4(KO)) or 1.8% isoflurane (EC95 for controls, lethal for KOs) led to a continued reduction in ATP concentrations. Control cells exposed to 1.8% isoflurane behaved as did mutants at .6% isoflurane. 0.6% isoflurane had no effect on control cells.

Conclusion: Isoflurane inhibits the function of mitochondrial complex I (6). The data here establishes that the mitochondrial inhibition leads to a decrease in presynaptic ATP concentration in excitatory neurons that, in turn, causes inhibition of endocytosis. This model is consistent with being the primary CNS effect of isoflurane.

Reference(s):

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3. PLoS One 7, e42904, 2012.
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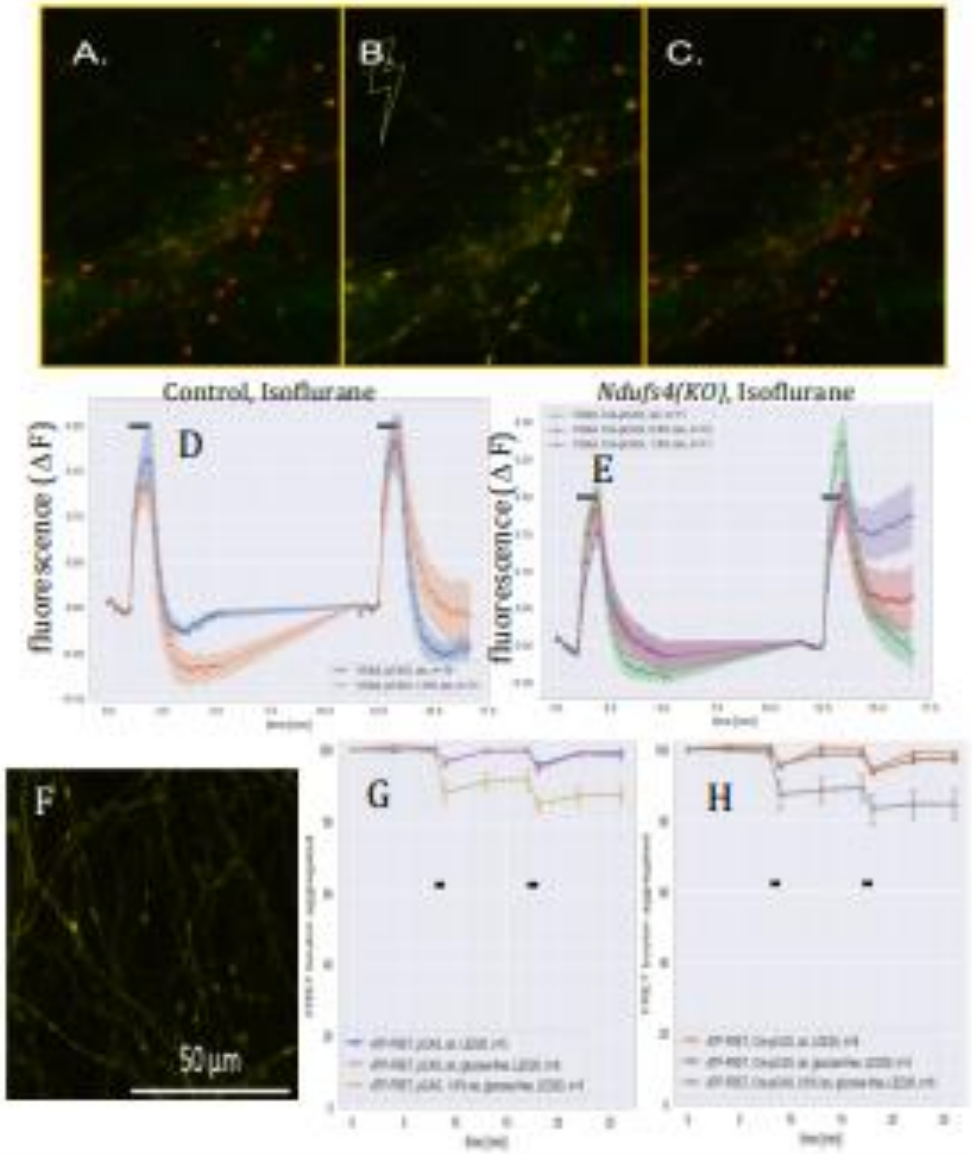

Figure 1. **A.** Representative pictures of pHluorin signal prior to high frequency stimulation (HFS), **B.** during HFS and **C.** after recovery from HFS. **D.** Response of pHluorin fluorescence (Δ F) to HFS with and without isoflurane. Control cultures in air (blue) or 1.8% isoflurane (red). The delay in recovery from HFS when exposed to isoflurane during the second peak indicates defective endocytosis. **E.** Mutant cultures in air (green), 0.6% isoflurane (red) or 1.8% isoflurane (purple). Again isoflurane inhibits endocytosis after the second HFS. In both genotypes s, the initial rise of Δ F is unchanged by isoflurane. These data indicate that endocytosis, but not exocytosis, is sensitive to isoflurane. **F.** Representative picture of FRET signal with ATP levels high. **G.** ATP levels reflected by FRET signal (y-axis). Control neurons in air, with (blue) or without (red) glucose (pyruvate present in both) drop ATP levels following HFS(black bars) but quickly recover. In the presence of 1.8% isoflurane, the EC_{95} for control animals (yellow), ATP levels do not recover. **H.** *Ndufs4 (KO)* cultures. Identical to G. but isoflurane (grey) is 0.6%, theiEC_{95} for *Ndufs4* animals.

Neuroscience in Anesthesiology and Perioperative Medicine-10 Modulation Of Microvascular Blood Flow And Stroke Outcome Via Gpr39 in Mice

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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 attributed 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 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 15 KO (8 males, 7 females) and 8 WT (4 males and 4 females) mice were used for the study. Brains were harvested at 24 hours of reperfusion, sliced coronally in 2-mm segments, sections stained with triphenyltetrazolium chloride (TTC), and infarcted areas measured after accounting for edema.

Results: Hemispheric infarct was 44.7% ± 3.31% in male GPR39 KO mice compared to 34.7% ± 5.23% in WT male littermates (mean ± sem, p=0.07). In females, infarct size was 30.3% ± 5.58% in GPR39 KO mice compared to 33.9% ± 1.45% in WT littermates (p = 0.34).

Conclusion: Our preliminary results suggest that GPR39 plays a sexually-dimorphic protective role in ischemic stroke, and that GPR39 may serve as a therapeutic target in stroke.

Reference(s):

1. J Neurochem 123: Suppl 2:2-11, 2012
2. Pharmacol Ther 179:31-46, 2017
3. J Cereb Blood Flow Metab 29:629-638, 2009
4. bioRxiv Sep. 19, 2018, https://doi.org/10.1101/420406

Neuroscience in Anesthesiology and Perioperative Medicine-11 D-amphetamine accelerates recovery of consciousness and respiratory drive after high-dose fentanyl in rats

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Introduction: Fentanyl causes dose-dependent somnolence and respiratory depression which can be lethal. Naloxone is efficacious for reversal of fentanyl overdose, but it has a short duration of action and produces undesirable side effects (e.g. reversal of analgesia, and precipitation of withdrawal symptoms in patients with opioid dependence). D-amphetamine (d-AMPH) has been shown to restore consciousness in rats anesthetized with propofol and sevoflurane.1 This study was conducted to test the hypothesis that d-AMPH accelerates recovery from fentanyl-induced unconsciousness and respiratory depression in rats.

Methods: All studies were approved by the Institutional Animal Care and Use Committee. Adult Sprague-Dawley rats (8 males and 8 females) with femoral arterial catheters were used. An intravenous catheter was placed in the lateral tail vein for drug administration. Fentanyl (55 µg/kg iv) was administered over 15 minutes, followed by a 2-minute infusion of d-AMPH (3 mg/kg iv) or saline (control) using a blinded, crossover design. Arterial blood gas analysis was performed before and after fentanyl administration, and 5, 15 and 60 minutes after D-AMPH administration. A blinded researcher scored the time to return of righting (ROR). A separate group of 3 rats underwent implantation of intracranial electrodes in the prefrontal cortex, and EMG electrodes in the trapezius muscles. These animals received the same protocol for fentanyl administration followed by d-AMPH or saline, and LFP/EMG were recorded until 30 minutes after return of righting (ROR).

Results: Some animals were excluded because they died, or the arterial catheter failed, prior to completion of all experiments. Compared to saline controls, D-AMPH accelerated ROR by 63% (from 19.2 ± 3.5 min to 12.2 ± 3.6 min, p = 0.0107, n=13). Within 5 minutes, D-AMPH hastened recovery of arterial pH (D-AMPH: 7.302 ± 0.025; saline: 7.156 ± 0.034, p = 0.0194, n = 9) and pO2 (D-AMPH: 82.6 ± 4.2 mmHg; saline: 68.5 ± 3.4 mmHg, p = 0.0501, n = 9) back towards baseline. In 3 separate rats, LFP recordings from the prefrontal cortex showed that fentanyl increased the power of broadband frequencies <20 Hz. Within 10 minutes of D-AMPH administration, the power in frequencies <20 Hz returned to baseline levels. However, after saline administration this increase in power persisted for >20 min, even once the animal recovered ROR.

Conclusion: After a high dose of fentanyl sufficient to induce unconsciousness and respiratory depression, d-AMPH accelerated recovery of consciousness and respiratory drive. Because d-AMPH has a longer half-life than naloxone and is not a direct opioid receptor antagonist, these results suggest that D-AMPH may be clinically useful as an alternative treatment for opioid overdose, particularly in the perioperative setting where reversal of analgesia is undesirable.

Reference(s): 1. Kenny et al, PLOS One 2015;10(7):e0131914.

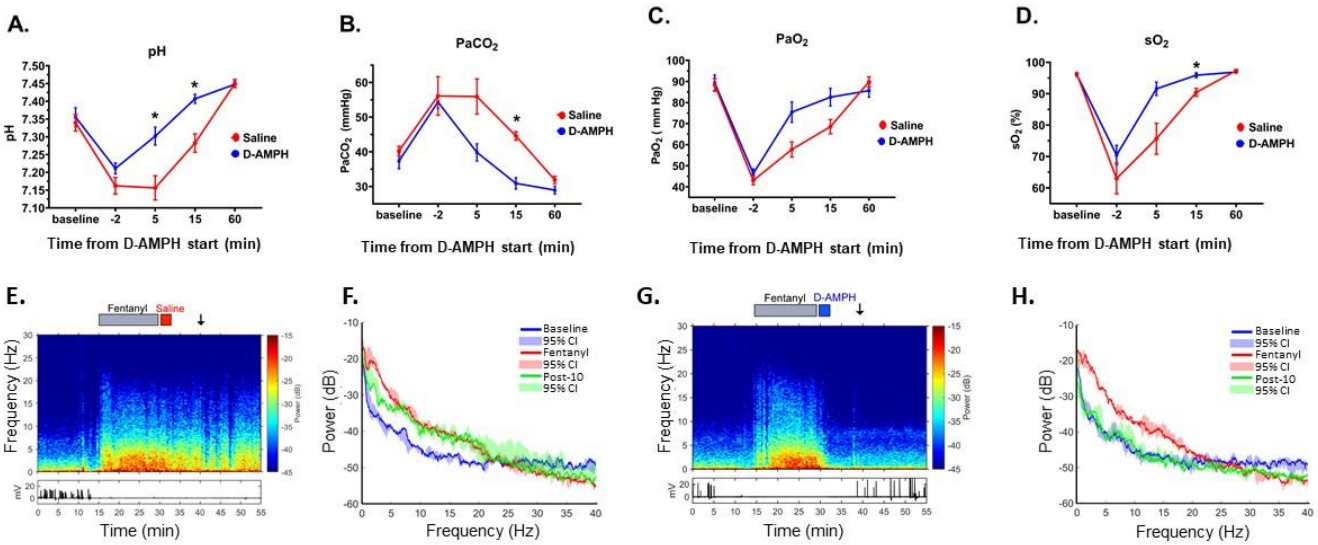

Figure 1. D-amphetamine (D-AMPH, 3 mg/kg) hastens recovery from fentanyl (55 µg/kg)-induced respiratory depression and loss of consciousness. A-D) Within 5-15 minutes of D-AMPH administration, arterial blood gas analysis shows hastened recovery towards baseline levels for pH (A), $PaCO_2$ (B), PaO_2 (C), and sO_2 (D). Time point "-2" is the end of the fentanyl infusion. Local field potentials (LFP) were recorded from the prelimbic cortex (E-H). Fentanyl induced heightened power in frequencies <20 Hz that was rapidly reversed after D-AMPH administration (G) but not saline (E). Power spectral density plots calculated at awake baseline, end of fentanyl infusion, and 10 minutes after D-AMPH administration show fentanyl-induced heightened power for frequencies <20 Hz after saline (F) that was reversed by D-AMPH (H) within 10 minutes.

Neuroscience in Anesthesiology and Perioperative Medicine-12 Intraoperative Frontal EEG Substitutes For Age in a Predictive Model Of PACU-Delirium

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Introduction: Postoperative delirium is a common complication that is associated with significant morbidity and mortality (1). Intraoperative frontal EEG allows for non-invasive monitoring of cortical activity, and specific EEG patterns are associated with delirium in the postanesthesia care unit (PACU-D) (2). In this study we compare the performance of a predictive model for PACU-D that includes intraoperative frontal EEG data to a model that does not include this information.

Methods: This study utilized data from a previously-published prospective multi-center observational study of intraoperative EEG activity and PACU-D and included 649 patients who underwent non-cardiac surgery requiring general anesthesia (2). Two logistic regression models were constructed to predict PACU-D. For Model 1, variables used in model construction included patient demographics, medical comorbidities, and intraoperative surgical and anesthetic management. For Model 2, these same variables were used as well as intraoperative frontal EEG data, including absolute alpha (8-12Hz) power, peak alpha frequency, spindle-dominant activity on emergence, and presence of burst suppression at any point during maintenance. Model Creation: Stepwise selection was applied to a training subset to identify variables that contributed significantly to model fit. Following this, purposeful selection was applied by iteratively removing each variable and recalculating variable coefficient estimates until only those variables that contributed to the Akaike Information Criteria (AIC, an estimator of model prediction error) of the model remained. The model was applied to a testing set, and model performance was evaluated. Outcome variables included AIC, receiver operating characteristic curve, positive predictive value, and negative predictive value.

Results: Nine significant predictors were identified in Model 1, and six predictors were identified in Model 2 (Table 1). Both models were good predictors of PACU-D (mean AUC Model 1 0.74 vs Model 2 0.74), however, Model 2 had a much lower AIC (Model 1: 570 vs Model 2: 410), which indicated Model 2 had decreased out-of-sample prediction error and improved generalizability. In Model 2, both age and history of stroke/neurodegenerative disorder were no longer selected as significant predictors. Among EEG variables, absolute alpha power during maintenance was a negative predictor for PACU-D (coeff. -0.0038, CI95% -0.0057, -0.0018). Figure 1 displays the overall performance distribution of each model.

Conclusion: The inclusion of intraoperative frontal EEG data resulted in an improved predictive model of PACU-D in which numerical age and history of neurodegenerative disease no longer contributed significantly to the model. Our findings additionally suggest a protective role of robust EEG activity in the alpha range. We interpret these findings to suggest that EEG reflects a patient's underlying brain health or 'cognitive age' better than chronological age alone, and that the use of intraoperative frontal EEG improves risk stratification and identification of patients who are most susceptible to develop PACU-D.

Reference(s):

1. Lancet 383, 911–922 (2014).
2. British Journal of Anaesthesia 122(5): 622-634 (2019).

	Model 1 (EEG-Excluded)			Model 2 (EEG-Included)		
Covariate	Coeff. estimate	95% CI	p-Value	Coeff. estimate	95% CI	p-Value
(Intercept)	-4.33	-5.26, -3.39	<0.001	-2.84	-3.76, -1.93	<0.001
Anesthesia Duration (min)	0.0042	0.0021, 0.0062	<0.001	0.0048	0.0021, 0.0075	<0.001
Stroke and/or Neurodegenerative Disease	1.53	0.080, 2.26	<0.001			
Use of Succinylcholine	0.81	0.32, 1.3	0.0012			
Emergence Duration (min)	0.005	0.002, 0.008	0.0019	0.0077	0.003, 0.012	0.0015
Gender (female)	0.55	0.10, 1.0	0.015	0.86	0.32, 1.4	0.0018
Absolute Alpha Power	n/a	n/a	n/a	-0.0038	-0.0057, -0.0018	<0.001
Adjunct Ketamine or Nitrous Oxide	1.38	0.51, 2.3	0.002	1.66	0.70, 2.6	<0.001
Propofol Infusion	1.03	0.21, 1.9	0.014			
Age (years)	0.018	0.0035, 0.033	0.015			
Preoperative Length of Stay (days)	0.047	0.0042, 0.089	0.031			
Pre-existing Renal or Hepatic Comorbidity				1.19	0.55, 1.8	<0.001

Table 1. Comparison of multivariable logistic regression models.

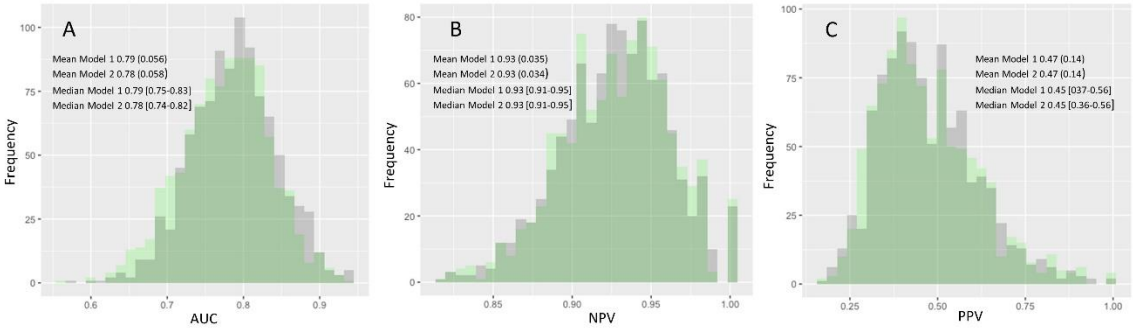

Figure 1: Stacked histograms comparing a) Area Under the Receiver Operating Characteristic Curve (AUC), b) Negative Prediction Value (NPV), and c) Positive Prediction Value (PPV) for an 80:20 train:test cross-validation with 1000-instance bootstrap for Model 1 (EEG-excluded, grey) and Model 2 (EEG-included, green). Legend data is presented as mean (sd) and median [IQR].

Neuroscience in Anesthesiology and Perioperative Medicine-13 A mutation in mitochondrial complex I increases sensitivity of a spinal cord TREK channel to volatile anesthetics in the mouse.

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Introduction: Volatile anesthetics (VAs) have a low margin of safety. Over time, vast improvements in ability to monitor their untoward side effects has minimized their associated morbidity. Discovering the mechanism of action of VAs could lead to rational drug design for future VAs, a decrease in unwanted effects such as neurotoxicity, as well as an understanding of the biology underlying consciousness. Defects in mitochondrial complex I profoundly sensitize the nematode C. elegans to VAs. This anesthetic hypersensitivity was extended across the animal kingdom by similar results in Drosophila, in mice and in children. Previous studies have shown that VAs increase outwardly rectifying currents through potassium K2P (TREK) channels (1,2) leading to neuronal quiescence. TREK-1 has also been shown to decrease halothane (HAL) inhibition of synaptic activity, demonstrating a presynaptic role (3). TREK-1(KO) animals were reported to be resistant to VAs (2). We find here that a complex I defect in the mouse, Ndufs4(KO), causes a striking increased sensitivity of TREK channel conductance to isoflurane in the spinal cord.

Methods: All animal experiments followed the recommendations were approved by the local IACUC. Mice were housed at 22°C with a 12-hour light-dark cycle and maintained on a standard rodent diet. Spinal cord slices were taken at the level of the lumbar enlargement from male and female mice, 23-30 days old. Anesthetic dose response curves and electrophysiology measurements were performed as previously described (4). Norfluoxetine was obtained from Cayman Chemical (Ann Arbor, MI), diluted to a final concentration of 20mcM in 1% DMSO. TREK-1(KO) animals were obtained from Jackson Laboratory (Bar Harbor, ME).

Results: Spontaneous spinal cord synaptic activity was not different between the mutant and control, with or without VA exposure. At 0.6% ISO (1.5X the Ndufs4(KO) EC50), in KO slices there was a dramatic increase in the holding current necessary for maintaining the resting membrane potential (Figure 1A,B). Similar changes were seen in the control cells only when the ISO concentration was raised to 1.8% (1.5X the control EC50). The current was completely blocked by norfluoxetine, an inhibitor of TREK K2P channels (Figure 1C). TREK-1(KO) animals were not resistant to isoflurane or halothane. We generated TREK-1(KO);NDUFS4(KO) double knockout animals. Measurements of the behavioral response of the double KO animal and electrophysiologic studies of spinal cord slices from the double KO animals are ongoing.

Conclusion: ISO increases an outwardly rectifying K+ current in ventral horn neurons from control mice as reported by others (5). We see this effect in the complex I mutant as well, but at much lower ISO concentrations than in controls (Figure 1A,B). These data reveal that TREK channels in Ndusf4(KO) are extremely hypersensitive to VAs in ventral cord neurons, unexpectedly linking mitochondrial status and TREK-1 channel function.

Reference(s):

1. Nat Neurosci. 2:422, 1999.
2. EMBO J. 23:2684, 2004.
3. Br J Pharmacol. 152(6):939, 2007.
4. Curr Biol. 26:2194, 2016.
5. J Neurosci. 30:7691, 2010.

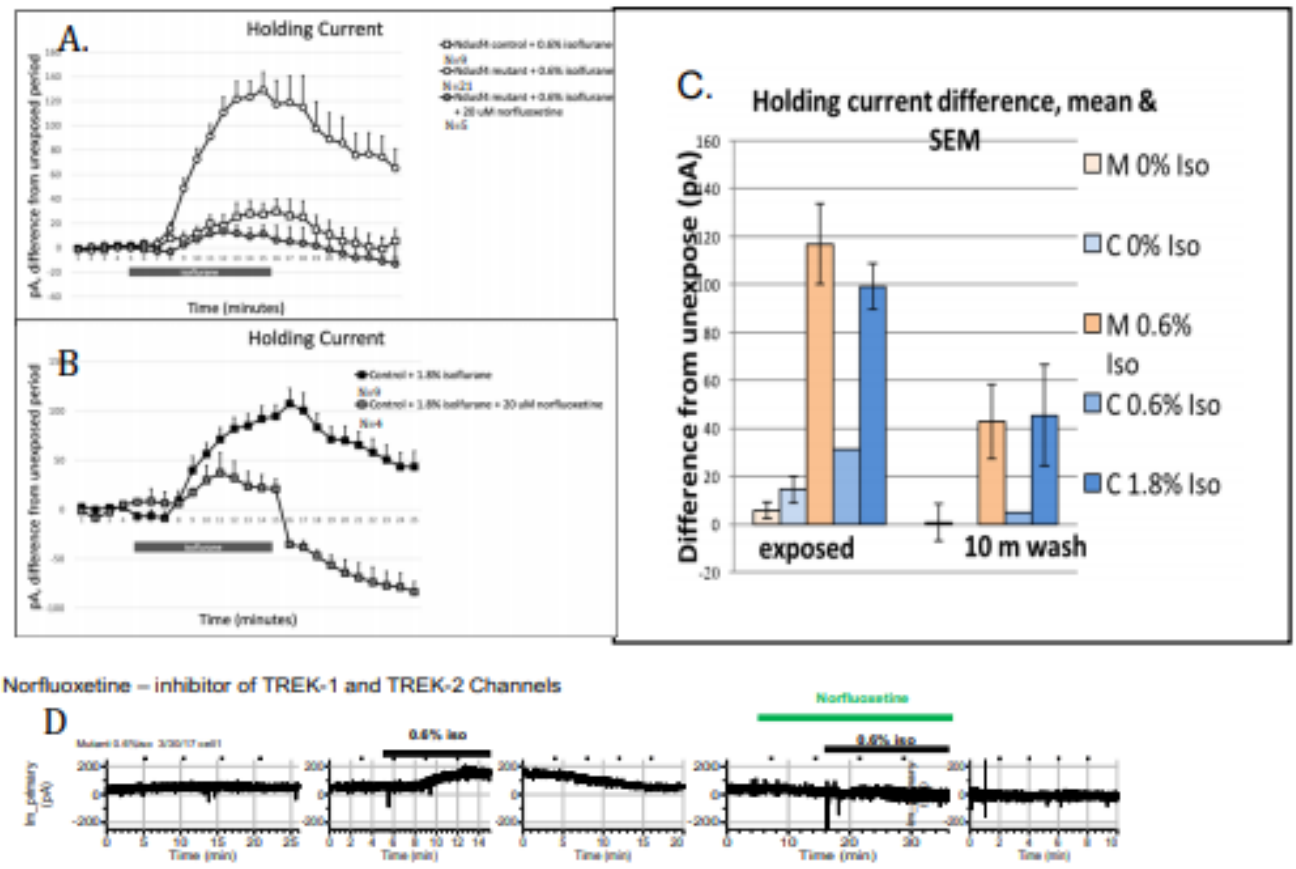

Figure 1. A. Holding currents for control and mutant spinal cord neurons in 0.6% isoflurane (Iso). Bar at bottom indicates time when Iso is applied; N indicated in legend in A and B. Holding current is increased in mutant at 0.6% Iso and blocked by norfluoxetine. **B.** Holding currents for control spinal cord neurons in 1.8% Iso. Holding current is increased in the control at 1.8% Iso and blocked by norfluoxetine. **C.** Mean values and SEM for the cells shown in A and B. Control and mutant cells at 0% Iso had similar holding currents (control not shown). **D.** An example of the effect of norfluoxetine to eliminate the increase in holding current in the mutant cells exposed to 0.6% Iso consistent with a role for TREK-1 or TREK-2 channels in conducting the increased current.

Neuroscience in Anesthesiology and Perioperative Medicine-14 Soluble Epoxide Hydrolase Inhibition and Delayed Cerebral Ischemia after Subarachnoid Hemorrhage

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Introduction: Epoxyeicosatrienoic acids (EETs) are arachidonic acid metabolites with multiple neurovascular actions, including suppression of endothelial inflammation and promotion of smooth muscle vasodilation.[1] Inhibition or deletion of EETs metabolizing enzyme, soluble epoxide hydrolase (sEH), decreases infarct size and improves neurobehavioral performance after cerebral ischemia in animal models.[2] Human genetic polymorphisms linked to increased sEH activity and decreased EETs availability are associated with increased mortality and risk of stroke after subarachnoid hemorrhage (SAH).[3] A novel pharmacological inhibitor of sEH, GSK2256294, has recently been demonstrated as safe and effective in healthy volunteers.[4, 5] We sought to evaluate the safety and pharmacodynamic effects of GSK2256294 in patients after aneurysmal SAH.

Methods: We conducted a phase 1b double-blind, placebo-controlled randomized trial of GSK2256294 in 20 patients admitted to the neuroscience ICU at a comprehensive stroke center with a diagnosis of aneurysmal SAH. Patients receive GSK2256294 or placebo daily for 10 days. Patients were monitored for adverse events during drug administration. At baseline, days 7 and 10, blood and cerebrospinal fluid (CSF) samples were collected and analyzed for eicosanoid levels, and a battery of inflammatory cytokines and endothelial injury biomarkers. Clinical outcomes were assessed at hospital discharge, and after 90 days. The primary study endpoint was the evaluation of safety based on the frequency of serious adverse events.

Results: 9 patients were enrolled in the placebo group and 10 in the GSK2256294 group. Patients in the GSK2256294 group tended to have higher GCS at admission. There were 5 serious adverse events in the GSK2256294 group and 5 serious adverse events in the placebo group, none of which were determined to be related to study drug administration. There was no difference between GSK2256294 and placebo in the 14,15 EET/DHET ratio measured in the CSF on day 7 or day 10, however, this ratio was significantly higher in the serum, comparing the GSK2256294 with the placebo group: absolute difference (95%CI): 0.18 (0.10; 0.26) at day 7 and 0.15 (0.09; 0.20) at day 10. Cytokines IFN-gamma, IL-1b, IL-8 and TNF-alpha were all lower at day 7 and day 10 in the GSK2256294 group compared to placebo, but none of the differences were statistically significant. There were no differences in the incidence of transcranial doppler or angiographic vasospasm or new stroke. There was a trend of shorter length of stay and better neurological and functional outcome at discharge and 90 day follow up in the GSK2256294 group vs placebo.

Conclusion: GSK2256294 is safe to administer in patients with SAH, and increases serum EETs levels compared to placebo. Pharmacologic sEH inhibition may reduce neuroinflammation after SAH and improve functional outcome as demonstrated by trends of decreased neuroinflammatory cytokines in the CSF following drug administration and favorable follow-up outcomes. A larger randomized trial is needed.

Reference(s):

1. Pharmacol Ther, 2017. 179: p. 31-46.
2. Stroke, 2015. 46(7): p. 1916-22.
3. J Neurosurg, 2014. 121(6): p. 1359-66.
4. Br J Clin Pharmacol, 2016. 81(5): p. 971-9.
5. Chest, 2017. 151(3): p. 555-563.

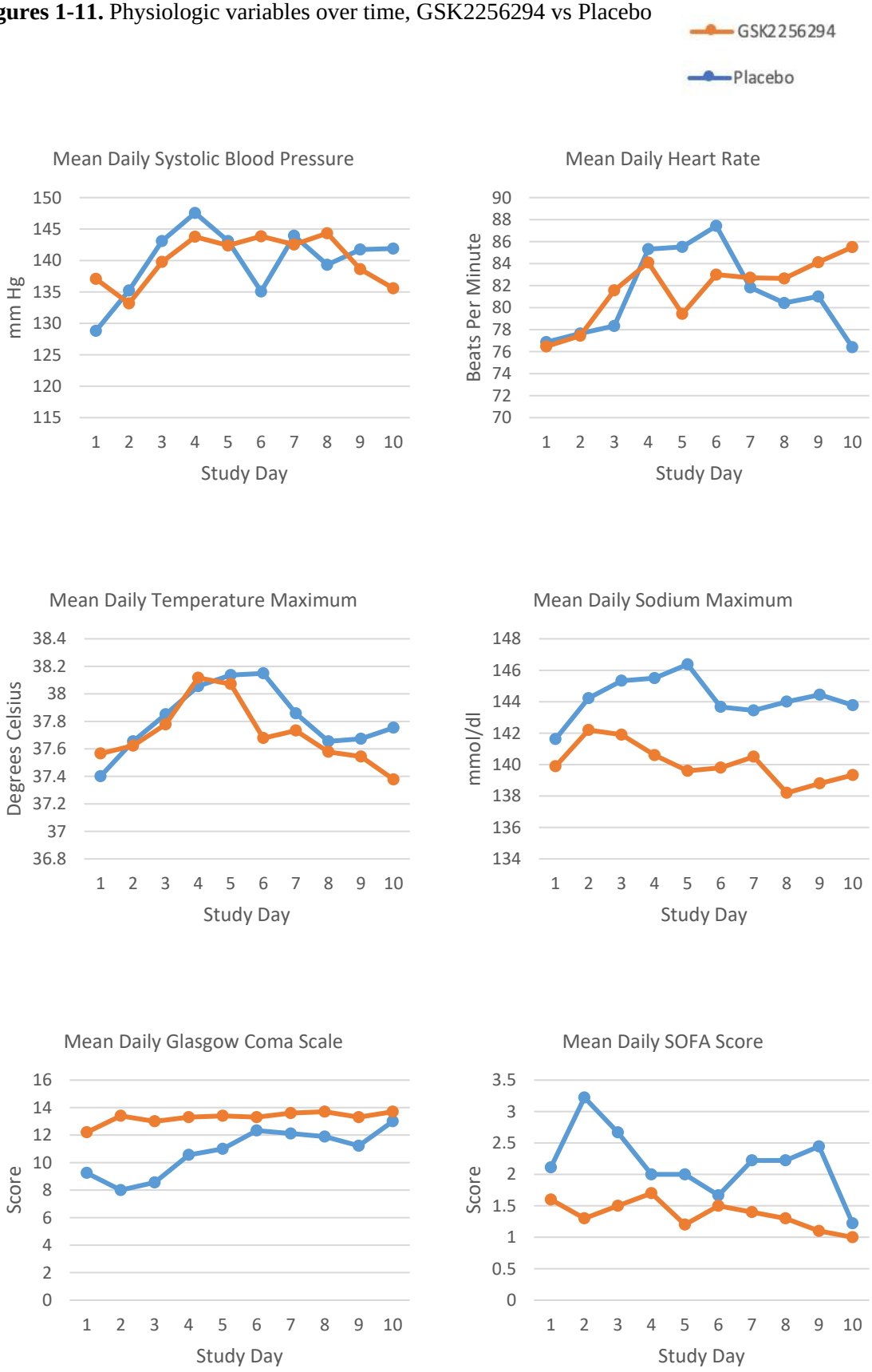
Table 1. Patient baseline characteristics. Data are expressed as mean ± SD unless otherwise specified.

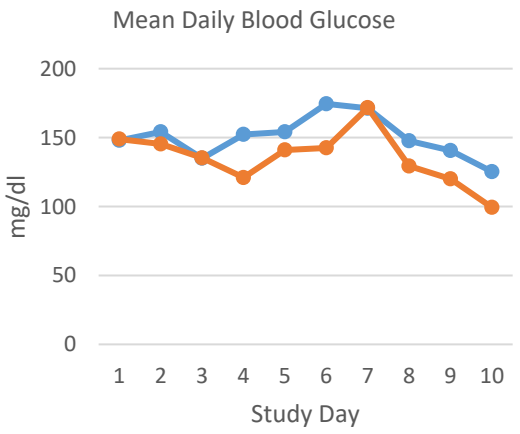
Characteristics	GSK2256294 (n=10)	Placebo (n=9)
Age, years	61.2 ± 11.2	60.4 ± 11.6
Female, n (%)	6 (60.0)	6 (66.7)
BMI (kg/m^2)	28.8 ± 6.6	27.7 ± 4.7
Race, n (%)		
White	8 (80.0)	8 (88.9)
Asian	2 (20.0)	0
Unknown	0	1(11.1)
Hispanic	0 (0)	2 (22.2)
Smoking		
Never/Passive Smoker	2 (20.0)	5(55.5)
Active	5 (50.0	3 (33.3)
Former	3 (30.0)	1 (11.1)
Substance Abuse, n (%)		
Charlson Comorbidity Score	2.4 ± 1.4	3 ± 2.3
Medical History, n (%)		
Hypertension	6 (60.0)	9 (100)
Seizure	0 (0)	0 (0)
Prior Brain Aneurysm	1 (10.0)	0 (0)
Medications, n (%)		
Anti-hypertensives	3 (30.0)	8 (88.9)
Anti-coagulants	0 (0)	2 (22.2)
Anti-platelets	2 (20.0)	2 (22.2)
Statins	1 (10.0)	1 (11.1)
Anti-diabetic agents	0 (0)	0 (0)
Hunt & Hess Scale	3 ± .94	3 ± 1
Modified Fisher Grade	3.9 ± .32	3.67 ± .71
GCS at Randomization	13.3 ± 2.7	10.7 ± 3.6
Location of Aneurysm, n (%)		
Anterior Cerebral	4 (40.0)	2 (22.2)
Artery/Branches	3 (30.0)	4 (44.4)
Middle Cerebral	1 (10.0)	0 (0.0)
Artery/Branches	2 (20.0	3 (33.3)
Posterior Cerebral		
Artery/Branches		
Vertebrobasilar System		
Treatment of Aneurysm, n (%)		
Craniotomy	4 (40.0)	2 (22.2)
Endovascular	6 (60.0)	6 (66.7)
Unsecured	0 (0)	1 (11.1)
Baseline Liver Function		
AST	22.7 ± 5.7	25.5 ± 11.8
ALT	27.5 ± 13.4	24.4 ± 15.7
Baseline QTc Interval (ms)	451.6 ± 24.3	456.4 ± 31.5
Admitted Intubated, n (%)	2 (20.0)	4 (44.4)

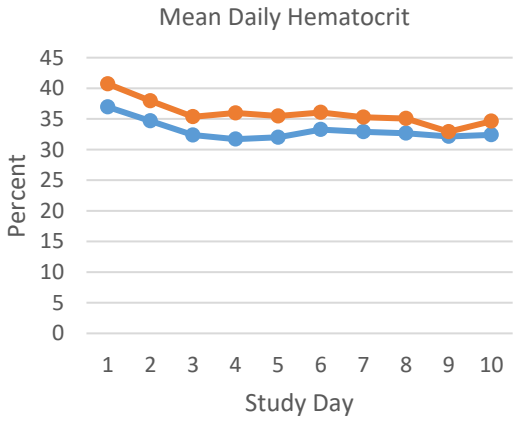
Table 2. Summary of Serious Adverse Events

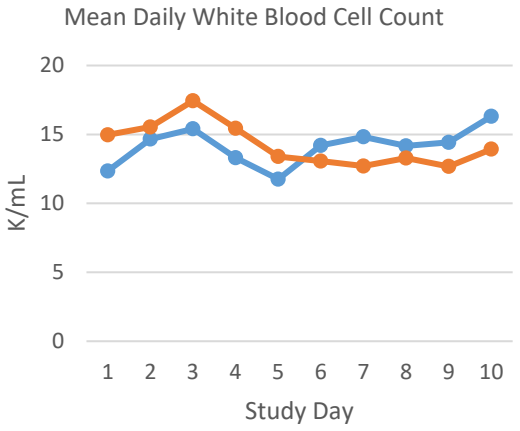
Study ID	Treatment	SAE Term	Fatal?	Expected?	Related?
OHSU-001	Placebo	Leukopenia	N	N	N
OHSU-004	Placebo	Aspiration pneumonia	N	Y	N
OHSU-004	Placebo	Rebleed of unsecured aneurysm	Y	Y	N
OHSU-008	GSK2256294	Femoral deep vein thrombosis	N	N	N
OHSU-038	Placebo	DCI with stroke event	N	Y	N
OHSU-039	GSK2256294	DCI, diffuse ACA/ MCA narrowing/ bifrontal infarctions	N	Y	N
OHSU-039	GSK2256294	Proximal LLE DVT	N	N	N
OHSU-046	GSK2256294	CLABSI	N	N	N
OHSU-046	GSK2256294	DCI	N	Y	N
OHSU-048	Placebo	ALI/ARDS	N	Y	N

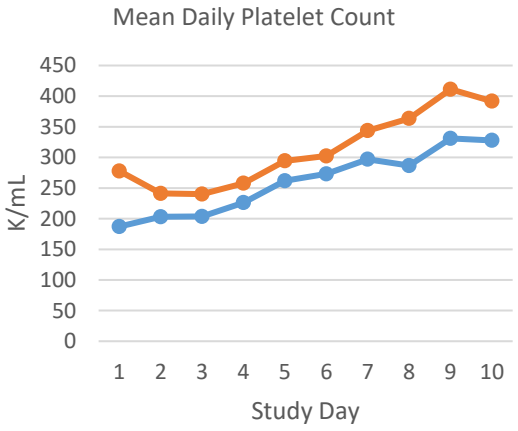
Figures 1-11. Physiologic variables over time, GSK2256294 vs Placebo




Mean Daily Blood Glucose
mg/dl
200
150
100
50
0
1 2 3 4 5 6 7 8 9 10
Study Day


Mean Daily Hematocrit
Percent
45
40
35
30
25
20
15
10
5
0
1 2 3 4 5 6 7 8 9 10
Study Day


Mean Daily White Blood Cell Count
K/mL
20
15
10
5
0
1 2 3 4 5 6 7 8 9 10
Study Day


Mean Daily Platelet Count
K/mL
450
400
350
300
250
200
150
100
50
0
1 2 3 4 5 6 7 8 9 10
Study Day

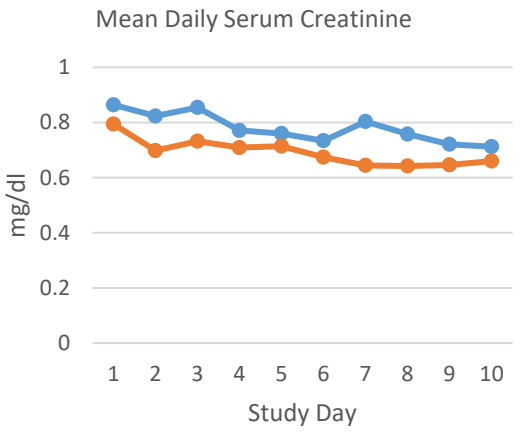

Mean Daily Serum Creatinine
mg/dl
1
0.8
0.6
0.4
0.2
0
1 2 3 4 5 6 7 8 9 10
Study Day

Table 3. Summary of safety and disease related events. Data are expressed as mean ± SD unless otherwise specified.

Characteristics	GSK2256294 (n=10)	Placebo (n=9)	Absolute difference or relative risk (95% CI)
Worst Headache Score	7.6 ± 2.7 (n=9)	6.5 ± 2.6 (n=4)	1.1 (-2.4 – 4.6)
Duration of EVD, days	11.6 ± 2.6	11.7 ± 3.9	-.10 (-4.1 – 3.9)
Required VP Shunt, n (%)	3 (30.0)	3 (33.3)	.90 (.24 – 3.38)
Cerebral salt wasting, n (%)	3 (30.0)	2 (22.2)	1.35 (.29 – 6.34)
Hypertonic saline used, n (%)	6 (60.0)	4 (44.4)	1.35 (.56 – 3.28)
NSTEMI/Cardiomyopathy, n (%)	0 (0)	0 (0)	
Thromboembolism, n (%)	2 (20.0)	0 (0)	
Seizure, n (%)	1 (10.0)	1 (11.1)	.9 (.07 – 12.38)
Day 7 Liver Function			
AST units	33.0 ± 7.7	39.8 ± 30.4	-6.8 (-30.5 – 17.0)
ALT units	51.4 ± 32.5	44.7 ± 35.7	6.7 (-26.3 – 39.7)
Change from baseline AST and ALT			
Any QTc >500ms, n (%)	0 (0)	0 (0)	
Any Infection, n (%)	4 (40.0)	6 (66.7)	.60 (.25 – 1.46)
UTI, n (%)	2 (20.0)	5 (55.6)	
Pneumonia, n (%)	1(10.0)	2 (22.2)	
Cellulitis, n (%)	1 (10.0)	0 (0)	
Bacteremia, n (%)	1 (10.0)	2 (22.2)	
Ventriculitis, n (%)	0 (0)	1 (11.1)	
Clostridium difficile, n (%)	0 (0)	1 (11.1)	
Shingles, n (%)	0 (0)	1 (11.1)	

Table 4. Clinical Outcomes. Data are expressed as mean ± SD unless otherwise specified.

Characteristics	**GSK2256294 (n=10)**	**Placebo (n=9)**	**Absolute difference or relative risk (95% CI)**
TCD MCA Vasospasm (LR>3)	4 (40.0)	5 (55.6)	P=.5
Maximum MCA Velocity	3.01 ± 1.36	3.37 ± 1.29	-.36 (-1.64 - .92)
Angiographic vasospasm	5 (50.0)	4 (44.4)	1.13 (.43 – 2.93)
New Stroke on imaging	1 (10.0)	1 (11.1)	.9 (.07 – 12.38)
ICU length of stay, days	12.9 ± 2.8	18.5 ± 7.9	-5.6 (-11.2 – -.04)
Hospital length of stay, days	16.9 ±3.3	28.8 ±19.8	-11.9 (-25.3 – 1.4)
Hospital Discharge			
mRS	3.4 ± 1.5	4.1 ± 1.4	-.71 (-2.1 - .7)
GCS	14.4 ± .97	12.6 ± 3.5	1.8 (-.6 – 4.3)
Discharged Home	7 (70.0)	2 (22.2)	3.2 (.9 – 11.4)
90 day follow up			
mRS	2.2 ± 1.6	3.3 ± 1.7	-1.1 (-2.7 - .5)
GOSE >4	4 (44.4)	2 (22.2)	1.8 (.4 – 7.6)
Living at Home	8 (80.0)	6 (66.7)	1.2 (.69 – 2.1)

Table 5. Serum Eicosanoid and Linoleic Acid Metabolite Ratios over Treatment Course

	GSK2256294 (n=10)	Placebo (n=9)	Absolute Difference (95% CI)
CSF			
14,15 EET/14,15 DHET			
Baseline	.08 ± .07	.08 ± .03	.001 (-.05 – .05)
Day 7	.17 ± .07	.19 ± .16	-.02 (-.14 – .09)
Day 10	.45 ±.78	.52 ± 1.04	-.07 (-1.1 – .95)
Serum			
14,15 EET			
Baseline	31.1 ± 11.3	24.0 ± 6.0	7.1 (-1.8 – 16.0)
Day 7	67.4 ± 31.0	21.8 ± 8.1	45.6 (23.1 – 68.1)
Day 10	55.8 ± 20.1	24.4 ± 11.3	31.3 (13.3 – 49.3)
14,15 EET/14,15 DHET			
Baseline	.14 ± .05	.13 ± .04	.016 (-.03 – .06)
Day 7	.30 ± .11	.12 ± .027	.18 (.10 – .26)
Day 10	.27 ± .065	.12 ± .016	.15 (.09 - .20)
9,10 EpOME / 9,10 DiHOME			
Baseline	.13 ± .07	.17 ±.12	-.37 (-.24 – .06)
Day 7	.37 ± .19	.15 ± .047	.23 (.09 – .37)
Day 10	.40 ± .21	.20 ± .14	.20 (.00 – .40)
12,13 EpOME / 12,13 DiHOME			
Baseline	1.02 ± .63	1.32 ± .95	-.31 (-1.1 – .47)
Day 7	6.0 ± 4.3	1.8 ± .92	4.2 (1.1 – 7.3)
Day 10	8.7 ± 7.1	1.7 ± .90	7.1 (1.3 – 12.8)

Table 6. Endothelial Injury and Inflammatory Biomarkers

	GSK2256294 (n=10)	Placebo (n=9)	Absolute Difference (95% CI)
Serum			
ICAM (ng/mL)			
Baseline	7.7	7.6	.07 (-3.6- 3.7)
Day 7	8.4	8.3	.12 (-6.8 – 7.1)
Day 10	17.8	6.7	11.1 (-11.3 – 33.5)
VCAM (ng/mL)			
Baseline	10.9	8.9	2.0 (-2.2 – 6.1)
Day 7	8.3	7.9	.37 (-2.1 – 2.8)
Day 10	8.9	7.9	1.0 (-1.7 – 3.8)
PECAM-1(ng/mL)			
Baseline	1.7	1.4	.28 (-.16 - .91)
Day 7	1.4	1.7	-.32 (-1.0 - .4)
Day 10	1.7	1.6	.13 (-.72 - .97)
E-Selectin (ng/mL)			
Baseline	53.8	44.5	9.3 (-15.5 – 34.1)
Day 7	46.6	48.0	-1.4 (-29.7 – 26.9)
Day 10	53.0	44.7	8.3 (-19.6 – 36.3)
P-Selectin (ng/mL)			
Baseline	1.8	1.3	.53(-.11 – 1.2)
Day 7	1.4	1.1	.33 (-.28 - .95)
Day 10	1.7	2.0	.31 (-2.0 – 1.3)
CSF			
IFN-g (pg/mL)			
Baseline	.81	.38	.43 (-.17 – 1.0)
Day 7	1.9	4.6	-2.6 (-7.2 – 1.9)
Day 10	1.5	5.8	-4.3 (-14.1 – 5.5)
IL-1b (pg/mL)			
Baseline	1.4	.48	.94 (0.81 – 2.7)
Day 7	1.6	5.0	-3.4 (-9.8 – 3.1)
Day 10	1.0	4.4	-3.4 (-10.4 – 3.5)
IL-6 (pg/mL)			
Baseline	1109.5	583.2	526 (-301.1 – 1353.9)
Day 7	2991.2	3417.9	-426.6 (-4185.1 – 3331.8)
Day 10	2089.4	2051.6	37.8 (-3764.8 – 3840.4)
IL-8 (pg/mL)			
Baseline	1074.2	1064.7	9.4 (-1538.0 – 1556.9)
Day 7	1652.4	3971.0	-2318.5 (-4745.2 – 108.2)
Day 10	1093.6	1485.8	-392.1 (-1384.2 – 599.9)
TNF-a (pg/mL)			
Baseline	5.9	3.0	2.8 (-4.4 – 10.0)
Day 7	7.8	13.1	-5.3 (-15.9 – 5.2)
Day 10	5.9	8.1	-2.3 (-10.7 – 5.5)

Neuroscience in Anesthesiology and Perioperative Medicine-15 Anesthesia and surgery induce age-dependent changes in behaviors and microbiota in mice

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Introduction: Delirium, a syndrome of confusion and inattention, is the most common postoperative complication in senior patients and is associated with accelerated cognitive decline and Alzheimer's disease and related dementia (ADRD) [1-2]. Senior patients are more likely than younger ones to develop postoperative delirium (POD) [3]. However, the neuropathogenesis of POD remains mostly unknown and no effective medication to prevent or treat POD. The gut microbiota contains up to 95% of the entire human microbiota [4]. Gut microbiota dysbiosis, a condition of microbiota imbalance or maladaptation inside the gut [5], which could lead to altered immune functions and associated with disorders of the immune, endocrine, and central nervous systems, including with POD [6]. Aging is associated with changes in the gut microbiota [7] and microbiota dysbiosis. Specifically, Alzheimer's disease (AD) patients have decreased microbial diversity and the changes in gut microbiota as compared to cognitively normal controls [8]. AD transgenic mice have a significant shift of the gut microbiota compared to wild-type mice [9]. Further, an imbalance in the gut microbiota in AD transgenic mice contributes to cognitive impairment and increased brain levels of Aβ. Neuroinflammation may contribute to the neuropathogenesis of POD. [10] However, while all patients may have surgery-induced neuroinflammation, not all patients develop POD. Thus, neuroinflammation alone (single-factor model of postoperative delirium) is not sufficient to cause POD. Instead, it is likely that an additional vulnerability or predisposing factor for neuroinflammation and delirium is required. We hypothesized that one of these changes is gut microbiota dysbiosis associated with aging. Therefore, the objective of the current study was to test the hypothesis that anesthesia/surgery causes age-dependent changes in the gut microbiota and delirium-like behavior in mice that is attenuated by preoperative prophylaxis with lactobacillis or a probiotics.

Methods: We set out to determine whether anesthesia/surgery causes age-dependent gut microbiota dysbiosis, changes in brain IL-6 level and mitochondrial function, leading to postoperative delirium-like behavior in mice. Female 9 or 18 months old mice received abdominal surgery under 1.4% isoflurane for two hours. We employed a battery of natural and learned behavioral tests to determine the delirium-like behavior [37], assessed the gut microbiota before and after the anesthesia/surgery by gene pyrosequencing of 16S rRNA, and measured levels of brain IL-6(ELISA), synaptic marker(Western blot) and mitochondrial function (Seahorse XFp Extracellular Flux Analyzer) as measures of neuroinflammation and cerebral dysfunction. For intervention, intragastric administration of lactobacillus (10 days) and probiotic (20 days) were used to mitigate the anesthesia/surgery-induced above changes.

Results: Firstly, compared 18 months vs. 9 months old mice, anesthesia/surgery induces greater postoperative delirium-like behaviors and cognitive impairment in 18 months old mice. Secondly, compared 18 months vs. 9 months old mice, anesthesia/surgery caused different alterations in gut microbiota, including change reduction rate in the levels of gut lactobacillusin 18, but not 9, months old mice. Moreover, compared 18 months vs. 9 months old mice, anesthesia/surgery increased brain IL-6 levels, decreased PSD-95 and synaptophysin levels, and mitochondrial dysfunction in 18 than 9 months old mice. Last, treatments with lactobacillus and probiotic mitigated the anesthesia/surgery-induced above changes.

Conclusion: In conclusion, we demonstrated that anesthesia/surgery induces age-dependent changes in the gut microbiota (reduction in lactobacillus), increases brain levels of IL-6, decreases levels of synaptic marker, and reduces mitochondrial function while also promoting development of postoperative delirium-like behaviors in the mice. Treatment with lactobacillus or probiotic prior to anesthesia/surgery mitigated these detrimental effects, strongly suggesting that abnormalities in the gut microbiota contribute to the development of postoperative delirium. As such, clinical investigations of this possibility seem warranted.

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1. Research Agenda on Delirium in Older Adults. 2015; 63(5):843-852.

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3.Postoperative delirium in the elderly. 1994; 73(5):673-687.

4.The Gut Microbiome Alterations and Inflammation-Driven Pathogenesis of Alzheimer's Disease-a Critical Review. 2018.

5. Dysbiosis in inflammatory bowel disease. 2004; 53(1):1-4.

6. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. 2016; 21(6):738-748.

7. Cognitive decline, dietary factors and gut-brain interactions. 2014; 136-137:59-69.

8. Gut microbiome alterations in Alzheimer's disease. 2017; 7(1):13537.

9. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. 2017; 7:41802..

10.The neuroinflammatory hypothesis of delirium. 2010; 119(6):737-754.

Figure 1

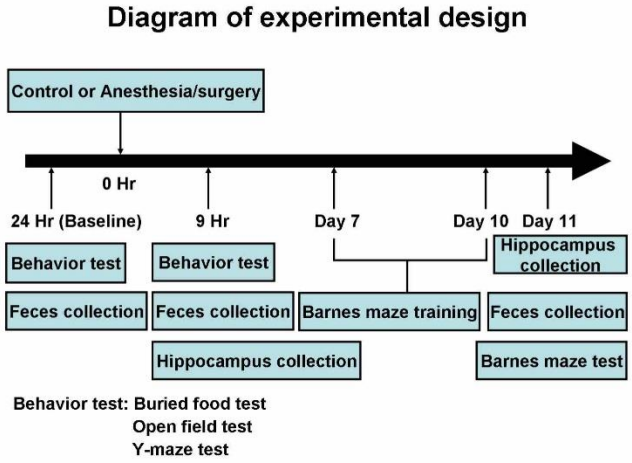
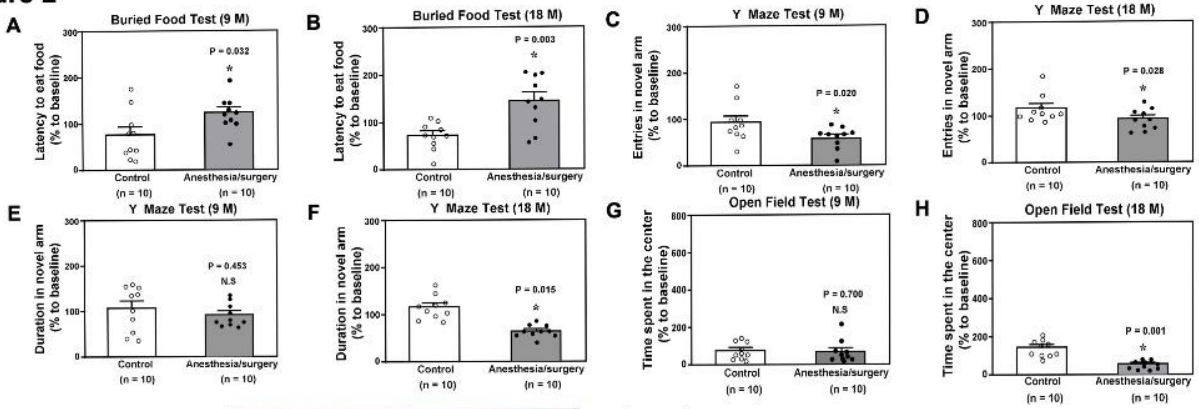


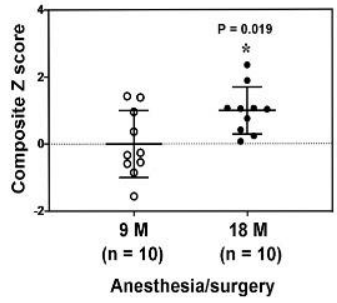
Diagram of experimental design
Control or Anesthesia/surgery
0 Hr
24 Hr (Baseline)
9 Hr
Day 7
Day 10
Day 11
Behavior test
Behavior test
Hippocampus collection
Feces collection
Feces collection
Barnes maze training
Feces collection
Hippocampus collection
Barnes maze test
Behavior test: Buried food test
Open field test
Y-maze test

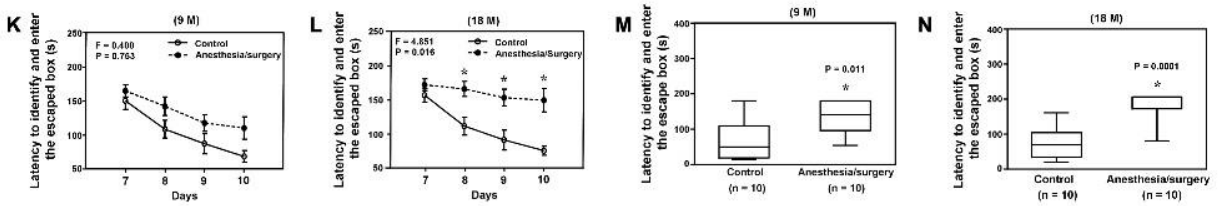
Figure 2

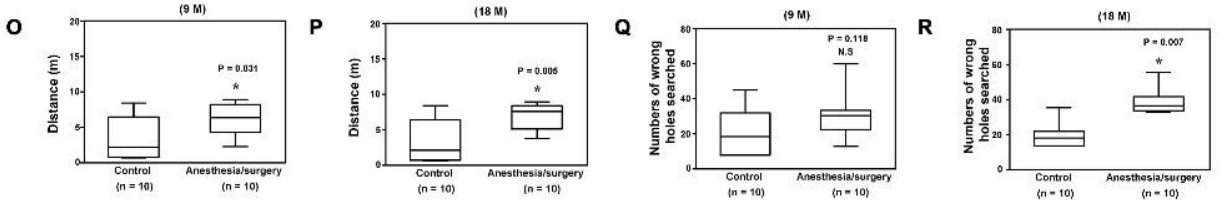


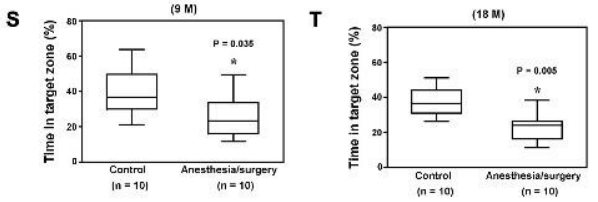
I

	9 M	18M
Buried food test		
Latency to eat food	↑	↑
Open field test		
Total distance	—	—
Time spent in the center	—	↓
Freezing time	—	—
Latency to the center	—	—
Y maze test		
Number of arm visits	—	—
Entries in novel arm	↓	↓
Duration in novel arm	—	↓









U

	9M	18M
Barnes maze training		
Latency	—	↑
Speed	—	—
Barnes maze test		
Latency	↑	↑
Target time	↓	↓
Wrong holes	—	↑
Distance	↑	↑

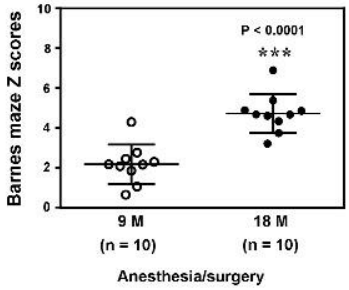


Figure 3

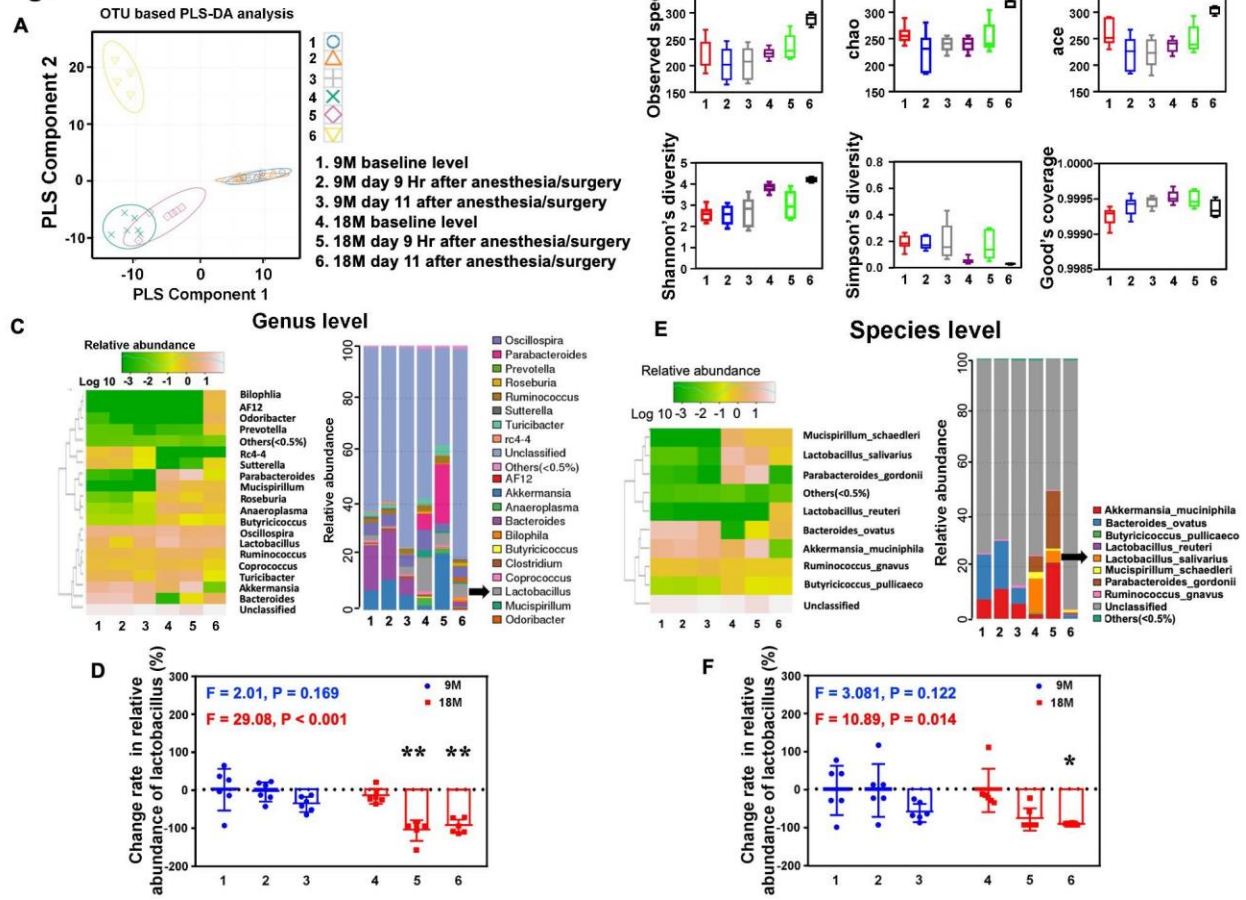

A
OTU based PLS-DA analysis
PLS Component 2
PLS Component 1
1. 9M baseline level
2. 9M day 9 Hr after anesthesia/surgery
3. 9M day 11 after anesthesia/surgery
4. 18M baseline level
5. 18M day 9 Hr after anesthesia/surgery
6. 18M day 11 after anesthesia/surgery
B
Observed species
chao
ace
Shannon's diversity
Simpson's diversity
Good's coverage
C
Genus level
Relative abundance
Log 10 -3 -2 -1 0 1
Bilophlia
AF12
Odoribacter
Prevotella
Others(<0.5%)
Rc4-4
Sutterella
Parabacteroides
Mucispirillum
Roseburia
Anaeroplasma
Butyricicoccus
Oscillospira
Lactobacillus
Ruminococcus
Coprococcus
Turicibacter
Akkermansia
Bacteroides
Unclassified
Relative abundance
Oscillospira
Parabacteroides
Prevotella
Roseburia
Ruminococcus
Sutterella
Turicibacter
rc4-4
Unclassified
Others(<0.5%)
AF12
Akkermansia
Anaeroplasma
Bacteroides
Bilophila
Butyricicoccus
Clostridium
Coprococcus
Lactobacillus
Mucispirillum
Odoribacter
E
Species level
Relative abundance
Log 10 -3 -2 -1 0 1
Mucispirillum_schaedleri
Lactobacillus_salivarius
Parabacteroides_gordonii
Others(<0.5%)
Lactobacillus_reuteri
Bacteroides_ovatus
Akkermansia_muciniphila
Ruminococcus_gnavus
Butyricicoccus_pullicaeco
Unclassified
Relative abundance
Akkermansia_muciniphila
Bacteroides_ovatus
Butyricicoccus_pullicaeco
Lactobacillus_reuteri
Lactobacillus_salivarius
Mucispirillum_schaedleri
Parabacteroides_gordonii
Ruminococcus_gnavus
Unclassified
Others(<0.5%)
D
Change rate in relative abundance of lactobacillus (%)
F = 2.01, P = 0.169
F = 29.08, P < 0.001
9M
18M
**
**
F
Change rate in relative abundance of lactobacillus (%)
F = 3.081, P = 0.122
F = 10.89, P = 0.014
9M
18M
*

Figure 4

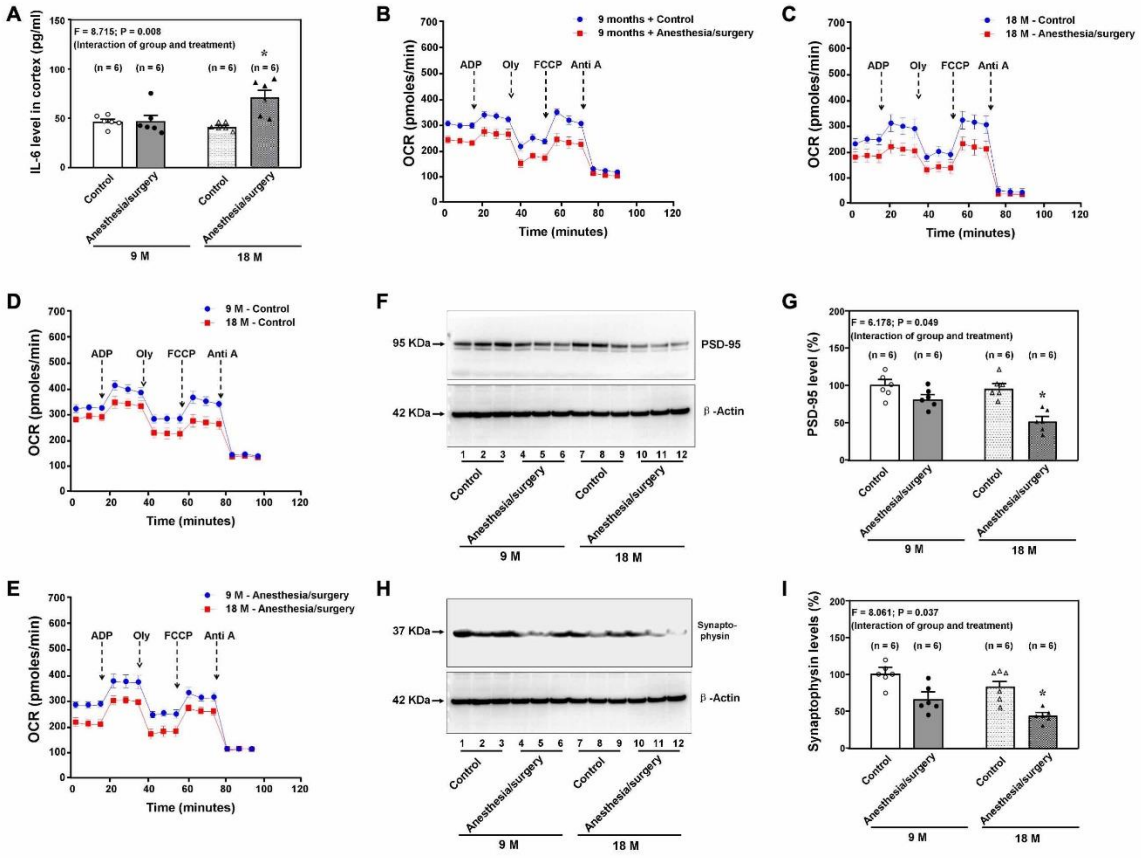
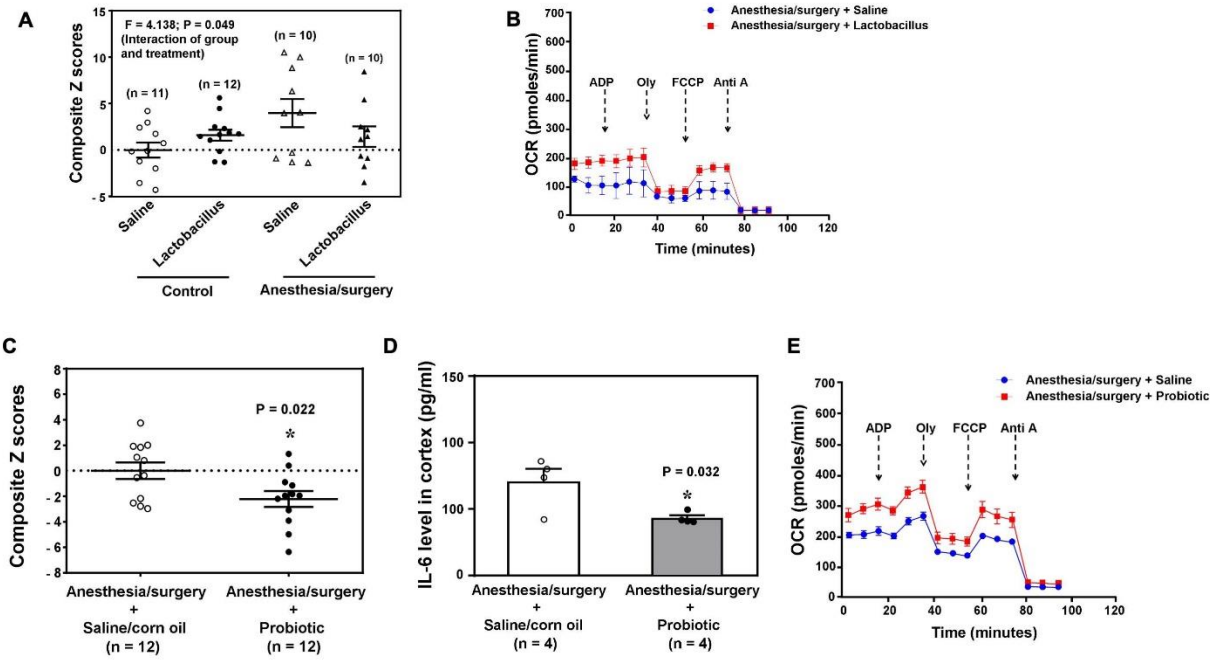

A
F = 8.715; P = 0.008
(Interaction of group and treatment)
IL-6 level in cortex (pg/ml)
(n = 6)
Control
Anesthesia/surgery
9 M
18 M
B
9 months + Control
9 months + Anesthesia/surgery
ADP
Oly
FCCP
Anti A
OCR (pmoles/min)
Time (minutes)
C
18 M - Control
18 M - Anesthesia/surgery
D
9 M - Control
18 M - Control
E
9 M - Anesthesia/surgery
18 M - Anesthesia/surgery
F
95 KDa
PSD-95
42 KDa
β -Actin
G
PSD-95 level (%)
H
37 KDa
Synapto-physin
I
Synaptophysin levels (%)

Figure 5


A
F = 4.138; P = 0.049
(Interaction of group and treatment)
Composite Z scores
(n = 11)
(n = 12)
(n = 10)
(n = 10)
Saline
Lactobacillus
Saline
Lactobacillus
Control
Anesthesia/surgery
B
Anesthesia/surgery + Saline
Anesthesia/surgery + Lactobacillus
OCR (pmoles/min)
ADP
Oly
FCCP
Anti A
Time (minutes)
C
Composite Z scores
P = 0.022
Anesthesia/surgery + Saline/corn oil (n = 12)
Anesthesia/surgery + Probiotic (n = 12)
D
IL-6 level in cortex (pg/ml)
P = 0.032
Anesthesia/surgery + Saline/corn oil (n = 4)
Anesthesia/surgery + Probiotic (n = 4)
E
Anesthesia/surgery + Saline
Anesthesia/surgery + Probiotic
OCR (pmoles/min)
ADP
Oly
FCCP
Anti A
Time (minutes)

Neuroscience in Anesthesiology and Perioperative Medicine-16 Preoptic Neurons That Promote Sleep and Wakefulness Do Not Alter Anesthetic Induction and Recovery Time in Mice

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Introduction: Growing correlative evidence supports the long-standing hypothesis that general anesthetics act on neural networks that regulate sleep.[1] The preoptic area of the hypothalamus is critical for sleep regulation.2,3 A subset of GABAergic neurons –presumably sleep-promoting– in the ventrolateral preoptic nucleus (VLPO) expresses Fos during anesthetic-induced unconsciousness and is directly activated by isoflurane.[4] Furthermore, lesions of the VLPO cause acute resistance to anesthetic induction.[4] However, no studies to date have investigated a causal role for preoptic neurons in general anesthetic mechanisms. We tested the hypothesis that chemogenetic activation of GABAergic or glutamatergic neurons in the median preoptic nucleus (MnPO) and VLPO would alter sleep/wake states and anesthetic state transitions.

Methods: All the procedures were approved by the Institutional Animal Care & Use Committee and conducted in accordance with The Guide. Male and female Vgat-cre (n=35) and Vglut2-cre (n=31) mice were injected with a viral vector for cre-dependent expression of the excitatory designer receptor hM3Dq in GABAergic or glutamatergic neurons in the MnPO or bilaterally in the VLPO. For anesthesia studies, mice received intraperitoneal injections of vehicle or the agonist for the designer receptors clozapine-N-oxide (CNO), and were anesthetized with 1.2% or 1.5% isoflurane for 30 minutes. Induction and recovery time were quantified, respectively, as time to loss and resumption of righting response. Data analysis was conducted by two investigators, one of whom was blinded to the treatment condition. For sleep/wake studies, a subset of mice was implanted with electrodes to record electroencephalogram (EEG) and electromyogram (EMG). After recovery and habituation, EEG and EMG were recorded continuously for 6 hours after injection of vehicle or CNO. Mice that did not express hM3Dq receptors, sham-injected, or naïve served as controls in sleep and anesthesia studies.

Results: Relative to vehicle, activation of GABAergic and glutamatergic neurons in the MnPO and VLPO did not alter anesthetic induction and recovery time. Activation of GABAergic neurons in the MnPO increased non-rapid eye movement (NREM) sleep (P=0.014) and decreased rapid eye movement (REM) sleep (P=0.005). Activation of glutamatergic neurons in the VLPO increased wakefulness (P=0.023) and decreased NREM (P=0.035) and REM sleep (P=0.017). Neither MnPO glutamatergic neurons nor VLPO GABAergic neurons altered sleep/wake states.

Conclusion: To our knowledge, this is the first causal investigation of preoptic neurons in anesthetic state transitions. These data suggest that activation of preoptic neurons that increase sleep or wakefulness does not alter anesthetic state transitions. The results imply that current correlative evidence for a mechanistic overlap of sleep and anesthesia at the level of individual preoptic nuclei, or even individual cell subtypes, might not necessarily have strong causal significance.

Reference(s):

1. Br J Anaesth 1994; 72: 506-8
2. Nature 2017; 545: 477-481
3. Curr Biol 2018; 28: 2263-2273 e4
4. Curr Biol 2012; 22: 2008-16

Neuroscience in Anesthesiology and Perioperative Medicine-17 Emergence EEG following cardiac surgery and association with clinical outcomes

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Introduction: Perioperative EEG monitoring can be used to identify cerebral activity which may have implications for postoperative cognition. (1-3) We hypothesized that a high proportion of cardiac surgical patients, who have unique surgical conditions, (4) would have EEG findings consistent with increased sedation and sought to associate these patterns with clinical outcomes.

Methods: Patients were eligible for inclusion in this observational study if they were undergoing elective cardiac surgery. Following induction of general anesthesia, we continuously collected EEG data using a SedLine Brain Function Monitor (Masimo Corporation, Irvine, CA) until extubation. EEGs were interpreted off-line using density spectral array (DSA) analysis for identification of prominent alpha power in the first postoperative hour by an expert reviewer who was blinded to clinical conditions. Additional clinical data were collected via retrospective chart review. Our primary outcome was the incidence of rapid extubation (within 4 postoperative hours) among patients. Results were analyzed using 2-sided Fisher's exact testing.

Results: 63 subjects were enrolled, 25 of whom were omitted due to data storage errors (21 patients), case cancellation (2), or investigator unavailability (2). 10 additional subjects were omitted due to poor quality DSA data. Thus, 28 patients were included in the final analysis. 14 underwent CABG procedures, 10 had valvular procedures, and 4 had other procedures (Figure 1). The median duration of postoperative mechanical ventilation was 381 minutes (IQR 250 - 508.5) in the entire sample, 282 min (IQR 200 - 400) for CABG patients, 484 min (IQR 407 - 551) for valve patients, and 279 min (143.5 - 503.3) for other patients. 7 patients were rapidly extubated (25%), including 28.6% of CABG patients, 10% of valve patients, and 50% of other patients. A total of 9 patients were determined to have prominent alpha power in the first postoperative hour (32.1%), including 4/14 CABG patients (28.6%), 5/10 valve patients (50%), and 0 other patients (Table 1). There were no significant differences in the proportion of patients in the entire sample who were rapidly extubated among those with alpha power versus without alpha power ($p = 0.25$), in the CABG cohort ($p = 0.60$), the valve cohort ($p = 0.50$), or the other-surgery cohort ($p = 1.00$) (Table 2). There were also no significant differences in the proportion of patients with prominent alpha between CABG, valve, or other procedures ($p = 0.25$) (Table 3).

Conclusion: In a heterogenous cohort of cardiac surgical patients, presence of alpha power on DSA analysis in the early postoperative period was uncommon, not significantly associated with rapid extubation, and not different between procedure subtypes. In this small exploratory study, the failure of alpha power to be significantly associated with rapid extubation may reflect inter-individual variation in cerebral physiology as well as indications for mechanical ventilation other than excessive sedation.

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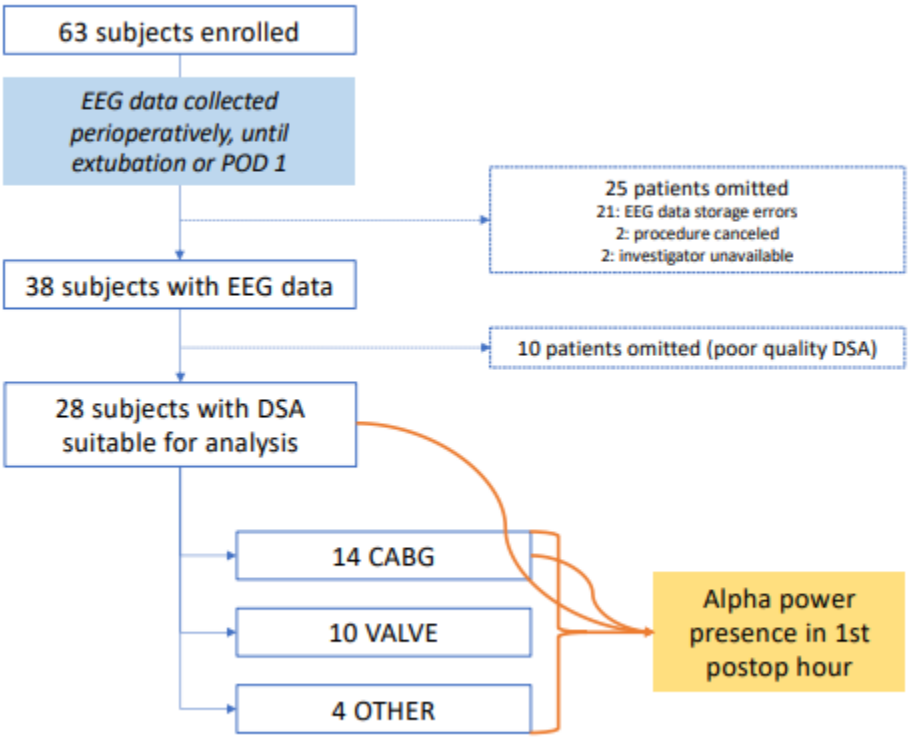
63 subjects enrolled
EEG data collected perioperatively, until extubation or POD 1
25 patients omitted
21: EEG data storage errors
2: procedure canceled
2: investigator unavailable
38 subjects with EEG data
10 patients omitted (poor quality DSA)
28 subjects with DSA suitable for analysis
14 CABG
10 VALVE
4 OTHER
Alpha power presence in 1st postop hour

Table 1. Clinical characteristics of patients in which perioperative EEG data were suitable for analysis.

	Entire cohort	CABG	Valve	Other
N	28	14	10	4
Age in years, median (IQR)	69 (57.8 – 75.3)	70 (66.5 – 74.3)	68 (56 – 76.8)	48.5 (41 – 59.8)
Male, %	75%	78.6%	60%	100%
ASA score, median (IQR)	4 (3 – 4)	3.5 (3 – 4)	4 (3 – 4)	3.5 (3 – 4)
Fentanyl mg in OR, median (IQR)	2 (1.5 – 2.6)	2.1 (1.5 – 2.5)	2.1 (1.8 – 2.9)	2 (1.8 – 2.2)
Midazolam mg in OR, median (IQR)	9 (5 – 12.5)	6.5 (4.3 – 10)	11 (7 – 14.8)	14 (7 – 20)
Propofol mcg/kg/min on ICU arrival, median (IQR)*	50 (37.5 – 50)	45 (32.5 – 50)	50 (32.5 – 50)	50 (50 – 50)
CPB duration in minutes, median (IQR)	91 (71.3 – 134.3)	74.5 (68.3 – 84.3)	151.5 (101.3 – 216.5)	131 (102.8 – 134.3)
Aortic cross clamp duration, median (IQR)	67 (48 – 94.5)	58 (48.5 – 73.5)	95 (74.3 – 155.3)	66 (20.3 – 106.5)
Postoperative mechanical ventilation duration in minutes, median (IQR)	381 (250 – 508.5)	282 (200 – 400)	484 (407 – 551)	279 (143.5 – 503.3)
Extubated within 4 hours (%)	7 (25%)	4 (28.6%)	1 (10%)	2 (50%)
Patients with alpha in spectral analysis of first postoperative hour (%)	9 (32.1%)	4 (28.6%)	5 (50%)	0 (0%)

***** One patient, who underwent valve replacement, left the OR on dexmedetomidine infusion instead of propofol. All other patients received propofol infusion as the sole ongoing sedative on transport to the ICU.

Table 2. Proportion of patients with or without prominent alpha power who were rapidly extubated (within 4 postoperative hours) among the entire sample and by procedural subtype.

		Alpha power present	Alpha power absent	P value*
Entire Sample	**Rapid extubation**	1 (14.2%)	6 (85.7%)	0.25
	Prolonged intubation	8 (61.5%)	13 (61.9%)	
CABG Only	**Rapid extubation**	1 (25%)	3 (75%)	0.60
	Prolonged intubation	3 (30%)	7 (70%)	
Valve Only	**Rapid extubation**	0 (0%)	1 (100%)	0.50
	Prolonged intubation	5 (55.6%)	4 (44.4%)	
Other Only	**Rapid extubation**	0 (0%)	2 (100%)	1.00
	Prolonged intubation	0 (0%)	2 (100%)	

* Fisher's exact testing, 2-sided.

Table 3. Comparison of the proportion of patients with alpha power within the first postoperative hour on DSA analysis among procedural subtypes. (CABG = coronary artery bypass graft)

	Alpha power present	Alpha power absent	P value*
CABG	4 (28.6%)	10 (71.4%)	0.25
Valve	5 (50%)	5 (50%)	
Other	0 (0%)	4 (100%)	

* Fisher's exact testing, 2-sided.

Neuroscience in Anesthesiology and Perioperative Medicine-18 Neurturin upregulates myeloid differentiation 1 (MD-1) mRNA in nonpeptidergic sensory afferents

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Introduction: Communication between nerves, keratinocytes and immune cells in the skin allows a robust and rapid response to invading pathogens. Skin is innervated by peptidergic (TRPV1+) and nonpeptidergic sensory afferents. Peptidergic afferents release neuropeptides (CGRP, substance P) that increase vasodilation and immune cell migration during inflammation. Nonpeptidergic afferents are relatively peptide poor and express glial cell line-derived neurotrophic factor family receptor alpha-2 (GFRα2), which binds neurturin (Nrtn), a growth factor expressed by keratinocytes. Nrtn expression is increased in the skin in response to the inflammatory agent imiquimod, suggesting a link between Nrtn, GFRα2+ afferents and immune signaling. (1, 2, 3) Towards understanding the role Nrtn and GFRα2+ afferents in immune signaling, we examined transgenic mice that overexpress Nrtn in keratinocytes (NrtnOE mice). These mice have increased density of GFRα2+ terminals in the skin (1) and, in response to Candida albicans (CA) infection, exhibit increased TNFα mRNA expression and faster clearance of CA relative to WT mice. In addition, NrtnOE mice showed increased TNFα release when challenged with complete Freund's adjuvant (CFA). Data also indicate that in response to Nrtn, DRG neurons increase mRNAs encoding myeloid differentiation 1 (MD-1), a secreted ligand that activates toll-like receptors (TLRs) 2 and 4 (4, 5) and increase TNFα.(6) Based on these findings, we hypothesized that Nrtn increases MD-1 expression in nonpeptidergic neurons via Nrtn/GFRα2 signaling. In this study, we identified the subtypes of neurons that express MD-1 and begin to address the role of neuron-derived MD-1 in the innate immune response.

Methods: NrtnOE and C57BL/6 (WT) mice were housed in an AAALAC approved facility. All protocols were approved by the University of Pittsburgh Institutional Animal Care and Use Committee. RNA from trigeminal (TG) and dorsal root ganglia (DRG) was isolated and MD-1 mRNA level determined using RT-PCR. Primary cultures of DRG neurons were prepared (7), incubated with growth factors for 5 days and MD-1 mRNA expression measured using RT-PCR. MD-1 protein from sciatic nerve, epidermis, DRG and TG was measured using SDS-PAGE and western blotting. RNAScope in situ analysis of MD-1 mRNA was performed according to the manufacturer's instructions. Images were acquired using a fluorescent microscope and analyzed using Image J.

Results: Sensory ganglia of NrtnOE mice have increased levels of MD-1 relative to WT ganglia. MD-1 mRNA was also increased in primary cultures of DRG neurons treated with Nrtn. In culture, glial cell line-derived neurotrophic factor (GDNF) also increased MD-1 mRNA, while artemin (Artn) did not. RNAScope analysis of TG and DRG localized MD-1 mRNA to GFRα2+ neurons. In addition, fluorescence intensity of MD-1 mRNA hybridization was significantly greater in NrtnOE ganglia. At the protein level there was no difference in the relative level of MD-1 in DRG, sciatic nerve and skin of NrtnOE and WT mice.

Conclusion: Data indicate that Nrtn/GFRα2 signaling regulates MD-1 mRNA expression in nonpeptidergic neurons. GDNF also increased MD-1 expression in primary cultures of DRG neurons, perhaps due to its known activation of GFRα2. (8) Artn, which only binds to GFRα3, which is only expressed by peptidergic afferents, did not increase MD-1 to the same level. There was no increase in MD-1 protein in the skin, DRG or nerve fibers of NrtnOE mice relative to WT. This may be due to the propensity of MD-1 to aggregate, i.e., recombinant MD-1 produced by Pichia pastoris has been shown to form aggregated complexes. (9) We hypothesize that release of MD-1 and its extracellular aggregation may facilitate 'trapping' of pathogens in the skin. In addition, MD-1 protein, but less so mRNA, is present in glabrous skin. Thus, the majority of MD-1 protein detected in skin may be derived from release by neuron terminals. Future studies will examine MD-1 distribution and release and how it may change in response to pathogen challenge.

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Neuroscience in Anesthesiology and Perioperative Medicine-19 Sex Hormones, Chloride Transporters, and Time: Critical Determinants for Anesthetic Neurotoxicity Susceptibility in Perinatal Rats

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Introduction: One of the most consistent preclinical findings in the field of neonatal anesthetic neurotoxicity is a cognitive deficit associated with early-life exposure to anesthetic drugs1,2. Our lab has previously found differences between male and female rats in their susceptibility to cognitive deficits after early-life volatile anesthetic exposure3,4. We also found that protein levels of the solute carrier family proteins NKCC1 and KCC2 correlated with susceptibility4. The relative expression of these molecules is thought to determine the function of the GABAAR activation, with high NKCC1 and low KCC2 leading to excitability from GABA modulation5. Given the differences in susceptibilities of male and female rats exposed on the same day, we hypothesized that there is a window of susceptibility which might altered so we manipulated androgen signaling, chloride transporter function and time of exposure to test this question.

Methods: To study the effect of androgen receptor blockade on anesthetic neurotoxicity, flutamide (250ug) was injected subcutaneously on postnatal days 2,4,6, in male rats that were subsequently exposed to 6 hrs. of 1MAC isoflurane on postnatal day 7. Cognitive function was later assessed in adulthood using a spatial memory task (Barnes Maze) and recognition memory tasks. In a separate cohort, protein levels of NKCC1 and KCC2 were measured from cortical lysates by western blot. To study the role of NKCC1 in the development of anesthetic mediated cognitive deficits, a NKCC1 inhibitor, bumetanide, was injected IP (1.8mg/kg) in male rats prior to postnatal day 7 isoflurane exposure. Animals were later tested for spatial memory deficits. To study the closure of the window of susceptibility in males, we exposed postnatal day 14 rats to the same 6 hr. isoflurane protocol and tested their spatial memory in adulthood. Statistical analysis was performed using Prism 8.3 software (GraphPad Software, San Diego, CA). Group size for behavior experiments was determined from previous studies. For all experiments, data was first subjected to Shapiro-Wilk normality testing which informed the choice of subsequent parametric or non-parametric statistical tests.

Results: Male rats exposed to flutamide prior to isoflurane exposure did not develop the spatial and recognition memory deficits that vehicle injected controls developed. Flutamide treated male animals also had changes in expression patterns of NKCC1 (decreased) and KCC2 (increased) at postnatal day 7 which were similar to levels seen in age matched females (which are protected for isoflurane neurotoxicity at this timepoint). Blockade of NKCC1 with bumetanide prior to isoflurane exposure protected animals relative to vehicle treated animals in the spatial memory task. Shifting the isoflurane exposure later to postnatal day 14 in males also preserved spatial memory performance in adulthood.

Conclusion: Male rats exposed to flutamide prior to isoflurane exposure did not develop the spatial and recognition memory deficits that vehicle injected controls developed. Flutamide treated male animals also had changes in expression patterns of NKCC1 (decreased) and KCC2 (increased) at postnatal day 7 which were similar to levels seen in age matched females (which are protected for isoflurane neurotoxicity at this timepoint). Blockade of NKCC1 with bumetanide prior to isoflurane exposure protected animals relative to vehicle treated animals in the spatial memory task. Shifting the isoflurane exposure later to postnatal day 14 in males also preserved spatial memory performance in adulthood.

