AUA 2021 Annual Meeting

Scientific Abstracts

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Airway Management

Airway Management - 1 Early Diagnosis Of Esophageal Intubation : First Auscultation Of The Armpits Versus Epigastrium?

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

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

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

Conclusion: The primary auscultation of the epigastrium allows a diagnosis of esophageal intubation much faster than that of armpits. In addition, taking Into account the urgency, the risk of anoxia, 'Bula-Bula's sign of cross' which prioritizes the primary exclusion of esophageal intubation by seeking in such a way: - vertical : the absence of esophageal intubation (1. presence of mist by compression of the thorax and 2. absence of rumbling by auscultation of the epigastrium) - horizontal : the symmetry of the ventilation (auscultation of the armpits : 3. left and 4. right), could improve the practice of endotracheal intubation. Key-words: intubation - esophageal - auscultation - armpits - epigastrium

References: 1. Confirmation of endotracheal tube position : a narrative review. J Intensive Care Med. 2009;24: 283-92. 2. Confirmation of tracheal intubation. In: Hagberg CA, cd. Bernumof and Hagberg's Airway Management, 3 rd Ed. Philadelphia : Elsevier Sauders. 2013; 657-84.

Airway Management - 2 Negative Pressure Airway Chamber: A Clinical Simulation Trial of an Isolation Chamber

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

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

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

Conclusion: The use of the NPAC device delayed the time to intubation (8.5 sec), endotracheal tube securement (5.2 sec), and the diagnosis of an airway emergency (17.0 sec). Some interruption to procedure flow when performed inside a restricted environment is to be expected, yet these short delays may not be clinically significant. To mitigate delays, practice using the chamber, and team planning on how and when to move it in an emergency should be completed in advance of the procedure. Reducing aerosol exposure to health care providers is vitally important, as is the ability to deliver much-needed oxygen therapy and

ventilation prior to intubation of a sick patient. This chamber may allow both of these considerations to be met in a safe manner and create improved intubating conditions where concerns for short delays are permissible.

References: References: 1. Exhaled air dispersion during bag-mask ventilation and sputum suctioning-Implications for infection control. Scientific Reports, 8(1), 1–8. 2018. 2. The coronavirus pandemic and aerosols: Does COVID-19 transmit via expiratory particles?. Aerosol Sci Technol. 0(0):1-4. 2020 3. COVID-19 and Risks Posed to Personnel During Endotracheal Intubation. JAMA. 323(20):2027-2028. 2020. 4. COVID-19 recommendations during airway manipulation. Canadian Anesthesiologists' Society, https://www.cas.ca/en/practice-resources/news/cas-articles/2020/covid-19-recommendations-during-airway-manipulation, March 16. 2020. 5. Aerosol boxes and barrier enclosures for airway management in COVID-19 patients: a scoping review and narrative synthesis. British Journal of Anaesthesia, 125 (6): 880e894 (2020)

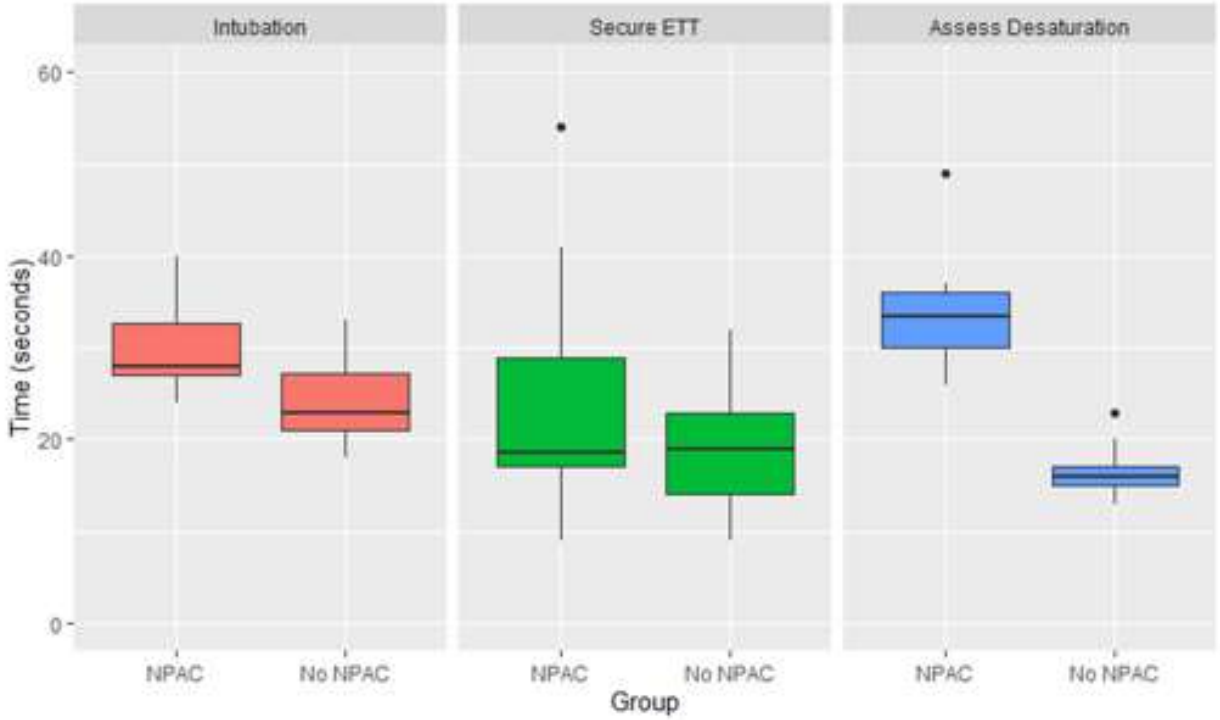

Figure 1: Box and whisker plot comparing time to complete intubation, secure endotracheal tube (ETT), and assess desaturation. Horizontal lines represents median with the box representing the interquartile range. One data point at 75 sec to intubate with the NPAC was censured for scaling.

Airway Management - 3 A Comparison Study Of Powered Air Purifying Respirator And N95 Use During Intubation Of Covid-19 Patients

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

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

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

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

References: 1. Rational use of personal protective equipment for coronavirus disease (COVID-19) and considerations during severe shortages. 2020. 2. To PAPR or not to PAPR? Can J Respir Ther. 50(3):87-90. 2014

Airway Management - 4 Effect of Low Left Paratracheal Compression on Carotid Blood Flow

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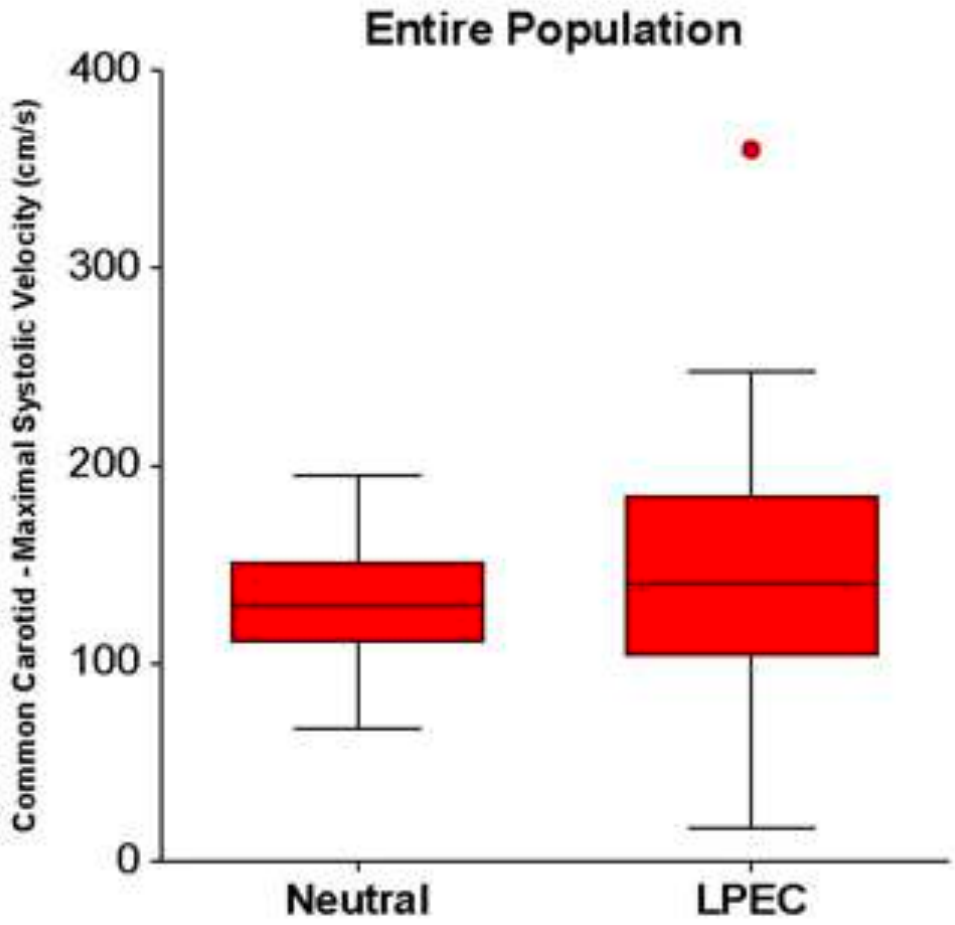
Introduction: For many years, cricoid pressure (Sellick maneuver) has been subject to debate. Recently, Gautier et al. demonstrated that a compression in the left paratracheal region could compress the esophagus. However, at this level, the left common carotid artery is closely located to the esophagus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

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

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

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

References: The effect of force applied to the left paratracheal oesophagus on air entry into the gastric antrum during positive-pressure ventilation using a facemask. Anaesthesia. 2019;74(1):22-8.


Entire Population
Common Carotid - Maximal Systolic Velocity (cm/s)
400
300
200
100
0
Neutral
LPEC

Airway Management - 5 Exploring The Association Between Provider Years In Training And Comfort And Fear Levels During Primary And Subsequent Intubation Attempts Of Covid-19 Patients

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

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

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

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

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model of improvement. 2020;35:450-457. 4. What factors affect the success rate of the first attempt at endotracheal intubation in emergency departments? 2013;30:888-892.

Airway Management - 6

Dexmedetomidine Use In Awake Fiber Optic Intubation Is Associated With Improved Patient Satisfaction And Comparable Rates Of Adverse Events

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

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

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

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

References: 1. J Clin Anesth. 2007 Mar;19(2):141–4. 2. Anaesthesia. 1999 Feb;54(2):146–65. 3. Anesth Analg. 2000 Mar;90(3):699–705. 4. Anesthesiology. 2000 Aug;93(2):382–94. 5. Am J Ther. 2016 Dec;23(6):e1788–800. 6. Anesthesiology. 1992 Dec;77(6):1125–33.

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

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

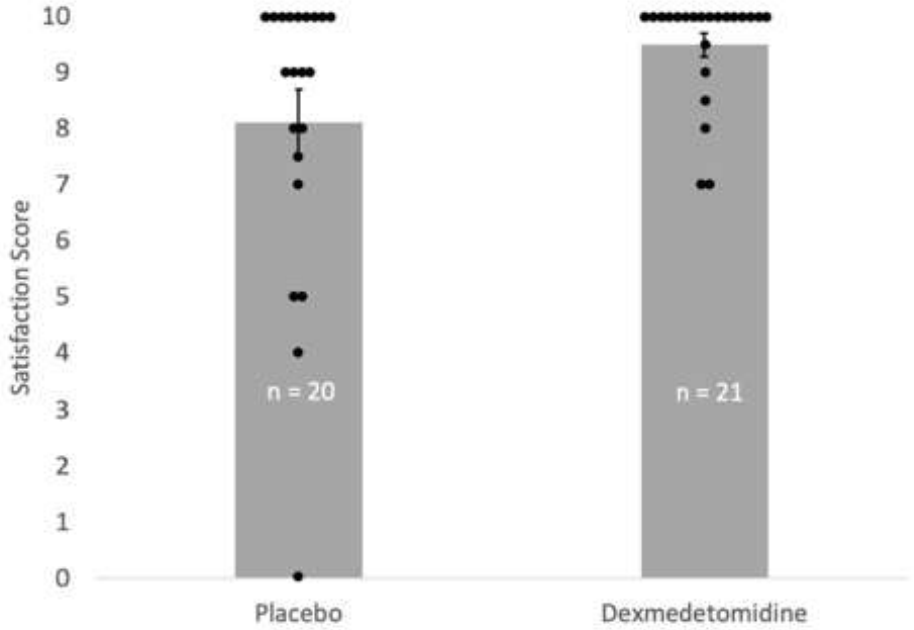

Figure 1. **Patient Satisfaction: Placebo vs. Dexmedetomidine.** Patients who received infusions of dexmedetomidine for >21 minutes reported higher satisfaction (M=9.5) compared to patients who received placebo (M=8.1) ($p<0.05$). Satisfaction was measured via survey and patients were asked to score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

Airway Management - 7 Investigation of Factors Affecting Providers' Fear of Contracting COVID-19 During Intubations: Results from a USA National Survey

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

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

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

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

References: 1. Healthcare worker infections and deaths due to COVID-19: A survey from 37 nations and a call for WHO to post national data on their website. 2021;102:239-241. 2. How Essential Is to Focus on Physician's Health and Burnout in Coronavirus (COVID-19) Pandemic?. 2020;12:e7538. 3. COVID-19 and Risks Posed to Personnel During Endotracheal Intubation. 2020;323:2027-2028. 4. COVID-19 Intubation Safety: A Multidisciplinary, Rapid-Cycle Model of Improvement. 2020;35(6):450-457. 5. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. 2020;395(10227):912-920. 6. Promoting resilience in

the acute phase of the COVID-19 pandemic: Psychological interventions for intensive care unit (ICU) clinicians and family members. 2020;12(S1):S105-S107. 7. Ultra Brief Psychological Interventions for COVID-19 Pandemic: Introduction of a Locally-Adapted Brief Intervention for Mental Health and Psychosocial Support Service. 2020;27(2):51-56.

Airway Management - 8 A Comparison of the Compression and Relaxation Characteristics of Polyvinyl Chloride Versus Reinforced Endotracheal Tubes

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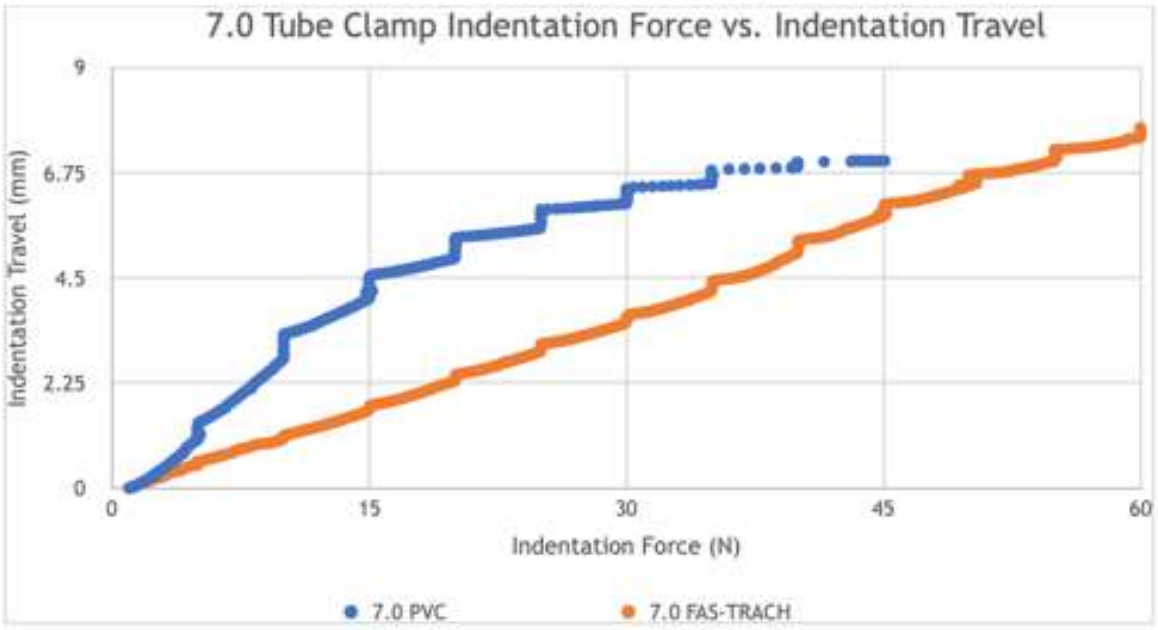
Introduction: Obstruction of endotracheal tubes can be caused by tube compression or kinking from extensive bite force. There are numerous case reports of ventilatory obstruction, requiring quick recognition and tube replacement to prevent desaturation and pulmonary edema related morbidities. Diagnostic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

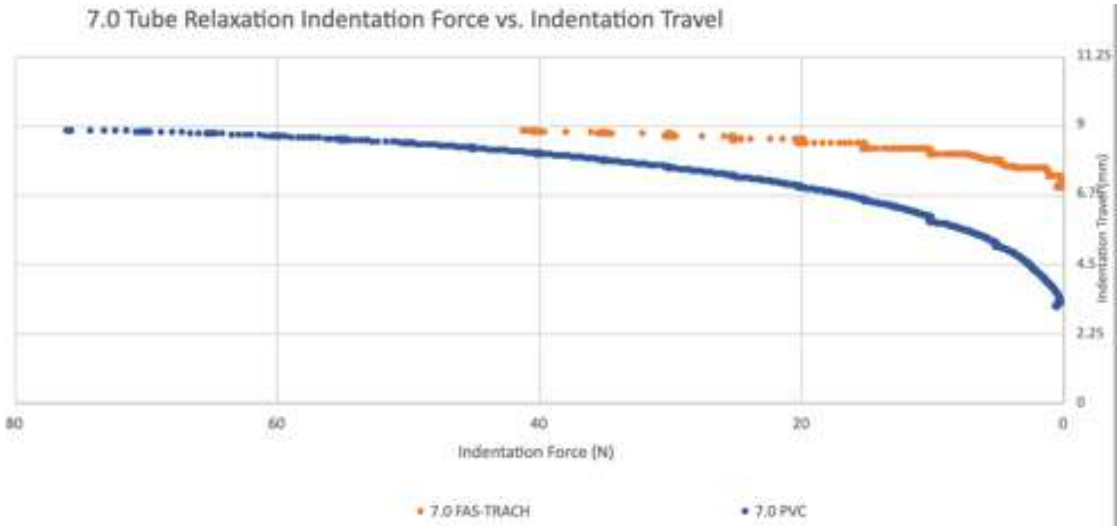
Methods: Increasing force was exerted on a PVC tube and on a reinforced (Fastrach--LMA America) tube by chisels mounted on a hydraulic press. Intermittent airflow was generated by a ventilator forcing air through the tubes as pressure was applied so that the inspiratory resistance (Rinsp) as well as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

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

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

References: 1. Anesth Analg. 1993;76(3):653-654. 2. Singapore Med J. 1999;40(3):174-175. 3. Indian J. Anaesth 2003; 47(1):48-4. 4. Int Arch Otorhinolaryngol. 2014;18(3):272-276.


7.0 Tube Clamp Indentation Force vs. Indentation Travel
Indentation Travel (mm)
9
6.75
4.5
2.25
0
0
15
30
45
60
Indentation Force (N)
7.0 PVC
7.0 FAS-TRACH


7.0 Tube Relaxation Indentation Force vs. Indentation Travel
11.25
9
6.75
4.5
2.25
0
Indentation Travel(mm)
80
60
40
20
0
Indentation Force (N)
7.0 FAS-TRACH
7.0 PVC

Airway Management - 9 A Comparison of Compression and Relaxation Characteristics in 7.0mm Versus 8.0mm Polyvinyl Chloride Endotracheal Tubes

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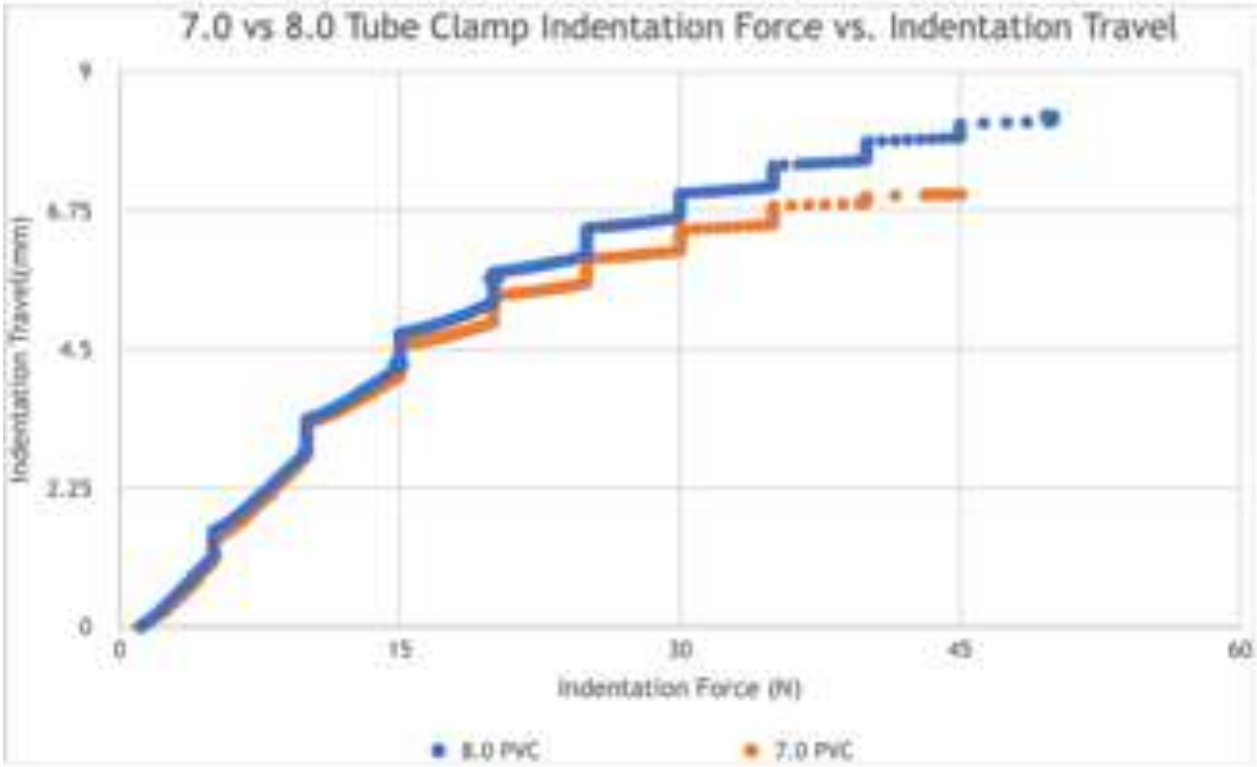
Introduction: Pressure exerted on endotracheal tubes by the bite force of a patient's teeth has been shown to cause ventilatory obstruction by producing compression on the tube. Depending on a patient's bite force, endotracheal tubes have been reported to become punctured or even severed completely.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

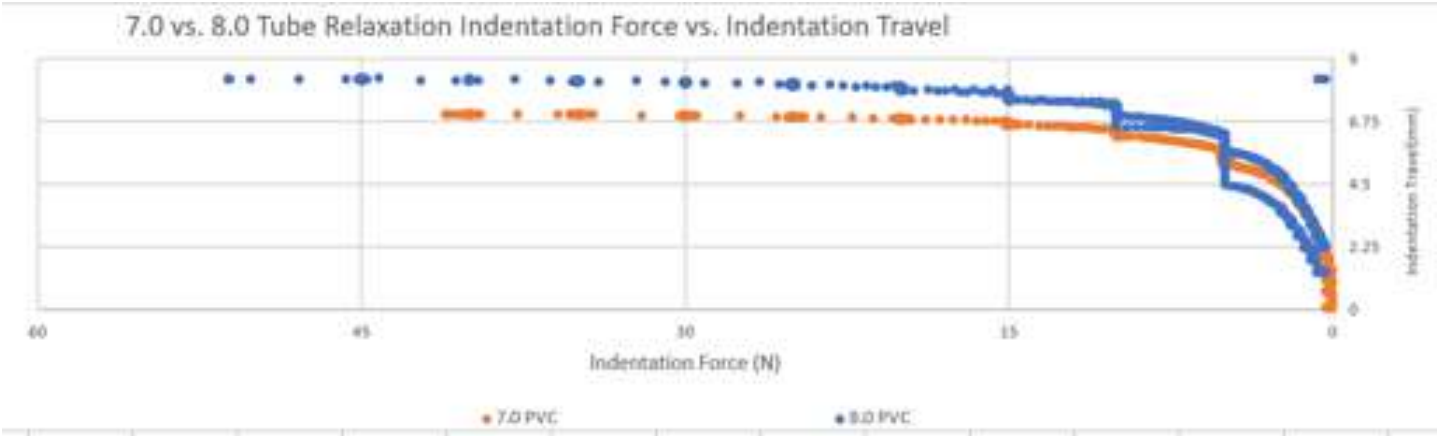
Methods: In order to compare the resistance of the 7.0 mm and 8.0 mm PVC endotracheal tubes, two chisels were attached to a hydraulic press to simulate the force applied by a patient's teeth. Once the respective tubes were in position, a ventilator generated simulated breaths through the endotracheal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

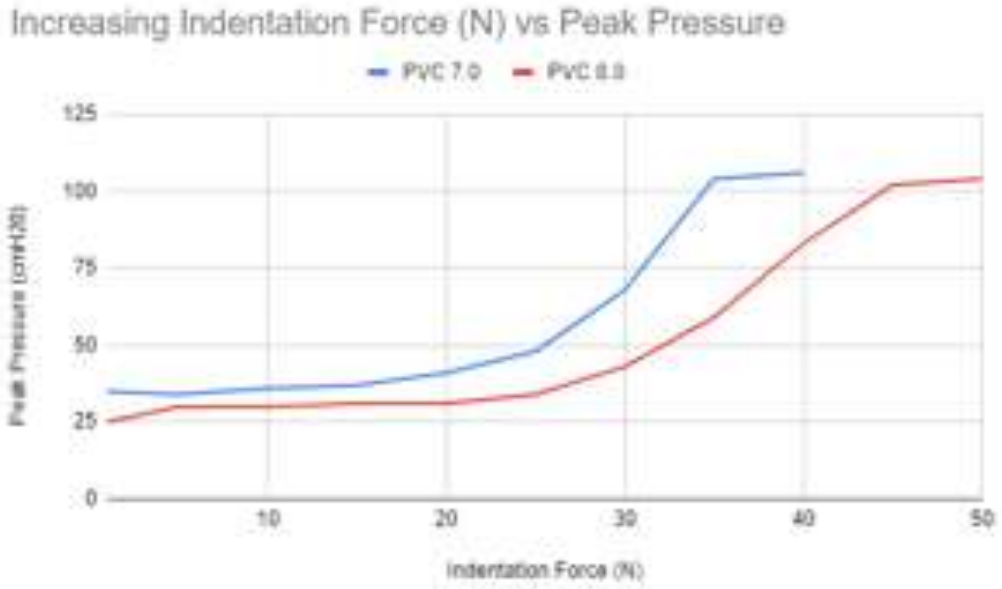
Results: Our results illustrate an inverse relationship with regards to resistance to indentation by force and recovery after relaxation between the 7.0 and the 8.0 PVC tubes (Figure 1, 2). At lower levels of force (0 - 15N), both tubes displayed similar levels of resistance to indentation. At levels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

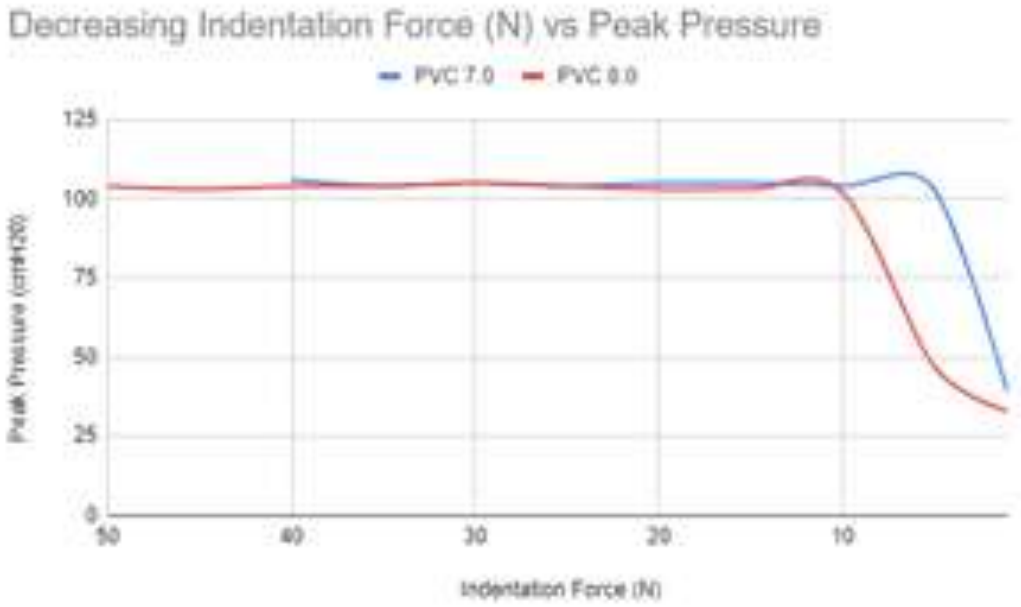
Conclusion: While the 8.0 PVC tube can withstand slightly greater indentation force, the 7.0 PVC tube is more effective in both resisting compression and recovering after the force is removed. Both tubes were nearly completely obstructed by a force around 50 newtons, a small fraction of the force applied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

References: 1. Korean journal of critical care medicine 32, 1 (2017): 70-73. 2. Indian journal of anaesthesia 57,4 (2013): 424. 3. Int Arch Otorhinolaryngol. 2014;18(3):272-276.


7.0 vs 8.0 Tube Clamp Indentation Force vs. Indentation Travel
Indentation Travel(mm)
9
6.75
4.5
2.25
0
0
15
30
45
60
Indentation Force (N)
8.0 PVC
7.0 PVC


7.0 vs. 8.0 Tube Relaxation Indentation Force vs. Indentation Travel
60
45
30
15
0
Indentation Force (N)
7.0 PVC
8.0 PVC


Increasing Indentation Force (N) vs Peak Pressure
PVC 7.0
PVC 8.0
125
100
75
50
25
0
10
20
30
40
50
Indentation Force (N)


Decreasing Indentation Force (N) vs Peak Pressure
PVC 7.0
PVC 8.0
125
100
75
50
25
0
50
40
30
20
10
Indentation Force (N)

Airway Management - 10 Investigation of Factors Affecting Providers' Comfort in Intubating COVID-19 Patients: Results from a USA National Survey

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

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

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

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

References: 1. Healthcare worker infections and deaths due to COVID-19: A survey from 37 nations and a call for WHO to post national data on their website. 2021;102:239-241. 2. How Essential Is to Focus on Physician's Health and Burnout in Coronavirus (COVID-19) Pandemic?. 2020;12:e7538. 3. COVID-19 and Risks Posed to Personnel During Endotracheal Intubation. 2020;323:2027-2028. 4. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. 2012;7:e35797. 5. Intubation and Ventilation amid the COVID-19 Outbreak: Wuhan's Experience. 2020;132:1317-1332.

Airway Management - 11 Effects Of Histones On Endothelial Barrier Function And Vascular Permeability In Cultured Human Endothelial Cell And Mice Lung

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[1]University of Maryland, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, MD, [3]University of Maryland, Baltimore, Baltimore, MD, [4]University of maryland, Baltimore, MD, [5]Dept of Medicine, University of Maryland School of Medicine, Baltimore, MD

Introduction: Disruption of endothelial barrier in the lungs leads to edema, inflammation and respiratory failure in acute respiratory distress syndrome (ARDS). Histones release into extracellular when cells undergo severe injury, generating immunostimulatory and cytotoxic effects in both sepsis and ARDS (1,2). However, cellular and molecular mechanisms of pathogenic effects triggered by extracellular histones remain unclear. This study investigated effects of extracellular histones on lung endothelial cell (EC) permeability in vitro and vascular endothelial barrier function in mice lungs.

Methods: Histone subunits induced endothelial cell permeability were assessed by ECIS and Xpert assay (3). Western blot was undergone after cultured endothelial cells were treated with histones. BAL was performed after mice treated with histones and LPS. Cell count and protein concentration were measured (4), and cytokine production was analyzed by ELISA.

Results: ECIS shows that histone mix had slight barrier protective activity during the first 2 hours. Histone H1 and H2A enhanced barrier integrity to a small extent. H3 and H4 significantly disrupt endothelial barrier in a dose dependent manner. Histone H2B shows weak barrier disruption effect. Cultured endothelial cells exposed to histone H3 demonstrated an increase in expression of ICAM, VCAM and p–MLC20 by WB analysis. Soluble ICAM and IL-8 also increased demonstrated by ELISA. Both H3 and H4 had significant impact on formation of paracellular gaps as shown by Xpert analysis. In vivo experiments found that there is an increase of lung vascular permeability to Evan blue and protein level in BAL after mice treated with histone mix.

Conclusion: Histone subunits exhibit differential effects on EC barrier function. High dose of H3 and H4 induced an increase inflammation markers ICAM1, VCAM and IL-8 as well as Rho signaling in pulmonary EC. H3 and H4 induced formation of stress fibers in pulmonary EC. Intravenous injection of histones increased lung vascular permeability for proteins without significant neutrophil infiltration. These results support the hypothesis that histones released from injured cells may serve as deleterious agents to the lungs and exacerbated ongoing sepsis and ARDS.

References: 1. Scuderi PE, MacGregro DA, Bowton DL, James RL. A laboratory comparison of three pulmonary artery oximetry catheters. Anesthesiology 1994;81:245-253. 2. Molnar Z, Umgelter A, Toth I et al. Continuous monitoring of ScvO2 by a new fibre-optic technology compared with blood gas oximetry in critically ill patients: a multicentre study. Intensive Care Med 2007;33:1767-1770. 3. Bland JM, Altman DJ. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;8:307-10.

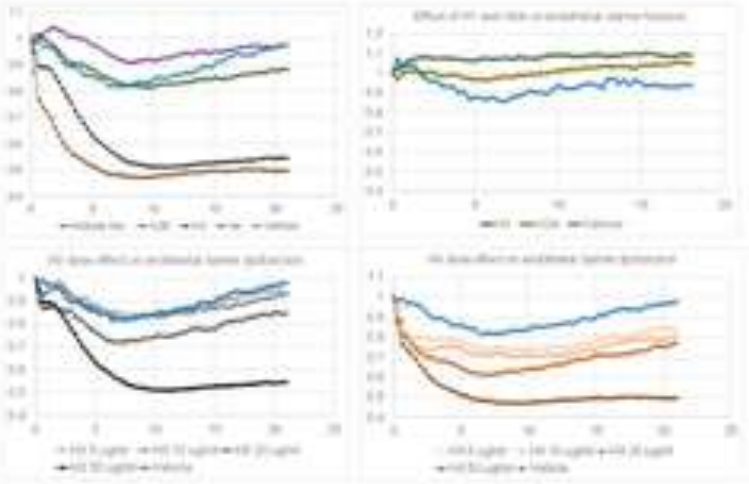

Figure 1. Effects of histones on endothelial barrier function. Histone samples were added to the wells of a 8W10E array and the trans-endothelial electrical resistance was measured by ECIS. A. Regulation of endothelial barrier function by histone mix (purple), histone H2B (green), H3 (black) and H4 (brown) as compared to the vehicle; B. Effect of H1 and H2A on endothelial barrier function as compared to the vehicle; C. The dose effect of H3 on EC barrier dysfunction; D. The dose effect of H4 on EC barrier dysfunction.

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Ambulatory Anesthesia

Ambulatory Anesthesia - 1 Postoperative Rescue Antiemetics in Adult Strabismus Surgery Under Combined Inhalational/Intravenous vs Inhalational Anesthesia

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

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

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

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

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

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

References: 1. Retrospective analysis of risk factors of postoperative nausea and vomiting in patients undergoing ambulatory strabismus surgery via general anaesthesia, Indian Journal of Anaesthesia 2020;64: 37 2. Evidence-based analysis of risk factors for postoperative nausea and vomiting, British Journal of Anaesthesia 2012;109:742

Table 1: Baseline Characteristics

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

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

Table 2: Intraoperative PONV Factors

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

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

Table 3: Postoperative

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

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

Ambulatory Anesthesia - 2 Tonsillar Hypertrophy Is Associated With Perioperative Complications In Pediatric Dental Procedures Under General Endotracheal Anesthesia

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

Introduction: General anesthesia (GA) is used in children undergoing comprehensive dental care when office based dentistry is not appropriate1. In our institution this is performed at both a freestanding ambulatory surgery center (ASC) and at the main hospital as an outpatient procedure. Appropriate patient selection for the ambulatory surgery center is vital to maintain both patient safety and workflow2. In general, American Society of Anesthesiologists (ASA) 1 and 2 patients are scheduled for the freestanding ambulatory center and ASA 3 and 4 patients for outpatient procedures at the main hospital. In addition to ASA status, patients with large tonsils (Brodsky Classification 3 or 4) are thought to have an increased risk of perioperative complications secondary to possible undiagnosed obstructive sleep apnea3 and are excluded from the ambulatory center. These exclusion criteria led to a significant backlog of dental cases at the main hospital of more than 9 months. In contrast, the ASC had only a 3 month backlog. We undertook this analysis to determine what, if any, patient comorbidities were associated with adverse outcomes in our pediatric dental population. In doing so, we aimed to determine whether our exclusion criteria could be safely modified to allow more GA dental procedures to be scheduled at the ASC.

Methods: A retrospective review of the electronic medical records of all ASA 1-3 pediatric patients (ages 2-17) having general anesthesia for dentistry at either the ambulatory surgery center or main hospital between June 2015 and March 2018 was undertaken. Age, race/ethnicity and gender distributions are shown in Table 1. All patients underwent inhalation induction and general endotracheal anesthesia with nasal intubation. Children with ASA 4 status or those who were undergoing extractions in preparation for cardiac surgery or who required a pediatric cardiac anesthesiologist were excluded from the analysis as they would be ineligible for the ASC regardless of outcome. A patient was considered to have an adverse outcome if at least one of the following occurred: 1) documented laryngospasm, 2) documented bronchospasm 3) three or greater intubation attempts 4) intraoperative hypoxia SpO2 <90% lasting more than one minute 5) respiratory complications requiring intervention in the post anesthesia care unit (PACU) or 6) escalation of care/unplanned admission. Independent variables analyzed included: age, sex, race/ethnicity, history of asthma, recent upper respiratory infection obesity (defined by BMI percentile >95% for age and sex), ASA status, and Brodsky tonsil size (0-2 versus 3-4).

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

Conclusion: Asthma and upper respiratory infections have been previously demonstrated to be associated with perioperative complications during anesthesia and sedation 45. While an association exists between tonsil size and obstructive sleep apnea6, there has not been a study demonstrating an association between enlarged tonsils and increased risk of adverse outcome in pediatric dentistry performed under general endotracheal anesthesia. These data support the risk stratification of patients according to tonsillar hypertrophy when assessing likelihood of perioperative complications. However, it should be noted that while

statistically significant, all of the composite adverse outcomes were managed without the need for escalation of care or admission, and no patient had respiratory issues in PACU.

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

Table 1. Independent variables

Ambulatory Anesthesia - 3 Intrathecal Morphine Does Not Increase Pour In Joint Arthroplasty Surgeries. A double Blind Rct

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Introduction: The changing health economy has driven the need for greater patient throughput, rapid turnover, and shorter hospital stays whilst retaining high-quality medical care. The use of intrathecal opioids has become a widely accepted technique for providing effective postoperative pain relief in joint arthroplasty surgeries1. However, intrathecal morphine (ITM) has its own adverse effects including urinary retention and delayed respiratory depression2. Postoperative urinary retention (POUR) is one of the main reasons for the delayed discharge following hip and knee arthroplasties. Early removal is important, as a risk of UTI is reported to rise 5% for each day a urinary catheter remains in situ3. Avoiding intrathecal morphine would benefit patients by decreasing complications associated with prolonged catheterization such as urinary tract infection and improve cost-effectiveness through the early discharge of patients4. Our aim was to evaluate, whether removing the intrathecal morphine would facilitate early removal of urinary catheters and earlier discharge from the hospital.

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

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

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

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

Table 1. Baseline characteristics

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

Table 2(a). Comparison of outcomes

Outcomes	ITM	Non-ITM	Difference (95%CI)*	p-values*
# Patients	48	51	(ITM vs. Non-ITM)	
Length of hospital stay (hrs.), median(IQR)	28 (25.4, 48)	43 (23.2, 68.5)	-15.3 (-29.9, -0.71)	0.04
Satisfaction, median (IQR)	6 (5, 6)	6 (5, 6)	0 (-0.47, 0.47)	0.99
First In&out Catheterization needed (hrs.) %(n)	37.5 (18)	35.3 (18)	2.2 (-16.8, 21.2)	0.81
Second In&out Catherization needed, %(n)	8.3 (4)	3.9 (2)	4.4 (-5.1, 13.9)	0.36
Catheter duration, (hrs.) %(n/N)	16.7 (3/18)	27.8 (5/18)	-11.1 (-38.0, 15.8)	0.41
VASm24	4.5 (3, 8)	6 (3, 7)	-1.0 (-3.10, 1.10)	0.35
VASm36	6 (5, 8)	6 (5, 7)	0.0 (-1.44, 1.44)	0.99
VASm48	7 (5, 8)	6 (5, 7)	1.0 (-1.32, 3.32)	0.39
VASr24	3 (1, 5)	3 (1, 5)	0.0 (-1.70, 1.70)	0.99
VASr36	4.5 (2, 6)	3 (2, 4)	1.0 (-0.98, 2.98)	0.32
VASr48	4 (3, 6)	2 (1, 3)	2.0 (0.73, 3.27)	0.002

Table 2(b)

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

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

Table 3. outcomes

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

Anesthetic Pharmacology

Anesthetic Pharmacology - 1 Pursuing the Next Generation of Anesthetic and Anticonvulsant Compounds

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

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

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

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

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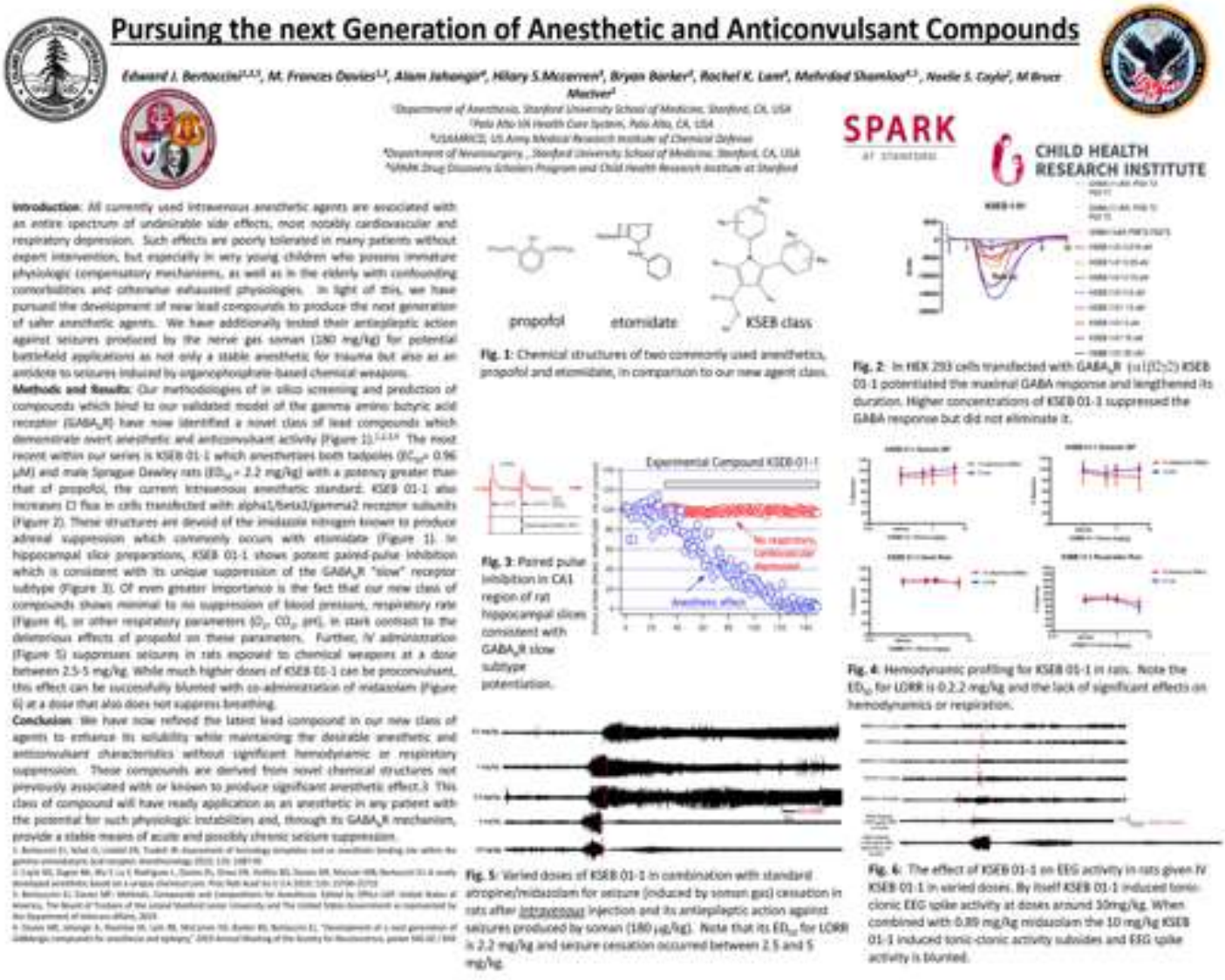

Anesthetic Pharmacology - 2 Structural Mechanism Of Lipid Modulation Of A Pentameric Ligand-Gated Ion Channel

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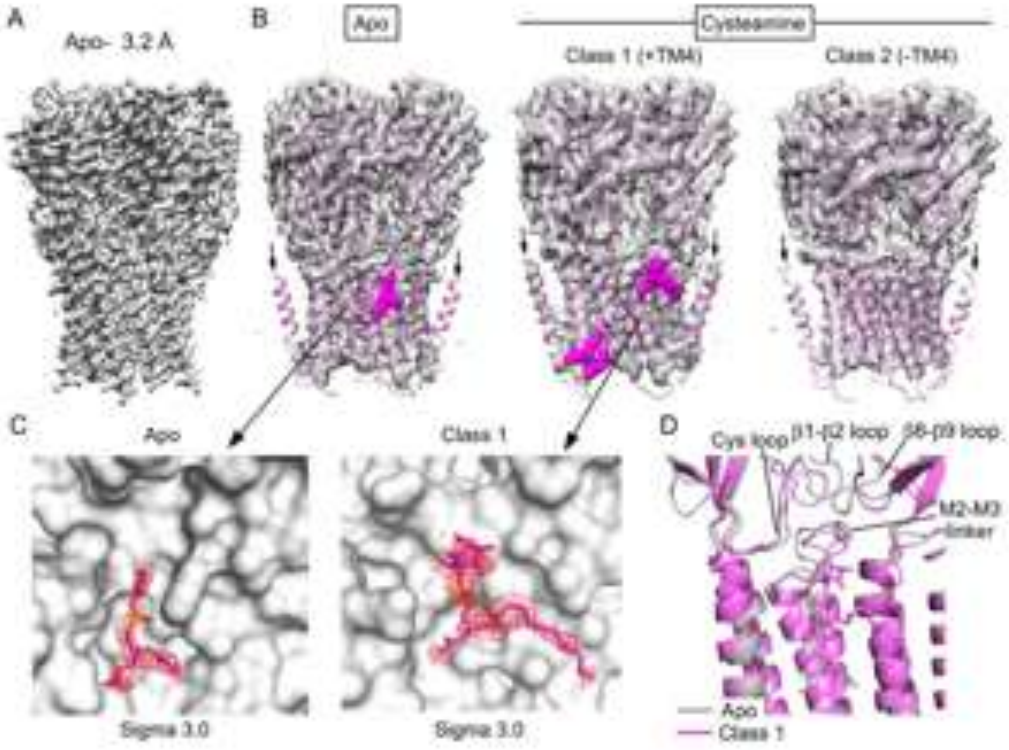
Introduction: Pentameric ligand-gated ion channels (pLGICs) such as the GABA(A) receptor and glycine receptor are essential determinants of synaptic neurotransmission and primary targets of anesthetics. Rational design of drugs that specifically target these ion channels requires a high resolution structural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

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

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

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



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

Anesthetic Pharmacology - 3 Ketamine Produces a Long-Lasting Enhancement of CA1 Neuron Excitability

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

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

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

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

Anesthetic Pharmacology - 4 Impact Of Polymorphisms In The Pharmacokinetic Pathway For Ondansetron On Ponv Treatment Efficacy

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

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

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

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

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Anesthetic Pharmacology - 5 Characters of Rapid Eye Movement Sleep Rebound After Sevoflurane Anesthesia

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

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

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

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

a mechanism for the REMS adaptations observed after SEVO.

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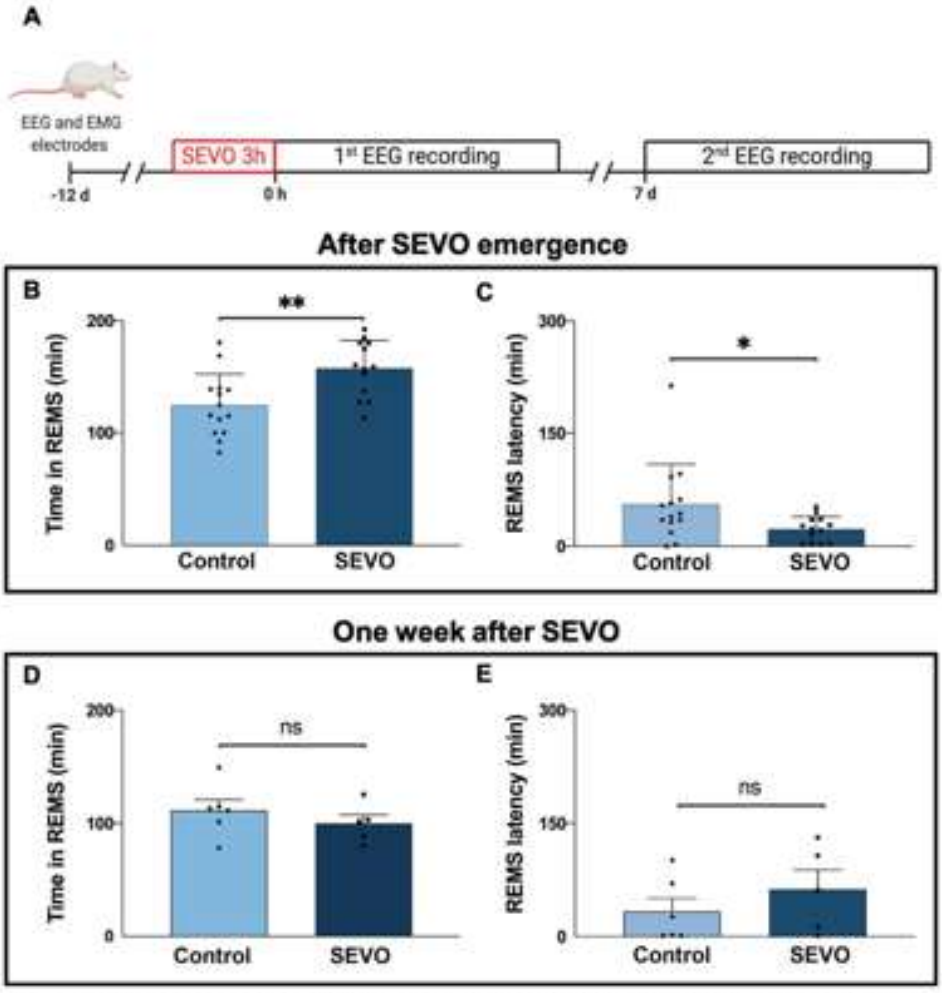

Fig. 1: A- Schematic of EEG/EMG experiments. **B-** Adult rats exhibit increased REMS duration in the 24 h following SEVO emergence. **C-** Time to REMS onset is significantly shorter in adult rats after emergence from SEVO than controls. **D, E-** There are no differences in REMS duration or latency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

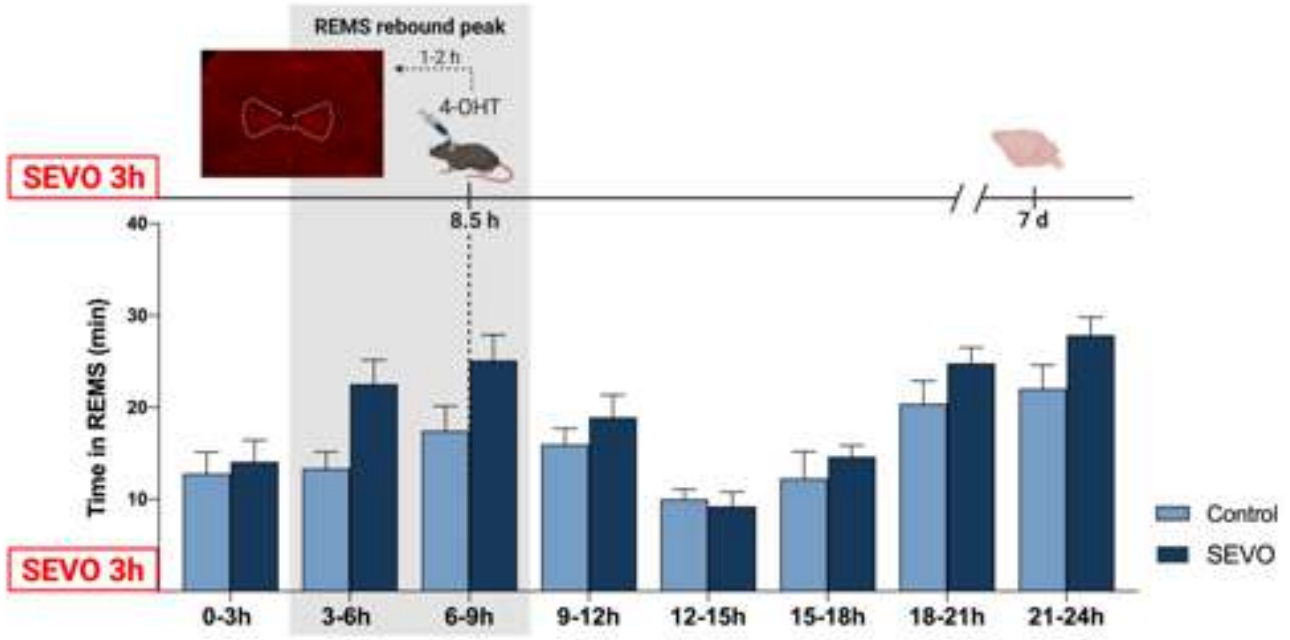

Fig. 2: Schematic of TRAP experiments. SEVO-exposed and control TRAP mice were injected with 4-OHT at 8.5 h after SEVO emergence. Injection of 4-OHT allowed tagging of active neurons in a 1- to 2- h window prior to the injection. Brains were collected 7 days after 4-OHT injection. Data expressed as mean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

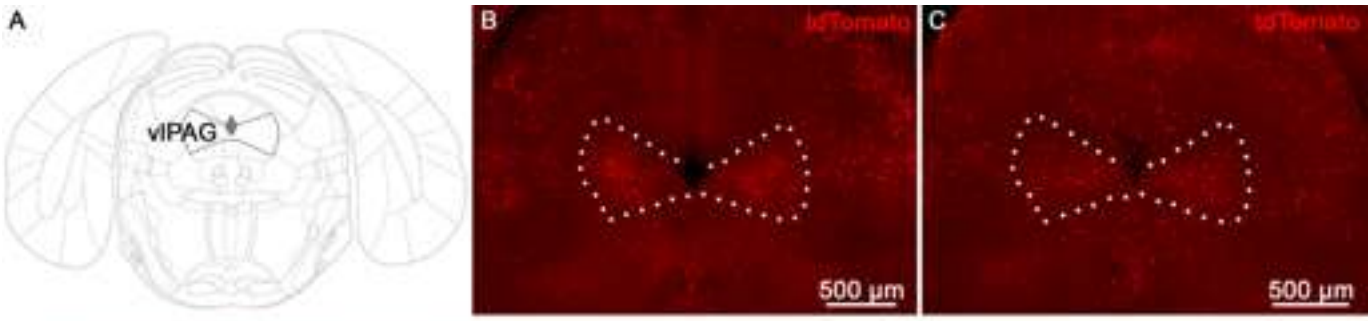

Fig. 3: A- Representative coronal map through the vlPAG adapted from the mouse brain atlas of Paxinos and Watson. **B-** Representative vlPAG image from a control TRAP mouse. **C-** Representative vlPAG image from a SEVO-exposed TRAP mouse. Red: tdTomato. Abbreviations: vlPAG: ventrolateral periaqueductal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

Anesthetic Pharmacology - 6 Comparison of the Effectiveness of Ascorbic Acid and Magnesium in Renal Ischaemia Reperfusion Model in Rats

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

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

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

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

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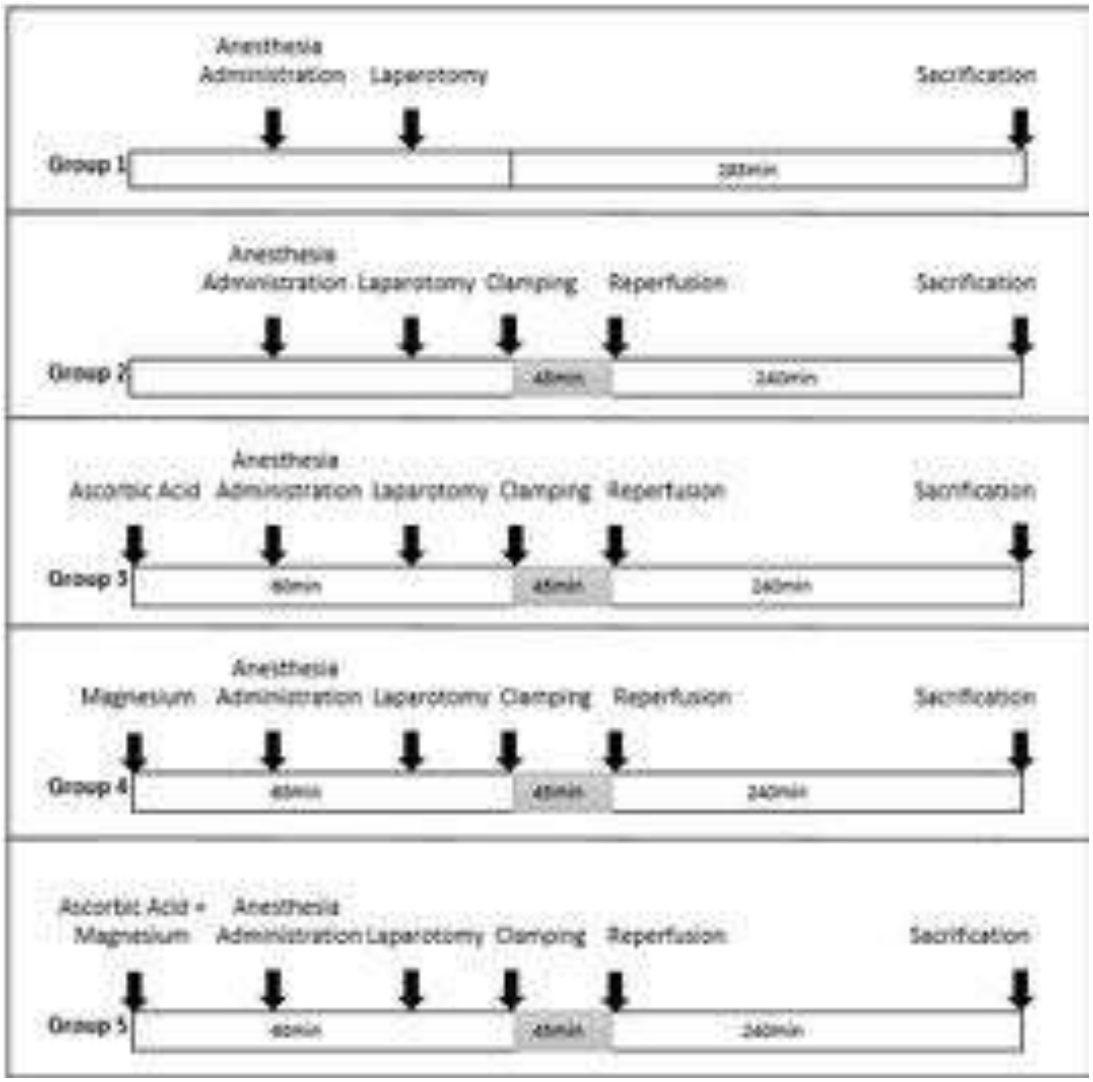

Anesthetic Pharmacology - 7

B2-Gaba$_a$ Receptors Strongly Modulate Sedation Induced By Isoflurane

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Introduction: The mechanisms of anesthesia induced by inhalational anesthetics remains incompletely understood. In part this is because the different endpoints of anesthesia - hypnosis, sedation, amnesia and immobility - can be produced by distinct mechanisms. Also, molecular studies have demonstrated that many ion channels involved in neural function can be modulated by inhaled agents. Here, we made use of the N265M point mutation in the $GABA_AR$ β2 subunit, which renders receptors completely insensitive to etomidate (Belelli et al., 1997) and partially insensitive to inhaled anesthetics (Nishikawa et al., 2002), to test whether β2-$GABA_A$ receptors contribute to the sedative and/or hypnotic effects of isoflurane.

Methods: All experiments were approved by the University of Wisconsin IACUC. β2-N265M mice were generated on a C57BL/6J background utilizing CRISPR-Cas9 technology and bred with 129X1/SvJ mice (Jackson Laboratories, Bar Harbor, Maine) to produce mice with a mixed background. Heterozygous offspring were bred together to create mutant (β2-N265M) and wild type (WT) mice used for experiments. Both male and female mice were used for experiments.

As a measure of hypnosis, we assessed the loss and recovery of the righting reflex under isoflurane anesthesia as previously described (McKinstry-Wu et al., 2019). Briefly, mice were housed in cylindrical cages and exposed to isoflurane in 100% oxygen for 4 hours. The righting reflex was assessed every 3 minutes. Mice were given 2 hours to reach a steady state of anesthesia, and data from 2-4 hours was used for analysis.

As a measure of sedation, we assessed movement in an open field. Mice were exposed to isoflurane anesthesia in 100% oxygen for 2 hours, which induced loss of spontaneous movement or righting reflex in all mice. Then, mice were placed in an 8" x 8" enclosure in room air to observe recovery of spontaneous movement. Mouse movement was tracked using Ethovision XT 15 software (Noldus Information Technology, Leesburg, Virginia).

Data analysis was performed using Excel (Microsoft, 2016) and R (R Foundation, v4.0.3). Groups of 2 conditions were compared using a Wilcoxon rank-sum test and multiple conditions were compared using a Kruskal-Wallis test with pairwise comparisons using a Wilcoxon rank-sum test and Holm correction.

Results: The isoflurane dose-response relationship did not differ between β2-N265M and WT mice: EC50(β2-N265M) = 0.56 ± 0.12%; EC50(WT) = 0.53 ± 0.06% (mean ± sd; n=8 of each genotype; p=0.56). However, isoflurane had very different effects on spontaneous movement as mice recovered from anesthesia. By the end of the 2nd minute of recovery, ambulation was present in 7 of 8 β2-N265M mice but only 4 of 8 WT mice. 10 minutes into the recovery period, β2-N265M mice had ambulated an average of 1263 ± 941 cm (n=8), whereas WT mice had ambulated only 299 ± 427 cm (n=8; p=0.04). In fact, this was not different from how far β2-N265M mice ambulated when not exposed to isoflurane (1791 ± 442 cm; n=8; p=0.70). Also, ambulation did not differ between β2-N265M and WT when the mice were not exposed to isoflurane (WT 1547 ± 815 cm; n=8; p=1.0).

Conclusion: Modulation of β2-GABAA receptors contributes strongly to isoflurane-induced sedation, but little if anything to loss of righting reflex. These findings mirror previous results obtained using the GABAergic anesthetics etomidate and propofol (Reynolds et al., 2003). Insofar as it remains debated whether the behavioral endpoints of inhalational anesthetics are due to small effects on a large number of molecular targets or large effects on a small number of molecular targets, our finding that a single point mutation of the GABAAR β2 subunit strongly influences sedation supports the notion that anesthetic action on a small number of critical targets mediates this endpoint.

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Anesthetic Pharmacology - 8 Selective Impairment Of Molecular Interaction Between Adp And Atp Synthase By Anesthetics

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Introduction: Isoflurane, sevoflurane, and desflurane have been shown to have different neurotoxic effects 1. However, the underlying mechanism at the single molecular level remains 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 assess whether different anesthetics can selectively impair the interaction of ADP and ATP synthase at a single molecular level.

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 employed a nanobeam technology-based single molecular dynamic interaction detection method 5 to determine the interaction of ADP and ATP synthase following the administration of isoflurane, sevoflurane, and desflurane. Each of resonance shifts, detected by a nanosensor, corresponded to single molecular interaction of ADP and ATP synthase. Finally, the single molecular dynamics computer simulation 5 was used to identify the binding sites between ATP synthase and each of the anesthetics.

Results: The Seahorse XFp Extracellular Flux Analyzer demonstrated that isoflurane, but not sevoflurane or desflurane, induced mitochondrial dysfunction in the H4-APP cells. The nanobeam technology-based single molecular dynamic interaction detection method demonstrated that isoflurane (Figure 1A) significantly impaired the interaction of ADP and ATP synthase as evidenced by the decreased numbers of resonance shift, longer duration between the resonance shifts and decreased disassociation constant (the bar graph). Neither sevoflurane (Figure 1B) nor desflurane (Figure 1C) impaired such interaction. Mechanistically, the single molecular dynamics computer simulation study, assessing the various energy binding ability and different binding dynamic activity, demonstrated that there were 14, 3 and 1 amino acid binding sites in ATP synthase by isoflurane (Figure 2 red), sevoflurane (Figure 2 green) and desflurane (Figure 2 yellow), respectively. Note that all the identified 14 binding sites in ATP synthase by isoflurane are dominated binding position of amino acid related to the generation of ATP.

Conclusion: These findings suggest that isoflurane has more binding sites with ATP synthase than sevoflurane or desflurane, which impairs the molecular interaction of ADP and ATP synthase, leading to the selective mitochondrial dysfunction and neurotoxicity observed following the administration of isoflurane but not sevoflurane or desflurane.

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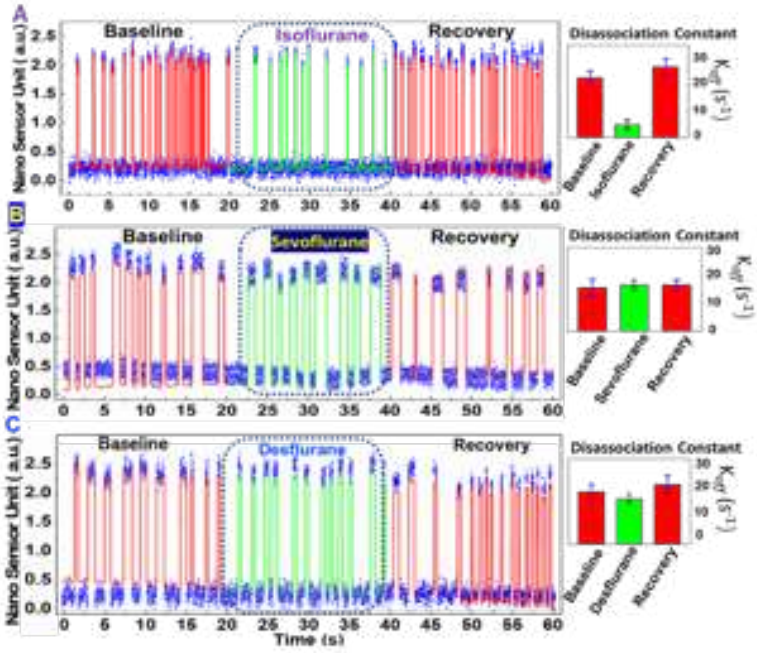
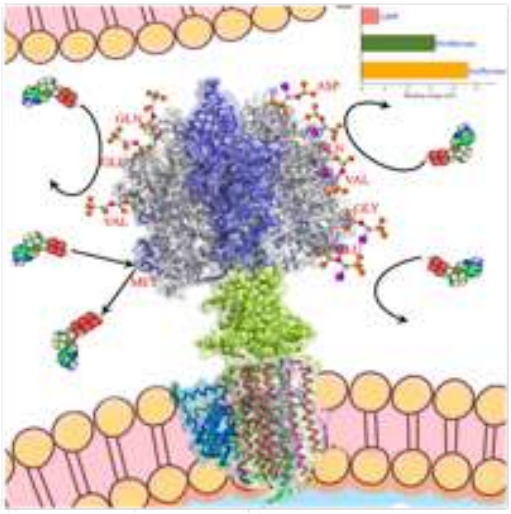


Figure 1. Isoflurane (A), but not Sevoflurane (B) or Desflurane (C), impairs the molecular interaction of ADP and ATP synthase.



	Isoflurane	Sevoflurane	Desflurane
ATP synthase F1 subunit	14 (-4.90 eV) (red)	3 (-3.67 eV) (green)	1 (-1.98 eV) (yellow)

Figure 2. The binding amino acid sites position of ATP synthase with Isoflurane (red), Sevoflurane (green) and Desflurane (yellow).

Blood Management

Blood Management - 1 Over-Transfusion in Pediatric Patients Intra-operatively. A Retrospective Observational Study at a Tertiary Pediatric Hospital.

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

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

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

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

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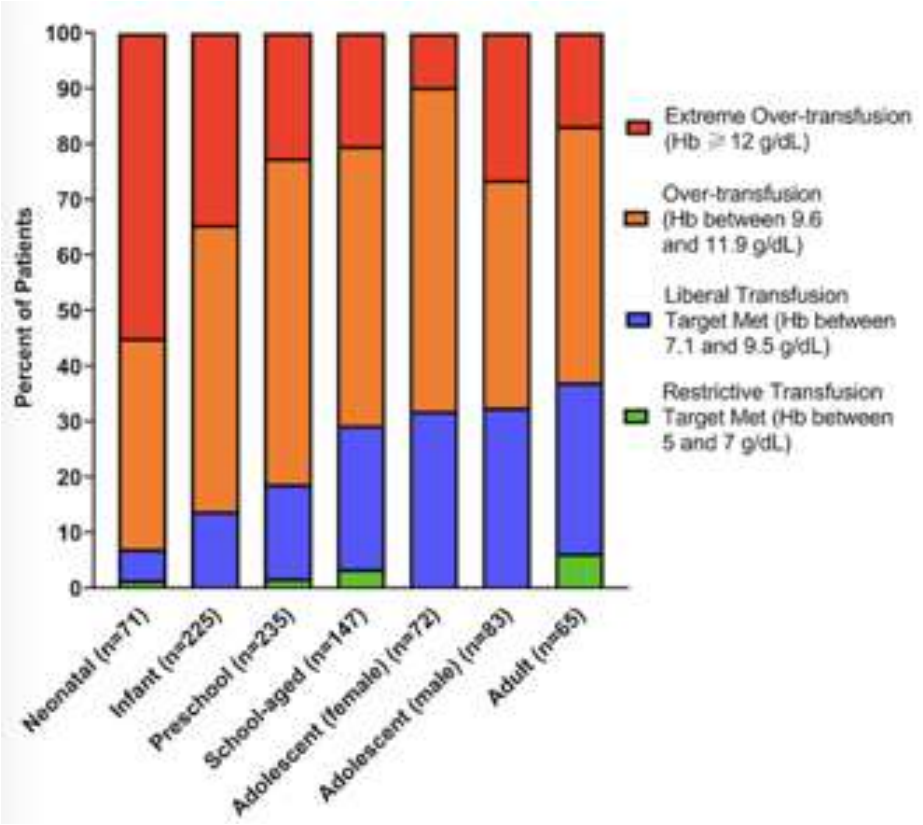

Table 1: Univariate Analysis of Intraoperative Over-transfusion based on 24-hour Hemoglobin Postoperatively (N=898)

Variable	Restrictive Transfusion Target Met (Hb between 5 and 7 g/dL)	Liberal Transfusion target met (Hb between 7.1 and 9.5 g/dL)
Number of Patients	**14**	**183**
Age Category		
Neonatal	1 (1.4%)	4 (5.6%)
Infant	0 (0%)	31 (13.8%)
Preschool	4 (1.7%)	40 (17%)
School-aged	5 (3.4%)	38 (25.9%)
Adolescent (female)	0 (0%)	23 (31.9%)
Adolescent (male)	0 (0%)	27 (32.5%)
Adult	4 (6.2%)	20 (30.8%)
Sex		
Male	9 (1.7%)	106 (20.3%)
Female	5 (1.3%)	77 (20.5%)
Weight (kg)	24.5 (16.4, 60)	21.4 (10.1, 45.9)
Pre-operative anemia		
Yes (n=513)	9 (1.8%)	141 (27.5%)
No (n=321)	4 (1.3%)	33 (10.3%)
Procedure Type		
General/GI	3 (0.7%)	75 (16.9%)
Ortho	1 (0.6%)	47 (25.8%)
Neuro	2 (2.3%)	12 (13.8%)
Plastics & Maxillary	4 (5.2%)	18 (23.4%)
Transplant	0 (0%)	17 (28.3%)
GU	0 (0%)	8 (38.1%)
ORL	1 (7.1%)	3 (21.4%)
Other	3 (21.4%)	3 (21.4%)
Emergent		
Yes (n=258)	7 (2.7%)	63 (24.4%)
No (n=577)	6 (1%)	110 (19.1%)
ASA-PS		
I	0 (0%)	4 (57.1%)
II	2 (2.5%)	25 (31.7%)
III	8 (1.5%)	112 (20.4%)
IV	4 (1.7%)	38 (16%)
V	0 (0%)	4 (16.7%)
VI	0 (0%)	0 (0%)
Surgery Duration (minutes)	194 (72, 285)	292 (159, 452)
Total Perioperative RBC Transfused (ml)	571 (366, 607)	312 (240, 610)
Total Perioperative RBC Transfused (ml/kg)	20.5 (16.6, 37)	16.9 (9.9, 29.5)
Perioperative administration of autologous RBC (cell saver)		
Yes	1 (0.7%)	26 (17.9%)
No	13 (1.7%)	157 (20.9%)
Perioperative administration of yellow blood products		
Yes	7 (2.5%)	75 (26.5%)
No	7 (1.1%)	108 (17.6%)

Categorical data are presented as n (row percent) and continuous data are presented as median (interquartile range).
Sample sizes are shown to indicate variables with missing data.
P values were calculated using the Chi-square test, Fisher's exact test or the Kruskal-Wallis test, as appropriate.
*Statistically significant.

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

Postoperative Outcome Variable	Restrictive Transfusion Target Met (Hb between 5 and 7 g/dL) [n=14]	Liberal Transfusion target met (Hb between 7.1 and 9.5 g/dL) [n=183]	Over-transfusion (Hb between 9.6 and 11.9 g/dL [n=461]
Length of Hospital Stay (days)	9 (5, 19)	12 (7, 39)	18 (8, 56)
Length of ICU stay (days)	2 (0, 4.7)	1.5 (0, 5.4)	2 (0.8, 7.7)
Postoperative intubation and/or mechanical ventilation	4 (28.6%)	73 (39.9%)	248 (53.8%)
Allergic Reaction	0 (0%)	6 (3.3%)	5 (1.1%)
Cardiac Arrest	0 (0%)	1 (0.6%)	8 (1.7%)
Heart Failure	1 (7.1%)	12 (6.6%)	30 (6.5%)
Neonatal Cardiac Failure	0 (0%)	0 (0%)	2 (0.4%)
Pulmonary Infection	8 (57.1%)	108 (59%)	335 (72.7%)
Renal Failure	2 (14.3%)	21 (11.5%)	32 (6.9%)
Sepsis	1 (7.1%)	24 (13.1%)	46 (10%)
Transfusion Reaction	0 (0%)	14 (7.7%)	18 (3.9%)
Wound Infection	0 (0%)	8 (4.4%)	22 (4.8%)
30-day mortality	1 (7.1%)	5 (2.7%)	10 (2.2%)

Data are presented as n (column percent) or median (interquartile range).

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

Multivariable median and logistic regression models were adjusted for age, ASA, procedure type, emergent status, and weight.

*Statistically significant.

Blood Management - 2 A retrospective study of the off-label Use of Activated 4-Factor Prothrombin Complex Concentrate in Neonates after Cardiac Surgery

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

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

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

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

effective hemostatic agent for rescue therapy in neonates with refractory bleeding after CPB.

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

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

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

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

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

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

[a]

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

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

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

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

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

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

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

Blood Management - 3 Reliability and Waste Reduction in Perioperative Blood Management: A Failure Modes and Effects Analysis

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

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

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

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

Blood Management - 4 Blood Product Utilization for Severe Anemia and Acute Kidney Injury at a Tertiary Hospital in Malawi

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

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

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

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

groups. Further research may focus on evaluation of different hemoglobin thresholds for severe anemia and/or improving the timely provision of blood products in this region.

Figure 1. Acute Kidney Injury Network Definitions

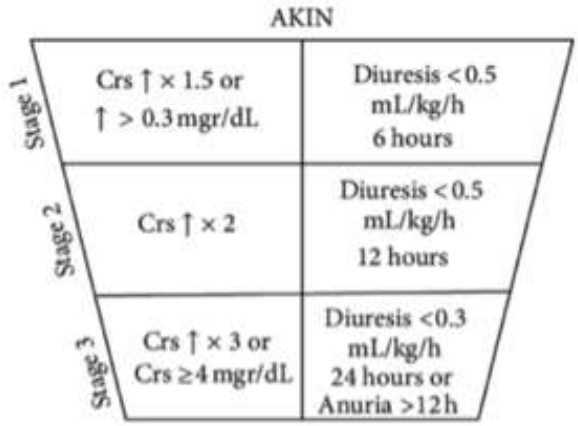

Table 1. Clinical traits of Obstetric and General Surgery Patients Admitted to the ICU of a tertiary hospital in Malawi, 2016-18			
	Overall (n=279)	**OBGyn (n=114)**	**General Surgery (n=165)**
Female	182 (65)	114 (100)	68 (41)
Age (years)	33 (16)	28 (8)	37 (19)
Admit From:			
High-Dependency Unit	57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

Outcomes			
Acute Kidney Injury			
Stage 1	31 (11)	18 (16)	13 (8)
Stage 2	78 (28)	28 (25)	50 (30)
Stage 3	45 (16)	14 (12)	31 (19)
Duration of mechanical ventilation, days	4.42 (5)	4.47 (5)	4.38 (5.5)
ICU Length of Stay, days	3.78 (5)	3.85 (5)	3.73 (5)
Hospital Length of Stay, days	13.9 (17)	14.4 (20)	13.6 (15)
ICU mortality	134 (48)	41 (36)	93 (56)
Hospital mortality	153 (55)	49 (43)	104 (63)

Table 2. Ordinal logistic regression for outcome of Acute Kidney Injury

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

Cardiovascular Anesthesiology

Cardiovascular Anesthesiology - 1 Iron Supplementation For Patients Undergoing Cardiac Surgery: A Systematic Review And Meta-Analysis Of Randomized-Controlled Trials

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

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

Results: Out of 1556 citations reviewed, five studies (n = 554 patients) met the inclusion criteria. The use of iron demonstrated no difference in transfusion incidence (RR 0.86; 95% CI 0.65 to 1.13). There was a low heterogeneity between studies (I2=0%). The trial sequential analysis suggested an optimal information size of 1132 participants, which the accrued information size did not reach.

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

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Cardiovascular Anesthesiology - 2 Effect of Exogenous Nitric Oxide Given During Cardiopulmonary Bypass on the Incidence of Postoperative Kidney Injury in Children

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

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

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

Conclusion: In this single center retrospective cohort study, we found no change in the incidence and severity of postoperative acute kidney injury after the

administration of exogenous nitric oxide into the cardiopulmonary bypass circuit in children.

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Table 1

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

*IQR= Interquartile range

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

Table 2

Creatinine	Control (N=321)		Intervention (N=296)		Difference between CrPre and Cr_{max}Post (95% CI between intervention andcontrol (95% CI)†	P value for change
	Mean (sd)	Difference between CrPre and Cr_{max}Post (95% CI)Avg. max	Mean (sd)	Difference between CrPre and Cr_{max}Post (95% CI)		
Preop	0.38 (0.19)	0.09 (0.07, 0.11)	0.39 (0.26)	0.08 (0.06, 0.10)	-0.01 (-0.04, 0.02)	0.535
POD 1	0.42 (0.22)		0.43 (0.21)			
POD 2	0.43 (0.19)		0.44 (0.27)			

CrPre = Preoperative creatinine; Cr_{max}Post= Peak postoperative creatinine
† After controlling for the effect of CPB time

Table 3: Effects in children less than 6 weeks of age

Creatinine	Control (N=54)		Intervention (N=49)		Difference in max. change (Intervention-control)†	P value for change
	Mean (sd)	Avg. max change from preop to POD1/POD2	Mean (sd)	Avg. max change from preop to POD1/POD2		
Preop	0.50 (0.19)	0.12 (0.06, 0.18)	0.46 (0.16)	0.06 (0.02, 0.10)	-0.05 (-0.13, 0.02)	0.18
POD 1	0.55 (0.22)		0.47 (0.15)			
POD 2	0.61 (0.28)		0.50 (0.19)			

† After controlling for the effect of CPB time

Table 4: Distribution of post-operative AKI between cohorts as defined by AKIN score

AKI Stages	Control (N=285)	Intervention (N=288)	Overall (N=573)
Stage 1	18 (6.3%)	24 (8.3%)	42 (7.3%)
Stage 2	15 (5.3%)	9 (3.2%)	24 (4.2%)
Stage 3	3 (1.1%)	3 (1.0%)	6 (1.1%)
Any stage	36 (12.6%)	36 (12.5%)	72 (12.6%)

Cardiovascular Anesthesiology - 3 Single Value Of Nephrocheck™ Performed At 4 Hours After Surgery Does Not Predict Acute Kidney Injury In Off-Pump Coronary Artery Bypass Surgery

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

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

Results: Thirteen patients developed AKI in the study cohort (14.4%) out of which 6 patients (6.6%) developed stage 1 AKI and the remaining 7 (7.8%) developed stage 2/3 AKI. Baseline renal parameters were similar between AKI and non-AKI group. The 4 hour post-operative Nephrocheck™ as compared to the preoperative NC, did not predict AKI. There were no significant differences in duration of mechanical ventilation, length of intensive care stay and hospital stay between the two groups (P>0.05). The Nephrocheck™ test performed at 4 hours after surgery did not identify patients at risk for developing AKI following OPCABG surgery.

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

NC- Nephrocheck™ value, S Cr- serum creatinine, eGFR-estimated glomerular filtration rate, LVEF-left ventricular ejection fraction, EuroSCORE- European System for Cardiac Operative Risk Evaluation, PA - pulmonary artery, MI-myocardial infarction, DM-diabetes mellitus, HTN-hypertension. Data are expressed as mean±SD. or number (percen

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

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

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

NC-NephroCheck™ value, S Cr- serum creatinine, eGFR-estimated glomerular filtration rate, LVEF-left ventricular ejection fraction, EuroSCORE- European System for Cardiac Operative Risk Evaluation, PA -pulmonary artery, MI-myocardial infarction, DM-diabetes mellitus, HTN-hypertension. Data are expressed as mean±SD. or number (percentage).

Cardiovascular Anesthesiology - 4

Off-Pump Technique May Prevent Deterioration Of Renal Function In Patients With Chronic Kidney Disease Undergoing Coronary Artery Bypass Grafting.

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

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

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

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

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

Table 1

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

*IQR= Interquartile range

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

Table 2

Creatinine	Control (N=321)		Intervention (N=296)		Difference between CrPre and $Cr_{max}Post$ (95% CI between intervention andcontrol (95% CI)†	P value for change
	Mean (sd)	Difference between CrPre and $Cr_{max}Post$ (95% CI)Avg. max	Mean (sd)	Difference between CrPre and $Cr_{max}Post$ (95% CI)		
Preop	0.38 (0.19)	0.09 (0.07, 0.11)	0.39 (0.26)	0.08 (0.06, 0.10)	-0.01 (-0.04, 0.02)	0.535
POD 1	0.42 (0.22)		0.43 (0.21)			
POD 2	0.43 (0.19)		0.44 (0.27)			

CrPre = Preoperative creatinine; $Cr_{max}Post$= Peak postoperative creatinine
† After controlling for the effect of CPB time

Table 3: Effects in children less than 6 weeks of age

Creatinine	Control (N=56)		Intervention (N=49)		Difference in max. change (intervention-control)†	P value for change
	Mean (sd)	Avg. max change from preop to POD1/POD2	Mean (sd)	Avg. max change from preop to POD1/POD2		
Preop	0.50 (0.19)	0.12 (0.06, 0.18)	0.46 (0.16)	0.06 (0.02, 0.10)	-0.05 (-0.13, 0.02)	0.18
POD 1	0.55 (0.22)		0.47 (0.15)			
POD 2	0.61 (0.28)		0.50 (0.19)			

† After controlling for the effect of CPB time

Table 4: Distribution of post-operative AKI between cohorts as defined by AKIN score

AKI Stages	Control (N=285)	Intervention (N=288)	Overall (N=573)
Stage 1	18 (6.3%)	24 (8.3%)	42 (7.3%)
Stage 2	15 (5.3%)	9 (3.2%)	24 (4.2%)
Stage 3	3 (1.1%)	3 (1.0%)	6 (1.1%)
Any stage	**36 (12.6%)**	**36 (12.5%)**	72 (12.6%)

Cardiovascular Anesthesiology - 5

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

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

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

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

Conclusion: Cardiovascular events were prevalent and associated with worse outcomes in hospitalized patients with COVID-19. Outcomes of cardiovascular

events in African American and white COVID-19 patients were similar except days to mortality. There were common and unique risk factors for cardiovascular events in African American COVID-19 patients when compared with white patients.

References: 1. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiology. 2020;5(7):811-818. 2. Ni W, Yang X, Liu J, et al. Acute Myocardial Injury at Hospital Admission Is Associated With All-Cause Mortality in COVID-19. J Am Coll Cardiol. 2020;76(1):124-125. 3. Shi S, Qin M, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur Heart J. 2020;41(22):2070-2079. 4. Heffernan KS, Michos ED, Gump BB. Coronavirus Disease 2019 (COVID-19) and Cardiac Injury. JAMA Cardiology. 2020;5(10):1198-1198. 5. Zakeri R, Bendayan R, Ashworth M, et al. A case-control and cohort study to determine the relationship between ethnic background and severe COVID-19. EClinicalMedicine. 2020;28. 6. Carrico R. Implementation of the Louisville COVID-19 Surveillance Protocol: Experiences from the University of Louisville Center of Excellence for Research in I

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

Variables	Cases without CV Events (n	Cases with CV Events (n=126)	P-values
Death	50 (8.7%)	57 (45.2%)	<0.001
LOS for survivors (Days) (IQR)[#]	5 (3,11)	9(6,18)	<0.001
Days to mortality for non-survivors (Days)	8(5,11)	10(6,15)	0.088
Demographics Morphometrics			
Age	57.8±19.37	66.8±15.2	<0.001
Female	330 (57.5%)	54(42.9%)	0.004
Male	244 (42.5%)	72(57.1%)	
Hispanic	77(13.4%)	4(3.2%)	<0.001
Non-Hispanic African American	179(31.2%)	41(32.5%)	
Non-Hispanic white	267 (46.5%)	76(60.3%)	
Non-Hispanic other	51(8.9%)	5(4.0%)	
Comorbidities			
Pulmonary comorbidity	256 (44.6%)	80 (63.5%)	<0.001
Pulmonary comorbidity count			
0	318(55.4%)	46(36.5%)	<0.001
1	174(30.3%)	50(39.7%)	
2-4	82(14.3%)	30(23.8%)	
Cardiovascular comorbidity	338(58.9%)	104(82.5%)	<0.001
Cardiovascular comorbidity count			
0	236(41.1%)	22(17.5%)	<0.001
1	125(21.8%)	21(16.7%)	
2-4	178(31.0%)	63(50.0%)	
5-8	35(6.1%)	20(15.9%)	
Renal disease	86(15.0%)	39(31.0%)	<0.001
Renal disease count			
0	488(85.0%)	87(69.1%)	<0.001
1	48(8.4%)	25(19.8%)	
2	38(6.6%)	14(11.1%)	
Diabetes	164(28.6%)	60(47.6%)	<0.001
Neoplastic/immune compromised diseases	47(8.2%)	20(15.9%)	0.013
Neoplastic/immune compromised disease			
0	527(91.8%)	106(84.1%)	0.026*
1	39(6.8%)	17(13.5%)	
2	8(1.4%)	3(2.4%)	
Laboratory Tests			
AST/ALT Ratio	1.5±0.77	1.7±0.83	0.003
Neutrophil/lymphocyte Ratio	6.4±7.69	9±10.74	<0.001
SaO2/FiO2 ratio	382.1±105.22	282.4±136.89	<0.001
WBC ($10^3/mm^3$)	7.4±4.43	8.6±5.72	0.026
Neutrophil percentage	71.5±13.53	75.4±14.24	0.002
Lymphocyte percentage	18.5±10.75	15.2±10.53	0.001
Neutrophil ($10^3/mm^3$)	7.8±13.03	8±9.63	0.013
Lymphocyte ($10^3/mm^3$)	1.7±3.3	1.5±2.92	0.001
Serum potassium (mmol/liter)	3.8±0.62	4.1±0.73	<0.001

Glucose (mg/dl)	145.7±80.01	165.3±91.96	0.001
BUN (mg/dl)	21±18.28	32.5±24.82	<0.001
Creatinine (mg/dl)	1.4±1.8	1.7±1.26	<0.001
Albumin(g/dl)	3.6±0.63	3.3±0.68	0.001
Bilirubin (mg/dl)	1±4.05	1.1±3.14	0.002
AST (units/liter)	55.7±64.38	83.6±168.01	0.033
INR	1.3±0.8	1.4±0.95	0.009
Procalcitonin (ng/ml)	2.3±22.06	2.2±6.15	<0.001
D-dimer (μg/ml fibrinogen equivalent unit	1729.9±4686.23	4741.5±13169.36	<0.001
Interleukin-6 (pg/ml)	95.7±131.58	190.8±266.21	0.001
CRP (mg/liter)	40.2±95.65	53.2±72.17	0.001
ABG FiO2 (%)	49.5±30.54	60.5±33.08	0.016
BNP (pg/ml)	1098.6±9406.06	823.5±1072.37	<0.001
NT-proBNP (pg/ml)	3374.8±17423.69	6168.1±15115.23	<0.001

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

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

	African American Patients (N=220)			**White Patients (N=424) (Non-Hispanic White and Hispanic)**			**African American vs. White Patients**	
Variables	**Without CV events**	**With CV events**	**P-values**	**Without CV events**	**With CV events**	**P-values**	**P-values without CV events**	**P-values with CV events**
Sample Size	179 (81.4%)	41 (18.6%)		344 (81.1%)	80 (18.9%)		1	
Death	14 (7.8%)	18 (43.9%)	**<0.001**	31 (9.0%)	37 (46.3%)	**<0.001**	0.767	0.958
LOS for survivors (Days) (IQR)#	5(2,11)	11(7.5,23.5)	**<0.001**	5(3,12)	9(5.5,16)	**<0.001**	0.419	0.257
Days to mortality for non-survivors (Days) (IQR)#	8.5(5.25,13.75)	6(5,10)	0.391	7(4,10.5)	12(8,15)	**0.004**	0.32	**0.031**
Age	57.2±17.67	68.5±12.26	**<0.001**	59±20.22	66±15.58	**0.003**	0.318	0.667
Sex: Female	107 (59.8%)	16(39.0%)	**0.025**	189(54.9%)	36(45.0%)	0.139	0.334	0.664
Male	72 (40.2%)	25(61.0%)		155(45.1%)	44(55.0%)			
Comorbidities								
Pulmonary comorbidity	93 (52.0%)	23 (56.1%)	0.760	147 (42.7%)	57(71.3%)	**<0.001**	0.055	0.143
Pulmonary comorbidity count								
0	86(48.0%)	18(43.9%)	0.7607	197(57.3%)	23 (28.8%)	**<0.001**	0.082	0.182
1	59(33.0%)	16(39.0%)		102(29.7%)	34 (42.5%)			
2-4	34(19.0%)	7(17.1%)		45(13.1%)	23 (28.8%)			
Cardiovascular comorbidity	120(67.0%)	36(87.8%)	**0.014**	194(56.4%)	64 (80.0%)	**<0.001**	**0.024**	0.413
Cardiovascular comorbidity count								
0	59(33.0%)	5(12.2%)	**<0.001***	150(43.6%)	16 (20.0%)	**<0.001***	**0.024**	0.741

1	44(24.6%)	6(14.6%)		71 (20.6%)	12 (15.0%)			
2-4	68(38.0%)	23(56.1%)		97 (28.2%)	39 (48.8%)			
5-8	8(4.5%)	7(17.1%)		26 (7.6%)	13 (16.3%)			
Renal disease	39(21.8%)	13(31.7%)	0.2523	46 (13.4%)	26 (32.5%)	**<0.001**	**0.019**	1
Renal disease count								
0	140(78.2%)	28(68.3%)	0.3647*	298 (86.6%)	54 (67.5%)	**<0.001***	**0.030**	0.638*
1	20(11.2%)	7(17.1%)		28 (8.1%)	18 (22.5%)			
2	19(10.6%)	6(14.6%)		18 (5.2%)	8 (10.0%)			
Diabetes	62(34.6%)	24(58.5%)	**0.008**	90 (26.2%)	36 (45.0%)	**0.001**	0.054	0.223
Neoplastic/immune compromised diseases	14(7.8%)	8(19.5%)	**0.039***	31 (9.0%)	11(13.8%)	0.214*	0.767	0.575
Neoplastic/immune compromised diseases count								
0	165(92.2%)	33(80.5%)	**0.021***	313 (91.0%)	69 (86.3%)	0.194*	0.813*	0.208*
1	11(6.2%)	8(19.5%)		26 (7.6%)	8 (10.0%)			
2	3(1.7%)	0(0.0%)		5 (1.5%)	3 (3.8%)			
Laboratory Tests								
AST/ALT Ratio	1.7±1	1.6±0.63	0.507	1.4±0.63	1.8±0.92	**<0.001**	**0.011**	0.733
Neutrophil/lymphocyte Ratio	6.3±10.49	8.5±6.79	**0.002**	6.5±6.06	9.6±12.44	**0.006**	**0.025**	
SaO2/FiO2 ratio	396.6±91.08	294.6±142.5	**<0.001**	377.5±108.0	268.1±132.9	**<0.001**	0.056	0.254
WBC(10^3/mm^3)	7.5±5.5	8.9±6.11	**0.017**	7.4±3.85	8.6±5.61	0.164	0.599	0.492
Hemoglobin (g/dl)	12.4±2.02	12.3±2.41	0.952	13±2.01	12.4±2.38	**0.026**	**<0.001**	0.795
Neutrophil percentage	70.3±13.07	75.3±13.36	**0.017**	72±13.78	76.4±14.08	**0.009**	0.135	0.566
Lymphocyte percentage	19.3±10.99	13.7±7.4	**0.004**	18.1±10.73	15.1±11	**0.015**	0.223	0.958
Neutrophil (10^3/mm^3)	7.8±14.07	7.4±6.89	**0.013**	7.8±12.47	8.5±10.96	**0.097**	0.08	0.975
lymphocyte(10^3/mm^3)	1.7±2.86	1.1±0.65	**0.079**	1.7±3.5	1.6±3.6	**0.006**	0.23	0.547
Serum potassium (mmol/liter)	3.8±0.63	4.3±0.74	**0.001**	3.9±0.63	4.1±0.73	**0.04**	0.865	0.091
Glucose@ (mg/dl)	142.5±76.29	193±113	**<0.001**	147.1±84.0	153.3±78.0	0.255	0.601	**0.004**
BUN(mg/dl)	22.5±17.9	37.6±32.8	**<0.001**	21.3±19.17	29.9±18.6	**<0.001**	0.509	0.393
Creatinine(mg/dl)	1.9±2.48	2.1±1.53	**0.001**	1.2±1.32	1.6±1.09	**<0.001**	**<0.001**	**0.005**
Albumin(g/dl)	3.6±0.6	3.2±0.73	**0.001**	3.6±0.65	3.4±0.65	0.068	0.926	0.093
Bilirubin(mg/dl)	1.5±7.12	0.9±0.57	**0.019**	0.7±0.64	1.2±3.91	0.069	0.285	0.119
AST (units/liter)	58.4±81.0	89.8±158.4	**0.029**	55.5±58.5	81.9±177.6	0.325	0.093	0.517
Procalcitonin(ng/ml)	4.1±34.14	1.2±2.58	**<0.001**	1.6±15.15	2.7±7.4	**<0.001**	0.214	0.445
D-dimer (µg/ml fibrinogen equivalent units)	2216±5512	6945±18717	**0.024**	1482±4462	3575±8726	**<0.001**	0.292	0.641
Interleukin-6 (pg/ml)	82.2±115.9	158.1±178.4	**0.012**	97.9±116.1	205.5±299.0	**0.039**	0.306	0.913
CRP (mg/liter)	37.2±59.51	65±69.47	**0.008**	43±114.11	47.4±73.95	**0.025**	0.717	0.248
BNP (pg/ml)	2749±17225	926.8±1396	**0.002**	439.3±1013	798.6±873.0	**0.002**	0.220	0.952
NT-proBNP (pg/ml)	4097±21360	2632±3772	**0.008**	3099±16290	7750±17860	**<0.001**	0.351	0.806

Note: Within each race, the patients with cardiovascular (CV) events were compared with those without CV events. African American and White patients were also compared among those without CV events (see the column "p-values without CV"), and among those with CV events (see the column "p-values with CV"), respectively.
*indicates Fisher's Exact Test. # indicates that median and interquartile range were reported.

Table 3. Factors Associated with Cardiovascular Events using Multiple Logistic Regression Model Data from the Entire Cohort, African American COVID-19 Patients, and White COVID-19 Patients.

	Entire cohort (N=700)		**African American Patients (N=220)**		**White Patients (N=424) (Hispanic + Non-Hispanic)**	
Variable	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age	1.008	(0.988, 1.028)	1.029	(0.991, 1.068)	1.008	(0.981, 1.035)
Race Non-Hispanic African American vs. Hispanic	**4.888**	**(1.01, 23.66)**				
Race Non-Hispanic others vs. Hispanic	2.432	(0.374, 15.82)				
Race Non-Hispanic white vs. Hispanic	4.639	(0.97, 22.18)				
Race Non-Hispanic African American vs. Non-Hispanic White	1.054	(0.590, 1.881)				
Male (vs. Female)	**1.737**	**(1.003, 3.01)**	1.417	(0.505, 3.979)	1.318	(0.620, 2.802)
SaO2/FiO2 ratio	**0.995**	**(0.993, 0.997)**	0.996	(0.991, 1.001)	**0.994**	**(0.991, 0.997)**
WBC	0.997	(0.940, 1.057)	0.918	(0.771, 1.092)	1.054	(0.962, 1.154)
Hemoglobin	1.05	(0.917, 1.203)	1.185	(0.925, 1.52)	1.039	(0.861, 1.254)
Lymphocyte percentage	1.009	(0.986, 1.033)	1.039	(0.986, 1.094)	0.999	(0.969, 1.030)
Lymphocyte	0.988	(0.959, 1.018)	0.978	(0.862, 1.109)	0.99	(0.959, 1.023)
Serum potassium	**1.557**	**(1.056, 2.296)**	2.156	(0.878, 5.293)	1.463	(0.868, 2.464)
Glucose	0.998	(0.995, 1.002)	0.997	(0.991, 1.003)	0.998	(0.992, 1.003)
BUN	0.994	(0.98, 1.009)	0.994	(0.963, 1.026)	0.99	(0.970, 1.010)
Albumin	**0.623**	**(0.411, 0.945)**	**0.165**	**(0.06, 0.454)**	1.048	(0.564, 1.946)
Bilirubin	1.000	(0.948, 1.055)	0.542	(0.235, 1.246)	1.157	(0.713, 1.878)
AST	1.002	(0.999, 1.004)	1.004	(0.998, 1.01)	1.002	(0.997, 1.007)
Pulmonary comorbidity count	1.016	(0.757, 1.364)	0.649	(0.336, 1.252)	1.382	(0.935, 2.044)
Cardiovascular comorbidity count	**1.297**	**(1.106, 1.521)**	1.258	(0.897, 1.763)	**1.326**	**(1.069, 1.645)**
Renal disease count	1.209	(0.754, 1.939)	1.147	(0.511, 2.577)	1.456	(0.724, 2.929)
Diabetes	1.512	(0.817, 2.796)	1.920	(0.577, 6.39)	2.059	(0.891, 4.758)
Neoplastic/immune compromised diseases count	1.622	(0.86, 3.059)	**5.157**	**(1.074, 24.77)**	1.967	(0.854, 4.53)

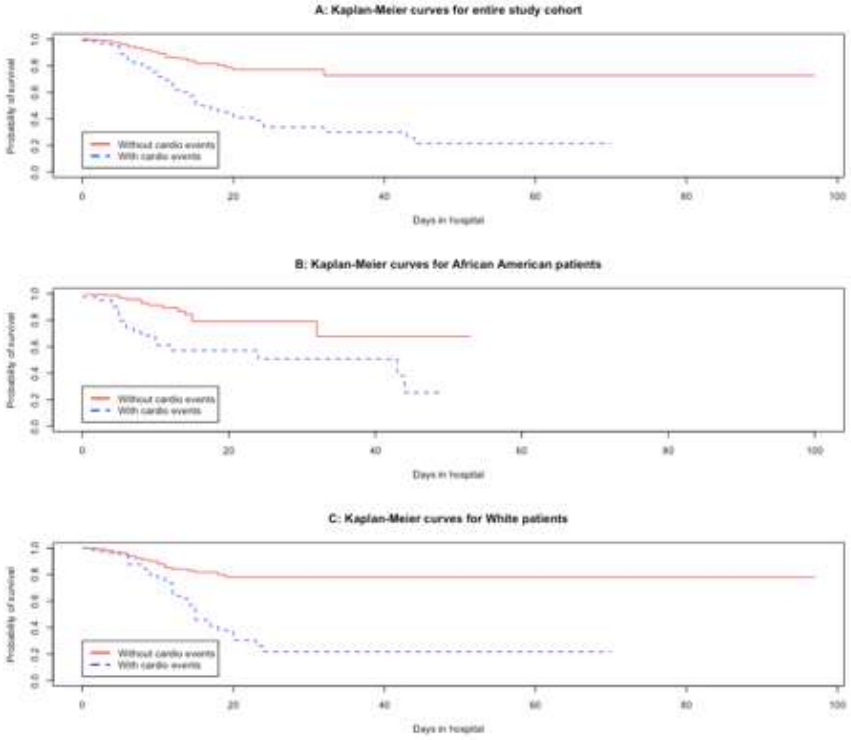
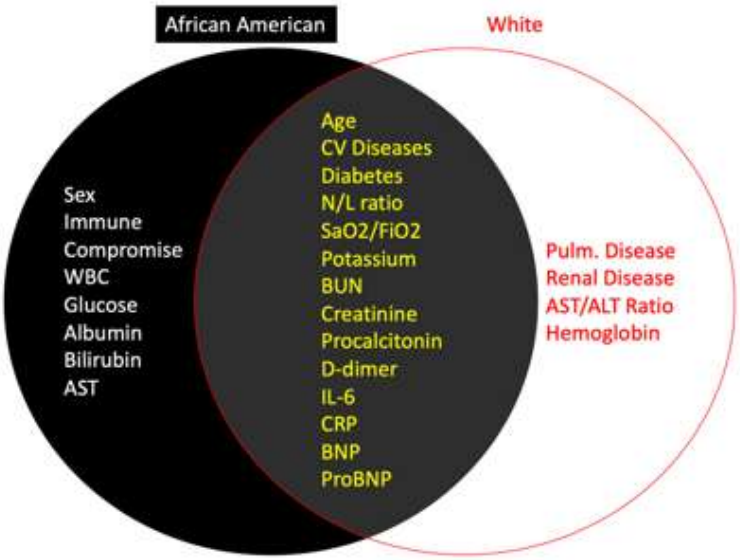

A: Kaplan-Meier curves for entire study cohort
Probability of survival
Without cardio events
With cardio events
Days in hospital
B: Kaplan-Meier curves for African American patients
Probability of survival
Without cardio events
With cardio events
Days in hospital
C: Kaplan-Meier curves for White patients
Probability of survival
Without cardio events
With cardio events
Days in hospital

Figure 2


African American
White
Sex
Immune
Compromise
WBC
Glucose
Albumin
Bilirubin
AST
Age
CV Diseases
Diabetes
N/L ratio
SaO2/FiO2
Potassium
BUN
Creatinine
Procalcitonin
D-dimer
IL-6
CRP
BNP
ProBNP
Pulm. Disease
Renal Disease
AST/ALT Ratio
Hemoglobin

Cardiovascular Anesthesiology - 6 The Effects of Phenylephrine and Haemorrhage on the Porcine Gut Mucosal Microcirculation

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

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

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

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

References: 1. Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. Intensive Care Medicine, 23(3): 276–281, 1997. 2. Perioperative Plasma Volume Expansion Reduces the Incidence of Gut Mucosal Hypoperfusion During Cardiac Surgery. Archives of Surgery, 130(4): 423, 1995. 3. Hemodynamic and Metabolic Effects of Hemorrhage in Man, with Particular Reference to the Splanchnic Circulation. Circulation Research, 18(5): 469-474, 1996.

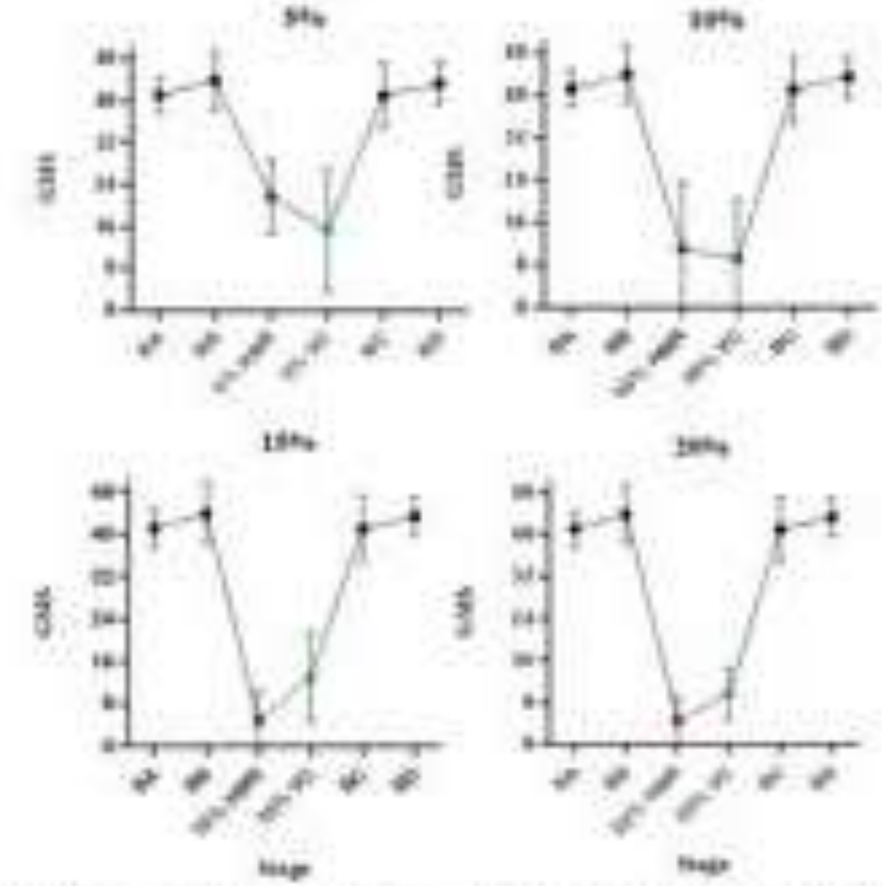

Figure 2: Graphs showing gut microcirculation scores (GMS) before and after phenylephrine administration at each percentage haemorrhage. Red points show haemorrhage alone (HMR stages) and green points are with phenylephrine present (VC stages). Stage IIIC follows blood re-transfusion and stage IIID follows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

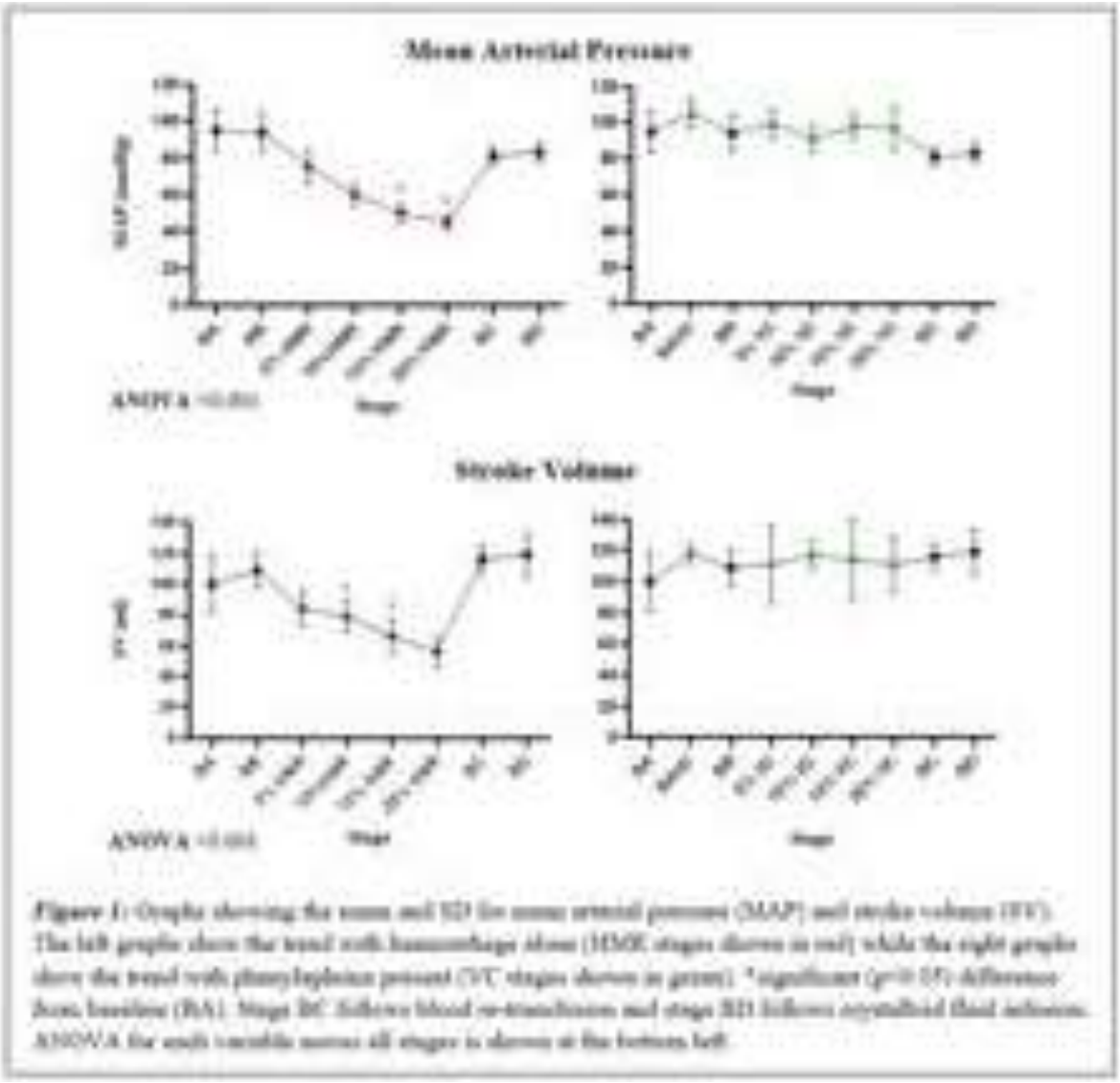

Figure 1: Graphs showing the mean and SD for mean arterial pressure (MAP) and stroke volume (SV). The left graphs show the trend with haemorrhage alone (HMR stages shown in red) while the right graphs show the trend with phenylephrine present (VC stages shown in green). * significant ($p<0.05$) difference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

Cardiovascular Anesthesiology - 7

Echocardiography As An Aid To Tracheal Extubation In Cardiac Surgical Patients

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

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

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

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

ECHOCARDIOGRAPHY AS AN AID TO TRACHEAL EXTUBATION IN CARDIAC SURGICAL PATIENTS

Dr. Roshini Sara Simon Dr. Anup Daniel Varghese Dr. Kumar Belani Dr. Muralidhar Kanchi

Key words: Echocardiography, Spontaneous breathing trial, Tracheal extubation

INTRODUCTION:

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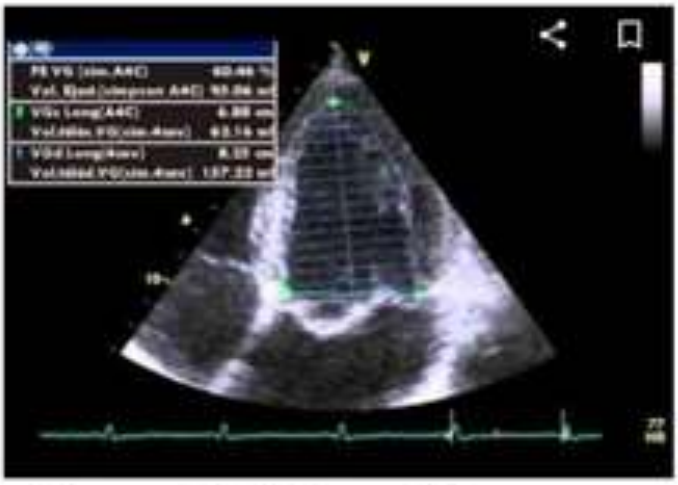
The following parameters were assessed: left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), pulmonary artery systolic pressure (PASP), E/A, E/e', inferior venacava (IVC) collapsibility index and right atrial pressure (RAP).



Measurement of EF by Simpsons method

RESULTS:

There were 400 patients who underwent elective cardiac surgery during the study period. The demographic, clinical and echocardiographic data are shown in the table. Amongst the echocardiographic parameters, EF and E/e' were significantly different in the short ventilation (SV) and delayed extubation (DE) group.

The sensitivity of EF and E/e' in predicting weaning failure were found to be 85% and 87.5% respectively while the specificity of E/e' was 97.6% and that of LVEF was found to be only 55.4%. There was no significant difference in other echocardiographic parameters.

2

Table 1: Demographic and preoperative data

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

Table 2: Echocardiographic data

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

CONCLUSION:

Echocardiography has a significant role in diagnosing and monitoring patients in intensive care units and provides information regarding patient suitability for extubation following cardiac surgery. Based on our findings in this study in patients undergoing elective cardiac surgery, echocardiography can be used to benefit the patient in terms of predictability of weaning the

patient from ventilator. E/e' has extreme sensitivity and predictability regarding extubation success. Ejection fraction also helps in predicting weaning failure, but specificity is less compared to E/e'.

Thus, we recommend the use of echocardiography to aid extubation in cardiac surgical patients as it helps in identifying difficult to wean patients which helps in better decision making and post-operative management in these patients which further improves the outcome of the surgery and benefit the patient.

Cardiovascular Anesthesiology - 8 Effect Of Neuraxial Anaesthesia On Left Ventricular Diastolic Function Assessed By Transthoracic Echocardiography.

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

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

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

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

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

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ABSTRACT

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

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

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

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

Keywords: Spinal anaesthesia, Neuraxial anaesthesia, transthoracic echocardiography, Diastolic function, Left ventricle.

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

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

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

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

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

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

Table 4: Left ventricular diastolic function parameters. E- transmitral E wave, A- transmitral A wave, E/A- transmitral E/A ratio, PVF S- pulmonary vein flow systolic wave, PVF D- pulmonary vein flow diastolic wave, PVF S/D ratio- pulmonary vein flow systolic/diastolic wave ratio, Sw e'- Septal wall tissue Doppler imaging measurement of the mitral annulus velocity E wave, Sw a'- Septal wall tissue Doppler imaging measurement of the mitral annulus velocity A wave. Sw E/e'- Septal wall transmitral pulse doppler E wave velocity/tissue Doppler imaging measurement of the mitral annulus velocity E wave, Lw e'- lateral wall tissue Doppler imaging measurement of the mitral annulus velocity E wave, Lw a'- lateral wall tissue Doppler imaging measurement of the mitral annulus velocity A wave, Lw E/e' – Lateral wall transmitral pulse doppler E wave velocity/tissue Doppler imaging measurement of the mitral annulus velocity E wave, DT- deceleration time, Vp- Propagation velocity, LA- left atrium. Data are represented as mean±SD.

Parameters	Baseline	20 minutes after spinal	40 minutes after spinal	60 minutes after spinal	*p*
E (m/s)	0.77±0.14	0.77±0.13	0.77±0.13	0.78±0.13	0.989
A (m/s)	0.60±0.13	0.59±0.13	0.59±0.11	0.58±0.11	0.922
E/A ratio	1.29±0.34	1.29±0.36	1.26±0.28	1.29±0.31	0.953
PVF S (m/s)	0.48±0.08	0.50±0.10	0.49±0.10	0.48±0.09	0.9

PVF D (m/s)	0.34±0.09	0.35±0.09	0.34±0.08	0.34±0.09	0.9
PVF S/D ratio	1.51±0.44	1.49±0.45	1.49±0.46	1.50±0.45	0.9
Sw e' (m/s)	0.10±0.03	0.10±0.03	0.10±0.03	0.09±0.02	0.707
Sw a' (m/s)	0.06±0.02	0.06±0.02	0.06±0.02	0.06±0.02	0.9
Sw E/e' ratio	7.95±2.92	7.73±2.65	8.19±3.64	8.06±3.09	0.8
Lw e' (m/s)	0.12±0.03	0.11±0.03	0.11±0.02	0.11±0.03	0.10
Lw a' (m/s)	0.07±0.02	0.07±0.02	0.07±0.02	0.07±0.02	0.75
Lw E/e' ratio	6.69±2.59	6.72±2.40	6.76±2.42	6.61±2.30	0.99
DT (msec)	144.88±30.73	151.48±29.33	150.14±27.93	151.68±29.08	0.6
Vp	60.20±6.8	60.60±5.19	59.12±5.66	59.86±5.11	0.6
LA volume index (ml/m^2)	22.98±6.32	23.43±6.63	23.88±6.74	24.05±6.89	0.8

Table 5: ASA gradings before and after neuraxial anaesthesia. ASE -American society of Echocardiography, DD-diastolic dysfunction

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

Cardiovascular Anesthesiology - 9 Higher Preoperative High-Density Lipoprotein Concentration Is Associated With A Lower Risk Of Acute Kidney Injury After Endovascular Aortic Repair

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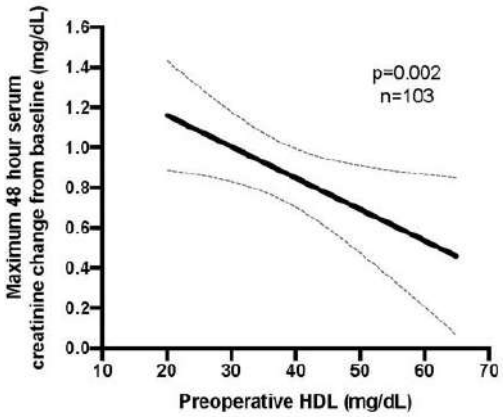
Introduction: Acute kidney injury (AKI) after endovascular aortic repair occurs in up to 20% of patients and is an independent predictor of death. Patients undergoing endovascular aortic repair have unique risk factors for AKI including exposure to radiocontrast, aortic clamping, and the potential for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

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

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

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



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

Cardiovascular Anesthesiology - 10

Intraoperative Use Of Methylene Blue For Vasoplegia In Cardiac Surgery Not Associated With Decreased Vasopressor Requirement

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

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

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

Conclusion: We unexpectedly found a higher pressor requirement associated with MB despite adjusting for baseline characteristics. Propensity score matching was performed to account for confounding factors which resulted in acceptable matches among all covariates (Figures 1 and 2). However, despite matching, the MB group still demonstrated higher pressor requirements. Given that these results conflict with existing literature, we think this is likely due to residual unobserved confounding by indication. For this reason, we elected to undertake an analysis to determine which covariates were most predictive of MB receipt. Prior studies have failed to identify a single or combination of factors as robust predictors of post-CPB VS and few cite endocarditis. Few studies have prospectively evaluated MB administration, though retrospective data suggests earlier (in the OR) vs. late administration (in the ICU) is protective for mortality and major adverse events (7). Only two studies have

evaluated prophylactic MB in cardiac surgery. These found benefit to MB but utilized weak predictive factors for VS and included small sample sizes (4,5). Importantly, not all studies, including our analysis, have found benefit to MB (8). Given our findings, we believe these data provide compelling preliminary results for a future randomized trial of MB use among endocarditis patients undergoing cardiac surgery. Further, the development of a more robust risk stratification profile may help in patient selection for further prospective studies.

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

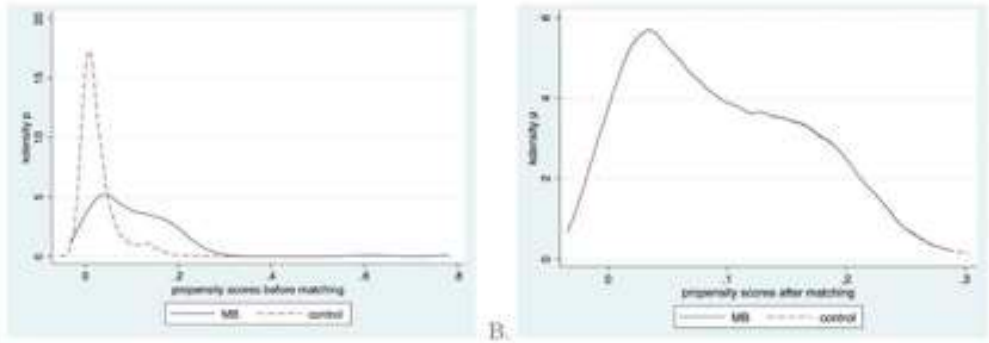
Characteristic (n = 9,616)	No MB Use (n = 9328)	MB Use (n = 288)	P value
Age (years)	62.55 (± 13.65) [95% CI 62.27-62.83]	56.68 (± 16.36) [95% CI 54.79-58.57]	<0.0001†
Sex - Female	3,029 (32.5%)	62 (21.5%)	<0.0001*
Male	6,299 (67.5%)	226 (78.5%)	
ASA Status 1	1 (<1%)	0 (<1%)	<0.0001*
Status 2	122 (1.3%)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

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

Table 2. Prediction model for methylene blue use.

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

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



A. B.

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

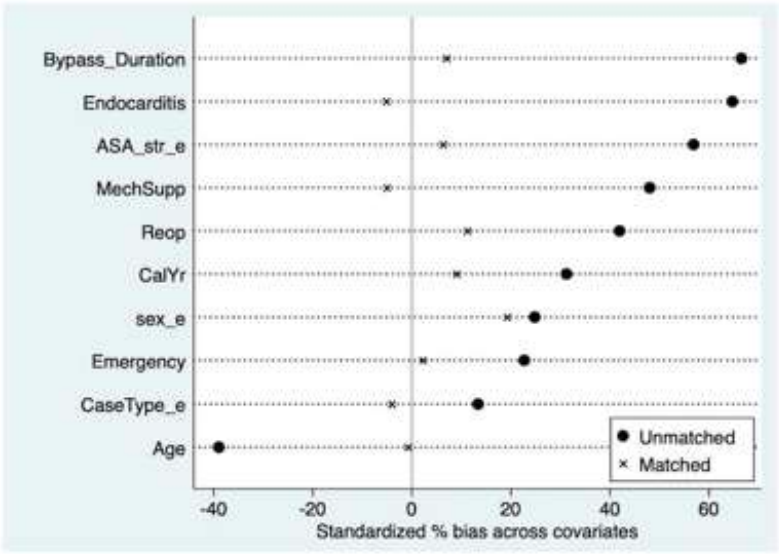


Figure 2. Standardized differences before and after propensity score matching comparing covariate values for patients receiving MB and controls. Balance can be judged as acceptable as imbalance for all variables was less than 20%. (ASA_str_e, ASA physical status; MechSupp, mechanical circulatory support;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

Cardiovascular Anesthesiology - 11

Life Impact Of Extracorporeal Life Support Due To Primary Graft Dysfunction In Patients After Orthotopic Heart Transplantation

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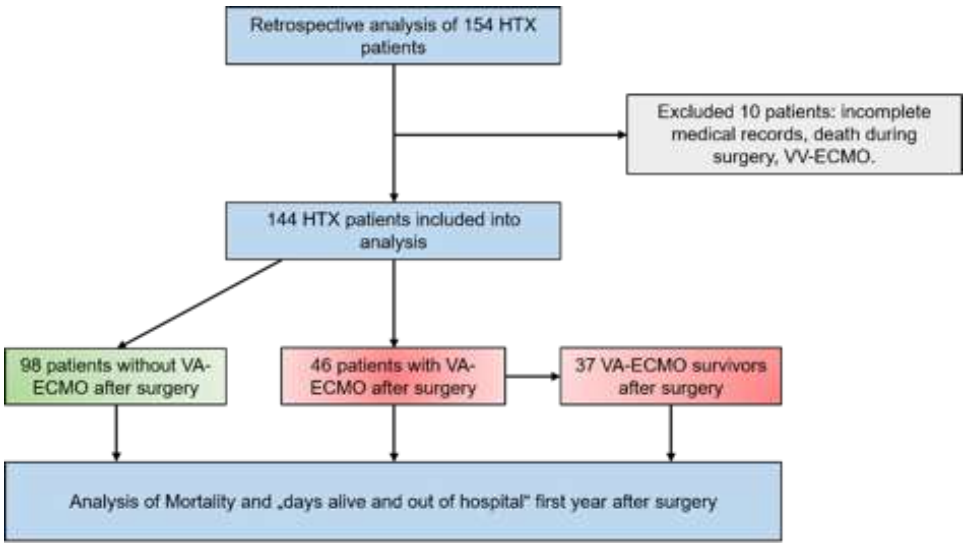
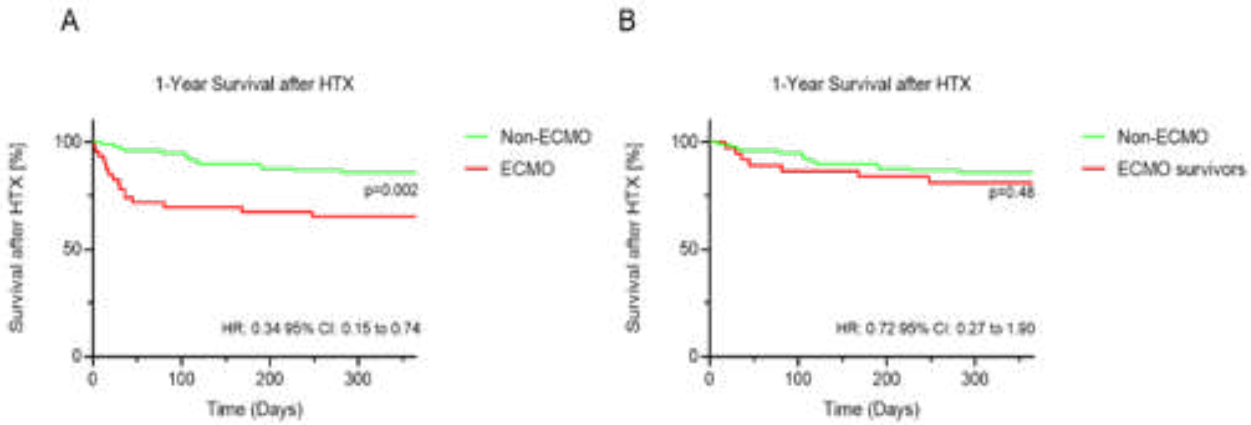
Introduction: Primary graft dysfunction (PGD) is a feared complication after orthotopic heart transplantation (HTX). These patients frequently receive veno-arterial extracorporeal membrane oxygenation devices (VA-ECMO) to overcome cardiac failure until graft recovery. Long-term survival of VA-ECMO survivors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

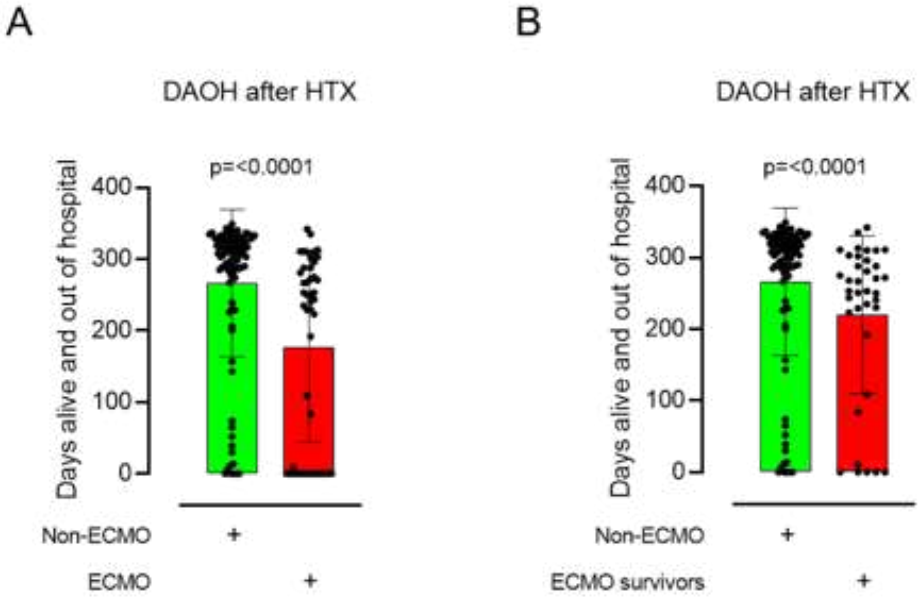
Methods: This retrospective single-center cohort study enrolled 144 HTX patients from 2010-2020 from the University hospital Duesseldorf HTX database. Study groups were divided in 98 patients without mechanical support and 46 patients with VA-ECMO due to PGD after HTX. A subgroup of 37 patients survived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

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

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


Retrospective analysis of 154 HTX patients
Excluded 10 patients: incomplete medical records, death during surgery, VV-ECMO.
144 HTX patients included into analysis
98 patients without VA-ECMO after surgery
46 patients with VA-ECMO after surgery
37 VA-ECMO survivors after surgery
Analysis of Mortality and „days alive and out of hospital" first year after surgery


A
1-Year Survival after HTX
Survival after HTX [%]
100
50
0
p=0.002
HR: 0.34 95% CI: 0.15 to 0.74
Non-ECMO
ECMO
0
100
200
300
Time (Days)
B
1-Year Survival after HTX
Survival after HTX [%]
100
50
0
p=0.48
HR: 0.72 95% CI: 0.27 to 1.90
Non-ECMO
ECMO survivors
0
100
200
300
Time (Days)


A
DAOH after HTX
Days alive and out of hospital
400
300
200
100
0
p=<0.0001
Non-ECMO
+
ECMO
+
B
DAOH after HTX
Days alive and out of hospital
400
300
200
100
0
p=<0.0001
Non-ECMO
+
ECMO survivors
+

Cardiovascular Anesthesiology - 12

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

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

[1]Vanderbilt University Medical Center, Nashville, TN

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

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

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

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

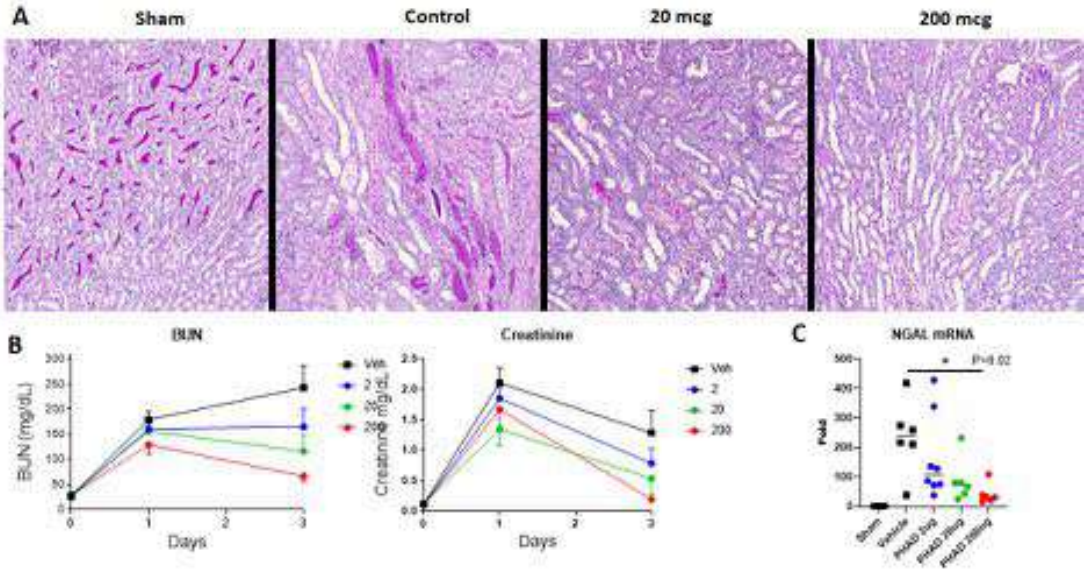


Figure. Kidney sections taken 3 days post 28-minute kidney ischemic insult and pretreated with 3D (6-Acyl) PHAD (**Panel A**). BUN and Creatinine change from baseline to 3 days post ischemic insult (**Panel B**). Day 3 NGAL mRNA post ischemic insult (**Panel C**).

Cardiovascular Anesthesiology - 13

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

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

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

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

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

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

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

Cardiovascular Anesthesiology - 14

Influence Of Respiration And Position On The Internal Jugular Vein Dimension In Cardiac Surgical Patients.

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Introduction: Internal jugular vein (IJV) is most frequently accessed site for central venous cannulation. Ultrasound guided right IJV catheterization is recommended to increase success of first attempt cannulation and decrease complications. This study was aimed to determine the influence of respiration on the dimension of the IJV and hence recommend the optimal time of IJV puncture with relation to the phase of respiratory cycle.

Methods: Forty adult patients who were scheduled for elective cardiac surgery ≥18 years were enrolled in the prospective observational study. The dimensions of the IJV was assessed during awake and intubated/ventilated conditions. Ultrasound probe of frequency 5-13 MHz was used (GE venue-40 ultrasound machine) in 4 different situations. During mechanical ventilation, a tidal volume of 8ml/kg without positive-end expiratory pressure (PEEP) was used. Size of internal jugular vein was compared in awake spontaneous and supine and 30° Trendelenburg position in inspiration and expiration and after anaesthesia with mechanical ventilation.

Results: There were 40 patients in the study, mean age was 52±10.6 years, mean body weight was 64.3±12.4 kg and height was 1.6±0.1 metre. The dimensions of IJV varied according to the phase of respiration and position. The width and depth of IJV was significantly increased during expiration in spontaneously breathing patients. There was statistically significant increase in width in Trendelenburg position. There was no significant change in IJV diameters both during inspiration and expiration in intubated and ventilated patients using a tidal ventilation of 8ml/kg with no positive-end expiratory pressure (PEEP).

Conclusion: Based on the observation, we recommend the use of Trendelenburg position in spontaneously breathing subjects and the IJV puncture to be timed to coincide expiration.

Cardiovascular Anesthesiology - 15

Volatile Anesthetics Loading Of The Sonoparticles; Preparation For Future Clinical Application

Amir Teimouri Dereshgi[1], Paul R Knight[1], Bruce A Davidson[1], Siavash Sedghi[1], Hilliard Kutscher[1], Nader D Nader[1]

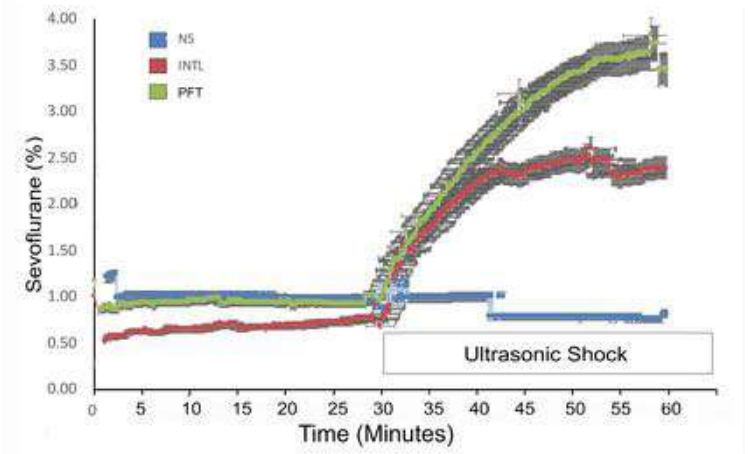
[1]University at Buffalo, Buffalo, NY

Introduction: Volatile anesthetics in clinical medicine are generally administered through inhalation. Intravenous administration of these agents requires emulsification or phospholipid particle loading due to their hydrophobic chemical structure. We have taken initial steps toward testing the feasibility and stability of sevoflurane-loaded sonoparticles. Perflutren is used as a contrast material in echocardiographic assessment of coronary perfusion, where the microspheres are ruptured under high mechanical index (> 0.8). This targeted release of sevoflurane could be used to precondition the ischemic myocardium to limit subsequent ischemia-reperfusion injury.

Methods: Sevoflurane 100ul was added to 1.7 mL microtubes containing 1.5 mL of normal saline (NS0.9%), intralipid 20% (INTL) or perflutren (PFT) vial and vigorously agitated for 45 seconds. The activation (loading) was confirmed with a milky appearance of the perflutren vial. Sealed glass tubes (10-mL) were attached to the gas analyzers (to measure the concentrations of sevoflurane) were primed with 4.5 mL NS0.9%. Following the initial mix of loaded samples, 500 uL from each sevoflurane containing solution was added to the measurement chamber. Sevoflurane concentration was analyzed in two phases lasting 30 minutes each. The initial phase of measurement was carried out without sonification, followed by 30 minutes of sonification. Measurements were taken every 5 seconds for a total duration of 60 minutes.

Results: Sevoflurane concentration had a decremental pattern in NS0.9% solution and continued to decrease after initiation of sonification. INTL and PFT solutions had relatively lower levels of sevoflurane compared to NS0.9% solution indicating a lower free vapor during the initial phase. On the other hand, both solutions released sevoflurane vapor in a stepwise fashion to a higher extent than that of NS0.9% solution during the sonification phase. (Figure 1)

Conclusion: Perflutren sonoparticles held sevoflurane contained and were able to release the vapor on demand when the particles were destroyed by ultrasonic energy. This observation may pave the road for targeted delivery of volatile anesthetic to organs like the myocardium under ultrasound guidance.



Cardiovascular Anesthesiology - 16

Cardiac Sodium Channel Mutations Are Associated with Sex-Specific Arrhythmias in Mice

Tim Lee[1], Kaley Hogarth[2], Elod Szabo[2], Jason Maynes[3]

[1]University of Toronto, Toronto, Ontario, [2]Hospital For Sick Children, Toronto, Ontario, [3]SickKids Hospital, Toronto, Canada

Introduction: The cardiac sodium channel Nav1.5 is encoded by the SCN5A gene and is normally responsible for initiating the action potential in the heart for coordinated cardiomyocyte contraction. The Nav1.5 channel can also reopen during cardiac repolarization, allowing a small sodium current to enter the cell (1). While this additional Nav1.5 activity is normally rare and innocuous, gain of function mutations, such as Arg222Gln, allow more substantial extra cation leak (2). These channelopathies occur in 1/2500 individuals and result in arrhythmogenic cardiac diseases, like long QT syndrome, and cardiomyopathies (3). Interestingly, males more often experience sudden cardiac arrest as a result of the channelopathy, indicative of an innate sex-dependent protection for females. We have examined the sex-specific effects of Nav1.5 mutation and investigated the protective mechanism present in females.

Methods: The human Arg222Gln mutation was knocked into exon 6 of the mouse SCN5A gene to produce viable adult animals. Under anesthesia, a three-lead electrocardiogram (ECG) was recorded using adult male and female mice, including both wild-type (WT) and mutant animals. Isoproterenol (β-adrenoreceptor agonist) was injected as an acute cardiac stressor to elicit electrophysiological changes. Echocardiograms were collected at baseline and after 30 days of transverse aortic constriction (TAC), a technique used to increase hypertrophic cardiac stress. Differentially expressed genes were measured in whole heart lysate using a chip-based microarray after TAC. Protein levels were quantified using Western blot and ELISA.

Results: ECG measurements revealed a prolonged QTc (0.064ms±0.006) and QRS interval (0.011ms±0.0003) in mutant males compared to WT males (0.036ms±0.008 and 0.0085ms±0.0004 respectively) ($P<0.05$). Mutant males had an observable sinus arrhythmia with bigeminies at baseline (RMSSD of beat-to-beat intervals of 4.597 vs 0.79 in WT males, $P<0.05$) whereas both WT and mutant females had no evidence of an arrhythmia. Upon acute cardiac stress, the arrhythmias seen in mutant males were ameliorated. At 30 days post-TAC, the ejection fraction (EF) of mutant males was 40%±9.9% lower compared to their WT counterparts ($P<0.05$), whereas no significant changes in EF were observed between female groups. Heart histopathology showed a 2-fold increase in fibrosis and a 3-fold increase in cardiomyocyte size in mutant males ($P<0.05$) compared to WT males. Transcript and protein levels of pyruvate dehydrogenase kinase 4 (PDK4), an inhibitor of pyruvate dehydrogenase (PDH) activity, was 6-fold higher in mutant males compared to WT males ($P<0.05$), no differences were seen between females. Interestingly, phospho-PDH levels and PDH activity was higher in mutant males compared to WT males ($P<0.05$) whereas PDH activity was lower in mutant females ($P<0.05$) compared to WT females with no significant difference in phospho-PDH levels.

Conclusion: We present a model of cardiac arrhythmia with significant functional, electrophysiological, and metabolic differences in male and female mice possessing the Arg222Gln Nav1.5 mutation. Female mice did not have adverse cardiac electrophysical changes and were resistant to spontaneous arrhythmias. Similarly, they are protected from cardiac dysfunction and fibrosis as a result of pressure overload. At least part of the protection was afforded by differential regulation of PDH activity. Male mice showed a significant increase in PDH activity to improve metabolic function in the cardiomyocyte, which appears to be a maladaptive response that did not occur in females. Future experiments will determine if these metabolic changes and the reduction in spontaneous arrhythmias are a direct result of sex hormones in the context of the Arg222Gln mutation.

References: 1. Clinical Spectrum of SCN5A Mutations. 4:569–579. (2018) 2. SCN5A variant R222Q generated abnormal changes in cardiac sodium current and action potentials in murine myocytes and Purkinje cells. 16:1676–1685. (2019) 3. Gating pore currents are defects in common with two Nav1.5 mutations in patients with mixed arrhythmias and dilated cardiomyopathy. 145:93–106. (2015)

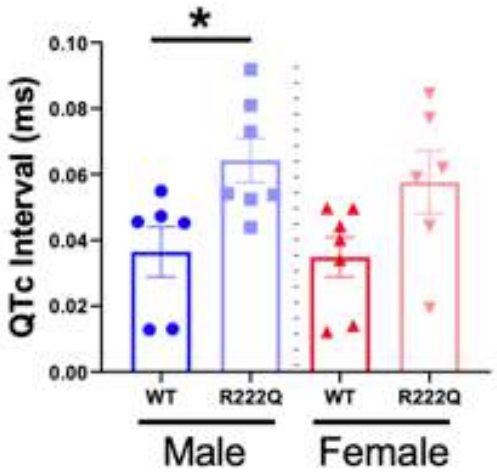


Figure 1: QTc interval of both wild-type and mutant (R222Q) male and female mice under anesthesia. Mutant male mice had significantly increased QTc interval ($P<0.05$) indicative of a long QT phenotype while mutant female QTc interval was not statistically significant.

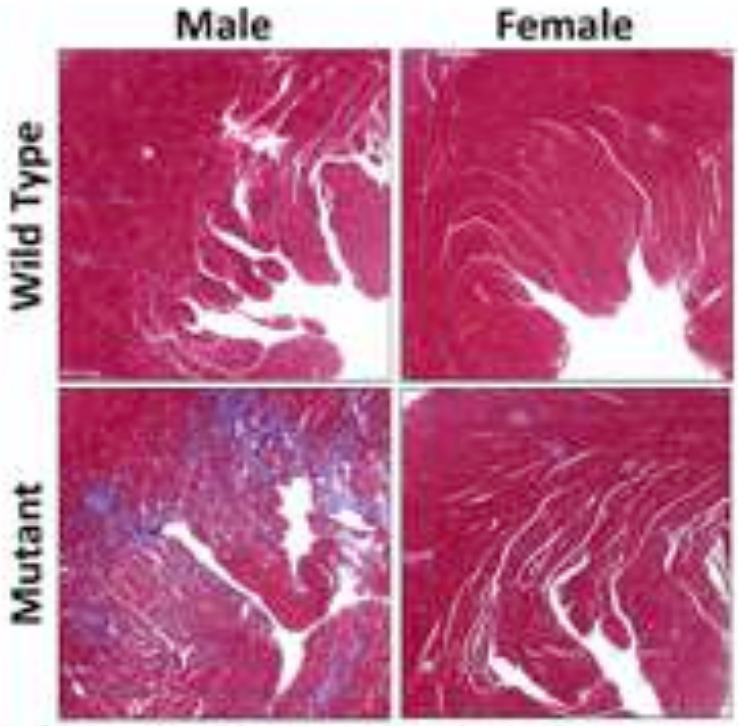


Figure 2: Trichrome staining of left ventricle sections from mice hearts 1 month post transverse aortic constriction. Mutant males (bottom left) had high amounts of fibrosis indicative of cardiac dysfunction as reflected in the reduce ejection fraction. All other animals had minimal fibrosis with no significant changes in their ejection fractions.

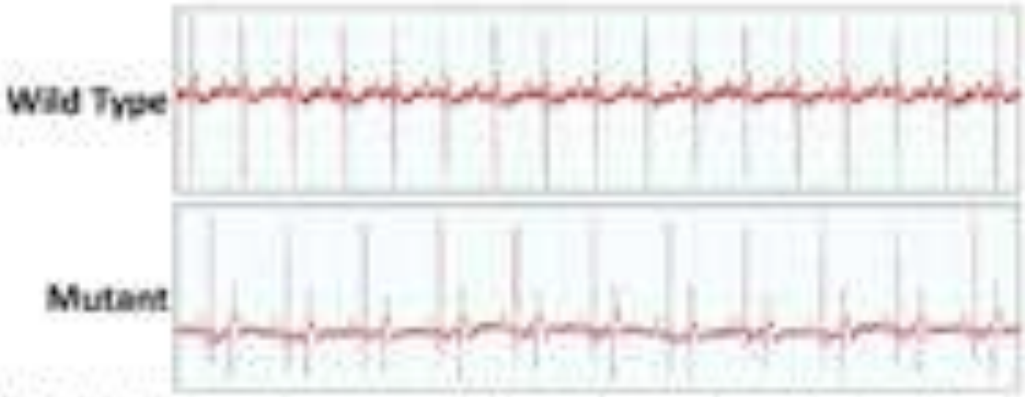


Figure 3: Sample electrocardiogram tracings of wild-type and mutant male mice at baseline under anesthesia. Wild-type mice presents a normal sinus rhythm while mutant mice posses a class sinus arrhythmia with bigeminism. These findings are indicative of abnormalities within the electrical conduction system of the heart in mutant male mice.

Cardiovascular Anesthesiology - 17 Left Ventricular Flow Change In Lvad Patient

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

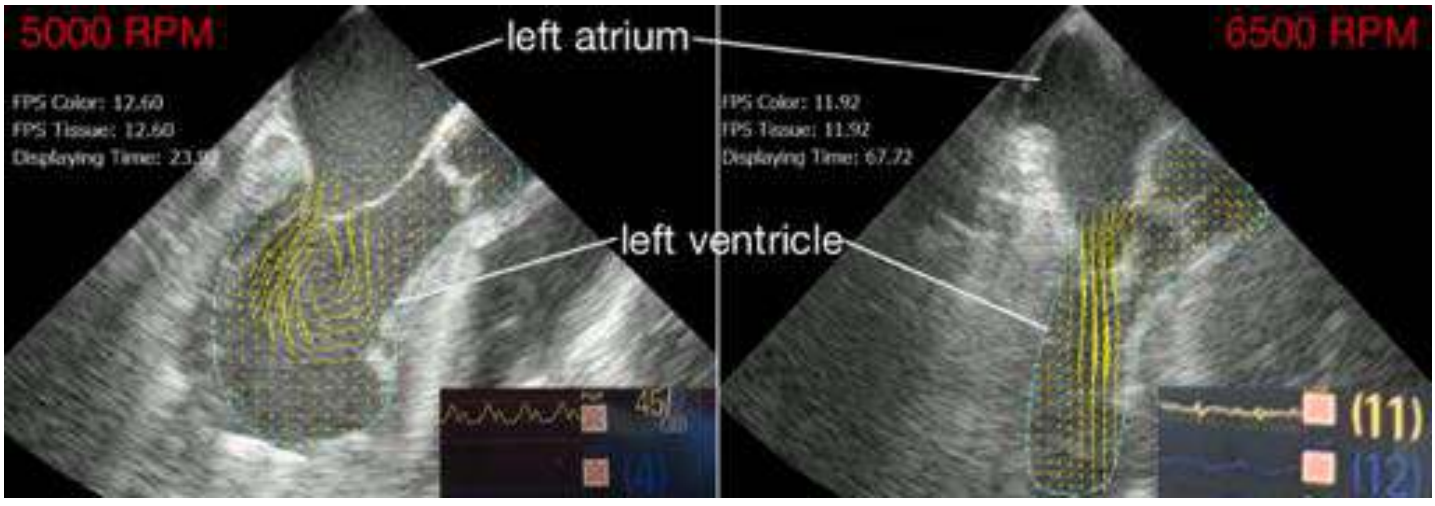
[1]Yodogawa Christian Hospital, Osaka, Osaka, [2]Yodogawa Christian Hospital, Osaka city, Japan, [3]Kyoto Prefectural University of medicine, Kyoto city, Kyoto prefecture

Introduction: Normal blood flow in the left ventricle, which demonstrates vortex ring formation during diastole, plays a very important role. The vortex ring facilitates inflow into the left ventricle, minimizes the dissipation of energy, preserves momentum, and redirects flow towards the left ventricular outflow tract in an energy-efficient manner. Right ventricular (RV) failure after left ventricular assist device (LVAD) implantation is a major cause of morbidity and mortality. LVAD flow can induce interventricular septal (IVS) flattening which in turn can cause RV failure, due to ventricular interdependence.

Methods: Vector flow mapping analysis was performed in a LVAD (HeartMateⅢ) implantation case. Left ventricular blood flow was monitored with increasing the pump rotating speed until interventricular septum was flattened whole cardiac cycle.

Results: At an optimal pump speed of 5000 RPM (left panel) the left heart appears appropriately filled with a normal vortex blood flow pattern (yellow arrows) during diastole. Concurrent pulmonary artery and central venous pressure (PAP, CVP) waveforms reflect preserved RV function. However, at an elevated pump speed of 6500 RPM (right panel), the left heart appears underfilled with IVS flattening, and vortex ring formation is lost. This resulted in a flat PAP waveform and increased CVP, consistent with RV dysfunction.

Conclusion: The loss of left ventricular vortex ring formation may identify RV failure in patients with an LVAD.



Cardiovascular Anesthesiology - 18

4d Flow Mri Analysis Improved Perioperative Management In A Patient With Severe Pulmonary Regurgitation And Pulmonary Artery Aneurysm

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

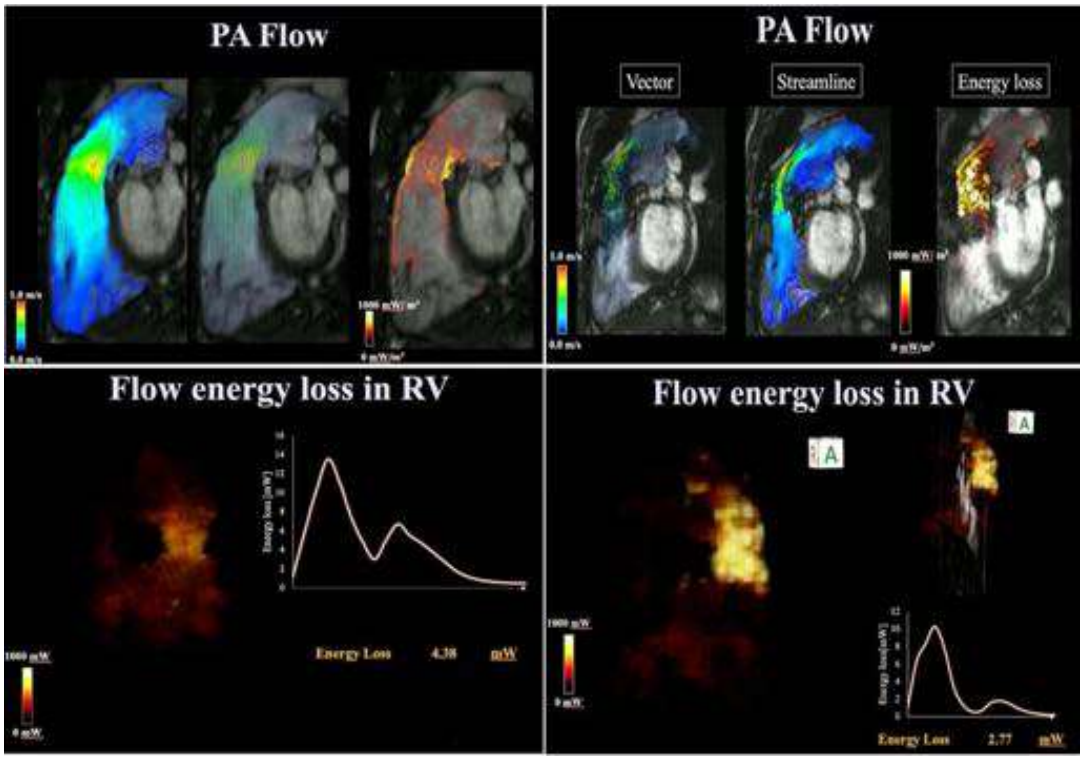
[1]Yodogawa Christian Hospital, Osaka, Osaka, [2]Yodogawa Christian Hospital, Osaka city, Japan, [3]Kyoto Prefectural University of medicine, Kyoto city, Kyoto prefecture

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

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

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

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



Cardiovascular Anesthesiology - 19

Impact of Obesity on Protocol-Driven Perioperative Management of Left Ventricular Assist Device Implanted via Less Invasive Surgery

Milica Bjelic[1], Ravie Abozaid[2], Heather Lander[1], Julie Wyrobek[3], Frane Paic[4], Yang Gu[5], Igor Gosev[1], Wendy Bernstein[1]

[1]University of Rochester Medical Center, Rochester, NY, [2]University of Rochester Medical Center, Rochester, Rochester, NY, [3]University of Rochester Medical Center, Rochester, United States of America, [4]University of Zagreb Medical School, Zagreb, Croatia, [5]University of Rochester, School of Medicine and Dentistry, Rochester, NY

Introduction: Left Ventricular Assist Device (LVAD) implanted via less invasive surgery (LIS) is considered a state-of-the-art approach with multiple potential benefits, including a lower incidence of right ventricle failure, decreased transfusion requirements, shorter mechanical ventilation, and decreased length of stay.1, 2 Obesity and its accompanying morbidities portray patients as poor surgical candidates due to the challenging perioperative care (difficult airway management, general anesthesia induction and maintenance, pain management, etc.).3 The present study compares the protocol-driven perioperative management and outcomes of patients who underwent less invasive LVAD implantation categorized based on body-mass index (BMI). We hypothesized that protocolized perioperative management with the LIS approach results in similar outcomes regardless of BMI.

Methods: We performed a single institution, retrospective review of all patients implanted with LVAD via LIS from 2018 to 2020. Patients were categorized based on pre-implant BMI in the following groups: Non-obese- BMI≤29.9 kg/m2, Obesity class I (OB1) - BMI=30-34.9 kg/m2, Obesity class II (OB2) - BMI=35-39.9 kg/m2, Obesity class III (OB3) - BMI≥40 kg/m2. Since 2018, LIS has become the standard approach at our institution. Enhanced recovery after surgery (ERAS) protocol was implemented with defined perioperative management (Figure 1). Primary outcomes were the absence of major complications and index-hospitalization survival. Secondary outcomes were the length of stay, discharge disposition, discharge opioid requirements, and the difference in anesthetic requirements.

Results: Of 161 patients implanted with LVAD via LIS in the study interval, patients' distribution through BMI groups were: Non-obese - 80 (49.7%), OB1- 40 (24.8%), OB2- 22 (13.7%), OB3- 19 (11.8%). The median age of the entire cohort was 57 years, with the youngest patients in the OB3 class (median age 49 years). Baseline patient characteristics (Table 1) were similar between the groups apart from pulmonary-capillary wedge pressure (p=0.011) and right ventricular stroke work index (p=0.004), which both had the highest values in the OB3 group. Intraoperatively (Table 2), airway managements were similar between the groups. Propofol and fentanyl requirements were similar among the group. Midazolam requirements were decreasing with an increase in BMI categories (p=0.001). The highest maximum glucose level in the OR occurred in patients in the OB2 group (218.5 (192.2-266) mg/dl) while the lowest was in Non-obese 187.5 (167.2-219.7)), p=0.001. Procedure time was prolonged proportionally to an increase in BMI, with the difference of 50 minutes between Non-obese and OB3 classes (p=0.004). Postoperatively (Table 3), mechanical ventilation time was increased as BMI increased (p=0.02), with the median time to extubation in Non-obese 12.7 hours to OB3 41.1 hours. Patients with lower BMI were more frequently discontinued from inotropic support within the first postoperative week (Non-obese, 80% vs. OB1, 92.5% vs. OB2, 68.2% vs. OB3, 63.2%; p=0.028). All major complications were similar between groups, as well as intensive care unit and hospital length of stay. Index-hospitalization survival in our LIS patients was 91.3%. However, there was a statistical significance when based on BMI groups (p=0.018), with the highest survival in the OB1 group (100%) and lowest in OB3 (78.9%). Discharge disposition and opioid requirements were similar between the groups.

Conclusion: Results of our study suggest that the protocol-driven LIS approach to LVAD implantation results in comparable outcomes regardless of patients` BMI status. The perioperative risk imposed by obesity could be mitigated with this strategy. Future trials are needed to confirm our data.

References: 1. J Heart Lung Transplant. 2020;39(1):37-44. 2. Curr Cardiol Rev. 2015;11(3):246-251. 3. Best Pract Res Clin Endocrinol Metab. 2013;27(2):247-260.

Table 1. Preoperative Patient Characteristics

BMI (kg/m²)	Non-obese BMI≤29.9	Obesity class I BMI 30-34.9	Obesity class II BMI 35-39.9	Obesity class III BMI≥40	p-value
Variables	(n=80)	(n= 40)	(n= 22)	(n= 19)	
Demographic characteristics					
Age, years, (median (IQR))	60 (50.2-66)	56 (48.5-64)	53 (41.2-58.2)	49 (37-55)	0.011*
Male, n (%)	67 (83.8%)	34 (85%)	19 (86.4%)	12 (63.2%)	0.156
White, n (%)	65 (81.2%)	28 (70 %)	15 (68.2%)	15 (78.9%)	0.386
NYHA functional class, n (%)					0.330
Class IIIb	9 (11.3%)	4 (10%)	5 (22.7%)	4 (21.1%)	
Class IV	71 (88.7%)	36 (90%)	17 (77.3%)	15 (78.9%)	
INTERMACS profile, n (%)					
Profile 1	30 (37.5%)	14 (35%)	7 (31.8%)	8 (42.1%)	0.903
Profile 2	9 (11.3%)	1 (2.5%)	3 (13.6%)	1 (5.3%)	0.285
Profile 3	38 (47.5%)	21 (52.5%)	10 (45.5%)	8 (42.1%)	0.888
Profile 4	3 (3.8%)	4 (10%)	2 (9.1%)	2 (10.5%)	0.333
Comorbidities, n (%)					
Ischemic cardiomyopathy	38 (47.5%)	18 (45%)	11 (50%)	3 (15.8%)	0.066
Stroke/TIA	10 (12.5%)	5 (12.5%)	4 (18.2%)	2 (10.5%)	0.872
Chronic renal failure	25 (31.3%)	15 (37.5%)	8 (36.4%)	4 (21.1%)	0.621
Diabetes	28 (35%)	19 (47.5%)	9 (40.9%)	5 (26.3%)	0.396
COPD	12 (15%)	9 (22.5%)	2 (9.1%)	2 (10.5%)	0.551
Past sternotomy	17 (21.3%)	6 (15%)	5 (22.7%)	3 (15.8%)	0.838
Pre-operative support, n (%)					
Inotropes	70 (87.5%)	32 (80%)	16 (81.8%)	15 (78.9%)	0.581
IABP	17 (21.3%)	7 (17.5%)	2 (9.1%)	2 (10.5%)	0.566
Impella	8 (10%)	3 (7.5%)	5 (22.7%)	4 (21.1%)	0.177
ECMO	18 (22.5%)	7 (17.5%)	3 (13.6%)	5 (26.3%)	0.705
Pre-operative hemodynamic parameters, (median (IQR))					
LVEF, %	19 (16-22)	19 (15.2-23)	23 (19-26.5)	17 (15-23)	0.068
Cardiac index, L/min/m²	1.8 (1.5-1.9)	1.7 (1.5-2.1)	1.9 (1.6-2.1)	1.8 (1.4-2)	0.668
PCW pressure, mmHg	24 (16.7-28)	25 (15.2-32)	31 (16.7-35)	33 (26-40)	0.011*
RA pressure, mmHg	12 (7-18.2)	13 (6-17)	15 (6.7-18.5)	19 (10-24.5)	0.152
RVSWI, mmHg x ml x m⁻²	451 (330-572.7)	396 (342-460)	550.6 (359-960.7)	643.5 (452-802.2)	0.004*

Abbreviations: COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCW, pulmonary-capillary wedge; RAP, right atrial; RVSWI, right ventricular stroke work index; TIA, transient ischemic attack; BTT, bridge to transplant;

*Statistical significance

Table 2. Intraoperative Data

BMI (kg/m²) Variables	Non-obese BMI≤29.9 (n=80)	Obesity class I BMI 30-34.9 (n= 40)	Obesity class II BMI 35-39.9 (n= 22)	Obesity class III BMI≥40 (n= 19)	p-value
Already intubated, n (%)	6 (7.5%)	3 (7.5%)	2 (9.1%)	1(5.3%)	0.968
Laryngoscopy, n (%)					0.259
Direct laryngoscopy	53 (71.6%)	24 (64.9%)	11 (55%)	9 (50%)	
Video laryngoscopy	21 (28.4%)	13 (35.1%)	9 (45%)	9 (50%)	
OR Anesthesia (median (IQR))					
Propofol- last dose, (mcg/kg/min)	50 (30-60)	50 (32.5-75)	50 (28.7-70)	50 (46.2 -71.2)	0.618
Midazolam- total dose, (mg/kg)	0.09 (0.06-0.14)	0.06 (0.04-0.12)	0.06 (0.04-0.08)	0.04 (0.03-0.07)	0.001*
Fentanyl- total dose, (mcg/kg)	7.7 (6.1-11.6)	7.7 (5.9-10.9)	6.6 (5.3-8.4)	7.1 (4.6-8.9)	0.284
Last OR temp, °C	36.8 (36.2-37.1)	36.8 (36.4-37.3)	36.7 (36.2-37.1)	36.8 (36.6-37.3)	0.382
Highest OR glycemia, mg/dl	187.5 (167.2-219.7)	193 (170.5-219)	218.5 (192.2-266)	206 (191-262)	0.001*
Received intraoperative blood product, n (%)					
Packed red blood cells	28 (35%)	9 (22.5%)	8 (36.4%)	7 (36.8%)	0.513
Fresh frozen plasma	19 (23.8%)	13 (32.5%)	2 (9.1%)	5 (26.3%)	0.222
Platelets	26 (32.5%)	13 (32.5%)	5 (22.7%)	6 (31.6%)	0.849
Cryoprecipitate	26 (32.5%)	13 (32.5%)	5 (22.7%)	6 (31.6%)	0.849
CPB time, minutes (median (IQR))	105.5 (84.2-122)	103 (80.5-121.7)	110 (91.7-137.5)	108 (97-134)	0.494
Surgery time, minutes (median (IQR))	280 (240-330)	298.5 (261-350.5)	320 (297-390)	330 (288-408)	0.001*
Delayed closure	17 (21.3%)	8 (20%)	8 (36.4%)	7 (36.8%)	0.258

Abbreviations: CPB, cardiopulmonary bypass; OR, operating room.

*Statistical significance

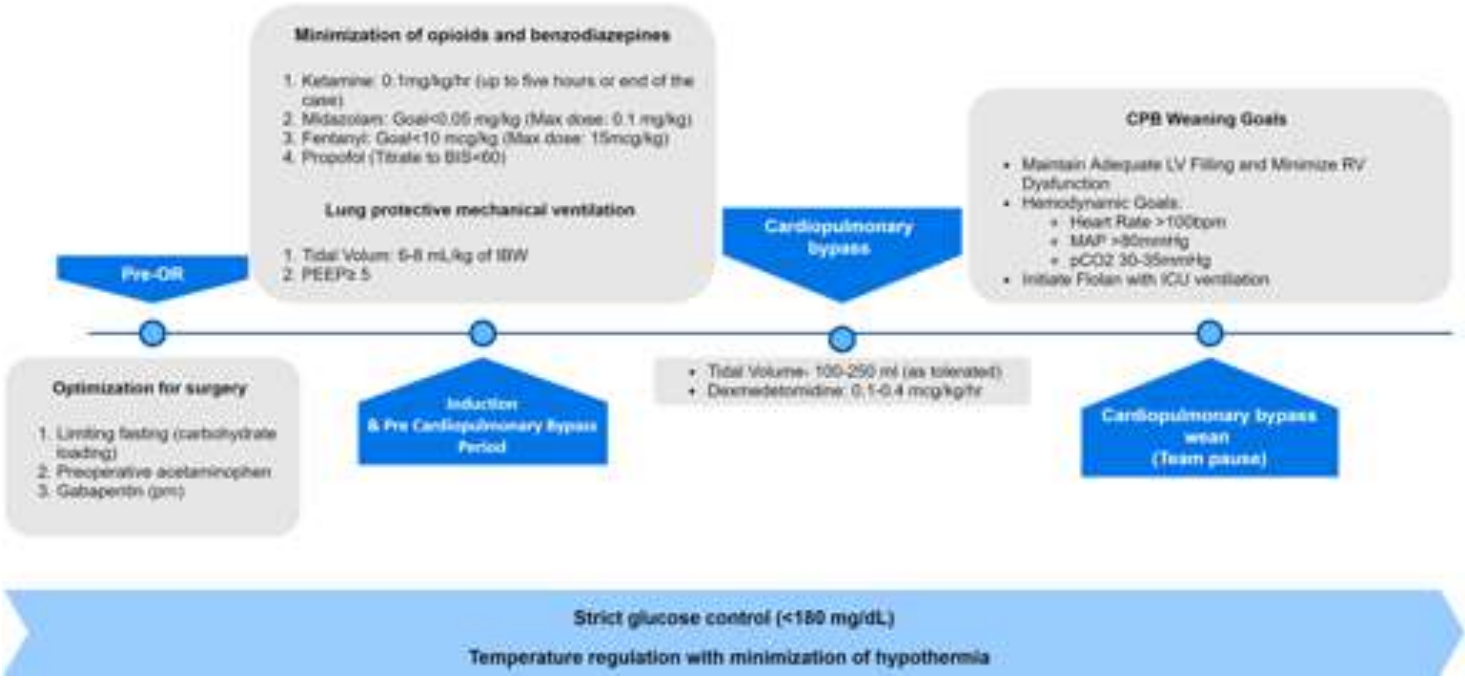
Table 3. Index Hospitalization Complications, Resource Utilization, and Survival

BMI (kg/m²) Variables	Non-obese BMI≤29.9 (n=80)	Obesity class I BMI 30-34.9 (n= 40)	Obesity class II BMI 35-39.9 (n= 22)	Obesity class III BMI≥40 (n= 19)	p-value
Mechanical ventilation time, hours (median (IQR))	12.7 (12.7-31.6)	16.8 (7.4-29.1)	24.1 (13.9-81.8)	41.1 (20.1-73)	0.002*
Chest tube output over 24 hours, ml (median (IQR))	987.5 (667.5-442.5)	910 (555.7-383.7)	1048 (772.7-1530)	1068 (840-1300)	0.504
Postoperative pain assessment- Numeric pain scale 1-10 (median (IQR))					
Pain score-24th hour	4 (0-7)	6 (2.2-9)	4.5 (0.7-8)	0 (0- 4.2)	0.006*
Pain score-48th hour	2 (0-6)	4 (0-6.7)	0 (0-3.5)	0 (0-5)	0.246
Number of nerve blocks, median (IQR))	1 (1-2)	2 (1-2)	1 (1-2)	2 (1-2)	0.185
Received postoperative blood product over 24 hours, n (%)					
Packed red blood cells	33 (41.3%)	13 (32.5%)	8 (36.4%)	7 (36.8%)	0.819
Fresh frozen plasma	21 (26.3%)	6 (15%)	6 (27.3%)	4 (21.1%)	0.535
Platelets	24 (30%)	8 (20%)	4 (18.2%)	2 (10.5%)	0.273
Cryoprecipitate	19 (23.8%)	7 (14.9%)	2 (5%)	1 (4.5%)	0.017*
Post-operative inotropic support, n (%)					
< 1 week	64 (80%)	37 (92.5%)	15 (68.2%)	12 (63.2%)	0.028*
1-2 weeks	12 (15%)	1 (2.5%)	3 (13.6%)	4 (21.1%)	0.086
2-4 weeks	2 (2.5%)	2 (5%)	2 (9.1%)	1 (5.3%)	0.378
> 4 weeks	2 (2.5%)	0 (0)	1 (4.5%)	1 (5.3%)	0.310
Major complications					
Unplanned RTOR	5 (6.3%)	2 (5%)	3 (13.6%)	1 (5.3%)	0.617
Infections	18 (22%)	9 (23.1%)	9 (40.9%)	5 (26.3%)	0.370
Cerebrovascular accident	7 (9%)	0 (0)	1 (4.5%)	1 (5.3%)	0.245
Respiratory failure	8 (10%)	4 (10%)	3 (13.6%)	5 (26.3%)	0.271
Hepatic failure	10 (12.5%)	4 (10%)	3 (13.6%)	3 (15.8%)	0.893
Renal failure	8 (10%)	7 (17.5%)	5 (22.7%)	5 (26.3%)	0.214
Right ventricular failure	5 (6.3%)	3 (7.5%)	3 (13.6%)	3 (15.8%)	0.389
Early outcomes					
ICU LOS, days, (median (IQR))	4 (3-10.7)	4 (3-6.7)	5 (3-16)	6 (4-19)	0.125
Hospital LOS, days, (median (IQR))	16.5 (13-24)	16 (13-29.7)	17 (14.5-22.7)	22 (12-38)	0.622
Index-hospitalization survival, n (%)	73 (91.3%)	40 (100%)	19 (86.4%)	15 (78.9%)	0.018*
Discharge disposition, n (%)					0.898
Home	61 (83.6%)	34 (85%)	15 (78.9%)	12 (80%)	
Rehab	12 (16.4%)	6 (15%)	4 (21.1%)	3 (20%)	
Discharge medication, n (%)					
GABA	35 (49.3%)	22 (55%)	9 (47.4%)	6 (40%)	0.795
ATC Acetaminophen	58 (72.5%)	31 (77.5%)	15 (68.2%)	11 (57.9%)	0.448
Opioids	25 (31.3%)	14 (35%)	6 (27.3%)	5 (31.1%)	0.883

Abbreviations: ATC, Around-the-Clock; GABA, Gamma-aminobutyric acid; ICU, Intensive care unit; LOS, length of stay RTOR, return to operating room.

*Statistical significance

INTRAOPERATIVE PROTOCOL



Critical Care

Critical Care - 1 Compassion And Humanism Play A Greater Role In Mitigating The Stress Of Covid 19 Amongst ICU Staff Than Wellness Programs.

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Introduction: The COVID 19 pandemic gripped the world at the beginning of this year and very quickly it was clear that ICU staff would have to take the major brunt of managing thousands of critically ill and dying patients. By March 2020 Boston was in the midst of its first surge and our hospital like others was dealing with hundreds of patients in all ICUs, as well as in surge ICUs that were staffed by nurses, CRNAs and physicians deployed from non-ICU settings. Even before the pandemic the rate of anxiety, depression as well as ethical and moral distress amongst staff was high in the critical care environment, however, since the pandemic began, multiple reports of work in the ICU significantly affecting the mental health of healthcare workers (HCWs), who stand in the frontline of this crisis have come forth. Several studies have shown that the pandemic has led to extraordinary amounts of stress on healthcare workers (HCWs). Some of the reasons for this include increased workload, physical exhaustion, inadequate personal equipment (PPE), risk of nosocomial transmission, and the need to make ethically difficult decisions on the rationing of resources may have dramatic effects on their physical and mental well-being. Their strength can be further compromised by isolation and loss of social support required for infection control, risk or infections of family and friends as well as new sudden changes to work locations and hours. HCWs are, therefore, especially vulnerable to mental health problems, including fear, anxiety, depression and burnout. Hospitals and organizations have added a multitude of wellness programs during the pandemic to provide staff with coping techniques, including online yoga sessions, meditation programs, stress hotlines and other virtual group activities whilst maintaining social distancing. The objective of this study was to evaluate the prevalence of anxiety, depression, ethical and moral distress among ICU HCWs based on job categories during the COVID-19 pandemic surge in our hospital, and to assess the value of wellness programs offered in mitigating this stress.

Methods: This study was approved as exempt by the Institutional review board. Between the months of March and May 2020, we conducted an online cross-sectional, mixed method survey across all ICUs of the Beth Israel Deaconess Medical center in Boston, USA. The survey link was advertised in all ICUs and weekly reminders were sent to all ICU staff. A cross-sectional online survey composed of 26 multiple choice and open-ended questions was administered between March and May 2020. We invited physicians, nurses, and respiratory technicians as well as certified nurse anesthetists who were deployed to work in ICUs due to the COVID 19 surge. A letter of information was attached to the link for the survey and completion of the questionnaire implied their consent. The survey instrument was developed using validated questions from the generalized anxiety disorder (GAD) screening tool and the depression screening tool developed by the Anxiety and depression association of America (Fig 1). In addition, other open-ended questions were tailored to focus on how respondents dealt with fear, anxiety, loss of control and stress of working in the front lines. A specific question was asked about how much wellness focused programs offered by their respective departments provided relief to HCWs.

Results: Our results show that although stress and anxiety were high among the HCW in the ICU, almost 70 % felt that the wellness resources being offered were not useful. The qualitative analysis revealed that compassionate interactions with the leadership and managers proved very useful and morale building for the nurses and doctors.

Conclusion: The stress of COVID 19 among frontline ICU health care workers is significant and can be mitigated by compassionate peer interaction and caring emotionally intelligent and mindful leadership. This may result in reduction of Burnout of the workforce and building resilience for future pandemic surges.

Stress Survey Analysis

Baseline Characteristics

Characteristic	N=67
Role, No. (%)	
Resident	15 (22.4)
Fellow	0 (0.0)
Attending	3 (4.5)
Respiratory Therapist	3 (4.5)
Nursing Professional	44 (65.7)
Other	2 (3.0)
Gender, No. (%)	
Female	56 (84.9)
Ethnicity, No. (%)	
Hispanic or Latino	4 (6.1)
Not Hispanic or Latino	58 (87.9)
Prefer not to answer	4 (6.1)
Race, No. (%)	
White	54 (81.8)
Black or African American	0 (0.0)
Asian	3 (4.6)
Native Hawaiian or other Pacific Islander	0 (0.0)
American Indian or Alaskan Native	0 (0.0)
Multi-Racial	0 (0.0)
Other	2 (3.0)
Prefer not to answer	7 (10.6)

Are you troubled by any of the following since the COVID-19 pandemic started?

Characteristic	(n=67) No. (%) of those who are troubled
Experience excessive worry	(n=60) 33 (54.1)
Worry excessive in intensity, frequency, or amount of distress it causes	(n=59) 27 (45.0)
Find it difficult to control the worry (or stop worrying) once it starts	(n=59) 28 (46.7)
Worry excessively or uncontrollably about minor things	(n=59) 20 (33.3)
Bothered by excessive worries more days than not, During the COVID-19 pandemic	(n=60) 24 (39.3)

During the past few weeks have you often been bothered by any of the following symptoms? Please select one option.

Symptom	N=67 No. (%)
Restlessness or feeling keyed up or on edge	(n=58)
Not at all	3 (5.1)
A little bit	18 (30.5)
Moderately	13 (22.0)
Quite a bit	18 (30.5)
Extremely	7 (11.9)
Irritability	(n=58)
Not at all	7 (11.9)
A little bit	15 (25.4)
Moderately	13 (22.0)
Quite a bit	20 (33.9)
Extremely	4 (6.8)
Difficulty falling/staying asleep or restless/unsatisfying sleep	(n=58)
Not at all	9 (15.3)
A little bit	7 (11.9)
Moderately	9 (15.3)
Quite a bit	22 (37.3)
Extremely	12 (20.3)
Being easily fatigued	(n=58)
Not at all	5 (8.5)
A little bit	12 (20.3)
Moderately	16 (27.1)
Quite a bit	16 (27.1)
Extremely	10 (17.0)
Difficulty concentrating or mind going blank	(n=57)
Not at all	12 (20.7)
A little bit	16 (27.6)
Moderately	9 (15.5)
Quite a bit	17 (29.3)
Extremely	4 (6.9)
Muscle tension	(n=58)
Not at all	11 (18.6)
A little bit	12 (20.3)
Moderately	9 (15.3)
Quite a bit	18 (30.5)
Extremely	9 (15.3)
How much do worry and physical symptoms interfere with your life, work, social activities, family, etc.?	(n=58)
Not at all	7 (11.9)

Mildly	22 (37.3)
Moderately	21 (35.6)
Severely	7 (11.9)
Very Severely	2 (3.4)
How much are you bothered by worry and physical symptoms (how much distress does it cause you)?	(n=58)
Not at all	6 (10.2)
Mildly bothered	20 (33.9)
Moderately bothered	21 (35.6)
Severely bothered	8 (13.6)
Very severely bothered	4 (6.8)

Over the last two weeks, how often have you been bothered by any of the following problems?

Problem	N=67 No. (%)
Little interest or pleasure in doing things	(n=58)
Not at all	21 (35.6)
Several days	23 (39.0)
More than half of the days	13 (22.0)
Nearly everyday	2 (3.4)
Feeling down, depressed or hopeless	(n=58)
Not at all	15 (25.4)
Several days	26 (44.1)
More than half of the days	14 (23.7)
Nearly everyday	4 (6.8)
Trouble falling or staying asleep, or sleeping too much	(n=58)
Not at all	10 (17.0)
Several days	21 (35.6)
More than half of the days	15 (25.4)
Nearly everyday	13 (22.0)
Feeling tired or having little energy	(n=58)
Not at all	7 (11.9)
Several days	24 (40.7)
More than half of the days	18 (30.5)
Nearly everyday	10 (17.0)
Poor appetite or overeating	(n=58)
Not at all	17 (28.8)
Several days	18 (30.5)
More than half of the days	15 (25.4)
Nearly everyday	9 (15.3)
Feeling bad about yourself - or that you are a failure or have let yourself or your family down	(n=58)

Not at all	31 (52.5)
Several days	16 (27.1)
More than half of the days	7 (11.9)
Nearly everyday	5 (8.5)
Trouble concentrating on things such as reading the newspaper or watching television	(n=58)
Not at all	34 (57.6)
Several days	14 (23.7)
More than half of the days	6 (10.2)
Nearly everyday	5 (8.5)
Moving or speaking so slowly that other people could have noticed? Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual	(n=58)
Not at all	47 (79.7)
Several days	8 (13.6)
More than half of the days	3 (5.1)
Nearly everyday	1 (1.7)
How difficult have the problems you experienced made it for you to do your work, take care of things at home, or get along with other people?	(n=54)
Not difficult	17 (30.9)
Somewhat difficult	30 (54.6)
Very difficult	6 (10.9)
Extremely difficult	2 (3.6)

In your opinion are the Wellness Resources being offered to you through your work helpful?

15 (30%) said yes, 35 (70%) said no

Comparing Genders

Are you troubled by any of the following since the COVID-19 pandemic started?

Characteristic	(n=56) No. (%) of women who are troubled	(n=11) No. (%) of men who are troubled	P-Value
Experience excessive worry	(n=51) 30 (58.8)	(n=9) 2 (22.2)	0.069
Worry excessive in intensity, frequency, or amount of distress it causes	(n=50) 25 (50.0)	(n=9) 2 (22.2)	0.16
Find it difficult to control the worry (or stop worrying) once it starts	(n=50) 27 (54.0)	(n=9) 1 (11.1)	0.027
Worry excessively or uncontrollably about minor things	(n=50) 19 (38.0)	(n=9) 1 (11.1)	0.148
Bothered by excessive worries more days than not, During the COVID-19 pandemic	(n=51) 18 (35.3)	(n=9) 6 (66.7)	0.137

During the past few weeks have you often been bothered by any of the following symptoms? Please select one option.

Symptom	(n=56) No. (%) of Women	(n=11) No. (%) of Men	P-Value
Restlessness or feeling keyed up or on edge	(n=50)	(n=8)	
Not at all	1 (2.0)	2 (25.0)	
A little bit	15 (30.0)	2 (25.0)	0.183
Moderately	11 (22.0)	2 (25.0)	
Quite a bit	17 (34.0)	1 (12.5)	
Extremely	6 (12.0)	1 (12.5)	
Irritability	(n=50)	(n=8)	0.421
Not at all	5 (10.0)	2 (25.0)	
A little bit	12 (24.0)	2 (25.0)	
Moderately	12 (24.0)	1 (12.5)	
Quite a bit	17 (34.0)	3 (37.5)	
Extremely	4 (8.0)	0 (0.0)	

Difficulty falling/staying asleep or restless/unsatisfying sleep	(n=50)	(n=8)	0.332
Not at all	6 (12.0)	3 (37.5)	
A little bit	7 (14.0)	0 (0.0)	
Moderately	7 (14.0)	1 (12.5)	
Quite a bit	19 (38.0)	3 (37.5)	
Extremely	11 (22.0)	1 (12.5)	
Being easily fatigued	(n=50)	(n=8)	0.535
Not at all	2 (4.0)	3 (37.5)	
A little bit	11 (12.0)	0 (0.0)	
Moderately	15 (30.0)	1 (12.5)	
Quite a bit	14 (28.0)	2 (25.0)	
Extremely	8 (16.0)	2 (25.0)	
Difficulty concentrating or mind going blank	(n=50)	(n=7)	0.206
Not at all	7 (14.0)	4 (57.1)	
A little bit	16 (32.0)	0 (0.0)	
Moderately	8 (16.0)	1 (14.3)	
Quite a bit	15 (30.0)	2 (28.6)	
Extremely	4 (8.0)	0 (0.0)	
Muscle tension	(n=50)	(n=8)	0.414
Not at all	8 (16.0)	3 (37.5)	
A little bit	10 (20.0)	1 (12.5)	
Moderately	8 (16.0)	1 (12.5)	
Quite a bit	16 (32.0)	2 (25.0)	
Extremely	8 (16.0)	1 (12.5)	
How much do worry and physical symptoms interfere with your life, work, social activities, family, etc.?	(n=50)	(n=8)	0.002
Not at all	3 (6.0)	4 (50.0)	
Mildly	19 (38.0)	3 (37.5)	
Moderately	19 (38.0)	1 (12.5)	
Severely	7 (14.0)	0 (0.0)	
Very Severely	2 (4.0)	0 (0.0)	
How much are you bothered by worry and physical symptoms (how much distress does it cause you)?	(n=50)	(n=8)	0.21
Not at all	3 (6.0)	3 (37.5)	
Mildly bothered	19 (38.0)	1 (12.5)	
Moderately bothered	17 (34.0)	3 (37.5)	
Severely bothered	7 (14.0)	1 (12.5)	
Very severely bothered	4 (8.0)	0 (0.0)	

Over the last two weeks, how often have you been bothered by any of the following problems?

Problem	(n=56) No. (%) of Women	(n=11) No. (%) of Men	P-Value
Little interest or pleasure in doing things	(n=50)	(n=8)	0.658
Not at all	17 (34.0)	4 (50.0)	
Several days	21 (42.0)	2 (25.0)	
More than half of the days	10 (20.0)	2 (25.0)	
Nearly everyday	2 (4.0)	0 (0.0)	
Feeling down, depressed or hopeless	(n=50)	(n=8)	0.048
Not at all	10 (20.0)	5 (62.5)	
Several days	23 (46.0)	2 (25.0)	
More than half of the days	13 (26.0)	1 (12.5)	
Nearly everyday	4 (8.0)	0 (0.0)	
Trouble falling or staying asleep, or sleeping too much	(n=50)	(n=8)	0.272
Not at all	7 (14.0)	3 (37.5)	
Several days	18 (36.0)	2 (25.0)	
More than half of the days	13 (26.0)	2 (25.0)	
Nearly everyday	12 (24.0)	1 (12.5)	
Feeling tired or having little energy	(n=50)	(n=8)	0.414
Not at all	3 (6.0)	4 (50.0)	
Several days	23 (46.0)	0 (0.0)	
More than half of the days	16 (32.0)	2 (25.0)	
Nearly everyday	8 (16.0)	2 (25.0)	
Poor appetite or overeating	(n=50)	(n=8)	0.071
Not at all	12 (24.0)	5 (62.5)	
Several days	16 (32.0)	1 (12.5)	
More than half of the days	13 (26.0)	2 (25.0)	
Nearly everyday	9 (18.0)	0 (0.0)	
Feeling bad about yourself - or that you are a failure or have let yourself or your family down	(n=50)	(n=8)	0.26
Not at all	25 (50.0)	6 (75.0)	
Several days	14 (28.0)	1 (12.5)	
More than half of the days	6 (12.0)	1 (12.5)	
Nearly everyday	5 (10.0)	0 (0.0)	
Trouble concentrating on things such as reading the newspaper or watching television	(n=50)	(n=8)	0.246
Not at all	30 (60.0)	4 (50.0)	
Several days	12 (24.0)	1 (12.5)	
More than half of the days	5 (10.0)	1 (12.5)	
Nearly everyday	3 (6.0)	2 (25.0)	
Moving or speaking so slowly that other people could have noticed? Or the opposite-being so fidgety or	(n=50)	(n=8)	1.0

restless that you have been moving around a lot more than usual			
Not at all	40 (80.0)	6 (75.0)	
Several days	6 (12.0)	2 (25.0)	
More than half of the days	3 (6.0)	0 (0.0)	
Nearly everyday	1 (2.0)	0 (0.0)	
How difficult have the problems you experienced made it for you to do your work, take care of things at home, or get along with other people?	(n=48)	(n=6)	0.082
Not difficult	13 (27.1)	4 (66.7)	
Somewhat difficult	27 (56.3)	2 (33.3)	
Very difficult	6 (12.5)	0 (0.0)	
Extremely difficult	2 (4.2)	0 (0.0)	

Interpretation of results: Over the last two weeks, 20% of female participants never felt down, depressed or hopeless, 46% felt down depressed or hopeless several days, 26% more than half of the days, and 8% nearly every day, compared to male survey participants where 62.5% never felt down, depressed or hopeless, 25% several days, 12.5% more than half of the days, and none nearly every day. There is a statistically significant difference in the amount that males and females felt down, depressed or hopeless (females felt this more often than males) (p=0.048).

All questions with ordinal responses can be interpreted similarly

In your opinion are the Wellness Resources being offered to you through your work helpful?

	(n=56) No. (%) Women	(n=11) No. (%) Men	P-Value
Wellness resources being offered are helpful No. (%) Yes	10/42 (23.8)	4/7 (57.1)	0.091

Comparing Profession (nurses versus not nurses)

Are you troubled by any of the following since the COVID-19 pandemic started?

Characteristic	(n=23) No. (%) of non-nurses who are troubled	(n=44) No. (%) of Nurses who are troubled	P-Value
Experience excessive worry	(n=20) 12 (60.0)	(n=41) 21 (51.2)	0.518
Worry excessive in intensity, frequency, or amount of distress it causes	(n=19) 9 (47.4)	(n=41) 18 (43.9)	0.802
Find it difficult to control the worry (or stop worrying) once it starts	(n=19) 9 (47.4)	(n=14) 19 (46.3)	0.941
Worry excessively or uncontrollably about minor things	(n=19) 7 (36.8)	(n=41) 13 (31.7)	0.695
Bothered by excessive worries more days than not, During the COVID-19 pandemic	(n=20) 8 (40.0)	(n=41) 16 (39.0)	0.942

During the past few weeks have you often been bothered by any of the following symptoms? Please select one option.

Symptom	(n=23) No. (%) of non-nurses	(n=44) No. (%) of Nurses	P-Value
Restlessness or feeling keyed up or on edge	(n=18)	(n=41)	
Not at all	3 (16.7)	0 (0.0)	
A little bit	6 (33.3)	12 (29.4)	0.136
Moderately	2 (11.1)	11 (26.8)	
Quite a bit	6 (33.3)	12 (29.3)	
Extremely	1 (5.6)	6 (14.6)	
Irritability	(n=18)	(n=41)	0.905
Not at all	2 (11.1)	5 (12.2)	
A little bit	6 (33.3)	9 (22.0)	
Moderately	2 (11.1)	11 (26.8)	
Quite a bit	7 (38.9)	13 (31.7)	
Extremely	1 (5.6)	3 (7.3)	
Difficulty falling/staying asleep or restless/unsatisfying sleep	(n=18)	(n=41)	0.02
Not at all	6 (33.3)	3 (7.3)	
A little bit	2 (11.1)	5 (12.2)	
Moderately	3 (16.7)	6 (14.6)	
Quite a bit	5 (27.8)	17 (41.5)	
Extremely	2 (11.1)	10 (24.4)	
Being easily fatigued	(n=18)	(n=41)	0.102
Not at all	4 (22.2)	1 (2.4)	
A little bit	4 (22.2)	8 (19.5)	
Moderately	4 (22.2)	12 (29.3)	
Quite a bit	3 (16.7)	13 (31.7)	
Extremely	3 (16.7)	7 (17.1)	
Difficulty concentrating or mind going blank	(n=18)	(n=40)	0.659
Not at all	5 (27.8)	7 (17.5)	
A little bit	4 (22.2)	12 (30.0)	
Moderately	3 (16.7)	6 (15.0)	
Quite a bit	5 (27.8)	12 (30.0)	
Extremely	1 (5.6)	3 (7.5)	
Muscle tension	(n=18)	(n=41)	0.003
Not at all	8 (44.4)	3 (7.3)	
A little bit	4 (22.2)	8 (19.5)	
Moderately	1 (5.6)	8 (19.5)	
Quite a bit	4 (22.2)	14 (34.2)	
Extremely	1 (5.6)	8 (19.5)	
How much do worry and physical symptoms interfere with your life, work, social activities, family, etc.?	(n=18)	(n=41)	0.385

Not at all	4 (22.2)	3 (7.3)	
Mildly	5 (27.8)	17 (41.5)	
Moderately	8 (44.4)	13 (31.7)	
Severely	0 (0.0)	7 (17.1)	
Very Severely	1 (5.6)	1 (2.4)	
How much are you bothered by worry and physical symptoms (how much distress does it cause you)?	(n=18)	(n=41)	0.059
Not at all	4 (22.2)	2 (4.9)	
Mildly bothered	6 (33.3)	14 (34.2)	
Moderately bothered	6 (33.3)	15 (36.6)	
Severely bothered	2 (11.1)	6 (14.6)	
Very severely bothered	0 (0.0)	4 (9.8)	

Over the last two weeks, how often have you been bothered by any of the following problems?

Problem	(n=23) No. (%) of non-nurses	(n=64) No. (%) of Nurses	P-Value
Little interest or pleasure in doing things	(n=18)	(n=41)	0.409
Not at all	8 (44.4)	13 (31.7)	
Several days	6 (33.3)	17 (41.5)	
More than half of the days	4 (22.2)	9 (22.0)	
Nearly everyday	0 (0.0)	2 (4.9)	
Feeling down, depressed or hopeless	(n=18)	(n=41)	0.107
Not at all	6 (33.3)	9 (22.0)	
Several days	10 (55.6)	16 (39.0)	
More than half of the days	1 (5.6)	13 (31.7)	
Nearly everyday	1 (5.6)	3 (7.3)	
Trouble falling or staying asleep, or sleeping too much	(n=18)	(n=41)	0.026
Not at all	7 (38.9)	3 (7.3)	
Several days	5 (27.8)	16 (39.0)	
More than half of the days	4 (22.2)	11 (26.8)	
Nearly everyday	2 (11.1)	11 (26.8)	
Feeling tired or having little energy	(n=18)	(n=41)	0.029
Not at all	6 (33.3)	1 (2.4)	
Several days	5 (27.8)	19 (46.3)	
More than half of the days	6 (33.3)	12 (29.3)	
Nearly everyday	1 (5.6)	9 (22.0)	
Poor appetite or overeating	(n=18)	(n=41)	0.079
Not at all	10 (55.6)	7 (17.1)	
Several days	3 (16.7)	15 (36.6)	

More than half of the days Nearly everyday	2 (11.1) 3 (16.7)	13 (31.7) 6 (14.6)	
Feeling bad about yourself - or that you are a failure or have let yourself or your family down	(n=18)	(n=41)	0.887
Not at all	9 (50.0)	22 (53.7)	
Several days	6 (33.3)	10 (24.4)	
More than half of the days	2 (11.1)	5 (12.2)	
Nearly everyday	1 (5.6)	4 (9.8)	
Trouble concentrating on things such as reading the newspaper or watching television	(n=18)	(n=41)	0.774
Not at all	10 (55.6)	24 (58.5)	
Several days	5 (27.8)	9 (22.0)	
More than half of the days	0 (0.0)	6 (14.6)	
Nearly everyday	3 (16.7)	2 (4.9)	
Moving or speaking so slowly that other people could have noticed? Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual	(n=18)	(n=41)	0.681
Not at all	14 (77.8)	33 (80.5)	
Several days	4 (22.2)	4 (9.8)	
More than half of the days	0 (0.0)	3 (7.3)	
Nearly everyday	0 (0.0)	1 (2.4)	
How difficult have the problems you experienced made it for you to do your work, take care of things at home, or get along with other people?	(n=15)	(n=40)	0.431
Not difficult	5 (33.3)	12 (30.0)	
Somewhat difficult	9 (60.0)	21 (52.5)	
Very difficult	1 (6.7)	5 (12.5)	
Extremely difficult	0 (0.0)	2 (5.0)	

In your opinion are the Wellness Resources being offered to you through your work helpful?

