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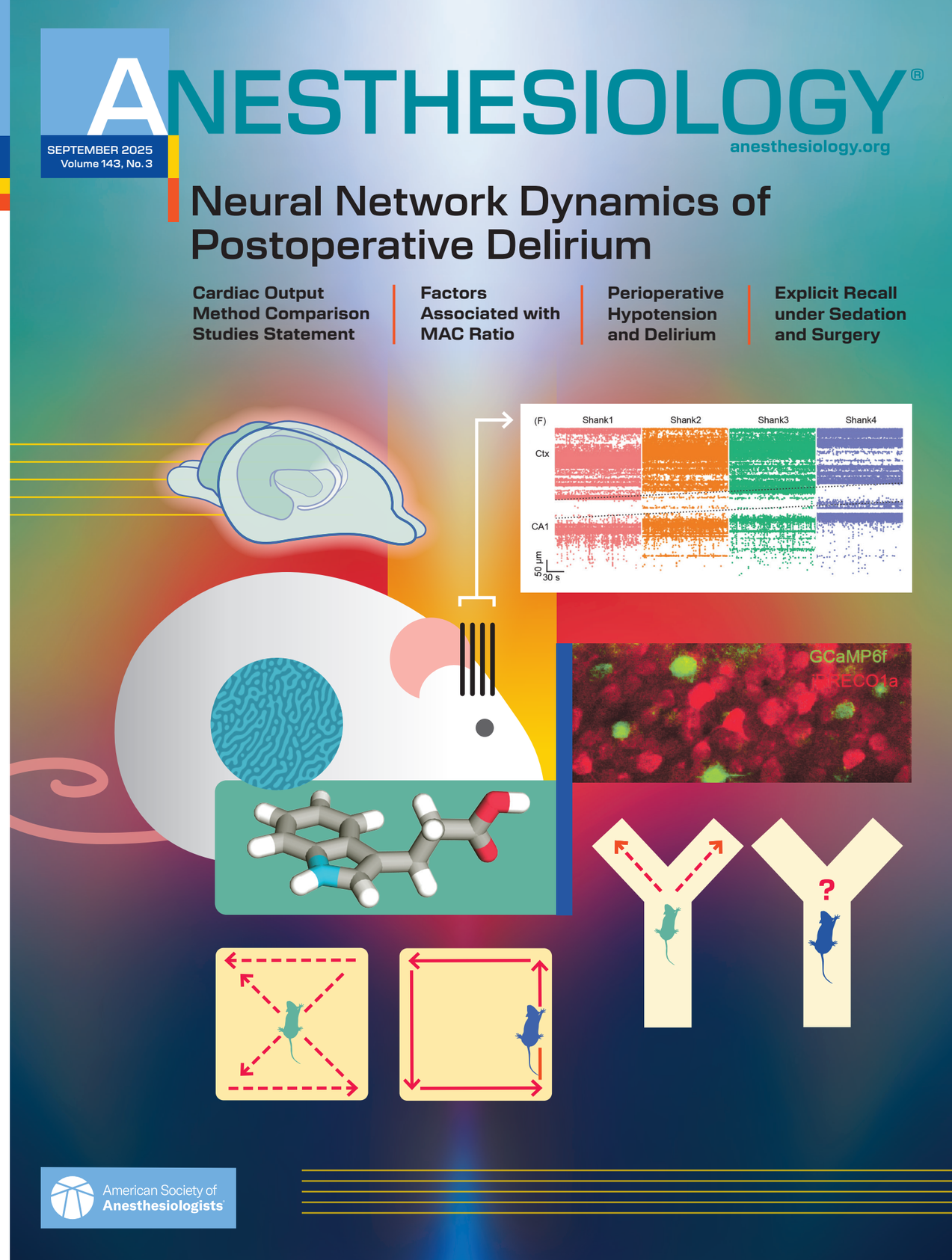
Neural Network Dynamics of Postoperative Delirium

Cardiac Output Method Comparison Studies Statement

Factors Associated with MAC Ratio

Perioperative Hypotension and Delirium

Explicit Recall under Sedation and Surgery



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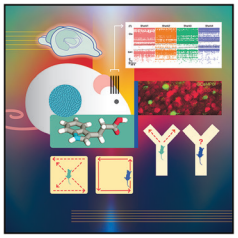
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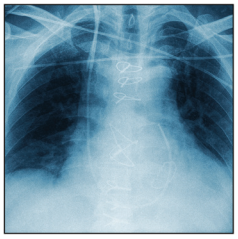
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THIS MONTH IN
ANESTHESIOLOGY®



625 Hippocampal Neural Dynamics and Postoperative Delirium–like Behavior in Aged Mice

Postoperative delirium is an important clinical entity, especially in at-risk populations. The electroencephalographic features of postoperative delirium are incompletely characterized. In aged mice, the combination of anesthesia and surgery decreased hippocampal interneuron activity and increased pyramidal neuron activity, as demonstrated by high-density silicon probe electrophysiologic recordings and *in vivo* calcium imaging. Pretreatment of mice before anesthesia and surgery with indole-3-proprionic acid, a gut microbiome metabolite, mitigated the development of postoperative delirium–like behavior, and these protective behavioral effects were correlated with the absence of changes in excitation inhibition balance when compared to control animals. *See the accompanying Editorial on* ***page 496****.* *(Image: A. Johnson, Vivo Visuals Studio.)*



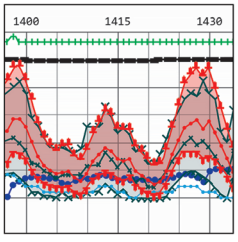
518 Statistical Analysis and Reporting of Cardiac Output Method Comparison Studies (COMPARE) Statement

Cardiac output is a key cardiovascular variable quantifying global blood flow. The measurement performance of cardiac output monitoring methods is investigated in validation studies, which are method comparison studies determining the agreement between cardiac output values measured with a test method and those measured with a reference method. The StatistiCal analysis and repOrting of cardiac output Method comPARison studiEs (COMPARE) statement provides a framework for designing, performing, and reporting cardiac output method comparison studies and includes a checklist of 29 items that are essential for reporting of those studies. *See the accompanying Editorial on* ***page 487****.* *(Image: Adobe Stock.)*



541 Clinical and Genetic Factors Associated with Intraoperative Minimum Alveolar Concentration Ratio: A Single-center Retrospective Cohort and Genome-wide Association Study

Minimum alveolar concentration (MAC) ratio is used as a standard pharmacologic dosing regimen for anesthetic delivery. In a large retrospective data set in adults undergoing general anesthesia with volatile anesthetics, the primary determinant of MAC ratio in clinical practice was blood pressure. Various factors known to influence MAC did not appear to influence clinical delivery of MAC ratio. A genome-wide association study failed to definitively identify novel variants at the level of genome-wide significance. However, eight variants located near six genes of neurologic relevance were identified at a lower level of evidence for an association. *See the accompanying Editorial on* ***page 491****.* *(Image: J. P. Rathmell.)*



559 Associations of Intraoperative Hypotension and Perioperative Blood Pressure with Delirium after Noncardiac Surgery: A Retrospective Cohort Analysis

Postoperative delirium after noncardiac surgery is a common and debilitating complication. A single-center cohort study of 38,940 noncardiac surgeries among adult patients observed postoperative delirium after 2,556 surgeries, for an incidence of 6.56%. Intraoperative hypotension, defined as area under the curve of a mean arterial pressure below 65 mmHg, was not associated with postoperative delirium (odds ratio, 1.000; 95% CI, 0.999 to 1.000). *See the accompanying Editorial on* ***page 493****.* *(Image: J. P. Rathmell.)*

 DOI: 10.1097/ALN.0000000000005668



570 Psychological Effects of Explicit Recall under Sedation and after Surgery (PEERS): A Prospective Cohort Study on 2,500 Patients

This 2,500-patient prospective cohort study found that explicit recall under sedation/regional anesthesia is relatively common, having occurred in 1 in 5 patients, but was not associated with adverse psychiatric consequences. Explicit recall *per se* during sedation/regional anesthesia did not increase the odds of developing psychiatric illness. Surgery itself carries significant risks of triggering depression and posttraumatic stress disorder that are severe enough to reach levels associated with suicidal ideation, requiring immediate mental care. This study reveals a significant, yet underappreciated, mental healthcare burden. *(Image: Adobe Stock.)*



680 A Pharmacist-partnered Opioid-tapering Service before Total Hip or Knee Arthroplasty: Qualitative Analysis of Patient Counseling Sessions

Recent evidence indicates that tapering opioids before total hip or knee arthroplasty improves postsurgical outcomes. This study qualitatively analyzed consultation sessions of patients receiving a pharmacist-partnered opioid-tapering service before total hip or knee replacement surgery to understand their experiences and attitudes. Qualitative themes included knowledge of upcoming surgery and desire to be fit for functional and social activities as motivating factors and recognition of psychosocial stressors as important barriers to overcome for successful tapering. A variety of initial attitudes were encountered (optimism, hesitancy, resistance) among patients who ultimately successfully tapered (opioid dose reduced to 50% of the baseline daily opioid dose). *(Image: Adobe Stock.)*



737 Potential Benefits of Medical Nutrition Therapy for Timely Ventilator Weaning in the Critically Ill

Nutritional support and metabolic assessment are crucial in weaning from invasive mechanical ventilation. This review explores strategies for metabolic assessment and tailored nutritional interventions and their impact on weaning outcomes, highlighting individualized nutritional interventions. *See the accompanying Editorial on* ***page 501****.* *(Image: Adobe Stock.)*



750 Anesthetic Amnesia: The Forgotten Importance of Forgetting?

This systematic review provides updated information, technologies, and opinions and discusses several clinically relevant applications of amnesia. Although the neuroscience of memory has advanced significantly over the past two decades, practitioners have struggled to successfully apply this knowledge in the clinical setting to improve patient experience. The purpose of this article is to stimulate relevant translational research; accordingly, this review does not delve deeply into the technicalities of the intricate neurobiology of memory but concentrates on clinical studies and their application. *(Image: Adobe Stock.)*

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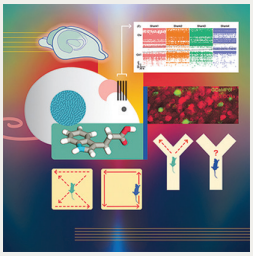
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The COMPARE statement provides a framework for designing, performing, and reporting cardiac output method comparison studies. Considering and reporting the items specified in the COMPARE checklist will help standardize cardiac output method comparison studies and increase the external validity of the results.

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The 2024 Rovenstine Lecture reflects on the COVID-19 pandemic, offering insights on leadership during a crisis, advances in medicine, and preparation for the future.

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ON THE COVER: While the clinical impact of postoperative delirium is well recognized, the underlying electrophysiologic mechanisms remain largely unknown, posing challenges for identifying effective treatments. In this issue of ANESTHESIOLOGY, Guo *et al.* investigated behavior and hippocampal neural dynamics before and after anesthesia and surgery in young and aged mice. In an accompanying editorial, Mintz and Vutskits discuss *in vivo* recordings of neural activity, the excitation–inhibition balance of neural networks, and the potential contribution of the gut microbiota to the onset of or protection from postoperative delirium. Cover illustration: A. Johnson, Vivo Visuals Studio.

- Guo *et al.*: Hippocampal Neural Dynamics and Postoperative Delirium–like Behavior in Aged Mice, p. 625
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Perioperative Medicine

CLINICAL SCIENCE

Clinical and Genetic Factors Associated with Intraoperative Minimum Alveolar Concentration Ratio: A Single-center Retrospective Cohort and Genome-wide Association Study

N. J. Douville, E. S. Jewell, X. Zhao, D. A. Colquhoun, E. Bertucci-Richter, S. Zöllner, R. P. Davis, S. S. Kumar, G. A. Mashour.....541

In a large retrospective data set in adults undergoing general anesthesia with volatile anesthetics, the primary determinant of minimum alveolar concentration (MAC) ratio in clinical practice was blood pressure. Various factors known to influence MAC did not appear to influence clinical delivery of MAC ratio. A genome-wide association study failed to definitively identify novel variants at the level of genome-wide significance. However, eight variants located near six genes of neurologic relevance were identified at a lower level of evidence for an association.

Associations of Intraoperative Hypotension and Perioperative Blood Pressure with Delirium after Noncardiac Surgery: A Retrospective Cohort Analysis

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A single-center cohort study of 38,940 noncardiac surgeries among adult patients observed a postoperative delirium after 2,556 surgeries, for an incidence of 6.56%. Intraoperative hypotension, defined as area under the curve of a mean arterial pressure below 65 mmHg, was not associated with postoperative delirium (odds ratio, 1.000; 95% CI, 0.999 to 1.000).

Psychological Effects of Explicit Recall under Sedation and after Surgery (PEERS): A Prospective Cohort Study on 2,500 Patients

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This 2,500-patient prospective cohort study found that explicit recall under sedation/regional anesthesia is relatively common, having occurred in 1 in 5 patients, but was not associated with adverse psychiatric consequences. However, in rare cases, 3 of 2,139 patients experienced pain and paralysis, which may carry different psychological implications. Additionally, surgery itself was a major psychological stressor, with 1 in 12 patients developing severe depression or posttraumatic stress disorder and 1 in 18 reporting suicidal ideation or seeking new psychiatric treatment postoperatively.

Association of Intraoperative Hypotension with Postoperative Nausea and Vomiting in Laparoscopic Gastrointestinal Surgery: A Secondary Analysis of a Randomized Trial

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Increased Plasma Fibroblast Growth Factor 23 and In-hospital Acute Kidney Injury after Cardiac Surgery

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BASIC SCIENCE

◆◇ **Hippocampal Neural Dynamics and Postoperative Delirium–like Behavior in Aged Mice**
S. Guo, L. Yang, W. Ding, T. M. Dagnew, Y. Gao, W. Wang, P. Wang, S. Huang, C. Ran, C. Wang, L. Shen, Q. Chen, O. Akeju, S. Shen.....625

In aged mice, the combination of anesthesia/surgery decreased hippocampal interneuron activity and increased pyramidal neuron activity, as demonstrated by high-density silicon probe electrophysiologic recordings and *in vivo* calcium imaging. Pretreatment of mice before anesthesia and surgery with indole-3-proprionic acid, a gut microbiome metabolite, mitigated the development of postoperative delirium–like behavior, and these protective behavioral effects were correlated with the absence of changes in excitation inhibition balance when compared to control animals.

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BASIC SCIENCE

◇ **A Pharmacist-partnered Opioid-tapering Service before Total Hip or Knee Arthroplasty: Qualitative Analysis of Patient Counseling Sessions**
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After successfully completing this activity, the learner will be able to evaluate the risk of prolonged QT interval from various methadone dosing regimens, design a strategy for perioperative methadone dosing that minimizes the risk of respiratory depression and maximizes the postoperative analgesic effect, and select a methadone dose based on the desired duration of analgesia.

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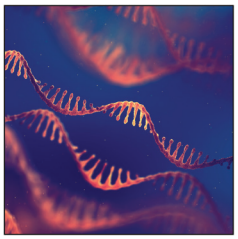
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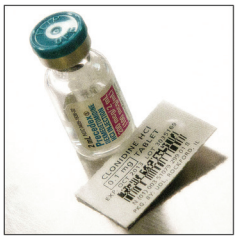
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Neuronal aging causes mislocalization of splicing proteins and unchecked cellular stress. Nat Neurosci 2025; 28:1174–84. PMID: 40456907.

The molecular mechanism underlying age-related dysfunction of neurons, a critically important driver of postoperative cognitive dysfunction, is poorly understood. This study explores the role of disrupted RNA biology using neurons differentiated from fibroblasts collected from aged humans that retained features consistent with senescence and compared them to neurons with early-life features generated from induced pluripotent stem cells. Proteomic analysis revealed that expression of RNA binding proteins is reduced in the aged *versus* young neuron models. Immunocytochemical analysis further showed that aged model neurons have a high rate of mislocalization of key components of the spliceosome, a group of RNA binding proteins that guard against translation errors by removing noncoding regions of the transcripts, to the cytoplasm, rather than to their correct location in the nucleus. Affinity pulldown mass spectroscopy indicates that the normal process to protect the cell from mislocalized spliceosome and transcript in aged model neurons *via* sequestration in structures called stress granules is impaired and that aged cells maintain chronically high loads of stress granules. The result is that aged model neurons challenged with the toxins thapsigargan and arsenite do not mount normal responses to cellular stress, as evidenced by reduced ubiquitylation and heat shock protein chaperone activity. *(Article Summary: C. David Mintz, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: Aging neurons exhibit impaired RNA processing that leads to cellular malfunctions particularly in the setting of stress, which indicates that RNA biology is a promising direction for future research in postoperative cognitive dysfunction.



Dexmedetomidine- or clonidine-based sedation compared with propofol in critically ill patients: The A2B randomized clinical trial. JAMA 2025; 334:32–45. PMID: 40388916.

Most patients undergoing mechanical ventilation receive sedation with propofol. Alpha-2 agonists—such as dexmedetomidine and clonidine—have been proposed as alternatives that may reduce the incidence of delirium and duration of mechanical ventilation. The A2B trial pragmatic randomized trial analyzed 1,404 patients (41 United Kingdom intensive care units; mean age, 59 yr; 64% male; mean APACHE-II score, 20.3) within 48 h of initiation of mechanical ventilation 1:1:1 to dexmedetomidine (n = 457), clonidine (n = 476), or propofol-based (n = 471) sedation to determine whether the two α-2 agonists reduced the primary outcome of time from randomization to extubation. Secondary and safety outcomes included among others delirium, adverse events related to sedation (*e.g.*, agitation), and bradycardia (less than 50 beats/min). Comparing each α-2 agonist to propofol, there was no difference in time to successful extubation for dexmedetomidine (hazard ratio, 1.09; 95% CI, 0.96 to 1.25) or clonidine (hazard ratio, 1.05; 95% CI, 0.95 to 1.17). There were also no differences in the rates of delirium or coma for dexmedetomidine (risk ratio, 0.94; 95% CI, 0.88 to 1.00) or clonidine (risk ratio, 0.97; 95% CI, 0.91 to 1.04). Compared to propofol, agitation and bradycardia were more common with dexmedetomidine (risk ratio for agitation, 1.54; 95% CI, 1.21 to 1.97; risk ratio for bradycardia, 1.62; 95% CI, 1.36 to 1.93) and clonidine (risk ratio for agitation, 1.55; 95% CI, 1.22 to 1.97; risk ratio for bradycardia, 1.58; 95% CI, 1.33 to 1.88). *(Article Summary: Jessica Spence, M.D., Ph.D. Image: J. P. Rathmell.)*

Take home message: This multicenter, pragmatic randomized controlled trial comparing dexmedetomidine- and clonidine-based sedation to propofol-based sedation in adults requiring mechanical ventilation in the intensive care unit found no difference in time to extubation or delirium but higher rates of agitation and severe bradycardia with dexmedetomidine- and clonidine-based sedation compared to propofol.



Modeling rapid language learning by distilling Bayesian priors into artificial neural networks. Nat Commun 2025; 16:4676. PMID: 40393968.

Humans can acquire language with striking speed and accuracy, but computational models have largely failed to reliably mimic this ability. This study aims to model such rapid language acquisition by developing an approach to bridge Bayesian models, which generalize well from few examples, and artificial neural networks, which scale well to large naturalistic datasets. The study introduces "inductive bias distillation," a meta-learning approach with three parts. First, a Bayesian model was applied to the building blocks of language in order to generate potential explanations of how language may work. Second, these potential explanations were used to generate a large number of learning tasks. Third, a neural network trained on the dataset of learning tasks. The resulting "prior-trained" neural network retained strong inductive biases akin to a Bayesian learner, enabling accurate learning of formal languages from fewer than 10 examples, while also maintaining flexibility to learn English syntax from 8.6 million words of speech from transcripts of parents speaking with children. Compared to standard neural networks, prior-trained models demonstrated improved performance on tests such as determining whether one idea follows from another (low-data tasks), nesting ideas within ideas (recursion), and using similar sentence structure (syntactic priming), while preserving comparable performance on predicting what comes next in sentences (perplexity). *(Article Summary: Mark C. Bicket, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: This computational study demonstrates that meta-learning can transfer the inductive biases of Bayesian language models into neural networks, enabling models that generalize well from small samples and scale to large naturalistic data, an advance toward modeling human-like language acquisition.



A focused update to the Clinical Practice Guidelines for the Prevention and Management of Pain, Anxiety, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2025; 53:e711–27. PMID: 39982143.

Critically ill patients often experience pain, anxiety, agitation, delirium, immobility, and sleep disruption during their intensive care unit (ICU) stay. In 2018, the Society of Critical Care Medicine issued clinical practice guidelines for prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. This article is an update and expansion of the previous version guidelines. Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, an interprofessional task force developed evidence-based recommendations focusing on five main contents: anxiety, agitation/sedation, delirium, immobility, and sleep disruption. For adult patients admitted to the ICU, the task force issued conditional recommendations to use dexmedetomidine over propofol for sedation in those with mechanical ventilation when light sedation and delirium reduction are of highest priorities (for intervention; moderate certainty of evidence), to provide enhanced mobilization/rehabilitation over usual mobilization/rehabilitation (for intervention; moderate certainty of evidence), and to administer melatonin over no melatonin (for intervention; low certainty of evidence); the task force was unable to issue recommendations on the use of benzodiazepines to treat anxiety (no recommendation; no evidence available), and for or against the use of antipsychotics over usual care to treat delirium (conditional recommendation; for intervention or comparison; low certainty of evidence). *(Article Summary: Dong-Xin Wang, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: In adult ICU patients, the updated guidelines conditionally recommend using dexmedetomidine over propofol for sedation, providing enhanced mobilization/rehabilitation, and administering melatonin; no recommendations are issued regarding use of benzodiazepines to treat anxiety and use of antipsychotics to treat delirium.



A comparison of intramuscular (Zimhi) and intranasal naloxone (Narcan) in reversal of fentanyl-induced apnea: A randomized, crossover, open-label trial. Nat Commun 2025; 16:4659. PMID: 40389500.

Potent opioids may induce respiratory depression followed by cardiac arrest, the primary cause of death in opioid overdose. Naloxone is an ideal drug to restore breathing following opioid-induced respiratory depression. In this randomized crossover, open-label trial, performed at the University of Leyden (September 2023 to September 2024), intramuscular *versus* intranasal application of naloxone was tested regarding efficacy to restore breathing after opioid-induced respiratory depression. In 18 opioid-naive participants, apnea was induced by 10 μg/kg intravenously applied fentanyl and after 2 min reversed by naloxone doses (intramuscular 5 mg/0.5 ml; intranasal 4 mg/0.1 ml) at 2-min intervals until adequate ventilation returned. Primary endpoint was defined as number of naloxone doses needed to restore proper ventilation. The same approach was chosen for participants with chronic opioid use. In the opioid-naive group, intramuscular naloxone doses were 1.5 (interquartile range, 1 to 2), for intranasal naloxone 2 (1 to 3), $P = 0.0002$, with no serious adverse events. Similarly in the exploratory adjunct study with six participants with chronic opioid consumption, intranasal naloxone was less efficient; muscle rigidity as well as mild to moderate withdrawal adverse events were observed in these subjects. *(Article Summary: Beatrice Beck-Schimmer, M.D. Image: Adobe Stock.)*

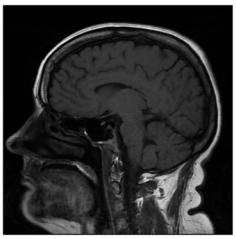
Take home message: This randomized crossover, open-label trial evaluates the efficacy of intramuscular *versus* intranasal naloxone application in two groups of volunteers—without and with chronic opioid consumption—after fentanyl-induced apnea. In both groups, intramuscular naloxone seems to be more efficient. Due to the small study, larger group trials are needed to verify these data.



Glucose-lowering medications, glycemia, and cognitive outcomes: The GRADE randomized clinical trial. JAMA Intern Med 2025; 185:778–87. PMID: 40388190.

Type 2 diabetes is a risk factor for cognitive impairment. It is not known whether specific second-line medical therapies in addition to metformin or improved glucose control modifies risk. This subanalysis of an open-label, randomized, multicenter randomized control trial across 36 U.S. clinical centers (GRADE trial) compared the second-line diabetes control agents: insulin glargine, glimepiride, liraglutide, or sitagliptin over a 4-yr follow-up period (2013 to 2021). A total of 3,721 individuals, 62.3% male, a mean 4.3 yr since diabetes diagnosis with a mean baseline hemoglobin A1c of 7.5% were included the final analysis. The primary outcome was cognitive function, assessed by the Digit Symbol Substitution Test (DSST), a sensitive marker of cerebrovascular damage. After mean follow-up of 4.1 yr, there was no difference in scores between treatment groups ($P = 0.59$). Four other secondary measures of cognitive performance also showed no differences between treatment. In secondary analyses, after adjustment for age, higher time-weighted hemoglobin A1c was associated with a modest decline in DSST score (β −1.02, $P < 0.001$), a finding of uncertain clinical significance. *(Article Summary: Douglas A. Colquhoun M.B.Ch.B., M.Sc., M.P.H. Image: Adobe Stock.)*

Take home message: This subanalysis of a randomized, parallel-arm trial reports no difference in primary cognitive outcome among second-line treatment choices used in addition to metformin or improved glucose control in patients with type 2 diabetes of relatively short duration (less than 10 yr). However, a small magnitude of cognitive decline was associated with worsening degrees of glycemic control.



General anaesthesia decreases the uniqueness of brain functional connectivity across individuals and species. Nat Hum Behav 2025; 9:987–1004. PMID: 40128306.

If phenomenological consciousness is the unique subjective experience of an individual, the question arises as to whether the distinctive patterns of brain function specific to each individual (termed *brain fingerprinting*) are lost under general anesthesia–induced unconsciousness? Using functional magnetic resonance imaging, patterns of brain functional connectivity were assessed in healthy subjects having propofol (n = 16) or deep sevoflurane (n = 15) anesthesia. Brain fingerprinting for an individual was quantified by consistency of functional connectivity matrices over time (*persistence*), and difference from other individuals (*diversity*). Sevoflurane anesthesia decreased persistence within subjects from: awake *versus* recovery = 0.60 ± 0.08, to awake *versus* anesthesia = 0.37 ± 0.08, $P < 0.001$; and reduced diversity between subjects. The suppression of individual distinctiveness with sevoflurane anesthesia was most marked in cortical regions that showed the largest interindividual variability when in the awake state. These were the higher-order association (transmodal) cortical regions—especially the default mode and frontoparietal networks. Unimodal somatomotor and visual cortices were least affected by anesthesia. Comparable results were seen with propofol anesthesia. Using dimension reduction methods to compare species, anesthesia was also found to reduce the diversity in cortical functional connectivity between humans and nonhuman primates (macaques, n = 9, isoflurane). *(Article Summary: Jamie Sleigh, M.D. Image: J. P. Rathmell.)*

Take home message: Deep anesthesia causes the functional connectome of each individual to become more similar to the functional connectomes of others.



Postoperative outcomes among sodium-glucose cotransporter 2 inhibitor users. JAMA Surg 2025; 160:681–9. PMID: 40305034.

Long-term use of sodium-glucose cotransporter 2 inhibitors (SGLT2i) is increasingly common among surgical populations, yet potential risks of postoperative euglycemic ketoacidosis (eKA) and downstream complications have not been rigorously evaluated. This retrospective, observational study of adult surgical patients across multiple Veterans Affairs Health Care System centers (June 2023 to August 2024; n = 7,439 SGLT2i users and 33,489 matched control patients; mean age, 68 yr; 96.5% male) studied associations between SGLT2i prescriptions and eKA (primary outcome), acute kidney injury (AKI), and 30-day mortality (secondary outcomes). SGLT2i use was defined as more than three outpatient prescription fills or most recent fill within 180 days before surgery. eKA was defined as a serum bicarbonate less than 18 mEq/l, base excess 5 mEq/l or less, or anion gap more than 12 mEq/l with glucose less than 200 mg/dl in the absence of lactate greater than or equal to 27 mg/dl within the first 7 postoperative days. eKA occurred in 29.7% of SGLTi users *versus* 27.6% of control patients; 30-day mortality in 1.1% *versus* 1.6%, respectively. After propensity score matching, SGLT2i use was associated with a small but significantly increased risk of eKA (odds ratio, 1.11; 95% CI, 1.05 to 1.17) but reduced risks of AKI (odds ratio, 0.69; 95% CI, 0.62 to 0.78) and mortality (odds ratio, 0.70; 95% CI, 0.55 to 0.88). *(Article Summary: Michael R. Mathis, M.D. Image: Adobe Stock.)*

Take home message: This multicenter, retrospective analysis of predominantly male Veterans Affairs registry data reports that long-term preoperative SGLT2i use was associated with 11% higher rates of postoperative eKA, but approximately 30% lower rates of AKI and 30-day postoperative mortality.



A broad-spectrum lasso peptide antibiotic targeting the bacterial ribosome. Nature 2025; 640:1022–30. PMID: 40140562.

Bacterial multiresistance to antibiotics is a global health crisis that has caused more than 4.5 million deaths in 2019. This study reports the identification and characterization of a new ribosome-targeting peptide that inhibits bacterial translation elongation and induces miscoding. The biologically active molecule with the name lariocidin was first isolated from *Paenibacillus sp.* and belongs to the family of lasso peptides named after their distinct structure mimicking a knotted fold or lariat. Lariocidin's cellular uptake is dependent on the membrane potential but does not rely on specific transporters. Its binding site to the small ribosomal 16S RNA subunit is different from sites of action of other ribosome-targeting antibiotics such as tetracyclines and aminoglycosides. Its mode of interaction is unique by arresting bacterial ribosomes at the start codon and by stalling them at internal codons of the open reading frame, while only marginally affecting eukaryotic translation. The efficacy of lariocidin was tested in a neutropenic murine model of thigh infection using the pathogen *Acinetobacter baumannii*, a multidrug-resistant strain with resistance to carbapenem. Treatment with lariocidin markedly reduced the bacterial burden in spleen, blood, and thigh, and 100% of the treated mice survived up to 28 h, whereas none of the vehicle control-treated mice survived. *(Article Summary: Michael Zaugg, M.D., M.B.A. Image: Adobe Stock.)*

Take home message: Lariocidin is a highly promising novel broad-spectrum antibiotic targeting the bacterial ribosome. It is unaffected by common resistance mechanisms, shows no toxicity to human cells, and is highly potent in a murine model of infection.

Postoperative Delirium & Neuronal Dynamics:

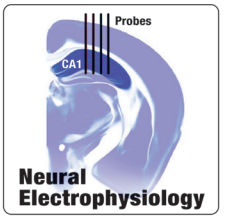


Postoperative delirium (POD) is common, but the electrophysiologic mechanisms remain largely unknown.

In this issue, Guo *et al.* investigated hippocampal neural dynamics and POD-like behaviors before and after anesthesia/surgery in adult (12–16 weeks) and aged (17–18 months) mice using a POD model.[1,2]

Insights from Aged Mice

Assessment of Hippocampal Neural Dynamics



Continuous recordings of hundreds of neuronal subtypes simultaneously at submillisecond resolution

What was measured:

Activity of hippocampal pyramidal neurons (excitatory) and interneurons (inhibitory).

How it was measured:

- High-density silicon probe electrophysiology (Neuropixels), allowing simultaneous, high-resolution recording of many single neurons.
- *In vivo* two-photon calcium imaging to visualize neuronal activity patterns in awake mice.

Relevance to POD:

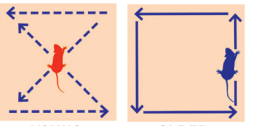
Circuit-level changes in excitation and inhibition may disrupt hippocampal information processing, providing a mechanistic link to POD-like behavior.

Assessment of POD-like Behavior*

Y MAZE TEST

Used to assess spontaneous alternation behavior and short-term spatial memory in mice.

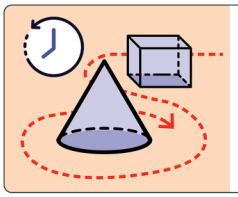




OPEN FIELD TEST

Mice were individually placed in the enclosure center, and latency to center, time spent in center, and time spent freezing were measured. Tests anxiety and arousal.

*All tests conducted at baseline and 9 h and 24 h postoperatively



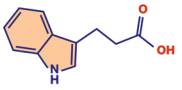
NOVEL OBJECT RECOGNITION

After previously exposing mice to two identical objects, NOR measures the exploration time when the prior object and a novel object are presented. Assesses recognition memory.



BURIED FOOD TEST

The time required for the mouse to find and eat buried food. Assesses alertness and consciousness.



PERIOPERATIVE COGNITIVE PROTECTOR?

Aged mice were pretreated with indole-3-propionic acid (IPA), a gut microbiome metabolite, to measure effects on POD-like behavior and neural activity.

Neural Electrophysiology

At 9 h after surgery, aged mice showed:

- **Increased activity of hippocampal pyramidal neurons** (excitatory cells)
- **Decreased activity of interneurons** (inhibitory cells)

By 24 h, neuronal activity and behavioral performance largely returned to baseline.

POD-like Behavior

At 9 h after surgery, aged mice demonstrated greater POD-like behavior compared to adult mice in all tested domains.

Values 24 h postoperatively were comparable to baseline levels, suggesting improvement in POD-like behavior.

CONCLUSION

Aged mice exhibit transient postoperative cognitive deficits driven by hippocampal excitation/inhibition imbalance, a possible neuronal mechanism of POD.

POD symptoms improved with pretreatment with gut-derived IPA, a potential future therapeutic for preventing or treating POD in aging populations.

IPA, indole-3-propionic acid; NOR, novel object recognition; POD, postoperative delirium.

Infographic created by Alexander S. Doyal, University of North Carolina at Chapel Hill; Jonathan P. Wanderer, Vanderbilt University Medical Center; and Holly Ende, Vanderbilt University Medical Center. Illustration by Annemarie Johnson, Vivo Visuals Studio. Address correspondence to Dr. Wanderer: jon.wanderer@vumc.org.

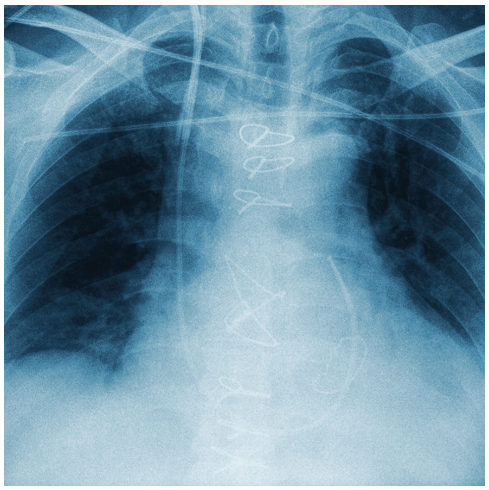
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Cardiac Output Measurement and Reporting: More Than Just Going with the Flow

Michael R. Mathis, M.D., Duminda N. Wijeysundera, M.D., Ph.D., Martin J. London, M.D.

Few clinicians would challenge the notion that maintenance of an adequate cardiac output to support end-organ perfusion is a critical component of safe perioperative care. However, the multiplicity of technologies promoted to measure cardiac output, how to judge the quality of such approaches, and how far to extend evidence derived from one measurement modality to another greatly complicate generalization of research to the bedside. These issues underpin the challenges and shortcomings of efforts to determine the clinical effectiveness of goal-directed hemodynamic therapies commonly involving optimizing cardiac output.[1] As a result, inconsistencies in cardiac output measurement methods and reporting pose serious challenges to the quality of health research.



"Accurate, reliable, noninvasive, and cost-effective cardiac output monitoring remains far from a solved problem, with limitations to currently available methods as abundant as the number of monitoring methods available."

In this issue of Anesthesiology, Saugel *et al.*[2] address these escalating challenges of rigor and reproducibility by comparing varied methods of cardiac output monitoring and reporting of research results and proposing a new framework for reporting of such results. Developed through a consensus process drawing from an expert group of anesthesiologists, critical care physicians, and biostatisticians, the StatistiCal analysis and repOrting of cardiac output Method comPARison studiEs (COMPARE) statement lays welcome groundwork for understanding the degree to which findings from a particular study using a given cardiac output monitoring method may be comparable to another study reporting on a different method. Key components include adopting elements from evolving reporting statements aimed at enhancing the quality and transparency of health research,[3,4] as well as nuances specific to cardiac output monitoring that have frequently been underreported or absent in earlier studies. Such nuances include the working principles and technical details of the cardiac output measurement method, as well as the timing (and, importantly, *trending*—the ability to track changes over time[5]) of measurements relative to other factors introduced within the setting in which comparisons were made.

Previous "uncontrolled" variation in the reporting of cardiac output monitoring studies hinder clinicians in effectively synthesizing different studies to understand how the monitors can improve patient care. There are solutions with foundational past precedents. From a general reporting perspective, broader consensus statements set expectations for how health research is published, such as Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for observational studies,[3] Consolidated Standards of Reporting Trials (CONSORT) for randomized trials,[4] and—perhaps the most directly related to the work by Saugel *et al.*[2]—the Guidelines for Reporting Reliability and Agreement (GRRAS).[6] Such consensus-based reporting standards allow clinicians and informaticians to more effectively synthesize evidence from

Image: Adobe Stock.

This editorial accompanies the article on p. 518. This article has an audio podcast.

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a diversity of studies to make informed decisions related to patient care and health services design. Similarly, from a methodologic perspective, consensus statements allow health researchers and clinical experts within a specific field to use more uniform terminologies, such as the STeP initiative for standardized definitions of perioperative outcomes[7] and the international initiative to develop a universal definition of heart failure.[8] These initiatives have enabled those groups to more effectively advance a shared understanding of the field and catalyze similar improvements to patient care and health services. This new COMPARE statement represents an important framework for advancing future health research and patient care in cardiac output monitoring.

To illustrate the value of the consensus statement, the clinician is now informed of the breadth of monitoring modalities available, the only two constants being the limitations to any given approach and the varied quality of study reports. For example, completely noninvasive cardiac output monitoring techniques currently include pulse wave analysis *via* wearable sensors,[9] bioimpedance or bioreactance measures from electrodes placed on the chest,[10] and pulse wave transit times based upon subtle time delays between electrocardiogram *versus* pulse oximeter waveforms.[11] Among surgical and critically ill patients, meta-analyses of the accuracy and precision of such measures compared to an invasive transpulmonary thermodilution reference standard suffer from high study heterogeneity, hindering more definitive intepretation.[12,13] Similarly, more invasive techniques span a wide range, including arterial line pulse contour analyses,[14] esophageal Doppler,[15] and partial carbon dioxide rebreathing.[16] Yet even for these more invasive measures, studies seeking to analyze their accuracy and precision across diverse patient populations are fraught with high heterogeneity in reporting, leading many studies to be excluded from meta-analyses.[17] Consequently, as additional studies continue to emerge comparing newly developed cardiac output monitoring techniques to reference standards—most recently those exploring measures in the setting of extracorporeal circulation[18,19]—what is clear is that this science demands a uniform approach to such comparison studies to advance evidence in a cohesive way.

In answering this call to action, notable strengths in how the COMPARE statement was developed include the involvement of a multidisciplinary steering committee, by which the project should be publicly registered within an international forum for enhancing the quality and transparency of health research[20] and through which checklist items were developed using a modified Delphi process with multiple rounds of revision. This process aligns with broader consensus reporting statements for health research,[3,4] serving to reinforce evolving standards stemming from methodologic advancements and feedback from the research community. Additionally, an emphasis on precision language in the consensus statement advances clarity of reporting in cardiac output comparison studies. Thus, checklist items should include clear identification of the test *versus* reference metrics of cardiac output monitoring, CO_{TEST} and CO_{REF}, with well-articulated technical and data extraction details for each approach. As recognized by the well-known late statistician Douglas Altman (of the Bland–Altman plot methodology used in cardiac output comparison studies), "readers should not have to infer what was probably done, they should be told explicitly."[21]

The statement also highlights core challenges to cardiac output monitoring, which can impede progress in research aimed at characterizing relationships between cardiac outcome and clinical outcomes. For example, the importance of the trending ability of a cardiac output measurement method is emphasized by the consensus statement. Given the dynamic nature of patient physiology in these settings, large fluctuations in cardiac output can occur over minutes or even seconds, meaning that cardiac output measured at a single time point may offer less clinical value than a series of measurements observed in the context of disease progression and treatment interventions.[22] Practicing clinicians are more interested in the ability of a cardiac output monitor to accurately track changes in cardiac output during resuscitation or ongoing bleeding, as opposed to whether the measurement at any individual time point is accurate. The trending ability of a particular cardiac output monitoring approach, assessed through specific methods such as polar plots[23] or Bayesian frameworks using previous knowledge of previous measurements,[24] is thus an important characteristic addressed by the statement.

The consensus statement also emphasizes precise reporting of how cardiac output data are recorded and extracted from a device, including averaging and operator-dependent effects. They underscore the importance of not accepting reports of cardiac output values at face value, without first understanding how the values may have been influenced by (1) beat-to-beat or second-to-second averaging computed automatically by the monitor and (2) inconsistencies in operator technique. Even thermodilution-based cardiac output monitoring, commonly used as a reference standard by which other methods are compared, poses multiple operator-dependent challenges to reliability.[25] Such issues challenge the use of thermodilution as the ideal reference standard upon which other cardiac output studies are compared, with alternative approaches prioritizing reliability, clinical availability, and scalability. Considering the multitude of challenges to cardiac output monitoring and the reporting thereof, applications of the COMPARE statement may prove to be a complex undertaking. Further guidance based on the experiences of investigative teams serving as early adopters of the statement will be of value to the health science community.

Accurate, reliable, noninvasive, and cost-effective cardiac output monitoring remains far from a solved problem, with limitations to currently available methods as abundant as the number of monitoring methods available. As new cardiac output monitoring methods evolve and are used to explore

fundamental relationships between end-organ perfusion and patient outcomes, so must a clinician's understanding of the strengths and limitations of each method. Toward this future state, the COMPARE statement is a laudable advance, providing a methodologic foundation for enhanced reporting of cardiac output measurement quality against established reference standards and enabling this science to progress in a more coordinated fashion.

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Competing Interests

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Are We Anesthetizing the Heart or the Brain (or Ourselves)?

Philip G. Morgan, M.D., Jamie W. Sleigh, M.D.

In the current issue of Anesthesiology, Douville *et al.* present a large retrospective study of surgical cases to determine what the primary drivers are for dosing of a general anesthetic.[1] For the study, they restricted the primary anesthetic agent to a volatile anesthetic, specifically isoflurane or sevoflurane with or without nitrous oxide. Propofol as an induction agent was allowed as was the use of an opioid for analgesia. Importantly, all patients were immobilized with muscle relaxant. The authors specifically asked what parameters serve to guide the delivery of volatile anesthetic concentrations—and, in particular, the role of intraoperative mean arterial pressure (MAP). To this end, they constructed multivariable models that included a wide range of covariates to control for confounding. These included preoperative data (sex, race, body mass index, American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status, history of drug or alcohol abuse, anemia, and hepatic and renal function), procedural data (surgical type and year), and anesthesia data (duration, blood product use, opioids, benzodiazepines, and vasoactive drugs). They also examined whether there was any association between genetic variants and the delivered volatile anesthetic concentrations.



"This study highlights the prevalence of MAP as a major driver for the dosing of volatile anesthesia in current practice… [I]t may be time for all of us to move on and actually monitor the brain."

The structural aspects of the study are well done, extremely well done. The main finding was that—after correction for confounding covariates—the concentration of volatile anesthetic used (quantified as minimum alveolar concentration [MAC] ratio) correlated most strongly with the mean arterial pressure of the patients. Those patients with a higher MAP had higher MAC ratios. To at least some anesthesiologists, this is so not surprising as to almost be a tautology. Most anesthesiologists (at least those trained before widespread use of processed electroencephalogram [EEG] monitoring) use hemodynamic factors, as indicators of autonomic response, to infer whether an immobilized patient is sufficiently anesthetized. Even though, as the authors correctly point out, this isn't an excellent direct measure of nervous system inhibition. The above correlation of MAP with anesthetic concentration is particularly true once the authors restrict their cohort to those receiving muscle relaxation. That removes the only other real measure of nervous system depth: movement. The authors do imply that there is almost no connection between the two (hemodynamic/autonomic nervous system and central nervous system [CNS] inhibition), although that may not be exactly correct. In the experience of most anesthesiologists, patients who are "CNS light" tend to have higher blood pressures.

However, Douville *et al.* do uncover a major surprise. One might expect that current physicians would more closely follow some form of processed EEG as a more direct CNS measure of anesthetic depth. Especially our younger colleagues have been trained in the era of commonly available processed EEG monitoring. Alas, it appears not to be so. This was surprising to the authors, that the old-fashioned way of following depth persists.

Image: J. P. Rathmell.

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Drug Titration Paradox

As illustrated and discussed by the authors, this study is a clear example of the phenomenon known as the drug titration paradox.[2] Even though increased volatile anesthetics will tend to *reduce* blood pressure in an individual patient (increased MAC ratio leads to decreased MAP), we see a *positive* correlation between MAC ratio and MAP when looking at the population level. This is because we have introduced the "intent of the anesthesia provider" who is pursuing a target MAP, so the causal direction is reversed (increased MAP leads to increased MAC ratio). The phenomenon is a version of Simpson's paradox, and there are disturbing implications for the interpretation of the results of this and almost all observational studies, because the results will strongly depend on the degree of titration that has been delivered by the anesthesia providers. To illustrate this, we can consider the two extreme cases: (1) when there is no titration and (2) when there is almost perfect titration. In the *absence of titration to MAP*, the MAC ratio delivery will be driven by other known and unknown factors. In broad terms, this results in the MAP correlating with the variation in underlying autonomic nervous system sensitivity of each patient, and having zero or a slight negative correlation with the MAC ratio. In contrast, if there is good titration, it is the MAC ratio (not the MAP) that is correlated with the variation in underlying autonomic sensitivity of each patient, and there is a positive correlation between MAC ratio and the MAP—as reported in this study. The real concern lies in the fact that most studies will have imperfect or mixed levels of titration. There will be some subgroups of patients receiving good titration and a positive MAC ratio:MAP correlation, and some receiving none or poor titration, showing a negative MAC ratio:MAP correlation—thus biasing toward a null result. More importantly, if we assume that the patient's genotype might be an important factor in controlling the variation in autonomic nervous system sensitivity to MAC ratio, then we could expect to see some link between genotype and MAP in the *absence* of titration, but between genotype and MAC ratio in the *presence* of titration, *i.e.*, the results of any study will be contingent on the diligence of titration of the anesthesia provider, not on the actual intrinsic responsiveness of the patient's physiology to anesthesia. In the current study, the demonstration of a positive MAP:MAC ratio correlation acts as a "quality control" to indicate the presence of quite strong titration of MAC ratio to MAP. This then supports the conclusion of a true negative result between genetic variants and delivered MAC ratio.

Genetic Studies

The authors then examine the genome-wide association results from their study to determine any genetic determinants of anesthetic dosing. There are three important points to consider in this aspect of the study. First, the authors did not follow any direct CNS measurement; instead, the results reflect responses of the cardiovascular system. Thus, the results are primarily looking at effectors of the hemodynamic system, not CNS function. Second, the clinical significance of the subthreshold genetic variants that the authors then linked with hemodynamic response seems uniformly weak. While the authors are justified in pointing out markers that approach significance, the results must be interpreted with extreme caution. Third, the reader must also remain aware that a genome-wide association study is primarily a mapping study, locating effectors of a trait to be near to a physical marker in the genome. In this case, it identifies genomic markers (not necessarily in genes) that segregate closely with some genomic element driving the hemodynamic response to anesthetics. It is not the same as exome mapping, which would identify changes *in identified genes* that linked to the hemodynamic response.[3] Despite this limitation, it is an excellent way to start such a search.

This study highlights the prevalence of MAP as a major driver for the dosing of volatile anesthesia in current practice. The efficacy of such practice is difficult to justify on the grounds that (1) volatile agents are relatively ineffective in controlling surges in blood pressure (MAC_{BAR} is typically almost twice $MAC_{incision}$), and (2) it is known that autonomic system responses are not reliably correlated with the state of consciousness. While this approach has served us fairly well during the past several decades, the results point out that it may be time for all of us to move on and actually monitor the brain.

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Competing Interests

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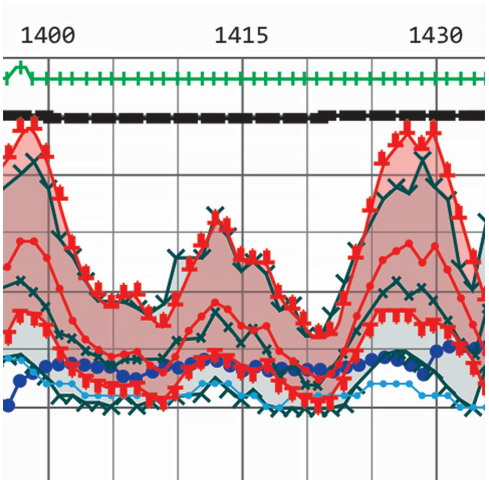
Wanted: Modifiable Risk Factors for Postoperative Delirium!

Yotam Weiss, M.D., Barak Cohen, M.D., Shiri Zarour, M.D.

Postoperative delirium is one of the most common complications in older patients recovering from surgery. Depending on the specific patient population, surgery type, and screening methods, research demonstrates that it affects between 10 and 50% of surgical patients older than 65 yr, which translates into millions of cases annually.[1] It is associated with prolonged hospital stay, increased healthcare costs, psychological distress for patients and families, and increased morbidity and mortality. Investigating predisposing and precipitating factors, particularly modifiable ones, is crucial for the development of preventive and therapeutic strategies.

In this issue of Anesthesiology, Rössler *et al.* report on their investigation of the possible relationship between intraoperative hypotension and postoperative delirium.[2] In their retrospective analysis of nearly 40,000 noncardiac surgeries, they found no causal association between the area under an intraoperative mean arterial pressure (MAP) threshold of 65 mmHg and postoperative delirium. Further analyses evaluating other methods to quantify intraoperative hypotension, postoperative hypotension, and blood pressure variability during and after surgery either found no associations or found statistically significant relationships with no clinically meaningful difference.

The lack of relationship between hypotension and postoperative delirium observed in this study may be partly explained by the relatively low incidence of delirium (6.5%). Postoperative delirium is a complex multifactorial phenomenon, and its diagnosis is often challenging due to its hallmark fluctuating nature. Any single questionnaire or test only captures a snapshot of the patient's cognitive state, often resulting in underdiagnosis. Retrospective review of physician and nursing charts can uncover missed cases, and validated tools such as the Chart-based Delirium Identification Instrument (CHART-DEL) are valuable for identification of delirious behaviors documented throughout the hospitalization.[3] Hopefully, artificial intelligence using large language models will assist us in efficiently reviewing patients' electronic medical records and in detecting previously undiagnosed cases of postoperative delirium.



"Paradoxically, the primary mechanisms by which general anesthetics induce hypotension may actually enhance cerebral blood flow and oxygen delivery, thereby mitigating potential effects of cerebral hypoperfusion and hypoxia."

Another ongoing debate concerns the optimal timing of screening; disoriented behavior in the postanesthesia care unit was traditionally considered as emergence delirium rather than postoperative delirium. However, growing evidence suggests that delirium that continues into the inpatient stay may begin as early as in the postanesthesia care unit, and that early recognition, even amid logistical challenges, may be critical.[4]

Undoubtedly, age is an independent risk factor for delirium. The preoperative cognitive state of patients is also strongly associated with postoperative delirium, as patients with lower cognitive reserve are at risk.[5] Similarly,

Image: J. P. Rathmell.

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frailty plays an important role in identifying patients at risk, but it is unclear whether the preoperative cognitive state or the cognitive reserve are modifiable.[6] Several studies have explored prehabilitation strategies, such as physical conditioning, nutritional support, cognitive training, and psychosocial interventions, with mixed results due to heterogeneous study designs and patient populations.[7] Since delirium also occurs in nonsurgical patients as well as before surgery, it is reasonable to assume that hospitalization, pain, and the unfamiliar environment are also contributing factors. However, by definition, postoperative delirium must occur after a surgical procedure, and surgery nearly always involves anesthesia. This raises important questions about the role of anesthesia in triggering or unmasking cognitive disturbances in at-risk individuals. It is therefore not surprising that intraoperative and anesthesia-related factors have been intensely investigated, although results remain inconclusive. Among these factors, intraoperative hypotension has received considerable attention.

Intraoperative hypotension has long been considered a plausible causal contributor to postoperative delirium, purportedly through mechanisms of cerebral hypoperfusion and reduced cerebral oxygen delivery.[8] Given that intraoperative hypotension is potentially modifiable, much research has previously evaluated its role in the development of postoperative delirium but has largely failed to identify a reliable causal relationship.[2,9]

It is surprising that while intraoperative hypotension is strongly associated with myocardial and kidney injury, this is not the case when the brain is the organ of interest. The answer to this discrepancy may lie within the unique cerebral hemodynamic profile of anesthesia-induced hypotension. Anesthesia-induced systemic hypotension is attributable to myocardial depression, systemic vasodilation, and decreased sympathetic activity. However, emerging evidence suggests that arterial dilatation with reduced systemic vascular resistance is the most significant factor.[10] Interestingly, systemic arterial dilatation is accompanied by cerebral arterial dilatation, increased cerebral blood flow, and improved cerebral oxygenation. These effects occur with both propofol and inhaled anesthetics.[11] Paradoxically, the primary mechanisms by which general anesthetics induce hypotension may actually enhance cerebral blood flow and oxygen delivery, thereby mitigating potential effects of cerebral hypoperfusion and hypoxia. Moreover, the decreased cerebral metabolic rate and oxygen demand attributed to general anesthesia further contribute to a favorable cerebral oxygen supply and demand balance.

This cerebral vascular response is different than the expected effects of hypotension in critically ill patients admitted to the intensive care unit, in patients having cardiac surgery, and in patients experiencing postoperative hypotension. In these clinical conditions, systemic hypotension is likely associated with impaired cerebral perfusion and oxygenation, and a causal relationship with postoperative delirium is therefore still plausible.

The complexity of postoperative delirium diagnosis and the unique cerebral vascular physiology warrant a comprehensive and nuanced approach to the study of hypotension and delirium. Future research should continue to advance postoperative delirium screening methods, focus on high-risk populations, and explore whether targeted intraoperative management can alter the postoperative cognitive trajectory.

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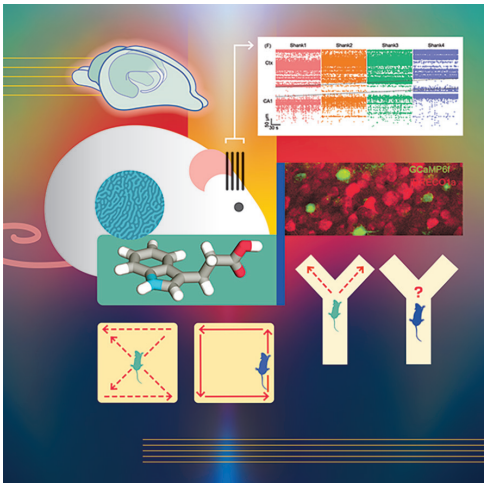
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Neural Network Dynamics of Postoperative Delirium: Is It All about Neurons Striking the Right Balance?

Cyrus David Mintz, M.D., Ph.D., Laszlo Vutskits, M.D., Ph.D.

The question of what the essential mechanisms are that cause postoperative delirium (POD) remains at the forefront of scientific inquiry in anesthesiology. The scope of the problem is immense: an estimated 37 to 46% of the surgical population suffers from POD, and the consequences include both substantial harm, with a 10 to 20% increase in mortality for every 2 days of delirium, and an estimated doubling of annual healthcare costs for patients who experienced POD in hospital.[1] The most prevalent electroencephalographic (EEG) signatures associated with POD comprise global cortical slow wave activity and decreased connectivity.[2] However, due to the limited spatial resolution of conventional EEG, we are still lacking an in-depth understanding of the nature of disarrayed neuronal function in POD, which in turn may better guide research to provide prevention or treatment. In this issue of Anesthesiology, Guo *et al.*[3] provide us with interesting new insights into high-resolution neural dynamics associated with the occurrence of POD-like behavior in rodents.[4] The authors performed anesthesia and surgery both in young adult and in aged mice, with the latter developing transient (up to 24 h) postoperative behavioral deficits reminiscent to human POD. Combining high-density silicon probes for EEG recordings with *in vivo* calcium imaging, Guo *et al.*[3] examined patterns of hippocampal neuronal activity at 9 and 24 h after anesthesia/surgery. The key finding is that, at 9 h, there was an increase in pyramidal cell activity and a decrease in interneuron activity in aged mice exhibiting behavioral anomalies corresponding to POD, but no such changes were found in young animals. In parallel with the normalization of behavior, neuronal activity patterns in the hippocampus were comparable to preoperative recordings at 24 h after anesthesia/surgery in aged animals. In an additional set of experiments, Guo *et al.*[3] also investigated the effects of pretreating aged animals with intraperitoneal injections of indole-3-proprionic acid (IPA), a metabolite in the tryptophan pathway produced by gut microbes, before anesthesia and surgery exposure. These investigations revealed that the IPA-pretreated animals had improved transient POD-related behavioral outcomes that correlated with a substantial normalization of hippocampal neuronal activity patterns in the postoperative period.



"[T]he technology applied by Guo *et al.* is an excellent opportunity to better explore gut–brain interactions in the perioperative context and beyond."

The major strength of these observations stems from the robust experimental approach allowing high-resolution *in vivo* recordings of neural activity patterns over time after anesthesia/surgery. So far, our understanding about the neural underpinnings of POD stemmed mostly from cortical EEG recordings, a technology that provides us with excellent temporal but poor spatial resolution of neuronal network dynamics. In experimental rodent research, using genetic tools and *in vivo* optical imaging, it is possible to monitor neuronal activity at the single-cell level, but the temporal resolution of this approach is strongly limited compared to electrophysiologic recordings. In their current article, Guo *et al.*[3] took advantage of a recently developed electrophysiologic monitoring system specifically

Image: A. Johnson, Vivo Visuals Studio.

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designed for recording neuronal activity with high temporospatial resolution in awake small laboratory rodents.[2] This approach allows continuous recordings of hundreds of neurons simultaneously at submillisecond resolution with high accuracy, and based on firing characteristics, neuronal subtypes can be identified with ease. While this sounds like the perfect approach to monitor neuronal network dynamics in awake animals exhibiting POD-like behavior, the technique is costly, it necessitates a substantial computing capacity, and implantation failures are not infrequent. It is therefore not surprising that while Guo *et al.*[3] provide us with recordings from hundreds of excitatory and inhibitory neurons, these observations are derived from just two animals per experimental group. In turn, this leads us to the eternal question of what the experimental unit should be in investigations in which neuronal network dynamics are analyzed at the single-cell level: the number of cells recorded or the number of animals included? Or does the field need to construct and validate a new paradigm incorporating both factors to serve as the standard? Indeed, despite the tremendous number of data obtained from these recordings, one may argue that important interindividual differences in network dynamic may exist, and relatedly, recordings from two animals may not be sufficient to depict the global picture. Hopefully, the continuous refinement of recording technologies and big data analysis will allow us to extend these observations to a larger cohort of animals in the near future.

The observations from Guo *et al.*[3] suggest that neuronal dysfunction underlying POD may reflect transiently altered excitation–inhibition (E/I) balance of neuronal networks. Excitation–inhibition balance is a basic feature of neural network function, and excitation–inhibition imbalance has been identified as a feature of a wide array of pathologic states involving cognitive dysfunction. Intriguingly, the direction of this shift in excitation–inhibition balance appears to be opposite to the one observed during general anesthesia, during which an overall decrease in neuronal network activities predominates. Indeed, the increased activity of hippocampal pyramidal neurons together with a concomitant decrease of inhibitory signaling observed by the authors shifts excitation–inhibition balance to a higher level of circuit activity. This, in turn, may result in a decrease of the signal-to-noise ratio of neuronal signaling, meaning that the network may be less responsive to behaviorally meaningful inputs.[5] Such a possibility provides us with an entirely new framework to understand the neurobiology of POD. Since the authors focused on the hippocampus, it remains to be determined whether the observed excitation–inhibition imbalance is limited to the hippocampal circuitry or also occurs in other brain regions involved in somatosensory and executive processing.

This study also provides us with food for thought on the potential contribution of the gut microbiota to the onset of or protection from POD. The fact that a 14-day pretreatment of aged animals with IPA, a metabolite of dietary tryptophan produced by gut microbiota, before anesthesia/surgery protected from both excitation–inhibition imbalance and the development of POD-like behavior not only provides us with further arguments between the causal link of neuronal network activity and the behavioral phenotype but also raises the possibility that "preconditioning" the gut microbiota before surgery may have therapeutic value in the prevention of POD. There is substantial literature demonstrating that disruptions of gut microbiome are correlated with alterations in cognition and behavior, including in human disease[6]; however, this study is one of few clear demonstrations of a mediator that explains how the gut and brain are connected. Whether administration of IPA in the early postoperative period reverses excitation–inhibition balance and restores normal behavior remains to be determined—a pretreatment approach is potentially much less practical to implement particularly given that we lack strong predictive indicators of which patients will have POD and which will not.

Like most high-quality preclinical work, this study not only sets new standards to investigate neuronal network dynamics in perioperative experimental research but also opens up possibilities to ask a whole new series of fundamental questions related to the mechanisms driving perioperative cognitive dysfunction. Understanding the molecular underpinnings driving the transient increase in excitatory neuronal network activity is one of them. In this regard, there is substantial experimental evidence suggesting that altered function in several neurotransmitter systems may be causally related to manifestations of POD.[7] A related question is whether transiently altered neuronal dynamics reflect the long(er)-term effects of anesthesia exposure itself or whether they are rather related to the surgery-induced inflammatory response. A distinct line of investigations should explore the question of whether the nature of excitation–inhibition imbalance related to POD-like behavior are comparable between different brain regions or, in contrast, this imbalance is region specific. Last but not least, the technology applied by Guo *et al.*[3] is an excellent opportunity to better explore gut–brain interactions in the perioperative context and beyond. While the puzzle of POD is far from being solved, the work from Guo *et al.*[3] constitutes a laudable and important piece along the way.

Competing Interests

Dr. Vutskits is a deputy editor for Anesthesiology. Dr. Mintz is an associate editor for Anesthesiology.

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"Bioblasts" in the Crosshairs—Again

Misha Perouansky, M.D., Philip G. Morgan, M.D., Ph.D.

Researchers, including anesthesiologists, repeatedly hear that one has to think "outside the box!" Certainly, most (not all) of drug development is not that, but rather the result of small chemical changes predicted to alter a pharmacokinetic characteristic of a current drug. However, in this month's Anesthesiology, we have a prime example of working outside the box and discovering a new, previously unsuspected, potential anesthetic target and agent. Somnay *et al.*,[1] in work from Richard Levy's laboratory, studied an undesired effect of propofol in mitochondria to lead them to a potentially new class of anesthetics.



"The amazing overall safety of general anesthetics obscures a fundamental fact: their desirable endpoint is an unphysiologically dysfunctional (comatose) brain… ."

The recent power failure on the Iberian Peninsula, causing a near-complete blackout in two European countries, reminded us that life as we enjoy it on the macroscopic scale is *manifest energy*. On the microscopic scale, the crucible of the cell's power grid in eukaryotes are mitochondria, power-*cum*-chemical plants integrated with signal processing centers. In 1894, Richard Altman referred to them as *bioblasts*, correctly intimating that they originated from once free-living organisms (the term *mitochondria* was coined in 1901 by Carl Benda). There, the sun's energy stored in foodstuff as high-energy electrons is extracted by reducing O_2 to H_2O. This energy is extracted primarily through oxidative phosphorylation: protons pumped against their electrochemical gradient from the mitochondrial core into the intermembrane space create a protonmotive force with an electrical ($\Delta\Psi_m$) and a chemical potential across the inner mitochondrial membrane. This potential of −90 mV facilitates the conversion of the sun's stored energy to adenosine triphosphate (ATP), a currency convertible on biologic exchanges, by powering the phosphorylation of adenosine diphosphate to ATP.