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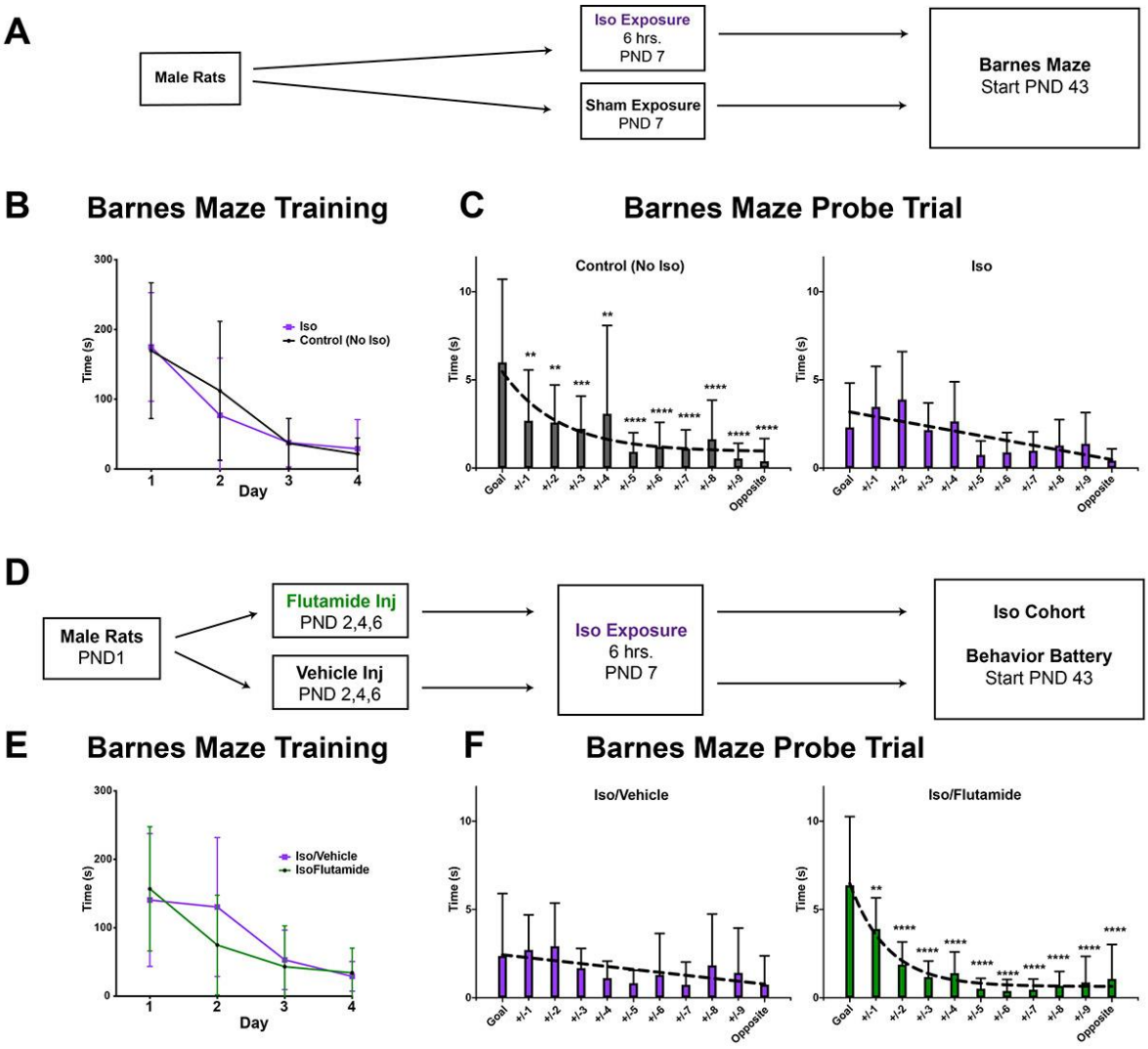
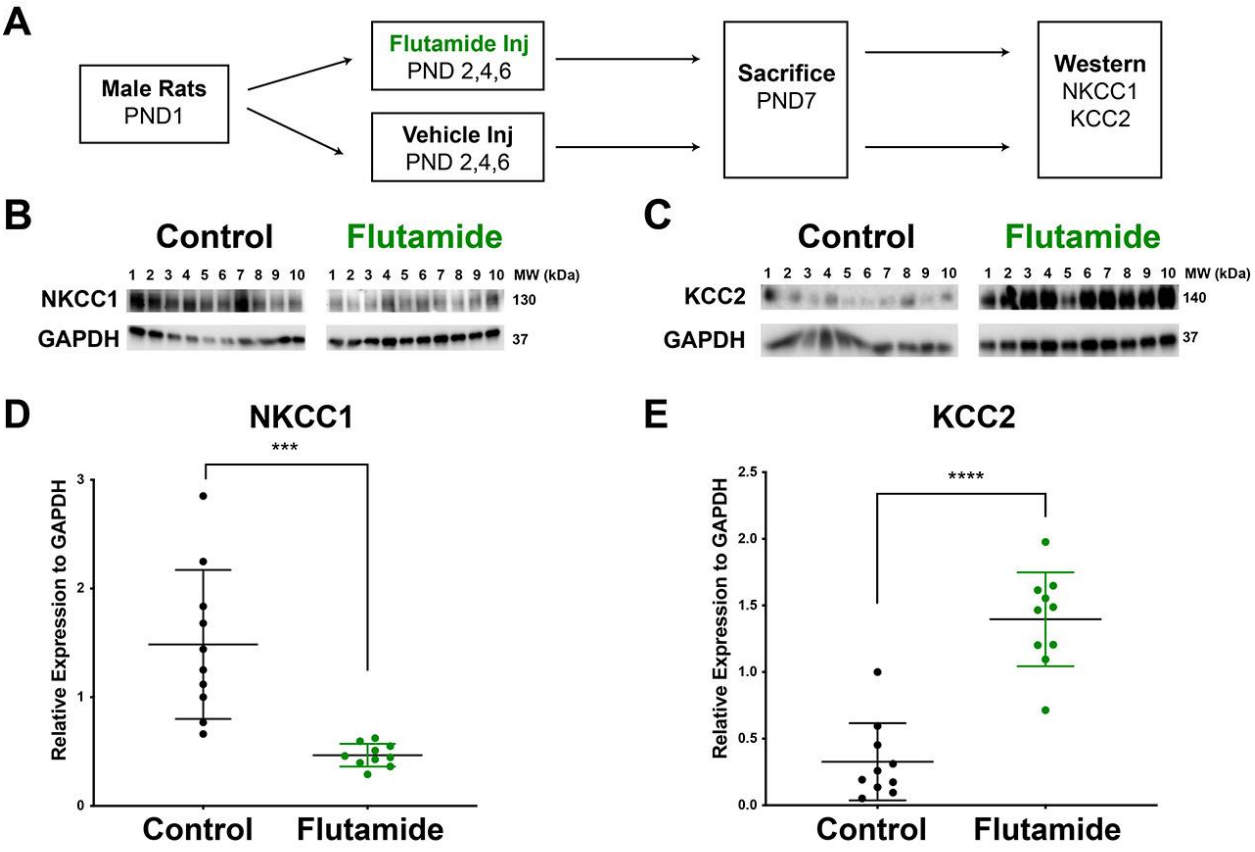


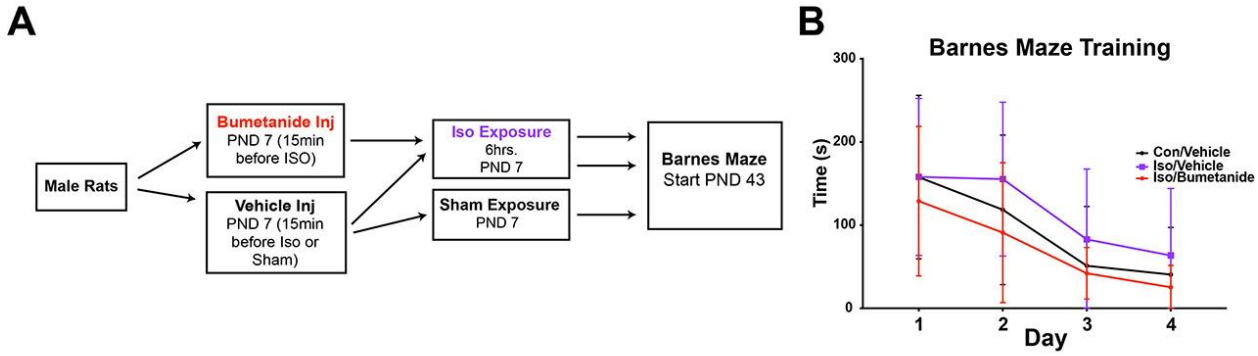
Flutamide protects against Spatial and Recognition Memory Deficits

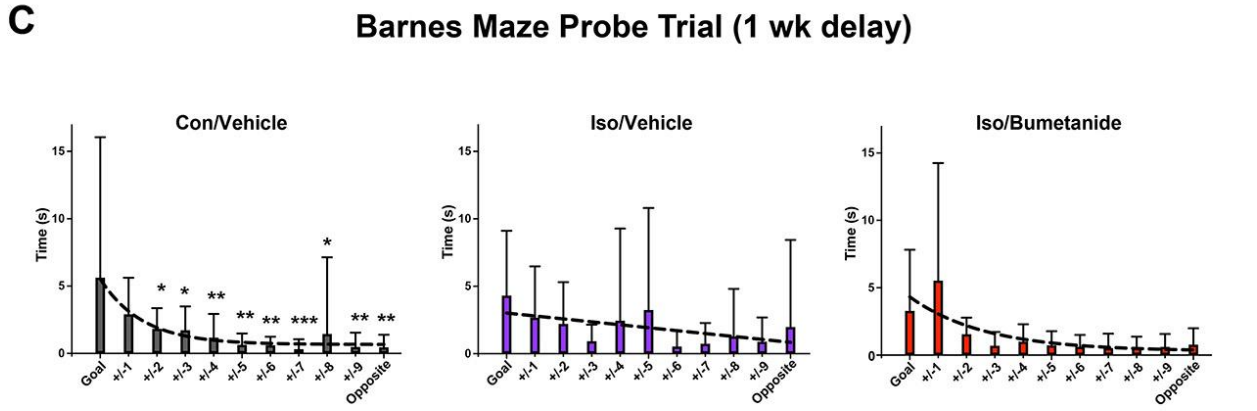
A. Experimental overview: male rats exposed to sham (n=17) or isoflurane (n=13) at PND7. Animals underwent Barnes Maze testing starting at PND 43. B. Behavior Training. All animals acquired the goal over the course of four training days C. Probe trial. Control animals differentiated the goal from every other averaged position by Dunnett's multiple comparison analysis. This pattern fit a curve with one-phase decay by extra sum of squares F-test ($F(1,140)=6.534, p=0.0117$). Isoflurane exposed animals were unable to differentiate any position from goal and showed a linear relationship among all positions ($F(1,184)=0.1769$, $p=0.6745$). D. Experimental overview: male rats were injected with flutamide (n=14) or vehicle (n=14) then exposed to isoflurane and subjected to behavior battery. E. Barnes Maze Training. No difference among acquisition. F. Probe trial. ISO/Veh animals did not differentiate the goal from other positions while ISO/flutamide treated animals successfully discriminated every position by Dunnett's multiple comparison. Curve fit for ISO/flutamide favored a one-phase decay ($F(1,151)=78.52$, $p<0.0001$). Error bars represent standard deviations. *$p<0.05$, ** $p<0.01$, ***$p<0.001$, ****$p<0.0001$

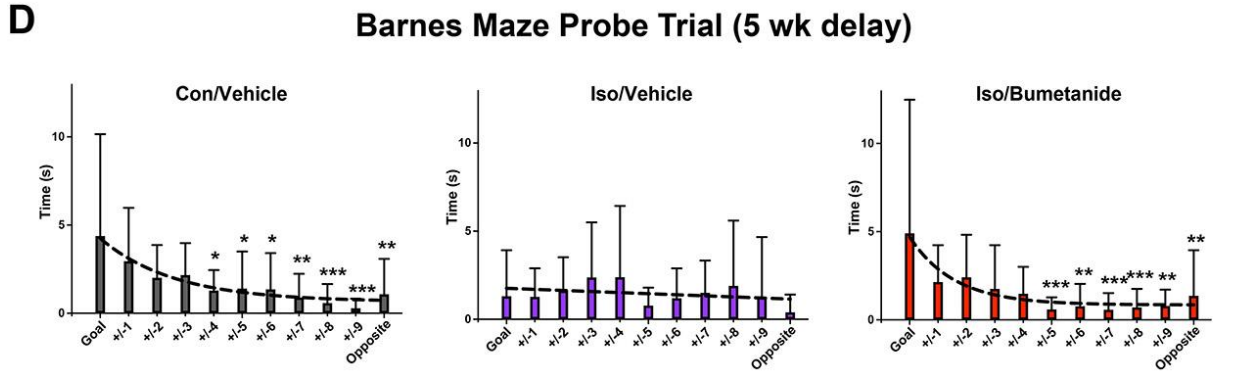


Flutamide Alters Chloride transporters at PND7

A. Experimental overview: male rats were injected with either flutamide (n=10) or vehicle (n=10) and sacrificed on PND7. B-C. Cortical lysates were made and subjected to western blot analysis for NKCC1 and KCC2. D-E. quantification of blot after normalization to GAPDH showed significant decrease in NKCC1 with flutamide treatment by unpaired t-Test ($p=0.002$) and a significant increase in KCC2 ($p<0.0001$). Error bars represent standard deviations. ***$p<0.001$, ****$p<0.0001$

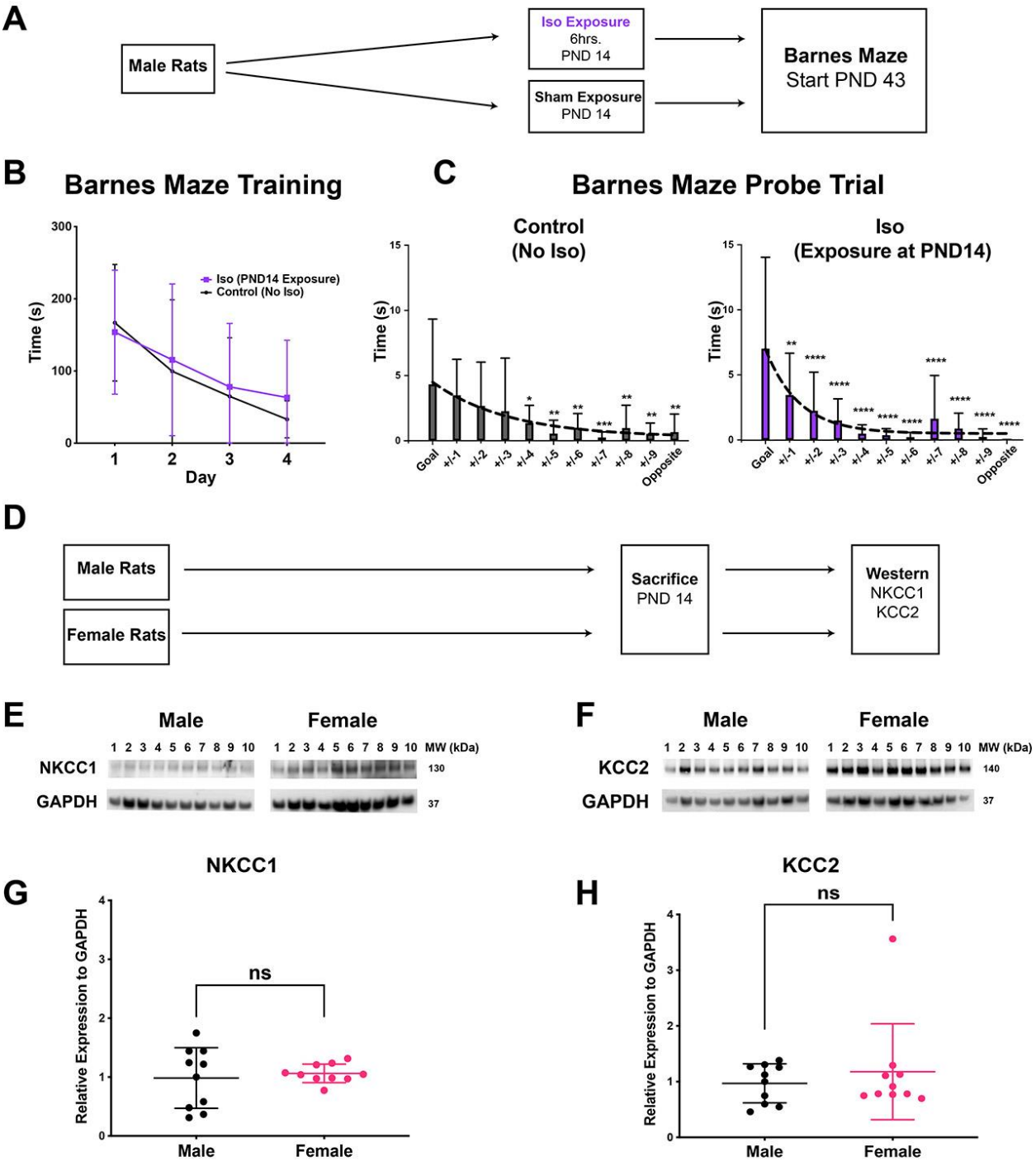






Bumetanide protects against recognition memory deficit

A. Experimental overview: Bumetanide (n=15) or vehicle (n=15) was injected prior to isoflurane exposure. Non-exposed, vehicle injected controls were also used (n=18). Barnes maze testing followed at PND43. B. All groups acquired the goal position over 4 days. C. Probe trial after 1 week showed no difference in goal vs other positions for either ISO/Veh or ISO/bumetanide by multiple comparison, but curve fit showed preference for linear fit by sum of squares F-test for ISO/Veh ($F(1,151)=1.864$, $p=0.1742$) and a one-phase decay for ISO/bumetanide ($F(1,162)=6.598$, $p=0.0111$). D. Repeat probe trial 5 weeks after initial acquisition showed significant differences in positions +/-5,6,7,8,9,opposite in the ISO/bumetanide, but no differences in the ISO/Veh. Error bars represent standard deviations. *$p<0.05$, ** $p<0.01$, ***$p<0.001$, ****$p<0.0001$



Male susceptibility window has closed by PND14, Chloride transporter levels are not different in males and females

A. Experimental overview: Male rats were exposed to isoflurane (n=15) or sham at PND14 (n=15) and underwent Barnes Maze testing at PND43. B. Both groups acquired the position of the goal hole. C. Both groups differentiated the goal from at least part of the maze by Dunnett's multiple comparison, and curve fit analysis favored one phase decay functions over linear (Fcontrol(1,162)=7.468, p=0.007; FISO (1,140)=27.91, p<0.0001). D. Experimental overview: male and female rats were sacrificed at PND14. E-F. Cortical lysates were subjected to western blot analysis for NKCC1 and KCC2. G-H. After normalization to GAPDH, neither protein showed a significant difference between male and females. Error bars represent

Neuroscience in Anesthesiology and Perioperative Medicine-20 Behavioral profiling in zebrafish identifies novel anesthetics.

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Introduction: Orchestration of animal behavior depends on the proper balance of excitatory and inhibitory neuronal signaling. GABA, the major inhibitory neurotransmitter, signals through a broad range of ionotropic receptors composed of pentameric combinations of at least 19 different subunits(1). These receptors mediate diverse phenotypes of GABAergic drugs including sedatives, hypnotics, anxiolytics, anxiogenics and anesthetics(2). However, due to the complexity of receptor subtypes, their pharmacology and behavioral consequences are poorly understood. Behavioral profiling in zebrafish will gain insight, here we present the use of zebrafish to understand known and identify novel sedatives and anesthetics.

Methods: Zebrafish larvae are small enough to fit in 96-well plates and are easily treated with compounds. We use specific behavioral profiles for anesthetic-related phenotypes, distinct from loss-of-motion behaviors(3). Using a behavioral profile specific to etomidate we queried a collection of quantified behaviors calculated from a phenotypic screen on zebrafish of 10,000 compounds. Similarity metrics like Pearson correlation were used to identify profiles similar to etomidate and propofol. Using structural clustering we organized and prioritized new hit compounds for further studies. Whole-mount immunostaining, image registration, and fluorescence intensity averaging was used to look at whole brain neural activity patterns(4). Automated adult zebrafish screening was developed to identify compounds that cross the blood brain barrier. Compounds that worked in adult fish were tested in mice for anesthesia by intraperitoneal injection.

Results: Using our previously described methods(3) we identified 60 structurally diverse compounds that phenocopied etomidate in vivo. We selected 26 that were in structurally unique classes to perform further investigations. Previous studies indicated that the larval blood brain barrier is not as robust as in adults(5). To identify translatable hits we performed a secondary screen in adult zebrafish in the top 26 hit compounds from structurally diverse classes. A subset of these hits in larvae translated to adults. Adult positive compounds tested in mice cause anesthesia. Whole brain imaging in larvae reveal that these translatable hits silence neural activity similar to etomidate.

Conclusion: Large-scale behavior-based chemical screens in zebrafish can identify novel anesthetics that translate to mammals. Here, we show behavioral profiling rapidly identifies new anesthetic-related compounds in vivo. Future studies will likely expand the utility of behavior-based chemical phenocopy screens and whole brain imaging to further understand sedatives and anesthetic like compounds.

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Neuroscience in Anesthesiology and Perioperative Medicine-21 Incidence of and Risk Factors for Emergence Delirium and Post-Operative Delirium in Neurosurgical Patients- A Prospective Cohort Study

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Introduction: Delirium after surgery is a spectrum of clinical syndrome constituting emergence delirium (ED) and/or post-operative delirium (POD). ED is a transient state (minutes to hours) of marked agitation or excessive sedation after the discontinuation of general anesthesia. POD is a fluctuating metal status commonly occurring between post operative day 1 to 3. The primary objective of this study was to evaluate the incidence of ED and POD in patients after neurosurgical procedures. The secondary objectives were: to examine the relationship between ED and POD and to identify peri- operative risk factors of ED and POD.

Methods: This is a prospective cohort study conducted at a tertiary referral neurosciences university hospital. After IEC approval ,we intended to study 200 neurosurgical patients undergoing cranial and spine surgeries from February 2018 onwards. Inclusion criteria were neurosurgical patients > 18 years with Glasgow coma scale (GCS) =15. Patients <18 years old and with GCS <15 are excluded.No preoperative sedation was administered to any patient prior to the completion of baseline delirium assessment. All study participants were assessed for pre-existing delirium using Confusion Assessment Method (CAM)[4]. Standard practices of anesthesia and postoperative care were provided for all patients. The attending anesthesiologists were free to select anesthetic drugs and techniques of their choice. Preoperative patient data and anesthetic details were retrieved from the electronic anesthesia record.Outcome measures included ED and POD. ED was assessed in the first hour of the postoperative period using sedation agitation score (SAS)[5] and highest score was considered for analysis. Patients with SAS of 4 were labelled as normal or having no ED. POD was evaluated using CAM (Supplements 1, 2) to identify presence of delirium at pre-determined time points- after 12 hours, 48 hours and 72 hours of surgery

Results: A total of four hundred and sixty-five patients undergoing elective cranial and spinal neurosurgery were screened during the study period. Of these, two hundred and thirty-eight patients were found eligible based on our selection criteria and consented for participation into the study.Two hundred neurosurgical patients completed all the assessments of our study outcomes during the study period and data of these patients were analyzed. Of these, 157 underwent cranial surgery and 43 underwent spine surgery. The [mean ± SD] age in years was 44 ± 14 and 133 patients were males in this study. Eighty-two of the 200 neurosurgical patients (41%) developed ED 9table 1). Patients with ED manifested with self-removal of intravenous lines, urinary catheters, random spitting and delayed ability for neurological assessment. All patients required more than one healthcare worker to hold and restrain the patient to the bed and few of them required pharmacological intervention and urgent imaging to exclude post-surgical complication. The incidence of POD in all neurosurgical patients was 20% (N=40). Those patients who developed POD required physical restraints in bed and occurrence of POD resulted in delayed discharge from high dependency unit to the ward. Patients with POD needed intravenous haloperidol bolus or dexmedetomidine infusion to control agitation. The incidence of ED and POD occurring in the same patient as a delirium spectrum was 15% (N=30).Incidences of ED-POD spectrum were 7% after spine surgeries and 17 % after cranial surgeries.As per the multivariate model, patients undergoing spine surgeries were found to have 44% less risk of ED than cranial surgeries ($p = 0.032$). Males were associated with 2.5 times higher risk of POD than females ($p = 0.005$), and presence of ED was associated with 1.8 times higher risk of POD ($p < 0.001$) (Figure 2). None of the other factors were significantly associated with ED or POD.

Conclusion: Incidences of ED and POD after neurosurgery were higher than that reported after non-neurosurgical procedures previously. Also, incidences of ED and POD was higher after cranial neurosurgery than spine surgery. Neurosurgical patients with predisposing (male gender) and precipitating (presence of ED) risk factors are at high risk for development of POD.Demonstration of ED and POD co-existing as a continuum of delirium syndrome is a novel finding of this observational study. This study also confirms that ED is a strong predictor of POD after neurosurgery.

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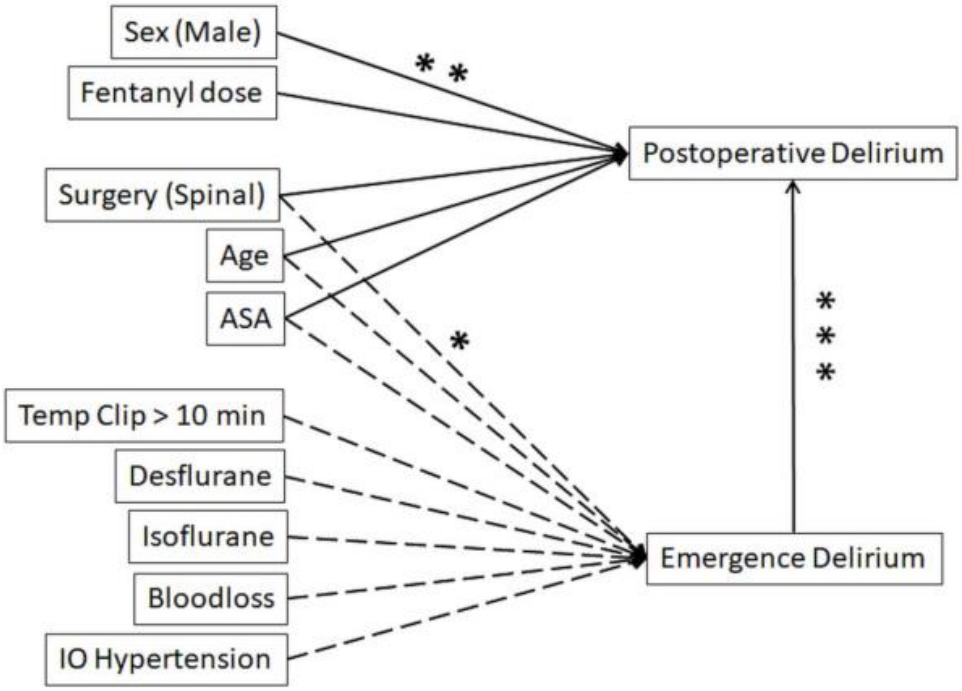
Table 1: Incidence of Emergence Delirium and Post-Operative Delirium

Surgical procedure (N)	Emergence delirium N (%)	Postoperative delirium N (%)
All Neurosurgical cases (200)	82 (41%)	40 (20%)
Spine surgery (43)	11 (26%)	4 (9%)
Cranial surgery (157)	70 (44%)	36 (23%)
a) Cerebrovascular surgery (Aneurysm + arterio-venous malformation) (18)	11 (61%)	4 (22%)
b) Surgery for supratentorial lesion (81)	33 (40%)	21 (26%)
c) Epilepsy surgery (4)	2 (50%)	1 (25%)
d) Endoscopic pituitary surgery (10)	5 (50%)	4 (40%)
e) Extradural surgery (18)	8 (44%)	2 (11%)
f) Infratentorial surgery (26)	11 (41%)	4 (14%)


Sex (Male)
Fentanyl dose
Surgery (Spinal)
Age
ASA
Temp Clip > 10 min
Desflurane
Isoflurane
Bloodloss
IO Hypertension
Postoperative Delirium
Emergence Delirium
* *
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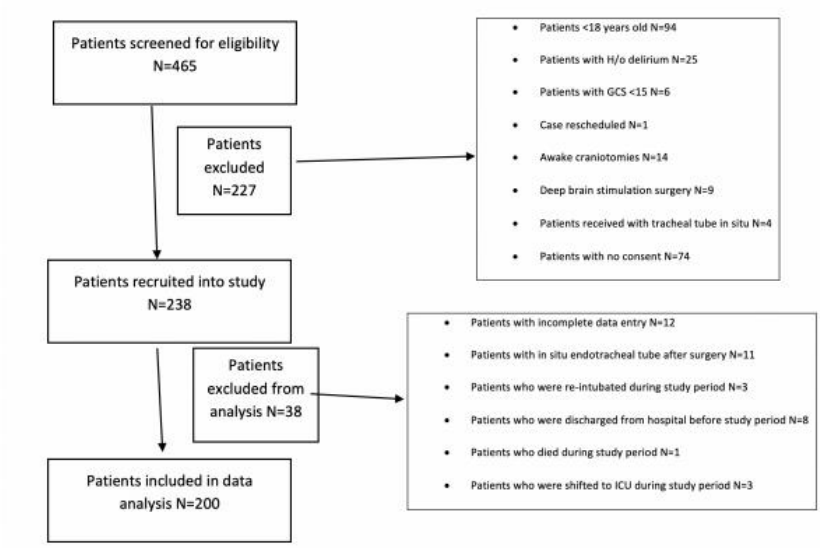
Patients screened for eligibility N=465
Patients excluded N=227
Patients <18 years old N=94
Patients with H/o delirium N=25
Patients with GCS <15 N=6
Case rescheduled N=1
Awake craniotomies N=14
Deep brain stimulation surgery N=9
Patients received with tracheal tube in situ N=4
Patients with no consent N=74
Patients recruited into study N=238
Patients excluded from analysis N=38
Patients with incomplete data entry N=12
Patients with in situ endotracheal tube after surgery N=11
Patients who were re-intubated during study period N=3
Patients who were discharged from hospital before study period N=8
Patients who died during study period N=1
Patients who were shifted to ICU during study period N=3
Patients included in data analysis N=200

Supplement 1: Confusion Assessment Method (CAM)

Diagnosis of Delirium by CAM requires presence of both features A and B	
A. Acute onset and fluctuating course	Is there an evidence of an acute change in mental status from baseline?
	Does the abnormal behavior
	• come and go? • fluctuate during the day? • Increase/decrease in severity
B. Inattention	Does the patient:
	• Have difficulty focusing attention • Become easily distracted • Have difficulty keeping track of what is said?
And the presence of either feature C or D	
C. Disorganized thinking	Is the patient's thinking
	• disorganized • incoherent
	For example, does the patient have
	• Rambling speech/irrelevant conversation • Unpredictable switching of subjects • Unclear or illogical flow of ideas
D. Altered level of consciousness	Overall what is the patient's level of consciousness:
	• Alert (normal) • Vigilant (hyper-alert) • Lethargic (drowsy but easily roused) • Stuporous (difficult to rouse) • Comatose (unarousable)

Supplement 2: Riker's Sedation Agitation (SAS) score

7	Dangerous agitation	Pulling at tracheal tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing side-to-side
6	Very agitated	Does not calm, despite frequent verbal reminding of limits; requires physical restraints, biting tracheal tube
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
4	Non-agitated, Calm and cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands , may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Neuroscience in Anesthesiology and Perioperative Medicine-22 Assessment of New Drug Class with both Anesthetic and Antiepileptic Efficacy on Mouse Neuronal and Astrocyte Mitochondrial Function

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Introduction: Our previous work has demonstrated efficacy of a new chemical class as both an anesthetic and an antiepileptic. Unlike propofol, these compounds produce minimal effects on breathing and hemodynamics in rats. They lack the free imidazole nitrogen of etomidate and therefore do not affect adrenal function. Both in silico and in vitro analyses show that their action is highly specific for a particular binding site within the GABA receptor. In order to advance pre-clinical testing, we screened one member of our class of compounds, KSEB 14-01, for mitochondrial toxicity in primary neuronal and astrocyte cultures from mouse.

Methods: Primary cerebral cortical astrocyte cultures were prepared from postnatal days 1–3 Swiss Webster mice and neuronal cultures were prepared from the cortices of embryonic day 15 or 16 Swiss Webster mice. Prior to treatment cell cultures were incubated with: Mitotracker Green (5μM) to assess mitochondrial density; TMRE (50nM) to asses mitochondrial membrane potential (Ïˆmito); dihydroethidium (10μM) to assess reactive oxygen species (ROS); and DAPI (1:10000) for cell counting. Cultures were then treated with either propofol or KSEB 14-01 (dissolved in 1:5000 DMSO) at final concentrations of 5, 10, or 30μM. ROS and Ïˆmito were measured hourly for 6h after treatment while mitochondrial density and cell proliferation were quantified 24h after treatment.

Results: No significant differences were observed in cell proliferation or mitochondrial density between treatments in either neuronal or astrocyte cultures. In primary neuronal cultures Ïˆmito was decreased at 6h with 5μM propofol and KSEB 14-01 treatment but remained stable with higher doses of propofol and KSEB 14-01. Neuronal ROS generation increased in all groups by 6h but was significantly lower with 10 and 30μM propofol and KSEB 14-01. In astrocyte cultures Ïˆmito was disrupted after 6h incubation with 5μM propofol and KSEB 14-01, while the two higher doses of propofol and KSEB 14-01 significantly preserved Ïˆmito. In all treatment groups astrocyte ROS generation was significantly increased after 6h, with no differences between groups.

Conclusion: Using live-cell fluorescent assays in mouse brain cell cultures with intact mitochondrial reticula, we demonstrate that KSEB 14-01 appears to positively modulate both neuronal and astrocyte mitochondrial function in a dose-dependent manner, similar in effect to propofol. Such mitochondrial preservation characteristics, without the associated detriment in breathing and hemodynamics, continue to favor the development of this new agent and further emphasize the value of such mitochondrial-based analyses. Future in vivo work is warranted to explore the potential role of mitochondrial function in the anesthetic effects of both propofol and KSEB 14-01.

Neuroscience in Anesthesiology and Perioperative Medicine-23 Behavioral and Cognitive Testing in 2-Year-Old Non-Human Primates After Single and Multiple Infant Isoflurane Exposures

Jose F Perez-Zoghbi[1], Viola Neudecker[1], Kristine Coleman[2], Martha Neuringer[2], Alexandra Bemis[2], Bess Glickman[2], Katie J Schenning[3], Damien Fair[3], Lauren D Martin4

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Introduction: Recent clinical studies with prospective assessments revealed that short time exposure of young children to inhaled anesthetics does not impair performance on intelligence tests but affects the children's social behaviors. In non-human primates (NHPs), infant anesthesia exposure causes neurobehavioral impairments, including delayed motor reflex development and increased anxiety-related behaviors assessed by provoked response testing. However, whether anesthesia exposure during infancy also alters spontaneous social behaviors in juvenile NHPs remains unknown. We hypothesized that multiple, but not single, 5-hour long anesthesia exposure in infant NHPs results in impairments in specific cognitive domains and affects anxiety and social behaviors at juvenile age.

Methods: Eight NHPs per group were exposed to isoflurane for 5 hours, either one-time (1X) or three-times (3X) between postnatal day 6 and 12, or a control group was handled similarly, but exposed to room air only. Cognitive testing, assessments of spontaneous behaviors in the home environment, and assessment of inhibition and anxiety behaviors using provoked response testing were performed during the second year of life.

Results: Juvenile NHPs did not show differences in cognitive functions tested, including working memory and cognitive flexibility, nor were there any differences in fine motor skills among groups. However, when observed in their home environment, NHPs in the 3X group showed significantly less close social behavior compared to controls and, provoked testing revealed that NHPs in the 1X group displayed increased anxiety-related behaviors (significantly increased teeth grinding duration and yawning frequency) and were more inhibited towards novel objects than controls.

Conclusion: After single and multiple infant isoflurane exposures, the 2-year-old juvenile NHPs showed a phenotype consisting of more anxious and inhibited behaviors, as well as decreased spontaneous interactions in social groups. However, this phenotype was not accompanied by impairments in any of the cognitive domains tested. These results suggest some parallels with findings in recent clinical studies where exposed children show no cognitive deficits, but secondary outcomes revealed behavioral alterations in social settings reported by parents and caregivers. Our results in NHPs may guide future research in the field of developmental neurotoxicity of anesthetics.

Neuroscience in Anesthesiology and Perioperative Medicine-24 Changes in Brain Functional Connectivity After Infant Anesthesia Exposure Are Associated With Alterations in Social Behaviors in Juvenile Non-Human Primates

Katie J Schenning[1], Oscar Miranda-Dominguez[1], Lauren D Martin[2], Kristine Coleman[3], Viola Neudecker[4], Jose F Perez-Zoghbi[4], Damien Fair[1], Ansgar Brambrink[5]

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Introduction: Recent clinical studies with prospective assessments suggest that anesthesia exposure at a young age does not affect general intelligence/IQ but may result in behavioral alterations later in life. Studies in animals including non-human primates (NHPs) demonstrate several functional alterations after infant anesthesia exposure. We recently found that juvenile 2-year-old NHPs show decreased close social behaviors after infant isoflurane exposure. This phenotype also consisted of increased inhibition and anxiety behaviors but we did not find cognitive impairments. However, whether anesthesia-induced behavioral alterations correlate with changes in functional connectivity of neuronal networks in the brain remains unknown. We hypothesized that isoflurane (ISO) exposures in the first two weeks of life result in changes in functional connectivity of 2-year-old NHPs, and that behavioral alterations at this age can be associated with connectivity changes in specific neuronal networks.

Methods: Resting state-functional connectivity MRI (rs-fcMRI) was performed in 2-year-old rhesus macaques that were exposed to 5 hours of ISO once (ISO 1, n=8), 3 times (ISO 3, n=7) or not at all (control, n=8). Blood-oxygen-level dependent (BOLD) contrast imaging data were grouped into seven neuronal networks and functional connectivity was determined within and between networks. To identify the associations between behavioral outcomes and functional connectivity, linear models using partial least squares regression were fit to predict outcome using connectivity values from different neuronal networks as predictors.

Results: We found that NHPs in the ISO 3 group displayed significantly increased functional connectivity between the auditory and insular-opercular networks compared to the control group, while in the ISO 1 group this increase did not reach significance. The alterations in close social behavior previously reported in these NHPs were correlated with functional connectivity within the insular-opercular network and between the default and dorsal attention networks.

Conclusion: Infant anesthesia exposure in NHPs causes changes in functional connectivity between specific neuronal networks evident at 2-years of age.

Neuroscience in Anesthesiology and Perioperative Medicine-25 Hormone-dependent recovery of hippocampal plasticity following pediatric cardiac arrest in mice.

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[1]University of Colorado, Aurora, CO, [2]University of Colorado, Denver, Aurora, CO, [3]University of Colorado, Anschutz Medical Campus, Aurora, United States of America

Introduction: Pediatric cardiac arrest is a common and devastating condition that remains poorly understood. The estimated incidence is >16,000 arrests per year in the US and unfortunately, the mortality rates are high, with brain injury being the most common cause of death. The sequelae of pediatric cardiac arrest results in a lifetime dependency for all aspects of care. Research on the impact of age on the brain's response to cerebral ischemia often focuses on neonatal or aged animals. In contrast, there are far fewer studies during the peri-pubertal developmental period. Addressing learning and memory deficits in children that have suffered cardiac arrest is critical to allowing survivors to achieve their full potential during critical school years. Here, we take advantage of our unique juvenile cardiac arrest mouse model to interrogate mechanisms of learning and plasticity deficits in the hippocampus.

Methods: Male and female juvenile mice (P21-25) were subjected to 8 minutes of cardiac arrest followed by cardiopulmonary resuscitation (CA/CPR). Mice were left hormonally intact or subjected to gonadectomy 5-7 days after CA/CPR with or without hormone replacement with dihydrotestosterone (males) or estrogen (females). Hippocampal plasticity was assessed by recording long-term potentiation (LTP) via extracellular field recordings in slices obtained from mice at 30 days after CA/CPR (P51-55).

Results: Neuronal injury was similar between males and females subjected to CA/CPR. At 7 days after CA/CPR, LTP was impaired in males and females compared to their respective shams. At 30 days after CA/CPR, LTP recovered to sham levels in hormonally intact mice. Ovariectomy in females or castration in males prevented the recovery in LTP observed at 30 days. Mice that received replacement of respective hormones showed LTP similar to hormonally intact CA/CPR mice and shams. Lack of recovery of LTP in gonadectomized mice correlated with a lack of recovery of BDNF levels seen in hormonally intact mice between 7 and 30 days.

Conclusion: Our results demonstrate a unique capacity for recovery of plasticity in juveniles that is not observed in adults after CA/CPR that occurs during puberty. Recovery of hippocampal plasticity is hormone dependent as removal of circulating hormones prior to puberty prevents juvenile recovery of LTP. Our results implicate circulating estrogen in females and androgens in males as key mediators of recovery observed between adolescence and adulthood, likely through regulation of BDNF expression in the hippocampus.

Neuroscience in Anesthesiology and Perioperative Medicine-26 Imaging Cortical Pain Circuitry During Nitrous Oxide Anesthesia in Mice

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Introduction: Inhalation of nitrous oxide (N2O) provides fast-acting analgesia that is sufficiently potent to be used as the sole anesthetic during labor and minor surgeries. Prior studies identified the midbrain periacqueductal gray (PAG) to be critical for the maintence of N2O induced-analgesia, however, whether N2O acts on brain regions upstream of the PAG, such as the anterior cingulate cortex (ACC), to initiate these effects remains unclear. In the present studies in the mouse, we monitored, over time, the in vivo activity of hundreds of individual ACC neurons during the induction to, and emergence from, N2O anesthesia. To further resolve how N2O acts on local ACC circuitry, we compared its effects on bulk activity (pan-neuronally) versus isolated subpopulations of molecularly-defined inhibitory interneurons (parvalbumin (PV+), somatostatin (SST+) or vasointestinal peptide (VIP+)). Our objective is to uncover the mechanisms through which a major anesthetic, N2O, produces analgesia.

Methods: In adult mice, we monitored the activity of neurons in the ACC, a region that is implicated in the affective component of pain and is a major source of afferent input to the PAG. Spontaneous neural activity was continuously monitored before, during, and after N2O anesthesia. Genetically encoded fluorescent reporters of neural activity (GCaMP6f) were virally delivered either (1) ubiquitously across neurons (bulk), or (2) specifically within molecularly-defined interneuron populations (PV+, SST+, or VIP+). Changes in GCaMP6f fluorescence were captured via Inscopix miniscopes.

Results: During the induction of N2O anesthesia, we observed a significant increase in the spontaneous activity of the bulk, SST+ and PV+ populations. Interestingly, SST+ interneurons have two activity peaks during N2O induction, an early phase that precedes increased activity in other populations, followed by a second phase that coincides with peak activities of the bulk and PV+ populations. Overall, VIP+ interneuron activity was unaffected during N2O induction. The activity of bulk, SST+, PV+, and VIP+ populations is greatly decreased during emergence from N2O, as compared to baseline activity prior to N2O exposure.

Conclusion: In patients and animals, decreases in ACC activity are generally associated with analgesia. Unexpectedly, N2O increased ACC activity, which is consistent with our hypothesis that the analgesic action of N2O involves the upstream activation of the PAG by the ACC. Importantly, we found that N2O differentially modulates the activity of functionally distinct subpopulations of ACC neurons, providing additional circuit mechanisms for explaining the analgesic effects of N2O. Lastly, we show that ACC activity is reduced during emergence from N2O, which may explain the cognitive effects witnessed after N2O anesthesia. As the recording arrangement permits concurrent behavioral analysis, we plan to probe the effects of N2O on noxious stimulus-evoked ACC activity and behavioral indices of nociceptive processing.

Neuroscience in Anesthesiology and Perioperative Medicine-27 Nicotinamide mononucleotide inhibits brain mitochondria fragmentation and free radicals generation following global cerebral ischemia in mouse

Tibor Kristian[1], Aaron Long[1], Nina Klimova[1]

[1]University of Maryland Baltimore, Baltimore, MD

Introduction: Global cerebral ischemia depletes brain tissue NAD+ leading to bioenergetics failure and cell death. The postischemic NAD+ levels can be replenished by the administration of nicotinamide mononucleotide (NMN), which serves as a precursor for NAD+ synthesis. We have shown that NMN administration shows protection against ischemic brain damage and inhibits post-ischemic hippocampal mitochondrial fragmentation. To understand the mechanism of NMN-induced modulation of mitochondrial dynamics and neuroprotection we used our transgenic mouse expressing mitochondria targeted fluorescent protein in neurons (mito-eYFP) and with disrupted gene of NAD+-dependent deacetylase sirt3 (SIRT3KO).

Methods: Animals were subjected to transient global cerebral ischemia and at 30 minutes of recovery a single dose of NMN (60 mg/kg) or PBS was administered via intraperitoneal (i.p.) injection. At 2, 4 and 24 hours of recovery brains were processed for analysis. Acetylation of isolated hippocampal mitochondrial proteins was determined using western blots as well as immunoprecipitation. Hippocampal mitochondria NAD+ levels were measured by cycling enzymatic assay. Post-ischemic reactive oxygen species (ROS) generation in brain was studied by treating the animals with dihydroethidium (DHE). DHE reacts with ROS generating fluorescent hydroxyethidium, which can then be visualized and quantified in brain tissue. Additionally, mito-eYFP brains were perfusion fixed and CA1 mitochondrial length measured using confocal microscopy with Volocity software. Brain section were also immunostained with fission active form of Drp1, pDrp1 (S616) antibody.

Results: Post-ischemic mitochondrial NAD+ levels were depleted leading to an increase in mitochondrial protein acetylation, high ROS production, and excessive mitochondrial fragmentation. Administration of a single dose of NMN normalized hippocampal mitochondria NAD+ pools, protein acetylation, and ROS levels. These changes were dependent on SIRT3 activity, which was confirmed using SIRT3KO mice. Ischemia induced increase in acetylation of the key mitochondrial antioxidant enzyme superoxide dismutase 2 (SOD2) that resulted in inhibition of its activity. This was reversed after NMN treatment leading to reduction of ROS generation and suppressed mitochondrial fragmentation. Specifically, we found that the interaction of mitochondrial fission protein, pDrp1 (S616), with neuronal mitochondria was inhibited in NMN treated ischemic mice.

Conclusion: Our data provides a novel link between mitochondrial NAD+ metabolism, ROS production, and mitochondrial fragmentation. Using NMN to target these mechanisms could represent a new therapeutic target for treatment of acute brain injury and neurodegenerative diseases.

Neuroscience in Anesthesiology and Perioperative Medicine-28 Plasma Neuronal Injury Biomarker, Tau, Is Associated with Postoperative Delirium & Predicts Resolution of Symptoms in a Prospective Cohort Study

Richard Lennertz[1], Tyler Ballweg[1], Cameron Casey[1], Marissa White[1], Amber Bo[1], Margaret Parker[1], Zahra Farahbakhsh[1], Austin Kayser[1], Alexander Blair[1], Heidi

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Introduction: Postoperative delirium is associated with a rise in the neuronal injury biomarker neurofilament light (NfL). We tested whether the neuronal biomarkers Tau and glial fibrillary acidic protein (GFAP) are superior for tracking acute injury and postoperative delirium.

Methods: 114 surgical patients were recruited into parallel prospective biomarker cohort studies with assessment of delirium severity and incidence (NCT03124303, NCT02926417). Plasma samples were sent for biomarker analysis for Tau, NfL and GFAP, as well as a panel of 10 cytokines. A priori we determined that any biomarker of interest would vary with delirium incidence, change proportionately to delirium severity and independently from inflammation (IL-8).

Results: GFAP levels showed no relationship to delirium. The change in Tau on postoperative day 1 was higher in patients with postoperative delirium (p=0.008) and correlated with delirium severity (r=0.38, p=0.0003). After adjusting for age, sex, preoperative cognition and change in IL-8, Tau remained significantly associated with delirium severity (p=0.017). Tau, but not NfL or IL-8, successfully classified delirium incidence (area under receiver operated curve, 0.70, 95% confidence interval 0.58 to 0.81) and predicted recovery of delirium symptoms (linear mixed effect model p=0.007 for interaction with time).

Conclusion: Changes in plasma tau were associated with delirium incidence and severity, and they resolved in conjunction with delirium symptoms. These finding support a possible causal role of neuronal injury with delirium pathogenesis. As Tau more closely tracked delirium status compared to other biomarkers, perhaps because it is cleared more quickly, the impact of perioperative Tau on long-term cognition merits further investigation.

Neuroscience in Anesthesiology and Perioperative Medicine-29 Propofol is associated with prolonged ICU and hospital length of stay and increased disability after endovascular treatment of unruptured cerebral aneursym

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Introduction: There are no current studies to assess the effects of intraoperative anesthetics for Unruptured intracranial aneurysm (UIA) management. We investigate the relationship between the choice of anesthetic and outcomes among UIA patients.

Methods: We performed a retrospective, cross-sectional analysis of data from the BIDMC anesthesia research repository for UIA management between 2014 - 2018.

Results: From a total of 1004 patients, 703 patients underwent endovascular treatment, and 301 patients underwent open craniotomy. Patients who underwent open craniotomy had a more extended follow-up period and increased Hospital and ICU length of stay (LOS). Still, there was no difference between neurological outcomes among the two groups. Looking at different anesthetic agents, the patients who received propofol had a more prolonged ICU and hospital LOS ($P<0.001$). Looking closer to this group of patients, the ones who received propofol had a more extended hospital and ICU LOS only if they had endovascular treatment ($P<0.001$). In univariate analysis of the choice of anesthetic agents, patients were stratified by Modified Rankin Scale (mRS) in three groups of neurologically intact, good, and poor outcomes. The proportion of patients who were not in the neurologically intact group was significantly higher among those who received propofol infusion during UIA treatment compare to those who did not receive propofol infusion during operation ($p=0.008$).

Conclusion: Long term neurological outcomes of both types of managements shows no differences. We also showed that propofol is associated with prolonged ICU and hospital length of stay and increased disability after endovascular treatment of the unruptured cerebral aneurysm.

Figure 1. Flow chart of inclusion criteria

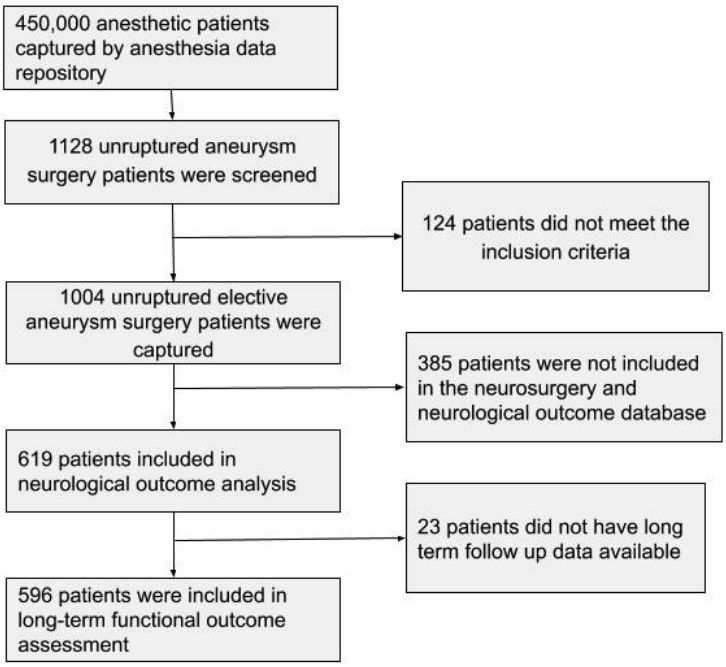
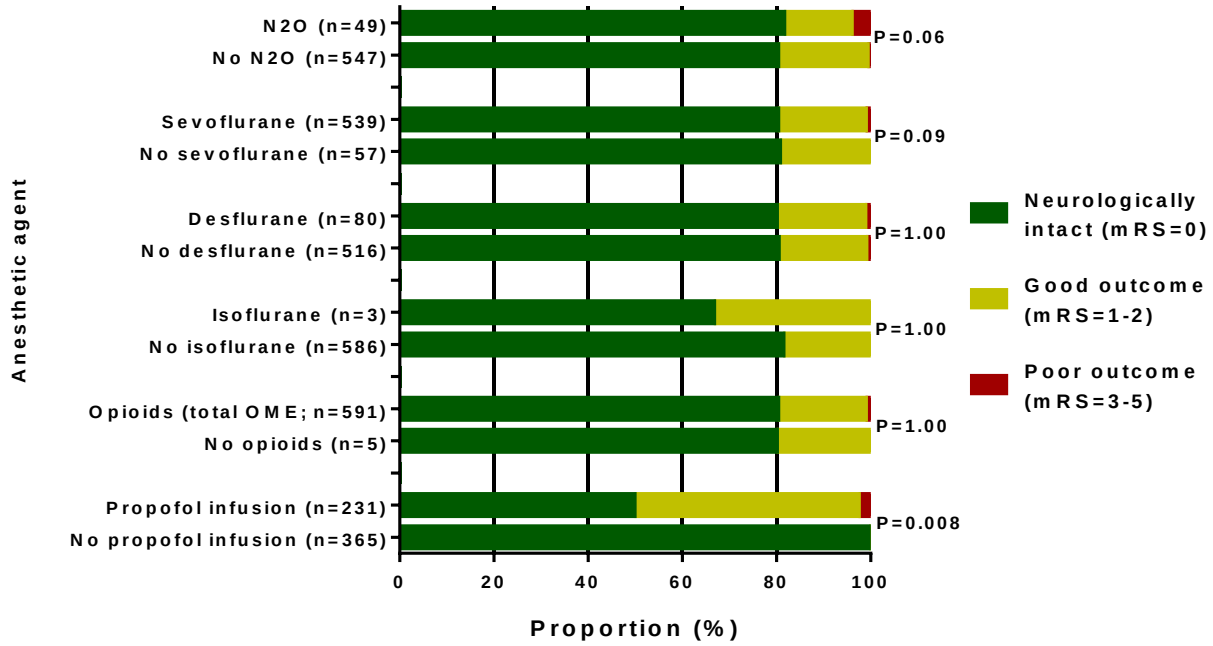


Figure 2. Anesthetic agent and functional outcome at last clinical visit



Follow up was 5 (IQR 1-12) months for endovascular and 8 (IQR 3-13) months for open craniotomy patients; mRS=modified Rankin Scale for Neurologic Disability; OME=oral morphine equivalent of opioid.

Table 1. Demographic and clinical features of the study cohort (Total N=1004)

	Endovascular N=703	**Open Craniotomy N=301**	**P value**
Demographic features			
Age (years)	59 ± 12	56 ± 11	< **0.001**
Sex			
Female	537(76%)	221 (73%)	0.35
Male	166 (24%)	80 (27%)	
BMI	28 ± 6	27± 5.7	0.08
ASA Status	2.7± 0.6	2.7 ± 0.5	0.89
Anesthetic agents			
N_2O			
Yes	52(8%)	21(6%)	0.91
No	651(92%)	280(94%)	
Sevoflurane			
Yes	636(90%)	274(91%)	0.87
No	67(10%)	27(9%)	
Desflurane			
Yes	69(10%)	36(12%)	0.36
No	634(90%)	265(88%)	
Isoflurane			
Yes	2(0.2%)	22(7%)	< **0.001**
No	701(99.8%)	279(93%)	
Opioids (total OME)			
Yes	682(97%)	300(99%)	**0.01**
No	21(3%)	1(1%)	
Propofol infusion			
Yes	675(96%)	300(99%)	**0.003**

No	28(4%)	1(1%)	
Treatment			
Clipping	0	301(100%)	
Coiling	283(40%)	0	
Stent-assisted coiling	48(7%)	0	
PED	6(1%)	0	
Coiling + PED	366(52%)	0	
Outcome parameters			
Follow Up (months)	5(IQR 1-12)	8(IQR 3-13)	< **0.001**
ICU admission			
Yes	480 (68%)	231(77%)	< **0.001**
No	223(32%)	70(23%)	
ICU Length of stay (days)	2(IQR 0-2)	2 (IQR 2-3)	< **0.001**
Hospital Length of stay (days)	2(IQR 2-3)	4 (IQR 3-5)	< **0.001**

BMI=Body Mass Index, ASA status= American Society of Anesthesiologists physical status, OME= Oral Morphine Equivalent of Opioid. Data are presented as mean ± standard deviation, median (interquartile range), or proportions, and compared using t-tests, Wilcoxon signed rank test, and chi-square tests, respectively.

Table 2. Comparison of outcome parameters among patients underwent unruptured aneurysmal surgery based on the anesthetic choice (N=1004)

Anesthetic Agent	**ICU Length of stay** (days)	**Hospital Length of stay** (days)
Propfol infusion		
Yes	2(IQR 2-3)	4(IQR 3-6)
No	2(IQR 0-2)	2(IQR 2-3)
P value	**< 0.001**	**< 0.001**
Sevoflurane		
Yes	2(IQR 0-2)	3(IQR 2-4)
No	2(IQR 0-2)	3(IQR 2-4)
P value	0.85	0.51
Desflurane		
Yes	2(IQR 0-2)	3(IQR 2-3)
No	2(IQR 0-3)	3(IQR 2-4)
P value	0.17	0.29
N_2O		
Yes	2(IQR 0-3)	3(IQR 2-4)
No	2(IQR 0-2)	3(IQR 2-4)
P value	0.98	0.68

Data are presented as median (interquartile range) and compared using Wilcoxon signed rank test.

Table 3. Comparison of outcome parameters among patients underwent unruptured aneurysmal surgery and were administered propofol based on the type of surgery (Total N=1004)

Propofol infusion	**ICU Length of stay** (days)	**Hospital Length of stay** (days)
Endovascular treatment (N= 703)		
Yes	2(IQR 2-15)	3(IQR 2-16)
No	2(IQR 0-2)	2(IQR 2-3)
P value	**< 0.001**	**< 0.001**
Open craniotomy (N= 301)		
Yes	2(IQR 2-3)	4(IQR 3-5)
No	2(IQR 0-3)	3(IQR 3-5)
P value	0.07	0.19

Data are presented as median (interquartile range) and compared using Wilcoxon signed rank test.

Neuroscience in Anesthesiology and Perioperative Medicine-30 Temporal trend of mechanical thrombectomy utilization in treatment of perioperative ischemic stroke following elective inpatient surgery in the United States

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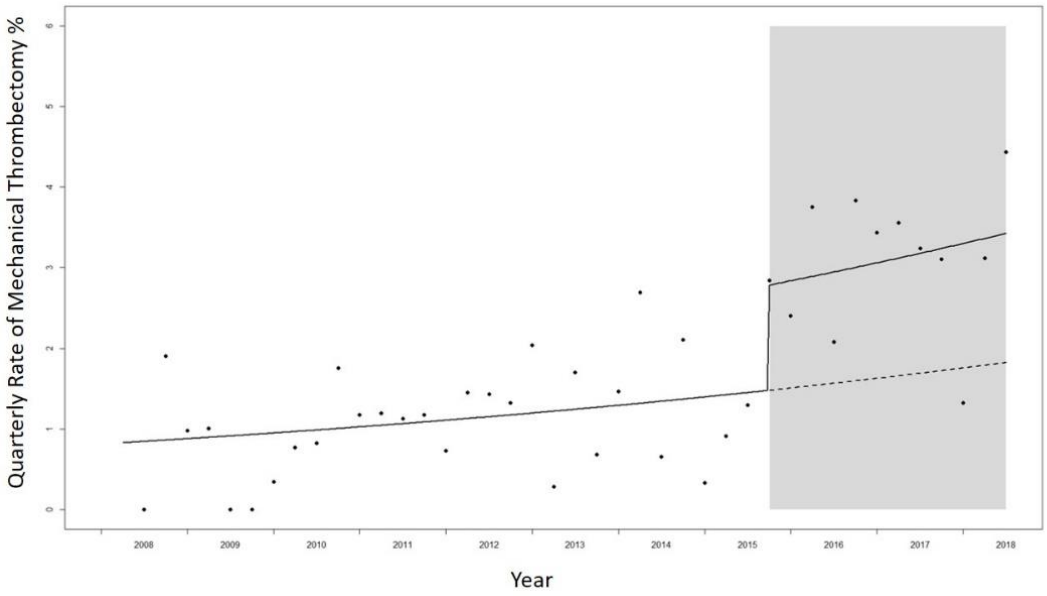
Introduction: Perioperative ischemic stroke significantly increases morbidity and mortality in patients undergoing elective surgery. Mechanical thrombectomy can improve outcomes of ischemic stroke caused by large vessel occlusion, but the frequency and trend of its utilization for treatment of perioperative ischemic stroke is not studied.

Methods: In this retrospective observational study using the Premier Healthcare Database, we identified adults who underwent elective inpatient surgery from 2008 to 2018. Patients with perioperative ischemic stroke were identified using the established International Classification of Diseases (ICD) ninth revision codes or equivalent ICD, tenth revision codes. Cases that underwent mechanical thrombectomy were further identified using established ICD9 and ICD10 procedure codes. Descriptive statistics were used to compare patient and center level characteristics between patients who received mechanical thrombectomy versus did not after perioperative ischemic stroke.

Results: Of 6,349,668 patients with elective inpatient surgery, 12,507 (0.2%) had perioperative ischemic stroke. The mean age (and standard deviation) of these patients was 69.5 (11.7) years, and 48.8% were female. Mechanical thrombectomy was used in 1.7% of all patients with perioperative ischemic stroke and its use increased from 0.0% in 3rd quarter, 2008 to 4.4% in 4th quarter, 2018. There was a significant increase in the use of mechanical thrombectomy after 3rd quarter, 2015 when mechanical thrombectomy use was incorporated in acute stroke treatment guideline (1.14% before 3rd quarter, 2015 versus 3.07% after; $p<0.0001$). Amongst patients with perioperative ischemic stroke, patients who received mechanical thrombectomy were more likely to have their surgery performed at a teaching institute (67.3% versus 53.9%).

Conclusion: Although there was a significant increase in rates of utilization of mechanical thrombectomy after guidelines were changed, rates of utilization remain low, especially in non-teaching hospitals. This highlights improvements in the management of perioperative ischemic strokes and further opportunities to improve outcomes.

Figure: Trend of patients treated with mechanical thrombectomy for perioperative ischemic stroke by quarter



Neuroscience in Anesthesiology and Perioperative Medicine-31 Transcriptomic Analysis of Thoracic Spinal Cords in Experimental Pulmonary Hypertension Reveals Novel Therapeutic Targets

Asif Razee[1], Jason Hong[2], Varina R Clark[3], Emma Said[3], Michael Zargari[1], Louis Saddic[3], Soban Umar[1]

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Introduction: Pulmonary hypertension (PH) is an incurable disease characterized by pulmonary artery pressure overload, right ventricular (RV) hypertrophy, failure, and death. PH is associated with sympathetic activation, however the involvement of spinal cord-lung-heart axis is yet to be investigated. Here, we performed the first ever transcriptome analysis of thoracic spinal cords in two pre-clinical rat models of PH using bioinformatics approach.

Methods: Male Sprague Dawley rats (~300g) received either Monocrotaline (MCT, 60mg/kg, s.c., n=8) and were followed for 30 days or Sugen (Su/Hx group, 20mg/kg, s.c., n=9) and kept in hypoxia (10% O2) for 3-wks followed by 2-wks of normoxia. Saline treated rats served as controls (CTRL, n=10). Echo and RV catheterization were performed terminally. Hearts, lungs and spinal cords were harvested and lung histology was assessed by Trichrome staining. RNASeq was performed on thoracic spinal cords. Differential expression analysis was conducted using R-program. RT-qPCR was performed for gene validation. Values are mean±SEM and $p<0.05$ is considered significant.

Results: Severe PH was confirmed by increased RV systolic pressure (RVSP, mmHg) in MCT (97.6±6.6) and Su/Hx (85.26±15.6) compared to CTRL (37.1±1.3; $p<0.05$). RV hypertrophy index (RV/LV+IVS) was significantly increased in MCT (0.82±0.07) and Su/Hx (0.61±0.1) compared to CTRL (0.27±0.01; $p<0.05$). MCT and Su/Hx rats demonstrated increased pulmonary vascular remodeling. RNASeq demonstrated differential expression of multiple pathways and genes in thoracic spinal cords of both models. Gene Set Enrichment Analysis revealed 14 significantly upregulated pathways in both MCT and Su/Hx among which 12 were overlapping. From these overlapping pathways 162 leading edge genes had significantly increased expression in MCT, 171 genes in Su/Hx and 168 overlapping genes in both models. Conversely, 9 pathways were significantly downregulated in MCT, among which 8 were overlapping in both models. From these overlapping pathways 77 leading edge genes had significantly decreased expression in MCT, 93 leading edge genes in Su/Hx and 360 overlapping genes in both. Both MCT and Su/Hx revealed similar significant up-regulation of hedgehog signaling, IL6 JAK STAT3 signaling, KRAS signaling, epithelial mesenchymal transition, apical junction and apical surface pathways and down-regulation of E2F target, DNA repair and fatty acid oxidation pathways. RNASeq data were validated with PCR by selecting several key dysregulated genes from hedgehog signaling (SLIT1), IL6 JAK STAT3 signaling and KRAS signaling (CNTFR), epithelial mesenchymal transition (TGFβ1), apical junction (VWF), apical surface (CX3CL1), E2F target (SMC4), DNA repair (RALA), and fatty acid metabolism (IDI1).

Conclusion: Severe PH in rats demonstrates characteristic transcriptome signature of thoracic spinal cords. Targeting these specific pathways and genes may yield novel therapeutic strategies for this incurable disease.

Obesity

Obesity-1 Impact of Perioperative IV Lidocaine Duration on Opioid Use, Pain Scores and Antiemetic Needs Following Sleeve Gastrectomy

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Introduction: Intravenous lidocaine (IVL) infusion is an effective analgesic in abdominal surgery[1]. Potential benefits of a prolonged IVL infusion following bariatric surgery have not been systematically investigated[2]. We hypothesized that extending IVL beyond the postoperative recovery room (PACU) stay to a total of 12 hours would reduce perioperative opioid consumption, VAS (0-10) pain scores and antiemetic use in the context of intraoperative multimodal opioid sparing analgesia.

Methods: Following IRB approval we retrospectively analyzed prospectively collected QA/QI data of 2 consecutive patient groups; Control (IVLP; before intervention) and Intervention (IVLF; after intervention implementation). All patients underwent laparoscopic sleeve gastrectomy (LSG) by a single surgeon (SS) under general anesthesia including standardized multimodal analgesia (acetaminophen, dexmedetomidine, ketamine, dexamethasone, lidocaine infusion). IVLP and IVLF groups received IV lidocaine at 1.5 mg/kg/hr adjusted body weight (100kg max) intraoperatively. In IVLP patients IVLido continued for 4 hours or to the end of their PACU stay and in IVLF patients IVLido was continued to the floor for a total of 12 hours. Data collection included demographic characteristics, in-hospital morphine milligram equivalent (MME) use, VAS 0 - 10 pain scores, and floor antiemetic use. Wilcoxon Rank Sum test was used to determine differences in median MME between groups. A multivariate regression accounting for age, gender, intraoperative multimodal analgesia, procedure duration, IVLF and intraoperative MME was employed to explore differences in total MME between groups. A $p < 0.05$ was considered statistically significant.

Results: Records of 117 patients met inclusion criteria, 46 and 71 for the IVLP and IVLF groups respectively. One patient in each group was excluded as an MME outlier. Demographic characteristics, opioid use, pain and antiemetic use outcomes are summarized in tables 1 and 2 respectively for all 115 patients. The IVLP group received lidocaine for a median of 4 hours and 46 minutes. Median Floor MME use was reduced by 29 mg (44%) in the IVLF group without reaching statistical significance ($p=0.11$). In this group there was also a trend for less total hospital stay MME (- 19.5 MME median, 17.7% reduction), and no difference in Floor antiemetic use compared to the IVLP group. In the multivariable logistic regression analysis there was no significant difference for total MME use adjusting for age, gender, intraoperative multimodal analgesia, procedure duration and IVLF, whereas floor VAS scores (floor) were significantly lower with greater age ($p < 0.001$) and in men compared to women ($p=0.025$).

Conclusion: In patients undergoing sleeve gastrectomy with multimodal intraoperative analgesia, extension of a lidocaine infusion from 4 to 12 hours perioperatively conferred a clinically meaningful reduction in total hospital and floor MME use. These consistent trends did not reach statistical significance. Pain control and antiemetic use on the floor were unaffected. In this population, a wide range of postoperative opioid consumption was observed resulting in a statistically non-significant outcome difference given our sample size. These results justify a larger, appropriately scaled study of extended perioperative IV lidocaine, and research to explain the wide range of postoperative opioid requirements in bariatric surgical patients. Our findings confirm the significance of age and gender for pain perception. Study limitations include the small sample size and the retrospective study design.

Reference(s): 1. Anesthesiology 2017;126:7292. Surg Obes Relat Dis 2017;13:523

Table 1. Demographic characteristics

Demographics	IVLP (n=45)	IVLF (n=70)	Total Cohort (n=115)	P-value
Age (years, mean/SD)	40.56 ± 11.55	41.56 ± 12.68	41.17 ± 12.21	0.66
Gender (F/M)	F: 34 (75.56%) M: 11 (24.44%)	F: 49 (70%) M: 21 (30%)	F: 83 (72.17%) M: 32 (27.83%)	0.516
BMI (kg/m^2)	44.87 ± 5.87	44.07 ± 7.05	44.38 ± 6.60	0.51
Procedure Duration (min, mean/SD)	53 ± 10	55 ± 26	54 ± 21	0.58
Number of intraop non-opioid analgesics used (median, range)	6 (2-8)	6 (4-8)	6 (2-8)	0.158
Median Preoperative baseline pain (VAS 0-10, range)	0 (0-8)	0 (0-8)	0 (0-8)	0.519

IVLP: IV Lidocaine to PACU, IVLF: IV Lidocaine to Floor, SD:Standard Deviation, F/M:female/male, BMI:Body Mass Index, VAS:Visual Analog Scale

Table 2. Outcomes

Outcomes	IVLP (n=45)	IVLF (n=70)	Total Cohort (n=115)	P-value
Total Hospital MME (median, range)	110.3 (10.5 – 532)	90.8 (6.7 – 365.5)	100.7 (6.7 – 532)	0.14
Floor MME (median (range))	65 (0-282.5)	36 (0- 301.5)	51 (0- 301.5)	0.11
Floor VAS (0-10, median, range)	3.5 (1.9 – 6.7)	3.8 (1.9 – 7.5)	3.7 (1.9 – 7.5)	0.42
No floor antiemetic requirement % (n)	53.3% (24)	44.3 % (31)	N/A	0.34

IVLP: IV Lidocaine to PACU, IVLF: IV Lidocaine to Floor, MME:Morphine Milligram Equivalents, VAS:Visual Analog Scale

Obstetric Anesthesiology

Obstetric Anesthesiology-1 Longitudinal Evaluation of Endothelial Function and Arterial Stiffness In Early vs. Late Onset Preeclampsia

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Introduction: Endothelial dysfunction (ED) and arterial stiffness (AS) appear to precede the clinical onset of preeclampsia (PE), and persistent ED is proposed as the underlying mechanism causing coronary artery disease and stroke later in life in women with a history of PE (1). Prior studies show up to 50% of women with early onset PE (EOPE) have ED years after delivery, while it is absent with late onset PE (LOPE) (2). We hypothesized that the prevalence of ED is greater with EOPE, and that in contrast to LOPE, features of AS are worse and persist well beyond postpartum in EOPE.

Methods: Women with PE were enrolled at the time of delivery and categorized as having EOPE (≤34 weeks) or LOPE (> 34 weeks) (4). The EndoPAT2000, validated for use in preeclampsia, was used to quantify ED with the reactive hyperemia index (RHI), and AS with augmentation index (AI) (2.3). Measures were taken longitudinally once at 24-72h after delivery and again at 6 weeks postpartum. Paired t-tests were used to compare RHI and AI, and Fisher's exact test was used to compare the proportion of ED and AS among women with EOPE versus LOPE.

Results: In this ongoing study, 17 women (8 EOPE, 9 LOPE) completed the 6-week follow up. There was no difference in the proportion of women with ED in the early or late onset PE groups after delivery (29 vs. 28% p=0.71) or at 6 weeks (33 vs. 50%, p=0.64). There was no difference in RHI at 6 weeks in the EOPE group (Delta RHI –0.00 [95% -0.70- 0.69]) or LOPE group (Delta RHI 0.15 [95% CI -0..45 - 0.75]). Both EOPE and LOPE patients had improvements in arterial elasticity as evidenced by lower AI at 6 weeks, however this change was only significant in the EOPE group (Delta AI 14.4% [95% CI 0.17-28], Pr(|T| > |t|) = 0.048).

Conclusion: We found endothelial dysfunction occurs equally in EOPE and LOPE and does not persist in women with EOPE. The overall lower prevalence of endothelial dysfunction after delivery may be due to intensive medical management of preeclampsia with magnesium and antihypertensives in the peripartum period (5). At 6 weeks, most women showed improved arterial elastance. Other biological measures (e.g. biomarkers) of endothelial dysfunction should be assessed to further examine the recovery trajectory of endothelial dysfunction among women with EOPE.

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5. Circulation. 2000;102:2353-2358

Obstetric Anesthesiology-2 Pharmacologic inhibitors of the calcium-activated chloride channel ANO1 have increased potency under inflammatory conditions in uterine smooth muscle

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Introduction: Inflammation is a complex process involved in many disorders. While inflammation may serve an adaptive role in normal physiology, inappropriately triggered inflammation can lead to disease. For example, it is recognized that inflammation plays a critical role both in the initiation of normal labor and as a pathological trigger to induce inappropriate preterm labor. [1, 2, 3] The Gallos lab has investigated the role of the calcium-activated chloride channel, ANO1, in uterine excitability and contractility and as a target for treating preterm labor. [4] As inflammation enhances uterine excitability and ANO1 is involved in uterine excitability, we questioned if an inflammatory milieu would enhance ANO1's role in uterine excitability and contractility.

Methods: With IRB approval (#AAAL4005), late gestation, human USM was harvested from healthy patients undergoing elective C-section. Tissues were enzymatically dissociated to establish in vitro primary cultures as well as cut into strips for ex vivo organ bath experiments. Strips and cells were treated with LPS 100 ng/mL or TNFα 10 ng/mL for 3 days, and acutely treated with ANO1 inhibitors MONNA or benzbromarone. Ex vivo uterine strip contractility was assessed mechanically as both integral force and motility index, while in vitro USM was assessed using the ratiometric fluorescent calcium indicator Fura-2 and a Flexstation 3 Platereader.

Results: MONNA and Benzbromarone show increased potency in reducing agonist-induced Ca2+ flux after receiving treatment with LPS 200 ng/mL for 3 days. MONNA IC50 for Thrombin (1 U/mL)-induced and oxytocin (500 nM)-induced Ca2+ release reduces from 27.9 to 22.9 µM ($p = 0.044$) and from 22.7 to 16.6 µM ($p = 0.0153$), respectively. Benzbromarone IC50 for Thrombin (1 U/mL)-induced Ca2+ release reduced from 10.57 to 8.55 µM ($p = 0.0478$). Organ bath experiments are still pending.

Conclusion: ANO1 has an upregulated role in uterine contractility in inflammatory conditions.

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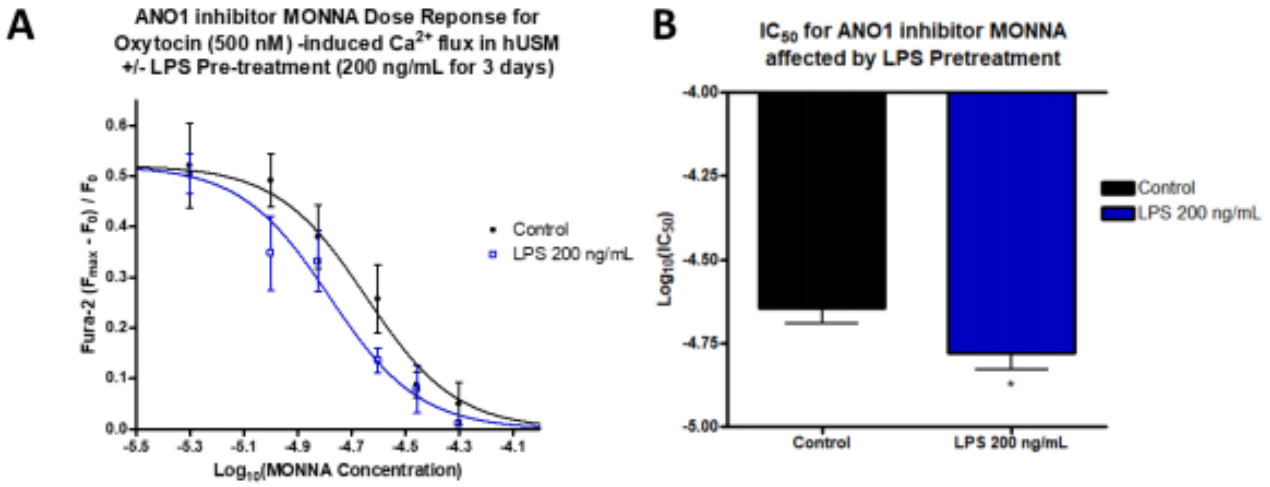

ANO1 inhibitor MONNA has increased potency under inflammatory conditions, generated by LPS 200 ng/mL pre-treatment for 3 days. A) A dose response of MONNA's effect on oxytocin-induced calcium flux in cultured hUSM cells. MONNA has a greater effect at each respective dose in hUSM pre-treated with LPS 200 ng/mL, with an overall left shift of the dose response curve. B) IC_{50} of MONNA's inhibition of oxytocin-induced Ca^{2+} flux between control and LPS pretreated hUSM, 22.7 µM vs. 16.6 µM ($p = 0.0153$), respectively.

Obstetric Anesthesiology-3 Patterns of Fibrinolysis Shutdown, Physiologic Fibrinolysis, and Hyperfibrinolysis in Postpartum Hemorrhage

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Introduction: Physiologic fibrinolysis (PHY), hyperfibrinolysis (HYP), and fibrinolysis shutdown (FSD) are described in traumatic hemorrhage based on thromboelastography (TEG). HYP and FSD are independently linked to trauma mortality. Postpartum hemorrhage (PPH) is a frequent, preventable cause of maternal death, but fibrinolysis phenotypes in PPH are not well-defined. Our primary aim was to describe fibrinolytic phenotypes in PPH. The secondary aim was to quantify outcomes associated with PHY, HYP, and FSD: mortality, thromboembolism, transfusion requirements, and intensive care unit (ICU) and hospital length of stay.

Methods: After IRB approval, TEG results and medical records for cesarean and vaginal deliveries from 1/1/2012 - 12/31/2016 at a high-risk center were reviewed. Cases with TEG done during PPH were included. Controls were cases where TEG was done for non-PPH reasons (i.e. routine cesarean with physician-judged increased risk for bleeding, with or without observed abnormal bleeding). Cases were excluded if percentage of fibrinolysis at 30 minutes (LY30) was missing or if antifibrinolytics/anticoagulants were given prior to TEG. Severe PPH was defined as 1) decrease in hemoglobin >4g/dL; 2) hemostatic procedure; 3) transfusion ≥4 red cell units; 4) blood loss (EBL) >2 liters; or 5) death [1]. Non-severe PPH was defined as EBL ≥500 mL (vaginal) and ≥1000mL (cesarean). FSD was defined as LY30 <0.8; PHY was LY30 0.08 to 3.0, and HYP was LY30>3.0. Descriptive statistics were performed for demographic variables. Odds ratios for severe PPH were calculated by fibrinolysis groups. PHY, FSD, and HYP rates were calculated and compared across hemorrhage groups. A P-value <0.05 was considered significant.

Results: 446 unique TEGs were performed on 196 cases during the study period. Demographic traits were similar between groups (Table 1). FSD was observed in 77.4% (345) TEGs, while PHY and HYP were observed in 15.7% (70) and 7.0% (31) respectively. Odds of FSD and PHY were not elevated for severe PPH, but odds of HYP was 4.5 times higher in severe PPH (OR 4.5, 95%CI 1.5-19.4, P=0.02, Table 2). TEG values (R and MA) were statistically, but not clinically, different across hemorrhage groups (Table 3). Fibrinogen levels were lower in severe PPH, but higher than the 150 mg/dL quoted in published literature[1] (severe PPH average fibrinogen, 260±140 mg/dL v. non-severe PPH 420±123 mg/dL v. no hemorrhage 389±144 mg/dL, P<0.001). Mortality, thromboembolism, transfusion requirement, and ICU length of stay were not different across PHY, HYP, and FSD groups. Hospital length of stay was longer for PHY (7.1±10.8 days v. FSD 5.0±5.4 days v. HYP 6.6±6.5 days, P=0.046).

Conclusion: FSD is common in PPH. Odds of HYP, but not FSD and PHY, are significantly elevated in severe PPH. These findings require corroboration by prospective evaluation.

Reference(s): 1. Charbit. J Thromb Haemost. 2007;5:266

Table 1. Demographic, obstetric, and laboratory characteristics of the study population.

	FSD [N=345]	PHY [N=70]	HYP [N=31]	*P*-value
Age (years)	30.68 ±5.54	30.77 ±5.85	31.16 ±6.23	0.90
Obstetric Characteristics				
Estimated gestational age (weeks)	35.59 ±5.95	35.20 ±4.86	35.91 ±4.12	0.82
Gravidity	2 (3)	2 (3)	3 (2)	0.60
Parity	1 (2)	1 (2)	1 (2)	0.18
BMI (kg/m^2)	33.48 ±7.62	31.11 ±6.41	32.88 ±4.15	0.11
Vaginal delivery (frequency)	11.01% [38]	17.14% [12]	9.68% [3]	0.33
Cesarean delivery (frequency)	85.09% [291]	77.94% [53]	90.32% [28]	0.21
Clinical Outcomes				
ICU LOS (days)	0.91 ±1.66	0.74 ±1.28	1.35 ±3.46	0.28
Death (frequency)	0	0	0	1.00
Hospital LOS (days)	5.03 ±5.44	7.07 ±10.83	6.55 ±6.49	0.046 *
Maternal blood transfusion (frequency)	43.48% [150]	41.43% [29]	54.84% [17]	0.43
Maternal thromboembolism (frequency)	0.58% [2]	0.0% [0]	0.0% [0]	1.00
Traditional Laboratory Values				
Fibrinogen (mg/dL)	291.64 ±155.90	288.51 ±126.47	297.90 ±135.31	0.80
Platelets (count per µL)	134.81 ±67.39	140.26 ±66.97	173.25±78.61	0.02 *

Data are reported as mean ± standard deviation, percentage [N], or median (IQR). FSD, fibrinolysis shutdown; PHY, physiologic fibrinolysis; HYP, hyperfibrinolysis; ICU, intensive care unit; LOS, length of stay; TXA, tranexamic acid; BMI, body mass index. Platelet counts and fibrinogen levels were drawn within 2 hours of TEG performance.

**P<0.05*

Table 2. Odds of fibrinolytic phenotypes given hemorrhage severity

	No Hemorrhage [N=134]	Non-severe PPH [N=78]	Severe PPH [N=234]
FSD [N=345]	reference	0.86 (0.44-1.74) *P* = 0.68	0.73 (0.43-1.2) *P* = 0.24
PHY [N=70]	reference	0.79 (0.35-1.7) *P* =0.56	0.88 (0.5 – 1.6) *P* =0.65
HYP [N=31]	reference	3.64 (0.93 – 17.6) *P* =0.07	4.53 * (1.5-19.4) *P* =0.016 *

FSD, fibrinolysis shutdown; PHY, physiologic fibrinolysis; HYP, hyperfibrinolysis; PPH, postpartum hemorrhage
**P<0.05*

Table 3. Clinical and TEG characteristics by hemorrhage phenotypes

	Severe PPH [N=234]	Non-severe PPH [N=78]	No Hemorrhage [N=134]	*P*-value
R time (min)	4.72 ±2.17	6.66 ±5.68	5.95 ±1.85	<0.0001 *
K time (min)	2.07 ±2.28	2.26 ±4.62	1.63 ±0.56	0.16
α Angle (degrees)	65.22 ±13.81	67.88 ±13.52	67.92 ±6.09	0.06
MA (mm)	62.02 ±14.15	65.78 ±26.07	67.43 ±17.51	0.01 *
LY30 (%)	1.36 ±4.94	0.91 ±2.40	0.45 ±0.92	0.08
Fibrinogen (mg/dL)	259.89 ±139.32	419.60 ±121.92	388.83 ±144.23	<0.0001 *
Cell salvage (mL)	330.26 ±400.05	31.84 ±80.81	8.37 ±41.11	<0.0001 *
Platelets (count per μL)	133.13 ±61.63	192.16 ±77.04	118.96 ±61.97	<0.0001 *
Vasopressor utilization (frequency)	48.67% [110]	31.58% [24]	43.55% [54]	0.03 *
TXA				
0g	81.33% [183]	100.00% [76]	100.00% [124]	
1g	16.89% [38]	0.00% [0]	0.00% [0]	<0.0001 *
2g	1.78% [4]	0.00% [0]	0.00% [0]	

Data are reported as mean ± standard deviation, or percentage [N]. TEG, thromboelastography; R, time to start forming clot; K, time until clot reaches a fixed strength; alpha angle, speed of fibrin accumulation; MA, maximum amplitude or the highest vertical amplitude of the TEG; LY30, lysis at 30 minutes
**P<0.05*

Obstetric Anesthesiology-4 Epidural Replacement Rate and Cost of Care Following Labor Epidural Analgesia at a Single Tertiary Care Hospital

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Introduction: Epidural analgesia is commonly used in alleviating labor pain due its effectiveness and superiority when compared to other methods of analgesia in alleviating labor pain (1). Prior studies have shown an epidural catheter failure rate average of 12% and 13% (2, 3). However, few studies have evaluated the effects of these rates on cost of healthcare. In this study, we determine the incidence of epidural failure in a single tertiary care hospital and review the total cost difference of epidural replacements with and without complications.

Methods: We conducted a retrospective cohort study of patients who received an epidural for labor analgesia at the University of Texas Medical Branch. This project has been approved by the University of Texas Medical Branch Institutional Review Board. We collected data from electronic health records at UTMB to identify parturients aged between 18 and 50 who had epidural anesthesia for planned vaginal delivery between November 2015 and February 2019. The epidural anesthesia procedures were identified using current procedural terminology code 01967. For the cost analysis, we estimated the total cost for the hospital stay for delivery and readmission if any. We first categorized patients into two groups by the presence of epidural replacement. Within each group, we further categorized the patients into three groups: 1) no headache or epidural blood patch (EBP), 2) with headache but no EBP, and 3) with EBP. Patients who had multiple orders for epidural anesthesia during the hospitalization were considered to have epidural replacement. All costs were adjusted to the same time period, using the consumer price index for medical care.

Results: We included 4973parturients in this study. The parturient characteristics during the inpatient visit for delivery are presented in Table 1. The incidence of epidural replacement rate noted in our patient population was 9.35%. Among 4973 parturients 465 of had epidural replacement within 24 hours of initial epidural placement. The median cost of care for parturients who had epidural replacement without complication such as PDPH was found as 20457.53 USD (Table 2). The median cost of care for parturients who had no epidural replacement without complication was found as 16272.40.

Conclusion: In our single institution study, the vast majority of labor epidurals are placed by resident trainees. The incidence of epidural replacement rate noted in our patient population was 9.35%. We found the average cost for the majority of our parturients who received epidurals was approximately $17,500. We found that the mere replacement of an epidural with no further signs of dural puncture headache increased cost by about $5000 or 29%. Despite the increased average cost, the range of costs was also very significantly increased, perhaps reflecting on the myriad reasons underlying the requirement for epidural replacement. We found approximately a 2% risk of headache in our epidurals. Of those patients with headache, patients were more than twice as likely to require an epidural blood patch if they had previously required replacement of their epidural versus if they did not. The patients that required an EBP after epidural replacement on average had the highest cost, 48% higher than the cost of single epidural alone.

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Table 1. Paturient characteristics at the inpatient visit for delivery

Paturient characteristic	Mean ± SD	Median
Age	27.4 ± 5.7	26.7
BMI[#]	32.3 ± 6.5	31.3
Gravidity	2.7 ± 1.7	2.0
Parity	1.7 ± 1.3	1.0
	N	%
Race/ethnicity		
Asian	168	3.75
African American	506	11.29
Caucasian/White	1197	26.70
Hispanic or Latino	2591	57.80
Other	21	0.47
Gravidity		
0-1	1277	28.49
2-3	2048	45.68
3-4	792	17.67
> 5	312	6.96
Unknown	54	1.20

[#]319 records did not have info on BMI.

Table 2. Cost associated with epidural anesthesia for planned vaginal delivery

Epidural replacement	**Headache**	**EBP**	**N**	**Mean ± SD[#]**	**Median[§]**
No	No	No	3928	17414.53 ± 6335.22	**16272.40**
	Yes	No	66	19201.23 ± 13686.01	17026.01
		Yes	20	23772.33 ± 6856.11	21359.12
Yes	No	No	450	22452.14 ± 13038.52	**20457.53**
	Yes	No	8	24935.07 ± 5093.90	24212.93
		Yes	7	25700.02 ± 4157.85	25279.51

[#] Total cost for the hospital stay for spontaneous vaginal delivery and readmission.

[§]Median costs were used in the Cost-Effectiveness model.

EBP: Epidural Blood Patch.

Pain Mechanisms

Pain Mechanisms-1 Decreased corticosterone contributes to hyperalgesia in Dahl S rats: an innovative model of persistent pain.

Adam Dziuba[1], Luiz F Ferrari[1], Lina Zickella[2], Michael Zickella[2], Norman E Taylor[1]

[1]University of Utah, Salt Lake City, UT, [2]Brigham Young University, Provo, UT

Introduction: Hypothalamic-pituitary-adrenal (HPA) axis (Fig 1) dysregulation is a key feature of many chronic pain conditions.[1-3] However, the mechanisms by which hypo-cortisol states contribute to persistent pain are not well delineated. We identified a rat strain, the Dahl S (SS) rat, that exhibits markedly low mechanical nociceptive thresholds at baseline, without a surgical or pharmacologic intervention. To understand the mechanisms responsible for this novel observation, we measured diurnal adrenocorticotropic hormone (ACTH) and corticosterone levels. From this data, we hypothesized that lower corticosterone levels in SS rats provides a permissive proinflammatory environment which leads to increased pain.

Methods: This study was approved by the authors' IRB for animal research. Hind paw withdrawal thresholds were measured in male and female SS, Sprague Dawley (SD), and Brown Norway (BN) rats using von Frey fibers and the Randall-Selitto test.[4] A separate group of SS and BN rats was handled daily for one week prior to the study. Blood was sampled by tail nick (n = 6/group) at 8:00 AM and 4:00 PM for the measurement of unstressed plasma ACTH and corticosterone concentrations by radioimmunoassay, as described previously.[5] A separate group of male SS and BN rats (n = 6/group) were treated with single daily i.p. injections of dexamethasone (1mg/kg) or vehicle (DMSO/saline) for 5 consecutive days. Paw withdrawal thresholds were measured with the Randall-Selitto test before, 2h and 24h after each treatment, then on days 3, 7, 10 and 17 after the last injection.

Results: We observed a markedly lower paw withdrawal threshold in both male and female SS rats at baseline, evaluated with von Frey fibers and the Randall-Selitto test, when compared to the SD and BN rats. We found that unstressed SS rats exhibit lower ACTH secretion and lower corticosterone baseline levels compared to BN rats (Fig 2), suggesting an abnormal function of the HPA axis. Treatment of male SS and BN rats with dexamethasone temporarily increased paw withdrawal thresholds in SS rats while having no significant effect in BN rats (Fig 3), suggesting that the low level of circulating glucocorticoids play a role in the nociceptive phenotype of SS rats.

Conclusion: Here we propose the SS rat as a novel model of idiopathic pain. This strain exhibits baseline mechanical hyperalgesia and hypo-corticosterone, traits that are found in many human chronic pain conditions. Our results indicate that further characterization of this rat strain can provide valuable information about the etiology of chronic widespread pain syndromes.

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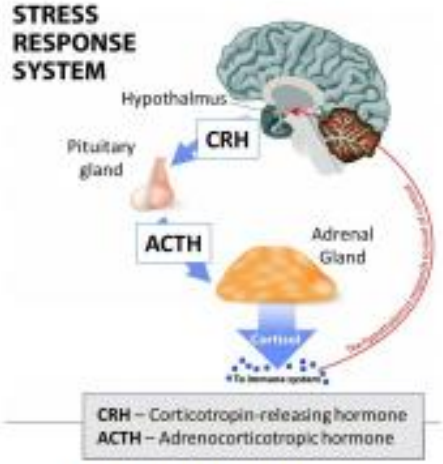

Figure 1. Schematic of the hypothalamic-pituitary-adrenal axis.

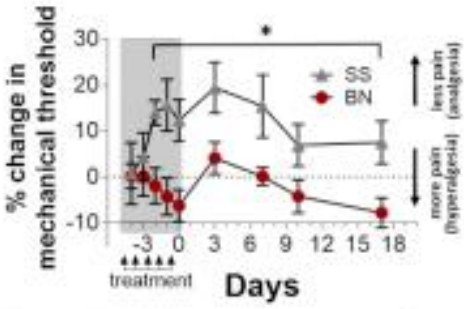

Figure 3. Dexamethasone reduces mechanical hyperalgesia in SS rats. SS rats (grey diamonds) treated with the glucocorticoid dexamethasone showed a significant increase in paw withdrawal thresholds, while there was no change in BN rats (black circles), indicating dexamethasone reduced mechanical hyperalgesia in SS rats. (* indicates significance $p<0.05$).

Methods: Male SS and BN rats (n=6/group) received baseline Randall Sellito testing. Single daily ip injections of dexamethasone (1mg/kg) or vehicle (DMSO/saline, data not shown) were then administered for 5 days. Paw withdrawal thresholds were measured each day 2hrs after drug administration. They were also measured on post treatment days 3, 7, 10 and 17.

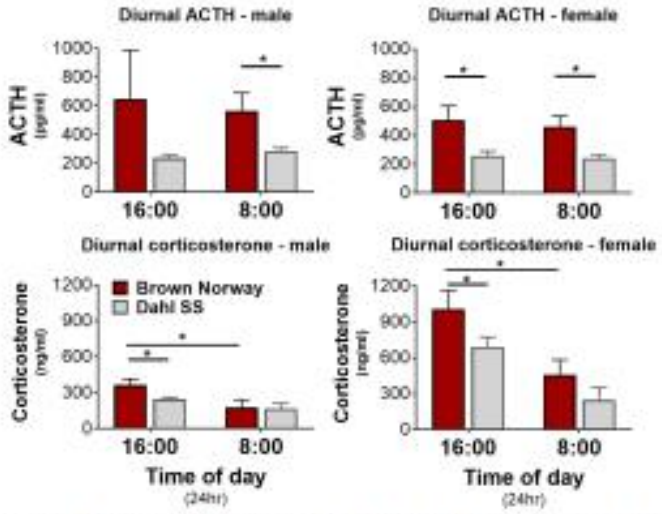

Figure 2. Plasma diurnal ACTH and corticosterone levels are significantly lower in SS rats. SS rats have significantly lower plasma ACTH levels than BN rats, without significant diurnal or sex differences (upper graphs). SS rats also demonstrate lower corticosterone levels, but in contrast with ACTH, demonstrate significant diurnal and sexual dimorphism, with higher levels at 16:00hr and in females in both SS and BN rats. (* indicates significance $p<0.05$).

Methods: Rats were handled daily for one week before being studied. Females and males were assessed on separate days. Blood was sampled by tail nick (n =6 per experimental group) for the measurement of plasma ACTH and corticosterone concentrations at 8:00 AM and 4:00 PM to assess the basal (unstressed) diurnal rhythm as described previously.[4] Plasma ACTH and corticosterone were measured via radioimmunoassay (MP Biomedicals, Solon, OH) as previously described.[5]

Pain Mechanisms-2 Neuroinflammation contributes to baseline hyperalgesia in Dahl S rats

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Introduction: One obstacle in preclinical pain research is that current animal models do not reproduce key characteristics of clinical pain. The resulting gap in translation between preclinical rodent studies and human clinical studies is a major topic of discussion in pain research. Virtually all rodent pain models must be induced using a chemical or surgical intervention, or by repeated exposure to an environmental stressor. Most frequently, these interventions are induced in rodent strains such as the Sprague Dawley rat or C57BL/6 mouse that have no particular genetic susceptibility to pain. This limits the applicability of the findings to humans, as many pain syndromes arise spontaneously without apparent precipitating factors. There is a critical need to develop animal models that reflect the genetic, environmental, sex-dependent, and psychologic aspects of human chronic pain conditions. We identified a rat strain, the Dahl S (SS) rat, that exhibits mechanical hyperalgesia and allodynia at baseline, without an external precipitating intervention. We hypothesized that the cause of the hyperalgesia was inflammatory in origin and investigated causes of systemic inflammation that lead to hyperalgesia in this strain.

Methods: This study was approved by the authors' IRB for animal research. CSF and plasma samples were obtained from anesthetized SS, Sprague Dawley (SD) and Brown Norway (BN) rats and analyzed using the LEGENDplexTM (Biolegend, San Diego, CA) bead-based immunoassay to quantify 13 cytokine and chemokine levels. A separate group of SS and BN rats were perfusion fixed with formalin and brains sectioned for immunohistochemical identification of microglia using the microglia marker EF calcium-binding protein (IBA-1). Total GFP stained area was quantitated as a surrogate for the degree of microglial activation. To determine if microglial inhibition ameliorated the hyperalgesia, single, daily ip injections of minocycline (30mg/kg) or vehicle (saline) were administered for 5 days to SS rats. Paw withdrawal thresholds were measured each day 24hrs after drug administration. They were also measured on post treatment days 3, 7, 10 and 17.

Results: The nociceptive cytokine IL-18 was significantly elevated in both (A) the plasma and (B) the CSF of SS rats compared with SD and BN rats (Fig 1). We then observed greater staining for IBA-1 in the periaqueductal gray, suggesting increased microglial activation (Fig 2). Microglia are known to be a source of CSF IL-18 when activated. SS rats treated with the microglial inhibitor minocycline showed significantly higher paw withdrawal thresholds than SS rats treated with vehicle, indicating minocycline reduced mechanical hyperalgesia (Fig 3) (ANOVA, $p<0.05$).

Conclusion: The results indicate that systemic and neural inflammation contribute to the baseline hyperalgesia of SS rats. These findings support the use of the SS rat as a novel tool to investigate mechanisms by which systemic inflammation contribute to persistent pain syndromes.

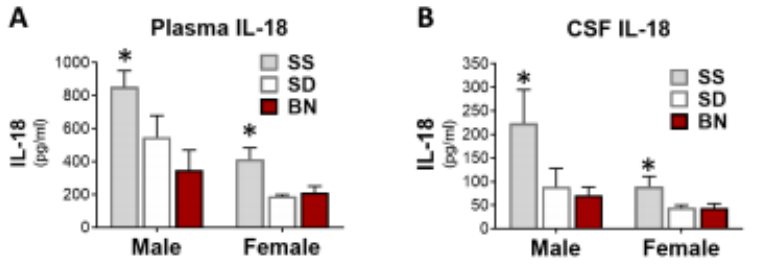

Figure 1. The nociceptive cytokine IL-18 is elevated at baseline in SS rats.

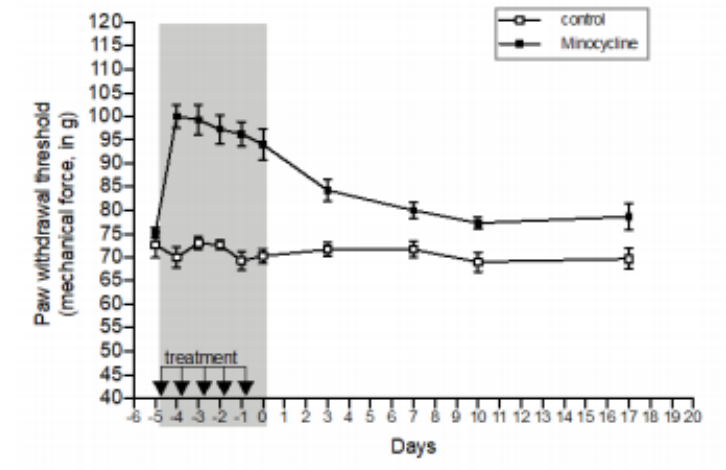

Figure 3. Minocyline reduces mechanical hyperalgesia in SS rats.

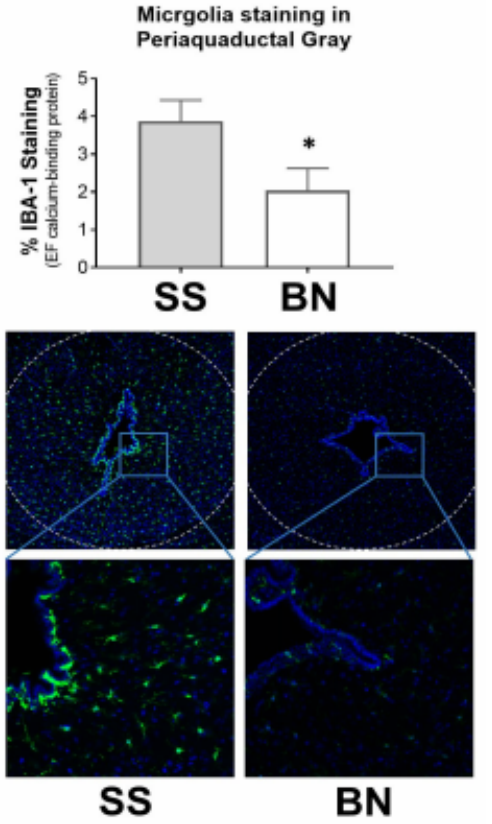

Figure 2. SS rats exhibit activated microglia in the periaqueductal gray.

Pain Medicine

Pain Medicine-1 Exploratory evaluation of the association between pain-related SNPs and postoperative opioid consumption after total knee arthroplasty

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Introduction: Conventional opioid prescribing practices face increasing scrutiny in all domains of healthcare.[1] Personalized medicine holds the promise to tailor pain management to the individual needs of patients. Pharmacogenetics uses genetic information to predict a response phenotype.[2] In the setting of increased total knee arthroplasty (TKA) and the current opioid crisis, an urgent knowledge gap exists regarding how to personalize opioid prescribing after TKA while improving pain management postoperatively. We sought to evaluate opioid related single nucleotide polymorphisms (SNPs) association with postoperative pain intensity and postoperative opioid consumption after TKA.

Methods: Secondary analyses were performed on a multi-site prospective cohort study of patients with knee osteoarthritis (OA) undergoing TKA. Following informed consent, participants completed pre-surgical assessments including pain (Brief Pain Inventory [BPI]), 'fibromyalgianess' (the Widespread Pain Inventory[WPI] and Symptom Severity[SS]), opioid consumption, pain catastrophizing (Pain Catastrophizing Scale[PCS]), depression, anxiety (PROMIS: Depression, Anxiety). Saliva samples were collected pre-surgically, using Gene Oragene self-collection kits for DNA collection(3). Genetic assay processing used the Infinium Global Screening Array, which combined multi-ethnic genome-wide content, curated clinical research variants, and quality control markers(3,4). Perioperative opioid use, ASA, length of stay and pain scores were extracted from the medical record. Primary objective was to evaluate the contribution of known pain-related SNPs to postoperative pain and postoperative opioid consumption using morphine milligram equivalents (MME), over and above demographic, clinical and psychosocial variables. Hierarchical multiple regression was conducted with postoperative pain, followed by postoperative MME, in a separate analysis, as the dependent variables. We controlled for demographic variables within the first step, clinical variables in the second step, psychosocial variables in the third step, followed by a specific SNP that was found to correlate with postoperative pain.