	(n=23) No. (%) of non-nurses	(n=44) No. (%) of Nurses	P-Value
Wellness resources being offered are helpful	8/17 (47.1)	7/33 (21.2)	0.059

CODING:
1. List most frequent topics about which you worry excessively or uncontrollably here. *Green- Personal safety and health (death, infected, isolation, burn-out); yellow- concern for others, guilt of infecting (family, patients); purple- worry of patient care; red- not enough staff; blue- worry about the future and finances; grey- lack of PPE; light blue- work related guilt and pressure, lack of support; maroon- sacrifice personal choices and responsibilities and events; teal- dying alone; bottle green- no difference*
dying of covid and family getting sick
causing more work than helping patients, not having enough staff.
I usually worry about how to handle COVID patients properly, doing the right thing for them, and how to best protect myself from being exposed.
Concern for my safety and the safety of those around me. Worry about the
Infecting my loved ones with COVID. Am I going to get COVID with the lack of PPE, how long can I take care of these extremely critically ill patients in these dangerous staffing ratios, when will I get burned out, guilty for not picking up more OT as management bounds me to pick up more
I worry I will get covid and end up on a vent. I worry I will bring it home to my family
How long this will last. Will my family get the virus and die?" How much longer can we work like this without losing it"
my house being a , gaining weight, dying, my family dying, life not returning to , my kids.
catching COVID and
Infecting my family. Unable to
How , life changing forever, the of , with poor prognosis, inability for family to visit, need to cancel
LONG TERM FROM THE DAMAGE FROM 2095 wearing Safety at work. Infected at work. Spreading to others. How I as a COVID RN have to wear a mask anywhere I go
Safety at work, exposure at work, infecting a friend family member. Getting sick myself. Long term health damage.
, doing a nursing task , leaving a task
, not being protected, being valued less than others
Getting covid or spreading it to loved ones.
Patients suffering without their support network, families fearful their family members are suffering and passing alone. It feels like the Recommended PPE is based on availability rather than best practice. Am I infecting my family. How can I give the best care when there are
I see adults the same age as my parents with no medical history decline rapidly to the point of intubation. I see them fail to recover. I see them transition to CMO and die alone in the hospital. I worry every single day that my parents will become one of those patients and that I won't make it in time to see them. I have nightmares wherein intubated patients and coworkers die in a COVID ward and realize I have no PPE. I am redeployed from a medicine unit to an ICU so I constantly worry that I don't belong or that I'm more in the way than helpful.


The number of deaths. Myself or my family becoming infected, cut off from family and
days. Also you worry about wearing the
Work place
I also worry about effects of
(ie my wedding
National management of crisis, lack of
public initiatives to relax social distancing
measures
Getting family sick, getting
the care being provided
my family getting sick, when I feel it will be safe to see my family
again
my newborn,
Getting friends/family sick since I am exposed to covid at work
for me & adult children
i worry about getting covid or exposing others to it, whether i will get the
need to be an
attending, i worry about my
them again
2. What scares you the most about coming to work in the ICU during this time?
getting sick
missing PPE
by doing things to them that ultimately will not help, being
and being stretched
not being able to provide the proper care because of shortage of
Bringing infection home
Feeling unsupported and burnt out.
The way
so rapidly and our
them
The amount of
exposure/treatment to these COVID patients
That the leaders know
Do we make changes
or because that is
all we have
I see so many young, previously healthy people dying and I think about how that could be me
being
and
in an area I am not proficient in
Being
or working long stressful hours
Lack of PPE and
because of it,
seeing as we
three icu
patients to 1 icu nurse
honestly, nothing does. The
in the but it what it is
Lack of support from roles higher up
inability to take breaks when needed (for mental
or physical reasons)
transmitting this virus to my family and them having a
the
there is no
Getting covid and working too hard
and working in dangerous conditions

2

Catching COVID
Inability to [redacted] Becoming exposed
Having [redacted] compounded with the day-to-day risk of exposing my family
Exposure to the virus and getting sick myself like these patients who have been [redacted] in the ICU
[redacted] if I will work with people I know. Unable to express my feelings to management
Becoming infected with covid. Not having adequate PPE at work. Unsafe [redacted]
[redacted]
Exposure to the virus, facing unsafe [redacted] situations
I'm afraid of not being able to give the best care due to staff, [redacted] shortages
Getting sick [redacted]
That we still have [redacted] That more young people / people with no medical histories will catch and die from this virus
Overall feel minimally [redacted] from pre covid in the work environment in terms of coming to work or "feeling scared"
Making [redacted] because PPE and other new protocols distract from doing our work the way we are used to. That I will be asked to take on more work than I can manage due to [redacted] The possibility of becoming sick or contaminating someone at home
Whether or not I am walking into minimal PPE. Will I have an admission that requires intubation, or I will have to respond to a code situation with the same expectation. Will I have to triple my assignment with a med-surg nurse. Or take two 1:1 patients because we don't have [redacted]
Bringing the virus home to my family
My infant nursing with inpatient EHR/EMC units/charting systems. Contracting the [redacted] or bringing it home to a family member.
Being an asymptomatic carrier and spreading COVID to colleagues
Contracting COVID and not knowing, then giving it to someone I love
I am [redacted] of getting Covid than I used to be. Now I'm more anxious about the working conditions and getting an overwhelming assignment that would have once been considered [redacted]
exposure to myself and bringing it home to my family, feeling as though I cannot provide adequate care
That I will get sick and expose my infant
Getting friends and family sick because I am exposed to covid at work
Not being able to [redacted] or getting sick myself and ending up a patient
Mistrust, the trust relationship between administration and nursing is broken.
Not having [redacted]
exposing others around me to covid

Where I'm working and if I'll have enough support
Risk for exposure
Getting sick
Me
My parents could be considered high-risk. I was most scared that I may bring it home to them even though I am being very careful at work.
I never know [redacted] until I arrive at the hospital. I dont know the people I am working with, what's supplies are. The assignments are very heavy and there is no one to help.
3. What fears do you have about your safety and health and that of your family?
family getting sick and myself
My family dying because I bring covid home to them
because of the pandemic, I feel very isolated from everybody since I must stay away from family and friends. I fear that I can get sick and nobody will be there to help me.
Oddly I am not worried about my own health
That I'll bring it home to my husband and son. That I'm not going to be [redacted] parents indefinitely because I am forced to work in a covid unit and potentially get exposed every shift
Mostly that I could infect my family. I do not fear so much for my self
After seeing people my age affected by the disease, I feel more anxiety about being exposed and the possibility of being intubated without family being able to be around. I also have a grandfather who lives at home with my parents who I fear exposing
High fears about bringing it home to someone else. So not [redacted] me most
Is the PPE enough to keep us safe? As I see more of my colleagues fall ill I worry more
I have a parent that is severely immunocompromised and I deliver groceries and am only next of kin.
Giving COVID to them
honestly not much I take the right steps in and out this place so that I wont have to worry too much about that.
As a nurse who is working in the Covid unit on west PACU. It concerns me being in an open room with positive patients all day with full PPE on for the 12 hour shifts.
I fear that any of us could get very sick and have a poor outcome
Exposing them to covid
giving it to my family and kids
I fear my husband getting sick and not being able to be with him if he did become ill
Bringing myself or my family
Spreading this to others if I don't shower frequently enough or doff my PPE appropriately
How [redacted] I need to take extreme precautions to ensure my family and I are safe
Fear that I will become infected/ be a carrier and infect my family
getting my family sick

Family getting sick and dying
I am afraid of infecting my family. I can't touch my children as a tave when they are scared and unsure and need hugs.
That I might [redacted] one of my icu patients
Somehow, I [redacted] myself, I take necessary precautions and don and doff PPE properly but I still think in a way I feel invincible even though I know I'm not. I think part of myself is convinced that I've already had COVID and am therefore immune, although I haven't been tested. I worry for the lives of my parents on a daily basis. It makes me physically ill.
health of family members is a concern
Wearing the same mask multiple days is so outside what used to be the acceptable norm. That myself or someone in my family could become infected and suffer alone. That my elderly mother could end up sick and [redacted]
I fear that I could be a carrier and not know it. I live with my 75 year old mother who is copd and compromised. I also have two children who I am trying to keep safe
I fear bringing the virus home to my family but my husband most of all since he has medical issues.
I have an [redacted], which means I could have a harder time fighting the virus than someone else who does not which makes me nervous for my own safety. My dad has COPD, so I worry about passing it along to him.
I fear my family will become affected.
I fear more for the health and safety of my family than [redacted]. I worry that if they contract covid they will not recover.
I'm most worried about my family. I don't personally live with them but I fear the thought of them ending up in the icu and looking like the patients I take care of
yes, more my family
That I have waited so long to be a mother and will die and not see him grow up.
I fear for my family getting sick, especially my parents getting very sick and ending up needing ICU care.
I [redacted] for my own health but am concerned about the well-being of my parents who are in their 60s and both medical professionals. I also worry that I won't be [redacted] extended family (brothers, nieces, nephews) for months to come.
[redacted]
I worry about my dad who is in dentistry contracting the virus and exposing my mom. I worry that i will expose other workers at work if i am a carrier
Contracting COVID and my immunocompromised husband getting it.
When will it be [redacted] seeing as we are constantly taking care of COVID patients?
That i could expose my 71 y o husband and 85 y o frail mother. My daughters all adult love in the same house as us and are strong and healthy so i don't fear as much for them
bringing covid home to my family
I'm afraid that I'm so young and new into my field that I shouldn't be feeling [redacted] yet, or even not wanting to do a job that I loved so much

I really am so [redacted] taking good care of my patients – which is completely [redacted] – that I really [redacted] about myself. I moved [redacted] to keep my partner safe and because I couldn't cope with being around anyone when I got home.
4. How do you balance your call of duty versus these fears? *Risk not well, no balance; yellow: avoid thinking, support group, distract, relax, yoga etc; blue: training, precautions, duty; grey: positive.*
[redacted]
I try to [redacted] of them, I [redacted] I try to focus [redacted]
N/A
[redacted]
As a critical care nurse, I just do [redacted] the volume is challenging and the larger assignments are a challenge but I just proceed through my shift knowing I [redacted]
I [redacted] sometimes to [redacted] when my duty is to care for the patient but I try to limit myself going in the rooms and [redacted]
I know that if I didn't come to work these [redacted] they need
do what I [redacted] employed
I [redacted] and hope I'm not intubated sedated and paralyzed one of these days
I come to work like if [redacted] Am I more proactive with social distancing, keeping my hands clean, not touching my face unless I'm in the bathroom? Yes.
Patients [redacted] and we need to get [redacted] My fellow nurse friends build each other up!
I go to work and * [redacted] *
by being [redacted]
?
[redacted] over PPE. Try to maintain hope.
Vent to colleagues
Thinking, look to peers for guidance
yoga and meditation, time with my significant other, touch
Stay away from family, there is [redacted]
[redacted] and distancing from my family
Stay informed [redacted]
continue [redacted] [redacted] on days off
Try to fully enjoy my days off. Try to spend some time outdoors every day that I'm not working. Stay in touch with family and friends. Talk about work/covid with my family at home but don't dwell excessively on the news. Watch movies or read books that take my mind off of things. Remind myself that when I go to work, I'm doing what I hope someone else would [redacted] the one who was the patient.

While I am home we do our best to get out and enjoy the fresh air safely. We try to stay busy, and I exercise daily while im home.
I try to be very careful about using my [redacted]. Once at work with a +COVID patient, I am so busy that I don't have time to think about my fears.
I decided to become a [redacted]. I would not be doing my duty as a nurse to have the skills, particularly the ICU skills, and not use [redacted] during this time.
I live alone, work every [redacted] in cases I'm needed when others cannot fill in.
I just do the [redacted] and remind myself these are unprecedented times and as long as I give everything I can with the resources I'm given I should try to relax
[redacted]
try to relax at home, do enjoyable things, play with my dog
Shut down my fears and focused [redacted]
I compartmentalize and just try to push through to [redacted] then have a hard time doing anything during my personal time
Compartmentalization
Jimily. I [redacted] before departing work
i want to [redacted] in which my skills are valuable so i make the [redacted] in the icu to help people and learn.
Just do the [redacted] and make sure I'm properly [redacted]
This is what we [redacted] for.
Call of [redacted] been a strong focus. I have few fears in life
I usually exercise but also unable to do that
Blank out the fears while I'm at work- come in and [redacted]. Handle everything else while at home.
Not really afraid
5. What frustrates you about your daily duties? *Red – no choice; yellow - futile care; green- moral dilemmas about care, personal skill, burnout, helplessness; grey- limited resources, unable to take care of patients, helpless to help colleagues; olive- improvements in pt condition; blue- discomfort of PPE, heavy workload; purple- changing policies, uncertainty; light blue- safety, lack of PPE.*
[redacted]
the amount of futile work I do: intubating patients that have no chance to recover, placing patients on prone position when there is no chance of survival (too many comorbidities, too many options given to families); families requesting unrealistic care: patient with a MOLST being intubated because family does not want to respect the MOLST;
Nothing
Having limited resources and feeling like I work in a third world country. Not being able to take care of my patients the way they deserve because I'm stretched so thin and my [redacted] heavy.
The [redacted] and multiple very sick patients.
What frustrates me is that policies are changed daily so I never really feel confident in having a plan of care in place. So I feel like the work I put in can just be for nothing sometimes.

I feel frustrated about the [redacted] and clean PPE, needing to recycle masks feels dirty and heightens my worry about their efficacy.
lack of [redacted]
The management can't figure out how [redacted], or take any of the icu nurses who are actually working with the patients [redacted]. Not to mention the trauma icu is staffing 3 icus currently (the PACU, rosenburg 6 icu, the TSICU and rosenburg 7 icu). the constant condescending texts from our manager or the emails she sends us are so rude and [redacted], demanding we pick up but [redacted]. I guess burn out isn't a thing in her mind. Perhaps they can suit up in PPE and help us out.
honestly nothing. I'm here to [redacted] in whatever need so that they can assist their patients
No one understands what it is like to work in these [redacted] units. No water. No food. Full PPE, heavy [redacted]. It's tough being physically and [redacted] drained and feelining [redacted]
the lack of [redacted] the PPE.
the [redacted]
Irritates me that we are [redacted] all the time, is having [redacted] PPE
Patients seem to improve [redacted]. It's hard to see the big picture.
The [redacted] and not being able to complete my previously assigned clinical rotations. 24 hour call in fall [redacted] an uncomfortable. I constantly [redacted]
[redacted] by management. Demands of over time by management [redacted]
[redacted] I am [redacted] to help
Being assigned assignments which were previously [redacted]
Shortages of [redacted] supplies
Not being able to freely [redacted] due to wearing [redacted] the time.
Providing interventions to patients who should be [redacted]. More and more I feel like I am torturing [redacted] by doing my job. I have cared for more than one patient whose living will states that they would not want these levels of care, yet the [redacted] to trach and PEG this person.
decrease in [redacted] and patient population/skills
Wearing and [redacted]. Not being able to freely enter and exit patient rooms and how that effects the [redacted]. The [redacted] atmosphere that sometimes exits in the unit. Lack of or shortage of [redacted].
Wearing a mask for [redacted] first thing. The cares we are [redacted] because it is out of the norm of how we care for our ICU patients. An when your patient is having an emergency or an issue, we have to do our best to [redacted] before we get into the room. Also the overflowing of trash is hard. Housekeeping wont always go in the room to help us so we find [redacted] taking trash out, and performing duties that go beyond what we normally do.
It is very difficult to use slow computers outside the room and deal with the constant alarms from infusion pumps. The noise level in the ICU is very high with so many team members in the ICU. The ICU is [redacted] with equipment which makes moving about slow. Running out of [redacted]. Gowns are used up quickly with multiple people using them to work inside patient rooms.

[redacted] from my normal position at HI (ie night shifts) are difficult.
Stress [redacted] and ICUs in particular. I want to help them but I can't imagine how difficult their lives must be right now. Also that patients aren't getting better, often suffering prolonged courses that I suspect will lead to high short and long term mortality.
Not being able to give the best care to all my patients due to the circumstances we are under.
Rotating models, constant supply and drug shortages, feeling like I'm not making good care of my patients-even though I'm [redacted]
sometimes [redacted] involving roles that I do not necessarily have training in.
[redacted] I [redacted] social nature of our jobs.
The [redacted] and hopelessness.
[redacted] routine. [redacted] changing.
Not having [redacted]
being a resident you feel sometimes like you have lack of control or any decision making capability independently so that can be frustrating.
The lack of PPE and the [redacted] for use.
Often times I feel unappreciated in my role.
General public disbelief in the situation and our stupid moronic President.
my [redacted] and how rude she was to all her staff.
Some responsibilities that we have to take [redacted] units- nothing too bad though.
Completely [redacted] and nurses in pacu that are sitting around and dont come and help.
6. What is your reactions's to the loss of control and fear of the unknown about the pandemic? How do you handle it? *Yellow- fear; green- angry; blue-work; purple- teamwork; red- personal ways; grey- sad.*
m afraid.
I become [redacted] and I find myself using foul language. I try not to think too much about things I have no control over; I try to protect myself and my mind from all this.
I don't freak out, I just do what I [redacted] every day.
It's scary.
I think we need to be flexible, this isn't what we trained to do, we are [redacted] go. The [redacted] has been extraordinary.
This is usually what worries me. I handle it by completely [redacted] work when I go home. I don't check the news, I don't look at my email, and I don't try talk about work. I only look at those things when I'm at work.
I am definitely scared and fearful for what the future holds. I try to handle it by [redacted] at a time and remembering that all pandemics eventually end.
I don't feel a total loss of control. Take [redacted]
Wine or other [redacted] vent to my husband or other [redacted] hang out with my dogs.

it sucks. Personally, I'm from New York City and would like to visit my family in he nearby future but just have [redacted]. Anyone can carry COVID. Symptoms are different so I guess we must continue to do what we are doing. it sucks seeing people dying on the new which is why I've been watching lesser and lesser. But coming to [redacted]
Fear of the unkown is one of the scariest things out there
It is hard. I', trying to stay positive but I have been a "[redacted]" (my own words) when I am at home
[redacted]
Sad, angry
Difficult to say. Some days [redacted] others. Try to control the [redacted] and let go of things outside of it.
More anxiety an apprehension than I usually have. Talking with family, [redacted]
Irritable. Through [redacted]
I have had to find outlets such as talking on the phone, [redacted]
with [redacted]
Anger, wanting to remove myself from contact from others even though normally a very outgoing social happy person
It makes me sad. My friends [redacted] I hike.
Try to live [redacted]
I maintain a [redacted] perspective on a day to day basis and form my thoughts and decisions based on the information at hand
I haven't been sleeping well for a while. Sometimes dry. Sometimes have bad dreams about work. Am sad that I can't fully enjoy my favorite time of year. I try to focus on the things I can control and to distract myself. Try to enjoy the now and be realistic about how life may continue to be different for a while. Think about what few good things may come out of this experience for the country as a whole. Remind myself that although the job is difficult, that I'm lucky to have a [redacted] to, unlike so many others.
We are here to do our [redacted] not, these are people and they are our patients. They deserve the best we can give.
My coping management for all [redacted] off creating things. I have many [redacted] on them every day I am off. I also am from a large family. It is hard for me not to see them. I am a planner and like to set up trips to see family by car and plane. Not being able to have dates set up to look forward to for a get away vacation or family reunion is tough.I have had to work 4 vacation days at the hospital recently with the loss of PTO. I am hoping the summer PTO will not be taken away. My strategy is to take each and week as it comes and help those patients within my care. Their struggles to survive are far more critical than my own needs.
I tend to [redacted] and not talk about it as much as I need to. This usually manifests [redacted] towards my loved ones, which is something I am trying to better manage. I have started [redacted] which is helping.
I exercise, [redacted] I also engage in [redacted] more frequently than usual.

I get anxious and I cry
[redacted] is helpful
Stress, cry more often
I compartmentalize [redacted] myself
Without routine, I've sacrificed many of my normal coping strategies - [redacted] with friends and family
Focus on [redacted] connecting to [redacted] neighbors
i try to take one day [redacted] i feel myself worrying about the future i try and remind yself to just focus on today
I just [redacted] Take a breather
I do the [redacted]
I don't let it [redacted] every day as I always have, try to love and laugh
na
Yoga and [redacted] work, getting out in nature. I have developed a skin rash that I believe is secondary to anxiety
7. What are some of the actions taken in the ICU that help your anxiety and fear? *Yellow- personal measures; pink- satisfaction; green- management measures; PPE, information; purple- friendship, camaraderie, support; light blue- unsupportive; blue- family communication; gray-mental help.*
?
None
making sure we have PPE, that we stay as informed as possible, bringing food, nurses to help us
Don't have much anxiety or fear
Daily walks with my son on my days off
Daily [redacted]
I actually felt better when we opened up the PACU as an ICU because there was a system. You donned on to get in and doffed off to get out and I felt more protected
Minimizing time spent in rooms, and placing bags (Ports in the room) helps. Also getting a Lucas has helped ease fear of CPR.
trying to learn new skills
None I don't even know that there is a number to call at BI if someone is feeling alone, isolated or depressed and if there was it was never communicated to us. The only number I know to call is the suicide hotline. In fact our manager sent us and email that said NOT to bother our resource nurse or clinical nurse specialist with personal issues as it is NOT their job.
Just seeing how my boss goes about her business is very inspiring. Also, the entire team. It motivates. Therefor, I have no time for anxiety or fear
Wearing N95 all of the time. Working with [redacted] that rise up to the challenge
being with my [redacted] all in this together. The food is a nice treat. I like the supplied scrubs too.

[redacted]
Helps to have [redacted] by my side that I love and respect
Improving the [redacted] ratio
Refocusing on [redacted] Talking with other [redacted] Reading [redacted]
None
Not very many [redacted]
[redacted]
None
[redacted] in common fears
supportive [redacted]
Sharing with [redacted] about them when we have the time [redacted] knowing that we have each others' backs and are helping each other get through every shift. Having the extra help of redeployed "med-surg" nurses [redacted] The intensivist staff has been amazing in assisting with [redacted] our care.
Working nights there is [redacted] for us to reach out on while were here. The prone team has been [redacted] But unfortunately we are multi-tasking as nurses, a housekeeper, and a sco re our shift due to the lack of [redacted] sometimes.
I feel good when the [redacted] plays over the hospital speakers. It makes all the work and stress worth it that some patients are making it home. I had spoken to management early in our quest to care for the COVID patients about all the stats within HEDAC news that were not showing positive information but rather ICU stats and with the radio and tv, death rates. All of us need some [redacted] to do the work we do.
There is a [redacted] that have been helpful in [redacted] and therefor burnout
[redacted]
Playing with [redacted]
[redacted] All the free food has been nice though and makes me feel [redacted]
having [redacted] having time for breaks
[redacted]
Venting with fellow [redacted]
Communication to [redacted]
i journal about [redacted] and talk [redacted] and family members [redacted] in the icu that helps me
[redacted] Our particular unit leadership (trauma) made it worse and it didn't have to be that way. They were [redacted] and didn't listen to any of our valid concerns. Just a little bit of support would have gone a long way in such circumstances. Threatening our jobs if we just had a question is not okay. In speaking w/ other coworkers, our lack of support is what caused most of the stress and anxiety.
Yoga, [redacted] and time away from work.
Weaning theVentilator settings and [redacted]

a manager that communicated with their staff
TPAC best because I am [redacted]. Other units offer no support
8. In your opinion are the Wellness resources being offered to you through your work helpful? If yes, please share which ones are specifically helpful to you? *Yellow- not used/ green- useful measures; red- outside chat.*
I haven't used them but it's nice to know they're there
Huddles
I can honest say that I feel that they all are
town halls and [illegible]
I actually have not utilized any of the wellness resources offered. I do appreciate all the food donated to us.
Yoga sessions, food delivery, [illegible] messages
2 weeks of free yoga at down under [illegible]
I have not personally used the Wellness Resources, but just knowing they are available helps to ease my concerns
exercise [illegible]
Exercise [illegible] helpful. I have tried the breathing exercises as well-hopeful that I can incorporate that into routine but hasn't happened yet
I have not used the resources, but I do think an effort is being made
Social work [illegible] our department and that was nice

OPEN CODING:

1. List most frequent topics about which you worry excessively or uncontrollably here.
2. What scares you the most about coming to work in the ICU during this time?
3. What fears do you have about your safety and health and that of your family?

Green-Personal safety and health (death, infected, isolation, burn-out; yellow- concern for others, guilt of infecting (family, patients); purple- worry of patient care; red- not enough staff; blue- worry about the future and finances; grey- lack of PPE; light blue- work related guilt and pressure, lack of support; maroon- sacrifice personal chores and responsibilities and events; teal- dying alone; bottle green- no difference.

4. How do you balance your call of duty versus these fears?

Red- not well, no balance; yellow- avoid thinking, support; green- distract, relax, yoga etc; blue- training, precautions, duty; grey- positive.

5. What frustrates you about your daily duties?

Red - no choice; yellow- futile care; green- moral dilemmas about care, personal skill, burnout, helplessness; grey- limited resources, unable to take care of patients, helpless to help colleagues, slow improvements in pt condition; blue- discomfort of PPE, heavy workload; purple- changing policies, uncertainty; light blue- safety, lack of PPE.

6. What is your reaction/s to the loss of control and fear of the unknown about the pandemic? How do you handle it?

Yellow- fear; green- angry; blue-work; purple- teamwork; red- personal ways; grey-sad

7. What are some of the actions taken in the ICU that help your anxiety and fear?

Yellow- personal measures, job satisfaction; green- management measures, PPE, information; purple- friendships, camaraderie, support; light blue- unsupportive; blue- family communication, professional help.

8. In your opinion are the Wellness resources being offered to you through your work helpful? If yes, please share which ones are specifically helpful to you?

Yellow- not used; green- useful measures; red- outside chat.

FOCUSED CODING:

Codes dealing with generalized worry in the time of COVID 19, specific about coming to work in the COVID ICUs as well as specific worries and anxieties about personal health and safety as well as that of family and loved ones:

Personal safety and health (death, infected, isolation, burn-out);
concern for others, guilt of infecting (family, patients);
worry of patient care;
not enough staff;
worry about the future and finances;
lack of PPE;
work related guilt and pressure, lack of support;
sacrifice personal chores and responsibilities and events;
dying alone;
no difference.

Codes dealing with frustrations experienced in working in COVID 19 ICUs:

No choice;
futile care;
moral dilemmas about care, personal skill, burnout, helplessness;
limited resources, unable to take care of patients, helpless to help colleagues, slow improvements in pt condition;
discomfort of PPE, heavy workload;
changing [illegible] uncertainty;
safety, lack of PPE.

Codes dealing with ways of handling fear and specific measures available in the ICU:

fear;
angry;
work;
tea[illegible]
personal [illegible]
sad;
personal measures, [illegible]
management [illegible] PPE, information;
friendships, camaraderie, [illegible]
unsupportive;

family

Codes dealing with experience of Wellness resources offered through work:

Not useful:

GROUPS:

1. **Negative emotions**
2. **Coping strategies**
3.
4.

EMERGENT THEMES:

1. **What was felt: Negative emotions**
2. **What was useful: Coping strategies,**
3. **What was not useful: Negative emotions**
4. **How can we improve?**


Open Coding
Focused coding
Groups
1. Negative emotions
2. Coping strategies
3. Positive reinforcements
4. Recommendations
Emergent themes
1. What was felt: Negative emotions
2. What was useful: Coping strategies, Positive reinforcements
3. What was not useful: Negative emotions
4. How can we improve? Recommendations

Critical Care - 2 Postoperative Acute Kidney Injury Is Associated With Progression Of Chronic Kidney Disease Independent Of Severity

Jamie Privratsky[1], Vijay Krishnamoorthy[1], Karthik Raghunathan[2], Tetsu Ohnuma[1], Mohammed Rasouli[3], Thorir E Long[4], Martin I Sigurdsson[5]

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Introduction: Both postoperative acute kidney injury (AKI) and preoperative chronic kidney disease (CKD) are associated with significantly worse short- and long-term outcomes following surgery. The relationship of both of these conditions to each other and to CKD progression after surgery remains poorly studied impeding efforts to reduce risk. The objective of our study was to determine whether postoperative AKI is independently associated with CKD progression within one year of surgery, in groups stratified by preoperative estimated glomerular filtration rate (eGFR), and to determine if a dose-response relationship exists. We hypothesized that AKI would be dose-dependently associated with an increased risk of CKD progression within one year of surgery, which would be exacerbated by preoperative kidney dysfunction.

Methods: Our study was a retrospective cohort study at the University Hospital in Iceland which serves about 75% of the population. Adults receiving their first major anesthetic between 2005-2018 were included in the initial cohort. Patients with end stage renal disease (ESRD); undergoing major urologic procedures; or having missing creatinine values for follow-up of GFR stage were excluded from analysis. Our primary exposure was postoperative AKI stage within 7 days after surgery classified by the kidney disease improving global outcomes (KDIGO) criteria. Our primary outcome was progression of CKD by at least one GFR category within 1-year following surgery. Multivariable Cox proportional hazards models were used to estimate hazards.

Results: A total of 7499 patients were studied. Patients who experienced postoperative AKI displayed faster time to CKD progression than patients who did not develop postoperative AKI; though, there did not appear to be additional risk based on severity of AKI (Figure 1). When plotted against time, patients with GFR category > 2 (eGFR < 90ml/min per 1.73m2) displayed faster progression to higher GFR category within 1 year of surgery (Figure 2). When stratified by both AKI stage and preoperative GFR category, patients with either postoperative AKI or GFR category > 2 were both at increased risk of progression to higher stage of CKD within 1 year following surgery; however, it again should be noted that there was not a dose response based on either variable (Figure 3). In the multivariable model adjusting for relevant risk factors including preoperative GFR category, post-operative AKI stage 1 (HR 2.76, 95% CI 2.19-3.48, p<0.001), stage 2 (HR 2.58, 95% CI 1.48-4.50, p<0.001), and stage 3 (HR 4.17, 95% CI 2.27-7.64, p<0.001) were all independently associated with GFR stage progression within 1 year following surgery. There was no dose-response relationship. Preoperative GFR category was found to be a confounder as it was independently associated with postoperative CKD progression (G2 60-89 ml/min/m2 [HR 4.33, 95% CI 2.82-6.67, p<0.001], G3a 45-59 [HR 4.37, 95% CI 2.76-6.93, p<0.001], and G3b 30-44 [HR 2.61, 95% CI 1.58-4.34, p<0.001]).

Conclusion: The development of postoperative AKI was independently associated with CKD progression within the year following surgery irrespective of AKI severity or baseline kidney function. Further, the presence of preoperative kidney dysfunction (increased GFR category) itself poses increased risk for postoperative CKD progression. These data suggest that the adoption of kidney protective practices is necessary whenever possible.

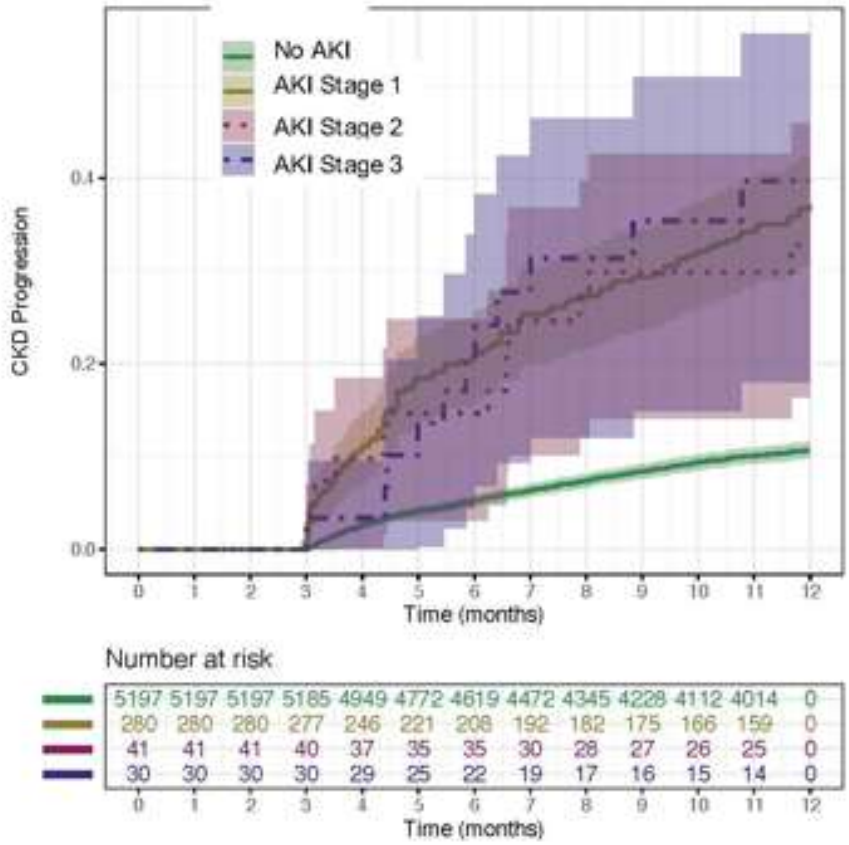

Figure 1: Unadjusted risk of GFR category after surgery versus time for patients who did or did not develop postoperative AKI. All AKI stages demonstrate increased risk of GFR category, though there is not a dose response relationship.

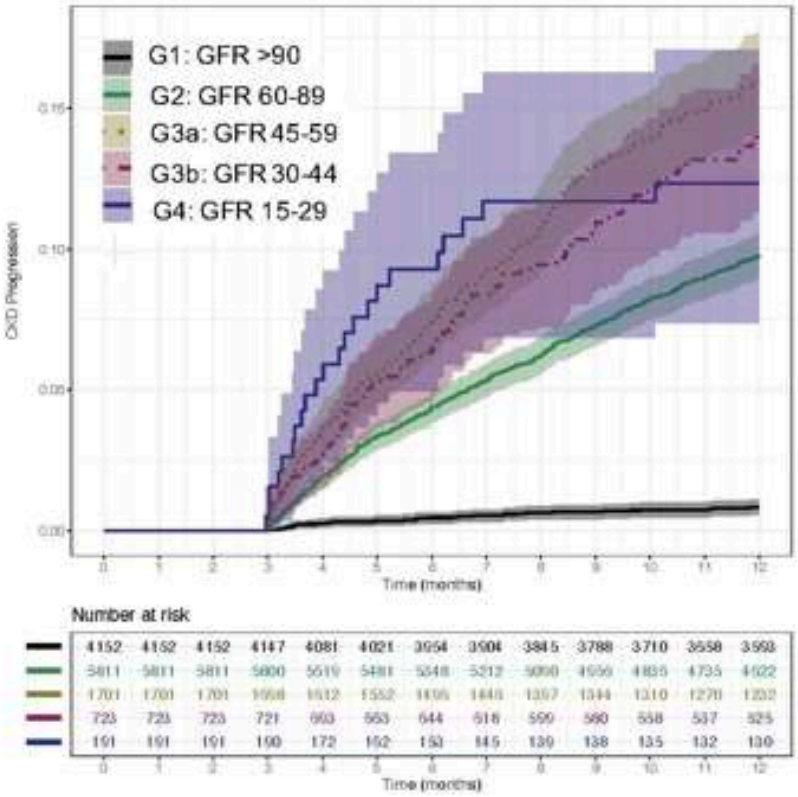

Figure 2: Unadjusted risk of GFR category after surgery versus time for GFR categories 2-4. All stages demonstrate increased risk of GFR category, though there is not a dose response relationship.

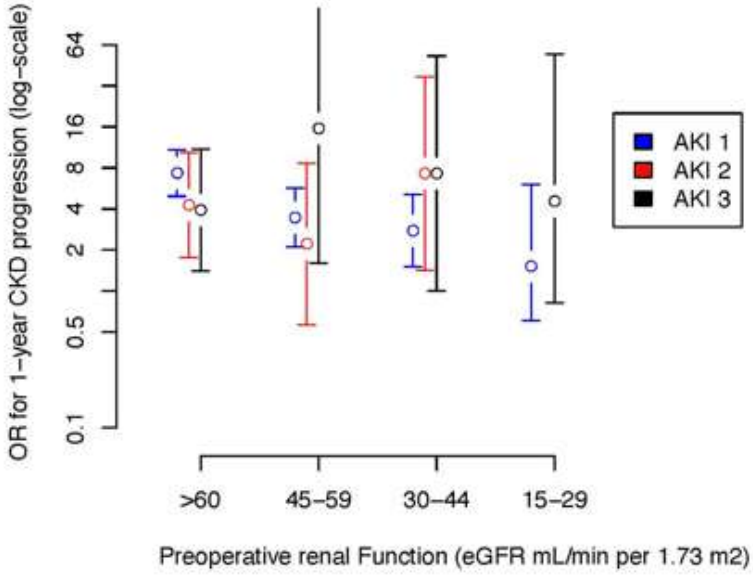

Figure 3: Unadjusted odds ratio for GFR category after surgery based on preoperative GFR category (eGFR) and postoperative AKI stage.

Critical Care - 3 Canadian Emergency Medicine and Critical Care Physician Perspectives on Pandemic Triage in COVID-19

Blair Bigham[1], Ali Mulla[2], Michael Christian[3]

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Introduction: Local and regional policies to guide the allocation of scarce critical care resources have been developed, but the views of prospective users are not understood. We sought to investigate the perspectives of Canadian acute care physicians towards triaging scarce critical care resources in the COVID-19 pandemic.

Methods: We rapidly deployed a brief survey to Canadian emergency and critical care physicians in April 2020 to investigate current attitudes towards triaging scarce critical care resources and identify subsequent areas for improvement. Descriptive and between-group analyses along with thematic coding were used.

Results: The survey was completed by 261 acute care physicians. Feelings of anxiety related to the pandemic were common (65%), as well as fears of psychological distress if required to triage scarce resources (77%). Only 49% of respondents felt confident in making resource allocation decisions. Both critical care and emergency physicians favored multidisciplinary teams over single physicians to allocate scarce critical care resources. Critical care physicians were supportive of decision making by teams not involved in patient care (3.4/5 vs 2.9/5 p=0.04), whereas emergency physicians preferred to maintain their involvement in such decisions (3.4/5 vs 4.0/5 p=0.007). Free text responses identified five themes for subsequent action including the need for further guidance on existing triage policies, ethical support in decision making, medico-legal protection, additional tools for therapeutic communications, and healthcare provider psychological support.

Conclusion: There is an urgent need for collaboration between policymakers and frontline physicians to develop critical care resource triage policies that wholly consider the diversity of provider perspectives across practice environments.

Critical Care - 4 Association between Cerebral Autoregulation as Estimated by Diffuse Correlation Spectroscopy and Neurologic Injury among Children on Extracorporeal Life Support

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Introduction: Extracorporeal Life Support (ECLS) is used in extreme physiologic shock states to support cardiopulmonary function and augment oxygen delivery. ECLS alters hemodynamics at the macro and micro circulatory levels and requires systemic anti-coagulation which may contribute to the risk of neurologic injury which occurs in ~13% of children. As post-ECMO neurological imaging is not widespread,1 this neuroinjury incidence is likely much higher (45-62%), as suggested by retrospective studies.2,3 Current neurologic monitoring modalities (NIRs, clinical exam) are not able to accurately determine risk or occurrence of neurologic injury. Imaging confirmation of injury with MRI, CT, or transcranial doppler are limited to single timepoint measurements, require advanced training to interpret, and are often not feasible during ECLS. Diffuse correlation spectroscopy (DCS) is a recently developed interferometric optical technique capable of dynamic measurement of microvascular regional cerebral blood flow through application of a simple, small light source and detector applied to the forehead. The correlation between DCS-measured cerebral blood flow and mean arterial pressure has been utilized as an autoregulatory index termed DCSx. Elevated DCSx measurement indicate disrupted cerebral autoregulation. We hypothesized disruption of cerebral autoregulation as indicated by increased DCSx is associated with neurologic injury among children on ECLS.

Methods: After obtaining IRB approval, we conducted a prospective cohort study of children under 18 years old on ECLS to assess the relationship between DCSx and neurologic injury. After obtaining consent, DCS measurement of regional cerebral blood flow data old was collected for a minimum of 1 hour daily unless precluded by clinical complexity, staff concerns, or parental request. Each unilateral (right or left sided) application of DCS was assessed as an independent measurement. DCSx was determined from Pearson correlation of cerebral blood flow and mean arterial blood pressure as previously described.5 Clinical vital signs including mean blood pressures measured by arterial line were recorded using medicollector data acquisition software. All relevant laboratory, ventilator, and type of ECLS were recorded. Head imaging including head US, head CT, and brain MRI were assessed by a blinded neuroradiologist to determine previously established pediatric neuroinjury scoring.4,5 The association between all DCSx measurements and neurologic injury was established through Spearman correlation. Spearmen correlation for the highest DCSx measurement and neurologic injury score was also calculated. Neuroimaging scores were dichotomized at a value of 10 as scores of 10 or greater signify more severe injury. DCSx was dichotomized at 0.5 as DCSx greater than 0.5 has been associated with cerebral dysregulation.6,7 Logistic regression defined the odds ratio for significant neurologic injury for patients with DCSx measures greater than 0.5.

Results: DCS data for 20 patients were collected. Imaging data were not available for 3 patients and there were incomplete clinical or DCS data for another 3 patients. Among the 14 patients included for analysis, 55 distinct DCS measurement episodes occurred. Descriptive statistics for baseline characteristics were calculated (Table 1). The Spearman correlation coefficient between all DCSx measures and neurologic injury was 0.55, P<0.001 (Figure 1). The Spearmen correlation for the highest DCSx measures for each patient and neurologic injury was 0.46, P=0.15. There was a significant difference in the odds of severe neurlogic injury for patients with a DCSx measurement greater than 0.5 (OR 13, 95% CI 2.66-63.6, P=0.002).

Conclusion: We identify a significant association between disruption in cerebral autoregulation measured by DCSx and neurologic injury. The odds of

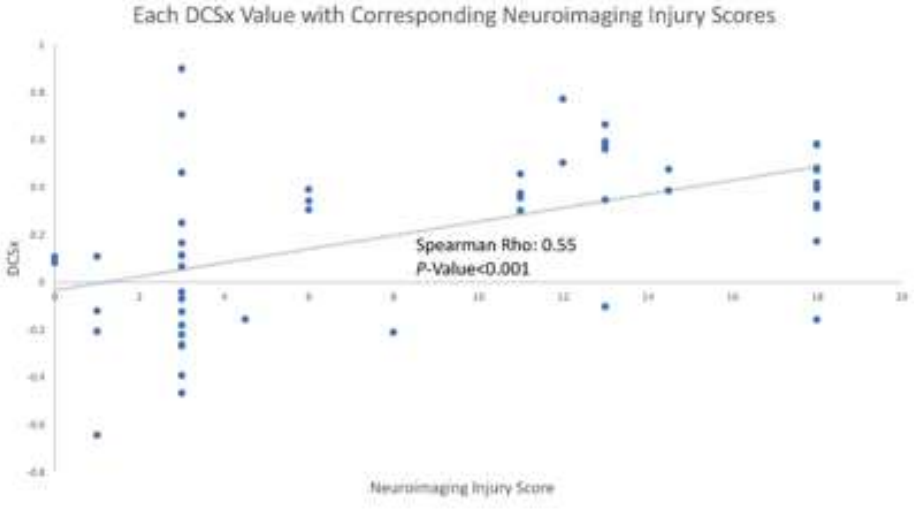
severe injury was higher for those patients with a DCSx measure>0.5. These results should be interpreted with caution as measures are limited to 1-hour time frame among relatively few patients. Our results may also be skewed by discrepancies in the number of measurements taken in individual patients. Despite limitations, these data suggest that dynamic measurement of DCSx may lead to earlier recognition of risk or occurrence of neurologic injury which could prompt changes in clinical management to ameliorate neurologic injury.

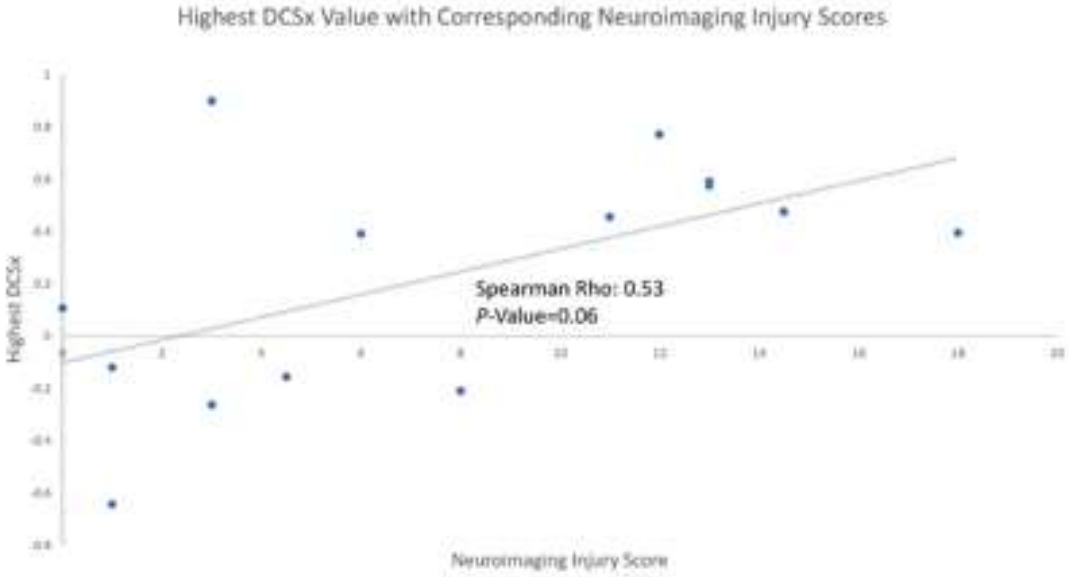
References: 1 Pediatric ECMO Research: The Case for Collaboration, Frontiers in Pediatrics 6 2018. 2 Utility of neuroradiographic imaging in predicting outcomes after neonatal extracorporeal membrane oxygenation, J. Pediatr. Surg. 47(1) 2012. 3 Cranial CT for diagnosis of intracranial complications in adult and pediatric patients during ECMO: clinical benefits in diagnosis and treatment, Acad. Radiol. 14(1) 2007. 4 Neonates treated with ECMO: predictive value of early CT and US neuroimaging findings on short-term neurodevelopmental outcome, Radiology 195(2) 1995. 5 Intracranial abnormalities in infants treated with extracorporeal membrane oxygenation: imaging with US and CT, Radiology 165(3) 1987. 6 Monitoring cerebral blood flow pressure autoregulation in pediatric patients during cardiac surgery, Stroke 41(9) 2010. 7 Noninvasive autoregulation monitoring with and without intracranial pressure in the naive piglet brain, Anesth Analg 111(1) 2010.

Table 1: Baseline Characteristics

CHARACTERISTIC	N=14 (%)
SEX	
MALE	8 (55.6)
FEMALE	6 (44.4)
AGE	2 (1.25,10)*
WEIGHT	11.6 (10.0, 56.5)*
ECPR OR CPR PRIOR TO ECMO	
YES	6 (44.4)
NO	8 (55.6)
ECMO CANNULATION	
VV	1 (11.1)
VA	13 (88.9)
MORTALITY WITHIN STUDY TIME FRAME	
YES	5 (38.9)
NO	9 (61.1)
HIGHEST LACTIC ACID	6.6 (3.7,10.1)
MEAN XA LEVEL	0.33 (95% CI 0.24-0.43)
HIGHEST OI	24.9 (95% CI 16.5-33.3)
IMAGING NEUROINJURY SCORE	7 (3,13)*

* Median values with interquartile ranges




Highest DCSx Value with Corresponding Neuroimaging Injury Scores
Highest DCSx
Neuroimaging Injury Score
Spearman Rho: 0.53
P-Value=0.06

Critical Care - 5 Incidence of Atrial Fibrillation in Single vs Bilateral Lung Transplantation Patients

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Introduction: Lung transplantation (LTx) is an important treatment option for patients with end-stage lung diseases such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis (IPF). Though LTx improves patient outcomes, the most frequent complications, such as infection and acute rejection, contribute to increased mortality in the immediate postoperative period [1]. LTx has also been associated with the development of atrial fibrillation (AF) [2], however, the relationship between LTx type and AF development postoperatively has been understudied. In this preliminary study, we assessed the incidence of AF development in unilateral and bilateral LTx patients.

Methods: A retrospective chart review was conducted on adult patients (≥18 years old) who underwent right, left, or bilateral LTx between April 2013 and June 2018 at our home institution. The outcome variables measured were the type of LTx (right, left, or bilateral) and whether or not the patient developed AF postoperatively during their hospital stay before discharge or death. The incidence of AF was compared between LTx type using the chi-squared test.

Results: A total of 431 patients that underwent right, left, or bilateral LTx were screened. Of those patients, 113 (26.2%) were diagnosed with AF. Left LTx had AF incidence of 30.1%, right LTx of 33.3%, and bilateral LTx of 22.5% (p=0.103) (Table 1). Results did not show a significant difference in the incidence of AF development between left vs right LTx (30.1% vs 33.3%, p=0.646). Incidence of AF development was lower in bilateral vs left LTx (22.5% vs 30.1%, p=0.133) and bilateral vs right LTx (22.5% vs 33.3%, p=0.058), indicating a trend in AF development in regard to LTx type. However, in comparing bilateral vs single (right and left) LTx, we found a statistically significant reduction in the incidence of AF development (22.5% vs 31.5%, p=0.038).

Conclusion: Preliminary data analysis showed a decreased incidence of AF in bilateral vs unilateral LTx. Haissaguerre et al. identify the critical role pulmonary veins play in the development of AF [3]. LTx involves the Cox Maze ('cut and sew') procedure in order to achieve pulmonary vein electrical isolation. This has been shown to mitigate AF in four vein (bilateral LTx) but not two vein (unilateral LTx) pulmonary isolation. Although the exact mechanism is not certain, the lower incidence of AF in bilateral LTx may be attributed to the prevention of pulmonary vein reconnection [2]. Known risk factors for AF include older age, IPF, coronary disease, enlarged left atrium, and use of postoperative vasopressors [4]. Though our study did not take into account these risk factors, future studies should control for them in order to help elucidate the relationship between AF and LTx type. A comprehensive understanding of the underlying mechanisms leading to AF development with respect to LTx type can help improve patient postoperative outcomes.

References: [1] 'Lung transplantation in idiopathic pulmonary fibrosis.' 12, (2018): 375-385. [2] 'Atrial fibrillation following lung transplantation: double but not single lung transplant is associated with long-term freedom from paroxysmal atrial fibrillation.' 31, (2010): 2774-2782. [3] 'Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins.' 339, (1998): 659-666. [4] 'Atrial fibrillation after pulmonary transplant.' 126, (2004): 496-500.

Table 1: Incidence of Atrial Fibrillation Development by Lung Transplantation Type

		Left LTx	**Right LTx**	**Bilateral LTx**
AF Development	No	72 (69.9%)	50 (66.7%)	196 (77.5%)
	Yes	31 (30.1%)	25 (33.3%)	57 (22.5%)

Critical Care - 6 Intestinal Macrophages Incorporate Microbiome Signals To Promote Wound Healing

Jim Castellanos[1]

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Introduction: Inflammatory bowel disease (IBD) results from a dysregulated interaction between the microbiota and a genetically susceptible host. Genetic studies have linked TNFSF15 polymorphisms and its protein TNF-like ligand 1A (TL1A) with IBD, but the functional role of TL1A in linking tissue homeostasis and intestinal inflammation is not known. Here, using cell-specific genetic deletion models, we show an essential role for the gut microbiome in directing intestinal macrophages to promote wound healing at the intestinal epithelium via TL1A.

Methods: Mice. C57BL/6, Itgax-cre, Rorc-cre, OT-II, Il1r-/-, Cx3cr1-GFP, Cx3cr1-CreER mice were purchased from The Jackson Laboratory. All mouse models were on C57BL/6 background. CX3CR1-DTR mice (Longman et al., 2014) were previously described. Il23rGFP mice were obtained from M. Oukka (Awasthi et al., 2009). Myd88-/- were obtained from J. Blander. MHCII□ILC3 mice were obtained from G. Sonnenberg (Hepworth et al., 2015). Tnfsf4flox were provided by T. Vyse and M. Botto (Cortini et al., 2017). Tnfrsf25-/- mice were obtained from Cancer Research UK (Wang et al., 2001). Generation of Tnfrsf25flox/flox mice is previously described (Shih et al., 2014). Tnfsf15flox/flox mice were generated at Cedars-Sinai by D. Shih and S. Targan. All experiments were performed with 6-8 week old littermates. Male and female mice were used with random and equal assignment of same sex to each experimental group. All vertebrate work was approved by the IACUC at Weill Cornell Medicine. Human IBD subjects. Endoscopic biopsies were obtained under an Institutional Review Board–approved protocol (1103011578) and informed consent was obtained at Weill Cornell Medicine (WCM) including patients >18 years of age. Active inflammation was defined by an endoscopic score of >2 and inactive disease was defined by an endoscopic score of 0. The age and gender of subjects included are as follows: Healthy controls-22, 38, 53, 55, 71, 72, 79 year old males and 36 year old female; Crohn's inactive-30, 52, and 57 year old males; Crohn's active-32, 36 year old males and 27, 44, 55, 55, 62, and 68 year old females. Statistical analysis. Statistical analysis was performed in GraphPad Prism or R software. Results represent mean ± s.e.m. and were analyzed by unpaired Student's t-test, Mann-Whitney test, one-way ANOVA, Log-rank (Mantel-Cox) test. Given that mouse experiments required littermate controls and complex genotyping, experimental group allocation was not blinded. No relevant exclusion criteria were applied.

Results: Using cell-specific genetic deletion models, we report an essential role for CX3CR1+ mononuclear phagocyte (MNP) TL1A in signaling through its cognate receptor death receptor 3 (DR3) on group 3 innate lymphoid cell (ILC3) to promote IL-22-dependent protection during acute colitis. Induction of intestinal MNP TL1A by IBD-associated adherent microbes confers TL1A-dependent protection from acute colitis. However, in contrast to this protective role in acute colitis, colitis-induced DR3-dependent expression of OX40L enables MHCII+ ILC3 to co-stimulate antigen-specific T cell proliferation and exacerbate chronic T cell-dependent colitis. Colonic biopsies from IBD patients revealed increased TL1A expression on MNPs and OX40L on ILC3 compared to healthy controls, highlighting the conserved TL1A-OX40L ILC3 axis in IBD. These results identify the mechanistic contributions of this IBD-linked pathway as a central regulator of ILC3 function in tissue homeostasis and wound healing.

Conclusion: Here we show a protective role for microbial induction of the IBD-linked protein TL1A in promoting ILC3-driven wound healing and uncover a pathogenic role for TL1A-induced expression of OX40L on ILC3s in driving chronic T cell colitis. A more thorough understanding of TL1A and group 3 innate lymphoid cell biology will lead to novel therapeutic approaches to wound healing in IBD and the preoperative environment.

Critical Care - 7 Prone Positioning is Associated with Improved Intensive Care Unit Survival Among Critically Ill Obese Patients with COVID-19

Nicholas Rizer[1], Blake Mergler[1], Benjamin Smood[1], Alexandra Sperry[1], Federico Sertic[1], Andrew Acker[1], Christian Bermudez[1], Jacob Gutsche[1], Asad A Usman[1]

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Introduction: The use of prone positioning has been widely reported in patients with coronavirus disease 2019 (COVID-19).(1) While prone positioning has been shown to have mortality benefit in patients with acute respiratory distress syndrome (ARDS), its specific benefit in obese patients is less clear. (2) For obese patients with ARDS, supine positioning has been shown to be particularly detrimental to respiratory status; however, there is also concern that prone positioning can lead to hepatic and renal derangements. (3–7) Here we present a retrospective cohort study among critically ill COVID-19 patients who received prone positioning in order to compare intensive care unit (ICU) mortality between obese and non-obese cohorts.

Methods: We designed a retrospective cohort study of all patients admitted to our center's ICU from 3/9/2020 to 4/19/2020 and underwent prone positioning. Patients were divided into two cohorts: body mass index (BMI) ≥ 30 kg/m2 and < 30 kg/m2. Cohorts were compared on survival to ICU discharge, secondary outcomes, demographic and clinical features. Univariate logistic regression was performed on pre-specified demographic features to test their association with survival at ICU discharge. Any variables with statistically significant associations with ICU survival were planned to be included in a multivariate logistic regression analysis. Data was manually extracted from the electronic medical record at our center by a trained team of physicians and researchers using a protocolized Case Record Form developed by the COVID-19 Critical Care Consortium and International Severe Acute Respiratory and Emerging Infection Consortium (CCCC/ISARIC) previously published elsewhere. (8)

Results: Demographic characteristics and initial vital signs for our patients are presented in Table 1. No significant demographic differences, aside from BMI, were noted between groups. There was no significant difference observed in the frequency of severe ARDS or SOFA scores among cohorts. Primary and secondary outcomes for patients with and without obesity are presented in Table 2. Proned obese patients were more likely to survive to ICU discharge than their non-obese counterparts (79% vs 33%, p = 0.03). ICU length of stay, duration of mechanical ventilation, time to initial proning, and duration of proning were similar between both groups. Univariate logistic regressions were performed on a set of pre-specified variables to test their association with survival to ICU discharge. The only covariates with a significant association were obesity (OR = 7.5, p = 0.03) and age (OR = 0.91, p = 0.03). Multivariate logistic regression revealed a significant mortality association with age (OR = 0.91, p = 0.04) and a trend towards survival among patients with obesity (OR = 8.5, p = 0.06).

Conclusion: Among patients who were proned for COVID-19 ARDS, obese patients were more than twice as likely to survive than non-obese patients, despite similar cohort composition and severity of illness. Improved survival among patients with obesity is concordant with prior non-COVID-19 literature suggesting unique detrimental effects with supine positioning in obese patients. (3,5) Proning is thought to be particularly effective in obese patients, given the substantial compressive effects of body habitus on the lung in obese patients. (9) Prior work has shown proning to improve ventilation in obese COVID-19 patients, however our study is the first to show a mortality beneifit to our knowledge. (10) Taken together with our work, proning may offer substantial therapeutic benefit in COVID-19 patients with obesity.

References: Arch Acad Emerg Med. 2020;8(1):e48. Chest. 2017;151(1):215-224. Anaesthesist. 2015;64:1-26. Expert Rev Respir Med. 2018;12(9):755-767. Eur Respir J. 2012;40(6):1568-1569. Crit Care Lond Engl. 2010;14(4):232. J Crit Care. 2014;29(4):557-561. BMJ. 2020;369:m1985. Chest. 2012;142(3):785-790. ERJ Open Res. 2020;6(2).

	Obese	Non-obese	p-value
Total (n)	19	9	
BMI (kg/m^2)*	38.8 (32.9 – 52.4)	26.4 (21.6 – 27.7)	1.6×10^{-4}
Age (years)	63 (47 – 66)	74 (52 – 75)	0.32
Sex			
Male (n)	10	5	1.0
Female (n)	9	4	-
Self-Reported Race			
White (n)	7	3	1.0
Black (n)	10	4	-
Asian (n)	0	2	-
Other (n)	2	0	-
Chronic Cardiac Disease* (n)	8	1	0.20
Hypertension* (n)	16	6	0.35
Chronic Pulmonary Disease (Not Asthma)* (n)	11	4	0.69
Asthma * (n)	5	2	1.0
Chronic Kidney Disease * (n)	3	1	1.0
Temperature (°F)*	99.7 (99.0 – 101.3)	100.5 (98.3 – 102.0)	0.56
Mean Arterial Pressure (mmHg)*	99.7 (89.7 – 117.3)	92.3 (76.0 – 108.0)	0.89
Heart Rate (min^{-1})*	106.0 (92.0 – 110.5)	93.0 89.0 – 117.0)	0.91
Respiratory Rate (min^{-1})*	28.0 (23.0 – 33.5)	32.0 (21.0 -36.0)	0.63
Pulse Oxygen Saturation (%)*	86.0 (75.0 – 92.0)	88.0 (83.0 – 93.0)	0.92
Severe ARDS (n)	16 (84%)	7 (78%)	1.0
SOFA Score$^{\Delta}$	9.0 (7.3 – 10.0)	6.0 (6.0 – 8.0)	0.24

Table 1: Demographic and Clinical Signs for Patients With and Without Obesity.

BMI : Body mass index. ARDS: Acute Respiratory Distress Syndrome. SOFA: Sequential Organ Failure Assessment. * - Data recorded at first presentation to facility. $^{\Delta}$ – Data recorded at admission to ICU.

	Obese (n=19)	Non-obese(n=9)	
Survival to ICU Discharge	15 (79%)	3 (33%)	0.03
Length of ICU Stay (days)	30 (22 -44)	38 (20 – 46)	0.50
Duration of Mechanical Ventilation (days)	26 (17.5 – 42.0)	32 (20 -44)	0.46
Time to Proning From ICU Admission (days)	1 (0 – 6)	3 (0 – 6)	0.24
Duration of Proning (days)	4 (2 – 5)	4 (2 – 6)	0.29
Use of ECMO	0 (0%)	1 (11%)	0.32
Use of vasopressors or inotropes	19 (100%)	9 (100%)	1.0

Table 2: Mortality and Secondary Outcomes in Patients With and Without Obesity.

ICU : Intensive care unit. ECMO : Extra-corporeal membrane oxygenation.

Critical Care - 8 Effectiveness of a Just in Time Educational Course Blending Remote Asynchronous Standardized Video Didactics and Live Simulation Scenario on Mechanical Ventilation for Non-Intensivist Training (VENT)

Brooke Albright-Trainer[1], Paul Miller[2], James Lavelle[3], Jonathan Nguyen[4], Jessica Feinleib[5]

[1]University of Virginia, Charlottesville, VA, [2]Veterans Health Administration, Orlando, FL, [3]VA Eastern Colorado Health Care System, Aurora , CO, [4]Central Virginia VA Health Care System, Richmond, VA, [5]Yale School of Medicine, New Haven, CT

Introduction: In anticipation of predicted ICU surges (1), the Veterans Health Administration sought novel methods of providing training for Non-Intensivists to better prepare them for managing critical patients with Acute Respiratory Distress Syndrome (ARDS) (2) requiring mechanical ventilation utilizing current evidence-based best practices (3,4). As multiple studies demonstrate the efficacy of simulation-based mechanical ventilation education (5), a standardized video didactic, cognitive aids (Fig 5), and live simulation scenario were developed to meet social distancing requirements and reduce travel. To evaluate this educational product, we designed and conducted a pilot study.

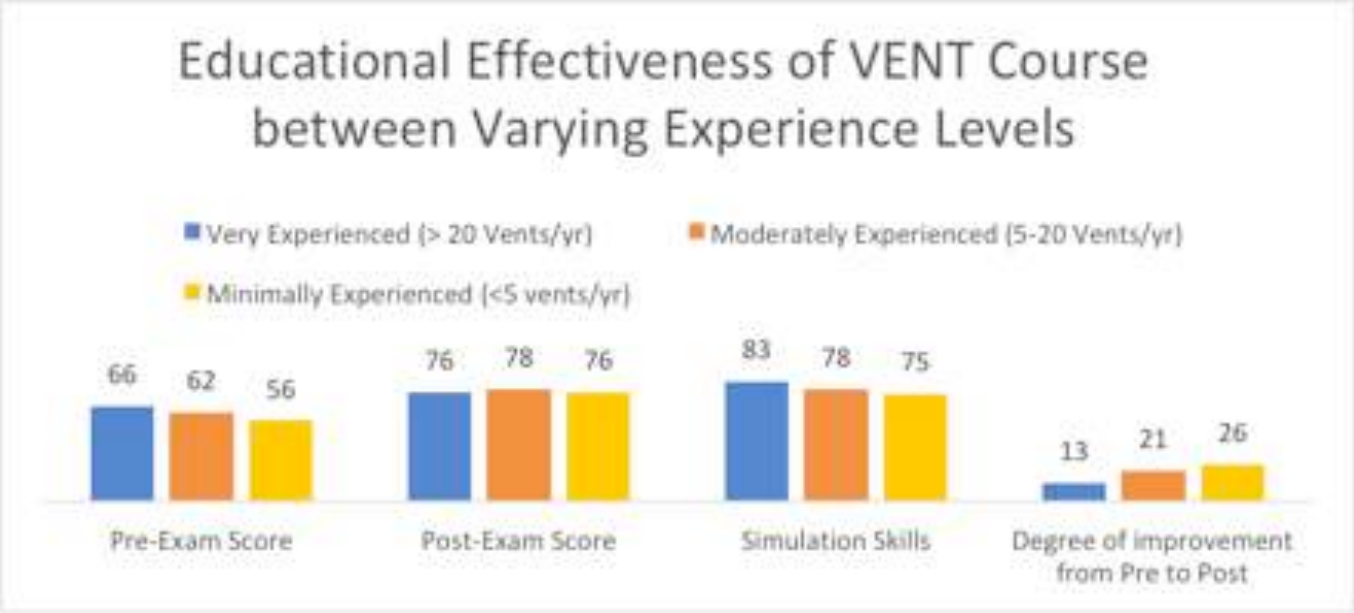
Methods: A multi-center prospective cohort study was designed to evaluate three outcomes of the VENT course: 1) feasibility; 2) educational effectiveness; and 3) clinical relevance. Multidisciplinary Non-Intensivists with varying levels of experience managing ventilators from high acuity hospital centers were recruited over three months. If study participants failed to complete any portion of the course curriculum and/or assessment tools they were eliminated from the analysis. The feasibility of the study was assessed at two study sites utilizing similar faculty and high-fidelity patient simulators. Each participant received the same video lecture, simulation scenario, and assessment tools at similar time intervals. The only difference between the sites was the type of advanced lung simulator and ICU ventilator used. The educational effectiveness was assessed by testing participants' baseline knowledge of mechanical ventilation concepts and management goals for ARDS and comparing it to an identical post course exam. Clinical relevance of the course was assessed using a Kirkpatrick's level 1 and 2 survey. (6) Analysis between individual cohorts as well as between learners with varying experience in managing ventilators was performed using a univariate and multivariate statistical analysis of variance.

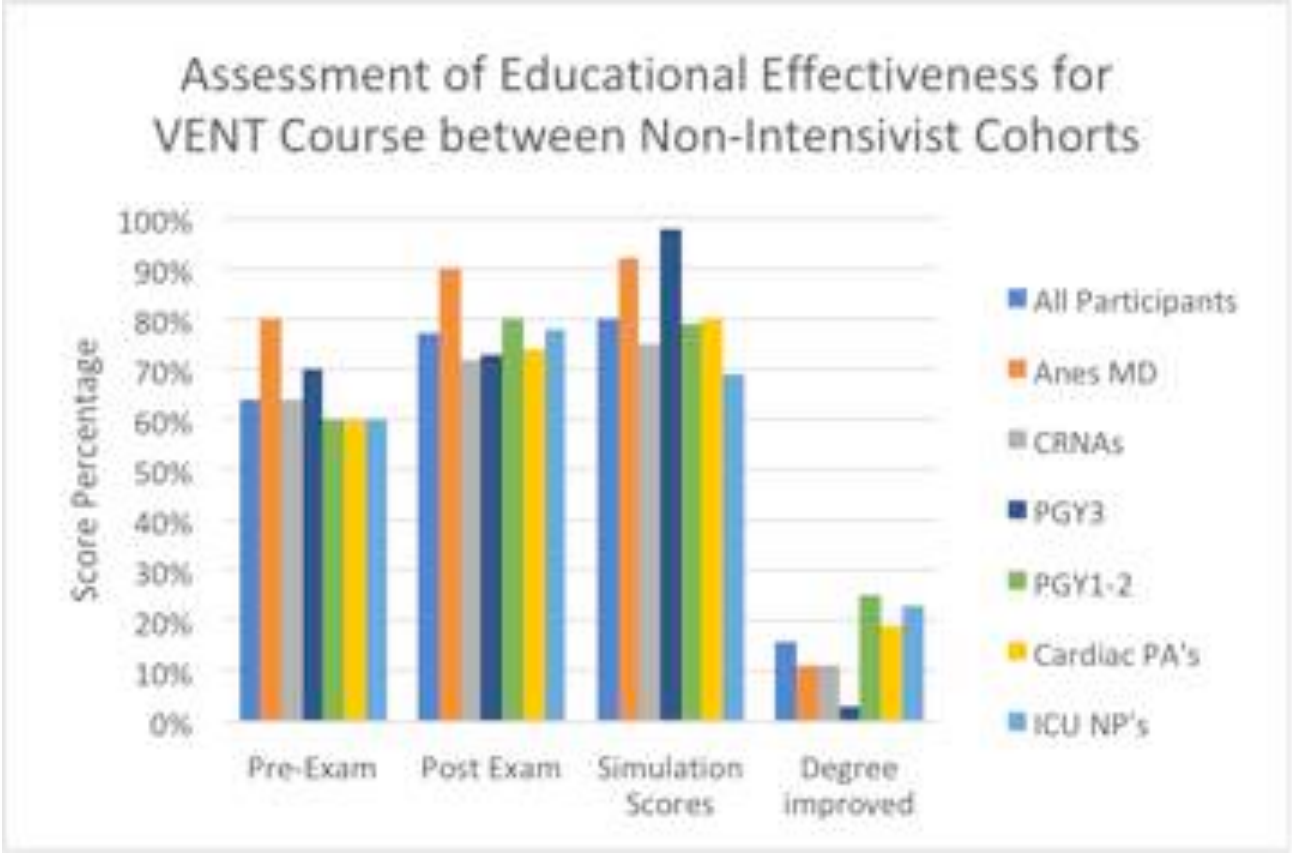
Results: Of thirty participants, twenty-six completed the study and were included in the analysis. (Fig 1) Outcome #1: Feasibility The pilot study revealed that advanced mechanical ventilation scenarios, including breath stacking and/or Auto-PEEP, were difficult to reliably reproduce with the QuickLung® simulator but was reliably reproduced with the IngMar ASL 5000™ lung simulator. Sixty-five percent of participants reported completing the video lecture in first sitting and most (92%) completed the entire video. All participants completed the live simulation scenario within one week of viewing the video and within 4 +/- 3 days from completion of the Pre-Test. On average, the Post-Test and Level 1-2 survey were completed 3 to 5 (+/- 7) days from the date of simulation performance. Outcome #2: Educational Effectiveness Despite the learners' difference in experience managing ventilators, all cohorts scored similarly on the post-test (76-78%). (Fig 2) Pre- to post-test scores improved (16%) in all cohorts. First and second-year residents improved the most (26 +/- 17%), followed by ICU Nurse Practitioners (23 +/- 17%). (Fig 3) Outcome #3: Clinical Relevance and Appropriateness All participants found the course relevant to their level of clinical training. Most participants found the video lecture (91%) and simulation scenario (100%) engaging. Although all participants believed they could apply the techniques and principles to their clinical practice, only 26% of participants strongly agreed they fully understood the materials and techniques after completing the entire course. Overall, 91% of participants believed that the training would enhance their ability to perform their clinical duties. (Fig 4)

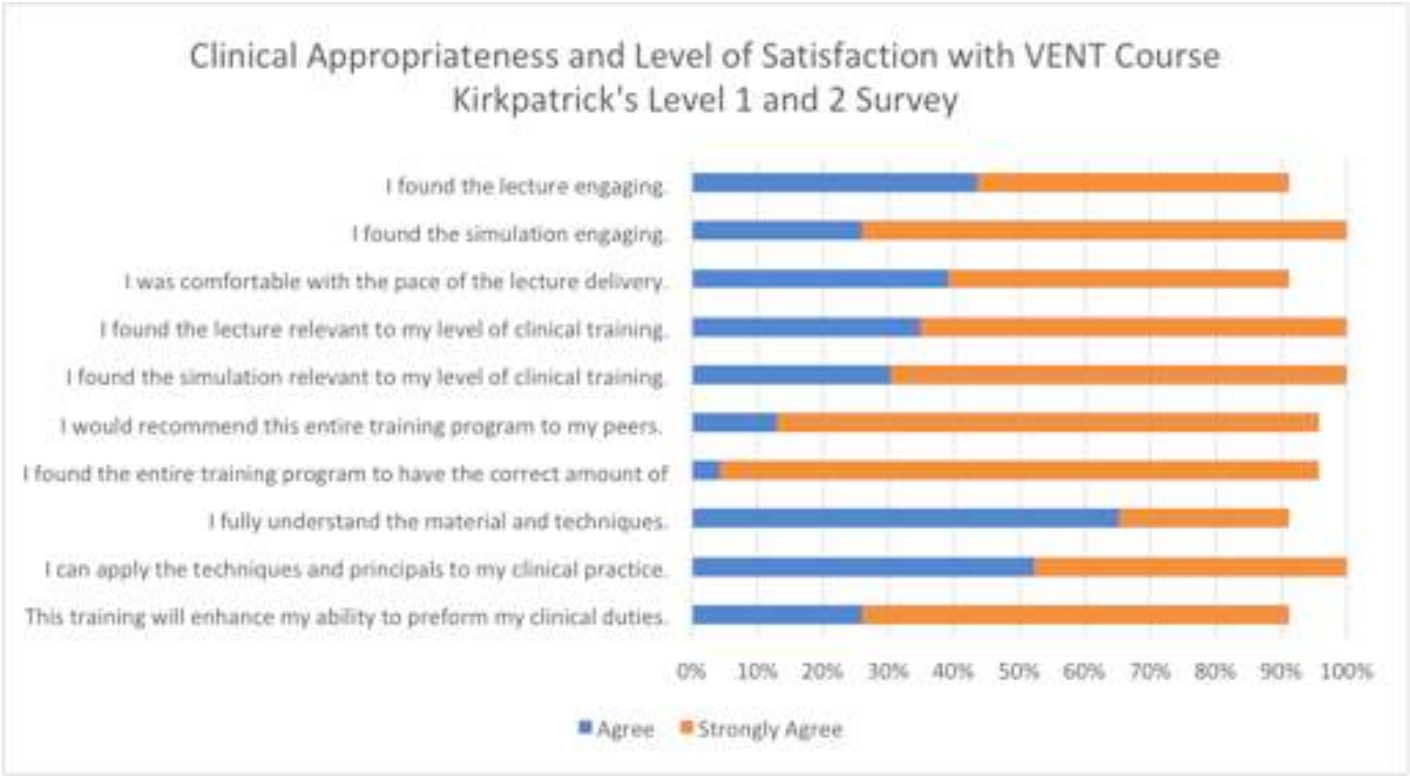
Conclusion: VENT course pilot data supports that remote asynchronous standardized video education paired with face-to-face high-fidelity simulation is feasible, educationally effective, and relevant. VENT is useful just-in-time training for a wide range of Non-

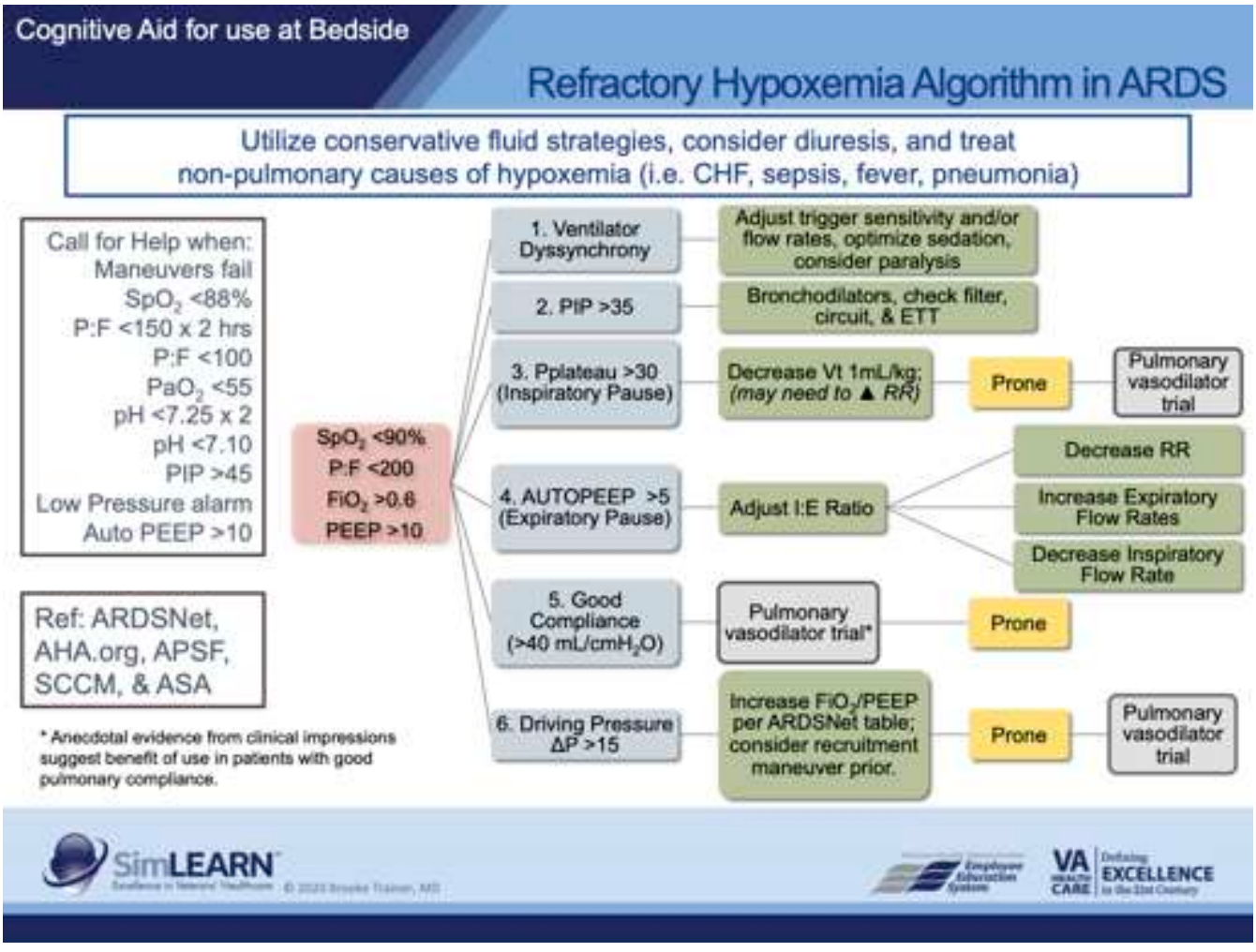
Intensivist healthcare providers prior to entrance into critical care environments. Even the most experienced providers find this program useful in reviewing evidence-based best practices for managing complex and challenging concepts associated with mechanical ventilation of patients with ARDS. Though educationally effective, VENT learners reported not fully grasping some concepts and post-tests revealed persistent knowledge gaps. Therefore, authors strongly recommend ICU Physician supervision of all VENT-trained Non-Intensivists.

References: 1. Critical Care 2020;24(1):516. 2. JAMA 2012; 307(23):2526-33. 3. Intensive Care Med 2016;42(5):699-711. 4. Intensive Care Medicine 2020; 46(7):1303-25. 5.Simul Healthcare 2017; 12(6):349-55. 6. Evaluating Training Courses: The Four Levels. 2nd Ed. San Francisco: Berrett-Koehler Publishers; 1998.


Educational Effectiveness of VENT Course between Varying Experience Levels
Very Experienced (> 20 Vents/yr)
Moderately Experienced (5-20 Vents/yr)
Minimally Experienced (<5 vents/yr)
66
62
56
76
78
76
83
78
75
13
21
26
Pre-Exam Score
Post-Exam Score
Simulation Skills
Degree of improvement from Pre to Post


Assessment of Educational Effectiveness for VENT Course between Non-Intensivist Cohorts
Score Percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Pre-Exam
Post Exam
Simulation Scores
Degree improved
All Participants
Anes MD
CRNAs
PGY3
PGY1-2
Cardiac PA's
ICU NP's


Clinical Appropriateness and Level of Satisfaction with VENT Course
Kirkpatrick's Level 1 and 2 Survey
I found the lecture engaging.
I found the simulation engaging.
I was comfortable with the pace of the lecture delivery.
I found the lecture relevant to my level of clinical training.
I found the simulation relevant to my level of clinical training.
I would recommend this entire training program to my peers.
I found the entire training program to have the correct amount of
I fully understand the material and techniques.
I can apply the techniques and principals to my clinical practice.
This training will enhance my ability to preform my clinical duties.
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Agree
Strongly Agree


Cognitive Aid for use at Bedside
Refractory Hypoxemia Algorithm in ARDS
Utilize conservative fluid strategies, consider diuresis, and treat non-pulmonary causes of hypoxemia (i.e. CHF, sepsis, fever, pneumonia)
Call for Help when:
Maneuvers fail
SpO2 <88%
P:F <150 x 2 hrs
P:F <100
PaO2 <55
pH <7.25 x 2
pH <7.10
PIP >45
Low Pressure alarm
Auto PEEP >10
Ref: ARDSNet, AHA.org, APSF, SCCM, & ASA
* Anecdotal evidence from clinical impressions suggest benefit of use in patients with good pulmonary compliance.
SpO2 <90%
P:F <200
FiO2 >0.8
PEEP >10
1. Ventilator Dyssynchrony
Adjust trigger sensitivity and/or flow rates, optimize sedation, consider paralysis
2. PIP >35
Bronchodilators, check filter, circuit, & ETT
3. Pplateau >30 (Inspiratory Pause)
Decrease Vt 1mL/kg; (may need to ▲ RR)
Prone
Pulmonary vasodilator trial
4. AUTOPEEP >5 (Expiratory Pause)
Adjust I:E Ratio
Decrease RR
Increase Expiratory Flow Rates
Decrease Inspiratory Flow Rate
5. Good Compliance (>40 mL/cmH2O)
Pulmonary vasodilator trial*
Prone
6. Driving Pressure ΔP >15
Increase FiO2/PEEP per ARDSNet table; consider recruitment maneuver prior.
Prone
Pulmonary vasodilator trial
SimLEARN
VA HEALTH CARE
EXCELLENCE

Critical Care - 9 The Neuroprotective Effects Of Metformin: Insights From Rodent Cardiac Arrest And In Vitro Ischemia-Reperfusion Of Neurons And Astrocytes

Santiago J Miyara[1], Muhammad Shoaib[2], Judith Aronsohn[3], Ernesto P Molmenti[4], Stacey Watt[5], Tai Yin[6], Linda Shore-Lesserson[3], Ata M Kaynar[7], Lance B Becker[6], Rishabh C Choudhary[6]

[1]Elmezzi Graduate School of Molecular Medicine / Feinstein Institutes for Medical Research, Manhasset, NY, [2]Feinstein Institutes for Medical Research / Donald and Barbara Zucker School of Medicine, Manhasset, NY, [3]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell / Department of Anesthesiology, Manhasset, NY, [4]North Shore University Hospital / Department of Surgery, Manhasset, NY, [5]University at Buffalo, Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, [6]Feinstein Institutes for Medical Research / Department of Emergency Medicine, Manhasset, NY, [7]U. of Pittsburgh / Departments of Critical Care Medicine and Anesthesiology & Perioperative Medicine, Pittsburgh, PA

Introduction: Brain damage due to ischemia-reperfusion injury (IRI) is an important challenge in post cardiac arrest syndrome (PCAS). Metformin is a widely available drug with numerous properties beyond its role in insulin resistance, including purported benefits in cardio and neuroprotection. Metformin's mechanisms of action are still under investigation, however, compelling evidence has shown the plurality and diversity of these mechanisms, which include modulation of oxidative stress and cell death in a cell-phenotype dependent fashion. Herein, we studied the effects of metformin on a rodent model of cardiopulmonary arrest. Furthermore, we explored the effects of metformin in vitro on single-cultures of astrocytes and neurons.

Methods: Adult male Sprague–Dawley rats experienced 10 min asphyxial cardiac arrest (CA) followed by resuscitation and received intravenously either metformin (100 mg/Kg in saline; n=16), or vehicle (saline; n=16) immediately following return of spontaneous circulation (ROSC). Survival and modified neurological deficit scores were monitored until 72 h post-ROSC with brains harvested from the surviving rats for histological evaluation. Brain protein carbonyl concentration was determined in both groups as a surrogate marker of reactive oxygen species (ROS) production. Nissl's staining was performed on the hippocampus CA1 region and dentate gyrus to determine neuronal morphology in both groups. Cell viability assay (WST-8) was assessed after 6 h of oxygen-glucose deprivation (OGD) and 20 h of reperfusion in single-cultures of neurons (mouse cell line HT-22) and astrocytes (mouse cell line C8-D1A).

Results: In the rodent model of CA, metformin treatment demonstrated an improved survival at 72 h from 43.8% to 68.8% (p= 0.0692; Kaplan-Meier Analysis with Gehan-Breslow-Wilcoxon test) (Fig.1). Metformin also significantly improved the neurological status at 72 h assessed by modified neurological deficit score when compared with vehicle (p= 0.0103) (Fig. 2). Metformin preserved neuron body integrity in both hippocampal CA1 and dentate gyrus regions observed by Nissl's staining, when compared with the noticeable neuronal body degeneration in the vehicle group (Fig. 3). Metformin treatment was associated with significantly lower protein carbonyl concentration, revealing significantly lower ROS production versus vehicle group (p= 0.0152). CA resulted in increased ROS production versus sham, determined by protein carbonyl concentration (p= 0.0012). Metformin significantly improved the cell viability of HT-22 neurons after 6 h of OGD and 20 h of reperfusion in a dose dependent manner [10 umol Metformin (p= 0.0425); 50 umol Metformin (p= 0.0336)] (Fig. 5A), but without significant impact on C8-D1A astrocytes (Fig. 5B).

Conclusion: Our results suggest that metformin improves survival and cell viability outcomes in both in vivo and in vitro models, respectively. Metformin treatment demonstrated increased neurological function and improved brain-cytologic morphology as well as decreased ROS production in our rodent CA model. Furthermore, metformin improved cell viability in single-cultures of HT-22 neurons, with no effect on C8-D1A astrocytes, after OGD and reperfusion, which was observed in a dose dependent fashion. Overall,

albeit at a very high dose, metformin could be a potential therapeutic intervention for improving survival and preventing neuronal death after cardiac arrest.

References: Wang, Y.W., He, S.J., Feng, X., Cheng, J., Luo, Y.T., Tian, L. and Huang, Q., 2017. Metformin: a review of its potential indications. Drug design, development and therapy, 11, p.2421. Zhu, J., Liu, K., Huang, K., Gu, Y., Hu, Y., Pan, S. and Ji, Z., 2018. Metformin improves neurologic outcome via amp-activated protein kinase–mediated autophagy activation in a rat model of cardiac arrest and resuscitation. Journal of the American Heart Association, 7(12), p.e008389. Yuan, R., Wang, Y., Li, Q., Zhen, F., Li, X., Lai, Q., Hu, P., Wang, X., Zhu, Y., Fan, H. and Yao, R., 2019. Metformin reduces neuronal damage and promotes neuroblast proliferation and differentiation in a cerebral ischemia/reperfusion rat model. Neuroreport, 30(3), pp.232-240.

Fig. 1

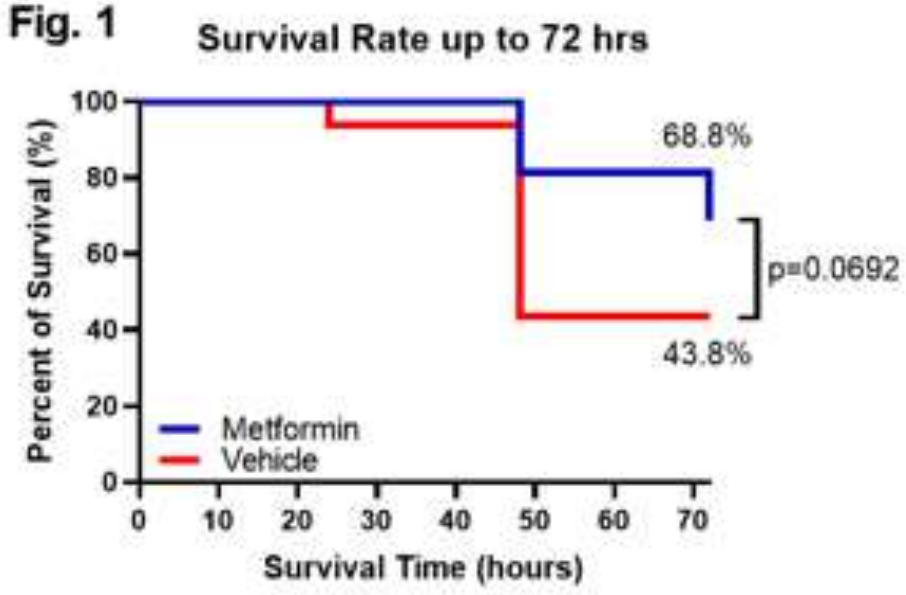


Fig. 2

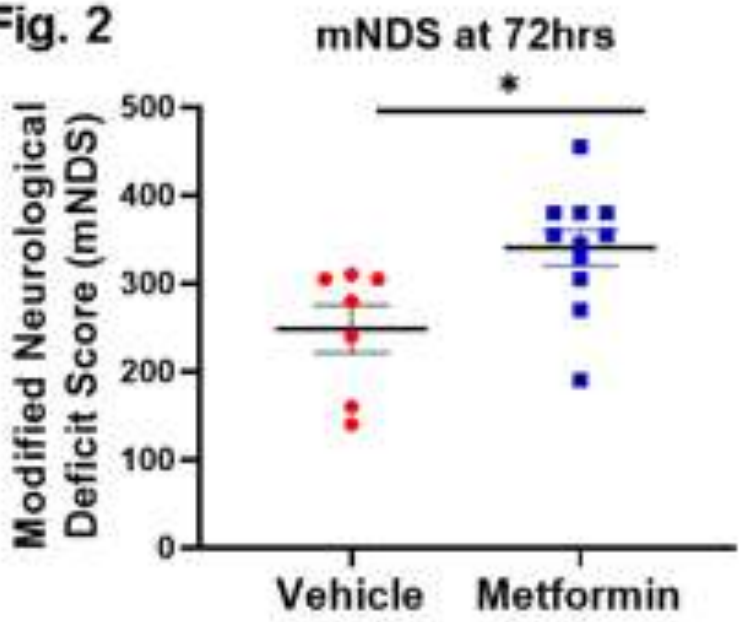

mNDS at 72hrs
*
Modified Neurological Deficit Score (mNDS)
500
400
300
200
100
0
Vehicle
Metformin

Fig. 3

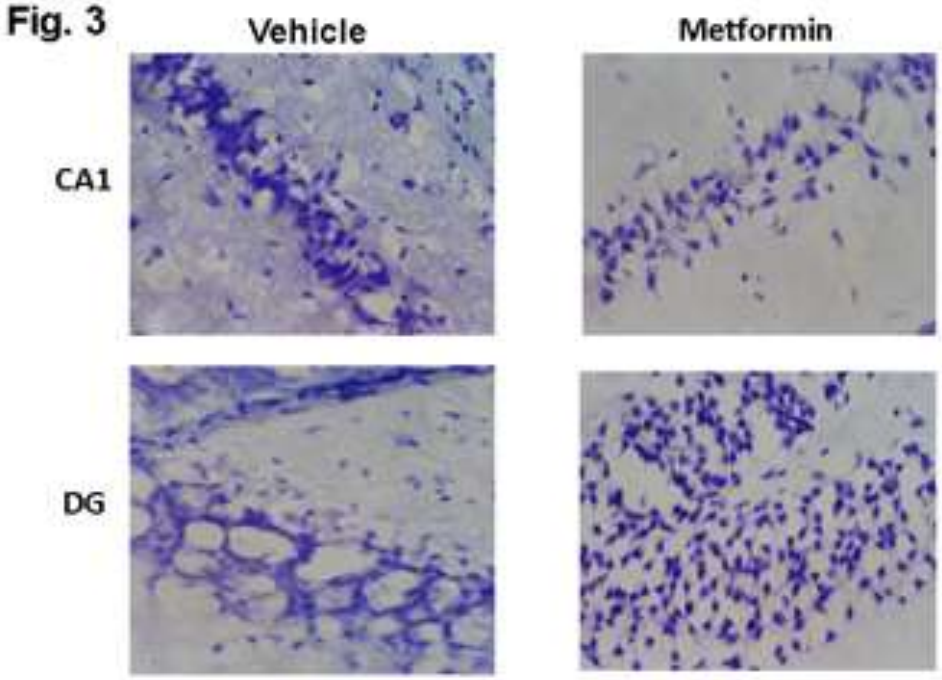

Vehicle
Metformin
CA1
DG

Fig. 4

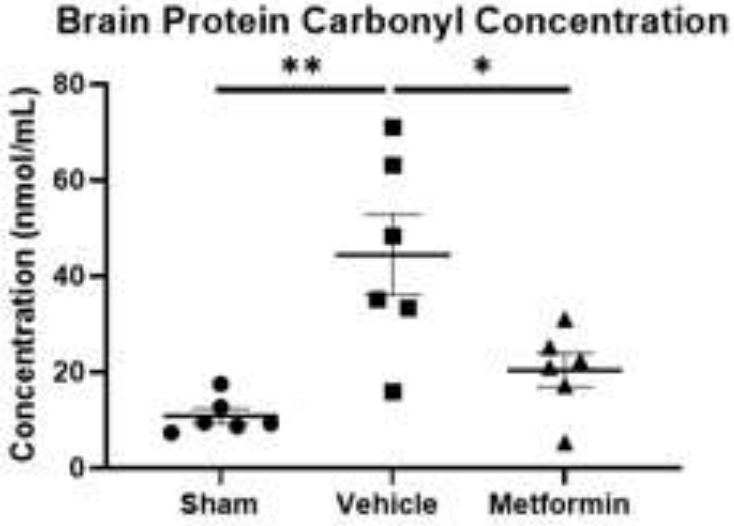


Fig. 5A

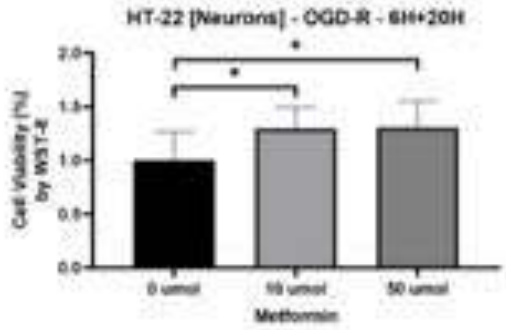
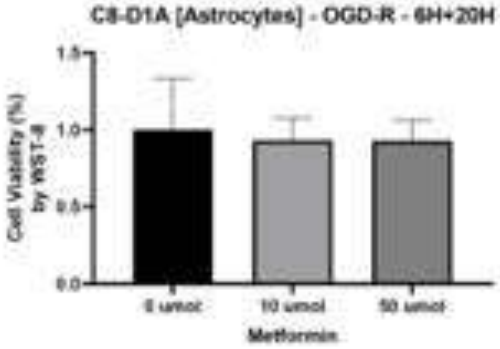


Fig. 5B



Critical Care - 10 Clinical Course of Critically Ill COVID-19 Patients with Tube Thoracostomy

Nicholas Rizer[1], Blake Mergler[1], Benjamin Smood[1], Alexandra Sperry[1], Federico Sertic[1], Andrew Acker[1], Christian Bermudez[1], Jacob Gutsche[1], Asad A Usman[1]

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Introduction: COVID-19 can cause acute respiratory failure requiring admission to the intensive care unit (ICU), mechanical ventilation, and potential ventilator associated complications. Notable among these, pneumothorax has been described in several reports of COVID-19 patients, with one case series from China reporting an incidence of 5.4% shortly after intubation. (1–4) Pneumothorax is known to cause significant morbidity and mortality, even necessitating tube thoracostomy. While tube thoracostomy has been reported in COVID-19 patients with pneumothoraces, there is limited information on the incidence and clinical course of critically ill COVID-19 patients with pneumothoraces requiring tube thoracostomy. We present here a case series of 4 critically ill COVID-19 patients necessitating 8 chest tubes.

Methods: We described a series of patients admitted to an intensive care unit at our center requiring tube thoracostomy for pneumothorax. Our center's electronic medical record was queried for all laboratory confirmed COVID-19 patients with tube thoracostomies admitted to the Intensive Care Unit (ICU) between March 9th, 2020 to April 19th, 2020. Data was manually extracted from the electronic medical record by a trained team of physicians and researchers using a protocolized Case Record Form developed by the COVID-19 Critical Care Consortium and International Severe Acute Respiratory and Emerging Infection Consortium (CCCC/ISARIC). (5) Additional information on tube thoracostomy technique, complications, and mechanical ventilation parameters prior to the procedure were obtained. Radiographic and clinical notes were reviewed for improvement of pneumothorax. Data collection was stopped on August 10th, 2020.

Results: We identified 69 patients admitted to an intensive care unit with COVID-19 from March 9th to April 19th 2020, with 8 chest tubes being placed between 4 patients (5.8%). Demographic information and clinical signs and symptoms at presentation are shown in Table 1. There was a prolonged duration of chest tubes in our patients (range 3-24 days; interquartile range: 18-20 days). 3 patients (75%) developed their initial pneumothoraces after 23 days, and all of these patients went on to develop contralateral pneumothoraces (See Table 2). Furthermore, all patients that developed delayed bilateral pneumothoraces, expired in the ICU (See Table 3). Patient 2 likely had an underappreciated hydropneumothorax at time of his first tube thoracostomy and necessitated a subsequent ipsilateral chest tube. 1 patient (25%) developed a ventilator associated pneumonia following chest tube placement. No patients (0%) developed significant bleeding or hemothorax following chest tube placement despite all patients being on therapeutic anti-coagulation.

Conclusion: Tube thoracostomy for pneumothorax appears to be a common and safe procedure in critically ill COVID-19 patients. The development of bilateral pneumothoraces after prolonged ICU admission appears to be a negative prognostic sign. This case series suggests that there may be a poor healing phenotype among critically ill COVID-19 patients with pneumothoraces and could inform management and prognosis in these patients.

References: Can Med Assoc J. 2020;192(19):E510. Korean J Radiol. 2020;21(5):541-544. J Travel Med. 2020;27(5). Br J Anaesth. 2020;125(1):e28-e37. BMJ. 2020;369:m1985.

Patient	1	2	3	4
Age	44	73	52	59
Sex	F	M	M	F
Race	White	White	White	Black
Body Mass Index (kg/m^2)	51.62	33.82	25.87	16.24
Admission Temperature (°F)	98.2	102.6	102	98.3
Admission Heart Rate (min^{-1})	155	125	87	144
Admission Blood Pressure (mmHg)	180/108	199/131	112/74	222/139
Admission Respiratory Rate (min^{-1})	16	39	30	42
Admission Oxygen Saturation	92%	64%	55%	85%
Initial Oxygen Therapy	Room Air	Room Air	Room Air	Room Air
Comorbidities	Hypertension	None	Hypertension, coronary artery disease, asthma, Hodgkin's Lymphoma (remote)	Scleroderma, chronic kidney disease, autoimmune hepatitis, interstitial lung disease
Presenting Symptoms	Fever, dyspnea, chest pain, fatigue, diarrhea, nausea, vomiting	Non-productive cough, dyspnea, fatigue, altered mental status	Non-productive cough, dyspnea, fatigue, anorexia, abdominal pain	Cough, dyspnea

Table 1. Demographics and Clinical Signs and Symptoms on Presentation.

Critical Care - 11 Awake Prone Position in Acute Hypoxemic Respiratory Failure secondary to COVID-19 Pneumonia: A Preliminary Systematic Review and Meta-Analysis

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Introduction: The use of prone position (PP) in moderate to severe ARDS requiring invasive mechanical ventilation improves oxygenation and reduces mortality. More recently, during the COVID-19 pandemic, use of high flow nasal cannula oxygen delivery has become commonplace with many experts recommending patients to self-prone. However, efficacy on awake PP is based on indirect evidence from mechanically ventilated patients, limited direct evidence and anecdotal observations. Whether PP results in reduced intubation rates, accelerated recovery, or a reduction in mortality remains largely unanswered. We conduct a systematic review and meta-analysis of the available evidence on the utility of awake PP in the management of the hypoxic non-intubated patient with COVID-19 pneumonia. Studying PP in the awake patient is complex, and it is imperative to elucidate how to effectively measure and monitor duration, continuity and positioning in order to elucidate meaningful clinical outcomes such as changes in intubation rates or mortality.

Methods: We searched databases including MEDLINE and Cochrane Library from December 1, 2019 to January 5, 2021 for studies describing the use of PP in the management acute hypoxemic respiratory failure from COVID-19 pneumonia. We selected for full review comparative studies, feasibility studies, and qualitative studies in hospitalized patients with COVID-19 requiring supplemental oxygenation who underwent awake self-prone positioning and abstracted oxygenation markers, intubation rates, ICU and hospital length of stay, mortality and adverse events..

Results: We abstracted data from 39 studies and 1,353 hospitalized adult patients with COVID-19 PNA who underwent non-invasive oxygen therapy managed with awake prone positioning. Observational data accounted for 95% (37/39) of studies and ubiquitously demonstrated improvement in oxygenation markers during PP with significant variability in sustained effects once re-supinated. There was limited non-comparative data on patient centered outcomes. 378 patients from 7/39 studies had a mean intubation rate of 23%. There was significant heterogeneity as to how standardized PP protocols were followed with a mean duration and overall continuity of PP being significantly shorter than in the reported literature pertaining to mechanically ventilated patients (16hrs). Only one randomized study was found with low adherence to prone position protocol being a major barrier to conclusive findings. We found an additional 29 ongoing clinical trials with only 5 of those being observational studies. The interventional arms of the remaining studies do not report or appear to lack a reliable way to monitor compliance to PP protocols. There was significant variability regarding initiation time, duration, continuity and type of prone position recorded.

Conclusion: In hospitalized non-intubated patients with hypoxemic respiratory failure secondary to COVID 19, prone position appears to temporarily improve oxygenation markers with low adverse events. Whether it results in more durable and meaningful outcomes such as a reduction in length of hospital stay, intubation rates and mortality remains unanswered. Fortunately, there is an abundance of ongoing interventional trials, some of which are intending to report comparative outcomes. However, we hypothesize that the heterogeneity in how prone position is being carried out among different groups and the lack of reliable monitoring to assess adherence to prone protocols may make it difficult to provide evidence-based recommendations on the role of awake self-prone position in respiratory failure.

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Critical Care - 12 Palliative Care Delivery Amongst Critically Ill Patients with COVID-19

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[1]Duke University School of Medicine, Durham, NC, [2]Duke University Hospital, Durham, United States of America, [3]Johns Hopkins School of Medicine, Baltimore, MD, [4]University of California San Francisco, San Francisco, United States of America, [5]Duke University Medical Center, Durham, NC, [6]Duke University, Durham, NC, [7]Duke University, Durham, United States of America

Introduction: COVID-19 has disproportionately affected older, comorbid adults with crucial implications on end-of-life decisions and necessity of Palliative Care delivery. Limited access to staff and services1 have impacted the quality of these two. COVID-19 has necessitated notable palliative care needs for symptom managements such as long-term dyspnea, isolation and the fear of dying alone2, advanced care planning, and prognostication. The benefits of palliative care in critically ill patients have been well-described3. Utilization of PC consultation in ICU patients with COVID-10 has been reported ~40%4, 5. However, these reports of PC have been single center and limited by small patient samples and local practices and/or capabilities. To Understand the variation of PC use amongst critically ill COVID-19 patients, we studied the use of palliative care in a large nationally representative dataset.

Methods: We analyzed data from the Premier Healthcare Database (Premier Inc., Charlotte NC), which is a hospital-based dataset of over 1000 US hospitals and nearly 10 million patients. Adults aged 18 years and older with an International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) were included. Only patients with a billing code for an ICU room for at least one day were included. A patient's first hospitalization for COVID-19 was included. Among this cohort, we examined the utilization of palliative care during the hospital encounter, using ICD-10 code Z51.5. Among patients exposed and unexposed to inpatient palliative care, we described demographic and clinical characteristics, facility characteristics, and the use of life-sustaining therapies such as cardiopulmonary resuscitation (CPR), hemodialysis, mechanical ventilation, and tracheostomies that are defined using ICD-10 codes and hospital charges.

Results: Among 14,745 ICU patients with a diagnosis of COVID-19, 3619 patients (24.5%) received a PC consultation. Of those who received a PC encounter, only 15.7% were 85 years or older. The majority of patients receiving a PC encounter were between 65-74 years old. Among patients exposed to PC utilization during hospital encounter, patients were predominantly male (57.8%), white (51.3%), non-Hispanic (59.3%), and those using Medicare (70.1%). PC encounters were most frequent in urban and teaching hospitals. In general, patients had a higher median vanWalraven scoare at baseline in the PC group (9 IQR 5-15) compared to the non-PC group (5 IQR 0-11). Life-sustaining therapies were higher in patients who had a PC encounter at some point in their hospitalization. Mortality was higher in the PC group compared to the non-PC group (76% vs. 24.3%) and ICU length of stay was longer (7 days [IQR 3, 14] vs. 5 days [IQR 2, 10]). Overall hospital length of stay was similar.

Conclusion: There is wide variation in the use of PC amongst COVID-19 patients admitted to the ICU. More than half of ICU patients older than 85 years did not have a coded PC encounter despite a recently published study showing a substantially higher odds of dying in this age group. Patients who underwent PC, had more comorbidities at baseline and had a much a higher in-hospital mortality. However, the majority of patients in the ICU with COVID-19 who had respiratory failure requiring mechanical ventilation (68.9%) and with renal and respiratory failure requiring dialysis and mechanical ventilation (64.7%) did not have a palliative care encounter code. This suggests an important and possibly large unmet need of palliative care in critically ill patients with COVID-19. Limitations include data-base specific limitations, including the inability to review individual medical records given the deidentified nature of the dataset, possibly missing data and the lack of granular level (e.g. laboratory, radiologic) data.

While charge/billing codes may not fully or accurately code for patient data compared to ICD codes, our previous work demonstrated improved data capture when using charge codes in addition to ICD codes. It is also possible that many hospitalized patients with COVID-19 are receiving PC consultations early in their hospital course and may not be transferred to the ICU based on advanced care plans. Also, while the ICD code for palliative care typically refers to specialized PC consultations, our results may not capture the majority of primary palliative care delivery (e.g. delivered by the primary ICU team).

References: 1.Feder S, Smith D, Griffin H, et al. 'Why Couldn't I Go in To See Him?' Bereaved Families' Perceptions of End-of-Life Communication During COVID-19. J Am Geriatr Soc. Dec 2020;doi:10.1111/jgs.16993 2.Wakam GK, Montgomery JR, Biesterveld BE, Brown CS. Not Dying Alone - Modern Compassionate Care in the Covid-19 Pandemic. N Engl J Med. Jun 2020;382(24):e88. doi:10.1056/NEJMp2007781 3.Aslakson RA, Curtis JR, Nelson JE. The changing role of palliative care in the ICU. Crit Care Med. Nov 2014;42(11):2418-28. doi:10.1097/CCM.0000000000000573 4.Sheehan J, Ho KS, Poon J, Sarosky K, Fung JY. Palliative care in critically ill COVID-19 patients: the early New York City experience. BMJ Support Palliat Care. Dec 2020;doi:10.1136/bmjspcare-2020-002677 5.Haydar A, Lo KB, Goyal A, et al. Palliative Care Utilization Among Patients With COVID-19 in an Underserved Population: A Single-Center Retrospective Study. J Pain Symptom Manage. 08 2020;60(2):e18-e21. doi:10.1016/j.jpainsymman.2020

Figure 1- Percentage of Covid-19 Patients with PC Consult by Hospital

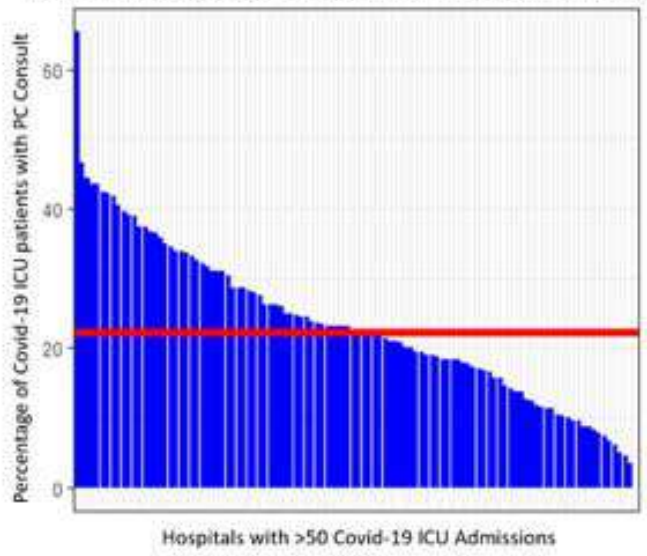

Table 1: Baseline Patient Characteristics and Presence or Absence of Palliative Care Consult

	Total ICU Patients (n= 14,745)	PC Consult (n= 3,619)	No PC Consult (n= 11,126)
Age Group			
18-64	7,377 (50.0%)	1,001 (27.7%)	6,376 (57.3%)
65-74	3,691 (25.0%)	1,060 (29.3%)	2,631 (23.6%)
75-84	2,513 (17.0%)	991 (27.4%)	1,522 (13.7%)
85+	1,164 (7.9%)	567 (15.7%)	597 (5.4%)
Gender			
Male	8,646 (58.6%)	2,092 (57.8%)	6,554 (58.9%)
Female	6,079 (41.2%)	1,525 (42.1%)	4,554 (40.9%)
Unknown	------	2 (< 1%)	18 (< 1%)
Race			
Asian	511 (3.5%)	119 (3.2%)	392 (3.5%)
Black	3,421 (23.2%)	768 (21.2%)	2,653 (23.8%)
Other	3,043 (20.6%)	688 (19.0%)	2,355 (21.2%)
Unknown	862 (5.9%)	189 (5.2%)	673 (6.0%)
White	6,908 (46.9%)	1,855 (51.3%)	5,053 (45.4%)
Ethnicity			
Hispanic	2,906 (19.7%)	528 (14.6%)	2,378 (21.4%)
Non-Hispanic	8,409 (57.0%)	2,147 (59.3%)	6,262 (56.3%)
Unknown	3,430 (23.3%)	944 (26.1%)	2,486 (22.3%)
Insurance			
Managed Care	2,407 (16.3%)	294 (8.1%)	2,113 (19.0%)
Medicaid	2,572 (17.4%)	461 (12.7%)	2,111 (19.0%)
Medicare	7,477 (50.7%)	2,537 (70.1%)	4,940 (44.4%)
Other	2,289 (15.5%)	327 (9.0%)	1,962 (17.6%)
VW Score at Baseline	6 [1, 11]	9 [5, 15]	5 [0, 11]

Table 2: Presence or Absence of Palliative Care Consult by Hospital Category

	Total ICU Patients (n= 14,745)	PC Consult (n= 3,619)	No PC Consult (n= 11,126)
Rural	1,415 (9.6%)	270 (7.5%)	1,145 (10.3%)
Urban	13,330 (90.4%)	3,349 (92.5%)	9,981 (89.7%)
Teaching	8,427 (57.2%)	2,260 (62.4%)	6,167 (55.4%)
Non-teaching	6,318 (42.9%)	1,359 (37.6%)	4,959 (44.6%)

Data presented as n (%)

Table 3: Presence of Absence of Palliative Care Consult by Method of Life-Sustaining Treatment

	Total ICU Patients (n= 14,745)	PC Consult (n= 3,619)	No PC Consult (n= 11,126)
CPR	1,136 (7.7%)	300 (8.3%)	836 (7.5%)
Hemodialysis	2,334 (15.8%)	749 (20.7%)	1,585 (14.2%)
Mechanical Ventilation	8,358 (56.7%)	2,599 (71.8%)	5,759 (51.8%)
Hemodialysis AND Mechanical Ventilation	1,945 (13.2%)	686 (19%)	1,259 (11.3%)
Tracheostomy	647 (4.4%)	184 (5.1%)	463 (4.2%)

Data presented as n (%)

Table 4: Presence or Absence of Palliative Care Consult by Outcome

	Total ICU Patients (n= 14,745)	PC Consult (n= 3,619)	No PC Consult (n= 11,126)
Hospital LOS	11 [6, 19]	11 [6, 20]	11 [6, 19]
ICU LOS	5 [2, 11]	7 [3, 14]	5 [2, 10]
In-Hospital Mortality	5,449 (37.0%)	2,749 (76.0%)	2,700 (24.3%)
Discharge to Hospice	Missing data?		

Data for Hospital and ICU LOS are presented as median, Q1, and Q3 whereas mortality and discharge to hospital data are presented as n (%)

Critical Care - 13 Effects of Blood Product Administration on Oxygen Dissociation Physiology of Patients Undergoing Cardiac Surgery

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Introduction: Despite advances in blood conservation, cardiac surgery remains as one the primary consumers of blood products with estimates that 40-95% of cardiac surgery patients receive at least one transfusion; this accounts for 20-25% of all transfusions yearly. [1][2] Acute reduction in red cell mass has been historically treated aggressively via transfusions but concerns with cost, side effects, blood supply, and more recently lack of efficacy has trended towards a more restrictive practice. [3][4] To help elucidate the curious marginal benefit/deleterious effects of PRBC transfusion, we theorized that the reduced P50 value in PRBCs would negatively affect cardiac surgery patients' post-transfusion P50 value, reflecting impaired oxygen delivery to end-organ tissues. Although there are small data sets regarding global P50 changes in infants who have undergone transfusion [5] and trauma patients [6], this is the first study to our knowledge designed to examine global P50 changes in adult cardiac surgery patients.

Methods: This was an IRB-approved retrospective study that included 1595 patients that underwent cardiac surgery Duke University Hospital, received intraoperative PRBCs, and had a pulmonary artery catheter placed. Point of care P50 analyzers have a high cost burden. Fortunately, P50 has been able to be calculated off of single mixed venous blood sample with an equation originally derived by Hill and has been examined by via sensitivity analysis to determine the error between P02 10-100, with the minimum errors between P02 20-45. [6] The number of PRBC transfused intraoperatively was recorded and then a P50 value was calculated at 12 hours and 24 hours post operating room. We assumed all patients initial P50 value was 27mmHg.

Results: Of the 1595 patients initially included in our study, 477 had the mixed venous blood gas we parsed for to calculate P50 and were ultimately included. [Table 1] The average number and standard deviation of PRBC, FFP, PLT, and cryoprecipitate given was 1.10 (2.74), 1.19 (2.48), 1.82 (1.45) and 1.35 (1.36) respectively. The average and standard deviation of P50 at 12 hours was 26.16 (2.19) mmHg and 26.28 (2.07) mmHg at 24 hours. Univariate analysis for blood products relation to P50 at 12 hours [n=256) and 24 hours (n=123) was performed. [Table 2] Although no statistical significance was found at 12 hours, the relationship between PRBC administration and PRBC was significant at 24 hours: -0.14 per PRBC given (sd=0.05) with a p-value of 0.0056.

Conclusion: Assuming that the initial P50 value of patients was 27mmHg initially, these results support our initial hypothesis that PRBC transfusion lowered the P50 value of postoperative cardiac surgery patients at the 24-hour measurement by -0.14mmHg per units of PRBC given. For platelets and cryoprecipitate, the effect was also significant with a larger effect size: -0.24 (sd=0.103) and -0.26 (sd=0.112) respectively; which may be a function that these products are usually only given after multiple PRBC transfusions. Further work to examine clinical outcomes with regards to P50 is needed, particularly with therapeutics on the horizon. [7]

References: 1. Optimal blood transfusion practice in cardiac surgery. J Cardiothorac Vasc Anesth 2018. 2. Blood transfusions in cardiac surgery: indications, risks, and conservation strategies. Ann Thorac Surg. 2014 3. TRICS Investigators and Perioperative Anesthesia Clinical Trials Group. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. N Engl J Med. 2017 4. Effects of red-cell storage duration on patients undergoing cardiac surgery. N Engl J Med. 2015 5. The effect of blood transfusion on the hemoglobin oxygen dissociation curve of very early preterm infants during the first week of life. Seminars in perinatology. 2002 6. A simple method to calculate P50 from a single blood sample. Int. J. Clin. Mon. Comp. 14, 109–111. 1997 7. Targeted O2 delivery by

low-P50 hemoglobin: a new basis for O2 therapeutics.
Am J Physiol Heart Circ Physiol. 2003

Table 1: Patient demographics, baseline characteristics, intra-op and post-op data [mean (sd) or median [IQR]; N (%)]

	N = 427
Demographics	
Age	59.98 (13.98)
Gender (M)	324 (67.9%)
BMI, n = 476	29.85 (6.95)
Race	
African American/Black	138 (28.8%)
White	306 (64.2%)
Asian	7 (1.5%)
American Indian/Alaskan Native	10 (2.1%)
Other	16 (3.4%)
Smoking status (Y)	38 (8.0%)
Baseline Characteristics	
ASA Status	
3	33 (6.9%)
4	428 (89.7%)
5	16 (3.4%)
Starting Hb, n = 450	12.00 (2.03)
Emergent (Y)	79 (15.7%)
Intra-op Data	
PRBC, units, n = 357	1.10 (2.74)
FFP, units, n = 357	1.19 (2.48)
Plt, units, n = 357	1.82 (1.45)
Cryo, units, n = 357	1.35 (1.36)
Post-op Data	
SvO2 - 12 hr, n = 338	66.84 (7.84)
SvO2 - 24 hr, n = 173	65.34 (2.07)
PO2 - 12 hr, n = 339	34.44 (4.99)
PO2 - 24 hr, n = 339	33.76 (5.07)
p50 - 12 hr, n = 338	28.16 (2.19)
p50 - 24 hr, n = 172	28.28 (2.07)
pH - 12 hr, n = 338	7.39 (0.05)
pH - 24 hr, n = 124	7.40 (0.05)
Hospital LoS, days	30.44 (26.40)
ICU LoS, hours	8.66 (2.22)

Table 2: Univariate model results

	12 Hr Model, n = 154		24 Hr Model, n = 121	
	Estimate	p-values	Estimate	p-values
PRBC	-0.04 (0.054)	0.4930	-0.14 (0.050)	0.0056
FFP	0.03 (0.055)	0.6470	-0.05 (0.062)	0.3450
Platelets	-0.01 (0.102)	0.8850	-0.24 (0.100)	0.0217
Cryoprecipitate	-0.03 (0.107)	0.7720	-0.26 (0.112)	0.0243

Critical Care - 14 Association of Initial Vasopressor Choice with Clinical and Functional Outcomes following Moderate-Severe Traumatic Brain Injury: a TRACK-TBI study

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Introduction: Early hypotension following moderate-severe traumatic brain injury is associated with increased mortality and worse long-term outcomes. Current guidelines support the use of intravenous vasopressors to maintain optimal blood pressure control and improve outcomes for patients; however, guidelines do not specify vasopressor type, resulting in variation in clinical practice. Existing studies comparing the utilization and efficacy of different vasopressors vary in their results. Therefore, we conducted a multicenter study to examine utilization patterns of different vasopressors in the management of early hypotension following TBI and their association with long-term clinical and functional outcomes.

Methods: In this retrospective cohort study of patients enrolled in the TRACK-TBI study, we examined adults with moderate-severe TBI (defined as Glasgow Coma Scale score <13) who were admitted to the ICU and received an intravenous vasopressor within 48 hours of admission. We excluded patients who received more than vasopressor in the first hour of admission (Figure 1). The primary exposure was initial vasopressor choice (phenylephrine versus norepinephrine) and the primary outcome was 6-month Glasgow Outcomes Scale Extended (GOSE) with secondary outcomes of length of hospital stay, length of ICU stay, in-hospital mortality, requirement of dialysis, and 6-month Disability Rating Scale (DRS). Descriptive statistics were used to examine the utilization patterns of initial vasopressors and demographic, clinical and facility characteristics of the cohort. Regression analysis was used to assess differences in outcome between norepinephrine and phenylephrine, with propensity-weighting to address selection bias due to both the non-random allocation of the treatment groups and subject drop-out.

Results: The final study sample included 157 patients, of whom 79 (50%) received norepinephrine and 66 (42%) received phenylephrine as their initial vasopressor (Table 1). 121 (77%) of patients in the study population were male, with a mean age of 43.1 years and arrival GCS of 5.0. Only 12 (8%) individuals received an initial vasopressor other than norepinephrine and phenylephrine. Of all subjects, 73 (54%) received a second vasopressor after at least one hour following administration of the first vasopressor, most commonly phenylephrine (Figure 2). Utilization of norepinephrine versus phenylephrine differed significantly only by clinical site; there was no association of initial vasopressor choice with demographic or clinical characteristics. For the 145 subjects with complete outcomes data, we found a mean (SD) 6-month GOSE of 3.4 and 3.8 for norepinephrine and phenylephrine, respectively. Choice of norepinephrine versus phenylephrine was not significantly associated with improved 6-month GOSE (weighted odds ratio 1.38, 95% CI 0.72-2.64, p=0.37) or any secondary outcome (Table 2).

Conclusion: Most patients with moderate-severe TBI commonly receive either phenylephrine or norepinephrine as first-line agents for hypotension following brain injury, with significant variability among hospitals. Initial choice of norepinephrine, compared to phenylephrine, was not associated with improved clinical or functional outcomes.

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adult patients with severe traumatic brain injury, does the use of norepinephrine for augmenting cerebral perfusion pressure improve neurological outcome? A systematic review. Injury. 2020;51(10):2129-2134.
Comparison of the cerebral effects of dopamine and norepinephrine in severely head-injured patients. Intensive Care Med. 2001;27(1):101-106.

Figure 1: Study population with inclusion and exclusion criteria

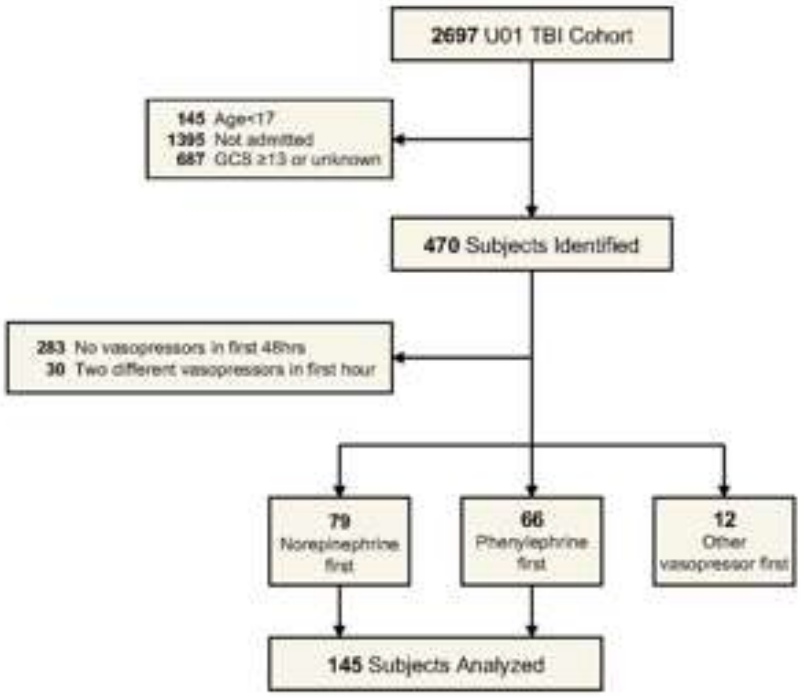
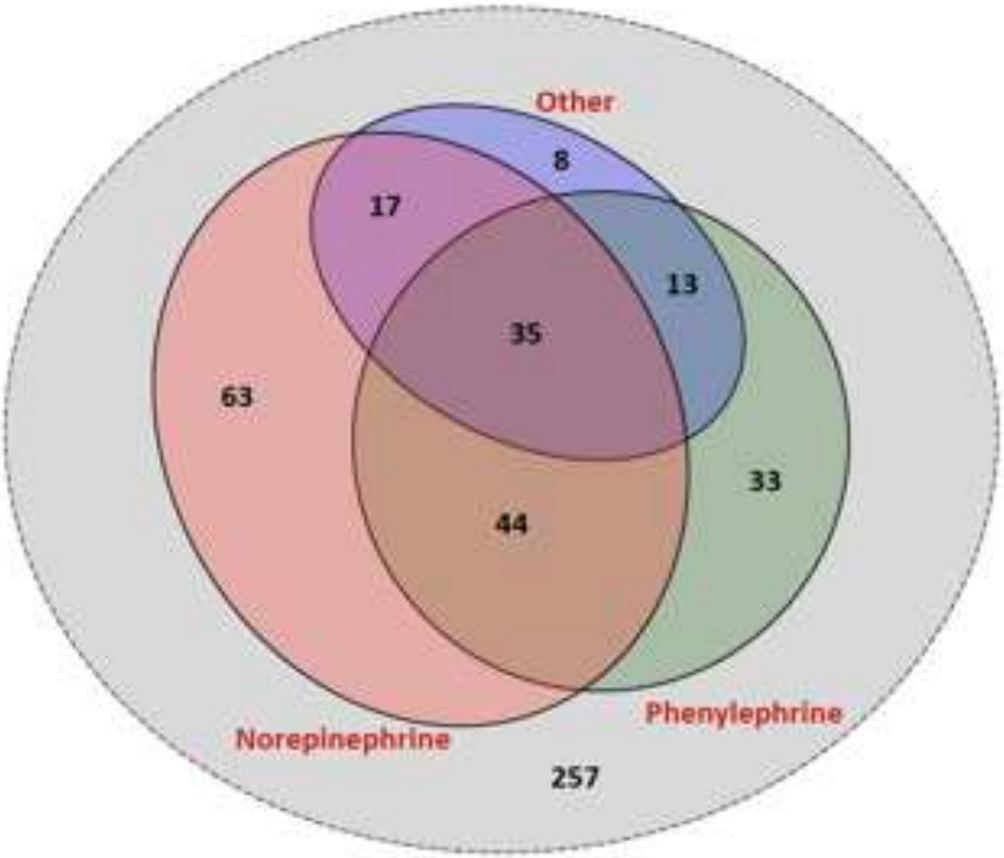


Figure 2: Multiple vasopressor utilization patterns



Vasopressor Use	N (%)
No Vasopressors	257 (55%)
Norepinephrine only	63 (13%)
Phenylephrine only	33 (7%)
Other only	8 (2%)
Norepineph. & Phenyleph.	44 (9%)
Norepinephrine & Other	17 (4%)
Phenylephrine & Other	13 (3%)
All three types	35 (7%)
Total Subjects	**470**

Area-Proportional
Venn Diagram

Table 1: Patient demographic, clinical, and facility characteristics

Variable		First IV Vasopressor		
	Total	Norepinephrine	Phenylephrine	Other
Subjects	**157**	**79 (50%)**	**66 (42%)**	**12 (8%)**
Had Second Vasopressor Type				
No	84 (46%)	54 (64%)	25 (30%)	5 (6%)
Yes	73 (54%)	25 (34%)	41 (56%)	7 (10%)
Mean (SD) hours	26.5 (38.9)	33.4 (43.9)	25.4 (38.3)	7.7 (8.3)
0-4 hours	26 (17%)	6 (23%)	16 (62%)	4 (15%)
4-24 hours	28 (18%)	11 (39%)	14 (50%)	3 (11%)
24+ hours	19 (12%)	8 (42%)	11 (58%)	0 (0%)
Site				
1	37 (24%)	30 (81%)	5 (14%)	2 (5%)
2	8 (5%)	3 (38%)	4 (50%)	1 (13%)
3	31 (20%)	7 (23%)	24 (77%)	0 (0%)
4	12 (8%)	11 (92%)	1 (8%)	0 (0%)
7	39 (25%)	18 (46%)	19 (49%)	2 (5%)
9	1 (1%)	0 (0%)	1 (100%)	0 (0%)
10	9 (6%)	5 (56%)	3 (33%)	1 (11%)
11	2 (1%)	1 (50%)	1 (50%)	0 (0%)
12	4 (3%)	1 (25%)	3 (75%)	0 (0%)
14	1 (1%)	0 (0%)	0 (0%)	1 (100%)
15	1 (1%)	0 (0%)	0 (0%)	1 (100%)
16	1 (1%)	0 (0%)	0 (0%)	1 (100%)
17	11 (7%)	3 (27%)	5 (45%)	3 (27%)
Age				
Mean (SD)	43.1 (17.3)	43.3 (17.8)	43.0 (17.1)	41.9 (15.5)
<20	9 (6%)	6 (67%)	3 (33%)	0 (0%)
20-29	38 (24%)	17 (45%)	17 (45%)	4 (11%)
30-39	29 (18%)	16 (55%)	12 (41%)	1 (3%)
40-49	26 (17%)	12 (46%)	10 (38%)	4 (15%)
50-59	27 (17%)	11 (41%)	14 (52%)	2 (7%)
60-69	13 (8%)	9 (69%)	4 (31%)	0 (0%)
70-79	13 (8%)	7 (54%)	5 (38%)	1 (8%)
80+	2 (1%)	1 (50%)	1 (50%)	0 (0%)
Sex				
Male	121 (77%)	63 (52%)	50 (41%)	8 (7%)
Female	36 (23%)	16 (44%)	16 (44%)	4 (11%)
Race				
White	123 (81%)	60 (49%)	54 (44%)	9 (7%)
Black	15 (10%)	10 (67%)	5 (33%)	0 (0%)

Other	13 (9%)	6 (46%)	6 (46%)	1 (8%)
Unknown	0	3 (50%)	1 (17%)	2 (33%)
Hispanic				
No	124 (82%)	62 (50%)	54 (44%)	8 (6%)
Yes	27 (18%)	15 (56%)	10 (37%)	2 (7%)
Unknown	6	2 (33%)	2 (33%)	2 (33%)
Education Years				
Mean (SD)	12.7 (2.7)	12.3 (3.1)	13.3 (2.3)	11.5 (2.1)
Less than high school	31 (24%)	23 (74%)	5 (16%)	3 (10%)
High school only	49 (38%)	18 (37%)	26 (53%)	5 (10%)
Some college	22 (17%)	11 (50%)	9 (41%)	2 (9%)
4yr degree	19 (15%)	10 (53%)	9 (47%)	0 (0%)
Post-graduate	7 (5%)	3 (43%)	4 (57%)	0 (0%)
Unknown	22	14 (64%)	13 (43%)	2 (7%)
Injury Cause				
MVC Occupant	40 (25%)	22 (55%)	14 (35%)	4 (10%)
MCC	19 (12%)	10 (53%)	9 (47%)	0 (0%)
MVC (cyclist or pedestrian)	25 (16%)	10 (40%)	13 (52%)	2 (8%)
Fall	38 (24%)	16 (42%)	20 (53%)	2 (5%)
Assault	9 (6%)	8 (89%)	1 (11%)	0 (0%)
Other/Unknown	26 (17%)	13 (50%)	9 (35%)	4 (15%)
Injury Cause				
Acceleration deceleration	80 (51%)	38 (48%)	37 (46%)	5 (6%)
Blow to head	45 (29%)	24 (53%)	18 (40%)	3 (7%)
Head against object	106 (68%)	54 (51%)	43 (41%)	9 (8%)
Crush	5 (3%)	1 (20%)	4 (80%)	0 (0%)
Blast	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ground level fall	22 (14%)	10 (45%)	11 (50%)	1 (5%)
Fall from height	41 (26%)	20 (49%)	19 (46%)	2 (5%)
Gunshot	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fragment	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	7 (4%)	1 (14%)	4 (57%)	2 (29%)
Unknown	1	1 (100%)	0 (0%)	0 (0%)
GCS ER Arrival				
Mean (SD)	5.0 (2.8)	5.0 (2.8)	5.2 (3.0)	4.6 (2.5)
Severe (3-8)	129 (82%)	66 (51%)	53 (41%)	10 (8%)
Moderate (9-12)	28 (18%)	13 (46%)	13 (46%)	2 (7%)
ISS Non-Head/Neck				
Mean (SD)	8.3 (9.2)	8.9 (10.3)	7.5 (7.7)	9.3 (9.3)
Unknown	3	0	1	2
AIS Head				

Mean (SD)	4.1 (1.1)	4.1 (1.0)	4.0 (1.3)	4.2 (1.6)
Unknown	3	0	1	2
ER SBP				
Mean (SD)	140 (34)	141 (35)	139 (31)	139 (44)
Unknown	5	3	2	0
ER MAP				
Mean (SD)	106 (26)	104 (27)	110 (26)	99 (25)
Unknown	23	8	15	0
ER Blood Transfusion				
No	158 (76%)	62 (53%)	45 (38%)	11 (9%)
Yes	38 (24%)	16 (42%)	21 (55%)	1 (3%)
Unknown	1	1 (100%)	0 (0%)	0 (0%)
Initial CT				
Negative	2 (1%)	1 (50%)	1 (50%)	0 (0%)
Positive	141 (99%)	71 (50%)	63 (45%)	7 (5%)
Unknown	14	7 (50%)	2 (14%)	5 (36%)
Rotterdam Score				
Mean (SD)	3.7 (1.3)	3.7 (1.2)	3.7 (1.4)	4.0 (1.4)
2	22 (16%)	9 (41%)	13 (59%)	0 (0%)
3	56 (40%)	28 (50%)	24 (43%)	4 (7%)
4	22 (16%)	13 (59%)	8 (36%)	1 (5%)
5	23 (16%)	15 (65%)	8 (35%)	0 (0%)
6	18 (13%)	6 (33%)	10 (56%)	2 (11%)
Unknown	16	8 (50%)	3 (19%)	5 (31%)
History of Hypertension				
No	108 (77%)	53 (49%)	46 (43%)	9 (8%)
Yes	33 (23%)	16 (48%)	14 (42%)	3 (9%)
Unknown	26	10 (63%)	6 (38%)	0 (0%)
History of TIA's				
No	141 (100%)	69 (49%)	60 (43%)	12 (9%)
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	26	10 (63%)	6 (38%)	0 (0%)
ER Mannitol/Hypersaline				
No	116 (74%)	63 (54%)	46 (40%)	7 (6%)
Yes	41 (26%)	16 (39%)	20 (49%)	5 (12%)
Placement of ICP Monitor (ED or first 24hrs)				
No	38 (24%)	15 (39%)	18 (47%)	5 (13%)
Yes	119 (76%)	64 (54%)	48 (40%)	7 (6%)

Mechanical Ventilation (ED or first 24hrs)				
No	12 (8%)	3 (25%)	3 (25%)	6 (50%)
Yes	145 (92%)	76 (52%)	63 (43%)	6 (4%)

Table 2: Association of initial vasopressor choice with primary and secondary outcomes

Outcomes		**First IV Vasopressor**		**Unweighted**		**Weighted**	
	Total	Norepinephrine	Phenylephrine	Effect size	p	Effect size	p
6-Month GOSE							
Data collected	118 (81%)	62 (78%)	56 (85%)	**OR**	**p**	**OR**	**p**
Mean (SD)	3.6 (2.4)	3.4 (2.4)	3.8 (2.4)	1.34 (0.70, 2.56)	373	1.38 (0.72, 2.64)	328
1	38 (32%)	22 (35%)	16 (29%)				
2	2 (2%)	0 (0%)	2 (4%)				
3	31 (26%)	19 (31%)	12 (21%)				
4	5 (4%)	1 (2%)	4 (7%)				
5	16 (14%)	7 (11%)	9 (16%)				
6	7 (6%)	3 (5%)	4 (7%)				
7	8 (7%)	5 (8%)	3 (5%)				
8	11 (9%)	5 (8%)	6 (11%)				
GOSE 1-4	76 (64%)	42 (68%)	34 (61%)	1.36 (0.64, 2.89)	426	1.38 (0.65, 2.93)	403
GOSE 5-8	42 (36%)	20 (32%)	22 (39%)				
Unknown	27	17	10				
6-Month DRS							
Data Collected	80 (55%)	39 (40%)	41 (62%)	**B**	**p**	**B**	**p**
Mean (SD)	4.7 (4.8)	4.8 (4.7)	4.5 (5.0)	-0.33 (-2.49, 1.83)	759	-0.43 (-2.66, 1.80)	700
Unknown	65	40	25				
Length of Hospital Stay (deaths treated as censored observations)				**HR**	**p**	**OR**	**p**
Mean (SE)	27.3 (1.8)	25.7 (2.3)	29.0 (2.7)	0.83 (0.57, 1.20)	825	0.88 (0.61, 1.27)	485
Length of ICU Stay (deaths treated as censored observations)				**HR**	**p**	**OR**	**p**
Mean (SE)	16.8 (1.8)	18.4 (1.6)	15.0 (1.7)	1.25 (0.86, 1.82)	251	1.23 (0.85, 1.80)	278
Discharged Alive				**OR**	**p**	**OR**	**p**
No	31 (21%)	19 (24%)	12 (18%)	1.43 (0.63, 3.21)	392	1.69 (0.73, 3.91)	220
Yes	114 (79%)	60 (76%)	54 (82%)				
Required Dialysis				**OR**	**p**	**OR**	**p**
No	140 (97%)	76 (96%)	64 (98%)	0.40 (0.04, 3.90)	427	0.76 (0.12, 4.77)	769
Yes	4 (3%)	3 (4%)	1 (2%)				
Unknown	1	0	1				

Critical Care - 15 Predicting Poor Outcome Of Covid-19 Patients On The Day Of Admission With The Covid-19 Score

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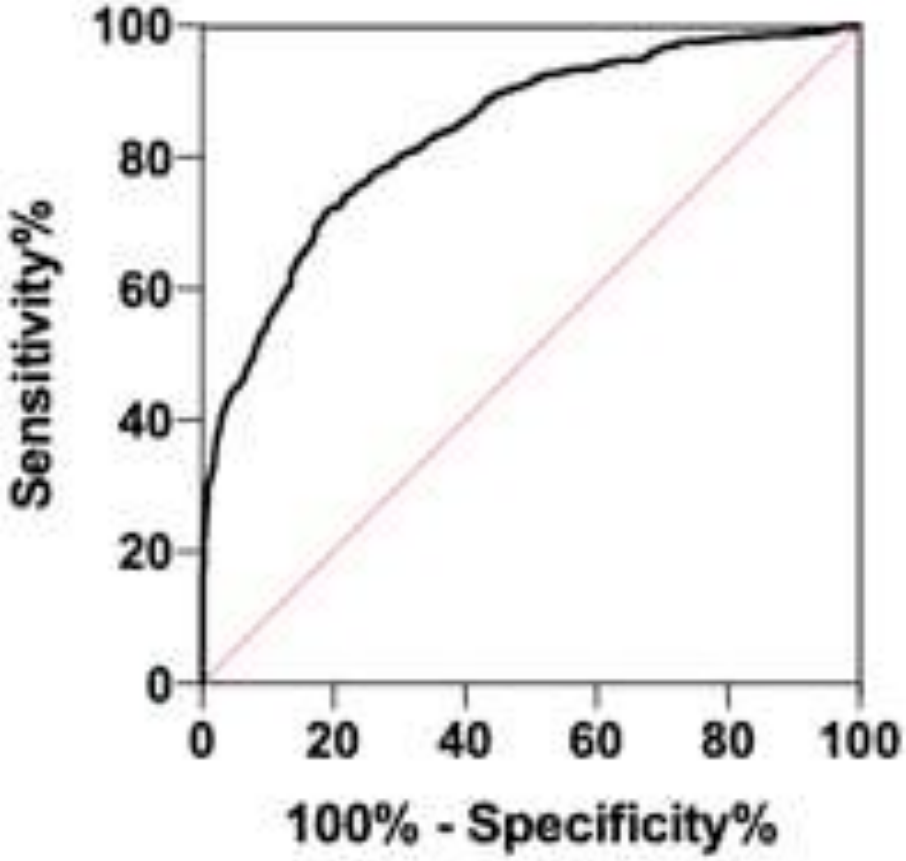
Introduction: From March to May 2020, New York City experienced a severe crisis of COVID-19 cases that resulted in a surge of patients who required hospital-level care. Although many patients recovered quickly, some progressed to develop severe COVID-19 characterized by multi-organ failure and death. There is an urgent need for objective clinical tools that can identify patients at risk for severe COVID-19 during admission to aid in triage. Laboratory tests are a promising source of easily obtained, objective data, and there is evidence that inflammatory laboratory markers and markers of cardiac, liver, and renal dysfunction may be associated with severe disease. The aim of this study is to determine which laboratory values on hospital admission can predict poor outcome in COVID-19 patients and to create a predictive COVID-19 score that can help practitioners triage patients on admission to the hospital.

Methods: This retrospective cohort study included all 2545 patients admitted to Columbia University Irving Medical Center, a tertiary academic medical center, with COVID-19 from March to May 2020. The primary combined endpoint was either intubation, stage 3 acute kidney injury (AKI) defined by Kidney Disease Improving Global Outcomes (KDIGO) criteria (increase in serum creatinine to 3 times baseline or to ≥4 mg/dL within seven days after admission), or death during hospitalization. Data were retrieved from electronic medical record systems. Laboratory tests available on admission in at least 70% of patients (and age) were included for univariate analysis. Tests that were statistically or clinically significant were then included in a multivariate binary logistic regression model using step-wise exclusion. 70% of all patients were used to train the model, and 30% were used as an internal validation cohort.

Results: Out of 2545 patients, 537 patients (21.1%) died, 309 patients (12.1%) were intubated, and 324 patients (12.7%) experienced stage 3 AKI. The primary combined endpoint was observed in 833 patients (32.7%). For the univariate analysis, 53 out of 99 laboratory tests (as well as race, sex and age) were available for ≥70% of patients on admission, and of these, 47 tests (and age) were significantly different between patients with and without the endpoint. For the multivariate analysis, we removed patients who were missing any of these variables, which yielded a final cohort of 1492 patients. The final multivariate model included age, albumin, creatinine, C-reactive protein (CRP) and lactate dehydrogenase (LDH). The area under the ROC curve was 0.850 (CI[95%]: 0.813, 0.889) (Figure 1), with a sensitivity of 0.800 and specificity of 0.761. The probability of experiencing the primary endpoint (i.e. the COVID-19 score) can be calculated as: P = [exp(−2.4475 x age - 0.6504 x albumin + 0.81926 x creatinine + 0.00388 x CRP + 0.00143 x LDH)] / {1+ [exp(−2.4475 x age - 0.6504 x albumin + 0.81926 x creatinine + 0.00388 x CRP + 0.00143 x LDH)]}.

Conclusion: Our study demonstrated that poor outcome in COVID-19 patients can be predicted on the day of admission with good sensitivity and specificity using age and a handful of laboratory tests (albumin, creatinine, C-reactive protein, lactate dehydrogenase). The COVID-19 score is potentially very useful for early identification of patients who are at risk for severe disease.

Figure 1. Receiver operating characteristic (ROC) curve of the admission COVID-19 score to predict the primary combined endpoint (either stage 3 acute kidney injury, intubation or death) in the internal validation cohort (n=447).



Critical Care - 16 The Immune Response Of Nasal Pcrv Vaccination Against *Pseudomonas Aeruginosa* In Rabbits.

Keita Inoue[1], Junya Ohara[2], Toshihito Mihara[2], Atsushi Kainuma[3], Yoshifumi Naito[4], Mao Kinoshita[3], Masaru Shimizu[5], Teiji Sawa[3]

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Introduction: Among the recent spread of multidrug-resistant bacteria, outbreaks of multidrug-resistant *Pseudomonas aeruginosa*(MDRP) are a serious concern not only making treatment difficult but also worsening the prognosis of infected patients. The development of an effective vaccine against *P. aeruginosa* as an alternative to conventional antimicrobial therapy has been highly anticipated. We have focused on the V antigen (PcrV), which inhibits the type III secretion system involved in the pathogenicity of virulent *P. aeruginosa*. In our previous studies, we examined the efficacy of PcrV vaccines by intraperitoneal and intranasal administration in mice[1,2]. In this study, we examined the immunity of nasal administration of PcrV vaccine in rabbits. As a formula of PcrV vaccine, we used CpG- oligodeoxynucleotide (ODN), K3 (5'-ATC GAC TCT CGA GCG TTC TC-3', synthesized by GeneDesign, Ibaraki, Japan) as an adjuvant, which induces Th1 type immune response by stimulating Toll-like receptor (TLR) 9.

Methods: Eleven-week-old rabbits (Japanese white species) were divided into four groups as follows, (1) PcrV alone 500Mg, n=3, (2) PcrV 500Mg + CpG-ODN 500Mg, n=3, (3) CpG-ODN alone 500Mg, n=1, (4) saline alone 2ml, n=1. The vaccines were intranasally administered on days 0, 7, and 14. The serum was obtained by collecting blood from the auricular vein of rabbits, and titer increases against PcrV were evaluated by ELISA.

Results: Results:
In rabbits vaccinated with either PcrV or PcrV + CpG, the anti-PcrV titers increased on day 30（group 1:1.22±0.15, group 2: 1.12±0.08), in comparison with the titers in the control rabbits vaccinated with CpG alone or saline alone (group 3: 0.09, group 4: 0.08). Fig. 1 Time-series data on changes in antibody titer in the course of vaccination Mean±SD).

Discussion:
While, in our previous study, a PcrV CpG ODN vaccine, which was administered either intraperitoneally or intranasally, successfully induced a significant increase of anti-PcrV titers in mice[1)2)]. On the other hand, in this study, PcrV vaccine alone increased anti-PcrV titer in rabbits.

Conclusion: The nasal administration of PcrV vaccine demonstrated the specific anti-PcrV titer increases, regardless of with or without the CpG-ODN adjuvant. Nasal administration of PcrV vaccine is attractive to induce specific immunity against a major virulence factor of *P. aeruginosa*.

References: 1) Microbiology and Immunology,61:64-74,2017 2) Microbiology and Immunology,62:774-785,2018

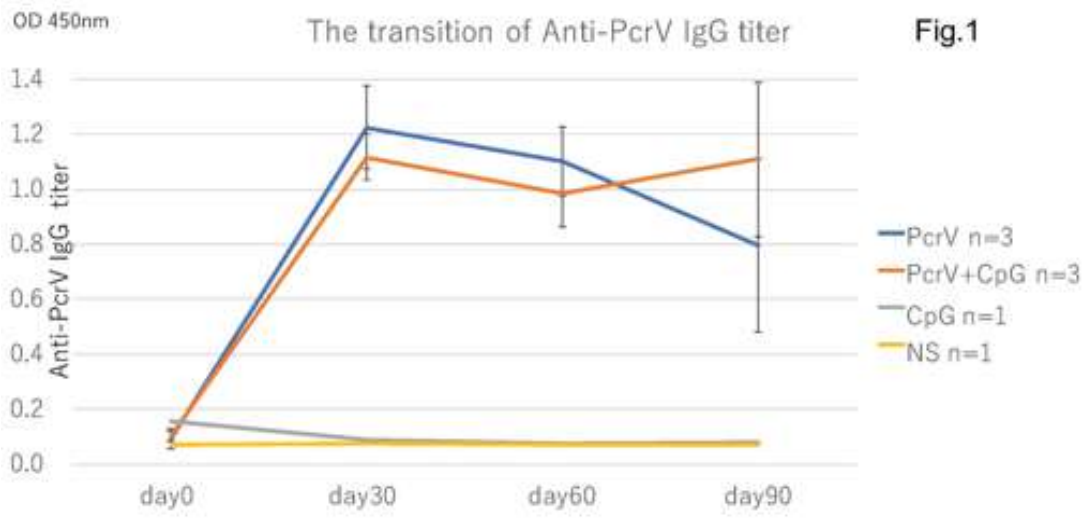

Fig.1

Critical Care - 17 Randomized Controlled Trial of the Efficacy and Safety of Sugammadex on Time-to-Extubation Following Cardiac Surgery

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Introduction: Residual neuromuscular blockade (NMB) represents a key factor leading to prolonged intubation after cardiac surgery(1) and has been associated with postoperative pulmonary complications(2,3). Sugammadex rapidly reverses NMB without adverse cardiovascular effects commonly seen with traditional NMB reversal agents (4). However, its use in the post cardiac surgery setting has not been investigated. We designed a randomized, controlled trial to determine the effectiveness of sugammadex in reducing time to extubation in mechanically ventilated patients admitted to the ICU after cardiac surgery.

Methods: This was a single center, randomized, double-blind, placebo-controlled trial. The study was approved by the institutional IRB, and all patients gave written informed consent preoperatively. Eligible participants were adult patients with preoperative left ventricular ejection fraction (LVEF) ≥45% undergoing elective aortic valve replacement (AVR), coronary artery bypass grafting (CABG) or a combination of the two. Exclusion criteria were: BMI>40, moderate to severe right ventricular dysfunction, estimated GFR <30 mL/min, home oxygen, chronic opioid use, neuromuscular disorders, cognitive impairment, emergency procedures, known allergy to rocuronium or sugammadex, anaphylactoid reaction intraoperatively, intraoperative hypoxia, cardiac arrest, sudden arrhythmia, postoperative ST changes postoperative bleeding (chest tube output >100cc/hr), temperature<35.5 or >38.3 degree C at ICU admission, or anticipated need for prolonged mechanical ventilation as determined by the treating team. Postoperatively, all patients were transferred to the ICU intubated and on a propofol and/or dexmedetomidine infusion. 30 minutes after the ICU admission, propofol was discontinued, and the participants were randomized to receive either sugammadex or placebo. Ten minutes after drug administration, if the patient was able to perform a head lift and remained hemodynamically stable, a spontaneous breathing trial (SBT) was initiated for 30 minutes. The patient was extubated if he/she was not hypoxic/ hypercapnic, had RSBI300 ml. The clinical decision to remove the endotracheal tube was determine by the treating team. If a patient failed the SBT, every attempt was made to correct the underlying reversible causes and the SBT was repeated once the cause was corrected or otherwise the patient was continued on mechanical ventilation. The primary study endpoint was time from study drug administration to extubation. Secondary endpoints were pulmonary function tests including negative inspiratory force (NIF), vital capacity (VC) at the time of extubation, and adverse events. The analysis was based on intention-to-treat. For the analysis of the primary endpoint, a two-sample Student's t-test was used to compare the time to extubation between the two groups. Frequency of adverse events were compared between the two groups using chi-square test.

Results: A total of 90 patients were randomized on an intention to treat basis of which 83 patients (Sugammadex=40, placebo=43) received sugammadex or placebo. The two groups were comparable with respect to demographic characteristics including age [sugammadex: 67 ± 8.45 vs. placebo: 64.4 ± 11.18 years], sex [women-sugammadex: 17.8% vs. placebo: 11.1%] and BMI [sugammadex: 29.39 ± 4.61 vs. placebo: 29.55 ±4.83 kg/m2]. Patients in sugammadex group had reduced time to extubation compared with the placebo group [sugammadex: 178 ± 130 minutes vs. placebo: 250.9 ± 201.9 minutes, difference 72.8 [95% CI:1.63-144.0] minutes, p=0.04]. There were no differences in NIF [sugammadex: -31.06 ± 15.90 vs. placebo: -29.22 ± 12.98, p=0.59] and VC [sugammadex:425 ± 466 ml vs. placebo: 470.7 ± 513.9 ml, p=0.68]. There were no difference in postoperative blood product requirements [sugammadex: 0.13 ± 0.76 vs. placebo: 0.04 ± 0.21 pRBC units, p=0.45] or dysrhythmias [sugammadex: 6.82% vs. placebo:13.33%, p=0.31] between the two groups. There were no serious adverse events in either group.

Conclusion: This randomized trial in patients undergoing cardiac surgery showed that Sugammadex administration decreased time to extubation by over one hour, without detectable difference in measures of pulmonary function. Larger trials may be required to confirm these findings and determine the clinical implications.

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Critical Care - 18 Effects Of Bacteriophage Therapy On Acute Lung Injury Caused By Pseudomonas Aeruginosa Pneumonia

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Introduction: Pseudomonas aeruginosa is a major opportunistic pathogen that causes acute and chronic infections. Recently, infections caused by multidrug-resistant P. aeruginosa(MDRP) have increased, and the emergence of pandrug-resistant P. aeruginosa has become a serious concern in hospitals worldwide. Bacteriophage therapy is expected to be an alternative choice of antimicrobial chemicals against multidrug-resistant bacteria. In this study, we examined the effects of bacteriophage therapy on acute lung injury caused by P. aeruginosa pneumonia.

Methods: Design: a prospective randomized and controlled animal study Setting: University laboratory Subjects: Male ICR mice This study was carried out under the Guidelines for Proper Conduct of Animal Experiments, Science Council of Japan. The protocol was approved by the Committee on the Ethics of Animal Experiments of Kyoto Prefectural University of Medicine. A bacteriophage φÜR18, which demonstrates the bactericidal activity against P. aeruginosa PA103, was isolated from sewage treatment plants at Hokkaido in Japan in advance, as reported previously A lethal dose(1.0×106CFU) of P. aeruginosa PA103 was intratracheally administered to the lungs of mice. Then, 5 minutes later, the solution(90ML) containing bacteriophage(treated group)(40×106PFU) or the saline alone(non-treated control group) was intratracheally administered. Body temperature, activity, and survival of mice were monitored for 24 hours. To measure the activity of mice, we measured the distance moved in the cage for 10 seconds 8 hours after infection.

Results: Regardless of the treated or non-treated, all mice once became severely hypothermic within 4 hours. However, after 8 hours, mice received bacteriophage recovered from hypothermia(32.3±1.1℃) while mice received saline remained hypothermic(29.2±0.8℃)($p<0.05$). After 12hours, the body temperature of the treated group was 34.5±1.5℃ while that of the control group was 29.1±0.8℃($p<0.05$). About the activity of mice, the average moving distance of the treated group was 26.5±12.0cm, while that of the saline group was 11.9±6.9cm($p<0.05$). Finally, 5 of 11 mice that received the bacteriophage survived for 24 hours. All mice(n=12) received saline died in 24 hours($p<0.05$).

Conclusion: The bacteriophage therapy improved the survival of mice intratracheally received a lethal dose of P. aeruginosa. The bacteriophage therapy in our animal model demonstrated its potential in the protection of acute lung injury caused by P. aeruginosa pneumonia.

Critical Care - 19 Endothelial Glycocalyx Degradation And Postoperative Acute Kidney Injury In Cardiac Surgery Patients

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Introduction: Acute kidney injury (AKI) occurs in an estimated 30% of cardiac surgery patients and is associated with increased mortality.[1,2] Intraoperative hyperoxia may promote the formation of reactive oxygen species (ROS) which have deleterious effects on renal permeability through oxidative stress.[1,3.] The glomerular endothelial glycocalyx is a critical regulator of renal permeability and is composed of glycosaminoglycans, proteoglycans, and other glycoproteins including syndecan-1, a heparan sulfate proteoglycan.[4] Surgery, cardiopulmonary bypass, and oxidative stress induce shedding of soluble syndecan-1, and plasma syndecan-1 concentrations reflect glycocalyx degradation.[3,5] We tested the hypotheses that increased endothelial glycocalyx damage is associated with AKI following cardiac surgery and that intraoperative normoxia decreases glycocalyx damage compared to hyperoxia.

Methods: We tested these hypotheses in a cohort of cardiac surgery patients enrolled in a randomized clinical trial of intraoperative normoxia (lowest fraction of inspired oxygen [FIO2] to maintain an arterial hemoglobin saturation of 95-97%) vs. hyperoxia (FIO2 =1).[6] Plasma concentrations of syndecan-1 were measured using an enzyme-linked immunosorbent assay (Abcam, Cambridge, MA) before surgery, immediately following cardiopulmonary bypass, and 6 hours after surgery. AKI was defined using KDIGO creatinine criteria. We measured the association between the area under the curve (AUC) of plasma syndecan-1 concentrations following CPB and 6 hours postoperatively and AKI using logistic regression adjusted for baseline syndecan-1 concentration, age, baseline estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula), and use of cardiopulmonary bypass. We measured the effect of intraoperative oxygen treatment on syndecan-1 concentration using the Mann-Whitney U test.

Results: One hundred thirty patients comprised the cohort. The median (10th, 90th percentile) participant age was 66 (50, 76) years, 33 (25%) were female, median baseline eGFR was 74 (43, 96) mL/min/1.73m2. Twenty-five participants (19%) developed AKI. Seventeen participants (13%) developed stage I AKI), 5 (4%) stage 2 AKI, and 3 (2%) stage 3 AKI. Median syndecan-1 concentrations were 155.6 ng/mL (69.6, 601.6) at baseline, increased to 333.4 (138.1, 798.7) ng/ml after CPB and decreased to 273.1 ng/mL (109.1, 934.1) 6 hours postoperatively. A 50 ng/ml increase of plasma syndecan-1 concentration AUC was independently associated with an 10% increase in the odds of AKI (OR 1.10; 95% CI: 1.00 to 1.20; P=0.04). Median (10th, 90th percentile) syndecan-1 AUCs were 330.5 ng/ml (137.8, 701.2) and 314.6 ng/ml (138.5, 1038.2) in patients receiving normoxia vs. hyperoxia, respectively (P=0.92).

Conclusion: Increased perioperative plasma concentrations of syndecan-1 were independently associated with postoperative AKI in patients undergoing cardiac surgery. Intraoperative normoxia vs. hyperoxia did not affect perioperative plasma concentrations of syndecan-1. Future investigations will test therapeutic interventions to decrease glycocalyx degradation and reduce postoperative AKI.

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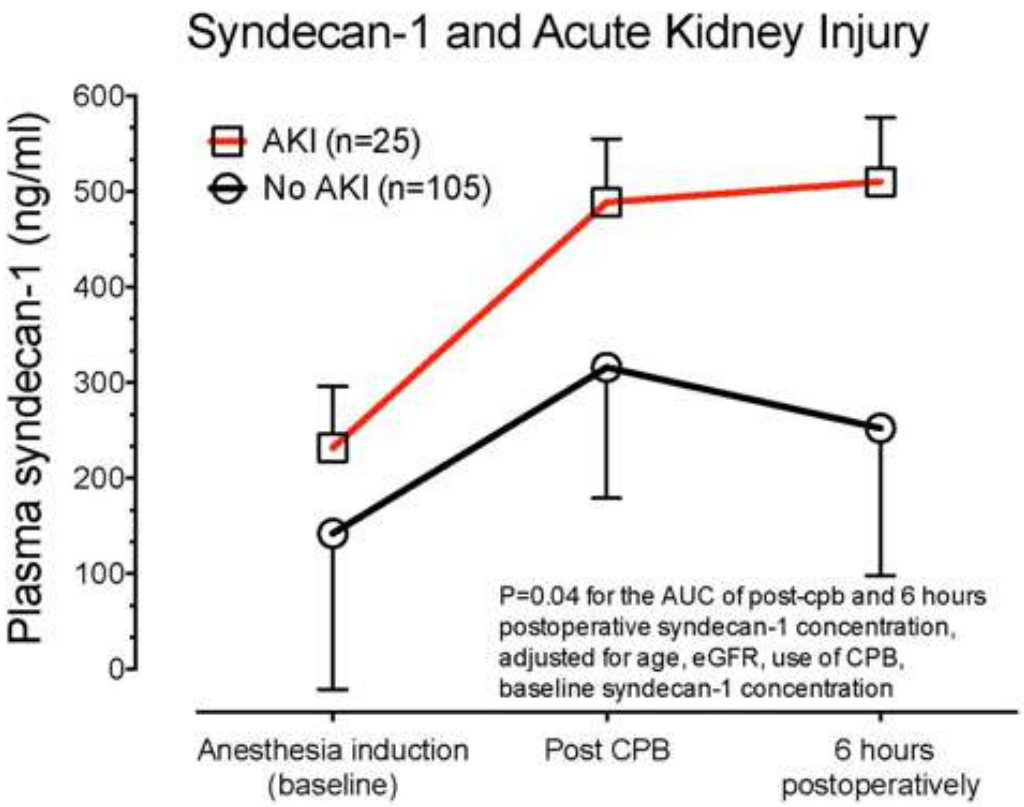
Syndecan-1 and Acute Kidney Injury
Plasma syndecan-1 (ng/ml)
600
500
400
300
200
100
0
AKI (n=25)
No AKI (n=105)
P=0.04 for the AUC of post-cpb and 6 hours postoperative syndecan-1 concentration, adjusted for age, eGFR, use of CPB, baseline syndecan-1 concentration
Anesthesia induction (baseline)
Post CPB
6 hours postoperatively

Critical Care - 20 Does Preventing Intubation in Covid-19 Save Lives? A Crush-Covid Multi-Center Study of the Outcomes of Advanced Respiratory Support Escalation in Covid-19

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Introduction: The COVID-19 disease caused by the SARS-CoV-2 virus has become an important illness since its identification. Intubation with mechanical ventilation is widely recognized as a necessary intervention for patients suffering from respiratory failure. Critically ill COVID-19 patients often present with severe hypoxia, prompting the need respiratory support. In the early months of the COVID-19 pandemic, hypoxic patients were intubated early in their course of disease to decrease aerosolization of the virus from non-invasive ventilation (NIV) measures (1). However, early reports revealed a high rate of mortality among intubated patients and ranged widely, reaching as high as 86% (2,3,4). Both High Flow Nasal Cannula (HFNC) and Non-Invasive Positive Pressure Ventilation (NIPPV) are proven modalities in non-COVID-19 pathologies. Data remains mixed on the aerosolizing risk of SARS-Cov-2 virus with these noninvasive strategies (5,6). Despite differing recommendations, the utility of NIV in COVID-19 remains unstudied. The literature currently lacks description of the outcomes between patients who were intubated immediately for respiratory failure due to COVID-19 versus intubating only after failing NIV methods. Some have argued that patients should be placed on mechanical ventilation early to prevent lung injury (7) while others argued against this (8). Our study aimed to describe the characteristics of patients who were intubated 'early,' defined as being intubated without NIV attempts, versus 'delayed', defined as intubated after failed initial NIV use. Our secondary aim was to characterize the use of NIV in COVID-19 to prevent intubation

Methods: We performed a multi-center retrospective cohort study to investigate the differences between those patients who were intubated early and those in which intubation was delayed by a trial of NIV. Patients were abstracted from a multicenter registry of hospitalized patients admitted between March 2020 and June 2020. Four tertiary care centers, University of Maryland Medical Center, Wake Forest Baptist Medical Center, Northeast Georgia Health System, and George Washington University Hospital contributed data to the registry contributed. Patients were divided into three cohorts, early intubation, delayed intubation, and non-invasive ventilation (NIV) methods only. An 'early' intubation was defined as intubation without demonstrated NIV failure, and delayed were those intubations that occurred after failed NIV. NIV methods included HFNC and NIPPV. Patients who were 18 years or older, had confirmed COVID-19 test, were admitted to the hospital, and required advanced respiratory support (HFNC, NIPPV, or intubated during their hospitalization) were included in the study.

Results: A total of 338 patients were collected on August 10, 2020 that met inclusion criteria. 127 patients were intubated early, without a trial of NIV prior to intubation, 101 intubated after failed NIV, and 110 who had NIV measures only. Pearson chi squared tests did not show any statistical demographic difference for age, race, BMI, and sex between the two groups. Mortality rates were significantly lower in the early group versus the delayed group, 37.8% vs 65.3% respectively. Crude odds ratio was 0.322 [0.187 – 0.556] ($p < 0.0001$), indicating the delayed intubated group had less odds of survival compared to the early. Stepwise logistic regression showed that age, gender, and institution were significant variables for adjustment. After controlling for these, the adjusted odds ratio 0.386 [0.204 – 0.721] ($p < 0.0001$), further indicating that even when controlled for age, gender, and institution, delayed intubation had less odds of survival. Secondary analysis showed that there were 92 patients who received HFNC alone, 5 NIPPV alone, and 13 received both. None of these 110 patients received mechanical ventilation during their hospital stay.

Conclusion: Our study suggests that HFNC and NIPPV may be useful modalities in the treatment of hypoxemia secondary to COVID-19 to prevent intubation. However, the likelihood of survival may decrease in those who fail these measures. Given the findings of our study, the authors believe a trial of NIV prior to intubation is reasonable, especially given the high mortality rates of intubation. Further randomized control trials are needed to not only evaluate the efficacy of NIV in COVID-19, but also quantify the risk of aerosolization to properly weigh the risks and benefits of this measure.

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Critical Care - 21 Optoacoustic Measurement of Central Venous Oxygen Saturation During Simulated Hemorrhage

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Introduction: Early identification and treatment of hemorrhagic shock is critical to reduce mortality. The development of noninvasive monitors to identify hemorrhage and monitor resuscitation is an area of ongoing research. The purpose of this study was to use lower body negative pressure (LBNP) to simulate hemorrhage in healthy volunteers to 1) observe its impact on central venous oxygen saturation (ScvO2) and 2) observe the correlation between ScvO2 measured by hemoximetric and optoacoustic (OA) measurement of oxygen saturation in the left innominate vein (LIV), which joins the right innominate vein to form the superior vena cava. Previous studies have demonstrated good correlations between in vivo oximetric measurements and concurrent hemoximetric measurements in blood samples from the pulmonary artery (bias and precision -1.12±3.29%) (1) and superior vena cava (-0.3±6.4%) (2).

Methods: In a protocol approved by the institutional review board, arterial and central venous catheters were placed in six healthy volunteers. Volunteers' lower abdomen and lower extremities were placed in the LBNP box. Ultrasound guidance was used for OA probe placement in the sternal notch. Hemoximetric and OA measurements were collected at -20, -40, -60, and -80 mmHg. If the patient became symptomatic or hemodynamically unstable, the negative pressure in the LBNP box was immediately released. Data were analyzed as recommended by Bland and Altman (3).

Results: The hemoximetric and OA measurements correlated well within six volunteers (bias and precision 2.45±6.45) (Figure).

Conclusion: Optoacoustic measurement of LIV oxygen saturation correlates well with hemoximetric measurements. In most volunteers, hemodynamic compensation prevented LBNP-induced hypotension until a critical level was reached, at which time blood pressure decreased too rapidly to reliably reduce venous oxygen saturation for an interval sufficiently long to permit measurements. Performance of this prototype OA system was similar to that of in vivo oximetry.

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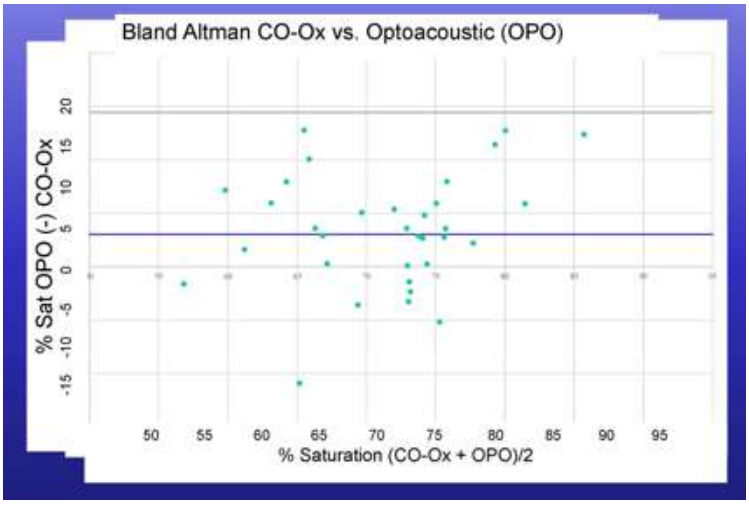

Critical Care - 22 Natural Killer Lymphocytes As Drivers Of Kidney Fibrosis After Acute Cardiac Dysfunction

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Introduction: Acute kidney injury (AKI) is a common sequela of perioperative critical illness, and is a cause of chronic kidney disease (CKD). The AKI to CKD transition presents an opportunity for early intervention to prevent CKD, for which there are currently no effective treatments. Our lab developed a novel model of critical illness-induced AKI, cardiac arrest and cardiopulmonary resuscitation (CA/CPR), in which all animals recover from AKI but nonetheless develop CKD at 7 weeks[1,2] (Fig. 1). We previously demonstrated that kidney inflammation occurs after CA/CPR[3]. The purpose of this study was to identify potential immune drivers of critical illness-induced CKD.

Methods: Experiments were approved by the Portland Veterans Affairs Medical Center Institutional Animal Care and Use Committee. Mice were anesthetized with isoflurane, then intubated. Cardiac arrest was induced by potassium chloride. After 7.5 minutes, chest compressions were initiated at a rate of 550 per minute, then intravenous epinephrine was administered. Chest compressions were discontinued after spontaneous electrocardiographic activity. Sham treated mice received 15 minutes of isoflurane anesthesia. To profile the immune landscape of the kidney after CA/CPR, we performed 11-color flow cytometry analysis at 1 day, 3 days, 7 days, and 49 days post cardiac arrest. PDGFRB expression was assessed to identify myofibroblasts, expansion of which signals the AKI to CKD transition[4]. Flow cytometry data were analyzed with FlowJo software. To identify potential NK cell-derived mediators of fibrosis, data from two previously published single cell RNA sequencing studies[5,6] were combined and analyzed using Seurat[7] in Rstudio.

Results: 77% of animals subjected to CA/CPR survived to the pre-designated endpoint. Mean (±S.D.) resuscitation time was 2.07±0.60 min, and mean epinephrine dose was 0.58±0.08 Mg/g. Seven distinct immune cell populations were identified in the kidney after CA/CPR (Fig. 2). While there was no increase in kidney T-cells or B-cells after CA/CPR, neutrophils increased starting at 1 day (878±676 neutrophils per million total cells in sham kidney vs. 44,636±31,893 per million in CACPR), peaked at 3 days (53,654±54,172 cells/million), then returned to baseline at 7 days. Monocytes peaked at 1 day (4,069±4,011 cells/million in sham vs. 23,284±20,185 cells/million in CA/CPR), then decreased to near baseline levels by 49 days (8,232±6,864 cells/million). Macrophages increased starting at 7 days (34,909±7,380 cells/million in sham vs. 97,502±8,057 cells/million in CA/CPR), and decreased at 49 days, but remained above baseline (49,381±31,803 cells/million). Natural killer (NK) cells were the only cell type that continually increased, starting at 1 day (4,688±4,738 cells/million in sham vs. 13,777±6,312 cells/million in CA/CPR), and remained elevated at 49 days (17,399±11,428 cells/million) (Fig. 3). PDGFRB+ cells increased starting at 7 days (12,778±7,695 cells/million in sham vs. 26,122±2,554 cells/million in CA/CPR) and remained elevated at 49 days (30,008±14,923 cells/million) (Fig. 4A and B). *Gzmb* (which codes for granzyme B), *Gzma* (granzyme A), *Prf1* (perforin 1), and *Ifng* (interferon gamma) were identified as potential NK cell-expressed mediators of myofibroblast expansion and fibrosis[8-10] (Fig. 4C and D).

Conclusion: CA/CPR induces acute and lasting renal inflammation. NK cells remain persistently elevated throughout the AKI to CKD transition, implicating these cells as potential drivers of kidney damage and fibrosis after acute cardiac dysfunction. Continuing experiments will investigate potential NK cell-derived mediators of myofibroblast expansion, such as granzyme B and interferon gamma.

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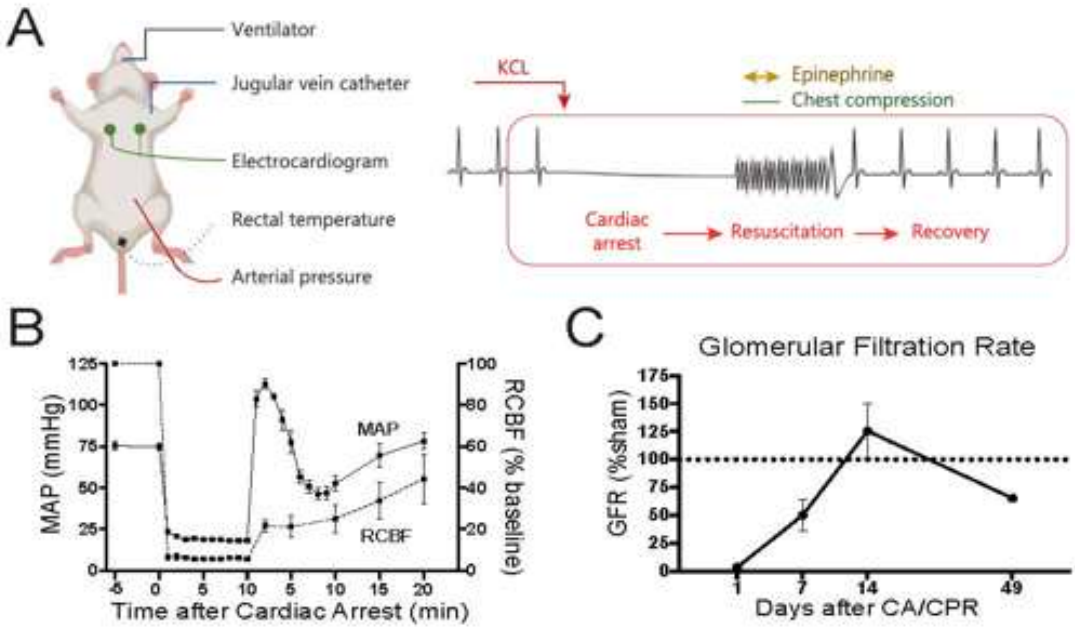

Figure 1. A mouse model of cardiac arrest and cardiopulmonary resuscitation. A) Schematic of CA/CPR experimental procedure. Adapted from ref. 1. B) Mean arterial pressure (MAP, solid lines, scale on left axis) and renal cortical blood flow (RCBF, dotted lines, scale on right Y axis) measurements after CA/CPR procedure. Return of spontaneous circulation was followed by relative hypertension then a gradual return to baseline. RCBF, in contrast, remained low after cardiac arrest and did not return to baseline within the 20-min follow-up period. *n*=5-6/group. Figure adapted from ref. 2. C) Glomerular filtration rate time course after CA/CPR, relative to sham. Results consist of data from ref. 2 and additional experiments combined. *n*=4-9/group. Error bars depict mean ± s.e.m.

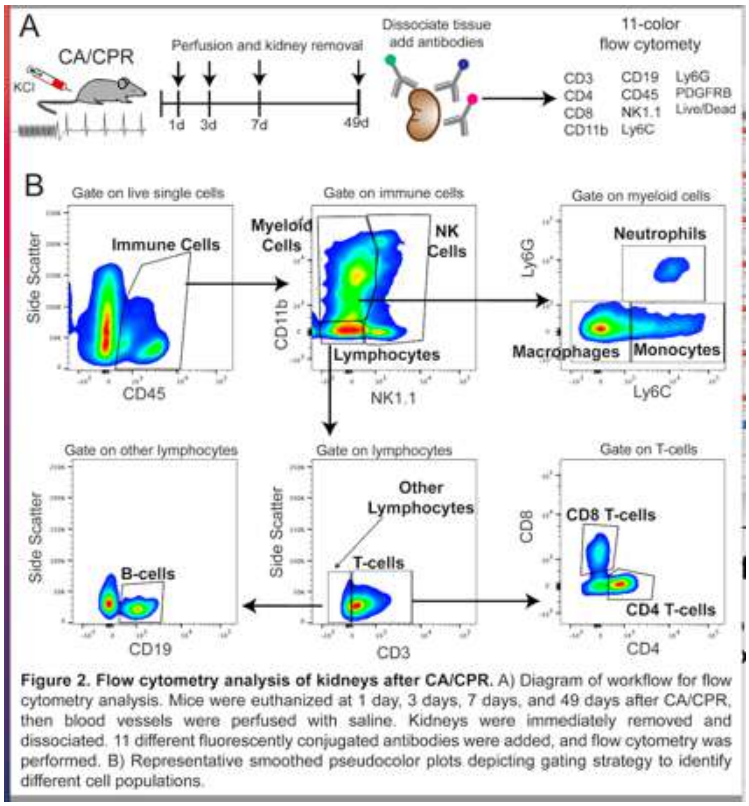

Figure 2. Flow cytometry analysis of kidneys after CA/CPR. A) Diagram of workflow for flow cytometry analysis. Mice were euthanized at 1 day, 3 days, 7 days, and 49 days after CA/CPR, then blood vessels were perfused with saline. Kidneys were immediately removed and dissociated. 11 different fluorescently conjugated antibodies were added, and flow cytometry was performed. B) Representative smoothed pseudocolor plots depicting gating strategy to identify different cell populations.

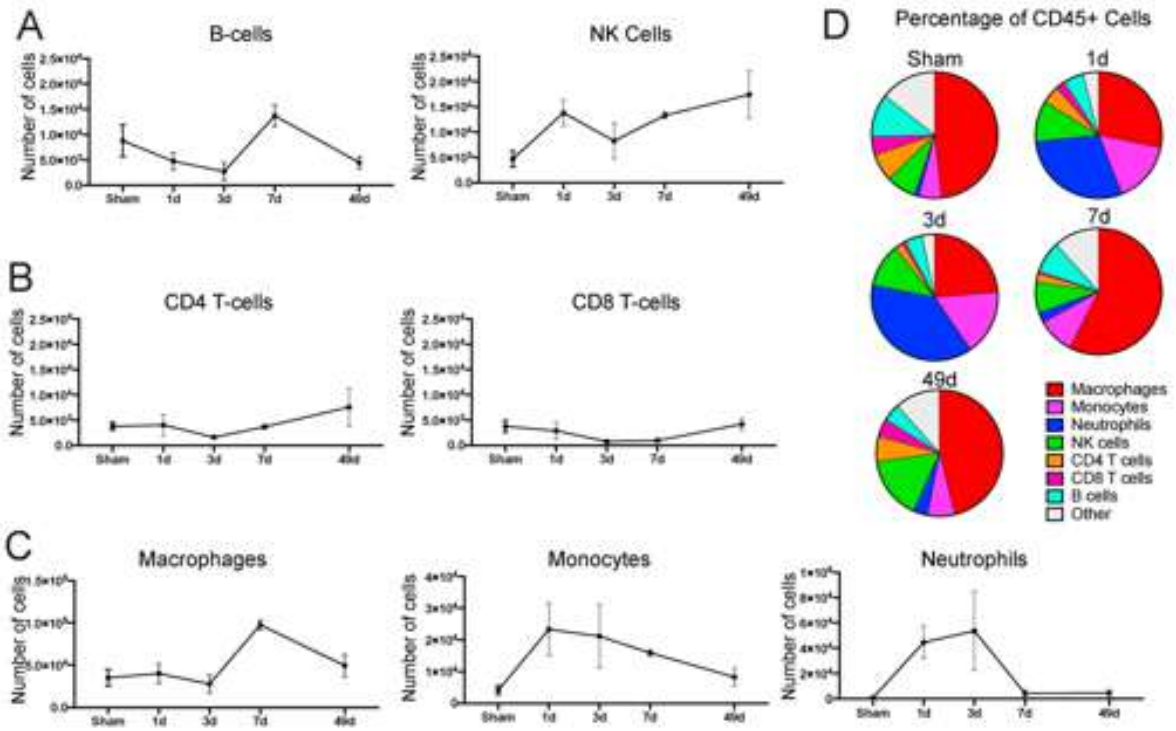

Figure 3. Immune cells infiltrate the kidney after CA/CPR. Time course quantification of different immune cell populations in the kidney, as identified by gating strategy depicted in Fig. 2. Number of cells = number of cells per one million live, single cells. Graphs depict lymphocytes (A), T-cells (B), myeloid cells (C). *n*=2-6/group. D) Relative number of cells as a percentage of total CD45+ cells in the kidney. Error bars depict mean ± s.e.m.

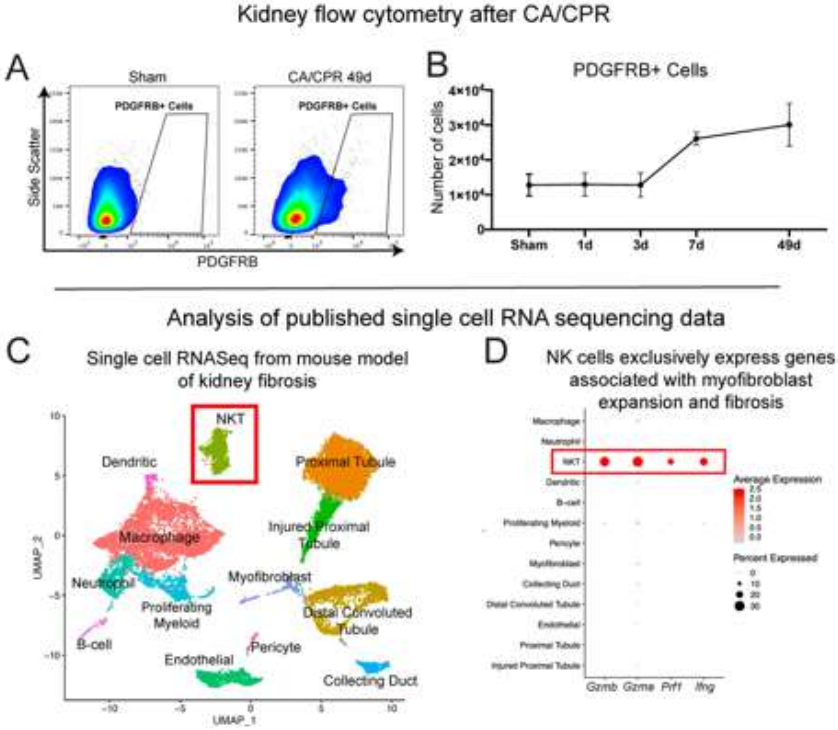

Figure 4. NK cells as drivers of myofibroblast expansion and kidney fibrosis. A) Representative flow cytometry plots of PDGFRB+ (a myofibroblast marker) cells in the kidney in sham mice and 49 days after CA/CPR. Plots depict live, single cells. Error bars depict mean ± s.e.m. B) Quantification of PDGFRB+ cells in the kidney after CA/CPR. d = days after CA/CPR. C) UMAP plots depicting compilation of two separate single cell RNA sequencing datasets (refs. 5 and 6) from mouse kidneys after unilateral ureter obstruction (a mouse model of kidney fibrosis). Each dot represents an individual cell. Clusters generated with Seurat. NKT = NK cells and T-cells. D) Dot plot depicting expression of NK cell-specific genes associated with myofibroblast expansion.

Critical Care - 23 Evaluation Of Covid-19 Treatments And Outcomes By Ethnicity And Race

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Introduction: As COVID-19 has infected large portions of the American population, several states and studies have found that different ethnic and racial groups have different outcomes. Several hypotheses exist as to why these outcomes differ including structural racism, socioeconomic status, adverse housing conditions, decreased access to healthcare, increased exposure to air pollution, treatment differences, and increased baseline co-morbidities. However, few studies have considered whether hospital treatments differ between racial and ethnic groups. We examined racial and ethnic differences in treatment and outcomes in critically ill patients with COVID-19.

Methods: Using the nationwide all-payer Premier Healthcare database (Premier Inc., USA) between April 1, 2020 and June 30, 2020, we examined the treatments and outcomes in 14,745 adult patients hospitalized with a diagnosis of COVID-19 (ICD-10 code U07.1) and with a hospital charge for intensive care across 438 hospitals in the United States. Patients less than 18 years of age were excluded. Our primary exposures were race and ethnicity while outcomes examined included in-hospital pharmacological treatments such as remdesivir, azithromycin, hydroxychloroquine, convalescent plasma, dexamethasone, and need for mechanical ventilation, and renal replacement. We also examined intensive care unit length of stay and in-hospital mortality. Descriptive statistics were used to examine the treatments and outcomes, stratified by race and ethnicity.

Results: Within the cohort, the overall use of hydroxychloroquine and azithromycin as therapy were high compared to remdesivir, convalescent plasma, and dexamethasone. Utilization of these drugs were statistically different. Hydroxychloroquine (p=0.084) and remdesivir (p=0.271) however, showed no difference in use within ethnic and racial groups, respectively. Additionally, there was no difference between use of noninvasive or invasive ventilation and renal replacement therapy (Table 1, 2, 3). We did not find differences in ICU length of stay, hospital length of stay or mortality by ethnicity or race.

Conclusion: Although differences in various treatments across race are statistically significant, the absolute difference in the use of these treatments are clinically minor. However, these analyses are unadjusted for severity of illness due to COVID-19. On the other hand, there are clinically and statistically meaningful differences by ethnicity. Hispanic patients were more likely to receive all therapies of interest minus hydroxychloroquine. However, these analyses are unadjusted for severity of illness due to COVID-19 or additional confounders. Additionally, differences within dexamethasone, convalescent plasma, and azithromycin therapies may be due to rapidly evolving data early in the pandemic, suggesting dissimilar treatment protocols across types of hospital institutions or geography. There was no difference in invasive mechanical ventilation nor in in-hospital mortality to explain prior data reported in previous studies. Lastly, based on previous data, a large proportion of patients with unknown ethnicity are uninsured. In our study, many of these patients who did not receive more costly therapies such as convalescent plasma, remdesivir, and tocilizumab, which likely skews the data.

Table 1: Treatment by Ethnicity

Patient Group	Ethnicity			P Value
COVID patients in ICU	Hispanic	Non Hispanic	Unknown	
(n=14745)	(n=2906, 19.7%)	(n=8409, 57.0)	(3431, 23.3%)	p-value
Dexamethasone for at least 5 days	114 (3.9%)	360 (4.4%)	180 (5.3%)	<0.001
*Remdesivir	241 (8.3%)	440 (5.2%)	71 (2.1%)	<0.001
*Convalescent plasma	147 (5.1%)	314 (3.7%)	88 (2.6%)	<0.001
Hydroxychloroquine	1069 (36.8%)	3147 (37.4%)	1109 (32.3%)	0.004
Azithromycin	1630 (56.4%)	3994 (47.5%)	1771 (51.6%)	<0.001
*Tocilizumab	757 (26.1%)	1617 (19.2%)	490 (14.3%)	<0.001
IMV	1633 (56.2%)	4448 (54.0%)	1177 (34.3%)	<0.001
NIV	694 (23.9%)	1921 (22.8%)	571 (16.6%)	<0.001
CRRT	12 (0.4%)	37 (0.4%)	11 (0.3%)	0.624
Dialysis	453 (15.6%)	1202 (13.9%)	579 (16.9%)	0.159

Data Represented as n(%)

Table 2: Treatments by Race

Patient Group	Race			P Values
COVID patients in ICU	Black/African American	White	Other	
(n=14745)	(n=3421; 23.2%)	(n=6908; 46.9%)	(4416; 30.0%)	p-value
Dexamethasone for at least 5 days	202 (5.9%)	332 (4.8%)	265 (6.0%)	0.010
Remdesivir	159 (4.7%)	352 (5.1%)	241 (5.5%)	0.271
Convalescent plasma	107 (3.1%)	288 (4.2%)	151 (3.4%)	0.013
Hydroxychloroquine	1314 (38.4%)	2323 (33.6%)	1788 (40.5%)	<0.001
Azithromycin	1689 (49.4%)	3420 (49.5%)	2299 (52.1%)	0.015
Tocilizumab	679 (19.9%)	1277 (18.5%)	908 (20.6%)	0.019
IMV	1976 (57.8%)	3547 (51.4%)	2835 (64.2%)	<0.001
NIV	810 (23.7%)	1667 (24.1%)	1110 (25.2%)	0.287
CRRT	20 (0.6%)	34 (0.5%)	5 (0.1%)	0.002
Dialysis	740 (21.6%)	821 (11.9%)	773 (17.5%)	<0.001

Data Represented as n(%)

ICU Patients (n=14745)	ICU LOS (days) mean SD, median [IQR 25 - 75]	In-hospital Mortality, n (%)
Ethnicity		
Hispanic (n=2906; 19.7%)	9.7 ± 10.1 6 [3, 13]	935 (32.2%)
Non-Hispanic (n=8409; 57.0%)	7.9 ± 8.5 5 [2, 10]	3097 (36.8%)
Unknown (n=3430; 23.3%)	7.8 ± 8.7 5 [2, 10]	1417 (41.3%)

ICU Patients (n=14745)	ICU LOS (days) mean SD, median [IQR 25 - 75]	In-hospital Mortality, n (%)
All ICU Patients (n=14745)	8.2 ± 8.9 5 [2, 11]	
Race		
Asian (n=511; 3.5%)	9.0 ± 9.1 6 [2, 13]	195 (38.2%)
Black (n=3421; 23.2%)	8.0 ± 8.3 5 [2, 11]	1260 (36.8%)
Other (n=3043; 20.6%)	9.1 ± 9.7 6 [2, 12]	1176 (38.6%)
Unknown (n=862; 5.8%)	9.4 ± 9.9 6 [3, 13]	373 (43.3%)
White (n=6908; 46.8%)	7.7 ± 8.6 5 [2, 10]	2445 (35.4%)

Critical Care - 24 CLABSI in COVID 19 in NYC Area Early 2020

Sofia Gilels[1], Shabaaz Baig[2], Carmine Gianatiempo[3], Jean D Eloy[4]

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Introduction: Central line associated bloodstream infections (CLABSI) are a significant cause of morbidity and mortality worldwide. Classified as a type of healthcare associated infection, CLABSI is defined as an infection of the bloodstream that develops within 48 hours of central line placement and is not related to another source of infection. Bloodstream infection is confirmed through laboratory analysis, with some of the most common pathogens noted as staph species, enterococci, and candida. Based on data from the years 2001 and 2009, the CDC estimated that CLABSI was noted in 43,000 cases in 2001 and 18,000 cases in 2009. This represented a 58% decrease. This reduction in the incidence of CLABSI is surmised to be due to the effort to advance the best practice evidence based guidelines for central line placement and maintenance. The mortality rate was estimated to be between 12-25%. The CDC also stated that 'Assuming that each CLABSI carries excess health-care costs of $16,550 and mortality of up to 25%, and that CLABSI reductions were steady during 2001–2009, the cumulative excess health-care costs of all CLABSIs prevented in ICUs could approach $1.8 billion, and the number of lives saved could be as high as 27,000 [3].' The Agency for Healthcare and Research Quality conducted a systematic review and reported that their estimate for CLABSI associated costs were even higher, with an average from the literature of $70, 696. With an estimated mortality rate of 12-25%, their healthcare associated cost savings were calculated to be $97,756,628–$244,270,620 [4]. In 2019, several patients in China were hospitalized with pneumonia like symptoms due to an unknown cause. The cause of these symptoms was discovered to be the novel coronavirus, Sars-CoV-2. The virus spread, covering the globe and beginning the COVID-19 pandemic. During the COVID-19 pandemic, the ICUs in the United States were overwhelmed with patients. At Englewood hospital, virtually all patients admitted to the ICU received central lines. However, while COVID-19 was not considered a causative factor for CLABSI, the number of CLABSI noted during the height of the pandemic skyrocketed. In this report we discuss the factors behind this drastic increase in CLABSI and what strategies we can implement to prevent this from occurring at other hospitals and to prepare for future pandemics.

Methods: Data was pulled on every patient identified with CLABSI between January 2020 and August 2020 at Englewood hospital in northern New Jersey. Variables identified included gender, age, admission date and reason, culture date, organism identified, and central line characteristics. Chart notes, provider comments, and COVID status were also noted.

Results: 26 total CLABSI events were noted, with 69% occurring in April alone. The months of March, April, and May, regarded as the height of the pandemic, accounted for 88% of the infections. Zero events were recorded in January and February. The three ICUs accounted for 92% of CLABSI. The most common infected line type was quad lumen with 69% followed by triple lumen at 19%. The most commonly infected placement was the right internal jugular with 73%. Group D enterococci (faecalis) was the most commonly seen organism with 69%. Males accounted for 77% of CLABSI. The significant increase in CLABSI during the height of the COVID pandemic raised concern for increased mortality and morbidity rates. Though guidelines documenting the best evidence-based practice for central line placement have been in place for many years, we found that the pandemic introduced new variables to consider and difficulties that now would require reevaluation of strategies that previously proved to be successful. Based on the Practice Guidelines for Central Venous Access 2020 by the American Society of Anesthesiologists (ASA) some of the best practices included usage of aseptic techniques, selection of catheter insertion site, usage of dressings, and catheter maintenance.

Conclusion: Innovation to decrease provider exposure using of pumps outside patient rooms with tubing extending via the ground. This led to concern as a source of infection. Enterococcus Faecalis as the majority bug identified in our data makes this unlikely. CLABSI increased mortality, particularly those in the ICU during the pandemic. Adherence to evidence-based guidelines is imperative. However, in the setting of new challenges, it is important to reevaluate protocols and reestablish guidelines such that they are sustainable.

References: [1] Durvasula R, Wellington T, McNamara E, Watnick S. Covid-19 and kidney failure in the acute care setting: our experience from Seattle. Am J Kidne Dis. 2020;76:4–6. 2) Bell T, O'Grady NP. Prevention of Central Line-Associated Bloodstream Infections. Infect Dis Clin North Am. 2017;31(3):551-559. doi:10.1016/j.idc.2017.05.007 3) Centers for Disease Control and Prevention (CDC). Vital signs: central line-associated blood stream infections--United States, 2001, 2008, and 2009. MMWR Morb Mortal Wkly Rep. 2011 Mar 4;60(8):243-8. PMID: 21368740. 4) Infections Avoided, Excess Costs Averted, and Changes in Mortality Rate. Content last reviewed January 2013. Agency for Healthcare Research and Quality, Rockville, MD. https://www.ahrq.gov/hai/cusp/clabsi-final-companion/clabsicomp4c.html

Critical Care - 25 Addition Of Standardized Focused Critical Care Echocardiography (Fcce) Learning Into Existing Critical Care Fellowship Training Programs: A Multi-Center Prospective Study Of Blended Learning

Nibras Bughrara[1], Whitney Tse[1], Oliver Panzer[2], Tim Tran[3], Habib Srour[4], Andrew Gold[5], Sumit Singh[6], Ranjit Deshpande[7], Ashar Ata[1], Lorna Workman[1], Aliaksei Pustavoitau[8]

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Introduction: Focused Critical Care Echocardiography (FCCE) is a time-sensitive examination performed by a non-cardiologist to evaluate cardiocirculatory or respiratory failure which can be performed serially to evaluate the impact of therapy. 'Non-traditional' users including intensivists have been using FCCE for over 20 years now. However, standardized FCCE training in anesthesiology critical care fellowship programs does not exist as there is a paucity of both evidence-based curricula and faculty proficient in this modality. Our goal is to examine the impact of a standardized 5-day curriculum of blended FCCE learning into existing Critical Care Medicine Fellowship training programs. Blended learning, or mixed-mode classes incorporates a portion of an educational process from web-based sources into an educational initiative.