However, for phosphorylation to occur, protons must return through complex V (ATP synthase) of the mitochondrial respiratory chain. The occasional protons leaking across the inner mitochondrial membrane bypassing complex V are "uncoupled" from ATP generation. This "constitutive" leak serves numerous physiologic functions. A precipitous, uncontrolled leak, by contrast, "short-circuits" the mitochondrion: $\Delta\Psi_m$ collapses, and maximal ATP supply decreases. This mechanism has been proposed and supported as a mechanism underlying propofol infusion syndrome.

Somnay *et al.*[1] reasoned that within regions of the cell where highest ATP demand exists, a collapse in the ability to generate ATP might result in the desired "anesthetic" phenotype. One such region, performing energy-intensive function, is the neuronal synapse. As a result, neuronal cell signaling is particularly susceptible to inhibition of mitochondrial production of ATP. Somnay *et al.*[1] show that a sudden dispersion of mitochondrial $\Delta\Psi_m$, by pharmacologic induction of proton leakage, contributes to loss of righting reflex, the lab-bench rodent analog of unconsciousness. This phenotype is presumably caused by energy shortage in regions of cells with continuous high energy needs, *i.e.,* neuronal synapses. In combination with extensive previous work showing that volatile anesthetics also act through interference with mitochondrial energy generation (by suppressing the build-up of $\Delta\Psi_m$), an energy-based mechanistic theory of anesthesia emerges. Notably, this current experimental project was driven by the search

Image: Adobe Stock.

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for pathways of propofol-induced toxicity but may provide an explanatory framework for both desirable and undesirable effects of general anesthetics.

It could be tempting to look at the current work as simply finding another drug that inhibits mitochondrial function to attain the anesthetic state. It is not that: *it is much more*. While testing their working hypothesis of propofol *toxicity* using the coenzyme Q analog Ub5, the authors discovered that the aspartate glutamate exchange protein Aralar is a potential anesthetic effector. Aralar is activated by Ub5 and contributes to its *toxic* effects. Pursuing toxicity, the authors discovered that Aralar recruitment also contributes to loss of the righting reflex from Ub5 injection in mice. Ironically, however, although propofol also induces a proton leak, it does so through an Aralar-independent mechanism.

Here, we have a classic example of working outside the box and discovering a new, previously unsuspected, anesthetic target. Will Aralar ascend to a clinically useful target? Or will the Venn diagram overlap with toxicity be too great? Propofol is a good example of when differences between the desirable (loss of consciousness) and undesirable effects (membrane leak and toxicity) are sufficiently large to accommodate a useful anesthetic. Where will Ub5, or similar drugs, land in this overlap? It is too early to tell, but the possibilities need to be explored. As the authors point out, there is much work yet to be done before knowing whether this particular target and/or this class of drugs will be useful.

The amazing overall safety of general anesthetics obscures a fundamental fact: their desirable endpoint is an unphysiologically dysfunctional (comatose) brain—arguably comparable to ventricular dysfunction for the heart. It is the rarity of anesthetic toxicity that should be surprising, not its existence. The approach illustrated in this article, however, of using undesired effects of anesthetics to lead us to potentially desired ones, is undeniably powerful. The authors are to be congratulated for pointing us in a new direction.

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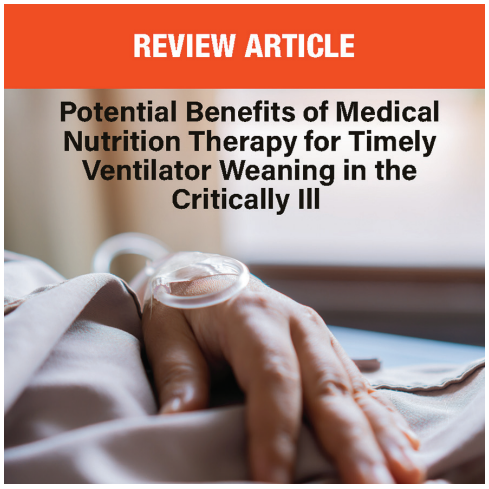
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Optimizing Nutrition to Reduce the Duration of Ventilation

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Prolonged or difficult weaning from invasive mechanical ventilation is a common and clinically significant challenge in the intensive care unit. In large cohorts of critically ill patients, invasive mechanical ventilation lasting more than 5 days occurs in a substantial proportion of cases.[1] Among the many contributing factors, inadequate nutrition resulting in muscle weakness or excessive energy intake—leading to increased carbon dioxide production—could impede weaning, even if this effect has not been studied so far. Consequently, the duration of weaning may serve as a pragmatic surrogate marker for nutritional adequacy (or inadequacy), particularly when functional outcomes remain under-reported and inconsistent in trials despite their clinical importance.[2,3]



"[T]ime to weaning represents a clinically meaningful, patient-centered endpoint that captures the complex interplay between metabolism, muscle function, and recovery."

In this issue of Anesthesiology, De Rosa *et al.*[4] provide an insightful narrative review examining nutritional strategies in relation to weaning. Their perspective evolved from a traditional "more is better" stance to the more nuanced "less is more" paradigm. This shift aligns with emerging trial evidence[5–7] supporting early macronutrient restriction and the concept of "permissive underfeeding" during the acute phase of critical illness.

The rationale for this approach lies in recognizing that overfeeding—before the patient has regained sufficient metabolic capacity—may be more harmful than beneficial, even when nutrition is recognized as important. The challenge remains in identifying the point at which the patient becomes "feeding responsive"[8]; that is, able to effectively metabolize increased nutritional intake. Similar caution applies to protein provision. Despite a strong theoretical rationale to deliver high protein doses to mitigate muscle wasting and promote anabolism, recent trials[9–11] have reported either neutral or adverse outcomes, including delayed weaning and increased complications.[12] These findings challenge long-standing assumptions and suggest that both timing and dose of protein require further individualization.

The use of markers of muscle protein catabolism, such as the urea-to-creatinine ratio, potentially help to detect the metabolic inflection point.[13] Meanwhile, indirect clinical indicators such as the intensity of the inflammatory response, hemodynamic stability, and insulin requirements are used to assess the ability to metabolize the macronutrients.[14]

At the bedside, indirect calorimetry remains the most accurate method to guide energy provision, enabling clinicians to avoid both early overfeeding (more than 50 to 70% of measured energy expenditure) and late underfeeding (less than 100% of energy expenditure). Although indirect calorimetry–guided nutrition has not yet demonstrated a definitive benefit on weaning duration, its physiologic rationale and individualization potential remain compelling. Complementary to this, functional imaging—particularly diaphragmatic ultrasound—offers a promising modality. While not ready for use in clinical practice routinely, it may be able to assess both respiratory muscle condition and the response to nutritional interventions.

Image: Adobe Stock.

This editorial accompanies the article on p. 737.

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Functional outcomes, including the duration of invasive mechanical ventilation and weaning success, are highly relevant endpoints in critical care nutrition trials. They offer greater clinical meaning than biochemical or surrogate outcomes and directly reflect the patient's physical recovery. However, functional outcomes such as muscular mass and function, rate of intensive care unit readmission, autonomy, activities of daily living, and return to work are likely influenced by several other factors including previous physical condition and the duration and magnitude of the acute phase of critical illness. Adequately powered trials should include hundreds of patients to allow an adjustment for these potential confounders. Future studies should prioritize such endpoints, particularly when evaluating the effects of manipulating macronutrient composition—carbohydrates, fats, and proteins—on ventilator liberation and respiratory function. Meanwhile, due to the lack of robust data on functional outcomes, currently available guidelines[15,16] only recommend that such measures (*e.g.*, physical strength or performance, hospital discharge disposition, and post–intensive care syndrome incidence rates) should be reported in future studies. Early macronutrient restriction is supported by the partially revised European Society for Clinical Nutrition and Metabolism guidelines,[16] *i.e.*, "energy delivery can be increased up to 80–100% of energy expenditure after day 3" and "1.3 g/kg protein equivalent per day can be delivered progressively."

Finally, once optimal macronutrient strategies are clarified, the evaluation of pharmaconutrients such as vitamin D, hydroxymethylbutyrate, and omega-3 fatty acids should also include weaning metrics as primary outcomes. These interventions, often targeting muscle preservation or metabolic modulation, may prove most valuable when aligned with individual recovery trajectories and functional benchmarks.

In conclusion, time to weaning represents a clinically meaningful, patient-centered endpoint that captures the complex interplay between metabolism, muscle function, and recovery. As De Rosa *et al.*[4] highlight, the integration of advanced monitoring tools and personalized nutritional strategies offers a pathway to optimized care. However, high-quality randomized controlled trials specifically targeting weaning-related outcomes are urgently needed to inform future practice. Until then, adopting a cautious, individualized, and function-oriented approach to nutrition may offer the best strategy for supporting critically ill patients through this pivotal phase of recovery.

Competing Interests

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ANESTHESIOLOGY®

Leveraging Large Language Models to Enhance Emotional Intelligence Training in Anesthesiology

Monika Nanda, M.B.B.S., M.P.H., Rodney A. Gabriel, M.D., M.A.S., Tetsuro Sakai, M.D., Ph.D., M.H.A.

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ABSTRACT

Emotional intelligence is essential for high-stakes interactions in the perioperative setting. Whether addressing patient concerns, resolving conflicts, or triaging cases, anesthesiologists rely on emotional intelligence for effective communication. However, stressors such as fatigue and heavy workloads can deplete the ability to sustain emotional intelligence during critical moments. Emotional intelligence can be strengthened with structured training. Large language models (LLMs), with their ability to generate empathetic responses, offer an innovative approach to enhancing emotional intelligence training in anesthesiology. LLMs can generate a variety of on-demand scenarios that can be fine-tuned, validated, and implemented by experts. They can be used to create tailored simulation scenarios for a variety of pedagogical methods to help clinicians prepare for emotionally charged conversations and enhance their communication skills. While not a replacement for human training, LLMs can serve as easily accessible supplemental tools to bolster clinicians' emotional intelligence skills when integrated with proper oversight.

(ANESTHESIOLOGY 2025; 143:504–8)

Emotional intelligence, defined as "the ability to recognize, understand, and deal skillfully with one's own emotions and the emotions of others,"[1] is an essential skill for high-stakes interactions in the perioperative setting. Emotional intelligence is a combination of self-awareness, self-regulation, empathy, compassion, motivation, and social skills.[2,3] Emotionally intelligent interpersonal communication is essential for effective leadership and teamwork[4–6], whether it is speaking up for patient safety, maintaining team morale, coordinating schedules, triaging cases, disclosing medical errors, managing a disruptive colleague, or providing constructive feedback to trainees. However, stressors such as fatigue and heavy workloads can deplete the ability to sustain emotional intelligence during critical moments, leading to breakdowns in communication or suboptimal teamwork. Anesthesiologists should be well trained and prepared for these vulnerable moments.

Research confirms that emotional intelligence can be strengthened through structured interventions.[7–9] Traditional approaches, such as standardized-patient role-plays or lecture-based workshops, help clinicians practice conflict resolution, self-awareness, and empathy.[10] In anesthesiology, simulation-based emotional intelligence training has also been proposed to augment these skills.[11] However, this is not widely implemented due to logistical constraints.

Recent advances in the "empathetic potential"[12] (Lee YK, Suh J, Zhan H, Li JJ, Ong DC. Large language models produce responses perceived to be empathic. Preprint. Posted online March 26, 2024. doi:10.48550/arxiv.2403.18148) of large language models (LLMs) provide a novel opportunity for anesthesiologists. The question is, can we tap into the power of a nonemotional yet emotionally intelligent resource to help us train for situations that demand a high degree of emotional intelligence? While preserving the essential human touch in difficult interactions, can LLMs bolster our capacity to communicate effectively when it matters most?

The Evolving Capabilities of LLMs

LLMs have demonstrated increasingly evolving capabilities in knowledge, reasoning, and creativity. In medical education contexts, LLMs have performed nearly on par with humans in oral and written board examinations across multiple fields.[13–15] Newer models often outperform previous versions, and they continue to evolve rapidly. They have also outperformed humans in emotional awareness evaluations such as the Levels of Emotional Awareness Scale[16] and can identify and respond to complex emotional cues, enabling validation of user feelings. This suggests that LLMs may respond to emotional content better than one might expect from a machine, an ability that could be harnessed in training scenarios.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

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More impressively, LLMs have shown potential in applying principles of the theory of mind and psychology,[16,17] forming the backbone of several personalized cognitive behavioral therapy models,[18–20] and excelling in traits we often think of as uniquely human: creativity, wit, humor,[21,22] and surprisingly, empathy and compassion.

How Do LLMs Generate Empathetic Responses?

The architecture of modern LLMs combined with the available computational resources have enabled deep learning models to process and respond to textual prompts in humanlike ways. The breakthrough in 2017 was the introduction of the "attention" mechanism in deep learning models (transformers).[23] Unlike previous approaches, "attention" allows the model to consider the context and relationship of words in a sentence, not just sequential order. This was key to advancing natural language processing, as it enabled understanding of linguistic structure and nuance, forming the basis of modern LLMs.[24] With more powerful computational resources, an extremely large corpus of text was then pretrained in such models, thus allowing the models to "self-learn" all the patterns and intricacies of human language, including text with empathetic and compassionate tones. This self-learning involves modeling millions to billions of parameters into the LLM, representing the patterns in sentences seen in the training sets. As a result, LLMs can statistically learn to identify emotional keywords and phrases and use them appropriately in responses.

Tapping LLMs' Potential for Emotional Intelligence Training in Anesthesiology

Interpersonal communication is a core competency expected of all physicians. LLMs offer a novel approach to bolstering these skills by generating on-demand, interactive role-play (Tamoyan H, Schuff H, Gurevych I. LLM role-play: Simulating human-chatbot interaction. Preprint. Posted online July 4, 2024. doi:10.48550/arxiv.2407.03974). A variety of teaching scenarios can be generated with prompts that can be tested, validated, and implemented by experts. Table 1 provides examples of difficult scenarios and suggested pedagogical methods that can be generated by LLMs.

In addition to generating scenario-based simulations, LLMs can cater to a variety of pedagogical methods typically applied in emotional intelligence training:

1. Narrative storytelling[25,26]: LLMs can generate scenarios or prompts that help foster empathy (*e.g.*, a story from a patient's perspective).

Table 1. Examples of EI Training Scenarios and Potential LLM-driven Pedagogical Methods

Category	Example/ Scenario	Key Learning Objectives	Suggested LLM-driven Approaches
1. Patient communication	Disclosing adverse events (*e.g.*, nerve block error); giving bad news (*e.g.*, surgical delay)	- Convey empathy and clarity - Apologize effectively - Provide next steps and reassurance	Role-play simulation: LLM simulates patient or family dialogue, guiding empathetic language and structured explanation.
2. Intrateam disagreements	Conflict about transfusion thresholds; scheduling disputes in the operating room	- De-escalate conflict - Use collaborative, respectful tone - Align on shared goals (patient safety)	Scenario practice: LLM role-plays a challenging colleague, offering real-time feedback on wording, tone, and conflict resolution strategies.
3. Professional feedback	Correcting a resident's oversight; coaching on unprofessional behavior	- Deliver constructive criticism - Maintain respectful relationships - Encourage reflection	Adaptive role-play: LLM simulates defensive resident responses, prompting the user to refine empathy, clarity, and problem-solving steps.
4. Family interactions	Explaining poor prognosis; responding to distressed relatives	- Validate strong emotions - Balance honesty with empathy - Build trust and rapport	Multiple-choice exercises: LLM provides different response options (empathetic *vs.* brusque). Learners select best approach, and LLM explains impact.
5. Narrative and storytelling	Vignettes capturing ethical dilemmas or emotional tension	- Identify empathetic *vs.* nonempathetic elements - Understand nuanced emotional cues	Story generation: LLM creates short narratives. Learners dissect missed opportunities for compassion, practice rewriting dialogue more sensitively.
6. Perspective-taking drills	Seeing a conversation from patient *vs.* clinician viewpoint	- Recognize emotional triggers - Understand how words might be perceived - Promote self-awareness	"Listener's view": LLM generates the inner thoughts of a patient or colleague reacting to certain language choices, highlighting emotional impact.
7. Emotion-recognition exercises	Detecting frustration or anxiety in a teammate using subtle cues during a surgical case	- Strengthen emotional awareness - Use self-regulation (*e.g.*, short pause, calm tone)	Sequential prompts: LLM presents incremental clues about emotional escalation, prompting learners to identify emotions and choose a de-escalation tactic.
8. De-escalation role-plays	Managing an angry surgeon in a high-pressure scenario	- Practice verbal diffusion - Maintain composure - Acknowledge concerns and find compromise	Stepwise simulation: LLM escalates the colleague's frustration in stages. The user responds, and AI critiques or suggests less inflammatory phrases.

AI, artificial intelligence; EI, emotional intelligence; LLM, large language model.

2. Multiple-choice empathy quizzes: The model presents a dialogue and asks the user to choose the most empathetic response, then explains why certain responses might escalate tension.
3. Perspective-taking drills[27]: The clinician can input a situation, and the LLM describes it from the patient's or colleague's perspective, helping the clinician understand how their words might be interpreted.
4. Emotion-recognition sequences: The LLM can prompt the user through stepwise identification of emotions (*e.g.*, recognizing anger *vs.* fear in a scenario) and practice self-regulation before responding.
5. De-escalation role-plays[28]: An LLM can simulate a difficult conversation (*e.g.*, an upset surgeon or patient), and the user can practice maintaining a calm tone and phrasing that defuses conflict.

Examples of LLM-generated emotional intelligence training scenarios are provided in Supplemental Digital Content 1 (https://links.lww.com/ALN/D982) and Supplemental Digital Content 2 (https://links.lww.com/ALN/D983). The first prompt used ChatGPT-o1 (OpenAI, USA, March 2025) to create a role-play script in which the anesthesiologist on call navigates two conflicting emergent cases. The second prompt used Gemini 2.0 Flash-Thinking model (Google AI, USA, March 2025) to create an adaptive role-play scenario to deliver empathetic feedback to a resident for insufficient setup before induction.

Preliminary data support these applications. In mental health contexts, LLM-powered chatbots have delivered immediate feedback on user interactions, helping participants refine their interpersonal skills.[29] Other studies report improved awareness of one's own language patterns after repeated sessions with LLM "coaches."[30] While randomized trials in anesthesiology are lacking, preliminary evidence suggests that repeated engagement with empathic prompts can accelerate learning.[31,32]

LLM-assisted emotional intelligence training shows promise but has limitations. LLMs simulate empathy from learned patterns, risking hollow or fabricated ("hallucinated") responses (Yao J-Y, Ning K-P, Liu Z-H, Ning M-N, Yuan L. LLM lies: Hallucinations are not bugs, but features as adversarial examples. Preprint. Posted online October 2, 2023. doi:10.48550/arxiv.2310.01469) if confronted with unfamiliar scenarios, although this can be addressed by fine-tuning prompts and with strategies such as retrieval-augmented generation.[33,34] LLM's reliance on potentially biased data[35] may reinforce stereotypes. Experts caution that LLMs, lacking a true moral framework, can mislead users who rely on them uncritically. Educators must supervise LLM outputs closely, ensuring they align with professional standards. LLMs have inherent vulnerabilities in privacy and security.[36] Publicly available LLM platforms do not meet confidentiality requirements, so scenarios must be de-identified or use hypothetical details. Further, there is limited evidence comparing empathetic responses from multiple available LLMs.[12] Additionally, overreliance on LLMs could dilute authentic human connection: no algorithm replaces the moral and emotional depth of genuine empathy, and users should approach LLM suggestions with discernment and consider strategies such as "human-in-the-loop."[37] Nonetheless, the potential is compelling: LLMs can generate near limitless variations of empathic scenarios catering to unique learning objectives.

In conclusion, LLMs offer an innovative approach to enhancing emotional intelligence training in anesthesiology because of their ability to generate a variety of on-demand scenarios that can be fine-tuned by experts. Beyond simulations, LLMs can create storytelling exercises, multiple-choice empathy assessments, and structured steps for emotion recognition and de-escalation, leaving the experts in charge of how to implement them. If thoughtfully integrated, respecting patient privacy and guided by expert oversight, LLM-generated emotional intelligence training scenarios could become a valuable supplement to existing methods. Future studies will determine the best ways to implement these tools in practice, but embracing innovation in this arena could enhance how we teach emotional intelligence in anesthesiology practice.

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Supplemental Digital Content

Supplemental Digital Content 1: LLM-generated Role-play for Scheduling Conflict, https://links.lww.com/ALN/D982
Supplemental Digital Content 2: LLM-generated Script for Adaptive Feedback, https://links.lww.com/ALN/D983

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ANESTHESIOLOGY®

Anesthesiology Clinical Trial Networks in the United States: A Report from the Anesthesia Research Council

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The Need for Large-scale Patient-centered Outcomes Research in Anesthesiology

Patient-centered outcomes research aims to generate knowledge to improve outcomes that are meaningful, valuable, and helpful to patients and their families.[1] For research comparing 2 or more treatment alternatives, this is often best achieved through the conduct of large-scale multicenter clinical trials. This approach provides a more accurate estimate of treatment effects than observational studies due to the use of randomization, allows for sufficient power when sample sizes are sufficiently large to detect small but clinically meaningful differences between treatment groups and effects in smaller subpopulations that may be more likely to benefit, and can create generalizable evidence when trials enroll diverse populations recruited from different care settings and environments. In addition to the potential benefit for patients, high-quality clinical research engages and educates clinicians in impactful science and contributes to the learning and professional development within the medical specialty overall. Within the United States, there is a significant need to establish high-functioning clinical research networks that facilitate the design, performance, and completion of such trials.

In 2016, the American Society of Anesthesiologists (ASA), the International Anesthesia Research Society (IARS), and the Foundation for Anesthesia Education and Research (FAER) created the Anesthesia Research Council (ARC).[1]

The ARC's mission is to provide "independent, trustworthy synthesis and advice to address complex challenges by mobilizing expertise, practice, and knowledge in science, engineering, and medicine."[2] The present report represents the work of the ARC Year 2 Working Group. This group was charged with: (1) summarizing the current state and future prospects of collaborative patient-centered outcomes research in anesthesiology in the United States; (2) identifying facilitators and barriers to establishing 1 or more collaborative, U.S.-based patient-centered outcomes research

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networks in anesthesiology; and (3) recommending specific actions that key stakeholders should undertake to transform the landscape of patient-centered outcomes research in anesthesiology in the United States over the next 5 to 10 years.

Existing Clinical Trial Networks and Resources in Anesthesiology

In working group discussions, we identified current U.S. and international patient-centered outcomes research networks in anesthesiology and other medical specialties that could serve as models for future U.S.-based anesthesia multicenter research networks. We then conducted informal interviews with leaders of these organizations and drew on the experiences of working group members within these organizations to learn more about the successes and challenges within these trial network groups. Interview notes were shared and discussed in working group meetings to identify barriers and facilitators to trial network function and operations, and generate potential recommendations.

While the working group considered multiple networks within and outside of anesthesiology, here we focus on 3 established anesthesia trial networks and 1 quality improvement collaborative that has built the infrastructure to support trials within the United States.

Australian and New Zealand College of Anaesthetists Clinical Trials Network, Australia and New Zealand

The Australian and New Zealand College of Anaesthetists (ANZCA) is the specialist medical college accredited to train anesthesiologists and support their continuing professional development. In 2003, after the successful collaborations of the Multicentre Australian Study of Epidural Anaesthesia (MASTER)[3] and the Bispectral index monitoring to prevent awareness during anesthesia (B-Aware)[4] Trial, investigators and the College established the ANZCA Clinical Trials Network (CTN). ANZCA CTN now has more than 70 participating sites across Australia and New Zealand. This CTN offers pilot grants and programs to support emerging researchers and maintains staff to support CTN operations, CTN-endorsed trials, and the network of ANZCA sites, investigators, and research coordinators. Strengths of the CTN include that it is embedded within ANZCA—with the college providing administrative support (ie, event planning, communications) as well as ongoing financial support. This ensures some sustainability and a high degree of ownership and pride among the Australian and New Zealand anesthesia research community. The network has grown to be a world leader in clinical trial methodology and delivery, completing numerous, large, international, multicenter trials within budget, at over 130 sites worldwide.[5–7]

Perioperative Anesthesia Clinical Trials (PACT), Canada

Within Canada, investigator-initiated studies led by academic centers (eg, PeriOperative ISchemic Evaluation [POISE-1] trial,[8] PeriOperative ISchemic Evaluation-2 [POISE-2] trial,[9,10] PeriOperative ISchemic Evaluation-3 [POISE-3] trial,[11] Blood Conservation Using Antifibrinolytics in a Randomized Trial [BART] trial,[12] Measurement of Exercise Tolerance before Surgery [METS] cohort study,[13] and Functional Improvement Trajectories After Surgery [FIT After Surgery] cohort study[14]) have helped build informal networks, and in 2010, the Perioperative Anesthesia Clinical Trials (PACT) Group was established as a formal collaborative network for multicenter studies in anesthesiology and perioperative medicine with support from the Association of Canadian University Departments of Anesthesiology (ACUDA).[15] PACT serves as a forum to foster collegial collaboration, refine study designs and grant proposals, identify partners for multicenter collaborations, and deliver educational content for researchers. Since its inception, the PACT group has steadily grown in membership, meeting attendance, and research success (as measured by publications and grants),[16] and has mentored and supported a new generation of physician-scientists within the Canadian anesthesiology community. The formal and informal mentorship provided by the group, along with opportunities to extend collaborative networks, has allowed early-career and midcareer investigators across different academic centers to achieve success in highly competitive peer-reviewed funding competitions.

Outcomes Research Consortium, Worldwide

The Outcomes Research Consortium is an academic research organization consisting of over 200 investigators at 50 different institutions in 25 countries across the world, headquartered now at the University of Texas, Houston.[17] Since its inception in 1990, the Consortium has published more than 2000 scientific papers and editorials, and has been involved in numerous clinical studies, including large international multicenter perioperative outcome trials.[18,19] The administrative hub provides protocol design review; project management, including investigator and site identification, site monitoring, and help with regulatory documentation; and biostatistics and data management services. Members are expected to actively collaborate (which is the only criteria for membership) and help complete studies. While members of the Consortium have successfully competed for federal funding, many studies have been sponsored by industry partnerships, which have provided a sustainable source of support for research activities.

Multicenter Perioperative Outcomes Group (MPOG), United States

The Multicenter Perioperative Outcomes Group (MPOG) is a collaborative of medical centers/hospitals, physicians, nurses, software developers, data scientists, statisticians, researchers, and administrators focused on promoting safe and evidence-based perioperative care through collaboration, research, education, and quality improvement. MPOG maintains a growing registry of over 23 million cases combining preoperative, intraoperative and postoperative

outcome data contributed by over 70 participating hospitals. Primarily, MPOG data has contributed to observational studies.[20,21] Now, MPOG has transitioned to also enable large, multicenter, pragmatic clinical trials given the robust electronic health record data collection platform and collaborative relationships. MPOG is now serving as the Data Coordinating Center for 3 distinct prospective clinical trials: Trajectories of Recovery after Intravenous Propofol versus inhaled VolatilE anesthesia (THRIVE),[22] a Patient-Centered Outcomes Research Institute (PCORI)-funded pragmatic clinical trial of 12,500 patients across approximately 20 U.S. hospitals (NCT05991453), an Agency for Health care Research and Quality's (AHRQ) funded cluster-randomized trial of precision feedback to anesthesia clinicians to improve clinical quality measurement performance (NCT05923463), and a multicenter cluster-randomized cluster-crossover trial of different intraoperative oxygenation strategies (IntraopOx) funded through the Initiative for Multicenter Pragmatic Anesthesiology Clinical Trials (IMPACT) award instrument.

Lessons Learned and Potential Threats to a Successful U.S. Anesthesia Clinical Trials Network

Several key factors to success emerged from examining existing trial networks and from discussions within the working group. Successful networks must (1) generate interest among stakeholders, (2) impact the field, (3) maximize efficiency, (4) create a culture of accountability, and (5) plan for growth.

Networks can generate interest among a variety of stakeholders by targeting clinically important outcomes, testing compelling interventions, and producing generalizable evidence. Several nonanesthesia networks in the United States were started in partnership with funding agencies, which allowed these networks to begin with administrative support, a clear directive, accountability to a funding agency, and seed money for trials. Achieving early successes engenders and propagates buy-in from funders, and achieving early success should be considered when selecting initial studies to serve as demonstration projects or when selecting sites for participation. Buy-in from both academic and community clinicians is critical, as clinicians are responsible for patient recruitment and study implementation and are the "end-users" of research results; individual clinicians having a sense of ownership over the research and being motivated to contribute to research efforts was highlighted as a major facilitator to completing studies in the ANZCA CTN. Professional societies can also play an important role in supporting a burgeoning research network, as they have in Australia and Canada. Established national organizations are well-suited to provide organizational and administrative support; additionally, societies communicate regularly with member clinicians, and their support serves to publicize and endorse a network's efforts.

Completing impactful studies demonstrates success. Scientific impact is generated by answering clinically important practice-changing questions through the completion of well-powered trials and the publication of results in high-impact journals. However, networks also have specifically focused on mentoring early-career investigators to broaden their impact on future research and the specialty. Lastly, to maximize generalizability of research, attention must be paid to participant and site (eg, community practices) diversity and to the incorporation of implementation science that better facilitates the translation of the generated knowledge into clinical practice.

Efficiency is a critical attribute for the success of a burgeoning trial network, as the efficient use of resources reduces incremental effort and financial requirements. While the United States lacks a formal trial network within anesthesiology, resources such as the Outcomes Research Consortium, MPOG, and existing networks from previously conducted or ongoing trials (eg, Regional versus General Anesthesia for Promoting Independence after Hip Fracture [REGAIN,][23] Postoperative Pulmonary Complications, Early Mortality, and Hospital Stay After Noncardiothoracic Surgery,[24] and Prophylactic Acetaminophen to Prevent Postoperative Delirium in Older Cardiac Surgical Patients [PANDORA])[25] may be leveraged or built on to maximize efficiency. To streamline the conduct of clinical trials, certain aspects of study conduct or data collection (eg, common data elements) should be standardized.

Establishing a culture of accountability at the outset of any trial network is essential. Individual sites should be held accountable for the science being conducted by maintaining robust processes for participant screening, participant recruitment, participant follow-up, and study oversite. A successful network provides "mentoring" of lower-performing sites from high-performing sites. The network should also aim to set and meet predesignated metrics to measure its own success (eg, completion of a certain number of trials, use of the network for federally funded trials), demonstrate return on investment, and establish the value of the network to all its member sites, funding agencies, and patients.

Although initial steps of any network will focus on establishing a footprint and sustainability, there is a need to plan for growth. The network and participating sites would ideally prepare to expand and create capacity to conduct different types of studies (eg, mechanistic, longitudinal, or translational studies) with different designs (eg, stepped wedge, cluster randomization, hybrid implementation, platform trials), as well as the creation of centralized shared resources, such as tools for data collection or training research personnel, research support services (eg, biostatistical consulting, institutional review board resources), and data repositories or biobanks.

While the U.S. health care system has many strengths that can be leveraged for running large-scale impactful clinical

trials, major challenges exist, chief of which is the need to obtain and maintain funding. This may be particularly difficult in anesthesiology which is not "organ-specific" and reaches patients across the life span, as existing funding structures in the United States (eg, National Institutes of Health [NIH]) are often directed to support research on a specific organ or patient population. Moreover, the high cost of clinical operations and strong economic pressure to generate revenue make the conduct of research costly and a secondary priority. Furthermore, even with successful networks, the need for continued funding is a constant threat across specialties and a concern for long-term sustainability. Another major obstacle is the decentralized national health care system. This framework presents challenges related to standardization of data collection and categorization, interoperability among informatics systems, and heterogeneity of local (institutional or state) research and clinical governance. Additionally, there can be significant resistance to change in health care settings. This may originate from health care providers who are comfortable with existing practices and systems, as well as from patients who may be concerned about privacy or the potential impacts of research on their clinical care. Other major obstacles include high per patient costs for clinical research, large administrative and regulatory burden to conduct research in the United States, and rules surrounding research conduct and data sharing. While not unique to multicenter trials, these challenges have a significant impact on design and performance of multicenter trials in the United States. Use of a single institutional review board (sIRB) and growth of pragmatic clinical trials are 2 facets of modern multicenter trials that address these issues.

Recommendations for Establishing an Impactful Patient-centered Outcome Research Network in Anesthesiology

We offer actionable recommendations for developing a patient-centered outcomes research network in the United States that conducts impactful clinical trials in anesthesiology, perioperative medicine, critical care, and pain medicine (table 1). The function of the network will be to serve as a repository of potential sites that investigators may consider approaching for participation in clinical trials. Over time, the network itself would serve the function of making collaborations function, retaining knowledge of past experiences regarding sites' performance and practical issues in the conduct of anesthesiology research. The proposed model differs from current research groups in 2 main ways. First, it would "democratize" research and allow for greater inclusivity and diversity of sites that have the potential to perform well and contribute to perioperative research. Second, for researchers without significant existing infrastructure within their institution, or for emerging researchers without existing relationships with other sites, the network will facilitate building connections among investigators and sites. We recommend creation of the **M**ulticenter **A**nesthesia **TRI**als for **A**dvancing **R**esearch and **C**linical **H**ealth (MATRIARCH) Network (fig. 1). Objectives of the MATRIARCH Network include:

- Connect investigators with sites and facilitate evaluation of potential sites
- Provide a framework for site onboarding and activation
- Streamline regulatory, informatics, and statistical support across sites
- Standardize data collection, outcomes assessments, and adverse event reporting across sites
- Establish resources (repository of site metrics, centralized data transfer processes and rules, standardization of data elements) and templates (protocol, budget, and subcontract templates) that enhance trial feasibility, efficiency, consistency, and funding application success
- Build enthusiasm and collegial collaboration for conducting anesthesia practice-changing clinical trials for all interested parties in academic anesthesiology (anesthesiology departments, hospital systems, anesthesia-based societies and journals, and funding agencies)

To meet these objectives, we recommend centralized administration of the MATRIARCH Network; promotion of the MATRIARCH Network and Network trials by national anesthesia organizations and foundations, academic medical centers, and community hospital systems; and establishment of ground rules for initial participation by institutions and investigators. These recommendations are not prescriptive but are intended to provide a framework and stimulus for advancing ARC's multicenter clinical trial Network initiative.

Network Support

We recommend that ARC's founding organizations and other bodies dedicated to advancing research in anesthesiology, nominally the ASA, the Association of University Anesthesiologists (Association of University Anesthesiologists), IARS, and FAER support the creation, maintenance, and success of the MATRIARCH Network. *Initial Steps* include supporting the development of a web-based platform that connects investigators and sites and providing administrative personnel support to facilitate access to the platform and to field queries from investigators and from participating and potential sites.

We encourage funding agencies, such as the NIH, to form specific programs that focus on patients receiving anesthesia and surgery, similar to how the NIH has created specific funding mechanisms like the Strategies to Innovate Emergency Care Clinical Trials Network (SIREN) Network and Cardiothoracic Surgical Trials Network (CTSN) for patients presenting to emergency departments and for cardiac surgery, respectively. Globally, more than 300 million surgeries are performed each year, and a substantial number suffer perioperative morbidity and poor recovery.

Table 1. Summary of Recommendations to Stakeholders for Patient-centered Outcome Research Network in Anesthesia and Perioperative Medicine

To the Anesthesia Research Council:
- Create the "MATRIARCH Network" by establishing bylaws, governance structure, and operating procedures

To ARC forming organizations (ASA, IARS, FAER):
- Allocate financial in-kind support to create and maintain a web-based MATRIARCH Network platform
- Provide administrative and informatics support that facilitates investigator and site (medical center, hospital, practice group, etc) access and use of the platform and Network
- Recognize and promote medical centers, institutions, and private practice groups that participate in the MATRIARCH Network

To department chairs and private practice group leadership:
- Value and reward physician and staff participation in Network trials through education, recognition, promotion, and allocation of protected time for research
- Establish and support local clinical research staff (research coordinators, regulatory personnel, informatics personnel) and infrastructure for completing clinical trials
- Establish and support local systems for engaging patients and the public to participate in clinical trials
- Support patient advocacy groups and inclusion of patients in clinical trial design and regulation
- Hospitals participating in research networks demonstrate a commitment to practicing evidenced based medicine and maintaining standards for quality improvement

To research funding agencies including but not limited to the NIH, the PCORI, and the DoD; foundations committed to safety and quality care; and other private entities:
- Prioritize research for multicenter clinical trials that aim to improve care for anesthesia/surgery, critically ill, and pain patient populations, specifically trials that use a network such as MATRIARCH

To existing anesthesia research networks including but not limited to the MPOG and the Outcomes Research Consortium:
- Partner with, collaborate with, and promote the MATRIARCH Network to best accomplish the shared mission of advancing care for anesthesia/surgery, critically ill, and pain patient populations

To principal and study site investigators:
- Participate and use the MATRIARCH Network to conduct research
- Hold oneself accountable to the rigorous conduct of science, the specialty of anesthesiology, and ultimately, patients
- Implement quality assurance and improvement strategies with frequent monitoring and feedback of sites, to improve the rigor of research

To consumers/patients:
- Remain open to opportunities to participate in research. This may improve your care and will generate evidence that allows investigators to test hypotheses and generate knowledge that will improve care for future patients.

ARC, Anesthesia Research Council; ASA, American Society of Anesthesiologists; DoD, Department of Defense; FAER, Foundation for Anesthesia Education and Research; IARS, International Anesthesia Research Society; MATRIARCH, **M**ulticenter **A**nesthesia **TRI**als for **A**dvancing **R**esearch and **C**linical **H**ealth; MPOG, Multicenter Perioperative Outcomes Group; NIH, National Institutes of Health; PCORI, Patient-Centered Outcomes Research Institute.

To improve care and outcomes for these patients, it is imperative that major funding agencies support practice-changing and practice-defining multicenter clinical trials in anesthesiology. The MATRIARCH Network could provide the infrastructure to address the large unmet need within perioperative research.

Network Function

Both the web-based platform and the MATRIARCH Network administrator will facilitate systematic and efficient review of sites and of studies/investigators. The platform will include lists of Network sites/centers with the requisite site and patient data that allow investigators to evaluate feasibility and subject characteristics. Data should be regularly updated (eg, quarterly, annually) and include patient and encounter data specific to perioperative, critical care, and pain research and site characteristics data such as research staff availability, presence of an anesthesia-led preoperative assessment facility or service, and prior study participation. Prior study participation data should include for each prior trial, the number of patients screened, the number eligible, the number consented, and the number who completed the study. Patient and encounter data necessary to evaluate a site include patient demographics (age, sex, race, ethnicity, body mass index), number and types of various surgeries (CPT codes), comorbidities (ICD codes), anesthesia type (general neuraxial, sedation, regional), disposition (outpatient, inpatient, day of admission), case duration, length of stay, and relevant outcomes. Data elements will be consistently defined and applied across sites, and the MATRIARCH Network will leverage existing national data harmonization, acquisition, and reporting efforts. For example, MATRIARCH perioperative electronic health record data for MPOG sites could be facilitated by existing MPOG central data rather than building de novo data extracts and transfers, building on existing validated MPOG phenotype definitions. This would limit site burden by leveraging existing data collection, cleaning/validation, and transfer procedures, while maintaining ample opportunity for non-MPOG sites to contribute and participate.

Sites will identify a site leader who will serve as liaison between investigators and the site and who will help identify relevant personnel at the site to vet and complete trials. Rather than receive proposals and select individual trials to support and complete across the Network, the MATRIARCH Network should function more as a networking site to connect investigators with sites and streamline onboarding of sites and execution of trials. Sites may participate in whichever trials they commit to and would not be confined to specific trials.

Longer term functions and benefits of the MATRIARCH Network include expansion of the administrative core to provide assistance and resources for automated electronic

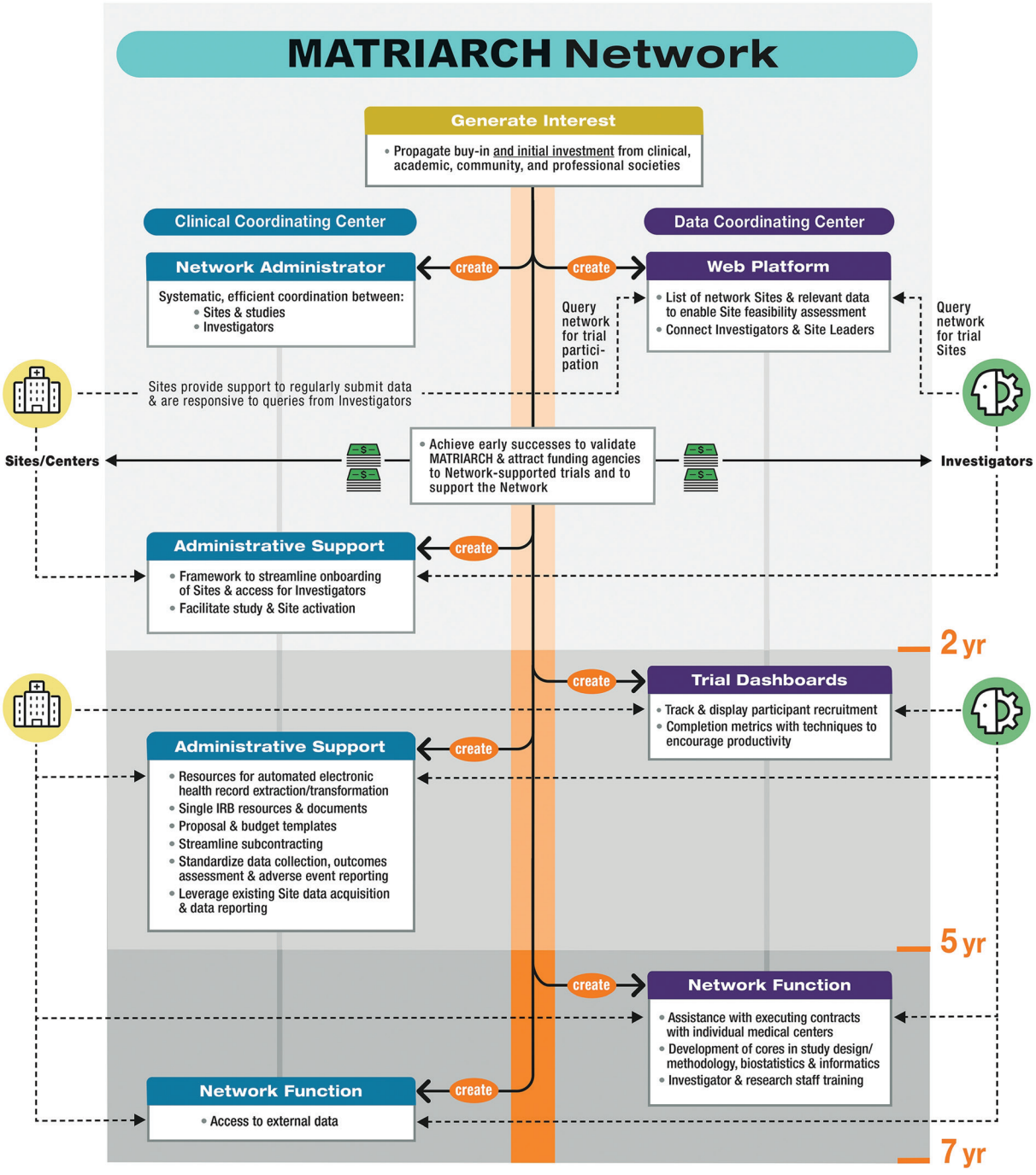


Fig. 1. MATRIARCH network. Proposed initiation and functionality of an anesthesiology clinical trials network (MATRIARCH). IRB, institutional review board; MATRIARCH, **M**ulticenter **A**nesthesia **TRI**als for **A**dvancing **R**esearch and **C**linical **H**ealth.

health record extract/transformation/load processes, sIRB resources and standardized documents, proposal templates to support resources/facilities sections for grant applications, text to support data sharing agreements, budget templates (customized to the study but then standardized across sites), and creation of trial dashboards that track and display participant recruitment and completion metrics with techniques to encourage productivity. Network capabilities and function could further expand to include access to external data (eg, National Surgical Quality Improvement Program [NSQIP], Centers for Medicare & Medicaid Services [CMS], National Death Index); assistance with executing contracts with individual medical centers; development of cores in study design/methodology, biostatistics,

and informatics; investigator and research staff training; and creation of a Clinical Coordinating Center (CCC) and a Data Coordinating Center (DCC) to execute trials.

Network Deliverables

Deliverables for MATRIARCH Network participating sites include opportunity to participate in multicenter trials; support for data sharing agreements, contracting, regulatory requirements and IRB; and the advancement of perioperative and critical care science. Requirements of sites include maintaining availability and responsiveness to investigators, sites within the network, and network staff/personnel; regular upload of aggregate deidentified patient/procedural data; and consideration of participation in trials. In the spirit of health equity and productivity, we recommend that all hospitals, medical centers, and health systems that express interest and meet requirements for communication and data reporting be eligible to join as a Network site and that principles of health equity should inform site selection to ensure all patient populations are included and to maximize generalizability of results.

Deliverables for investigators/trialists include access to the MATRIARCH Network's sites and centers; exposure to relevant site-specific perioperative summary data that allows assessment of site feasibility for potential inclusion; tools to facilitate patient and community engagement; and standardized regulatory, data acquisition, and trial start-up documents for site initiation, trial performance, and funding application submissions. Access to site data for individual investigators/trials requires the investigator's site to participate actively and adhere to minimum data standards. This will promote growth of the Network and provide accountability between investigators and sites.

Network Promotion

For such a network to succeed, institutions and departments should prioritize and value participation in large multicenter trials. This includes education on research within residency and department seminar and conference offerings, implementation of behavioral approaches to enhance enrollment,[26] partnerships with payors (Medicare, insurers) to fund research, and PhD programs in perioperative clinical research. The cost and availability of clinical research coordinators and the need for nonclinical time of coinvestigators pose barriers. Thus, commitment from institutions and departments to support nonclinical time for faculty and to support clinical research efforts will be necessary to facilitate the conduct of large multicenter trials and enrollment of many patients in a reasonable period. We encourage departments and hospital systems to create and support internal clinical research cores that include trial coordinators, research nurses, and trial regulation/contracting/IRB expertise. Institutional promotion committees should reward the contribution of local investigators for their active participation in multicenter trials based on site trial metrics (overall and study specific). Large anesthesia practice groups should also participate in pragmatic clinical trials, especially as advanced electronic health record (EHR) and information technology (IT) capabilities across the group make it possible to automate granular capture of monitor and medication use, patient risk factors, and intraoperative vital signs for large numbers of patients.[27] Collaboration with community practices can provide academic anesthesiologists with large volumes of common cases for analysis.

The launch and success of the MATRIARCH Network requires a stepwise and incremental approach that focuses on the *Initial Steps* outlined above. There are numerous important clinical questions to address (table 2). Network success further requires 1 or more initial trials to incorporate the Network into their trial start-up, performance, and close-out/completion procedures.. This will provide opportunity to create and refine Network functionality and efficiency. Such trials will need to secure funding and support independent of the MATRIARCH Network, as the Network is untested and unvalidated, whereas subsequent trials can tout use of the Network as a strength to recruit sites, recruit participants, and conduct high-quality perioperative science efficiently and effectively.

Conclusions

Developing a patient-centered outcomes research network has a unique opportunity to transform anesthesiology and critical care medicine in providing clinical practice-changing trials and ultimately improving patients' outcomes and public health.

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Table 2. Examples of Potential Impactful Multicenter Clinical Trial Questions in the Specialty with Patient-centered Outcomes

- Does routine implementation of preoperative screening for cognitive dysfunction result in a reduction in the use of high-risk medications and result in less postoperative delirium?
- Do opioid-sparing techniques alter the risk of persistent opioid use after surgery?
- Does a management approach aimed at reduction of hypotension reduce postoperative organ dysfunction compared to usual care?
- Does protocolized neuromuscular blockade and reversal management based on quantitative monitoring reduce the occurrence of postoperative pulmonary complications compared to subjective monitoring?
- Does implementation of a department wide patient satisfaction survey after each anesthetic with routine feedback to faculty and department leaders impact provider behavior, patient satisfaction, subjective symptoms (pain, nausea, etc) and readmissions?
- Does supraglottic airway management reduce the risk of postoperative pulmonary complications compared to endotracheal intubation for surgeries commonly managed with either technique?

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Competing Interests

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Supplemental Digital Content

Table S1: Acronyms, https://links.lww.com/ALN/E113

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Statistical Analysis and Reporting of Cardiac Output Method Comparison Studies (COMPARE) Statement

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ABSTRACT

Cardiac output is a key cardiovascular variable quantifying global blood flow. The measurement performance of cardiac output monitoring methods is investigated in validation studies, which are method comparison studies determining the agreement between cardiac output values measured with a test method and those measured with a reference method. The StatistiCal analysis and repOrting of cardiac output Method comPARison studiEs (COMPARE) statement provides a framework for designing, performing, and reporting cardiac output method comparison studies and includes a checklist of 29 items that are essential for reporting of those studies. Considering and reporting the items specified in the COMPARE checklist will help standardize cardiac output method comparison studies and increase the external validity of the results.

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Cardiac output—the volume of blood pumped by the heart per minute—is a key cardiovascular variable quantifying global blood flow. Numerous validation studies were and are being performed to test the measurement performance of cardiac output monitoring methods.[1–4] From a methodologic perspective, these validation studies are method comparison studies in which the agreement between cardiac output values measured with a test method (CO_{TEST}) and values measured with a reference method (CO_{REF}) is determined.

Cardiac output method comparison studies can differ regarding the study design, the cardiac output measurement methods, the clinical setting and patient population, the methods for data sampling and processing, the statistical analyses, and the definitions for "clinically acceptable agreement" between CO_{TEST} and CO_{REF}. Although there are previous publications on performing cardiac output method comparison studies,[5–9] there is no generally accepted standard for how such studies should be designed, performed, and reported. This makes it difficult to assess the internal and external validity of study results.

Cardiac output method comparison studies should be reported transparently and comprehensively with regard to

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Abbreviations: **COMPARE**, StatistiCal analysis and repOrting of cardiac output Method comPARison studiEs; **CONSORT**, Consolidated Standards of Reporting Trials; **CO_{REF}**, cardiac output values measured with a reference method; **CO_{TEST}**, cardiac output values measured with a test method; **GRRAS**, Guideline for Reporting Reliability and Agreement Studies; **PRISMA**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **STARD**, Standards for Reporting Diagnostic Accuracy; **STROBE**, Strengthening the Reporting of Observational Studies in Epidemiology

what was planned, what was done, what was found, and what conclusions were drawn. Therefore, we aimed to develop reporting guidelines analogous to those established for other study types.[10–15] We therefore established a network of clinical researchers, methodologists, and journal editors to develop recommendations on how to perform and report cardiac output method comparison studies: the StatistiCal analysis and repOrting of cardiac output Method comPARison studiEs (COMPARE) statement.

A detailed review of methods to measure cardiac output is beyond the scope of our article. Measuring cardiac output in clinical practice remains challenging because it is a dynamic variable determined by cardiac stroke volume and heart rate, both of which can change rapidly in response to physiologic and clinical factors making reliable real-time measurements technically demanding. There are invasive, minimally invasive, and noninvasive methods to measure cardiac output in perioperative and intensive care medicine.[16] Indicator dilution methods, such as pulmonary artery thermodilution[17–19] and transpulmonary thermodilution,[20,21] are considered clinical reference methods against which other cardiac output monitoring methods are compared. However, indicator dilution methods provide cardiac output values intermittently and do not measure cardiac output *directly*. Rather, they calculate cardiac output based on downstream changes in indicator concentration after the upstream injection of an indicator, which introduces variability related to injectate timing, indicator volume, and patient-specific factors.[22] Due to these inherent limitations, indicator dilution methods cannot be considered true "gold standards." Additionally, indicator dilution methods are invasive and can cause complications, although severe complications are rare.[23,24] Over the past decades, various minimally invasive and noninvasive cardiac output monitoring methods have been developed, including pulse wave analysis, bioimpedance/bioreactance, pulse wave transit time, and ultrasound Doppler methods.[16,25–29]

Aims and Intent of the COMPARE Statement

The COMPARE statement is a checklist and guideline to provide a framework for reporting cardiac output method comparison studies. It can also help design and perform these studies. Here, we present the COMPARE statement and provide methodologic background regarding transparent reporting. We recommend using the COMPARE checklist when reporting cardiac output method comparison studies and advise authors to consider all checklist items in their articles. Using and reporting the statistical methods according to the checklist will help standardize cardiac output method comparison studies and increase the external validity of the results. Even though this checklist may (in part) be applicable to other method comparison studies (*e.g.*, blood pressure, respiratory rate), we emphasize that this checklist was specifically developed for cardiac output method comparison studies. The checklist can be applied to any cardiac output monitoring method used in any setting (including anesthesiology/perioperative medicine, intensive care medicine, emergency medicine, and cardiology). While we primarily focus on clinical method comparison studies in humans (volunteers or patients), the COMPARE statement also applies to experimental method comparison studies in animals or studies using simulated data.

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Development of the COMPARE Statement

The coordinators (B.S. and K.K.) defined the scope of the statement and conceived the basic framework of the COMPARE statement in 2019. They invited additional experts (A.H., J.R., M.F., R.H.T., and S.T.V.) in anesthesiology, intensive care medicine, and biostatistics to form a key group of experts steering the project (steering committee). The project was registered at https://www.equator-network.org on December 4, 2021.

The steering committee members searched and reviewed literature published on cardiac output method comparison studies (including original method comparison studies, previous recommendations,[5–9] and articles describing relevant methodologic research). Steering committee members extensively communicated by email and phone; wrote, iteratively reviewed, and revised draft versions of the COMPARE statement and checklist; and met in virtual meetings on August 6, 2021, July 25, 2023, and July 31, 2023.

Additional expert researchers and journal editors were identified by steering committee members based on relevant publications and through personal recommendations by other experts. The additional expert researchers and journal editors were informed about the aim of the COMPARE project and invited to contribute to and finalize the COMPARE statement and checklist. No minimum or maximum sample size was placed on the number of experts. We aimed to compose a diverse group of experts to achieve geographical and disciplinary diversity and include key stakeholder groups, including clinician scientists (anesthesiologists and intensivists), statisticians and data scientists, biomedical engineers, and journal editors. As the COMPARE statement is very technical, we deliberately did not include patient representatives. The 7 steering committee members and the 16 expert researchers and journal editors formed the group of authors.

The final COMPARE checklist items were developed using a modified Delphi process. The Delphi surveys were designed using the online platform LimeSurvey (LimeSurvey GmbH, Germany). Links to the Delphi surveys were sent *via* email to the 7 steering committee members and the 16 expert researchers and journal editors, who answered the Delphi surveys individually online.

The first round of the Delphi process was conducted between September 6, 2024, and September 19, 2024 (initial email sent on September 6, 2024, and reminder email sent on September 15, 2024). In the first round, we asked respondents to rate each checklist item as "essential for inclusion," "desirable for inclusion," "possibly include," and "can be omitted" (supplemental table 1, https://links.lww.com/ALN/E9). Agreement was considered when the respondents agreed that a checklist item was desirable or essential for inclusion. Checklist items with an agreement of 70% or greater were carried over to the second round. Checklist items with an agreement rate of less than 70% were excluded, merged, or revised—and re-evaluated in the second round. Respondents were also invited to comment on the checklist items. Free text responses were collected and analyzed by B.S. and K.K.. The 7 steering committee members and 16 expert researchers and journal editors completed the first Delphi survey.

The second round of the Delphi process was conducted between September 22, 2024, and October 2, 2024 (initial email sent on September 22, 2024, and reminder email sent on September 30, 2024). In the second round, respondents could agree or not agree to each checklist item (supplemental table 2, https://links.lww.com/ALN/E9). The 7 steering committee members and 16 expert researchers and journal editors completed the second Delphi survey. All authors approved the final version of the COMPARE statement and checklist and decided on the strategy for disseminating the COMPARE statement and checklist.

Components of the COMPARE Statement

The COMPARE statement is a checklist of 29 items that are essential for the reporting of cardiac output method comparison studies (table 1). These items relate to the article's title and abstract (item 1), the introduction (items 2 to 5), methods (items 6 to 18), results (items 19 to 22), discussion (items 23 to 26), conclusion (item 27), and other information (items 28 and 29).

Justification of Checklist Items

In the following text, we discuss and explain the 29 items of the COMPARE checklist (table 1).

Title and Abstract

1(*a*). Include the Terms "Cardiac Output" and "Method Comparison Study" in the Title and Abstract

An appropriate title accurately informs about the study type and helps ensure correct indexing of articles in electronic literature databases. Clearly identify the study as a cardiac output method comparison study by including the terms *cardiac output* and *method comparison* or *method comparison study* in the title and abstract. Notably, no specific Medical Subject Headings terms exist for method comparison studies.

1(*b*). Provide a Structured Summary of Study Background, Objectives, Design, Methods, Results, and Conclusions

The abstract should cover all key information about the study, including the background and rationale of the study, the study objectives, the study design, the measurement methods, the analysis methods, the main numeric results (see section 20), and conclusions that are substantiated by the main results. Align the conclusion in the abstract with the conclusion in the main text of the article.

Table 1. The Statistical Analysis and Reporting of Cardiac Output Method Comparison Studies (COMPARE) Statement: Checklist of Items that Should Be Addressed in Cardiac Output Method Comparison Studies

Section	Item	Recommendation
Title and abstract	1	(*a*) Include the terms "cardiac output" and "method comparison study" in the title and abstract (*b*) Provide a structured summary of study background, objectives, design, methods, results, and conclusions
Introduction		
Background and study rationale	2	Describe the background of the study and justify the need for the study
Test method	3	Briefly describe the test method for cardiac output measurement
Reference method	4	State the reference method for cardiac output measurement
Objectives and research hypotheses	5	State the study objectives and research hypotheses
Methods		
Study design	6	Describe the study design
Study registration	7	State study registration with date
Ethics approval	8	Provide details of ethics committee approval
Informed consent	9	Describe how written informed consent for study participation was obtained from subjects
Data availability and sharing	10	Describe how raw data can be accessed
Setting	11	Describe the study setting, list participating sites, and state relevant dates, including recruitment and data collection periods
Subjects	12	(*a*) Describe the study population (*b*) List the inclusion and exclusion criteria
Measurement methods	13	(*a*) Describe the test method for cardiac output measurements (including device name, manufacturer, and hardware/firmware/software version numbers) (*b*) State the reference method for cardiac output measurements (including device name, manufacturer, and hardware/firmware/software version numbers) (*c*) Provide or refer to a (brief) description of the working principles of the test method and reference method for cardiac output measurements
Data collection	14	(*a*) Explain how cardiac output was measured using the test method (*b*) Explain how cardiac output was measured using the reference method (*c*) Describe where and when cardiac output was measured (*d*) Explain any interventions or procedures performed during the study (*e*) Describe how data were recorded and extracted from measurement devices (*f*) Describe how data were sampled or processed before statistical analyses
Bias	15	Describe efforts to prevent or reduce bias
Sample size	16	Explain how the sample size was determined
Statistical methods	17	(*a*) State descriptive statistical methods used to characterize subjects (*b*) State descriptive statistical methods used to quantify and illustrate cardiac output measurements (*c*) Provide a clear notation of commonly used terms (*d*) Describe methods used to analyze the agreement between cardiac output values measured with the test method and the reference method (*e*) Describe methods used to analyze the trending ability of the test method (*f*) If applicable, state any other analyses (*g*) Give details of the software used for statistical analyses
Criteria for agreement	18	Consider defining thresholds/criteria for clinically acceptable agreement between cardiac output values measured with the test method and the reference method and for clinically acceptable trending ability of the test method
Results		
Subjects	19	(*a*) Report numbers of subjects at each stage of the study (*b*) Provide reasons for nonparticipation/exclusion of subjects at each state (*c*) Provide a flow chart of subject inclusion/exclusion
Descriptive results	20	(*a*) Present subject characteristics (*b*) Report the number of cardiac output measurements and measurement pairs (*c*) Report descriptive statistics of the distribution of cardiac output values measured with the test method and the reference method (*d*) Present a scatter plot of cardiac output values measured with the test method and the reference method (*e*) Consider reporting a correlation coefficient for cardiac output values measured with the test method and the reference method
Main results	21	(*a*) Report numerical results of Bland–Altman analysis and present a Bland–Altman plot (*b*) Report the percentage error between cardiac output values measured with the test method and the reference method (*c*) If applicable, present the results of analyses assessing the trending ability of the test method
Other analyses	22	Report other analyses
Discussion		
Key results	23	Summarize the main results and qualify the measurement performance of the test method

(*Continued*)

Table 1. (Continued)

Section	Item	Recommendation
Interpretation	24	Give an overall interpretation of results considering results from similar studies and other relevant evidence
Generalizability	25	(*a*) Discuss the generalizability (external validity) of the study results (*b*) Justify the reference method (*c*) Justify the thresholds/criteria for clinically acceptable agreement between cardiac output values measured with the test method and the reference method and for clinically acceptable trending ability of the test method
Limitations	26	Discuss the limitations of the study
Conclusions	27	(*a*) State whether the cardiac output measurement performance of the test method was clinically acceptable (*b*) If applicable, state whether the trending ability of the test method was clinically acceptable
Other information		
Funding	28	Give the source of funding
Conflicts of interest	29	Report conflicts of interest of all investigators and authors

Introduction

2. Background and Study Rationale: Describe the Background of the Study and Justify the Need for the Study

The introduction should provide important background information summarizing what is already known about the topic. The need for the study can be justified based on existing knowledge gaps (*i.e.*, what is not known) or the need for confirmation or knowledge gain (*i.e.*, what needs to be replicated, tested, or refined). Set the stage for the study by describing it as a method comparison study.

3. Test Method: Briefly Describe the Test Method for Cardiac Output Measurement

The main purpose of a method comparison study is to investigate the measurement performance of the test method used to measure CO_{TEST}. Therefore, readers must understand the underlying technology and measurement principles of the test method and its current clinical applications. References may provide additional (technical) information for interested readers. Explicitly state which method is the test method, for example: "method X (test method)." There may be more than one test method in one study.

4. Reference Method: State the Reference Method for Cardiac Output Measurement

The reference method used to measure CO_{REF} should be clearly stated in the introduction, for example: "method Y (reference method)." This will help readers understand which methods were compared. Referrals to literature can provide additional (technical) information. Indicator dilution methods—pulmonary artery thermodilution and transpulmonary thermodilution—are considered clinical reference methods for cardiac output measurements[22,30] but have their own immanent limitations and measurement errors.[22,31–33] More direct measurements, such as ultrasonic flow probes, are more invasive and require open-chest conditions with direct access to the ascending aorta and are thus usually not clinically available outside experimental settings. Minimally invasive and noninvasive methods,[16,25–29] such as pulse wave analysis, bioimpedance/bioreactance, or pulse wave transit time, should not be used as reference methods. Whether ultrasound Doppler methods can be considered reference methods for measuring cardiac output is a matter of debate. Cardiac output measurements with ultrasound Doppler methods and cardiac output measurements with indicator dilution methods are not interchangeable.[34] In addition, the cardiac output measurement performance of ultrasound Doppler methods depends on operator skills and patient factors. However, ultrasound Doppler methods may be the only available method in neonates and small children.