Results: A total of 246 patients were enrolled. Genetic samples were available for 205 participants. Quality control procedures including principle component analysis (PCA) were used to investigate population structure and identical by descent analysis to check relatedness.(5) Six samples with call rates <85% and 1 pair of unexpected duplicates were excluded, resulting in 197 (80%) subjects included in these analyses. Mean age of participants was 65 years(SD 7.9), 60% female, and 90% non-Hispanic white. Genotypes were sequenced on Illumina Global Screening Array v2+multi disease content. ANOVA F-statistics checked association of postoperative MME and postoperative pain to 14 previously reported pain-associated SNPs. SNP rs2740574(G) was the most significantly associated SNP in our dataset. For SNP rs2740574(G) 95% of the cohort of patients had two A alleles while the other 5% had a one or two G allele. In the regression analysis, demographic variables added non-significantly to the model, clinical variables accounted for 23.3% of the variance in postoperative MME, and psychosocial variables added non-significantly to the model. The addition of genetic factor SNP rs2740574(G), explained an additional 4% of the variance, after controlling for demographic, clinical and psychosocial variables [$F(1,106)=6.16$; $\beta=-.218$ $p=.015$]. The final model explained 37% of variance in MME [$F(18,106)=3.46$; $p<0.001$]. In addition, in the final model only age ($\beta=-.219$,$p=.016$), postoperative pain ($\beta=.402$,$p<0.001$), ASA ($\beta=.170$,$p=.050$), LOS ($\beta=.195$,$p=.032$), catastrophizing ($\beta=.213$,$p=.034$) and SNP rs2740574(G) ($\beta=-.218$,$p=.015$) were statistically significant. SNP rs2730574(G) did not meaningfully contribute to postoperative pain regression analyses when controlling for demographic, clinical and psychosocial variables (F change $p>0.05$).

Conclusion: In this prospective cohort study of patients undergoing TKA for OA, SNP rs2740574(G) was associated with higher opioid consumption postoperatively. Higher postoperative MME use was also associated with younger patients, longer hospitalizations, and higher pain scores, ASA classifications and baseline pain catastrophizing scores. These results suggest that there may be SNPs that potentially influence opioid consumption, which could lead to a more tailored pain management strategy for each individual patient.

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Pain Medicine-2 Chronic Pain after Orthopedic Procedures using Tourniquet in order to Minimize Blood Loss

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Introduction: Tourniquet use in orthopedic surgeries has been common practiced to aid in minimizing blood loss (1). Although this technique is common, very little research has evaluated the development of post-surgical chronic pain (PSCP) after tourniquet use. Previous publications have shown that the use of tourniquet during orthopedic surgical procedures may contribute to further muscle atrophy and chronic neuropathic pain (2, 3). This is of particular interest given that recent animal research has shown ischemic reperfusion injury, edema and tissue inflammatory changes immediately after tourniquet release that could lead to reductions in pain threshold in the first few days after tourniquet use (4, 5, 6). The purpose of our study was to determine incidence of PSCP and possible factors associated with the onset of PSCP following application of tourniquet during orthopedic surgeries to minimize intraoperative blood loss.

Methods: In our retrospective chart review, we collected clinical and surgical data on patients who received a tourniquet during an orthopedic limb surgery between the years of 01/01/2012 and 12/31/2014 at Massachusetts General Hospital. There were no exclusion criteria applied to this cohort. We conducted phone interviews using a survey that assessed the incidence of, factors associated with, and individual characteristics of PSCP. A total of 111 patients were called (64 patients received surgery in 2012 and 47 patients received surgery in 2013). 77 patients were lost to follow-up, and a total of 34 patients were included in the final cohort with both clinical data and follow-up data. Outcome variables included incidence of PSCP. Statistical methods used for analysis included a linear mixed effects regression adjusted for tourniquet time, ASA class, weight, and surgeon.

Results: Only subjects that successfully completed follow-up phone interviews were included in our final cohort. Subjects that were lost to follow-up were excluded from our study. In our cohort, we looked at individual demographic and surgical variables for patients who experienced PSCP and those who did not (Table 1). There was an even split of 17 patients each that experienced PSCP and did not experience Complex Regional Pain Syndrome (CRPS). While none of the subgroups in the study were significant to the outcome of PSCP with a p value <0.05, the standardized mean difference for age, gender, race, height, weight, ASA class, and year of surgery resulted in values >0.2, indicating that the effect size of these variables may be meaningful to the prevalence of PSCP.

Conclusion: Our results show that tourniquet use may be a contributing factor for the development of chronic pain after orthopedic limb surgeries. The tourniquet time during orthopedic surgeries was not significantly associated with the development of PSCP. Certain demographics including age, weight, and ASA classification at the time of procedure were meaningful to the prevalence of PSCP. We hope to use this study to continue to understand how to improve the current practices of tourniquet use in orthopedic surgery to minimize the incidence of PSCP.

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Pain Medicine-3 Automated Screening of New Glycinergic Modulators as Potent Analgesics

Yan Xu[1], Qiang Chen[1], Kerryann Koper[1], Nicole Brandon[1], Pei Tang[1]

[1]University of Pittsburgh School of Medicine, Pittsburgh, PA

Introduction: We previously demonstrated that the analgesic effect of ï□„9-tetrahydrocannabinol (THC), a major active component of marijuana, is mediated by potentiating function of glycine receptors (GlyRs) through binding to a transmembrane domain site.1,2 Using in silico screening and electrophysiology,3 we also identified lead compounds that bind to the THC site but are unlikely to produce psychoactive side effects. Their analgesic effects were further substantiated by in vivo tests in inflammatory and neuropathic pain models in mice and rats, respectively. To expand these findings and ultimately to identify potent analgesics for clinical applications, we must establish high throughput assays for a larger pool of compounds. Here, we report on how to effectively overcome issues stemming from the hydrophobic nature of compounds in an automated high throughput electrophysiology system so that a robust and reliable platform can be established to screen new glycinergic positive modulators as potent analgesics.

Methods: A stable HEK cell line expressing human α3GlyRs was developed. An automated patch clamp system, IonFlux (Fluxion Biosciences, Alameda, CA), was used for measuring the functional modulation of α3GlyRs by compounds. Compounds were dissolved in DMSO before dilution by extracellular solution into desired concentrations containing 1% DMSO. 1% pluronic reagent was included in individual samples to increase microfluidics and facilitate transporting hydrophobic compounds to cells. Two protocols were tested to quantify potency and efficacy of analgesic candidates: (1) preincubate the compound before applying glycine (~EC10) and (2) apply compound and glycine (~EC10) simultaneously. Concentrations of compounds spanned at least five orders of magnitude so that a reliable EC50 could be fit from the concentration response curve. Bromo-propofol, a known positive modulator of α3GlyRs, was used as a positive control for evaluating assay performance.

Results: Protocol 1 significantly improves data reproducibility and quality of potency and efficacy measurements. A longer preincubation time may increase potentiation slightly at a given compound concentration, but in most cases 1 min preincubation is sufficient to generate reliable data without challenging the limit of cells' lifetime in the IonFlux sample plate. In contrast, protocol 2 yields higher uncertainty in both potency and efficacy measurements, presumably due to insufficient compound interaction with cells. Using the positive control bromo-propofol, we observed scattered results from repeated measurements without preincubation, while protocol 1 gives reproducible data that agree well with previously published results.4

Conclusion: The study establishes a new high-throughput in vitro method to effectively and reliably search for glycinergic modulators as novel analgesics. The method can be easily adapted for high-throughput hydrophobic candidate drugs acting on other ion channels.

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Pain Medicine-4 More Sopor, Less Dolor: A Systematic Review and Meta-analysis on the Impact of Cannabinoids on Sleep Health and Pain in Patients with Chronic Neuropathic Pain

Daniel Kapustin[1], Anuj Bhatia[2], Hance Clarke[3], Aditya Trivedi[4], Aidan L McParland[5], Alexandra Davidson[6], Richard Brull[2], Mandeep Singh[7]

[1]University of Toronto Faculty of Medicine, Toronto, Canada, [2]Department of Anesthesia, University Health Network, Women's College Hospital, Toronto, Canada, Toronto, Ontario, [3]Toronto General Hospital, Toronto, Canada, [4]McMaster University, Hamilton, Canada, [5]28 Tranby Ave, Toronto, Ontario, [6]University of Toronto Faculty of Medicine, Toronto, Ontario, [7]University of Toronto, Toronto, Ontario

Introduction: Neuropathic pain (NP) syndromes are debilitating conditions which can impact sleep health and overall quality of life significantly.[1] Pharmacological treatment with cannabinoids has not been evaluated for its impact on sleep health (sleep quality and daytime somnolence). The objectives of this systematic review and meta-analysis (SR-MA) were to determine the effect of cannabinoids on sleep quality, pain control, and patient impression of treatment efficacy.

Methods: We reviewed randomized controlled trials comparing synthetic and natural cannabinoids (CB) to placebo in patients with central and peripheral neuropathic pain syndromes. A systematic search of the standard literature databases from database conception to July 2019 was carried out with the help of an information specialist. Inclusion criteria were randomized controlled trials evaluating the pharmacological treatment of NP syndromes using cannabinoids, with an active treatment or a placebo as a comparator. Data on eleven-point (0-11) numerical rating scales for pain and sleep quality, incidence of daytime somnolence, nausea, and dizziness as adverse effects, and patient global impression of change (PGIC) scores were recorded. Meta-analysis using the random effects model was conducted where appropriate.

Results: Of the 3536 studies screened, a total of 8 randomized controlled trials including 1051 patients (placebo: 478 patients; CB: 573 patients) with neuropathic pain were included. Cannabinoids most commonly included in the studies were Sativex (GW-1000-02), Nabilone, and medical cannabis preparations with THC dose ranging from 1mg to 130mg per day. Pain scores were significantly reduced in the CB group (standardized mean difference, SMD = -0.50, 95% CI -0.79 to -0.22, p=0.001) compared to placebo (Figure 1). Significant improvement in sleep quality (Figure 2) was also observed in the CB group (SMD=0.39, 95% CI 0.18 to 0.60, p<.001). Additionally, patients in the CB group were more likely to report improvement in PGIC scores (OR=2.3, 95% CI 1.37 to 3.7, p=0.001) compared to patients treated with placebo (Figure 3). Notably, CB-treated patients were more likely to experience daytime somnolence (OR=2.2, 95% CI 1.3 to 3.9, p=0.004), nausea (OR=1.7, 95% CI 1.1 to 2.5, p=0.02), and dizziness (OR=3.8, 95% CI 2.6 to 5.7, p<.001).

Conclusion: Cannabinoids are useful agents for NP as evidenced by significant improvement in pain, sleep quality, and PGIC. However, these benefits were noted at the expense of several adverse events including daytime somnolence. With the advent of new agents and more refined cannabis derivatives, further research is needed to comprehensively explore treatment effectiveness. Moreover, future work should incorporate clinically validated measures of sleep health to better evaluate this outcome.

Reference(s): 1: Ferini-Strambi L. Neuropathic Pain and Sleep: A Review. Pain and therapy. 2017;6:19-23

Study name	Dose	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Berman 2004	129.6 mg THC / day	-0.490	0.208	0.043	-0.898	-0.081	-2.351	0.019
Berman 2004	129.6 mg THC + 120mg CBD / day	-0.489	0.209	0.044	-0.899	-0.079	-2.336	0.020
Nurmikko 2007	129.6 mg THC + 120mg CBD / day	-1.579	0.205	0.042	-1.981	-1.178	-7.707	0.000
Rog 2005	129.6 mg THC + 120mg CBD / day	-0.734	0.254	0.065	-1.232	-0.235	-2.884	0.004
Toth 2012	1-4mg nabilone /day	-0.677	0.403	0.163	-1.467	0.114	-1.678	0.093
Ware 2010	25mg of 2.5%, 3x/daily	-0.114	0.305	0.093	-0.712	0.485	-0.372	0.710
Ware 2010	25mg of 6%, 3x/daily	-0.028	0.309	0.095	-0.633	0.577	-0.091	0.928
Ware 2010	25mg of 9.4%, 3x/daily	-0.424	0.308	0.095	-1.028	0.181	-1.374	0.170
Langford 2013	32.4 mg THC + 30 mg CBD/day	-0.129	0.109	0.012	-0.342	0.084	-1.184	0.236
Serpell 2014	64.8 mg THC + 60 mg CBD/day	-0.189	0.128	0.016	-0.440	0.061	-1.481	0.139
Guido van Amerongen 2017	16mg THC	-0.803	0.424	0.180	-1.635	0.028	-1.893	0.058
		-0.503	0.146	0.021	-0.789	-0.217	-3.447	0.001

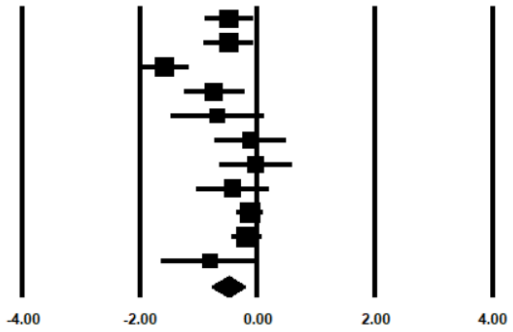

Figure 1. Forest plot evaluating changes in patient daily pain scores in CB and placebo groups

Study name	Dose	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Berman (1) 2004	129.6 mg THC + 120mg CBD	0.493	0.209	0.044	0.082	0.903	2.352	0.019
Berman (2) 2004	129.6 mg THC / day	0.697	0.211	0.045	0.283	1.112	3.299	0.001
Serpell 2014	64.8 mg THC + 60 mg CBD/day	0.347	0.129	0.017	0.095	0.599	2.700	0.007
Langford 2012	32.4 mg THC + 30 mg CBD/day	0.023	0.109	0.012	-0.190	0.236	0.211	0.833
Rog 2005	129.6 mg THC + 120mg CBD	0.772	0.255	0.065	0.271	1.272	3.022	0.003
Toth 2012	1-4mg nabilone /day	0.739	0.405	0.164	-0.055	1.534	1.824	0.068
Ware (1) 2010	25mg of 2.5%, 3x/daily	0.061	0.305	0.093	-0.538	0.659	0.198	0.843
Ware (2) 2010	25mg of 6%, 3x/daily	0.221	0.310	0.096	-0.386	0.828	0.714	0.476
Ware (3) 2010	25mg of 9.4%, 3x/daily	0.534	0.310	0.096	-0.075	1.142	1.720	0.085
		0.390	0.105	0.011	0.184	0.597	3.713	0.000

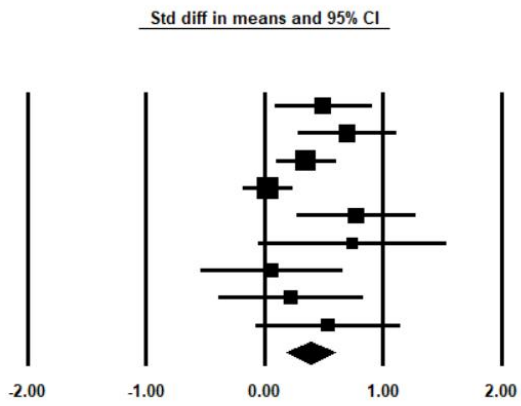

Figure 2. Forest plot evaluating changes in patient sleep quality in CB and placebo groups

Study name	Dose	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Rog 2005	129.6 mg THC + 120mg CBD / day	2.520	0.690	9.204	1.398	0.162
Toth 2012	1-4mg nabilone /day	10.286	1.018	103.948	1.975	0.048
Serpell 2014	64.8 mg THC + 60 mg CBD/day	1.762	1.080	2.875	2.267	0.023
Langford 2013	32.4 mg THC + 30 mg CBD/day	1.470	0.991	2.181	1.913	0.056
Nurmikko 2007	Blank	4.583	2.058	10.209	3.726	0.000
		2.250	1.373	3.688	3.216	0.001

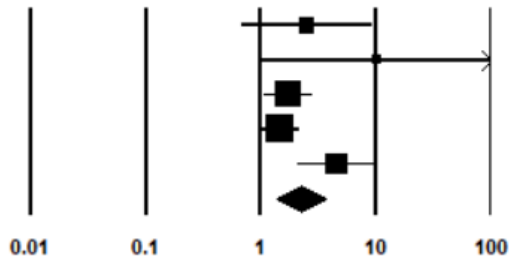

Figure 3. Forest plot evaluating changes in PGIC scores (odds ratios) in CB and placebo groups

Pain Medicine-5 Postoperative Pain in Pediatric Scoliosis Repair: Comparing Subjective and Objective Pain Scores

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Introduction: Scoliosis is a multidimensional deformity of the thoracolumbar spine, and can be categorized as idiopathic, congenital, or neuromuscular. Adolescent idiopathic scoliosis is the most common variant seen. Since severity of symptoms is associated with progression of this disease, surgical correction is undertaken based on a Cobb angle of >40 to 50 degrees. Patients undergoing this surgical correction experience severe pain in the postoperative period, and intraoperative and postoperative management of these patients varies. Postoperative management commonly includes the use of opioid-based patient-controlled analgesia (PCA) and adjuncts such as valium and ketorolac. We present here the initial results of prospective review of 122 cases including idiopathic, congenital, and neuromuscular scoliosis at a quaternary freestanding children's hospital that is a leading center for scoliosis repair.

Methods: We prospectively gathered data over a one year period. Data extracted included demographics, perioperative management, length of stay, and blood management techniques employed. Data relating to the intraoperative and postoperative care and hospital course was recorded using a RedCap database. Inclusion criteria were age between 5 and 18 years, and procedure of posterior spinal instrumentation and fusion or anterior spinal instrumentation and fusion. All personal health identifiable data were de-identified. Institutional review board approval was obtained prior to the start of data collection. Pain scores as recorded in the electronic medical record were reported. Both Numeric Rating Scale (NRS) patient reported data and nurse-reported Face, Legs, Activity, Cry, Consolability (FLACC) Scale data were recorded.

Results: Our preliminary data totals 122 records included for analysis. 91 patients had idiopathic scoliosis repair, 16 had congenital scoliosis repair, and 12 had neuromuscular scoliosis repair. Average age was 14.1 years (s.d. 2.24 years). Pain scores in the post-anesthesia recovery unit and on post-operative days 0, 1 and 2 were examined. Scores differed by scoliosis type, with significantly higher NRS scores reported by congenital scoliosis patients on post-operative days 0, 1 and 2 ($p<0.05$) and significantly higher FLACC scores reported on post-operative days 0 and 1. FLACC scores were significantly lower than NRS scores for all types of scoliosis throughout the hospital stay ($p<0.05$).

Conclusion: Though scoliosis is commonly considered to be one of the more painful pediatric surgeries, objective data on post-operative pain has been sparse. These data represent a unique opportunity to examine post-operative pain scores and how they differ by types of scoliosis in a large, single-center series. The results have implications for pain management, particularly given the discrepancies between the objective FLACC and subjective NRS scores in all types of scoliosis.

Reference(s): Altaf, F., et al., Adolescent idiopathic scoliosis. BMJ, 2013. 30(346). Yamada, K., et al., Etiology of idiopathic scoliosis. Clin Orthop Relat Res, 1984(184): p. 50-7. Machida, M., Cause of idiopathic scoliosis. Spine (Phila Pa 1976), 1999. 24(24): p. 2576-83. Giampietro, P.F., et al., Congenital and idiopathic scoliosis: clinical and genetic aspects. Clin Med Res, 2003. 1(2): p. 125-36.

Pain Medicine-6 Reducing postoperative opioids consumption with intraoperative methadone in long oral and maxillofacial surgeries

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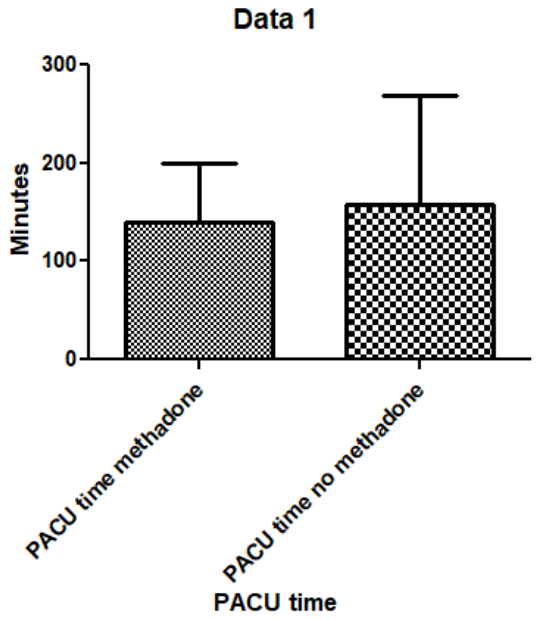
Introduction: This is a retrospective study that explored the effectiveness of intra-operative iv methadone used in reducing the post-operative opioids consumption in Oral and Maxillofacial (OMF) Surgeries of 4 hours or longer. Due to the clinical course of OMF surgeries, patient usually stays as inpatient for less than 48 hours and a portion of these patients will be discharged on post-op day 1. We compared the patient group with intra-op iv Methadone (10mg) to the regular management group where other opioids are administrated. Our result demonstrated that lower dose of methadone administration introperatively associated with significant clinical reduction in post-op opioids requirement. No side effects from medication observed in the methadone group. We recommend low dose Methadone as prefered opioids for these long OMF cases.

Methods: This is a retrospective cohort study. We reviewed OMF surgery cases which longer than 4 hours for surgical time in the lasts 10 years from 2009 to 2019. From the recent years, Methadone 10mg iv has been used for intra-op pain management. We studied inpatients only and excluded patients that were chronically on opioids medication, Methadone, or Suboxone treatment in both groups. The patient age is between 18-65 with no other major organ disease, no allergy to opioids. Group 1, 28 cases with intra-op Methadone administration (10mg iv) were selected as treatment group. Group 2, 28 cases without intra-op methadone administration were selected as control group. The control group is age/gender/surgery time matched to the treatment group.The post-operative pain management in both groups were kept identical which were managed by primary team. The pain medication in both groups includes: NSAIDs, Tylenol and Opioids. The pain scale of each patient was evaluated by the nursing team or primary team, and then the primary team decided which pain medication should be administrated for pain management. We compared the PACU stay time, opioid consumption in PACU time, opioid consumption in 24 hours after PACU, and opioid consumption in 24-48 hours after PACU between two groups with t test. All the opioids were converted to Morphine Milligram Equivalent (MME) using Stanford Opioid equivalent Dosing table.

Results: Result is done using t test and showing as Mean ± SEM. There is NO significant difference in the PACU stay time between Methadone treatment group (139.8 ± 11.24 mins) and control group (157.9 ± 20.87 mins) (p=0.45. 95% confidence interval -65.66 to 29.44). There is NO significant difference in the PACU time opioid consumption between Methadone treatment group (12.57 ± 2.624 MME) and control group (15.18 ± 2.526 MME) (p=0.48, 95% confidence interval -9.915 to 4.701). There is significant difference in oipoid consumption in the 24 hours after PACU period. Methadone treatment group (24.93 ± 4.738 MME) vs. control group (45.29 ± 7.864 MME) (p=0.0308, 95% CI -38.78 to -1.937). Most patient were discharged within 48 hours. There are only 9 patients in the Methadone group and 11 patients in the control group remained inpatient by 48 hours after PACU. This makes the result of 24-48 hours post PACU less reliable. The result shows NO significant difference in oipoid consumption in the 48 hours after PACU period, Methadone treatment group (13.07 ± 4.298 MME) vs. control group (15.43 ± 5.516 MME) (p=0.73, 95% CI -16.39 to 11.67).

Conclusion: 1. Intra-op iv Methadone (10mg) can be used safely as primary analgesia medication for OMF surgeries longer than 4 hours. No side effect from Methadone was recorded. 2. Methadone takes longer to reach the full effect, it does not affect the over all PACU stay time comparing to other opioid medication. 3. Low dose of Methadone provided significant pain relief and reduced the opioid consumption significantly within 24 hours after patients left PACU, but does not reduce the opioid consumption in the PACU period. 4. There is no difference in the inpatient time observed from our limited cases using methadone comparing to other regular management. 5. Despite the long time to reach the full efficacy, methadone provides similar pain relief in the immediately post-op period comparing to other short/long acting opioids which was demonstrated as no difference in the PACU opioids consumption.

Reference(s): Intraoperative methadone improves postoperative pain control in patients undergoing complex spine surgery. Anesth Analg. 2011 Jan;112(1):218-23.
Intraoperative Methadone for the Prevention of Postoperative Pain: A Randomized, Double-blinded Clinical Trial in Cardiac Surgical Patients. Anesthesiology. 2015 May;122(5):1112-22.
Intraoperative methadone: rediscovery, reappraisal, and reinvigoration? Anesth Analg. 2011 Jan;112(1):13-6.
Treatment of postoperative pain in oral and maxillofacial surgery Br J Oral Maxillofac Surg. 2000 Dec;38(6):588-592.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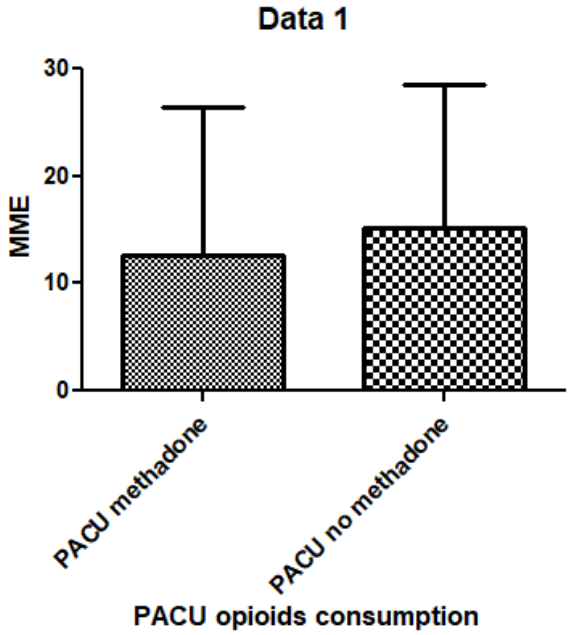
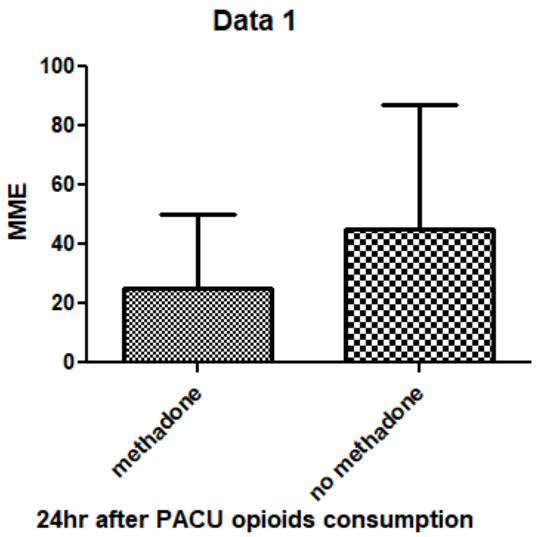
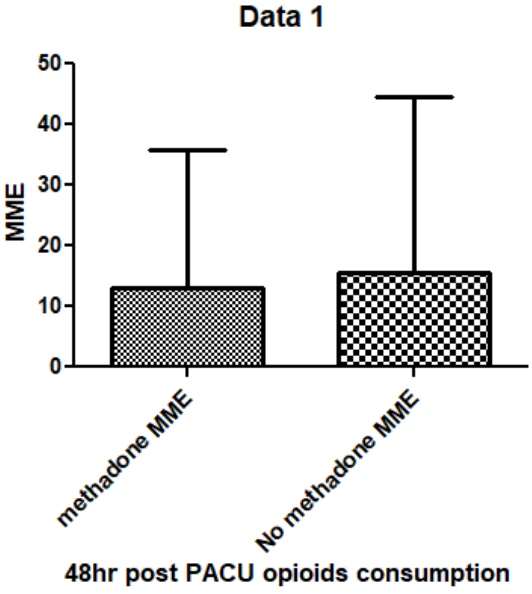
300
200
100
0
Minutes
PACU time methadone
PACU time no methadone
PACU time


Data 1
30
20
10
0
MME
PACU methadone
PACU no methadone
PACU opioids consumption



24hr after PACU opioids consumption



48hr post PACU opioids consumption

Pain Medicine-7 Perioperative Assessment of Opioid Induced Hyperalgesia using Quantitative Sensory Testing: A Pilot Study

Kelsei Brown[1], Christina Hayhurst[2], Stephen Bruehl[3], David A Edwards[3]

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Introduction: Opioid induced hyperalgesia (OIH) is a syndrome of paradoxically increased nociceptive responsiveness following opioid analgesia. OIH is characterized by increased perceived pain intensity over time, spreading of pain to locations distinct from the initial painful site, increased sensitivity to external stimuli and central sensitization (1,2). Under recognition of OIH in the perioperative period is a risk factor for chronic post-surgical pain (3). Additionally, the influence of opioids on pain thresholds in the perioperative period had yet to be studied. Our study aimed to evaluate OIH through demonstrating alterations in mechanical pain threshold (MPT) as a measure of hyperalgesia, assessing differences in self-reported pain interference, and characterizing central sensitization (indexed by temporal summation) following surgical insult and administration of opioid analgesia.

Methods: Opioid naïve patients, with no chronic pain diagnosis, and no previous thoracic surgery were included. Data were collected 3-4 hours preoperatively, 24 hours postoperatively, and 3 weeks postoperatively. Participants completed the PROMIS-29 v2.1 profile to assess for changes in pain interference from the preoperative to 3-week postoperative visit. Von Frey filaments were used to determine MPT on the dorsum of the hand ipsilateral to the surgical incision and at the surgical site. One contact was made with each filament in ascending order until participants indicated they felt a 'pinprick' sensation. The pressure (in grams) applied at this threshold percept was recorded as the MPT. Temporal summation assessment was conducted using a 6.10g Von Frey filament applied to the dorsum of the contralateral hand, with pain ratings (0-10) obtained after the initial stimulus and immediately following a train of 10 stimuli applied at 1 sec intervals. Temporal summation was defined as the final pain rating minus the initial rating.

Results: Thirteen (6 male; 7 female) patients undergoing thoracic surgery (mean age = 56.2 +/- SD 16 years) were included. Patients were exposed to a mean of 39.5 +/- 20.2 morphine milligram equivalents (MME) intraoperatively and 34.1 +/- 28.1 MME 24 hours postoperatively. Mean MPT (in grams) at the ipsilateral hand was 32 +/- 84.7 preoperatively and 42.3 +/- 98.4 at 3-weeks postoperatively. There was no significant differences in MPT on the ipsilateral hand, temporal summation, or pain interference when comparing preoperative status to 3 weeks postoperatively. There was a significant increase in MPT at the surgical site 24 hours postoperatively (p= 0.02).

Conclusion: Surgical- and opioid- induced hyperalgesia was not detected after thoracic surgery in opioid naïve patients. Our study did not demonstrate significant changes in ipsilateral MPT, temporal summation or pain interference in the perioperative period. Increased MPT at the surgical site may be due to cutaneous nerve damage, edema, or even opioid analgesia itself. Our study was limited by low statistical power due to the small sample and by use of a single modality of quantitative sensory testing (QST). Detection of OIH may be possible with the addition of alternative QST methods.

Reference(s): Review of the Performance of Quantitative Sensory Testing Methods to Detect Hyperalgesia In Chronic Pain Patients on Long-term Opioids. Vol. 122(3), pp. 677-685, 2015. Differential Opioid Tolerance and Opioid-induced Hyperalgesia: A Clinical Reality. Vol. 124(2), pp. 483-488, 2016. Perioperative opioid analgesia -- when is enough too much? A review of opioid-induced tolerance and hyperalgesia. Vol. 393(10180), pp.1558-1568, 2019.

Pain Medicine-8 Long–term Outcome of Complex Regional Pain Syndrome Diagnosed and Treated in Childhood and Adolescence

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Introduction: Complex Regional Pain Syndrome (CRPS) is a disease state that usually follows trivial or mild limb injury or surgery, and which results in longstanding severe spontaneous physical pain, hyperalgesia and allodynia, sensory distortion, and perfusion alteration of the affected body part, which is generally one or more limbs. While the short-term prognosis of pediatric CRPS is thought to be better than that of adult CRPS, less is known of the long-term outcome of pediatric CRPS. The aim of this study was to describe recurrent or persistent long-term symptoms of pain or physical disability and quality of life in adults who were diagnosed with CRPS and treated during childhood or adolescence.

Methods: "Potential study subjects were identified through a search of Lucile Packard Children's Hospital Pediatric Pain Management Clinic patients whose charts were coded with CRPS type 1 or type 2 between the years 1994 and 2018. Those who were above eighteen years old at the time of subject identification were mailed consents and surveys. The first part of the survey consisted of general questions focused on the current state of the previously affected CRPS limb. The second part of the questionnaire included the SF-8 Health Survey, which is a validated survey of health-related quality of life. Participation was voluntary subsequent to completion of written informed consent; no financial incentives were provided. The SF-8 survey is composed of 8 questions designed to quantify a health-related quality of life score. Using a scoring key from Optum®, the survey results were reported in summary scales of Physical Component Score (PCS) and Mental Component score (MCS). The scores were scaled based on norm-based scoring (NBS) such that each scale is scored to have a mean of 50 and a standard deviation of 10. When a participant's scale score is less than 45 or a group mean scale score is below 47, health status is below the average range [1]. The general population norm is built into the scoring algorithm for NBS and simplifies the interpretation. Parametric and nonparametric variables were compared using single-tailed Student t tests with Bonferroni corrections for multiple comparisons. Statistical significance was defined as $p < 0.05$. Univariate analysis was done based on Fisher's exact test for predictors of gender, race (white and non-white), and ethnicity, and based on the Wilcoxon test for the predictors of age at CRPS diagnosis and time elapsed from diagnosis to survey."

Results: Our study had a 55% overall survey response rate. Of the 53 study patients, 68% reported some degree of pain at the time of the survey. There were no significant associations between reported race and reports of pain versus no pain. Only age at CRPS diagnosis versus follow-up pain had a p value less than 0.05. Using logistic regression for predicting at least some pain based on the age of CRPS diagnosis, we found that each increment of one year of age at diagnosis increased the odds of having some pain at the time of the survey by a factor of 1.61, an increase of 61% ($p=0.0049$). The time from diagnosis to the time of survey completion did not predict the presence of pain at the time of survey ($p = 0.0625$). Neither age at the time of CRPS diagnosis nor the amount of time that had elapsed between diagnosis and the survey were significant predictors of pain as an ordinal.

Conclusion: The majority (68%) of patients completing a survey reported some degree of CRPS-related pain, and each increasing year of age at CRPS diagnosis increased the odds of some pain by 61%. A later onset of CRPS in adolescence portends a worse prognosis of having pain in adulthood. In terms of health-related quality of life, in our cohort there were lower SF-8 scores in the composite physical component score of 44.4 (95% CI 3.3) and the composite mental component score of 43.4 (95% CI 3.4). These quality of life scores are congruent with the finding that most patients have pain in their young adult years. It is encouraging that only a minority of patients (32%) had symptoms that had spread to other limbs, and only 38% of patients felt that their symptoms warranted further evaluation and treatment. We believe awareness of these findings is important for pediatric patients and their parents to understand the expected trajectory of CRPS. Perhaps greater insight into these long-term outcomes and disabilities and further attention to managing expectations of treatments may help improve their quality of life as adults.

Reference(s): User’s manual for the SF-36v2 Health Survey 3rd ed. QualityMetric Incorporated 2011;6-8.

Patient Characteristics

	Male (%)	**Female** (%)
GENDER	12 (23%)	41 (77%)
AGE	**Range**	**Mean ± SD**
Age at survey (yr)	18 - 27	19.1 ± 2.0
Age at diagnosis (yr)	9 - 17	13.5 ± 2.2
Time from treatment to survey (yr)	1.55 - 13.46	6.0 ± 2.98
SYMPTOMS	**Yes** (%)	**No** (%)
Pain at time of survey	36 (68.0%)	17 (32.1%)
Spread of symptoms	17 (32.1%)	36 (67.9%)
Recurrent symptoms requiring treatment	20 (37.7%)	33 (62.3%)

Pain Medicine-9 A Predictive Model for 2-Week Postoperative Opioid Use Following Ambulatory Joint Arthroscopy

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[1]University of California San Diego School of Medicine, La Jolla, CA, [2]University of California, San Diego, La Jolla, United States of America, [3]University of California, San Diego, La Jolla, CA, [4]University of California, San Diego, La jolla, United States of America, [5]University of California, San Diego, La jolla, CA

Introduction: The number of joint arthroscopy procedures performed in the ambulatory surgery setting is steadily increasing. Management of perioperative pain in ambulatory surgery is challenging and necessitates communication between anesthesiologists, surgeons and patients, as well as early interventions to manage pain experienced after surgery. Unfortunately, there are very few studies that have examined risk factors for continued postoperative opioid use in the outpatient setting. We developed a predictive model to identify variables predictive of need to refill opioid prescription 2 weeks postoperatively.

Methods: A predictive model was developed using single institutional data from patients undergoing joint arthroscopy (knee arthroscopy, anterior cruciate ligament repair, hip arthroscopy, shoulder arthroscopy, or rotator cuff repair) from 2018-2019 using various demographic, comorbidity, intraoperative and recovery room data. The primary outcome was need to refill opioid prescription after 2 weeks. Variables were entered into a multivariable logistic regression model if they met a significant level of $p<0.05$ on univariate analysis. The final model was built using a combination of forward selection and backwards elimination based on the Akaike Information Criterion. Variables were allowed to stay in the model if significance level of $p<0.1$. The final model was then validated on bootstrapped samples (R=1,000) and the average area under the receiver operating characteristic curve (AUC) and Hosmer-Lemeshow (HL) p-value for discrimination and goodness-of-fit, respectively, were reported. The odds ratio (OR) and 95% confidence interval (CI) for each covariate was reported.

Results: There were a total of 406 patients included in the analysis. The rate of 2-week opioid use was 14.8% (n=60). The final model included: native English speaker (OR 0.23, 95% CI 0.07 - 0.82, p = 0.02), alcohol use (OR 4.33, 95% CI 1.77 - 10.62, p = 0.001), active smoker (OR 2.89, 95% CI 1.27 - 6.52, p = 0.01), hypertension (OR 2.19, 95% CI 0.99 - 4.85, p = 0.05), history of anxiety and/or depression (OR 1.76, 95% CI 0.92 - 3.38, p = 0.09), chronic pain (OR 3.40, 95% CI 1.46 - 7.88, p = 0.004), and total intravenous morphine equivalents use in the recovery room (OR 1.06, 95% CI 1.01 - 1.12, p = 0.01). The average AUC calculated from the bootstrapped samples was 0.748 (95% CI 0.675 - 0.821) and the average HL-test p-value was p = 0.86.

Conclusion: This predictive model revealed that in patients undergoing ambulatory joint arthroscopy, the need to refill opioid prescriptions 2 weeks after surgery were increased in those who were native English speakers, had alcohol use, active smoking, hypertension, history of anxiety and/or depression, chronic pain and total intravenous morphine equivalents use in the recovery room. We hope that with this information, we can better predict who is at risk for chronic opioid use and therefore improve patient education and intervene earlier to attempt to decrease long term postoperative opioid use.

Pain Medicine-10 ACETAMINOPHEN, UNDERUTILIZED IN OLDER ADULT TRAUMA PATIENTS

Justin G Vaughan[1], Matthew Fuller[2], Karthik Raghunathan[3], Vijay Krishnamoorthy[3], George Kasotakis[2], Suresh Agarwal[1], Krista L Haines[4]

[1]Duke University Hospital, Durham, NC, [2]Duke University Hospital, Durham, United States of America, [3]Duke University, Durham, NC, [4]Duke University, Durham, United States of America

Introduction: Given the vulnerability of older patients and opioid associated morbidity, this study focused on pain medication escalation in the immediate post-operative setting. The purpose of this study was to determine the frequency of acetaminophen use in post-operative older adult trauma patients once able to tolerate oral medications.

Methods: From 2008-2014, 175,787 older adult trauma patients (≥65) suffered falls (E880-E888) resulting in hip fractures requiring femur or hip fixation (79.15,79.35,78.55,81.51,81.52) and were recorded in the Premier database. Patients were excluded if they were admitted to the ICU prior to surgery or on POD 1 or 2 had concurrent tibia/fibula procedures, or were above the 95th percentile for opioid use on their last hospital day. We examined patients to identify the frequency of opioid medication administration without prior acetaminophen exposure in the post-operative setting. To examine the use of opioids used the day before and day of discharge, a mixed effects linear regression model was fit with fixed effects for patient demographics, hospital characteristics, patient comorbidities, surgery type, and co-treatments, as well as a random intercept for each hospital to control for patient clustering. Main exposure was acetaminophen on DOS or postoperatively before receipt of opioid/acetaminophen combination drugs or oral opioids.

Results: In this analysis, 8%(15,428) of patients received opioid medications without first being administered acetaminophen, and only 19.8%(38080) of patients received acetaminophen prior to opioids. Of this cohort, 81.6% were Caucasian, 74% were female, average age was 82 years, and 26.4% (50801) of patients were given a combination acetaminophen/opioid pill before Tylenol or opioids. Tylenol first was associated with reduced opioids on day before and day of discharge (3.60 MME less [3.41, 3.79]; p<.0001).

Conclusion: There is clearly potential to improve delivery of non-opioid medications, including acetaminophen, prior the administration of opioid-based medications. According to this data 1/3rd (34%) of older adult patients would benefit from acetaminophen as first line analgesia, minimizing the exposure of older adult trauma patients to the side effects and addiction potential of opioids.

Pain Medicine-11 Norepinephrine differentially modulates nociception in a stress- and sex-dependent manner in mice

Loc V Thang[1], Manish K Madasu[2], Makenzie R Norris[1], Jazmin R Garcia[1], Priyanka Chilukuri[1], Sreemathi Palanisamy[2], Ream Al-Hasani[2], Jordan G McCall[1]

[1]Washington University in St. Louis, Saint Louis, MO, [2]Saint Louis College of Pharmacy, Saint Louis, MO

Introduction: Psychological stress can either suppress or enhance pain. The precise mechanisms of how stress induces analgesia or hyperalgesia is unclear. Similar to chronic pain, stress-related psychiatric disorders such as depression and anxiety have poorly understood pathophysiology. Both chronic pain and stress lead to adaptations sharing significant overlapping physiology such that tricyclic and SNRI antidepressants are effective in treating chronic pain. Therefore, norepinephrine (NE) is likely one of the key neurotransmitters regulating pain processing during stress. Locus coeruleus (LC), a brainstem nucleus, supplies most of the NE released in the brain and spinal cord. Previously we showed that increased tonic LC noradrenergic activity drives acute antinociception in mice. LC neurons that project to the dorsal spinal cord are thought to promote descending pain modulation. This view is also consistent with behavioral studies that support the antinociceptive effects of NE mediated by spinal alpha-2-adrenergic receptors (α2-ARs). Growing evidence suggests that chronic pain may derive from dysregulation of the descending pain inhibitory pain pathways. Recent studies demonstrate that α2-ARs in the dorsal root ganglion (DRG) inhibit transient receptor potential cation channel subfamily V member 1 (TRPV1), a polymodal molecular integrator in the pain pathway expressed in Aδ and C fiber nociceptors. This study examines, in mice, 1) the effect of NE on TRPV1 signaling in sensory neurons during chronic stress and 2) the role of LC-NE activity in stress-induced analgesia.

Methods: We used 3 models of chronic stress: 1) a 10-day social isolation stress (SIS), 2) a 3-week chronic mild stress (CMS), and 3) 30-minute acute restraint stress (ARS). For SIS, animals were singly-housed in standard home cages with ad libitum food and water. For CMS, a series of seven stressful events (removal of nesting for 24 h, 5 min forced swim stress at 15°C, 8 h food and water deprivation, damp bedding overnight, white noise, cage tilt, and disrupted home cage lighting) were randomly shuffled and repeated over a 3-week period. For ARS, animals were restrained in a conical tube for 30 minutes in some experiments this restraint was repeated 3 times with 5 days inter-stress intervals. We evaluated mechanical sensitivity with the von Frey assay and thermal sensitivity with a 45ºC or 55ºC hot plate. To study Ca+2 dynamics, we used Ca+2 imaging in the present of TRPV1 agonist, capsaicin (200 nM), with or without pre-application of NE (10 μM), the α2-AR agonist guanfacine (10 μM), or α2-AR antagonist atipamezole (10 μM). To inhibit LC-NE neurons, AAV5-EF1α-DIO-hM4Di-mCherry was injected into the LC of Dbh-Cre mice. JHU37160 (0.1 mg/kg i.p), a DREADD receptor agonist, was used to activate hM4Di in LC-NE neurons, 3 weeks post-injection.

Results: SIS increases paw-withdrawal thresholds to mechanical and thermal stimuli in both male and female mice ($p<.01$, Student's T-test). In contrast, CMS did not alter either mechanical or thermal nociception. For ARS, the first exposure to 30 minutes of restraint stress increases jump latency on a 45ºC hot plate. This effect is lost after the 2nd exposure but decreases with the 3rd exposure ($p<.001$, two-way ANOVA with Sidak posthoc test). Using Ca2+ imaging, we show that SIS blunts TRPV1-mediated Ca2+ mobilization in sensory neurons from male mice ($p<.001$, Student's T-test). Furthermore, both NE and the α2-AR agonist guanfacine inhibit TRPV1 activation in the DRG of male group-housed mice, but not in group-housed females or singly-housed mice of either sex. These results are reversed by the α2-ARs antagonist, atipamezole. Inhibiting LC-NE neurons, through activation of hM4Di, prevents acute restraint stress-induced analgesia in mice.

Conclusion: This study shows different stress models distinctly alter nociception. Interestingly, first time exposure to acute restraint stress is antinociceptive, but repeated exposure converts to pronociception. Therefore, this paradigm might be a good model to study the effect of stress chronicity on nociception. The reduction in TRPV1-depdent calcium signaling may help explain the mechanism for social isolation stress-induced antinociception in male mice, but suggests this phenomenon is NE-independent in female mice. This effect of stress-induced antinociception may involve LC-NE spinal projections or peripheral sources of NE.

Pain Medicine-12 The Impact of Non-Steroidal Anti-Inflammatory Drugs on Older Adult Trauma Patients with Hip Fractures

Justin G Vaughan[1], Krista L Haines[2], Matthew Fuller[3], Vijay Krishnamoorthy[4], Karthik Raghunathan[4], George Kasotakis[3], Raquel R Bartz[4], Suresh Agarwal[1], Tetsu Ohnuma[4]

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Introduction: Non-Steroidal Anti-Inflammatory Drugs (NSAID) are frequently incorporated into multimodal pain control treatment plans. A major goal of multimodal therapy is improved pain control while simultaneously reducing the amount opioids used. This reduction in opioid morbidity allows for improved patient outcomes. Falls are a frequent source of morbidity and mortality in trauma. This study focused on the impact NSAIDs have on hospital length of stay (LOS), perioperative bleeding, opioid consumption, and intensive care unit (ICU) admission rates in adult fall trauma patients undergoing hip surgery. Given the mechanism of injury and surgery type studied, this project focused on the older adult population.

Methods: Using the Premier database, a retrospective cohort study of 190,057 adult trauma patients over a 6-year period (2008-2014) was performed. Patients aged 65 or older undergoing hip repair surgeries (E codes 880-888) following fractures due to falls (ICD9 codes: 79.15,79.35,78.55,81.51,81.52) were analyzed to determine the impact of NSAIDs on LOS, ICU admissions, bleeding risk, and opioid requirements. Billing data from the database was used to determine the outcomes measured. A mixed effects logistic regression model with the receipt of NSAIDs on DOS as the outcome was utilized to explore the impact of NSAIDs on these patients. Fixed effects were included for patient and hospital characteristics, patient comorbidities, co-treatments, and surgery type. The type I error rate was set at 0.05 as the threshold for statistical significance. Analysis were performed using SAS version 9.4 (SAS Institute; Cary, NC).

Results: Provided the mechanism of injury and surgery studied the average age of the population studied was 83 years old. NSAIDs had a positive impact in reducing the hospital LOS 5.61 days vs. 5.96 days, 0.18 days shorter, 95% CI [-0.24, -0.12]; p < .0001) and decreasing ICU admissions (9.73% vs. 10.59%; OR: 0.91, 95% CI [0.86, 0.96]; p < .0001). Despite increased transfusion requirements on POD1 (OR: 1.15 [1.11, 1.20]; p<.0001), no overall increase in bleeding was noted throughout the hospital admission (40.83% vs. 43.18%; OR 1.02 [0.99, 1.05]; p<.0001). Overall NSAIDs did decrease the amount of opioids prescribed (12.01 MME vs. 11.43 MME β = -0.23 mg (or MME), 95% CI [0.41, -0.06]; p = .2625)

Conclusion: NSAID use on the day of surgery was associated with improved hospital LOS and decreased ICU admissions. Although NSAIDs were associated with an increase in bleeding on POD1, no overall increase in bleeding rates were identified over the entire admission. A decrease in opioid prescribing during these hospitalizations was found. To our knowledge, this is the first study focused linking NSAIDs to decreased ICU admission rate in older adult trauma patients after surgery.

Patient Safety

Patient Safety-1 Improving Basic Preventive Measures in the Perioperative Arena to Reduce S. aureus Transmission and Surgical Site Infections, a Randomized Trial

Randy W Loftus[1], Franklin Dexter[1]

[1]University of Iowa, Iowa City, IA

Introduction: Surgical site infections increase patient morbidity and healthcare cost (1-4). The Centers for Disease Control and Prevention emphasizes improved basic preventive measures to reduce bacterial transmission and infections for patients undergoing surgery (5,6). We sought to determine whether improved basic preventive measures can reduce perioperative S. aureus transmission and surgical site infections.

Methods: We conducted a one-year randomized clinical trial (9/20/2018-9/20/2019) with a 60-day follow-up period at the University of Iowa. Nineteen surgeons and their associated patients (N=236) were randomized 1:1 via a random number generator to sustained improvements in perioperative provider hand hygiene, vascular care, environmental cleaning, and patient decolonization efforts or to usual care. S. aureus transmission (primary outcome) was assessed by the number of isolates transmitted and by the incidence of transmission occurring among patient care units. Patients were followed for 60 postoperative days to assess for the development of surgical site infections according to National Healthcare Safety Network definitions (secondary outcome). Observers were blinded to patient groupings during assessment of outcome measures.

Results: Treatment reduced the mean (± standard deviation) number of transmitted perioperative S. aureus isolates (1.25 ± 2.11 control vs. 0.47 ± 1.13 treatment, Wilcoxon-Mann-Whitney test P=0.002). Treatment reduced the incidence of S. aureus transmission (incidence risk ratio 0.56; 95% CI 0.37-0.86, P=0.008; clustering by surgeon, 95% CI 0.42-0.76, P<0.001). Approximately 4% of patients (11/236) suffered from surgical site infections, 7.69% in the control group (10/130) and 0.94% (1/106) in the treatment group. Transmission was associated with an increased risk of surgical site infection (11.0% [8/73] with transmission vs. 1.8% [3/163] without, risk ratio 5.95, 95% CI 1.63-21.80, P=0.004). Treatment reduced the risk of surgical site infection (Cox regression hazard ratio 0.12; 95% CI 0.015-0.918, P=0.041; with clustering by surgeon, 95% CI 0.027-0.506, P=0.004).

Conclusion: Improved basic preventive measures in the perioperative arena can reduce S. aureus transmission and surgical site infections.

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2. Infect Control Hosp Epidemiol 2012; 33: 283-91.
3. Clinical Infectious Diseases 2009; 48:1–12.
4. Surg Infect (Larchmt) 2012; 13: 307-1.
5. http://www.whitehouse.gov/the-press-office/2014/09/18/fact-sheet-obama-administration-takes-actions-combat-antibiotic-resistan. FACT SHEET: Obama Administration Takes Actions to Combat Antibiotic-Resistant Bacteria. The White House, Office of the Press Secretary. Accessed September 1st, 2018.
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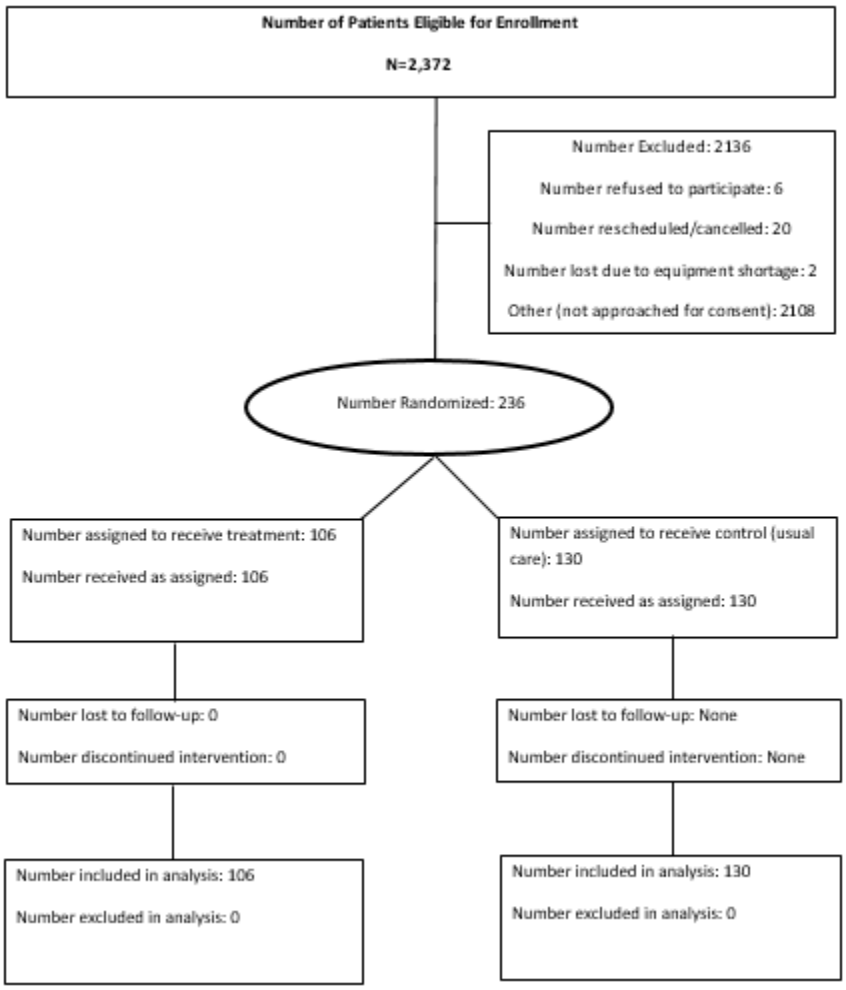
Table 1: Baseline Patient and Procedural Demographics	**Treatment**	**Control**
Baseline Patient and Procedural Demographics by Treatment N (%)	106 (44.92)	130 (55.08)
Age > 50 N (%)	88 (83.02)	81 (62.31)
Female N (%)	43 (40.57)	113 (86.92)
ASA > 2 N (%)	62 (58.49)	44 (33.85)
Dirty or Infected Site N (%)	3 (2.83)	6 (4.62)
Duration > 2 Hours N (%)	97 (91.51)	119 (91.54)
Plastic surgery N (%)	1 (0.94)	27 (20.77)
Orthopedic surgery N (%)	27 (25.47)	20 (15.38)
General abdominal surgery N (%)	5 (4.72)	6 (4.62)
Preoperative decolonization strategy		
Nasal mupirocin and chlorhexidine for 5 days N (%)	27 (25.47)	20 (15.38)
Chlorhexidine for day before and morning of surgery N (%)	55 (51.89)	80 (61.54)
No protocol N (%)	24 (22.64)	30 (23.08)
Discharge location		
Same day	27 (25.47)	54 (41.54)
Floor	69 (65.09)	73 (56.15)
Intensive care unit	10 (9.43)	3 (2.31)
	Yes	**No**
Baseline Patient and Procedural Demographics by *S. aureus* Transmission N (%)	73 (30.93)	163 (69.07)
Age > 50 N (%)	48 (65.75)	121 (74.23)
Female N (%)	53 (72.60)	103 (63.19)
ASA > 2 N (%)	27 (36.99)	79 (48.47)
Dirty or Infected Site N (%)	5 (6.85)	4 (2.45)
Duration > 2 Hours N (%)	68 (93.15)	148 (90.80)
Plastic surgery N (%)	11 (15.07)	17 (10.43)
Orthopedic surgery N (%)	12 (16.44)	35 (21.47)
General abdominal surgery N (%)	4 (5.48)	7 (4.29)
Preoperative decolonization strategy		
Nasal mupirocin and chlorhexidine for 5 days N (%)	12 (16.44)	35 (21.47)
Chlorhexidine for day before and morning of surgery N (%)	45 (61.64)	90 (55.21)
No protocol N (%)	16 (21.92)	38 (23.31)
Discharge location		
Same day	25 (34.25)	56 (34.36)
Floor	43 (58.90)	99 (60.74)
Intensive care unit	5 (6.85)	8 (4.91)

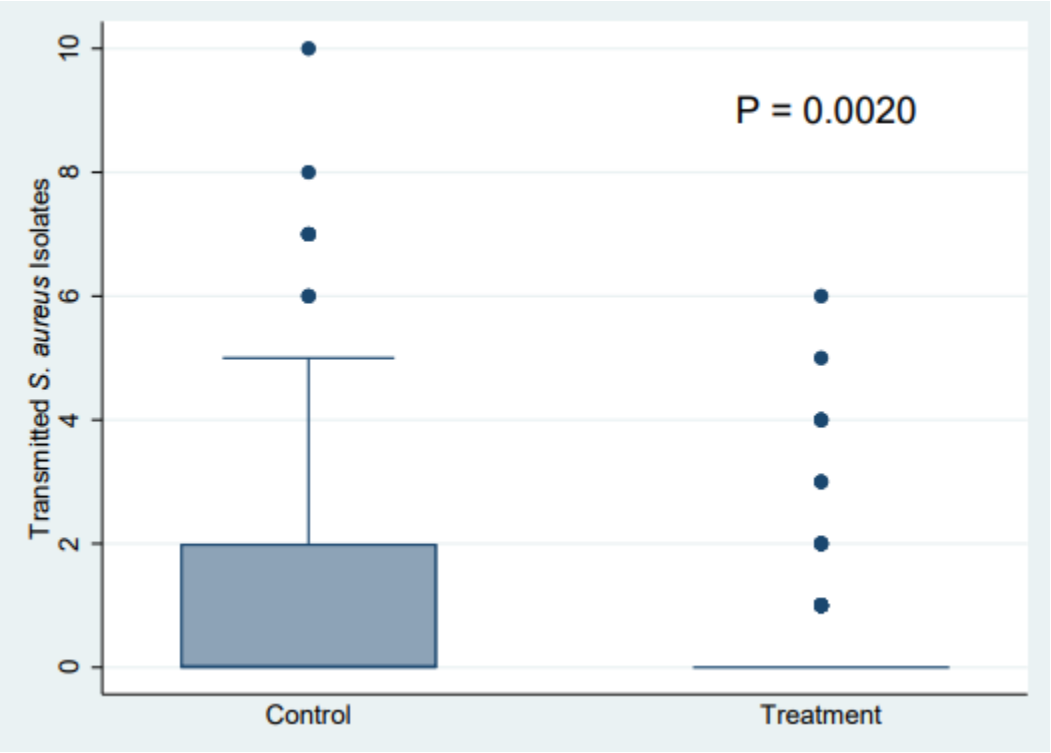
Table 2: *S. aureus* Reservoir Exposure, Transmission and SSI Development by Surgeon and Treatment

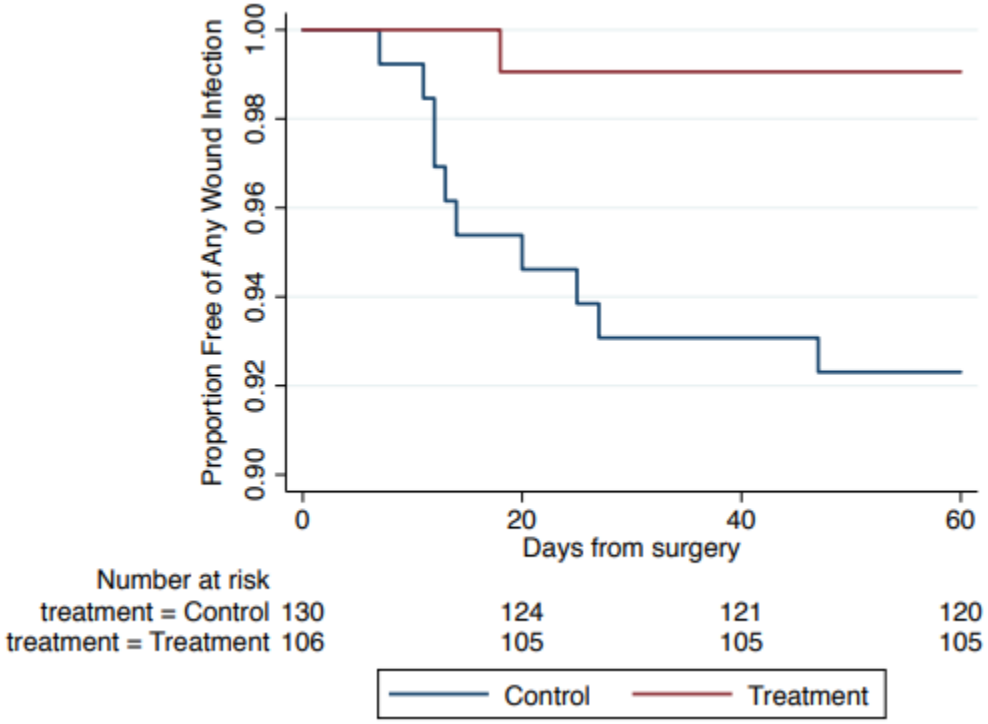
Surgeon	Treatment	No. Cases	Isolates Transmission N (%)	Transmission N (%)	Surgical Site Infection N (%)
7	1	41	23 (46)	10 (45.5)	1 (100)
8	1	27	15 (30)	7 (31.8)	0
9	1	4	7 (14)	2 (9.1)	0
10	1	16	4 (8)	3 (13.6)	0
11	1	6	0 (0)	0 (0)	0
12	1	6	0 (0)	0 (0)	0
14	1	3	0 (0)	0 (0)	0
16	1	1	0 (0)	0 (0)	0
18	1	1	1 (2)	0 (0)	0
19	1	1	0 (0)	0 (0)	0
Total		**106**	**50**	**22**	**1**
1	0	45	41 (25.3)	19 (38)	5 (50)
2	0	26	42 (25.9)	12 (24)	2 (20)
3	0	19	35 (21.6)	7 (14)	2 (20)
4	0	6	4 (2.5)	2 (4)	0
5	0	20	12 (7.4)	5 (10)	0
6	0	8	13 (8)	3 (6)	1 (10)
15	0	1	0 (0)	0 (0)	0
17	0	2	7 (4.3)	0 (0)	0
13	0	3	8 (4.9)	2 (4)	0
Total		**130**	**162**	**50**	**10**

Treatment 0=usual practice, 1= program

Fig. 1. Patient Randomization Profile




P = 0.0020
Transmitted S. aureus Isolates
0
2
4
6
8
10
Control
Treatment


Proportion Free of Any Wound Infection
0.90
0.92
0.94
0.96
0.98
1.00
0
20
40
60
Days from surgery
Number at risk
treatment = Control 130 124 121 120
treatment = Treatment 106 105 105 105
Control
Treatment

Patient Safety-2 The Difficult Airway Response Team Program: Twelve Years of Lessons Learned and Ongoing Innovations

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[1]Johns Hopkins Hospital, Baltimore, MD, [2]JOhns, Baltimore, MD, [3]Johns Hopkins Hospital, baltimore, MD

Introduction: We previously described the implementation and lessons learned from the Difficult Airway Response Team (DART) program, a multidisciplinary collaboration between anesthesiologists, otolaryngologists, emergency physicians, and trauma surgeons (Figs. 1, 2).1-3. Innovations in 2018 included our One Breath From Death Perioperative Integrative Medicine Consultation for survivors of failed/difficult airway management.4. We report on aspects of our 12-year experience with the DART program.

Methods: This IRB-approved study included all events for which DART was activated to manage adult patients from July 2008 to July 2018. The DART database was used to collect demographic and event data, including intubation technique and success or failure of each attempt. Chi-squared testing with pairwise Bonferroni correction ($p \leq 0.05/6 = 0.0083$ statistically significant) was used to compare intubation technique success rates. Linear regression was used to model the change in technique prevalence over time.

Results: During the period studied, 729 DART activations were recorded (57.8% male, average age ± standard deviation=55.6±16.7 years). The predominant locations for DART activation were intensive care units (n=373, 51.1%) and the emergency department (n=143, 19.6%). Of the 729 patients, 125 (17.1%) were transported to the operating room for management. Risk factors for DART activation included known difficult airway, angioedema, current tracheostomy, airway bleeding, and body mass index > 30. The primary techniques used were video laryngoscopy (VL), direct laryngoscopy (DL), fiberoptic bronchoscopy (FOB) techniques, rigid laryngoscopy (RL), and surgical airway; supgraglottic airway was used as part of airway management in 58 (8.0%) activations. Linear regression showed a significant increase over time in the percentage of attempts with VL (slope=3.0%/year, 95% confidence interval=1.8%–4.2%, p=0.0005). Chi-squared analysis revealed higher rates of success for FOB techniques (133/179, 74.3%) than for either DL (143/277, 51.6%) or VL (142/267, 53.2%) ($p<0.00001$ for both). RL (48/74, 64.9% successful) was associated with higher success rates than DL (p=0.04) or VL (p=0.07), but these results were not significant after Bonferroni correction. Fifty-six patients (7.7%) required a surgical airway (cricothyroidotomy or tracheostomy) (Figs. 3-5). No airway-related mortalities, malpractice claims, or sentinel events occurred during DART activations.

Conclusion: The DART program has successfully prevented airway-related mortality through multidisciplinary collaboration, promoted wellness for practitioners and patient survivors through Integrative Medicine, and received national and international recognition for Best Clinical Poster and changing clinical practices in airway management.5,6. Institutions should consider customizing the DART program to optimize their clinical practice.

Reference(s):

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4. Expert Panel Session and Poster Presentation. World Airway Management Meeting (WAMM). Amsterdam, Netherlands, Nov 2019
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6. Anesth Analg Most Important Airway Papers, 2015-2019. Anesth Analg 2015; 121(1): 127-139, World Airway Management Meeting (WAMM), Amsterdam, Netherlands, Nov. 2019

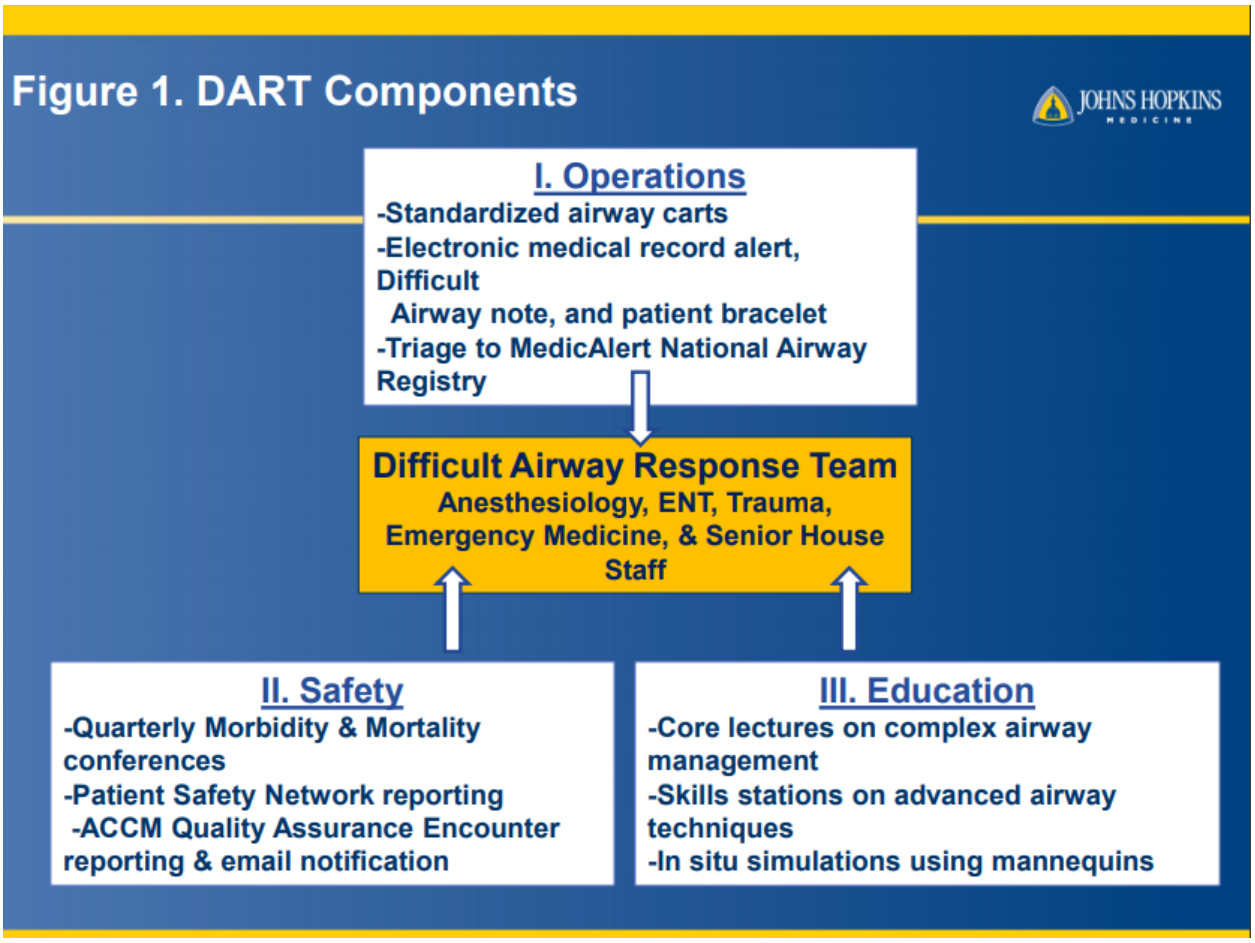
Figure 1. DART Components
JOHNS HOPKINS MEDICINE
I. Operations
-Standardized airway carts
-Electronic medical record alert, Difficult Airway note, and patient bracelet
-Triage to MedicAlert National Airway Registry
Difficult Airway Response Team
Anesthesiology, ENT, Trauma, Emergency Medicine, & Senior House Staff
II. Safety
-Quarterly Morbidity & Mortality conferences
-Patient Safety Network reporting
-ACCM Quality Assurance Encounter reporting & email notification
III. Education
-Core lectures on complex airway management
-Skills stations on advanced airway techniques
-In situ simulations using mannequins

Figure 2. Lessons learned and innovations from the DART Program: 2008-present

1. Communication is critical: clarify attending roles when you arrive at the bedside: "Who's in charge?"
2. Customize a standardized approach for airway management to optimize the expertise of all specialties.
3. Incorporate "Just-in-Time" training to maintain fiberoptic intubation and bronchoscopy skills – they remain the gold standard for awake intubation and select asleep airway management.
4. A surgical airway is not a failed airway and might be first choice technique
5. Transporting select high risk patients to an operating environment might optimize successful airway management.
6. Pre-existing front of neck airways are potentially difficult airways and might require multidisciplinary airway interventions.
7. Collect and use data to continually improve.
8. Create a pediatric DART Program as indicated.
9. Do not forget the second victim and the aftermath of adverse airway events for providers.
10. Consider creating a One Breath from Death Perioperative Integrative Program for survivors of failed/difficult airway management.

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Figure 3. Patient predisposing factors, 2008-20018.

Patient predisposing factors	Total #	% of Adult DARTs
History of COPD	74	10.2
History of Head and Neck Tumor	149	20.4
History of Difficult Airway	201	27.6
Current C-spine injuries	79	10.8
Current Angioedema	48	6.6
Current Airway Bleeding	104	14.3
BMI ≥ 30	276	37.9
Current Trach	101	13.9
Total DARTs	**729**	-

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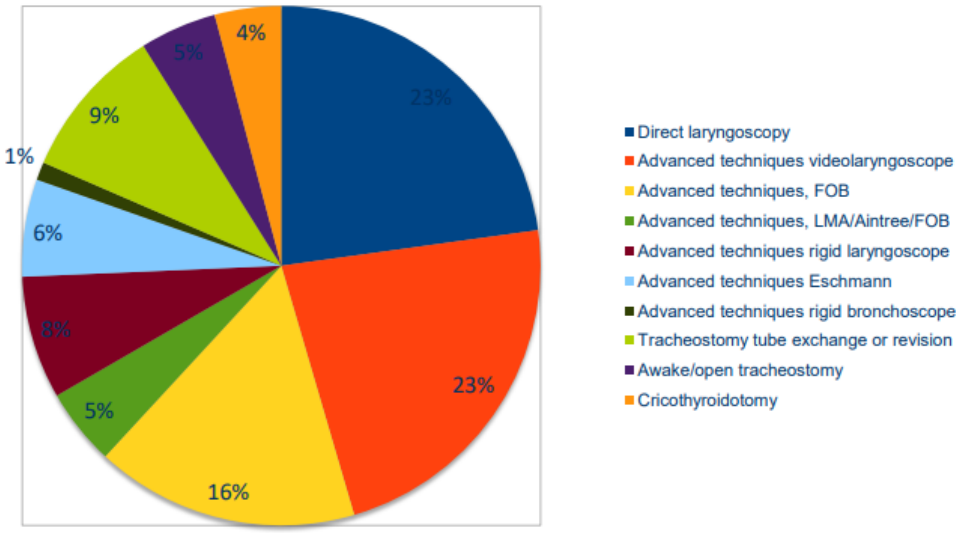
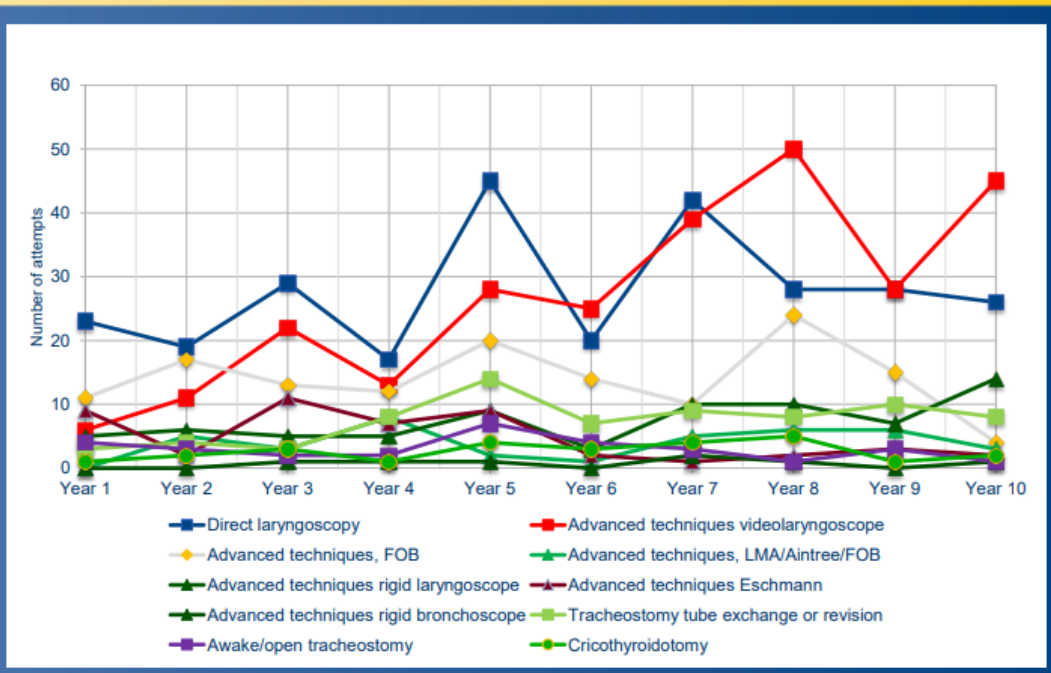
Figure 4. Total succsful DART techniques, 2008-2018.



JOHNS HOPKINS MEDICINE

Figure 5. Total DART techniques by year, 2008-2018.



Patient Safety-3 Predicting Need for Language Translation During Emergence from Anesthesia for Non-Native English Speaking Patients

Tracy Dinh[1], Christopher Awounou[2], Nicholas Lyon[1], Sean O'Connor[1], Avery Tung[3], David Glick[1]

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Introduction: As the United States becomes more culturally diverse, the number of patients whose native language is not English is likely to increase. Current evidence suggests that such patients experience more difficulty communicating with healthcare providers[1,2] and are often not offered an interpreter[3]. During emergence from anesthesia, response to verbal commands is often used to assess anesthetic depth and whether patients may be safely extubated. We have previously observed that non-native English speaking patients may preferentially respond to commands in their native language during anesthetic emergence. How to predict which patients respond preferentially to their native language, however, is incompletely understood. We hypothesized that poor familiarity with English during the awake state would predict a preferential response to the native language during emergence.

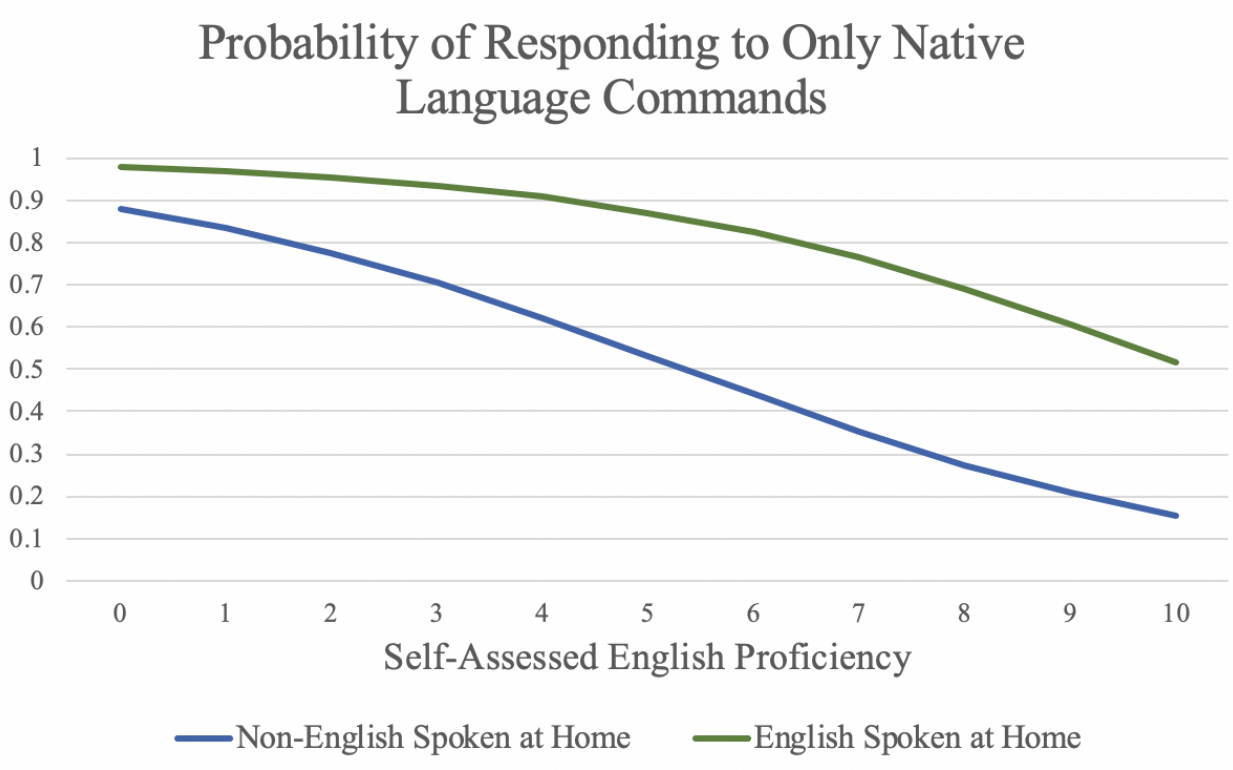
Methods: Non-native English speaking adult patients scheduled for surgical procedures were administered a survey in the preoperative area prior to surgery. The survey asked about the age English was learned, what language is spoken at home, and what language they dream in. Participants were also asked to assess their native and second language proficiencies on a scale of 1-10. During emergence from anesthesia, participants were then given the commands 'open your eyes', 'squeeze my finger', and 'wiggle your toes' alternating between English and their native language using an iPad. The relationship between survey responses and response to native language commands only was then assessed using logistic regression.

Results: Of the 106 patients who were consented, 80 completed the protocol. 26 patients were excluded due to a change from general to regional anesthesia, change in length of surgery, and delayed communication with the anesthesia team. Univariate regression identified age English was learned, self-assessed English proficiency, and language spoken at home as significantly associated with response to native language. After multivariable logistic regression, self-assessed English proficiency ($p=0.03$) and language spoken at home ($p=0.02$) remained significant. As shown in the figure, patients who speak their native language at home and rate their English proficiency ≤ 7 have a greater than 75% chance of responding to only their native language. Patients who speak English at home who also rate their English proficiency ≤ 2 also have a greater than 75% chance of responding to only native language commands.

Conclusion: In this prospective trial of non-native English speakers we demonstrated that many non-native English speakers emerging from anesthesia preferentially respond to commands given in their native language during emergence from anesthesia. After multivariable analysis, both language spoken at home and self-assessed English proficiency correlated with the patient response to only native language commands. Further work is needed to better identify patients who are likely to respond to their native language during anesthesia emergence and who may benefit translation services during that time.

Reference(s):

1. JAMA. 1995;273(9):724-28.
2. Health Aff (Millwood). 2007 Oct;26(5):1258–68.
3. Am J Prev Med. 2003;24(3 Suppl):68-79.


Probability of Responding to Only Native Language Commands
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
1
2
3
4
5
6
7
8
9
10
Self-Assessed English Proficiency
Non-English Spoken at Home
English Spoken at Home

Patient Safety-4 Impact of Environmental Stimulation on Opioid Induced Respiratory Depression

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Introduction: Iatrogenic opioid-induced respiratory depression (OIRD) carries high risk of adverse outcome, with one report citing death or severe brain injury in 75% of affected hospitalized patients.1,2 Recognition of OIRD is challenging, as 1/3 cases occur during continuous pulse oximetry, and 16% within 15-minutes of an apparently uneventful interaction with a caretaker.3 Many suspect that environmental factors such as intermittent conversation or pain, involving neocortical circuitry, may confound the clinical assessment of a patient for signs of opioid toxicity. Pupillary unrest in ambient light (PUAL) is the bilaterally asynchronous, periodic fluctuation in pupil diameter that occurs normally in the human eye within characteristic frequency ranges, thought to be mediated by fluctuating activity in the Edinger Westphal (EW) nucleus.4,5 Portable infrared pupillometers, in conjunction with Fourier Transformation waveform analysis, can measure PUAL. Preliminary studies have suggested that PUAL declines after opioid administration, although a quantitative relationship to opioid has not been systematically established.4,6 We hypothesized that the impact of participation in conversation would mitigate OIRD during remifentanil infusion in volunteer subjects, but that PUAL would consistently decline and remain depressed in accordance with increasing opioid concentration.

Methods: After receiving approval from the UCSF IRB, we conducted a cross-over study of healthy volunteers undergoing two sequential remifentanil infusion protocols, separated by a 30-minute washout period. In Study A, investigators continuously engaged the subject in conversation, while in Study B, a quiet environment was maintained; the study sequence (A/B versus B/A) alternated with each successive enrolee. In each 35-minute test sequence, vital signs and pupil measurements were taken every 2.5 minutes. From 0-10 minutes, remifentanil was infused (at 0.2µg/kg/min x 5 minutes, then 0.3µg/kg/min x 5 minutes, then stopped), and from 10-35 minutes, no drug was given. During a 30-minute rest period between, no measurements were taken. To evaluate PUAL as an indicator of opioid effect, we examined the correlation between PUAL and specific study time-points. During infusion (0-10 minutes) and recovery (10-35 minutes), with incrementally increasing and declining opioid concentrations, we applied the pharmacokinetic model by Minto to estimate remifentanil concentration versus time.7 Analyses were performed using Stata 16.

Results: Baseline PUAL and average diameter measurements did not differ significantly between Run 1 versus 2, or between Study A versus B. In serial pupil measurements taken at 2.5-minute time points during the remifentanil infusion, corresponding with incremental increasing estimated opioid concentrations, PUAL decline was profound and consistent, progressing from baseline to zero to near-zero values (average overall decline 96%, ANOVA F-statistic 94.4, Bartlett chi2 = 182.38, $P < 0.001$). Maximum pupil diameter decline was less pronounced and did not approach a defining lower boundary (average 49%, Bartlett chi2 63.77, $P < 0.001$). Moderate respiratory depression (CO_2 increase ≥ 15% above baseline) occurred more often in Study B (in 20/20 subjects) versus Study A (in 14/20 subjects, Fisher exact $p = 0.02$). Significantly, oxyhemoglobin desaturation occurred more often in Study B (19/20) versus Study A (10/20 subjects, Fisher exact $p = 0.003$, Figure 2), occurring ~2 minutes sooner in Study B versus A (409 ± 159 versus 557 ± 132 seconds, $P = 0.0179$).

Conclusion: Healthy volunteers receiving intravenous remifentanil experienced more frequent respiratory depression and oxyhemoglobin desaturation when the infusion was conducted in a non-stimulating versus stimulating, verbally interactive setting. In contrast to respiratory outcomes, the decline in PUAL did not differ between these two environments. We propose that PUAL represents a robust signal of central opioid effect that is more sensitive than pupil diameter and, unlike measures of ventilatory depression, is not affected by interactions or other common forms of stimulation within the environment. We propose that low or absent values of PUAL will identify patients at risk for deterioration who warrant additional precautions, especially in circumstances where environmental or noxious stimulation might be abruptly withdrawn.

Reference(s):

1. J Addict Med. 2019 Apr 2. doi: 10.1097/ADM.0000000000000536.
2. PLoS ONE 11(2): e0150214. https://doi.org/10.1371/journal.pone.0150214.
3. Anesthesiology 2015; 122: 659–65.
4. Anesth Analg 2017; 124: 915-21.
5. Investigative Ophthalmology and Visual Science 2017; 58: 197-203.
6. Anesth Analg Practice 2018; 10: 279-82.
7. Anesthesiology 1997; 86: 24-43.
8. Anaesthesia 1981; 36: 37-9.

Table 1: Respiratory parameters during remifentanil infusions, by temporal sequence (run) and Study A versus B (interactive versus non-interactive protocols)

Measurement	Run 1	Run 2	Interactive	Non-interactive
Respiratory Depression (≥ 15% CO_2 Increase)	15 (0.75)	19 (0.95)	14 (0.70)	20 (100)^
Highest CO_2 (mm Hg)	47.41 (43.30-51.52)	46.93 (44.06-49.81)	43.37 (40.66-46.09)	50.97^^ (47.62-54.32)
Highest CO_2 Increase (%) above Baseline	26.6 (19.5-33.7)	32.8 (26.4-39.1)	21.3 (15.0-27.7)	37.5 (32.5-42.5)*
Time (Seconds) from Start of Remifentanil to Desaturation	479 ± 149	444 ± 179	557 ± 132	409 ± 159**
Oxyhemoglobin Desaturation, n (%)	13 (65)	16 (80)	10 (50)	19 (95)***

^ Respiratory Depression, defined as highest CO_2 ≥ 15% above baseline, did not differ significantly between Runs 1 and 2 (Fisher exact p = 0.1820) but was significantly more frequent in the non-interactive Study B versus interactive Study A (Fisher exact p = 0.020).
^^ The highest CO_2 was significantly greater during the non-interactive study than the interactive study (p = 0.0007)
* Maximum percent rise in CO_2 was significantly greater in non-interactive Study B compared to interactive Study A; t-statistic = 4.22 with 37 DF, P = 0.0007. However, the difference between Run 2 versus Run 1 was not statistically significant (p = 0.182).
** Time from start of remifentanil infusion until onset of desaturation was significantly longer among subjects in interactive Study A versus non-interactive Study B; t-statistic = -2.52, P = 0.0179.
*** Oxyhemoglobin desaturation occurred significantly more often in the non-interactive Study B versus the interactive Study A (2-sided Fisher exact P = 0.002); frequency difference between Run 1 and Run 2 did not differ statistically (p = 0.480).

Table 2: PUAL measurements during experiments, by temporal sequence (run) and Study A versus B (interactive versus non-interactive protocols)

Measurement	Run 1	Run 2	Interactive	Non-interactive
PUAL at Baseline	0.269 ± 0.106	0.259 ± 0.102	0.265 ± 0.107	0.263 ± 0.101
Lowest PUAL	0.001 ± 0.008#	0.007± 0.008#	0.007 ± 0.009#	0.011 ± 0.007#
Maximum PUAL Decline (% Baseline)	95.65 ± 4.71	96.54 ± 4.31	96.39 ± 5.01	95.79 ± 3.98

Difference between baseline and nadir PUAL values, t-test of equal variance, $P < 0.0001$
No significant differences in lowest values of PUAL were observed in sequential or interactive versus non-interactive runs.

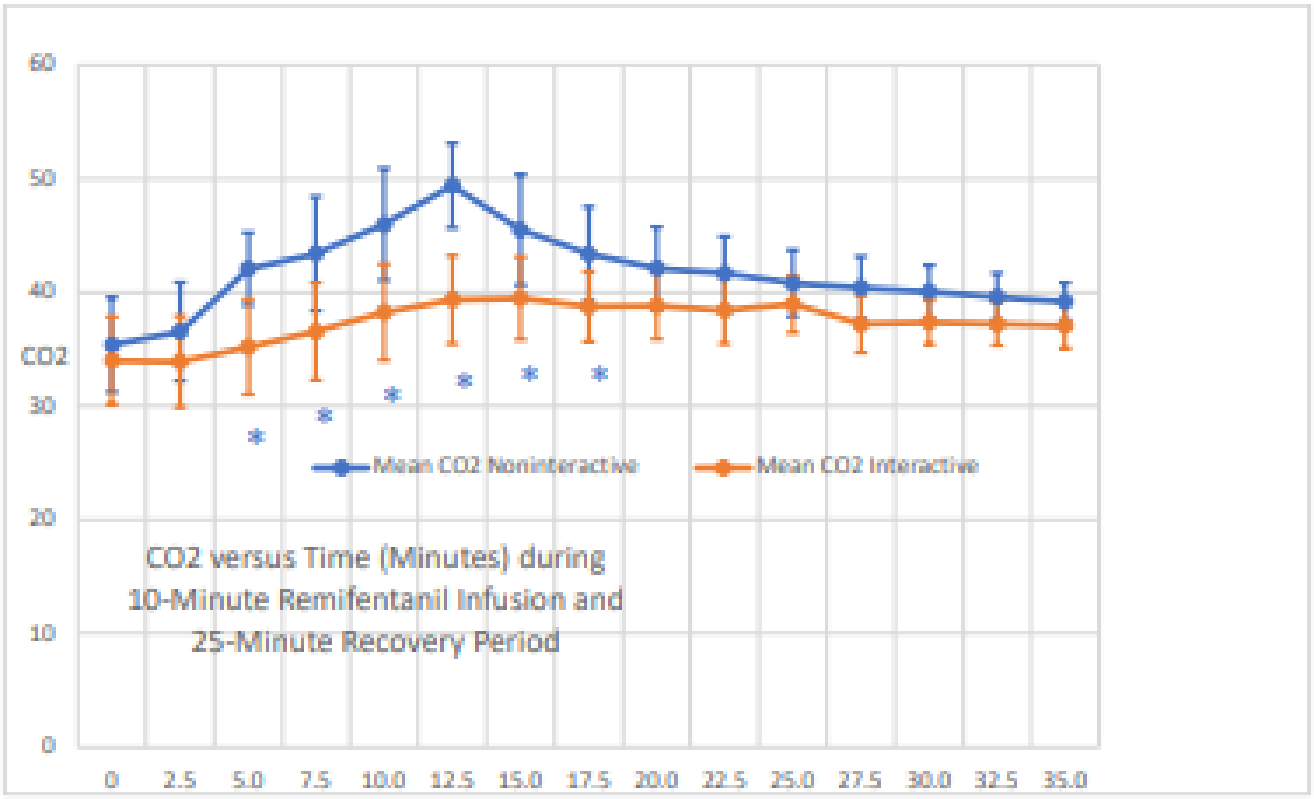

Figure 1: Transcutaneous CO_2 increase was more pronounced during the non-interactive versus interactive experiments, differing significantly at 5.0 – 17.5 minutes

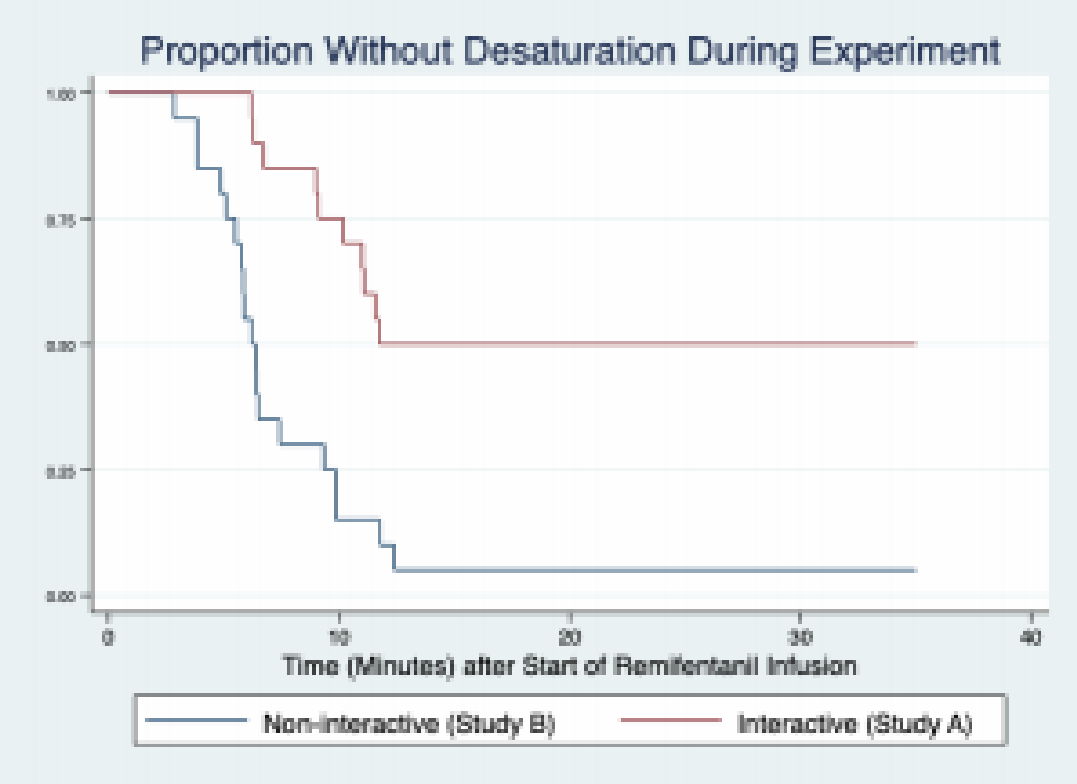

Figure 2: Among the interactive experiments, oxyhemoglobin desaturation was less frequent, (in 10/20 subjects versus 19/20 non-interactive subjects); when it did occur, events were later in the course of the experiment, corresponding to higher estimated opioid concentrations. Interactive protocol HR = 0.229 (0.104 – 0.503), LR chi2 = 14.41, p = 0.0001.