Methods: Our methodology is an adapted version from a study originally performed by Bughrara et al (1). After IRB approval, 36 critical care fellows at seven large academic medical centers participated in the study during 2019-2020 academic year. Educational activities followed outline of 4-days fundamental Critical Care Ultrasound course and 1-day advanced course developed by SCCM (Appendix 1). Standardized 30 MCQs knowledge tests created by the SCCM were the main assessment tool. All participating fellows received a pre-test at the beginning of the academic year, a post-test immediately after the course, and retention test during the last month of the academic year. Tested items included identification and acquisition of standard transthoracic views, recognition of cardiac structures and interpretation of images from presented clinical cases. Test scores were recorded and ranged from 1 to 30. Departing 10 fellows (academic year 2018-2019) from 3 institutions completed the retention at the end of their academic year, and their test scores were compared with the retention test scores of the 16 fellows at the same 3 institutions who took the 5-day course in the following academic year. Additionally, the pre-test scores and post-test scores for the 36 fellows who did the 5-day course were compared for improvement. Both parametric (Student's T, Paired T, Fisher's Exact) and non-parametric (Mann-Whitney, Wilcoxon signed-rank) tests were used as appropriate.

Results: 36 fellows in 7 institutions completed the 5-day standardized training course. Mean (SD) scores were available for 27 fellows who took pretest (18.0 (4.6)), 35 fellows who took post-test (24.8 (3.1)) and 33 fellows who completed retention test (25.2 (2.4)). Missing test data is related to pending IRB approval to use pretest scores (n=9) and off-cycle fellowship participation (n=3). Based on the passing score of 21/30 (70%) on the standardized test validated by SCCM, the passing rates for pre, post and retention tests were 29.6%, 88.6% and 97.0% respectively. The pre- and post-test scores were available for 26 fellows with a mean improvement of 6.5 (95% CI: 5.1 to 7.8, $p<0.001$). Among those who completed the course post and retention test scores were available for 32 fellows with a non-significant change in scores of 0.06 (95% CI: 0.7 to -0.8, $p<0.568$). The mean test scores of the 10 fellows that did not participate in the 5-day course was 22.2 and was lower by 2.9 units compared to the mean retention scores of 16 fellows from the same 3 institutions who completed the course which was 25. The corresponding pass rates among those not participating in the course was 60% and was significantly lower as compared to 93.8% among those who participated.

Conclusion: A 5-day course of blended FCCE learning in critical care fellowship programs results in rapid acquisition and retention of knowledge and improves FCCE knowledge test scores compared to alternative educational modalities. In addition, we were able to overcome other major obstacles to implement FCCE training like the paucity of trained faculty and lack of standardized curriculum. Implementation of the described course across medical centers will result in sustained passing score FCCE knowledge acquisition among critical care fellows.

References: 1) Bughrara NF, Meuli M, Renew JR, et al. How well do residents retain focused transthoracic echocardiography (FoTE) knowledge after a four-day extensive training program: a multicenter prospective study of anesthesiology residents. Abstract presented at: Anesthesiology of the American Society of Anesthesiologists; October 13-17, 2018; San Francisco, California.

Dear fellows,

Welcome to our Comprehensive Critical Care Echocardiography Hands-On training program, please find the Agenda below. You will be relieved of any clinical duties from 8:00 AM to 4:00 PM on the course days.

Agenda:

Monday September 7th:

8-11:30 am	Basic Physics and Knobology, Fundamental Windows and Views, Lung ultrasound
12:15 – 1 pm	Lunch and Clinical cases 1, Introduction to perceptual Adaptive learning Modules (PALMs)
1- 4 pm	SICU 1:1 Scanning with report generation for each patient scanned

Tuesday September 8th:

8-12 am	Assessment of Left ventricular systolic function, Intra Vascular Volume Assessment, point of care ultrasound in cardiac arrest
12- 1pm	Lunch and Clinical Cases 2
1-4 pm	PACU/SICU 1-1 Scanning

Monday September 15th:

8-12 am	Basic evaluation of RV, Pulmonary Embolism, Vascular Ultrasound, Pericardial tamponade
12-1 pm	Lunch and Clinical Cases 3
1-4 pm	SICU 1-1 Scanning

Tuesday November 16th:

8-12 am	Echo approach to shock, EASy- FAST, CC Echo limitation, CCE Board Certification
12- 1pm	Lunch and Clinical cases 4
1- 4 pm	SICU 1-1 Scanning

Friday January 21st

8-4 pm	Advanced hemodynamic measurements, advanced evaluation of left and right ventricular function, focus transesophageal echocardiography, focus echocardiograph evaluation in life support, the Histology in the ICU, valvular assessment in the critically ill.

- *By the end of October, a portfolio of at least 20 supervised CCE studies (performed with report generation) must be achieved by the trainee.*

Critical Care - 26 Respiratory Non-Invasive Venous waveform Analysis (RIVA) for Assessment of Respiratory Distress in COVID-19 Patients: An Observational Study

Bret Alvis[1], Lexie Vaughn[1], Jeffrey Schmeckpeper[1], Jessica Huston[2], Marisa Case[1], Matthew Semler[1], JoAnn Lindenfeld[1], Colleen Brophy[3], Kyle Hocking[4]

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Introduction: In well under a year, the coronavirus 2 (SARS-CoV-2) has spread globally leading to a global pandemic that has crippled both economies and healthcare.1,2 Evaluation and management of COVID-19 depends on the severity of the disease.2 Unfortunately, knowing whose symptoms will remain mild and who will acutely progress to severe respiratory failure have proven very difficult and, often, requires observation in a hospital setting.2 This sudden deterioration of patients with COVID-19 into critical illness is a major concern.3 Rapid and effective triage is critical for early treatment and effective allocation of hospital resources.3 This observational study describes a post-hoc discovery of the novel respiratory signal (RIVA) that has not been described to date. We report the relationship of the relative amplitude of the venous waveform to COVID-19 and the potential triage ability it holds for screening patients need for oxygen support therapy.

Methods: This is a post-hoc analysis of respiratory data from a single institution observational study of non-invasive venous waveform analysis (NIVA). Peripheral venous waveforms were recorded (Figure 1) from admission to discharge in enrolled COVID-19+ patients and healthy age-matched controls. Data were analyzed in LabChart 8 to transform venous waveforms to the frequency domain using Fast Fourier Transforms (FFT; Figure 2 &3). The peak respiratory frequency was normalized to the peak cardiac frequency to generate respiratory non-invasive venous analysis respiratory indexes (RIVA-RI). Paired Fisher's exact tests were used to compare RIVA-RI on admission and discharge. A nonparametric one-way ANOVA was used for multiple comparisons between groups for RIVA-RI, respiratory rate, and SpO2.

Results: In total, 50 COVID-19+ patients admitted to Vanderbilt University Medical Center from April-September 2020 were enrolled. Forty-five patient's venous waveforms were blindly analyzed and compared against 34 age-matched healthy controls. The RIVA RI for COVID-19+ patients requiring oxygen support during hospitalization (median = 0.27, IQR 0.11 – 1.28, n = 34) was significantly higher ($p < 0.01$; 95% CI 0.4008 – 2.037) than the RIVA RI for COVID-19 negative controls (median = 0.06, IQR 0.03 – 0.14, n = 34 and the RIVA RI for those same patients at time of discharge ($p = 0.02$, 95% CI 0.1023 – 1.939; median = 0.12, IQR 0.05 – 0.56, n = 24; Figure 4). RIVA RI of 0.64 demonstrated an AUC of 0.64 (sensitivity=92%, specificity=47%; Figure 5) as a predictor for requiring supplemental oxygen therapy during hospitalization. Positive predictive value was 93%. There was no significant difference ($p = 0.13$, 95% CI -0.7309 – 8.28) in the respiratory rate between COVID-19+ patients that required oxygen support during hospitalization (median= 20, IQR 19 - 25, n = 34) and those that did not require oxygen support during hospitalization (median=17, IQR 16 - 18, n =10) or between COVID-19+ patients on admission to the hospital (median= 20, IQR 19 - 25, n = 34) and at discharge (median=19, IQR 17 - 20, n = 27; $p = 0.66$, 95% CI -1.944 – 4.974). COVID-19+ patients that required oxygen support during hospitalization had a significantly lower oxygen saturation (SpO2) on admission (median= 93%, IQR 91 – 95%, n = 34; $p < 0.01$, 95% CI 2.536 – 8.727) and at discharge (median=93, IQR 92 – 95%, n = 27; $p < 0.01$, 95% CI 0.8066 – 7.426) than COVID-19 positive patients that did not require oxygen support during hospitalization (median=96, IQR 94 - 98, n = 10).

Conclusion: The peripheral venous waveform signal is able to be captured non-invasively in hospitalized COVID-19 patients. RIVA RI is a novel physiological measurement with a promising ability to predict the need for oxygen support therapy in COVID-19 patients. With the exploding need for efficient and correct triage, RIVA monitoring could aid clinicians in caring for

patients both at home and at the hospital and potentially prevent unnecessary hospitalizations.

References: 1. Klompas M. Coronavirus Disease 2019 (COVID-19): Protecting Hospitals From the Invisible. Ann Intern Med 2020; 172(9): 619-20. 2. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. N Engl J Med 2020. 3. Liang W, Yao J, Chen A, et al. Early triage of critically ill COVID-19 patients using deep learning. Nat Commun 2020; 11(1): 3543.

Figure 1. Picture representation of RIVA device used to capture the venous waveforms that contain the cardiac and respiratory harmonics in COVID-19 and control subjects.

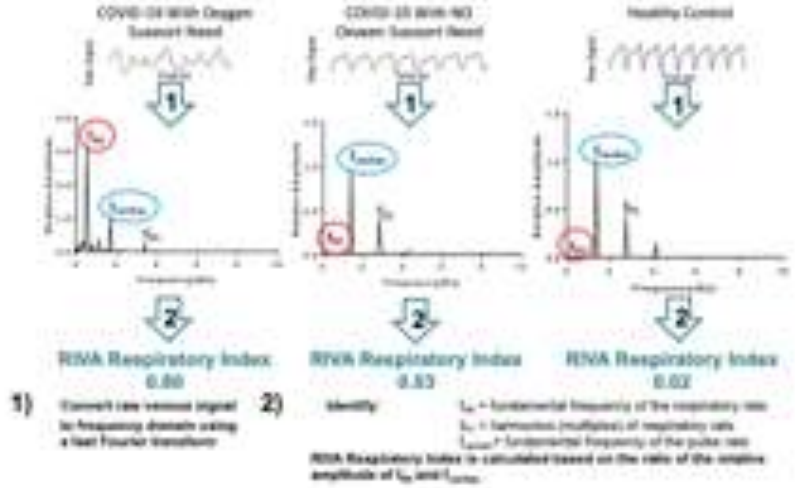

Figure 2. Representative RIVA respiratory signals from subjects with high to low risk of O_2 support need (left to right). Raw signals are transformed from the time domain (top) to the frequency domain (bottom) (1). The relative amplitude of the respiratory rate (f_{Resp} fundamental frequency) compared to the relative amplitude of the pulse rate ($f_{Cardiac}$) is used to calculate a RIVA Respiratory Index.

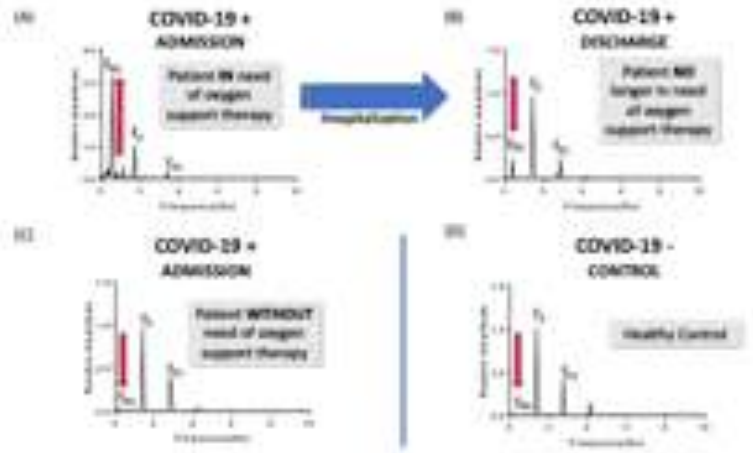

Figure 3. Representative examples of f_{AI} amplitude changes in the frequency domain recorded in COVID-19+ subjects. The fast fourier transform (FFT) of venous waveform recorded using non-invasive venous waveform analysis (NIVA) in COVID-19+ subjects admitted requiring oxygen support therapy (A) and at time of discharge when oxygen support was no longer required (B). A representative FFT of a COVID-19+ subject that did not require any oxygen support therapy and, for comparison, the FFT of a COVID-19 – healthy control subject (D). Abbreviations: COVID 19+ = positive for the SARS-CoV-2 virus; COVID-19- = negative for the SARS-CoV-2 virus.

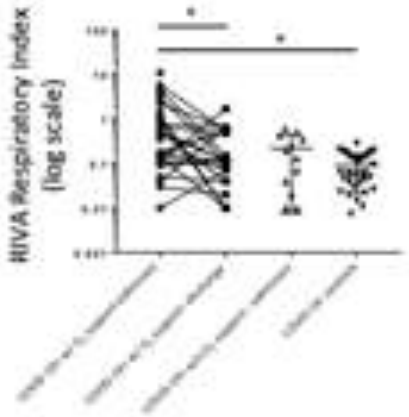

Figure 4. RIVA Respiratory Index (RIVA RI) for COVID-19 positive patients and COVID-19 negative controls. Venous waveforms were obtained using the RIVA device for patients admitted to Vanderbilt University Medical Center (VUMC) with COVID-19 from April - September 2020. The amplitude of the respiratory signal relative to the amplitude of the cardiac signal was derived from the venous waveforms after fast Fourier transformation and this ratio represents the RIVA RI. The RIVA RI for COVID-19 positive patients (COVID-19+) admitted to the hospital and requiring oxygen support during hospitalization (median = 0.27, n = 34) was significantly higher ($p < 0.01$, 95% CI 0.4008 – 2.037) than the RIVA RI for COVID-19 negative controls (median = 0.06, n = 34). The RIVA RI for COVID-19 + patients that required oxygen support was also significantly higher ($p = 0.02$, 95% CI 0.1023 – 1.939) than the RIVA RI for those same patients at time of discharge (median = 0.12, n = 24). The RIVA RI was not significantly different ($p = 0.09$, 95% CI -0.1242 – 2.265) for COVID-19+ patients that required oxygen support during hospitalization and those COVID-19+ patients that never required oxygen support during hospitalization (median = 0.2, n = 11). Statistical analysis was completed using ANOVA with multiple comparisons between groups. Horizontal bars with star (*) demonstrate statistical significance.

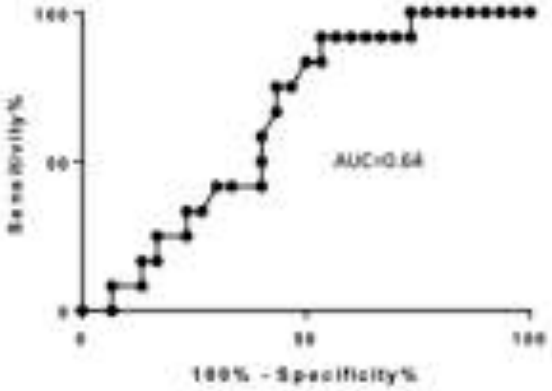

Figure 5. AUC for predicting oxygen requirement with RIVA RI. A RIVA RI of ≥ 0.6 demonstrates 92% sensitivity (95% CI, 61.52% to 99.79%) and 47% specificity (95% CI, 28.34% to 65.67%) for predicting need for oxygen support during admission for COVID-19 positive patients with an area under the ROC curve of 0.6431.

Critical Care - 27 Combined Use of ECMO, Prone Positioning, and APRV in the Management of Severe COVID-19 Patients

Stephanie Ong[1], Hossam Tantawy[2], Roland Assi[2], Astha Chichra[2], Miriam Treggiari[2]

[1]University of Toledo, Toledo, OH, [2]Yale University, New Haven, CT

Introduction: The ongoing COVID-19 pandemic has resulted in an overwhelming number of ICU admissions, posing a significant challenge for the ICU community. Acute Respiratory Distress Syndrome (ARDS) is one complication of severe COVID-19 infection and may lead to rapid clinical deterioration, warranting extracorporeal membrane oxygenation (ECMO) in the most critical cases. A recently conducted literature review reported that the mortality rates for patients with COVID-19 admitted to the ICU is 40%, and 45% for those with associated ARDS. [1] In the context of the current pandemic, there have been reports of small series regarding the role of ECMO on patient outcomes. One retrospective cohort study reported a 57% mortality rate in COVID-19 ARDS patients on ECMO compared to 63% in those only mechanically ventilated, but this difference was not significant. [2] Another retrospective cohort study of COVID-19 patients with ARDS who received ECMO found a 60-day mortality of 31% and a 90-day mortality of 36%. [3] During the COVID-19 pandemic, we have employed an unconventional mix of therapeutic modalities while managing COVID-19 patients with severe, refractory ARDS, including prone positioning while on ECMO. We designed a study to evaluate the safety, physiologic changes in oxygenation and hemodynamic profile, and complications observed during ECMO, prone positioning, and APRV in a cohort of patients who received veno-venous (VV) ECMO support for COVID-19-associated ARDS.

Methods: This retrospective cohort study included adult patients with COVID-19-associated ARDS who required VV-ECMO. Three intervention groups were defined: patients who received ECMO support (ECMO only), and patients who underwent prone positioning prior to or after ECMO (prone only) and while on ECMO (ECMO + prone). In addition to demographics of the entire cohort, we collected physiologic variables and ventilation settings at four time points for each modality: pre (prior to intervention), 1h-post (within one hour after intervention), 6h-post (six hours after intervention), and 24h-post (24 hours after intervention). Patients were placed in the prone position by a dedicated prone team consisting of three nurses, who regularly proned patients throughout the hospital, a respiratory therapist, a perfusionist, and the patient's bedside nurse. Patients were ventilated with either assist-control or airway pressure release ventilation (APRV). Patient tolerance of the intervention(s) was evaluated through changes in vital signs, ventilation settings, and pressor requirements before and after intervention initiation. We also documented the frequency of intervention-related complications, such as deep tissue injury and cannula damage. Post-intervention (1h-, 6h-, and 24h-post) continuous variables were compared with baseline (pre) using one-sample paired t-tests. We used Bonferroni correction to account for multiple comparisons. A two-sided alpha level of 0.05 was required for statistical significance.

Results: We included 14 patients (mean age 48.1 [SD 9.3] years, male [100%]) who received VV-ECMO support, with ten undergoing prone positioning while not on ECMO, and seven while on ECMO (Table 1). Thirteen patients were ventilated using APRV while on ECMO. Patients on ECMO had an improvement in oxygen saturation, PaO_2/FiO_2 ratio, and minute ventilation up to 24 hours post intervention (Table 3). Vasopressor requirements increased with ECMO support at 1h- and 24h-post time points. Prone positioning, while on and not on ECMO, was not associated with clinically significant hemodynamic or respiratory changes. All patients sustained deep tissue injuries, but only those on the face or chest were related to prone positioning. One patient required cannula replacement due to cannula damage. The overall in-hospital mortality was 43%.

Conclusion: The use of VV-ECMO, prone positioning, and APRV in a select population of patients with COVID-19 ARDS was generally overall well-tolerated, however, the physiologic improvements observed were marginal. Patients sustained deep tissue injuries that resolved without further complications and were not entirely related to prone positioning. Cannula complications were rare (one patient), and the patient would have likely required cannula exchange regardless of prone positioning. Given the impact of these complications on patient care, it is critical for clinicians to be aware of these risks and be prepared to address them should they arise.

References: 1. Critical care (London, England), 24, 516-16, 2020. 2. Critical Care Medicine, 48, 1289-95, 2020. 3. The Lancet Respiratory Medicine, 8, 1121-31, 2020.

Table 1. Patients' demographics and baseline characteristics at hospital admission.

Variable	N (%)	Mean (SD)
Age (y)	14 (100)	48.1 (9.3)
Gender		
Male	14 (100)	
Race		
White or Caucasian	6 (43)	
Black or African American	2 (14)	
Other / Not Listed	6 (43)	
BMI (kg/cm^2)	14 (100)	36.5 (6.2)
SOFA Score (0 - 24)		
ECMO	12 (86)	12.6 (1.2)
Prone	13 (93)	11.9 (1.3)
APRV	9 (64)	11.6 (4.5)
WHO Illness Severity Score	14 (100)	5.9 (1.4)
4 Hospitalized, O_2 mask or nasal cannula	4 (29)	
5 Non-invasive ventilation or high-flow O_2	1 (7)	
6 Intubation and mechanical ventilation	1 (7)	
7 Ventilation + additional organ support	8 (57)	
ECMO duration (days)	14 (100)	22.2 (7.5)
Prone Only	10 (66.7)	
Duration (hours)		14.6 (3.8)
Sessions		2.1 (1.4)
Prone + ECMO	7 (46.7)	
Duration (hours)		16.2 (2.9)
Sessions		4 (3.6)

Table 2. Patients' characteristics at hospital discharge.

Variable	N (%)	Mean (SD)
ICU stay (days)	14 (100)	37.4 (13.8)
Hospital stay (days)	14 (100)	41.7 (18.2)
WHO Illness Severity Score	14 (100)	5.6 (2.3)
2 Limitation of activity	1 (7)	
3 Hospitalized, no O_2 therapy	1 (7)	
4 Hospitalized, O_2 mask or nasal cannula	5 (36)	
6 Intubation and mechanical ventilation	1 (7)	
8 Death	6 (43)	

Table 3. Changes in Vital Signs and Ventilator/ECMO Settings Before and After the Intervention. Data are expressed as mean (SD).

Variable	Pre	1 h-post	6 h-post	24 h-post	p-values*
ECMO					
Temperature (°C)	37.2 (2.2)	36.9 (0.61)	36.4 (0.7)	36.6 (0.17)	> 0.99; 0.784; > 0.99
HR (beats/min)	113.2 (13.8)	97.2 (12.6)	87.4 (20.0)	93.6 (19.9)	0.001; 0.0004; 0.117
RR (breaths/min)	30.9 (4.3)	17.9 (10.5)	16.7 (9.1)	11.6 (6.4)	0.230; 0.023; 0.075
Systolic BP (mmHg)	113.8 (16.6)	116.3 (19.5)	109.4 (12.0)	117.8 (21.7)	> 0.99; 0.837; > 0.99
O_2 Saturation (%)	90 (5.3)	98.5 (2.5)	97.9 (2.2)	96.4 (2.9)	0.009; 0.009; 0.021
ECMO Sweep (L/min)	NA	5.2 (1.9)	4.6 (1.4)	5.7 (1.4)	
PaO_2/FiO_2 Ratio (mmHg)	93.4 (35.4)	213.4 (126.1)	210.4 (94.3)	222.3 (67.0)	0.027; 0.039; 0.002
Tidal Volume (mL/kg)	370.7 (68.5)	329.9 (123.6)	228.1 (115.8)	181 (123.7)	0.515; 0.0002; 0.001
Total RR (breaths/min)	29.2 (5.1)	17.7 (10.6)	14.8 (6.8)	11.6 (5.7)	0.047; 0.0004; 0.0007
Minute Ventilation (L/min)	10.7 (2.0)	5.7 (3.9)	3.0 (2.1)	2.1 (1.4)	0.034; 0.00001; 0.000002
PEEP (cmH_2O)	16 (3.3)	16.3 (3.1)	15.6 (3.0)	14.5 (2.8)	> 0.99; > 0.99; > 0.99
Plateau Pressure (cmH_2O)	34.9 (5.2)	34.7 (5.0)	31.3 (4.2)	26.8 (6.1)	> 0.99; 0.449; 0.130
Prone Positioning while Not on ECMO					
Temperature (°C)	37.7 (1.5)	38.1 (1.5)	38.4 (1.1)	37.4 (1.9)	0.223; 0.532; > 0.99
HR (beats/min)	98.9 (18.1)	98.5 (17.1)	107.1 (18.4)	106.2 (19.8)	> 0.99; 0.496; > 0.99
RR (breaths/min)	27.6 (5.3)	24.6 (7.5)	28.3 (4.6)	32.5 (2.7)	> 0.99; > 0.99; > 0.99
Systolic BP (mmHg)	119.3 (11.2)	129.2 (25.3)	113 (14.0)	120.2 (13.0)	0.844; 0.366; > 0.99
O_2 Saturation (%)	91.4 (4.5)	93.5 (3.9)	94 (3.3)	92.9 (5.0)	0.361; 0.206; 0.713
PaO_2/FiO_2 Ratio (mmHg)	98.5 (32.8)	124.3 (53.2)	123.2 (41.5)	118.2 (46.3)	0.170; 0.087; 0.396
Tidal Volume (mL/kg)	387.3 (48.7)	376.2 (33.7)	364 (42.9)	374.7 (69.7)	> 0.99; 0.512; > 0.99
Total RR (breaths/min)	26.7 (4.5)	28.8 (3.5)	28.9 (3.8)	28.6 (3.8)	0.220; 0.080; 0.282
Minute Ventilation (L/min)	10.4 (2.3)	10.9 (1.8)	10.6 (2.1)	10.8 (2.8)	0.955; > 0.99; > 0.99
PEEP (cmH_2O)	15.3 (1.7)	15.8 (2.7)	15.2 (2.5)	14.8 (2.2)	1; 0.585; 0.507
Plateau Pressure (cmH_2O)	35.3 (5.2)	34.8 (4.5)	33.7 (3.3)	32.5 (2.7)	0.960; 0.740; 0.107
Prone Positioning while on ECMO					
Temperature (°C)	36.7 (0.36)	36.6 (0.18)	36.7 (0.15)	36.6 (0.11)	> 0.99; > 0.99; 0.891
HR (beats/min)	102.3 (26.3)	100.6 (23.6)	91.3 (17.2)	95.9 (22.9)	> 0.99; 0.436; > 0.99
RR (breaths/min)	9.8 (3.5)	13.2 (4.3)	11.8 (10.3)	13 (9.1)	0.187; > 0.99; 0.799
Systolic BP (mmHg)	133.3 (20.8)	131.4 (20.3)	126.1 (16.2)	109.4 (10.5)	> 0.99; > 0.99; 0.038
O_2 Saturation (%)	92.1 (3.4)	94.9 (3.6)	95.4 (3.3)	95.7 (2.9)	0.307; 0.223; 0.145
ECMO Sweep (L/min)	6.1 (2.4)	6.1 (2.4)	6.8 (1.8)	6.5 (2.1)	
PaO_2/FiO_2 Ratio (mmHg)	76.6 (10.0)	90.5 (30.4)	94.3 (28.4)	81.7 (31.9)	0.605; 0.397; > 0.99
Tidal Volume (mL/kg)	244.1 (148.4)	190.7 (147.0)	192.1 (145.1)	241.6 (140.0)	0.752; 0.838; > 0.99
Total RR (breaths/min)	10.7 (5.9)	16.1 (13.8)	13 (10.0)	13.3 (11.6)	0.796; > 0.99; > 0.99
Minute Ventilation (L/min)	2.1 (1.2)	2.3 (1.9)	2.1 (1.8)	2.5 (1.4)	> 0.99; > 0.99; > 0.99
PEEP (cmH_2O)	13.7 (3.7)	13.7 (3.7)	13.7 (3.7)	13.7 (3.7)	NA; NA; NA
Plateau Pressure (cmH_2O)	28.9 (5.5)	28.9 (5.5)	28.9 (5.5)	28.9 (5.5)	NA; NA; NA

HR heart rate, *RR* respiratory rate, *BP* blood pressure, *ECMO* extracorporeal membrane oxygenation, *PaO2* partial pressure of oxygen in arterial blood, FiO_2 fraction of inspired oxygen, *PEEP* positive end-expiratory pressure.

* p-values comparing pre *versus* the post-intervention time points; 1 h (1st p-value), 6 h (2nd p-value), 24 h (3rd p-value). P-values are adjusted for multiple comparisons using Bonferroni corrections.

Critical Care - 28 Cardiac Output Estimation by Multi-Beat Analysis of Arterial Blood Pressure Waveform versus Continuous Pulmonary Artery Thermodilution in Post Cardiac Surgery Intensive Care Unit Patients

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Introduction: Cardiac output estimation is a critical component of monitoring critically ill patients after cardiac surgery. We sought to access the correlation between cardiac output estimation using a novel multi-beat analysis of arterial blood pressure waveform versus a traditional continuous pulmonary artery catheter guided thermodilution method.

Methods: After institutional review board approval, we prospectively enrolled adult cardiac surgical patients recovering post-operatively in the cardiovascular surgical intensive care unit of our tertiary care university hospital. Eligible patients had a functioning pulmonary artery catheter (PAC) and a radial artery line. Continuous thermodilution cardiac output measurements (CO-CTD) obtained via the PAC were retrieved from the electronic medical records (EMR) at a resolution of one measurement every 15 minutes. The arterial blood pressure waveform was fed into the Argos CO monitor (Retia Medical; Valhalla, NY, USA) via a reusable cable connected to the bedside patient monitor. The Argos monitor analyzes the arterial line blood pressure waveform using multi-beat analysis (MBA) and provides CO estimates (CO-MBA) once every 5 seconds. For every available CO-CTD measurement, CO-MBA was averaged over the preceding 30 minutes, in order to obtain paired CO-CTD and CO-MBA measurements.
Correlation between CO-CTD and CO-MBA was computed within subjects, taking repeated observations into account and removing the between subject variability. Agreement between CO-CTD and CO-MBA was assessed via Bland-Altman analysis, accounting for multiple observations within patients. Specifically, the difference between CO-MBA and CO-CTD was modeled as $D_{ij}=\mu+b_i+\epsilon_{ij}$ where D_{ij} is the difference between CO-MBA and CO-CTD, μ is the bias, b_i is the intercept specific to the ith subjects, and ϵ_{ij} is the residual for the jth measurement in the ith subject. The overall variance of D_{ij} is given by the sum of the variances of b_i and ϵ_{ij}.

Results: Out of the 26 eligible patients, 1 was rejected due to unavailability of continuous thermodilution CO measurements (CO-CTD) from the PAC. One patient was further excluded due to underdamped arterial BP waveforms evident in square wave tests performed throughout the recording. Median length of monitoring where measurement of CO-CTD overlapped with CO-MBA was 14 hours and 15 minutes. A total of 1012 paired measurements across 24 patients was available for final analysis. Mean CO-CTD was 5.12 L/min and mean CO-MBA was 5.54 L/min. Paired observations showed a moderate correlation ($r= 0.62$, $p<0.001$) across a range of values of CO-CTD and CO-MBA. (Figure 1) Bland-Altman plot of the difference between CO-MBA and CO-CTD, plotted against their mean, for all paired measurements showed a mean of differences (bias) of 0.43 L/min +- 1.08 L/min, 95% limits of agreement -1.69 to 2.55 L/min, and a percentage error of 39.4 %. (Figure 2)

Conclusion: Cardiac output measurements using a novel multi-beat analysis of radial artery pressure waveform are moderately correlated with the traditional more-invasive pulmonary artery thermodilution guided cardiac output measurements. Our results agree with a previous validation of the MBA method in 31 post-cardiac surgery patients in the ICU, where a percentage error of 40.7% was reported. Pending larger datasets, intensivists and anesthesiologists have the option of using a relatively non-invasive, easy to use method of cardiac output estimation in post cardiac surgery patients.

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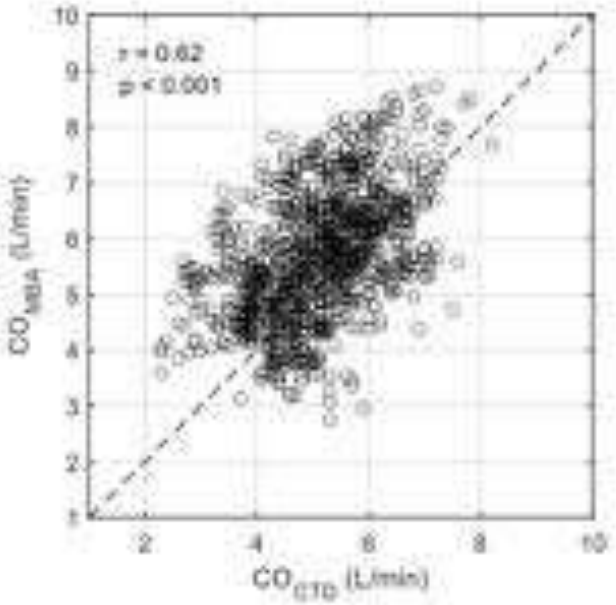
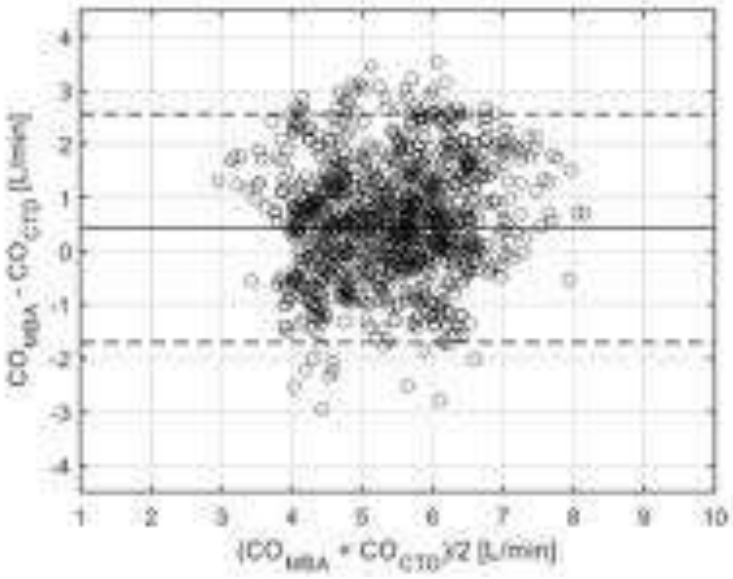
Journal of Clinical Monitoring and Computing 2020
Aug;34(4):643-648.





Critical Care - 29 Proning in the ICU for Management of SARS from COVID-19

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Introduction: Since the initial reports of the novel coronavirus, SARS-CoV-2, from the Wuhan province in China, this outbreak has rapidly spread to other countries in the world (1-6). Although most patients with this infection (COVID-19) are either asymptomatic or have mild upper respiratory track symptoms; patients with comorbidities are prone to developing a pneumonic process leading to severe acute respiratory syndrome (SARS) requiring invasive positive pressure pulmonary ventilation. We examined the role of proning during the management of SARS during the initial weeks of COVID-19 epidemic at a tertiary referral medical center in New Orleans.

Methods: Following IRB approval, all adult patients from the 13th of March to the 8th of April 2019 with a diagnosis for COVID-19 infection and who required invasive positive pressure pulmonary ventilation from SARS were entered into this study. Diagnosis for COVID-19 was based upon a single positive nasopharyngeal swab or tracheal aspirate obtained through the endotracheal tube with a real-time polymerase chain reaction for SARS-CoV-2 (7). Categorical variables were presented as counts and percentages with 95% confidence intervals (CI) with differences between the groups assessed using chi-square tests with P values set for statistical significance at <.005 (8) to reduce the risk of false discovery rates (9). Measures of effect size were expressed as percentages with 95% CI (10-12).

Results: Forty-two of 211 patients with SARS were proned (20% CI 15-26%) during the course of their hospital stay. Most patients underwent this procedure within the first week following ICU admission (Figure 1). The outcomes from proning are shown in Table 1. Hospital mortality rates were higher in proned patients when compared to patients who were not proned with a risk difference of 23% CI 8-35.1% (Table 1). SpO2 nadirs measured at admission and for the first seven days of hospital admission are shown individually and as box plots (Fig. 2). There were no discernable differences in the nadir SpO2 values in SARS patients who underwent proning (blue box plots) versus SARS patients who did not undergo this procedure (red box plots; Fig. 2).

Conclusion: Proning is not supported as a therapeutic modality as hospital mortality rates were higher in this patient population.

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Figure 1

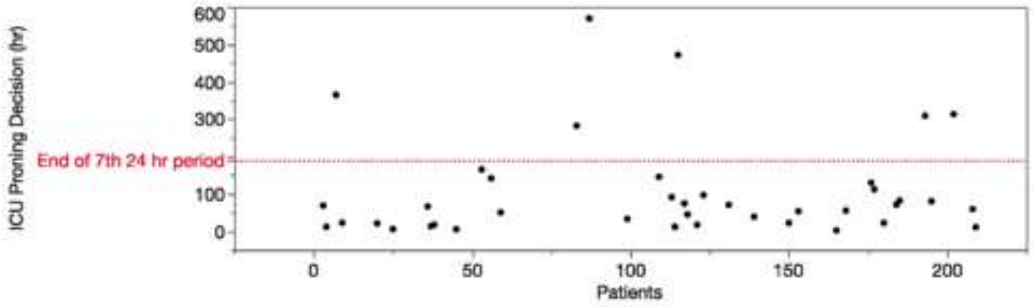


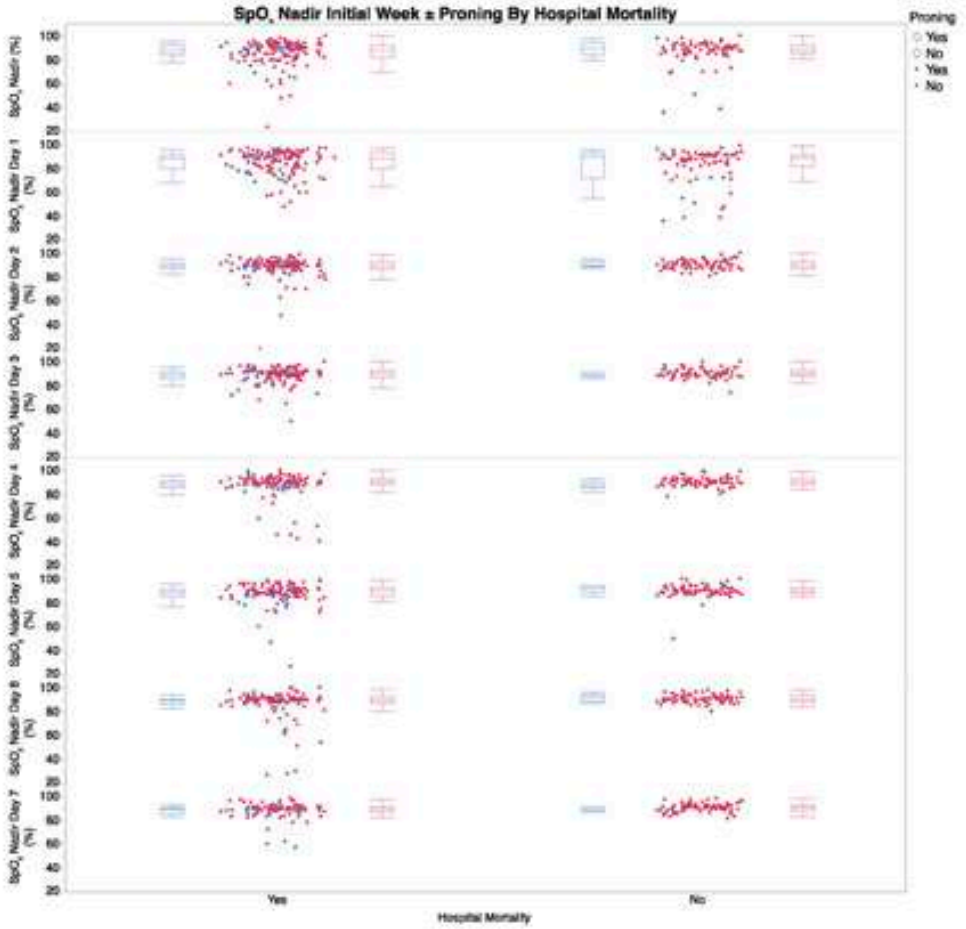
Table 1

Hospital Mortality Rates by Proning in SARS Patients with COVID-19 who Required Invasive Pulmonary Ventilation

		Proning		
	n (%)	Yes	No	Risk Differences % [CI]
Hospital Mortality	Yes	35 (83.3)	7 (16.7)	23 CI [8-35.1]
	No	102 (60.4)	67 (39.6)	

n (%): number and percentage of patients; CI: 95% confidence interval. ChiSquare=7.8, P=.0052; P values <.005 are statistically significant.

Figure 2



Legend: SpO_2 nadirs during the initial hospital course of stay individually expressed as dots and summated as box plots. Blue box plots and dots are proned patients; Red box plots and red dots are non-proned patients.

Critical Care - 30 The Role Of An Amyloid Beta–Trpm2 Interaction In Causing Post-Stroke Cognitive Impairment And Synaptic Dysfunction

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Introduction: Despite the increasing use of thrombolytics and mechanical thrombectomy in acute stroke management, cognitive impairments and memory loss remain a chronic problem afflicting stroke survivors. It is increasingly clear that in addition to neuronal injury following cerebral ischemia, impaired functional networks contribute to long-term deficits in learning, memory, and executive function. The mechanisms underlying these changes are poorly defined, but may involve perturbations in pathways involved in both neurodegeneration and oxidative stress. In this study, we used both behavioral paradigms and electrophysiological assessment of synaptic potentiation in mice subjected to a large-vessel ischemic stroke to evaluate the role of amyloid beta and the ion channel TRPM2 in mediating hippocampal dysfunction after a stroke.

Methods: Extracellular field recordings of CA1 neurons were performed in acute hippocampal slices prepared 30 days after recovery from transient middle cerebral artery occlusion (MCAo, 45 min) in adult (6-8 week) mice. Long-term potentiation (LTP) was then assessed to evaluate for synaptic plasticity. A behavioral fear conditioning paradigm was used to evaluate contextual memory 30 days after MCAo. An ELISA assay was used to quantify soluble Aβ40 and 42 from the hippocampus of MCAo and sham mice. To evaluate if Aβ42 impairment of LTP is dependent on TRPM2, a calcium-permeable ion channel that regulates neuronal damage during ischemia, slices were treated with Aβ42 oligomers with and without our newly developed peptide inhibitor of TRPM2 (tatM2NX) and LTP was measured. Finally, the ability of TRPM2 to alter cognitive impairments after a stroke were assessed by treating MCAo mice with a tatM2NX inhibitor 29 days following the stroke and performing behavioral analysis.

Results: Recordings obtained in brain slices 30 days after MCAO exhibited near complete loss of LTP (161±9%, n=6 in sham compared to 115±4%, n=7 30 days after MCAO) in the ipsilateral hippocampus. Similar deficits in LTP were observed in the contralateral hippocampus. Impairments in memory function, measured using contextual fear conditioning, were consistent with our LTP findings. MCAO decreased freezing behavior, indicating lack of memory (65±7% in sham mice (n=6) and 37±7% in MCAO mice, n=7). We observed a 61% increase in Aβ40 and a 48% increase in Aβ42 in the hippocampus 30 days after MCAo. Consistent with previous studies, we observed that addition of Aβ42 oligomers (500 nM) impaired LTP (160±9%, n=5 in control compared to 104±6%, n=3 Aβ42). This impaired LTP was prevented with co-application of the TRPM2 channel inhibitor tatM2NX (145±13%, n=3), demonstrating that TRPM2 is a downstream target of Aβ. MCAO mice treated with tatM2NX (20 mg/kg iv injection 24 hr before testing) on day 29 post MCA demonstrated increasing freezing to 72±5% (n=9), suggesting improved contextual memory and highlighting the role of role of TRPM2 channels in post-stroke cognitive impairment.

Conclusion: These data indicate that MCAo causes hippocampal dysfunction consistent with post-stroke cognitive impairment. Our data implicates increased levels of soluble Aβ42 in the hippocampus following stroke, resulting in activation of TRPM2 channels and impaired synaptic plasticity. Therefore, reducing soluble Aβ42 and/or inhibition of TRPM2 channels at chronic time points following ischemia may represent a novel strategy to improve functional recovery following stroke.

Economics, Education and Policy

Economics, Education and Policy - 1

Implementation of a Diversity, Equity, and Inclusion (DEI) Curriculum to Residents: Workshops Targeted at Enhancing Performance Regarding Unconscious Bias, Allyship, and Microaggression

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Introduction: The rate of burnout seems to be more prevalent among women, trainees, and perioperative specialties, particularly general surgery. In 2018, a cross-sectional national survey of general surgery residents (n=7409) demonstrated that 31.9% reported discrimination based on their self-identified gender and 16.6% reported racial discrimination. Furthermore, patients and their families were the highest source for racial discrimination as reported by 47.4% of residents and gender discrimination as reported by 43.6% of residents. There is unfortunately not much guidance for physicians and hospitals to navigate ways of effectively balancing medical personnel's employment rights, patients' interests, and the duty to treat. Utilizing the framework of the Kirkpatrick Evaluation Model, this graduate medical education training series focuses on transferring DEI knowledge (level 2) into applied behaviors (level 3). The DEI curriculum centers around three core concepts including unconscious bias, microaggressions, and allyship. The series' objective is to curate facilitated spaces that will support faculty and residents in their ability to effectively engage in difficult dialogues and take action to support the lives of people who have long been marginalized within healthcare and society.

Methods: This study is a pretest-posttest design of a 4-series workshop utilizing activities to enhance competence and performance around unconscious bias, allyship, and microaggression. A needs assessment survey was administered at the end of an introductory session, which highlighted national data regarding mistreatment and discrimination of residents and each workshop session's goals and objectives. The diversity curriculum is being administered in a virtual format to all first-year clinical anesthesia residents and senior general surgery resident (PGY-4 and PGY-5) at UCSF from August 2020 to April 2021. The remaining anesthesia and surgery residents will be surveyed as a control group in April 2021. A post-curriculum survey will be administered after each 2-hour workshop and 6 months later after the fourth 2-hour (DEI) workshop to the participating residents. The anesthesia residents have didactic protected non-clinical time composed of lectures, workshops, and simulations every two weeks where half of the class is expected to attend. This recurring two-hour block was used to coordinate the availability of the senior surgery residents. The University of California San Francisco Institution Review Board deemed this study exempt from review (5/14/20). The survey items were adapted from previously published and validated instruments. Pretest cognitive interviews were conducted with 2 anesthesia fellows to assess the overall clarity, coherence, and balance of each survey question. The surveys were then iteratively revised and retested in a larger sample of 10 second-year and 6 fourth-year medical students prior to administration of the surveys to the resident participants.

Results: We used a previously published assessment tool that consists of 5 Likert-scaled items to assess the concepts around unconscious bias, allyship, and frequency of conflict resolutions around microaggression. Participants provided demographic data including race, gender, sexual orientation, specialty, and previous experience with formal training for conflict resolution. The needs assessment surveys included questions about the curriculum's relevance to their future workplace career, the effectiveness of the facilitation, and whether they would recommend it to other peer colleagues. Lastly, the survey allowed residents to leave comments about what they thought were the most effective portions of the introductory DEI session and suggestions on how to improve the workshop. Twenty-four residents attended the introductory DEI session and completed the needs assessment online survey, giving us a response rate of 100% from twenty first-year clinical anesthesia residents and four senior surgery residents. Of those who responded, 87.5% felt that the workshop demonstrated the importance of the DEI curriculum to their training, that the workshop was relevant to their

workplace, and that they would recommend the workshop to their peers (Table 1).

Conclusion: While primary care specialties have addressed educational tools for DEI, perioperative specialties have done little to address this gap among trainees within graduate medical education programs demonstrating the need for this curriculum.

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Table 1. Resident Evaluations of Introductory DEI Workshop (N = 24)

Statement	Strongly disagree	Somewhat disagree	Neutral	Somewhat agree	Strongly agree
This introductory workshop showed me that a DEI curriculum is important to my training.	0.00%	4.17%	8.33%	37.50%	50.00%
I believe this workshop is relevant to my workplace.	0.00%	0.00%	12.50%	20.83%	66.67%
I would recommend this workshop to my peers.	0.00%	0.00%	12.50%	41.67%	45.83%

Estimating Preventable COVID-19 Infections Related to Elective Outpatient Surgery: A Quantitative Model

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Introduction: As the number of suspected and confirmed COVID-19 cases in the US continues to rise, the US surgeon general, Centers for Disease Control and Prevention, and several specialty societies have issued recommendations to consider canceling elective surgeries. However, these recommendations have also faced controversy and opposition.

Methods: Using previously published information and publicly available data on COVID-19 infections, we calculated a transmission rate and generated a mathematical model to predict a lower bound for the number of healthcare-acquired COVID-19 infections that could be prevented by canceling or postponing elective outpatient surgeries. Since Washington (WA) was affected early on by the COVID-19 pandemic in the US and has relatively reliable data on COVID-19 infections compared to other US states, we used WA as a test case for our model.

Results: Our model predicts that over the course of 30 days, at least 75.9 preventable patient infections and at least 69.3 preventable healthcare worker (HCW) infections would occur in WA state alone if elective outpatient procedures were to continue as usual.

Conclusion: In the absence of COVID-19 testing, canceling elective outpatient surgeries during the COVID-19 pandemic could prevent a large number of patient and healthcare worker infections. With appropriate data, our model can also provide predictions for different regions and time ranges, and thus may be a useful policy tool.

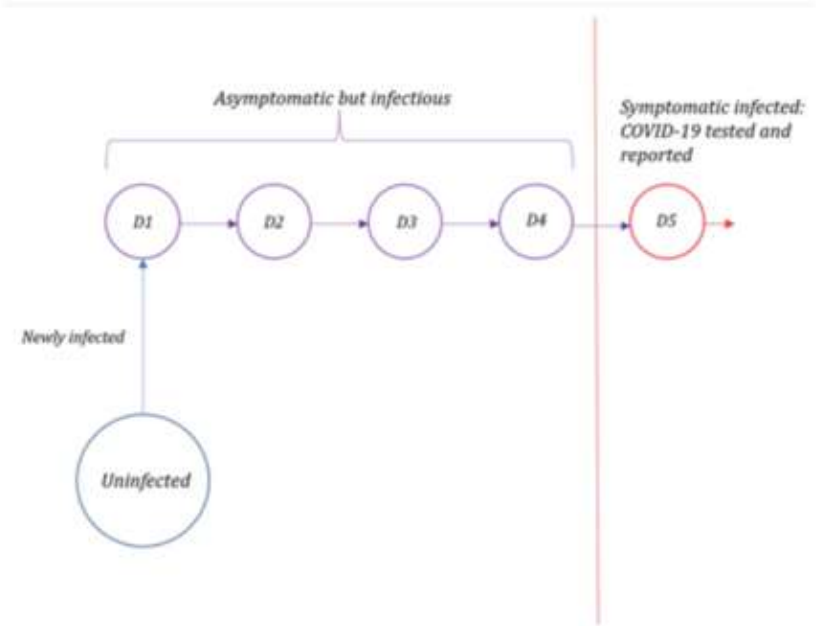

Figure 1. Timeline of Infection for Confirmed COVID19 Cases. After infection, the individual can transmit the infection to others but does not become symptomatic until day 5, at which point they become eligible for COVID19 testing and their infection is discovered and reported.

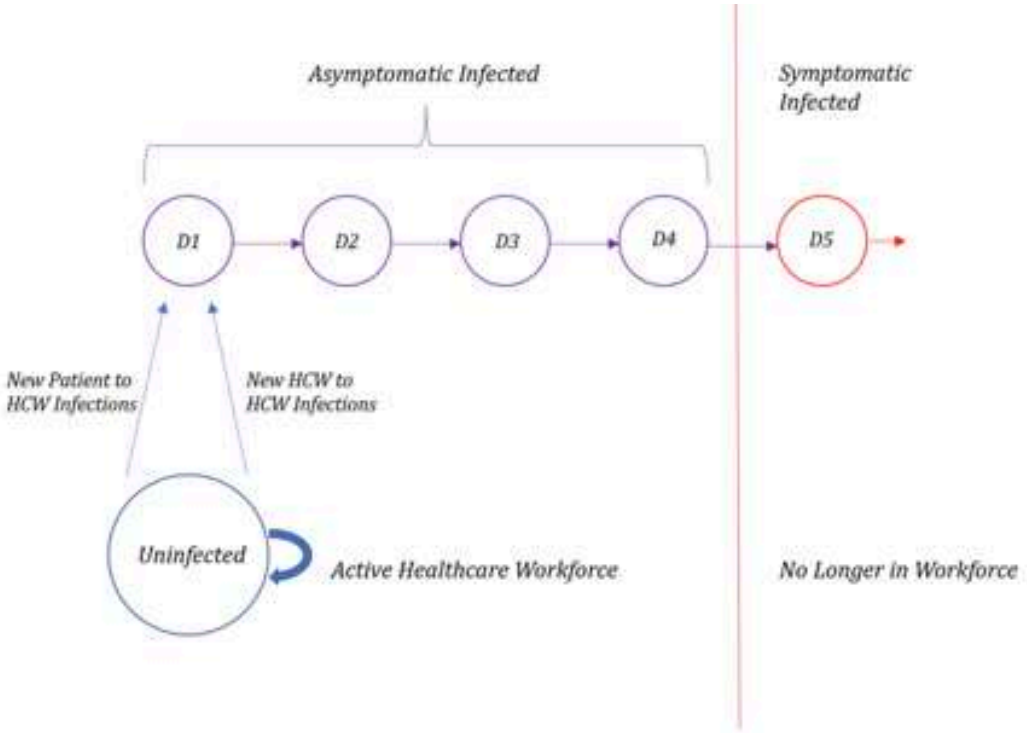

Figure 2. Markov Chain for Healthcare Workers. Healthcare workers (HCW) who are uninfected on any given day can either stay uninfected or become newly infected, at which point they would proceed to day 1 of infection the next day. Individuals who are infected will proceed to the next day of infection with each passing day. On days 1-4 of infection, infected HCW are asymptomatic and therefore continue to fully participate in the workforce, exposing other individuals to the risk of COVID19 infection. On day 5 of infection, infected individuals begin showing symptoms, at which point they may no longer participate in the perioperative workforce.

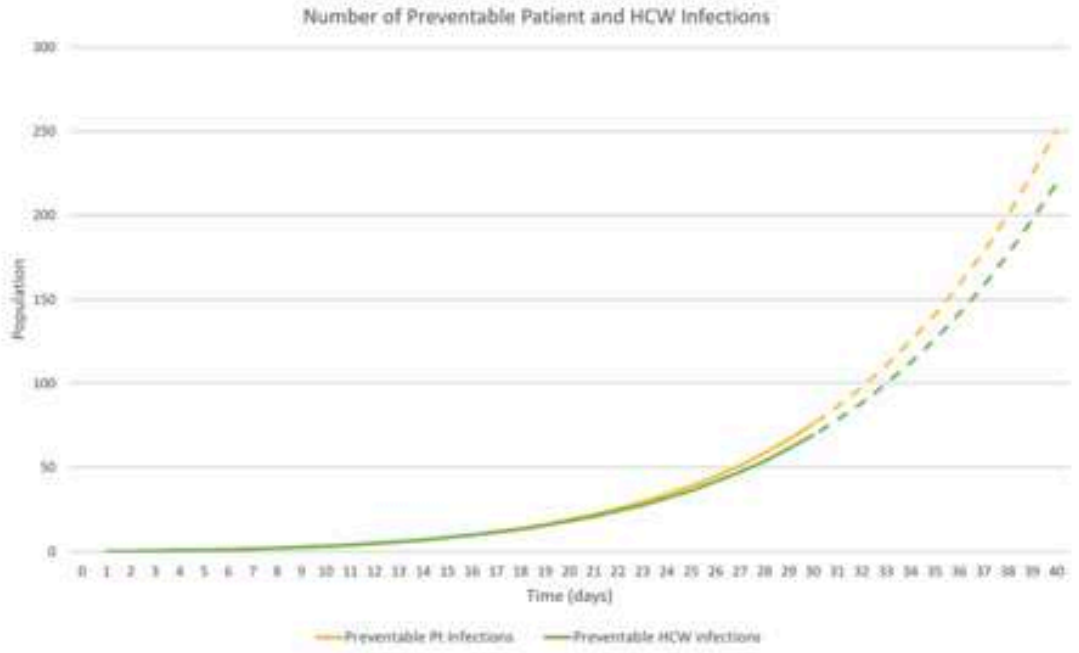

Figure 3. Number of Preventable Patient and HCW Infections. In the early phase of the pandemic, preventable patient infections (yellow line) and preventable HCW infections (green line) exhibit exponential growth, reaching a cumulative number of 75.9 preventable patient infections and 69.3 preventable HCW infections attributed to outpatient elective surgery. The dashed lines represent projections if the same surgical volume were to continue, but that is unlikely to happen given that HCW staffing would become an issue and start to limit case volume.

Economics, Education and Policy - 3

Effects Of Stress On Learning Cardiopulmonary Resuscitation

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Introduction: Cardiopulmonary resuscitation is a crucial skillset which can be taught using high-fidelity simulation. Simulation is a recognised method for teaching procedural skills(1). Stress may have crucial impact on the learning process(2)(3)(4). The influence of stress and cognitive load on the learning process is not entirely known(5). Over one semester, we investigated the possible influence of context sensitive stress on the learning Cardiopulmonary resuscitation teaching sessions in a view to assess the possible effects of stress and changes in cognitive load on student performance.

Methods: Using an experimental approach, 107 students performed baseline and second CPR simulations before and after their teaching sessions. Baseline and second simulations were recorded and graded. Teaching sessions were randomised into two groups. The control group received the traditional CPR training, the intervention group was taught with various stress factors. Students then repeated the simulation at the end of the semester. All simulations were graded using the standard checklist. Stressors mimicked typical emergency resuscitation factors such as anxious relatives and inexperienced colleagues. The cognitive load and perceived stress were quantified using validated questionnaires and scoring scales respectively to assess cognitive load and stress: baseline before the CPR course, before and after all simulations. Data sets were considered incomplete if students did not participate in all simulations. 93 participants submitted a baseline stress questionnaire before the study.107 students enrolled in the simulations, 21 did not participate in baseline performance and 18 were excluded due to protocol violations. 83 students attempted the stress scoring scales, 6 of which were not completed, 15 were excluded from analysis due to protocol violations. 72 participants attempted the cognitive load questionnaire, 19 of which were not completed and 6 were excluded due to protocol violations. A Mann-Whitney-U-Test was used to analyse checklist performances and the unpaired Student's t-test to quantify group differences and questionnaire results.

Results: Identifying characteristics showed a female preponderance, 64,9 %. Thirteen percent of students reported previous medical experience such as nursing or paramedic experience. The mean age was 25 years ranging from 21 to 37. During the baseline simulation we found no differences in performance scores between the intervention group (MRank=31,51) and control group (MRank=37,49), U=476.500, Z=-1.262, p=.207. In the second simulation the scores for the intervention group were (MRank=25,48) and control group (MRank=30,61), U=307.500, Z=-1.214, P=.225. Final simulation results showed for the the intervention group (MRank=31,21), control group (MRank=33,87), U=469.000, Z=-.600, p=.549. The baseline stress score prior to study begin for the intervention group was (M=18.973 SD=7.057), control group (M=16.676 SD=7.972), t(72)=1.312, p=.194. The stress scores before and after the three simulations did not show any differences between the intervention and control group. The stress test score before the final simulation performance was (M=10.094 SD=2.632) and control (M=10.300 SD=2.336),t(60)=-.325, p=.746. After the intervention the score for the stress group was (M=32.875 SD=5.852) and the control (M=31.759 SD=5.069), t(59)=.793, p=.431. Cognitive load scores showed significant differences between the two groups reflecting an increased cognitive load by the intervention group (M=40.23 SD=7.274) and the control (M=33.17 SD=5.393), t(42)=3.503, p=0.001, d=6.578.

Conclusion: Results indicate that addition of a stressor to the learning environment does not significantly influence learner's performance in the cardiopulmonary resuscitation during a high-fidelity simulation training as evidenced by the unchanged p values throughout the tests. However, the perceived cognitive load was increased. As medical professionals often face stressful environments, the study shows stress may not negatively affect the learning process (6). Further research would be required to investigate

if various forms of stress could be beneficial (7). Stress and increased cognitive load may not have any negative impacts on learning.

References: 1.Technology-enhanced simulation in emergency medicine: a systematic review and meta-analysis. Acad Emerg Med. 2013 Feb;20(2):117-27 2. Glucocorticoids in the prefrontal cortex enhance memory consolidation and impair working memory by a common neural mechanism. Proc Natl Acad Sci USA 107(38): 16655-16660 3. Negative affect impairs associative memory but not item memory. Learn Mem 21(1): 21-27 4. Enhanced memory for emotional material following stresslevel cortisol treatment in humans Psychoneuroendocrinology 26: 307-317 5. Evaluation of cognitive load and emotional states during multidisciplinary critical care simulation sessions. BMJ Stel 2018;4:87–91 6. Impact of Stress and Glucocorticoids on Schema-Based Learning. Neuropsychopharmacology. 2017 May;42(6):1254-1261 7. Adding emotional stressors to training in simulated cardiopulmonary arrest enhances participant performance. Med Educ. 2010 Oct;44(10):1006-15

Economics, Education and Policy - 4 How Anesthesiologists Conceptualize and Experience Crisis: A Qualitative Analysis

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Introduction: By tacit convention, the term 'crisis' is often used by medical professionals with reference to a 'turning point' characterized by 'a distinct possibility of a highly undesirable outcome.' However, though the anesthesia crisis resource management (ACRM) model is now widely taught and implemented in perioperative emergencies, it is not understood precisely how anesthesiologists conceptualize and recognize crises and thus apply ACRM principles in practice. To address this gap in knowledge, we conducted a prospective and exploratory qualitative analysis aiming to pinpoint themes underlying the definition and features of the concept of 'crisis' in the field of anesthesiology.

Methods: This prospective observational study was IRB-approved and integrated into a mandatory, recurring ACRM course at a freestanding simulation center. Over a 15-month period, a total of 91 attending anesthesiologists who were enrolled in the ACRM curriculum participated in 20 structured focus groups addressing the questions (1) 'How do you define a crisis?' and (2) 'How do you know when you are in a crisis?' Focus groups were video-recorded and facilitated by the investigators, who performed real-time transcription and coding with member-checking of participant dialogue. A separate researcher then viewed a random sampling of 10 video recordings to verify the accuracy and quality of the coding process. Two investigators next developed and assigned categories to coded material, after which an additional round of analysis was performed to derive themes inductively with constant comparison to the data. Finally, three separate researchers reviewed all themes and categories to ensure validity.

Results: Attending anesthesiologists with a diverse array of professional experiences and backgrounds from across the United States were enrolled in the study (Table 1). Four central themes emerged from 16 categories applied methodically to coded focus group dialogue (Figure 1). According to these themes, the concept of a 'crisis' is characterized or understood by anesthesiologists as: (1) a scenario involving imminent or refractory patient deterioration requiring time-sensitive resource mobilization, (2) a situation evoking negative emotions in the clinician with congruent affective or physiologic responses, (3) a context influenced by or deviating from safety culture, and (4) pronounced changes in a provider-specific sense of situational control.

Conclusion: Apart from the conventional understanding of a 'crisis' as a critical event marked by an increased potential for patient harm, anesthesiologists also define and recognize crises as situations that provoke powerful psychological and physiological responses in the provider, that alter the clinician's perception of control, and that hinge upon the principles of safety culture. From these findings, several hypotheses emerge that may guide future research in the realms of patient safety and ACRM-focused education. Namely, for a crisis to be recognized and managed effectively, it is possible that (1) institutions need to cultivate robust cultures of safety, (2) educators should teach ACRM principles with careful attention to clinicians' past experiences and individual skill sets, and (3) anesthesiologists may be best served by acknowledging and normalizing the emotional reactions that inevitably arise in perioperative emergencies.

References: 1. Crisis. Merriam-Webster Online Dictionary. Retrieved December 28, 2020 from https://www.merriam-webster.com/dictionary/crisis. 2. Gaba, David M. et al. Crisis Management in Anesthesiology, 2nd Ed. Elsevier Saunders: Philadelphia, 2015.

Table 1. General participant and focus group characteristics. Focus groups consisted of board-certified/board-eligible U.S. attending anesthesiologists with representation from all recognized subspecialties.

Genders	30 (33%) female, 61 (67%) male
Time from Medical School Graduation	Median: 16 years (range: 4-43)
Regional Affiliations	65 (71%) from local academic centers, 26 (29%) from outside of the greater Boston area
Focus Group Size	Median: 4 participants (range: 2-7)

Figure 1. Themes surrounding the characteristics of perioperative crisis grouped with corresponding categories, definitions, and representative quotes. Dialogue elements were coded in real time with member-checking by investigators. Quotes were obtained from review of video footage.

Theme	Category	Definition of Category	Sample Quote
Crisis is a rare or time-sensitive situation marked by objective clinical deterioration, often refractory to initial treatments, in which help is needed to enact interventions necessary to mitigate the potential for patient harm.	DNGR	There is an increased potential for decompensation or serious harm to the patient.	*"For the patient, it means they're decompensating. I mean, that's a crisis."*
	FAIL	A clinician's treatments or interventions fail to produce meaningful effects.	*"Patient's condition [is] worsening despite interventions expected to produce results."*
	HELP	A clinician (1) needs additional help or (2) experiences a mismatch between required and available resources.	*"The resources I have are outstripped by the demands."*
	RARE	The scenario is objectively uncommon or improbable.	*"Beyond the normal scope of practice—nonroutine."*
	REAC	The clinician cannot stand by and must actively respond to a situation.	*"Needs urgent action to turn things around."*
	TIME	The clinician (1) needs to act immediately or urgently or (2) develops a sense that time is running out.	*"I can't do things fast enough."*
	TRIG	Contextual triggers or clinical signs suggest that the patient's status is changing adversely.	*"You've reached that cusp where it can deteriorate very quickly."*
Crisis is a powerful emotional event that may feature physiological responses and negative self-referential thinking that affect the clinician's actions.	FEEL	The clinician (1) feels overwhelmed, distressed, or panicked, or (2) otherwise negatively emotionally responds to an event.	*"I'm cursing in my head [and] feel overwhelmed."*
	GRAV	The situation instills a self-referential sense of gravity, personal risk, guilt, or vulnerability in the provider.	*"I'm asking myself: how would I explain this to the family?"*
	PHYS	The clinician experiences (1) signs of sympathetic arousal or (2) impaired cognition as a result of an autonomic response.	*"My heart rate goes up…my ST changes are worse than the patient's."*
Crisis is caused by activation or disturbance of a team's shared sense of safety culture, which may influence the clinician's ability to act.	TEAM	Dysfunctional team dynamics or communication errors increase the potential for a poor outcome.	*"[There are] two different event managers arguing back and forth."*
	VOIC	A sense of safety culture is either reinforced or violated by verbal or nonverbal interactions with other providers.	*"It's just not the fault of the anesthesiologist all the time."*
Crisis is marked by a change in a clinician's individual sense of control over a situation, which may be influenced by task load, lack of information, or an inability to determine next steps in management.	INFO	The clinician lacks or is unable to access necessary data to manage an event.	*"Is there something else I'm missing?"*
	LOAD	An objective increase in cognitive or physical task load arises.	*"[The] amount of mental energy needed to think of steps gets in the way of treatment."*
	LOSS	The clinician (1) experiences a loss of control, great uncertainty, or chaos or (2) cannot anticipate future events.	*"I don't have a Plan A, B, C, D..."*
	PROV	The clinician's unique prior experiences, specialty training, or individual perspectives drive a change in management.	*"Crisis is in the eye of the beholder."*

Economics, Education and Policy - 5

Publication Misrepresentation Amongst Pediatric Anesthesiology Fellowship Applicants: A Retrospective Single Center Cohort Study

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Introduction: Introduction: Many medical specialties have found publication misrepresentation in residency and fellowship applications, but pediatric anesthesia fellowship application data is lacking (1-4). We sought to determine the prevalence of publication misrepresentation among pediatric anesthesia fellowship applications.

Methods: Methods: In this retrospective cohort study, fellowship applications to Stanford University's pediatric anesthesiology fellowship program from 2009 to 2019 were reviewed. Only peer-reviewed journal articles listed as accepted or published were included. Nine additional variables were collected: applicant age, gender, citizenship status, American vs. international medical school, public vs. private medical school, allopathic doctor versus osteopathic doctor, number of years between college and medical school, additional degrees, and application year. The primary outcome was the rate of publication misrepresentation, defined as peer-reviewed journal citations listed on the application that could not be verified or on which the applicant was not listed as an author. Secondary outcomes were the associations between publication misrepresentation and the additional collected variables.

Results: Results: 1293 peer-reviewed journal publications from 880 applicants were reviewed. 3.6% of all citations listed as peer-reviewed journal articles were misrepresented and 9.2% of all applicants with at least 1 publication had ≥ 1 misrepresented publications. 27.7% of publications labelled 'misrepresented' were located in our search of databases but did not have the applicant as an author, and 72.3% could not be located using the search databases. None of the 9 collected variables were significantly associated with publication misrepresentation.

Conclusion: Publication misrepresentation exists in pediatric anesthesiology fellowship applications, and admission committees should be cognizant of the issue. While rates were low compared to those found in other studies, we found that one in 11 applications with at least one publication had PM. We hope these, and previously published, findings encourage ERAS and fellowship admissions committees to consider methods to improve application publication accuracy and to discourage PM.

References: 1. Branco BC, Inaba K, Gausepohl A, et al. Nonverifiable research publications among applicants to an academic trauma and surgical critical care fellowship program. J Am Coll Surg. 2012;215(3):337-342. 2. Chung CK, Hernandez-Boussard T, Lee GK. “Phantom” Publications Among Plastic Surgery Residency Applicants. Annals of Plastic Surgery. 2012;68(4):391-395. doi:10.1097/sap.0b013e31823d2c4e 3. Gasior AC, Marty Knott E, Fike FB, et al. Ghost publications in the pediatric surgery match. Journal of Surgical Research. 2013;184(1):37-41. doi:10.1016/j.jss.2013.04.031 4. Katz ED, Shockley L, Kass L, et al. Identifying inaccuracies on emergency medicine residency applications. BMC Med Educ. 2005;5:30.

Figure 1. Publication misrepresentation among applicants to a single pediatric anesthesiology fellowship.

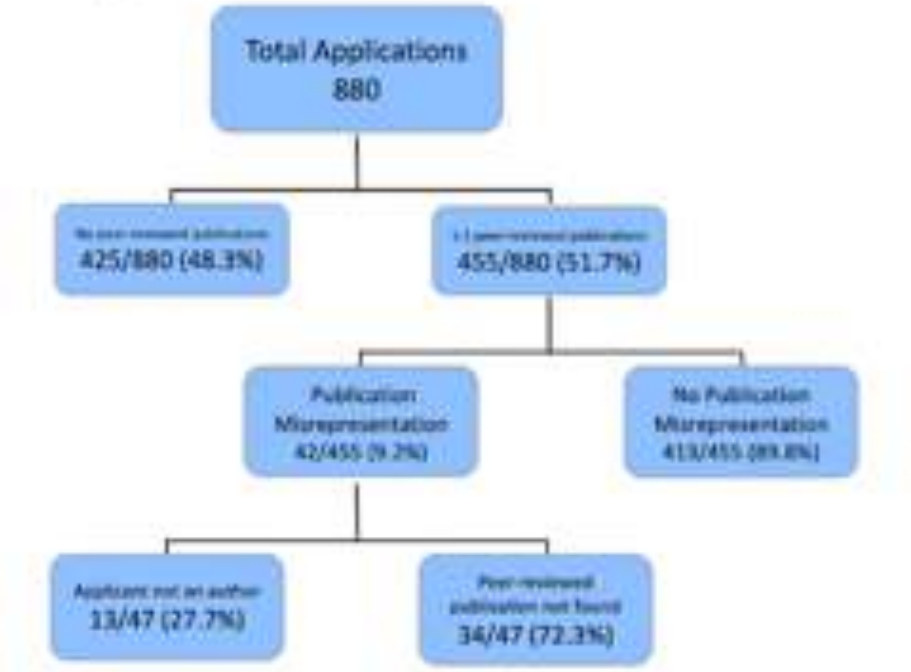
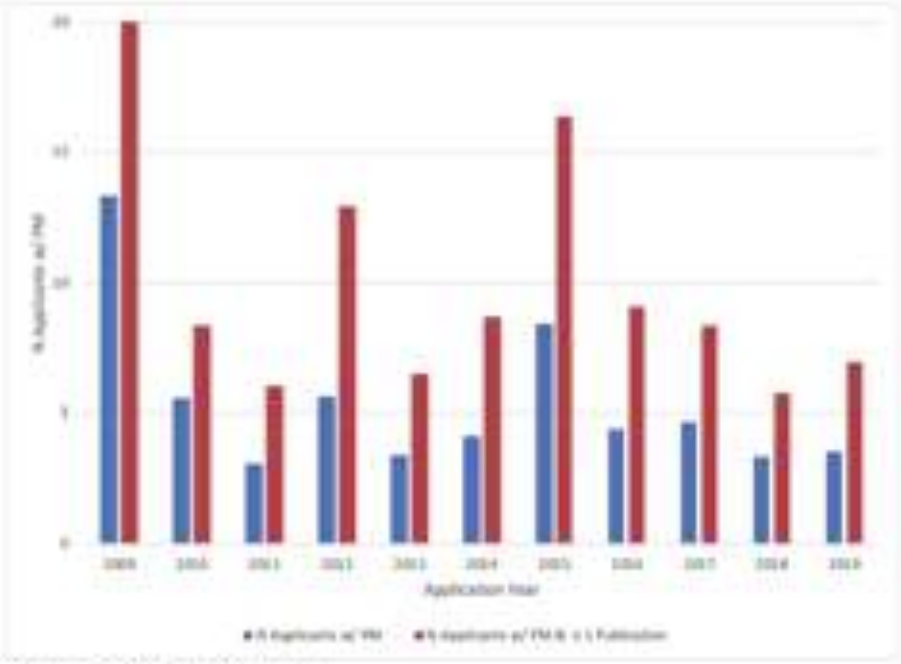


Figure 2. Percentage of PM for all applicants (blue), and percentage of PM for applicants with ≥ 1 listed publication (red) by year.



PM, publication misrepresentation

Economics, Education and Policy - 6 The Anesthetic Room Adjacent To The Operating Room - Mandatory Or Outdated?

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Introduction: Nowadays, operation wings are planed with anesthetic rooms adjacent to each operating room. This allows for induction of anesthesia, while in the operating room the scrub nurses and surgeons get prepared for the operation. Having these perioperative procedures paralleled is supposed to save time, thus improving workflow, allowing for a decrease in turn-over-time, and improved OR-efficacy, thus guaranteeing more cases per time (1). In the here presented study, we challenge the economic advantage of anesthetic procedure rooms, since the anesthetic processes can easily be paralleled within the operating room itself. This saves the invest of building extra anesthetic rooms including its expensive equipment.

Methods: We moved our Department of Gynecology from an operating room with adjacent anesthetic procedure rooms for induction of and emergence from anesthesia to an operating room without such anesthetic rooms. No other changes were made. We compared work flow and turnover times for 3 months in each setting. For statistical analysis, we used an unpaired Student's t-test. Significance was defined as $p<0.05$.

Results: The results are summarized in Table 1. There was no significant difference in turn-over-time, nor was the operating room itself significantly less occupied with adjacent anesthetic rooms. The OR efficacy, calculated as the ratio of the patients operating time over the related OR-occupancy, did not differ.

Conclusion: In the field of gynecology with the majority of cases requiring a general anesthesia, extra anesthetic rooms have no advantage. Kinetics of modern anesthetics allow for fast induction and emergence of anesthesia (2). Our data show, that adjacent anesthetic rooms do not serve to improve the ORs efficacy. Since technically equipped anesthetic rooms adjacent to the OR are expensive, a return on invest in terms of a higher throughput cannot be achieved. In future, operating wings can be planned without adjacent anesthetic rooms.

References: 1: Example of cost calculations for an operating room and a post anesthetic care unit. Anaesth Crit Care Pain Med 2015, 34: 211-215 2: Pharmacoeconomics in anaesthesia: what are the issues? Eur J Anaesthesiol supp 2001, 23: 10-15

Table 1	operating time (Min)	OR occupany (Min)	turn-over-time (Min)	OR-efficacy (%)
OR with adjacent anesthetic rooms (N=236)	47.5 +/- 47.3	74.7 +/- 57.4	47.6 +/- 18.6	57.4 +/- 40.5
stand-alone OR (N= 254)	50.4 +/- 56.1	75.7 +/- 66.0	41.6 +/- 17.0	58.6 +/- 40.5

Economics, Education and Policy - 7

Representation Of Women As Editors In Anesthesiology Journals

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Introduction: Although there has been a considerable increase in female representation in medicine, a gender gap still exists with regards to leadership positions. This gender discrepancy has been identified in the field of anesthesiology, in terms of first and senior authorship, as well as in general composition of editorial boards in Anesthesiology and Anesthesia and Analgesia. The goal of this study is to examine the representation of women in the top high impact anesthesia journals with respect to the hierarchy of different editorial positions.

Methods: A comprehensive search was performed for anesthesiology journals indexed in the Scimago Journal and Country Rank in May 2020, and the top 20 journals were analyzed. Editorial board members were ranked on a scale of 1-5 depending on their title, with 1 being the highest ranking (editor-in-chief) and 5 being the lowest (associate/assistant editors) (Table 1). Female representation within each category was calculated.

Results: Overall, women occupied 19% of editorial board positions. All editor-in-chiefs (rank 1) and assistant/associate/deputy editor-in-chiefs (rank 2) were males. Females consisted of 17.1% of executive/section/senior editors (rank 3), 17.9% of editors (rank 4), and 20.6% of associate/assistant editors (rank 5) (Figure 1).

Conclusion: These findings suggest that, in anesthesiology journals, women are underrepresented at all editorial levels, especially at levels of higher ranking.

Table 1
Editorial title classification and ranking

Numerical Ranking	Editorial Titles
1	Editor-in-chief
2	Associate editor–in-chief Assistant editor-in-chief Deputy editor-in-chief
3	Executive editors Senior editors Section editors Executive section editors
4	Editors Editorial board/international editorial board Editorial office Other editors: Social media editors, Statistical editors, Social media editor, CME editor, Infographic editor, Language editor, Proof editor, Managing editor, Editorial coordinator, Laboratory investigations editor, education editor, review articles editor, update editor, guest editor
5	Associate editors Associate editorial board Assistant editors Guest editors

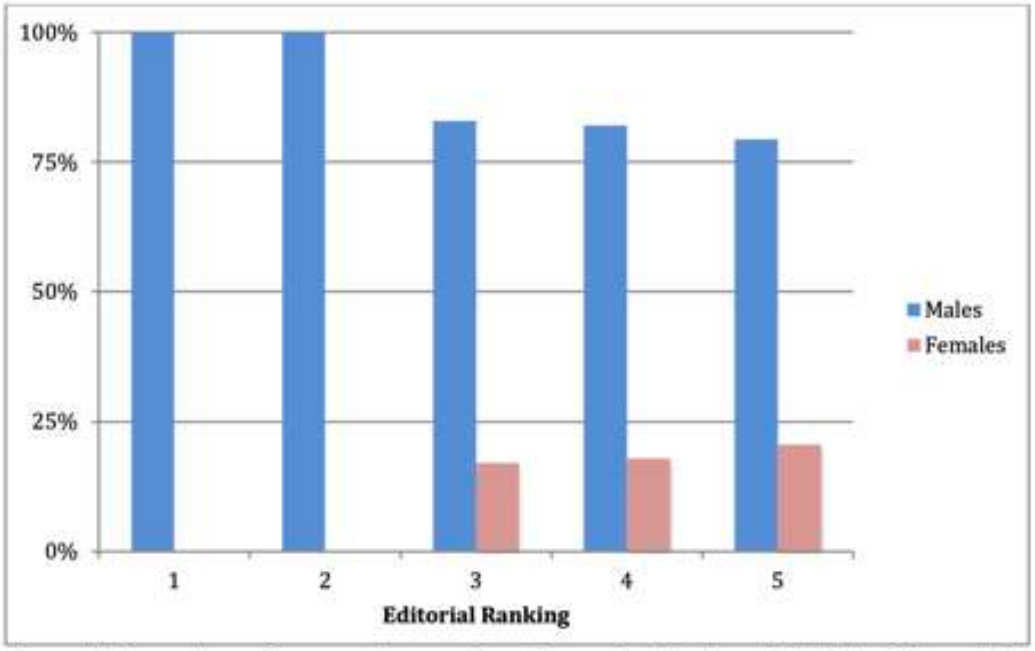

Figure 1. Percentage of men and women in various editorial roles divided into 5 hierarchical categories, with 1 being the highest journal position and 5 being the lowest.

Economics, Education and Policy - 8

Impact Of Near-Miss Pediatric Intraoperative Adverse Events On Anesthesiology Residents

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Introduction: Pediatric anesthesiology residents, by nature of their training, will be involved in near-miss intraoperative events. The psychological and physical consequences of being involved in these near-miss events is not described in the literature and may not be recognized as significant by their supervising physicians. In comparison, the concept of the 'second victim' and the impact of catastrophic events on physician wellness has previously been well documented.[1] Near-miss intraoperative adverse events have the potential to elicit similar emotional responses to intraoperative death,[2] yet residency programs typically fail to proactively address aftermath management of these events.[3] The purpose of this study was to characterize the impact of near-miss pediatric intraoperative adverse events on anesthesiology residents and determine desirable support and wellness initiatives.

Methods: Following ethics board approval, a survey administered via REDCap was e-mailed to all second to fifth year anesthesiology residents, as well as 2019 and 2020 graduates of the residency program. The survey was an adaptation of the previously validated Second Victim Experience and Support Tool.[2] This tool asks participants to evaluate their experiences with adverse patient safety events and rank their desirable support options on a five-point Likert scale. When completing the survey, respondents were asked to specifically reflect on any near-miss pediatric intraoperative adverse events. Scores of four or higher represented a negative second victim effect of these experiences or a desirable support option. Descriptive statistics were used for analysis.

Results: Participants by year of residency training are outlined in Table 1. 35 of 66 eligible participants responded to the survey and 30 surveys were fully complete. This corresponds to a response rate of 45%. 27 of 30 respondents indicated at least one second victim response. On average respondents indicated a second victim response to 5 of the survey's 29 questions. Questions with the highest second victim response included fear of future occurrences, fear of patient care inadequacy, and embarrassment. The most desirable forms of support were peer support and a discussion with the residency site director to discuss the event.

Conclusion: The majority of anesthesiology residents in this particular program reported a range of both physical and psychological consequences following a near-miss pediatric intraoperative adverse event. Responses reaching threshold for 'second victimization' were related to fears about current and future patient care, as well as personal embarrassment. In addition to intraoperative death, residency programs must acknowledge near-miss intraoperative adverse events as significant and provide necessary support.

References: [1] The impact of perioperative catastrophes on anesthesiologists: Results of a national survey. 114: 596-603. 2012. [2] The second victim experience and support tool: Validation of an organizational resource for assessing second victim effects and the quality of support resources. 13: 93-102. 2017. [3] Anaesthetists' attitudes to intraoperative death. 22: 938-941. 2005.

Table 1. Participants by year of residency training

Residency year	n (%)
Second	4 (13%)
Third	8 (27%)
Fourth	7 (23%)
Fifth	6 (20%)
Graduated (2019 or 2020)	5 (17%)
Total Complete Responses	30 (100%)

Economics, Education and Policy - 9

Assessing Interrater Reliability Of A Faculty-Provided Feedback Rating System

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Introduction: Feedback is pivotal to promoting resident growth and development; therefore, it is crucial to assess the quality and utility of feedback being provided.[1] Having an accurate, reliable feedback rating system can help programs ensure accurate, reliable assessments of feedback, enabling them to assess the impacts of educational interventions aiming to improve the quality and utility of feedback. Our research group previously created a seven-item feedback rating system to accomplish this.[2] However, to this point we have only utilized it as a group where all raters must come to a consensus on ratings. In order to evaluate the scale for use by independent raters, we sought to explore the inter-rater reliability (IRR) of this rating system with faculty educators newly trained on said rating system.

Methods: [2]Our research group previously created a seven-item feedback rating system developed by three anesthesiologists, each with over 5 years of educational experience.[2] We recruited three anesthesiology faculty volunteers from an academic medical center, including the residency program director and two associate residency program directors. Participants were trained on the seven-item feedback rating system in which the presence or absence of six predefined feedback traits are assessed on a binary scale and the overall utility of feedback with regards to devising a resident performance improvement plan is assessed on an ordinal scale from 1 to 5 (Table 1). Participants were trained as a group by a creator of the rating system via a series of three sixty-minute teleconference workshops and three independent rating exercises using deidentified feedback examples which were previously rated by consensus of the creators of the rating system (Figure 1).[2] During workshops, the trainer polled participants on their ratings and encouraged discussion when ratings differed between members to assess rationale. Each workshop covered 20 feedback comments randomly pulled from the pool of 1,925 previously rated examples and was constructed to have an equal distribution of utility scores (four for each score). The IRR was measured after each independent rating exercise, with results used to identify areas to focus on in subsequent training sessions. The IRR for feedback trait categories was measured using R[3,4] to calculate Gwet's first-order agreement coefficient (Gwet's AC1)[5] and interpreted using Landis & Koch's rule of thumb.[6] Unlike Cohen's Kappa,[7] Gwet's AC1 allows for chance-correlated agreement calculations between more than two raters and is robust against a 'Kappa paradox,' which can occur in datasets where one classification is observed substantially more than the other possible classification(s).8 The IRR for utility scores was measured using R[3,9] to calculate intraclass correlation (ICC - two-way random effects, consistency, multiple raters/measurements),[10] and interpreted using Koo & Li's guidelines.[11]

Results: On the final rating exercise, participants achieved near-perfect IRR on two feedback traits (Gwet's AC1 ≥ 0.81: Actionable - 0.88, Professionalism / Communication - 0.83), substantial IRR on three feedback traits (Gwet's AC1 of 0.61 - 0.80: Behavior Focused - 0.80, Detailed - 0.74, Specific - 0.67), and moderate IRR for Negative Feedback (Gwet's AC1 of 0.41 - 0.6: 0.54). For utility score, IRR on the final exercise was on the cusp of excellent with an ICC of 0.90 (95% CI of 0.80 - 0.96). IRR for each feedback trait and utility score are reported in detail for each rating exercise and for all combined rating exercises in Tables 2 and 3.

Conclusion: At the end of a series of training sessions and rating exercises, participants achieved high IRR on six of seven rating categories and moderate IRR on the remaining category. Therefore, when this instrument is utilized by trained, expert educators, reliable assessments of faculty-provided feedback can be made, enabling programs to assess the quality and utility of their feedback and the impact of any educational interventions designed to improve feedback.

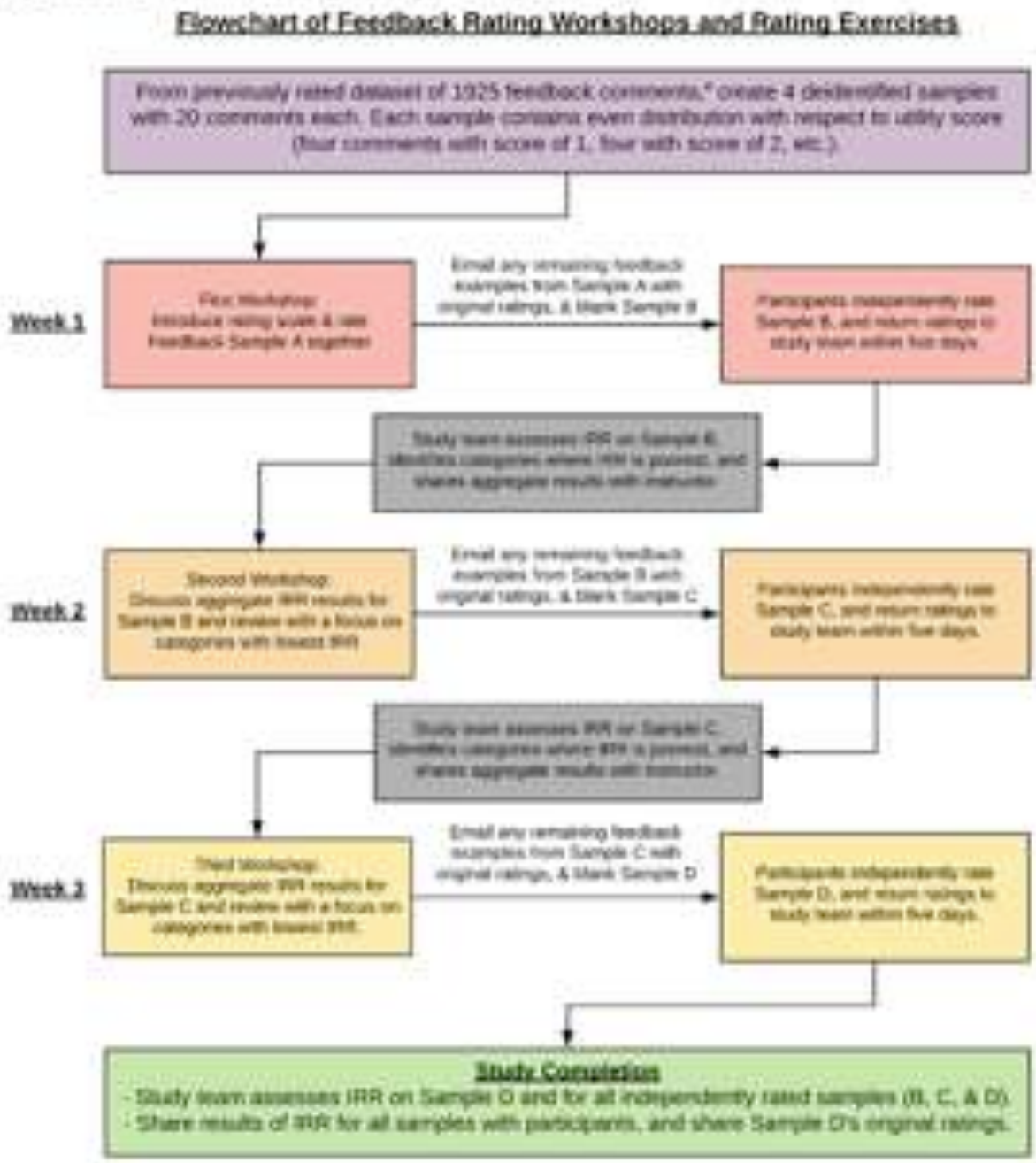
References: 1. Feedback in clinical medical education. 777-781. 1983. 2. Enhancing Feedback on Professionalism and Communication Skills in Anesthesia Residency Programs. 25:620-631. 2017. 3. R: A language and environment for statistical computing. 2017. 4. irrCAC: Computing Chance-Corrected Agreement Coefficients (CAC). 2019. 5. Handbook of inter-rater reliability: How to estimate the level of agreement between two or multiple raters. 2001. 6. The Measurement of Observer Agreement for Categorical Data. 33(1):159–174. 1977 7. A coefficient of agreement for nominal scales. 20(1):37–46. 1960. 8. High Agreement and High Prevalence: The Paradox of Cohen's Kappa. 11:211-218. 2017. 9. irr: Various Coefficients of Interrater Reliability and Agreement. 2019. 10. Forming Inferences about Some Intraclass Correlation Coefficients. 1:30-46. 1996. 11. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. 15:155-163. 2016.

Table 1. Definitions for utility and the six feedback traits with emblematic examples.*

Term	Definition	Example†
Actionable	Identifies areas for residents to work on improving.	"Consider thinking out loud when going through your difficult airway algorithm."
Behavior Focused	Notes something done by the resident as modifiable or changeable. Raters differentiated the definition of a behavior from a characteristic, or personality attribute of the resident.	Behavior: "The resident placed lines with enthusiasm." Characteristic: "The resident was enthusiastic."
Detailed	Provides ample information describing observed cases or actions which occurred, but not necessarily how a resident performed.	"There were many difficult airway patients today, including a cervical spine injury case."
Negative Feedback	Notes areas the resident could improve on. Does not necessarily have to be hurtful or personal.	"The resident had trouble identifying areas of bronchial anatomy with the bronchoscope."
Professionalism / Communication	Notes an exceptional level of planning, preparation, and/or communication or a lack of such.	"The resident was prepared with a McGrath and a difficult airway cart in case DL failed, and discussed their intubation approach plan with the OR team ahead of time." "The resident did not have a readily accessible bailout option in case of DL failure."
Specific	Provides information related to the resident's actions.	"The resident used manual inline stabilization when intubating the cervical spine injury patient."
Utility	Assessment of whether feedback can help devise a performance improvement plan for the resident.	High-Utility Example: "Did a great job, just needs to work on thinking and doing things quickly on their feet. For example, after we put in the LMA in our converted MAC, the patient was coughing and not tolerating the LMA. Rather than use their drawn up syringe of propofol and giving a bolus dose, they used the pump to try and deliver a bolus dose which took slightly longer. I think with time in their training, they will naturally continue to improve in this area."

*Adapted from table in *Using Machine Learning to Evaluate Attending Feedback on Resident Performance* by Neves SE, Chen MJ, et. al in *Anesth Analg [online ahead of print, 2020]*.
†Examples provided for Actionable, Behavior Focused, Detailed, Negative Feedback, Professionalism / Communication, and Specific are synthetic examples created to exemplify statements containing their respective feedback traits. The example for utility is a genuine, deidentified feedback comment left by faculty on a resident's performance which achieved the maximum utility score (5 out of 5); this example was also edited to use gender neutral pronouns.

Figure 1. Flowchart of feedback rating workshops and rating exercises.



*Previously rated dataset of 1925 feedback comments was collected during a prior study, where all these raters would come to a consensus on ratings.[7]

Table 2. Table of inter-rater reliability and percent agreement for feedback trait ratings.

	Sample B (n=20)		Sample C (n=20)		Sample D (n=20)		Combined Samples B,C, & D (n=60)	
	Gwet's AC1[a]	Percent Agreement[b]	Gwet's AC1[a]	Percent Agreement[b]	Gwet's AC1[a]	Percent Agreement[b]	Gwet's AC1[a]	Percent Agreement[b]
Actionable	0.88 (Substantial)	83%	0.56 (Moderate)	0.73%	**0.88** (Almost Perfect)	93%	0.70 (Substantial)	83%
Behavior	**0.83** (Almost Perfect)	87%	0.8 (Substantial)	0.83%	0.80 (Substantial)	83%	**0.81** (Almost Perfect)	84%
Detailed	0.54 (Moderate)	77%	**0.81** (Almost Perfect)	0.90%	0.74 (Substantial)	87%	0.69 (Substantial)	84%
Negative Feedback	0.88 (Substantial)	83%	0.47 (Moderate)	0.73%	0.54 (Moderate)	77%	0.56 (Moderate)	78%
ProfComm[c]	0.29 (Fair)	63%	0.55 (Moderate)	0.77%	**0.83** (Almost Perfect)	87%	0.57 (Moderate)	76%
Specific	0.2 (Slight)	60%	0.33 (Fair)	0.67%	0.67 (Substantial)	83%	0.40 (Fair)	70%

[a]Gwet's AC1: Gwet's first-order agreement coefficient.[3] Gwet's AC1 was calculated using R.[14] Results for Gwet's AC1 are reported with the value followed by interpretation in parentheses per Landis & Koch's interpretations for kappa values and strength of agreement,[5] and are likewise color-coded as follows:
< 0.00 is poor (unused), 0.00 to 0.20 is slight agreement (red), 0.21 to 0.40 is fair (orange), 0.41 to 0.60 is moderate (yellow), 0.61 to 0.80 is substantial (blue), and 0.81 to 1.00 is almost perfect (green and bold font).
[b]Percent Agreement represents the percent of feedback examples on which all three participants unanimously agreed on whether the feedback trait was present in an example or not.
[c]ProfComm: Abbreviation for Professionalism / Communication trait.

Table 3. Table of intraclass correlation and agreement rates for utility score ratings.

	ICC[a]	Adjacent Agreement[b]
Sample B (n=20)	0.95 (Excellent), 95% C.I. [0.88 - 0.98]	95%
Sample C (n=20)	0.75 (Good) 95% C.I. [0.88 - 0.98]	55%
Sample D (n=20)	0.90 (Good), 95% C.I. [0.88 - 0.98]	95%
Combined Samples B, C, & D (n=60)	0.87 (Good) 95% C.I. [0.88 - 0.98]	82%

[a]ICC: Intraclass correlation - Two-way random effects, consistency, multiple raters/measurements.[15] Reported as the calculated ICC value with interpretation in parentheses followed by the 95% confidence interval. Interpretations for ICC values taken from Koo & Li's guidelines, where values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively.[15] Calculations performed using R.[14]
[b]Adjacent Agreement represents the percent of examples on which all three participants' utility score ratings had a range of one or less (ex: scores of 3/4/3, 2/2/2, and 5/5/4).

Economics, Education and Policy - 10

Curriculum Innovation: Introduction to Hospice and Palliative Medicine during the Clinical Base Year

Michael Wadle[1], Annette Rebel[1], Robert Weaver[1], Jessica McFarlin[1]

[1]University of Kentucky, Lexington, KY

Introduction: Even before the American Board of Anesthesiology recognized hospice and palliative medicine (HPM) as a subspecialty in 2006, this field of medicine has emerged as integral to the practice of anesthesiology. Anesthesiologists comprise only a small fraction of HPM physicians, but the clinical skills and practical knowledge required to care for such patients complements anesthesiology training. Despite this, few residency programs provide formal rotations in this discipline, probable due to limited ability to offer dedicated rotations in this field. We explored if a short exposure (2 days) in palliative care medicine during the PGY-1 year would be sufficient to relate the essential components of HPM to anesthesiology residents, increasing their understanding and ability to integrate HPM knowledge/procedures into patient care.

Methods: As a curriculum innovation, we created a novel HPM course, incorporated into a preexisting chronic pain medicine rotation during the clinical base year of the anesthesiology residency. The PGY-1 residents spent 2 days with the institutional in-patient palliative care service, receiving on-line and in-person education and joining the team for rounds and patient care. After completion of the rotation, the participating residents were surveyed on the merits and contributions of added course into the Chronic pain rotation. The survey form is shown in Figure 1.

Results: The Hospice and Palliative Medicine course was implemented in 7/2018, with the first PGY-1 residents participating in September 2018. Eleven (of twenty eight) residents completed the post experience survey (n=8 for 2018-2019; n=3 for 2019-2020). The survey responses were de-identified pre-analysis. Figure 2 demonstrates results pertaining to residents' prior exposure to palliative care. 73% of total residents surveyed had completed an ICU rotation prior to this palliative care experience: 63% of PGY-1 residents during the 2018-2019 year and 100% of residents during the 2019-2020 year. 45% of total residents surveyed reported previous exposure to palliative medicine prior to this palliative care experience: 38% of PGY-1 residents during the 2018-2019 year and 67% during the 2019-2020 year. Figure 3 demonstrates the results pertaining to residents' impressions of palliative medicine after the rotation. 100% of responders indicated they agreed or strongly agreed the rotation helped them understand the ASA guidelines regarding code status preference in the setting of procedure risk. 100% of responders agreed or strongly agreed the HPM rotation helped them understand how palliative care can modify plans and contribute to the care of seriously ill patients. 100% of responders indicated they agreed or strongly agreed the palliative care experience improved their anesthesiology training.

Conclusion: Our findings affirm that a short exposure to HPM is supportive and efficient in introducing HPM principles into the formal anesthesiology residency curriculum. Further studies will be needed to explore if the short-term exposure has impact on dependent anesthesiology care areas (perioperative medicine, critical care medicine) and if residents consider additional training time in HPM for elective rotations at a later stage of their residency.

Preview Form

Printed on Jan 14, 2021

medhub

Resident Evaluation of Palliative Care Consult Experience

● Insufficient contact to evaluate

Dear Resident, we are evaluating the Palliative Care Consult component during the Chronic Pain rotation and would like to ask for your input about your experience. As this is a new component of the rotation, we are working to make it the best experience possible, and are very interested in all of your feedback. Thank you!

1. Please reflect and describe one thing you learned or experienced during your time on Palliative Medicine that was the most valuable to you. *

	Strongly Agree	Agree	Disagree	Strongly Disagree	NA
2. This educational experience met the goals and objectives.	○	○	○	○	○
3. I was provided with adequate time for education/discussion with faculty on service.	○	○	○	○	○
4. This experience helped raise my awareness of how Palliative Medicine contributes to the care of my patients.	○	○	○	○	○
5. After the palliative care experience, I recognize the framework for a goals-of-care discussion with a patient with a serious illness.	○	○	○	○	○
6. The palliative care experience helped me to develop an understanding how palliative care involvement can modify the care plan for a patient with a serious illness.	○	○	○	○	○
7. After the palliative care experience, I understand the ASA guidelines for confirmation, suspension and modification of code status preferences in the context of procedural risk.	○	○	○	○	○
8. The palliative care experience improved my anesthesiology training.	○	○	○	○	○
9. The course material was sufficient and supplemented the learning experience.	○	○	○	○	○
10. I was satisfied with the overall learning experience on palliative care.	○	○	○	○	○
11. I would recommend this educational experience to other learners.	○	○	○	○	○

12. How many days did you spend in palliative care during your chronic pain rotation?


(e.g., 0, 1, 2, 3, more than 3)
Too little
Just right
Too much
N/A
1
2
3
4
5
0
13. The length of time I spent on the Palliative Care Consult service was
14. Did you review the goals and objectives of the rotation?
Yes
15. Did you review the online communication modules during the rotation?
Yes
16. Did you review the recommended reading material (DNR and perioperative care)?
Yes
17. Did you complete an ICU rotation (either in residency or medical school) prior to this Chronic Pain rotation?
Yes
18. Did you have any previous exposure to Palliative Medicine prior to this rotation?
N/A
19. If you had prior exposure to Palliative Medicine prior to this rotation, please describe:
20. Additional comments or suggestions regarding this educational experience
Submit completed evaluation
Submit

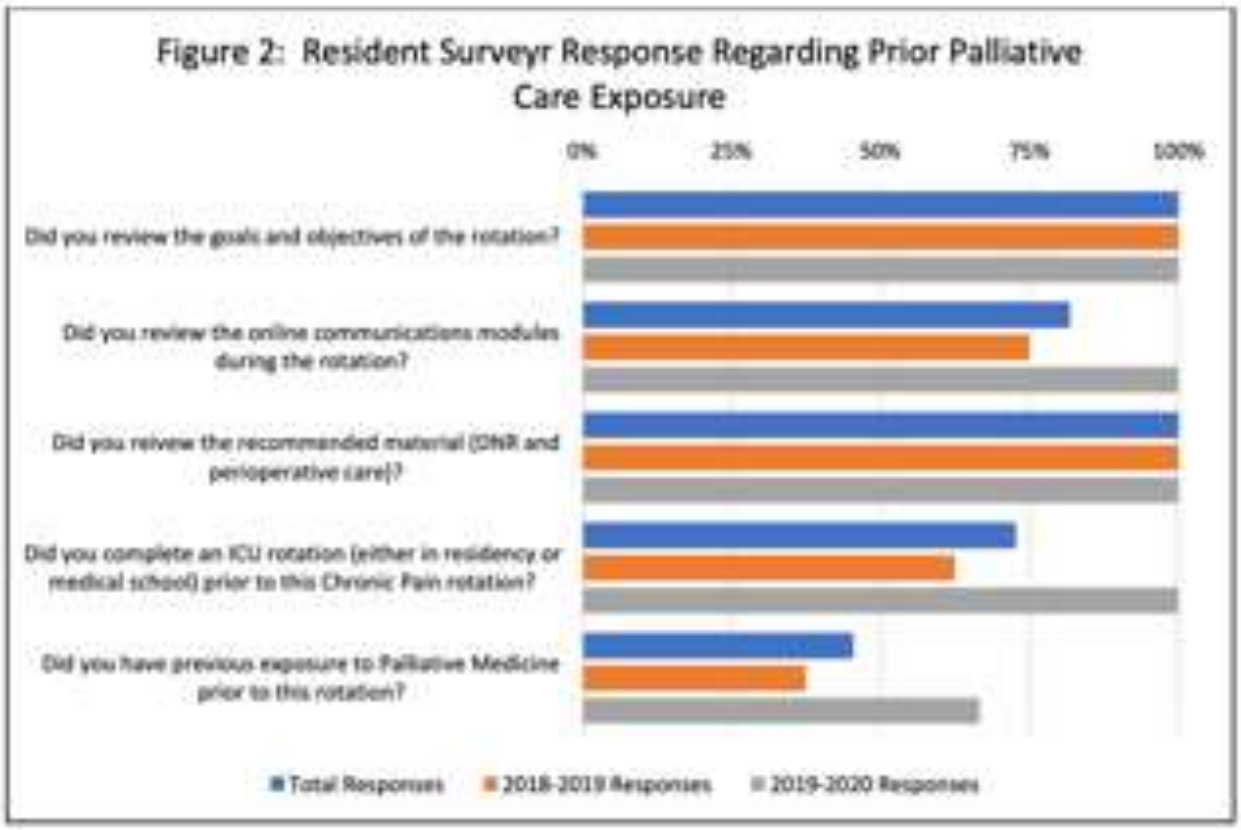


Figure 2: Resident Surveyr Response Regarding Prior Palliative Care Exposure
0%
25%
50%
75%
100%
Did you review the goals and objectives of the rotation?
Did you review the online communications modules during the rotation?
Did you reivew the recommended material (DNR and perioperative care)?
Did you complete an ICU rotation (either in residency or medical school) prior to this Chronic Pain rotation?
Did you have previous exposure to Palliative Medicine prior to this rotation?
Total Responses
2018-2019 Responses
2019-2020 Responses

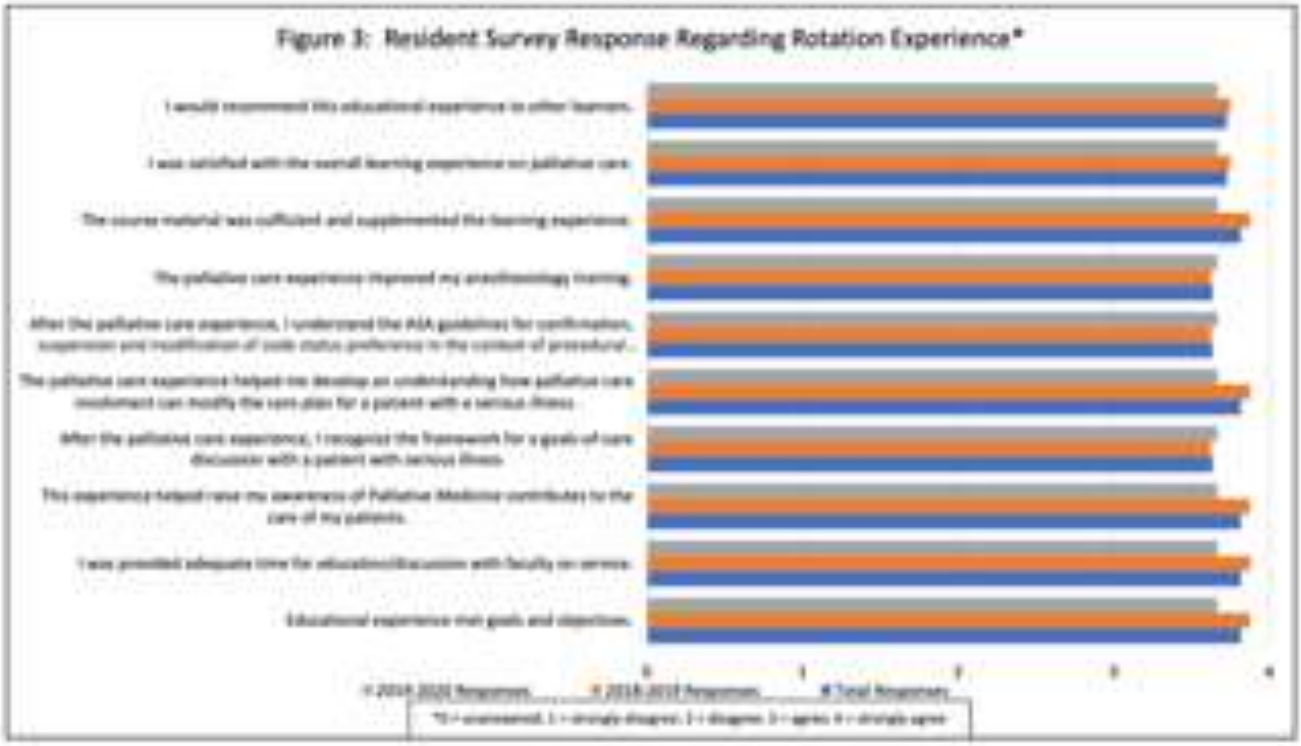


Figure 3: Resident Survey Response Regarding Rotation Experience*
I would recommend this educational experience to other learners.
I was satisfied with the overall learning experience on palliative care.
The course material was sufficient and supplemented the learning experience.
The palliative care experience improved my anesthesiology training.
After the palliative care experience, I understand the ASA guidelines for confirmation, suspension and modification of code status preference in the context of procedural...
The palliative care experience helped me develop an understanding how palliative care involvement can modify the care plan for a patient with a serious illness.
After the palliative care experience, I recognize the framework for a goals of care discussion with a patient with serious illness.
This experience helped raise my awareness of Palliative Medicine contributes to the care of my patients.
I was provided adequate time for education/discussion with faculty on service.
Educational experience met goals and objectives.
0
1
2
3
4
2019-2020 Responses
2018-2019 Responses
Total Responses
*0 = unanswered, 1 = strongly disagree, 2 = disagree, 3 = agree, 4 = strongly agree

Economics, Education and Policy - 11

Effect Of The Covid-19 Pandemic On Attitudes Of Health Care Sector Employees On Resource Conservation, Healthcare Pollution And Environmental Sustainability.

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Introduction: Climate change has negative impacts on human health and is a growing public health crisis. (1, 2) In turn, the health care sector is a significant contributor to greenhouse gas and other environmental emissions. Energy consumption by facilities, pharmaceutical and equipment manufacturing, and biomedical waste management have sizeable environmental impacts. The United States health care sector contributes 8-9% of the nation's greenhouse gas emissions. (3, 4) Globally, the sector also contributes to air, water and soil pollution. (5) Resource conservation is one approach to reducing health care-related environmental harm. The need for resource conservation applies to both pandemic and climate change related disasters. The covid-19 pandemic created an unparalleled demand for intensive care unit beds, personal protective equipment, sedation medications, ventilators and other resources. The surge in demand and the supply chain interruption due to illness and economic shutdown, together, resulted in dramatic supply shortages leading many institutions to ration resources. The objective of this survey was to understand knowledge, beliefs and attitudes towards climate change and resource conservation in the context of the Covid-19 pandemic.

Methods: From May to September 2020, we e-mailed a link to an optional, anonymous 10 question survey to all 29,000 employees at a 2,500 bed health care system within the United States. As the survey met institutional requirements for quality improvement projects, no IRB approval was required. Informed consent from the participants was obtained at the start of the survey. At the time of initial survey distribution, the health system had just passed the peak of the first wave of Covid-19 admissions. The survey was adopted from a prior survey of health professional student knowledge, attitudes and beliefs about climate change, pollution, and resource conservation in health care. (6) Descriptive statistics were used for data analysis.

Results: Of the nearly 29,000 employees, 3,204 employees participated in the survey (approximately 11% overall). Participants included: 2,389 clinical/support staff (74.56%) and 815 administrative staff (17.34%). A majority (85.26%) of clinical/support staff respondents agreed or strongly agreed that healthcare workers are responsible for conserving resources and preventing healthcare pollution within their professional practice. Most clinical/support staff respondents (93.1%) and administrative staff respondents (92.54%) agreed or strongly agreed that they use resources according to hospital policy. As a result of the Covid-19 pandemic, 74.51% of clinical/support staff respondents agreed or strongly agreed with efforts to limit unnecessary orders or use of clinical supplies, medications, and tests. 76.60% further supported extending these efforts beyond the Covid-19 pandemic. Amongst the administrative staff, 77.89% agreed or strongly agreed with efforts to limit unnecessary orders or use of supplies and 83.38% supported continuing these efforts into the future. Only 16.33% of clinical/support staff and 13.90% of administrative respondents agreed or strongly agreed that they will go back to the usual way of ordering and using supplies and devices once Covid-19 related shortages are no longer of concern.

Conclusion: Health care sector employees, clinical and non-clinical, agree that they have a responsibility towards judicious use of resources and to decrease healthcare pollution. There is an interest in continuing the resource conservation policies and practices that started in the Covid-19 pandemic. Hospital policies heavily influence employee behavior, thus there is a need to amend system level policies to encourage and enforce environmentally sustainable practices. The lessons learned during this global pandemic likely need directed action to reinforce resource conservation behaviors, to better manage future pandemics, weather-related disasters, and prevent pollution.

References: 1. Climate change: challenges and opportunities for global health. JAMA. 2014;312(15):1565-1580. doi:10.1001/jama.2014.13186 2. Washington, DC: US Global Change Research Program; 2016. The Impacts of Climate Change on Human Health in the United States: A Scientific Assessment. http://dx.doi.org/10.7930/J0R49NQX 3. United States Health Care Pollution and Public Health Damages: An Update. Health Affairs 2020, 39 (12):2071-2079. DOI: 10.1377/hlthaff.2020.01247 4. Reducing Pollution From the Health Care Industry. JAMA.2019;322(11):1043–1044. doi:10.1001/jama.2019.10823 5. The environmental footprint of health care: a global assessment. Lancet Planet Health. 2020;4(7):e271–9. 6. Medical, nursing, and physician assistant student knowledge and attitudes toward climate change, pollution, and resource conservation in health care. BMC Med Educ 2020, 20: 200.

Economics, Education and Policy - 12 The Role of Medical Students during Difficult Airway Management: Education and Contribution Beyond Intubation

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Introduction: Medical students may participate actively in patient care during their anesthesia clerkship, including airway management (1). In high-intensity situations, such as difficult airway management, it may be difficult for medical students to find a contributory role. However, students lose educational opportunities if they only observe without participating actively (2). We examined cases in which medical students actively participated and played a role in difficult airway management.

Methods: Approval and waiver of consent was obtained. Patients with expected difficult airways were recruited. Patients met at least one of four inclusion criteria for the study: 1) one or more abnormal airway index(es); 2) expected challenges with intubation, ventilation or oxygenation by clinician judgement; 3) patient history or comorbidities suggesting difficult airway management; 4) planned use of specialized device for intubation and ventilation. For inclusion in this subanalysis, the procedure had a medical student who actively participated as a member of the clinical anesthesia team. Trained research assistants, who were not part of the clinical team, observed airway management and recorded events in real-time. Data analysis was conducted in Microsoft Excel and Stata/MP 15.0.

Results: Of 1355 total cases in the study, 34 cases (2.5%) were included in our subanalysis as medical students played an active role in airway management (see Table 1 for demographics). Patients underwent the following procedures: 18 gastrectomy/gastric bypass; 6 thyroidectomy/parathyroidectomy; 3 orthopedic; 2 urology; 5 others, including ENT and general surgery. 5 (15%) patients required three or more attempts to visualize vocal cords and 3 (9%) patients required three or more attempts to place the endotracheal tube. 27 (79%) patients required maneuvers during intubation; 20 required lip retraction and 17 required anterior laryngeal pressure. 7 (21%) patients required three or more maneuvers during bag mask ventilation (BMV). All medical students assisted with intubation and/or ventilation. Medical students assisted with maneuvers required during ventilation, such as adjusting the adjustable pressure-limiting valve. In 17 cases (50%), the medical student successfully performed laryngoscopy and endotracheal tube placement with clinician guidance. In the other 17 (50%) cases, students played a supportive role in intubation, such as attempted laryngoscopy and/or ETT placement, placed ETT while clinician performed laryngoscopy, or performed maneuvers such as lip retraction or anterior laryngeal pressure with clinician direction. Medical students also observed patients for complications related to physiologic changes, oxygenation, ventilation, aspiration, and debriefed the case with the attending and research assistants (see Figure 1).

Conclusion: In high-intensity situations such as difficult airway management, we found that medical students assisted with multiple facets including patient assessment, preparation, induction, intubation, and ventilation. These cases demonstrate the situational and educational benefits of having students assist in complex cases and participate in subsequent debriefing. Having additional personnel to perform maneuvers and monitor hemodynamic changes was helpful for the clinical team. Even though medical students did not always have the opportunity to intubate or reintubate after an unsuccessful attempt, they developed a holistic understanding of clinical decision-making in difficult airway management, which is more valuable than simply knowing how to intubate. Through real-time challenges, students learned to identify relevant comorbidities, prepare an anesthetic-airway plan, and anticipate complications. Practical experience with difficult airway management may augment learning and performance in other disciplines such as surgery and critical care, and during situations such as emergency codes.

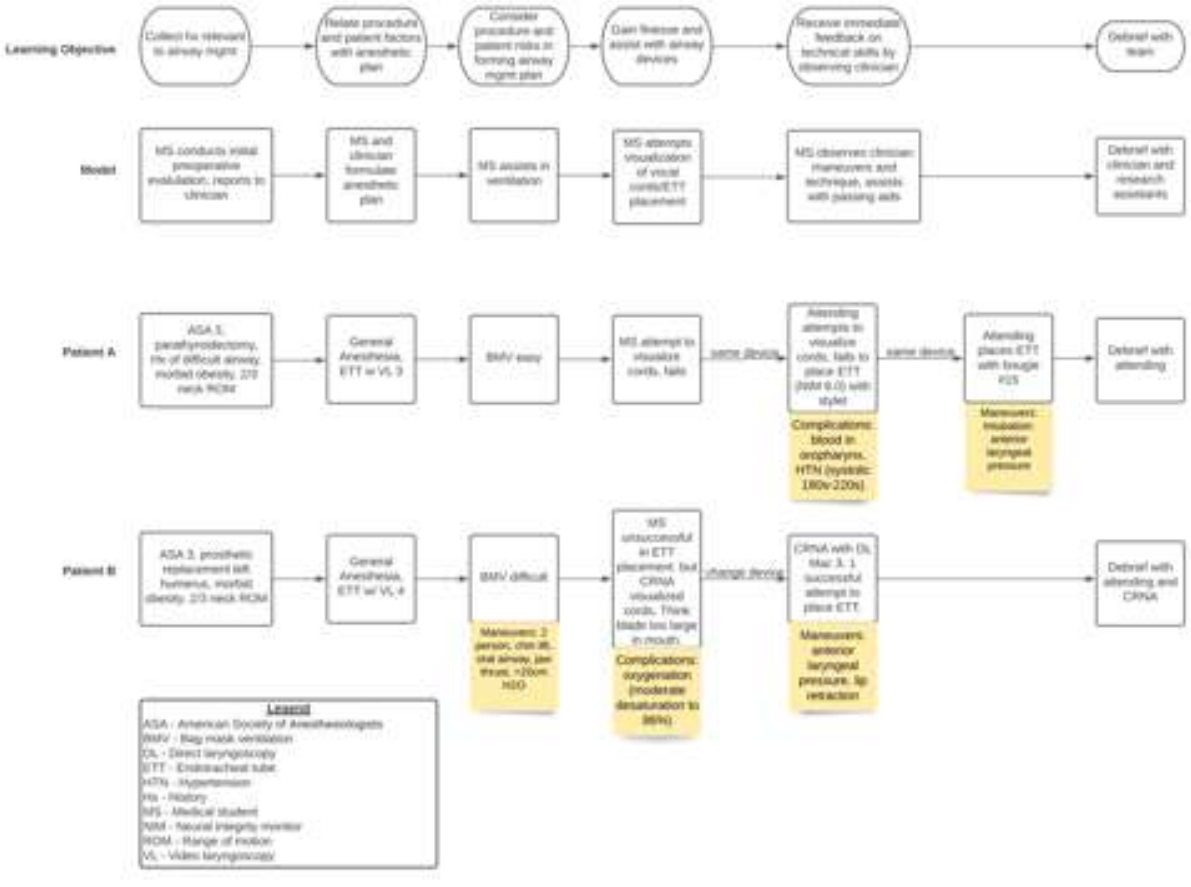
References: 1) Anesthesia & Analgesia, 126(5), 1687-1694, 2018. 2) Medical Education, 52, 34-39, 2017

Table 1. Demographics

Patient Characteristics	
Characteristic	**All patients (N=34)**
Age (y) (median, IQR)	47 [42-57]
Weight (kg) (median, IQR)	117.5 [93.0-135.9]
Height (cm) (median, IQR)	165 [160.0-173.3]
BMI (kg/m^2) (median, IQR)	41.9 [36.3-47.7]
Sex (n, %)	Female: 24 (69%) Male: 10 (31%)
ASA classification (n, %)	
I/II	10 (29%)
III/IV	25 (71%)
Expected Difficult Airway* (n, %)	32 (94%)
Number (%) with at least 1 abnormal airway index	16 (46%)
1 abnormal	9 (26%)
2 abnormal	4 (12%)
3 abnormal	3 (9%)
Medical Students (N=34)	
MS2 (n, %)	5 (15%)
MS3 (n, %)	7 (21%)
MS4 (n, %)	19 (56%)
Not stated (n, %)	3 (8%)

*determined by patient history on chart, patient or family statement of previous history of difficult airway, and physical exam

Figure 1. Medical Student Role in Difficult Airway Management



Economics, Education and Policy - 13 The Value Of Just-In-Time In-Situ Simulation Training As A Preparedness Measure For The Perioperative Care Of Covid-19 Patients.

Liana Zucco[1], Michael J Chen[1], Nadav Levy[1], Allison Hyatt[1], Jeffrey R Keane[1], Richard pollard[1], John D Mitchell[1], Satya Krishna Ramachandran[1]

[1]Beth Israel Deaconess Medical Center, Boston, MA

Introduction: In anticipation of a surge of COVID-19 patients and the associated risks posed to healthcare workers involved in aerosol-generating procedures such as tracheal intubation, the rapid redesign of workflow processes was required to prepare staff to safely care for COVID-19 patients within the perioperative setting.[1] In March 2020, simulations were rapidly developed, and delivered through just-in-time (JIT) training, an educational technique known for its efficacy and ability to promote confidence in performing specific tasks.[2-5] Simulations were conducted in-situ in operating rooms (OR) to identify site-specific latent hazards and opportunities for improvement.[6,7]

Methods: Based on available evidence, the Anesthesia Quality, Safety and Innovation group created new standard operating procedures (SOP's), cognitive aids (i.e.: single-page checklists) and established a core development group to facilitate training efforts (Figure 1). Four training simulations were developed with a focus on minimizing viral exposure and transmission risk in the perioperative setting (Figure 2; A: pre-op huddle & OR set up for COVID-19 case; B: donning & doffing PPE; C: transfer of a COVID-19 patient from the ICU to the OR; and D: airway management with enhanced infection control measures. Over 3 weeks, JIT in-situ training sessions were delivered up to twelve times per day to a total of 428 perioperative staff within a healthcare network which provides care in a metropolitan area containing nearly 5 million people. Comprehensive evaluation of this training method was performed using a post-simulation survey, which collected Likert scale assessments and free text responses from 110 participants. Post-simulation feedback helped facilitate iterative changes to training and organizational SOP's. Compliance with COVID precautions in the OR was retrospectively reviewed over 6 months (March-August 2020) after JIT in-situ training was initially delivered.

Results: Survey responses (n=110) for each of the four simulations reported increased knowledge of and comfort in adopting new workflows post-sim (all p-values < 0.00001; Figure 3), and >90% of respondents agreed or strongly agreed that this training would impact their future practice (Figure 4). Free text responses were notable for identifying areas to improve upon, expressing appreciation of the timeliness of this training, and praising the 'hands-on' nature of in-situ simulation and inter-professional collaboration (Figure 5). Compliance with COVID precautions in practice was found to be 95% (121 out of 127 cases) and associated with lower than expected healthcare worker infection rates within the network during this same time period (<1%).

Conclusion: The JIT in-situ training method as a preparedness measure for perioperative care of COVID-19 patients demonstrates this approach is a notable training method during a crisis. Participants highly regarded the content and delivery of training and were themselves integral to improving organizational SOP's and further training materials. We encourage institutions to consider this approach for any refresher training on subsequent COVID-19 surges or other crises that require timely, effective training.

References: 1. Risks to healthcare workers following tracheal intubation of patients with COVID-19: a prospective international multicentre cohort study. 75:1437-1447. 2020. 2. Just-in-time simulation-based training. 26: 866–868. 2017. 3. Perceptions on the Impact of a Just-in-Time Room on Trainees and Supervising Physicians in a Pediatric Emergency Department. 8: 754–758. 2016. 4. Qualitative evaluation of just-in-time simulation-based learning: The learners' perspective. 8: 43–48. 2013. 5. Effect of just-in-time simulation training on provider performance and patient outcomes for clinical procedures: a systematic review. 1: 94-102. 2015. 6. Use of in situ simulation to evaluate the operational readiness of a high-consequence infectious disease

intensive care unit. 75:733-738. 2020. 7. Detecting latent safety threats in an interprofessional training that combines in situ simulation with task training in an emergency department. 3:1-7. 2018.

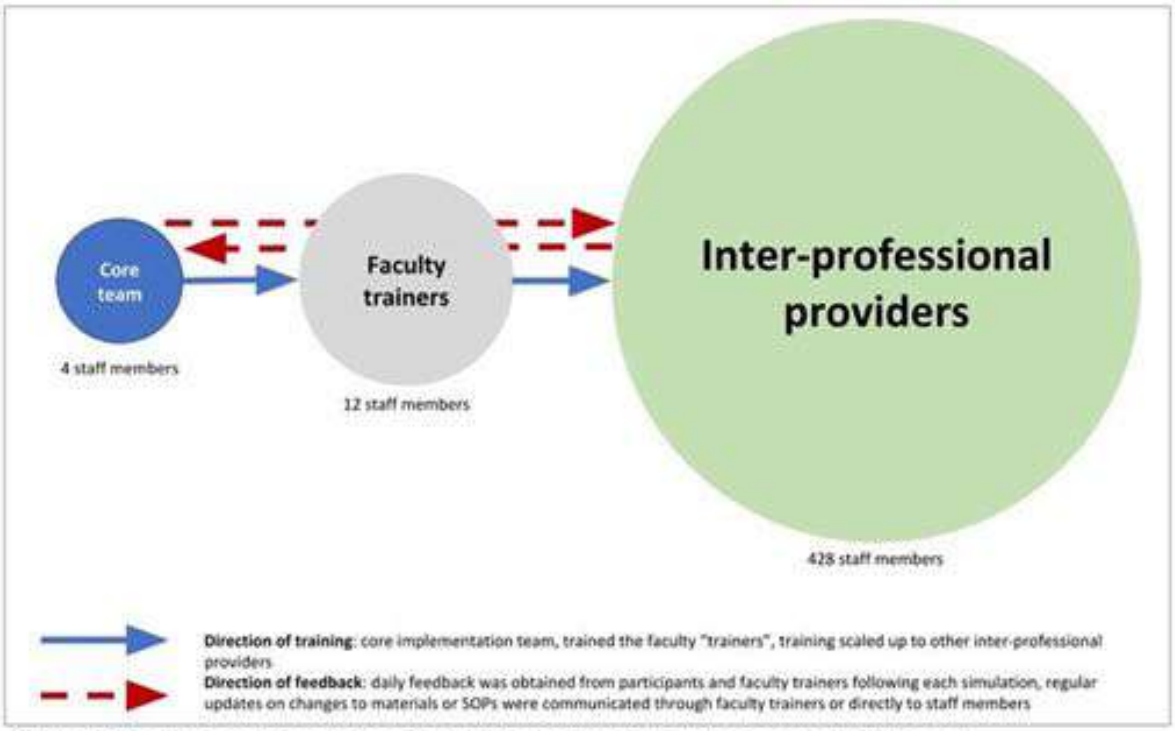


Figure 1. Schematic representation of the simulation implementation team and framework.

Figure 2. JIT in-situ simulation training stations. A: Pre-op huddle & OR set up for COVID-19 case. B: Donning & doffing PPE. C: Transfer of a COVID-19 patient from the ICU to the OR. D: Airway management with enhanced infection control measures

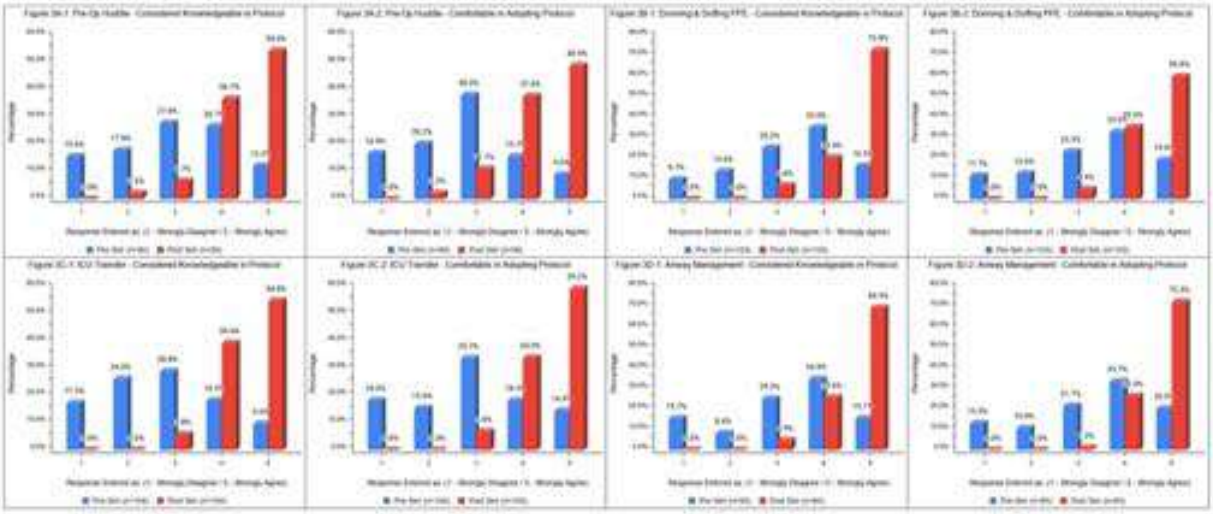


Figure 3. Pre-post simulation training survey results for all 4 simulation stations. Results for each simulation station (labeled A-D) on knowledge of protocols (labeled "...-1") and comfort in adapting protocols (labeled "...-2") are expressed as percentage of responses. Pre-simulation responses are noted in blue; post-simulation responses are in red. X-axes represents 5-point Likert scale (1=strongly disagree, 5=strongly agree).

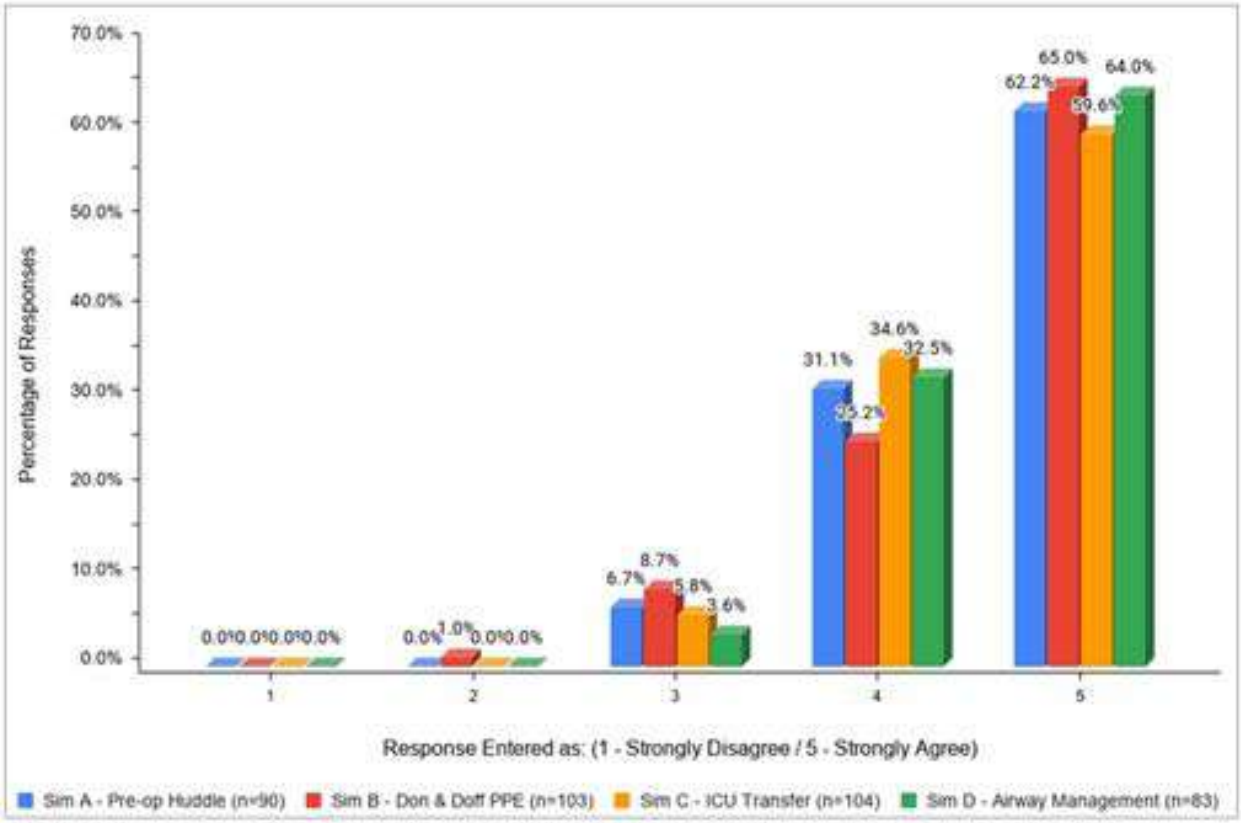


Figure 4. Survey results for perceived impact of JIT simulation training on clinical practice. Results are expressed as percentage of responses for each simulation drill. Simulations are labeled to aid interpretation as follows: sim A – pre-operative huddle (blue), sim B – donning & doffing PPE (red), sim C – intensive care unit (ICU) transfer (orange) and sim D – airway management using enhanced infection control measures (green). X-axis represents a 5-point Likert scale (1=strongly disagree, 5=strongly agree). Mean scores for sim A: 4.6 (SD=0.6), sim B: 4.5 (SD=0.7), sim C: 4.5 (SD=0.6) and sim D: 4.6 (SD=0.5).

Summary of Themes	Quotes
Simulation content and materials: Preference for greater number of clinical scenarios, use of visual materials to aid in learning and clarification of minor points in our protocols.	"Scenarios chosen were very clear, practical and common situations" "Content could have included emergency situations (stat calls, traumas, combative patients, extreme respiratory depression) ... videos or pictures would also have been helpful."
Relevance to practical skills: Appreciation of the ability to practice a clinical skill not often performed and be "hands-on" in the process	"Donning and doffing was important to practice, as its not done regularly enough." "The hands-on nature of the ICU transfer was useful to me ... it gave me the opportunity to test my abilities and be familiar with the process"
Relevance to clinical experience: Recognition of training as an opportunity to discuss upcoming or unanticipated hazards/safety issues	"Simulation got you thinking about the issues in dealing with a COVID-19 patient, and helped you learn from others' trial and errors." "I'm grateful to have had the training since none has been done at my facility. I had to lead a team for a suspected COVID-19 case today and I'm not sure how I could have done this without having had the training"
Perceived benefits of training: Increased awareness of new protocols, as well as comfort in adopting new protocols. Training method provided a forum to review protocols step-by-step, engage in teamwork, hear from others' experiences, and offer feedback. Contribution in alleviating anxieties about personal HCW safety in the workplace.	"It really helps the nursing staff in preparing to care for these patients and increases communication between the disciplines" "The simulations provided an opportunity to hear about the most up-to-date protocol/policy changes, and also about complaints" "This help[ed] prepare me to manage a COVID-19 case, I felt much more confident and comfortable following these simulations"
Perceived failures of training: Challenging to extrapolate lessons simulation into real life. Difficulty in keeping up to date due to frequent changes in hospital policy/guidelines.	"The knowledge that the content might be changing daily, impacted my learning" "The protocol changed after I did the simulation, but I wasn't aware of this change"
Inter-professionalism/Collaboration: Appreciation noted when groups contained multiple disciplines, and seen as a missed opportunity when logistical barriers & COVID-19 precautions occasionally resulted in groups where all disciplines were not equally represented.	"I found it most useful when there was nursing and anesthesia collaborating in the sim. There was a great discussion between the two disciplines on different ways to troubleshoot issues that were uncovered" "Assigned groups could have been better organized, fewer anesthesia providers, etc"
Leadership: Perception of leadership support within the organization	"Getting a feel for how thoughtful leadership was taking the situation"

Figure 5. Qualitative analysis of free text responses.
*COVID-19: Coronavirus disease 2019, HCW: healthcare worker, ICU: intensive care unit, JIT: just-in-time.

Economics, Education and Policy - 14

Impact of COVID-19 on Free-standing Pediatric Ambulatory Centers

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Introduction: Cost containment remains an important driving force in healthcare. In children, this has become vital as the healthcare landscape remains unpredictable without specific healthcare mandates and no firm re-authorization of the Children's Health Insurance Program (CHIP). Additionally, increasing bed shortages during seasonal periods make it imperative to develop strategies to deal with variations in surgical volumes and healthcare resources. The COVID pandemic has made this environment even more uncertain. As this pandemic is a novel and new situation, no one knows its true effect on work flow efficiency, cost, and patient flow. Also, what is the cost of social distancing and sanitization measures? Are these costs being configured into the charges or is that the cost of doing business? With these decreasing margins, will ambulatory centers function and thrive pre-COVID. There have been necessary changes to the workflow due to precautions taken for COVID 19. Although various societal task forces have given roadmaps for reopening (ASA), it is up to individual institution to outline their re-opening strategy. We integrated our EMR/financial data to look at cost during period of 3/2019-9/2019 versus 3/2020-9/2020 for otolaryngology cases.

Methods: We o
and financial dat

Results: 2019 2020
Total Case count 2984 1673
Demographics
Male 639 331
Female 542 295
Race
African American 52 117
Asian 16 29
Multi-racial 25 0
Payors
Medicaid 37% 41%
Medicaid/private 6% 8%
Private 55% 50%
Self-pay 8% 6%
Average Cost of PPE $11.47 $30.02
per Case

Results

	2019	2020
Total Case count	2984	1673
Demographics		
Male	639	331
Female	542	295
Race		
African American	52	117
Asian	16	29
Multi-racial	25	0
Payors		
Medicaid	37%	41%
Medicaid/private	6%	8%
Private	55%	50%
Self-pay	8%	6%
Average Cost per Case		
	$11.47	$30.02

Conclusion: In the age of cost containment and decreasing resources, measures for safety comes at a price. During the COVID pandemic months, we had also limited testing availability and could only use screening questions which increased our costs in terms of personal equipment, social distancing, and sanitizing. Our freestanding ambulatory care center not only experienced decreased volume (56%) but increasing cost of business. More research needs to be done in viability of maintaining a free standing ambulatory center during a pandemic.

References: 1. Blumenthal et al. Covid 19 implications for healthcare system. NEJM. July 2020
2. Hospitals and Health Systems face unprecented financial pressures due to COVID 19. https://www.aha.org/guidesreports/2020-05-05-hospitals-and-health-systems-face-unprecedented-financial-pressures-due

Economics, Education and Policy - 15

Practical Experience Of Residents In A Colombian Anesthesiology Program Compared To The Accreditation Council For Graduate Medical Education (Acgme) And The Johns Hopkins Hospital Suggested Standards

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Introduction: Assuring quality in medical education, is a universal goal that must be achieved by every single residency program in anesthesiology. They should be able to provide theoretical basics and practical scenarios, that allows the student to apply their knowledge to real life situations, and to develop all the required skills to become a qualified physician (1). Many countries in cooperation with formal institutions, like the Accreditation Council for graduate medical education (ACGME), have established competencies and minimal caseloads, to achieve this goal (2,3). Unfortunately, in Colombia, since there are no regulatory organizations in charge of this issue and there is no precise knowledge about the real exposure of residents during their training, the adequate number of cases has not been yet standardized. The aim of this study is to describe and compare the practical experience of residents in an anesthesiology program in Colombia, with the minimum standards established by the ACGME and the Johns Hopkins Hospital.

Methods: This was a cross-sectional study, conducted in a hospital, linked to an anesthesiology program in Bogotá, Colombia. All cases in which 10 residents participated during their years of training (between 2015 and 2020) were included. As established by the teaching program, each resident had to register all the data related to the procedures they were involved, in a mobile Software (HanDBase v4.9.079. DDH Software.) Outcome variables were the number of cases performed by each resident, patients baseline features, ASA classification and type of procedure. Anesthetic techniques were described to characterize the procedures and its complexity, that each resident had to encounter during their training period. After a descriptive analysis of the values, all the caseloads were organized and compared with the minimum standard procedures, listed by the two selected organizations.

Results: From 11711 cases of 10 eligible residents, 1652 were excluded, due to inconsistent and incomplete data. A total of 10059 cases were included (51.3% female patients and 70.1% adults). On average, each resident participated in 1006±122 cases during their training period (Table 1). The number of cases per resident, according to age range and ASA physical status classification, are shown in Table 2 and 3. Residents were mainly involved in procedures from general surgery (n=1836,18.3%), orthopedics (n=1679,16.7%) and obstetrics (n=1087, 10.8%). The total average procedures of our residents exceeded in most of the categories, the standards suggested by ACGME (n=400). In comparison with the standards of Johns Hopkins Hospital (n=1416.1), there is a considerable difference of 410.1 procedures (Table 4)

Conclusion: To our knowledge, this is the first time that the caseload of residents has been described for an anesthesiology program in Colombia. There was a high number of cases that were excluded due to incomplete data, an issue that needs to be addressed for future studies of this type. Regardless, this study aims to establish a starting point, to formulate the minimum number of cases in a realistic manner, and to assess the optimization of quality standards in our setting. This 3-year program ensures an extensive clinical experience for the residents during their training period, comparable to American standards.

References: 1. American Osteopathic Association and American Osteopathic College of Anesthesiologists 2012:3. 2. About Us [Internet]. Acgme.org. 2020 Available from: https://www.acgme.org/About-Us/Overview. 3. Accreditation Council for Graduate Medical Education

(ACGME) 2020:31-34. 4. Residency – Program Details – Johns Hopkins Anesthesiology & Critical Care Medicine [Internet]. Anesthesiology.hopkinsmedicine.org. 2020. Available from: https://anesthesiology.hopkinsmedicine.org/residency/residency-program-details/

Table 1. Number of cases per resident

Resident	10059	
1	850	8%
2	999	10%
3	1078	11%
4	942	9%
5	956	10%
6	1191	12%
7	944	9%
8	1120	11%
9	837	8%
10	1142	11%
Average	1005,9	

Table 2. Number of cases per resident according to age range

Anesthesia according to age range	Resident 1 n=850	Resident 2 n=992	Resident 3 n=1075	Resident 4 n=935	Resident 5 n=945	Resident 6 n=1190	Resident 7 n=942	Resident 8 n=1119	Resident 9 n=822	Resident 10 n=1142	n=10012	Average
Anesthesia for children under 3 years of age	14	20	11	8	12	25	8	15	4	20	157	14
Anesthesia for children between 3 months to 3 years	59	85	54	58	94	83	66	86	60	82	727	73
Anesthesia for children between 3 to 12 years	87	149	116	122	119	156	123	146	129	145	1286	129
Anesthesia for people older over 12 years old	690	738	894	747	720	926	745	872	635	895	7862	786

Table 3. Number of cases per resident according to ASA physical status classification

ASA	Resident 1 n=850	Resident 2 n=999	Resident 3 n=1078	Resident 4 n=942	Resident 5 n=956	Resident 6 n=1191	Resident 7 n=944	Resident 8 n=1120	Resident 9 n=837	Resident 10 n=1142	n=10059	Average
I	212	296	299	302	249	341	215	304	226	309	2753	275
II	370	396	500	330	383	449	409	437	338	374	3986	399
III	253	276	232	276	308	366	255	314	240	337	2857	286
IV	14	30	43	32	16	28	45	47	27	113	395	40
V	1	1	1	2	0	0	17	12	0	9	43	4
VI	0	0	3	0	0	7	3	6	6	0	25	3

ASA: American Society of Anesthesiologists.

Table 4. Comparison with ACGME and the Johns Hopkins Hospital minimum standards (4)

Medical specialty	ACGME standards n=400	The Johns Hopkins Hospital average n=1416.1	Anesthesiology program in Colombia average n=1006
Anesthesia for Vaginal Delivery including High-Risk OB	40	118.9	40
Anesthesia for Cesarean Section	20	59.8	117
Anesthesia for Children 3-12 YO	75	237.1	129
Anesthesia for Children 3 months-3YO	20	89.8	73
Anesthesia for Children <3 months old	5	65	14
Anesthesia for Cardiac Surgery including CPB	20	41	25
Anesthesia for Major Vascular Surgery	20	36.4	17
Anesthesia for Non-Cardiac Intrathoracic Surgery	20	16	35
Anesthesia for Intracranial Surgery	20	162.1	44
Patients Undergoing Anesthesia in which Epidural Analgesia/Anesthesia is Used	40	192.7	78
New Acute or Chronic Pain Patient Evaluation	20	105.7	20
Anesthesia for Patients with Complex, Life-Threatening Injuries (Trauma)	20	48.8	0*
Patients Undergoing Anesthesia in which Spinal Anesthesia is Used	40	101.3	97
Peripheral Nerve Blocks	40	101.5	73

ACGME: Accreditation Council for Graduate Medical Education; OB: obstetrics; YO: years old; CPB: cardiopulmonary bypass.

*This item was not available for inclusion in the third group

Economics, Education and Policy - 16

Investigating Gender Disparities in Case Assignments in an Academic Anesthesiology Department: Implications for Pay and Productivity

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Introduction: Gender bias has been described in anesthesiology.(1,2) Inequalities in compensation and career advancement have been reported.(3,4) Gender-based assumptions, such as the perception of women as less agentic (associated with stereotypically masculine qualities such as independence and ambition) and more communal (associated with stereotypically feminine qualities such as gentleness and dependence), are a possible explanation for these gender-based discrepancies.(5) Case scheduling within academic anesthesia departments consists of assigning attending anesthesiologists (attendings) to supervise up to four Certified Registered Nurse Anesthetists (CRNAs) or up to two resident physicians (residents). By supervising CRNAs, the attending has the potential to oversee more cases and may have a greater opportunity to earn American Society of Anesthesiologists (ASA) units and Relative Value Units (RVUs). We hypothesized that female anesthesia attendings are assigned at increased frequency to residents and produce less ASA units and less RVUs, compared to male colleagues.

Methods: This retrospective cohort study qualified for IRB exemption. We reviewed attending assignments within our high-risk operating suite. Inclusion criteria were generalist attendings who worked a minimum of ten days in the high-risk operating suite in a supervisor role between January 1, 2020 and May 15, 2020. Attending assignments are determined by a rotating group of schedulers. Past assignments with respect to CRNA versus resident supervision is generally not considered by schedulers. Pediatric and cardiac attendings who were more likely to receive low ratio resident assignments were excluded. Primary endpoints were type of assignment (CRNA versus resident), ASA unit production, and RVU production. The analysis was by intention-to-treat. Data were analyzed using R Project version 4.0.3. We tested for treatment differences using Welch's t-test for mean comparisons of quantitative data and the chi-squared test for binary characteristics.

Results: Thirteen male and seven female attendings met eligibility criteria. Attendings assigned CRNAs completed a mean of 16 cases per day whereas those assigned residents completed a mean of 6 cases per day. Male attendings were more likely to be Caucasian than female attendings (Table 1). Female attendings generated more RVUs working with residents compared with CRNAs (5.3 RVUs vs. 3.1 RVUs, $p<0.01$). Male attendings generated more RVUs working with residents compared with CRNAs (4.0 RVUs vs 2.8 RVUs, P=0.07) (Table 2). Male and female attendings were equally assigned to residents (60.8% vs. 55.7%) (p=0.75) (Table 3). Overall, there was a trend towards greater RVU production in female attendings (4.3 vs. 3.6, p=0.21), but there was no difference in ASA unit production (99.8 vs. 99.3, p = 0.94) (Table 3).

Conclusion: Our hypothesis was incorrect. Male and female attendings were equally assigned to residents. While we did not measure implicit bias in schedulers, our results suggest a lack of gender-based implicit bias with regards to frequency of CRNA assignments. Interestingly, we found that there is greater opportunity to earn RVUs working with residents, compared with CRNAs. This may be due to a preferential assignment of complex cases to residents, which often require more RVU generating procedures, such as invasive monitors. The trend of greater RVU production in female attendings suggests that female attendings may be assigned higher complexity cases. This study is limited to our anesthesia department and may not be generalizable to institutions with different scheduling practices and case mixes. It has been suggested that gender-based pay discrepancy can be corrected with the implementation of a compensation plan that includes objective evaluation measures.(6) A multi-centered study is suggested to determine if gender-based differences in anesthesia attending assignments may help explain the gender pay gap.

References: 1. Int Anesthesiol Clin. 2018;56(3):21–43. 2. Br J Anaesth. 2020;124(3):e134-e147. 3. Eur J Anaesthesiol EJA. 2016;33(8):588–590. 4. Anesthesiol J Am Soc Anesthesiol. 2015;123(5):997-1012. 5. Trans Am Clin Climatol Assoc. 2015;126:197-214. 6. Ann Surg. 2018;268(3):479-487.

Table 1: Subject Baseline Attending Characteristics Stratified by Sex

	Female (n = 7)	Male (n = 13)
Caucasian race, n (%)	3 (42%)	12 (92%)
Attending experience (years), mean	8	7
Fellowship trained, n (%)	4 (57%)	8 (61%)

Table 2. Average RVUs by Sex and Whether Worked with Residents

	Average Units Generated		
	Male	Female	Total
Worked with CRNAs	2.8	3.1	2.9
Worked with Residents	4.0	5.3	4.4
Student T-Test	-1.8	-2.9	-3
p-value	0.07	<.01	<.01
n	100	53	153

Table 3: Trial Endpoints Stratified by Sex

	Female (n = 7)	Male (n = 13)	p value
Assignment to Residents, %	55.7	60.8	0.75
ASA units, mean	99.8	99.3	0.94
RVUs (all cases), mean	4.3	3.6	0.21

Economics, Education and Policy - 17

The Development of a Template for Learning Anesthetic and Airway Management: the Medical Student Perspective

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Introduction: Medical students learn about anesthesiology through independent reading, observation, teaching from clinicians, and active participation. New learners must develop skills to assess and prepare patients, choose anesthetic techniques and airway devices, and understand when and how to use aids and maneuvers for intubation and ventilation. Medical students tend to focus on intubations during their clinical rotation in anesthesia, and most studies on medical students learning anesthesiology have studied best practices for teaching intubations to medical students (1-5). Though intubation is an important clinical skill in airway management, redirecting learners to appreciate the multiple dimensions of anesthetic and airway management may be more comprehensive. We present a learning guide for medical students to understand the phases of anesthetic and airway management to optimize their learning potential and utilize their skill sets.

Methods: We divided anesthetic and airway management into seven phases: patient chart review, preoperative evaluation, preparation/premedication, induction, intubation, maintenance, and extubation. For each phase, we separated the clinical course into tasks (interventions and actions by the anesthesia team) and events (complications).

Results: The template was developed by anesthesiologists and medical students. It was used to introduce medical students on a clinical anesthesia elective clerkship to anesthetic and airway management (Figure 1). During procedures, from the preoperative evaluation to the patient exiting the operating room, medical students referenced the guide with consideration to patient risk factors. Medical students were encouraged to record clinical events in relation to interventions employed by the anesthesiologist (see Figure 2 and Figure 3).

Conclusion: Our template encouraged medical students to participate in every phase while they maintained a high-level understanding of goals in anesthetic and airway management. A recent survey showed that clinical anesthesia teaching for U.S. medical students occurred in the operating room during the clinical years, and 68% of responding clinician teachers reported that they had no formal training for faculty teachers (6). This report highlights the need for structure not only in anesthesia teaching, but also in student-driven learning in clinical environments. Our proposed template would be easy to bring to the operating room and reference throughout a procedure. Further work on best practices for teaching and learning in anesthesia would optimize clinical learning for medical students.

References: 1) Anaesthesia. 61(11), 1093-1099, 2006. 2) Journal of the Royal Society of Medicine. 85(10), 603, 1992. 3) Anesthesia & Analgesia. 113(3), 586-590, 2011. 4) Anaesthesia. 65(7), 674-678, 2010. 5) Medical Education Online. 16(1), 7309, 2011. 6) Anesthesia & Analgesia, 126(5), 1687-1694, 2018.

Figure 1. Learning Template for Anesthetic and Airway Management

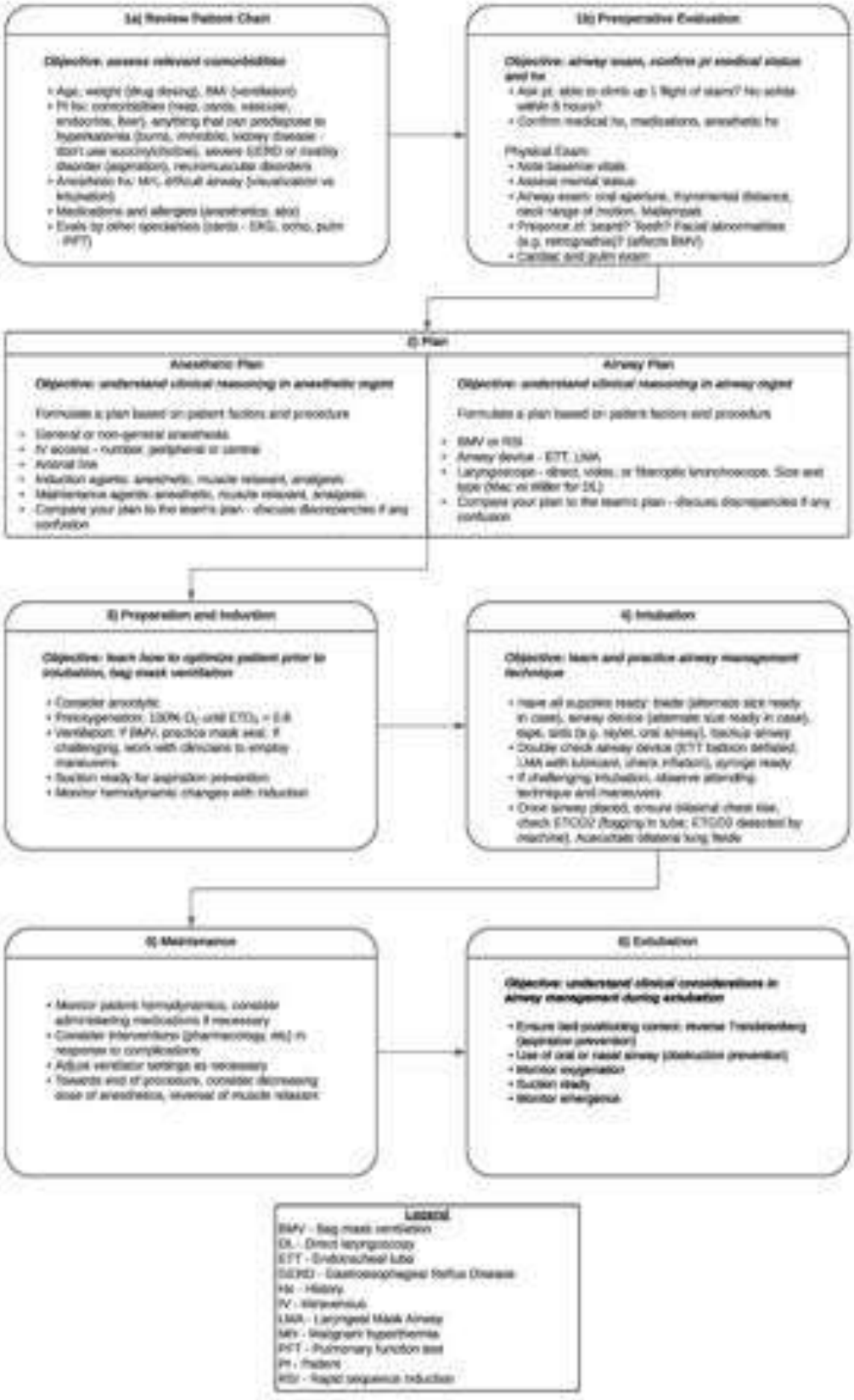

Figure 2. Learning Worksheet for Anesthetic and Airway Management

		Medical Student Assisting Task	CLINICIAN TASK: Intervention	CLINICIAN TASK: Intubation	EVENTS*: Ventilation	EVENTS*: Physiologic	EVENTS*: Oxygenation	EVENTS*: Aspiration	EVENTS*: Other
1	Pre-operative Evaluation								
2	Preparation/ Premedication								
3	Induction								
4	Intubation								
5	Maintenance								
6	Extubation								

*For events, record complications experienced. Ventilation includes increases in end-tidal CO2 or periods of apnea. Physiologic changes include large variations in blood pressure or heart rate. Oxygenation includes desaturations. Aspiration includes aspirations risks such as vomiting or dislodging endotracheal tube.

Figure 3. Example of Completed Learning Worksheet for Anesthetic and Airway Management

		Medical Student Assisting Task	CLINICIAN TASK: Intervention	CLINICIAN TASK: Intubation	EVENTS*: Ventilation	EVENTS*: Physiologic	EVENTS*: Oxygenation	EVENTS*: Aspiration	EVENTS*: Other
1	Pre-operative Evaluation	40yo male w stable angina, morbid obesity, OSA, GERD, Mallampati 3, beard undergoing femoral bypass graft, cardiac workup normal. No solids for 6h. Baseline vitals 142/86, HR 90, SpO2 99%							
2	Preparation/ Premedication	Help transport pt to OR. My anesthetic plan: general anesthesia, BMV (Trendelenberg for aspiration prevention), 7.5mm ETT with VL #4 due to Mallampati 3. Start A-line due to: obesity (BP cuff likely inaccurate) and two peripheral IVs. NG tube? Compare to team	administered 5mg midazolam. Ordered beside EKG			tachycardic and hypertensive			sweating, anxious
3	Induction	Suction ready. Ask team if I can perform BMV. Expect to be challenging due to beard, so oral airway ready. My induction plan: lidocaine + propofol + rocuronium. Compare to team	Clinician demonstrated jaw thrust, inserted oral airway, rotated patient head to right, squeezed bag		Laborious. Required two-hand BMV. Max detected ETCO2 54mmHg		89%		
4	Intubation	Ask team if I can perform intubation. Supplies ready. Once tube placed, check for ETT fogging, bilateral chest rise, ETCO2 detected. Ask clinician for ventilation settings. Ask clinician if I can place peripheral IV	Guided my left hand to performing laryngoscopy, provided cricoid pressure. Administered fentanyl in response to physiologic changes. Administered A-line	Vocal cords difficult to visualize, required few attempts		BP 182/126, HR 101, went back down after fentanyl	Dropped to 94%		
5	Maintenance	My maintenance plan: sevoflurane + propofol, rocuronium (vascular procedure, don't want patient to move) fentanyl if needed. Monitor hemodynamics.	Administered phenylephrine (drip), norepinephrine, fentanyl, adjusted propofol and sevoflurane in response to hemodynamic changes		ETCO2 35-45mmHg	BP 174/119 HR 98 after first incision	97-99%		
6	Extubation	Trendelenberg, oral and nasal airway ready. Suction ready.	Decreased anesthetic dosing 15-30 minutes before end of procedure. Suction NG tube. Twitch monitor showing residual paralysis, administered suggemadex				dropped to 93% during extubation	Some fluid in NG tube, suctioned	

*For events, record complications experienced. Ventilation includes increases in end-tidal CO2 or periods of apnea. Physiologic changes include large variations in blood pressure or heart rate. Oxygenation includes desaturations. Aspiration includes aspirations risks such as vomiting or dislodging endotracheal tube.

Economics, Education and Policy - 18

Promoting Perioperative Neuroscience Exchange And Excellence: Neuroanesthesia Program Relations (Npr) Committee For International Council On Perioperative Neuroscience Training (Icpnt)

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Introduction: International council on perioperative neuroscience training (ICPNT) is the first international and non-ACGME accreditation council for an anesthesia subspecialty fellowship training. The ICPNT was created in 2019, given increasing interest internationally for standardization and accreditation of neuroanesthesia fellowship programs. One of the unique services that ICPNT offers is a collaborative sharing of educational, scientific, and professional resources between programs. With this mission in mind, the Neuroanesthesia Program Relations (NPR) committee was created. In this abstract, we seek to present the launching of collaborative activities of NPR committee in an effort to promote and connect neuroanesthesia education and training in fellowship programs around the world.

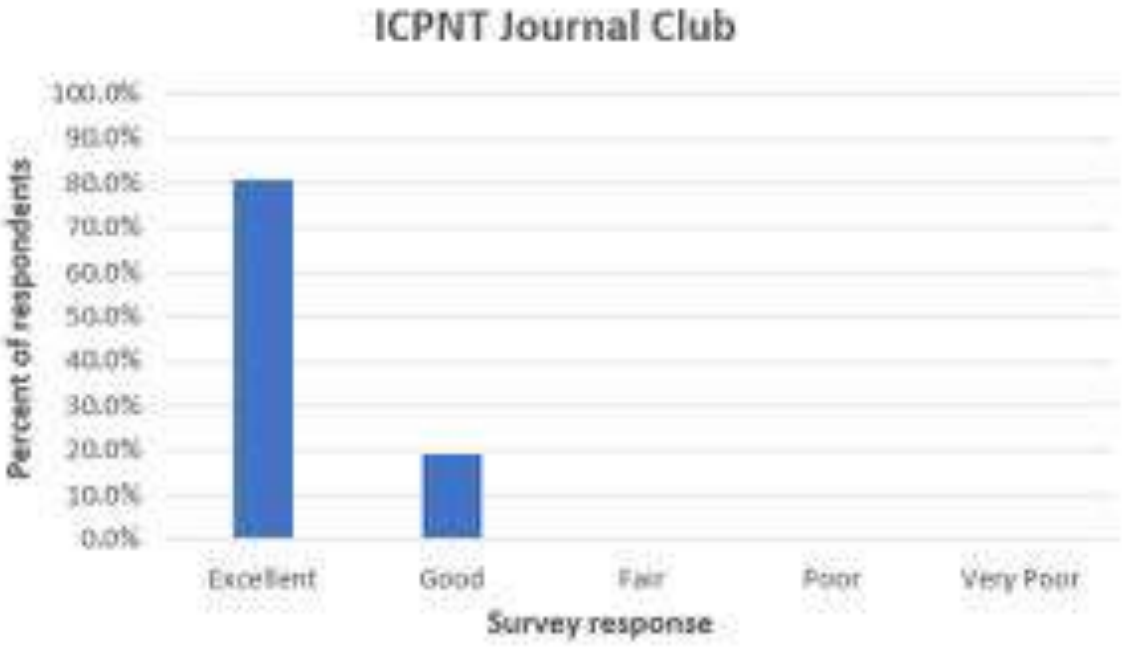
Methods: A number of activities were designed as part of this effort to be a center for education in neuroanesthesia. NPR organized its first patient safety session on 'Crisis management in neuroanesthesia' at the 2020 annual meeting of Society of Neuroscience for Anesthesiology and Critical Care (SNACC). The other goal is to offer the 'ICPNT rounds' regularly, similar to grand rounds. The aim is to enable fellows in the ICPNT accredited fellowship programs to present at journal clubs, to facilitate case-based discussions and to organize academic seminars using online video communication platforms. The online platform has greatly facilitated the international programs to participate the virtual NPR activities, despite the time zone laps. Up to date, ICPNT has conducted three webinars. The first, a seminar with timely discussion on 'Neurological Manifestations of COVID-19 ' after the initial surge of the pandemic (June 2020). More recently, a journal club was conducted to discuss three recent articles in areas of perioperative management of neurological surgical patients (November 2020). Participant feedback was collected after the journal club. It was followed by a case based reasoning webinar: ' When the Going Gets Tough - The Tough Get Going!' (January 2021).

Results: Our first NPR/ICPNT webinar on case-based discussions welcomed 98 registrants, including neuroanesthesia faculty, fellows, and residents. They represent medical institutions located at continents around the globe: Africa, Asia, Europe, North America, Oceania, and South America. (Figure 1) The first NPR/ICPNT journal club was also well-attended by 100 registrants from around the world. Our post-event survey demonstrated that 81.8% of respondents rated it as excellent and 18.2% as good, respectively (n=26). (Figure 2)

Conclusion: The Neuroanesthesia Program Relations committee (NPR) for ICPNT creates an international collaborative platform for the accredited programs which may wary widely in their neuroanesthesia practices, to share academic resources and to learn from each other's experiences. This program represents an opportunity for fellows and faculty to gain worldwide exposure of educational presentations. We believe this is one of the first such innovative educational efforts in sub-specialty education.

References: 1. J. Neurosurg. Anesthesiol.. 25(1):1-7. 2013. 2. J Neurosurg Anesthesiol. Jan;33(1):82-86. 2021

ICPNT Webinar Registrants Map



Economics, Education and Policy - 19 The Development Of Laryngoscopy: A Historical Crossroads For Anesthesiology & Laryngology

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[1]*Boston Children's Hospital, Boston, MA*

Introduction: The relationship of laryngoscopy to anesthesiology and otolaryngology was not always well established, and geographic and historical simultaneity were insufficient.

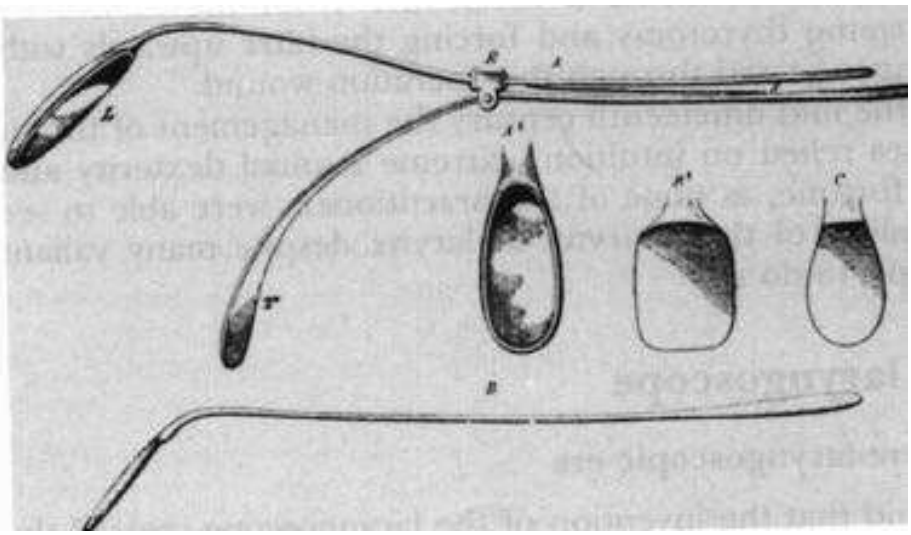
Methods: Historical review.

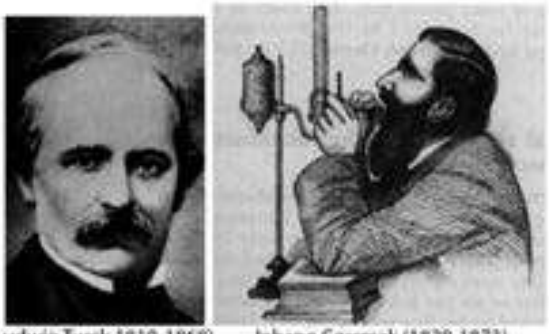
Results: Galen demonstrated that the larynx was the instrument of the voice by sectioning the recurrent laryngeal nerve. Antyllus described laryngotomy for airway obstruction around 425 A.D.(1) Roger Frugardi and his contemporaries utilized the spongia somnifera a millennium ago for surgical anesthesia at Salerno. Guy de Chauliac asserted direct observation as the basis of anatomy.(2) The visualization of a living larynx waited until Babington developed his "glottiscope" palatal mirror/tongue retraction system in 1829. (Fig. 1) Laryngology and anesthesiology crossed paths at the Allgemeine Krankenhaus in Vienna. Turck used a laryngoscope in 1857, although Czermak published his own observations in 1858.(5) At the same time, Niemann isolated and von Anrep noted the numbing action of cocaine. Freud, also at the Allegemeine Krankenhaus, mentored Karl Koller, a medical student, who presented his finding that cocaine could be used to anesthetize the cornea. Shortly thereafter, Jelineck published "Cocaine as an anaesthesia and analgesia for the mucous membrane of the pharynx and larynx."(6) (Fig.2) But the techniques were not combined. In 1859 Mackenzie was taught the use of the laryngoscope by Czermak. Mackenzie relied on the patient sucking ice and taking an occasional inhalation of chloroform.(7) While Macewen was the first to intubate the trachea by the tactile method.(8,9) Kirstein was the first (1895) to examine the larynx directly; Killian (1896) was so impressed, he devoted his entire practice to endoscopy.(10) (Fig. 3) O'Dwyer digitally intubated the trachea in order to treat diphtheria, but the method was not used by him for delivery of anesthesia. This technique was adapted for anesthetic purposes by Kuhn in Germany. Neither a general nor a local anesthetic was administered initially, but Kuhn, using topical cocaine, made his patients more comfortable for intubation prior to the chloroform or ether.

In 1912, Elsberg reported intratracheal insufflation anesthesia with subsequent intubation of the trachea. He stated "ever since I have made use of the laryngoscopic introducer of…Jackson, I have never had much difficulty."(11) One year later, Janeway reported on his modification of the three-sided Jackson direct laryngoscope: "...it is deficient at the side…permitting…the withdrawal of the instrument without the necessity of pushing the catheter through it…to insert the catheter without detaching it from the tubing connecting…the gas bag."(12) (Fig. 4)

Conclusion: The relationship of laryngoscopy to anesthesiology and otolaryngology was now well established. The anesthetized airway (topically) or patient (with inhalation anesthesia) could be examined for diagnostic purposes by suspension laryngoscopy or have his trachea intubated with the assistance of a specially modified laryngoscope.

References: 1. Otol H & N Surg 1982; 90:226-232 2. Trans Amer Acad Opth Otol 1974; 78:15-20 3. Proc. Roy. Soc. London 1855;7:399 4. Trans. Sec. Lar. VIIth Cong Med 1881;3:197 5. Otolaryngology. London: Butterworths, 1990:290 6. Wien. Med. Woch. 1884;34:1334 7. Philadelphia: Lindsay and Blakiston, 1865:160. 8. Br Med Jour 1880; 2:122-125. 9. Br Med Jour 1880; 2:163-165. 10. Larynxwand. Jena: G. Fischer, 1890:77 11. New York State Journal of Medicine 1912;12:524-528 12. Annals of Surgery 1913;58:927-933

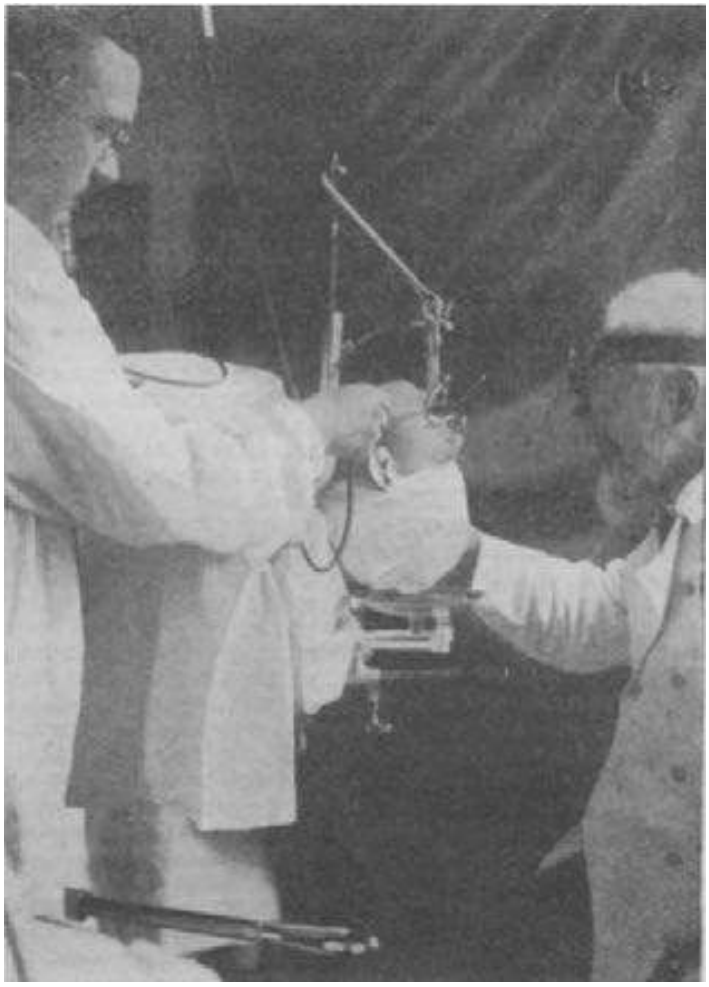


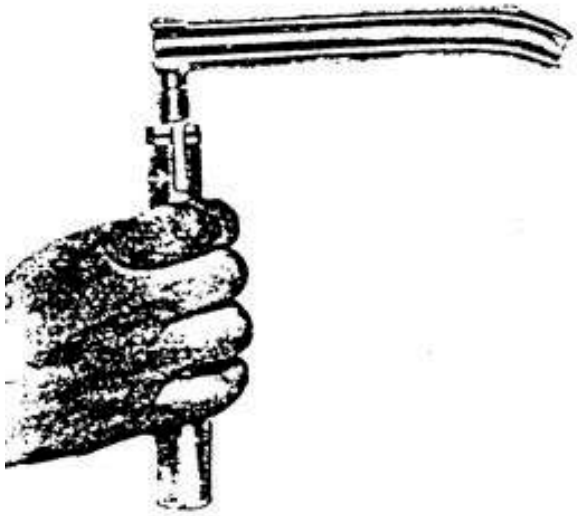


Ludwig Turck 1810-1868) Johann Czermak (1828-1873)

Karl Koller (1857-1944

Edmund Jelineck (1852-1928)





Economics, Education and Policy - 20

Forging Interprofessional Education in the Perioperative Setting in the Time of COVID 19

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Introduction: The COVID 19 pandemic has wreaked havoc among healthcare staff and the population. I, in these trying times when fear, stress and anxiety run high, interprofessional communication and support for each other and teams are essential to keep the morale of the staff high. A recent survey done at BIDMC in the COVID ICUs and surge ICUs showed that stress and anxiety were indeed at a very high level and open-ended responses revealed that staff preferred strong camaraderie and interprofessional communication. I, in light of the pandemic, which highlighted the importance of interprofessional communication and teamwork, we plan to improve the interprofessional education we offer to Anesthesiology and Surgery trainees as well as to nurses.

Methods: The COVID 19 pandemic has wreaked havoc among healthcare staff and the population. I, in these trying times when fear, stress and anxiety run high, interprofessional communication and support for each other and teams are essential to keep the morale of the staff high. A recent survey done at BIDMC in the COVID ICUs and surge ICUs showed that stress and anxiety were indeed at a very high level and open-ended responses revealed that staff preferred strong camaraderie and interprofessional communication. I, in light of the pandemic, which highlighted the importance of interprofessional communication and teamwork, we plan to improve the interprofessional education we offer to Anesthesiology and Surgery trainees as well as to nurses.

Results: The COVID 19 pandemic has wreaked havoc among healthcare staff and the population. I, in these trying times when fear, stress and anxiety run high, interprofessional communication and support for each other and teams are essential to keep the morale of the staff high. A recent survey done at BIDMC in the COVID ICUs and surge ICUs showed that stress and anxiety were indeed at a very high level and open-ended responses revealed that staff preferred strong camaraderie and interprofessional communication.ii In light of the pandemic, which highlighted the importance of interprofessional communication and teamwork, we plan to improve the interprofessional education we offer to Anesthesiology and Surgery trainees as well as to nurses.

Conclusion: So far this project has received excellent feedback and we hope to continue the relevance and touching on the stressful issues that may hinder smooth perioperative patient care, especially during the pandemic. We also hope to evolve into other multi-professional arenas such as OR and ICU.

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Economics, Education and Policy - 21

Percentage Of Cases In Pairs And Triplets Of Operating Rooms Of Sufficient Duration To Accommodate A 30-Minute Breast Milk Pumping Session By Supervising Anesthesiologists

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Introduction: The US Fair Labor Standards Act requires "reasonable break time" for a woman "to express breast milk for her nursing child for 1 year after the child's birth each time such employee has need to express the milk." The Accreditation Council for Graduate Medical Education (ACGME) includes "clean and private facilities for lactation" as a common program requirement. Breastmilk pumping sessions are challenging to arrange for US anesthesiologists because clinical care is organized with supervision of multiple anesthetics simultaneously. We previously quantified the minimum percentages of cases for which there could reliably (>95%) be at least 30 minutes during the surgical time when the anesthesia provider could receive a break. We repeated for the anesthesiologist covering multiple anesthetics and with her operating rooms (ORs) covered by another anesthesiologist.

Methods: This historical cohort study was performed using 4 yr of anesthetic and surgical times from the surgical suites of a large US teaching hospital. The first 3 yr of historical data were applied to the final 1 yr period, the latter used in the results.

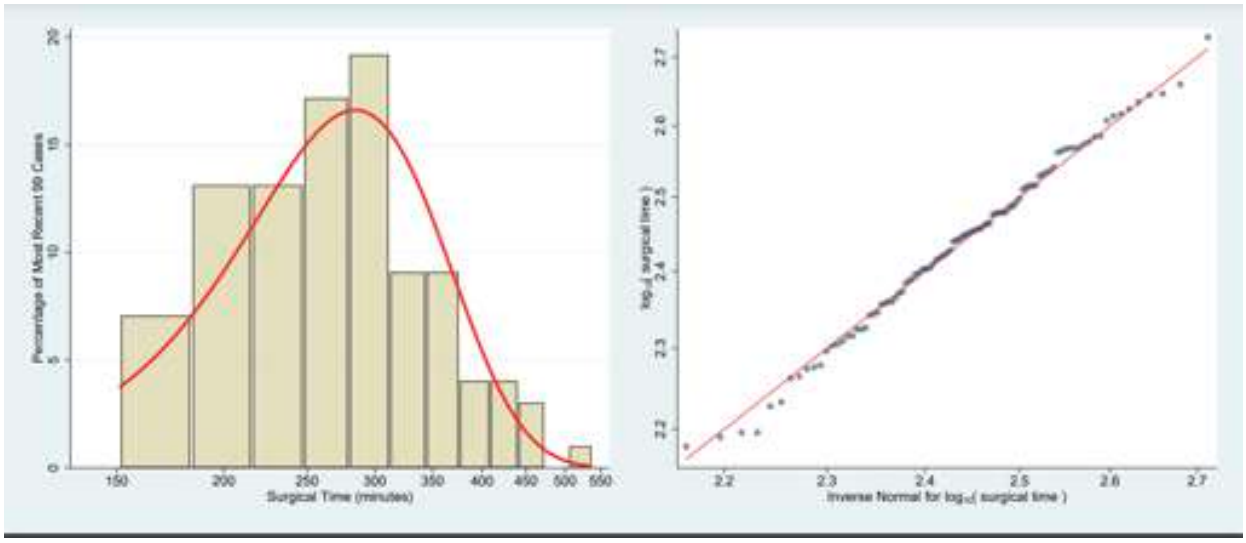
Previously, we calculated 5% lower prediction bounds of individual cases' surgical times using the 3 historical years, based on 2-parameter log-normal distributions classified by the primary surgical procedure (Healthcare Common Procedure Coding System) used for anesthesia billing. The prediction bounds were applied to actual surgical start times during the final 1 yr. For example, Fig 1 shows surgical times of the most recent 99 cases (during the 3 yr period) for 55866, "Laparoscopy, surgical prostatectomy ... includes robotic assistance." The probability plot shows excellent fit to a log-normal distribution, Shapiro-Wilk P=0.84. Fig 2 shows the corresponding cumulative distribution function, up to the 50th percentile. The red line shows exponential (a posteriori Student t distribution), based on N=3 cases, using the same mean and SD in the log scale as for the blue line. The blue line is based on 99 historical cases. The 5% lower prediction bound with N=3 cases is less (124 min) than for N=99 because with N=3 there is considerable uncertainty in the estimated mean and SD. These 5.0% lower prediction bounds are accurate, coverage 4.86% (99% confidence interval 4.55%-5.19%, N=30,357). To appreciate their used, 39% of cases were reliably (>95%) of sufficient duration for the anesthesia provider in that one OR to receive a 30-min break for breast milk pumping session between 15-min after the start of surgery and procedure end. This 39% was much less than the 72% of the surgical times being that long because the 5% prediction bounds account accurately for uncertainty in the duration of each case.

Our focus of the current study was pairs and triplets of simultaneous cases, as supervised by individual anesthesiologists. The sequentially numbered ORs were treated as having cyclic adjacency (e.g., for the 36 OR adult surgical suite, room 1 was paired with rooms 36 and 2, room 2 was paired with rooms 1 and 3, etc.). For each of the two adjacent rooms, the maximum overlapping period was calculated. Sample sizes are in the Table.

Results: For the large majority of all cases (>2/3rd), an anesthesiologist supervising 3 ORs would lack a reliable 30-minute period of overlapping surgical times ($P < 0.0001$). An anesthesiologist working at the ambulatory surgery center, with shorter duration cases, would have an even smaller chance per case, 10% (9% to 11%).

For approximately 42% (41%-43%) of sufficiently long individual cases, there was absence of a continuous 30-minute period during which both of the 2 adjacent rooms' cases also were suitable for the anesthesiologist to receive a break.

Conclusion: Our analyses make multiple assumptions that are deliberately unrealistic (e.g., anesthesiologists' responsibilities are only ongoing cases and not their patients in the post-anesthesia care unit). Nevertheless, there was no practical mechanism for an anesthesiologist supervising 3 ORs to start cases, be relieved for a breast milk pumping session, and then return in time for the end of the anesthetics (e.g., tracheal extubation). Therefore, departments with anesthesiologists who are breastfeeding should consider having options for temporary clinical assignments, commensurate with training and experience, that do not require supervising >2 ORs.


Percentage of Most Recent 99 Cases
0
5
10
15
20
150
200
250
300
350
400
450
500
550
Surgical Time (minutes)
log10 surgical time)
2.2
2.3
2.4
2.5
2.6
2.7
Inverse Normal for log10(surgical time)

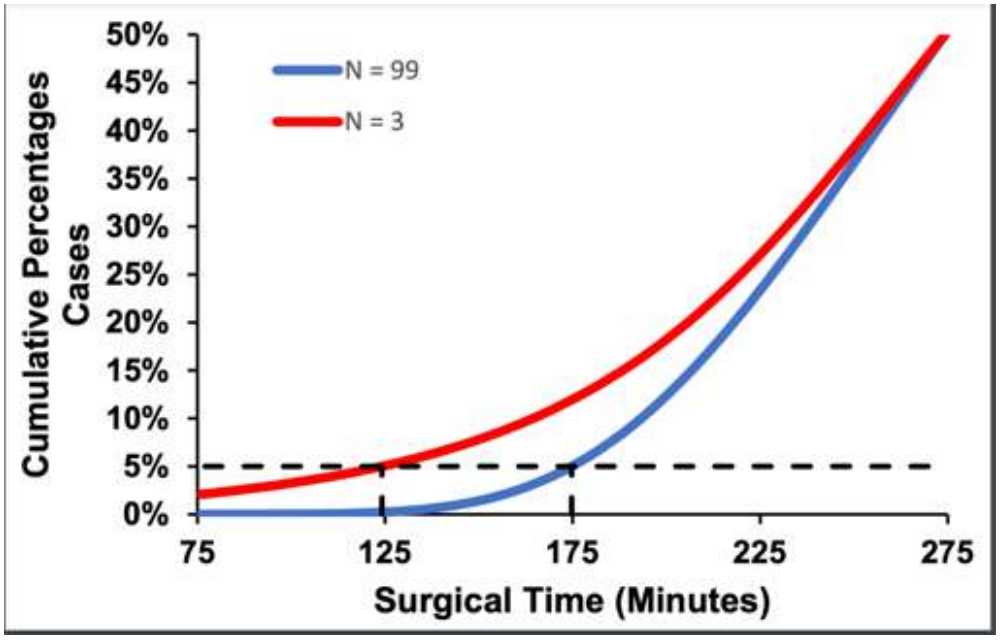

Cumulative Percentages Cases
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
N = 99
N = 3
75
125
175
225
275
Surgical Time (Minutes)

Table. Periods with at least 30 minutes from 15 minutes after the start of surgery but before the end of the procedure

	All Cases Combined	Ambulatory Surgery Center	Children's Hospital	Children's Hospital Elective Cases	Adult Surgical Suite	Adult Surgical Suite Elective Cases
N of column, single cases' 5% lower bounds	30,357	7987	4872	4163	17,498	13,411
Single cases reliably ≥ 30 min from (surgery start + 15 min)	11,932	1439	1009	882	9484	8012
%, denominator is row 1	**39%**[a]	18%[b]	21%	21%	54%	60%[c]
lower 99%CI	**39%**	17%	19%	20%	53%	59%
upper 99% CI	**40%**	19%	22%	23%	55%	61%
Pairs of adjacent cases best chance reliably ≥ 30 min overlap	11,271	1322	929	808	9020	7589
%, denominator is row 1	37%	17%	19%	19%	52%	57%
lower 99% CI	36%	16%	18%	18%	51%	56%
upper 99% CI	38%	18%	21%	21%	52%	58%
Pairs of adjacent cases least chance reliably ≥ 30 min overlap	7795	835	837	526	6323	5099
%, denominator is row 1	26%	10%	13%	13%	36%	38%
lower 99% CI	25%	10%	12%	11%	35%	37%
upper 99% CI	26%	11%	14%	14%	37%	39%
Triplets of adjacent cases reliably ≥ 30 min overlap	6928	821	618	508	5489	4296
%, denominator is row 1	23%	**10%**[a]	13%	12%	31%	32%[c]
lower 99% CI	22%	**9%**	12%	11%	30%	31%
upper 99% CI	23%	**11%**	14%	14%	32%	33%
Two-sided P-value making comparison with 1/3[d]	**< 0.0001**[e]	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.0014
Single cases but not triplets reliably with ≥ 30 min	6928	821	618	508	5489	4296
%, denominator is row 2	**42%**[a]	43%	39%	42%	42%	46%
upper 99% CI	**41%**	40%	35%	38%	41%	45%
lower 99% CI	**43%**	46%	43%	47%	43%	48%
Two-sided P-value making comparison with 1/3[d]	**< 0.0001**	< 0.0001	0.0003	< 0.0001	< 0.0001	< 0.0001

Economics, Education and Policy - 22

Creating a Programmatic System of Assessments for Evaluation of Anesthesiology Residency Milestone Achievement

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Introduction: In 2015 the Accreditation Council for Graduate Medical Education (ACGME) and the American Board of Anesthesiology (ABA) published a revised list of knowledge, skills, and behaviors that represent competency in anesthesiology[1]. This information was presented in the form of core competencies, sub-competencies, and specific developmental milestones[2]. Competency assessment and documentation of milestone achievement is required by the ACGME for accreditation, however the ACGME did not include tools to assess milestone achievement. In 2018, a set of core, case-based entrustable professional activities (EPAs) was developed for United States anesthesiology residency training[3]. Each EPA was mapped to the ACGME milestones; however, if a resident performed at the expected level of competency for graduation, they would only reach graduation targets for 10 (40%) of ACGME sub-competencies (Figure 1). The specific nature of some milestones – particularly those in the sub-competencies of practice-based learning and improvement, systems-based practice, interpersonal communication, and professionalism – made them difficult to assess by case-based EPAs. The aim of this project was to develop a set of additional competency assessments that, when combined with the 20 core EPAs, resulted in a system that informs the majority of anesthesiology milestones and sub-competencies.

Methods: In the first phase of the study, a modified Delphi process was used to reach consensus on a set of additional assessments using a panel of education experts (Figure 2). All surveys, communication, and data collection were completed virtually. For each survey round, panelists were asked to include or exclude each assessment and provide comments. They were also able to propose new assessments. The results from each round were reviewed by the research coordinators (ZG, GW). Items that did not reach the threshold for inclusion or exclusion were carried into the next round's survey, and were modified based on panelist comments in the prior round. This process was repeated until the committee reached consensus on all proposed assessments. In the second phase of the study, panelists were assigned to fully define the assessments. The definitions followed templates provided by the research team, and included learning objectives, background information, and expected behaviors at different levels of learner competency that were mapped to milestones. The full definitions and milestone mappings were reviewed by the entire expert panel. The research team revised the assessments based on reviewer comments. The revised assessments were sent back to the panel for comment and this process was repeated until no further comments were received. The primary outcomes of this study were 1) A consensus list of new assessments with full definitions and 2) Milestone coverage of new assessments.

Results: The panel reached consensus to include 7 special assessments, 7 OSCEs, and 1 EPA (Figure 3). Each assessment includes a detailed description, expected behaviors with examples, and milestones achieved for demonstrated behaviors. Assessments were uploaded using software from MyTipReport (MyTipReport LLC, Richmond, Virginia). The new suite of assessments covers 144 non-patient care milestones (87.8%) and 23 (92%) of ACGME sub-competencies (Figure 4).

Conclusion: A modified Delphi process was used to develop and refine a set of assessments to complement 20 core cased-based EPAs for anesthesia residents training in the United States. Overall, 15 assessments were developed and approved by a committee of experts in anesthesia education. The new assessments create a programmatic system and structured method to evaluate achievement of the majority of ACGME anesthesiology milestones. These new assessments primarily evaluate non-patient care sub-competencies including interpersonal communication skills, professionalism, problem-based learning and improvement, and systems-based practice. The milestones not covered by this system of proposed assessments are either not suitable for evaluation with direct observation of trainees at single points in time or are aspirational in nature. Future directions are focused on studying the reliability and validity of the individual and full suite of assessments. The assessments will be examined for feasibility of implementation, inter-rater reliability, and construct validity.

References: 1. The Anesthesiology Milestone Project (2015 revision). The Accreditation Council for Graduate Medical Education and The American Board of Anesthesiology; 2015. 2. The Next GME Accreditation System — Rationale and Benefits. 366(11):1051–56. 2012. 3. Development and Pilot Testing of Entrustable Professional Activities for United States Anesthesiology Residency Training. Anesth Analg. Accepted for publication 1/8/2021.

Assessment	Assessment	Assessment
OSCE 1: Adverse Event	**Special Assessment 1: Leadership of quality and/or safety initiative**	**Entrustable Professional Activity: Leadership and Management of a Team**
OSCE 2a: Patient Conflict	**Special Assessment 2: Review of personal outcomes**	
OSCE 2b: Patient and family Conflict	**Special Assessment 3: Giving and Receiving feedback**	
OSCE 3: Staff Conflict	**Special Assessment 4: Teaching Others**	
OSCE 4a: Ethical Issue surgeon	**Special Assessment 5: Crisis Management**	
OSCE 4b: Ethical Issue family	**Special Assessment 6: Development and modification of an individual learning plan**	
OSCE 5: Physician Impairment	**Special Assessment 7: Demonstration of basic professionalism and personal wellness behavior**	

Figure 1. In-app screenshot: sub-competency achievement of a trainee who accomplishes all milestones covered by core EPAs. "G" designates graduation targets for US anesthesia trainees.

Figure 4. In-app screenshot: sub-competency achievement of a trainee who accomplishes all milestones covered by new suite of assessments. "G" designates graduation targets for US anesthesia trainees.

Geriatric Anesthesia

Geriatric Anesthesia - 1 Preoperative Cognitive Impairment And Frailty Are Risk Factors For Adverse Postoperative Outcomes After Perioperative Potentially Inappropriate Medication Administration

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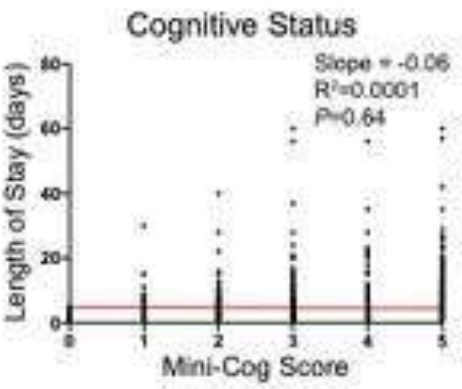
Introduction: The American Geriatrics Society maintains a list of potentially inappropriate medications (PIMs) best avoided in adults ≥65 years (1). Recent best-practice guidelines recommend avoiding perioperative administration of these medications in all geriatric surgical patients (2,3). However, it is unclear whether PIM administration increases the incidence of poor postoperative outcomes in at-risk older adults. We investigated whether preoperative frailty or cognitive impairment increases the risk for poor postoperative outcomes after perioperative PIM administration.

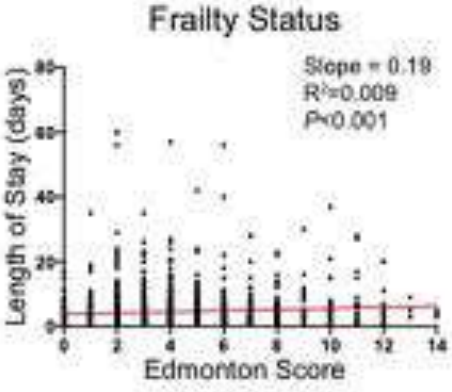
Methods: We performed a retrospective study of patients ≥65 years that underwent elective inpatient surgery at a large academic medical center from February 2018 to January 2020. Edmonton Frail Scale and Mini-Cog screening tools were administered to all patients at their preoperative clinic visit. A Mini-Cog score 0-2 was considered cognitive impairment, and frailty was defined by an Edmonton Frail Scale score≥ 8. The effects of preoperative frailty, cognitive impairment, and perioperative PIM administration on length of hospital stay and discharge disposition were assessed. One-way ANOVA or t-test was used to compare average length of hospital stay or discharge disposition. Linear regression analysis was used to determine relationships between frailty status, cognitive status, PIM administration, and length of stay.