5. Objectives and Research Hypotheses: State the Study Objectives and Research Hypotheses

It is important to state the specific objectives and aims of the study, for example: "We aimed to determine the agreement between cardiac output measured using method X and cardiac output measured using method Y." This should also include the population and clinical setting, for example: "in patients having major abdominal surgery" or "in patients with septic shock." It is also important to state whether a prespecified research hypothesis was examined, for example: "We hypothesized that the agreement between cardiac output measured using method X and cardiac output measured using method Y is clinically acceptable." In this case, explicitly define prespecified criteria for clinically acceptable agreement between CO_{TEST} and CO_{REF} (see section 18). Investigating whether the trending ability of the test method is clinically acceptable may also be a research objective.

Methods

The methods section should report in detail how CO_{TEST} and CO_{REF} were measured. The methods section should especially focus on how measurements were performed,

including data recording, data sampling, and data processing. Additionally, it should provide a detailed description of the statistical methods of data analysis. Methods should be described in sufficient detail to allow the study to be replicated.

6. Study Design: Describe the Study Design

Present the study design and identify the study as a cardiac output method comparison study. Most method comparison studies are prospective studies. However, if simultaneous cardiac output measurements by different methods have been recorded and stored, method comparison studies can also be performed as retrospective studies. It is thus also important to identify the method comparison study as a prospective or retrospective study.

7. Study Registration: State Study Registration with Date

Register prospective studies before starting data collection. Study registration needs to include study methodology and planned statistical analyses. Study registration is essential to demonstrate that data collection and analysis were performed as planned. State the registry, the identifier number, and the date of registration. In the registration, if applicable, explicitly define prespecified criteria for clinically acceptable agreement between CO_{TEST} and CO_{REF} and for clinically acceptable trending ability of the test method (see section 18).

8. Ethics Approval: Provide Details of Ethics Committee Approval

Method comparison studies will almost always require approval by an institutional review board or ethics committee. The name of the respective institutional review board or ethics committee, the date of approval, and the study identifier should be stated.

9. Informed Consent: Describe How Written Informed Consent for Study Participation Was Obtained from Subjects

Method comparison studies will almost always require written informed consent from participating subjects. It should be clearly stated when and how written informed consent was obtained and who provided it. In some cases, institutional review boards may waive the need for written informed consent, which should also be clearly stated and justified. It may also be necessary to state the legal basis of data processing and sharing.

10. Data Availability and Sharing: Describe How Raw Data Can Be Accessed

Contemporary scientific work should include a best effort to make data publicly available. Such effort is especially apparent for relatively low-sensitivity data such as cardiac output measurements. Hence, we recommend providing deidentified data in a publicly available repository. In any case, include a statement that informs readers if, where, and how they can access the raw data and provide specific reasons for any limitations on data availability.

11. Setting: Describe the Study Setting, List Participating Sites, and State Relevant Dates, Including Recruitment and Data Collection Periods

Cardiac output method comparison studies can be performed in different settings, most often in intensive care units or operating rooms. State when and where the study was performed, list and characterize participating sites, and state relevant dates, including recruitment and data collection periods.

12. Subjects

12(*a*). Describe the Study Population

Cardiac output method comparison studies can be performed in different populations (*e.g.*, critically ill patients, patients having surgery, or volunteers). Clearly describe the study population.

12(*b*). List the Inclusion and Exclusion Criteria

List inclusion and exclusion criteria as they are important for the interpretation of the results. Exclusion criteria often are determined by contraindications for or limitations of cardiac output measurement methods.

13. Measurement Methods

13(*a*). Describe the Test Method for Cardiac Output Measurements

Clearly describe the test method (or methods in studies with more than one test method) used to measure CO_{TEST}. Provide (technical) details to expand on what has already been explained in the introduction section of the article. Provide the device name, manufacturer, and hardware/firmware/software version numbers. The version is important because different versions may exhibit substantially different measurement performances.

13(*b*). State the Reference Method for Cardiac Output Measurements

State and (briefly) describe the reference method used to measure CO_{REF}. Provide the device name, manufacturer, and hardware/firmware/software version numbers.

13(*c*). Provide or Refer to a (Brief) Description of the Working Principles of the Test Method and Reference Method for Cardiac Output Measurements

To permit individual articles to stand for themselves and increase readability, provide or refer to a (brief) description of the measurement principles of the test method and the reference method. Depending on the novelty of the test and reference methods, this may be a detailed description with technical details—or less detailed when the method is already well established. Additional technical details may be presented in the supplemental digital content. In either case, adequate information or references should be provided to enable interested readers to find technical details of the methods used.

14. Data Collection

14(*a*). Explain How Cardiac Output Was Measured Using the Test Method

Provide a clear and detailed description of how CO_{TEST} was measured. This will help readers who are not familiar with the test method understand how CO_{TEST} was measured and allow them to replicate the study. If applicable, calibration procedures and intervals should be provided, as well as any other relevant information that may have influenced CO_{TEST}.

14(*b*). Explain How Cardiac Output Was Measured Using the Reference Method

Provide a clear and detailed description of how CO_{REF} was measured. If applicable, calibration procedures and intervals should be reported, as well as any other relevant information that may have influenced CO_{REF} measurements.

14(*c*). Describe Where and When Cardiac Output Was Measured

Describe where and when CO_{TEST} and CO_{REF} were measured. Provide details on measurement points or intervals, and, in case of continuous measurements, measurement periods. Describe whether CO_{TEST} and CO_{REF} were measured simultaneously or consecutively. If applicable, explain how CO_{TEST} and CO_{REF} were synchronized.

14(*d*). Explain Any Interventions or Procedures Performed during the Study

Specific maneuvers or interventions may deliberately be performed as part of the study to induce cardiac output changes or as part of routine care. A wide range of cardiac output values is desirable when evaluating the measurement performance and trending ability of CO_{TEST}. Explain all interventions or procedures performed during the study that may have affected CO_{TEST} and CO_{REF}.

14(*e*). Describe How Data Were Recorded and Extracted from Measurement Devices

Provide information about how CO_{TEST} and CO_{REF} data were recorded and extracted from the devices. For most cardiac output monitoring systems, cardiac output values displayed on the screen are averaged over a certain period of time or over a certain number of heart beats. State whether averaged cardiac output data were extracted—or beat-by-beat or second-to-second raw data. Raw measurement data should directly and digitally be extracted from the measurement devices. However, some devices may not allow users to directly extract these data and require workarounds, which need to be transparently explained or provided as supplemental digital content. Whenever operator-dependent reference methods such as ultrasound Doppler methods are used, the handling of any operator-dependent effect should be described (*e.g.*, providing details on how interoperator agreement was quantified).

14(*f*). Describe How Data Were Sampled or Processed before Statistical Analyses

Provide detailed information on CO_{TEST} and CO_{REF} data sampling and processing before the statistical analysis. Data sampling and processing may substantially influence the results of comparative statistics.[35] Data sampling describes how measurements are chosen, for example, within a specific period, from the overall set of measurements. Data processing describes any processing of raw measurement data, for example, data transformation and aggregation. Depending on how measurement data are recorded, data may already be processed by the measurement device. This includes calibration and averaging procedures, as well as the exclusion of outliers.

15. Bias: Describe Efforts to Prevent or Reduce Bias

The results of method comparison studies are prone to different types of biases.[36,37] Selection bias occurs when the subjects included in the study are not representative of the target population. In method comparison studies, this bias affects the generalizability of the results and the translation of the results in clinical practice. Selection bias should be considered when designing the study so that representative subjects are planned to be included. Conscious or unconscious influence on the measurements may lead to observer bias. Subjective influences on data collection must thus be prevented. To avoid researcher bias, data processing and analysis—and the definition of clinically acceptable agreement between CO_{TEST} and CO_{REF}—must not be changed after the results have become known (see also section 18). Publication bias can occur when study results are not or not completely published. The COMPARE statement and the checklist are intended to help avoid incomplete data reporting. Address any efforts that have been made to prevent or reduce different types of bias.

16. Sample Size: Explain How the Sample Size Was Determined

Explain and justify the sample size estimation.[38] Consider both the number of subjects and the number of measurements per subject. The number of measurements per subject is often large in method comparison studies when cardiac output is repeatedly measured per subject (*e.g.*, serial indicator dilution measurements, continuous pulmonary artery thermodilution, beat-to-beat pulse wave analysis).

The sample size may be justified by a certain precision of estimation (*e.g.*, concerning the width of CI of the limits of agreement), by the anticipated power of statistical hypothesis testing (*e.g.*, testing the limits of agreement against prespecified thresholds), or based on pragmatic considerations.[39,40] A sample size estimation that takes replicate measurements per subject into account and therefore directly relates to cardiac output method comparison studies is not well established,[41] and it has been suggested to use simulation studies in such a case.[42] Treating replicate measurements as independent is

not recommended as it leads to limits of agreement that are too narrow,[43] which may result in positively biased assumptions about power and precision.

A sample size estimation should be reported in such detail that it is reproducible. For the sake of transparency and reproducibility, provide the (pseudo-)code used for the sample size estimation. Assumptions should be justified by reference to published data, own preliminary pilot studies, or the relevance of effect sizes.

17. Statistical Methods

17(*a*). State Descriptive Statistical Methods Used to Characterize Subjects

Clearly state the descriptive statistical methods used to characterize subjects in the article.

17(*b*). State Descriptive Statistical Methods Used to Quantify and Illustrate Cardiac Output Measurements

State descriptive statistics used to characterize the distribution of CO_{TEST} and CO_{REF}, such as mean, SD, and range. Describe how you report the range and distribution of cardiac output measurements and the relation of CO_{TEST} and CO_{REF}. We recommend that cardiac output data should be visualized in a scatter plot with CO_{REF} on the *x*-axis and CO_{TEST} on the *y*-axis. For optimal visualization and interpretation of this scatter plot, the *x*- and *y*-axes should have the same scaling and length and cover all pairs of measured cardiac output values. The identity line (*i.e.*, line of equality)—a line with a slope of 1 and an intercept of 0—should be added as it reflects the line of perfect agreement.

In addition to the scatter plot, the relation between CO_{TEST} and CO_{REF} can be quantified by the correlation coefficient.[44] In case of repeated cardiac output measurements, one may consider using the within-subject correlation coefficient.[45] Other statistical measures, such as the intraclass correlation coefficient or concordance correlation coefficient, can also be used to explicitly quantify agreement.[46] All of these coefficients should be interpreted with caution and reported for descriptive purposes only, as they either measure relation instead of agreement or have been shown to be affected by between-subject variability.[41] To support comparability between studies, different types of correlation coefficients can be reported.

17(*c*). Provide a Clear Notation of Commonly Used Terms

Provide a clear notation of commonly used terms. For example, the terms *trueness*, *accuracy*, and *bias* are used interchangeably but may occasionally be defined differently.[8,9] Similarly, the definition of the *limits of agreement* (see section 17[*d*]) may vary, assuming either a normal distribution or a *t* distribution for the differences in cardiac output measurements. Provide a detailed and unambiguous introduction of such terms and give computational details where possible.

17(*d*). Describe Methods Used to Analyze the Agreement between Cardiac Output Values Measured with the Test Method and the Reference Method

Describe the methods used to quantify the agreement between CO_{TEST} and CO_{REF}. The use of the Bland–Altman analysis and visualization by Bland–Altman plots is recommended.[39,47] If applicable, Bland–Altman analysis needs to account for repeated measurements per individual. Describe in full detail how Bland–Altman analysis was performed, including distributional assumptions and calculations. We recommend subtracting CO_{REF} from CO_{TEST} in the analysis and plots. This will result in positive differences when CO_{TEST} is higher than CO_{REF} and *vice versa*.

Two major statistical measures are derived from Bland–Altman analysis and should be reported as follows:

1. The mean of the differences is used to infer any systematic deviation of methods, *i.e.*, an average underestimation or overestimation of CO_{TEST} compared to CO_{REF}. It is calculated as the mean of all single differences between CO_{TEST} and CO_{REF}. If a dependency of method agreement on the magnitude of cardiac output measurements is assumed from the Bland–Altman plot (*i.e.*, if $CO_{TEST} - CO_{REF}$ seems to depend on the cardiac output level), a regression model of the differences against the mean values should be used to fit this nonconstant relation. Consider reporting the 95% CI—or pointwise intervals in case of a regression model—and the standard error of the mean of the differences.
2. The 95% limits of agreement represent a 95% prediction interval of the differences between CO_{REF} and CO_{TEST}. They describe the methods' agreement on the measurement level, covering about 95% of the (expected) differences. Assuming a normal distribution of the differences, they are calculated as the mean of the differences $\pm$ 1.96 $\times$ SD of the differences. Exact *t* values can be used instead of 1.96 if a *t* distribution is assumed, for example, in case of smaller sample sizes. In cardiac output method comparison studies, it is important to use Bland–Altman analysis for repeated measurements.[41,43] Treating measurements as independent instead would lead to an underestimation of the SD of differences and consequently to limits of agreement that are too narrow.[39]

Additionally, the percentage error should be reported, which is the one-sided width of the 95% limits of agreement divided by the mean cardiac output multiplied by 100. The percentage error is intended to facilitate the comparison of the agreement between CO_{REF} and CO_{TEST} across studies, although the absolute values of CO_{REF} and CO_{TEST} may substantially differ among studies.[48] However, the percentage error quantifies agreement on a relative scale and depends on the variability of both CO_{TEST} and CO_{REF}, which may differ between studies or simply cannot be derived from the reported data.[49,50] Percentage errors,

therefore, must be interpreted with caution. Percentage error thresholds that have been proposed to determine acceptable agreement between CO_{TEST} and CO_{REF} are based on the strong assumption of a measurement error that is considered universal for any cardiac output measurement reference method.[49,50] Such an assumption is unlikely to be valid in most method comparison studies in which different reference methods are used in different clinical settings. If at all necessary, such a criterion for acceptable agreement should be prespecified and determined for each study.

In any case, the precision of estimates should be reported through 95% CI around the 95% limits of agreement. In the absence of analytical solutions, these can be derived from sampling methods, such as bootstrapping.

The Bland–Altman analysis can also be performed in a Bayesian framework,[51] as an alternative to the original and popular frequentist approach described above. By estimating the posterior probability distribution of differences, one can directly infer the limits of agreement within which a difference lies with a probability of 95%, without having to explicitly consider the uncertainty associated with estimating the limits of agreement, *i.e.*, by considering their 95% credible intervals (the Bayesian CI). Previous knowledge about the mean and the SD of differences is needed to inform the estimation of the posterior probability distribution by the choice of a previous probability distribution. Further, the Bayesian approach must be able to handle repeated measurements to be suitable for cardiac output method comparison studies. The frequentist and the Bayesian approach produce similar results in large-sample studies.

17(*e*). Describe Methods Used to Analyze the Trending Ability of the Test Method

Describe the methods used to analyze the trending ability of the test method in the article. Trending ability refers to the ability of the test method to adequately track changes in CO_{REF}. Several methods have been described to investigate the trending ability.[52,53] The four-quadrant plot analysis[53] is widely used. A four-quadrant plot is a scatter plot showing differences between consecutively measured CO_{REF} on the *x*-axis and CO_{TEST} on the *y*-axis. When CO_{REF} and CO_{TEST} change in the same direction (*i.e.*, concordant measurements), the resulting data points are displayed in the upper right quadrant of the four-quadrant plot when cardiac output increases or in the lower left quadrant when cardiac output decreases. Data points on the identity line of the four-quadrant plot correspond to concordant changes of CO_{REF} and CO_{TEST} with equal absolute changes. When CO_{REF} and CO_{TEST} change in opposite directions (*i.e.*, CO_{TEST} decreases while CO_{REF} increases or *vice versa*; discordant measurements), the resulting data points are displayed in the upper left quadrant or lower right quadrant of the four-quadrant plot. The concordance rate can be calculated as the number of concordant CO_{REF} and CO_{TEST} pairs divided by all CO_{REF} and CO_{TEST} pairs.

To exclude small cardiac output changes that may be attributed to noise rather than true changes in cardiac output, a quadratic exclusion zone at the center of the four-quadrant plot is often applied. Data points within this exclusion zone are excluded from quantitative analysis. Authors can individually define exclusion zones using absolute or relative thresholds but should do so *a priori* and justify their definition.

Notably, the four-quadrant plot-derived concordance rate provides a basic assessment of the cardiac output trending ability of CO_{TEST}, essentially determining whether CO_{REF} and CO_{TEST} change in the same direction but not accounting for the magnitude of these cardiac output changes. Therefore, more advanced methods for assessing the cardiac output trending ability remain an active area of research.

17(*f*). If Applicable, State Any Other Analyses

Provide a description of any other analyses performed as part of the study, for example, analysis of subgroups and sensitivity analyses. State whether these analyses were planned *a priori* or *post hoc*.

17(*g*). Give Details of the Software Used for Statistical Analyses

Give details of the software used for statistical analyses, including the software name and version. This supports the replicability of the analyses. Sharing analysis codes is recommended.

18. Criteria for Agreement: Consider Defining Thresholds/Criteria for Clinically Acceptable Agreement between Cardiac Output Values Measured with the Test Method and the Reference Method and for Clinically Acceptable Trending Ability of the Test Method

Consider defining thresholds or criteria for clinically acceptable agreement between CO_{TEST} and CO_{REF} and for the clinically acceptable trending ability of the test method. For example, using the frequentist approach of Bland–Altman analysis (see section 17[*d*]), acceptable agreement could be concluded when the limits of agreement are within or statistically significantly different from threshold values.[40] Using the Bayesian approach, the probability that differences are within threshold values may have to exceed a certain value (usually 95%) to conclude acceptable agreement.[51]

State whether the thresholds or criteria have been defined *a priori* or *post hoc*. *A priori* definition is preferred and should be detailed in the study protocol and study registration. Otherwise, exploratory results of the cardiac output method comparison should simply be described without concluding whether or not the agreement between CO_{TEST} and CO_{REF} or the trending ability of the test method are clinically acceptable.

Results

19. Subjects

19(*a*). Report Numbers of Subjects at Each Stage of the Study

Report the number of subjects assessed for eligibility, the number of subjects included in the study, the number of subjects in whom measurements were performed, and the number of subjects included in the final analysis.

19(*b*). Provide Reasons for Nonparticipation/Exclusion of Subjects at Each State

Provide reasons for not including or excluding subjects at each stage in the article.

19(*c*). Provide a Flow Chart of Subject Inclusion/Exclusion

Provide a flow chart to illustrate the number of subjects at each stage, starting with subject screening and ending with the final analyses in the article.

20. Descriptive Results

20(*a*). Present Subject Characteristics

Present subject characteristics that may be important for interpreting the results using descriptive statistics. Additional background information on the subjects' medical history, ambulatory medication, and type of surgery may be provided. Any disease states known to affect cardiac output or cardiac output measurements should be reported (*e.g.*, valvular disorders, heart failure, vascular disease).

20(*b*). Report the Number of Cardiac Output Measurements and Measurement Pairs

Separately report the number of CO_{TEST} and CO_{REF} and the number of CO_{TEST} and CO_{REF} pairs in total and per subject. Also, report the number of excluded measurements and measurement pairs and the number of measurements and measurement pairs included in the final analysis. Report descriptive statistics of the number of measurement pairs per subject.

When multiple cardiac output measurements are performed and averaged (*e.g.*, when measuring cardiac output with indicator dilution methods), consider reporting the individual cardiac output values that were averaged and individual values that were excluded. For studies using operator-dependent reference methods such as ultrasound Doppler methods, consider reporting characteristics of the operators, including their level of experience.

20(*c*). Report Descriptive Statistics of the Distribution of Cardiac Output Values Measured with the Test Method and the Reference Method

Report descriptive statistics of the distribution of CO_{TEST} and CO_{REF}, *e.g.*, mean, SD, and range. Describe whether methods accounting for repeated measurements were used.

20(*d*). Present a Scatter Plot of Cardiac Output Values Measured with the Test Method and the Reference Method

Present a scatter plot of CO_{TEST} and CO_{REF} (detailed description in section 17[*b*]).

20(*e*). Consider Reporting a Correlation Coefficient for Cardiac Output Values Measured with the Test Method and the Reference Method

Consider reporting a correlation coefficient of CO_{TEST} and CO_{REF} (detailed description in section 17[*b*]).

21. Main Results

21(*a*). Report Numerical Results of Bland–Altman Analysis and Present a Bland–Altman Plot

Report the mean of the differences between CO_{TEST} and CO_{REF} (optionally with 95% CI or standard error), and the 95% limits of agreement with 95% CI (detailed description in section 17[*d*]). Present a Bland–Altman plot.[5,54,55]

21(*b*). Report the Percentage Error between Cardiac Output Values Measured with the Test Method and the Reference Method

Report the percentage error between CO_{TEST} and CO_{REF} (optionally with 95% CI; detailed description in section 17[*d*]).

21(*c*). If Applicable, Present the Results of Analyses Assessing the Trending Ability of the Test Method

If applicable, report the results of analyses performed to assess the trending ability of the test method. For example, present four-quadrant plot analyses and report the concordance rate (detailed description in section 17[*d*]).

22. Other Analyses: Report Other Analyses

If applicable, report other analyses according to their description in the methods section.

Discussion

23. Key Results: Summarize the Main Results and Qualify the Measurement Performance of the Test Method

Summarize the main results of the study, especially the agreement between CO_{TEST} and CO_{REF}. State whether you reject or accept your primary hypothesis and restate it. Qualify the measurement performance of the test method considering how you defined thresholds or criteria for clinically acceptable agreement between CO_{TEST} and CO_{REF} and for clinically acceptable trending ability of the test method.

24. Interpretation: Give an Overall Interpretation of Results Considering Results from Similar Studies and Other Relevant Evidence

Interpret the results of the study in the context of the results of previous studies.

25. Generalizability

25(*a*). Discuss the Generalizability (External Validity) of the Study Results

Discuss the generalizability (external validity) of the study results. Discuss the characteristics of the study population, the clinical context in which measurements were obtained, and how these aspects relate to the eventual intended use of the test method.

25(*b*). Justify the Reference Method

Justify the used reference method. In studies that use operator-dependent reference methods (such as ultrasound Doppler methods), we recommend reporting the rationale for using this reference method.

25(*c*). Justify the Thresholds/Criteria for Clinically Acceptable Agreement between Cardiac Output Values Measured with the Test Method and the Reference Method and for Clinically Acceptable Trending Ability of the Test Method

Justify the used thresholds or criteria for clinically acceptable agreement between CO_{TEST} and CO_{REF} and for clinically acceptable trending ability of the test method.

26. Limitations: Discuss the Limitations of the Study

List and discuss the limitations of the study. Limitations can be related to the study design, setting, subjects, measurement methods, data collection, sample size, and statistical methods—among many other things. Especially expand on the limitations of the reference method. Discuss sources of potential bias. Discuss both the direction and magnitude of any potential bias.

27. Conclusions

27(*a*). State Whether the Cardiac Output Measurement Performance of the Test Method Was Clinically Acceptable

State whether the cardiac output measurement performance of the test method was clinically acceptable considering how you defined thresholds or criteria for clinically acceptable agreement between CO_{TEST} and CO_{REF}.

27(*b*). If Applicable, State Whether the Trending Ability of the Test Method Was Clinically Acceptable

If applicable, state whether the trending ability of the test method was clinically acceptable considering how you defined thresholds or criteria for clinically acceptable trending ability of the test method.

Other Information

28. Funding

Give the source of funding (if applicable, include information on who provided the devices used in the study) and the role of the funders for the current study.

29. Conflicts of Interest

Report conflicts of interest of all investigators and authors.

Implications and Limitations

We devolved the COMPARE statement to provide researchers, journal editors, and reviewers a framework for designing, performing, and reporting cardiac output method comparison studies. Using the COMPARE statement and defining it as mandatory when publishing cardiac output method comparison studies will help standardize these method comparison studies and increase the external validity of study results. We thus strongly recommend using the COMPARE statement to ensure complete and transparent reporting of study results.

The COMPARE statement differs fundamentally from previously published guidelines including the Standards for Reporting Diagnostic Accuracy (STARD)[56,57] guidelines, which provide general guidance on reporting studies on diagnostic tests. COMPARE also differs from the Guideline for Reporting Reliability and Agreement Studies (GRRAS).[58] Both STARD and GRRAS have broad scopes and do not address key aspects that are essential for designing and reporting cardiac output method comparison studies (supplemental table 3, https://links.lww.com/ALN/E9).

In the COMPARE statement, we particularly focused on statistical methods, which are a cornerstone of method comparison studies. Notably, statistical methods may evolve over time, and new approaches may be developed. Therefore, we emphasize that the COMPARE statement is an evolving guideline requiring perpetual evaluation and, if necessary, revisions. We plan to regularly update the COMPARE statement in response to comments, experiences, and new evidence. We encourage authors and researchers to develop and apply innovative methods in addition to established statistical methods.

The final COMPARE checklist items were developed using a modified Delphi process that consisted of two Delphi surveys rounds *via* an online platform. Although the diverse group of experts was carefully selected based on the scientific contribution of the experts to the literature of cardiac output method comparison studies, our article reflects expert knowledge of a limited number of individuals. There thus remains some risk of bias. Our group of experts did not include lay members or patient representatives of the target population (*i.e.*, patients in whom cardiac output monitoring methods are used).

In summary, the COMPARE statement includes a checklist of 29 items and provides a framework for designing, performing, and reporting cardiac output method comparison studies. Considering and reporting the items specified in the COMPARE checklist will help standardize cardiac output method comparison studies and increase the external validity of the results.

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Support was provided solely from institutional and/or departmental sources.

Competing Interests

Dr. Saugel is a consultant for Edwards Lifesciences (Irvine, California), Philips North America (Cambridge, Massachusetts), GE Healthcare (Chicago, Illinois), Maquet Critical Care (Solna, Sweden), Pulsion Medical Systems (Feldkirchen, Germany), Vygon (Aachen, Germany), Retia Medical (Valhalla, New York), Masimo (Neuchâtel, Switzerland), and Dynocardia (Cambridge, Massachusetts); has received institutional restricted research grants from Edwards Lifesciences, Baxter (Deerfield, Illinois), GE Healthcare, CNSystems Medizintechnik (Graz, Austria), Pulsion Medical Systems, Vygon, Retia Medical, and Osypka Medical (Berlin, Germany); has received honoraria for giving lectures from Edwards Lifesciences, Philips Medizin Systeme Böblingen (Böblingen, Germany), Baxter, GE Healthcare, CNSystems Medizintechnik, Getinge (Gothenburg, Sweden), Pulsion Medical Systems, Vygon, Masimo, and Ratiopharm (Ulm, Germany); was a consultant for and has received institutional restricted research grants from Tensys Medical (San Diego, California); and is an Editor of the *British Journal of Anesthesia*. Dr. Flick is a consultant for and has received honoraria for giving lectures from Edwards Lifesciences and has received honoraria for consulting and giving lectures from CNSystems Medizintechnik. Dr. Rinehart is a consultant for and receives royalties from Edwards Lifesciences, now Becton Dickinson (Franklin Lakes, New Jersey), and has ownership interests of Perceptive Medical (Newport Beach, California). Dr. Thiele has consulted for Philips Medical (Andover, Massachusetts), Edwards Lifesciences, and Noninvasix (Galveston, Texas), and has received honoraria for giving lectures from Metronic (Minneapolis, Minnesota). Dr. Cannesson is a consultant for Edwards Lifesciences and Masimo; receives research support from Edwards Lifesciences; receives royalties from Edwards Lifesciences and Sironis (Newport Beach, California); and has ownership interests in Sironis and Perceptive Medical. Dr. Cecconi is a consultant for Edwards Lifesciences, Directed Systems (Cambridge, United Kingdom), and GE Healthcare. Dr. Chew has received honoraria and lecture fees from Edwards Lifesciences, AOP Health (Vienna, Austria), and Philips Healthcare (Eindhoven, The Netherlands). Dr. De Backer has received honoraria and lecture fees from Edwards Lifesciences, Philips, and AOP Health. Dr. Joosten is a consultant for Edwards Lifesciences and has ownership interests in Perceptive Medical. Dr. Khanna consults for Medtronic (Boulder, Colorado), Edwards Lifesciences, Philips Research North America, GE Healthcare, Potrero Medical (Hayward, California), Sentinel Medical (Jacksonville, Florida), Retia Medical, Nihon-Kohden USA (Irvine, California), Caretaker Medical (Charlottesville, Virginia), TNO (The Hague, The Netherlands), Bayer Corporation (Whippany, New Jersey), Fifth Eye Inc. (Ann Arbor, Michigan), Pharmazz Inc. (Willowbrook, Illinois), Viatris (Canonsburg, Pennsylvania), Innoviva Specialty Therapeutics (Waltham, Massachusetts), and Zynex Medical (Boulder, Colorado) and has ownership interests with BrainX LLC (Cleveland, Ohio). Dr. Levy is a steering committee member for Bayer (Leverkusen, Germany), Grifols (Barcelona, Spain), Octapharma (Paramus, New Jersey), Takeda (Boston, Massachusetts), and Werfen (Bedford, Massachusetts), none of which are associated with hemodynamic monitoring. Dr. Meidert has received honoraria for giving lectures from Edwards Lifesciences. Dr. Messina received payments or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events from Vygon (Écouen, France), Philips, and Edwards Lifesciences. Dr. Monnet is a consultant for and has received institutional restricted research grants and honoraria for giving lectures from Pulsion Medical Systems; is a consultant for and has received institutional restricted research grants and honoraria for giving lectures from Baxter Healthcare; is a consultant for and has received institutional restricted research grants and honoraria for giving lectures from Becton Dickinson; has received honoraria for giving lectures from Masimo (Irvine, California); is an Editor of *Annals of Intensive Care*; and belongs to the editorial board of *Critical Care*. Dr. Pinsky is a consultant for Edwards Lifesciences, now Becton Dickinson. Dr. Kouz is a consultant for and has received honoraria for giving lectures from Edwards Lifesciences and is a consultant for Vygon (Aachen, Germany). The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental material, https://links.lww.com/ALN/E9
Supplemental Table 1. Results of Delphi Round 1 (n = 23 participants)
Supplemental Table 2. Results of Delphi Round 2 (n = 23 participants)
Supplemental Table 3. Practical importance of items addressed in the StatistiCal analysis and repOrting of cardiac output Method comPARison studiEs (COMPARE) statement

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ANESTHESIOLOGY®

2024 Emery A. Rovenstine Memorial Lecture: Our Finest Hour—How Anesthesiologists Saved Countless Lives during the COVID-19 Pandemic

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ABSTRACT

Pandemics shape history and leave lasting impacts on society and healthcare practices. The 2024 Rovenstine lecture debriefs the experience of anesthesiologists and leadership during the COVID-19 pandemic and reflects on emergency preparedness, crisis management, scientific advances, lessons from the crisis response, posttraumatic stress and burnout, and the importance of leadership in a crisis.

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The Rovenstine lecture was created shortly after Dr. Emery Rovenstine's death in 1962 to honor his enormous contributions to our specialty. Dr. Rovenstine was inspired to pursue a career in medicine after witnessing the suffering of World War I soldiers in the field. He first struggled to build a general practice, and then became one of two residents under Dr. Ralph Waters at the University of Wisconsin in Madison. In 1935, he was named chair of the Department of Anesthesiology at Bellevue Hospital in New York City (New York) and was the first to set up a nerve block clinic. He served on the Army Advisory Board during World War II and was responsible for an order to place army hospital operating rooms under the charge of anesthesiologists. He was the cofounder of the American Society of Anesthesiologists (ASA; Schaumburg, Illinois), becoming its president in 1943. He was also a founder of the New York Postgraduate Assembly (New York, New York) and the American Board of Anesthesiology, and he received the ASA's Distinguished Service Award in 1957.

A quote from Dr. Rovenstine is resonant: "The ultimate goal is the patient's need and whatever service may best apply it with reasonable economy and convenience." How foresighted this was of him to pinpoint the factors that later were to become the crucial goals of the healthcare community and the public that are now called the triple aim: quality, cost, and access to healthcare.

The famous Aqualumni tree[1] (fig. 1) created by Dr. Lucian Morris and his wife, Jean, was first displayed at the 1984 ASA annual meeting to celebrate the genealogy of American anesthesiologists. The roots denote the triple mission of academic departments: clinical care, teaching, and research. The trunk represents Dr. Ralph Waters, who established the world's first anesthesiology residency program at the University of Wisconsin. The branches were the trainees of Dr. Waters who went on to become department chairs across the United States.

Dr. Rafael Ortega and his colleagues recently published an updated version of this genealogy[2] where anesthesiologists might be able to trace their lineage back to Dr. Rovenstine or Dr. Waters. I saw that I was only four chairs removed from the first in the United States. I hope we all appreciate the giants who came before us, who, like Dr. Rovenstine's generation, went through World War I, World War II, and the great flu pandemic of 1918. Perhaps spurred by this massive human suffering, medicine made large advances, especially in anesthesiology.

There is a scene in the movie *Apollo 13* where Gene Kranz, the flight director, overhears the National Aeronautics and Space Administration (NASA; Washington, D.C.) director, Chris Kraft, saying this could be the worst disaster that NASA has ever experienced. Gene's memorable response was, "With all due respect, sir, I believe this is gonna be our finest hour." Indeed it was. The mission to land on the moon was doomed, but the ingenuity and dedication of the NASA team saved the astronauts from certain death. That is how I remember that devastating first year of the COVID-19 pandemic as ASA president. It was the collective finest hour of anesthesiologists. Debriefing this collective and yet also private traumatic experience seemed important to me to help us through the recovery phase of the pandemic, celebrate our advances in medicine, and prepare for the future.

Early Days of the COVID-19 Pandemic

Pandemics are not new to civilizations. One of the worst pandemics in recorded history was the plague, or Black

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Fig. 1. The Aqualumni tree. Reprinted courtesy of the Wood Library-Museum of Anesthesiology (Schaumburg, Illinois).

Death. In the fourteenth century, Europe was the hardest hit, with as much as half of the continent's population, or about 25 million, dying of the disease within 4 yr. The influenza pandemic of 1918 killed 50 million people, with one-fifth of the world's population infected. Young adults were among the hardest hit, along with the elderly and young children. Despite our modern age of medicine, COVID-19 killed at least 7.3 million people, with about a million of those from the United States. COVID-19 has accounted for 1 in 20 deaths worldwide since the beginning of 2020.

Pandemics shape history and leave lasting impacts on society and healthcare practices. So how will COVID-19 shape us in the future? The beginning of COVID-19 and a timeline of ASA's response started on December 12, 2019, when concerns began about a new respiratory virus in the Wuhan province of China. On January 7, 2020, public health officials in China identified a novel coronavirus as the causative agent. On January 20, China confirmed human-to-human transmission had been occurring. That very same day, the first recorded case in the United States occurred in Washington state: a 35-yr-old American citizen who had traveled from Wuhan, China. The first official case in Italy was recorded on February 21. The ASA Board of Directors met in person February 28, and that was the last face-to-face meeting for almost two years.

The United States was caught flatfooted with limited personal protective equipment (PPE) and a failed Centers for Disease Control and Prevention (CDC; Atlanta, Georgia) testing strategy when the emergency was declared by the president on March 12. We were lured into thinking that this virus would be like Middle East respiratory syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), which had limited impact in the United States, but this time was different. This coronavirus could be transmitted through aerosols that linger in the air and, just as important, could infect people who never became symptomatic or only mildly so, unlike MERS and SARS. The asymptomatic were the perfect transmission vehicles for this novel virus, which enabled rapid transmission around the world.

With a nationwide emergency, bans on elective surgery ensued to conserve scarce PPE and redeploy resources to intensive care units (ICUs). This was controversial in parts of the United States that had not seen any COVID-19 cases and created economic hardships for anesthesiologists. In those early days, I received an unprecedented volume of emails. Clearly, the ASA had to reorganize itself to deal with this emergency. However, ASA had no manual or other planning document on dealing with a disaster of this magnitude. So I relied on my firsthand experiences with natural disasters as well as the training I had received as a hospital leader in the Hospital Incident Command System approach. On a Sunday afternoon in mid-March, Paul Pomerantz (then ASA CEO) and I discussed how we were going to handle this disaster. He had already organized the ASA staff, who would be working remotely, and I organized the COVID Council like a Hospital Incident Command structure where you have key leaders who can provide input, provide guidance, and share the workload. In any disaster, it is critical to have a command structure that is agile. We were not going to have the luxury of months to refine and perseverate on every word of an ASA statement.

We tapped into other committees and sister organizations as needed. I did not appreciate the depth of ASA volunteers until this moment. The ASA COVID-19 Clinical Task Force, also known as the COVID Council, consisted of the executive committee of myself, Beverly Philip, Randy Clark, and Linda Mason, as well as the Administrative Council with the other officers: Ken Elmassian, Ron Harter, Pat Giam, Jeff Mueller, Michael Champeau, Andy Rosenberg, Don Arnold, and Kraig de Lanzac. In addition to the Administrative Council, the chairs of key committees and the Anesthesia Patient Safety Foundation (APSF; Schaumburg, Illinois) were also part of the COVID Council. Other committee leaders were brought in to help with frequently asked questions, as well as providing expertise in our town hall webinars. These COVID Council calls also included key ASA staff leaders—Brian

Reilly, Manuel Bonilla, Matthew Popovich, Marc Bernstein, Maureen Geoghegan, Nora Matus, Joseph Szokol, and Sarah Bruce—led by Paul Pomerantz. I had daily communications with many of them, and they did an excellent job supporting the physician leaders in dealing with the onslaught of issues affecting our members and patients. Managing through a crisis is a team sport, and I had the dream team.

In Thinking about Emergency Planning, There Are Five Stages

1. The prevention stage involves taking measures to prevent emergencies from occurring in the first place. It includes identifying potential hazards, assessing the risks, and taking steps to reduce or eliminate them. Examples might include things like sanitation to prevent a cholera epidemic or information technology security to prevent cyberattacks.
2. The mitigation stage involves taking actions to reduce the impact of an emergency. It includes developing plans and procedures, training personnel, and conducting exercises to test the plans. For many natural disasters, this might include reinforcing buildings, installing storm windows, and having emergency power.
3. The preparedness stage includes developing emergency plans, stockpiling supplies, and training personnel. For a hurricane, where I live, we have drills every June and increase our supply PAR levels. This came in handy with the 2024 IV solution shortages. We had extra PAR levels on hand for hurricane threats that we were able to use until we adjusted to more drastic conservation measures.
4. The response stage involves responding to the emergency. It includes activating the emergency plan that you have developed, mobilizing resources, and initiating responses. The priorities are twofold: prevent loss of life, then loss of property.
5. The recovery stage involves recovering from the emergency, restoring the essential services, repairing damage, and returning to normal operations. This should include trauma-informed care and debriefing on what went well and what could be improved in the future. After major natural disasters, the recovery stage can take years.

In March 2020, we were beyond prevention, although the government attempted this early on with travel bans. In retrospect, the virus was here well before the travel bans. We were in a combination of mitigation, preparation, and response, depending on where one lived. Mitigation involved limiting disease transmission to ensure we could maintain hospital capacity. It was done by the old-fashioned methods of quarantining those who are sick, limiting person-to-person contact, and barriers like masks.

Controversy arose, not unlike in the flu pandemic of 1918. I received an email from an anesthesiologist who was fired for wearing a mask in a hallway. The hospital administration did not want to scare people, or at least that is what he was told. The CDC was late in either recognizing or acknowledging that this virus was being transmitted through aerosols. It was obvious for many of us who tracked the rapid expansion across China, then Italy, as well as the reports of transmission during a choir practice, and the cruise ship quarantined off the coast of Japan. In those well-documented situations, it was clear people were being infected through the air and not merely droplet contact.

Principles to remember in response to a crisis are to preserve life first and property second. The priorities became what I call the three Ps: physicians, patients, and pennies. The first statement ASA published advocated that every anesthesia professional have access to N95 respirators or the equivalent when doing aerosol-generating procedures like intubations. This was not without significant discussion by the ASA COVID Council, mainly because of the shortage of N95 respirators. This illustrates a principle I think is useful for the future. Protect our people. If we get sick, who is going to take care of our patients? It is like those instructions you receive every time you fly: "Put your mask on first before you put on your child's." It was better to mitigate the shortages by reusing and resterilizing the N95s than anesthesia professionals going completely without. ASA quickly got concurrence with the APSF, the American Association of Nurse Anesthetists (Rosemont, Illinois), and the American Academy of Anesthesiologist Assistants (Middleton, Wisconsin). We were the first medical organization advocating this. We then addressed what resources were needed to help physicians take care of their patients, and finally, addressed how practices could stay in business and meet payroll.

The ASA responded with many resources and communicated these in new ways. For the first time, we did town halls to deliver just-in-time education. We were all learning along the way. As ASA president, I was fortunate to know our surgeon general, Dr. Jerome Adams, an anesthesiologist, as well as Dr. Brett Giroir, a pediatric critical care physician who was the assistant secretary of Health and Human Services (Washington, D.C.). Relationships in a crisis do matter.

Our chief advocacy officer, Manny Bonilla, also had many relationships, which I am sure helped us get invited to a White House Task Force conference call on March 16 with several other medical organizations present. After the president, vice president, and other leaders on the call introduced themselves and thanked us for our work, it became a free-for-all with people talking over each other. One physician association leader discussed the impending mental crisis. Another wanted payment for telemedicine. I did not think those were the highest priorities at that time, and I voiced my concern about the impending ventilator shortage that needed to be addressed. That got the attention of the White House Task Force. Soon after that call ended, my office phone rang with a 202 area code: Washington, D.C.

It was Dr. Deborah Birx saying the situation was critical, worse than I could imagine. They were estimating a need of 200,000 ventilators, and the U.S. stockpile had only 10,000 ventilators, which were probably all going to be deployed to New York City. I then informed her that ASA and APSF had a plan to convert our anesthesia gas machines to ICU ventilators. Drs. Butch Loeb and Jeff Feldman had been working around the clock on this problem along with the Food and Drug Administration and the machine manufacturers. We could add an estimated 80,000 ventilators with these conversions. ASA held a town hall meeting on March 19, where Drs. Loeb and Feldman explained how to convert our anesthesia gas machines to ICU ventilators. Dr. George Williams provided education on ICU management and especially ventilation management for COVID-19 patients. More than 8,000 attended this town hall, and that same week, New York City had to convert anesthesia gas machines to become ICU ventilators to save patient lives.

One of the positive aspects I saw in this crisis was the willingness of organizations, groups, and individuals to come together. This was especially true in our medical communities, where information was freely shared, and many volunteers, including anesthesiologists, went to hard-hit areas. We worked with our specialties in sister organizations like the Society of Critical Care Anesthesiologists (Milwaukee, Wisconsin), Society of Critical Care Medicine (Mount Prospect, Illinois), American College of Chest Physicians (Glenview, Illinois), and the American College of Thoracic Surgeons (Chicago, Illinois) to create a statement about the dangers of coventing patients or putting multiple patients on one ventilator. This should not be done in lieu of converting our anesthesia gas machines. Unfortunately, in the current guidance issued by the Administration for Strategic Preparedness and Response (Washington, D.C.), otherwise known as ASPR, there is no mention of anesthesia gas machine conversions as a resource. Anesthesiologists need to have a voice in these government organizations. We have the expertise and the on-the-ground reality to inform better planning for the future. Society for Ambulatory Anesthesia (Milwaukee, Wisconsin), Society for Obstetric Anesthesia and Perinatology (Lexington, Kentucky), Society of Critical Care Anesthesiologists, Society for Neuroscience in Anesthesiology and Critical Care (Raleigh, North Carolina), and APSF leaders and members all contributed to our frequently asked questions and town hall meetings. Special thanks go to our critical care medicine colleagues who created an ICU bootcamp to help our physicians who were not practicing in the ICU refresh their skills so they could also help in the ICUs.

ASA worked at the national level advocating for anesthesia professionals having access to appropriate respirators, and to use the Defense Production Act to acquire and manufacture more PPE. We worked with the Food and Drug Administration, not just with our anesthesia gas machine conversions but also mitigating and managing our drug shortages. We worked with the federal government advocating for financial help to our practices, which were struggling with the loss of elective surgeries that occurred with the initial shutdowns but also were affected by the rolling waves of COVID variants that also limited available beds and other resources.

In the early days of the pandemic, the ASA became a connector and supporter where we learned from each other and sometimes just commiserated with each other. I received poignant emails from some of my women colleagues with young newborns and young children at home who were going to work, worried about infecting their loved ones. Was proper use of PPE enough? Should I be living with my family? As it turns out, proper PPE did work, but we did not know that then. All I could do was listen because I did not have the answers to their questions. We were all doing our best with limited knowledge at that time.

COVID-19 Research and Vaccine Development

Research was pivotal in saving lives during the pandemic. The challenge editors faced was the trade-off in publishing studies with small numbers quickly and without the usual iterative process of peer review *versus* better powered studies with more scrutiny. Any small study with seemingly positive results had widespread press attention. The public was desperate for any quick fixes like chloroquine. When many larger studies proved that chloroquine did not work, we had disbelief from many in the public. We have a challenge communicating how science works and its limits and a lot of work to do in rebuilding trust in our communities.

Despite the challenges in effectively communicating in the early stages of the pandemic, we witnessed early and marked declines in mortality. In a study published in 2021, Asch *et al.*[3] showed that mortality dropped almost 50% in the first 6 months of the pandemic for patients admitted with a diagnosis of COVID-19. In another study, Finelli *et al.*[4] studied more than 42,000 patients in more than 200 hospitals, which also showed an improvement in mortality, especially in those older than 50 yr (fig. 2). In a *JAMA Internal Medicine* commentary provided by Drs. Boudourakis and Uppal,[5] they posit that the reasons for the decreases in mortality may include increased clinical experience that we got in caring for patients requiring ventilators in different stages of COVID, the use of prone positioning, steroids, remdesivir, and the use of noninvasive ventilation. But there are other nonmedical possibilities. Perhaps patients in the initial period were admitted with more serious disease, or there were hospital capacity issues that degraded care, or early on with less use of PPE, people had larger infective doses of COVID. The improvements in mortality in such a brief time were hard-fought at the bedside and in our research communities and were impressive. A 50% reduction in mortality. That is amazing.

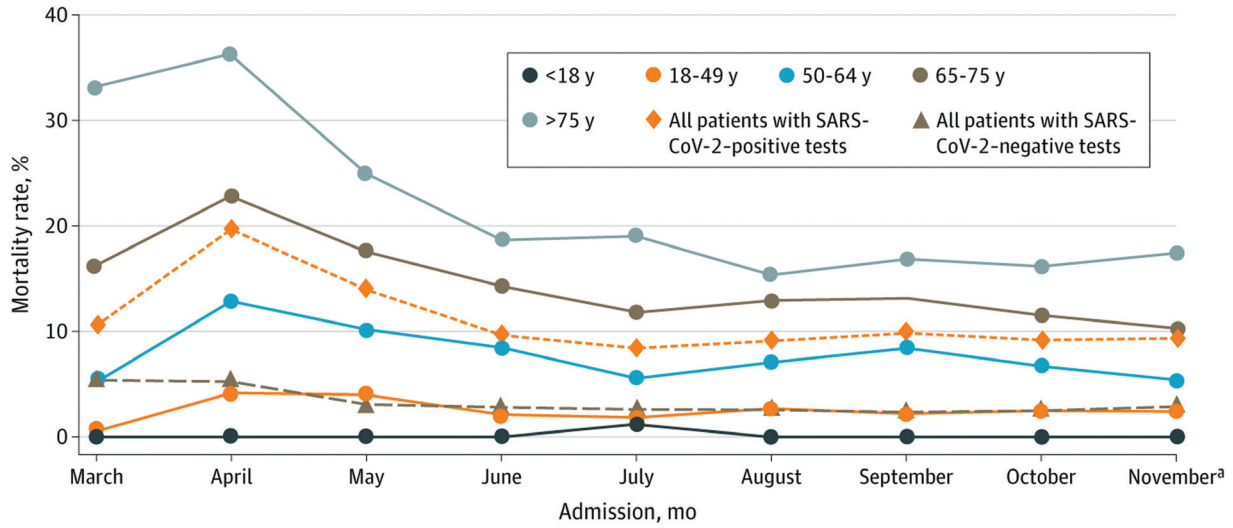


Fig. 2. In-hospital mortality rates by month of admission among patients with SARS-CoV-2–positive and SARS-CoV-2–negative tests. The assessment period was from March 1 to November 21, 2020, and included data from 42,604 patients cared for in 209 hospitals. [a]The November time period extended from November 1 to November 21, 2020. Reprinted from Finelli L, Gupta V, Petigara T, Yu K, Bauer KA, Puzniak LA: Mortality among US patients hospitalized with SARS-CoV-2 infection in 2020. JAMA Netw Open 2021 4:e216556. doi: 10.1001/jamanetworkopen.2021.6556.

One of the major accomplishments in this pandemic was the development of the mRNA COVID-19 vaccine and its rapid deployment. The story of the mRNA vaccine is fascinating, and this research will open a new age of medical miracles. While the public worried that the innovative technology was rushed and was not safe, the truth is that this was 40 yr in the making. I want to share the story of Katalin Karikó, who, along with her colleague Drew Weissman, won the Nobel Prize for Medicine in 2023.

Dr. Karikó, who was born in 1955, grew up in a small home in Hungary without running water, a refrigerator, or a television. Her father was a butcher, her mother a bookkeeper. She excelled in science and earned her Ph.D. in biochemistry in 1982. When her laboratory lost funding in 1985, she immigrated to the United States with her husband, 2-yr-old daughter, and money smuggled inside her daughter's teddy bear and landed a postdoctoral fellowship at Temple University (Philadelphia, Pennsylvania). Despite her lack of continued grant funding, and being demoted by the University of Pennsylvania (Philadelphia, Pennsylvania), she persisted in her belief of the future of mRNA for vaccine development and cancer treatment.

Her collaboration with Drew Weissman eventually led to our current mRNA technology. Karikó and Weissman figured out how to reduce the immune response to mRNA by one simple nucleoside replacement. This key finding was rejected by the prestigious journals *Science* and *Nature* but was finally accepted in *Immunity*. In the United States, this paper caught the attention of a group of researchers, professors, and venture capitalists, who formed Moderna (Cambridge, Massachusetts) and BioNTech (Mainz, Germany). These companies worked for years with no products to show for it. Moderna partnered with the National Institutes of Health (Bethesda, Maryland) and Defense Advanced Research Projects Agency (Arlington, Virginia) in vaccine development for Zika. Pfizer signed a deal with BioNTech to deliver mRNA vaccines for the flu. After years of mRNA clinical work built on decades of basic research, scientists developed a COVID-19 vaccine with astonishing speed. On January 11, 2020, Chinese researchers published the genetic sequence, and 48 h later, Moderna had finalized its mRNA recipe. By late February, batches of the vaccine had been shipped to Bethesda for clinical trials. The federal government's Operation Warp Speed invested billions of dollars into vaccine candidates and supported the manufacturing of them. This is an example like the moonshot when the government partners with researchers and private industry to accomplish an exceedingly difficult goal.

After 40 yr of wandering in the deserts of research, despite the setbacks and naysayers, finally Karikó and Weissman reach the promised land, seeing their grit pay off in profound ways, saving millions of lives in the pandemic and many future lives to come. The future of this technology is breathtaking. It is not just about vaccines, although infectious diseases continue to kill millions a year around the globe, especially with a hard impact on children. In the case of infectious diseases, these molecules are designed to better recognize the pathogens in our body for search and destruction, or in some cases, ensure that the pathogens have not incapacitated or bypassed our normal immune response. Cancer is another rich area of research for this technology. By taking our own cancer cells, a personal mRNA vaccine

is made, which will help our immune system search for and destroy similar tumor cells. Or, in the case of amyloidosis, a small interfering RNA will silence messenger RNA to suppress those genes that make amyloid.

Lessons from Crisis Response

During the early days of the COVID-19 response, I also learned that on-the-ground information is critical. When there is a crisis, even those who are normally competitors need to come together and share resources. Perhaps because Texas experiences a lot of natural disasters, we do have a robust emergency management system. One of the principles used is that the regional communities need to work together before asking the state government for assistance, and I saw that work well in my community and others.

I know that Dr. Marc Boom, the CEO of the Methodist Healthcare System in Houston, led 6:30 AM daily calls with the other CEOs of the regional health systems to understand what capacity existed and which hospitals were overextended. Not surprisingly, the county hospital in Houston filled up first, and the other private hospitals began to take all new incoming patients in a round robin fashion. My calls were usually in the evening, when we could divide up the 10% of what we asked for in state resources. We all had each other's cell numbers and could easily ask for help with just random shortages, like glucose test strips, to see if anybody had any to spare. I learned that was not always the case in the other states, where there was a lack of coordination of local, regional, and state resources. I urge any of you who are leaders in your hospitals or communities to develop relationships with your community leaders and understand the emergency management system. Sometimes they need to hear your voice to improve a response in the future.

After Hurricane Harvey, I complained to our local and state management leaders that Texas needed to develop specialized medical shelters. When I was working with my team to evacuate children at home on ventilators or other technologies, I found it was almost impossible. They could not go to a general shelter, and hospitals outside our regions did not want them because they did not meet admission criteria. Some of these families did not have the ability to manage a ventilator alone. They depended on private duty nurses or other expertise in the home. We now have that specialized medical shelter and Air Force base in San Antonio with nurses, therapists, dialysis, *etc.*

My colleague Dr. Meera Gangadharan *et al.*[6] have nicely described why anesthesiologists are especially suited in being involved with disaster planning, training, and response. All communities are at risk for disasters. One disaster not discussed in their research, which is becoming much more common, is a cybersecurity event that can take down the electronic medical records, phone systems, and other systems that we depend on to take care of our patients. This is not only very disruptive but can lead to patient deaths. I urge everyone to develop policies, plans, and procedures for maintaining patient safety and care for these more frequent events.

Psychological Perspectives on the Natural History of a Disaster

The natural history of a disaster can be viewed from a psychological perspective.[7] Phase one, or the predisaster phase, is characterized by fear and uncertainty. The specific reactions a community experiences depends on the type of disaster. Disasters with no warning can cause feelings of vulnerability and a lack of security, fears of the future, unpredicted tragedies, and a loss of sense of control, or the loss of the ability to protect yourself and your family. On the other hand, disasters with warning can cause guilt or self-blame for failure to heed the warnings. The predisaster phase may be as short as hours or even minutes, such as during a terrorist attack, or it may be as long as several months, such as during hurricane season.

Phase two or the impact phase is characterized by a range of intense emotional reactions. As with the predisaster phase, specific reactions also can depend on the type of disaster that is occurring. Slow, low-threat disasters have psychological effects that are different from a rapid, dangerous disaster. As a result, these reactions can range from shock to overt panic. Initial confusion and disbelief and denial typically are followed by a focus on self-preservation and family protection. The impact phase is usually the shortest phase of the six phases of a disaster.

Phase three, or the heroic phase, is characterized by a high level of activity with a low level of productivity, and during this phase, there is a sense of altruism, and many community members exhibit adrenaline-induced rescue behavior. As a result, risk assessment can sometimes be impaired.

The heroic phase often quickly passes into phase four, the honeymoon phase, which is characterized by a shift in emotion, and during this phase, disaster assistance is hopefully readily available. Community bonding occurs. Optimism exists that everything is going to get better quickly. As a result, numerous opportunities are available during this time for providers and organizations to establish and build rapport with those affected and for them to build relationships with stakeholders.

The honeymoon phase typically only lasts a few weeks. Phase five, the disillusionment phase, is in stark contrast to the honeymoon phase. During this phase, communities and individuals realize the limits of disaster assistance. As optimism turns to discouragement, and stress continues to take its toll, negative reactions such as physical exhaustion and substance use may begin to surface. The increasing gap between need and assistance leads to feelings of abandonment, especially as the larger community returns to business as usual. There may be an increased demand for services as individuals and communities begin to accept support. This disillusionment phase can last months and even years.

It is often extended by one or more trigger events, usually including the anniversary of the disaster.

And finally, phase six, a reconstruction phase, is characterized by an overall feeling of recovery. Individuals and communities begin to assume responsibility for rebuilding their lives, and people adjust to the new normal while continuing to grieve losses. The reconstruction phase often begins around the anniversary of the disaster and may continue for some time beyond that. After catastrophic events, the reconstruction phase may last for years.

We are still seeing the aftermath of the COVID-19 pandemic with staffing shortages due to accelerated retirements and burnout while our aging population needs more healthcare services. It is important for us to realize that crisis care affects the mental health of those providing it. We need to pay more attention to the caregivers.

Posttraumatic Stress and Burnout among Physicians

In a 2024 *JAMA Network Open* publication,[8] a meta-analysis of physician posttraumatic stress disorder (PTSD) during COVID-19 showed a pooled estimate of physician PTSD of 18% compared with 4 to 5% in the general population (table 1). Women had a prevalence rate almost twice as high as men. More research is needed to understand the risk factors that contribute to PTSD so that we can improve physician wellness.

In an article published in fall 2024 in the *Journal of Healthcare Management*,[9] Carlasare *et al.* surveyed 3,671 physicians, with 1,162 or almost 32% responding. The study looked at burnout, perceived organizational support, and professional fulfillment using some standardized instruments. In their study, women and physicians with children under 18 scored significantly lower on the perception of organizational support. Specialties like anesthesiology and emergency medicine also scored poorly. It was also noted that a single-point increase in the perception of organizational support results in 21% lower odds of burnout and 32% higher odds of professional fulfillment.

Table 1. Mean of PTSD Prevalence for Each Specialty*

Specialty	Prevalence
Emergency medicine	23.4%
Anesthesiology	16.1%
Surgery	22.4%
Family medicine	31.2%
Critical care	14.8%
Internal medicine	21.9%

*Fifty-seven studies with a total of 28,965 participants and 25 countries were included in the analysis, with 18.3% of physicians reporting symptoms consistent with posttraumatic stress disorder (PTSD). The pooled odds ratio for female (*vs.* male) physicians was 1.93. Data from Kamra M, Dhaliwal S, Wenshan L, et al.: Physician posttraumatic stress disorder during COVID-19: A systematic review and meta-analysis. JAMA Netw Open 2024;7:e2423316. doi: 10.1001/jamanetworkopen.2024.23316.

I certainly saw this during our own organization with COVID. I could see our women faculty at the end of their ropes when schools announced they were going to be late opening in fall 2020 after having been closed in the spring and summer. That was when we decided to hire some schoolteachers and opened our abandoned business spaces and auditorium to allow our staff to bring their children under 18 yr to the workplace, a safe place with teachers who could support their online learning. Now, staff could go home with homework completed and not a second job. Organizations need to think more about providing tangible support like this and not just meditation rooms. How we care as employers and leaders can positively influence our employees and those around us.

Trauma-informed Leadership

What is trauma-informed leadership? If I had to sum it up, it is simply asking and listening and caring about the people you work with. Drs. Shanafelt, Ripp, and Trockel from Stanford University School of Medicine (Stanford, California) and Icahn School of Medicine (New York, New York) conducted eight listening sessions with about 69 clinicians during that very first week of COVID to explore what they were worried about, what they needed from their leaders, and what tangible supports would be most helpful[10]:

1. Hear me. Listen to people on the front line. Address their concerns as much as organizations and leaders can.
2. Protect me. Reduce the risk of healthcare professionals acquiring infection or being the portal of transmission to their family members. In other words, make sure you have PPE.
3. Prepare me. Provide training and support so I can take great care of my patients.
4. Support me. Provide support that acknowledges our human limitations in a time of extreme work hours, uncertainty, and intense exposure to critically ill patients.
5. Care for me. Provide holistic support for the individual and their family if they must be quarantined.

As leaders, we need to ensure that in the heat of a crisis, we don't forget to take the time to actively listen and do what we can to respond to the needs of our people.

Conclusions

In conclusion, these are my learnings and take-home messages to think about for the future. First, research is about taking risks and learning from failures. For decades, we have tried to find an HIV vaccine. Did you know that 90% of COVID vaccines that made it into clinical trials used technology that could be traced back to the prototypes in HIV trials? These rabbit holes and dead ends have begotten an

explosion of technologies for a new golden age of medicine. Without Karikó and Weissman's heroic efforts to make mRNA technology work, the world would have no Moderna or BioNTech. Without government funding and philanthropies, both companies would have been bankrupt before the 2020 vaccines. Without the work of international scientists decoding the secrets of the coronavirus spike proteins several years ago with MERS and SARS, we may not have known to target it. It is about planting seeds. Only some will germinate and grow. A few more will produce fruit. It is up to us as a society and professional organization to plant seeds and fertilize and water them.

Second, we all need to prepare for disasters and hope we never have to use our plans. I hope you do not have to experience another pandemic or a mass casualty event or a cyberattack, but just as with our anesthesia training, preparing for the worst can help us remain calm and focused in the event of a crisis. It will also save lives. I also cannot stress enough the value of relationships. Know whom to call to ask for help in your hospital, your community, your state, and your national association, the ASA. Know how to call a friend.

Third, as in any crisis, we will always have limited information, but we cannot be paralyzed by that. This is another good reason anesthesiologists make good crisis leaders.

I want to thank all of you who took care of your patients, regardless of the personal risks involved. I want to thank all the researchers who persevered in finding the best treatments and vaccines. Were there people who died because of a lack of resources that we would ordinarily have saved? Yes, but realize you did your best under difficult circumstances. That is why we call it crisis level of care. All of us lost someone—a friend, a colleague, a family member, or a patient—to COVID. We can honor them by continuing our work to advance and advocate for science, educate the public and the next generation of anesthesiologists, and provide leadership in our communities in planning for future disasters.

Acknowledgments

I thank the members of ASA for stepping up and providing care in our ICUs during the COVID-19 pandemic. You were problem solvers when we ran out of PPE or other drugs and supplies when taking care of our patients. You were an example to all of medicine of what it means to be a physician and demonstrated the versatility of anesthesiologists. While we have a shared grief for the many losses we experienced during the COVID-19 pandemic, I want us to also celebrate our many victories, the lives we saved then, and the lives we will save in the future with the knowledge we gained.

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Competing Interests

The author declares no competing interests.

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ANESTHESIOLOGY®

Clinical and Genetic Factors Associated with Intraoperative Minimum Alveolar Concentration Ratio: A Single-center Retrospective Cohort and Genome-wide Association Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Minimum alveolar concentration (MAC) ratio is used as a standard pharmacologic dosing regimen for anesthetic delivery.
- Despite extensive knowledge of what influences MAC in controlled studies, the determinants of clinical delivery of MAC ratio are largely unknown.

What This Article Tells Us That Is New

- In a large retrospective data set in adults undergoing general anesthesia with volatile anesthetics, the primary determinant of MAC ratio in clinical practice was blood pressure. Various factors known to influence MAC did not appear to influence clinical delivery of MAC ratio.
- A genome-wide association study failed to definitively identify novel variants at the level of genome-wide significance. However, eight variants located near six genes of neurologic relevance were identified at a lower level of evidence for an association.

ABSTRACT

Background: Minimum alveolar concentration (MAC) is a standard dosing metric for general anesthesia. Although influences of MAC have been identified in controlled studies, the determinants of clinical delivery of MAC ratio are largely unknown. To address this knowledge gap, the authors performed this single-center retrospective study. The primary objective was to understand factors associated with MAC ratio, as indexed by the end-tidal volatile anesthetic concentration, for a given case. It was hypothesized that mean arterial pressure (MAP) was strongly associated with anesthetic delivery; a secondary objective was to perform a genome-wide association study to identify genetic variants associated with MAC ratio in clinical practice.

