Weill Cornell Medicine
Anesthesiology

16th Annual Research Exposition

November 2024

12 TUE

Opening and Faculty Presentations
3:00-4:00 pm | M309 and P300

Special Research Talk
4:00-4:30 pm | M309 and P300

Reception
4:30-5:00 pm | P3 Corridor

Oral Abstract Presentations
5:00-6:00 pm | P300

14 THU

Joseph F. Artusio Jr. Resident/Trainee Research Expo Afternoon
3:00-4:30 pm | Griffis Faculty Club

TUESDAY, NOVEMBER 12TH

Oral Presentations
3:00-4:00 pm

"How dying cells get recognized: structure and mechanism of a human apoptotic scramblase"

Alessio Accardi, Ph.D.
Professor of Physiology and Biophysics in Anesthesiology
Professor of Biochemistry
The Accardi Lab
Weill Cornell Medicine

"The power (and pitfalls) of pharmaco-epidemiology"

Hannah Wunsch, M.D., MSc
Professor of Anesthesiology
Vice Chair for Research
Director of Outcomes Research
Weill Cornell Medicine

Special Research Talk
4:00-4:30 pm

"Using data science to journey from retrospective observational research to prospective patient-centered clinical trials"

Sachin Kheterpal, M.D., MBA
Professor of Anesthesiology
Co-Director of the Precision Health Initiative
Associate Dean for Research Information Technology
University of Michigan Medical School

THURSDAY, NOVEMBER 14TH

Joseph F. Artusio Jr. Resident/Trainee Research Expo Afternoon
3:00-4:30 pm

Oral presentations of award winning abstracts
Moderated poster session

Department of Anesthesiology • 525 East 68th Street, P3
For more information contact: **Michele Steinkamp, RN**
212-746-2953 or mls9004@med.cornell.edu

Welcome to the 16th Annual Research Exposition

Tuesday, November 12th 2024

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Reception

4:30-5:00 pm | P3 Corridor

Oral Abstract Presentations

5:00-6:00 pm | P300

"Determinants of delayed recovery of consciousness after analgosedation discontinuation in the Intensive Care Unit: insights from patients with COVID-19 hypoxemic respiratory failure"
Seyed Safavynia, M.D., Ph.D.

"The cryo-EM structure and physical basis for anesthetic inhibition of the THIK1 K2P channel"
Elena Riel, Ph.D.

"Racial disparities in the adherence to an Enhanced Recovery After Cesarean Protocol (ERAC): A retrospective observational study, 2016-2020"
Abbey Gilman, B.S.

"Isoflurane and sevoflurane inhibit mammalian sodium channel subtype Nav1.3"
Jiaxin (Jessica) Xiang, M.Eng.

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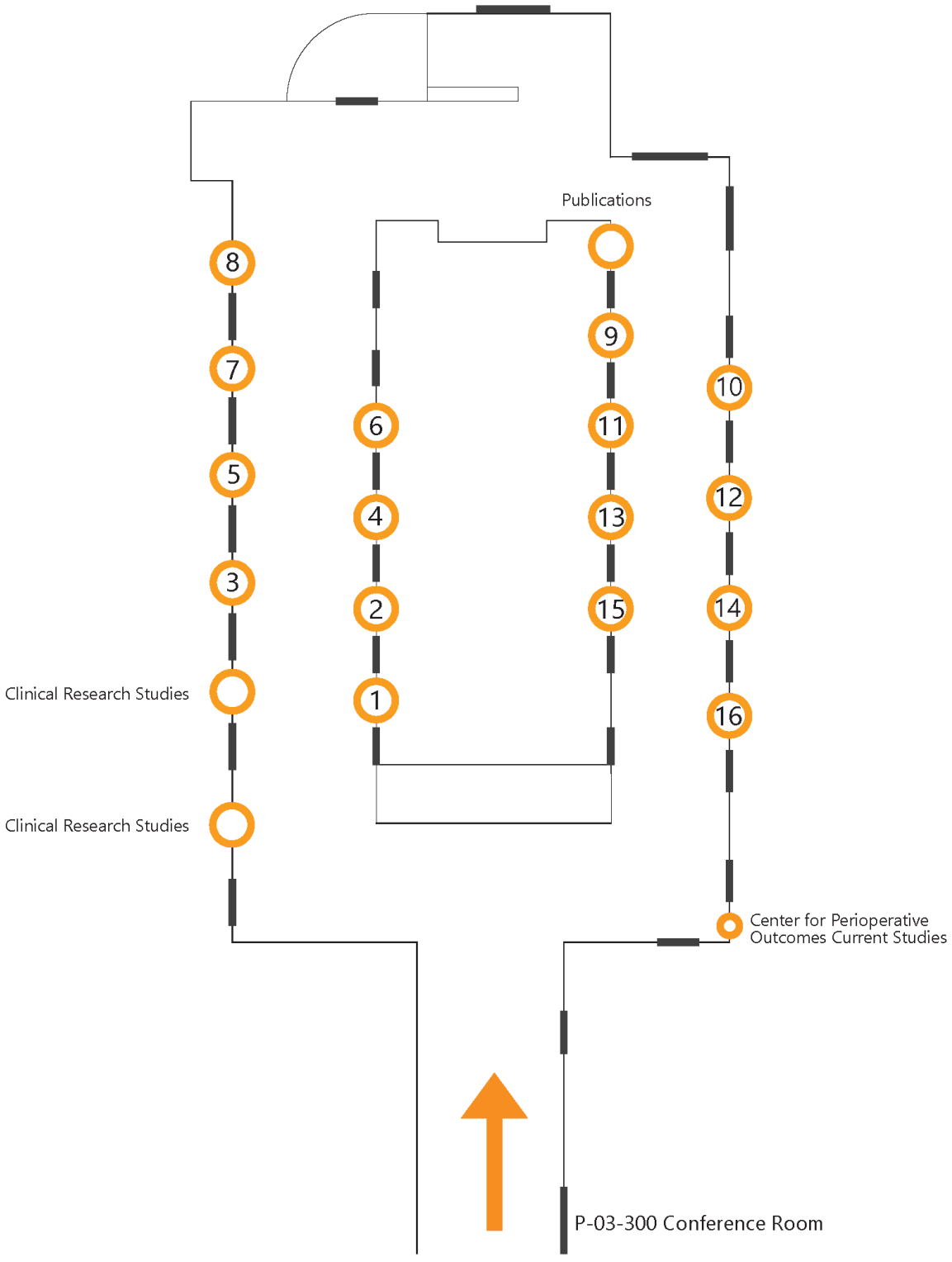
P-03 Poster Map



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3. **Establishing a Vital Sign Registry for Digital Health Research and Algorithm Development**
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4. **User Experience and Efficacy of Low Dose Naltrexone: A Patient Survey**
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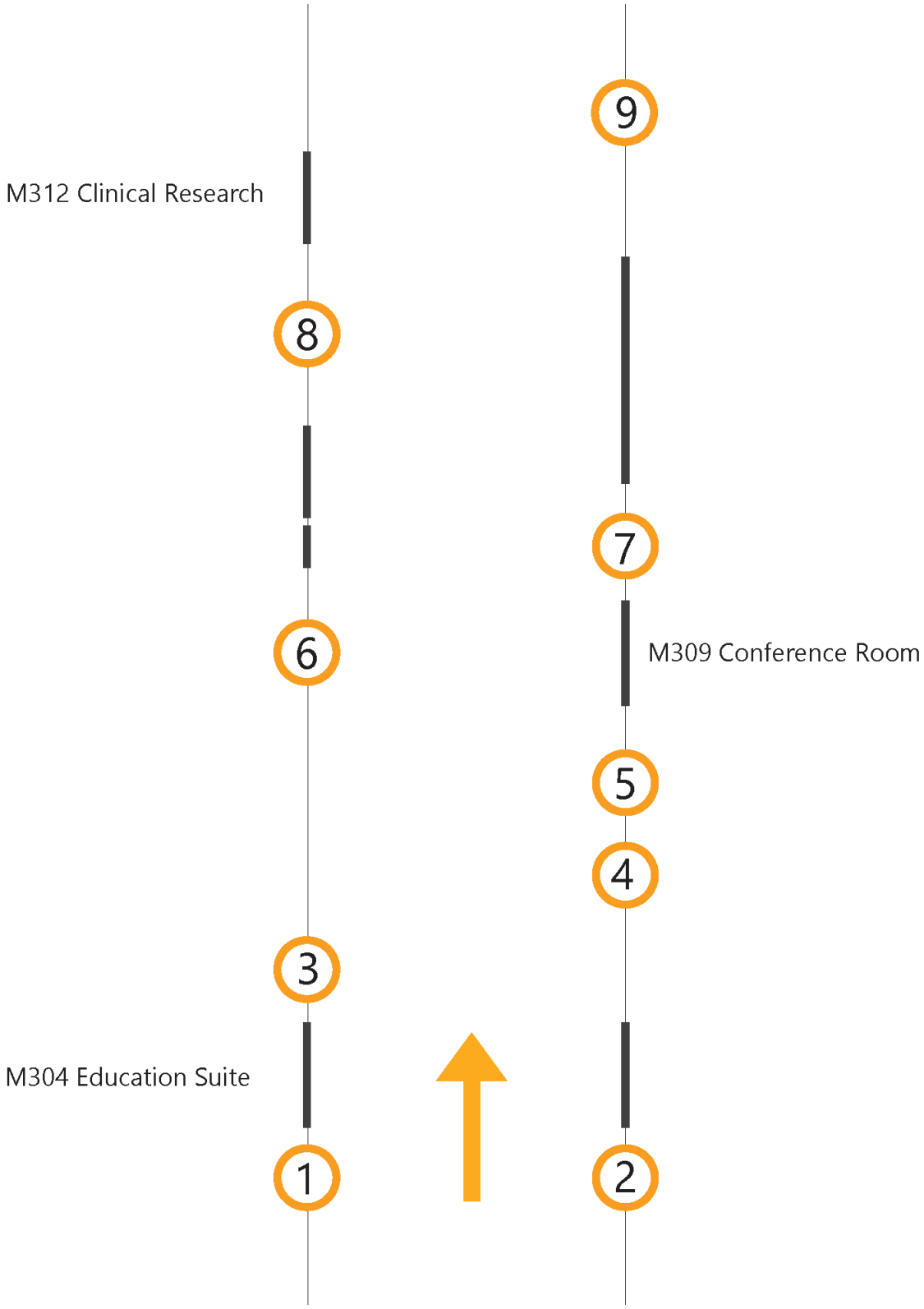

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Clinical Research, Quality Improvement, and Center for Perioperative Outcomes Posters

An Interpretable Model for Predicting Preoperative Cardiorespiratory Fitness Using Wearable Data in Free-Living Conditions

Richard Boyer [1,*], Iqram Hussain [1], Julianna Zeepvat [1], Cary Reid [2], Sara Czaja [2], Kane Pryor [1]
1. Dept of Anesthesiology, Weill Cornell Medicine, New York, NY
2. Division of Geriatrics and Palliative Medicine, Weill Cornell Medicine, New York, NY

Introduction

- Predicting preoperative cardiorespiratory fitness (CRF) is essential for assessing surgical risk, but formal testing methods like CPET or 6MWT are impractical for preoperative screening.
- Wrist-worn devices with actigraphy and heart rate monitoring can now estimate physiological measures, offering an alternative.
- Our aim was to investigate whether the 6MWT distances can be predicted using a wearable preoperative CRF model for older adults.

Methods

- We analyzed heart rate and activity data from 65 older adults wearing Fitbit devices over a 1-week preoperative period during their usual daily activities before major noncardiac surgery.
- We used a machine-learning ensemble regression model to predict CRF based on 6MWT outcomes, applying Shapley Feature attribution to identify key wearable data features contributing to personalized fitness prediction.

Wearable Features Assessed – Definitions

Activity States & Metabolic Equivalent of Task (MET):
- Light activity: 1<METs≤2
- Moderate-low activity: 2<METs≤4
- Moderate-high activity: 4<METs≤6
- Vigorous activity: 6<MET

Heart Rate Variability (HRV) Features:
- SDNN, RMSSD, and SDSD
- pNN50
- Respiratory Sinus Arrhythmia (RSA)
- LF/(LF + HF), HF/(LF + HF), LF/HF
- Entropy
- Fractal Detraction analysis (DFA1, DFA2)
- Poincare plot (Slope)

Heart Rate (HR) Recovery Features:
- 5th min HR recovery
- 4th min HR recovery
- 3rd min HR recovery
- 2nd min HR recovery
- 1st min HR recovery

Other Features
- aEEmax , HR slope/work (calories) , HR intercept/work (calories)

Target Variable: 6MWT

- Data partition: Training dataset (80%) and testing dataset (20%).
- Machine-learning algorithms: Random forest classifier, Gradient boosting classifier.
- Interpretation: Shapley Value.

Hypothesis

We conducted a prospective, observational clinical study to test the hypothesis that wearable measurements of cardiorespiratory fitness (CRF) are predictive of postoperative complications in older adult patients undergoing major surgery.

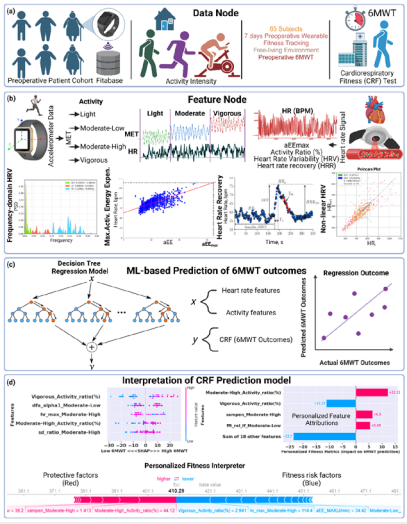

Figure 1: Comprehensive system architecture for predicting 6MWT outcomes using wearable fitness trackers and explainable AI techniques. (a) Collection of heart rate and activity data from fitness trackers. (b) Feature Node: Extraction of physiological and activity features. (c) Machine Learning Framework to predict cardiorespiratory fitness (CRF). (d) Model Interpretation and Personalization.

Results

- Adults with higher CRF showed increased levels of MVPA, aEEmax, HRR, and non-linear HRV, which correlated with better 6MWT outcomes.
- Regression models (random forest and linear regression) predicted CRF with R^2 values of 0.91 and 0.81, respectively (Fig. 2).
- Shapley Feature Attribution revealed MVPA, aEEmax, HRR, and non-linear HRV as key indicators of improved CRF performance (Fig. 3).

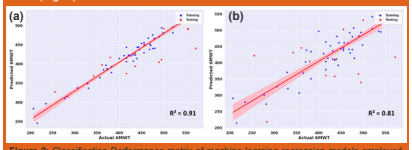

Figure 2: Classification Performance matrix of machine-learning regression models employed for estimating 6MWT (6-Minute Walk Test) performance.

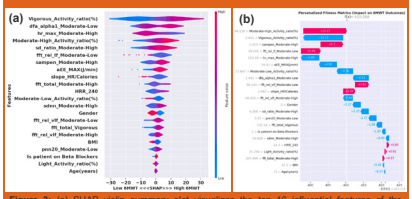

Figure 3: (a) SHAP violin summary plot visualizes the top 16 influential features of the Random Forest Regression (RFR) model for predicting 6MWT, (b) SHAP waterfall plot illustrating heart rate trends as explanations for a 'typical individual' in predicting 6MWT performance.

Conclusions

- Wearable cardiorespiratory fitness monitors have strong potential for preoperative assessment of CRF in older adult surgical patients and is a promising tool for geriatric surgical risk stratification.

Application of the Patient Priorities-Aligned Decision-Making Model of Care in The Pain Management Setting

Lisa R. Witkin, MD, MS[1], Abha Kasubhai, BA[1], Jerad H. Moxley, PhD[2], Elaine Wethington, PhD[2], Cary Reid, MD, PhD[2]

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Introduction

Aligning care with patients' priorities has been shown to improve outcomes for older patients with multiple chronic conditions in the primary care setting [1]. Patient-priority directed care (PPC) consists of eliciting and documenting a patient's goals and preferences by a trained member of the healthcare team [2]. Providers then develop treatment plans that align with patients' goals and preferences [3]. Patients suffering with chronic pain may have multiple competing goals, such as pain intensity reduction, improvement of physical function, and increase in their quality of life. Eliciting their preferences and values may influence clinical decision-making and help to optimize and tailor pain care.

This national survey study sought to determine pain management physicians' attitudes, preferences, and beliefs regarding patient-centered care models, and gauge respondents' willingness to adopt a patient priorities model in their respective practices. As a related goal, we sought to understand respondents' practice patterns regarding incorporating patient priorities and values into care decision-making.

Methods

A one-time Qualtrics survey was distributed to board-certified pain management physicians nationwide via the physician membership of the American Academy of Pain Medicine (AAPM), IQVIA, and through Weill Cornell Medicine pain alumni listservs. Participants were compensated for their survey completion with a $20 gift card [4].

Results

212 surveys were collected (5/8/2023 through 8/23/2023) and analyzed. Most respondents were male (73.3%). All but one reported offering multidisciplinary pain care. The two largest settings were private practice (53.9%) and academic (32.0%). Most respondents reported that it would be at least somewhat useful (98.5%) to understand patients' health goals and personal values in formulating a pain treatment plan. 89.7% reported they were at least somewhat likely to adopt these techniques in their practice. 79.0% reported that their older chronic pain patients would be at least somewhat likely to undertake a values exploration process. Factors influencing patients' receptivity to adopting a PPC approach were categorized into patient characteristics (45.1%), financial status (11.8%), age (24.8%), diagnosis (25.5%), treatments (15.7%), and treatment preferences (17%). Key barriers to implementing a PPC approach in pain medicine practices included burnout, integration into the EHR (electronic health record), time constraints, staffing/support, reimbursement, provider acceptance, patient acceptance, and knowledge and training.

Conclusions

While most pain practitioners report that PPC would be useful to understand patients' health goals and values, respondents identified multiple barriers to implementing such an approach in pain medicine practices. Further research is needed to identify the feasibility, acceptability, and efficacy of using PPC in diverse pain care settings.

Table 1: Types of Patients Most Receptive to Adopting a PPC Model

Code	Number of Respondents that Reported Code
Characteristics (45.1%)	
Motivated	23
Educated	12
No time restrictions/flexibility	7
Actively engage in treatment	10
Open-minded/reflective	5
Financial Status (11.8%)	
High SES	6
Low SES	1
Age (24.8%)	
Younger	16
Middle-aged	5
Older	9
Diagnosis (25.5%)	
Facial pain	1
Spinal pain	3
Centralized pain	3
Multiple pain conditions	2
Chronic pain	11
Terminal diagnosis	3
Comorbid mental health disorders	2
Treatment (15.7%)	
Exhausted other treatment options	5
Not on opioids	7
Patient Treatment Preferences (17%)	
Improving their QoL/Functionality	4
Alternative/holistic therapies	8

Figure 1: Likelihood to Adopt PPC Model of Care Techniques in Practice

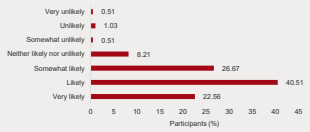
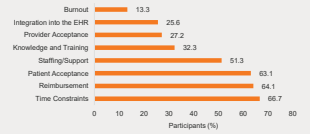


Figure 2: Barriers to Implementation



Acknowledgements

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References

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3. Tinetti ME, Esterson J, Ferris R, Posner P, Blaum CS. Patient Priority-Directed Decision Making and Care for Older Adults with Multiple Chronic Conditions. Clin Geriatr Med. 2016;32(2):261-75.
4. Leung GM, Ho LM, Chan MF, JM MJ, Wong FK. The effects of cash and lottery incentives on mailed surveys to physicians: a randomized trial. J Clin Epidemiol. 2002;55(8):801-7.

Establishing a Vital Sign Registry for Digital Health Research and Algorithm Development

Iqram Hussain, Joseph Scarpa, Julia Scarpa, Andrew Milewski, Kane Pryor, Richard Boyer *

Weill Cornell Med, New York, NY

Dept of Anesthesiology, Weill Cornell Medicine, New York, NY

Introduction

- Intraoperative vital sign monitors produce analog signals (e.g., ECG, EEG, AWP, ART) and digital signals (e.g., HR, BP, temperature).Practical challenges (software/network/server limitations) result in most of this data being discarded.
- Our objective is to create a comprehensive Vital Sign Registry at Weill Cornell Medicine (WCM) for clinical research and algorithm development.

Methods

- The study uses minicomputers with **Vital Recorder** software to collect real-time vital sign data (analog and digital) from patient monitors and anesthesia machines in operative rooms.
- Data is routed through a central hub, backed up to NAS, and periodically stored in the in-house cloud.
- The system integrates vital signs with clinical events and patient outcomes, ensuring anonymization and compliance with privacy regulations like HIPAA.

Vital Sign Registry

Data Collection System:

- Hardware: Minicomputers equipped with Vital Recorder software.
- Data Sources: Analog and digital signals from standard patient monitors in WCM/NYP operative rooms.
- Real-Time Acquisition: Continuous monitoring of vital signs and event data.

Data Management:

- Storage: Periodic backups to WCM ITS-supported in-house cloud storage.
- Integration: Linking vital sign data with clinical events and patient outcomes.
- Anonymization: Data is anonymized to ensure compliance with HIPAA and other privacy regulations.

Vital Signals:

- IntelliVue Patient Monitor: ECG, plethysmography, heart rate, blood pressures, oxygen saturation, temperature, gas concentrations, etc.
- Aisys CS2 Anesthesia Machine: Gas concentrations, ventilatory volumes, flows, airway pressures
- Masimo Sedline: (EEG) L1, L2, R1, R2, L1L2, R1R2

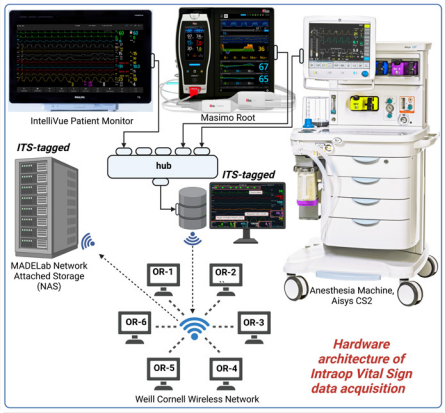


Figure 1: Schematic representation of intraoperative vital signs data collection and dataset creation.

Expected Outcomes

- Scope:
  - Registry will include intraoperative data from thousands of patients across various surgical and critical care scenarios.
  - Supports retrospective and prospective studies.
- Key Contributions:
  - Enables research into hemodynamic changes, drug effects, and clinical outcomes.
  - Facilitates development of AI-driven predictive analytics for improved care and decision-making.