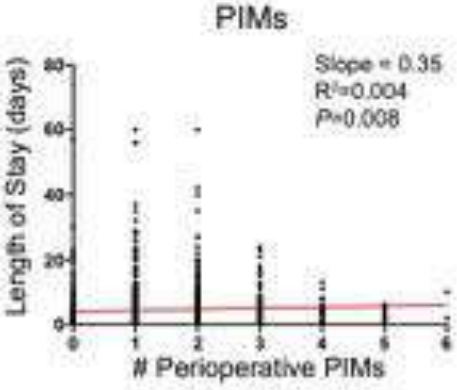
Results: 1,627 patients (mean age 73.7±6.3 years, 49.1% male) were included (Table 1). 72% of frail patients and 71% of patients with Mini-Cog 0-2 received at least one PIM (Table 2). Perioperative administration of at least one PIM was associated with longer hospital stay after surgery (3.00±4.83 days vs. 4.84±5.65 days, P<0.001). Linear regression analysis demonstrated an association between Edmonton Frail Scale score and length of stay (R^2=0.009, F=14.2, P<0.001), as well as number of PIMs and length of stay (R^2=0.004, F=7.2, P=0.007) (Fig. 1). Frail patients that received PIMs had a longer length of stay than non-frail patients who received PIMs (4.67±5.63 days vs. 6.26±6.00 days, P=0.009) (Table 3). While PIMs had no effect on discharge disposition for cognitively intact and nonfrail patients, cognitively impaired patients that received at least one PIM were more likely to discharge to a care facility than cognitively intact patients that received at least one PIM (36% vs. 30%, P=0.02). In addition, frail patients that received at least one PIM were more likely to discharge to a care facility than frail patients that did not receive any PIMs (41% vs 60%, P<0.001) (Table 4).

Conclusion: PIM administration to cognitively impaired and frail older adults is common in the perioperative period, and associated with increased length of hospital stay. Preoperative frailty and cognitive impairment increase the detrimental effects of perioperative PIMs, and should be screened for preoperatively to guide perioperative medication administration.

References: 1. J Am Geriatr Soc, 67, 674-694. 2019. 2. Anesthesia & Analgesia, 127, 1406-1413. 2018. 3. Anesthesia & Analgesia, 130, 1572-1590. 2020.







Patient Characteristics	
Age, yr (SD)	73.7 (6.3)
Male Sex, n (%)	800 (49.1)
ASA Class, n (%)	
I	7 (0.4)
II	450 (27.7)
III	948 (58.4)
IV	219 (13.5)
Procedure Department, n (%)	
Orthopedic	569 (35.0)
Cardiac	261 (16.1)
General	220 (13.5)
Neurosurgery	161 (9.9)
Otolaryngology	98 (6.0)
Vascular	92 (5.7)
Urology	82 (5.0)
Gynecology	17 (1.0)
Other	124 (7.6)
Type of Anesthesia, n (%)	
General	1168 (71.7)
MAC	299 (18.3)
Nerve Block	68 (4.2)
Spinal	48 (2.9)
Epidural	45 (2.8)
Cogntivie Status, n (%)	
Mini-Cog 3-5	1450 (89.1)
Mini-Cog 0-2	177 (10.9)
Frailty Status, n (%)	
Edmonton 0-7	1428 (87.8)
Edmonton 8+	199 (12.2)

Number of PIMs	Mini-Cog 3-5 (n=1450)	Mini-Cog 0-2 (n=177)	Edmonton 0-7 (n=1428)	Edmonton 8+ (n=199)
0	268	50	269	49
1	505	58	496	67
2	460	54	454	60
3	172	13	166	19
4	31	2	30	3
5	12	0	11	1
6	2	0	2	0

Group	n	Mean±SD	Comparison	P-value	Comparison	P-value
Mini-Cog 3-5	1450					
PIM (-)	268	2.93±4.85	Mini-Cog 3-5	**<0.001**	Mini-Cog 3-5 PIM (-)	>0.99
PIM (+)	1182	4.85±5.71	PIM (-) vs. PIM (+)		Mini-Cog 0-2 PIM (-)	
Mini-Cog 0-2	177					
PIM (-)	50	3.36±4.75	Mini-Cog 0-2	0.18	Mini-Cog 3-5 PIM (+)	>0.99
PIM (+)	127	4.92±5.11	PIM (-) vs. PIM (+)		Mini-Cog 0-2 PIM (+)	
Edmonton 0-7	1428					
PIM (-)	269	2.79±4.70	Edmonton 0-7	**<0.001**	Edmonton 0-7 PIM (-)	>0.99
PIM (+)	1159	4.67±5.63	PIM (-) vs. PIM (+)		Edmonton 8+ PIM (-)	
Edmonton 8+	199					
PIM (-)	49	3.21±4.53	Edmonton 8+	0.05	Edmonton 0-7 (+)	**0.009**
PIM (+)	150	6.26±6.00	PIM (-) vs. PIM (+)		Edmonton 8+ (+)	

Group	n	Discharge Home	Discharge to CF	Percentage CF	Comparison	P-value	Comparison	P-value
Mini-Cog 3-5	1446							
PIM (-)	265	198	67	25%	Mini-Cog 3-5	0.82	Mini-Cog 3-5 PIM (-)	0.48
PIM (+)	1181	869	312	26%	PIM (-) vs. PIM (+)		Mini-Cog 0-2 PIM (-)	
Mini-Cog 0-2	177							
PIM (-)	50	35	15	30%	Mini-Cog 0-2	0.48	Mini-Cog 3-5 PIM (+)	**0.02**
PIM (+)	127	81	46	36%	PIM (-) vs. PIM (+)		Mini-Cog 0-2 PIM (+)	
Edmonton 0-7	1428							
PIM (-)	269	207	62	23%	Edmonton 0-7	>0.99	Edmonton 0-7 PIM (-)	**0.01**
PIM (+)	1159	893	266	23%	PIM (-) vs. PIM (+)		Edmonton 8+ PIM (-)	
Edmonton 8+	199							
PIM (-)	49	29	20	41%	Edmonton 8+	**0.02**	Edmonton 0-7 (+)	**<0.001**
PIM (+)	150	60	90	60%	PIM (-) vs. PIM (+)		Edmonton 8+ (+)	

Geriatric Anesthesia - 2 Cognitive Trajectory Before And After Elective Total Joint Arthroplasty In A Population-Based Cohort Of Older Adults

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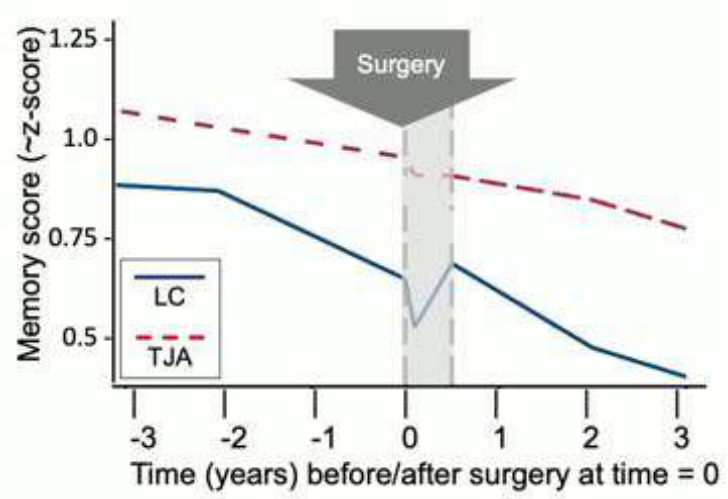
Introduction: Following total joint arthroplasty (TJA) of the hip or knee, 10-15% of older adults experience a decrement in neuropsychiatric test performance lasting 3 months or longer. However, it is not known whether this decrement represents a change in longitudinal rate of cognitive decline compared with pre-TJA cognitive trajectory.

Methods: We studied Health and Retirement Study (HRS) participants, a longitudinal population-based cohort of Americans, linked to Medicare fee-for-service billing records. Participants underwent TJA between 1998 and 2016 at age 65 or older. We compared TJA recipients to laparoscopic cholecystectomy (LC) recipients, who undergo surgery and a hospital stay of comparable duration. We modeled covariate-adjusted 'memory score,' a Z-scored summary measure of biennial HRS cognitive test scores and proxy cognition reports,(1) using multivariable linear mixed effects models with linear splines (a priori: knots at -2, 0, 0.5, 2y, and a discontinuity at time=0). The a priori primary outcome was change in rate of memory decline in the interval [2 to 0 years before surgery], versus [0.5 to 2 years after surgery], chosen to align with time to clinical benefit from TJA and exclude the 0-6 month period of initial recovery from surgery.

Results: 1,575 participants underwent TJA (474 hip, 1,101 knee) and 296 underwent LC. After TJA, participants' memory score declined 0.006 [-0.022 to 0.034] units/year more slowly (p=0.67), and LC recipients declined 0.003 [-0.098 to 0.092] units/year more quickly (p=0.95), compared to their own preoperative rate of cognitive change. The change was not significantly different between TJA and LC recipients (difference-in-differences, -0.009 [-0.11 to 0.092] units/year, p=0.86). In both groups, the change in cognitive slope represents a difference of fewer than 2 months of cognitive aging, which is unlikely to be clinically significant.

Conclusion: On average, older adults who undergo TJA do not experience a clinically or statistically significant change in longitudinal cognitive prognosis following surgery, compared to preoperative trajectory or to older adults who undergo LC.

References: (1) Alz Dis Assoc Disord Jul-Sep 2013;27(3):207-12.



Geriatric Anesthesia - 3 Postoperative Delirium in non-ICU High Risk Geriatric Patients

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Introduction: The American college of surgeons defines high risk geriatric patients as those who are frail or age ≥ 85 years (HRGP). Frailty and age are associated with higher postoperative complications, including postoperative delirium (POD). Most associations between HRGP and POD have been determined in surgical populations requiring post-operative icu admission. However, it is not clear whether being a HRGP is a strong risk factor for POD in surgery not requiring ICU admission. Our aim was to determine the association between HRGP and POD in surgical patients recovering in the PACU.

Methods: Patients undergoing surgery at a single institution from 1/1/2018-3/1/2020 were studied. The Edmonton frailty score was used to assess for frailty, with a score ≥ 6 defined as frail. CAM-ICU and 4AT were used to assess for POD with possible POD defined as CAM-ICU positive or 4AT score ≥4, and possible cognitive impairment defined as 4AT score 1-3, at any time on the surgical ward postoperatively. Eligibility criteria included age ≥ 65 years undergoing non-ICU surgery, with documented preoperative Edmonton frailty score assessment and POD evaluations. Groups were divided into HRGP and non-HRGP and compared. Multivariate modelling incorporating age, sex, race, anesthesia technique (spinal/epidural vs regional vs MAC vs general), surgical service, and surgical urgency (elective vs urgent vs emergency surgery) was used to determine relationships of HRGP with possible POD, length of stay, discharge disposition, and mortality.

Results: 410 patients were included with 129 HRGP. Incidence of POD and possible cognitive impairment were 15.5% vs 3.6% and 8.5% vs 2.5% comparing HRGP vs non-HRGP; Fishers exact p<0.0001. Length of stay (6.0 ± 6.9 days vs 4.2 ± 4.6 days; p=0.0098) was increased, but PACU length of stay (5.7 ± 3.5 h vs 5.5 ± 2.7 h; p=0.6) and mortality (7.7% vs 5.3%; p=0.3) were similar comparing HRGP vs non-HRGP. Comparing HRGP vs non-HRGP, 55% vs 88% (p<0.0001) were discharged to home. Neither gender nor race were associated with POD. In comparison to general surgery, neurosurgical procedures had an increased risk of POD (OR 3.8 [1.3-11.1]; p=0.009). In multivariate modelling frailty (OR 3.4 [1.8-6.4]; p=0.0002), age (OR 1.1 [1.0-1.1]; p=0.04), and ASA status (OR 2.6 [1.4-5.0]; p=0.003) were risk factors for POD; however, surgical urgency (OR 1.7 [0.2-16.7]; p=0.6) and anesthetic technique (spinal vs general: OR 0.8 [0.2-3.8]; p=0.9) were not.

Conclusion: HRGP undergoing surgery with PACU recovery have a higher incidence of POD and are less likely to be discharged home. Frailty, age, and ASA status are strong risk factors for POD in this population, but gender, surgical urgency, and anesthetic technique are not. These results emphasize the importance of preoperative frailty assessment in determining risk of postoperative geriatric syndromes in patients undergoing non-ICU procedures.

Global Health

Global Health - 1 Influence Of Pandemic On Self-Protection Simulation Performance

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Introduction: SARS-CoV-2 (COVID) is a pandemic unlike any seen in over a century. Highly infectious pathogens pose a significant threat to healthcare workers around the world, especially for those who come in direct contact with infected patients. Despite only accounting for approximately 3% of the global population, healthcare workers constitute roughly 14% of COVID infections.[1] This demonstrates the need to improve self-protection and infection control strategies. Simulation training is an effective educational approach in training.[2,3] However, it is unclear how training in the midst of an active pandemic impacts healthcare worker learning. The purpose of this study was to compare performance of novice trainees instructed by newly trained trainers in simulation courses for either Ebola virus disease (EVD) or COVID. We hypothesized that performance would be superior in the COVID group due to the ongoing pandemic.

Methods: The EVD and COVID groups both consisted of 4 trainers and 8 trainees who volunteered to participate in this study. Trainees completed a demographic and confidence survey prior to beginning a two-part training course for EVD or COVID. Part 1 included online knowledge-based training with pre- and post-tests. Part 2 consisted of simulation tasks using procedural and team-based checklists. Trainee team performance was evaluated by trainers in real-time using a performance assessment tool. Trainers took a train the trainer (TTT) course for EVD or COVID prior to training trainees. The TTT course included both on-line and in-person practice. Simulation tasks and checklists were developed using evidence based safe practice guidelines for common tasks performed when caring for EVD or COVID patients. The tasks were designed for teams of 3 individuals ('supervisor', 'provider', and 'buddy'). The structure of the training for this course was mastery-based learning in which steps were repeated until performed correctly. Errors were defined as any action that led to risk of infection or contamination. The primary outcome was trainee performance, measured by the number of steps required to complete each task. Performance was further dichotomized into those who repeated at least one step and those who did not. Secondary outcomes included time to complete each task and pre- vs. post-training confidence. Demographic and performance data were compared across the two groups with Chi-square tests of homogeneity for categorical data; continuous data were evaluated with t-tests of means and Wilcoxon rank-sums tests of medians, as appropriate.

Results: There was no significant difference in demographic characteristics or pre- vs. post-test knowledge scores between the two groups [Table 1]. Performance was described as the number of participants that repeated at least one step for each task [Table 2]. Participants in the COVID group performed better than the EVD group on the 'Doffing Gown with N95' task (P=0.02). Overall, the COVID group had fewer repeated steps; however, difference in performance between the two groups for the other tasks was not statistically significant. The COVID group took less time on average to complete all tasks [Table 3], however, only the 'Doffing Gown with N95' was completed significantly faster in the COVID group compared to the EVD group (P=0.04). There was no statistically significant change in confidence levels for either the EVD or COVID group [Table 4].

Conclusion: We found that the COVID group significantly differed in one training scenario and tended to perform better than the EVD group. These findings suggest that training for a real pandemic enhances learning of self-protection skills to a greater degree than training for a seemingly hypothetical threat, such as EVD. This study provides insight into the education, performance, and preparedness of healthcare workers to protect themselves while caring for patients with highly contagious pathogens.

References: 1. WHO Director General's opening remarks at the media briefing on COVID 19-14 December 2020. Accessed on Jan 14th 2021. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---14-december-2020 2. Developing Nation's Experience in Using Simulation-Based Training as a Preparation Tool for the Coronavirus Disease 2019 Outbreak. Anesth Analg. 2021;132(1):15-24. 3. Simulation as a critical resource in the response to Ebola virus disease. Simul Healthc 2014;9:337-8.

Table 1. Demographic characteristics of trainee cohorts

	EVD trainees N=8		COVID trainees N=8		p-value
	n	(%)	n	(%)	
Gender					
Female	7	(87.5)	5	(62.5)	0.25
Male	1	(12.5)	3	(37.5)	
Education					
Baccalaureate	7	(87.5)	7	(87.5)	1.00
Masters	1	(12.5)	1	(12.5)	
MD	0	(0.0)	0	(0.0)	
Other	0	(0.0)	0	(0.0)	
Specialized Education					
Medical Fellowship	0	(0.0)	0	(0.0)	0.52
Medical Residency	0	(0.0)	0	(0.0)	
Nursing Specialty Training	1	(12.5)	2	(25.0)	
Other	7	(87.5)	6	(75.0)	
None	0	(0.0)	0	(0.0)	
Current Employment					
Hospital Staff	1	(12.5)	0	(0.0)	0.30
Medical Staff	0	(0.0)	0	(0.0)	
Resident	0	(0.0)	0	(0.0)	
Student	7	(87.5)	8	(100.0)	
Score on didactic					
Pre-test	18.0	±2.3	15.8	±3.6	0.18
Post-test	24.1	±1.1	23.3	±2.7	0.41
pre/post test change	6.1	±2.6	7.4	±5.1	0.54

Table 2. Providers with at least one repeated step

Task	EVD # providers	EVD >1 repeated step	COVID # providers	COVID >1 repeated step	chi² p-value
Donning Gown with N95	7	0	5	1	0.26
Doffing Gown with N95	7	4	7	0	0.02
Don Coverall with N95	6	1	6	0	0.34
Doff coverall with N95	8	4	7	1	0.14
Spill Cleanup	8	2	5	0	0.22

Table 3. Average time (min) to complete task

Task	EVD mean ±Std	COVID mean ±Std	P-value
Donning Gown with N95	13.6 ±3.3	10.8 ±2.5	0.14
Doffing Gown with N95	11.0 ±3.8	7.1 ±2.1	0.04
Don Coverall with N95	13.6 ±3.0	12.7 ±2.3	0.56
Doff coverall with N95	14.6 ±2.9	10.3 ±1.1	0.27
Spill Cleanup	11.0 ±2.8	10.0 ±2.3	0.64

Table 4. Change in confidence score indicating self-assessed readiness to care for patients.

		EVD N=8 Median (IQR)	COVID N=8 Median (IQR)	Rank-Sum Test P-value
Total Score		1.7 (1.3-2.0)	1.4 (1.0-1.5)	0.22
Q1	Confidence in ability to care for patient with Ebola	3.0 (1.0-3.0)	2.0 (1.0-2.5)	0.37
Q2	The level of protective equipment used during care is adequate to prevent contamination	0.5 (0.0-1.0)	0.0 (0.0-1.0)	0.56
Q3	While working in an Ebola Clinical unit, my team is confident	2.0 (0.5-2.5)	2.0 (1.0-2.5)	0.87
Q4	If I care for a patient with Ebola, my loved ones, coworkers, and patients are at risk for contracting disease from me	1.5 (1.0-2.0)	2.0 (1.0-2.0)	0.91
Q5	Trust our team of coworkers to practice 100% accountability for their own actions and for our own teammates actions	0.5 (0.0-1.5)	1.0 (0.5-1.5)	0.41
Q6	My new background knowledge of Ebola has improved my ability to care for someone with the disease	1.0 (1.0-2.5)	1.0 (1.0-1.5)	0.68
Q7	I believe my infection control techniques will help reduce my risk of exposure to Ebola	2.0 (0.5-3.0)	1.0 (0.0-1.0)	0.08
Q8	Confident in my ability to recognize signs and symptoms of heat stress in myself and my team members	1.0 (0.0-1.0)	1.0 (0.5-1.5)	0.49
Q9	I feel proficient in donning and doffing PPE	3.0 (1.5-3.0)	2.0 (1.0-3.0)	0.44
Q10	I feel competent to perform my duties in PPE	2.0 (1.0-3.0)	1.0 (1.0-2.0)	0.35

Global Health - 2 Quantitative Fit-Testing Of A Locally Produced, Reusable, Valved Half-Face Respirator During Covid-19 Pandemic.

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Introduction: The COVID-19 pandemic continues to stimulate demands for respiratory protective equipment, hence increased interest in developing reusable respirators (1). Validation of such devices is challenging. We present the development of a reusable, silicone, valved respirator combined with pleated-membrane filters (Duo). To validate its performance, we quantitatively fit-tested (QNFT) and compared Duo with disposable N95 respirators.

Methods: A multidisciplinary team used 3D-printing and silicone casting to develop the Duo. A prospective observational cohort study was then conducted on 41 healthcare workers (HCWs). Users were tested on Duo and disposables by QNFT according to industry standards. Lastly, volunteers scored the comfort and breathability of Duo.

Results: Duo was designed, modified, and produced locally using 3D printing and silicone molding techniques.Figure 1 depicts a fully assembled Duo respirator. HCW characteristics are detailed in Table 1. Table 2 depicts the distribution of participant demographics, anthropometric characteristics, and types of 3M N95 respirators. Passing rates in Duo and disposable N95 respirators by QNFT were 100% and 58.5%. Heat maps illustrating individual participant success rates across seven different maneuvers are depicted in Figures 2. Median QNFT overall scores were 2947 and 77.2 respectively. The median scores for stationary and dynamic maneuvers of the Duo were 3179 and 2794 and of the disposable respirator was 84 and 73 ($p < 0.0001$). Visualization of pairwise comparison of log10 adjusted overall fit-factors for 41 participants are shown in Figure 3. Average comfort and breathability scores of the Duo were 3.9/5 and 4.2/5. Estimated unit cost for a production run of 1000 are $25-CAD in materials and 35 minutes of labor.

Conclusion: We present a locally-manufactured valved respirator that can match the filtration efficiency of commercial N95s and may be used in case of disruption of the supply chain. Effective protection and comfort may increase the compliance and safety of HCW during extended wear.

References: Centers for Disease Control and Prevention. Strategies for Optimizing the Supply of N95 Respirators. (2020).

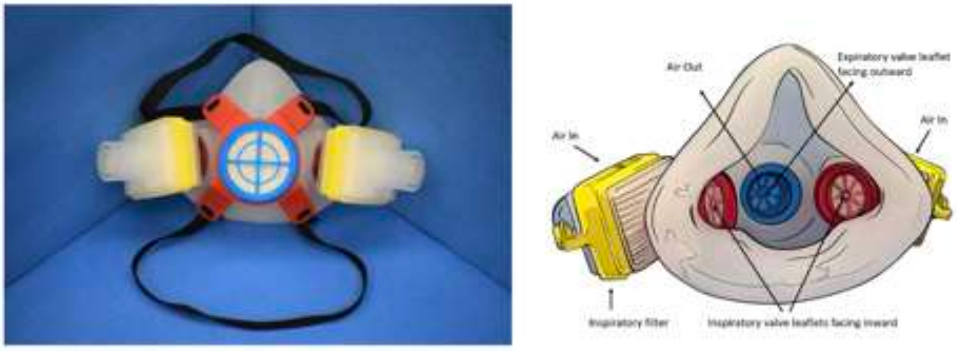

Figure 1. A fully assembled Duo respirator ready for testing (left) with unidirectional air flow through inspiratory valve leaflets (Air in) and through expiratory valve leaflet (Air Out) on the right

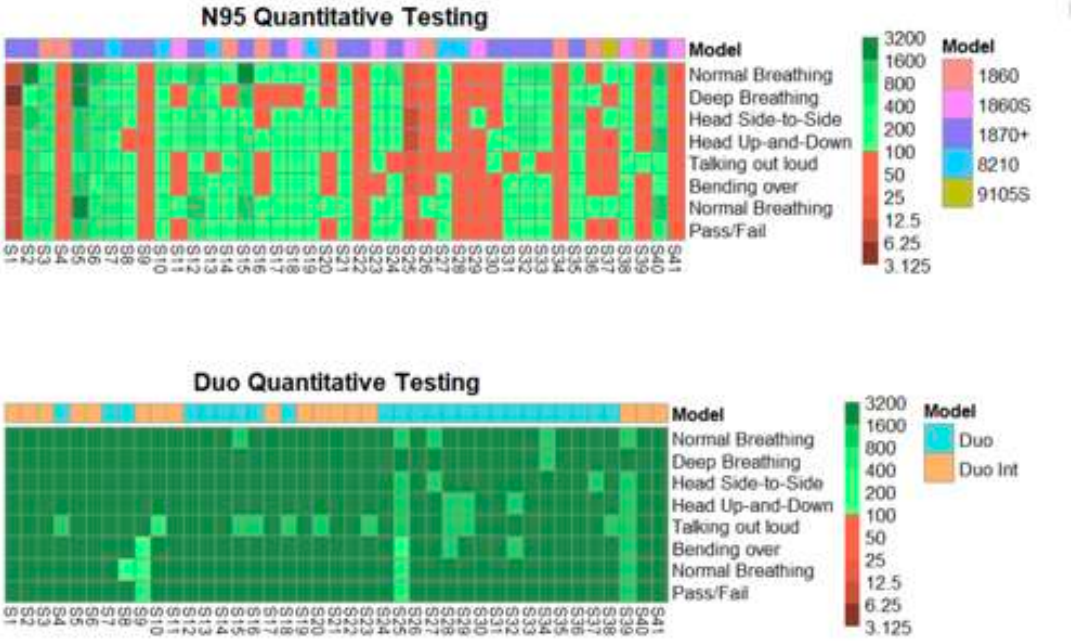

Figure 2. Representation of success rate of disposable N95 and Duo respirator throughout the 7 runs of test on 41 participants. Green indicates pass (fit-factor of 100 or greater) and red indicates fail (fit-factor less than 100).

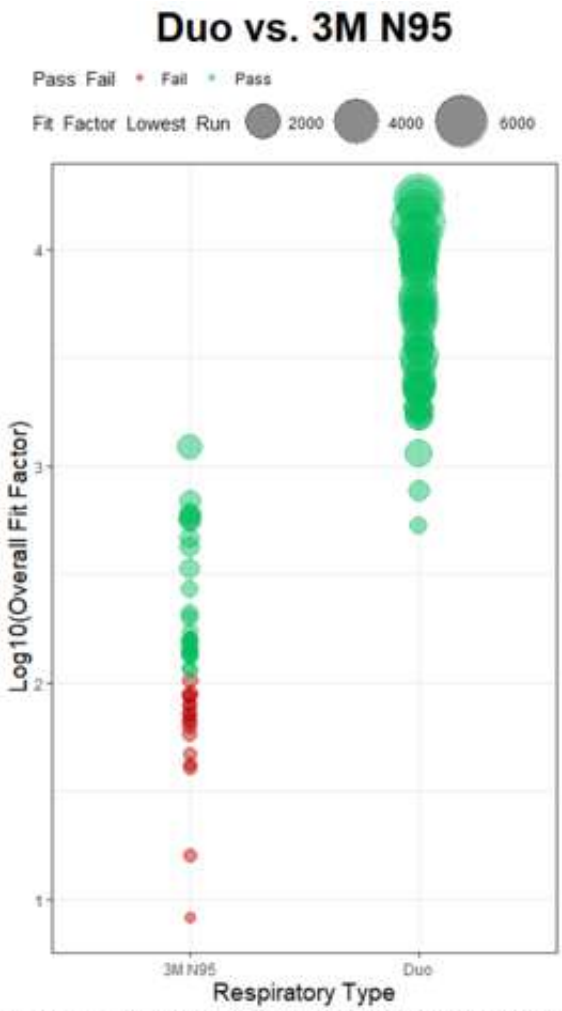

Figure 3. Log10 group comparison between disposable N95 and Duo overall fit factors for 41 participants. The overall fit-factor was defined as the harmonic mean of the seven individual run fit-factors.

Participant Demographics	**N = 41**
Age, mean (SD), y	36.1 (7.0)
Female – no./total (%)	20/41 (48.8%)
Body Mass Index, categorical no./total (%)	
Under-weight (BMI<18.5 kg/m2)	0/41 (0.0%)
Normal weight BMI (18.5 - 25 kg/m2)	33/41 (80.5%)
Overweight BMI (25-30 kg/m2)	6/41 (14.6%)
Obese BMI (>30 kg/m2)	2/41 (4.9%)
Body Mass Index, mean (SD), kg/m^2	22.90 (3.3)
Anthropometric	
Face Width mean (SD), mm	133.15 (11.6)
Face Length mean (SD), mm	120.10 (9.3)
Menton-sellion distances mean (SD), mm	103.79 (8.7)
NIOSH panel	
1 no./total (%)	2/41 (4.9%)
2 no./total (%)	0/41 (0.0%)
3 no./total (%)	7/41 (17.1%)
4 no./total (%)	4/41 (9.8%)
5 no./total (%)	3/41 (7.3%)
6 no./total (%)	5/41 (12.2%)
7 no./total (%)	8/41 (19.5%)
8 no./total (%)	1/41 (2.4%)
9 no./total (%)	2/41 (4.9%)
10 no./total (%)	2/41 (4.9%)
NA no./total (%)	7/41 (17.1%)
Disposable N95 Model	
1860 no./total (%)	9/41 (21.9%)
1860S no./total (%)	7/41 (17.1%)
1870+ no./total (%)	18/41 (43.9%)
8210 no./total (%)	6/41 (14.6%)
9105S no./total (%)	1/41 (2.4%)

Table 1. Demographics, Anthropometric Characteristics, and Qualitatively Fitted disposable N95 Model.

	Disposable N95 Test		P-Value
	Pass no./total (%) 24/41 (58.5%)	Fail no./total (%) 17/41 (41.5%)	
Demographic			
Age mean (SD), y	35.7 (7.1)	36.6 (7.0)	P = 0.681
Female sex – no./total (%)	11/24 (45.8%)	9/17 (52.9%)	P = 0.654
BMI, mean (SD), kg/m²	22.84 (3.5)	22.94 (3.3)	P = 0.979
BMI			
Normal weight no./total (%)	21/24 (87.5%)	12/17 (70.6%)	P = 0.047
Overweight no./total (%)	1/24 (4.2%)	5/17 (29.4%)	
Obese no./total (%)	2/24 (8.3%)	0/17 (0.00%)	
Anthropometric			
Face width mean (SD), mm	132.21 (9.1)	134.47 (14.7)	P = 0.3399
Face length mean (SD), mm	119.79 (7.4)	120.53 (11.6)	P = 0.7707
Menton-sellion distance mean (SD), mm	102.38 (7.6)	105.79 (10.0)	P = 0.1978
NIOSH panel			
1 no./total (%)	2/24 (8.3%)	0/17 (0.0%)	P = 0.210
2 no./total (%)	0/24 (0.00%)	0/17 (0.0%)	
3 no./total (%)	5/24 (20.8%)	2/17 (11.8%)	
4 no./total (%)	2/24 (8.3%)	2/17 (11.8%)	
5 no./total (%)	2/24 (8.3%)	1/17 (5.9%)	
6 no./total (%)	5/24 (20.8%)	0/17 (0.00%)	
7 no./total (%)	4/24 (16.7%)	4/17 (23.5%)	
8 no./total (%)	1/24 (4.2%)	0/17 (0.00%)	
9 no./total (%)	1/24 (4.2%)	1/17 (5.9%)	
10 no./total (%)	0/24 (0.00%)	2/17 (11.8%)	
NA no./total (%)	2/24 (8.3%)	5/17 (29.4%)	
Disposable N95 model (3M)			
1860 no./total (%)	2/24 (8.3%)	7/17 (41.2%)	P = 0.016
1860S no./total (%)	3/24 (12.5%)	4/17 (23.5%)	
1870+ no./total (%)	14/24 (58.3%)	4/17 (23.5%)	
8210 no./total (%)	5/24 (20.8%)	1/17 (5.9%)	
9105S no./total (%)	0/24 (0.00%)	1/17 (5.9%)	

Table 2. Demographic Anthropometric Characteristics and disposable N95 Model Distribution Based on Success of disposable N95 Fit Test.

Global Health - 3 A Randomized Comparison of Educational Booster Strategies on Team-based Clinical Performance During C-Section in Kenya

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Introduction: Large deficiencies in the quantity of healthcare workers in low-resource settings contributes to poor anesthesia-related outcomes including maternal mortality. Educational interventions to improve training and care are often limited by access and cost. High-fidelity simulation improves individual and team clinical performance in a variety of settings but gains often decay over time and methods to extend the efficacy of such training remain uncertain. Advances in short message service (SMS) technology and increased cellular accessibility may provide a means to supplement in-person training courses (Butler 2015), although data on the use of such technology for medical education in low- and middle-income countries (LMICs) is limited (Gomez 2018). This study seeks to evaluate SMS quizzing compared to additional in-person simulation sessions for improving long-term retention of skills for obstetric care during C-section in a low-resource setting.

Methods: Multidisciplinary high-fidelity simulation training in obstetric management was provided on-site to multiple hospitals in Kenya through the Mobile Obstetric Simulation Training (MOST) course. Hospitals were randomized for course participants to receive booster education to reinforce initial training through either quizzes distributed via SMS two to three times per week over a period of 8 months, or an in-person refresher course conducted four months after the initial training utilizing small group discussion and low-fidelity simulation. SMS quizzing was conducted with the application QuizTime which allows for tracking of individual participant performance over time. The primary outcome was team performance during actual C-Section cases. Assessment was performed using the 'Safe C-Section Team Checklist' (Alexander 2019) as assessed by blinded observers. Performance was measured during two-week intervals at baseline, and immediately, eight and twelve months after the MOST course (Figure 1). Performance was evaluated using two-tailed, unpaired or paired Student's t-test, as appropriate. Patient demographics and additional measures of team performance including duration of surgery, maternal deaths, and neonatal deaths or stillbirths were collected, as well.

Results: MOST training was conducted at three sites, two of which were assigned to SMS booster and one to in-person booster. Out of 42 users registered to participate in SMS quizzing, 76% responded to multiple quiz questions during the study period. Baseline clinical performance was comparable between SMS and in-person groups (16.4 vs 16.2 out of 18 checklist items, $p=0.72$). Both groups improved in performance following the course. By month 8 the in-person follow-up group returned to baseline performance, and at 12-months was performing below baseline (14.9 vs. 16.2 checklist items, $p<0.001$). In contrast, performance of the SMS group remained elevated until month 12 and had higher measured performance at 8 and 12 months than the in-person group (Figure 2). A high percentage of C-sections were urgent or emergent in both groups (Table 1).

Conclusion: Educational interventions that demonstrate reliable improvement in clinical performance and outcomes are critical for environments with fewer material and human resources commonly encountered in LMICs. This study demonstrates the feasibility of SMS-based quizzing as an educational tool to supplement in-person training among medical providers in Kenya. SMS-based quizzing was also associated with prolonged performance improvement following in-person simulation training compared to an in-person refresher course. Given the costs associated with training courses in these settings, use of a low-cost automated quizzing system may be particularly advantageous. Funding for this study has been provided by the Foundation for Anesthesia Education and Research (FAER).

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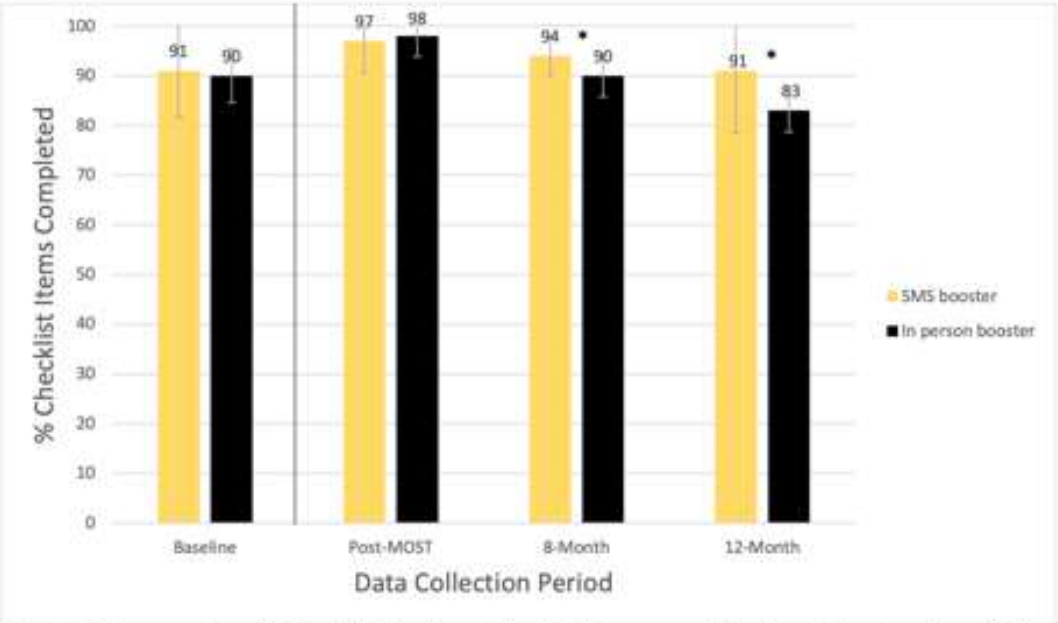

Figure 2. The percentage of Safe C-Section Team Checklist items completed for routine C-sections for the SMS and in-person booster groups at baseline and immediately, 8-months and 12-months following Mobile Obstetric Simulation Training (MOST). Error bars indicate 1 standard deviation above and below mean performance. Mean performance compared between groups at each time point using unpaired, two-tailed Student's t-test. *p<0.01.

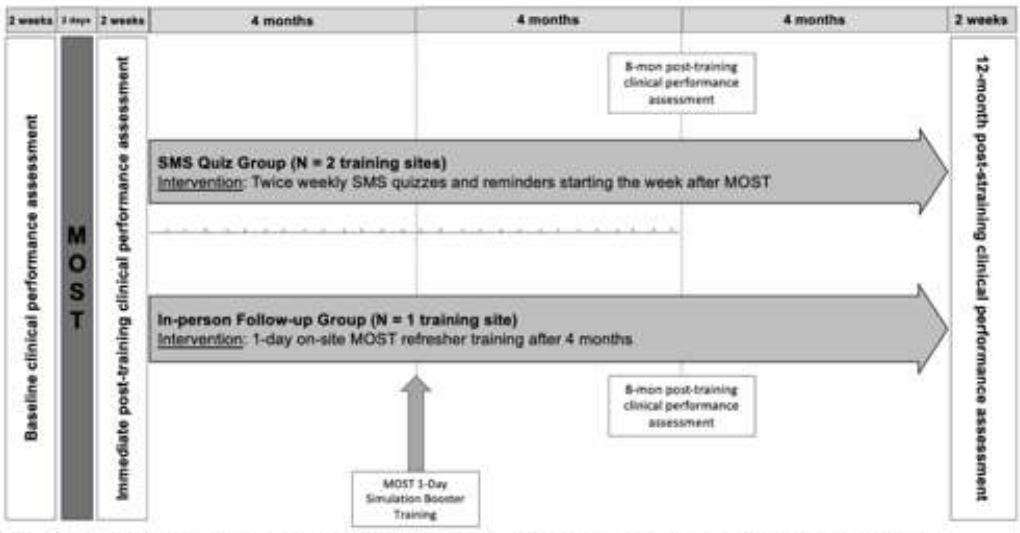

Figure 1. Study design demonstrating collection of clinical performance data for SMS Quiz and In-person Booster groups at four time points.

Table 1. Comparison of clinical performance and outcomes for SMS booster and in-person booster groups at timepoints before and after Mobile Obstetric Simulation Training (MOST) course. Mean checklist performance was compared between groups using unpaired, two-tailed Student's T-test. *p<0.01

	SMS Booster Group	In-person Booster Group
Safe C-Section Checklist Items (out of 18)		
Baseline	16.4	16.2
Post-MOST	17.5 (1.12)	17.7
8-month	16.9*	16.2
12-month	16.4*	14.9
Surgery Duration (minutes)		
Baseline	34	33
12-month	36	48
Clinical Outcomes		
Observations	171	89
Maternal deaths	0	0
Neonatal deaths/stillbirths	7 (4.1%)	3 (3.4%)
Urgent/emergent	149 (87%)	56 (63%)

Liver

Liver - 1 A Retrospective Cohort Study of Pediatric Patients Undergoing Early Extubation After a Staged Laparotomy

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Introduction: Congenital portosystemic shunts, otherwise known as Abernethy malformations, are a condition in which splanchnic blood bypasses the liver and drains directly into the systemic circulation. The approximate incidence of this malformation is 1:30,000 births with less than 300 cases reported in the literature.[1] Currently, these patients undergo temporary portosystemic shunt ligation and remain intubated in the intensive care unit (ICU) for approximately 5 days before returning to the operating room for permanent ligation.[2] However, there is substantial evidence that prolonged mechanical ventilation after surgery leads to higher costs, longer ICU and hospital length of stay (LOS), and higher mortality.[3, 4] In contrast, early extubation in pediatric patients undergoing liver transplantation and congenital cardiac surgery experienced shorter ICU admission, hospital LOS, and decreased cost.[5, 6, 7] However, there is a paucity of data regarding the effect of early extubation in pediatric patients undergoing staged laparotomy. Therefore, we designed this retrospective cohort study to (1) examine whether early extubation between the two stages of an Abernethy shunt ligation had an effect on ICU and total hospital LOS, and (2) determine if there was a difference in duration of scheduled opioids and benzodiazepine administration in patients who were extubated early.

Methods: A retrospective cohort study was performed to examine all patients who underwent a two-stage ligation of a portosystemic shunt at Ann & Robert H. Lurie Children's Hospital of Chicago from January 2016 to August 2020. Patients who were electively extubated between the two operations were considered to be in the early extubation cohort and were compared to a cohort of patients that were not extubated between stages. The primary outcome was total ICU LOS. Secondary outcomes of interest were total hospital LOS, duration of scheduled opioid administration, duration of scheduled benzodiazepine administration, methadone prescribed on discharge, need for adjuvant sedatives (ketamine, dexmedetomidine, clonidine), and in-hospital cardiac arrest. We report descriptive summaries of collected data as medians with interquartile ranges (IQRs) for continuous data and counts and frequencies (%) for categorical data. The paired Wilcoxon signed-rank test was used to evaluate differences for continuous variables, while the Fisher's exact test was used to evaluate categorical variables. Outcome data were analyzed using logistic regression with calculation of odds ratios, 95% confidence intervals (CI), and P-values.

Results: Thirteen patients with type 2 congenital portosystemic shunts were identified, 6 of whom were extubated early. Among the study participants, the median age was 5 years old (IQR 2.8-16). Patients in the early extubated group were significantly older than those who were not extubated. There were no differences in preoperative laboratory test results, preoperative shunt occlusion pressures, and American Society of Anesthesiologists (ASA) physical status classification between the two cohort groups. Patients who were in the early extubation cohort had significantly shorter ICU LOS (8 days, IQR 6-9) and total hospital LOS (13.5, IQR 11-14) than that of the non-extubated cohort ($p<0.01$). The total duration of mechanical ventilation was also significantly shorter in the extubated group, 1 (IQR 0-2) day versus 11 (IQR 9-17) days respectively. Patients who were extubated early received significantly fewer days of scheduled opioids (6.5 days vs. 27 days) and fewer days of scheduled benzodiazepines (0 days vs. 14 days). Significantly more patients in the non-extubated group (5 versus 0 patients) required methadone at discharge ($P=0.03$). No patients in either cohort needed to be reintubated in the ICU.

Conclusion: This study showed that an early extubation approach among patients who are undergoing a staged surgical procedure is associated with improved outcomes. Patients who were extubated early not only consumed less benzodiazepines and opioids, but also had significantly shorter ICU and hospital LOS. We believe that early extubation among

patients undergoing staged portosystemic shunt ligation is safe and beneficial. While this study consisted solely of patients undergoing Abernethy ligations, this proof of concept could have greater implications for all pediatric patients undergoing staged operations.

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Table 1. Univariable Analysis of Patients Undergoing Portosystemic Ligation

Baseline Characteristic	All Patients, n = 13 (100%)	Extubation Median, IQR/n (%)		P-value
		Extubated, n = 6 (46.2%)	Not Extubated, n = 7 (53.8%)	
Gender, n (%)				
Male	4 (30.8)	1 (16.7)	3 (42.9)	
Female	9 (69.2)	5 (83.3)	4 (57.1)	0.55
Age at surgery, years	5, 2.8-16	16, 4-16	2.8, 1.3-12	0.03
Preoperative Lab				
Hemoglobin	12.8, 11.7-13.8	12.8, 11.7-13.8	12.8, 11.2-14.1	0.94
Platelet	220, 200-270	248, 206-303	210, 194-223	0.15
INR	1.1, 1.0-1.3	1.1, 1.0-1.1	1.2, 1.0-1.3	0.23
Preoperative Pressures				
Nonoccluded Shunt Pressure	9, 6-11	9, 6-9	10, 8-11	0.57
Occluded Shunt Pressure	24, 16-29	24, 19-27	23.5, 16-29	0.74
ASA Physical Status Classification, n (%)				
2	3 (23.1)	2 (33.3)	1 (14.3)	0.55
3	10 (76.9)	4 (66.7)	6 (85.7)	
Weight	16.0, 12.2-71.6	59.8, 16.0-71.6	12.2, 10.9-75.8	0.11
BMI	16.0, 15.1-22.2	20.0, 14.9-23.5	16.6, 15.1-22.2	0.66
Shunt Type				
2a	1 (7.7)	1 (16.7)	0	0.01
2b	6 (46.2)	0	6 (85.7)	
2c	6 (46.2)	5 (83.3)	1 (14.3)	
History of Pulmonary Disease	3 (23.1)	0	3 (42.9)	0.19

ASA, American Society of Anesthesiologists; BMI, body mass index; INR, international normalized ratio; IQR, interquartile range

Table 4. Univariable Analysis of Patients Undergoing Portosystemic Ligation

Baseline Characteristic	All Patients, n = 13 (100%)	Extubation Median, IQR/n (%)		OR (95% CI)	p-value
		Extubated, n = 6 (46.2%)	Not Extubated, n = 7 (53.8%)		
Total Days Scheduled Opioid	14, 7-27	8.5, 6-9	27, 15-33	0.87 (0-0.91)	<0.01
Total Days Scheduled Benzodiazepine	9, 0-14	0, 0-8	14, 9-28	0.60 (0.08-0.96)	0.01
Adjuvants					
Ketamine	4 (30.8)	2 (33.3)	2 (28.6)	1.25 (0.12-13.24)	0.85
Clonidine	4 (30.8)	1 (16.7)	3 (42.9)	0.27 (0.019-3.65)	0.32
Dexmedetomidine	9 (69.2)	3 (50.0)	6 (85.7)	0.17 (0.01-2.36)	0.18
Discharged on Methadone	5 (38.4)	0	5 (71.4)	0.52 (0-0.83)	0.03
Total Length of Mechanical Ventilation, days	8, 1-11	1, 0-2	11, 9-17	0.64 (0-0.88)	<0.01
Cardiac Arrest	1 (7.7)	0	1 (14.3)	1.17 (0-45.5)	0.35
Total ICU Stay, days	10, 8-20	8, 6-9	20, 13-20	0.52 (0-0.88)	<0.01
Total Hospital Stay, days	19, 14-28	13.5, 11-14	28, 19-33	0.59 (0.20-0.83)	<0.01

OR, odds ratio

Liver - 2 An Analysis of Postoperative Strokes following Introduction of Goal-Directed Coagulation Management Guidelines during Liver Transplantation

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Introduction: Early liver transplantation (LT) was frequently associated with significant hemorrhagic diathesis due to surgical technique and to end-stage liver disease (ESLD) coagulopathy.1 Although advances in control of surgical hemorrhagic diathesis have occurred, the underlying coagulation abnormalities observed in ESLD patients continue to be problematic.2 In 2018, the International Liver Transplant Society proposed coagulation management guidelines to assist LT centers.3 The purpose of this study was to measure our version of these recommendations on a prospective cohort on the incidences of stroke following LT.4

Methods: Following IRB approval, all adult (≥18 years of age) patients with ESLD undergoing LT were entered into this study. Categorical variables were presented as counts and percentages. Risk differences with CI were calculated for the probabilities of postoperative stroke following introduction of goal-directed coagulation management guidelines during hepatic LT.5

Results: The incidences of postoperative strokes following LT are shown in Tables 1 and 2. The incidence of postoperative ischemic stroke was not clinically different following introduction of the goal-directed coagulation management guidelines (Table 1). However in Table 2, no postoperative hemorrhagic strokes were observed in patients following LT following introduction of goal-directed coagulation management guidelines (Table 2).

Conclusion: The results from this preliminary study cautiously suggest an improvement in postoperative hemorrhagic stroke rates but not in postoperative ischemic stroke rates following the introduction of the goal-directed coagulation management guidelines.

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Table 1: The Incidence of Postoperative Ischemic Stroke following Introduction of Intraoperative Goal-Directed Coagulation Management Guidelines (GDCMG)

		Postoperative Ischemic Stroke		
	Patients n(%)	Yes	No	Totals
Intervention	GDCMG	2 (2.7)	72 (97.3)	74
	Control	19 (1.7)	1121 (98.3)	1140
	Totals	21	1193	1214

n (%): number and percentage of patients. Risk Differences: -0.01 [-0.5 to 0.2]

Table 2: The Incidence of Postoperative Hemorrhagic Stroke following Introduction of Intraoperative Goal-Directed Coagulation Management Guidelines (GDCMG)

		Postoperative Hemorrhagic Stroke		
	Patients n(%)	Yes	No	Totals
Intervention	GDCMG	0 (0)	74 (100)	74
	Control	14 (1.2)	1126 (98.8)	1140
	Totals	14	1200	1214

n (%): number and percentage of patients. Risk Differences due to Intervention: 0.01 [-0.02 to 0.02]

Liver - 3 Endothelial Activation by Liver Reperfusion Injury in Transplantation

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Introduction: Hepatic ischemia-reperfusion injury (IRI) is a pathological process associated with systemic effects upon restoration of blood flow to the liver.[1] Graft reperfusion during liver transplantation (LT) induces an inflammatory insult that is precisely defined in time (by the unclamping of the portal vein). Ample evidence suggests that the severity of liver ischemia-reperfusion injury (IRI) is associated with end-organ injury such as acute kidney injury (AKI).[2] Hepatic IRI is a complex process involving many different cell types. Endothelial dysfunction may be one process contributing to post-LT organ failure. We hypothesize that liver IRI leads to endothelial activation and contributes to organ injury.[3] To investigate whether or not liver IRI leads to the production of circulating factors that cause endothelial dysfunction, we developed a novel translational model of ex vivo stimulation of cultured pulmonary human microvascular ECs (HMVECs) with sera from LT patients (LT sera). We assessed perturbation of endothelial barrier function using trans-endothelial electrical resistance (TEER)[4] and quantified inflammatory cytokines in culture supernatants.

Methods: Paired sera specimens were collected from 65 human subjects undergoing LT as part of the Mild Hypothermia and AKI in LT (MHALT) trial (NCT03534141), at baseline (start of surgery) and 2 hours after reperfusion of the portal vein. The research was approved by the IRB and all subjects or their legal surrogates provided informed consent and HIPAA authorization for the use of biospecimens in research. According to the MHALT trial protocol, subjects were randomized to normothermia (36.5-37.5 °C) throughout the operation, or mild hypothermia (34-35 °C) from the start of surgery until portal vein reperfusion. Deidentified clinical data were extracted from the electronic medical record.

For cellular assays, pulmonary HMVECs were grown to confluence on 96-well electrode arrays. LT sera were then added to wells to a final concentration 5%, and TEER was continuously measured over 24 h. Lipopolysaccharide (LPS) served as a positive control. Cytokines (IL-6, IL-8, CCL2) were quantified in HMVEC supernatants by ELISA at 24 h. TEER was continuously measured as a surrogate of barrier integrity (ECIS®, Applied Biophysics). Cytokine levels were compared between the two time points using Wilcoxon matched-pairs signed-rank tests. Comparisons were stratified by study arm (normothermia vs. mild hypothermia). Analyses were performed using GraphPad Prism 7.0e.

Results: Sera from most of the LT patients (n=63, 97%) did not reduce TEER, a surrogate for endothelial barrier function, either at the start of surgery or 2 h post-reperfusion, similar to medium controls (Fig. 1A and B). However, post-reperfusion sera from two patients (3%) strongly induced HMVEC barrier disruption as evidenced by a drop in TEER of similar magnitude to that triggered by LPS (Fig. 1C and D). Both of these subjects had profound liver IRI with markedly elevated postoperative aspartate aminotransferase levels (> 10,000 U/L).

In general, LT sera obtained 2 h post-reperfusion stimulated HMVECs to produce higher levels of inflammatory cytokines IL-6, IL-8, and CCL2 as compared with baseline sera (Fig. 2A, D, and E). However, we observed significant heterogeneity – most notably in two distinct populations with respect to IL-6 production (Fig. 2A, C). Production of IL-8 correlated strongly with CCL2 (R2=0.84) but not IL-6 (R2=0.03). Post-reperfusion sera from patients randomized to mild hypothermia generally stimulated more cytokine production (Fig. 2C, F, I) than did sera from normothermic patients (Fig. 2B, E, H).

Conclusion: Sera from LT patients 2 h after portal vein reperfusion are capable of activating cultured primary HMVECs. This finding suggests the presence of a circulating factor or factors downstream of liver reperfusion that lead to endothelial activation and dysfunction. However, we observed significant heterogeneity among different subjects, and only a rare subset of patients with severe IRI yielded sera capable of disrupting endothelial barrier function ex vivo. Future work will explore additional earlier and later time points to better understand the kinetics of release of endothelial-active factors into the circulation after liver IRI. Multivariate analysis may help understand how patient, graft, and procedural factors contribute to the observed heterogeneity in ability of LT sera to stimulate inflammatory cytokine production.

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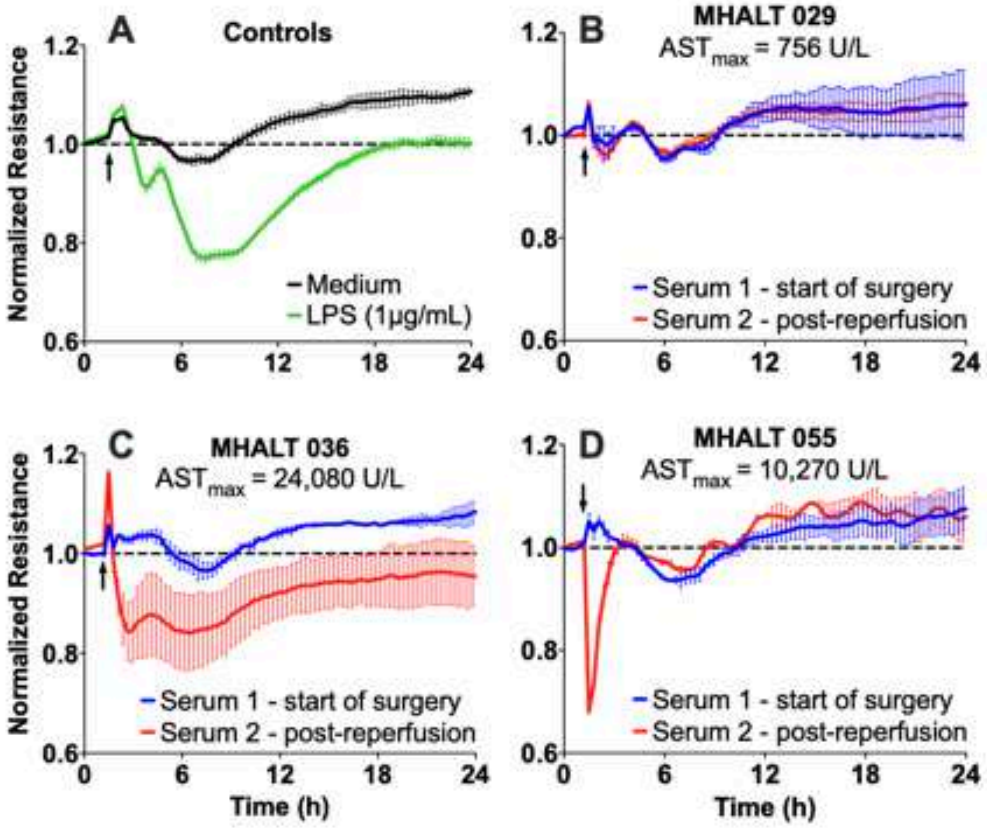

Figure 1. Trans-endothelial electrical resistance measurements of cultured pulmonary HMVECs on 96-well electrode arrays upon application of (*A*) controls or (*B-D*) 1% serum from MHALT study subjects. *Arrow* indicates approximate time of stimulation. *(B)* Subject with minimal IRI showing no effect on endothelial resistance. (*C-D*) Two subjects with severe IRI (peak AST > 10,000) where post-reperfusion sera (*red*) caused a strong decrease in HMVEC resistance consistent with increased permeability (similar to LPS). Sera from the start of surgery (*blue*) had minimal effect on the resistance.

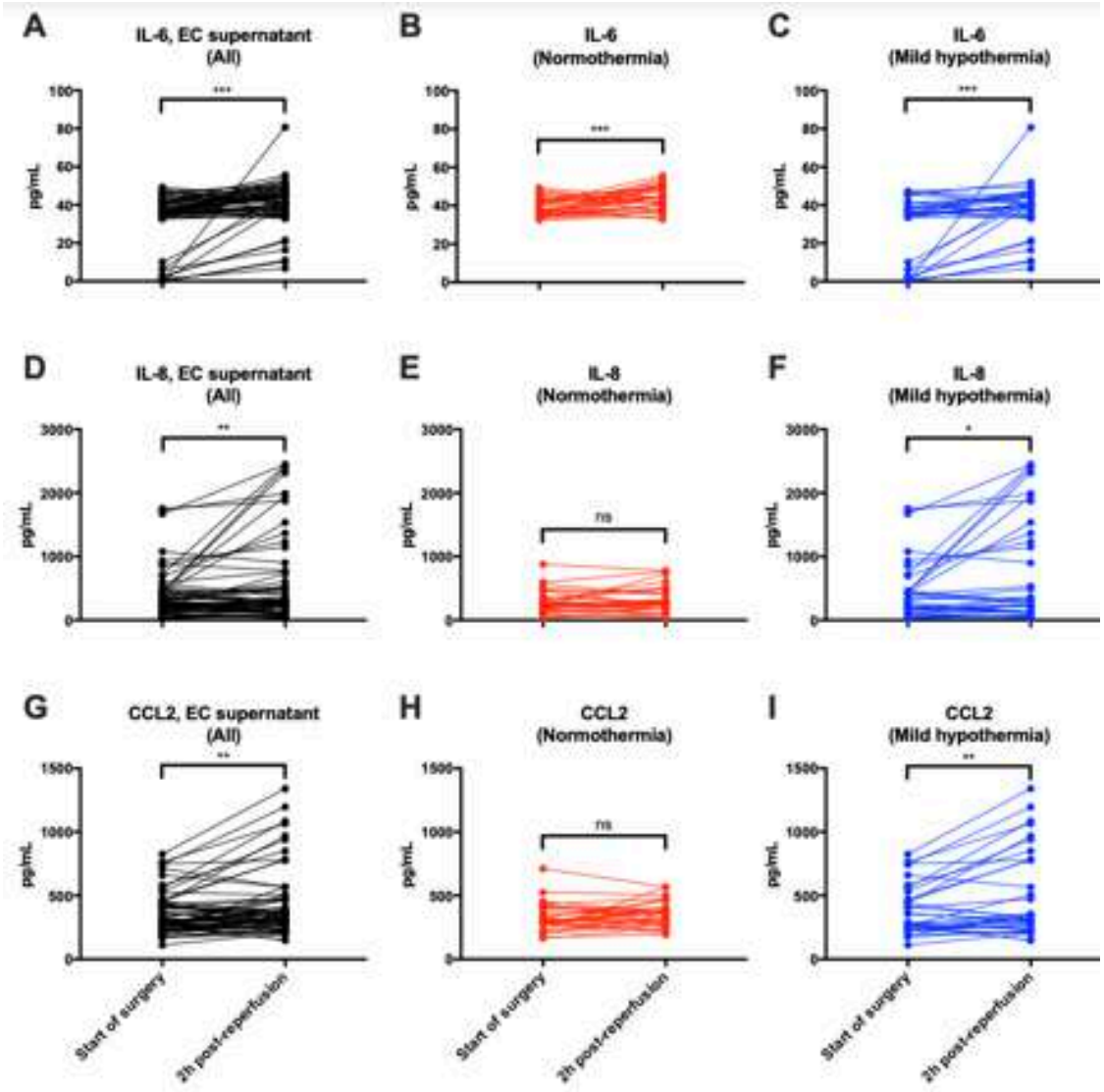

Figure 2. Concentration of cytokines interleukin (IL)-6, IL-8, and chemokine (C-C motif) ligand 2 (CCL2) present in HMVEC supernatant after stimulation with 5% serum from LT patients for 24 h. Sera were collected at the start of surgery (baseline) and 2 h after portal vein reperfusion in each patient. Brackets indicate Wilcoxon matched-pairs signed-rank tests (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Analysis is stratified by randomization arm of the MHALT clinical trial (*red*, normothermia; *blue*, mild hypothermia).

Neuroscience in Anesthesiology and Perioperative Medicine

Neuroscience in Anesthesiology and Perioperative Medicine - 1 A Machine Learning Approach for Predicting Real Time Risk of Intraoperative Hypotension in Traumatic Brain Injury

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Introduction: Traumatic brain injury (TBI) is a major cause of death, disability and health care utilization (1,2). Episodes of hypotension after TBI are associated with worse outcomes (3,4). Studies have shown preoperative risk factors for intraoperative hypotension (5). Our aim was to build a model to predict the real- time risk of intraoperative hypotension in TBI patients, identify the features that may contribute to intraoperative hypotension and understand the advantage of using machine learning methods (which are less interpretable, but better capture non-linear structure and interactions between variables) over traditional statistical methods in this model.

Methods: This was a retrospective and prognostic study that analyzed TBI patients undergoing neurosurgical procedures for 1005 patients at Harborview Medical Center (an academic level 1 trauma center caring for patients from the Pacific Northwest) between 2008 and 2017. The patients were divided into a training dataset used for model development and a testing data set used for estimating model performance; there was no overlap in patients between the two data sets. The clinical event was intraoperative hypotension, defined as mean arterial pressure (MAP) < 65 mmHg for five or more consecutive minutes (Figure). We developed two types of models: one based on preoperative patient-level predictors and one based on intraoperative predictors that were available minute by minute. For each of these models, we took two approaches to predict the occurrence of an event: a logistic regression model and a gradient boosting tree model. Model performances were evaluated with area under the ROC curve (ROC-AUC) and under the precision-recall curve (PR-AUC); we present results from the test set. The contribution of predictor variables were evaluated.

Results: 45.7% of the patients in the training set and 43.4% of patients in the test set had at least one episode of hypotension. Model performance based on preoperative predictors was poor, with an ROC-AUC of 0.55 logistic regression models and ROC–AUC of 0.47 for the gradient boosting model. The ROC-AUC for the intraoperative logistic regression model was 0.80 (95% CI: 0.78–0.83), and for the gradient boosting model was 0.83 (95% CI: 0.81–0.85). The PR-AUC for the intraoperative logistic regression model was 0.16 (95% CI: 0.12-0.20), and for the gradient boosting model was 0.19 (95% CI: 0.14-0.24). By both ROC- and PR-AUC metrics, the XGBoost intraoperative model had higher predictive performance than the logistic intraoperative model (ΔROC-AUC: 0.03, 95% CI: 0.01-0.04, p<0.001; ΔPR-ROC: 0.03, 95% CI: 0.00-0.06, p=0.023). Features related to MAP (current MAP, recent averages and recent variance) emerged as most predictive in both the logistic regression and gradient boosting models.

Conclusion: This study developed a model for real-time prediction of intraoperative hypotension in patients with TBI, and demonstrated that machine learning techniques achieve better performance than traditional statistical techniques. ML allows the analysis of a large set of features with more complex interactions through efficient computing techniques (6). Features representing the temporal trend of MAP are key for predicting future hypotension, while preoperative risk factors are poor predictors for intraoperative hypotension. The combination of computationally efficient models with a streamlined set of key features lays the groundwork for developing real-time intraoperative decision support in TBI.

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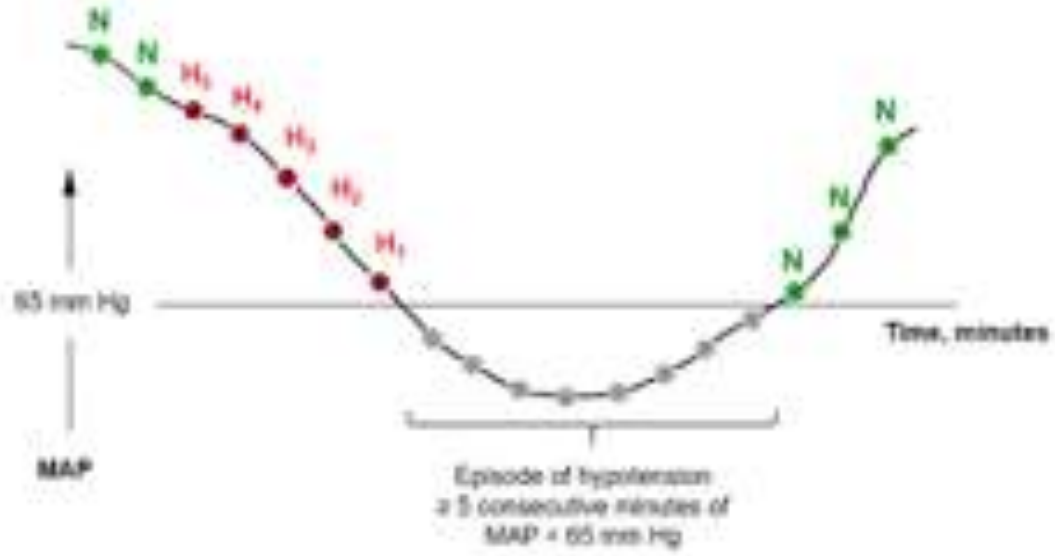
FIGURE. Use of timing in definition of intraoperative hypotension.



Neuroscience in Anesthesiology and Perioperative Medicine - 2 Ketamine Dissociation Triggers A Universal Switch In Neuronal Activity Across Neocortex

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Introduction: Since antiquity indigenous cultures have used plant-derived medicines to create a state of internally generated experiences divorced from reality for medicinal and religious purposes. Recently, clinical trials revealed that a single dose of dissociative agents produces robust and durable improvements in diverse, treatment-resistant psychiatric disorders, and that the dissociative experience itself is a powerful predictor of clinical response1–7. The neuronal and circuit mechanisms underlying the dissociative experience, however, remain unknown.

Methods: Two-photon microscopy in living cortex.

Results: Here, using in vivo calcium imaging, we found that ketamine-induced dissociative state is accompanied by a switch in cortical network activity – active neurons become suppressed while previously silent neurons become activated. All the while the net cortical activity is preserved. Ketamine-induced switch in network activity is universal across excitatory neurons in all cortical layers and regions, and all major genetically-defined interneuron subtypes. Cortical application of ketamine or combined pharmacologic blockade of cortical NMDA receptors and HCN1 channels was sufficient to recapitulate the activity switch and impaired sensorimotor processing.

Conclusion: These experiments reveal that the neocortex contains two largely non-overlapping distributed neuronal populations: one engaged in processing sensory stimuli, the other giving rise to the dissociative state. Identification of this dissociative circuit lays the groundwork for mechanistic understanding of the therapeutic efficacy of dissociative agents.

Neuroscience in Anesthesiology and Perioperative Medicine - 3 State Decoupling of the C. Elegans Neural System Under Anesthesia and During Emergence.

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Introduction: Essentially all multicellular organisms are susceptible to exposure to volatile anesthetic agents (1,2). In mammals, EEG is the usual method for detecting resultant changes in neural function. Many EEG patterns have been empirically characterized in the anesthetized brain (3,4), but the causal relationship is unclear. This limitation can be overcome by functional fluorescent imaging in the nematode C. elegans, a well-established model for anesthetics, allowing the activity of individual neurons to be captured simultaneously across the majority of the nervous system (5).

Methods: The predominant hypothesis is that anesthesia results from a disruption in coordinated neural activity, causing dissociation between stimuli and behavior (6). Thus, metrics based on information theory have been explored such as mutual information (MI) (7), which measures the entropy shared between two sources, and transfer entropy (TE) (8), which measures the future entropy of a source that can be predicted from another source but not from itself. The application of MI and TE directly to EEG data has an unclear neuronal basis, whereas functional imaging in C. elegans can identify the activity state of individual neurons and their temporal relation. C. elegans data were obtained in a total of 10 specimens progressively equilibrated to atmospheres of 4% and 8% isoflurane (1.3 and 2.6 MAC) with volumetric fluorescent imaging performed with a diSPIM microscope, using 5mW 488nm and 561nm lasers to excite cytoplasmic GCaMP6s and nuclear RFP fluorophores respectively. For each animal, N=120 neurons were tracked in the head region using the fixed RFP, and their activity extracted using fluctuations in GCaMP6s fluorescence. Data were quantized to 4 levels (9), producing a 2-bit value for each neuron at each imaging timestep. For each neuron pair in each animal ($X,Y \in N, X \neq Y$), joint entropies were calculated for the past and future states of X and Y (Xp,Yp,Xf,Yf). These entropies can be recombined to produce the metrics of MI and TE (Fig 1), but also to derive arbitrarily any other information metric (10). We arrive at a novel metric, state decoupling, that quantifies the degree of independent information unique to individual neurons across time. To evaluate state decoupling over time, C. elegans were anesthetized with 4% isoflurane and then exchanged to fresh buffer to achieve a gradual emergence over 2 hours with continuous imaging.

Results: Figure 2 shows the collection of the entropy regions for MI (Fig 2A1) for C. elegans when under 0%, 4% and 8% isoflurane (Fig 2A2). Figures 2B1 and 2B2 show these results for TE. No statistically significant differences were detected between any pair of conditions. However, the entropy collection shown in Figure 2C1 indicates the extent to which the state of each source is informationally decoupled from any of the others, and we therefore give this novel metric the name of state decoupling. The 4% isoflurane group is statistically significantly different from both the 0% isoflurane group ($P < 0.00001$) and the 8% isoflurane group ($P < 0.0001$), as shown in Figure 2C2. During emergence from isoflurane 4%, state decoupling progressively resolves from the level seen in these anesthetized animals to the level seen in an unexposed control group. Figure 3 shows the recovery of state decoupling for the emerging anesthetized specimens, versus state decoupling in control specimens. Black lines show time-smoothed averages, though individual anesthetized specimens show significant cyclical non-smooth recovery. Controls evince a slow downward drift in state decoupling, most likely an artifact of slow, progressive photobleaching of the fluorophores under prolonged imaging producing a gradual artifactual suppression of the apparent activity.

Conclusion: State decoupling has a straightforward biological interpretation that parallels its mathematical definition: it quantifies individual neurons becoming decoupled from their previous state and the state of surrounding neurons. Under moderate anesthesia (1.3 MAC), increased state decoupling represents induced

disorder of the usual functioning of the neuronal system. Under profound anesthesia (2.6 MAC), C. elegans evinces episodes of quiescence in which individual neurons are stuck in either an inactive or active state. This simplification decreases state decoupling as the neural state appears more predictable, but actually represents a diminished repertoire of states and transitions that the system can enact.

References: [1] Does natural selection explain the universal response of metazoans to volatile anesthetics? Anesth Analg 2008;107:862-3 [2] Why can all of biology be anesthetized? Anesth Analg 2008;107:859-61 [3] General anesthesia and altered states of arousal: a systems neuroscience analysis. Ann Rev Neurosci 2011; 34:601-28 [4] Reconfiguration of network hub structure after propofol-induced unconsciousness. Anesthesiology 2013;119:1347-59 [5] Collapse of Global Neuronal States in Caenorhabditis elegans under Isoflurane Anesthesia. Anesthesiology 2020;133:133-44 [6] The Biology of General Anesthesia from Paramecium to Primate. Curr Biol 2019;29:1199-210 [7] A mathematical theory of communication. Bell System Technical Journal 1948;27:379-423 [8] Measuring information transfer. Phys Rev Lett 2000;85:461-4 [9] A threshold selection method from gray-level histograms. IEEE Trans on Systems, Man, Cybernetics 1979;9:62-6 [10] On the amount of information. Theory of Probability 1962;7:439-4

Figure 1

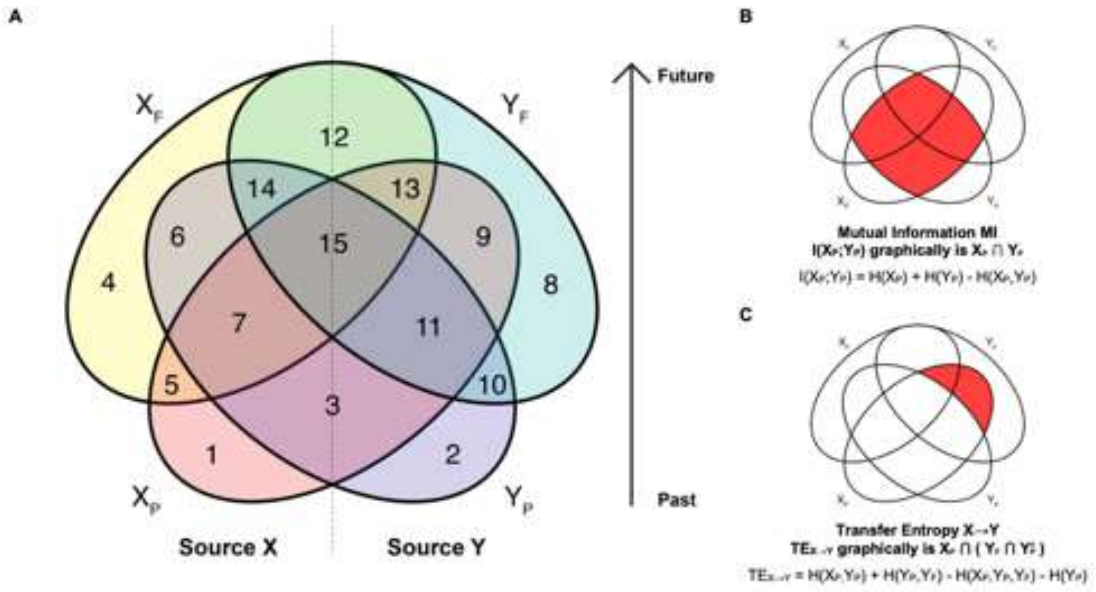


Figure 2

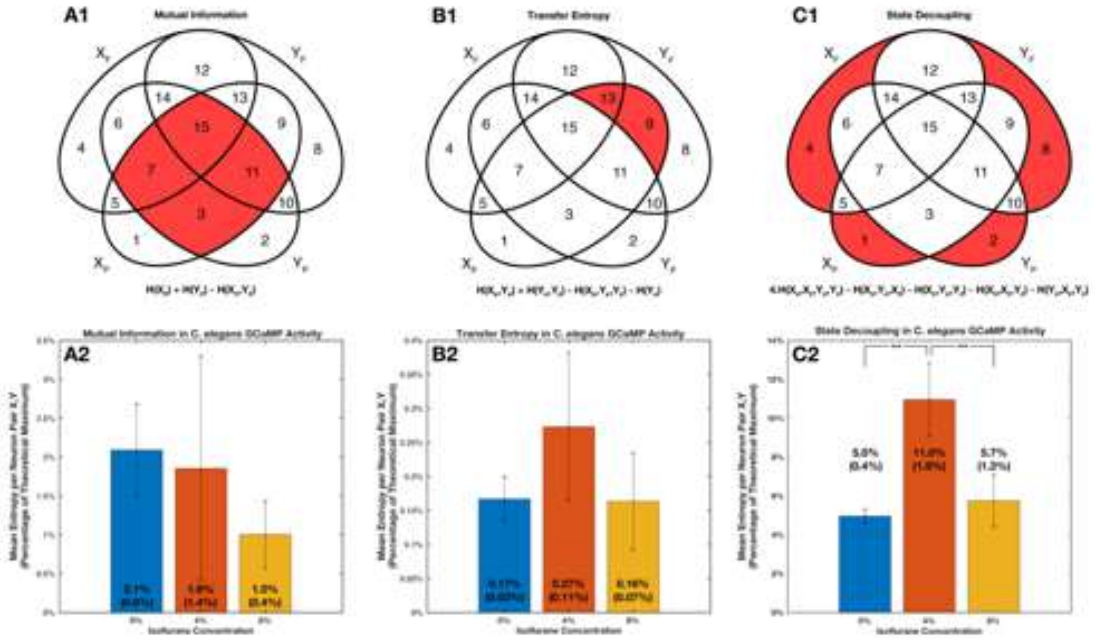
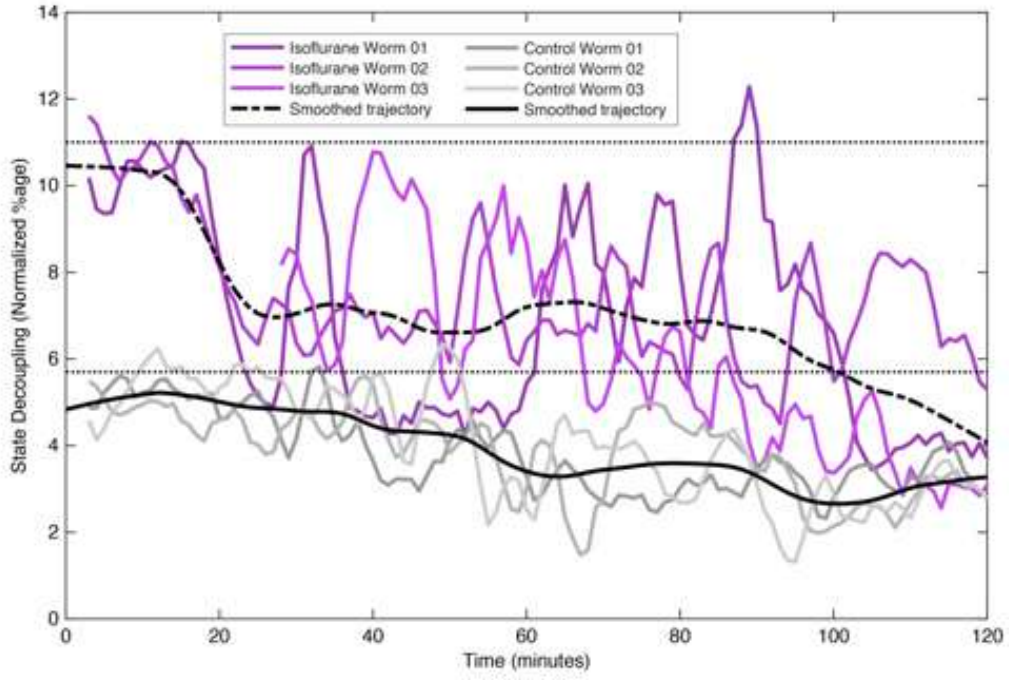


Figure 3



Neuroscience in Anesthesiology and Perioperative Medicine - 4 Whole-Brain Network Connectivity Changes With Midazolam Sedation During Task Performance And Periodic Pain: A Functional Mri Study In Healthy Young Adults

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Introduction: Despite the widespread use and well-known pharmacology of midazolam, the brain network correlates of its action, especially during pain, are less well characterized. Though converging evidence suggests that decreases in long range Functional Connectivity (FC) is a feature of anesthetic-induced unconsciousness [1], FC under conscious sedation is more varied. Previous studies of fMRI-based FC under midazolam have employed independent component analysis (a data-driven approach) to organize brain areas into large resting-state networks. The first of these found increased FC in the mid-cingulate and decreased FC in the posterior cingulate, with the component they identified as default-mode network [2]. A subsequent study showed mixed non-robust results, with both increased and decreased FC throughout the brain [3]. A recent study in older adults showed midazolam-associated increases in FC between networks labelled default-mode (predominantly posterior cingulate and medial prefrontal areas) and salience (notably including insula and dorsal anterior cingulate) [4]. This is a focused secondary analysis of data from a within-subject crossover imaging study comparing midazolam and ketamine on multiple behavioral and imaging endpoints. We used background FC as a dynamic measure of midazolam's effect on neural communication, during a novel experimental paradigm of memory encoding during the periodic aversive experience of acute pain. Our previous FC analysis focused on anatomical seed regions with known roles in memory, fear, and pain processing. From these seed regions, we found predominantly increased FC to targets throughout the brain [5]. In this current expanded network-level whole-brain analysis, we anticipated widespread increased FC under midazolam, compared to saline.

Methods: Data is from 16 healthy volunteers (age 25.7 ± 5.3 years, 11 male), who underwent fMRI (3 T BOLD, TR=1 s, 2.3 mm isotropic) under saline, followed by a target-controlled infusion of midazolam (effect-site concentration 10 ng/ml). Light sedation was achieved, with all subjects able to respond to voice. Under both saline and midazolam conditions, subjects performed a memory encoding task [6] with 270 auditory word items. One-third of these were immediately followed by painful (subjective rating 7/10) electric nerve stimulation to their left index finger. FMRI data were processed and analyzed using Conn Toolbox [7]; motion parameters, CSF signal, and task-event timing were removed by regression. The Saline > Midazolam contrast (looking for drug-induced differences in FC) was calculated using 30 standard network regions of interest (defined from resting-state data from the Human Connectome Project; cerebellum and brain stem excluded). Fig. 1 shows anatomic locations of selected networks used as seed and target regions of interest in the analysis. Significant FC changes were adjusted for an analysis-level false detection rate of $p < 0.05$ (correcting for multiple comparisons).

Results: Fig. 2 shows FC differences between networks for saline versus midazolam conditions. Increased (blue hue) FC under midazolam was found between 29/30 networks investigated. The majority of changes were localized to nodes in the parietal, posterior temporal, and occipital lobes. The identified FC changes crossed functional network labels, including between nodes within the default-mode, visual, language, and sensorimotor networks. Fig. 3 graphically displays the network FC changes overlaid anatomically on the brain. This allows visualization of the overall pattern of increased FC from posterior network nodes to nearby targets, as well as to a sparser array of more anterior target nodes centered in the prefrontal cortex and anterior temporal lobes.

Conclusion: These findings add to the previous resting-state (pain-free) studies of midazolam, which overall show mixed results for direction, magnitude, and locations of connectivity change under the drug. In

this clinically relevant paradigm of a memory task **during periodic painful stimulation, light sedation with midazolam caused robust increases in background network connectivity throughout the brain**, with predominance of posterior FC changes. These findings support that behavioral context, including pain, may influence anesthetic effects on brain networks. Further, we found increases in FC during conscious sedation, which differ from broad decreases seen under general anesthesia.

References: [1] Anesth Analg, 2016. 123(5): 1228-1240. [2] Hum Brain Mapp, 2008. 29(7): 839-47. [3] Hum Brain Mapp, 2015. 36(11): 4247-61. [4] Anesth Analg, 2020. 130(1): 224-232. [5] Anesth Analg, 2020. 130(5), Meeting Supplement: 397-399. [6] Exp Brain Res, 2019. 237(7): 1615-1627. [7] Brain Connect, 2012. 2(3): 125-41.

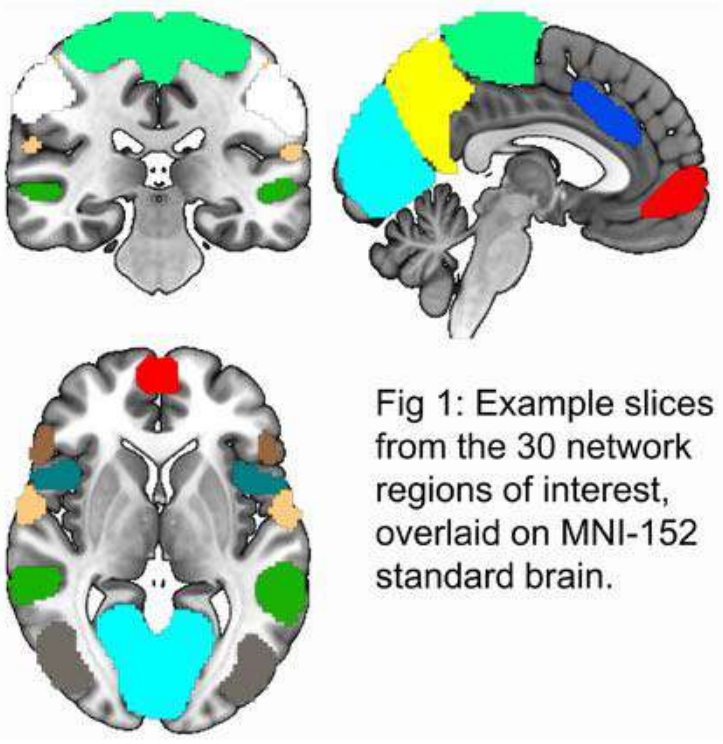

Fig 1: Example slices from the 30 network regions of interest, overlaid on MNI-152 standard brain.

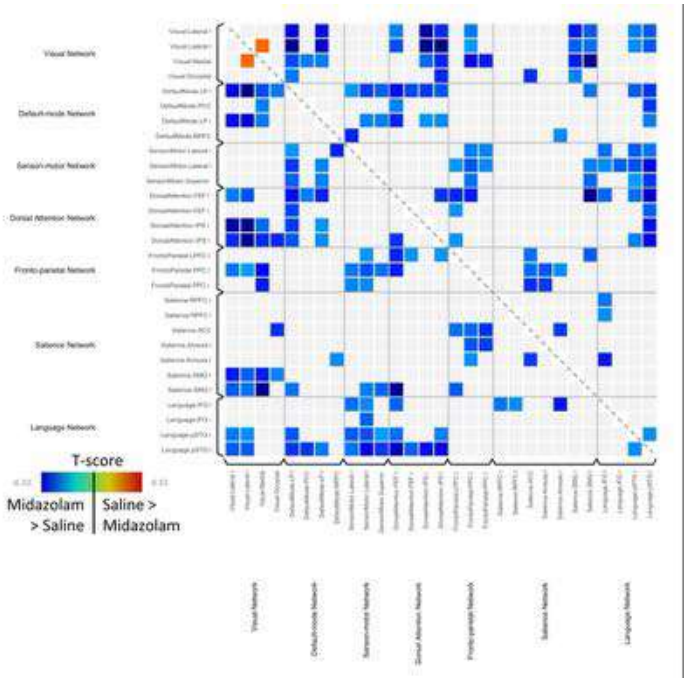

Fig 2: Connectivity contrast matrix, showing between-network differences in functional connectivity comparing saline to midazolam conditions.

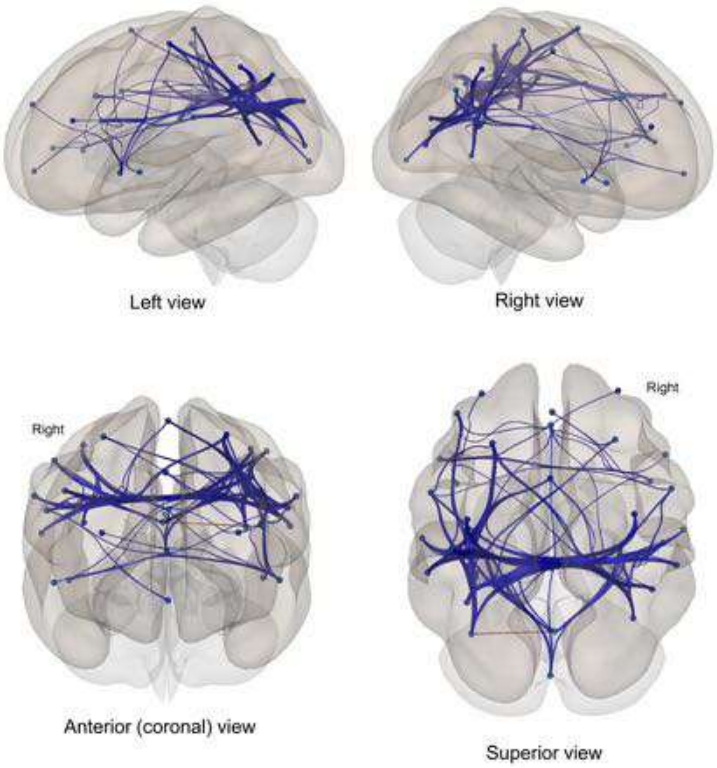

Fig 3: Anatomical visualization of between-network changes in functional connectivity comparing, saline to midazolam conditions. Views are slightly oblique from four labelled perspectives.

Neuroscience in Anesthesiology and Perioperative Medicine - 5 Using The 5-Choice Serial Reaction Time Task To Measure Cognitive Recovery In Rats Following Anesthetic Emergence

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Introduction: While healthy adults recover cognitive function rapidly following anesthesia, cognitive complications such as post-operative delirium become more prevalent as we get older [1]. As the proportion of elderly continues to increase globally, understanding how the brain restores neurocognition following anesthetic-induced breaks in consciousness becomes a more clinically and neurophysiologically important question to address. In rodents, levels of consciousness are traditionally captured by physiological responses such as the return of righting reflex (RORR) and electroencephalographic recordings; however, the return of cognitive function is more difficult to assess. The advent of touchscreen operant chambers with programmable tasks has vastly improved our ability to measure more complex cognitive features in animals, though their usage in anesthesia research has been limited. The 5-choice serial reaction time task (5-CSRTT), an analog to human continuous performance tasks, measures aspects of working memory, sustained attention, and inhibitory control using a fully automated system [2]. Previous work has demonstrated that exposure to isoflurane anesthesia produces no long-term consequences in rat 5-CSRTT performance, but how quickly performance recovers has not been established [3]. Here we use the 5-CSRTT to capture cognitive recovery trajectories in rats immediately following emergence from both inhaled and intravenous anesthetic regimens. By assessing the recovery trajectories of cognitive function in young, healthy rats we establish a foundation for which future models of post-anesthetic cognitive impairment may be compared.

Methods: Sprague Dawley rats (4 males and 4 females) were trained to perform the 5-CSRTT (Fig. 1). In a 5-CSRTT trial, the rat attends a 5-windowed screen for the appearance of a white square in 1 of 5 locations. The rat must recall and select the correct location via nose poke within 5s to receive a food reward. Selecting the wrong tile (incorrect responses) or not responding (omissions) are punished with a time-out. Primary outcome measures were accuracy (% correct responses) and omissions (% of trials with no response). Rats were trained until they could perform the 5-CSRTT with >80% accuracy and <20% omissions, after which they were tested once per week following anesthesia. The following anesthetic regimens were tested: 2% isoflurane for 1h (ISO), 3% sevoflurane for 20 min (SEVO), 10mg/kg I.V. propofol (PROP), 35 µg/kg and 20 µg/kg IV dexmedetomidine over 10 min (high and low DEX), and 50 mg/kg I.V. ketamine over 10 min (KET). Rats recovered from anesthesia in the 5-CSRTT testing chamber where they could initiate trials ad libitum during a 2-3h period. Recovery of low omission rate is the time from RORR to when a response is made in ≥4 out of 5 consecutive trials and is a metric of sustained attention. Recovery of accuracy performance is the time from RORR to when ≥4 out of 5 consecutively responded trials are correct and is a metric of working memory. Recovery trajectories were analyzed by survival curve comparison using a Mantel-Cox test.

Results: The time to recover accuracy performance ($\chi2 = 21.37$, $p = 0.0007$) and low omission rates ($\chi2 = 27.95$, $p < 0.0001$) on the 5-CSRTT following RORR varied among anesthetic regimens. Recovery of accuracy performance, a measure of working memory, was achieved in 87% of rats following SEVO, in 75% of rats following PROP, in 62% of rats following ISO and KET, and 37% and 25% of rats following either low or high doses of DEX (Fig. 2). Recovery of low omission rates, a measure of sustained attention, was achieved in 87% of rats following ISO, SEVO, and PROP, in 37% of rats following KET, in 12% of rats following low dose of DEX, and no rats recovered a low omission rate following high doses of DEX. RORR was unrelated to cognitive recovery (Table 1).

Conclusion: Using the 5-CSRTT, we found that metrics of working memory and sustained attention follow anesthetic-specific trajectories. The return of cognitive function is most delayed following dexmedetomidine and is most rapidly recovered

following sevoflurane anesthesia. Importantly, RORR – which is widely used to measure the return of consciousness in animals models – is not predictive of how quickly cognitive function returns. Overall, we demonstrate that the 5-CSRTT can be exploited to track real-time cognitive recovery in trained rats following anesthetic emergence to capture clinically relevant neurocognitive function.

References: 1. Lancet, 383, 911-22, 2014 2. Psychopharmacology, 163, 362-80, 2002 3. Front Behav Neurosci, 13, 76, 2019

Figure 1

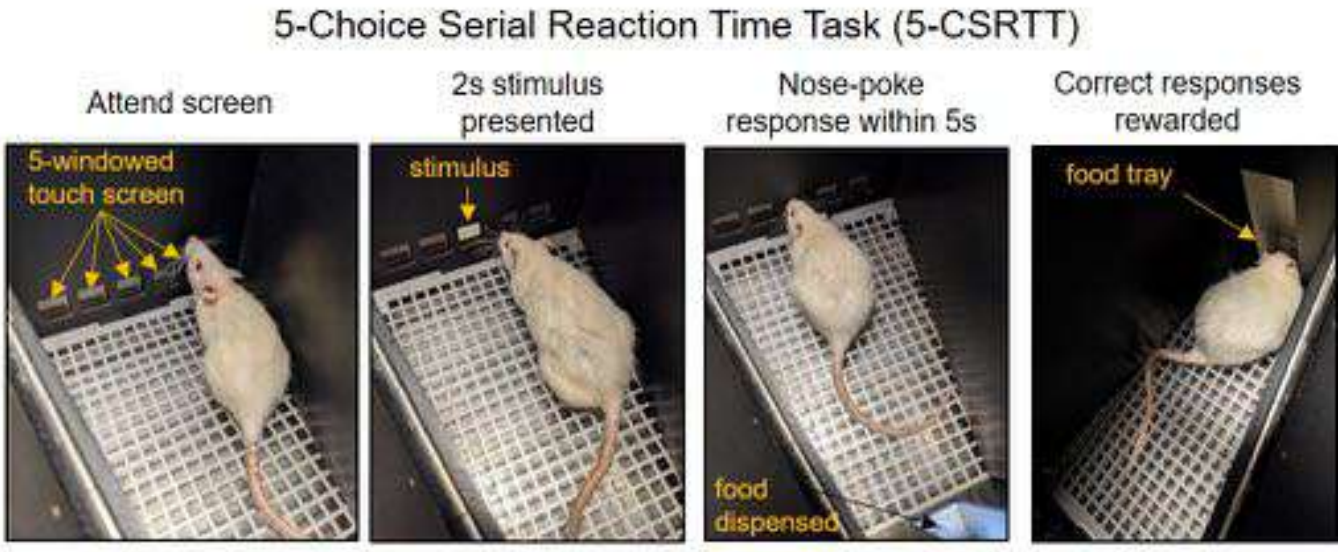

Figure 2

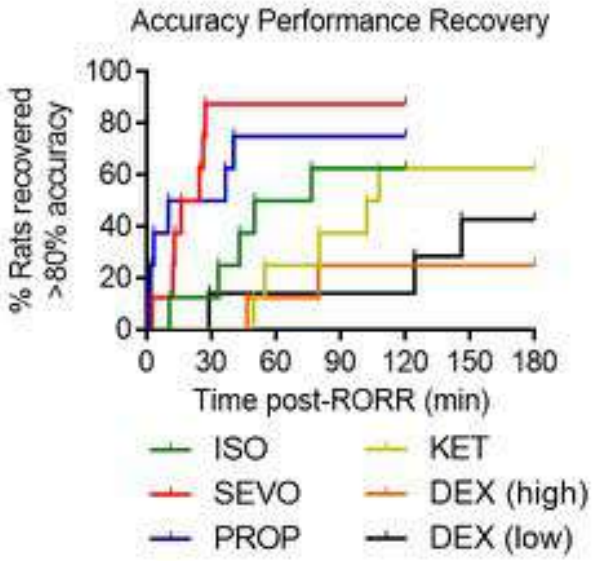

Figure 3

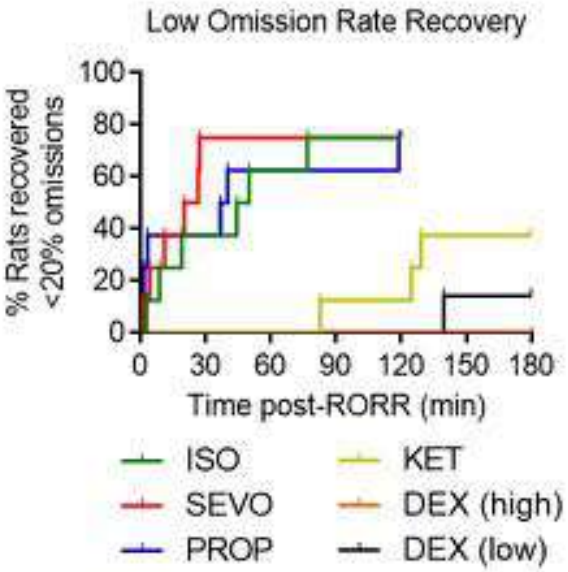

Table 1

	RORR (min)		Median recovery time (min post-RORR)	
	Mean	S.D.	Accuracy performance	Omission performance
ISO	10.2	5.4	63.1195	47.1631
SEVO	7.5	2.5	20.16	23.4503
PROP	12.9	2.4	23.27	38.475
KET	75.0	20.8	104.886	Undefined
DEX (high)	35.4	10.6	Undefined	Undefined
DEX (low)	49.8	20.2	Undefined	Undefined

Neuroscience in Anesthesiology and Perioperative Medicine - 6 Modulation of Resistance to State Transitions is Dose Independent Across Volatile Anesthetics

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[1]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

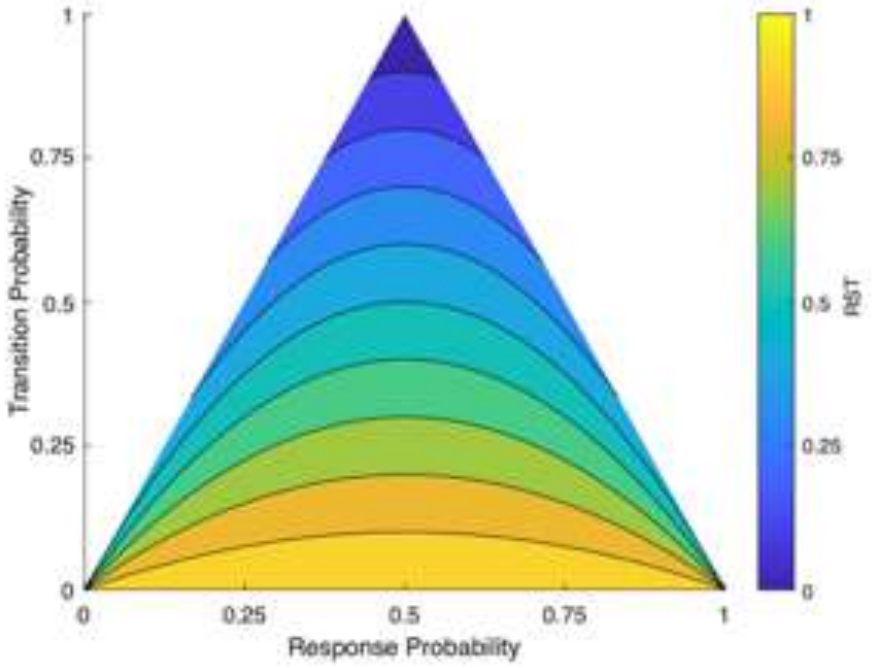
Introduction: Recent studies have begun to investigate the relationship between population-based and individual-based anesthetic pharmacology (1-3). At steady state concentrations, population level measures of anesthetic potency are constant, yet they mask spontaneous fluctuations in behavioral arousal observed between the responsive and unresponsive states within individuals (2). These changes in behavioral arousal demonstrate resistance to state transitions (RST), a tendency to remain in the same arousal state upon repeated behavioral assessment. Volatile anesthetics differentially modulate RST at equipotent concentrations (3). However, it remains unclear whether this observation is dose dependent. Furthermore, the relationship between RST and transition probability have not been fully explored. We hypothesize that RST is a novel feature of state transitions independent of drug dosing or potency.

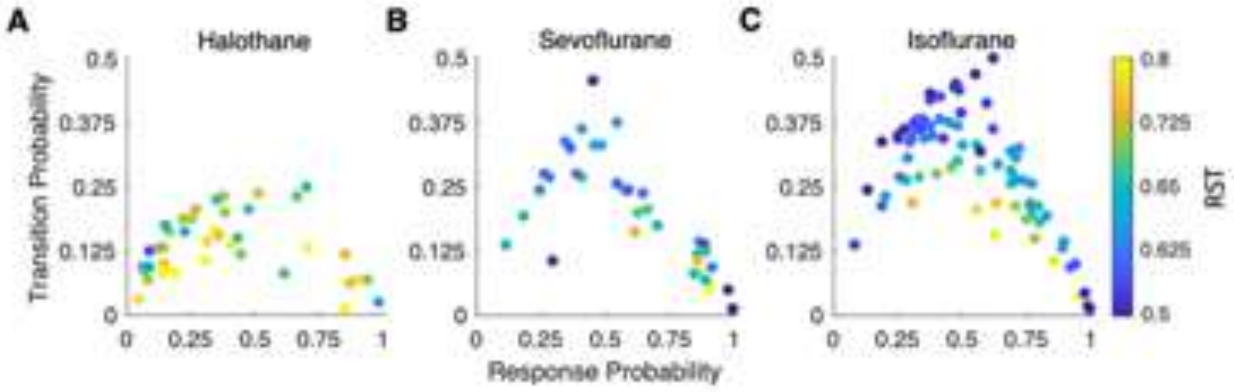
Methods: Adult (14-24 weeks old) C57Bl/6 mice (n=140 in total) were exposed to steady state concentrations of isoflurane (0.3%, 0.4%,0.6%, 0.7% atm), sevoflurane (0.5%, 1.0% atm), or halothane (0.4%, 0.5% atm). After a 2-hour equilibration period, righting reflex assessments were performed every 3 minutes for 2 hours on 4 separate occasions. Results were used to determine transition probability matrices for each individual. Response probability, transition probability, and RST were computed from the transition probability matrices. A 2x2 transition probability matrix can be fully described by 2 parameters (a and b), where a corresponds to the probability of staying responsive on two consecutive righting reflex assessments, and b corresponds to the probability of staying unresponsive on two consecutive righting reflex assessments. Response probability, transition probability, and RST can be analytically be derived using a and b. Equations for said features are found below. TPM=[a 1-a;1-b b] Response Probability=(1-a)/(2-a-b) Transition Probability=2(1-a)(1-b)/(2-a-b) RST=(a+b)/2 A linear regression was used to compare predicted and experimental transition probabilities. Analyses were performed in Matlab 2020b.

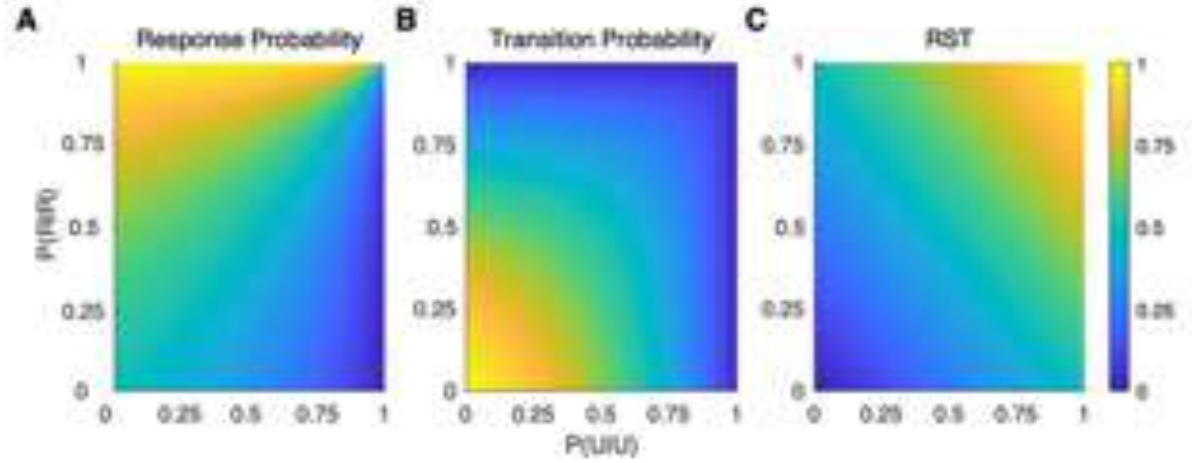
Results: At steady state concentrations, a 2x2 transition probability matrix is sufficient to describe experimental transition probabilities, regardless of anesthetic choice or dose. There is a unique relationship between response probability, transition probability, RST, and the defining parameters of the transition matrix. Transition probability and RST are distinct measures of state transition characterization, explaining differences between RST and measures of transition likelihood based on stochastic switching between a 2-well energy landscape (1,3).

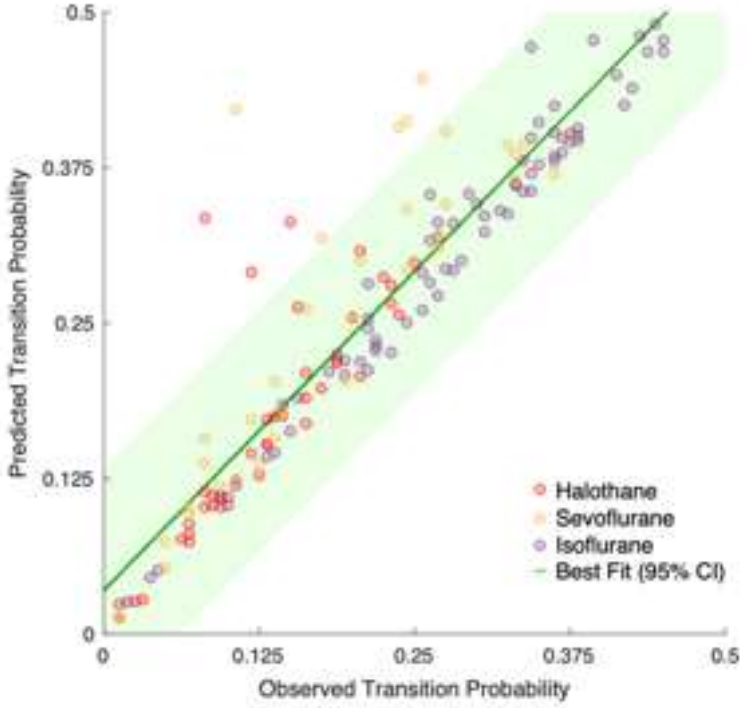
Conclusion: RST is a novel means of characterizing state transitions. While unique to the anesthetic choice, RST does not depend on anesthetic dose, and is distinct from more traditional measures of anesthetic potency. In combination with seemingly random fluctuations in arousal, assessment of RST offers additional insights for precision-based practice.

References: 1. Proekt, A., & Hudson, A. E. (2018). A stochastic basis for neural inertia in emergence from general anaesthesia. British journal of anaesthesia, 121(1), 86-94. 2. McKinstry-Wu, A. R., Wasilczuk, A. Z., Harrison, B. A., Bedell, V. M., Sridharan, M. J., Breig, J. J., Pack, M., Kelz, M.B., & Proekt, A. (2019). Analysis of stochastic fluctuations in responsiveness is a critical step toward personalized anesthesia. Elife, 8, e50143. 3. Wasilczuk, A. Z., Harrison, B. A., Kwasniewska, P., Ku, B., Kelz, M. B., McKinstry-Wu, A. R., & Proekt, A. (2020). Resistance to state transitions in responsiveness is differentially modulated by different volatile anaesthetics in male mice. British Journal of Anaesthesia, 125(3), 308-320.


Transition Probability
Response Probability
RST
0
0.25
0.5
0.75
1


A
Halothane
B
Sevoflurane
C
Isoflurane
Transition Probability
Response Probability
RST
0
0.125
0.25
0.375
0.5
0.625
0.75
0.875
1


A
Response Probability
B
Transition Probability
C
RST
P(I|I/I)
P(U|U)
0
0.25
0.5
0.75
1


Predicted Transition Probability
Observed Transition Probability
0
0.125
0.25
0.375
0.5
Halothane
Sevoflurane
Isoflurane
Best Fit (95% CI)

Neuroscience in Anesthesiology and Perioperative Medicine - 7 EEG-Derived State Dynamics At EC50 Isoflurane in Mice

Andrew McKinstry-Wu[1], Andrzej Wasilczuk[2]

[1]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA

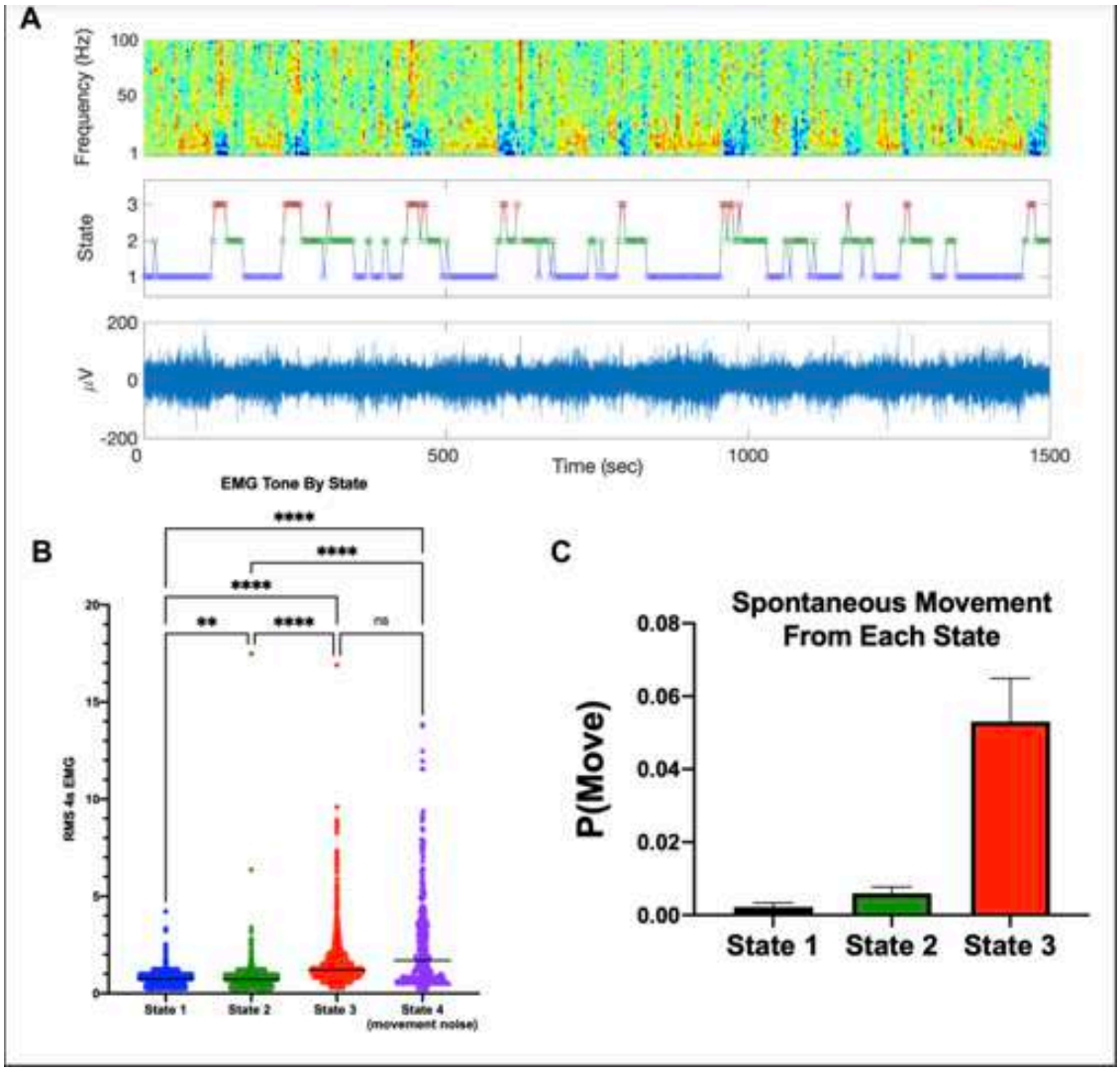
Introduction: Spontaneous shifts among distinct neurophysiologic states occur at steady-state anesthesia, even in the absence of significant external stimulation (1,2). Spontaneous arousals only occur from certain states, and a behavioral correlate of spontaneous state switching occurs near population anesthetic EC50 (1,3). Previous studies of anesthetic-induced neurophysiologic states and arousals either terminated with arousal or altered anesthetic concentration before the full range of state dynamics could be assessed. Here, we examine mouse electroencephalographic states at population EC50 for isoflurane in order to examine the relationship between neurophysiologic state dynamics and patterns of spontaneous arousal at the intersection of aroused and anesthetized behavioral states.

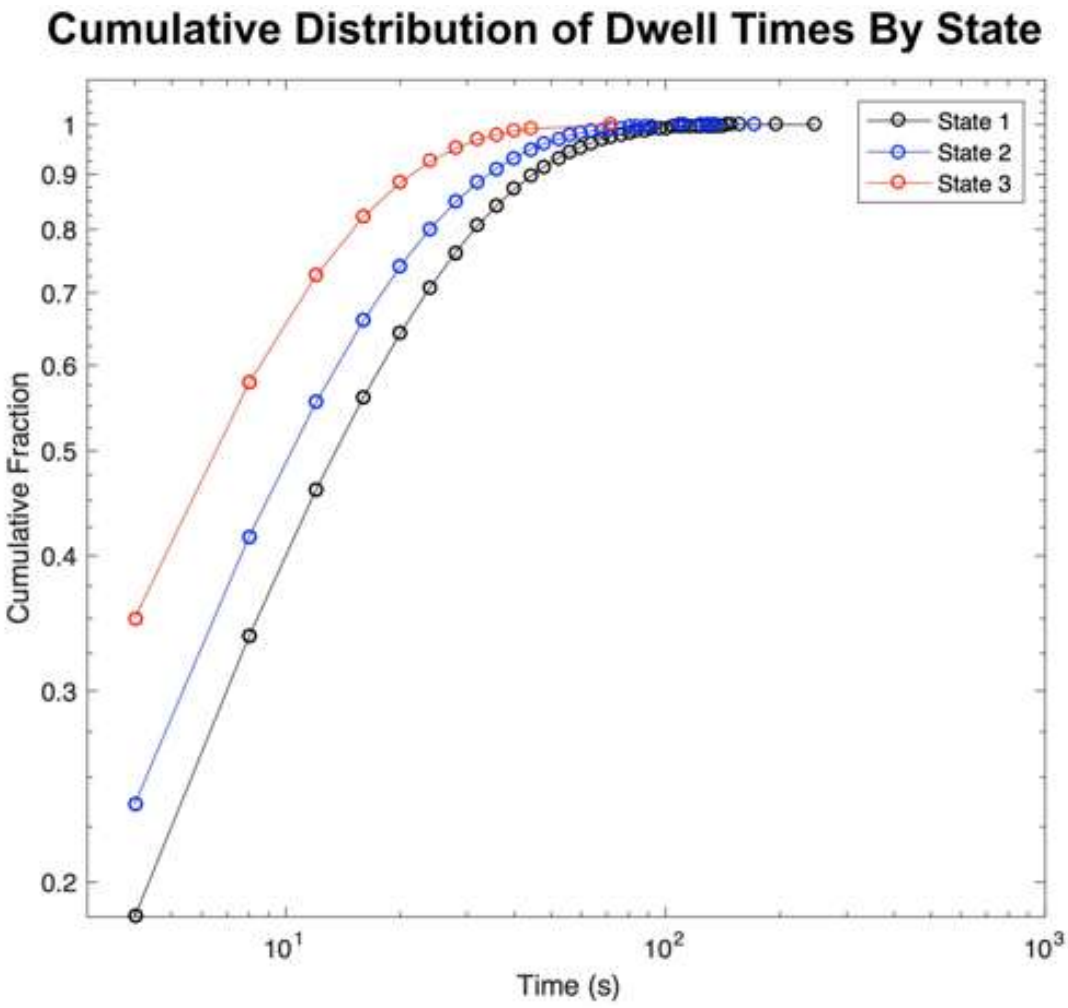
Methods: Male C57/B6 mice (n=6) were chronically implanted with 25 lead EEG and 4 EMG as previously described (1). After a 2 week recovery, they were exposed to 0.6% isoflurane unrestrained in open chambers with continuous acquisition of EEG and EMG. Analyses were performed on 4 contiguous hours of acquisition with minimal artifacts beginning at least 90 minutes after the start of exposure. EEG was band pass filtered from 1 to 100 Hz, and EMG high pass filtered at 15 Hz, with root mean squared of 4 second windows of EMG used for analysis. EEG signals were mean rereferenced and multitaper spectral analysis with 4 second non-overlapping windows performed in Matlab. Spectral states were determined using optimized kmeans clustering (silhouette method) of the first 10 principle components spectra of the 12 EEG leads of the right hemisphere across animals, base on methods used by Hudson et al. (2). All analyses were performed using Matlab with the Chronux toolbox and PRISM. Alpha of 0.05 (corrected for multiple comparisons where appropriate) was used for all statistical tests.

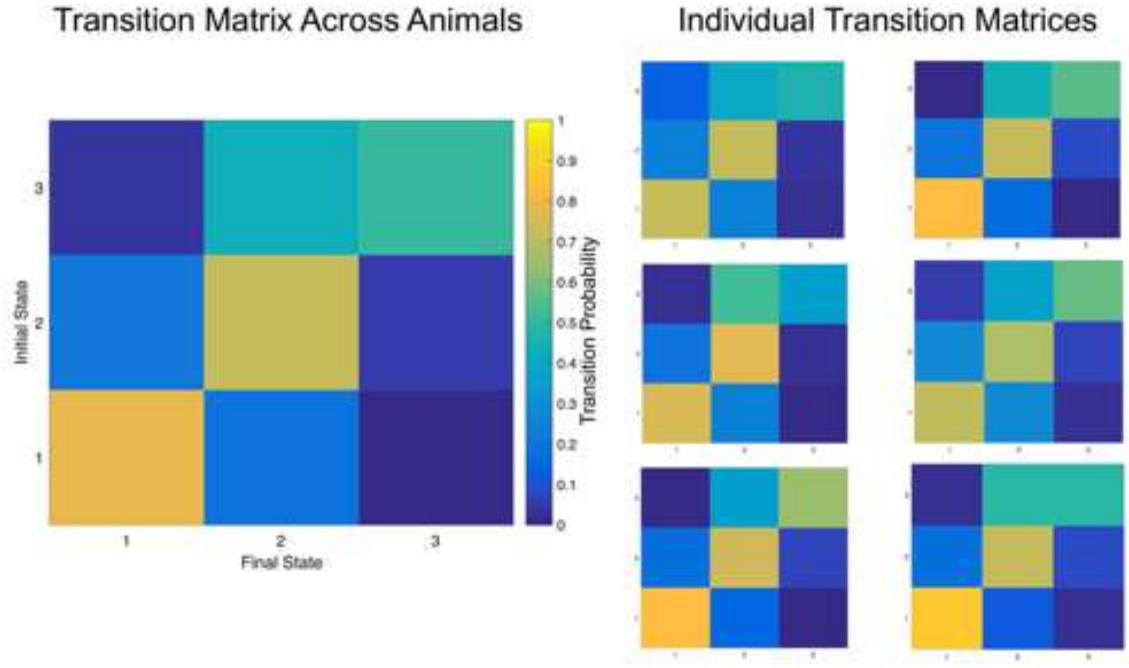
Results: At steady-state isoflurane, we found 4 clusters in the EEG data representing 3 EEG states with distinct spectral signatures and EMG tone and 1 cluster associated with movement artifact (Fig 1A,B). While spontaneous movement (and consequent movement artifact) occurred subsequent to each of the three states, it was vastly more likely to occur following state 3 (Fig 1C.) Dwell time distributions for states under isoflurane, as in rats, are consistent with those expected from a Markov process, but the observed distribution in mice were markedly shorter than those observed in rats (Fig 2, Ref 1:Fig S7.) We thus modelled EEG-derived state transitions as a Markov chain, estimating transition probability matrices for each animal and across animals. Transitions among all states occurred, though transition between states 1 and 3 occurred at a lower probability, and did not occur in all animals (Fig 3). State transitions showed significant autocorrelation, suggesting a cyclic process, with all mice displaying period lengths between 93 and 227 seconds (Fig 4.) The total amount of time spent in spontaneous arousal/movement in a given individual, which could be considered an individual's anesthetic sensitivity, best tracks with lower values of a measure of systemic state stability derived from the estimated Markov matrix, the mixing time (Fig 5.)

Conclusion: We have found that at steady-state isoflurane, mice spontaneously fluctuate through a limited set of EEG-derived states. These states, though similar to those described in rats, are shorter in duration. Spontaneous arousals occur predominantly from a single state. State stability, as measured by mixing time, is a better predictor of aroused/spontaneously moving time than any single state prevalence. Unlike previous characterizations of such states, the states we observe are oscillatory. Whether the combined oscillatory nature of state transitions and the state-specificity of spontaneous arousals/movement has implications for times to emergence from anesthesia is an open question, as are means of manipulation of state stability or oscillatory period.

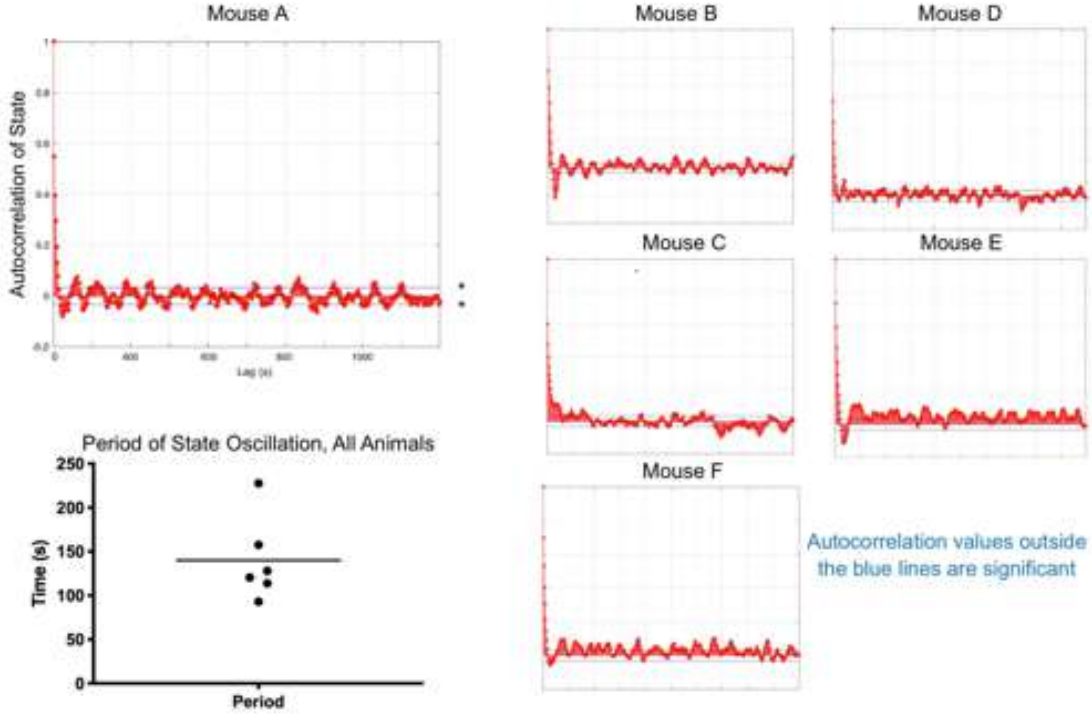
References: 1. Proc Natl Acad Sci USA. 2014. Jun 24;111(25):9283-8. 2. Anesthesiology. 2019. Jun;130(6):870-884. 3. Elife. 2019. Dec 3;8:e50143. 4. J Vis Exp. 2016. Nov 26;(117):54908. 3.

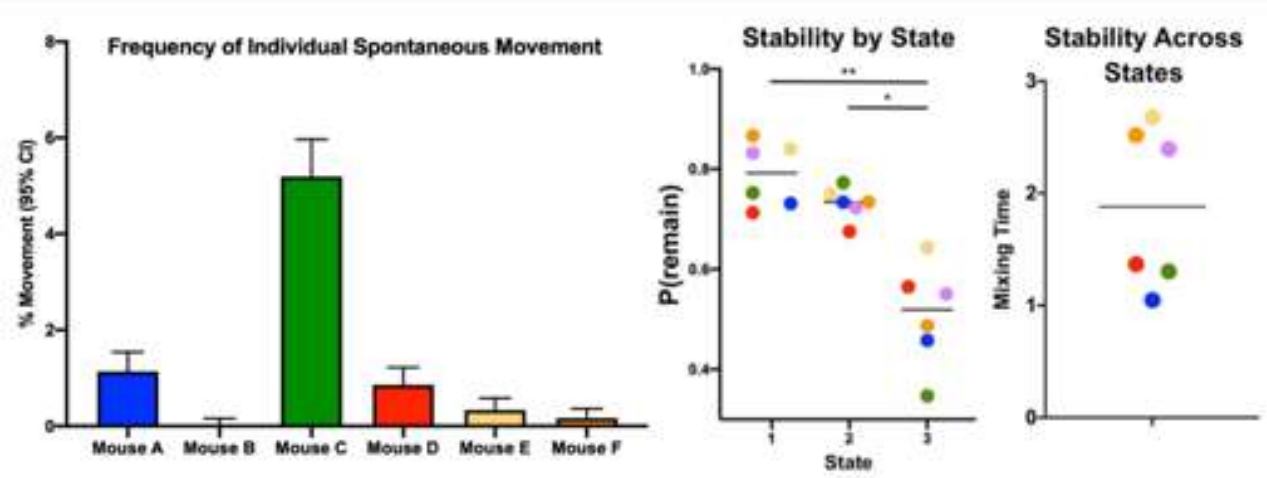



Cumulative Distribution of Dwell Times By State
State 1
State 2
State 3
Cumulative Fraction
Time (s)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
10^1
10^2
10^3


Transition Matrix Across Animals
Individual Transition Matrices
Initial State
Final State
Transition Probability
1
2
3
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9

State Dynamics Are Oscillatory





Neuroscience in Anesthesiology and Perioperative Medicine - 8 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 due to impaired microvascular reperfusion, which limits the benefit from large-vessel recanalization (1). Microvascular blood flow is regulated by a number of molecules including P450 eicosanoids whose levels are known to be altered in stroke (2,3). We have recently identified GPR39 as a dual sensor for two vasoactive P450 eicosanoids: the vasodilator and neuroprotective 14,15-epoxyeicosatrienoate (14,15-EET) and vasoconstrictor and neurotoxic 15-hydroxyeicosatetranoate (15-HETE) (4). GPR39 is expressed in arteriolar vascular smooth muscle cells and peri-capillary pericytes. Thus, GPR39 is uniquely positioned to sense the balance of vasoactive eicosanoids and modulate microvascular blood flow during and following stroke. To investigate the role of GPR39 in stroke, we have generated a global GPR39 knock-out (KO) mouse via CRISPR/Cas9 deletion of the receptor's first exon, eliminating expression of GPR39. We tested the hypothesis that GPR39 KO mice sustain larger infarcts, associated with lower microvascular reperfusion after transient focal cerebral ischemia compared to wild-type (WT) littermates with intact GPR39.

Methods: A 60-min middle cerebral artery occlusion (MCAO) was induced in 3-month old male and female mice using a silicone coated filament introduced through an external carotid stump under isoflurane anesthesia. A total of 26 KO (14 males, 12 females) and 18 WT (9 males and 9 females) mice were used for the study. Brains were harvested at 24 hours of reperfusion, sliced coronally in 2-mm segments, sections and stained with triphenyltetrazolium chloride (TTC) for measurement of infarcted areas after accounting for edema. Optical microangiography (OMAG) imaging was used to measure microvascular perfusion over the ischemic penumbra at baseline and 24 hours after MCAO in separate groups of 10 WT and 8 KO male mice.

Results: Striatal infarct size was 69.3% ± 3.51% in male GPR39 KO mice compared to 47.15% ± 3.19% in WT male littermates (mean ± sem, $p<0.0005$). In females, infarct size was 50.9% ± 7.24% in GPR39 KO mice compared to 48.3% ± 6.35% in WT littermates ($p = 0.81$). Two-way ANOVA demonstrated significant difference between male GPR39 KO and WT hemispheric and striatal infarct size ($P=0.038$). OMAG demonstrates decreased red blood cell flux in deeper cortical layers after MCAO, with GPR39 KO mice showing decreased microvascular reperfusion in deeper cortical layers compared to WT.

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

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

Neuroscience in Anesthesiology and Perioperative Medicine - 9 Imaging Cortical Circuitry during General Anesthesia-Induced Analgesia

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Introduction: General anesthetics work in a concentration-dependent manner on the central nervous system (CNS) to induce loss of consciousness and block the experience of pain. Interestingly, however, with nitrous oxide anesthesia and during the initial stages of diethyl ether anesthesia, analgesia can be produced independently of loss of consciousness. In contrast, isoflurane and sevoflurane, which are halogenated ethers, unquestionably produce unconsciousness, but produce little to no pain relief at subanesthetic doses. As the effects of general anesthetics on pain processing circuits in the brain are largely unexplored, the mechanisms that underlie the analgesic actions of certain general anesthetics are unknown. In the present studies in the mouse, we investigated the influence of non-analgesic (isoflurane) and analgesic (nitrous oxide) anesthetics on the anterior cingulate cortex (ACC), a brain region that encodes affective/emotional, but not sensory/discriminative, features of the pain experience. We continuously monitored, over time, the in vivo activity of hundreds of individual ACC neurons during the induction to, and emergence from, isoflurane or nitrous oxide anesthesia. Our objective is to uncover the mechanisms through which general anesthetics alter the perception of pain.

Methods: In adult mice, we continuously monitored the spontaneous activity of neurons in the ACC before, during, and after the inhalation of (1) isoflurane or (2) nitrous oxide anesthesia. Concentrations of anesthetic gases were monitored using a Datex Ohmeda S/5 patient monitor. Virally delivered, genetically encoded fluorescent reporters of neural activity were expressed ubiquitously across neuronal subtypes (AAV1-Synapsin-GCaMP6f). To capture GCaMP6f fluorescence, we implanted a gradient index (GRIN) lens into the ACC and monitored fluorescence changes with an Inscopix nVista (v3) head-mounted miniscope. Imaging data were recorded and processed with Inscopix nVista (v1.1.0) and Inscopix Data Analysis (v1.1.1) software, respectively and with custom-written MATLAB (R2017b) code. As individual fluorescence changes produced by an active neuron do not necessarily correspond to a single action potential, we classified these as events.

Results: Consistent with previous studies demonstrating that the global activity of the cerebral cortex is decreased during general anesthesia, we find that the rate of spontaneous neural activity decreases with increasing concentrations of isoflurane. Interestingly, isoflurane-induced alterations of ACC activity have two clear phases, a transient increase in ACC activity (1.2-1.4 fold increase from baseline) at low concentrations (>0 – 0.4% isoflurane), followed by a steep decline, and then cessation, as the concentration increased (>1% isoflurane). Surprisingly, and in sharp contrast, during the inhalation of nitrous oxide, we observed a significant increase in spontaneous activity of ACC neurons. Furthermore, we found that nitrous oxide also increases the activity of ACC neurons in two waves, with modest increases below 30% (1.5-2 fold increase from baseline) and greater increases above 30% (3-4 fold increase from baseline).

Conclusion: We conclude that non-analgesic and analgesic general anesthetics differentially alter neural activity in the ACC, a region of the brain that is a major contributor to the pain percept. In both patients and animals, decreases in ACC activity are generally associated with analgesia. Therefore, our finding that nitrous oxide, an analgesic, increased ACC activity, and that isoflurane, which is non-analgesic, decreases ACC activity, was unexpected. Of particular interest, nitrous oxide concentrations above 20-30%, which are considered analgesic in patients, are comparable to the concentrations that produced dramatic increases in neural activity in the mouse ACC. Additionally, preliminary data from our lab dissecting the effects of general anesthetics on functionally distinct neurons within the ACC (i.e., excitatory vs subtypes of inhibitory), suggest that the analgesic potential of a general anesthetic results from the preferential modulation of the activity of particular subtypes of

neurons. Our findings indicate that selectively modulating the activity of subtypes of ACC neurons, thereby disrupting pain processing by specific ACC circuits, provide an advantageous target to guide the development of novel classes of general anesthetics that exhibit increased analgesic potency.

Neuroscience in Anesthesiology and Perioperative Medicine - 10

Perioperative neurocognitive and neuroimaging trajectories in older APOE4 carriers vs non-carriers: A prospective cohort study

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Introduction: Neurocognitive disorder postoperative is a cognitive deficit of >1 or >2 SDs that occurs 1-12 months after surgery when accompanied by a subjective cognitive complaint.[1] A smaller group of neurocognitively vulnerable patients may have more significant postoperative cognitive decline than these objective thresholds, perhaps related to genetic polymorphisms associated with increased dementia risk.[1] Thus, we examined the effect of *APOE4*, the most common genetic variant associated with late-onset Alzheimer's disease (AD), on perioperative neurocognition in older patients.

Methods: The observational cohort study Markers of Alzheimer's Disease and neuroCognitive Outcomes after Perioperative Care (MADCO-PC) enrolled English-speaking patients ≥ 60 years (N=140) scheduled for non-neurologic, non-cardiac surgery under general anesthesia with a planned hospital stay.[2] Cognitive testing was completed before and six weeks after surgery using our established cognitive assessment battery.[3] Assessments were categorized into four cognitive domains by factor analysis. These four domains were averaged together to create the continuous cognitive index (CCI); a positive score indicates cognitive improvement and vice versa. CSF samples were collected before, 24 hours and six weeks after surgery via lumbar punctures. CSF amyloid beta1-42, t-tau, and p-tau181p levels were measured per Alzheimer's Disease Neuroimaging Initiative study methods.[4] Patients were PCR genotyped for *APOE4* as described.[5] Patients underwent resting state functional magnetic resonance imaging (rs-fMRI) before and 6 weeks after surgery; data processing and analyses were performed as described.[6]

Results: Complete assessments were available for 52 patients (Fig 1). No significant differences in baseline CSF AD biomarker concentrations were seen between *APOE4*-positive and -negative groups except for baseline Aβ levels, which were higher in *APOE4*-negative patients compared with *APOE4*-positive patients (p=0.0011) in accord with prior studies.[4] After multiple comparison corrections, there were no significant *APOE4*-related differences for Aβ, pTau, Tau, pTau/Aβ, and Tau/Aβ over time (p > 0.05 for all). There were no significant *APOE4*-related differences in CCI change from before to 6-weeks after surgery (p=0.8273), nor in the percentage of *APOE4* carriers vs non-carriers who had a ≥1 SD drop in ≥1 cognitive domain from before to 6 weeks after surgery (p=0.7478) (Fig 2). *APOE4* carriers (vs non-carriers) had significant greater rs-fMRI functional connectivity differences between left posterior cingulate and left angular/supramarginal gyrus region and between right entorhinal cortex and left inferior frontal lobe region before surgery, and this connectivity pattern decreased to a greater extent following surgery in *APOE4* carriers vs non-carriers, resulting in a postoperative "normalization" of functional connectivity between these brain regions in *APOE4* carriers (Fig 3).

Conclusion: In older surgery patients, there was no *APOE4*-related difference in post-operative changes in cognition or CSF AD biomarkers, though *APOE4* carriers (vs non-carriers) had a greater post-operative drop in rs-fMRI connectivity between specific brain regions. Since increased functional brain connectivity has previously been suggested to act as a compensatory mechanism to maintain normal cognition in *APOE4* carriers[7], the loss of this increased functional connectivity pattern following surgery in *APOE4* carriers may later contribute to the interaction effect previously observed between *APOE4* and surgery exposure for cognitive decline.[1] Future studies should thus examine 1-year and 5-year postoperative cognitive follow-up data to determine if this 6-week postoperative decrease in functional hyperconnectivity between specific brain regions in *APOE4* carriers is associated with worsened long-term cognitive trajectories. Lastly, these findings represent the first evidence for a genetic variant associated with altered brain functional connectivity patterns weeks after surgery/anesthesia.

References: 1. Surgery is associated with ventricular enlargement as well as cognitive and functional decline. 12, 590-597 (2016).
2. Intraoperative Frontal Alpha-Band Power Correlates with Preoperative Neurocognitive Function in Older Adults. 11, 24 (2017).
3. 18F-florbetapir Positron Emission Tomography-determined Cerebral beta-Amyloid Deposition and

Neurocognitive Performance after Cardiac Surgery. 128, 728-744 (2018).
4. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. 65, 403-413 (2009).
5. The Effect of Propofol Versus Isoflurane Anesthesia on Human Cerebrospinal Fluid Markers of Alzheimer's Disease: Results of a Randomized Trial. 52, 1299-1310 (2016).
6. Relative effect of APOE ε4 on neuroimaging biomarker changes across the lifespan. 87, 1696-1703 (2016).
7. Meta-analysis of cognitive ability differences by APOE genotype in young humans. 94, 49-58 (2018).

Figure 1: MADCO-PC surgical patients consort diagram

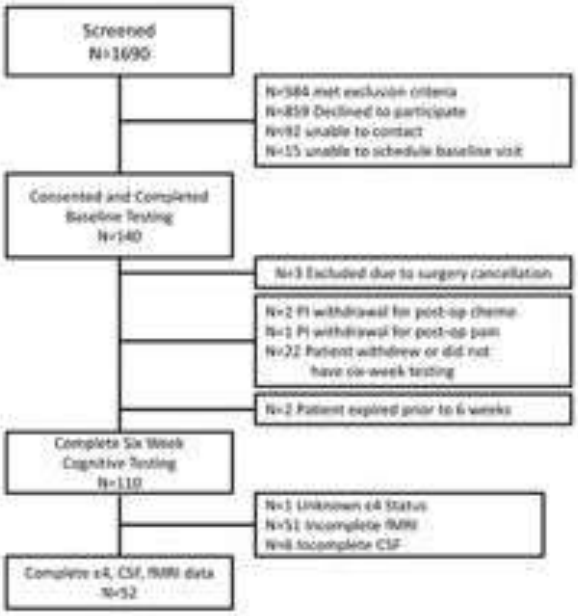
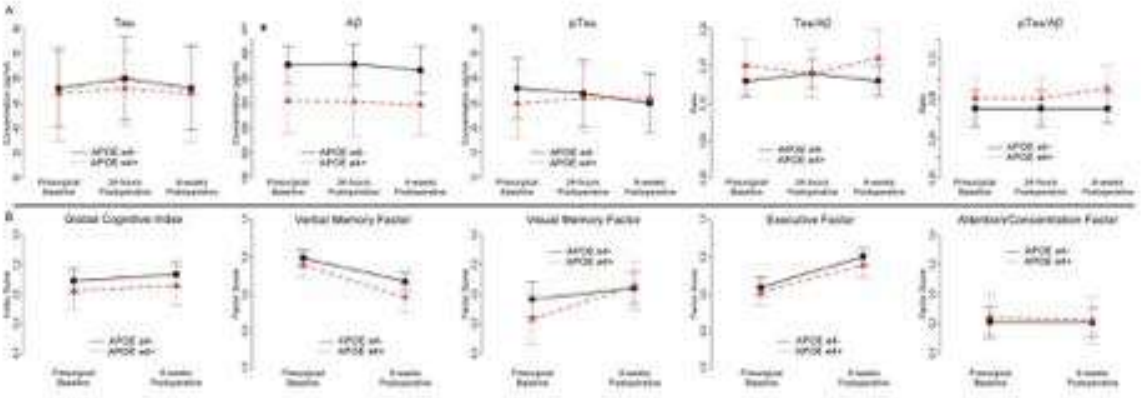


Figure 2: Perioperative neurocognitive trajectories by APOE4 genotype
A. Perioperative CSF AD biomarker trajectories. * indicates $p < 0.05$
B. Indicated cognitive trajectories



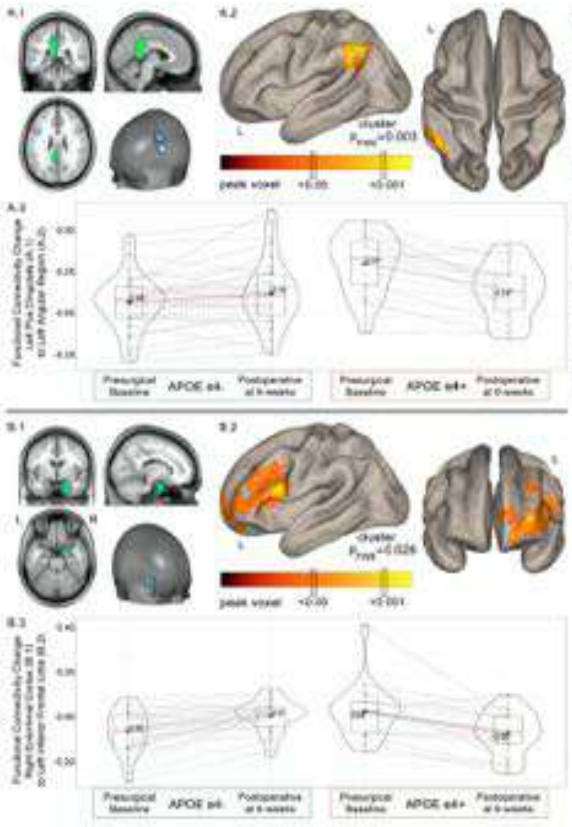


Figure 3: APOE4-related perioperative neurocognitive neuroimaging changes in older adults

A.1. *aparc*left posterior cingulate cortex Alzheimer's disease-risk seed region-of-interest (Neuromorphometrics ROI Atlas).
A.2. left angular/supramarginal gyrus region demonstrating statistically significant (peak $p<0.001$; cluster p-FWE<0.05) resting-state functional connectivity change from presurgical baseline to 6-week postoperative between APOE ε4 carrier and non-carrier groups for A.1. seed ROI.
A.3. distribution of resting-state functional connectivity values (Fisher *z*) for APOE groups between A.1. and A.2. regions at presurgical baseline and postoperatively at 6-weeks.

B.1. *aparc* right amygdala cortex Alzheimer's disease-risk seed region-of-interest (Neuromorphometrics ROI Atlas).
B.2. left inferior frontal lobe region demonstrating statistically significant (peak $p<0.001$; cluster p-FWE<0.05) resting-state functional connectivity change from presurgical baseline to 6-week postoperative between APOE ε4 carrier and non-carrier groups for B.1. seed ROI.
B.3. distribution of resting-state functional connectivity values (Fisher *z*) for APOE groups between B.1. and B.2. regions at presurgical baseline and postoperatively at 6-weeks.

Neuroscience in Anesthesiology and Perioperative Medicine - 11 The effect on cerebral oxygen saturation of vasopressors administered to treat intraoperative hypotension: a Bayesian network meta-analysis

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[1]Stanford University School of Medicine, Palo Alto, CA, [2]MMIMSR, MM (DU), Mullana-Ambala, India, [3]Stanford University, Stanford, CA, [4]Washington University in Saint Louis, St.Louis, MO, [5]Washington University in Saint Louis, Saint Louis, MO

Introduction: The optimal choice of vasopressor for managing hypotension during surgery is unclear. One of the main concerns in the setting of intraoperative hypotension is cerebral perfusion. Cerebral blood flow (CBF) is tightly regulated by a set of powerful mechanisms that include cerebral autoregulation, neurovascular coupling and carbon dioxide reactivity (1). CBF decreases passively if mean arterial pressure (MAP) falls below the lower limit of cerebral autoregulation, exposing the patient to possible cerebral hypoperfusion which has been associated with worst postoperative outcomes, such as delirium and postoperative cognitive dysfunction (2). The mainstay of management of intraoperative hypotension is the use of vasopressors. Different vasopressors have different pharmacological effects on cerebral hemodynamics (3) and there is no consensus on the best agent to use in each situation. We therefore performed a network meta-analysis (NMA) to pool and analyze data comparing various vasopressors used for the treatment of intraoperative hypotension.

Methods: Randomized control trials were searched in Embase, Ovid Medline, Scopus, Cochrane Central Register of Controlled Trials, and Web of Science until April 14, 2020. We included studies that enrolled adult patients (at least 18 years old) undergoing surgery under spinal/general anesthesia, that compared at least two vasopressors for the treatment of hypotension. The primary outcome assessed was the change in cerebral oxygen saturation (ScO2) as measured by cerebral oximetry following the administration of vasopressors.

Results: Of the 51 full-text manuscripts we reviewed, 9 were deemed eligible for our final network analysis. We included a total of 399 patients. The network geometry across outcomes revealed a majority of studies comparing phenylephrine with ephedrine, relative to other intervention comparisons, as shown in Figure 1. Our Bayesian network meta-analysis showed the likelihood that dopamine, ephedrine, and norepinephrine had the lowest probability of adversely affecting ScO2 as measured by cerebral oximetry. The suggested rank order from our analysis was Dopamine<Ephedrine<Norepinephrine<Phenylephrine, as shown in Figure 2. Because of the inherent imprecision when collecting direct/indirect comparisons, the rank orders suggested are possibilities rather than absolute ranks.

Conclusion: The results of our NMA suggest the possibility that dopamine and ephedrine are the vasopressors that better preserve ScO2, followed by norepinephrine. When compared to any of the other vasopressors, phenylephrine resulted to decrease ScO2. More research into these agents and preferably multi-drug trials are required to improve the strength of the evidence and to inform clinical practice. From the studies included in this NMA, it appears that the role of cardiac output needs to be taken into account when evaluating the effect of a vasopressor treatment on CBF/ScO2.

References: 1) Meng L, et al. Cardiac Output and Cerebral Blood Flow: The Integrated Regulation of Brain Perfusion in Adult Humans. Anesthesiology 2015;123:1198-208. 2) Maheshwari K, et al. Association Between Perioperative Hypotension and Delirium in Postoperative Critically Ill Patients: A Retrospective Cohort Analysis. Anesthesia and analgesia 2020;130:636-43. 3) Jentzer JC, et al. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. J Cardiovasc Pharmacol Ther 2015;20:249-60.

Figure 2. Network plot

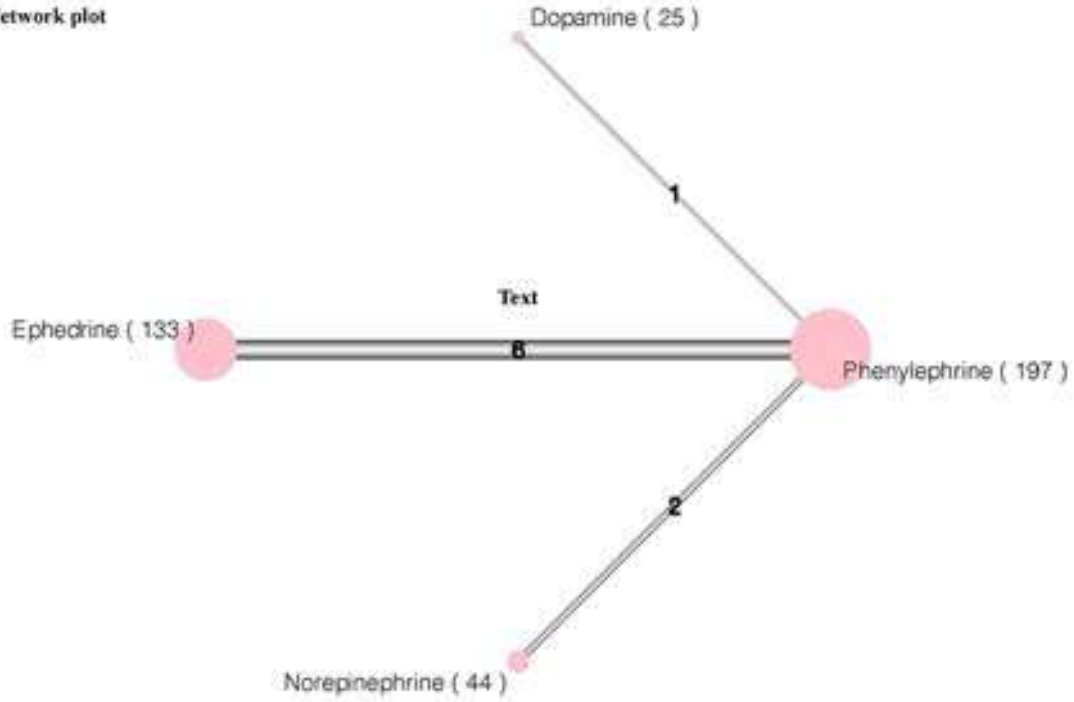
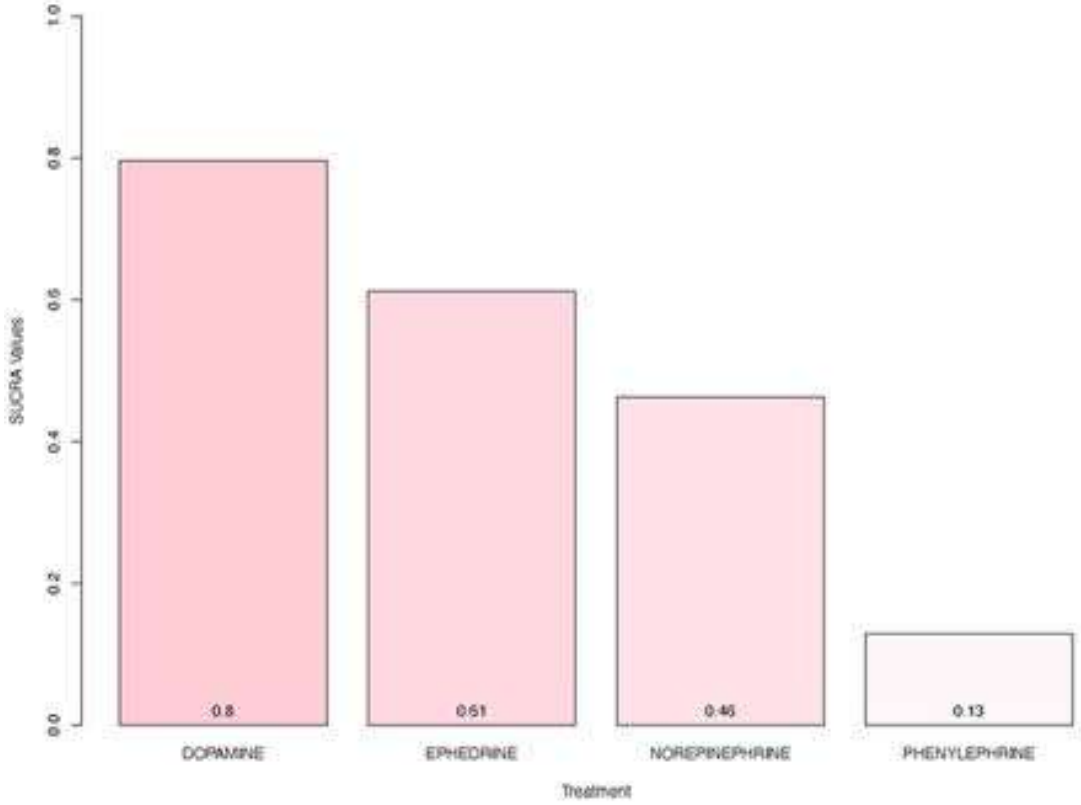


Figure 2. Surface Under the Cumulative Ranking (SUCRA) plot



Neuroscience in Anesthesiology and Perioperative Medicine - 12 Neuron-glia crosstalk plays a major role in the neurotoxic effects of ketamine via extracellular vesicles

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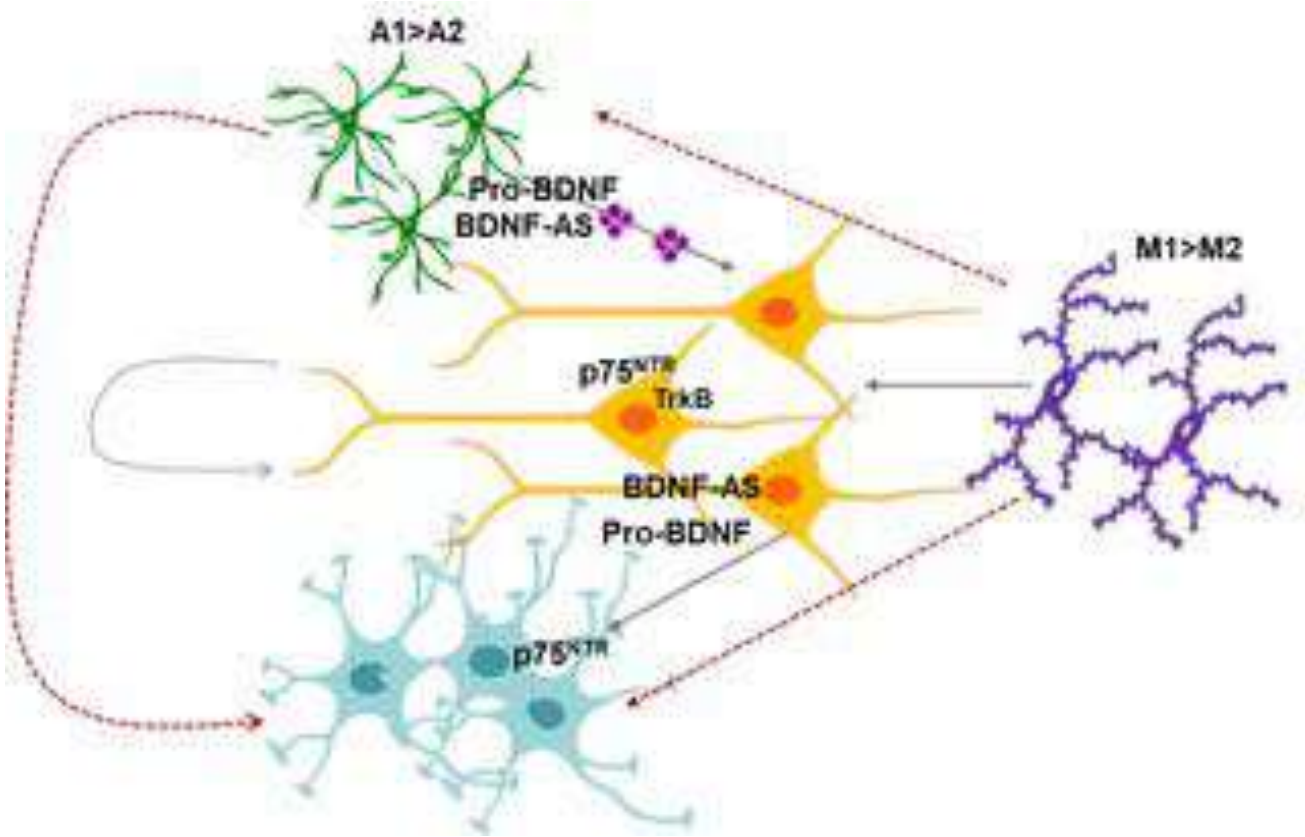
Introduction: There is overwhelming evidence from animal studies that general anesthetics (GA) lead to neurodevelopmental abnormalities including cell death, cognitive and behavioral changes.(1) Human studies have not been conclusive and are challenging since they must account for numerous confounding factors. There is now powerful evidence for non-cell autonomous mechanisms(2) in almost every pathological condition in the brain, especially relevant to glial cells(3), mainly astrocytes and microglia, that exhibit structural and functional contacts with neurons. These interactions were recently reported to occur via the secretion of extracellular vesicles (EVs) that play important roles in both physiological and pathological pathways(4). EVs carry a specific cargo consisting of RNA molecules, proteins and lipids. Dysregulated EV-related cargo and communication have been implicated in a variety of pathological conditions(5), including stroke, brain injury and neurodevelopmental disorders. Here, we employed primary human neural cells to analyze ketamine effects, focusing on the functions of glial cells and their polarization/differentiation state. We also explored the roles of extracellular vesicles (EVs) and different components of the BDNF pathway.

Methods: Ketamine effects on neuronal and glial cell death were analyzed using live/dead assay, caspase 3 activity and PARP-1 cleavage. Astrocytic (A1 vs. A2) and microglial (M1 vs. M2) cell differentiation were determined using RT-PCR and phagocytosis assays. The impact of the neuron-glial cell interactions in the neurotoxic effects of ketamine was analyzed using transwell cultures. The roles of the brain-derived neurotrophic factor (BDNF) pathway, including levels of BDNF, pro-BDNF, the lncRNA BDNF-AS and the receptors p75 and TrkB were analyzed using RT-PCR, ELISA western blot and gene silencing. EVs secreted by ketamine-treated cells were isolated, characterized and analyzed for their effects in neuron-glia cell interactions. The results are presented as the mean values ± SE. Data were analyzed using analysis of variance or a Student's t test with correction for data sets with unequal variances.

Results: Ketamine induced neuronal and oligodendrocytic cell apoptosis and promoted the expression of pro-inflammatory astrocytes (A1) and microglia (M1) phenotypes. Astrocytes and microglia enhanced the neurotoxic effects of ketamine on neuronal cells, whereas neurons increased oligodendrocyte cell death. Ketamine modulated different components in the BDNF pathway: decreasing BDNF secretion in neurons and astrocytes while increasing the expression of p75 in neurons and oligodendrocytes. In addition, ketamine treatment increased the lncRNA BDNF-AS levels and the secretion of pro-BDNF secretion in both neurons and astrocytes. We found an important role of EVs secreted by ketamine-treated astrocytes in neuronal cell death. Using knockdown experiments, we demonstrated that EVs secreted from ketamine-treated astrocytes expressed high levels of BDNF-AS and that silencing of the expression of this lncRNA in astrocytes abrogated the increased ketamine toxicity in neuron-astrocytes co-cultures, indicating a role for EV-associated BDNF-AS in this effect.

Conclusion: Ketamine exerted a complex neurotoxic effect on neural cells by impacting both neuronal and glial cells, therefore indicating that ketamine neurotoxicity involves both autonomous and non-cell autonomous mechanisms. We identified the role of different components of the BDNF pathway expressed by neurons and glial cells as major regulators of ketamine effects. Finally, we demonstrated for the first time a role of EVs as important mediators of ketamine effects by the delivery of specific non-coding RNAs between cells. These results may contribute to a better understanding of cellular and molecular mechanisms underlying ketamine neurotoxic effects in humans and to the development of potential approaches to decrease its neurodevelopmental impact.

References: 1. Jevtovic-Todorovic, V. Anesthetics. in The Curated Reference Collection in Neuroscience and Biobehavioral Psychology (2016). doi:10.1016/B978-0-12-809324-5.03913-4. 2. Zanghi, C. N. & Jevtovic-Todorovic, V. A holistic approach to anesthesia-induced neurotoxicity and its implications for future mechanistic studies. Neurotoxicol. Teratol. (2017) doi:10.1016/j.ntt.2016.12.004. 3. Zhang, Y. et al. Ketamine within clinically effective range inhibits glutamate transmission from astrocytes to neurons and disrupts synchronization of astrocytic SICs. Front. Cell. Neurosci. (2019) doi:10.3389/fncel.2019.00240. 4. Basso, M. & Bonetto, V. Extracellular vesicles and a novel form of communication in the brain. Frontiers in Neuroscience (2016) doi:10.3389/fnins.2016.00127. 5. Datta Chaudhuri, A. et al. Stimulus-dependent modifications in astrocyte-derived extracellular vesicle cargo regulate neuronal excitability. Glia (2020) doi:10.1002/glia.23708.



A diagram summarizing the roles of neuron-glia interactions, the BDNF pathway and extracellular vesicles in ketamine's effects. The effects of ketamine on various components of the BDNF pathway, the interactions of neuron and glial cells and the role of EVs as mediators of these interactions are depicted in this diagram.

Neuroscience in Anesthesiology and Perioperative Medicine - 13 Altered Brown Adipose Mitochondrial Respiration in Fragile X Syndrome Mice

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Introduction: Mitochondrial proton leak is a physiological process that is integral to thermoregulation and metabolic homeostasis[1]. Brown adipose tissue (BAT) mitochondria primarily generate heat via uncoupled respiration due to the excessive proton leak mediated by uncoupling proteins (UCPs)[2]. We have previously reported coenzyme Q (CoQ) deficiency in the forebrain mitochondria of newborn Fragile X Syndrome (FXS) mice (Fmr1 KO) that lack fragile X mental retardation protein (FMRP)[3]. This defect resulted in inefficient thermogenic mitochondrial respiration and hyperthermia due to a pathologically open mitochondrial permeability transition pore. Because the phenotype of these uncoupled forebrain mitochondria was highly reminiscent of the metabolic features of BAT mitochondria[4], and that FMRP is ubiquitously expressed, we hypothesized that Fmr1 KO BAT mitochondria would demonstrate discrete defects. Using a top down approach, we aimed to characterize the effect of FMRP deficiency on BAT mitochondria in newborn FXS mice.

Methods: Interscapular BAT mitochondria from ten-day-old male Fmr1 KO and FVB control mice were isolated and tested. Immunoblot analysis for UCP-1 was performed and electron transport chain (ETC) complex activities and oxidative phosphorylation were assessed using spectrophotometry and polarography, respectively. Mitochondrial CoQ levels were quantified and source of proton leak was determined using specific inhibitors. We evaluated 5-6 animals per cohort per assay. Significance was assessed with non-parametric Kruskal-Wallis test and post hoc Bonferroni correction set at $p < 0.05$.

Results: Immunoblot analysis demonstrated no significant difference in steady-state BAT UCP-1 expression in Fmr1 KOs relative to controls. Fmr1 KO BAT mitochondria demonstrated significantly slower state 3, dinitrophenol (DNP)-induced state 3, and oligomycin-induced state 4 oxygen consumption rates and lower membrane potentials for all substrates assessed. There was no significant difference in steady-state ETC complex kinetic activities between strains for the majority of enzymes. However, the linked kinetic activities of complexes I+III and II+III were significantly decreased in Fmr1 KOs, suggesting CoQ deficiency. Spectrophotometric quantification of mitochondrial CoQ content confirmed significantly decreased CoQ levels in Fmr1 KOs. Modular kinetics analyses revealed impaired substrate oxidation in Fmr1 mutants and pathologically increased proton conductance relative to controls, albeit at relatively low oxygen consumption rates. Grossly, Fmr1 KO BAT fat pads were visibly smaller than controls and weighed significantly less as a fraction of total body weight.

Conclusion: Our findings suggest defective BAT mitochondrial respiration in the setting of FMRP deficiency. Specifically, we identified CoQ deficiency, impaired substrate oxidation, and relatively lower membrane potentials in BAT mitochondria from newborn Fmr1 KO mice. Although our data provide further evidence of a link between FMRP and CoQ biosynthesis, the results highlight the importance of CoQ in developing tissues and suggest tissue-specific differences in the effects of CoQ deficiency. Because BAT mitochondria are primarily responsible for regulating core body temperature, the defects we describe in Fmr1 KOs could manifest as an adaptive downregulated response to hyperthermia or could result from FMRP deficiency directly. Given that anesthetic agents can interfere with the ETC[5] and induce hypothermia[6], future work will focus on mechanisms of anesthetic-induced thermodysregulation with a specific focus on BAT mitochondria and CoQ.

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Neuroscience in Anesthesiology and Perioperative Medicine - 14 Isoflurane exposure disrupts metabolic fluxes in neonatal brain

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Introduction: Volatile anesthetics are widely utilized in modern medicine, yet their precise targets and underlying molecular mechanisms remain poorly defined. While these anesthetic agents are considered safe in healthy individuals, there is evidence of anesthetic sensitivity and toxicity in select clinical populations, including children with mitochondrial disease (1). Recent animal studies have also demonstrated that neonatal mammals and developing invertebrates are susceptible to CNS damage following extended exposure to volatile anesthetics (2). Together, these data suggest that the toxic effects of volatile anesthetics may be mediated by molecular mechanisms that are unique to neonates. We have recently uncovered that volatile anesthetic exposure results in significant reductions of circulating ketone and glucose levels in neonatal mice. Here, we have elucidated a novel molecular mechanism that underlies the potent metabolic effects of volatile anesthetic exposure specific to neonates.

Methods: All rodent experiments were approved by the Institutional Animal Care and Use Committee of Seattle Children's Research Institute. Blood ß-hydroxybutyrate and glucose levels were measured using point-of-care ketone/glucose meters. To investigate the dynamic metabolic changes with isoflurane exposure, we developed a novel ex vivo metabolomic assay that utilizes stable isotope tracing with 13C-glucose. Statistical analyses were performed using GraphPad Prism.

Results: Isoflurane exposure led to a rapid and sustained depletion of circulating levels of ß-hydroxybutyrate in neonatal mice at postnatal day 7 (P7). The disruption in ketogenesis was observed at varying concentrations of isoflurane, even those well below the anesthetizing dose of 1.5%. However, in adolescent animals at P30, isoflurane had no impact on blood ketone levels. Isoflurane exposure also resulted in profound hypoglycemia, which was attenuated by ß-hydroxybutyrate, but not glucose, injections. Given that both ß-hydroxybutyrate and glucose are key metabolic substrates for the brain, we developed a novel metabolomic assay to examine the effects of isoflurane on dynamic metabolic fluxes in neonatal cortex ex vivo. Isoflurane exposure led to striking TCA cycle perturbations. Percentage of 13C-labeled citrate was increased by threefold in the 1.5% isoflurane exposed group as early as 2 minutes (6.50% vs. 2.21%, $p<0.05$). There was also a significant elevation of labeled isocitrate that persisted up to 30 minutes (24.80% vs. 18.21%, $p<0.05$). While pyruvate levels did not differ between groups, isoflurane exposure caused a nearly threefold increase in labeled lactate and alanine levels at 5 minutes (all $p<0.001$). A concomitant treatment of ß-hydroxybutyrate attenuated the increase in labeled citrate and isocitrate in the isoflurane exposed group but had no effects on lactate or alanine.

Conclusion: We developed a targeted metabolomic approach to study dynamic metabolic flux through glycolysis and TCA cycle in neonatal brain. Our data demonstrate that short-term exposure to volatile anesthetics results in substantial disruptions in cerebral metabolism, including a striking accumulation of citrate and isocitrate. Our results uncover a novel molecular mechanism that underlies the physiologic effects of volatile anesthetics on neonatal metabolism. These mechanistic links reveal potential therapeutic targets for the prevention of volatile anesthetic induced neurotoxicity in vulnerable populations.

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Neuroscience in Anesthesiology and Perioperative Medicine - 15 Isoflurane specifically inhibits endocytosis due to acute ATP depletion in mouse neurons: a mechanism of action for volatile anesthetics

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Introduction: Volatile anesthetics (VAs) selectively inhibit mitochondrial complex I of the electron transport chain; defects in complex I cause VA hypersensitivity in nematodes, flies, mice and humans (1-4). Spontaneous excitatory presynaptic frequencies are decreased by VAs (5). The pattern of presynaptic inhibition in hippocampal CA1 neurons is consistent with failure of neurotransmitter cycling and is seen at lower VA concentrations in the mitochondrial mutant, Ndufs4(KO), than in wildtype. In order to identify which synaptic functions are most sensitive to VA inhibition, we investigated synaptic vesicle cycling during exposure to isoflurane (ISO) in hippocampal cultures from Ndufs4(KO) and wild type mice. We also investigated the relationship between intracellular ATP and vesicle dynamics in this system.

Methods: All studies were approved by the local IACUC committee. Cells from the hippocampus of P0-P1 Ndufs4 floxed mice were grown in culture for 7-10 days. Cells were transfected with a construct containing a FRET sensor to measure relative ATP concentrations, VGLUT1-pHluorin to measure synaptic vesicle cycling and an mCherry-synaptophysin (to identify synaptic boutons) (6). To generate Ndufs4(KO) cells, Cre-recombinase was also transfected into cells from Ndufs4 floxed mice. Increases in pHluorin fluorescence were recorded upon high frequency stimulation (HFS) with and without ISO. Cells were supplemented with pyruvate to support mitochondrial function while glucose was varied to restrict or support glycolysis. Extracellular acidification was used to measure reuptake of synaptic vesicles into the presynaptic cell.

Results: At baseline, mitochondrial respiration is similar in control and Ndufs4(KO) hippocampal cultures indicating similar baseline energy stores (Fig 1). At physiologic concentrations of glucose, in both genotypes high frequency stimulation (HFS) increased VGLUT1-pHluorin fluorescence (synaptic vesicle exocytosis) followed by rapid return to baseline (endocytosis) (Fig 2A). Endocytosis, but not exocytosis, was delayed in both wildtype and KO cultures exposed to ISO at their behavioral EC95 (WT, 1.8% isoflurane, 0.74mM; KO, 0.6% isoflurane, 0.25mM) (Fig 2B). Exposure to high concentrations of glucose to artificially support glycolysis and with pyruvate to support mitochondrial respiration led to improved endocytosis in ISO (Fig 2C). Decreased extracellular glucose greatly increased the endocytosis blockade by ISO (Fig 2D). HFS did not prolong decreases in ATP concentrations in boutons of either genotype when not exposed to ISO (Fig 3A). HFS of cells superfused with ISO at their EC95s and glucose/pyruvate as in Figure 2, reduced ATP concentrations to similar degrees in both genotypes, matching their whole animal behaviors (Fig 3B-C). Extracellular acidification caused a return of pHluorin fluorescence to baseline (Fig 4) indicating that the block in endocytosis, associated with decreased ATP levels, occurred at reuptake of synaptic vesicles into the presynaptic cell (Fig 5). Legends. Fig 1. Oxygen uptake from control and KO cells shows similar baseline and stimulated rates when neurons are quiescent, indicated similar ATP production. Fig 2.A Exocytosis (upslope of fluorescence) and endocytosis (downslope) during HFS stimulation (blue bars) are rapid in absence of ISO for WT and KO cells. B-C. Endocytosis shows an increasing defect in presence of ISO as glucose is restricted. Fig 3.A. ATP levels decrease during HFS stimulation but recover rapidly in absence of ISO. B-C. ATP levels show an increasing deficit as glucose is restricted in the presence of ISO. Fig 4. Fluorescence rapidly decreases when acidic buffer (MES, pH 5.5) is superfused showing that pHluorin is on the cell surface. Fig 5. The resulting model for the action of ISO at the presynapse to inhibit neurotransmission.

Conclusion: The data indicate that clinical concentrations of isoflurane inhibit mitochondrial ATP

production with resulting failure of presynaptic endocytosis. Endocytosis is blocked at the step of reuptake of synaptic vesicles from the presynaptic cell surface. Inhibition of presynaptic mitochondrial complex I occupies a central role in the mode of action of VAs, the failure of synaptic transmission.

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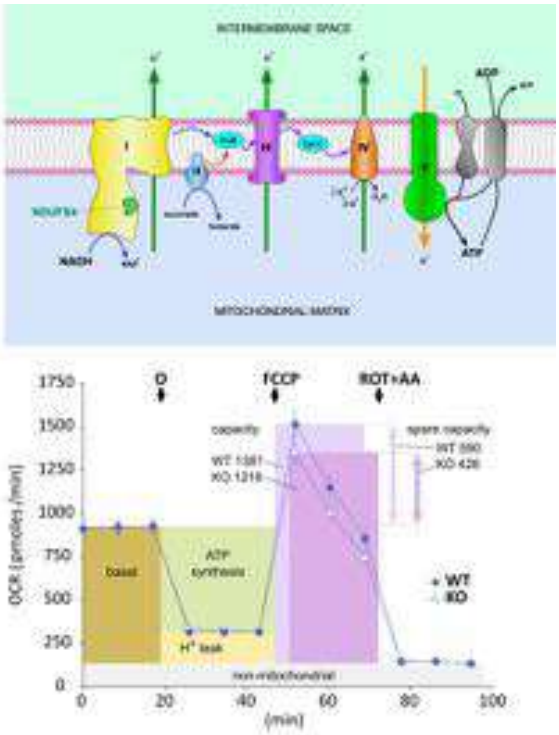
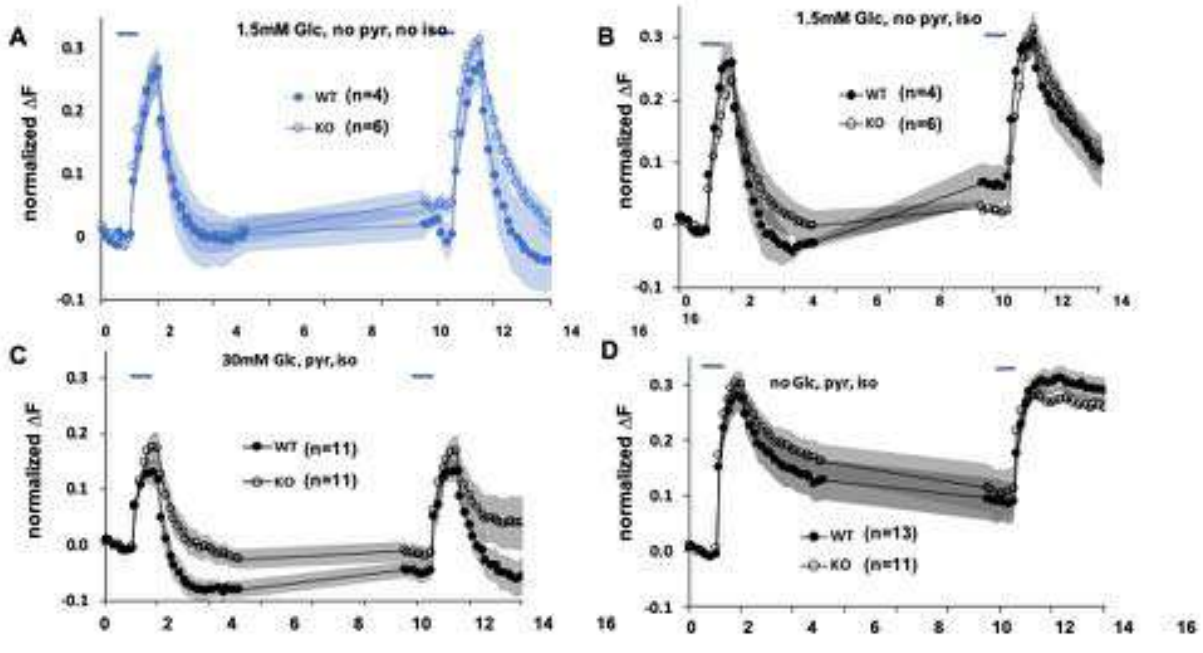
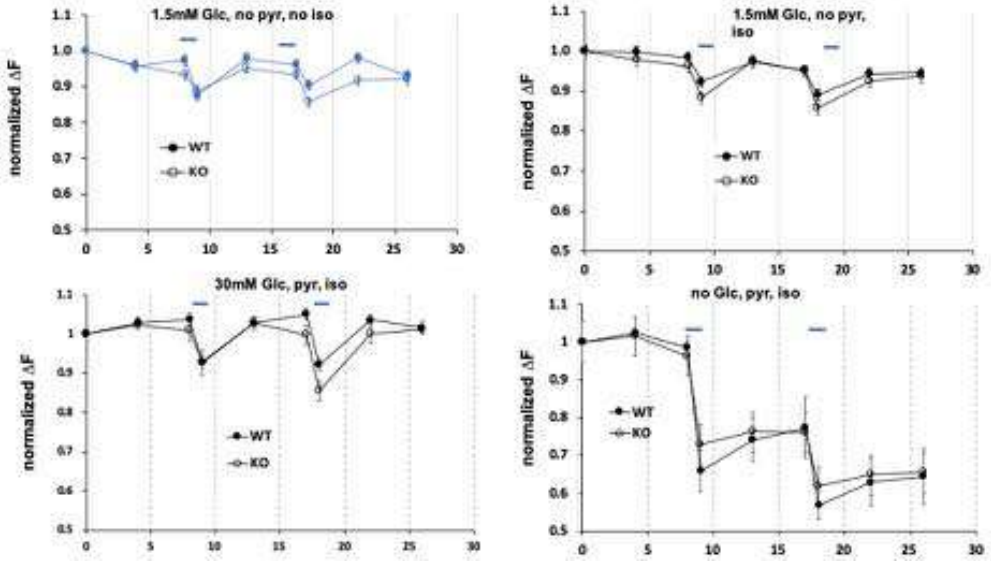
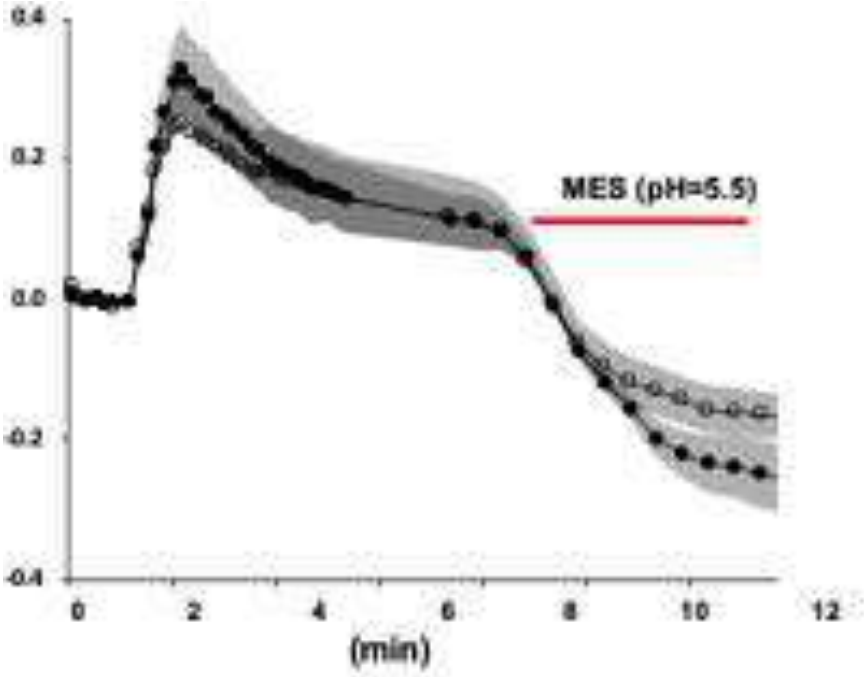
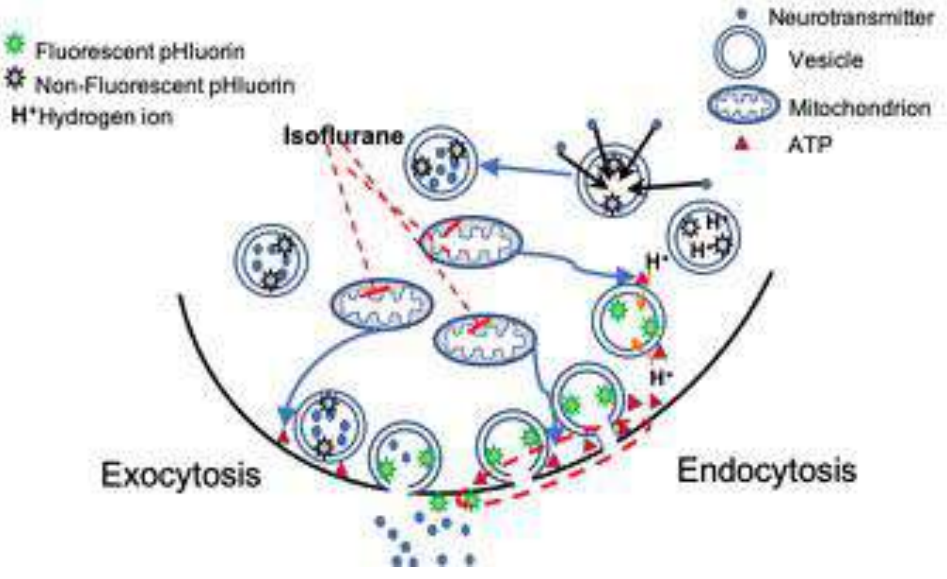
Figure 1






1.5mM Glc, no pyr, no iso
1.5mM Glc, no pyr, iso
30mM Glc, pyr, iso
no Glc, pyr, iso
normalized ΔF
WT
KO


MES (pH=6.5)
(min)


Fluorescent pHluorin
Non-Fluorescent pHluorin
H+Hydrogen ion
Neurotransmitter
Vesicle
Mitochondrion
ATP
Isoflurane
Exocytosis
Endocytosis

Neuroscience in Anesthesiology and Perioperative Medicine - 16

Electroencephalographic Characteristics Associated with the Use of Dexmedetomidine During Supratentorial Craniotomies

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Introduction: Neurosurgical procedures involving eloquent cortex and critical neurovascular structures require extensive multimodal neuromonitoring to allow the assessment of different anatomical brain structures . The most common neuromonitoring modalities employed during supratentorial brain surgeries are electroencephalography (EEG), motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP). It is particularly challenging to optimize the anesthesia approach for the simultaneous acquisition of EEG and MEPs. To allow reliable simultaneous neuromonitoring of EEGs and MEPs, the neuroanesthesiology team at Yale New Haven Hospital has successfully introduced the use of dexmedetomidine in combination with reduced MAC of sevoflurane and opioids, as a balanced protocol for multimodal neuromonitoring during supratentorial brain surgeries. Currently there are limited data available regarding the characteristics of intraoperative EEG changes associated with the use of dexmedetomidine in adult patients undergoing neurosurgical procedures. We designed a retrospective observational study to determine differences in intra operative EEG signals resulting from the use of dexmedetomidine, compared with a balanced general anesthesia using propofol without dexmedetomidine.

Methods: This retrospective cohort study was approved by the Yale IRB with a waiver of informed consent. Eligible patients were adults older than 18 years of age, who underwent elective supratentorial brain tumor resections or carotid endarterectomy, with intraoperative use of continuous EEG monitoring, and a surgical duration >2 hours. EEG and Data Processing Intraoperative EEG was recorded using an 8 channel Cadwell Intraoperative Monitoring System.For each patient, a total of 9 high quality EEG recordings (free from noise and artifacts) were collected on a 3-3-3 basis corresponding to beginning-mid-end of procedure, during which infusions of propofol and/or dexmedetomidine were stable. Conversion of the raw EEG file to the European Data format was performed by data extraction software commercialized by Cadwell. The unprocessed electroencephalogram and its spectrogram were used to characterize the EEG signature.(3,4) The EEG data was merged with demographics, anesthesia, medications and physiology data abstracted from the Electronic Health Record. During the EEG intervals, the following data were recorded: Rate and dose of propofol or dexmedetomidine infusions, MAC of sevoflurane, vitals including blood pressure, end tidal CO2, temperature, respiratory rate and any medication bolus. We categorized patients into 2 groups: 1. Utilization of propofol infusion as part of intra operative anesthesia without dexmedetomidine (Prop group); and 2. Utilization of dexmedetomidine infusion (without propofol) as part of intra operative anesthesia (Dex group). We compared patients' characteristics between the two groups using two-sample Student's t-test for continuous variables or chi-square test for categorical variables. A two-sided alpha level less than 0.05 was required for statistical significance. In this report, we present preliminary data for the first 27 patients included.

Results: 16 patients were in the Dex group and 11 in the Prop group. Mean surgery duration was 224 (SD 114) min in the Dex group and 187 (SD 93) min in the Prop group. Average infusion rate of dexm was 0.62 mcg/kg/hour and average infusion rate of prop was 80 (SD 24) mcg/kg/min. Average infusion rate of remifentanil was 0.2 (SD 0.06) mcg/kg/min in the Dex group and 0.18 (SD 0.04) mcg/kg/min in the Prop group. Sevoflurane MAC was 0.89 (SD .26) in the Dex group and 0.46 (SD 0.39) in the Prop group ($p<0.01$). Hemodynamic profiles were comparable between the two groups. Fig 1 and 2 show a representative spectrogram of two patients that received either propofol or dexmedetomidine. Patterns suggest higher global suppression & greater power in theta range for the prop group. There was greater power in the alpha range with spindles in the 12-15 Hz range for the dex

group. Both groups showed the greatest power in the delta range

Conclusion: We found higher global suppression and greater power in theta range for the propofol group, while there was greater power in the alpha range with spindles in the 12-15 Hz range for the dexmedetomidine group.This is important to correctly interpret EEG signals and choose the optimal combination of anesthetic techniques during supratentorial craniotomies in which EEG monitoring is utilized.

References: REFERENCES 1) Baylor University Medical Center Proceedings. 2001 Jan; 14 (1),13-21, 2) Paediatr Anaesth. 2009 Dec;19(12):1175-83. 3) PLoS One. 2016; 11(10). 4) Anesthesiology, 2014 month V 121, No 5, pages, 2014

Figure 1.

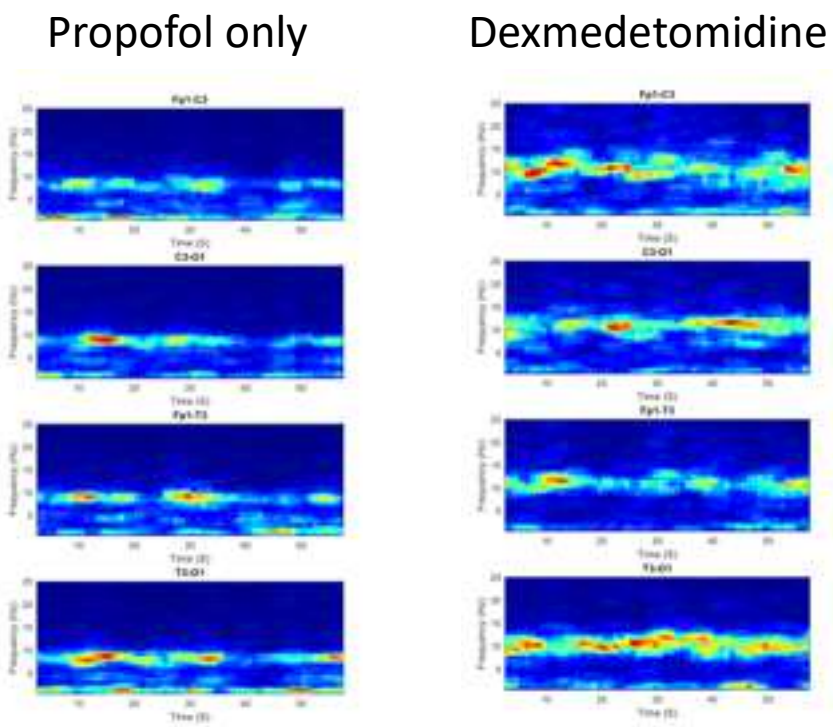
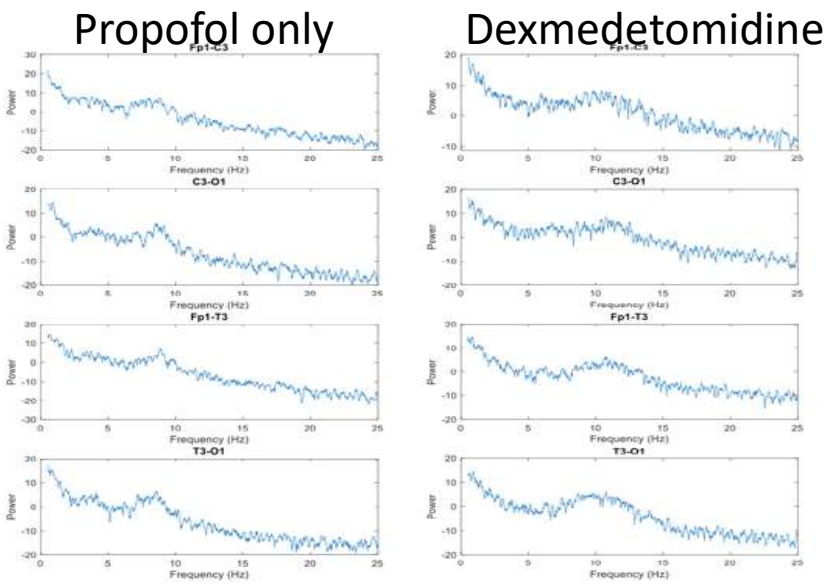


Figure 2.


Propofol only
Dexmedetomidine
Fp1-C3
C3-O1
Fp1-T3
T3-O1
Power
Frequency (Hz)

Neuroscience in Anesthesiology and Perioperative Medicine - 17 Brain-wide unbiased mapping of neuronal activity pinpoints ketamine's interaction with the opioid system in mice

Daniel Ryskamp[1], Tuuli Hietamies[2], Sofia Schlozman[2], Pierre Llorach[2], Juliana S Salgado[2], Daniel A Barbosa[3], Boris D Heifets[4]

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Introduction: A diagnosis of depression strongly predicts poor postoperative outcomes, including chronic pain and opioid use disorder. Perioperative interventions for depression are largely absent because available treatments have limited efficacy and are difficult to implement on a perioperative timetable. Considerable evidence now shows that ketamine (KET) has a rapid-onset, large effect size for the treatment of depression. Developing safer, better KET-like drugs requires a clear understanding of KET's mechanism of action. KET's mechanism involves NMDA receptor (NMDAR) antagonism, but other NMDAR antagonists fail to mimic the diversity of KET's clinical effects. We recently found that the antidepressant effect of KET is blocked by the opioid receptor antagonist naltrexone (NAL) in humans[1]. This finding adds to evidence for a complex interaction between KET and the opioid system, as KET can also markedly potentiate opioid analgesia and prevent opioid-induced hyperalgesia. We hypothesize that a discrete set of neuronal circuits exist that are activated by KET, but not by KET + NAL. Here, we use an unbiased, whole-brain approach to identify brain regions in which neuronal activity is selectively modulated by KET in an opioid receptor-dependent manner.

Methods: All mouse experiments were approved by the Stanford IACUC. Mice were injected with either KET (10 mg/kg i.p.) with or without pre-injection of an opioid receptor antagonist, naltrexone (NAL; 5 mg/kg i.p.) 30 min prior. Mice were perfused 90 min after injection of ketamine with 4% PFA, brains were bisected, made optically transparent with the iDISCO+ protocol, and immunolabeled for cFos to fluorescently label neurons that were active during KET exposure. Light sheet microscopy was used to acquire Z-stacks spanning each hemisphere. Using open-source software (MIRAcL[2] and Ilastik[3]), we registered images to the Allen brain atlas5, detected active cells based on sparse user input and machine learning, and quantified voxelized regional cell counts.

Results: The total number of cFos+ (active) neurons was similar in KET (114322 ± 9912 cells; N = 10) and NAL/KET hemispheres (123174 ± 11471 cells; N = 7). Counts from 486 grey matter regions were normalized to total counts. We found that NAL significantly decreased the number of cFos+ cells in layer 5 of the lateral agranular retrosplenial cortex (KET = 0.005071 ± 0.00037 vs. KET + NAL = 0.003902 ± 0.000358 cells/total brain cells; p = 0.0453) and of the ventral retrosplenial cortex (KET = 0.006853 ± 0.000421 vs. KET + NAL = 0.005622 ± 0.000303 cells/total brain cells; p = 0.0461). NAL, also suppressed activity in the adjacent posteromedial visual area (layer 5) and anteromedial visual area (layer 6a) in addition to a number of subcortical regions such as the inferior colliculus, substantia nigra pars reticulata, arcuate hypothalamic nucleus, superior olivary complex (periolivary region), pontine reticular nucleus medial vestibular nucleus, and facial motor nucleus. NAL also enhanced activity in several regions including the temporal association areas, primary somatosensory areas, intercalated amydalar nucleus, and pre/parasubthalamic nucleus.

Conclusion: Through unbiased whole-brain mapping of neurons differentially activated by SAL/KET vs NAL/KET, we identified a novel network of brain regions that may mediate some of KET's opioid receptor-dependent clinical effects. Recent data suggests that a 1-3-Hz rhythm in layer 5 neurons of the retrosplenial cortex is associated with dissociation from drugs or certain seizures[4]. Ketamine injection drives cFos expression in layer 5 neurons of the retrosplenial cortex[4] in an opioid-receptor dependent manner, suggesting a role for dissociation and opioid receptor activation in the antidepressant effect of KET. Future work will test for causal links between these structures'

activity and ketamine's efficacy in animal models of pain and depression.

References: 1) Am J Psychiatry, 175 (12), 1205-1215, 2018 2) https://github.com/mgoubran/MIRACL 3) https://github.com/ilastik 4) Nature, 586(7827):87-94, 2020

Neuroscience in Anesthesiology and Perioperative Medicine - 18 Brain wide mapping of neuronal activity evoked by MDMA, a rapid-acting therapy for post-traumatic stress disorder

Daniel Ryskamp[1], Pierre Llorach[2], Sofia Schlozman[2], Zahra Rastegar[2], Juliana S Salgado[2], Tuuli Hietamies[2], Daniel A Barbosa[2], Daniel Cardozo Pinto[2], Peter Neuman[2], Michel Hell[3], Kevin Beier[2], Robert C Malenka[2], Boris D Heifets[4]

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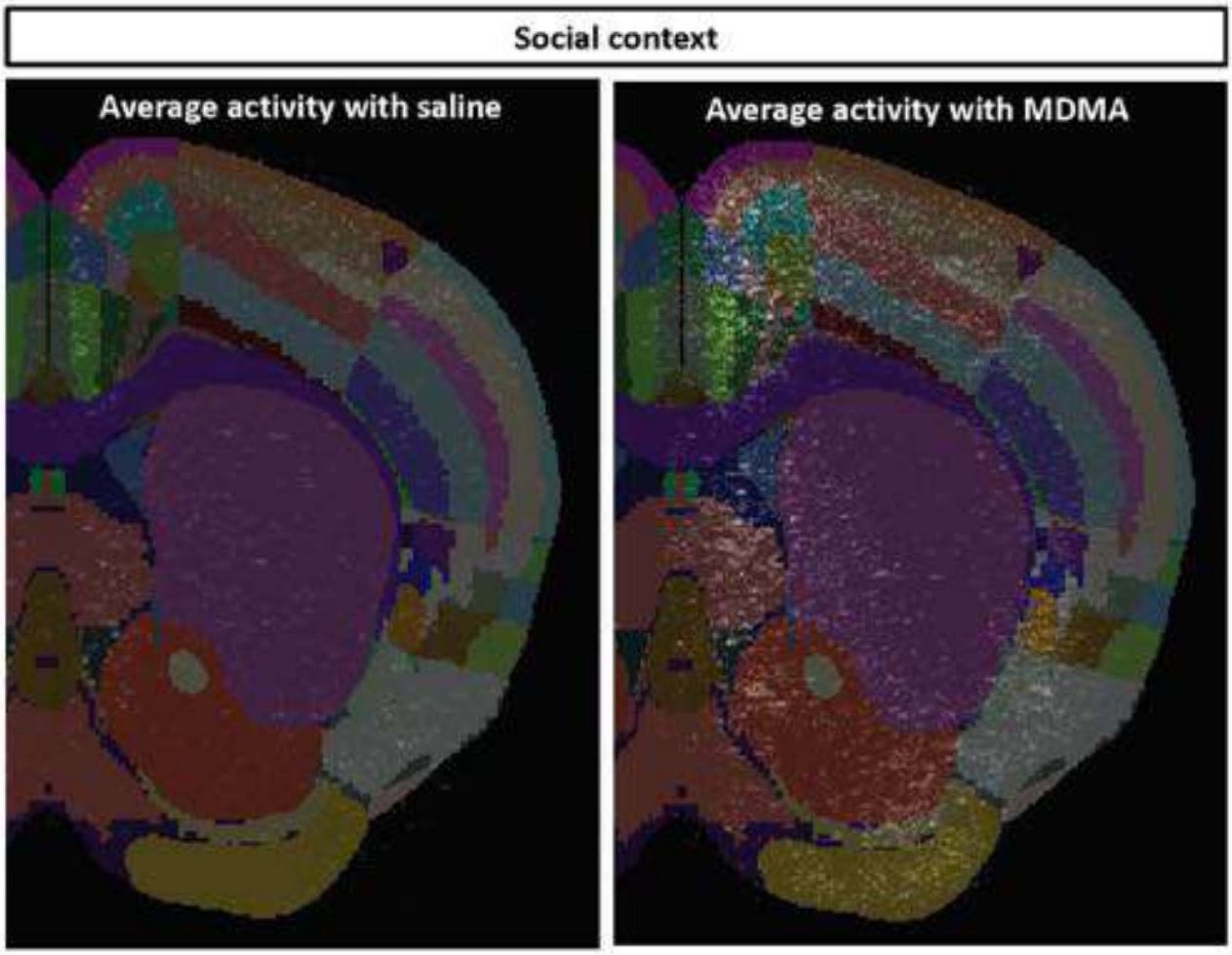
Introduction: Psychiatric diagnoses, including depression and post-traumatic stress disorder (PTSD), strongly predict poor postoperative outcomes, including chronic pain and opioid use disorder. Perioperative interventions for psychiatric risk are largely absent because available treatments have limited efficacy and are difficult to implement on a perioperative timetable. Recent evidence supports the efficacy of rapid-acting therapies in treating psychiatric diseases, with notable results from pharmacotherapy with drugs like ketamine, a well-known anesthetic, and MDMA, a substituted amphetamine. We focus here on MDMA, the recreational drug known as 'ecstasy', which has a large effect size for the treatment of PTSD. For patients with PTSD in therapy, MDMA fosters strong feelings of social connection, empathy and trust. However, MDMA has abuse potential, and long-term heavy use is associated with a host of neurological, psychiatric and cardiovascular complications. Improving on MDMA to develop a safe, rapid treatment for patients with PTSD requires an understanding of the neural circuit mechanism underlying MDMA's therapeutic effects. We have shown that a mouse model recapitulates the prosocial effects of MDMA, key to MDMA's therapeutic effect in humans. We now use an unbiased, whole-brain approach to identify brain regions in which neuronal activity is modulated by MDMA in non-social and social contexts in mice.