Methods: The primary outcome was mean age-adjusted MAC ratio during the maintenance phase of anesthesia. The primary exposure variable was mean MAP during the same time window. The correlation between the outcome, exposure, and a variety of demographic, laboratory, procedural, and anesthetic covariates was assessed in adjusted multivariable linear regressions. Next, the authors performed two genome-wide association studies of clinically delivered MAC ratio.

Results: Of the 30,125 cases included in the final dataset, mean ± SD age-adjusted MAC ratio was 1.066 ± 0.173, and mean MAP was 82 ± 10 mmHg. MAP was associated with MAC ratio in the overall model (β = 0.0028; 95% CI, 0.0024 to 0.0032; $P < 0.0001$). A variety of demographic (*e.g.*, female sex: β = –0.0182; 95% CI, –0.0219 to –0.0144; $P < 0.0001$), laboratory, surgical, and anesthetic factors were also associated with anesthetic agent concentration. Eight variants located near six genes (*DPH6*, *CPM*, *EEFSEC*, *SGSM1*, *CDH9*, and *DISC1*) reached the lower suggestive threshold ($P < 1 \times 10^{-6}$) in one but not both models; none exceed the threshold for genome-wide significance ($P < 5 \times 10^{-8}$).

Conclusions: The hypothesis was verified that MAP was associated with clinical delivery of MAC ratio. The authors also characterized practice patterns of inhalational anesthetic management and identified numerous covariates that need to be accounted for when modeling anesthetic requirements. Female patients received lower doses of anesthetic, despite evidence that they have a higher requirement. While genome-wide association studies failed to identify novel variants at the level of genome-wide significance ($P < 5 \times 10^{-8}$), multiple mechanistically plausible genes were suggested. Notably, the *DISC1* gene has been shown to impact resting-state brain activations under general anesthesia with isoflurane and has been linked to abnormal sleep/wake patterns.

(Anesthesiology 2025; 143:541–58)

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Abbreviations: **ASA**, American Society of Anesthesiologists; **EtAA**, end-tidal anesthetic agent; **GEE**, generalized estimating equation; **MAC**, minimum alveolar concentration; **MAP**, mean arterial pressure

Minimum alveolar concentration (MAC) is historically defined as the steady state alveolar concentration that results in immobility in 50% of humans in response to a noxious stimulus[1] and has been the standard measure of potency for inhaled anesthetics since its introduction.[2] A variety of patient (*e.g.*, age, pregnancy), physiologic (*e.g.*, electrolyte abnormalities, anemia, hypercarbia), and pharmacologic (*e.g.*, concurrent medications, acute intoxication, and chronic alcohol use) factors influence anesthetic potency.[2] Modern anesthesia machines typically display both (1) end-tidal anesthetic agent (EtAA) concentration and (2) age-adjusted MAC ratio,[3] allowing clinicians to titrate their individual anesthetic plan and avoid anesthetic concentrations associated with awareness.[4] Although the influences on MAC are well-known, little is known about what factors that influence clinical delivery of MAC ratio in real-world practice. Even less is known about the genetics underlying anesthetic requirement and anesthetic dose, despite recent studies showing genetic associations with intravenous anesthetic requirement.[5]

To address the knowledge gap between factors known to influence anesthetic requirement and those actually impacting delivery of MAC ratio, we performed a retrospective analysis of cases employing inhaled agents as the primary means of general anesthesia. The primary objective for this study was to understand the factors impacting average age-adjusted MAC ratio for a given case. We hypothesized that hemodynamic factors, specifically mean arterial pressure (MAP), were associated with anesthetic dosing. A secondary objective was to conduct a genome-wide association study to identify genetic variants associated with intraoperative anesthetic dosing.

Materials and Methods

Study Design

All study procedures were approved by the University of Michigan Institutional Review Board (HUM00127909; Ann Arbor, Michigan). We followed the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines, an extension of the existing STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for the characterization of the MAC phenotype[6] and the STrengthening the REporting of Genetic Association Studies (STREGA) guidelines for the genetic analyses.[7] Informed patient consent was waived because no experimental patient care interventions were involved in the conduct of the study. Study methods including data collection, outcomes, and statistical analyses were established *a priori*, reviewed, and approved by the Anesthesia Clinical Research Committee (Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan, May 1, 2023).[8]

Study Population

Adult patients (18 yr or older) who had a surgical procedure employing inhalational anesthetic at Michigan Medicine between January 1, 2014, and March 11, 2023, were included in this observational cohort study. A representative sampling window for the maintenance phase of anesthesia was established from 30 min after intubation to 30 min before extubation. Only cases with greater than 60 min of valid ventilator and hemodynamic data during the maintenance phase were included in the final analysis. Cases with a gap between consecutive MAC or MAP measurements exceeding 5 min were also excluded from subsequent analyses. Additional details surrounding data extrapolation and algorithm for matching the MAC ratio and MAP time matrices can be found in the appendix.

Patient-specific exclusion criteria were pregnancy and American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status V/VI. Procedural exclusions were (1) cardiac surgery (or documented cardiopulmonary bypass), (2) lung transplantation, and (3) liver transplantation. Total intravenous anesthesia cases (or alternatively, cases using either a propofol or dexmedetomidine infusion), cases employing multiple volatile anesthetic agents, and those without muscle relaxant administration were also excluded.

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 491. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a visual abstract available in the online version.

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The large number of qualifying cases enabled us to apply restrictive inclusion and exclusion criteria to ensure relatively homogeneous case selection. In the absence of neuromuscular blockade, some clinicians might be employing a higher anesthetic dose to suppress patient movement. This dose could be approximately 30 to 40% higher than a comparable case with neuromuscular blockade, where the primary motivation is to prevent awareness.[9] In the interest of curating a uniform cohort, we focused on the more common anesthetic strategy (inhalational anesthetic plus neuromuscular blockade) and excluded the less common strategy (inhalational anesthetic without neuromuscular blockade).

Based upon the practice pattern at Michigan Medicine, during the study timeframe, only cases using sevoflurane or isoflurane (with and without nitrous oxide) were included. Total MAC ratio was calculated by adding the contribution of nitrous oxide to that of either sevoflurane or isoflurane in cases with two hypnotic agents.[10] Additional sensitivity analyses for single-agent cases were calculated to account for the expected stabilizing hemodynamic impact of nitrous oxide with volatile anesthetic.[11]

Data Sources

Our study leveraged perioperative data (local repository) of the Multicenter Perioperative Outcomes Group (Ann Arbor, Michigan) database.[12] The Multicenter Perioperative Outcomes Group is a multicenter registry of perioperative data extracted from the electronic health record for the purpose of research, education, and quality improvement.[12] Qualifying cases met previously validated criteria for data completeness and quality.[13] When possible, validated algorithms for concepts including case duration, inhaled anesthetic during maintenance phase of anesthesia, total intravenous anesthetic, and procedure class were employed.

Outcomes

The primary outcome was mean EtAA concentration during the maintenance phase of anesthesia, expressed in (age-adjusted) MAC units[10] for comparison purposes. End-tidal anesthetic concentration was also recorded minute by minute to allow correlation with dynamic intraoperative parameters. Although MAC is a single fixed number (*e.g.*, 2.1% for sevoflurane) that does not change with dynamic intraoperative factors, we report our anesthetic dosing in age-adjusted MAC units for ease of interpretation and comparison across patients and anesthetic agents. For simplicity's sake, "mean end-tidal volatile anesthetic concentration during maintenance phase of anesthesia, expressed in age-adjusted MAC units" will be henceforth referred to as "MAC ratio."

Exposure Variable

Mean MAP during the maintenance phase of anesthesia was the primary exposure variable. To facilitate subanalysis of dynamic changes through the intraoperative course, MAP measurements were matched to correspond to the timing of MAC ratio data collection.

Covariates

Patient-specific, physiologic, and pharmacologic factors known to influence anesthetic potency were extracted from the electronic health record. The covariates related to past history of (1) alcohol abuse or (2) drug abuse were derived using Elixhauser classifications[14] applied to International Classification of Diseases billing information, as previously described.[15] Quantitative variables—(1) age (years), (2) body mass index (kg m^{-2}), (3) ASA Physical Status Classification System (individual levels), (4) duration of inhalational anesthetic (minutes), (5) intraoperative transfusion (units), and (6) anesthesia base units assigned to the case based on surgical procedure type acting as proxy of case complexity—were treated as continuous variables in the analysis. Concurrent medications were selected based upon mechanisms for impacting MAC, data availability, and distribution within our surgical population. Therefore, the (1) collection window (*i.e.*, overall case *vs.* maintenance phase of anesthesia), (2) standardized *versus* absolute units, and (3) selection of continuous *versus* categorical variables differed between medications. Induction dose of propofol, total ephedrine dose, doses for benzodiazepines and opioids (normalized by patient weight and case duration), and the use of intraoperative epinephrine, vasopressor infusion, and α2-agonists were included as covariates.

Additionally, a *post hoc* sensitivity analysis was performed in response to peer review assessing the confounding effect of total vasopressor dose (expressed as norepinephrine equivalents) between anesthesia start and end.[16]

Genotype

Genetic data were obtained from Michigan Medicine's Michigan Genomics Initiative, Freeze 6.[17] Study participants provided written informed consent for obtaining genetic data, and protocols were reviewed and approved by the institutional review board.[18] Due to the retrospective design of this study and the use of deidentified data, the need for additional informed patient consent was waived by both boards. Full details and characterization of genotype for both cohorts have been previously described.[19,20]

Statistical Analyses

Perioperative and intraoperative characteristics were summarized using means and SDs for continuous variables and counts and percentages for categorical covariates. Balance between groups was assessed using standardized differences, with a standardized difference greater than 0.2 considered unbalanced.

We assessed the association between MAP and age-adjusted MAC ratio in an adjusted multivariable linear regression.[15] In prespecified sensitivity analyses, we repeated the models in the subset of cases using (1) single-agent isoflurane (model 2) and (2) single-agent sevoflurane (model 3) for anesthetic choice. P value < 0.05 was selected *a priori* to denote statistical significance. We also created a prediction curve to demonstrate the expected age-adjusted MAC ratio at different MAP values. These curves were created by using multivariable regression to predict the age-adjusted MAC ratio from MAP values while holding the other independent variables constant. Mean values were used for continuous variables, and the most common category was used for categorical variables, except for biologic sex, for which female was used, and year, for which the mean year of 2018 was used.

We also investigated the relationship between MAC ratio and MAP within individual cases (intracase as opposed to intercase association) using generalized estimating equations (GEEs). A directed acyclic graph representing the hypothesized causal pathway is shown in the Supplemental Digital Content, Figure 1 (https://links.lww.com/ALN/E58). Note the bidirectional relationship between MAP and MAC ratio.

Impact of Processed Electroencephalography on Practice

We assessed whether processed electroencephalography (EEG), specifically SedLine Brain Monitoring (Masimo, USA), impacted practice patterns. SedLine use began in 2022 with limited but increasing uptake.[21] While the relatively limited sample size precluded meaningful regression analysis, we elected to describe this sample with descriptive statistics. Additionally, in two *post hoc* sensitivity analyses, we repeat the original regression (1) on all cases (with and without SedLine data), beginning after the first documented use of SedLine, and (2) with a term quantifying the interaction between MAP and year of surgery included in the model.

Genome-wide Association Study

We performed a genome-wide association study on the outcome mean age-adjusted MAC ratio during the maintenance phase of anesthesia using the Scalable and Accurate Implementation of GEneralized mixed model (SAIGE) linear regression model with kinship adjustment on genetic data from a European cohort in the Michigan Genomics Initiative, Freeze 6,[22] as previously described.[23] In brief, the European population was defined using the majority admixture global ancestry fraction (Q-value). For association tests, we used TOPMed reference panel and excluded variants[24] with low imputation quality (R-squared less than 0.3) or very rare minor alleles (minor allele frequency less than 0.1% or minor allele count less than 20). Genome-wide significance threshold ($P < 5 \times 10^{-8}$) was selected *a priori* for identification of novel loci,[25,26] and a lower threshold ($P < 1 \times 10^{-6}$) was selected as a *suggestive* threshold (and to allow future *replication* of reported loci).[19,27,28] The 5×10^{-8} threshold established for genome-wide significance minimizes false positives by correcting for the high number of associations tested across the entire genome, ensuring robust and reproducible genetic findings. This standard threshold for genome-wide association studies was chosen to control for the high number of statistical tests performed across the entire genome, thereby minimizing the risk of false-positive findings. The 1×10^{-6} threshold adopted in our study is a commonly used and accepted threshold for "suggestive" significance.[28] Reporting associated loci at $P < 1 \times 10^{-6}$ allows the broader scientific field to replicate (or fail to replicate) the finding, which then either increases or decreases the proof of the association. Variants identified at this less stringent threshold should not be viewed as significant novel associations, as adoption leads to increased rate of false discovery.[25] Furthermore, if our hypothesis is proven true that anesthetic delivery, in the absence of neurobiological markers like the electroencephalogram, is being titrated to cardiovascular parameters, then the genome-wide association study may detect genetic variants that are associated with the cardiovascular rather than neurologic effects of volatile anesthetics.

Genome-wide association for average age-adjusted MAC ratio (inverse normalized) during the maintenance phase of anesthesia was assessed in two linear regression models. Model 1 controlled for (1) age, (2) genotypic sex, (3) body mass index, (4) mean MAP, (5) duration of inhalational anesthetic exposure, (6) year of surgery, (7) genotyping chip, and (8) the first 10 principal components. Controlling for principal components in a genome-wide association study helps alleviate the effect of population stratification caused by differences in allele frequencies resulting from systematic differences in genetic ancestry.[29] Genetic principal components were calculated using linkage disequilibrium-pruned directly assayed genotypes. Variants with a minor allele frequency less than 1% were removed before thinning variants with a squared correlation greater than 0.5 within a walking window of 500 variants and a step size of 5 using PLINK, an open source whole genome analysis toolset (Boston, Massachusetts).[30] Principal components for participants unrelated to the third degree or closer (determined using Kinship-based INference for GWAS [KING] v2.2.7)[31] were computed with FlashPCA2 v2.0,[32] and related participants were then projected onto the resulting principal component space. These genetic principal components are reflective of genetic ancestry and used to control for population stratification.

In model 2, we controlled for the full range of patient, surgical, and anesthetic factors. In addition to the variables from model 1, we controlled for (1) ASA Physical Status, (2) history of alcohol abuse, (3) history of drug abuse, (4) body region, (5) emergency surgery, (6) anesthesia base units, (7) intraoperative oral morphine equivalents (normalized), (8) induction dose of propofol (milligrams),

(9) intraoperative ephedrine dose, and (10) vasopressor requirement.

Results of the genome-wide association studies were visualized and top hits annotated using the *gwasTools* repository (https://github.com/ilarsf/gwasTools) with the option to set a suggestive significance threshold (*--sigthreshold*) of 1×10^{-6}. The Manhattan plot was annotated with quasi-independent top hits by creating 1-Mb regions centered around variants with *P* values less than 1×10^{-6} and combining overlapping intervals.

Results

Patient and Procedural Characteristics

Of 194,650 cases initially screened (adult patients, with inhaled anesthetic between January 1, 2014, and March 11, 2023), 30,125 were included in our final cohort. Figure 1 shows the derivation of this cohort. Missing data for each variable are described further in the Supplemental Digital Content, table 1 (https://links.lww.com/ALN/E58). Major reasons for case exclusion were (1) use of propofol infusion (or total intravenous anesthetic; n = 30,083), (2) cardiac surgery (or cardiopulmonary bypass; n = 19,955), and less than 60 min of valid ventilation (and MAC ratio) data (n = 54,317; fig. 1).

Within the final cohort, patients were average ± SD age 56 ± 18 yr with average ± SD body mass index 29.4 ± 7.3 kg m^{-2}, and 43.1% were female. A total of 1,450 (4.8%) of patients had a past history of alcohol abuse (by Elixhauser comorbidity index),[14] and 1,539 (5.1%) had a history of drug abuse. Average ± SD duration of inhalational anesthetic was 3.97 ± 1.93 h. In terms of intraoperative anesthetic management, (1) 9,299 (30.9%) required a vasopressor infusion, (3) mean ± SD induction dose of propofol was 1.65 ± 0.75 mg/kg, and (4) average ± SD intraoperative opioid requirement was 0.24 ± 0.13 oral morphine equivalents/kg/h during the maintenance phase of anesthesia. Full details on patient and procedural characteristics can be found in table 1.

Practice Patterns for Volatile Anesthetic Administration

Of the 30,125 cases included in the final dataset, 14,437 (47.9%) used only isoflurane, 2,592 (8.6%) used only sevoflurane, and 13,099 (43.5%) used a combination of two inhalational agents (*e.g.*, isoflurane plus nitrous oxide or sevoflurane plus nitrous oxide; Supplemental Digital

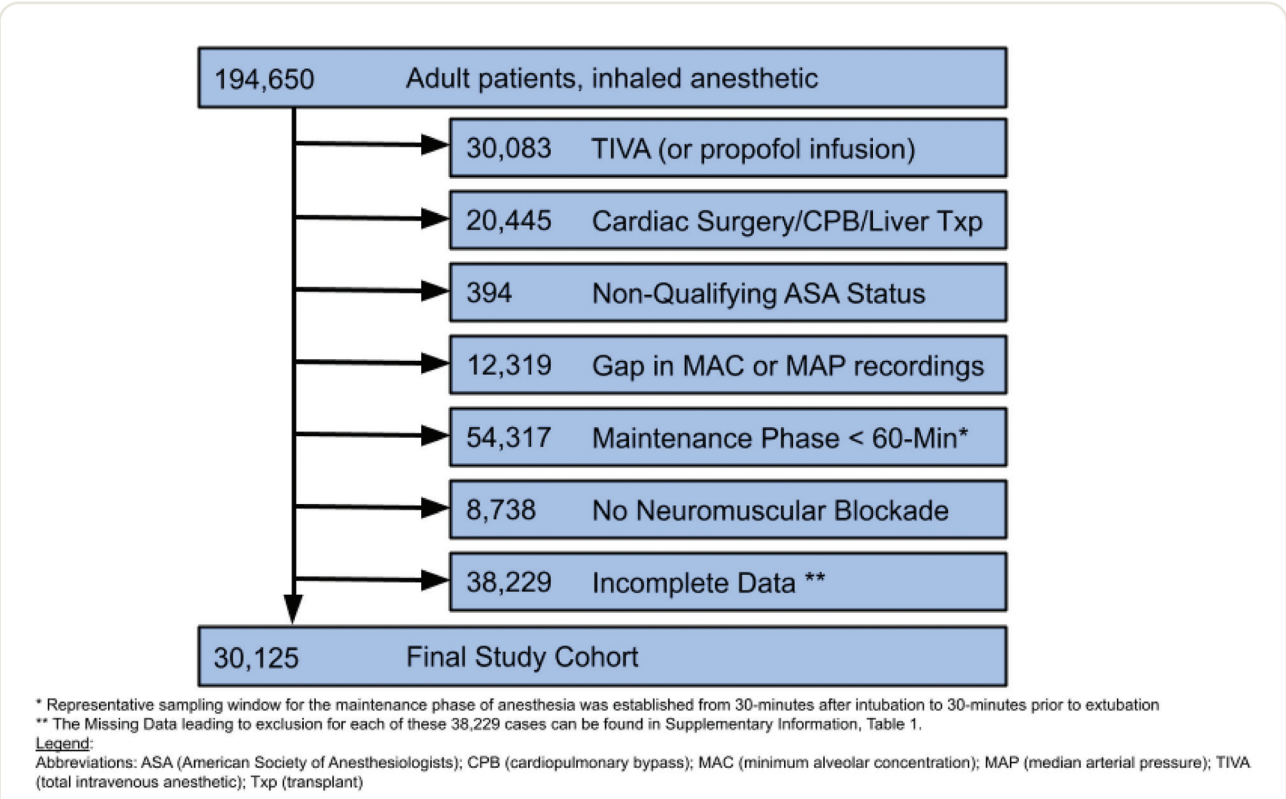


Fig. 1. Derivation of the study cohort. *Representative sampling window for the maintenance phase of anesthesia was established from 30 min after intubation to 30 min before extubation. **The missing data leading to exclusion for each of these 68,357 cases can be found in Supplemental Digital Content, Table 1 (https://links.lww.com/ALN/E58). ASA, American Society of Anesthesiologists; CPB, cardiopulmonary bypass; MAC, minimum alveolar concentration; MAP, mean arterial pressure; TIVA, total intravenous anesthetic; Txp, transplant.

Table 1. Characteristics of Full Cohort

Category and Characteristic	Full Cohort (n = 30,125) Mean/N	SD/ Percent
Demographic information and social history		
Age, yr	56	17.6
Female sex	12,982	43.1
Race		
White	26,451	87.8
Black	3,015	10.0
Asian or Pacific Islander	659	2.2
Body mass index, kg/m^2	29.4	7.3
ASA Physical Status		
I	549	1.8
II	7,915	26.3
III	19,069	63.3
IV	2,592	8.6
Previous history of alcohol abuse	1,450	4.8
Previous history of drug abuse	1,539	5.1
Preoperative laboratories		
Sodium		
Hyponatremia	2,740	9.1
Normal or hypernatremia	27,385	90.9
Hemoglobin		
Severe anemia (< 8.0 g/dl)	1,074	3.6
Mild anemia (8.0–13.5 g/dl)	16,651	55.3
Normal or elevated (≥ 13.5 g/dl)	12,400	41.2
eGFR		
Stage 1 (≥ 90 ml/min/1.73 * m^2)	15,208	50.5
Stage 2 (60–89)	9,407	31.2
Stage 3a (45–59)	2,189	7.3
Stage 3b (30–44)	1,038	3.5
Stage 4 (15–29)	706	2.3
Stage 5 (< 15)	1,577	5.2
Aspartate aminotransferase		
Normal (< 34 U/l)	22,991	76.3
High (≥ 34 U/l)	7,134	23.7
International normalized ratio		
Low or normal (< 1.1)	21,873	72.6
High (≥ 1.1)	8,252	27.4
Surgical and procedural details		
Body region		
Abdomen	8,941	29.7
Extremities	5,157	17.1
Genitourinary	5,847	19.4
Head and neck	3,089	10.3
Radiologic	2,486	8.3
Spine	1,453	4.8
Thorax	3,152	10.5
Emergency surgery	2,774	9.2
Year of surgery		
2014	2,846	9.4
2015	3,890	12.9
2016	4,034	13.4
2017	3,798	12.6
2018	3,544	11.8
2019	3,492	11.6
2020	2,729	9.1
2021	2,818	9.4
2022	2,468	8.2
2023	506	1.7
Intraoperative details		
Age-adjusted MAC	1.006	0.173
Mean arterial pressure, mmHg	81.8	9.9
Duration of inhalational anesthetic, h	3.97	1.93
Anesthesia CPT units	8.1	3.2
Induction dose of propofol, mg/kg	1.65	0.75
Total intraoperative opioid, OME/kg/h	0.24	0.13
Ephedrine dose, mg	4.0	9.0
α2-Agonist	5,753	19.1
Vasopressor infusion	9,299	30.9
Epinephrine administered	406	1.35

AKI, acute kidney injury; ASA, American Society of Anesthesiologists; CPT, Current Procedural Terminology; eGFR, estimated glomerular filtration rate; MAC, minimum alveolar concentration; OME, oral morphine equivalents.

Content, table 2, https://links.lww.com/ALN/E58). Mean ± SD age-adjusted MAC ratio was 1.006 ± 0.173. There were small differences between age-adjusted MAC ratio among the isoflurane, sevoflurane, and two-agent subgroups (Supplemental Digital Content, table 3, https://links.lww.com/ALN/E58). For example, the mean ± SD age-adjusted MAC ratio for the isoflurane-only group was 0.944 ± 0.147 compared to 1.060 ± 0.179 in the sevoflurane-only group ($P < 0.0001$).

The mean average ± SD MAP among all included cases was 82 ± 10 mmHg, which is very similar to cases employing isoflurane only (mean ± SD, 82 ± 10 mmHg) and sevoflurane only (mean ± SD, 80 ± 11 mmHg; Supplemental Digital Content, table 3, https://links.lww.com/ALN/E58). Histograms showing the distribution of MAC ratio and MAP for the overall cohort (and subcohorts used in sensitivity analyses) are visualized in the Supplemental Digital Content, figure 2 (https://links.lww.com/ALN/E58). Additionally, institutional practice has changed during the course of the study period, with the predominant single-agent inhalational anesthetic transitioning from isoflurane to sevoflurane. Nitrous oxide, in the setting of two-agent inhalational anesthetic (*i.e.*, isoflurane plus nitrous oxide or sevoflurane plus nitrous oxide) also decreased sharply toward the conclusion of the study period (Supplemental Digital Content, table 2, https://links.lww.com/ALN/E58).

Multivariable Linear Regression: Average MAP during Maintenance Phase

MAP was associated with age-adjusted MAC ratio in the overall model (β = 0.0028; 95% CI, 0.0024 to 0.0032; $P < 0.0001$; table 2) and each of the sensitivity analyses (Supplemental Digital Content, table 4, https://links.lww.com/ALN/E58). This implies that every 10-mmHg increase in average MAP is associated with a 0.028 increase in average age-adjusted MAC ratio for that case, holding other covariates constant. If we assume that a change in

MAC ratio of 0.1 is clinically meaningful, a MAP difference of 30 mmHg would be required to exert a clinically meaningful change. The interaction between MAP and duration of inhalational anesthetic was also associated with average MAC ratio during the maintenance phase ($P < 0.0001$). A variety of demographic factors were found to be associated with MAC ratio, notably (1) female sex ($\beta = -0.0182$; 95% CI, –0.0219 to –0.0144; $P < 0.001$), (2) Black race ($\beta = 0.0096$; 95% CI, 0.0036 to 0.0156; $P = 0.0016$), and (3) previous history of drug abuse ($\beta = 0.0159$; 95% CI, 0.0078 to 0.0239; $P < 0.0001$). Laboratory studies consistent with (1) anemia, (2) renal dysfunction, and (3) elevated international normalized ratio ($\beta = -0.0067$; 95% CI, –0.0109 to –0.0026; $P = 0.0015$) were also associated with MAC ratio. Emergency surgery ($\beta = -0.0231$; 95% CI, –0.0294 to –0.0168; $P < 0.0001$) and larger cases (by Anesthesia Current Procedural Terminology units; $\beta = -0.0072$; 95% CI, –0.0079 to –0.0066; $P < 0.0001$) were associated with lower MAC ratio. Intraoperative medications, including (1) induction dose of propofol ($P < 0.0001$), (2) total intraoperative opioid ($\beta = 0.0950$; 95% CI, 0.0792 to 0.1109; $P < 0.0001$), (3) ephedrine dose ($\beta = -0.0009$; 95% CI, –0.0011 to –0.0007; $P < 0.0001$), and (4) use of a vasopressor infusion ($\beta = -0.0691$; 95% CI, –0.0734 to –0.0648; $P < 0.0001$) were all associated with average MAC ratio. The full results from the regression model are in table 2. Goodness-of-fit for the full model was quantified using the Akaike information criterion (–27,813.4) and Bayesian information criterion (–27,406.0) compared to –20,258.3 and –20,241.7 for the null models, respectively. The greater values for the full model indicated that including the variables in the multivariable regression improved the fit over the null model.

The effect remained consistent on *post hoc* sensitivity analysis controlling for total vasopressor dose (Supplemental Digital Content, table 5, https://links.lww.com/ALN/E58). Furthermore, cumulative vasopressor dose was also associated with age-adjusted MAC ratio ($\beta = -1.5304 \times 10^{-5}$; 95% CI, -2.1067×10^{-5} to -9.5410×10^{-5}; $P < 0.0001$) in this model.

A curve showing the predicted MAC ratio at different MAPs generated for a representative patient, selected from informative, average, or most common covariate (*i.e.*, 56-yr-old woman, ASA III, nonemergency surgery, *etc.*), is shown in the Supplemental Digital Content, figure 3 (https://links.lww.com/ALN/E58).

Intracase Relationship between MAC Ratio and MAP

The previously described analytical approach assesses the relationship between average MAP and average MAC ratio on an overall case basis but fails to characterize the temporal relationship between the exposure and outcome variable *within* a given case. Specifically, exposure to inhalational anesthetic *decreases* MAP,[33] but the anesthesia provider may actively *downtitrate* the anesthetic in response to those hemodynamic changes. This bidirectional relationship between MAP and MAC ratio is illustrated in the directed acyclic graph (Supplemental Digital Content, figure 1, https://links.lww.com/ALN/E58). Further complicating this relationship is a variable lag time between dose and response, which may vary as a function of inhalational anesthetic selection, concentration of inhaled anesthetic, total fresh gas flow, and provider attentiveness. We illustrate each of these characteristic temporal relationships between MAC ratio and MAP within a single case each in figure 2. Figure 2A demonstrates a period of high (set) MAC ratio, with a corresponding decrease in MAP. Figure 2B shows a period of hypertension, preceding uptitration of MAC ratio by the provider. In response to the uptitration of MAC ratio (in fig. 2B), the MAP continues to decrease until the provider responds by downtitrating the MAC ratio. In practice, the parameters have a circular relationship. In some epochs, MAP determines MAC ratio, and in others, MAC ratio determines MAP. Figure 2C incorporates the Patient State Index, a validated metric for depths of anesthesia,[34] from one of the limited number of cases with processed EEG data available (SedLine monitor, Masimo). In this figure, MAC ratio is titrated in response to a cardiovascular parameter (hypertension), despite the neurologic metric (Patient State Index) indicating an appropriate depth of anesthetic.

Just as MAP was associated with MAC ratio when considering the cumulative distribution of these measures for each case ($\beta = 0.0028$; 95% CI, 0.0024 to 0.0032; $P < 0.0001$), the relationship persisted ($\beta = 0.0013$; 95% CI, 0.0012 to 0.0013; $P < 0.0001$) when the repeated-measures distribution of MAP and MAC ratio data was included in our GEE models (Supplemental Digital Content, table 6, https://links.lww.com/ALN/E58).

Impact of Processed EEG on Age-adjusted MAC Ratio

Twenty-five patients had processed EEG data that were accessible for inclusion in the analysis. Cases utilizing EEG had a lower average MAC ratio (1.005 *vs.* 1.052; standardized difference, 0.249) and higher average MAP (86 mmHg *vs.* 82 mmHg; standardized difference, 0.328) when compared to the population not using EEG during the same period. Full comparison of the EEG cohort and the non-EEG population can be found in the Supplemental Digital Content, table 7 (https://links.lww.com/ALN/E58). The relationship between average Patient State Index (over the maintenance phase of anesthesia) and age-adjusted MAC ratio can be visualized in the scatterplot (Supplemental Digital Content, figure 4, https://links.lww.com/ALN/E58). In a *post hoc* sensitivity analysis of cases occurring after the introduction of SedLine at our institution (*i.e.*, after the first case with SedLine data), MAP was no longer significantly associated with MAC ratio ($\beta = 0.0000$; 95% CI, –0.0019 to 0.0018; $P = 0.9863$; Supplemental Digital Content, table 8,

Table 2. Multivariable Linear Regression of Factors Associated with End-tidal Volatile Anesthetic Concentration (Expressed as Age-adjusted Minimum Alveolar Concentration; n = 30,125)

	β	95% CI		*P* Value
Primary exposure variable				
Average mean arterial pressure, mmHg	0.0028	0.0024	0.0032	< 0.0001
Interaction of mean arterial pressure with duration of anesthesia, h	0.0002	0.0001	0.0003	< 0.0001
Demographic information and social history				
Age, yr	0.0001	0.0001	0.0002	0.2284
Female sex	–0.0182	–0.0219	–0.0144	< 0.0001
Race				
White	Reference			
Black	0.0096	0.0036	0.0156	0.0016
Asian or Pacific Islander	–0.0043	–0.0161	0.0075	0.4750
Body mass index, kg/m^2	0.0004	0.0001	0.0007	0.0049
ASA Physical Status				
I	Reference			
II	0.0021	–0.0114	0.0155	0.7636
III	–0.0172	–0.0307	–0.0036	0.0128
IV	–0.0453	–0.0603	–0.0302	< 0.0001
Previous history of alcohol abuse	0.0048	–0.0036	0.0131	0.2623
Previous history of drug abuse	0.0159	0.0078	0.0239	0.0001
Preoperative laboratories				
Sodium				
Hyponatremia	Reference			
Normal or hypernatremia	0.0043	–0.0019	0.0105	0.1720
Hemoglobin				
Severe anemia (< 8.0 g/dl)	–0.0217	–0.0318	–0.0115	< 0.0001
Mild anemia (8.0–13.5 g/dl)	–0.0068	–0.0108	–0.0029	0.0007
Normal or elevated (≥ 13.5 g/dl)	Reference			
eGFR				
Stage 1 (> 90 ml/min/1.73 * m^2)	Reference			
Stage 2 (60–89)	–0.0045	–0.0088	–0.0002	0.0396
Stage 3a (45–59)	–0.0112	–0.0184	–0.0040	0.0024
Stage 3b (30–44)	–0.0140	–0.0239	–0.0040	0.0060
Stage 4 (15–29)	–0.0171	–0.0290	–0.0052	0.0049
Stage 5 (< 15)	–0.0117	–0.0208	–0.0025	0.0123
Aspartate aminotransferase				
Normal (< 34 U/l)	Reference			
High (≥ 34 U/l)	–0.0025	–0.0067	0.0017	0.2513
International normalized ratio				
Low or normal (< 1.1)	Reference			
High (≥ 1.1)	–0.0067	–0.0109	–0.0026	0.0015
Surgical/procedural details				
Body region				
Abdomen	Reference			
Extremities	0.0677	0.0622	0.0731	< 0.0001
Genitourinary	0.0152	0.0097	0.0207	< 0.0001
Head and neck	–0.0137	–0.0201	–0.0073	< 0.0001
Radiologic	0.0214	0.0143	0.0285	< 0.0001
Spine	0.0295	0.0207	0.0384	< 0.0001
Thorax	0.0118	0.0049	0.0186	0.0007
Emergency surgery	–0.0231	–0.0294	–0.0168	< 0.0001
Anesthesia CPT units	–0.0072	–0.0079	–0.0066	< 0.0001
Year of surgery				
2014	Reference			
2015	–0.0054	–0.0128	0.0020	0.1529
2016	–0.0126	–0.0200	–0.0053	0.0008
2017	–0.0004	–0.0078	0.0071	0.9240
2018	–0.0194	–0.0270	–0.0118	< 0.0001
2019	–0.0300	–0.0376	–0.0224	< 0.0001
2020	–0.0210	–0.0291	–0.0129	< 0.0001
2021	–0.0161	–0.0241	–0.0080	0.0001
2022	–0.0069	–0.0153	0.0015	0.1086
2023	0.0464	0.0319	0.0609	< 0.0001

(*Continued*)

Table 2. (Continued)

	β	95% CI		*P* Value
Anesthetic management				
Duration of inhalational anesthetic, h	–0.0192	–0.0271	–0.0112	< 0.0001
Blood products (units transfused)	–0.0010	–0.0024	0.0004	0.1701
Induction dose of propofol, mcg/kg	0.0116	0.0091	0.0142	< 0.0001
Benzodiazepine dose, equivalents/kg/min	11.0565	–15.1097	37.2227	0.4076
Total intraoperative opioid, OME/kg/h	0.0950	0.0792	0.1109	< 0.0001
Ephedrine dose, mg	–0.0009	–0.0011	–0.0007	< 0.0001
α2-Agonist	0.0000	–0.0046	0.0047	0.971
Vasopressor infusion	–0.0691	–0.0734	–0.0648	< 0.0001

Akaike information criterion, –27,813.4 (null model, –20,258.3). Bayesian information criterion, –27,406.0 (null model, –20,241.7). Adjusted R^2 of the full model, 0.223. AKI, acute kidney injury; ASA, American Society of Anesthesiologists; CPT, Current Procedural Terminology; eGFR, estimated glomerular filtration rate; MAC, minimum alveolar concentration; OME, oral morphine equivalents.

https://links.lww.com/ALN/E58). Furthermore, when an interaction term between year of surgery and MAP was included in another *post hoc* sensitivity analysis, the impact of MAP on MAC ratio increased (β = 0.0037; 95% CI, 0.0030 to 0.0043; $P < 0.001$), and the interaction term was significant for most years (Supplemental Digital Content, table 9, https://links.lww.com/ALN/E58).

Genome-wide Association Study

Genotype was available on 14,326 patients in our cohort. Median genomic control λ values calculated across included variants (minor allele frequency 0.1% or greater and minor allele count greater than 20) were 0.930 and 0.936 for models 1 and 2, respectively (Supplemental Digital Content, figure 5, https://links.lww.com/ALN/E58).[35] No variants exceeded our threshold for genome-wide significance ($P < 5 \times 10^{-8}$); however, a total of eight variants—(1) rs133291820 (chr15:35990586:G:T), (2) rs149242519 (chr12:68964597:G:C), (3) rs75322273 (chr3:128412109:C:G), (4) rs145507201 (chr14:83193976:A:G), (5) rs79410601 (chr3:128367187:C:T), (6) rs6004287 (chr22:24805779:C:T), (7) rs542418051 (chr5:27637801:C:T), and (8) rs201683942 (chr1:232039266:T:C)—exceeded the suggestive ($P < 1 \times 10^{-6}$) threshold in at least one of our models (tables 3 and 4). Manhattan plots for the two models can be found in figure 3. The Manhattan plots were annotated with quasi-independent top hits by creating 1-Mb regions centered around variants with *P* values less than 1×10^{-6} and combining overlapping intervals (accounting for slight differences in annotated variants between fig. 3 and tables 3 and 4).

Discussion

We report the results of a single-center retrospective study characterizing the delivery of MAC ratio during routine clinical care. Although the therapeutic target of inhaled anesthetics is the nervous system, clinical practice appears to be driven primarily by the cardiovascular system and converges on a MAC ratio of 1.0, despite this being the EC_{50}. Conversely, factors that are known to influence MAC, such as previous history of alcohol abuse, benzodiazepine dose, and administration of an α2-agonist, do not appear to influence the delivery of MAC ratio. These results suggest a fundamental dissociation between (1) the neurobiology and pharmacology of general anesthesia, and (2) our routine monitoring and management strategies for inhaled anesthetics. A further dissociation found in this study is between the known increased anesthetic requirements in females and the delivery of lower MAC ratios compared to males. In terms of genetic factors, genome-wide association studies did not identify novel variants associated with anesthetic dosing at the level of genome-wide significance ($P < 5 \times 10^{-8}$), but eight variants located near six genes (*DPH6*, *CPM*, *EEFSEC*, *SGSM1*, *CDH9*, and *DISC1*) reached the suggestive threshold ($P < 1 \times 10^{-6}$; tables 3 and 4). Specifically, (1) *EEFSEC* appeared in both models, (2) *CPM* and *DPH6* appeared only in model 1 (the basic model), and (3) *SGSM1*, *CDH9*, and *DISC1* appeared only in model 2 (the full clinical model; tables 3 and 4).

Relationship between Hemodynamic Parameters and MAC Ratio

As expected, average MAP during the maintenance phase had a strong association with mean MAC ratio during the same time frame. For every 10 mmHg that MAP increases, the MAC ratio would be expected to increase by 0.03. This suggests that, after achieving a level considered sufficient for unconsciousness, inhaled anesthetic concentrations and MAC change as a function of blood pressure. A representative patient with an average MAP of 60 mmHg would be expected to have an age-adjusted MAC ratio of 0.91 (95% CI, 0.902 to 0.919), while the same patient with an average MAP of 90 mmHg would be expected to have a MAC ratio of 1.02 (95% CI, 1.015 to 1.030; Supplemental Digital Content, figure 3, https://links.lww.com/ALN/E58).

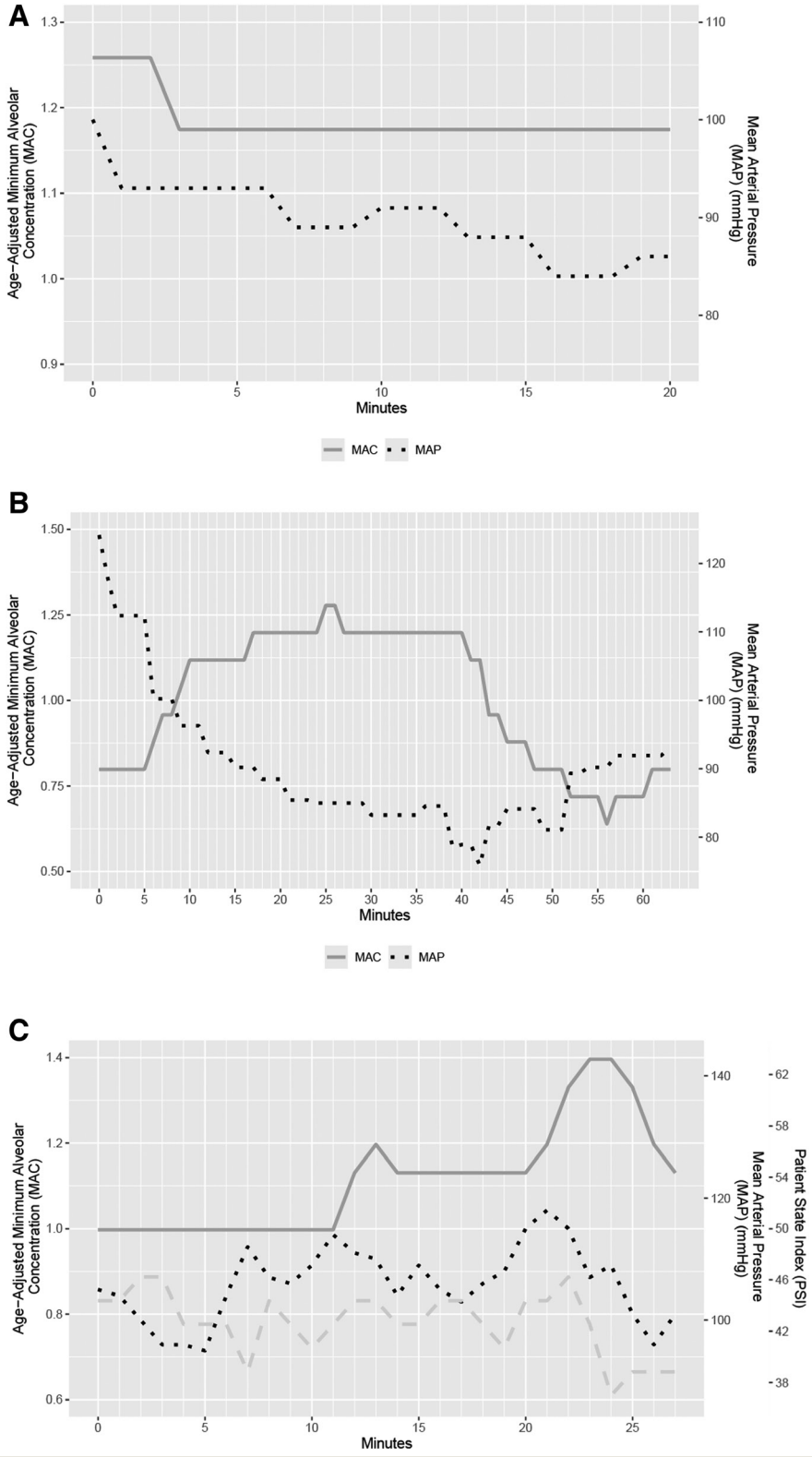


Fig. 2. Representative curves illustrating relationship between anesthetic titration and blood pressure within a single case. (*A*)Hemodynamic change in response to inhalational anesthetic. (*B*)Titration of inhalational anesthetic in response to blood pressure. (*C*) Titration in response to cardiovascular parameter (hypertension) despite neurologic metric indicating appropriate anesthetic depth. MAC, minimum alveolar concentration; MAP, mean arterial pressure.

Table 3. Genome Wide Association Study (GWAS) Results: $P \leq 1 \times 10^{-6}$, Minor Allele Frequency ≥ 1%. Model 1: GWAS Performed on Mean Age-adjusted MAC, Controlling for Age, Genotypic Sex, Intraoperative Mean Arterial Pressure, Body Mass Index (kg/m^2), Year of Surgery, Duration of Inhalational Anesthetic Exposure, Microarray Chip, and PC 1 to 10

Chr	Pos	Allele 1	Allele 2	Effect AF	SNP	Gene	OR	SE	*P* Value
15	35,990,586	G	T	0.3186	rs13329182	*DPH6*	1.07	0.0131	2.89×10^{-7}
12	68,964,597	G	C	0.0147	rs149242519	*CPM*	1.28	0.0491	4.42×10^{-7}
3	128,412,109	C	G	0.0215	rs75322273	*EEFSEC*	0.80	0.0436	6.06×10^{-7}
14	83,193,976	A	G	0.0163	rs145507201		1.27	0.0474	6.39×10^{-7}

AF, allelic frequency; SE, standard error; SNP, single nucleotide polymorphism; OR, odds ratio; PC, principal component.

Table 4. Genome Wide Association Study (GWAS) Results: $P \leq 1 \times 10^{-6}$, Minor Allele Frequency ≥ 1%. Model 2: GWAS Performed on Mean Age-adjusted MAC, Controlling for Age, Genotypic Sex, Intraoperative Mean Arterial Pressure, Body Mass Index (kg/m^2), Year of Surgery, Duration of Inhalational Anesthetic Exposure, Microarray Chip, ASA Physical Status, History of Alcohol Abuse, History of Drug Abuse, Body Region, Emergency Surgery, Anesthesia Base Units, Intraoperative Oral Morphine Equivalents (Normalized), Induction Dose of Propofol (mg), Intraoperative Ephedrine Dose, Vasopressor Requirement, and PC 1 to 10

Chr	Pos	Allele 1	Allele 2	Effect AF	SNP	Gene	OR	SE	*P* Value
3	128,367,187	C	T	0.0214	rs79410601	*EEFSEC*	0.81	0.0412	2.46×10^{-7}
14	183,193,976	A	G	0.0163	rs145507201		1.25	0.0445	3.52×10^{-7}
22	24,805,779	C	T	0.5235	rs6004287	*SGSM1*	0.95	0.0112	7.41×10^{-7}
5	27,637,801	C	T	0.0069	rs542418051	*CDH9*	1.40	0.0686	9.36×10^{-7}
1	232,039,266	T	C	0.0011	rs201683942	*DISC1*	2.36	0.1758	9.74×10^{-7}

AF, allelic frequency; SE, standard error; SNP, single nucleotide polymorphism; OR, odds ratio; PC, principal component.

Just as MAP was associated with MAC ratio when considering the cumulative distribution of these measures for each case ($\beta = 0.0028$; 95% CI, 0.0024 to 0.0032; $P < 0.0001$), the relationship persisted ($\beta = 0.0013$; 95% CI, 0.0012 to 0.0013; $P < 0.0001$) when the repeated-measures distribution of MAP and MAC ratio data was included in our GEE models. The first methodologic approach accounted for between-case variability, and the second considered both within-case and between-case variability. The fact that estimates of these two different methods of analysis show similar patterns of the association of MAP with MAC ratio suggests a robust finding. While this relationship is more complex, due to the drug titration paradox (described more fully later in the Discussion section), it supports our hypothesis that providers uptitrate MAC ratio in response to hypertension.

While anesthetic requirement can be reflected through hemodynamic parameters (*e.g.*, hypertension in a patient with inadequate depth of anesthesia), the appropriateness of titrating a neurologic endpoint (in this case, MAC ratio) based upon a cardiovascular parameter (in this case, MAP) suggests a gap in the foundations of clinical practice. We demonstrate this phenomenon with an illustrative example showing MAC ratio titration in response to a cardiovascular parameter (hypertension), despite the neurologic metric (Patient State Index, one metric for depth of anesthesia)[34] indicating an appropriate concentration of anesthetic (fig. 2C).

Differentiating between statistical and clinical significance is essential. If we assume that a change in MAC ratio of 0.1 is clinically meaningful, a MAP difference of 30 mmHg would be required to exert a clinically meaningful change. There are multiple reasons why this effect size might not initially seem clinically relevant. First, the phenotype captures the *average* MAC ratio during an entire case, while MAC ratio titration in response to hemodynamic extremes is likely a transient phenomenon, with regression to more normally distributed values over time. For example, in figure 2B, MAC ratio is briefly titrated to greater than 1.25 due to hypertension, but as the blood pressure falls, the MAC ratio is also downtitrated. Despite the relatively large change in MAC ratio in response to changes in MAP, the average MAC ratio for the illustrative window remained near 1. Building upon this, average MAC ratio has a very narrow range of values within our study. Specifically, the 95% CI for the overall study cohort was 1.0075 to 1.0036 (range, 0.0039). In practical terms, that means a 10-mmHg change in blood pressure (corresponding to 0.03 change in average MAC ratio) might shift MAC delivery outside the MAC range delivered for 95% of cases.

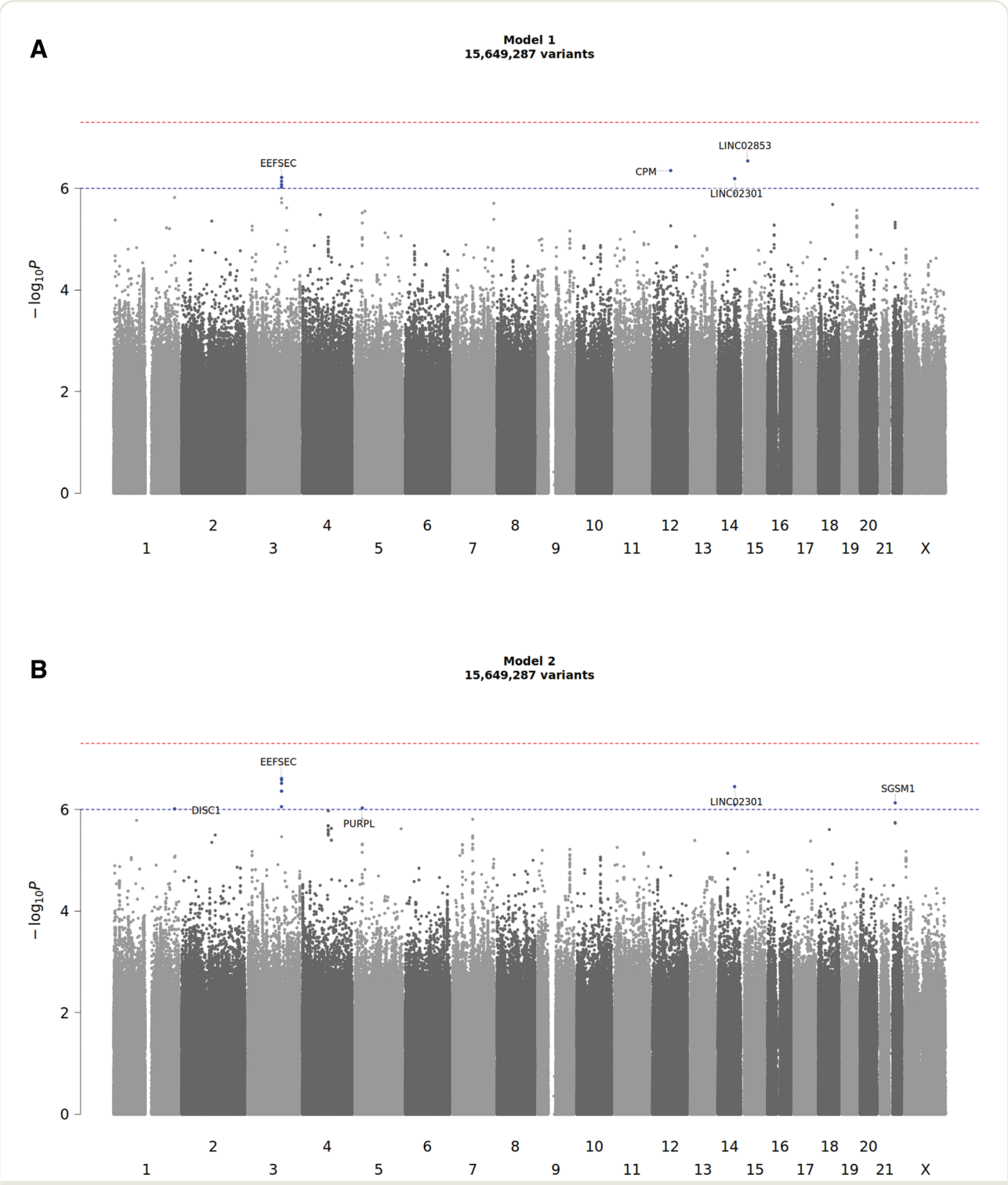


Fig. 3. Manhattan plots for genome-wide association study of minimum alveolar concentration delivered. (*A*) Model 1. (*B*) Model 2.

Potential Disparities in MAC Ratio

Sex-based Differences in Anesthetic Requirement. In recent publications, female patients have been found to have a higher anesthetic requirement than males (*i.e.*, increased resistance to the hypnotic effects of volatile anesthetics,[36] faster recovery,[37] and greater incidence of awareness under general anesthesia).[38] Our finding that females receive lower average MAC than male patients, even when controlling for a variety of patient, anesthetic, and surgical factors, raises a

potential disparity in care and warrants further investigation in multicenter studies.

Race-based Differences in Anesthetic Requirement. Our model shows that Black patients receive a statistically significant increased dose of inhaled anesthetic (β = 0.0096; 95% CI, 0.0036 to 0.0156; P = 0.0016) compared to White patients. Whether this is of clinical significance is unclear. One potential explanation is that the genetic variants dictating anesthetic requirements vary with ancestry.[39] Alternatively, race (as adjusted in our regressions) may be associated with other latent confounders that need to be identified and controlled in future models. A final explanation is that we have identified a racial disparity in anesthetic delivery that merits further investigation. As such, the finding should be viewed as hypothesis-generating. The limited ancestral diversity of the population genotyped in the Michigan Genomics Initiative precludes full study on ancestral differences in anesthetic requirement; however, future work can explore this and other exploring perioperative phenotypes in larger, more diverse data sources.[40]

Drug Titration Paradox

The relationship between anesthetic dosing and MAP, which we have attempted to characterize in this study, is an example of the "drug titration paradox," a phenomenon originally described in the relationship between propofol concentration and Bispectral Index (Medtronic, USA).[41] This paradox has also been demonstrated with the titration of end-tidal sevoflurane concentration.[42] Pharmacologic principles dictate that "more drug should produce more effect"; however, when a drug is titrated to a specified effect level, the typical dose-effect relationship is reversed (*i.e.*, "more drug produces less effect").[43] Schnider and Minto hypothesize the bulk of pharmacodynamic variation in anesthetic delivery can be explained by factors such as surgical stimulation, hemodynamics, sepsis, and genetic/epigenetic factors.[42,44] Studying medication effects by titration to a clinical endpoint (as opposed to using high-resolution pharmacokinetic-pharmacodynamic methodology) can lead to numerous incorrect apparent associations.[43] In our study, the pharmacodynamic effect (*i.e.*, volatile anesthetic causing hypotension) is not in question.[33] Instead, our study goal is to quantify this relationship, a necessary first step if other factors impacting anesthetic dosing are to be understood. As such, the problem is complex, and any true index of titration of relationship between MAP and anesthetic dosing can only be detected at the within-patient level, which we have attempted to do through GEEs presented in Supplemental Digital Content, table 6, (https://links.lww.com/ALN/E58).

Comparison to Expected Results

While hemodynamics are the most obvious metric guiding titration of anesthetic dosing (in paralyzed patients without processed EEG), our research raises the question of the appropriateness of titrating a neurologic metric in response to a cardiovascular parameter and quantifies/characterizes this practice so that it can be controlled for in future models. In addition to characterizing titration of MAC ratio in response to hemodynamics, we demonstrate a variety of factors that are known to influence the delivery of MAC ratio,[2] including (1) opioids, (2) α2-agonists, (3) ephedrine, (4) chronic alcohol abuse, and (5) anemia. Despite a theoretical association with anesthetic requirement, the extent to which providers incorporate these factors into their clinical practice had not previously been quantified. Our study demonstrated that intraoperative use of ephedrine and preoperative anemia were associated with lower anesthetic delivery. Intraoperative opioid dose (oral morphine equivalents per kilogram per hour) was associated with higher MAC ratio (0.095; 95% CI, 0.079 to 0.111; P < 0.0001), despite numerous studies showing reduction in MAC with use of opioid analgesics.[45] Healthier patients may receive a larger dose of opioid and also require a higher MAC ratio (despite the fact that the administration of those opioids decreases MAC). Also, somewhat surprisingly, the dose of benzodiazepines was not found to be associated with the average MAC ratio (11.188; 95% CI, –14.984 to 37.361; P = 0.402). While chronic alcohol and drug use (specifically, cocaine) should both increase MAC ratio based on knowledge of MAC determinants,[2] our data showed that history of drug use (β = 0.016; 95% CI, 0.008 to 0.024; P < 0.0001) but *not* history of alcohol abuse (β = 0.005; 95% CI, –0.004 to 0.013; P = 0.2623) was associated with increased MAC ratio in clinical practice.

A variety of other covariates (*e.g.*, obesity)[46] are not thought to modulate anesthetic requirement, but were shown to be significantly associated with the average MAC ratio. Other surgical and anesthetic factors that were found to be significant in our study (*e.g.*, duration of inhalational anesthetic and emergency surgery) have not been previously characterized and should be viewed as hypothesis-generating.

Intraoperative Processed EEG

Cases employing intraoperative processed EEG were associated with decreased volatile anesthetic exposure (and higher MAP) when compared to those without EEG (Supplemental Digital Content, table 7, https://links.lww.com/ALN/E58). Furthermore, the relationship between age-adjusted MAC ratio and Patient State Index, a metric used to assess depth of anesthesia,[34] is complex (Supplemental Digital Content, figure 4, https://links.lww.com/ALN/E58). Considerable variability in age-adjusted MAC ratio exists within the range of patient state indices consistent with optimal hypnotic state for general anesthesia.[47] For example, the patient with lowest average Patient State Index in our cohort had the second lowest MAC ratio (0.650 to 21.211), whereas another patient

was outside the optimal hypnotic range (25 to 50) despite a MAC ratio greater than 1.0 (1.100 to 52.245). This characterization, albeit highly limited, cautions against trying to use age-adjusted MAC ratio as a proxy for anesthetic depth. A more sophisticated phenotype for anesthetic requirement might titrate processed EEG measurement to a narrow band (or alternatively, a consistent electroencephalographic waveform pattern) and then quantify the anesthetic dosage delivered to maintain that level.

Furthermore, both sensitivity analyses confirm changes in practice and suggest an altered relationship between MAP and MAC ratio through the course of the study window. Notably, the MAC ratio was no longer associated with MAP when restricted to cases after the introduction of processed EEG (Supplemental Digital Content, table 8, https://links.lww.com/ALN/E58). Because of the limited sample size and *post hoc* nature of this analysis, we caution that this finding should be viewed as hypothesis-generating. Specifically, we hypothesize that the dependence of MAC ratio on MAP changed over the time course of the study and that the use of SedLine decreases (or even eliminates) this dependence. Further studies are necessary to better characterize how processed EEG impacts titration of inhalational anesthetic.

Results of Genome-wide Association Study

A recently published study identified two genetic variants associated with propofol requirement at the level of genome-wide significance ($P < 5 \times 10^{-8}$).[5] Our study assessed genetic associations with a related phenotype, inhaled anesthetic delivery. Although our results suggested several variants (and associated genes) that may be associated with inhaled anesthetic requirement, no variants reached the level of genome-wide significance. This likely results from different genetic mechanisms for metabolism and sensitivity to inhaled anesthetics compared to propofol. Additionally, our genome-wide association study used a phenotype for inhaled anesthetic *delivered*, which does not necessarily reflect inhaled anesthetic *required*. Alternatively, our study could have been underpowered to detect novel associations. While numerous loci reached the "suggestive" threshold ($P < 1 \times 10^{-6}$), these should not be viewed as significant novel associations, as adoption of less stringent thresholds leads to increased rate of false discovery.[25] Instead, we report these findings to accumulate and aggregate information on anesthetic requirements, allowing the scientific community to replicate (or fail to replicate) them in future studies and meta-analyses. The Scalable and Accurate Implementation of GEneralized mixed model (SAIGE) methodology selected for our genome-wide association studies enables us to control for a large number of clinical covariates, in addition to case–control imbalance and sample relatedness.[22] We present basic and full clinical models, a similar approach to previous genome-wide association studies.[18,19,23,48] Because our sample size is sufficiently large and we excluded rare variants (minor allele frequency less than 1%), we would expect the model containing the more complete list of clinical variables to be more accurate, but there is always the potential for statistical variation or error. Increased consistency in the variants suggested between the two models presented would increase our confidence in model validity.

Of particular interest for future research is the variant *rs201683942*, which was located on chromosome 1 near the gene *DISC1*. *DISC1* is a protein-coding gene involved in neurite outgrowth and cortical development.[49] Notably, mutations in *DISC1* have been shown to impact resting-state brain activations under general anesthesia with isoflurane[50] and have been linked to abnormal sleep/wake patterns[51] in mouse models. Additionally, the genes *CPM*, *EEFSEC*, and *SGSM1* have been implicated in a variety of neurologic processes and conditions, including (1) neurodegeneration (*EEFSEC*),[52] (2) neuronal function (*SGSM1*),[53] and (3) myelination within the central and peripheral nervous system (*CPM*).[54] As our study demonstrated titration of MAC ratio in response to hemodynamics, the suggested association of genes known to play a role in higher-order neurologic processes (and not cardiovascular or autonomic functions) is surprising and should be viewed as hypothesis-generating.

Study Strengths and Limitations

A strength of our study was the use of a validated data collection method (covariates, exposure variables, and outcome). This enabled a diverse collection of perioperative variables to be automatically queried and adjusted for in our regression models. We also assessed genetic associations between a large number (15,649,287) of genetic polymorphisms across a large number of patients and surgical procedures (14,326).[19]

The study was designed to assess practice within a very homogenous cohort (volatile anesthetic, more than 60 min, muscle relaxation), minimizing confounds due to other procedures and anesthetic regimens (*e.g.*, combined inhaled and intravenous anesthetic). The large number of general anesthetics performed during the study window (194,650 cases initially screened) allowed us to be selective, excluding a large number of patients at each step (fig. 1), while still ensuring high statistical power of the final cohort (30,125 cases). Our decision to perform complete case analysis despite some data being missing in a nonrandom way (*i.e.*, healthier patients and smaller procedures are less likely to obtain preoperative studies) could potentially introduce bias into our analysis.[55] After comparing the distribution of all covariates between the whole cases and the complete cases (based on their standardized differences), we found that the complete cases are representative in our study; thus, the decision was made to perform complete case analyses.

In terms of limitations, the retrospective nature of the study precludes causal inference, which potentially limits the impact of our findings on clinical practice. Discharge coding errors or misclassification may have also contributed

to the observed change in outcome.[56] Furthermore, there are limitations associated with use of the Elixhauser Comorbidity Index.[22] Diagnoses based on International Classification of Diseases, Ninth and Tenth Revisions, are often nonspecific and reflect conditions with markedly different severity and definitions.[15] Additionally, characterizing the relationship between MAC and MAP is complicated by the fact that a change in MAC potentially leads to a change in MAP (due to impact on β-adrenergic activity and the resulting vasodilatory effect of inhaled anesthetic),[33] *and* a change in MAP can potentially lead to a change in MAC (due to the anesthesia clinician titrating the inhaled anesthetic due to perceived under- or overdosing). GEE models account for within-subject correlations while accounting for "between-subject" variations by specifying a "working correlation structure" that describes how observations within a subject are correlated.[57,58] Finally, the imperfect study outcome/endpoint intrinsically limits the conclusions that can be drawn from the genetic analysis. Specifically, if MAC (in the absence of direct neurobiological markers like EEG) is being titrated to cardiovascular, as opposed to neurologic, parameters, it raises the question of whether our genetic study actually reveals genes impacted by the cardiovascular, instead of neurologic, effects of volatile anesthetics.