Figure 2: Schematic representation of the Vital Recorder, intraoperative vital sign data acquisition software, cable of gathering real-time data from patient monitor, anesthesia machine, Masimo brain function monitor, and other OR equipments.

Conclusions

- Significance:
  - A vital step in leveraging large-scale datasets for advancing healthcare research and algorithm development for improving patient care and treatment protocols.
  - Lays the foundation for scalable, data-driven solutions in critical care and perioperative medicine.
- Future Directions:
  - Expansion of the registry to include outpatient settings.
  - Collaboration with external institutions for multicenter studies.

Acknowledgments

- We thank Weill Cornell ITS for technical support and WCM/NYP for operational collaboration.

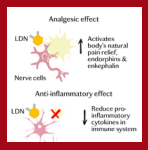
Weill Cornell Medicine
Anesthesiology

User Experience and Efficacy of Low Dose Naltrexone: A Patient Survey

Tiffany Lin, MD, David Cabello, BS, Abha Kasubhai, BA,
Virginia Tangel, MA MSc, Neel Mehta, MD.

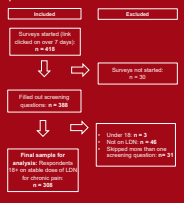
Introduction

- Low-dose naltrexone (LDN) is an opioid receptor antagonist with emerging off-label use in chronic pain management. Administered in doses typically between 1-5mg, LDN exhibits both analgesic and anti-inflammatory properties.
- Although anecdotal evidence supports LDN's efficacy for pain conditions such as fibromyalgia, complex regional pain syndrome, painful diabetic neuropathy, and multiple sclerosis, limited data exist on its clinical usage, dosing patterns, and side effects.



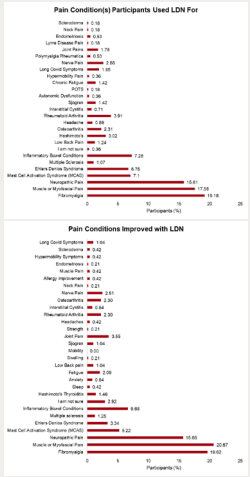
Methods

- We conducted a prospective cross-sectional survey using Qualtrics, distributed through LDN Research Trust newsletters and online support groups. Eligible participants (n=308) were adults who had used LDN for at least 60 days to treat chronic pain. The survey collected demographic information, dosing regimens, indications, pain relief, and side effects. Descriptive statistics were used to analyze responses.



Results

- The majority of respondents were women (92%) between 45-74 years old, with 69% holding a bachelor's degree of higher. Fibromyalgia (19.2%), muscle pain (17.6%), and neuropathic pain (15.8%) were the most common indications for LDN. The median daily dose was 4.5mg, with 87% following a titration schedule. Significant pain relief was reported by 79% of participants. Vivid dreams (57%) and sleep disturbances (55%) were the most frequently reported side effects, with most resolving over time or through dose adjustments. Five patients discontinued LDN due to side effects, including muscle or nerve pain.



Discussion

- This is the first large-scale survey to describe LDN prescribing practices and patient experiences in chronic pain management. Results align with previous studies on LDN efficacy, particularly for inflammatory pain conditions. Despite promising results, 21% of the patients experienced minimal improvement, suggesting individualized dosing strategies may be necessary. Side effects were common but mostly transient, further supporting LDN's safety profile.
- LDN is a well-tolerated, potentially effective treatment for chronic pain, particularly in women with conditions like fibromyalgia. Further research is needed to optimize dosing and investigate LDN's full potential as a non-opioid alternative in chronic pain management.

Limitations

- The population was a convenience sample of patents who are active in online groups who discuss LDN use.
- The ration between LDN support group respondents with favorable experiences versus failures of therapy is not completely clear, given that both parties may either stay engaged or drop out of a support group.
- The predominant response by women survey participants may not be reflective of the population at large.
- The survey relied on self-reported data, which may introduce bias in terms of symptom reporting and side effect attribution.
- The absence of a control group makes it difficult to conclusively attribute improvements in pain to LDN, rather than a placebo effect or the natural course of the disease.

Weill Cornell Medicine
Anesthesiology

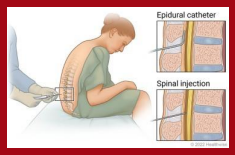
Patients' perspectives on non-utilization of neuraxial epidural analgesia: A qualitative study

Eliana Weinstein, BS; Jaime Aaronson, MD; Sharon Abramovitz, MD; Danielle McCullough, MD;
Ruth Gotian, EdD, MS; Robert White, MD, MS

FAER
Foundation for Anesthesia Education and Research

Introduction

- Over 25% of women who undergo vaginal birth do not receive neuraxial labor analgesia, and few studies have examined patient-level factors
- Studies have identified widespread variation in labor neuraxial analgesia usage by race, ethnicity, and geographic location
- One study of 50 women interviewed in Houston identified fears of paralysis, belief that women should cope with labor pain, fears about chronic back pain, and that friends and family advised them against it as reasons for avoiding neuraxial analgesia
- We aimed to provide a qualitative analysis of the factors important in pregnant women's decision to opt-out of neuraxial analgesia for labor and delivery using a semi-structured interview approach



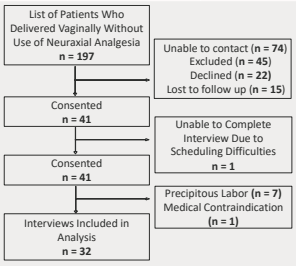
Methods

- Eligibility: delivered vaginally within 6 months without use of neuraxial labor analgesia, English speaking, no medical contraindications to neuraxial labor analgesia or pregnancy loss
- Participants were contacted, consented, and scheduled for 1-hour semi-structured Zoom interview
- Interviews were transcribed, then coded in Dedoose
- We analyzed data using sequential and iterative open, axial, and selective coding consistent with grounded theory
- Themes were identified using number of participants who mentioned the theme

Results

- We identified **five themes** encompassing the factors participants considered when making their pain management decision:

1. Patient preferences for a natural birth experience		
"I'm not against pain management in other areas, but there's just something about this experience that I wanted to be able to feel and experience."	"I wanted to feel my body. I wanted to feel my legs. I wanted to feel the pushing. I wanted to feel every single thing."	"Being able to move around was so great, laying on my back I think would have just exasperated things"
2. An empowering and supportive labor environment		
"everyone was just very friendly, very welcoming. It seemed like they were going out of their way to really help us and provide us what we needed in that given moment."	"All of our physicians and nurses and everyone involved, all the care team throughout the entire hospital stay was really wonderful."	"I feel like I had the best of both worlds. I feel like I had access to the best medicine in the world literally, like in case anything went wrong. Then I also feel I was able to do it both times, like on my own terms."
3. Preparation or preparedness for a birth without medication		
"I went into the experience with a battery of options. So I knew that, and I believed that I can't really know what's going to feel best in the moment. So I'm going to need a lot of options."	"I feel like all the techniques I followed- having doula, breathing, music, affirmation, having my partner and my husband know what to do and he also understood the process."	"I am really happy that I had a doula, I'm incredibly happy that I went to a birth class, I'm really happy that I listened to these birth stories, I talked to friends, I read, I was very well informed."
4. Positive outlook on labor pain		
"this idea that labor was going to be excruciatingly painful is something that has come up in our culture. So that really helped us understand that we got this."	"I tried to think of it as intense that the more intense it was the faster I was progressing and that really helped me stay in like a positive mindset."	"women have been doing this for millions of years and if he is head down and he's healthy and I'm healthy, then my body is capable of doing that"
5. Information, misinformation, knowledge gaps, and fears about the epidural		
"I know it's not necessarily true, but I did have this idea that it can slow down labor and then if you slow down labor, you're more likely to get a C section."	"mostly the needle going into the back and then the outcome of the effects of the medication, not feeling my legs, because I never experienced that."	"I've had friends and siblings that had epidural and some of them they complain about back pain, and some of them don't."



Discussion

- Participants expressed the value of **personal preferences** coupled with a **desire for more information** on both the epidural and non-pharmaceutical pain management options
- A **positive outlook on labor pain** and an **empowering environment** enabled our participants to be successful in their goal. The perception of pain—shaped by the social environment and contextual factors—may affect how women experience and respond to labor pain4
- Understanding patients' perspectives labor pain management can guide patient-provider interactions centered on **mutual understanding, evidence-based medicine, and honoring patients' wishes**
- **OB anesthesiology consults** can be incorporated into routine obstetrical visits, and early identification of patients who are considering natural delivery can help identify patients for whom a consult prior to labor may be especially useful

Limitations

- There is a sampling and recall bias; social desirability
- This study was conducted at a single urban center
- We did not consider perspectives of women who wanted to not use an epidural but ultimately received one
- Themes were identified by using number of individual participants who mentioned the theme (rather than number of total mentions)
- All participants expressed overall satisfaction with their care
- **Future studies** should explore perspectives on pain relief during labor for women who delivered without an epidural and were not satisfied with their care

Beliefs, perspectives, and experiences with non-use of epidural analgesia for labor: A breakdown by race and educational background

Eliana Weinstein, BS; Jaime Aaronson, MD; Sharon Abramovitz, MD; Danielle McCullough, MD; Ruth Gotian, EdD, MS; Robert White, MD, MS

Weill Cornell Medicine Anesthesiology

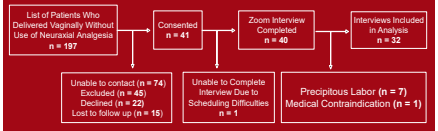
FAER Foundation for Anesthesia Education and Research

Introduction

- Non-Hispanic White women are more likely to receive neuraxial labor analgesia for labor than Black or Hispanic women
- Maternal age, education, culture, pain perception, and parity have been described as associated with disparities in epidural usage on the patient-level
- One study observed that Black teenage women focused more on medical risks of epidurals than White middle- and upper-class women, who viewed epidurals as a safe way to avoid labor pain

Methods

- Eligibility: delivered vaginally within 6 months without use of neuraxial labor analgesia, English speaking, no medical contraindications to neuraxial labor analgesia or pregnancy loss
- Participants were contacted, consented, and scheduled for 1-hour semi- structured Zoom interview
- Interviews were transcribed, then coded in Dedoose (Los Angeles, CA: SocioCultural Research Consultants, LLC) according to grounded theory
- Themes were identified using number of participants who mentioned the theme
- Responses were stratified according to race/ethnicity grouping, and according to highest educational degree



Results

- 5 core themes remained consistent; differences among subthemes are highlighted in dark gray.

Theme	Subtheme	Non-White (N=16) (%)	White (N=16) (%)	High school graduate or GED completed (N=2)	Some college credit but no degree (N=3) (%)	Bachelor's degree (N=14) (%)	Master's degree (N=10) (%)	Doctorate or Professional degree (N=3) (%)
Patient preferences for a natural birth	Prefer to avoid medication during childbirth	16 (100)	16 (100)	2 (100)	3 (100)	14 (100)	10 (100)	3 (100)
	Prefer to avoid interventions	10 (62.5)	10 (62.5)	1 (50)	1 (33.33)	9 (64.3)	6 (60)	3 (100)
	Desire to take an active role in the birthing process, or for mobility during labor	6 (37.5)	13 (81.25)	0	0	9 (64.3)	8 (80)	3 (100)
An empowering and supportive labor environment	Sense of trust and support	16 (100)	16 (100)	2 (100)	3 (100)	14 (100)	10 (100)	3 (100)
	Communication or rapport with physician/staff	16 (100)	15 (93.75)	2 (100)	3 (100)	14 (100)	10 (100)	2 (66.67)
	Feeling of comfort and safety	13 (81.25)	11 (68.75)	2 (100)	2 (66.67)	9 (64.3)	9 (90)	2 (66.67)
	Autonomy	9 (56.25)	12 (75)	0	1 (33.33)	11 (78.6)	7 (70)	2 (66.67)
	Desire for or appreciatio n for physicians who are open- minded	11 (68.75)	10 (62.5)	1 (50)	2 (66.67)	9 (64.3)	6 (60)	3 (100)
Preparation or preparedness for a birth without medication	Success in plan	16 (100)	16 (100)	2 (100)	3 (100)	14 (100)	10 (100)	3 (100)
	Used non- pharmacological strategies for pain management at time of labor and delivery	16 (100)	13 (81.25)	2 (100)	3 (100)	13 (92.9)	9 (90)	2 (66.67)
	Breathing and relaxation techniques	9 (56.25)	11 (68.75)	1 (50)	3 (100)	9 (64.3)	6 (60)	1 (33.33)
	Positioning techniques	8 (50)	8 (50)	0	0	4 (28.6)	5 (50)	8 (50)
	Exercise or movement	6 (37.5)	6 (37.5)	0	1 (33.33)	7 (50)	3 (30)	1 (33.33)
	Touch/press ure	7 (43.75)	5 (31.25)	0	1 (33.33)	3 (21.4)	6 (60)	2 (66.67)
Positive outlook on labor pain	Perceived ability and strength	15 (93.75)	15 (93.75)	2 (100)	2 (66.67)	13 (92.9)	10 (100)	3 (100)
	Confidence to deliver without an epidural, or pride in successful delivery without one	13 (81.25)	14 (87.5)	2 (100)	2 (66.67)	11 (78.6)	9 (90)	3 (100)
	Notion that labor pain is experienced differently by different people	14 (87.5)	13 (81.25)	2 (100)	3 (100)	12 (87.5%)	7 (70)	3 (100)
	Positive mindset	12 (75)	12 (75)	1 (50)	1 (33.33)	11 (78.6)	8 (80)	3 (100)
	Natural part of the birthing process	5 (31.25)	10 (62.5)	0	0	6 (42.9)	7 (70)	3 (100)
	Means to an end, temporary	6 (37.5)	8 (50)	0	1 (33.33)	7 (50)	6 (60)	0

Theme	Subtheme	Non-White (N=16) (%)	White (N=16) (%)	High school graduate or GED completed (N=2)	Some college credit but no degree (N=3) (%)	Bachelor's degree (N=14) (%)	Master's degree (N=10) (%)	Doctorate or Professional degree (N=3) (%)
Information, misinformation, knowledge gaps, and fears about the epidural	Friends	12 (75)	14 (87.5)	1 (50)	2 (66.67)	13 (92.9)	7 (70)	3 (100)
	Partner	11 (68.75)	15 (93.75)	1 (50)	3 (100)	12 (87.5%)	7 (70)	3 (100)
	Family members	12 (75)	13 (81.25)	2 (100)	2 (66.67)	12 (87.5%)	7 (70)	2 (66.67)
	OBGYN	13 (81.25)	12 (75)	1 (50)	3 (100)	11 (78.6)	8 (80)	2 (66.67)
	Social media (e.g., Instagram, Facebook, TikTok, YouTube)	10 (62.5)	5 (31.25)	1 (50)	1 (33.33)	7 (50)	4 (40)	2 (66.67)
	Doula or midwife	6 (37.5)	9 (56.25)	1 (50)	0	6 (42.9)	6 (60)	2 (66.67)
	Fears about the epidural	12 (75)	16 (100)	1 (50)	2 (66.67)	14 (100)	8 (80)	3 (100)
	Needles	4 (25)	9 (56.25)	1 (50)	1 (33.33)	8 (57.1)	3 (30)	0
	Staying still or sitting up for the procedure	5 (31.25)	5 (31.25)	1 (50)	1 (33.33)	4 (28.6)	4 (40)	1 (33.33)
	Faulty insertion	4 (25)	7 (43.75)	0	1 (33.33)	4 (28.6)	4 (40)	2 (66.67)
	That it would not work	3 (18.75)	6 (37.5)	1 (50)	1 (33.33)	3 (21.4)	2 (20)	2 (66.67)
	The unknown	2 (12.5)	5 (31.25)	1 (50)	0	4 (28.6)	2 (20)	0
	Dosing would be off	4 (25)	1 (6.25)	1 (50)	0	3 (21.4)	1 (10)	0
	Lack of control	2 (12.5)	3 (18.75)	1 (50)	0	3 (21.4)	1 (10)	0
	Side effects or complicatio ns from the epidural	15 (93.75)	10 (62.5)	2 (100)	2 (66.67)	10 (71.4)	8 (80)	3 (100)
	Back pain	12 (75)	4 (25)	2 (100)	2 (66.67)	7 (50)	4 (40)	1 (33.33)
	Paralysis	4 (25)	2 (12.5)	1 (50)	0	2 (14.3)	2 (20)	1 (33.33)
	Headache	1 (6.25)	4 (25)	0	0	1 (7.14)	3 (30)	1 (33.33)
	Effects on the baby	1 (6.25)	4 (25)	0	1 (33.33)	2 (14.3)	2 (20)	0
	Slows down labor	2 (12.5)	3 (18.75)	0	0	2 (14.3)	2 (20)	1 (33.33)
	Did not have much of an understanding before labor or had unanswered questions	7 (43.75)	6 (37.5)	1 (50)	2 (66.67)	7 (50)	3 (30)	0

Discussion

- Broad themes as well as knowledge barriers transcended racial and educational strata in our sample
- Some subthemes (e.g., fear of needles) showed differences among subgroups
- Our results contrast with those of Dillaway and Brubaker, who found that Black teenage women and White middle- and upper-class women had different ways of viewing epidurals
- Our contrasting findings may be attributed to the fact that:
  - 1) The Black women in their study decided to forego epidural usage vs. the White women in their study used epidurals, whereas all the women in our study did not use epidurals;
  - 2) Their study participants were treated in different hospitals, versus our participants were treated in the same hospital
- Given that prior studies have identified differences in neuraxial analgesia by state and race, future research should explore if these differences are due to differences in patients' perspectives, disparities in care, or other factors

Limitations

- There is a sampling and recall bias; social desirability
- This study was conducted at a single urban center
- We did not consider perspectives of women who wanted to not use an epidural but ultimately received one
- Themes were identified by using number of individual participants who mentioned the theme (rather than number of total mentions)
- All participants expressed overall satisfaction with their care

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Accurate prediction of respiratory gating windows using long, short-term—memory deep learning

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Memorial Sloan Kettering Cancer Center

INTRODUCTION

Although it has been proposed and attempted for treating patients, respiratory-gated radiotherapy (RGRT) has not been widely used in radiotherapy clinics: To date, real-time external indicators cannot provide accurate and reliable signals to turn radiation beams on and off within the desired gating windows. Owing to their inaccuracies, correlation-based, intra-fractional motion prediction models require frequent radiographic imaging to ensure the target is within the beam, precluding widespread application of these models for clinical purposes.

With the recent advances in deep learning (DL) and its applications in radiotherapy—including image segmentation and image modality conversion—many DL algorithms have been developed and tested, such as U-net-based convolution neural networks. The long short-term—memory (LSTM) algorithm has been thoroughly investigated in computer-vision research for automatic driving, including single-point forecasting in the immediate future and multi-point to multi-point learning and prediction [1-3]. The potential to employ LSTM models over longer timeframes, such as the 10-20 minute needed for radiotherapy, has yet to be explored.

AIM

We explored the potential of the LSTM network to predict long-term internal motion based on external waveforms, aiming for a clinical RGRT application. Using the long short-term memory (LSTM) deep learning (DL) network, we developed a subject-specific, cross-dataset model that predicts long-term motion. We evaluated the model's beam-triggering accuracy during respiratory-gated radiotherapy.

METHODS

In this IRB-approved study, concurrent external-bellows and internal-navigator waveforms were acquired during 4DMRI scans for 10 volunteers. Each volunteer was scanned twice: Scans lasted 5-10min, and 15-20min elapsed between scans. The LSTM-DL algorithm was trained on 50% of each volunteer's first scan, and the remaining 50% was used to evaluate how accurately the algorithm could predict internal motion from external waveforms. The timing of respiratory peaks and beam triggering were calculated from the predicted waves, and the accuracy was assessed against the internal ground truth. The percentage harm (%harm, % beam-on time that target is outside gating windows) and gating efficiency (%effic, % of time the target is within the gating windows and the beam is on) were found for the predicted waveforms and compared to the %harm and %effic when the original or phase-shift-corrected (SPC) external waveforms were used for respiratory gating.

RESULTS

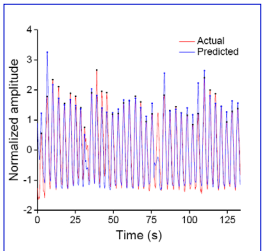

Figure 1. An example of the actual (red) diaphragm motion and the waveform predicted by the LSTM-DL algorithm (blue). The temporal locations of the actual and predicted peaks are marked by black and blue dots, respectively.

Table 1. Error in predicting the temporal locations of the waveform's peaks. Means (s) ± std.

	Scan 1			Scan 2		
Vol	Initial error (s)	PSC error (s)	LSTM error (s)	Initial error (s)	PSC error (s)	LSTM error (s)
1	0.203±0.088	0.236±0.079	0.056±0.043	0.135±0.082	0.250±0.083	0.100±0.032†
2	0.748±0.206	0.183±0.100	0.062±0.080	0.283±0.139	0.325±0.133	0.115±0.038
3	0.174±0.062	0.281±0.065	0.075±0.048	0.233±0.161	0.300±0.071	0.271±0.442†
4	0.600±0.100	1.350±0.071	0.300±0.203	0.150±0.125	0.771±0.706	0.490±0.315
5	0.199±0.191	0.293±0.147	0.180±0.205†	0.180±0.097	0.171±0.096	0.077±0.042
6	0.722±1.031	0.553±0.895	0.175±0.688	0.369±0.497	0.544±0.603	0.146±0.491
7	1.836±1.268	1.525±0.608	0.447±0.450	0.302±0.175	0.745±0.503	0.378±0.313†
8	1.118±0.251	0.315±0.219	0.118±0.084	1.360±0.280	0.137±0.126	0.111±0.084
9	1.678±1.572	1.383±1.181	0.237±0.185	0.593±0.771	0.338±0.160	0.079±0.037
10	0.302±0.301	0.578±0.173	0.139±0.126	0.200±0.094	0.533±0.076	0.050±0.035
Avg.	0.758±0.577	0.670±0.507	0.179±0.116	0.381±0.350	0.411±0.214	0.182±0.141

†Not statistically significant

The error for the LSTM model was less than the initial error for 9 volunteers in the first scan (one-sided Mann-Whitney U test, $p < 0.005$) and no different for one volunteer (for whom most of the peaks of the navigator and bellows waveforms were already well aligned). Across all volunteers, the LSTM performed better than the initial waveforms ($p = 0.0023$) and the PSC method ($p = 0.0018$). In the second scan, the error for the LSTM model was less than the initial error for six volunteers ($p < 0.05$), no different for three volunteers, and worse for one volunteer. Across all volunteers, the LSTM performed better than the initial waveforms ($p = 0.0188$) and the PSC method ($p = 0.0106$). After correcting the large residual phase shift for volunteers 4 and 7, the error for the LSTM model decreased to 0.240±0.371 s and 0.328± 0.134 s, respectively, neither of which was was statistically different from the initial error.