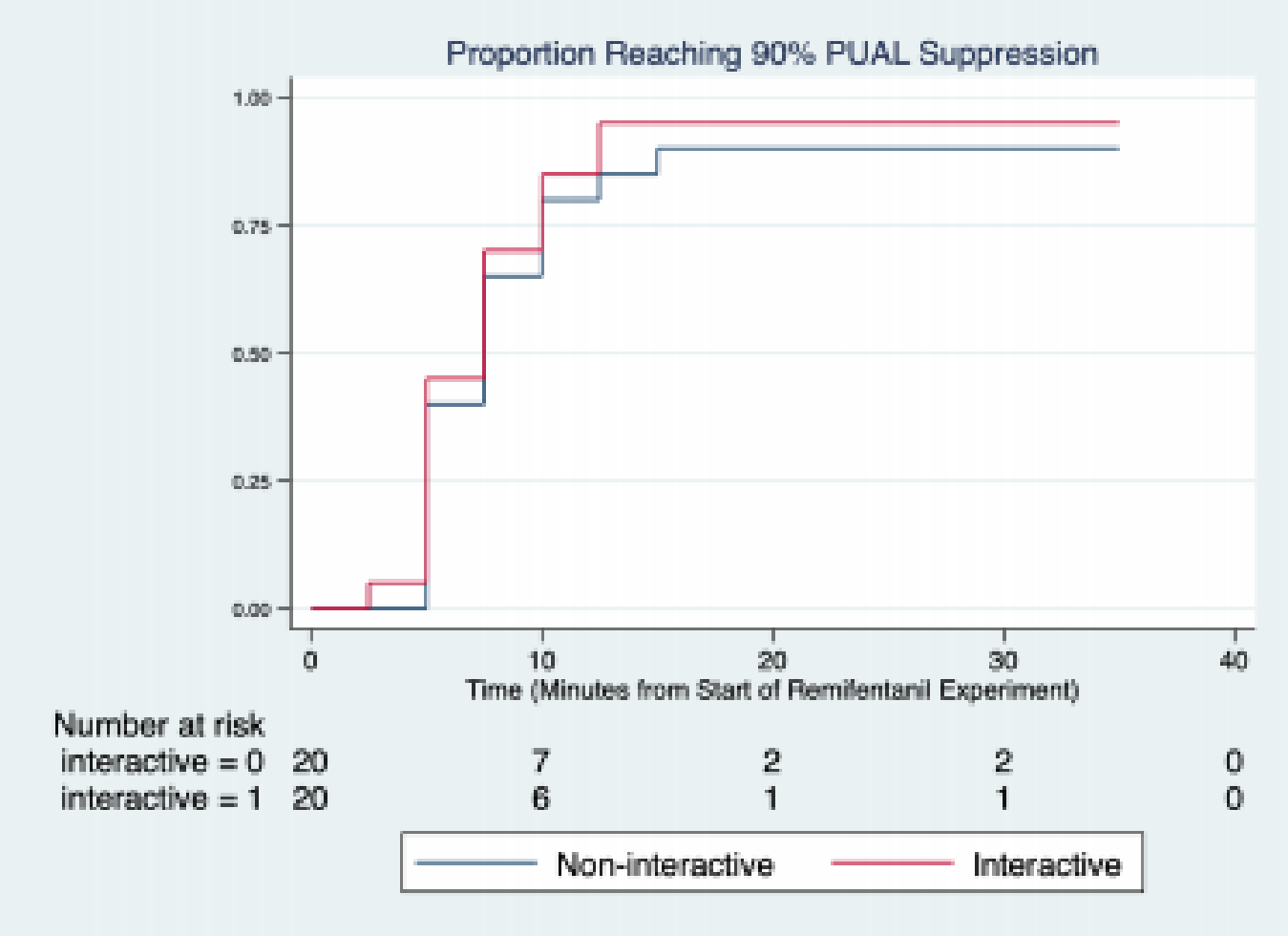

Figure 3: The proportion of subjects reaching ≥ 90% PUAL suppression did not differ in the interactive versus non-interactive protocols, HR = 1.193 (0.624 – 2.278), LR chi2 = 0.29, p = 0.593.

Patient Safety-5 Contextual Factors Influencing Anesthesiologists' Identification of Crises in a Simulated Perioperative Emergency

Lukas Matern[1], Roxane Gardner[2], Jenny Rudolph[3], Rebecca D Minehart[4]

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Introduction: Optimal management of life-threatening perioperative emergencies often hinges upon anesthesia providers recognizing and then alerting others to crises, frequently by calling for help to mobilize key resources. However, triggers for crisis recognition may vary greatly between providers, confounding the implementation of crisis management principles. In this mixed-methods study, we aimed to (1) pinpoint factors influencing clinicians' identification of crises within a perioperative simulation and (2) assess for differences in crisis recognition between observers and active participants in the simulation.

Methods: This IRB-approved study was integrated into a mandatory, recurring course at a freestanding simulation center. Over a 10-month period, a total of 60 attending anesthesiologists from across the U.S. completed a standardized, high-fidelity simulation featuring a case of anaphylactic shock in a low-resource ambulatory surgery setting. In each session, one participant served as the active 'hot seat' participant (HSP) instructed to manage a simulated patient and call for help at the time of crisis. The remaining 2-5 clinicians functioned as 'cool seat' observers (CSOs) who viewed the case via one-way mirrors and recorded the times at which they believed crises occurred. Video footage was reviewed for contextual elements surrounding the crises identified by HSPs and CSOs, including simulated patient vital signs, participant dialogue and behaviors, and airway interventions. Qualitative factors were then categorized by investigators, and descriptive statistics and unpaired t-tests were used to summarize data and compare HSP and CSO groups.

Results: We analyzed data from 60 subjects (19 HSP, 41 CSO). Collectively, HSPs and CSOs identified crises at mean simulated patient vital signs of SBP 92 mmHg, DBP 52 mmHg, MAP 65 mmHg, HR 112 bpm, RR 18 breaths/min, and SpO2 94% (Table 1). We found no meaningful differences between HSP and CSO groups with respect to vital signs at times of recognized crises or times from crisis to airway escalation (Figure 1), though CSOs exhibited variability relative to their HSP counterparts in when they identified crises (Figure 2). The most frequent crisis triggers for CSOs were respiratory concerns (59%), help requests or prompts (34%), and calls for escalated care (27%) (Table 2).

Conclusion: Anesthesiologists identified crises as simulated patients approached hypotension per common definitions (SBP < 90 mmHg or MAP < 65 mmHg). Both participants and observers noted crises based on similar metrics. The most common trigger for crisis recognition among observers was escalation of respiratory support, suggesting that airway and pulmonary findings may powerfully influence anesthesiologists' perceptions of crises despite variability between individual cases. Our findings may guide more effective teaching and application of crisis management principles, particularly in low-resource settings in which standardized triggers to call for help could be employed.

Reference(s): Gaba DM, Fish KJ, Howard SK, Burden AR. Crisis Management in Anesthesiology, 2nd Ed. Elsevier Saunders: Philadelphia, 2015.

Figure 1. Distributions of the simulated patient's vital signs, including SBP, DBP, MAP, HR, RR, and SpO2, at the times of identified crises as well as times from crisis identification to airway escalation with differences between "hot seat" participant (HSP) and "cold seat" observer (CSO) groups. For the purpose of this study, airway escalation was defined as the institution of positive-pressure airway support, most commonly with the use of a bag-valve mask device. P-values were obtained via unpaired t-tests.

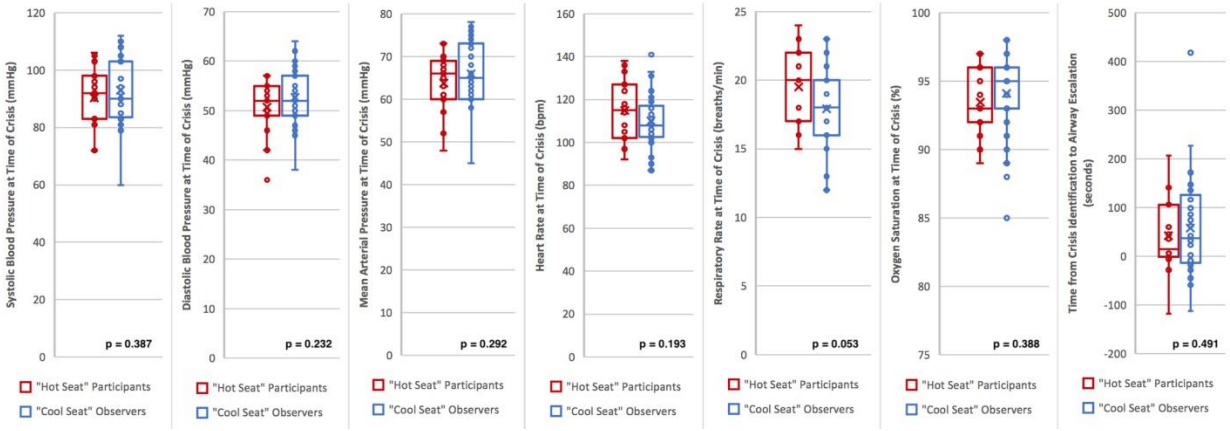

Figure 2. Representation of variability in the time from the "cool seat" observer's identified crisis to the "hot seat" participant's call for help (at 0 seconds). Positive values indicate that the observer identified a crisis prior to the participant's help request, while negative values indicate that the observer identified a crisis after the participant's help request. Each marker represents a single "cool seat" observer (n = 41).

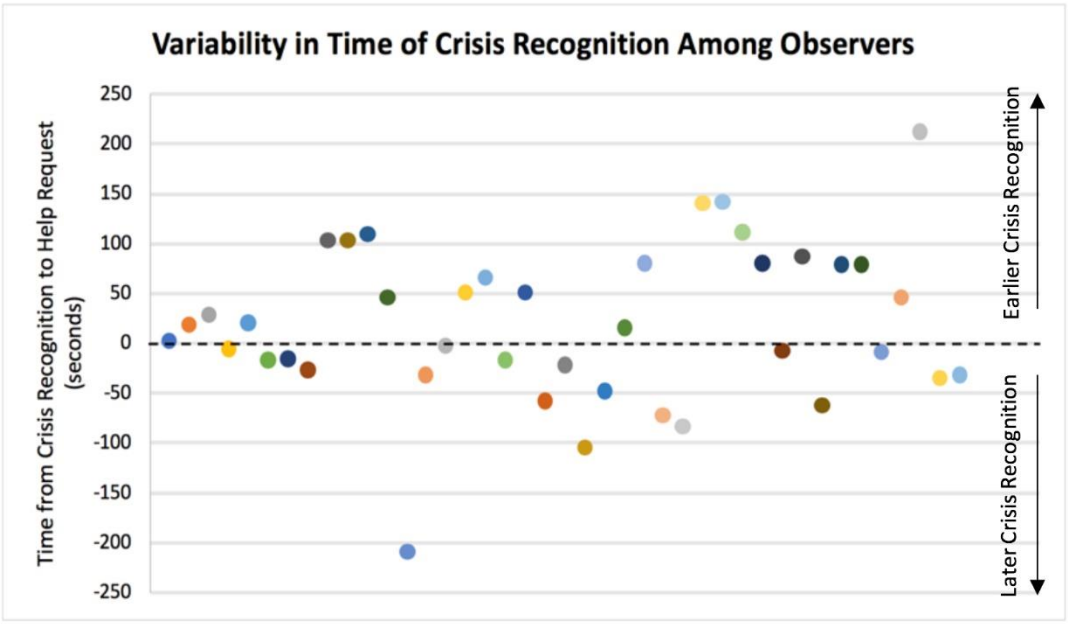

Table 1. Simulated patient vital signs, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), and oxygen saturation by pulse oximetry (SpO2), at the time of recognized crisis. Included are aggregated data from all simulation "hot seat" participants (n = 19) and "cool seat" observers (n = 41). For "hot seat" participants, the time of help request was used as a proxy for crisis recognition.

	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	RR (breaths/min)	SpO2 (%)
Median	90	52	66	110	19	94
Mean	92	52	65	112	18	94
Std. Dev.	11	6	7	13	3	3
Range	60-112	36-64	45-78	87-141	12-24	85-98

Table 2. Major contextual factors identified qualitatively as triggers for crisis recognition among "cool seat" observers (n = 41) with percentage of observers responding to each trigger.

Factor	Definition	Observers (%)
Respiratory concerns	(1) Requests or orders for additional respiratory supportive measures by the participant, including oxygen delivery, positive-pressure breathing support, or airway interventions, and (2) signs or symptoms of respiratory deterioration in the patient that might warrant acute intervention.	59%
Help request or prompt	(1) Requests for additional assistance by the participant or (2) prompts by simulation confederates to call for help. Included requests for help from respiratory therapy and ancillary staff.	34%
Escalation of care	Requests by the participant to obtain medications or position the patient for imminent resuscitation efforts. Included flattening the bed, obtaining a code cart or cardiopulmonary resuscitation equipment, ordering more frequent assessments, and requesting transport of the patient to the OR environment.	27%
Evolving anaphylaxis	(1) Lines of inquiry into symptoms of allergic reactions or anaphylaxis, (2) claims made by participants or confederates with respect to hypersensitivity reactions, or (3) requests for medications used to treat anaphylaxis other than epinephrine or respiratory interventions (e.g., corticosteroids).	20%
Epinephrine	Requests for epinephrine to be prepared or administered to the patient. Included doses of epinephrine appropriate for anaphylaxis management rather than those used in cardiac arrest.	15%
Vague statements	Miscellaneous comments or behaviors occurring within the simulation that did not suggest an evolving patient crisis related to anaphylaxis or impending hemodynamic deterioration.	10%
Scarce resources	Suggestions or comments made within the simulation with respect to help or resources being limited or unavailable due to the constraints of the perioperative setting.	7%

Pediatric Anesthesiology

Pediatric Anesthesiology-1 Evaluation of a Novel Method for Lung Isolation using a High Fidelity Infant Mannequin - Preliminary Results

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

Introduction: Techniques of lung isolation and one-lung ventilation for infants can be challenging; several methods using an Arndt bronchial blocker have been described[1-5]. We developed a novel device[6], whereby the bronchial blocker is securely attached to the outside of an endotracheal tube (ETT) before intubation and blocker placement. This study compares the novel device with five previously published methods.

Methods: After ethics approval, 18 pediatric anesthesiologists and 18 anesthesia residents were recruited to participate in a simulation study with a high fidelity infant mannequin[7]. Following one practice laryngoscopy and intubation attempt, each participant trialed six different methods for extra-luminal bronchial blocker placement in a semi-randomized order, ensuring that each method tested occupied the first position in the trial three times for each cohort of eighteen study subjects (Figure 1). The six methods tested were: Novel method[6], Bent blocker[1], Endobronchial ETT placement of blocker[2], Blind insertion of blocker[3], Blocker looped to endotracheal tube[4], and Blocker looped to bronchoscope[5]. The primary outcome was total time to lung isolation, defined as the time between the laryngoscope entering the oral cavity to confirming blocker placement by ventilation. Secondary outcome measurements included time for laryngoscopy and ETT intubation with confirmation of lung ventilation, time for blocker placement following successful intubation with ETT, and placement method preference before and after completion of the trial. Three independent mixed effects models were used to determine whether the novel method was faster than the other methods, while controlling for each participant. Time for laryngoscopy and ETT intubation was used as the outcome variable for one model, time for blocker placement following successful intubation for the second, and total time to lung isolation for the third. For all three models, blocker method was used as a fixed variable, with the novel method as the reference category, and participant as the random variable.

Results: Data from 18 pediatric anesthesiologists were available for analysis. The novel method was as fast as, or faster than, all methods tested for both time to laryngoscopy and ETT intubation (Figure 2) and total time to lung isolation (Figure 3). The total time to lung isolation with the novel method was significantly faster than the endobronchial ETT (91 sec; 95% CI: 36-146; p=0.002) and blind methods (97 sec; 95% CI: 42-152; p=0.001). Most (12/18) pediatric anesthesiologists changed their preferred method of blocker placement after completion of the trial (Figure 4).

Conclusion: The novel method of extra-luminal bronchial blocker placement shows promise as an alternative method for lung isolation in infants. Of the five published methods tested, the bent blocker method was the most consistent, fastest, and preferred method. The novel method using a new device, consisting of a bronchial blocker securely attached to the exterior of an ETT, compares favorably to the bent blocker method with faster times to intubation, blocker placement, and similar post-trial method preference. The simplicity of the design, low cost, and ease of use may allow early adoption in developing countries. The new device and novel method of placement may have other advantages including: a) security of the blocker once positioned, b) opportunity to delay lung isolation until after patient positioning, c) ease of repositioning a misplaced blocker, d) improved accuracy of placement, and e) improved success with blind placement. Alternate patient populations including rapid lung isolation in adults with massive pulmonary hemorrhage, unilateral lung trauma, and lung isolation for large bronchial tree air leaks, may also benefit from this approach. Further clinical trials are needed.

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4. Can J Anesth. 2006;53(2):159-61
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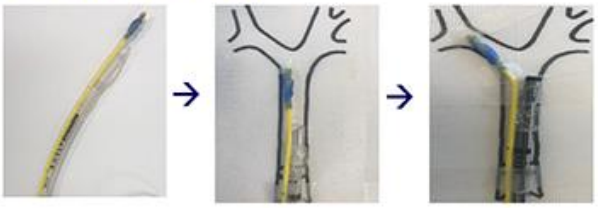
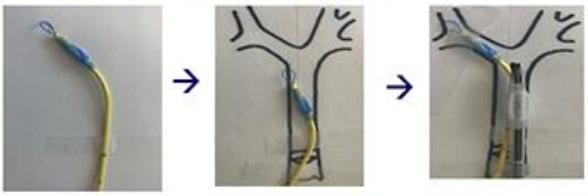
Novel Method



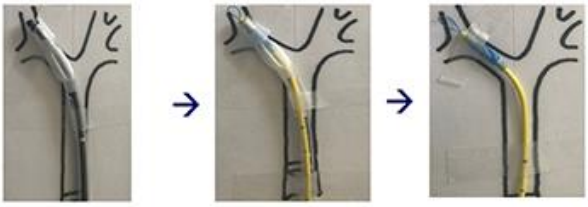
Intubate with novel device and direct blocker into bronchus.

Bent Blocker Method



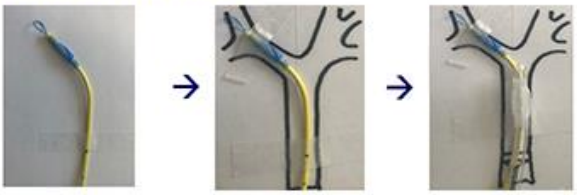
Bend blocker to 35-45^{o}, intubate with blocker, followed by ETT, and direct blocker into bronchus.

Endobronchial Intubation Method



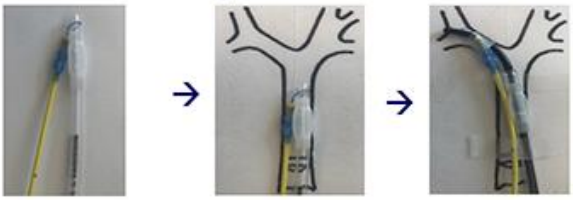
Intubate and direct ETT into bronchus. Insert blocker into ETT and remove ETT. Reintubate with 2nd ETT.

Blind Method



Bend blocker to 35-45^{o}, intubate with blocker and blindly direct into bronchus. Intubate with ETT.

Blocker Looped to ETT



Attach loop to ETT tip. Intubate, direct scope into bronchus. Slide blocker over scope.

Blocker Looped to Bronchoscope

Scope into ETT and attach loop to scope. Intubate and direct scope/blocker into bronchus.

Figure 1. *Bronchial blocker placement methods*

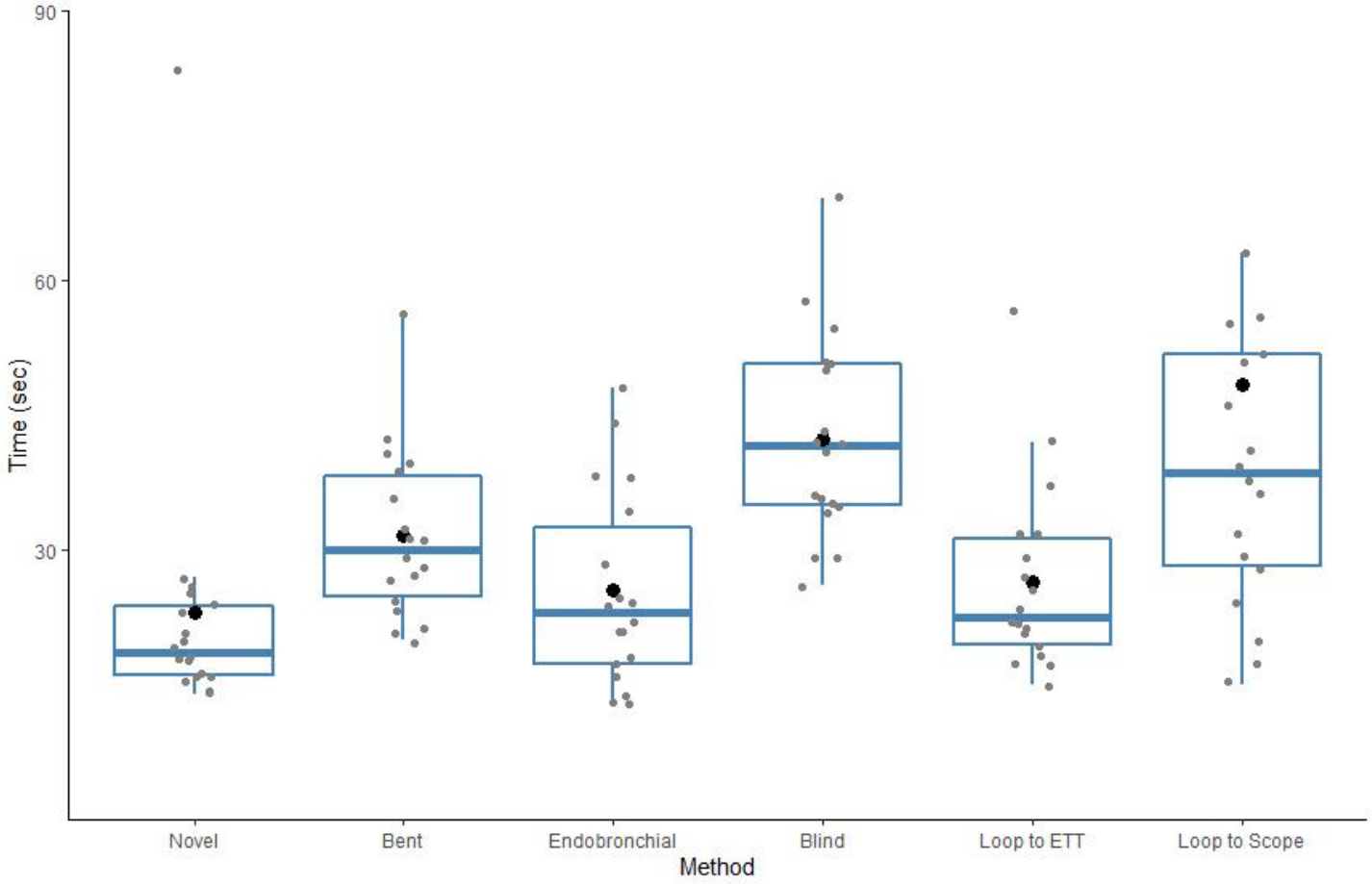


Figure 2. *Time from laryngoscope entering the oral cavity to intubation and confirmation of ventilation. One outlier was censored in the Loop to Scope method at 228 seconds.*

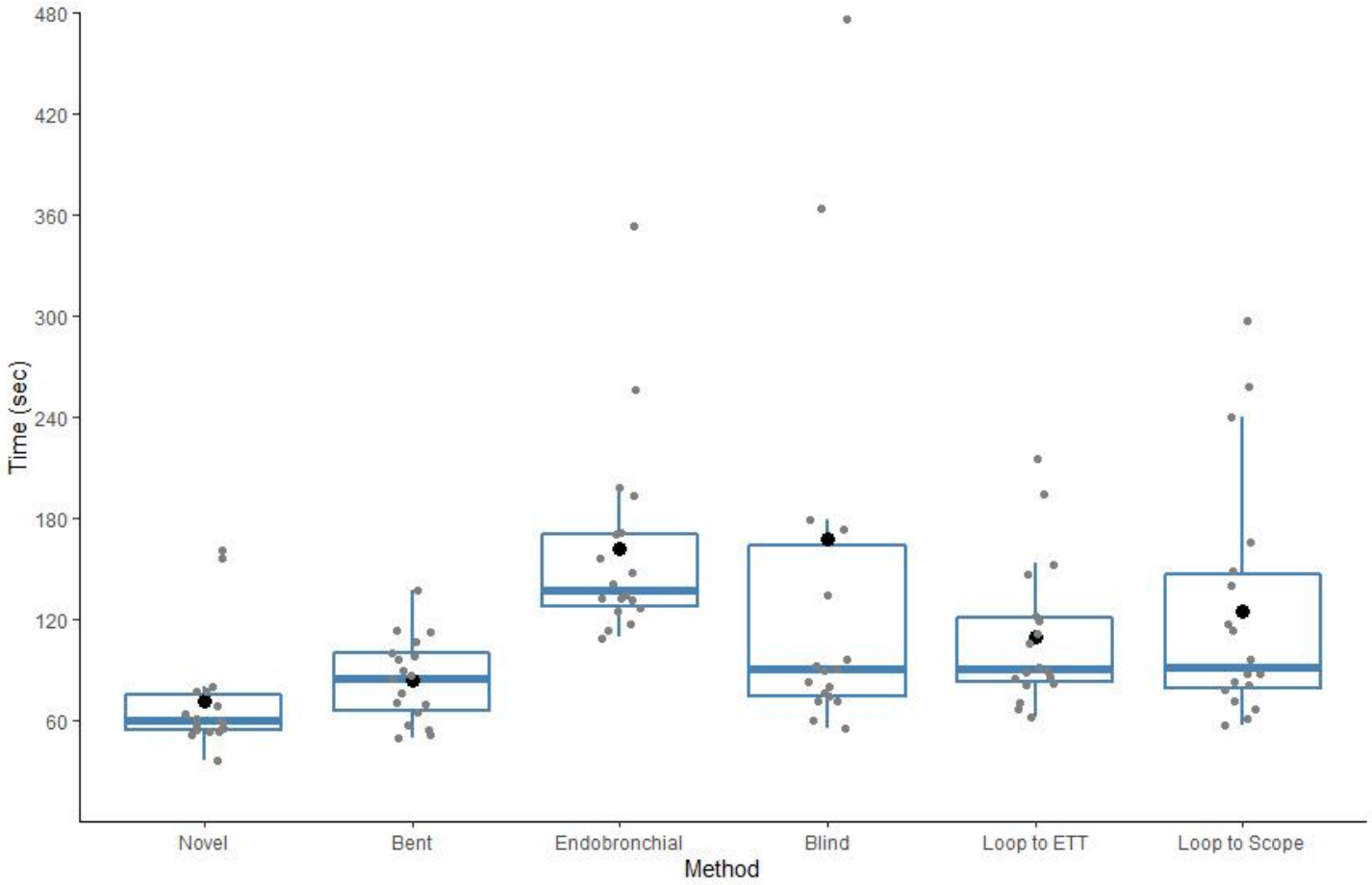


Figure 3. *Total time to lung isolation; from laryngoscope entering the oral cavity to confirmation of blocker placement. One outlier was censored in the blind method at 756 seconds.*

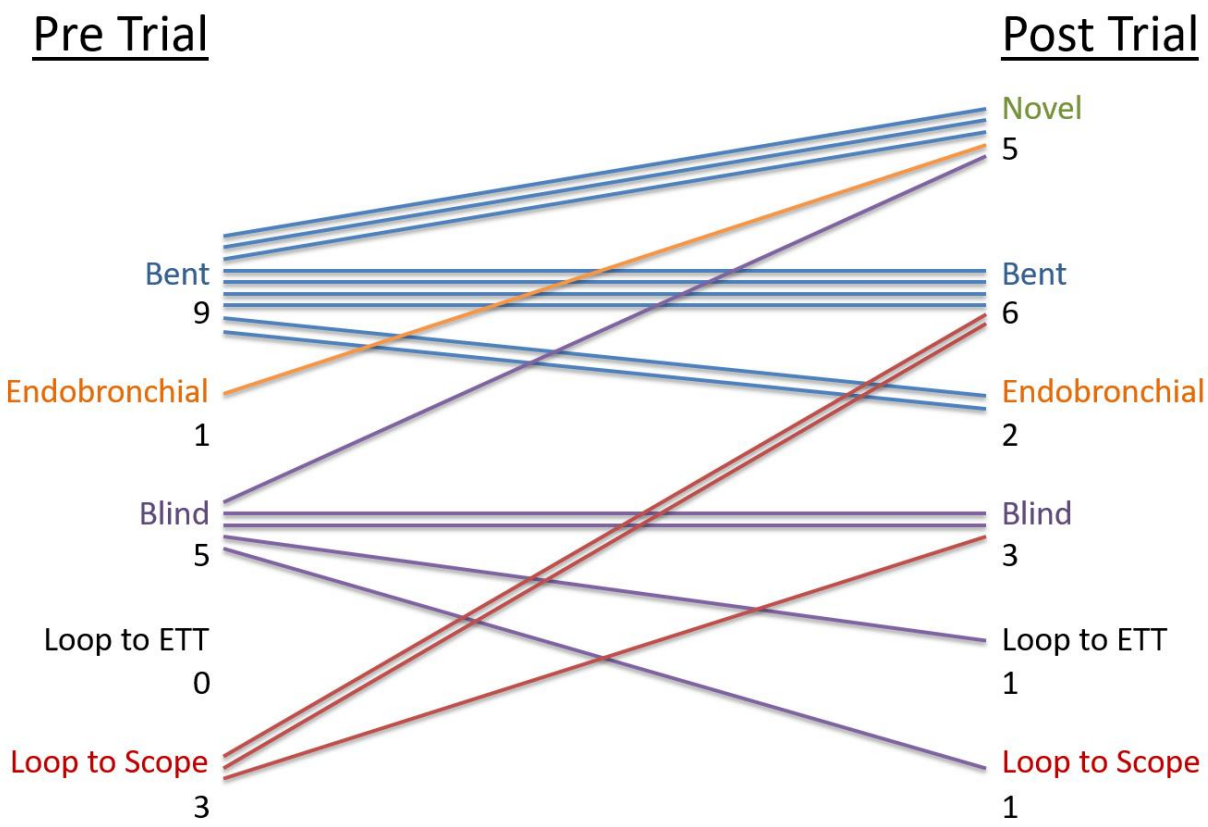


Figure 4. *Change in method preference among the 18 anesthesiologists.*

Pediatric Anesthesiology-2 Anesthesia management for pediatric patients with high risk Williams syndrome - a quality improvement study

Alexander R Schmidt[1], Thomas Collins[2], Yamini Adusumelli[2], Chandra Ramamoorthy[2], Kirstie L MacMillen[2], Manchula Navaratnam[2]

[1]Stanford University, School of Medicine, Palo Alto, CA, [2]Stanford University,School of medicine, Palo Alto, United States of America

Introduction: Over 80% of patients with Williams syndrome (WS) have structural cardiovascular abnormalities,[1] predisposing them to a risk of adverse cardiac events (ACE) during general anesthesia (GA).2,3 Intravenous (IV) induction of GA is usually preferred for high risk patients however, mask induction with volatile anesthesia is sometimes necessary especially in younger patients and those with difficult IV access when they present on the day of the intervention. In 2017 there was a change in anesthesia management at our institution which is a national referral center for WS. Based on a 3-staged risk category (RC) for WS patients (Table 1)[4], patients are admitted for IV pre-hydration the evening before (high RC), 2 hours prior to GA (moderate RC) or they received standard care (low RC). The aim of this quality improvement study was to evaluate if a change in anesthesia management based on risk stratification and pre-operative IV hydration and IV induction decreased the incidence of ACE during GA induction in WS patients

Methods: After IRB approval, we identified all pediatric patients with WS who underwent GA for catheterization lab procedures, cardiovascular or non-cardiovascular surgery, or diagnostic imaging between 11/2008 and 08/2019. We reviewed electronic anesthesia records and compared the intervention group (IG, 03/17 - 08/19) to a historical control group (HG, 11/08 - 02/17). Primary outcome were ACE (defined as cardiac arrest, CPR, arrhythmias or ST-segment changes) within 60 minutes after GA induction. Secondary outcome were more than two inotrope bolus given and the percentage change in the systolic blood pressure during GA induction. Standardized mean difference (SMD) was calculated, with a SMD >0.2 suggesting clinically significant difference between the groups.

Results: We identified 142 patients with WS, of these 48 underwent 118 GAs. In the HG 27 patients had 67 GAs, and 28 in the IG had 51 GAs. Risk category, procedure data and induction type for each group are shown in Table 2. The incidence of ACE in the HG was 6% vs 2% in the IG (SMD=0.207), see Table 3. The frequency of more than two inotrope bolus given was 13.4% in the HG vs 11.8% in the IG (SMD=0.069) and the median drop of the systolic blood pressure was 17.5% (IQR: 5-30%) in the HG vs 9% (IQR: 5-18%) in the IG (SMD=0.419).

Conclusion: This is the first quality improvement study investigating an adapted anesthesia management strategy in WS patients with regard to ACE during GA induction. The results suggest a clinically significant reduction of ACE and a more stable systolic blood pressure during GA induction in patients who received pre-operative IV hydration and an IV induction. The presence of IV access allowed for titration of induction drugs, an immediate response to arterial hypotension and the pre-induction initiation of inotropic support. The presented risk stratification for IV placement and an adapted anesthesia management should be considered in WS patients.

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4. Peri-procedural risk stratification and management of patients with Williams syndrome. Congenital heart disease. 2017;12:133-42.

Table 1: Procedural risk stratification categories for patients with Williams syndrome.

Low Risk Category	Moderate Risk Category	High Risk Category
Age >20 years	Hypertension	Age <3 years
No or mild supravalvar or branch PA stenosis	Moderate supravalvar or branch PA stenosis	History of ACE
Normal ECG	Mild BiVOTO	Preprocedural arrhythmia
No renal artery involvement	Renal artery stenosis	BiVOTO of ≥ moderate severity
	Renal dysfunction	SVAS gradient of ≥40mmHg *and* the presence of LV hypertrophy
	QTc on ECG >450 ms, but <500 ms	Coronary artery involvement
	Airway abnormalities, lung disease, or severe gastroesophageal reflux	Diffuse stenosis of the thoracic aorta
		RV pressure ≥75% systemic
		≥Moderate LV or RV hypertrophy
		Symptoms or ECG signs of ischemia
		QTc on ECG ≥500 ms

PA indicates pulmonary artery; ECG, electrocardiogram; biVOTO, bilateral ventricular outflow tract obstruction; SVAS, supravalvar aortic stenosis; LV, left ventricle; QTc, corrected QT interval; ACE, adverse cardiovascular event; RV, right ventricle; ms, milliseconds

Table 2: ASA score, risk category, procedures performed and induction type among study patients.

		Historical Control Group n=67		Intervention Group n=51	
	Age (years)	4.7	± 4.5	5.9	± 6.6
ASA score	2	6	9.0%	2	3.9%
	3	37	55.2%	29	56.9%
	4	24	35.8%	20	39.2%
Williams Risk Category	low	0	0%	7	13.7%
	moderate	22	32.8%	10	19.6%
	high	45	67.2%	34	66.7%
Procedure	Cath Lab	14	20.9%	17	33.3%
	CV surgery	24	35.8%	12	23.5%
	Non-CV surgery	18	26.9%	11	21.6%
	Imaging	11	16.4%	11	21.6%
Induction type	Mask	48	71.6%	5	9.8%
	intravenous	19	28.4%	46	90.2%

Data presented as mean (± standard deviation) or as count (percent). ASA indicates American Society of Anesthesia; CV, cardiovascular.

Table 3: Detailed patient data for the adverse cardiac events within 60 minutes after anesthesia induction in patients with Williams syndrome.

Historical Group (n=67)							
Patient	WRC	age (yrs)	weight (kg)	ASA score	induction type	ACE (n=4 / 6%)	SMD
1	moderate	7,0	18,9	3	mask	Arhythmia	0.207
2	high	0,2	5	4	mask	ST elevation	
3	high	0,6	7,5	4	IV	ST depression	
4	high	1,0	8,45	4	mask	CPR	
Intervention Group (n=51)							
Patient	WRC	age (yrs)	weight (kg)	ASA score	induction type	ACE (n=1 / 2%)	
1	high	0,7	6,639	4	IV	ST changes	

WRC, Williams risk category; ACE, adverse cardiac events; IV, intravenous; CPR, cardio pulmonary resuscitation; SMD, Standardized mean difference between the two groups for ACE.

Pediatric Anesthesiology-3 Anesthesia and Neurotoxicity in the Nonhuman Primate: A Critical Review of Experimental Design, Conduct and Reporting

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Introduction: Nonhuman primates (NHP) have been employed in research into anesthesia-related neurodevelopmental delay in order to overcome limitations attendant conducting these studies in rodents (1-2). The NHP, by virtue of its neurodevelopmental proximity to humans, offers potentially the opportunity to derive more reliable insight into the occurrence of and mechanisms contributing to anesthesia and neurotoxicity (3). Utilizing an animal of the same taxonomy order as humans should however also demand the application of more stringent animal research guidelines and the highest quality in experimental design and monitoring. The Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines, developed to improve reproducibility and reduce unnecessary use of animals, has been adopted by many journals, to include Anesthesiology, as the standard on enforcing quality experimental design and reporting in animal research. The increased size of the NHP neonate should also allow one to control the anesthetic management and monitoring to human standards (4-5). Herein we have conducted a critical review of the non-human primate studies focused on experimental design, procedures, reporting, consistency of results, and adherence to American Society of Anesthesiologist (ASA) monitoring and ARRIVE guidelines.

Methods: A literature search of PubMed from 2005 through November 2019 was conducted. Full-text, peer-reviewed original research articles in English were retrieved. Studies describing anesthetic related outcomes in neonatal nonhuman primates aged P5 - P40 were included. Studies were first categorized according to species and primary outcomes reported. From these studies we extracted data documenting anesthetic, route, dose, frequency and duration of exposures, type of ventilation, anesthetic monitoring, mortality, vitals and blood gases. Additionally, we assessed adherence to the ASA monitoring and ARRIVE guidelines. Each study was then graded using a 38-point ARRIVE Guideline Checklist.

Results: A total of 18 studies were identified for inclusion in this review (Figure 1). Table 1 summarizes characteristics of included studies. Our analysis found zero (0/18) studies met full ASA standards on basic anesthesia monitoring. Zero (0/18) studies reported supervision by a qualified pediatric anesthesia provider. One (1/18) study reported a failed intubation rate of 20% (6 of 30 animals). A single study (1/18) employed arterial blood gas data to validate adequacy of ventilation. Additionally, zero (0/18) studies reported all items on the established ARRIVE guideline. Conflicting results were found in 9/18 (50%) studies on issues of whether isoflurane causes neuroapoptosis, regions of the brain affected by anesthetics, and whether volatile agents cause anxious behaviors. Four (4/18) ketamine studies were found administering up to 12-fold the recommended pediatric dose. Two (2/18) studies provided a priori power calculation to justify sample size used. Blinding was used in data collection for only 9/18 (50%) studies and in data analysis for 0/18 (0%) studies.

Conclusion: Our review identified important deficits in study design and execution, to include adherence to even basic standards such as ASA monitoring and ARRIVE guidelines, potentially limiting benefits that could have been achieved through the employment of this most sentient model to clarify an area of research already clouded with controversy.

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3. Comparative aspects of the brain growth spurt. 3:79-83. 1979.
4. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. 8: e1000412. 2010.
5. Reporting of Preclinical Research in Anesthesiology: Transparency and Enforcement. 124:763-765. 2016.

Figure 1. PRISMA flowchart: methodology applied and results.

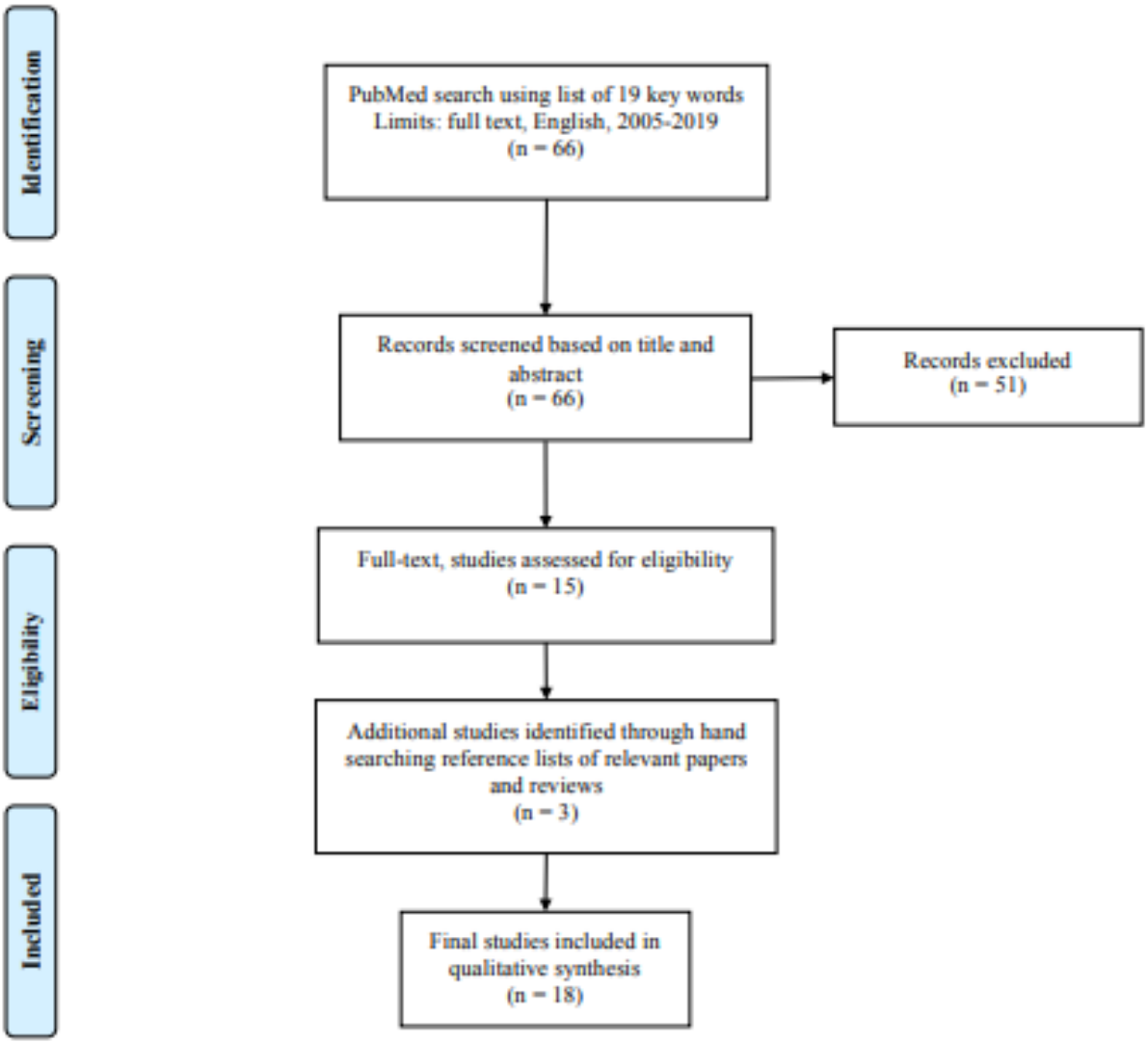

Table 1. Nonhuman Primate Study Characteristics

Year	Citation	Species	Age	Anesthetic	Dose/Route	Duration	Outcome
2007	Slikker	Macaca mulatta	G122	Ket	20-50 mg/kg/h (IV)	24h	Neuroapoptosis
			P5-6	Ket	20-50 mg/kg/h (IV)	24h	Neuroapoptosis
			P35-37	Ket	20-50 mg/kg/h (IV)	24h	Neuroapoptosis
			P5	Ket	20-50 mg/kg/h (IV)	3h	Neuroapoptosis
2009	Zou	Macaca mulatta	P5	Ket	20-50 mg/kg/h (IV)	3h	Neuroapoptosis
			P5-6	Ket	20-50 mg/kg/h (IV)	9h	Neuroapoptosis
			P5-6	Ket	20-50 mg/kg/h (IV)	24h	Neuroapoptosis
2010	Brambrink	Macaca mulatta	P6	Iso	0.7-1.5% (I)	5h	Neuroapoptosis
2011	Paule	Macaca mulatta	P5,6	Ket	20-50 mg/kg/h (IV)	24h	Behavior
2011	Zou	Macaca mulatta	P5-6	N2O	70% Anesth. Chamber	8h	Neuroapoptosis
			P5-6	Iso	1% vaporizer, Anesth. Chamber	8h	Neuroapoptosis
			P5-6	N2O+Iso	70% + 1% Anesth. Chamber	8h	Neuroapoptosis
2012	Brambrink	Macaca mulatta	G120	Ket	48.1-86.5 mg/kg/h (IV)	5h	Neuroapoptosis
			P6	Ket	18.4 - 56.0 mg/kg/h (IV)	5h	Neuroapoptosis
2012	Brambrink	Macaca mulatta	P6	Iso	0.7-1.5% (I)	5h	Neuroapoptosis
2012	Zhang	Macaca mulatta	P5-6	N20 + Iso	70% N20 + 1% Iso (I)	8h	18F-FEPPA uptake by microPET/CT
2013	Creeley	Macaca mulatta	G120	Pro	350-450 mcg/kg/min (IV)	5h	Neuroapoptosis
			P6	Pro	300-400 mcg/kg/min (IV)	5h	Neuroapoptosis
2015	Zhou	Macaca fascicularis	P6	Sev	2.0-2.6% (I)	5h	Behavior, Protein Expression
2015	Liu	Macaca mulatta	P5-6	Sev	2.5%, Anes Chamber	9h	Neuroapoptosis, Lipid Metabolism
2015	Raper	Macaca mulatta	P6-10, 14d later, 28d later	Sev	2% (I)	4h (3x)	Behavior
2016	Zhang	Macaca mulatta	P5-6	Sev	2.5% (I)	8h	18F-FEPPA uptake by microPET/CT
2017	Schenning	Macaca mulatta	P20	Iso	1.3-2.5% (I)	5h	Neuroapoptosis
			P40	Iso	1.3-2.5% (I)	5h	Neuroapoptosis
2017	Coleman	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	Macaca mulatta	P6-10, 14d later, 28d later	Sev	2% (I)	4h (3x)	Vision impairment
2017	Noguchi	Macaca mulatta	P6	Iso	0.7-1.5% (I)	3h	Neuroapoptosis
2018	Raper	Macaca mulatta	P6-10, 14d later, 28d later	Sev	2% (8% max with 100% O2) (I)	4h (3x)	Behavior

Pediatric Anesthesiology-4 Association Of Race and Ethnicity with Postoperative Analgesic Administration and Pain Scores in Pediatric Patients: A Single-Center Study of 29,614 Surgical Cases

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Introduction: Disparities in the medical and surgical care of adults of different races and ethnicities have detrimental health outcomes.1,2 However, few studies have been published regarding pediatric healthcare disparities, and particularly the perioperative care of children. We are investigating the association between race and ethnicity and pediatric postoperative analgesic administration, pain scores, and related adverse events at a tertiary care children's hospital.

Methods: The medical records of children ≤18 years old undergoing general anesthesia and surgery from May 2014 to August 2019 are included. The exposure is racial and ethnic groups: Asian, Black, Hispanic, Other, Pacific Islander, and White non-Hispanic (White-nH). The primary outcome is PACU weight-adjusted morphine equivalent dose (MED, mg kg-1). Secondary outcomes are: PACU mean pain score (0-10), PACU length of stay, and PACU anti-emetic administration (any vs none). The association of race or ethnicity with each outcome is modeled using linear or logistic regression as appropriate, adjusting for confounders and covariates.

Results: 29614 cases are included (39.0% Hispanic, 33.8% White-nH, 18.5% Asian, 2.0% Black, 1.3% Pacific Islander, 5.3% Other race or ethnicity. In the PACU, no race or ethnicity was associated with receipt of a higher or lower MED. Asian, Black, and Pacific Islander were associated with lower mean PACU pain scores, and Other race was associated with higher mean PACU pain scores, than White-nH. Compared to White-nH Pacific Islanders were estimated to be discharged sooner from the PACU. Asian, Hispanic, and Pacific Islander were associated with lower odds of receiving anti-emetic drugs than White-nH. See quantitative results in Table 1.

Conclusion: Given the adverse events associated with both too little and too much analgesic administration, poor pain control, and postoperative nausea and vomiting, investigations on differences in postoperative pain medication administration, pain scores, and associated adverse events in children of different races and ethnicities are important.3 The differences of the PACU pain scores of some races and ethnicities compared to White-nH found here, while statistically significant, are not clinically significant. The decreased PACU length of stay of Pacific Islander patients compared to White-nH patients (6.4 minutes) while statistically significant, is also not clinically significant. White-nH were found to be more likely to receive antiemetics than Asian, Hispanic, and Pacific Islander patients. The reason(s) for this difference are not apparent but may be a result of cultural differences in nursing assessment of nausea, patient expression of nausea, patient understanding of medication availability for nausea, and/or language differences between healthcare providers and patients and their caregivers. (Additional analyses of inpatient outcomes are pending but will be available before the AUA/IARS meeting in May 2020.)

Reference(s):

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2. National Center for Health Statistics (US). Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities. Hyattsville, MD: National Center for Health Statistics (US), 2016.
3. Long DR, Lihn AL, Friedrich S, et al. Association between intraoperative opioid administration and 30-day readmission: a prespecified analysis of registry data from a healthcare network in New England. Br J Anaesth. 2018;120:1090–1102.

Association Of Race and Ethnicity with Postoperative Analgesic Administration and Pain Scores in Pediatric Patients: A Single-Center Study of 29,614 Surgical Cases

Table 1

PACU Opioid Dose mg/kg (weight-adjusted morphine equivalents)			
Race	Change in dose	(95% Conf. Interval)	p-value
Asian	-0.001	(-0.002, 0.0001)	0.094
Black	-0.002	(-0.005, 0.001)	0.304
Hispanic	-0.001	(-0.002, 0.0002)	0.119
Other	0.000	(-0.002, 0.001)	0.608
Pacific Islander	-0.003	(-0.007, 0.0003)	0.069
White-nH	Reference		

PACU Mean Pain Score (pain scale of 0-10)			
Race	Change in score	(95% Conf. Interval)	p-value
Asian	-0.134	(-0.179, -0.089)	**<0.001**
Black	-0.119	(-0.231, -0.007)	0.037
Hispanic	-0.019	(-0.055, 0.018)	0.314
Other	0.073	(0.001, 0.145)	**0.046**
Pacific Islander	-0.214	(-0.351, -0.077)	**0.002**
White-nH	Reference		

PACU Length of Stay (minutes)			
Race	Change in LoS	(95% Conf. Interval)	p-value
Asian	-0.65	(-2.056, 0.763)	0.368
Black	-1.04	(-4.578, 2.493)	0.563
Hispanic	-0.06	(-1.208, 1.081)	0.913
Other	-1.17	(-3.432, 1.101)	0.314
Pacific Islander	-6.35	(-10.642, -2.063)	**0.004**
White-nH	Reference		

PACU Anti-Emetic Medications (any vs none)			
Race	Odds Ratio	(95% Conf. Interval)	p-value
Asian	0.735	(0.613, 0.881)	**0.001**
Black	0.685	(0.436, 1.075)	0.100
Hispanic	0.738	(0.641, 0.849)	**<0.001**
Other	0.763	(0.568, 1.025)	0.073
Pacific Islander	0.402	(0.205, 0.786)	**0.008**
White-nH	Reference		

Pediatric Anesthesiology-5 Rates of, and Risk Factors for, Chronic Pain in Children and Young Adults Before and After Surgery

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Introduction: Approximately 20% of U.S. adults have chronic pain,1 and the annual economic burden attributed to chronic pain is >$500 billion.2 Those who develop chronic pain are more likely to have a large number of health issues.3,4 The incidence of CPSP for adults ranges from 5-85%, depending on the type of surgery.5 In the single meta-analysis published on the subject in children, the median prevalence of CPSP was 20%;6 however, this prevalence was based on just four studies, 628 subjects, and a limited selection of surgeries. Therefore, we are investigating the incidence of, and risk factors for, chronic post-surgical pain in a cohort of pediatric patients from 0 to 21 years of age, before and after surgery as well as compared to a non-surgical reference sample using a national insurance provider claims database.

Methods: Using the Optum Clinformatics„¢ Data Mart Database, a de-identified prescription and medical claims database from a large national insurance provider, we identified patients in each of five age groups (0-2 years, 2-6 years, 6-12 years,12-18 years, and 19-21 years) who underwent anesthesia and surgery between January 1, 2003 to December 31, 2017. Inclusion criteria: 0-21 years of age; enrolled in the insurance at least one year prior to surgery and remained enrolled for at least one year following surgery; had an anesthesia CPT code within one day of their surgical CPT code. Exclusion criteria: had any anesthesia claim either in the 365-3 days prior to their surgery date or in the 3-365 days following their surgery date, surgery was within a length-of-stay greater than 30 days at the hospital. Chronic pain diagnosis was established by searching the year before and after surgery for 1) chronic pain ICD codes and 2) the same acute pain ICD code reported on two medical claims more than three months apart.

Results: The Optum database contained data on 72,395,344 unique individuals, 21,247,237 (29.35%) of whom were aged under 22 at enrollment. There were 755,244 0-21 year-olds who met our inclusion and exclusion criteria. Results are summarized in Table 1. (Pending results: Rates of chronic pain in a non-surgical reference sample and risk factors associated with CPSP are pending but will be available before the annual AUA/IARS meeting in May 2020.)

Conclusion: The rates of CPSP across all 1300 of the most frequent pediatric surgeries in this retrospective cohort study were found to be increased after surgery and similar to those from prospective studies of CPSP in children,7 including a recent study study that found chronic pain rates of 8.2% for children 6-17 years of age.8 Rates of CPSP for the most frequent 20 surgeries and the 20 surgeries with the highest rates will be further investigated. Additionally, we will analyze risk factors for CPSP among patients who undergo surgery. Further investigation is necessary as the impact of life-long pain after surgery in childhood carries significant risks health and economic risks.

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3. J Pain Res. 2016;9:457-467.
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5. Pain Rep. 2017;2(6):e627.
6. J Pain. 2017;18(6)
7. The Journal of Pain. 2017;18(4):S1. doi:10.1016/j.jpain.2017.02.002
8. JAMA Pediatrics. 2019;173(12):1203. doi:10.1001/jamapediatrics.2019.3826

Table 1: Rates of chronic pain before and after surgery in children and young adults

Age Group	# Surgeries	# Chronic Pain Before (%)	# Chronic Pain After (%)	Relative Risk (95% CI)
0 to < 2	115,114	172 (0.15%)	344 (0.30%)	2.00 (1.67-2.40)
2 to < 6	113,976	479 (0.42%)	518 (0.45%)	1.08 (0.95-1.22)
6 to <12	108,743	1,412 (1.30%)	1,775 (1.63%)	1.26 (1.17-1.35)
12 to <19	181,848	12,641 (6.95%)	15,058 (8.28%)	1.19 (1.16-1.22)
19 to 21	76,476	5,162 (6.75%)	5,762 (7.53%)	1.12 (1.07-1.16)

Pediatric Anesthesiology-6 Association Between Subsequent Papilloma Excision Procedures and Propofol Anesthetic Requirements

Thomas M Austin[1], Joelle Karlik[2], Humphrey Lam[2], stuart Lehn[2], Laura Gilbertson[2]

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Introduction: Laryngeal papillomatosis is the most common benign neoplasm of the pediatric larynx (1). Surgical removal of tumors at frequent intervals to relieve the symptoms of airway obstruction remains the primary choice of management (2). In order to provide proper anesthetic conditions, a total intravenous anesthetic (TIVA) with propofol may be used to maintain spontaneous ventilation as well as a deep plain of anesthesia (3). However, tolerance to propofol may occur in painful surgical procedures (4). Because of this, we sought to examine if there is a correlation between the number of papilloma excision procedures and the propofol anesthetic requirements in this patient population.

Methods: We evaluated all pediatric patients who underwent at least one papilloma excision procedure at the Egleston and Scottish Rite Hospitals from January 2014 to August 2019 whose general anesthetic consisted primarily of a propofol TIVA. In order to control for potential confounders while accounting for within-patient correlation, repeated measures ANCOVA models were created with the random intercept set to each patient. All analyses were performed using the R software package (version 3.6.1) with p-values < 0.05 considered statistically significant.

Results: 107 procedures on 14 individual patients were included in this analysis. The mean (± standard deviation) age and weight of this cohort were 7.4 (± 3.9) years and 38.3 (±23.3) kg, respectively. After controlling out other surgical and anesthetic factors, propofol administration increased with each subsequent procedure (0.14 mg/kg per procedure; 95% CI: 0.02 to 0.22; $p = 0.002$; Table 1a). This increase in propofol use was correlated with an increase in PACU length of stay (1.27 min per 1 mg/kg; 95% CI: 0.08 to 2.39; $p = 0.042$; Table 1b). Utilizing remifentanil was associated with shorter PACU times while ketamine was associated with longer PACU times (Table 1b).

Conclusion: Patients presenting for papilloma excision provide a challenge for anesthesiologists due to the need to provide an adequate depth of anesthesia while maintaining spontaneous ventilation. To accomplish this, the dose of propofol has to be adjusted very accurately. These patients present for multiple subsequent excisions and our analysis confirms that the propofol dose increased with each successive procedure. This information is essential for anesthesiologists as it can be very challenging to adjust the anesthetic for these patients with each consecutive anesthetic.

Reference(s):

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Table 1a. Predictors of Intraoperative Propofol Dose (mg/kg)*

Characteristic	Estimate	95% CI	*P*-value
Procedure Number	0.14	0.02 to 0.22	0.002
Dexmedetomidine Used (Y vs N)	-0.84	-2.77 to 1.25	0.401
Remifentanil Used (Y vs N)	-1.94	-4.16 to 0.40	0.098
Ketamine Used (Y vs N)	-1.51	-4.17 to 1.16	0.279
Morphine Equivalents (mg/kg)	3.31	-1.45 to 8.12	0.187
Anesthesia Duration (min)	0.09	0.07 to 0.11	<0.001

CI = confidence interval.

*Results are based on a repeated measures ANCOVA model with a random intercept set to each individual patient. Procedure number, morphine equivalents, and anesthesia duration were modeled as continuous variables and other characteristics were modeled as nominal variables. *P*-value < 0.05 was considered statistically significant.

Table 1b. Predictors of PACU stay (min)*

Characteristic	Estimate	95% CI	*P*-value
Propofol Dose (mg/kg)	1.27	0.08 to 2.39	0.042
Procedure Number	0.56	0.29 to 1.17	0.049
Dexmedetomidine Used (Y vs N)	0.67	-9.22 to 9.88	0.893
Remifentanil Used (Y vs N)	-17.33	-33.18 to -3.04	0.030
Ketamine Used (Y vs N)	38.39	18.46 to 56.84	<0.001
Morphine Equivalents (mg/kg)	5.18	-23.15 to 30.37	0.725
Anesthesia Duration (min)	-0.03	0.29 to 1.17	0.727

CI = confidence interval.

*Results are based on a repeated measures ANCOVA model with a random intercept set to each individual patient. Propofol dose, procedure number, morphine equivalents, and anesthesia duration were modeled as continuous variables and other characteristics were modeled as nominal variables. *P*-value < 0.05 was considered statistically significant.

Pediatric Anesthesiology-7 Prolonged Neuromuscular Block after Rocuronium Administration in Laparoscopic Pyloromyotomy Patients

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Introduction: Pyloromyotomy is one of the most common surgeries performed on infants (1). Due to the probable full stomach in these patients, a rapid sequence induction (RSI) is the preferred method of induction. As there are significant concerns with the use of succinylcholine in this surgical population, rocuronium is frequently used instead (2). Because of the potential for prolonged neuromuscular blockade in these short procedures, we sought to determine if there is a correlation between the dose of rocuronium, likelihood of being reversible with neostigmine at the end of surgery, and out of operating room time (OOR).

Methods: Following IRB approval, we evaluated all neonates who underwent laparoscopic pyloromyotomy at the Egleston and Scottish Rite Hospitals from April 2014 to August 2018 and received rocuronium and neostigmine. Qualitative neuromuscular monitoring was used on all patients in this cohort. Prolonged block was defined as neostigmine given after at least five minutes following surgical end while OOR was defined as the surgical end time to the time leaving the operating room. A logistic regression was performed to determine the association between rocuronium dose and prolonged block while a multivariable median regression was performed to ascertain the correlation between rocuronium dose and OOR. Due to non-linearity, rocuronium dose was fit utilizing linear splines with one knot at 0.48mg/kg, resulting in two linear segments each with its own p-value. This cut point was determined by the Muggeo method.1 All analyses were performed using the R software package (version 3.6.1).

Results: 306 patients were included in this analysis with a median rocuronium dose of 0.41mg/kg (range 0.02 - 1.25mg/kg). Prolonged block occurred in 85 (27.8%) patients. After accounting for surgery time, rocuronium dose was directly associated with prolonged block (odds ratio 1.33; 95%CI: 1.16 to 1.54; $p < 0.001$; Table 1a). For a 20 minute surgery (median surgical length), the odds of a prolonged block with rocuronium doses of 0.30 and 1.20 mg/kg were 27.4% (95% CI: 20.7 - 35.3%) and 83.5% (95% CI: 64.5 - 94.3%), respectively. Doses of rocuronium above 0.48 mg/kg were linearly correlated to median OOR time (1.43 min per 0.1 mg; 95%CI: 0.71 to 2.56; $p = 0.007$; Table 1b).

Conclusion: Patients undergoing laparoscopic pyloromyotomy present a challenge due to the need to balance a rapid sequence induction with the quick duration of the surgical procedure. To avoid prolonged neuromuscular blockade, rocuronium is often dosed lower than the standard RSI dose. Although dose was associated with prolonged block and higher doses were correlated with median OOR, there was still a rather high probability of prolonged neuromuscular block even at low doses of rocuronium. Because of this, reversal with sugammadex should be considered in these patients when using rocuronium.

Reference(s):

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2. Ped Anesth 2013; PMID: 22784242.

Table 1a. Predictors of Prolonged Neuromuscular Block at Surgical End*

Characteristic	Odds Ratio	95% CI	*P*-value
Rocuronium Dose (per 0.1 mg/kg)	1.33	1.16 to 1.54	<0.001
Rocuronium Duration (min)	0.95	0.92 to 0.98	0.003

CI = confidence interval.

*Results are based on a logistic regression model with the response variable being neostigmine given ≥ 5 minutes after surgical end time. Rocuronium duration was defined as time from rocuronium administration to surgery end. Both predictors were modeled as categorical variables. *P*-value < 0.05 was considered statistically significant.

Table 1b. Association between Rocuronium Dose and Median Out of Operating Room Time

		§Unadjusted			¥Adjusted		
Outcome	**Dose**	**Coefficient***	**95% CI**	**P-value**	**Coefficient***	**95% CI**	**P-value**
OOR (min)	≥ 0.48 mg/kg	1.52	0.95 to 2.54	<0.001	1.43	0.71 to 2.56	0.007
OOR (min)	< 0.48 mg/kg	-0.94	-1.66 to 0.91	0.066	-0.71	-1.39 to 0.15	0.092

CI = confidence interval; OOR = out of operating room time

* Per 0.1mg/kg

§ Results are based on a simple quantile regression with the tau set to 0.5 (median). Out of operating room time was defined as surgical end time to the time when the patient left the operating room. Due to non-linearity, rocuronium dose was fit utilizing linear splines with one knot at 0.48mg/kg, resulting in two linear segments each with its own p-value.

¥Based on a multivariable quantile regression with the tau set to 0.5 (median). Out of operating room time was defined as surgical end time to the time when the patient left the operating room. Due to non-linearity, rocuronium dose was fit utilizing linear splines with one knot at 0.48mg/kg, resulting in two linear segments each with its own p-value. Variables controlled for included preoperative serum bicarbonate level, propofol dose, end-tidal carbon dioxide at start of emergence, prematurity, opiate use, and hospital. P-values <0.05 was considered statistically significant.

Pediatric Anesthesiology-8 Infant spinal anesthesia reduces r-FLACC scores and pain medication consumption compared to general anesthesia in the post anesthesia recovery unit and during inpatient admission

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Introduction: Spinal anesthesia (SA) has become a popular anesthetic method in premature infants undergoing infraumbilical surgery. SA in premature infants can decrease the risk of postoperative apnea, maintain hemodynamic stability, and improve operating room and post anesthesia recovery unit utilization (1,2,3). SA has been shown in the adult population to reduce postoperative pain and opioid consumption in comparison to general anesthesia (GA) for lower abdominal surgery (4). However, there is limited research on the effect of SA on postoperative pain in the pediatric population (5). We hypothesized that in addition to the previously shown benefits, SA could improve postoperative pain control and decrease consumption of analgesics in infants compared to GA.

Methods: We performed a prospective observational study of 20 infants younger than 60 weeks postmenstrual age undergoing inguinal herniorrhaphy at our children's hospital. 10 infants were anesthetized with SA using a previously described infant spinal anesthesia protocol (3) and were compared with 10 age-matched infants anesthetized with general endotracheal anesthesia followed by caudal anesthesia. IRB approval and parental consent were obtained to perform the study and utilize patient data. All patients underwent bilateral inguinal herniorrhaphy. Detailed patient demographics are outlined in Table 1. The mean postmenstrual age was 44.3 weeks for infants undergoing SA and 43.8 weeks for infants undergoing GA. All infants undergoing SA received intrathecal plain 0.5% bupivacaine at a dose of 1 mg/kg without any additional sedatives. Infants undergoing GA received mask induction with sevoflurane and oxygen, 1 mcg/kg of fentanyl and 0.2 mg/kg of cisatracurium for endotracheal intubation, and a single caudal injection of 0.2% ropivacaine at a dose of 1 ml/kg. All 20 infants were admitted for postoperative apnea monitoring. We measured and compared the revised and individualized Face, Legs, Activity, Cry and Consolability (r-FLACC) scores in the postoperative care unit (PACU) and during the rest of the inpatient admission for all 20 infants. In addition, we measured and compared the mg/kg acetaminophen consumption between the SA and GA groups during inpatient admission. All comparisons between these metrics were performed using unpaired t-test, and statistical significance were calculated using GraphPad Prism.

Results: In the PACU, mean r-FLACC scores in infants who received SA at 15, 30, and 45 minutes were 0.17, 0.44, and 0.17 respectively, compared to 0.22, 2.00, and 3.22 in infants who had GA (Figure 1A). R-FLACC scores were significantly lower in infants who received SA at 30 and 45 minutes, with p-values of 0.01 and <0.0001, respectively. During inpatient admission, infants who received SA had significantly lower r-FLACC scores of 0.33 and 0.33 at 2 and 4 hours respectively, compared to 2.22 (p=0.02) and 2.56 (p=0.005) for infants who received GA (Figure 1B). During their inpatient admission, infants who had SA received 25.14 mg/kg of total acetaminophen compared to 39.14 mg/kg of total acetaminophen for infants who had GA (p=0.03) (Figure 1C). All infants in the spinal group required only acetaminophen during their PACU and inpatient stay. One infant in the GA group required intravenous fentanyl during their PACU stay. One different infant in the GA group required a dose of oral oxycodone during their inpatient stay.

Conclusion: In summary, spinal anesthesia in infants significantly reduces r-FLACC scores in the PACU and inpatient unit compared to general anesthesia for infants undergoing bilateral inguinal herniorrhaphy. Furthermore, spinal anesthesia also reduced the overall acetaminophen consumption during the patient's inpatient admission compared to general anesthesia in our cohort. This study is the first to compare postoperative pain and analgesics as a primary outcome between SA and GA in infants younger than 60 weeks postmenstrual age. Further studies are needed to examine this benefit in a larger cohort of infants. GA is associated with insufflation of the gastrointestinal tract during positive pressure ventilation as well as airway instrumentation. The lack of these may explain the increased comfort in infants undergoing SA as reflected by their r-FLACC scores (Figure 2).

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Table 1: Patient demographic data.

	Spinal Anesthesia	General Anesthesia
Number of patients	10	10
Gestational age (weeks)	36 +/- 2.8	37 +/- 2.6
Age at time of surgery (weeks)	7.5 +/- 1.5	6.8 +/- 1.2
Postmenstrual age at time of surgery (weeks)	44.25 +/- 2.28	43.75 +/- 2.4

Figure 1A: r-FLACC Score in PACU

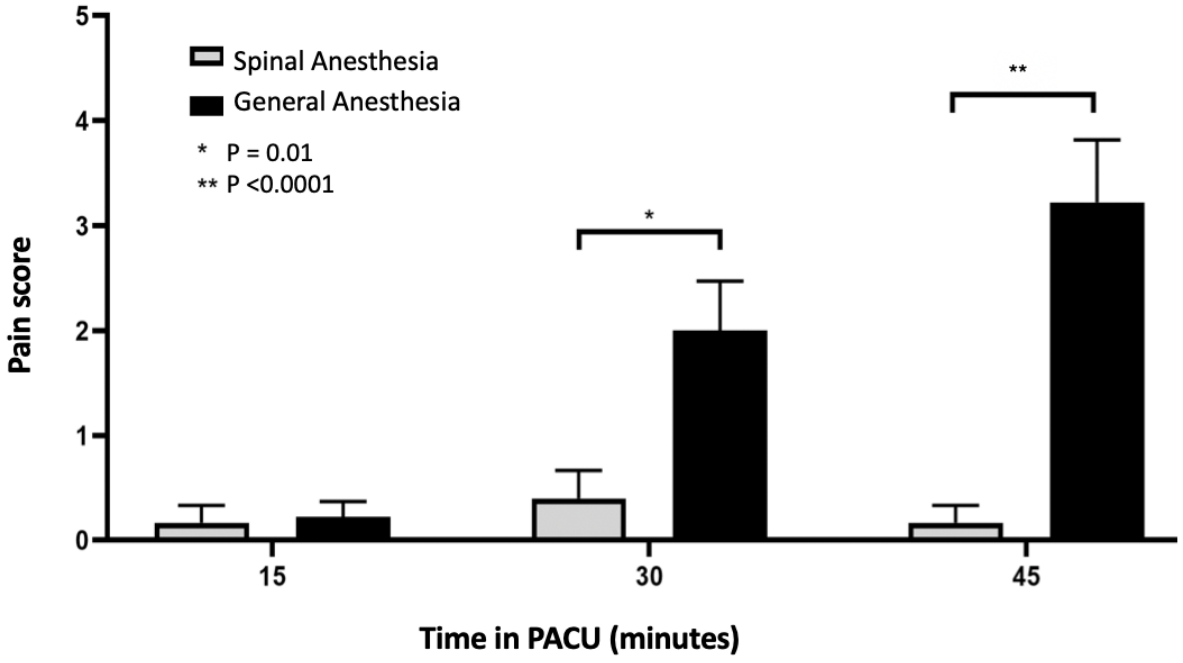


Figure 1B: r-FLACC Score in Inpatient Unit

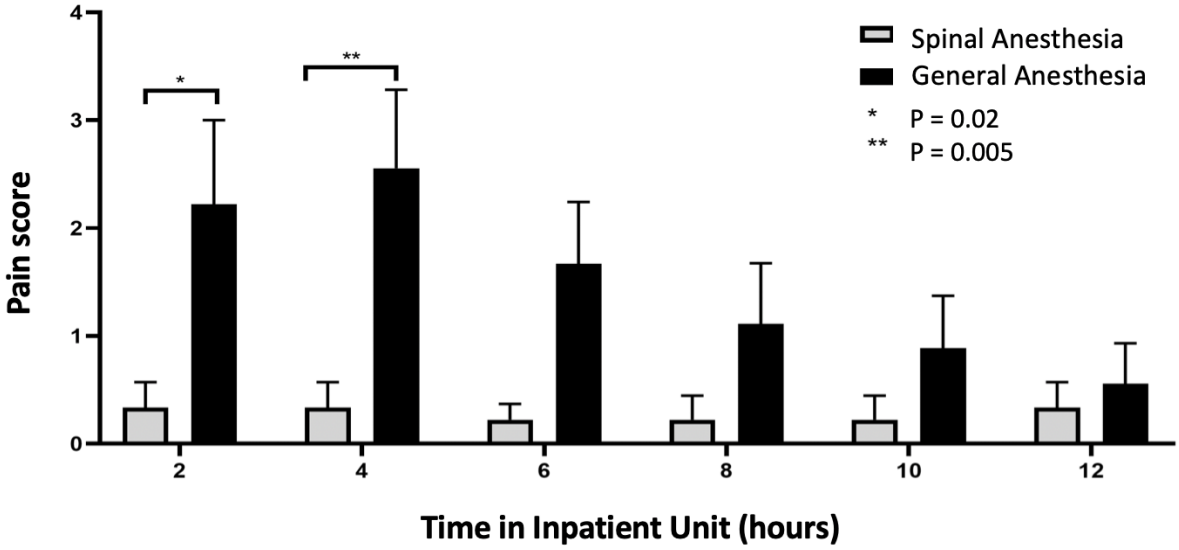
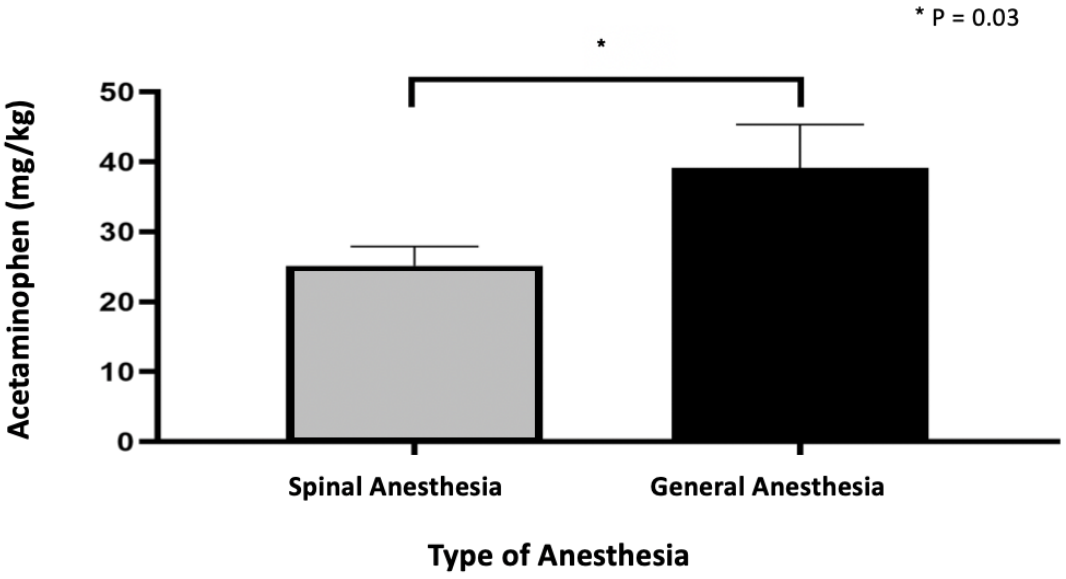


Figure 1C: Inpatient Total Acetaminophen Consumption



Pediatric Anesthesiology-9 Early ketorolac use not associated with increased risk of complications in posterior spinal fusion for adolescent idiopathic scoliosis: a case-control study

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Introduction: Ketorolac is a potent non-steroidal anti-inflammatory drug (NSAID) commonly used after major surgery for analgesia.1 However, despite its analgesic efficacy in treating moderate to severe pain, it is often withheld due to concerns about its effects on platelet function and bleeding risk2 as well as bone growth and healing3. We used a database of children undergoing posterior spinal instrumentation and fusion (PSIF) for adolescent idiopathic scoliosis (AIS) to test the hypothesis that intraoperative ketorolac would increase the rate of pseudoarthrosis at one year compared to use after the first postoperative day (POD1) as well as increase the risk of hematologic complications in the postoperative period.

Methods: We searched an established database of patients who had surgery for AIS to identify patients who received intraoperative ketorolac and those who did not receive the drug. We compared pseudoarthrosis rates in the group who received ketorolac versus those who did not receive the drug. We then searched the electronic medical record to identify postoperative transfusion rates, estimated intraoperative blood loss (EBL), drain output on the POD1, and opioid use on the POD1. Continuous variables were analyzed with a two-tailed Student's T test with unequal variance, and dichotomous variables were analyzed with a Fischer's Exact Test using Microsoft Excel for Mac (Redmond, WA).

Results: 70 participants were included in the analysis. A total of 17 people received intraoperative ketorolac (24.3%). There were no significant differences in demographic or surgical variables (Table 1). There were no differences in the rates of pseudoarthrosis in the two groups (0% vs. 0%, p=1). There were no significant differences in transfusion rates, EBL, drain output, or opioid use on the first POD (Table 2).

Conclusion: Intravenous ketorolac may be safe to use intraoperatively in children undergoing posterior spinal fusion for adolescent idiopathic scoliosis surgery. Further studies should confirm the safety of early ketorolac use and study its benefit in terms of pain scores and patient-reported outcomes.

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2. Chan, D.K. and Parikh, S.R. (2014), Perioperative ketorolac increases post-tonsillectomy hemorrhage in adults but not children. The Laryngoscope, 124: 1789-1793.
3. Wheatley BM, Nappo KE, Christensen DL, et al. Effect of NSAIDs on Bone Healing Rates: A Meta-analysis. JAAOS. 2019; 27(7): e330-e336.

Table 1. Demographic and surgical variables of early vs. late ketorolac groups. Continuous variables expressed as mean (SD).

	Early ketorolac	No early ketorolac
n	17	53
Female (%)	68	65
Age (yr)	16.3 (1.3)	15.5 (1.9)
Levels fused	9.2 (3.2)	10.5 (2.2)
Height (cm)	163.9 (9.9)	164.2 (11.2)
Weight (kg)	61 (12.8)	59.6 (17)

Table 2. Primary and secondary outcomes in early ketorolac group compared to late ketorolac group. Continuous variables expressed as mean (SD).

	Early ketorolac	No early ketorolac	P
Non-union at 1 year (%)	0	0	1
Postoperative transfusion (%)	5/17 (29)	9/53 (17)	0.31
Intraoperative blood loss (mL)	541.2 (261.2)	635.9 (338.7)	0.81
Drain output on POD 1 (mL)	296.5 (86.5)	385.1 (170)	0.99
Opioid use POD1 (MME/kg)	0.98 (0.36)	1.38 (0.69)	0.99

Pediatric Anesthesiology-10 A NOVEL METHOD TO DETECT CHANGES IN PERMEABILITY TRANSITION PORE VOLTAGE GATING IN NEONATAL MOUSE HEART MITOCHONDRIA

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Introduction: The mitochondrial permeability transition pore (mPTP) is a voltage-gated, non-selective channel present on the inner mitochondrial membrane (1, 2). The mPTP plays a fundamental role in the pathophysiology of a variety of 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 of 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 the voltage threshold for mPTP opening in isolated mitochondria using polarography and a TPP+ selective electrode. Using this approach, we identified differences in voltage gating in mitochondria from Fragile X Syndrome (FXS) mice versus controls.

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 assessed using succinate, rotenone and oligomcyin. In separate experiments, CsA was added at specific membrane potential levels as the proton motive force declined in order to determine open or closed mPTP probability. We evaluated 3-11 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 relatively low membrane potentials, suggesting open mPTP probability at or near 100%. Conversely, both groups showed CsA insensitivity at relatively high membrane potential mitochondria, suggesting closed mPTP probability. At a median membrane potential, we found open mPTP probability to be 80% in FVB controls samples compared to 40% in Fmr1 KOs.

Conclusion: 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 permits assessment of both physiological and pathological regulation of the mPTP given that it does not induce the pore to open, per se. Thus, it will have utility when investigating the role of the mPTP in health and disease.

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Pediatric Anesthesiology-11 Sevoflurane Induction with Propofol Bolusing in Human Infants is Associated with Discontinuity on the Electroencephalogram

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Introduction: 'Deep anesthesia,' as defined by low amplitude waveform activity on the electroencephalogram (EEG) less than 25 microVs and lasting greater than 2 seconds, is common during routine conduct of anesthesia in infants. This finding is termed EEG discontinuity1,2. The purpose of this present study was to determine the prevalence of EEG discontinuity during sevoflurane induction and the factors associated with it.

Methods: After IRB approval, we prospectively recruited pediatric patients presenting for surgery requiring general anesthesia. We excluded those with prematurity, neurologic injury, or congenital heart disease. Sevoflurane was used for inhalational induction without nitrous oxide or midazolam premedication. The conduct of the induction following sevoflurane was otherwise not restricted. We used the microEEG system (Biosignal Group Corp., Acton, MA)3 to obtain baseline and sevoflurane induction video-EEG. Two neurologists analyzed recordings using Persyst software (Persyst Corp., Solana Beach, CA). Baseline demographics were reported as medians and interquartile ranges or counts and percentages. The number of discrete EEG discontinuity events was recorded as well as their duration. End tidal sevoflurane concentration and other drug administrations were documented in real time and extracted post-hoc from EPIC (EPIC Systems Corp., Verona, WI). We performed univariate analysis of clinical characteristic among those with EEG discontinuity versus those without using (i) the Wilcoxon Rank-Sum test for continuous variables or (ii) Fisher's Exact test for categorical variables. A p value <0.05 was considered statistically significant and all tests were two tailed. We fit logistic regression models with age, maximum etSEV, and propofol bolus hypothesized a priori to be clinically meaningful predictors of EEG discontinuity. This is a secondary analysis of a pilot observational study in which we set a goal of obtaining 50 interpretable recordings a priori without formal power analysis4. Statistical analyses were done using STATA 13.1 (STATA Corp., College Station, TX).

Results: The median cohort age was 7.6 months, IQR (4.9, 9.8) (Table 1). 20 subjects (37.0%) exhibited EEG discontinuity with 22 total discrete events, the majority occurring after propofol bolus (Table 2). On univariate analysis, EEG discontinuity was statistically significantly associated with propofol co-administration during sevoflurane induction, p<0.001. For every 1 mg/kg of propofol administered during sevoflurane induction, the odds of EEG discontinuity was increased by 2.9, 95% CI[1.72 - 4.74] while adjusting for age and maximum end tidal sevoflurane and this association was statistically significant, p<0.001 (Table 3).

Conclusion: While EEG discontinuity is present in preterm infants during normal sleep-wake cycling, its presence in full-term infants is non-physiologic and abnormal5. However, the short-term and long-term clinical meaningfulness of neurophysiologic changes during pediatric anesthesia remain largely unknown. Prior studies have found the period of anesthesia induction is associated with a greater number of discontinuity events as well as younger age, propofol bolus, and need for advanced airway management1,2. Epileptiform changes has also been detected4. This study demonstrates an overall high prevalence of low amplitude waveform activity on the EEG (20/54 subjects, 37.0%) during routine pediatric anesthesia induction using sevoflurane alone and, in particular, with superimposed propofol bolusing. While we know EEG discontinuity is not a normal finding in the usual clinical setting5, its significance during anesthesia is unclear. This study was not powered to follow postoperative outcomes. Subjects who did receive propofol received a median dose of 2.71 mg/kg IQR (2.0, 3.3). More research is necessary to clarify the clinical meaningfulness of EEG discontinuity during anesthesia.

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2. Anesthesia Analgesia. doi: 10.1213/ANE0000000000004221. 2019
3. Epilepsy Behavior. 34:81-5. 2014
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5. Journal of Clinical Neurophysiology. 2:89-103. 1985

Table 1. Cohort Demographics and Clinical Characteristics

	Overall (n=54)	No EEG Discontinuity (n=34)	EEG Discontinuity (n=20)	p value*
Age (mo.s)	7.6 (4.9, 9.8)	7.4 (4.9, 9.8)	7.6 (5.0, 9.9)	0.94
Weight (kg)	8.9 (6.7, 10.4)	8.7 (6.8, 10.2)	9.4 (6.0, 10.5)	0.61
Male gender	41 (75.9)	28 (82.4)	13 (65.0)	0.15
Discontinuity on EEG				<0.001
Sevoflurane only	33 (61.1)	28 (82.4)	5 (25.0)	
Sevoflurane and propofol	21 (38.9)	6 (17.6)	15 (75.0)	
Epileptiform EEG	4 (7.4)	1 (2.9)	3 (15.0)	0.14
Max et_{SEV} (%)	6.1 (5.5, 6.6)	6.1 (5.5, 6.5)	6.1 (5.5, 6.6)	0.14
Et_{CO2} min (mmHg)	15.5 (10.0, 20.5)	16.5 (11.0, 21.5)	14.5 (9.5, 19.5)	0.31
Et_{CO2} max (mmHg)	36.5 (32.0, 41.0)	35.5 (30.0, 39.5)	39.5 (33.0, 44.5)	0.10
Propofol administration				
Number	21 (38.9)	4 (11.8)	17 (85.0)	<0.001
Dose (mg/kg)	0 (0, 2.6)	0 (0, 0)	2.71 (2.0, 3.3)	<0.001
Fentanyl				0.36
Fentanyl given	28 (51.9)	16 (47.1)	12 (60.0)	
Fentanyl not given	26 (48.2)	18 (52.9)	8 (40.0)	
Induction time (min)	6 (3, 9)	6 (3, 7)	6 (3, 9)	0.32

*"No EEG Discontinuity" group compared to "EEG Discontinuity" group

Table 2. Characteristics of EEG discontinuity events (n=20)

	Overall (n=20)	Sevoflurane alone (n=5)	Propofol bolus (n=15)	p value
Total number of discontinuity events	22	7	15	-
Discontinuity events by subject	1 (1, 1)	1 (1, 1.5)	1 (1, 1)	0.05
Duration of discontinuity events (sec)	135 (10, 307)	78 (7, 445)	144 (19, 307)	0.88
Et_{SEV} when discontinuity begins (%)	4.2 (2.9, 5.0)	4.2 (3.8, 6.5)	4.4 (2.9, 5)	0.54
Time to onset from propofol injection to appearance of EEG discontinuity (sec)	-	-	15 (5, 28)	-

Table 3. Univariable logistic regression model of the association between EEG discontinuity and clinical characteristics

	Odds Ratio	p value	95% confidence interval
Age (mo.s)	0.96	0.51	[0.85 – 1.09]
Propofol (yes/no)	42.50	<0.001	[8.49 – 212.80]
Propofol (mg/kg)	2.86	<0.001	[1.72 – 4.74]
Epileptiform EEG	5.82	0.14	[0.56 – 60.31]
Max et_{SEV}	1.01	0.98	[0.50 – 2.02]
Et_{CO2} min	0.97	0.48	[0.89 – 1.05]
Et_{CO2} max	1.08	0.09	[0.99 – 1.18]
Fentanyl (yes/no)	1.69	0.36	[0.55 – 5.17]

Table 4. Multivariable logistic regression model of the association between EEG discontinuity and propofol administration*

	Odds Ratio	p value	95% confidence interval
Model 1			
Age (mo.s)	0.98	0.86	[0.81 – 1.20]
Max et_{SEV}	0.98	0.98	[0.37 – 2.62]
Propofol (yes/no)	37.05	<0.001	[7.34 – 187.08]
Model 2			
Age	1.01	0.91	[0.86 – 1.19]
Max et_{SEV}	0.95	0.90	[0..39 – 2.32]
Propofol (mg/kg)	2.73	<0.001	[1.63 – 4.55]

Pediatric Anesthesiology-12 A Retrospective Review of the Assigning Practices of American Society of Anesthesiology-Physical Status Scores by Pediatric Anesthesiologists for Patients with Retinoblastoma

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Introduction: ASA scores are used to assess preoperative physical status and quantify perioperative risk. The application of the ASA scoring guidelines for patients with cancer remains undefined, and few studies have assessed the standardization of ASA score assignment practices in the context of cancer.1 This study investigates the ASA score assigning practices for patients with retinoblastoma (RB) at a pediatric cancer hospital with the goals of: justifying current ASA assignment practices with regard to cancer prognosis and type of treatment, and proposing a guideline for assigning ASA scores to patients with localized cancer.

Methods: Medical records of patients assigned to a retinoblastoma protocol at a pediatric cancer hospital were retrospectively reviewed. Patients were selected based on the stratum to which they were assigned within the protocol (enucleation-only stratum). One-hundred fourteen patients were evaluated. ASA scores given before enucleation were compared with those after enucleation to determine if removal of localized cancer influenced ASA assigning practices. A single, summarized ASA-PS score was calculated for each patient pre- and post-enucleation by using the median of all ASA-PS scores pre- and post-enucleation, respectively. The summarized ASA-PS and individual ASA-PS scores were both described by reporting the median (range) and mean [standard deviation (± SD)] pre- and post-enucleation. A sign test was used to evaluate the median difference between the summarized ASA-PS scores.

Results: Of the 114 patients evaluated, 70 were excluded because they were assigned to a chemotherapy and/or radiation therapy stratum; 3 patients were excluded due to the presence of a comorbidity other than RB thus, 41 patients were included. These 41 patients underwent a total of 118 pre-enucleation anesthetics and 518 post-enucleation anesthetics (Figure 1). The most common ASA score given was III (83.2% of pre-enucleation anesthetics and 90.2% post-enucleation). Thirty-four (82.9%) patients maintained the same median summarized ASA-PS score pre- and post-enucleation, and seven (17.1%) patients had increased median summarized ASA-PS scores post-enucleation (Table 1). Collectively, this suggests that the median summarized ASA-PS score increased following enucleation (Figure 2).

Conclusion: In the absence of severe systemic impact of the disease, its treatment, or other comorbidities, patients with localized cancer could justifiably be categorized as ASA II or I. In our study however, anesthesiologists routinely assigned patients with RB as ASA III, and excision of the tumor produced variable ASA score assigning practices. Our findings demonstrate a high-degree of interrater variability (Figure 3), and suggest a need for a sample cancer diagnosis in the ASA guidelines, as was done with renal and cardiovascular disease in 2014.2 As such, we have provided an example of a cancer-specific ASA guideline using RB as a model (Table 2).

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Table 1: Summarized ASA-PS Score Characteristics

	Pre-Enucleation N=41(%)	Post-Enucleation N=41(%)	p-value
Number of ASA scores			
Mean ± SD	2.9 ± 0.4	12.6 ± 7.9	<0.0001[T]
Median (IQR)	3.0 (3.0 - 3.0)	12.0 (6.0 - 16.0)	<0.0001[W]
Minimum – Maximum	2.0 - 4.0	2.0 - 35.0	<0.0001[P]
Any anesthesia-related complication			
No	31 (75.6)	32 (78.0)	1.000[M]
Yes	10 (24.4)	9 (22.0)	
Median Summarized ASA score			
1	1 (2.4)	0 (0.0)	<0.0001[S]
2	6 (14.6)	0 (0.0)	
3	34 (82.9)	41 (100.0)	
Mean ± SD	2.8 ± 0.5	3.0 ± 0.0	0.0096[T]
Median (IQR)	3.0 (3.0 - 3.0)	3.0 (3.0 - 3.0)	0.0147[W]
Minimum – Maximum	1.0 - 3.0	3.0 - 3.0	0.0190[P]

T=paired t-test, W=Wilcoxon signed-rank test/Sign test, P=Permutation test, M=McNemar's chi-square test, S=Symmetry test

Table 2. Suggested ASA-PS [a] scores for a sample patient with a "general" cancer diagnosis as well as a RB [b] diagnosis

ASA-PS Classification	Systemic implications of a "general" cancer diagnosis	Systemic implications of RB (utilizing IRSS [c]) [3]
ASA-PS I	-Localized cancer without systemic impact; no metastasis -No chemotherapy/radiation - No other comorbidities	-IRSS Stage 0: Patient treated conservatively -IRSS Stage I: Eye enucleated, completely resected histologically -No other comorbidities
ASA-PS II	-Localized cancer, mild comorbid impact -Less toxic or more targeted therapies (e.g., implanted radiation device)	-IRSS Stage II: Eye enucleated, microscopic residual tumor -Targeted or locally delivered chemotherapy/radiation (e.g., intravitreal chemo or brachytherapy)
ASA-PS III	-Metastatic cancer, moderate comorbid impact -Systemic chemotherapy/ radiation -Moderate systemic effect of localized cancer (e.g., dehydration/malnutrition, paraneoplastic syndrome)	-IRSS Stage III: Regional extension -IRSS Stage IV: Metastatic disease a. Hematogenous metastasis (without CNS [d] involvement) b. CNS extension -Systemic chemotherapy, external beam radiation therapy
ASA-PS IV	Life-threatening metastatic disease (e.g., cerebral, cardiac, pulmonary), severe comorbid impact	-IRSS Stage IV: Metastatic disease that is a constant threat to life (e.g. CNS metastasis with elevated ICP [e], liver metastasis causing liver failure)
ASA-PS V	Severe metastatic burden (e.g., impending cerebral herniation) in which patient is not expected to survive (e.g., palliation procedure)	- IRSS Stage IV: Metastatic disease leading to significant morbidity in which the patient is not expected to survive without the procedure (e.g., craniotomy for impending cerebral herniation secondary to CNS metastasis)
ASA-PS VI	Patient declared brain-dead	Patient declared brain-dead

[a] ASA-PS: American Society of Anesthesiology-Physical Status, [b] RB: retinoblastoma, [c] IRSS: International Retinoblastoma Staging System, [d] CNS: central nervous system, [e] intracranial pressure

Figure 1. CONSORT diagram of the study.

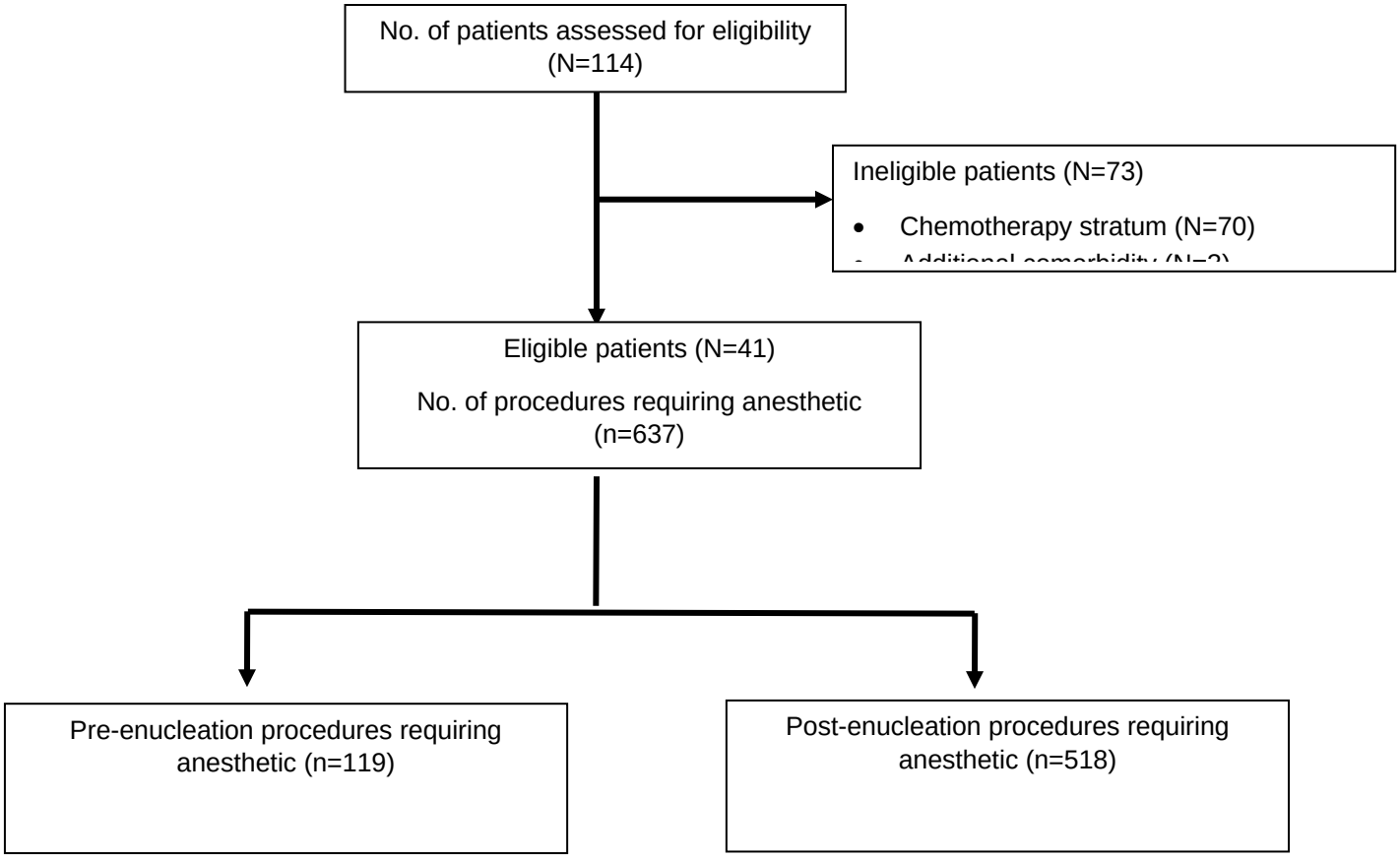


Figure 2: A visualization of the Median Summarized ASA-PS Scores over time (pre- vs post-enucleation) by patient

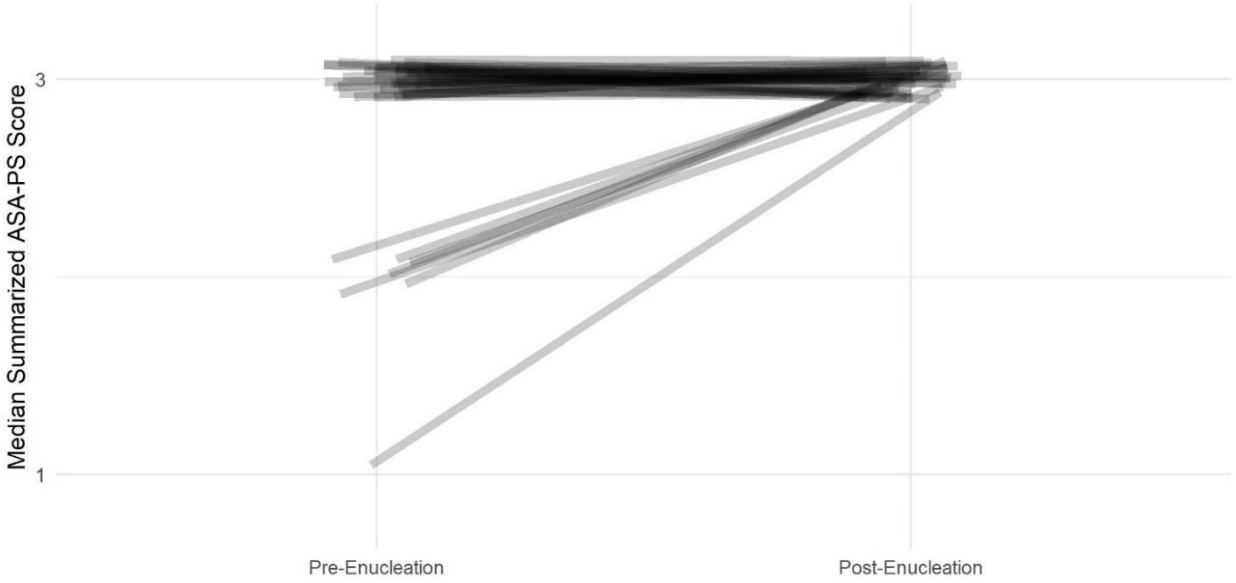
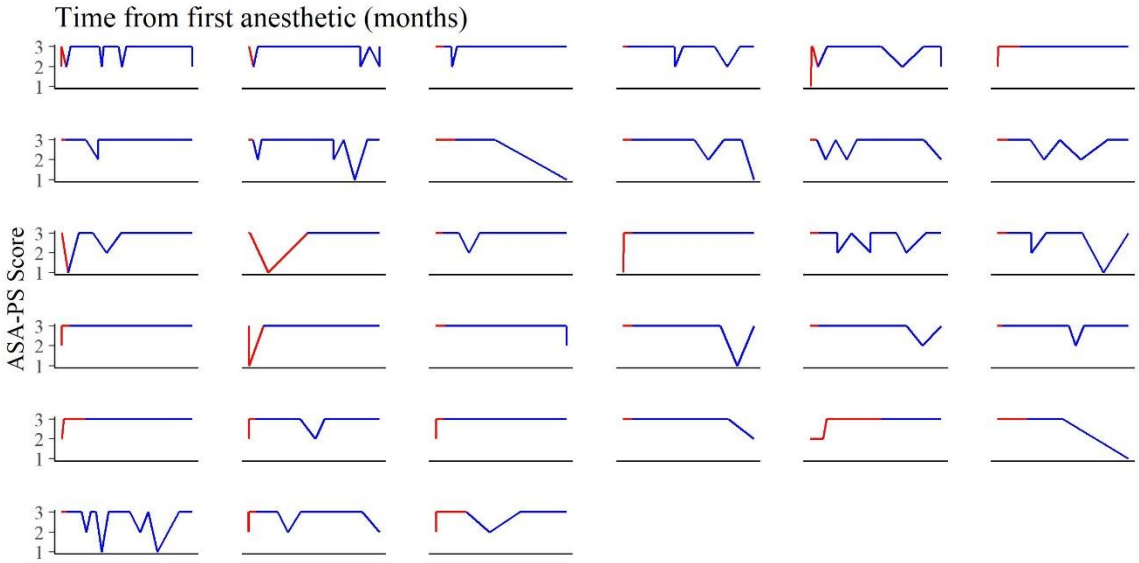


Figure 3: A visualization of the ASA Scores over time for patients whose score experienced changed.