Conclusions

Despite the limitations, the data support the hypothesis that the clinical delivery of MAC ratio, which is intended as a dosing framework for the central nervous system effects of anesthetics, is most closely associated with the cardiovascular factor MAP in clinical practice. Some factors known to affect MAC did not appear to influence MAC ratio; conversely, factors influencing MAC ratio are not known to influence MAC. Furthermore, we identified demographic/social, laboratory, surgical/procedural, and anesthetic covariates that need to be accounted for when modeling anesthetic dosage. Notably, female patients received lower mean MAC ratios, despite evidence that they have a higher anesthetic requirements.[36] While genome-wide association studies failed to identify novel variants at the level of genome-wide significance ($P < 5 \times 10^{-8}$), eight variants located near six genes (*DPH6*, *CPM*, *EEFSEC*, *SGSM1*, *CDH9*, and *DISC1*)—several with neurobiological relevance—reached the suggestive threshold ($P < 1 \times 10^{-6}$).

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Competing Interests

Dr. Colquhoun reports receiving an honorarium from Medscape, Inc., (New York, New York) and previous research support paid to the University of Michigan from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Rahway, New Jersey), Chiesi, USA (Cary, North Carolina), and GE Healthcare (Chicago, Illinois) unrelated to the current work. Dr. Kumar received funding from Edwards Lifesciences (Irvine, California), Haisco Pharmaceuticals (Bridgewater, New Jersey), and HemoSonics, LLC (Durham, North Carolina). The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental Information, https://links.lww.com/ALN/E58

Figure 1. Directed Acyclic Graph Showing the Hypothesized Causal Pathways.

Figure 2. A. Histogram of MAC. B. Histogram of MAP.

Figure 3. Predicted Minimum Alveolar Concentration Curve for Representative Patient at Different Mean Arterial Pressures.

Figure 4. Scatterplot Depicting the Relationship between Average Patient State Index (over the Maintenance Phase of Anesthesia) and Age-adjusted MAC Ratio.
Figure 5. Quantile–Quantile (Q-Q) Plots. A. Model 1. B. Model 2.
Table 1. Missing Data Table.
Table 2. Temporal Changes in Practice Patterns Surrounding the Use of Inhalational Anesthetic.
Table 3. Distributions for MAC and MAP in the Study Population. A. Minimum Alveolar Concentration. B. MAP.
Table 4. Multivariable Linear Regression of Factors Associated with End-tidal Volatile Anesthetic Concentration (Expressed as Age-adjusted Minimum Alveolar Concentration)—Sensitivity Analyses of Cases Utilizing (1) Isoflurane Only and (2) Sevoflurane Only
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Table 9. Multivariable Linear Regression of Factors Associated with End-tidal Volatile Anesthetic Concentration (Expressed as Age-adjusted Minimum Alveolar Concentration) with Interaction Term between Year of Surgery and MAP (n = 30,125)—*Post Hoc* Sensitivity Analysis

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Appendix. Data Extrapolation and Algorithm for Matching the MAC Ratio and MAP Time Matrices

MAC values were typically captured (and extracted) on a 1-minute basis (during the period of inhalational anesthetic). Invasive blood pressure measurements (*i.e.*, arterial monitor) were captured on a 1-minute basis. Noninvasive blood pressure measurements (*i.e.*, oscillometric sphygmomanometer) were obtained during the same time window at the discretion of the clinical provider and subject to the expected physiologic and technologic limitations (for example, cuff disconnect with position, failed readings due to body habitus, *etc.*). At our institution, noninvasive blood pressure is typically recorded 3-minute basis. To account for the resulting differences in the "time matrix" between the MAP and MAC measurements, we assumed a linear change between two known conditions (up to the established 5-min time "gap"), and resulting minute-by-minute values were extrapolated in increments with no value recorded (see examples below). When no bound values are known (for example, start or end of case), the nearest value was propagated, up to the 5-min "gap."

An illustrative example of this methodology follows:

Minute	Recorded MAC	MAC in Study	Recorded MAP	MAP in Study
0	0.7	0.7	NA	88
1	0.6	0.6	NA	88
2	0.6	0.6	88	88
3	0.6	0.6	NA	88.33
4	0.6	0.6	NA	88.66
5	0.7	0.7	89	89
6	0.7	0.7	NA	88
7	0.7	0.7	NA	87
8	0.7	0.7	86	86
9	0.7	0.7	NA	86
10	0.7	0.7	NA	86

NA, not applicable

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Associations of Intraoperative Hypotension and Perioperative Blood Pressure with Delirium after Noncardiac Surgery: A Retrospective Cohort Analysis

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ABSTRACT

Background: Postoperative delirium is a common and serious complication after noncardiac surgery. A possible precipitating factor may be perioperative hemodynamic changes, with subsequent changes in brain perfusion. This study aims to investigate whether intraoperative hypotension, perioperative average blood pressure, or blood pressure variability are associated with postoperative delirium.

Methods: The authors conducted a retrospective cohort study analyzing adult noncardiac surgery patients from a single academic center between 2018 and 2022. The primary exposure was intraoperative hypotension, defined as area under the curve of intraoperative mean arterial pressure (MAP) less than 65 mmHg. Secondary exposures were intraoperative and postoperative time-weighted average of MAP. The outcome was the incidence of postoperative delirium, assessed twice daily using the brief Confusion Assessment Method and Confusion Assessment Method for Intensive Care Unit.

Results: The authors included 38,940 noncardiac surgeries. The incidence of postoperative delirium was 6.56%. In the primary analysis, the authors found no significant association between the intraoperative area under the curve of MAP less than 65 mmHg and postoperative delirium (odds ratio [OR], 1.000; 95% CI, 0.999 to 1.000; $P = 0.17$). In the secondary analyses, association with intraoperative time-weighted average MAP was linear, where increasing MAP was associated with lower delirium risk (OR, 0.993; 95% CI, 0.990 to 0.996; $P < 0.001$). Postoperatively, the authors identified one change point for time-weighted average MAP at 88 mmHg—where increasing increments of MAP were associated with lower risk of delirium when MAP was less than 88 mmHg (OR, 0.995; 95% CI, 0.992 to 0.998; $P < 0.001$), but higher risk of delirium when MAP was 88 mmHg or greater (OR, 1.022; 95% CI, 1.019 to 1.027; $P < 0.001$).

Conclusions: Intraoperative hypotension and intraoperative average blood pressure were not associated with postoperative delirium. Postoperative higher average blood pressures demonstrated a statistically significant association with delirium; however, this finding lacks clinical relevance.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative delirium after noncardiac surgery is a common and debilitating complication.
- Existing observational and prospective interventional research provides conflicting evidence on the causal relationship between intraoperative hypotension and delirium. Postoperative hypotension is poorly studied.

What This Article Tells Us That Is New

- A single-center cohort study of 38,940 noncardiac surgeries among adult patients observed a postoperative delirium after 2,556 surgeries, for an incidence of 6.56%.
- Intraoperative hypotension, defined as area under the curve of a mean arterial pressure below 65 mmHg, was not associated with postoperative delirium (odds ratio, 1.000; 95% CI, 0.999 to 1.000).

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Abbreviations: **AUC**, area under the curve; **bCAM**, brief Confusion Assessment Method; **CAM**, Confusion Assessment Method; **CAM-ICU**, Confusion Assessment Method for Intensive Care Unit; **ICU**, intensive care unit; **IQR**, interquartile range; **MAP**, mean arterial pressure; **OR**, odds ratio; **TWA**, time-weighted average

Postoperative delirium is a prevalent and serious complication after noncardiac surgery, particularly among older adults.[1,2] Characterized by acute and fluctuating disturbances in attention, cognition, and consciousness, postoperative delirium is associated with increased morbidity, extended hospital stays, and higher healthcare costs.[1,3,4] Despite its incidence and impact on patient experience and outcomes, the pathophysiology of postoperative delirium remains poorly understood, and treatment is challenging, making prevention the preferable approach.[5] Thus, identifying risk factors—especially modifiable ones—is crucial for its prevention and management.[6]

One area of growing interest is the role of blood pressure dynamics in the development of postoperative delirium. During the intraoperative and postoperative periods, blood pressure can fluctuate significantly, with hypotension particularly common.[7] Hypotension may lead to hypoperfusion and subsequent organ damage, to which especially the heart and kidneys but also the brain may be susceptible.[8] Previous studies have shown an association between intraoperative hypotension and mortality, as well as acute kidney injury and myocardial injury.[9,10] Presumably, hypotension could also lead to brain hypoperfusion and delirium.[11] There are, however, equivocal data on perioperative hypotension and development of delirium.[12–16] Wachtendorf *et al.* retrospectively identified a mean arterial pressure (MAP) of less than 55 mmHg to be associated with a duration-dependent increase in odds of postoperative delirium.[15] However, more recently, Zarour *et al.* found that a more common definition of intraoperative hypotension—area under a MAP threshold of 65 mmHg—was not associated with postoperative delirium in elderly patients having elective noncardiac surgery.[17] These findings still need to be confirmed in other cohorts.

In addition to hypotension, rapid blood pressure changes may especially interfere with cerebral autoregulation and lead to changes in brain perfusion.[18] One study found that increased blood pressure variability—defined as greater fluctuations in blood pressure during surgery—rather than absolute or relative hypotension was predictive of postoperative delirium.[19]

This study aims to investigate whether intraoperative hypotension, perioperative average blood pressure, or blood pressure variability are associated with the development of postoperative delirium. Specifically, we tested the primary hypothesis that in patients having noncardiac surgery, postoperative delirium is more common if patients are exposed to longer and more severe episodes of intraoperative hypotension—which we defined as area under the curve (AUC) of MAP less than 65 mmHg. We further tested the secondary hypothesis, that postoperative delirium is associated with decreasing intraoperative and postoperative average MAP, and the exploratory hypothesis that postoperative delirium is associated with increased intraoperative and postoperative blood pressure variability.

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Materials and Methods

We conducted a retrospective cohort analysis to assess the association between intraoperative hypotension and postoperative delirium among adults who had noncardiac surgery at the Cleveland Clinic from 2018 to 2022. A data analysis and statistical plan was written and filed with an institutional review board. Approval was obtained before data were accessed (institutional review board No. 22-882; approval date, June 26, 2023); thereafter, the only changes to the analysis were due to independent request during the review process.

Patients 18 yr or older having noncardiac surgery, with at least 48 h postoperative hospitalization, and having blood pressure recorded in preanesthesia care evaluation clinic or other preoperative appointments within 6 months before surgery were included in the study. Patients who had preexisting dementia or cognitive impairment, neurologic surgery, fewer than 1 delirium assessment per day, inadequate blood pressure measurements on the regular ward (reading gaps longer than 8 h while in regular nursing floor or fewer than four measurements per day), or missing baseline variables were excluded from the analysis.

Exposure

Invasive blood pressure was recorded at 1-min intervals intraoperatively, and noninvasive blood pressure were recorded at 1- to 5-min intervals. Postoperative blood pressures were recorded at 15-min intervals in the postanesthesia care unit and 4-h intervals on surgical wards. All the postoperative MAP measurements before first positive delirium assessment on the ward (or postoperative day 4, which came first) were used.

The primary exposure was intraoperative hypotension. We defined hypotension as AUC of MAP less than 65 mmHg. The intraoperative period was defined as the interval between anesthetic induction and emergence.

The secondary exposure was the time-weighted average (TWA) of intraoperative and postoperative MAP (TWA-MAP).

As an exploratory exposure, we analyzed intraoperative and postoperative blood pressure fluctuations

through both average real variability of MAP, and variability independent of mean of MAP. Average real variability of MAP is an index representing short-term, reading-to-reading, within-subject variability in blood pressure.[20] Variability independent of mean of MAP also represents within-subject blood pressure variability, however independent of mean blood pressure levels.[21] We report further details about average real variability and variability independent of mean in the Supplemental Digital Content Methods (https://links.lww.com/ALN/E13).

We removed artifacts of intraoperative and postoperative blood pressures using the following rules, in order: (1) blood pressures documented as artifacts; (2) pressures out of range defined by (a) systolic blood pressure greater than or equal to 300 or systolic blood pressure less than or equal to 20 mmHg, (b) systolic blood pressure less than or equal to diastolic blood pressure plus 5 mmHg, or (c) diastolic blood pressure less than or equal to 5 mmHg or diastolic blood pressure greater than or equal to 225 mmHg; (3) abrupt changes defined by systolic blood pressure change greater than or equal to 80 mmHg within 1 min in either direction or abrupt systolic blood pressure changes greater than or equal to 40 mmHg within 2 min in both directions.

Outcome

Our primary outcome was presence of postoperative delirium as defined by versions of the Confusion Assessment Method (CAM). Delirium is most formally diagnosed using criteria described in the *Diagnostic and Statistical Manual of Mental Disorders*. However, various alternative instruments have been developed and validated to facilitate the diagnosis of delirium. CAM is the most frequently used delirium detection tool. It is a validated method for clinicians without psychiatric training to identify and recognize delirium quickly and accurately.[22] The CAM includes four features from the *Diagnostic and Statistical Manual of Mental Disorders* diagnostic criteria found to have the greatest ability to distinguish delirium from other types of cognitive impairment. There is also a CAM for Intensive Care Unit (CAM-ICU) version for use with nonverbal mechanically ventilated patients.

Both the CAM and the CAM-ICU have demonstrated sensitivity of 94 to 100%, specificity of 90 to 95%, and high interrater reliability.[23] There is also a brief version of the CAM, the brief CAM (bCAM), which facilitates rating of the four core CAM features with a sensitivity of 80 to 84% and specificity of 87 to 95%.[24,25] Per local routine at the study center, bCAM is assessed on admission and then twice daily by nurses for patients in regular wards, and CAM-ICU is assessed in ICUs on admission, then every 4 h, or with changes in patient condition. We retrieved delirium assessments from end of surgery until postoperative day 4 or discharge, whichever came first.

Statistical Analysis

Potential confounding variables for which we adjusted in all analyses are listed in table 1. Individual variables were censored and no longer considered for adjustment if they occurred after a positive delirium assessment. Demographic and intraoperative characteristics were described using mean ± SD or median [interquartile range (IQR)] for continuous variables and frequency and percentage for categorical variables, and compared by postoperative delirium using two-sample *t* test or Wilcoxon rank-sum test based on the distribution for continuous variables and Pearson's chi-square test for categorical variables.

In the primary analysis, the exposure was the AUC of MAP less than 65 mmHg. Association of AUC of MAP less than 65 mmHg with postoperative delirium was assessed through multivariable generalized mixed-effects logistic regression model accounting for within-patient correlation among repeated surgeries from the same patient. We first tested the nonlinear relationship between exposure and postoperative delirium by adding a restricted cubic spline with 3 knots at the 10th, 50th, and 90th percentile of the exposure to the above model. If a nonlinear relationship was observed and tested statistically significant, segmented regression approach was used to estimate the change point of the intraoperative AUC of MAP less than 65 mmHg in its association with postoperative delirium. Specifically, change point was estimated using segmented logistic regression model by treating all surgeries as independent. The 2.5th and 97.5th percentiles of the distribution of the change points from the bootstrapping 1,000 resamples were used to estimate the 95% CI of the change point. We performed sensitivity analyses with the intraoperative AUC of MAP less than 65 mmHg categorized by quartiles, as well as a subgroup analysis of age greater than 65 yr. When defining quartiles at the 25th, 50th, and 75th percentiles of the AUC of MAP, we assigned all zero values to the first quartile, and then split the remaining values by the 50th and 75th percentiles.

In the secondary and exploratory analyses, association between each exposure and postoperative delirium was assessed through the same approach as the primary analysis using multivariable generalized mixed-effects logistic regression model, adjusting for with-patient correlation among repeated surgeries from the same patient. Nonlinear relationship was tested and change point analysis was performed on each exposure.

Full models for all analyses are shown in Supplemental Digital Content tables 1 to 6 (https://links.lww.com/ALN/E13). All analyses were performed based on a significance level of 0.05. SAS software (version 9.4, USA) and R statistical software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) were used.

Sample Size Consideration

We used all the noncardiac surgeries eligible for the study period. Given the large sample size of 38,940 noncardiac

Table 1. Patient Characteristics and Surgical Information by Postoperative Delirium

Factor	Overall (N = 38,940)	No Delirium (N = 36,384)	Delirium (N = 2,556)	*P* Value
Age, yr	60.2 ± 15.2	59.8 ± 15.2	65.0 ± 13.8	*< 0.001**
Race				*0.049*†
Caucasian	31,965 (82.1)	29,911 (82.2)	2,054 (80.4)	
African American	5,603 (14.4)	5,194 (14.3)	409 (16.0)	
Other	1,372 (3.5)	1,279 (3.5)	93 (3.6)	
Sex, female	20,234 (52.0)	19,023 (52.3)	1,211 (47.4)	*< 0.001*†
Body mass index, kg/m^2	29.6 ± 7.6	29.6 ± 7.6	29.5 ± 7.9	0.44*
ASA Physical Status				*< 0.001*‡
I to II	4,725 (12.1)	4,662 (12.8)	63 (2.5)	
III	25,854 (66.4)	24,511 (67.4)	1,343 (52.5)	
IV	8,361 (21.5)	7,211 (19.8)	1,150 (45.0)	
Baseline MAP, mmHg	91.2 ± 12.3	91.3 ± 12.2	89.2 ± 13.4	*< 0.001**
Charlson Comorbidity Index	2.0 [0.00, 4.0]	2.0 [0.00, 4.0]	3.0 [2.0, 6.0]	*< 0.001*‡
Preoperative use of benzodiazepines	5,926 (15.2)	5,384 (14.8)	542 (21.2)	*< 0.001*†
Preoperative use of antipsychotics	5,677 (14.6)	5,059 (13.9)	618 (24.2)	*< 0.001*†
Preoperative use of midazolam	18 (0.05)	17 (0.05)	1 (0.04)	0.99§
Diabetes w/o chronic complications	10,018 (25.7)	9,060 (24.9)	958 (37.5)	*< 0.001*†
Hypertension uncomplicated	23,781 (61.1)	21,841 (60.0)	1,940 (75.9)	*< 0.001*†
Peripheral vascular disease	3,175 (8.2)	2,820 (7.8)	355 (13.9)	*< 0.001*†
Depression	6,699 (17.2)	6,072 (16.7)	627 (24.5)	*< 0.001*†
Patent foramen ovale	198 (0.51)	171 (0.47)	27 (1.06)	*< 0.001*†
Schizoaffective disorder	216 (0.55)	181 (0.50)	35 (1.4)	*< 0.001*†
Ischemic stroke or transient ischemic attack	353 (0.91)	238 (0.65)	115 (4.5)	*< 0.001*†
Vision impairment	524 (1.3)	435 (1.2)	89 (3.5)	*< 0.001*†
Smoking history	21,074 (54.1)	19,536 (53.7)	1,538 (60.2)	*< 0.001*†
Drug abuse	845 (2.2)	767 (2.1)	78 (3.1)	*0.002*†
Alcohol abuse	704 (1.8)	591 (1.6)	113 (4.4)	*< 0.001*†
Type of surgery				*< 0.001*†
Operations on the nervous system	1,858 (4.8)	1,706 (4.7)	152 (5.9)	
Operations on the nose, mouth, and pharynx	349 (0.90)	311 (0.85)	38 (1.5)	
Operations on the respiratory system	2,789 (7.2)	2,622 (7.2)	167 (6.5)	
Operations on the cardiovascular system	2,414 (6.2)	2,227 (6.1)	187 (7.3)	
Operations on the hemic and lymphatic system	357 (0.92)	336 (0.92)	21 (0.82)	
Operations on the digestive system	14,223 (36.5)	13,444 (37.0)	779 (30.5)	
Operations on the urinary system	3,181 (8.2)	3,065 (8.4)	116 (4.5)	
Operations on the male genital organs	696 (1.8)	679 (1.9)	17 (0.67)	
Operations on the female genital organs	1,149 (3.0)	1,112 (3.1)	37 (1.4)	
Operations on the musculoskeletal system	8,238 (21.2)	7,677 (21.1)	561 (21.9)	
Operations on the integumentary system	2,473 (6.4)	2,288 (6.3)	185 (7.2)	
Operations on other system	1,213 (3.1)	917 (2.5)	296 (11.6)	
Emergency surgery	1,656 (4.3)	1,336 (3.7)	320 (12.5)	*< 0.001*†
Year of surgery				0.27‡
2018	10,022 (25.7)	9,363 (25.7)	659 (25.8)	
2019	9,920 (25.5)	9,295 (25.5)	625 (24.5)	
2020	8,476 (21.8)	7,929 (21.8)	547 (21.4)	
2021	9,246 (23.7)	8,618 (23.7)	628 (24.6)	
2022	1,276 (3.3)	1,179 (3.2)	97 (3.8)	
Duration of surgery, h	3.9 [2.6, 5.7]	3.9 [2.6, 5.6]	4.6 [2.7, 8.0]	*< 0.001*‡
Anesthesia type				*< 0.001*†
General	31,106 (79.9)	28,875 (79.4)	2,231 (87.3)	
Regional	2,319 (6.0)	2,218 (6.1)	101 (4.0)	
Combined regional and general	5,515 (14.2)	5,291 (14.5)	224 (8.8)	
Intraoperative RBC transfusion amount, cc	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 350.0]	*< 0.001*‡
Estimated blood loss, cc	75.0 [10.0, 250.0]	75.0 [10.0, 200.0]	150.0 [10.0, 500.0]	*< 0.001*‡
Intraoperative phenylephrine dose, mg	0.40 [0.00, 2.5]	0.35 [0.00, 2.3]	0.90 [0.10, 5.4]	*< 0.001*‡
Intraoperative use of epinephrine	1,479 (3.8)	1,124 (3.1)	355 (13.9)	*< 0.001*†
Intraoperative ephedrine dose, mg	0.00 [0.00, 10.0]	0.00 [0.00, 10.0]	0.00 [0.00, 10.0]	0.54‡
Intraoperative use of norepinephrine	2,567 (6.6)	1,962 (5.4)	605 (23.7)	*< 0.001*†
Intraoperative use of vasopressin	804 (2.1)	510 (1.4)	294 (11.5)	*< 0.001*†
Intraoperative opioid dose, IV morphine equivalent in mg	20.0 [10.0, 29.0]	20.0 [10.0, 29.0]	20.0 [10.0, 31.7]	0.45‡
Postoperative use of benzodiazepines	9,238 (23.7)	8,926 (24.5)	312 (12.2)	*< 0.001*†
Postoperative use of antipsychotics	8,065 (20.7)	7,682 (21.1)	383 (15.0)	*< 0.001*†
Postoperative use of propofol	3,957 (10.2)	3,080 (8.5)	877 (34.3)	*< 0.001*†

(*Continued*)

Table 1. (Continued)

Factor	Overall (N = 38,940)	No Delirium (N = 36,384)	Delirium (N = 2,556)	*P* Value
Postoperative use of dexmedetomidine	702 (1.8)	551 (1.5)	151 (5.9)	*< 0.001*†
Postoperative opioid dose, IV morphine equivalent in mg	12.0 [0.00, 51.0]	14.0 [0.00, 54.0]	5.0 [0.00, 25.0]	*< 0.001*‡
Preoperative hemoglobin, g/l	12.8 ± 2.0	12.8 ± 2.0	12.2 ± 2.2	*< 0.001**
Postoperative lowest hemoglobin, g/l	9.7 ± 2.0	9.7 ± 2.0	8.4 ± 1.8	*< 0.001**
Postoperative highest creatinine, mg/dl	0.96 [0.76, 1.3]	0.95 [0.76, 1.3]	1.1 [0.82, 1.8]	*< 0.001*‡
Postoperative average pain, NRS	4.0 ± 1.9	4.1 ± 1.9	3.4 ± 2.0	*< 0.001**
ICU admission	7,589 (19.5)	5,775 (15.9)	1,814 (71.0)	*< 0.001*†

Statistics presented as mean ± SD, median [25th percentile, 75th percentile], or N (column %). Values with $P < 0.05$ are italicized to signify statistical significance.
P values: *Satterthwaite *t* test, †Pearson's chi-square test, ‡Wilcoxon rank-sum test, §Fisher's exact test.
ASA, American Society of Anesthesiologists; IV, intravenous; MAP, mean arterial blood pressure; NRS, numeric rating scale; RBC, red blood cells; w/o, without.

surgeries, a small odds ratio of 1.0004 would achieve greater than 90% power based on the 6% incidence of postoperative delirium and a 0.05 significance level.

Results

Data analysis included a total of 38,940 noncardiac surgeries from 32,007 patients between 2018 and 2022, with an overall incidence of postoperative delirium of 6.56% (Supplemental Digital Content fig. 1, https://links.lww.com/ALN/E13). The median of the number of CAM tests was 9 [IQR, 7 to 11] per surgery. Patient characteristics and surgical information are summarized in table 1.

Primary Analysis

The median of intraoperative AUC of MAP less than 65 mmHg was 20 mmHg · min [IQR, 0 to 80]. The association between AUC of MAP less than 65 mmHg and postoperative delirium was linear ($P = 0.63$ for the nonlinear term) and not statistically significant (odds ratio [OR], 1.000; 95% CI, 0.999 to 1.000; $P = 0.17$). The sensitivity analysis showed that the AUC of MAP quartiles was not associated with postoperative delirium ($P = 0.53$). A subgroup analysis repeated the same models in older patients with age 65 yr or older, where the relationship remained nonsignificant between intraoperative AUC of MAP less than 65 mmHg ($P = 0.084$) and postoperative delirium (table 2).

Secondary Analyses

The association of intraoperative TWA-MAP with postoperative delirium was linear ($P = 0.080$ for the nonlinear term; fig. 1A). When intraoperative TWA-MAP increased 1 mmHg · min, the odds of delirium would decrease 0.7% (OR, 0.993; 95% CI, 0.990 to 0.996; $P < 0.001$; table 3). In the subgroup of age 65 yr or older, the relationship between intraoperative TWA-MAP and postoperative delirium was linear and not statistically significant (OR, 0.999; 95% CI, 0.996 to 1.002; $P = 0.46$).

The association of postoperative TWA-MAP with postoperative delirium was nonlinear (fig. 1B), with one change point at 88 (95% CI, 85 to 89). When postoperative TWA-MAP was less than 88 mmHg, the estimated odds ratio of postoperative delirium per 1-mmHg increment increase of TWA-MAP was 0.995 (95% CI, 0.992 to 0.998; $P = 0.001$), meaning risk decreased with increasing TWA-MAP. When postoperative TWA-MAP was above 88 mmHg, the estimated odds ratio was 1.022 (95% CI, 1.019 to 1.027; $P < 0.001$), meaning risk would increase with increasing TWA-MAP (table 3). In the subgroup of the patients with age 65 yr or older, the relationship between postoperative TWA-MAP and postoperative delirium was linear and positive with an estimated odds ratio of 1.007 (95% CI, 1.003 to 1.010; $P < 0.001$).

Exploratory Analyses

The association of intraoperative average real variability of MAP with postoperative delirium was nonlinear (fig. 2A), with an estimated change point at 2.6 (95% CI, 2.1 to 3.2). When intraoperative average real variability of MAP was below the change point, it was not associated with postoperative delirium (odds ratio for postoperative delirium, 0.996; 95% CI, 0.964 to 1.030; $P = 0.83$). Above the change point, increasing intraoperative average real variability of MAP was associated with lower delirium risk: the estimated odds ratio for postoperative delirium was 0.951 (95% CI, 0.933 to 0.969; $P < 0.001$). The association of intraoperative variability independent of mean of MAP was not statistically significant (table 4).

The association of postoperative average real variability of MAP with postoperative delirium was nonlinear (fig. 2B), with one change point at 5.5 (95% CI, 4.4 to 5.7). When postoperative average real variability of MAP was less than 5.5, increasing average real variability was associated with a lower delirium risk with an estimated odds ratio of postoperative delirium of 0.716 (95% CI, 0.693 to 0.740; $P < 0.001$). When postoperative average real variability of MAP was above 5.5, increasing average real variability was associated with a higher delirium risk with an estimated odds ratio of 1.059 (95% CI, 1.052 to 1.066; $P < 0.001$; table 4).

Table 2. Primary Analysis: Estimated Odds Ratio of Postoperative Delirium by Intraoperative Hypotension Defined as Area under the Curve (AUC) of Mean Arterial Pressure (MAP) Less than 65 mmHg

	Univariable Analysis			Multivariable Analysis	
Factor	**No Delirium (N = 36,384)**	**Delirium (N = 2,556)**	***P* Value**	**Adjusted OR (95% CI)**	***P* Value**
AUC of MAP < 65 mmHg, mmHg · min	18.0 [0.00, 75.0]	60.0 [9.0, 192.0]	< 0.001	1.0000 (0.9999–1.0001)	0.17
AUC of MAP < 65 mmHg quartiles					
AUC = 0	10,353 (28.5)	433 (16.9)	< 0.001	Reference group	
0–20	8,621 (23.7)	396 (15.5)		0.997 (0.925–1.074)	0.93
20–80	8,878 (24.4)	623 (24.4)		1.040 (0.967–1.119)	0.29
>80	8,532 (23.4)	1,104 (43.2)		1.042 (0.963–1.128)	0.31
Subgroup of age ≥ 65 yr	**No Delirium (N = 15,590)**	**Delirium (N = 1,450)**	***P* Value**		
AUC of MAP < 65 mmHg, mmHg · min	22.0 [0.00, 81.0]	58.0 [9.0, 175.0]	< 0.001	1.0001 (1.0000–1.0003)	0.084
AUC of MAP < 65 mmHg quartiles					
0–1	4,390 (28.2)	267 (18.4)	< 0.001	Reference group	
1–24	3,652 (23.4)	231 (15.9)		1.005 (0.930–1.087)	0.90
24–87	3,886 (24.9)	364 (25.1)		1.013 (0.938–1.094)	0.75
>87	3,662 (23.5)	588 (40.6)		1.056 (0.971–1.149)	0.20

Univariable analysis presented as median [P25, P75] or N (%) comparing exposures using Wilcoxon rank-sum test. Multivariable generalized mixed-effects logistic regression model was used to estimate the odds ratio of postoperative delirium for each exposure. Adjusted covariates included all variables in table 1.

OR, odds ratio.

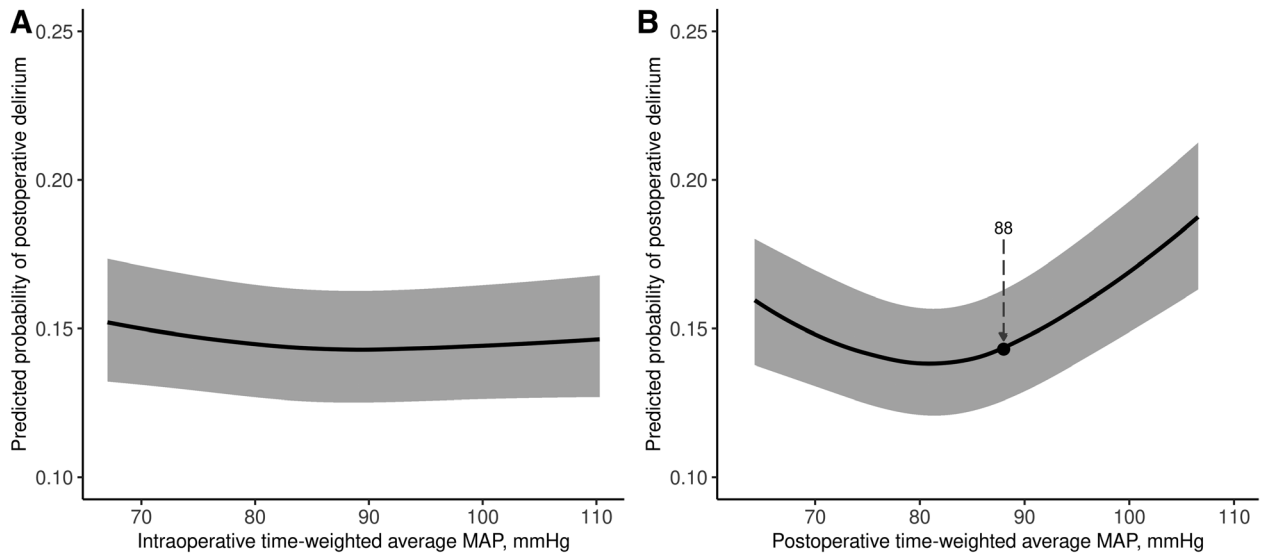


Fig. 1. Secondary analysis. (*A*) Linear relationship of intraoperative time-weighted average mean arterial blood pressure (MAP) with postoperative delirium. (*B*) Nonlinear relationship of postoperative time-weighted average MAP with postoperative delirium. Multivariable generalized mixed-effects logistic regression model was used to estimate the probability of postoperative delirium with adjustment of covariates in table 1. *Arrows* indicate the change point of the slope.

The association of postoperative and variability independent of mean of MAP with postoperative delirium was nonlinear, with one change point at 0.123 (95% CI, 0.111 to 0.128). When postoperative variability independent of mean of MAP was less than 0.123, the estimated odds ratio of postoperative delirium was 0.851 per 0.01-unit increment increase (95% CI, 0.836 to 0.866; $P < 0.001$); when postoperative variability independent of mean of MAP was above 0.123, the estimated odds ratio was 1.023 (95% CI, 1.015 to 1.030; $P < 0.001$; table 4).

Table 3. Secondary Analysis: Estimated Odds Ratio of Postoperative Delirium by Intraoperative and Postoperative Time-weighted Average (TWA) Mean Arterial Pressure (MAP)

	Univariable Analysis			Multivariable Analysis		
Factor	**No Delirium (N = 36,384)**	**Delirium (N = 2,556)**	***P* Value**	**Segments***	**Adjusted OR† (95% CI)**	***P* Value**
Intraoperative time-weighted average MAP, mmHg	85.3 ± 9.2	83.0 ± 9.4	< 0.001	Linear relationship	0.993 (0.990–0.996)	< 0.001
Postoperative time-weighted average MAP, mmHg	82.7 ± 9.2	82.9 ± 11.4	0.24	< 88 mmHg	0.995 (0.992–0.998)	0.001
				≥ 88 mmHg	1.022 (1.019–1.027)	< 0.001
Subgroup of age > 65 yr	**No Delirium (N = 15,590)**	**Delirium (N = 1,450)**	***P* Value**			
Intraoperative time-weighted average MAP, mmHg	86.0 ± 8.9	83.5 ± 9.2	< 0.001	Linear relationship	0.996 (0.979–1.013)	0.63
Postoperative time-weighted average MAP, mmHg	81.9 ± 8.8	82.2 ± 10.7	0.29	Linear relationship	1.046 (1.028–1.065)	< 0.001

Univariable analysis presented as mean ± SD or median [P25, P75] comparing exposures using two-sample *t* test or Wilcoxon rank-sum test. Multivariable generalized mixed-effects logistic regression model was used to estimate the odds ratio of postoperative delirium for each exposure. Adjusted covariates included all variables in table 1.

*Nonlinear relationship between exposures and postoperative delirium was tested by adding a restricted cubic spline with 3 knots at the 10th, 50th, and 90th percentile of exposures to the above logistic regression model. If a nonlinear relationship was observed and tested statistically significant, segmented regression approach was used to estimate the change point of the exposures. †The adjusted odds ratio of TWA-MAP was estimated using an increment of 5 mmHg.

OR, odds ratio.

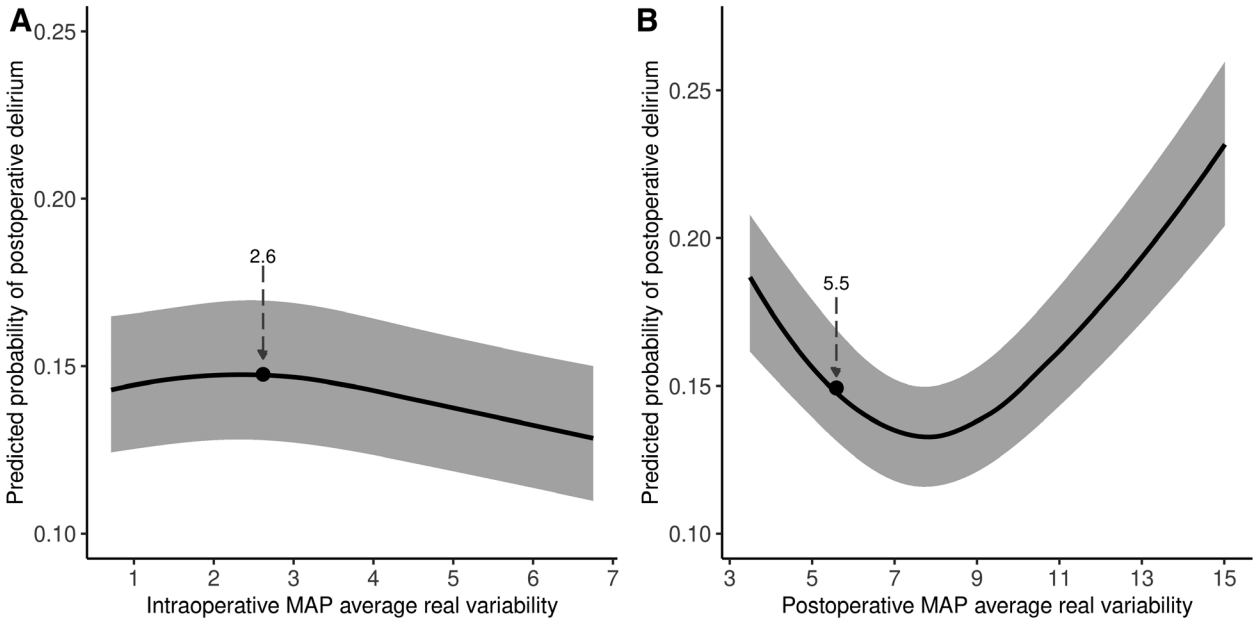


Fig. 2. Exploratory analysis. (*A*) Nonlinear relationship of intraoperative mean arterial blood pressure (MAP) average real variability with postoperative delirium. (*B*) Nonlinear relationship of postoperative MAP average real variability with postoperative delirium. Multivariable generalized mixed-effects logistic regression model was used to estimate the probability of postoperative delirium with adjustment of covariates in table 1. *Arrows* indicate the change point of the slope.

Discussion

In this retrospective, single-center cohort study of 38,940 noncardiac surgeries, we found that intraoperative hypotension, defined by the AUC of MAP less than 65 mmHg, was not associated with postoperative delirium—neither in our full sample nor in a subgroup of older patients aged 65 yr and above.

Previous data on intraoperative hypotension and delirium have been equivocal. A systematic review from 2018 found no significant relationship between hypotension and delirium.[13] Since then, Wachtendorf *et al.* retrospectively analyzed a large

Table 4. Exploratory Analysis: Estimated Odds Ratio of Postoperative Delirium by Intraoperative and Postoperative Mean Arterial Pressure (MAP) Variability Measurements

	Univariable Analysis			Multivariable Analysis		
Factor	**No Delirium (N = 36,384)**	**Delirium (N = 2,556)**	***P* Value**	**Segments***	**Adjusted OR† (95% CI)**	***P* Value**
Intraoperative MAP average real variability	2.3 [1.6, 3.4]	2.9 [2.1, 3.8]	< 0.001	< 2.6	0.996 (0.964–1.030)	0.83
				≥ 2.6	0.951 (0.933–0.969)	< 0.001
Postoperative MAP average real variability	7.4 [6.0, 9.0]	7.4 [5.6, 10.0]	0.14	< 5.5	0.716 (0.693–0.740)	< 0.001
				≥ 5.5	1.059 (1.052–1.066)	< 0.001
Postoperative MAP variation independent of mean	0.14 ± 0.03	0.15 ± 0.04	< 0.001	< 0.123	0.851 (0.836–0.866)	< 0.001
				≥ 0.123	1.023 (1.015–1.030)	< 0.001

Univariable analysis presented as mean ± SD or median [P25, P75] comparing exposures using two-sample *t* test or Wilcoxon rank-sum test. Multivariable generalized mixed-effects logistic regression model was used to estimate the odds ratio of postoperative delirium for each exposure. Adjusted covariates included all variables in table 1.

*Nonlinear relationship between exposures and postoperative delirium was tested by adding a restricted cubic spline with 3 knots at the 10th, 50th, and 90th percentile of exposures to the above logistic regression model. If a nonlinear relationship was observed and tested statistically significant, segmented regression approach was used to estimate the change point of the exposures. †The adjusted odds ratio was estimated using an increment of 1 for average real variability and 0.01 for variation independent of mean.

cohort of more than 300,000 patients having noncardiac surgery.[15] They found that a MAP less than 55 mmHg but no relative decrease from baseline blood pressure was associated with a duration-dependent increase in odds of postoperative delirium—especially in longer cases. Another smaller retrospective study of 605 older patients having thoracic and orthopedic surgery found MAP 65 mmHg or less for 5 min or more to be associated with an increased incidence of delirium.[26,27] In a retrospective study of around 1,000 critically ill patients, Maheshwari *et al.* found intraoperative hypotension, defined as TWA of MAP less than 65 mmHg, was moderately associated with higher odds of postoperative delirium.[14] Finally, most recently Zarour *et al.* found that a more common definition of intraoperative hypotension—area under a MAP threshold of 65 mmHg—was not associated with postoperative delirium in elderly patients having elective noncardiac surgery.[17] Using the same definition as Zarour *et al.*, we were able to replicate and validate their findings in another, much larger cohort. However, the only randomized trial—assigning 322 patients aged more than 65 yr to either low MAP (60 to 70 mmHg) or high MAP (90 to 100 mmHg) during general anesthesia—found a relative risk of 0.48 (95% CI, 0.25 to 0.87; $P = 0.02$) for postoperative delirium with the higher MAP target.[28] Actual intraoperative MAP in each group was not reported in this trial. Thus, further prospective data are warranted.

Our secondary analysis used intraoperative and postoperative average blood pressure, defined as TWA-MAP, as the exposure. Here, the statistically significant association of intraoperative TWA-MAP and postoperative delirium—increasing blood pressure was linearly associated with lower delirium risk—was small and not clinically important. Postoperatively, both lower and higher average blood pressures seemed to be associated with higher risk of delirium. In a nonlinear relationship resembling a U shape, we identified the change point to be at a MAP of 88 mmHg. Segmented regression revealed both blood pressure segments—if the blood pressure decreased below or increased above 88 mmHg—to be statistically significantly associated with delirium. The odds ratio is—similar to the intraoperative analysis—small, and its clinical importance questionable. Previous studies on postoperative blood pressure and delirium are sparser.[29] However, postoperative blood pressure perturbations are common and often undetected by routine vital sign assessments.[7,30] A general consensus on an upper limit in noncardiac surgery is not supported.[31] Maheshwari *et al.* found a 10-mmHg reduction in the lowest mean pressure on each day in the critical care unit to be significantly associated with a higher risk of delirium.[14] Our data join the body of evidence that postoperative blood pressure should also be an area of focus in research. Importantly, while we identify high average blood pressures as potentially harmful, this finding was incidental and should only be seen as hypothesis-generating.

In our sensitivity analysis of patients aged 65 yr and older, the results were similar to the main analysis in a comprehensive cohort. While the incidence of postoperative delirium is known to increase substantially with increasing age, in our study, the aged brain did not seem to be more susceptible to hypotension or hypertension. Likely other mechanisms contribute to the risk of delirium in older patients.[32]

In our exploratory analysis, we identified blood pressure lability, defined as MAP average real variability and variability independent of mean, to be associated with postoperative delirium. Again, the associations were statistically significant but small and likely lack clinical relevance. Intraoperatively, we observed a very weak association for average real variability of MAP and none for variability independent of mean of MAP. This may be due to the overall low median of average real variability of MAP during the intraoperative period, suggesting that MAP did not fluctuate markedly or rapidly between measurements during general anesthesia. Methodologically, this could

be expected as sampling rate during anesthesia is higher, which is known to reduce average real variability.[33] During the postoperative period, both low and high blood pressure variation was associated with an increased delirium risk. Hirsch *et al*. also found that an increasing blood pressure variance was associated with higher delirium risk.[19] This could represent a causal effect, where cerebral autoregulation may be more susceptible to rapid changes in perfusion—or, due to the fact that blood pressure variability is related to a variety of separate predisposing and precipitating factors for delirium: old age, hypertensive or cardiac comorbidities, perioperative blood loss or intravascular volume shifts, or pain.[19,34]

Limitations of our study were the retrospective design, with its inherent restrictions: there may have been unmeasured confounders, and causality cannot be shown. This is especially important regarding hypotension and postoperative outcomes, where randomized trials are often not able to replicate the detrimental effects described in observational studies.[35] Delirium can be difficult to diagnose reliably; thus, rates of delirium vary not only by study population but also by the used diagnostic criteria. Our hospital uses the bCAM for delirium assessment in postoperative patients, which has a sensitivity of 80 to 84% and may thus miss some events.[24,25] The high median number of conducted bCAMs per surgery suggests reliable assessment.

In conclusion, intraoperative hypotension and intraoperative average blood pressure were not associated with the development of postoperative delirium, either in the general population or among older patients. Postoperative higher average blood pressures were statistically significantly associated with delirium; however, this finding lacks clinical relevance.

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Competing Interests

The authors declare no competing interests.

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Supplemental Digital Content

Supplemental content, https://links.lww.com/ALN/E13
Supplemental Methods. Average real variability and variation independent of mean.
Supplemental Figure 1. Flowchart.
Supplemental Table 1. Full model of the primary analysis.
Supplemental Table 2. Full model of the secondary analysis – intraoperative TWA MAP.
Supplemental Table 3. Full model of the secondary analysis – postoperative TWA MAP.
Supplemental Table 4. Full model of the exploratory analysis – intraoperative ARV MAP.
Supplemental Table 5. Full model of the exploratory analysis – postoperative ARV MAP.
Supplemental Table 6. Full model of the exploratory analysis – postoperative VIM MAP.

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ANESTHESIOLOGY®

Psychological Effects of Explicit Recall under Sedation and after Surgery (PEERS): A Prospective Cohort Study on 2,500 Patients

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ABSTRACT

Background: Explicit recall occurring during sedation/regional anesthesia is common but has long been assumed to have no sequelae. A prospective cohort study was conducted to determine the incidence of explicit recall experience under sedation/regional anesthesia, as well as to assess the recall experiences that are associated with psychological consequences.

Methods: The study prospectively recruited 2,500 adults who underwent elective total hip or knee arthroplasty under sedation/regional anesthesia from September 2021 to March 2024 at University Hospital in London, Ontario, Canada. The primary exposure was recall experience, assessed using the modified Brice questionnaire. The co-primary outcomes included probable depression (defined as a Patient Health Questionnaire score of 8 or higher) and suspected posttraumatic stress disorder (PTSD) symptoms (defined as a Post-traumatic Stress Disorder Checklist for Civilians score of 13 or higher) at 6 weeks postoperatively. The association between specific recall experiences and the co-primary outcomes was evaluated by multivariable regression analysis. Additionally, the incidence and mental health burden related to the psychological effects of surgery in the entire cohort were assessed.

Results: A total of 2,138 patients were included in the final analysis. Explicit recall was reported by 475 participants (22.2%) but was not associated with the co-primary outcomes. Regarding surgery's overall impact, 61 participants (5%) developed new probable depression, 105 participants (5%) reported suspected PTSD, and 95 patients (4.4%) developed new suicidal ideation postoperatively. The authors estimated that 1 in 18 patients required new psychiatric consultation.

Conclusions: Explicit recall *per se* during sedation/regional anesthesia did not increase the odds of developing psychiatric illness. Surgery itself carries significant risks of triggering depression and PTSD that are severe enough to reach levels associated with suicidal ideation, requiring immediate mental care. This study reveals a significant, yet underappreciated, mental healthcare burden.

(Anesthesiology 2025; 143:570–81)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Explicit recall during sedation/regional anesthesia is common
- Awareness under general anesthesia is associated with a high risk of posttraumatic stress disorder and other long-term psychological consequences

What This Article Tell Us That Is New

- This 2,500-patient prospective cohort study found that explicit recall under sedation/regional anesthesia is relatively common, having occurred in 1 in 5 patients, but was not associated with adverse psychiatric consequences
- However, in rare cases, 3 of 2,139 patients experienced pain and paralysis, which may carry different psychological implications
- Additionally, surgery itself was a major psychological stressor, with 1 in 12 patients developing severe depression or posttraumatic stress disorder and 1 in 18 reporting suicidal ideation or seeking new psychiatric treatment postoperatively.

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Abbreviations: **ASA**, American Society of Anesthesiologists; **IQR**, interquartile range; **NAP5**, National Audit Project 5; **OR**, odds ratio; **PACU**, postanesthesia care unit; **PCL-C**, Post-Traumatic Stress Disorder Checklist for Civilians; **PHQ-9**, Patient Health Questionnaire-9; **PTSD**, posttraumatic stress disorder

Explicit recall occurring during sedation in surgery is common and generally expected, with the long-standing misconception that it has no sequelae. In contrast, awareness during general anesthesia is a rare but devastating complication that could lead to serious psychological consequences such as flashbacks, nightmares, depression, and in some cases, posttraumatic stress disorder (PTSD).[1–3] However, two recent studies[4,5] suggest that explicit recall during sedation may cause comparable psychological distress to those associated with awareness under general anesthesia. The 5th National Audit Project (NAP5) of the Royal College of Anaesthetists (United Kingdom)[4] reviewed cases of patients who spontaneously reported accidental awareness across 329 hospitals in the United Kingdom and Ireland in a 1-yr period and incidentally found that one-third of patients who reported awareness were under sedation. Many of these patients experienced long-term psychological sequalae, and some pursued legal action based on uninformed consent.

Our current understanding of explicit recall under sedation is limited due to the retrospective nature and reliance on self-reporting data in previous studies.[4,5] There has been a lack of analysis to identify specific recall experiences or risk factors that may contribute to psychological consequences. Furthermore, surgery itself, along with the entire perioperative experience—including the underlying condition necessitating surgery, surgical outcomes, complications, and the recovery experience—can serve as a significant lifelong stressor. This may potentially trigger psychiatric conditions that interact with recall experiences, an area that remains underexplored.

In this prospective cohort study, we primarily aimed to determine the incidence of explicit recall under sedation/regional anesthesia in adults, and to identify whether explicit recall experiences—or specific elements of those experiences (*e.g.*, feeling pain and paralysis)—were associated with psychiatric sequelae. As secondary objectives, we examined potential risk factors for explicit recall and whether miscommunication or unmet expectations contributed to patients' experiences and satisfaction. We also summarized patients' perspectives on their recall events. Additionally, we explored the risks of developing new PTSD, depression, and suicidal ideation after surgery in the overall surgical cohort and estimated the added mental healthcare burden.

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Materials and Methods

Study Design and Setting

This is a single-center, prospective cohort study involving adult patients who underwent elective total hip or knee replacement surgery under sedation/regional anesthesia. The primary exposure was explicit recall. The co-primary outcomes were suspected PTSD and probable depression at postoperative 6 weeks. After obtaining ethics approval on April 7, 2020 (approval 114966, principal investigator: Chui) and trial registration at ClinicalTrials.gov on February 9, 2021 (NCT04747379), the study took place at the University Hospital, London Health Science Center, London, Ontario, Canada.

Participants

We included all adult participants (age 18 yr or older) who were scheduled for elective total knee or hip replacement surgery under sedation/regional anesthesia, were able to communicate in English, and had American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status of I to IV. We excluded patients who were unable to provide informed consent, who received or converted to general anesthesia, and who were unable to complete the survey or follow-up assessments.

We focused on a single surgical population for several reasons: (1) obesity and multiple comorbidities are common, making sedation challenging and increasing the risk of sedation failure and explicit recall; (2) it allows for better verification of intraoperative events and reduces confounding variables; and (3) our center is one of the highest-volume joint replacement centers in Canada, with a strong follow-up rate.

Primary Exposure

The primary exposure (explicit recall) was assessed in the postanesthesia care unit (PACU) using a modified Brice questionnaire (five questions),[6] a widely used tool for evaluating awareness under general anesthesia. All patients were assessed within a standardized 6-h window while in the PACU. The 6-h window was implemented to account for occasional prolonged PACU stays due to hospital bed shortages, thereby ensuring a consistent assessment timeframe. To account for timing effects,[7–9] this assessment was repeated on postoperative day 1. The Michigan Awareness Classification[10] was employed to categorize levels of sensation during recall as auditory, tactile, pain, paralysis, or a

combination of pain and paralysis. Additionally, we recorded patients' perceptions and the estimated duration of their recall experiences.

Co-primary Outcomes

We focused on depression and PTSD, as these two psychological consequences were most commonly reported after awareness under general anesthesia (supplemental table 1, https://links.lww.com/ALN/E78). PTSD was assessed by the Post-Traumatic Stress Disorder Checklist for Civilians (PCL-C) questionnaire at postoperative 6 weeks.[11–13] Depression symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) at baseline and postoperative 6 weeks.[14–16] Suicidal ideation was identified based on the ninth question of PHQ-9. Although both outcomes were defined using highly accurate screening tools, definitive diagnoses require detailed diagnostic interviews conducted by psychiatrists. We used the terminology of "probable" and "suspected" to reflect these limitations, which also correspond with the disease surveillance framework adopted by the World Health Organization, classifying the likelihood of diagnosis from suspected to probable to confirmed.[17]

Data Measurement

The study procedure and participant timeline are outlined in supplemental table 2, (https://links.lww.com/ALN/E78). All interviewers received standardized training. The outcome assessors were blinded to recall status. All data was directly entered into the REDCap study database.

Study Size

Our sample size was powered to assess the incidence of recall with psychological consequence using population prevalence technique.[8] Based on previous studies[4,5] reporting the incidence of self-reported awareness under sedation at 0.1 to 0.5%, we estimated that a minimum sample of 1,799 patients would be required to detect an incidence of 0.3% with 99% confidence, and we further increased to 2,500 participants with consideration of an anticipated 20% loss to follow-up rate.

Statistical Analysis

Demographic and perioperative variables were summarized, and a study flow chart was created.

Impact of Explicit Recall. Descriptive statistics were used to examine the incidence of explicit recall under sedation/regional anesthesia in PACU and postoperative day 1. Sex differences were assessed. The details of recall experiences, initial emotional responses to the recall events, and patient satisfaction were summarized.

For the primary analysis, to assess the risk of explicit recall experience toward the development of suspected PTSD (PCL-C score of 14 to 30) and probable depression (PHQ-9 score of 10 to 27), we performed univariable logistic regression to assess whether explicit recall was associated with either co-primary outcome. This was followed by an assessment of individual element of recall experiences, such as auditory recall, feeling pressure, feeling pain and paralysis, among others. Multivariable logistic regression analysis was conducted only to evaluate the association between feeling pain and paralysis (the only individual element of recall experiences that was significant in univariable analysis) and the two co-primary outcomes with adjustment for confounders listed in table 1. Given the small number of events, feeling pain and paralysis and the wide CI reflect imprecision in the estimates. To address potential bias due to sparse data, we also conducted penalized logistic regression using Firth's method. To further contextualize these associations, we present 2 × 2 contingency tables (supplemental table 9, https://links.lww.com/ALN/E78) to illustrate the raw frequency of outcomes by exposure status.

The severity of harm (using modified National Patient Safety Agency score) according to suspected PTSD and probable depression were reported. The modified National Patient Safety Agency classification of harm that was devised for use in the NAP5 study[4] to assess psychological impact on the patients was used (supplemental table 3, https://links.lww.com/ALN/E78).

For the secondary analysis, the risk factors for explicit recall—considered as the secondary outcome—were assessed using univariable logistic regression analysis. Factors that might lead to sedation failure, such as obesity, obstructive sleep apnea, history of drug abuse, and the choice of sedatives, were explored.

A previous study[4] suggested that miscommunication and failure to manage patients' expectations were the major factors affecting future outcomes and any subsequent legal action. We assessed patient expectations and communication between the patients and healthcare providers. Wilcoxon rank sum test was used to test the difference of expectation scores, a self-report scale from 0 to 100, between groups who were informed or not informed by the healthcare provider before surgery. Patient satisfaction toward healthcare providers was assessed in a 5-point scale.

Impact of Surgery. To assess the impact of surgery on the development of psychiatric symptoms, we evaluated changes in the severity of depressive symptoms before and after surgery using the McNemar's chi-square test. The occurrence of PTSD after surgery was also determined.

We estimated the mental healthcare burden by determining the number of new psychiatric consultations potentially required. We defined the minimum healthcare burden as the new psychiatric consultations needed if the patient had new onset of moderate or severe depression (PHQ-9 score of 10 or higher), PTSD (PCL-C score of 14 or higher) and a willingness to seek professional help or had suicidal ideation regardless of willingness to seek assistance. The

Table 1. Multivariable Logistic Regression Analysis of Factors That Were Associated with Probable Depression and Suspected PTSD at Postoperative 6 Weeks

	Probable Depression (PHQ-9 Score of 10 to 27)		Suspected PTSD (PCL-C Score of 14 to 30)	
Variables	**Odds Ratio (95% CI)**	***P* value**	**Odds Ratio (95% CI)**	***P* Value**
Patient factors				
Age	1.0 (1.0–1.0)	0.005*	1.0 (1.0–1.0)	0.05
Female sex	1.2 (0.9–1.6)	0.22	1.1 (0.7–1.7)	0.8
ASA III or IV (I and II as base)	1.5 (1.1–2.0)	0.01*	1.0 (0.6–1.6)	0.9
Hypertension	1.2 (0.9–1.6)	0.13	1.4 (0.9–2.1)	0.2
Coronary artery disease	1.5 (0.9–2.3)	0.1	0.6 (0.2–1.7)	0.4
Congestive heart failure	0.6 (0.2–2.2)	0.4	0.6 (0.07–5.6)	0.7
Valvular heart disease	2.0 (0.7–5.2)	0.2		
Atrial fibrillation	1.6 (1.0–2.6)	0.05	2.1 (1.0–4.5)	0.04*
COPD	1.1 (0.6–2.4)	0.7	1.5 (0.5–4.7)	0.5
Asthma	1.0 (0.7–1.5)	0.8	1.1 (0.6–2.0)	0.7
Sleep apnea	1.3 (0.9–1.7)	0.1	2.3 (1.5–3.6)	< 0.0001
Morbid obesity	1.0 (0.7–1.6)	0.8	1.0 (0.5–1.9)	0.9
Diabetes	0.8 (0.6–1.1)	0.2	0.5 (0.3–1.0)	0.06
Stroke	1.5 (0.8–2.8)	0.18	1.5 (0.6–4.1)	0.4
History of depression	1.5 (1.1–2.2)	0.03*	2.2 (1.3–3.7)	0.002*
History of PTSD	2.3 (0.9–5.9)	0.07*	4.5 (1.5–13.2)	0.006*
History of other psychiatric illness	1.1 (0.7–1.85)	0.8	0.9 (0.4–2.0)	0.9
History of chronic opioid uses	3.6 (1.2–10.6)	0.02*	0.7 (0.09–6.0)	0.8
History of substance abuse	0.5 (0.2–1.2)	0.1	1.1 (0.4–3.0)	0.8
Explicit recall experience				
Feeling pain and paralyzed	8.9 (0.8–101.0)	0.08	26.7 (2.2–315)†	0.009*

*The following factors were considered as potential confounders in the multivariable regression analysis: age, female sex, ASA Physical Status III or IV (with I and II as the reference), hypertension, coronary artery disease, congestive heart failure, valvular heart disease, atrial fibrillation, COPD, asthma, sleep apnea, morbid obesity, diabetes, previous stroke, history of depression, history of PTSD, other psychiatric illnesses, chronic opioid use, and history of substance abuse. †To address concerns related to model performance in the context of low event rates, we conducted a Hosmer–Lemeshow goodness-of-fit test, which yielded a chi-square of 6.96 ($P = 0.54$), indicating adequate model fit with no evidence of poor calibration. Model selection statistics included an Akaike information criterion of 784.08 and a Bayesian information criterion of 903.10. The Brier score was 0.0459. The calibration plot was reasonably well fit visually. These values reflect a balance between model fit and complexity, with lower values generally preferred, although this criterion is not definitive in causal inference settings. Given the small number of outcome events, we additionally applied Firth's penalized logistic regression to reduce bias and improve estimate stability. The odds ratio for "feeling pain and paralyzed" using Firth's method was 3.04 (95% CI, 0.94 to 5.13; $P < 0.004$), consistent in direction with the standard logistic regression but with improved robustness.

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; PCL-C, Post-Traumatic Stress Disorder Checklist for Civilians; PHQ-9, Patient Health Questionnaire-9; PTSD, posttraumatic stress disorder.

types of medical assistance requested and the reasons for their decline were summarized. All patients with new-onset major depression, suicidal ideation, or PTSD were referred to their family physicians for further care. All statistical analysis was performed using STATA (version 14). *P* values less than 0.05 are accepted as statistically significant.

Data Sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request. However, access to the data is subject to restrictions due to ethical/legal/privacy concerns. The data may be shared after appropriate approval of the institutional review board or ethics committee.

Results

From September 2021 to March 2024, we screened the eligibility of 2,724 patients and excluded 224 patients for reasons detailed in figure 1. A total of 2,500 patients were consented and included. After enrollment, 231 patients were excluded: the majority (n = 133) due to drowsiness in PACU and 95 patients due to conversion to general anesthesia. The remaining reasons for exclusion are detailed in figure 1. Ultimately, 2,138 patients were included in the final analysis.

This cohort consisted of patients aged 66.3 ± 10.9 yr with a body mass index of 31.6 ± 6.8 kg/m^2. Approximately half of the patients (n = 1,139, 53%) were female. The vast majority (n = 2,018, 95%) were classified as ASA Physical Status II or III and had a wide range of medical comorbidities, as listed in table 2.