Table 2. Percent harm (%harm)

	First scan			Second scan		
Vol	Initial	PSC	LSTM	Initial	PSC	LSTM
1	25.8	6.1	1.3	7.8	0.0	0.0
2	53.7	14.6	2.2	37.9	0.0	0.0
3	2.7	0.0	0.0	9.1	0.0	0.0
4	46.0	5.1	4.6	44.5	71.0	23.7
5	26.5	20.5	14.2	24.8	19.8	11.6
6	32.5	11.7	6.1	36.1	13.5	5.8
7	53.7	5.5	6.4	30.1	89.6	17.6
8	77.2	11.6	5.3	79.7	24.0	8.0
9	79.1	60.5	9.6	31.9	23.3	1.4
10	54.0	35.3	23.0	69.4	50.6	15.1
Avg.	45.1±22.6	17.1±17.3	7.3±6.5	37.1±21.9	29.2±29.7	8.3±8.0

Table 3. Percent efficiency (%effic)

	First scan			Second scan		
Vol	Initial	PSC	LSTM	Initial	PSC	LSTM
1	53.2	67.2	74.0	55.4	59.9	62.5
2	22.2	40.5	91.6	37.0	60.8	77.4
3	61.2	64.6	64.1	54.6	60.7	68.8
4	34.0	62.0	84.2	33.3	17.7	61.8
5	53.0	58.9	57.9	44.9	48.0	55.3
6	32.4	40.3	62.3	38.3	51.9	69.5
7	26.5	54.9	69.9	41.9	6.4	48.4
8	10.7	42.0	96.5	12.2	45.7	99.1
9	13.5	25.8	82.5	40.9	46.3	42.8
10	32.6	43.5	72.6	18.4	30.4	59.1
Avg.	33.9±16.2	50.0±12.8	75.6±12.2	37.7±13.1	42.8±17.8	64.5±15.0

Compared to the initial %harm, the LSTM models reduce the %harm for all volunteers in the first ($p < 0.001$) and second ($p = 0.001$) scans. Although the LSTM models outperformed the PSC method for 9 volunteers in the first scan for 7 volunteers in the second, the change was not statistically significant. Correcting the large residual phase shifts for volunteers 4 and 7 in the second scan reduced the %harm to 10.0 and 0.2, respectively, and the %harm across all volunteers for the LSTM models was then statistically lower than the PSC method ($p = 0.039$). The LSTM models enhance the %effic for all volunteers in the first ($p < 0.001$) and second ($p < 0.001$) scans. The LSTM models outperformed the PSC method for 9 volunteers in the first scan and for 9 volunteers in the second scan, and the improvement across all volunteers was statistically significant ($p < 0.001$ in first scan, $p = 0.007$ in the second scan). Correcting the large residual phase shifts for volunteers 4 and 7 in the second scan further enhanced the %effic yielded by the LSTM models to 72.0 and 58.5, respectively.

DISCUSSION

- In the first scan, the LSTM model significantly reduced the average error in locating the respiratory peaks 0.76±0.58s to 0.18±0.12s, and performed better than the PSC method (0.67±0.51s). Similarly, the LSTM model significantly reduced the average error in locating peaks during the second scan from 0.38±0.35s to 0.18±0.14s, and performed better than the PSC method (0.41±0.21s).
- The LSTM model significantly reduced the %harm in both scans from 45±23% down to 7±7% in the first scan and from 37±22% to 8±8% in the second scan. Moreover, the LSTM model yielded that a %harm that was either better than the PSC method or 0% in 9 out of 10 volunteers in scan 1 and in all volunteers for scan 2.
- The improvement in the %harm did not require a loss in efficiency; the LSTM model enhanced the %effic across all volunteers (from 34±16% to 76±12% on average in the first scan, and from 38±13% to 65±15% in the second scan). The %effic obtained by the LSTM model almost always exceeds that for the PSC method.

CONCLUSION

The LSTM model accurately predicts internal-organ motion from external-motion data and often surpasses the accuracy of a physical model. Over longer times (>20min), the accuracy of the LSTM model may decrease as new irregularities occur outside of the training datasets. The stability of the long-term LSTM prediction could likely be improved further through an adaptive approach that incorporates the motion measured on the day of clinical application.

ACKNOWLEDGEMENTS

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Association between ε-aminocaproic acid administration and seizure risk in cardiothoracic intensive care unit patients

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Introduction

Tranexamic acid (TXA) and the less-potent aminocaproic acid (ACA)[1] are commonly used antifibrinolytic agents in the perioperative setting to reduce allogenic transfusion and decrease hemorrhage-associated mortality[2]. Despite these demonstrated benefits, there is concern that antifibrinolytic administration may confer an increased risk of convulsive seizures in humans[3], which is corroborated by animal data[4]. These studies point to a potential mechanism for cortical hyperexcitability as TXA and ACA can act as competitive antagonists to both gamma aminobutyric acid (GABA) and glycine receptors[5]. Indeed, recent large human trials studying TXA have shown a strong association with postoperative seizures[3,6].

Despite large human trials, meta-analyses have not corroborated an association between TXA and seizure. This discrepancy may be partially explained by the fact that seizure is not a consistent secondary outcome in many studies, and when seizure is reported, it is largely based on the clinical presentation and not electrographic findings. Moreover, the potential association between ACA and seizure activity is not well-studied. This gap in knowledge is underscored in cardiothoracic (CT) surgery patients who are routinely administered antifibrinolytics and are at high seizure risk from neurological complications.

We sought to investigate the association between ACA and seizure risk in patients hospitalized in the CT ICU. We hypothesized that ACA administration may confer cortical hyperexcitability (enhanced propensity of cortical neurons to produce action potentials) and increase seizure risk.

Methods

We obtained EMRs of patients admitted to the CT-ICU at NYP-Cornell who underwent continuous EEG (cEEG) monitoring from 01/01/2015 to 04/30/2034. Inclusion criteria included administration of ACA within 5 days of EEG monitoring and having neuroimaging on record during the index admission. After appropriate exclusions, we analyzed a total of 224 patients, of which 102 (45%) demonstrated markers of cortical hyperexcitability, 26 (12%) exhibited electrographically-proven seizure, and 47 (21%) had an acute cerebral infarction during admission (Table 1).

Table 1. Characteristics of the patients.

Characteristic	All Patients (N = 224)	Received aminocaproic acid (N = 118)	No aminocaproic acid (N = 106)	p-value*
Median aminocaproic acid dose (IQR) – g	N/A	14.3 (0 – 17.2)	N/A	N/A
Median age (IQR) – yr	68.0 (58.7 – 75.2)	70.0 (63.0 – 76.0)	65.5 (55.2 –75)	0.045
Male sex – no. (%)	132 (58.9)	66 (55.9)	66 (62.3)	0.34
Race				
White	92 (41.1)	43 (36.4)	49 (46.2)	0.17
Asian	27 (12.0)	18 (15.2)	9 (8.5)	0.15
Black	25 (11.2)	13 (11.0)	12 (11.3)	1
Median weight (IQR) – kg	72.0 (61.2 – 82.0)	72.0 (60.0 – 82.8)	71.7 (62.0 – 79.9)	0.76
Cardiopulmonary bypass (CPB) during index admission – no. (%)	90 (40.2)	84 (71.2)	6 (5.7)	$6.53*10^{-26}$
Median total CPB time (IQR) – min.	0 (0 – 110.0)	98.0 (0 – 145.5)	0 (0 – 0)	$3.14*10^{-22}$
History of stroke prior to admission – no. (%)	46 (20.5)	25 (21.2)	21 (19.8)	0.87
History of seizures/epilepsy prior to admission – no. (%)	4 (1.8)	2 (1.7)	2 (1.9)	1
Acute cerebral infarction during index admission – no. (%)	47 (21.0)	34 (28.8)	13 (12.3)	0.0029
Brain hemorrhage during index admission – no. (%)	22 (9.8)	7 (5.9)	15 (14.1)	0.045
Electrographic seizure – no. (%)	26 (11.6)	19 (16.1)	7 (6.6)	0.035
Markers of cortical hyperexcitability	102 (45.4)	61 (51.7)	41 (38.7)	0.060

*Calculated via two-tailed Student's t-test (for continuous data) or Fisher's exact test (for categorical data)

Results

Univariate logistic regression modeling demonstrated that ACA confers a 75% increase in risk of seizure for every 100mg/kg of medication administered (OR = 1.75, p = 0.000050). Acute cerebral infarction and CPB during admission were also found to significantly increase the risk of seizure, the latter increasing risk nearly four-fold (Table 2). On multivariate analysis (*modeling seizure as a function of (1) ACA dose (100mg/kg), (2) acute cerebral infarction during admission, and (3) time on CPB*), both ACA and cerebral infarction (but not CPB) were found to be significant predictors of seizure (ACA dose (100mg/kg): $OR_{adjusted}$ = 1.50, p = 0.029 | acute cerebral infarct: OR_{adj} = 2.60, p = 0.043). There was no significant interaction between cerebral infarction and ACA (p = 0.41), however, cerebral infarction was found to to act as a mediator in the association between ACA and seizure risk (Sobel test p-value = 0.043).

Table 2. Univariate logistic regression. Outcome: electrographic seizure.

Independent variable	OR	p-value	95% CI
Total ACA dose (100mg/kg)	1.75	**$5.031*10^{-5}$**	1.35 – 2.33
CPB during index admission (yes/no)	4.85	**0.00070**	2.027 – 12.94
Total CPB time (min)	1.0074	**0.0011**	1.0029 – 1.012
Sex (reference: Female sex)	0.47	0.071	0.20 – 1.063
Age	1.034	0.059	1.00 – 1.073
History of stroke prior to admission	0.47	0.24	0.11 – 1.43
Brain hemorrhage during index admission	1.23	0.75	0.27 – 3.97
Acute cerebral infarction during index admission	3.99	**0.0015**	1.68 – 9.40
History of seizures/epilepsy prior to admission	No convergence		

We next examined the effects of ACA on cortical hyperexcitability (CH). Univariate logistic regression demonstrated that ACA increases risk of CH by 51% for every 100mg/kg of medication (OR = 1.51, p = 0.00014). CPB, age, and female sex were found to be additional significant risk factors (Table 3). However, on multivariate analysis (*modeling CH as a function of (1) ACA dose (100mg/kg), (2) acute cerebral infarction during admission, (3) time on CPB, (4) age, and (5) sex*), ACA was no longer found to be significantly associated with CH, although the trend for increased risk persisted (OR_{adj} = 1.22, p = 0.22). Female sex and age were found to be significant independent risk factors in the multivariate model (female sex: OR_{adj} = 2.69, p = 0.0009 | age: OR_{adj} = 1.031, p = 0.0060).

Table 3. Univariate logistic regression. Outcome: Makers of cortical hyperexcitability.

Independent variable	OR	p-value	95% CI
Total ACA dose (100mg/kg)	1.51	**0.00014**	1.23 – 1.88
CPB during index admission (yes/no)	3.42	**$1.64*10^{-5}$**	1.97 – 6.026
Total CPB time (min)	1.0068	**0.00040**	1.0032 – 1.011
Sex (reference: Female sex)	0.34	**0.00015**	0.20 – 0.59
Age	1.028	**0.0060**	1.0086 – 1.050
History of stroke prior to admission	1.0059	1.00	0.52 – 1.93
Brain hemorrhage during index admission	0.53	0.18	0.19 – 1.30
Acute cerebral infarction during index admission	1.32	0.39	0.69 – 2.53
History of seizures/epilepsy prior to admission	1.20	0.86	0.14 – 10.15

Lastly, we examined the effects of ACA on risk of acute cerebral infarction. Considering the antifibrinolytic effect of ACA, not surprisingly, it was found to significantly elevate the risk of having a cerebral infarction on univariate analysis (54% elevation in risk for every 100mg/kg of ACA administered; OR = 1.54, p = 0.00014). CPB was also found to be a significant risk factor (OR = 2.73, p = 0.0028) (Table 4). On multivariate logistic regression (*modeling acute cerebral infarction as a function of (1) ACA dose (100mg/kg), (2) time on CPB, (3) age, and (4) history of stroke prior to admission*), ACA was the only significant predictor of cerebral infarction, increasing risk of infarction by 60% for every 100mg/kg of ACA administered (OR_{adj} = 1.60, p = 0.0042).

Table 4. Univariate logistic regression. Outcome: Acute cerebral infarction during index admission.

Independent variable	OR	p-value	95% CI
Total ACA dose (100mg/kg)	1.54	**0.00014**	1.24 – 1.94
CPB during index admission (yes/no)	2.73	**0.0028**	1.42 – 5.35
Total CPB time (min)	1.0050	**0.010**	1.0011 – 1.0088
Sex (reference: Female sex)	0.83	0.57	0.43 – 1.60
Age	1.025	0.060	1.00 – 1.052
History of stroke prior to admission	1.67	0.18	0.77 – 3.46

Conclusions

- Aminocaproic acid (ACA) increases the risk of electrographically demonstrated seizure in the CT ICU patient population, even after adjusting for acute cerebral infarction. ACA also increases the risk of acute brain infarction in the same patient population.
- Acute cerebral infarction does not demonstrate statistical interaction with ACA. Thus, infarction does not exert effect modification effects on the association between ACA and seizure. However, infarction does act as a mediator (at least partially) in the relationship between ACA and seizure.

Limitations

- Low number of seizure events (26), does not permit a multivariable model to accommodate more than 3 variables, due to risk of overfitting.
- Selection bias likely exists in this dataset to some degree, since most patients undergoing cEEG monitoring had a witnessed clinical event suspicious for seizure.

Acknowledgements

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Improving Ultrasound Access in the Operating Room

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Presenter: Olivia Henry | 5.23.2024

Problem Statement

Ultrasound machines are frequently used in the operating room for vascular access. When available, they aid in **difficult line placement** and decrease time to place an arterial line, intravenous line or central line.

Due to increasing demand and limited supply, locating an ultrasound when needed may be difficult. **Delays in ultrasound delivery** can and do lead to delays in the OR, incurring significant costs for the hospital and fueling frustration among patients, surgical teams and anesthesiologists.

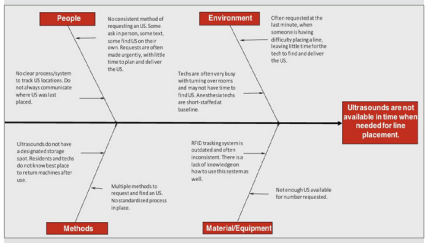
Objectives

- Design a system for quantifying delays in delivering an ultrasound to the OR when requested
- Reduce the amount of time to **deliver an ultrasound machine to the OR** following a request

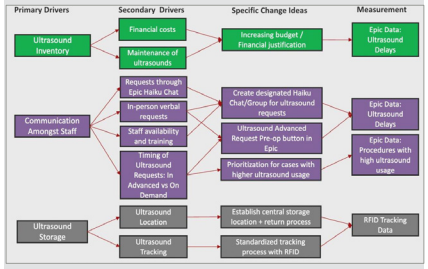
Methods

- Developed a **process map** with key stakeholders
- Clarified the workflow for requesting, finding and delivering an ultrasound to the OR
- **Collected data on number of requests and delays** by having anesthesia technicians fill out ultrasound request cards for each ultrasound request
- Revised the data collection to utilize existing anesthesia technician Haiku group chat **to track and measure ultrasound requests and delivery times**

FISHBONE DIAGRAM



KEY DRIVER DIAGRAM



Results

- There was no **formalized process for ultrasound requests**
- US machines were difficult to locate
- US delivery was prioritized to pediatric and patients.
- US Machines were sequestered by clinicians due to perception they would not be available when needed
- Data on Delays is presented in the table:

Total Requests Documented	37
Average Time from Request Received to US Delivery	17 minutes
# of Cases with US Delays	16 (43%)

Future Directions

- The purchase of **two additional ultrasounds** has been authorized.
- Our next step will be creating a Haiku chat dedicated to equipment requests for anesthesia clinicians and technicians
- **The plan is to automate this into a "button "**that the anesthesiologist can use to automatically send an ultrasound request
- Use of **RFID technology** to help track and locate ultrasound machines

Tylenol, Toradol, and Heparin, Oh My! Reducing inappropriate dosing of commonly administered perioperative medications

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Problem Statement and Objectives

Problem Statement:

- Medication dosing and timing is not always clear as the patient moves through pre-op, intra-op, and post-op phases of care
- This may lead to over- or under- dosing of medications in the perioperative period

Objective/Aim Statement:

- Quantify the incidence of mistimed medication errors for common perioperative medications
- Identify key drivers behind these errors
- Decrease the percentage of cases where patients receive mistimed medications by 10% over a 3-month period

Methods and Design

- Retrospective review of all ambulatory or same-day admit adult surgical cases over a 6-month period
- Specifically identify cases using acetaminophen, subcutaneous heparin, and/or celecoxib/ketorolac
- Review repeat dosing and timing intervals
- Chart review of specific cases

Baseline Data

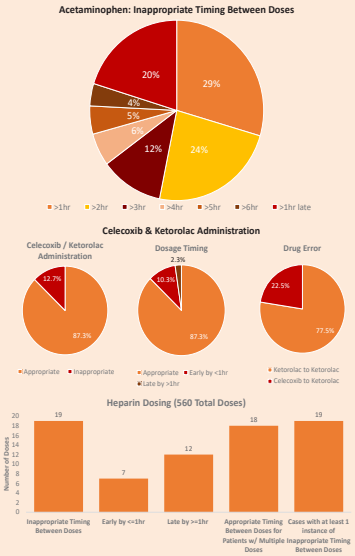


Figure 1: Fishbone Diagram

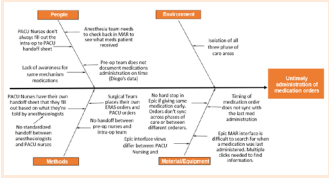
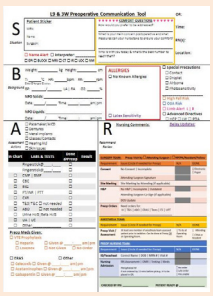


Figure 2: Perioperative Communication Tool



Results

- SQ Heparin: 7 instances of misadministration reviewed
  - 5 Pre-Op -> PACU
  - Short cases
  - 1 OR -> OR
  - 1 Pre-Op -> OR -> PACU
- Tylenol: 42 instances of misadministration reviewed
  - Combination of pre-op -> OR -> PACU
  - No clear pattern
- Celecoxib/Ketorolac: 42 instances of misadministration reviewed
  - Majority Celecoxib Pre-Op -> Ketorolac OR

Interventions and Next Steps

- Updated perioperative nursing communication tool to document intra-op administration of acetaminophen, ketorolac, and heparin in a more thorough handoff
- Utilize intra-operative debrief to inform surgical team of last medication dose ahead of PACU order placement
- EMR enhancement to show recent administrations of medications to all providers regardless of their baseline EMR views

Implementation of a Formalized Handoff Between the Acute Pain and Intraoperative Anesthesiology Team for Perioperative Procedures

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Purpose

Currently there exists no formal handoff system between the acute pain/regional anesthesiology team and the intraoperative anesthesiology team after patients receive preoperative regional and neuroaxial anesthesia procedures. This absence can lead to breakdowns in communication, suboptimal care, and negative patient outcomes. Transitions in patient care have shown to contribute to a higher risk for adverse events[1,2].

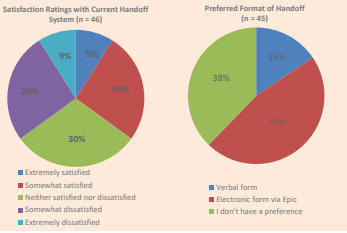
Study Aims:

- **Primary Goal**: Achieve completion of handoff between regional anesthesia providers and the intraoperative anesthesia team 75% of the time over a 6-month period
- **Identify** the most essential pieces of information to be included in the handoff
- **Develop** a standardized Epic handoff macro including this information

Investigation Methods

- **Baseline Pre-Implementation Survey**
  - Sent to all anesthesiology attendings, residents, CRNAs, and regional anesthesiology fellows
  - Assessed respondents' preferred format of handoff
  - Identified key pieces of information to be included in the handoff
- **Create Epic Handoff Documentation**
  - Automatically included as required "Event" when regional procedure is performed outside of the OR
  - Regional anesthesiology team educated on macro use
  - Handoff information also sent as Haiku message

Figure 1: Pre-Implementation Survey Results



In an ideal world, what information would you like to be included in the handoff (select all that apply): (n = 46)

Item	Percentage	Count
Baseline Vitals	41%	19
Baseline Mental Status	50%	23
Fluids Administered	30%	14
Indication: Surgical anesthesia or postoperative analgesia	65%	30
Expected duration of the block, additives in the block, dosage of meds administered	80%	37
Plan for in-situ catheters	59%	27
Type of procedure	43%	20
Medications administered	80%	37
Adverse events	65%	30
Initial assessment of procedure	22%	10
DVT prophylaxis	11%	5
Test dose	35%	16
Additional history	13%	6
Other	11%	5

Figure 2: Epic Handoff Macro

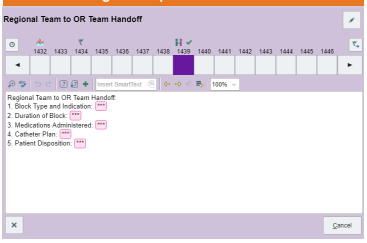
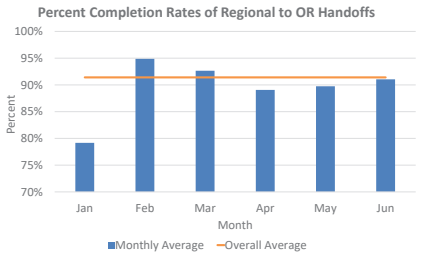
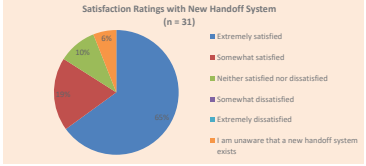


Figure 3: Completion Rates of Handoff Event

Go-Live Date	1/24/2024 @ 5PM
Data Period	1/25/2024 - 6/30/2024
Total Cases w/ Macros	382
Total Cases w/ Event Comments	346
Completion Rate	91%



Post-Implementation Results



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Type and Screens

Who Needs One? Who is Responsible?