Methods: All mouse experiments were approved by the Stanford IACUC. Brain-wide activity, indexed by the immediate early gene Fos, was imaged for two distinct behavioral states (social and nonsocial) in each mouse by sequential use of the TRAP2 activity reporting and conventional cFos staining. TRAP2 mice (Targeted Recombination in Active Populations 2)[1] contain a genetic construct that allows the neuron firing-dependent Fos promoter to drive expression of CreER, a recombinase sensitive to 4-hydroxytamoxifen (4-OHT). TRAP2 mice were crossed to a Cre-dependent reporter line (Ai14). 4-OHT transiently enables CreER to trigger permanent expression of the fluorophore tdTomato (encoded by Ai14). To map MDMA effects in a non-social environment, TRAP2;Ai14 mice were singly housed and i.p. injected with saline or MDMA (7.5 mg/kg), along with 4-OHT (50 mg/kg). 1 day later mice were regrouped with littermates. To map prosocial effects of MDMA in the same mice, after 2 weeks mice were again injected with saline or MDMA (7.5 mg/kg). 90 minutes later mice were perfused with 4% PFA to capture expression of Fos, analogous to the tdTomato label generated by the TRAP2 technique. Brains were bisected, made optically transparent with the iDISCO+ protocol, and immunolabeled. Light sheet microscopy was used to acquire Z-stacks spanning each hemisphere. Using open source software[2,3], we registered images to the Allen brain atlas[4], detected active cells based on sparse user input and machine learning, and quantified voxelized regional cell counts. Activity maps were compared for MDMA and saline in each behavioral context (social and nonsocial).

Results: Counts from 486 grey matter regions (MDMA, N=7; saline, N=6) were normalized to total counts. MDMA significantly enhanced neuronal activity relative to saline in several pre-frontal cortical regions in both social and non-social contexts, including the prelimbic area, agranular insular areas, infralimbic area, dorsal anterior cingulate area, and orbital areas. In the social context only, MDMA enhanced activity in several areas including the nucleus accumbens, lateral amygdalar nucleus, taenia tecta, rhomboid nucleus, and intermediodorsal nucleus of the thalamus. In the non-social context only, MDMA selectively decreased activity in several regions including the pre/post subiculum, superior colliculus, red nucleus and posterior pretectal nucleus.

Conclusion: Through unbiased whole-brain mapping of neurons differentially activated by saline vs MDMA in social and non-social contexts we identified a novel network of regions that may mediate some of MDMA's prosocial effects. Future work will test for causal links between these structures' activity and MDMA's effects on mouse sociability and relief from traumatic experiences. Characterizing circuits that are selectively modulated by MDMA in a social context may yield novel targets for noninvasive brain stimulation therapy and safe, rapid treatment for PTSD.

References: 1) Science, 357 (6356), 1149-1155, 2017 2) https://github.com/mgoubran/MIRACL 3) https://github.com/ilastik 4) https://mouse.brain-map.org/



Neuroscience in Anesthesiology and Perioperative Medicine - 19

Pharmacological restoration of anti-nociceptive functions in the rat prefrontal cortex relieves chronic pain

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Introduction: Chronic pain affects one in four adults, and effective non-sedating and non-addictive treatments are urgently needed. Pain is known to trigger responses in neurons of the cerebral cortex, and these neuronal responses in turn determine how pain is processed and regulated at the behavioral level. Meanwhile, chronic pain can alter synapses and circuits in the cortex, resulting in abnormalities in pain perception. In particular, the prelimbic prefrontal cortex (PL-PFC) has been shown to play an important role in the top-down regulation of sensory inputs. Therefore, this cortical region may form an important therapeutic target for chronic pain. To date, however, few studies have examined pharmacological agents that could target maladaptive changes in the PL-PFC to regulate chronic pain. AMPAkines are a class of compounds that are able to enhance glutamate transmission in a use-dependent manner by binding to an allosteric site on the AMPA (Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor. Emerging data from animal studies suggest that AMPAkines can relieve symptoms of acute incisional and inflammatory pain. However, cortical mechanisms for the anti-nociceptive effects of AMPAkines remain unknown. In this study, we investigated the impact of AMPAkines on the anti-nociceptive function of neurons in the PL-PFC in a well-known neuropathic pain model.

Methods: Silicon probes were implanted in the PL-PFC for in vivo recording of neuronal spike activities in response to peripheral noxious (pin prick) or non-noxious (vF filaments) stimuli from freely moving Sprague-Dawley rats. The impact of chronic neuropathic pain induced by a spared nerve injury (SNI) model was evaluated by basal and peak firing rates extracted from each individual neuron's perievent time histograms. Then we studied how the PL-PFC neuronal abnormality in the chronic pain state was rescued by system administration of a well-established AMPAkine (CX546). In addition, we compared the chronic pain relief effects between system and intracranial administration of CX546 through mechanical allodynia and cold allodynia tests. Furthermore, optogenetic and pharmacological modulations of the PL-PFC neurons were used to verify whether CX546 could target AMPA receptors in the PL-PFC to relieve pain. During the mechanical allodynia and cold allodynia tests, we interfered PL-PFC through either shining yellow light on the halorhodopsin expressed pyramidal neurons or injecting AMPA receptor antagonist (NBQX) intracranially into the PL-PFC. For unpaired data, a Mann Whitney test was used. For paired data, a Wilcoxon matched-pairs signed rank test was used. For all tests, a p value < 0.05 was considered statistically significant.

Results: The authors found that neurons in the PL-PFC increase their firing rates in response to noxious stimulations; chronic pain, however, suppresses this cortical pain response. CX546, meanwhile, restores the anti-nociceptive response in PL-PFC neurons to reduce chronic pain. Furthermore, the authors found that optogenetic inactivation of the pyramidal neurons in the PL-PFC as well as direct administration of AMPA receptor antagonists in the PL-PFC blocked anti-nociceptive effects of CX546.

Conclusion: In this study, we have shown that pyramidal neurons in the PL-PFC increase their firing rates in response to noxious stimulations and that chronic pain suppresses these nociceptive responses. AMPAkines, however, can restore anti-nociceptive regulatory function of neurons in the PL-PFC to deliver analgesic effects in chronic pain states. A combination of analgesic and respiratory-stimulating properties makes AMPAkines an intriguing treatment choice for persistent neuropathic pain. More generally, our results indicate that drugs targeting the endogenous cortical pain-regulatory system are likely to have important roles in the treatment of chronic pain.

Neuroscience in Anesthesiology and Perioperative Medicine - 20

Neuroinflammation in a Mouse Model of Delirium Superimposed on Parkinson's Disease

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Introduction: Millions of Americans live with neurodegenerative conditions including Parkinson's disease (PD) and routinely require surgical interventions, such as orthopedic surgery. These potentially life-saving procedures often increase the risk for postoperative cognitive complications, like delirium, which in many cases associated with a worse prognosis and even death. Currently, no study has attempted to model the effects of surgery on the PD-vulnerable brain.

Methods: We used a well-established familial PD mouse model leucine-rich repeat kinase 2 (LRRK2) G2019S, the most prevalent kinase gain-of-function mutation, and subjected mice to orthopedic surgery under isoflurane anesthesia and analgesia. LRRK2 (Het) at 6 and 12-months of age, both male and female, were assessed for glial activation and changes in PD pathology 24 hr after surgery.

Results: Surgery induced a robust neuroinflammatory response in the hippocampus, evidenced by changes in Iba-1 immunoreactivity and CD68 expression within Iba-1-positive cells both in 6 and 12-month-old LRRK2 (males and females) after surgery. Microglial activation was accompanied by changes in astrocytes/GFAP expression and AQP-4, suggesting a dysfunction in the neurovascular unit in these mice. These changes were not limited to the hippocampus but were also observed in the prefrontal cortex.

Conclusion: Together, these findings suggest that mice with pre-existing PD pathology are more vulnerable to postoperative neuroinflammation and neurovascular dysfunction, which may drive delirium onset. Future work will define whether surgery alters PD-pathological hallmarks phospho-tau/α-synuclein and the behavioral effects of delirium-like behavior.

This work is funded by the 2020 NIDUS Pilot Award to RV.

Neuroscience in Anesthesiology and Perioperative Medicine - 21 Trek channels do not affect volatile anesthetic sensitivity in mice

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Introduction: The Trek channels, members of the two-pore domain K+ (K2P) channel family, contribute to background or "leak" potassium currents and are important for maintaining the resting membrane potential in neurons. Electrophysiological experiments have established that volatile anesthetics activate both Trek-1 and Trek-2, while behavioral experiments have suggested that Trek-1-/- mice are resistant to volatile anesthetics (VAs) (1-3). However, this resistance was measured by evaluating emergence following exposure to a high dose of anesthetic, rather than averaging induction and emergence values to determine the EC50 as established by Sonner and colleagues (4). Here we evaluated both induction and emergence from VAs in mice deficient in Trek-1 (Trek-1-/-) as well as mice missing all three Trek channels (Trek-1-/-, Trek-2-/-, Traak-/-) to determine whether knocking-out these channels confers resistance to VAs and ultimately whether these channels contribute to a molecular mechanism underlying VA activity.

Methods: All experiments were approved by the Institutional Animal Care and Use Committee of Seattle Children's Research Institute. Response to a non-damaging tail clamp was measured during exposure to each halothane and isoflurane. Measurements were made in Trek-1-/- as well as mice missing all three Trek channels (Trek-1-/-, Trek-2-/-, and Traak-/-), and were compared to C57Bl6, wild-type or heterozygous siblings (N ≥ 8/genotype). Genotype was confirmed by PCR and qRT-PCR. Animals were exposed to increasing or decreasing concentrations of the VA in steps of 0.2% with 10-minute incubation periods. Induction and emergence measurements reflect the mean of the concentrations bracketing the response and lack response to the tail clamp. Emergence was measured in one of two ways. The first, by decreasing anesthetic concentration directly following induction measurements. The EC50 for these animals was determined by averaging the induction and emergence measurements. The second method for measuring emergence, was to expose animals to a high dose of anesthetic and decrease anesthetic concentration until the animal responded to the tail clamp. No induction data was collected for these mice. Data was evaluated for normality with the Shapiro Wilk test and compared using one-way ANOVA and Dunnett's multiple comparisons test.

Results: Compared to wild type or heterozygous controls (EC50(H); 1.19%, N=18: EC50(I); 1.22%, N=18) we found no resistance to halothane or isoflurane in either Trek-1-/- (EC50(H); 1.18%, N=10; p=0.984: EC50(I); 1.11%, N=9; p=0.134) or Trek-1-/-, Trek-2-/-,Traak-/- (EC50(H); 1.22%, N=12; p=0.6469: EC50(I); 1.25%, N=12; p=0.816) mice. Neither induction nor emergence values were significantly different in KO mice compared to controls, and there was no significant difference in EC50 values. Furthermore, we failed to replicate the resistance to VAs observed in Trek-1-/- mice following exposure to a high dose of VA (not shown).

Conclusion: We find that knocking-out Trek channels in mice has no significant impact on the tail-clamp response to VAs. While we corroborated earlier evidence (1,2) that that these channels are activated by VAs, our data suggest that this activation does not change sensitivity for response to a painful stimulus during VA exposure. Overall, this indicates it is unlikely these channels play a central role in the primary molecular mechanism underlying VA activity.

Work supported by grants: Anesthesiology & Perioperative Medicine Research Training NIH-GM086270 and A Mouse Model Linking Anesthetic Sensitivity to Mitochondrial Function NIH-GM105696

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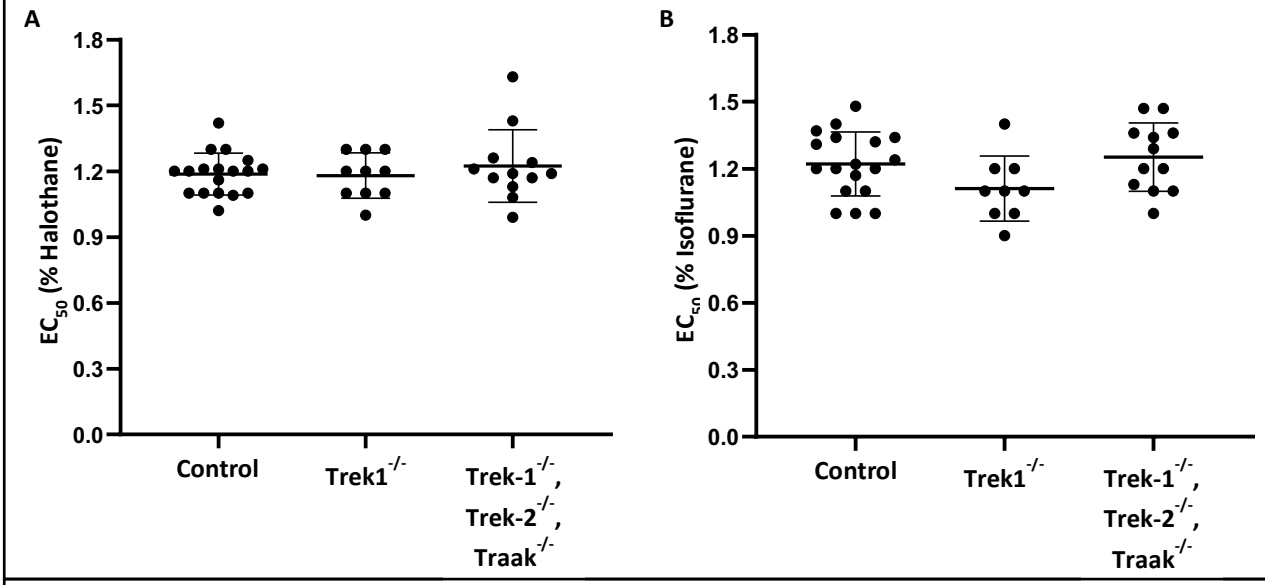

Figure 1. The EC_{50} for Halothane and Isoflurane do not change in Trek KO mice. Graphs show A) EC_{50} for Halothane (H) and B) EC_{50} for Isoflurane (I). Line indicates EC_{50} , error bars = ±SD. Wild type or heterozygous controls, N=18 (H), N=18 (I); Trek-$1^{-/-}$ N=10 (H) p=0.984, N=9 p=0.134 (I); Trek-$1^{-/-}$, Trek-$2^{-/-}$,Traak$^{-/-}$ N=12 (H) p=0.6469, N=12 (I) p=0.816. Comparisons made with ANOVA and Dunnett's multiple comparisons test.

Neuroscience in Anesthesiology and Perioperative Medicine - 22 Ketamine Response of Rat Cortical Mechanisms in Pain Aversion

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Introduction: Chronic pain is known to enhance aversive behavior towards peripheral acute nociceptive stimuli. This response is evident in patients with chronic pain syndromes such as fibromyalgia or persistent postoperative pain. However, there is a lack of understanding of the neural mechanisms that are involved in this enhanced aversion, hampering the development of novel analgesics. The rat prelimbic prefrontal cortex (PL-PFC), an analog to the human dorsolateral PFC, has been shown to undergo structural and activity alterations during chronic pain conditions. Ketamine is a well-known pharmacological agent used to reduce the aversive component of pain, and it has been shown to alter cortical plasticity to selectively regulate the aversive response to peripheral nociceptive inputs. Ketamine has also been shown to reshape synaptic activities in the PL-PFC under conditions of chronic stress. However, it is not yet understood whether ketamine could specifically alter PL-PFC functions in chronic pain conditions.

Methods: Neural activity in the PL-PFC is measured by calcium imaging in freely-behaving rats in response to either a noxious or non-noxious peripheral stimulus. After data processing and motion correction, cells are extracted and classified to produce output cell contours and activity traces through a constrained non-negative matrix factorization for endoscopic data. Afterward, neurons are registered across recording sessions based on their contours and spatial footprints. Furthermore, to identify functionally specific neurons corresponding to changes in calcium activity, the z-scored average activity of 0-5 seconds post stimulus with 200 ms bins and a 2 s moving window is then compared to 2 s baseline activity pre stimulus using a ranksum test. To understand neural changes in response to persistent pain and to ketamine analgesia, we perform a series of calcium imaging recordings in the PL-PFC. First, a baseline recording is performed in freely moving rats, before and after a noxious or non-noxious acute peripheral stimulus in the paw contralateral to the gradient index (GRIN) lens implant. Next, the rat receives a Complete Freund's Adjuvant (CFA) injection to induce chronic inflammatory pain. We then perform another calcium imaging recording after CFA injection to assess how persistent pain alters acute nociceptive processing. Following the recording, we administer ketamine or saline to these rats. Finally, two days after the ketamine or saline injection, we repeat calcium imaging recordings to understand how ketamine alters cortical activity in the chronic pain state.

In addition to neural recordings, pain aversion behavior is studied through a conditioned place aversion assay. The rat first moves freely between two chambers during a preconditioning phase. Next, during the conditioning stage, one chamber is paired with a noxious stimulus, whereas the opposite chamber is not paired with any stimulus. During the testing phase, the rat is again allowed to move freely between the chambers, without additional stimuli. Avoidance of the stimulus-paired chamber indicates an aversive association. Differences in times within each chamber is compared using a Student's t-test.

Results: In the naïve condition, neurons in the PL-PFC demonstrate an increase in calcium activity, indicative of increased neural activity, in response to an acute noxious stimulus. However, this neural response to noxious inputs is suppressed by the presence of chronic pain. A single dose of ketamine, meanwhile, restores the endogenous nociceptive response in neurons in the PL-PFC. These changes in neural activity are reflected in changes in pain aversive behavior as well. We show that while chronic pain enhances the aversive response to acute noxious stimuli, ketamine inhibits this enhanced pain aversion. Furthermore, inhibition of the PL-PFC removes this anti-aversive effect of ketamine, whereas direct blockade of NMDA receptors in the PL-PFC achieves similar anti-aversive effects as ketamine.

Conclusion: These results indicate that ketamine targets neurons in the PL-PFC to reduce the affective symptoms of chronic pain.

Neuroscience in Anesthesiology and Perioperative Medicine - 23 Resting calcium concentrations and action potential-driven fluxes in the endoplasmic reticulum are modulated by extracellular calcium in hippocampal neurons of rats

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Introduction: The endoplasmic reticulum (ER) forms a tubular network that extends throughout neurons and their axons and serves as an intracellular calcium (Ca2+) store with profound influence on neuronal and synaptic function.1,2 At rest, cytosolic Ca2+ ([Ca2+]cyto)is influenced in part by the balance of Ca2+ fluxes into (via the sarco(endo)plasmic reticulum ATPase (SERCA)) and out of (via ryanodine receptors and IP3 receptors) the ER. During action potential (AP) firing, Ca2+ influx across the plasma membrane, that increases [Ca2+]cyto, can in principle enhance Ca2+ flux across both into and out of the ER since both SERCAs and RyRs are activated by Ca2+. To investigate how the concentration of Ca2+ in the ER lumen ([Ca2+]ER) is controlled, we utilized genetically-encoded Ca2+ indicators targeted to the ER and cytosol both at rest and during (AP)-driven fluxes at different external Ca2+ concentrations ([Ca2+]e). Our data show that the ([Ca2+]ER) in axons shows a steep dependence on changes in [Ca2+]cyto and always favors a net Ca2+ uptake rather than release from this store.

Methods: Protocols were approved by the Weill Cornell Medicine IACUC. Hippocampi from P0-1 Sprague-Dawley rats of both sexes were dissected, digested, dissociated, and plated onto coverslips coated with poly-O-ornithine. ER-Halo-GCaMP6-150, synaptophysin-GCaMP6f, and mRuby-synapsin were transfected on DIV 6-8 with Ca2+ phosphate-mediated gene transfer. Experiments were performed on DIV 14-21. For ratiometric ER Ca2+ imaging, JaneliaFluor (jF)-635 was loaded onto cells at a final concentration of 500 nM in the incubator for 30 min, followed by washing for ≥30 min in media. Coverslips were loaded onto a custom perfusion and stimulation chamber, perfused with Tyrode's solution buffered to pH 7.4 at 100 µL min-1, maintained at 37°C with an objective heater, and imaged with a custom-built, laser-illuminated epifluorescence microscope and Andor iXon+ EMCCD. Solutions with different Ca2+ concentrations (in mM: 0.8, 1.2, and 2.0, with changes in divalence offset by adjusting magnesium concentrations) were perfused for 5 min prior to stimulating with a train of 1 ms field depolarizations to elicit APs. Ionomycin 500 µM was washed in buffer with 4 mM Ca2+ and pH 6.9 at the end of experiments with GCaMP6f to convert fluorescence to absolute Ca2+ concentrations using the in vitro properties of the indicator.2 ImageJ was used for image analysis, and statistical analysis was performed in Prism v8. Comparisons of groups were analyzed with repeated-measures one-way ANOVA and Tukey's post-test, with significance defined as $p < 0.05$.

Results: [Ca2+]ER was measured with a novel ratiometric, ER-targeted, genetically-encoded Ca2+ indicator, GCaMP6-150 fused to HaloTag and labeled with the far-red fluorescent dye, jF-635 (Figure 1, A-H). Decreasing [Ca2+]e (in mM) from 2.0 to 1.2 caused a decrease in [Ca2+]ER, but there was no change in resting [Ca2+]ER due to a change from 1.2 to 0.8 (Figure 1, I and K). However, net influx of Ca2+ into the ER due to a brief AP train was not significantly different between 1.2 and 2.0 [Ca2+]e, but influx was lowered at 0.8 [Ca2+]e (Figure 1, I and J). [Ca2+]cyto was measured at different extracellular Ca2+ concentrations with synaptophysin-GCaMP6f, which is targeted to presynaptic nerve terminals (Figure 2A). Changing [Ca2+]e minimally affected resting [Ca2+]cyto (Figure 2, B and C) but potently modulated influx caused by a brief AP train (Figure 2, B and D). Comparison of resting and AP-driven [Ca2+]cyto and [Ca2+]ER reveals that resting [Ca2+]ER increased disproportionately at 2.0 mM [Ca2+]e (Figure 3A), while ER Ca2+ influx was significantly inhibited at 0.8 versus 1.2 mM [Ca2+]e despite similar Ca2+ influx (Figure 3B).

Conclusion: Resting [Ca2+]ER is modulated by [Ca2+]e while cytosolic levels are minimally affected. AP-driven Ca2+ uptake by the ER is also sensitive to [Ca2+]e independent of cytosolic changes. Although cytosolic influx was similar between 0.8 and 1.2 mM [Ca2+]e, ER Ca2+ uptake was significantly lowered at 0.8 and to a greater degree than the relative change from 2.0 to 1.2 mM [Ca2+]e despite similar resting [Ca2+]ER. These findings suggest that decreasing [Ca2+]e below the physiologic level of 1.2 mM impairs the ability of the ER to uptake Ca2+.

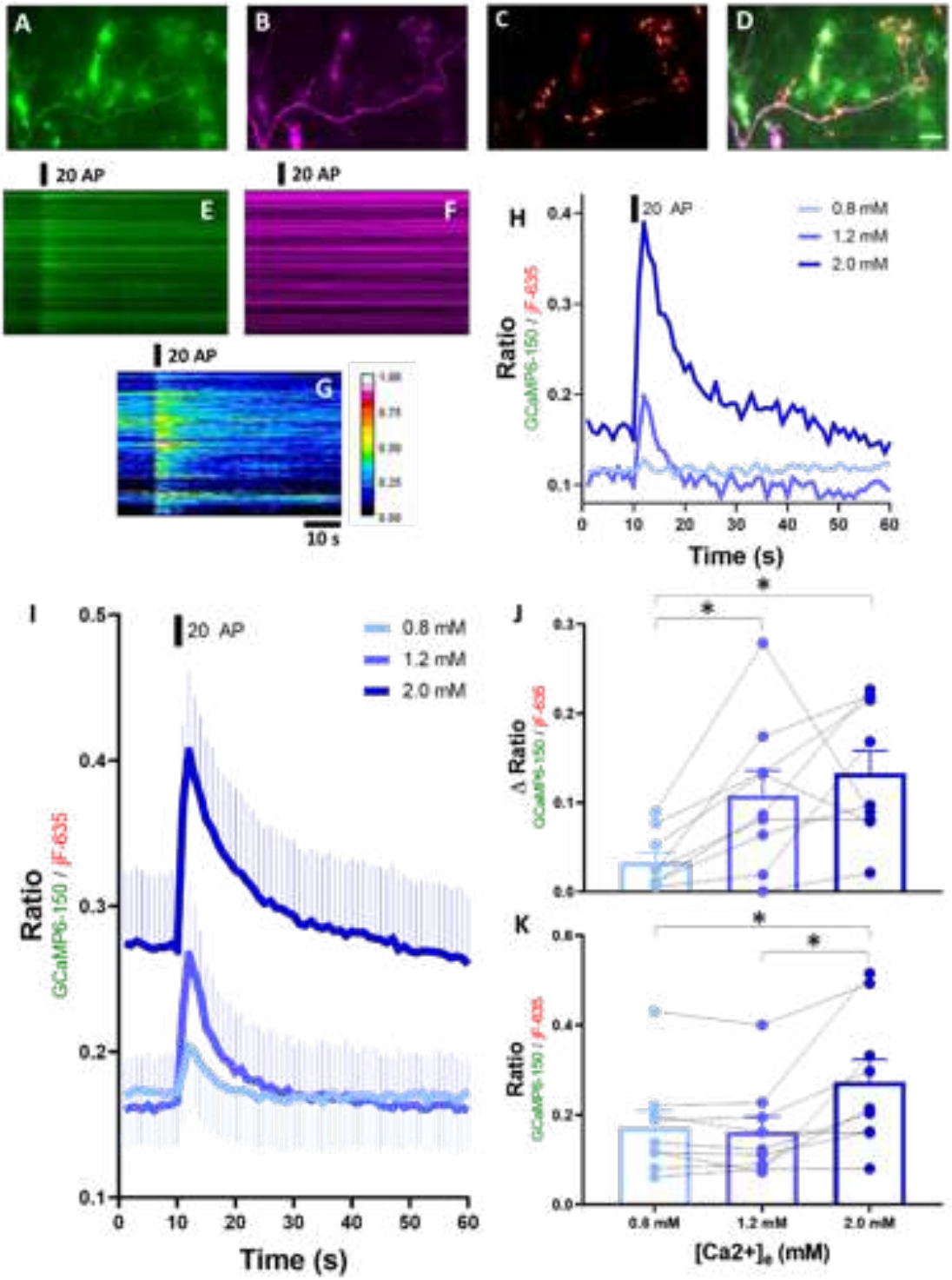

Figure 1. Resting and action potential-driven flux of Ca^{2+} in the endoplasmic reticulum is responsive to extracellular Ca^{2+} concentrations. (A-D) Neuronal ER Ca^{2+} was measured with a low-affinity, genetically-encoded Ca^{2+} indicator, GCaMP6-150 (A), fused to HaloTag, allowing covalent binding of the fluorogenic dye jF-635 (B). This construct is targeted to the ER and enables ratiometric imaging of ER Ca^{2+}. Co-expression of mRuby-synapsin identifies presynaptic nerve terminals (C, merged D, scale bar = 20 µm). (E-G) Kymographs showing fluorescence intensity along the length of the axon of the neuron shown above. A brief action potential (AP) train (20 AP in 1 s) causes an increase in fluorescence intensity due to a net uptake of Ca^{2+} in the ER (E). Fluorescence is converted into a ratiometric ratio representing ER Ca^{2+} levels (G) by comparing to jF-635 (F). (H) The 20 AP stimulus was performed in different

extracellular Ca^{2+} concentrations (in mM): 0.8, 1.2, and 2.0. (I) Mean ER Ca^{2+} responses at different extracellular Ca^{2+} concentrations (n = 9 neurons; error bars are SEM). (J,K) Summary of resting ER Ca^{2+} ratio (J) and change in ER Ca^{2+} ratio (K) following 20 AP stimulus (n = 9, one-way ANOVA with Tukey's post-test, * $p < 0.05$, comparisons not shown were not statistically significant).

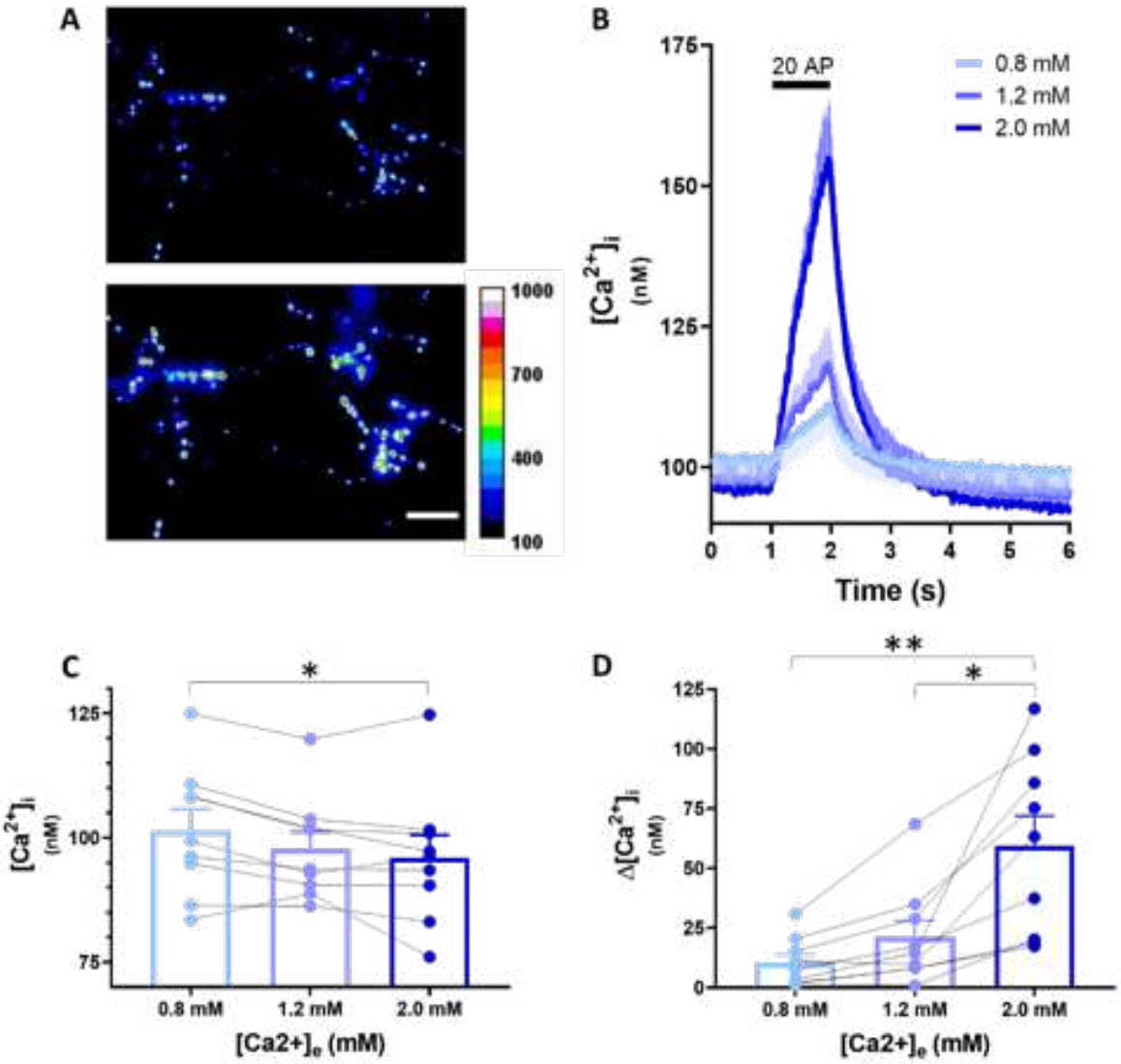

Figure 2. Extracellular Ca^{2+} concentration minimally affects resting cytosolic Ca^{2+} but potently controls stimulated influx. (A) Presynaptic cytosolic Ca^{2+} was measured with synaptophysin-GCaMP6f, a genetically-encoded Ca^{2+} indicator localized to nerve terminals (top, prestimulus; bottom, peak of stimulus with 20 AP; scale bar = 20 µm; calibration bar in arbitrary fluorescence units). (B) Mean cytosolic Ca^{2+} concentrations with 20 AP train performed at different extracellular Ca^{2+} concentrations (in mM): 0.8, 1.2, and 2.0 (n = 9 neurons, error bars are SEM). (C-D) Resting (C) and change in Ca^{2+} with 20 AP (n = 9, one-way ANOVA with Tukey's post-test, * $p < 0.05$, ** $p < 0.01$, comparisons not shown were not statistically significant).

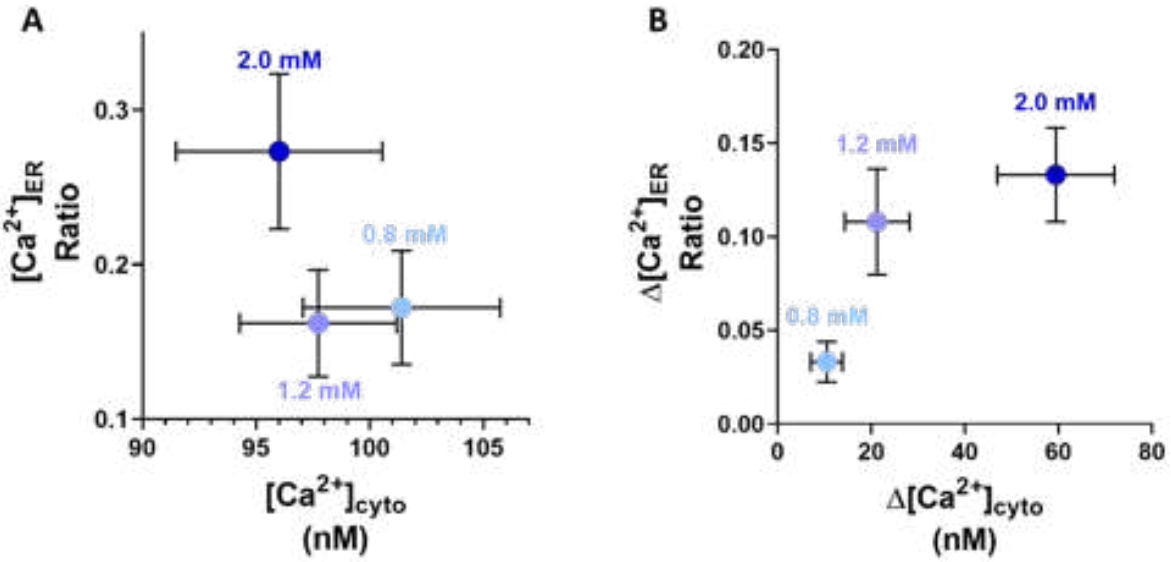

Figure 3. Comparison of resting and AP-driven fluxes of ER and cytosolic Ca^{2+}. (A) Resting ER Ca^{2+} ratio is compared to cytosolic Ca^{2+} at different extracellular Ca^{2+} concentrations (data from Figures 1 and 2). (B) Net change due to 20 AP train of ER Ca^{2+} ratio and cytosolic Ca^{2+} concentrations at different extracellular Ca^{2+} concentrations (data from Figures 1 and 2).

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Hippocampal engrams recapitulate contextual memory formation, its suppression by etomidate, and its persistence in mice lacking α5-$GABA_A$ receptors in interneurons

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Introduction: Hippocampal "place cells" were discovered 50 years ago,[1] and they remain one of the most interesting and intensely studied neuronal correlates of behavior. Place cells fire preferentially when animals traverse specific locations, and their combined activities permit an accurate reconstruction of the animal's position in space. They become reactivated when the animal re-enters the same environment, forming an 'engram' that remains stable for long periods of time (weeks). These same cells undergo 'remapping' when the animal enters a new environment. Studies of place cells have thus provided strong evidence that the hippocampus encodes a cognitive map, with the engram representing the memory of a specific environment.[2] In the present study we sought to capture engram formation using a genetically-encoded calcium sensor and a new optical recording methodology that permits the simultaneous recording of activity in several hundred cells.[3] We examined what an amnestic dose of etomidate does to engram formation and stability, and how engram formation persists under etomidate when α5-$GABA_A$Rs that serve as its amnestic target are eliminated.

Methods: With institutional IACUC approval, a virus encoding the fluorescent calcium binding protein GCaMP6f under the control of the CaMKIIa promoter was injected into the dorsal hippocampus of wild type (WT) mice and mice lacking α5-GABAARs in interneurons (α5-GABAAR-interneuron knockout; α5-i-KO). Two to three weeks later a baseplate with integrated GRIN lens was implanted over the hippocampus, enabling attachment of a miniature endoscopic camera (Inscopix nVoke) that was used to capture the activity of underlying CA1 pyramidal neurons. Optical recordings of cellular activity were performed in an arena that permitted simultaneous capture of the mouse's position using Noldus Ethovision. Recording sessions lasting 10-minutes were performed twice weekly with two sessions per day separated by four hours (a.m. and p.m.). New sets of visual, tactile, and odor cues were used each day to create new contexts, in order to test for memory encoding and recall. Fluorescence image processing was performed using an integrated software system (IDPS, Inscopix). Registration of spatial location with cell firing, further characterization of place cell properties, and statistical analysis were performed using custom-written MATLAB routines.

Results: In both WT and α5-i-KO mice, transient fluorescent activity was observed in up to 364 cells within a single field of view when mice were placed in the recording arena. Approximately one quarter to one third of these cells exhibited place-specific firing, as determined by the mutual information between spatial location and firing rate. Place fields became apparent several minutes into the session, grew in number and intensity over the first five minutes, and were stable for the remainder of the 10-minute session. When mice were placed back into the same arena four hours later, these same cells exhibited similar patterns of spatially modulated firing, demonstrating that they had formed stable engrams that could be recalled. The similarity between a.m. and p.m. sessions was quantified by the population vector (PV) correlation between position-specific firing rate maps. Administration of etomidate 2-10 mg/kg IP to WT mice 30 minutes prior to the a.m. session resulted in dose-dependent reductions in both place cell formation during the a.m. session and PV correlations between a.m. and p.m. sessions, with complete loss of significant PV correlation at 7 mg/kg. By contrast, α5-i-KO mice injected with 7 mg/kg etomidate formed place cells during the a.m. session, and they retained a high PV correlation between a.m. and p.m. sessions, indicating that they had successfully formed stable engrams despite the administration of etomidate.

Conclusion: These results demonstrate that engram formation in the hippocampus can serve as a measure of contextual memory formation or its impairment by amnestic agents. In addition, the correspondence between these results and the behavioral measure of memory presented in a companion abstract further strengthens the conclusion that α5-$GABA_A$ receptors on interneurons serve as a target for etomidate-induced amnesia. This model of 'conscious amnesia' will enable further mechanistic studies using precise

genetic targeting and control of cellular activity via optogenetic and pharmacogenetic means.

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Neuroscience in Anesthesiology and Perioperative Medicine - 25 Etomidate-induced amnesia is mediated by α5-$GABA_A$ receptors located on inhibitory interneurons

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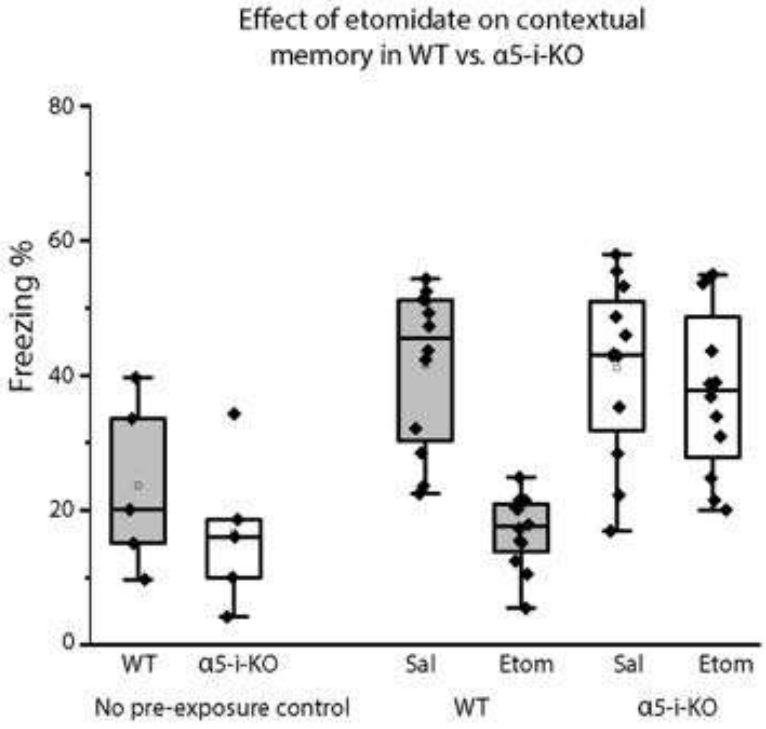
Introduction: Suppression of memory is one of the primary goals of general anesthesia. In studies of the underlying mechanism, etomidate has proved exceptionally useful because it is highly selective for $GABA_A$ receptors, its physicochemical properties make it amenable to use both in vivo and in vitro, and it potently blocks memory formation. Previous investigations showed that etomidate blocks both long term potentiation of excitatory synapses (LTP – a cellular model of memory) and contextual memory (a surrogate for episodic memory) by targeting $GABA_A$Rs that incorporate α5 subunits (α5-$GABA_A$Rs).[1,2] These receptors are concentrated in the hippocampus and are located primarily on pyramidal neurons. We reported recently, however, that selectively eliminating α5-$GABA_A$Rs from hippocampal pyramidal neurons did not interfere with etomidate's ability to suppress LTP in vitro,[3] suggesting thatα5-$GABA_A$Rs on non-pyramidal cells might be instrumental in etomidate-induced amnesia. Here, we tested this hypothesis by selectively eliminating α5-$GABA_A$Rs from inhibitory interneurons and measuring etomidate suppression of contextual memory.

Methods: With institutional IACUC approval, experiments were performed using α5-$GABA_A$R-interneuron knockout (α5-i-KO) mice. α5-$GABA_A$Rs were selectively eliminated from interneurons by crossing mice carrying a 'floxed' Gabra5 gene with mice expressing cre-recombinase under the control of the Gad2 promoter. To test the ability of etomidate to interfere with hippocampus-dependent contextual memory formation, we used the Context Pre-exposure Facilitation Effect (CPFE) paradigm.[4] On day 1, wild type (WT) or α5-i-KO mice were administered saline or etomidate 7 mg/kg IP, and 30 minutes later they were placed in an experimental chamber containing visual and tactile cues. They remained there for 10 minutes to allow them time to form a memory of the context. They were placed back in that context on day 2, and after a delay of 15 seconds (to allow them to recall the context) they were administered a 2-second 1.0 mA foot-shock, then removed after 30 seconds. On day 3 they were placed in the same context, and the amount of time they spent 'freezing' (a rodent expression of fear) over the first three minutes was used as a measure of the memory for context they had formed on day 1. Mice that had not been pre-exposed on day 1 served as controls. Anxiety was assessed using the elevated plus maze (EPM) test. Sedation was assessed by measuring the time spent exploring during the 10-minute pre-exposure session. Results are presented as mean±sem. Statistical comparisons were performed using Student's t-test.

Results: No-pre-exposure control mice had low freezing scores (no-pre-ctrl: WT 23±5%, α5-i-KO 17±5%, n=5 each), demonstrating the 'immediate shock deficit' described previously.[5] Both WT and α5-i-KO mice injected with saline displayed significantly higher freezing scores (WT-sal 41± 3 %, α5-i-KO-sal 41±4 %, n=12 each, $p<0.01$ vs. no-pre-ctrl), at levels not different from each other ($p=0.5$), demonstrating that the pre-exposure resulted in contextual memory formation, and that eliminating α5-$GABA_A$Rs from interneurons did not itself interfere with memory. Administration of etomidate significantly reduced freezing scores in WT mice (α5-i-KO-sal 17±2%, n=12, $p=0.01$ vs. WT-sal) but not in α5-i-KO mice (α5-i-KO-sal 37±4%, n=12, $p=0.47$ vs. WT-sal). The two genotypes did not display different levels of anxiety (EPM open arm time: WT 13±4%, α5-i-KO 30±8%, n=6, $p = 0.09$), and etomidate-induced sedation did not differ between genotypes (day 1 exploration: WT 9.7±2%, α5-i-KO 9.5±2%, n=12 each, $p=0.9$).

Conclusion: Etomidate impaired contextual memory formation in WT mice but not in mice lacking α5-$GABA_A$Rs in interneurons, supporting the hypothesis that α5-$GABA_A$Rs on interneurons are instrumental in producing this essential endpoint of anesthesia. Which of the many subtypes of interneurons are involved, and whether other anesthetics share this mechanism, are interesting unanswered questions.

References: 1. J. Neurosci. 26, 3713-3720 (2006) 2. Anesthesiology 111, 1025-1035 (2009) 3. J. Neurosci. 35, 9707-9716 (2015) 4. J Neurosci. 24, 2431-2439 (2004) 5. Anim. Learn. Behav. 18, 364-270 (1990)


Effect of etomidate on contextual memory in WT vs. α5-i-KO
Freezing %
80
60
40
20
0
WT
α5-i-KO
Sal
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Sal
Etom
No pre-exposure control
WT
α5-i-KO

Obesity

Obesity - 1 The benefits of transversus abdominis plane (TAP) block in bariatric surgery: a systematic review and meta-analysis

Chenchen Tian[1], Yung Lee[2], Yvgeniy Oparin[2], Dennis Hong[2], Harsha Shanthanna[2]

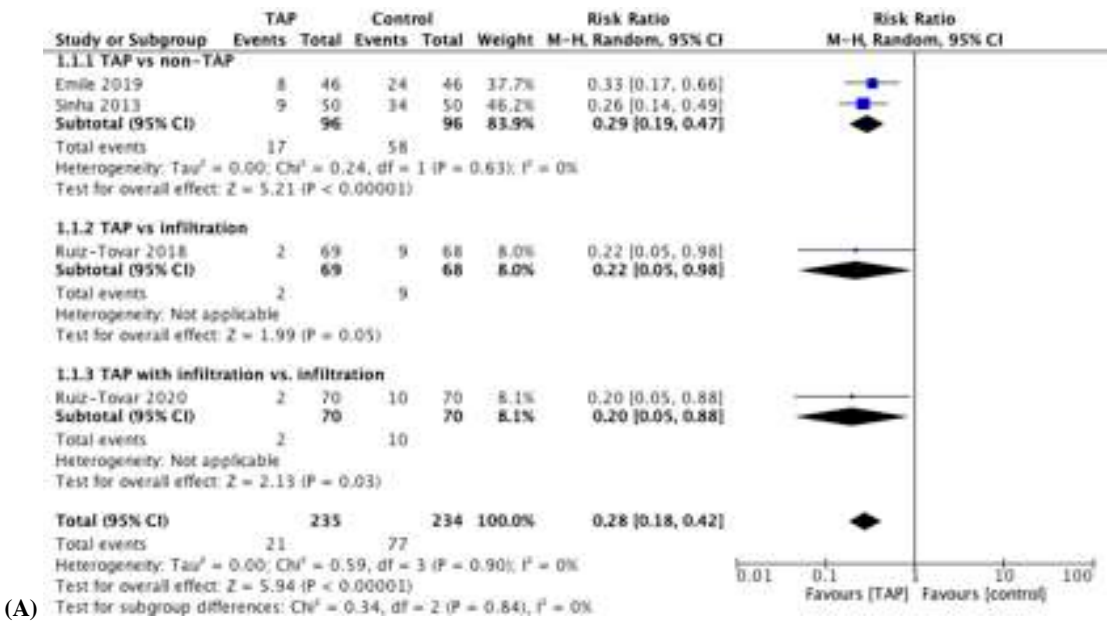
[1]University of Toronto, Toronto, Canada, [2]McMaster University, Hamilton, Canada

Introduction: Patients undergoing bariatric surgery are at increased risk of having poorly controlled postoperative pain with analgesic challenges, including the increased prevalence of obstructive sleep apnea and associated opioid-induced respiratory depression. The transversus abdominis plane (TAP) block has demonstrated to be a safe and effective procedure at reducing postoperative pain and opioid consumption for a variety of abdominal surgeries. We aimed to determine the benefits of TAP block on postoperative analgesia and recovery in bariatric surgery through a systematic review and meta-analysis of randomized controlled trials (RCTs) and non-randomized studies.

Methods: A comprehensive search was conducted within MEDLINE, EMBASE, and CENTRAL databases from inception to April 2020 for studies using TAP block in bariatric surgeries on postoperative outcomes. Outcomes were pooled using random effects model and reported as relative risks (RR) or mean differences (MD) with 95% confidence intervals (CIs). We adhered to PRISMA reporting guidelines. Two investigators independently extracted data. Effect estimates were pooled using random-effect meta-analysis. Certainty of evidence was rated using the GRADE framework. Primary outcomes included postoperative pain scores, opioid consumption, and recovery related outcomes (e.g. length of stay, time to ambulation). We hypothesized that TAP block would be beneficial to these outcomes in promoting postoperative recovery measures.

Results: Twenty-one studies (15 RCTs [n=1410] and six non-randomized studies [n=1959]) were included. Among RCTs, the TAP block group required fewer opioid rescues (RR 0.28; 95% CI 0.18 to 0.42, P<0.001; figure 1A) (moderate quality); reduced total opioid use over 24 hours (MD –8.33; 95% CI –14.78 to –1.89, P=0.01; figure 1B); significantly lower pain scores at 6 hours (MD –1.52; 95% CI –1.90 to –1.13, P<0.01; figure 2A) and 12 hours (MD –0.95; 95% CI –1.34 to –0.56, P<0.001; figure 2B) on a 0-10 pain scale (moderate quality); and decreased time to ambulation (MD –1.12 hours; 95% CI –1.50 to –0.73, P<0.001; figure 3) (high quality). No difference was observed for nausea and vomiting or hospital length of stay. Meta-analyzed outcomes from observational studies supported these results, suggesting decreased postoperative pain and opioid consumption.

Conclusion: The present study suggests that performing the TAP block in bariatric surgery is safe and effective in reducing postoperative opioid requirements and lowering pain scores up to 24h after surgery, while reducing time to ambulation, with moderate to high certainty of evidence. Limitations we observed included that studies varied with respect to type of surgeries and components of comparator multimodal analgesia, contributing to heterogeneity and operative differences (five laparoscopic ports for LSG and six for LRYGB, operative time), leading to variation in visceral pain. Lastly, there was significant variation of TAP block technique across all studies. Taken together, these findings are of particular importance in the bariatric population who are at increased baseline risk for opioid-induced complications, such as respiratory depression, and would benefit from an analgesia regimen aimed at limiting such risks in the postoperative period. Further research might aim to determine optimal TAP block technique and also to firmly establish a high-quality evidence to support clinical decisions.



(A)

(B)

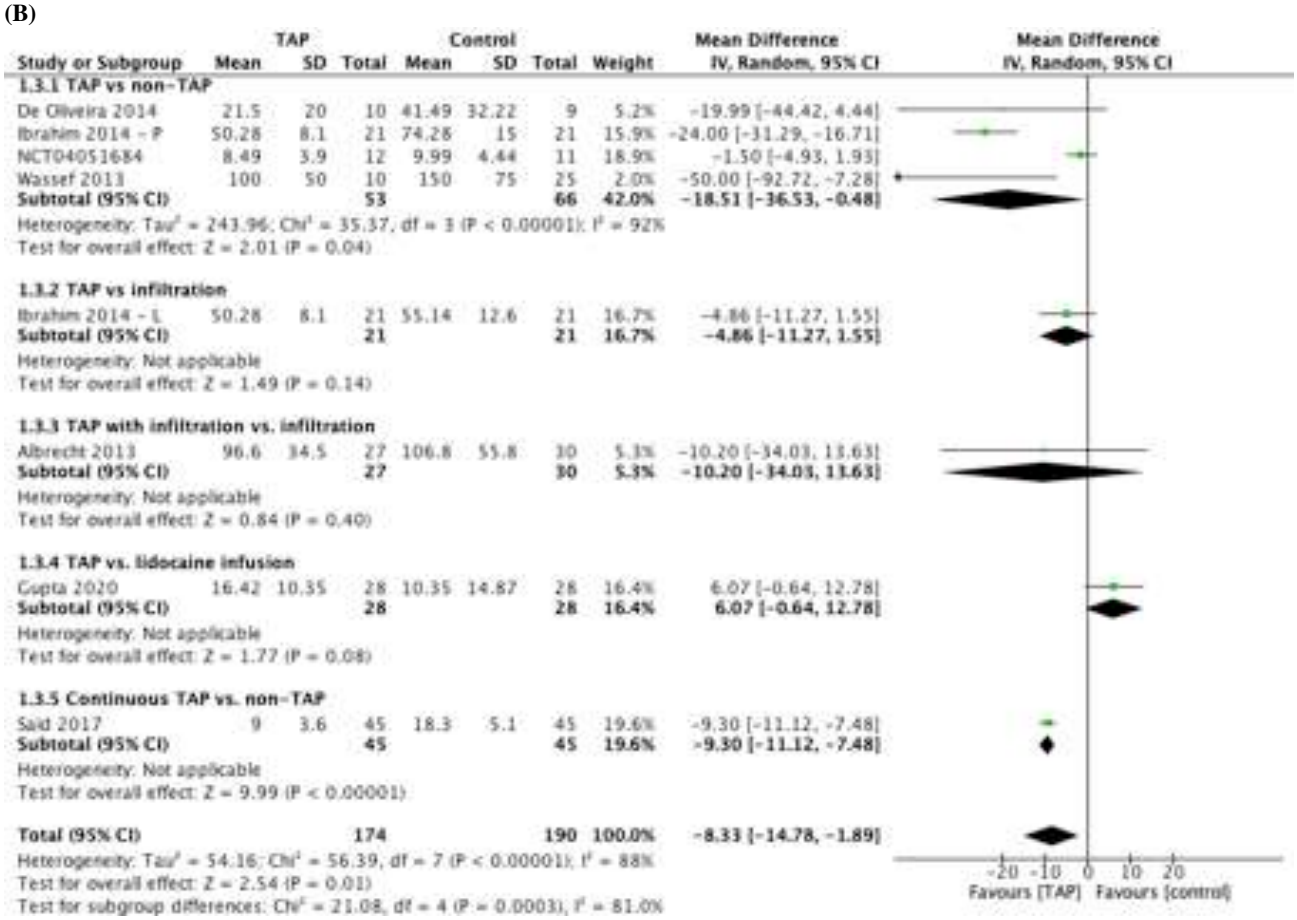


Figure 1. Random-effects meta-analysis forest plots for RCTs comparing TAP block versus control group on (A) requirement of opioid rescue and; (B) 24-hour total opioid requirement in OME (oral morphine equivalents).

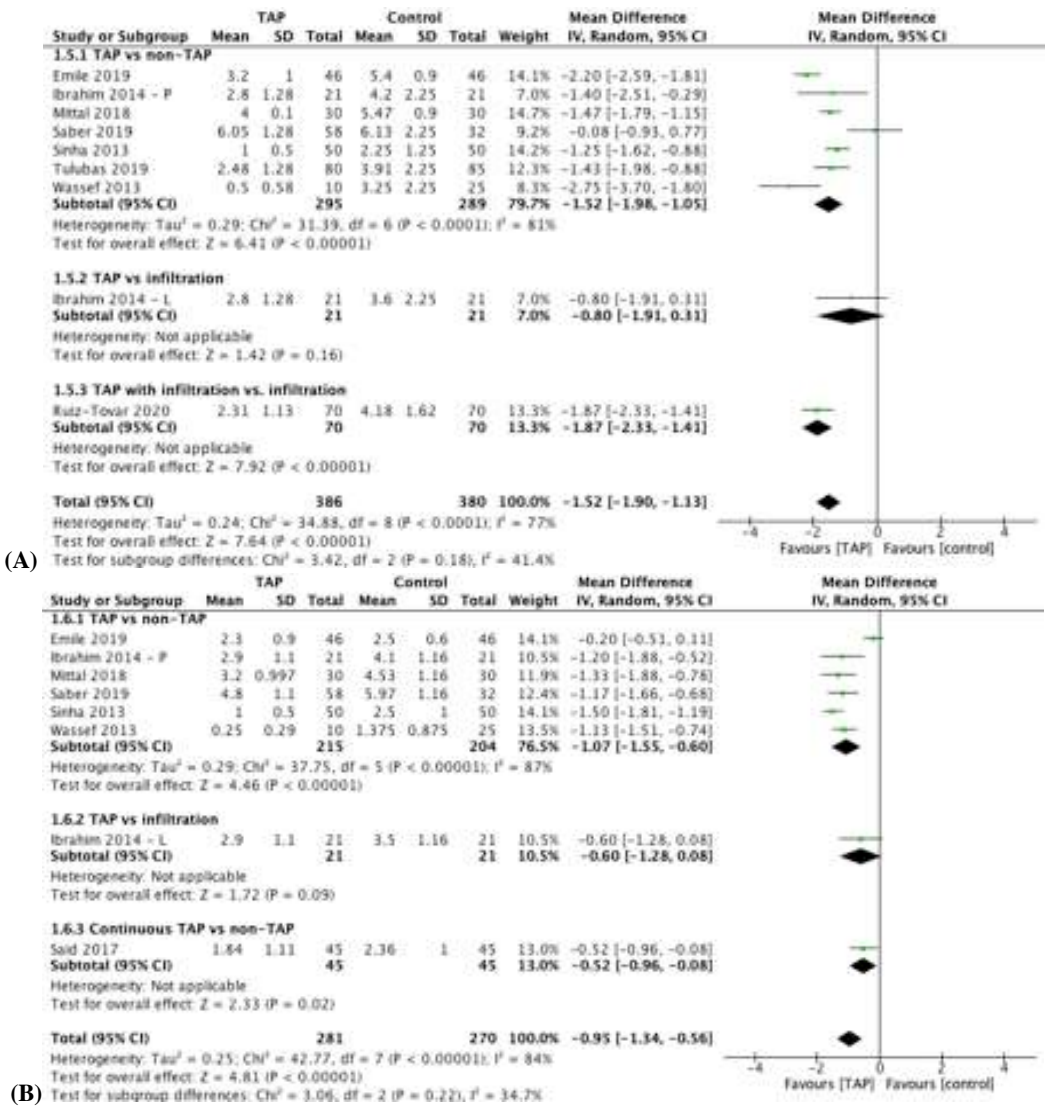


Figure 2. Random-effects meta-analysis forest plots for RCTs comparing TAP block versus control group on postoperative pain scores (numeric pain scale 0-10) at (A) 6-hours; and (B) 12-hours.

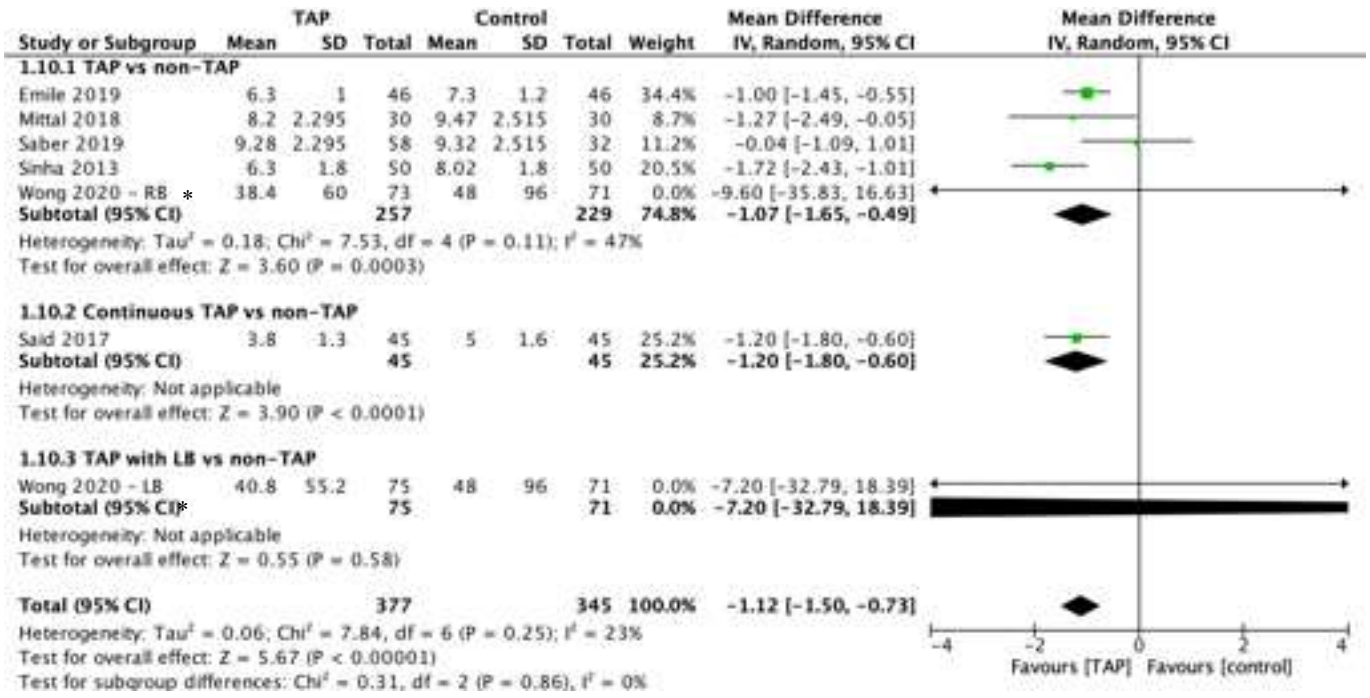


Figure 3. Random-effects meta-analysis forest plots for RCTs comparing TAP block versus control group on time to first ambulation in hours. RB, regular bupivacaine; LB, liposomal bupivacaine.
* The confidence intervals from Wong 2020 were extremely wide and not entirely displayed in the figure.

Obstetric Anesthesiology

Obstetric Anesthesiology - 1 The effect of ERAS on opioid use and opioid prescribing behaviors for opioid naive patients undergoing cesarean section

Erica Langnas[1], Zachary Matthay[1], Andrew Lin[1], Rosa Rodriguez-Monguio[1], Catherine Chen[1]

[1]UCSF, San Francisco, CA

Introduction: Cesarean sections are the most common inpatient surgical procedure performed in the United States, with approximately 1.3 million cases performed annually [1]. Almost all women undergoing cesarean section are exposed to opioids during their inpatient stay [2]. Between 1 in 300 to up to 1 in 45 women who received an opioid prescription after cesarean section develop new persistent opioid use [2,3]. Furthermore, 83% of women undergoing cesarean section report having leftover prescription opioids, potentially contributing to non-medical use of these products by others [4]. Enhanced Recovery after Surgery (ERAS) has emerged as a promising tool to reduce opioid use after surgery [5-9]. However, implementation of such protocols can have unintended effects on provider prescribing patterns, but these effects have not been described in the literature for ERAS implementation in patients undergoing cesarean section. To better understand the impact of ERAS implementation on provider opioid and non-opioid pain medication prescribing behavior, we performed a single center interrupted time series analysis comparing provider opioid prescription behavior pre and post ERAS adoption for cesarean sections.

Methods: We conducted a retrospective observational cohort study of adult opioid-naïve patients undergoing cesarean section from 2/1/2015 through 12/31/2019 at the University of California San Francisco Medical Center. Data were summarized using descriptive statistics and chi-squared tests were used to compare patient characteristics pre and post ERAS implementation. An interrupted time-series analysis (ITSA) was used to model the changes in pain medication prescribing associated with the implementation of ERAS to account for pre-existing temporal trends. All ITSAs were performed using the ordinary least squares method with Newey-West standard errors. A Cumby-Huizinga test was used to assess for temporal autocorrelation, and standard error adjustments were incorporated for up to a 12-month lag in our models. As a sensitivity analysis, we examined whether patient characteristics or prescribing provider type impacted the models when included as covariates. None of these significantly altered the association of ERAs with the pain medication outcome variables and were therefore not included in the final models. All data analyses were performed in Stata (Version 15, Stata Corps).

Results: In total, 2249 opioid naïve patients underwent cesarean section. In our pre-ERAS group, 21.01% were opioid free in the 24 hours prior to discharge compared to 49.76% in our post-ERAS group ($p < 0.01$) and pre-ERAS 95.35% were discharged with an opioid prescription compared to 80.72% of the post-ERAS group ($p<0.01$). Post-ERAS, we observed an increase in the percent of discharge prescriptions with a total daily OME of 90 or more (11.35% vs 61.35%, $p < 0.01$) and a reduction of discharge prescriptions with a total daily OME of less than 50 (79.86% vs 25.85%, $p<0.01$). Prior to ERAS, both the strength (daily OMEs) and total OMEs prescribed at discharge were decreasing (daily OMEs by -0.50/month and total OMEs by 2.3/month, both $p<0.01$). However, there was a sharp increase in the strength of discharge opioid prescriptions associated with ERAS implementation (level shift up in daily OMEs by 35, $p<0.01$), followed by a month to month decrease in daily OMEs of 1.4/month (figure 1, $p<0.01$). Total OMEs showed both an immediate decrease (level shift down) in total OMEs by 50/month ($p<0.01$), and a post eras trend of 3.8 fewer OMEs/month. Pre-ERAS, there was no significant trend in the percent of patients receiving opioid refills within 90 days. Rates of 90-day opioid refills decreased by 4.96% ($p=0.04$) immediately following ERAS implementation, and this rate remained stable during the post-ERAS period.

Conclusion: This is the first study to report an unintended consequence on provider opioid prescribing patterns in the immediate post-ERAS period for patients undergoing cesarean section. While ERAS led to an increase in opioid free pain control prior to discharge, we observed an increase in discharge prescription daily OMEs. Most notably, more patients received >90 daily OMEs on their discharge

prescription, a dose that is associated with increased risk of misuse and overdose. Although this finding did not lead to increases opioid refills, this study highlights the importance of early and continued evaluation after new pain medication prescribing interventions.

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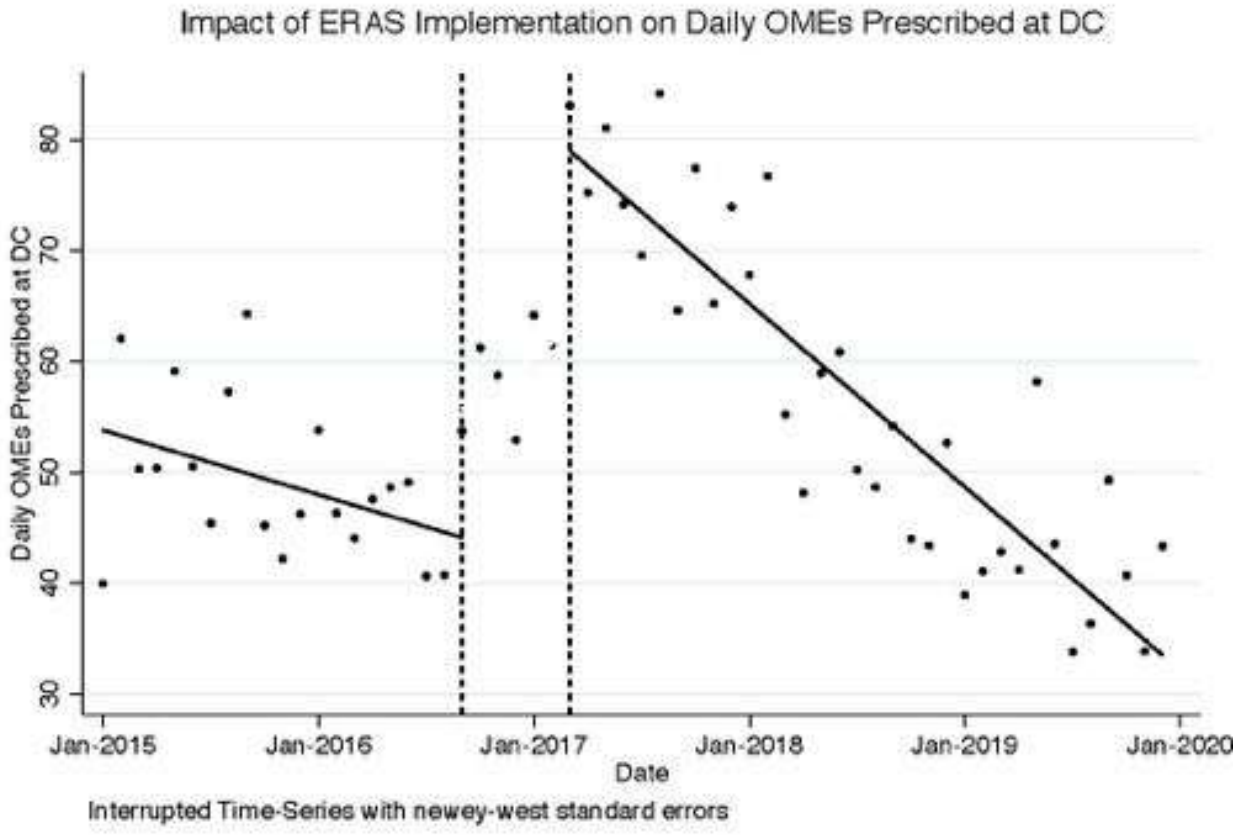


Obstetric Anesthesiology - 2 Can the Gender of the Neonate Affect Intra-cesarean Nausea and Vomiting?

Danielle Levin[1], Rohan Shah[2], Kate Balbi[2], Shaul Cohen[2]

[1]St. Elizabeth's Medical Center, Brighton, MA, [2]Rutgers - Robert Wood Johnson Medical School, New Brunswick, NJ

Introduction: 73-80% of parturients who undergo cesarean section under regional anesthesia experience intraoperative nausea.1-2 Not only is nausea an unpleasant physical condition, but intraoperative vomiting can cause additional challenges, such as inadvertent surgical trauma, increased risk of bleeding, and aspiration pneumonitis.3-4 Various prophylactic antiemetic medications exist, but they are not entirely effective and may have multiple adverse effects. Knowing which parturients are at a higher risk of experiencing intraoperative nausea and vomiting could help anesthesiologists provide appropriate prophylactic antiemetic management. Semizet al.5 suggested that parturients who have a female neonate have a significantly higher rate of intraoperative nausea and vomiting than parturients who have a male neonate. To our knowledge, no other study has yet validated these findings. The goal of our retrospective study was to compare the rate of nausea and vomiting experienced by parturients undergoing cesarean section under combined spinal-epidural anesthesia who had female neonates with those that had male neonates.

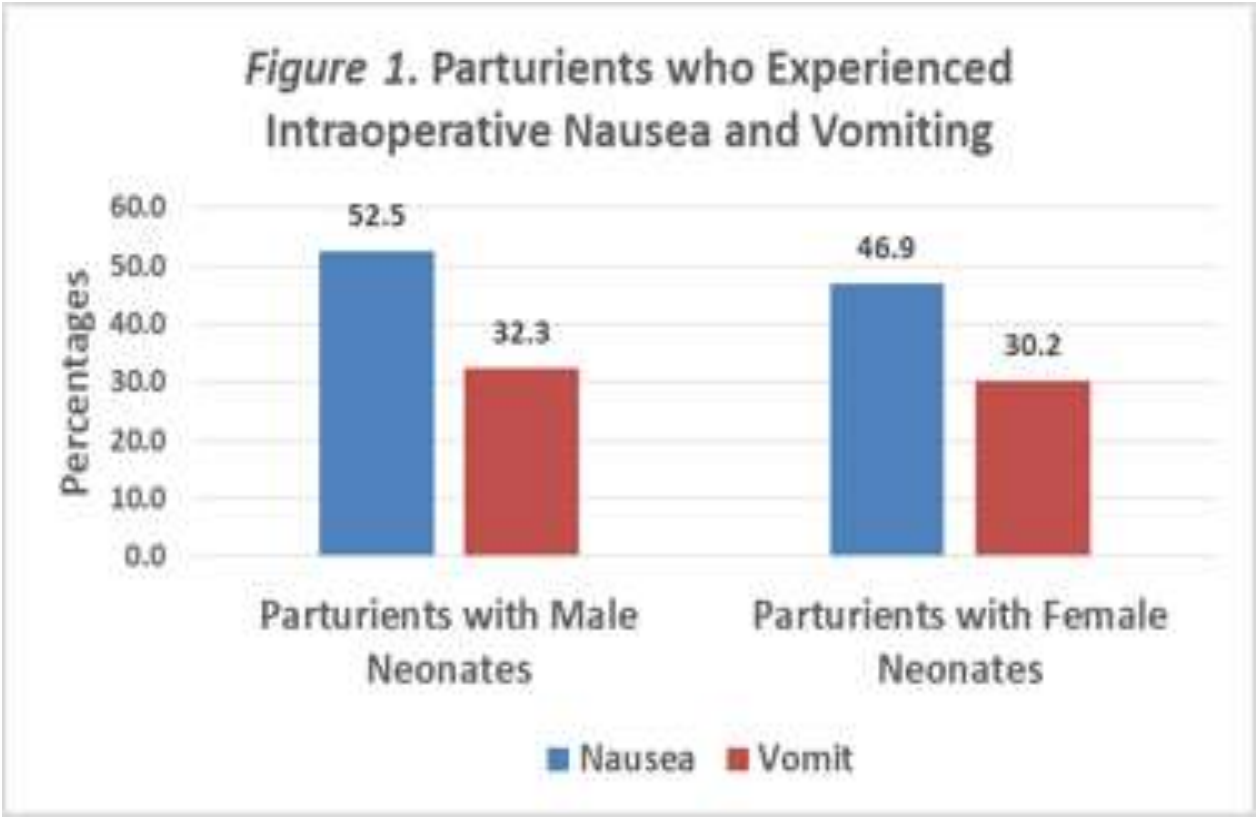
Methods: Following IRB approval, 195 parturients who underwent elective cesarean section under combined spinal-epidural anesthesia between 09/2016 and 06/2019 were analyzed. Group I (n = 99) had male neonates, and Group II (n = 96) had female neonates. The rate of nausea and vomiting were compared between the two groups. Excel version 2013 was used for Chi-squared test and Student T-test analysis of our data.

Results: Baseline characteristics were similar between the two groups (Table 1). The rate of intraoperative nausea was similar between the two groups (Group I - 52.5%, Group II - 46.9%, P = 0.43). The rate of intraoperative vomiting was also similar between the two groups (Group I - 32.3%, Group II - 30.2%, P = 0.75) (Figure 1).

Conclusion: In our cohort of parturients, the gender of the neonate did not appear to have a significant effect on whether a parturient experienced intra-cesarean nausea or vomiting. Based on our findings, we were unable to validate Semizet al.'s5 results. We will continue to explore other risk factors that may contribute to intra-cesarean nausea and vomiting to further improve parturient satisfaction and safety during delivery.

References: 1. Effectiveness of P6 Stimulation for Reduction of Nausea and Vomiting During Caesarean Section Under Combined Spinal-Epidural Anaesthesia: A Randomised Controlled Trial. Turk J Anaesthesiol Reanim. 2019;47(2):120-127. 2. The antiemetic efficacy and safety of prophylactic metoclopramide for elective cesarean delivery during spinal anesthesia. Reg Anesth. 1992;17(3):126-130. 3. Interventions for preventing nausea and vomiting in women undergoing regional anaesthesia for caesarean section. Cochrane Database Syst Rev. 2012(9):Cd007579. 4. Delayed surgical emphysema, pneumomediastinum and bilateral pneumothoraces after postoperative vomiting. Br J Anaesth. 1993;71(2):296-297. 5. Prediction of intraoperative nausea and vomiting in caesarean delivery under regional anaesthesia. J Int Med Res. 2017 Feb;45(1):332-339. doi: 10.1177/0300060516680547. Epub 2017 Jan 17.

Table I. *Patient and procedural characteristics*			
Characteristics	**Male Neonate (n=99)**	**Female neonate (n=96)**	**P-value**
Age (years)	31.8 ±6.0	31.8± 5.3	0.98
BMI	31.5± 6.5	31± 6.5	0.55
Gestational age (wks)	38.7± 1.0	38.5± 1.8	0.25
Hypotension, n (%)	48 (49%)	43 (45%)	0.61
Hypoxia, n(%)	0	0	1
Blood loss (mL)	776.0± 123.7	807.0± 199.0	0.19
Surgery duration (min)	62.6± 17.4	63.9± 16.8	0.61
Continuous variables were expressed as mean ± standard deviation, and P values were calculated using the Student T-test. Categorical variables were expressed as number (percentage), and P values were calculated using the chi-square test. P<0.05 were considered statistically significant. ‡Hypotension was defined as an SBP <90 mm Hg at any point.[6]			



Obstetric Anesthesiology - 3 Does the Timing of P6 stimulation Affect Intra-cesarean Nausea and Vomiting? A Retrospective Study.

Danielle Levin[1], Rohan Shah[2], Kate Balbi[2], Shaul Cohen[2]

[1]St. Elizabeth's Medical Center, Brighton, MA, [2]Rutgers - Robert Wood Johnson Medical School, New Brunswick, NJ

Introduction: Approximately 80% of parturients experience nausea and vomiting during cesarean section1 when no prophylactic antiemetic treatment is given. While intravenous antiemetic medications have been advocated to prevent intraoperative nausea and vomiting during cesarean section, they are not entirely effective and may carry multiple adverse effects, including the development of gastrointestinal, renal, neurological, cardiovascular, and allergic reactions.2-7 In our recent randomized clinical trial, we found that a non-pharmacological method, P6 stimulation, reduces intraoperative nausea and vomiting, without any side effects. We conducted a 3.5 year retrospective review to evaluate whether a 1-hour pre-treatment with P6 stimulation prior to the initiation of combined spinal epidural anesthesia (CSE) could further reduce the rate of intraoperative nausea and vomiting.

Methods: Following IRB approval, a chart review from June 2015 to December 2018 was conducted: Group I (n=67) began receiving transcutaneous point P6 stimulation on the right wrist 1 hour prior to induction of CSE and continued receiving it throughout the cesarean section (Figure 1). Group II (n=45) began receiving P6 stimulation immediately prior to CSE administration and continued receiving it throughout the cesarean section. Group III (n=60) did not receive P6 stimulation. The P6 stimulator output current was adjustable from 0-70mA by a control dial that had ten different knob settings. The device was turned on gradually to the highest level of intensity tolerated by the patient. Evidence of N&V was collected intraoperatively. Excel and IBM SPSS Statistics V22.0 were utilized for Chi-squared test, T-test, and ANOVA analyses.

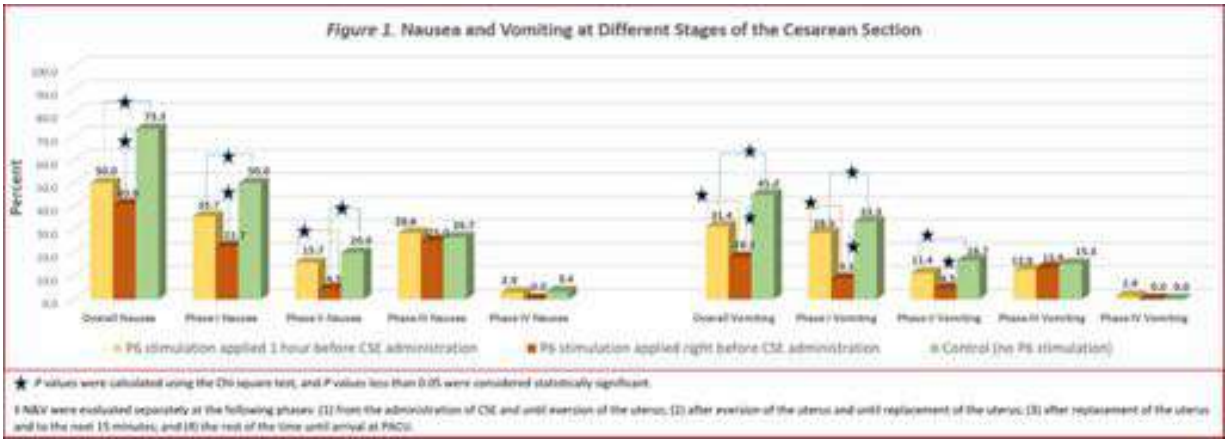
Results: Baseline characteristics were similar between the three groups (Table 1). Markedly fewer patients experienced intraoperative vomiting in the Immediate P6 group (18.2%) than in the 1-hour P6 pretreatment group (31.4%, P=0.04). Interestingly, patients in the Immediate P6 group tolerated a significantly lower level of P6 stimulation (36.9±11.5mA) than in the 1-hour P6 pretreatment group (42.7±9.6mA, P<0.005). Furthermore, fewer patients experienced intraoperative nausea and vomiting in each of the treatment groups than in the control group (P<0.05).

Conclusion: Higher P6 stimulation for longer period of time before the induction of CSE did not further reduce the incidence of nausea and vomiting in our patients undergoing cesarean section. We suspect that P6 stimulation overtime increases patient tolerance and makes it less effective. P6 stimulation continues to be a simple, non-invasive, effective prophylactic alternative antiemetic treatment that could be of great interest to patients and obstetric anesthesiologists who prefer less invasive care with fewer side effects for cesarean section performed under CSE. We recommend applying prophylactic antiemetic P6 right before initiation of CSE for cesarean section.

References: 1. The antiemetic efficacy and safety of prophylactic metoclopramide for elective cesarean delivery during spinal anesthesia. RegAnesth. 1992;17(3):126-130. 2. Interventions for preventing nausea and vomiting in women undergoing regional anaesthesia for caesarean section. Cochrane Database Syst Rev. 2012(9):Cd007579. 3. Prophylaxis of intra- and postoperative nausea and vomiting in patients during cesarean section in spinal anesthesia. Med SciMonit. 2013;19:993-1000. 4. Intraoperative nausea and vomiting during cesarean section under regional anesthesia. Int J ObstetAnesth. 2005;14(3):230-241. 5. Placental transport of metoclopramide: assessment of maternal and neonatal effects. Can AnaesthSoc J. 1983;30(5):487-492. 6. Study protocol: a double blind placebo controlled trial examining the effect of domperidone on the composition of breast milk. BMC Pregnancy Childbirth. 2006;6:17.

Table I. **Patient and procedural characteristics**				
Characteristics	P6 stimulation applied 1 hour before CSE administration (n = 67)	P6 stimulation applied right before CSE administration (n = 45)	Control Group (no P6 stimulation) (n = 60)	*P*-value
Age (years)	31.3 ± 5.1	31.8 ± 4.7	30.8 ± 4.8	0.59
Gestational age (weeks)	38.6 ± 1.4	38.3 ± 1.5	38.2 ± 2.4	0.44
BMI (kg/m²)	30.5 ± 5.9	34.0 ± 9.2	31.6 ± 7.0	0.05
Hypertension, n (%)	45 (67.2)	23 (53.5)	32 (53.3)	0.16
Hypotension, n (%)	32 (47.8)	26 (59.1)	31 (53.4)	0.58
Hypoxia, n (%)	0 (0)	0 (0)	0 (0)	1
Surgery duration (min)	60.8 ± 17.5	65.4 ± 24.3	63.5 ± 21.4	0.52
P6 stimulation level	6.1 ± 1.4	5.3 ± 1.6	N/A	0.005
CSE induction position				
• Right lateral, n (%)	24 (35.8)	16 (36.4)	13 (21.7)	0.15
• Sitting, n (%)	43 (64.2)	28 (63.6)	47 (78.3)	0.15

Continuous variables were expressed as mean ± standard deviation, and P values were calculated using the one-way ANOVA test. Categorical variables were expressed as number (percentage), and P values were calculated using the chi-square test. P<0.05 were considered statistically significant.



Obstetric Anesthesiology - 4 ED90 of Oxytocin Infusion During Cesarean Delivery in Non-laboring Preeclamptics receiving Magnesium Sulfate Therapy and Normotensives: An Up-Down Sequential Allocation Dose-Response Study

Devansh Garg[1], Asha Tyagi[2], Aparna Mohan[3], Yuvraj Singh[3], Ankit Luthra[4], Rajeev K Malhotra[5]

[1]University College of Medical Sciences, NEW DELHI, Delhi, [2]university College Of Medical Sciences & Gtb Hospital, Delhi, India, [3]University College Of Medical Sciences, New Delhi, India, [4]university College Of Medical Sciences And Gtb Hospital, Delhi, India, [5]Delhi Cancer Registry, Dr BRAIRCH, All India Institute of Medical Sciences; Delhi, India., New Delhi, India

Introduction: Oxytocin administration during cesarean delivery is first-line therapy for prevention of uterine atony.(1,2) Preeclamptic patients may be receiving magnesium sulfate for seizure prophylaxis, a drug with known tocolytic effect.(3,4)Thus we hypothesized that the dose of oxytocin required to attain an adequate uterine tone during cesarean delivery in preeclamptic patients receiving preoperative magnesium sulfate may be greater than otherwise healthy normotensive parturients. However, there is no study evaluating minimum effective dose of oxytocin during cesarean delivery in preeclamptics.The present study evaluated the minimum effective dose of prophylactic oxytocin infusion for achieving satisfactory uterine tone during cesarean delivery, in non-laboring preeclamptic patients receiving magnesium sulfate treatment, and compare it with a control group of normotensives (without magnesium sulfate treatment).Herein,the ED90 was taken to represent the "minimum effective dose" since it would represent the dose likely to be successful in 90% patients and hence a clinically acceptable goal.

Methods: This single-blinded dual-arm dose finding study was based on 9:1 biased sequential allocation design which compared minimum effective dose of oxytocin infusion for achieving satisfactory uterine tone during cesarean delivery, defined as the ED90.From the total of 150 patients who were assessed for inclusion there were 52 preeclamptics and 98 normotensives. Since 25 and 58 of them respectively did not meet the inclusion criteria, 27 and 40 patients each were included in the preeclamptic and normotensive group (Fig. 1).
The anesthetic management for these patients was standardized as per routine practice. Oxytocin infusion was initiated upon clamping of umbilical cord at 13 IU/h for the first patient in both groups. Uterine tone was graded as satisfactory or unsatisfactory by the obstetrician, 4 minutes after initiation of the oxytocin infusion. Doses of oxytocin infusion for subsequent patients were decided by response in previous patient of the group; it was increased by 2 IU/h after unsatisfactory response, and decreased by 2 IU/hr or maintained at same after satisfactory response in a ratio of 1:9. This method of biased allocation was implemented by drawing black and white marbles, kept in a ratio of 1:9, out of an opaque bag. Oxytocin associated side effects were also noted.Hypotension was defined as a fall in systolic blood pressure >20% from baseline or <90 mmHg. For comparative analysis, student's unpaired t-test was used to compare parametric and Mann-Whitney U test for non-parametric data. Dose-response data for both groups was evaluated using log-logistic function in R version 3.1.0 and ED90 estimates derived from fitted equations using delta method.

Results: All non-laboring parturient >18 years age, whether preeclamptics receiving magnesium sulfate therapy, or normotensives without magnesium sulfate therapy, posted for cesarean delivery under spinal block were enrolled.Exclusion criteria included patient refusal, need for general anesthesia, presence of active labor, use of oxytocin in preoperative period; history of previous PPH, more than one uterine surgery, or bleeding disorders; and presence of abnormal placentation or uterine fibroid. Those with any contraindication to spinal block such as hemodynamic instability, infection at site of injection, coagulopathy etc. were also excluded.
The ED90 of oxytocin was significantly greater for preeclamptic as compared to normotensive group [24.9 IU/hr (95% CI: 22.4 – 27.5) and 13.9 IU/hr (95% CI: 12.4 – 15.5) respectively]; (Fig. 2)difference in dose requirement was 10.9 IU/hr (95% CI: 7.9 to 14.0) (P <0.001).The demographic as well as obstetric details were not significantly different between both groups (Tables 1 and 2). The baseline mean arterial pressure was significantly higher for the preeclamptic group (P <0.001, Table 1).Number of patients with oxytocin related adverse effects was significantly greater in preeclamptic as compared to normotensive group (100% versus 67.5% respectively, P = 0.001). Hypotension was significantly greater for the preeclamptic group (92.6% versus 62.5%, P = 0.005).Other side effects(Table 3) were either statistically similar in both groups or infrequent or absent.

Conclusion: Patients of preeclampsia receiving preoperative magnesium therapy need a greater intraoperative dose of oxytocin to achieve a satisfactorily contracted uterus after fetal delivery.

References: 1.Oxytocin Protocols for Cesarean Delivery. Int Anesthesiol Clin. 2014;52:48–66. 2.Hypertensive disorders.Chestnut's Obstetric Anaesthesia, 5th ed; 2014:826-850. 3.Hypertension in Pregnancy, 2013. Available at at www.acog.org. Accessed on December 30, 2018. 4.Effect of magnesium sulfate on oxytocin-induced contractility in human myometrium: an in vitro study. Can J Anesth. 2017;64:744–753.

Figure 1: CONSORT diagram for patient enrollment

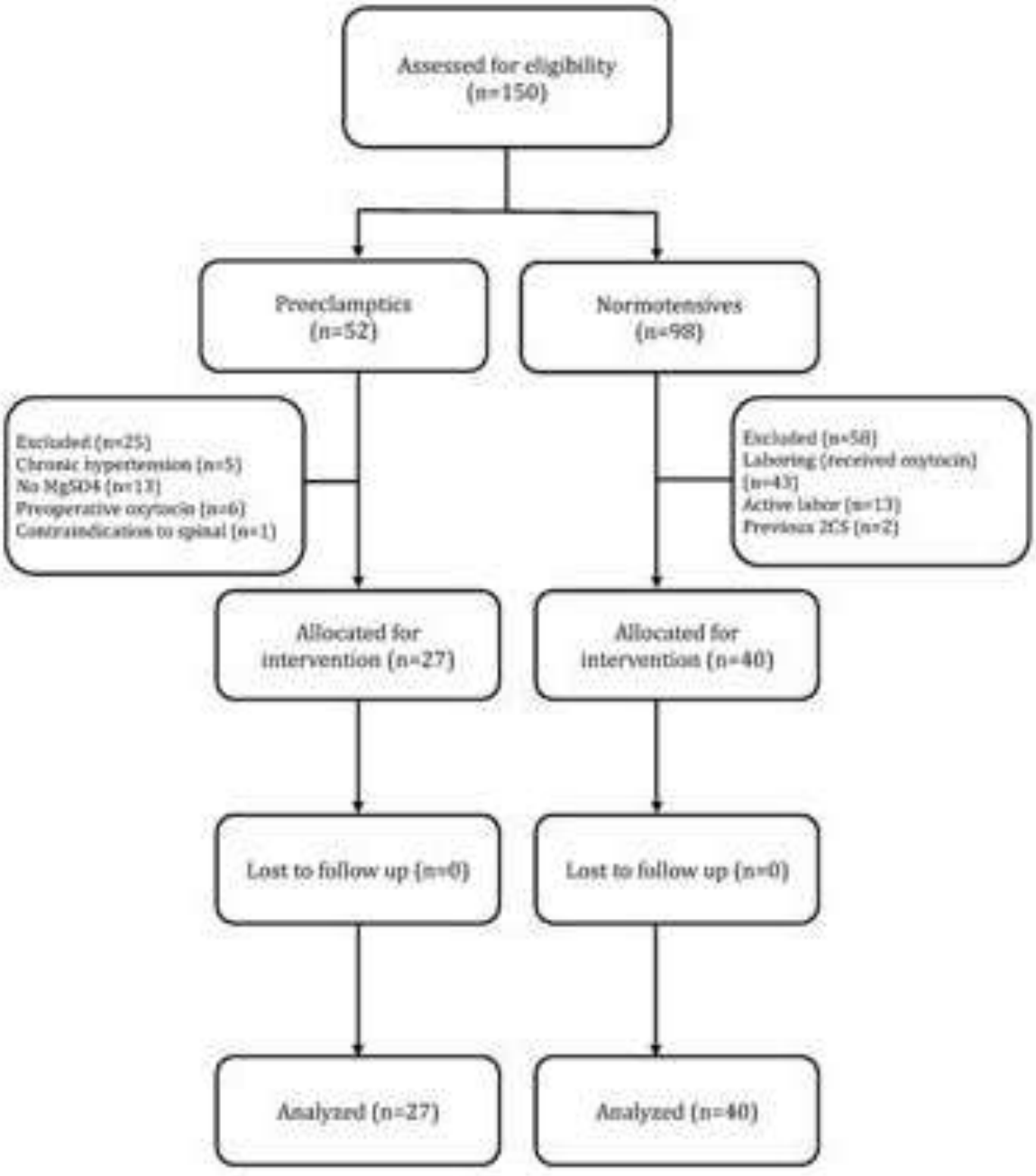


Figure 2. Sequence of successful and failed doses for oxytocin infusion in the normotensive and preeclamptic group.

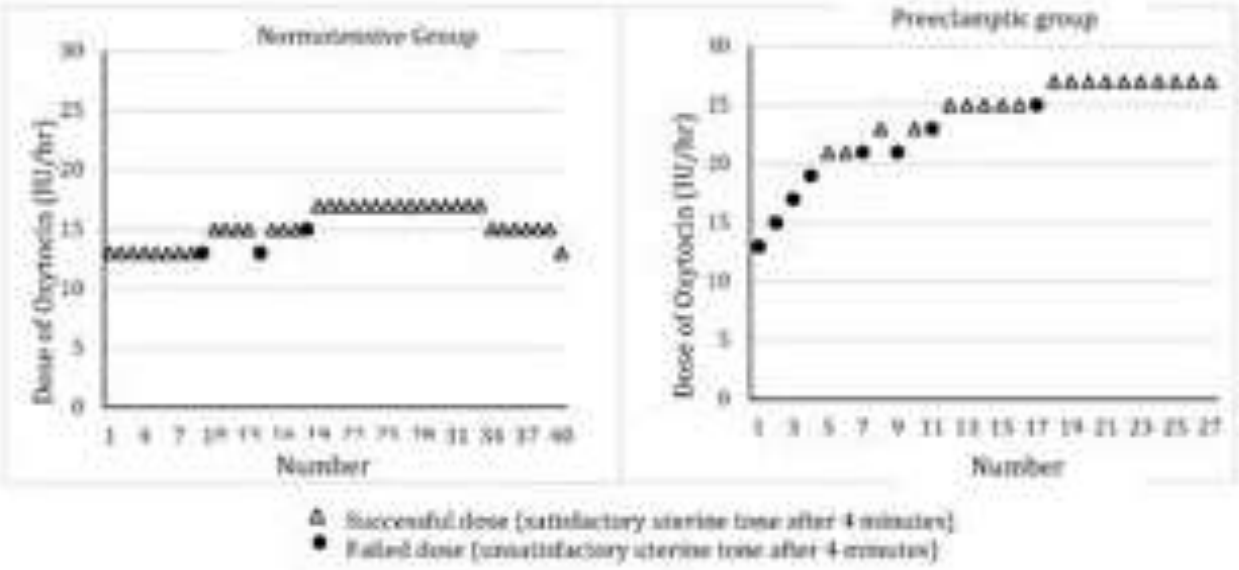


Table 1. Comparison of demographic characteristics

Characteristic	Normotensives (n = 40)	Preeclamptics (n = 27)	Standardized mean difference	P-value
Age, years	25.9 (3.2)	26.8 (4.9)	-0.109	0.391[a]
Height, cm	154.8 (5.8)	156.9 (7.9)	-0.152	0.228[b]
Weight, Kg	64.1 (11.5)	66.5 (12.1)	-0.102	0.420[b]
Body mass index, kg/m^2	26.6 (4.1)	27.0 (4.7)	-0.045	0.764[b]
Basal mean arterial pressure, mmHg	126.3 (9.6)	151.3 (18.9)	-0.833	<0.001[a]
Basal heart rate, bpm	96.5 (5.6)	94.3 (15.5)	-0.094	0.557[a]

Values are mean (SD)
[a]Welch test (unequal variances)
[b]Unpaired Student t-test (equal variances)

Table 2. Comparison of obstetric parameters

Characteristic	Normotensives (n = 40)	Preeclamptics (n = 27)	Standardized mean difference	P-value
Gravidity	2 [2-3]	2 [1-3]	0.063	0.269[a]
Parity	1 [0.25-1]	1 [0-1]	0.208	0.109[a]
Period of gestation, weeks	38.0 [36.5 – 39.9]	37.1 [34.2 – 39.2]	0.159	0.111[a]
Previous cesarean delivery	11 (27.5%)	6 (22.2%)	0.497	0.625[b]
Multiple gestation	0 (0%)	1 (3.7%)	---	0.403[b]
Baby weight, kg	2.5 (0.6)	2.2 (0.7)	0.230	0.092[c]
Duration of surgery; mins	54.0 (12.4)	51.7 (14.0)	0.087	0.489[c]

Values are mean (SD), median [IQR] or number of patients (%).
[a]Mann Whitney U test.
[b]Chi-square Fisher's exact test.
[c]Unpaired students t-test (equal variances).

Table 3. Comparison of efficacy and side-effects of prophylactic intraoperative oxytocin infusion

Characteristic	Normotensives (n = 40)	Preeclamptics (n = 27)	MD*/OR** [95% CI]	P value
Duration of oxytocin infusion; mins	44.8 (11.0)	42.1 (11.6)	2.7 [-3.0 to 8.4]*	0.342[c]
Estimated blood loss	450 [350-537]	500 [400-600]		0.069[a]
Intraoperative blood loss > 500 ml	10 (25%)	13 (48.1%)	2.8 [1.0-7.9]**	0.050[b]
Intraoperative blood loss > 1000 ml	1 (2.5%)	0 (0%)		0.408[b]
Decrease in hemoglobin (%)	13.9 (6.1)	12.1 (7.2)	1.7 [-1.5 to 5.1]*	0.278[c]
Hypotension[1]	25 (62.5%)	25 (92.6%)	7.5 [1.55-36.27]**	0.005[b]
Need of vasopressor	17 (44.7%)	18 (66.7%)	2.7 [1.0-7.5]**	0.052[b]
Dose of vasopressor (mg)	0 [0-5.25]	6 [0-12]	-	0.002[a]
Nausea/vomiting	7 (17.5%)	6 (22.2%)	1.4 [0.4-4.6]**	0.632[b]
Intraoperative fluid volume, ml	1500 [1250 – 1600]	1000 [1000 - 1500]		0.003[a]
Time for placental separation; mins	1 [0.9 – 2]	1.1 [1-2]		0.324[a]

Values are mean (SD), median [IQR], or number of patients (%).
[1]Fall in systolic blood pressure of >20% below baseline or <90 mmHg, whichever was higher.
MD=mean difference, OR=odds ratio, CI=confidence interval.
[c]Unpaired student t-test, [b]Chi-square/Fisher's exact test, [a]Mann Whitney-U test.

Obstetric Anesthesiology - 5 Intrinsic Risk of Cesarean delivery Assessed as the Incidence of Postpartum Acute Kidney Injury: A Retrospective Large Database Propensity Score Matched Study

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Introduction: Cesarean delivery (CD) is the most commonly performed major abdominal surgery with the attendant risk of perioperative complications.[1] The advantages of CD have been established in certain well-defined cases where CD clearly leads to improved maternal and fetal outcomes.[2] However, there is growing concern that the overall increasing rate of CD has not been accompanied by decreases in maternal or neonatal morbidity or mortality.[3]. The driving force behind the high CD rate is multifactorial and complex, with modifiable factors such as patient preferences and practice variation among clinicians.[4] A key element driving the increasing rate is the perception of safety associated with CD.[5]

The perioperative risks of non-CD abdominal surgeries are well established.[6] Acute kidney injury (AKI) is a commonly used variable in studying perioperative risk because it is well-defined.[7] AKI in pregnancy is a known obstetric complication associated with adverse maternal and fetal outcomes.[8] The incidence of pregnancy-related AKI ranges from 2.7 to 6.3 per 10,000 deliveries, with a temporal trend showing increasing rates of pregnancy-related AKI.[9] In the same period, there has been a concurrent increase in the rate of CD.[10] However, it is challenging to determine the intrinsic risk of CD for AKI because of selection bias; parturients undergoing CD likely have either pregnancy-related or preexisting comorbidities which led to the CD.[11] Therefore, even though some studies assess the risks associated with CD, the key question whether CD imposes an intrinsic risk and the effect size of this risk has not been explored. In this study, we address this question. We hypothesized that CD is associated with an increased risk of AKI compared to VD. We tested this hypothesis with a large-scale, retrospective, controlled study.

Methods: In this retrospective cohort study, we used a large commercial insurance claims database to identify deliveries between 2016 and 2018. The primary exposure of interest was CD. Using propensity score matching, we generated a final sample of matched pairs of CD and VD that were balanced with respect to 25 antepartum characteristics associated with maternal morbidity and mortality. Associations between delivery mode, VD vs. CD, and the risk of postpartum AKI (as defined by previously validated ICD-10-CM diagnostic codes) were determined after adjusting for antepartum comorbidities and postpartum events associated with AKI. Secondarily, we evaluated the impact of postpartum AKI on length of hospital stay (LOHS). We performed additional sensitivity analyses to test the robustness of our findings among several clinically important subgroups including: parturients without any comorbidities, parturients without clear indications for CD as defined by the Society for Maternal Fetal Medicine, and parturients with a clear indication for CD (fetal malpresentation).

Results: The propensity-score matched-pairs cohort was from 117,592 deliveries (Fig 1). After matching, the two groups were well-balanced with respect to all antepartum characteristics (Fig 2). The incidence of postpartum AKI (Fig 3) was 22 per 10,000 deliveries in the CD group, vs. 8 per 10,000 in the VD group (adjusted odds ratio = 3.03; 95% CI, 2.18 to 4.22; $P < 0.001$). The median LOHS [IQR] was longer in patients who developed postpartum AKI after VD (3 [2-4] days vs. those who did not, 2 [2-3] days; $P < 0.001$) and after CD (5 [4-7] days vs. 3 [3-4] days; $P < 0.001$). The association between CD and an increased risk of postpartum AKI remained significant in all additional sensitivity analyses performed, supporting the robustness of our findings.

Conclusion: Our results from this large-scale retrospective controlled study demonstrate that CD is associated with a significantly higher risk of postpartum AKI compared to VD. Since CD contributes to an increased rate of repeat CD in the subsequent delivery, the true risk of CD for postpartum AKI and other complications are likely higher than what we observed in this study. Parturients, families, and healthcare providers must carefully weigh the risks and benefits for both the parturients and their babies when a decision is made to have a CD. Further studies are needed to identify modifiable factors for AKI and to develop effective interventions to prevent and treat this perioperative complication.

References: 1. HCUP Statistical Briefs. 2010: Statistical Brief #149.
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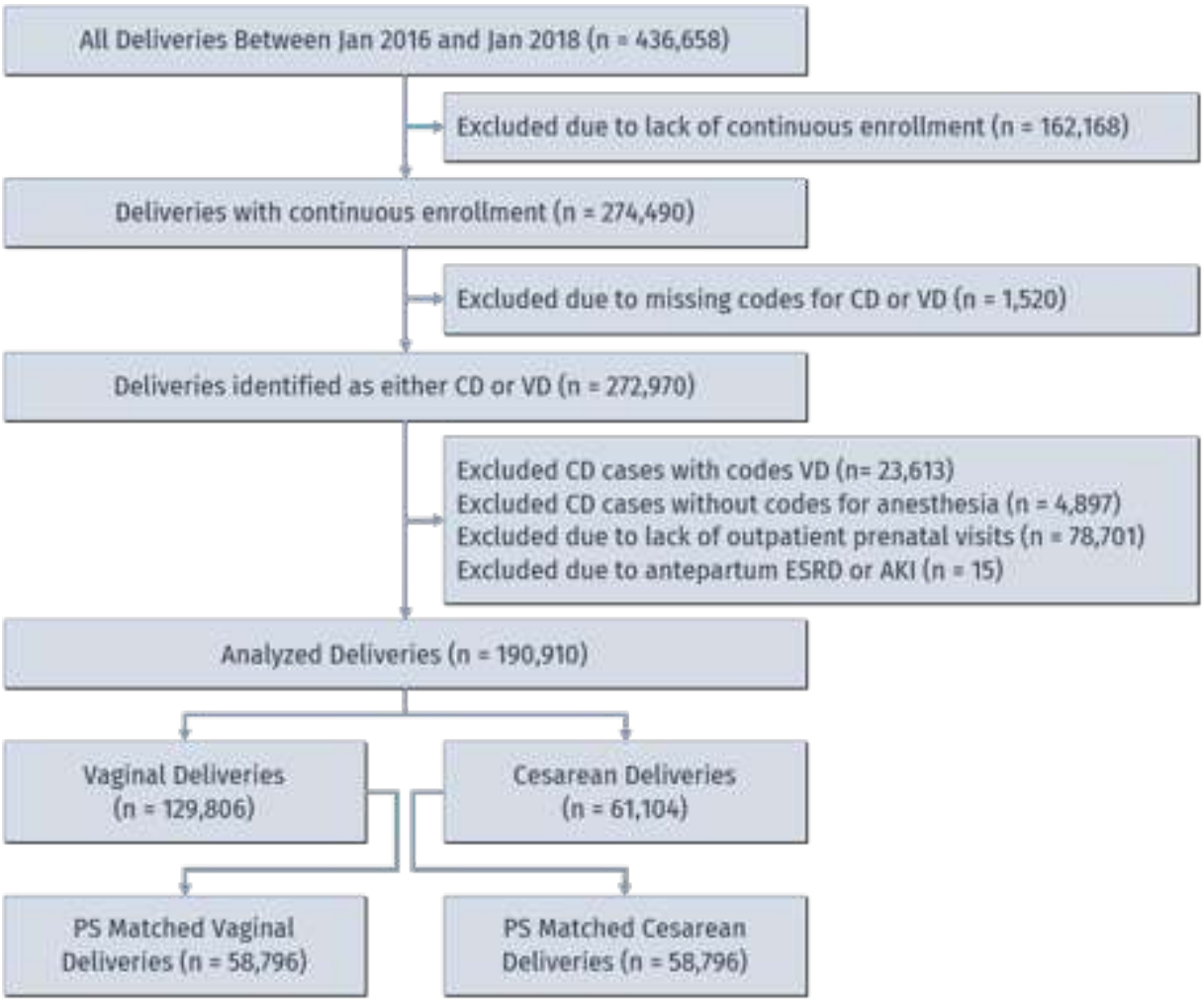
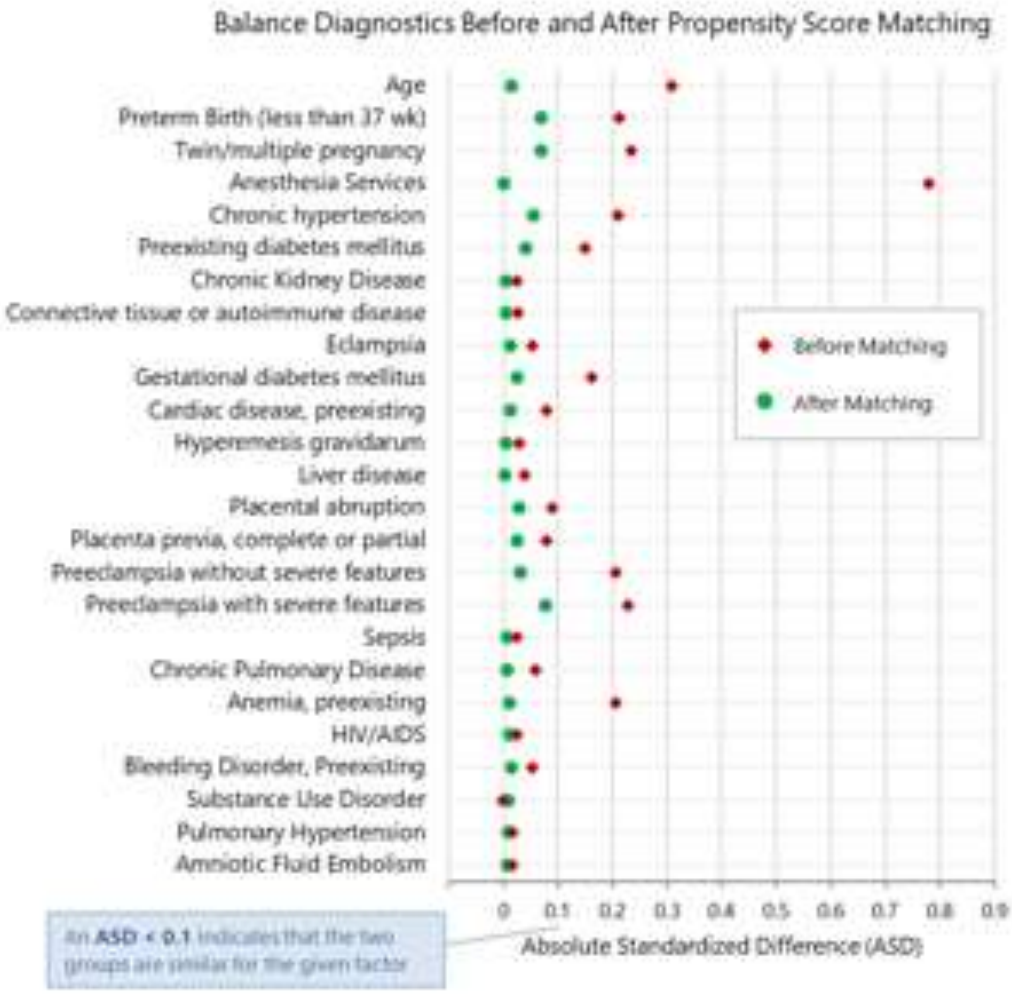




	Unmatched Cohort		1:1 Matched Cohort	
	VD (n=129,806)	CD (n=61,104)	VD (n=58,796)	CD (n=58,796)
Postpartum AKI	81 (0.06)	198 (0.32)	49 (0.08)	159 (0.27)
Blood Product Transfusion	566 (0.44)	743 (1.22)	339 (0.58)	635 (1.08)
Sterilization Surgery	2,857 (2.20)	7,295 (11.94)	1,394 (2.37)	6,910 (11.75)
Hysterectomy	41 (0.03)	120 (0.20)	18 (0.03)	104 (0.18)
LOHS, median [IQR]				
Without Postpartum AKI	2 [2-3]	3 [3-4]	2 [2-3]	3 [3-4]
With Postpartum AKI	3 [2-4]	5 [4-7]	3 [2-4]	5 [4-7]

Obstetric Anesthesiology - 6 Assessment of left ventricular diastolic function by analyzing intraventricular pressure difference during third trimester of pregnancy

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

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

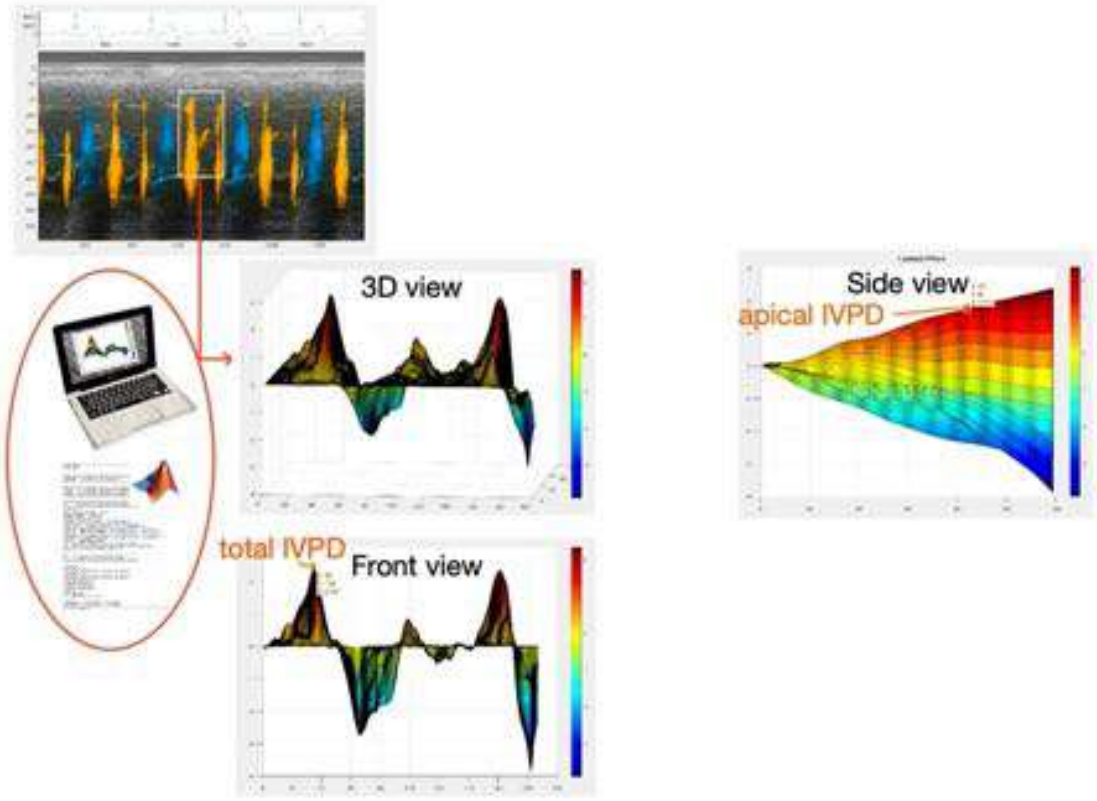
Introduction: Physiologic and hemodynamic changes during pregnancy have been well investigated[1]. However, changes in left ventricular (LV) diastolic function associated with pregnancy is not fully understood[2]. Recently, the intraventricular pressure difference (IVPD) which is the driving force of the LV suction is drawing attention as a crucial parameter of diastolic function[3]. The purpose of the present study was to investigate LV diastolic function during the third trimester of pregnancy assessed using conventional echocardiographic parameters and IVPD.

Methods: This is a prospective observational study. We performed transthoracic echocardiography in healthy pregnant women in the third trimester and non-pregnant controls, and assessed left ventricular diastolic function using the following parameters: end diastolic and end systolic diameter of LV (Dd, Ds); mitral inflow peak velocities in early diastole (E wave) and late diastole (A wave); E/A ratio; tissue Doppler-derived peak velocities in early diastole at lateral and septal basal regions (lateral e' and septal e'); and IVPD. We stored color M-mode Doppler images of the mitral inflow and estimated IVPD using an in-house MATLAB code (MathWorks, MA, USA). Wilcoxon rank-sum test was used to compare the parameters in pregnant and non-pregnant groups. A p-value less than 0.05 was considered statistically significant.

Results: We included 20 pregnant women and 19 non-pregnant controls. Dd was not significantly different between the two groups whereas Ds was significantly higher in pregnant group than non-pregnant group (Ds: 28.15 mm [24.85 to 30.05] vs 25.6 mm [22.5 to 27.4], p<0.05). E wave was not significantly different between the two groups, whereas A wave was higher and E/A was lower in pregnant women compared to those in non-pregnant controls (A wave: 50.6 cm/sec [45.93 to 62.73] vs 38.5 cm/sec [35.1 to 42.1], p<0.0005, E/A: 1.33 [1.17 to 1.54] vs 1.73 [1.52 to 1.94], p<0.0005). Also, lateral e' and septal e' were significantly lower in pregnant women. (lateral e': 12.77 cm/sec [10.73 to 14.94] vs 16.31 cm/sec [13.25 to 19.92], p<0.005, septal e': 10.41 cm/sec [8.32 to 11.80] vs 13.93 cm/sec [12.03 to15.24], p<0.0001). There was no significant difference in IVPD (total IVPD: 3.43 mmHg [2.70 to 4.33] vs 4.32 mmHg [2.92 to 5.36] p=0.18; apical IVPD: 1.94 mmHg [1.55 to 2.69] vs 2.21 mmHg [1.82 to 2.86]), p=0.48).

Conclusion: We found that IVPD doesn't change during the third trimester of pregnancy although conventional parameters of LV diastolic function are altered. Our results suggest that the heart adapts to meet the significant increase in total blood volume during pregnancy by increasing atrial contraction and maintaining the ventricular sucking force.

References: 1. Circulation. 2014; 130:1003-1008. 2. Circulation. 1999; 99:511-517. 3. Am. J. Physiol. Heart Circ. Physiol. 2001;280:2507-2515.


3D view
Side view
apical IVPD
total IVPD
Front view

Pain Mechanisms

Pain Mechanisms - 1 What Predicts the Outcome of Postsurgical Neuropathic Pain rather than Numbness? A Prospective, Longitudinal Assessment of Chronic Postmastectomy Sensory Disturbances out to 1 year Postop

Kristin L Schreiber[1], Kelsey Mikayla Flowers[2], Natt Zinboonyahgoon[2], Yun-Yun K Chen[2], Robert R Edwards[2]

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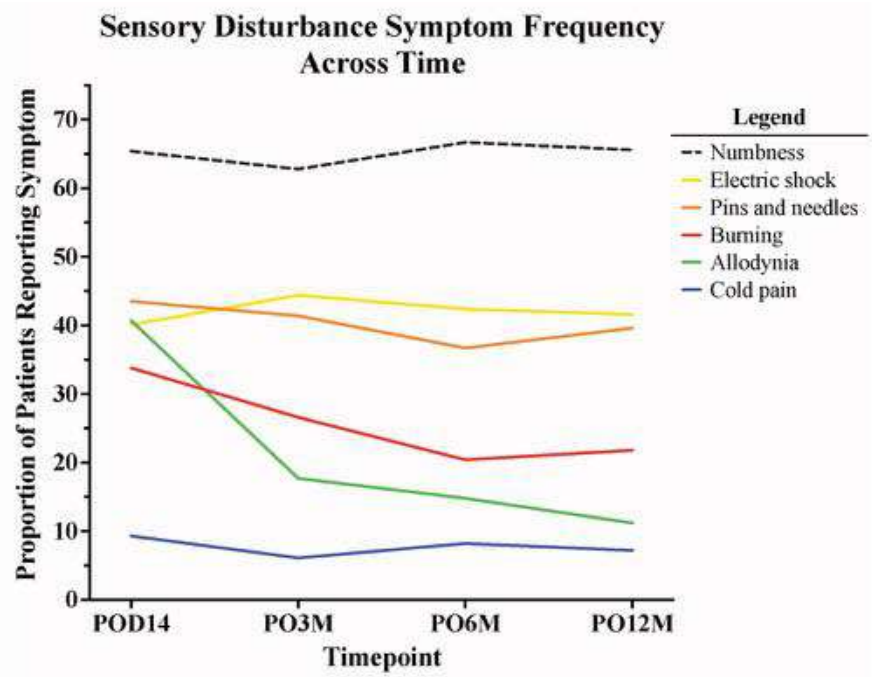
Introduction: Both painful (e.g.,burning, stabbing, and allodynia) and non-painful (numbness) sensory disturbances may arise after surgical injury of peripheral nerves, and may significantly impact patients' lives if persistent. Most questionnaire-based measures of neuropathic pain combine painful neuropathic symptoms together with the more benign, and arguably adaptive, symptom of numbness, in a single score. The purpose of this prospective longitudinal study was to investigate the overlap and divergence of surgical, psychosocial and psychophysical predictors of painful neuropathy vs numbness throughout the first year after breast surgery.

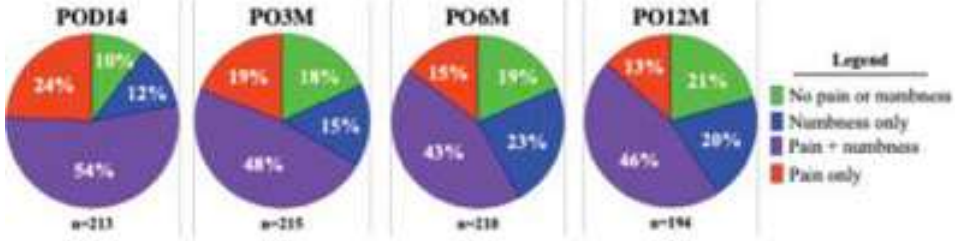
Methods: Patients (n=259) undergoing lumpectomy or mastectomy completed the Breast Cancer Pain Questionnaire(BCPQ) preoperatively and postoperatively at 2 weeks, 3, 6 and 12 months, including a question about numbness and a validated subscale assessing the presence of painful neuropathic symptoms (NeuPPS), including pins and needles, electric shock, heat/burning, allodynia, and pain from cold temperatures. Additional validated psychosocial questionnaires and psychophysical testing (bedside QST) were also completed at baseline.

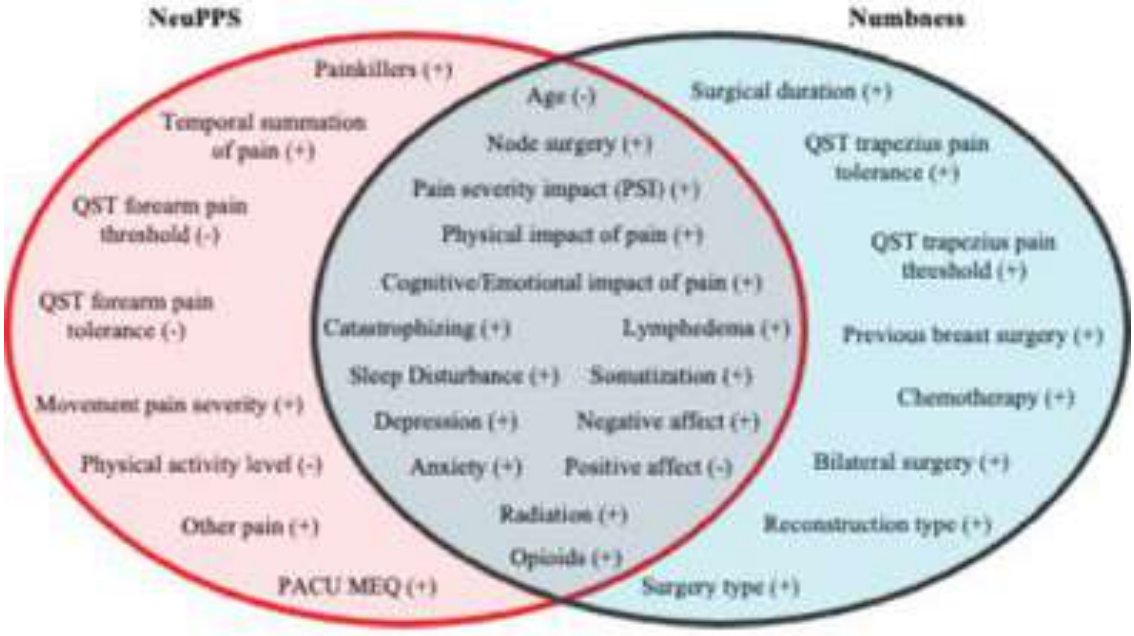
Results: Numbness was the most frequently reported sensory disturbance, present in approximately 50% of patients, and stable across time. NeuPPS was highest at 2 weeks, decreasing over time ($F(1,124)=37.71$, $p<.001$). Both NeuPPS and numbness were closely associated with greater clinical pain severity and impact, as well as associated with younger age, axillary surgery, and psychosocial factors including anxiety and catastrophizing. Interestingly, many surgical and treatment factors, including greater surgical extent, bilateral surgery, surgical duration, and chemotherapy were associated with greater numbness, but not NeuPPS. Conversely, other chronic pain, lower activity level, larger perioperative opioid requirement, higher temporal summation of pain, and lower pressure pain threshold and tolerance were associated with NeuPPS, but not numbness.

Conclusion: Identifying factors that uniquely predict numbness compared to those that uniquely predict painful neuropathic symptoms may offer insight into the pathophysiologic plasticity underlying persistent postsurgical pain in those patients that develop this outcome.

References: Mejdahl MK, Christensen KB, Andersen KG. Development and Validation of a Screening Tool for Surgery-Specific Neuropathic Pain: Neuropathic Pain Scale for Postsurgical Patients. Pain physician. 22:E81-E90, 2019 Schreiber K, Zinboonyahgoon N, Flowers KM, Hruschak V, Fields K, Patton M, Azizoddin D, Soens M, Schwartz E, King T, Partridge A, Pusic A, Edwards R. Prediction of Persistent Pain Severity and Impact 12 months after Breast Surgery using comprehensive Preoperative Assessment of Biopsychosocial Pain Modulators. Annals of Surgical Oncology. [accepted 27-Oct-2020], in press


Sensory Disturbance Symptom Frequency Across Time
Proportion of Patients Reporting Symptom
70
60
50
40
30
20
10
0
POD14
PO3M
PO6M
PO12M
Timepoint
Legend
Numbness
Electric shock
Pins and needles
Burning
Allodynia
Cold pain


POD14
PO3M
PO6M
PO12M
10%
12%
24%
54%
n=213
19%
18%
15%
48%
n=215
15%
19%
43%
23%
n=210
13%
21%
20%
46%
n=196
Legend
No pain or numbness
Numbness only
Pain + numbness
Pain only


NeuPPS
Numbness
Painkillers (+)
Temporal summation of pain (+)
QST forearm pain threshold (-)
QST forearm pain tolerance (-)
Movement pain severity (+)
Physical activity level (-)
Other pain (+)
PACU MEQ (+)
Age (-)
Node surgery (+)
Pain severity impact (PSI) (+)
Physical impact of pain (+)
Cognitive/Emotional impact of pain (+)
Catastrophizing (+)
Lymphedema (+)
Sleep Disturbance (+)
Somatization (+)
Depression (+)
Negative affect (+)
Anxiety (+)
Positive affect (-)
Radiation (+)
Opioids (+)
Surgical duration (+)
QST trapezius pain tolerance (+)
QST trapezius pain threshold (+)
Previous breast surgery (+)
Chemotherapy (+)
Bilateral surgery (+)
Reconstruction type (+)
Surgery type (+)

Pain Mechanisms - 2 Leveraging TRPV1 genetic divergence between avian and mammalian species to develop a TRPV1^{K710N} knock-in mouse and a novel analgesic

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Introduction: Pain afflicts ~1 in 5 individuals worldwide and treatment for pain, such as opioids, can lead to secondary health problems including abuse, addiction, and overdose. Therefore, there is an unmet need to understand the molecular mechanism of pain and in doing so, develop novel analgesics. One target is the transient receptor potential vanilloid 1 channel (TRPV1), a cation channel triggering calcium influx in the presence of noxious stimuli[1]. Interestingly avian species, unlike mammalian species, have a limited response to capsaicin; accredited to the genetic divergence of the TRPV1[2]. Here, we questioned whether introducing a genetically divergent avian TRPV1 sequence by CRISPR/Cas9 to rodents limits pain responses without exacerbating cellular injury.

Methods: To identify genetically divergent TRPV1 residues between avian and mammalian species, multiple sequence alignment was performed. These identified variants were analyzed using Chimera using the rat TRPV1 crystal structure (PDB ID: 3J5P)[3]. Next, a TRPV1^{K701N} knock-in mouse was created by CRISPR/Cas9 gene-editing. To evaluate behavioral differences in response to noxious stimuli, wild type TRPV1 and TRPV1^{K701N} mice were exposed to capsaicin-laced bird food, intraplantar capsaicin, or intraplantar Brp lysophosphatidic acid (Brp-LPA, an analogue of LPA that directly targets TRPV1 at K710) [4]. Primary dorsal root ganglion (DRG) neurons were also isolated from wild type TRPV1 and TRPV1^{K701N} mice and capsaicin-induced calcium influx was measured. Further, a cell-permeable peptide (V1-Cal, $_{701}$RAITILDTEKS$_{711}$+TAT) targeting the K710 TRPV1 region was injected in the paw to evaluate the capsaicin-induced nociception in wild type TRPV1 and TRPV1^{K701N} mice. Finally, cardiomyocytes were isolated from the wild type TRPV1 and TRPV1K701N mice and subjected to cellular injury (hydrogen peroxide (H2O2) or hypoxia/reoxygenation). Data were analyzed using ANOVA followed by Tukey's post hoc analysis. Significance was set at $P < 0.05$.

Results: We identified ~60 non-conserved amino acids when comparing avian with mammalian TRPV1 by multiple sequence alignment. Among these residues, we focused on the C-terminus TRP domain (687-711), which is critical for TRPV1 channel gating[3, 5]. Unlike mammals having K710, birds have N710 in the TRP domain (Figure 1a). Substitution of K710 to N710 changes the structure of the TRP domain α-helix (Figure 1 b, c). CRISPR/Cas9 gene-edited TRPV1^{K701N} knock-in mice were generated and verified by sequencing (Figure 1 d, e). When exposed to the bird food containing capsaicin, behavioral response was markedly decreased for TRPV1^{K701N} mice relative to wild type TRPV1 mice (Figure1 f, g, 15±6 vs. 50±6 instances of paw withdrawal/10 min, n=10, P<0.0001). Moreover, paw-licking time after capsaicin or Brp-LPA injection was reduced in TRPV1^{K701N} mice relative to wild type TRPV1 mice (Figure 1h, Capsaicin: 27±4 sec vs. 57±6 sec, respectively, n=10, P=0.0001; Figure 1i, Brp-LPA: 50±6 sec vs. 80±5 sec, respectively, n=8, P<0.0001). The peak intracellular calcium influx (Δ ratio 340/380) was also lower in TRPV1^{K701N} DRG cells (n=13) than wild type TRPV1 DRG cells (n=14) (0.07±0.01 vs. 0.12±0.02, ratio of 340/380, respectively, P=0.030 from 3 biological replicates). When subjecting wild type TRPV1 mice to acute capsaicin, V1-cal peptide substantially reduced the nociceptive response to capsaicin relative to the vehicle peptide (TAT) -treated rodents (Figure 1j, 32.8±4.4 vs. 86.0±6.9 sec, respectively, n=8, P<0.001). TRPV1^{K701N} mice treated with V1-cal had similar behavioral responses relative to TAT-treated mice. In addition, following H_2O_2 treatment or hypoxia/reoxygenation, TRPV1^{K701N} cardiomyocytes had more calcein-AM stained viable cells and less PI stained dead cells, as well as slightly increased cell viability measured by MTT compared to the wild type cardiomyocytes.

Conclusion: We generated a novel TRPV1^{K701N} mouse based upon avian and mammalian genetic differences. Introducing this avian variant into rodents mitigates TRPV1-mediated response to noxious stimuli with an added benefit of reducing cellular injury. Together, these data unlock a crucial genetic difference between avian and mammalian species regulating TRPV1-mediated pain responses that was leveraged to develop a novel analgesic.

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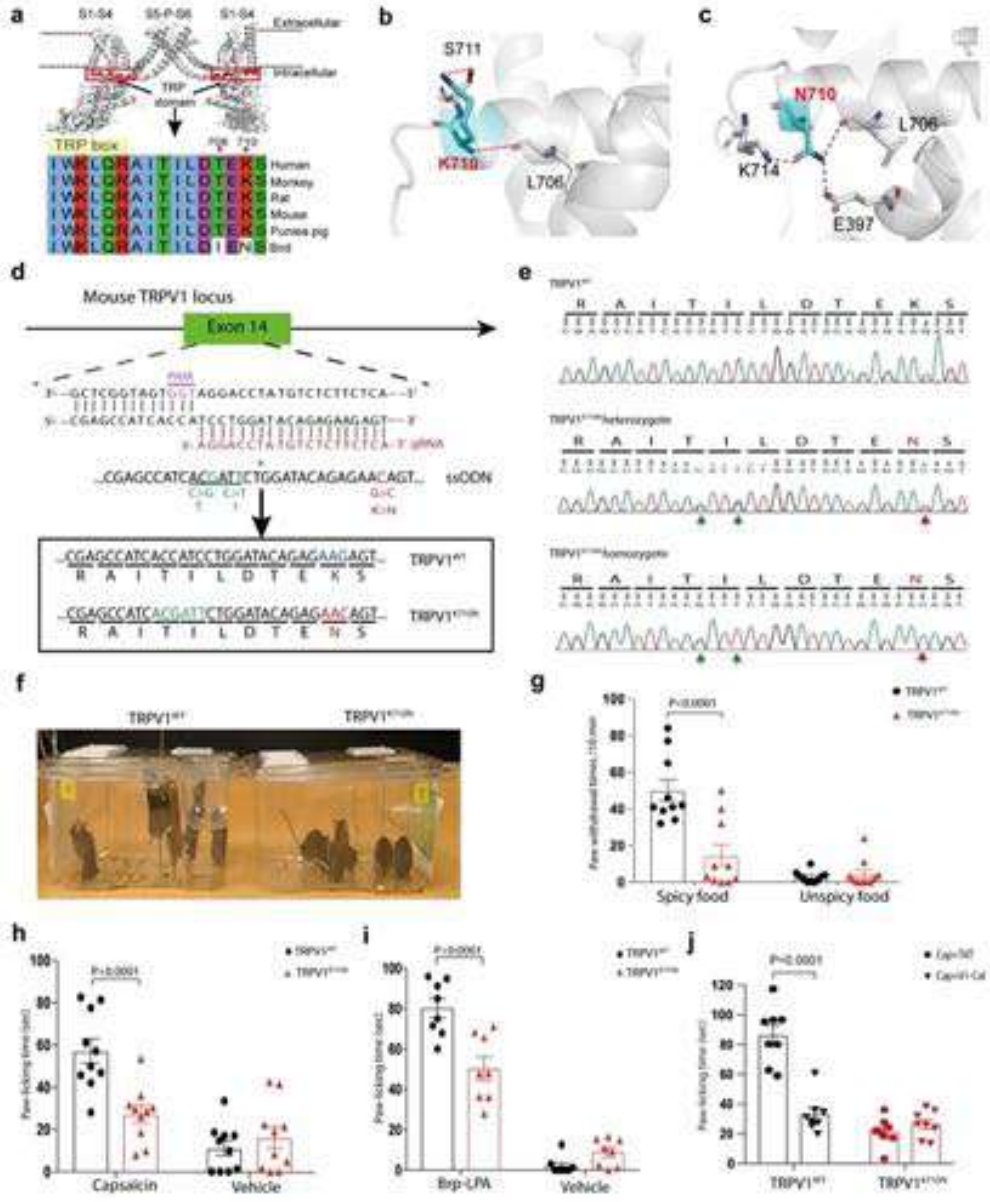

Figure 1 (a) Sequence alignment of the C-terminus TRP domain for mammalian and avian TRPV1. The zoom-in view of 3D structure of **(b)** wild type rat TRPV1, **(c)** K710N, based on the closed-state rat TRPV1 molecular model (PDB ID: 3J5P). **(d)** Design of gRNA, ssODNs lead to the K710N mutation (red) and two silent mutations (green) in the protospacer adjacent motif (PAM, purple). **(e)** Representative DNA sequencing data for wild type (WT) TRPV1, TRPV1^{K710N} heterozygotes (double peaks), or TRPV1^{K710N} homozygotes (single peak). **(f)** Representative image showing the difference in response to capsaicin-laced food for wild type TRPV1 and TRPV1^{K710N} mice. **(g)** Paw withdrawal behavior for wild type TRPV1 and TRPV1^{K710N} mice exposed to capsaicin-laced bird food or regular bird food. **(h)** Pain behavior induced by paw-injection of capsaicin or vehicle for wild type TRPV1 and TRPV1^{K710N} mice. **(i)** Pain behavior induced by paw-injection of Brp-LPA or vehicle in wild type TRPV1 and TRPV1^{K710N} mice. **(j)** Pain behavior induced by paw-injection of capsaicin after V1-cal or TAT in wild type TRPV1 and TRPV1^{K710N} mice.

Pain Mechanisms - 3 Morphine Tolerance and Reward is Regulated by Aldehyde Dehydrogenase-2 in Mice

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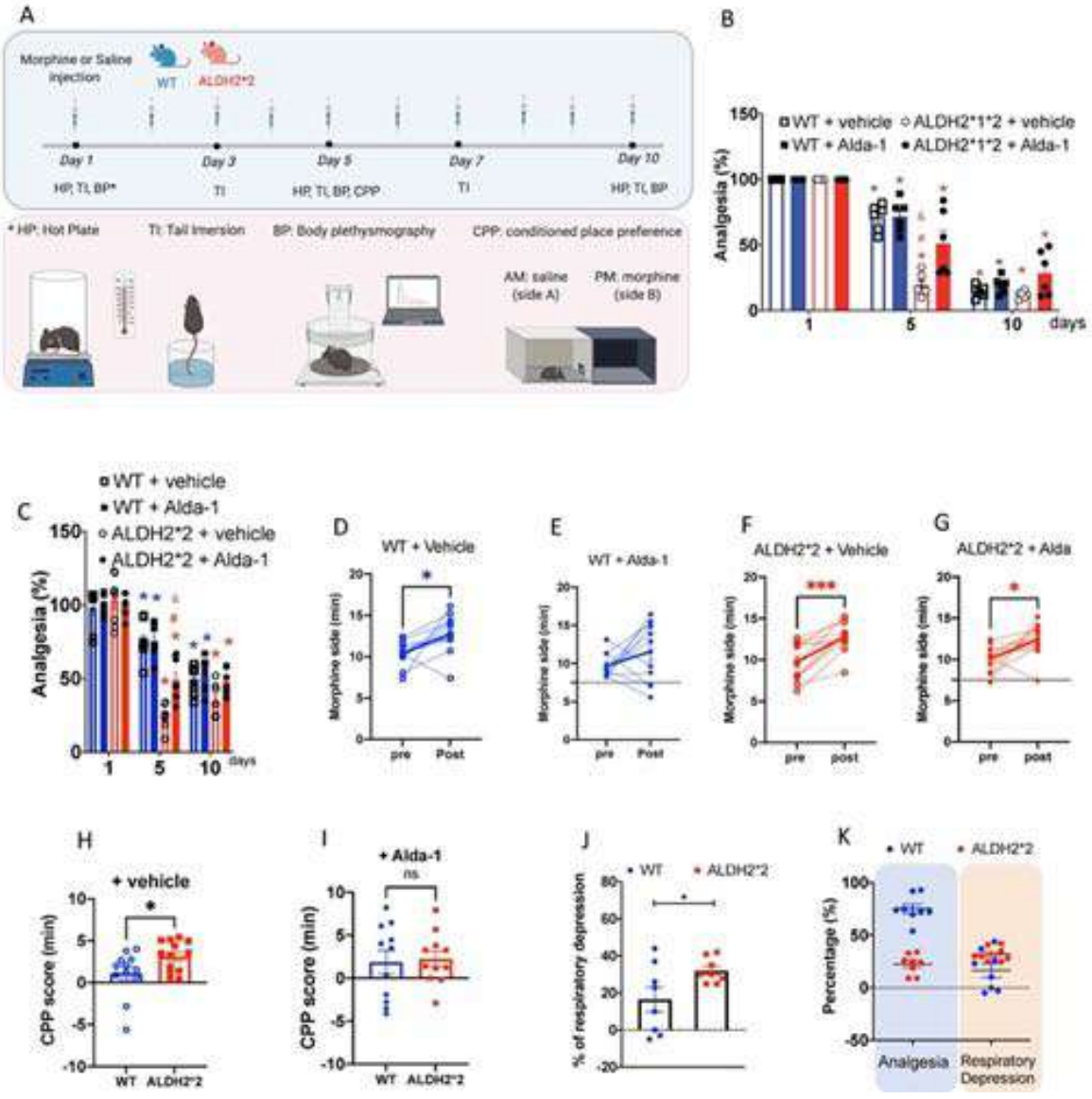
Introduction: Aldehyde dehydrogenase-2 (ALDH2) plays a key role in controlling toxic aldehydes involved in inflammatory and neuropathic pain development. This enzyme also converts aldehyde metabolites of amine neurotransmitters, including dopamine, norepinephrine, and serotonin, to less reactive forms[1]. An aldehyde dehydrogenase 2 (ALDH2) genetic variant, ALDH2E487K or ALDH2*2, is present in 540 million people world-wide, mostly of East Asian descent, which has impaired enzymatic activity (~ 60-90% versus wild type). Genomic studies revealed that opioid-dependence in Asians is higher than in population controls[2]. However, whether this genetic variant contributes to opioid-induced side effects including tolerance and addiction is unclear. Therefore, our aim was to investigate whether ALDH2 modulates opioid-induced tolerance and opioid reward in wild-type (WT) and ALDH2*2 mice. Further, we determined whether Alda-1, a small molecule activator of ALDH2, reverses these effects.

Methods: ALDH2*2 mice were generated as previously described[3] with the specific inactivating point mutation in ALDH2 that occurs in the East Asian population. Male and female WT C57BL/6J and ALDH2*2 mice (10-12 weeks) received morphine 10 mg/kg (s.c.), once daily for 10 days (Fig. 1a). A subset of these mice also received the ALDH2*2 activator Alda-1 (16 mg/kg/day, s.c. by osmotic pump) for the duration of morphine treatments. To measure morphine analgesia, the hot plate and tail flick tests were conducted on days 1, 3, 5, 8 and 10, thirty minutes after morphine administration. To investigate reward-related behavior with morphine, an unbiased conditioned place preference (CPP) paradigm was performed. In addition, respiratory function was monitored by whole body plethysmography (Fig. 1a). All procedures were approved by the Administrative Panel on Laboratory Animal Care at Stanford University. Data were analyzed by t-test (CPP experiments) or two-way ANOVA with post-hoc Bonferroni correction (hot plate, tail immersion and respiratory function studies). Statistical significance was indicated by *p<0.05.

Results: Morphine was analgesic in ALDH2*2 or WT mice on day 1 of treatment as evidenced by increased latency to withdrawal in the hot plate and tail flick assays. This analgesic effect was decreased in ALDH2*2 mice at day 5, compared to WT mice in the hotplate (21.5±4% vs 72.9±5.8% of analgesia, respectively, *p<0.05, n=8/group, Fig. 1b) and tail flick (32±5% vs 89±8.2% of analgesia, respectively, *p<0.05, n=8/group, Fig. 1c) assays, suggestive of analgesic tolerance. Alda-1 partially reversed this morphine tolerance in ALDH2*2 mice, compared to vehicle-treated controls at day 5 (48±4% vs 20% of analgesia, respectively, *p<0.05, n=8/group). No differences were detected in the sensitivity to hot plate or tail immersion tests in saline-treated control animals. ALDH2*2 mice presented increased preference for the morphine-paired compartment compared to WT (Δ pre- and post-morphine): 3.11±0.7s, vs 1.09±0.7s, respectively, n=12/group, (Fig. 1 d, f) suggesting that these mice may develop morphine-induced reward despite being tolerant to the analgesic effect. Alda-1 prevented morphine-induced reward effects in both WT and ALDH2*2 mice (Fig. 1 e, g). Importantly, ALDH2*2 mice also displayed increased respiratory depression at day 5 compared to WT mice (32±2% vs 16.5±6%, respectively, n=8/group, Fig. j), however, no differences were detected at day 10 (12.2±4% and 14.5±4%, respectively, n=8/group).

Conclusion: Our findings indicate that ALDH2 regulates morphine analgesic tolerance and reward. Further, East Asians with the ALDH2*2 genetic variant (ALDH2E487K) may experience enhanced tolerance to the analgesic effect of opioids, however, may still remain susceptible to respiratory depression (Fig. 1k). Patients with an ALDH2*2 genetic variant may therefore be at greater risk of respiratory depression as opioid dose escalation to mitigate analgesic tolerance may be more common and should be carefully monitored.

References: 1 Annu Rev Pharmacol Toxicol. 2015; 55:107-27, 2 Drug Alcohol Depend. 2012;120: 220–24,3Sci Transl Med 6:251ra118, 2014 Funding: FAPESP 2018/19332-7; NIGMS MIRA AWARD GM 119522; NINDS R35GM137906, K08 MH110610, Department of Anesthesia FIDL 2020



Pain Mechanisms - 4 A hindered HCN1-selective inhibitor is antihyperalgesic in a rat spared nerve injury neuropathic pain model

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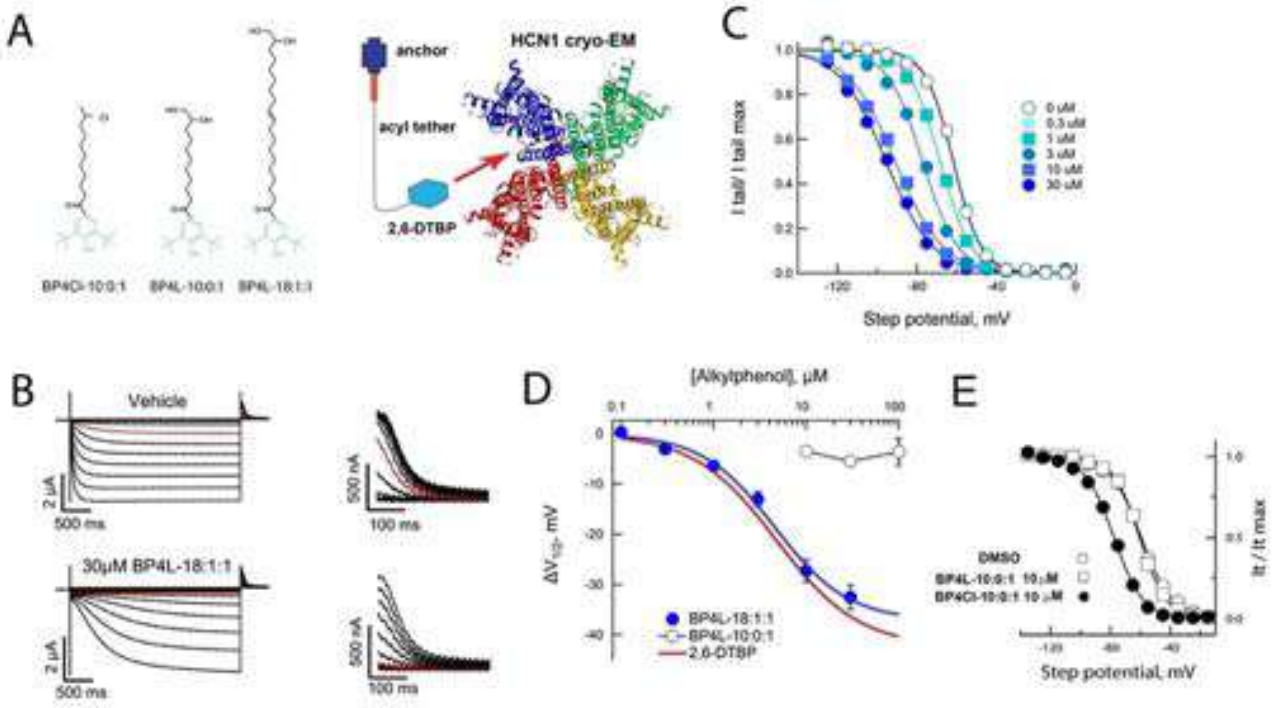
Introduction: Chronic pain, which includes neuropathic pain, impairs an individual's quality of life, is widely prevalent, and has significant economic cost. Pharmacologic intervention is a mainstay for the treatment of neuropathic pain [1]. First-line therapy includes the antidepressant duloxetine and/or an antiepileptic α2-δ ligand (ex., gabapentin), though both have poor (or no) efficacy [2, 3] and dose-limiting side effects [1, 4, 5]. Opioids are effective in relieving acute nociceptive pain, but are of little use in treating neuropathic pain [6-12], and the inappropriate use of opioid pain relievers has contributed to the opioid crisis [13-16]. Thus, there is a critical need for the development of safe, effective non-opioid antihyperalgesics.
We have previously demonstrated that 2,6-di-tert-butylphenol (2,6-DTBP) inhibits gating of HCN1 channels [17, 18], and that such inhibition is HCN1 selective [17]. We [17] and others [19] have also demonstrated that 2,6-DTBP is antihyperalgesic. The successful development of an HCN1-selective therapeutic with minimal, or no, adverse central side-effects requires that the drug not cross the blood:brain barrier due to widespread HCN1 expression in the human brain. Here we provide proof-of-principle that a potent and novel "hindered" HCN1-selective inverse agonist is an effective antihyperalgesic with therapeutic potential.

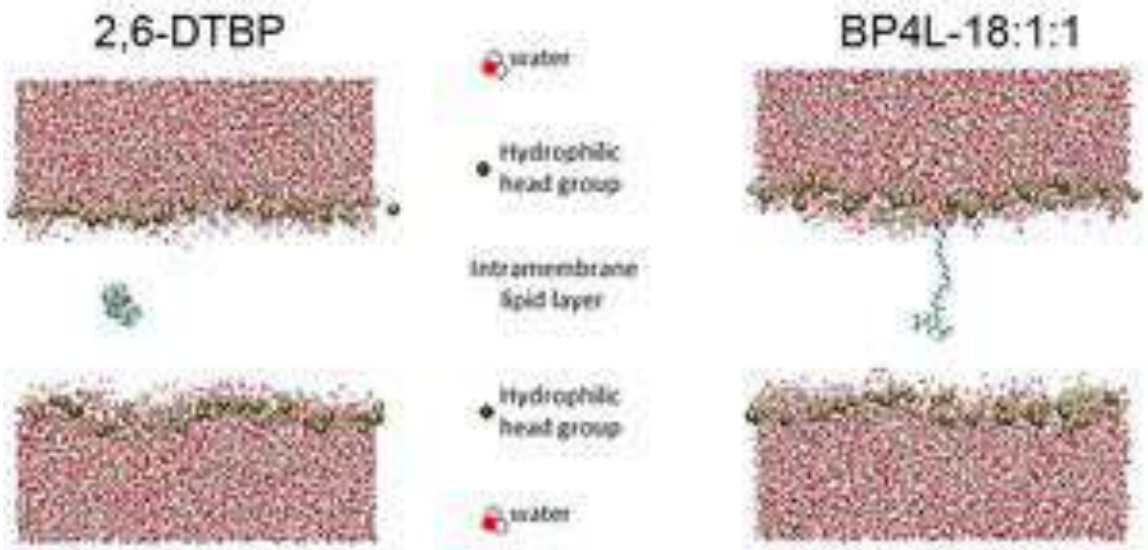
Methods: In vitro studies: Two-electrode voltage clamp (TEVC) was used to record I(h) currents from Xenopus oocytes in which mHCN1 was heterologously expressed as previously described [17, 18]. Chemical synthesis: Using 2,6-DTBP as the starting pharmacophore, we synthesized a series of novel derivatives via direct acylation of 2,6-DTBP to yield diol (BP4L-10:1:1 and BP4L-18:1:1) and Cl- (BP4-10:0:1) modified substances as prototypes. The synthetic procedure provides access to variable carbon length modifications that can mimic acylglycerols present in the bilayer and control depth of penetration of the pharmacophore into bilayers. Structures were confirmed using NMR.
In silico modeling: The starting configurations for the small molecules in the dierucoyl-phosphocholine (DEPC) lipid bilayer were constructed using CHARMM-GUI [20]. Each simulation system contained 200 lipids (100 lipids in each leaflet) and one drug molecule. Each system was simulated for 200 ns in the semi-isotropic ensemble. The CHARMM36 force field was used to model the lipids [21].
In vivo studies: All behavioral studies were performed following IACUC approval and in accordance with both institutional and Federal guidelines. The antihyperalgesic efficacy of BP4L-18:1:1 was tested against mechanical and thermal stimuli using the adult rat spared nerve injury (SNI; [22]) model of neuropathic pain in both male and female rats. Mechanical nociception & hyperalgesia: Exaggerated responses to mechanical stimuli were measured using von Frey filaments. Thermal and cold allodynia and hyperalgesia: Thermal hyperalgesia were measured by changes in sensitivity to temperature. A Hargreaves radiant heat source was used (IITC Life Science; Woodland Hills, CA) to test for heat hypersensitivity. Cold allodynia was determined by measuring aversive behaviors caused by evaporation of a drop of acetone. Safety testing: Rats were assessed using open field and rotarod testing at 3-6 hr post-drug administration. Cardiovascular testing: Heart rate and non-invasive blood pressure were measured in a separate cohort of rats using a Kent CODA non-invasive blood measuring systems (Kent Scientific Corp., Torrington, CT).

Results: BP4L-18:1:1 (Fig 1) inhibits HCN1-dependent Ih currents in Xenopus oocytes (Fig 1B-D); such inhibition depends on length of the tether and the identity of the substituent at the end of the acyl chain (Fig 1D-E). In silico, the hydrophilic diol is effectively retained by the phosphate head-group region of a lipid bilayer whereas the lipophilic 2,6-DTBP moiety is freely mobile within the lipid core (Fig 2). In vivo, BP4L-18:1:1 administered via oral gavage relieves mechanical hyperalgesia and thermal allodynia/hyperalgesia in a dose-dependent manner with equal efficacy in male (n = 36; Fig 3) and female (n = 36; Fig 4) rats. There was no sedation, motor coordination, or hemodynamic changes following 1 or 7 day administration of BP4L-18:1:1 (Fig 5).

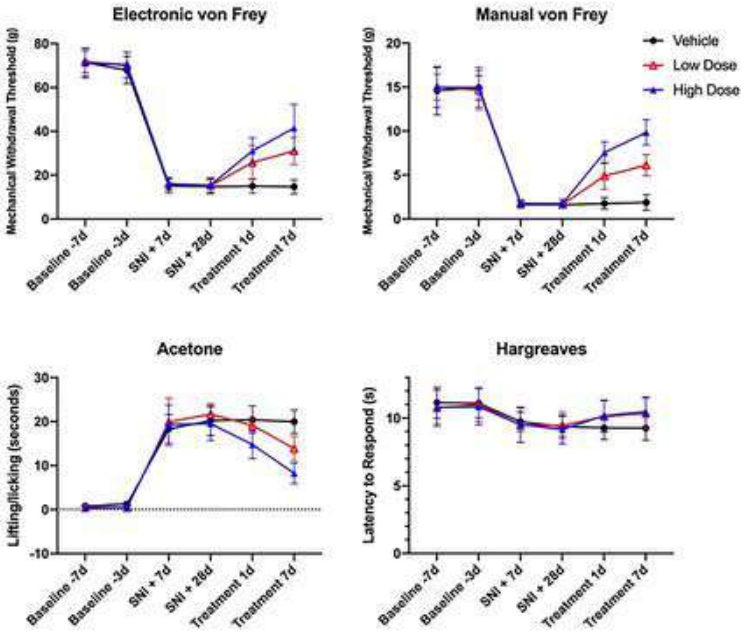
Conclusion: These data provide evidence that a "hindered" HCN1-selective inverse agonist is an effective antihyperalgesic with no apparent side effects and which has therapeutic potential.

References: 1. Nat Rev Dis Primers, 2017, 3: 17002. 2. JAMA, 2013, 309(13): 1359-67. 3. Cancer, 2007, 110(9): 2110-8. 4. BMJ, 2009, 339: b3002. 5. Lancet Neurol, 2015, 14(2): 162-73. 6. Curr Opin Neurol, 2009, 22(5): 467-74. 7. Br J Anaesth, 2008, 101(1): 48-58. 8. JAMA, 2018, 320(23): 2448-2460. 9. Cochrane Database Syst Rev, 2017, 5: CD012499. 10. Cochrane Database Syst Rev, 2017, 5: CD011669. 11. Cochrane Database Syst Rev, 2016, 10: CD011605. 12. Cochrane Database Syst Rev, 2016, 7: CD010692. 13. Int J Drug Policy, 2014, 25(6): 1124-30. 14. Medicine (Baltimore), 2019, 98(20): e15425. 15. MMWR Morb Mortal Wkly Rep, 2017, 66(26): 697-704. 16. JAMA Netw Open, 2018, 1(2): e180217. 17. J Pharmacol Exp Ther, 2013, 345: 363-373. 18. Biochem Pharmacol, 2019, 163: 493-508. 19. J Clin Invest, 2016, 126(7): 2547-60. 20. J Comput Chem, 2008, 29(11): 1859-65. 21. J Phys Chem B, 2010, 114(23): 7830-43. 22. Pain, 2000, 87(2): 149-58.



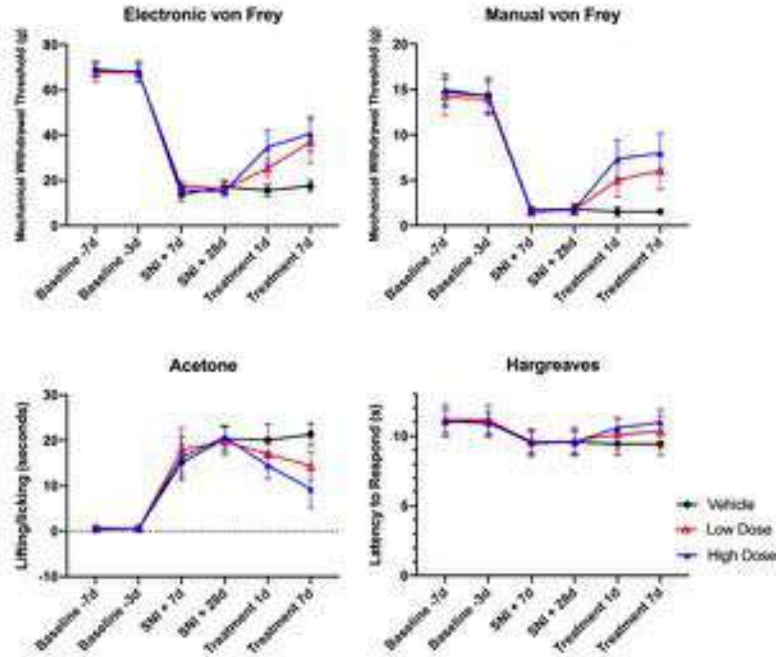


Male Rats

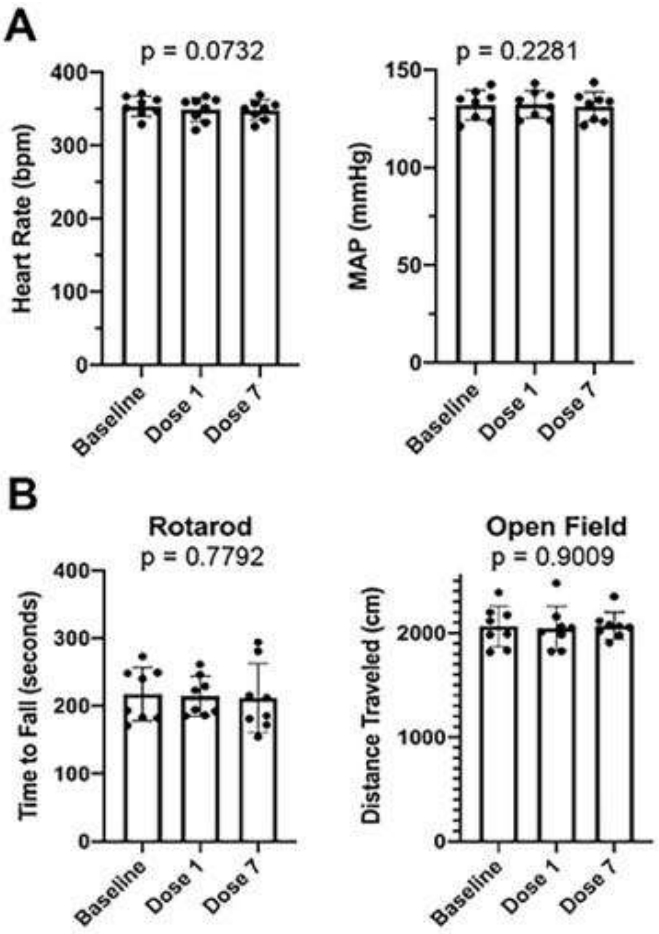


Timepoint	Comparison	Electronic von Frey	Manual von Frey	Acetone	Hargreaves
	ANOVA	F(10, 165) = 13.58	F(10, 165) = 19.74	F(10, 165) = 11.72	F(10, 165) = 10.47
Treatment, 1 day	Vehicle vs. Low Dose	p = 0.0014	p < 0.0001	NS; p = 0.4224	NS; p = 0.1428
	Vehicle vs. High Dose	p < 0.0001	p < 0.0001	p = 0.0006	NS; p = 0.1036
	Low Dose vs. High Dose	NS; p = 0.1645	p = 0.0003	p = 0.0014	NS; p = 0.9895
Treatment, 7 day	Vehicle vs. Low Dose	p < 0.0001	p < 0.0001	p < 0.0001	p = 0.0435
	Vehicle vs. High Dose	p < 0.0001	p < 0.0001	p < 0.0001	p = 0.0200
	Low Dose vs. High Dose	p = 0.0244	p < 0.0001	p < 0.0001	NS; p = 0.9609

Female Rats



Timepoint	Comparison	Electronic von Frey	Manual von Frey	Acetone	Hargreaves
	ANOVA	F(10, 165) = 25.97	F(10, 165) = 16.25	F(10, 165) = 10.89	F(10, 165) = 11.42
Treatment, 1 day	Vehicle vs. Low Dose	p < 0.0001	p < 0.0001	NS; p = 0.0502	NS; p = 0.2466
	Vehicle vs. High Dose	p < 0.0001	p < 0.0001	p = 0.0010	p = 0.0038
	Low Dose vs. High Dose	p = 0.0037	p = 0.0221	NS; p = 0.2751	NS; p = 0.4391
Treatment, 7 day	Vehicle vs. Low Dose	p < 0.0001	p < 0.0001	p < 0.0001	NS; p = 0.1111
	Vehicle vs. High Dose	p < 0.0001	p < 0.0001	p < 0.0001	p = 0.0008
	Low Dose vs. High Dose	NS; p=0.6061	NS; p > 0.0862	p < 0.0071	NS; p > 0.2666


A
p = 0.0732
Heart Rate (bpm)
400
300
200
100
0
Baseline
Dose 1
Dose 7
p = 0.2281
MAP (mmHg)
150
100
50
0
Baseline
Dose 1
Dose 7
B
Rotarod
p = 0.7792
Time to Fall (seconds)
400
300
200
100
0
Baseline
Dose 1
Dose 7
Open Field
p = 0.9009
Distance Traveled (cm)
2000
1000
0
Baseline
Dose 1
Dose 7

Pain Mechanisms - 5 Evidence of Anxiety but not Depression in a novel rat model of Fibromyalgia

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Introduction: The Fibromyalgia syndrome (FMS) is one of the most common chronic widespread pain syndromes in the US and has a profound cumulative impact on the nation. Diagnosis of FMS relies on nonspecific clinical characteristics including chronic widespread pain, tenderness to pressure stimuli, fatigue, sleep disturbances, mood impairments, and cognitive difficulties. Despite similar prevalence, several studies have shown anxiety, but not depressive symptoms, appear to be causally associated with pain and pain interference in FMS patients.[3-5] Current FMS rodent models rely on measurements of thermal and mechanical hyperalgesia alone, and do not incorporate the other comorbid symptoms. We have identified the Dahl S rat as a novel model of FMS which exhibits spontaneous hyperalgesia. We hypothesized that it would also demonstrate symptoms consistent with anxiety but not depression.

Methods: We used the forced swim test and elevated plus maze behavioral studies to determine if male Dahl S (SS) rats exhibit signs of anxiety and depression compared to Sprague Dawley (SD) and Brown Norway (BN) rats. The forced swim test is used to assess depression-like behavior by measuring rodent behavioral despair. After a 15-minute pretest swim as a stressor event, the rat is observed during a subsequent 5-minute forced swim. Its failure to persist in escape-oriented behavior during the test is measured as immobility or freezing time (seconds). The elevated plus maze is a validated behavioral test for anxiety in rodent models. Less time spent exploring the open arms is indicative of higher levels of anxiety.

Results: SS rats (n=6) exhibited signs of anxiety by spending significantly less time in the open arms of the maze compared to BN and SD rats (Fig 1). In contrast, SS rats do not exhibit signs of depression, as they spent significantly less time frozen (i.e. not swimming) during the test (Fig 2).

Conclusion: Of all of the mood disturbances, several investigations show that anxiety and related hypervigilance symptoms are most associated with pain symptomatology in FMS,[6] and that anxious mood is not a reaction to the disease, but may represent a predisposing factor.[3-5] These results indicate that SS rats demonstrate idiopathic, persistent pressure point sensitivity and anxiety, which are traits shared with FMS patients, and conclude that SS rats demonstrate improved face and construct validities over other FMS rodent models.

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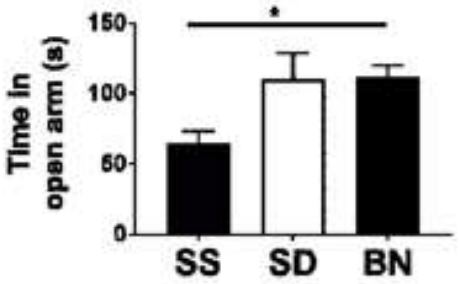

Figure 1. SS rats exhibit signs of anxiety. SS rats spent significantly less time in the open arms of an **elevated plus maze,** suggesting they exhibit greater anxiety than SD or BN rats. (n=6, *p<0.05, ANOVA).

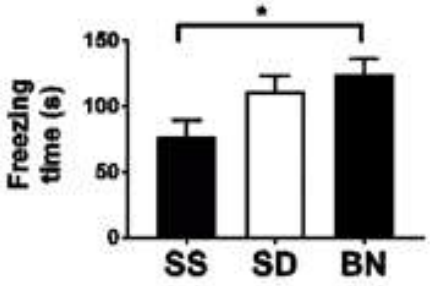

Figure 2. SS rats *do not* exhibit signs of depression. SS rats spent significantly less time frozen (not swimming) in the **forced swim test,** suggesting they do not exhibit signs of depression compared to SD or BN rats. (n=6, *p<0.05, ANOVA).

Pain Medicine

Pain Medicine - 1 Social Isolation-Induced Worsening of Chronic Pain: The Protective Effect of Introversion

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Introduction: The COVID-19 pandemic social distancing mandates have increased levels of social isolation, a change which appears to have impacted some chronic pain patients more than others. Previous research suggests that feelings of loneliness and sleep disturbance may importantly modulate pain. In the present study, we examined whether the personality trait of introversion served as a protective factor against worsening pain interference during conditions of social isolation, and whether this was related to differences in sleep disturbance and loneliness.

Methods: Chronic pain patients in Massachusetts (n=150) completed electronic questionnaires 4-8 weeks after the state-wide social distancing mandate. Validated questionnaires included the Brief Pain Inventory(BPI), Myers-Briggs introversion/extroversion subscale (1-10), UCLA Loneliness and PROMIS Sleep Disturbance short forms. Change scores were calculated by subtracting recalled scores from current scores. Linear regression was used to assess association between factors, and mediation analyses were used to assess the degree to which other factors mediated the relationship between introversion and change in pain interference.

Results: Introversion scores were inversely related to increased pain interference since social distancing (Rho=-0.194, p=0.017), such that patients with higher introversion scores showed little to no change in pain interference, compared to more extroverted patients. Higher introversion was also associated with lower increases in sleep disturbance (Rho=-0.163, p=0.046) and loneliness (Rho=-0.279, p=0.001) since social distancing. Multiple simple mediation analyses revealed that the relationship between introversion and change in pain interference was partially mediated by differential changes in sleep disturbance and loneliness.

Conclusion: Chronic pain patients experience varying degrees of worsening of pain interference with social distancing, which may be partially explained by their degree of introversion/extroversion. In particular, more introverted patients appeared to be partially protected, experiencing less of an increase in loneliness and sleep disturbance and, in turn, less of an increase in pain interference.

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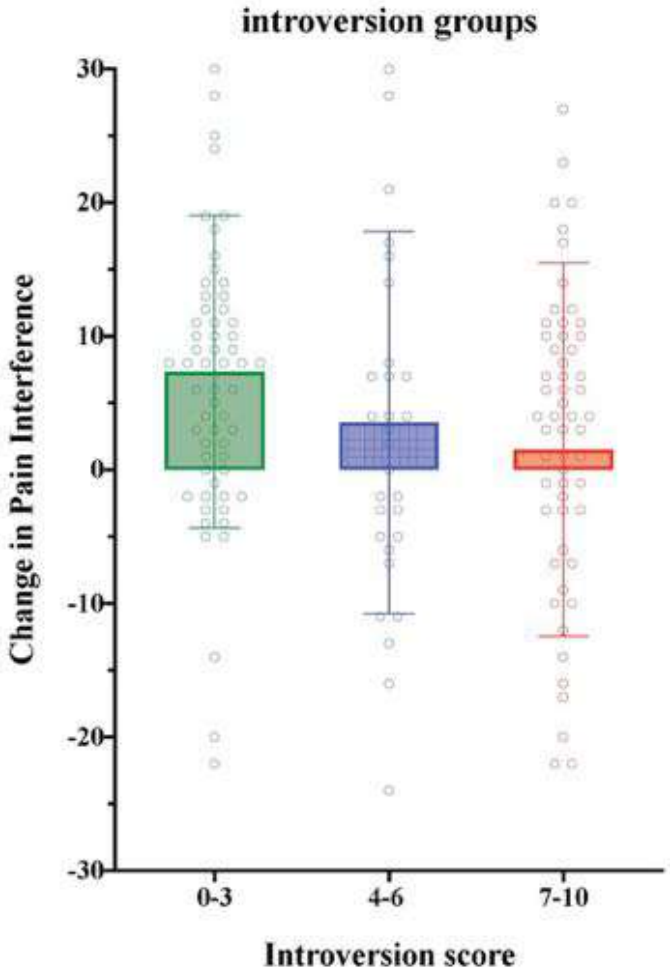
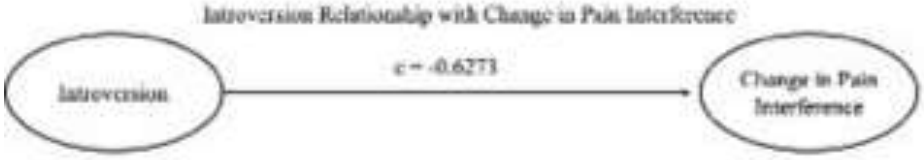
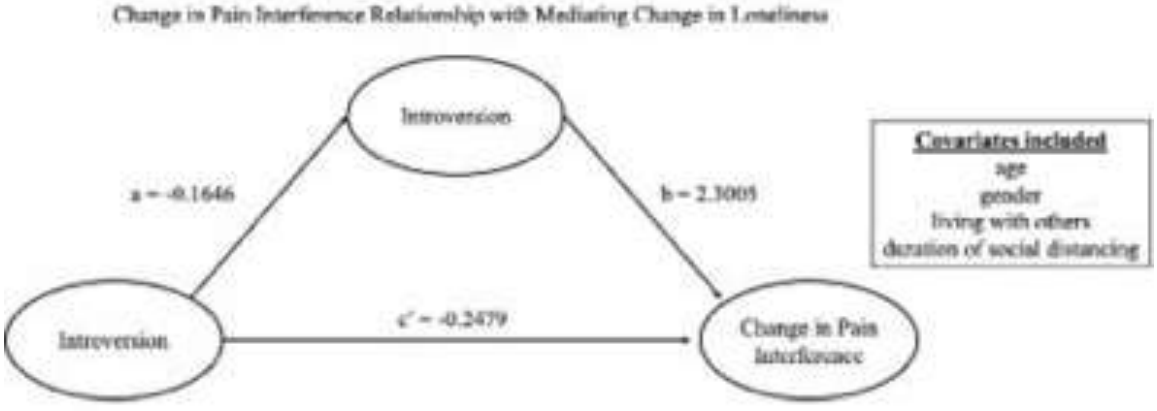

introversion groups
Change in Pain Interference
30
20
10
0
-10
-20
-30
0-3
4-6
7-10
Introversion score


Introversion Relationship with Change in Pain Interference
Introversion
c = -0.6273
Change in Pain Interference


Change in Pain Interference Relationship with Mediating Change in Loneliness
Introversion
a = -0.1646
b = 2.3005
Introversion
c' = -0.2479
Change in Pain Interference
Covariates included
age
gender
living with others
duration of social distancing

Pain Medicine - 2 Association of Postoperative Opioid Misuse with Prolonged Postoperative Pain, Opioid Use, and Delayed Recovery

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Introduction: Opioid exposure during surgical recovery is associated with risks such as the development of new persistent postoperative opioid use. With prolonged postoperative opioid exposure, little is also known about the resulting risks for developing opioid misuse. Currently, available measures of opioid misuse have not been validated among surgical patients, and the link between postoperative opioid misuse and postoperative pain, opioid use, and recovery long after hospital discharge has not been examined.

Methods: A secondary analysis of the Stanford Accelerated Recovery Trial, a randomized, double-blinded trial was conducted at a single-center of 422 participants in a mixed surgical cohort between May 25, 2010, and July 25, 2014. Of the 422 patients enrolled, 381 patients on post-operative opioids with 7.6 % missing data were included in the analysis. After discharge from surgery, a modified Brief Pain Inventory was administered over the phone to assess pain related to the surgical site using the Numeric Pain Rating Scale, opioid medication use, and recovery. Calls occurred daily for the first 3 months, weekly thereafter up to 6 months, and monthly thereafter until patients reached pain cessation, opioid cessation, and full recovery up to 2 years after surgery, amounting to 19,511 distinct postoperative calls. The presence of opioid misuse behavior was defined as any use of opioid medication for sleep or using more opioid than prescribed. Multivariate Cox proportional hazards regression was conducted for time to opioid cessation (defined as the first of 5 consecutive days of no opioid use), pain cessation (defined as the first of 5 consecutive days of 0 out of 10 pain on the NRS) and surgical recovery (defined as a 'yes' response to the question of complete surgical recovery). Data-mining algorithms were applied using the R programming language, version 3.3 (R Foundation), and subsequent statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc).

Results: Postoperative opioid misuse was significantly associated with an increased time to pain resolution (hazard ratio [HR], 0.52; P < 0.001), delayed opioid cessation (HR, 0.44; P < 0.001) and prolonged surgical recovery (HR, 0.67; P <0.001).

Conclusion: These findings suggest the presence of postoperative opioid misuse is associated with worse postoperative outcomes including prolonged pain, opioid use, and delayed recovery. Future studies are needed to replicate these findings, and to validate postoperative opioid misuse assessments.

Pain Medicine - 3 Best pre-discharge time intervals of opioid intake as predictor of post-discharge opioid use after surgery to inform opioid prescribing

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Introduction: Following inpatient surgery, opioids are often prescribed using a one-size-fits-all regimen rather than a patient-centered approach.(1) To reduce the quantity of unnecessary opioids prescribed post-discharge, it has previously been demonstrated that pre-discharge opioid use is the most reliable and practical predictor of post-discharge opioid intake following surgery.(2-4) However, the most appropriate pre-discharge time frame to be used for the prediction of post-discharge opioid use is not known. While longer time frames before discharge could yield more comprehensive information on analgesic requirements, they would more likely include the immediate post-operative period during which analgesic requirements could be lower (e.g., from residual local anesthetic effect) or higher (e.g., from the more recent response to tissue damage). Conversely, shorter (<24h) time frames closer to discharge may be unevenly impacted by diurnal/nocturnal variations in activity. This study investigated the strength of the association between the quantity of opioids taken during four pre-discharge time frames (48h, 24h, 12h, and 6h) and self-reported opioid intake over four weeks post-discharge after three categories of inpatient surgery (Cesarean section, thoracic surgery, and gastrointestinal surgery). We hypothesized that the 24h pre-discharge time frame would show the strongest correlation with post-discharge use.

Methods: The local institutional review board approved this study prior to enrollment of the first patient. Written informed consent was obtained from all subjects or their legal surrogates. This study was prospectively registered at clinicaltrials.gov, NCT03034278. We conducted a secondary analysis of outcomes reported in three prospective cohort studies in 587 adult patients undergoing Cesarean section, thoracic, and gastrointestinal surgery.(3-5) These patients were followed with four weekly surveys that yielded >80% response rates.(3-5) For this study, pre-discharge opioid use during four pre-discharge time frames: 48h, 24h, 12h, and 6h was assessed by individual chart review of the electronic medication administration records. These quantities were converted to oral milligram morphine equivalents (MME) for comparison.(6-7) Since these records listed medication administration hourly, discharge times were rounded to the nearest hour. Data for patients with hospital stays less than 48 hours were excluded. Spearman rank correlation coefficients were calculated to estimate the association between the quantity of opioids taken pre-discharge with self-reported cumulative opioid use during the first four weeks following discharge.

Results: We found the strongest association with post-discharge opioid use for the 24h window ($\rho=0.59$, $p < 0.01$). The weakest correlations were with the 48h and 6h windows ($\rho=0.55$, $p < 0.01$, $\rho=0.49$, $p < 0.01$), Table 1. Our hypothesis that the 24h window provides the most useful pre-discharge opioid intake information for predicting opioid use following discharge was confirmed.

Conclusion: When comparing different time frames of pre-discharge opioid intake in 587 patients who underwent inpatient surgery, we found that 24h pre-discharge opioid use yields the strongest association with four-week post-discharge opioid use. Consistent with our findings, guidelines for post-discharge prescriptions after surgery recommend a tiered approach toward determining the total quantity of opioids to be prescribed.(8) The feasibility and effectiveness of using 24h pre-discharge opioid intake to appropriately inform post-discharge analgesic prescriptions deserves further study.

References: 1. Opioid Use and Storage Patterns by Patients after Hospital Discharge following Surgery. PLoS One. 2016 Jan 29;11(1):e0147972. 2. Correlation between 24-Hour Predischarge Opioid Use and Amount of Opioids Prescribed at Hospital Discharge. JAMA Surg. 2018;153:e174859. 3. Postdischarge Pain Management after Thoracic Surgery: A Patient-Centered Approach. Ann Thorac Surg. 2020;110:1714-21. 4. Predicting Opioid Use Following Discharge after Cesarean Delivery. Ann Fam Med. 2020;18:118-26. 5. Opioid and Non-Opioid Utilization at Home Following Gastrointestinal Procedures. Surg Endosc. 2020;34:304-11. 6. Clinical application of opioid equianalgesic data. Clin J Pain. 2003 Sep-Oct;19(5):286-97. 7. Association of increased postoperative opioid administration with non-small-cell lung cancer recurrence: a retrospective analysis. Br J Anaesth. 2014 Jul;113 Suppl 1:i88-94. 8.A Pathway for Developing Postoperative Opioid Prescribing Best Practices. Ann Surg. 2020 Jan;271(1):8

Pre-discharge time frames	Spearman rank correlation ρ	P value
6 hours	0.49	<0.01
12 hours	0.56	<0.01
24 hours	0.59	<0.01
48 hours	0.55	<0.01

Table 1: Correlations of opioid intake during different pre-discharge time frames with post-discharge opioid use in surgical patients.

Pain Medicine - 4 The Effect of Covid-19 on the Opioid Epidemic

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Introduction: The opioid epidemic is a serious national crisis that has detrimental impacts on both public health, and social and economic welfare. Therefore, any efforts to combat the opioid epidemic, including minimizing or weaning opioid prescriptions, and using other modes of analgesia when possible are undeniably necessary in this day and age. With the onset of Covid-19 pandemic, healthcare providers abruptly changed their care delivery. In-person clinic visits were changed to telemedicine, and elective cases were cancelled. Due to a growing concern that chronic pain patients may have limited resources from this unprecedented time of social and economic shutdown, organizations such as American Medical Association and Drug Enforcement Administration have supported implementing measures to ensure these patients achieve adequate pain control by increasing access to pain medications, but at the cost of reducing barriers and restrictions to controlled substances. Some of these policies include allowing all 'authorized practitioners' to prescribe controlled substances via telemedicine without first conducting an in-person examination, and removing existing barriers for patients, which includes dose, quantity, refill restrictions on controlled substances. Given the cancellation of elective interventional pain management procedures and relaxed regulations on controlled substances during the Covid-19 pandemic, it is reasonable to suspect a dramatic increase in opioid prescription during this time. However, to my understanding, there are no reports measuring the rate of opioid prescriptions during the pandemic although there has been numerous reports of increased rates of opioid-overdose related cases when compared to previous years. Our study focused on the change in opioid consumption in chronic pain patients who were unable to undergo their interventional pain procedure during the Covid-19 pandemic. By demonstrating whether or not there has been a significant increase in opioid consumption in this patient population, we can justify the efficacy and necessity of these procedures. A significant increase can also support the importance of creating protocols that allow for elective interventional pain procedures to continue during the next pandemic.

Methods: Our study took place at King's County Hospital Center. It is a retrospective chart review study that looked at chronic pain patients who were scheduled for an interventional pain procedure from the months of March 1st to May 30th, 2020 using EPIC and QuadraMed. Study has been approved to be IRB exempt. Subjects were classified into groups based on their cancelled interventional pain procedure, including ESI, SI joint injections, and intra-articular facet joint injections. For each patient, the frequency and dose of each opioid prior to and after notification of their cancelled procedure were recorded. The change in opioid consumption was calculated by measuring the change in morphine milligram equivalents per day (MME/day).

Results: A total of 22 subjects were included in the study. 91% were female and 9% were male. The mean change in opioid consumption (MME/day) in all subjects showed a statistically significant increase of +14.96 (95% CI [2.04, 27.87], p = 0.02). The mean change in opioid consumption was determined for subjects categorized based on procedure scheduled. The mean changes in opioid consumption (MME/day) in subjects scheduled for lumbar ESI (7 subjects), SI joint injection (4 subjects), intra-articular facet joint injection (6 subjects), both intra-articular facet joint injection and SI joint injection (5 subjects) were +9.64 (95% CI [-5.72, 25.01], p = 0.17), +1.13 (95% CI [-2.45, 4.71], p = 0.39), +26.92 (95% CI [-23.49, 77.32], p = 0.23), and +19.1 (95% CI [-13.20, 51.40], p = 0.17). Subjects were also stratified based on whether or not they received the same procedure in the past. Subjects who received the same procedure in the past (8 subjects) showed a mean change in opioid consumption of +31.44 (95% CI [-3.86, 66.73], p = 0.07), while subjects who were scheduled to receive the procedure for the first time (14 subjects) showed a mean change in opioid consumption of +5.54 (95% CI [-1.50, 12.57], p = 0.11).

Conclusion: The mean change in opioid consumption (MME/day) in all subjects showed a statistically significant increase (+14.96 MME/day, p-value = 0.02). This may justify the need for a protocol that allows for elective interventional pain procedures to continue in a future pandemic.

References: 1. Data Overview." Opioid Overdose, Centers for Disease Control and Prevention, 2019. 2. What impact has COVID-19 had on outpatient visits? (n.d.). Commonwealth Fund. https://www.commonwealthfund.org/publications/2020/apr/impact-covid-19-outpatient-visits 3. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse; Phillips JK, Ford MA, Bonnie RJ, editors. Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. Washington (DC): National Academies Press (US); 2017 Jul 13. 4, Trends in Opioid Use, Harms, and Treatment. 4. COVID-19: DEA and SAMHSA guidance for treating opioid use disorders via Telehealth. (n.d.). JD Supra. https://www.jdsupra.com/legalnews/covid-19-dea-and-samhsa-guidance-for-62582/ 5. Knopf, A. (2020). AMA COVID-19 recommendations: MAT, pai

	Total number of subjects	Mean change in opioid consumption (MME/day)	p-value
Lumbar ESI	7	9.64 CI[-5.72, 25.01]	0.17
SI joint injection	4	1.13 CI[-2.45,4.71]	0.39
Intra-articular facet joint injection	6	26.92 CI[-23.49,77.32]	0.23
Intra-articular facet join injection + SI joint injection	5	19.1 CI[-13.20,51.40]	0.17
Patients who received procedure in the past	8	31.44 CI[-3.86,66.73]	0.07
Patients receiving procedure for the first time	14	5.54 CI[-1.50,12.57]	0.11

Total change in opioid consumption (MME/day) in all subjects				
Subject	Sex	Opioid consumption prior to cancelled procedure (MME/day)	Opioid consumption after cancelled procedure (MME/day)	Change in MME/day
1	F	[illegible]	[illegible]	[illegible]
2	F	0	45	45
3	F	[illegible]	[illegible]	[illegible]
4	F	[illegible]	[illegible]	[illegible]
5	F	[illegible]	[illegible]	[illegible]
6	F	[illegible]	[illegible]	[illegible]
7	F	[illegible]	[illegible]	[illegible]
8	F	[illegible]	[illegible]	[illegible]
9	F	[illegible]	[illegible]	[illegible]
10	F	[illegible]	[illegible]	[illegible]
11	F	[illegible]	[illegible]	[illegible]
12	F	[illegible]	[illegible]	[illegible]
13	F	[illegible]	[illegible]	[illegible]
14	F	[illegible]	[illegible]	[illegible]
15	F	[illegible]	[illegible]	[illegible]
16	F	[illegible]	[illegible]	[illegible]
17	F	[illegible]	[illegible]	[illegible]
18	F	[illegible]	[illegible]	[illegible]
19	F	[illegible]	[illegible]	[illegible]
20	M	[illegible]	[illegible]	[illegible]
21	F	[illegible]	[illegible]	[illegible]
22	M	[illegible]	[illegible]	[illegible]
Mean				[illegible]
p-value				[illegible]

Pain Medicine - 5 Association between the Number of Prescribers of Concurrent Opioid and Benzodiazepine Medications and the Risk of Overdose: A Retrospective Analysis

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Introduction: Previous work has shown that having a greater number of providers involved in prescribing opioids is associated with an increased risk of an emergency room visit or inpatient admission for overdose.1 Furthermore, concurrent prescriptions of opioids and benzodiazepines have been associated with an increased risk of overdose compared to prescriptions for either drug class alone.2,3 However, it remains unknown if there is a relationship between the number of providers responsible for prescribing concurrent opioids and benzodiazepines and the risk of overdose. This study used a large national database of health insurance claims to examine this question.

Methods: The data consist of administrative health claims provided by the Optum©'s Clinformatics® Data Mart. The final sample included 2,000,529 patients aged 18-89 with no history of cancer and any concurrent benzodiazepine and opioid prescriptions between January 1, 2003 and June 30, 2019. The primary outcome was whether a patient had an emergency room visit or inpatient admission for overdose which occurred within 30 days of being prescribed both a benzodiazepine and an opioid. Using previously described methods,4,5 we defined overdose to be an admission or visit with ICD-9 or ICD-10 codes indicating poisoning by benzodiazepine-based tranquilizers, opioids, sedatives, or hypnotics. Our independent variable of interest was the number of unique providers responsible for prescribing benzodiazepines and opioids for each patient based upon the National Provider Identifier (NPI) associated with each prescription. We analyzed the distribution of demographic and comorbidity data using descriptive statistics including means and 95% confidence intervals. We then estimated the association between the number of prescribers and the risk of overdose by using multivariable proportional hazard regression modeling, which included adjustments for potential confounders including age, sex, patient comorbidities, as well as the average daily doses of benzodiazepines and opioids in diazepam milligram equivalents (DME) and morphine milligram equivalents (MME) respectively. The model aggregated data in 30-day intervals of continuous concurrency of benzodiazepine and opioid prescriptions for each patient. Gaps in concurrency less than 30 days were considered continuous, while gaps greater than 30 days were treated as separate events in the model. The number of prescribers was measured using the NPI associated with each prescription and was modeled based upon whether the patient had one, two, three, or four or more prescribers of benzodiazepines or opioids during each 30-day period. Hazard ratios were then calculated comparing the risk of overdose for patients with two, three, and four or more providers compared to having one provider.

Results: The average age of was 51 years (SD 16 years), with 1,301,038 (64.8%) female patients. The average duration of concurrency was 129 days (SD 248 days), and the average number of providers was 2.0 (SD 0.5 providers). 11,838 (0.6%) patients had an overdose event. Prior to adjustment, the risk of overdose was higher for increasing number of providers compared to 1 provider prescribing concurrent benzodiazepine and opioid medications (2 providers: hazard ratio 1.24, 95% CI 1.17 to 1.31, p<0.001; 3 providers: hazard ratio 2.24, 95% CI 2.10 to 2.40, p<0.001; 4+ providers: hazard ratio 4.45, 95% CI 4.11 to 4.82, p<0.001). After adjusting for potential confounders, the risk of overdose remained higher when a greater number of providers were responsible for prescribing concurrent benzodiazepine and opioid therapy compared to 1 (2 providers: hazard ratio 1.08, 95% CI 1.02 to 1.15, p=0.008; 3 providers: hazard ratio 1.42, 95% CI 1.33 to 1.52, p<0.001; 4+ providers: hazard ratio 2.10, 95% CI 1.93 to 2.28, p<0.001) (Table 1, Figure 1).

Conclusion: In this retrospective analysis of 2,000,529 patients with concurrent prescriptions for benzodiazepines and opioids, an increased number of providers responsible for prescribing these medications was associated with an increased risk of an emergency room visit or inpatient admission for overdose. This increased risk was also observed after adjusting for patient demographics, comorbidities, and the doses of opioid and benzodiazepine being prescribed. These results provide support for policies which encourage the fewest possible number of providers to manage prescriptions for medications associated with a potentially synergistic risk of overdose.

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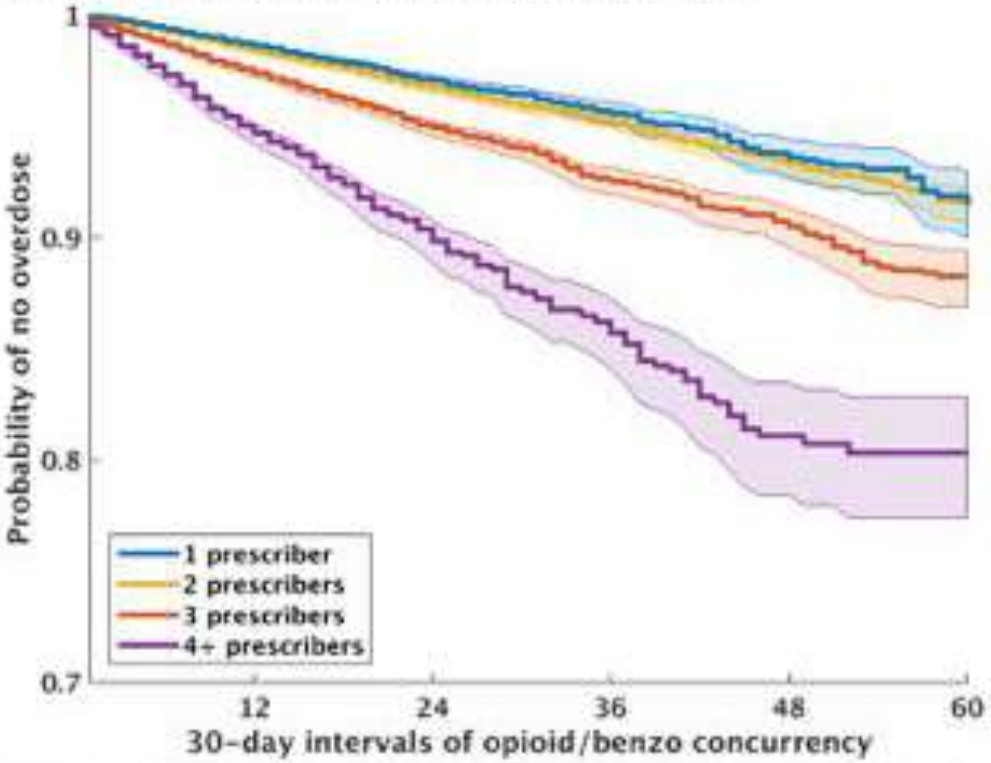
Table 1. Primary outcomes

Number of prescribers	Unadjusted		Adjusted	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-Value
2 prescribers	1.24 (1.17 to 1.31)	P<0.001	1.08 (1.02 to 1.15)	P=0.008
3 prescribers	2.24 (2.10 to 2.40)	P<0.001	1.42 (1.33 to 1.52)	P<0.001
4+ prescribers	4.45 (4.11 to 4.82)	P<0.001	2.10 (1.93 to 2.28)	P<0.001

The unadjusted and adjusted results of the hazard analysis show an association between having a greater number of prescribers for concurrent opioids and benzodiazepines and increased risk of having an emergency room visit or inpatient admission for overdose.

Figure 1: Kaplan-Meier survival curve for the probability of overdose



The Kaplan-Meier curve for the probability of overdose is shown. A greater number of providers was associated with increased risk of overdose.

Pain Medicine - 6 Positive airway pressure therapy for chronic pain in patients with obstructive sleep apnea - a systematic review

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Introduction: Patients with chronic pain often have sleep-disordered breathing (SDB), which includes obstructive sleep apnea (OSA) [1]. Evidence has demonstrated that individuals with chronic pain who report higher pain intensity also experience greater sleep impairment and vice versa [2]. The standard management of OSA is positive airway pressure therapy (PAP). Although there is robust evidence supporting PAP's use in improving the Apnea-Hypopnea Index of OSA, its use in improving pain is mostly unknown. Our goal was to evaluate whether PAP for OSA in the chronic pain population improves pain outcomes, including pain intensity, tolerance, and threshold.