The surgical duration was 97 ± 30 min (table 2). Almost all patients (n = 2,133, 99.7%) received spinal anesthesia, with (28%) or without (72%) supplementary nerve block (supplemental table 4, https://links.lww.com/ALN/E78). Propofol was used as a sedative in 96% of patients (n = 2,041), administered with or without supplementary

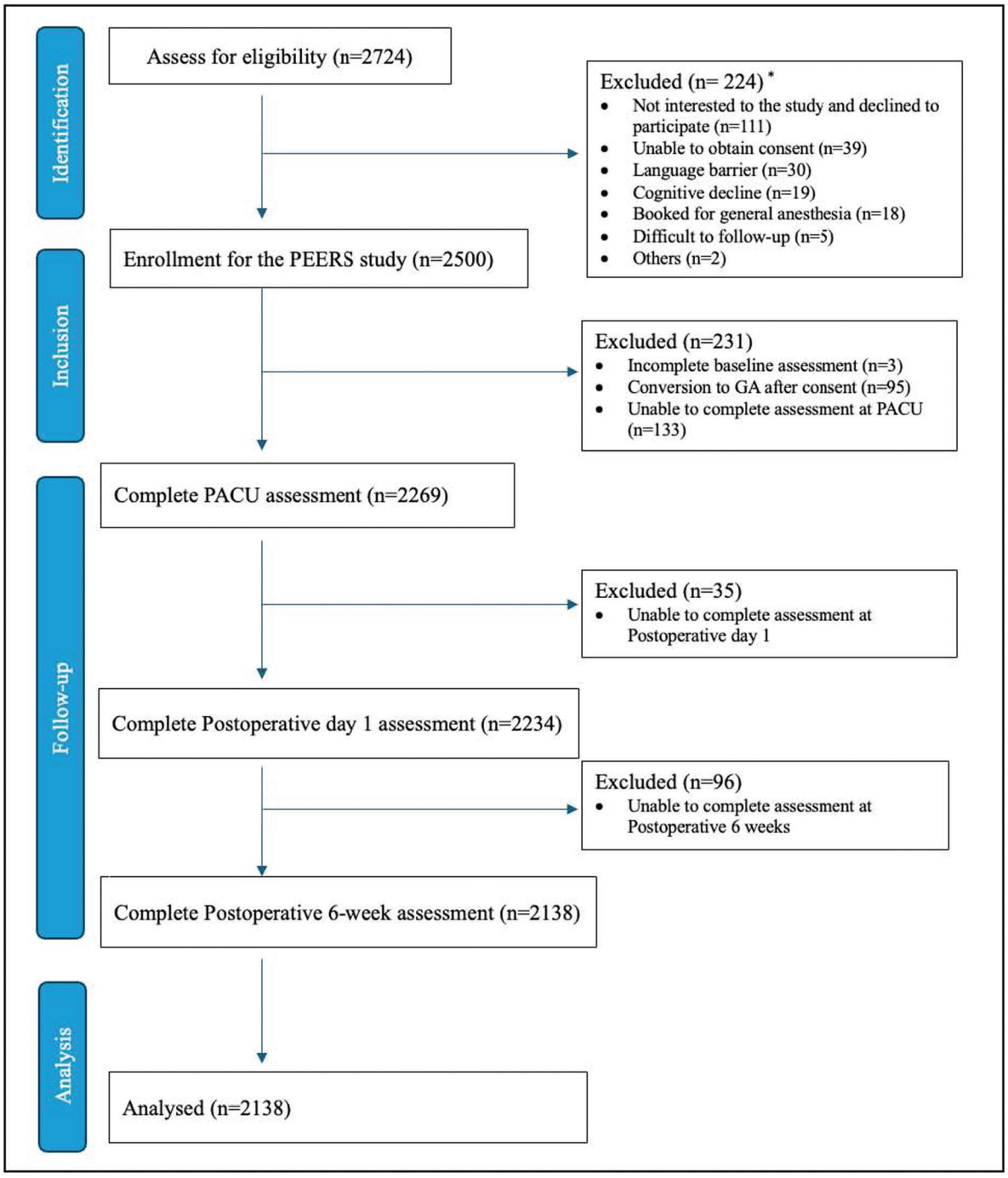


Fig. 1. Study flow chart. *Unable to obtain consent refers to cases in which the study team was unable to contact the patients or complete the consent process before surgery. Difficult to follow-up: These patients were from another province or city, came to our site only for surgery, and did not plan to have any follow-up at our hospital after the surgery. Others: These patients were assessed at our site but had surgery at other hospitals. GA, general anesthesia; PACU, postanesthesia care unit; PEERS, Psychological Effects of Explicit Recall under Sedation and after Surgery.

Table 2. Patient and Surgical Demographics

Variables	Patients with Recall Experience (n = 475)	Patients with No Recall Experience (n = 1,663)	Total (n = 2,138)
Age, yr	66.0 ± 10.4	66.4 ± 10.9	66.3 ± 10.9
Height, cm	169 ± 10	169 ± 10	169 ± 10
Weight, kg	96.3 ± 24.9	89.2 ± 20.5	90.8 ± 21.7
Body mass index, kg/m^2	33.5 ± 7.9	31.1 ± 15.2	31.6 ± 6.8
Female sex, n (%)	265 (56)	874 (53)	1,139 (53)
ASA Physical Status, I/II/III/IV, n (%)	4/151/286/34 (1/32/60/7)	25/616/965/57 (2/37/58/3)	29/767/1,251/91 (1/36/59/4)
Medical comorbidities, n (%)			
Hypertension	263 (55)	863 (52)	1,126 (53)
Coronary artery disease	25 (5)	123 (7)	148 (7)
Congestive heart failure	6 (1)	13 (1)	19 (1)
Valvular heart disease	2 (0)	22 (1)	24 (1)
Atrial fibrillation	31 (7))	97 (6)	128 (6)
COPD	11 (2)	46 (3)	57 (3)
Asthma	65 (14)	180 (11)	245 (12)
Sleep apnea	119 (25)	304 (18)	423 (20)
Morbid obesity	80 (17)	136 (8)	216 (10)
Diabetes mellitus	66 (31)	286 (15)	352 (17)
Stroke	18 (4)	54 (3)	72 (3)
Depression	49 (10)	228 (14)	277 (13)
History of PTSD	8 (2)	15 (1)	23 (1)
Baseline suicidal ideation	27 (6)	102 (6)	62 (3)
Other psychiatric history	27 (6)	102 (6)	129 (6)
Chronic opioid users	3 (1)	12 (1)	15 (1)
History of substance abuse	15 (3)	53 (3)	68 (3)
History of recall experience in previous surgery	31 (7)	79 (5)	110 (5)
History of difficult airway	2 (0.4)	0 (0)	2 (0.1)
History of chronic kidney disease	12 (3)	38 (2)	50 (2)
Surgical demographics			
Surgical diagnosis, n (%)			
Osteoarthritis	419 (89)	1,462 (88)	1,881 (88)
Rheumatoid arthritis	0 (0)	6 (0.3)	6 (0.3)
After trauma or injury	5 (1)	21 (1)	26 (1.2)
Avascular necrosis	5 (1)	22 (1)	27 (1.3)
Hardware failure due to previous surgery	27 (6)	103 (6)	130 (6)
Deformities	1 (0)	6 (0.4)	7 (0.3)
Others	15 (3)	41 (2)	56 (3)
Surgical procedure, n (%)			
Total hip replacement	187 (40)	846 (51)	1,033 (48)
Total knee replacement	283 (60)	812 (49)	1,095 (51)
Other*	2 (0.4)	3 (0.2)	5 (0.2)
Surgical duration, min	100 ± 32	93 ± 30	97 ± 30

The parametric data are presented as mean ± SD, and the categorical data are presented as number (frequency).

*Other surgeries include patients who underwent either unicondylar knee arthroplasty or a combination of femur open reduction and internal fixation and total knee replacement.

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; PTSD, posttraumatic stress disorder.

opioids during the procedure. Midazolam and ketamine were used in 26% (n = 560) and 14% (n = 308) of the patients, respectively. Additionally, 38 patients (1.8%) did not receive any sedatives. The choices and doses of sedatives are listed in supplemental table 4 (https://links.lww.com/ALN/E78).

Explicit Recall under Sedation

Approximately one-fifth of patients (n = 475, 22.2%) reported experiencing explicit recall under sedation/regional anesthesia. The incidence of explicit recall was similar between men (n = 210 of 999, 21%) and women (n = 265 of 1,139, 23%). Additionally, the incidence of explicit recall was comparable between patients assessed in the PACU and those assessed on postoperative day 1 (22.2% [n = 475] *vs.* 22.7% [n = 486]; supplemental table 5, https://links.lww.com/ALN/E78).

In terms of the content (or types) of recall experiences (supplemental fig. 1, https://links.lww.com/ALN/E78), the vast majority of patients (n = 466, 21.8%) experienced auditory perception. Visual perceptions, such as seeing flashes or lights, were reported by 7.6% of patients (n = 163). Feeling nonpainful pressure and paralysis was reported by 5.1% (n = 110) and 5% (n = 107) of patients, respectively. Pain was reported by 0.7% (n = 14) of patients, and

feeling both pain and paralysis was reported by 0.1% (n = 3) of patients. Dreaming was reported by 4.6% (n = 99) of patients, although no patients reported nightmares.

For those who reported explicit recall, the estimated median (interquartile range [IQR]) duration of explicit recall was 4 (1 to 30) minutes. The majority of patient-reported recall experiences occurred in the middle of surgery (n = 306, 14%), followed by the end of surgery (n = 171, 8%), and then the beginning (n = 128, 7%). A significant proportion of patients (n = 121, 6%) were uncertain about the timing of their experiences. This time pattern was consistent across all types of recall experiences (supplemental fig. 1, https://links.lww.com/ALN/E78).

Consequences of Explicit Recall. In the univariable analysis (supplemental tables 7 and 8, https://links.lww.com/ALN/E78), explicit recall, *per se*, showed no association with probable depression (odds ratio [OR], 0.9; 95% CI, 0.7 to 1.3; $P = 0.8$), suspected PTSD (OR, 1.1; 95% CI, 0.7 to 1.7; $P = 0.7$), or suicidal ideation (OR, 1.1; 95% CI, 0.7 to 1.8; $P = 0.6$) at 6 weeks postoperatively. However, feeling pain and paralysis was significantly associated with increased rates of suspected PTSD (OR, 39; 95% CI, 3.5 to 434; $P = 0.003$) and probable depression (OR, 12.5; 95% CI, 1.1 to 138; $P = 0.04$). Feeling pain alone was also associated with increased odds of suspected PTSD (OR, 5.4; 95% CI, 1.5 to 19; $P = 0.01$). Other types of recall experiences did not show associations with these psychological consequences. The severity of harm was reported in supplemental fig. 2 (https://links.lww.com/ALN/E78).

In the multivariable regression, after adjustment for potential confounders, feeling pain and paralysis was still significantly associated with increased rates of suspected PTSD (PCL-C score of 15 or higher[11]; OR, 26.7; 95% CI, 2.2 to 315; $P = 0.009$; table 1). However, it was no longer statistically significantly associated with probable depression (OR, 8.9; 95% CI, 0.8 to 101; $P = 0.08$). Despite the wide CI—reflecting the low number of exposed individuals and events—model diagnostics indicated adequate fit, with a Hosmer–Lemeshow test chi-square of 6.96 ($P = 0.54$). The association between feeling pain and paralysis and suspected PTSD remained statistically significant in the Firth model (OR, 3.0; 95% CI, 0.94 to 5.13; $P < 0.004$), yielding a more stable but directionally consistent estimate. The results of 2 × 2 contingency tables in supplemental table 9 (https://links.lww.com/ALN/E78) also support the direction of the observed associations, particularly for suspected PTSD.

For the results of secondary analysis, explicit recall was more likely to be experienced by patients with ASA scores of III or IV (OR, 1.3; 95% CI, 1.0 to 1.6; $P = 0.02$), sleep apnea (OR, 1.5; 95% CI, 1.2 to 1.9; $P = 0.001$), and morbid obesity (OR, 2.3; 95% CI, 1.7 to 3.1; $P < 0.0001$, supplemental table 6, https://links.lww.com/ALN/E78). Patients with no sedation were obviously more likely to have recall experiences (OR, 5.6; 95% CI, 2.9 to 10.8; $P < 0.0001$). Patients who received midazolam had a higher risk of recall (OR, 1.5; 95% CI, 1.2 to 1.9; $P < 0.0001$); however, the median (25th to 75th IQR) dose of midazolam was only 1 (1 to 2) mg. In contrast, patients who received propofol had a much lower risk of recall (OR, 0.1; 95% CI, 0.1 to 0.2; $P < 0.0001$), which was likely related to the adequate infusion dose being administered.

Regarding communication and management of patient expectations, slightly less than half of the patients (n = 990, 46%) reported that healthcare providers mentioned the possibility of explicit recall before surgery. This finding corresponds closely to the proportion of patients (n = 1,073, 50%) who reported that their actual experience matched their expectations. However, one-fifth of patients (n = 248, 20%) indicated that their actual experience only matched with half of their expectations. Interestingly, despite half of the patients not being informed of the potential for explicit recall, there was no significant difference in terms of expectation scores between those who had previous discussions and those who did not (100 *vs.* 94.5, $P = 0.8$). The median (IQR) patient satisfaction score was generally high at 93 (73 to 100) of 100; however, scores were significantly lower in patients who developed new suicidal ideation, depression, and PTSD than those who did not (median [IQR], 65 [56 to 76] *vs.* 94 [79 to 100], $P < 0.0001$; 90 [70 to 100] *vs.* 93 [77 to 100], $P < 0.003$; and 69 [50 to 98] *vs.* 93 [78 to 100], $P < 0.001$, respectively). There was no effect of preoperative discussion of recall experience on satisfaction score ($P = 0.5$). The details of patient satisfaction toward healthcare providers are listed in supplemental fig. 3 (https://links.lww.com/ALN/E78).

Patient Perspectives

Patients were asked to describe their experiences in greater detail if they wished. While many did not elaborate, some provided vivid descriptions, such as the following:

- "I heard people talking and the hammering sounds. I could feel the vibration coming from my leg going up to my spine."
- "I felt my leg was separated from me and lying beside me. I woke up two to three times in the OR while they were placing my knee in position."

Regarding pain, many patients did not specify its exact location. However, some reported pain during hammering, at the tourniquet site, or the surgical site (hip and knee). Others mentioned pain at the intravenous site or at the shoulder due to lateral positioning. One patient vividly described hearing noises and feeling pain with each staple being applied.

For paralysis, many patients acknowledged the expected sensation of paralysis due to spinal anesthesia, describing it as a feeling of heaviness and total immobility, such as: "I felt paralysis from my waist down—very heavy

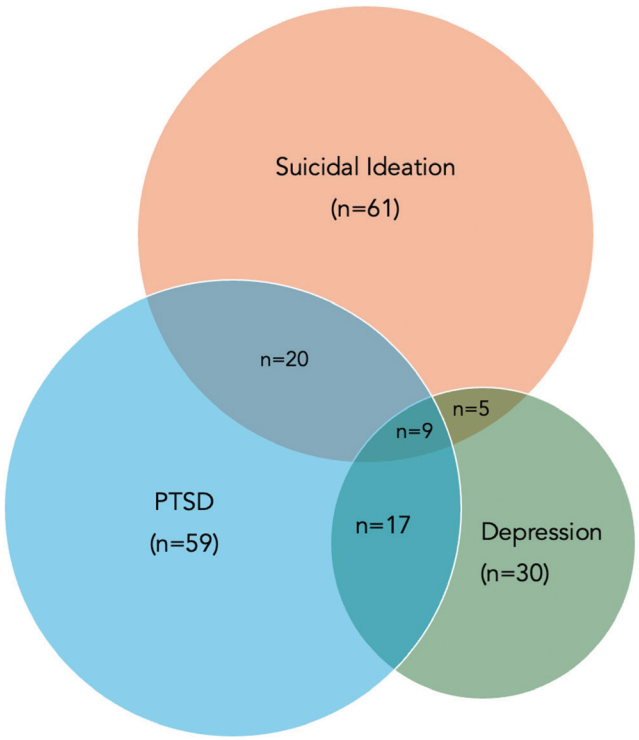
and completely immobile." Some also referred to the tugging of their arms and body during surgery. However, this expected sensation of paralysis often evoked negative reactions. Patients described it as a "weird feeling" or "astounding, bizarre, and scary." For example: "I felt like a lead balloon." Others expressed feelings of extreme fear, helplessness, and frustration. One patient shared: "I felt very scared during and after this surgery and with the anesthesia. I have flashbacks of the OR and lying on the OR table."

Psychological Consequence of Surgery

When considering the effect of surgery as a whole, we observed a significant increase in patients who developed new depression symptoms in all levels of severity after surgery ($P < 0.0001$; McNemar's chi-square test; fig. 2; table 3). At baseline, one-quarter of patients had probable depression (*i.e.*, PHQ-9 score of 5 or higher), in which 20% (n = 423) had mild depression, 6% (n = 129) had moderate depression, 2% (n = 33) had moderately severe depression, and 0.4% (n = 8) had severe depression. At postoperative 6 weeks, almost two-fifths of patients had probable depressive symptoms (*i.e.*, PHQ-9 score of 5 or higher), in which 27% (n = 582) had mild depression, 11% (n = 224) had moderate depression, 3% (n = 59) had moderately severe depression, and 0.6% (n = 13) had severe depression.

PTSD (A-PCLs score of 15 or higher[11]) was found in 5.0% (n = 105) of patients. New suicidal ideation was found in 4.4% (n = 95) of patients (fig. 2).

Worst Experience during Surgery. The majority of patients (89% or n = 1,893) reported no unpleasant experiences during surgery. Among the 245 patients who did report unpleasant experiences, 65 cited postoperative pain, 47 were related to spinal anesthesia, and 29 to uncomfortable positioning. Notably, only 27 patients (1.3%) identified recall as their most unpleasant experience, with intraoperative pain mentioned by 6 patients (0.3%). Additionally, two patients reported oversedation as the most unpleasant experience. Further details are presented in supplemental figure 4 (https://links.lww.com/ALN/E78). Importantly, feeling upset about the surgical experience at postoperative day 1 was associated with increased probable depression (OR, 1.4; 95% CI, 1.2 to 1.7; $P < 0.0001$) as well as suspected PTSD



PTSD	59
PTSD + Suicidal Ideation	20
PTSD + Depression	17
PTSD + Depression + Suicidal Ideation	9
Suicidal Ideation	61
Suicidal Ideation + Depression	5
Depression	30

Fig. 2. New onset psychiatric symptoms after surgery. The diagram depicts the number of patients who developed new-onset suicidal ideation, posttraumatic stress disorder (PTSD), or moderately severe to severe depression (Patient Health Questionnaire-9 [PHQ-9] score greater than 14) at 6 weeks postoperatively. These figures represent only newly emergent psychiatric symptoms, as patients with preexisting psychiatric conditions at baseline were excluded. Specifically, individuals who had moderately severe to severe depressive symptoms (PHQ-9 score greater than 14) before surgery were not included, even if their depressive symptoms persisted or worsened postoperatively—from moderately severe (PHQ-9 score of 15 to 19) to severe (PHQ-9 score of 20 to 27).

Table 3. Number of Patients with No to Severe Depression Assessed by PHQ-9 Depression at Baseline and 6 Weeks after Surgery

	Postoperative 6 Weeks					
Baseline	No (0 to 4	Mild (5 to 9)	Moderate (10 to 14)	Moderately Severe (15 to 19)	Severe (20 to 27)	Total Number
Normal	1030	378	115	19	3	1,545
Mild (5 to 9)	181	151	69	18	3	422
Moderate (10 to 14)	35	43	33	13	5	129
Moderately severe (15 to 19)	10	8	7	6	2	33
Severe (20 to 27)	3	2	0	3	0	8
Total number	1,259	582	224	59	13	

PHQ-9, Patient Health Questionnaire-9.

(OR, 1.4; 95% CI, 1.1 to 1.8; $P = 0.01$) at postoperative 6 weeks.

Mental Healthcare Burden of Explicit Recall and Surgery

A total of 184 patients (8.6% of 2,138) were identified as suffering from clinically significant psychiatric illness after surgery. This included 61 patients with new moderate to severe depression, 105 patients with PTSD symptoms, and 95 with new suicidal ideation, with some patients presenting with more than one mental condition, illustrated in figure 2. At least 123 patients (5.8% of 2,138) required new mental health services, which included 28 patients requested for further medical advice and those with suicidal ideation. We estimate this mental health burden could result in an additional 6,786 psychiatric service requirements in Canada, considering approximately 117,000 total hip and knee joint arthroplasties are performed annually.[18] The types of health professionals sought and reasons for not seeking help are detailed in supplemental figure 5 (https://links.lww.com/ALN/E78).

Discussion

This large-scale prospective cohort study examined the psychological impact of explicit recall under sedation/regional anesthesia and postsurgery. Explicit recall under sedation/regional anesthesia occurred in 1 of 5 patients and was not linked to psychiatric consequences. No difference in incidence between sex was observed. However, in rare cases—3 of 2,139 patients (1 in 713)—experiencing pain and paralysis under sedation/regional anesthesia during surgery may be associated with increased odds of developing PTSD. Additionally, 1 in 12 patients undergoing major hip and knee replacement developed new clinically significant depression, PTSD, or suicidal ideation postoperatively, with 1 in 18 actually requiring new psychiatric services. Given the high volume of hip and knee replacements in Canada and globally, this novel insight highlights a significant, yet underappreciated, mental health burden.

This study addresses several knowledge gaps. First, patients who experience awareness during general anesthesia report feeling partially conscious and enduring excruciating pain while being unable to move, which leads to feelings of terror and violation.[19,20] While such reports are most commonly associated with general anesthesia, a few participants (n = 3) in our study described similar experiences under sedation/regional anesthesia. The combination of helplessness due to paralysis and the sensation of pain appears to be a key factor contributing to psychological effects, regardless of whether the patient is under sedation/regional anesthesia or general anesthesia. Despite our analysis demonstrating a consistent direction of the observed association, the small number of such cases limits the precision of our estimates. Therefore, these findings should be interpreted cautiously but highlight an important area for further research. Additionally, it remains challenging to determine whether these feelings stem from a failure of regional anesthesia, sedation, or both. The low event rate of these experiences in this study limited our ability to identify specific risk factors. Second, the NAP5 study[4] estimated the incidence of "accidental awareness" during sedation to be 1:15,000, similar to the 1:19,000 for general anesthesia. However, the incidence of awareness may be significantly underestimated, as structured interviews revealed a five-fold higher rate (0.1%) compared to self-reported cases (0.02%).[21] Our study found that the incidence of explicit recall involving pain and paralysis occurred in approximately 0.14% (3 of 2,139 patients), much higher than previously reported incidence[4] and aligning more closely with the 0.13% (1 in 800) incidence of awareness under general anesthesia determined from structured interview studies.[22] However, the incidence may depend on the depth of sedation and choice of sedatives, which, in turn, are influenced by factors like obesity and sleep apnea. Third, the NAP5 study[4] postulated that miscommunication or unmet expectations contribute to the impact and legal actions after explicit recall. In contrast, we found that most patients had clear expectations about their surgeries, even though only half were informed about the possibility of recall. This likely reflects the use of information pamphlets and educational videos, as well as the advanced educational background of

our population, where self-research is common. Last, the quality of sedation plays a crucial role in the occurrence of explicit recall, pain, and paralysis, which is also influenced by patient factors such as obesity and sleep apnea. Identifying vulnerable patients and optimizing sedation, along with potential nonpharmacologic strategies, such as intraoperative auditory stimuli, which form implicit memories even under general anesthesia,[23] may mitigate postoperative depression and PTSD.

Our study found a notably high incidence of new suicidal ideation along with depression and PTSD that developed after surgery. The results are consistent with a matched case-control study[24] that reported PTSD in approximately 20% of patients (44 of 219). Other smaller studies reported varying PTSD rates of 20 to 34% after lumbar spine surgery,[25,26] lung resection surgery,[27] abdominal aortic repair surgery,[28] gynecologic cancer surgery,[29] and cesarean delivery.[26] A recent retrospective study using U.S. insurance data found that 7 to 19% of patients had depression consultation within 1 yr after surgery.[30] Collectively, these findings indicate that the onset of psychiatric illness after surgery is likely a valid observation. However, this study is the first to show that these new psychiatric illnesses are not only prevalent but also severe enough to reach levels associated with suicidal ideation, requiring immediate mental health care.

Undergoing major surgery is a significant lifetime stressor for many patients. While not completely identical to the PTSD experienced in the civilian population, traumatic events such as intensive care unit admission[31–33] and serious intraoperative events (such as cardiac arrest,[34] heart attack,[35] stroke[36]) are likely the contributors for healthcare-related PTSD. The causes likely stem from health-related thought intrusions or perceived threats to life.[37] Previous studies have also linked a history of psychiatric illness, lack of social support, and dissociation during surgery to the onset of PTSD.[27,24–26] Our study found that a history of multiple medical comorbidities, depression, or PTSD were linked to an increased risk of postoperative depression, PTSD, and suicidal ideation after surgery (supplemental tables 7 and 8, https://links.lww.com/ALN/E78). The extrapolated mental health burden could be substantial, including direct costs such as long-term medication and indirect costs like lost productivity. Subsyndromal symptoms, which were not assessed in this study, may also face significant functional impairments over time, potentially leading to a greater long-term healthcare burden.

Limitations

This study has several limitations: (1) Our co-primary outcomes—suspected PTSD and probable depression—were assessed using screening tools. These instruments are known for their high accuracy and are effective in determining the need for further psychiatric referral and thus the healthcare burden. Given the scale of this study, conducting comprehensive psychological assessments was also deemed impractical. (2) PTSD symptoms typically evolve over time after a traumatic event, with a median duration of 60 months. Our study employed a single time-point outcome measurement. Although the longitudinal course of perioperative psychiatric illness remains unclear, this single time-point assessment is adequate to demonstrate the association and provides a snapshot of the short-term impact. (3) The implications of implicit recall and patients' past traumatic experience were not explored in this study. (4) The incidence of self-reported awareness under sedation varies widely, ranging from 0.007 to 0.03% in previous studies.[4,38] This variability presents significant challenges for sample size calculation, resulting in a low event rate in this study.

Additionally, our study's generalizability is limited due to its single-center design and its focus solely on joint replacement surgeries. However, this study design benefits from the ability to verify intraoperative events. Furthermore, we did not examine other factors such as postoperative pain, delirium, and their interactions, which might also contribute to psychological consequences after surgery.

Conclusions

Our results suggest that while explicit recall under sedation/regional anesthesia is relatively common, it does not appear to be associated with adverse psychiatric outcomes. However, certain types of recall—such as experiences involving pain and paralysis—may carry different psychological implications, underscoring the need for further investigation. Additionally, surgery itself poses a substantial lifetime risk of triggering severe depression and PTSD with the risk up to the level of suicidal ideation, thereby adding to the mental healthcare burden. These adverse psychological effects are often overlooked, yet they present modifiable factors that could be addressed. Further investigation is crucial.

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Competing Interests

Dr. Naudie has disclosed a relationship with Smith & Nephew (Mississauga, Ontario, Canada). Dr. Yang has

disclosed relationships with the Canadian Anesthesiologists' Society (Toronto, Ontario, Canada), the Canadian Institutes of Health Research (Ottawa, Ontario, Canada), and the Heart and Stroke Foundation (Toronto, Ontario, Canada). None of these relationships has a direct impact on the content of this article. The other authors declare no competing interests.

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Supplemental Digital Content

Supplementary Information, https://links.lww.com/ALN/E78
Supplementary Table 1. Main outcome measures.
Supplementary Table 2. Participant timeline and study procedure.
Supplementary Table 3. Modified National Patient Safety Agency classification.
Supplementary Table 4. Anesthetic techniques.
Supplementary Table 5. Explicit recall experience.
Supplementary Table 6. Factors associated with recall under sedation.
Supplementary Table 7. Factors linked to depression and PTSD at 6 weeks postoperatively.
Supplementary Table 8. Factors linked to suicidal ideation at 6 weeks postoperatively.
Supplementary Table 9. Unadjusted associations between elements of recall experience and psychological outcomes at postoperative 6 weeks (suspected PTSD and probable depression).
Supplementary Figure 1. Timing of specific explicit recall experience.
Supplementary Figure 2. National Patient Safety Agency harm classification in postoperative depression and PTSD.
Supplementary Figure 3. Patient satisfaction toward healthcare providers.
Supplementary Figure 4. Most unpleasant surgical experience reported on day 1.
Supplementary Figure 5. Mental health burden and service needs after surgery/recall.

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ANESTHESIOLOGY®

Association of Intraoperative Hypotension with Postoperative Nausea and Vomiting in Laparoscopic Gastrointestinal Surgery: A Secondary Analysis of a Randomized Trial

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ABSTRACT

Background: Few studies have examined the association between intraoperative hypotension and postoperative nausea and vomiting (PONV), and no definitive conclusions have been established. This study investigated the association between intraoperative hypotension and PONV in patients undergoing laparoscopic gastrointestinal surgery.

Methods: This secondary analysis of a randomized trial included adult patients at high risk for PONV undergoing laparoscopic gastrointestinal surgery. Intraoperative hypotension was quantified as a time-weighted average mean arterial pressure (TWA-MAP) less than 65 mmHg. Primary and secondary outcomes were PONV within 0 to 24 h and 25 to 120 h after surgery, respectively. The authors assessed the association between intraoperative hypotension and outcomes using restricted cubic splines and multiple logistic regression models, adjusting for potential confounders. Sensitivity analyses were conducted using various mean arterial pressure thresholds (70, 60, 55 mmHg) and metrics (area under the curve [AUC], duration) with similar models.

Results: In total, 1,093 patients were included (median age, 56 yr; 1,054 [96.4%] women). The medians [interquartile ranges] of TWA-MAP less than 65 mmHg, AUC, and duration of mean arterial pressure less than 65 mmHg were 0.03 [0.00, 0.14] mmHg, 6.33 [0.17, 30.17] mmHg · min, and 1.83 [0.17, 7.00] min, respectively. The overall incidence of PONV within 0 to 24 h and 25 to 120 h after surgery was 40.4% and 42.9%, respectively. No exposure–response relationship was found between TWA-MAP less than 65 mmHg and either the primary or secondary outcome. Compared with the first tertile of TWA-MAP less than 65 mmHg, patients in the second and third tertiles did not have a higher risk of primary outcome (adjusted odds ratio, 0.92 [95% CI, 0.67 to 1.24; $P = 0.569$] and 0.95 [95% CI, 0.70 to 1.30; $P = 0.755$], respectively) or secondary outcome (adjusted odds ratio, 1.05 [95% CI, 0.77 to 1.42; $P = 0.772$] and 0.86 [95% CI, 0.63 to 1.18; $P = 0.360$], respectively). Intraoperative hypotension was not associated with PONV in any sensitivity analyses.

Conclusions: Intraoperative hypotension was not associated with PONV in patients at high risk of PONV who underwent laparoscopic gastrointestinal surgery.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative nausea and vomiting (PONV) is common after general anesthesia; while a range of risk factors for PONV has been identified, clinicians and patients need better information on modifiable risk factors for PONV
- Intraoperative hypotension has been hypothesized to be a modifiable risk factor for PONV, but past studies examining the association between hypotension and PONV are limited by issues with confounding control, data quality, and lack of information on symptoms beyond 24 h after surgery

What This Article Tells Us That Is New

- The authors conducted secondary analysis of 1,093 patients at high risk for PONV who underwent general anesthesia for laparoscopic gastrointestinal surgery in a randomized trial carried out at a major teaching hospital in China; this study collected detailed information on PONV symptoms up to 120 h after anesthesia based on patient and family interviews
- Using robust trial data that included detailed outcome information, the authors found no association between intraoperative hypotension and the adjusted odds of PONV within 0 to 24 h after surgery or within 25 to 120 h after surgery; these results were consistent across models that used a range of different approaches to defining intraoperative hypotension

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Abbreviations: **AUC**, area under the curve; **AUC-MAP**, area under the curve of mean arterial pressure; **AUC-ROC**, area under the receiver operating characteristic curve; **DBP**, diastolic blood pressure; **FDP-PONV**, Fosaprepitant plus Dexamethasone and Palonosetron for Postoperative Nausea and Vomiting; **IQR**, interquartile range; **MAP**, mean arterial pressure; **OR**, odds ratio; **PACU**, postanesthesia care unit; **PONV**, postoperative nausea and vomiting; **SBP**, systolic blood pressure; **STROBE**, Strengthening the Reporting of Observational Studies in Epidemiology; **TWA**, time-weighted average; **TWA-MAP**, time-weighted average mean arterial pressure; **VIF**, variance inflation factor

Postoperative nausea and vomiting (PONV) is a common, distressing, and costly complication of general anesthesia.[1–4] Recognizing PONV risk factors facilitates more accurate risk stratification and perioperative prevention. However, many of these risk factors have been incompletely defined. Previous studies have identified several risk factors associated with PONV, including female sex, younger age, history of PONV or motion sickness, nonsmoking status, use of opioids, duration of anesthesia, and type of surgery (*e.g.*, cholecystectomy, laparoscopy, and gynecologic procedures).[5] Despite this knowledge, many of these factors, such as sex and age, are not modifiable. Therefore, exploring modifiable risk factors holds greater potential for effective prevention strategies.

Intraoperative hypotension is a common occurrence during anesthesia and may represent a potentially preventable condition deserving investigation due to its possible role in the development of PONV.[6,7] However, its association with PONV remains understudied. Pusch *et al.*[8] reported that a significant drop in systolic blood pressure (SBP) during anesthesia induction was associated with an increased incidence of PONV within 0 to 2 h and 2 to 24 h after gynecologic surgery (n = 300). However, Kranke *et al.*[9] subsequently highlighted methodologic limitations in this study, particularly insufficient adjustment for confounding variables. Similarly, Nakatani *et al.*[10] linked intraoperative SBP reductions to PONV in patients undergoing thyroid surgery (n = 247). Large-scale database analyses by Maleczek *et al.*[11] and Goss *et al.*[12] further demonstrated that intraoperative hypotension significantly increased PONV risk in the postanesthesia care unit (PACU), but no assessment was made after discharge from the PACU. In summary, previous studies have been limited by small sample sizes or reliance on retrospective data across various surgical types. Moreover, while PONV can occur within 0 to 24 h or even more than 24 h after surgery,[13,14] most research has narrowly focused on early PONV in the PACU, with less attention paid to its occurrence after PACU discharge, particularly beyond 24 h.[11,12] Thus, further investigation into the association between intraoperative hypotension and prolonged PONV is warranted to clarify this complex relationship.

Therefore, we aimed to evaluate the independent association between intraoperative hypotension and PONV in a large cohort of patients at high risk of PONV undergoing laparoscopic gastrointestinal surgery. Specifically, we tested the hypothesis that intraoperative hypotension is associated with PONV within 0 to 24 h after surgery. Second, we tested the hypothesis that intraoperative hypotension is associated with PONV within 25 to 120 h after surgery.

Materials and Methods

Trial Design

This is a secondary analysis of data from a previously published randomized, controlled, double-blind trial (Fosaprepitant plus Dexamethasone and Palonosetron for Postoperative Nausea and Vomiting [FDP-PONV] trial) conducted between April 2021 and April 2022 (registered at clinicaltrials.gov [NCT04853147]).[14] Ethics approval for the FDP-PONV trial was obtained from the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (Guangzhou, China; No. 2021ZSLYEC-78), and all participants provided written informed consent for trial participation.

The current study also received ethical approval (No. 2024ZSLYEC-444), and the requirement for informed consent was waived because it used only anonymous data from a previous trial. This article adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (STROBE Checklist, Supplemental Digital Content 1, https://links.lww.com/ALN/E48).

Participants

This secondary analysis included all participants enrolled in the FDP-PONV trial between April 2021 and April 2022, excluding participants who did not undergo laparoscopic gastrointestinal surgery and those who lacked records of invasive blood pressure monitoring. The FDP-PONV trial enrolled patients (age 18 to 75 yr) with Apfel score 3 or greater who were scheduled for laparoscopic gastrointestinal surgical procedures during general anesthesia. The Apfel score includes four risk factors—female

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sex, nonsmoking status, history of motion sickness or PONV, and postoperative opioid use—with each factor contributing one point.[15] Patients were excluded if they had an American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status IV or greater; severe hepatic dysfunction; contraindications to fosaprepitant, 5-hydroxytryptamine type 3 receptor antagonists, or dexamethasone; preoperative use of medications with known antiemetic properties; or mental disorders or inability to communicate, or were pregnant or breastfeeding.

Summary of the Original Trial

Details regarding the inclusion and exclusion criteria for the FDP-PONV trial are available in a published article[14] and Supplemental Digital Content 2 (https://links.lww.com/ALN/E49). The FDP-PONV trial assessed whether the addition of fosaprepitant to dexamethasone and palonosetron reduced the incidence and severity of PONV. Before the induction of anesthesia in the operating room, patients were randomly assigned to receive a 30-min intravenous infusion of fosaprepitant or placebo solution. At the time of anesthesia induction, all patients in both groups received intravenous administration of dexamethasone (5 mg) and palonosetron (0.075 mg) to prevent PONV. We implemented a standardized anesthetic protocol using only propofol, remifentanil, and cisatracurium during induction and maintenance of anesthesia. Other medications, such as inhalational anesthetics, midazolam, and fentanyl, were not administered. Total intravenous anesthesia was performed *via* effect-site target-controlled infusion of propofol (2 to 6 μg/ml; Schnider model) and remifentanil (2 to 6 ng/ml; Minto model). When surgery was completed, each patient underwent surgical site infiltration with 0.5% ropivacaine. Neuromuscular blockade was reversed with neostigmine based on clinical indicators at the discretion of the attending anesthesiologist, and its use was recorded as part of the intraoperative data. An intravenous patient-controlled analgesia pump delivering hydromorphone was then initiated for postoperative pain management.

Data Collection

Demographic data, medical history, intraoperative characteristics, and detailed information regarding PONV were obtained from the records of the FDP-PONV trial. Before anesthesia induction, patients underwent distal radial artery puncture for continuous invasive blood pressure monitoring when necessary. The anesthesia information management system (Beijing WFMY Tech Co., Ltd., China) automatically recorded and stored these measurements every 10 s. We removed artifacts based on the following sequential rules[16–18]: (1) SBP 300 mmHg or greater or SBP 20 mmHg or less; (2) SBP less than or equal to diastolic blood pressure (DBP) plus 5 mmHg; and (3) DBP 5 mmHg or less or DBP 225 mmHg or greater.

Exposure

The primary exposure variable was intraoperative hypotension, defined as an intraoperative mean arterial pressure (MAP) value less than 65 mmHg. The threshold was chosen because MAP less than 65 mmHg is commonly associated with organ injury.[17,19,20] Since both the duration and depth of hypotension may affect the studied outcomes, we assessed intraoperative hypotension severity using the time-weighted average MAP (TWA-MAP) less than 65 mmHg. TWA-MAP was calculated by dividing the area under the curve of MAP (AUC-MAP) less than 65 mmHg by the time interval between the first and last MAP measurements.[18,21] The detailed calculation of TWA-MAP less than 65 mmHg is shown in Supplemental Digital Content 3 (https://links.lww.com/ALN/E50).

Outcomes

The primary outcome was the occurrence of PONV within 0 to 24 h after surgery, and the secondary outcome was the occurrence of PONV within 25 to 120 h after surgery. PONV was defined as nausea, retching, or vomiting.[22] Data on outcomes were derived from records of the FDP-PONV trial. In the FDP-PONV trial, participants, along with their family members, were instructed to record the occurrence and timing of PONV symptoms as they happened. Trained and blinded investigators then conducted structured follow-up interviews with participants every 24 h during the first 120 h after surgery. Data on PONV were systematically collected from the participants themselves, their family members, or medical staff to ensure accuracy and completeness.

Confounding Variables

Potential confounders were predefined according to existing evidence or their association with the studied outcomes in the univariate logistic regression analyses ($P < 0.05$; tables S1 and S2, Supplemental Digital Content 4, https://links.lww.com/ALN/E51). The following eight variables were selected as potential confounders for the association between intraoperative hypotension and the primary outcome: sex, age, nonsmoking status, history of motion sickness and/or PONV, standardized self-rating anxiety scale scores, prophylactic therapy for PONV, nasogastric tube placement, and duration of anesthesia. Regarding the association between intraoperative hypotension and secondary outcome, all these eight variables, along with body mass index, history of hypertension, and history of chemotherapy, were selected as potential confounders. These confounding variables were sequentially included in the restricted cubic splines and multiple logistic regression models.

Sample Size Considerations

The incidence of PONV within 0 to 24 h after surgery was 40.6% (468 of 1,154) in the FDP-PONV trial. To account for

10% of the patients who might not have undergone laparoscopic gastrointestinal surgery or received invasive blood pressure monitoring, the target sample size was set to 1,038, with an expectation of approximately 422 PONV events occurring. To ensure the stability of the logistic regression models in the current study, we adhered to the "10 events per variable" rule of thumb, allowing for up to 42 predictor parameters to be included.[23,24] Consequently, in our models, we strictly limited the number of adjusted confounders to no more than 42, ensuring both model stability and interpretability.

Sensitivity Analysis

We conducted the following sensitivity analyses to confirm the robustness of our results. The first one was conducted to explore the association between the cumulative duration or AUC of MAP less than 65 mmHg and PONV, as it is more clinically applicable. Another sensitivity analysis was carried out to explore the association between intraoperative hypotension defined by other MAP thresholds (MAP less than 70, 60, and 55 mmHg) and PONV, as the MAP threshold for intraoperative hypotension definition was varied.

Statistical Analysis

Before the analysis, a prespecified statistical analysis plan was developed and approved by investigators. Subsequently, data completeness was verified against the source data. For the primary outcome, the data completeness was 100%. Regarding the secondary outcome, 17 patients (1.5% of

Table 1. Patients' Baseline and Intraoperative Characteristics According to Tertiles of Time-weighted Average Mean Arterial Pressure (TWA-MAP) Less than 65 mmHg

	Total (n = 1,093)	First Tertile (n = 359)	Second Tertile (n = 370)	Third Tertile (n = 364)	*P* Value
Female sex	1,054 (96.4)	348 (96.9)	353 (95.4)	353 (97.0)	0.425
Age, yr	56 [48, 65]	56 [49, 64]	55 [48, 63]	58 [47, 66]	0.240
ASA Physical Status					0.167
I	36 (3.3)	9 (2.5)	13 (3.5)	14 (3.8)	
II	1,007 (92.1)	327 (91.1)	340 (91.9)	340 (93.4)	
III	50 (4.6)	23 (6.4)	17 (4.6)	10 (2.7)	
BMI, kg/m^2	22.2 [20.0, 24.4]	22.7 [20.4, 25.0]	22.2 [20.4, 24.6]	21.5 [19.5, 23.6]	< 0.001
Nonsmoking status	1,079 (98.7)	355 (98.9)	367 (99.2)	357 (98.1)	0.418
History of motion sickness and/or PONV	624 (57.1)	212 (59.1)	201 (54.3)	211 (58.0)	0.400
Apfel score for the risk of PONV					0.256
3	522 (47.8)	162 (45.1)	189 (51.1)	171 (47.0)	
4	571 (52.2)	197 (54.9)	181 (48.9)	193 (53.0)	
Migraine	120 (11.0)	39 (10.9)	42 (11.4)	39 (10.7)	0.959
Diabetes mellitus	101 (9.2)	44 (12.3)	29 (7.8)	28 (7.7)	0.055
Hypertension	233 (21.3)	89 (24.8)	78 (21.1)	66 (18.1)	0.091
History of chemotherapy	292 (26.7)	101 (28.1)	93 (25.1)	98 (26.9)	0.654
SAS score (standardized)	31.2 [28.8, 35.0]	32.5 [28.8, 36.2]	31.2 [27.5, 36.2]	31.2 [28.8, 35.0]	0.341
Type of surgery					0.058
Gastrectomy or small intestinal resection	139 (12.7)	37 (10.3)	59 (15.9)	43 (11.8)	
Colon resection	491 (44.9)	153 (42.6)	162 (43.8)	176 (48.4)	
Rectal resection	459 (42.0)	167 (46.5)	147 (39.7)	145 (39.8)	
Other	4 (0.4)	2 (0.6)	2 (0.5)	0 (0.0)	
Prophylactic PONV therapy					< 0.001
Dexamethasone +palonosetron	544 (49.8)	211 (58.8)	189 (51.1)	144 (39.6)	
Fosaprepitant +dexamethasone +palonosetron	549 (50.2)	148 (41.2)	181 (48.9)	220 (60.4)	
Intraoperative F_{IO_2}, %	45.0 [40.0, 50.0]	45.0 [40.0, 50.0]	45.0 [40.0, 50.0]	45.0 [40.0, 50.0]	0.264
Intraoperative use of neostigmine	689 (63.0)	232 (64.6)	237 (64.1)	220 (60.4)	0.448
Nasogastric tube placement	145 (13.3)	43 (12.0)	52 (14.1)	50 (13.7)	0.675
Duration of anesthesia, min	209.0 [170.0, 270.0]	212.0 [169.5, 272.0]	208.5 [171.2, 275.0]	204.5 [167.8, 258.0]	0.317
Intraoperative blood pressures					
Patients with ≥1 consecutive min of a MAP < 65 mmHg	379 (34.7)	0 (0.0)	83 (22.4)	296 (81.3)	< 0.001
Patients with any MAP readings < 65 mmHg	835 (76.4)	101 (28.1)	370 (100.0)	364 (100.0)	< 0.001
Lowest MAP, mmHg	58 [52, 64]	67 [64, 70]	57 [52, 60]	53 [49, 55]	< 0.001
TWA-MAP < 65 mmHg, mmHg	0.03 [0.00, 0.14]	0.00 [0.00, 0.00]	0.03 [0.01, 0.05]	0.20 [0.14, 0.36]	< 0.001

Data are presented as n (%) or median [interquartile range]. The tertiles were categorized according to the distribution of TWA-MAP <65 mmHg across the cohort. The ranges for each tertile are as follows (mmHg): first tertile, 0 to 0.006; second tertile, 0.006 to 0.092; third tertile, 0.092 to 1.351.

ASA, American Society of Anesthesiologists; BMI, body mass index; F_{IO_2}, fractional inspired oxygen tension; PONV, postoperative nausea and vomiting; SAS, self-rating anxiety scale; MAP, mean arterial pressure; TWA-MAP, time-weighted average mean arterial pressure.

1,093) had missing data that were not imputed. Continuous variables were analyzed using ANOVA and reported as mean ± SD when normally distributed, whereas others were analyzed using the Kruskal–Wallis test and reported as medians with interquartile ranges (IQRs). Categorical variables were analyzed using the chi-square or Fisher exact test, as appropriate, and reported as frequencies with percentages.

We categorized patients into tertiles of intraoperative hypotension metrics (time-weighted average [TWA], AUC, or cumulative duration) and compared their characteristics across tertiles. To explore the exposure–response relationship between intraoperative hypotension and the studied outcomes, we utilized restricted cubic splines with three knots placed at the 10th, 50th, and 90th exposure percentiles, adjusting for potential confounders in model 3. In addition, we explored the association between exposure and outcomes using multiple logistic regression models: model 1, unadjusted; model 2, adjusted for sex; and model 3, adjusted for all potential confounders. Odds ratio and 95% CI were used to estimate the effect size. The goodness-of-fit and discriminatory power of multivariable logistic regression were assessed through Hosmer–Lemeshow test and the area under the receiver operating characteristic curve (AUC-ROC), respectively. Multicollinearity assessment among covariates was performed by calculating variance inflation factors (VIFs). The full model was considered to be appropriate based on three criteria: (1) a nonsignificant Hosmer–Lemeshow test result ($P > 0.05$); (2) an AUC-ROC value exceeding 0.5[25]; and (3) a VIF value less than 5.

Subgroup analyses were conducted based on prophylactic PONV therapy, Apfel score for the risk of PONV, age (less than 50 or 50 yr or more), history of hypertension, history of diabetes mellitus, and type of surgery to evaluate the interaction of these factors with the association between TWA-MAP less than 65 mmHg and the primary outcome.

All analyses were performed using R software 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/, accessed March 25, 2024). All statistical tests were two-sided, and statistical significance was set at $P < 0.05$.

Results

Study Cohort

A total of 1,154 patients age 18 to 75 yr who were enrolled in the FDP-PONV trial were screened, of whom 1,093 (94.7%) remained in our analysis after exclusion. All patients included in our study underwent laparoscopic gastrointestinal surgery during general anesthesia between April 2021 and April 2022. Of the eligible patients, 1,093 (100%) underwent follow-up within 0 to 24 h after surgery and were included in the primary analysis, and 1,076 (98.4%) underwent follow-up within 25 to 120 h after surgery and were included in the secondary analysis (fig. S1, Supplemental Digital

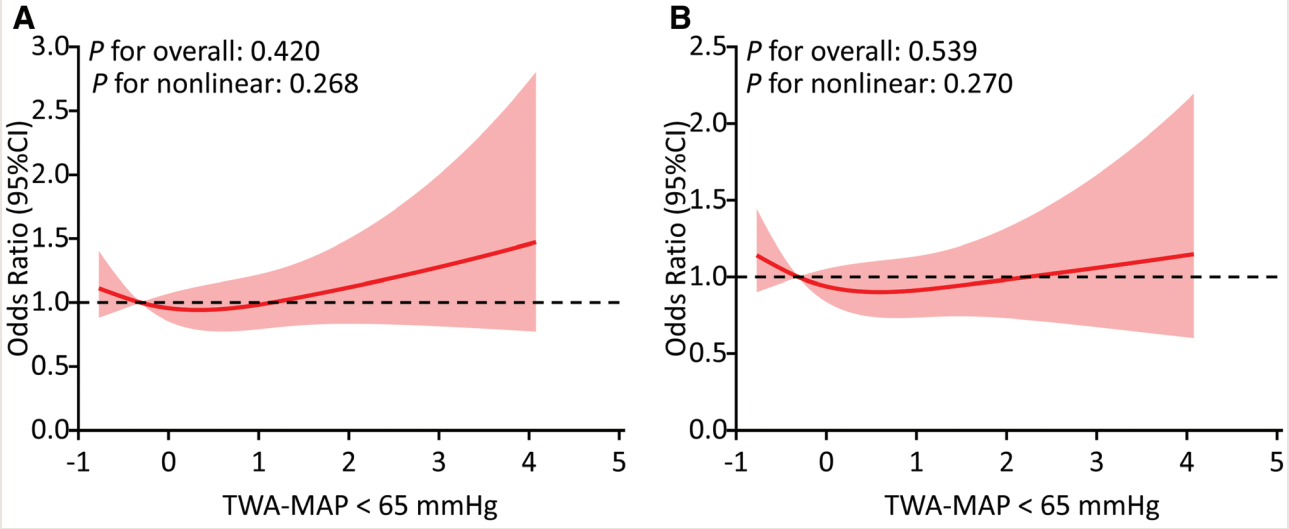


Fig. 1. Restricted cubic splines (RCS) for the association of time-weighted average mean arterial pressure (TWA-MAP) less than 65 mmHg with postoperative nausea and vomiting (PONV). (*A*) RCS for the association of TWA-MAP less than 65 mmHg with PONV within 0 to 24 h after surgery. The model was adjusted for eight variables: sex, age, nonsmoking status, history of motion sickness and/or PONV, standardized self-rating anxiety scale scores, prophylactic therapy for PONV, nasogastric tube placement, and duration of anesthesia. (*B*) RCS for the association of TWA-MAP less than 65 mmHg with PONV within 25 to 120 h after surgery. The model was adjusted for all eight variables along with body mass index, history of hypertension, and history of chemotherapy. The *x*-axis represents the standardized value of TWA-MAP less than 65 mmHg. The *y*-axis represents the odds ratios of outcomes, corresponding to a 1-SD increment in the TWA-MAP less than 65 mmHg. Odds ratios were depicted by *solid lines* and 95% CIs by *shaded areas*.

Content 5, https://links.lww.com/ALN/E52). Among the 1,093 patients analyzed, 1,054 (96.4%) were women. The median [IQR] age and body mass index were 56.0 [48.0, 65.0] yr and 22.2 [20.0, 24.4] kg/m^2, respectively. A total of 1,007 (92.1%) patients were classified as American Society of Anesthesiologists Physical Status II. When intraoperative hypotension is defined as a MAP less than 65 mmHg for at least 1 min, the incidence is 34.7% (379 of 1,093). When intraoperative hypotension is defined as any occurrence of mean arterial pressure less than 65 mmHg, the incidence is 76.4% (835 of 1,093). The median [IQR] of lowest MAP was 58 [52, 64] mmHg (table 1). The overall medians [IQRs] of TWA-MAP less than 65 mmHg, AUC-MAP less than 65 mmHg, and cumulative duration of MAP less than 65 mmHg, were 0.03 [0.00, 0.14] mmHg, 6.33 [0.17, 30.17] mmHg · min, and 1.83 [0.17, 7.00] min, respectively (table 1; table S3, Supplemental Digital Content 4, https://links.lww.com/ALN/E51). The tertile groups of TWA-MAP less than 65 mmHg differed significantly in body mass index, prophylactic PONV therapy, incidence of intraoperative hypotension, and lowest MAP ($P < 0.001$; table 1).

Primary Outcome

The overall incidence of PONV within 0 to 24 h after surgery was 40.4% (442 of 1,093 patients). The incidence of PONV was comparable among the TWA tertile groups within 0 to 24 h after surgery: first tertile, 43.2% (155 of 359 patients); second tertile, 39.5% (146 of 370 patients); and third tertile, 38.7% (141 of 364 patients; $P = 0.427$). After adjusting for potential confounders, no exposure–response relationship was found between TWA-MAP less than 65 mmHg and PONV within 0 to 24 h after surgery in the restricted cubic splines ($P_{overall} = 0.420$; $P_{nonlinear} = 0.268$; fig. 1). Multiple logistic regression models revealed that a TWA-MAP less than 65 mmHg was not associated with PONV within 0 to 24 h after surgery (models 1 to 3). In model 3, compared with the first tertile of TWA-MAP less than 65 mmHg, patients in the second and third tertiles had comparable odds of PONV 0 to 24 h after surgery, with adjusted odds ratio of 0.92 (95% CI, 0.67 to 1.24; $P = 0.569$) and 0.95 (95% CI, 0.70 to 1.30; $P = 0.755$), respectively (fig. 2).

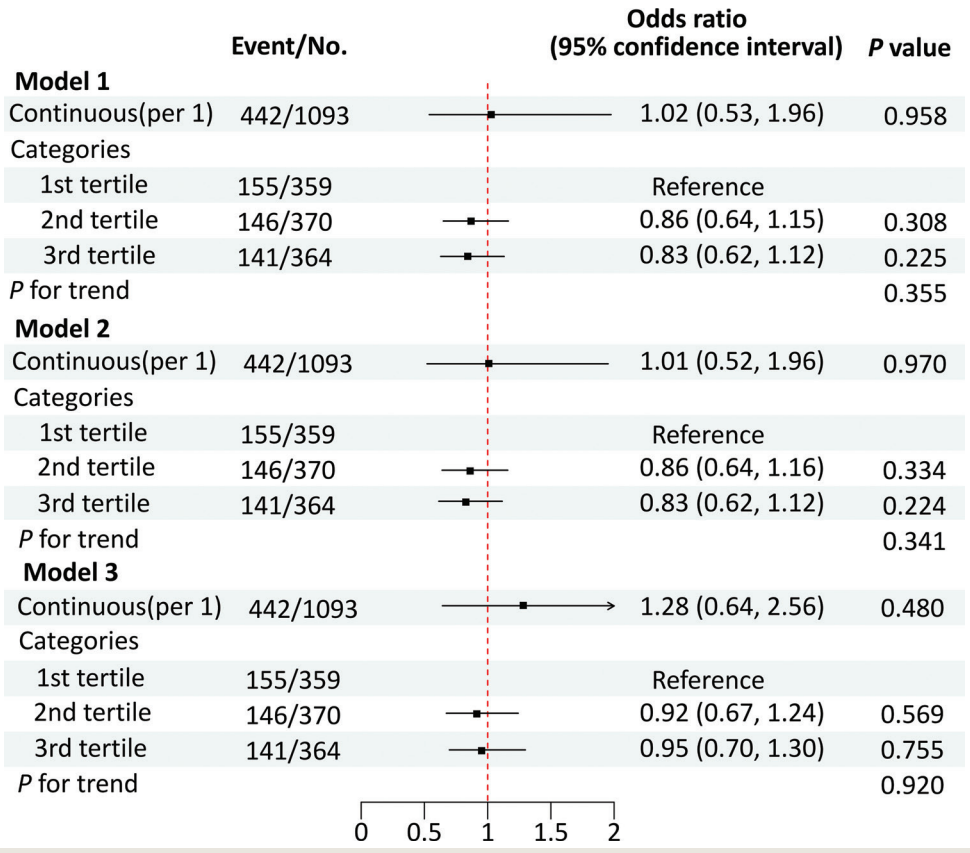


Fig. 2. Forest plot for multiple logistic regression models to show the association of time-weighted average mean arterial pressure less than 65 mmHg with postoperative nausea and vomiting within 0 to 24 h after surgery. Model 1 was unadjusted. Model 2 was adjusted for sex. Model 3 was adjusted for sex, age, nonsmoking status, history of motion sickness and/or postoperative nausea and vomiting (PONV), standardized self-rating anxiety scale scores, prophylactic therapy for PONV, nasogastric tube placement, and duration of anesthesia. "Per 1" indicates a 1-unit increment in the corresponding exposure variable (as a continuous variable).

Subgroup analysis also revealed no significant interaction between several factors (prophylactic PONV therapy, Apfel score for the risk of PONV, age, history of hypertension, history of diabetes mellitus, or type of surgery) and the association of TWA-MAP less than 65 mmHg with PONV occurring within 0 to 24 h after surgery (fig. 3).

Secondary Outcome

The overall incidence of PONV within 25 to 120 h after surgery was 42.9% (462 of 1,076 patients). The incidence of PONV was comparable between the TWA tertile groups within 25 to 120 h after surgery: first tertile, 42.9% (152 of 354 patients); second tertile, 44.8% (162 of 362 patients); and third tertile, 41.1% (148 of 360 patients; $P = 0.614$). After adjusting for potential confounders, no exposure–response relationship was found between TWA-MAP less than 65 mmHg and PONV within 25 to 120 h after surgery in the restricted cubic splines ($P_{overall} = 0.539$; $P_{nonlinear} = 0.270$; fig. 1). Multiple logistic regression models revealed that TWA-MAP less than 65 mmHg was not associated with PONV within 25 to 120 h after surgery (models 1 to 3). In model 3, compared with the first tertile of TWA-MAP less than 65 mmHg, patients in the second and third tertiles had comparable odds of PONV 25 to 120 h after surgery, with adjusted odds ratio of 1.05 (95% CI, 0.77 to 1.42; $P = 0.772$) and 0.86 (95% CI, 0.63 to 1.18; $P = 0.360$), respectively (fig. 4).

Sensitivity Analyses

Intraoperative hypotension was not associated with primary or secondary outcome in any of the sensitivity analysis.

First, when MAP less than 65 mmHg was quantified by either AUC or cumulative duration, no exposure–response relationship was found between AUC-MAP less than 65 mmHg or cumulative duration of MAP less than 65 mmHg and either the primary or secondary outcomes (figs. S2 and S3, Supplemental Digital Content 5, https://links.lww.com/ALN/E52). After adjusting for potential confounders, compared with the first tertile of both AUC-MAP less than 65 mmHg and cumulative duration of MAP less than 65 mmHg, patients in the second and third tertiles had comparable odds of both the primary and secondary outcomes (table 2; table S4, Supplemental Digital Content 4, https://links.lww.com/ALN/E51).

Second, when intraoperative hypotension was defined by other MAP thresholds (MAP less than 70, less than 60, and less than 55 mmHg), no exposure–response relationship was found between TWA, AUC, or cumulative duration under these MAP thresholds and either the primary or secondary outcome (figs. S4 and S5, Supplemental Digital Content 5, https://links.lww.com/ALN/E52). After adjusting for potential confounders, compared with the first tertile of each measure (TWA, AUC, or duration), patients in the second and third tertiles exhibited comparable odds for both primary and secondary outcomes (tables S5 to S10, Supplemental Digital Content 4, https://links.lww.com/ALN/E51).

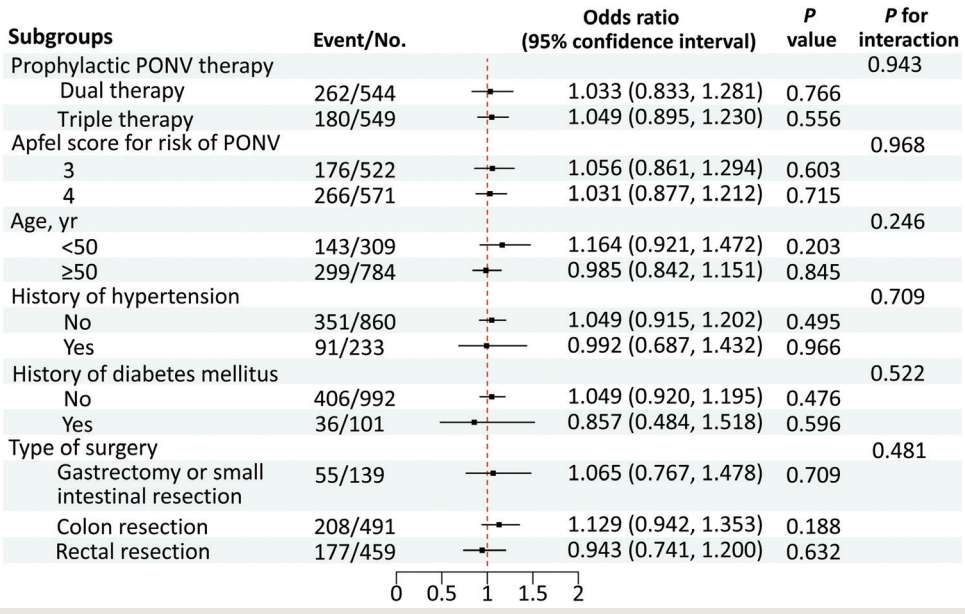


Fig. 3. Subgroup analyses for the association of time-weighted average mean arterial pressure less than 65 mmHg with postoperative nausea and vomiting (PONV) within 0 to 24 h after surgery. For prophylactic PONV therapy, dual therapy represents therapy with dexamethasone and palonosetron, and triple therapy represents therapy with fosaprepitant plus dexamethasone and palonosetron.

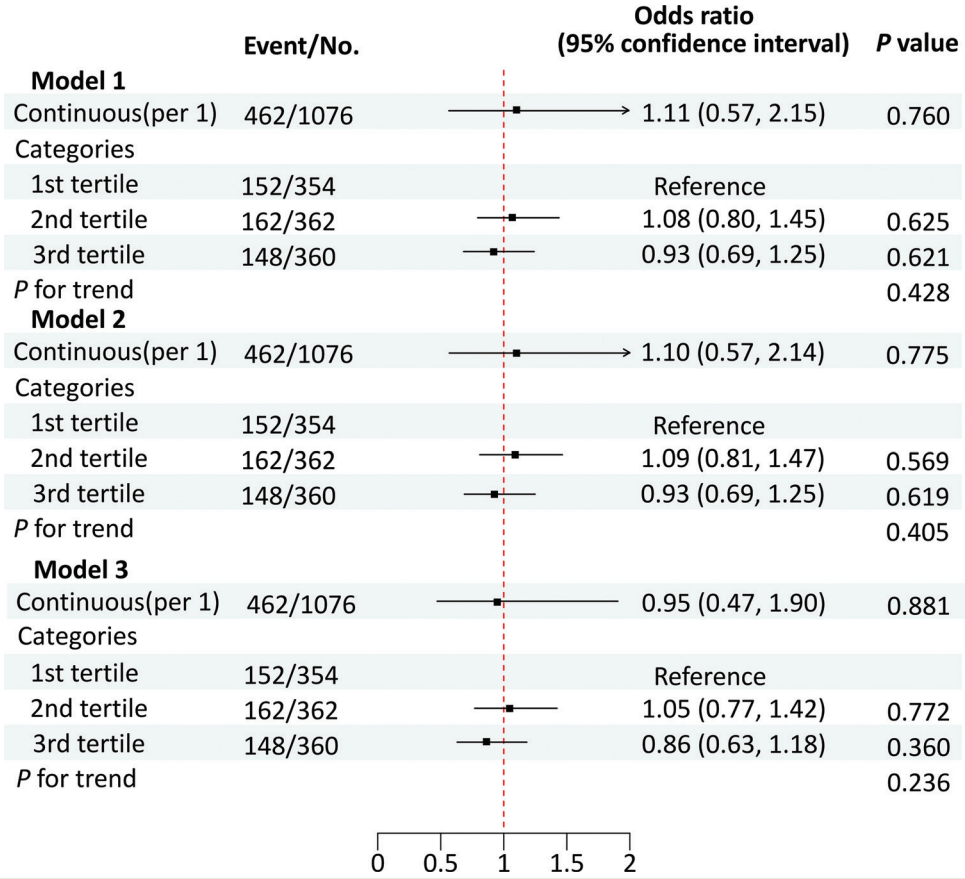


Fig. 4. Forest plot for multiple logistic regression models to show the association of time-weighted average mean arterial pressure less than 65 mmHg with postoperative nausea and vomiting within 25 to 120 h after surgery. Model 1 was unadjusted. Model 2 was adjusted for sex. Model 3 was adjusted for sex, age, body mass index, nonsmoking status, history of hypertension, history of chemotherapy, history of motion sickness and/or postoperative nausea and vomiting (PONV), standardized self-rating anxiety scale scores, prophylactic therapy for PONV, nasogastric tube placement, and duration of anesthesia. "Per 1" indicates a 1-unit increment in the corresponding exposure variable (as a continuous variable).