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Purpose

The lack of an immediately available Type and Screen (T&S) in the perioperative period where blood product transfusion is indicated can result in increased utilization of emergency uncrossmatched products, posing risks to patients and resource burdens to the blood bank. Contributing factors include: subjectivity of current institutional guidelines for ordering T&S prior to scheduled procedures, as well as other systems issues.

Study Aims:

- **Investigate** - incidence of uncrossmatched blood transfusions
- **Evaluate** - result time of T&S and barriers to meeting the institutional standard of 120 minutes
- **Increase** - % of T&S resulted prior to case start in OR

Investigation Methods

Emergency Blood Orders Chart Review Jan 2021 - Aug 2023

- Classified by service
- Filtered by ED admit vs outpatient admit

Type and Screen Orders Oct 2023 - Dec 2023

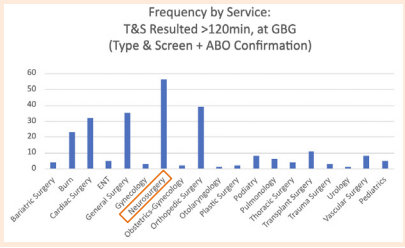
- Classified by service
- T&S result times within 45 min, 90 min, 100 min, & 120 min

Chart review of NSGY cases where emergency blood was transfused; when T&S resulted after case end

Table 1: Blood Order Results

	T&S + ABO Confirmation Order Count	Yes	No
Specimen Received Before Case Start?	4526	88.62%	11.38%
T&S Resulted before Case Start?	3822	74.84%	25.16%
T&S Resulted before Case End?	4769	93.38%	6.62%
T&S Resulted within 45min of Specimen Received?	762	14.92%	85.08%
T&S Resulted within 1hr of Specimen Received?	2037	39.89%	60.11%
T&S Resulted within 90min of Specimen Received?	4119	80.65%	19.35%
T&S Resulted within 100min of Specimen Received?	4383	85.82%	14.18%
T&S Resulted within 120min of Specimen Received?	4688	91.80%	8.20%

Graph 1: Frequency by Service – T&S Resulted >120 min



Proposed Solutions

Safety Events Dashboard for Blood Bank

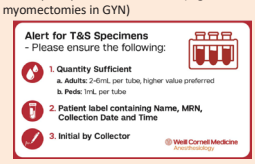
- Develop systematic process for reporting safety incidents related to T&S
- Categorize common reasons for T&S result delays (e.g. truncated specimen label, insufficient specimen quantity, delayed transport time)

Perioperative Staff Education

- In-service education for perioperative nursing and patient assistant staff regarding proper specimen collection and transport (see below)

Clarify Department Specific Guidelines on T&S Ordering

- Educate specific surgical departments regarding bleeding risk and need for pre-op T&S to be ordered (e.g. craniotomies in NSGY, myomectomies in GYN)



Future Directions

Follow up metrics 3 months post-intervention

Develop clearer institutional guidelines for T&S ordering based on surgical procedure and historic needs for transfusion

Abbreviations: T&S: type and screen, NSGY: neurosurgery, GYN: gynecology

Factors associated with poor intraoperative perfusion and postoperative complications in otolaryngological autologous tissue transfers

In press, Anaesthesia and Intensive Care (2024)

Adriano A Bellotti, Steven C Eastlack, Wesley H Stepp, Joshua B Cadwell and Alan M Smeltz

Introduction

- Autologous tissue transfers involve moving tissue to reconstruct defects after tumor excision or trauma.
  - Flap surgeries maintain an intact blood supply.
  - Grafts rely on new blood vessel growth (neovascularization).
  - Free flap surgeries are complex, lengthy procedures involving multiple surgical specialties.
- Major complications include:
  - arterial thrombosis
  - delayed healing
  - Infection
  - tissue ischemia/necrosis
- Leading cause of flap failure: vascular compromise (from intravascular thrombosis or vessel obstruction)
- Goal-directed perfusion for hemodynamic management:
  - Predicting poor perfusion remains a challenge.
  - Liberal fluid strategy to avoid vasopressors can have negative effects, like edema.
  - Pulse pressure variation (PPV) for hypotension management but hasn't been studied in flap surgeries.
- **The study aims to identify modifiable hemodynamic factors to improve tissue perfusion outcomes, hypothesizing that elevated PPV leads to postoperative complications.**

Methods

- Retrospective observational study was conducted at a single academic tertiary care centre (IRB 12-1087).
- 1,355 adult patients who underwent otolaryngological flap or graft reconstructions under general anaesthesia.
- Modified Vasopressor Ionotrope Score (VIS):
  VIS = 10×phenylephrine (ug) + 0.123×ephedrine (ug) + 100×epinephrine (ug) + 10,000×vasopressin (units) + 100×norepinephrine (ug)
- Outcomes:
  - acute kidney injury (as defined by KDIGO criteria)
  - lactic acidosis (plasma lactate > 2 mmol/L)
  - complications requiring take-back surgery within 7 days (thrombosis, infection, fistula formation, haematoma)

Results

Table 2. Univariate regression analysis of patient comorbidities, perioperative variables and study outcomes.

	AKI		Hyperlactataemia		Take-back surgery	
Parameter	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
DM1 or DM2	1.870 (1.232 to 2.839)	**0.003**	1.756 (1.224 to 2.519)	**0.002**	0.873 (0.334 to 2.280)	0.781
Hypertension	1.537 (1.090 to 2.169)	**0.014**	1.125 (0.843 to 1.500)	0.423	0.563 (0.269 to 1.181)	0.128
Afib/flutter	2.076 (1.147 to 3.757)	**0.016**	0.748 (0.393 to 1.425)	0.377	0.438 (0.059 to 3.256)	0.419
CHF	2.218 (1.121 to 4.388)	**0.022**	1.195 (0.609 to 2.346)	0.605	2.118 (0.624 to 7.190)	0.228
CVA	0.277 (0.066 to 1.158)	0.078	0.859 (0.407 to 1.813)	0.689	0.666 (0.089 to 4.985)	0.692
COPD	0.845 (0.469 to 1.522)	0.574	0.336 (0.177 to 0.638)	**0.001**	1.084 (0.376 to 3.129)	0.881
CKD	4.256 (2.565 to 7.062)	**<0.001**	1.756 (1.061 to 2.904)	**0.028**	0.375 (0.051 to 2.781)	0.337
Patient age, years	1.016 (1.004 to 1.029)	**0.012**	0.993 (0.983 to 1.002)	0.135	0.984 (0.963 to 1.006)	0.154
BMI, kg/m²	1.010 (0.985 to 1.036)	0.420	1.059 (1.037 to 1.081)	**<0.001**	0.978 (0.926 to 1.032)	0.416
Maximum dose vasopressor						
Phenylephrine, µg	1.000 (1.000 to 1.000)	0.786	1.000 (1.000 to 1.000)	0.725	1.000 (1.000 to 1.000)	0.184
Ephedrine, µg	1.000 (1.000 to 1.000)	0.260	1.000 (1.000 to 1.000)	0.121	1.000 (1.000 to 1.000)	0.777
Epinephrine, µg	1.000 (1.000 to 1.000)	0.437	1.000 (1.000 to 1.000)	0.161	1.000 (1.000 to 1.000)	0.442
Vasopressin, units	0.969 (0.856 to 1.097)	0.615	1.0542 (0.881 to 1.262)	**0.021**	0.891 (0.658 to 1.205)	0.452
Norepinephrine, µg	1.000 (0.998 to 1.002)	0.923	0.999 (0.993 to 1.005)	0.241	0.991 (0.977 to 1.004)	0.174
VIS, unitless	1.000 (1.000 to 1.000)	0.333	1.000 (1.000 to 1.000)	0.238	1.000 (1.000 to 1.000)	0.696
Crystaloid, ml	1.000 (1.000 to 1.000)	0.456	1.000 (1.000 to 1.000)	0.736	1.000 (1.000 to 1.000)	0.915
Colloid volume, ml	1.000 (1.000 to 1.000)	**0.038**	1.001 (1.000 to 1.001)	**<0.001**	1.000 (1.000 to 1.001)	0.551
IV fluid (all types), ml	1.000 (1.000 to 1.000)	0.616	1.000 (1.000 to 1.000)	0.806	1.000 (1.000 to 1.000)	0.922
MAP <65 mmHg	0.908 (0.634 to 1.301)	0.600	1.109 (0.827 to 1.486)	0.489	1.412 (0.722 to 2.75)	0.313
Max PPV, dimensionless	1.032 (1.011 to 1.054)	**0.003**	1.022 (1.004 to 1.041)	**0.014**	1.045 (1.005 to 1.086)	**0.027**
Time-average max PPV	1.038 (1.014 to 1.063)	**0.002**	1.028 (1.007 to 1.050)	**0.008**	1.031 (0.986 to 1.078)	0.174
Nadir Hb, g/l	0.903 (0.826 to 0.988)	**0.025**	0.973 (0.906 to 1.045)	0.455	1.000 (0.838 to 1.192)	0.997
Case duration, min	1.001 (1.000 to 1.002)	0.145	1.003 (1.002 to 1.004)	**<0.001**	1.003 (1.001 to 1.006)	**0.003**

Bold font denotes variables which were statistically significant following Bonferroni correction ($P < 0.017$). Italics are added to signify variables with pre-correction significance only ($0.05 > P > 0.017$). Patient factors (excluding age and BMI) as well as MAP < 65 mmHg represent binary variables; all other variables are continuous. Vasopressor agents are presented as the max dose over 30-min window; for IV fluids, a simple cumulative dose is shown.
Epinephrine (adrenaline); norepinephrine (noradrenaline).
AKI: acute kidney injury; OR: odds ratio; CI: confidence interval; DM: diabetes mellitus; Afib/flutter: atrial fibrillation/flutter; CHF: congestive heart failure; CVA: cerebrovascular accident; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; BMI: body mass index; VIS: Vasopressor-Inotrope Score; IV: intravenous; MAP: mean arterial pressure; PPV: pulse pressure variation; Hb: haemoglobin.

Table 3. Multivariate regression analysis of selected predictor variables and study outcomes.

	AKI		Hyperlactataemia		Take-back surgery	
Parameter	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Case duration, min	1.000 (0.998 to 1.001)	0.595	1.002 (1.001 to 1.003)	**0.003**	1.004 (1.001 to 1.007)	**0.007**
Maximum PPV, dimensionless	1.318 (1.100 to 1.581)	**0.003**	1.065 (0.911 to 1.245)	0.429	1.254 (0.879 to 1.790)	0.212
Nadir Hb, g/l	0.940 (0.845 to 1.044)	0.247	0.997 (0.914 to 1.087)	0.941	1.114 (0.908 to 1.367)	0.300
Vasopressin, units	0.976 (0.931 to 1.023)	0.311	1.032 (0.997 to 1.067)	0.070	0.920 (0.767 to 1.103)	0.367
Colloid, ml	1.000 (1.000 to 1.001)	0.327	1.000 (1.000 to 1.000)	0.376	1.000 (0.999 to 1.001)	0.825
CVA, binary	0.137 (0.029 to 0.642)	**0.012**	0.659 (0.291 to 1.492)	0.316	0.972 (0.117 to 8.131)	0.979
CKD, binary	3.621 (1.997 to 6.569)	**<0.001**	2.106 (1.175 to 3.776)	**0.012**	0.445 (0.053 to 3.672)	0.451
BMI, kg/m²	1.008 (0.978 to 1.039)	0.599	1.059 (1.034 to 1.084)	**<0.001**	0.963 (0.905 to 1.025)	0.237
COPD, binary	0.679 (0.354 to 1.303)	0.244	0.373 (0.190 to 0.733)	**0.004**	1.284 (0.398 to 4.143)	0.675

Bold text indicates statistically significant variables following Bonferroni correction ($P < 0.017$).
AKI: acute kidney injury; OR: odds ratio; CI: confidence interval; PPV: pulse pressure variation; Hb: haemoglobin; CVA: cerebrovascular accident; CKD: chronic kidney disease; BMI: body mass index; COPD: chronic obstructive pulmonary disease.

Discussion

- Pulse pressure variation (PPV) is a marker of preload responsiveness (dynamic indicator of location on the Frank Starling curve) → guides administration of fluids and vasopressors.
  - Result: max PPV is an independent risk factor for AKI.
  - PPV monitoring can reduce risk of AKI.
  - Cannot comment on PPV assocaition with take-back surgery: a future cohort study would be necessary.
- Result: there is no apparent increase in the incidence of flap/graft dysfunction in conjunction with catecholamines.
  - Composite variable reflective of total vasoactive dose burden (VIS) was also not significantly associated with poor outcomes.
- Result: univariate regression suggests an association between vasopressin and elevated lactate.
  - Possibly confounded by the complicated clinical situations in which vasopressin is typically required.
  - Since vasopressin is not a first-line agent for hypotension, its use likely signals significant vasoplegia or hypovolemia.
  - Vasopressin use is more likely an effect rather than a cause of an underlying process associated with poor perfusion.
  - Association with poor outcomes was not recapitulated in the multivariate analysis.
- Study limitations:
  - retrospective design
  - low take-back surgery rate
  - insufficient power to assess flap failure outcomes
- Conclusion: Rather than restricting fluids or avoiding vasopressors, avoid extremes in max PPV and limit time under anaesthesia.
  - Case duration association with take-back surgery was likely confounded by surgical difficulty (hard to control).
  - On the contrary, PPV is well-understood and readily modifiable.

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Multicenter Perioperative Outcomes Group (MPOG)

Local MPOG Leadership: Hugh Hemmings, MD, PhD. Patricia Mack, MD. Kane Pryor, MD. Zachary Turnbull, MD, MBA, MS.

Department of Anesthesiology 16th Research Exposition | November 12, 2024

Investigators:

Hugh Hemmings, MD, PhD. Kane Pryor, MD. Lisa Rong, MD. Virginia Tangel, MA, MSc. Zachary Turnbull, MD, MBA, MS. Robert White, MD, MS. Hannah Wunsch, MD, MSc.

Background

The Multicenter Perioperative Outcomes Group (MPOG [http://mpog.org]; founded 2008) is a perioperative registry of anesthesia care comprised of electronic health records from institutions located in the U.S. and the Netherlands of surgical and diagnostic procedures. It contains over 24 million cases and 408 million medication records. The overall purpose of the database is to create a resource for clinical researchers to investigate outcomes following surgery. MPOG combines electronic health record and administrative data to facilitate the analysis of the interplay between patient comorbidities, surgical procedures, perioperative care, interventions, and postoperative outcomes. Researchers can query the database and access an adequate number of patient records to identify trends that are not visible in single institutions.

Research

The goal of MPOG research is to accelerate outcomes research, investigate perioperative adverse events and publish in high impact journals to advance knowledge and improve patient care.

Quality

Our goal is to improve the care of patients undergoing anesthesia by reducing unexplained variation in practice and collaborating with anesthesia providers to define best practices.

Participants

There are currently 71 medical centers that contribute to the MPOG database, including:

- Weill Cornell
- University of Michigan
- Columbia University
- Stanford
- Johns Hopkins
- NYU Langone
- Duke University
- Yale University
- Vanderbilt University
- Dartmouth College
- Memorial Sloan Kettering Hospital
- University of Pennsylvania

Updates

We are adding NYP Brooklyn Methodist Hospital and NYP Queens Hospital as participants to the MPOG database and will be contributing their perioperative data for quality assurance purposes. This integration will occur in the near future.

MPOG MULTICENTER PERIOPERATIVE OUTCOMES GROUP

Current MPOG Projects in Progress

- *Virginia's studies*: define reference ranges for intraoperative hemodynamic measures for healthy pediatric patients undergoing non-cardiac surgery.
- *Dr. Rong's study*: describe benzodiazepine use and sources of variation during non-operating room cardiac procedures across patients, clinicians, and institutions.
- *Dr. Pryor's study*: determine (i) whether patients undergoing (a) major inpatient surgery, (b) minor inpatient surgery, or (c) outpatient surgery have a superior quality of recovery after INVA or TIVA and (ii) whether TIVA confers no more than a small (0.2%) increased risk of intraoperative awareness than INVA.
- *Dr. White's study*: examine the sensitivity of individual clinician process quality metrics to patient- and census tract-level social determinants of health (SoDH).
- *Dr. Wunsch's study*: determine whether patients with a known history of polio receive different anesthetic care compared with similar individuals without polio AND whether anesthetic complications differ for those who have a known history of polio compared with similar individuals without polio.

Project Intake

If you are interested in doing an MPOG project, please scan the QR code and enter a project request.

ACC/AHA/ASE/ASNC/HFSA/ HRS/SCAI/SCCT/SCMR/STS 2024 Appropriate Use Criteria for Multimodality Imaging in Cardiovascular Evaluation of Patients Undergoing Nonemergent, Noncardiac Surgery.

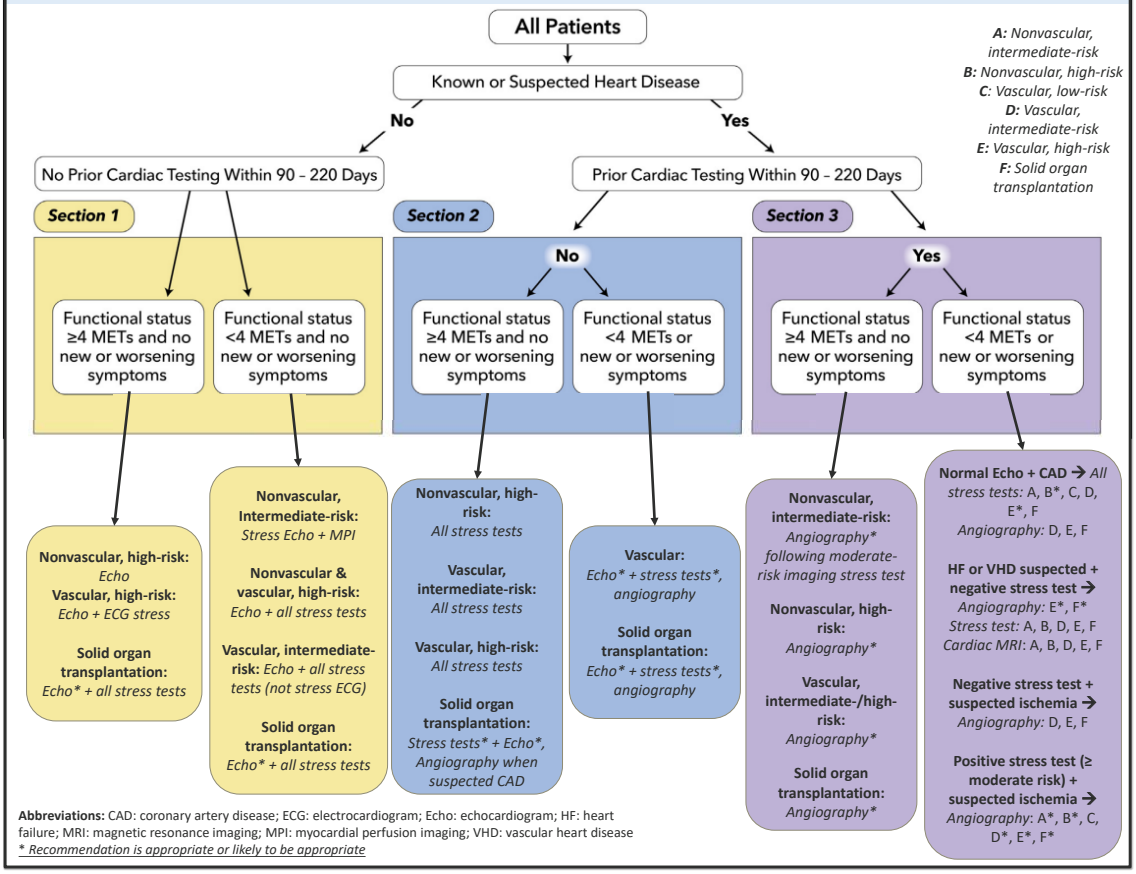
*** The American Society of Anesthesiologists affirms the value of this document.**
ASA representative Lisa Q. Rong, MD, FACC, co-author on the Rating Committee

Weill Cornell Medicine

Background & Purpose:

- This appropriate use criteria (**AUC**) addresses the use of **multimodality imaging** in the **preoperative evaluation** of patients undergoing nonemergent noncardiac surgery.
- The vast number of available new and old imaging modalities are **constantly evolving and being validated**, and it is **not universally known which imaging tests are best for nuanced clinical scenarios**
- The purpose of this AUC is to **provide a framework to identify the value of imaging** in patients stratified by the presence or absence of **underlying cardiac disease** or **the spectrum of altered functional status** before surgery.
- **Methods:** An independent rating panel scored the **182 clinical scenarios** on a scale of 1 to 9
  - » Scores 7 to 9 = *modality is considered appropriate;*
  - » 4 to 6 = *modality may be appropriate*;
  - » 1 to 3 = *modality is rarely considered appropriate*

FIGURE 1 Guide to Tables for Cardiac Imaging in Patients Undergoing Nonemergent, Noncardiac Surgery



Abbreviations: CAD: coronary artery disease; ECG: electrocardiogram; Echo: echocardiogram; HF: heart failure; MRI: magnetic resonance imaging; MPI: myocardial perfusion imaging; VHD: vascular heart disease

** Recommendation is appropriate or likely to be appropriate*

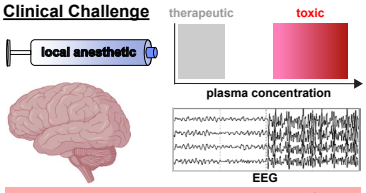
Basic Science Posters

Weill Cornell Medicine
Anesthesiology

Comparison of Presynaptic Inhibition of Calcium Influx in Glutamatergic and GABAergic Neurons by Lidocaine

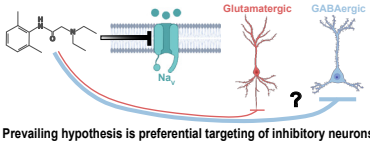
Daniel Cook[1], MD, Kirsten Bredvik[2], BS, Timothy Ryan[1,2], PhD
Department of Anesthesiology[1] and Biochemistry[2], Weill Cornell Medicine, New York, NY

Clinical Challenge



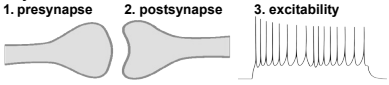
Local anesthetics are indispensable drugs for surgery and medical procedures. Intravascular overdose often leads to neurotoxicity, which can progress to seizures.[1]

Models of local anesthetic neurotoxicity



Prevailing hypothesis is preferential targeting of inhibitory neurons[2]

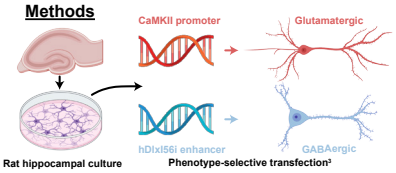
May involve differential modulation of:
1. presynapse 2. postsynapse 3. excitability

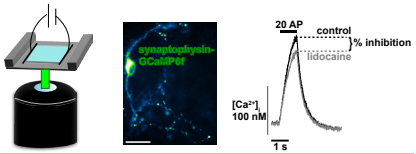


Research Question

Does the prototypical local anesthetic, lidocaine, preferentially inhibit nerve terminals of GABAergic neurons compared to glutamatergic neurons?