Methods: We performed a systematic search for studies published after 1990, utilizing Medline, Medline In-Process/ePubs, Embase, Cochrane CENTRAL, and the Cochrane Database of Systematic Reviews. Blocks of search terms included 'chronic pain,' 'sleep disorders,' and 'positive airway pressure.' Two reviewers independently performed the abstract and full-text screening, data extraction, and study quality appraisal.

Results: Of 1,982 initial results, ten studies met the inclusion criteria. These studies included 323 chronic pain patients with OSA who underwent PAP and 64 chronic pain patients with OSA who were not adherent to PAP. The average age was 52 ± 12 years, and 80% were male. Six studies investigated chronic headaches. One study investigated chronic non-headache pain. Three studies focused on patients' pain tolerance or threshold (surrogate markers of pain outcomes). Of the six studies examining headaches, five demonstrated improved pain outcomes at follow-up, ranging from one-day to 42 months. In one study, PAP resulted in a decreased morning headache prevalence; but, the result was non-significant ($p = 0.065$). The study examining PAP's effect on non-headache pain found that PAP didn't significantly decrease pain intensity ($p > 0.05$). Out of three studies measuring pain tolerance or threshold, PAP significantly improved these outcomes in two studies ($p = 0.03$ and $p = 0.01$). Conversely, in another cohort study, PAP for one month resulted in a decreased pain threshold ($p = 0.027$).

Conclusion: In chronic pain patients with OSA, we found that PAP decreased chronic headaches. Our results also support the idea that PAP may increase pain threshold and tolerance. However, a gap in the literature exists regarding PAP's effectiveness in improving chronic non-headache pain. One study found a lack of pain intensity improvement, which may be due to patients with more psychiatric comorbidities and more neuropathic pain. Another study also found a lack of PAP effectiveness, which may be due to unfamiliarity with PAP, causing muscle tension and lower pain thresholds. The advancement of this understanding would help inform the promotion of OSA screening in patients with chronic pain, pain management in OSA patients, and PAP's potential use as an adjunct/alternative therapy to current analgesics.

Table 1. Study outcomes

Study	Study Design; Population [n]	Pain classification	PAP therapy duration	Outcome Measure	Conclusion	Effect of PAP
Chronic pain						
Pocalis, 1995	Pre-post cohort; 14	Headache type: •Cluster: 1 •Migraine: 5 •Tension: 3 •Mixed: 5	CPAP; range, 4–36 months	Morning headache questionnaire: Frequency of waking up with a headache (never, 'rarely', 'weekly', or 'nightly'. 'Weekly or 'nightly' considered symptomatic	CPAP; 50% overall showed headache improvement •Cluster: 1/1 •Migraine: 3/5 •Tension: 0/3 •Mixed: 3/5	Positive
Loh, 1999[9]	Retrospective pre-post cohort; 25	Headache type: •Headache AM: 23 •Tension: 12 •Migraine: 9 •Cervicogenic: 5 •Cluster: 1 •Other: 12	CPAP; duration NR	Telephone interview: Numerical rating scale of headache improvement: 0-100% (in increments of 10%), lowest to highest	Headache AM or cluster: CPAP average of 80% headache improvement Tension, migraine, or cervicogenic: CPAP; minimal improvement	Positive
Goksan, 2009	Retrospective pre-post cohort; 76	Headache AM; 76	CPAP; follow up; 1 day, 1 week, and 1 month	Morning headache questionnaire: Presence of morning headache (yes/no)	1 day, 1 week, 1 month headache improvement; 72.4%, 84.2%, 92.1% showed headache improvement	Positive
Kallweit, 2011	Pre-post cohort; 11	Migraine; 11	CPAP; 12 months	Migraine disability assessment scale	Attack frequency post-CPAP vs baseline: 0.1 ± 0.3 vs. 5.8 ± 7.8 attacks per month (p < 0.05) Attack duration post-CPAP vs baseline: 0.5 ± 0.7 vs. 8.4 ± 11.9 hours (p = 0.05) Intensity of attacks (VAS) post-CPAP vs. baseline: 2.1 ± 3.2 vs. 7.4 ± 1.7 (p = 0.001) Workdays lost post-CPAP vs. baseline: 0.2 ± 0.3 vs. 1.8 ± 2.2 days/month (p = 0.05) Acute antimigraine medication post-CPAP vs. baseline: 0 vs. 6.5 ± 8.0 units/month (p = 0.05)	Positive

Cruz, 2012	Pre-post cohort; 97	Headache AM; 10	APAP; 6 months	Sleep Disorder Questionnaire Presence of morning headache; 5-point Likert scale, '4' or '5' considered symptomatic	Post-APAP vs. baseline: 3.0% vs. 10.0% considered symptomatic (p = 0.065)	Negative
Johnson, 2013[a]	Retrospective cohort; CPAP adherent: 27 CPAP non-adherent: 6	Headache-type: • Migraine • Tension • Post-traumatic • Medication-overuse • Total: 27	CPAP range, 18–42 months	Telephone interview Headache improvement definition: ≥50% reduction in headache severity and frequency	CPAP adherent vs. CPAP non-adherent or no CPAP: 78% vs. 33% or 42% showed headache improvement (p = 0.045)	Positive
Jacobs, 2018	Retrospective cohort; CPAP adherent: 35 CPAP non-adherent: 58	Non-malignant pain	CPAP: 12 months	Numerical Categorical Scale Pain intensity scored from 0-10, lowest/highest	CPAP adherent at 12 months vs. baseline: 1.9 ± 1.5 vs. 2.1 ± 1.4 (p > 0.05) CPAP non-adherent at 12 months vs. baseline: 2.6 ± 1.5 vs. 2.7 ± 1.4 (p > 0.05)	Negative
Pain tolerance or threshold						
Orem, 2010[b]	Randomized blinded crossover; 11	Pain tolerance	CPAP: 3 days[c]	Pain Matcher Pain tolerance scored from 0-99, lowest/highest	Mean tolerance post-high CPAP Rx vs baseline: 28.4 ± 16.0 vs. 21.2 ± 10.9 (p = 0.03) Mean tolerance post-low CPAP Rx vs. baseline: 23.9 ± 12.4 vs. 21.2 ± 10.9 (p = 0.44)	Positive
Khalid, 2011	Pre-post cohort; 12	Pain threshold	CPAP: follow up 2 nights, and 6–8 weeks	Finger Withdrawal Latency Testing Time until finger was withdrawn from heat source in seconds	Post-CPAP (2 nights) vs. baseline 13.7 ± 5.1 vs. 9.8 ± 1.3 sec. (p = 0.01) Post-CPAP (6-8 weeks) vs. CPAP discontinuation 21.1 ± 16.2 vs. 11.5 ± 5.9 sec., (p = 0.03)	Positive
Jhaveri, 2016	Pre-post cohort; 15	Pain threshold	CPAP: 1 month	Digital Dashboard Algometer (in kg/m²)	Post-CPAP therapy vs. baseline: 1.51 vs. 2.02 (p = 0.027)[d]	Negative

[a]Headache-types were not mutually exclusive.
[b]Distribution of headache-types not stated.
[c]Subjects randomized to 2 consecutive 3-day sequences, either beginning with low CPAP or high CPAP.
[d]Low CPAP: 4 cm H_2O, high CPAP: 5 to 10 cm H_2O auto-adjusted CPAP.
[e]All pain models analyzed displayed similar significant decreases in pain threshold.

Pain Medicine - 7 Preclinical evaluation of a novel glycinergic analgesic for treatment of chronic pain in rodents

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Introduction: About 10% of the world's population suffers from chronic pain. Current treatment relies heavily on opioids, which carry the risk of drug abuse. The discovery and development of effective analgesics devoid of the potential for abuse are urgently needed. Glycine receptors (GlyRs) are the major inhibitory ion channels in the spinal cord and brain stem. Positive allosteric modulators (PAMs) capable of enhancing glycinergic tone are expected to reduce nociceptive signaling and potentially serve as effective analgesics for chronic pain.1-3 We previously identified MJPY1 as an α3GlyR-selective PAM through structure-based screening and electrophysiology measurements4, 5. Here, we report in vivo studies of MJPY1 as a novel analgesic that presents a new opportunity for future non-opioid treatment of chronic pain.

Methods: All protocols and procedures involving animals were approved by the University of Pittsburgh Institutional Animal Care and Use Committee. Chronical pain models were generated using male Sprague-Dawley rats and male CD1 mice at the age of 6 weeks. Neuropathic pain was induced by a chronic constriction injury (CCI) of the left sciatic nerve of rats. Inflammatory pain was induced by subcutaneous (s.c.) injection of Complete Freund's Adjuvant (CFA, 1 mg/ml) to the plantar surface of the left rear paw of mice (5 μL) or rats (50 μL CFA diluted by pH 7.4 PBS to 100 μL). Behavioral assessment of chronic pain in the absence and presence of MJPY1 was conducted at least 10 days after CCI or 24 hrs after CFA injection to allow neuropathic or inflammatory hyperalgesia to fully develop. Rodents with sham surgical operation or saline injection were used as negative controls for CCI and CFA groups, respectively. Antinociceptive effects of MJPY1 on neuropathic or inflammatory hyperalgesia were quantified by the percent maximum possible effects (%MPE) in the thermal place preference test (TPPT)6, Hargreaves test and Von Frey test. Morphine (5 mg/kg, s.c.) and pregabalin (30 mg/kg, s.c.) were used as positive analgesic controls in TPPT. The non-opioid mode of MJPY1 action was established by conducting Hargreaves and Von Frey tests in the absence and presence of naloxone, an antagonist of opioid receptors. At least 6 rodents were used for each testing condition. Data were collected 1.5 hrs post MJPY1 administration, fit to the Hill equation, and are expressed as means ± SEM. Statistical analyses were conducted with one-way ANOVA and Dunnett's post hoc test to compare results generated with and without MJPY1 treatment.

Results: In the TPPT, MJPY1 (3mg/kg, s.c.), along with morphine (5 mg/kg, s.c.) and pregabalin (30 mg/kg, s.c.), alleviated cold allodynia of CCI rats so that they spent a significantly ($p<0.0001$) longer time on the cold plate (12.5 ± 0.5°C vs 30° ± 0.5°C) than those receiving only vehicle. CCI rats or CFA mice showed dose-dependent responses to MJPY1 (i.p. or s.c.) in both Hargreaves and von Frey tests, demonstrating high MJPY1 potency (≤ 2.8mg/kg) and efficacy (>70% MPE) on thermal and mechanical hypersensitivity in both pain models. A battery of in vivo tests was performed to assess the potential of MJPY1 for substance use disorder. We found that MJPY1 alleviated neuropathic pain in CCI rats independent of opioid receptors. Antinociceptive effects produced by MJPY1 (3 mg/kg, s.c.) on CCI rats showed no statistical difference between groups with and without the administration of naloxone (3 mg/kg, s.c.) in Hargreaves ($p=0.15$) and von Frey ($p=0.1$) tests based on statistical analyses with unpaired t-tests. Substance use disorder potential, such as drug seeking and reward behaviors, were investigated using the conditioned place preference test in naïve rats with repeated exposures to MJPY1. Rats conditioned with different doses of MJPY1 (1, 3, and 10 mg/kg, s.c.) or vehicle did not develop place preference in conditioning and post-conditioning tests. In contrast, rats conditioned with morphine (5 mg/kg, s.c.) showed a significant preference to the compartments paired with morphine in post-conditioning tests based on two-way repeated-measures ANOVA, Bonferroni post hoc test ($p < 0.001$).

Conclusion: MJPY1 is an effective analgesic with high potency against hyperalgesia in rodent models of chronic pain. Furthermore, MJPY1 neither acts through opioid receptors nor leads to development of reward behaviors associated with abuse liability. These qualities make MJPY1 an attractive alternative to current chronic pain treatments.

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new therapeutic target in pain pathways. Curr Opin Investig Drugs 7, 48-53 (2006). 3. Fast synaptic inhibition in spinal sensory processing and pain control. Physiol Rev 92, 193-235 (2012). 4. Structure-Based Discovery of Novel Glycinergic Modulators. Biophys J 112, 556a (2017). 5. Ensemble-based virtual screening for cannabinoid-like potentiators of the human glycine receptor α1 for the treatment of pain. J Med Chem 58, 2958-2966 (2015). 6. A Thermal Place Preference Test for Discovery of Neuropathic Pain Drugs. ACS Chem Neurosci 11, 1006-1012 (2020).

Pain Medicine - 8 Morphine causes Reduced Tumor Growth through Modulation of IDH1 Activity in Glioma Xenograft Mouse Model

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Introduction: Analgesic agents are a common component of the chemotherapeutic treatment plan for cancer patients. However, the impact of these agents on disease progression through off-target effects is often overlooked. Our lab has found that morphine is a partial inhibitor of Isocitrate Dehydrogenase 1 (IDH1), a key metabolic enzyme of particular interest in the field of glioma research. IDH1 is responsible for the production of α-ketoglutarate in the cytosol but is mutated in >80% of low-grade gliomas. Mutated IDH1 no longer produces α-ketoglutarate, instead the oncometabolite 2-hydroxyglutarate (2HG) is made resulting in epigenetic hypermethylation and dysregulated cellular metabolism (Dang et al. 2009). Contrary to expectation, IDH1 mutant gliomas are slower growing and more responsive to antineoplastic agents, leading to improved patient prognosis (Minniti et al. 2014). Moreover, this mutation is not commonly found in more aggressive tumors like high-grade gliomas, also referred to as glioblastoma (GBM). We sought to determine if the inhibition of IDH1 by morphine in GBMs could mimic the beneficial IDH1 mutation phenotype observed in low grade gliomas.

Methods: U87 glioblastoma cells (IDH1 wild type) were treated in vitro with clinically relevant serum concentrations of morphine (0.1-10μM) or equipotent hydromorphone (0.01-1μM) for 7 days. Hydromorphone has no effect on IDH1 activity and served as a negative opiate control. Targeted metabolomics was done by LC/MS and DNA methylation was quantified by ELISA assay. SCID-nude mice were inoculated with U87 cells to examine intraperitoneal tumor growth as approved by the hospital for Sick Children Animal Committee. Mice were given daily subcutaneous injections of high or low morphine (5mg/kg or 10mg/kg) or hydromorphone (2mg/kg). Tumor size was measured for 30 days by caliper then resected for histopathology. Staining of TUNEL and ki67 proteins were quantified for apoptosis and proliferation, respectively. Cooperative capacity of morphine to potentiate the effect of antineoplastic agent temozolomide (TMZ)(Stupp et al. 2005), was determined following 36 hours of treatment by measuring in vitro U87 cell viability. Statistical significance was determined by One-way ANOVA with post-hoc Dunnett correction or Kruskal-Wallis testing with post hoc Dunn's correction as indicated in figure subtext. Fold change values are presented in the following section as treatment/vehicle with 95% confidence interval.

Results: Following 7 days of treatment, we observed an intercellular dose-dependent increase in 2HG oncometabolite levels (1.8±0.66, $p<0.01$) and a corresponding increase in DNA methylation levels (1.9±0.80, $p<0.05$) with morphine, but not hydromorphone treatment (Fig. 1 and 2). Mice inoculated with subcutaneous U87 cells began developing solid tumors by day 18 of treatment. Morphine treated mice had significantly smaller tumors throughout the treatment period compared to other groups. Upon resection, tumors from morphine treated mice were considerably smaller by weight than vehicle (0.27±0.096, $p<0.01$) (Fig. 3). We found significantly higher levels of TUNEL (2.7±2.0, $p<0.01$) and lower levels of ki67 (0.76±0.11, $p<0.01$) staining in morphine treated tumors, compared to vehicle (Fig. 4). Co-treatment of U87 cells with morphine and temozolomide reduced cell viability to 82% compared to either morphine (97%) or temozolomide (88%) alone ($p<0.05$) (Fig. 5). Hydromorphone and temozolomide co-treatment did not significantly impact cell viability.

Conclusion: Our research has shown that morphine treatment in glioblastoma cells, through its interaction with IDH1, is able to increase levels of oncometabolite 2HG as well as DNA methylation levels, much like the phenotype observed in IDH1 mutant gliomas. Morphine was able to significantly impact tumor size in our xenograft model by means of decreased proliferation and increased apoptosis. Furthermore, the combined treatment of GBM cells with morphine and TMZ potentiated the effect of the chemotherapeutic agent, much like the impact of the IDH1 mutation in low grade gliomas. Thus, we conclude that the interaction between morphine and IDH1 results in the mimicking of the beneficial IDH1 mutation phenotype. Imitating this phenotype in high grade gliomas may improve patient prognosis and extend survival. Finally, our research illustrates that choice of opiate can significantly impact and alter the course of disease, thus supporting the need for personalized medicine.

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Figure 1: Relative 2HG Metabolite Levels. Blue bars indicated levels of morphine treated samples, while green bars represent hydromorphone treated samples. Values are normalized to vehicle. Statistical significance is determined by One-Way ANOVA with post hoc Dunnett's multiple comparison correction.

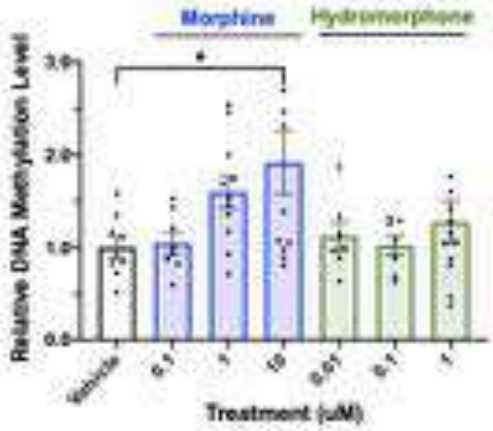

Figure 2: Relative DNA Methylation Levels. Blue bars indicated levels of morphine treated samples, while green bars represent hydromorphone treated samples. Values are normalized to vehicle. Statistical significance is determined with a nonparametric Kruskal-Wallis test and Dunn's post hoc correction.

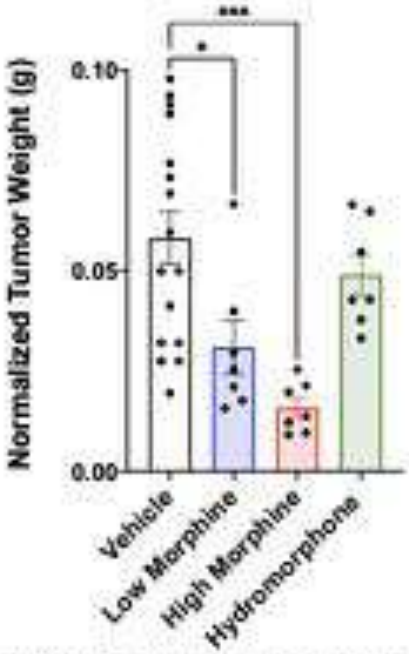

Figure 3: Mouse Tumor Weight. Tumor weight was measured immediately after resection and was normalized to mouse body weight. Statistical analysis was performed using a nonparametric Kruskal-Wallis test with Dunn's post hoc multiple comparison correction

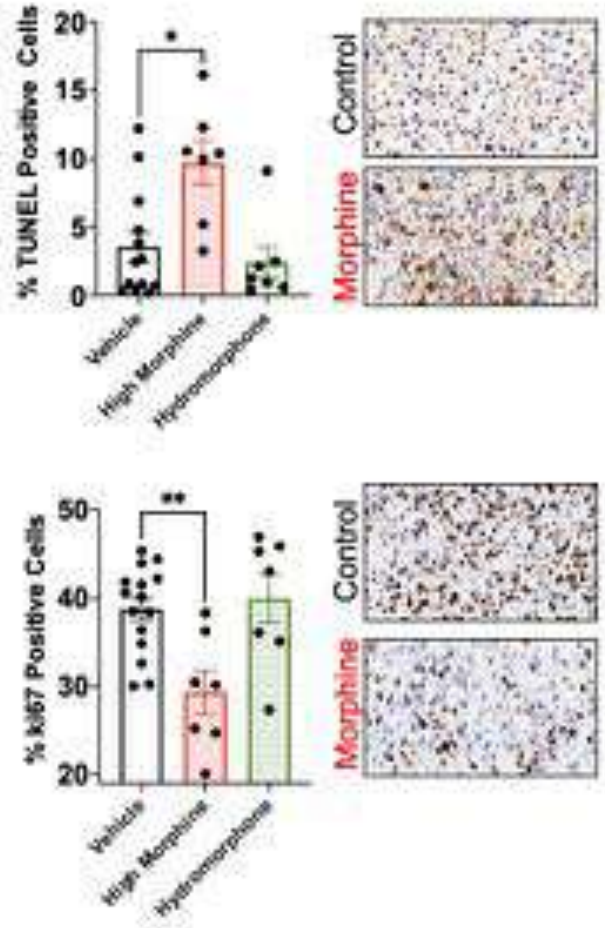

Figure 4: Mouse Tumor Histopathology. Representative images of U87 mouse tumors stained for TUNEL (top) and ki67 (bottom) to quantify apoptosis and proliferation, respectively. Quantification of positively stained nuclei, which appear brown in the images, is found in the left panel. Statistical analysis was done with a nonparametric Kruskal-Wallis test and Dunn's post hoc correction.

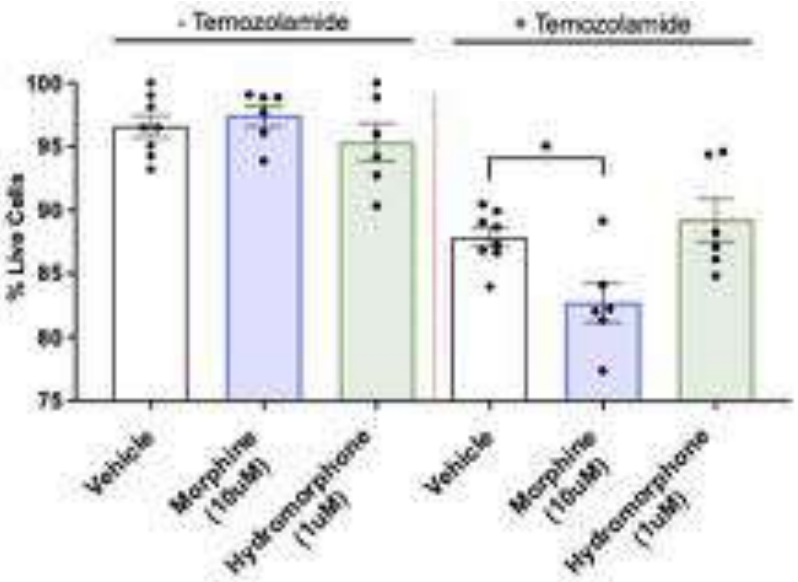

Figure 5: Opiate Cotreatment with Temozolomide. Left panel represents cell viability after 36 hours of treatment with opiates only. Right panel shows cell viability after 36 hours of TMZ and opiate cotreatment. Statistical analysis was done using One-way ANOVA with Dunnett's post hoc multiple comparison correction.

Patient Safety

Patient Safety - 1 Team factors influence emotions and stress in a non-operating room anesthetizing location. A Qualitative interview study among anesthesia clinicians.

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Introduction: Care for patients in non-operating room anesthesia (NORA) locations is associated with multiple challenges, including working with unfamiliar teams and equipment in a location distant from the resources the standard operating room (OR) offers (1-3). Anesthesia clinicians generally consider working in the NORA environment demanding which may contribute to feelings of stress and burnout among anesthesia clinicians (4). To date, no qualitative studies exist to describe the impact of those challenges on anesthesia clinicians. In addition, the difference in type and invasiveness of procedures in NORA and OR settings often complicates direct comparisons. Our institution is uniquely positioned to examine the impact of the NORA environment in our hybrid magnetic resonance imaging OR suite (MRI-OR) which is several minutes walking distance from the regular OR. Comparable craniotomy and spine surgery cases are performed in both locations, which allows to isolate the effect of the environment on anesthesia clinicians' perceptions of stress. This study utilizes qualitative interviews to characterize the workload, emotions, and stress experienced by anesthesia clinicians during similar cases in the two different environments.

Methods: Synthesizing literature about human factors and challenges in NORA locations, we developed an open-ended interview guide to explore the following key areas that may influence experiences in providing anesthesia care: environment, equipment, people, processes, and culture (1-3,5,6). The study population consisted of anesthesia clinicians at a single institution who were involved in patient care in both the regular OR and a specific NORA location (the MRI-OR). Sampling was purposive to include 8-12 nurse anesthetists, anesthesiology residents, and attendings. Interviews were recorded and transcribed, then coded and analyzed using a qualitative data analysis program. The analytic strategy was developed using a mixed deductive and inductive approach with some codes being pre-determined based on literature-derived challenges and other additional codes being identified based on iterative review of the data. Member-checking was performed to validate the results (7).

Results: Saturation of major themes was achieved after ten interviews with 2 residents, 4 attending anesthesiologists, and 4 nurse anesthetists. Table 1 displays the emerging themes (remoteness, team factors, culture, unfamiliarity, and safety protocols) with representative quotes. Every interviewee mentioned the remoteness of MRI-OR (for a total of 35 excerpts), but team factors were discussed most frequently (54 excerpts from 9 interviews). Higher workload, anxiety, and stress in the MRI-OR were identified uniformly by the interviewees (Table 2). Asked about the main determinant of emotions and stress, five of ten interviewees named team factors – both within the anesthesia care team and between the anesthesia and OR – as the most important determinant, while remoteness and unfamiliarity were less frequently reported (2 interviewees for each).

Conclusion: Our findings corroborate that known challenges of the NORA environment increase the workload, anxiety, and stress for anesthesia clinicians (Figure 1). Some of the identified challenges, for instance the physical location within the healthcare institution, are hardly modifiable, but the large emphasis on team factors in our study is notable and points towards team training initiatives as opportunities to alleviate the stress experienced by clinicians in the NORA environment. For other healthcare settings, clinician stress has been linked to provider burnout and medical errors (8). Conversely, physician well-being has been postulated as a quality indicator (9). While a large retrospective study finds that most adverse events were less frequently reported for the NORA environment compared to the OR, the mortality rate for some NORA locations including radiology and cardiology was actually higher (1). Given the rising incidence of NORA procedures – which already

comprise more than 30% of anesthesia cases – , it is critical for optimal patient safety to improve workload and stress for the clinicians working in these environments. Future investigations are needed to examine the effect of multi-disciplinary team training on both provider stress and patient safety in NORA locations.

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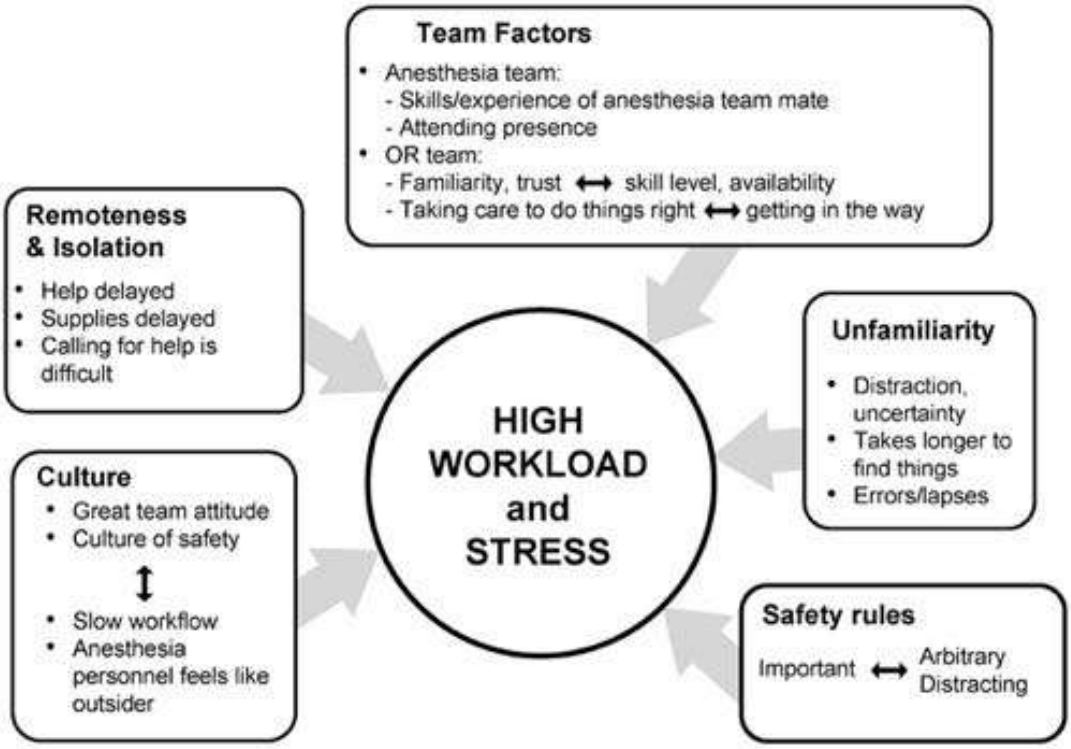
Table 1 - The most salient themes affecting anesthesia clinicians in the non-operating room environment, a MRI-hybrid operating room ("CSI"), compared to the regular operating room (" main OR")

Theme	N (interviews, excerpts)	Representative quotes
[illegible] Due to its location distant from the regular OR, help or supplies arrive later to CSI. Communicating to/from CSI is hard because use of personal devices and pagers is restricted in CSI	10, 30	"Can be farther from help, should something kind of go wrong" (A, CRNA) "In the main OR, we have access to multiple phones [...] in CSI sometimes, that's a little bit more challenging. We don't have our beepers. We don't have cellphones." (C, resident)
Team Factors The CSI-relevant skills and availability of the anesthesia team members and the OR personnel, familiarity with the surgeons, and quality of teamwork influence the work day of anesthesia clinicians	9, 54	"So the circulating nurse may not be paying attention quite as much to what I'm doing [...] in CSI because they're focused on their own part" (C, resident) "it just raises the stress level of the room if there are people who aren't comfortable being there" (G, CRNA)
Culture The CSI OR team is generally perceived as helpful with a great attitude, yet some interviewees describe a sense of being an "outsider" to that team. The workflow is slow with extra attention given to safety protocols.	8, 38	"I'm always a visitor to that team. [...]. There's not a feeling of inclusion, but I'm clearly a visitor down there" (E, attending) "You know, the main OR is slow. CSI is even slower." (F, CRNA)
Unfamiliarity with Environment and Equipment The differences in equipment and environment and the presence of environment-specific rules/restrictions creates a sense of unfamiliarity and distraction.	8, 36	"People operating [...] in an environment that they're not 100% comfortable I think poses a risk to the patient in general." (F, CRNA) "with the MRI cases we can't use the syringe pumps so [...] you have to sort of adjust how you're [...] running your infusions" (G, CRNA)
Safety protocols and processes Safety rules and protocols in CSI, such as ferromagnetic item counts and restricted use of non-MRI-compatible equipment, are viewed as important for safety, but also as difficult, distracting, or arbitrary.	8, 24	"Well, you have the steps that are required because you are working in with an MRI and I think those are reasonable [...] given the fact we've got a big magnet sitting there" (E, attending) "So there certainly is a very sort of stringent adherence to some regulations that don't always make a lot of sense to me." (E, resident)

Table 2 Workload and emotions in the non-operating room environment, a MRI-hybrid operating room ("CSI"), compared to the regular operating room (" main OR").

Theme/Sentiment	N (interviews coded)	Representative quotes
Workload in CSI Workload in CSI is described as higher, in part due to the need to follow protocols and to plan ahead for any additional needs	10, 29	"I think overall the workload of the entire team is quite a bit more. Positioning, making sure there's no metal [...]" (H, CRNA) "Of having to be, again, extra mindful of having sort of every piece of equipment and every medication that one could foreseeably need. I think it's objectively more... requires more preparation up front." (I, resident)
Emotions in CSI Working in CSI is associated with feelings of stress, anxiety, and frustration, despite positive feelings about some aspects	10, 19	"The mental work we've already gone over, and so the mental work is much higher, and that's where the stress comes from." (E, attending) "I think when I'm working in CSI, my guard is a little bit higher. My threshold to call for help is a little bit lower. I think my adrenaline sympathetic system is a little bit more in overdrive." (C, resident) "I love working in the CSI. The reasons for that are the people that we work with down there tend to be very helpful in facilitating the care of the patient [...]." (D, attending)



Patient Safety - 2 Four-fold increase in case capture after implementation of an electronic anesthesia reporting system compared to paper reporting

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Introduction: True quality assurance and process improvement requires accurate outcomes data measurement as well as non-punitive reporting (1). Underreporting exists in a voluntary and non-anonymous incident reporting system (2). Minor incidents may be underreported compared to major incidents. To improve peri-anesthesia event capture, providers were transitioned from paper reporting to an electronic capture system with a prompted quality improvement (QI) reporting response. This retrospective observational study compares the incidence of encounters with adverse events during two consecutive 42 month periods. Laryngospasm and cardiopulmonary resuscitation (CPR) events were utilized as surrogates for minor and major events, respectively (3).

Methods: The incidence of voluntarily reported events was calculated from 1/2014 - 6/2017 (paper) and 7/2017 - 9/2020 (electronic). Differences in reported case rates were determined using Student's t-test univariately. In order to adjust for background trends, an interrupted time series analysis was performed with the interruption occurring when the electronic QI reporting system was implemented (7/2017 or study month 43). Due to lack of linearity in the QI case rate before and after implementation, the time variables were represented as B splines in the statistical model. Lastly, the standard errors were modeled as being temporally correlated with an autoregressive 1 correlation structure. All analyses were performed with R 4.0.2.

Results: QI cases for a total of 81 months were included in this analysis ranging from a case report rate of 0.6-22.9 per 1000 anesthetics (Figure 1). Univariately, there was an increase in case report rate with electronic reporting (9.75 more captured cases per 1000 anesthetics per month, 95% CI 8.3-11.2, P-value < 0.001). On the interrupted time series analysis, this difference in captured cases per month increased to 13.7 cases per 1000 anesthetics (95% CI 8.3-19.1, P-value < 0.001), representing a four-fold increase in captured QI cases with the implementation of electronic reporting. There was not an increase in CPR events with electronic reporting (P-value = 0.84), but laryngospasm reports increased three-fold (P-value = 0.001).

Conclusion: Implementation of an electronic QI case reporting system improved peri-anesthesia adverse event capture by a four-fold increase. The lack of increase in CPR events suggests that the increase in total reported cases is not simply due to more overall events, but to more efficient capture of all events, particularly minor events. More accurate adverse event data collection should help in identifying common system risk factors and lead to targeted QI initiatives.

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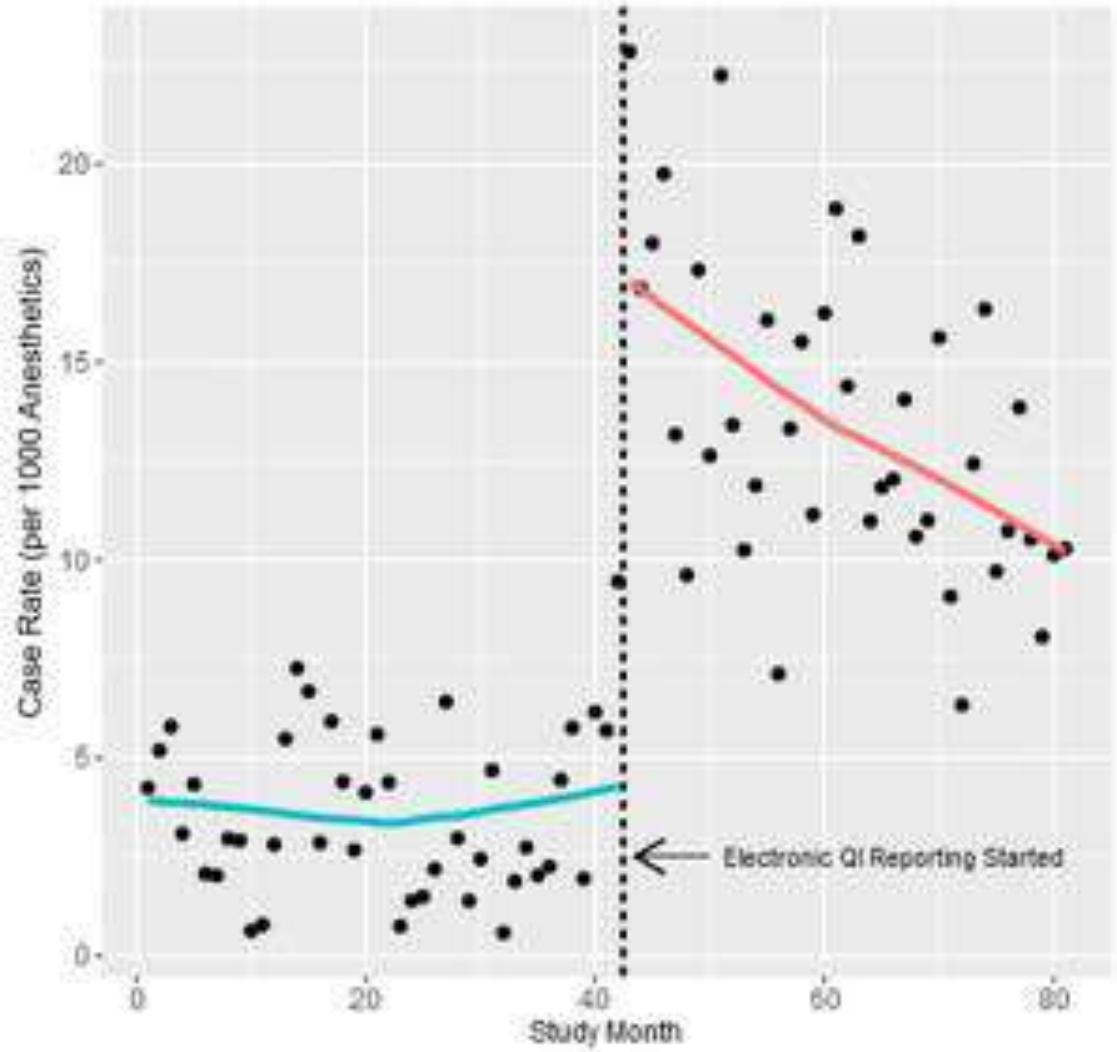
Figure 1. QI Cases Over Time



Patient Safety - 3 Impact of PPE Type and Healthcare Worker Characteristics on Perioperative Communication

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Introduction: The use of extensive PPE during for the care of patients with SARS-CoV-2 has significantly impacted the ability of healthcare providers to communicate with each other and with their patients. Challenges in communication represent a risk to patient safety and have motivated the use of written signs, call backs, and other techniques (1-5). However, it is unclear whether certain types of PPE or certain characteristics of healthcare providers impact their ability to communicate effectively. This study examines how specific types of PPE as well as specific healthcare worker characteristics impair communication in the perioperative setting. We also examine the ability of an Iasus GP-3 throat microphone to improve communication between providers wearing PPE.

Methods: QUALITATIVE ASSESSMENT: 75 healthcare workers at Memorial Hospital West completed a 19 item survey (Figure 1) to qualitatively assess the impact of gender, age, healthcare role (preop nursing, recovery nursing, OR nursing, surgeon, surgery assistant, anesthesia), native language (English, other), respirator type (N95, P100) and eye protection type (face shield, goggles) on employee perception of communication. Data analyzed using Microsoft Power BI and are presented in Figure 2. QUANTITATIVE ASSESSMENT: The Bamford-Kowal-Bench(BKB) sentence list, a benchmarked tool for evaluating comprehension of verbal communication, was utilized to analyze communication between healthcare workers wearing varying PPE. Variables in the quantitative analysis included distance between workers (3 versus 6 feet), phone versus in person communication, and ambient noise level (60 dB, 90dB). An Iasus GP3-R throat microphone was utilized for speakers to assess its efficacy as an intervention. Data were analyzed using Microsoft Power BI and results are presented in Figures 3, 4, and 5.

Results: QUALITATIVE SURVEY Responses from a standard survey (Figure 1) were compiled and analzyed using microscft power BI. Responses were not statistically different between male and female workers, nor were they statistically different between native English speakers and non-native English speakers. However, as shown in Figure 2, results were statistically different between younger cohorts (21-30, 31-40 year old) and more mature workers (41-50, 51-60 year old). These differences appeared in both speaker and listener roles. In this survey there was a non-statistically significant difference between individuals who routinely wore P100 respirators and those who wore N95 (p=0.12). QUANTITATIVE ASSESSMENT Comprehension of a standard set of BKB phrases were studied under several standard conditions (distance apart, phone versus in person, background noise 60 dB versus 90 dB). For consistency, we utilized a set of 4 speakers between 41-50 year old (male native English, female native English, male native Spanish, female native Spanish). Figure 3 demonstrates that non-native speakers wearing P100 respirators were more poorly understood under most conditions. Gender of speaker did not influence these results. While the combination of face shield + P100 appeared worse than goggles + p100, the difference was not statistically significant. Figure 4 demonstrates the effect of an Iasus GP-3 throat microphone on in person BKB phrase comprehension. Participants were kept 6 feet apart with a background noise level of 90 dB for this portion of the work because the baseline comprehension scores were lowest. The throat microphone produced an impressive improvement in comprehension of all speakers, but failed to statistically improve the comprehension of non-native speakers wearing P100 respirators. Figure 5 demonstrates the impact of the Iasus GP-3 throat microphone on comprehension via phone using 90 dB background noise for both listener and speaker. Again, the throat microphone produced an impressive improvement in comprehension, but not statistically so

in the case of non-native speakers wearing P100 respirators.

Conclusion: This study demonstrates that multiple factors influence the quality of comprehension when wearing PPE. These include speaker respirator type, native language, and the age of both the listener and speaker. The use of Iasus GP3-R throat microphone improved comprehension except in the case of non-native speakers wearing a P100 respirator. Limitations include sample size, the use of only two respirator types, and the simulated setting, which may not reflect clinical practice.

References: 1. World Health Organization. Interim guidance 19 March 2020. 2020.. 2. Arthroscopy. 2020; s(28): p. 1690-1698. 3. J Am Coll Surg. 2020 Jun;230(6):1098-1101 4. Surg Clin North Am. 2015; 95(4): p. 869-884. 5. Arch Surg. 2010; 145(6): p. 582-588.

Figure 1. Qualitative survey of healthcare worker perception of communication when wearing PPE.

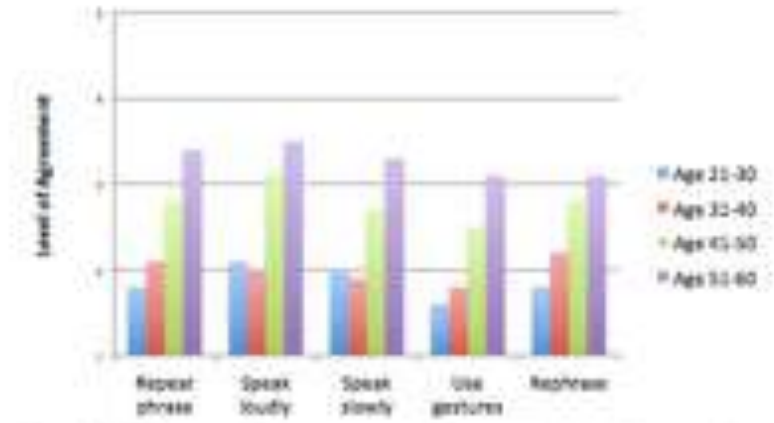

Figure 2. Data from qualitative survey regarding communication when wearing PPE. . In chart, 1 = never and 5 = always. Responses between male/female and native/non-native speakers were not statistically different but there was a statistically significant difference between 21-30 /31-40 and 50-61 year old participants (p<0.05).

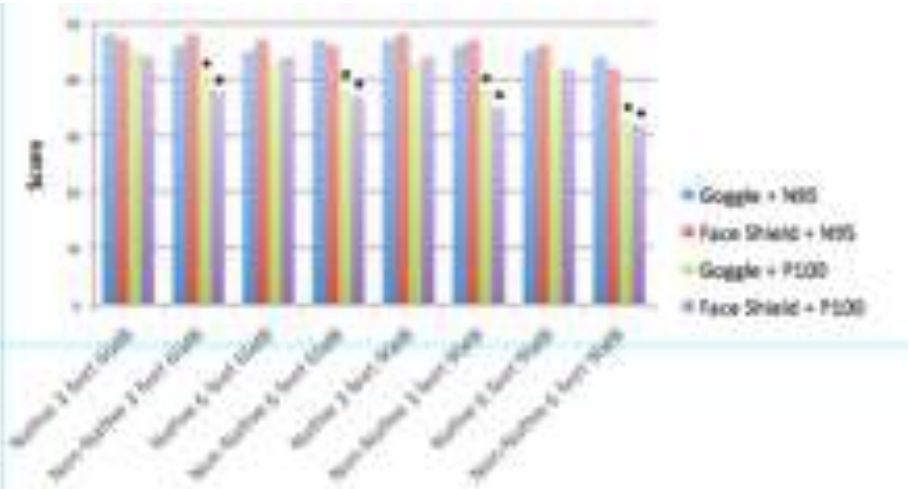

Figure 3. Evaluation of in person standardized phrase comprehension under standard conditions. Male and Female speakers between ages 41-50 recited standard phrases from the Bamford Kowal-Bench (BKB) to listeners under the conditions shown. Compared to speakers with N95, scores with speakers wearing P100 respirators were consistently lower, particularly with non-native speakers (* = $p < 0.05$).

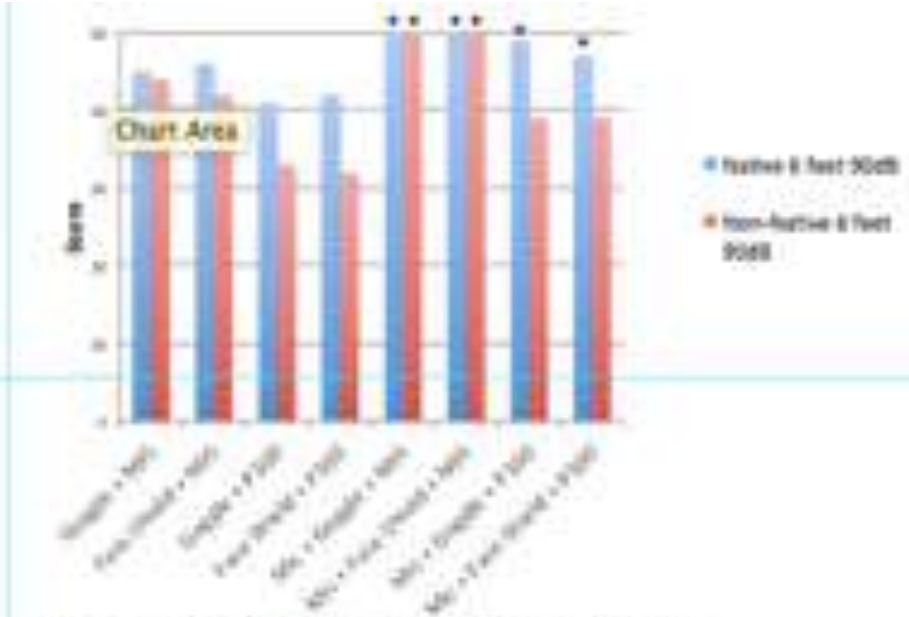

Figure 4. Impact of Jawz Throat Microphone on BKB Phrase comprehension under standard conditions. The throat microphone improved comprehension in all groups, but improvement with non-native speakers wearing P100 respirator was not statistically significant.

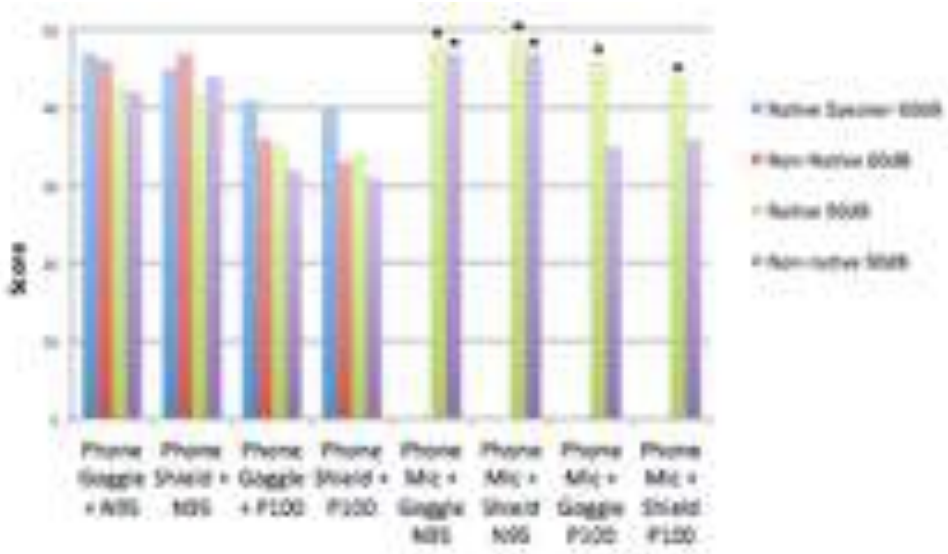

Figure 5. Evaluation of BKB phrase comprehension via phone call under standardized conditions. An Isolus GP3-R throat microphone showed a statistically significant improvement in comprehension in all groups except non-native speakers wearing P100 respirators (* p<0.05).

Patient Safety - 4 Non-Operating Room Anesthesia Care and Crisis Management in a Hybrid Magnetic Resonance Imaging-Operating Room: A Human Factors-based Assessment

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Introduction: Human factors and ergonomics (HFE) research in healthcare focuses on the interactions of humans with the complex and dynamic systems in which they provide patient care. This discipline has informed process improvement, patient safety, and provider well-being initiatives in many clinical work settings, including the perioperative environment.[1-3] More than 30% of anesthetic cases take place in non-operating room anesthesia (NORA) environments,[4] which are challenging for anesthesia clinicians to navigate.[5] Operating in this stressful environment may have detrimental effects on physician well-being, performance, and patient safety, making this fertile ground for HFE research.[6,7] At our institution, several near misses in a specific NORA site – a hybrid MRI-OR – prompted this investigation. Our objective was to generate an inventory of clinically relevant differences between this MRI-OR and the standard operating room (OR), describe these differences within an HFE framework, and determine how these differences might affect the ability of anesthesia clinicians to respond to a crisis.

Methods: In an iterative process, three anesthesia clinicians and an operating room manager with expertise in both MRI-OR and OR created an inventory of differences between the typical steps and tasks required for patient care in the two settings during a hypothetical brain tumor resection. Next, we determined how these differences may affect clinician task load using the domains of the NASA Task Load Index (NASA-TLX). This instrument was originally developed for pilots and military personnel and has been extensively studied and validated in many different environments, including medicine and specifically anesthesiology. It considers 6 domains – mental demand, physical demand, temporal demand, performance, effort, frustration.[8] Coding of the identified task differences continued until a consensus was reached. Finally, we identified in a similar fashion aspects of crisis management which are likely to be affected by these differences in task load.

Results: Multiple differences in anesthesia-care related tasks were identified, spanning the entire continuum from preoperative case preparation to postoperative transport. Table 1 displays illustrative examples. The differences were most likely to increase the temporal and mental demand and effort for anesthesia clinicians working in the MRI-OR compared to the OR. Similarly, multiple important steps in crisis management were found to be different in the MRI-OR environment – involving more personnel and increased effort and temporal demand (Table 2).

Conclusion: An HFE framework allows for a systematic assessment of the dynamic and interdependent components of a work system that influence clinician well-being and patient outcomes. Our analysis outlined important differences in the MRI-OR and OR settings and their implications for crisis management. This approach highlights concrete elements in the work environment that can be effectively targeted by guided interventions aimed to ease clinician mental and temporal load and enhance crisis management. For the MRI-OR in the present study, possible interventions include (1) simplification and standardization of equipment and processes; (2) formalized education about the differences that cannot be eliminated; (3) development of physical barriers to prohibit errors associated with some of these differences, and (4) standardization of roles and tasks during a crisis. Finally, creation of standardized location-specific cognitive aids to make this information available at the point of care is likely to decrease the workload for clinicians, particularly during a crisis. This systematic, HFE-informed approach can be used as a template for other NORA environments, thereby enhancing both clinician well-being and patient safety in our growing and heterogenous NORA landscape.

References: 1. Bailliere's Clin Anaesthesiol, Vol 10, Pg. 278, 1996. 2. Anesthesiol Clin, Vol 36, Pg. 17 – 29, 2018. 3. Qual Saf Health Care, Vol 15, Pg. i50 – 58 , 2006. 4. Anesth Analg, Vol 124, Pg.1261 – 1267, 2017. 5. Anesthesiol Clin, Vol 34, Pg. 223 – 240, 2016. 6. BMJ STEL, Vol 4, Pg. 112 – 116, 2018. 7. Health Care Manage Rev. Vol. 32, Pg. 203 – 212. 2007. 8. Proceedings of the Human Factors and Ergonomics Society Annual Meeting, Vol 50, Pg 904– 908, 2006.

Table 1: Illustrative examples of anesthesia-relevant task differences for a routine brain tumor resection in the MRI-OR vs OR, NASA-TLX domains affected, and implications for anesthesia clinicians

Phase/Step	Task differences for MRI-OR vs OR	NASA -TLX*	Implications for anesthesia clinicians
Preparation			
Exposure	• Exposure to MRI-OR environment and case type may be more infrequent.	M E	• Less familiarity with environment leads to higher cognitive load and effortful processing rather than relying on "muscle memory" during case preparation and plan execution.
Case set up on day of procedure	• MRI-OR suite requires badge access. • Prior to OR entry, ferromagnetic personal items have to be removed/stored.	M T E F	• Extra processes are required to access this environment. • May correspond with increase in the temporal and mental demand and effort domains.
Operating Room Set-up			
Safety check	• MRI-OR safety equipment check includes additional equipment (e.g., code drug box, airway grab bag).	M T E	• Although the additional time needed to check for these items is small, the mental demand to remember, and the effort required to do it increase the workload.
Ferrous item count	• A two-person ferromagnetic object count is required in MRI-OR before patient enters room to avoid accidents in the magnetic field of the MRI scanner. • Count repeated at pre-defined time-points intraoperatively.	M T F	• Process is time-consuming and may disrupt regular workflow of these two independent clinicians.
Supplies planning	• Planning for medication/supplies unavailable in the regular anesthesia cart is more important in MRI-OR due to the time-inefficient process of having items delivered as needed. • Any ferromagnetic piece of equipment must be added to the object count sheet.	Ph M T F	• Clinicians need to anticipate which non-routine items might be needed and how urgently these items might be needed. • Clinicians must either (1) physically retrieve the items from the OR area themselves or (2) ask a colleague to do this for them. • Clinicians need to be aware of ferromagnetic concerns and regulations in the MRI-OR.
Case Execution			
Induction	• Patient/airway is typically located far from anesthesia machine due to the size and layout of MRI-OR.	M T E	• Extra person with anesthesia expertise is required to perform routine ventilation from anesthesia machine during induction sequence.
Positioning	• Patient in MRI-OR is typically positioned with arms tucked in by their side. • Loops in IV tubing or monitor cables have to be avoided to prevent radiofrequency-induced heat/burn injury during MRI scan. • Skin-to-skin and skin-to-tubing/cable points of contact must be padded with gauze to prevent moisture build-up and burn injury during MRI scan.	Ph M T E	• This time- and labor-intense process is performed by MRI-OR nurse and tech team in parallel with anesthesia team. • May result in "competing workflow" as the anesthesia team may still need to acquire more intravascular access sites or connect infusions and monitor cables. This leads to a high workload and the need for "multitasking" for the anesthesia team.
Extubation	• Patients are often extubated out of reach from anesthesia machine in MRI-OR. • Long suction tubing is required to reach patient's head.	M T E P	• Additional personnel must be available for safe extubation, as patient may still require assisted ventilation post-extubation. • Long suction tubing may become entangled or disconnected.
Transfer from room	• Portable oxygen tanks are prohibited in the MRI-OR.	M T E	• Requires advanced planning and decision making for patients who cannot tolerate a brief period without supplemental oxygen while being transferred from MRI-OR to hallway.

: The North American Space Association (NASA) has developed a task load index tool (NASA-TLX) to grade tasks using 6 different domains which contribute to task load. The TLX domains are Physical demand (Ph**), Mental demand (**M**), Temporal demand (**T**), Effort (**E**), Performance (**P**), Frustration (**F**). Abbreviations: **OR**: Operating Room; **MRI-OR**: Magnetic resonance imaging-operating room, a specific operating room remote from other ORs.*

Table 2: Illustrative examples of anesthesia-relevant task differences for non-routine anesthesia care in the MRI-OR vs OR

Equipment or Process	Task differences for MRI-OR vs OR	NASA-TLX*	Implications for anesthesia clinicians in times of crisis
Code cart	• Code cart and defibrillator prohibited in the MRI-OR while magnet is in the room due to ferromagnetic properties.	M T E	• Clinicians recall that the normal code cart is unavailable while the MRI magnet is in the room. • Deviation from usual crisis management can increase mental demand by forcing effortful processing.
Airway management	• Access to patient's airway in the MRI-OR is often complicated by the patient's position, turned 180 degrees away and far from the anesthesia machine. • Patient inaccessible due to being fully wrapped in multiple layers of drapes during MRI scans.	Ph M T	• Physically impossible for a single clinician to assess the airway while controlling the anesthesia machine/adjust ventilation. • Clinicians need to be aware of the 'airway grab bag', which allows a single person to provide positive pressure ventilation without simultaneously controlling the anesthesia machine. • Clinicians must rely on help from other MRI-OR team members to obtain access to the patient under the surgical drapes.
Availability of help	• The MRI-OR is located several minutes walking distance from the ORs.	M E P	• Arrival of additional personnel or equipment to MRI-OR is delayed due to its remote location two levels below the standard ORs. • Imparts a sense of vulnerability and isolation on the clinician.
Cognitive Aids/2-way communication	• Personal devices are restricted in MRI-OR, limiting access to the internet and digital cognitive aids. • Phone lines and internet are disabled during MRI scanning.	M T E F	• Limits (1) communication between anesthesia care team members, (2) access to the internet and digital cognitive aids. • Additional time and effort are required to access information needed for diagnosis and management of a crisis.

*: *The North American Space Association (NASA) has developed a task load index tool (NASA-TLX) to grade tasks using 6 different domains which contribute to task load. The TLX domains are Physical demand (**Ph**), Mental demand (**M**), Temporal demand (**T**), Effort (**E**), Performance (**P**), Frustration (**F**). Abbreviations: **OR**: Operating Room; **MRI-OR**: Magnetic resonance imaging operating room, a specific operating room remote from other ORs.*

Patient Safety - 5 A Quality Improvement Project to Improve Medication Administration by Anesthesia Providers during Non-OR Airway Emergencies

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Introduction: Inconsistent medication administration during airway emergencies outside of operating rooms (ORs) can impact patient safety [1-2]. Untimely and inappropriate documentation of medications administered during these emergencies can interfere with anesthesia providers' ability to distinguish between deterioration in patient condition due to hemodynamic effects of the medication or due to worsening of medical condition [3]. Recognizing this challenge interferes with optimal decision-making, treatment, and continuum of care [3], a quality improvement project was instituted to reduce lapses in medication documentation administered during non-OR airway emergencies by anesthesia providers. The goal was to standardize documentation of medications administered during non-OR airway emergencies in the electronic health record (EHR).

Methods: Prior process: Upon activation of an out-of-OR airway emergency, the assigned anesthesia response team including a senior resident and an attending anesthesiologist responded to the emergency. The airway team carried the 'emergency airway drug kit' (figure 1) and 'airway box' (supplies) to the emergency location. During each airway emergency, anesthesia providers were expected to document the drug administration details in the airway intubation note. In the case that additional or controlled medications were needed during this process, nursing staff dispensed those medications with an override of the 'pyxis' machine i.e., medications were removed in the absence of an order. During a review of this process, providers discovered that used and unused/wasted medications were not documented consistently in the EHR and used medications were not charged to the patient. Intervention: In January 2018, members from the Department of Anesthesiology and Perioperative Medicine Quality Improvement Committee (AQIC) along with representatives from the Department of Pharmacy and Nursing worked with Information Technology (IT) to develop a physician order set in the EHR, called Powerplan (Cerner) that would help document the medications administered during a non-OR airway emergency. The EHR linked the order set to a universal 'Intubation Note' that all anesthesia providers were asked to use during each emergency airway procedure. The order set contained built-in details of medications administered, including the drug name and dose. Figures 2-3 outline the physician order set. Administered medications, now visible real time in the EHR, were officially considered to be 'tasked off' by an anesthesia provider. This allowed for nurses to chart any excess or unused medications. To overcome inaccurate billing, disposal, and drug waste, as well as to standardize the availability of required medications, the pharmacy provided and replenished the 'emergency airway kit' after each use. So, each time the emergency airway kit was used, providers returned the kit to the pharmacy with the patient's identification label and obtained a new kit. In order to check adherence with the process and identify the opportunities for improvement, a monthly report was compiled of all non-OR emergency airways managed by the anesthesia providers. The monthly adherence rate was calculated as the number of correctly documented intubation notes out of the total number of non-OR airway emergencies performed. After plotting the results over time, the QI team fit a regression line and evaluated whether a significant trend existed over time.

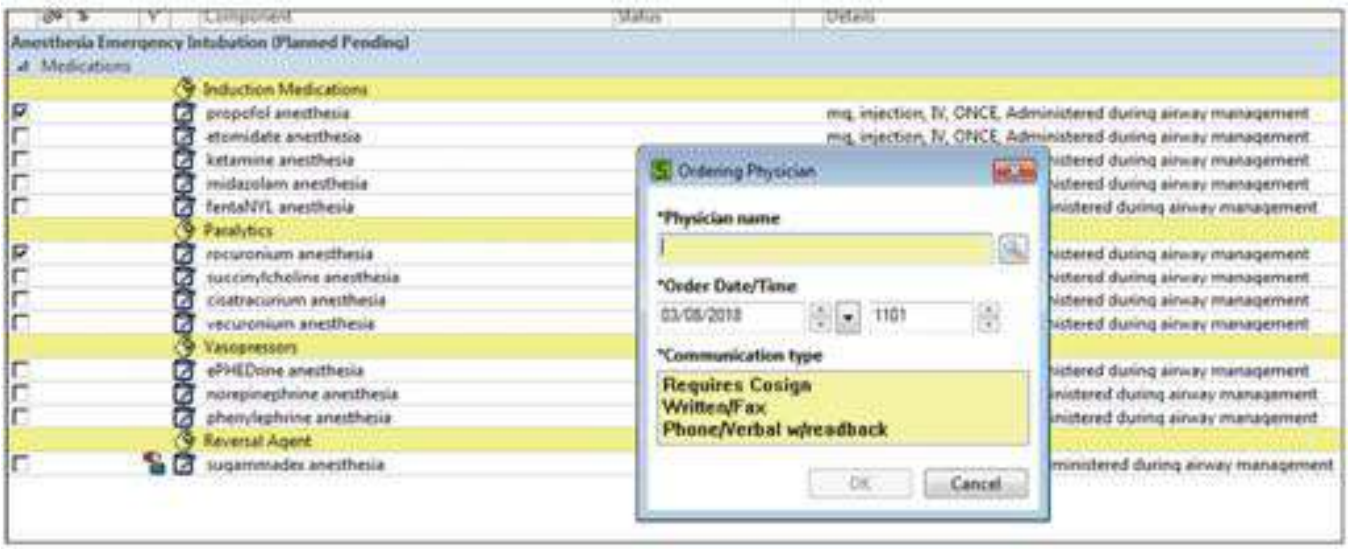
Results: From January 2018 to November 2020, anesthesia providers managed a total of 1505 out-of-OR emergent airways, an average of 43 per month. As seen in figure 4, adherence rates ranged from 69% (March, 2018) to as high as 100% in four different months. The regression line (figure 5) showed a significant upward trend in the adherence rates over time ($p<0.001$).

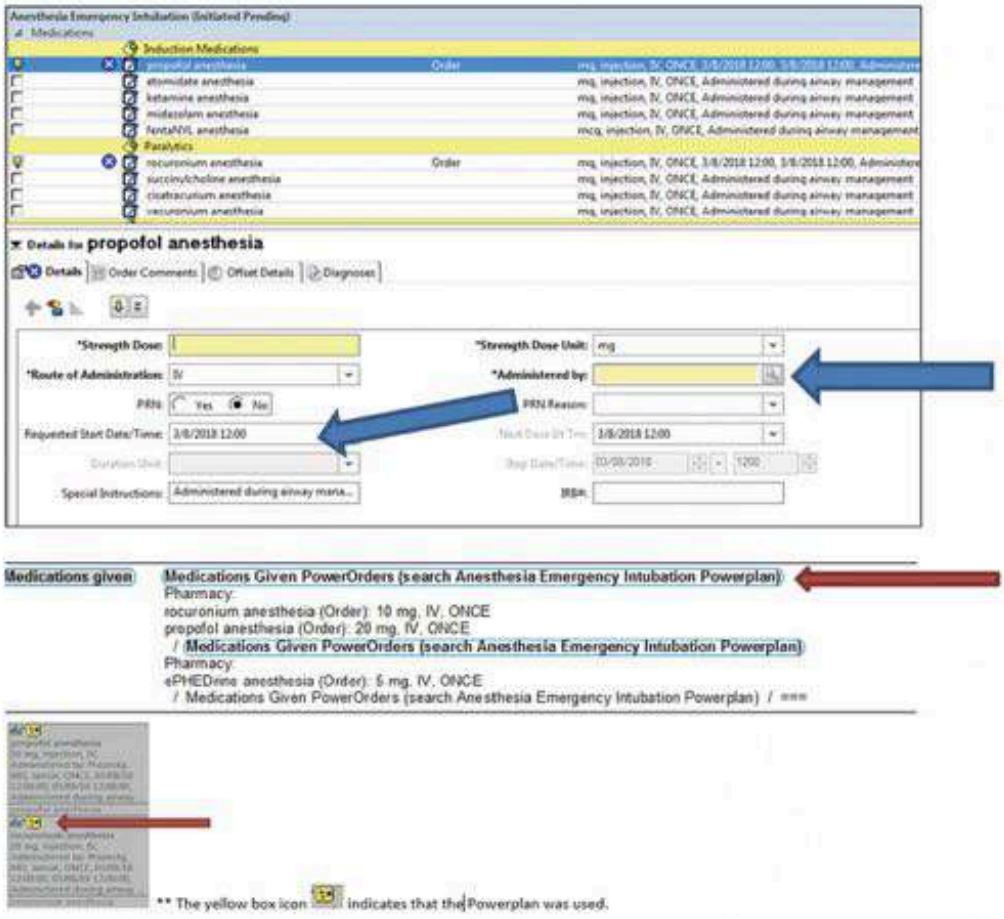
Conclusion: The multidisciplinary QI initiative significantly improved the documentation of medication administered during out-of-OR emergent airways by anesthesia providers. Appropriate documentation during similar high-risk procedures ensures accurate and timely recording in the EHR and ultimately improves patient safety. Additionally, appropriate medication documentation allows providers to track wastage and dispose of excess controlled medications, minimizing concerns related to charge capture and controlled substance misuse.

References: 1. Moyen, E., Camiré, E., & Stelfox, H. T. (2008). Clinical review: medication errors in critical care. Critical care (London, England), 12(2), 208. https://doi.org/10.1186/cc6813 2. Mark, L. J., Herzer, K. R., Cover, R., Pandian, V., Bhatti, N. I., Berkow, L. C., Haut, E. R., Hillel, A. T., Miller, C. R., Feller-Kopman, D. J., Schiavi, A. J., Xie, Y. J., Lim, C., Holzmueller, C., Ahmad, M., Thomas, P., Flint, P. W., & Mirski, M. A. (2015). Difficult airway response team: a novel quality improvement program for managing hospital-wide airway emergencies. Anesthesia and analgesia, 121(1), 127–139. https://doi.org/10.1213/ANE.0000000000000691 3. Hammer, A., Wagner, A., Rieger, M. A., Manser, T., & WorkSafeMed Project Consortium# (2019). Assessing the quality of medication documentation: development and feasibility of the MediDocQ instrument for retrospective chart review in the hospital setting. BMJ open, 9(11), e034609. https://doi.org/10.1136/bmjopen-2019-034609

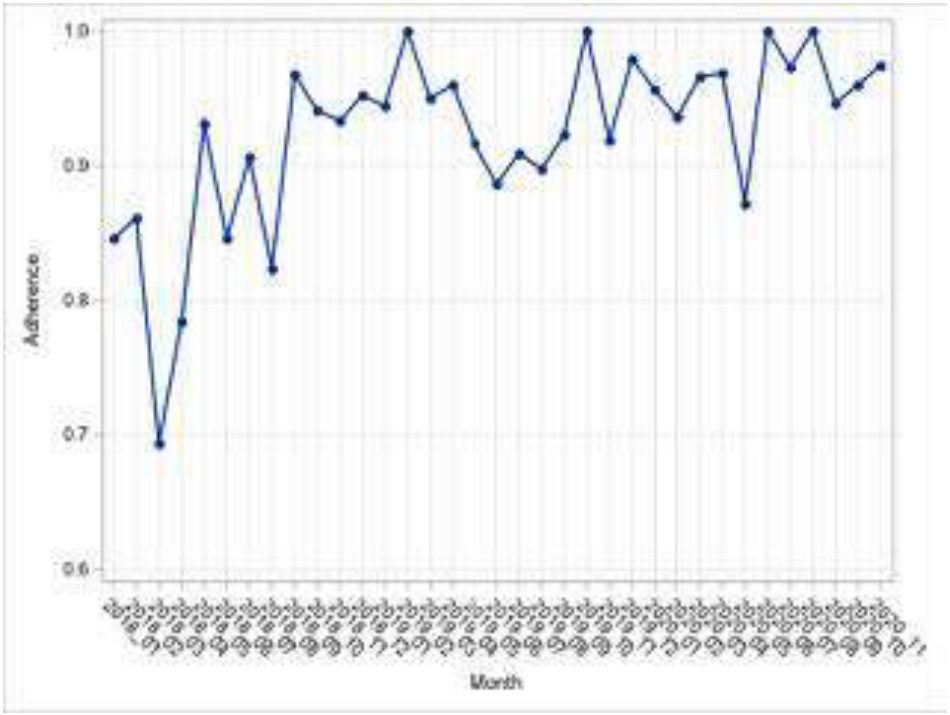
Emergency Drug Kit consists of:

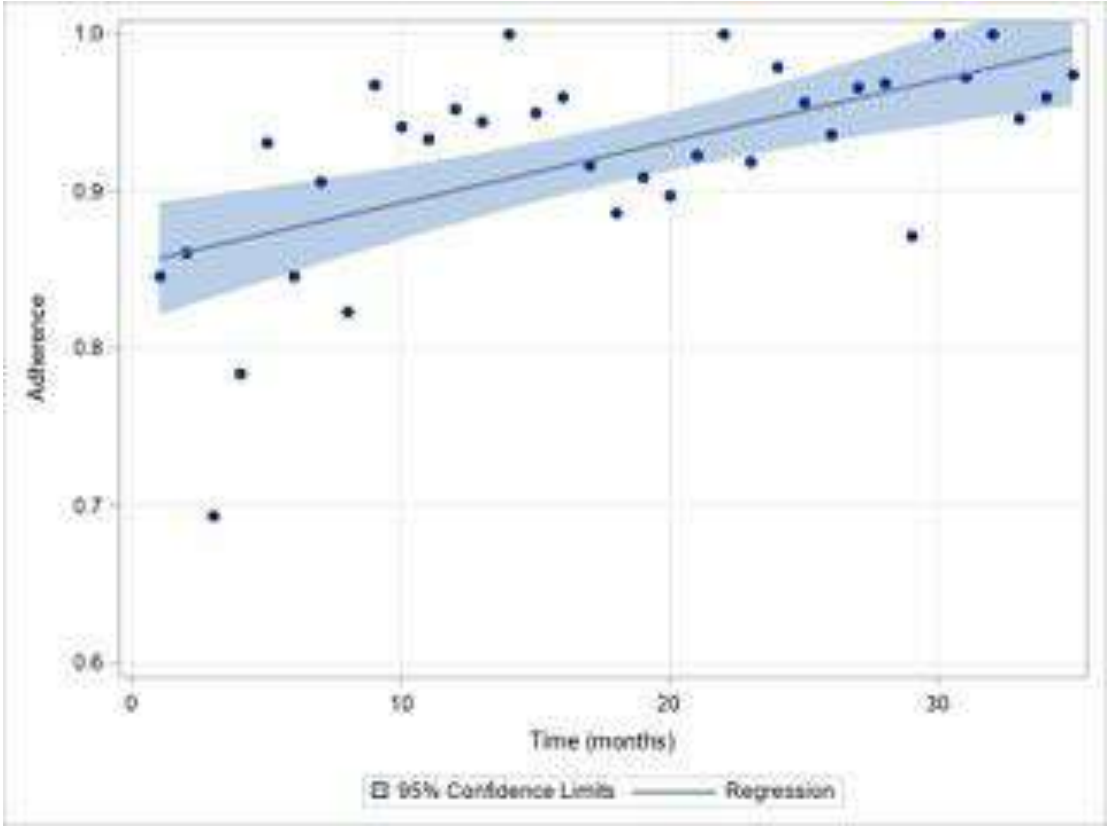
Ephedrine 25 mg/5 ml syringe #1
Epinephrine 100 mcg/10 ml syringe # 2
Etomidate 20 mg/10 ml vial #1
Phenylephrine 1000 mcg/10 ml #2
Propofol 200 mg/20 ml vial #2
Rocuronium 50 mg/5 ml syringe #2
Succinylcholine 200 mg/10ml syringe #2
Sugammadex #8 (2 ml)
Sodium chloride 0.9% syringe #2
10 ml syringes #2
18 g needles #2
Alcohol packets




Anesthesia Emergency Intubation (Initiated Pending)
Medications
Induction Medications
propofol anesthesia
etomidate anesthesia
ketamine anesthesia
midazolam anesthesia
fentaNYL anesthesia
Paralytics
rocuronium anesthesia
succinylcholine anesthesia
cisatracurium anesthesia
vecuronium anesthesia
Details for propofol anesthesia
Details
Order Comments
Offset Details
Diagnoses
*Strength Dose:
*Strength Dose Unit: mg
*Route of Administration: IV
*Administered by:
PRN:
PRN Reason:
Requested Start Date/Time: 3/8/2018 12:00
Special Instructions: Administered during airway mana...
IBW:

Medications given
Medications Given PowerOrders (search Anesthesia Emergency Intubation Powerplan)
Pharmacy:
rocuronium anesthesia (Order): 10 mg, IV, ONCE
propofol anesthesia (Order): 20 mg, IV, ONCE
/ Medications Given PowerOrders (search Anesthesia Emergency Intubation Powerplan)
Pharmacy:
ePHEDrine anesthesia (Order): 5 mg, IV, ONCE
/ Medications Given PowerOrders (search Anesthesia Emergency Intubation Powerplan) / ***
** The yellow box icon indicates that the Powerplan was used.


1.0
0.9
0.8
0.7
0.6
Adherence
Month


1.0
0.9
0.8
0.7
0.6
Adherence
0
10
20
30
Time (months)
95% Confidence Limits
Regression

Patient Safety - 6 Comparison of ToFscan and TetraGraph during Recovery of Neuromuscular Function in the Post Anesthesia Care Unit

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Introduction: Residual neuromuscular blockade (RNMB) is common in the post-anesthesia care unit (PACU) when neuromuscular blocking agents (NMBAs) are used intraoperatively(1-3). The use of quantitative neuromuscular monitors can reduce the number of patients with RNMB and its associated complications(4-6). The ToFscan (Drager, Germany) is a standalone acceleromyography (AMG)-based quantitative monitor; the TetraGraph (Senzime, Sweden) is a standalone electromyography (EMG)-based quantitative monitor. The aim of this randomized, multi-center trial is to compare the performance of the two quantitative monitors throughout various stages of neuromuscular recovery with assessments obtained subjectively by using a peripheral nerve stimulator (PNS). The secondary aim was to determine the overall incidence of postoperative residual weakness and identify whether subjective evaluation provides a reliable indication of adequate neuromuscular function recovery.

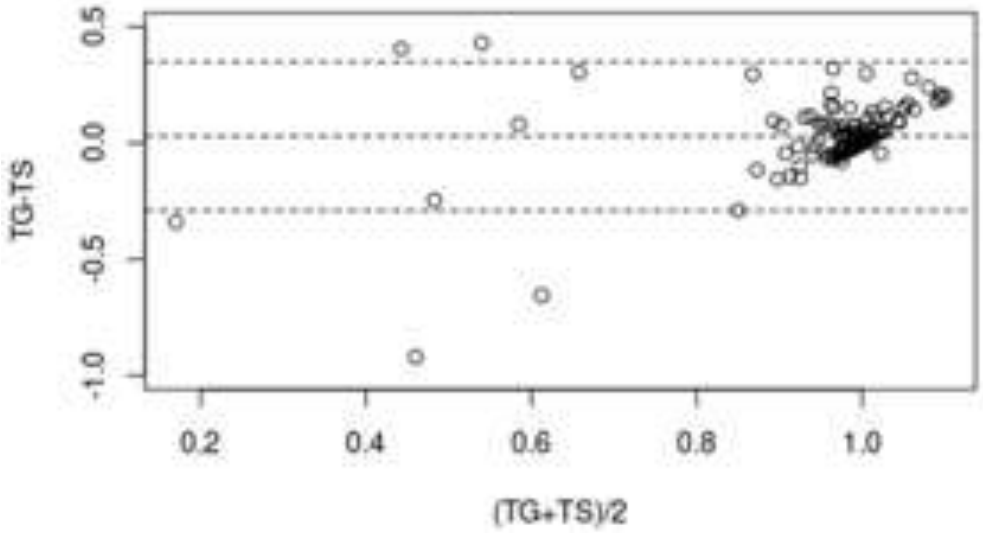
Methods: After IRB approval, consenting adult patients scheduled for elective surgery requiring neuromuscular blockade were enrolled. Intraoperative NMBA management and reversal were at the discretion of the anesthesiologist. Upon arrival to PACU, the ToFscan (TS) and TetraGraph (TG) were placed on opposite arms (dominant and non-dominant hand), based on randomization. Train-of four (TOF) stimulation was performed twice at 50 mA every 15 sec at three time intervals: upon arrival to the PACU (t = 0), and 5 min (t = + 5 min), and 10 min (t = + 10 min) after PACU arrival. RNMB was defined as a mean ratio (TOFR) < 0.9 obtained by either device. A paired t-test compared the mean score for a device in the 3 time periods. Bland-Altman plots expressed the agreement between the two devices. The association between the type of antagonism and RNMB incidence was tested using Fisher's exact test and Wilcoxon rank sum test.

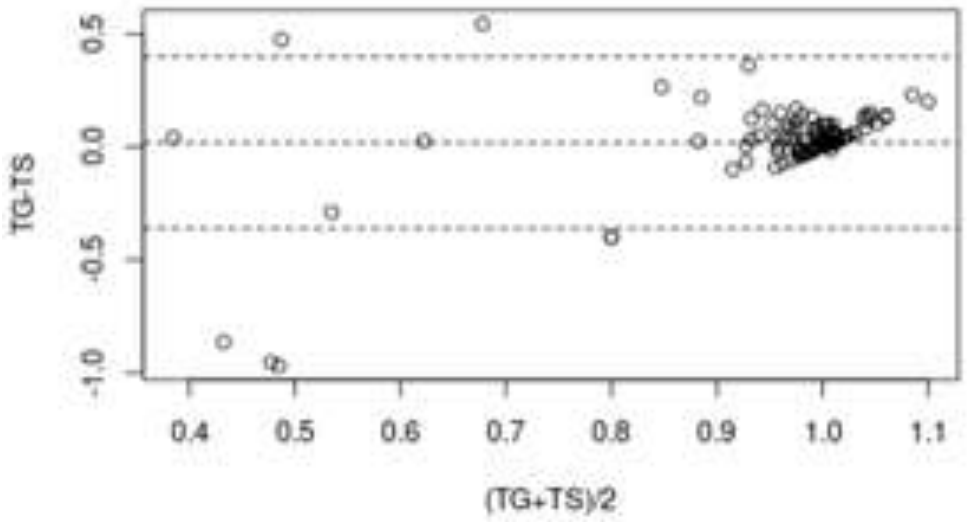
Results: Patients (n=120) from three institutions were enrolled. Five were excluded due to technical issues. TOFRs were higher at all time intervals in the TG compared with TS group. There was no significant difference in the mean TOFRs obtained with the TG and TS at t = 0, and t = + 5. At (t = + 10), there was a statistically significant difference in mean TOFRs obtained with the TG and TS, (0.99 ± 0.14 vs 0.94 ± 0.12, P < 0.001, respectively). The bias between the two devices at t = 0 was 0.03 (95% CI, -0.29 to 0.35, P=0.26; Fig 1a). The bias between the two devices at t = + 5 min was 0.02 (95% CI, -0.36 to 0.40, P=0.54; Fig 1b), and at t = + 10 min it was 0.05 (95% CI, -0.25 to 0.36, P=0.77). The use of a peripheral nerve stimulator (vs. quantitative neuromuscular monitor) was associated with higher incidence of RNMB (75.0% vs 25.0%, p=0.012, respectively). The use of neostigmine (vs. sugammadex) was associated with a higher incidence of RNMB (56.2% vs 43.8%, p < 0.001, respectively) when measured at extubation.

Conclusion: This multi-center study demonstrates that the TS and the TG devices provide similar quantitative neuromuscular measurements and they can be used interchangeably in the clinical setting. These measurements differed after the first 10 PACU minutes, as the variability of the TS-obtained measurements increased. This decreased consistency of the AMG-based TS monitor data may be due to the awakening of PACU patients who exhibited involuntary and voluntary withdrawal movements following neurostimulation, thus affecting the consistency of AMG (but not EMG) data. The results suggest that the two technologies yield comparable neuromuscular recovery data, but the TS is more prone to unreliable data in awakening PACU patients. As reported previously, subjective evaluation of neuromuscular responses to PNS is unreliable and results in postoperative neuromuscular weakness.

References: 1. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. Anesth Analg. 2010;111(1):120-8. 2. Postoperative residual block after intermediate-acting neuromuscular blocking drugs. Anaesthesia. 2001;56(4):312-8. 3. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology. 2003;98(5):1042-8.

4. The implementation of quantitative electromyographic neuromuscular monitoring in an academic anesthesia department. Anesth Analg. 2014;119(2):323-31. 5. The Implementation of Quantitative Electromyographic Neuromuscular Monitoring in an Academic Anesthesia Department: Follow-Up Observations. Anesth Analg. 2015;121(3):836-8. 6. Intraoperative acceleromyography monitoring reduces symptoms of muscle weakness and improves quality of recovery in the early postoperative period. Anesthesiology. 2011;115(5):94





Patient Safety - 7 Intralesional bleomycin injection and skin hyperpigmentation: A retrospective review of a single centers' experience with a standardized skin-protective protocol

Jacob Heninger[1], Daniel Thompson[2]

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Introduction: Bleomycin is a cytotoxic antibiotic that can be used to treat vascular anomalies given its sclerosing effect on vascular endothelium. With systemic use, bleomycin is known to cause flagellate hyperpigmentation; however, there is evidence that even the smaller doses used for more targeted, localized injections can precipitate skin hyperpigmentation. Given the use of bleomycin to treat vascular malformations has increased in recent years, we implemented a skin protective protocol aiming to mitigate this preventable side effect. Of particular concern is the development of hyperpigmentation in areas of skin micro-trauma, such as on the face from taping endotracheal tube and eyes, and on the chest from sticky ECG leads. The shearing force from tape removal or the pressure from monitor cords and gown folds can cause the drug to leak into the interstitial space, where it is unable to deactivated due to the lack of bleomycin hydrolase, leading to darkening of the skin. The exact incidence of this complication is unknown but thought to be underreported. We conducted a retrospective chart review of patients who underwent intralesional bleomycin injection since implementation of our skin protective protocol to evaluate its impact on hyperpigmentation.

Methods: Cases performed from November 2019 to December 2020 were obtained for chart review. Age, bleomycin dose, anatomic location of lesion, type of lesion, adherence to protocol, side-effects and length of follow up were recorded. The charts were reviewed for adherence to skin precaution protocol and all post procedure notes were reviewed for documentation of skin hyperpigmentation. The protocol emphasizes avoidance of adhesives and minimizing pressure points to the patient. All gowns are removed to prevent the folds from creating pressure points, and the patient lies on a smooth flat surface, typically the flat side of egg create foam. Intravenous lines are secured with cotton roll and self-adherent elastic wrap with 2 transparent dressings stuck to each other to create a viewing window. Endotracheal tubes are secured with padded ties and the eyes are lubricated with ointment as opposed to tape. The adhesive of ECG leads is removed and immersed in jelly on the chest. The SpO2 probe adhesive sticker is removed and bare probe is secured around a finger with self-adherent elastic wrap. Prior to implementation, anesthesiology, interventional radiology, and nursing staff were educated via grand rounds, department emails and a written protocol. All necessary supplies are stocked and stored in a bucket near the interventional radiology suite.

Results: Since the implementation of the skin protective protocol in November 2019, 12 patients received a total of 35 injections of bleomycin (5-10mg per injection) for various vascular malformations. Skin protective precautions were employed in all cases. Only 1 patient was lost to follow up. 2 patients scratched around the vascular access site in the PACU and developed hyperpigmentation both of which resolved. 1 patient developed a rash at the IV site (antecubital fossa) which was evaluated by dermatology and deemed to be a viral exanthem. Ages, anatomic location, number of injections per patient and length of follow up are presented in table 1.

Conclusion: Since the implementation of a skin protective protocol, no cases of skin hyperpigmentation attributable to adhesive or pressure points were discovered on retrospective chart review. The protocol was followed 100% of the time with no identifiable barriers to implementation. There are numerous limitations of this single center retrospective review. The small sample size limits generalizability. Follow up was limited and patients were not formally assed for hyperpigmentation. Documented adherence to the protocol does not ensure that such measures were actually taken. Post procedure documentation may be inaccurate. Given the ethical concerns of conducting a trial where skin protection measures are forgone, this retrospective review aims to inform and present our

results regarding skin hyperpigmentation after intralesional bleomycin injections. Given that the only cases of hyperpigmentation were due to patients scratching themselves post procedurally, administering an antihistamine intraoperatively may decrease incidence of scratching. Future studies are needed to further evaluate the true incidence of hyperpigmentation following intralesional bleomycin injection and efficacy of skin protective measures.

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Patient Safety - 8 The addition of a PACU transfer to the flow of ICU-bound postoperative patients is not associated with increased complication rates

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Introduction: Perioperative handovers are a potential source of patient harm. Standardization of handoffs from the operating room (OR) to the intensive care unit (ICU) has been demonstrated to improve communication and outcomes, but prior studies have not included patients admitted to the ICU via the post anesthesia care unit (PACU). The purpose of this study was to determine whether a PACU transfer prior to ICU admission (i.e., an additional handoff) is associated with patient outcomes for ICU-bound postoperative patients.

Methods: This IRB-approved, retrospective observational cohort study was conducted at a large tertiary care independent academic medical center. This project was part of a research study to standardize OR-to-ICU handoffs. Electronic medical record patient-level data from calendar year 2017 were combined with outcome data from Vizient. All patients transmitted from the OR to the ICU (with or without an intervening PACU stop) were deemed eligible. Patients with missing data on preoperative location were excluded. The primary outcome was a composite rate of major postoperative complications, including in-hospital stroke, myocardial infarction, aspiration pneumonia, and postoperative infection. We used bivariate statistical testing to compare cohort demographics and tested the association of a PACU stop with postoperative complications using a negative binomial model that adjusted for patient age, gender, comorbidities, and surgery type.

Results: Of all eligible patients (n=915), 567 underwent direct OR-to-ICU handovers and 348 included an additional PACU transfer (OR-to-PACU-to-ICU). Group demographics differed based on gender and age, with direct OR-to-ICU transfers including more male (64.5% vs. 50.0%, $p<0.001$) and older (66.7 vs. 63.3 years, $p=0.004$) patients. Cardiac surgery patients comprised a majority direct OR-to-ICU observations (74.6%), while neurosurgery patients were most represented among OR-to-PACU-to-ICU observations (39.4%). After multivariable adjustment, there was no statistically significant difference in the rate of postoperative complications between the two groups (10.0% vs 14.4% for OR-to-ICU and OR-to-PACU-to-ICU flows, respectively, $p>0.05$).

Conclusion: The addition of a PACU transfer was not associated with greater rates of postoperative complications among patients requiring postoperative ICU-level care. Additional research is needed to determine how to measure the effects of patient flow on outcomes, including ways to adjust for confounding by indication.

Patient Safety - 9 Intraoperative Handoffs' Impact on Surgeon-Anesthesiologist Relations

Aubrey L Samost-Williams[1], Allison Doney[1], May Pian-Smith[2]

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Introduction: Intraoperative handoffs are a high-risk time in a patient's perioperative care, yet there remains no standard approach for information to be passed along. Retrospective studies have shown that the number of anesthesia providers in a case was correlated with incidence of surgical complications [1,2]. Even beyond this, intraoperative handoffs when done well can facilitate communication in the surgeon-anesthesiologist dyad [3]. In this study, we sought to understand the content of intraoperative handoffs and the role that the anesthesia handoff plays in promoting multi-disciplinary communication.

Methods: This was an observational study using a convenience sample of operating room cases at a large academic medical center. Handoffs were observed by members of the research team as well as by trained anesthesia clinicians receiving handoffs. Subjects giving handoff were unaware of the observations. Data were analyzed first with descriptive statistics. Paired t tests and ANOVA was used to assess for differences between role groups, surgery type, break time, and anesthesia versus multidisciplinary surgical information. All statistics were done with Microsoft Excel. This quality improvement initiative was IRB exempt.

Results: 45 lunch break handoffs and 35 end-of-day handoffs were observed. The most common elements of the intraoperative handoffs were surgical procedure (95.1%) and past medical history (88.9%) with the leas common being surgery specific medications (28.4%) and tasks to do (37.1%). 5.7% of handoffs included an introduction of the new anesthesia provider to the surgical team. Handoffs were broken down first by role group – anesthesiologist, nurse anesthetist, or trainee. These role groups included significantly different information in their handoffs ($p<0.001$). Figure 1 shows the elements included by role group. Handoff elements were then classified as multidisciplinary or anesthesia specific. Multidisciplinary elements were overall passed along in 42.9% of handoffs versus anesthesia specific elements in 61.0% of handoffs observed ($p=0.2$) with no significant differences by role group, shown in Figure 2.

Conclusion: Handoffs are an opportunity to share information amongst anesthesiologists and anesthetists and an opportunity to deliberately reinforce information sharing and alignment with surgical colleagues. When we start cases at our institution we have a multidisciplinary huddle where the surgeon-anesthesiologist dyad communicates about the patient and the procedure as well as sharing names to facilitate communication throughout the case. When we hand over the case to a new anesthesia team, we have lost that direct multidisciplinary communication, and key surgical information, such as surgery specific conditions, are not passed along more than half the time. Additionally, without introducing new team members to the surgical team we have raised the barrier to communication across the drapes that we had sought to lower by sharing names during the pre-operative huddles. Intraoperative handoffs have real impacts on quality of care, and based on our data, we argue that some of that impact comes from disruption to the surgeon-anesthesiologist dyad function.

References: Anesthesiology 2014; 121: 695-706 JAMA 2018; 319 (2): 143-153 Anesthesiology 2018; 129: 402-405

Figure 1: Percentage of handoffs including each listed element broken down by provider role group.

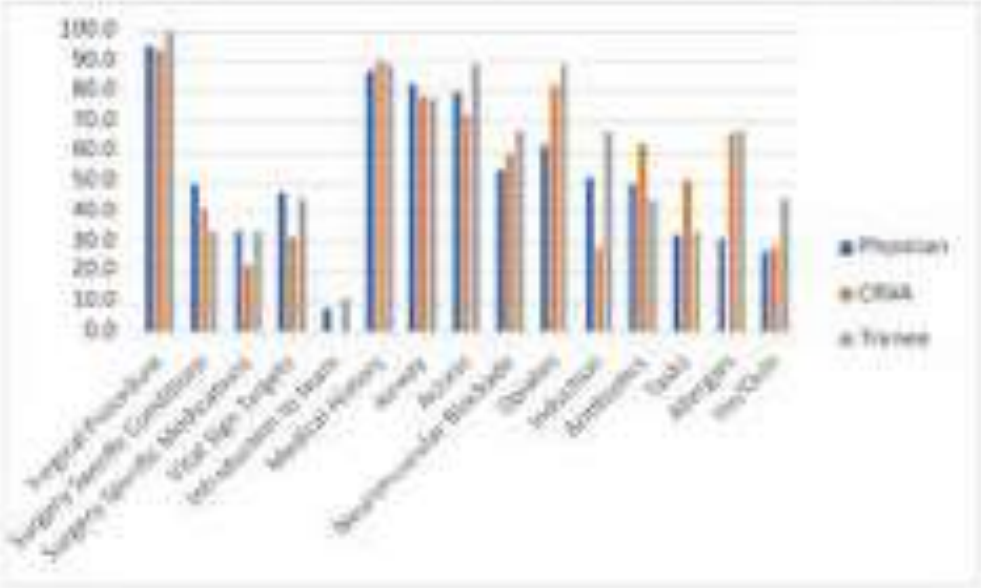
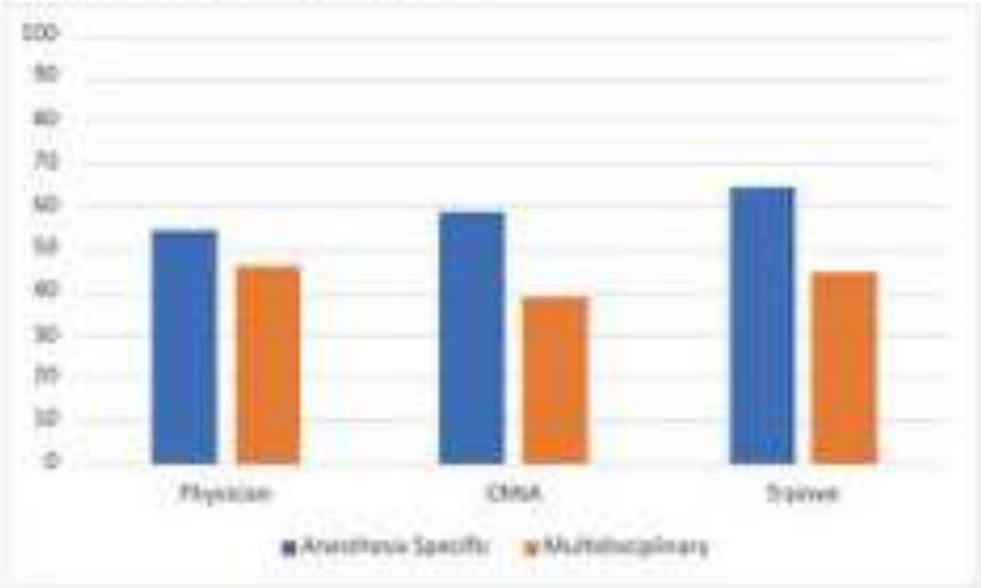


Figure 2: Percentage of handoffs including anesthesia specific elements versus multidisciplinary elements broken down by role group



Patient Safety - 10 Limitations of Colorimetric $etCO_2$ Detection during Cardiopulmonary Resuscitation

William J Cleveland[1], Alyssa K Streff[1], Matthew Barajas[1], Matthew J Hampton[1], Zhu Li[1], Matthias L Riess[2]

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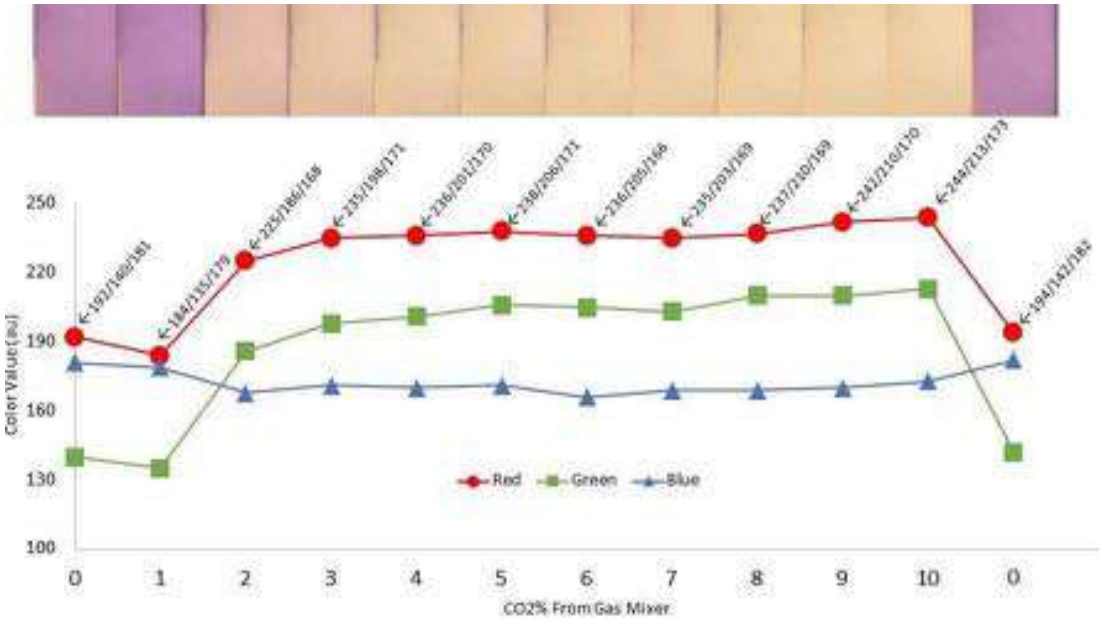
Introduction: During cardiopulmonary resuscitation (CPR), display of end tidal carbon dioxide ($etCO_2$) is critical for two reasons: 1) to determine proper placement of the endotracheal tube, and 2) to assess cardiac output during CPR and/or return of spontaneous circulation (ROSC). Colorimetric $etCO_2$ detectors allow for rapid and instant visual feedback of the $etCO_2$. However, these devices rely on optically differentiating a gradient between two different colors. We investigated how well colorimetric $etCO_2$ detection is able to differentiate between different CO_2 concentrations between 0 and 10% (0 and 76 mmHg) and, thus, would be suitable for use in confirming proper endotracheal tube placement vs assessing cardiac output.

Methods: A tank of 100% CO_2 and a tank of 100% O_2 were connected to an electronically controlled gas mixer (GSM-4, CWE Inc) that allows for precise control of the gas composition. Its output was connected in line with a colorimetric $etCO_2$ (Easy Cap II CO_2 Detector, Nellcor) and an electronic capnograph (Capnogard $ETCO_2$ Monitor 1265, Novametrix) to verify the chosen percentage of CO_2. The percentage of CO_2 was then increased from 0% up to 10% in increments of 1% and back down to 0% to ensure the color change was reversible. A video camera was used to monitor the color change in the detector and shots from the video were analyzed using color analysis software to determine the Red/Green/Blue (RGB) color values of the detector.

Results: Changes in the color of the $etCO_2$ detector as well as their respective RGB values are displayed for each CO_2% level (Fig 1). The largest change occurred between 1% and 2% CO_2 when the color changed from purple to yellow with corresponding RGB values changing from 184/135/179 to 225/186/168, respectively. Otherwise, all further changes in RGB values were relatively small with equally small changes in the color of the detector.

Conclusion: Based on the unexpectedly limited visual changes in the colorimetric $etCO_2$ detector, it is possible to use it to determine the proper placement of an endotracheal tube, providing the $etCO_2$ is 2% or higher. Meaningful changes in $etCO_2$ beyond 2%, however, cannot be discriminated so that colorimetric $etCO_2$ detection is not useful during CPR to assess the quality of chest compressions or ROSC. Instead, if available, quantitative capnography should be used during CPR.



Patient Safety - 11 Sedation with Monitored Anesthesia Care: An Examination of Perceptions and Educational Directions

Priscilla Nelson[1], Jonas Nelson[2], Linda Gerber[3], Sarah Wu[1], Patricia F Mack[4]

[1]New York Presbyterian / Weill Cornell Medical College, New York, NY, [2]Memorial Sloan Kettering Cancer Center, New York, NY, [3]Weill Cornell Medical College, New York, NY, [4]Weill Cornell Medicine, New York, NY

Introduction: Moderate to deep sedation, commonly referred to as Monitored Anesthesia Care (MAC), is increasingly utilized in both the operating room (OR) and non-operating room (NORA) settings. However, MAC has been associated with an increase in morbidity and mortality. In a recent examination of malpractice claims for NORA cases, most of the morbidity and mortality stemmed from over-sedation without vigilant monitoring and was felt to be preventable.(1,2) Additionally, a growing body of literature continues to caution against MAC in higher-risk patients. An understanding of surgeon and anesthesiologist perceptions of MAC is needed to better direct educational initiatives to improve patient care.

Methods: A project-specific questionnaire was developed with stakeholder engagement to address perceptions of safety, efficiency, and patient experience related to MAC (Figure 1).

The survey was administered using the Qualtrics platform to surgeons across specialties and anesthesiologists at a single urban, academic institution. Cohorts were compared by training background, the volume of cases under MAC, and length of time in practice.

Results: One-hundred forty physicians completed the survey(77 surgeons and 63 anesthesiologists)(Table 1). Differences were noted across training backgrounds, with surgeons more likely to believe that patients under MAC had "lighter" anesthetic compared to general anesthesia (GA)(Figure 2, Table 2). Surgeons were more likely to agree that a good MAC was one in which a patient was unaware and did not move. Subgroup analyses demonstrated that surgeons who performed a higher volume of MAC cases more strongly agreed patients desired MAC compared to GA.

Conclusion: Perceptions of MAC differ between surgeons and anesthesiologists. Surgeons tended to believe MAC is safer, yet preferred characteristics most anesthesiologists attribute to GA. Anesthesiologists demonstrated more caution when answering questions regarding the depth of anesthesia and airway protection. This study presents focused topics for educational initiatives and research to improve communication and shared decision-making regarding MAC.

References: 1. Bhananker SM, Posner KL, Cheney FW, Caplan RA, Lee LA, et al. Injury and liability associated with monitored anesthesia care: a closed claims analysis. Anesthesiology 2006:104:228-234. 2. Woodward ZG, Urman RD, Domino KB Safety of Non-Operating Room Anesthesia: A Closed Claims Update. Anesthesiology clinics 2017:35:569-581.

Figure 1—Monitored anesthesia care perception survey

Years in practice

Percentage of cases under monitored anesthesia care (0%–25%, 26%–50%, 51%–75%, 76%–100%)

Surgical specialty (for surgeon survey)

For the following questions, please indicate if you **agree or disagree**

OR[a] turnover will be quicker if the patient is under MAC[b]

Patients prefer MAC to GA[c]

Patients under MAC are not as deep as patients under GA

The quality of recovery is better with MAC

There is less postoperative nausea and vomiting with MAC than GA

Postoperative cognitive function is better with MAC than GA

Patients will be discharged sooner with MAC than GA

The airway is usually easier to manage with MAC than GA

There is greater hemodynamic stability with MAC than GA

In a patient with multiple comorbidities, (CHF, pHTN, OSA, COPD, CKD) MAC is generally safer

A good MAC is one where the patient is unaware

A good MAC is one where a patient does not move

There are fewer adverse anesthetic events with MAC than GA

a- OR = operating room; b- MAC = monitored anesthesia care; c- GA = general anesthesia

Figure 2—Surgeon vs. Anesthesiologist Perceptions of MAC. MAC = monitored anesthesia care, GA = general anesthesia.

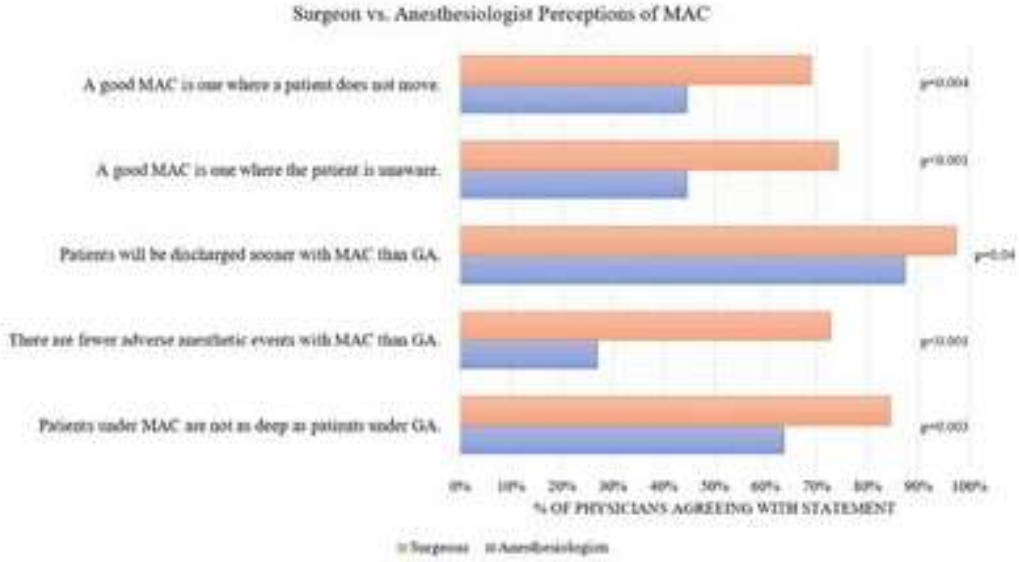


Table 1—Survey respondent demographics

	n	% of specialty	% of overall
Anesthesiologists	63		45%
Surgeons	77		55%
Bariatric surgery	3	4%	2%
Electrophysiology	3	4%	2%
Endocrine surgery	2	3%	1%
Gastroenterology	16	21%	11%
General surgery	10	13%	7%
Trauma surgery	5	6%	4%
Interventional neuroradiology	3	4%	2%
Interventional radiology	12	15%	9%
Neurosurgery	6	8%	4%
Otolaryngology	10	13%	7%
Plastic surgery	4	5%	3%
Vascular surgery	3	4%	2%
TOTAL	140		
Surgeon respondents, % MAC[a] cases*			
0–50	48		
51–100	28		
Anesthesiologist < 10 years in practice§	28		
Anesthesiologist ≥ 10 years in practice	27		
Surgeons < 10 years in practice‖	36		
Surgeons ≥ 10 years in practice	34		

	Median	IQR	p-value
Years in practice anesthesia	9	4–20	0.74
Years in practice surgery	9	5–17	

[a] MAC = monitored anesthesia care.

*76/77 surgeons provided data on % of MAC cases; § 55/63 anesthesiologists provided data on years in practice; ‖ 70/77 surgeons provided data on years in practice.

Table 2—Anesthesiologists vs. Surgeons Perceptions

Respondents who agree with the following statement: n, (%)	Anesthesiologists (n = 63)		Surgeons (n = 77)		p-value
	63	(%)	77	(%)	
Safety					
Patients under MAC[a] are not as deep as patients under GA[b]	40	(63.5)	65	(84.4)	0.003
Postoperative cognitive function is better with MAC than GA	50	(79.4)	66	(85.7)	0.24
The airway is usually easier to manage with MAC than GA	7	(11.1)	14	(18.2)	0.24
There is greater hemodynamic stability with MAC than GA	48	(76.2)	48	(62.3)	0.08
In a patient with multiple comorbidities, MAC is generally safer	35	(55.6)	38	(49.4)	0.47
There are fewer adverse anesthetic events with MAC than GA	17	(27.0)	56	(72.7)	<0.001
Efficiency					
OR[c] turnover will be quicker if the patient is under MAC	50	(79.4)	69	(89.6)	0.09
Patients will be discharged sooner with MAC than GA	55	(87.3)	75	(97.4)	0.04
A good MAC is one where the patient is unaware	28	(44.4)	57	(74.0)	<0.001
A good MAC is one where a patient does not move	28	(44.4)	53	(68.8)	0.004
Patient Experience					
Patients prefer MAC to GA	41	(65.1)	58	(75.3)	0.15
The quality of recovery is better with MAC	54	(85.7)	70	(90.9)	0.28
There is less postoperative nausea and vomiting with MAC than GA	58	(92.1)	71	(92.2)	1

a- MAC = monitored anesthesia care; b- GA = general anesthesia; c- OR = operating room.

Pediatric Anesthesiology

Pediatric Anesthesiology - 1 Enhanced Recovery after Pediatric Congenital Heart Repair with Erector Spinae Plane Blockade: An Ongoing Prospective, Randomized Controlled Trial

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[1]Stanford University School of Medicine, Stanford, CA, [2]Lucile Packard Children's Hospital Stanford, Stanford, CA

Introduction: Children who undergo congenital heart repair are at high risk for morbidity. Prolonged postoperative intubation is associated with high mortality, long ICU stays, and long hospital stays. While intubated, children are typically sedated with opioids, which are associated with increased risks of pneumonia. Bilateral ESPB catheters have been described as effective regional anesthesia during cardiac surgery1. Unlike paravertebral blocks, the ESPB is superficial with a lower risk of pneumothorax. Given the potential opioid-sparing benefits of ESPB catheters, we report the preliminary findings of an ongoing prospective, randomized controlled trial examining bilateral ESPB compared to standard of care (SOC). The primary aim was to determine whether lidocaine ESPB reduces CVICU length of stay (LOS) compared to SOC. Secondary aims examined time to extubation and total opioid consumption.

Methods: After IRB approval, patients were randomized to SOC control or treatment (ESPB). Patients in the treatment group received bilateral T7 ESPB catheters, with lidocaine 0.25% 1.5 mg/kg (max 20mL) through each catheter prior to surgery, followed by alternating-side lidocaine boluses every 2 hours postoperatively. Both groups received a standardized postoperative pain management regimen: acetaminophen 15 mg/kg every 6 hours, ketorolac 0.5 mg/kg every 6 hours for 6 doses, and as needed parenteral morphine, oral ibuprofen, and oral oxycodone. Inclusion criteria were patients age 0-21 years old undergoing these congenital heart surgeries: atrial septal defect repair, ventricular septal defect repair, anomalous aortic origin of a coronary artery repair, and left ventricular or right ventricular outflow repairs. Exclusion criteria were patients weighing <5kg, patients who were clinically unstable or requiring emergent surgery, and patients with pre-existing kidney or liver insufficiency.

Results: At the time of submission, 28 patients, ages 2 months to 19 years were enrolled. 14 patients were randomized to control and 14 to ESPB . Compared to SOC patients, ESPB patients had a lower mean total opioid consumption, measured in morphine equivalents per weight in kg (2.607 ± 1.440 vs. 6.367 ± 9.585, p =0.1922, Figure 1) and a shorter mean time to Extubation (15.86 ± 7.049hrs vs. 22.24 ± 32.14hrs, p=0.4750, Figure 2) but a longer CVICU LOS (55.71 ± 37.72hrs vs. 34.86 ± 19.28hrs, p=0.0769, Figure 3), though all the differences were not yet statistically significant. No adverse events were recorded in either group. Data collection is ongoing; final presentation will include aggregate results from patients collected to date.

Conclusion: Given the increasing use of regional during cardiac surgery1, this study may yield important findings to help guide clinical indications for ESPB during pediatric heart repair.

References: (1) Current Opinion in Anaesthesiology. 32(5):674-682. 2019.

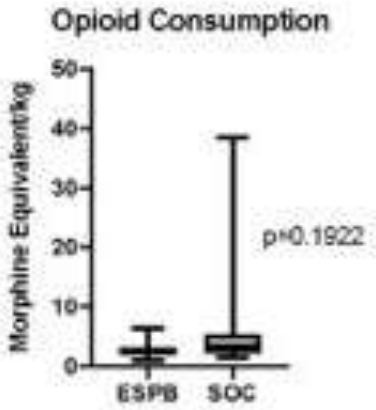

Figure 1. Total opioid consumption (in morphine equivalents per weight in kg) of ESPB and SOC patients. ESPB patients had a lower mean total opioid consumption than SOC patients, though not statistically significant (2.607 ± 1.440 vs. 6.367 ± 9.585, p =0.1922).

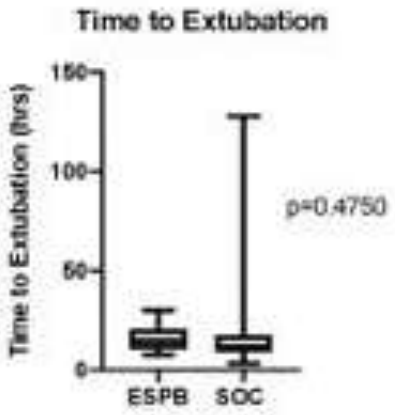

Figure 2. Time to Extubation of ESPB and SOC patients. ESPB patients had a shorter mean time to Extubation compared to SOC patients, though not statistically significant (15.86 ± 7.049 vs. 22.24 ± 32.14, p=0.4750).

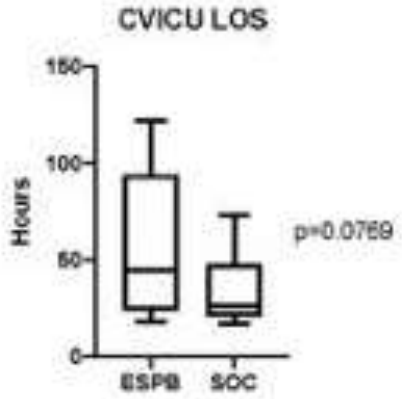

Figure 3. CVICU Length of Stay (in hours) of ESPB and SOC patients. SOC patients had a shorter mean CVICU LOS compared to ESPB patients, though not statistically significant (34.86 ± 19.28 vs. 55.71 ± 37.72, p=0.0769).

Pediatric Anesthesiology - 2 Association Between Intra-Operative Ketorolac Administration During Pediatric Adenotonsillectomy and Reduced Post-Operative Pain After Discharge

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Introduction: Adenotonsillectomy (T+A) is one of the most common pediatric surgical procedures performed in the United States. Sleep disordered breathing and obstructive sleep apnea (OSA) as the indication for T+A has increased significantly over the past ten years and is now the most common indication for this procedure in children (1). Opioids continue to be the primary pain medication for these procedures, however studies have shown that patients with OSA have significantly increased sensitivity to opioids which result in post-operative respiratory depression and apnea when administered at standard opioid dosing protocols (1-3). Unfortunately, poor pain control and subsequent dehydration continues to be a main factor in post-operative Emergency Department (ED) visits and hospital readmissions. The most recent data estimates the overall ED return rate at 13.3% for all children who underwent T+A (4). Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) that possesses similar efficacy to morphine without the side effects of respiratory depression, nausea and vomiting (5). Importantly, ketorolac has a synergistic effect when combined with opioids resulting in a lower dose of opioid required to achieve the same level of analgesia. In this study, we aim to determine if there is a significant correlation between intra-operative administration of ketorolac in pediatric T+A and the rate of post-operative pain after discharge resulting in post-operative phone calls, emergency room visits and readmission to the hospital.

Methods: After IRB approval, information was collected from pediatric patients who underwent tonsillectomy at either a free-standing pediatric hospital or a pediatric outpatient surgical center over a 5-year period by two pediatric otolaryngologists. The primary outcome of this analysis was significant postoperative pain after leaving the hospital/surgical center. This was defined as a phone call to the surgeon regarding post-surgical pain, an ED visit due to post-surgical pain, and/or a hospital admission due to post-surgical pain. In addition, the lone secondary outcome was significant postoperative bleeding defined as an ED visit for post-surgical bleeding, a hospital admission due to post-surgical bleeding, and/or returning to the operating room for post-surgical bleeding. Logistic mixed effects regression models were used to determine significant predictors for the outcomes. Variables accounted for included age, ASA classification, surgical location, inpatient vs outpatient, intraoperative steroid use, intraoperative dexmedetomidine use, perioperative morphine equivalents, surgical time, and surgeon. All analyses were performed with R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results: 878 patients were included with a median [IQR] age of 6 [4, 9] years. 39.2% of patients in this sample received intraoperative ketorolac. Significant postoperative pain at home and significant postoperative bleeding occurred in 157 (17.9%) and 21 (2.4%) patients, respectively. Intraoperative ketorolac was associated with a decreased incidence of significant postoperative pain (adjusted odds ratio [aOR] 0.65, 95%CI 0.44 to 0.95, P-value = 0.027, Table 1) without an apparent increase in significant postoperative bleeding (adjusted odds ratio [aOR] 0.96, 95%CI 0.35 to 2.44, P-value = 0.932, Table 1). However, this latter analysis is underpowered due to a low event rate.

Conclusion: OSA predisposes children to respiratory depression and apnea after opioid administration, prompting providers to minimize the amount of narcotics these patients recieve. Therefore, patients undergoing T+A often experience significant post-operative pain resulting in frequent phone calls, ED visits and readmissions after discharge. These incidences are not only unpleasant for the patient and caregiver, but they place significant burden on the hospital system. This study demonstrates that intraoperative ketorolac administration during T+A reduces post-operative pain and the incidence of these

untoward events. It also appears that ketorolac does not increase the adverse event of post-operative bleeding, although a larger cohort is needed to further delineate this outcome.

References: 1. Recurrent hypoxemia in young children with obstructive sleep apnea is associated with reduced opioid requirement for analgesia. Anesthesiology 2004; 100:806-10. 2. Effects of OSA, inhalational anesthesia, and fentanyl on the airway and ventilation of children. J Appl Physiol 2002; 92:1987-94. 3. An anesthetic management protocol to decrease respiratory complications after adenotonsillectomy in children with severe sleep apnea. Anesth Analg 2010; 110:1093-101. 4. Causes and costs for ED visits after pediatric adenotonsillectomy. Otolaryngol. Head Neck Surg. 2015; 152:691-696. 5. Ketorolac for postoperative pain management in children. Drug Saf 1997; 16(5):309-29.

Table 1. Association between intraoperative ketorolac use and outcomes

		†Unadjusted			‡Adjusted		
Outcomes	Levels	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Significant Postoperative Pain	Intraoperative Ketorolac vs None (Referent)	0.61	0.41 to 0.90	0.009	0.65	0.44 to 0.95	0.027
Significant Postoperative Bleeding	Intraoperative Ketorolac vs None (Referent)	0.77	0.26 to 2.07	0.656	0.96	0.35 to 2.44	0.932

CI = Confidence Interval.

†Based on Fisher's Exact Test. P-values <0.05 considered statistically significant.

‡Based on mixed effects logistic regression models after control of various patient, surgical, and analgesic variables. Variables accounted for included age, ASA classification, surgical location, inpatient vs outpatient, intraoperative steroid use, intraoperative dexmedetomidine use, perioperative morphine equivalents, surgical time, and surgeon. P-values <0.05 considered statistically significant.

Pediatric Anesthesiology - 3

Temperature Management for Paediatric Patients undergoing outpatient (OP) Magnetic Resonance Imaging (MRI) scans under General Anaesthetics (GA)

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Introduction: MRI is increasingly used for diagnosis and disease monitoring in the paediatric population. However, some, especially those with neurodevelopmental conditions, require a GA to tolerate the scans. Radiofrequency waves tend to increase body temperature, whilst MRI suites are usually kept cool and GA results in a general body temperature reduction. Research studies looking at temperature changes in paediatric patients (Ppts) undergoing MRI scans have shown mixed results[1][2]. The aim of the project is to assess temperature changes in Ppts undergoing OP MRI scans under GA and evaluate adequacy of current departmental practices in temperature management due to anecdotal concerns for hyperthermia.

Methods: Data prospectively collected over four month period across two MRI suites;1.5T and 3T. Data collected included basic demographics (age, gender, indications for scan), temperature pre- and post-scan using tympanic temperature probes. Other factors that may influence temperature changes also assessed include scan duration, ambient temperature and humidity and temperature management adopted (clothing choice, heating/cooling methods) during GA and in PACU. Data analysed using Excel™ and statistical significance calculated using two tailed paired T test.

Results: Fifty Ppts were included, 21 females and 29 males at mean age 4.24 years (95% CI 3.49 - 4.99) and mean weight 17.25kg (95%CI 15.13 - 19.38). 74% (37/50) scans were indicated for neuro-oncology or neurodevelopmental reasons. 68% (34/50) patients were scanned in 3T suite. Mean scan duration was 58.98 mins (95% CI 52.09 - 65.87), with mean scan room temperature 19.39°C and humidity 50.34%. Mean pre-scan temperature was 36.62°C (95% CI 36.50 - 36.75) dropping to mean post-scan temperature 36.43°C (95% CI 36.29 - 36.57; p=0.028). The mean temperature change was a decrease of 0.15°C (95% CI -0.33 - + 0.03). 14 % (7/50) patients were hypothermic (<36°C) post scan (mean 35.61, 95% CI 35.22 - 35.90), 4 in 1.5T group and 3 in 3T group. 92% (46/50) patients were covered with a blanket during the scan, whilst the rest were not covered. 22% (11/50) required additional blankets in PACU. No patients were hyperthermic (>37.5°C) and there was no delay discharge in any of the patients.

Conclusion: Our study has shown a statistically significant decrease in temperature for Ppts undergoing MRI with 14% hypothermic post scan, although this does not translate into a clinical significance. We did not observe a correlation between temperature change in relation to strength of magnet, duration of scan or patient weight. This is likely to reflect the complex physiological interactions at play. It is recommended extra vigilance is taken with the temperature management of these patients.

References: 1. Temperature management and radiofrequency heating during paediatric MRI scans. Vol 8 (1); 2019 2. Association Between Magnetic Resonance Imaging in Anesthetized Children and Hypothermia. Vol 4 (4); e181, 2019

Pediatric Anesthesiology - 4 Protocols in Pediatric Ambulatory Surgeries Do Not Decrease Disparities: A Single-Center Retrospective Study

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Introduction: Racial/ethnic disparities exist in the perioperative care of children. Non-Hispanic Black (NHB) children have higher perioperative morbidity and mortality compared to their non-Hispanic White (NHW) counterparts (1). Minority children receive opioids in the post-anesthesia care unit at different rates than NHW children (2,3), and racial/ethnic differences in administration of regional anesthetics in children may also exist (4). Enhanced recovery after surgery (ERAS) protocols aim to standardize care and are associated with decreased racial/ethnic disparities in adults (5). While pediatric ERAS protocols are less common, it has been hypothesized that they may also ameliorate disparities (6). We examined the effect of protocolized pediatric anesthetic care on reducing intraoperative racial/ethnic disparities for three well-established markers of quality of care: administration of antiemetics, non-opioid analgesic adjuvants, and regional anesthetics. We hypothesized protocol-driven approaches would decrease disparities by supporting objective intraoperative decision-making and decreasing provider-related variation.

Methods: Study design: retrospective cohort study using a level 1 pediatric hospital's medical record data for: 1) knee, foot, and ankle (KFA) orthopedic surgery (patients ≤18 years old), or 2) circumcision (patients ≤3 years old) from 2014-2019. Exposure: protocol (intraoperative administration of ≥1 antiemetic, ≥1 non-opioid analgesic, and a regional anesthetic). Exposure was determined by surgical location (the protocol was implemented at our ambulatory center but not our main campus). Primary outcomes: administration of 1) an antiemetic (ondansetron/dexamethasone), 2) a non-opioid analgesic (acetaminophen/ketorolac), and 3) a regional anesthetic (caudal/pudendal block for circumcision, and lower extremity block for KFA surgery). Statistical analysis: we calculated the rate of each outcome, stratified by exposure and racial/ethnic subgroup (Hispanic, NHW, NHB, Non-Hispanic Asian [NHA], and Other) and estimated the Wald binomial confidence interval for each.

Results: 4,185 patients were included in our study (Table 1). 1,904 (45.5%) were treated at our ambulatory center and received protocolized care. A majority (71.0%) were male. Surgical distribution varied, with a higher proportion of circumcisions done at the ambulatory center and a higher proportion of KFA surgeries at our main campus. There were no differences in location of surgery by race/ethnicity. Among patients who underwent KFA surgery and received protocolized care, NHW patients were more likely than all other racial/ethnic subgroups to receive: 1) an antiemetic (97.2%, 95% CI 95.6-98.8), with Hispanic patients significantly less likely (88.4%, 82.8-93.9) and 2) a regional block (80.1%, 76.1-84.0), with NHB patients least likely (70.0%, 58.4-81.6). NHW (83.1%, 79.4-86.8) and Other (88.4%, 83.2-93.6) patients were also most likely to receive a non-opioid analgesic, while Hispanic patients were least likely (76.0%, 68.6-83.3) (Figures 1, 2, and 3). In patients who underwent circumcision, all racial/ethnic subgroups were more likely to receive a regional block if they underwent protocolized care. However, differences between groups persisted, and NHB patients continued to be least likely to receive a regional block (86.1%, 79.4-92.9), while NHA patients were almost ten percent more likely (95.8%, 92.7-98.8). Overall protocol adherence to administer prophylactic antiemetics and non-opioid analgesics was low. Patients in the protocolized care group were less likely than those in the non-protocolized group to receive antiemetic and non-opioid analgesic medications.

Conclusion: We found persistence of racial/ethnic disparities with protocolized care. While protocols were associated with improved care for most NHW patients – particularly in KFA surgery and with the provision of a regional block – this was not the case for other racial/ethnic groups. Specifically, NHB and/or Hispanic patients were identified repeatedly as less likely to receive antiemetics, non-opioid analgesics, and/or regional anesthetics. Our findings suggest that implicit biases persist despite the implementation of protocolized anesthetic care.

References: 1. Pediatrics. 2020;146(2):e20194113. 2. J Health Care Poor Underserved. 2010;21(1):229-236. 3. Pediatrics. 2012;129(5):832-838. 4. Anesth Analg. 2020;131(1):255-262. 5. Ann Surg. 2018;268(6):1026-1035. 6. Anesthesiol Clin. 2020;38(2):327-339

Table 1: Characteristics of the Study Population

	Overall	Ambulatory Center (Protocol)	Main Campus (No Protocol)
N (%)	4185	1904 (45.5)	2281 (54.5)
Demographic Characteristics			
Sex (Male) (%)	2971 (71.0)	1486 (78.0)	1485 (65.1)
Race/Ethnicity (%)			
NHW	2145 (51.3)	961 (50.5)	1184 (51.9)
NHB	354 (8.5)	161 (8.5)	193 (8.5)
Hispanic	549 (13.1)	230 (12.1)	319 (14.0)
NHA	461 (11.0)	250 (13.1)	211 (9.3)
Other (Non-Hispanic)	676 (16.2)	302 (15.9)	374 (16.4)
Age in years (%)			
0-3	1824 (43.6)	1173 (61.6)	651 (28.5)
>3-10 (only KFA subgroup)	657 (15.7)	138 (7.2)	519 (22.8)
>10-18 (only KFA subgroup)	1704 (40.7)	593 (31.1)	1111 (48.7)
Surgery Type			
Circumcision	1513 (36.2)	1089 (57.2)	424 (18.6)
Knee/Foot/Ankle	2672 (63.8)	815 (42.8)	1857 (81.4)
Outcomes			
Received Antiemetic (%)	2954 (70.6)	1116 (58.6)	1838 (80.6)
Received Non-opioid Analgesic (%)	2445 (58.4)	773 (40.6)	1672 (73.3)
Received Regional Block (%)	3058 (73.1)	1615 (84.8)	1443 (63.3)

Figure 1
Antiemetic Administration by Surgery and Race/Ethnicity

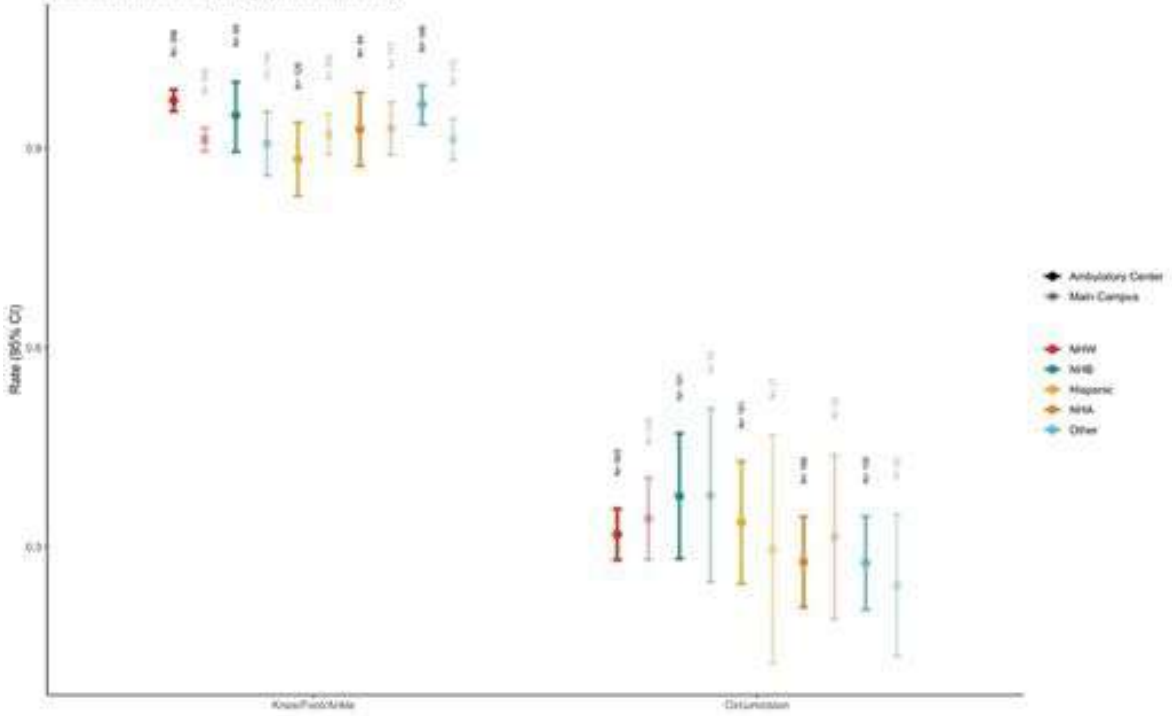


Figure 2

Analgesic Administration by Surgery and Race/Ethnicity

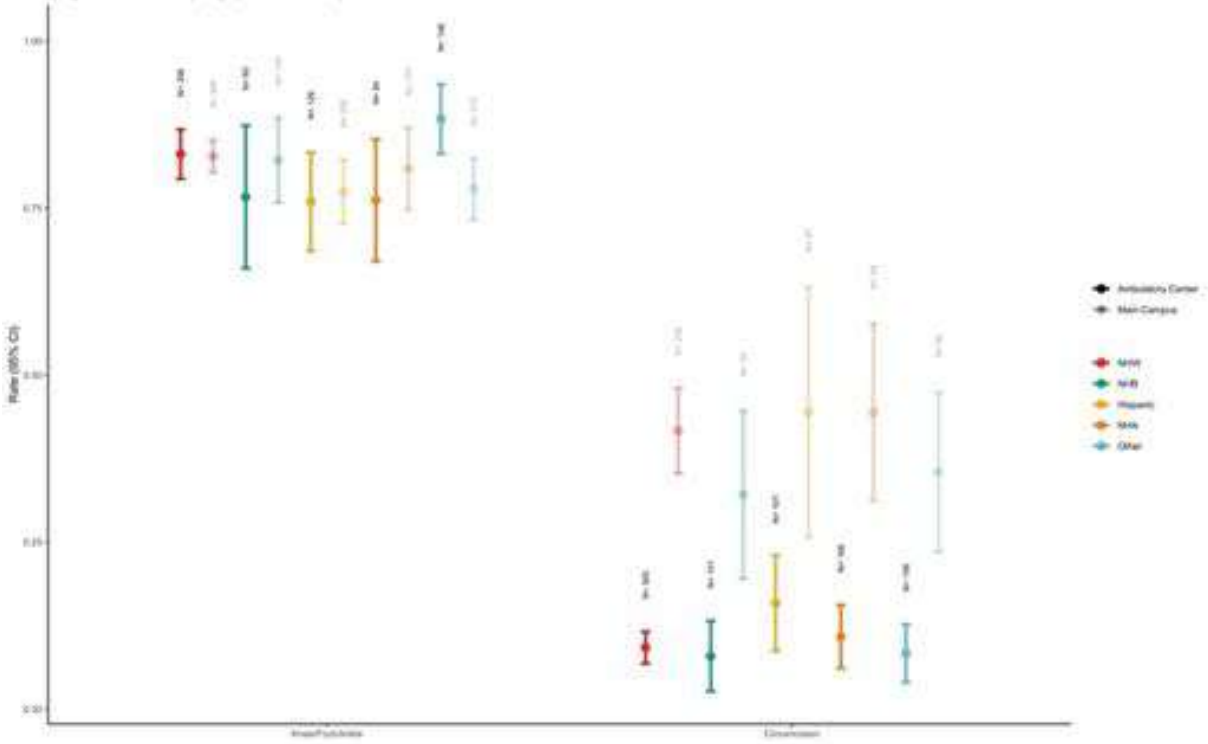
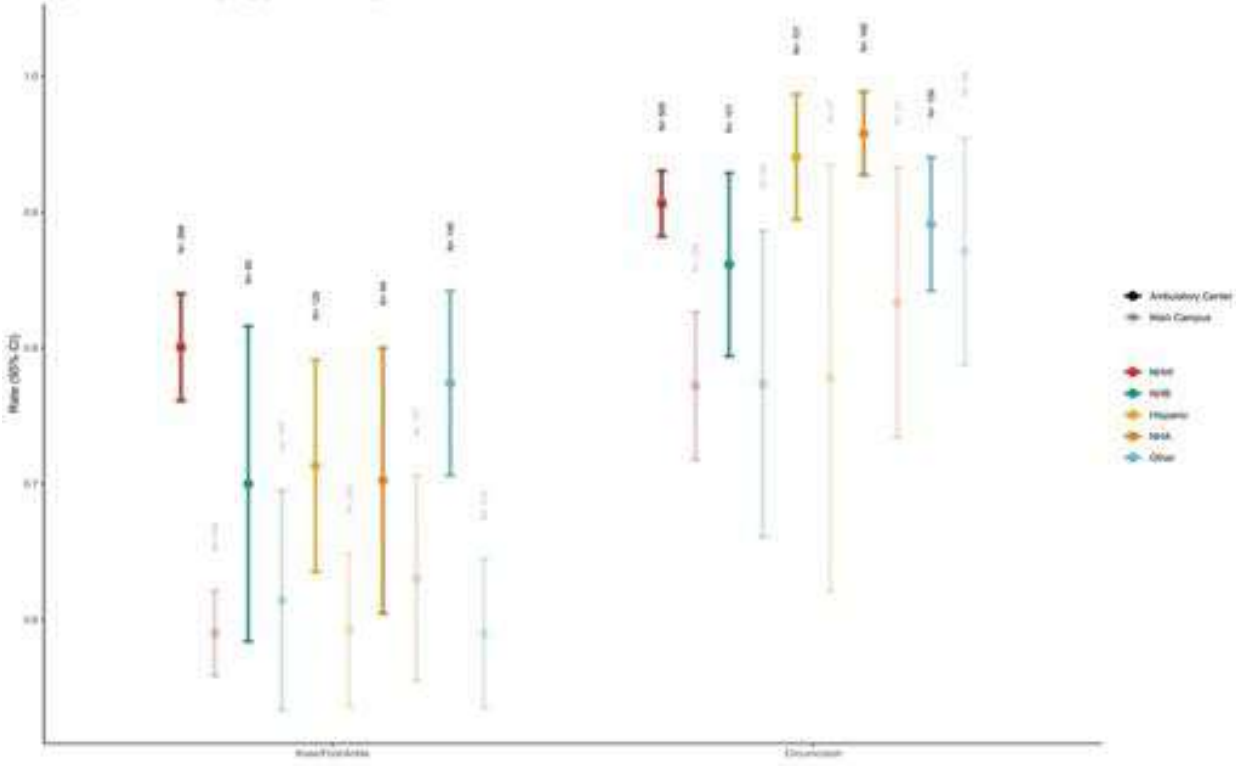


Figure 3

Regional Block Administration by Surgery and Race/Ethnicity



Pediatric Anesthesiology - 5 Anesthesia and Neurotoxicity Study Design, Execution, and Reporting in the Nonhuman Primate: a Deep Dive

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Introduction: Concern for role of anesthesia in developmental delay in children primarily originated from neonatal rodent and non-human primate (NHP) studies, yet prospective clinical trials, including Pediatric Anesthesia Neuro Development Assessment (PANDA) and General Anesthesia versus Spinal Anesthesia (GAS), have largely not supported this concern (1-2). Largely relying on these neonatal animal studies, the FDA issued the 2016 'Drug Safety Communication' warning on general anesthetics as potentially neurotoxic agents to young children (3). Lately, the legitimacy of the rodent data has been called into concern by recent studies on confounding factors of hypoxia and hypercarbia during experiments (4-6). However, the validity NHP data has not been reviewed in a systematic fashion. Herein, we present an objective and quantitative assessment of published NHP study rigor in experimental design, conduct, and reporting of outcomes.

Methods: We conducted a systematic MEDLINE search from 2005 to November 2019 focusing on animals between postnatal age 0 to 40 days who underwent anesthetic exposure (Figure 1). Article screening and data extraction were conducted by 2 independent reviewers, with all conflicts reviewed and resolved by the principal investigator. A total of eighteen manuscripts were included (Table 1). We extracted anesthetic, route, dose, frequency and duration of exposures, age at exposure, ventilation, mortality, sample size, vitals, blood gases, anesthesia monitoring, behavioral and neuroapoptosis outcomes. We also assessed adherence to the ASA (American Society of Anesthesiologist) monitoring and ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. Data were summarized as median (25th-75th percentile) and mean (SD).

Results: Important deficits in study design, execution, and reporting were identified in neonatal NHP studies. Critical issues identified in study design included (Table 2): lack of blinding in data acquisition (56%) and analysis (100%), supratherapeutic (4-12 fold) maintenance dosing in 28% of studies, lack of sample size justification (89%) resulting in a mean (SD) sample size of 6 (3) animals per group. Critical items identified in the conduct and reporting of studies included (Table 3): documentation of anesthesia provider (0%), electrocardiogram monitoring (40%), arterial monitoring (5%), spontaneous ventilation employed (40%), failed intubations resulting in commingling ventilated and unventilated animals in data analysis, inaccurate reporting of failed intubation, and only 50% reporting on survival. Inconsistencies were also noted in drug related induction of neuroapoptosis and region of occurrence. Further, 66-100% of behavior outcomes were not significantly different from controls (Figure 2).

Conclusion: Important deficits in study design, execution, and reporting were identified in neonatal NHP studies. These results raise concern for the validity and reliability of these studies and may explain in part the divergence from results obtained in human neonates.

References: 1. Association Between a Single General Anesthesia Exposure Before Age 36 Months and Neurocognitive Outcomes in Later Childhood. 2016;315:2312-2320. 2. Neurodevelopmental outcome at 5 years of age after general anesthesia or awake-regional anesthesia in infancy (GAS): an international, multicenter, randomized, controlled equivalence trial. 2019;393:664-677. 3. FDA Drug Safety Communication. 2016; https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-results-new-warnings-about-using-general-anesthetics-and. Accessed January, 12, 2021. 4. Physiological disturbance may contribute to neurodegeneration induced by isoflurane or sevoflurane in 14 day old rats. 2014;9:e84622. 5. Relevance of experimental paradigms of anesthesia induced neurotoxicity in the mouse.

2019;14:e0213543. 6. Hypoxia, hypercarbia, and mortality reporting in studies of anesthesia-related neonatal neurodevelopmental delay in rodent models: A systematic review. 2020;37:70-84.

Table 1. Nonhuman primate study characteristics.

Year	Citation	Species	Age	Anesthetic	Dose/Route	Duration	Outcome
2007	Ikkink et al.[11]	Macaca mulatta	G122	Ket	20-30 mg kg^{-1} h^{-1} (i.v.)	24h	Neuroapoptosis
			P5-6	Ket	20-30 mg kg^{-1} h^{-1} (i.v.)	24h	Neuroapoptosis
			P35-37	Ket	20-30 mg kg^{-1} h^{-1} (i.v.)	24h	Neuroapoptosis
			P5	Ket	20-30 mg kg^{-1} h^{-1} (i.v.)	3h	Neuroapoptosis
2009	Zou et al.[12]	Macaca mulatta	P5	Ket	20-30 mg kg^{-1} h^{-1} (i.v.)	3h	Neuroapoptosis
			P5-6	Ket	20-30 mg kg^{-1} h^{-1} (i.v.)	9h	Neuroapoptosis
			P5-6	Ket	20-30 mg kg^{-1} h^{-1} (i.v.)	24h	Neuroapoptosis
2010	Brambrink et al.[13]	Macaca mulatta	P6	Iso	0.7-1.5% (I)	5h	Neuroapoptosis
2011	Paule et al.[14]	Macaca mulatta	P5-6	Ket	20-30 mg kg^{-1} h^{-1} (i.v.)	24h	Behavior
2011	Zou et al.[15]	Macaca mulatta	P5-6	N2O	70% (I)	8h	Neuroapoptosis
			P5-6	Iso	1% (I)	8h	Neuroapoptosis
			P5-6	N2O+Iso	70% N2O + 1% Iso (I)	8h	Neuroapoptosis
2012	Brambrink et al.[16]	Macaca mulatta	G120	Ket	10.1-60.5 mg kg^{-1} h^{-1} (i.v.)	5h	Neuroapoptosis
			P6	Ket	18.4 - 56.0 mg kg^{-1} h^{-1} (i.v.)	5h	Neuroapoptosis
2012	Brambrink et al.[17]	Macaca mulatta	P6	Iso	0.7-1.5% (I)	5h	Neuroapoptosis
2012	Zhang et al.[18]	Macaca mulatta	P5-6	N2O + Iso	70% N2O + 1% Iso (I)	8h	18F-FEPPA uptake by PET/CT
2013	Creeley et al.[19]	Macaca mulatta	G120	Pro	350-850 mg kg^{-1} min^{-1} (i.v.)	5h	Neuroapoptosis
			P6	Pro	300-600 mg kg^{-1} min^{-1} (i.v.)	5h	Neuroapoptosis
2013	Zhou et al.[20]	Macaca fascicularis	P6	Sev	2.0-2.6% (I)	5h	Behavior, Protein Expression
2013	Liu et al.[21]	Macaca mulatta	P5-6	Sev	2.5% (I)	9h	Neuroapoptosis, Lipid Metabolism
2013	Rajan et al.[22]	Macaca mulatta	P6-10, 14d later, 28d later	Sev	2% (I)	4h (3x)	Behavior
2014	Zhang et al.[23]	Macaca mulatta	P5-6	Sev	2.5% (I)	8h	18F-FEPPA uptake by PET/CT, Neuroapoptosis
2017	Schenning et al.[24]	Macaca mulatta	P20	Iso	1.3-2.5% (I)	5h	Neuroapoptosis
			P40	Iso	1.3-2.5% (I)	5h	Neuroapoptosis
2017	Coleman et al.[25]	Macaca mulatta	P6, P9, P12	Iso	0.7-1.5% (I)	5h (3x)	Behavior
			P6	Iso	0.7-1.5% (I)	5h	Behavior
2017	Alvarado et al.[26]	Macaca mulatta	P6-10, 14d later, 28d later	Sev	2% (I)	4h (3x)	Vision impairment
2017	Noguchi et al.[27]	Macaca mulatta	P6	Iso	0.7-1.5% (I)	5h	Neuroapoptosis
2018	Rajan et al.[28]	Macaca mulatta	P6-10, 14d later, 28d later	Sev	2% (8% rises with 100% O2) (I)	4h (3x)	Behavior

i.v.: intravenous; I: inhaled; G: gestational; P: postnatal; Ket: ketamine; Iso: isoflurane; N2O: nitrous oxide; Pro: propofol; Sev: sevoflurane; 14d: 14 days; 28d: 28 days; 18F-FEPPA: 18F-labeled fluoroethoxybenzyl-N-(4-phenoxypyridin-3-yl) acetamide; PET-CT: positron emission tomography–computed tomography.

Table 3: Summary of anesthesia monitoring

Characteristics	Exposed (n=18 studies)	Unexposed (n=18 studies)
Overall mortality, No. (%)	1 (6)	0 (0)
Perioperative mortality, No. (%)		
Reported all animals survived	9 (50)	
Did not mention survival or mortality	9 (50)	
Ventilation, No. (%)		
Controlled	11 (61)	
Spontaneous	4 (22)	
Not specified	3 (17)	
Fraction of inspired oxygen, No. (%), %		
Not specified	13 (72)	
50	4 (22)	
100	1 (6)	
Recovery after anesthesia, No. (%)		
Room air	17 (94)	
Not specified	1 (6)	
ASA Monitoring, No. (%)		
Presence of anesthesia personnel	0 (0)	0 (0)
Pulse oximetry	17 (94)	6 (33)
Heart rate	17 (94)	6 (33)
Capnography	17 (94)	5 (28)
NIBP	16 (89)	6 (33)
Temperature	16 (89)	11 (61)
ECG	10 (83)[a]	0 (0)
Electrocardiogram	7 (39)	0 (0)
Intubation Reporting, No. (%)		
Pre-oxygenation	0 (0)	
Skill level of personnel intubating	0 (0)	
Number of attempts	0 (0)	
MAP, median [25th-75th], mmHg		
Nadir MAP (n = 5 exposed, 2 unexposed)	78 [55-82]	60 [62-69]
Venous blood gases, median [25th-75th], mmHg		
Nadir pH (n = 3)	7.31 [7.28-7.31]	7.36 [7.36-7.36]
Peak PCO2 (n = 3)	60 [59-64]	43 [43-43]
Nadir PO2 (n = 3)	28 [25-28]	25 [25-25]
Arterial blood gas, mmHg		
Nadir pH (n = 1)	7.29	
Peak PCO2 (n = 1)	69	
Nadir PO2 (n = 1)	231	
Monitoring frequency, median [25th-75th], hr		
Blood pressure (n = 14 exposed, 6 unexposed)	0.25 [0.25-0.50]	2 [1.8-3]
Heart rate (n = 15 exposed, 6 unexposed)	Cont [Cont-0.08]	1.5 [1.5-1.8]
End-tidal CO2 (n = 15 exposed, 5 unexposed)	Cont [Cont-0.08]	1.5 [1.5-1.5]
Pulse oximetry (n = 15 exposed, 6 unexposed)	0.25 [0.08-1]	1.5 [1.5-1.8]
Temperature (n = 14 exposed, 11 unexposed)	1 [0.25-2]	1 [twice²-1.5]
Blood gases (n = 14 exposed, 9 unexposed)	2 [1.5-3]	twice [twice-2]
Blood gas monitoring, No. (%)		
VBG	11 (61)	9 (50)
ABG	1 (6)	0 (0)

NIBP: Non-invasive Blood pressure; MAP: Mean arterial pressure; FIO2: Fraction inspired oxygen; Cont: Continuous; VBG: Venous blood gas; ABG: Arterial blood gas; PO2: partial pressure of oxygen; PCO2: partial pressure of carbon dioxide. [a]Only 12 studies were mechanically ventilated where FIO2 was measurable. [b]At baseline and after recovery

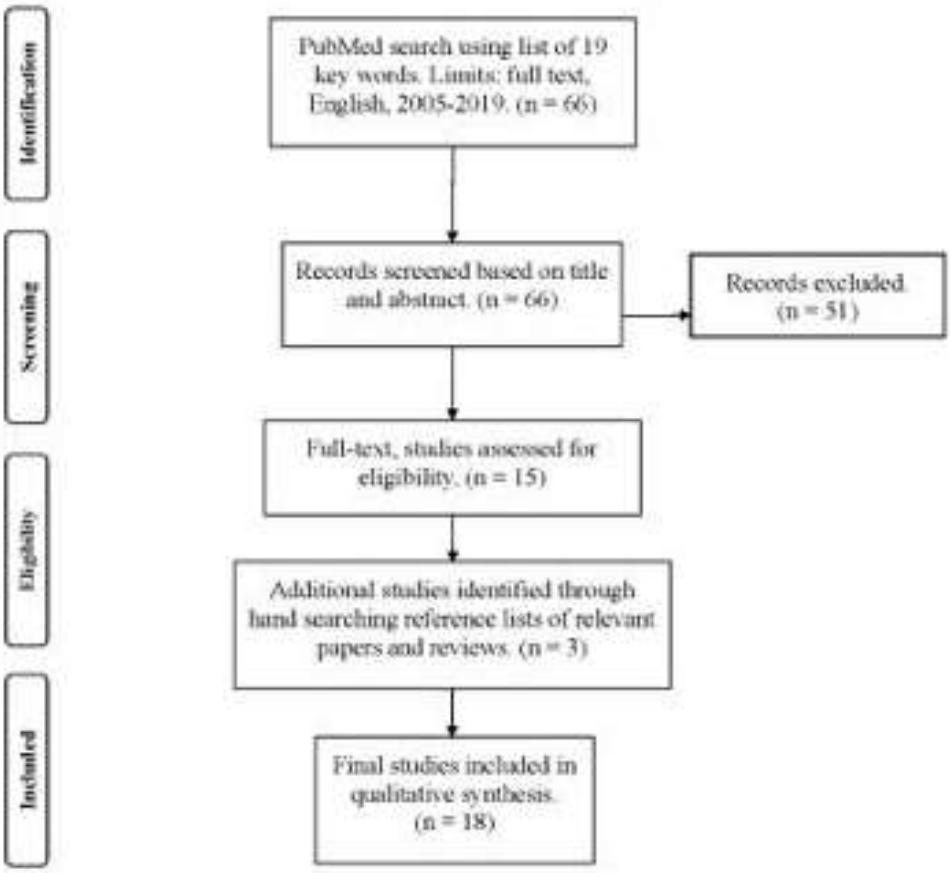

Figure 1. PRISMA flow chart: methodology applied and results.

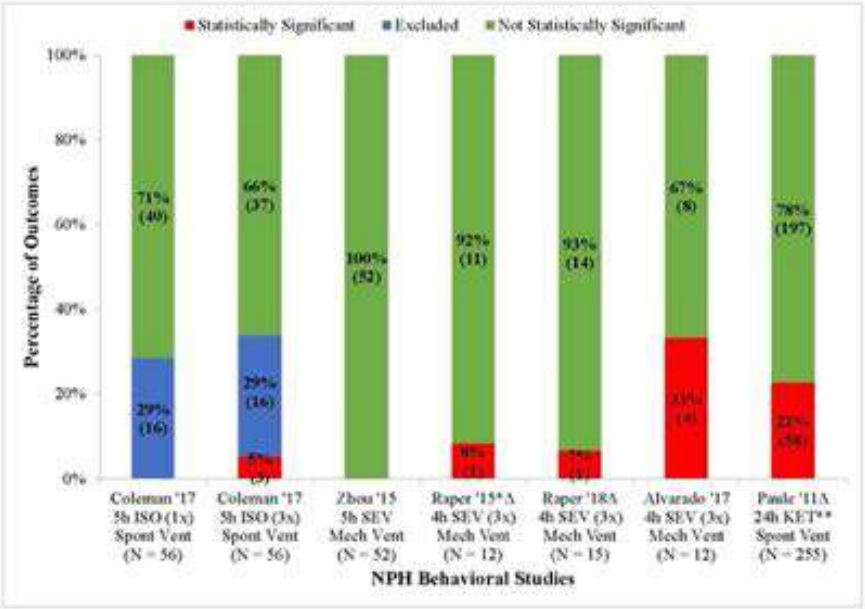

Figure 2. Behavioral study outcome breakdown. ISO: isoflurane; SEV: sevoflurane; KET: ketamine; Mech Vent: mechanical ventilation; Spont Vent: spontaneous ventilation. *Same test no longer statistically significant at 2-year follow up in Raper 2018. **Anesthetic Overdose by 4 to 11-fold. Δ: Rater not blinded.

Pediatric Anesthesiology - 6 Applying Machine Learning to Identify Pediatric Patients at Risk of Critical Perioperative Adverse Events: using the APRICOT Dataset

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Introduction: Literature on pediatric anesthesia focuses on clinical audits of morbidity and mortality from a single institution or country, which were not sufficiently powered to study rare, severe complications or mortality. The APRICOT (Anesthesia PRactice In Children Observational Trial) study aimed to identify the incidence, nature, and outcome of serious perioperative adverse events (PAEs) in children undergoing anesthesia, and the associated potential risk factors, using traditional statistical methodology. Anesthesia risk is currently calculated on a population 'one size fits all' basis, perhaps modified by the presence of certain known risk factors. However, each child presents a unique clinical picture and to incorporate this into individualized risk prediction is not yet possible. Experienced clinicians will recognize risk factors, especially for children who are ASA III or higher. The availability of a precision medicine approach to risk calculation for children generally considered 'low risk' enables anesthesia teams to better prepare the appropriate level of care for these children. Here we present a high performance machine learning model for classification of patients as high or low risk for a PAE as a secondary use of the APRICOT dataset.

Methods: APRICOT studied the primary endpoint of incidence of perioperative severe critical events in 30 874 children undergoing anesthetic procedures across 33 European countries. Severe critical events defined by APRICOT were laryngospasm, bronchospasm, pulmonary aspiration, drug error, anaphylaxis, cardiovascular instability, neurological damage, peri-anesthetic cardiac arrest and post-anesthetic stridor. The critical event rate was 4.7%. We identified 27 425 patients (88% of the registry) categorized as ASA I or II, presenting for their first procedure and whose PAE was not caused by drug error. This subset experienced 1087 PAEs, for a rate of 4%. We handled missing fields using multiple imputation for continuous variables and random draw for discrete variables. A 25:1 class imbalance existed in the original dataset. Several sampling techniques were tested, of which under-sampling of the majority class produced the most effective results. Data was split in a stratified fashion 17:1 between training and testing. K-fold stratified cross validation was used for training (k=5). Models were built using random forest, extreme gradient boosting (XGB), XGB with histograms, Naïve-Bayes, k-nearest neighbor, AdaBooster, multi-level perceptron neural networks and support vector machines. A stacked classifier composed of random forest, XGB and XGB with histograms was also built. Model performance was evaluated using accuracy, AUROC, positive predictive value and negative predictive value. This study was classified as IRB exempt.

Results: The top performing single model was extreme gradient boosting and achieved an accuracy between 0.7 and 0.8, an AUROC of 0.6-0.7, a maximum positive predictive value (PPV) of 0.13 and a negative predictive value (NPV) greater than 0.9. The stacked classifier models had an accuracy in excess of 0.8, AUROC of 0.7-0.8, a maximum PPV of 0.15 and a NPV in excess of 0.97. Our results show that airway interface, in-patient status and history of influenza are the most substantial predictive factors for severe PAEs. This study demonstrates the application of machine learning to classify risk in healthy children undergoing anesthesia. Our models show an AUROC that is considered acceptable when using a highly imbalanced dataset. However, even our best performing stacked model demonstrates a low PPV- as do many other models trained on clinical data, where class imbalance is common. This suggests that the most clinical utility may lie in using the high NPV as a screening tool to identify patients at low risk for PAE.

Conclusion: Individually identifying patients at low risk of severe critical PAE has clinical utility through helping clinicians to identify cases that have a low likelihood of care escalation to greater than routine levels. This may help in stratifying patients to receive care at satellite sites, or in informing the managing clinician's decisions in teaching and levels of supervision. We will continue to develop our work with providers to increase clinical confidence in the model, including the development of interpretability. We aim to produce a calculator and intuitive user interface using visual analytics methods so that front line clinical staff can use the models in real-time.

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Pediatric Anesthesiology - 7 The Conundrum of Opioid Use in the Neonatal Intensive Care Unit (NICU): Providing Comfort or Aggravating Development?

Kunal Sualy[1], Sneh Koul[2], Jordan Hernandez[2], Victoria Schaal[2], Ann Anderson-Berry[1], Somwmya Yelamanchili[2], Steven J Lisco[2], Mohanad Shukry[1], Sneham Tiwari[2], Gurudutt Pendyala[2]

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Introduction: Newborns in intensive care unit (ICU) settings post-surgery are often treated for prolonged periods with sedative medications, including opioids. Whilst developmental neurotoxicity associated with anesthetic agents has received attention from anesthesiologists for decades, it is still common practice to expose infants or toddlers to such agents during pediatric surgery. Studies suggest almost all general anesthetics could potentially induce structural and functional changes in the brain of neonatal animals(1). Moreover, large-scale clinical studies also indicated learning disabilities and behavioral disturbances in some children are correlated with surgery under anesthesia before 4 years of age, especially in children undergoing multiple surgeries under general anesthesia(2). Evidence from studies conducted in animal models, including rodent(3) and non-human primates(4), suggest the possibility early developmental exposure to general anesthesia (GA) has harmful consequences for brain development. Although nearly all the evidence in human studies and animal models relates to GA as practiced in operating room (OR) settings, the FDA has issued a warning regarding the of risks associated with medications described as 'sedation drugs' used during surgery and other procedures(5). The current proposal focuses on fentanyl, a mu opioid-receptor agonist, which is used commonly as part of GA, as well as to promote sedation in the neonatal intensive care unit (NICU). Of note, the duration of exposure may be the most critical difference between ICU sedation and OR GA, as NICU sedation can continue for days or even weeks. This leaves open an important question with potentially substantial public health ramifications: Does sedation for infants and young children as practiced in ICU settings have the potential to cause harm to the developing brain? Based on these factors, and the absence of any clear and comprehensive literature on long-term exposure of analgesics/sedatives, there is a compelling rationale and pressing need to study the effects of ICU-type sedation on the developing brain. Accordingly, our proposed studies will focus on testing the outcomes associated with long-term exposure of fentanyl in pre-term infants (23-36 week gestation) vs term infants (37-40 week gestation) on synaptogenesis – a key process of formation of synapses during brain development and subsequent impairment of behavioral outcomes at a later stage of life.

Methods: The current study focused on rat pups at postnatal (P) 3 and 7 that mimic the pre-term and term infants equivalent in humans, respectively. Pups were injected with subcutaneous fentanyl at doses similar to seen in the NICU population for 11 and 7 days for the two groups. At P14 (represents peak synaptogenesis in rodents), body weights, lengths and head size circumference were measured, along with isolation of brains and blood plasma. The remainder of the pups underwent behavioral testing at P45 and P90.

Results: Our preliminary results demonstrated that P3 animals had a marked reduction in the physical attributes compared to the control and P7 animals. Currently, molecular and behavioral studies are in progress and will be discussed in further detail at the conference.

Conclusion: The studies proposed are timely, novel and importantly help delineate the long-term exposure of Fentanyl in pre-term vs term infants on synaptogenesis and subsequent impairment of behavioral outcomes at a later stage of life. The outcomes will then help the pediatric clinical community to help decipher the conundrum of the safety of opioids use in neonates.

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Pediatric Anesthesiology - 8 Association between S100β, NSE and BDNF levels and different exposure time of general anesthetics in pediatric patients undergoing non-cardiac surgeries

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Introduction: Compelling evidence from preclinical studies using neonatal rodent models has demonstrated detrimental effects of general anesthetics on the developing brain after prolonged exposure. Some of these clinical studies suggest that children may develop cognitive and behavioral impairment if exposed to more than one surgery with anesthesia before the age of 4 yr. However, the lack of studies evaluating long-term anesthesia exposure and its impact on the developing human brain has limited diagnostic and therapeutic options. The present study investigated the effect of general anesthetics on serum brain-derived neurotrophic factor (BDNF), calcium-binding protein β (S100β) and neuron specific enolase (NSE) protein concentrations in pediatric patients aged <4 yr and 4-17 yr undergoing long (>3 hr) vs. short duration (<1 hr) non-cardiac surgeries. We hypothesized that prolonged anesthesia and surgery will reduce a known neurotrophic agent that attenuates neuroinflammation (BDNF) and increase the biomarkers known to be elevated due to the neuronal cell damage (S100β and NSE).

Methods: To investigate the effect of general anesthetics and surgery on serum concentration of S100β, NSE, BDNF in pediatric patients aged (<4 yr and 4-17 yr) (n=10/group), we collected blood samples before and after surgery. We determined the protein levels by ELISA on 3 pooled samples per group due to the limited amount of serum. Data analysis was performed using Graph Pad Prism software ($P<0.05$).

Results: Patients aged <4 yr undergoing lengthy surgeries (>3 hr) had statistically significant differences (*$P<0.05$, **$P<0.01$) in the serum protein concentration of S100β, NSE, and BDNF, before vs. after the surgery, as compared to patients with short surgery durations (<1 hr) (Figures A-B). In addition, the pediatric population aged 4-17 yr showed smaller (S100β) or no differences (BDNF) in biomarker levels as a function of duration of surgery (Figures C-D).

Conclusion: These preliminary results suggest that the serum concentration level of S100β, NSE, and BDNF correlate with the duration of surgery for patient aged <4 yr. These effects might point to a greater detrimental effect of surgery and anesthesia in younger children that may contribute to developmental neurotoxicity.

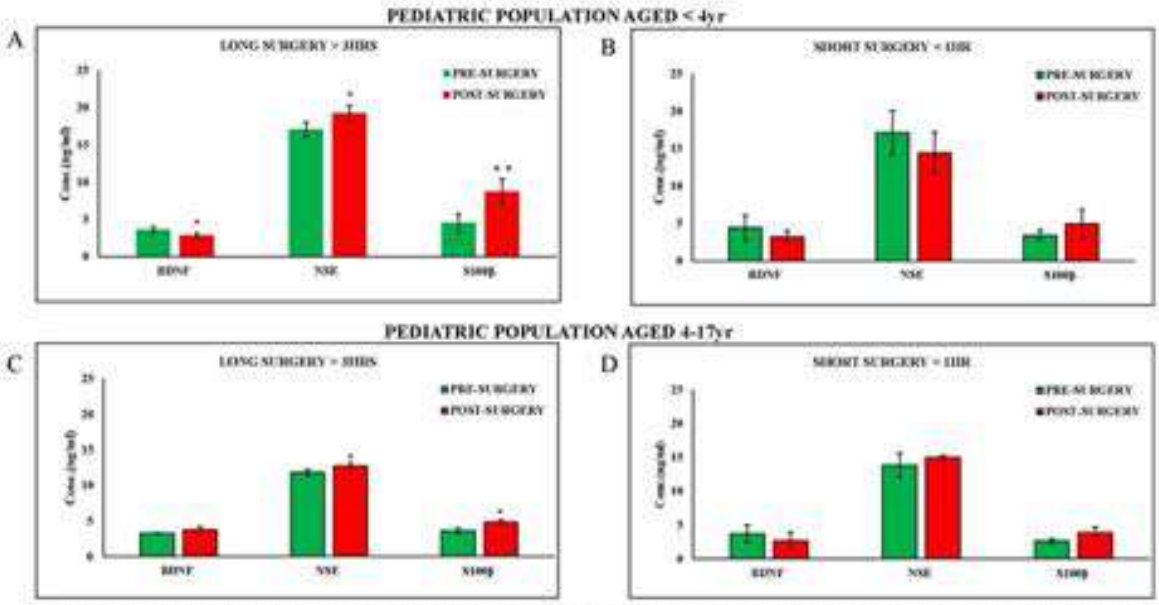

Figure: The serum concentration of BDNF, NSE and S100β in non-cardiac pre and post operative surgery were measured by sandwich ELISA (A) >3hrs & age <4 yr (B) <1hr & age <4 yr (C) >3hrs & age 4-17 yr. (D) <1hr & age 4-17 yr The protein expression of BDNF, NSE and S100β are shown in ng/mL. Data represent mean ± SD (n = 3). *P < 0.05, **P < 0.01 by Student's t-test.

Pediatric Anesthesiology - 9 A Survey of the Global Impact of COVID-19 on the Practice of Pediatric Anesthesia: a study from the PEACOC group

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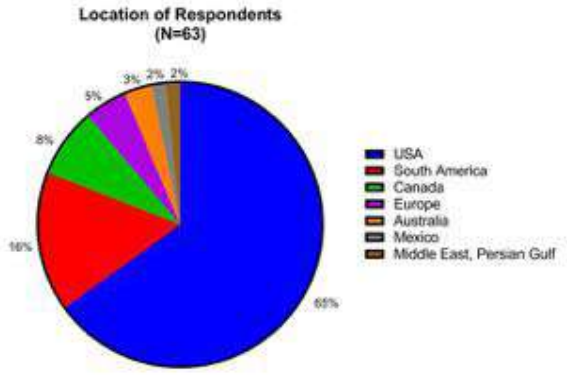
Introduction: The COVID-19 global pandemic has upended traditional hospital policies regarding preoperative testing, personal protective equipment, staffing, and visitation. No data exist on how the pediatric perioperative experience has changed for patients and providers due to the pandemic. With this study, we sought to survey pediatric centers and highlight how COVID-19 has altered the delivery of care by pediatric anesthesiologists, the practice of pediatric anesthesia, and its economic impact. Responses showed COVID-19 has strained healthcare resources, and drastically changed the environment in which pediatric anesthesiologists practice.

Methods: Institutional Review Board (IRB) exemption was obtained from Boston Children's Hospital. A prospective survey questionnaire concerning four major domains (testing, safety, clinical management/policy, economics) was developed. It was pilot tested for clarity and content by members of the Pediatric Anesthesia COVID-19 Collaborative (PEACOC). The survey was administered by email to all PEACOC members on September 1, 2020. There were no exclusion criteria. Respondents had 6 weeks to complete the survey and were instructed to answer the questions based on their institution's practice during September 1 - October 13, 2020. If an institution had several anesthesiologists as members of PEACOC, they were instructed to select a representative to respond. Respondents were instructed to answer the questions based on the current situation at their institutions during the study period September 1-October 13, 2020. Individual institution data were fully de-identified, so study authors knew only that a member from the corresponding institution had completed the survey. Descriptive statistical analysis was performed by statisticians at Boston Children's Hospital.

Results: 63 institutions (100% response rate) participated in the COVID-19 Pediatric Anesthesia Survey. 41 hospitals (65%) were from the United States, and 35% included other countries. N95 masks were available to anesthesia teams at 91% of institutions (95% CI: 80%-96%). The most common PPE worn by anesthesiologists while caring for an untested, patient under investigation (PUI), or COVID-19 positive patient were N95 masks (89%), face shields or goggles (86%), hat/bonnet (79%), and gloves (71%). In the event of a shortage of PPE, 51% of institutions allowed anesthesiologists to use their own equipment. Patient PCR testing for COVID-19 was required for elective surgery in 65% of hospitals and for urgent surgery in 56% of hospitals. Thirteen percent of respondents (n=8) reported that PCR testing was not used at their institution. Perioperative screening questionnaires were used at 92% of institutions. COVID-19 testing criteria of anesthesia staff and guidelines to return to work varied by institution. Seventy-one percent of hospitals have airway barrier methods utilized when intubating a PUI or COVID-19 positive patient. In 38 institutions of the 45, it was at the discretion of the anesthesiologist in which age group airway barriers were utilized. During the care of a COVID-19 positive patient or PUI 65% of institutions had a designated spotter available for donning and doffing of PPE, however during the off hours this safety feature was only available in 35% of institutions. Structured simulation training aimed at improving COVID-19 safety and patient care occurred at 62% of institutions. Pediatric anesthesiologists were economically affected by losses of incentive pay, retirement matching, vacation time and restriction of personal travel. Incentive pay was negatively impacted at 46% of institutions (95% CI: 33% - 59%) during the pandemic, vacation time was reduced at 27% of hospitals (95% CI: 17% - 40%), and personal travel restrictions were implemented at 62% (95% CI: 49% - 74%). Sixty-eight percent (95% CI: 55% - 79%) of respondents indicated that staff are not given the choice regarding working with COVID-19 positive patients.

Conclusion: Our data indicate that the COVID-19 pandemic has impacted the testing, safety, clinical management, and economics of pediatric anesthesia practice. Lessons learned from the operational challenges posed by COVID-19 should be used to inform preparation for similar challenges in the future. Further investigation into the long-term consequences for the specialty are indicated

Figure 1. Description of Respondent Characteristics



Demographics and Respondent Characteristics	
Variable	n (%)
Primary Practice Setting	
Public (government supported)	16 (27%)
Private (non-government supported)	15 (24%)
Academic	41 (65%)
Other	0 (0%)
Number of Hospital Beds Dedicated to Pediatric Population	
0 – 50	4 (6%)
50 – 100	9 (14%)
100 – 250	21 (33%)
250 – 500	22 (35%)
> 500	7 (11%)
Primary Site of Practice	
Free standing pediatric hospital	36 (57%)
Pediatric hospital within an adult hospital	20 (32%)
Adult hospital	7 (11%)

Figure 2. COVID-19 Testing of Pediatric Anesthesia Staff

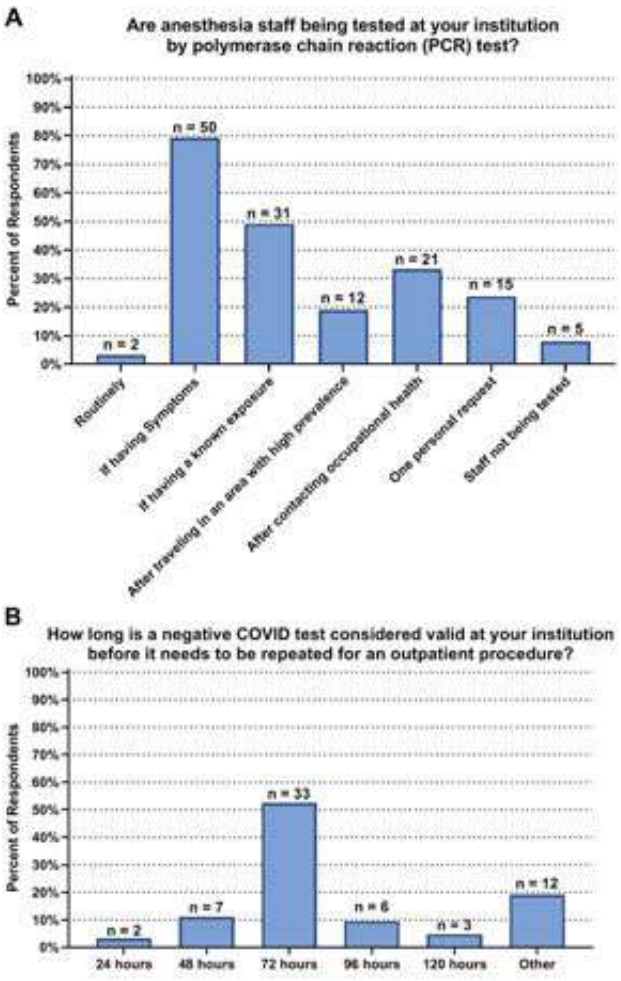
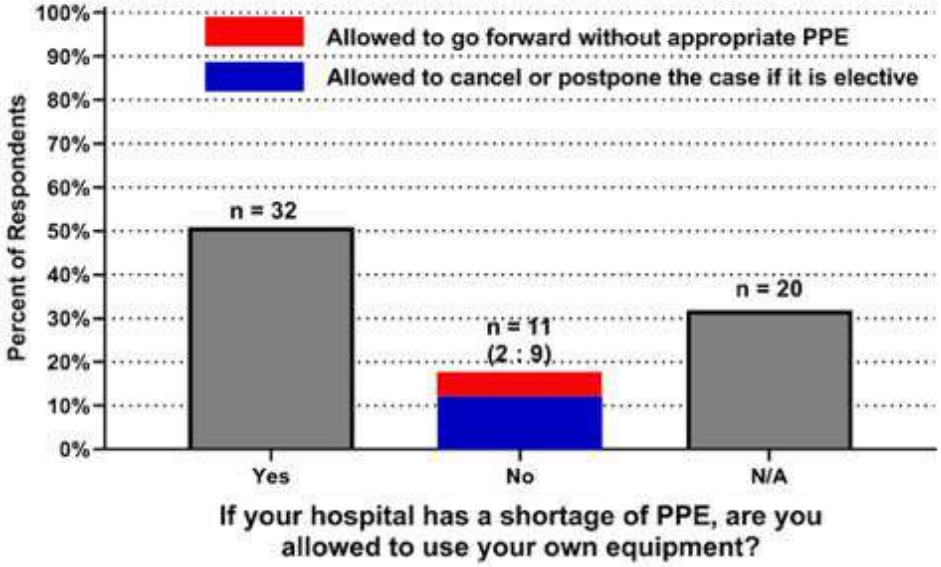


Figure 3. PPE during a Shortage



Pediatric Anesthesiology – 10 Short Term Mortality After Anesthesia for Non-Surgical Indications Among Children with Complex Chronic Conditions in the United States

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Introduction: Children with complex chronic conditions (CCCs) often require anesthesia for non-surgical indications, such as diagnostic imaging, and minimally invasive cardiac or interventional radiology procedures. Children with CCCs are more likely to suffer adverse events after even low risk anesthetics, however little data regarding outcomes after non-surgical anesthetics currently exists. We hypothesized that non-surgical anesthetics would be followed by death within three days at a rate comparable to low-risk non-cardiac surgery.

Methods: Using the Pediatric Health Inpatient Sample database 4/1/2016 to 10/31/2018, we measured the incidence of death following non-surgical and surgical anesthetics in neonates, infants, and children with CCCs, including cardiac procedures, imaging, interventional radiology, endoscopy, and oncology procedures. We examined first anesthetics of last hospitalizations each year, and used multivariable logistic regression to calculate incidence of death after each procedure type.

Results: Fifty-nine percent of patients received a non-surgical anesthetic during the study period. 51,170 (38%) were performed for non-surgical indications (11% cardiac procedures, 30% diagnostic imaging, 40% interventional radiology, 18% endoscopy, and 17% oncology procedures); 134,564 were performed for surgery. Death within three days of the anesthetic occurred in 0.8% (319/38,546) of children, 1.6% (104/6,480) of infants, and 5.2% (322/6,236) of neonates. Table 1 shows the incidence of death within three days of anesthesia performed in children during elective hospitalizations. Non-surgical cardiac procedures had a higher incidence of death than cardiac surgery (one in 278 vs. one in 769). The incidence of death after imaging (one in 667), interventional radiology (one in 588), and endoscopy (one in 1,429) was similar to high-risk non-cardiac surgery (one in 1,111). For urgent/emergent hospitalizations (Table 2), in children the incidence of death after non-surgical cardiac procedures was comparable to cardiac surgery (one in 36). The incidence of death after imaging and interventional radiology procedures was comparable to high-risk non-cardiac surgery (one in 78). Similar results were seen among infants and neonates, except that non-surgical cardiac procedures were more than 10x as likely to be followed by death within three days than cardiac surgery.

Conclusion: Over one third of the anesthetics in this population are for non-surgical indications; almost 1% of children with a CCC die a short duration after, with higher incidence among infants and neonates. Mortality after imaging and interventional radiology procedures was comparable to high-risk non-cardiac surgery in children, and twice as high as high-risk non-cardiac surgery among infants and neonates. Future research should examine whether anesthesia staffing or technique contribute to these outcomes.

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Table 1. Indicence of Mortality within Three Days of Anesthesia for Children > 1 Year Presenting for Anesthesia for Surgery and Non-Surgical Indications During Elective Hospitalizations

	Marginal Probability % (95%CI)	Number Needed to See Effect
Surgery		
Cardiac Surgery	0.13 (0.08, 0.18)	769
High Risk Non-Cardiac Surgery	0.09 (0.07, 0.12)	1111
Low Risk Non-Cardiac Surgery	0.02 (0.01, 0.03)	5000
Non-Surgical Indication		
Cardiac Procedures	0.36 (0.23, 0.48)	278
Imaging	0.15 (0.1, 0.21)	667
Interventional Radiology	0.17 (0.11, 0.22)	588
Endoscopy	0.07 (0.04, 0.09)	1,429
Oncology	0.04 (0.02, 0.06)	2,500

Table 2. Incidence of Mortality within Three Days of Anesthesia for Patients Presenting for Anesthesia for Surgery and Non-Surgical Indications During Urgent / Emergent Hospitalizations

	Marginal Probability % (95%CI)	Number Needed to See Effect
Neonates		
Surgery		
Cardiac Surgery	1.35 (0.94, 1.75)	74
High Risk Non-Cardiac Surgery	3.45 (3.01, 3.9)	29
Low Risk Non-Cardiac Surgery	1.31 (0.99, 1.63)	76
Non-Surgical Indication		
Cardiac Procedures	15.68 (13.07, 18.29)	6
Imaging	4.34 (3.18, 5.5)	23
Interventional Radiology	8.2 (7.19, 9.22)	12
Endoscopy	5.15 (4.01, 6.29)	19
Oncology	3.84 (2.09, 5.6)	26
Infants		
Surgery		
Cardiac Surgery	0.18 (0.07, 0.29)	556
High Risk Non-Cardiac Surgery	0.74 (0.59, 0.9)	135
Low Risk Non-Cardiac Surgery	0.17 (0.1, 0.23)	588
Non-Surgical Indication		
Cardiac Procedures	3.32 (2.37, 4.27)	30
Imaging	2.07 (1.58, 2.55)	48
Interventional Radiology	2.07 (1.61, 2.53)	48
Endoscopy	0.66 (0.32, 1.01)	152
Oncology	0.7 (0.25, 1.15)	143
Children		
Surgery		
Cardiac Surgery	2.81 (2, 3.61)	36
High Risk Non-Cardiac Surgery	1.29 (1.11, 1.46)	78
Low Risk Non-Cardiac Surgery	0.19 (0.14, 0.24)	526
Non-Surgical Indication		
Cardiac Procedures	2.82 (2.32, 3.31)	35
Imaging	1.41 (1.22, 1.61)	71
Interventional Radiology	1.33 (1.15, 1.51)	75
Endoscopy	0.52 (0.39, 0.66)	192
Oncology	0.47 (0.34, 0.61)	213

Pediatric Anesthesiology - 11 CYP2B6 and POR polymorphisms influence metabolism and clinical outcomes of perioperative methadone in children

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Introduction: Methadone is a long-acting opioid agonist, with actions on NMDA and SNRI pathways. It is being increasingly used for perioperative analgesia in both adults and children, due to minimal abuse potential and beneficial effects in terms of minimal opioid induced hyperalgesia, opioid sensitization and chronic pain prevention. CYP2B6 is the most significant enzyme that mediates de-methylation and elimination of methadone [1-5]. CYP enzymes (3A4, 3A5 and 3A7) require electron transfer through the P450 oxidoreductase (POR) [6]. Polymorphisms in the CYP2B6 as well as POR genes can potentially influence the individual variability in clinical response to methadone. Studies have associated CYP2B6 and POR polymorphisms with methadone response and dose requirements [1-6]. But these are adult studies in the setting of methadone maintenance therapy (MMT) for opioid use disorders (OUD). The current study is focused on assessing the influence of CYP2B6 and POR genetic variants on pharmacokinetics (PK) and clinical outcomes of perioperative methadone therapy in children.

Methods: Adolescents undergoing posterior spinal fusion (PSF) for idiopathic scoliosis or pectus excavatum (PE) repair were included in this prospective observational study. They received methadone intraoperatively (0.1 mg/kg IV, maximum 5 mg) and postoperatively every 12 h for 3-5 doses (0.1 mg/kg PO, maximum 5 mg) as part of multimodal analgesic protocol. Blood samples were collected up to 72 hours post-operatively for measurement of plasma levels of R- and S-methadone and primary metabolite: 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) chiral assay; Metabolite to parent ratios of R-, S- and total methadone were calculated. Genotyping was also performed using Whole genome sequencing (WSG) analysis at 40x coverage (mapped to hg19). Aldy, a high-throughput sequencing data analysis tool was used to identify the genotypes of relevant, highly polymorphic genes from the mapped data. Outcomes: The primary PK outcome measure was metabolite to parent drug ratios for R- and S-methadone. The primary clinical outcome measure was analgesia: described by pain scores and opioid consumption (other than methadone). The secondary clinical outcomes included adverse events like postoperative nausea and vomiting (PONV), respiratory depression (RD) and heart-rate corrected QT (QTc) interval prolongation. The effect of genotypes on outcomes like maximum and median pain score, morphine equivalent dose and PONV were analyzed using univariate regression and multiple regression analyses (adjusted for BMI, age and the type of surgery).

Results: A total of 50 children were enrolled in the study. Adolescents that were poor metabolizers (*6/*6) had >2-fold lower metabolite/drug ratios, compared with normal (*1/*1) or rapid metabolizers (*1/*22) (Fig.1). Beside PK variability, we identified novel associations between methadone induced PONV (increased risk) and CYP2B6 SNPs, rs1038376 (P=.005), rs10853744 (P=.024), rs7250601 and rs7250991 (P=.022), as well as maximum post-surgical pain (rs11882424, P=.007). Also, POR rs1057868 TT and CT genotypes (with anticipated higher CYP3A4 activity, higher methadone inactivation and higher requirements of non-methadone opioids) was associated with higher incidence of PONV than the wild type, CC (P=.026); the higher total opioid use in those with PONV (P = .005, R2 = 0.21) supports this association (Fig.2).

Conclusion: Along with the CYP2B6 genotype mediated metabolic variability, this study demonstrates positive associations of CYP2B6 polymorphisms with methadone induced PONV and maximal pain scores. We also found POR polymorphisms that are associated with an increased risk of PONV, secondary to increased opioid requirements. Genetic polymorphisms could explain variable clinical responses to perioperative methadone. More, well-powered studies are required to establish robust

associations and also to examine other genes influencing pharmacokinetics and pharmacodynamics of methadone, to enable development of a multi-gene predictive model. Genotyping might hold the key to personalize perioperative methadone use in children, to ensure efficacy and safety.

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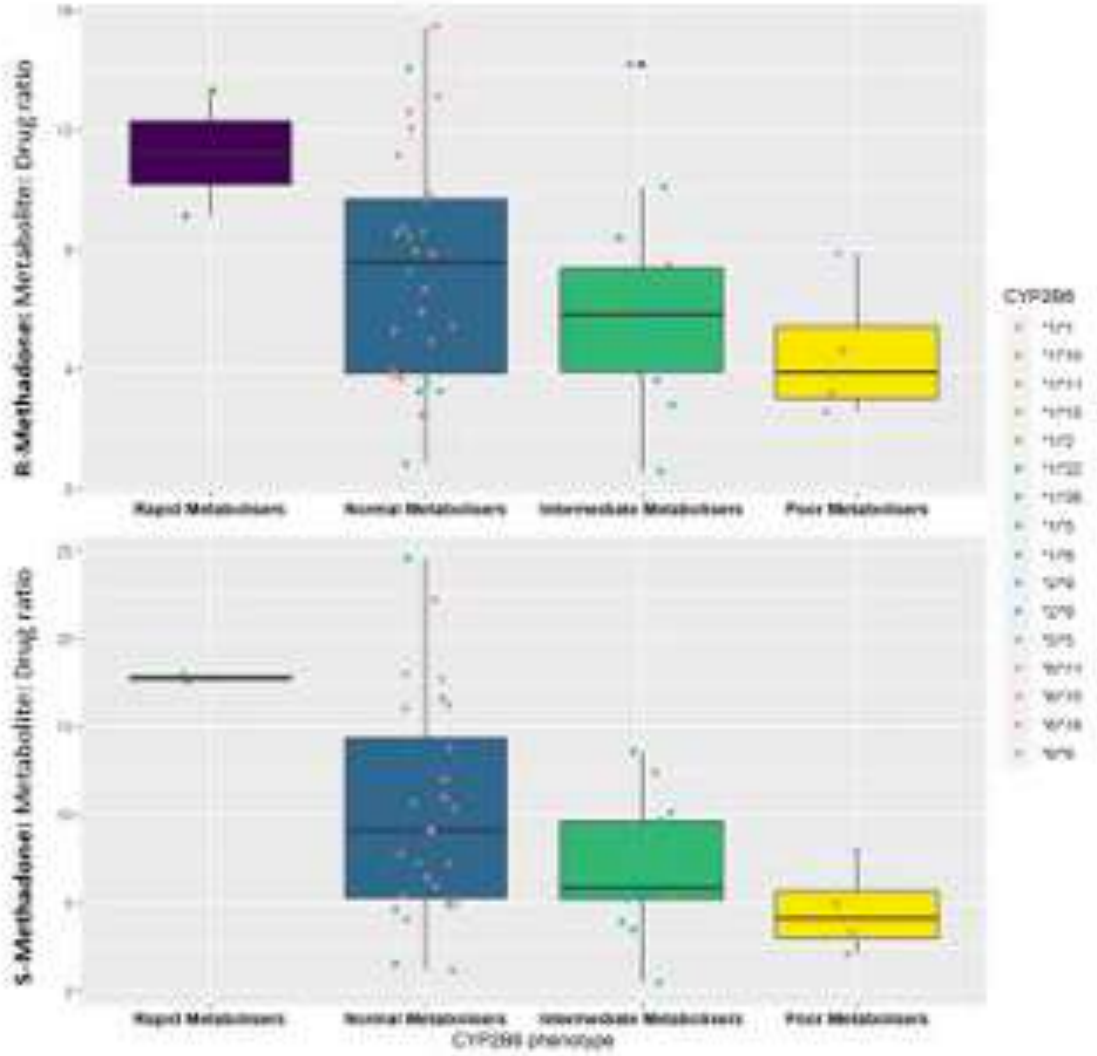

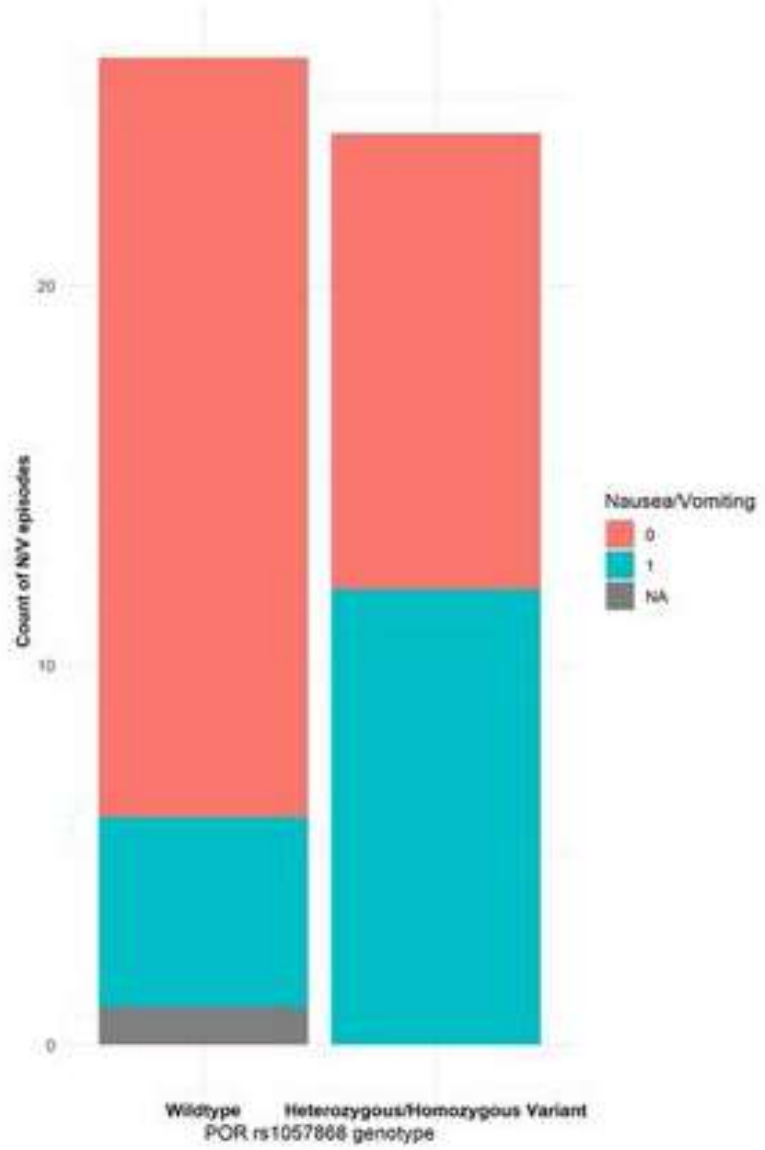
Count of N/V episodes
20
10
0
Nausea/Vomiting
0
1
NA
Wildtype
Heterozygous/Homozygous Variant
POR rs1057868 genotype

Pediatric Anesthesiology - 12 Present Anesthesiology Practices in the Context of Patent Foramen Ovale: PFO Anesthesiology Survey

Huynh Nguyen[1], Ricardo Falcon[2], Tim Petersen[2], Codruta Soneru[3]

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Introduction: Many institutions have no stated standard of care for perioperative management of spine surgery patients with PFO. Patients who undergo posterior spinal fusion are at risk for pulmonary air embolism (1,2,3). However, patients with PFO are at risk of paradoxical air embolism, in which air passes from the right atrium to the left and then systemic circulation possibly causing stroke, myocardial or other organ infarction, cardiovascular collapse, or mortality. We conducted a survey to learn whether standards are arising surrounding: 1) routine preoperative echocardiography for spinal fusion patients, and 2) any PFO defect closure prior to spinal surgery.

Methods: We surveyed 350 pediatric anesthesiologists in multiple states to identify perioperative anesthesia practice patterns related to posterior spinal fusion patients.

Results: There were 49 respondents, of whom 46 completed the survey. Most respondents' practice involved OR care for surgical patients (81%) and spine surgery patients (92%). Our respondents were generally experienced; 63% had been practicing anesthesia for >10 years, and 88% had completed a fellowship in pediatric anesthesia. A minority of anesthesiologists (6%) would routinely perform or order echocardiograms on surgery patients with idiopathic scoliosis, but 35% would for those patients with neuromuscular scoliosis. For patients with known PFO, most respondents (61%) would not advise/require device closure prior to spinal fusion, consistent with most of them not having ever experienced a spinal fusion surgery complicated by a significant air embolism (82%) or paradoxical air embolism (86%).

Conclusion: Consistent with previous studies, we found that most anesthesiologists would perform echocardiograms in at least some patients presenting for spine surgery; however, most would not do so if the patient was otherwise healthy with idiopathic scoliosis despite a 3.6% risk of undiagnosed heart defect (4). Most respondents would not advise/require device closure of the defect prior to spinal fusion, contrary to a study suggesting that patients with PFO should undergo closure of the defect prior to procedures with air embolism risk (5). Our response rate was somewhat low, so we cannot definitely determine whether preoperative echocardiogram is becoming standard of care for all spinal fusion patients. However, we can say that many anesthesiologists would not routinely require PFO closure prior to spinal fusion. Given the risk of fatal events from paradoxical air embolism after spinal fusion, this is an area that requires further research.

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Pediatric Anesthesiology - 13 Modeling Intraoperative Opioid Administration Variation: A Single-Center Retrospective Cohort Study of Children

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Introduction: Determining the appropriate intraoperative opioid dose requires anesthesiologists to analyze and integrate numerous patient and healthcare details to effectively manage nociception and analgesia while minimizing risk of opioid-related adverse health outcomes.[1] Guidelines informing intraoperative analgesic administration are not clearly delineated for different patient populations or types of surgery. However, administration of too little or too much opioid has negative consequences.[2,3] Comprehensive investigation of anesthesia providers' opioid administration patterns and patient and healthcare contributions to intraoperative administration practices may inform practice and improve patient outcomes. We sought to determine variables associated with variance in the intraoperative opioid dose administered to children.

Methods: Patient, surgery, and anesthesia details were extracted for all surgeries at a single pediatric center from May 2014 to August 2019. Variables expected to impact intraoperative opioid dose administration were selected. Filtration criteria, including exclusion of the highest 0.5% of weight-normalized opioid doses, were applied to obtain a final case cohort for primary analyses: univariable modeling determined the association of each variable with intraoperative opioid dose; parameters for multivariable machine learning models were optimized on ,Öì of the final case cohort; the model best able to predict intraoperative opioid dose was trained and tested with 30-fold cross-validation to determine a coefficient of determination (R^2) for the final case cohort. Secondary analyses with the best performing model were conducted to understand the impact of varying the threshold of weight-normalized outlier exclusion, and to determine model performance for select surgery types.

Results: The final cohort included 33,631 surgical cases. Univariable modeling identified variables with the greatest impact on intraoperative opioid dose: patient weight (R^2 24.84%), patient age (R^2 23.68%), surgery type (R^2 19.64%) (Table 1). Multivariable model optimization identified gradient boosting as the most predictive model. With the final case cohort, this model achieved an R^2 of 58.6% (interval 46.4% to 69.2%). Varying the stringency of the weight-normalized-dose outlier threshold from 0 to 1% of cases resulted in R^2 varying from 42.3% to 59.2% (Figure 1). The mean R^2 for the five selected common surgeries ranged from 39.6% to 48.7%.

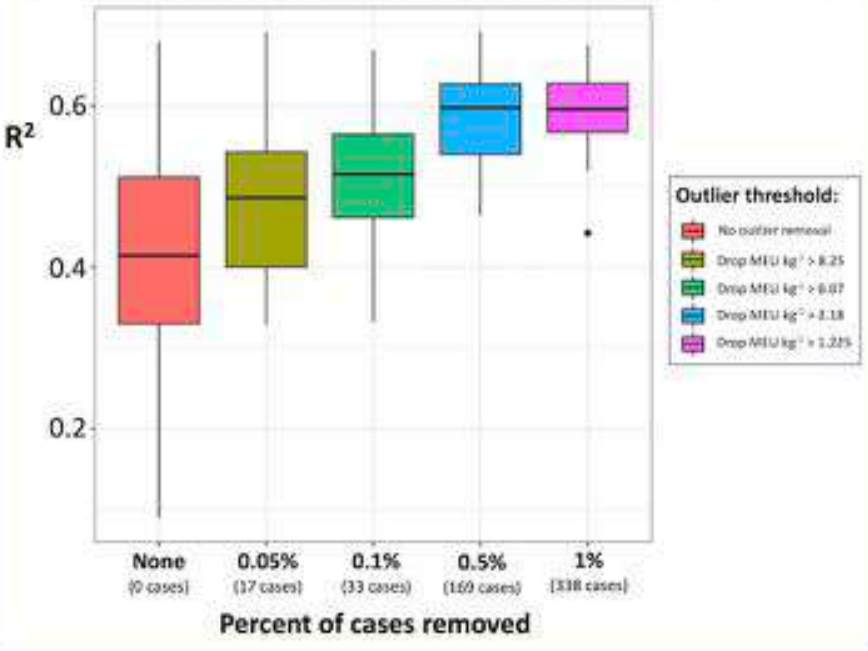
Conclusion: Multivariable modeling explains a modest proportion of variation in intraoperative opioid dose delivered to children; however, greater than 40% of variation is not explained by the captured features. Additional healthcare and patient features, including innate differences in patient nociception and opioid sensitivity (as indicated by physiological parameters), likely play significant roles in intraoperative opioid dose delivery variation. Future efforts to optimize intraoperative analgesia delivery must acknowledge and account for this unexplained variation.