Model Fit/Diagnostics

All full models were deemed appropriate, since all the *P* values from the Hosmer–Lemeshow tests were greater than 0.05, the AUC-ROC values were greater than 0.6, and the VIFs were less than 2.

Discussion

Using various thresholds to define intraoperative hypotension (mean arterial pressure less than 70, less than 65, less than 60, and less than 55 mmHg) and different metrics to quantify hypotensive exposure (TWA, AUC, and cumulative duration), we found no statistically significant association between intraoperative hypotension and PONV within 0 to 24 h or 25 to 120 h after surgery in patients at high risk of PONV undergoing laparoscopic gastrointestinal surgery.

Currently, studies examining the association between intraoperative hypotension and PONV are limited, and there are no uniform criteria for defining intraoperative hypotension or definitive conclusions regarding its association with PONV. Pusch *et al.*[8] conducted a prospective observational study including 300 women undergoing elective gynecologic surgery, and found that patients whose SBP decreased by more than 35% from their preanesthesia baseline during the induction of general anesthesia had an increased incidence of PONV within 0 to 24 h after surgery. However, a decrease in SBP during the maintenance phase of general anesthesia did not significantly affect the incidence of PONV. Nakatani *et al.*[10] carried out a retrospective cohort study and reported that intraoperative hypotension—defined as SBP below baseline levels measured before anesthesia induction—was related to PONV in a cohort of 247 patients undergoing thyroidectomy. Maleczek *et al.*[11] performed a retrospective analysis of 38,577 adults using the perioperative database with the records of intraoperative blood pressure and PONV in the PACU. The results showed that a MAP less than 50 mmHg for at least 1.8 min or MAP less than 60 mmHg for at least 6 min during anesthesia was

Table 2. Association of Intraoperative Hypotension Quantified by Area under the Curve (AUC) or Cumulative Duration of Mean Arterial Pressure (MAP) Less than 65 mmHg with Postoperative Nausea and Vomiting (PONV) within 0 to 24 h after Surgery

		Model 1		Model 2		Model 3	
	Event/No.	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
AUC-MAP < 65 mmHg							
Continuous (per 1)	442/1,093	1.00 (1.00–1.00)	0.615	1.00 (1.00–1.00)	0.622	1.00 (1.00–1.01)	0.281
Categories							
1st tertile	156/356	Reference		Reference		Reference	
2nd tertile	143/374	0.79 (0.59–1.07)	0.125	0.80 (0.59–1.07)	0.138	0.84 (0.62–1.14)	0.260
3rd tertile	143/363	0.83 (0.62–1.12)	0.229	0.83 (0.62–1.12)	0.228	0.94 (0.69–1.28)	0.702
P value for trend			0.489		0.472		0.952
Duration of MAP < 65 mmHg							
Continuous (per 1)	442/1,093	1.00 (0.98–1.01)	0.624	1.00 (0.98–1.01)	0.648	1.00 (0.98–1.02)	0.854
Categories							
1st tertile	145/331	Reference		Reference		Reference	
2nd tertile	156/392	0.85 (0.63–1.14)	0.276	0.85 (0.63–1.15)	0.287	0.95 (0.70–1.29)	0.739
3rd tertile	141/370	0.79 (0.58–1.07)	0.126	0.79 (0.58–1.07)	0.125	0.90 (0.66–1.24)	0.524
P value for trend			0.205		0.199		0.558

Data are presented as odds ratios and 95% CI. Multiple logistic regression models were established. Model 1, unadjusted; model 2, adjusted for sex; model 3, adjusted for all confounders. "Per 1" indicates a 1-unit increment in the corresponding exposure variable (as a continuous variable).

AUC, area under the curve; OR, odds ratio; MAP, mean arterial pressure.

associated with an increased risk of PONV in the PACU. Goss *et al.*[12] conducted a retrospective analysis of perioperative data from 18,674 adults using electronic anesthesia records and the hospital's patient data management system. Their results revealed that intraoperative hypotension was significantly associated with an increased risk of PONV during PACU stay. In contrast, our study found no statistically significant association between intraoperative hypotension and PONV within 0 to 24 h or 25 to 120 h after surgery, which seemed to be inconsistent with previous studies.

Several factors may explain the inconsistency among these findings, including variations in sample size, observation time windows for PONV, the number of adjusted confounders, patient population selection, definitions of intraoperative hypotension, and intervals of blood pressure measurement. The study conducted by Pusch *et al.* (n = 300) has a relatively small sample size. Additionally, potential confounders such as the duration of anesthesia, smoking history, or previous history of PONV were not adjusted for—a limitation also highlighted by Kranke *et al.*[9] Similarly, the study by Nakatani *et al.*,[10] with a sample size of n = 247, also involved a limited number of participants. Two large-scale studies by Maleczek *et al.*[11] (n = 38,577) and Goss *et al.*[12] (n = 18,674) utilized database-derived data. However, the reported incidence of PONV in these two studies (approximately 11%) was notably lower than that observed in nondatabase studies.[14,26–29] Potential biases in the database, such as underreporting of PONV cases by PACU healthcare providers and follow-up durations restricted to the PACU period, may have contributed to this lower incidence. These factors could also influence the observed association between intraoperative hypotension and PONV.

Our study represents a secondary analysis of a randomized, controlled, double-blind trial, with a relatively large sample size of 1,093 participants.[14] The rigorous follow-up protocol employed in the randomized trial likely minimized the underreporting of PONV events, providing a more accurate and comprehensive assessment of their occurrence. Additionally, optimizing prophylactic therapy for high-risk patients is particularly meaningful, as the incidence of PONV remains high even when combined prophylactic drugs are used. Since our study focused on identifying additional modifiable risk factors for PONV in a high-risk patient cohort, the observed incidence of PONV was relatively high. Moreover, most previous studies have relied on intermittent measurements of blood pressure taken every 1 to 5 min,[8,11,12] but our study collected information regarding intraoperative hypotension from a continuous invasive blood pressure monitoring system with measurements recorded every 10 s. This high-frequency monitoring ensured that the information regarding hypotension was accurately captured. Of note, while previous investigations have predominantly examined early PONV (0 to 24 h after surgery),[11,12] our study extends this evaluation to the under-investigated phenomenon of delayed PONV (more than 24 h after surgery), which represents a clinically significant yet underinvestigated phenomenon. Although less frequent than early PONV, delayed symptoms significantly impair nutritional recovery and independently prolong hospitalization,[30] underscoring its clinical relevance. The risk factors and mechanisms of PONV within these two distinct time windows may differ.[31] Our analysis provides novel insights into the association between intraoperative hypotension and delayed PONV, addressing this critical knowledge gap.

This study has several strengths. First, it was a secondary analysis of a randomized controlled trial with a large sample size to investigate the association between intraoperative hypotension and PONV. Information regarding PONV was prospectively collected from a previous trial to avoid recall bias. Second, potential confounders were minimized by focusing on laparoscopic gastrointestinal surgeries under total intravenous anesthesia, with standardized PONV prophylaxis and uniform postoperative pain management. Third, we employed multiple models to adjust for various confounders step by step and conducted extensive sensitivity analyses using different criteria for quantifying intraoperative hypotension. These rigorous methods ensured robust and reliable findings regarding the association between intraoperative hypotension and PONV.

The current study has several limitations. First, while conducted at a tertiary referral center (Sixth Affiliated Hospital of Sun Yat-sen University) specializing in gastrointestinal surgery, the single-center design may affect generalizability. Second, our exclusive focus on high-risk PONV patients (Apfel 3 to 4) undergoing elective laparoscopic gastrointestinal procedures, while methodologically advantageous for controlling confounders, may limit extrapolation to other surgical populations. Third, the study population was predominantly women, which may limit the generalizability of the findings to male patients.

In summary, within the range of hypotension observed in our data, intraoperative hypotension was not associated with increased odds of PONV in patients at high risk of PONV undergoing laparoscopic gastrointestinal surgery.

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Competing Interests

The authors declare no competing interests.

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Supplemental Digital Content

Supplemental Digital Content 1. STROBE checklist, https://links.lww.com/ALN/E48
Supplemental Digital Content 2. Inclusion and exclusion criteria of FDP-PONV trial, https://links.lww.com/ALN/E49
Supplemental Digital Content 3. Calculation of time-weighted average MAP less than 65 mmHg, https://links.lww.com/ALN/E50
Supplemental Digital Content 4. Supplementary tables, https://links.lww.com/ALN/E51
Supplemental Digital Content 5. Supplementary figures, https://links.lww.com/ALN/E52

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ANESTHESIOLOGY®

Increased Plasma Fibroblast Growth Factor 23 and In-hospital Acute Kidney Injury after Cardiac Surgery

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Acute kidney injury (AKI) is common after cardiac surgery with cardiopulmonary bypass and is associated with increased morbidity
- Its diagnosis is most commonly based on standardized criteria using elevations in serum creatinine
- Alternate biomarkers have been proposed, although only limited data are currently available
- A leading candidate is plasma fibroblast growth factor 23 (FGF23), a glycoprotein that increases phosphate excretion, among other actions

What This Article Tells Us That Is New

- This observational prospective study of 173 patients undergoing nonemergent cardiac surgery analyzed changes in C-terminal (cFGF23) and intact, full-length FGF23 (iFGF23) at 6 h after termination of bypass to assess relations with in-hospital AKI using Kidney Disease: Improving Global Outcomes serum creatinine criteria by 7 days postoperatively (or sooner if discharged earlier)
- AKI was detected in 18.5% of the cohort
- Two-fold increases in either cFGF23 or iFGF23 were associated with similar elevated odds of developing postoperative AKI

ABSTRACT

Background: Acute kidney injury (AKI) occurs in 20 to 30% of cardiac surgery patients and is most often classified as mild. A previous study reported that intact fibroblast growth factor 23 (iFGF23) and C-terminal fibroblast growth factor 23 (cFGF23) measured after cardiopulmonary bypass (CPB) were associated with severe AKI after cardiac surgery but did not analyze the association between iFGF23 and all-stage AKI. The primary aim of the study was to determine whether FGF23 biomarker measurements 6 h after CPB were associated with all-stage AKI after cardiac surgery.

Methods: This prospective observational study included 173 patients undergoing nonemergent coronary artery bypass graft (CABG) and/or valve surgery on CPB. The primary study outcome was all-stage postoperative in-hospital AKI defined using the Kidney Disease: Improving Global Outcomes serum creatinine criteria through postoperative day 7, or earlier if the hospital stay was less than 7 days. Plasma iFGF23 and cFGF23 were measured 6 h after the end of CPB.

Results: A total of 32 patients developed in-hospital postoperative AKI (18.5%) by the seventh postoperative day. The incidence of AKI was 18.5% in CABG patients, 14.3% in valve surgery patients, and 41.2% in combined CABG valve patients. A two-fold increase in cFGF23 was associated with 1.57 greater predicted odds of developing in-hospital postoperative AKI (odds ratio [OR], 1.57; 95% CI, 1.26 to 1.96; $P < 0.0001$). This association remained significant after adjusting for clinical covariates (OR, 1.40; 95% CI, 1.10 to 1.77; $P = 0.006$) and after adjusting for preoperative Cleveland Clinic score (OR, 1.54; 95% CI, 1.22 to 1.95; $P = 0.0003$). A two-fold increase in iFGF23 was associated with 1.59 greater predicted odds of developing in-hospital postoperative AKI (OR, 1.59; 95% CI, 1.08 to 2.35; $P = 0.018$).

Conclusions: Early postoperative measurements of cFGF23 and iFGF23 are associated with all-stage AKI after cardiac surgery. The utility of these biomarkers for risk classification in cardiac surgery patients remains to be determined.

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Abbreviations: AKI, acute kidney injury; **AUC**, area under the receiver operating characteristic curve; **CABG**, coronary artery bypass surgery; **cFGF23**, C-terminal fibroblast growth factor 23; **CKD**, chronic kidney disease; **CPB**, cardiopulmonary bypass; **eGFR**, estimated glomerular filtration rate; **FDR**, false discovery rate; **FGF**, fibroblast growth factor; **iFGF23**, intact fibroblast growth factor 23; **IGFBP-7**, insulin-like growth factor-binding protein-7; **IL-18**, interleukin-18; **IQR**, interquartile range; **KDIGO**, Kidney Disease: Improving Global Outcomes; **NGAL**, neutrophil gelatinase-associated lipocalin; **OR**, odds ratio; **POD**, postoperative day; **TIMP-2**, tissue inhibitor of metalloproteinase 2

Among the 2 million patients who undergo cardiac surgery worldwide each year, approximately 20 to 30% develop in hospital postoperative acute kidney injury (AKI).[1] The mortality associated with AKI varies significantly, ranging from 3.5% in mild cases to 17.9% in severe cases.[2] This is concerning since AKI after cardiac surgery is significantly associated with increased short-term and long-term morbidity, mortality, and hospitalization costs.[1,3,4] Cardiac surgery invokes perioperative inflammatory, oxidative, and nephrotoxic physiologic stresses that can increase susceptibility to renal hypoxia.[5] Presently, assessing a rise in serum creatinine and a decline in urine output after cardiac surgery are the main clinical approaches to identifying postoperative AKI. However, there is typically a significant lag between a clinically relevant decline in glomerular function and subsequent clinical diagnosis of AKI, assessed by rise in serum creatinine.[6] This lag, which is secondary to time for plasma creatinine accumulation after kidney injury,[7] hemodilution on cardiopulmonary bypass,[8,9] and postoperative fluid resuscitation,[10] can be pronounced in cardiac surgery patients.

Plasma fibroblast growth factor 23 (FGF23) is an osteocyte- and osteoblast-derived glycoprotein that acts on the kidneys to increase phosphate excretion in urine, among a myriad of physiologic functions. Its action is mediated by FGF receptor R1 and α-klotho, which serve as coreceptors for FGF23, and heparan sulfate, which facilitates FGF receptor R1 dimerization.[11,12] α-Klotho increases receptor binding affinity to FGF23 in the kidney and parathyroid gland, functioning to reduce blood phosphate levels and inhibit the production of $1,25(OH)_2$ vitamin D.[13] The expression of α-klotho is reduced in patients with chronic kidney disease (CKD), which has led to its investigation as a biomarker of kidney dysfunction.[14,15]

In ambulatory patients who have CKD, plasma FGF23 levels rise as kidney function declines,[16] and plasma FGF23 concentration is an independent risk factor for progression of CKD[17] and for mortality in dialysis patients.[18] The plasma concentrations of both iFGF23 and cFGF23 measured preoperatively[19–21] and after cardiopulmonary bypass (CPB)[22–24] have been found to be early markers of AKI after cardiac surgery. In one study that enrolled infants undergoing cardiac surgery, cFGF23 measured after CPB was associated with severe AKI, with an area under the receiver operating characteristic curve (AUC) of 0.74.[23] Another study reported an association between post-CPB cFGF23 and all-stage AKI in adult cardiac surgical patients, with an AUC of 0.78 (0.72 to 0.84).[22] However, the study did not examine the association between iFGF23 and all-stage AKI. The primary hypothesis of our study is that at 6 h after CPB, plasma cFGF23, iFGF23, and the empiric numeric ratio of cFGF23/iFGF23 will be associated with the development of in-hospital AKI after cardiac surgery.

Materials and Methods

Study Population

A total of 190 patients scheduled for nonemergent coronary artery bypass graft (CABG) and/or valve surgery on CPB at the University of Texas Southwestern Medical Center in Dallas, Texas, were prospectively enrolled into the parent observational cohort study, with retrospective use of collected clinical data and use of plasma biobank samples needed for this study (ClinicalTrials.gov NCT01258231). Exclusion criteria for enrollment included the inability to give informed consent, age of less than 20 yr, preoperative hematocrit of less than 25%, or known infection with human immunodeficiency virus (HIV) or untreated hepatitis C virus. A total of 17 enrolled subjects were excluded from study analyses because they required preoperative renal replacement therapy (n = 3), they withdrew from the study before postoperative day 4 (n = 4), surgery was aborted (n = 1), they had missing biomarker data (n = 3), or they did not have samples for analysis (n = 6). Altogether, 173 patients were included in the final analysis. These patients underwent surgery between May 5, 2015, and May 31, 2018. The study was approved by the University of Texas Southwestern Medical Center's Institutional Review Board, and all subjects provided written informed consent.

Clinical Data

Patient demographics, comorbid conditions, medications, surgical characteristics, and postoperative details during the primary surgical hospitalization were collected using a standardized case report form. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Texas Southwestern Medical Center and supported by CTSA grant No. UL1 TR003163 from the National Center for Advancing Translational Science, a component of the National Institutes of Health (Bethesda, Maryland).[25,26] Diabetes was defined as requiring preoperative insulin or oral hypoglycemic medications. Preoperative anemia was defined by the World Health Organization (Geneva, Switzerland) cutoffs of less than 12 g/dl in women and less

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than 13 g/dl in men.[22] Preoperative β-blocker use was defined as administration within 24 h preoperatively. Preoperative history of thyroid disease was defined as history of hypothyroidism or hyperthyroidism and/or taking thyroid hormone replacement therapy at the time of surgery. Other preoperative medications were evaluated, if found on the patient's home medication list on the same day of surgery or on the patient's hospital medication list if the patient was hospitalized before surgery. Preoperative eGFR was determined by the 2021 Chronic Kidney Disease–Epidemiology Collaboration equation, which does not include race as a variable.[27]

Plasma Biomarkers

Biomarker data included C-terminal FGF23 (cFGF23), which is the sum of the C-terminal fragment and full-length, intact full-length FGF23 (iFGF23), and serum creatinine. The two assays of FGF23 were commercial enzyme-linked immunosorbent assay kits for cFGF23 (Quidel, USA), which measures full-length and C-terminal fragment of FGF23 and iFGF23 (Immutopics, USA), which only measures full-length FGF23. FGF23 concentrations were right skewed in distribution and thus transformed using the natural log to normalize distributions for analyses. Plasma samples were centrifuged at 1,227*g* for 15 min at 4°C, and aliquots were stored at −80°C until thawed for batch analysis.

Biomarker Prediction Variable Definitions

Measurements of iFGF23 and cFGF23 were defined as the value that occurred 6 h after separation from CPB. The empiric numerical ratio of cFGF23 and iFGF23 in clinical units was also evaluated as a predictor of AKI. The window of 6 h postoperative CPB was selected at the suggestion of peer reviewers because it preceded in time the onset of postoperative in-hospital AKI in the current study sample. Of the postoperative in-hospital AKI events, 50% occurred on postoperative day (POD) 1, 34.4% on POD 2, and the remaining 15.6% occurred on PODs 3 to 6.

Study Outcomes

The primary study outcome was postoperative in-hospital AKI, which was operationally defined using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for serum creatinine: a rise in postoperative serum creatinine compared to preoperative serum creatinine that was greater than or equal to 0.3 mg/dl within the first 48 h after surgery or greater than or equal to 1.5 times the preoperative serum creatinine at any time through postoperative day 7 or earlier if hospital stay was less than 7 days.[28]

Statistical Analysis

The sample size was one of convenience, based on resources available to measure FGF23. Demographic and clinical characteristics were described using the sample mean (SD) or median (IQR) for continuous variables and the frequency (percentage) for categorical variables. To identify any differences between the characteristics of patients who did and did not develop postoperative in-hospital AKI, the two–independent sample *t* test, with the Satterthwaite method for unequal variances, or the median two-sample test (continuous variables) and Fisher's exact test (categorical variables) were used.

Logistic regression, with penalized maximum likelihood estimation along with Firth's bias correction (to limit bias due to small samples), was implemented to estimate the odds of postoperative in-hospital AKI from the biomarkers. Odds ratios associated with AKI were expressed to correspond to a two-fold increase in the biomarker level. cFGF23 and iFGF23 values, as well as the cFGF23/iFGF23 ratio, were assessed alone in separate simple logistic regression models for association with postoperative in-hospital AKI and then were evaluated in separate multiple logistic regression models with adjustment for the covariates (covariates are specified below *via* clinical models 1 and 2, respectively). AUC was used to demonstrate the discriminative ability of the logistic regression models.

Covariates of clinical model 1 included age, sex, preoperative eGFR ml · min^{-1} · 1.73 m^{-2}, preoperative left ventricular ejection fraction, body mass index (kg/m^2), CPB time (min), and history of CKD, which emerged from the LASSO-penalized variable selection algorithm, with the Bayesian information criterion, in the context of a multiple logistic regression model for the outcome of AKI. This process and method (L1 regularization) balanced model fit and parsimony, which helped to prevent overfitting.[29] These covariates also have been reported in previous studies[6,30,31] as risk factors for AKI after cardiac surgery. The covariates in clinical model 2 consisted of the Cleveland Clinic score, which is one of the few externally validated preoperative risk score for predicting severe AKI after cardiac surgery.[32] The covariates from models 1 and 2 were selected *a priori* and then included in the above-mentioned multiple logistic regression models.

Statistical analyses were carried out using SAS software, version 9.4 (SAS Institute, Inc., USA). The level of significance was set at $\alpha = 0.05$ (two-tailed), and the false discovery rate (FDR) procedure[33] was used to control false positives over the multiple tests. The FDR approach controls the number of false discoveries in those tests that result in a significant result. An FDR-adjusted *P* value of 0.05 implies that 5% of significant tests will result in false positives.

Results

Characteristics of the Study Population

Of the 173 patients, 75.1% were male, 64.2% were non-Hispanic white, and the mean age of the patients was 61.3 ± 12.1 yr (range, 29 to 83 yr). The mean body mass index

was 30.1 ± 6.4 kg/m^2. The mean preoperative eGFR and preoperative creatinine were 79.8 ± 20.4 ml · min^{-1} · 1.7 m^{-2} and 1.1 ± 0.4 mg/dl, respectively. The median in-hospital length of stay was 6 days (IQR, 4 days). Patient characteristics are summarized in table 1.

The incidence of postoperative in-hospital AKI by the seventh postoperative day was 18.5% (n = 32). AKI developed in 18.5% of CABG patients, 14.3% of valve surgery patients, and 41.2% of combined CABG valve patients. The median (IQR) time between the end of surgery and

Table 1. Characteristics of 173 Patients Who Underwent Cardiac Surgery with CPB Stratified by the Occurrence of Postoperative In-hospital AKI

Patient Characteristics	All (N = 173)	AKI (n = 32)	No AKI (n = 141)	*P* Value	FDR
Preoperative characteristics					
Age, mean ± SD, yr	61.26 ± 12.09	62.00 ± 11.31	61.09 ± 12.29	0.702	0.830
Male, n (%)	130 (75.14)	26 (81.25)	104 (73.76)	0.498	0.741
Race, n (%)				0.350	0.594
White	111 (64.16)	20 (62.50)	91 (64.54)		
Hispanic	33 (19.08)	5 (15.63)	28 (19.86)		
Black	19 (10.98)	3 (9.38)	16 (11.35)		
Other	10 (5.78)	4 (12.50)	6 (4.26)		
BMI, mean ± SD, kg/m^2	30.05 ± 6.44	33.09 ± 5.30	29.37 ± 6.49	0.003	0.039
Obesity, BMI > 30 kg/m^2, n (%)	75 (43.35)	24 (75.00)	51 (36.17)	0.0001	0.004
Diabetes mellitus, n (%)	54 (31.21)	10 (31.25)	44 (31.20)	0.999	0.999
Hypertension, n (%)	136 (78.61)	30 (93.75)	106 (75.18)	0.018	0.067
Hypercholesterolemia, n (%)	124 (71.68)	22 (68.75)	102 (72.34)	0.669	0.815
Tobacco smoking, n (%)				0.584	0.771
Current smoker	12 (6.94)	3 (9.38)	9 (6.38)		
Past smoker	82 (47.40)	13 (40.63)	69 (48.94)		
Never smoker	79 (45.66)	16 (50.00)	63 (44.68)		
Baseline eGFR, mean ± SD, ml · min^{-1} · 1.73 m^{-2}	79.76 ± 20.40	75.72 ± 23.09	80.67 ± 19.71	0.216	0.427
Baseline eGFR < 60 ml · min^{-1} · 1.73 m^{-2}, n (%)	27 (15.61)	6 (18.75)	21 (14.89)	0.593	0.771
Left ventricular ejection fraction, mean ± SD, %	55.22 ± 11.58	50.71 ± 12.60	56.24 ± 11.13	0.011	0.061
History of preoperative arrhythmia, n (%)	28 (16.18)	8 (25.00)	20 (14.18)	0.181	0.415
History of heart failure, n (%)	46 (26.59)	12 (37.50)	34 (24.11)	0.127	0.310
History of thyroid disease, n (%)	23 (13.29)	0 (0.00)	23 (16.31)	0.008	0.052
History of chronic kidney disease, n (%)	17 (9.83)	7 (21.88)	10 (7.09)	0.019	0.067
Cleveland Clinic preoperative score, mean ± SD	2.24 ± 1.84	2.81 ± 2.14	2.11 ± 1.75	0.053	0.159
Preoperative medications					
ACEI or ARB, n (%)	97 (56.07)	20 (62.50)	77 (54.61)	0.438	0.683
ACE or ARB within 48 h of surgery, n (%)	56 (32.37)	12 (37.50)	44 (31.21)	0.532	0.741
Number of concurrent inotropes and vasopressors, mean ± SD	1.87 ± 1.04	2.06 ± 1.16	1.83 ± 1.01	0.272	0.482
Loop diuretic, n (%)	52 (30.06)	13 (40.63)	39 (27.66)	0.199	0.427
Statin, n (%)	123 (71.10)	22 (68.75)	101 (71.63)	0.829	0.951
β-Blocker (within 24 h of surgery), n (%)	107 (61.85)	23 (71.88)	84 (59.57)	0.230	0.427
Calcium channel blocker, n (%)	38 (21.97)	7 (21.88)	31 (21.99)	0.999	0.999
Aspirin, n (%)	115 (66.47)	21 (65.63)	94 (66.67)	0.999	0.999
Nonaspirin platelet inhibitor, n (%)	21 (12.14)	4 (12.50)	17 (12.06)	0.999	0.999
Surgical, intraoperative, and postoperative characteristics					
CPB time, median (IQR), min	120 (50)	128 (84.50)	119 (46)	0.221	0.427
Aortic cross-clamp time, minutes, median (IQR)	84 (39)	89.50 (43)	83 (34)	0.411	0.668
Type of cardiac surgery, n (%)					
CABG only	65 (37.57)	12 (37.50)	53 (37.59)	0.999	0.999
CABG plus valve	17 (9.83)	7 (21.88)	10 (7.09)	0.019	0.067
Valve only	91 (52.60)	13 (40.62)	78 (55.32)	0.079	0.220
Reoperative cardiac surgery, n (%)	17 (9.83)	6 (18.75)	11 (7.80)	0.092	0.239
Nadir intraoperative hemoglobin, mean ± SD, g/dl	8.26 ± 1.63	8.13 ± 1.78	8.29 ± 1.60	0.632	0.795
Fluid balance 6 h postoperative to POD 1, median (IQR), ml	−300 (804)	−32 (731.50)	−366 (774)	0.013	0.063
Intraoperative PE transfusion, n (%)	51 (29.48)	11 (34.38)	40 (28.37)	0.523	0.741
PE transfused intraoperative + 24 h after surgery, n (%)	40 (23.12)	12 (37.50)	28 (19.86)	0.039	0.127
ICU length of stay, median (IQR), days	2 (3)	4 (5.50)	2 (3)	0.0003	0.006
Hospital length of stay, median (IQR), days	6 (4)	9 (11)	6 (4)	0.005	0.049
Urine output first 24 h after surgery, median (IQR), l	0.80 (0.38)	0.63 (0.39)	0.83 (0.31)	0.007	0.052

The data are shown as *n* (%) for categorical variables and mean ± SD or median (IQR = difference between the 75th and 25th percentiles) for continuous variables.

ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin-II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; FDR, false discovery rate; ICU, intensive care unit; IQR, interquartile range; *P*, two-tailed *P* value; PE, packed erythrocyte; POD, postoperative day.

diagnosis of AKI using KDIGO serum creatinine criteria was 30.8 (30.9) h. Of the 173 patients, KDIGO stage 1 AKI occurred in 13.9% (n = 24), stage 2 AKI occurred in 3.5% (n = 6), and stage 3 AKI occurred in 1.2% (n = 2). The median (IQR) time between FGF23 measurement and diagnosis of AKI was 27.5 (31.2) h, with a range of 4.7 to 144.4 h.

FGF23 Biomarker Levels Stratified by In-hospital AKI

Box plots of the natural log FGF23 biomarker levels across the perioperative timepoints stratified by the occurrence of AKI *versus* no AKI are shown in figure 1. Patients with AKI had significantly greater cFGF23 values at the 6-h post-CPB timepoint than patients without AKI ($P < 0.05$). Patients with AKI had significantly greater iFGF23 values at the timepoint than patients without AKI ($P < 0.05$). Patients with AKI also had significantly greater cFGF23/iFGF23 ratio values at the timepoint than patients without AKI ($P < 0.05$).

Association of Postoperative Biomarker Levels with In-hospital AKI

Table 2 shows the logistic regression results of the association of clinical covariates, the Cleveland Clinic score, and the individual biomarker levels with in-hospital AKI. Table 2 also shows the association of in-hospital AKI with

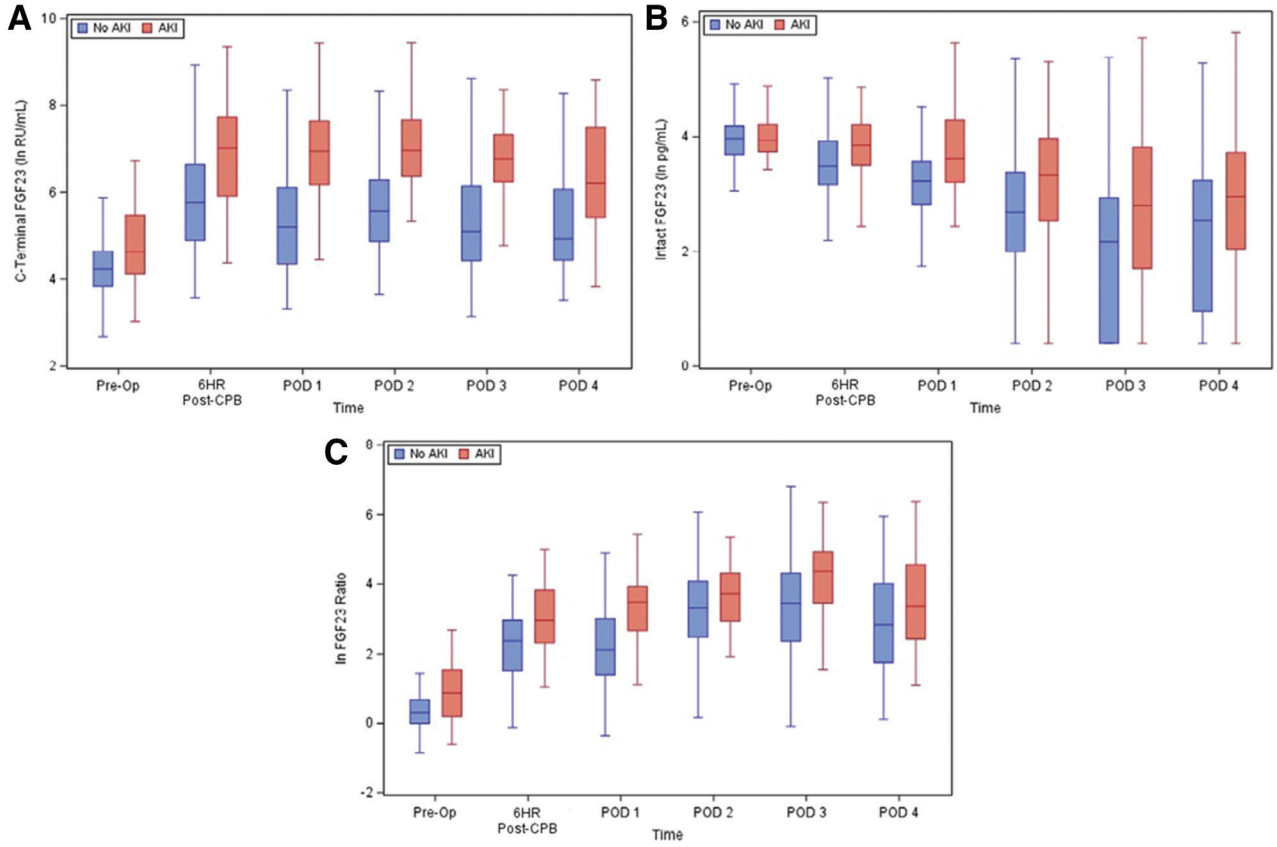


Fig. 1. (*A*) Box plot of the natural log (ln) cFGF23 biomarker levels across the perioperative timepoints stratified by the occurrence of acute kidney injury (AKI) *versus* no AKI. For AKI and no AKI, respectively, cFGF23 was measured preoperatively (n = 32, n = 141), 6 h after cardiopulmonary bypass (n = 29, n = 135), postoperative day (POD) 1 (n = 31, n = 137), POD 2 (n = 31, n = 137), POD 3 (n = 30, n = 136), and POD 4 (n = 31, n = 116). Note that patients with AKI had significantly greater C-terminal FGF23 values at each timepoint than patients without AKI ($P < 0.05$). (*B*) Box plot of the ln iFGF23 biomarker levels across the perioperative timepoints stratified by the occurrence of AKI *versus* no AKI. For AKI and no AKI, respectively, iFGF23 was measured preoperatively (n = 32, n = 141), 6 h post–cardiopulmonary bypass (n = 29, n = 135), postoperative day (POD) 1 (n = 31, n = 137), POD 2 (n = 31, n = 137), POD 3 (n = 30, n = 136), and POD 4 (n = 31, n = 116). Note that patients with AKI had significantly greater intact FGF23 values at each timepoint (except for preoperatively) than patients without AKI ($P < 0.05$). (*C*) Box plot of the ln FGF23 ratio across the perioperative timepoints stratified by the occurrence of AKI *versus* no AKI. For AKI and no AKI, respectively, the FGF23 ratio was measured preoperatively (n = 32, n = 141), 6 h after cardiopulmonary bypass (n = 29, n = 135), postoperative day (POD) 1 (n = 31, n = 137), POD 2 (n = 31, n = 137), POD 3 (n = 30, n = 136), and POD 4 (n = 31, n = 116). Note that patients with AKI had significantly greater FGF23 ratio values at each timepoint than patients without AKI ($P < 0.05$). cFGF23, C-terminal fibroblast growth factor 23; CPB, cardiopulmonary bypass; iFGF23, intact fibroblast growth factor 23.

the biomarker levels adjusted for the clinical covariates and the Cleveland Clinic score, respectively.

C-terminal FGF23. A two-fold increase in cFGF23 (denoting C-terminal peptide plus full-length FGF23) at 6 h post-CPB was associated with 1.57 greater predicted odds of developing in-hospital AKI (odds ratio [OR], 1.57; 95% CI, 1.26 to 1.96; AUC, 0.73; $P < 0.0001$; FDR, 0.0009; fig. 2). The association remained statistically significant after adjusting for the covariates in model 1 (adjusted OR, 1.40; 95% CI, 1.10 to 1.77; AUC, 0.81; $P = 0.006$; FDR, 0.009) and the Cleveland Clinic score in model 2 (adjusted OR, 1.54; 95% CI, 1.22 to 1.95; AUC, 0.73; $P = 0.0003$; FDR, 0.0012).

Intact FGF23. Patients with a two-fold increase in iFGF23 (at 6 h post-CPB) were 1.59 times more likely to develop postoperative in-hospital AKI (OR, 1.59; 95% CI, 1.08 to 2.35; AUC, 0.67; $P = 0.018$; FDR, 0.023; fig. 3). The association, however, was not statistically significant after adjusting for the covariates in model 1 (adjusted OR, 1.29; 95% CI, 0.84 to 2.01; AUC, 0.79; $P = 0.243$; FDR, 0.243) and the Cleveland Clinic score in model 2 (adjusted OR, 1.45; 95% CI, 0.95 to 2.20; AUC, 0.66; $P = 0.082$; FDR, 0.092).

FGF23 Ratio. A two-fold increase in the FGF23 ratio (at 6 h after CPB) was associated with 1.71 greater predicted odds of developing in-hospital AKI after CBP surgery (OR, 1.718; 95% CI, 1.27 to 2.31; AUC, 0.71; $P = 0.0004$; FDR, 0.0012; fig. 4). The association remained statistically significant after adjusting for the covariates in model 1 (adjusted OR, 1.56; 95% CI, 1.13 to 2.15; AUC, 0.80; $P = 0.006$; FDR, 0.009) and the Cleveland Clinic score in model 2 (adjusted OR, 1.65; 95% CI, 1.23 to 2.23; AUC, 0.72; $P = 0.0009$; FDR, 0.002). Figure 5 shows the plot of each FGF23 biomarker against the FGF23 ratio.

Discussion

In this prospective cohort study of adult cardiac surgery patients, we determined that postoperative cFGF23 and iFGF23 measured 6 h after CPB were significantly associated with all-stage in-hospital AKI after cardiac surgery, but only cFGF23 remained statistically significant after adjusting for clinical covariates. The ratio of cFGF23/iFGF23 was examined to evaluate the relative effect of the two biomarkers on postoperative in-hospital AKI. While the FGF23 ratio was associated with all-stage in-hospital AKI, the scatter plot (fig. 5) of each FGF23 biomarker against the FGF23 ratio revealed that cFGF23 was the main contributor. Our

Table 2. Logistic Regression Results of the Relationship of the Clinical Variables (Covariates) and Postoperative 6 h Biomarker Levels (Independent Variables) with the Development of Postoperative In-hospital AKI (Dependent Variable)

Clinical Variables	Odds Ratio (95% CI)	AUC (95% CI)	*P* Value	FDR
Clinical model 1		0.78 (0.71–0.87)		
Age, yr	1.01 (0.97–1.05)		0.571	
Sex (male *vs.* female)	1.75 (0.58–5.28)		0.317	
Preoperative eGFR, ml · min^{-1} · 1.73 m^{-2}	0.99 (0.98–1.03)		0.559	
Preoperative LVEF, %	0.96 (0.93–0.99)		0.036	
BMI, kg/m^2	1.09 (1.02–1.16)		0.007	
History of CKD, %	3.68 (0.79–16.92)		0.098	
CPB time, min	1.01 (0.99–1.02)		0.078	
Clinical model 2		0.60 (0.48–0.71)		
Cleveland Clinic score	1.21 (0.99–1.47)		0.056	
Biomarkers alone in Separate Models (6 h after CPB)				
iFGF23 (ln pg/ml)	1.59 (1.08–2.35)	0.67 (0.57–0.76)	0.018	0.0231
cFGF23 (ln RU/ml)	1.57 (1.26–1.96)	0.73 (0.63–0.83)	< 0.0001	0.0009
ln FGF23 ratio	1.71 (1.27–2.31)	0.71 (0.60–0.81)	0.0004	0.0012
Biomarkers in separate models adjusted by the covariates in clinical model 1				
iFGF23 (ln pg/ml)	1.29 (0.84–2.01)	0.79 (0.71–0.87)	0.243	0.243
cFGF23 (ln RU/ml)	1.40 (1.10–1.77)	0.81 (0.73–0.89)	0.006	0.009
ln FGF23 ratio	1.56 (1.13–2.15)	0.80 (0.72–0.89)	0.006	0.009
Biomarkers in separate models adjusted by the covariate in clinical model 2				
iFGF23 (ln pg/ml)	1.45 (0.95–2.20)	0.66 (0.56–0.77)	0.082	0.0923
cFGF23 (ln RU/ml)	1.54 (1.22–1.95)	0.73 (0.63–0.84)	0.0003	0.0012
ln FGF23 ratio	1.65 (1.23–2.23)	0.72 (0.62–0.83)	0.0009	0.002

Clinical model 1 consisted of six preoperative and one intraoperative clinical variables that emerged from the LASSO-penalized variable selection algorithm, with the Bayesian information criterion, in the context of a multiple logistic regression model for the outcome of AKI. Clinical model 2 consisted of the Cleveland Clinic score, which is a preoperative risk score for predicting AKI after cardiac surgery. Biomarker data were transformed using the ln, and the odds ratios associated with AKI were expressed to correspond to a 2-fold increase in the biomarker level. The FDR procedure was used to control false positives over the multiple tests.

AKI, acute kidney injury; AUC, area under the receiver operating characteristic curve; BMI, body mass index; cFGF23, C-terminal FGF23; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; FDR, false discovery rate; FGF23 ratio, C-terminal/intact; eGFR, estimated glomerular filtration rate (ml · min^{-1} · 1.73 m^{-2}); iFGF23, intact FGF23; ln, natural log; LVEF, left ventricular ejection fraction (%); *P*, raw two-tailed *P* value; RU, relative units.

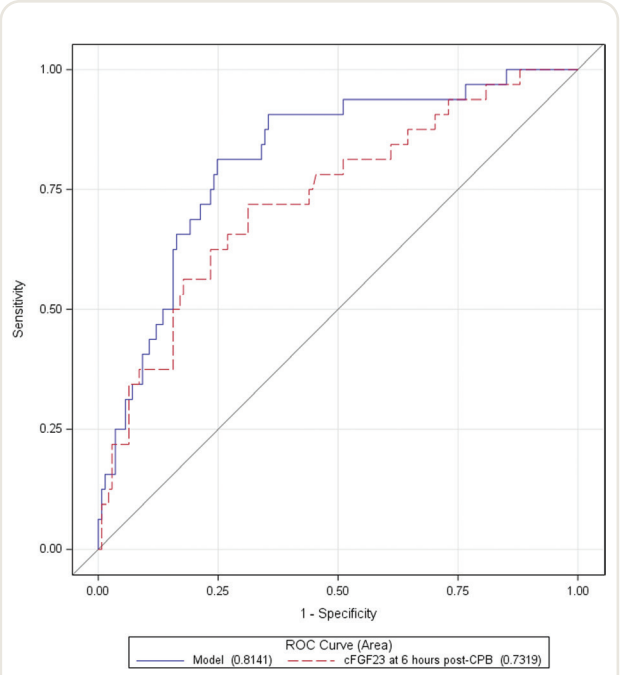


Fig. 2. Receiver operating characteristic (ROC) curves for C-terminal fibroblast growth factor 23 (cFGF23). The *red curve* is from the model that only included cFGF23 6 h after cardiopulmonary bypass (area under the ROC curve [AUC] = 0.7319), while the *blue curve* ("Model") is from the full covariate-adjusted model that included cFGF23, age, sex, preoperative estimated glomerular filtration rate, preoperative left ventricular ejection fraction, body mass index, history of chronic kidney disease, and cardiopulmonary bypass (CPB) time (AUC = 0.8141). Pairwise comparison of these two ROC curves revealed that the cFGF23-only model was significantly different from the full covariate-adjusted model ($P = 0.010$).

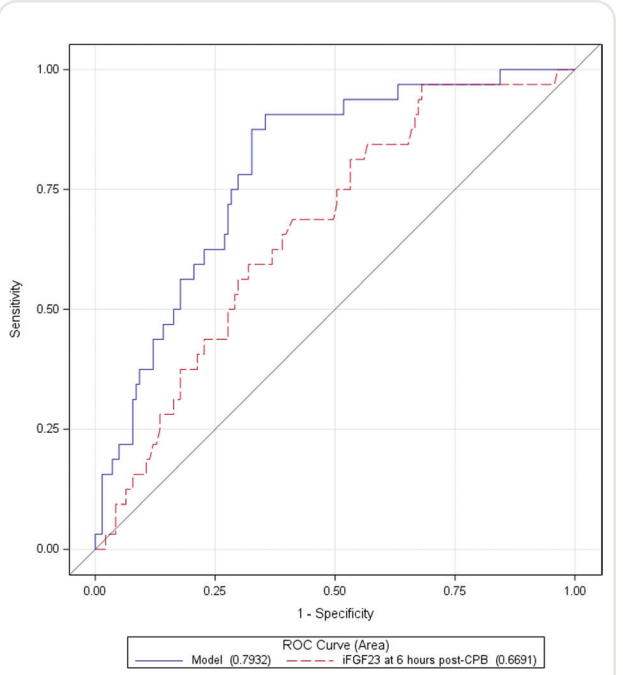


Fig. 3. Receiver operating characteristic (ROC) curves for iFGF23. The *red curve* is from the model that only included iFGF23 6 h after cardiopulmonary bypass (area under the ROC curve [AUC] = 0.6691), while the *blue curve* (model) is from the full covariate-adjusted model that included iFGF23, age, sex, preoperative estimated glomerular filtration rate, preoperative left ventricular ejection fraction, body mass index, history of chronic kidney disease, and cardiopulmonary bypass (CPB) time (AUC = 0.7932). Pairwise comparison of these two ROC curves revealed that the iFGF23-only model was significantly different from the full covariate-adjusted model ($P = 0.015$).

study also tested the predictive accuracy of cFGF23 and iFGF23 concentrations and found that cFGF23 had better performance in discriminating between patients who developed in-hospital postoperative AKI *versus* those who did not develop in-hospital postoperative AKI (AUC = 0.73). Adjusting cFGF23 for covariates including demographics, comorbidities, and CPB time improved the predictive performance of the model. While our study focused primarily on the unadjusted association between FGF23 biomarkers and the AKI outcome, the adjusted results suggest that cFGF23 can be integrated with clinical variables to enhance AKI detection.

FGF23 is produced by osteoblasts and osteoclasts and functions as an important regulator of mineral homeostasis. Intact FGF23, which is biologically active, can be cleaved into its N-terminal and C-terminal fragments. cFGF23 is not biologically active but acts as a competitive antagonist of iFGF23, and its generation may be inhibited by higher circulating concentrations of plasma iFGF23.[34] Previous observational studies performed in adult[20] and pediatric patients[19,21] undergoing cardiac surgery found that increased preoperative cFGF23 level was associated with postoperative AKI. cFGF23 may have been a marker of preoperative inflammation or subclinical kidney dysfunction in these studies. Early post-CPB concentrations of cFGF23 were also found to predict postoperative AKI. Leaf *et al.*[22] measured cFGF23 preoperatively, at the end of CPB, and on PODs 1 and 3 and found that post-CPB and POD 1 cFGF23 concentrations were significantly associated with in-hospital postoperative AKI, even when adjusted for age, preoperative glomerular filtration rate, and CPB time. Their study also matched 18 patients who developed severe AKI with 18 patients who did not develop AKI in a nested case-control analysis and found significantly higher levels of iFGF23 in the severe AKI group. The results of our study confirmed the finding that early post-CPB measurements of cFGF23 are associated with all-stage AKI after cardiac surgery. We expanded on the study by Leaf *et al.*[22] by also examining iFGF23 in our entire cohort rather than a subgroup of patients who developed severe AKI. Our study findings suggest that both iFGF23 and cFGF23 measured 6 h after CPB are associated with all-stage in-hospital AKI after cardiac surgery. We found that cFGF23 had the better

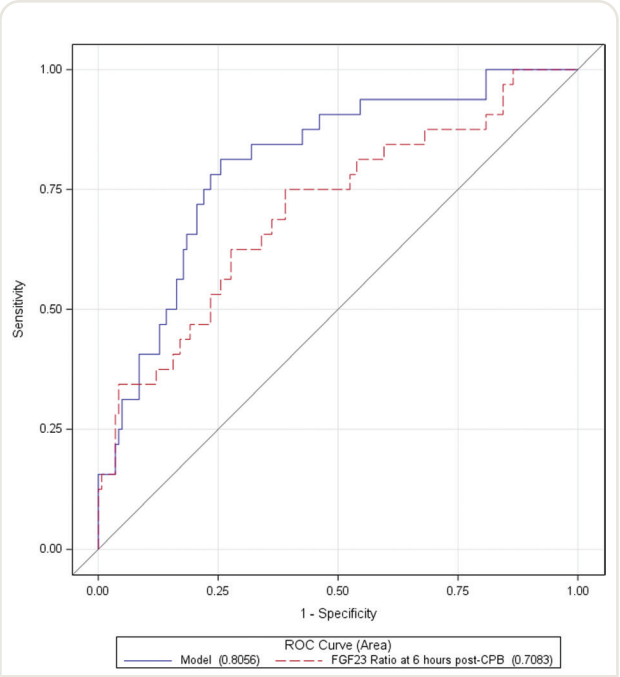


Fig. 4. Receiver operating characteristic (ROC) curves for FGF23 ratio. The *red curve* is from the model that only included FGF23 ratio 6 h after cardiopulmonary bypass (area under the ROC curve [AUC] = 0.7083), while the *blue curve* (model) is from the full covariate-adjusted model that included FGF23 ratio, age, sex, preoperative estimated glomerular filtration rate, preoperative left ventricular ejection fraction, body mass index, history of chronic kidney disease, and cardiopulmonary bypass (CPB) time (AUC = 0.8056). Pairwise comparison of these two ROC curves revealed that the FGF23 ratio-only model was significantly different from the full covariate-adjusted model ($P = 0.008$).

predictive value (AUC) for AKI compared to iFGF23 and the cFGF23/iFGF23 ratio.

Our study supports the role of FGF23 as an early biomarker of post–cardiac surgery AKI, with a median time of biomarker measurement 28 h before diagnosis of AKI using KDIGO serum creatinine criteria. Other biomarkers that have been investigated as early predictors of post–cardiac surgery AKI include plasma and urine neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, interleukin-18 (IL-18), tissue inhibitor of metalloproteinase 2 (TIMP-2), and insulin-like growth factor-binding protein-7 (IGFBP-7). Among these, urine and plasma NGAL is effective in predicting AKI in children and adults without CKD but is less predictive in adults with CKD.[35] Cystatin C and IL-18 have been found to have lower predictive value for early AKI in some studies of cardiac surgery patients.[36,37] TIMP-2*IGFBP-7 has been found to be predictive of moderate to severe AKI[38,39] but less effective in predicting mild AKI.[40,41] This suggests a critical gap in prediction because even mild AKI is associated with long-term adverse outcomes.[42] The diagnostic performance of our biomarkers (AUC, 0.69 to 0.73) was similar to that of other biomarkers for detection of AKI including urine TIMP-2*IGFBP-7 (AUC, 0.66),[43] urine NGAL (AUC, 0.71),[43] plasma NGAL (AUC, 0.71),[37] urine IL-18 (AUC, 0.66),[37] urine cystatin C (AUC, 0.71),[37] and plasma cystatin C (AUC, 0.63).[37] Each of these pooled AUCs were derived from meta-analyses of cardiac surgery studies that measured biomarkers during the intraoperative or early postoperative timepoints and evaluated all-stage in-hospital postoperative AKI.

The results of our study with FGF23 biomarkers suggest that they have the potential to identify patients at risk for all-stage AKI early and with competitive performance compared to other biomarker candidates. This may enable the implementation of therapies to reduce the severity and progression of AKI. Preoperative and intraoperative therapies that have been shown to reduce the incidence of post–cardiac surgery AKI such as amino acid infusions,[44] goal-directed oxygen delivery,[45] and the KDIGO bundle of care[41,46] can be tested early in the postoperative period in high-risk patients identified using FGF23.

Our study was limited by its single-center and observational design. Larger studies are warranted to evaluate the performance of iFGF23 and cFGF23 in the prediction of each stage of AKI individually and to develop cut points for clinical use. Reduced binding of FGF23 to α-klotho may also explain the increased plasma concentration of FGF23 in patients with AKI.[14] The interplay between FGF23 and α-klotho in post–cardiac surgery AKI should be investigated in further studies.

In conclusion, both intact and C-terminal FGF23, when used separately, are early predictors of in-hospital AKI in cardiac surgery patients. While the empiric numerical ratio of cFGF23/iFGF23 is also associated with the AKI outcome, the relationship is primarily driven by cFGF23. Further research is necessary to determine the biologic mechanism associating FGF23 with post–cardiac surgery AKI and to determine the utility of FGF23 in the risk classification and management of post–cardiac surgery AKI.

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Competing Interests

Dr. Neyra has consulted for Vantive (Santa Clara, California) and CovarsaDx (Downey, California). Dr. Jessen is a shareholder in United Health Products, Inc. (Mt. Laurel, New Jersey); Palantir Technologies, Inc. (Denver, Colorado); Cerebras Systems, Inc. (Sunnyvale, California); Applied Materials, Inc. (Santa Clara, California); Advanced Micro Devices, Inc. (Santa Clara, California); and Allogene Therapeutics, Inc. (San Francisco, California). Dr. Moe is an unpaid advisor to Epok Therapeutics (Toronto, Canada). Dr. Fox is a member of the University of Michigan Frenkle

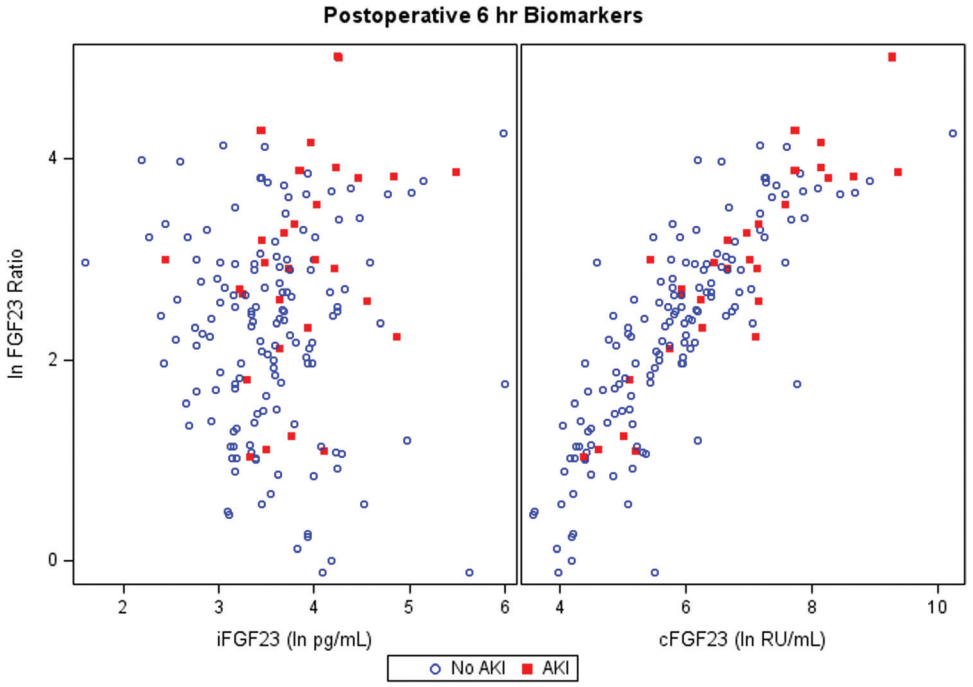


Fig. 5. Plot of each FGF23 biomarker against the FGF23 ratio. The biomarkers and the ratio were transformed using the natural log (ln). AKI, acute kidney injury.

National Advisory Board (Ann Arbor, Michigan). The other authors declare no competing interests.

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ANESTHESIOLOGY®

Analgesic Benefits of Motor-sparing Fascial Plane Blocks in Comparison to Periarticular Local Infiltration Analgesia for Total Hip Arthroplasty: A Network Meta-analysis

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ABSTRACT

Background: Periarticular local infiltration analgesia has become an important mainstay of multimodal analgesia after elective total hip arthroplasty (THA). However, the role of novel motor-sparing fascial plane blocks—with or without periarticular local infiltration analgesia—has not been fully elucidated for patients undergoing THA. The authors conducted a network meta-analysis evaluating the relative analgesic effectiveness of motor-sparing fascial plane blocks (quadratus lumborum, erector spinae, and pericapsular nerve group blocks) and periarticular local infiltration analgesia for adult patients undergoing THA.

Methods: Randomized trials examining single-injection quadratus lumborum, erector spinae, or pericapsular nerve group blocks, or periarticular local infiltration analgesia, for THA were sought. The primary outcome was area under the curve (AUC) rest pain scores during the period from 0 to 24 h. Secondary outcomes included rest pain scores at 0, 6, 12, and 24 h; postoperative function at 6, 12, and 24 h; analgesic consumption at 0 to 24 h; incidence of opioid-related side effects; and incidence of block-related complications. Network meta-analysis was performed using a frequentist approach.

Results: A total of 44 trials (3,579 patients) evaluating the quadratus lumborum block, erector spinae block, pericapsular nerve group block, or periarticular local infiltration analgesia for THA were considered. Network meta-analysis was used to derive the probability of each intervention being the most effective as compared to the others (P score). For AUC 0 to 24 h rest pain, periarticular local infiltration analgesia was the most effective intervention, as demonstrated by a P score of 89%. For postoperative analgesic consumption, the quadratus lumborum block was the most effective intervention, with a P score of 88%. This was followed by the pericapsular nerve group block (74%), the erector spinae block (38%), and periarticular local infiltration analgesia (42%).

Conclusions: Periarticular local infiltration analgesia alone provides the most consistent improvements in postoperative rest pain, analgesic consumption, and functional recovery after THA. The addition of a quadratus lumborum block or pericapsular nerve group block to periarticular local infiltration may further improve analgesic outcomes.

(ANESTHESIOLOGY 2025; 143:604–24)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Periarticular local infiltration analgesia has become an important mainstay of multimodal analgesia after elective total hip arthroplasty.
- The benefit of novel motor-sparing fascial plane blocks, in both the presence and the absence of surgical local anesthetic infiltration, is unclear.

What This Article Tells Us That Is New

- This network meta-analysis included 44 trials to compare the relative analgesic effectiveness of ultrasound-guided, motor-sparing fascial plane blocks (quadratus lumborum [n = 259], erector spinae [n = 111], and pericapsular nerve group blocks [n = 683]) and periarticular local infiltration analgesia (n = 1,010) for adult patients undergoing total hip arthroplasty.
- For pain at rest during the first 24 h, local infiltration had the highest likelihood of benefit (P score, 89%), followed by quadratus lumborum (75%) and lower scores for erector spinae (32%), pericapsular nerve group blocks (26%), and control (28%).
- When combined with local infiltration, both quadratus lumborum (93%) and pericapsular nerve group block (89%) had high P scores, indicating a higher likelihood of benefit over local infiltration alone (60%).
- Local infiltration analgesia alone provides the most consistent improvements in analgesic and functional outcomes after total hip arthroplasty. Adding quadratus lumborum or pericapsular nerve group block to local infiltration may further improve analgesic outcomes.

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Abbreviations: **AUC**, area under the curve; **GRADE**, Grading of Recommendations, Assessment, Development and Evaluation; **OR**, odds ratio; **SMD**, standard mean difference; **THA**, total hip arthroplasty; **VAS**, visual analog scale

Total hip arthroplasty (THA) is one of the most common and successful orthopedic procedures[1] performed. Local anesthetic-based regional anesthesia techniques can enhance early mobilization, decrease hospital time, and improve satisfaction after THA.[2] While periarticular local infiltration analgesia is an important mainstay of multimodal analgesia,[3] the role of novel motor-sparing fascial plane blocks, including the pericapsular nerve group block,[4] erector spinae plane block,[5] and the quadratus lumborum block[6]—with or without periarticular local infiltration—has not been fully elucidated for patients undergoing THA. Although the analgesic effectiveness of these fascial plane blocks has been assessed in isolation compared to control (*i.e.*, unimodal or multimodal analgesia), their effectiveness relative to each other and to periarticular local infiltration remains unclear, precluding the standardization of a regional anesthesia regimen for THA.

The aim of this network meta-analysis was to further evaluate the comparative analgesic effectiveness (pain and opioid consumption) of motor-sparing fascial plane blocks, periarticular local infiltration analgesia, and parenteral analgesic alone in adult patients undergoing THA. Our secondary aim was to assess the impact of each approach on postoperative function and the incidence of opioid related side effects. Finally, we also aimed to assess the incremental impact of adding a motor-sparing fascial plane block to preexisting periarticular local infiltration analgesia for THA. A frequentist approach was used for the network meta-analysis, and P scores for being the most effective intervention were calculated.

Materials and Methods

The authors prepared the manuscript in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines[7] and its extension statement for network meta-analyses.[8] The protocol for this network meta-analysis was registered with the International Prospective Register of Systematic Reviews under the identification No. CRD42024564145. We specifically sought studies evaluating the analgesic efficacy of motor-sparing fascial plane blocks for adult patients undergoing THA. There were no protocol deviations or amendments made to the protocol after registration.

Eligibility Criteria

We sought randomized trials that evaluated the analgesic effectiveness of single-injection motor-sparing fascial plane blocks or periarticular local infiltration analgesia in adult patients undergoing unilateral or bilateral primary THA. The motor-sparing fascial plane blocks considered for this network meta-analysis included the pericapsular nerve group block, erector spinae plane block, and quadratus lumborum block. We also considered those studies where periarticular local infiltration analgesia was performed by the surgeon. With the increasing popularity of anterior hip arthroplasty, ambulatory THA, and favorable pain trajectories, we chose to focus on single-injection techniques; studies that used continuous catheter-based nerve block techniques were excluded. No restriction was placed on the type of local anesthetic and solution used for the motor-sparing fascial plane block and periarticular local infiltration analgesia, respectively. We did not include trials investigating regional anesthetic modalities for minor hip surgeries, including hemiarthroplasty and hip arthroscopy. In regard to anesthetic modality, we considered surgeries performed under general anesthesia or a spinal anesthetic with or without spinal morphine. We included studies that performed an epidural only if it was *not* continued for postoperative analgesia. We excluded all studies of volunteers, dose-ranging studies, or those without an intervention/comparator being either (1) a motor-sparing fascial plane block or (2) periarticular local infiltration analgesia. No language restriction was placed on study inclusion, and all non-English trials were translated using an online translator.

Search Strategy

A search strategy was developed by an evidence-based medicine librarian with experience in systematic reviews

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and meta-analyses (T.S.) for the following databases from inception until January 9, 2024: U.S. National Library of Medicine Database (MEDLINE) and Excerpta Medica Database (EMBASE). The search strategies were developed using a variety of Boolean phrases, keywords, and subject headings related to the regional anesthetic approaches of interest. The full search strategies for the databases can be viewed in Supplemental Digital Content A (https://links.lww.com/ALN/E59). We also screened all the reference lists of all potentially eligible trials and previous direct meta-analyses for additional citations that satisfied the inclusion criteria. Citations published as abstracts were included in this network meta-analysis only if their full data were made available by the corresponding author. We included only indexed citations in this network meta-analysis; indexed abstract presentations were considered only if the full data were made available by the corresponding author.

Selection of Included Studies

Two authors (N.H. and A.T.F.) independently screened the initial results generated by the search strategy based on title and abstract alone. After this, any potentially eligible citation had their full-text version retrieved for screening by the same two independent reviewers. In the case of disagreement between the two reviewers on full-text eligibility, a discussion was initiated until a consensus was reached. If a consensus could not be reached after a discussion, a third reviewer (F.W.A.) assessed the full-text trial and made the final decision.