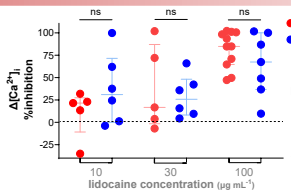
Methods



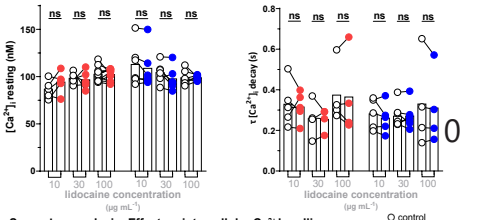


Fluorescence imaging of the genetically-encoded Ca^{2+} indicator, GCaMP6f, targeted to nerve terminals by synaptophysin and driven to fire action potentials (APs) by field depolarization. Lidocaine inhibition of synaptic function was quantified as the relative decrease of Ca^{2+} influx into nerve terminals compared to control. Scale bar = 20 µm.

ACKNOWLEDGEMENTS
This research is supported by the National Institutes of Health (K08GM148935 to DCC; NS036942 and NS11739 to TAR). Figures were created with Biorender.com. Statistical analysis was performed with GraphPad Prism v10. We thank Giulia Dalaty for research technical support.



Effect on presynaptic Ca^{2+} influx
Lidocaine administered in a range of clinically relevant toxic doses. GCaMP6f converted into net intracellular Ca^{2+} change. Dots are individual cells, lines are median and interquartile range. Analyzed with Mann-Whitney test, ns $p > 0.05$.



Secondary analysis: Effect on intracellular Ca^{2+} handling
Resting $[Ca^{2+}]_i$ and decay from peak after stimulation. Dots are individual cells, bars are mean. For decay data, cells with single exponential fit $R^2 < 0.8$ were excluded. Analyzed with paired t-test, ns $p > 0.05$.

control
lidocaine, glutamatergic
lidocaine, GABAergic

Conclusions

Our results do not support preferential presynaptic inhibition of glutamatergic compared to GABAergic neurons. Future experiments will identify the molecular factors determining the unexpected variability of neuronal inhibition by lidocaine.

References
1) Di Gregorio et al. *Reg Anesth Pain Med.* 2010; 35:181-187. 2) El-Boghdadly et al. *Local Reg Anesth.* 2018; 11:35-44.
3) Farrell et al. *bioRxiv* 2024.02.15.580492

The mechanism of PI(4,5)P2 inhibition of rod Cyclic Nucleotide-Gated (CNG) channel

Taehyun Park and Crina M. Nimigean*

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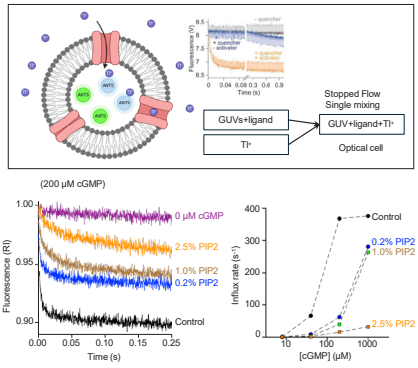
PIP2 serves as an anchor to lower the cGMP sensitivity of rod Cyclic Nucleotide-Gated (CNG) channel

Phosphatidylinositol-4,5-bisphosphate (PIP2) functions as a pivotal signaling lipid that governs numerous ion channels[1,2,3]. Although prior studies have indicated PIP2's inhibitory impact on rod cyclic nucleotide-gated (CNG) channels[4], the underlying mechanism has remained elusive. In this study, we elucidate the molecular inhibitory mechanism of PIP2 on the human rod CNG channel, CNGA1. Consistent with previous findings, both ensemble and single-channel assays of purified CNGA1 channels show a nearly complete inhibition of ion flux in the presence of PIP2 accomplished by lowering cGMP sensitivity. To gain further insight we determined the structures of CNGA1 embedded in lipid nanodiscs in the presence and absence of cGMP as well as in the presence and absence of PIP2. In the absence of cGMP, only closed states were determined. In the presence of cGMP however, PIP2 led to the disappearance of the open state found in the absence of PIP2, indicating that PIP2 binding prevents channel opening. A lipid density fitting well a PIP2 molecule not observed in apo structures was detected in the intermediate and closed states, located between the voltage-sensing and pore domains of adjacent subunits. This density precisely accommodates a PIP2 molecule. To open, the pore must undergo dilation and rotation, accompanied by lifting of the cytosolic domains, C-linker and CNBD, which are triggered by cGMP binding to the cyclic nucleotide-binding domain (CNBD). PIP2 binding prevents the translation outwards and rotation of the S6 as well as the elevation of the C-linker, preventing channel opening and locking the channel in the intermediate state. Here, we propose that PIP2 serves as an anchor for holding the transmembrane domain in close state, sterically inhibiting the dilation of the pore domain and the elevation of the cytosolic domain, essential for pore opening in rod CNG channel.

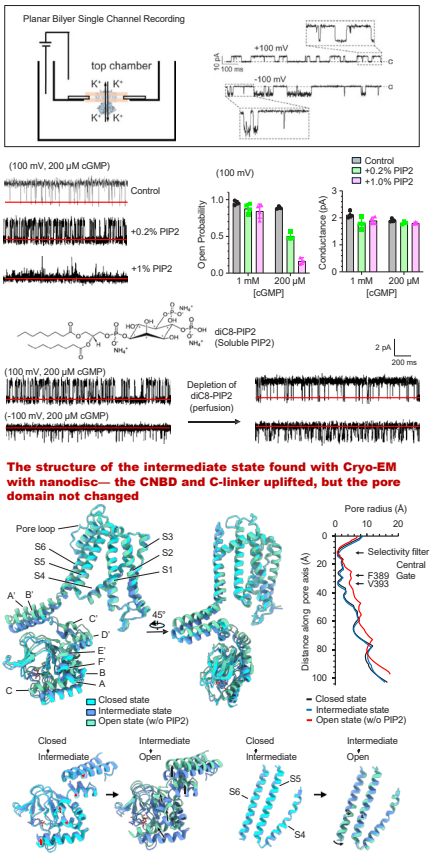
Reference

1. Whorton et al., Cell. 147:199–208 (2011)
2. Large et al., Cell Calcium. 45:574–582 (2009)
3. Riel et al., Journal of General Physiology. 154:e202112989 (2021)
4. Womack et al., J. Neurosci. 20:2792–2799 (2000)
5. Xue et al., Neuron 109, 1302–1313 (2021)

PIP2 lowers the open probability and the cGMP sensitivity of CNGA1

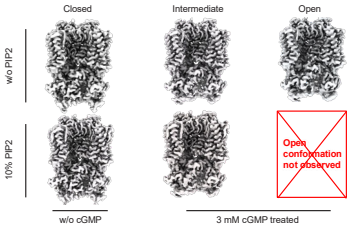


Single channel recording shows the consistent result of the inhibitory activity of PIP2, depending on the cGMP level

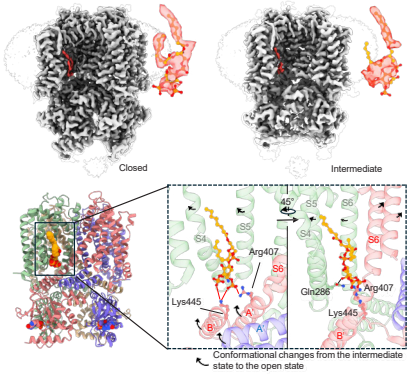


The structure of the intermediate state found with Cryo-EM with nanodisc— the CNBD and C-linker uplifted, but the pore domain not changed

With PIP2, the open conformation is not observed with saturating cGMP

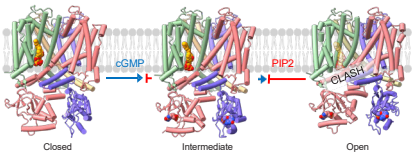


PIP2 interacts the residues on the C-linker and S4, sterically inhibiting the cytosolic domain lifting



Summary

PIP2 inhibits CNGA1 with the steric hindrance to disturb the cytosolic domain from uplifting and triggering the pore domain open, which makes more cGMP needed for the channel open.



Acknowledgements

NYU Langone Health's Cryo-Electron Microscopy Laboratory (RRID: SCR_019202)
NIH R01 GM088352

A Structural Biology 3D-Viewer Compatible File Format for Localization Atomic Force Microscopy Maps

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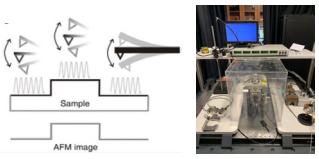
Abstract

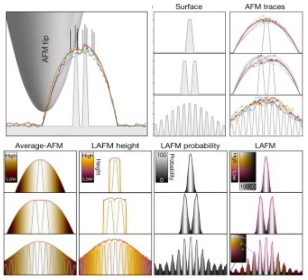
Cryogenic electron microscopy (cryo-EM), X-ray crystallography, and nuclear magnetic resonance (NMR) contribute structural data that are interchangeable, cross-verifiable, and visualizable on common platforms making them powerful tools for our understanding of protein structures. Unfortunately, atomic force microscopy (AFM) has so far not found ways to interface with the other structural biology methods, because it did not produce data and files that were comparable with other techniques and/or readable in the common structure visualization software. Recently, we developed localization AFM (LAFM) a method that allowed to extract high-resolution structural information from AFM data. Here, we build on LAFM and develop a pipeline that transforms AFM data into 3D density files (MRC/AFM1) that are readable by the programs commonly used to analyze and interpret structural data (*eg.* Chimera). The 3D-LAFM density data could also serve as a force field to seek the most probable atomic model underlying the AFM data obtained at physiological conditions using molecular dynamics flexible fitting (MDFF). This approach enabled detailed comparisons of the conformations of a single transporter at different stages along its transporting cycle. We show that the method can transform LAFM maps into files that are useful for the structural biology community. We anticipate that the new file format will find wide application and bring AFM into the structural biology community, allowing AFM researchers to deposit AFM data in common repositories in a format that is readable in structural biology software and be compared with data from other techniques.

Backgrounds

- **High-speed atomic force microscopy**



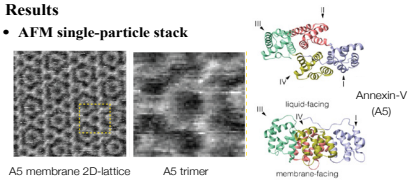
- **Localization atomic force microscopy (LAFM) algorithm**



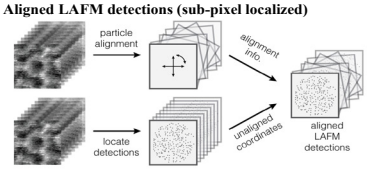
Merging sub-pixel localized local maxima (free-of-convolution) from AFM images breaks the spatial resolution limit of AFM

Results

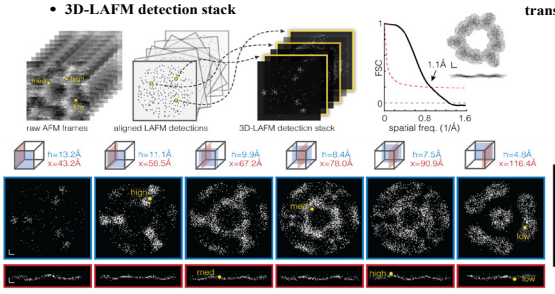
- **AFM single-particle stack**



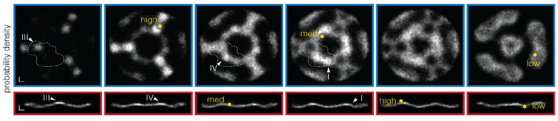
- **Aligned LAFM detections (sub-pixel localized)**



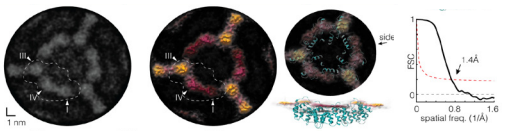
- **3D-LAFM detection stack**



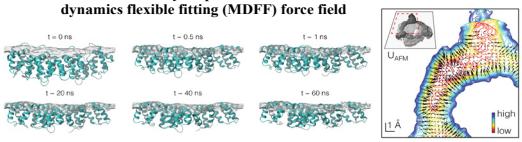
- **3D-LAFM density map**



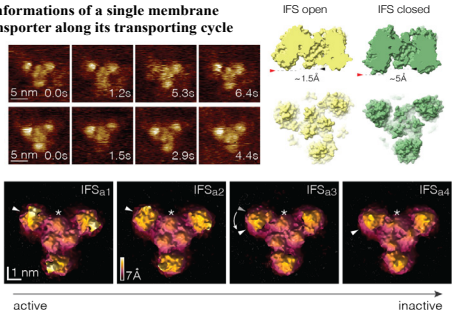
- **3D-LAFM detection evaluation**



- **3D-LAFM density map as a molecular dynamics flexible fitting (MDFF) force field**



- **Conformations of a single membrane transporter along its transporting cycle**



Acknowledgement

Funding: Work in the Scheuring laboratory was supported by grants from the National Institute of Health (NIH), National Center for Complementary and Integrative Health (NCCIH), DP1AT010874 and National Institute of Neurological Disorders and Stroke (NINDS), R01NS110790.

Heath et al., *Nature*, 2021
Jiang et al., in press
Jiang et al., in preparation

Comparative Analysis of 405 nm Illumination and 530 nm Light Scattering Methods for Distinguishing Hemodynamic from Neural Signals in GCaMP Imaging

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Introduction

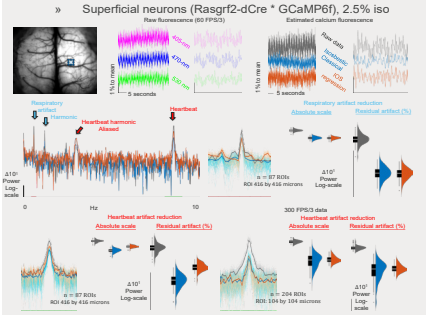
- Green fluorescent protein (GFP)-derived genetically encoded fluorescent indicators, such as GCaMP, are the most widely used neural activity indicators but face significant challenges due to their absorption and emission spectra overlapping with hemoglobin, which is abundant in brain tissue.
- Traditionally, this issue has been addressed using the Beer-Lambert law-based approach, which utilizes 530-nm illumination to detect intrinsic optical signals (IOS) in order to distinguish neural signals from artifacts caused by variations in tissue hemoglobin levels (hereafter, the IOS method).
- Recently, the isosbestic method, which employs 405-nm illumination to generate neural activity-insensitive fluorescence in order to extract neural signals from raw data, has gained popularity for its ease of experimental setup.
- However, the optical properties of 405-nm photons differ significantly from those at 470 nm, with a higher absorption coefficient by hemoglobin and increased tissue scattering.
- In this study, we compare the effectiveness of the isosbestic method and the IOS method in canceling respiratory and heartbeat-induced artifacts in calcium imaging. Our results show that while the isosbestic method demonstrates a non-inferior accuracy compared to the IOS reference method, its accuracy is dependent on neuronal depth. To address this limitation, we propose a novel regression approach to enhance the accuracy of the isosbestic method.

Material and Methods

- Widefield fluorescence/scattering imaging setup with three excitation wavelengths: 405, 470, and 530 nm. Emission: 525/50 nm.
- Cranial window in two strains of transgenic mice
  - » Rasgrf2-dCre x GCaMP6f (Layer 2/3 neurons)
  - » Thy1-GCaMP6f (Kim 5.5) (Majorly Layer 5 neurons)
- Sequential multi-wavelength imaging at 60 FPS or 300 FPS.
- Experimental conditions: deep anesthesia to quench spontaneous neural activity
- Algorithms
  - » Classical: $\delta I_t / \delta I_{r,t}$, where $\delta I_t = I_t / I_{t_0}$(470 nm) $\delta I_{r,t} = I_{r,t} / I_{r,t_0}$ (530 nm or 405 nm)
  - » Regression: $\delta I_t / \{\beta \delta I_{r,t} + C\}$, β & C determined by linear regression, PCA, or robust PCA
- Performance evaluation: Artifact cancellation (respiration, heartbeat)

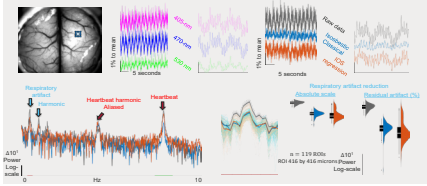
Results

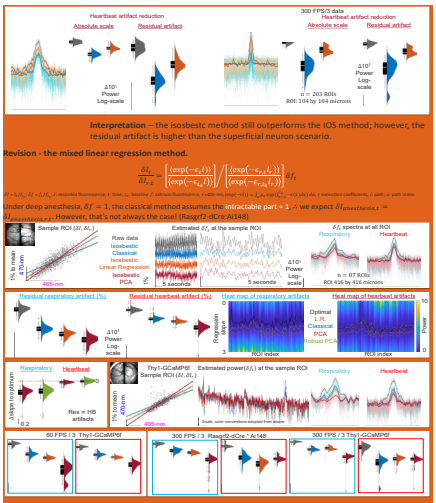
- The isosbestic method (405-nm) is more superior compared to the IOS reference method (530-nm) in terms of removing hemodynamic artifacts, particularly hearbeat-associated artifacts, regardless of neuron depth.
  - » Superficial neurons (Rasgrf2-dCre * GCaMP6f), 2.5% iso



Interpretation – IOS images are superposition of all levels; whereas, isosbestic images guarantees the image depth.

  - » Deep neurons (Thy1-GCaMP6f (Kim 5.5)), 2.5% iso





Conclusion

- The isosbestic method outperformed the IOS method
- The classical method does not completely remove hemodynamic artifacts
- The PCA methods outperformed the classical and simple linear regression method in terms of removing hemodynamic artifacts
- Deep anesthesia may be used as a hemdynamic calibration tool

Discovering Neuronal Firing Codes underneath Slow Waves: A Novel Approach in Rodent Models of Anesthesia and Sleep

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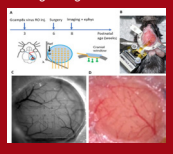
# Equal contribution; $ Corresponding authors (jyl9010@med.cornell.edu)

Introduction

- Slow waves are key features of general anesthesia (GA) and resemble those in slow-wave sleep (SWS).
- The similarity of neuronal firing patterns between GA and SWS remains debated.
- We introduce a novel approach combining EEGs and optical recordings in transgenic mice to capture large-scale neuronal activity.
- Our method also allows cortical electrical stimulation, enabling direct comparison of cortical states during anesthetic-induced and SWS slow waves.

Material and Methods

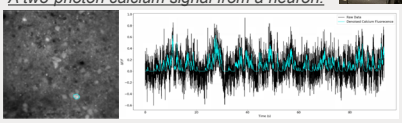
- Firing patterns of individual neurons over a large brain area
  - » Vgat-Cre/tdTomato transgenic mice + pGP-AAV-syn-jGCaMP8s-WPR (PhP.eB)
  - » 4-mm curved cranial window by glass window with ECOG
  - » Epifluorescence imaging with Bruker 2P+ Olympus 20X/1.0 920-nm excitation
- Concurrent extracellular electrophysiology recording
  - » The old method (left)
    - Bone screws anterior-posteriorly
    - Site-specific recording and intervention via a sharp electrode by penetrating the PDMS elastomer film
  - » The new method - transparent electrode array (right) with reference electrode anterior
    - Wires: Nano-meshed, Au:PEDOT/PSS
    - Parylene C embedding with glass window.



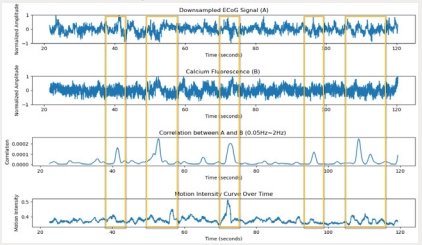
- GA
  - » Isoflurane
- SWS models
  - » Dexmedetomidine (100 mcg/g IP or 75 mcg/g RO)
  - » 24-hour sleep-deprivation

Results

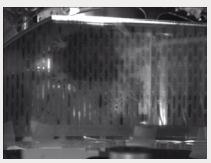
A two-photon calcium signal from a neuron.



Correlation Analysis between ECoG and Calcium Fluorescence Signals



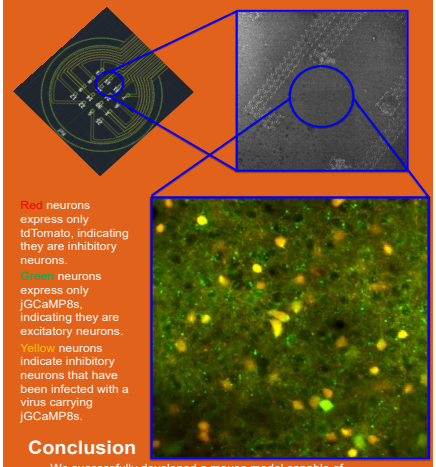
Downsampled ECoG Signal (A) is the signal obtained from the electrode in the transparent ECoG electrode array closest to the microscope observation window. **Calcium Fluorescence (B)** represents the fluorescence signal of jGCaMP8s located 150 micrometers below the brain surface. Since the decay time of the jGCaMP8s fluorescence signal is less than 500 ms, we used wavelet transform to calculate the correlation coefficient between signals A and B within the bandwidth of 0.05 Hz and 2 Hz. Meanwhile, we used the optical flow method to calculate the mouse's **motion intensity** from the behavioral camera. As indicated in the signal intervals marked by yellow boxes, there is a noticeable change in the mouse's motion intensity during periods when signals A and B are highly correlated. This suggests that the calcium fluorescence and electrophysiological signals we captured together detected movement-related events.



Behavioral camera, observing the activity of the laboratory rodent from a bottom-up perspective.

Calcium imaging under the new ECoG array

- Two-photon imaging



Red neurons express only tdTomato, indicating they are inhibitory neurons.

Green neurons express only jGCaMP8s, indicating they are excitatory neurons.