References: [1.] Brown EN, Pavone KJ, Naranjo M. Multimodal General Anesthesia: Theory and Practice. Anesth Analg. 2018;127(5):1246-1258. [2.] Shafi S, Collinsworth AW, Copeland LA, et al. Association of Opioid-Related Adverse Drug Events With Clinical and Cost Outcomes Among Surgical Patients in a Large Integrated Health Care Delivery System. JAMA Surg. 2018;153(8):757-763. [3.] Oderda GM, Evans RS, Lloyd J, et al. Cost of opioid-related adverse drug events in surgical patients. J Pain Symptom Manage. 2003;25(3):276-283.

Table 1. Results of univariable regression models relating each feature of interest to the total amount of oral morphine equivalent units (MEU) of opioids utilized intraoperatively.

Feature	Number of categories	Median [interquartile range]	R^2
Weight (kilograms)	NA	22.2 [13.4-43.0]	**24.84%**
Age (years)	NA	6.6 [2.7-11.9]	**23.68%**
Surgery type	224	NA	**19.64%**
Primary surgeon	122	NA	**12.48%**
Anesthesia duration (hours)	NA	1.6 [1.1-2.5]	**11.71%**
Procedure duration (hours)	NA	0.7 [0.3-1.3]	**11.66%**
Surgical service	26	NA	**7.97%**
Sum RVUs	NA	8.8 [4.3-16.5]	**6.64%**
Case complexity classification (based on RVUs)	3	NA	**4.68%**
Primary anesthesiologist	68	NA	**3.60%**
Patient class (inpatient, outpatient, surgery admit)	3	NA	**3.10%**
Weight percentile for age (0 - 100%)	NA	0.6 [0.3-0.9]	**1.56%**
Overweight (weight percentile > 85)	2	NA	**1.41%**
History of chronic pain	2	NA	**1.00%**
Postoperative disposition (PACU, ICU)	2	NA	**0.47%**
Intraoperative non-opioid analgesics (0, ≥1)	2	NA	**0.47%**
Presence of anesthesia trainee (resident, fellow)	2	NA	**0.29%**
History of mood disorder	2	NA	**0.26%**
Race	8	NA	**0.22%**
Case year (2014 - 2019)	6	NA	**0.20%**
History of obstructive sleep apnea	2	NA	**0.08%**
ASA class (I - VI)	6	NA	**0.06%**
Ethnicity	5	NA	**0.04%**
Gender	2	NA	**0.02%**
History of substance use disorder	2	NA	**0.02%**
Intraoperative remifentanil	2	NA	**0.01%**
History of personality disorder	2	NA	**0.01%**

Figure 1. R^2 Sensitivity to Outliers (box and whisker plot given cross validation)



Pediatric Anesthesiology - 14 A Novel Method To Detect Changes In Mitochondrial Permeability Transition Pore Voltage Gating In Isolated 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 for pore opening, calcium is used to trigger the permeability transition, leading to collapse of the membrane potential, rapid uncoupling of oxidative phosphorylation, and swelling (5). We aimed to develop a method to detect mPTP opening without inducing it to open, per se. We hypothesized that we could determine the threshold for opening by monitoring sensitivity to the inhibitor cyclosporine A (CsA) relative to the mitochondrial membrane potential. We describe a novel method to assess for voltage threshold for mPTP opening in isolated mitochondria using polarography and a TPP+ selective electrode. We hypothesized that using this approach, we could identify differences in voltage gating in cardiac mitochondria from Fragile X Syndrome (FXS) mice which were previously found to have excess CoQ and increased closed probability of the mPTP.

Methods: The care of mice was in accordance with NIH and CUMC IACUC guidelines. We evaluated cardiac mitochondria harvested from male Fmr1 KO mice (FXS) along with FVB controls on P10. Oxygen consumption and mitochondrial membrane potential were measured simultaneously using polarography and a TPP+ selective electrode. Complex II-dependent proton leak respiration was initiated using succinate, rotenone and oligomycin. In separate experiments, CsA was added at three specific TPP+ voltage levels (low, intermediate and high) relative the TPP+ standard as the proton motive force declined in order to determine open or closed mPTP probability. We evaluated up to 11 mice per group. Significance was assessed via chi-squared test with set $p < 0.05$.

Results: Mitochondria from both Fmr1 KOs and FVB controls demonstrated CsA sensitivity at low membrane potentials, suggesting open mPTP probability at or near 100%. Conversely, both groups showed CsA insensitivity at high membrane potential mitochondria, indicating closed mPTP probability. At median membrane potentials, we found significant differences between strains, with open mPTP probability in 89% of FVB controls and only 45% in Fmr1 KOs.

Conclusion: Here we describe a new technique to assess the voltage threshold for mPTP opening in isolated mitochondria by monitoring sensitivity to CsA over a range of mitochondrial membrane potentials during oligomycin-induced state 4 respiration. Using our novel technique, we were able to identify differences in voltage gating of the mPTP between Fmr1 KO and FVB controls. This technique will permit assessment of both physiological and pathological regulation of the mPTP without the need to induce the pore to open. Thus, it will have utility when investigating the role of the mPTP in health and disease.

References: 1. J. Bioenerg. Biomembr. 24:111-7, 1992 2. Apoptosis 12:815-33, 2007 3. Cell Cycle 9:3442-8, 2010 4. Dev. Biol. 426:1-7, 2017 5. FEBS J. 273:2077-99, 2006

Pediatric Anesthesiology - 15 Evaluation of opioid usage in the early postoperative period for pediatric patients with scoliosis following surgical correction

Esteban Esquivel[1], William Johnson[1], Elizabeth Rossmann Beel[1], Nihar Patel[1], Kim-Phuong Nyguyen[1], Michael Zelisko[1], Eduardo Medellin[1], Andrew Lee[1], THIEN-DUY TRAN[1], HILLARY CLOYD[1], ANGELA MEDELLIN[1], Chris D Glover[1]

[1]Baylor College of Medicine, Houston, TX

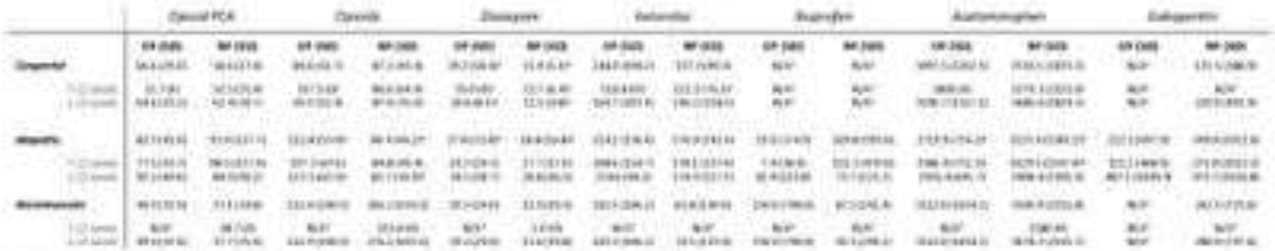
Introduction: Scoliosis is a multidimensional deformity of the thoracolumbar spine that may require surgical correction as the severity of symptoms worsens with disease progression. Postoperative management includes the use of opioid-based patient-controlled analgesia (PCA) and adjuncts without a consensus on optimal perioperative management. This lack of consensus combined with current societal concerns around opioid abuse and dependency led us to evaluate the perioperative opioid use characteristics of our scoliosis population while in the hospital and at follow up.

Methods: This retrospective comparative study included pediatric patients from December 2014 to March 2017 who underwent posterior spinal instrumentation and fusion for repair of idiopathic, neuromuscular, or congenital scoliosis. 130 patients met inclusion criteria. The primary outcome was long-term opioid use noted by active use of an opioid agent at the first postoperative follow up. The doses and amounts of opioids and adjuvants given in the early postoperative period (postop day 0 to postop day 5) were analyzed. Opioids were converted to morphine milligram equivalents (MME). The data are presented as Mean ± SD. Continuous variables were examined for normality and the data were analyzed using independent t-tests or Whitney U-tests.

Results: In our cohort, 42.3% (N=55) required opioid medications at their first follow up visit. The total amounts for both opioid PCA and PRN opioids during the early postoperative time period were not significant when looking at patients on and off opioid therapy at follow up. Patients on opioids at follow up received larger amounts of diazepam (On opioids: 26.3±23.3 mg; Not on opioids: 16.8±16.6 mg; $p<0.05$). Patients not on opioids at follow up received larger amounts of acetaminophen (On opioids: 2818.6±986.4 mg; Not on opioids: 3341.3±1536.1 mg; $p<0.05$). When stratified by types of scoliosis, the idiopathic scoliosis group that required opioids at follow up received higher amounts of PRN opioids and diazepam while those not requiring opioids received higher amounts of acetaminophen. Additionally, the idiopathic scoliosis patients who underwent surgical repair of ≥ 13 levels and were requiring opioids at follow up received higher amounts of PRN opioids (complete subgroup analysis shown in Table 1). None of the patients were given epidural analgesia or ketamine.

Conclusion: Providing sufficient analgesia during the immediate time period after surgery remains a critical aspect of the recovery for these patients undergoing scoliosis repair. There is not an obvious link between opioid usage during the early postoperative period and at postoperative follow up. In our cohort, those requiring more diazepam and PRN opioids specifically in the idiopathic scoliosis population were requiring opioid medications at their follow up while those not requiring opioids received more acetaminophen. Additional studies that include data from multiple institutions can be used to create a best practice guideline.

Mean Cumulative Amount of Medication Administered (POD0-POD5)



	Opioid PCA		Opioids		Diazepam		Ketorolac		Ibuprofen		Acetaminophen		Gabapentin	
	CP (SD)	**NP (SD)**	**CP (SD)**	**NP (SD)**	**CP (SD)**	**NP (SD)**	**CP (SD)**	**NP (SD)**	**CP (SD)**	**NP (SD)**	**CP (SD)**	**NP (SD)**	**CP (SD)**	**NP (SD)**
Cigarette	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	N/A*	N/A*	[illegible]	[illegible]	N/A*	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	N/A*	N/A*	[illegible]	[illegible]	N/A*	N/A*
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	N/A*	N/A*	[illegible]	[illegible]	N/A*	[illegible]
Alcohol	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Marijuana	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	N/A*	[illegible]	N/A*	[illegible]	N/A*	[illegible]	N/A*	N/A*	N/A*	N/A*	N/A*	[illegible]	N/A*	N/A*
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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Pediatric Anesthesiology - 16 Reduction of preoperative anxiety using Virtual Reality vs midazolam: A randomized controlled trial

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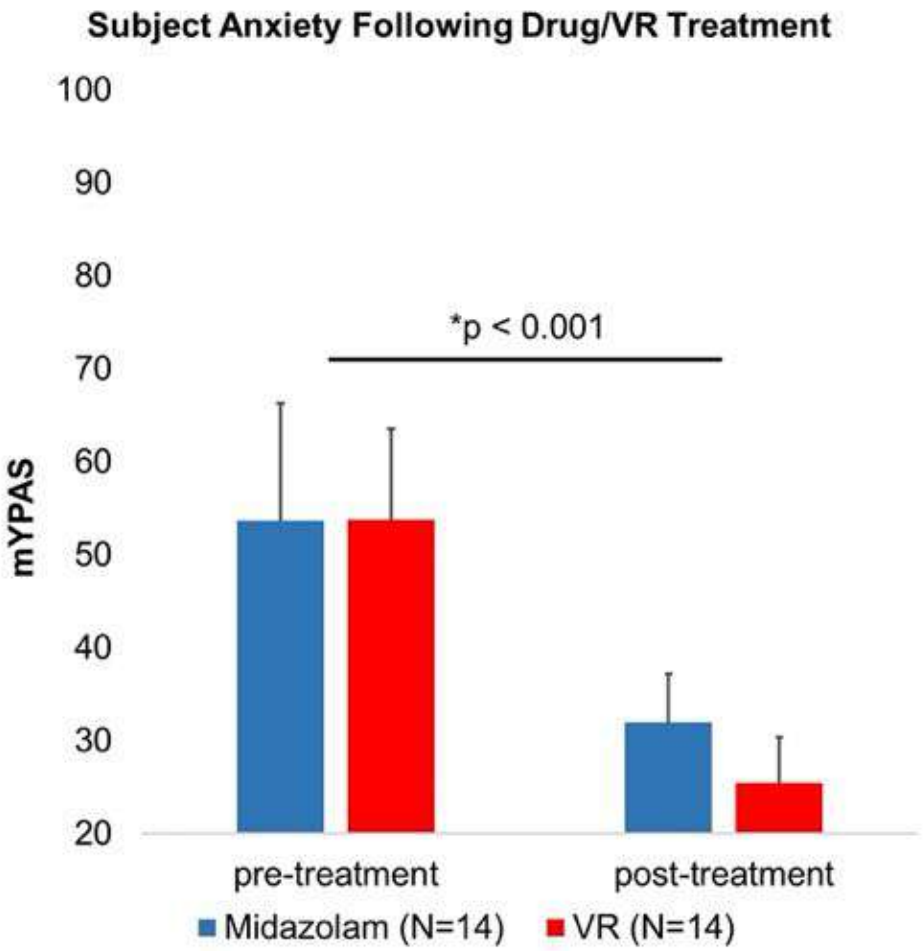
Introduction: More than 50% of pediatric patients experience significant stress and anxiety prior to surgery[1]. High anxiety can result in increased postoperative pain, increased analgesic consumption and delayed recovery[2]. In order to reduce this preoperative anxiety, multiple therapeutic modalities have been developed, including the use of distraction, such as playing video games, watching movies, and listening to music. In severe cases of anxiety, anxiolytic and sedative medications like midazolam are used. However, given the acknowledged drawbacks of medications, including the risk of paradoxical reactions to the drug, alternatives to medication for reducing preoperative anxiety in patients may be useful. Our study compares the use of Virtual Reality (VR) to midazolam in reducing preoperative anxiety in surgical patients, and assesses differences in induction compliance, emergence delirium, pain scores, and opioid use in VR vs midazolam-treated patients.

Methods: 28 first-time surgical patients between the ages of 5-11 undergoing tonsillectomy or tonsillectomy and adenoidectomy procedures were randomly assigned to either receive midazolam (0.5mg/kg up to 25mg) or play an interactive underwater-themed immersion game using VR. The Modified Yale Preoperative Anxiety Scale (mYPAS) was administered by a single child life specialist preoperatively, and only patients who reached a threshold of >40 on mYPAS scoring were enrolled (scale range: 23-100). Additional anxiety measurement was tested using the adult and child State-Trait Anxiety Inventory (STAI). Midazolam or VR was administered prior to transport to the OR, and mYPAS was scored again at the time of separation from family. The Induction Compliance Checklist (ICC) was utilized for further data collection and assessment of patients at the time of anesthesia induction. VR-treated patients continued use of the VR headset up to and through mask induction. A standardized anesthesia induction protocol was used for all patients. The Pediatric Anesthesia Emergence Delirium scale (PAED) was administered at emergence, post-operatively. Postoperative nurses scored pain and administered IV pain medication as needed. Group means and standard deviations were reported and compared with 2-sided t tests.

Results: Interim results showed that 57% of first-time surgery patients scored with mYPAS had scores >40, indicating anxiety. The mYPAS anxiety scores dropped 21.6 ±12.5 points following midazolam treatment ($p<0.001$) and dropped 28.4 ±9.8 points following VR treatment ($p<0.001$). There was no significant difference in mYPAS scores between groups following treatment (midazolam= 32.0±5.2; VR= 25.4±4.9; $p= 0.12$). There were no significant differences between midazolam and VR-treated groups in the Induction Compliance Checklist (ICC), emergence delirium (PAED), peak postoperative pain scores, and medication use for pain control, post-operatively. This study is currently ongoing.

Conclusion: Based on these results, VR appears to provide an equivalent alternative to midazolam in reducing preoperative anxiety. Distraction and immersion with VR can help minimize preoperative anxiety during peak stress events, including separation from parents, arrival in the OR, and anesthetic induction. VR was equivalent to midazolam in preoperative induction compliance, and, postoperatively, patients in both groups had similar emergence delirium, pain scoring, and pain medication use. The patient population for this study was limited and additional studies will be necessary to confirm if the conclusions formed are generalizable to the entire pediatric population, including patients with developmental delays and previous surgical experience undergoing a variety of procedures.

References: 1. Archives of Pediatrics and Adolescent Medicine, Vol 150, p. 1238 –1245, 1996. 2. Pediatrics, Vol 118(2), p. 651-658, 2006.


Subject Anxiety Following Drug/VR Treatment
100
90
80
70
60
50
40
30
20
mYPAS
*p < 0.001
pre-treatment
post-treatment
Midazolam (N=14)
VR (N=14)

Pediatric Anesthesiology - 17 Meditative Virtual Reality for Parents with Limited English Proficiency During Pediatric Anesthesia: Emerging Data from a Prospective, Randomized, Controlled Trial

Charles K Lee[1], Ahtziri Fonseca[2], Kylie Burdsall[1], Sam Rodriguez[2], Fatima Rodriguez[2], Thomas Caruso[2]

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Introduction: Many parents experience periprocedural anxiety about their child's operation, and it can be compounded by language and cultural barriers. Preoperative anxiety may adversely affect overall satisfaction, postoperative compliance with their child's care, and future medical contacts.1-3 The primary aim was to study anxiety in parents with limited English proficiency (LEP) while their child was under anesthesia after a meditative virtual reality experience. The secondary aim explored parental satisfaction.

Methods: The inclusion criteria of this IRB approved, prospective, randomized pilot study were parents of a child with an estimated duration of anesthesia of at least one hour, self-identified as having LEP, and whose primary language was Spanish. During their child's operation, parents were randomized into either intervention (VR) or standard of care (SOC). Pre-anxiety level was measured using a visual analog scale (VAS) from 0-10. SOC parents sat in a room for 6 minutes and those in the VR group were guided through a 6-minute meditation using a Spanish VR experience. Post-anxiety scores was measured for both groups. Adverse events, including nausea, headaches, dizziness and eye strain, were recorded. A satisfaction survey was administered. A priori, given a power of 80%, alpha 0.05, effect size of 50%, and average pre-anxiety score of 6.5±2.5, indicated a sample size of 18. To account for dropouts and missing data, we target an enrollment of 40. Statistical analysis was performed using GraphPad-Prism.

Results: At the time of submission, 13 parents were enrolled, with ten (77%) parents in the VR group and three (23%) in the control group. All parents self-identified as native Spanish speakers with LEP and none had previously utilized meditative VR. There were no differences in mean pre-anxiety VAS score between VR and SOC group (6.15 ± 2.82 vs 7.50 ± 1.83; p=0.4578). The mean post-anxiety score for the VR group was 1.91 ± 1.65, which was significantly lower than both the VR pre-score of 6.15 ± 2.82 (p=0.0004) and the SOC post-score of 6.70 ± SD=2.21 (p=0.0017, Figure 1). VR parents had a significant reduction in anxiety change compared to SOC (mean reduction of 4.24 ±2.44 vs 0.80 ± 0.69, p=0.0385, Figure 2). There were no adverse events reported in the VR group. All parents reported they would use VR meditation in the future.

Conclusion: Given the cultural boundaries that those with LEP face in the unfamiliar hospital environment, coupled with the added stress of a child needing anesthesia, parental anxiety should be attended to by perioperative clinicians. The initial data from this RCT suggests that VR meditation represents a novel, low cost tool to effectively address parental anxiety in those with LEP.

References: References 1. Journal of Clinical Anesthesia. 26(4): 325-9. 2014 2. Academic Pediatrics. 17(4): 403-410. 2017 3. Journal of Abnormal Child psychology. 38(7): 897-909. 2010

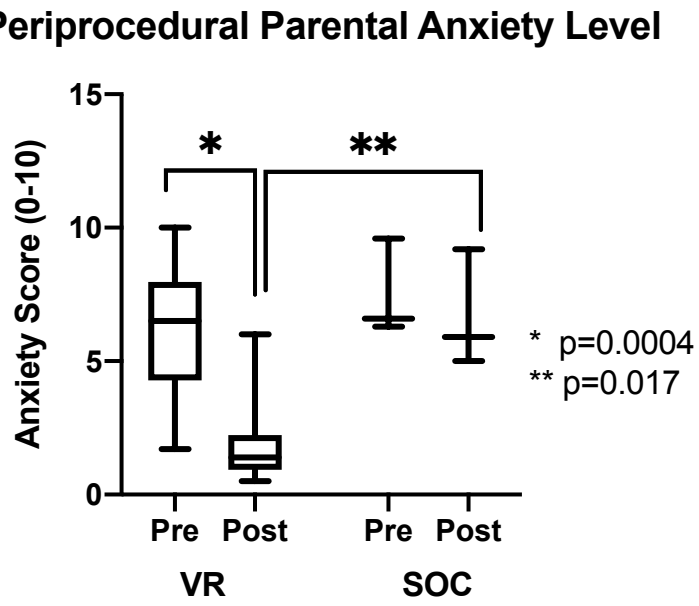

Figure 1.
Mean anxiety scores of LEP parents with and without the meditative VR experience. Parents who underwent the VR experience had significantly lower anxiety level when compared to their anxiety level before the VR experience (p=0.0004) and also lower when compared to the SOC group (p=0.017).

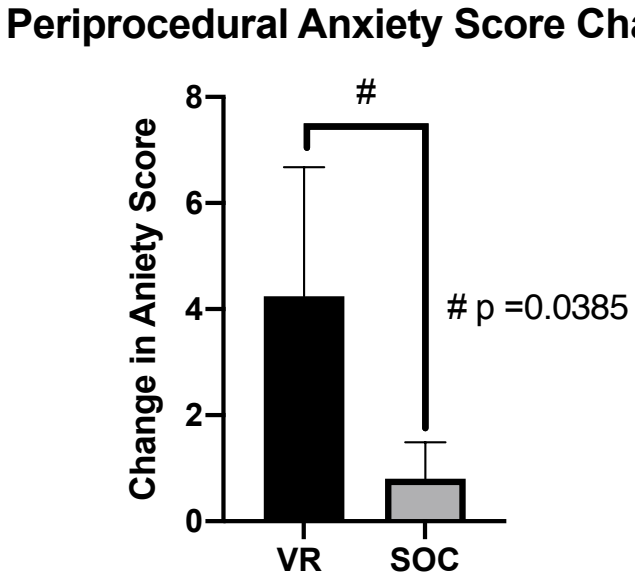

Figure 2.
Periprocedural anxiety score changes of LEP parents with and without the meditative VR experience. There was a significant reduction in anxiety score in parents who had a meditative VR experience compared with those who did not (mean reduction 4.24 ±2.44 vs 0.80 ± 0.69, p=0.0385).

Pediatric Anesthesiology - 18 The Association of Race and Ethnicity with Postoperative Analgesic Administration and Pain Scores in Children: 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 exist and may have detrimental health outcomes.1,2 However, few studies have been published regarding pediatric healthcare disparities, and fewer still on the perioperative care of children. We investigated 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 perioperative medical records of children ≤18 years old undergoing concurrent general anesthesia and surgery from May 2014 to August 2019 was included. The exposure was racial and ethnic groups: Asian, Black, Hispanic, Pacific Islander, and reference category White non-Hispanic (White-nH). The primary outcome was post-anesthesia care unit (PACU) weight-adjusted morphine equivalent dose (mg kg-1). Secondary outcomes are: PACU mean pain score (categorized as mild vs moderate/severe), PACU length of stay (minutes), PACU anti-emetic administration (any vs none), inpatient weight-adjusted morphine equivalent dose (mg kg-1); inpatient mean pain score (0-10 scale), hospital length of stay (hours), and inpatient anti-emetic administration (any vs none). Inpatient outcomes were analyzed for White-NH, Asian and Hispanic groups only. The association of race or ethnicity with each outcome was 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, and 1.3% Pacific Islander). PACU results: Asian was associated with 20% reduction in odds of receiving narcotics (odds ratio (OR) 0.8, 95% confidence interval [CI] 0.72, 0.88) and a 34% reduction in odds of a moderate or severe mean pain score, (OR 0.66 95% C.I 0.54, 0.80). Hispanic was associated with a .003 MEU kg-1 decrease in opioid dose (95% C.I -0.005, 0.000). Asian and Hispanic had lower odds of receiving anti-emetics, Asian OR 0.78 (95% C.I 0.64, 0.94) Hispanic OR 0.78 (95% C.I. 0.67, 0.91). Pacific Islander was associated with 6.3 minutes reduction in LOS (95% C.I -10.99 to -1.68) . There was no difference in antipruritic given between groups. Inpatient results: Asian and Hispanic were associated with reduction in odds of receiving an antipruritic, Asian OR 0.33 (95% C.I 0.17, 0.64) and Hispanic OR 0.41 (95%CI 0.25, 0.68). Asian was associated with a 42% reduction in odds of receiving narcotics (OR 0.58, 95% C.I 0.44, 0.78). Asian was associated with a 48% reduction in odds of moderate-severe mean pain score (OR 0.52, 95% C.I 0.40, 0.69). In patients administered opioids, there was no significant difference in the MEU kg-1 . There was no difference in the hospital length of stay.

Conclusion: Administration of both too little and too much opioid are associated with adverse outcomes. Thus, investigations into differences in postoperative pain medication administration, pain scores, and associated adverse events in children of different races and ethnicities are important.3 Compared to the reference group (White-nH), Asian children received less opioids both in the PACU and inpatient. Interestingly, Asian children had lower odds of having moderate or severe pain. However, there was no difference in the MEU kg-1 if they received an opioid. The decrease in opioids could explain the decrease in the need for anti-emetics and antipruritics. There was no difference in the length of stay in the PACU or hospital length of stay. These differences could be a result of cultural differences in defining pain, nausea, or concerns from parents of the side effect profile of the pain medication and refusing treatment. Further investigation is warranted to understand if the differences found are due to cultural differences or institutional unconscious bias.

References: 1. Institute of Medicine (US) Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care. In: Smedley BD, Stith AY, Nelson AR, eds. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC: National Academies Press; 2003. 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.

Table 1: PACU Results

Race	Opioid Received (any vs none)		Mean Pain Score (mild vs moderate/severe)		Opioid Dose mg kg^{-1} (morphine equivalents)	
	Odds Ratio	(95% Conf.Interval)	Odds Ratio	(95% Conf.Interval)	Change in dose	(95% Conf.Interval)
Asian	**0.80**	**[0.72, 0.88]**	**0.66**	**[0.54, 0.80]**	-0.002	[-0.006, 0.001]
Black	1.00	[0.78, 1.27]	0.68	[0.43, 1.09]	-0.007	[-0.015, 0.002]
Hispanic	1.07	[0.98, 1.16]	0.99	[0.86, 1.14]	**-0.003**	[-0.005, 0.000]
Pacific Islander	0.79	[0.57, 1.08]	1.19	[0.72, 1.97]	-0.01	[-0.022, 0.001]
White-nH	Reference		Reference		Reference	

Table 2: Inpatient Results

Race	Opioid Received (any vs none)		Mean Pain Score (mild vs moderate/severe)		Opioid Dose mg kg^{-1} (morphine equivalents)	
	Odds Ratio	(95% Conf.Interval)	Odds Ratio	(95% Conf.Interval)	Change in dose	(95% Conf.Interval)
Asian	**0.58**	**[0.44, 0.78]**	**0.52**	**[0.40, 0.69]**	-0.007	[-0.019, 0.005]
Hispanic	1.07	[0.85, 1.34]	0.94	[0.76, 1.15]	-0.004	[-0.013, 0.006]
White-nH	Reference		Reference		Reference	

Pediatric Anesthesiology - 19 Surgery in Pediatric Patients During the Covid-19 Pandemic in New York City

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Introduction: The World Health Organization declared COVID-19 as a pandemic in March 2020 (1). A statewide elective surgery ban was implemented in New York from March 23 to June 7, 2020. During this period, all pediatric patients in the 10 New York Presbyterian network hospitals who required urgent or emergent surgical procedures were cohorted at Morgan Stanley Children's Hospital/Columbia University Irving Medical Center (MSCH/CUIMC). In adult surgical patients with COVID-19, an increased risk for adverse perioperative outcomes has been reported (2-4), but no similar data exist in pediatric patients. We report the incidence of COVID-19 and the demographic and clinical characteristics of pediatric patients who underwent urgent or emergent surgical procedures at MSCH/CUIMC during the period of elective surgery ban.

Methods: The study was approved by the institutional review board. We abstracted data from the electronic medical record of all patients aged 0-20 years who underwent surgery at MSCH/CUIMC from 3/23/2020 to 6/7/2020. Patients were classified as COVID-positive if they had documentation of a positive result on nasal swab samples by reverse-transcriptase-polymerase chain reaction assay within 21 days before or after their surgical procedure. Index cases are defined as the first known procedure during the study period. Index cases were included for analysis of patient demographics. All procedures were analyzed for procedure-related characteristics. Comparative analysis of demographic and clinical data elements between COVID-positive and negative cohorts was conducted using Fisher exact tests. A p-value <0.05 was considered statistically significant.

Results: A total of 505 surgical procedures were performed in 451 patients during this time period, of which 32 procedures (6.3%) were performed in 21 COVID-positive children. In those procedures involving COVID-positive patients, 78% (25/32) were diagnosed pre-operatively. There was no significant difference in the prevalence of COVID positivity across sex, age, race, or ethnicity groups; however, it is notable that for all patients, race and ethnicity had missing data or declined reporting in >25% of cases. The prevalence of COVID positivity in Medicaid insured children was more than twice the prevalence in commercially insured children (6.8% vs 2.6%, p=0.04). COVID-positive patients were more likely to undergo more than one surgical procedure (5/16, 23.8% vs 31/399, 7.2%, p=0.02), and were more likely to have ASA class designations of III, IV, or V compared to I or II (22/32, 69.8% vs 224/473, 47.4%, p=0.03). Emergent case status and surgical procedure type were not significantly different between positive and negative groups. Thirty-day mortality rate was low overall (4/505, <0.1%), and no deaths occurred in the COVID-positive group. (Details in Tables 1 and 2.)

Conclusion: This study reports a higher prevalence of COVID-19 in pediatric patients undergoing urgent and emergent surgical procedures in the New York City region compared to reports from other institutions in the US (<1%) (5). COVID-positive and COVID-negative pediatric patients did not differ significantly in age, sex, race, or ethnicity. They did not differ in the types of surgical procedures and 30-day mortality. However, a greater percentage of COVID-positive patients were insured under Medicaid indicating possible poorer socioeconomic status. COVID-positive patients were clinically more complex as shown by their higher ASA physical class and having more surgical procedures. Future research is needed to examine the perioperative and long-term outcomes of pediatric surgical patients with the diagnosis of COVID-19.

References: 1. WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020. Published March 11, 20. Accessed November 24, 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 2. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. EClinicalMedicine 2020;21: 100331. 3. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. Lancet 2020;396(10243): 27-38. 4. Perioperative morbidity and mortality of patients with COVID-19 who undergo urgent and emergent surgical procedures. Ann Surg. 2020. DOI: 10.1097/SLA.0000000000004420. 5. Incidence of COVID-19 in Pediatric Surgical Patients Among 3 US Children's Hospitals. JAMA Surg. 2020;155(8): 775-7.

Table 1: Characteristics of children who received surgical procedures stratified by COVID-19 status

	COVID Negative		COVID Positive		p-value
	n	%	n	%	
Total Number	430	95.3	21	4.7	
Sex					1
Female	174	40.5	8	38.1	
Male	256	59.5	13	61.9	
Age (Years)					0.25
Under 1	138	32.1	3	14.3	
1 to 2	57	13.3	4	19.0	
3 to 11	117	27.2	6	28.6	
12 to 18	99	23.0	8	38.1	
19 to 20	19	4.4	0	0	
Race					0.45
White	214	49.8	8	38.1	
Black	51	11.9	5	23.8	
Asian	10	2.3	0	0	
Native American	3	0.7	0	0	
Other/Declined/Missing	152	35.3	8	38.1	
Ethnicity					1
Hispanic	114	26.5	5	23.8	
Not Hispanic	198	46.0	10	47.6	
Other/Declined/Missing	118	27.4	6	28.6	
Payor					0.04
Medicaid	205	47.7	15	71.4	
Non-Medicaid	225	52.3	6	28.6	
Multiple Procedures					0.02
No	399	92.8	16	76.2	
Yes	31	7.2	5	23.8	

Table 2: Surgical procedures stratified by COVID-19 status

	COVID Negative		COVID Positive		p-value
	n	%	n	%	
Total Number	473	93.7	32	6.3	
COVID-19 Diagnosis					
Pre-Operative			25		
Post-Operative			7		
Procedure Type					0.24
Cardiothoracic	94	19.9	12	37.5	
ENT	43	9.1	3	9.4	
Eye	19	4.0	0	0	
General Surgery	185	39.1	9	28.1	
Gynecology	4	0.8	1	3.1	
Neurosurgery	26	5.5	0	0	
OMFS	2	0.4	0	0	
Orthopedic	64	13.5	6	18.8	
Plastic	11	2.3	0	0	
Urology	25	5.3	1	3.1	
Emergent Case					0.1
No	347	73.4	19	59.4	
Yes	126	26.6	13	40.6	
ASA Class					0.03
I, II	249	52.6	10	31.3	
III, IV, V	224	47.4	22	68.8	
Death Within 30 Days					1
No	469	99.2	32	100	
Yes	4	0.8	0	0	

Perioperative Anesthesia

Perioperative Anesthesia - 1 Effects of end-tidal carbon dioxide on postoperative nausea and vomiting

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Introduction: Postoperative nausea and vomiting (PONV) is one of the most common post-surgical complications. Proposed mechanisms of action include compression of gastrointestinal mucosa and hypoperfusion of emetic centers which may be improved by hypercapnia induced vasodilation. Mild hypercapnia has been shown to increase perfusion, leading to improved cardiac index, hemodynamics, oxygenation, and reduced emergence time.1 The relationship between carbon dioxide levels and PONV is unclear and studies have found conflicting results. One randomized controlled trial showed a fivefold decrease in PONV with hypercapnia while another showed no difference.2,3 This study will examine the relationship between end-tidal carbon dioxide (EtCO2) levels and PONV in surgical patients.

Methods: 474 patients who underwent total knee arthroplasty under general anesthesia between October 2018 and July 2019 at the Mayo Clinic in Phoenix, Arizona were identified for a retrospective analysis. Patient records were reviewed for risk factors of PONV including age, gender, smoking history, PONV history, preoperative antiemetic administration, and inhaled anesthetic administration. Patients receiving total intravenous anesthetic (TIVA) or regional anesthesia were excluded. 343 patient records had intraoperative EtCO2 data. Median EtCO2 levels for the duration of the anesthetic (OEtCO2), last 30 minutes prior to extubation (30EtCO2), and final 10 minutes prior to extubation (10EtCO2) were calculated. Administration of a postoperative antiemetic in the recovery room was used as proxy for PONV. Hypocapnic (mmHg<36) and hypercapnic (≥36) groups were identified. Logistic regression was used for each group as well as dichotomous groups (<36 or ≥36).

Results: The incidence of PONV as measured by antiemetic administration was 12.2% (42/343). Patients who were administered an antiemetic were more likely to be female (69% vs 48%, p-value 0.01). However, other risk factors such as smoking history, age, a history of PONV were not significant. Median (Q1, Q3) EtCO2 for the OEtCO2, 30EtCO2, and 10EtCO2 groups were 34.3 (32.7, 36.0), 38.1 (35.1, 41.4), 38.9(35.1, 43.4). Rates of antiemetic administration are reported in Table 1. No statistical relationship is seen within or across groups. Logistic regression of continuous EtCO2 levels showed odds ratios and p-value of OEtCO2 1.03 (0.586), 30EtCO2 1.01 (0.683), and 10EtCO2 0.98 (0.576). EtCO2 levels evaluated as dichotomous groups (<36, ≥36), likewise, did not show a significant relationship with odds ratios (p-values) of OEtCO2 1.215 (0.631), 30EtCO2 1.253 (0.538), and 10EtCO2 1.114 (0.767).

Conclusion: The results of this study do not show any relationship between intraoperative EtCO2 levels and PONV rates in the PACU. There is controversy in the literature regarding this relationship with recent randomized controlled trials finding both significant and insignificant results.2,3 This study contributes to the body of knowledge available and indicates that a relationship may not exist. However, this study is limited by relatively few data points greater than 40 mmHg EtCO2. Large randomized controlled prospective trials are needed to more effectively determine the existence of a relationship between EtCO2 and PONV.

References: 1. Akca O, et al. Anesthesiology 97:801-806. 2. Golparvar M, et al. Advanced Biomedical Research. 2014;3(1):84. 3. Son J-S, et al. Surgical Endoscopy. 2017;31(11):4576-4582.

Table 1: $EtCO_2$ separated by duration of anesthesia			
	Number of patients receiving PACU Antiemetic / total patients (%)		
$EtCO_2$, mmHg	**<36**	**≥36**	**OR (p-value)**
$EtCO_2$ full duration of anesthesia	32/257 (12.5%)	10/86 (11.6%)	1.215 (0.631)
$EtCO_2$ 30 min prior to extubation	14/113 (12.4%)	28/230 (12.2%)	1.253 (0.538)
$EtCO_2$ 10 min prior to extubation	13/104 (12.5%)	29/239 (12.1%)	1.114 (0.767)

Perioperative Anesthesia - 2 Changes in analgesic strategies for lobectomy from 2009 to 2018

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Introduction: Thoracic surgery is associated with significant postoperative pain. Inadequate pain control can exacerbate pulmonary complications by worsening lung restriction, decreasing ventilation, reducing clearance of secretions, and increasing atelectasis in the perioperative period.[1] Moreover, poorly controlled postoperative thoracic pain may also lead to the development of chronic pain.[2] Since pain is a major modifiable factor affecting patient perioperative morbidity and mortality following thoracic surgery,[3] this provides an opportunity for the healthcare team to optimize patient outcomes with a strategic pain management.[4] There are many ways to manage postoperative pain in thoracic surgery. For thoracic surgery, there is currently no multicenter study that characterizes the recent usage in neuraxial techniques and multimodal analgesia in the U.S. The objective of this study was to depict changes over time in the usage of epidural analgesia and nonopioid analgesics and to examine whether there was any change in opioid administration for open and video-assisted lobectomy.

Methods: We conducted a retrospective study by querying the Premier Healthcare database for adult patients undergoing open or video assisted thoracic surgery (VATS) lobectomy from 2009 to 2018. The outcome of interest was changes in the receipt of epidural analgesia and nonopioid and opioid analgesics as measured by charges on the day of surgery. We also evaluated postoperative average daily opioid use. We used multivariable logistic and linear regression models to examine the association between utilization of each analgesic modality and year.

Results: We identified 81,380 patients undergoing lobectomy: 36,775 (45.12%) patients had open lobectomy and 44,605 (54.81%) patients had VATS lobectomy. Median age for both cohorts was 65 years. Fifty percent of open cohort and 45% of VATS cohort were male. Predicted probabilities and values of use of analgesic techniques, medications, and opioid consumption by year using that were estimated using multivariable logistic and linear regression models. Epidural analgesia use decreased from 29.6% in 2009 to 14.7% in 2018 for open lobectomy ($P < 0.0001$), and from 14.2% in 2009 to 4% in 2018 for VATS lobectomy ($P < 0.0001$). Nonopioid local and systemic analgesics, including liposomal bupivacaine, oral and intravenous acetaminophen, gabapentinoids, ketamine, dexmedetomidine, COX-2 inhibitors, and dexamethasone increased over time for both open and VATS lobectomy. On the contrary, the use of intravenous nonsteroidal anti-inflammatory drugs declined over time. Use of patient-controlled analgesia decreased, while opioid consumption on the day of surgery increased and postoperative opioid consumption remained relatively stable over time.

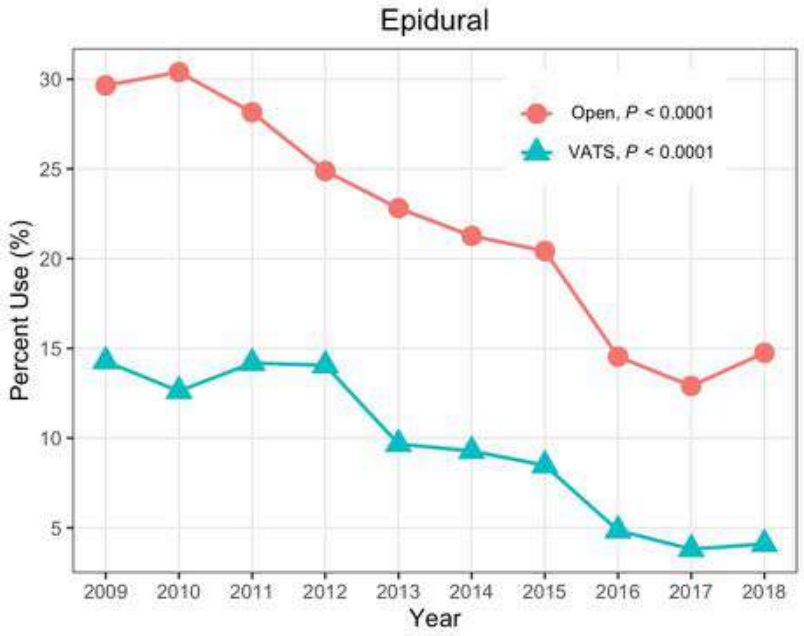
Conclusion: In this large sample of patients undergoing open and VATS lobectomy, utilization of epidural analgesia declined, use of non-opioid analgesics increased, opioid consumption on day of surgery increased, and postoperative daily opioid consumption initially declined but slowly increased back to its level in 2009. This suggests that the analgesics chosen to replace epidurals for lobectomy patients might not be as effective at reducing opioid use. Further research will be required to examine the association of these changes with outcomes.

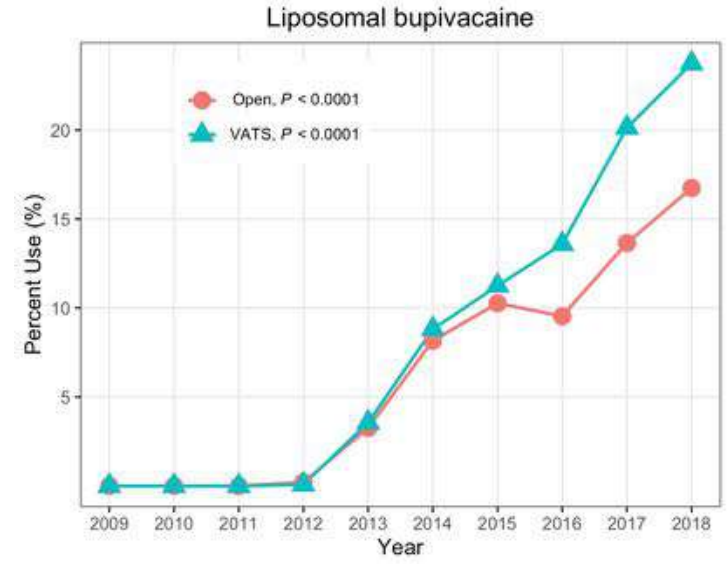
References: Thompson C, French DG, Costache I. Pain management within an enhanced recovery program after thoracic surgery. J Thorac Dis. 2018;10(Suppl 32):S3773-S3780. Richebe P, Capdevila X, Rivat C. Persistent Postsurgical Pain: Pathophysiology and Preventative Pharmacologic Considerations. Anesthesiology. 2018;129(3):590-607. Kaiser AM, Zollinger A, De Lorenzi D, Largiadèr F, Weder W. Prospective, randomized comparison of extrapleural versus epidural analgesia for postthoracotomy pain. Ann Thorac Surg. 1998;66(2):367-372. Gottschalk A, Cohen SP, Yang S, Ochroch EA. Preventing and treating pain after thoracic surgery. Anesthesiology. 2006;104(3):594-600.

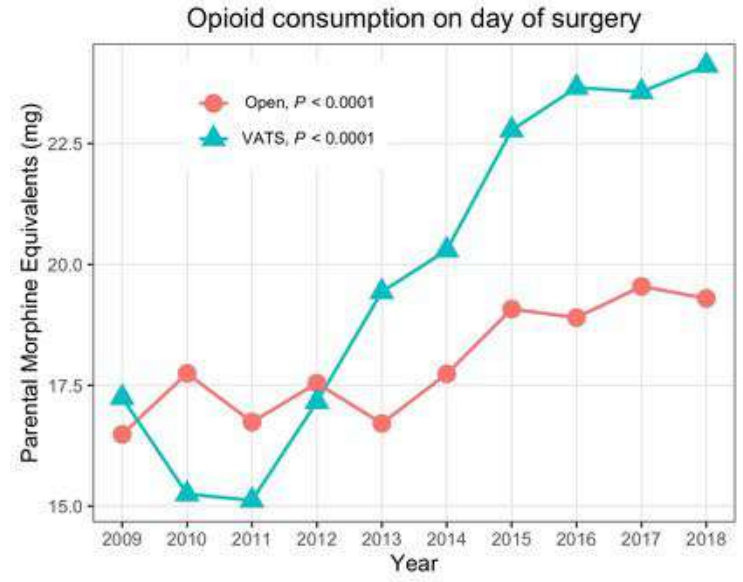
Table 1. Patient baseline characteristics and comorbidities and hospital-related characteristics

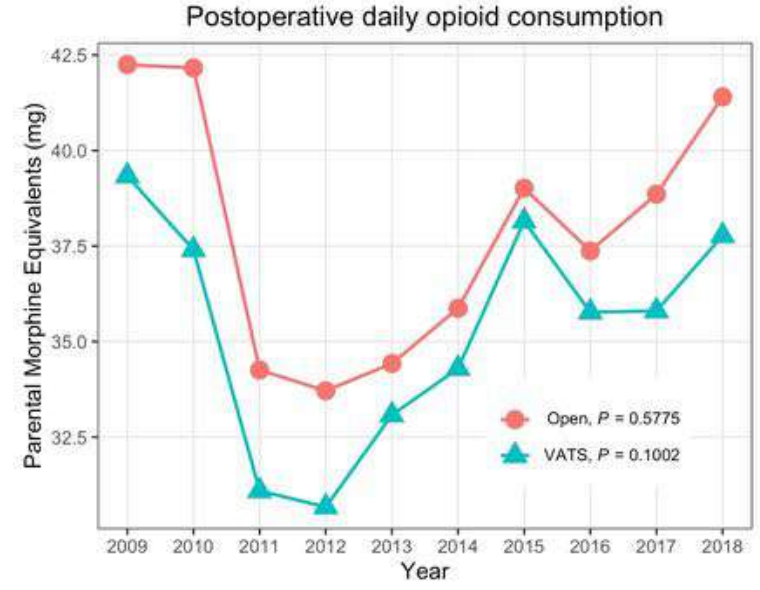
	Open Lobectomy (n = 36,775)	VATS Lobectomy (n = 44,605)
Age, ± SD (years)	65.5 ± 12.2	65.1 ± 12.9
Male [no. (%)]	18325 (49.8)	20145 (45.2)
Race [no. (%)]		
African Americans	2739 (7.4)	3473 (7.8)
Caucasians	29898 (81.3)	36706 (82.3)
Other	4138 (11.3)	4426 (9.9)
Payor [no. (%)]		
Managed care organization	8069 (21.9)	10643 (23.9)
Medicaid	2469 (6.7)	3097 (6.9)
Medicare	22729 (61.8)	26671 (59.8)
Other	3508 (9.5)	4194 (9.4)
Comorbidity		
Congestive heart failure	1621 (4.4)	1716 (3.8)
Valvular disease	1328 (3.6)	1517 (3.4)
Pulmonary circulation disease	430 (1.2)	261 (0.6)
Peripheral vascular disease	3271 (8.9)	3069 (6.9)
Paralysis	58 (0.2)	59 (0.1)
Other neurological disorders	1438 (3.9)	1584 (3.6)
Chronic pulmonary disease	18606 (50.6)	19203 (43.1)
Diabetes without chronic complications	6296 (17.1)	6973 (15.6)
Diabetes with chronic complications	1350 (3.7)	1888 (4.2)
Hypothyroidism	4410 (12)	5557 (12.5)
Renal failure	2393 (6.5)	2623 (5.9)
Liver disease	616 (1.7)	850 (1.9)
Peptic ulcer Disease excluding bleeding	72 (0.2)	104 (0.2)
Acquired immune deficiency syndrome	38 (0.1)	60 (0.1)
Lymphoma	303 (0.8)	395(0.9)
Metastatic cancer	5499 (15)	4176 (9.4)
Solid tumor without metastasis	4865 (13.2)	4996 (11.2)
Rheumatoid arthritis/collagen vascular disease	1301 (3.5)	1677 (3.8)
Coagulopathy	578 (1.6)	663 (1.5)
Obesity	4233 (11.5)	5236 (11.7)
Weight loss	1337 (3.6)	994 (2.2)
Fluid and electrolyte disorders	1953 (5.3)	1626 (3.6)
Chronic blood loss anemia	124 (0.3)	98 (0.2)
Deficiency Anemias	3077 (8.4)	2593 (5.8)
Alcohol abuse	1047 (2.8)	967 (2.2)
Drug abuse	425 (1.2)	442 (1)
Psychoses	719 (2)	850 (1.9)

Depression	4153 (11.3)	4964 (11.1)
Hypertension	23057 (62.7)	26401 (59.2)
Teaching hospital	18530 (50.4)	27146 (60.9)
Rural hospital	3275 (8.9)	3327 (7.5)
Hospital number of beds [no. (%)]		
0-99	344 (0.9)	310 (0.7)
100-199	2003 (5.4)	2022 (4.5)
200-299	4749 (12.9)	4851 (10.9)
300-399	6957 (18.9)	6843 (15.3)
400-499	7372 (20)	6679 (15)
500+	15350 (41.7)	23900 (53.6)
Fiscal year [no. (%)]		
2009	2486 (6.8)	1212 (2.7)
2010	2922 (7.9)	1807 (4.1)
2011	3460 (9.4)	2405 (5.4)
2012	3404 (9.3)	2541 (5.7)
2013	3591 (9.8)	2865 (6.4)
2014	3602 (9.8)	2975 (6.7)
2015	3653 (9.9)	3350 (7.5)
2016	5380 (14.6)	9484 (21.3)
2017	4968 (13.5)	10497 (23.5)
2018	3309 (9)	7469 (16.7)




Liposomal bupivacaine
Open, P < 0.0001
VATS, P < 0.0001
Percent Use (%)
20
15
10
5
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year


Opioid consumption on day of surgery
Open, P < 0.0001
VATS, P < 0.0001
Parental Morphine Equivalents (mg)
22.5
20.0
17.5
15.0
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year


Postoperative daily opioid consumption
Parental Morphine Equivalents (mg)
42.5
40.0
37.5
35.0
32.5
Open, P = 0.5775
VATS, P = 0.1002
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year

Perioperative Anesthesia - 3 Unintended consequences of the 2016 CDC opioid prescribing guidelines on opioid dispensing after surgery

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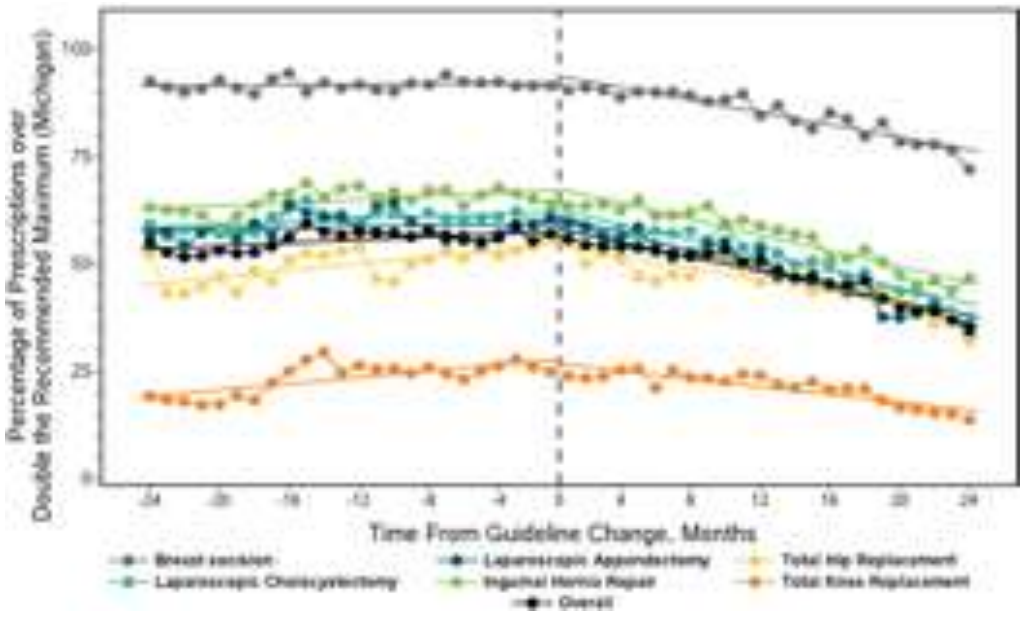
Introduction: Opioids are frequently overprescribed after common surgeries.(1,2) Excess supply leads to increased community availability and subsequent risk of diversion,(3,4) and may contribute to adverse outcomes, including new long-term use.(5,6) In 2016, the US Centers for Disease Control (CDC) released guidelines on opioid prescribing for pain management, including a recommendation for acute pain management. While the guideline was not intended to address postoperative pain management, observers have noted potential unintended impacts of this guideline on opioid prescribing after surgery. We hypothesize that the guideline release did affect opioid dispensing after surgery.

Methods: We performed a retrospective interrupted time series analysis involving 361,556 privately insured opioid-naïve patients undergoing 8 general and orthopedic surgeries between 2014 and 2018. The primary outcome was the total amount of opioids dispensed in the first prescription filled within 7 days after surgery in morphine milligram equivalents (MME); secondary outcomes included the total amount of opioids prescribed within 30 days after surgery and the incidence of any opioid refill within 30 days. To characterize absolute levels of opioid dispensing, we compared the amount dispensed in initial prescriptions with available procedure-specific recommendations based on anticipated pain severity.

Results: The total amount of opioids dispensed in the first prescription after surgery decreased over the 2 years following the CDC guideline release, compared to an increasing trend over the 2 years prior (pre-release trend: 1.43 MME/month (95% Confidence Interval (CI): 0.62, 2.24, P=0.001); post-release trend: -2.18 MME/month (95% CI: -3.01, -1.35, P<0.001); trend change: -3.61 MME/month (95% CI -4.87, -2.35, P<0.001)). Changes in initial dispensing amount trends were greatest for patients undergoing hip or knee replacement (-8.64 MME/month (95% CI -11.68, -5.60, P<0.001)). Minimal changes were observed in rates of refills over time (net change: 0.14%/month (95% CI 0.06, 0.23, P=0.001)). Absolute amounts prescribed remained high throughout the period, with 47.7% of patients treated in the post-guideline period receiving at least twice the initial opioid dose anticipated to treat postoperative pain based on available procedure-specific recommendations.

Conclusion: Opioid dispensing after surgery decreased markedly after the 2016 CDC guideline release, compared to an increasing trend over the two years prior, suggesting unintended impacts of the guideline on postoperative pain management. Absolute amounts prescribed for surgery remained high over the study period, supporting further efforts to improve postoperative pain management.

References: 1. Prescription Opioid Analgesics Commonly Unused After Surgery: A Systematic Review. JAMA Surg. 2017;152(11):1066-1071. 2.Inappropriate opioid prescription after surgery. Lancet. 2019;393(10180):1547-1557. 3. Chronic Opioid Use After Surgery: Implications for Perioperative Management in the Face of the Opioid Epidemic. Anesth Analg. 2017;125(5):1733-1740. 4.Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. Ann Intern Med. 2017;167(5):293-301. 5. Long-term analgesic use after low-risk surgery. Arch Intern Med. 2012;172(5):425-430. 6.New Persistent Opioid Use After Minor and Major Surgical ProceduresiS Adults. JAMA Surg. 2017;152(6):e170504. 7. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. JAMA. 2016;315(15):1624-1645. 8.Michigan Opioid Prescribing Engagement Network (OPEN). URL: https://michigan-open.org/prescribing-recommendations


Percentage of Prescriptions over Double the Recommended Maximum (Michigan)
100
75
50
25
0
-24
-20
-16
-12
-8
-4
0
4
8
12
16
20
24
Time From Guideline Change, Months
Breast excision
Laparoscopic Cholecystectomy
Laparoscopic Appendectomy
Inguinal Hernia Repair
Overall
Total Hip Replacement
Total Knee Replacement

Perioperative Anesthesia - 4 Association between Preoperative Systemic Inflammation and Major Adverse Cardiovascular Events after Noncardiac Surgery – A Multicenter Prospective Cohort Study

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Introduction: Each year more than 200 million people worldwide undergo noncardiac surgery of whom about 5% will develop cardiovascular complications.(1) Therefore, prevention and early recognition of major adverse cardiovascular events (MACE) is crucial. Recent studies demonstrated the important role of systematic inflammation in the development of MACE.(2) Neutrophil-lymphocyte ratio (NLR) is a low cost and widely available marker of systemic inflammation that may be associated with cardiovascular disease as well. While there are some promising data on its predictive value for myocardial injury,(3) the use of NLR to enhance preoperative risk assessment for MACE remains underexplored. The aim of this study was to answer the question if an elevated preoperative NLR (defined as NLR>4) is independently associated with MACE at 30 days after noncardiac surgery.

Methods: This study reports prospectively collected data of a multicentre cohort study (NCT02573532) that included patients undergoing major noncardiac surgery aged ≥ 65 years OR ≥ 45 years in presence of a history of coronary artery disease, peripheral arterial disease or stroke. NLR was assessed within 7 days prior to surgery. The primary endpoint was MACE at 30 days after surgery. Secondary outcomes included MACE at 1 year, all-cause mortality at 30 days and 1 year and the occurrence of perioperative myocardial injury (PMI) defined as an increase in hsTNT ≥ 14 ng/l within the first 3 postoperative days. The discrimination of NLR for the events of interest was quantified using the area under the receiver operating characteristics curve (AUC). The independent association between NLR and MACE was calculated using multivariable Cox regression with predefined covariables.

Results: Among 4828 patients (55% male, mean age 74±8 years), we registered 312 MACE at 30 days and 577 at 1 year. The AUC for 30-day and 1-year MACE was 0.65 [95% confidence interval (CI) 0.62-0.68] and 0.62 [95% CI 0.60-0.65], respectively (see figure 1). The adjusted hazard ratios for preoperative NRL>4 were 1.99 [95% CI 1.53-2.6] for 30-day and 1.57 [95% CI 1.31-1.89] for 1-year MACE (see figure 2). All-cause mortality was 3.1% at 30 days and 12.5% at 1 year. The AUC of NLR for 30-day and 1-year all-cause mortality was 0.73 [95% CI 0.69-0.78] and 0.66 [95% CI 0.63-0.68], respectively. The AUC for PMI was 0.59 [95% CI 0.57-0.61] and the adjusted odds ratio was 1.53 [95% CI 1.26-1.98].

Conclusion: Preoperative systemic inflammation as defined by NLR > 4 was independently associated with MACE at 30 days and 1 year after noncardiac surgery. Our findings support the potential value of NLR as a low-cost approach to enhance preoperative risk stratification in noncardiac surgery patients.

References: 1. Devereaux PJ, Sessler DI. Cardiac complications in patients undergoing major noncardiac surgery. N Engl J Med. 2015;373:2258-2269. 2. Hansson G. Inflammation, Atherosclerosis, and Coronary Artery Disease. N Engl J Med. 2005;352;16:1685-1695. 3. Ackland GL, Abbott TEF, Cain D, et al. Preoperative systemic inflammation and perioperative myocardial injury: prospective observational multicentre cohort study of patients undergoing non-cardiac surgery. Br J Anaesth. 2019;122:180-187.

Figure 1:

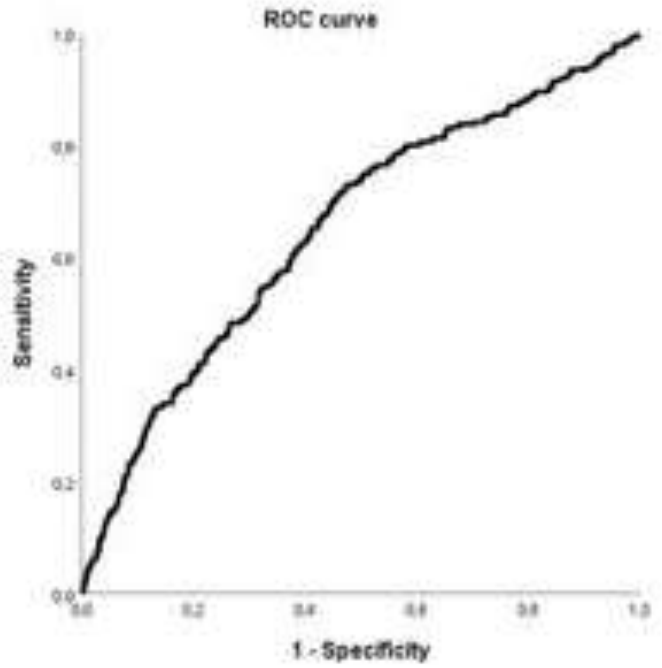
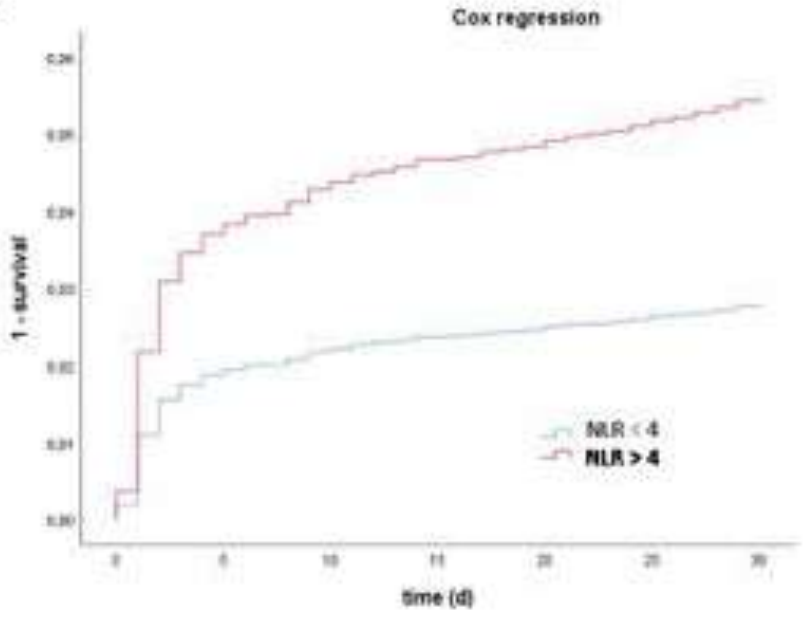


Figure 2:



Perioperative Anesthesia - 5

Postoperative Complications Associated with Differing Neuromuscular Blockade Reversal

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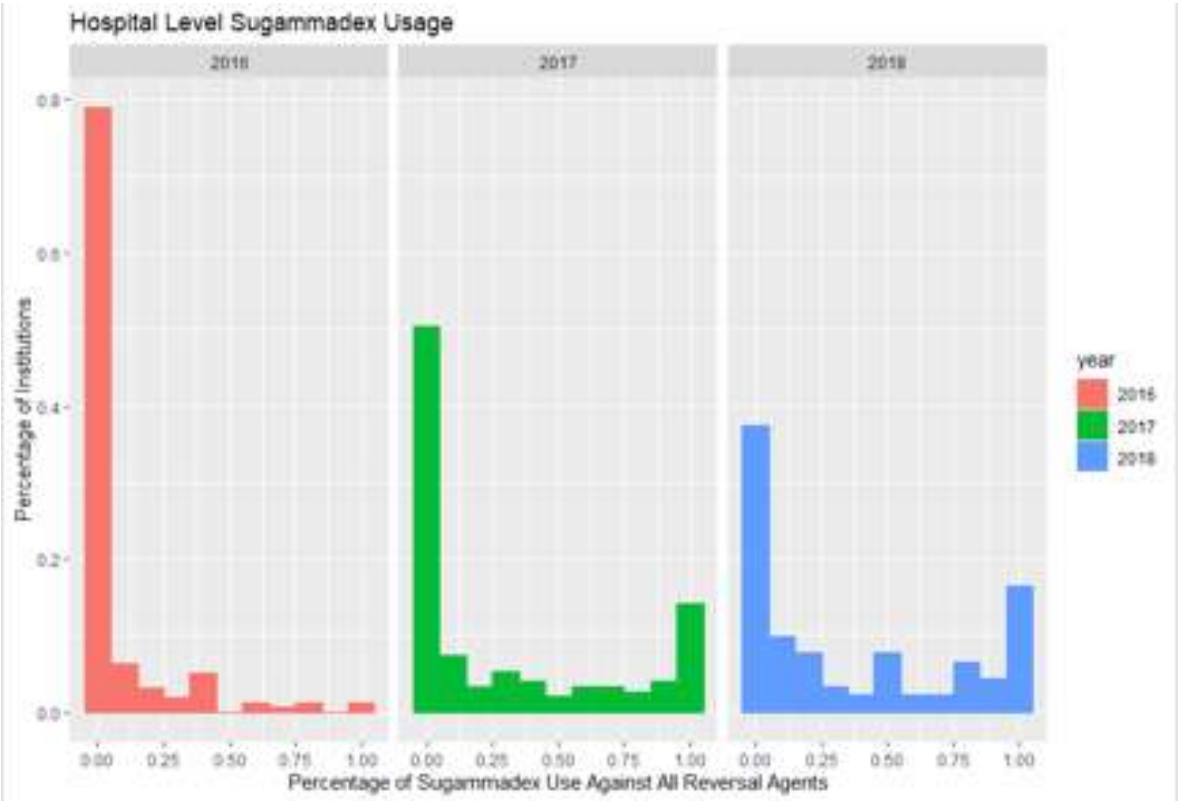
Introduction: Residual neuromuscular blockade remains a significant risk factor for postoperative complications. (1) Recently, a large observational matched-cohort study of inpatient surgeries demonstrated that use of Sugammadex resulted in a significant decrease in postoperative pulmonary complications. (2) However, there is little evidence regarding the use of Sugammadex in outpatient surgery. Therefore, we sought to examine the association between utilization of Sugammadex (versus Neostigmine) for NMBA reversal and Discharge Disposition (discharge to home: primary outcome) and Complications (anaphylaxis and postoperative pulmonary complications: secondary outcome) after laparoscopic cholecystectomy.

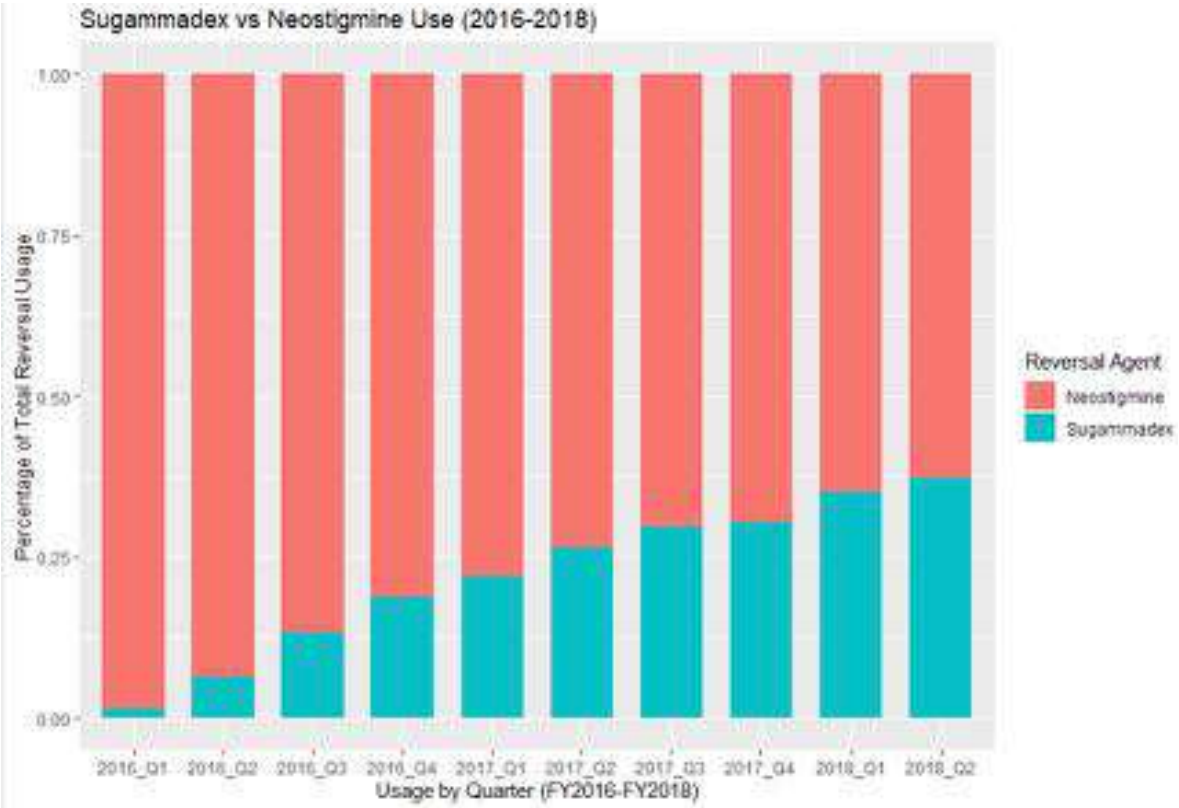
Methods: In this retrospective observational cohort study, the US nationwide all-payer Premier Healthcare database (Premier Inc., USA) from 2016 to 2018 was queried for the International Classification of Diseases, Ninth Revision (ICD-9) and tenth (ICD-10) procedure codes for laparascopic cholecystectomy. Inclusion criteria consisted of patients undergoing laparascopic cholecystectomy with a same day surgery designation, receipt of rocuronium or vecuronium, reversal with either neostigmine or Sugammadex. Patients less than 18 years of ages were excluded along with hospitals without Sugammadex charges, and patients that received both neostigmine and Sugammadex. We examined patterns of use of Sugammadex use over time and Institutional variation in use (Figures 1 and 2). We compared baseline characteristics as well as outcomes in patients who had received either neostigmine vs Sugammadex. Statistical significance was determined using Chi Square or Kruskall Wallis tests as appropriate.

Results: Our study cohort consisted of 32,789 adults who had undergone laparoscopic cholecystectomy with a 'same day surgery' designation between 2016 and 2018, and who were admitted from home, receiving either rocuronium or vecuronium, and receiving either Sugammadex (n=6736) or Neostigmine (n=26,503). The use of Sugammadex increased markedly over the study period and by Q1 2018, Sugammadex was utilized by 40% of institutions. 99.7% of patients receiving Sugammadex vs 98.6% receiving neostigmine were discharged to home ($p< 0.0001$). The need for postoperative mechanical ventilation was significantly great in the neostigmine group ($p=0.035$) but no differences were observed for non invasive ventilation and anaphylaxis.

Conclusion: In 32,789 patients undergoing Lap Chole in a Same Day Surgery setting, utilization of Sugammadex increased significantly reaching 40% of institutions in 2018. Patients who received Sugammadex had higher rates of discharge to home versus Patients who received Neostigmine. There were no differences in PPCs or readmissions. Given the baseline differences between the two groups, risk-adjusted studies are needed to draw further inferences regarding the impact of type of NMBA reversal on important outcomes after Same Day Surgery.

References: 1) McLean DJ, Diaz-Gil D, Farhan HN, Ladha KS, Kurth T, Eikermann M. Dose-dependent Association between Intermediate-acting Neuromuscular-blocking Agents and Postoperative Respiratory Complications. Anesthesiology 2015;122:1201–13. 2) Kheterpal S, Vaughn MT, Dubovoy TZ, Shah NJ, Bash LD, Colquhoun DA, Shanks AM, Mathis MR, Soto RG, Bardia A, Bartels K, McCormick PJ, Schonberger RB, Saager L. Sugammadex versus Neostigmine for Reversal of Neuromuscular Blockade and Postoperative Pulmonary Complications (STRONGER): A Multicenter Matched Cohort Analysis. Anesthesiology 2020;132:1371–81.


Hospital Level Sugammadex Usage
2016
2017
2018
Percentage of Institutions
0.0
0.2
0.4
0.6
0.8
0.00
0.25
0.50
0.75
1.00
Percentage of Sugammadex Use Against All Reversal Agents
year
2016
2017
2018


Sugammadex vs Neostigmine Use (2016-2018)
Percentage of Total Reversal Usage
0.00
0.25
0.50
0.75
1.00
2016_Q1
2016_Q2
2016_Q3
2016_Q4
2017_Q1
2017_Q2
2017_Q3
2017_Q4
2018_Q1
2018_Q2
Usage by Quarter (FY2016-FY2018)
Reversal Agent
Neostigmine
Sugammadex

Perioperative Anesthesia - 6

Intraoperative hypotension before critical care admission is common but not associated with in hospital mortality in non-cardiac surgery.

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Introduction: At the time of ICU admission after non cardiac surgery, it is not always possible to predict which patients will further decompensate. Since intraoperative hypotension has been associated with acute kidney injury, myocardial injury and 30 day mortality, many advocate looking at intraoperative hypotension at time of ICU admission to project future clinical course. Previous analysis has quantified intraoperative hypotension by time weighted average under different blood pressure thresholds and absolute time under certain thresholds. No study has evaluated a population of exclusively ICU patients. We sought to first quantify the magnitude and time below different blood thresholds in patients requiring critical care after non cardiac surgery and then explore the association between these data and in-hospital mortality.

Methods: We identified a retrospective cohort of 10,014 elevated risk non cardiac surgery patients cared for at Johns Hopkins hospital from July 2016 to October 2018 (Table 1). All patients that had an ICU stay after their surgery were included. Exclusion criteria included availability of discharge date, more than one surgery, insufficient data recorded for blood pressure measurements taken from the arterial line, and ASA physical status V (Figure 1). 3991 intraoperative records were included in analysis. Derived feature calculation: Area under and over time-weighted average curve of MAP were calculated for each patient episode. In particular, total area of the curve and the area between the set baseline and the curve were calculated. Example time-weighted average curves of MAP are shown in Figure 2. Main outcome: In hospital mortality. Statistical Analysis: Mann Whitney analysis comparing the mean values for Area under MAP threshold and time weighted area under MAP threshold between the alive versus deceased group. Data analysis and representation were performed using Python Libraries of Pandas, Numpy, and Scipy.

Results: Intraoperative hypotension ranging from MAP 45 to 65 mmHg and hypertension ranging from MAP 70 to 90 mmHg for multiple cumulative duration in minutes was common. There was no association with intraoperative hypotension or hypertension with in-hospital mortality (Figures 3 and 4).

Conclusion: Despite previous literature associating periods of hypotension below MAP thresholds of 50 to 65 mmHg and kidney and myocardial injury, we saw no association with in-hospital mortality in a population of surgical patients requiring post-operative critical care. Upon ICU admission, looking at the time below target threshold and magnitude below threshold likely does not reveal clinically useful information about the risk of in-hospital mortality. Our next steps are to examine other pertinent patient centered outcomes such as length of stay and cardiac and renal injury as they relate to intraoperative blood pressure management. One of our study's strengths is exploring multiple MAP thresholds instead of one single cut-off threshold to define intraoperative hypotension/hypertension. Both additional severity (area under MAP threshold) and averaged (time- weighted average under MAP threshold) characterizations were comparable with our main characterization of duration below the threshold. Several limitations were present in this study. First, the data was measured in one university hospital limiting generalizability. Second, some blood pressure recordings were accepted by clinical judgment. Third, we did not account for intravenous fluids, volatile anesthesia, inotropes, and vasopressors, which have a substantial contribution to intraoperative hypotension, though this is dependent on the institution's protocols and anesthetists' preferences. These variables may have been sources of confounding.

References: Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. British journal of anaesthesia. 2019;122(5):563-574. Postoperative Hypotension after Noncardiac Surgery and the Association with Myocardial Injury. Anesthesiology. 2020. Intraoperative Mean Arterial Pressure Variability and 30-day Mortality in Patients Having Noncardiac Surgery. Anesthesiology. 2015;123(1):79-91. Intraoperative blood pressure variability predicts postoperative mortality in non-cardiac surgery—A prospective observational cohort study.International Journal of Environmental Research and Public Health,16(22). https://doi.org/10.3390/ijerph16224380 Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocar- dial injury after noncardiac surgery: A retrospective cohort analysis. Anesthesiology 2017; 126:47–65

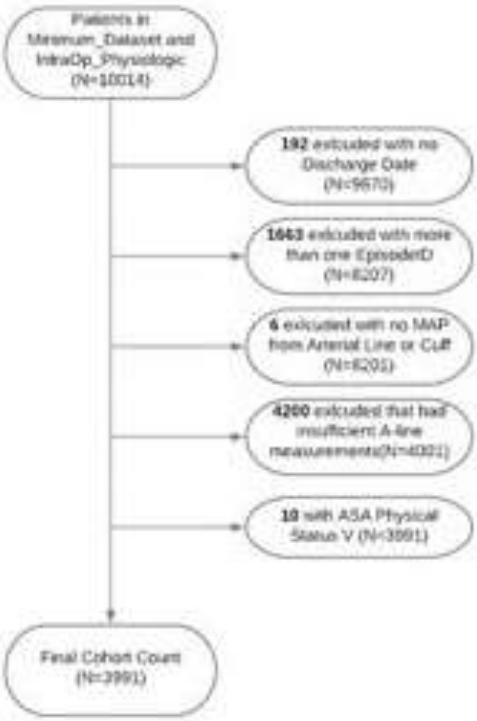

Figure 1. Data Preprocessing – Application of Exclusion Criteria

		Missing	Overall	Alive	Deceased	P Value	Test
n			3991	3734	257		
Age, mean (SD)		0	59.2 (15.8)	58.1 (15.7)	82.8 (10.6)	<0.001	Two Sample T-test
Gender, n (%)	F	0	2061 (51.6)	1911 (51.2)	150 (58.4)	0.025	Chi-squared
	M		1930 (48.4)	1823 (48.8)	107 (41.6)		
FirstRace, n (%)	Declined to Answer	0	9 (0.2)	9 (0.2)	0 (0.0)	<0.001	Chi-squared (warning: expected count < 5)
	Non-White		1479 (37.1)	1392 (37.3)	87 (33.9)		
	Unknown		42 (1.1)	39 (1.0)	3 (1.2)		
	White or Caucasian		2461 (61.7)	2294 (61.5)	167 (65.0)		
BMI, mean (SD)		71	29.0 (7.4)	29.0 (7.3)	27.4 (8.6)	<0.001	Two Sample T-test
LOS, mean (SD)		0	7.6 (8.4)	7.4 (7.1)	12.5 (22.4)	<0.001	Two Sample T-test
ASA_PhysicalStatus, n (%)	I	0	71 (1.8)	68 (1.8)	3 (1.2)	<0.001	Chi-squared (warning: expected count < 5)
	II		1964 (49.2)	1915 (51.3)	49 (19.1)		
	III		1602 (40.1)	1458 (39.1)	144 (56.0)		
	IV		367 (9.2)	287 (7.7)	80 (31.1)		
	Unknown		71 (1.8)	68 (1.8)	3 (1.2)		
	V		16 (0.4)	8 (0.2)	8 (3.1)		
	VI		10 (0.3)		10 (3.9)		
SmokingStatus, n (%)	Never Smoker	0	2213 (55.5)	2113 (56.6)	100 (38.9)	<0.001	Chi-squared (warning: expected count < 5)
	Smoker		1767 (44.3)	1608 (43.1)	159 (61.9)		
	Unknown		11 (0.3)	13 (0.3)	0 (0.0)		

Table 1. Characteristics of Study Population

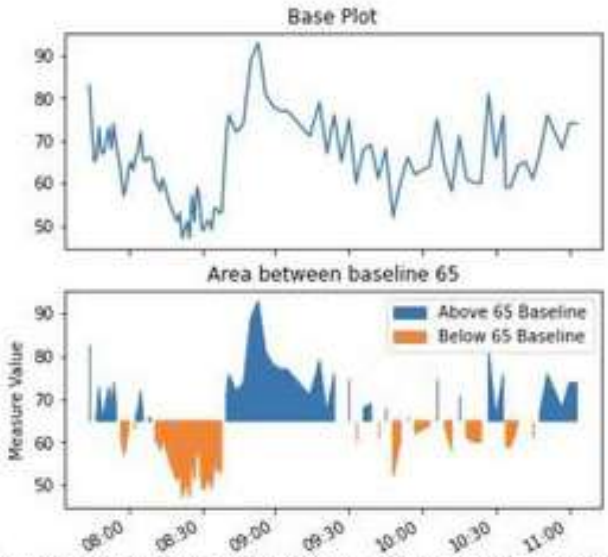

Figure 2. Sample time-weighted average curve of MAP from a single episode. Base plot shows a regular time-weighted average curve, and the second graph shows the curve separated by 65mmHg 'normal' line.

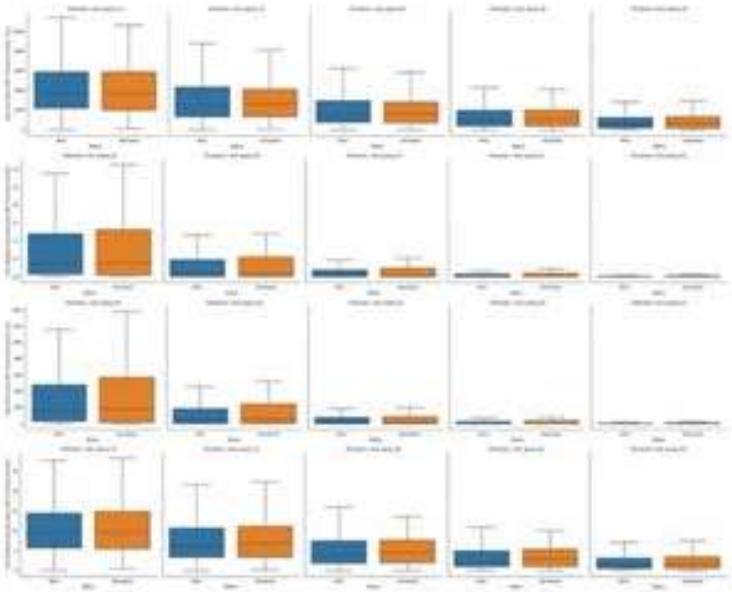

Figure 3. Association of Intraoperative Hypotension and Hypertension, as Total Area and TWA-MAP Under/Above multiple MAP Thresholds, and In-hospital Mortality

Threshold	Status	median_TWA-MAP	P-value	mean_TWA-MAP	P-value	median_Total Area	P-value	mean_Total Area	P-value
AUC_below_45	Alive	0	[illegible]	[illegible]	[illegible]	0	[illegible]	[illegible]	[illegible]
AUC_below_45	Deceased	0		0.273490987		0		72.28618448	
AUC_below_50	Alive	0	[illegible]	[illegible]	[illegible]	0	[illegible]	[illegible]	[illegible]
AUC_below_50	Deceased	0		0.440939426		0		[illegible]	
AUC_below_55	Alive	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
AUC_below_55	Deceased	[illegible]		0.463305472		7.333333333		181.7654062	
AUC_below_60	Alive	[illegible]	[illegible]	[illegible]	[illegible]	41.25	[illegible]	[illegible]	[illegible]
AUC_below_60	Deceased	[illegible]		[illegible]		58		236.67307	
AUC_below_65	Alive	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
AUC_below_65	Deceased	[illegible]		[illegible]		[illegible]		[illegible]	
AUC_above_70	Alive	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
AUC_above_70	Deceased	[illegible]		11.07202664		[illegible]		4125.144239	
AUC_above_75	Alive	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
AUC_above_75	Deceased	[illegible]		[illegible]		[illegible]		[illegible]	
AUC_above_80	Alive	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
AUC_above_80	Deceased	4.546747967		5.792713639		[illegible]		[illegible]	
AUC_above_85	Alive	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
AUC_above_85	Deceased	[illegible]		[illegible]		[illegible]		[illegible]	
AUC_above_90	Alive	[illegible]	[illegible]	[illegible]	0.1422221	142.6666667	[illegible]	[illegible]	[illegible]
AUC_above_90	Deceased	[illegible]		[illegible]		[illegible]		[illegible]	

Table 2. Association of Mean and Median Intraoperative Hypotension and Hypertension, as Total Area and TWA-MAP Under/Above multiple MAP Thresholds, and In-hospital Mortality

Perioperative Anesthesia - 7 Feasibility of Blood Flow Restriction Exercise Prehabilitation to Attenuate Postoperative Loss of Function after Total Knee Replacement: A Randomized Pilot Study

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Introduction: Prehabilitation is an expanding tool in Anesthesiology to improve postoperative outcomes of patients undergoing major surgeries such as total knee arthroplasty (TKA). TKA is associated with significant morbidity and mortality (1,2). Up to 20% of patients have reported dissatisfaction with postoperative outcomes (3,4,5). A meta-analysis of studies evaluating lower limb strength for up to 3 years after TKA revealed decreased strength in multiple leg muscle groups after TKA compared to controls, despite routine physical therapy/rehabilitation in the first months after surgery (5). Because knee replacement surgery is an elective surgery, interventions applied during the preoperative period are feasible. However, the available studies show mixed results (6,7,8). Based on this dilemma, blood flow restriction (BFR) exercise may provide an alternative. The BFR exercise entails the concurrent application of a tourniquet on a limb during exercise. The BFR exercise has been shown to improve muscle mass in a shorter period of time and at a lower exercise intensity and it appears to be an attractive alternative for patients who cannot undergo a lengthy exercise program secondary to pain and a limited time schedule (9,10). Based on these findings, we tested the feasibility of a low-resistance exercise protocol with blood flow restriction (BFR) in the preoperative period for patients awaiting TKA.

Methods: Our pilot randomized control study was approved by the Institutional Review Board and participants provided written informed consent. Ten patients were included to study the feasibility of BFR exercise in the preoperative period in older patients undergoing unilateral TKA. Patients were randomized to undergo the BFR exercise ('BFR' group) 4 weeks prior to TKA or standard of care (no exercise, 'Control' group). After random assignment to the BFR exercise group and determination of the 1RM, participants engaged 2 days per week with at least 2 days apart in a center-based exercise intervention for 4 weeks. We tested the following parameters 4 to 5 weeks preoperatively and 2 weeks postoperatively: the Short Physical Performance Battery (SPPB), the 6-Minute Walk Test (6MWT), leg strength of the operative leg (peak torque knee extension), and pain score (numerical rating scale). Anesthetic and postoperative management was similar among patients; all surgeries were performed under a spinal anesthetic and regional anesthesia including a femoral nerve catheter and sciatic nerve single-injection regional anesthetic. Measures were summarized as means and standard deviations (± SD) for continuous measures and counts for categorical measures. Differences scores between baseline and follow-up were reported as mean differences with 95% confidence intervals (95%CI). To compare difference between groups, linear regression analyses were run with follow-up measurement as dependent variable and group and baseline measures as independent variables. By including baseline measurement as an independent variable, a 'residual change score' across time points was created; thus, an effect of group assignment would then be interpreted as an effect on the change from baseline to follow-up. $P < 0.05$ was considered statistically significant. All analyses were conducted in JMP Pro 15.0.

Results: Ten patients were included in this study (total n=10; n=6 BFR exercise group, n=4 No exercise group). Table 1 reports baseline patient demographics, for full sample and stratified by group. The average age of patients was 67.2 and average BMI was 31.2. The majority of the sample were women and non-Hispanic, white. There were significant group differences in change for SPPB ($p = 0.011$, Figure 1). The BFR group, on average, showed less decline in SPPB following surgery (-2.2, 95%CI:-4.4,0.1) compared to no exercise group (-4.8, 95%CI:-7.8,-1.7). Group differences for SMW ($p = 0.626$), leg strength ($p=0.852$), and pain ($p=0.713$), did not achieve statistical significance.

Conclusion: Findings show that BFR exercise was feasible preoperatively and, more importantly, it was associated with significantly less decline in physical function measured by the SPPB when compared to the control group without any complications in patients undergoing a TKA. Additionally, and as anticipated, our findings suggest across all measurements a clinically significant decline in physical function following elective TKA, indicating the need for prehabilitation.

References: 1. J Bone Joint Surg Am. 2005;87:1487–97. 2. Arthritis Rheum. 2012;64: 3839–49. 3. Knee Surg Sports Traumatol Arthrosc. 2011;19:1442–52. 4. BMJ Open. 2012;2:e000435. 5. Knee. 2014;21:12–20. 6. Arch Phys Med Rehabil. 2013; 94 (1): 164-76. 7. J Arthroplasty. 1998; 13: 414-21. 8. Arthritis Rheum. 2006; 55: 700-8. 9. Acta Physiol Hung. 2013; 100 (4): 419-26. 10. Am J Physiol Endocrinol Metab. 2014; 306 (10): E1198-204.

	Total Sample n=10	BFR Exercise n=6	No Exercise n=4
Age, mean year ± SD	67.2 ± 7.1	66.5 ± 9.0	68.3 ± 3.9
Gender, n for women	7/10	4/6	3/4
Ethnicity, n for non-Hispanic	9/10	6/6	3/4
Race, n for white	9/10	6/6	3/4
BMI, mean ± SD	31.2 ± 5.4	29.7 ± 4.7	33.3 ± 6.3

Table 1. Baseline patient demographics, for full sample and stratified by group.

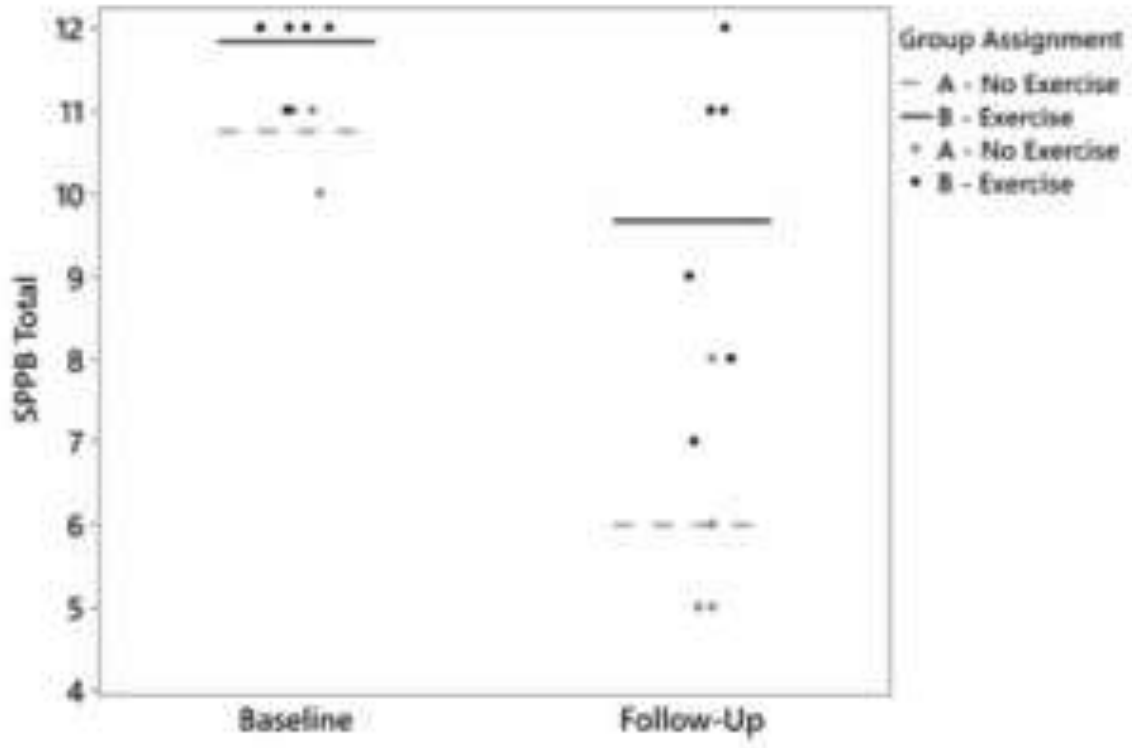

Figure 1. Short Physical Performance Battery (SPPB) scores at baseline to follow-up, stratified by group. Horizontal lines represent group means, dots represent individual patient values.

Perioperative Anesthesia - 8 Natural Language Processing Predicts ASA Physical Status Classification from Pre-operative Note Text

Philip Chung[1], Christine T Fong[1], Vikas O'Reilly-Shah[2]

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Introduction: Large studies have demonstrated the value of the American Society of Anesthesiologists Physical Status Classification System (ASA-PS) as an independent predictor of post-operative morbidity and mortality. Prediction of ASA-PS has value for a variety of reasons; prior approaches to this prediction task have used tabular data.[1,2] In the present work, we describe using neural natural language processing (NLP) to predict ASA-PS. Neural NLP combines linguistics, deep learning, and statistics in order to create numerical representations of text data, allowing for development of predictive models utilizing a sequence of words as input data. We hypothesized that text from the 'History of Present Illness' (HPI) section of the anesthesiology pre-operative evaluation note would predict the ASA-PS assigned by the anesthesiologist on day of surgery.

Methods: Data was extracted from the electronic health record at the University of Washington Medical Center and affiliated hospitals and clinics. Inclusion criteria was all patients who had surgery from Jan 1, 2018 – Oct 31, 2019 who also had a pre-anesthesia preoperative evaluation note with a 'History of Present Illness' (HPI) section in the medical record prior to the surgery. We do not distinguish between emergent (presence of ASA-PS 'E' modifier) and non-emergent cases. The model was trained using transfer learning, starting with the Bio+Clinical BERT model and fine-tuned on our task by adding a linear classification layer to perform multi-class sequence classification.[3] Model performance was evaluated on validation and test sets by receiver operator characteristic (ROC) curve, area under ROC curve (AUC), precision-recall (PR) curve, and average precision for predicting each ASA-PS class as well as micro-average of all classes.

Results: Our dataset is comprised of 28244 unique surgical procedures, randomly split into a training set of 25392 samples (90%) and test set of 2852 samples (10%). The distribution of ASA-PS among patients is described in Figure 1. Given the rarity of ASA V and VI, these classes were merged with ASA IV forming a compound class 'ASA IV-VI'. To control for class imbalance, the training data was randomly resampled to boost minority classes and generate an augmented dataset with 12000 samples from each class (48000 total), which was again randomly split into training set of 38400 samples (80%) and validation set 9600 (20%). The model was trained for 150 epochs on the training set with batch size of 256, learning rate of 5 x 10-5 with AdamW optimizer, 10% dropout, and cross-entropy loss. Training and validation loss both decreased with number of training samples, suggesting that the model did not overfit on the training set. We achieve micro-averaged AUC of 0.96 on the validation set and 0.8 on the test set (Figure 2). Micro-averaged average precision is 0.90 on the validation set and 0.50 on the test set (Figure 3).

Conclusion: Our NLP model performs well on predicting ASA I & IV-VI with AUC 1.0 & 0.97 on the validation set and 0.9 & 0.81 on the test set, respectively. Model performance suffers particularly with patients assigned ASA II or ASA III, which suggests that the truncated HPI input may not always be descriptive enough to accurately categorize these patients. Additionally, ASA-PS has been shown to have moderate inter-rater reliability among anesthesiologists, and our NLP model may have difficulty accounting for inter-rater differences.[4] However, even when our model misclassifies ASA-PS, it typically only does so by one ASA-PS class (Figure 4). This suggests that the NLP model is able to correlate the presence of specific words and its contextual meaning in natural language to a patient's underlying perioperative risk. Additional investigation using explainable artificial intelligence techniques is needed to determine whether this is the case. Our results demonstrate that HPI text alone can predict ASA-PS well. We plan to include additional data in this prediction task as well to build on these results to predict additional elements of perioperative patient risk. The use of neural NLP for perioperative risk stratification based on naturally acquired medical language appears to be promising.

References: 1. ASA class is a reliable independent predictor of medical complications and mortality following surgery. International Journal of Surgery. 2015;18:184-190 2. Development and validation of a predictive model for American Society of Anesthesiologists Physical Status. BMC Health Serv Res. 2019;19(1):859

3. Publicly Available Clinical BERT Embeddings. arXiv:190403323 [cs]. http://arxiv.org/abs/1904.03323 4. Reliability of the American Society of Anesthesiologists physical status scale in clinical practice. Br J Anaesth. 2014;113(3):424-432

ASA Physical Status	Training Set	Test Set
I	1992 (7.8%)	224 (7.8%)
II	7824 (30.8%)	884 (31.0%)
III	11438 (45.0%)	1288 (45.2%)
IV	3953 (15.6%)	446 (15.6%)
V	166 (0.7%)	10 (0.4%)
VI	19 (0.1%)	0 (0%)
Total	**25392**	**2852**

Figure 1: Distribution of ASA Classes in training and test dataset prior to data augmentation.

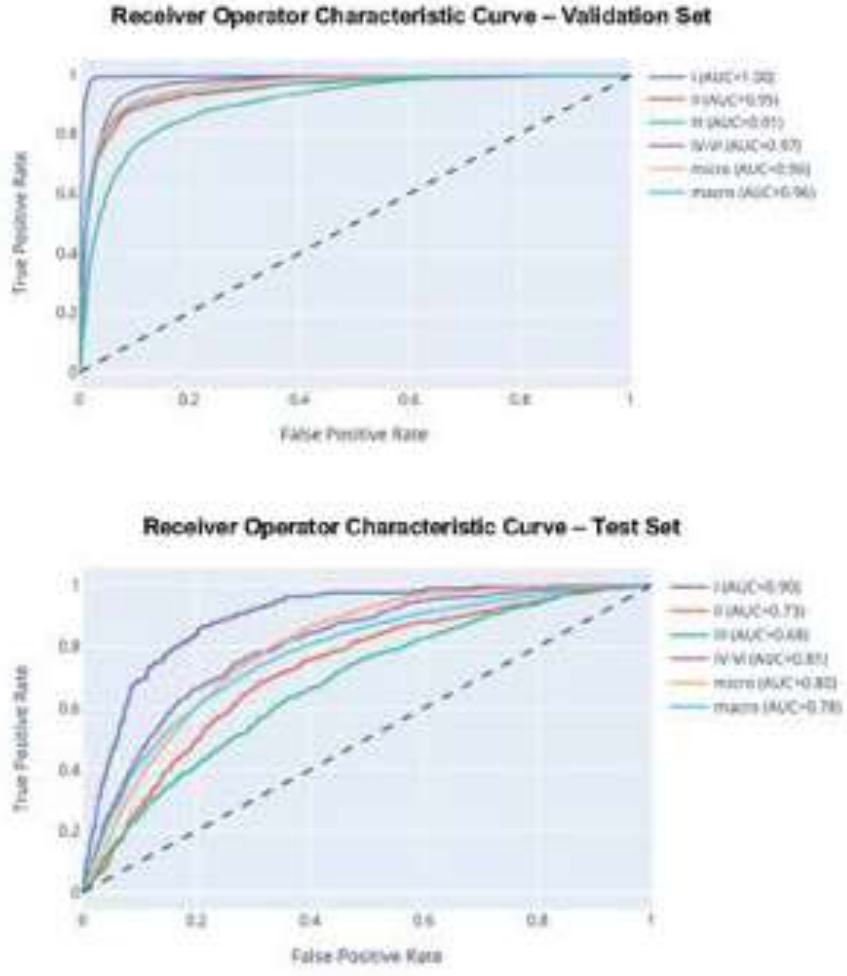

Figure 2: Receiver operator characteristic (ROC) curve for predicting each ASA-PS category in the validation set and test set. Also plotted is the micro-average and macro-average ROC across all classes. Area under ROC curve (AUC) is noted in the legend next to each class.

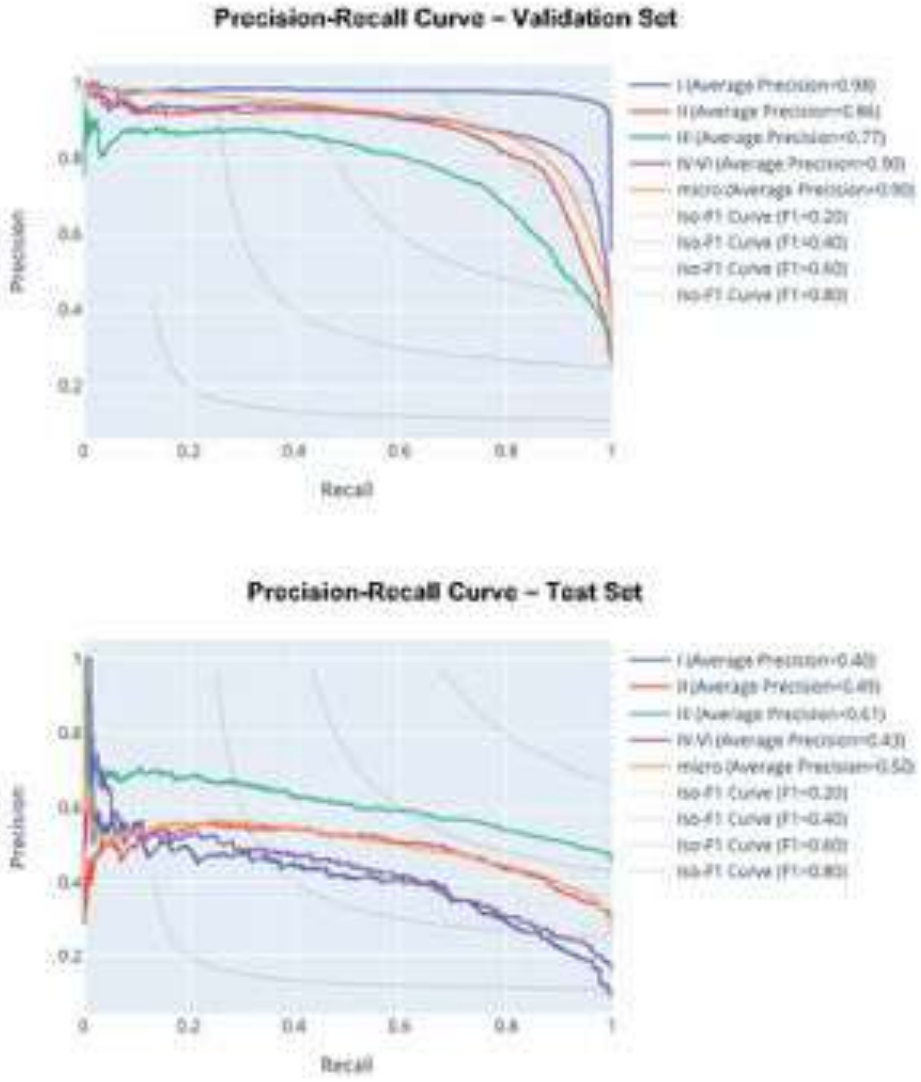

Figure 3: Precision-recall (PR) curve for predicting each ASA-PS category in the validation set and test set. Also plotted is the micro-average PR curve across all classes. Average precision is noted in the legend next to each class.

Confusion Matrix – Validation Set					
		True ASA-PS			
		I	**II**	**III**	**IV-VI**
Predicted ASA-PS	**I**	92.9%	0.6%	0.2%	0%
	II	6.1%	84.0%	15.7%	2.0%
	III	0.7%	13.6%	78.2%	18.8%
	IV-VI	0.3%	1.8%	5.9%	79.2%
	Total	*100%*	*100%*	*100%*	*100%*

Confusion Matrix – Test Set					
		True ASA-PS			
		I	**II**	**III**	**IV-VI**
Predicted ASA-PS	**I**	41.8%	12.1%	1.0%	0.3%
	II	48.7%	52.8%	24.4%	8.3%
	III	8.7%	32.0%	61.0%	50.7%
	IV-VI	0.8%	3.1%	13.6%	40.7%
	Total	*100%*	*100%*	*100%*	*100%*

Figure 4: Confusion Matrices for validation and test set with predicted ASA-PS normalized for each true ASA-PS class. Predictions are made by our fine-tuned model. Cells shaded in green represent correct predictions. Majority of incorrect classifications are a single ASA-PS class off from the true ASA-PS.

Perioperative Anesthesia - 9

Antidepressant Effect of Intraoperative Ketamine in Patients with Major Depression Undergoing Surgery: An Open-Label Pilot Study

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Introduction: Depression strongly predicts postoperative chronic pain[1], and optimizing this risk factor may improve outcomes. Ketamine is a well-investigated rapid-acting therapy for major depression[2], yet it is unclear whether ketamine is effective in reducing depressive symptoms when administered with other anesthetics during surgery. The purpose of this pilot study was to determine whether intravenous ketamine administered intraoperatively to clinically depressed patients undergoing joint replacement surgery is associated with reduced depressive symptoms postoperatively. We also explored whether intraoperative electroencephalogram (EEG) predicts ketamine response.

Methods: IRB approval was obtained for this open-label pilot study conducted at a tertiary academic medical center. Five patients with moderate-to-severe depression were recruited from an orthopedic surgery clinic. Each participant received intravenous ketamine (0.5 mg/kg administered over 40 minutes) with routine anesthesia during total joint replacement surgery. Montgomery-Asberg Depression Rating Scale (MADRS) was used to rate depression severity before and after surgery. Mean and standard deviations are described at each assessment time point. Power spectral density analysis of EEG data obtained from a commercially-available EEG monitor was used to identify the alpha peak frequency (APF) of each patient before and after ketamine administration. The association between MADRS and APF was assessed with simple linear regression.

Results: On average, there was a 40% decrease in MADRS scores from preoperative baseline to postoperative day 1 (mean=28.2 [SD=3.1] to mean=17.0 [SD=13.0]). This antidepressant effect was sustained at postoperative day 14 (52% decrease in MADRS, to mean=13.6 [SD=12.6]). Ketamine administration shifted the mean APF from 10.2 to 8.1 Hz. Individual shifts in APF predicted the decrease in MADRS scores.

Conclusion: Clinically depressed patients undergoing joint replacement surgery experienced reduced depressive symptoms after receiving ketamine intraoperatively, which correlated with EEG. This preliminary data from an uncontrolled open label study demonstrates feasibility for an appropriately powered randomized, placebo controlled trial.

References: 1. Depression and postoperative complications: an overview. BMC Surgery. 2016; 16:5.2. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychological Medicine. 2015; 45(4):693-704.

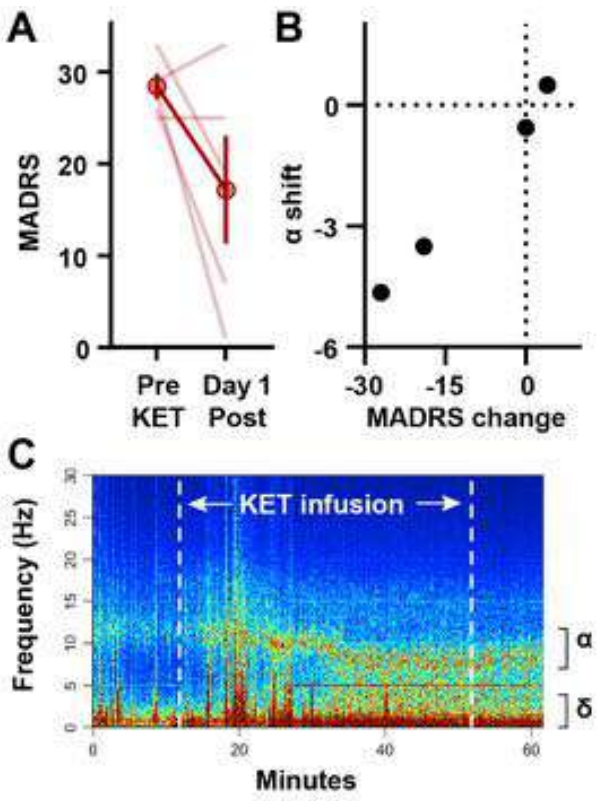

Fig. 1. A. Depression score (MADRS) pre and post ketamine. B. Shift in EEG alpha peak vs. MADRS change. C. Example density spectral array during ketamine + anesthesia

Perioperative Anesthesia - 10

Retrograde Amnestic Effect of Midazolam on Post-Operative Word Recall

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[1]University of Chicago Pritzker School of Medicine, Chicago, IL, [2]University of Chicago, Chicago, IL

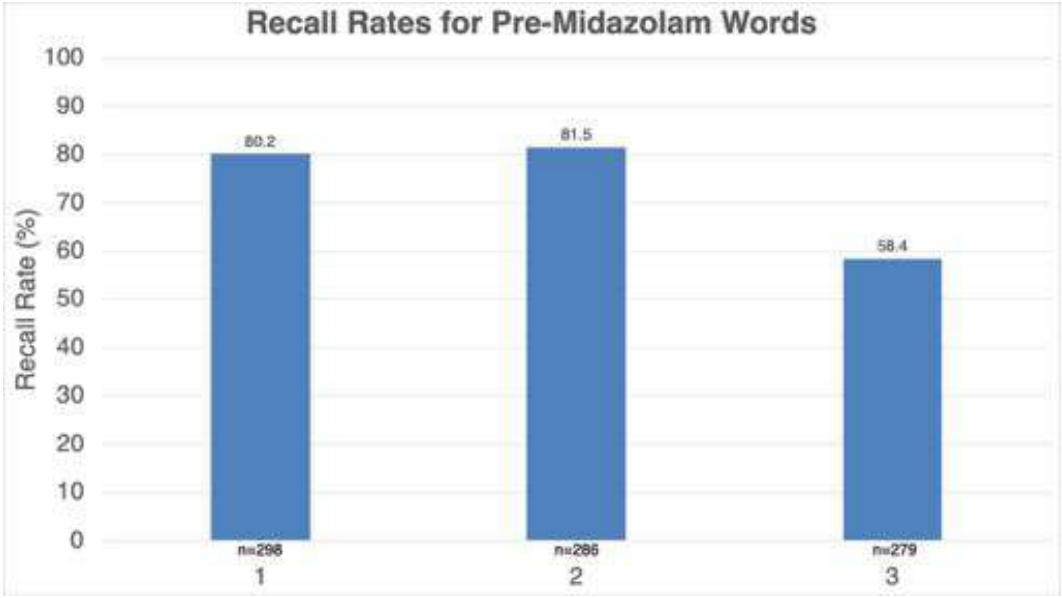
Introduction: Benzodiazepines, like midazolam, are commonly used as sedatives and anxiolytics in the perioperative setting. They are known to cause anterograde amnesia, but they are not classically associated with retrograde amnesia. There is, however, some limited research suggesting a possible retrograde amnestic effect for benzodiazepines in animals, and there are scattered case reports of retrograde amnestic effects of midazolam in the clinical setting. The current study demonstrates a statistically and clinically significant occurrence of retrograde amnesia in a series of patients given midazolam preoperatively as part of a clinical research study.

Methods: Following Institutional Review Board approval, a total of 363 patients undergoing general anesthesia for a surgical procedure consented to participate in this study. Each patient was given six equally memorable words preoperatively to remember. Words 1, 2, and 3 were given 5 minutes, 3 minutes, and 1 minute before administration of midazolam, respectively; word 4 was given during administration of midazolam; words 5 and 6 were given 1 minute and 3 minutes after the administration of midazolam, respectively. The words were given only once, and patients were asked to repeat each word to confirm that they heard it correctly. Following their operation, each patient was asked to recall the six words given to them before the operation. Which, if any, words each patient recalled post-operatively were recorded. Word recall rates for words 1, 2, and 3 (words given before administration of midazolam) were calculated and used for analysis in this study.

Results: Figure 1 shows the post-operative recall rates of words 1, 2, and 3. The number of patients used in analysis for word recall is shown under each bar and the y-axis designates the recall rate. Although all three words were given before administration of midazolam, there is a markedly diminished recall rate for word 3 compared to words 1 and 2 (where the recall rates were nearly identical). The recall rates for word 1 and 2 were 80.2% and 81.5%, respectively, while the recall rate for word 3 was only 58.4%. The difference in proportion of correct recall between words 1 and 3, as well as words 2 and 3, were both found to be statistically significant ($p<0.0001$). The difference in proportion of correct recall between words 1 and 2 was not statistically significant ($p=0.6974$).

Conclusion: Midazolam is a benzodiazepine that is known to cause anterograde amnesia. Our results suggest it also has a significant retrograde amnestic effect. Although words 2 and 3 are given only two minutes apart, that two-minute difference is enough to show an approximate 20% reduction in overall recall rate for patients in our study. This retrograde amnestic effect in the preoperative area could lead to a failure to recall important instructions or the considerations discussed in the process of informed consent. More studies are needed to more clearly delineate the timing and character of this retrograde amnestic effect.

References: Roth T, Roehrs T, Wittig R, Zorick F. Benzodiazepines and memory. Br J Clin Pharmacol. 1984; 18(Suppl 1):45S-49S. Mejo SL. Anterograde amnesia linked to benzodiazepines. Nurse Pract. 1992; 17(10):44, 49-50. Timi$\acute{f}$á T, Joksimovi$\acute{f}$á S, Mili$\acute{f}$á M, Divljakovi$\acute{f}$á J, Batini$\acute{f}$á B, Savi$\acute{f}$á MM. Midazolam impairs acquisition and retrieval, but not consolidation of reference memory in the Morris water maze. Behav Brain Res. 2013; 241:198-205. Semba K, Adachi N, Arai T. Facilitation of Serotonergic Activity and Amnesia in Rats Caused by Intravenous Anesthetics. Anesthesiol J Am Soc Anesthesiol. 2005; 102(3):616-623.


Recall Rates for Pre-Midazolam Words
Recall Rate (%)
100
90
80
70
60
50
40
30
20
10
0
80.2
81.5
58.4
n=298
n=286
n=279
1
2
3

Perioperative Anesthesia - 11

Association of a FDA Warning on Hydroxyethyl Starch solutions with Bleeding After Major Spine Surgery: Differences between Hospitals That Did Versus Did Not Switch to Albumin

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[1]Duke University School of Medicine, Durham, NC, [2]North Carolina State University, Raleigh, NC

Introduction: After the Food & Drug Administration (FDA) issued a 'black box' safety warning for the perioperative use of Hydroxyethyl Starch (HES) in June 2013, its usage in noncardiac surgery decreased in many US hospitals (Figure 1, top). Many hospitals that moved away from the use of HES switched to Albumin ('Albumin Switchers', AS), while others did not ('Crystalloid Switcher', CS) (Figure 1, bottom). Albumin usage has been associated with smaller transfusion volumes in sepsis. We tested the hypothesis that patients undergoing major spine surgery where significant blood loss can occur, transfusion and bleeding would be decreased in the AS hospitals more than in the CS hospitals.

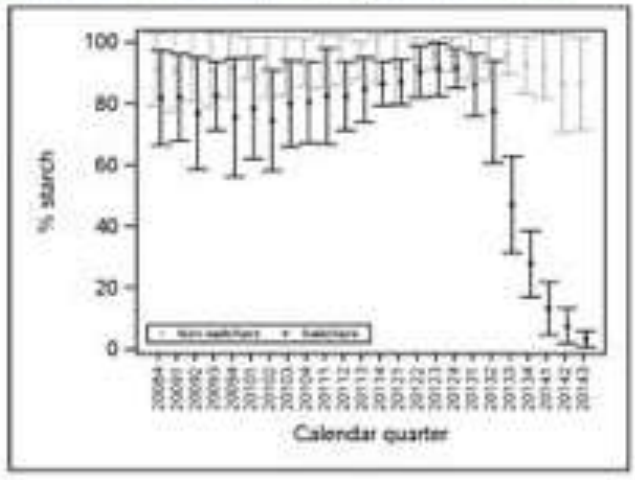
Methods: Approval was obtained from the IRB at Duke University Health System. The study population consisted of patients undergoing major spine surgeries between July 2012 and June 2014. Data was obtained from surgery (ICD9 Codes, 81.08, 81.07, 81.06, 81.02) in hospitals who contribute to Premier Healthcare Database (PHD), a de-identified administrative and financial dataset, between July 2012 and June 2014. Only hospitals who perform at least ≥ 50 such procedures every quarter were included. The exposures were treatment in either the year pre-warning or the year post-warning, within AS or within CS hospitals. The outcome was a composite of either bleeding (defined by ICD diagnosis codes 998.11 or 998.12) or transfusions (identified by ICD Procedure code 99.1 and by Charge Codes). Information on baseline covariates that were extracted from PHD included socio-demographics, comorbidities (defined using Elixhauser's ICD9 code-based algorithms), and various cotreatments. Standardized Mean Differences (SMDs in means or proportions) were computed for over 80 covariates between patients treated pre- versus post-warning within a) AS hospitals and b) within CS hospitals. Propensity scores were computed as the probability of treatment pre- versus post-warning (Standardized Mortality Ratio-weighting). SMDs were also computed between patients treated in AS versus in CS hospitals, and propensities computed as the probability of treatment in either type of hospital. Propensity density plots were examined (Figure 2). Using Segmented Regression of Interrupted Time Series analysis, we estimated risk-adjusted differences in outcomes pre-versus post-warning within AS (difference 1), and within CS (difference 2). The difference-in-differences (DiD) was calculated as difference 1 minus difference 2. This represents the change in outcomes attributable to the change in fluid choice after the FDA-warning, adjusted for differences in patient attributes and temporal trends.

Results: Of the 79 'switcher' hospitals where 5,965 patients underwent major spine surgery between July 2012 and June 2014, 29 were AS hospitals where 3,937 patients were treated (1,426 pre-warning versus 2,511 post-warning), and 50 were CS hospitals where 2,028 patients were treated (1,313 pre-warning versus 715 post-warning). Based on average SMDs <|0.1|, and on common support (overlap) in propensity density plots (Figures 2 and 3), confounding was less likely when comparing patients treated pre- versus post-warning within AS and within CS hospitals, but not when comparing patients treated in AS versus CS hospitals as a whole. Focusing on pre- versus post-warning differences, in unadjusted analyses, we observed a decrease in the outcome within the AS hospitals versus an absolute reduction of 1.9% or 38% in relative terms regarding bleeding / transfusions (increase within CS hospitals, Table 1). In propensity adjusted segmented regression analysis, the DiD estimate corresponded to a 72% reduction (95%CI, 1%-92% reduction) in the risk of the outcome in AS hospitals, when compared to CS hospitals (relative risk 0.28, 95% CI 0.08 - 0.99, p<0.05).

Conclusion: A 2013 FDA warning on HES solutions was followed by a significant decrease in the perioperative use of HES on the day of major spine surgeries in 79 US hospitals. In risk-adjusted analyses, we observed a statistically significant decrease in the proportion of patients with either bleeding or need for transfusions in the 29 hospitals that had 'switched' from HES to Albumin, when compared to the 50 hospitals that had not. Further research is needed to understand how FDA warnings impact upon clinical practice and future patient outcomes.

References: 1. Krishnamoorthy V, Ellis AR, McLean DJ, et al. Bleeding After Musculoskeletal Surgery in Hospitals That Switched From Hydroxyethyl Starch to Albumin Following a Food and Drug Administration Warning. Anesth Analg. 2020;131(4):1193-1200. 2. Tseng C-H, Chen T-T, Wu M-Y, Chan M-C, Shih M-C, Tu Y-K. Resuscitation fluid types in sepsis, surgical, and trauma patients: a systematic review and sequential network meta-analyses. Crit Care. 2020;24(1):693. 3. Tse EYW, Cheung WY, Ng KFJ, Luk KDK. Reducing Perioperative Blood Loss and Allogeneic Blood Transfusion in Patients Undergoing Major Spine Surgery. JBJS. 2011;93(13):1268.

Figure 1: Perioperative Use of HES declined drastically after the FDA warning in 79 US hospitals conducting at least 50 major spine procedures every quarter between July 2012 and June 2014 (top panel). Among these 79 hospitals, the use of albumin increased rapidly in 29 AS hospitals (black bars) but not in 50 CS hospitals (grey bars), bottom panel



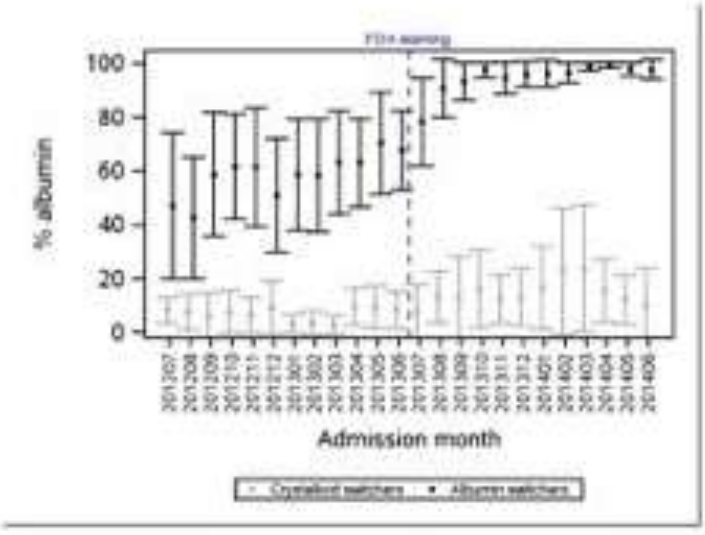


Figure 2: Propensity density plots. There is significant overlap (top panels) where the propensity is the probability of treatment pre- versus post-warming (AS hospitals top left and CS hospitals top right). This suggests that patients are, on average, comparable pre- versus post-warming within AS and CS hospitals, in contrast, in the bottom panel the propensity is the probability of treatment in AS versus CS hospitals. The figure suggests that patients are, on average, less comparable when contrasted across AS versus CS hospitals.

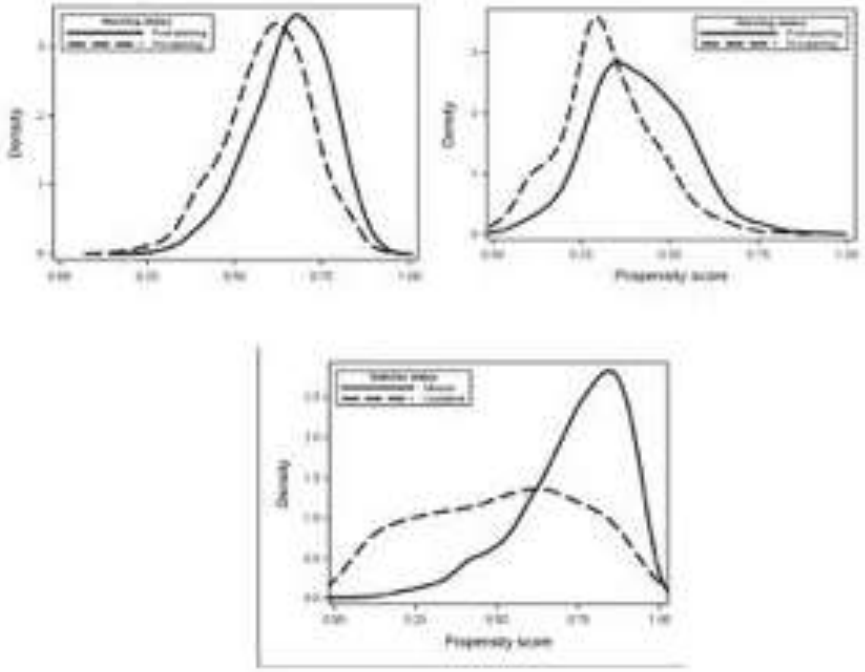
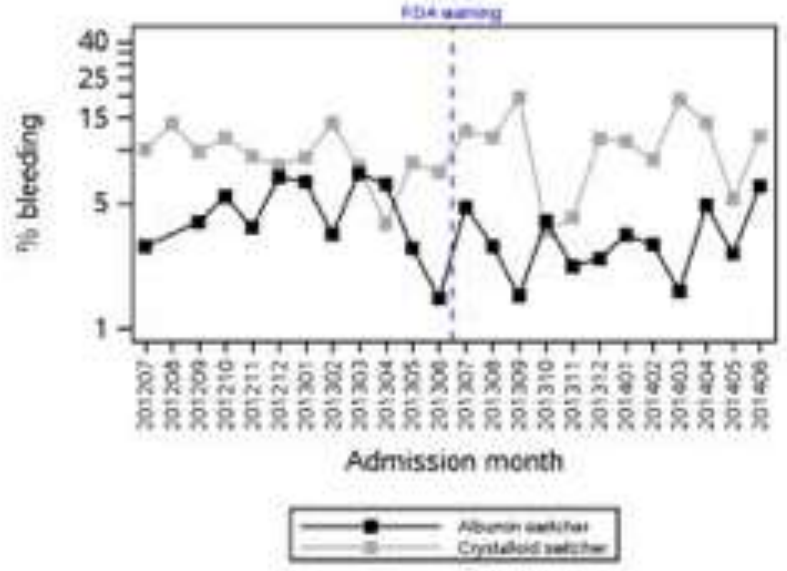


Figure 3: SMDs in Socio-demographics, Co-morbidities, and Co-treatment characteristics across: a) patients in AS pre- versus post- warning, unadjusted (open triangles) and propensity score adjusted (filled triangles) b) patients in CS pre- versus post- warning, unadjusted (open circles) and propensity score adjusted (filled circles), and c) patients treated in AS versus CS over the entire time period, unadjusted (open squares) and propensity score adjusted (filled squares)

Table 1: Number of patients - overall and bleeding - in AS and CS hospitals, Pre- and Post-Warning

	Total Patients	Bleeding	Proportions	Differences	DinD
Albumin Pre	1426	60	4.2%	Difference 1 = Absolute Decrease in Bleeding of 0.9%	D2 minus D1 = 1.9% absolute difference in rate of bleeding (equivalent to a relative reduction of 36% in AS)
Albumin Post	2511	83	3.3%		
Crystalloid Pre	1313	126	9.6%	Difference 2 = Absolute Increase in Bleeding of 1%	
Crystalloid Post	715	76	10.6%		

Figure 4: Changes over time in the proportion of patients with bleeding in AS and CS groups through the study period



Perioperative Anesthesia - 12 Evaluating Subjective Cognitive Complaint and Informant-Reported Questionnaires Used for Subjective Cognitive Decline Screening in Older Adults: A Systematic Review

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Introduction: A spectrum of cognitive impairment exists, starting with subjective cognitive decline (SCD), followed by mild cognitive impairment (MCI) and dementia.[1] SCD may represent at-risk persons progressing to MCI. Screening for SCD is advantageous due to easy administration and low cost.[2] The objective of this systematic review is to identify the most common subjective and informant-reported individual questions in subjective cognitive complaint and informant-reported questionnaires used to assess cognitive impairment of elderly patients that are also correlated with standardized tests.

Methods: We searched Medline, PubMed, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database, Emcare Nursing, Web of Science, Scopus, CINAHL, ClinicalTrials.Gov, and ICTRP between January 1, 2010 to August 31, 2020. The search process followed the PRISMA guideline. We included studies that evaluated subjective cognitive complaints and informant-reported questions in patients aged 50 years old or more. Data on validation and prevalence were extracted for the SCC questionnaire as a whole as well as for each individual question. Questions are grouped under the six domains of cognitive function described by the Neurocognitive Work Group which include: complex attention, executive function, learning and memory, language, perceptual–motor function, and social cognition.

Results: A total of 28,407 patients were included from 22 studies that assessed 21 subjective complaint questionnaires and nine informant-reported questionnaires. The most common subjective cognitive complaints were those assessing learning and memory, specifically, anterograde memory. This was closely followed by spatial orientation and executive function (Table 1). The most common informant-reported questions were those assessing executive function, temporal orientation, and learning and memory. Fifteen articles included questionnaires assessing learning and memory. Of these, seven showed a positive association between the subjective/informant-reported questions related to anterograde memory and cognitive measure tests.

Conclusion: Questions assessing learning and memory were most associated with results from standardized tests assessing cognitive impairment. Study results are consistent with the fact that Alzheimer's disease and amnestic MCI are defined by deficits in memory, and that these conditions make up the majority of dementia and MCI cases among elderly patients.[3] Therefore, assessing learning and memory plays a key role in evaluating SCD in elderly patients. Thus, the results from this review contribute to knowledge for perioperative healthcare professionals regarding the use of subjective cognitive complaints and informant-reported complaints for SCD screening in busy clinic settings.

References: 1. Alzheimer's Dement. 2014, 10, 844–852. 2. J. Alzheimer's Dis. 2015, 48, S63–S86. 3. Neurology 1992, 42, 115–119.

Table 1. Most Common Questions.

Neurocognitive Domain	Learning and Memory						Perceptual-Motor Function	Executive Function	Language	Complex Attention
Question Category	Anterograde memory (e.g. do you/does the patient have difficulty remembering things that have happened recently?)	Ability to remember and/or keep appointments (e.g. do you/does the patient have trouble remembering appointments?)	Forgetfulness of common objects (e.g. do you/does the patient lose objects more often that you did previously?)	Temporal orientation (e.g. do you/does the patient have trouble remembering the time/date?)	Comparing own memory to others of similar age (e.g. do you/does the patient think that your memory is poorer than that of other people your age?)	Remembering routine tasks (e.g. do you/does the patient have trouble remembering how to turn off the stove or lights?)	Spatial orientation (e.g. do you/does the patient have trouble finding your way around familiar streets?)	Executive function (e.g. do you/does the patient have trouble working household appliances?)	Language (e.g. do you/does the patient have trouble finding the right word to describe something you know well?)	Ability to follow a conversation (e.g. do you/does the patient have trouble following TV program or a book?)
Number of Studies (SCC)	11	9	7	5	4	4	9	7	6	6
Number of Studies (Informant-report questions)	4	2	0	5	0	0	1	6	2	3

Perioperative Anesthesia - 13

Neuromuscular Blockade Usage and Reversal Trends in U.S. Inpatients

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Introduction: As an important component of general anesthesia, whose use may vary by patient and procedural characteristics, neuromuscular blockade (NMB) utilization patterns have changed in recent years in the U.S. We sought to describe how clinical characteristics among those receiving NMB and NMB reversal agents have changed in the inpatient setting since the U.S. introduction of sugammadex (December 2015).

Methods: A retrospective longitudinal analysis of a large all-payer national electronic healthcare database (Premier Healthcare Database, PHD) assessed U.S. adult inpatients who received rocuronium and/or vecuronium (without renal failure, myasthenia gravis or pyridostigmine therapy) between January 2014 and June 2019.

Results: Approximately 4.3 million adults undergoing inpatient procedures received rocuronium or vecuronium (+/- succinylcholine) overall, the vast majority of whom were given rocuronium alone (86.0%), or in combination with succinylcholine (4.8%). Trends show modest increases in the use of rocuronium alone compared to decreases in combination with succinylcholine between 2016 and 2019 (Figure 1). Between 2014 and 2016, almost two-thirds of inpatients were reversed with neostigmine, and just over one-third were not actively pharmacologically reversed (ie. spontaneous reversal). Since then, both the use of neostigmine and spontaneous reversal have decreased over time, reaching lows of 38.3% and 27.6%, respectively, with NMB reversal with sugammadex reaching 34.2% by June 2019 (Figure 2). On average, patients were 58.2 years old, more often women (55.3%), the majority were white (78.4%), non-Hispanic (93%), and undergoing a musculoskeletal (37.2%) or digestive (29.1%) procedure. Overall, the proportion of elderly among the study population increased in later years; in concurrent years, those reversed with sugammadex tended to more often be older than the neostigmine population and younger than those spontaneously reversed (Figure 3). Over time, overall, and within each NMB reversal group, the proportion of patients with any comorbidities increased, as did most individual comorbidities (Figure 4). Generally, those spontaneously reversed and reversed with neostigmine tended to most, and least often have comorbidities, respectively.

Conclusion: In a large population of US adult inpatients administered NMBs, we observed an increase in age, number and frequency of comorbidities, and an increase in pharmacologic reversal compared to spontaneous reversal between 2014 and 2019. Additional research to understand how these NMB treatment patterns continue to change in light of the increasing efforts to expand capacity and shift patient care out of the inpatient hospital setting, accompanying the unprecedented burden on the US healthcare systems in 2020 is warranted.

Figure 1: *NMB with rocuronium alone rises, other combinations decline*

Figure 2: *Spontaneous NMB and Neostigmine Use Decline with Introduction of Sugammadex*

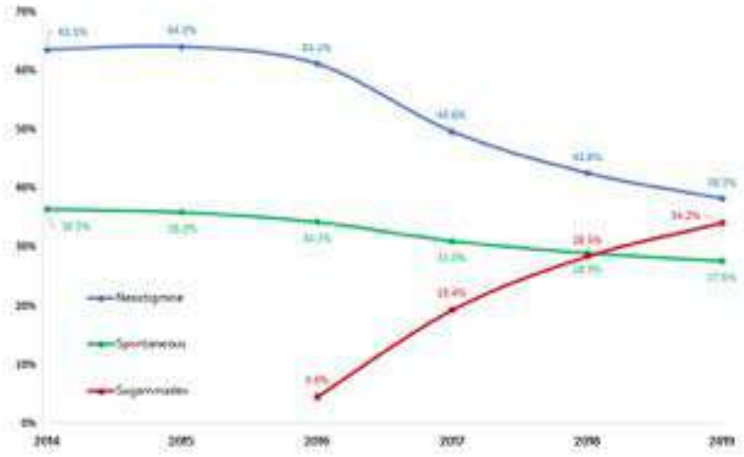


Figure 3: *Population Ages Over Time and Across All NMBRA Types*

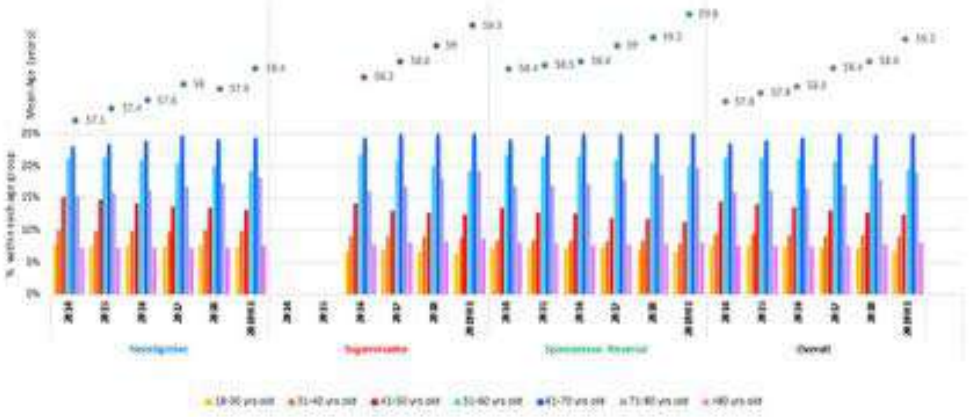
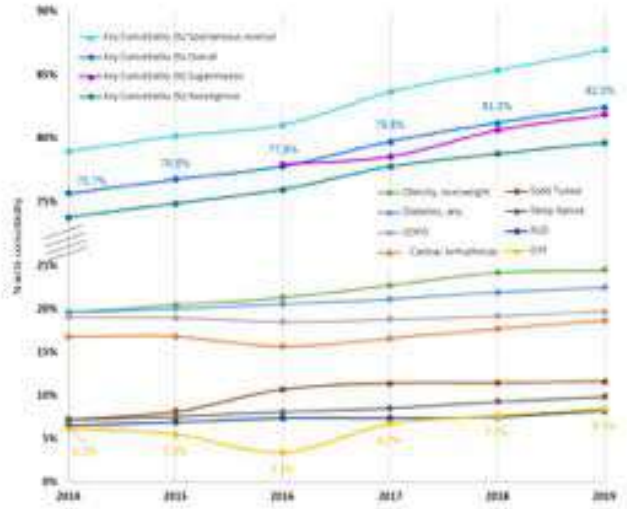


Figure 4: *Comorbidities Increase Over Time and Across All NMB Reversal Types*



Perioperative Anesthesia - 14 Patient and Procedural Characteristics Associated with Neuromuscular Blockade Reversal Choices in the U.S. Inpatient Setting

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Introduction: Patient, provider, and environmental factors impact patient care. As an important component of general anesthesia, whose use is also impacted by budgetary pressures, we sought to understand factors impacting the use of neuromuscular blockade (NMB) reversal agents in inpatients since the U.S. introduction of sugammadex (December 2015).

Methods: A retrospective longitudinal analysis of a large all-payer national electronic healthcare database (Premier Healthcare Database, PHD) assessed U.S. adult inpatients using rocuronium and/or vecuronium (without renal failure, myasthenia gravis or pyridostigmine therapy) between January 2014 and June 2019. Multivariable logistic regression assessed the independent association of patient, site and procedural characteristics with NMB reversal choice (active vs. spontaneous 2014-2019, and neostigmine vs. sugammadex 2016-2019).

Results: Approximately 4.3 million inpatients, across 909 sites, received rocuronium or vecuronium (+/- succinylcholine). Between 2014 and 2016, about two thirds were reversed with neostigmine and one third spontaneously reversed. Since then, the frequency of both have decreased, while the use of sugammadex increased to 34.2% and active reversals overall, reaching 73%, by June 2019. The most common types of procedures were musculoskeletal (35.9%), digestive (28.5%) and cardiovascular (12.2%). NMB reversal choice varied by procedure type with cardiovascular procedures being most often spontaneously reversed, and digestive procedures most often actively reversed (Figure 1). Patients with comorbidities were also actively reversed less frequently than the overall population; patients with cardiovascular comorbidities were actively reversed the least often (Figure 2). Multivariable analyses showed time to have a strong, positive independent association with patients' likelihood to be pharmacologically reversed between 2014 and 2019, as well as a patients' likelihood to be reversed with sugammadex compared to neostigmine among those actively reversed between 2016 and 2019. Several other patient, site and procedural characteristics were associated with NMB reversal choice independent of time, NMB agent, and each other. While the associations of patient and procedural characteristics including age and comorbidities were more pronounced when comparing choice of active vs. spontaneous reversal, the independent associations of time, race, ethnicity, and geographic region were more pronounced on choice of reversal agent (sugammadex vs. neostigmine) .

Conclusion: Among U.S. adult inpatients administered NMBs, we observed complex relationships between patient, site, regional, procedural characteristics and NMB management choices. Observations suggest that patient and procedural characteristics are important factors in NMB reversal choices in whether a patient is pharmacologically reversed, while external factors may be more influential in impacting choice of pharmacological reversal agent when a patient is actively reversed. Additional research to understand how these associations may continue to shift with increasing economic pressures on the U.S. healthcare system is warranted.

Figure 1: *NMB Reversal Choice Varies by Type of Procedure*

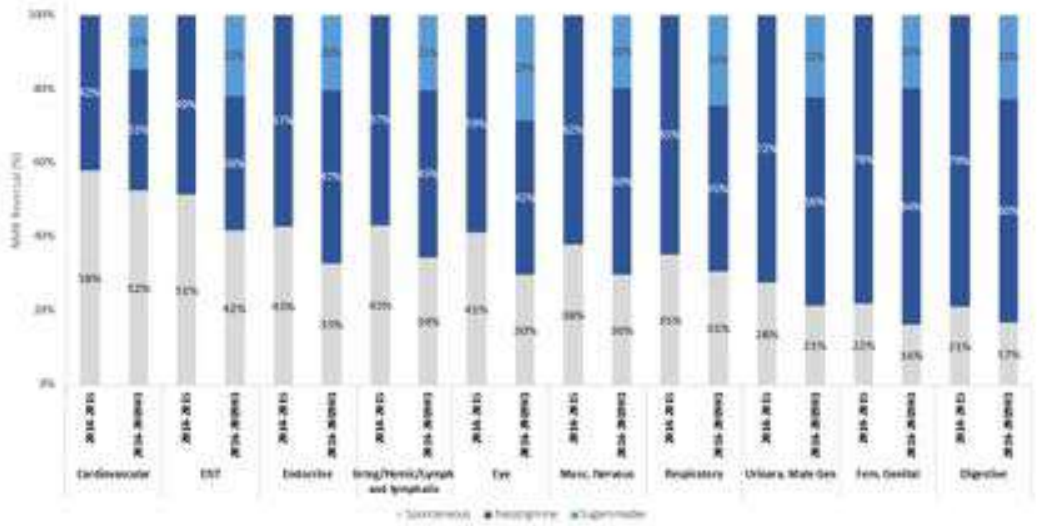
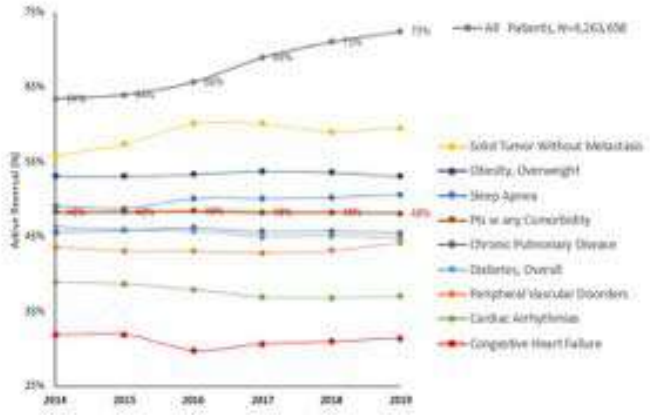


Figure 2: *Patients with Comorbidities are less often actively reversed*



Perioperative Anesthesia - 15

Anesthesia and the gut microbiome: exploring the effects of isoflurane, propofol, and supplemental oxygen in a murine model of general anesthesia

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Introduction: Derangements in the composition and/or function of the intestinal microbiota, a state known as microbial dysbiosis, have been shown to alter local and systemic immune responses rendering the host more susceptible to infection. The gut microbiome provides crucial molecular cues directly through microbial surface antigens, and indirectly by regulation of biochemical pathways and the synthesis of metabolites which in turn influence innate and adaptive responses essential to host immunity. For example, gut-derived short chain fatty acids exert anti-inflammatory properties by strengthening gut mucosal integrity and promoting T-reg differentiation, and amino acids like arginine contribute to macrophage and T-cell activation[1]. Thus far, however, little is known about the effects of anesthetic practices on the gut microbiome and related metabolites, largely due to a paucity of investigations. We have shown in a previous study that after four hours of general anesthesia with isoflurane, the composition of the murine intestinal microbiome is altered up to seven days after exposure[2]. However, the contribution of inhaled oxygen to these alterations, and whether these findings extended to intravenous anesthetics, remains incompletely understood. Moreover, whether the effects of anesthetics on the gut microbiome also confer changes in microbial-mediated metabolites has been unexplored altogether. We hypothesized that practices commonly employed in the operating room – such as the administration of supplemental oxygen as well as inhaled and intravenous anesthetics – result in distinct changes in the gut microbial environment and are accompanied by derangements in microbial-mediated metabolites. To this end, we used a multi-omics approach including 16s rRNA sequencing and untargeted metabolomics in a mouse model to explore how brief exposure to 100% oxygen, isoflurane, and propofol separately affect the gut microbiota and associated metabolites.

Methods: Briefly, 12-14 week-old C57/BL6 cagemates were exposed to one of four interventions (n=8 per group): 100% oxygen, 1.5% isoflurane in 100% oxygen, intravenous propofol infusion (equivalent to 200ug/kg/hr), and intravenous intralipid. Fecal samples were collected immediately prior to exposure, and at 3 and 7 days after. At each time point, samples from each mouse were divided and sent for both 16s rRNA sequencing to generate taxonomic profiles, and untargeted metabolomics by gas chromatography-mass spectrometry (GC-MS) for identification of fecal metabolites. We then analyzed the changes over time in taxonomic profiles to species-level resolution, and metabolic products, both within each exposure type and between groups. Finally, we used multivariate analyses to identify significant associations between microbial species and specific metabolites. Comparisons were made between exposure to isoflurane and oxygen, propofol and intralipid, and isoflurane and propofol.

Results: We found that both exposure to oxygen and isoflurane resulted in specific, and sometimes opposing, alterations in the composition of the gut microbiota. Differences were particularly notable in the abundances of several species belonging to the genera Lachnospiraceae and Ruminococcaceae (Clostridiales order) which have been implicated in host immune responses and short-chain fatty acid production. While exposure to oxygen alone increased the abundance of these taxa in day 3 and day 7, these populations declined significantly in the isoflurane group. In contrast, propofol and intralipid yielded significantly different effects on other members of the Clostridiales order: taxa from the genera Peptococcus and Hespellia increased in abundance at day 7 after intralipid, but decreased after propofol. We also found that different exposures resulted in characteristic alterations in metabolic pathways. For example, exposure to isoflurane was associated with significant increases in the concentration of argininate and arginine when compared to oxygen and propofol. Finally, we discovered over 30 significant, microbiome-

metabolite pairs in our multivariate analysis and identified distinct metabolic changes that are a result of both exposure-specific as well as microbiota-specific interactions.

Conclusion: The present study confirmed that multiple therapies routinely used during the provision of general anesthesia are associated with significant alterations in the gut microbiota and their metabolites, and have the potential to shape key immune responses.

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Perioperative Anesthesia - 16 Predictive Analytics for Inpatient Postoperative Opioid Use in Patients Undergoing Mastectomy

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Introduction: The use of opioids in patients undergoing mastectomy is a particular challenge, having to balance the management of acute pain while minimizing risks of continuous opioid use postoperatively. The goal of this study is to identify risk factors and to develop machine-learning based models to predict patients who are at higher risk for acute postoperative opioid use after mastectomy. The ability to predict patients' postoperative pain could have significant impact on preoperative counseling and patient satisfaction. Additionally, the predictive ability may direct different pain management techniques perioperatively (i.e. intercostal cryoanalgesia or two-level paravertebral catheters) [1-3].

Methods: In this retrospective cohort study, we collected data from all patients that underwent mastectomy procedure from either of two surgeons from 2019 to 2020. The primary outcome of interest was binary and defined as oxycodone milligram equivalents (OME) greater than or equal to the 75% of OME use on postoperative day 1. We included a number of surgical and patient characteristics as independent variables. We performed multivariable logistic regression, lasso, ridge regression, and elastic net regression to develop predictive models. Model performance (area under the receiver operating characteristics curve [AUC]) was calculated via 10-fold cross-validation. Odds ratio (OR) and 95% confidence intervals (CI) were reported for significant predictors.

Results: There was a total of 148 patients that underwent mastectomy included in our final analysis. The medium [quartiles] postoperative day 1 opioid use was 5mg OME [0, 25mg OME] with a range from 0mg to 211.2mg OME. We separated the population into two cohorts, one with less than the third quartile of OME (25mg OME) and another with ≥ third quartile (n = 38). Table 1 lists the patient characteristics in both cohorts. On crude analysis, the only covariate that was statistically significantly different in both cohorts was whether patient was post-menopausal (42.7% vs. 21.1% in the lower versus higher opioid use cohorts, respectively, p = 0.03). We performed a multivariable logistic regression model with variable selection in order to identify specific covariates associated with opioid use and to develop a predictive model. From this model (Table 2), the most protective factors against higher opioid use was being post-menopausal (OR 0.13, 95% CI 0.03 – 0.61, p = 0.009) and cancer diagnosis (OR 0.19, 95% CI 0.05 – 0.73, p = 0.01). The predictive model had an AUC of 0.777 (95% CI 0.699 – 0.855) and the HL-test demonstrated adequate goodness-of-fit (p=0.59) (Figure 1). On 10-fold cross-validation, the average AUC was 0.725 (95% CI 0.572, 0.876). Compared to our reference model, there were no statistically significant differences between AUCs among each model: multivariable logistic regression including all variables (p=0.92), ridge regression (p=0.39), lasso (p=0.22), and elastic net regression (p=0.15).

Conclusion: We developed a predictive model to identify patients who are at high risk for higher acute opioid use after mastectomy. Using different machine learning approaches, we found that logistic regression performed just as well as other methodologies. The model had excellent discrimination and included predictors such as post-menopausal, age, race, bilateral surgery, mastectomy with tissue expander placement, cancer diagnosis, depression, substance abuse history, smoking, hypertension, and asthma. Post-menopausal woman and those with a cancer diagnosis had less odds for requiring higher amounts of opioids in the acute setting. While debated, some studies have shown that post-menopausal women have higher pain tolerance while others have shown lower sensitivity to analgesics [4-5]. Women who choose prophylactic mastectomy over breast conserving treatment have higher rates of psychological distress (anxiety, depression, and pain catastrophizing) which is associated with higher postoperative pain levels [6-7]. Cancer diagnosis as a protective factor may in part be due to higher rates of resilience among this group and the association between resilience and decreased risk of high intensity

acute post-operative and chronic pain [6]. Additional research is necessary to determine an appropriate methodology to apply this model in clinical settings and determine the most effective preventative measures to reduce opioid use among high-risk patients.

References: [1] Percutaneous peripheral nerve stimulation and other alternatives for perineural catheters for postoperative analgesia. 2019;33:37-46. [2] Two-Level Continuous Thoracic Paravertebral Nerve Blocks Providing Opioid-Free Postoperative Analgesia After Latissimus Dorsi Flap Breast Reconstruction: A Case Report. 2018;11:118-120. [3] Ultrasound-guided percutaneous intercostal cryoanalgesia for multiple weeks of analgesia following mastectomy: A case series. 2020;73:163-168. [4] Comparison of experimental and acute clinical pain responses in humans as pain phenotypes. 2004;5:377-384. [5] Gender and age influences on human brain mu-opioid receptor binding measured by PET. 1999;156:842-848. [6] Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: A population-based cohort study. 2014;155:232-243. [7] Influences on decision-making for young women undergoing bilateral prophylactic mastectomy. 2018;101:318-323.

	OME <75% quartile		OME ≥75% quartile		
	n	%	n	%	p-value
Total	110		38		
Mastectomy Surgery					
Node Dissection Involvement	40	36.4	12	31.6	0.74
Tissue Expander Placement	21	19.1	9	23.7	0.71
Bilateral Surgery	58	52.7	22	57.9	0.72
Cancer Diagnosis	83	75.5	23	60.5	0.12
Age (years), mean [SD]	45.5 [17.1]		40.5 [13.1]		0.06
Male Sex	11	10.0	3	7.9	0.95
BMI ≥ 35kg/m2	11	10.0	2	5.3	0.58
White Race	61	55.5	26	68.4	0.23
Non-English speaker	21	19.1	4	10.5	0.34
Transgender	24	21.8	11	28.9	0.51
Post-menopausal	47	42.7	8	21.1	0.03
ASA Physical Status Score					0.25
1	13	11.8	7	18.4	
2	46	41.8	19	50.0	
3	51	46.4	12	31.6	
Active Smoker	1	0.9	2	5.3	0.33
Active Alcohol Use	43	39.1	19	50.0	0.32
Chronic Opioid Use	0	0.0	2	5.3	0.11
Illicit Drug Use	1	0.9	1	2.6	0.99
Marijuana Use	6	5.5	5	13.2	0.23
Preoperative Vital Signs					
Systolic Blood Pressure	116.5 [17.3]		112.6 [14.1]		0.19
Heart Rate	77.1 [14.2]		73.5 [11.6]		0.13
Comorbidities					
Diabetes Mellitus	6	5.5	1	2.6	0.79
Chronic Kidney Disease	4	3.6	0	0.0	0.54
Obstructive Sleep Apnea	5	4.5	3	7.9	0.71
Depression	30	27.3	6	15.8	0.23
Anxiety	24	21.8	9	23.7	0.99
ADHD	3	2.7	3	7.9	0.36
Fibromyalgia	2	1.8	2	5.3	0.58
Hypertension	29	26.4	4	10.5	0.07
COPD	1	0.9	1	2.6	0.99
Asthma	16	14.5	2	5.3	0.22
Congestive Heart Failure	0	0.0	0	0.0	0.99
Coronary Artery Disease	1	0.9	0	0.0	0.99

Table 1. Patient characteristics of the two study cohorts. Abbreviations: ADHD = attention-deficity hyperactive disorder, OME = oxycodone milligram equivalents; SD = standard deviation

	OR (95% CI)	p-value
Post-menopausal	0.13 (0.03 - 0.61)	0.009
Age (years)	1.04 (0.99 - 1.09)	0.12
Mastectomy with Tissue Expander Placement	2.12 (0.73 - 6.17)	0.17
Bilateral Surgery	0.36 (0.11 - 1.17)	0.09
Cancer Diagnosis	0.19 (0.05 - 0.73)	0.01
White Race	2.95 (1.17 - 7.42)	0.02
Depression	0.31 (0.09 - 1.07)	0.06
Substance Abuse History	16.11 (0.66 - 391.8)	0.09
Active Smoker	30.99 (1.36 - 703.6)	0.03
Hypertension	0.28 (0.06 - 1.20)	0.09
Asthma	0.19 (0.03 - 1.09)	0.06

Table 2. Results of the multivariable logistic regression, in which the outcome was oxycodone equivalents ≥ 75% quartile on postoperative day 1. The final model was developed by a combination of forward selection and backwards elimination based on the Akaike Information Criterion. Only covariates with p<0.2 were allowed to stay in the final model. Abbreviations: CI= confidence interval, OR = odds ratio

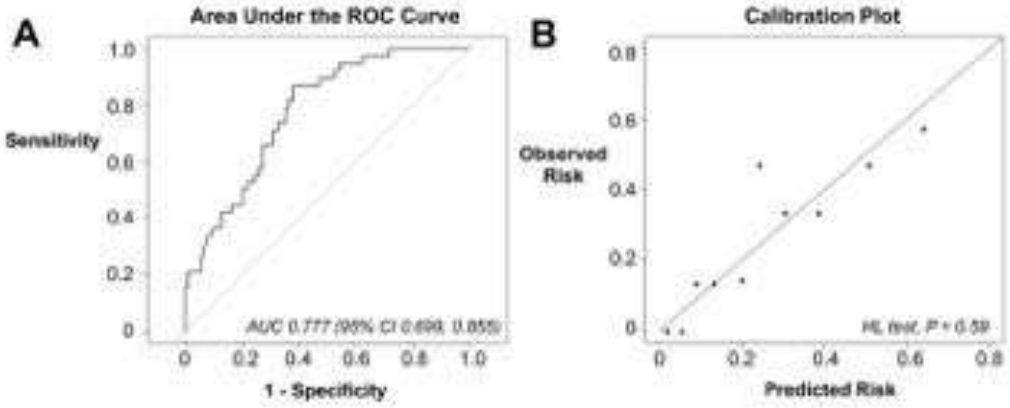

Figure 1. Performance of the multivariable logistic regression with variable selection predicting patients at risk for higher acute opioid use on postoperative day 1. A) area under the receiver operating characteristics curve and B) calibration plot illustration goodness-of-fit. Abbreviations: AUC = area under the receiver operating characteristics curve, CI = confidence interval, HL = Hosmer-Lemeshow, ROC = receiver operating characteristics

Perioperative Anesthesia - 17

Comparison of visual and electromyography assessments in response to train-of-four stimulation

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Introduction: Neuromuscular blocking agents (NMBAs) are a class of medications routinely used during anesthesia to facilitate endotracheal intubation and optimize surgical conditions. However, these medications are also associated with respiratory complications in the early postoperative period due to residual neuromuscular blockade (RNMB)(1-3). Even when neuromuscular blockade is reversed in the operating room, postoperative RNMB continues to be a common problem in the post-anesthesia care unit (PACU), and a significant number of patients have objective evidence of muscle weakness. The use of quantitative monitoring was shown to reliably reduce the incidence of postoperative residual weakness and ensuing complications. Many clinicians default to the antiquated and unreliable practice of subjective monitoring, which includes visual or tactile evaluation of the train-of-four (TOF) in response to neurostimulation provided by peripheral nerve stimulation. The aim of this study is to correlate electromyographic responses of the adductor pollicis muscle obtained with the TetraGraph (Senzime AB, Uppsala, Sweden) monitor with visual (subjective) assessment of the thumb movement, throughout various stages of neuromuscular blockade.

Methods: After IRB approval, 20 adult patients scheduled for elective surgery requiring neuromuscular blockade were screened and enrolled after giving written informed consent. Intraoperative NMBA management and antagonism was at the discretion of the anesthesiologist. Prior to induction of anesthesia, Tetragraph electrodes were placed over the ulnar nerve and the thumb randomly assigned to their dominant or non-dominant hand. Anesthesia providers were blinded to the TetraGraph values during the entire procedure. After every dose of NMBA administration, and before and after sugammadex antagonism, a set of EMG measurements was obtained, and the researcher asked the provider to give a subjective assessment of the TOF count based on the visual assessment following peripheral nerve stimulation of ulnar nerve with TetraGraph. A paired sample t-test was used to compare the mean score in the different time periods.

Results: Twenty patients (aged 58 ± 14 yr) were enrolled in the study. One patient was excluded due to profuse sweating that precluded the electrodes of either monitor from adhering to the skin. Anesthesia providers were CRNAs in all cases. In the 19 patients, a total of 218 observation pairs were collected. Compared to TetraGraph, anesthesia providers subjectively assessed a higher TOF count in 114 (53%) observations and a lower count in 18 (8%) observations. Intraoperatively, providers assessed a higher TOF count especially during maintenance and before sugammadex. There was a significant difference obtained from measurements obtained just prior to maintenance dosing that maintained neuromuscular blockade, and before sugammadex (95% CI; -1.22 to 0.55, p <0.001) and (95% CI; -1.87 and -0.33, p 0.007) respectively. Medians were 0 for objective assessment and 1 for subjective. IQR was 1-0 and 4-2 respectively. The incidence of residual paralysis was 16% at the time of extubation.

Conclusion: This study demonstrated that anesthesia providers assessed a significantly higher TOF count using visual assessment than the quantitative data obtained from the TetraGraph. The subjective assessment of TOF count may affect clinical care, and lead to inappropriate administration of NMBAs and/or premature administration of the reversal agents. Subjective evaluation may provide inaccurate information and assessment of full recovery compared to objective evaluation placing the patients at increased risk of residual block and attendant complications.

Perioperative Anesthesia - 18 An evaluation on a low dose of ketamine preventing from post-induction hypotension in general anesthesia

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Introduction: Post-induction hypotension (PIH) is common in general anesthesia (1), directly resulting in intraoperative hypotension (2). Although etomidate is widely employed to minimize blood pressure drop, PIH is still occurred often during the induction of general anesthesia (3). Ketamine has a positive effect on hemodynamic changes, increasing heart work, heart rate, and blood pressure (4). This study is to investigate whether PIH can be prevented by a low dose of ketamine administered in the induction of general anesthesia.

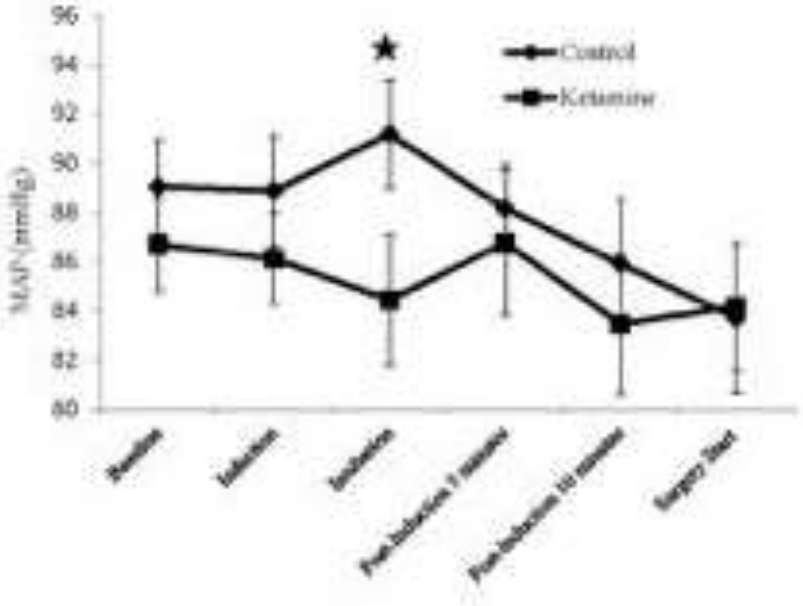
Methods: In this randomized controlled clinical trial, sixty American Society of Anesthesiology (ASA) I and II patients aged 15-60 years scheduled for elective surgery under general anaesthesia were randomized into two groups: Ketamine group: received intravenous induction with midazolam (0.05mg/kg), fentanyl (4Mg/kg), etomidate (0.4mg/kg) ketamine (0.25mg/kg) and cisatracurium (0.2mg/kg)intravenously; Control group: received introvenous induction with midazolam (0.05mg/kg), fentanyl (4Mg/kg), etomidate (0.4mg/kg) and cisatracurium (0.2mg/kg). Patients with cardiovascular complications (hypertension, heart disease, arrhythmia), respiratory diseases (upper respiratory infection, airway stenosis), allergic to anesthesia, mental disease, epilepsy, a history of drug and alcohol abuse, diabetes, opiate-dependence were excluded. General anaesthesia was standardized in both groups. The patients and physicians administering anaesthesia were blinded to the study. Hemodynamic responses were evaluated by determining blood pressure. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at different times (pre-induction 5 min, induction, intubation, post-induction 5min, post-induction 10 min, surgery start), and the mean arterial pressure (MAP) was calculated via the formula: MAP=(SBP + 2×DBP)/3. Data were showed as mean ± standard error (M±SEM), analyzed using GraphPad Prism 5.01 statistical software. T-tests were used to compare the two groups. A satistical significance was set at $P<0.05$.

Results: A low dose of ketamine during the induction did not critically increase MAP in the ketamine group compared with the control goup at different peri-induction time: Baseline ($P>0.05$), Induction ($P>0.05$), Post-Induction 5 minutes ($P>0.05$), Post-Induction 10 minutes ($P>0.05$), and Surgery Start ($P>0.05$). However, it can significantly reduce the increase of MAP during Intubation compare with the control group ($P=0.027$) (Figure 1). A limitation is that side effects of ketamine are not monitored in this study.

Conclusion: An induction of general anesthesia with a low dose of ketamine cannot show a significant advantage in stablizing MAP in the peri-induction. However, it prevents blood pressure from critically fluctuating in the process of intubation.

References: 1. Jor O, Maca J, Koutna J, Gemrotova M, Vymazal T, Litschmannova M, et al. Hypotension after induction of general anesthesia: occurrence, risk factors, and therapy. A prospective multicentre observational study. J Anesth. 2018;32(5):673-80. 2. Sudfeld S, Brechnitz S, Wagner JY, Reese PC, Pinnschmidt HO, Reuter DA, et al. Post-induction hypotension and early intraoperative hypotension associated with general anaesthesia. Br J Anaesth. 2017;119(1):57-64. 3. Masoudifar M, Beheshtian E. Comparison of cardiovascular response to laryngoscopy and tracheal intubation after induction of anesthesia by Propofol and Etomidate. J Res Med Sci. 2013;18(10):870-4. 4. Smischney NJ, Beach ML, Loftus RW, Dodds TM, Koff MD. Ketamine/propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent: a randomized, controlled trial. J Trauma Acute Care Surg. 2012;73(1):94-101.

Figure 1 The effect of an induction with a low dose of ketamine on mean arterial pressure (MAP) in the peri-induction period.



Perioperative Anesthesia - 19 Combined general/epidural anesthesia vs general anesthesia on the postoperative inflammation or stress response: a systematic review and meta-analysis

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Introduction: Local and systemic inflammation is common after surgery and is associated with morbidity and mortality. The use of epidural analgesia is thought to improve postoperative outcomes through pain reduction and opioid sparing. The present study aimed to assess whether addition of epidural anesthesia or analgesia (EA) to general anesthesia (GA) was associated with altered inflammatory response after surgery.

Methods: We systematically searched PubMed, Central, EMBASE, CINAHL, Google Scholar and Web of Science citation index, for clinical studies comparing the two techniques. We carried out a meta-analysis to evaluate the postoperative plasma levels of cytokines including Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α), IL-1β, IL-4, IL-8, IL-10, as well as C-Reactive Protein (CRP) and cortisol, after EA plus GA or GA alone.

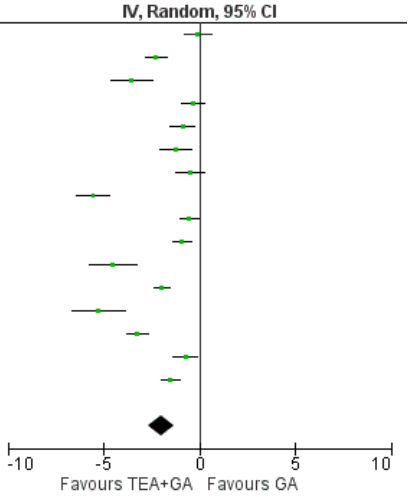
Results: The literature search was last updated on Oct 10th, 2020. We identified a total of 20 studies which compared postoperative inflammatory mediators with EA plus GA compared to EA alone. EA plus GA was associated with significantly lower serum levels of IL-6, TNF- α, CRP, as well as cortisol and other pro-inflammatory cytokines. In cancer surgery, EA plus GA was also associated with lower postoperative cytokines (Fig 1).

Conclusion: Our meta-analysis indicates that EA plus GA is associated with diminished postoperative inflammatory response. This offers an alternative explanation for the benefit of epidural analgesia on postoperative outcomes. Considering the link between postoperative inflammation and recurrence after cancer surgery, this is an area that warrants further research.

References: Myocardial, inflammatory, and stress responses in off-pump coronary artery bypass graft surgery with thoracic epidural anesthesia. Ann Thorac Surg. 2009;87(4):1119-1126. Effects of Different Anaesthesia Methods on Perioperative Cellular Immune Function and Longterm Outcomes in Patients Undergoing Radical Resection of Esophageal Cancer: A Prospective Cohort Study. Anesthesiology & Pain Medicine. 2020;epub ahead of print. Modulation of CCL2 Expression by Laparoscopic Versus Open Surgery for Colorectal Cancer Surgery. Surg Laparosc Endosc Percutan Tech. 2019;29:101-108. Comparative Study between General Anesthesia versus General Anesthesia Combined with Thoracic Epidural Analgesia on Cytokine Response in Laparoscopic Cholecystectomy Patients. Open Journal of Anesthesiology. 2020;10(06):247-262. Thoracic epidural analgesia inhibits the neuro-hormonal but not the acute inflammatory stress response after radical retropubic prostatectomy. British journal of anaesthesia. 2013;110(5).

	TEA+GA			GA				Std. Mean Difference		Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**	**IV, Random, 95% CI**
Yokoyama 2005	350	196.77	15	372.58	222.58	15	6.3%	-0.10 [-0.82, 0.61]	2005	
Caputo 2009	60.55	7.09	36	77.69	7.91	38	6.5%	-2.25 [-2.84, -1.67]	2009	
Moselli 2011	171.15	15.89	18	1,226.19	416.67	17	5.8%	-3.55 [-4.65, -2.45]	2011	
Hadimioglu 2012	4,651.16	3,455.15	21	6,245.85	5,847.17	25	6.5%	-0.32 [-0.90, 0.26]	2012	
Xu 2014	26.75	6.84	20	33.6	8.32	20	6.4%	-0.88 [-1.53, -0.23]	2014	
Fares 2014	55.2	24.6	15	80.6	13.7	15	6.2%	-1.24 [-2.03, -0.45]	2014	
Gu 2015	0.1173	0.0255	14	0.14	0.0563	15	6.3%	-0.50 [-1.24, 0.24]	2015	
Tan 2016	86.94	13.6	53	187.25	21.45	53	6.1%	-5.55 [-6.40, -4.69]	2016	
Sun 2016	95.49	12.7	36	101.64	10.25	36	6.6%	-0.53 [-1.00, -0.06]	2016	
Yan 2019	95.2	6.8	37	102.5	9.1	37	6.6%	-0.90 [-1.38, -0.42]	2019	
Wang 2019	27.24	1.33	20	33.58	1.42	20	5.6%	-4.52 [-5.73, -3.30]	2019	
Hou 2019	140.2	20.58	60	177.22	17.03	60	6.6%	-1.95 [-2.38, -1.51]	2019	
Duque 2019	38.8	5	20	71.5	7	19	5.3%	-5.29 [-6.68, -3.90]	2019	
Xu 2020	21.5	1.5	55	28	2.4	55	6.5%	-3.23 [-3.80, -2.65]	2020	
Elsayed 2020	17	2.9	20	19.4	3.6	20	6.4%	-0.72 [-1.36, -0.08]	2020	
Cong 2020	109.52	25.6	40	152.6	30.5	40	6.5%	-1.52 [-2.02, -1.02]	2020	
Total (95% CI)			**480**			**485**	**100.0%**	**-1.99 [-2.67, -1.31]**		

Heterogeneity: Tau² = 1.76; Chi² = 266.46, df = 15 (P < 0.00001); I² = 94%
Test for overall effect: Z = 5.76 (P < 0.00001)



Perioperative Anesthesia - 20 Risk prediction of perioperative neurocognitive disorders in surgical patients

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Introduction: Perioperative neurocognitive disorders (PND) are one of the main current anesthetic challenges. PND are caused by the non-resolution of an inflammatory cascade that involves circulating high molecular group box 1 (HMGB1) and interleukin-6 (IL6) levels (1-5). Identifying patients at risk of PND would improve perioperative management.

Methods: A prospective trial was conducted in 2019 on 17 surgical patients at the University Hospital of Charleroi (Charleroi, Belgium). Each patient underwent a mini mental state examination (MMSE) and laboratory tests (IL-6 and HMGB1 by ELISA) prior to surgery (T0). IL6 and HMGB1 were again assayed 6 (T6) and 24 (T24) hours after surgery and MMSE after 6 weeks and 3 months, respectively. The 6-week change in MMSE was predicted from log-transformed IL6 and HMGB1 levels recorded from baseline to 24h post-surgery by multiple regression analysis.

Results: MMSE scores dropped from (mean ± SD) 25.8 ± 4.2 at baseline to 23.6 ± 4.8 after 6 weeks ($p<0.01$). IL6 increased from 31.2 ± 33.9 to 290 ± 277 pg/ml (24h) and HMGB1 from 38.9 ± 85.6 to 91.1 ± 170 pg/ml ($p<0.0001$). A significant relationship ($R^2=0.79$, $p=0.039$) was found between the 6-week change in MMSE (ΔMMSE6W) and the serial IL6 and HMGB1 measurements:
[ΔMMSE6W = 39 + 4.32 x log(IL6 T0) – 3.49 x log(IL6 T6) – 6.99 x log(IL6 T24) + 1.75 x log(HMGB1 T0) – 11.7x log(HMGB1 T24) – 0.85 x log(IL6 T0) x log(HMGB1 T0) + 0.40 x log(IL6 T6) x log(HMGB1 T6) + 2.12 x log(IL6 T24) x log(HMGB1 T24)].
This model which includes multiplicative effects of IL6 and HMGB1 allows predicting the risk of PND (drop of MMSE score) in surgical patients

Conclusion: Identifying patients at risk of PND development remains a challenge. Based on the predictive model, a decrease in MMSE scores 6 weeks post-operatively could be predicted relying on serum IL6 and HMGB1 levels. Large prospective studies are needed to confirm this finding.

References: (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

Dependent Variable: [illegible]

Number of Observations Read	17
Number of Observations Used	17

Analysis of Variance

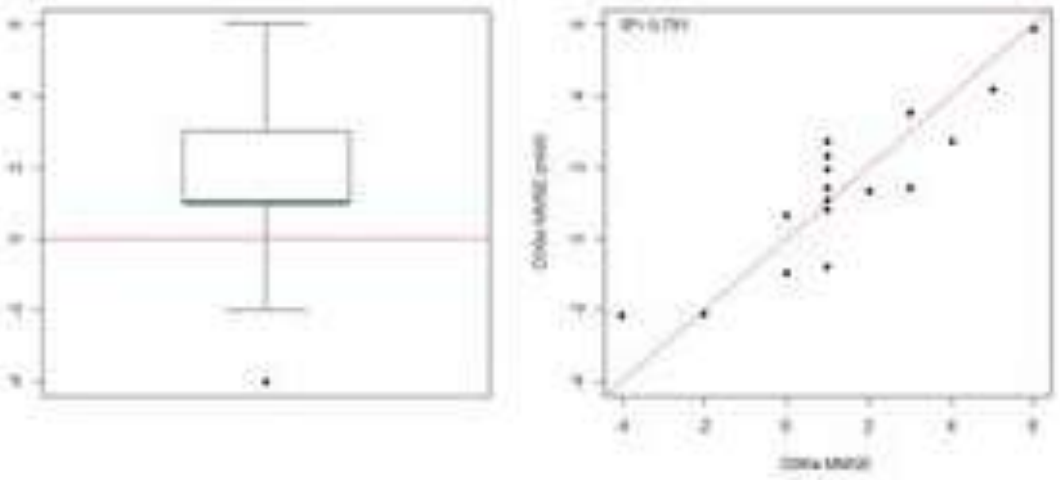
Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	8	72.89024	9.11128	3.79	0.0366
Error	8	19.22749	2.40343		
Corrected Total	16	92.11705			

Root MSE	1.55030	R-Square	0.7913
Dependent Mean	1.a1176	Adj R-Sq	0.5825
Coeff Var	109.81281		

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	1	38.80346	13.03752	2.98	0.0175
[illegible]	1	4.31767	1.42653	3.03	0.2104
[illegible]	1	-2.48695	0.83508	-4.19	0.0031
[illegible]	1	-8.38130	2.24442	-3.11	0.0164
lnlength1	1	1.75187	1.67047	1.05	0.3249
[illegible]	1	-11.71439	3.25369	-3.59	0.0071
[illegible]	1	-0.85291	0.43776	-1.95	0.0673
[illegible]	1	0.99596	0.20037	1.99	0.0636
[illegible]	1	2.11898	0.61468	3.45	0.0067

Image 1



Perioperative Anesthesia - 21

Acetylcholine Esterase Inhibitor Galantamine's Effect on Central and Peripheral Cholinergic Transmission and Resulting Attenuation of Murine Allergic Lung Inflammation

Maya Mikami[1], Elvedin Lukovic[2], Gene T Yocum[1], Aisha Kuforiji[3], Charles W Emala[1]

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Introduction: Inflammatory responses in many peripheral diseases are modulated by parasympathetic neural outflow from the central nervous system (CNS) that includes efferent fibers of the vagal nerve, the neurotransmitter acetylcholine (ACh) and α7 subunit-containing nicotinic acetylcholine receptors (α7nAChR)[1]. ACh activates both muscarinic and nicotinic ACh receptors which are both known to be involved in the regulation of immune function, allergic lung inflammation and the clinical symptoms of asthma. We previously reported that galantamine reduced murine allergic lung inflammation likely due to an increase in ACh levels following ACh esterase inhibition. Currently, we sought to determine whether the mechanism(s) of galantamine-mediated attenuation of allergic lung inflammation involved centrally- or peripherally-expressed muscarinic receptors and/or peripheral α7nAChRs.

Methods: Studies were approved by the institutional IACUC. C57BL/6J mice were treated with house dust mite (HDM) antigen for 10d. During the 10d sensitization, mice received daily i.p. galantamine (5mg/kg). Separate groups of mice were simultaneously treated with daily i.p. injections of methyllycaconitine citrate (MLA) (α7nAChR antagonist), scopolamine methyl bromide (SMB) (muscarinic antagonist without CNS penetration), scopolamine hydrobromide (SHB) (muscarinic antagonist with CNS penetration) or vehicle. Bronchoalveolar lavage (BAL) was performed for cell counts and protein. Blood and lungs were collected for cytokine analysis. In separate experiments, mice were HDM sensitized for 3 weeks +/- daily galantamine, and their respiratory system mechanics were measured using FlexiVent.

Results: MLA reversed galantamine's action in attenuating HDM-induced plasma IL-6 increases but had no effect on reversing lung IL-4 levels and BAL protein. Intraperitoneal co-administration of SMB did not reverse galantamine's effect on BAL protein or lung IL-4. SHB also did not reverse galantamine's effect on BAL protein or lung IL-4, but plasma IL-6 levels with SHB/galantamine were reversed to sensitized levels. Central airway resistances in mice treated with galantamine during the HDM sensitization were the same as the resistances measured in unsensitized vehicle-treated mice.

Conclusion: Attenuation of nasal HDM-induced allergic lung inflammation by systemic administration of an ACh esterase inhibitor galantamine was not solely attributable to α7nAChR signaling likely due to differential expression of nicotinic receptors in cell types involved in inflammation. Systemic but not peripheral muscarinic antagonism reversed galantamine's effects suggesting a role of central muscarinic receptors in lung anti-inflammation. Although ACh is classically considered detrimental to airway function, chronic galantamine treatment even with HDM sensitization did not increase airway resistance. These findings suggest that galantamine can be used to attenuate allergic lung inflammation without airway constriction.

References: 1. Nature (2003) 421: 384-388.

Regional Anesthesia

Regional Anesthesia - 1 Association between regional anesthesia and analgesic outcomes: a single-center retrospective study of 2,761 pediatric regional anesthetics

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[1]Stanford Universisty, Stanford, CA, [2]Stanford University School of Medicine, Stanford, CA, [3]Stanford University School of Medicine, STANFORD, CA, [4]Stanford Unviersity, Stanford, CA

Introduction: Results from adult clinical trials show that perioperative regional anesthesia often improves analgesic outcomes.(1,2,3) Significantly fewer pediatric studies have been published. A 2018 systematic review of pediatric regional anesthesia outcomes included 40 randomized controlled trials with 2,408 patients (study arm size ranged from 5-73, the majority were 20-40) with most studies reporting a decrease in postoperative pain and opioid consumption. However some studies did not show an analgesic benefit of regional anesthesia for certain procedures. (4) As most pediatric studies are small trials conducted under idealized conditions, we sought to explore pediatric analgesic outcomes in a large pragmatic study. We hypothesized that children who received regional anesthesia (both single-shot and catheter-based) would have reduced perioperative opioid consumption and pain scores compared to patients without a regional anesthetic.

Methods: Using our institution's electronic medical record, we identified patients ≤18 years of age who underwent surgery from May 2014 to August 2019. Inclusion criteria: surgeries with regional anesthesia performed in at least one of the included cases. Exclusion criteria: postoperative ICU admission, ASA class ≥4, ≥1 operation performed during the same anesthetic, and non-operative procedures. Regional anesthetics were categorized as catheter-based blocks and single-shot blocks. Primary outcome: PACU opioid exposure (any/none) and dose. Secondary outcomes: intraoperative and inpatient opioid exposure (any/none) and dose, procedure and anesthesia lengths, PACU length of stay, and mean postoperative pain scores (mild vs moderate/severe). Mild pain was defined as numeric rating scale 0-3, while moderate/severe was defined as 4-10. Linear and logistic regressions were used to estimate the association of exposure to regional anesthesia with outcomes; adjustments were made for possible confounders.

Results: 13,526 eligible procedures met inclusion criteria; 2,761 (20.4%) regional anesthetics were performed. Cohort demographics are summarized in Table 1. Regional anesthesia was significantly associated with having an opioid-free intraoperative anesthetic (Table 2). For patients who did receive opioid intraoperatively, catheter-based regional anesthesia had an associated intraoperative reduction of 0.035 mg kg-1 oral morphine equivalents (MEUs) while single-shot blocks had a reduction of 0.038 mg kg-1 MEUs. Regional anesthesia had a weaker association with having an opioid-free PACU course. For patients who did receive opioid in the PACU, regional anesthesia was not associated with a significant difference in dose received. The difference in procedure length for patients who received single-shot blocks was +8 minutes and for patients who received regional catheters was +19 minutes. Odds of having moderate/severe PACU pain scores was slightly higher in catheter block patients whereas the single-shot block group had similar pain scores to patients who did not undergo regional anesthesia. Preliminary analysis of inpatient outcomes data showed a small decrease in probability of opioid exposure in the catheter block group, and no major difference in the probability of opioid exposure in the single-shot block group. At 12-24 hours, the single-shot group patients had a slightly higher probability of higher pain scores compared to no-block and catheter block patients.

Conclusion: While evidence from prospective trials under idealized conditions with stringent inclusion and exclusion criteria suggests regional anesthesia improves postoperative pain parameters, results from large pragmatic studies are lacking. In this retrospective review of children undergoing routine care in the perioperative setting, regional anesthesia was associated with a statistically significant decrease

in intraoperative opioid exposure and administration. Furthermore, there was a significant difference in PACU opioid administration but no clinically significant difference in PACU pain severity, corroborating the opioid-sparing effect of single-shot blocks. Inpatient outcome results suggest a small decrease in opioid exposure in patients who receive a catheter-based block. Our results suggest that in real-world conditions, regional anesthesia may play an opioid-sparing role intraoperatively and in the PACU, but it is unclear if meaningful differences in analgesic outcomes occur beyond this.

References: 1. Chen et al. Medicine (Baltimore). 2019;98(49):e18220. 2. Tan et al. Medicine (Baltimore). 2019;98(48):e17967. 3. Zhou et al. Medicine (Baltimore). 2019;98(42):e17545. 4. Kendall et al. Local Reg Anesth. 2018;11:91-109.

Table 1: Cohort Demographics

	Intraoperative Block Type							
	No Block		Catheter Block		Single Shot Block		Total	
	#	%	#	%	#	%	#	%
Female	4401	(40.66)	188	(42.25)	670	(28.93)	5259	(38.66)
Male	6364	(59.12)	257	(57.75)	1646	(71.07)	8267	(61.12)
Mean age (yrs), (sd)	8.04	(5.20)	11.88	(5.55)	7.35	(6.12)	8.06	(5.42)
ASA class								
1	4655	(43.24)	141	(31.69)	1336	(57.69)	6132	(45.33)
2	4603	(42.76)	186	(41.80)	765	(33.04)	5552	(41.05)
3	1507	(14.00)	118	(26.52)	217	(9.37)	1842	(13.62)
Disposition								
Hospital Outpatient Surgery	7669	(71.24)	103	(23.15)	1868	(80.68)	9640	(71.27)
Inpatient	856	(7.95)	29	(6.52)	62	(2.68)	1047	(7.74)
Surgery Admit	2140	(19.88)	313	(70.34)	386	(16.67)	2839	(20.99)
Intralipid reinfiltrated								
No	10094	(93.77)	427	(95.96)	2263	(98.58)	12804	(94.66)
Yes	671	(6.23)	18	(4.04)	33	(1.42)	722	(5.34)
History of OSA								
No	10318	(95.85)	440	(98)	2278	(98.36)	13036	(96.36)
Yes	447	(4.15)	<10	(2)	38	(1.64)	490	(3.62)
History of chronic pain								
No	10269	(95.34)	372	(83.60)	2094	(90.41)	12755	(94.30)
Yes	476	(4.42)	73	(16.40)	222	(9.59)	771	(5.70)
Overweight								
No	6709	(62.32)	297	(66.74)	1545	(66.71)	8551	(63.22)
Yes	4037	(37.50)	148	(33.26)	771	(33.29)	4956	(36.64)
Unknown	19	(0.18)	0	(0.00)	0	(0.00)	19	(0.14)
History of mood disorder								
No	10651	(98.94)	436	(98)	2301	(99.35)	13388	(98.96)
Yes	114	(1.06)	<10	(2)	15	(0.65)	136	(1.01)

Table 2: Regression Analysis of Analgesic Outcomes

Association Evaluated	Regression Model	Confounders Adjusted	Regression Result
Opioid exposure intraoperative if receiving regional anesthesia	Logistic	Procedure, procedure length	OR for having intraoperative opioid exposure: *Catheter block*: 0.21 (95% CI: 0.13-0.32) *Single-shot block*: 0.13 (95%CI: 0.11-0.16)
Total intraoperative opioid dose for patients who did receive intraoperative opioid	Linear	Procedure, procedure length, use of intraoperative remifentanil	Total intraoperative opioid dose lower by mg/kg MEUs: *Catheter block*: 0.035 (95% CI: 0.056-0.014 decrease) *Single-shot block*: 0.038 (95% CI: 0.047-0.029 decrease)
Opioid exposure in PACU if receiving regional anesthesia	Logistic	Procedure, age	OR for having PACU opioid exposure: *Catheter block*: 0.58 (95% CI: 0.36-0.96) *Single-shot block*: 0.89 (95%CI: 0.78-1.02)
Total opioid dose in PACU for patients who did receive PACU opioid	Linear	Procedure, age	Total opioid dose lower by mg/kg MEUs: *Catheter block*: 0.002 (95%CI: -0.019-0.02) *Single-shot block*: -0.004 (95% CI: -0.009, 0.001)
Intraoperative time difference between patients who did and did not receive regional anesthesia	Linear	Procedure, age, anesthesiologist, surgeon, ASA class, case complexity	Intraoperative time difference in minutes: *Catheter block*: +20.4 (95% CI: 18.0-22.8-0.38) *Single-shot block*: +8.4 (95% CI: 7.8-9.6)
Mean PACU pain score (categorized as 0-3 for low pain or ≥4 for high pain)	Logistic	Procedure, sex, age, history of chronic pain or mood disorders	OR for high pain: *Catheter block*: 1.79 (95% CI: 1.32-2.43) *Single-shot block*: 1.04 (95% CI: 0.83-1.30)

Regional Anesthesia - 2 Comparison of Analgesic Efficacy of Ultrasound Guided Suprascapular Nerve Block (Anterior Approach) Versus Interscalene Brachial Plexus Block in Adults Undergoing Arthroscopic Shoulder Surgery

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Introduction: Interscalene brachial plexus block (ISB), is gold-standard for shoulder surgeries (1). However, it can block the phrenic nerve causing hemi-diaphragmatic paresis (HDP), leading to post-operative respiratory distress in patients with pre-existing respiratory disease, obstructive sleep apnea or morbidly obese (2, 3). Different strategies for decreasing phrenic nerve involvement with ISB have been investigated, including lowering the concentration and volume of local anesthetic to 5 ml; but still, the incidence of diaphragmatic involvement remains significantly high (upto 45%). Suprascapular nerve block-anterior approach (SSB-A) performed more distal than ISB can spare the phrenic nerve (4,5). This study compares the analgesic efficacy of ultrasound guided (USG) SSB-A with ISB and the incidence of HDP post-block. The primary objective of this study was to compare the duration of analgesia of ultrasound guided (USG) SSB-A and ISB in adults undergoing arthroscopic shoulder surgery. The secondary objectives of this study were to compare the quality of analgesia, change in diaphragmatic excursion and pulmonary function tests (PFTs) post-block.

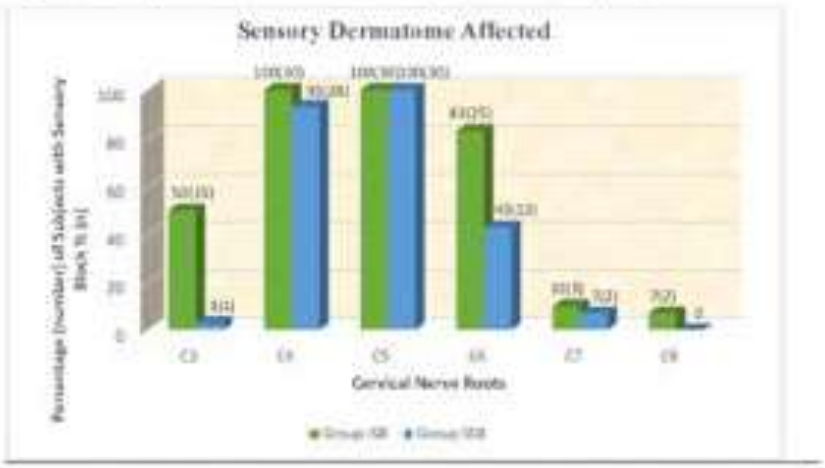
Methods: After IRB approval, this randomized, double blind prospective study was conducted in consenting 60 ASA I/II adults (18-65yrs), undergoing unilateral arthroscopic shoulder surgery. They were randomized by a computer-generated table to receive either USG SSB-A (n = 30) or ISB (n = 30) using 10 ml of 0.5% bupivacaine with 4 mg dexamethasone (Figure1). Baseline ultrasound evaluated diaphragmatic excursion (during quiet breathing and sniffing) and pulmonary function tests (PFTs) values were recorded. Sensory dermatomes, diaphragmatic excursion and PFTs were assessed 60 mins post-block. All patients received general anesthesia consisting of fentanyl/propofol/vecuronium/O2/air/sevoflurane (MAC0.8-1) as per institutional protocol. Post-operative rescue analgesia was provided by IV PCA morphine (1 mg bolus and 10 min lockout). The primary outcome was duration of regional analgesia i.e. time from block to first rescue analgesic (i.e., IV PCA morphine). Secondary outcomes were postoperative NRS pain scores (0-10) at 4h, 6h, 8h, 12 h and 24 h, total 24 h morphine consumption, diaphragmatic excursion, PFTs and sensory dermatomes affected. Statistical Analysis: For intergroup differences, Pearson's chi-square/ Fisher Exact test was used for categorical variables, Unpaired t test for normally distributed quantitative variables and Mann Whitney test for non-normally distributed quantitative variables. For intra-group differences, Paired t test was used. P value <0.05 was considered significant.

Results: Demographic profile of the two groups were similar. Duration of regional analgesia was also similar, (mean ± SD, SSB-A group: 1,345 ± 182 min and ISB group: 1,375 ± 156 min, p=0.5) and 24 h morphine consumption (mean) was <1 mg in both groups, highlighting superior quality of both blocks. NRS scores on physical activity (cough or deep breathing) were similar between the 2 groups (Table 1).However, distribution of NRS scores at rest were significantly different between Group SSB-A and Group ISB at 4h, 6h and 8h (Table 1); but likely clinically irrelevant. Post block diaphragmatic excursion on surgical side was significantly decreased in Group ISB (44%) than in group SSB-A (11%), but this was associated with a significant compensatory increase in diaphragmatic excursion on the non-surgical side (Table 2). The incidence of HDP post-block was significantly higher in group ISB compared to group SSB-A (Table 3). There was a decrease in PFT values in both the groups post-block (Table 3), but was greater decrease in group ISB (25%) than in group SSB-A (10%). Sensory dermatomes affected are shown in Figure 2. None of the patient developed any respiratory distress/ desaturation or any other complication.

Conclusion: SSB-A is a non-inferior regional analgesic approach for arthroscopic surgery as compared to ISB and has the advantage of preserving diaphragmatic function by sparing phrenic nerve. Hence, SSB-A can be a potentially safer analgesic technique in patients with pre-existing decreased respiratory reserve; like chronic obstructive lung disease, obstructive sleep apnea or morbidly obese.

References: 1. Abdallah F, et al. Will the Real Benefits of Single-Shot Interscalene Block Please Stand Up? A Systematic Review and Meta-Analysis. Anesth Analg. 2015;120 (5):1114–29. 2. Urmey WF, McDonald M: Hemidiaphragmatic paresis during interscalene brachial plexus block: Effects on pulmonary function and chest wall mechanics. Anesth Analg 1992; 74:352–7. 3. El-Boghdadly K, et al. Phrenic Nerve Palsy and Regional Anesthesia for Shoulder Surgery: Anatomical, Physiologic, and Clinical Considerations. Anesthesiology. 2017;127(1):173–91. 4. Siegenthaler A, et al. Ultrasound-guided suprascapular nerve block, description of a novel supraclavicular approach. Reg Anesth Pain Med. 2012;37(3):325–8. 5. Laumonerie P, et al. Ultrasound-guided proximal suprascapular nerve block: A cadaveric study. Clin Anat N Y N. 2018;31(6):824–9.

Figure 2. Sensory dermatomes affected in Group ISB and Group SSB-A



Group ISB = Interscalene brachial plexus block; Group SSB-A = Suprascapular nerve block (anterior approach). Values are expressed as Percentage (Number)

Table 2. Diaphragmatic Excursion before block and 60 min after block in Group ISB and Group SSB-A

	Pre-Block (cms) Mean ± SD	Post-Block (cms) Mean ± SD	p-value	Percentage change
GROUP ISB				
• **DE S_I quiet**	1.32 ± 0.31	0.73 ± 0.29	**<0.001**	-44 (-60, -33)
• **DE S_I sniff**	1.99 ± 0.64	1.30 ± 0.53	**<0.001**	-47 (-60, -30)
• **DE NS_I quiet**	1.39 ± 0.30	1.90 ± 0.54	**<0.001**	35 (5, 68)
• **DE NS_I sniff**	1.94 ± 0.44	2.60 ± 0.79	**<0.001**	30 (5, 64)
GROUP SSB-A				
• **DE S_I quiet**	1.51 ± 0.36	1.27 ±0.37	**0.001**	-11 (-26, 0)
• **DE S_I sniff**	2.12 ± 0.52	1.88 ± 0.51	**0.025**	-7 (-22, 4)
• **DE NS_I quiet**	1.38 ± 0.24	1.40 ± 0.34	0.008	1 (-3, 17)
• **DE NS_I sniff**	2.09 ± 0.48	2.13 ± 0.56	0.555	-5 (-9, 14)

ISB = Interscalene brachial plexus block; SSB-A = Suprascapular nerve block (anterior approach); DE S_I quiet = Diaphragmatic excursion on surgical side during quiet breathing; DE S_I sniff = Diaphragmatic excursion on surgical side during sniff; DE NS_I quiet = Diaphragmatic excursion on Non-surgical side during quiet breathing; DE NS_I sniff = Diaphragmatic excursion on Non-surgical side during sniff. Pre-Block and Post-Block values are expressed as Mean ± SD, Percentage change expressed as Mean (IQR).

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram

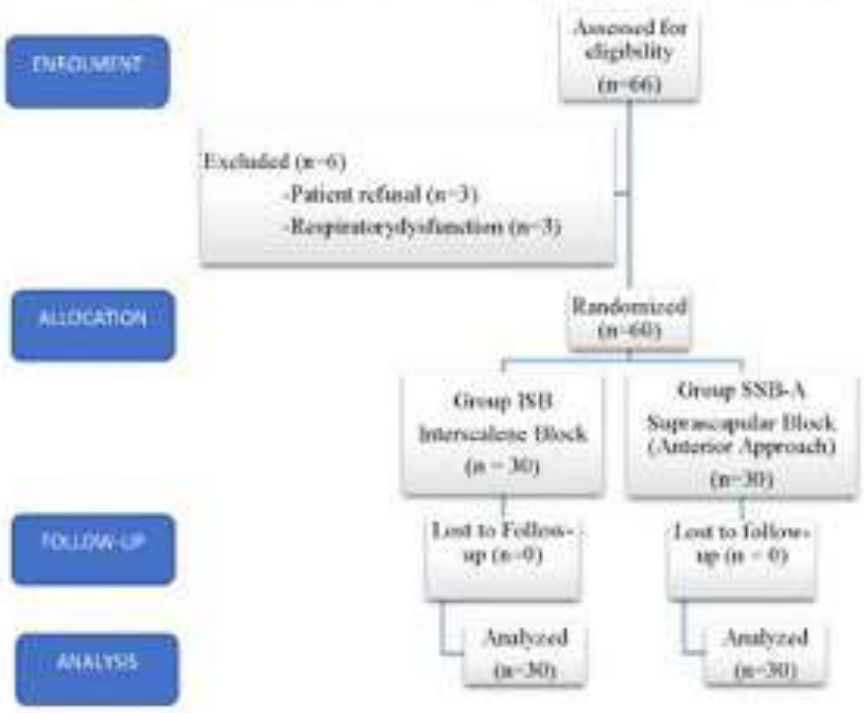


Table 1. Postoperative NRS Scores in Group ISB and Group SSB-A at Rest and Activity (cough or deep breathing)

Time after block	Group ISB	Group SSB	p-value
4 hour			
• **Rest**	0 (0, 0)	0.5 (0, 1)	**0.006**
• **Activity**	1 (0, 1)	1 (0, 2)	0.171
6 hour			
• **Rest**	0 (0, 0)	0 (0, 1)	**0.025**
• **Activity**	1 (0, 1)	1 (0, 2)	0.406
8 hour			
• **Rest**	0 (0, 0)	0 (0, 1)	**0.040**
• **Activity**	1 (1, 1)	1 (0, 2)	0.346
12 hour			
• **Rest**	0 (0, 1)	0.5 (0, 2)	0.114
• **Activity**	1 (1, 2)	1 (1, 2)	0.431
24 hour			
• **Rest**	1 (0, 2)	1 (0, 3)	0.703
• **Activity**	2 (1, 3)	2 (1, 4)	0.768

ISB = Interscalene brachial plexus block; SSB-A = Suprascapular nerve block (anterior approach); NRS =Numerical Rating Scale. Values are expressed as Median (Interquartile Range).