Pediatric Anesthesiology-13 Development and Validation of a Machine Learning Algorithm for Prediction of Prolonged Opioid Use After Surgery in Adolescents and Young Adults

Trisha Jani[1], Andrew T Ward[2], Beth De Souza[3], Nicholas Bambos[1], Thomas A Anderson[3]

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Introduction: Long-term opioid use has significant negative healthcare consequences 1–3. While associations between prolonged opioid use after surgery (POUS) and patient variables have been examined in some adolescent and teenage populations,4–6 there is a lack of accurate risk predictions for children who undergo surgery and develop prolonged opioid use. We hypothesized that machine learning techniques may be utilized to build predictive algorithms for use in clinical scenarios to identify adolescents and young adults at increased risk of POUS.

Methods: Using a de-identified prescription and medical claims database from a large national insurance provider, we identified patients aged 12–21 who underwent anesthesia and surgery between January 1, 2011 and June 30, 2017 and were enrolled for at least one year prior to surgery and at least six months following surgery. The primary outcome was POUS, defined as having filled ≥1 opioid prescription 90–180 days after surgery. Variables capturing clinical, demographic, socioeconomic, diagnostic, medical utilization, and medication information from the 365 days before surgery were extracted and engineered. Five machine learning algorithms (random forests (RF), logistic regression with an L2 penalty (LRL2), logistic regression with a lasso penalty (LRLasso), gradient boosting machines (GBM), and extreme gradient boosting models (XGBoost)) were trained to predict POUS at two clinical intervention points: the day of surgery and 14 days after surgery (common surgical follow-up visit time). For each intervention point, for each model, hyperparameters were tuned using 5-fold cross-validation, and model performances were assessed on a 20% held-out test set.

Results: 186,493 patients aged 12–21 years met inclusion/exclusion criteria; 8,410 (4.5%) had POUS. The average patient age was 17.5 years at the time of surgery, and 49.6% were female. The rates of POUS in adolescents and young adults who underwent the ten most common surgeries ranged from 2.1% ('Dental') to 5.6% ('Other therapeutic procedures on muscles and tendons'). See Table 1 for quantitative results. Gradient boosting machines had the strongest test performance for day-of-surgery prediction. Extreme gradient boosting had the strongest test performance for 14-days-after-surgery prediction. Prediction performance for some individual surgeries was even stronger. The variables most used in prediction included information about previous opioid prescriptions, overall medical utilization, opiate agonist and muscle relaxant prescriptions, abdominal pain, and history of mental health and substance use disorders.

Conclusion: We designed a machine learning algorithm for predicting whether adolescents and young adults will develop prolonged opioid use after surgery. For some individual surgeries, this algorithm's performance may be well-suited to identify high-risk patients and inform clinical intervention strategies.

Reference(s): Br J Clin Pharmacol. 2009;67(2):172-179. The Primary Care Companion For CNS Disorders. 2012. doi:10.4088/pcc.11m01326 Neurosci Biobehav Rev. 2012;36(9):2056-2068. Journal of Craniofacial Surgery. 2018;29(7):1697-1701. doi:10.1097/scs.0000000000004762 Pediatrics. 2018;141(1). doi:10.1542/peds.2017-2439 JAMA Internal Medicine. 2019;179(2):145. doi:10.1001/jamainternmed.2018.5419

Table 1: Rates of POUS and Machine Learning Performance by Surgery

Surgery	Number of surgeries	Number of POUS cases (%)	Day of Surgery AUC (GBM)	14 Days After Surgery AUC (XGBoost)
Most common surgeries				
Other OR therapeutic procedures on joints	4097	224 (5.5)	0.699	0.711
Tonsillectomy and/or adenoidectomy	3822	164 (4.3)	0.698	0.702
Dental	2999	64 (2.1)	0.696	0.727
Arthroscopy	2709	101 (3.7)	0.669	0.679
Excision of semilunar cartilage of knee	2518	89 (3.5)	0.609	0.640
Appendectomy	2315	105 (4.5)	0.745	0.741
Other OR therapeutic procedures on bone	2207	104 (4.7)	0.726	0.706
Other OR therapeutic procedures on nose; mouth and pharynx	2021	82 (4.1)	0.667	0.683
Other therapeutic procedures on muscles and tendons	1892	106 (5.6)	0.700	0.718
Other fracture and dislocation procedure	1853	57 (3.1)	0.734	0.752
Surgeries with highest performance				
Inguinal and femoral hernia repair	494	14 (2.8)	0.851	0.874
Extracorporeal lithotripsy; urinary	193	15 (7.8)	0.847	0.858
Myringotomy	448	17 (3.8)	0.823	0.845
Endoscopy and endoscopic biopsy of the urinary tract	195	14 (7.2)	0.815	0.831
Transurethral excision; drainage; or removal urinary obstruction	190	16 (8.4)	0.781	0.806
Incision and drainage; skin and subcutaneous tissue	194	15 (7.7)	0.804	0.800
Other OR therapeutic procedures; female organs	783	66 (8.4)	0.775	0.792
Other vascular catheterization; not heart	139	13 (9.4)	0.768	0.790
Laparoscopy (GI only)	351	39 (11)	0.772	0.785
Arthroplasty knee	413	18 (4.4)	0.781	0.782

Figure 1: Receiver operating characteristic curves for machine learning models to predict prolonged opioid use after surgery on the day of surgery (left) and 14 days after surgery (right). Performance was assessed on a 20% held-out test set. Legend entries denote the AUC for each method with 95% confidence intervals.

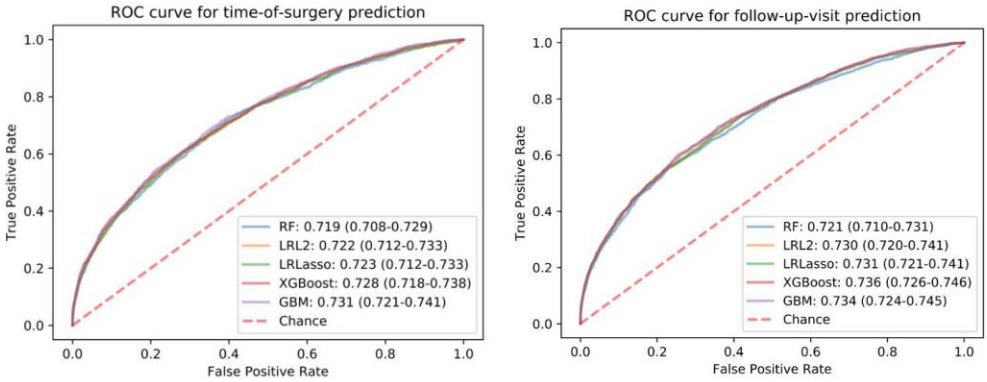
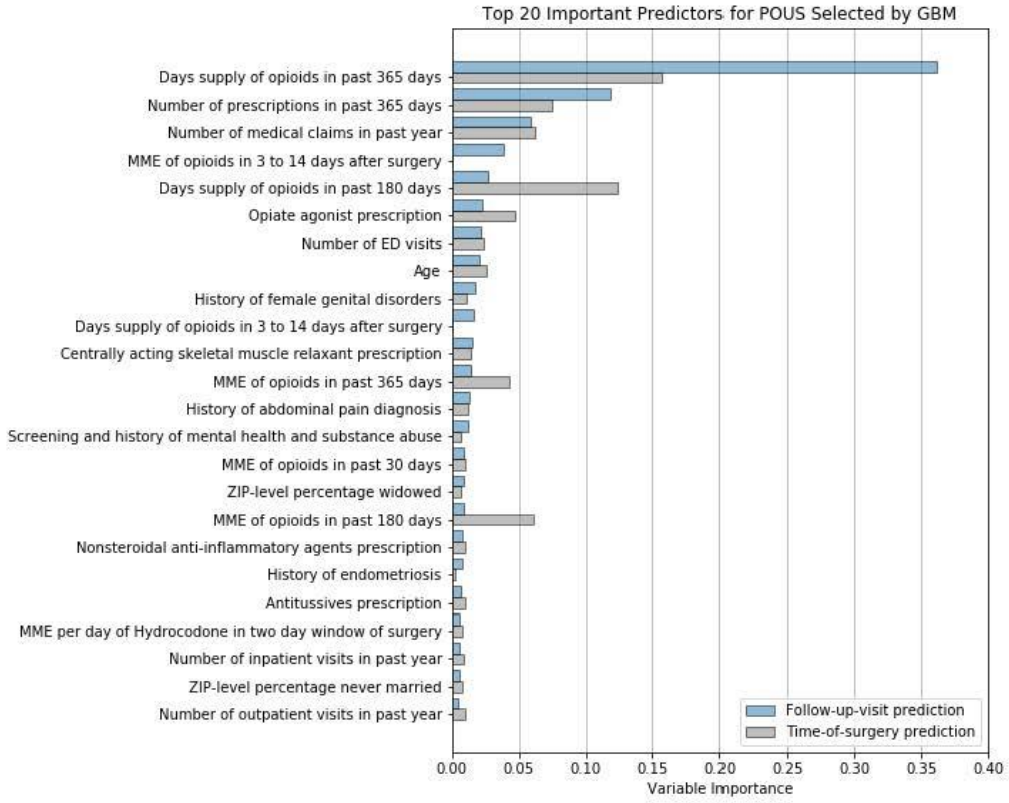


Figure 2: Variable importance provides a measure of how useful a given variable was in constructing the gradient boosting machine model. The twenty most important variables for the GBM model predicting POUS on the day of surgery and 14 days after surgery are compared. MME and days supply of opioids in the 3-14 days after surgery were not included in the time-of-surgery model.



Pediatric Anesthesiology-14 Continuous infusion of Lidocaine for Erector Spinae Plane Blocks in Pediatric Cardiothoracic Surgery is Lidocaine Safe

David A Rosen[1], Joshua D Eaton[1], Ashley L Petrone[1], Robert A Gustafson[1]

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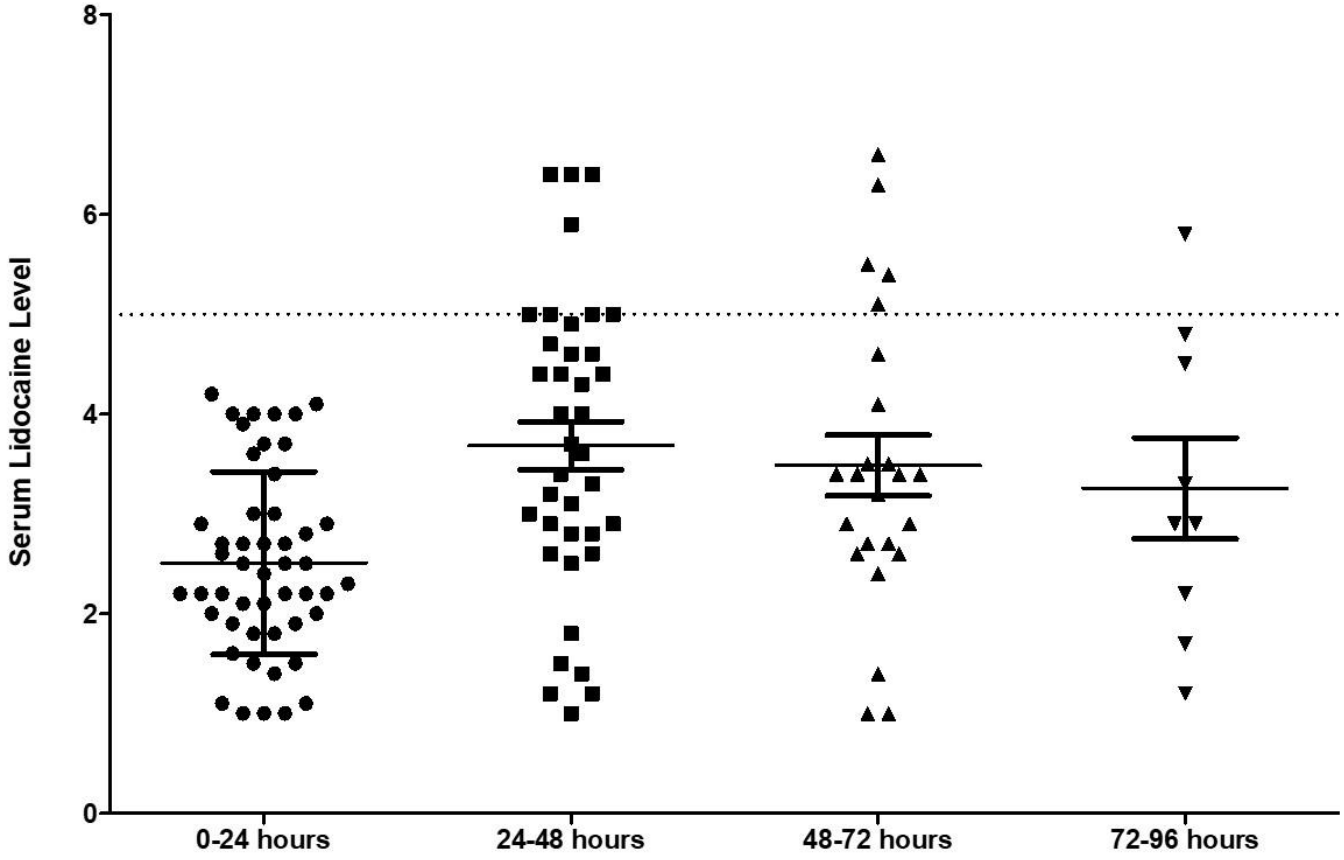
Introduction: Pain relief in Children undergoing cardiothoracic is surgery is a critical portion of their intraoperative and postoperative care. While there are many different approaches to achieving this goal regional analgesic techniques have become attractive as they provide analgesia without the complications associated with narcotics. The erector spinae plane block (ESPB) has been used at our institution for the past two years and has become the predominant mode of postoperative analgesia in these patients. The ESPB has been able to significantly reduce the need for postoperative narcotics. A concern in this population is the pharmacokinetics of local anesthetics in the ESPB. Intravenous infusions of lidocaine are frequently used in this population for control of arrhythmias. Intravenous lidocaine Infusion rates from 10-40 mcg/kg/min are used to maintain lidocaine in the therapeutic range. The purpose of this study was to determine the incidence of toxic levels of local anesthetic associated with the ESPB when lidocaine infusion levels were maintained in the range usually considered safe and effective for controlling ventricular arrhythmias.

Methods: This study approved by the WVU institutional review board for human subjects. Children 3 months to 18 years coming for cardiothoracic surgery were entered into the study if they received an ESPB for their cardiothoracic surgery, and had a continuous infusion of lidocaine in the postoperative period. Lidocaine infusion were maintained at rates less than 40 mcg/kg/min combined for all catheters the patient had placed. Lidocaine levels were obtained every 24 hours while ESPB catheters were infusing. Lidocaine levels greater than 5.0 mcg/ml were considered toxic.

Results: Sixty-four patients have received lidocaine infusions for their ESPB. All lidocaine infusions were infused at rates less than or equal to 40 mcg/kg/min total regardless of the number of catheters in place. No patients had levels outside of the therapeutic range on post op day 1. On post op day two 4 patients had levels above 5 mcg/ml. Three of these patients were 1 year of less and one was 17 years. The highest lidocaine level in these 4 patients on day one was 3.7 mcg/ml. At 48-72 hours 5 patients had levels above 5 and only one of these had abnormal value at 48 hours. None of these patients had signs of local anesthetic toxicity.

Conclusion: Amide local anesthetics are widely used because of their duration of action, and their lack of allergic reactions. The uptake of these local anesthetics varies by location of the block. The uptake of local anesthetic placed in the erector spinae plane in children has not been well studied. Additionally, the impact of cardiothoracic surgery on the kinetics of this block has not been studied. This study documents that lidocaine levels exceeding therapeutic levels (5 mcg/ml) can be seen in pediatric patients with continuous ESPB despite maintaining the lidocaine infusion rates at accepted intravenous infusion rates. Lidocaine was chosen because of the ease in obtaining serum blood levels. Toxic levels with amide local anesthetics are more common in younger children because of immaturity of their metabolic systems and low concentrations of the alpha 1-acid glycoprotein. This along with the results of our study support the recommendation that 2-Chloroprocaine be the local anesthetic of choice for ESPB in children less than 6 months. Additionally bypass and hepatic congestion in some of these cardiac lesions may further depress metabolism. Some of the highest levels on Day 1 were observed in Fontan Patients. The fact that toxic concentrations were not observed on day 1 probably relates to the increased volume of distribution for the local anesthetics which becomes full as the continuous infusion of local anesthetics persisted. 3.7 mcg/ml was the highest level recorded on post op day 1 in those patients that developed toxic levels on post op day 2. Conclusion: Children undergoing cardiothoracic procedures with ESPB can develop toxic lidocaine levels on day 2 despite receiving lidocaine infusion rates generally considered safe. These patients had no outward signs of Lidocaine toxicity. Because of the elevated serum levels found in our study we recommend using lidocaine for ESPB in children undergoing cardiothoracic procedures, and obtaining daily lidocaine levels to avoid toxicity.


Serum Lidocaine Level
8
6
4
2
0
0-24 hours
24-48 hours
48-72 hours
72-96 hours

Pediatric Anesthesiology-15 EFFECTS OF GENERAL ANESTHETICS AND DIFFERENT EXPOSURE TIME ON THE SERUM BIOMARKERS OF BRAIN INJURY IN PEDIATRIC POPULATION UNDERGOING NON-CARDIAC SURGERIES

Tarun Pant[1], Richard J Berens[2], Amy Henry[3], Susan P Taylor[4], 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

Introduction: Preclinical investigations have consistently demonstrated neuroanatomical changes and life-long cognitive deficits following exposure to common anesthetics early in life. Recent reports from clinical studies, such as the Pediatric Anesthesia Neurodevelopment Assessment (PANDA) and the General Anesthesia compared to Spinal anesthesia (GAS) trials have indicated that single anesthesia exposure or short sevoflurane exposure (<1hr) to healthy children younger than 3 years do not cause significant adverse effects. However, the Mayo Anesthesia Safety in Kids Study found that multiple exposures are associated with a pattern of changes in specific neuropsychological domains that is associated with behavioral and learning difficulties. In the present study, we tested the hypothesis that general anesthetics may significantly alter the expression profile of biomarkers of brain injury in pediatric patients (<4 yrs.) having a lengthy surgery (>2.7hrs.) as compared to those with short duration surgery (<1hr).

Methods: To elucidate the effect of short and long duration of general anesthetics on pediatric population (n=10/ group) the blood samples were collected before and after surgery. We examined the mRNA expression of different biomarkers in the serum using reverse transcription quantitative polymerase chain reaction (qRT-PCR). Additionally, to identify the underlying mechanisms and signaling network of anesthetic-induced neurotoxicity we used PCR array (RT2 profiler PCR array) containing 84 genes specific to human neurotoxicity pathways. Moreover, we are in the process of determining the protein expression of biomarkers using the monoclonal antibodies by sandwich ELISA. Data analysis was performed using Graph Pad Prism software and the significance was set at $P<0.05$.

Results: Our study demonstrates that pediatric population having a long-term anesthetic exposure (>2.7hrs.) have an elevated expression change post-surgery in several brain biomarkers like BDNF, MBP, NSE, and S100-B, as compared to pediatric patients with short surgery duration (<1hr, $*P<0.05$, Figure). The Human neurotoxicity PCR array showed that longer exposure of anesthetics elicited dysregulation of several mRNA genes. Bioinformatics analysis on these deregulated genes indicates the linkage to neuro inflammatory and neuronal apoptotic pathways which may contribute to neurodegeneration.

Conclusion: The preliminary results of our investigation indicate that longer exposures to general anesthetics elicit the expression of several brain injury biomarkers that may contribute to neurotoxicity in the pediatric population.

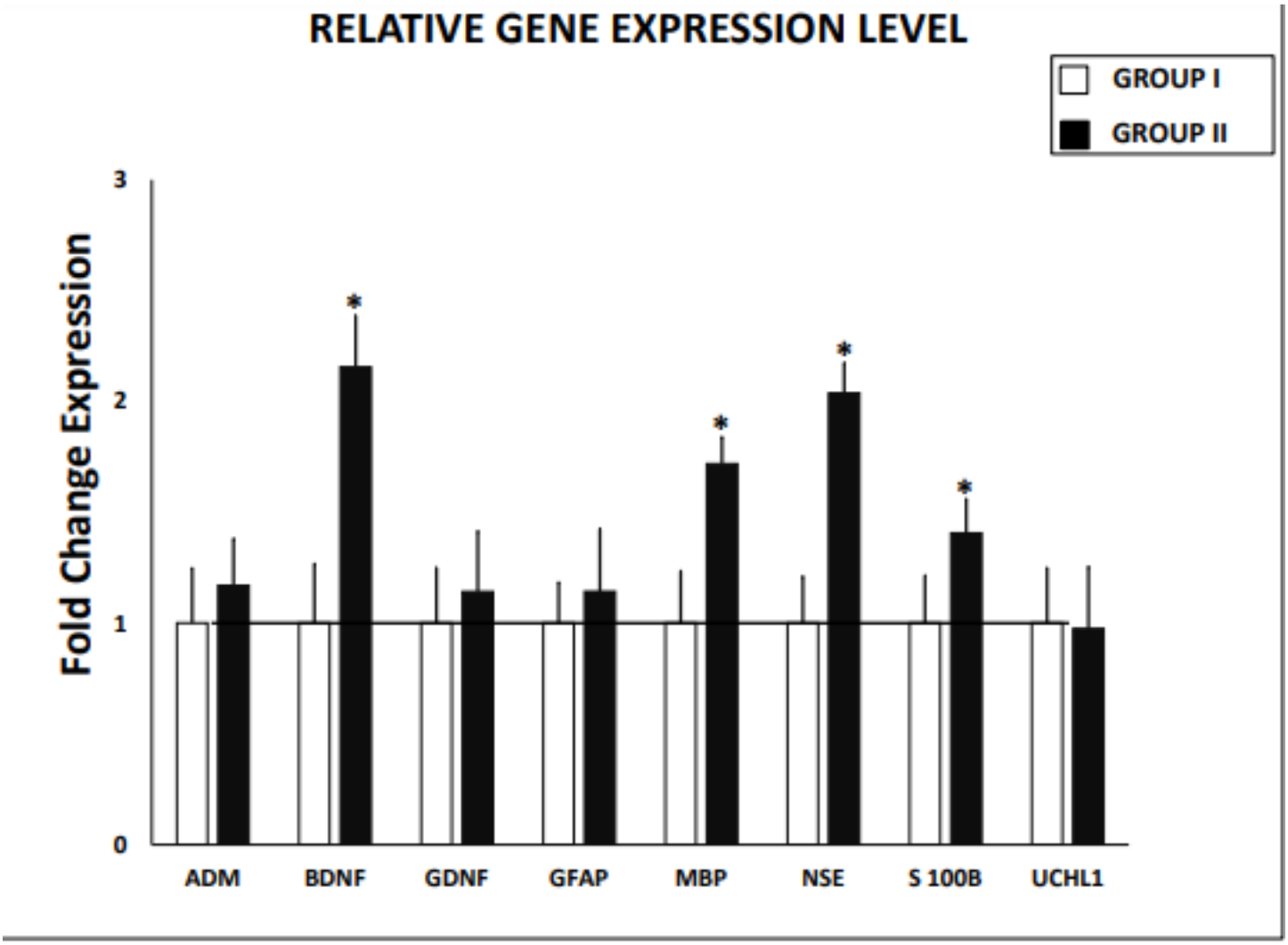


Figure: Normalization expression analysis of a set of target genes Adrenomedullin (ADM), Brain-derived neurotrophic factor (BDNF); Glial cell-derived neurotrophic factor (GDNF); Glial fibrillary acidic protein (GFAP); Myelin Basic Protein (MBP); Neuron Serum Enolase (NSE); Calcium-binding protein B (S100B); Ubiquitin C-terminal hydrolase-L1 (UCH-L1) in post-operative surgery samples using 18srRNA as a reference gene. The relative normalized expression levels are depicted as means ± standard error of the mean (SEM) of ten biological replicates and corresponds to the ratio between post operative surgery samples for duration <1hr & age <4 yrs. **(GROUP I)** and duration >2.7 hrs. & age <4 yrs. **(GROUP II)**. Each sample was conducted in triplicate (*n* = 3) Statistical significances **(*P≤0.05)** between the two means were determined by unpaired two tailed t-test using GraphPad Software, Inc., La Jolla, CA, USA).

Perioperative Anesthesia

Perioperative Anesthesia-1 Factors and clinical outcomes associated with preoperative Do-Not-Resuscitate designation differ across surgical groups: an analysis of the National Surgical Quality Improvement Database

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[1]University of California, San Francisco, San Francisco, CA, [2]Duke University, Durham, NC, [3]Duke University School of Medicine, Durham, NC, [4]Duke University Medical Center, Durham, NC

Introduction: The role of do-not-resuscitate (DNR) orders pose a unique clinical challenge in the preoperative setting [1]. Patients with pre-existing DNR orders who undergo surgical procedures have been shown to have a higher risk of perioperative mortality [2] and increased length of stay and postoperative complications [3]. Still, there is limited research elucidating the patient factors associated with a DNR designation, as well as the factors associated with key outcomes for interest for individuals with a DNR designation. The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database provides a cohort of patients with DNR information along with relevant procedural and demographic information. In addition, Clinical Classifications Software (CCS) classes can be leveraged to identify three broad disease/procedure groups of interest: colorectal, vascular, and orthopedics. We use the data from the NSQIP database to: a) identify factors associated with a pre-existing DNR designation in homogeneous cohorts of patients undergoing colorectal, vascular and orthopedic procedures; b) identify preoperative factors that are associated with 30-day mortality, death prior to discharge and length of stay in these patients; and c) identify unique phenotypes of patients with pre-existing DNR orders who develop various patient-centric outcomes.

Methods: Using data from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database, patients with a pre-existing DNR were queried. The most common procedures in the vascular, orthopedic and colorectal classes were included based on Current Procedural Terminology (CPT) codes. Demographic and baseline characteristics were summarized using mean with standard deviation, median with interquartile range or frequency with percentage where appropriate. To identify variables associated with pre-existing DNR, 30-day mortality, death at discharge, increased length of stay for each disease/procedure group, a pseudo machine learning algorithm using Least Absolute Shrinkage and Selection Operator (LASSO) was used. Adjusted logistic/linear regression models were also postulated.

Results: Between the years of 2010-2013, 2,001,405 unique observations were initially queried from the NSQIP database. Applying inclusion and exclusion criteria, 211,420 unique observations remained in the dataset. Of this cohort, patients with a 'yes' designation for DNR were included in this study, totaling 2755 unique observations of which 1,149 patients in the colorectal group, 736 patients in the orthopedics group and 870 patients in the vascular group. Baseline clinical and demographic information is shown in TABLE 1 and outcome information is shown in TABLE 2. Of patients with a pre-existing DNR on day of surgery, 30-day mortality for colorectal, orthopedic and vascular subsets was 27.2%, 15.4% and 19.5%, respectively. Death at discharge across groups were 10.3%, 4.9% and 6.1%, respectively. Length of hospital stay was highest in colorectal patients. LASSO analysis demonstrated unique odds ratios for a number of different parameters some of which were associated with increased or decreased association with the outcomes of interest, even across different surgical groups. Typically, parameters corresponding to increased comorbidities and baseline illness were associated with having a pre-existing DNR, increased 30-day mortality, risk of death at discharge and increased length of stay. Parameters showing discrepant risk (increased versus decreased) were noted across all surgical classes for each outcome. Some of these included a male gender, increased age, higher BMI and Hispanic descent. Additionally, odds ratios had dramatically different values for individual parameters across different surgical classes.

Conclusion: Using a machine learning methodology, we show that patients with pre-existing DNR at time of common colorectal, orthopedic or vascular procedures carry different risks for morbidity and mortality. This is important because it demonstrates that (1) there are distinct phenotypes of DNR patients in the preoperative setting that carry unique risk profiles for perioperative morbidity and mortality; (2) a personalized risk assessment prior to undergoing certain procedures in DNR patients can be performed for specific surgical subsets; and (3) patient-centered outcomes beyond mortality alone should be used when communicating risk to clinicians, patients and families.

Reference(s):

[1] JAMA 1991, 266(17):2407-2412
[2] Ann Surg 2012, 256(3):453-461.
[3] Arch Surg 2011, 146(8):922-928

Figure 1: CONSORT Diagram for Inclusion and Exclusions for Both Study Aims

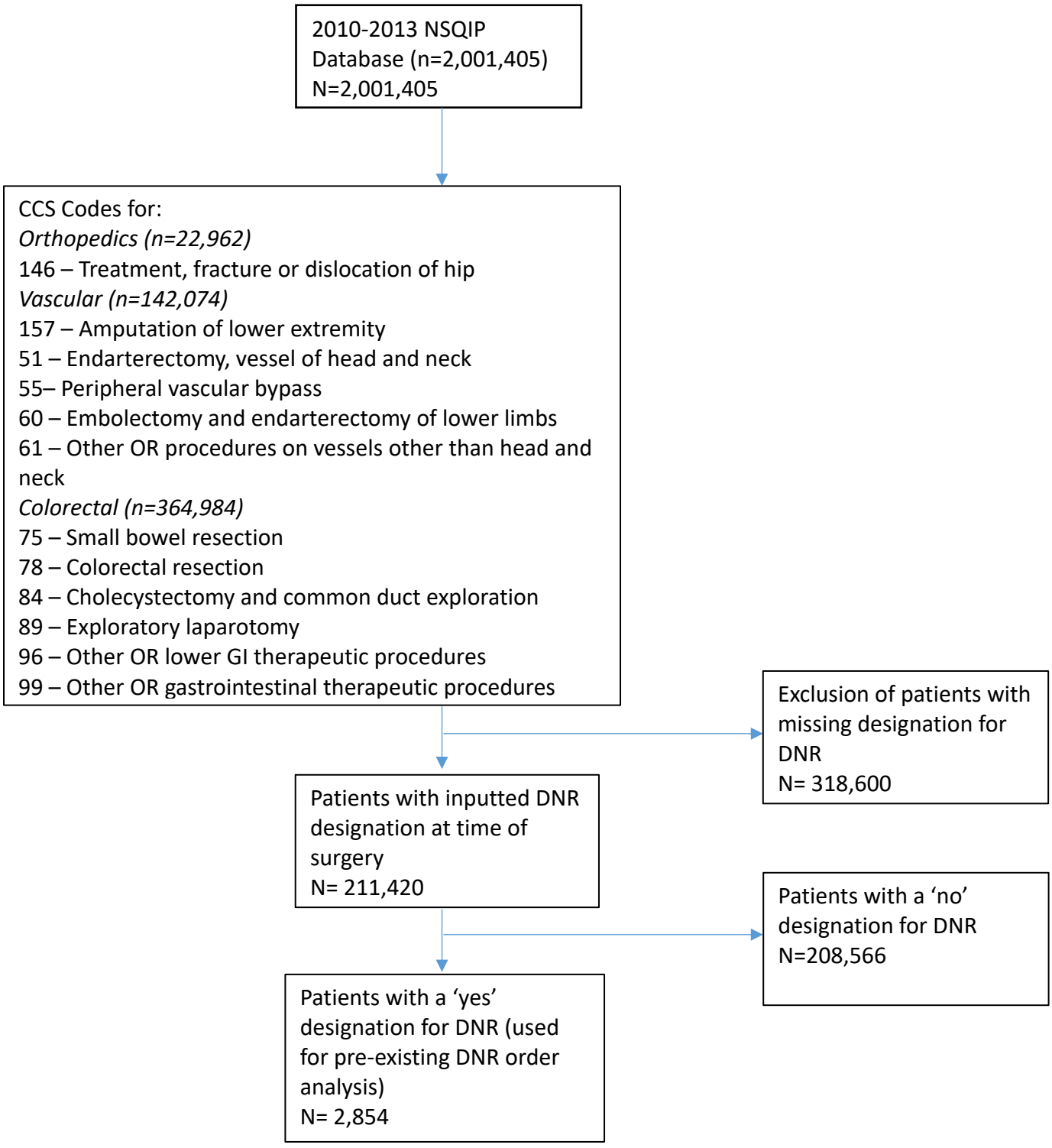


Figure 2: Adjusted Odds Ratios for Selected Predictors of a Pre-existing DNR Order (By Surgical Group)

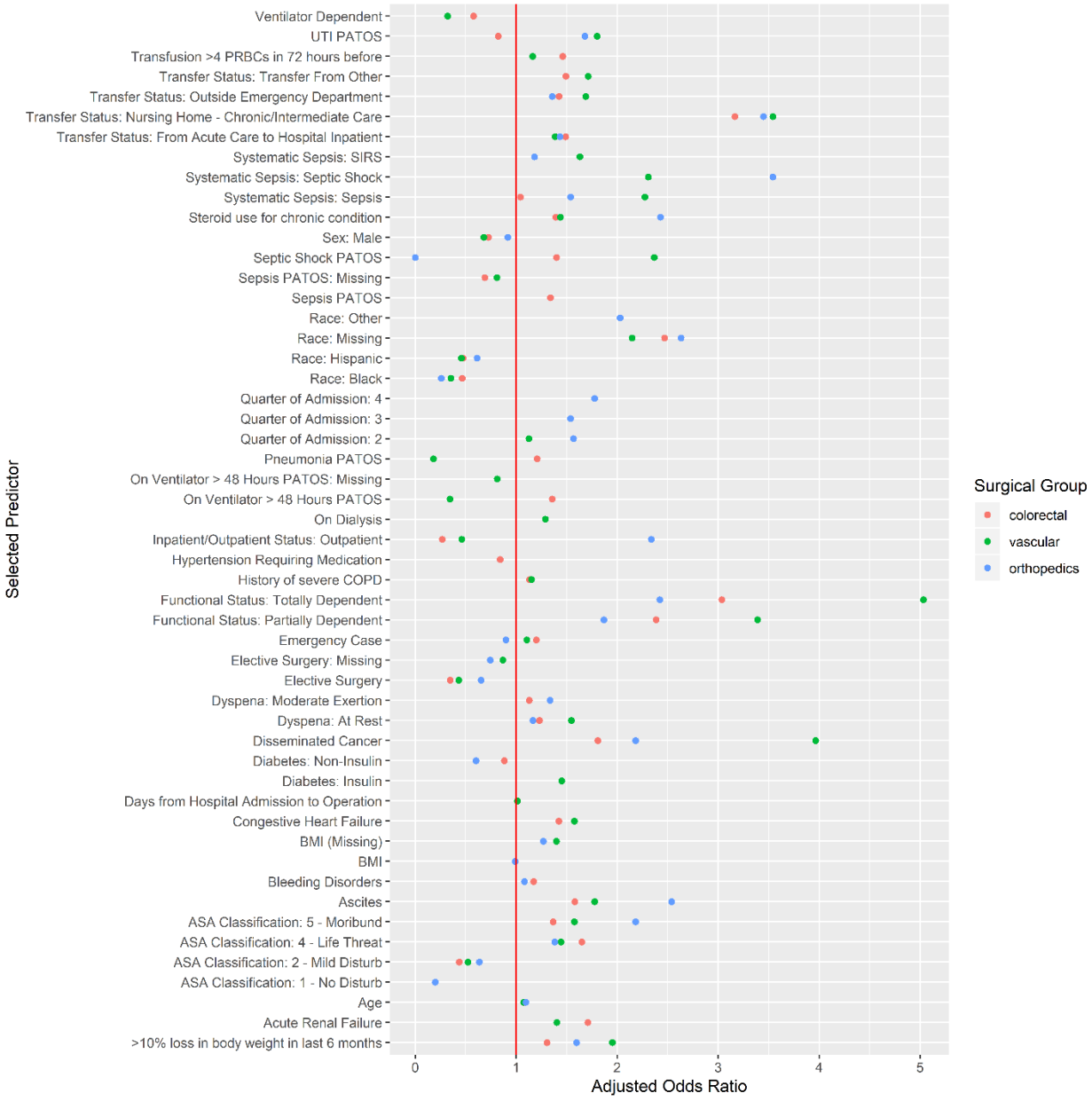


Figure 3: Adjusted Odds Ratios for Selected Predictors of 30-Day Mortality (By Surgical Group)
(Adjusted Odds Ratios > 5 are shown as 5 on this graph)

Figure 4: Adjusted Estimates for Selected Predictors of Total Hospital Length of Stay (By Surgical Group)

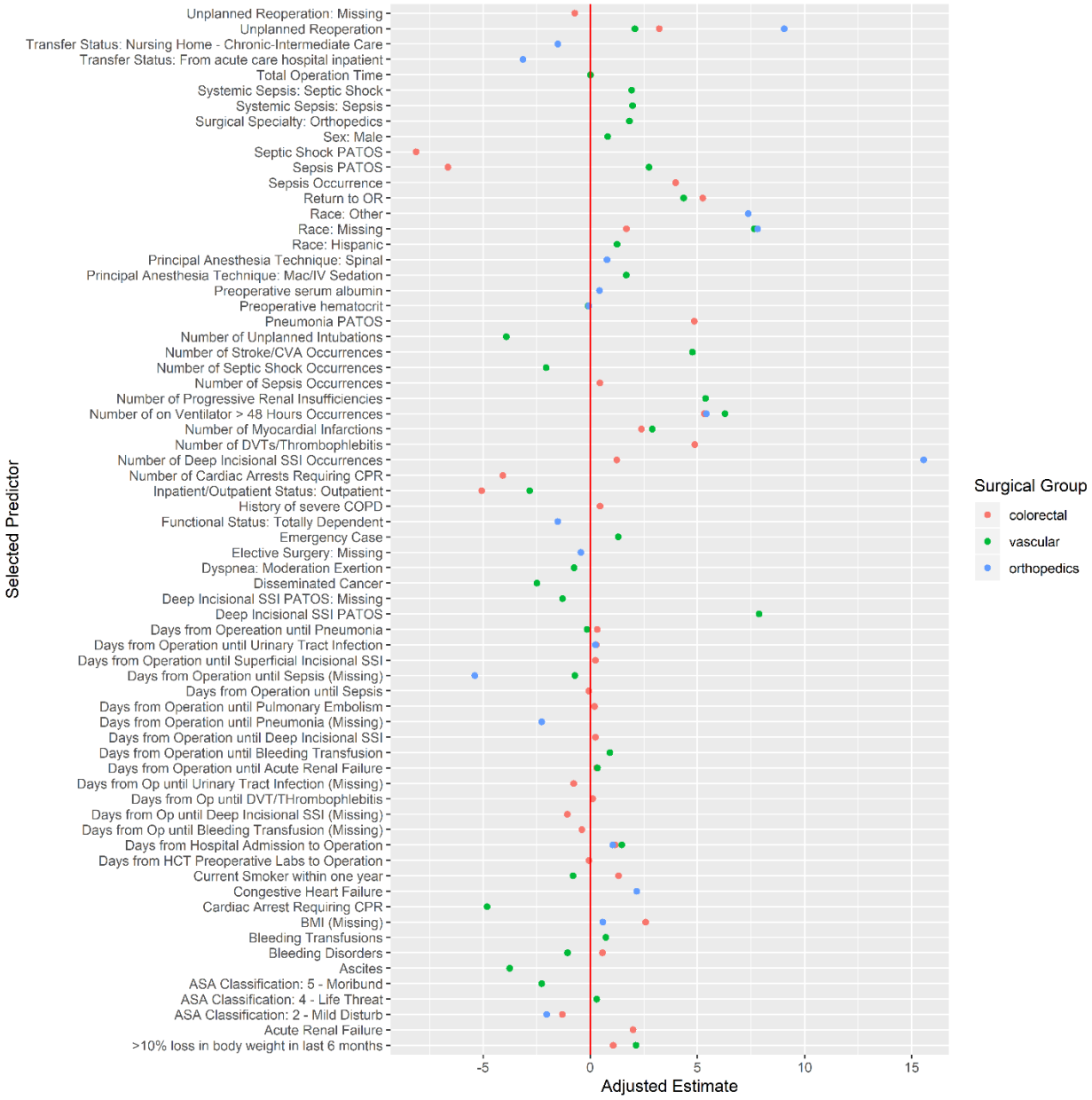
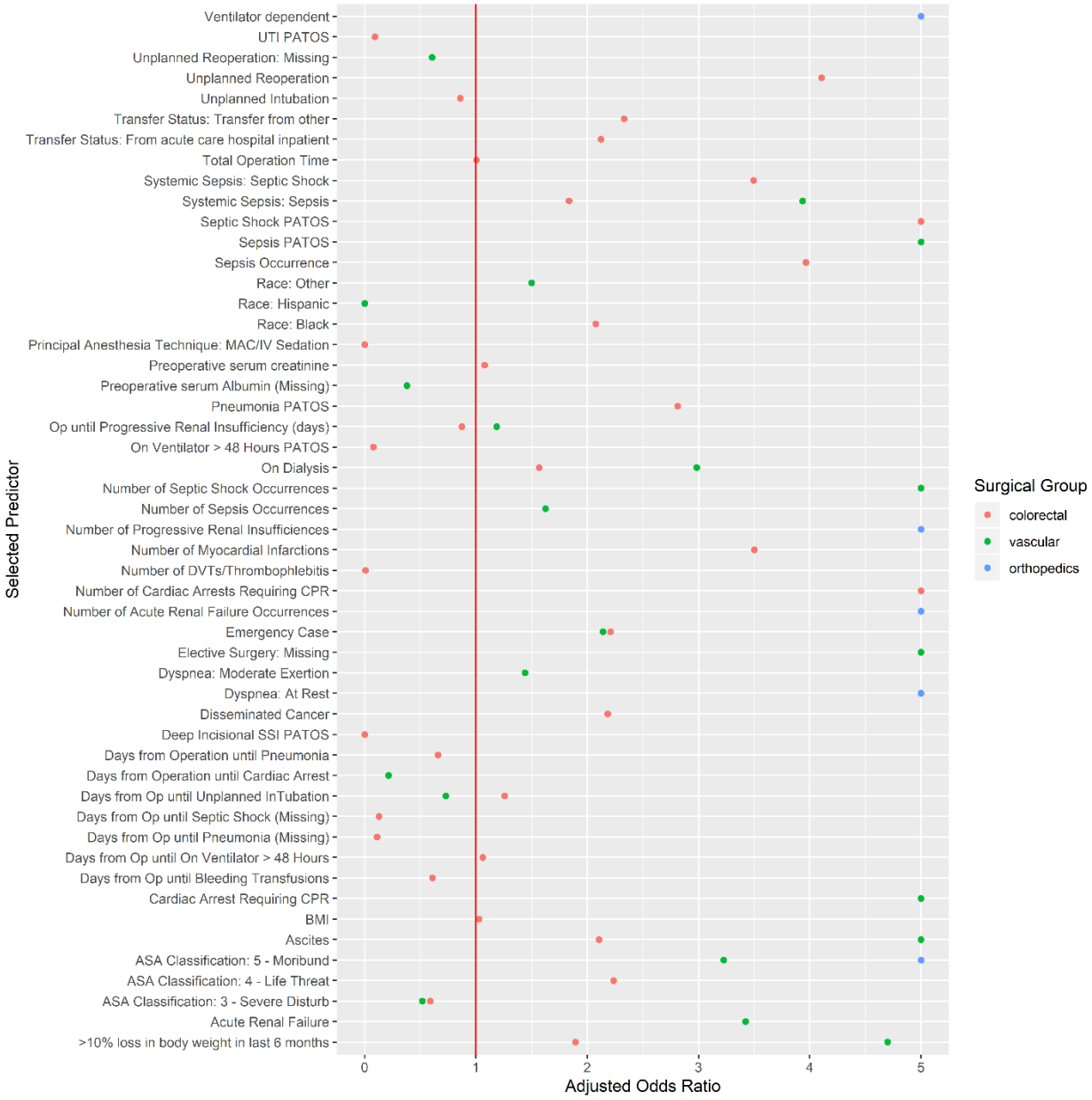


Figure 5: Adjusted Odds Ratios for Selected Predictors of Death During Hospitalization Surgical Group) (Adjusted Odds Ratios > 5 are shown as 5 on this graph)



Perioperative Anesthesia-2 Isolated intravenous anesthetic doses have small effects on BIS index during volatile-based anesthesia in surgical patients: A single-institution retrospective study

Michael P Schnetz[1], James W Ibinson[1], Aman Mahajan[1], Ata M Kaynar[1], Keith M Vogt[1]

[1]University of Pittsburgh, Pittsburgh, PA

Introduction: The bispectral index is a mathematical measure of phase coherence across frequency spectrum, based on Fourier transformation [1]. The BISTM monitor, which employs bispectral electroencephalography (EEG) analysis in a proprietary algorithm, has come into widespread use [2]. Because of similar spectral effects on the EEG seen with propofol and volatile anesthetics [3], the device has robust performance for depth of consciousness monitoring to most commonly-used anesthetic regimens. However, other hypnotic agents are known to induce different spectral patterns of EEG changes [3], and the calculated BIS index can change discordantly with depth of anesthesia when high-doses of some agents are given [4]. However, this phenomenon has not been systematically explored in the setting of typical clinical practice. The purpose of this study was to determine the changes in BIS index seen in response to isolated administration of common anesthetic medications in a retrospective review of electronic anesthesia record data captured from routine clinical administration of volatile-based anesthetics. We focused on bolus administration of 5 key agents of interest. We hypothesized that significant decreases in BIS index would occur for midazolam and propofol and that a significant increase would be seen with ketamine. Assessments of BIS index changes with dexmedetomidine and fentanyl administrations were exploratory, with clinically-insignificant differences expected.

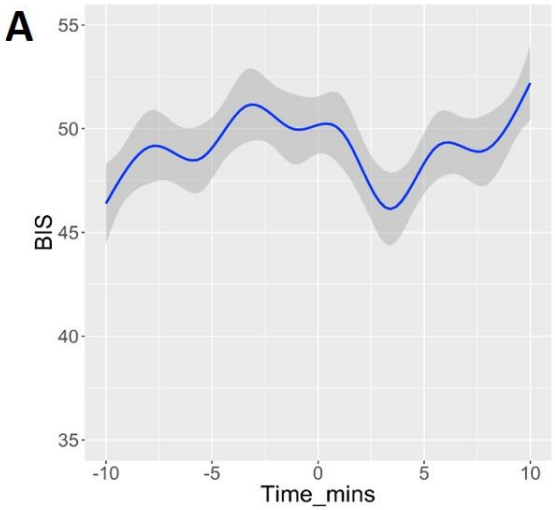
Methods: This retrospective study was exempted by the local institutional review board. Electronic anesthesia record data for surgical cases between 2011 and 2018 were obtained from one quaternary hospital in an urban academic health system. Cases were excluded if there were no BIS index or end-tidal anesthetic gas concentration measurements recorded, this yielded 70,642 cases for analysis, which was performed in RStudio (Version 1.1.442), running R version 3.4.4. Isolated administrations of midazolam, propofol, ketamine, dexmedetomidine, and fentanyl were identified, when no other drug administrations occurred in the preceding or following 10 minutes, creating a 20-minute analysis window. Average BIS index and minimum alveolar concentration (MAC) values were plotted over these time windows. MAC values were calculated from volatile agent concentrations (isoflurane = 1.17%, sevoflurane”‰=”‰1.8%, & desflurane”‰=”‰6.6%), and were not age-adjusted. Because volatile anesthetic concentration was not held constant during the analysis window, the ratio of BIS index to MAC value (BIS/MAC ratio) was calculated before and after each administration. This effectively normalizes changes in BIS index for concomitant changes in MAC, which is particularly important as the delivered MAC of volatile anesthetic can certainly directly affect the BIS index. Aggregate BIS/MAC ratio values before and after drug administration were statistically compared using the Kruskal-Wallis test; we had conservatively chosen $p < 0.005$ to indicate statistical significance in this large dataset.

Results: Specific values for the number of isolated drug administration windows, median drug dose, and median BIS/MAC ratio before and after drug administration are listed in the figures. Timecourse plots for the BIS index (panel A) and MAC (panel B) are also shown. Aggregate BIS/MAC ratio data was not normally distributed and is displayed using violin plots (panel C). The median changes in BIS/MAC ratios, from before to after drug administration, were: decrease by 6.1 for midazolam, decrease by 5.8 for propofol, increase by 3.2 for ketamine, decrease by 3.3 for dexmedetomidine, and decrease by 2.3 for fentanyl. All changes in BIS/MAC ratio were statistically significant ($p< 0.005$).

Conclusion: Based on a retrospective analysis of electronic anesthesia record data, from surgical cases employing a volatile anesthetic, clinically-used doses of common intravenous anesthetic and analgesic agents have a small overall impact on the ratio of BIS index to MAC concentration. For the agents that would intuitively be expected to significantly decrease the BIS index, midazolam and propofol, we observed a decrease of about 6 in BIS/MAC ratio. Smaller decreases of 2-3 were seen with dexmedetomidine and fentanyl. Importantly, our data suggests that bolus ketamine (median dose 20 mg) only increased the BIS/MAC ratio by 3. This contrasts with previous work showing large BIS index increases with high-dose ketamine [4].

Reference(s):

1. Rev Bras Anestesiol, 2012. 62(1): p. 105-17.
2. J Clin Monit Comput, 2017. 31(2): p. 281-289.
3. Anesthesiology, 2015. 123(4): p. 937-60.
4. Br J Anaesth, 2018. 121(6): p. 1242-1248.



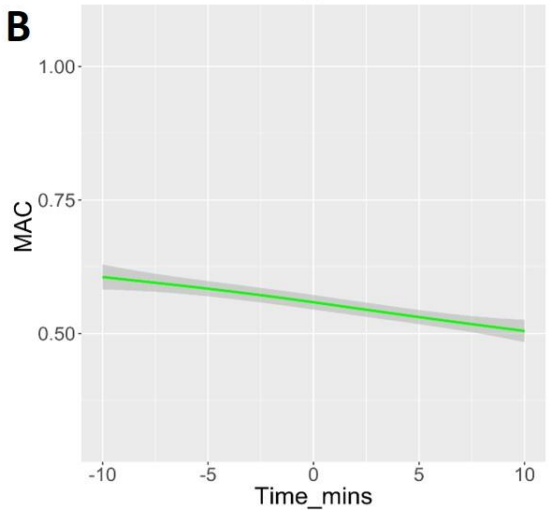
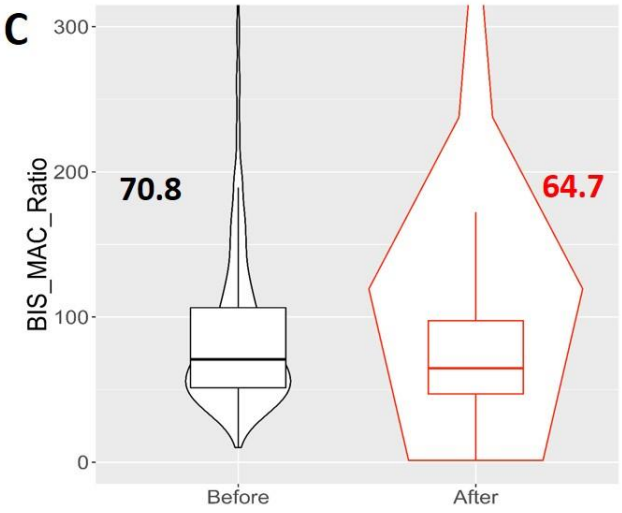
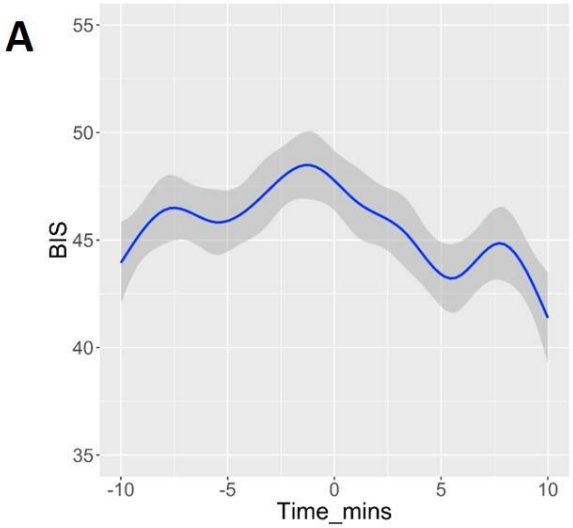


Figure 1 - Midazolam

- Data from 10718 isolated drug administrations
- Median dose = 2 mg

Panel A and B show BIS index and MAC values, respectively, for the 10 minutes before and after drug administration (occurring at time =0). Panel C shows the distribution of BIS/MAC ratio values before (black) and after (red) over the entire 10 minute window. Median values are listed numerically next to the violin plots.





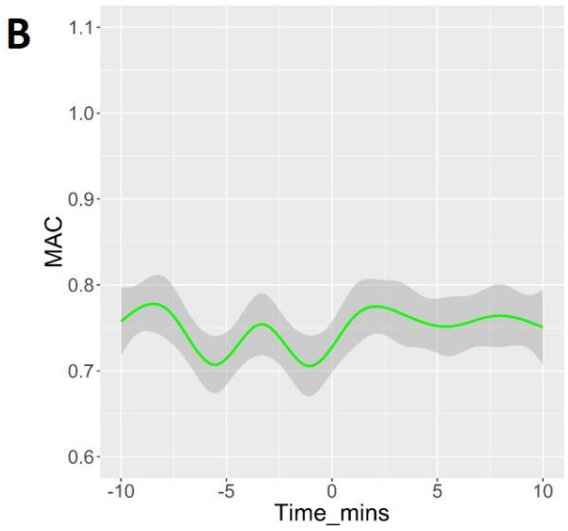
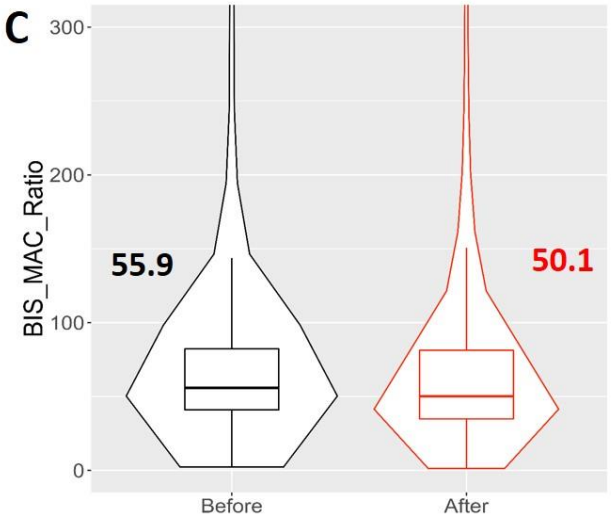


Figure 2 - Propofol

- Data from 1119 isolated drug administrations
- Median dose = 40 mg

Panel A and B show BIS index and MAC values, respectively, for the 10 minutes before and after drug administration (occurring at time =0). Panel C shows the distribution of BIS/MAC ratio values before (black) and after (red) over the entire 10 minute window. Median values are listed numerically next to the violin plots.



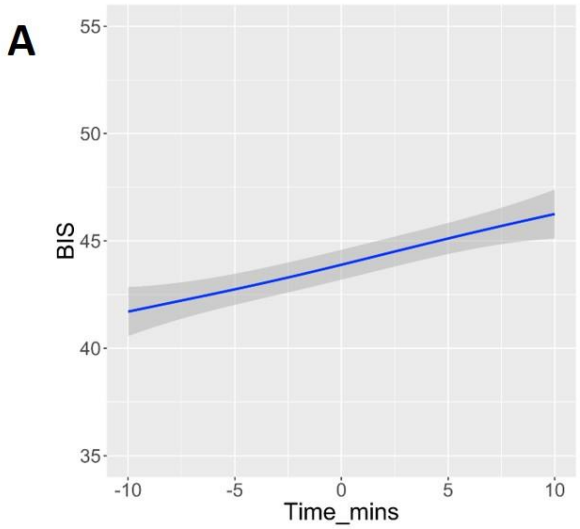
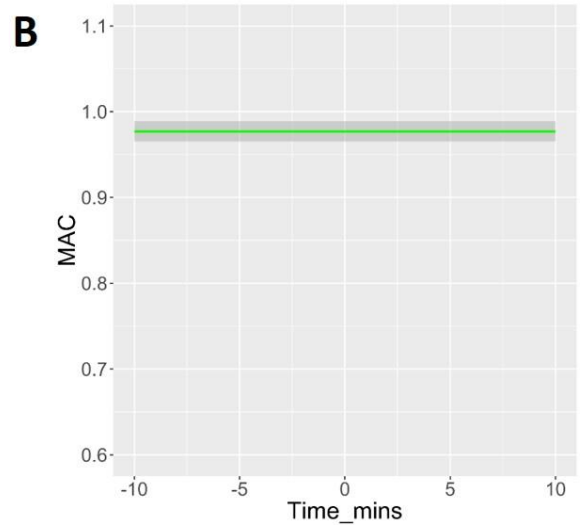
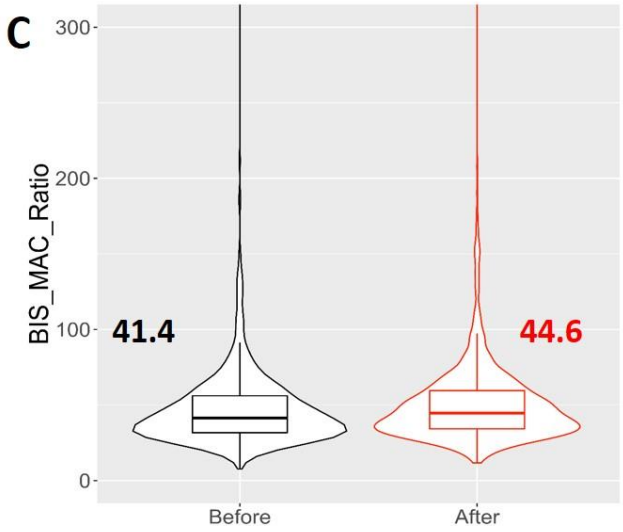


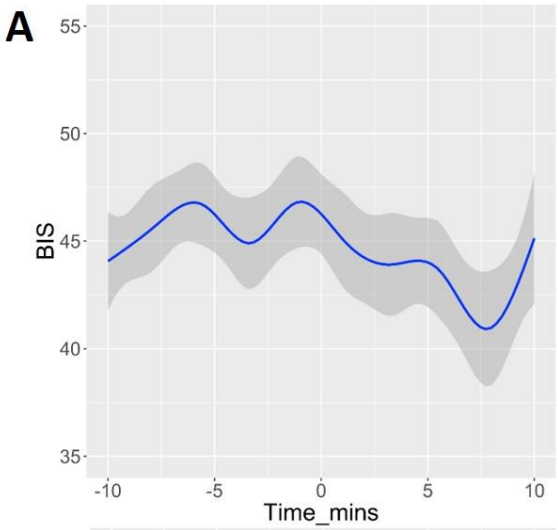
Figure 3 - Ketamine

- Data from 470 isolated drug administrations
- Median dose = 20 mg

Panel A and B show BIS index and MAC values, respectively, for the 10 minutes before and after drug administration (occurring at time =0). Panel C shows the distribution of BIS/MAC ratio values before (black) and after (red) over the entire 10 minute window. Median values are listed numerically next to the violin plots.







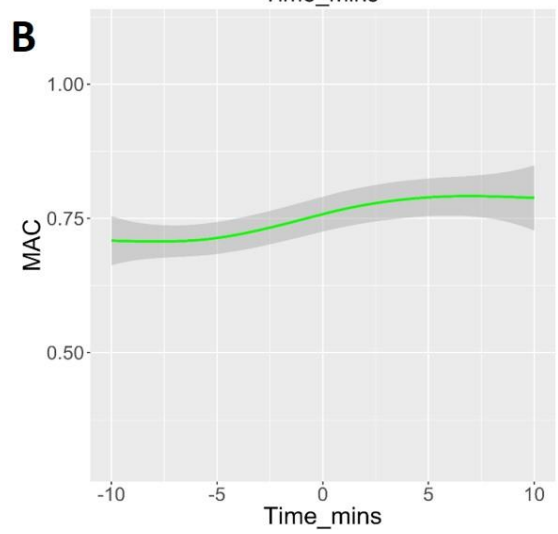
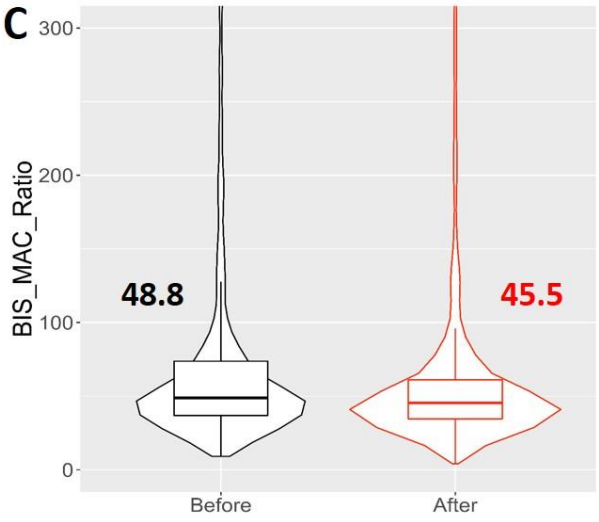
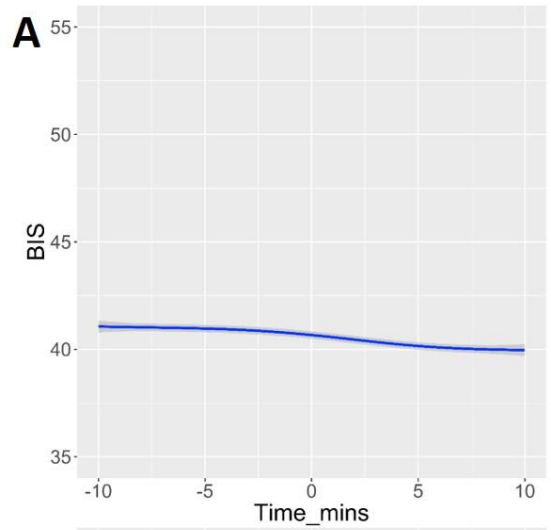


Figure 4 - Dexmedetomidine

- Data from 734 isolated drug administration
- Median dose = 12 mcg

Panel A and B show BIS index and MAC values, respectively, for the 10 minutes before and after drug administration (occurring at time =0). Panel C shows the distribution of BIS/MAC ratio values before (black) and after (red) over the entire 10 minute window. Median values are listed numerically next to the violin plots.





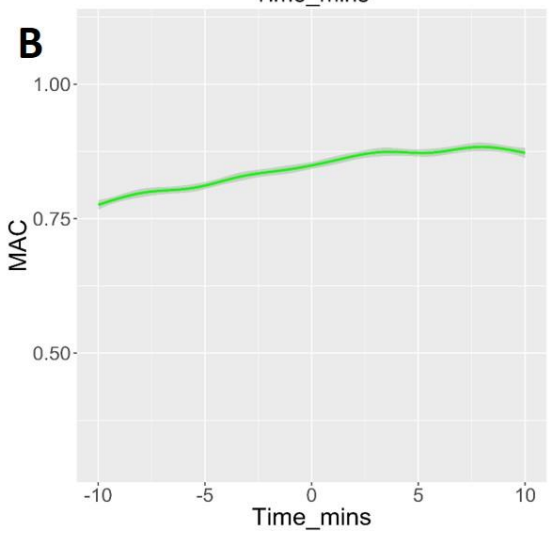
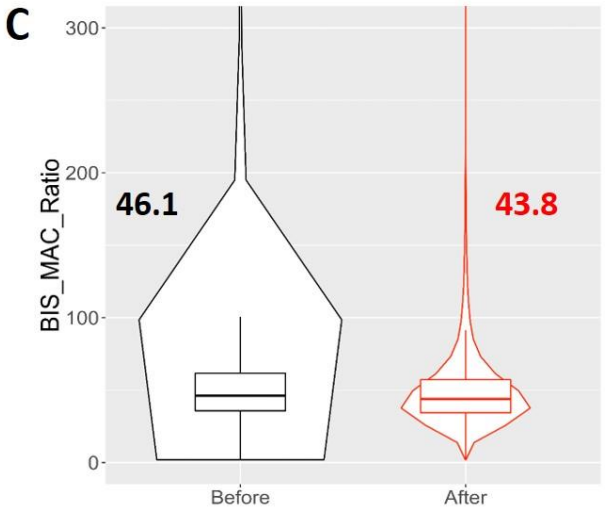


Figure 5 - Fentanyl

- Data from 15705 isolated drug administrations
- Median dose = 50 mcg

Panel A and B show BIS index and MAC values, respectively, for the 10 minutes before and after drug administration (occurring at time =0). Panel C shows the distribution of BIS/MAC ratio values before (black) and after (red) over the entire 10 minute window. Median values are listed numerically next to the violin plots.



Perioperative Anesthesia-3 Perioperative colloid choice and effects on bleeding in patients undergoing musculoskeletal surgery

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Introduction: The use of colloids such as hydroxyethyl starch (HES) and albumin is common for intravenous fluid resuscitation in the perioperative period. [1, 2] Meta-analyses comparing albumin with HES (human-derived versus synthetic colloids respectively) in patients with sepsis and in patients undergoing cardiac surgery (with cardiopulmonary bypass) have found that red blood cell transfusions are reduced when albumin is used.[3, 4] However, HES continues to be used worldwide in non-cardiac surgical settings. Our study compares the association of albumin versus HES with major perioperative bleeding in musculoskeletal surgery, the most common surgery performed in the United States.

Methods: In this retrospective cohort study, we extracted data from the Premier Healthcare Database (Premier Inc., Charlotte, NC, USA) between October 2008 and September 2014, a period of time prior to a safety warning about HES in United States (when HES was still widely used). We identified patients who underwent elective inpatient surgery on the musculoskeletal system and received either albumin or hydroxyethyl starch (HES). Patients who received both albumin and HES were excluded from the study. The primary outcome was major perioperative bleeding; secondary outcomes were acute renal failure and prolonged postoperative length-of-stay (>75th%ile), as a surrogate for significant in-hospital complications. We examined differences in baseline characteristics - demographics, comorbidities, and co-treatments. We then conducted propensity-score weighted analysis to ensure comparability of study groups prior to examining outcome differences.

Results: We identified 579,392 patients who underwent surgery in the musculoskeletal system. Only 43,454 received colloids on the day of surgery. After excluding dual colloid recipients (n= 2,243), 41,211 (94.8%) were included in the analysis: 12,803 in the albumin in the albumin group and 28,408 in the HES group. As shown in table 1, there were minor differences between the two groups that were resolved upon propensity-score weighting. This include: van walraven score, which was lower in the albumin group; the higher rate of regional anesthesia (spinal or epidural) that was noted in the albumin vs. starch group; and the use of anti-fibrinolytic medications was noted to be higher in the HES vs. albumin, 19.3% and 13.9% respectively. The propensity-score weighted mean van Walraven score in patients receiving albumin was 0.59, compared to 0.58 in patients that received HES (standardized mean difference= 0.003). There was no difference in the use of anti-platelet medication or anti-thrombotic medication in either group before or after propensity-score weighting. However, the high rate of non-steroidal anti-inflammatory drugs (NSAIDs) usage noted in the albumin group persisted even after propensity-score weighting (standardized mean difference = 0.24 and 0.21 before and after propensity-score weighting respectively). The primary analysis indicated that the rate of major perioperative bleeding was higher in those exposed to HES compared with those receiving albumin . The rate of major bleeding was 16.8% in patients exposed to albumin, compared with 18.5% in those exposed to HES, [Relative Risk 0.89 (95% CI 0.84-0.93)]. We observed no significant difference in secondary outcomes.

Conclusion: Compared with albumin, exposure to HES on the day of musculoskeletal surgery was associated with an increased risk of major perioperative bleeding. Given that HES continues to be used as a colloid in multiple patient populations worldwide, further studies examining the safety of HES solutions are needed.

Reference(s):

1. Cochrane Database of Systematic Reviews, 2, 2013.
2. The Journal of the American Society of Anesthesiologists, 123(6), 1385-93, 2015.
3. The Annals of Thoracic Surgery, 72(2), 527-33, 2001.
4. British Medical Journal, 346, f839, 2013.

Figure 1: Patients undergoing surgery on musculoskeletal system, colloid by type

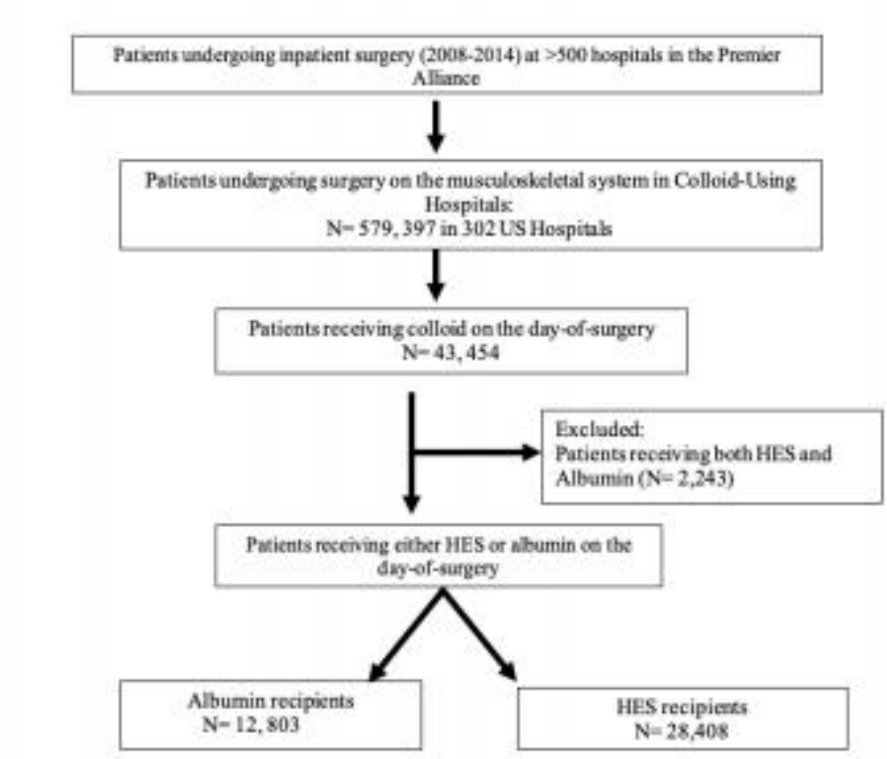

Figure 2: Comparability of patients treated with albumin vs. HES

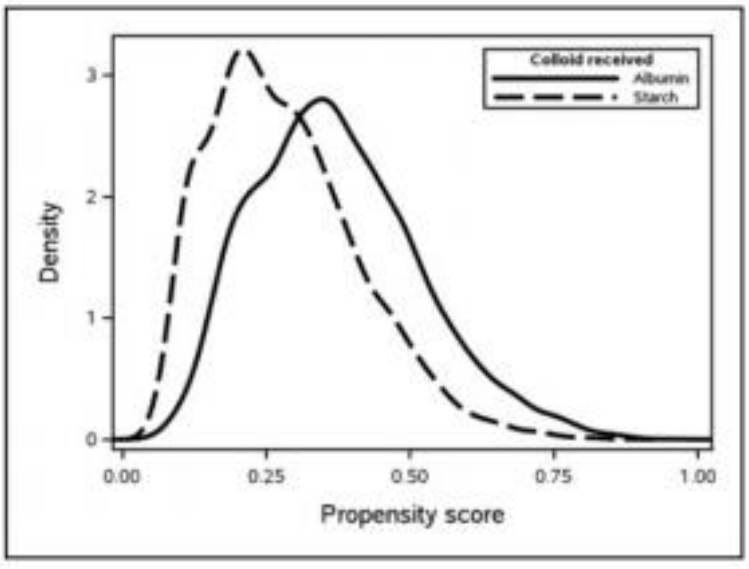

Table 1:

Variable	Albumin (unweighted)	Starch (unweighted)	SAMD (unweighted)	Albumin (weighted)	Starch (weighted)	SAMD (weighted)
Age	65.1 (11.8)	65.4 (12.3)	0.02	65.4 (12.0)	65.4 (12.3)	0.00
Black (ref. white)	7.2%	8.8%	0.06	9.2%	8.8%	0.01
Other race (ref. white)	20.2%	10.2%	0.28	9.8%	10.2%	0.01
Male (ref. female)	41.4%	41.2%	0.00	41.1%	41.2%	0.00
van Walraven score	8.2 (3.6)	8.6 (4.2)	0.10	8.6 (4.0)	8.6 (4.2)	0.00
Anti-fibrinolytic medication	13.9%	19.3%	0.15	18.2%	19.3%	0.03
Anti-platelet medication	2.5%	2.7%	0.01	2.8%	2.7%	0.00
Anti-thrombotic medication	80.6%	78.6%	0.05	78.6%	78.6%	0.00
Analgesia, NSAID, parenteral	40.7%	29.4%	0.24	39.2%	29.4%	0.21
Anesthesia, regional, spinal/epidural	27.1%	13.3%	0.35	14.8%	13.3%	0.04
Anesthesia, epidural	10.2%	4.4%	0.22	5.1%	4.4%	0.03

Perioperative Anesthesia-4 Improving Surgical patient knowledge and safe use of opioids- a Randomized Controlled Trial

Helen R Doherty[1], Enoch Lam[2], Tania Di Renna[1], Junior Chuang[3], Frances F Chung[4], David Urbach[1], David T Wong[5], Jean Wong[6]

[1]University Health Network (UHN), Toronto, Ontario, [2]Toronto Western Hospital, UHN, Toronto, Ontario, [3]University of Toronto, Toronto, Ontario, [4]University of Toronto Faculty of Medicine, Toronto, Ontario, [5]Toronto Western Hospital, Toronto, Ontario, [6]University of Toronto, Toronto, ONTARIO

Introduction: Opioids are associated with post-operative respiratory depression and complications.[1] It is currently not routine practice to provide patient education materials for safe opioid use.[2] The objective of our study is to evaluate the impact of an educational pamphlet for surgical patients. We hypothesize that this will increase knowledge about safe use, proper storage and disposal of opioids.

Methods: This multi-center randomized controlled study recruited 100 patients in the pre-operative assessment clinic. Inclusion criteria were English-speaking, ≥18 years of age, able to give informed consent. Exclusion criteria were non-English speaking, on opioids for chronic pain or within the past 30 days. All patients completed a baseline knowledge questionnaire; developed by us, as a literature search found no existing questionnaires validated for our purpose. There were 35 True/False questions and 3 single answer questions, giving a maximum score of 38. Patients were randomized to either the intervention - educational pamphlet, or control group - standard care (no pamphlet). Questionnaires were repeated immediately post-education in the intervention group and at 15 and 30 days after surgery by telephone or email in both groups. The primary outcome was improvement after education in number of correctly answered safe use questions from baseline. Secondary outcomes were 15 and 30-day score, and percentage answering safe storage and disposal questions correctly in both groups. Primary outcome was analyzed using repeated measure analysis of variance (rANOVA). Secondary outcomes and patient characteristics were compared using pooled t-test for continuous variables and chi-square analysis for categorical variables.

Results: Table 1 shows questionnaire scores in the two groups. Scores in the intervention group (mean ± SD) immediately post-education were higher (34.2 ± 4.0) than baseline (27.8 ± 5.3). The difference between mean scores and baseline was 6.4 (95% CI 4.9–8.0) immediately post-intervention, 3.8 (95% CI 2.1-5.5) at 15 days and 4.6 (95% CI 2.9-6.3) at 30 days. The results from rANOVA suggest that the score across different follow up periods for each subject is dependent on whether the intervention was applied ($P<0.05$). At 15 and 30 days, scores in the intervention group (mean ± SD) were significantly higher than in the control group at 31.6 ±3.5 compared to 29.1 ±3.6, and 32.4 ±3.3 compared to 30.5 ±3.8 (Table 1). For knowledge on safe storage, there was no significant difference between intervention vs. control groups at 15 and 30 days. For safe disposal, a correct answer was given (intervention vs. control group) by 97.5% vs. 92.5% at 15 days ($P=0.30$) and 100% vs. 89.7% at 30 days ($P<0.05$).

Conclusion: Our results show a significant improvement in knowledge on safe opioid use after using an education pamphlet and retention of knowledge 15 and 30 days after surgery. We also found higher levels of knowledge in the intervention than control group at 15 and 30 days after surgery.

Reference(s):

1. Curr Opin Anaesthesiol 2016; 29(1): 134–140.
2. American College of Surgeons Patient Education Opioid Workgroup 2018. Safe and Effective Pain Control After Surgery [pamphlet].

Table 1: Questionnaire scores in the Control and Intervention groups over time.

	Questionnaire scores out of 38 (mean ± SD)		Difference (control - intervention)	t Value	P Value
	Control	Intervention			
Pre-education	28.3 ± 5.8	27.8 ± 5.3	0.44	0.40	0.69
Post-education	-	34.2 ± 4.0*	-	-	-
15 Days	29.1 ± 3.6	31.6 ± 3.5*	-2.55	-3.24	0.0017
30 Days	30.5 ± 3.8	32.4 ± 3.3*	-1.97	-2.43	0.0174

* score significantly higher than pre-education value ($P<0.05$ and difference in means was significant)

Perioperative Anesthesia-5 Association between the Trajectory of Preoperative Opioid Use and Postoperative Opioid Use, Adverse Events, and Economic Outcomes: A Retrospective Analysis

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[1]Stanford University, Stanford, CA, [2]Stanford University School of Medicine, Stanford, CA

Introduction: Chronic preoperative opioid use has been associated with numerous worse perioperative outcomes.1–5 However, it remains unknown how changes in the amount of opioid used in the weeks to months leading up to surgery affect postoperative outcomes. To examine this question, this study used a large database of healthcare claims to determine whether a decrease or increase in daily opioid dose before surgery is associated with differences in postoperative outcomes compared to patients whose opioid use was stable.

Methods: The data consist of administrative health claims provided by the Optum©'s Clinformatics® Data Mart. The final sample included 43,065 chronic opioid users (filled ≥10 prescriptions or ≥120 days prescribed for opioids in the year prior to surgery), aged 18-89 who underwent one of 10 common procedures between 2003-2017. The primary outcomes were whether patients used any opioid during postoperative days 91-365, and if so, the average daily dose prescribed, and the average daily dose of opioid prescribed during postoperative days -7-30. Secondary outcomes included the probability of an adverse event, healthcare costs, and hospital length of stay within the first 30 days after discharge. Our independent variable of interest was whether the patient decreased or increased their opioid use prior to surgery. To measure this, we compared the average daily opioid dose in MMEs for two time periods: preoperative days 91-365 and preoperative days 7-90. Patients with a ≥20% decrease between these periods were classified as opioid-reducers, patients who remained within ±20% were classified as opioid-stable, and patients with a ≥20% increase were classified as opioid-escalators. We estimated the association between a decrease or increase in preoperative opioid use and postoperative opioid use by using multivariable regression models, which included adjustments for potential confounders including age, sex, procedure type, year of surgery, patient comorbidities, as well as the average daily dose of opioid during preoperative days 91-365 and 7-90.

Results: The average age of was 62.1 years (SD 13.6 years), with 28,698 (66.6%) female patients. During preoperative days 7-90, 9,326 (21.7%) patients decreased their opioid use, 17,964 (41.7%) increased their opioid use, while the remaining 15,775 (36.6%) had stable opioid use. After adjusting for potential confounders, the probability of using any opioid during postoperative days 91-365 was lower for both opioid-decreased (88.8%, 95% CI 88.0 to 89.5%, odds ratio 0.33, 95% CI 0.30 to 0.37, P<0.001) and opioid-increased patients (93.6%, 95% CI 93.2 to 94.0%, odds ratio 0.62, 95% CI 0.56 to 0.68, P<0.001) compared to opioid-stable patients (96.0%, 95% CI 95.7 to 96.3%). Among patients who used opioids in postoperative days 91-365, the average daily opioid dose was not different for either opioid-decreased or opioid-increased patients compared to opioid-stable patients. During postoperative days -7-90, the average daily opioid dose was higher for opioid-decreased patients (difference 3.2 MMEs, 95% CI 2.3 to 4.1, P<0.001), but not different for opioid-increased patients compared to opioid-stable patients.

Conclusion: In this retrospective analysis of 43,065 chronic opioid users aged 18-89 undergoing one of 10 common surgeries, a change in daily dose of opioid weaning opioid use by at least 20% in the 90 days before surgery was associated with decreased odds of continuing to require opioids during postoperative days 91-365 compared to patients whose opioid doses remained stable throughout the preoperative year. This was true for either patients who decreased or increased their opioid dose preoperatively, though patients who increased their dose were more likely to continue to use opioids than patients who decreased their dose. However, while changes in preoperative opioid use were independently associated with decreased postoperative opioid use, the strongest predictor in our model of opioid use in both the immediate postoperative period and long-term was the daily dose of opioid being used in the 90 days before surgery. This suggests that stable chronic opioid use is an especially tenacious challenge, and that preoperative opioid weaning should be considered as additional potentially highly impactful optimization for chronic opioid users undergoing surgery.

Reference(s):

1. Preoperative Opioid Misuse is Associated With Increased Morbidity and Mortality After Elective Orthopaedic Surgery. Clin. Orthop. Relat. Res. 473, 2402–2412 (2015).
2. Preoperative Opioid Use is Independently Associated With Increased Costs and Worse Outcomes After Major Abdominal Surgery. Ann. Surg. 265, 695–701 (2017).
3. Preoperative Opiate Use Independently Predicts Narcotic Consumption and Complications After Total Joint Arthroplasty. J. Arthroplasty 32, 2658–2662 (2017).
4. Impact of preoperative opioid use on total knee arthroplasty outcomes. Journal of Bone and Joint Surgery - American Volume 99, 803–808 (2017).
5. A pilot cohort study of the determinants of longitudinal opioid use after surgery. Anesth. Analg. 115, 694–702 (2012).

Table 1. Patient characteristics

Variable	Opioid-stable patients (N = 15,775)	Opioid-decreased patients (N = 9,326)		Opioid-increased patients (N = 17,964)	
			P-value		P-value
Demographics, [SE]					
Age, mean, years	63.3 [0.1]	61.0 [0.2]	<0.001	61.7 [0.1]	<0.001
Female, %	66.1 [0.4]	69.7 [0.5]	<0.001	65.5 [0.4]	0.24
Year of surgery, mean	2012.0 [0.0]	2011.5 [0.0]	<0.001	2011.2 [0.0]	<0.001
Narcotic use in preoperative year, [SE]					
Number of opioid prescriptions	13.7 [0.1]	11.6 [0.7]	<0.001	12.5 [0.1]	<0.001
Number of days with opioid prescription	279.5 [0.6]	207.3 [0.8]	<0.001	212.4 [0.6]	<0.001
Average daily morphine milligram equivalents prescribed in preoperative days 365-91	39.0 [0.3]	32.9 [0.4]	<0.001	22.1 [0.2]	<0.001
Average daily morphine milligram equivalents prescribed in preoperative days 90-7	39.5 [0.3]	14.6 [0.2]	<0.001	42.7 [0.3]	<0.001
Type of surgery, % [SE]					
Total knee arthroplasty	36.1 [0.4]	32.5 [0.5]	<0.001	34.2 [0.4]	<0.001
Total hip arthroplasty	15.6 [0.3]	14.4 [0.4]	0.01	26.9 [0.3]	<0.001
Laparoscopic cholecystectomy	26.7 [0.0]	26.9 [0.5]	0.75	21.8 [0.3]	<0.001
Open cholecystectomy	1.8 [0.1]	1.7 [0.1]	0.67	1.6 [0.1]	0.13
Laparoscopic appendectomy	3.2 [0.1]	3.3 [0.2]	0.65	2.7 [0.1]	0.007
Open appendectomy	0.7 [0.1]	0.8 [0.1]	0.31	0.5 [0.1]	0.004
Cesarean section	1.0 [0.1]	5.0 [0.2]	<0.001	1.3 [0.1]	0.01
Functional endoscopic sinus surgery	6.8 [0.2]	7.9 [0.3]	0.001	5.7 [0.2]	<0.001

Variable	Opioid-stable patients (N = 15,775)	Opioid-decreased patients (N = 9,326)		Opioid-increased patients (N = 17,964)	
			P-value		P-value
Transurethral resection of the prostate	2.8 [0.1]	2.8 [0.2]	0.68	1.9 [0.1]	<0.001
Simple mastectomy	2.8 [0.1]	4.7 [0.2]	0.06	3.4 [0.1]	<0.001
Comorbidities, % [SE]					
Congestive heart failure	15.7 [0.3]	15.9 [0.4]	0.64	14.1 [0.3]	<0.001
Cardiac arrhythmias	31.4 [0.4]	31.0 [0.5]	0.55	29.7 [0.3]	0.001
Valvular disease	20.6 [0.3]	21.3 [0.4]	0.22	19.4 [0.3]	0.005
Pulmonary circulation disorders	7.1 [0.2]	7.4 [0.3]	0.34	6.5 [0.2]	0.05
Peripheral vascular disorders	24.2 [0.3]	23.4 [0.4]	0.16	21.7 [0.3]	<0.001
Hypertension, uncomplicated	81.0 [0.3]	76.3 [0.4]	<0.001	77.4 [0.3]	<0.001
Hypertension, complicated	17.9 [0.3]	17.9 [0.4]	0.88	16.6 [0.3]	0.001
Paralysis	2.4 [0.1]	2.5 [0.2]	0.49	2.0 [0.1]	0.02
Other neurological disorders	11.7 [0.3]	12.7 [0.3]	0.02	10.5 [0.2]	<0.001
Chronic pulmonary disease	44.9 [0.4]	44.6 [0.5]	0.62	41.7 [0.4]	<0.001
Diabetes, uncomplicated	35.0 [0.4]	34.2 [0.4]	0.23	32.1 [0.3]	<0.001
Diabetes, complicated	16.7 [0.3]	16.5 [0.4]	0.69	14.3 [0.3]	<0.001
Hypothyroidism	31.1 [0.4]	32.5 [0.5]	0.02	29.0 [0.3]	<0.001
Renal failure	16.3 [0.3]	15.9 [0.4]	0.34	14.4 [0.3]	<0.001
Liver disease	18.2 [0.3]	18.8 [0.4]	0.26	17.1 [0.3]	0.009
Peptic ulcer disease	5.7 [0.2]	6.0 [0.2]	0.24	5.9 [0.2]	0.44
AIDS/HIV	0.3 [0.0]	0.5 [0.1]	0.09	0.4 [0.0]	0.20
Lymphoma	1.5 [0.1]	1.7 [0.1]	0.18	1.6 [0.1]	0.65

Variable	Opioid-stable patients (N = 15,775)	Opioid-decreased patients (N = 9,326)		Opioid-increased patients (N = 17,964)	
			P-value		P-value
Metastatic cancer	2.6 [0.1]	2.7 [0.2]	0.59	2.6 [0.1]	0.87
Solid tumor without metastases	15.6 [0.3]	15.6 [0.4]	0.95	14.2 [0.3]	<0.001
Rheumatoid arthritis/collagen vascular diseases	25.8 [0.3]	26.2 [0.5]	0.55	23.4 [0.3]	<0.001
Coagulopathy	7.4 [0.2]	8.6 [0.3]	<0.001	7.0 [0.2]	0.20
Obesity	32.6 [0.4]	31.8 [0.5]	0.19	31.8 [0.3]	0.14
Weight loss	12.0 [0.3]	12.5 [0.3]	0.29	10.7 [0.2]	<0.001
Fluid and electrolyte disorders	30.8 [0.4]	32.4 [0.5]	0.008	29.5 [0.3]	0.008
Blood loss anemia	3.7 [0.2]	4.3 [0.2]	0.02	4.1 [0.1]	0.04
Deficiency anemia	16.2 [0.3]	16.8 [0.4]	0.19	15.2 [0.3]	0.008
Alcohol abuse	5.0 [0.2]	5.6 [0.2]	0.04	5.5 [0.2]	0.04
Drug abuse	12.5 [0.3]	13.4 [0.4]	0.04	10.0 [0.2]	<0.001
Psychoses	5.3 [0.2]	6.7 [0.3]	<0.001	5.4 [0.2]	0.54
Depression	44.9 [0.4]	45.9 [0.5]	0.13	42.6 [0.4]	0.05

[a]Values are reported with their standard errors of the mean. P values were computed using Chi-squared and two-sample t-tests for categorical and continuous variables respectively.

Table 2. Primary outcomes

	Opioid-stable patients	Opioid-decreased patients			Opioid-increased patients		
Probability of any opioid prescribed in postoperative days 91-365, %	*Unadjusted*						
	95.4% (95.0 to 95.7%)	85.4% (84.7 to 86.1%)	Odds ratio		91.2% (90.8 to 91.6%)	Odds ratio	
			0.28 (0.26 to 0.31)	P<0.001		0.50 (0.46 to 0.55)	P<0.001
	Adjusted						
	96.0% (95.7 to 96.3%)	88.8% (88.0 to 89.5%)	0.33 (0.30 to 0.37)	P<0.001	93.6% (93.2 to 94.0%)	0.62 (0.56 to 0.68)	P<0.001
Average daily opioid prescribed in postoperative days 91-365, morphine milligram equivalents	*Unadjusted*						
	39.2 (38.5 to 39.9)	24.6 (23.7 to 25.4)	Difference		35.5 (34.6 to 36.3)	Difference	
			-14.6 (-15.7 to -13.6)	P<0.001		-3.7 (-4.8 to -2.7)	P<0.001
	Adjusted						
	34.8 (34.2 to 35.3)	35.4 (34.6 to 36.2)	0.7 (-0.3 to 1.6)	P=0.17	34.2 (33.7 to 34.8)	-0.5 (-1.3 to 0.3)	P=0.20
Average daily opioid prescribed in postoperative days -7 to 90, morphine milligram equivalents	*Unadjusted*						
	54.3 (53.6 to 55.0)	35.9 (35.1 to 36.7)	Difference		56.2 (55.4 to 57.1)	Difference	
			-18.4 (-19.5 to -17.3)	P<0.001		1.9 (0.8 to 3.0)	P=0.001
	Adjusted						
	50.9 (50.4 to 51.4)	54.1 (53.3 to 54.8)	3.2 (2.3 to 4.1)	P<0.001	50.5 (50.0 to 51.0)	-0.4 (-1.1 to 0.4)	P=0.34

The probabilities, average daily dose of opioid, healthcare costs and number of days admitted are reported as unadjusted values. Odds ratios, differences, and P-values were adjusted for age, sex, type and year of surgery, and medical comorbidities. For the calculation of the average daily dose of opioid, patients who were not prescribed any opioid in the referenced time period were excluded from the analysis to prevent downward biasing of the results. Values are reported with their 95% confidence intervals.

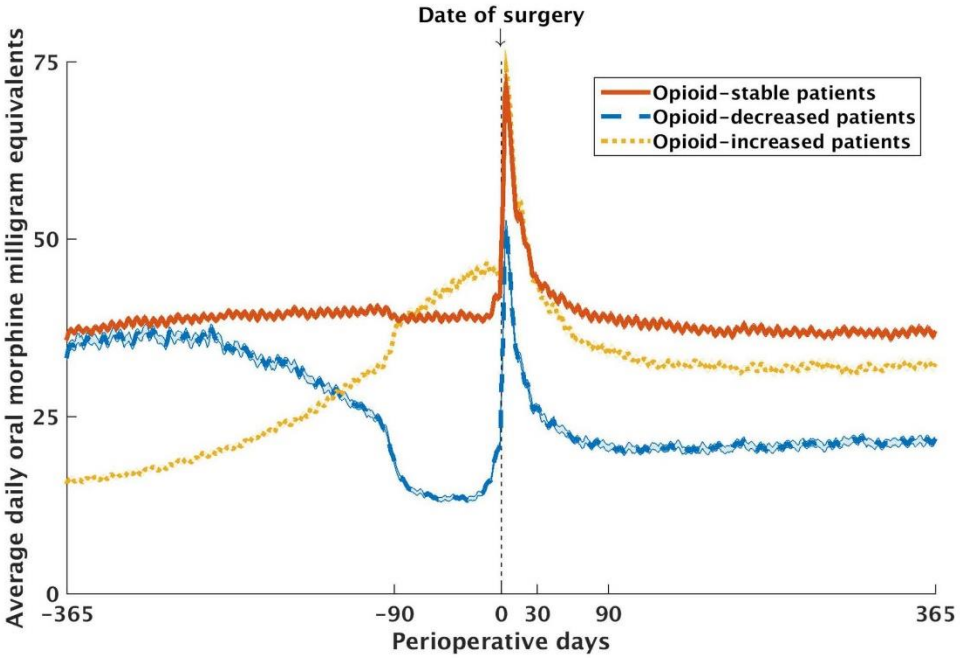
Table 3. Secondary outcomes in postoperative days 0-30

	Opioid-stable patients	Opioid-decreased patients			Opioid-increased patients		
Probability of surgical site infection, %	*Unadjusted*						
	2.1% (1.8 to 2.3%)	2.4% (2.1 to 2.7%)	Odds ratio		2.3% (2.1 to 2.5%)	Odds ratio	
			1.16 (0.97 to 1.38)	P=0.10		1.13 (0.97 to 1.30)	P=0.12
	Adjusted						
	1.6% (1.4 to 1.8%)	1.9% (1.6 to 2.2%)	1.22 (1.02 to 1.47)	P=0.03	1.7% (1.5 to 1.9%)	1.08 (0.92 to 1.27)	P=0.37
Probability of urinary tract infection, %	*Unadjusted*						
	6.7% (6.3 to 7.1%)	7.1% (6.6 to 7.6%)	Odds ratio		6.8% (6.5 to 7.2%)	Odds ratio	
			1.07 (0.96 to 1.18)	P=0.22		1.02 (0.94 to 1.11)	P=0.64
	Adjusted						
	5.1% (4.8 to 5.5%)	5.4% (5.0 to 5.9%)	1.06 (0.95 to 1.18)	P=0.28	5.2% (4.9 to 5.6%)	1.01 (0.92 to 1.12)	P=0.77
Probability of pneumonia, %	*Unadjusted*						
	3.2% (2.9 to 3.5%)	3.0% (2.7 to 3.4%)	Odds ratio		2.7% (2.5 to 3.0%)	Odds ratio	
			0.94 (0.81 to 1.09)	P=0.39		0.84 (0.74 to 0.95)	P=0.006
	Adjusted						
	2.3% (2.1 to 2.5%)	2.2% (1.9 to 2.5%)	0.96 (0.82 to 1.12)	P=0.60	2.0% (1.8 to 2.2%)	0.89 (0.77 to 1.02)	P=0.10
Probability of venous thromboembolism, %	*Unadjusted*						
	3.5% (3.2 to 3.7%)	3.8% (3.4 to 4.2%)	Odds ratio		3.5% (3.2 to 3.7%)	Odds ratio	
			1.10 (0.96 to 1.26)	P=0.19		1.01 (0.90 to 1.13)	P=0.90
	Adjusted						
	2.4% (2.2 to 2.7%)	2.8% (2.5 to 3.2%)	Odds ratio		2.2% (2.0 to 2.5%)	Odds ratio	
			1.18 (1.02 to 1.37)	P=0.03		0.92 (0.81 to 1.05)	P=0.22

	Opioid-stable patients	Opioid-decreased patients			Opioid-increased patients		
Total healthcare costs, US$	*Unadjusted*						
	$46,864 (46,207 to 47,520)	$44,958 (44,102 to 45,814)	Difference		$51,322 (50,664 to 51,979)	Difference	
			-$1,906 (-2,985 to -827)	P=0.001		$4,458 (3,528 to 5,387)	P<0.001
	Adjusted						
	47,579 (46,967 to 48,191)	47,909 (47,044 to 48,773)	Difference		49,162 (48,539 to 49.785)	Difference	
			329 (-707 to 1,366)	P=0.53		1,583 (677 to 2,489)	P=0.001
Number of days admitted	*Unadjusted*						
			Difference			Difference	
	3.4 (3.3 to 3.4)	3.4 (3.4 to 3.5)	0.0 (0.0 to 0.1)	P=0.43	3.6 (3.5 to 3.6)	0.2 (0.1 to 0.2)	P<0.001
	Adjusted						
	3.5 (3.4 to 3.5)	3.5 (3.4 to 3.6)	Difference		3.5 (3.4 to 3.5)	Difference	
			0.0 (-0.1 to 0.1)	P=0.90		0.0 (-0.1 to 0.0)	P=0.20

The probabilities, average daily dose of opioid, healthcare costs and number of days admitted are reported as unadjusted values. Odds ratios, differences, and P-values were adjusted for age, sex, type and year of surgery, and medical comorbidities. Values are reported with their 95% confidence intervals. Regression models were also created for the probability of sepsis, myocardial infarction, narcotic overdose, and death within 30 days after surgery, but these events were too infrequent for the model to converge, and thus were excluded.