Yellow neurons indicate inhibitory neurons that have been infected with a virus carrying jGCaMP8s.

Conclusion

- We successfully developed a mouse model capable of simultaneously recording electrophysiological signals and calcium fluorescence signals.
- Experimental results demonstrate that our electrophysiological and calcium fluorescence signals show a strong correlation and the neuronal events can be simultaneously detected across systems.
- The next step will involve studying the difference in cortical states in GA and SWS mouse models based on electrophysiological signals and calcium signals from excitatory and inhibitory neurons.

Isoflurane and sevoflurane inhibit mammalian sodium channel subtype $Na_v1.3$

Jiaxin Xiang[1], Karl F. Herold[1], Jimcy Platholi[1,2], Hugh C. Hemmings, Jr.[1,3]

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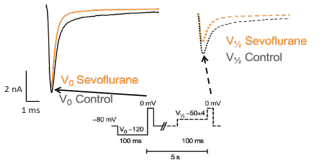
Weill Cornell Medicine

Introduction:

Volatile anesthetics have been widely used in clinical applications for more than 170 years, but the molecular mechanisms by which these drugs work are incompletely understood. A role of ion channels as critical targets for anesthesia has been proposed, including voltage-gated sodium channels (Na_v). Volatile anesthetics inhibit the neuronal subtypes $Na_v1.1$, $Na_v1.2$ and $Na_v1.6$ in a voltage-dependent manner [1,2], but their effects on $Na_v1.3$, a subtype abundantly expressed in developing brain as well as in mature neurons following injury or disease, are unknown. Activation of $Na_v1.3$ increases susceptibility to hyperexcitability with multiple $Na_v1.3$ variants identified in patients with epilepsy [3,4]. We investigated the effects of the volatile anesthetics isoflurane and sevoflurane on $Na_v1.3$ function using patch-clamp electrophysiology.

Volatile anesthetics inhibit peak Na^+ current (I_{Na}) in a voltage-dependent manner

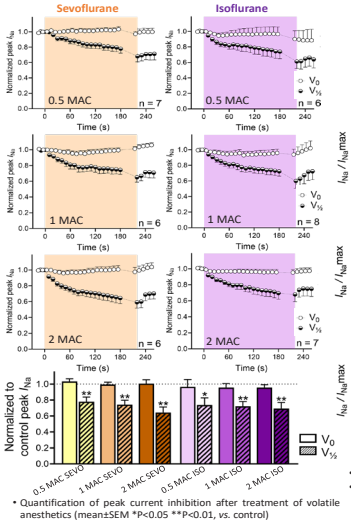


- Macroscopic Na^+ current traces elicited with the given stimulation protocol (see inset).

Methods:

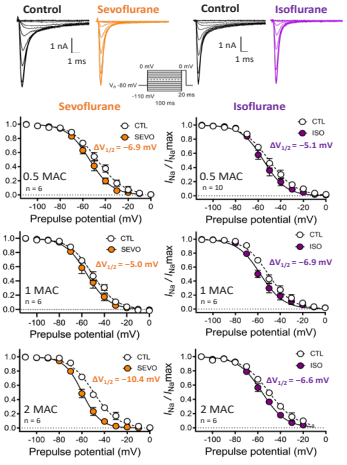
Human embryonic kidney HEK293T cells grown on 12-mm glass coverslips were co-transfected with human $Na_v1.3$ cDNA, $h\beta_1$, and pEGFP as a marker. The whole-cell voltage-clamp method was used to record Na^+ currents from transfected cells in the absence or presence of clinical concentrations of anesthetics.

Sevoflurane (SEVO) and isoflurane (ISO) inhibit $Na_v1.3$ peak Na^+ current (I_{Na}) in a voltage-dependent manner



- Quantification of peak current inhibition after treatment of volatile anesthetics (mean±SEM *P<0.05 **P<0.01, *vs.* control)

Volatile anesthetics left shift the voltage-dependance of half maximal inactivation ($V_{1/2}$)

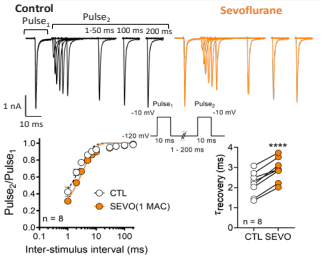


- Normalized peak I_{Na} plotted against the pre-pulse potential
- Fitted with two-state Boltzmann distribution to determine $V_{1/2}$

References:

[1] J of Pharm. and Experi. Therapeu. 2019; 369: 200-211.
[2] J Gen Physiol 2014; 144 (6): 545-560.
[3] Neurobiol Dis. 2014 Feb;62:313-22.
[4] Exp Neurol. 2010 20420834.

Sevoflurane slows recovery from inactivation



Results:

- Clinical concentrations of isoflurane and sevoflurane **significantly inhibit** $Na_v1.3$ peak Na^+ current in a voltage-dependent manner.
- Isoflurane and sevoflurane also shifted $Na_v1.3$ $V_{1/2inact}$ toward **hyperpolarized potentials**.
- Sevoflurane **increased** the time it takes for $Na_v1.3$ channel to **recover after inactivation**.

Conclusions:

- Clinical concentrations of isoflurane and sevoflurane **inhibit** $Na_v1.3$ function confirming $Na_v1.3$ as a **potential target** for volatile anesthetics.
- Modulation of $Na_v1.3$ by volatile anesthetics may influence **anesthetic neurotoxicity** in developing or injured brain.
- These effects on voltage-dependent inhibition of peak Na^+ current and the leftward shift in $V_{1/2inact}$ are **comparable to anesthetic effects on other mammalian Na_v subtypes,** which suggests a conserved mechanism.

Supported by NIH Grant 5R01GM058055-24 (HCH)

Structural basis of closed groove scrambling by a TMEM16 protein

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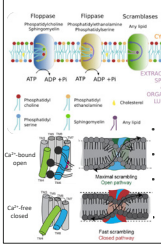
1 Department of Anesthesiology, Weill Cornell Medical College; 2 Physiology, Biophysics and Systems Biology Graduate Program, Weill Cornell Medical College; 3 Department of Physiology and Biophysics, Weill Cornell Medical College; 4 Department of Biochemistry, Weill Cornell Medical College

ABSTRACT

Activation of Ca^{2+}-dependent TMEM16 scramblases induces the externalization of phosphatidylserine, a key molecule in multiple signaling processes. Current models suggest that the TMEM16s scramble lipids by deforming the membrane near a hydrophilic groove, and that Ca^{2+} dependence arises from the different association of lipids with an open or closed groove. However, the molecular rearrangements involved in groove opening and of how lipids reorganize out side the closed groove remain unknown. Using cryogenic electron microscopy, we directly visualize how lipids associate at the closed groove of Ca^{2+}-bound nhTMEM16 in nanodiscs. The 2.6 Å resolution of the cryoEM map in the Ca^{2+}-bound closed state enables us to visualize how lipid reorganize outside a closed groove resulting in a pronounced thinning of the membrane that could facilitate scrambling. Structure-based mutagenesis of lipid-interacting residues suggests that residues coordinating outer leaflet lipids have an important role specifically in closed groove scrambling. Structural and functional analyses suggest Ca^{2+} binding induces the sequential appearance of two π-helical turns in the groove-lining TM6 helix. Disruption of a salt bridge connecting two sides of the groove favors a closed groove and prevents formation of the second π-helical turn, a key role of this rearrangement in groove opening. Finally, we find that the choice of scaffold protein and lipids affects the conformations of nhTMEM16 and their distribution, highlighting a key role of these factors in cryoEM structure determination. Our findings provide the structural basis for closed groove scrambling and reveal how lipid scrambling can occur outside a closed groove by membrane thinning.

INTRODUCTION



Physiological role of scrambling

- Activated scramblases externalize PS on the extracellular leaflet.
- PS exposure is critical for cell signaling pathways regulating blood coagulation, apoptosis, autophagy and cell-cell fusion.

Closed groove scrambling is supported by

- Basal activity of lipid scrambling is observation in many TMEM16 scramblases when the groove is closed.
- The professional lipid scramblases TMEM16s and Xkrs function as non-selective scramblases
- The mammalian scramblase TMEM16F has a stable closed state.

However…

- Direct information on how lipids interact with a closed groove during scrambling is lacking.

QUESTIONS

1) How do TMEM16s interact with lipids during scrambling when groove is closed?
2) What are the conformational rearrangements critical for groove opening?

RESULTS

The conformational landscape of nhTMEM16 depends on the environment

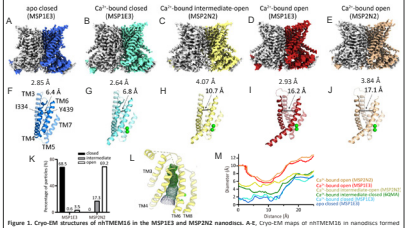


Figure 1. Cryo-EM structures of nhTMEM16 in the MSP1E3 and MSP2N2 nanodiscs. A-E, Cryo-EM maps of nhTMEM16 in nanodiscs formed from a 7:3 mix of DOPC:DOPG lipids and MSP1E3 (**A-C**) or MSP2N2 (**D-E**) scaffold proteins. (**A**) Ca^{2+}-free, closed groove, (**B**) Ca^{2+}-bound, closed groove, (**C**) Ca^{2+}-bound, open groove, (**D**) Ca^{2+}-bound, intermediate-open groove, and (**E**) Ca^{2+}-bound, open groove. **F-I**, The groove in the different conformations is viewed from the plane of the membrane. Ca^{2+} ions are shown as green spheres. **K**, The percentage of particles with a closed (black bar), intermediate (gray bar), or open (white bar) groove conformation in the datasets of Ca^{2+}-bound nhTMEM16 in MSP1E3 or MSP2N2 nanodiscs. Here, intermediate does not distinguish between the intermediate-open and -closed conformations. **L**, The accessibility of the permeation pathway of nhTMEM16 in the intermediate conformation is visualized using the program Hole. **M**, The inner diameter of the permeation pathway of nhTMEM16 in MSP1E3 or MSP2N2 nanodiscs and in the published the diameter of a putative ion conduction pathway measured in different states with Hole.

Structural basis of membrane thinning at the closed groove of nhTMEM16

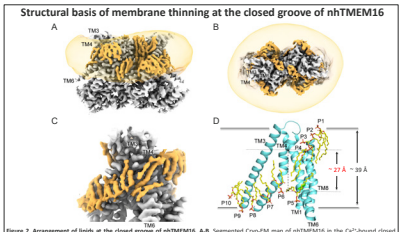


Figure 2. Arrangement of lipids at the closed groove of nhTMEM16. A-B, Segmented Cryo-EM map of nhTMEM16 in the Ca^{2+}-bound closed state (gray) and the associated lipids (orange) viewed from the membrane plane (**A**) and from the extracellular side (**B**). The map showing the density of the nanodisc membrane is low-pass filtered to 12 Å and shown in transparent orange. **C,** View of the lipids outside of the closed groove from the plane of the membrane. **D,** Stick representation of the ten pathway lipids colored in yellow (P1-P10). Dashed arrow indicates the distance between the phosphate atoms of the last lipid from the inner (P6) and outer (P4) leaflets (~27 Å) and the measured membrane thickness (~39 Å). Lipids were built up to the phosphate atom in the head. Ca^{2+} ions are displayed as green spheres.

1) There is a pronounced thinning of the membrane at the closed groove

Interactions important for closed –but not open– groove scrambling

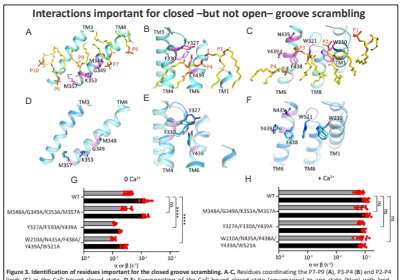


Figure 3. Identification of residues important for the closed groove scrambling. A-C, Residues coordinating the P7-P9 (**A**), P3-P4 (**B**) and P2-P4 lipids (**C**) in the Ca^{2+}-bound closed state. **D-F:** Superposition of the Ca^{2+}-bound closed state (aquamarine) to apo state (blue) with lipid-coordinating residues shown as sticks. **G-H,** Forward (α) and reverse (β) scrambling rate constants of the mutants of nhTMEM16 aimed at disrupting the protein-lipid interactions (shown in **A-C**) measured in 0 (**G**) or 0.5 mM Ca^{2+} (**H**). Bars are averages for α (black) and β (gray) (N ≥ 3), error bars are S. Dev., and red circles are values from individual repeats. The statistical significance of the effects of the mutants on the scrambling rate constants was evaluated with a two-sided Student's t-test with a Bonferroni correction. **** denotes p<10^{-5} after Bonferroni correction.

2) Lipid interacting residues at outer leaflet are important for closed-groove scrambling

Steps in groove opening of nhTMEM16

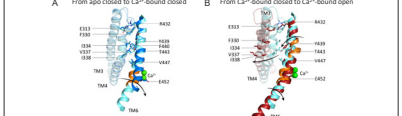


Figure 4. Role of the E313-R432 salt bridge in groove opening. A-B, Structural comparisons of the groove in apo (blue) vs Ca^{2+}-bound closed (cyan) (**A**) and Ca^{2+}-bound closed (cyan) vs open (red) states (**B**). Arrows denote rotations in the TM6. Sidechains of E313 and R432, and of the residues forming the TM4-TM6 interface are shown as sticks. π-helical turns are colored in orange. Ca^{2+} ions are displayed as green spheres.

Disruption of the E313-R432 salt bridge favors a closed groove

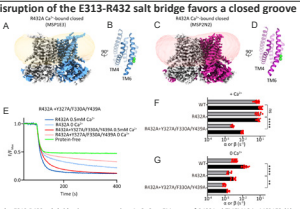


Figure 5. Role of the E313-R432 salt bridge in groove opening. A, C, Cryo-EM maps of R423A nhTMEM16 in MSP1E3 (**A**) or MSP2N2 (**C**) nanodiscs. One protomer is colored in gray and the other in light blue (**A**) or magenta (**C**). The density of the nanodisc membrane is low pass filtered to 7 Å and shown in transparent orange (**A**) and red (**C**). **B, D,** Views of the groove from the plane of the membrane. TM4 and TM6 are shown in cartoon representation and labelled. Ca^{2+} ions are displayed as green spheres. **E,** Representative traces of the dithionite induced fluorescence decay in the scrambling assay for protein free liposomes (green), or R432A nhTMEM16 and the quadruple mutant R432A+Y327A/F330A/Y439A nhTMEM16 in the presence (dark blue and dark red) and absence (light blue and light red) of Ca^{2+}. **F-G,** Forward (α) and reverse (β) scrambling rate constants of the mutants measured in 0.5 mM (**F**) or 0 Ca^{2+} (**G**). Bars are averages for α (black) and β (gray) (N ≥ 3), error bars are S. Dev., and red circles are values from individual repeats. The statistical significance of the effects of the mutants on the scrambling rate constants was evaluated with a two-sided Student's t-test with a Bonferroni correction. ** denotes p<0.001 and **** denotes p< 10^{-5} after Bonferroni correction.

Straightening of TM6 is important for closed-groove scrambling

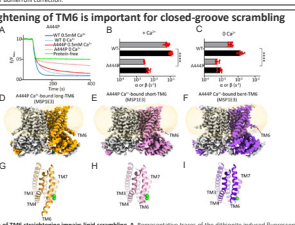


Figure 6. Disruption of TM6 straightening impairs lipid scrambling. A, Representative traces of the dithionite induced fluorescence decay in the scrambling assay in protein-free liposomes (green) or proteoliposomes reconstituted with WT and A448P nhTMEM16 in the presence (dark blue and dark red) and absence (light blue and light red) of Ca^{2+}. **B-C,** Forward (α) and reverse (β) scrambling rate constants of the mutants measured in 0.5 mM (**B**) or 0 Ca^{2+} (**C**). Bars are averages for α (black) and β (gray) (N ≥ 3), error bars are S. Dev., and red circles are values from individual repeats. The statistical significance of the effects of the mutants on the scrambling rate constants was evaluated with a two-sided Student's t-test with a Bonferroni correction. **** denotes p<10^{-5} after Bonferroni correction. **D-F**, Cryo-EM maps of **A448P** nhTMEM16 in MSP1E3 nanodiscs in the long TM6 state (**D**), short TM6 state (**E**) and bent TM6 state (**F**). One protomer is colored in gray and the other in orange (**D**), pink (**E**), and purple (**F**). The density of the nanodisc membrane is low pass filtered to 7 Å and shown in transparent orange. **G-I**, The groove in the long TM6 (**G**), short TM6 (**H**) and bent TM6 (**I**) states is viewed from the plane of the membrane. Transmembrane helices are labelled and Ca^{2+} ions are displayed as green spheres.

CONCLUSIONS

- We used cryoEM to image the fungal nhTMEM16 scramblase in lipid nanodiscs formed from different scaffold proteins and found this to affect both the conformations adopted by nhTMEM16 and their distribution.
- The 2.64 Å resolution structure of Ca^{2+}-bound closed nhTMEM16 reveals how lipids arrange near the groove, thus showing how the scramblase thins the membrane outside a closed groove.
- Mutating residues that coordinate outer leaflet lipids near the closed groove impairs scrambling only in the absence of Ca^{2+}, suggesting these interactions play a specific role in closed-groove scrambling.
- Structural analysis of the transition of nhTMEM16 from closed to open state suggests that the E313-R432 salt bridge could be involved in groove opening. Disruption of this interaction by the R432A mutation trapped nhTMEM16 in a closed-groove conformation, suggesting the salt bridge is critical for groove opening.

Acknowledgements

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Cryo-EM structures and functional characterization of the human TMEM16E scramblase and GDD associated mutations

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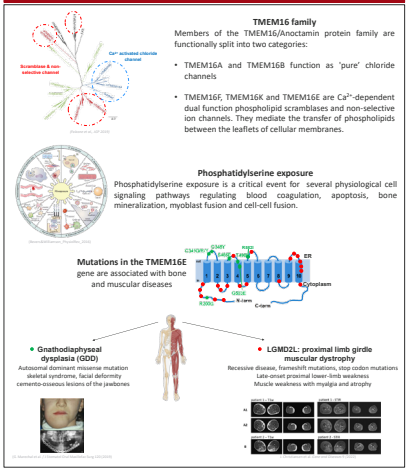
ABSTRACT

The TMEM16 (ANOctamin) family of proteins encodes for Ca^{2+}-activated chloride channels and phospholipid scramblases. Our understanding of mammalian TMEM16s function primarily stems from studies on the murine TMEM16F homologue, a dual function non-selective channel and scramblase that resides on the plasma membrane. However, the function of most of the other 9 human TMEM16 homologues remains poorly understood, as they primarily localize to intracellular compartments such as the endoplasmic reticulum (ER) and the Golgi apparatus. For example, the TMEM16E (ANOS or GDD1) family member primarily localizes to the ER and is highly expressed in bone and skeletal muscle, where it plays a vital role in muscle repair and bone mineralization. Strikingly, whereas loss-of-function mutations in human TMEM16E are associated with recessive forms of limb-girdle muscular dystrophy-2L and distal Miyoshi muscular dystrophy-3, gain of function mutations cause the autosomal dominant bone disease gnathodiaphyseal dysplasia (GDD). However, the structure of TMEM16E and the molecular mechanisms underlying the pathogenesis of these genetic disorders remains poorly understood.

To address this knowledge gap, we purified and reconstituted human TMEM16E in proteoliposomes and showed it functions as a Ca^{2+}-dependent phospholipid scramblase. CryoEM imaging shows that hTMEM16E adopts the canonical dimeric butterfly fold of TMEM16 proteins, with each protomer forming an independent lipid permeation groove. In the absence of Ca^{2+}, hTMEM16E adopts a closed groove conformation, with a straight TM6 helix and severely tilted TM3 and TM4 helices. Surprisingly, no structural rearrangements occur upon Ca^{2+} binding in the groove lining TM3, TM4, or TM6 helices. Interestingly, our map shows that in saturating ligand concentrations only one of the two orthosteric Ca^{2+} binding sites is occupied, possibly rationalizing the weaker Ca^{2+}-dependence of hTMEM16E compared to other family members. Notably, the cytosolic allosteric Ca^{2+} site is occupied, suggesting this site might play a regulatory role in hTMEM16E activity.

To gain insights into the pathogenesis of GDD, we investigated the recently reported mutation Arg582Ile, in the extracellular TM5-TM6 loop . Using a cell-based scrambling assay we found that whereas WT hTMEM16E shows Ca^{2+}-dependent scrambling activity, the R582I mutant displays constitutive, Ca^{2+}-independent activity. The cryoEM structure of R582I hTMEM16E in the presence and absence of Ca^{2+} are very similar to the respective WT structures, with the notable difference that Ca^{2+} binding to the orthosteric site appears weakened. These results suggest that in hTMEM16E Ca^{2+}-dependent scrambling entails minimal conformational rearrangements, possibly just changes in the occupancy of the orthosteric and/or allosteric binding sites.

INTRODUCTION



TMEM16 family

Members of the TMEM16/Anoctamin protein family are functionally split into two categories:

- TMEM16A and TMEM16B function as 'pure' chloride channels
- TMEM16F, TMEM16K and TMEM16E are Ca^{2+}-dependent dual function phospholipid scramblases and non-selective ion channels. They mediate the transfer of phospholipids between the leaflets of cellular membranes.

Phosphatidylserine exposure

Phosphatidylserine exposure is a critical event for several physiological cell signaling pathways regulating blood coagulation, apoptosis, bone mineralization, myoblast fusion and cell-cell fusion.

Mutations in the TMEM16E gene are associated with bone and muscular diseases

Questions

1) **What is the structure of TMEM16E?**
2) **What are the functional effects and the structural rearrangements associated with the novel GDD mutation R582I ?**

Acknowledgements

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METHODS and RESULTS

Ca^{2+} bound human TMEM16E adopts a closed groove conformation

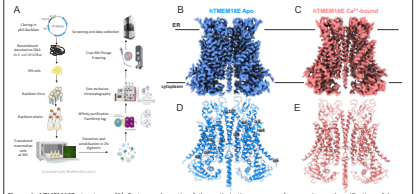


Figure 1. hTMEM16E structures. (A) Cartoon schematic of the optimization process of expression and purification of human TMEM16E protein for CryoEM. Cryo-EM map of hTMEM16E in digitonin in absence (**B**) and in presence (**C**) of calcium at 3.3 Å and 3.2 Å, respectively. Cartoon representation of the Ca^{2+}-free (light blue) (**D**) and Ca^{2+}-bound hTMEM16E-WT (light pink) (**E**) dimer. Both structures superimpose with a root mean square deviation (RMSD) of 1.2 Å. Transmembrane helices are labelled, and the membrane boundary is indicated.