Table 3. Pulmonary Function Test and Hemi-diaphragmatic Paresis Data at Baseline and 60 min Post-Block

	Group ISB	Group SSB-A	p-value
Pulmonary Function Test	**Actual Value (% change)**	**Actual Value (% change)**	
• FVC (L/min)	Pre-block: 2.87 ± 0.90 Post-block: 2.07 ± 0.89 (-25%); **p<0.001**	Pre-block: 2.70 ± 0.72 Post-block: 2.38 ± 0.67 (-11%) * **p<0.001**	**< 0.001**
• FEV_1 (L/min)	Pre-block: 2.61 ± 0.73 Post-block: 1.99 ± 0.83 (-27%) **p<0.001**	Pre-block: 2.58 ± 0.62 Post-block: 2.31 ± 0.62 (-10%) * **p<0.001**	**0.003**
• PFR (L/min)	Pre-block: 6.94 ± 1.89 Post-block: 5.76 ± 2.15 (-11%) **p<0.001**	Pre-block: 7.47 ± 1.69 Post-block: 6.92 ± 2.31 (-5%) * p=0.07	0.08
Hemi-diaphragmatic Paralysis	**Number (%)**	**Number (%)**	**p- value**
None (<25%)	5 (17%)	20 (67%)	**<0.001**
Partial (25-75%)	24 (80%)	10 (33%)	**<0.001**
Complete (>75%)	1 (3%)	0	0.31

ISB = Interscalene brachial plexus block; SSB-A = Suprascapular nerve block (anterior approach); FVC= Forced vital capacity; FEV_1 = forced expiratory volume in 1 second; PFR= Peak expiratory flow rate; L=Liter; Complete HDP: 75-100% decreased excursion or paradoxical movement of diaphragm; Partial HDP: 25-75% decrease; None : <25% decrease in diaphragmatic excursion. Pre-Block and Post Block values are expressed as Mean ±SD; Percentage change expressed as Median; Hemi-diaphragmatic paralysis expressed as n (%) = Number (Percentage)

Respiration

Respiration - 1 Deterioration of Oxygenation Index and Oxygen Saturation Index after intubation predicts mortality in critically ill COVID-19 patients

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Introduction: Acute hypoxemic respiratory failure is a major cause of death from Coronavirus disease 2019 (COVID-19). We examined if PaO2/FiO2, Oxygenation Index (OI), SpO2/FiO2 and Oxygen Saturation Index (OSI), used to assess the severity of respiratory failure in ARDS, predict mortality in intubated COVID-19 patients.

Methods: In this single-centered retrospective cohort study we enrolled 68 critically ill adult patients with confirmed COVID-19 infection requiring mechanical ventilation. Respiratory and other physiological variables were recorded on the day of intubation (day 0), post-intubation days 3 and 7. The association between physiological parameters, PaO2/FiO2, OI, SpO2/FiO2 and OSI with mortality were analyzed using logistic and multivariate regression. The area under the receiver-operating characteristic curve (AUC) for mortality was calculated. Significant predictors of mortality were identified in bivariate analysis and were entered into multivariate analysis to identify independent predictors of in-hospital mortality.

Results: The ARDS severity indices PaO2/FiO2, OI, SpO2/FiO2 and OSI were not statistically different in surviving versus non-surviving patients on the first day of intubation. Three days after intubation, however, they were significantly worse in the non-surviving patients. The ARDS severity indices continued to worsen in the non-survivors, but improved in survivors on day 7, resulting in an even greater group difference (PaO2/FiO2 106.3 [94.2] vs. 178.0 [69.3], p<0.001; OI 150.0 [118.4] vs. 61.5 [46.7], p<0.001; SpO2/FiO2 130 [90] vs. 230 [50] p<0.001; OSI 14.7 [13.2] vs. 6.5 [5.4], p<0.001, respectively). All measures were independently associated with hospital mortality, with significantly greater odds ratios (ORs) observed on day 7. The AUC for mortality prediction was greatest on intubation day 7 (AUC =0.775, 0.808, 0.830 and 0.828 for PaO2/FiO2, OI, SpO2/FiO2 and OSI, respectively) compared to days 0 and 3.

Conclusion: ARDS severity indices are not of prognostic value on the day of intubation but deteriorate within three days in non-surviving COVID-19 patients. Saturation based measurements are of similar prognostic value as measures that rely on invasive blood gas monitoring, and can reliably predict mortality in patients with acute hypoxemic respiratory failure due to SARS-CoV-2 infection.

Characteristic	Survivors	Non-survivors	p
Age in years (SD)	58.1 (16.3)	68.3 (10.8)	0.0036
Gender			
Female (n (%))	7 (21.21%)	15 (42.86%)	0.0565
Male (n (%))	26 (78.79%)	20 (57.14%)	0.0565
Race			
White (n (%))	9 (31.03%)	7 (20.59%)	0.6544
African American (n (%))	14 (48.28%)	18 (52.94%)	0.6544
Asian	0 (0%)	1 (2.94%)	0.6544
Other (n (%))	0 (0%)	1 (2.94%)	0.6544
Unknown	6 (20.69%)	7 (20.59%)	0.6544
Ethnicity			
Hispanic	14 (42.42%)	9 (25.71%)	0.1455
Non-hispanic	19 (57.58%)	26 (74.29%)	0.1455
BMI	31.89 (8.43)	33.48 (7.66)	0.4731
SOFA	8 (2.30)	9 (3.42)	0.4768
APACHE II	21.2 (6.8)	20.3 (10.5)	0.8314
Charlson Comorbidity Index	3.5 (2.9)	5.9 (2.2)	0.0004
Myocardial Infarction	1 (3.03%)	10 (28.57%)	0.0043
Congestive Heart Failure	4 (12.12%)	9 (25.71%)	0.1543
Peripheral Vascular Disease	3 (9.09%)	5 (14.29%)	0.5064
Cerebrovascular disease	5 (15.15%)	4 (11.43%)	0.6507
Chronic Obstructive Lung Disease	3 (9.09%)	6 (17.14%)	0.3275
Liver Disease	1 (3.03%)	0 (0%)	0.4821
Chronic Kidney Disease	2 (6.06%)	10 (28.57%)	0.0149
Diabetes Mellitus	13 (39.39%)	26 (74.29%)	0.0036
Laboratory Parameters			
C-reactive Protein (mg/dL)	119.4 (121.0)	113.8 (110.9)	0.8532
D-dimer (mcg/mL)	1.6 (2.4)	3.2 (6.8)	0.2059
Hemoglobin (mg/dL)	12.1 (2.2)	11.9 (1.7)	0.7908
Procalcitonin	1.2 (3.1)	3.0 (5.8)	0.1084
Creatinine (mg/dL)	1.2 (1.3)	1.9 (1.9)	0.0734
Respiratory paramaters			
PEEP (CmH2O))	10.2 (3.3)	11.8 (3.1)	0.045
FiO2 %	69.3 (21.7)	73.6 (21.1)	0.4113
MAP (cm H2O)	14.3 (3.5)	16.5 (3.7)	0.0183
Tidal Volume (ml)	446.3 (41.7)	420.5 (65.7)	0.0565
Days ventilated	13.9 (9.1)	14.7 (8.3)	0.7304
ICU legnth of stay (days)	13.7 (7.7)	15.8 (8.5)	0.3652
Hospital length of stay (days)	21.6 (10.2)	16.9 (8.7)	0.0859

Table 1. Clinical characteristics of the COVID-19 patients with acute hypoxic respiratory failure requiring intubation. Values are presented as mean (%), mean (SD) when normally distributed or median (IQR).

	Intubation day	Survivors	Non-survivors	P
Lung Compliance	Day 0	18.8 [IQR 18.5]	16.8 [IQR 7.8]	0.105
	Day 3	19.4 [IQR 22.4]	14.6 [IQR 7.2]	0.014
	Day 7	21.5 [25.3]	15.8 [IQR 9.9]	0.007
PaO2/FiO2 Ratio	Day 0	118.1 [IQR 103.3]	105.0 [IQR 78.1]	0.432
	Day 3	140.2 [IQR 109.6]	101.0 [IQR 61.4]	0.004
	Day 7	178.0 [IQR 69.3]	106.3 [IQR 94.2]	<0.001
Oxygenation Index	Day 0	82.9 [IQR 95.3]	116.0 [IQR 90.8]	0.165
	Day 3	84.8 [IQR 86.1]	135.0 [IQR 129.7]	0.003
	Day 7	61.5 [IQR 46.7]	150.0 [IQR 118.4]	<0.001
SpO2/FiO2 Ratio	Day 0	1.5 [IQR 0.8]	1.2 [IQR 0.7]	0.217
	Day 3	2.1[IQR 0.9]	1.3 [IQR 0.9]	0.003
	Day 7	2.3 [IQR 0.5]	1.3 [IQR 0.9]	<0.001
Oxygen Saturation Index	Day 0	10.9 [IQR 7.8]	12.2 [IQR 9.2]	0.052
	Day 3	8.0 [IQR 10.0]	12.0 [IQR 11.7]	0.006
	Day 7	6.5 [IQR 5.4]	14.7 [IQR 13.2]	<0.001

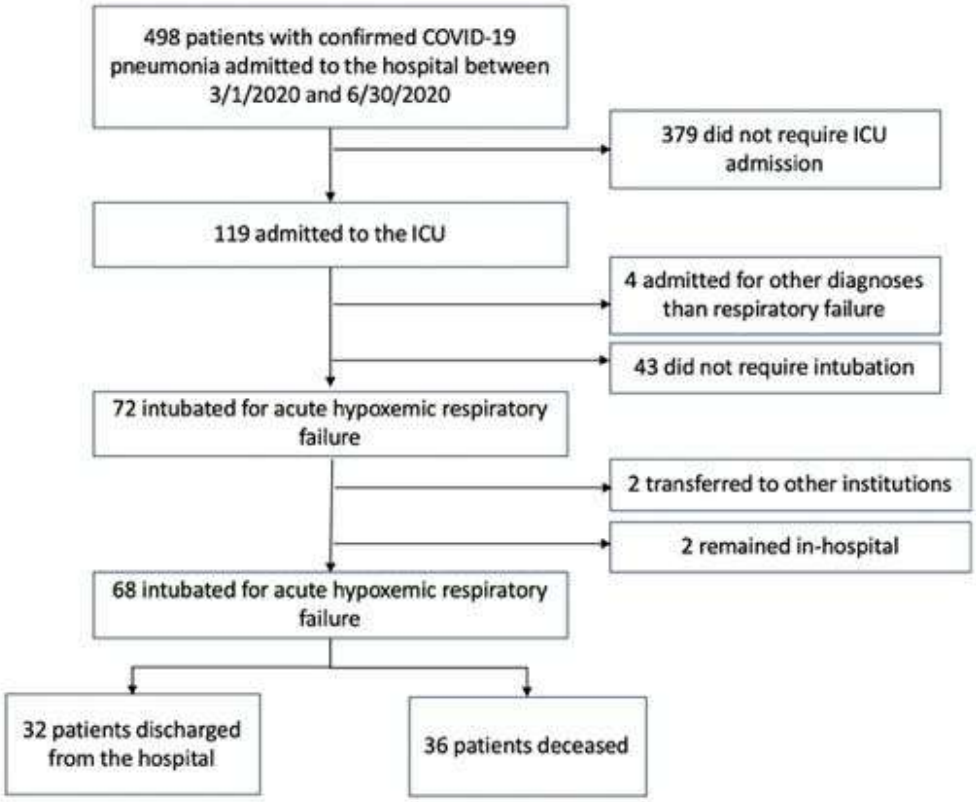
Table 2. ARDS severity indices for COVID-19 survivors and non-survivors on days 0, 3 and 7 after intubation; data presented as median [Interquartile Range].

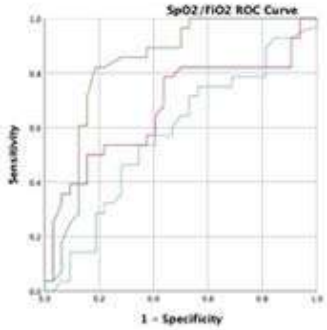
Day 0	Unadjusted OR (95% CI
Crs (per 10 ml/cmH2O decrease)	1.644 (0.951, 2.839)
PaO2/FiO2 (per 10 mmHg decrease)	1.020 (0.951, 1.083)
OI (per 10 cmH2O/mmHg increase)	1.041 (0.961, 1.116)
SpO2/FiO2 (per 10 unit decrease)	1.051 (0.961, 1.161)
OSI (per cmH2O increase)	1.107 (0.996, 1.230)

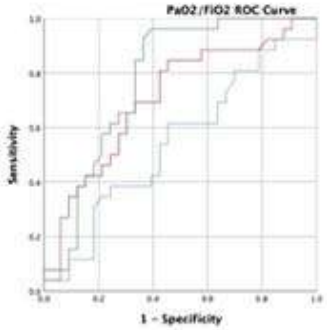
Day 3	Unadjusted OR (95% CI
Crs (per 10 ml/cmH2O decrease)	1.930 (1.149, 3.219)
PaO2/FiO2 (per 10 mmHg decrease)	1.104 (1.020, 1.207)
OI (per 10 cmH2O/mmHg increase)	1.093 (1.020, 1.207)
SpO2/FiO2 (per 10 mmHg decrease)	1.138 (1.041, 1.243)
OSI (per cmH2O increase)	1.092 (1.017, 1.173)

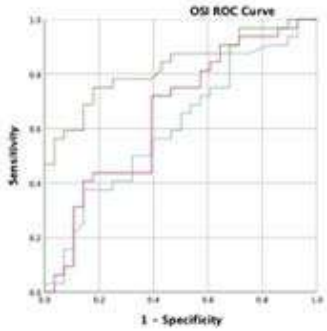
Day 7	Unadjusted OR (95% CI
Crs (per 10 ml/cmH2O decrease)	2.119 (1.207, 3.772)
PaO2/FiO2 (per 10 mmHg decrease)	1.149 (1.041, 1.268)
OI (per 10 cmH2O/mmHg increase)	1.267 (1.105, 1.452)
SpO2/FiO2 (per 10 unit decrease)	1.293 (1.138, 1.466)
OSI (per cmH2O increase)	1.275 (1.120, 1.451)

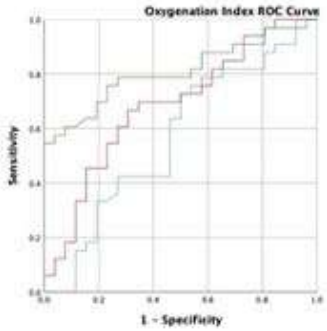
Table 3. Unadjusted and multivariate adjusted odds ratio of death for Crs, PaO2/FiO2, OI, SpO2/FiO2, and OSI.


498 patients with confirmed COVID-19 pneumonia admitted to the hospital between 3/1/2020 and 6/30/2020
379 did not require ICU admission
119 admitted to the ICU
4 admitted for other diagnoses than respiratory failure
43 did not require intubation
72 intubated for acute hypoxemic respiratory failure
2 transferred to other institutions
2 remained in-hospital
68 intubated for acute hypoxemic respiratory failure
32 patients discharged from the hospital
36 patients deceased


SpO2/FiO2 ROC Curve
Sensitivity
1 - Specificity


PaO2/FiO2 ROC Curve
Sensitivity
1 - Specificity


OSI ROC Curve
Sensitivity
1 - Specificity


Oxygenation Index ROC Curve
Sensitivity
1 - Specificity


Source of the Curve

Respiration - 2 The TMEM16A Antagonist Benzbromarone Decreases β2-Adrenergic Receptor Desensitization in Human Airway Smooth Muscle In Vitro

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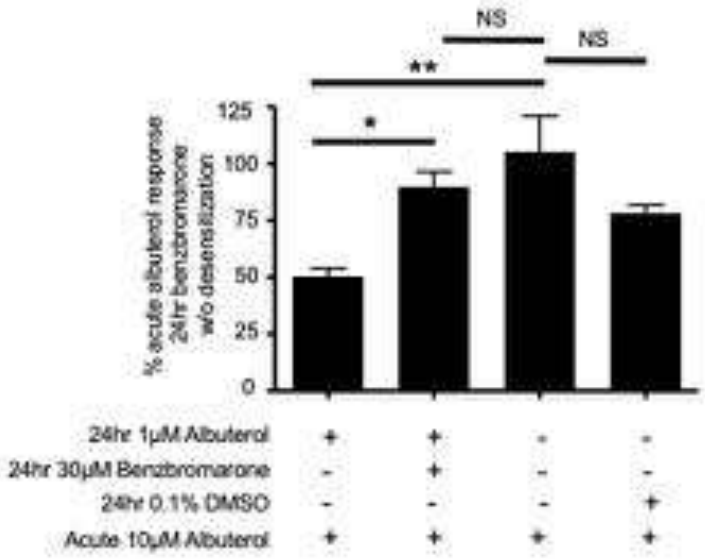
Introduction: We have previously shown that antagonism of the calcium-activated chloride channel, TMEM16A (also known as ANO1), exerts a pro-relaxant effect in airway smooth muscle (ASM). TMEM16A antagonism may thus serve as a novel therapeutic for bronchoconstrictive diseases such as asthma. We have previously demonstrated that TMEM16A antagonism-mediated relaxation is still effective after β-adrenoreceptor desensitization ex vivo and in vivo. In the current study, we hypothesized that concurrent treatment with the TMEM16A antagonist benzbromarone during desensitization with a β2-agonist would attenuate β2-adrenergic receptor (βAR) functional desensitization.

Methods: Primary human bronchial ASM cells were purchased from Lonza and maintained in Lonza smooth muscle growth media in 95% air/5%CO2. Cells were desensitized with 1 MM albuterol with or without 30 MM benzbromarone for 24 hrs.

Subsequently, to confirm functional desensitization, cells were treated with an acute dose of 10 MM albuterol. The measurement of cAMP levels was assayed via ELISA (Enzo) and values were normalized to protein levels (BCA assay) (Thermofisher). Data are expressed as mean±SEM and as a percent of the acute albuterol response after overnight benzbromarone treatment without β2-agonist-mediated desensitization. One-way ANOVA and Bonferroni post-hoc was performed with Prism 4 (Graphpad).

Results: Human ASM cells treated for 24hr with 1 μM albuterol ("desensitizing albuterol") subsequently exhibited reduced cAMP production in response to 10 μM acute albuterol compared to cells not treated for 24hr with albuterol (50.4±4.19% vs.105 ±15.8% $p<0.001$, n=5-7). Co-incubation of 30 μM benzbromarone with desensitizing albuterol, increased the subsequent cAMP response to acute albuterol compared to desensitized cells without concurrent benzbromarone (89.8±7.75% vs. 50.4±4.19%, $p<0.01$, n=7). Co-incubation with benzbromarone during β2-agonist-mediated sensitization restored cAMP levels to the levels in non-desensitized controls (89.8±7.75%, n=7 vs.105±15.8%, n=5, respectively).

Conclusion: Concurrent treatment of TMEM16A antagonist benzbromarone and β2-agonist reduces percent β2AR functional desensitization, which suggests that treatment with the TMEM16A antagonist benzbromarone could help attenuate desensitization to β2-agonist.



Respiration - 3 Mechanical power during general anesthesia and postoperative respiratory complications: A hospital registry study

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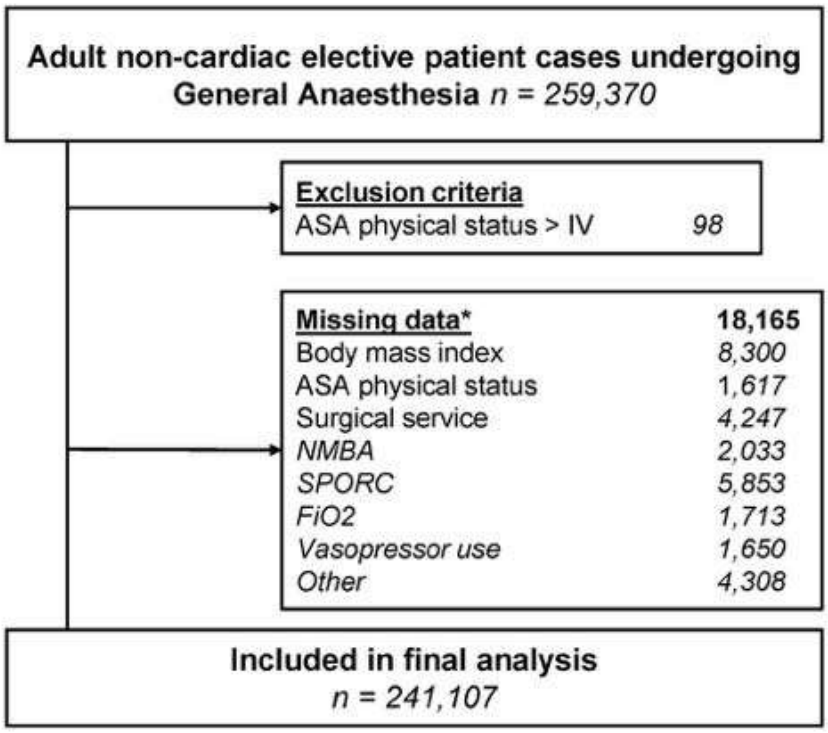
Introduction: Postoperative respiratory complications and respiratory failure occur in over 11 million patients each year and have been linked to the physico-mechanical parameters of mechanical ventilation, including stress from inspiratory pressure, strain from tidal volume, and cyclic repetition through the respiratory rate [1, 2]. Mechanical power is a concept that integrates these parameters and estimates the energy delivered to the respiratory system [3]. Although controversies exist with regards to its computation [4], mechanical power derived from a simplified calculation [5] has been associated with increased mortality in critically ill patients [6]. It remains unknown how intraoperative mechanical power during general anesthesia influences the occurrence of postoperative respiratory failure, and whether this integrative concept provides additional value compared to its individual components.

Methods: In this retrospective cohort study, we investigated the association between mechanical power and postoperative respiratory failure requiring re-intubation in adult patients with American Society of Anesthesiologists status I-IV, undergoing non-cardiac surgery, between 2006 and 2018 at Beth Israel Deaconess Medical Center and Massachusetts General Hospital in Boston, MA. The median intraoperative mechanical power was estimated from median values of intraoperative tidal volume, respiratory rate and inspiratory pressures using a previously validated method [5]. The primary outcome was postoperative emergent re-intubation within seven days after surgery. The secondary outcome was post-extubation hypoxemia <90% hemoglobin oxygen saturation. We applied multivariable logistic regression analysis to adjust for potential confounding factors including patient demographics, comorbidities, procedural severity, and intraoperative factors. We compared the area under the receiver operating characteristics curve (ROC-AUC) for predicting postoperative reintubation solely based on mechanical power, respiratory rate, or tidal volume.

Results: 241,107 out of 259,370 patients were included (Figure 1). Patient and perioperative characteristics are depicted in Table 1. The median intraoperative mechanical power was 6.7 [IQR 4.7; 9.2] J/min (Figure 2). Emergent postoperative reintubation occurred in 2,524 (1.1%) cases and post-extubation hypoxemia in 11,155 (4.6%) patient cases. Increased intraoperative mechanical power was associated with an increased risk of postoperative re-intubation (aOR 1.06 [95%CI 1.05; 1.08], per every J/min increase, p<0.001, Figure 3). This association was robust in high-risk patients after excluding ambulatory patients and surgeries less than 3 hours (n= 71,805, aOR 1.05 [1.04; 1.07], p<0.001). Increased intraoperative mechanical power was further associated with higher odds of post-extubation hypoxemia (aOR aOR 1.05, [1.05; 1.06], p<0.001). Finally, mechanical power predicted PRC better than tidal volume or respiratory rate alone (ROC-AUC 0.57, 0.49 and 0.51, respectively, p<0.001).

Conclusion: A high intraoperative mechanical power is associated with increased risk of emergent re-intubation after surgery and general anesthesia. Our findings suggest that this integrative concept adds additional information compared to established parameters such as tidal volume or respiratory rate. Adjustment of intraoperative tidal volume, inspiratory pressure and respiratory rate should aim at reducing mechanical power.

References: [1] BMJ.2015;351:h3646 [2] Br J Anaesth.2020;125:e130-e139 [3] Intensive Care Med. 2016;42(10):1567-75 [4] Intensive Care Med. 2021;47(1):130-2 [5] Crit Care.2020;24:417 [6] Intensive Care Med. 2018;44(11):1914-22



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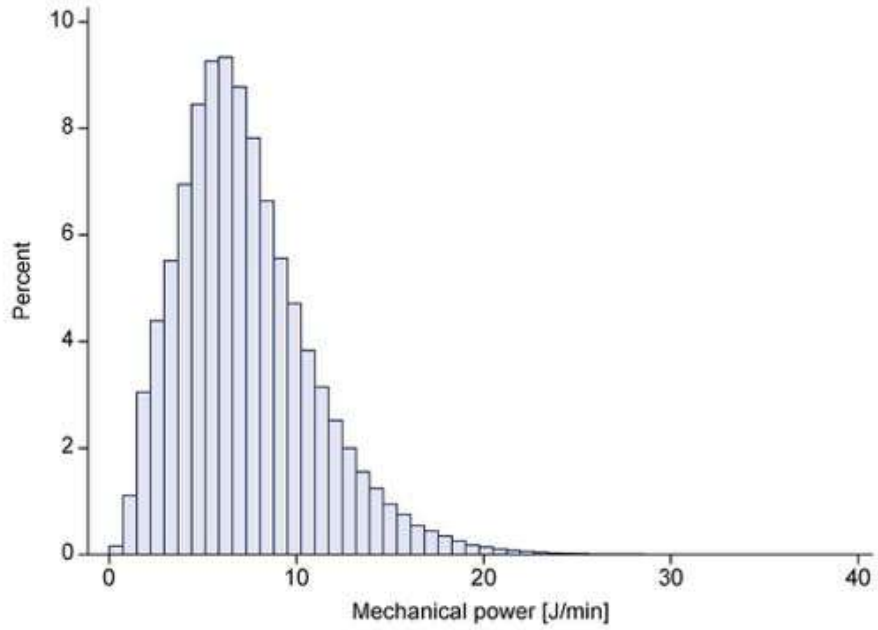

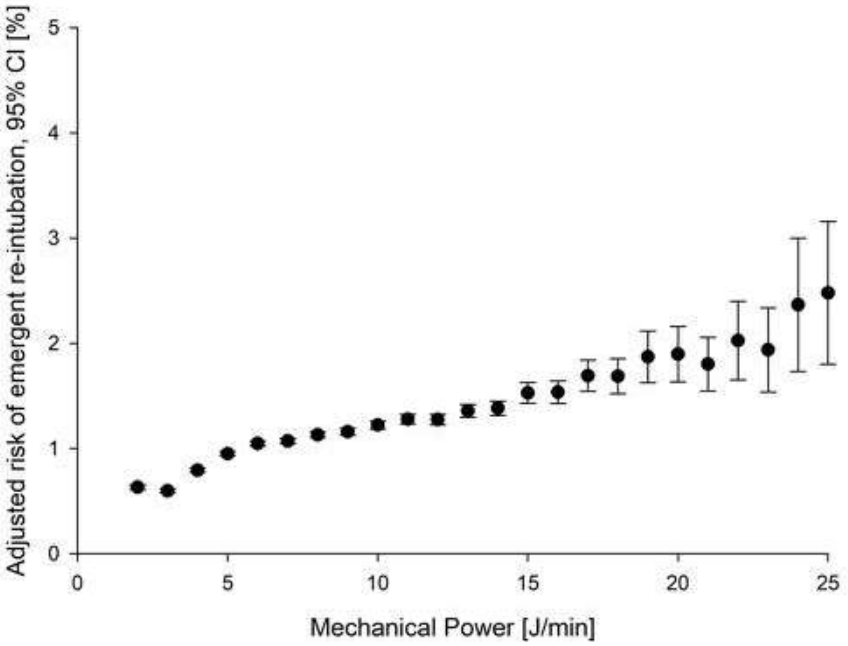

	No postoperative reintubation	Postoperative reintubation
N	238,583	2,524
Age, years	54.4 ± 16.2	62.3 ± 15.0
Female sex	134,645 (56.4%)	1,191 (47.2%)
Body mass index, kg/m²	28.6 ± 6.9	28.5 ± 7.5
ASA status	2 (2, 3)	3 (3, 3)
ASA status ≥3	80,349 (33.7%)	1,917 (76.0%)
Charlson Comorbidity Index	1 (0, 3)	3 (1, 6)
SPORC	2 (0, 3)	5 (3, 6)
History of COPD	12,623 (5.3%)	383 (15.2%)
History of chronic heart failure	13,827 (5.8%)	555 (22.0%)
Smoking history	27,913 (11.7%)	371 (14.7%)
Type of surgery		
General	40,644 (17.0%)	292 (11.6%)
Gynecology	24,857 (10.4%)	63 (2.5%)
Neurosurgery	15,656 (6.6%)	301 (11.9%)
Orthopedic	50,614 (21.2%)	552 (21.9%)
Plastic	15,910 (6.7%)	55 (2.2%)
Oncological	11,610 (4.9%)	68 (2.7%)
Thoracic	15,739 (6.6%)	406 (16.1%)
Transplant	4,364 (1.8%)	89 (3.5%)
Urological	20,819 (8.7%)	74 (2.9%)
Vascular	9,186 (3.9%)	261 (10.3%)
Other	29,182 (12.2%)	363 (14.4%)
Duration of surgery, min	134 (86, 207)	203 (130, 319)
Work relative value units	13.2 (7.4, 19.9)	20.1 (12.3, 26.7)
Vasopressor requirement	129,942 (54.5%)	2,065 (81.8%)
Fluids, ml	1,000 (750, 1,800)	1,600 (1,000, 3,000)
Tidal volume, ml per kg IBW	8.3 ± 2.2	8.2 ± 2.1
Peak inspiratory pressure, cmH₂O	20.1 ± 6.5	22.6 ± 6.1
Positive end-expiratory pressure, cmH₂O	4.1 (2.0, 5.0)	5.0 (2.5, 5.1)
Respiratory rate, 1/min	12 (10, 13)	12 (10, 13)
Inspiratory oxygen fraction, %	55.8 ± 17.5	63.48 ± 19.8
Mechanical Power, J/min	7.3 ± 3.6	8.1 ± 3.7
30-day mortality	954 (0.4%)	251 (9.9%)
Hospital length of stay, days	2 (1, 5)	13 (8, 22)

Data are expressed as mean±SD, median (IQR), or frequency (percent)
ASA, American Society of Anesthesiologists; SPORC, Score for the Prediction of Postoperative Respiratory Complications

Respiration - 4 STIL-STRONGER: Association of Sugammadex Use with the Incidence of Postoperative Pulmonary Complications in a Population at Increased Risk

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Introduction: Sugammadex selectively reverses rocuronium and vecuronium induced neuromuscular blockade (NMB) and was introduced to the US in December 2015. The STRONGER Study demonstrated an association between sugammadex use and decreased odds of postoperative pulmonary complications (PPCs).[1] It is not known if this effect is present in patients thought to be at increased risk of PPCs.[2] We therefore evaluated the association of NMB reversal choice with incidence of PPCs in this subset of the STRONGER cohort.[1]

Methods: After obtaining IRB approval, using data from the Multicenter Perioperative Outcomes Group Database,[3] we conducted a retrospective matched cohort study. Noncardiac, nonemergency adult (>18yrs) surgical inpatients were included if they had general anesthesia with an endotracheal intubation, received rocuronium and/or vecuronium, were reversed with neostigmine (27 to 77 mcg/kg) or sugammadex (1.8-4.4mg/kg) and were considered at increased risk of a PPC based on: [ASA Physical Status (PS) of 3 or 4]; AND [Age > 80 or Procedure Length > 2hrs]; AND [Intrathoracic or Abdominal Surgery]. As in STRONGER[1], cases were included if administered neostigmine between January 2014 and the date sugammadex was first used at that site, or administered sugammadex 6 months after first use of sugammadex at that site and August 31st 2018. Patients were excluded if they: were intubated prior to OR or transferred from the ICU, underwent liver or lung transplantation, received both sugammadex and neostigmine, were reversed to facilitate neuromuscular monitoring, had myasthenia gravis, were taking pyridostigmine chronically, had renal failure, lacked follow up or exposure data. The cases were matched 1:1 based on several patient and procedural characteristics (See Table 1). A conditional logistic regression model estimated the association between postoperative pulmonary complications (defined as ICD 9/10 coded diagnoses of Respiratory Failure or Pneumonia) and the choice of neuromuscular blockade reversal.

Results: 16,042 cases from 12 institutions were eligible for matching and resulted in 3,817 matched pairs. The distribution of match characteristics of the matched and un-matched populations are presented in Table 1. Additional characteristics after matching are presented in Table 2. The primary outcome occurred in 5.9% (n=225) of patients reversed with neostigmine and 2.6% (n=99) of those reversed with sugammadex ($p < 0.01$) – Figure 1. After adjustment, the use of sugammadex was associated with a decreased odds of the occurrence of a PPC (OR: 0.44, 95% CI: 0.33-0.59 $p < 0.0001$, Figure 2), of respiratory failure (OR: 0.32 CI: 0.21-0.5 $p < 0.0001$) and of pneumonia (OR: 0.51, 0.36-0.72 $p < 0.0001$).

Conclusion: In a multicenter cohort of US patients at increased risk of postoperative pulmonary complications presenting for major surgery, the use of sugammadex was associated with decreased odds of subsequent occurrence of postoperative pulmonary complications compared to neostigmine.

References: 1. Kheterpal S et al. Anesthesiology. 2020 Jun;132(6):1371-1381. 2. Canet J et al. Anesthesiology. 2010 Dec;113(6):1338-50. 3. Colquhoun DA et al. Anesth Analg. 2020 May;130(5):1133-1146

Figure 1 - Incidence of Primary Outcome and component parts in the Sugammadex vs Neostigmine Groups

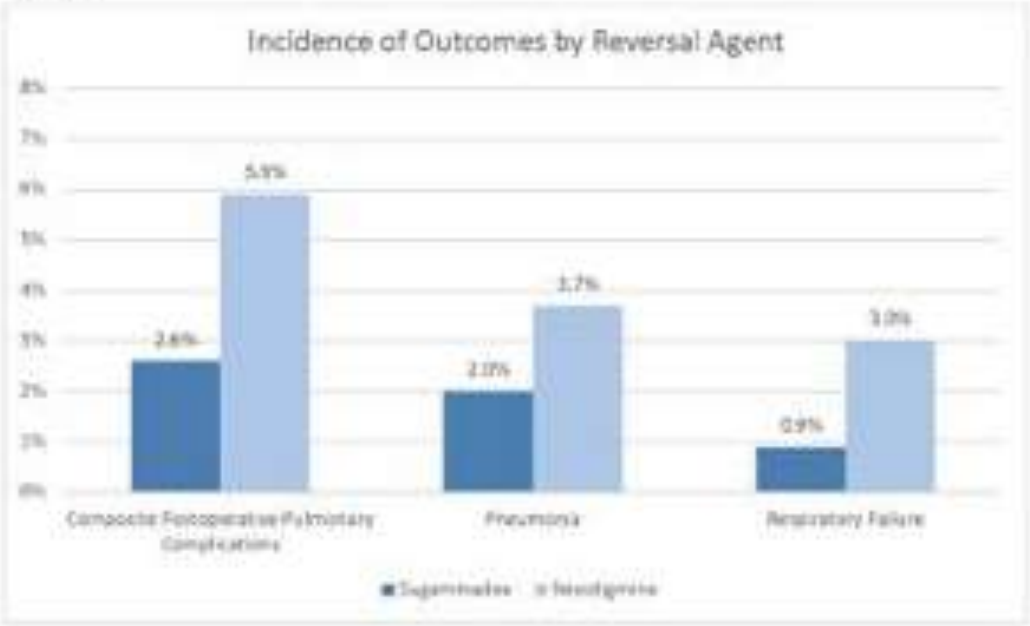

Figure 2 – OR Plot for Model Covariates for the Conditional Logistic Regression Model Examining the Association Between Neuromuscular Blockade Reversal Agent Selection and Development of Postoperative Pulmonary Complication.

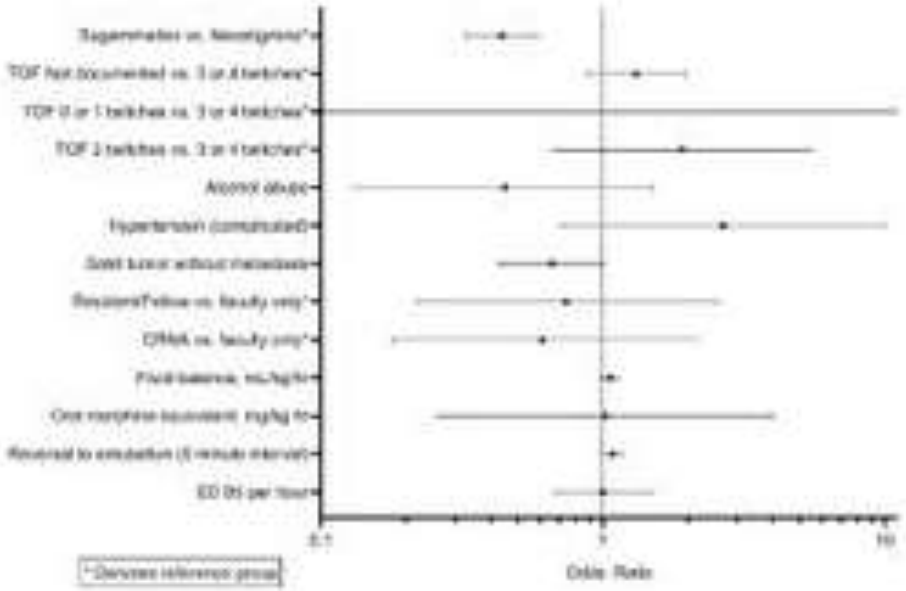

Table 1 – Patient demographics and case characteristics of matched and unmatched sugammadex cases and neostigmine cases.

Covariate Used for Matching:	Matched Cases		Unmatched Cases			
			Unmatched Sugammadex Cases		Unmatched Neostigmine Cases	
	N=3,817		N=1,689		N=6,719	
	N	Column %	N	Column %	N	Column %
Age*						
18-40 years	251	6.6%	198	11.6%	807	8.9%
41-50 years	408	10.7%	195	11.5%	817	12.2%
51-60 years	896	23.5%	341	20.2%	1,836	25.7%
61-70 years	1,251	32.8%	463	27.4%	2,099	31.2%
71-80 years	773	20.3%	345	20.4%	1,150	17.1%
81-90+ years	238	6.2%	149	8.8%	600	8.9%
Sex:						
Male	1,774	46.5%	799	47.3%	3,646	54.3%
Female	2,043	53.5%	887	52.5%	3,066	45.6%
ASA Status:						
3	3,784	99.1%	1,528	90.5%	6,583	97.9%
4	33	0.9%	161	9.5%	136	2.0%
WHO BMI:						
Underweight	22	0.6%	43	2.5%	160	2.4%
Normal	888	23.1%	378	23.2%	1,541	24.7%
Overweight	1,188	31.1%	414	25.4%	1,796	28.8%
Class I	771	20.5%	360	22.0%	1,289	20.6%
Class II	429	11.4%	213	13.3%	714	11.5%
Class III	501	13.3%	209	12.6%	738	11.8%
Select Elixhauser Comorbidities:						
Cardiac Arrhythmias	453	11.9%	578	34.2%	1,179	19.0%
Chronic Pulmonary Disease	579	13.2%	559	33.1%	1,621	24.1%
Congestive Heart Failure	50	1.3%	193	11.4%	423	6.3%
Liver Disease	140	3.7%	232	13.7%	625	9.3%
Paralysis	8	0.2%	48	2.7%	68	1.0%
Body Region/Type of Procedure:						
Intrathoracic Non-Cardiac	454	11.9%	432	25.6%	1,390	20.7%
Abdominal	3,363	88.1%	1,257	74.4%	5,329	79.3%
Type of neuromuscular blockade:						
Rocuronium only	2,849	74.6%	1,093	64.7%	5,239	78.0%
Vecuronium or (Rocuronium and Vecuronium)	868	23.4%	596	35.3%	1,480	22.0%

Table 2 - Patient demographics and case characteristics of non-matched covariates after matching sugammadex

	Sugammadex Cases N=1817		Neostigmine Cases N=1817		
	N	%	N	%	Absolute Standardized Difference
Last TOF documented within 30 minutes of extubation					0.32
Not documented	961	15.2%	1,426	37.4%	
0 or 1 twitches	171	4.6%	63	1.7%	
2 twitches	196	5.1%	100	2.6%	
3 or 4 twitches	2,485	65.1%	2,228	58.4%	
General Anesthesia Technique					0.09
GA yes, volatile yes	3,730	97.7%	3,774	98.9%	
GA yes, no volatile, no nitrous	80	2.1%	37	1.0%	
GA yes, nitrous yes	7	0.2%	6	0.2%	
Other Elixhauser comorbidities					
AIDS/HIV	8	0.2%	4	0.1%	0.03
Alcohol Abuse	10	0.3%	48	1.3%	0.12
Blood Loss Anemia	67	1.8%	40	1.0%	0.06
Coagulopathy	119	3.0%	100	2.6%	0.03
Deficiency Anemia	151	4.0%	105	2.8%	0.07
Depression	398	10.4%	500	13.1%	0.08
Diabetes (complicated)	51	1.4%	38	0.9%	0.04
Diabetes (uncomplicated)	709	18.6%	700	18.3%	0.01
Drug Abuse	62	1.6%	58	1.5%	0.01
Fluid/Electrolyte Disorders	414	10.8%	447	11.7%	0.03
Hypertension (complicated)	61	1.6%	23	0.6%	0.10
Hypertension (uncomplicated)	2,094	54.9%	2,112	55.3%	0.01
Hypothyroidism	442	11.6%	469	12.3%	0.02
Lymphoma	35	0.9%	44	1.2%	0.02
Metastatic Cancer	736	19.3%	699	18.3%	0.03
Other Neurological Disorders	91	2.4%	111	2.9%	0.03
Peptic Ulcer Disease, Excluding Bleeding	46	1.2%	48	1.3%	0.01
Peripheral Vascular Disorders	171	4.5%	172	4.5%	0.00
Psychoses	14	0.4%	28	0.7%	0.04
Pulmonary Circulation Disorders	92	2.4%	93	2.4%	0.00
Rheumatoid Arthritis Collagen Vascular Diseases	91	2.4%	89	2.3%	0.00
Solid Tumor Without Metastasis	2,198	57.6%	1,607	42.1%	0.31
Valvular Disease	118	3.1%	132	3.5%	0.02
Weight Loss	297	7.8%	329	8.6%	0.03
Primary In-Room Provider					0.11
Faculty Only	158	4.1%	103	2.6%	
Resident/Fellow	2,029	53.2%	2,199	57.6%	
CRNA	1,631	42.7%	1,516	39.7%	
Estimated Blood Loss					0.09

0-500 ml	3,429	89.8%	3,322	87.0%	
501-1000 ml	260	6.8%	330	8.6%	
>1000 ml	128	3.4%	165	4.3%	
Surgical Duration					0.02
>=2 hrs	3,710	97.2%	3,699	96.9%	
<2 hrs	107	2.8%	118	3.1%	
Sugammadex Dosing Range					
1.8 to 2.2 mg/kg	2,231	58.4%			N/A
>2.2 AND < 3.6 mg/kg	1,106	29.0%			
3.6 to 4.8 mg/kg	478	12.5%			
Neostigmine Dosing Range					
27 to <40 mcg/kg	N/A		1,295	34.0%	N/A
=>40 AND =<60 mcg/kg			2,048	53.6%	
>60 to 77 mcg/kg			475	12.4%	
	Median	IQR	Median	IQR	Standardized Difference
Surgical duration, hours	3.5	[2.5,4.5]	3.5	[2.5,4.5]	0.01
Fluid balance, mL/kg/hr	3.1	[1.8, 4.6]	3.6	[2.2, 5.5]	0.21
Intraop PRBC Transfusions (Units)	0	[0,0]	0	[0,0]	0.02
Intraop FFP Transfusions (Units)	0	[0,0]	0	[0,0]	0.01
Oral Morphine Equivalent, mg/kg hr	0.23	[0.16, 0.31]	0.24	[0.09, 0.36]	0.04
Median ventilator driving pressure	16	[13, 21]	17	[13, 22]	0.09
Age (years)	64	[54, 71]	65	[54, 71]	0.02
Time from last NMB dose to first reversal (15 minute interval)	4	[2.8, 5.9]	4.1	[2.8, 5.8]	0.00
Time from first reversal to Extubation (5 minute interval)	2.6	[1.4, 4.7]	3.4	[1.2, 5.2]	0.14
Time from last NMB to extubation (15 minute interval)	5	[3.7, 7.0]	5.4	[3.0, 7.3]	0.09
ED SS per hour	1.3	[1.1, 1.7]	1.3	[1.0, 1.6]	0.12

Respiration - 5 Impact of hyperoxia on renal tissue oxygenation, reactive oxygen species production, and oxidative damage in a murine ischemia reperfusion model

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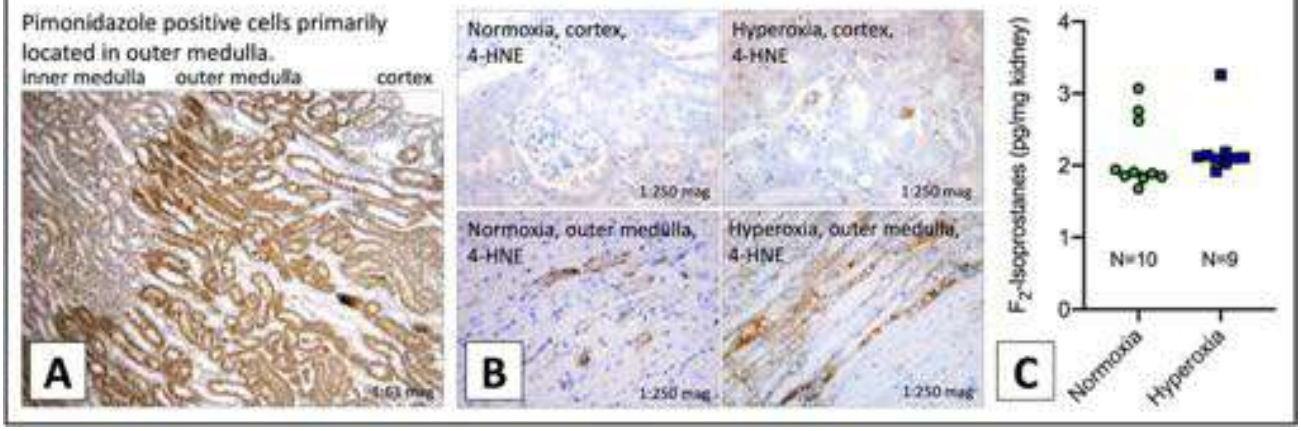
Introduction: Acute kidney injury (AKI) affects 10% of patients following major surgery and is independently associated with extra-renal organ injury, increased duration of hospitalization, long-term development of chronic kidney disease and dialysis, and death. Perioperative renal ischemia and reperfusion (IR) is common and contributes to the development of AKI, in part, by increasing production of reactive oxygen species (ROS) and leading to oxidative damage. Patients are frequently given excess oxygen during surgery (hyperoxia) to reduce hypoxia, but hyperoxia constricts arterioles and may shunt blood away from some tissue beds. The impact of hyperoxia on tissue oxygenation, reactive oxygen species production, and oxidative damage during perioperative IR is unclear. We hypothesized that hyperoxia during renal IR affects kidney hypoxia, ROS production, and oxidative damage.

Methods: We randomly assigned 8-week-old FVBN male mice (N=20) to receive hyperoxia (100% oxygen) or normoxia (room air) during dorsal unilateral nephrectomy with contralateral renal ischemia/reperfusion surgery as follows. Mice were anesthetized with intraperitoneal ketamine/xylazine, the dorsal flanks were shaved and prepped for surgery, and we administered the assigned oxygen treatment through a nose cone for the remainder of the experiment. We dissected the right kidney through a dorsal lateral incision and then ligated, removed, and discarded it. We then exposed the left kidney through a contralateral incision, dissected the renal hilum, and placed a clamp on the renal artery and vein. At 30 minutes of ischemia, the clamp was released. Following 30 minutes of reperfusion, the animals were sacrificed via terminal bleed, and the left kidney was harvested and bisected. Half the kidney was placed in formalin for fixation and pimonidazole and 4-hydroxy-2-nonenal (4-HNE) staining, and half the kidney was snap frozen in liquid nitrogen for F2-isoprostane quantification by gas chromatography/mass spectrometry. Pimonidazole forms adducts with thiol-containing peptides under hypoxic conditions and therefore serves as a tissue hypoxia marker. 4-HNE is a product of ROS-mediated oxidation of cellular polyunsaturated fatty acids, thus 4-HNE serves as a ROS marker. F2-isoprostanes are end products of non-enzymatic arachidonic acid peroxidation that quantify oxidative damage in vivo.

Results: One mouse assigned hyperoxia died following anesthesia. The 19 remaining mice survived IR surgery and completed the study. Pimonidazole staining (hypoxia marker) was primarily located in the outer medulla (Panel A), consistent with corticomedullary ischemia, and was similar in mice treated with hyperoxia or normoxia. Renal 4-HNE staining (ROS marker) was increased in mice treated with hyperoxia. 4-HNE staining was primarily located in the outer medulla (Panel B). Renal F2-isoprostanes (oxidative damage markers) were 2.2 ± 0.4 pg/mg kidney in mice treated with hyperoxia and 2.1 ± 0.5 pg/mg kidney in mice treated with normoxia. (Panel C)

Conclusion: Hyperoxia during renal IR did not appear to affect the degree of hypoxia in the kidney, but medullary ROS production and renal F2-isoprostanes appeared to be increased in mice treated with hyperoxia, compared to mice treated with normoxia during renal IR. In subsequent studies we will determine if indeed hyperoxia during renal IR increases renal oxidative damage, if molecular markers of hypoxia and oxidative damage are associated with kidney injury, and if hyperoxia during renal IR affects kidney injury in mice and AKI in surgical patients.

Figure. Renal IR led to tissue hypoxia post reperfusion in both groups (pimonidazole, **Panel A**), but ROS (4-HNE, **Panel B**) and oxidative damage (F_2I, **Panel C**) appeared higher in hyperoxia treated animals.



Respiration - 6 Inhibition of phospholipase C in human airway epithelial cells with ginger metabolite-inspired compounds

Elvedin Lukovic[1], Benjamin Redenti[1], Yingdong Zhu[2], Shengmin Sang[2], Charles W Emala[1]

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Introduction: Asthma causes pathological alterations in airway smooth muscle (ASM), and chronic inflammation and mucus production in airway epithelium (AE). Available therapies provide poor symptom management in ~40% of severe asthmatic patients, indicating the need for novel treatment alternatives. Our lab has demonstrated that 6-shogaol (6S), a primary constituent of ginger, its metabolites, and synthetic derivatives (Fig. 1A) relax ex vivo human ASM, and attenuate intracellular calcium ($[Ca^{2+}]_i$) increases and IP_3 synthesis, likely by inhibition of phospholipase C (PLC). These compounds may also affect airway epithelial PLC, which has been implicated in the expression and secretion of mucins and inflammatory cytokines that are upregulated in asthma. Thus, we hypothesize that ginger constituents, metabolites, and synthetic derivates will also inhibit airway epithelial PLC and prevent PLC-mediated $[Ca^{2+}]_i$ increases.

Methods: Gingerols, shogaols, 6S metabolites, or synthetic derivatives (Fig. 1A) were assayed for their ability to inhibit bradykinin-induced increases in $[Ca^{2+}]_i$ in airway epithelial cells (NCI-H292 and BEAS-2B). Cells were loaded with a Ca^{2+}-specific ratiometric fluorophore Fura-2 AM (5 μM), pretreated with 6S derivatives (50 μM) and challenged with the Gq-coupled ligand bradykinin (10 μM) to measure $[Ca^{2+}]_i$ fluorescence. Statistical analysis included one-way ANOVA with Dunnett's post-test, and was performed using GraphPad Prism version 4.0 for Windows, GraphPad Software.

Results: As prior studies suggested that ASM relaxation by ginger phytochemicals is caused by inhibition of ASM phospholipase C (PLC)-mediated increases in $[Ca^{2+}]_i$, we measured the effects of 6S metabolites and derivatives on $[Ca^{2+}]_i$ in human AE cells. Pretreatment of BEAS-2B cells with M9, a major 6S metabolite, and M14-4, a synthetic derivative of metabolite M14, significantly reduced bradykinin-induced increases in intracellular calcium compared to vehicle (49.7 ± 10%, $p < 0.001$, and 69.4 ± 5%, $p < 0.05$, respectively, n = 6-8) (Fig. 1B).

Conclusion: 6S metabolites and metabolite-based novel synthetic derivatives attenuate the rise of Gq-mediated $[Ca^{2+}]_i$. Since these Gq-coupled pathways regulate mucin and cytokine production in airway epithelial cells, these compounds offer promise as inhibitors of these pathologic contributions to airway asthmatic responses. This may be the first class of drugs, by targeting two key pulmonary cell types (ASM and AE), that could control both asthma progression and exacerbation.

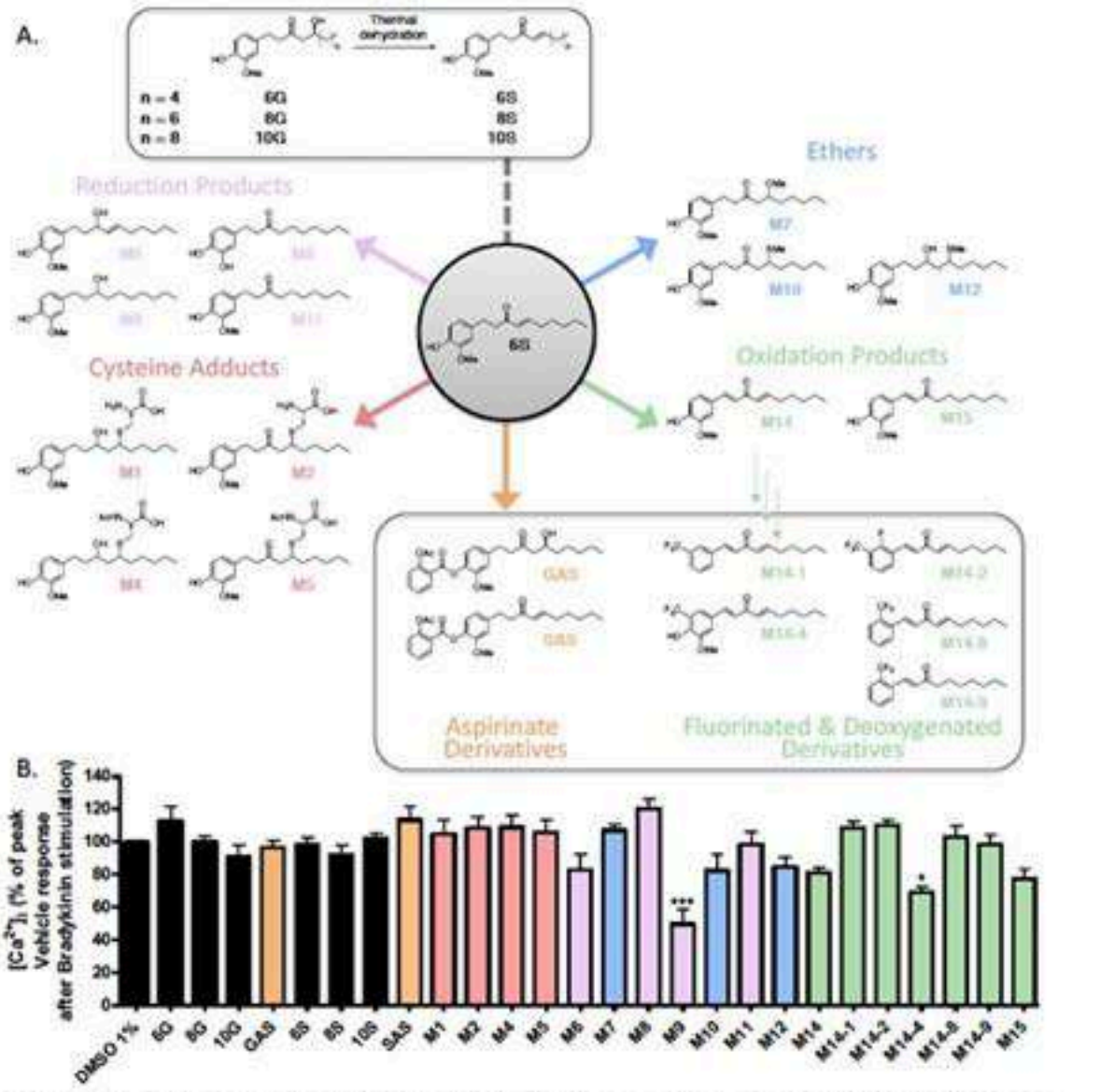

Fig 1. A natural ginger constituent 6-shogaol (6S), its human metabolites and synthetic derivatives as modulators of airway epithelial cell response to inflammatory stimuli. A. Structures of gingerols, shogaols, 6-shogaol (6S) human metabolites, and synthetic derivatives of 6S. B. Inhibition of increases in $[Ca^{2+}]_i$ in BEAS-2B human bronchial epithelial cells pretreated with either vehicle (1% DMSO), gingerols, shogaols, or shogaol derivatives (50 μM) stimulated by bradykinin (10 μM). * $p < 0.05$; *** $p < 0.001$ compared to vehicle, n = 6-8.

Respiration - 7 Separation of cardiogenic oscillations from airflow waveforms using singular spectrum analysis

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Introduction: In the clinical application of pressure support ventilation for intubated patients in the operating room or ICU, superimposed airflow fluctuations due to cardiac contractility can inadvertently trigger ventilator support in the absence of patient respiratory effort. This phenomenon has been described in case reports in which such ventilator autotriggering resulted in high minute ventilation and required manual increase of the trigger threshold or the level of PEEP to eliminate it (1). Extraction of cardiogenic oscillations from the respiratory flow pattern using signal separation techniques would improve performance of this ventilation mode. This study applied singular spectrum analysis to isolate cardiogenic oscillations from high-resolution airflow data during pressure support ventilation in patients undergoing general endotracheal anesthesia.

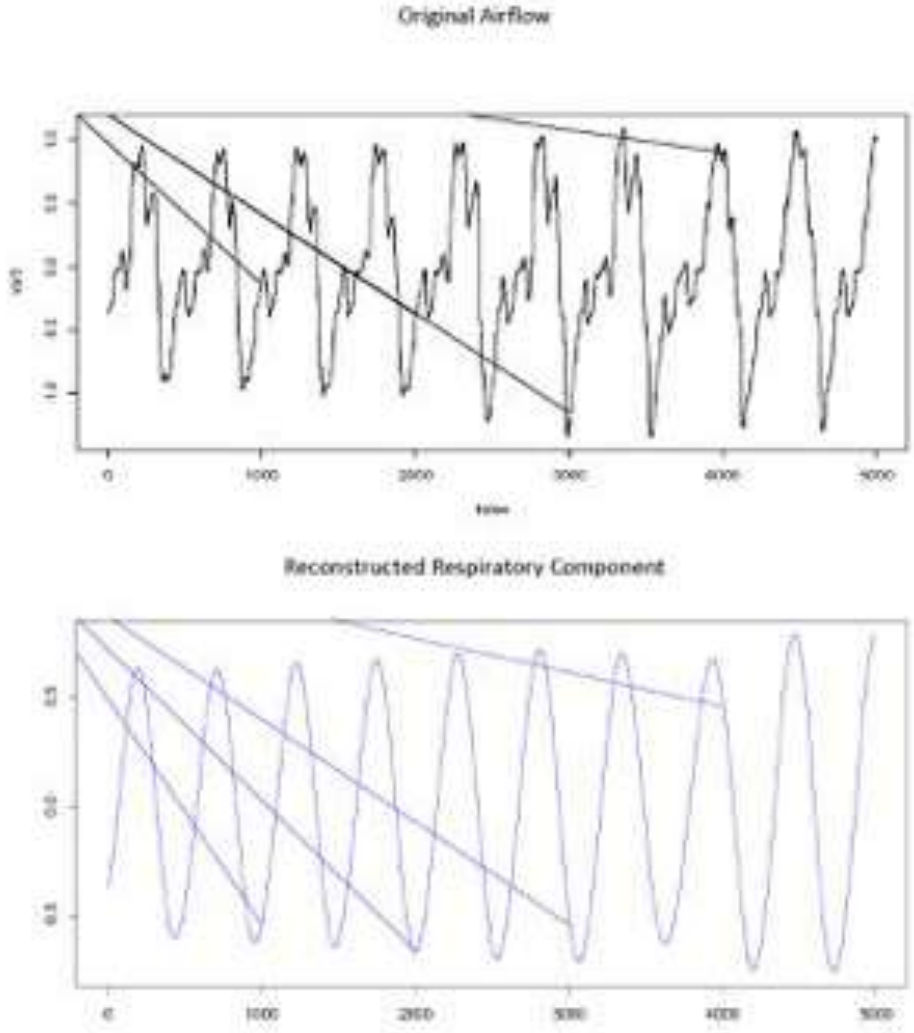
Methods: Institutional IRB approval was obtained for this study. When pressure support ventilation was selected by the anesthesiologist caring for an adult patient undergoing general endotracheal anesthesia in the operating room, de-identified end-tidal CO2 and airflow data were collected at a rate of 125Hz from the intraoperative monitoring systems for up to 10 minutes using MediCollector Bedside software (MediCollector LLC, Winchester, MA). Simultaneous electrocardiogram data were collected at 250Hz for reference purposes. Data was collected from ten patients.
Singular spectrum analysis (SSA) was performed to separate respiratory and cardiogenic waveforms within the airflow data. SSA is a model-free approach which separates a time series into trend, oscillatory components and noise (2). The one-dimensional time series values are embedded into a trajectory matrix consisting of time-lagged segments of the original series, followed by singular value decomposition of the trajectory matrix yielding a collection of eigenvalues and corresponding eigenvectors. The reconstruction procedure groups together eigenvectors corresponding to, in this case, oscillatory signals and computes the resultant matrix for each group. Diagonal averaging applied to these matrices produces reconstructed time series components. Singular spectrum analysis was performed on normalized airflow data using the Rssa package in R (3). The window length used to construct the trajectory matrix was set at 675; with a data sampling rate of 125Hz this spans at least one period of a typical respiratory cycle. Paired eigenvectors corresponding to oscillatory components within the original signal were identified by the magnitude and similarity of the singular values, weighted correlation plots and periodograms of the elementary eigenvectors in the decomposition. Selected pairs were utilized to reconstruct the cardiogenic and respiratory waveforms from the original airflow signal. The cardiogenic waveform was compared to the reference ECG.

Results: In the airflow signal, the main sources of variation are the respiratory excursions and cardiogenic oscillations. The respiratory excursions are more slowly varying and of significantly higher magnitude; these were reconstructed from the first pair of elementary matrices corresponding to the two leading singular values obtained in the decomposition. The cardiogenic waveform was reconstructed from elementary matrices corresponding to singular values 5 and 6. Figure 1 shows the normalized airflow signal over 40 seconds in a patient under general anesthesia receiving pressure support ventilation, the reconstructed respiratory and cardiogenic components and the contemporaneous ECG signal. The reconstructed cardiogenic component reproduces the patient heart rate consistent with that of the reference ECG signal.

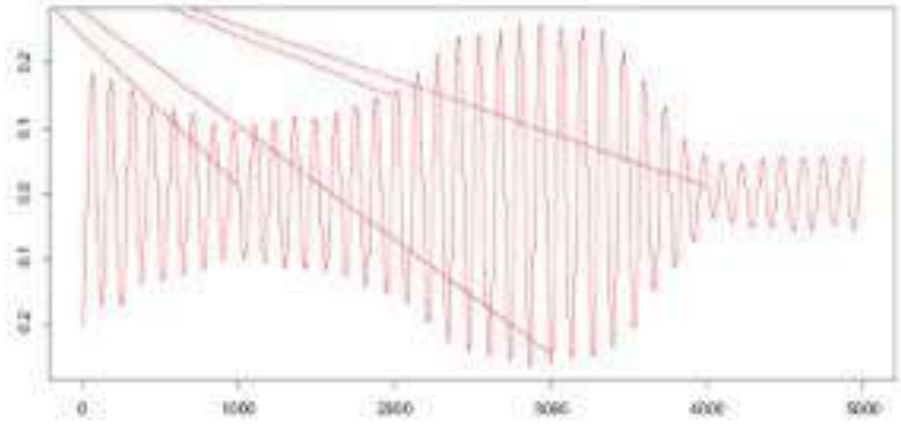
Conclusion: Separation of cardiogenic oscillations from the respiratory excursions in airflow signals can be applied to suppress autotriggering during pressure support ventilation. This type of biomedical signal is characterized by spectral overlap between the higher amplitude respiratory component and the lower amplitude cardiogenic component. Singular spectrum analysis was applied for extraction and separation of respiratory and cardiogenic contributions to the airflow signal with accurate extraction of the cardiogenic waveform.

References: 1. Anesth Analg 2009;109:470-2. 2. Singular spectrum analysis for time series. Heidelberg, Springer 2013. 3. Computational Statistics and Data Analysis 2014;71:934-54.

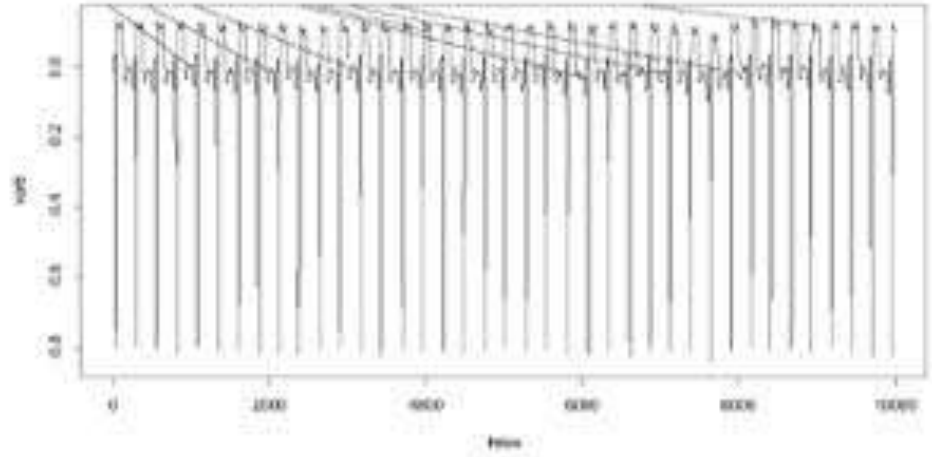
Figure 1



Reconstructed Cardiogenic Component



Reference ECG Signal



Sleep Medicine

Sleep Medicine - 1 Sleep Medicine and Anesthesia Core Curriculum Topics for Anesthesia Residency – A Modified Delphi Technique Survey

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Introduction: Sleep disorders affect up to 25% of the general population and are prevalent in surgical patients. Patients with sleep-disordered breathing such as obstructive sleep apnea (OSA), central sleep apnea, and sleep-related hypoventilation are at an increased risk of adverse perioperative events. Despite the potential impact of sleep-disordered breathing to the practice of anesthesia, the key topics of sleep medicine that should be included in anesthesia residency curricula have not been well-defined. The objective of this study was to determine the high priority sleep medicine topics that should be included in the education of anesthesia residents based on the insight of experts in the fields of Anesthesia and Sleep Medicine.

Methods: Two iterations of a prospective cross-sectional survey of 58 experts in the fields of Sleep Medicine and Anesthesia based on the Delphi technique were used to establish consensus on the sleep medicine topics that should be incorporated into anesthesia residency curricula. Experts were identified based on their publication record and include key opinion leaders, educational experts, and members of the Society of Anesthesia and Sleep Medicine (SASM). An initial topic list was generated by content experts based on well-known Sleep Medicine resources and guidelines from the SASM. The initial survey was a 17-item online questionnaire requesting feedback on the initial topic list through the use of 5-point Likert scale ratings, and open response questions inviting novel topic suggestions. The process was repeated in the second survey with the new topics identified in the initial iteration. The level of agreement used to define consensus for inclusion of a topic was over 80% of all experts selecting 'agree' or 'strongly agree' on the 5-point Likert Scale. Responses to the survey questions were analyzed with descriptive statistical methods and presented as percentages of participants selecting 'agree' and 'strongly agree'. A Mean Agreement Score (weighted average of ratings on the 5-point Likert scale) was determined to represent the distribution of ratings amongst participants. A weighted mean with standard deviations was calculated for the Mean Agreement Score.

Results: A total of 33 (57%) invited experts responded to the initial survey, and 28 (48%) responded to the second round. Most of the participants were anesthesiologists (82%) and 18% were sleep medicine physicians. The majority of participants (42%) had 11-20 years in practice and most survey respondents were from the United States (70%). The topics that were found to have 100% 'strong agreement' amongst experts were 1) the influence of opioids and anesthetics on control of breathing and upper airway obstruction; 2) potential interactions of wake-promoting/hypnotic medications with anesthetic agents; 3) effects of sleep and anesthesia on upper airway patency; 4) anesthetic considerations of OSA; and 5) postoperative respiration monitoring strategies for sleep-disordered breathing. Other topics identified as high priority for inclusion into anesthesia residency curricula (Mean Agreement Score 4.8-4.99) were 1) the effects of anesthetic drugs on respiratory control [4.97 (0.17)]; 2) mechanism of action and pharmacologic effects of hypnotic medications [4.85 (0.36)]; 3) relationship between pain, analgesia, and sleep [4.85 (0.44)]; 4) sleep assessment questionnaires and scales [4.88 (0.33)]; 5) OSA definition, epidemiology, risk factors, and perioperative management [4.94 (0.24)]; and 6) obesity hypoventilation syndrome, central sleep apnea, and periodic breathing anesthetic considerations and perioperative management [4.82 (0.39-0.53)]. The topics which had less than 80% agreement amongst the expert panel included the anesthetic implications of other sleep disorders, future pathways in sleep medicine and anesthesia, indications and efficacy of various surgical airway modification options to treat OSA, anesthesia for the fiberoptic diagnosis of OSA, impact of sleep deprivation on the immune system and pulmonary muscle function, the effect of alcohol and other recreational drugs on sleep, and CPAP therapy compliance strategies.

Conclusion: We provide a framework of key sleep medicine topics that can be incorporated into future design of anesthesia residency training curricula. The results of our survey will be instrumental to program directors and specialty boards in defining specific topics of sleep medicine deemed most important for the practice of anesthesiology.

Table 1. Sleep Medicine topics and their level of agreement for inclusion in the Sleep Medicine and Anesthesia core curriculum for anesthesia residency (n=33)

Topic	Mean Agreement Score* (SD)	No. of participants in agreement** (%)	No. of participants who strongly agree (%)
Definition and physiology of sleep			
• Sleep stages and cycle	4.48 (0.76)	30 (91)	20 (61)
• Circadian rhythms	4.12 (1.02)	27 (82)	14 (43)
• Overview of functional neuroanatomy of sleep	4.24 (1.00)	27 (82)	17 (52)
• Cardiovascular and respiratory regulation during sleep	4.70 (0.53)	32 (97)	24 (73)
Pharmacology and sleep			
• Hypnotic medications: mechanisms of action and pharmacologic effects	4.85 (0.36)	33 (100)	28 (85)
• Wake-promoting medications: mechanisms, efficacy and adverse events	4.70 (0.47)	33 (100)	23 (70)
• Potential interactions with anesthetic agents	5.00	33 (100)	33 (100)
• Influence of opioids and anesthetics on control of breathing and upper airway obstruction	5.00	33 (100)	33 (100)
Sleep physiology and anesthesia			
• Similarities and differences between sleep, anesthesia, and coma	4.70 (0.53)	32 (97)	24 (73)
• EEG activity in sleep stages and anesthesia	4.36 (0.93)	28 (85)	19 (58)
• Effects of anesthetic drugs on respiratory control	4.97 (0.17)	33 (100)	32 (97)
• Effects of sleep and anesthesia on upper airway patency	5.00	33 (100)	33 (100)
• Sleep and circadian rhythm in the preoperative period	4.30 (0.77)	27 (82)	16 (49)
• Pain, analgesia, and sleep	4.85 (0.44)	32 (97)	29 (88)
• Effects of anesthesia and surgery on sleep and circadian rhythms	4.67 (0.54)	32 (97)	23 (70)
Effects of anesthesia and surgery on sleep and circadian rhythms			
• Acute and chronic sleep deprivation	4.45 (0.56)	32 (97)	16 (49)
• Interaction between sleep deprivation and anesthesia	4.64 (0.49)	33 (100)	21 (64)
Methods to assess sleep			
• Sleep-related history and physical examination	4.58 (0.56)	32 (97)	20 (61)
• Questionnaires and scales (STOP-BANG, the Berlin Questionnaire, Epworth sleepiness scale etc.)	4.88 (0.33)	33 (100)	29 (88)
• Actigraphy, Respiratory, Polygraphy, Polysomnography	4.27 (0.88)	29 (88)	15 (46)
• Potential methods to use in the perioperative setting	4.67 (0.54)	32 (97)	23 (70)
Obstructive sleep apnea (OSA)			
• Definition, epidemiology and risk factors	4.94 (0.24)	33 (100)	31 (94)
• Clinical presentation	4.79 (0.48)	32 (97)	27 (82)
• Anesthetic considerations	5.00	33 (100)	33 (100)

• OSA in children and pregnant patients	4.70 (0.59)	31 (94)	25 (76)
• Pathophysiology of upper airway collapse in OSA	4.79 (0.48)	32 (97)	27 (82)
• Co-morbidities and complications	4.76 (0.56)	31 (94)	27 (82)
• Treatment options (surgery, CPAP and oral appliances)	4.79 (0.48)	32 (97)	27 (82)
• Perioperative guidelines and management	4.94 (0.24)	33 (100)	31 (94)
Central sleep apnea and periodic breathing			
• Definition, epidemiology and risk factors	4.67 (0.54)	32 (97)	23 (70)
• Clinical presentation	4.55 (0.56)	32 (97)	19 (58)
• Anesthetic considerations	4.82 (0.46)	32 (97)	28 (85)
• Treatment	4.64 (0.60)	31 (94)	23 (70)
• Perioperative management	4.82 (0.39)	33 (100)	27 (82)
Obesity hypoventilation syndrome			
• Definition, epidemiology and risk factors	4.76 (0.56)	31 (94)	27 (82)
• Clinical presentation	4.67 (0.60)	31 (94)	24 (75)
• Anesthetic considerations	4.82 (0.53)	31 (94)	29 (88)
• Perioperative implications and management	4.82 (0.53)	31 (94)	29 (88)
Anesthetic implications of other sleep disorders			
• Overview and anesthetic implications of non-respiratory sleep disorders	4.19 (1.09)	25 (76)	17 (53)
• Central disorders of hypersomnolence: Narcolepsy	3.91 (0.96)	23 (70)	9 (28)
• Central disorders of hypersomnolence: Idiopathic hypersomnia	3.66 (1.15)	20 (61)	8 (25)
• Circadian rhythm sleep-wake disorders	3.72 (1.11)	20 (61)	9 (28)
• Parasomnias	3.56 (1.13)	18 (55)	7 (21)
• Restless legs syndrome	3.69 (1.15)	21 (64)	8 (25)
Sleep in the hospitalized patient			
• Implications of sleep disturbances to patient health	4.34 (1.07)	28 (85)	19 (59)
• Sleep hygiene in perioperative and critical care setting	4.44 (0.95)	27 (82)	21 (66)
• Sleep and strategies to improve sleep in ICU	4.56 (0.84)	30 (91)	22 (69)
• Pain, analgesia, and disrupted sleep	4.78 (0.49)	31 (94)	26 (81)
Impact of sleep deprivation on physician wellness			
• Performance deficit during sleep deprivation	4.47 (0.72)	28 (85)	19 (59)
• Strategies for good sleep hygiene	4.50 (0.72)	28 (85)	20 (63)
• Sleep, stress, and burn out	4.53 (0.67)	29 (88)	20 (63)
• Effects of shift work on sleep	4.44 (0.67)	29 (88)	17 (53)
Obstructive sleep apnea			
• Differences between clinical presentation of pediatric vs. adult OSA	4.21 (0.96)	23 (82)	13 (46)
• When questionnaires (e.g. STOP-Bang, Berlin Questionnaire, Epworth sleepiness scale) are not applicable	4.54 (0.51)	28 (100)	15 (54)
• Indications and efficacy of various surgical airway modification options to treat OSA (e.g. drug induced sleep endoscopy and genioglossus stimulation)	4.11 (0.83)	22 (79)	10 (36)

• Anesthesia for the fiberoptic diagnosis of OSA and its anatomical location	4.11 (1.03)	20 (71)	13 (46)
• Role of oxygen therapy in patients at risk for OSA	4.54 (0.58)	27 (96)	16 (57)
Impact of sleep deprivation			
• Impact of sleep deprivation on immune system	4.00 (0.00)	21 (75)	9 (32)
• Impact of sleep deprivation on pulmonary muscle function	4.07 (0.90)	22 (79)	10 (36)
• Sleep deprivation and delirium	4.61 (0.69)	25 (89)	20 (71)
• Effect of alcohol and other recreational drugs on sleep	4.21 (0.83)	21 (75)	13 (46)
Non-invasive ventilation			
• Different non-invasive ventilation modalities and their indications in sleep-disordered breathing	4.79 (0.42)	28 (100)	22 (79)
• CPAP therapy compliance strategies	4.29 (0.85)	21 (75)	15 (54)
• Pressure considerations in sleep-disordered breathing	4.32 (0.77)	25 (89)	13 (46)
• Mask interface options	4.25 (0.75)	25 (89)	11 (38)
• Advanced PAP therapies for complicated sleep-disordered breathing	4.07 (0.90)	22 (79)	10 (36)
Perioperative considerations in sleep-disordered breathing			
• Postoperative respiration monitoring strategies	5.00	28 (100)	28 (100)
• Preoperative considerations in sleep-disordered breathing	4.89 (0.42)	27 (96)	26 (93)
• Indications for and appropriate use of high care and intensive care facilities	4.75 (0.52)	27 (96)	22 (79)
• Indications for Sleep Medicine consultation	4.54 (0.69)	27 (96)	17 (61)
Future pathways in Sleep Medicine and Anesthesia			
• Sleep medicine and fellowship training	3.75 (1.00)	17 (61)	7 (25)
• Pathways to certification in Sleep Medicine	3.71 (1.08)	18 (64)	7 (25)
• What a Sleep Medicine practice could look like (e.g. in academic vs. private practice setting)	3.32 (1.22)	15 (54)	4 (14)

*Data are presented as means of ratings on a 5-point Likert scale, where 5 indicates strong agreement and 1 indicates strong disagreement.
**Percentage of participants who selected either "agree" or "strongly agree"

Sleep Medicine - 2 Can the complete blood count be used as a reliable screening tool for obstructive sleep apnea?

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Introduction: Obstructive sleep apnea (OSA) is a common disorder, defined by nocturnal intermittent hypoxia. Hypoxia has been shown to cause increases in erythropoietin production and inflammation. [1,2] Thus, we hypothesized that the complete blood count (CBC) parameters would reflect the hypoxic burden in OSA, and may act as an inexpensive alternative clinical tool for the screening and assessment of OSA patients. The objective of this study was to evaluate whether nocturnal intermittent hypoxia and severity of OSA, as measured by the apnea-hypopnea index (AHI) and mean oxygen saturation (SpO2), affect hematological parameters as measured by the CBC.

Methods: This post-hoc analysis included 941 surgical patients enrolled from 2007 to 2017 from two hospitals. Consented patients, aged ≥18 years, underwent a portable sleep apnea study (Embletta or ApneaLink Plus). Pre-operative CBC data was extracted from electronic medical records. Patients were stratified according to their AHI scores, into no OSA (AHI <5), mild (AHI ≥5 – <15), moderate (AHI ≥15 – <30), and severe (AHI ≥30) OSA groups. Patients on OSA therapy were excluded from this study. One-way analysis of variance or Kruskal-Wallis tests were conducted to examine the difference in severity of OSA for continuous variables, and chi-square tests were conducted for categorical variables. A Pearson correlation analysis was used to examine the association between mean SpO2, body mass index (BMI), age, and the different hematological parameters. Multivariable regression analysis was preformed to examine the predictors of intermittent hypoxia by considering confounding factors including age, BMI, sex, and hypertension.

Results: There were 244 patients without OSA, 294 with mild, 223 with moderate, and 180 with severe OSA. Patients had a mean age 63(11) years, BMI 31(7) kg/m2, and 50% were male. There were significant differences among BMI, age, gender, hypertension, mean SpO2, hemoglobin, hematocrit and basophils for the different severity of OSA. Further, post hoc analysis showed a difference between the different severities of OSA for the significant variables. Compared to patients with no OSA, those with severe OSA had lower mean SpO2 (Figure 1A). Hemoglobin was significantly different between patients with moderate OSA vs no OSA, as well as severe OSA vs no OSA (Figure 1B). Hematocrit and basophils were significantly different between severe OSA vs no OSA. For mean SpO2, there were negative associations with body mass index (r= -0.287; P<0.001), age (r=-0.077; P=0.021), hemoglobin (r=-0.208; P<0.001), hematocrit (r=-0.220; P<0.001), red blood cells (r=-0.107; P=0.001), mean corpuscular volume (MCV) (r=-0.159; P<0.001), mean corpuscular hemoglobin (r=-0.142; P<0.001), and basophils (r=-0.091; P=0.007). All analyzed parameters remained within normal clinical range. Controlling for age, BMI, sex and hypertension, multivariable regression identified hemoglobin and MCV to be an independent predictor of hypoxia defined by mean SpO2.

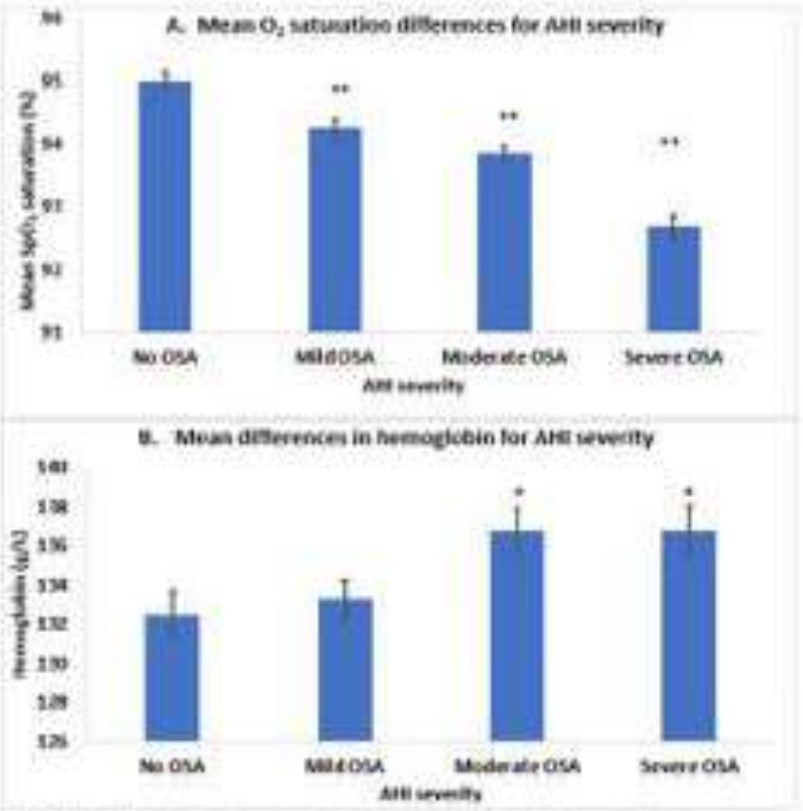
Conclusion: This study demonstrated significant associations among hemoglobin, hematocrit, MCV, and basophils, with both SpO2 and AHI. Using mean SpO2, we identified hemoglobin and MCV as significant independent predictors of hypoxia in OSA patients. However, all of the CBC parameters were within normal clinical ranges. Thus, while we have found modest changes among the CBC to reflect the hypoxic burden seen in OSA, no single parameter can aid reliably in the prediction or assessment of OSA.

References: 1. Am J Respir Crit Care Med. 2006;174(7):824-830. 2. Eur Arch Otorhinolaryngol. 2017;274(6):2505-2512.

Figure

Figure 1. (A) shows that there was a significant difference in the severity of OSA for mean oxygen saturation. Further post-hoc analysis showed that there was a significant difference between no OSA and mild OSA (P<0.01), no OSA and moderate OSA (P<0.01), and no OSA and severe OSA (P<0.01).

Figure 1. (B) shows that there was a significant difference in the severity of OSA for hemoglobin. Further post-hoc analysis showed that there was a significant difference between no OSA and moderate OSA (P<0.05), no OSA and severe OSA (P<0.05).



*p<0.05, **p<0.01. Vertical lines on the bars represent standard error of the mean.
Abbreviation: AHI, Apnea hypopnea index; OSA, Obstructive sleep apnea; SpO_2, Oxygen saturation

Sleep Medicine - 3 Perioperative Adherence to Continuous Positive Airway Pressure and its Effect on Postoperative Nocturnal Hypoxemia in Obstructive Sleep Apnea Patients: a Prospective Cohort Study

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Introduction: Although continuous positive airway pressure (CPAP) is the first line treatment for obstructive sleep apnea (OSA) patients, the perioperative adherence rate is unclear. The objective of this study was to determine the perioperative adherence rate of patients with OSA with a CPAP prescription and the effect of adherence on nocturnal oxygen saturation.

Methods: This prospective cohort study included adult surgical patients with a diagnosis of OSA with CPAP prescription undergoing elective non-cardiac surgery. Patients were divided into CPAP adherent and non-adherent groups based on duration of usage (≥ 4h/night). Overnight oximetry was performed preoperatively and on postoperative night 1 and 2 (N1, N2). The primary outcome was adherence rate and secondary outcomes were nocturnal oxygen saturation. A linear fixed effects model was used to test the relationship between CPAP adherence and oxygen saturation, adjusted for supplemental O2 therapy.

Results: One hundred and thirty-two patients completed the study. CPAP adherence was 61% preoperatively, 58% on postoperative N1, and 59% on N2. Forty-nine percent were consistently CPAP adherent pre- and postoperatively. Using a linear fixed effects regression, oxygen desaturation index (ODI) was significantly improved by CPAP adherence ($p = 0.0011$). The interaction term CPAP x N1 was significant ($p = 0.0015$), suggesting that the effect of CPAP adherence varied on N1 vs preoperatively. There was no benefit of CPAP adherence on postoperative mean SpO2, minimum SpO2, and percentage of sleep duration with SpO2 <90%. Supplemental oxygen therapy was higher in the CPAP non-adherent group vs adherent group on N1 (47% vs 9.8%, $p < 0.001$).

Conclusion: Among patients with a preoperative CPAP prescription, approximately 50% were consistently adherent. CPAP adherence was associated with improved preoperative ODI and the benefit was maintained on N1 and improved pain control. These modest effects may be underestimated by a higher severity of OSA in the CPAP adherent group and a higher rate of oxygen supplementation in the non-adherent group.

Technology, Computing and Simulation, Equipment Monitoring

Technology, Computing and Simulation, Equipment Monitoring - 1 Evaluation of the efficacy and safety of a novel dermatotomy device for central venous cannulation

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Introduction: Central venous cannulation (CVC) is one of the most common procedures performed in the United States. More than 5 million CVC's are performed annually in the United States. Dermatotomy incision and dilation are important steps for CVC. A precise incision is necessary to ensure success, minimize bleeding, and avoid the need for a second dermatotomy. The Guideblade® is a novel wire-guided scalpel that utilizes the Seldinger's technique to facilitate the dermatotomy incision. The hypothesis that the Guideblade® is a safe and effective instrument for performing the dermatotomy for CVC was tested.

Methods: In an IRB-approved protocol, cardiac surgical and major vascular patients who required CVC insertion were enrolled after written informed consent. CVC was performed according to the institutional protocol. The CVC catheter type, triple lumen catheter (ABG+ Multiple-Lumen Central Venous Catheterization, Arrow Inc®, Reading, PA), Introducer catheter (ARROWg+ard Blue PSI kit Cath-Gard, Arrow Inc®, Reading, PA), and Multi-lumen access catheter (MAC®, Arrow Inc®, Reading, PA) was chosen by the attending anesthesiologist. It was common practice to place two central lines (double sticks) for cardiac operations. The Guideblade®, was used to create the dermatotomy incision after guidewire insertion. The number of dermatotomies required, dilations required, catheter insertion attempts, wire kinking, or need for additional tools for CVC were recorded. The primary outcome was the rate of successful CVC without additional equipment. The secondary outcomes were bleeding at the insertion site at 30 min after CVC and immediately after operation.

Results: 99 patients, 61 (61.6%) male and 38 (38.4%) female, participated in the study with 187 CVC procedures. The mean and standard deviation (mean+SD) of body weight (kg), height (cm) and BMI (kg/m2) were 85+22, 172+10 and 29+6. 89 (89%) patients received 2 central lines. 13% of patients had abnormal baseline coagulation defined as INR > 1.5 or aPTT >48 seconds. 98% of patients received heparin during the procedure with a mean maximum ACT value of 708+180 seconds. All CVC procedures were performed by anesthesiology residents or cardiothoracic anesthesiology fellows. CVC was successful without need for additional equipment in 100%. Only a single dermatotomy was required for CVC in 90% (89 out of 99 patients). There were no observations of of wire kinking or user injury. Bleeding at the insertion sites was classified as 'no bleeding' or 'minimal bleeding' at 30 min after insertion in 90% and 86% at the conclusion of surgery. Two patients required sutures at their CVC sites to stop bleeding. One patient required oxidized regenerated cellulose powder application at the CVC site.

Conclusion: The novel, wired-guided scalpel, Guideblade®, was safe and effective for performing the dermatotomy incision for CVC with a 100% success rate and a very high first attempt success rate with no report of user injuries. It may also help decrease bleeding at the insertion site by improving the precision of the dermatotomy and avoiding the need for multiple dermatotomy incisions for CVC.(Guideblade® used for the study were supplied by Ambitus Medical Supplies LLC)

References: 1. Central Line Proficiency Test Outcomes after Simulation Training versus Traditional Training to Competence. Ann Am Thorac Soc. 2017 Apr;14(4):550-554

Technology, Computing and Simulation, Equipment Monitoring - 2 High Fidelity CRISPR Libraries to Interrogate Anesthetic Coding and Non-Coding Genetic Susceptibilities

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Introduction: High-throughput CRISPR screens accelerate the discovery of novel genetic susceptibilities pertinent to human health. Already CRISPR screens are being utilized to uncover gene susceptibilities relevant to cancer and neurodegenerative disease processes (1,2). The ease and effectiveness of CRISPR screens derives from the technology's simplicity in needing only two components for its use: an enzyme that cleaves double stranded DNA (CRISPR endonuclease) and a targeting element (Guide RNA) that directs the endonuclease to its target. Genome-wide collections of Guide RNAs (gRNAs) form CRISPR libraries that allow for highly customizable and robust interrogation of a genome. Importantly, the accuracy of CRISPR libraries depends on the ability of gRNAs to precisely direct a CRISPR endonuclease to its intended target. Non-precise gRNAs are capable of generating complex genomic rearrangements that can disrupt the organization and regulation of a genome. This consideration takes on added importance when CRISPR libraries are used to investigate non-coding regulatory elements such as microRNAs. Many current genome-wide CRISPR libraries contain non-specific gRNAs that add substantial noise to screen results. This noise confounds the output of CRISPR screens and creates false positive and false negative hits. At present, no CRISPR gRNA libraries exist that guarantee high fidelity gRNAs against both coding and non-coding elements in both the human and mouse genomes. We utilized our GuideScan and CSC softwares to design ultra-specific CRISPR gRNA libraries to interrogate all coding genes and all microRNAs in both the human and mouse genomes. Recent studies have highlighted the importance of genomics in suggesting new avenues of anesthetic discovery and therapeutic involvement (3). We will use our high-fidelity CRISPR gRNA libraries to prospectively interrogate how anesthetic exposure affects human cell proliferation following coding gene or microRNA knockout. Overall, CRISPR screens, using high fidelity gRNA libraries, promise to accelerate the development of anesthetic genomics.

Methods: Enumeration of Guide RNA (gRNA) Targets We constructed retrieval trees (tries) consisting of all possible 20mer Cas9 gRNA target sites in the mouse and human genomes as previously published (4). Unlike the original tries reported in GuideScan (4), these were constructed without alternative chromosome data and thus produce a more accurate description of the off-target space of individual gRNAs. To determine the mismatch neighborhood for each gRNA in the library, we traversed each of their sequences through the trie to exhaustively determine all neighbors up to and including Hamming and Levenshtein distances of 3. Specificity scores for each gRNA was computed using Hamming distance neighbors as previously described (4) Cutting Efficiency Determination The cutting efficiency of gRNAs was done through computing Rule Set 2 scores for all gRNAs in the human and mouse libraries (5). Rule Set 2 is a gradient boosted regression tree model that quantifies gRNA cutting efficiency with higher scores being indicative of more pronounced cutting efficiency (5). Guide RNA Library Design Guide RNA libraries were constructed for all coding genes and all microRNAs in the human and mouse genomes. Guide RNA specificity was determined by using the GuideScan software to select gRNAs that were maximally unique to their target feature. The target features of these libraries being human and mouse coding genes and microRNAs. After determining each feature's set of maximally unique gRNAs, we selected for the final library those gRNAs with the highest Rule Set 2 scores. In this manner we designed genome-wide libraries against human and mouse coding and non-coding features that are maximally specific and efficient at cutting their genomic targets. We will use these libraries to prospectively interrogate how anesthetic exposure affects human cell proliferation following coding gene or microRNA knockout.

Results: CRISPR libraries containing non-specific gRNAs limit screen utility (Fig 1a-d) as non-specific gRNAs confound screen readout (Fig 1e). GuideScan libraries eliminate non-specific gRNAs and are designed to be maximally specific and efficient at cutting target loci.

Conclusion: GuideScan libraries contain maximally specific and efficient gRNAs capable of targeting all coding genes and microRNAs in human and mouse genomes. These libraries are prerequisite for anesthetic CRISPR screens.

References: 1: High-Resolution CRISPR Screens Reveal Fitness Genes and Genotype-Specific Cancer Liabilities, Cell, 163, 1515-1526, 2015 2: CRISPR-based functional genomics for neurological disease, Nature Reviews Neurology, 16, 465–480, 2020 3: Microdeletion in a FAAH pseudogene identified in a patient with high anandamide concentrations and pain insensitivity, British Journal of Anaesthesia, 123, 249-253, 2019 4: GuideScan software for improved single and paired CRISPR guide RNA design, Nature Biotechnology, 35, 347, 2017 5: Optimized sgRNA design to maximize activity and minimize off-target effects of CRISPR-Cas9, Nature Biotechnology, 34, 184-191, 2016

Figure 1

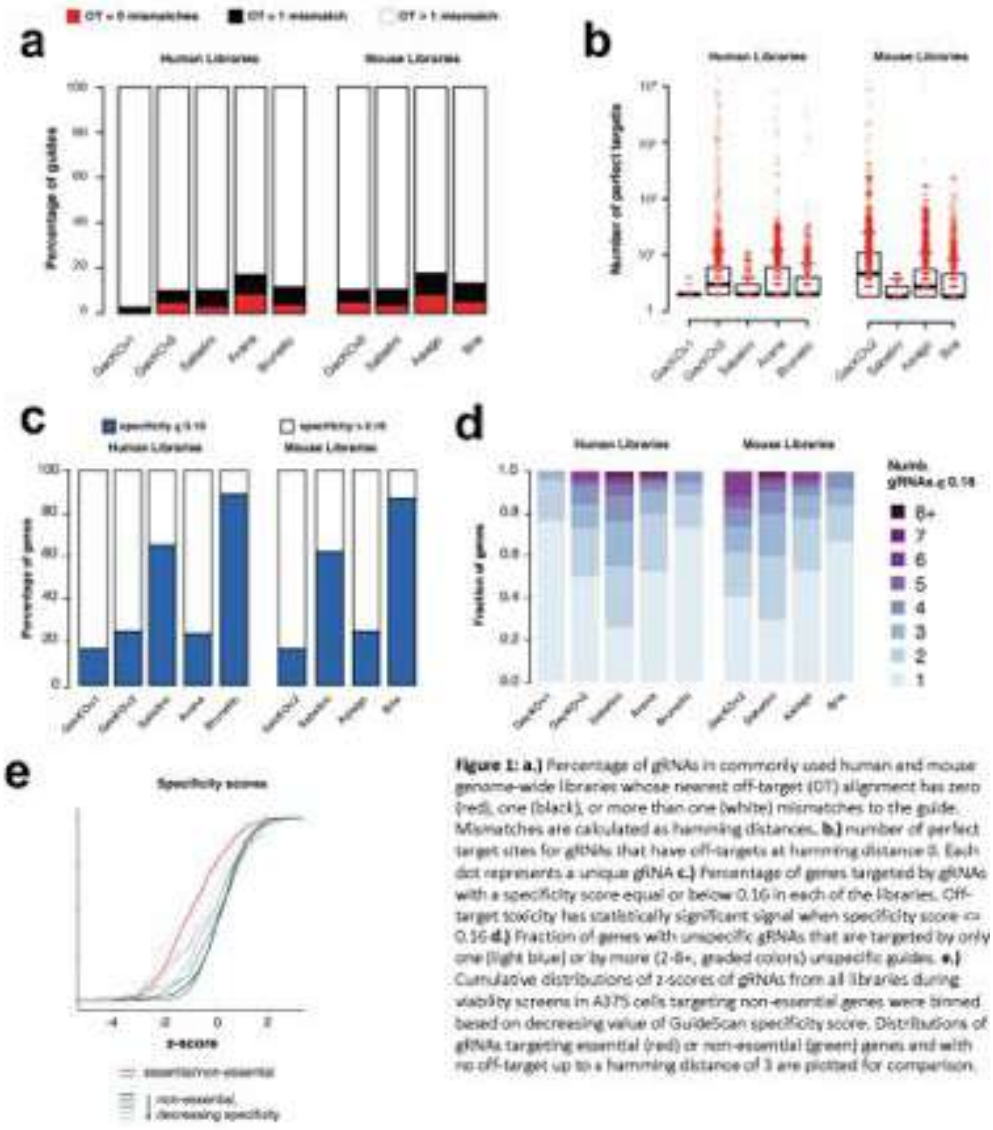

Figure 1: a.) Percentage of gRNAs in commonly used human and mouse genome-wide libraries whose nearest off-target (OT) alignment has zero (red), one (black), or more than one (white) mismatches to the guide. Mismatches are calculated as hamming distances. **b.)** number of perfect target sites for gRNAs that have off-targets at hamming distance 0. Each dot represents a unique gRNA **c.)** Percentage of genes targeted by gRNAs with a specificity score equal or below 0.16 in each of the libraries. Off-target toxicity has statistically significant signal when specificity score <= 0.16 **d.)** Fraction of genes with unspecific gRNAs that are targeted by only one (light blue) or by more (2-8+, graded colors) unspecific guides. **e.)** Cumulative distributions of z-scores of gRNAs from all libraries during viability screens in A375 cells targeting non-essential genes were binned based on decreasing value of GuideScan specificity score. Distributions of gRNAs targeting essential (red) or non-essential (green) genes and with no off-target up to a hamming distance of 3 are plotted for comparison.

Technology, Computing and Simulation, Equipment Monitoring - 3 Towards a user-centered design of a display interface for machine learning predictions of postoperative complications

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Introduction: Postoperative death and complications such as acute kidney injury are common [1-2]. Some of these adverse outcomes can be prevented through intraoperative risk mitigation, requiring early identification of at-risk patients. Telemedicine can augment risk stratification and provide guidance on mitigation strategies while bedside clinicians are occupied with other tasks. We have developed machine learning (ML) tools to assist in prediction of postoperative death and acute kidney injury during surgery [3-4]. To make such tools effective and user-friendly to clinicians, we need to understand the intraoperative clinician information workflow. Our aims in this study were (1) to characterize the content needs for an ML display interface to support intraoperative decision making and (2) to ascertain the optimal structural format for the content.

Methods: Attending anesthesiologists, certified registered nurse anesthetists (CRNAs), and anesthesiology residents who work in the intraoperative telemedicine suite at our institution were recruited for focus group interviews. Focus groups were conducted by the first and senior authors using a semi-structured interview guide. Activities included (1) discussion of workflows for selecting patients to evaluate, conducting comprehensive patient case reviews, and estimating risk for postoperative complications; (2) a card sorting activity to classify information elements to include, to maybe include, or to not include in a display interface showing ML predictions for postoperative complications; and (3) discussion of preferences among display formats for each content element. Participants completed card sorts independently and then discussed the rationale behind their choices, attempting to reach consensus within each focus group. Focus groups were audio-recorded, transcribed, and qualitatively analyzed using thematic analysis. Two authors openly coded each transcript independently. Recurring patterns or combinations of codes that yielded sub-themes leading to overarching themes were identified and iteratively analyzed, until consensus was achieved. Card sort results were tallied for frequencies.

Results: Twenty clinicians (8 attending anesthesiologists, 3 CRNAs, and 9 residents) participated in six focus groups. Three themes emerged during the qualitative analysis. First, clinicians wanted to identify patients for whom they can take action to prevent complications. They felt ML could assist by identifying patients with an elevated risk and a large portion of the risk driven by modifiable factors. Second, clinicians performed case reviews using a systematic approach, frequently starting with the pre-anesthesia clinic note and mirroring the approach they use when personally caring for patients in the operating room. An ideal ML tool would be accessible from within the existing case review workflow and might reduce time spent reviewing onerous parts of the medical record such as flowsheets. Finally, clinicians preferred display formats that minimize the energy and time spent interpreting complex data. They identified several strategies such as simplifying interface display layout, indicating risk level with color (e.g., red for high risk), hovering for details, and showing risk trends over time with graphs. Card sort results are shown in Table 1 (individual participant sorts) and Table 2 (consensus sorts from each focus group). All participants agreed on including the variables contributing to the risk prediction and the name of the scheduled surgery in the display. There was also strong interest in seeing the quantitative predicted risk and the change over time. They expressed mixed opinions about other elements, such as whether and how to convert numeric risk predictions to 'high risk' and 'low risk' categories.

Conclusion: The results suggest that telemedicine clinicians are more likely to accept ML-augmented interface displays if contents are simple to use, flag patients at elevated risk, and highlight actionable risks and potential mitigation strategies. Our finding that information and decision making workflows of

telemedicine clinicians mirrored bedside practices can be leveraged in the design of clinical decision support tools for both telemedicine and bedside intraoperative care decision making processes. Insights from this study inform our ongoing and planned research including prototype development, prototype testing using simulated patient cases, and lastly a large-scale evaluation and implementation trial.

References: 1. Lancet 2019; 393: 401 2. Ann Surg 2015; 261: 1207-1214 3. Br J Anaesth 2019; 123: 688-695 4. AMIA Annu Symp Proc 2019; 2019: 343-352

Table 1. Clinician preferences for elements to include in the display interface.
Results from individual participant card sorts (N = 20)

Display Element	Yes – Definitely include in the display n (%)	Maybe – Maybe include in the display n (%)	No – Do not include in the display n (%)
Quantitative predicted risk (percentage)	16 (80%)	4 (20%)	0 (0%)
Confidence interval around quantitative predicted risk	5 (25%)	10 (50%)	5 (25%)
Qualitative predicted risk (high/average/low)	8 (40%)	7 (35%)	5 (25%)
Change in predicted risk in last 15 minutes	11 (55%)	6 (30%)	3 (15%)
Variables contributing to this patient's predicted risk	13 (65%)	6 (30%)	1 (5%)
Average risk for all patients at the hospital	1 (5%)	3 (15%)	16 (80%)
Average risk for patients undergoing the same surgery	5 (25%)	12 (60%)	3 (15%)
Average risk for patients of the same age	1 (5%)	14 (70%)	5 (25%)
Predicted risk from preoperative information only	9 (45%)	8 (40%)	3 (15%)
Patient identifiers	8 (40%)	7 (35%)	3 (15%)
Name of scheduled surgery	16 (80%)	4 (20%)	0 (0%)
Patient age	14 (70%)	5 (25%)	1 (5%)

Table 2. Clinician preferences for elements to include in the display interface.
Results from consensus card sorts within each focus group (N = 6)

Display Element	Yes – Definitely include in the display n (%)	Maybe – Maybe include in the display n (%)	No – Do not include in the display n (%)	Not sorted (consensus not achieved) n (%)
Quantitative predicted risk (percentage)	5 (83%)	1 (17%)	0 (0%)	0 (0%)
Confidence interval around quantitative predicted risk	1 (17%)	5 (83%)	0 (0%)	0 (0%)
Qualitative predicted risk (high/average/low)	2 (33%)	3 (50%)	1 (17%)	0 (0%)
Change in predicted risk in last 15 minutes	5 (83%)	1 (17%)	0 (0%)	0 (0%)
Variables contributing to this patient's predicted risk	6 (100%)	0 (0%)	0 (0%)	0 (0%)
Average risk for all patients at the hospital	0 (0%)	0 (0%)	6 (100%)	0 (0%)
Average risk for patients undergoing the same surgery	1 (17%)	5 (83%)	0 (0%)	0 (0%)
Average risk for patients of the same age	0 (0%)	5 (83%)	1 (17%)	0 (0%)
Predicted risk from preoperative information only	2 (33%)	3 (50%)	0 (0%)	1 (17%)
Patient identifiers	2 (33%)	1 (17%)	1 (17%)	2 (33%)
Name of scheduled surgery	6 (100%)	0 (0%)	0 (0%)	0 (0%)
Patient age	3 (50%)	3 (50%)	0 (0%)	0 (0%)

Technology, Computing and Simulation, Equipment Monitoring - 4 Efficacy of COVID-19 specific simulation training in improving intubator's experience during intubation of COVID-19 patients

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Introduction: Since the start of the pandemic, approximately 3.2% of patients with COVID-19 required intubation and mechanical ventilation at some point during their treatment course (1). Intubators are at particular risk of infection due to the aerosol-generating nature of the procedure. Simulation training (ST) offers an opportunity for trainees to enhance knowledge and skills in airway management (2,3) and has been used as a training tool to prepare health providers for airway management of COVID-19 patients. The purpose of this study is to explore the demographics of providers participating in COVID-19 specific ST and the efficacy of ST in improving provider experience during the intubation of COVID-19 patients.

Methods: In this multicenter cross-sectional national study, electronic surveys were disseminated using a snowball sample approach to intubators from 32 hospitals between 9/2020 and 12/2020. Surveys were pilot tested for reliability. The survey assessed providers' comfort of intubating and fear of contracting COVID-19 during COVID-19 intubations using 1-10 scale. Various demographic and exposure factors were also collected. Simulation training group (ST) and no simulation training group (non-ST) were compared using the Mann-Whitney U test, Fisher's exact test, and Chi-square test of homogeneity. Statistical significance was declared at $p<0.05$.

Results: A total of 186 surveys from 32 hospitals were analyzed after excluding surveys that reported no experiences with COVID-19 intubations. From 32 hospitals, 28 hospitals (87.5%) had providers participating in ST. Within those hospitals, the attendance of ST ranged from 44.4% to 100.0%. From 186 providers, 62 providers (33.3%) reported participating in a ST. Of those, 45 (72.6%) of them reported that the ST helped reduce their fear of intubating COVID-19 patients. More women participated in the ST compared to men (n=36, 58.1% vs. n= 26, 41.9%; p=0.049). There was no difference in the number of COVID-19 intubations and COVID-19 exposure factors between the two groups. Providers in the ST group reported a higher level of comfort level with intubating COVID-19 patients than providers in the non-ST group (median=9, IQR= 3-10 vs. 8, 1-10; p=0.021).

Conclusion: Our study demonstrated that COVID-19 specific intubation simulation training improved providers' comfort level during COVID-19 intubations. Moreover, the majority of providers reported reduction in fear of intubating COVID-19 patients after participating in a simulation training. Simulation training on intubation may be implemented as part of airway management training for health care providers during the COVID-19 pandemic as well as in novel pandemic situations to help providers' comfort and fear. Additional studies with a larger sample size from diverse institutions are recommended to explore the efficacy of the simulation training.

References: 1. Intubation and Ventilation amid the COVID-19 Outbreak: Wuhan's Experience. Anesthesiology. 131(6):1317-1332. 2020 2. COVID-19 pandemic preparation: using simulation for systems-based learning to prepare the largest healthcare workforce and system in Canada. Adv Simul (Lond). 5:22. 2020 3. The usefulness of 3-dimensional virtual simulation using haptics in training orotracheal intubation. Biomed Red Int. 534097. 2013

Technology, Computing and Simulation, Equipment Monitoring - 5 Non-invasive assessment of the effect of noradrenalin continuous dosing on left ventricular end-systolic elastance, arterial elastance and end-diastolic volume, analyzing eight cases of bleeding.

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[1]Fukui Saiseikai Hospital, Fukui, Japan, [2]University of Fukui Hospital, Fukui, Japan, [3]Department of Human and Artificial Intelligent Systems, University of Fukui, Fukui, Japan, [4]Department of Integrative and Systems Physiology, Faculty of Medical Sciences, University of Fukui, Fukui, Japan

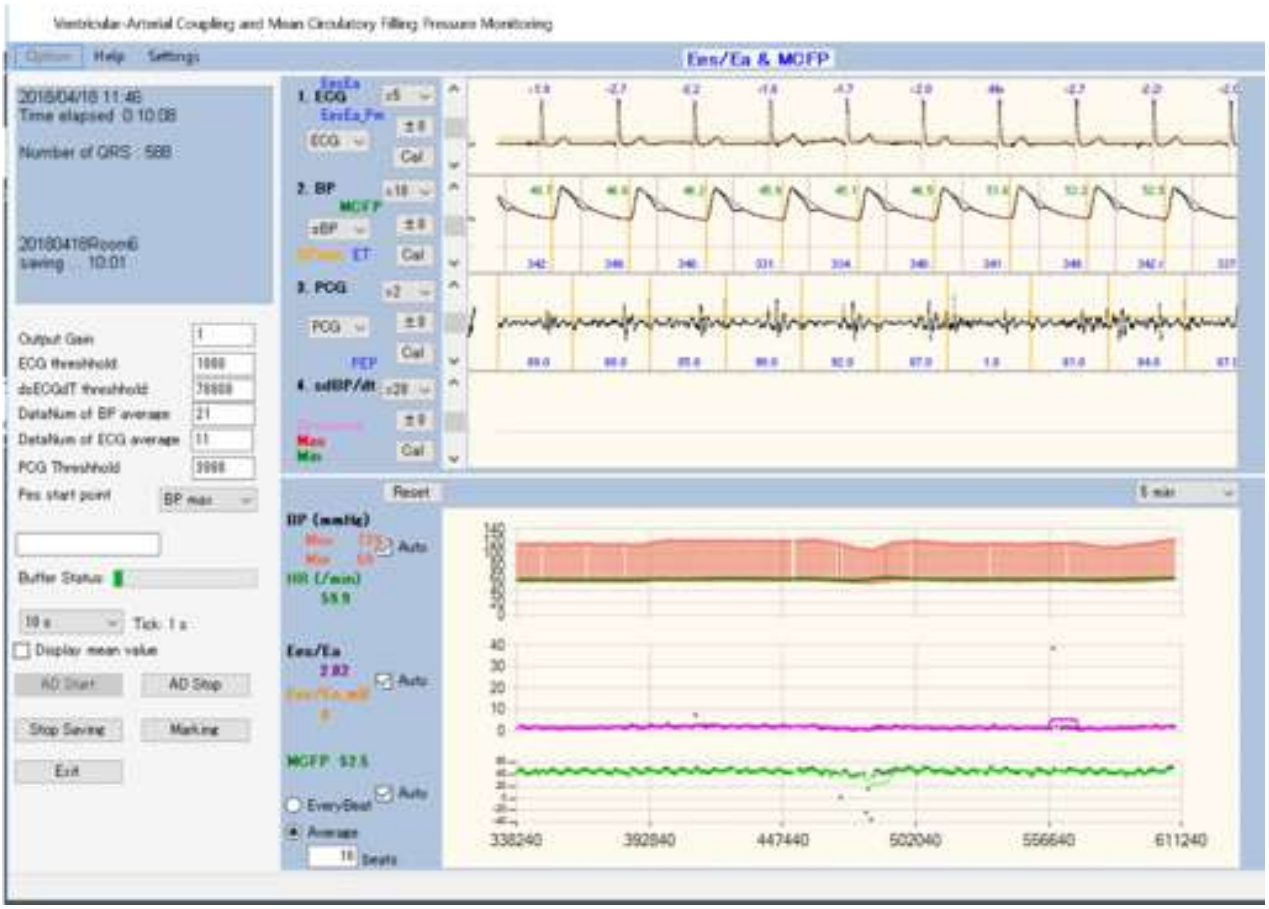
Introduction: The changes in stroke volume (SV) and systemic vascular resistance (SVR) in response to vasopressors are well known. However, it is unclear that the effect of the vasopressors on left ventricular end-systolic elastance (Ees), atrial elastance (Ea), and left ventricular end-diastolic volume (Ved). The present study aimed to assess the changes in Ees, Ea, Ved associated with noradrenalin continuous dosing in several cases of bleeding.

Methods: This is a pilot retrospective observational study. We enrolled patients who underwent non-cardiac surgeries with clinical indication of radial arterial blood pressure. We recorded electrocardiogram, radial arterial waveform, and phonocardiogram. Then we measured the pre-ejection period (PEP), ejection time (ET), end- systolic pressure (Pes), and diastolic pressure (Pd) using a computer-automated technique. We calculated the ventricular aortic coupling (Ees/Ea) using PEP, ET, Pes, and Pd as described previously[1]. Furthermore, we calculated Ees and Ea separately, and Ved with SV obtained from FloTrac sensor®(Edwards Lifesciences, CA, USA). We extracted those variables as well as heart rate (HR), and mean arterial pressure (MAP) at 2 points, 1 minute before increasing (or decreasing) noradrenalin continuous dosing and 5 minutes after the conversion. Noradrenalin dose was up to 0.5 Mg/kg/min. We used paired t-test to compare pre and post those variables as stated before. We standardized Ea, Ees, and Ved using body surface area(BSA). We calculated BSA with Du bois formula[2]. Statistical significance was set at $p<0.05$.

Results: We analyzed 8 bleeding cases using noradrenalin for keeping the blood pressure. In 4 cases, which we increased the continuous dose of noradrenalin, MAP, and Ea×BSA increased significantly from 66±5.0 to 90±15 mmHg, $p<0.05$; from 2.3±0.3 to 2.9±0.3 mL×m^2/mmHg, $p<0.05$, respectively. On the other hand, we observed no significant changes in HR, Ees×BSA and Ved/BSA (from 83±10 to 85±8.0 bpm, $p=0.24$, 3.8±2.0 to 5.7±3.2 mL×m^2/mmHg, $p=0.11$; from 50±9.1 to 53±11 mL/m^2, $p=0.15$, respectively). In another 4 cases, which we decreased the continuous dose of noradrenalin, MAP, Ea×BSA, and Ees×BSA decreased significantly from 94±10 to 82±4.6 mmHg, $p<0.05$; from 2.4±0.5 to 2.0±0.4 mL×m^2/mmHg, $p<0.05$; from 4.4±1.1 to 2.6±0.6 mL×m^2/mmHg, $p<0.05$, respectively. Ved/BSA increased significantly from 65±7.3 to 74±6.1 mL/m^2, $p<0.05$. There were no significant changes in HR (from 82±6.5 to 79±7.0 bpm, $p=0.27$).

Conclusion: Our method enabled further assessment of the effects of continuous noradrenalin dosing. Noradrenalin elevates blood pressure by increasing left ventricular afterload. Our results are consistent with the action mechanism proposed previously.

References: [1]Anesthesiology 2000; 92:1769-1776
[2]Aech Intern Med 1916;17:863-71


Ventricular-Arterial Coupling and Mean Circulatory Filling Pressure Monitoring
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AD Start
AD Stop
Stop Saving
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2.82
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Technology, Computing and Simulation, Equipment Monitoring - 6 Comparison of Supervised Machine Learning Techniques for Prediction of Blood Products Transfusion after High Risk Cardiac Surgery

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Introduction: Cardiac surgeries carry a significant risk for requiring allogeneic blood transfusion, which is associated with increased morbidity and mortality [1,2]. Application of machine learning and artificial intelligence (AI) to large clinical data sets may be of great clinical value in enhancing clinical prognostic and therapeutic abilities [3]. In this study we hypothesize that machine learning techniques can be used to identify risk factors and predict incidence of allogeneic blood transfusion based on preoperative and intraoperative data, in high-risk cardiac surgeries. Additionally, we compared the ability to predict blood transfusion among several supervised machine learning algorithms.

Methods: A cross-sectional study with data from 313 patients who underwent high risk cardiac surgery (repeat sternotomies, thoracic aortic repairs, multiple valve repairs, coronary bypass grafts, either alone or in combination on cardiopulmonary bypass (CPB)) during 2019-2020 was created. Exclusion criteria were hemodynamic instability, severely reduced left ventricular function, and hematocrit <30%. The database contained demographic, medical history, transfusion, laboratory and surgical data. The five supervised learning techniques we used were logistic regression, support-vector machines (SVM), classification trees, random forests, and extreme gradient boosting (XGBoost). For logistic regression, two different variable selection techniques were assessed: (1) variables with $p<0.05$ in single-variable selection in a multi-variable regression model, and (2) a forward-backward stepwise regression model. Each machine learning model's hyperparameters were tuned using an exhaustive grid search with quality judged by the accuracy score (ACC) from leave-one-out cross-validation (LOO-CV) out-of-sample predictions. Final model forms were evaluated and compared on their ability to predict allogenic blood transfusion using accuracy (ACC), area under the receiver operating characteristic curve (AUC), and balanced F-score based on the out-of-sample predictions of each round of LOO-CV.

Results: By both ACC (0.757) and F-score (0.797), the best-performing model for predicting allogeneic blood transfusion using preoperative and intraoperative data was an XGBoost model. Averaging feature importance across all rounds of LOO-CV for the XGBoost model indicates that the most important features for predicting the need for allogeneic blood transfusion were: patient's weight, EuroSCORE, INR after separation from CPB, need for circulatory arrest, and use of acute normovolemic hemodilution (ANH). By AUC (0.815) the best performing model was a multi-variable logistic regression using variables with $p<0.05$ in single-variable logistic regression models (Figure 1). The significant ($p<0.05$) variables in the final logistic regression model were: INR and platelet count after separation from CPB, need for circulatory arrest, and use of ANH (negative predictor).

Conclusion: Important risk factors for allogenic blood transfusion in patient who underwent high risk cardiac surgery, that were consistently present in the highest scoring models were INR after separation from CPB, need for circulatory arrest and utilization of ANH (negative predictor). Logistic regression and XGBoost held the best predictive ability across techniques, depending on the quality metric used. This study informs the selection of machine learning and statistical techniques for prediction of allogeneic blood utilization.

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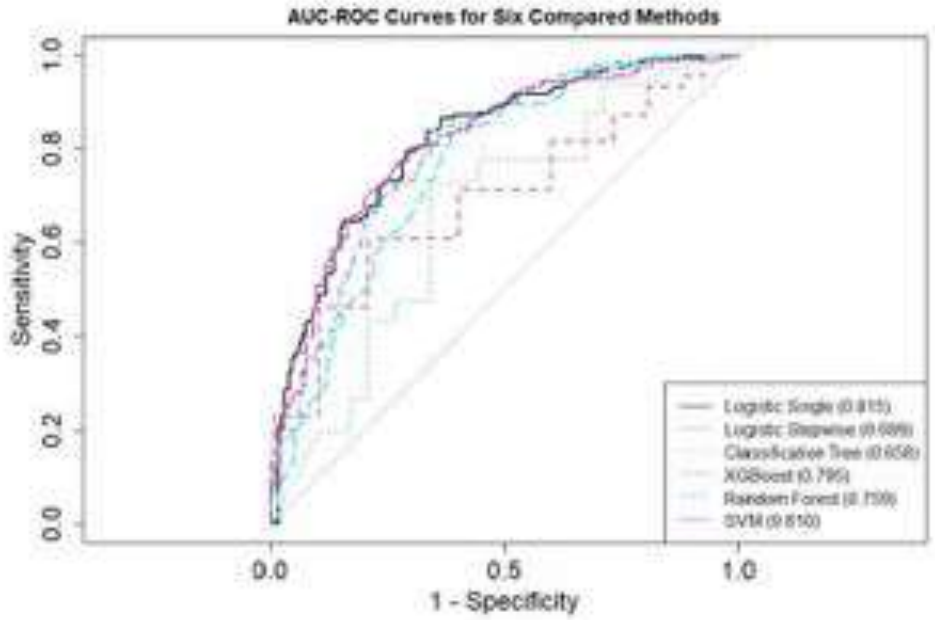

Figure 1: Receiver operating characteristic (ROC) curves are shown for the final model of each of the 6 assessed techniques and the corresponding areas under curve (AUCs) are presented in the figure legend. By AUC (0.813), the best performing model was a multi-variable logistic regression using variables with p<0.05 in single-variable logistic regression models.

Technology, Computing and Simulation, Equipment Monitoring - 7 A Prospective, Single Center Study of the Effects of Modulating Music in the Operating Room

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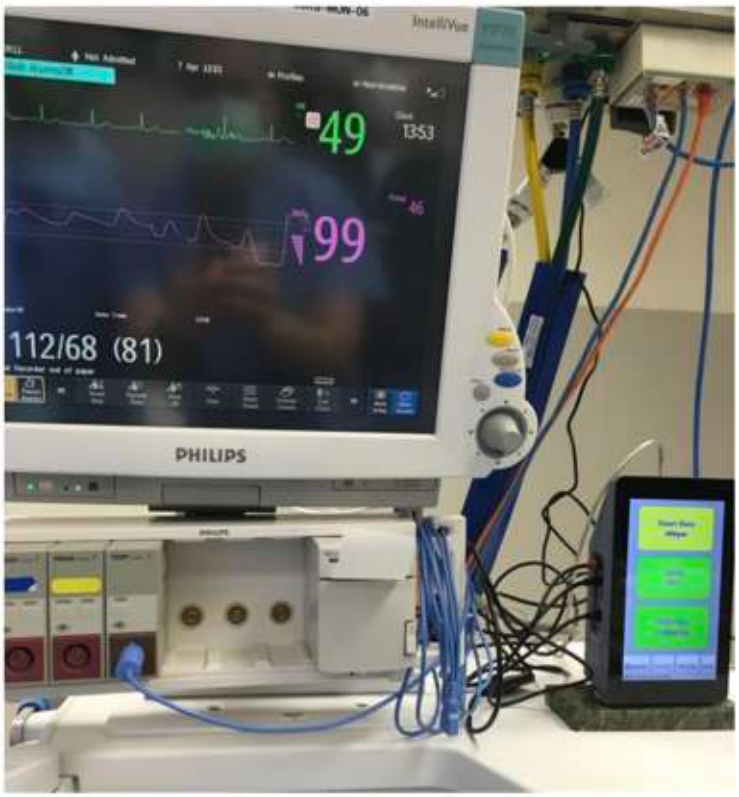
Introduction: Music is played in about 53-72% of surgical operations performed in the operating room (OR). Studies on music in the OR have resulted in mixed data on the potential benefits and harms (Weldon et al., 2015). While music is thought to have a calming effect in some cases, it can impair vital communication between staff members. Several studies have found music during procedures to be a cause of distraction and lowered performance, particularly in training (Miskovic et al., 2008). Weldon et al. analyzed video recordings of operating rooms and found that almost 2% of requests were repeated between the operating team when music was playing, in contrast to only 0.3% when music was absent. In a survey of 200 anesthesiologists, 51% felt music was distracting when a problem was encountered during the surgery, 25% felt that music reduced their vigilance and impaired their communication, and 11.5% felt the music might interfere with attention to alarms (Hawksworth et al., 1997). The effect of modulating music volume during critical times of surgery, however, has not been quantitatively researched as a possible opportunity to lessen the negative impact of music during surgery. We are testing a music volume controller that integrates operating room music with vital sign data from the anesthesia monitor. Using the CanaryBox (CB), background music volumes are reduced or silenced based on flexible algorithms for heart rate, oxygen saturation or blood pressure.

Methods: This study examines whether clinician performance is improved with the reduction of music volume during critical alarm events. We are collecting data from 100 surgical cases: 50 intervention and 50 control. Data is collected throughout each case by having anesthesia providers press a button on a keypad each time they recognize an alarm as true or false. A study coordinator provides training for each anesthesia provider. In addition, the study coordinator, who is not involved in providing care, is present in the OR during the case and uses a laptop to record the approximate time that each alarm occurs, as well as the qualitative details about the alarm. Throughout the intervention case, the CB lowers music by one-half or shuts the music off depending on the patient's vitals. The CB also records exact time stamps of the alarm, which are compared with the anesthesia provider's button presses and the study coordinator's recordings of the alarm details using a script written in MATLAB. Anesthesia providers also complete post-procedure surveys designed to measure whether in-room anesthesia providers find the volume adjusting device to be useful and beneficial.

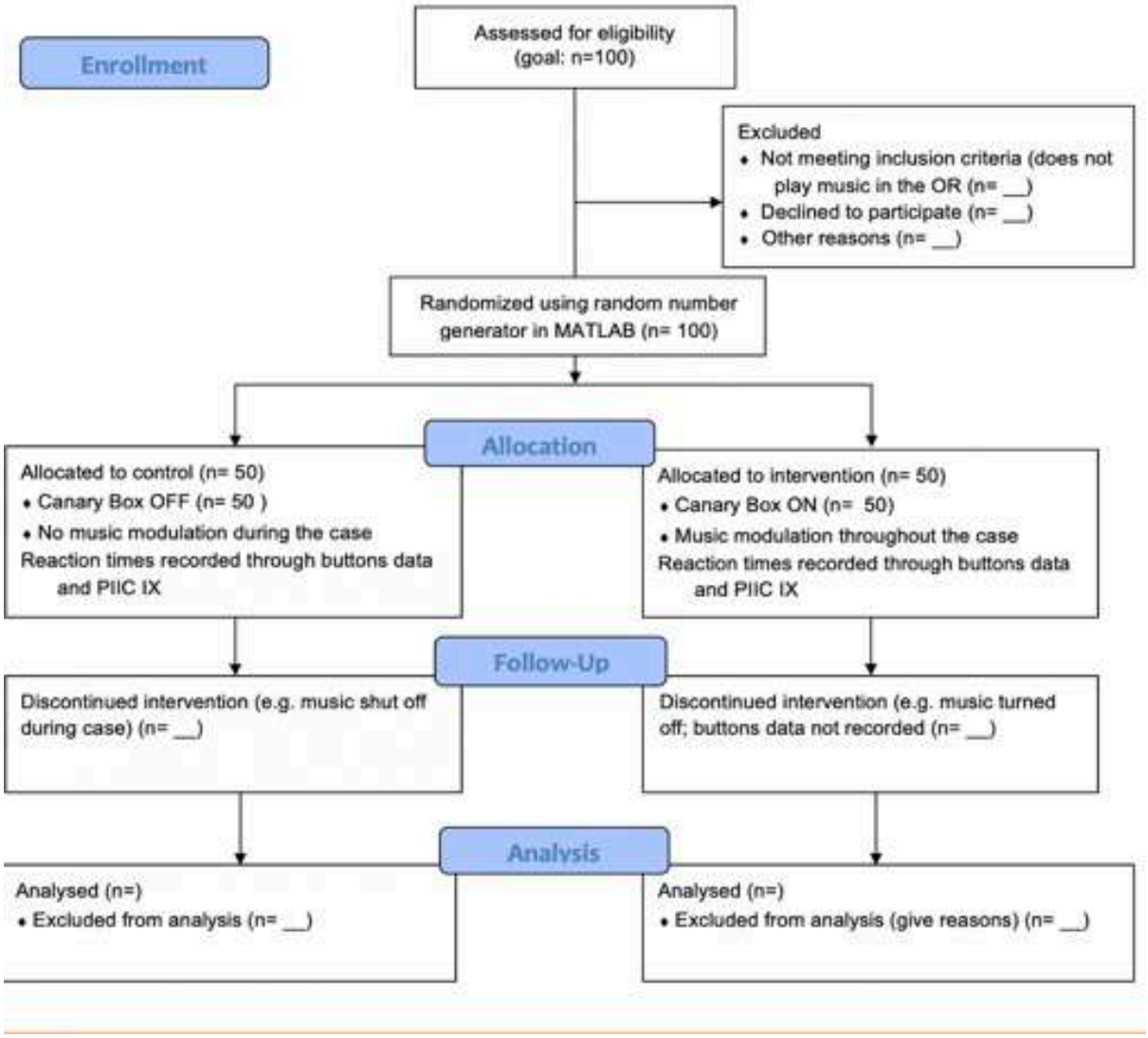
Results: We qualitatively analyzed preliminary data to assess the impact of the CB. After implementing the music modulating device in 30 procedures, we surveyed anesthesiologists and operating room personnel and found that 29 of 30 participants would use the controller again, and 27 of 30 rated the device as working well. We expect to complete our quantitative data collection by March 2021. We hypothesize that anesthesia providers will be able to detect important alarms more quickly and accurately when the background music is reduced during critical events. Response time will be measured as the latency between when the vitals monitor triggers an alarm and when the anesthesia provider responds to the alarm, measured in milliseconds. The study coordinator response data allows us to see the difference is response time with reduced cognitive load. The effects of intervention on the average response time will be assessed using a t-test that compares mean response times of the intervention and exposure group. Random intercept indexed by study participant will be used to account for the fact that one provider may participate in the study up to three times. Intervention effects will be estimated with Wald-type 95% confidence interval and tested using a Wald-type test.

Conclusion: Information gathered in this study will advance our understanding of how music volume affects anesthesia provider reaction times, which may benefit both surgeons and anesthesia providers in the future. The survey will help the experimenters understand the potential quantitative and qualitative benefits and drawbacks to the utilization of the music volume reduction device. The study not only assesses whether or not response times are improved with music modulation but also creates a new paradigm for assessing reaction times of anesthesia providers in the OR setting.

References: Weldon, S.-M., Korkiakangas, T., Bezemer, J., & Kneebone, R. (2015). Music and communication in the operating theatre. Journal of Advanced Nursing, 71(12), 2763–2774. Miskovic, D., Rosenthal, R., Zingg, U., Oertli, D., Metzger, U., & Jancke, L. (2008). Randomized controlled trial investigating the effect of music on the virtual reality laparoscopic learning performance of novice surgeons. Surgical Endoscopy, 22(11), 2416–2420 Hawksworth, C., Asbury, A. J., & Millar, K. (1997). Music in theatre: Not so harmonious. Anaesthesia, 52(1), 79–83. MacDonald, A., & Schlesinger, J. (2017). Canary in an operating room: Integrated operating room music. 5.



	Full volume	*Half volume*	*Music off*
Oxygen saturation (SpO_2) %	$90 \leq SpO_2$	$85 \leq SpO_2 < 90$	$SpO_2 < 85$
SpO_2 delay		20 seconds	10 seconds
Heart Rate (HR) bpm	$50 \leq HR \leq 130$	$40 \leq HR < 50$, or $130 < HR \leq 150$	$HR < 40$, or $HR > 150$
HR delay		20 seconds	10 seconds
Systolic Blood Pressure (SBP) mm Hg	$80 \leq SBP \leq 170$	$70 \leq SBP < 80$, or $170 < SBP \leq 190$	$SPB < 70$, or $SPB > 190$
SBP delay		60 seconds	30 seconds



Technology, Computing and Simulation, Equipment Monitoring - 8 Device assessment for the application of computer vision to identification drug vials and syringes during anesthesia care

Kelly Michaelsen[1], T. Andrew Bowdle[1], Srdjan Jelacic[2], Shyamnath Gollakota[1], Ananditha araghu@cs.washington.edu[1]

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Introduction: Real-time video data collection in the operating room (OR) coupled with computer vision algorithms to identify syringes, vials and drug administration events may improve patient safety and record keeping. In a study of anesthesia records, drugs were omitted from the electronic medical record in 15% of instances and the documented drug matched the administered drug name and dose 83% of the time1. Drug administration errors in anesthesia are common, can result in morbidity or mortality, and should be preventable. Numerous attempts to minimize drug errors and improve documentation have resulted in incremental improvement but these efforts generally require additional steps by providers2–4. This study assesses commercially available point of view (POV) cameras in terms of their ability to record syringes and detect text in an OR environment.

Methods: Only devices that had battery and video recording capabilities of greater than one hour, and no restriction of the wearer's visual field (Microsoft Hololens, Google Glass Enterprise, Axon Body Flex 2 and GoPro Hero 8) were included in this study. Initial comparisons were performed with a single provider performing a series of vial to syringe drug transfers to determine if cameras could visualize the text and actions. Optical character recognition was performed after image cropping using an off-the-shelf online tool5. GoPro images at 1080p and 4K resolution were analyzed to assess the effects of distance and camera resolution on syringe label readability at four-inch intervals from the edge of the anesthesia cart to 30 inches away. Frame rate was compared using two GoPro cameras, one at 30 and one at 60 frames per second (FPS) for a low light simulation, as might be encountered in a darkened operating room with static and moving image targets to understand image blur. After Institutional Review Board exemption, the POV cameras were used in the OR to record case preparation and assess wearability and durability.

Results: Initial testing looked at the field of view (FOV) of each camera and the effects on the wearer's visual field. Figure 1 shows each device being worn by the author and FOV when standing eight inches from an anesthesia cart. In simulation and OR, Microsoft Hololens and Google Enterprise frequently missed syringes and vials during manipulation by the anesthesia providers as these events were outside the FOV of the provider. The Axon Flex 2 and GoPro have much greater flexibility in angle and orientation and were able to record drug preparation events, especially when the GoPro was mounted vertically. Figure 2 shows cropped images from each device for a single syringe and the optical character recognition output for propofol (protamine results were unobtainable; this syringe was much further from the camera as it was at the back of the tray). Figure 3 illustrates the impact of resolution on optical character recognition. Propofol label text was unrecognizable at distance > 6 inches using 1080 image resolution while propofol label was partially recognizable up to 24 inches using 4K resolution. Figure 4 shows static and motion low light images of propofol syringe label obtained with the GoPro camera at 12 inches. Sixty FPS images were noisier than 30 FPS in a low light conditions, impacting optical character recognition, but had less image blur with motion.

Conclusion: POV camera recording can detect vial and syringe manipulations by anesthesiologists. Of the four cameras tested, the GoPro camera provided the greatest image quality, visualizing all drug preparation events during a case turnover in multiple FOV settings and allowed for optical character recognition of the majority of characters on the syringe label, even when the provider was standing more than a foot from the anesthesia cart.

References: 1. Avidan, A., Dotan, K., Weissman, C., Cohen, M. J. & Levin, P. D. Accuracy of manual entry of drug administration data into an anesthesia information management system. Can J Anesth/J Can Anesth 61, 979–985 (2014). 2. Bowdle, T. A. et al. Facilitated self-reported anaesthetic medication errors before and after implementation of a safety bundle and barcode-based safety system. British Journal of Anaesthesia 121, 1338–1345 (2018). 3. Eagle, B., Williams, D. & Dingley, J. Investigation of Two Prototypes of Novel Noncontact Technologies for Automated Real-Time Capture of Incremental Drug Administration Data From Syringes. Anesthesia & Analgesia 125, 458–466 (2017). 4. Alapetite, A. Speech recognition for the anaesthesia record during crisis scenarios. International Journal of Medical Informatics 77, 448–460 (2008). 5. CLOVA OCR - 네이버 클로바. https://clova.ai/ocr.

Figure 1: View of Anesthesia Cart from Left Top to Bottom-Google Enterprise, Microsoft Hololens, Axon Flex 2. Images on the Right are from GoPro with different fields of view and GoPro headmount design below.

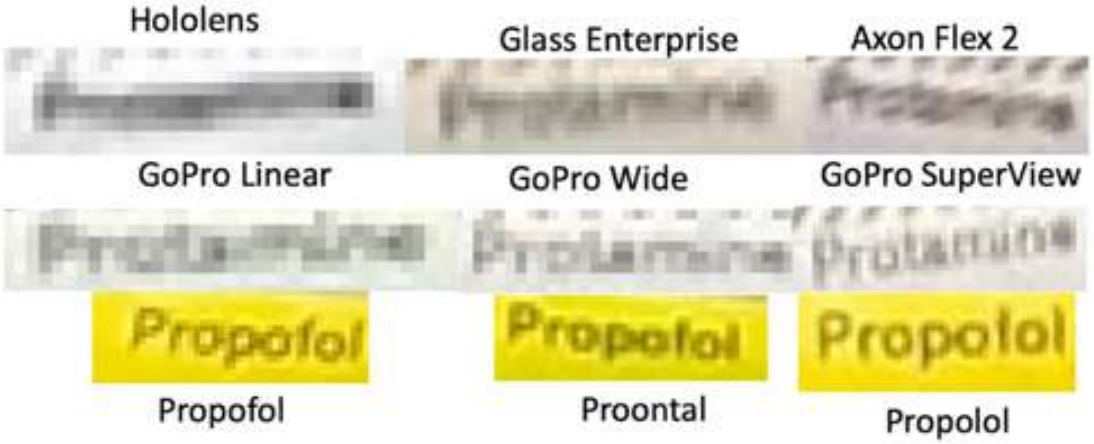

Figure 2: Zooming in on the labels for protamine (top two rows) and propofol (bottom two rows) for different cameras and three FOV settings for the GoPro. Character recognition results are shown for propofol only below those images (protamine was unrecognizable in all cases).

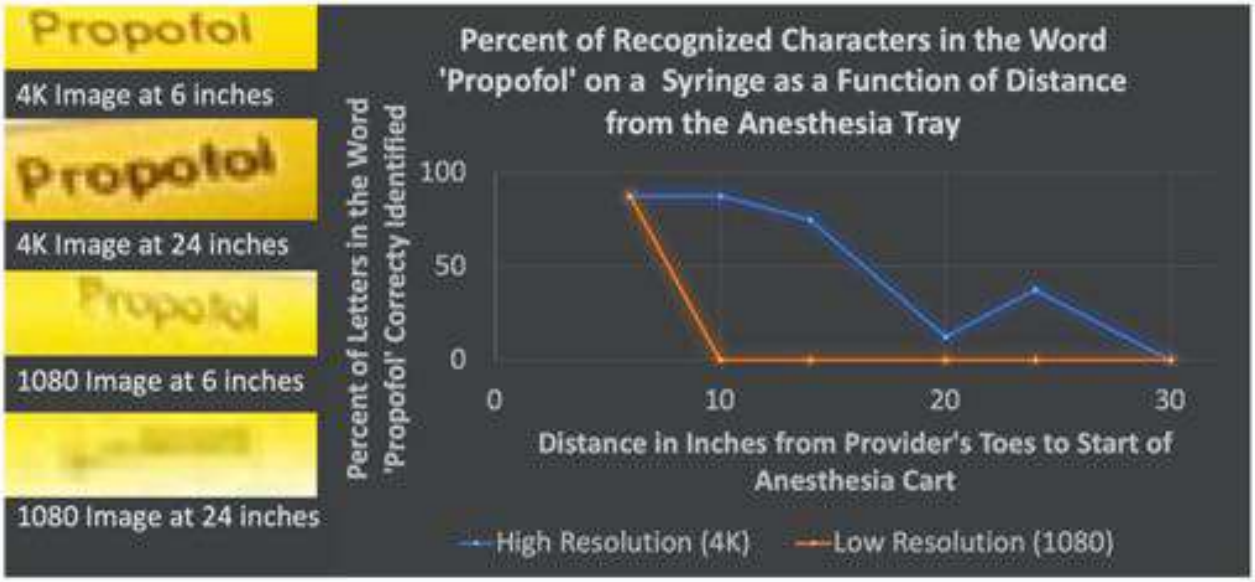

Figure 3: Higher resolution imaging improves optical character recognition of a syringe label

Figure 4: In dark rooms, lower frames per second (FPS) performs better at optical character recognition (OCR) in static conditions (left), but has more blur with movement (right)

Technology, Computing and Simulation, Equipment Monitoring - 9 Clevidipine infusion dose accuracy: How does pump-driven continuous delivery of a lipid emulsion compare to a saline solution in a laboratory model?

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Introduction: Critically ill or anesthetized patients commonly receive treatment with potent, fast-acting medications delivered by pump-driven, continuous, intravenous infusion. Infusion rates are titrated stepwise up or down over short intervals, e.g. 5 minutes, according to physiologic responses. Depending on the clinical setting and drug formulation, initial flow rates may range from < 0.5 ml/hr to > 30 ml/hr. Most potent drugs are formulated for infusion in aqueous solutions, e.g. normal saline (NS). However, hydrophobic drugs may be formulated as lipid emulsions (LE). Clevidipine is a key example of a hydrophobic drug formulated in a LE and infused at low flow rates. Infusion pumps often exhibit inaccurate delivery of aqueous solutions at low flow rates thereby contributing to dose errors. Lipid emulsions and aqueous solutions have different physical and chemical properties. How will the characteristics of LE infusion delivery at low flow rates compare to an NS infusion? In a laboratory model of continuous intravenous infusion, where flow rates could be accurately measured, we asked whether pump-driven delivery of a 20% emulsion differs from delivery of NS.

Methods: A representative clinical large volume pump (LVP) and a representative clinical syringe pump (SP) delivered continuous infusions of either a lipid emulsion, (LE, 20% w/v) or NaCl (NS, 0.9% w/v). New disposables were used for each experiment. A balance with a resolution of 0.1 mg measured delivery by weight over time. Weight/time data were converted to ml/hr. In the first protocol, each pump delivered the LE or the NS continuous infusions in steps of 5 minutes duration, exponentially ascending from 0.5 -32 ml/h and descending from 32 – 0.5 ml/hr. Delivery data for each 5 min step were compared to the expected delivery rate and then analyzed by mean flow rate error (%), averaged across 3 identical experiments. Data were compared using a Kruskal-Wallis test followed up by a Dunn's test for multiple comparisons corrections. In a second protocol, LE or NS infusions flowed continuously for 2 hours at a rate of 0.5 ml/hr. Data were compared by two-sample t-test or Mann Whitney U test depending on data distribution The results were represented graphically, and numerically, with the key outcome values being mean flow rate, mean flow rate % error and the duration of no flow periods.

Results: Each pump delivered the LE and NS infusions similarly in both ascending and descending steps across the flow rate range of 0.5 to 32 ml/hr (Figure 1 A & B, Table 1 A & B). Only at 32 ml/hr were there statistically significant differences in flowrate between emulsion and aqueous solutions, however, the mean flowrates are comparable, the mean flowrate error is low, and at 32 ml/hr the difference is not clinically relevant. Each pump delivered the LE and NS infusions similarly at a continuous flow of 0.5 ml/hr over 2 hours for each interval epoch of 30 minutes duration (Figure 2 A & B, Table2 A & B). There were no statistically significant differences. Both pumps exhibited periods of no flow for both fluids, defined as flow 50% below the set rate (i.e. <0.25 ml/hr). The longest periods of no flow were at least one minute and, in some cases, longer than 2 minutes.

Conclusion: We show that clinical infusion pumps with different mechanisms of action, in this study a syringe pump and a large volume pump, delivery by continuous infusion of a lipid emulsion (20%) was similar to delivery of an aqueous solution (normal saline) under clinically relevant conditions, stepwise escalating doses, stepwise decreasing doses, and continuing infusion. Both pumps, for both fluids, exhibited periods of no flow. The relevance of this finding may depend on the drug's circulating half-life. For commonly used critical care medications that are potent, rapid acting, and frequently administered by pump-driven continuous effect-titrated infusion, we conclude that differences in the diluent formulation (aqueous vs. emulsion) will not detectably influence delivery to cause unusual or unexpected under- or over- dosing. Specialized management of clevidpine infusions is not required for accurate dosing in pump driven infusions.

Figure 1 A & B

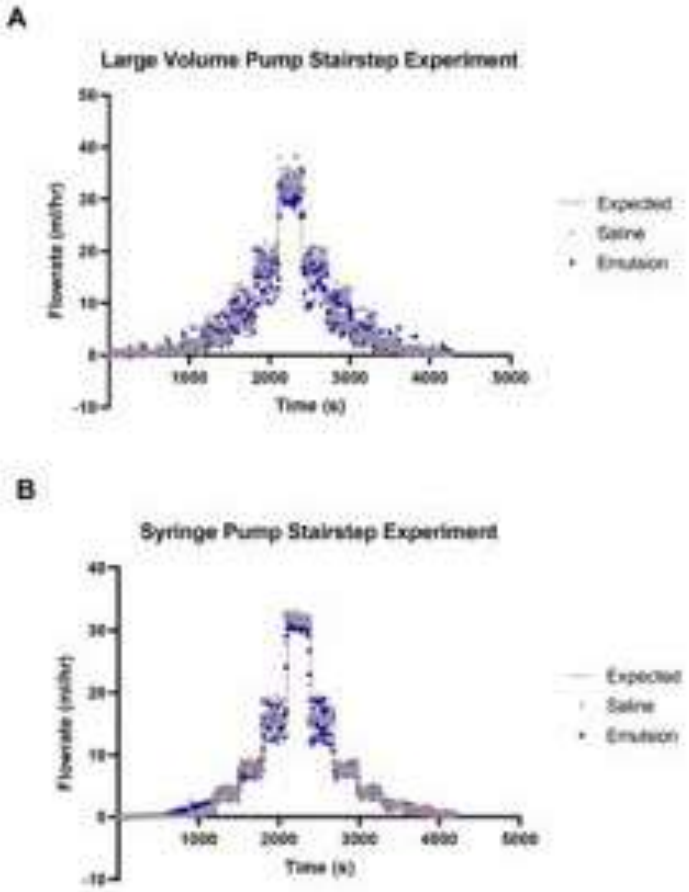

Figure 1.
Flowrate was calculated over 5 s windows with a 2 minute startup before data collection. Flowrate was set to 0.5 ml/hr and then doubled to 1 ml/hr after 10 minutes, and subsequently doubled every 5 minutes until reaching 32 ml/hr, after which it was halved every 5 minutes until reaching 0.5 ml/hr. Representative individual experiments

Figure 2 A & B

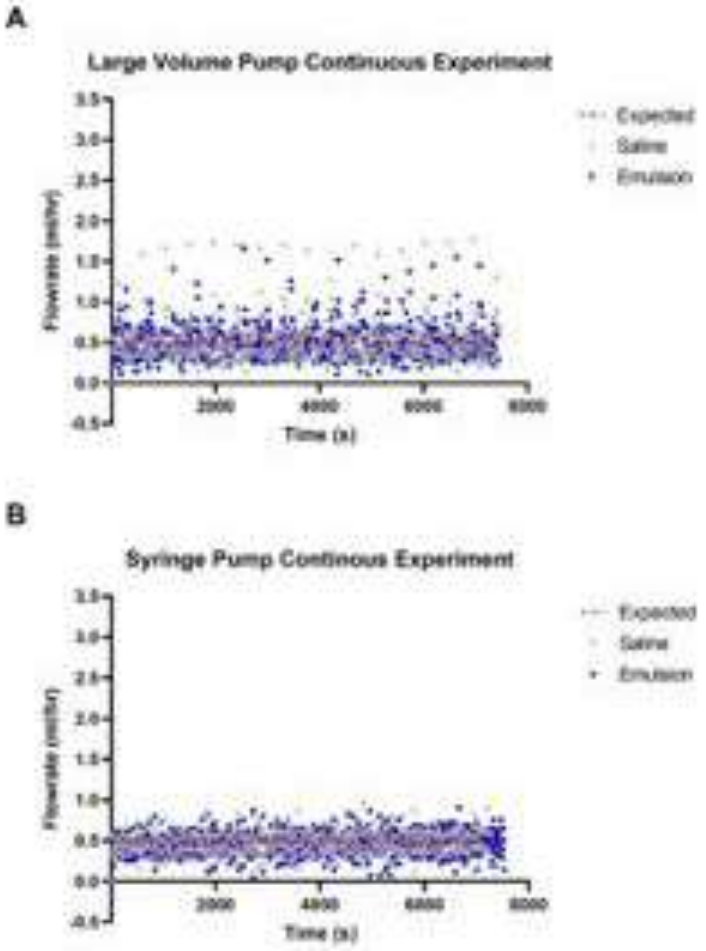

Figure 2.
Flowrate was calculated over 10 s windows and then graphed over a 2 hour period. Both pumps were primed and ran for sufficient time to prevent any startup delay in the flow. Representative individual experiments

Table 1 Stairstep

A

Large Volume	Average Flowrate (ml/hr)		Dunn's Test	Mean Flowrate Error (%)	
Expected Flowrate (ml/hr)	Intralipid	Saline	Probability	Intralipid	Saline
0.5	0.4314	0.3748	1	13.72	25.03
1	0.9734	0.9849	1	2.66	1.51
2	2.0312	2.0846	1	1.56	4.23
4	4.1802	4.2685	1	4.50	6.71
8	8.2368	8.4973	1	2.96	6.22
16	16.3852	16.9272	1	2.41	5.79
32	31.4242	32.6291	0.0049	1.80	1.97
16	15.8571	16.5262	1	0.89	3.29
8	7.9430	8.3441	1	0.71	4.30
4	3.9715	4.1576	1	0.71	3.94
2	2.0138	2.0724	1	0.69	3.62
1	0.9473	1.0288	1	5.27	2.88
0.5	0.5347	0.5256	1	6.95	5.13

B

Syringe	Average Flowrate (ml/hr)		Dunn's Test	Mean Flowrate Error (%)	
Expected Flowrate (ml/hr)	Intralipid	Saline	Probability	Intralipid	Saline
0.5	0.0119	0.0289	1	97.62	94.22
1	0.2054	0.2042	1	79.46	79.58
2	0.8095	1.2355	0.098	59.52	38.22
4	3.3457	3.6885	0.4774	21.36	7.79
8	7.4846	7.7529	0.8318	6.44	2.59
16	15.5716	15.9930	1	2.68	0.04
32	30.5231	31.4000	0.0009	4.62	1.88
16	15.0500	15.3167	1	5.94	4.27
8	7.5364	7.6663	1	5.79	4.17
4	3.3807	3.8302	1	5.48	4.25
2	1.9125	1.9081	1	4.37	4.59
1	0.9620	0.9549	1	3.80	4.51
0.5	0.5149	0.5078	1	2.97	1.57

Table 1

Mean Flowrate Error was calculated $Error\ (\%) = \left|\frac{Average\ Flowrate - Expected\ Flowrate}{Expected\ Flowrate}\right| * 100.$

Table 1 Stairstep

A

Large Volume	Average Flowrate (ml/hr)		Dunn's Test	Mean Flowrate Error (%)	
Expected Flowrate (ml/hr)	Intralipid	Saline	Probability	Intralipid	Saline
0.5	0.4314	0.3748	1	13.72	25.03
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16	16.3852	16.9272	1	2.41	5.79
32	31.4242	32.6291	0.0049	1.80	1.97
16	15.8571	16.5262	1	0.89	3.29
8	7.9430	8.3441	1	0.71	4.30
4	3.9715	4.1576	1	0.71	3.94
2	2.0138	2.0724	1	0.69	3.62
1	0.9473	1.0288	1	5.27	2.88
0.5	0.5347	0.5256	1	6.95	5.13

B

Syringe	Average Flowrate (ml/hr)		Dunn's Test	Mean Flowrate Error (%)	
Expected Flowrate (ml/hr)	Intralipid	Saline	Probability	Intralipid	Saline
0.5	0.0119	0.0289	1	97.62	94.22
1	0.2054	0.2042	1	79.46	79.58
2	0.8095	1.2155	0.098	59.52	38.22
4	3.3457	3.6885	0.4774	21.36	7.79
8	7.4846	7.7929	0.8318	6.44	2.59
16	15.5716	15.9930	1	2.68	0.04
32	30.5231	31.4000	0.0009	4.62	1.88
16	15.0500	15.3167	1	5.94	4.27
8	7.5164	7.6663	1	5.79	4.17
4	3.8307	3.8302	1	5.48	4.25
2	1.9125	1.9081	1	4.37	4.59
1	0.9620	0.9549	1	3.80	4.51
0.5	0.5149	0.5078	1	2.97	1.57

Table 1

Mean Flowrate Error was calculated $Error\ (\%) = \left|\frac{Average\ Flowrate - Expected\ Flowrate}{Expected\ Flowrate}\right| * 100.$

Technology, Computing and Simulation, Equipment Monitoring - 10 Central Lines in Virtual Reality, Procedural Training in the Era of COVID-19

Alexander Pop[1], Sal Salavat Yulaman[2], Raymond Powers[1], Richard Goldmann[1], Lionel Willams[1], Sanjay Thomas[1]

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Introduction: In excess of 5 million Central Venous Catheters (CVC) are placed annually in the United States. Unfortunately, this life-saving procedure also has many complications associated with its placement. Adverse events pertaining to CVC placement have been shown to significantly increase morbidity, mortality, and cost to American healthcare (1). More ubiquitously available CVC training resources are needed to address this issue. Vassar Brothers Medical Center in Poughkeepsie, New York, does not currently have a formal training program regarding CVC placement. Furthermore, the coronavirus (COVID-19) pandemic has proven to be incredibly disruptive to this type of procedural medical education. Virtual Reality (VR) technology has seen a tremendous increase in investment, popularity, and in its applications. VR can be utilized in novel training programs to teach students and medical professionals. A scoping review of 21 papers found that 74% of these studies concluded more efficacious learning through the use of VR (2). Furthermore, physicians that learned through VR modalities were found to have better accuracy in their respective medical practice (3). A VR based curriculum would be especially useful when teaching procedures such as CVC placement. This technology would afford medical professionals 360-degree, immersive, procedural training. This firsthand experience would be from a skilled physician's eyes performing said procedure, while additional educational media (e.g., diagrams, checklists, narration) is interjected in the virtual world. Traditionally, such an educational experience could only be offered through direct observation of procedures being performed on patients. Direct observation/participation would not only put patients at a greater risk of procedural complications but could also increase transmission of diseases such as COVID-19. VR technology can now make firsthand accounts of procedures ubiquitously and remotely available, without risking patient or student health. Participants can determine and increase their competency regarding a specific procedure prior to performing on a patient. Through the use of our novel VR based CVC curriculum, we aim to increase the cumulative CVC knowledge and confidence of our participants.

Methods: This preliminary phase of our VR CVC training program started in July 2020 and ended in October 2020. 14 participants consisting of Nuvance Health transitional year residents participated. Participants first took a pre-training questionnaire testing core CVC subjects. Participants then put on the VR headset and completed the instructional CVC VR program. Subsequently, participants took a post-training questionnaire testing core CVC subjects. These assessments consisted of 10 multiple choice questions testing core CVC parameters. The 10 parameters that were compared pre- and post-training are described in Figure 2. Participant knowledge and confidence were evaluated through questionnaires pre- and post-training. These assessments consisted of 10 multiple choice questions testing core CVC parameters. Pre- and post-training questionnaire data comparison was analyzed through paired t-tests, with significance set to $\alpha = .05$.

Results: Paired t-tests were significant for a post-intervention increase in all tested parameters (figure 2). Correct patient positioning responses increased by a mean of 42.9 % (90% CI 18.5 - 67.2, $p < 0.05$). Correct steps regarding sterile technique increased by a mean of 71.4 % (90% CI 49.2 - 93.6, $p < 0.001$). Correct responses regarding vascular anatomy of the neck increased by a mean of 50.0 % (90% CI 25.4 - 74.6, $p < 0.05$). Femoral vascular anatomy correct responses increased by a mean of 42.9 % (90% CI 12.3 - 73.4, $p < 0.05$). Correct steps regarding inadvertent arterial access increased by a mean of 57.1 % (90% CI 32.8 - 81.4, $p < 0.001$).

Conclusion: We attribute much of this drastic improvement in all tested CVC knowledge and confidence parameters to the use of a virtual medium. The applications of VR technology in procedural medical education are innumerable. Our VR program affords medical professionals a full sensory, immersive experience of CVC placement without having to step foot in a hospital. As we expand this program, we aim to correlate Central Line-Associated Bloodstream Infection rates to the incorporation of our VR curriculum.

References: 1. Kornbau C, Lee KC, Hughes GD, Firstenberg MS. Central line complications. Int J Crit Illn Inj Sci 2015;5:170-8. 2. Samadbeik Mahnaz, Yaaghobi D, Bastani P, Abhari S, Rezaee RA, Garavand Ali. The Applications of Virtual Reality Technology in Medical Groups Teaching. J Adv Med Educ Prof. 2018 Jul;6(3):123–129. 3. Remtulla R. The Present and Future Applications of Technology in Adapting Medical Education Amidst the COVID-19 Pandemic. JMIR Med Educ. 2020;6(2):e20190. Published 2020 Jul 17. doi:10.2196/20190

Figure 1. Example of our VR Curriculum and Setup

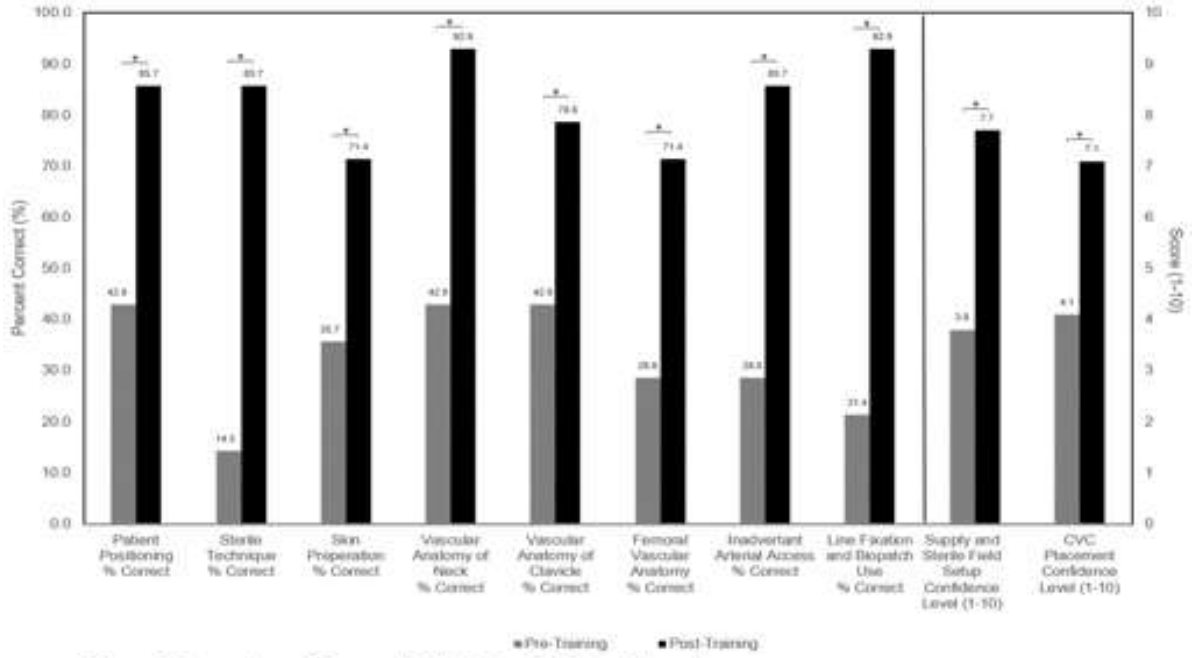
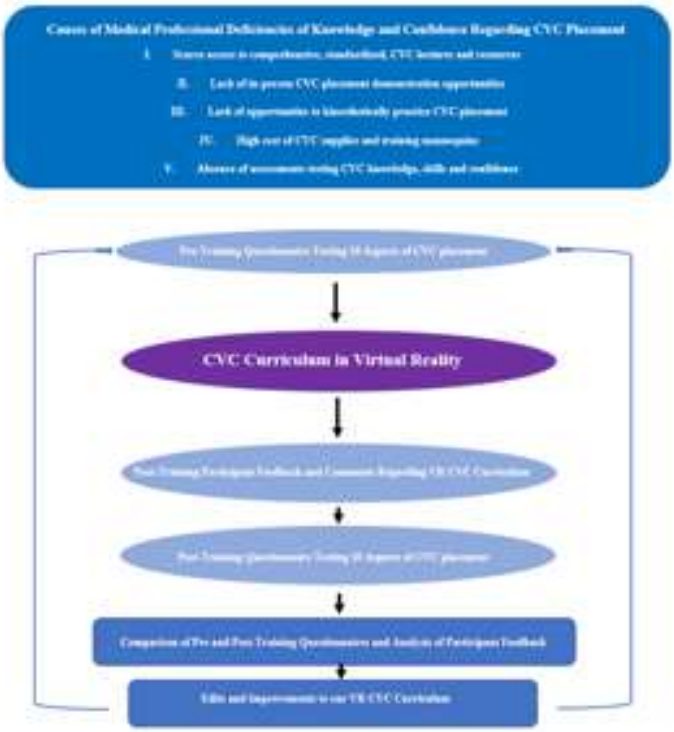


Figure 2. Comparison of Pre and Post Training CVC Questionnaires

Left panel shows an increase in objective CVC knowledge after training. Right panel shows an increase in participant confidence level. Paired t-test showed a significant increase for all 10 parameters ($p < 0.05$).


Causes of Medical Professional Deficiencies of Knowledge and Confidence Regarding CVC Placement
I.
II.
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IV.
V.
CVC Curriculum in Virtual Reality

Technology, Computing and Simulation, Equipment Monitoring - 11 A finite element model for isoflurane release from perfluorocarbon nanoemulsions as a predictor of bolus dosing and time to effect in a rodent model.

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Introduction: Research efforts to bioengineer safe and stable injectable volatile anesthetic emulsions have recently increased but with most efforts failing due primarily to problems with long-term stability of the emulsion or toxicity of the ingredients1. Our group has developed and successfully tested in both small animals (rodents) and large animals (dog) an ultra-stable perfluorocarbon-based isoflurane emulsion2,3 with no exhibited acute or long-term side effects. Ultimately, these emulsions could be used for both induction and maintenance of anesthesia through total intravenous protocols with the development of successful dosing algorithms. In this study we utilized computational finite element modeling (FEM) to determine the release profile of isoflurane from our perfluorocarbon carrier nanoemulsions and further, correlated the predicted dose rate ([mMiso]/s) with time to loss of all reflexes in induction of anesthesia.

Methods: In this study, 10 independent isoflurane/perfluorocarbon nanoemulsion preparations, manufactured and characterized as previously described2-4, were utilized in induction studies with 36 male Lewis rats with protocol approval from the University of Miami Leonard M Miller School of Medicine IACUC. Animals were continuously infused (0.8 – 2.0 µL/min g-1) with isoflurane nanoemulsions using a syringe pump (Harvard Apparatus) until effect, determined by loss of all reflexes (loss of righting reflex, ciliary reflex and pain sensation). Post-hoc, FEM (Diffusion) was utilized to examine the release of isoflurane from the nanoparticles into the blood compartment. A simple dynamic model was generated of a representative nanoparticle suspended in an aqueous sphere representing the interparticle distance within the bloodstream. As infusion continues, the outer sphere contracts around the nanoparticle, representing the increased number of nanoparticles infused and the decreasing interparticle distance. The model was solved for the duration of infusion in 0.1s increments. The final modeled molar concentration of isoflurane was recorded. Least squares regression curve fitting of the modeled infusion profile was performed using Prism GraphPad v8.4.3 for Mac and the rate constant was recorded for comparison. Multiple variables were correlated with the time to loss of all reflexes to determine if any were predictive for dosing.

Results: All 36 animals were safely and smoothly induced with no untoward effects. The release curves were exponential in nature, in line with typical diffusion/release profiles (Fig. 2). There was a significant correlation between the time to effect and the molar change in blood concentration ([mMIso]/s) determined by the finite element accumulation (Fig. 3A, Pearson R = 0.98, P < 1.0 x 10-15). The mean effective dose was 0.10 ± 0.016 [mMiso]/s with a coefficient of variation of 16%.

Conclusion: This preliminary study indicates that induction of surgical anesthesia with our IV isoflurane nano-emulsion is safe and effective in the small animal model and that dosing can be predicted using finite element models with a significant correlation to effect time observed. Of interest, the assumptions of the model held and simple single compartment isoflurane accumulation was significantly predictive of time to effect. With further study and fine-tuning, these models could be implemented to aid in the determination of dosing algorithms for automated delivery (TIVA).

References: 1. Journal of Pharmacological Sciences 100: 2685-2692 (2008) 2. Colloids Surfaces B: Biointerfaces 172:797-805 (2018) 3. Anesthesia & Analgesia 128(5): 65-66 (2019) 4. Vibrational Spectroscopy 109: Article # 103095 (2020)

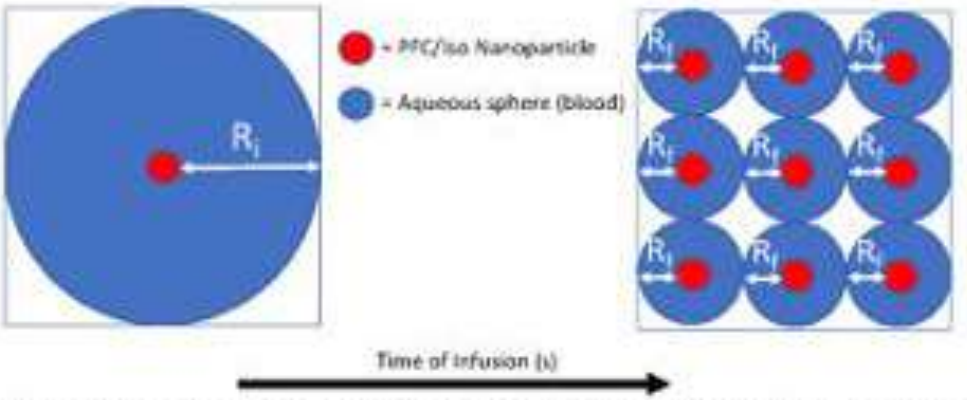

Figure 1: Schematic representation of finite element model. A 2D model was developed containing an inner, unchanging sphere of isoflurane/perfluorocarbon nanodroplets (red) and an outer sphere representing the aqueous/blood compartment between adjacent droplets during infusion (blue). As infusion continues, the distance between droplets is reduced and the outer sphere diameter decreases with a concurrent exponential/plateau increase in the concentration of isoflurane.

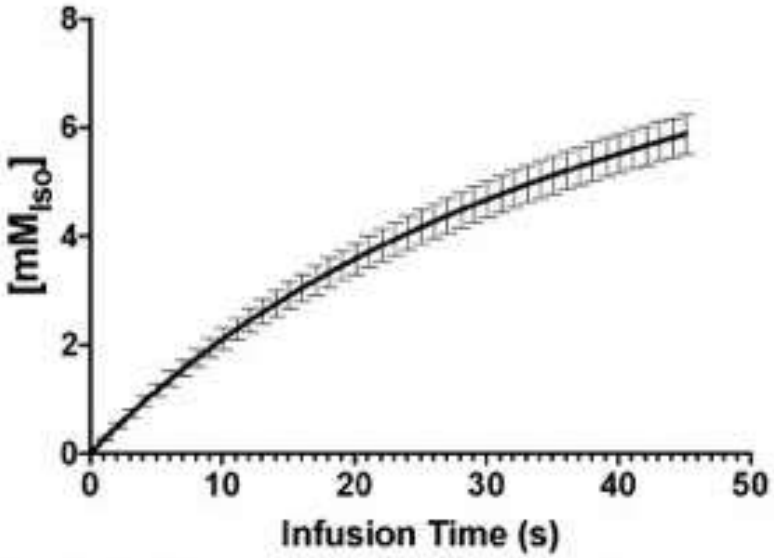

Figure 2: Mean FEM-derived infusion profile for effective dose of isoflurane/perfluorocarbon nanoemulsions.

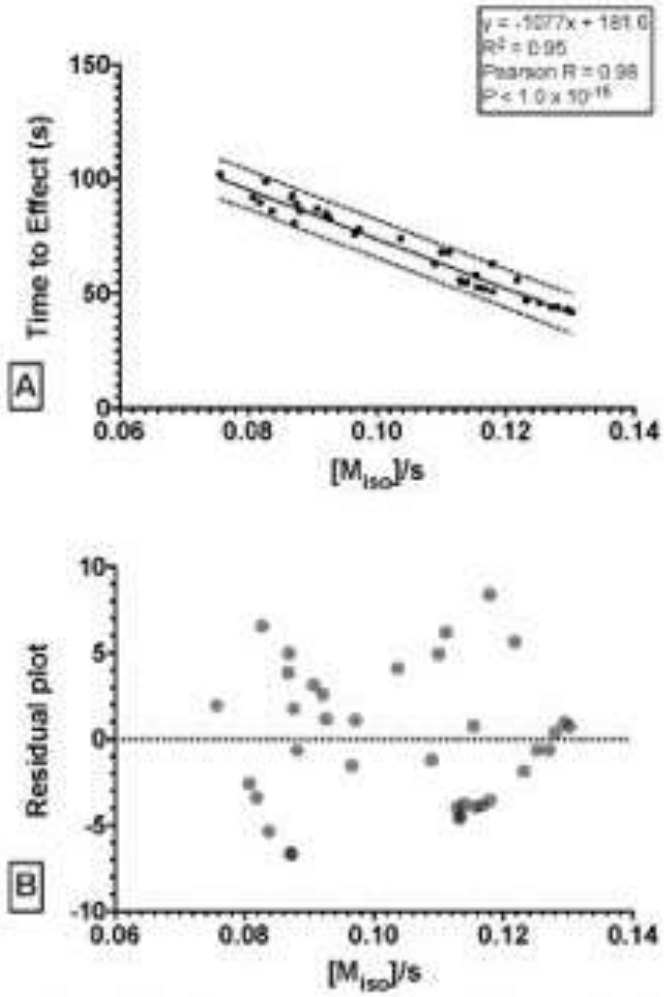

Figure 3. Correlation of rate of molar isoflurane blood concentration increase with the time to effect of induction infusions in 36 individual infusions. There was a significant correlation between the two metrics and the residual plot was balanced with no indication of outliers, heteroscedasticity, y-axis imbalance or non-linearity.

Technology, Computing and Simulation, Equipment Monitoring - 12

Implementation Of An Automated Time-Tracking System To Accurately Document Billable Time For Physician Anesthesiologists

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Introduction: Many clinical anesthesia environments have separate documentation processes that indicate the conclusion of medical direction in the electronic health record (EHR) and the related overtime payroll claim of "extended hours".

Prior to 2014, the Vanderbilt University Medical Center's Department of Anesthesiology attendings documented the beginning (start time) and end (end time) of medical direction for every operating room case within Vanderbilt's Perioperative Information Management System (VPIMS). When the latest medical direction end time was after 5pm on a weekday, the physician manually recorded their extended hours on a separate paper form called a "yellow sheet". Yellow sheet data were manually collated by administrative staff and hand-keyed into the department's payroll system. Business Office analysis illustrated that the manual yellow sheet extended hours were greater than represented by the medical record end times.

On 4/1/2014, our Department of Anesthesiology implemented OpenTempo, physician scheduling software, to automate extended hours submissions into the payroll system. We performed an analysis to understand the impact of this implementation on overtime payroll claims.

Methods: Following IRB approval, data were extracted from our Perioperative Data Warehouse (PDW) over the time period between 1/1/2013 and 12/31/2015. The pre-intervention period was defined as 1/1/2013 through 3/31/2014 and after a six-month wash-in period the post-intervention period was defined as 10/1/2014 through 12/31/2015. 6,708 anesthetic records for attending anesthesiologists not on "first call" that had end times after 5pm in Vanderbilt University Adult Hospital and Monroe Carell Jr. Children's Hospital at Vanderbilt operating rooms were analyzed.

During the preintervention period, the difference between the latest documented medical direction end time for the attending anesthesiologist from VPIMS (VPIMS end time) and the reported end time documented on a departmental "yellow sheet" (manual payroll end time) was calculated. For the post-intervention period, the difference between the VPIMS end time and the automatically recorded end time from OpenTempo (automated payroll end time) was calculated. A Mann-Whitney U-Test and Fisher Exact Test were performed on the data. Data analysis was done using Microsoft SQL Server and Microsoft Excel.

Results: Following implementation of the automated time-tracking system, the median difference between the VPIMS end time and payroll end time decreased 6 minutes. The mean of the end time differences decreased from 9.65 minutes pre-intervention to 1.75 minutes post-intervention (p-value < 0.0001) illustrating statistical significance for the intervention.

During the pre-intervention phase, there were 121 occurrences of a difference in VPIMS versus manual end times of greater than 60 minutes. Post-intervention, the number of cases with a discrepancy greater than 60 minutes between VPIMS end time and the automated end times decreased to 49 occurrences, a decline of 59.5% . A similar trend was seen for discrepancies of greater than 30 minutes (319 occurrences pre-intervention versus 165 occurrences post-intervention) and greater than 15 minutes (707 pre-intervention versus 307 post-intervention). [Fisher exact test p-value 0.07338]

Conclusion: After implementation of an automated extended hours recording system, a statistically significant decrease between the recorded time of medical direction on the EHR and the reported end time in the payroll system was observed. We expect that the decreased difference will result in a sustained decrease in payroll expenses.

Trauma

Trauma - 1 Reduction in Cerebral Blood Flow During Aeromedical Evacuation-Relevant Hypobaria Following Rat Traumatic Brain Injury

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Introduction: Simulated aeromedical evacuation (AE), or hypobaria equal to 8000 ft cabin pressure, worsens neurologic and neuropathologic outcomes after traumatic brain injury (TBI) in several animal models and species (1-5); however, the underlying mechanisms responsible for this form of secondary brain injury are unknown. This study tested the hypothesis that cerebral blood flow (CBF) is reduced following TBI in rats and is further reduced during exposure to AE- relevant hypobaria at 24 hr post-injury.

Methods: All animal protocols were approved by the Univ. of Maryland, Baltimore Institutional Animal Care and Use Committee and by the US Air Force Research Oversight and Compliance Division (SGE-C). The animal TBI model consisted of controlled cortical impact with adult male rats. Shams underwent anesthesia and craniotomy but no impact. Naïve rats had no surgery. Magnetic resonance imaging (MRI) and spectroscopy (MRS) measurements were performed 1 week prior to Sham or CCI, 1 day after CCI, followed by during 6 hr AE, and at 14 days post-injury. For each 2 hr scan, isoflurane anesthetized rats were placed in an MRI-compatible, custom built hypobaric chamber and then positioned within the bore of the 7 Tesla magnet. MRI and MRS measurements during AE were made under a combination of normoxic (30-40% O2) or hyperoxic (100% O2) conditions and normobaric (sea level) or hypobaric (equivalent to 8000 ft) barometric pressures. Arterial spin labeling was used to measure brain region-specific blood flow.

Results: Cerebral blood flow was reduced by 30 to 40% in the ipsilateral cortex and hippocampus at 24 hr post-CCI. Additional reductions in CBF were observed during exposure of CCI rats to normoxic or hyperoxic hypobaria in the ipsilateral and contralateral hippocampus and thalamus. This reduced CBF occurred under both normoxic and hyperoxic conditions. Moreover, blood flow in the thalamus was reduced by an additional 40% specifically in Shams exposed to hypobaria. Rats in the Sham group underwent a craniotomy, which results in mild inflammation and tissue damage. We therefore included an additional group of naïve rats to detect any effects of hypobaria on uninjured rats. Remarkably, there was a small, 10% reduction in CBF during exposure to hypobaria, relative to the flow rate present prior to hypobaric exposure. Lactate levels present in the ipsilateral cortex one day after CCI rose to 7 times greater than baseline. Lactate rose an additional 46% in rats under normobaric hyperoxia compared to levels present a 4 hr prior to exposures. There was a 45% increase in lactate when rats were exposed to normobaria under 100% O2. Lactate present in the cortex of all groups normalized by 14 days post-injury. There was also a 65% reduction in ipsilateral glutathione one day following CCI, followed by an additional 60% reduction during exposure to normobaria under 100% O2.

Conclusion: Exposure to AE-relevant hypobaria one day after moderate TBI or Sham surgery reduced CBF in the cerebral cortex and hippocampus. During flight, there was an increase in cortical lactate in rats exposed to normobaria under 100% O2 compared to rats exposed to hypobaria under 100% O2. Thus, being exposed to normobaria under 100% O2 creates more metabolic stress than hypobaria under high O2. Cortical glutathione levels fell after TBI and were exacerbated by exposure to normobaria under 100% O2. This finding indicates that there is more oxidative stress when exposed to normobaric hyperoxia compared to hyperbaric hyperoxia. When comparing the CBF and neurochemical outcomes across the animal groups, the CCI group that fared the best was the one with rats maintained under normobaric and normoxic conditions. These results support the recommendation that TBI patients should either wait at least several days before flying or fly at cabin pressures higher than those typically used. In addition, the use of unnecessarily high levels of supplemental O2 should be avoided during flights as hyperoxia can worsen oxidative stress and metabolic dysfunction.

References: 1. Aeromedical evacuation-relevant hypobaria worsens axonal and neurologic injury in rats following underbody blast-induced hyperacceleration. J Trauma Acute Care Surgery 83(1 Suppl 1):S35-S42 (2017) 2. Simulated aeromedical evacuation exacerbates experimental brain injury, J. Neurotrauma 33:1292-302 (2016) 3. Hypobaria during aeromedical evacuation exacerbates histopathological injury and modifies inflammatory response in rats exposed to blast overpressure injury. J Trauma Acute Care Surg. 87:205-213.(2019) 4. Hypobaria during long-range flight resulted in significantly increased histopathological evidence of lung and brain damage in a swine model. J Trauma Acute Care Surg. 86:116-122 (2019) 5. Hypobaric hypoxia exacerbates the neuroinflammatory response to traumatic brain injury. J Surg Res. 165:30-7 (2011)

Trauma - 2 Induction in Trauma Patients: Etomidate vs. Propofol on Mortality and Hemodynamics

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Introduction: Traumatic injury is the leading cause of death for adults under age 45.[1] When trauma patients require emergent surgery, an ongoing question is whether anesthetic induction with etomidate is more hemodynamically stable and results in better long-term survival than propofol. [2] Because trauma victims are often hypovolemic due to hemorrhage, vasodilatory effects of propofol may cause or worsen hemodynamic instability. Conversely, although anesthetic induction with etomidate may be more hemodynamically stable, suppressive effects of etomidate on adrenal function may worsen long term outcomes after surgery.[3,4] To evaluate the impact of induction agent on peri-induction hemodynamic variables and postoperative outcome, we reviewed intra and postoperative outcomes in emergent trauma cases from an urban Level I trauma center.

Methods: Because all data were deidentified, this study was exempt by the Institutional Review Board. We conducted a retrospective chart review of all patients who underwent emergent trauma surgery on the day of admission from an urban Level I trauma center from May 1 to November 9, 2020. Data collection included demographic information, ASA physical status score, method of injury, blood transfusion prior to induction, hemodynamic variables (systolic and diastolic blood pressure and heart rate), and time of intubation (night vs. day). Our primary outcomes included change in blood pressure and heart rate post induction, and mortality in the operating room or during the hospitalization. Data were analyzed between groups using t-test for continuous variables and chi-squared test for categorical variables.

Results: During the study period, 183 patients underwent emergent surgery on the day of admission. The average age was 32.9 years (SD=13.1), and average weight was 82.0 kg (SD=23.4). The mechanism of injury was penetrating in 154 of 183 patients (84.2%). We excluded 47 patients who were intubated before the operating room or who received induction agents other than propofol or etomidate. Of the remaining 136 patients, 96 were induced with propofol (70.6%), and 40 with etomidate (29.4%). The average propofol dose was 1.61 mg/kg (SD=0.71) while etomidate was 0.22 mg/kg (SD=0.065). Demographic, time of induction, and baseline hemodynamic data did not differ between the propofol and etomidate groups (Table 1). More patients who were transfused prior to the operating room received etomidate (70.0% etomidate vs. 38.5% propofol; $p < 0.001$) (Table 1). Outcomes, including changes in hemodynamic variables post-induction (blood pressure and HR), mortality in the operating room, and mortality during the hospitalization did not differ between patients induced with propofol and those induced with etomidate (Table 2).

Conclusion: In this study of 136 trauma patients who underwent emergent surgery at an urban level 1 trauma center, we found that peri-induction changes in hemodynamic variables, operating room and overall mortality did not differ between patients induced with etomidate or propofol. Although most demographic data were similar between groups, patients who had been transfused prior to surgery were more likely to receive etomidate. Although limited by our retrospective study design, our findings suggest that propofol may be used safely in trauma patients. Further work is needed to clarify the role of induction agent in outcome after emergent trauma surgery.

References: 1. NVSS. 2016 Feb;65(2):1–95. 2. Eur J Trauma Emerg Surg. 2015 Aug;41(4):405–11. 3. Etomidate. In: StatPearls [Internet]. 2020 Aug 10. 4. J Emerg Med. 2012 Nov 1;43(5):e277–82.

Table 1. Demographics and characteristics of trauma patients in the Propofol vs. Etomidate group

	Propofol (n=96)	Etomidate (n=40)	P value
Age (SD)	32.3 (12.3)	36.4 (15.9)	0.154
Weight in kg (SD)	81.5 (24.0)	83.6 (23.1)	0.631
SBP < 90*	3 (3.4%)	3 (9.4%)	0.219
MAP (SD)	101.4 (21.5)	102.6 (24.3)	0.800
PP (SD)	50.2 (19.9)	43.2 (17.8)	0.076
HR (SD)	94.3 (18.9)	96.0 (18.9)	0.664
ASA Score (SD)	2.5 (1.4)	2.85 (1.4)	0.163
Penetrating trauma	88 (91.7%)	31 (77.5%)	**0.023**
Blood transfusion pre-induction	37 (38.5%)	28 (70.0%)	**0.001**
6AM-6PM	36 (37.5%)	17 (42.5%)	0.586

*n=87 for propofol, n=32 for etomidate
SBP= systolic blood pressure, MAP= mean arterial pressure (mmHg), PP= pulse pressure (mmHg), HR= heart rate (beats per minute), ASA score = American Society of Anesthesiology physical status score

Table 2. Mortality & hemodynamic outcomes of trauma patients in the Propofol vs. Etomidate group

	Propofol (n=96)	Etomidate (n=40)	P value
Mortality in operating room	1 (1.1%)	1 (2.5%)	0.520
Mortality during hospitalization	4 (4.2%)	4 (10.0%)	0.188
SBP < 90*	16 (17.4%)	5 (12.8%)	0.514
MAP (SD)	90.4 (24.5)	95.4 (28.9)	0.316
PP (SD)	52.6 (21.6)	53.3 (19.8)	0.864
HR (SD)	104.1 (17.0)	106.1 (21.2)	0.606

*n=92 for propofol, n=39 for etomidate
SBP= systolic blood pressure, MAP= mean arterial pressure (mmHg), PP= pulse pressure (mmHg), HR= heart rate (beats per minute)

Trauma - 3 Comparison of Intravenous Waveform Analysis to Current Markers for Detection of Hemorrhage in a Rat Model

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Introduction: Quantification of hemorrhage and assessment of volume status remain challenging, particularly in the perioperative period. Central venous pressure (CVP) poorly correlates with volume status. Dynamic measurements such a pulse pressure variation (PPV), stroke volume variation (SVV) and systolic pressure variation (SPV) are predictive of cardiac preload only within a narrow set of clinical parameters (1). Obtaining serial measurements of left ventricular end diastolic area (LVEDA) is often impractical. Intravenous waveform analysis (IVA) is a novel method of volume status assessment which relies on spectral frequency analysis of amplitudes within the intravenous waveform. We hypothesized that IVA would be superior to current clinical markers in assessing intravascular volume during hemorrhage.

Methods: Ten male Sprague Dawley rats were anesthetized, intubated, and mechanically ventilated. Intravascular volume was altered through stepwise hemorrhage totaling 20% of the estimated blood volume (EBV) over 50 min. 2% of the EBV was removed over 1 minute every 5 minutes for 10 repetitions. PPV and SPV were derived from femoral arterial pressure tracings. Right ventricular base diameter (RVd), LVEDA, SVV and cardiac output (CO) were measured via echocardiography. Fast Fourier transformation was performed on the femoral venous waveform and the amplitude of the primary frequency, F1, was analyzed. The F1 frequency corresponded with heart rate measured on ECG. Data was evaluated as percent change from baseline. Repeated measures ANOVA analysis with pairwise comparisons and Bonferroni correction was performed. If either interval of comparison was non-normally distributed Dunn's test was used. Significance was set at p=.05.

Results: IVA amplitude F1 differed significantly from baseline with loss of 2% of the EBV, p=.0001 (95% CI -44% to -24%). CO also fell at loss of 2% EBV, p=.004 (95% CI -18% to -2%). Notably F1 continued to fall significantly over the first four intervals while cardiac output did not, Table 1. CVP was able to detect a loss of 6% EBV, p=.012 (95% CI -28% to -2%). All other markers required hemorrhage of ≥8% of the EBV to achieve statistical significance, Table 2. Heart rate and RVd did not change significantly at any interval.

Conclusion: In this study, IVA displayed a higher sensitivity to change in volume status than cardiac output and was able to estimate blood loss with higher precision. Additionally, it outperformed commonly used static, dynamic and echocardiographic markers of volume status including CVP, PPV, and LVEDA. Clinically the advantage of IVA stems from its practicality. IVA can be performed via a venous catheter, making this minimally invasive technique more available than invasive volume status assessment methods or repeat ultrasonography. Further work is required in assessing both its prediction of volume responsiveness in resuscitation and its applicability in varying clinical scenarios, e.g., spontaneously breathing, open chest, non-supine subjects.

References: 1. 'Arterial pulse pressure variation with mechanical ventilation.' American Journal of Respiratory and Critical Care Medicine 199.1 (2019): 22-31.

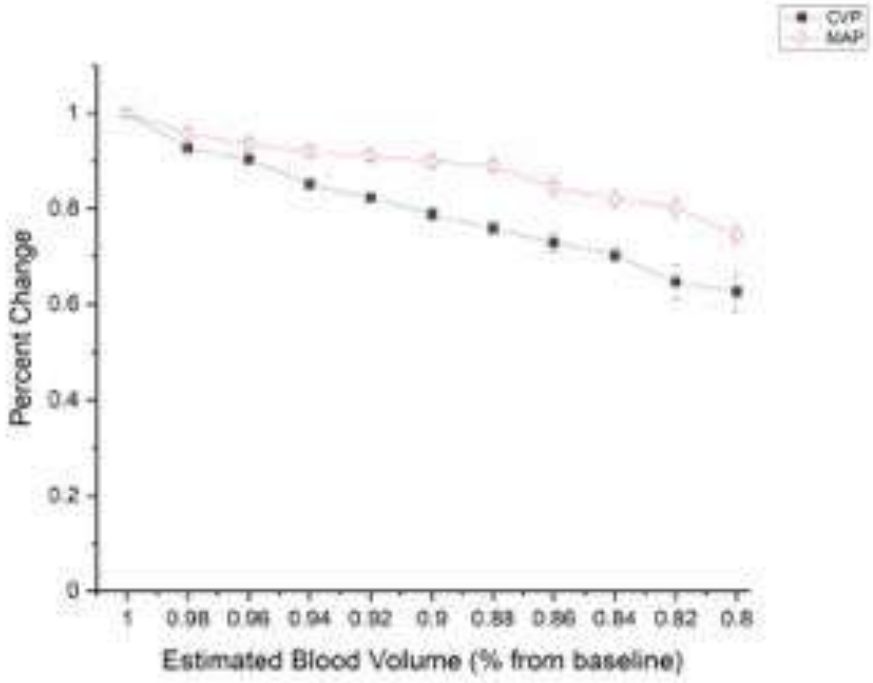

Figure 1. Mean value and standard error are displayed for central venous pressure and mean arterial pressure at each interval of the experimental protocol. Values are displayed as percent change from baseline measurements.

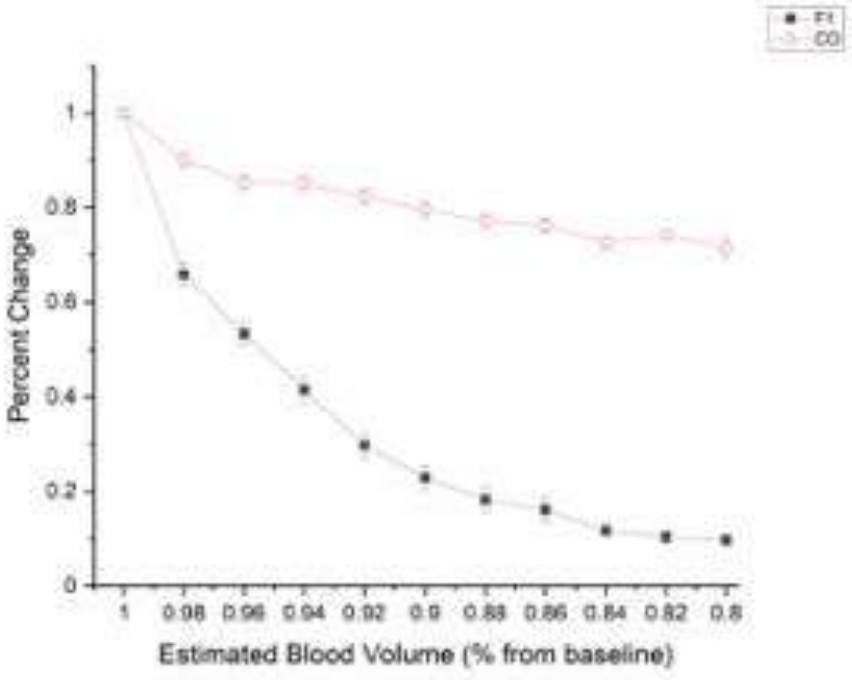

Figure 1. Mean value and standard error are displayed for the F1 amplitude derived from intravenous waveform analysis and cardiac output measured by transthoracic echocardiography at each interval of the experimental protocol. Values are displayed as percent change from baseline measurements.

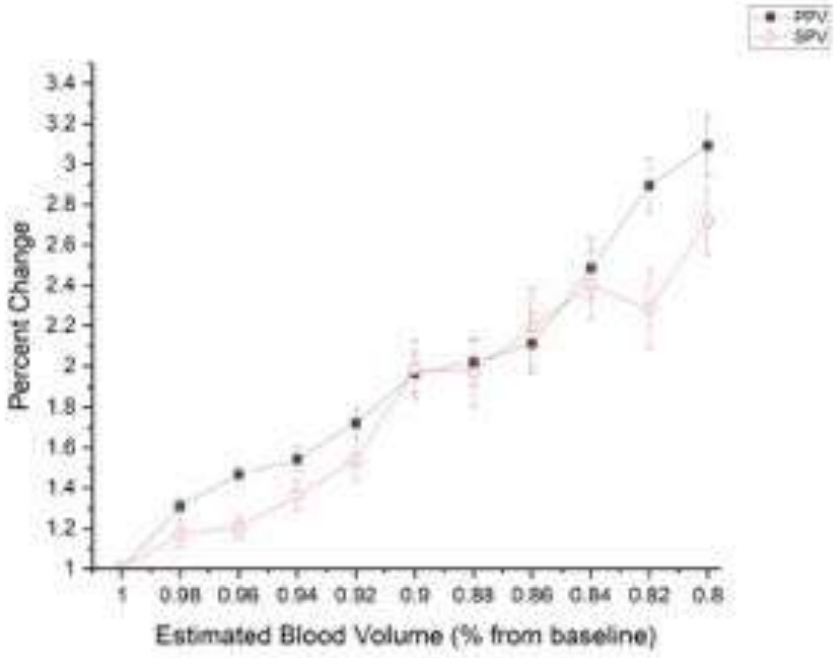

Figure 1. Mean value and standard error are displayed for the pulse pressure variation and the systolic pressure variation derived from femoral arterial line transduction at each interval of the experimental protocol. Values are displayed as percent change from baseline measurements.

Table 1.

	F1 amplitude		Cardiac Output	
Blood loss (experimental interval)	P value	95% Confidence interval as % change	P value	95% Confidence interval as % change
0% to 2% (1)	0.0001	-44% -24%	0.004	-18% -2%
2% to 4% (2)	0.0028	-22% -2%	1.000	-12% +3%
4% to 6% (3)	0.0068	-22% -2%	1.000	-8% +7%
6% to 8% (4)	0.0094	-22% -1%	1.000	-11% +4%
8% to 10% (5)	1.0000	-17% +3%	1.000	-10% +5%

Table 1. The P values and 95% Confidence Intervals are displayed for both the F1 amplitude derived from intravenous waveform analysis and the cardiac output measured via transthoracic echo. Values are displayed for evaluation amongst time points separated by one experimental interval. F1 was sensitive to early blood loss and was able to discern between loss of 0%, 2%, 4%, 6% and 8% of the estimated blood volume.

Table 2.

Variable	Blood loss Required for Significant Change	P value	95% Confidence Intervals
FI	2%	0.0001	-44% -24%
CO	2%	0.004	-18% -2%
CVP	6%	0.011	-28% -2%
PPV	8%	0.005	+12% +132%
EDV	8%	0.017	-26% -1%
MAP	10%	0.017	-19% -1%
SPV	10%	0.001	+27% +170%
SVV	14%	0.002	+17% +146%
HR	N/A	1.000	-4% +5%
RVd	N/A	1.000	-15% +7%

Table 2: The smallest amount of blood loss required for statistically significant deviation from baseline for each parameter is displayed.