Figure 1. Average daily dose of opioid prescribed during the 2-year perioperative window



Compared to perioperative days -365 to -91, opioid-stable patients maintained their average daily opioid dose within ±20% during perioperative days -90 to -7, while opioid-decreased patients reduced their average daily dose by at least 20%, and opioid-increased patients escalated their average daily dose by at least 20% in the same period.

Perioperative Anesthesia-6 Effect of Fluid Administration Rates in CRS/HIPEC Surgeries on Postoperative Complication Rates and Hospital Length of Stay

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Introduction: Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is an important therapeutic option for selected patients with peritoneal surface malignancies and is associated with improved prognosis and quality of life. {Raspe} This procedure requires complex perioperative management by anesthesiologists due to associated physiologic disturbances, increased intra-abdominal pressure, systemic hypo-/hyperthermia, increased metabolic rate, and pain management. As the number of centers performing CRS/HIPEC increases, optimized and standardized anesthetic management is critical to ensure the best patient outcomes and hospital resource utilization. {Maciver} In particular, proper intraop fluid management remains controversial. {Colantonio} In this retrospective study, we examine the relationship between fluid management technique and outcomes of hospital length of stay and encountered complications including anastomotic leaks, bowel leaks, fistulae, intra-abdominal abscesses, and surgical site infections.

Methods: We identified patients who underwent CRS/HIPEC (open and laparoscopic) from May 2014 to February 2018 at the UCSD Health System from a database maintained by the Department of Surgery and approved by the IRB. All data was collected retrospectively. Variables of interest were intraop crystalloid and colloid volumes; patients were excluded if these volumes could not be collected. Other variables were body mass index (BMI), American Society of Anesthesiologists (ASA) Physical Status class, preop functional status with ≥4 metabolic equivalents (METs), preop serum glucose, highest intraop glucose, lowest intraop pH, lowest intraop base excess, intraop urinary output, duration of surgery, estimated blood loss (EBL), Peritoneal Cancer Index, # of visceral resections, and # of anastomoses created. Outcome variables were development of anastomotic leaks, bowel leaks, and/or fistulae; intra-abdominal abscess(es); surgical site infection; and hospital length of stay (LOS). No collected patients died postoperatively, so mortality was not used. We calculated infusion rates in mL/hr with the formula (volume)/(duration of surgery). Infusion volumes and duration of surgery were then removed. We designated infusion rates as primary predictors and all other variables as covariates. We applied univariable regression for each outcome and selected covariates with $p<0.20$. We then applied multivariable regression for each outcome using the primary predictors and the previously selected covariates. For categorical predictors with more than 2 categories, overall Wald test p-values were recorded. We treated ordinal predictors as continuous variables. We performed all statistical analyses using SPSS (IBM SPSS Statistics, Version 26.0. IBM Corp., Armonk, NY).

Results: Demographics 173 patients were identified. Descriptive statistics are listed in Table 1. Mean BMI was 27.37. Most patients were ASA 3 (140 out of 173). Mean crystalloid rate was 628.82 mL/hr. Mean colloid rate was 165.19 mL/hr. Mean LOS was 11.09 days. The most frequent complication was surgical site infection (12 out of 173). Univariable analysis Univariable regression results are found in Table 2. Higher maximum intraop glucose, higher colloid infusion rates, and higher EBL were significantly associated with developing anastomotic leaks, bowel leaks, and/or fistulae. Higher EBL volumes and more anastomoses created intraoperatively were significantly associated with developing intra-abdominal abscesses formation. Lower BMI was significantly protective against developing surgical site infections, while lower values for lowest intraoperative pH were significantly promotive for developing surgical site infections. Multivariable analysis Multivariable regression results are found in Table 3. After adjusting for selected covariates, both infusion rates were not significant for any outcomes. Higher EBL was a significant predictor for developing anastomotic leaks, bowel leaks, and/or fistulae, and intra-abdominal abscesses. Surgical site infection did not have any significant predictors. The number of anastomoses created was a significant predictor for LOS by a mean of +1.4 days/anastamosis.

Conclusion: This interim analysis indicates no trends towards increased complication rates, including surgical site infection, with crystalloid and colloid administration, acidosis, hyperglycemia and functional status of the patients during CRS/HIPEC. These findings may change in the final analysis.

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Table 1 - Patient demographics and perioperative clinical data

Characteristic	Mean	SD
BMI	27.37	6.43
ASA Status	N	%
2	29	16.8
3	140	80.9
4	4	2.3
METs	N	%
<4	8	4.6
>=4	157	90.8
Unknown	8	4.6
Preop glucose (mg/dL)	105.82	32.80
Highest intraop glucose (mg/dL)	170.32	41.17
Lowest intraop pH	7.33	0.06
Lowest intraop base excess	-5.17	2.74
Urinary output (mL)	960.93	669.32
Crystalloid rate (mL/hr)	628.82	254.84
Colloid rate (mL/hr)	165.19	116.58
EBL (mL)	192.69	188.61
Peritoneal Cancer Index	12.92	7.10
Number of Visceral Resections	N	%
0	25	14.5
1	55	31.8
2	50	28.9
3	21	12.1
4	19	11.0
5	3	1.7
Number of Anastomoses Created	N	%
0	80	46.2
1	58	33.5
2	28	16.2
3	6	3.5
4	1	0.6
Anastomotic Leak/Bowel Leak/Fistula	N	%
No	168	97.1
Yes	5	2.9
Intra-Abdominal Abscess	N	%
No	166	96.0
Yes	7	4.0
Surgical Site Infection	N	%
No	161	93.1
Yes	12	6.9
LOS (days)	11.09	6.90

BMI, Body mass index; ASA, American Society of Anesthesiologists; METs, metabolic equivalents; EBL, estimated blood loss; LOS, length of stay.

Table 2 – Univariable regression analysis of postoperative outcomes

	Anastomotic Leak/Bowel Leak/Fistula		Intra-Abdominal Abscess		Surgical Site Infection		LOS	
Predictor	Odds ratio Mean (95% CI)	p-value	Odds ratio Mean (95% CI)	p-value	Odds ratio Mean (95% CI)	p-value	Coefficient Mean (95% CI)	p-value
BMI	0.997 (0.867,1.147)	0.969	0.996 (0.884,1.122)	0.948	1.089 (1.009,1.175)	0.028*	0.011 (-0.151,0.173)	0.891
ASA Status		1.000		0.979		0.999		0.819
2 (reference)								
3	59832403.371 (0.000, ...)		1.254 (0.145,10.826)		1.038 (0.215,5.010)		-0.892 (-3.683,1.899)	
4	1.000 (0.000, ...)		0.000 (0.000, ...)		0.000 (0.000, ...)		-0.578 (-7.875,6.719)	
METs		0.999		0.999		0.071**		0.634
<4	0.000 (0.000, ...)		0.000 (0.000, ...)		4.900 (0.874,27.466)		1.216 (-3.815,6.247)	
>=4 (reference)								
Preop glucose (mg/dL)	0.984 (0.926,1.047)	0.613	0.997 (0.970,1.025)	0.835	1.005 (0.991,1.019)	0.516	-0.014 (-0.048,0.019)	0.393
Highest intraop glucose (mg/dL)	1.017 (1.001,1.033)	0.033*	1.013 (0.998,1.027)	0.085**	1.004 (0.991,1.017)	0.579	0.032 (0.006,0.057)	0.014*
Lowest intraop pH	0.015 (0.000,14163.210)	0.551	0.460 (0.000,110056.234)	0.902	0.000 (0.000,0.316)	0.027*	-22.520 (-39.629,-5.412)	0.010*
Lowest intraop base excess	0.883 (0.645,1.209)	0.438	0.843 (0.646,1.100)	0.208	0.840 (0.681,1.037)	0.105**	-0.552 (-0.928,-0.176)	0.004*
Urinary output (mL)	1.000 (0.999,1.001)	0.851	0.999 (0.998,1.001)	0.513	1.000 (0.999,1.001)	0.859	0.001 (-0.001,0.002)	0.414
Crystalloid rate (mL/hr)	0.995 (0.989,1.001)	0.095**	0.997 (0.992,1.001)	0.141**	0.999 (0.996,1.002)	0.406	-0.003 (-0.007,0.001)	0.118**
Colloid rate (mL/hr)	1.008 (1.001,1.014)	0.017*	0.997 (0.990,1.004)	0.444	1.002 (0.997,1.007)	0.466	0.006 (-0.003,0.014)	0.223
EBL (mL)	1.004 (1.001,1.007)	0.003*	1.004 (1.001,1.007)	0.002*	1.002 (1.000,1.004)	0.100**	0.010 (0.005,0.015)	0.000*
Peritoneal Cancer Index	1.105 (0.976,1.252)	0.114**	1.019 (0.917,1.132)	0.722	1.032 (0.951,1.119)	0.451	0.180 (0.036,0.325)	0.014*
Number of Visceral Resections	1.450 (0.745,2.824)	0.275	1.614 (0.911,2.857)	0.101**	1.215 (0.775,1.906)	0.396	1.614 (0.821,2.406)	0.000*
Number of Anastomoses Created	1.601 (0.666,3.847)	0.293	2.329 (1.118,4.852)	0.024*	1.589 (0.877,2.877)	0.127**	2.235 (1.100,3.369)	0.000*

Odds-ratio values that are too large to be displayed are denoted with ellipses. * highlights significant values, based on α=0.05. ** highlights variables with p-values less than 0.20 and are selected to be included in the multivariable analysis.

BMI, Body mass index; ASA, American Society of Anesthesiologists; METs, metabolic equivalents; EBL, estimated blood loss; LOS, length of stay; CI, confidence interval.

Table 3 – Multivariable regression analysis of postoperative outcomes

	Anastomotic Leak/Bowel Leak/Fistula		Intra-Abdominal Abscess		Surgical Site Infection		LOS	
Predictor	Odds ratio Mean (95% CI)	p-value	Odds ratio Mean (95% CI)	p-value	Odds ratio Mean (95% CI)	p-value	Coefficient Mean (95% CI)	p-value
BMI					1.061 (0.972,1.157)	0.186		
METs						0.232		
<4					3.303 (0.465,23.455)			
>=4 (reference)								
Highest intraop glucose (mg/dL)	1.016 (1.001,1.033)	0.174	1.008 (0.990,1.027)	0.384			0.008 (-0.021,0.036)	0.589
Lowest intraop pH					0.000 (0.000,296.558)	0.238	-10.129 (-35.358,15.100)	0.429
Lowest intraop base excess					1.024 (0.732,1.432)	0.892	-0.055 (-0.639,0.529)	0.852
Crystalloid rate (mL/hr)	0.995 (0.988,1.002)	0.187	0.999 (0.994,1.004)	0.603	0.999 (0.997,1.002)	0.717	-0.001 (-0.005,0.003)	0.558
Colloid rate (mL/hr)	1.007 (0.999,1.016)	0.101	0.995 (0.987,1.004)	0.284	1.000 (0.995,1.006)	0.866	0.002 (-0.007,0.012)	0.608
EBL (mL)	1.004 (1.000,1.007)	0.035*	1.004 (1.000,1.008)	0.029*	1.001 (0.998,1.003)	0.637	0.004 (-0.002,0.010)	0.173
Peritoneal Cancer Index	1.041 (0.865,1.252)	0.671					0.073 (-0.087,0.234)	0.366
Number of Visceral Resections			0.999 (0.994,1.004)	0.509			0.404 (-0.734,1.542)	0.484
Number of Anastomoses Created			0.995 (0.987,1.004)	0.096	1.631 (0.818,3.254)	0.165	1.445 (0.003,2.887)	0.050*

Odds-ratio values that are too large to be displayed are denoted with ellipses. * highlights significant values, based on α=0.05. Blank cells indicate that the predictor was not selected for this multivariable analysis.

BMI, Body mass index; METs, metabolic equivalents; EBL, estimated blood loss; LOS, length of stay; CI, confidence interval.

Perioperative Anesthesia-7 Development of a mouse model of Intensive Care Unit postoperative delirium

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Introduction: Intensive care unit (ICU) postoperative delirium (POD) is an acute form of brain failure characterized by fluctuating level of consciousness, inattention, memory deficits and disorganized thinking1-9. Its pathophysiology remains largely unknown, mainly owing to the lack of animal models to study its basic mechanisms2,3,5,9. Hence, we set out to develop a translationally relevant mouse model of delirium that faithfully recapitulates the realism of the perioperative setting by replicating anesthesia, surgery and ICU conditions (A/S/I). We hypothesized that A/S/I would induce changes in mice behavior and gene expression consistent with the features of human delirium.

Methods: Sixty 18-20 month old male mice were tested in the Y-maze, buried food test, simple discrimination task of the attentional set-shifting test and open field test at baseline. The following day they were randomized to A/S/I or control group. A/S/I mice received laparotomy under sevoflurane anesthesia (3 hours), sedation with propofol (2 hours) and ICU conditions, i.e., intermittent lights, sounds and cage shaking (12 hours). Controls did not receive A/S/I. Mice were tested in the Y-maze, buried food, attentional tasks and open field tests at the end of ICU conditions (0h) and every 6 hours up to 24 hours. Mice hippocampi were collected following the behavioral assessments at 24h and processed for qPCR gene expression analysis. Two-tailed Mann-Whitney test was used for statistical analysis. Behavioral data are presented as mean ± S.E.M. Gene data are expressed as fold change relative to controls. Four mice did not survive A/S/I, therefore their data were excluded from analysis. All studies were approved by the Institutional Animal Care and Use Committee.

Results: A/S/I decreased the entries in the Y-maze novel arm at 0h ($P=0.001$), 6h ($P<0.001$), 18h ($P=0.002$) and 24h ($P=0.029$), and increased the latency to find food in the buried food test at 18h ($P=0.035$) and 24h ($P=0.027$). A/S/I increased the trials to criterion in the reverse compound discrimination ($P=0.013$) and extradimensional shift task ($P<0.001$) of the attentional test. The changes were independent of motor performance assessed in the open field test (data not shown). A/S/I impaired expression of calcium-independent protein kinase C10 (-4.97 fold change), alpha synuclein11 (-3.78 fold change), tropomyosin receptor kinase A12 (-2.27 fold change) and syntaxin1a13 (-1.50 fold change) relative to controls.

Conclusion: In aged mice, a combination of anesthesia, surgery and ICU conditions induced deficits in memory, attention, thought organization and cognitive flexibility with acute onset and fluctuating course. It also impaired expression of key genes that regulate synaptic exocytosis, synaptic plasticity and memory consolidation in the hippocampus. A/S/I-induced behavioral and gene expression impairments are consistent with the features of human delirium and support the use of our model for mechanistic studies of ICU POD.

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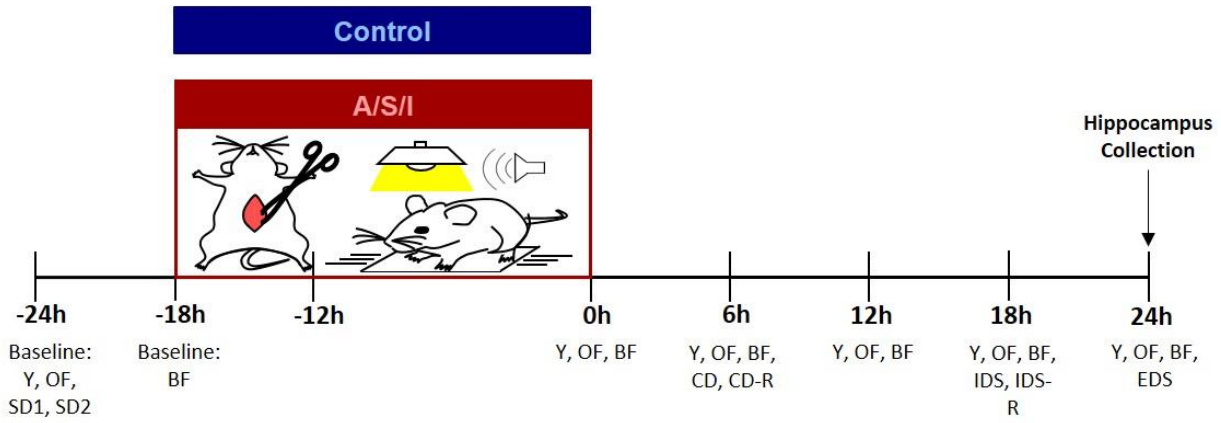

Figure 1. Schematic representation of the experimental design. A/S/I: anesthesia + surgery + ICU conditions. Y: Y-maze test. BF: Buried food test. SD: simple discrimination test. CD: compound discrimination test. CD-R: reverse compound discrimination test. IDS: intra-dimensional shift test. IDS-R: reverse intra-dimensional shift test. EDS: extra-dimensional shift test. OF: open field test.

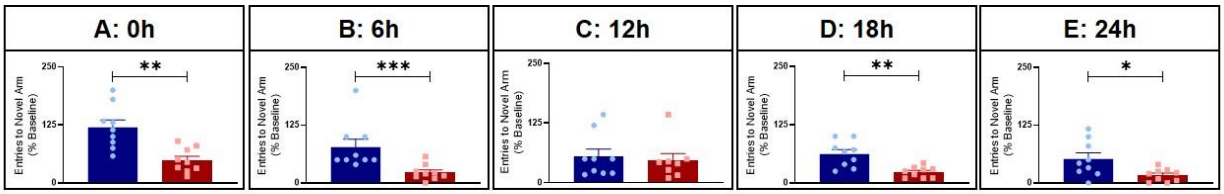

Figure 2. Effects of Anesthesia/Surgery/ICU on mice behavior in the Y-maze. Panels A, B, D and E: A/S/I decreased the number of entries in the novel arm of the Y-maze as compared to controls at 0h (panel A, p= 0.001), 6h (panel B, p<0.001), 18h (panel D, p=0.002) and 24h (panel E, p=0.029). Panel C: there were no differences in the number of entries in the Y-maze novel arm between A/S/I and control mice at 12h (p=0.588). N=9 Control and N=9 A/S/I mice. Time is expressed in hours from the end of ICU conditions.

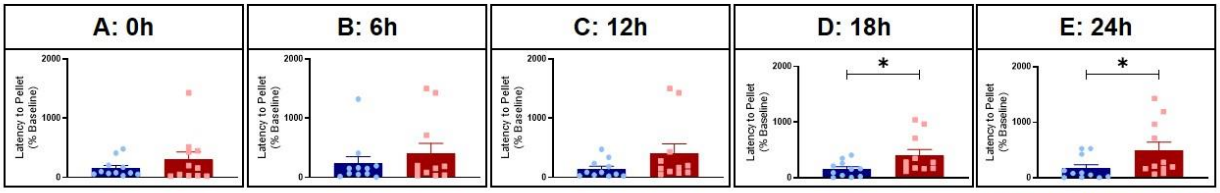

Figure 3. Effects of Anesthesia/Surgery/ICU on mice behavior in the BFT. Panels A-C: there was no difference in the latency to find a buried cereal between A/S/I and control mice at 0h (panel A, P=0.949), 6h (panel B, P=0.478) and 12h (panel C, P=0.116). Panels D and E: A/S/I mice took significantly longer to find a buried sweet cereal compared to control mice at 18h (panel D, p=0.035) and 24h (panel E, p=0.027). N=11 Control and N=11 A/S/I mice. Results are mean ± S.E.M, with individual data represented. Time is expressed in hours from end of ICU conditions.

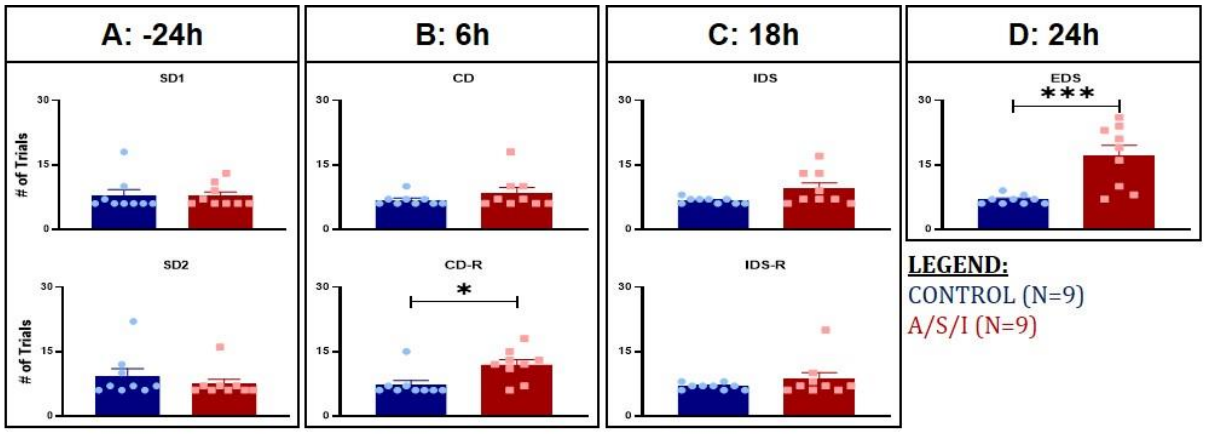

Figure 4. Effects of Anesthesia/Surgery/ICU on mice behavior in the AST. Panel A: there were no differences in baseline performance on the SD tasks between A/S/I and control mice (top panel, P=0.753; bottom panel, P=0.322). Panel B: While A/S/I and control mice performance on the CD task was not significantly different (top panel, P=0.514), A/S/I mice required a significantly higher number of trials to achieve criterion in the CD-R task (bottom panel, P=0.013) compared to controls. Panel C: there were no differences in performance in the IDS and IDS-R tasks between A/S/I and control mice (top panel, P=0.111 and bottom panel, P=0.659). Panel D: A/S/I mice exhibited difficulties finding the reward in the EDS task compared to controls (P<0.001). SD: simple discrimination; CD: compound discrimination; CD-R: reverse compound discrimination. IDS: intra-dimensional shift; IDS-R: reverse intra-dimensional shift. EDS: extra-dimensional shift. N= 9 Control and N=9 A/S/I mice. Results are mean ± S.E.M, with individual data represented. Time is expressed in hours from end of ICU conditions.

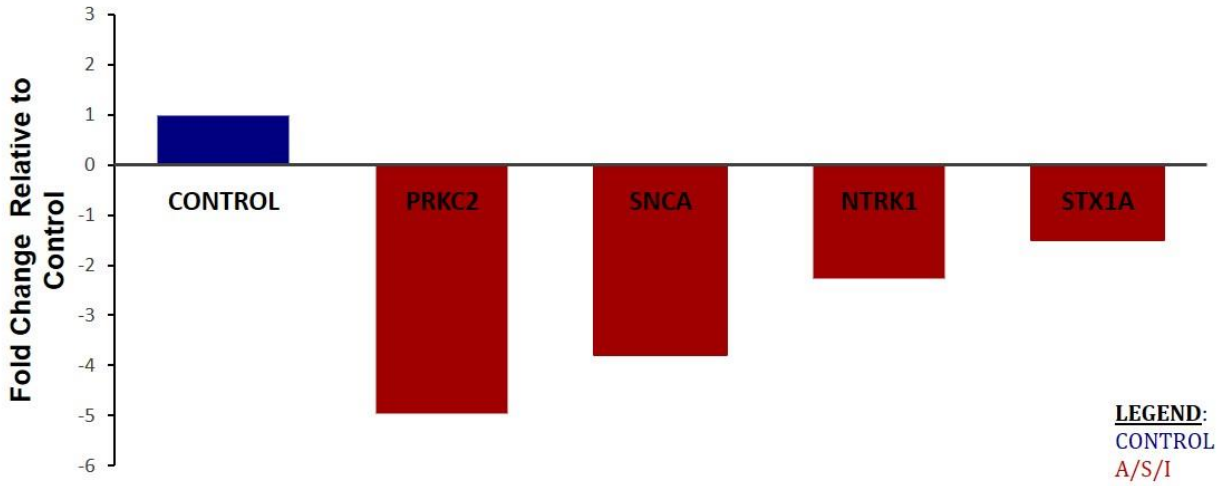

Figure 5. Effects of Anesthesia/Surgery/ICU on hippocampal expression of genes regulating synaptic vesicle exocytosis and plasticity: A/S/I impaired expression of calcium-independent protein kinase C (-4.9 fold change), alpha synuclein (-3.78 fold change), tropomyosin receptor kinase A (-2.26 fold change) and syntaxin1a (-1.49 fold change) relative to controls. N=3 pooled A/S/I hippocampi and 3 control hippocampi. PRKC2: Calcium-independent protein kinase C; SNCA: Alpha Synuclein; NTRK1: Tropomyosin receptor kinase A; STX1A: Syntaxin1A

Perioperative Anesthesia-8 The Impact of Surgeon Gender on Add-on Case Wait Time

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Introduction: Communication is an essential part of effective team work and patient safety, particularly in the fast-paced, high acuity setting of the operating room.[1] Yet, inter-professional and gender hierarchies complicate teamwork and communication amongst surgeons, anesthesiologists and perioperative nurses.[1] Recent studies suggest that gender in both internists and surgeons may impact patient outcomes,2-4 and that the gender of medical team members can impact effective team dynamics and communication.5-7 The purpose of our study was to determine whether the gender of the attending surgeon impacts how quickly an 'add-on' surgery case is moved into an operating room. We also investigated whether this difference, if one exists, affects patient outcome.

Methods: The Anesthesia Research Data Repository was queried for surgical add-on cases performed at our academic medical center between August 2014 and December 2018. Cardiac surgery cases, patients ≤ 18 years old and patients with an ASA score of 6 were excluded from the cohort. Analyses were carried out using the complete-case method. The exposure was defined as the gender of the attending surgeon. The primary outcome, add-on case wait time, was defined as the time elapsed between the booking of an add-on case and the anesthesia B-time (in-room time). Secondary outcomes included ICU admission within 7 postoperative days, 30-day mortality, hospital length of stay, and adverse discharge disposition. Zero-truncated negative binominal regression and logistic were used to evaluate the association between the gender of the surgeon and the endpoints, as appropriate. Analyses were adjusted for a priori defined covariates including acuity of the add-on case, emergency status, night-time surgery, weekend surgery, patient ASA classification, and Charlson Comorbidity Index. To assess if case acuity, as categorized by our institution's booking codes, moderates the association of surgeon's gender and add-on case wait time, the interaction term 'case acuity (A to E) * surgeon's gender (male/female)' was added to the primary regression model in an exploratory analysis. Furthermore, we tested the strength of the association in sensitivity analyses by analyzing only surgeries performed on the same day booked, additionally adjusting for the service, gender proportion on a service level, or post-operative ICU requirement.

Results: The studied cohort consisted of 18,371 adult, non-cardiac add-on cases. (Figure 1.) Female gender in attending surgeons was significantly associated with a shorter add-on case wait time, both in the crude analysis (IRR 0.792 [0.759-0.827], p<0.001) and adjusted for confounders (aIRR 0.934 [0.907-0.962], p<0.001.) Female gender in the surgical attending was significantly associated with a shorter add-on case wait time in every category of case acuity except the most emergent class (A: <30mins,) where male gender of the surgical attending was associated with a shorter add-on case wait time. (Figure 2, Table2) Sensitivity analyses confirmed robustness of the association between female surgeon gender and shorter add-on case wait time. (Table 2) We found no association between the gender of attending surgeon and ICU admission within 7 postoperative days, 30-day mortality, hospital length of stay, or adverse discharge disposition (Table 2.)

Conclusion: In this hospital-based registry study of 18,371 add-on surgical cases performed over a 4.5-year time frame, we found that female gender of the attending surgeon is significantly associated with a shorter add-on case wait time. This association was robust in every category of case acuity, except for the emergent category, where male gender of the surgical attending was associated with a shorter add-on case wait time. The differential impact of surgeon gender on add on case wait time based on case acuity suggests that multiple mechanisms are at play. Further investigation is warranted.

Reference(s):

1. British Journal of Anaesthesia. 2018 Nov;121(5):997-999
2. JAMA Intern Med. 2017 February 01; 177(2):206-213
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5. British Journal of Anaesthesia, 119(4):697-702 (2017)
6. Critical Care Medicine Volume 45, Number 7, July 2017
7. PNAS Vol. 115, no. 29, 7575-7580. July 2018.

Figure 1. Flow of the study patients.

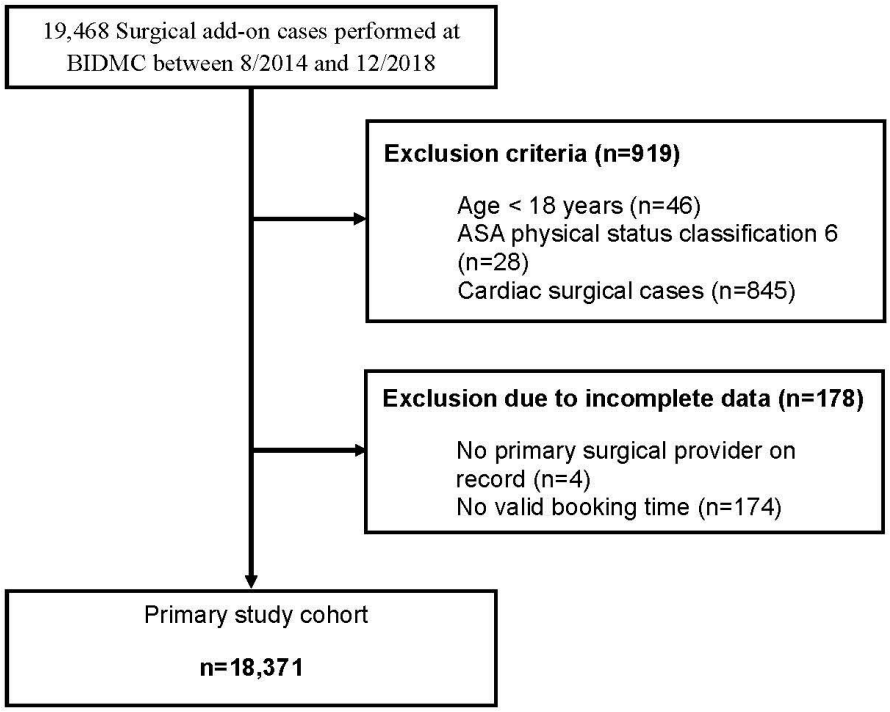

Figure 2. Predicted add-on case wait time by gender of the primary surgical provider, stratified by acuity of the case.

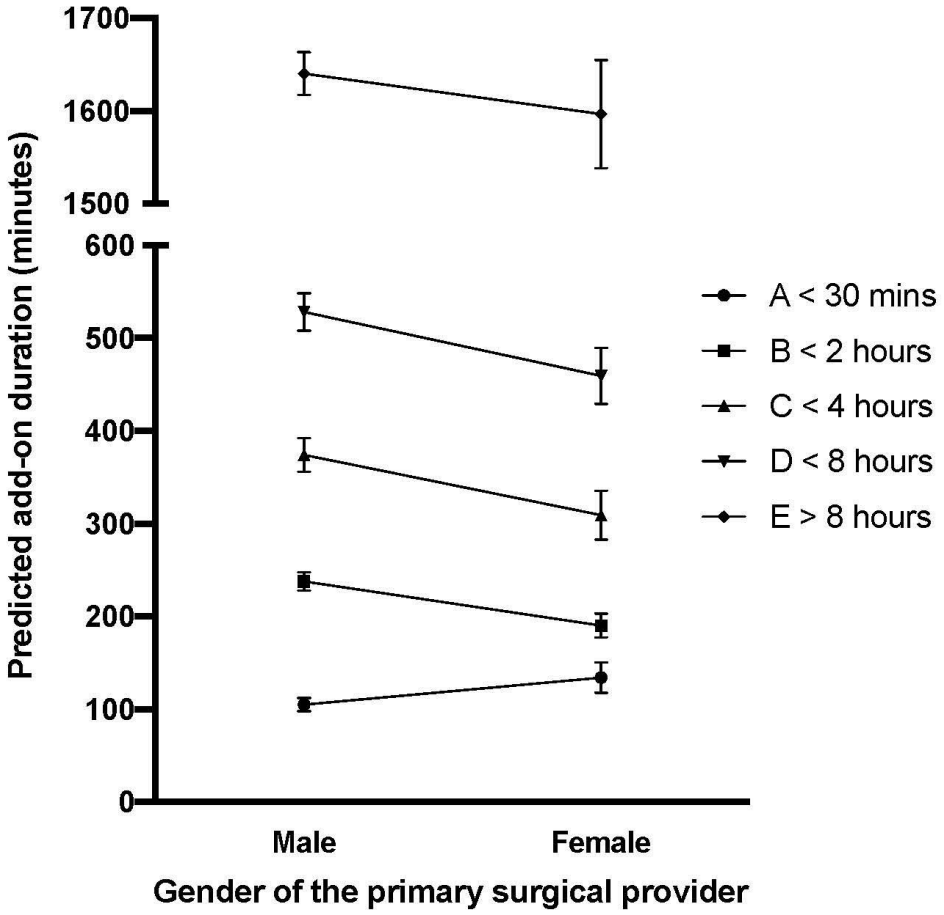

Table 1. Characteristics of the study cohort.

Patient characteristics		Female Surgeon (n=2983)	Male Surgeon (n=15388)
Median (interquartile range) add-on case wait time, minutes		464 (138, 1362)	963 (306.5, 1623.5)
ICU admission within 7 postoperative days		585 (19.6%)	3577 (23.3%)
Hospital length of stay		4 (1, 10)	7 (3, 14)
Adverse discharge disposition		360 (12.7%)	3117 (21.0%)
30-day mortality		86 (2.9%)	632 (4.1%)
Acuity of the add-on case			
	A < 30 mins	146 (4.9%)	484 (3.1%)
	B < 2 hours	494 (16.6%)	1345 (8.7%)
	C < 4 hours	296 (9.9%)	933 (6.1%)
	D < 8 hours	489 (16.4%)	1514 (9.8%)
	E > 8 hours	1558 (52.2%)	11112 (72.2%)
Add-on score*			
	0	83 (2.8%)	422 (2.7%)
	1	1656 (55.5%)	9914 (64.4%)
	2	1022 (34.3%)	4420 (28.7%)
	3	222 (7.4%)	632 (4.1%)
Emergency case		1282 (43.0%)	5082 (33.0%)
Surgery at night		1154 (38.7%)	3891 (25.3%)
Surgery on the weekend		770 (25.8%)	3746 (24.3%)
Surgical service			
	Colorectal Surgery	61 (2.0%)	611 (4.0%)

Dental / Oral	88 (3.0%)	236 (1.5%)
Ear Nose Throat	18 (0.6%)	118 (0.8%)
Eye	16 (0.5%)	111 (0.7%)
General Surgery	419 (14.0%)	500 (3.2%)
Gastroenterology	43 (1.4%)	84 (0.5%)
Gynecology	1020 (34.2%)	313 (2.0%)
Neurosurgery	233 (7.8%)	903 (5.9%)
Orthopedic Surgery	303 (10.2%)	4886 (31.8%)
Plastic Surgery	7 (0.2%)	871 (5.7%)
Podiatry	117 (3.9%)	690 (4.5%)
Surgical oncology	55 (1.8%)	74 (0.5%)
Thoracic Surgery	80 (2.7%)	1194 (7.8%)
Transplant Surgery	345 (11.6%)	214 (1.4%)
Trauma / Surgical Critical Care	144 (4.8%)	3024 (19.7%)
Urology	29 (1.0%)	558 (3.6%)
Vascular Surgery	5 (0.2%)	1000 (6.5%)
American Society of Anesthesiologists physical status classification		
1	586 (19.6%)	1356 (8.8%)
2	999 (33.5%)	4326 (28.1%)
3	979 (32.8%)	7127 (46.3%)
4	388 (13.0%)	2410 (15.7%)
5	31 (1.0%)	169 (1.1%)
Median (interquartile range) Charlson Comorbidity Index	0 (0, 3)	1 (0, 4)

* Add-on score: Scoring systems used to quantify operation room readiness of the patient (i.e. completion of work-up consults, waiting time, expected time to hospital discharge after completion of the surgery)

Table 2: Summary of primary, secondary and sensitivity analyses.		
Primary Analysis: Association of gender of the primary surgical provider and add-on case wait time	Female Surgeon	p-value
Crude Analysis, IRR [95% CI]	0.792 [0.759 - 0.827]	< 0.001
Adjusted Analysis, aIRR [95% CI]	0.934 [0.907 - 0.962]	< 0.001
Secondary Analyses: Association of gender of the primary surgical provider and secondary outcomes		
ICU Admission within 7 postoperative days, aOR [95% CI]* (n=11,913)	0.879 [0.746 – 1.034]	0.123
30-day Mortality, aOR [95% CI]	1.052 [0.802 - 1.382]	0.713
Hospital length of stay, aIRR [95% CI]	0.979 [0.931 - 1.031]	0.424
Adverse discharge disposition, aOR [95% CI]	1.079 [0.934 - 1.246]	0.3

Regression models were adjusted for a priori defined covariates reflecting case and patient's characteristics (acuity of the add-on case, add-on score, emergency status, night surgery, weekend surgery, ASA status, Charlson Comorbidity Index).

*adjusted for the propensity of ICU admission based on the following covariates: age, gender, BMI, Charlson Comorbidity Index, duration of surgery, duration of intraoperative hypotension, emergency status, work RVUs ASA physical status, fluid resuscitation (colloids and crystalloids), PRBC units, vasopressor requirement, median intraoperative PEEP and PIP, dose of ND-NMBAs, median S/F ratio, surgical service and procedural severity score for morbidity (Thevathasan et. al. Anesthesia and Analgesia 2019)

Perioperative Anesthesia-9 Postoperative Depression after Major Surgery: A Comparative Analysis Using a National Claims Database

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Introduction: Depression is the largest contributor to global disability.1 Aside from surgical disease, major surgery itself could increase the risk of depression. The incidence of postoperative depression has been described in small cohort studies lacking preoperative confounder control or direct comparisons of risk from other surgeries.2,3,4 Given its substantial impact on postoperative recovery we investigated the risk of depression after common major surgeries, hypothesizing that surgeries with higher degrees of stress, pain, complications, or cognitive dysfunction would have an increased risk of postoperative depression.

Methods: Retrospective cohort study with claims from the Optum© Clinformatics® Database of 75 million patients. Cardiac, thoracic, hip, or laparoscopic cholecystectomy (lap CCY) surgery patients between 2004-2019 were screened. Exclusion criteria were previous depression, adjustment disorder, prescription for an anti-depressant or comparator surgery within 365 days before surgery. Death or disenrollment during follow-up (365 days) was censored. The primary outcome was depression, defined by either a new ICD9/10 depression diagnosis code or a new prescription for an antidepressant. A secondary outcome requiring both a diagnosis and a prescription was also analyzed. Covariates included demographics, predictors of depression, and comorbidities. Primary and secondary outcomes were analyzed with multivariate logistic regression. Adjusted analysis included a propensity score matched (PSM) model with preoperative confounders based on prior reports and clinical knowledge. 1:1 matching with a 1% caliper was used. A $P<0.05$ was considered significant. Lap CCY was chosen a priori as the referent group (OR=1). The primary comparison was cardiac surgery versus lap CCY patients. Repeated analyses then explored the risk between thoracic and hip surgery versus lap CCY patients. No adjustments were made for multiple comparisons.

Results: The PSM cohort contained data from 66,097 cardiac surgery (CS) and lap CCY patients (Figure 1, Table 1). The odds of the primary and secondary outcome were significantly higher for CS than for lap CCY patients [OR(95%CI) 1.56(1.50,1.61) $P<0.001$, (1.76(1.63, 1.9), $P<0.001$), respectively] (Table 2). Thoracic (1.33(1.26, 1.41), $P<0.001$) and hip fracture surgery (1.96(1.88, 2.03), $P<0.001$) patients were also at increased risk, however the odds were significantly less for hip replacement patients (0.82(0.79, 0.86), $P<0.001$) (Table 3, Figure 2).

Conclusion: After controlling for preoperative confounders, the odds of developing new depression after cardiac, thoracic, and hip fracture surgery are significantly higher than for patients undergoing lap CCY. Surgery and the associated postoperative period may be uniquely associated with depression, apart from surgical disease. Surgical approach or indication may also influence risk. Further investigation is necessary to identify predictors and preventative targets for postoperative depression after major surgery.

Reference(s):

1. Depression and other common mental disorders: global health estimates. World Health Organization;2017
2. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet. 2003;362(9384):604-609.
3. Risk factors for postoperative anxiety and depression after surgical treatment for lung cancer. European Journal of Cardiothoracic Surgery. 2016;49(1):e16-e21.
4. Onset of depression in elderly persons after hip fracture: implications for prevention and early intervention of late-life depression. Journal of the American Geriatrics Society. 2007;55(1):81-86.

Table 1 Baseline demographics stratified by surgery type

	Unmatched Cohort			Propensity Matched Cohort		
	Laparoscopic Cholecystectomy	Cardiac Surgery	Absolute Standardized Difference†	Laparoscopic Cholecystectomy	Cardiac Surgery	Absolute Standardized Difference
N	325,952	122,770	-	66,097	66,097	-
Age	51.92 (17.8)	66.8 (12)	0.979	68.1 (13.2)	66.6 (13.2)	0.112
Gender						
Male	113,485 (34.8%)	90,907 (74%)	0.857	45,783 (69.3%)	44,799 (67.8%)	0.032
Female	212,433 (65.2%)	31,838 (25.9%)		20,301 (30.7%)	21,287 (32.2%)	
Low Income Subsidy	11,652 (3.6%)	6,887 (5.6%)	0.112	5,198 (7.9%)	4,483 (6.8%)	0.027
Race						
White	216,376 (66.4%)	89,163 (72.6%)		46,399 (70.2%)	47,000 (71.1%)	
Asian	7,946 (2.4%)	3,043 (2.5%)	0.212	1,849 (2.8%)	1,723 (2.6%)	0.028
Black	27,811 (8.5%)	9,986 (8.1%)		5,379 (8.1%)	5,142 (7.8%)	
Hispanic	44,290 (13.8%)	9,422 (7.7%)		6,099 (9.2%)	5,747 (8.5%)	
Charlson Comorbidity Score*	171.17 (385.31)	338.87 (516.41)	0.368	285.7 (489.4)	268.1 (478.3)	0.036
Angina	8,198 (2.5%)	46,748 (38.1%)	0.986	6,526 (9.9%)	7,550 (11.4%)	0.050
Myocardial infarction	2,693 (0.8%)	25,711 (20.9%)	0.682	2,222 (3.4%)	2,902 (4.4%)	0.053
Percutaneous Coronary Intervention	1,378 (0.4%)	7,204 (5.9%)	0.316	1,329 (2%)	1,805 (2.7%)	0.047
Coronary Heart Disease	1,034 (0.3%)	46,437 (37.8%)	1.087	1,034 (1.6%)	1,711 (2.6%)	0.072
Congestive heart failure	4,342 (1.3%)	15,404 (12.5%)	0.452	3,853 (5.8%)	4,451 (6.7%)	0.037
Smoking	42,486 (13%)	27,378 (22.3%)	0.245	8,974 (13.6%)	9,154 (13.8%)	0.008
Diabetes	42,788 (13.1%)	35,674 (29.1%)	0.398	12,816 (19.4%)	12,181 (18.4%)	0.025
Hyperlipidemia	98,816 (30.3%)	71,404 (58.2%)	0.584	25,172 (38.1%)	25,701 (38.9%)	0.016
Hypertension	111,870 (34.3%)	77,604 (63.2%)	0.604	29,417 (44.5%)	29,377 (44.4%)	0.001
Obesity	47,392 (14.5%)	16,195 (13.2%)	0.039	5,939 (9.0%)	6,151 (9.3%)	0.011
Chronic Kidney Disease	35,247 (10.8%)	27,635 (22.5%)	0.318	11,225 (17%)	10,831 (16.4%)	0.016
Chronic Pulmonary Disease	54,440 (16.7%)	35,188 (28.7%)	0.289	19,163 (29%)	17,687 (26.8%)	0.050
Lung Cancer	1,262 (0.4%)	742 (0.6%)	0.031	514 (0.8%)	424 (0.6%)	0.016
Osteoarthritis	43,779 (13.4%)	22,777 (18.6%)	0.140	14,968 (22.6%)	13,580 (20.5%)	0.051
Cognitive Disorder	3,979 (1.2%)	1,972 (1.6%)	0.033	1,649 (2.5%)	1,392 (2.1%)	0.026
Alcohol Abuse	2,348 (0.7%)	1,536 (1.3%)	0.054	629 (1.0%)	588 (0.9%)	0.006

Values are reported as N (%) or mean (SD) depending on variable type

†Absolute standardized difference is calculated as the difference in group means or proportions divided by the square root of the pooled variance. A value less than 0.1 signifies a negligible difference

**Summed over 365-day period*

FIGURE 1: CONSORT DIAGRAM – CARDIAC SURGERY VS LAPAROSCOPIC CHOLECYSTECTOMY

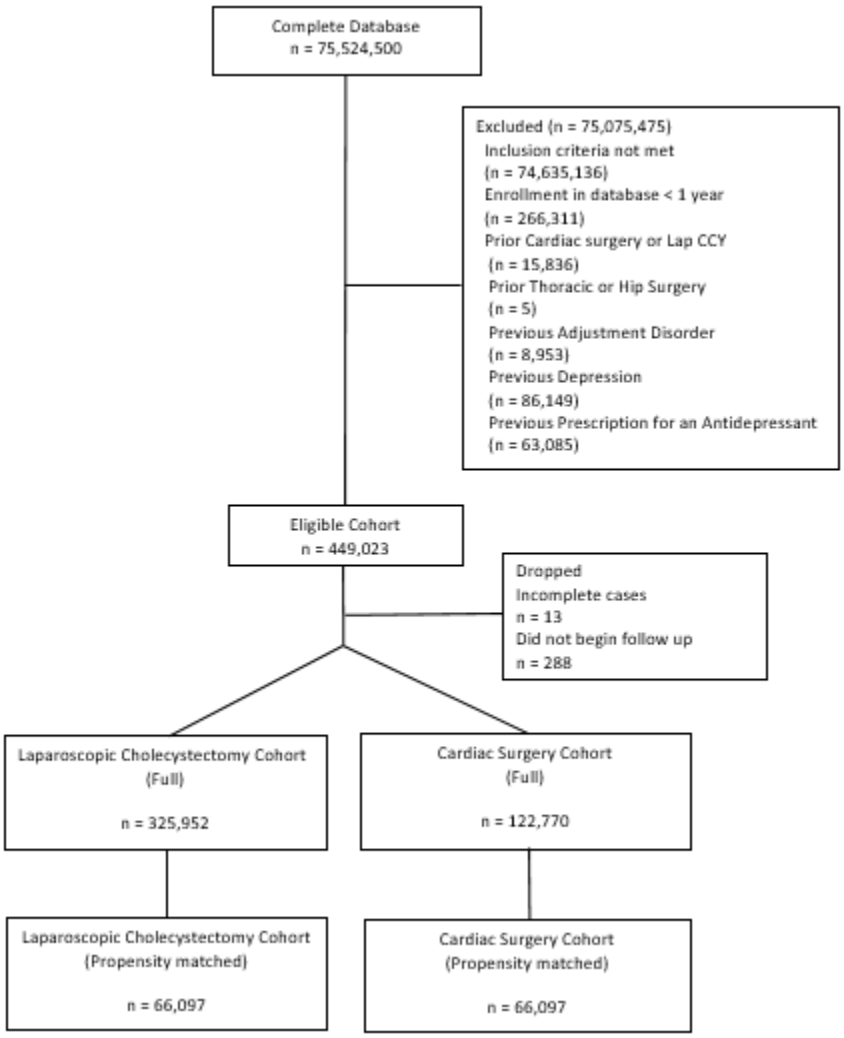

Table 2: Primary and secondary outcomes after cardiac surgery as compared to lap CCY.

	Odds Ratio (95% CI)	P
New depression OR a new prescription		
Unadjusted	1.57 (1.54, 1.60)	<0.001
Propensity score matched	1.56 (1.50, 1.61)	<0.001
New depression AND a new prescription		
Unadjusted	1.60 (1.53, 1.67)	<0.001
Propensity score matched	1.76 (1.63, 1.9)	<0.001

Table 3: Odds of the Primary Outcome for Other Surgeries Compared to Lap CCY

	Odds Ratio (95% CI)	p
Thoracic Surgery		
Unadjusted	1.71 (1.57, 1.72)	<0.001
Propensity score matched	1.33 (1.26, 1.41)	<0.001
Thoracotomy		
Unadjusted	2.09 (1.99, 2.19)	<0.001
Propensity score matched	1.62 (1.49, 1.76)	<0.001
VATS		
Unadjusted	1.57 (1.52, 1.63)	<0.001
Propensity score matched	1.24 (1.16, 1.32)	<0.001
Hip Surgery		
Hip Fracture Surgery		
Unadjusted	2.48 (2.43, 2.53)	<0.001
Propensity score matched	1.96 (1.88, 2.03)	<0.001
Hip Replacement		
Unadjusted	0.81 (0.79, 0.83)	<0.001
Propensity score matched	0.82 (0.79, 0.86)	<0.001

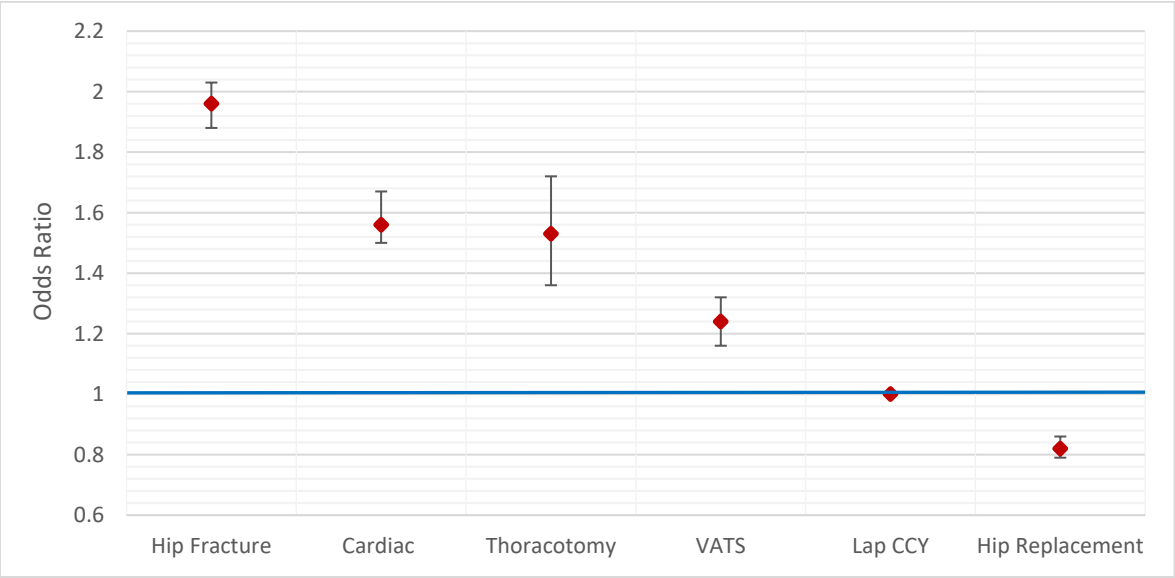

Figure 2: Odds of new depression (diagnosis or prescription) after various major surgeries.
Lap CCY was assigned as referent (OR=1)

Perioperative Anesthesia-10 Establishing the “New Normal': Biostatistics of the Average Patient Undergoing Anesthesia at a University Medical Center

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Introduction: Since the 1970s, medical literature has defined the average patient as a 70kg male, however as the population of the United States struggles with increasing rates of obesity, it is unlikely that today's average patient truly weighs 70kg1. In 2017, the National Center for Health Statistics reported an obesity prevalence of 39.8% in the adult population , as well as a 9% increase in obesity rates over a 15-year period (2,3). As such, it is unlikely that 70kg remains an accurate surrogate weight for the average patient. Given this, we sought to identify an observed average weight, as well as other focused health metrics for surgical patients at a single university hospital.

Methods: After obtaining IRB approval, all patients age 18 or older who received anesthetics in an operating environment between January 1 and December 31, 2015 were identified. Extracted data included: medical record number, age, weight, body mass index (BMI), American Society of Anesthesiology (ASA) score and the first recorded set of vital signs limited to heart rate and mean arterial blood pressure (MAP). We excluded patients with an ASA score of 6, and those over 80 years of age due to the disproportionally small number of patients within that group. Patients who had multiple anesthetics were screened to include only their first anesthetic for 2015. Data points for weight, BMI, heart rate, MAP, and ASA score were extracted and imported into the electronic database Research Electronic Data Capture (REDCap). Descriptive statistical analysis was performed looking at the dataset as a whole as well as by gender specific age-by-decades (categories of 19-30, 31-40, 51-60, 61-70, and 71-80), with the exception of the category 'age'.

Results: 19,522 patients were identified who required operative anesthesia during 2015. Females comprised 53.5% of patients and had an average age of 54.7 ± 16 y. The average age for males was 54.7 ± 16 y. Demographic and vital sign data, stratified by both gender and age-by-decade, are shown in Table 1. Similar trends were evident for both females and males when the data was considered by decades of age. For weight and BMI, the 19-30y decade had the lowest average values; and values increased to a high for the 41-50y decade, and then decreased to the 71-80y decade. The average heart rate measured fell within established normal ranges for all decades. There was a steady decrease sequentially from the 19-30y decade (for males, 19-30y and 31-40y decades had similar values) to the 71-80y decade. The MAP value measured also exhibited sequential changes across the decades, increasing from a low for the 19-30y decade to a high for the 71-80y decade. ASA Score: Analysis of ASA status by age-decade is shown in Figure 1. For the 3 lowest age decades, the highest percentage of patients were ASA-2, and patients with ASA status scores ≤ 2 constituted the majority (≥57%). For the three oldest age decades, the highest percentage of patients were ASA status 3, and ASA status scores ≥3 constituted the majority (≥58%). ASA status 5 was <1% for all age decades.

Conclusion: Our data reflects national trends of increasing rates of obesity and hypertension. The average patient weight of 83.5 and 94.1kg for females and males, respectively, is notably higher than the historical average of 70kg1. Additionally, using the Center for Disease Controls (CDC) criteria for obesity (BMI<30kg/m2), the average surgical patient over the age of 31, regardless of gender, would qualify as obese2. Our findings also show that the bulk of our surgical patient population has hypertension when MAP is calculated using the highest allowable blood pressure per the 2017 ACA/AHA Guidelines4. Perhaps the best metric utilized in this analysis for overall health status is the ASA physical status classification system5. ASA-3 status corresponds to 'severe systemic disease', and for all ages above 50, the majority of the surgical patients were ASA status ≥3, as well as 43% of 41-50 year olds. The majority of surgical patients under age 41 were ASA status ≤2, corresponding to 'mild systemic disease', yet even this group demonstrated hypertension. We found that regardless of age or gender, the average patient is likely to weight more than 70kg. Our data also suggests that at equivalent age ranges, males tend to have higher weight, BMI and MAP compared to females. Anesthesia providers should consider current population trends and the potential impact on the delivery of anesthesia.

Reference(s):

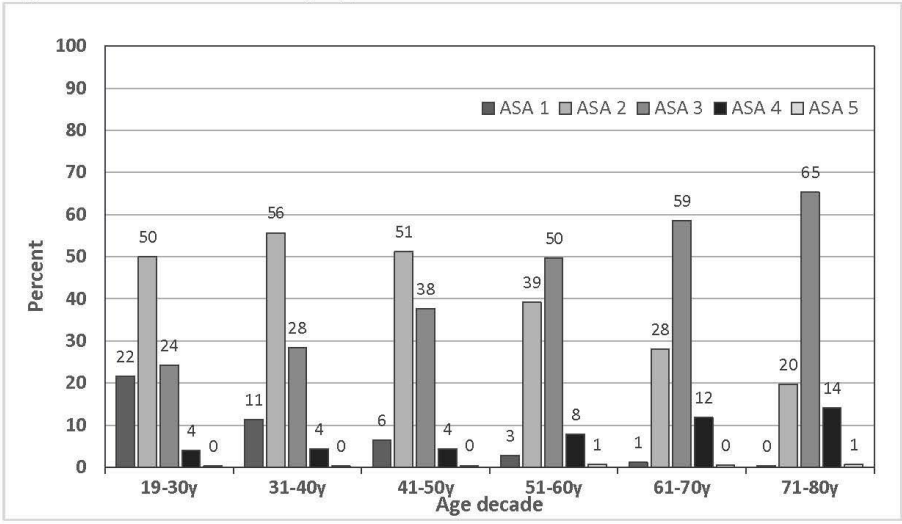
1. Evid Based Med. 2013;18(1):21-22.
2. Centers for Disease Control and Prevention: Overweight & Obesity, Defining Adult Overweight and Obesity. 2017
3. NCHS Data Brief No. 288: Prevalence of Obesity Among Adults and Youth: United States, 2015–2016. 2017

Table 1. Demographic and vital sign data by decade and gender

Age (years)	Sex	N	Variable	N	Mean	Std Dev
19-30	Female	1294	Weight (kg)	986	74.9	26.9
			BMI (kg/m^2)	942	28.8	9.7
			First HR (bpm)	1293	83.5	26.6
			First MAP (mmHg)	1283	97.6	14.7
	Male	1068	Weight (kg)	791	80.5	23.1
			BMI (kg/m^2)	765	26.0	7.29
			First HR (bpm)	1066	81.0	28.2
			First MAP (mmHg)	1058	99.1	14.4
31-40	Female	1548	Weight (kg)	1273	84.3	27.1
			BMI (kg/m^2)	1214	31.7	9.9
			First HR (bpm)	1546	80.2	25.5
			First MAP (mmHg)	1542	102.1	15.6
	Male	943	Weight (kg)	641	94.3	28.2
			BMI (kg/m^2)	616	30.0	8.3
			First HR (bpm)	940	81.4	30.3
			First MAP (mmHg)	922	104.4	16.4
41-50	Female	1836	Weight (kg)	1483	87.6	27.5
			BMI (kg/m^2)	1421	32.8	9.9
			First HR (bpm)	1831	78.4	25.8
			First MAP (mmHg)	1824	107.4	16.7
	Male	1091	Weight (kg)	818	100.1	28.2
			BMI (kg/m^2)	786	31.6	8.1
			First HR (bpm)	1087	77.9	29.4
			First MAP (mmHg)	1069	109.9	17.3
51-60	Female	2165	Weight (kg)	1693	86.3	25.7
			BMI (kg/m^2)	1632	32.4	9.3
			First HR (bpm)	2160	76.9	29.5
			First MAP (mmHg)	2139	110.4	17.7
	Male	2061	Weight (kg)	1523	97.4	27.0
			BMI (kg/m^2)	1453	31.1	8.5
			First HR (bpm)	2053	74.1	32.6
			First MAP (mmHg)	2015	111.5	17.4

61-70	Female	2064	Weight (kg)	1575	85.1	25.2
			BMI (kg/m^2)	1518	32.7	9.4
			First HR (bpm)	2058	76.5	31.5
			First MAP (mmHg)	2027	113.9	19.1
	Male	2241	Weight (kg)	1657	96.0	23.8
			BMI (kg/m^2)	1608	31.0	7.4
			First HR (bpm)	2234	72.1	36.4
			First MAP (mmHg)	2186	113.6	18.5
71-80	Female	1525	Weight (kg)	1153	78.3	20.3
			BMI (kg/m^2)	1114	30.7	7.9
			First HR (bpm)	1520	73.4	36.3
			First MAP (mmHg)	1493	116.8	19.8
	Male	1687	Weight (kg)	1201	91.9	19.8
			BMI (kg/m^2)	1162	30.0	6.98
			First HR (bpm)	1684	70.6	40.7
			First MAP (mmHg)	1650	116.0	19.2

Figure 1. ASA Status Class by Age Decade



Perioperative Anesthesia-11 The influence of daily habits on perioperative neurocognitive disorders in patients scheduled for non-cardiac surgery. An observational study

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Introduction: Perioperative neurocognitive disorders (PND) remain an important complication, caused by the non-resolution of an inflammatory cascade. (1) (2) (3) (4) Methods of identifying patients who are likely to develop PND would improve overall perioperative support of these patients. We aimed to investigate whether the sedentary behavior of the elderly surgical patient was associated with PND and increased peripheral inflammatory markers.

Methods: 38 patients scheduled for non-cardiac surgery were included in this prospective observational study from January until July 2019 at the CHU de Charleroi, Charleroi, Belgium. Prior to surgery, patients were asked questions regarding their daily habits. Sedentary behavior was assessed via IPAQ (international physical activity questionnaire). Baseline MMSE (mini mental state examination) testing was conducted and a baseline blood sample was taken. Six and 24 hours after surgery, blood samples were again taken. Patients' MMSE were re-evaluated 6 weeks and 3 months after surgery. Circulating IL-6 and HMGB1 levels were analyzed through ELISA.

Results: Six weeks postoperatively MMSE decreased from baseline. (Figure 1) Sedentary behavior was not associated with a decrease in MMSE. Patients who spoke more than one language ($p=0.028$) and who were self-sufficient ($p=0.0083$) scored better on the MMSE six weeks postoperatively. (Table 1) Surgery was associated with an increase in peripheral IL-6 ($p<0.0001$). (Figure 2) Interestingly, IL-6 increased from baseline to 24 hours in patients who underwent general and genitourinary surgeries while in those who underwent orthopedic surgery, it achieved its maximum at 6 hours and then decreased. An increase in IL-6 levels was not associated with sedentary behavior. (Table 2) The postoperative rise in IL-6 was increased in elderly patients ($p=0.0044$). It was lower when patients took less psychoactive drugs ($p=0.041$) and when work-related IPAQ was high ($p=0.024$). Surgery was associated with an increase in peripheral HMGB1($p<0.0001$). (Figure 3) No statistically significant association was found between HMGB1 and pre-existing/baseline patient characteristics.

Conclusion: Surgery is associated with an increase in peripheral IL-6 and HMGB1 and with cognitive impairment 6 weeks postoperatively. Preoperative sedentary behavior is neither a risk factor for PND nor associated with an increase in peripheral inflammation, findings that correspond with pre-clinical data. (5) The putative effect of preoperative lifestyle in surgical patients should be further tested in randomised controlled trials, ideally with a battery of memory tests, instead of a single test.

Reference(s):

1. J Neuroinflammation. 13: 211, 2016
2. Anesthesiology. 120: 1160, 2014
3. Ann Neurol. 70: 986, 2011
4. JCI Insight. 2: e91229, 2017
5. Front Immunol. 8: 1768, 2017

Table 1. Evolution of MMSE with respect to time and baseline parameters (N=38)

Variable	Estimate (SE) Time 3w vs. 0	Estimate (SE) Time 6m vs. 0h	Estimate (SE) parameter	P-value time	P-value parameter
Age (years)	-2.10 (0.56)	-1.72 (0.68)	-0.071 (0.11)	0.0012	0.53
Gender (Male vs. Female)	-2.11 (0.56)	-1.74 (0.68)	0.23 (1.41)	0.0011	0.87
BMI (kg/m²)	-2.14 (0.56)	-1.77 (0.68)	-0.077 (0.13)	0.0010	0.55
Education level (ordinal)	-2.13 (0.56)	-1.79 (0.68)	1.36 (0.72)	0.0010	0.069
Number of languages known (ordinal)	**-2.16 (0.56)**	**-1.83 (0.68)**	**1.44 (0.63)**	**0.0008**	**0.028**
Working (Yes vs. No)	-2.10 (0.56)	-1.72 (0.68)	2.95 (1.64)	0.0012	0.080
Marital status (Divorced vs Married)	-2.11 (0.56)	-1.74 (0.68)	-0.080 (1.75)	0.0011	0.95
Marital status (Widow vs. Married)			0.65 (2.13)		
Self-sufficient (Yes vs. No)	**-2.09 (0.55)**	**-1.69 (0.68)**	**6.44 (2.31)**	**0.0013**	**0.0083**
Living situation (Number of people)	-2.12 (0.56)	-1.74 (0.68)	0.67 (1.10)	0.0011	0.55
Number of alcoholic drinks/week (sqrt)	-2.12 (0.56)	-1.75 (0.68)	0.48 (0.53)	0.0011	0.37
Smoking Status (Current vs. no)	-2.13 (0.56)	-1.75 (0.68)	-0.38 (1.52)	0.0010	0.12
Smoking Status (Ex vs. no)			-3.50 (1.73)		
Surgery (Orthopedic vs. General)	-2.12 (0.56)	-1.77 (0.68)	-1.52 (1.76)	0.0010	0.34
Surgery (Genitourinary vs. General)			-2.47 (1.67)		
Number of psychoactive meds (sqrt)	-2.11 (0.56)	-1.74 (0.68)	-0.91 (1.75)	0.0011	0.61
Type 2 Diabetes (Yes vs. No)	-2.10 (0.56)	-1.73 (0.68)	-2.82 (1.50)	0.0012	0.068
MMSE baseline (/30)	**-2.10 (0.53)**	**-1.62 (0.63)**	**0.92 (0.067)**	**0.0007**	**<0.0001**
IPAQ work-related (hours/week) (sqrt)	-2.09 (0.56)	-1.72 (0.68)	2.49 (1.40)	0.0013	0.084
IPAQ transport-related (hours/day) (sqrt)	-2.11 (0.56)	-1.75 (0.68)	0.78 (1.45)	0.0011	0.59
IPAQ household-related (hours/day) (sqrt)	-2.11 (0.56)	-1.74 (0.68)	1.00 (1.39)	0.0011	0.48
IPAQ leisure time-related (hours/day) (sqrt)	-2.13 (0.56)	-1.77 (0.68)	3.32 (1.75)	0.0010	0.066
IPAQ sitting time (hours/day) (sqrt)	-2.11 (0.56)	-1.74 (0.68)	-1.75 (1.53)	0.0011	0.26
Energy (METS-min) (sqrt)	-2.10 (0.56)	-1.74 (0.68)	0.045 (0.083)	0.0012	0.59
GDS	**-2.12 (0.56)**	**-1.72 (0.68)**	**-0.47 (0.14)**	**0.0011**	**0.0015**
Intra-operative ketamine (mg) (sqrt)	-2.10 (0.58)	-1.87 (0.71)	0.34 (0.27)	0.0015	0.20
IL6 baseline (pg/ml) (log)	-2.03 (0.63)	-1.55 (0.77)	-0.31 (0.46)	0.0080	0.50
IL6 increase until 24 hours (Yes vs. No)	-1.15 (0.71)	-1.38 (0.82)	1.47 (1.56)	0.16	0.35
HMGB1 baseline (pg/ml) (log)	-2.21 (0.62)	-1.77 (0.75)	0.13 (0.46)	0.0027	0.77
HMGB1 increase until 24 hours (Yes vs. No)	-1.32 (0.72)	-1.48 (0.86)	0.13 (1.76)	0.12	0.94

Table 2. Evolution of IL6 with respect to time and baseline parameters (N=38)

Variable	Estimate (SE) Time 6h vs. 0	Estimate (SE) Time 24h vs. 0h	Estimate (SE) parameter	P-value time	P-value parameter
Age (years)	**1.66 (0.22)**	**2.04 (0.24)**	**0.13 (0.041)**	**<0.0001**	**0.0044**
Gender (Male vs. Female)	1.67 (0.22)	2.06 (0.24)	0.75 (0.54)	<0.0001	0.18
BMI (kg/m²)	1.70 (0.23)	2.11 (0.25)	0.027 (0.049)	<0.0001	0.59
Education level (ordinal)	1.67 (0.22)	2.06 (0.24)	-0.27 (0.29)	<0.0001	0.35
Number of languages known (ordinal)	1.66 (0.22)	2.05 (0.24)	-0.027 (0.25)	<0.0001	0.95
Working (Yes vs. No)	1.67 (0.22)	2.06 (0.24)	-0.79 (0.63)	<0.0001	0.23
Marital status (Divorced vs Married)	1.66 (0.22)	2.05 (0.24)	0.19 (0.63)	<0.0001	0.60
Marital status (Widow vs. Married)			-0.85 (0.95)		
Self-sufficient (Yes vs. No)	1.66 (0.22)	2.05 (0.24)	-0.53 (1.10)	<0.0001	0.63
Living situation (Number of people)	1.66 (0.22)	2.05 (0.24)	0.038 (0.42)	<0.0001	0.93
Number of alcoholic drinks/week (sqrt)	1.67 (0.22)	2.06 (0.24)	-0.078 (0.22)	<0.0001	0.72
Smoking Status (Current vs. no)	1.66 (0.22)	2.05 (0.24)	-0.45 (0.63)	<0.0001	0.58
Smoking Status (Ex vs. no)			-0.73 (0.71)		
Surgery (Orthopedic vs. General)	**1.66 (0.36)**	**2.82 (0.34)**	**xT0: 0.17 (0.73)**	**<0.0001**	**t x surgery : 0.031**
			xT6: 0.25 (0.75)		
			xT24: -1.22 (0.78)		
Surgery (Genitourinary vs. General)			**xT0: -0.56 (0.68)**		
			xT6: -0.59 (0.68)		
			xT24: -1.97 (0.70)		
Number of psychoactive meds (sqrt)	**1.68 (0.22)**	**2.08 (0.24)**	**-1.25 (0.59)**	**<0.0001**	**0.041**
Type 2 Diabetes (Yes vs. No)	1.67 (0.22)	2.05 (0.24)	0.79 (0.64)	<0.0001	0.22
MMSE baseline (/30)	1.66 (0.22)	2.05 (0.24)	0.029 (0.074)	<0.0001	0.70
IPAQ work-related (hours/week) (sqrt)	**1.68 (0.22)**	**2.06 (0.24)**	**-1.55 (0.65)**	**<0.0001**	**0.024**
IPAQ transport-related (hours/day) (sqrt)	1.66 (0.22)	2.05 (0.24)	-0.36 (0.63)	<0.0001	0.57
IPAQ household-related (hours/day) (sqrt)	1.67 (0.22)	2.06 (0.24)	-0.30 (0.53)	<0.0001	0.57
IPAQ leisure time-related (hours/day) (sqrt)	1.67 (0.22)	2.06 (0.24)	-0.86 (0.66)	<0.0001	0.21
IPAQ sitting time (hours/day) (sqrt)	1.66 (0.22)	2.05 (0.24)	0.058 (0.62)	<0.0001	0.93
Energy (METS-min) (sqrt)	1.66 (0.22)	2.05 (0.24)	-0.012 (0.032)	<0.0001	0.71
GDS	1.66 (0.22)	2.05 (0.24)	0.039 (0.062)	<0.0001	0.54
Intra-operative ketamine (mg) (sqrt)	1.69 (0.23)	2.10 (0.25)	0.029 (0.10)	<0.0001	0.78
IL6 baseline (pg/ml) (log)	**1.63 (0.22)**	**2.00 (0.24)**	**0.86 (0.084)**	**<0.0001**	**<0.0001**
HMGB1 baseline (pg/ml) (log)	1.67 (0.22)	2.05 (0.24)	0.097 (0.18)	<0.0001	0.59

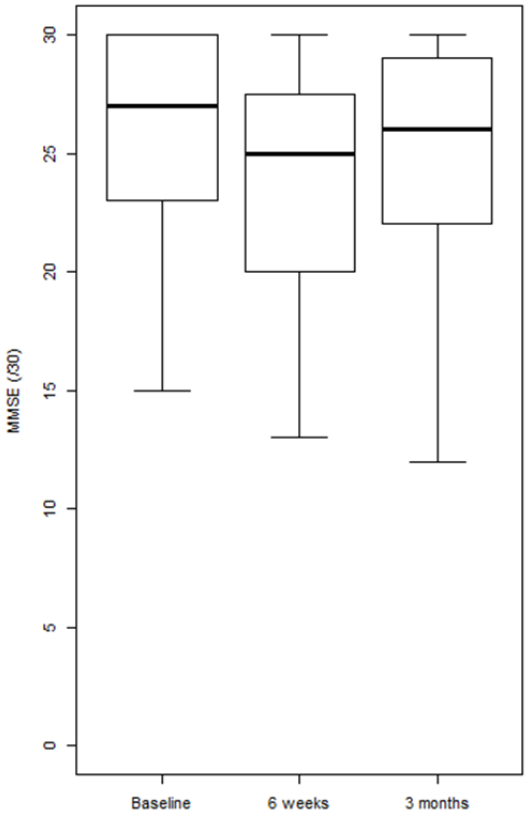

Figure 1: Evolution of MMSE

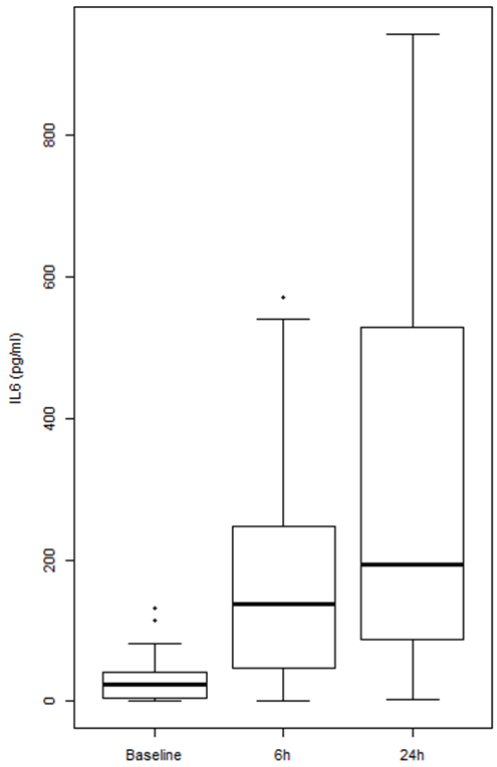

Figure 2 : Evolution of IL-6

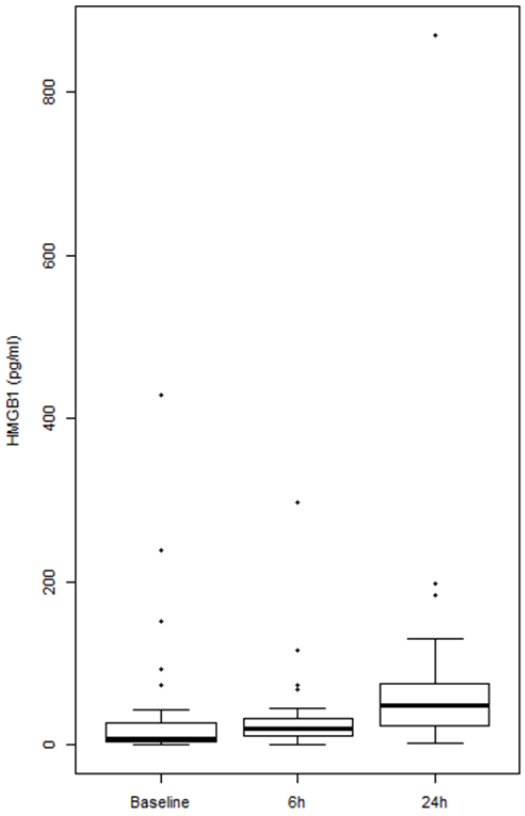

Figure 3: Evolution of HMGB1

Perioperative Anesthesia-12 Epidemiology of Opioid-Related Disorders in Critically Ill Pediatric Patients in US Children's Hospitals, 2010-2017

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Introduction: Recent data have demonstrated growing rates of ingestion-related hospitalizations and admissions to the pediatric intensive care unit (PICU)1-2. Other than the risks associated with opioid poisoning and neonatal opioid withdrawal syndrome, the impact of the opioid epidemic on the pediatric patient population has not been well studied. Very little is known about the prevalence of other opioid-related disorders (ORDs) in critically ill, hospitalized pediatric patients. We sought to examine the epidemiology of ORDs in the PICU population and describe patient characteristics in this cohort.

Methods: We performed a retrospective analysis of the Pediatric Health Information System database (38 tertiary US children's hospitals) from discharge years 2010-2017 for patients ≤20 years in the PICU, excluding neonates. The ORD group was defined using ICD-9/10-CM codes for ORDs based on a prior publication3 and classified into sub-categories: opioid dependence and withdrawal (OD/W), opioid abuse, opioid use, adverse effects of opioids, opioid ingestion, and not otherwise specified (DX NOS). We examined patient characteristics by various subgroups including age (infants and toddlers <2 years, children 2-11 years, adolescents 12-20 years as recommended by the American Academy of Pediatrics), race or ethnicity (Non-Hispanic African American/Asian/Caucasian, Hispanic, or other), and hospital census region (midwest, northeast, south, or west as defined by the US Census Bureau). Descriptive statistics were summarized with frequencies and percentages. The Cochran-Armitage test for trend was used to assess changes in rate over time.

Results: A total of 488,855 patients of 633,404 PICU discharges were included in the analysis, and 1.5% was in the ORD group (n=7,241). OD/W accounted for 47.4% of ORDs followed by ingestion (22.5%) (Table 1). 16.1% did not have an ORD on admission, suggesting iatrogenic etiology. While opioid ingestion rates decreased from 4.0 to 2.4 per 1,000 PICU patients from 2010 to 2017 (p for trend, <0.001), rates of OD/W doubled from 5.4 to 10.9 per 1,000 PICU patients (p for trend, <0.001) (Figure 1). Presumed iatrogenic ORD rates also increased from 0.7 to 4.6 per 1,000 PICU patients (p for trend, <0.001). ORDs occurred most frequently in adolescents (45.2%) except for OD/W, which were mostly diagnosed in <2 year olds (64.5%) (Table 2). 37.7% (184,129 patients of 248,945 PICU discharges) of the overall cohort were under age 2 years, and 1.7% was in the ORD group (n=3,245). 32.6% of the ORD group were post-op surgical patients. ORDs occurred most frequently in the southern census hospital region (40.3%) and Caucasian Non-Hispanic population (55.0%) (Table 3).

Conclusion: Although opioid ingestion rates declined from 2010 to 2017, OD/W rates doubled and iatrogenic ORD rates increased more than 5-fold in this large multicenter study. OD/W occurred most frequently in patients under age 2 years, and approximately one third of patients with ORDs were post-op surgical patients. More research is needed to elucidate risk factors and outcomes of critically ill pediatric patients with ORDs, particularly those of iatrogenic origin.

Reference(s):

1. National trends in hospitalizations for opioid poisonings among children and adolescents, 1997 to 2012. JAMA Pediatr. 2016;170(12):1195-1201.

2. Opioid-Related Critical Care Resource Use in US Children's Hospitals. Pediatrics. 2018;141(4):e20173335.

3. Trends in Opioid-Related Inpatient Stays Shifted After the US Transitioned to ICD-10-CM Diagnosis Coding in 2015. Med Care. 2017 Nov;55(11):918-23.

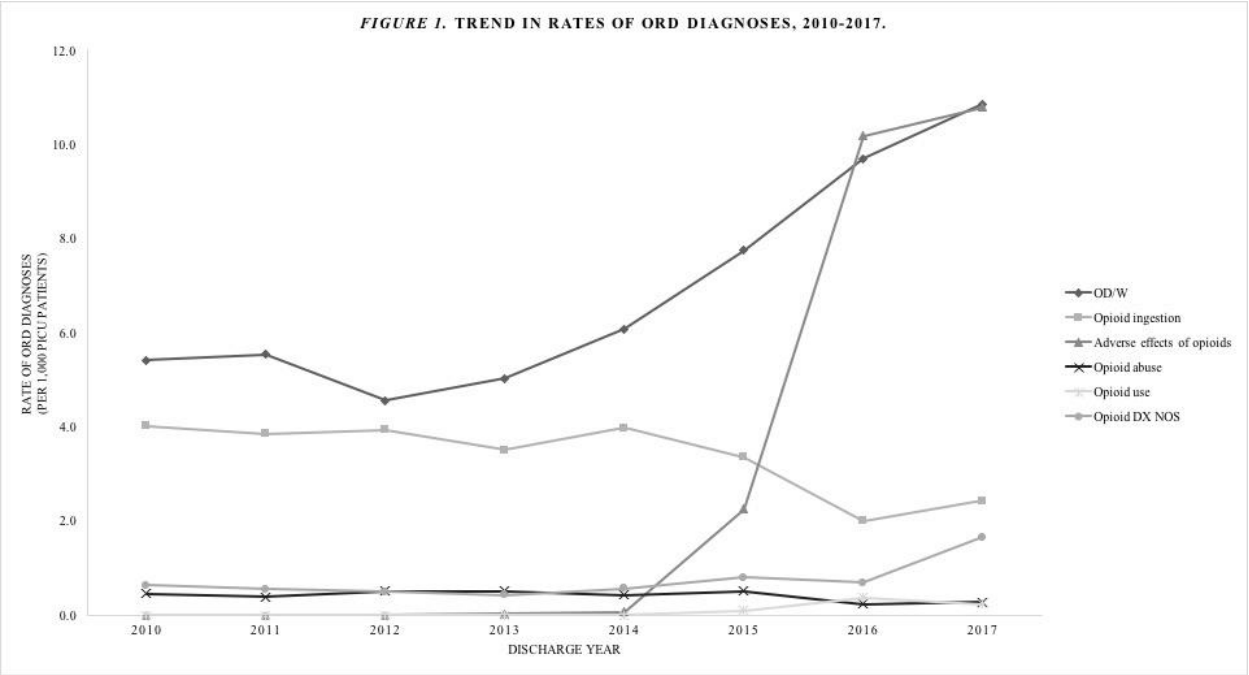

Table 1. **Overall Distribution of ORDs in the PICU Population, 2010-2017.**		
	n	%
OD/W	3,432	47.4
Opioid ingestion	1,630	22.5
Adverse effects of opioids	1,569	21.7
Opioid DX NOS	365	5.0
Opioid abuse	199	2.7
Opioid use	46	0.6
	7,241	*100.0*

***Table 2*. Distribution of ORD Groups by Age.**			
		n	%
Adverse effects of opioids	<2 years	342	21.8
	2-11 years	561	35.8
	12-20 years	666	42.4
		1,569	*21.7*
Opioid abuse	<2 years	3	1.5
	2-11 years	1	0.5
	12-20 years	195	98.0
		199	*2.7*
OD/W	<2 years	2,213	64.5
	2-11 years	781	22.8
	12-20 years	438	12.8
		3,432	*47.4*
Opioid DX NOS	<2 years	167	45.8
	2-11 years	122	33.4
	12-20 years	76	20.8
		365	*5.0*
Opioid ingestion	<2 years	508	31.2
	2-11 years	361	22.1
	12-20 years	761	46.7
		1,630	*22.5*
Opioid use	<2 years	12	26.1
	2-11 years	9	19.6
	12-20 years	25	54.3
		46	*0.6*

Table 3. **Distribution of Race or Ethnicity by Hospital Census Region in the ORD Cohort.**			
		n	%
Midwest	African American Non-Hispanic	262	15.5
	Asian Non-Hispanic	46	2.7
	Caucasian Non-Hispanic	1,117	66.1
	Hispanic	131	7.7
	Other	135	8.0
		1,691	*23.4*
Northeast	African American Non-Hispanic	210	17.4
	Asian Non-Hispanic	28	2.3
	Caucasian Non-Hispanic	683	56.5
	Hispanic	109	9.0
	Other	178	14.7
		1,208	*16.7*
South	African American Non-Hispanic	624	21.4
	Asian Non-Hispanic	36	1.2
	Caucasian Non-Hispanic	1,517	52.0
	Hispanic	508	17.4
	Other	234	8.0
		2,919	*40.3*
West	African American Non-Hispanic	88	6.2
	Asian Non-Hispanic	80	5.6
	Caucasian Non-Hispanic	667	46.9
	Hispanic	466	32.7
	Other	122	8.6
		1,423	*19.7*

Perioperative Anesthesia-13 Adjusted Composite Morbidity/Mortality Rate Stratified by Anesthesiology Attending Staffing Ratio

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Introduction: In the United States, anesthesia services may be delivered in one of two systems: a single attending anesthesiologist in a procedural room or a care team model where one attending anesthesiologist supervises a nurse anesthetist, anesthesia assistant, or anesthesiology resident in two or more operating rooms concurrently. The ratio of anesthesiologist to the number of rooms covered is known as their staffing ratio. While much of the current anesthesia service staffing research has focused on provider type (independent nurse anesthetist versus anesthesiologist), little attention has been paid to evaluating the impact of varying staffing ratios of anesthesiologists across multiple operating rooms. With one exception [1], the current literature suggests no difference in quality based on anesthesia provider type [1–6]. There are presumed benefits of lower staffing costs, but limited research into investigating potential risks patients face with increasing anesthesiologist responsibility. We hypothesized that increasing the number of rooms an anesthesiologist oversees is associated with an increased risk of morbidity and mortality for patients under their care.

Methods: Data was obtained from the Multicenter Perioperative Outcomes Group database, a comprehensive perioperative patient registry based on electronic healthcare data from over 50 hospitals. Operative cases were selected for patients greater than two years of age who underwent surgery between 1/1/2010 and 10/31/2017. Cardiac, liver transplant, cataract, organ procurement, and labor epidural procedures were excluded. Anesthesiologist sign in/out times are recorded accurately due to compliance and reimbursement impact. Cases with inappropriate data, including irreconcilable concurrencies, were excluded from analysis. Exposure measure (TWA): Sign in/out times between anesthesia start and end were used to calculate a single staffing ratio for each operative case, using the time-weighted average (TWA) of the individual staffing ratios and reported as a continuous variable. TWA was categorized into 4 levels used in our regression models: 1, 1<TWA<=2, 2<TWA<=3 and 3<TWA<=4. Primary Outcome: A composite of in-hospital mortality and six major morbidities, composed of cardiac, respiratory, gastrointestinal, urinary, bleeding, and infection groupings based on the U.S. Agency for Healthcare Research and Quality's Clinical Classifications Software categories for International Classification of Diseases. Statistical Analysis: Propensity score matching methods were applied to create a balanced sample with respect to patient, procedure, and hospital level confounders. We implemented a sequential modeling approach using logistic regression where propensity scores were estimated for two TWA levels at a time, using 1<TWA<=2 as the reference group. Cases were matched based on estimates of the propensity scores for groups 1 vs. 2; 2 vs. 3 and 2 vs. 4. After matching, we assessed the association between TWA staffing ratio and the collapsed composite primary outcome using a multivariable conditional logistic regression modeling.

Results: This study analyzed matched samples consisting of 607,380 patients across 23 institutions. Propensity score matching resulted in a cohort with absolute standardized differences < 0.10 across all comparisons for six covariates: gender, ASA status, number of Elixhauser comorbidities, general anesthesia, neuraxial/regional anesthesia technique, and emergency surgery. The propensity model also accounted for institution. Covariates with SD ≥ 0.10 such as age, BMI, anesthesia CPT group, surgical service category, and anesthesia duration were included in the multivariable model as potential confounders. We observed an incremental increase in the adjusted composite morbidity/mortality rate with increasing TWA staffing ratio group. Going from a staffing ratio between 1<TWA≤2 to 3<TWA≤4 the rate increased from 5.18% to 5.85% (adjusted odds ratio 1.136 [95% CI 1.081 - 1.195], p-value <0.0001), representing a relative 12.9% increase in risk. A step-like increase is observed in adjusted odds ratio, as comparison of 2<TWA≤3 to 3<TWA≤4 was 1.082 (95% CI 1.028 - 1.140).

Conclusion: After controlling for observed patient and procedure factors, we observed a 13% increase in relative risk associated with attending anesthesiologist staffing ratio going from 1<TWA≤2 to 3<TWA≤4. These data quantify a potential patient and safety risk associated with increasing staffing ratio.

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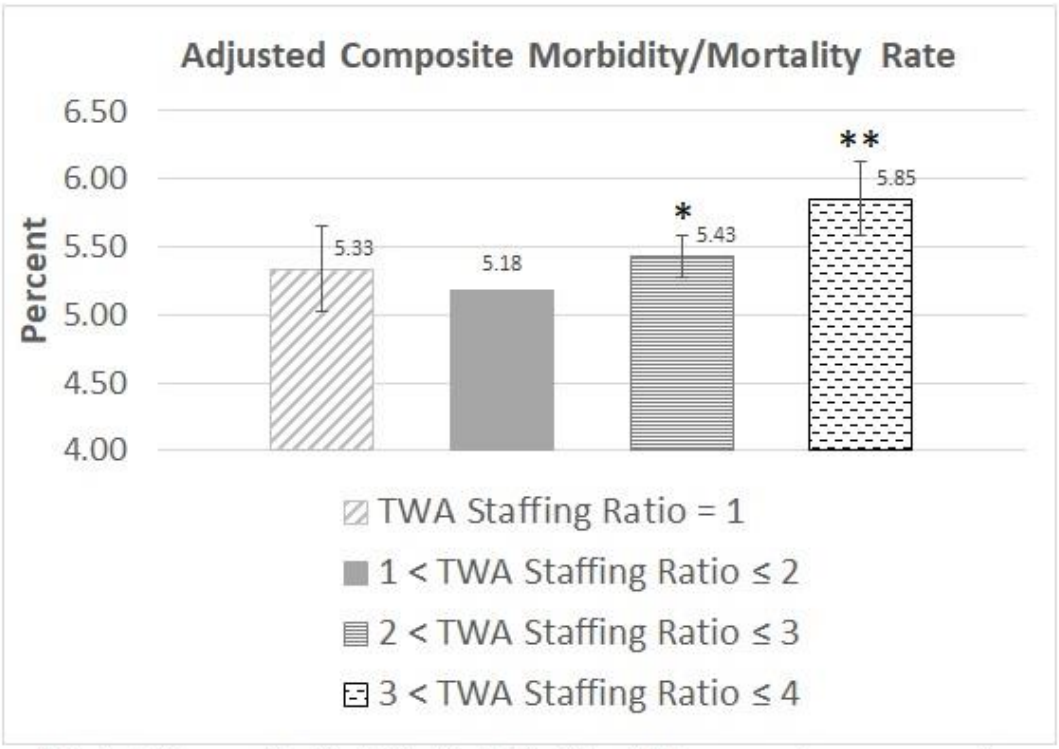

Figure: Adjusted Composite Morbidity/Mortality Rate. Values are shown composite morbidity/mortality percentage for four time-weighted average (TWA) staffing ratio groups (TWA=1, 1<TWA<=2, 2<TWA<=3, 3<TWA<=4). Data is labeled for p-values 0.001<p<0.05 (*) and p<0.001 (**).

Perioperative Anesthesia-14 COMPARISON OF THROMBOELASTOGRAPHY WITH CONVENTIONAL COAGULATION TESTS TO EVALUATE THE HAEMOSTATIC PROFILE OF PATIENTS WITH PRIMARY BRAIN TUMOUR UNDERGOING SURGERY

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Introduction: Brain cancer accounts for approximately 1.4% of all cancers and 2.3% of all cancer related deaths(1). Hemostasis is a complex dynamic process involving bleeding and thrombosis as two extreme ends. Traditional plasma-based coagulation assays, provide little information about the dynamics of the clot formation or the quality of clot. Thrombolastography measures viscoelastic changes of the entire clotting process. This study was undertaken to compare thromboelastography with conventional coagulation"¬ tests(PT, aPTT, INR) to evaluate the trends in haemostatic profile and identify specific patterns in coagulation abnormalities if any, of patients "¬with primary brain tumour undergoing surgery."¬

Methods: We designed a prospective observational study in patients with primary brain tumors, undergoing craniotomy for surgical management of the same. Informed written consent was obtained from all the patients enrolled in the study. Forty patients were enrolled from the elective neurosurgical operation list with the diagnosis of supratentorial primary brain tumor. All the patients belonged to American Society of Anesthesiologists (ASA) Physical Status grades I, II& III. All the patients had a Glasgow Coma Scale (GCS) of E4V5M6. A standard anaesthesia regime was followed for all the patients. Samples for thromboelastography (TEG) and conventional tests were taken in the preoperative period, then after removal of tumor, and start of hemostasis and on the first postoperative day. SPSS V.21 statistical package was used.Mean, Mode, Median and Paired t test, Chi square test were done with a $p<0.05$ was taken as statistically significant.

Results: Inclusion criteria included all newly diagnosed patients with primary brain tumours larger than 4 cm in maximum diameter on CT or MRI. Exclusion criteria were patients with a history of haematological or coagulation disorders, those taking anticoagulant therapy, and those with chronic disease-for example, liver cirrhosis or renal failure will be excluded.All 40 patients enrolled in our study had supratentorial brain tumor, of which 22 were glioma and 18 were meningioma. Out of these 40 patients, 20 were male and 20 were female. All the patients were demographically statistically similar. The baseline parameters of all the patients were within normal range and they remained hemodynamically stable through out perioperative period. Intraoperative bleeding was calculated to be 737.7 (±185.6) ml. PRBC were transfused in 17 patients, FFP in 13 but no platelet transfusion was done. In our study we found that there was a universal trend towards hypercoagulability (Persistent decrease in R & K values and Persistent increase in MA &α Angle) in all the TEG parameters measured intraoperatively and post operatively. The conventional tests remained within normal limit except for a slight prolongation in PT, INR and aPTT value intra operatively.

Conclusion: Brain tumors are prone to develop hypercoagulability and are at risk for thromboembolic complications. Thromboelastography maybe useful in identifying these abnormalities. Further evaluation of the role of Thromboelastography in identifying those patients who will be at risk to develop thromboembolic complications can improve our perioperative management of patients with brain tumors.

Reference(s): Ann Card Anaesth. 2018;21:151-157. J Adv Res Med 2018;5: 32-35.

Perioperative Anesthesia-15 Use of BIS in Memory Recall and Recognition

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Introduction: The Bispectral Index Monitor (BIS Medtronic-Covidien, Dublin, Ireland) was developed to monitor the depth of anesthesia and reduce incidence of intraoperative awareness, which studies have shown correlates with the development of posttraumatic stress disorder (PTSD). This study focuses on delineating what BIS readings mean in the context of perioperative memory formation-and subsequent memory retrieval- and the impact BIS monitoring may have on reducing negative sequelae associated with intraoperative awareness.

Methods: Following Institutional Review Board approval, 363 patients undergoing general anesthesia were approached in the pre-op area and provided consent. A total of six words were administered in the preoperative state for later recall and timed with the administration of a physician-determined dosage of midazolam. Words 1, 2, and 3 were given 5 minutes, 3 minutes, and 1 minute prior to the administration; word 4 was given during the administration, and words 5 and 6 were given 1 minute and 3 minutes after the administration of midazolam respectively. At each time point, the patient's BIS score was recorded. Immediately after the operation, patients were approached in the post-op area and asked to recall the six preoperative words given to them. BIS scores for each word were then correlated with the successful or unsuccessful recall of the associated word. Within 24 hours after the procedure, patients were contacted and asked to recall the words given to them and were asked to open an envelope containing 6 study words and 18 other words and identify any words that they had missed. Any word that was only remembered after looking at the list was considered a successful recognition of the word but not a successful recall.

Results: Figure 1 shows rate of recall and recognition by BIS score, stratified into six groups by BIS score. Higher BIS scores correlated with both higher rates of recall and recognition of a word at 24 hours. Rates of recognition were consistently higher than rates of recall among every stratified BIS score group.

Conclusion: By examining the relationship between recall and recognition, we were able to demonstrate consistently higher levels of 24 hour word recognition when compared to word recall. This demonstrates that while some patients may not endorse overt recall of perioperative events, memories of such events can still be triggered with prompting. These findings may help further elucidate the connection between intraoperative awareness events and development of subsequent PTSD due to latent memories.