Ca^{2+} binding does not induce any conformational rearrangements

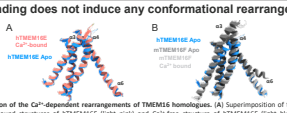


Figure 2. Comparison of the Ca^{2+}-dependent rearrangements of TMEM16 homologues. (A) Superimposition of the α-helices 3–6 between the Ca^{2+}-bound structures of hTMEM16E (light pink) and Ca^{2+}-free structure of hTMEM16E (light blue) displaying no structural rearrangement upon Ca^{2+} binding. **(B)** Superimposition of the α-helices 3–6 between mTMEM16F in both Ca^{2+}-bound (light gray) and Ca^{2+}-free (dark grey) state and hTMEM16E in absence of Ca^{2+} (light blue) showing the TMEM16E α-helix-6 in the same conformation of the Ca^{2+} bound TMEM16F.

Only one of the two orthosteric Ca^{2+} binding sites is occupied

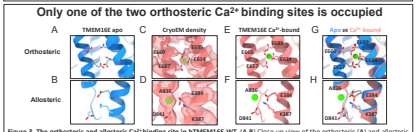
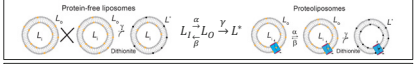


Figure 3. The orthosteric and allosteric Ca^{2+}-binding site in hTMEM16E-WT. (A-B) Close-up view of the orthosteric (**A**) and allosteric (**B**) Ca^{2+} binding sites of hTMEM16E in the absence of Ca^{2+}. **(C-F)** Close-up view of the cryoEM density maps and model (**E**) for the orthosteric (**C, E**) and allosteric (**D, F**) sites in 0.5 mM Ca^{2+}. Density for a single Ca^{2+} ion is visible in the orthosteric site. **(C)** Overlay of the orthosteric (**G**) and allosteric (**H**) sites show lack of rearrangements in the Ca^{2+} sites.

In vitro phospholipid Scramblase Assay



Purified hTMEM16E is a Ca^{2+}-dependent scramblase

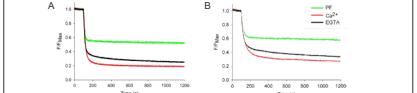
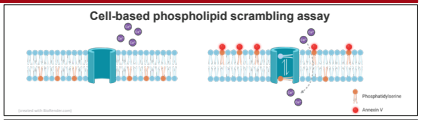


Figure 4. Functional characterization of purified hTMEM16E. A-B Representative time courses of dithionite-induced fluorescence decay in protein-free liposomes (green) or in hTMEM16E proteoliposomes with (red) or without (black) Ca^{2+}. Liposomes were formed from (**A**) soybean polar lipids and cholesterol, or (**B**) a 2:1:1 mixture comprised of 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE, C18:0), 1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-L-serine (POPS 16:0-18:1 PS) and 1-palmitoyl-2-oleoyl-glycero-3-phosphocholine (POPC, 16:0-18:1).

Cell-based phospholipid scrambling assay



The R582I GDD mutant is constitutively active in cells

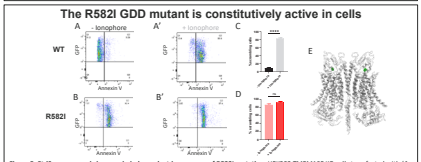


Figure 5. PtdSer exposure is ionomycin independent in presence of R582I mutation. HEK293 TMEM16F KO cells transfected with (**A, A'**) $TMEM16E_{GFP}$-GFP wild-type and (**B, B'**) p.Arg582Ile (R582I), were incubated and stained with Alexa647-conjugated Annexin-V and DAPI in absence (**A, B**) or in presence (**A', B'**) of Ca^{2+} ionophore. Data were collected with BD Fortessa Cell Analyzer. (**C, D**) Quantification of the cell population DAPI negative, GFP positive and Annexin-V positive in presence and in absence of Ca^{2+} ionophore. The cells expressing TMEM16E WT (**C**) show scrambling activity only in presence of Ca^{2+} ionophore, on the contrary TMEM16E R582I (**D**) expressing cells are active in the absence of Ca^{2+} ionophore. (**E**) hTMEM16E atomic model showing the position of the R582I (green) mutation in external loop between α-helices 5 and 6.

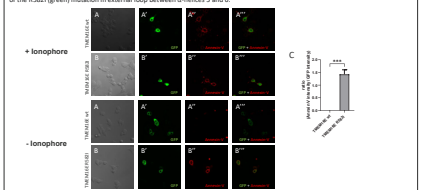


Figure 6. Cell-based scrambling assay in presence and absence of Ca^{2+} ionophore. (**A – B'''**) Confocal images of HEK293 TMEM16F KO cells transfected with (**A – A'''**) $TMEM16E_{GFP}$ GFP wild-type and (**B – B'''**) p.Arg582Ile (R582I), stained with Alexa555-conjugated Annexin-V in presence or in absence of Ca^{2+} ionophore. (**A, B**) show transmission light, (**A', B'**) green channel (GFP), (**A'', B''**) red channel (Alexa555) and (**A''', B'''**) merge of green and red channels. (**C**) Whereas the TMEM16E wild-type is not scrambling in absence of the Ca^{2+} ionophore, the mutation TMEM16E R582I is showing scrambling activity.

The R582I mutant weakens Ca^{2+} density in the orthosteric site

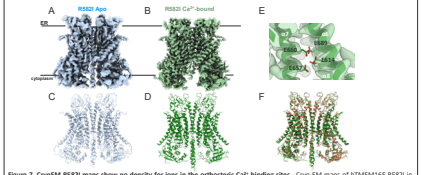


Figure 7. CryoEM R582I maps show no density for ions in the orthosteric Ca^{2+} binding sites. Cryo-EM maps of hTMEM16E R582I in digitonin in absence (**A**) and in presence (**B**) of calcium at 3.49 Å and 3.25 Å, respectively. Cartoon representation of the Ca^{2+}-free (light blue) (**C**) and Ca^{2+}-bound hTMEM16E-R582I (light green) (**D**) dimer. (**E**) Close view of the residues coordinating the orthosteric Ca^{2+} binding site for R582I (green) showing weak density for the R582I. The cryo-EM density of hTMEM16E-R582I map is superimposed on the respective refined model. (**F**) Superimposition of the Ca^{2+} bound structures of the hTMEM16E-WT (light pink) and the R582I displaying no structural rearrangement.

SUMMARY

Human TMEM16E

- In absence of Ca^{2+}, hTMEM16E adopts a pre-activated closed groove conformation, with a straight α6 helix and preformed Ca^{2+} binding site.
- The α3 and α4 helices are severely tilted compared to other TMEM16 scramblase structures.
- Ca^{2+}-binding does not induce conformational rearrangements in TMEM16E as the groove lining α3, α4, or α6 helices do not move.
- We detect density for only one Ca^{2+} ion in the orthosteric binding sites. Other TMEM16s homologues have two Ca^{2+} ions in these sites.
- Purified TMEM16E mediates Ca^{2+}-dependent scrambling when reconstituted in proteoliposomes.

GDD associated TMEM16E mutation

- The R582I GDD mutant, like other GDD mutants, is constitutively active in cells. Thus, basal cellular Ca^{2+} concentrations are sufficient to activate the mutant protein.
- CryoEM imaging shows that Ca^{2+} binding to the orthosteric site appears weakened in the mutant.
- Apo and Ca^{2+}-bound R582I hTMEM16E are very similar to the *WT apo* structure.

The Dynamic Interplay of Membrane Proteins is Lipid-Modulated

Lipid-Dependent Membrane Protein Dynamics and Interactions

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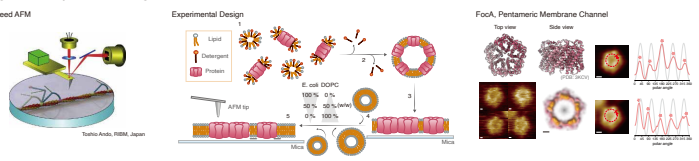
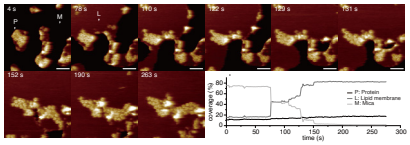
Abstract

The solvent of membrane proteins are the membrane lipids in which they are embedded. Therefore, the nature of the lipids that surround membrane proteins impact their dynamics and interactions. Unfortunately, how membrane proteins dynamically interact is difficult to study, and little is experimentally known how membrane proteins interplay in a membrane at the molecular scale. Here, we used high-speed atomic force microscopy (HS-AFM) dynamic imaging of a well-controlled bottom-up system consisting of two aquaporin-fold membrane proteins, pentameric FocA and tetrameric GlpF, that interact in membranes composed of varying amounts of DOPC and E. coli lipids. We find that the lipid environment significantly influences membrane protein mobility and interaction, with increased E. coli lipid content reducing protein movement, while DOPC-rich environments promote mobility. Furthermore, the supramolecular structure of the membrane proteins and protomer interactions in clusters are also lipid modulated, where E. coli lipids favor specific protein-protein interactions, whereas greater interaction variability is found in DOPC. These findings highlight the role of lipids in regulating protein diffusion and interactions and suggest that lipid-protein interaction energetics play a significant role in controlling membrane protein interactions and supramolecular assembly.

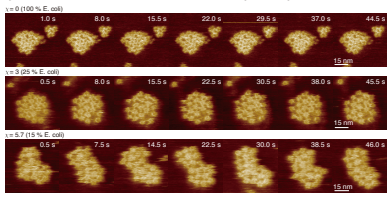
Background & Experimental Design



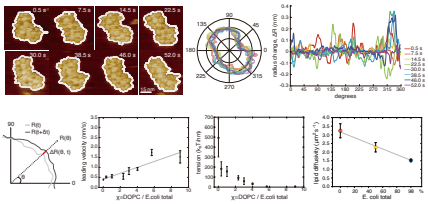
Lipid membrane fusion process with reconstituted FocA liposomes on a mica



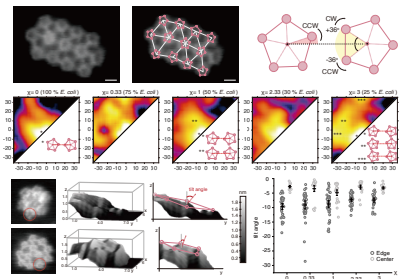
Dynamics of Protein Clusters Under Different Lipid Compositions



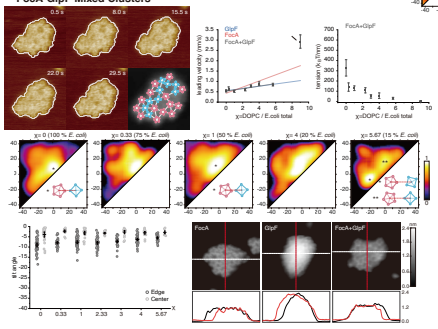
Protein Cluster Dynamics and Energetics in Varying Lipid Compositions



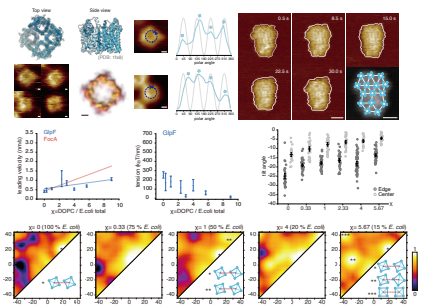
FocA-FocA Interactions are Lipid-Dependent



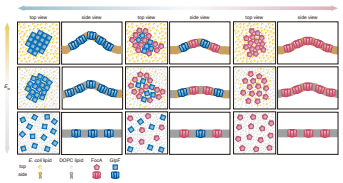
FocA-GlpF Mixed Clusters



GlpF-GlpF Interactions are Lipid-Dependent



Lipid-dependent and protein-dependent membrane protein clustering



Acknowledgments

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We thank the WCM Imaging Facility (Optical Microscopy Core) for their support with FRAP experiment.

Clinical Research Studies

1. **Evaluation of Wearables for Preoperative Cardiorespiratory Fitness Screening and Risk Stratification in Geriatric Surgery**
   PI: *Richard Boyer, MD, PhD*
   Protocol #: 21-04023531
   This prospective, observational clinical study tests the hypothesis that wearable measurements of cardiorespiratory fitness (CRF) are predictive of postoperative complications in older adult patients undergoing major surgery.

2. **Identifying Neurocognitive Outcomes and Electroencephalography Correlates in Elderly Patients Following Transcatheter Aortic Valve Replacement Performed Under Sedation: A Pilot Study**
   PI: *Diana Khatib, MD*
   Protocol #: 21-01023123
   The overall purpose of this pilot study is to examine the incidence and prevalence of post-operative delirium (POD) and associated neurocognitive changes in patients undergoing transcatheter aortic valve replacement (TAVR) procedures and additional procedures under monitored anesthetic care (MAC). Additionally, Sedline EEG monitoring and recording are completed during the procedure to explore the possible correlation between intraprocedural EEG changes and the development of neurocognitive changes.

3. **A Sequenced Strategy for Improving Outcomes in People with Knee Osteoarthritis Pain (SKOAP)**
   PI: *Neel Mehta, MD*
   Protocol #: 20-09022645
   This is a multi-center, randomized, controlled trial with two phases to investigate both non-invasive treatments, including physical therapy and duloxetine, as well as minimally invasive treatments, including steroid injections, GNB, and RFA, to treat knee osteoarthritis pain. It is conducted in collaboration with John's Hopkins University and Duke University.

4. **A 5-year Superion(R) IDS Clinical Outcomes Post-Approval Evaluation (SCOPE)**
   PI: *Neel Mehta, MD*
   Protocol #: 21-04023564
   This is a prospective, multi-center, single-arm observational post-approval study to compile real-world outcomes as well as evaluate the safety and effectiveness of the Superion® IDS in routine clinical practice. The Superion® IDS is an FDA approved non-fusion, spinal column load-sharing device that uses "indirect" compression to stabilize the spine for patients with lumbar spinal stenosis.

5. **Trajectories of Recovery after Intravenous propofol versus inhaled VolatilE anesthesia (THRIVE) trial**
   PI: *Kane Pryor, MD*
   Protocol Number #: 23-09026456
   This is a multi-institutional, randomized, comparative effectiveness trial to determine whether total intravenous or inhaled volatile anesthesia yields superior patient experience, safety, and recovery. THRIVE is conducted in collaboration with The University of Michigan and Washington University in St. Louis.

6. **Impact of surgical revascularization strategy on left ventricular function, myocardial perfusion and clinical outcomes**
   PI: *Lisa Rong, MD, MSCE, FASE, FACC*
   Protocol #: 21-05023605
   This is a prospective study designed to test the central hypothesis that early improvement in myocardial strain will be less with multiple arterial grafting (MAG) than single arterial grafting (SAG) (stemming from less initial increase in myocardial perfusion) requiring increased pharmacologic support (vasopressor and inotropes), and that early left ventricular (LV) strain recovery will predict better clinical outcomes than conventional indices (LV ejection fraction, volume).

7. **Non-Invasive Monitoring of Brain Activity in Altered Conscious States**
   PI: *Seyed A. Safavynia, MD, PhD*
   Protocol #: 18-01018908
   This study will use functional near-infrared spectroscopy (fNIRS) and electroencephalography (EEG) to monitor brain activity in delirious and lucid states during recovery from general anesthesia. By analyzing hemodynamic and electrical activity within the brain, we will quantify differences in cerebral hemodynamics and cortical connectivity during episodes of PACU delirium. This study is sponsored by the Foundation for Anesthesia Education and Research and the Charles A. Frueauff Foundation.

8. **Feasibility Study for Measuring Frailty with Passive, In-Situ Gait Monitoring**
   PI: *Joseph Scarpa, MD, PhD*
   Protocol #: 21-01023137
   This is a feasibility study that aims to assess the predictive capability and social acceptability of contactless sensors (depth cameras and floor-mounted accelerometers) to predict frailty and postoperative outcomes. In collaboration with Virginia Tech Civil and Environmental Engineering.

9. **Molecular Profiling of Surgical Inflammation and Postoperative Complications**
   PI: *Joseph Scarpa, MD, PhD*
   Protocol #: 24-05027534
   This is a prospective, observational, cohort study that seeks to identify molecular characteristics of immune cells and peripheral blood to predict postoperative pain and cognition dysfunction. It also strives to characterize age- and sex-specific immune responses to surgical inflammation.

10. **Cerebrovascular Dynamics and Cognition in Patients with Advanced Heart Failure and Left-Ventricular Assist Devices**
    PI: *Julia Scarpa, MD, PhD*
    Protocol #: 24-03027250
    The overall objective of this study is to determine the role of cerebral hemodynamics in cognitive outcomes for advanced heart failure patients receiving Left-Ventricular Assist Devices (LVADs). Patients will be cognitively assessed, as well as monitored with an ambulatory physiologic research device (NINscan) to assess neurophysiology and cerebrovascular dynamics. We hypothesize that we will be able to detect an objective cerebrovascular signature prior to LVAD implantation that can predict postoperative cognitive function, quality of life (QoL), and Days Alive and at Home (DAH) at 6 and 12 months.

11. **Frailty and Autonomic Dysfunction as Predictors of Intra- and Post-operative Morbidity: A Prospective Study**
    PI: *Julia Scarpa, MD, PhD*
    Protocol #: 22-03024487
    The overall objective of this prospective, observational study is to determine the role of preoperative frailty and autonomic dysfunction on perioperative hemodynamic stability and morbidity. Subjects will complete questionnaires and will be monitored with an ambulatory physiologic research device (NINscan) throughout the preoperative evaluation, the intraoperative course, and the immediate postoperative period to assess cardiovascular stability, cerebrovascular parameters, and perfusion-related morbidity. We hypothesize that preoperative frailty and autonomic function classifications will correlate with increased incidence and severity of perioperative hemodynamic instability and morbidity.

12. **PENG vs Femoral Block for Hip Fracture Pain in the Emergency Department, A Pragmatic Cluster Crossover Trial**
    PI: *Tiffany Tedore, MD*
    Protocol #: 24-07027709
    This cluster crossover study plans to compare the efficacy of the PENG block to the femoral block for the reduction in hip fracture pain prior to surgery and determine whether the blocks have different efficacy in intracapsular versus extracapsular hip fractures.

13. **Assessment of Preoperative Gastric Content with Ultrasound in Patients taking GLP1 Agonists**
    PI: *Marissa Weber, MD*
    Protocol Number #: 23-09026457
    This prospective study investigates delayed gastric emptying in surgical patients taking GLP1 agonists. Point-of-Care Gastric Ultrasound (POCUS) will be used to investigate the presence of preoperative full stomachs in these patients. It is conducted in collaboration with the Hospital for Special Surgery.

Chart, Observational, & Survey Studies

1. **Low Dose Naltrexone (LDN) Dosing Regimen and Side Effect Patient Survey**
   PI: *Neel Mehta, MD*
   Protocol #: 22-11025360
   This study uses a survey questionnaire to gather information about LDN dosing regimens and side effects, and which chronic pain conditions LDN was prescribed for.

2. **Delayed Recovery of Consciousness after Anesthetic Coma in Survivors of COVID-19 Hypoxemic Respiratory Failure**
   PI: *Seyed A. Safavynia, MD, PhD*
   Protocol #: 20-08022490
   This is a retrospective analysis of clinical data from critically-ill NewYork-Presbyterian/Weill Cornell COVID-19 patients, with a primary aim to characterize functional neurophysical changes associated with delayed recovery of consciousness in severe COVID. It is conducted in collaboration with the Columbia University Irving School of Medicine and sponsored by the JumpStart Research Career Development Grant.

Registry Studies

1. **Leveraging ROTEM to Greater Advantage**

   PI: *Meghann Fitzgerald, MD, Andrew Milewski, MD, PhD*
   Protocol #: 23-08026373
   This protocol establishes a retrospective and prospective registry of ROTEM curves and coagulation profiles from ROTEM tests performed across this institution. Through a variety of analytical and machine-learning approaches, we aim to develop algorithms that predict the trajectories of ROTEM curves in real time to enable early estimation of ROTEM parameters and, consequently, to accelerate decisions making for targeted transfusion therapy in bleeding patients.

2. **Weill Cornell Center for Human Rights Registry**
   PI: *Gunisha Kaur, MD, MA*
   Protocol #: 18-10019677
   This study aims to create a database for clients seeking services at the Weill Cornell Center of Human Rights (WCCHR).

3. **Weill Cornell Center for Human Rights Registry Torture Scar Database Project**
   PI: *Gunisha Kaur, MD, MA*
   Protocol #: 24-04027389
   This study aims to use the Weill Cornell Center of Human Rights (WCCHR) Registry database to compile a repository of torture scar images, with the aim of developing an AI-based system for identification and classification of these scars. Through machine learning (ML), we seek to develop a robust model capable of recognizing torture scars with high accuracy.

4. **Spinal Cord Stimulator Implant Registry**
   PI: *Neel Mehta, MD*
   Protocol #: 18-11019714
   This study aims to create a registry that collects longitudinal data from the approximately 300-400 patients pre- and post-implantation of SCS currently treated by the Pain Management clinic. We intend to collect over the lifetime of the device and include factors like trends comparing efficacy against various diagnoses, opioid use, and pain scores.

5. **Creation of an electroencephalography (EEG) registry to study functional neuronal changes in patients with altered conscious states**
   PI: *Seyed A. Safavynia, MD, PhD*
   Protocol #: 24-04027309
   The study aims to create a registry of subjects with EEG and clinical parameters which encompass a variety of neurophysiological profiles. We will then identify the relative contributions and interactions of clinical parameters with the development of distinct EEG signatures and examine the relationship between these EEG signatures and neurological outcomes.

6. **Pediatric Difficult Intubation (PeDI) Registry - Improving Safety and Quality of Airway Management in Children with Difficult Airways**
   PI: *Aarti Sharma, MD*
   Protocol #: 16-02016988
   This is an observational, multi-center data collection study to establish a registry that will allow participating institutions to assess the outcomes of care of children with Difficult Direct Laryngoscopy (DDL) and to facilitate comparison to the other institutions' difficult airway management practices and outcomes. It is conducted in collaboration with the Children's Hospital of Philadelphia.

7. **Perioperative Investigative Collaboration for Neonates, Infants, and Children**
   PI: *Roshan Patel, MD*
   Protocol #: 23-03025814
   This study aims to create a multicenter collaborative registry framework to capture observational data relating to the perioperative course and management of infants and children receiving anesthesia care.