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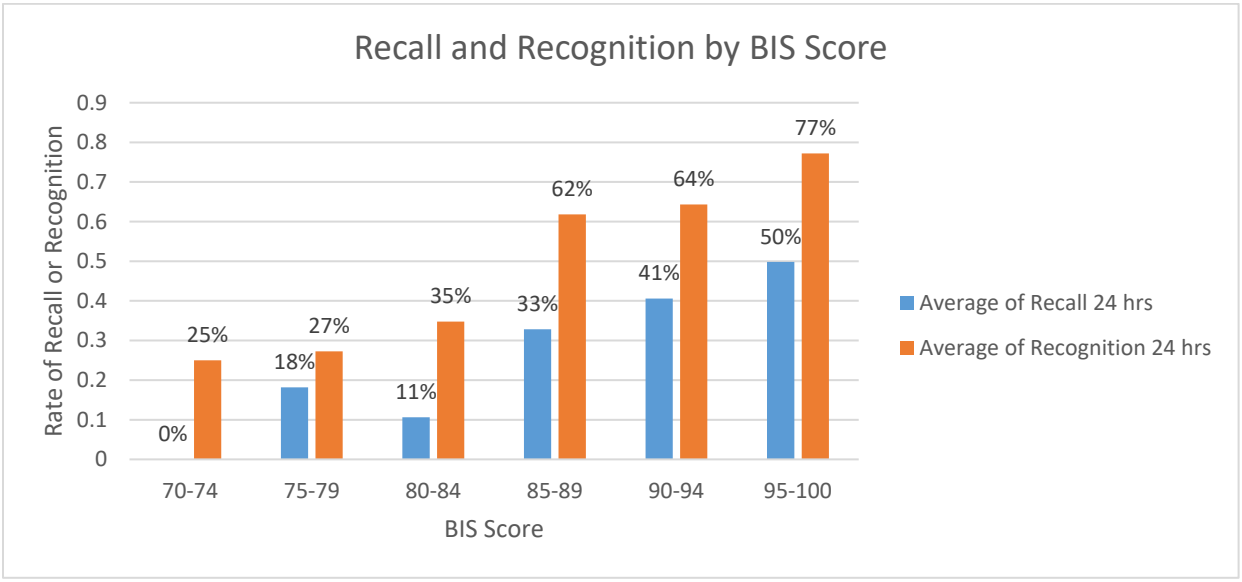
Recall and Recognition by BIS Score
Rate of Recall or Recognition
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0%
25%
18%
27%
11%
35%
33%
62%
41%
64%
50%
77%
70-74
75-79
80-84
85-89
90-94
95-100
BIS Score
Average of Recall 24 hrs
Average of Recognition 24 hrs

Perioperative Anesthesia-16 OSNAP: Prospective randomized investigation to enhance recovery after shoulder arthroplasty

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Introduction: Sleep deprivation is associated with significant adverse effects on bone metabolism, bone mass, and recovery from post-surgical pain. We hypothesize that a multimodal sleep pathway, including non-pharmacological sleep hygiene interventions and the use of zolpidem and melatonin, can improve patient sleep and analgesia after undergoing total shoulder arthroplasty.

Methods: We performed a prospective randomized control study in which anatomic and reverse total shoulder arthroplasty patients were treated with or without an interventional sleep pathway (Orthopedic Sleep and Novel Analgesia Pathway [OSNAP]). All patients underwent a standardized multimodal analgesia protocol with a interscalene nerve block and scheduled acetaminophen, naproxen, gabapentin, and opioids as needed for breakthrough pain (Table 1). OSNAP included nursing directed non-pharmacological measures to promote sleep hygiene and pharmacological interventions with melatonin and zolpidem (Table 2).

Results: 124 patients were enrolled (63 control, 61 interventional) with similar demographics. The interventional OSNAP group had a trend towards lower pain scores compared to the control group (Postoperative Day 0: 2.6 ± 1.83 vs. 3.24 ± 3.02, Day 1: 4.04 ± 2.25 vs. 4.55 ± 2.24). The OSNAP group experienced significantly longer sleep periods based on wrist worn actigraphy (total time in bed [9.31 ± 1.74 vs. 8.2 ± 2.1 hours] and total sleep time [6.88 ± 1.88 vs. 5.59 ± 2.07 hours]), improved sleep quality on the Leeds Sleep Evaluation Questionnaire (LSEQ, 50.29 ± 19.72 vs 39.11 ± 30.63), and higher satisfaction with the inpatient management of pain (82% vs. 73%) and sleep (75% vs. 67%). There was no difference in perioperative complications or length of stay.

Conclusion: In the setting of a modern regional anesthesia and multimodal analgesia recovery plan for total shoulder arthroplasty, the use of an inpatient sleep pathway appears to be safe and associated with benefits of a potentially improved analgesia, extended sleep periods, improved patient reported sleep quality, and higher patient satisfaction.

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Table 1: Multimodal Analgesia Pathway	
Preoperative Analgesia	• Celecoxib 400mg oral • Gabapentin 600mg oral • Acetaminophen oral/intravenous 1000mg • Single-shot interscalene block with 15-20 mL of 0.5% ropivacaine prior to surgery
Postoperative Analgesia	• Naproxen 500mg oral every 12 hours • Gabapentin 300mg oral every 8 hours • Acetaminophen 1000mg oral/intravenous every 8 hours
	• Oxycodone 5-10mg oral every 4 hours as needed for moderate pain • Hydromorphone 0.2-1mg intravenous every 2 hours for severe break through pain

Table 2: Orthopaedic Sleep and Novel Analgesia Pathway (OS-NAP)	
Nursing directed measures (non-pharmacological interventions) to optimize daytime activities, minimize daytime sleep, minimize delirium risk, and improve sleep duration and hygiene.	Encourage fluids/oral intake Fluids within reach of patient at all times
	Activity and sensory devices: • Walker/commode to bedside • Hearing aids, glasses, and dentures to bedside • Use Pocket Talker at all times when communicating with patients who are hard of hearing
	Daytime: • Open blinds and turn on lights • Prevent/minimize daytime napping • No caffeine after 1200 • Turn off TV when not in use
	Nighttime: • Close blinds and turn off lights • Earplugs, turn off TV • Avoid vitals between hours of 2200 and 0600; exception to current vitals order
	Encourage family to bring in familiar objects from home, visit during daytime hours, discuss current events and reminisce with patient
	Up to chair for all meals Ambulate in halls Provide patient with therapeutic activities as appropriate for cognitive state
Pharmacological treatments to reduce sleep latency and improve sleep cycle	• Zolpidem 5mg at night 2100 • Melatonin 3mg at night 2100
Preoperative Analgesia	• Celecoxib 400mg oral • Gabapentin 600mg oral • Acetaminophen oral/intravenous 1000mg • Single-shot interscalene block with 15-20 mL of 0.5% ropivacaine prior to surgery
Postoperative Analgesia	• Naproxen 500mg oral every 12 hours • Gabapentin 300mg oral every 8 hours • Acetaminophen 1000mg oral/intravenous every 8 hours • Oxycodone 5-10mg oral every 4 hours as needed for moderate pain • Hydromorphone 0.2-1mg intravenous every 2 hours for severe break through pain
Safety measures:	Continuous pulse oximetry overnight to monitor respiratory status
	Nasal cannula oxygen as needed to maintain O2 saturation at night

Perioperative Anesthesia-17 Evaluating the Utilization of Single-Use Bair Paws Gown for Perioperative Warming: A Case Study

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Introduction: Inadvertent perioperative hypothermia affects 25~ 90% of the patients. The American Society of Anesthesiologists practice guidelines recommend temperature monitoring and maintaining normothermia during surgery to improve surgical outcomes in wound healing, infection rate reduction, and adverse cardiac events prevention. Bair Paws gown is a single-use forced-air warming system that intends to provide comfort to patients and maintain normothermia in the perioperative period.

Methods: This observational study evaluated the effective utilization of the single-use Bair Paws gown across three time periods: preoperative, intraoperative and postanesthesia care unit (PACU) at two tertiary medical centers in our healthcare system. 676 and 144 surgical cases were observed at the two different hospital sites. Each patient was given a Bair Paws gown in the preoperative area and was transported to the operating rooms with the same warming gown.

Results: Among the 820 cases observed, only 3-13% of the cases actually utilized the Bair Paws system for preoperative warming and only 21-33% of the cases used Bair Paws gown for intraoperative warming. Additional single-use Bair Hugger blankets were used for intraoperative warming instead of Bair Paw gowns, which were discarded unused in the operating rooms. The limitations of Bair Paws gown that were observed include uncomfortable designs reported by patients and inflexible manipulation for the prone position as well as chest/thoracic surgeries during intraoperative warming.

Conclusion: The data of gross underutilization from the observations prompted us to rethink the effectiveness of Bair Paws gown as a mean to achieve normothermia in the perioperative setting. With the rising healthcare costs and the operating rooms' significant contribution to landfill waste and carbon footprint, we should continue to analyze our use of single-use devices. This study indicates a suboptimal use of Bair Paws further contributes to landfill waste, carbon footprint, and increase our healthcare cost. Therefore, the value of the Bair Paws for perioperative warming deserved to be reviewed with further scrutiny, and more effective alternatives need to be explored.

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	Hospital 1	Hospital 2
Preoperative Warming	3.0% (20/676)	12.5% (18/144)
Intraoperative Warming	21.3% (144/676)	33.3% (48/144)

Table 1. Bair Paws gowns utilization (warming unit turned on) in the perioperative setting at two tertiary hospital sites.

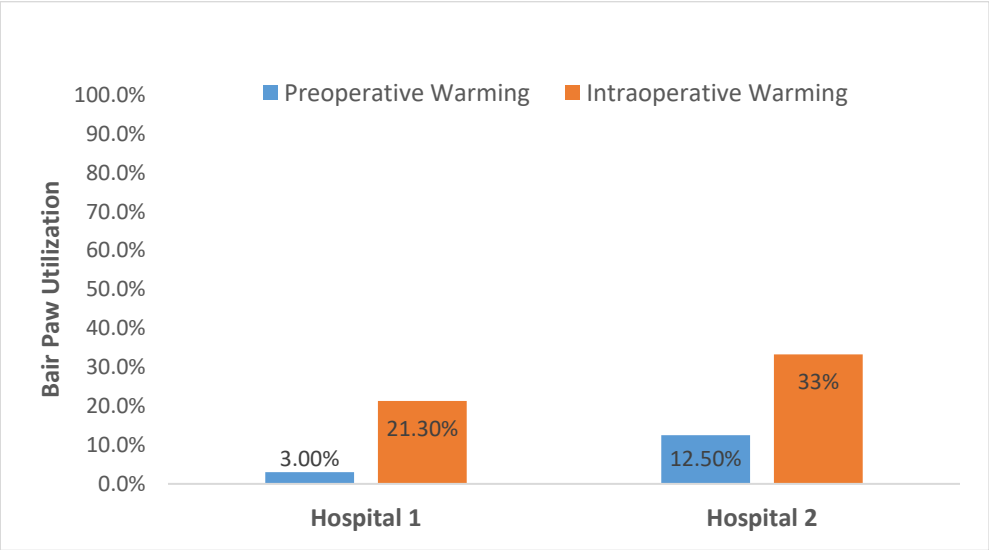

Figure 1. Bair Paws gowns utilization (warming unit turned on) in the perioperative setting at two tertiary hospital sites.

Perioperative Anesthesia-18 Multimodal Analgesia and Opioid Prescribing Patterns at Discharge for Opioid Naive Surgical Patients

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Introduction: The use of multimodal analgesic approaches for the management of acute post-operative pain has proven effective in reducing inpatient opioid requirements. However, it remains unclear if inpatient use of multimodal analgesia is associated with decreased day of discharge prescribing of opioid pain medications. We sought to understand whether the pre-discharge pain regimen, which includes opioids and non-opioids, was associated with discharge prescribing practices of opioid pain medications in surgical patients.

Methods: This was a retrospective analysis of the electronic medical record system at a single academic institution between June 2012 and December 2018. We studied adult patients (18+ years) who were opioid naïve and underwent surgery requiring an inpatient stay of at least 24 hours after surgery. We calculated the total opioids administered in oral morphine equivalents (OME) within the 24 hours prior to discharge and the total daily OME prescribed on the discharge opioid prescription. Multimodal analgesia was defined as the use of acetaminophen, NSAIDs, gabapentinoids, or neuraxial/peripheral nerve blocks with active infusions in the 24 hours prior to discharge. We defined high-dose opioid prescribing as receipt of >90 daily OME on the discharge prescription. We compared total daily OMEs consumed in the 24H prior to discharge to total daily OMEs on the discharge prescription and identified risk factors for high-dose prescribing practices (> 90 daily OME). We also investigated whether multimodal analgesia use in the 24H prior to discharge was associated with a reduction in high-dose discharge opioid prescriptions. Means, medians and interquartile ranges were used to visualize annual trends. An adjusted odds ratio was performed to identify factors for receiving a discharge opioid prescription > 90 daily OME. For categorical values we chose the following reference values: female, white, 2018, length of stay < 3 days, general surgery.

Results: 32,511 patients met inclusion criteria. Mean age was 55, 52% were female, and the mean length of stay was 3.4 days. 83 %of patients were discharged with an opioid prescription. The median OME administered in the 24 hours prior to discharge started at 31 OME (IQR 7.5, 71.5) in 2013 and steadily decreased to 19.8 OME by 2018 (IQR 0, 52.5). Median daily OME on the discharge prescription was 90 OME during 2014-2017, but decreased to 60 OME in 2018. In 2013, 34.1% of patients with a discharge opioid prescription received a total daily dose > 90 OME; this percentage declined to 17.7% by 2018. Use of multimodal analgesic agents during the final 24 hours of hospitalization peaked in 2018 with 80.3%, 27.1% and 34.1% receiving an acetaminophen, an NSAID, or a gabapentinoid, respectively. Of the 8,052 patients who did not require any opioids and did not have an active neuraxial or peripheral nerve catheter infusion in the 24 hours prior to hospital discharge, 58.7% were prescribed opioids at hospital discharge. Median daily OME on the discharge prescription was 30 OME (IQR 0, 80) and 10% of these patients received a discharge prescription exceeding 90 daily OME. The surgical services for which the patients had the highest odds of receiving a high-dose discharge opioid prescription were orthopedics [(AOR), 4.662; 95% CI, 4.138-5.252] and thoracic surgery [AOR, 3.122; 95% CI, 2.450-3.978]. Other significant predictors that increased the odds of receiving a high-dose prescription were male sex [adjusted odds ratio (AOR) 1.132; 95% CI 1.060-1.209], length of hospital stay over 6 days [AOR 2.158; 95% CI 1.968-2.366]), and a history of anxiety [AOR 2.626; 95% CI 1.415-4.868]. Black and Asian patients were less likely to receive a high-dose prescriptions compared to White patients (AOR 0.782; 95% CI 0.675-0.907 and AOR 0.837; 95% CI 0.754-0.928, respectively]. There was no difference in high-dose opioid discharge prescriptions (>90 daily OME) in patients who received neuraxial or peripheral nerve catheters, acetaminophen, gabapentinoids, or NSAIDs in the 24 hours prior to discharge compared to patients who did not receive multimodal analgesia.

Conclusion: High-risk opioid discharge prescribing persists in surgical patients, even among patients who did not require any opioids in the 24 hours prior to discharge. Use of multimodal analgesia during the hospital admission did not decrease the odds of receiving a high-dose opioid prescription at discharge.

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Perioperative Anesthesia-19 HDL-microRNAs are associated with acute kidney injury after cardiac surgery

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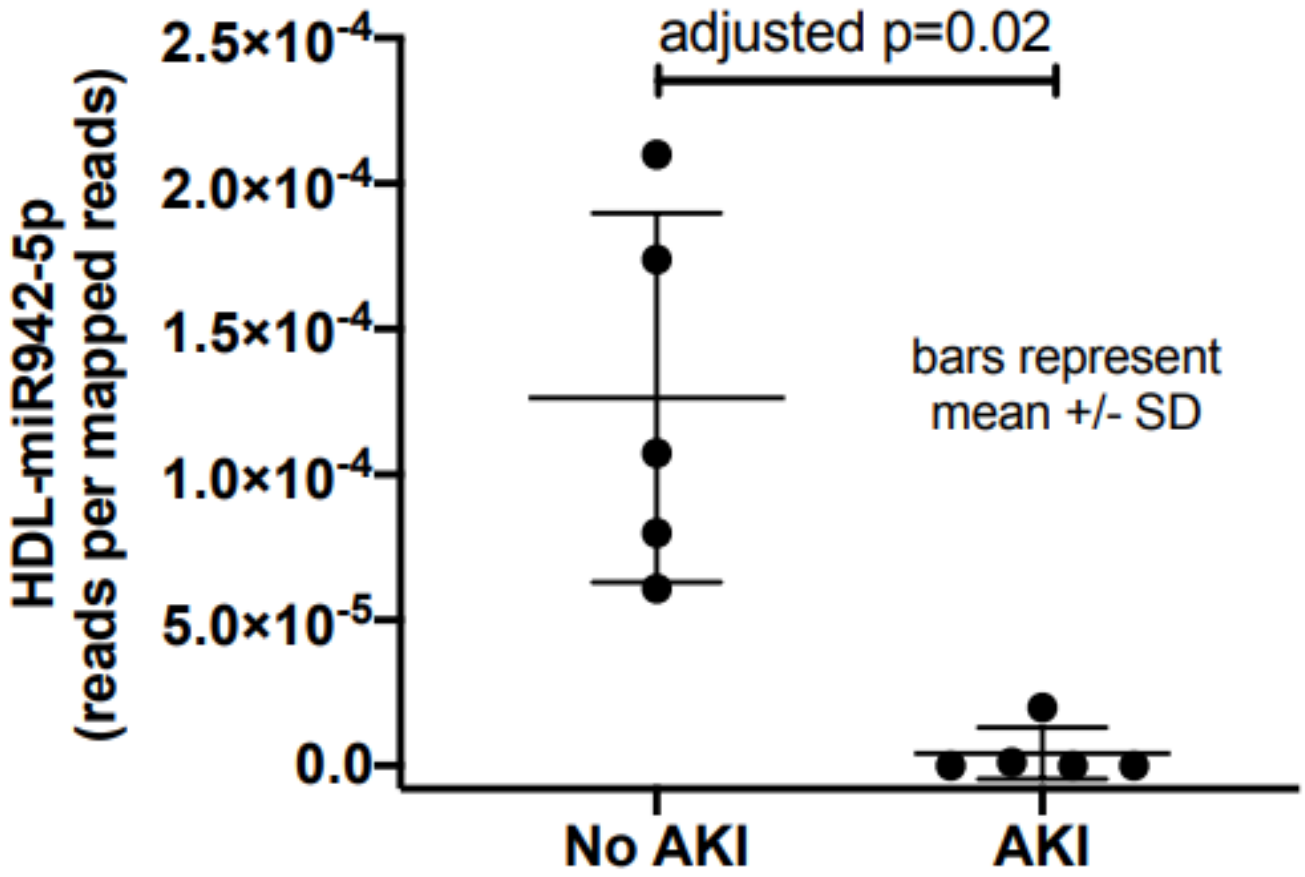
Introduction: Acute kidney injury (AKI) after cardiac surgery occurs in 25% of patients and independently predicts death. Higher preoperative high-density lipoprotein (HDL) concentrations are associated with less AKI after cardiac surgery. HDL can transport and deliver microRNAs (miRNAs) to cells expressing the SR-B1 receptor including macrophage, endothelial, and renal proximal tubule cells. miRNAs bind mRNA transcripts, inhibit translation, and alter cellular function. We tested the hypothesis that specific HDL-miRNAs are associated with less AKI after cardiac surgery.

Methods: We isolated, sequenced, and quantified the miRNAs present on HDL five cardiac surgery patients who developed KDIGO AKI and five patients who did not. AKI and non-AKI patients were matched on baseline eGFR, the Thakar score for predicting dialysis following cardiac surgery, and duration of cardiopulmonary bypass. We used commercial isolation kits, RT-PCR, and the NextSeq500 high-throughput sequencing system. miRNAs were identified in plasma and HDL samples collected prior to surgery and on postoperative day 1. High quality unique reads were mapped to the human genome using Bowtie1, allowing for 1 mismatch and the miRNA database miRBase22.1. Mann-Whitney-U tests were used to compare miRNAs differentially carried on the HDL of patients who did and did not develop AKI. A Bonferroni correction was used to account for error inflation due to multiple comparisons.

Results: HDL-miRNA quantity increased 3.3-fold on average (95% CI: 2.3-7.3 fold) during surgery. Seven preoperative HDL-miRNAs had >10-fold expression difference in patients who did and did not develop AKI, while postoperative HDL-miRNAs expression did not differ between patient groups. HDL-associated miR-942-5p was 65.3-fold greater in patients who did not develop AKI compared to patients that did ($p<0.0001$, $p=0.02$ after Bonferroni correction, Figure). miR-942-5p promotes the activation and resolution of renal inflammation by regulating transcription cofactor NF-ÎºB and promotes anti-apoptotic signaling pathways that reduce renal tubular damage in preclinical models of renal ischemia and reperfusion injury. In addition, HDL-miR-143-3p was 6.5-fold lower and HDL-miR146b-5p was 17.3-fold lower in patients who did not developed AKI compared to patients who did develop AKI. miR-143-3p is an miRNA that promotes vascular contractility and endothelial mitochondrial ROS production and miR146b-5p is an miRNA that facilitates cisplatin-induced renal epithelial apoptosis. However, differences in these miRNAs did not reach statistical significance.

Conclusion: HDL-miRNA cargo varies between patients that do and do not develop AKI after cardiac surgery and changes in the perioperative period. Patients that did not develop AKI after cardiac surgery had higher HDL-miR-942-5p quantities than patients who did develop AKI after cardiac surgery. Future studies will characterize the effects of HDL-miR-942-5p on acute renal injury in vivo.


adjusted p=0.02
HDL-miR942-5p
(reads per mapped reads)
2.5×10-4
2.0×10-4
1.5×10-4
1.0×10-4
5.0×10-5
0.0
bars represent
mean +/- SD
No AKI
AKI

Perioperative Anesthesia-20 Sugammadex versus neostigmine for reversal of rocuronium neuromuscular block in patients having neurointerventional Cather based procedures

Eva Rivas[1], Mauro Bravo[2], Maged Y Argalious[3], Sandeep Khanna[3], Edward J Mascha[4], Guangmei Mao[5], Daniel I Sessler[5], Ehab Farag[6]

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Introduction: Cerebral neurointerventional procedures have become increasingly common during the last decades. They required dense neuromuscular blocks during the procedure. The end-time is difficult to predict, but when the procedure ends, the block must be reversed quickly to permit neurological evaluation. We tested the hypothesis that sugammadex reverses deep neuromuscular blocks faster than neostigmine reverses moderate neuromuscular blocks.

Methods: Sixty-nine patients having catheter-based cerebral neurointerventional procedures from Jan 2018 to Oct 2019 at the Cleveland Clinic Main Campus were randomized to: 1) deep neuromuscular block (post-tetanic count 1) and sugammadex (4 mg/kg) as reversal agent; or, 2) moderate neuromuscular block (train of four [TOF] 1) during the procedure and neuromuscular reversal with neostingmine (0.7 mg/kg to a ceiling dose of 5mg). Neuromuscular block was induced with rocuronium and continuously monitoring during the procedure and for 90 min after reversal agent administration. Recovery of diaphragmatic function was assessed by ultrasound before the procedure and 90 min after the administration of the reversal agent during normal and deep breathing. The primary outcome was the number of minutes required to reach TOF ratio greater 0.9 after the administration of reversal agent. Recovery times were compared with a Wilcoxon test, and the difference between post- and preoperative diaphragmatic contraction distance were compared with paired T-test.

Results: Among 68 patients finally analyzed, 35 were assigned to receive sugammadex and 33 to neostigmine. Baseline characteristics and surgery factors were reasonably balanced in the two treatment groups (absolute standardized difference <0.48). The median time to reach TOF ratio ≥0.9 was 3 (IQR: 2, 3) minutes in patients given sugammadex and 8 (IQR: 5, 10) minutes in those given neostigmine. Sugammadex was significantly faster, with a median difference of 5 minutes (95% confidence interval: 3, 6; P<0.001). Sugammadex and Neostigmine did not differ on the change in preoperative to postoperative diaphragmatic function.

Conclusion: Sugammadex reversed deep rocuronium neuromuscular blocks considerably faster than neostigmine reversed moderate neuromuscular blocks in patients having neurointerventional Cather based procedures.

Table 1. Baseline characteristics by treatment groups

N = 68	Sugammadex (N=35)	Neostigmine (N=33)	ASD
Age (year)	54 ± 15	59 ± 12	0.35
Female	27 (77)	19 (58)	0.43
Weight (Kg)	92 ± 28	90 ± 32	0.05
ASA (%)			0.24
I	0 (0.0)	0 (0.0)	
II	3 (9)	1 (3)	
III	32 (91)	32 (97)	
Race (%)			0.25
African American	3 (9)	3 (9)	
Asian	0 (0.0)	1 (3)	
Caucasian/white	32 (91)	29 (88)	
Arterial hypertension	23 (66)	20 (61)	0.11
Asthma	3 (8.6)	3 (9.1)	0.02
Chronic pulmonary disease	3 (8.6)	5 (15)	0.20
Obstructive sleep apnea	4 (11)	6 (18)	0.19
Diabetes mellitus	6 (17)	4 (12)	0.14
Myocardial infarction	1 (2.9)	1 (3.0)	0.01
Ischemic heart disease	2 (5.7)	0 (0.0)	0.35
Neurologic diseases	7 (20)	9 (27)	0.17
Chronic pain requiring opioids	1 (2.9)	0 (0.0)	0.24
Current smoker	8 (23)	5 (15)	0.20
Current recreational drug user	35 (100)	33 (100)	<0.001
Alcohol abuse	1 (2.9)	0 (0.0)	0.24
Cancer	2 (5.7)	0 (0.0)	0.35
No medical history	3 (8.6)	3 (9.1)	0.02

Data are presented as mean (SD) or N (%) appropriately

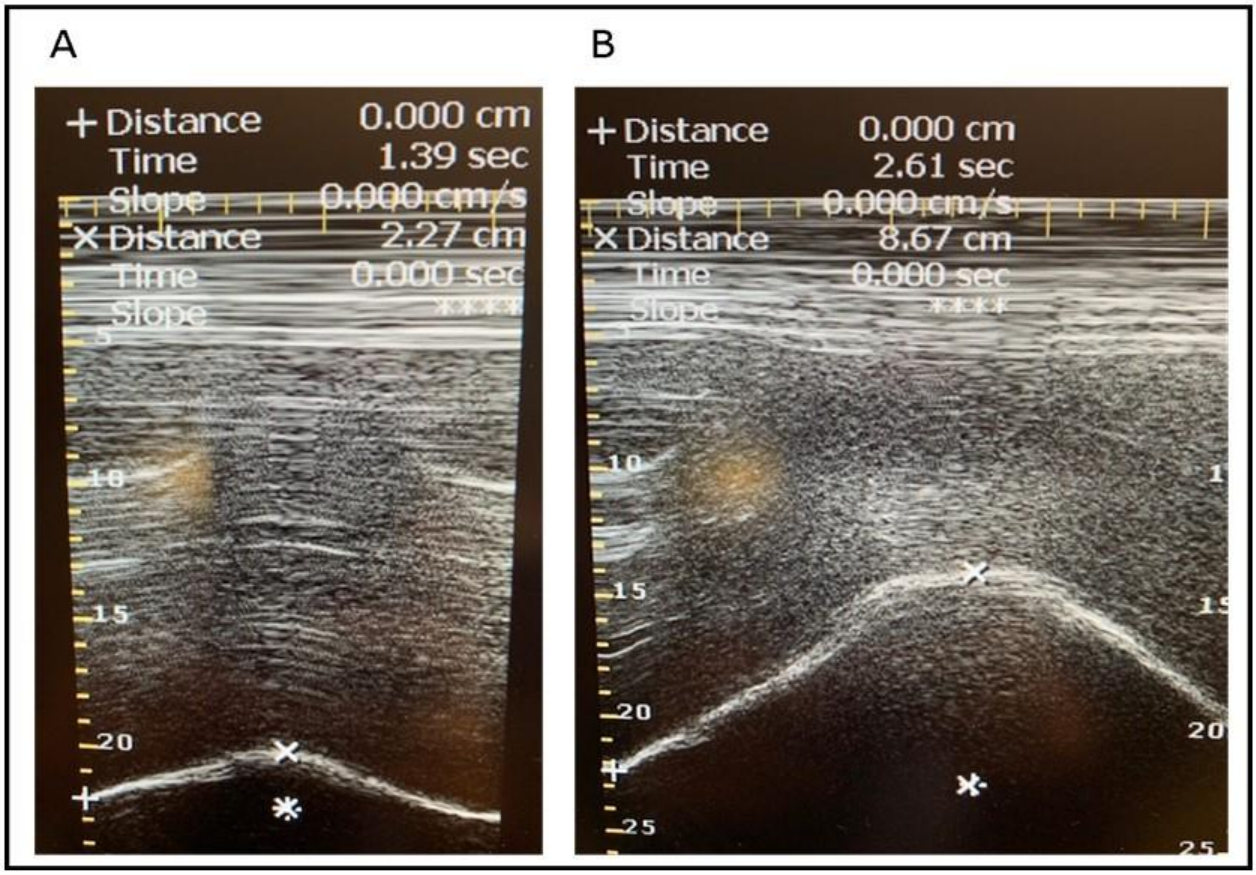

Figure 1. Diaphragmatic function ultrasound assessment during normal (A) and deep breathing (B).

Perioperative Anesthesia-21 The Impact of Perioperative Sleep Health on Patient-Centred Outcomes Following Elective Major Joint Arthroplasty - A Systematic Review

Ayesha Khan[1], Richard Brull[2], Aneesh Thakore[3], Zikra Awosanmi[4], Vivek Kumar[4], Anuj Bhatia[5], Miki Peer[6], Mandeep Singh[7]

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Introduction: Sleep health disruptions have been associated with heightened pain perception and poor quality of life in the general population. However, this association has not been evaluated in the perioperative setting, where surgical trauma and inadequate pain negatively impacts quality of recovery and functional outcomes. The objective of this qualitative systematic review was to evaluate the impact of perioperative sleep health disruption on patient-centred outcomes such as pain control, functional recovery and quality of life following total joint arthroplasty.

Methods: A search of all electronic databases including: Medline, Medline In-Process, ePUB, Embase, CCTR, CDSR, PsychINFO, Biosys Previews, Web of Science (Clarivate), Scopus (Elsevier), PubMed, ClinicalTrials.gov, and WHO ICTRP was conducted from database inception to February 15, 2019. Inclusion criteria were observational studies (including cohort, cross-sectional, and case-control) and randomized controlled trials of patients undergoing major joint arthroplasty in the lower limb with mention of sleep health and pain as measures or outcomes of interest. Article screening and data extraction were conducted by 2 independent reviewers, with all conflicts reviewed and resolved by the principal investigator. Critical appraisal and risk of bias were assessed using the Cochrane Risk of Bias Tool (RCTs) and RoBANS tool (observational studies). Patient-centered postoperative outcomes including sleep, pain intensity and perception for acute and persistent pain, quality of life, functioning, and recovery were extracted. Sleep health domains that were assessed included sleep quality and sleep patterns-total sleep time, sleep latency, night awakenings, and sleep efficiency. Qualitative literature review was performed.

Results: Out of the initial 28,500 studies identified, 17,651 were assessed for eligibility. Of these, 31 articles evaluating 5,247 patients were included. Ten of these articles were randomized control trials RCT and the rest were observational studies. Majority of the studies had a low risk of bias, and high risk of bias resulted mainly for failing to account for confounders such as sleep environment and external factors (Figures 1a and 1b). There was considerable heterogeneity observed in the choice of validated tools used to assess sleep health, pain, functioning, and quality of life (Tables 2a, 2b, and 3). Nevertheless, we aggregated data on sleep health domains to assess their associations with patient-centred outcomes. From the included studies, 29/31 (94%) looked at sleep outcomes [predominantly sleep efficiency (45%), sleep duration (39%), and sleep satisfaction and/or quality (39%)] with 1/31 (3%), 18/31 (58%), and 10/31 (32%) assessing preoperative, postoperative, and intraoperative sleep outcomes, respectively. Most studies (28/31,90%) examined pain outcomes (most commonly pain intensity) with 0 (0%), 12 (39%), and 16 (52%) assessing preoperative, postoperative, and perioperative pain outcomes respectively. Nearly half of the included studies included measures of physical functioning (42%). Poor sleep quality was associated with worse pain and functional recovery outcomes in observational studies (Table 2a and 2b). Of the eight RCTs (Table 3) involving use of a pain intervention post-operatively (i.e. rofecoxib, diclofenac and gabapentin), 4 (50%) reported an improvement in postoperative sleep. Similarly, of the two RCTs involving a sleep intervention (i.e. melatonin, zolpidem), 1 (50%) reported improved postoperative analgesia reported improved analgesia post-operatively.

Conclusion: Significant heterogeneity was observed in the use of validated tools to assess sleep health in the perioperative setting. Furthermore, sleep health disruption, especially patient-reported sleep quality, was associated with worsening of acute as well as persistent post-surgical pain, physical functioning, and quality of life. More research is needed to comprehensively assess sleep health as a predictive factor for relevant patient centred outcomes.

Figure 1a. Risk of Bias Assessment Tool for Non-Randomized Studies Table

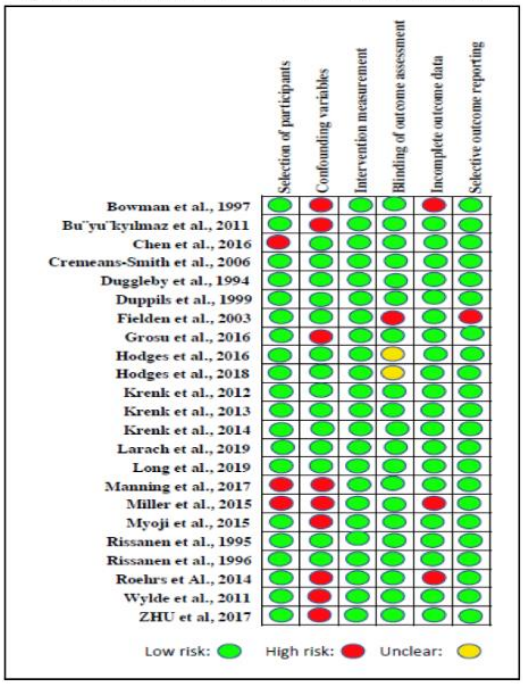

Figure 1a. RoBANS (Risk of bias assessment tool for non-randomized studies) summary table among observational studies evaluating sleep health association, at various different stages of surgical setup, with postoperative pain outcomes and pain-related impacts on physical functioning and quality of life.

Figure 1b. Cochrane Risk of Bias Assessment of Randomized Controlled Trials Table

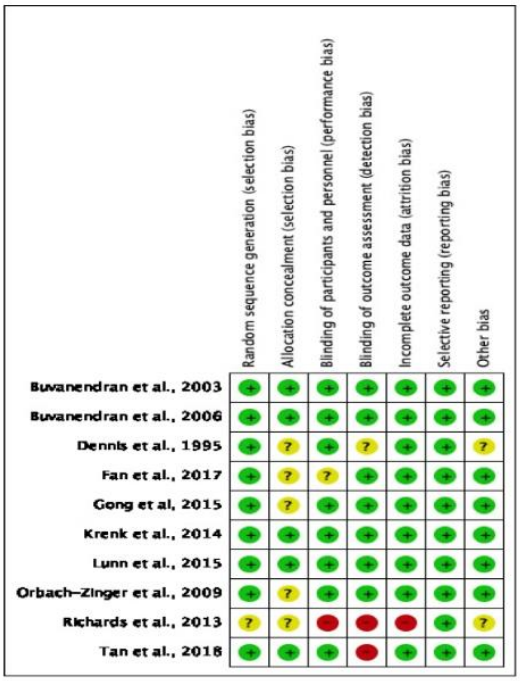

Figure 1b. Cochrane risk of bias summary table among trial evaluating the effects of various interventions in the management of postoperative physical functioning and pain-related sleep disturbance

Table 1. Summary Table of All Included Studies

Study	Study Type		Sleep Domains								Pain Assessment Domains					QOL and Function		
	RCT	Observational	Sleep Quality	Sleep Continuity or Efficiency	Alertness/sleepiness	Sleep Duration (TST)	Pre-operative Sleep	Post-operative Sleep	Sleep Domain Correlation with QOR, QOL, and/or Pain	Validated Tools for Sleep measurement	Pain Intensity	Pre-operative Pain	Post-operative Pain	Pain Correlation with Periop Sleep, Functioning, or QOL	Validated Tools for pain measurement	Overall QOL	Validated Tools for QOL measurement	PhysicalFunctioning
Bowman et al., 1997		*	*					*		*	*	*	*		*			
Buvanendran et al., 2003	*		*	*				*			*	*	*	*	*			*
Buvanendran et al., 2006	*		*					*			*	*	*		*			*
Büyükyılmaz et al., 2011		*	*	*	*	*		*	*	*	*		*	*	*			
Chen et al., 2016		*	*	*	*		*	*		*	*	*	*		*			
Cremeans-Smith et al., 2006		*	*	*	*	*	*	*	*	*	*	*	*	*	*			*
Dennis et al., 1995	*		*	*		*		*			*		*		*			*
Duppils et al., 1999		*																
Fan et al., 2017	*		*				*	*		*	*	*	*		*			*
Fielden et al., 2003		*	*	*	*	*	*	*	*	*								
Gong et al., 2015	*		*	*		*		*	*	*	*		*	*	*			*
Grosu et al., 2016		*	*					*		*	*	*	*	*	*	*		
Hodges et al., 2016		*																
Hodges et al., 2018		*	*			*		*	*		*	*	*	*	*	*		*
Krenk et al., 2012		*	*		*	*	*	*		*	*	*	*		*			
Krenk et al., 2013		*	*			*		*		*	*	*	*		*			*
Krenk et al., 2014	*		*	*		*	*	*		*	*	*	*		*			
Krenk et al., 2014		*	*	*	*	*		*		*	*		*		*			
Larach et al., 2019		*	*				*	*		*	*	*	*		*			*
Long et al., 2019		*																
Lunn et al., 2015	*		*					*		*	*		*		*			
Manning et al., 2017		*	*	*	*	*	*	*		*								
Miller et al., 2015		*		*		*		*		*	*		*	*	*			
Myoji et al., 2015		*	*	*	*	*	*	*	*	*	*		*		*			
Orbach-Zinger et al., 2009	*		*					*					*		*			
Richards et al., 2013	*		*					*		*	*		*	*	*			*
Rissanen et al., 1995		*	*				*	*	*	*	*	*	*	*	*	*	*	*
Rissanen et al., 1996		*	*				*	*		*	*	*	*		*	*	*	*
Roehrs et Al., 2014		*		*	*	*	*		*	*	*	*	*		*			*
Tan et al., 2018	*		*	*				*			*		*	*	*			*
Wylde et al., 2011		*	*	*				*			*	*	*	*	*			
ZHU et al, 2017		*	*					*		*	*		*	*	*			

*RCTs *Observational studies

Table 1. Summary table outlining outcome domains, their correlations, and validated tools used for all included (RCTs and observational) studies.

Abbreviations: QOL- Quality of Life; QOR- Quality of Recovery; RCT- Randomized Controlled Trial; TST- Total Sleep Time

Table 2a. Observational Studies Descriptive Table

Table 2a. Descriptive Summary Table of Observational Studies

Study	Type of Study	Sleep Outcome		Pain Outcome		Results	Confounding (Influencer) Factors
		Measure	Tool	Measure	Tool		
Bowman et al., 1997	Observational: Descriptive Study	Sleep satisfaction	Likert scale (for sleep satisfaction)	Pain perception; Intensity	VAS	Pain scores declined in the postoperative period; intervention worsened delirium, which, inturn, impacted sleep	Cohort type; age; gender; unequal sample sizes
Büyükyılmaz et al., 2011	Observational: Descriptive Correlational (Cohort) Study	Sleep quality, latency, effiency, duration, disturbance,	PSQI	Pain intensity	VAS 10 cm; MPQ-SF; PPI index; BPI	Correlation between postoperative pain intensity and quality of sleep; Most significant contributing factor to poor sleep quality was pain	Variablility in types of surgery
Chen et al., 2016	Observational: Prospective Cohort	latency, effiency, duration, disturbance, daytime sleepiness	PSQI; ESS	Pain intensity	VAS 10 cm	Decrease pain intensity 4-weeks, 6 weeks, 3-mo, 6-mo postoperatively; no correlation between sleep quality and pain; Initial decrease in sleep quality postoperatively with gradual improvement overtime	-
Cremeans-Smith et al., 2006	Observational: Prospective Cohort	Sleep quality, latency, effiency, duration, disturbance, daytime	PSQI	Pain frequency	AIMS2	Positive relationship between postop sleep disurbance, pain intensity, and functioning limitation;: Postop sleep disruption mediated the relationship between pain and functional limitations; increase pain intensity is associated	-
Duggleby et al., 1994	Observational: Cohort	Sleep disturbance	No validated tool	Pain intensity	VAS 10 cm	Decrease in pain and sleep disturbance postoperatively; significant correlation of pain on sleep disturbance	-
Duppils et al., 1999	Observational: Cohort	-	-	-	-	Sleep and pain were not outcomes of assessment in this study	
Fielden et al., 2003	Observational: Cohort	Sleep quality; daytime sleepiness; sleep duration	ESS; Sleep questionnaire			Postoperatively, sleep duration increased by 20 minutes; improvement in sleep quality and sleep effiecency for elderly patients compared to preoperative levels;	-
Grosu et al., 2016	Observational: Prospective Cohort	Sleep quality	BPI	Pain intensity	MPQ-SF; BPI; VDS	Positive evolution of pain intensity postoperatively; Significant correlation between all aspects of postop pain on sleep quality	Depression; gender
Hodges et al., 2016	Observational: Longitudinal Cohort	Not applicable	Not applicable	Not applicable	Not applicable	-	-
Hodges et al., 2018	Observational: Longitudinal Cohort	Sleep quality	Sleep questionnaire	Pain intensity	WOMAC	Postoperative sleep disruption correlated with fatigue; fatigue correlated with QOL; correlation between pain, sleep, fatigue, and	-

Table 2b. Observational Studies Descriptive Table

Table 2b. Descriptive Summary Table of Observational Studies

Study	Type of Study	Sleep Outcome		Pain Outcome		Results	Confounding (Influencer) Factors
		Measure	Tool	Measure	Tool		
Krenk et al., 2012	Observational: Prospective Cohort	Sleep quality	EEG; AASM; hypnogram; PSQI	Pain intensity	VAS	No association between postoperative sleep disturbance and level of pain; postoperative pain affected sleep; sleep quality worsened postoperatively	-
Krenk et al., 2013	Observational: Cohort	Overall sleep	Actigraphy; sleep diary	Pain intensity	10cm VAS	No association between postoperative pain, activity or sleep parameters; inital increase in pain followed by improvement postoperatively; postop increase daytime sleepiness and decrease nighttime sleep duration	-
Krenk et al., 2014	Observational: Cohort	Sleep quality, latency, effiency, duration, disturbance	PSQI	Pain intensity	NPRS	No statistical difference in patients with and without POCD and pain and sleep quality postoperatively	-
Manning et al., 2017	Observational: Prospective Cohort	Sleep quality; disturbance; habits; daytime sleepiness	ESS; Subjective sleep questionnaire			Sleep disturbance increased immediate postop period; improvement in sleep quality gradually chronic postop period;	Gender; patient anticipation of outcome of interest
Miller et al., 2015	Observational: Cohort	Sleep effieciency; duration; quality	Actigraphy	Pain intensity	10cm VAS	Immediate postoperative period- increased pain intensity correlated with decreased sleep duration	Surgery type
Myoji et al., 2015	Observational: Cohort	Sleep duration; sleep-wake rhythm	Actigraphy; questionnaire	Pain intensity	10cm VAS	Pain intensity improved postoperatively from preop levels; postoperative sleep time associated with pain intensity levels; increase sleep time caused decrease in pain intensity	Gender
Rissanen et al., 1995	Observational: Cross-sectional	Sleep quality	NHP	Pain intensity	HRQOL; NHP	Improvement in pain and physical ability in postop group; with inturn improved sleep quality, QOL and physical function (ADL) in postop group vs preop group;	-
Rissanen et al., 1996	Observational: Prospective Cohort	Sleep quality	NHP	Pain intensity	NHP; HRQOL; ADL	Improvements in QOL, functioning ability, pain intensity, sleep quality, and physical ability- gradually following surgery	-
Roehrs et Al., 2014	Observational: Randomized Feasibility Study	Sleep hygiene; sleep-wake timing; TST; TIB; sleep quality; daytime sleepiness	Actigraphy; sleep diary (1 week preop; concurrent); ESS	Pain intensity	10cm VAS	Postoperative pain intensity was lower with sleep extension; Preop sleep exension correlated with (improved) postop pain, physical function, QOL vs no preop sleep extension which resulted in greater postop pain	Duration of study
Wylde et al., 2011	Observational: Cohort	Sleep disturbance	Nonvalidated sleep questionniare	Pain intensity	10cm VAS; MPQ-SF	Pain intensity was greater preop vs postop; postop pain intensity was highest POD1, causing the greatest sleep disturbance; Decline in intensity POD2 POD3; Acute postop pain was associated with sleep disturbance	Gender; Anesthesia type administered
ZHU et al, 2017	Observational: Cross-sectional	Sleep quality; sleep disturbance	BPI questionnaire	Pain intensity	BPI; PPSMB	Greatest postop pain intensity at POD1 with gradual decline thereafter; negative correlation of pain intensity on sleep quality and disturbance; pain induced sleep disturbance	Unequal cohort groups; age; gender

Table 2a and 2b. Brief descriptive table for all included observational, highlighting sleep and pain outcome, the measures evaluated, the tools used for measurement, any confounding factors, and the conclusive result.

Sleep Tools Abbreviations: AASM- American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events; BPI- Brief Pain Inventory questionnaire EEG- Electroencephalogram; ESS- Epworth Sleepiness Scale; NHP- Nottingham Health Profile; PSQI- Pittsburgh Sleep Quality Index

Pain Tools Abbreviations: ADL- Activities of Daily Living; BPI- Brief Pain Inventory questionnaire; HRQOL- Health Related Quality of Life; MPQ-SF- Short-form McGill Pain Questionnaire; NHP- Nottingham Health Profile; NPRS- Numeric Pain Rating Scale; PPI- Present Pain Intensity Index; PPSMB- Postoperative Pain Self-Management Behaviour; VAS- Visual Analog Scale; WOMAC- Western Ontario and McMaster Universities Osteoarthritis Index

Other Abbreviations: POCD- Postoperative Cognitive Decline; QOL- Quality of Life

Table 3. Randomized Controlled Trials Descriptive Table

Desciptive summary of Randomized Contolled Trials

Study	Type of Study	Sleep Outcome		Surgical Time-Period	Pain Outcome		Surgical Time-Period	Results
		Measure	Tool		Measure	Tool		
Buvanendran et al., 2006	RCT	Sleep disturbance	No validated tool	Postoperative sleep (POD 1)	Pain intensity	VAS 10 cm	Preoperative and intraoperative pain (3, 9, 24, and 30-h after surgical incision)	Intervention decreased postoperative pain; positive correlation of VAS scores with CSF PEGE2 and IL-6 levels and negative correlation with postoperative sleep disturbance;
Dennis et al., 1995	RCT	Sleep duration; sleep disturbance	No validated tool	Postoperative sleep (24-hr postop)	Pain intensity	VAS 10 cm	Postoperative pain (24-hrs postop)	No difference in pain intensity before and after intervention; no correlation of sleep and pain; no significance in postoperative sleep
Fan et al., 2017	RCT	Sleep quality	100mm VAS	Preoperative (1 day preop) and postoperative sleep (POD 1,3,5,7)	Pain intensity	VAS 10cm	Preoperative (1 day preop) and postoperative pain (POD 1, 3, 5, 7)	No difference in pain intensity preoperatively and postoperatively between both groups; decrease postoperative sleep quality in placebo group; increase postop sleep quality in intervention group
Gong et al., 2015	RCT	Sleep quality	PSG; objective sleep assessment	Poatoperative sleep (POD 1, 3, 5, 7, 11, 14)	Pain intensity	VAS	Post-operative pain (POD 1, 3, 5, 7, 11,14)	Improved postop sleep quality in intervention group decreased pain intensity; improved pain intensity improved QOR; positive correlation between improved sleep quality and pain on functional recovery
Krenk et al., 2014	RCT	Sleep quality; sleep stages	EEG; self report	Preoperative (1 night, 3 days prior to surgery) and postoperative	Pain	10cm VAS	Preoperative (1 night, 3 days prior to surgery) and postoperative	Postoperative pain intensity and opioid consumption did not change with intervention; no improvement in sleep stages; significant improvement in postop sleep quality and fatigue for intervention group
Lunn et al., 2015	RCT	Sleep quality	11-p NRS	Postoperative sleep (POD 0-6)	Pain intensity; ambulation	100mm VAS	Post-operative pain (4, 6, 24, 28, 32, 48 hours postoperatively & POD 3-6)	No difference postoperatively in pain level and ambulation in both groups; improvement in sleep quality in acute postoperative period for both groups
Orbach-Zinger et al., 2009	RCT	Sleep Quality	Sleep Quality Questionnaire		Pain intensity	VAS		Intervention and placebo showed no improvement in postop pain; no impact on postoperative sleep quality
Richards et al., 2013	Randomized open label	Sleep quality	BPI-SF	Postoperative sleep (0-48 hours after first dose)	Pain Intensity	NPRS, BPI-SF	Postoperative pain (0-48 hours after first dose)	Postoperative pain interference with physical activity, sleep quality, and mood was lower in intervention (morphine) group;
Tan et al., 2018	RCT	Sleep disturbance	non-validated questionnaire	Postoperative sleep (POD 1, 2, 3)	Pain intensity	10cm VAS	Postoperative pain (2, 4, 8, 12, 24, 48, 72 hours postoperatively & upon discharge)	Postoperative pain was lower in femoral nerve block group vs ACB group; positive correlation of pain intensity on improved physical functioning (strength); no impact or association of pain on sleep in both groups

Table 3. Brief descriptive table for all randomized controlled trials, highlighting sleep and pain outcome, the surgical time-period these outcomes were assessed in, the measures evaluated, along with the tools used for the measurements, and the conclusive results.

Sleep Tools Abbreviations: BPI-SF- Brief Pain Inventory-Short-Form; EEG- Electroencephalogram; NRS- Numeric Rating Scale; PSG- Polysomnography; VAS- Visual Analog Scale

Pain Tools Abbreviations: BPI- Brief Pain Inventory; NPRS- Numeric Pain Rating Scale; QOR- Quality of Recovery; VAS- Visual Analog Scale

Other Abbreviations: ACB- Adductor Canal Block; CSF- Cerebrospinal Fluid; IL-6- Interleukin 6; PGE2- Prostaglandin E2; POD- Postoperative Day; RCT- Randomized Controlled Trial

Regional Anesthesia

Regional Anesthesia-1 Association between regional anesthesia and analgesic outcomes: a single-center retrospective study of 2038 pediatric regional anesthetics

James J Xie[1], Beth De Souza[1], Ellen Wang[1], Thomas A Anderson[1]

[1]Stanford University School of Medicine, 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) (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 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 performed ≥20 times; regional anesthesia performed in 10-90% of included surgeries. Exclusion criteria: postoperative ICU admission, ASA class ≥4, ≥1 operation performed during the same anesthetic, and non-operative procedures. Primary outcome: PACU opioid exposure and dose. Secondary outcomes: intraoperative and inpatient opioid exposure and dose, procedure and anesthesia lengths, PACU length of stay, and postoperative pain scores. Linear and logistic regressions were used to estimate the association of exposure to regional anesthesia with outcomes; adjustments were made for possible confounders such as age, procedure length, use of remifentanil during the procedure, and comorbidities affecting pain.

Results: 5478 eligible procedures met inclusion criteria; 2038 (37.2%) regional anesthetics were performed. See quantitative results in Table 1. Regional anesthesia was significantly associated with having an opioid-free anesthetic. For patients who did receive opioid intraoperatively, regional anesthesia had an associated intraoperative reduction of 0.03 mg/kg oral morphine equivalents. For patients who did receive opioid in the PACU, regional anesthesia was not associated with a significant change in dose received. Procedures with regional anesthesia were 20.5 minutes longer. Mean PACU pain scores were not different between patients who received regional anesthesia and those who did not.

Conclusion: While evidence from prospective trials under idealized conditions with stringent inclusion/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, the effect of regional anesthesia techniques on postoperative pain scores and perioperative opioid consumption were assessed. Pre-incision regional anesthesia is associated with a statistically significant decrease in intraoperative and PACU opioid administration, while there is no major difference in PACU pain severity. This corroborates the opioid sparing effect of regional anesthesia. Meanwhile, regional anesthesia may increase intraoperative anesthesia time. These results suggest that even in real-world conditions, regional anesthesia remains an important component of multimodal analgesia in pediatric perioperative care. (Additional analyses of inpatient pain outcomes are pending but will be available before the AUA/IARS meeting in May 2020.)

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Table 1:

Association Evaluated	Regression Model	Confounders Adjusted	Regression Result
No opioid exposure intraoperatively	Logistic	Procedure, procedure length	OR for no intraoperative opioid exposure: 7.6 (95% CI: 6.1-9.3, p<0.001)
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 0.03mg/kg (95% CI: 0.01-0.04mg/kg decrease, p<0.001)
No opioid exposure in PACU	Logistic	Procedure, age	OR for no PACU opioid exposure: 1.17 (95%CI: 1.02-1.35, p=0.029)
Total opioid dose in PACU for patients who did receive PACU opioid	Linear	Procedure, age	Total opioid dose lower by 0.003mg/kg (95%CI: 0.004mg/kg decrease-0.012mg/kg increase, p=0.33)
Time between induction of anesthesia and extubation	Linear	Procedure, age	20.5 minute increase (95% CI: 17.3-23.8 minute increase, p<0.001)
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: 1.27 (95% CI: 0.96-1.68, p=0.10)

Regional Anesthesia-2 An Interactive Serious Game to Teach Sonoanatomy: Prospective Multicenter Randomized Control Trial

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Introduction: Serious games have emerged as an engaging and efficient alternative to standard anatomy education modalities such as textbooks, online resources, didactics and point-of-care training [1,2]. Trainees have specifically shown interest in utilizing drawing-based games to learn sonoanatomy. No prior studies have evaluated the use of a serious game to teach sonoanatomy for ultrasound-guided regional anesthesia (UGRA).

Methods: A web-based interactive drawing game was developed to teach sonographic anatomy necessary for the performance of four common peripheral nerve block procedures. Users progress through multiple game levels to first identify anatomy in schematic diagrams and then utilize an interactive drawing tool to identify the precise sonographic borders of each relevant structure. A randomized, single-blinded, control trial of resident-level anesthesiology trainees across three academic institutions compared a classic annotated image approach to anatomy education (CONTROL) with the interactive structure identification game (GAME). 25 residents were enrolled via a recruitment email sent to the entire class. Approval was obtained from the Columbia University Medical Center institutional review board. After informed consent, subjects completed an anatomic knowledge test prior to completion of the web modules, immediately following completion of the web modules, and then again one week and six weeks later. Percentage improvement in test scores from baseline were compared between the two groups, as well as results of self-reported engagement surveys. Students T-Test was used to compare the trial's two arms.

Results: 25 subjects were enrolled in the study and completed all components (13 in the GAME group and 12 in the CONTROL group). In both groups, scores improved from pretest to posttest, but returned to baseline by week 6. There were no significant differences in scoring between the two groups on pretest, post-test, nor one-week and six-week follow up tests (Table 1). Follow-up surveys demonstrated positive attitudes towards both standard online pre-learning and gaming for learning sonoanatomy without any consistent differences between the two modalities (Table 2).

Conclusion: A serious game to teach sonoanatomy improved anatomy knowledge in the short-term in a similar fashion to web-based training. Despite prior studies reporting student interest in drawing-based tools to learn anatomy, our randomized control trial suggests that drawing tools do not appear to significantly improve sonoantomy knowledge retention. Nonetheless, trainees rated both gaming and online learning as effective, engaging, and enjoyable learning modalities for sonoanatomy that are preferred over textbook education. Finally, given the gradual loss of knowledge by trainees over the six week our study suggests that spaced learning may be critical to ensure long term sonoanatomy knowledge retention.

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Table 1: Change in performance over time between the Sonoanatomy Training Tool (GAME) compared t
a static image tool (CONTROL).

Average Quiz Score (% correct) [Mean (SD)]							
	Pre-Test	Post-Test	P Value (Compared to Pretest)	1 Week	P Value (Compared to Pretest)	6 Week	P Value (Compared to Pretest)
GAME	59 (17)	77 (14)	<0.01	62 (12)	0.6	57 (17)	0.9
CONTROL	57 (19)	86 (14)	<0.01	71 (16)	0.06	62 (20)	0.6
P Value (GAME vs. CONTROL)	0.83	0.10		0.10		0.57	

Table 2: Self-reported participant interest and engagement in using the Sonoanatomy Training Tool (GAME) compared to a static image tool (CONTROL). Agreement with statement was reported on Likert scale (5 = Strongly Agree, 1 = Strongly Disagree). The values reported are in the format: average (standard deviation).

Survey Question:	GAME [Mean (SD)]	CONTROL [Mean (SD)]	P value
The training module I completed six weeks ago is a very effective tool for learning ultrasound anatomy.	4.00 (1.00)	3.83 (0.93)	0.67
This training module taught me ultrasound anatomy more effectively than if I were to have spent the same time studying from a textbook.	3.77 (1.09)	3.92 (0.99)	0.73
I found the training module engaging and enjoyable.	4.15 (0.09)	3.92 (0.99)	0.54
I would prefer learning from this training module to learning from a textbook.	4.00 (1.15)	4.25 (0.99)	0.56

Regional Anesthesia-3 Quality of Analgesia at Twenty Four Hours after using Dexamethasone and Dexmedetomidine as a Perineural Adjunct for Interscalene Brachial Plexus Block

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Introduction: Recent literature has demonstrated the improvement in analgesia from addition of different additives to the perineural solution. Specifically, dexmedetomidine and dexamethasone have been used in studies with typically positive results. Of note the two drugs have also been reported to have neural protective effects. Our institution began using a solution containing dexmedetomidine and dexamethasone on our single shot blocks to improve analgesia and extend the length of the block. All other patients who received a continuous block with a catheter did not traditionally get the additives. However, after noticing great results from the patients who received single shot blocks containing the additives we decided to expand this to the continuous patients as well. Our initial observation after utilizing these additives in our injection was improvement in pain control generally for all types of blocks. However, we noticed the biggest effect with interscalene and supraclavicular blocks. We were noticing a dense block lasting 36-48hrs where as 0.5% ropivicaine alone would last at most 18hrs. Patients were having lower pain scores at 24 hrs with the additives and thus overall improved satisfaction. Prior patients noted pain increased significantly after termination of the initial block and initiation of the 0.2% ropivicaine pain ball. For shoulder surgery, use of the arm and hand is not necessary until 72 hrs post op unlike hip and knee surgery where post-operative mobility is crucial. Thus shoulder surgery is an ideal situation to utilize a prolonged dense block as long as patients' have no problem with the numbness/muscle weakness for that period of time. We decided we wanted to focus on interscalene or supraclavicular for shoulder and elbow shoulder respectively.

Methods: We retrospectively reviewed data from patients who were at Tulane Lakeside Hospital Metairie Louisiana from 10/1/19- 12/1/19 who underwent interscalene or supraclavicular continuous peripheral nerve block. Patients were divided into three groups based on which additives they received within the local anesthetic solution. Patients in the control group, received no additives. Patients in the second group received only dexamethasone. Patients in the third group received dexamethasone and dexmedetomidine. For every interscalene and supraclavicular block patients received 20ml of 0.5% ropivicaine. If patient's were in group 2 or 3 they received 2mg dexamethasone in the injectate, If the patients were in group 3 they also received 1mcg/kg of dexmedetomidine in the injectate. Patients were then contacted at 24hrs post block to assess their pain score based on visual analog scale. IRB was consulted prior to submission however was determined to be waved as this projected was solely retrospective and involved no patient identifiers. Off laberl usage of dexmedetomidine was used however the study was retrospective thus consent can not be obtained retrospectively. Any future research using this method will involve IRB approval

Results: There was a total of 105 patients included in this retrospective review. There were 38 patients in the group that received dexmedetomidine and dexamethasone, 29 patients in the group that received dexamethasone only, and 38 patients in the group that received no additives. Pain score at 24 hours post block between dexmedetomidine plus dexamethasone, dexamethasone, and no additives groups were analyzed using anova. Based on analysis, there was a significant result with a p value of 0.006. All groups were then individually analyzed with a student T test. Dexmedetomidine plus dexamethasone group was found to have lower pains scores at 24 hrs compared to the other 2 groups with p values less than 0.05. However, there was no difference in pain scores between the dexamethasone and no additive groups.

Conclusion: The purpose of the study was to retrospectively review our regional anesthesia history and observe if there was improvement in patient satisfaction from the addition of dexmedetomidine and/or dexamethasone. We found that overall patients had a more satisfied block at 24hrs with both drugs added to the ropivicaine injection. However, this demonstrates the need for further prospective investigation. Anecdotally, we observed longer block duration with this additive group yet had no established method to record this information. We plan to prospectively record pain scores at 24 and 48hrs, block duration, and morphine equivalent consumption in the near future.

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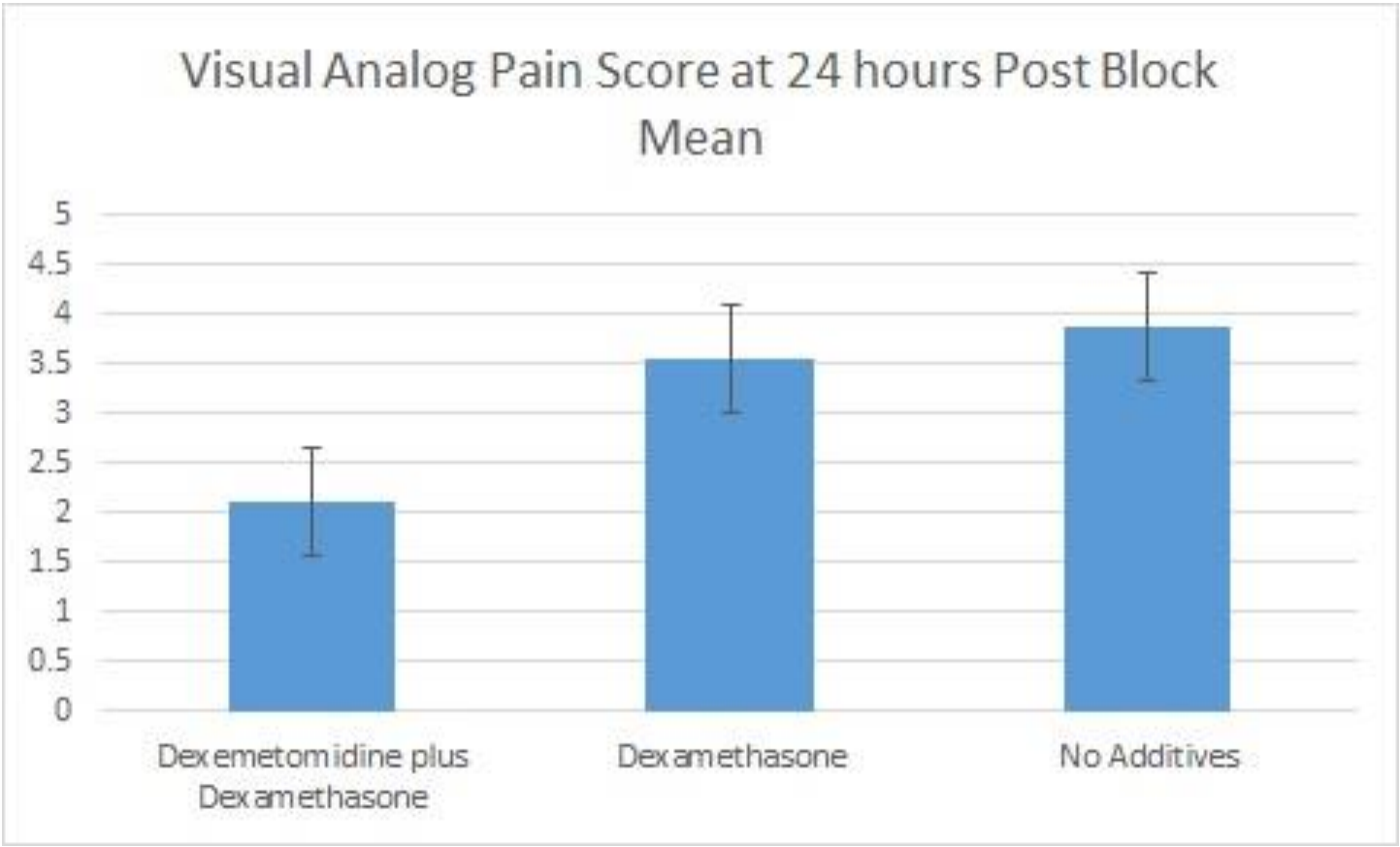
Visual Analog Pain Score at 24 hours Post Block Mean
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Dexemetomidine plus Dexamethasone
Dexamethasone
No Additives

Respiration

Respiration-1 Oral ginger prevents gut microbiome changes in house dust mite (HDM) antigen-induced allergic asthma in mice

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Introduction: Microbial dysbiosis in the gut and the lung is increasingly recognized as being associated with the incidence and severity of asthma [1]. The efficacy of medications, especially orally administered ones, may be influenced by the patient's microbial composition. Despite current treatments for asthma (e.g., β-agonists and inhaled corticosteroids), approximately 40% of severe asthmatics have inadequate control of the disease, and many use alternative medicines, like ginger, for symptom management. Previously, we demonstrated that crude ginger and its purified components, including 6-shogaol, relax airway smooth muscle (ASM) ex vivo [2, 3] and reduce lung inflammation in vivo [4]. We hypothesize that orally administered ginger decreases inflammatory changes in the murine house dust mite (HDM) antigen model of asthma in part by preventing disruption of the commensal gut and lung microbiota.

Methods: Mouse ginger pretreatment and HDM sensitization: All animal studies were approved by the IACUC. Wild-type C57BL/6J 8-12 week-old male mice were co-housed. Mice were briefly anesthetized with isoflurane and pretreated with ginger (40 mg/kg in 2% hydroxypropyl methylcellulose w/v and 2.5% polyethylene glycol w/v) or vehicle via oral gavage once a day for 3 weeks. After this 3-week pretreatment period, mice were randomized to receive intranasal HDM antigen (30 µg in 25 µL PBS) or vehicle once a day, while continuing oral ginger or vehicle twice each day. Fecal pellets were collected at the beginning and end of treatment and stored (-80 oC). Bronchoalveolar lavage: At the end of the treatment period, anesthetized mice were tracheostomized for bronchoalveolar lavage (BAL) (2 mL PBS per mouse). Samples were centrifuged at 800 g x 10 min to remove mucus and cellular debris, and the supernatant was centrifuged at 22 000 g x 30 min to pellet microbial particles, which were resuspended in PBS (100 µL) and stored (-80 oC). Microbiome sample preparation and sequencing: DNA extraction, amplicon library preparation, cleaning, and dilution were performed by the Center for Metagenomics and Microbiome Research (CMMR) at Baylor College of Medicine. Sequence data were analyzed using ATIMA (Agile Tool for Incisive Microbial Analyses).

Results: Intranasal exposure of mice to HDM antigen for 10 days (Fig. 1A) induced a strong inflammatory response characterized by peribronchial and perivascular leukocyte infiltration. HDM also led to increased BAL total cell counts, primarily eosinophils and lymphocytes, which were also present in mice pre- and co-treated with oral whole ginger. The gut microbiota of mice that were sensitized with HDM showed a distinct shift away from control mice. In contrast, the gut microbiota from mice treated with ginger + HDM retained a microflora profile similar to control mice (Fig 1B). The HDM-treated mice had increased Bacteroidetes and Proteobacteria, and decreased Verrucomicrobia. Specifically, they had lower abundance of the family Lachnospiraceae (phylum Firmicutes, class Clostridia), which has been linked to asthma development in children as these bacteria produce short chain fatty acids (SCFAs), known anti-inflammatory microbial metabolites. The lung microbiota under these experimental circumstances did not show a significant shift in bacterial communities (Fig 1C), although there are notable decreases in the abundance of the class Bacilli with HDM treatment. Lactobacilli, which belong to this class, have been implicated in the prevention of asthma development.

Conclusion: Disturbances in the gut microbiome are linked to an increased incidence and severity of asthma. Ginger and its components have been shown to be protective in the allergic inflammatory model of murine asthma [4]. Here we showed that the gut microbial communities were affected by intranasal HDM treatment and that this change was prevented by oral ginger. These results suggest a possible mechanistic link between ginger's effect on the gut microbiome and ginger's anti-inflammatory effect on the lungs in this murine model of asthma.

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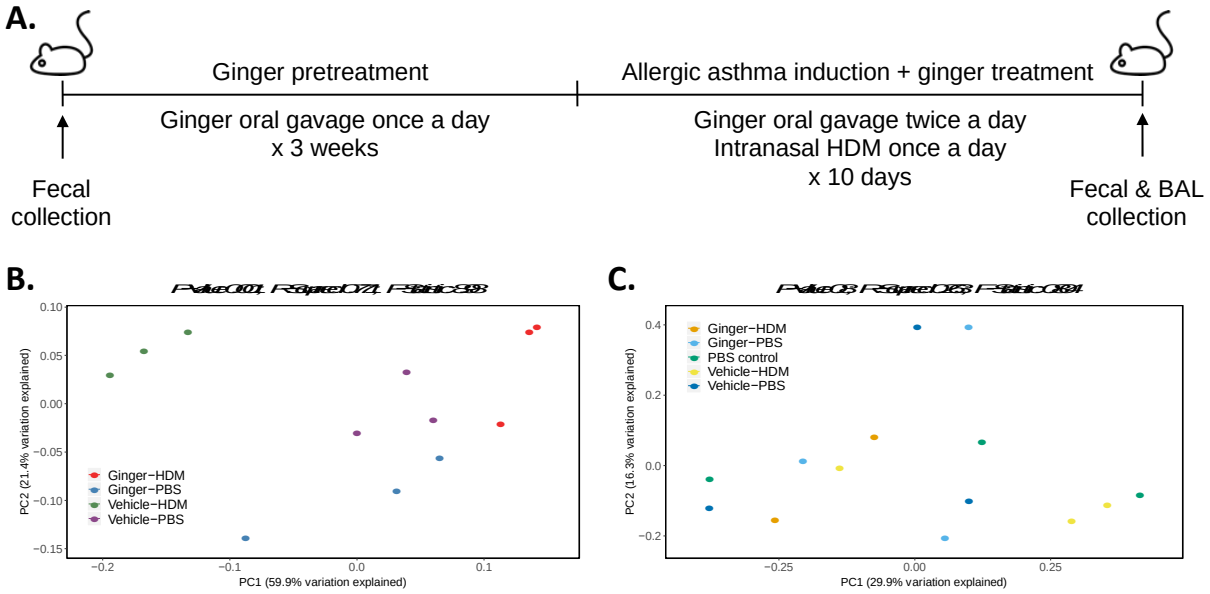

Figure 1. House dust mite (HDM) antigen induces allergic response in lungs and a shift in the gut microbiota, which is reversed with oral ginger. Experimental schematic is shown in A. Principal coordinate analysis (PCoA) of weighted UniFrac distances was performed on controls (Vehicle-PBS), HDM (Vehicle-HDM), ginger (ginger-PBS), and ginger + HDM (Ginger-HDM) samples (B, C). HDM sensitization changes the gut microbiota significantly (B) but not the lung microbiota (C). The closer two points are to each other, the more similar they are. Variance among samples is represented by the X and Y axes, where the percentage noted represents the proportion of all variance represented on that axis. The higher the number, the greater the dissimilarity a given distance along that axis represents. n = 3.

Sleep Medicine

Sleep Medicine-1 Sleep Disturbance in the First Year After Breast Surgery: A Prospective Longitudinal Study of Association with Pain, Opioid Use, and Psychosocial Factors

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Introduction: Sleep disturbance is often associated with greater pain (1-2) and pain persistence (3) and is an important negative sequela that may occur post-surgically. In this prospective longitudinal study of women undergoing breast cancer surgery, we investigated sleep disturbance preoperatively and periodically up to one year. We assessed the relationship of demographic, medical, and psychological factors with sleep disturbance, and its association with acute and persistent postsurgical pain, as well as anesthetic requirement in the perioperative period.

Methods: Women ages 18-80 (n=259) underwent breast-conserving surgery, mastectomy, or mastectomy with reconstruction. PROMIS Sleep Disturbance short form captured extent of sleep disturbance preoperatively and at 2 weeks, 6 and 12 months after surgery. Pain severity, frequency, and physical, cognitive and emotional impact of pain, as well as psychosocial traits, and sensitivity to pain using a brief bedside quantitative sensory test were also longitudinally assessed.

Results: "Sleep disturbance was variable amongst individual patients but stable over the course of the study, and moderately correlated with pain severity and impact at all timepoints (þ=0.14- 0.51,p's<0.001). Greater sleep disturbance at baseline was also associated with younger age lower physical activity, opioid use, catastrophizing, depression, anxiety, somatization, and lower pressure pain thresholds and tolerance on bedside quantitative sensory testing. Multivariate assessment of sleep disturbance across the first year after surgery using a general estimating equation (GEE) revealed axillary node dissection (vs no lymph node procedure (β=2.24), younger age (β=-0.11), baseline pain (β=0.21) and opioid use (β=3.1), anxiety (β=0.38), and lower positive affect (β=-0.12), as independent predictors.

Greater sleep disturbance was also modestly associated with higher midazolam and opioid amounts used in the perioperative period (þ=0.13-0.24,p's<0.001). Furthermore, opioid use at 2 weeks, 3 months, and 12 months was associated with a higher baseline sleep disturbance score."

Conclusion: Sleep disturbance varies amongst individuals in the first year after surgery, and is associated with greater perioperative benzodiazepine and opioid utilization, longer term opioid use, and long term pain outcomes. Predictors of greater sleep disturbance in the first year after mastectomy include demographic factors such as age and education, as well as psychosocial variables including anxiety and affect, as well as baseline pain and opioid use.

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Technology, Computing and Simulation, Equipment Monitoring

Technology, Computing and Simulation, Equipment Monitoring-1 Impact of patient position and artifacts on intraoperative processed electroencephalogram monitoring of burst suppression.

Devon Pleasants[1], Rochelle Zak[2], Liza Ashbrook[3], Christopher J Tang[1], Sanam Tabatabai[1], Danielle L Tran[4], Jacqueline Leung[1], Laura Sands[5]

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Introduction: Burst suppression is a waveform pattern observed through electroencephalography (EEG) that is linked to a diminished level of metabolic brain activity [1]. Recent evidence suggests that intraoperative burst suppression during general anesthesia may be associated with a higher incidence of postoperative delirium [2], however the mechanism for this association is undefined. Accurately quantifying burst suppression is important to understanding it's impact on postoperative cognitive outcomes. A previous study [3] suggested that burst suppression determined through a processed EEG is less accurate in predicting postoperative delirium when compared to off-line visual analysis by neurologists. We performed a follow-up study to further investigate the reasons for discordance between burst suppression as measured by a machine vs. neurologist.

Methods: The inclusion criteria were patients ≥ 40 years of age, undergoing major, elective, non-cardiac surgery requiring general anesthesia with an expected hospital stay of at least three days. All patients were monitored intraoperatively with continuous processed EEG using a SEDLine® monitor. The raw EEG data were reviewed visually in an off-line setting by neurologists in 30-second epochs, and each epoch was assigned an estimated duration of burst suppression in whole seconds. Burst suppression was quantified by the SEDLine® monitor in the form of the burst suppression ratio (BSR). A computer algorithm was used to convert the BSR into a raw duration (seconds) of burst suppression and was partitioned into the same 30-second epochs reviewed by the neurologists. SEDLine® generated estimates were considered to be accurate if there was a <10% difference in duration when compared with the neurologists' estimation. Each 30-second epoch was also visually assessed for significant signal artifact (such as wavering baseline, electro-cautery interference, etc.) lasting for ≥3 seconds within a single 30-second epoch.

Results: 23,354 30-second epochs (194 hours) of intraoperative EEG data were reviewed across 45 patients. 84.5% (±17.4%) of the 23,354 epochs analyzed had processed EEG estimates of burst suppression concordant with the neurologists' estimates. Epochs with artifact were significantly more likely to have discordance between the SedLine® and neurologists' estimates (P<0.0001, Table 2). Cases where the patient was prone during surgery had significantly more epochs that were discordant (P<0.0001, Table 3). Prone patients also had a significantly higher incidence of EEG artifact (P<0.0001, Table 4).

Conclusion: Processed EEG monitoring is less accurate in measuring intraoperative burst suppression when there is increased EEG artifact and when the patient is prone, generally as an association of having increased artifact in that position. These are potentially important limitations when using real-time processed EEG for monitoring burst suppression.

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Impact of patient position and artifacts on intraoperative processed electroencephalogram monitoring.

Table 1: Summary		
	Epochs in Agreement (>10% error)	**Epochs with Artifact (>3 second)**
All patients (n=45)	84.5% (±17.4%)	12.1% (±11.3%)
Prone Surgery (n=15)	75.2% (±14.5%)	20.9% (±15.8%)
Supine Surgery (n=30)	91.5% (±10.8%)	7.4% (±4.4%)

Table 2: Chi-square analysis – Artifact presence vs. Epoch Agreement			
Artifact vs. Agreement	**Epochs that Agree** Error ≤ 10% (n = 19618)	Epochs that **Disagree** Error > 10% (n=3736)	**P- Value**
Epochs with Artifact (n=2613)	2043	570	P = 0.0001
Epochs without Artifact (n=20741)	17575	3166	

Table 3: Chi-square analysis - Surgery Position vs Epoch Agreement			
Surgery Position vs. Agreement	**Epochs that Agree** Error ≤ 10% (n = 19717)	**Epochs that Disagree** Error > 10% (n=3637)	**P-value**
Epochs from **Prone Cases** (n=9132)	7010	2122	P < 0.0001
Epochs from **Supine Cases** (n=14222)	12707	1515	

Table 4: Chi-square analysis - Surgery Position vs Artifact Presence			
Surgery Position vs. Artifact	**Epochs with Artifact** (n=2613)	**Epochs without Artifact** (n=20741)	**P-value**
Epochs from Prone Cases (n=9132)	1572	7560	P < 0.0001
Epochs from Supine Cases (n=14222)	1041	13181	

Technology, Computing and Simulation, Equipment Monitoring-2 Detection of Regional Spinal Cord Ischemia with Fiber Optics and Diffuse Correlation Spectroscopy During Balloon Aortic Occlusion in a Porcine Model

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Introduction: Thoracic and thoracoabdominal aortic reconstruction/stenting not infrequently results in spinal cord ischemia, paresis, and paralysis. Current motor and somatosensory electrophysiological intraoperative monitoring techniques do not directly detect changes in blood flow, lack specificity for spinal cord injury, exhibit poor temporal resolution and offer no spatial resolution. These deficiencies limit a surgeon's confidence in the technique and ability to quickly modify the repair to restore spinal cord blood flow. We have developed and extensively tested a single level (1-3), and now a multi-sensor fiber optic epidural device employing diffuse correlation spectroscopy (DCS), designed to measure spinal cord blood flow at multiple (3) regions, Figure 1. The three sets of detectors are separated by 10 cm. Herein we test the hypothesis that the FLOXsp (Flow-Oxygenation for Spinal Cord) device, can detect spinal cord ischemia with high temporal resolution and regional specificity.

Methods: This work was conducted with approval for the local IACUC. Four domestic male/female pigs, weighing 50-70 kg, were employed in these studies. Under general anesthesia, and with ultrasound guidance, a right 16 G femoral artery catheter was placed to allow for arterial pressure monitoring. Through the contralateral femoral artery a ER-REBOA intra-aortic balloon catheter (Prytime Medical, Boerne, TX) was introduced via a 7 Fr sheath. This balloon catheter also allows for the measurement of intra-aortic pressure, superior to the level of balloon inflation. The pigs were then placed in a prone position and an L-3-4 laminotomy was created. The FLOXsp probe was then placed into the epidural space through the laminotomy, advanced into position with fluoroscopic guidance, and the anatomic position (vertebral level) of each set of detectors documented (Figure 2a). Using the same laminotomy, an 8 mm diameter laser Doppler flow (LDF) probe (Moor Instruments, Wilmington DE) was placed directly upon the spinal cord, inferior to the most proximal set of detectors on the FLOXsp probe (Figure 2a). The Moor tissue LDF probe, an FDA approved device, was employed to confirm changes in flow identified with the FLOXsp device. Following Figure 2a, the REBOA balloon was first advanced to the level of the proximal descending thoracic aorta, and above the most distal detector set on the FLOXsp probe. The balloon was then sequentially withdrawn and inflated to occlude the aorta at five pre-defined locations (color coded on Figure 2a). Positions were as follows: 1) superior to the distal FLOXsp detector, 2) between the distal and central FLOXsp detector, 3) between the central and proximal FLOXsp detector, 4) between the proximal FLOXsp detector and the LDF probe, and 5) below the LDF probe. At each location balloon inflation was verified fluoroscopically, and with sustained loss of inferior femoral arterial pressure. Changes in flow were documented at each of the three FLOXsp detectors, as well as at the LDF probe. Balloon inflation was maintained at each position for 5 minutes and flow was allowed to return to baseline prior to movement and reinflation.

Results: Figure 2b depicts the characteristic regional changes in blood flow sensed by the FLOXsp device and the LDF probe in response to balloon inflation at each level, in a single pig, as the balloon was moved from its most superior position to its final position below all sensors. Flow (DCS), as measured at the three FLOXsp detector regions and the LDF probe, are depicted on the left y-axis, while time is depicted on the x-axis. Matching colored arrows can be found on Figures 2a and 2b, indicating balloon position. The mean FLOXsp (DCS) blood flow response measured above balloon occlusion at any position was slightly elevated (7±37%), while mean FLOXsp (DCS) blood flow below the level of balloon occlusion dropped by 51±29% ($p<0.001$). Predicted region-related changes in flow as measured with the FLOXsp matched changes detected by the single LDF detector.

Conclusion: The FLOXsp device is able to immediately detect and regionally discriminate changes in spinal cord blood flow during aortic occlusion. This device may have utility in monitoring for spinal cord ischemia in thoracic and thoracoabdominal aortic surgery.

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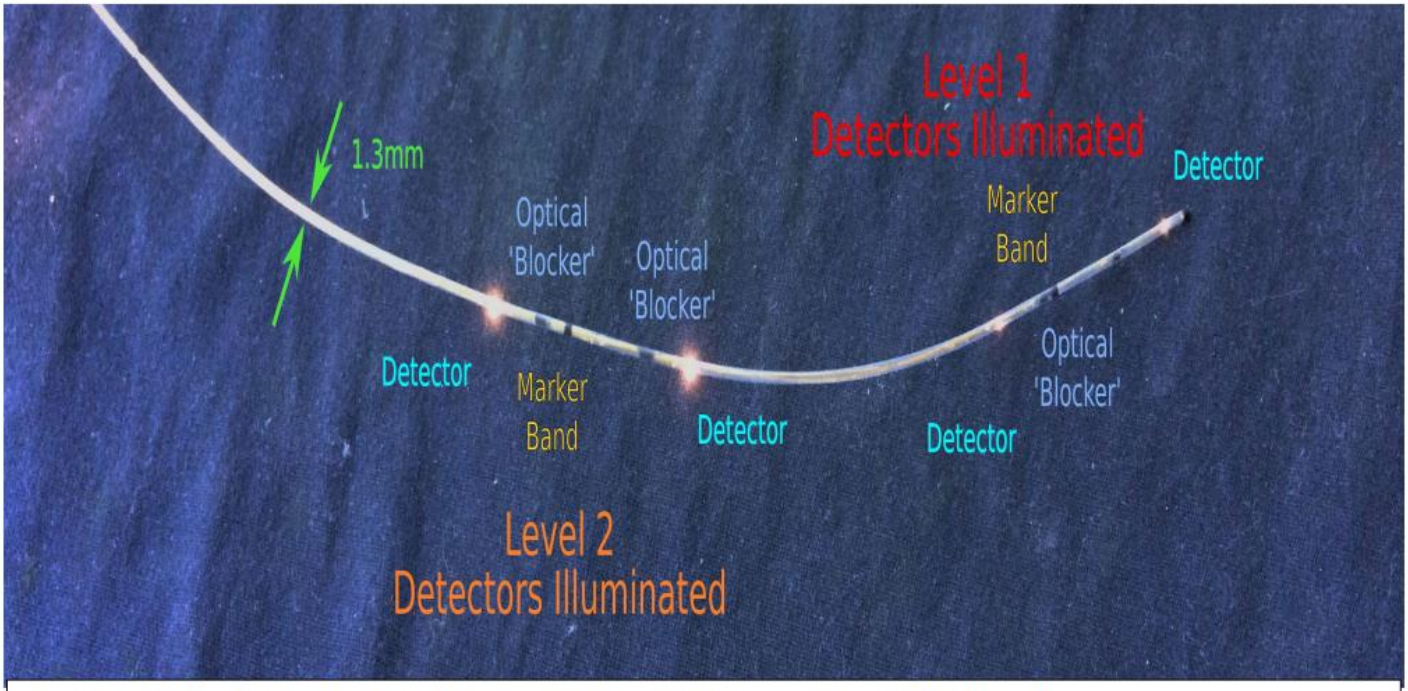

Figure 1. FLOX$_{SP}$ Multi-level probe. Two (of three) detector sets are illuminated.

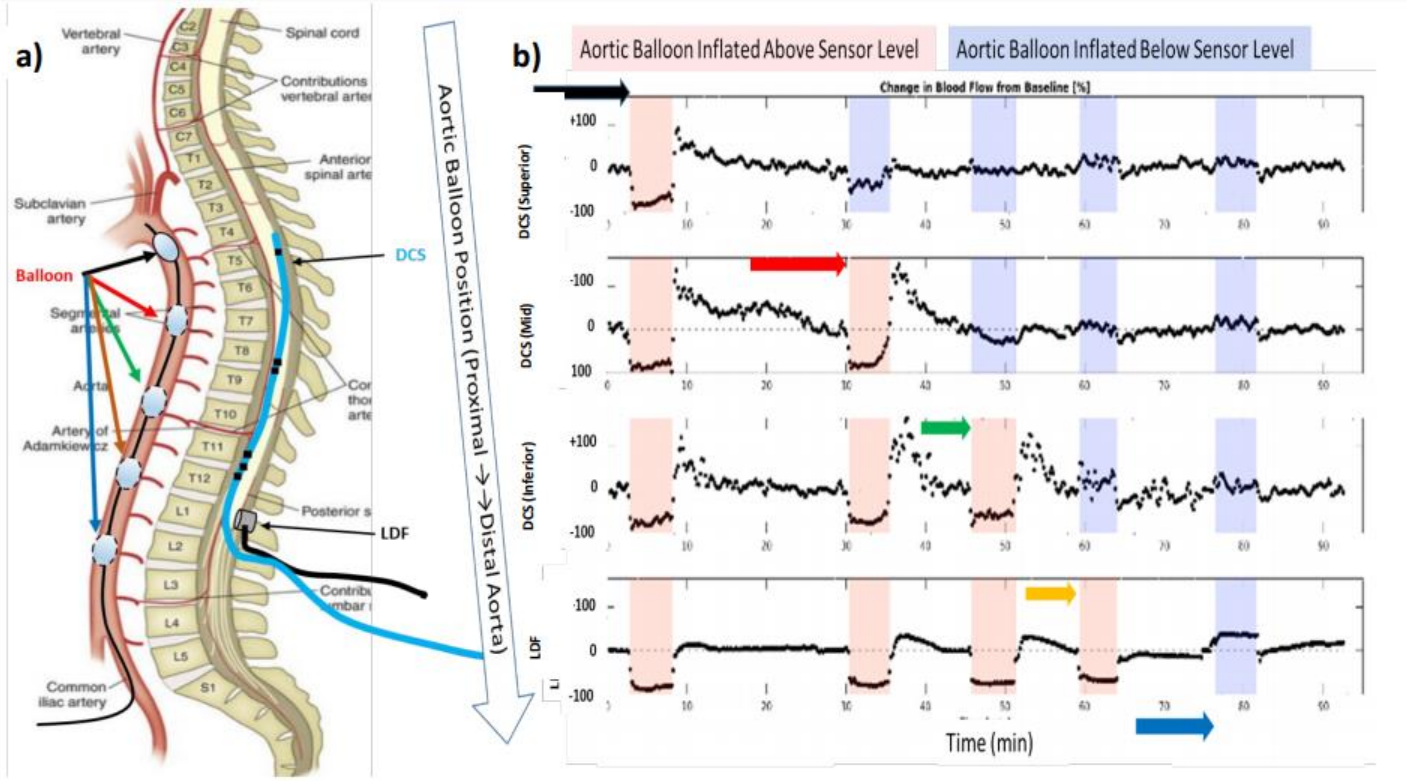

Figure 2. a) Position of ER-REBOA balloon in relationship to FLOXsp probe. **b)** FLOXsp (DCS) blood flow and LDF responses to balloon inflation from superior to inferior positions.

Technology, Computing and Simulation, Equipment Monitoring-3 Assessing Anesthesia Residents' Cognitive Load through Digital Biomarkers during a Simulation-Based Crisis Resource Management (CRM) Training.

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Introduction: Cognitive load reflects the balance between demand and available resources within working memory.1 Learning processes and outcomes are intrinsically related to the level of cognitive load imposed by teaching activities and cognitive overload can negatively impact learning and long-term retention.2,3 The aim of this study was to investigate anesthesia residents' cognitive load through heart rate variability (HRV) during different phases of a simulation-based Crisis Resource Management (CRM) training.

Methods: A 2-hour high-fidelity simulation-based CRM training program was developed. Each session was composed of an introductory lecture + pre-briefing, 2 scenarios each followed by a debriefing. Two of the following scenarios were conducted in each session: intraoperative hemorrhage, preoperative anaphylaxis, complicated vaginal delivery, postpartum hemorrhage, high spinal anesthesia, bradycardia, ventricular fibrillation and laryngospasm. Participants were anesthesia residents, wearing a chest strap with a heart rate sensor capable of detecting continuous electrical heart signals, calculate interbeat intervals (R-R intervals) in milliseconds, and transmit data via Bluetooth connection to a smart watch. Raw data were processed generating more than 40 HRV parameters. We selected the high frequency/low frequency ratio (LF/HF ratio) that is a validated proxy for cognitive load.4 The parameter HF/LF ratio was calculated using a 1-minute time window, allowing comparison across the different phases of the CRM training. A mixed model analysis with repeated measures was performed.

Results: A total of 16 anesthesia residents participated in 7 sessions. Eight participants (50%) were female, 12 were PGY-2 (75%), 3 PGY-4 (18.8%) and 1 PGY-5 (6.3%). The average age was 29.9 + 4.1 years. Analysis of learners' cognitive load (HF/LF ratio) demonstrated statistically significant differences across distinct phases of the simulation training ($F = 7.004$, $p < 0.001$). As shown in Figure 2, maximum cognitive load occurred during the first scenario (6.93 + 0.48), with the lowest cognitive load occurring during the second debriefing (3.56 + 0.43). Pairwise comparison (Bonferroni adjustment) showed a statistically significant difference between scenario 1 and debriefing 1 ($p = 0.025$); and debriefing 2 and all phases: pre-brief/lecture ($p = 0.04$), scenario 1 ($p < 0.001$), debriefing 1 ($p = 0.002$), scenario 2 ($p=0.047$).

Conclusion: In this pilot study, we used an objective digital biomarker (HRV) to measure the cognitive load of anesthesia residents during simulation-based CRM training. Our findings revealed that the cognitive load (HF/LF ratio) imposed during simulation activities is higher than the normal range in adults (1.5-2.5). However it appears to fluctuate across different simulations phases. Cognitive load was higher during scenarios compared to debriefings, and learners completed the last debriefing session with the lowest cognitive load across all phases. This data suggests that simulation-based training may have the positive effect of decreasing learners' cognitive load, releasing working memory and potentially enhancing information storage into long-term memory. Future studies should investigate the relationship between decreased cognitive load, performance and long-term knowledge/skills retention.

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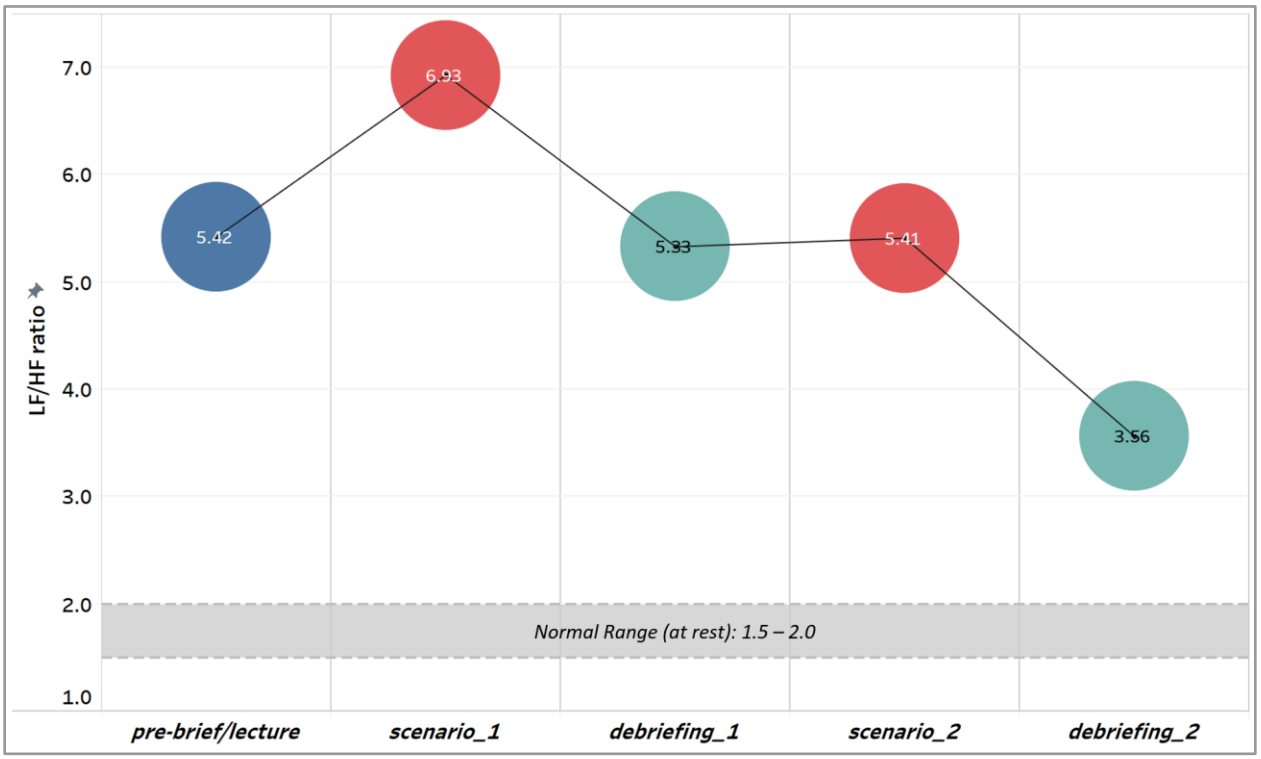
7.0
6.0
5.0
4.0
3.0
2.0
1.0
LF/HF ratio
6.93
5.42
5.33
5.41
3.56
Normal Range (at rest): 1.5 – 2.0
pre-brief/lecture
scenario_1
debriefing_1
scenario_2
debriefing_2

Technology, Computing and Simulation, Equipment Monitoring-4 Lag time in drug delivery by continuous intravenous infusion: direct comparison of peristaltic and syringe pump performance reveals similar effects of dead volume but different startup characteristics

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Introduction: Drug delivery by continuous infusion is prone to time lags between the initiation of an infusion and achievement of the intended delivery rate [1]. At least 3 factors contribute to time lags: 1) dead volume size, (2) the ratio between total system flow and dead volume, and (3) startup delay [2,3]. Dead volume is the total volume contained within catheters, tubing, and connectors from the point where drug and carrier flow streams meet to the patient's blood. Startup delay refers to the intrinsic mechanical properties of the system that the pump must overcome when the pump is turned on [4]. Two common infusion pump types are peristaltic and syringe pumps. Peristaltic pumps use linearly arranged rollers to sequentially compress the tubing of an infusion set, causing forward displacement of fluid in discrete boluses. Syringe pumps use a piston to push a plunger through a fluid-filled syringe. They are preferred for low flow rate delivery (< 5 mL/hr) because continuous flow improves accuracy. The potential clinical impact of long lag times to achieve intended drug delivery rates is a recognized safety concern [5]. We directly compare the performances of a representative peristaltic pump and a representative syringe pump on delivery lag time at clinically relevant flow rates.

Methods: We used established methods [6,7] to quantify delivery of methylene blue (MB, 0.1 mg/mL). Our setup contained two peristaltic pumps (Sapphire; QCOR Medical) or two syringe pumps (Medfusion 2500; Smiths Medical). One pump delivered MB as the model drug, while the other delivered saline as the carrier. In an adult model system, the carrier pump was set to a rate of 10 mL/h and the drug pump was set to a rate of 3 mL/h (5 mcg/min). In a pediatric model system, the carrier pump was set to a rate of 1.5 mL/h and the drug pump was set to a rate of 0.5 mL/h (0.833 mcg/min). A manifold connected the drug and carrier fluid pathways to the distal lumen of a 7Fr triple lumen adult catheter or a 5Fr double lumen pediatric catheter, with manufacturer reported dead volumes of 0.39 mL and 0.26 mL, respectively. MB delivery was quantified by spectrophotometric absorbance. Delivery curves were modeled and compared by multivariable fractional polynomial methods. Post-hoc pairwise comparisons were performed using two sample t-test. The time required to reach 5% (T5), 50% (T50), and 95% (T95) of the intended delivery rate was estimated and reported.

Results: Effects of Startup + Dead Volume The combined effects of startup delay and dead volume on the time required to reach a target delivery rate were studied by turning on the drug pump to initiate MB flow into an ongoing continuous carrier flow. The time required for the drug pump to overcome startup and for the MB to flow through the dead volume to reach the intended delivery rate was measured. Adult Model: The ability to overcome the combined effects of startup delay and dead volume differed between syringe and peristaltic pumps ($p < 0.001$). T5, T50, and T95 were shorter for the peristaltic pump compared to the syringe pump. Pediatric Model: The ability for the pumps to overcome the combined effects of startup delay and dead volume differed between syringe and peristaltic pumps ($p < 0.001$). T50, and T95 were shorter for the syringe pump, while T5 was shorter for the peristaltic pump. Dead Volume Effects To isolate the time lag due to dead volume from that of startup, the carrier and drug infusion pumps were run separately prior to the experimental start. The drug infusion was then directed into the main fluid pathway. The time required for MB to flow through the dead volume and reach the intended delivery rate was measured. Adult Model: The ability for the pumps to overcome dead volume was overall similar between syringe and peristaltic pumps. Pediatric Model: The ability for the pumps to overcome dead volume was overall similar between the two pumps. The T50 was shorter for the syringe pump, while T5 and T95 were similar.

Conclusion: Dead volume and mechanical startup in carrier-based infusion systems cause substantial time lags to reach intended delivery rates when initiating drug infusions. Peristaltic and syringe pumps are similarly susceptible to dead volume effects. Startup performance differed between peristaltic and syringe pumps; their relative performance may be dependent on flow rate. Clinicians must not expect the two types of pumps to perform interchangeably in terms of mechanical startup.

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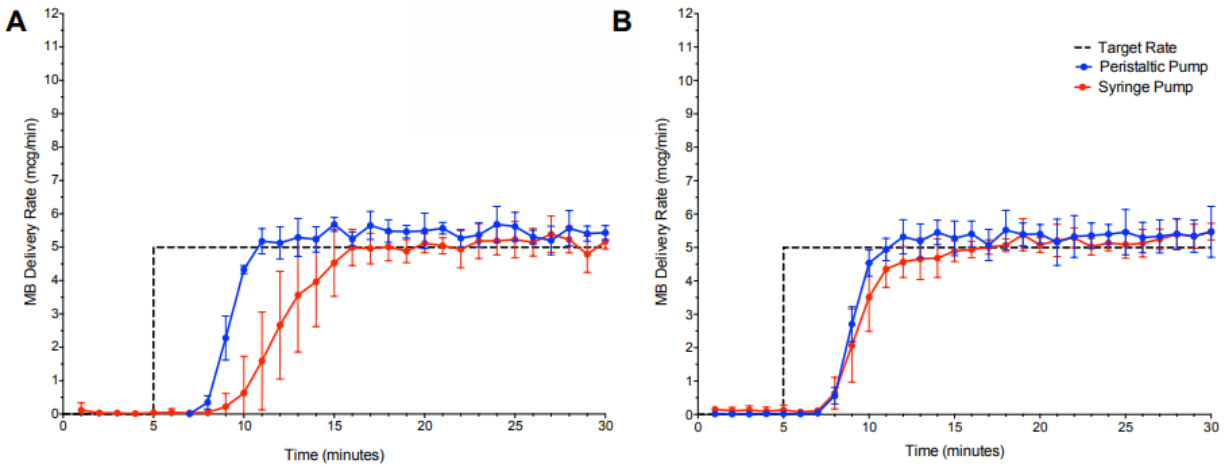

Figure 1. Results from the adult model system. Panel A shows the combined effects of startup delay and dead volume on the initiation of a drug infusion. Panel B shows the effects of dead volume alone on the initiation of a drug infusion.

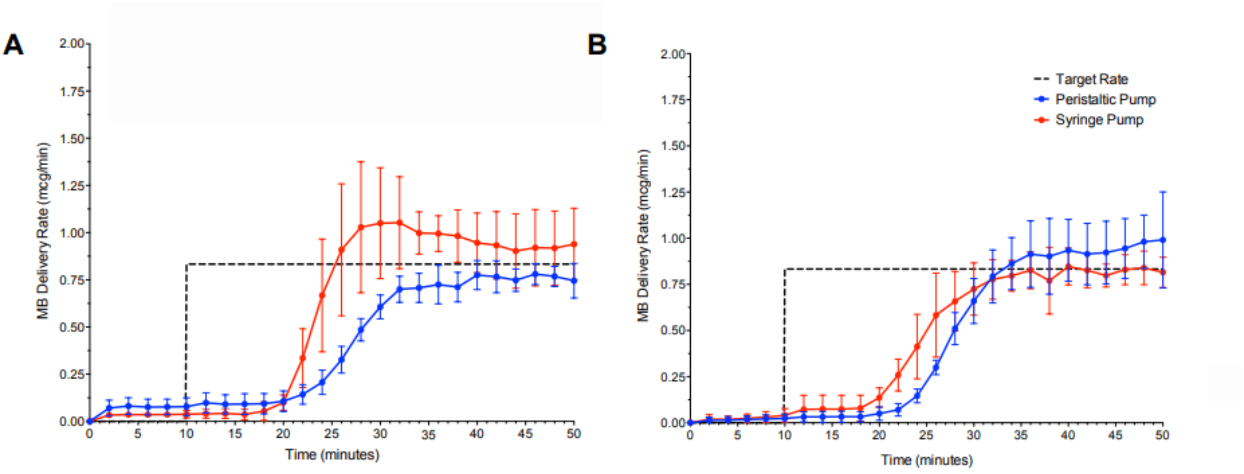

Figure 2. Results from the pediatric model system. Panel A shows the combined effects of startup delay and dead volume on the initiation of a drug infusion. Panel B shows the effects of dead volume alone on the initiation of a drug infusion.

Table 1. Time to achieve 5% (T5), 50% (T50), and 95% (T95) of the intended delivery rate after initiation of a drug infusion in an adult model (13 mL/h total flow)

Startup + Dead Volume Effects		Mean (minutes)		Statistics	
	n	**Peristaltic Pump**	**Syringe Pump**	**Difference [95% CI]**	**P value**
5%	5	2.732	5.064	-3.417 [-4.165, -0.499]	*0.0233*
50%	5	4.104	6.960	-3.687 [-4.974, -0.738]	*0.0196*
95%	5	5.688	10.368	-3.305 [-8.542, -0.818]	*0.0278*
Dead Volume Effects		Mean (minutes)		Statistics	
	n	**Peristaltic Pump**	**Syringe Pump**	**Difference [95% CI]**	**P value**
5%	5	2.476	1.412	1.820 [-0.512, 2.640]	0.138
50%	5	3.928	4.328	-1.315 [-1.191, 0.391]	0.248
95%	5	5.552	6.740	-1.590 [-2.960, 0.584]	0.157

Table 2. Time to achieve 5% (T5), 50% (T50), and 95% (T95) of the intended delivery rate after initiation of a drug infusion in a pediatric model (2 mL/h total flow)

Startup + Dead Volume Effects		Mean (minutes)		Statistics	
	n	**Peristaltic Pump**	**Syringe Pump**	**Difference [95% CI]**	**P value**
5%	8	0.350	4.838	-3.035 [-7.766, -1.211]	*0.0120*
50%	8	17.113	12.909	6.889 [2.905, 5.502]	*< 0.001*
95%	8	29.485	15.987	5.762 [8.192, 18.803]	*< 0.001*
Dead Volume Effects		Mean (minutes)		Statistics	
	n	**Peristaltic Pump**	**Syringe Pump**	**Difference [95% CI]**	**P value**
5%	8	6.810	3.430	1.351 [-2.034, 8.794]	0.200
50%	8	17.255	14.603	3.779 [1.045, 4.260]	*0.00500*
95%	8	24.483	19.437	1.830 [-0.973, 11.065]	0.0926

Technology, Computing and Simulation, Equipment Monitoring-5 Applying Three-Dimensional Multi-Objective Optimization to the Perioperative Services

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[1]University of Vermont, Burlington, VT, [2]Oxford University Hospitals, Oxford , United Kingdom, [3]UAMS, Little Rock, AR, [4]University of Vermont Medial Center, Burlington, VT

Introduction: Although the chief objectives of operating room management are to maximize clinical productivity and minimize under and over-utilized time, multi-objective optimization problems are often very challenging to solve. Despite these challenges, considering multiple criteria undoubtedly leads to better informed decisions. With the advent of data science, multi-objective optimization will enable hospital administrators understand the trade-offs between financial and operational measures. Previously, Tsai et al. demonstrated that it is possible to apply performance frontiers as an economic framework to operating room management metrics of under and over-utilized time [1]. In this article, we expand the previous narrative by using multi-objective optimization to extend the two-dimensional analysis with performance frontiers to three dimensions. Herein, we evaluate the Pareto optimality of an ACS service model on General Surgery (GS) by utilizing three metrics: under-utilized time, over-utilized time, and a financial productivity metric.

Methods: The following monthly summed OR management data were extracted from WiseOR® (Palo Alto, CA), for two years prior and two years after the October, 2015 ACS implementation: out-of-block minutes, after-hours minutes, and opportunity-unused minutes. Monthly block metrics were calculated as follows: Over-utilized time = After-hours minutes + Out-of-block minutes Under-utilized = Opportunity-unused minutes. From financial reports, we obtained monthly work Relative Value Units (wRVUs) and clinical Full Time Equivalents (FTEs) for faculty of the GS service. As Paine et al. did, we used the wRVU/FTE ratio to quantify the financial impact on the GS service of the implementation of the ACS model of care [2]. Under-utilized time, over-utilized time and productivity over the four-year span were then normalized independently of one another to lie between zero and one. Because this multi-objective optimization was performed in the three-dimensional space, the hyperplanes are thus the two-dimensional planes. In three-dimensional space, we randomly assigned underutilization to the x-axis, overutilization to the y-axis, and productivity to the z-axis. Using the programming language Python, the pre-transition and post-transition data were then plotted on the hyperplanes as shown in Figures 1 and 2. The Pareto-optimal sets are the points in which none of the other solutions are superior in the other objectives represented in the space. In both the two-dimensional and three-dimensional multi-objective analyses, the optimal solutions are those that minimize under-utilized and over-utilized time, but maximize productivity, representing the common challenge of conflicting criteria. To address this issue, the direction of the z-axis representing productivity was reversed. Hence, the Pareto-optimal set consists of the outer edge of points closest to the origin (x, z) = (0, 1) and (y, z) = (0, 1) in two-dimensions and (x, y, z) = (0, 0, 1) in three dimensions. The (x, z) and (y, z) coordinates of the pre- and post-transition Pareto-optimal sets were extracted from the two hyperplanes of Figures 1 and 2 to interpolate quadratic surfaces as shown in Figure 3.

Results: The results show that the GS post-transition Pareto-surface is contained within a much smaller volume of space than the GS pre-transition Pareto-surface. In the (x,y) space, the post-transition surface lies closet to the origin representing optimality, however it is higher in its z-elevation, representing lower productivity than the pre-transition surface. This decrease in productivity is due to significant decrease in after-hours case volume. Paine et al. found that over this transition, GS was increased the number of wRVUs generated during normal-hours to compensate for lost after-hours productivity [4]. Hence, the general surgeons were actually more productive during normal hours in the post-transition period [4].

Conclusion: Pareto optimization allows for evaluation of common issues of under-utilized time and over-utilized time in the context of other variables [3]. The Pareto frontier enables operating room managers to track management metrics and their interdependent interactions across time [4]. There is no limitation to the variables that can be analyzed in the context of multi-objective optimization, but it is up to the model user to define the variables based on outcomes that are goals in the context of their healthcare organization.

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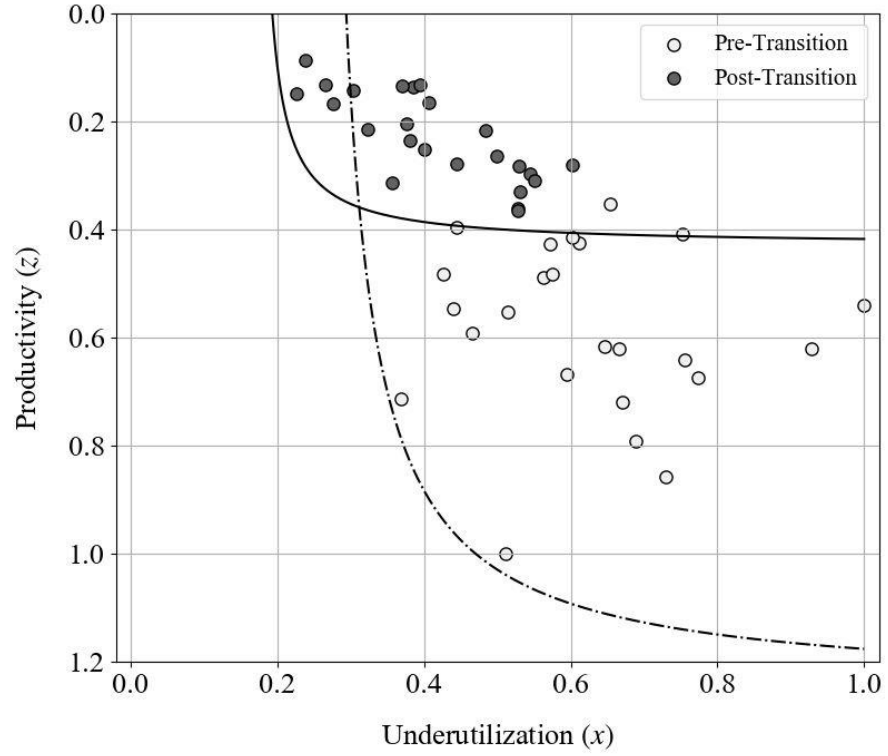

Figure 1

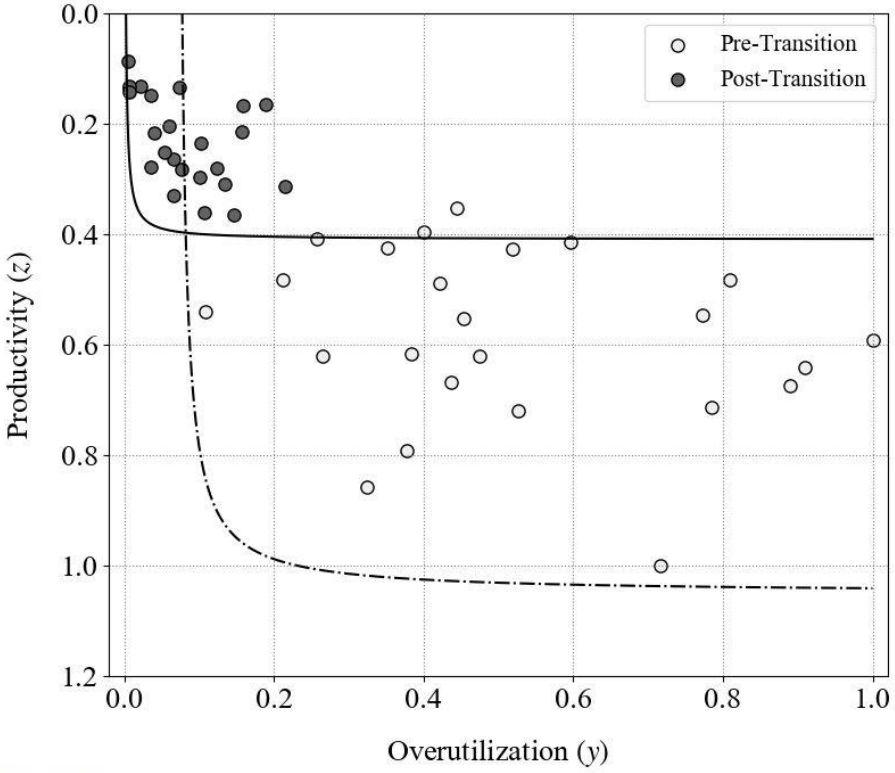

Figure 2

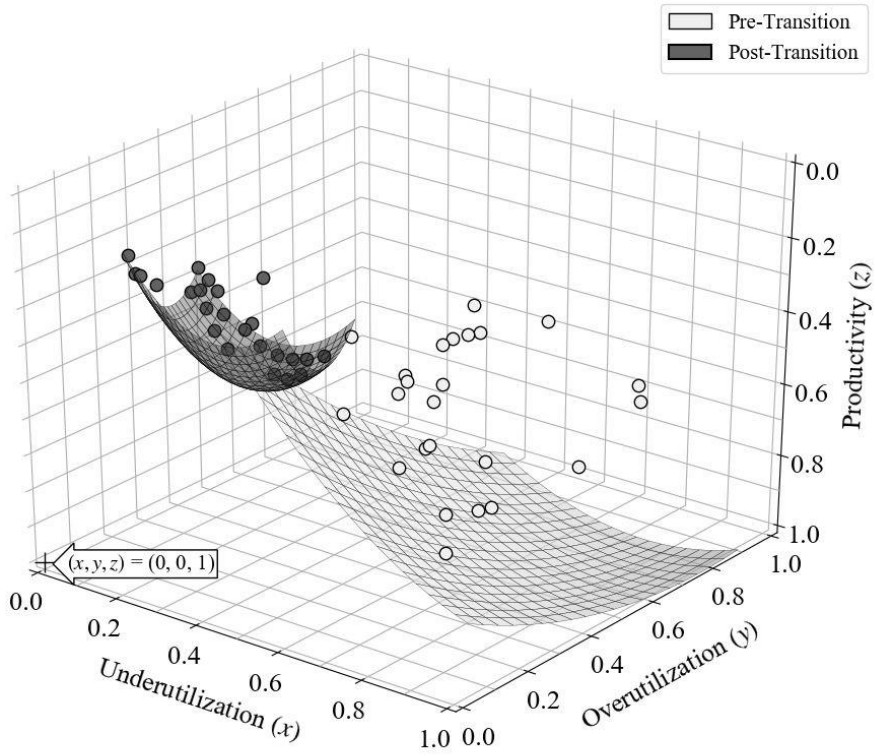
Pre-Transition
Post-Transition
Productivity (z)
0.0
0.2
0.4
0.6
0.8
1.0
(x, y, z) = (0, 0, 1)
Underutilization (x)
Overutilization (y)

Figure 3

Technology, Computing and Simulation, Equipment Monitoring-6 Custom EEG Setup for Direct Comparison of the Patient State Index and Bispectral Index- A Pilot Study

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Introduction: In recent years, the use of processed electroencephalography (EEG) monitors has increased in an effort to closely monitor the impact of anesthetic medications during surgery. Intraoperative use of EEG monitors such as the bispectral index (BIS) and the patient state index (PSI) may be associated with enhanced early recovery times and decreased anesthetic exposure (1,2). Comparative studies between these two indices have applied both commercial sensors simultaneously but size restrictions necessitate that one of the arrays must be placed in a location not consistent with manufacturer recommendations, resulting in compromised accuracy of the collected data (3,4). We present a novel system with a custom-built interface box employing universal neonatal electrodes whose small size allows us to accurately and concurrently compare intraoperative BIS and PSI indices. As proof of concept we present comparative data collected during propofol administration for induction of general anesthesia.

Methods: This was a sponsored, prospective, nonrandomized clinical study that received approval from the Institutional Review Board. All patients provided written informed consent prior to initiation of any study procedures. Data from five adult patients scheduled for elective surgery under general anesthesia were analyzed. Six electrodes (Kendall 1050NPSM Neonatal Electrodes) were applied at locations matching the SedLine sensor array along with five additional sensors applied at BIS Sensor locations (Figure 1). A custom-built interface box was created to allow concurrent use of shared electrode positions and simultaneous connection to the BIS and SedLine monitors. In the operating room, sensors were connected to the interface box. Baseline values were recorded with the patient's eyes closed for 3 min prior to propofol administration. The SedLine Root monitor and BIS system were connected to a computer (Windows Pro PC) for data recording using Masimo Automated Data Collection (proprietary, 2017 version 10.4) and Rugloop (2018 version 10.10) software, respectively. BIS and PSI values were continuously recorded during the induction with propofol.

Results: Three male and two female patients: mean age 65 ± 8.3 years, average weight 88 ± 11.9 kg, average propofol dose 2.78 mg/kg, range 2.38 to 3.10mg/kg were analyzed. PSI, right and left BIS values recorded during the initial 20 minutes of the case are presented in Figure 2.

Conclusion: Our findings demonstrate that this custom interface can provide reliable collection of concurrent BIS and PSI indices in an intraoperative setting. Initial results reveal differences in responses. A larger clinical study utilizing this custom setup is currently underway to characterize differences between PSI and BIS during administration of anesthetic agents over a wide range of EEG activity. This system will allow us to accurately assess the performance of both indices across the entire range of clinical anesthesia.

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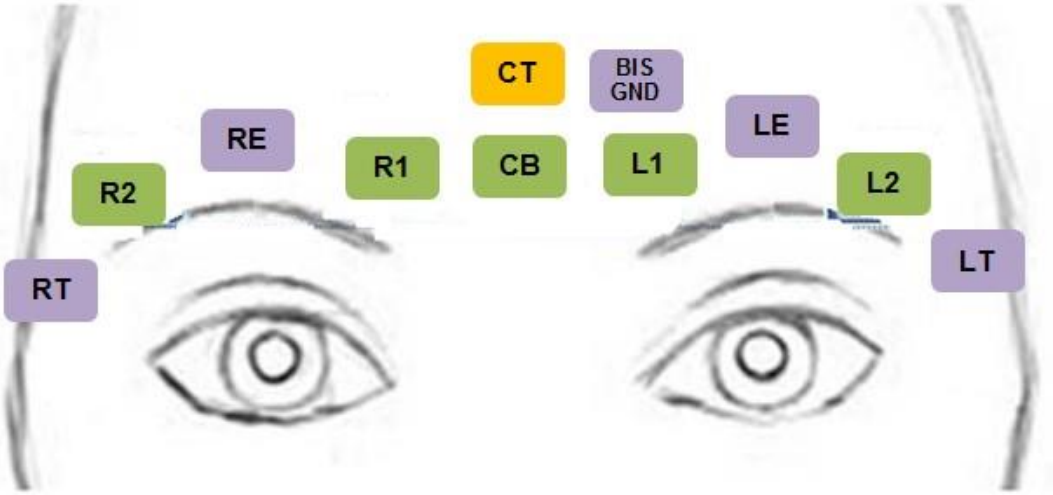
FIGURE 1

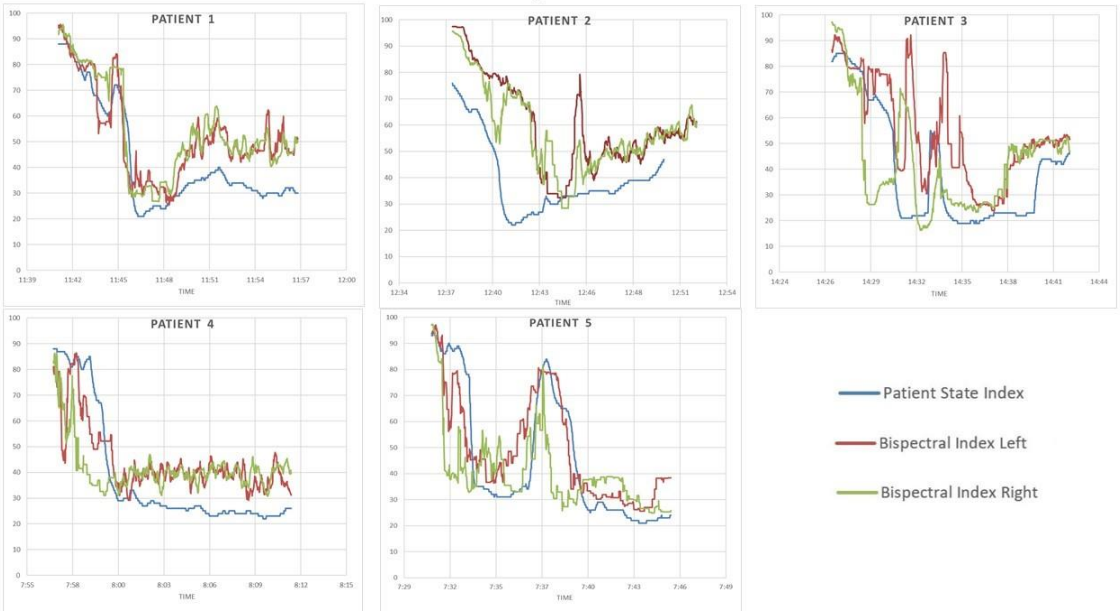


SedLine Electrode Positions

SedLine and BIS Shared Electrode Positions

BIS Electrode Positions

Figure 2



Technology, Computing and Simulation, Equipment Monitoring-7 Examining the correlation between Altmetric Attention Score and Citations in the Anesthesiology Literature

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Introduction: Traditionally accepted measures of determining the quality and impact of scientific research have focused on article citation number and impact factor of the journal where the article was published.1 However, with the rise of digital technology and use of social media platforms used to disseminate research information, impact may also be assessed through these channels. Alternative-level metrics (Altmetrics), are a new measure used to assess the overall impact of scientific publications.2 Altmetrics compile the number of mentions that an article receives across the most commonly used social media platforms such as Twitter, Facebook, and blogs and research websites. The primary objective of this study is to explore the relationship between bibliometrics and Altmetric scores of the 50 most frequently cited articles published in the top anesthesiology journals in 2016.

Methods: We identified the top 10 most-cited articles for the 5 journals with the highest impact factor in 2016 (Anesthesiology, British Journal of Anaesthesia, European Journal of Anaesthesiology, Anaesthesia and Anesthesia & Analgesia). Citation count by Scopus and Altmetric scores were recorded for each of the articles. The journal impact factor in 2016, date of Twitter account development, and total number of tweets were recorded for each of the journals. The Altmetric scores for the top 50 cited articles in the journals were determined as well as the average altimetric and citation score per journal. Descriptive statistics were performed and variables were analyzed in Microsoft excel using Pearson's correlation testing.

Results: A total of 50 articles were analyzed. The highest Altmetric score for any article was 349, mean (standard deviation[SD]) was 57.4 (22.6) and highest citation score was 119, mean (SD) was 34.2 (55.2). The journal with the highest mean article Altmetric score was Anesthesiology, which also had the highest impact factor. In 2016, Altmetric scores and citation numbers showed a moderate positive correlation (r=0.43), although Altmetric scores correlated weakly with journal impact factor (r=0.30). There was strong correlation between the journal impact factor and average Altmetric score of articles from that journal and a moderate correlation between number of overall tweets by journal and the average altmetrics score of articles from that journal (r=0.55). The strongest correlations were found between journal impact factor and citation counts (r=0.71), and the journal impact factor and average citation counts of articles from that journal (r=0.91).

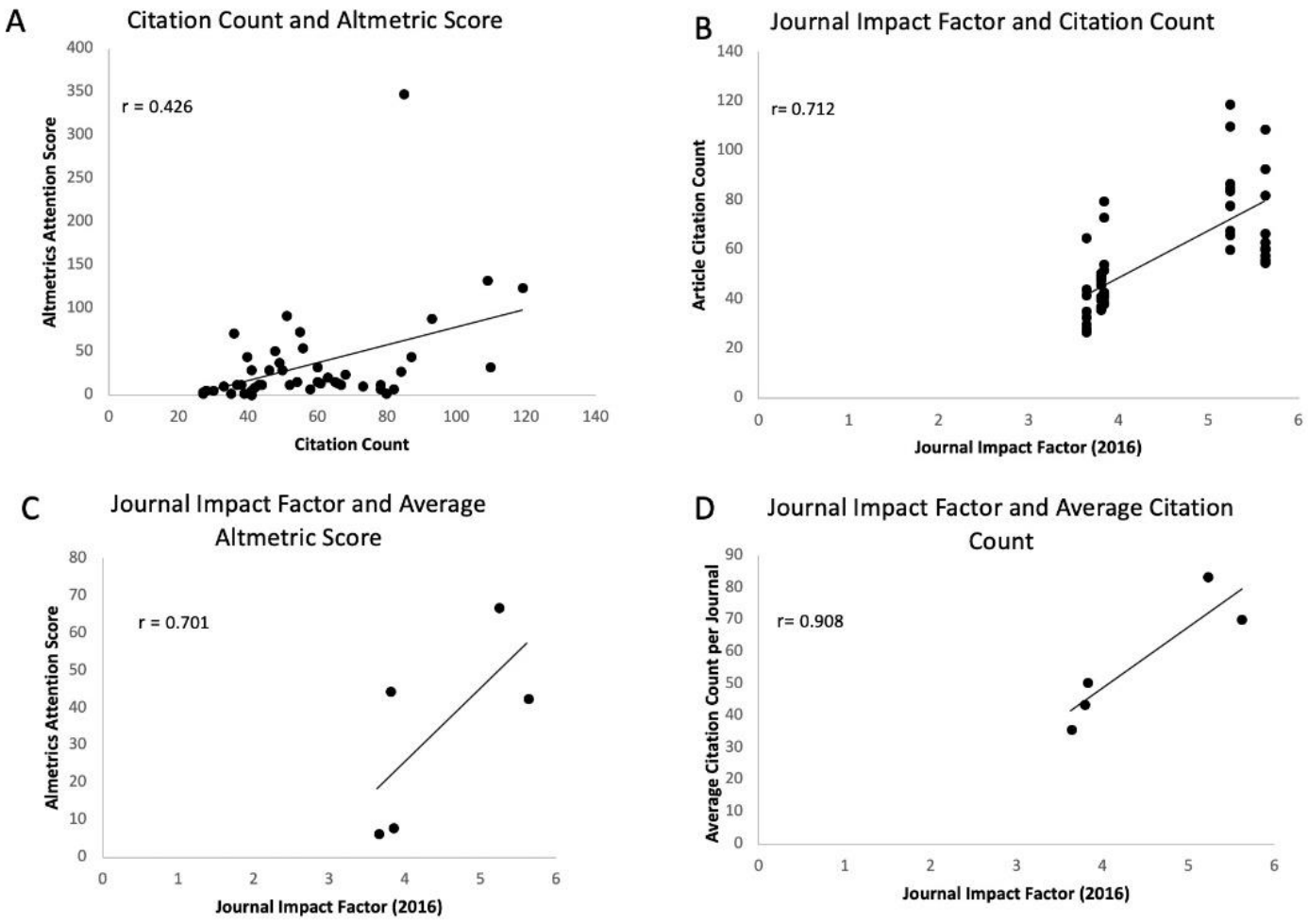
Conclusion: This study is the first analysis of Altmetric scores for the top cited articles in Anesthesiology. We demonstrated that Altmetric score is moderately correlated with citations count in the anesthesiology literature and average Altmetric score is correlated with overall number of journal tweets for the top papers in anesthesiology. As social media influence continues to increase, future research is needed to better understand the relationship between traditional metrics and alternative metrics over time and to determine how social media exposure impacts articles and journals.

Reference(s):

1. Barbic D, Tubman M, Lam H, Barbic S. An Analysis of Altmetrics in Emergency Medicine. Acad Emerg Med 2016;23:251-68.

2. Nocera AP, Boyd CJ, Boudreau H, Hakim O, Rais-Bahrami S. Examining the Correlation Between Altmetric Score and Citations in the Urology Literature. Urology 2019;134:45-50.

Figure: Correlations between Altmetric Score, Journal Impact Factor, and Citation Count



Technology, Computing and Simulation, Equipment Monitoring-8 The Kaplan-Meier Model Overestimates The Probability Of Healthcare-Associated Infections In ICU Patients

Ksenia Ershova[1], Martin Wolkewitz[2], Oleg Khomenko[3], Olga Ershova[4], Vladimir Zelman[5]

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Introduction: Outcome research in critical care is often focused on the occurrence of complications over time during an Intensive Care Unit (ICU) stay, and the method to do this research is usually a time series analysis. The Kaplan-Meier model is most frequently used to analyze these time series. Used mostly for survival data, it is also popular for evaluating the probability of various complications in the ICU [1]. One important assumption of the Kaplan-Meier model, is that patients who dropped out from the observation, due to discharge or death, have the same risk of complication as those who stayed, which is not accurate for healthcare-associated infections (HAI). There is an alternative model that accounts for competing events, events that preclude the occurrence of complications [2]. It was previously shown that Kaplan-Meier model overestimates the risk of complications in ICU patients [3], however, there is no such data for the risk of HAIs. In this study we compared the performance of the Kaplan-Meier and competing risk models to analyze the probability of HAIs in the ICU.

Methods: An infection surveillance database was prospectively collected in the neurosurgical ICU from 2011-2018. All patients who stayed for >48 hours were included. Three types of HAI were analyzed: urinary tract infections (UTI), ventriculitis/meningitis (HAVM), and pneumonia. The Nelson-Aalen model was used to demonstrate instantaneous hazard. The cumulative probabilities of each infection through day 60 in the ICU estimated by the Kaplan-Meier and competing risk models were compared.

Results: Of the 2,918 included patients, 797 of the patients had UTIs, 307 had HAVMs, and 673 of them had pneumonia. The instantaneous hazard of all three HAIs was non-monotonous over time. It increased rapidly from day 0 to days 10-15 in the ICU and then fluctuated around the higher values of hazard (Figure 1, A1-C1). Cumulative incidence over an eight-year study period calculated per 100 ICU patients was 27.3 for UTI, 10.5 for HAVM, and 23.1 for pneumonia. These values also corresponded to the highest probability of infections in the competing risk model (Figure 1, A2-C2). The Kaplan-Meier model overestimated the cumulative probability of all three infections at day 60 in the ICU: for UTI 2.9 times (0.77 vs 0.27), for HAVM the difference was 4.2 times (0.42 vs 0.1), and for pneumonia 3.2 times (0.72 vs. 0.22), Figure 1, A3-C3. By the end of the study, the at risk number, the number of patients who remained in the ICU by day 60, was 166. This number constituted a significant dropout rate.

Conclusion: We showed that the immediate risk of HAIs in the ICU is non-linear and depends on the number of days patients already spent in the unit. Therefore, it is of interest to study the cumulative probability of HAIs in a time series analysis. As our study demonstrated, in a situation of substantial patient dropout due to discharge or death, the Kaplan-Meier model significantly overestimated a cumulative incidence of UTIs, HAVM, and pneumonia. The competing risk model accounts for the dropout and therefore is recommended when studying the probability of HAIs in the ICU.

Reference(s):

1. Zhang et al. 2019. “The Cumulative Venous Thromboembolism Incidence and Risk Factors in Intensive Care Patients Receiving the Guideline-Recommended Thromboprophylaxis.” Medicine 98 (23): e15833.

2. Fine, Jason P., and Robert J. Gray. 1999. “A Proportional Hazards Model for the Subdistribution of a Competing Risk.” Journal of the American Statistical Association 94 (446): 496–509.

3. Lacny et al. 2018. “Kaplan-Meier Survival Analysis Overestimates Cumulative Incidence of Health-Related Events in Competing Risk Settings: A Meta-Analysis.” Journal of Clinical Epidemiology 93 (January): 25–35.

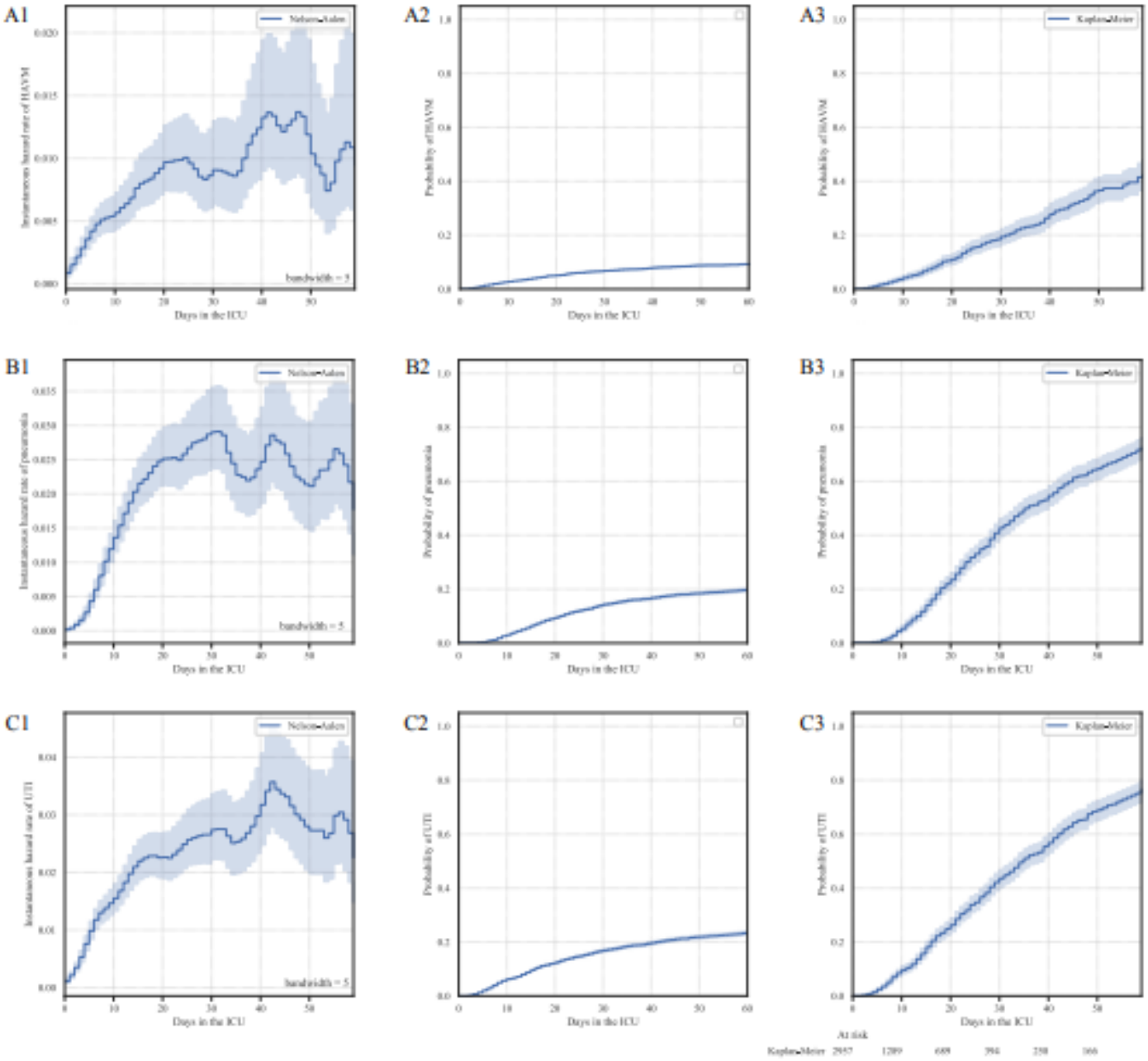


Figure 1. Probability of different healthcare-associated infections in the neurosurgical ICU in 2011-2018. **A1-A3**: Healthcare-associated ventriculitis and meningitis (HAVM); **B1-B3**: Pneumonia; **C1-C3**:Urinary tract infections (UTI). **A1, B1, C1**: Kernel-smoothed function of instantaneous hazard of infections depending on the number of days in the ICU, Nelson-Aalen estimate. **A2, B2, C2**: Cumulative probability of infections depending on the number of days in the ICU while accounting for discharge (death) as competing events (competing risk model). **A3, B3, C3**: Cumulative probability of infections depending on the number of days in the ICU when discharge (death) is censored (Kaplan-Meier model).

Technology, Computing and Simulation, Equipment Monitoring-9 High Fidelity CRISPR Libraries to Interrogate Anesthetic Genetic Susceptibilities

Alexendar R Perez[1]

[1]*University of California, San Francisco, San Francisco, CA*

Introduction: CRISPR technology allows for the versatile and permanent modification of DNA through a two component system: a targeting element (Guide RNA) and an endonuclease that cleaves double stranded DNA. CRISPR mediated DNA cleavage allows for the generation of loss-of-function perturbations or precisely engineered modifications of genomic loci. The ease and effectiveness of CRISPR technology in inducing these changes, makes it an ideal tool for genetic screens as it allows for the robust interrogation of virtually any genomic locus. The fidelity of these screens depends on precise targeting by Guide RNAs (gRNA). Guide RNAs must uniquely identify a genetic locus and a complete knowledge of potential off-target sites is essential for precise targeting. Current genome-wide CRISPR libraries contain numerous non-specific gRNAs that create false negatives and false positives in genetic screens. Though the effects of these false negatives and false positives can be corrected computationally, no CRISPR gRNA library currently exists that guarantees high fidelity gRNAs against a broad array of coding sequences. We have utilized our GuideScan software to generate rules defining the design of ultra-specific CRISPR gRNAs libraries for both human and mouse genomes (1). Such libraries are important if investigators utilize CRISPR screens to interrogate the genetic susceptibilities of patients to anesthesia. Recent studies have highlighted the importance of genetics in suggesting new avenues of anesthetic discovery and therapeutic development (2). However, these studies depend on retrospective genotype identification. CRISPR screens, using high fidelity gRNA libraries, allow for prospective identification of genetic targets in human or mouse cells under anesthetic exposure.

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 (1). Unlike the original tries reported in GuideScan (1), 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 were computed using Hamming distance neighbors as previously described (1) Computational Adjustment of Off-Target Effects: A computational adjustment that corrects for off-target effects called the CRISPR Specificity Correction (CSC) was developed by training a Gradient Boosted Regression Tree on gRNA library log2 fold change depletion. A total of 426 features were used in learning. Feature importances for this model were extracted and specificity features, which serve as confounders in this setting, were extracted and modeled with a mathematical correction that was demonstrated to robustly eliminate false positive and negatives. Guide RNA Library Design Guide RNA libraries were constructed using the GuideScan software for the selection of uniquely targeting gRNAs. These gRNAs were filtered such that off-target effects, as measured by the degree of computational correction, were minimal. The GuideScan gRNAs were directly compared against published libraries of gRNAs using positive and negative selection screens. Prior to deploying the libraries, global GuideScan specificity scores were computed for each library and directly compared.

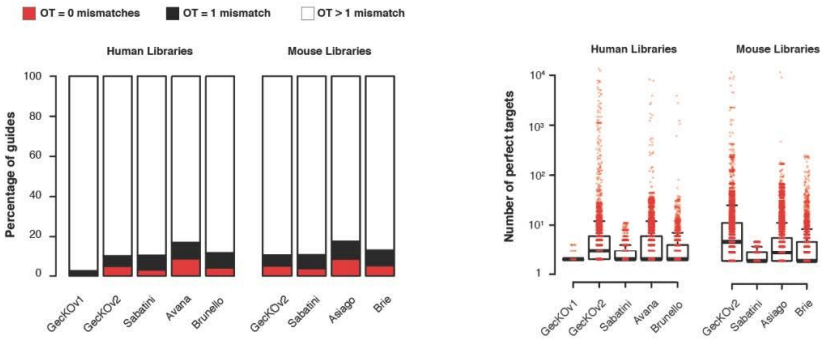
Results: The enumeration and specificity computation of gRNAs allowed for the construction of GuideScan gRNA libraries that were composed exclusively of uniquely targeting gRNAs. Furthermore, the CRISPR Specificity Correction (CSC) was able to robustly account for library gRNA off-target effects. Overall, GuideScan gRNA libraries showed the highest and most robust specificity in targeting genomic loci.

Conclusion: GuideScan libraries contain the most specific gRNAs reported to date and allow for highly precise targeting of loci. These libraries will be deployed to precisely screen for novel genetic susceptibilities to anesthesia.

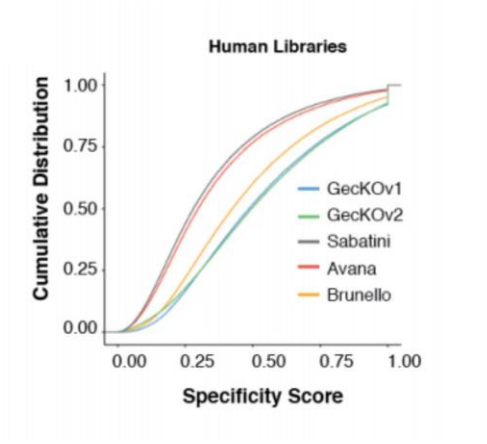
Reference(s):

1: GuideScan software for improved single and paired CRISPR guide RNA design, Nature Biotechnology, 35, 347, 2017

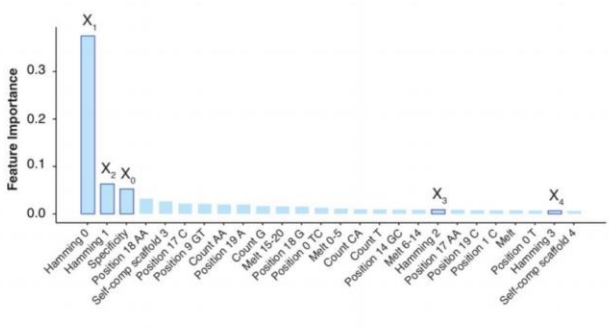
2: Microdeletion in a FAAH pseudogene identified in a patient with high anandamide concentrations and pain insensitivity, British Journal of Anaesthesia, 123, 249-253, 2019

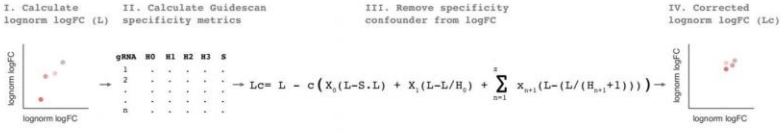

OT = 0 mismatches
OT = 1 mismatch
OT > 1 mismatch
Human Libraries
Mouse Libraries
Percentage of guides
100
80
60
40
20
0
GeckOv1
GeckOv2
Sabatini
Avana
Brunello
GeckOv2
Sabatini
Asiago
Brie
Human Libraries
Mouse Libraries
Number of perfect targets
10^4
10^3
10^2
10^1
1
GeckOv1
GeckOv2
Sabatini
Avana
Brunello
GeckOv2
Sabatini
Asiago
Brie

1

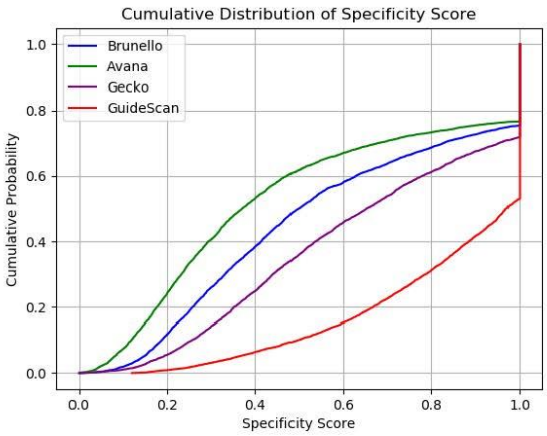

Human Libraries
Cumulative Distribution
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
Specificity Score
GecKOv1
GecKOv2
Sabatini
Avana
Brunello

2


Feature Importance
0.3
0.2
0.1
0.0
X_1
X_2
X_0
X_3
X_4
Hamming 0
Hamming 1
Specificity
Position 18 AA
Self-comp scaffold 3
Position 17 C
Position 9 GT
Count AA
Position 19 A
Count G
Melt 15-20
Position 18 G
Position 0 TC
Melt 0-5
Count CA
Count T
Position 14 GC
Melt 6-14
Hamming 2
Position 17 AA
Position 19 C
Position 1 C
Melt
Position 0 T
Hamming 3
Self-comp scaffold 4


I. Calculate lognorm logFC (L)
II. Calculate Guidescan specificity metrics
III. Remove specificity confounder from logFC
IV. Corrected lognorm logFC (Lc)
lognorm logFC
lognorm logFC
gRNA H0 H1 H2 H3 S
1
2
n
$Lc = L - c\left(X_0(L-S.L) + X_1(L-L/H_0) + \sum_{n=1}^{x} x_{n+1}(L-(L/(H_{n+1}+1)))\right)$
lognorm logFC
lognorm logFC

3


Cumulative Distribution of Specificity Score
Brunello
Avana
Gecko
GuideScan
Cumulative Probability
Specificity Score
0.0
0.2
0.4
0.6
0.8
1.0

Technology, Computing and Simulation, Equipment Monitoring-10 The Rapid Pulse Confirmation Device: An observational study of a prototype device designed to detect return of spontaneous circulation (ROSC) and quantify chest compression efficacy

Jonathan Bond[1], Michael Ritchie[1]

[1]West Virginia University, Morgantown, WV

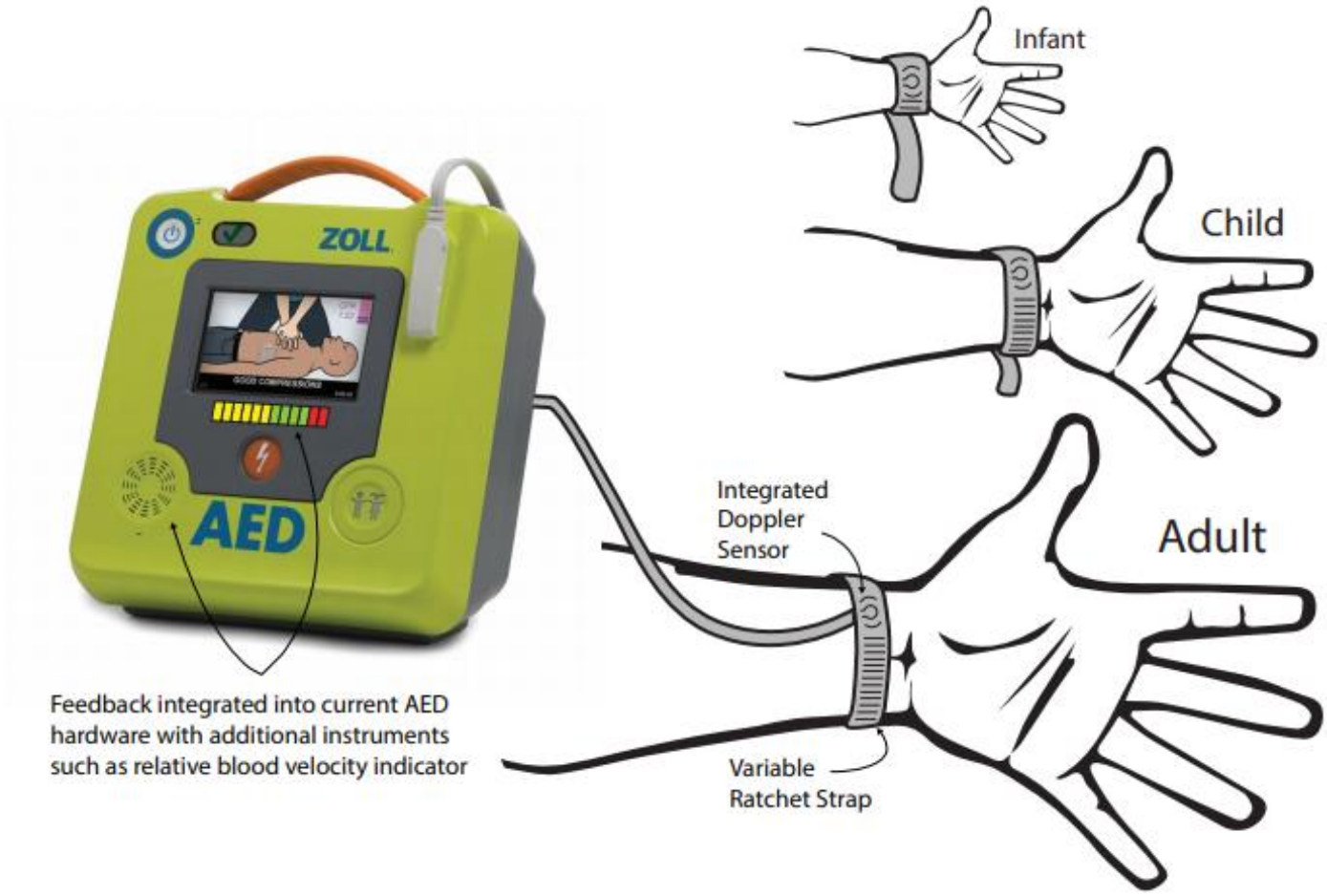
Introduction: Effective chest compressions are essential to the survival of a cardiac arrest requiring cardiopulmonary resuscitation (CPR). Major challenges to providing effective chest compressions are frequent interruption of compressions, insufficient force applied to the chest and low rate of compression. To potentially solve the issues of evaluating the chest compression effectiveness and minimization of the time interval of pulse checks, the authors have constructed a novel device that can be rapidly applied to an arresting patient and evaluate the current state of the circulatory system using a processed Doppler signal. It is designed to be applied over a major artery and detects the Doppler shift of red blood cells to gauge red blood cell velocity and rate of pulsation during compressions and pulsatile blood flow indicative of ROSC during pulse checks. The overall goal of the device is to provide feedback on compression efficacy beyond the American Heart Association depth based approach and increase accuracy while decreasing time required for pulse checks.

Methods: The observation study was designed to assess the viability and functionality of the RPC device prototype in a controlled cardiac arrest environment. Specifically, the data was obtained with the goal being to evaluate initial device performance with the specific observation of the device's ability to detect pulsatile blood flow in comparison with indwelling brachial arterial catheter tracings. Secondary data collected for comparison of RPC device feedback in relation to TEE, pulse oximetry, and ECG. Patients were assessed for inclusion and exclusion criteria in the pre-operative area on the morning of the scheduled cardiac surgery. The left carotid artery was selected due to the convenience of access near the head of the bed and way from the draped sterile field. After the patient had been rewarmed, the RPC device, brachial arterial catheter tracing, and the pulse oximeter were observed for the detection of pulsatile blood flow. The time of detection of the RPC device and the invasive arterial blood pressure were recorded. Observations were made concerning device audible and visual feedback of pulsatile blood flow as well as correlation with other clinical monitors including ECG, transesophageal echocardiography and pulse oximetry. Cardiopulmonary bypass pump flow was recorded if applicable.

Results: The population studied were patients > 18 years of age undergoing valve repair/ replacement surgery, coronary artery bypass surgery or a combination of the procedures who required cardiopulmonary bypass. Further inclusion and exclusion criteria can be seen in Figure 2. A total of 10 patients were enrolled according to the inclusion and exclusion criteria above. BMI range from 24.8 to 39.9 representing patients of normal body habitus to obese body habitus. The average detection time of the RPC device was within one minute of the brachial artery catheter with an SD of 1 minutes. The difference in RPC pulse rate reading and arterial line pulse reading was 3 beats per minute with a standard deviation of 14. Average blood pressure values at the time of detection of ROSC was systolic blood pressure of 77 millimeters of mercury (mmHg) with an SD 11 mmHg and mean arterial pressure of 57 mmHg with an SD 13 mmHg. The data is summarized in Figure 3.

Conclusion: A device that can be quickly applied during a cardiac arrest that would give meaningful feedback about the efficacy of circulation during chest compression as well as substantially reduce pulse check interval could prove beneficial to cardiopulmonary resuscitative efforts both in and outside the hospital. The goal of this quasi-experimental observational study was to assess the ability of the RPC device to detect the return of spontaneous circulation. A patient preparing to separate from CPB often has a lower body temperature, requires ionotropic and/or vasopressor support, has 'stunned' myocardial tissue, and may have fluctuating effective circulatory volume. Many parallels can be drawn between the patient state described above and that of a spontaneous cardiac arrest patient. The observations made in this study showed the device to be able to detect return of pulsatile flow within an average of one minute of detection by an indwelling brachial arterial line. We plan to expand study of the device to spontaneous arresting patients as well as to an animal model to determine limits and significance of detection data.

Reference(s): Dick, Wolfgang F., et al. 'The carotid pulse check revisited: what if there is no pulse?.' Critical care medicine 28.11 (2000): N183-N185. Kleinman, Monica E., et al. '2017 American Heart Association focused update on adult basic life support and cardiopulmonary resuscitation quality: an update to the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care.' Circulation 137.1 (2018): e7-e13. Adedipe, Adeyinka A., et al. 'Carotid Doppler blood flow measurement during cardiopulmonary resuscitation is feasible: a first in man study.' Resuscitation 96 (2015): 121-125. Zengin, Suat, et al. 'Comparison of manual pulse palpation, cardiac ultrasonography and Doppler ultrasonography to check the pulse in cardiopulmonary arrest patients.' Resuscitation 133 (2018): 59-64 Kucewicz, John C., et al. 'Towards a non-invasive cardiac arrest monitor: An in vivo pilot study.' Resuscitation 134 (2019): 76-80.


ZOLL
AED
Feedback integrated into current AED hardware with additional instruments such as relative blood velocity indicator
Infant
Child
Adult
Integrated Doppler Sensor
Variable Ratchet Strap

Inclusion:

18 or older

Left ventricular ejection fraction (LVEF) >40% on pre-operative echocardiogram

Patient with single cardiac valve disease to be repaired during a scheduled surgery

Patient undergoing coronary artery bypass

A combination procedure of criteria 3 and 4

Exclusion:

Redo procedure

Emergency procedure

Arterial stents in the radial, ulnar, brachial, femoral, or carotid arteries

History of peripheral arterial bypass

History of any degree of carotid artery stenosis

Thoracic outlet syndrome

Valvular heart disease NOT being repaired day of surgery

Heart rhythm other than sinus before the scheduled procedure (occasional PVC's ok) as determined by pre-operative EKG

Figure 2- Inclusion and Exclusion Criteria

Subject Number	Sex	BMI	Difference in Time (mins) RPC vs BAC	Difference in Time (mins) pulse oximeter vs RPC	Pulse Difference RPC vs BAC (BPM)
1	male	27.01	-1	-4	0
2	male	24.85	0	-13	-1
3	male	39.69	-3	-14	2
4	female	29.74	-4	-5	0
5	male	30.29	-2	-3	9
6	female	33.15	0	-12	-16
7	female	24.79	0	-2	0
8	female	33.01	0	2	40
9	male	39.9	0	0	-2
10	male	27.82	0	-1	2

Figure 3- Observations of the function of the RPC device versus brachial artery catheter and pulse oximeter in time of detection of pulsatile flow in minutes and beats per minute (BPM) pulse reading.

Patient	Sex	BAC Systolic Pressure (mmHg)	BAC Diastolic Pressure (mmHg)	BAC Mean Arterial Pressure (mmHg)
1	male	62	48	52
2	male	84	37	52
3	male	90	63	72
4	female	75	39	51
5	male	87	65	72
6	female	89	76	80
7	female	74	67	69
8	female	60	53	55
9	male	88	74	78
10	male	69	51	57

Figure 4- The blood pressures (systolic, diastolic, and systolic) at time of BAC detection of pulsatile flow are included to assess device performance at hypotensive pressures.

Technology, Computing and Simulation, Equipment Monitoring-11 Recycling Discarded Anesthesia and Other Equipment in a Patch Clamp Setup for Electrophysiological Recordings in Neuronal Cells.

Maksym Doroshenko[1], Eugene Fu[2], Dennis Patin[2], Roy C Levitt[3], Konstantinos D Sarantopolous[2]

[1]University of Miami / Jackson Memorial Hospital, Miami, FL, [2]University of Miami, Miami, FL, [3]University of Miami, Miami , FL

Introduction: Conducting basic science research, and in particular electrophysiological research, can be very challenging and costly these days. This is more difficult in clinical anesthesiology departments due to the significant costs involved, especially if no dedicated funds from grants are available. On the other hand, research equipment such as set-ups for electrophysiology (patch clamp) recordings are necessary not only for comprehensive basic research focusing on pain mechanisms, but also essential for the professional development and involvement in basic research of residents and junior faculty. Preparing a functional patch clamp setup requires not only basic equipment, such as an inverted microscope, amplifier, digitizer and computer with software, but the manufacturing of a functional and low-noise perfusion system, recording bath chamber and suction for draining the solutions used in the experiments. Some of the components of the latter parts can be easily available in the operating room setting or the procedure rooms in the pain clinics. These include clean, non-contaminated material such as IV and arterial line tubing, stopcocks, manifolds and syringes. Other parts may not be available but can be purchased at very low cost.

Methods: "We have hereby presented the use of recycled anesthesia equipment, as well as other gear used in hospitals for various purposes, but utilized in completing a functional patch clamp set up for electrophysiological recordings. The used anesthesia equipment includes: 1. Unused syringes (clean, non contaminated) obtained from procedure trays, and utilized instead of being discarded. 2. Three-way stop-cocks, obtained from lines that were not used. 3. Plastic IV or arterial line tubing (clean, uncontaminated) obtained from opened packages, but not used. 4. Iodine applicator sponges and gauze were used to clean the recording chamber after experiments. All the above used equipment was clean and non-contaminated. It was obtained from opened procedure trays or line packages that - for various reasons - were not used and were about to be discarded. Nurses and residents were advised to keep that gear for future possible use in the lab. Other equipment. 1. Removable mounting putty and dental or museum wax (purchased from pharmacies or other stores) was used to secure the recording chamber and stage in place. 2. Damage-free hanging strips were used to secure tubing and cables in place. 3. Aluminum foil was used to cover the Faraday cage for improved electromagnetic isolation Suction system. Suction system is necessary to allow drainage of the perfusion solutions from the recording chamber. However, not all laboratory rooms are equipped with a negative pressure vacuum system in the wall. On the other hand, portable vacuum pumps can generate vibrations and electrical noise that is unacceptable for electrophysiological recordings. We used a simple and inexpensive aquarium air flow pump, that was modified into a vacuum suction pump after we reversed its internal valve. This was positioned onto a few plastic gloves to absorb any vibrations. This pump costs less than $10, and is essentially noiseless while it does not generate any electrical interference, but strong enough to provide adequate suction. Finally, small Cuban coffee cups, offered for free in most local coffee shops were used to place solutions or to cover vials containing solutions."

Results: Utilizing above parts made possible the completion of a functional patch clamp set up, saving money that would have otherwise been spent in purchasing specialized tubing or establishing a costly perfusion and vacuum suction system. This set-up has already being used in obtaining patch clamp recordings from neuronal cells in the current clamp and voltage clamp configurations.

Conclusion: We suggest that in an era of financial constraints, anesthesia equipment and disposable gear that is unused, clean and non-contaminated, to be kept for any future possible application in basic science labs, instead of being discarded.

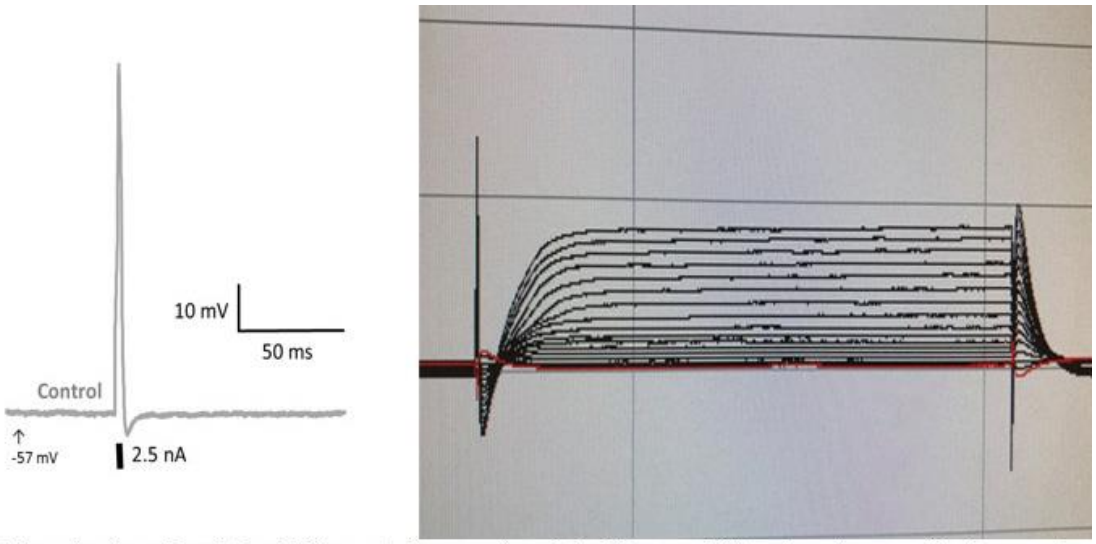


Fig. 1: Examples of recordings obtained. Left - current clamp recording of mice DRG neuron. Right - voltage clamp recordings in successive voltage clamp steps from -60mV poential.

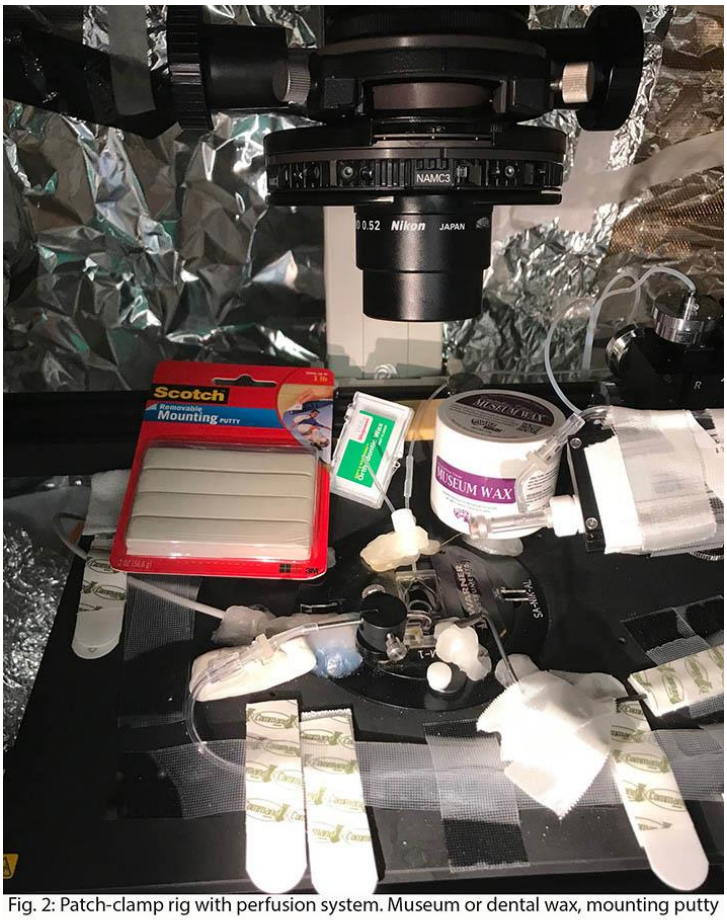


Fig. 2: Patch-clamp rig with perfusion system. Museum or dental wax, mounting putty and strips were used to secure and adjust the perfusion system, made from IV tubing. Aluminum foil covers the Faraday cage for improved electromagnetic isolation.

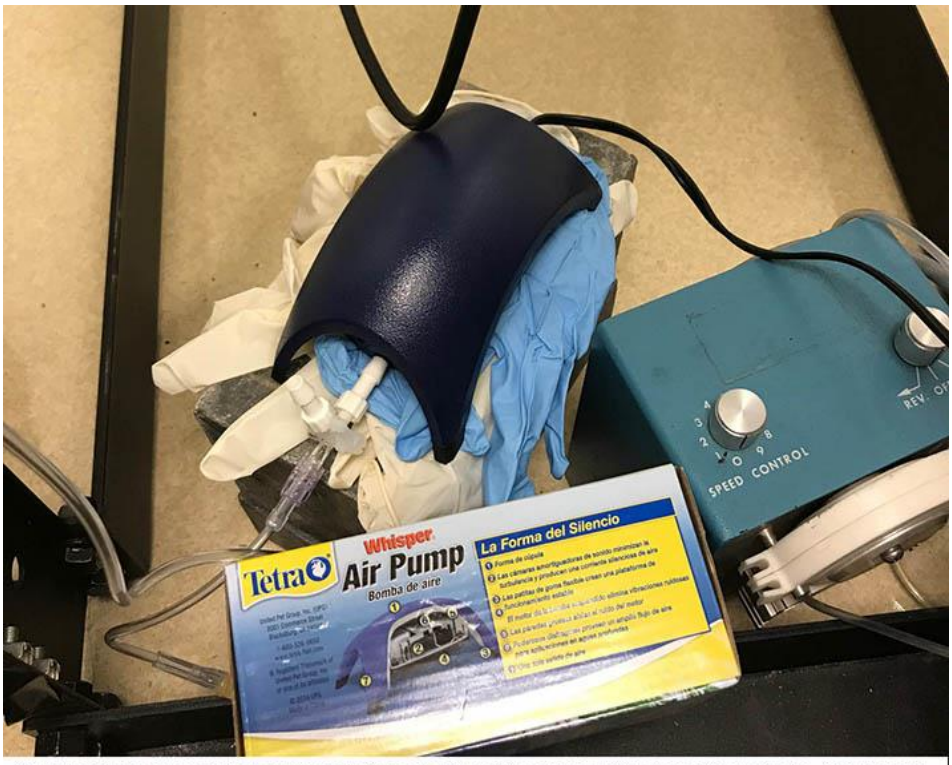


Fig. 3: Modified vacuum suction pump made from aquarium air flow pump with reversed internal valve. Pump is positioned on few plastic gloves to absorb any vibrations.

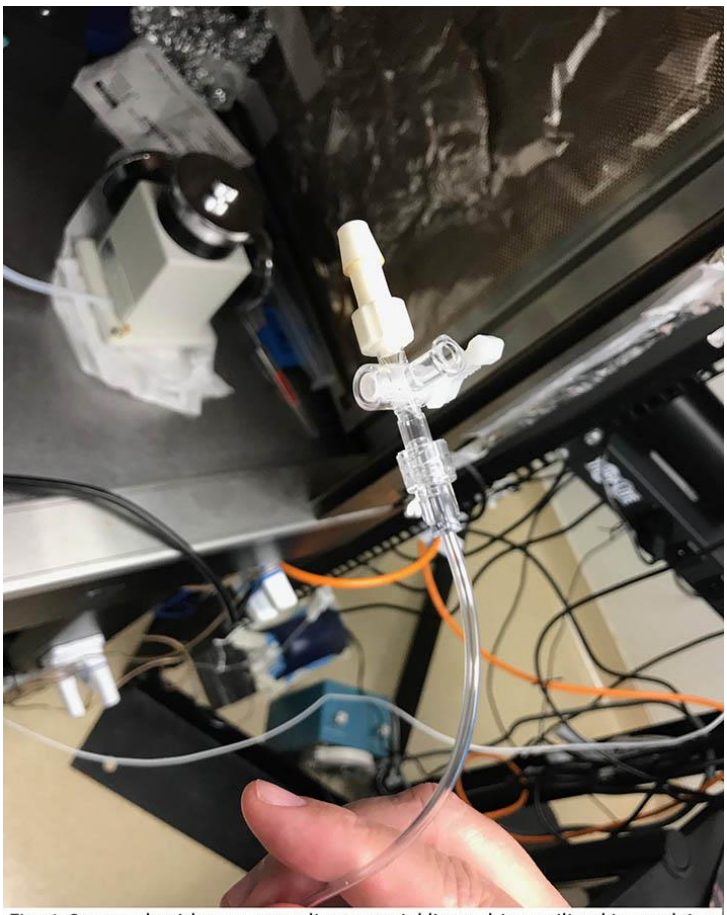


Fig. 4: Stopcock with non-compliant arterial line tubing utilized in applying negative pressure to break cellular membrane attached to patch pipette.

Fig. 5: Unused syringes from procedure trays, manifolds, sponges and sphenopalatine block catheters utilized in perfusion system and intracellular/extracellular solutions management.

Technology, Computing and Simulation, Equipment Monitoring-12 Virtual reality-based Advanced Cardiac Life Support training experience for anesthesia residents

Vikas Kumar[1], MARIA G SANCHEZ[1]

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Introduction: Cardiac arrest is the leading cause of mortality in and out of the hospital and correct management significantly increases chances of survival. Virtual Reality (VR) based medical education is a new concept with significant growth in the last few years and ACLS VR was only introduced very recently. VR devices provide immersive and experiential learning with real patient encounters to facilitate interaction and feedback and can be accomplished in any setting. The added benefit of VR is that it provides cost-saving measures and flexible scheduling in comparison to traditional mannequin based training. VR can also help prepare the learners before their ACLS certification course provided by AHA and this may improve the success rate and confidence levels and prevent decay of knowledge and skills after certification because of the ability to repeat as many times as needed to achieve competency. We are proposing a pilot study to assess the feasibility of VR based ACLS education for anesthesia residents because of many advantages including the ability to apply the deliberate practice, follow up the progress of learners, less space and resource requirements and much lesser cost compared to mannequin based training. In this study, we will be exploring their experience with VR based ACLS education and training.

Methods: The aims of the study are to: 1. Get a background of every individual and their level of training 2. Assess these individuals in the current ACLS knowledge with a Pre-test 3. Undergo the VR ACLS training 4. Assess the individuals post VR ACLS training with a post-test 5. Compare the knowledge; the level of comfort, confidence and any other benefits seen in VR based ACLS training. Method: 16 anesthesia residents were surveyed before and after VR based ACLS experience. There was a pre-VR and post VR test to determine the level of confidence and knowledge among the participants of this study. First, the participants undergo a Pre-ACLS questionnaire and a Pre-ACLS test on knowledge. Then the participants are introduced to Virtual Reality and taught how the ACLS VR will function. After this, the participants undergo the scenario in the VR ACLS training. The participants are asked the appropriate responses to different scenarios seen in any ACLS scenario including management of complete heart block, tachyarrhythmias, asystole, ventricular fibrillation,. The VR software then determines if the participants had the appropriate responses for each scenario. If the responses were appropriate, the scenario continues forward, if incorrect the VR software then tells the participant the correct response to the scenario. This continues until the end of the ACLS code which may last for 25-30 minutes per resident. Once the ACLS code ends, the participants then review all their incorrect responses during their scenario. This is followed by a Post-ACLS questionnaire and Post-ACLS test to determine if there is a difference in confidence and knowledge in the participants.

Results: 56% had never experienced VR before, but about 50% were confident in using VR. 43.8% of residents were at 1 on the scale of 1 to 5 where 1 was least and 5 most confident in managing cardiac arrest as a team leader. Last ACLS certification by AHA varied mostly from 3-12 months for about 95 % of residents. 75 % of residents had never participated in code as a team leader. 80% of residents mentioned VR as very realistic, and valuable. 70% of residents scored less than 50% in rhythm recognition and management. More than 90% of participants valued VR as very useful to learn ACLS.

Conclusion: VR based simulation education may be a way to teach learners to provide experiential learning, considering the fact that VR is less resource-intensive and more cost-effective. The results of our study showed that VR provides immersive and realistic experience and can be very useful. We will need larger studies across different specialties and more learners to prove the efficacy of ACLS VR and compare it with other methods of teaching ACLS.

Score on Critical Rhythms in VR:	Score on General Management in VR	On a scale of 1 - 5 how confident are you being the leader of a code?	On a scale of 1 - 5 how helpful did you feel that the VR simulation was in helping you learn/review ACLS?	On a scale of 1 - 5 how much did you enjoy the VR simulation for ACLS training?
30	38	1	5	5
32	40	4	5	5
20%	50%	3	4	4
20%	50%	3	4	4
40	46	5	5	5
50	58	3	5	3
20	46	1	4	1
20	38	1	5	3
40	62	1	5	5
10	38	1	2	3
20	42	1	5	5
40	38	3	4	4
25	54	1	2	5
20	38	1	4	4
40	42	4	4	3
36	44	3	4	5

On scale of 1 - 5 how user friendly did you feel that simulation was?	On a scale of 1 - 5 how realistic did the Virtual Reality simulation feel?
3	4
3	4
3	4
3	4
4	4
2	2
1	3
3	4
5	5
3	3
4	4
3	3
3	3
3	4
3	4
4	4

Trauma

Trauma-1 Chronic restraint-induced psychological stress increases homocysteine levels and worsens anxiety-like behavior and fine motor deficits in rats with mild traumatic brain injury

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Introduction: United States service members suffer substantial psychological stress on the battle field and during combat simulation activities. These stressful conditions cause biochemical changes including increased homocysteine (hcy) levels (Pharmacol Biochem Behav. 2004; 77(2):269-73; Med Sci Monit. 2012; 18(12):CR771-776), a stress biomarker associated with several neurological disorders including stroke. Our current study demonstrated that experimental induction of hcy accumulation exacerbates oxidative stress, blood brain barrier dysfunction, inflammation and functional deficits in rats with mild traumatic brain injury (mTBI). In this study, we tested the hypothesis that chronic psychological stress alters hcy metabolism and worsens TBI pathological outcomes.

Methods: Male Sprague Dawley rats (250-300g) were subjected to stress via restraint for 1hr/day for seven consecutive days. On day 8, they underwent surgery for mTBI induction by Controlled Cortical Impact (CCI) method or sham operation over the left parietal cortex under anesthesia. Following CCI/sham surgery, rats (n = 8-12/group), were assessed for a battery of behavioral tasks including anxiety, working memory and motor activity. Rats were euthanized 24 hours, 7-days (n = 4-6/group) or 30 days post-injury (pi). Plasma and brain were collected for histological or biochemical analyses including hcy measurements and analysis for markers of oxidative stress, cell death and inflammation. Statistical analysis was performed by one-way ANOVA with Tukey-Kramer post-test analysis. Results expressed as Mean ± SEM. All procedures were approved by the University of Maryland Institutional Animal Care and Use Committee and the USAF/USAMRMC Animal Care and Use Review Office.

Results: Restraint induced stress increased plasma hcy levels in sham and CCI rats compared to non-restrained rats. Hcy concentration at day 1-pi was 9.23 ± 1.16μM and 11.79 ± 2.25μM in restrained shams and CCI rats respectively compared to 5.88 ± 1.08 μM and 6.8 ± 1.25μM in non-restrained. Similar results were obtained at day 7-pi. Behavioral assessments showed that restraining increased anxiety-like behavior in shams at day 2-pi, reducing their exploration time by 32% compared to non-restrained shams ($p < 0.05$). This deficit was aggravated by mTBI with 51% decrease of maze exploration time ($p < 0.001$) compared to non-restrained rats and persisted up to day 8-pi ($p < 0.05$). Similarly, fine motor activity was impaired in restrained CCI-rats up to 16 days-pi versus non-restrained shams ($p < 0.01$). Moreover, restrained-CCI rats had delayed recovery and exhibited significantly greater deficits than non-restrained rats at day 16-pi ($p < 0.05$).

Conclusion: In summary, restraint induced chronic stress increase plasma hcy concentration and worsens TBI-associated anxiety-like behavior and fine motor performance. Funding: US Air Force FA8650-17-2-6H10

Reference(s): de Oliveira AC, Suchecki D, Cohen S, D'Almeida V. (2004). Acute stressor-selective effect on total plasma homocysteine concentration in rats. Pharmacol. Biochem. Behav.; 77(2):269-73.

Kade G, Antosiewicz S, Nowak Z, Wańkowicz Z. (2012). Albuminuria and hyperhomocysteinemia as cardiovascular risk factors in potentially healthy soldiers: A long-term observation. Med Sci Monit.; 18(12):CR771-776.

Trauma-2 A machine learning approach to automated Glasgow Coma Scale estimation using continuous vital signs

Peter F Hu[1], Shiming Yang[2], Chienyu Lin[2], Samuel Galvagno[1], Catriona H Miller[3], Colin Mackenzie[4], Peter Rock[4]

[1]University of Maryland Baltimore, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, United States of America, [3]Air Force Research Labs, Baltimore, MD, [4]University of Maryland School of Medicine, Baltimore, MD

Introduction: The Glasgow Coma Scale (GCS) is a measure of a patient's neurological critical illness, based on evaluation of severity of eye, verbal and motor responses. The GCS is widely used in assessing trauma patients and is part of many scoring systems such as the SOFA score and the revised Trauma Score (RTS). A worsening GCS should warrant prompt patient reassessment and possible interventions. Obtaining a GCS requires a trained medical personal. Our prior work suggested that changes in GCS result in changes in vital sign characteristics that can be quantified by machine learning [1]. We investigated whether these subtle changes in vital signs could be used to predict GCS. We hypothesized that we could estimate the GCS using available vital signs. We propose a machine learning algorithm to estimate GCS using automated, non-invasive vital signs (VS).

Methods: We studied adult (age≥18 years old), trauma patients from 2009-2017. We partitioned the dataset into training and testing sets. The first 7 years of data were used for training. The last two years of data were used for evaluating how the model could perform on 'new' data. We designed variables from ECG (electrocardiogram), PPG (photoplethysmography) and blood pressure using both the actual values for heart rate, oxygen saturation and blood pressure, as well as features of the ECG and PPG waveforms. We calculated the accumulated 'dose' of VS in abnormal ranges (e.g. HR > 120 bpm, SBP<70mmHg, SpO2<92%, etc.). We also derived heart rate variability (HRV) from ECG and PPG waveforms. A regression tree model was trained to estimate GCS, given the past 15 minutes of VS observed for a patient. With this model, we tested its performance in a two-year new dataset. We aggregated the GCS scores into three severity categories: severe (GCS≤8), moderate (GCS 9-12), and mild (GCS 13-15). The comparison between actual GCS and the model estimated GCS in the 3 severity categories are reported in the multi-class confusion matrix table (Table 1).

Results: With University of Maryland School of Medicine Institutional Review Board (IRB) approval, we collected continuous VS and admission GCS from 2009-2017. From 2009 - 2015 there were 22,481 cases that were used to develop the GCS estimation model. We reserved 6819 cases from 2016-2017 for testing. In the testing set, the mean age was 43.8 (±19.6 SD) y/o. and 70.6% were male. GCS was severe in 534 (7.8%) cases, moderate in 247 (3.6%) cases, and mild in 6038 (88.6%) mild. The VS based estimation model had 80.5%, 55.5% and 99.95% true positive rate for severe, moderate and mild groups (Table 1) respectively. Our model has good performance in estimating severe or mild GCS category cases, but not moderate severity GCS.

Conclusion: Testing of a GCS estimation model on a large dataset shows that it is possible to use automated, continuous, VS features to estimate GCS severity categories. This approach could allow more frequent monitoring of injured patients' GCS and give early warnings for unfavorable changes in GCS.

Reference(s): Hu P, Lee CH, Yang S, Li Y, Rock P. Predicting Need For Intubation In The Field: Comparison Of Glasgow Coma Scale To Vital Signs (Poster Presentation) Association of University Anesthesiologists (AUA) 64th Annual Meeting. Washington DC. May 4-6, 2017.

Table 1. The confusion matrix of estimated GCS vs the reported GCS.

	Estimated			
	GCS	≤8	9-12	13-15
True	≤8 (Severe)	430 (80.5%)	0 (0%)	104 (19.5%)
	9-12 (Moderate)	1 (0.4%)	137 (55.5%)	109 (44.1%)
	13-15 (Mild)	3 (0.05%)	0 (0%)	6035 (99.95%)

Trauma-3 Can Machine Learning Using Automated Vital Signs Estimate Findings Of Focused Assessment With Sonography For Trauma (FAST) Exam?

Peter F Hu[1], Shiming Yang[2], Peter Rock[3], Florian Stumpf[2], Chienyu Lin[2], Sarah Murthi[2], Catriona H Miller[4], Colin Mackenzie[3], Samuel Galvagno[1], William Teete

[1]University of Maryland Baltimore, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, United States of America, [3]University of Maryland School of Medicine, Baltimore, MD, [4]Air Force Research Labs, Baltimore, MD

Introduction: The Focused Assessment with Sonography for Trauma (FAST) is a bedside ultrasound exam that looks for free fluid around the heart or abdominal organs after trauma. It is rapid, non-invasive, portable and cheaper than CT. However, the exam requires clinicians' expertise to interpret which is scarce in natural disaster scene or remote rural areas. We hypothesized that a model derived from the combination of analysis of non-invasive continuous vital signs (VS) and the type of injury could estimate the FAST exam results (Positive or Negative).

Methods: With University of Maryland School of Medicine Institutional Review Board (IRB) approval, we studied trauma patients older than 18 years of age from 2016-2017. We developed three VS based models for the estimation of FAST exam results. The three FAST exam results estimation models are (1) shock index = heart rate/systolic blood pressure (SI=HR/SBP); (2) VS based bleeding risk index (BRI) [1]; and (3) a regression model based on continuous VS features and type of injury. We designed continuous VS features from ECG (electrocardiogram), PPG (photoplethysmography) and blood pressure using both the actual values for heart rate, oxygen saturation and blood pressure, as well as features of the ECG and PPG waveforms. We calculated the accumulated 'dose' of VS in abnormal ranges (e.g. HR > 120 bpm, SBP<70mmHg, SpO2<92%, etc.). We also derived heart rate variability (HRV) from ECG and PPG waveforms. The area under the Receiving Operating Curve (AUROC) was used to compare the models. Delong's method was used to test the difference between AUROCs.

Results: 6,594 patients had a FAST. The cohort mortality was 4.1% (272). The exam was positive in 4.6% of the patients. The mean age was 41.7 (±19 SD) y/o. 73.4% were male and 11.2% had penetrating injury. Using SI, or BRI or VS and injury type to estimate FAST exam, the three models achieved AUROCs of 0.68, 0.74 and 0.81 respectively. The model using VS and injury type is significantly better than the other two models ($p<0.001$).

Conclusion: A positive FAST exam is a strong indicator of the need for a transfusion and other life-saving interventions. However, it requires expert clinicians to perform such exam. Using variables derived from automated VS, we found that the likelihood of having a positive FAST exam can be estimated and used to assist emergency patient triage and care.

Reference(s): S. Shackelford, S. Yang, P.F. Hu, C. Miller, A. Anazodo, S. Galvagno, Y. Wang, L. Hartsky, R. Fang, C. Mackenzie, Predicting Blood Transfusion using Automated Analysis of Pulse Oximetry Signals and Lab Values, J. of Trauma and Acute Care Surgery, 2015; 79(4) p S175-80

Trauma-4 Directly Cooling Gut Prevents Mortality in the Rat Model of REBOA Management of Lethal Hemorrhage

Bingren Hu[1], Chunli Liu[2], Dong Yuan[1]

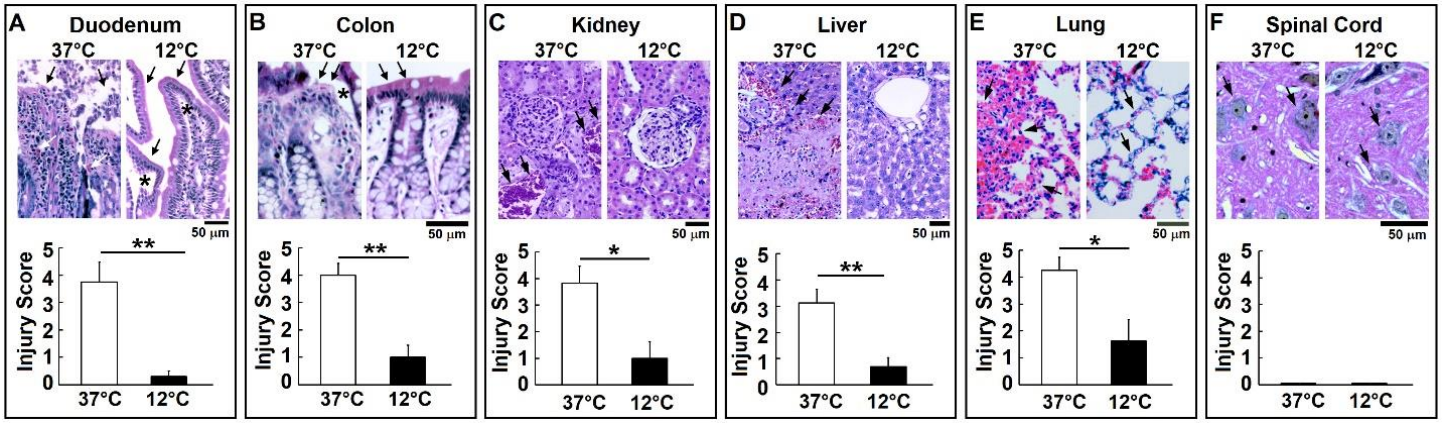
[1]University of Maryland School of Medicine, Baltimore, MD,
[2]Baltimore VA, Baltimore, MD

Introduction: Non-compressible torso hemorrhage (NCTH) is the leading cause of preventable death following trauma. A cutting-edge technique, known as resuscitative endovascular balloon occlusion of the aorta (REBOA), can now be used to manage previously uncontrollable hemorrhage. This benefit, however, must be weighed against the serious aftereffects of distal organ ischemia-reperfusion injury (IRI). This study uses a novel direct gut cooling technique to mitigate distal organ IRI.

Methods: A new rat model of lethal hemorrhage was established by bleeding of 50% of the total blood volume via inferior vena cava over a 20 min period. A novel TransRectal Abdominal Colon (TRAC) temperature management device was positioned in the descending colon and activated at 5 min after induction of hemorrhage either to maintain intra-colon wall temperature at about 37°C (TRAC 37°C) or to cool it rapidly to 12°C (TRAC 12°C). The upper body temperature was maintained at as close to 37°C as possible in both groups during the period of REBOA management of hemorrhage. A 2F Fogarty balloon catheter was inserted via the right femoral artery into the descending aorta at about 2 cm above diaphragm for the implementation of REBOA. At 20 min after induction of hemorrhage, the REBOA balloon was inflated. After 20 min of REBOA occlusion of descending aorta, the balloon was deflated and the shed blood was returned. The temperature management was continued for additional 180 min to maintain the colon wall temperature either at 37°C or 12°C during the post-REBOA period.

Results: All rats subjected to 20 min of REBOA management of lethal hemorrhage at TRAC 37°C had severe abdominal organ injury, and severe functional deficits, and died within 24 h with 100% mortality. By contrast, directly cooling the colon wall to 12°C with TRAC device virtually abolished mortality, as well as dramatically improved arterial blood gas (ABG) parameters as well as liver and kidney functions, prevented the abdominal organ injury, and reduced the functional deficits after the REBOA management of lethal hemorrhage.

Conclusion: The combination of REBOA and TRAC management of rat lethal hemorrhage offers extraordinary functional improvement and amazing tissue protection, and abolishes mortality.


A
Duodenum
37°C
12°C
50 μm
Injury Score
**
37°C
12°C
B
Colon
37°C
12°C
50 μm
Injury Score
**
37°C
12°C
C
Kidney
37°C
12°C
50 μm
Injury Score
*
37°C
12°C
D
Liver
37°C
12°C
50 μm
Injury Score
**
37°C
12°C
E
Lung
37°C
12°C
50 μm
Injury Score
*
37°C
12°C
F
Spinal Cord
37°C
12°C
50 μm
Injury Score
37°C
12°C

Trauma-5 Interferon-β plays a detrimental role in experimental traumatic brain injury by enhancing neuroinflammation that drives chronic neurodegeneration

James P Barrett[1], Rebecca J Henry[1], Kari Ann Shirey[1], Sarah Doran[1], Rodney Ritzel[1], Victoria Meadows[1], Stefanie Vogel[2], Alan I Faden[1], Bogdan A Stoica[1], David J Loane[1]

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Introduction: Following traumatic brain injury (TBI), activation of microglia and peripherally derived inflammatory macrophages occurs in association with tissue damage. Recent evidence has suggested that Type I Interferons (IFNs) play a role in the inflammatory response following central nervous system (CNS) injury. The present study examined the role of IFN-β in mediating the inflammatory response following TBI, and evaluated the effects of IFN inhibition on secondary neuroinflammatory responses and long-term neurological recovery.

Methods: Study 1: WT mice were anesthetized (100 mg/kg sodium pentobarbital, I.P.) at 3 and 60 days post-injury (dpi). Mice were transcardially perfused with ice-cold 0.9% saline (100 ml). Ipsilateral cortical and hippocampal tissue were rapidly dissected and snap-frozen on liquid nitrogen for RNA or protein extraction. Study 2: WT and IFN-β-/- sham-injured (n=6) or CCI (n=6) of mice were anesthetized (100 mg/kg sodium pentobarbital, I.P.) at 3 days post-injury (dpi) and transcardially perfused with ice-cold 0.9% saline (100 ml). Ipsilateral cortical and hippocampal tissue were rapidly dissected and snap-frozen on liquid nitrogen for RNA and protein extraction. Study 3: WT and IFN-β-/- sham-injured or CCI (n=8-15) mice were anesthetized (100 mg/kg sodium pentobarbital, I.P.). All animals underwent motor function testing (beam walk) on 1, 3, 7, 14, 21 and 28 dpi. Cognitive function was assessed using the Y-maze (8 dpi) and the Novel Object Recognition test (NOR; 18 dpi). At 28 dpi animals were anesthetized (100 mg/kg sodium pentobarbital, I.P.) and transcardially perfused with ice-cold 0.9% saline (100 ml), followed by 300 ml of 4% paraformaldehyde. Brains were removed and post-fixed in 4% paraformaldehyde overnight, and cryoprotected in 30% sucrose for histological analysis. Study 4: Antibody to the type I IFN receptor (αIFNAR; 0.5 mg/ml) or isotype control IgG1 was delivered i.c.v. via osmotic pump infusion to WT CCI mice (n=7-9/group). The dose of αIFNAR was chosen based on prior studies demonstrating neutralization of type I IFN in a mouse model of aging (Baruch et al. 2014). Sham WT mice (n=6) were used as control. All animals underwent motor function testing (beam walk) on 1, 3, 7, 14, 21 and 28 dpi, and cognitive function was assessed using the Y-maze (8 dpi) and Novel Object Recognition test (NOR; 18 dpi). At 28 dpi animals were anesthetized (100 mg/kg sodium pentobarbital, I.P.) and transcardially perfused with ice-cold 0.9% saline (100ml), followed by 300 ml of 4% paraformaldehyde. Brains were removed and post-fixed in 4% paraformaldehyde overnight, and cryoprotected in 30% sucrose for histological analysis.

Results: TBI increased expression of DNA sensors cyclic GMP-AMP synthase (cGAS) and Stimulator of Interferon Genes (STING). Additionally, mRNA expression of IFN-β and other IFN-related and neuroinflammatory genes were were upregulated early and persistentlyacutely after TBI. TBI induced expression of proinflammatory mediators in the cortex and hippocampus of WT mice, whereas levels were mitigated in IFN-β-/- mice. Moreover, long-term microglia activation, cognitive and motor function impairments were decreased in IFN-β-/- TBI mice compared to their injured WT counterparts; improved neurological recovery was associated with reduced lesion volume and hippocampal neurodegeneration in IFN-β-/- mice. Continuous central administration of a neutralizing antibody to the IFN-∝/β receptor (IFNAR) for 3 days, beginning 30 minutes post-injury, reversed early cognitive impairments in TBI mice and led to transient improvements in motor function. However, anti-IFNAR treatment did not improve long-term functional recovery or decrease TBI neuropathology at 28 days post-injury

Conclusion: In summary, TBI induces a robust neuroinflammatory response that is associated with increased and persistent expression of IFN-β and other IFN-related genes. Inhibition of IFN-β reduces post-traumatic neuroinflammation and neurodegeneration, resulting in improved neurological recovery. Thus, IFN-β may be a potential therapeutic target for TBI.

Trauma-6 MiR-711 regulates neuronal DNA-damage and apoptosis mechanisms after irradiation

Boris Sabirzhanov[1], Oleg Makarevich[2], Alan I Faden[3], Bogdan A Stoica[1]

[1]UMB, Baltimore, MD, [2]Univerisity of Maryland School of Medicine, Baltimore, MD, [3]University of Maryland School of Medicine, Baltimore, MD

Introduction: Brain exposure to ionizing radiation can cause DNA damage and neuronal cell death. The neurotoxic effects of irradiation therapy for brain tumors contributes to patients' progressive neurodegeneration and neurological deficits. Yet, the mechanisms that govern the opposing processes of neuronal DNA repair and cell death, including the regulatory roles of microRNAs following irradiation, remain largely unknown.

Methods: We examined the molecular mechanisms that control neuronal DNA damage/repair and intrinsic apoptotic pathways following X-ray exposure in primary cortical neurons in vitro and the brain in vivo.

Results: Irradiation in primary cortical neurons induced a dose-dependent activation of DNA damage and apoptotic pathways as well as an associated miR-711 up-regulation. The resulting neuronal cell death involved sequential up-regulation of BH3-only, pro-apoptotic Bcl-2 family members Puma, Noxa and Bim; mitochondrial release of cytochrome c and AIF-1 and caspase-dependent and -independent neuronal apoptosis. Induction of miR-711 may play an important role in irradiation-induced neuronal cell death due to the downregulation of its targets, pro-survival genes Akt and Ang-1, negative regulators of BH3-only molecules. Inhibition of IR-induced miR-711 attenuates degradation of Akt and Ang-1 mRNAs in the RNA-induced silencing complex (RISC) and thus increases their neuronal levels leading to a shift away from apoptotic processes and in favor or neuronal survival mechanisms. Accordingly, administration of Ang-1 decreased IR-induced neuronal apoptosis. Inhibition of miR-711 also rescued expression of novel targets, DNA repair genes Rad50 and Rad54l2, by preventing their degradation in the RISC. Rescued Rad50 and Rad54l2 expression following miR-711 inhibition may underpin the increased elimination of γH2A.X and 53BP1 foci, consistent with an enhancement of DNA repair. Importantly, we confirmed key aspects of the changes in miR-711, DNA repair and apoptotic pathways following brain irradiation in vivo.

Conclusion: Together, these data indicate that miR-711 contributes to post-irradiation neuronal cell death through multi-factorial processes, including the induction of p53-dependent pathways that converge upon mitochondria to activate intrinsic apoptosis and the inhibition of DNA repair capacity. Thus, targeting irradiation-induced miR-711 elevation may be a potentially important therapeutic target to limit post-irradiation neuronal cell death.