8. **Perioperative Transesophageal Echocardiography Registry**
   PI: *Lisa Q. Rong, MD*
   Protocol #: 17-08018484
   The goal of this study is to establish a retrospective and prospective pre-, intra-, and postoperative anesthesia echocardiography data registry for subjects who have received anesthesia services for cardiac surgery with intraoperative transesophageal echocardiography at New York-Presbyterian Hospital/Weill Cornell Medical College since 2010.

9. **Chronic Pain Registry**
   PI: *Lisa Witkin, MD*
   Protocol #: 17-05018203
   This study aims to establish a retrospective chronic pain patient data registry for patients with chronic pain, and to use the patient data registry, Practice Based Evidence (PBE), and Clinical Practice Improvement (CPI) methodology to identify specific pain management interventions that are most effective for specific patient types with chronic pain.

10. **The Development and Implementation of a Collaborative Health Outcomes Information Registry for the Weill Cornell Multidisciplinary Spine Center**
    PI: *Lisa Witkin, MD*
    Protocol #: 17-01017897
    This study aims to develop and implement a patient-reported outcomes data collection system for the Weill Cornell Center for Comprehensive Spine Care. Ideally, this will allow ongoing treatment to be determined by the patients' response and progress and can improve evidence-based medicine guidance of treatment. It is sponsored by the Applebaum Foundation.

Global Health Studies

1. **Chronic Pain Diagnosis and Treatment in Torture Survivors**
   PI: *Gunisha Kaur, MD, MA*
   Protocol #: 20-10022730
   The goal of this 3-part study is to characterize the diagnosis of chronic pain in torture survivors. This investigation is funded by the National Institutes of Health K23 Grant.

   Aim 1: Study Aim 1 assesses whether the application of a validated pain screen, the Brief Pain Inventory Short Form, can supplement the United Nations Istanbul Protocol and improve its sensitivity for pain detection, as compared to the gold standard (a pain specialist evaluation).

   Aim 2: This sub-study aims to qualitatively assess the challenges and acceptability of our proposed, evidence-based somatic pain treatment model - physical therapy and/or non-opioid analgesics and/or trigger point injections - and to receive feedback in terms of challenges, limitations, and acceptability of the interventions.

   Aim 3: This sub-study aims to assess the feasibility of recruiting and retaining participants in a digital pain treatment program over six months by enrolling 20 participants into a digital program of pain, stress, and cardiovascular health monitoring.

2. **Digital Solutions to Reduce Maternal Morbidity and Mortality in Pregnant Refugee Women**
   PI: *Gunisha Kaur, MD, MA*
   Protocol #: 24-01026913
   The overall objective of this project is to increase the detection of gestational hypertension and reduce the incidence of severe maternal morbidity and mortality among pregnant refugee women. The goal of this specific investigation is to maximize the performance of a digital cardiovascular monitoring system to detect hypertension in pregnant refugees through clinical training and validation.

Education Studies

1. **Pain Simulation Education Curriculum**
   PI: *Daniel Pak, MD*
   Protocol #: 22-01024333
   The purpose of this project is to collect and analyze the outcome measures of the Weill Cornell Tri-Institutional Pain Fellows in using a spine simulator model on several different simulated procedures and analyze this information to measure milestones and evaluate their performance throughout the year. In addition, survey responses pre-session and post-session will be used to collect feedback from the fellows.

2. **Anesthesiology Education Research Registry**
   PI: *Kane Pryor, MD*
   Protocol #: 14-03014915
   This study aims to design and establish a registry to assess the utility of various metrics in predicting anesthesiology resident performance outcomes.

Center for Perioperative Outcomes Studies

1. **Multicenter Perioperative Outcomes Group (MPOG) and Anesthesiology Performance Improvement and Reporting Exchange (ASPIRE) Performance Site**
   PI: *Hugh C. Hemmings, MD, PhD*
   Protocol #: 12-08012817
   The primary objective of this study is to assess the impact of provider feedback on anesthesiology quality measures on patient outcomes. This project will provide Weill Cornell Medicine, NYP Brooklyn Methodist Hospital, and NYP Queens Anesthesiologists with individualized feedback of their performance on anesthesiology quality metrics. Their individualized performance is based on information extracted from the anesthesia information management system (AIMS). This feedback, given on a monthly basis, will hopefully lead to positive behavior changes among the anesthesiology providers, which will result in better care for patients.

2. **Primary Graft Dysfunction in the Black Heart Transplant Recipient with SDOH**
   PI: *Mandisa Jones, MD*
   Protocol #: 23-03025844
   The proposed study will explore risk factors associated with primary graft failure in Black heart transplant recipients and assess the contribution of severe primary graft failure to in-hospital and one-year mortality within this population. The primary outcome is a binary measure of primary graft failure within 24 hours of transplant. Secondary outcomes are mortality during the transplant admission and mortality in the first-year-post-transplant.

3. **Reference values for post-induction hemodynamic measures in pediatric patients undergoing general anesthesia for non-cardiac surgery**
   PI: *Kane O. Pryor, MD*
   Protocol #: 23-02025736
   The primary objective of this study is to define reference ranges for intraoperative hemodynamic measures (heart rate, systolic blood pressure, diastolic blood pressure) for pediatric patients classified as ASA-PS 1 or 2 and undergoing general anesthesia for both operative and non-operative non-cardiac procedures according to age group, sex, and body temperature. The primary goal is to develop a holistic hemodynamic reference standard for use in the intraoperative setting.

4. **Multicenter Analysis of Benzodiazepine Use in Patients Undergoing Non-Operating Room Cardiac Procedures**
   PI: *Lisa Q. Rong, MD*
   Protocol #: 22-04024670
   In this retrospective cohort study, we use a multicenter perioperative electronic medical record data to identify practice patterns regarding benzodiazepine use in non-operating room cardiac procedures that require anesthetic management. We hypothesize that patient, clinician, and institutional factors will be independently associated with benzodiazepine use during non-operating room anesthesia (NORA) procedures, and that the majority of the variation in benzodiazepine use will be explained by institution and clinician rather than patient factors.

5. **Evaluation of a Novel Patient Monitor in the Perioperative Setting**
   PI: *Zachary A. Turnbull, MD, MBA, MS*
   Protocol #: 22-05024803
   This is a dual-center, pre-/post-, observational study. In this proposed study, we aim to evaluate the impact of a novel patient monitor, known as the Philips Visual Patient Monitor (VP), on deviations from expected physiologic ranges. This novel monitor, which was developed in a collaboration between faculty at University of Zurich Hospital and Philips, features a patient aviator to provide visual cues for common physiologic deviations, such as bradycardia.

6. **SONAR: Perioperative Readiness Tool?**
   PI: *Zachary A. Turnbull, MD, MBA, MS*
   Protocol #: 23-01025642
   This study seeks to leverage SONAR (an acronym for Surgery, Operating Room, Preoperative Nursing, Anesthesia, Preoperative Complete), an electronic tool in Epic that visually tracks preoperative readiness, to improve first case on time start rates and the case turnover time by allowing care teams to proactively be aware of and identify gaps in OR case preparation.

7. **The impact of team familiarity on operational efficiency and postoperative outcomes**
   PI: *Zachary A. Turnbull, MD, MBA, MS*
   Protocol #: 23-09026546
   The primary objective of this study is to quantitatively measure the relationship between team familiarity, operational efficiency, and postoperative outcomes. Team familiarity will be defined as how often attending anesthesiologists and surgeons have worked together. Our aim is to study the relationship between team familiarity and (1) operational efficiency, which will focus on post-operative time points (procedure end to anesthesia end time) and (2) PACU outcomes (LOS and pain control measurements).

8. **Disparities in anesthesia type received for cesarean delivery and investigation into racial and ethnic concordance between the patient and anesthesia team and patients' satisfaction with pain management during cesarean delivery**
   PI: *Robert S. White, MD, MS*
   Protocol #: 23-12026870
   The overall purpose of this study is to use United States Anesthesia Partners (USAP) staff files and the USAP clinical case and quality data warehouse to examine if patient race/ethnicity or other social determinants of health (such as geocoded area deprivation index and related geospatial measures) are associated with the type of anesthesia (general or regional) administered in cesarean deliveries. A secondary objective of this study is to look at patient outcomes by type of anesthesia (general or regional) including patient length of stay, markers of severe maternal morbidity (SMM), and patient completed satisfaction survey.

9. **Health Disparities in Obstetrical Care and Delivery Outcomes Before and After Implementation of an Enhanced Recovery After Surgery Protocol**
   PI: *Robert S. White, MD, MS*
   Protocol #: 21-10024035
   The first aim of this study is to study the effect that Enhanced Recovery After Surgery for Cesarean Delivery (ERAS-CD) implementation has on postoperative complications and readmissions after planned and unplanned cesarean deliveries. We also plan to analyze the impact of patient race/ethnicity, spoken language, and insurance status on postoperative complications and readmissions.

10. **MPOG: Racial disparities in cesarean delivery anesthesia type by race/ethnicity and social determinants of health**
    PI: *Robert S. White, MD, MS*
    Protocol #: 23-04025937
    The overall purpose of this study is to use the MPOG database to examine if patient race/ethnicity is associated with the type of anesthesia (general or regional) administered in cesarean deliveries. Our primary covariate of interest is recorded patient race/ethnicity (unordered: white [reference category], Black, Hispanic, Other, or Unknown). Other patient-level variables that will be abstracted for each admission include demographic information (age; ASA PS classification system score 1-6) and a validated obstetric comorbidity index used to predict maternal end-organ injury or inpatient mortality, which has also been shown to predict general anesthesia for cesarean delivery use.

11. **Multicenter Perioperative Outcomes Group (MPOG) Geo-Coding and Sensitivity of ASPIRE Process Metrics to Social Determinants of Health**
    PI: *Robert S. White, MD, MS*
    Protocol #: 23-07026284
    This is a multicenter, retrospective study. We will use quantitative methods to investigate individual clinicians' equitable adherence with guidance-congruent surgical care. Our hypotheses are (1) Patient Black race predicts passing a composite of certain ASPIRE metrics and (2) Census tract-level (CT-level) social determinants of health (SoDH) "Neighborhood disadvantage" (ND) predicts passing ASPIRE metrics.

12. **The Development and Implementation of a Collaborative Health Outcomes Information Registry (CHOIR) for the Weill Cornell Multidisciplinary Spine Center**
    PI: *Lisa Witkin, MD, MS*
    Protocol #: 17-01017897
    This study aims to develop and implement a patient-reported outcomes data collection system for the Weill Cornell Center for Comprehensive Spine Care. Ideally, this will allow ongoing treatment to be determined by the patients' response and progress to improve evidence-based medicine guidance of treatment.

13. **Assessment of anesthetic considerations for polio survivors**
    PI: *Hannah Wunsch, MD*
    Protocol #: 24-04027402
    The overall purpose of this study is to determine whether patients with a known history of polio receive different anesthetic care compared with similar individuals without polio AND whether anesthetic complications (e.g. slow wakeup, postoperative respiratory failure) differ for those who have a known history of polio compared with similar individuals without polio.

14. **Assessment of care and outcomes for patients treated for tuberculosis in 1947 during the MRC streptomycin trials**
    PI: *Hannah Wunsch, MD*
    Protocol #: 24-04027312
    The overall purpose of this study is to describe, in detail, the characteristics of the patients and the hospital care provided to individuals in the Streptomycin trials published in 1948. This work will elucidate the patient experience and details of the care provided in this important historic trial.

15. **Intraoperative blood pressure reference values for neonates undergoing non-cardiac surgery under general anesthesia**
    PI: *Hannah Wunsch, MD*
    Protocol #: 24-04027342
    The primary aim of this study is to describe the distribution of values for blood pressure (BP, both ascertained from invasive and non-invasive measurements) in term and preterm neonates undergoing noncardiac surgery under GA at three time points: before induction, before incision, and post-incision. The goal is to create a multidimensional model of BP reference ranges, factoring in age (chronological, gestational, and postmenstrual age), weight, and height.

16. **Redefining temperature cut-offs for infection concern in older adults**
    PI: *Hannah Wunsch, MD*
    Protocol #: 24-07027723
    The purpose of this study is to redefine temperature cut-offs for infection concern in older adults using TriNetX data and EHR data from WCM, Columbia, and the University of Miami Hospital and Clinics. Our objectives are to (1) describe the temperatures of ICU patients and identify current temperature triggers at which infection is suspected in U.S. ICU patients, stratified by age and other potential modifiers, (2) characterize ICU patients' baseline (outpatient) temperatures and evaluate whether the change in temperature from their individual baselines (delta t) during critical illness is an earlier and more sensitive indicator of infection than standard temperature cutoffs, and (3) create a personalized definition of fever to more accurately prompt concern for infection.

Upcoming Studies

1. **Molecular Dynamics of Human Epithelial Wound Healing**
   PI: *Jim Gonzalez Castellanos, MD, PhD, MFA*
   Protocol #: 24-08027804
   This observational study aims to understand the clinical, cellular, and microbiologic characteristics associated with epithelial wound healing in burn ICU patients. The hypothesis of this study is that clinical, cellular, and microbiologic signatures stratify epidermal wound healing, and novel markers will allow for improved prediction of epidermal wound healing, skin graft rejection and infection susceptibility. Burn patients with wounds requiring surgical intervention will be considered for enrollment in this study. Clinical data, surgical biopsies and skin swabs will be collected in the operating room and/or ICU at the initiation of surgical intervention. Subsequent samples will be collected between week 0 and 104, depending on surgical need for intervention.

2. **The PROTECT Trial: PeRiOperTive Enhancement of Cognitive Trajectory**
   PI: *Lisbeth Evered, PhD*
   Protocol #: Pending
   The primary aim of this multisite, prospective, pragmatic, randomized controlled trial is to demonstrate that older people (65 years and over) who undergo supported perioperative optimization strategies have a decreased incidence of perioperative neurocognitive disorders (PND) over 3 months compared to people who receive standard care. Patients will be randomized to receive perioperative optimization (treatment arm) or current standard of care (control arm). Both study groups will undergo daily delirium assessments throughout the postoperative period, alongside evaluation of perioperative neurocognitive disorder at baseline and 3 and 12 months postoperatively.

3. **The Society for the Advancement of Transplant Anesthesia (SATA) - Liver Transplant Anesthesia Quality Improvement Database**
   PI: *Christine Lennon, MD*
   Protocol #: 24-10028045
   The purpose of this study is to gain insight into preoperative patient condition, intraoperative surgical and anesthetic treatment practice, anesthetic outcomes and complications, and patient outcomes in the care of liver transplant recipients at the center level for research and quality improvement, as well as to establish practice patterns and knowledge of outcomes on a national scale.

4. **A Prospective, Multi-Center, Randomized, Controlled Trial to Compare the Safety and Efficacy of Ultra Low Frequency Spinal Cord Stimulation Plus Conservative Medical Management (CMM) to CMM Alone in the Treatment of Chronic Axial Low Back Pain with Prominent Nociceptive Etiology (fULFill Study)**
   PI: *Neel Mehta, MD*
   Protocol #: 24-10028108
   This is a prospective, multi-center, randomized, controlled trial in which subjects with chronic, intractable axial low back pain with prominent nociceptive features will be randomized 2:1 into either Ultra Low Frequency (ULF) therapy combined with conventional medical management (CMM) or CMM alone. It is conducted in collaboration with Presidio Medical, Inc.

5. **AI-Powered End-of-Life Care Training**
   PI: *John Rubin, MD*
   Protocol #: 24-10028129
   This study aims to improve the communication skills and perceived confidence of residents who interact with patients approaching the end of life. It strives to accomplish this through the utilization of an Artificial Intelligent Conversational Agent that has already been developed and is capable of realistic conversations to train physicians to have difficult conversations.

Recruitment Completed Studies

1. **Multicenter Intraoperative Discomfort during Cesarean Delivery**
   PI: *Sharon Abramovitz, MD*
   Protocol #: 23-10026623
   This is a multi-center prospective observational cohort study to better understand the intra-operative pain experience during cesarean delivery with neuraxial anesthesia. It is conducted in collaboration with Stanford University.

2. **Cognitive and Functional Consequences of COVID-19**
   PI: *Lisbeth Evered, PhD*
   Protocol #: 20-08022498
   This is an observational pilot study that will utilize responses from an online survey completed by COVID-19 positive patients to identify the rate of cognitive decline, disability and psychological factors in COVID-19 positive patients at 6-24 months post positive test and determine a severity-response in outcomes between those who were treated as outpatients vs ward inpatients vs ICU intubated and ventilated patients.

3. **Pediatric Craniofacial Surgery Perioperative Registry (PCSPR)**
   PI: *Jennifer Lee, MD*
   Protocol #: 15-04016130
   This is a multi-center registry to capture information relating to the perioperative course and management of children undergoing craniofacial reconstructive surgery. The aggregate multi-institutional data set will be used for benchmarking for national quality improvement efforts. It is conducted in collaboration with the Children's Hospital of Philadelphia.

4. **Self-Management of Chronic Pain Using PainDrainer**
   PI: *Neel Mehta, MD*
   Protocol #: 19-04020168
   This is a single-arm open concept trial (SAC) to evaluate if PainDrainer, a digital pain coach based on artificial intelligence (AI), will improve the self-management of chronic pain and increase quality of life. It is conducted in collaboration with Lund University.

5. **PROtective ventilation with high versus low PEEP during one-lung ventilation for THORacic surgery - PROTHOR: A randomized control trial**
   PI: *Matthew Murrell, MD, PhD*
   Protocol #: 17-01017890
   This is a multi-center, randomized, controlled trial investigating the use of a higher or lower PEEP strategy in reducing postoperative pulmonary complications in patients undergoing thoracic surgery with one-lung ventilation. It is conducted in collaboration with Technische Universität Dresden.

6. **Carotid Doppler Imaging Correlation with Pulmonary Artery Catheters As A Marker For Fluid Responsiveness**
   PI: *James Osorio, MD*
   Protocol #: 19-11021076
   This prospective pilot study evaluates the use of carotid doppler imaging, specifically measuring carotid blood flow, corrected carotid flow time, and respiratory variation in peak carotid velocity, to assess if these measures can be used as a reliable marker for fluid responsiveness when compared to the use of Pulmonary Artery catheters in mechanically ventilated, postoperative cardiac surgery patients.

7. **Pilot Study: Determining the Presence of Perioperative Optic Nerve Sheath Diameter Changes after Cardiac Surgery**
   PI: *James Osorio, MD*
   Protocol #: 19-09020866
   The primary objective of this study is to assess if there is an increase in optic nerve sheath diameter (ONSD) after cardiac procedures. Additionally, as a secondary objective, the study is evaluating if an increase in ONSD may be associated with an increased risk of postoperative delirium.

8. **A Randomized Controlled Study to Evaluate the Safety and Effectiveness of Boston Scientific Spinal Cord Stimulation (SCS) Systems in the Treatment of Chronic Low Back and/or Leg Pain with No Prior Surgeries (WaveWriter-SOLIS)**
   PI: *Daniel Pak, MD*
   Protocol #: 21-04023563
   This prospective, multi-center randomized controlled trial with a parallel group design evaluates the safety and effectiveness of the Boston Scientific WaveWriter™ Spinal Cord Stimulation (SCS) Systems with multiple modalities compared to Conventional Medical Management (CMM) in patients with chronic low back and/or leg pain who have not undergone spinal surgery.

9. **Benzodiazepine-free cardiac anesthesia for the reduction of postoperative delirium (B-Free)**
   PI: *Kane Pryor, MD*
   Protocol #: 19-11021136
   This is a pragmatic, multicenter, cluster crossover trial to evaluate whether a policy limiting the use of intraoperative benzodiazepine (B-Free) reduces postoperative delirium when compared to a policy of liberal benzodiazepine administration. The trial is run by the Population Health Research Institute (PHRI) and is endorsed by the Canadian Perioperative Anesthesia Clinical Trials group. The study is funded by the Canadian Institutes of Health Research (CIHR).

10. **Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome II (OPTIMISE II) Trial**
    PI: *Kane Pryor, MD*
    Protocol #: 18-04019164
    This is an open, international, multi-center, randomized controlled trial of cardiac output-guided fluid therapy with low dose inotrope infusion compared to standard of care in subjects undergoing major elective gastrointestinal surgery. It is sponsored by Queen Mary University of London.

11. **Preoperative Transglomerular Gradient and the Risk of Developing AKI in Patients undergoing Elective Cardiac Surgery: The PRO - AKI study**
    PI: *Ankur Srivastava, MD*
    Protocol #: 22-03024560
    The primary objective of this study is to investigate the effect of the preoperative transglomerular pressure gradient on the development of acute kidney injury (AKI) in patients undergoing elective cardiac surgery. The secondary objective of this study is to investigate the effects of preoperative pulmonary artery pressure, cardiac output, cardiac index, anemia, and MAP on the development of AKI in patients undergoing elective cardiac surgery.

12. **A Survey of Obstetrical Anesthesia Health Equity Practices at Academic Centers in the United States (US)**
    PI: *Robert White, MD, MS*
    Protocol #: 22-09025245
    This study utilized an internet-based Qualtrics survey questionnaire to collect qualitative information regarding obstetrical anesthesia practice patterns concerning healthcare disparities and efforts to address these disparities on the labor and delivery unit. It is sponsored by the Foundation for Anesthesia Education & Research.

13. **Patients Perspectives on Non-Utilization of Neuraxial Labor Analgesia During Labor and Delivery**
    PI: *Robert White, MD, MS*
    Protocol #: 22-05024854
    This is a qualitative study that utilized open-ended individual interviews to understand patient-level factors (ex: maternal age, education, culture, pain perception, and parity) for declining or waiving access to neuraxial labor analgesia during labor and delivery. It is sponsored by the Foundation for Anesthesia Education & Research.

14. Applying the Patient Priorities-Aligned Decision-Making Model in a Pain Management Setting

PI: *Lisa Witkin, MD*

Protocol #: 22-08025126

This study utilized an anonymous Qualtrics survey to evaluate the attitudes, preferences, and beliefs regarding patient-centered care models of board-certified pain management physicians across the country from a variety of backgrounds and practice settings as well as their willingness to adopt a patient priorities model.

15. Physicians' Perspectives and Utilization of Patient-Reported Outcomes to Guide Clinical Decision-Making

PI: *Lisa Witkin, MD*

Protocol #: 22-01024354

This is a qualitative study that used semi-structured interviews to evaluate the implementation of an electronic patient-reported outcomes registry in the pain management division of Weill Cornell Medicine in order to understand providers' beliefs and experiences using the data and how it affects their patient interactions and discussions, and how it guides their clinical decision-making.