Data Extraction

A data extraction form was created in Microsoft Excel (USA) by a coauthor (N.H.) and piloted and validated by a second coauthor (A.T.F.). Data extraction was then carried out by a coauthor (N.H.) and validated by another coauthor (A.T.F.). Any discrepancies in data extraction resulted in a discussion until a consensus was reached. If a consensus could not be reached, then a third author (F.W.A.) assessed the data point in question and made the final decision. The data extraction form collected information regarding the following variables: type of surgery; primary outcome of study; regional anesthetic technique performed and block technique; medications used for periarticular local infiltration analgesia; type of surgical anesthetic used (general or spinal anesthesia); inclusion of spinal morphine; preoperative, intraoperative, and postoperative analgesic modalities; rest pain scores for all time points up until 24 h with measures of variance; analgesic consumption for all time points up until 24 h with measures of variance; postoperative function at 6 h, 12 h, and 24 h with tools used for measurement and measures of variance; opioid related side effects; and block-related adverse events. The primary sources of data were tables and in-text reported values; for data reported in purely graphical form, extraction was performed using graph-digitizing software (Engauge Digitizer version 12.1, USA).

Risk of Bias Assessment

The methodologic quality of all included trials was assessed using the Cochrane Collaboration Risk of Bias 2.0 tool.[9] Each study was evaluated using a set of predefined domains related to bias due to deviations from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain was rated as having a low risk, some concern, or high risk of bias. The overall risk of bias was also classified. Specifically, a trial was rated as having a high risk of bias if any one domain had a high-risk bias, or some concerns of bias if at least two domains had an unclear risk of bias.

Certainty of Evidence Assessment

The strength of evidence for all statistically pooled outcomes was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group guidelines.[10] Each outcome was evaluated using a set of predefined domains related to study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence within the network estimates. The certainty of evidence was rated as being of high certainty, moderate certainty, low certainty, or very low certainty. We additionally used a partially contextualized approach to assess the quality of the primary outcome based on P score rankings.[11] For this, evidence was downgraded if any discrepancies existed between the magnitude of the effect size and P score ranking.

Primary and Secondary Outcomes

The primary outcome of this network meta-analysis was the area of the curve rest pain scores between 0 to 24 h for the network comparison of the motor-sparing fascial plane blocks, periarticular local infiltration analgesia, and control (*i.e.*, parenteral analgesia). The secondary outcomes of this meta-analysis included postoperative analgesic consumption in milligrams of oral morphine during the period from 0 to 24 h; postoperative function at 6, 12, and 24 h; incidence of postoperative opioid related side effects (*i.e.*, nausea or vomiting and pruritus); and incidence of block-related complications.

Measurement of Outcome Data

To improve interpretability, all rest pain severity data were converted to an equivalent score on the 0- to 10-cm visual analog scale score, with 0 cm representing no pain and 10 cm representing the worst pain imaginable.[12] All analgesic consumption data were converted milligrams of oral morphine. For postoperative functional recovery, based on

previous work,[6] we anticipated that a wide variety of instruments and tools would be used for functional assessment. As such, we statistically pooled data based whether continuous, dichotomous, or both types of data were reported.

Statistical Analysis

For all continuous data, we sought the mean ± SD. If these data were not available, then statistical conversions were made to derive the mean and SD using available data (*i.e.*, median and interquartile range).[13] For instances where a median was reported and sufficient data were not available for conversion to a mean, the median was used to approximate this value, and the SD was inputted using data from the included trials.

For all rest pain data, when data were presented at time points *different* from our prespecified time points (0, 6, 12, and 24 h), we included these data if they differed by only 2 h (*i.e.*, 10-h time point included in 12-h time point). For the AUC analysis, we included only those studies that included rest pain score data for all time points (0, 6, 12, and 24 h). To conduct this analysis, three time intervals were considered, namely, 0 to 6 h, 6 to 12 h, and 12 to 24 h. The AUC for each study was then calculated using the trapezoid method with associated variance.[14] The units for this analysis was centimeters per hour.

Postoperative function data were pooled according to our previous methods since we expected differences in reporting and instruments used for assessment.[6] As such, we planned to report (1) the standardized mean difference if all trials used a continuous scale that measured the same theme; (2) a log[odds ratio (OR)] if a variation of continuous and dichotomous outcomes was reported that measured the same theme; or (3) an OR if all trials reported dichotomous outcomes measuring the same theme. For instances in which a log[OR] was calculated, this was done for trials reporting a continuous functional outcome using the formula log[OR] = standardized mean difference ($\pi / \sqrt{3}$).[15,16]

Network Meta-analysis

We performed a network-analysis for primary and secondary outcomes using a frequentist approach and a random effects method.[17,18] We assumed an equal variance for all comparisons.[17,18] Each node within the network corresponded to an intervention/comparator, and any regional anesthetic technique that was not attached to any other node in the network was excluded from analysis. Due to the risk of imprecision, we also excluded those direct comparisons with only one study investigating their use. For continuous variables, we presented the data in the form a league table with a mean difference and 95% CI. For dichotomous variables, we presented the data in a similar format except with an OR and 95% CI. For the presentation of postoperative functional recovery, a league table was also created, but the method for presentation (standardized mean difference *vs.* OR with 95% CI) was dependent on the type of data reported. Finally, per frequentist methods, a P score for each intervention was calculated using point estimates and standard errors.[19] The P score is the probability of an intervention being the best for a specific outcome. The score can range from 0 to 1, with 0 corresponding to a 0% probability of being the best intervention and 1 corresponding to a 100% probability of being the best intervention.[19,20]

Assessment of Inconsistency and Coherence

Inconsistency for all pooled outcomes was assessed through the calculation of Tau and I^2 values. Substantial heterogeneity in the pooled estimate was considered to be present with I^2 values greater than 50%.[21] To evaluate network consistency and incoherence,[22] a node-split forest plot comparing direct and indirect estimates was created for each outcome. Degree of inconsistency was also visually assessed by creating a heat plot for the primary outcome when at least one closed loop was present within the network. Homogeneity was assessed qualitatively by evaluating the equivalence in study characteristics between pairwise comparisons.

When substantial heterogeneity was present in the primary outcome, we conducted additional analyses based on the following covariates: nature of THA (inpatient *vs.* ambulatory); type of postoperative analgesia (multimodal *vs.* unimodal); type of surgical anesthetic (spinal *vs.* general anesthesia); and inclusion of spinal morphine (yes *vs.* no).

Ancillary Analyses

For the primary outcome, we conducted two additional analyses. First, we assessed transitivity by conceptually evaluating the similarity of patients and interventions across the included trials. For this, we specifically assessed the baseline characteristics of patients and block techniques across included trials. Second, we conducted two additional exploratory analyses for the primary outcome. The first exploratory analysis was to assess the incremental benefit of adding a motor-sparing fascial plane block to preexisting periarticular local infiltration analgesia. Since several of the motor-sparing fascial plane blocks are only now gaining popularity, with scant evidence supporting them, we explored the impact of excluding the comparisons with fewer than two trials. The second exploratory analysis was to assess the impact of quadratus lumborum block approach (anterior, posterior, or lateral). For this, based on the available data, we conducted either (1) subgroup analysis based on quadratus lumborum block approach, or (2) sensitivity analysis based on exclusion of a quadratus lumborum block approach if it was only performed by one study.

We created contributions matrices for all outcomes to assess the percentage contribution of each direct estimate

to the network meta-analysis. We also created funnel plots for all outcomes to assess for the risk of small study effects/publication bias.[23]

Interpretation of Results

All outcome data for rest pain severity at individual time points were interpreted in light of the minimal clinically important difference in visual analog scale pain scale score for THA (1.49 cm).[24] The AUC of this minimal clinically important difference was calculated for three-time intervals (0 to 6 h, 6 to 12 h, and 12 to 24 h) and was used for interpretation of our AUC analysis; this threshold is 34.27 cm · h. All postoperative opioid data were interpreted in light of a minimal clinically important difference of 30 mg oral morphine.[25]

Data Management

Forest and funnel plots were generated using the "netmeta" package for R software (version 2.9-0, R Core Team, Vienna, Austria).[26] Risk of bias plots were created using the *robvis* tool. GRADE tables were created using the CINeMA tool.[27]

Results

The initial search strategy identified a total of 624 citations. Of these, 567 were excluded based on title and abstract alone. The remaining 57 citations had their full-text versions retrieved for review. After full-text screening, 13 citations were excluded due to having an illegible (1) study intervention/comparator,[28–35] (2) study design,[36,37] or (3) patient population.[38–40] Thus, a total of 44 randomized trials[4,5,41–82] were included in the network meta-analysis. The full flow diagram for study inclusion can be viewed in figure 1.

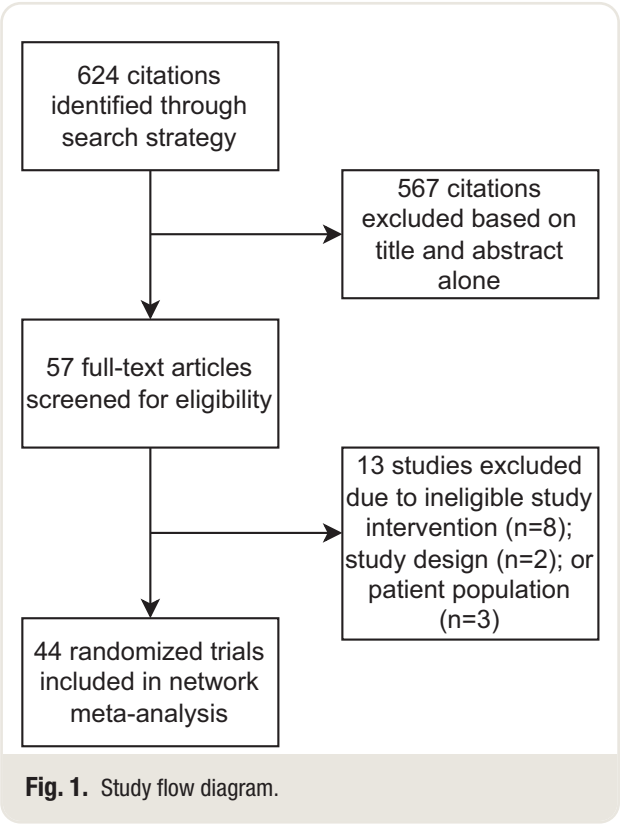


Fig. 1. Study flow diagram.

Study Characteristics

Across all studies, there were a total of 3,579 patients randomized. A total of 19 studies[4,5,42,43,48,52,53,55,62–67,71,74,78–80] performed THA under general anesthesia, whereas 24 studies[41,45–47,49–51,54,56–61,68–70,72,73,75–77,81,82] performed a spinal anesthetic; 1 study[44] utilized both approaches. For those that performed spinal anesthesia, only one study[56] included spinal morphine in their local anesthetic solution. A total of 43 studies[4,5,41–73,75–82] performed unilateral THA, whereas 1 study[74] performed bilateral THA with each patient serving as their own control. THA was performed on inpatients in all 44 studies.[4,5,41–82] Postoperative rest pain scores and analgesic consumption within the first 24-h period were assessed by 44[4,5,41–82] and 37 studies,[4,5,41–46,48,49,51,53–56,58–73,75,77,78,80–82] respectively. Postoperative function was assessed by 31 studies.[4,5,42–55,57,59,61,63,66–68,72,75–79,81] The outcomes assessed by all included trials can be viewed in table 1.

In regard to regional anesthetic group allocation, 259 patients received quadratus lumborum block, 111 received erector spinae plane block, 683 received pericapsular nerve group block, and 1,010 received periarticular local infiltration analgesia. There was one additional study[52] that randomized patients to receive quadratus lumborum block with periarticular local infiltration (40 patients), one[57] to erector spinae plane block with periarticular local infiltration (40 patients), and two[4,77] to pericapsular nerve group block with periarticular local infiltration (75 patients). In regard to quadratus lumborum block approach, seven studies used an anterior approach,[42,51,52,60,68,79,81] and one study used a posterior approach.[67] All motor-sparing fascial plane blocks were performed with ultrasound guidance, and the block techniques can be viewed in table 2. Broadly, the local anesthetic volume varied from 20 to 40 ml, and four studies[46,51,76,79] included additives in their block solution, including epinephrine, dexmedetomidine, or dexamethasone. For periarticular local infiltration analgesia, 10 studies used local anesthetic alone,[4,52,55,57,61,63,64,68,69,82] whereas 17 studies[41,44,46,48–50,56,66,70–77,80] had a solution of other analgesic or adjunct agents alongside the local anesthetic.

The pre- and postoperative analgesic strategies employed by the trials can be viewed in table 3. Preoperative analgesia was provided by 22 studies.[4,41,43,45,47,49,51,52,54,57,62–64,68–70,72,75,76,79,80,82] The vast majority of studies employed a multimodal analgesic strategy in the postoperative phase[4,5,41,43–61,63–70,72,73,75–80,82]; however, five studies[42,62,71,74,81] used a unimodal approach.

Table 1. Outcomes Assessed by Included Studies

First Author, Year	Interventions (n)	Sample Size (n)	Anesthetic Modality	Rest Pain		Analgesic Consumption		Functional Recovery	Opioid-related Side Effects
				Early	Late	Early	Late		
Abduallah, 2020[60]	1. Quadratus lumborum block (30) 2. Control (30)	60	Spinal	•		•			•
Amato, 2022[62]	1. Pericapsular nerve group block (34) 2. Control (34)	68	General	•	•	•	•		•
Bernaus, 2022[82]	1. Periarticular local infiltration analgesia (32) 2. Control (31)	63	Spinal	•	•	•	•		
Bravo, 2023[46]	1. Pericapsular nerve group block (30) 2. Periarticular local infiltration analgesia (30)	60	Spinal	•	•	•	•	•	•
Brixel, 2021[67]	1. Quadratus lumborum block (50) 2. Control (50)	100	General	•		•		•	•
Busch, 2010[44]	1. Periarticular local infiltration analgesia (32) 2. Control (32)	64	Spinal or general	•	•	•		•	
Chan, 2022[5]	1. Erector spinae plane block (36) 2. Control (35)	71	General	•		•		•	•
Chung, 2022[43]	1. Pericapsular nerve group block (36) 2. Control (36)	56	General	•		•		•	•
den Hartog, 2015[73]*	1. Periarticular local infiltration analgesia (50) 2. Control (25)	75	Spinal	•	•	•	•		•
Dobie, 2012[50]	1. Periarticular local infiltration analgesia (50) 2. Control (46)	96	Spinal	•				•	
Domagalska, 2023[59]	1. Pericapsular nerve group block (245) 2. Control (244)	489	Spinal	•	•	•	•	•	
Et, 2023[68]	1. Pericapsular nerve group block (30) 2. Quadratus lumborum block (30) 3. Periarticular local infiltration analgesia (30)	90	Spinal	•	•	•	•	•	•
He, 2020[51]	1. Quadratus lumborum block (44) 2. Control (44)	88	Spinal	•	•	•	•	•	•
Hirasawa, 2018[74]†	1. Periarticular local infiltration analgesia (40) 2. Control (40)	40	General	•	•				
Hofstad, 2015[75]	1. Periarticular local infiltration analgesia (58) 2. Control (58)	116	Spinal	•		•		•	
Hu, 2021[52]	1. Quadratus lumborum block with periarticular local infiltration analgesia (40) 2. Periarticular local infiltration analgesia (40)	80	General	•	•		•	•	•
Hu, 2023[4]	1. Pericapsular nerve group block with periarticular local infiltration analgesia (45) 2. Periarticular local infiltration analgesia (45)	90	General	•	•	•	•	•	•
Iglesias, 2023[76]	1. Lumbar plexus block (20) 2. Pericapsular nerve group block (20) 3. Periarticular local infiltration analgesia (20)	60	Spinal	•	•		•	•	•
Kukreja, 2023[54]	1. Pericapsular nerve group block (61) 2. Control (61)	122	Spinal	•	•	•	•	•	•
Lennon, 2021[57]	1. Erector spinae plane block with periarticular local infiltration analgesia (32) 2. Periarticular local infiltration analgesia (32)	64	Spinal	•				•	
Lin, 2022[77]	1. Pericapsular nerve group block with periarticular local infiltration analgesia (30) 2. Periarticular local infiltration analgesia (30)	60	Spinal	•		•	•	•	
Liu, 2011[72]	1. Periarticular local infiltration analgesia (41) 2. Control (41)	82	Spinal	•	•	•	•	•	•
Lunn, 2011[70]	1. Periarticular local infiltration analgesia (60) 2. Control (60)	120	Spinal	•		•			
Manuwong, 2019[81]	1. Quadratus lumborum block (20) 2. Control (20)	40	Spinal	•		•		•	•
Medhat, 2023[58]	1. Pericapsular nerve group block (23) 2. Erector spinae plane block (23) 3. Control (23)	69	Spinal	•		•			•
Mostafa, 2023[78]	1. Pericapsular nerve group block (25) 2. Control (25)	50	General	•		•		•	

(*Continued*)

Table 1. (Continued)

First Author, Year	Interventions (n)	Sample Size (n)	Anesthetic Modality	Rest Pain		Analgesic Consumption		Functional Recovery	Opioid-related Side Effects
				Early	Late	Early	Late		
Murphy, 2012[69]	1. Periarticular local infiltration analgesia (45) 2. Control (46)	91	Spinal	•	•	•	•		•
Nakai, 2013[71]	1. Periarticular local infiltration analgesia (28) 2. Control (26)	54	General	•		•			•
Pandazi, 2013[41]	1. Periarticular local infiltration analgesia (21) 2. Epidural (21) 2. Control (21)	63	Spinal	•		•			•
Parvataneni, 2007[49]	1. Periarticular local infiltration analgesia (35) 2. Control (26)	71	Spinal	•	•	•		•	•
Pascarella, 2021[47]	1. Pericapsular nerve group block (30) 2. Control (30)	60	Spinal	•	•		•	•	•
Solovyova, 2013[80]	1. Periarticular local infiltration analgesia (35) 2. Periarticular local infiltration analgesia with catheter (35) 2. Control (35)	105	General	•	•	•	•		•
Tan, 2019[61]	1. Periarticular local infiltration analgesia (75) 2. Control (79)	154	Spinal	•		•	•	•	
Titman, 2018[64]	1. Periarticular local infiltration analgesia (20) 2. Control (20)	40	General	•		•			
Townsend, 2022[45]	1. Erector spinae plane block (32) 2. Control (31)	63	Spinal	•	•	•	•	•	
Tulgar, 2018[65]	1. Quadratus lumborum block (20) 2. Erector spinae plane block (20) 3. Control (20)	60	General	•		•			•
Villatte, 2016[48]	1. Periarticular local infiltration analgesia (20) 2. Control (20)	40	General	•	•	•	•	•	•
Ruan, 2022[42]	1. Quadratus lumborum block (20) 2. Control (20)	40	General	•		•		•	•
Wang, 2023[79]	1. Quadratus lumborum block (45) 2. Pericapsular nerve group block (45)	90	General	•	•		•	•	•
Xiao, 2021[63]	1. Periarticular local infiltration analgesia (40) 2. Wound infiltration (40) 3. Control (40)	120	General	•	•	•	•	•	•
Ye, 2023[66]	1. Pericapsular nerve group block (40) 2. Periarticular local infiltration analgesia (40)	80	General	•	•	•	•	•	•
Zheng, 2022[56]	1. Pericapsular nerve group block (30) 2. Periarticular local infiltration analgesia (30)	60	Spinal	•		•	•		•
Zheng, 2022b[53]	1. Pericapsular nerve group block (34) 2. Control (36)	70	General	•	•	•	•	•	•
Zoric, 2014[55]	1. Periarticular local infiltration analgesia (31) 2. Control (30)	61	General	•	•	•	•	•	•

Patients presented are the number randomized.

*Study was a three-armed trial with two groups that received different techniques to perform periarticular local infiltration analgesia. †Bilateral total hip arthroplasty performed.

The risk of bias assessment for all included studies can be seen in Supplemental Digital Content B (https://links.lww.com/ALN/E60).

Primary Outcome

Area under the Curve Pain Scores from 0 to 24 h. A total of 18 studies[41,46,48,50,51,54–56,60,63,65–68,72,76,79,81] encompassing 1,355 patients reported rest pain severity scores at 0, 6, 12, and 24 h and were thus included in this outcome. There were 21 pairwise comparisons and 4 regional anesthetic approaches in the analysis, namely quadratus lumborum block, erector spinae plane block, pericapsular nerve group block, and periarticular local infiltration analgesia (fig. 2). Overall, when compared to parenteral analgesia alone (*i.e.*, control), periarticular local infiltration analgesia provided a significant improvement in AUC rest pain during the period from 0 to 24 h by a mean difference (95% CI) of –8.06 cm · h (–14.10 to –2.02; $P = 0.009$; fig. 2); however, this did not surpass the threshold for clinical importance. In contrast, no difference was observed when the quadratus lumborum block, erector spinae plane block, or pericapsular nerve group block was compared to control (fig. 2). Across all regional anesthetic approaches, periarticular local infiltration analgesia was

Table 2. Details of Analgesic Modalities for Included Studies

	Analgesic Modality			
First Author, Year	**Local Infiltration Analgesia**	**Quadratus Lumborum Block**	**Erector Spinae Plane Block**	**Pericapsular Nerve Group Block**
Abduallah, 2020[60]		30 ml 0.25% bupivacaine		
Amato, 2022[62]				20 ml 0.50% bupivacaine
Bernaus, 2022[82]	120 ml 0.20% ropivacaine			
Bravo, 2023[46]	60 ml 0.25% bupivacaine + epinephrine + ketorolac			20 ml 0.50% bupivacaine + epinephrine
Brixel, 2021[67]		30 ml 0.33% ropivacaine		
Busch, 2010[44]	100 ml 400 mg ropivacaine + ketorolac + epinephrine + morphine			
Chan, 2022[5]			40 ml 0.25% levobupivacaine	
Chung, 2022[43]				25 ml 0.50% ropivacaine
den Hartog, 2015[73]	100 ml 0.20% ropivacaine + epinephrine			
Dobie, 2012[50]	120 ml 0.125% levobupivacaine + epinephrine			
Domagalska, 2023[59]				20 ml 0.50% ropivacaine
Et, 2023[68]	30 ml 0.50% bupivacaine	30 ml 0.50% bupivacaine		20 ml 0.50% bupivacaine
He, 2020[51]		20 ml 0.33% ropivacaine + dexmedetomidine + dexamethasone		
Hirasawa, 2018[74]	60 ml solution of 40 ml 0.75% ropivacaine + morphine + methylprednisolone + ketoprofen + epinephrine			
Hofstad, 2015[75]	150 ml 0.20% ropivacaine + epinephrine			
Hu, 2021[52]	30 ml 0.33% ropivacaine	30 ml 0.33% ropivacaine		
Hu, 2023[4]	20–40 ml 0.50% ropivacaine			20 ml 0.50% ropivacaine
Iglesias, 2023[76]	80 ml 0.25% bupivacaine + epinephrine + morphine + ketorolac			20 ml 0.25% bupivacaine + epinephrine
Kukreja, 2023[54]				25 ml 0.50% bupivacaine
Lennon, 2021[57]	100 ml 0.20% ropivacaine		30 ml 0.20% ropivacaine	
Lin, 2022[77]	100 ml 0.10% ropivacaine + epinephrine			20 ml 0.50% bupivacaine
Liu, 2011[72]	60 ml solution of 30 mg bupivacaine + morphine + betamethasone + epinephrine			
Lunn, 2011[70]	150 ml solution of 0.20% ropivacaine + epinephrine			
Manuwong, 2019[81]		N/S		
Medhat, 2023[58]			20 ml 0.25% bupivacaine	20 ml 0.25% bupivacaine
Mostafa, 2023[78]				20 ml 0.25% bupivacaine
Murphy, 2012[69]	60 ml 150 mg levobupivacaine			
Nakai, 2013[71]	30 ml solution of 20 ml 0.50% bupivacaine + morphine + epinephrine			
Pandazi, 2013[41]	100 ml solution of 0.30% ropivacaine + morphine + epinephrine + methylprednisolone + clonidine			
Parvataneni, 2007[49]	0.50% bupivacaine + morphine + epinephrine + methylprednisolone			
Pascarella, 2021[47]				20 ml 0.375% ropivacaine
Solovyova, 2013[80]	50 ml 0.20% ropivacaine + epinephrine + ketorolac			
Tan, 2019[61]	200 ml (maximum) 0.20% ropivacaine			
Titman, 2018[64]	150 ml 0.20% ropivacaine			
Townsend, 2022[45]			30 ml 0.375% ropivacaine	
Tulgar, 2018[65]			20 ml 0.50% bupivacaine + 10 ml 2.00% lidocaine + 10 ml normal saline	20 ml 0.50% bupivacaine + 10 ml 2.00% lidocaine + 10 ml normal saline
Villatte, 2016[48]	100 ml solution containing 235 mg ropivacaine + epinephrine			
Ruan, 2022[42]		30 ml 0.375% ropivacaine		
Wang, 2023[79]		30 ml 0.33% ropivacaine + epinephrine		20 ml 0.50% ropivacaine + epinephrine
Xiao, 2021[63]	80 ml 0.25% ropivacaine			

(*Continued*)

Table 2. (Continued)

First Author, Year	Analgesic Modality: Local Infiltration Analgesia	Quadratus Lumborum Block	Erector Spinae Plane Block	Pericapsular Nerve Group Block
Ye, 2023[66]	30 ml 0.33% ropivacaine + epinephrine			20 ml 0.50% ropivacaine + epinephrine
Zheng, 2022[56]	100 ml solution of 20 ml 0.75% ropivacaine + ketorolac + epinephrine		30 ml 0.50% ropivacaine	
Zheng, 2022b[53]				20 ml 0.50% ropivacaine
Zoric, 2014[55]	80 ml 0.20% ropivacaine			

N/S, not specified.

observed to have the highest P score probability (89%) of being the most effective intervention for improving AUC rest pain during the period from 0 to 24 h. This was followed by the quadratus lumborum block (75%), erector spinae plane block (32%), and control (28%). The pericapsular nerve group block was found to have the lowest P score probability at 26% (fig. 2). The risk of publication bias was moderate (Supplemental Digital Content C, https://links.lww.com/ALN/E61), and the GRADE quality of evidence ranged from low to moderate across the comparisons (Supplemental Digital Content D, https://links.lww.com/ALN/E62).

This analysis was characterized by inconsistency ($Tau^2 = 61.83$; $I^2 = 95.50\%$). As a result, we conducted additional subgroup/sensitivity analysis based on *a priori* covariates. The hierarchy of P scores did not change when subgroup analysis was performed based on (1) type of surgical anesthetic, with periarticular infiltration analgesia still being the best performing intervention for both general (84%)[48,55,63,65–67,79] and spinal anesthetics (81%)[41,46,50,51,54,56,60,68,72,76,81]; or (2) type of postoperative analgesia, with periarticular infiltration analgesia still being the best performing intervention for both multimodal (83%)[41,46,48,50,51,54–56,60,63,65–68,76,79] and unimodal analgesic (84%)[72,81] strategies. For those studies that performed a spinal anesthetic, exclusion of the one study that used spinal morphine[56] did not change the hierarchal rank, with periarticular infiltration analgesia still being the intervention with greatest probability of being optimal (80%). Subgroup/sensitivity analysis was not performed for type of surgery, since all studies[41,46,48,50,51,54–56,60,63,65–68,72,76,79,81] performed THA on an inpatient basis.

We conducted two additional exploratory analyses. The first exploratory analysis was based on the inclusion of studies that performed a motor-sparing fascial plane block alongside periarticular local infiltration analgesia.[4,52] This was done to better understand the incremental benefit of adding a motor-sparing fascial plane block to preexisting periarticular local infiltration. Two additional studies were included in this analysis that assessed the (1) quadratus lumborum block with periarticular local infiltration analgesia[52] and (2) pericapsular nerve group block with periarticular local infiltration analgesia.[4] The P score probability of being the most effective intervention was higher for those studies that combined periarticular infiltration with either the quadratus lumborum block (93%) or pericapsular nerve group block (89%) than with periarticular local infiltration analgesia alone (60%). The second exploratory analysis was to assess the impact of quadratus lumborum block technique on our results. Exclusion of the single study[67] performing a posterior quadratus lumborum from the analysis did not significantly alter P score probabilities from the primary pooled analysis, with periarticular local infiltration analgesia still having the highest probability (85%) of being the most effective intervention for improving AUC rest pain during the period from 0 to 24 h, followed by the quadratus lumborum block (81%).

Secondary Outcomes

Rest Pain Severity at Individual Time Points. Zero Hours (Postanesthesia Care Unit)

A total of 26 studies[41,46,48,50,51,54–56,58,60,63–68,70–76,79–81] encompassing 1,966 patients reported rest pain severity scores at 0 to 2 h (Supplemental Digital Content E, https://links.lww.com/ALN/E63). There were 32 pairwise comparisons and 4 regional anesthetic approaches in the analysis. Ranked based on P score, periarticular local infiltration analgesia was found to be the most effective intervention for this outcome (80%). This was followed by the erector spinae plane block (73%), quadratus lumborum block (51%), and pericapsular nerve group block (41%). Control was found to have the lowest P score probability at 5%. This analysis was characterized by a high level of inconsistency ($Tau^2 = 0.16$; $I^2 = 79.80\%$); however, the risk of publication bias was low (Supplemental Digital Content C, https://links.lww.com/ALN/E61). The GRADE quality of evidence was ranged from very low to high across the comparisons (Supplemental Digital Content D, https://links.lww.com/ALN/E62).

Table 3. Analgesic Regimens

First Author, Year	Preincisional	Postoperative
Abduallah, 2020[60]	None	Intravenous paracetamol 1,000 mg every 6 h; intravenous morphine 3 mg as needed
Amato, 2022[62]	Oral acetaminophen 975 mg once; oral oxycodone 5 mg once	Oral oxycodone 5 mg or hydromorphone 2 mg as needed; intravenous hydromorphone 0.5 mg as needed
Bernaus, 2022[82]	Oral acetaminophen 1,000 mg once; oral celecoxib 200 mg once	Oral celecoxib 200 mg every 12 h; oral acetaminophen 1,000 mg every 8 h; oral morphic chloride 10 mg as needed
Bravo, 2023[46]	None	Oral acetaminophen 1,000 mg every 6 h; oral ketoprofen 100 mg every 8 h; PCA morphine
Brixel, 2021[67]	None	Intravenous acetaminophen 1,000 mg every 6 h; intravenous ketoprofen 100 mg every 12 h; PCA morphine
Busch, 2010[44]	None	Oral acetaminophen–oxycodone 325–650/5–10 mg; oral acetaminophen 325 mg; PCA morphine
Chan, 2022[5]	None	Oral paracetamol 500–4,000 mg daily; oral ibuprofen 200 to 400 mg daily or oral diclofenac 25 to 100 mg daily; oral tramadol 50 to 200 mg daily; oral gabapentin 100 to 900 mg daily or oral pregabalin 25 to 150 mg daily; PCA fentanyl
Chung, 2022[43]	Oral acetaminophen 1,000 mg once; intravenous ketorolac 30 mg once	Oral acetaminophen 325 mg every 12 h; oral tramadol 37.5 mg every 12 h; PCA fentanyl
den Hartog, 2015[73]	None	Oral paracetamol 1,000 mg every 6 h; oral celecoxib 200 mg daily; oral gabapentin 300 mg daily; oral tramadol 100 mg daily; oral piritramide 10 mg every 4 h as needed
Dobie, 2012[50]	None	Intravenous acetaminophen 1,000 mg every 6 h for 36 h; oral tramadol 100 mg every 4–6 h as needed; oral co-codamol 30–500 mg every 4–6 h as needed; intravenous morphine 10 mg as needed every 4–6 h
Domagalska, 2023[59]	None	Intravenous acetaminophen 1,000 mg every 6 h; intravenous 1,000 mg metamizole every 6 h; intravenous ketorolac 50 mg every 12 h; intravenous morphine 5 mg as needed
Et, 2023[68]	Intravenous paracetamol 1,000 mg once	Intravenous paracetamol 1,000 mg every 8 h; oral diclofenac 50 mg every 8 h; oral oxycodone 5 mg as needed
He, 2020[51]	Intravenous acetaminophen 1,000 mg once	Intravenous parecoxib 40 mg every 12 h for 48 h; oral acetaminophen 500 mg every 6 h until discharge; PCA morphine as needed or oral oxycodone every 12 h as needed
Hirasawa, 2018[74]	None	Oral lornoxicam 4 mg every 8 h; rectal diclofenac 50 mg as needed
Hofstad, 2015[75]	Intravenous acetaminophen 1,000–2,000 mg once	Oral nonsteroidal anti-inflammatory drugs and acetaminophen at regular intervals; oral oxycodone and intravenous morphine as needed
Hu, 2021[52]	Oral loxoprofen 180 mg once; oral nonsteroidal anti-inflammatory drug once	Oral celecoxib 200 mg every 12 h; intravenous morphine 10 mg as needed
Hu, 2023[4]	Oral celecoxib 200 mg every 12 h 1 day before surgery	Oral celecoxib 200 mg every 12 h; intravenous morphine 10 mg as needed
Iglesias, 2023[76]	Oral paracetamol 500 mg every 12 h 1 day before surgery; oral gabapentin 300 mg once	Intravenous paracetamol 500 mg every 8 h; intravenous etoricoxib 60 mg every 12 h; oral gabapentin 300 mg nightly; oral tramadol 50 mg as needed
Kukreja, 2023[54]	Oral paracetamol 1,000 mg once; oral celecoxib 200 mg once	Oral paracetamol; oral celecoxib; oral oxycodone 5 mg as needed; intravenous hydromorphone 1 mg every 6 h as needed
Lennon, 2021[57]	Oral acetaminophen 1,000 mg once; oral pregabalin 75 mg once	Oral tramadol 50 mg once; oral acetaminophen 1,000 mg every 6 h; oral celecoxib 200 mg every 12 h; oral pregabalin 25 mg at night; oral tapentadol 50 mg every 12 h; intravenous tapentadol 50–100 mg as needed; intravenous hydromorphone 2–4 mg as needed
Lin, 2022[77]	None	Oral acetaminophen and nonsteroidal anti-inflammatory drugs; tramadol, oxycodone, or fentanyl as needed
Liu, 2011[72]	Oral celecoxib 200 mg once	Oral celecoxib 200 mg every 12 h; PCA morphine
Lunn, 2011[70]	Oral acetaminophen 2,000 mg once; oral celecoxib 400 mg once; oral gabapentin 600 mg once	Oral acetaminophen 2,000 mg; oral celecoxib 400 mg; oral gabapentin 600 mg; intravenous sufentanil 5 mcg as needed; oral oxycodone 5 mg as needed
Manuwong, 2019[81]	None	PCA morphine
Medhat, 2023[58]	None	Intravenous 1,000 mg paracetamol every 8 h; intravenous 2 mg morphine as needed
Mostafa, 2023[78]	None	Intravenous paracetamol 1,000 mg every 8 h; intravenous morphine 3 mg as needed
Murphy, 2012[69]	Intravenous paracetamol 1,000 mg once; rectal diclofenac 100 mg once	Oral paracetamol 1,000 mg every 6 h; oral diclofenac 75 mg every 12 h; oral oxycontin 10 mg every 12 h; PCA opioid
Nakai, 2013[71]	None	Rectal diclofenac as needed
Pandazi, 2013[41]	Intravenous lornoxicam 8 mg once; intravenous paracetamol 600mg once	Intravenous lornoxicam 8 mg every 12 h; oral paracetamol 500 mg every 6 h; PCA morphine as needed
Parvataneni, 2007[49]	Oral celecoxib 200–400 mg once; oral oxycodone 10–20 mg once	Intramuscular ketorolac 15–30 mg every 6 h as needed; oral celecoxib 200 mg daily; oral oxycodone 10–20 mg every 12 h; oral acetaminophen 1,000 mg every 6 h
Pascarella, 2021[47]	Intravenous acetaminophen 1,000 mg once; intravenous ketorolac 30mg once	Intravenous ketorolac 60 mg every 24 h; intravenous acetaminophen 1,000 mg every 8 h; PCA sufentanil as needed
Solovyova, 2013[80]	Oral celecoxib 200 mg once; oral pregabalin 75 mg once	Oral celecoxib 200 mg every 12 h; oral pregabalin 50 mg every 12 h; oral acetaminophen 975 mg every 6 h; intravenous hydromorphone as needed; PCA hydromorphone
Tan, 2019[61]	None	Oral oxycodone 10–20 mg every 12 h; oral paracetamol 1,330 mg every 8 h; oral meloxicam 15 mg daily; PCA fentanyl as needed

(*Continued*)

Table 3. (Continued)

First Author, Year	Preincisional	Postoperative
Titman, 2018[64]	Intravenous paracetamol 1,330 mg once	Intravenous paracetamol 1,330 mg every 8 h; oral celecoxib 200 mg every 12 h; Intravenous morphine 1 mg as needed; PCA morphine as needed
Townsend, 2022[45]	Oral acetaminophen 975 mg once; oral pregabalin 50–100 mg once	Oral acetaminophen 975 mg every 8 h; oral pregabalin 25–50 mg every 12 h; intravenous ketorolac 15–30 mg every 8 h for three doses, then oral celecoxib 200 mg every 12 h; PCA hydromorphone; oral oxycodone 2.5–10 mg every 4 h as needed
Tulgar, 2018[65]	None	Intravenous paracetamol 1,000 mg every 8 h; PCA tramadol; intravenous fentanyl 25 mcg as needed; intramuscular diclofenac 75 mg as needed
Villatte, 2016[48]	None	Intravenous paracetamol 1,000 mg every 6 h for 2 days followed by oral paracetamol 1,000 mg every 6 h; intravenous ketoprofen 100 mg every 12 h; PCA morphine for 2 days followed by oral tramadol 50–100 mg every 6 h; intravenous morphine 5–10 mg every 6 h as needed
Ruan, 2022[42]	None	PCA oxycodone
Wang, 2023[79]	Oral celecoxib 200 mg every 12 h 1 day before surgery	Oral celecoxib 200 mg every 12 h; intravenous 10 mg morphine as needed
Xiao, 2021[63]	Oral celecoxib 200 mg every 12 h 1 day before surgery	Oral celecoxib 200 mg every 12 h; oral oxycontin 10 mg every 12 h as needed; intravenous morphine 5 mg as needed
Ye, 2023[66]	None	Oral celecoxib 200 mg every 12 h; intravenous 10 mg morphine as needed
Zheng, 2022[56]	None	Oral naproxen/esomeprazole 500/20 mg; intramuscular dexketoprofen 50 mg as needed; PCA fentanyl
Zheng, 2022b[53]	None	Oral ketorolac; oral acetaminophen; intravenous tramadol as needed; intravenous butorphanol as needed
Zoric, 2014[55]	None	Intravenous paracetamol 1,000 mg every 6 h; intravenous nefopam 60–120 mg daily; intravenous morphine 2–4 mg as needed; intravenous ketoprofen 100 mg as needed; PCA morphine as needed

PCA, patient-controlled analgesia.

Six Hours

A total of 26 studies[41–43,46,48,50,51,54–56,60,63–70,72–74,76,79,81,82] encompassing 1,908 patients reported rest pain severity scores at 6 h (Supplemental Digital Content F, https://links.lww.com/ALN/E64). There were 30 pairwise comparisons and 4 regional anesthetic approaches in the analysis. Ranked based on P score, the quadratus lumborum block was found to be the most effective intervention for this outcome (71%). This was followed by periarticular local infiltration analgesia (65%), the pericapsular nerve group block (56%), and the erector spinae plane block (51%). Control was found to have the lowest P score probability at 6%. This analysis was characterized by a high level of inconsistency ($Tau^2 = 0.65$; $I^2 = 88.20\%$), and evidence was downgraded due to the risk of publication bias (Supplemental Digital Content C, https://links.lww.com/ALN/E61). The GRADE quality of evidence was ranged from very low to high across the comparisons (Supplemental Digital Content D, https://links.lww.com/ALN/E62).

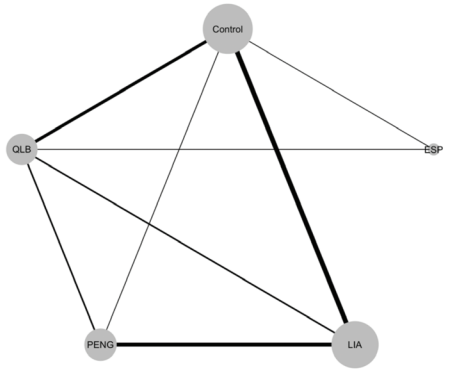
Twelve Hours

A total of 21 studies[41,43,46,48,50,51,54–56,58,60,63,65–68,72,76,79,81,82] encompassing 1,537 patients reported rest pain severity scores at 12 h (Supplemental Digital Content G, https://links.lww.com/ALN/E65). There were 27 pairwise comparisons and 4 regional anesthetic approaches in the analysis. Ranked based on P score, periarticular local infiltration analgesia was found to be the most effective intervention for this outcome (79%). This was followed by the pericapsular nerve group block (73%), quadratus lumborum block (71%), and control (24%). The erector spinae plane block found to have the lowest P score probability at 3%. This analysis was characterized by a high level of inconsistency ($Tau^2 = 0.28$; $I^2 = 84.50\%$); however, the risk of publication bias was low (Supplemental Digital Content C, https://links.lww.com/ALN/E61). The GRADE quality of evidence was ranged from low to high across the comparisons (Supplemental Digital Content D, https://links.lww.com/ALN/E62).

Twenty-four Hours

A total of 35 studies[5,41–43,45–51,54–56,58–63,65–69,71–76,78–81] encompassing 3,063 patients reported rest pain severity scores at 24 h (Supplemental Digital Content H, https://links.lww.com/ALN/E66). There were 42 pairwise comparisons and 4 regional anesthetic approaches in the analysis. Ranked based on P score, the pericapsular nerve group block was found to be the most effective intervention for this outcome (64%). This was followed by the quadratus lumborum block (63%), periarticular local infiltration analgesia (63%), and erector spinae plane block (45%). Control was found to have the lowest P score probability at 14%. This analysis was characterized by a high level of inconsistency ($Tau^2 = 0.37$; $I^2 = 92.20\%$); however, the risk of publication bias was low (Supplemental Digital Content C, https://links.lww.com/ALN/E61). The GRADE quality of evidence was ranged from low to high across the comparisons (Supplemental Digital Content D, https://links.lww.com/ALN/E62).

A



B

Control				
-0.73 (-16.22,14.76)	Erector Spinae Plane Block			
8.06 (2.02,14.10)*	8.79 (-7.40,24.97)	Periarticular Local Infiltration Analgesia		
-0.47 (-8.05, 7.11)	0.26 (-16.42,16.94)	-8.53 (-15.00,-2.05)*	Pericapsular Nerve Group Block	
6.00 (-0.66,12.66)	6.73 (-8.74,22.19)	-2.06(-9.30, 5.17)	6.47 (-1.53,14.47)	Quadratus Lumborum Block

C

Intervention	P-Score
Periarticular Local Infiltration Analgesia	89%
Quadratus Lumborum Block	75%
Erector Spinae Plane Block	32%
Control	28%
Pericapsular Nerve Group Block	26%

Fig. 2. (*A*) Network plot for area under the curve rest pain from 0 to 24 h; (*B*) league table representing the mean difference (95% CI) for area under the curve rest pain scores between regional anesthetic approaches. Values greater than 0 represent worsened area under the curve rest pain (*red shading*). (*C*) P score for the probability of being the most effective intervention. Values could range from 0 to 1, with 1 indicating a 100% probability of being the most effective intervention. *$P < 0.05$.

Postoperative Function. For all postoperative function data, a log[OR] with 95% CI was calculated since a variation of continuous and dichotomous outcomes was reported by included studies. A full list of functional assessments included in each pooled estimate can be viewed in Supplemental Digital Content S (https://links.lww.com/ALN/E77).

Six Hours

A total of eight studies[43,46,56,59,68,70,76,79] encompassing 924 patients reported postoperative function at 6 h (Supplemental Digital Content I, https://links.lww.com/ALN/E67). There were nine pairwise comparisons and three regional anesthetic approaches in the analysis. Ranked based on P score, the pericapsular nerve group block was found to be the most effective intervention for this outcome (78%). This was followed by periarticular local infiltration analgesia (51%) and the quadratus lumborum block (37%). Control was found to have the lowest P score probability at 34%. This analysis was characterized by a high level of inconsistency ($Tau^2 = 1.44$; $I^2 = 80.70\%$); however, the risk of publication bias was low (Supplemental Digital Content C, https://links.lww.com/ALN/E61). The GRADE quality of evidence was very low across the comparisons (Supplemental Digital Content D, https://links.lww.com/ALN/E62).

Twelve Hours

A total of six studies[42,43,59,68,72,79] encompassing 825 patients reported postoperative function at 12 h (Supplemental Digital Content J, https://links.lww.com/ALN/E68). There were eight pairwise comparisons and three regional anesthetic approaches in the analysis. Ranked based on P score, periarticular local infiltration analgesia was found to be the most effective intervention for this outcome (94%). This was followed by the pericapsular nerve group block (63%) and the quadratus lumborum block (35%). Control was found to have the lowest P score probability at 8%. This analysis was characterized by a high level of inconsistency

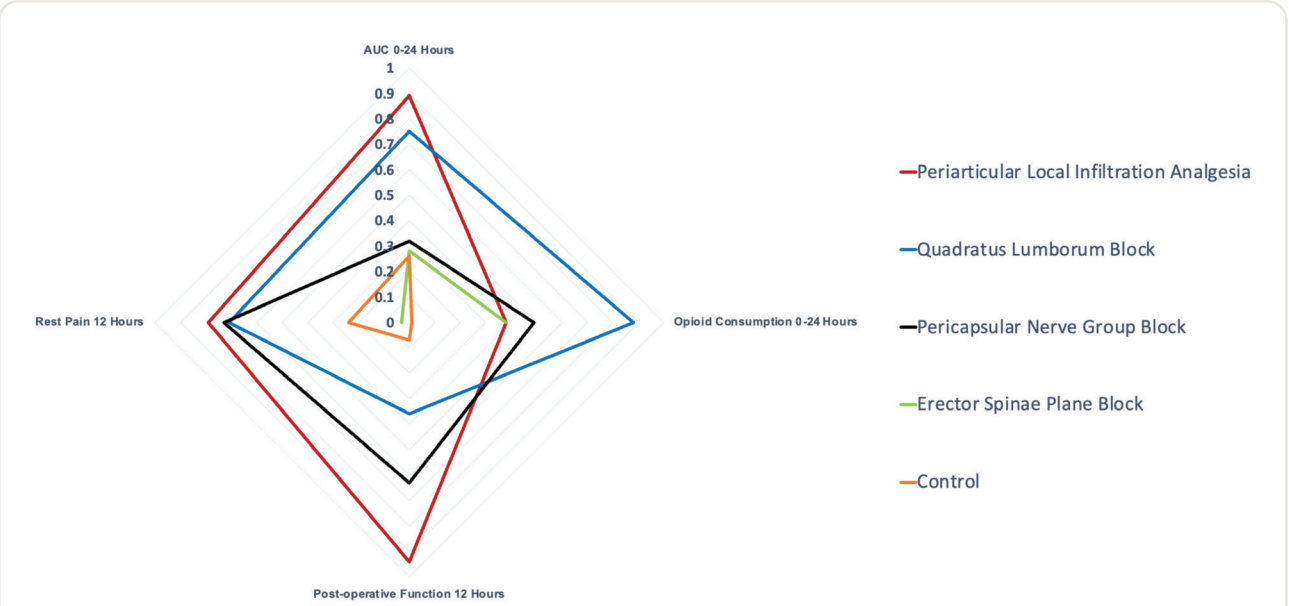


Fig. 3. Star plot of P scores evaluating the probability of being the most effective intervention across pain, analgesic, and function outcomes. P score values can range between 0 and 1, with higher P scores indicating higher probability of being the most effective intervention. AUC, area under the curve.

(Tau^2 = 6.15; I^2 = 93.00%); however, the risk of publication bias was low (Supplemental Digital Content C, https://links.lww.com/ALN/E61). The GRADE quality of evidence was very low across the comparisons (Supplemental Digital Content D, https://links.lww.com/ALN/E62).

Twenty-four Hours

A total of 18 studies[5,43,45–50,54–56,61,63,66–68,75,79] encompassing 1,504 patients reported postoperative function at 24 h (Supplemental Digital Content K, https://links.lww.com/ALN/E69). There were 18 pairwise comparisons and 4 regional anesthetic approaches in the analysis. Ranked based on P score, the pericapsular nerve group block was found to be the most effective intervention for this outcome (93%). This was followed by the erector spinae plane block (62%), periarticular local infiltration analgesia (57%), and control (22%). The quadratus lumborum block was found to have the lowest P score probability at 17%. This analysis was characterized by a high level of inconsistency (Tau^2 = 0.15; I^2 = 43.00%); however, the risk of publication bias was low (Supplemental Digital Content C, https://links.lww.com/ALN/E61). The GRADE quality of evidence ranged from very low to moderate across the comparisons (Supplemental Digital Content D, https://links.lww.com/ALN/E62).

Postoperative Opioid Consumption. A total of 28 studies[5,41–46,51,54–56,58–63,65–68,71,72,75,78,80–82] encompassing 2,389 patients reported postoperative analgesic consumption from 0 to 24 h (Supplemental Digital Content L, https://links.lww.com/ALN/E70). There were 34 pairwise comparisons and 4 regional anesthetic approaches in the analysis. Ranked based on P score, the quadratus lumborum block was found to be the most effective intervention for this outcome (88%). This was followed by the pericapsular nerve group block (74%), erector spinae plane block (49%), and periarticular local infiltration analgesia (38%). Control was found to have the lowest P score probability at 0%. This analysis was characterized by a high level of inconsistency (Tau^2 = 61.65; I^2 = 90.20%); however, the risk of publication bias was low (Supplemental Digital Content C, https://links.lww.com/ALN/E61). The GRADE quality of evidence was ranged from low to high across the comparisons (Supplemental Digital Content D, https://links.lww.com/ALN/E62).

Opioid-related Side Effects. We evaluated several opioid-related side effects, which were categorized according to type of side effect.

Nausea and/or Vomiting

A total of 23 studies[5,42,43,46,47,51,54–56,58,60,62,63,65–68,71–73,79–81] encompassing 1,595 patients assessed postoperative nausea/vomiting (Supplemental Digital Content M, https://links.lww.com/ALN/E71). There were 29 pairwise comparisons and 4 regional anesthetic approaches in the analysis. Ranked based on P score, the erector spinae block was found to be the most effective intervention for this outcome (92%). This was followed by the quadratus lumborum block (76%), pericapsular nerve group block (46%), and periarticular local infiltration analgesia (28%). Control was found to have the lowest P score probability at 8%. This analysis was characterized by a low level of inconsistency

($Tau^2 = 0.059$; $I^2 = 7.80\%$), and the risk of publication bias was low (Supplemental Digital Content C, https://links.lww.com/ALN/E61). The GRADE quality of evidence was ranged from very low to moderate across the comparisons (Supplemental Digital Content D, https://links.lww.com/ALN/E62).

Pruritus

A total of eight studies[46,51,56,60,62,63,68,81] encompassing 528 patients assessed postoperative pruritus (Supplemental Digital Content N, https://links.lww.com/ALN/E72). There were 10 pairwise comparisons and 3 regional anesthetic approaches in the analysis. Ranked based on P score, the quadratus lumborum block was found to be the most effective intervention for this outcome (81%). This was followed by the periarticular local infiltration analgesia (50%) and control (48%). The pericapsular nerve group block was found to have the lowest P score probability at 21%. This analysis was characterized by a low level of inconsistency ($Tau^2 = 0.0$; $I^2 = 0.0\%$), and the risk of publication bias was low (Supplemental Digital Content C, https://links.lww.com/ALN/E61). The GRADE quality of evidence ranged from very low to low across the comparisons (Supplemental Digital Content D, https://links.lww.com/ALN/E62).

Urinary Retention

A total of six studies[46,51,63,67–69] encompassing 501 patients assessed postoperative urinary retention (Supplemental Digital Content O, https://links.lww.com/ALN/E73). There were eight pairwise comparisons and three regional anesthetic approaches in the analysis. Ranked based on P score, the quadratus lumborum block was found to be the most effective intervention for this outcome (83%). This was followed by periarticular local infiltration analgesia (64%) and control (28%). The pericapsular nerve group block was found to have the lowest P score probability at 24%. This analysis was characterized by a low level of inconsistency ($Tau^2 = 0.0$; $I^2 = 0.0\%$), and the risk of publication bias was low (Supplemental Digital Content C, https://links.lww.com/ALN/E61). The GRADE quality of evidence was low across the comparisons (Supplemental Digital Content D, https://links.lww.com/ALN/E62).

Other Side Effects

Five studies[43,46,51,68,81] assessed the incidence of postoperative respiratory depression, and no events were recorded for patients who received the quadratus lumborum block, pericapsular nerve group block, periarticular local infiltration analgesia, or control. No study assessed the incidence of constipation.

Block-related Adverse Events. A total of 30 studies[5,41–49,53–55,57,58,60–67,70–72,74,76,78,79] inclusive of 1,252 patients assessed block-related complications. Across all patients, 13 adverse events were reported, which included 3 cases of hematoma with the quadratus lumborum block,[60] 5 cases of hematoma with the pericapsular nerve group block,[78] 3 cases of hematoma with sham block (*i.e.*, control),[78] one case of prolonged motor weakness with the quadratus lumborum block,[42] and one case of prolonged motor weakness with the erector spinae plane block.[5]

Ancillary Analyses

Evaluation consistency between the direct and indirect estimates did not reveal significant difference between the estimates for most comparisons (Supplemental Digital Content P, https://links.lww.com/ALN/E74); this was also demonstrated *via* inspection of the heat plot for the primary outcome (Supplemental Digital Content Q, https://links.lww.com/ALN/E75). Further, the contribution matrix for the primary outcome of area under the curve rest pain suggested that most data originated from studies that had either a low or unclear risk of bias (Supplemental Digital Content Q, https://links.lww.com/ALN/E75). Finally, due to a perceived similarity between patients and motor-sparing techniques, data were not further downgraded for transitivity.

Discussion

The results of our network meta-analysis suggest that periarticular local infiltration analgesia alone for THA most consistently improves postoperative pain scores across 24 h, analgesic consumption, and postoperative functional recovery (fig. 3). In the absence of periarticular local infiltration, the quadratus lumborum block achieves the greatest improvement in postoperative pain across 24 h and analgesic consumption, whereas the pericapsular nerve group block achieves the greatest postoperative function. Our ancillary analysis also suggests an incremental analgesic benefit when a quadratus lumborum block or periscapular nerve group block is added to periarticular local infiltration analgesia; however, the quality of the available data is low. Finally, the erector spinae plane block performs the least consistently for analgesia and functional benefits when compared to other motor-sparing fascial plane blocks. Taken together, our results support the continued use of periarticular infiltration analgesia, with or without the quadratus lumborum block or pericapsular nerve group block, to optimize postoperative analgesia and functional recovery after elective THA.

Local anesthetic-based analgesia after THA is predicated on capturing the innervations to both the anterior and posterior capsule of the hip joint[83] as well as the incisional area. The anterior capsule is supplied by the articular branches of the femoral and obturator nerves, and the posterior capsule is supplied by the articular branches of the sciatic nerve and nerves to the quadratus femoris,[83] while the incisional area is innervated by the lateral femoral cutaneous nerve.[84] Furthermore, the density of innervation may differ across the hip joint, with the capsule itself having a relatively low density of innervation when compared to the fascial planes,[85] and the anterior capsule in specific receives the large majority of the sensory innervation.[86] Guided

by surgeons' direct visualization of the joint and incision, local anesthetic infiltration can anesthetize the entire joint space, as well as the incision, which is densely innervated.[85] Targeted local anesthetic deposition also reduces the risk of motor weakness and potential falls that may be associated with fascial plane blocks (and peripheral blocks), which is particularly valuable in the setting of ambulatory THA.[87] On the downside, the periarticular infiltration technique has some limitations that may potentiate interest in complimentary or alternative interventions. For example, infiltration requires large volumes of dilute local anesthetic, which necessarily limits the duration of action[88] and is operator-dependent.[89] Indeed, a study of periarticular infiltration analgesia for THA[90] indicated that single-injection infiltration is likely to require postoperative "rescue" supplementation with narcotic medications in 81% of patients, which was significantly greater than what is observed in patients who received a sham injection or no block.[90] That said, when performed by expert hands, such as the "operators" in the clinical trials included in this review, periarticular infiltration demonstrated superiority over all other comparators. The interpretation of this variation may be that the infiltration technique possesses very good internal validity in studies, but differing performance of the infiltration technique by surgeons[91,92] in actual clinical practice may limit the generalizability of its benefits. Further, the variation in its effectiveness may be based on the location of deposition of the local anesthetic solution, whether into the ligaments of the capsule, its tendons, or the surrounding fascial planes, anatomical structures that have varying high densities of nerve tissue.[85]

On the other hand, fascial plane blocks capitalize on the availability of portable high-resolution ultrasound to visualize intermuscular fascial planes where terminal nerve branches are located, offering the advantage of technical ease and theoretically safeguarding peripheral nerves against the risk of needle trauma and nerve injury.[93] The quadratus lumborum block targets the femoral, obturator, and sciatic nerves as these nerves originate from the lumbar plexus,[94,95] which is believed to anesthetize both the anterior and posterior hip capsule. The pericapsular nerve group block targets the articular branches of the femoral and obturator nerves at the level of the ilium proximal to the acetabulum,[96] which ought to anesthetize the anterior capsule. However, local anesthetic spread along fascial planes may be unreliable, especially if small volumes are used, potentially leading to reduced and/or inconsistent effectiveness.[97–99] Further, the risk of unwanted motor block after the quadratus lumborum block or pericapsular nerve group block is real,[100,101] as has also been observed in this network meta-analysis, leading to increased risk of falls, delays in physiotherapy, and failure of outpatient THA. As for the erector spinae block, its analgesic benefits have recently been attributed to local anesthetic spread to the dorsal and ventral rami of the spinal nerves[102] rather than terminal nerve branches. However, cadaveric studies provide conflicting evidence regarding local anesthetic spread with this block, which is in keeping with the limited improvement in clinical outcomes that we observed in this network meta-analysis.

Combining novel fascial plane blocks with periarticular infiltration is also practiced for analgesia after THA. Our limited ancillary analysis signals promising incremental benefits to performing an additional quadratus lumborum block or pericapsular nerve group block, as has been discussed elsewhere.[96,103] Nonetheless, further research is needed to corroborate this finding and to definitely demonstrate that the magnitude of additional benefit is actually clinically important. Mechanistically, the additional benefits may be a result of the dense nociceptive innervation of the anterior rim of the hip joint that is derived from the femoral nerve.[89] Finally, stacking interventions leads to an additive effect of their respective risks, including injury and local anesthetic toxicity, warranting careful consideration of risks and benefits.[104,105]

Our results from the AUC analysis suggest statistically significant improvements in rest pain during the period from 0 to 24 h with periarticular infiltration but questionable clinical importance. First, clinically important difference values are patient-specific and may not apply well to meta-analyses. Therefore, we cannot dismiss a subjective perceived benefit of periarticular infiltration in some patients. Second, the AUC analysis may be limited due to the loss of temporal resolution.[106] Thus, one could argue that periarticular infiltration provides greater benefit in postanesthesia care unit, which is primarily driving the overall AUC estimate.

It is also important to highlight the contextual use of P scores in our network meta-analysis. The P scores inherently considers standard error and allows for a clinically easy way to assess relative effectiveness of interventions, which are already part of everyday clinical practice. The P scores we have observed acknowledge that all interventions may be beneficial right from the outset, and the likelihood of one being significantly inferior is slim. Our network meta analysis helps identify the optimal intervention across the majority of clinically important domains. In that, the actual P scores are only a means to an end.

Limitations

There are notable limitations of this network meta-analysis. First, we included motor-sparing fascial plane blocks that are more commonly used for THA; however, there are several other block techniques that we did not consider due to their potential impact on postoperative function, including the fascia iliaca block[107] and the psoas compartment block.[108] Second, some centers may employ the use of continuous catheter-based approaches for these blocks, and the effectiveness of these was not explored in this review. Third, our primary and many of our secondary outcomes were characterized by a high level of inconsistency. This may be due to several factors, including but not limited to difference in block technique and in surgical approach, such as anterior *versus* posterolateral THA. This may limit the external

validity of our findings. However, our subgroup analysis did not identify considerable variations in P score rank from the primary analysis. Fourth, the majority of included trials used postoperative multimodal analgesia.[109] While certainly advantageous, this may limit the perceived effectiveness of regional anesthetic approaches and lead to falsely low effect sizes. Nonetheless, this constitutes the "universal" care standard, which supports the external validity of our findings. Fifth, a variety of different standardized and unstandardized instruments was used to assess postoperative function. Further, both dichotomous and continuous outcomes were statistically pooled together for this outcome. This may ultimately increase the uncertainty in this outcome and generalizability. Sixth, patient-level data were not collected for our analysis. As a result, we were unable to determine if baseline characteristics (*i.e.*, preoperative pain or functional status) were similar between control and intervention groups, or if these characteristics were associated with certain benefits from the addition of a motor-sparing fascial plane block. Future studies should consider inclusion of this in order to better understand whether these techniques might be more useful to certain patient subgroups (*i.e.*, those with preexisting pain or opioid use or certain patient demographics).

Conclusions

The results of our network meta-analysis suggest that periarticular local infiltration analgesia alone appears provide the most consistent improvements in postoperative rest pain, analgesic consumption, and functional recovery after THA. If a motor-sparing fascial plane block is considered, the quadratus lumborum block and the pericapsular nerve group block, in combination with periarticular local infiltration analgesia, may further optimize analgesic outcomes. Finally, the erector spinae plane block appears to perform poorly across the majority of postoperative clinical outcomes.

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Competing Interests

The authors declare no competing interests.

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Supplemental Digital Content

Supplemental Digital Content A - Search strategies, https://links.lww.com/ALN/E59
Supplemental Digital Content B - Risk of bias assessment, https://links.lww.com/ALN/E60
Supplemental Digital Content C - Funnel plots for publication bias, https://links.lww.com/ALN/E61
Supplemental Digital Content D - GRADE assessments, https://links.lww.com/ALN/E62
Supplemental Digital Content E - Network analysis for 0-2 hour rest pain, https://links.lww.com/ALN/E63
Supplemental Digital Content F - Network analysis for 6 hour rest pain, https://links.lww.com/ALN/E64
Supplemental Digital Content G - Network analysis for 12 hour rest pain, https://links.lww.com/ALN/E65
Supplemental Digital Content H - Network analysis for 24 hour rest pain, https://links.lww.com/ALN/E66
Supplemental Digital Content I - Network analysis for 6 hour post-operative function, https://links.lww.com/ALN/E67
Supplemental Digital Content J - Network analysis for 12 hour post-operative function, https://links.lww.com/ALN/E68
Supplemental Digital Content K - Network analysis for 24 hour post-operative function, https://links.lww.com/ALN/E69
Supplemental Digital Content L - Network analysis for 0-24 hour opioid consumption,https://links.lww.com/ALN/E70
Supplemental Digital Content M - Network analysis for post-operative nausea/vomiting, https://links.lww.com/ALN/E71
Supplemental Digital Content N - Network analysis for post-operative pruritis, https://links.lww.com/ALN/E72
Supplemental Digital Content O - Network anlaysis for post-operative urinary retention, https://links.lww.com/ALN/E73
Supplemental Digital Content P - Node split plots for pooled outcomes, https://links.lww.com/ALN/E74
Supplemental Digital Content Q - Heat plot for primary outcome, https://links.lww.com/ALN/E75
Supplemental Digital Content R - Contributions matrix for primary outcome, https://links.lww.com/ALN/E76
Supplemental Digital Content S - Measurement tools for functional outcomes, https://links.lww.com/ALN/E77

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Hippocampal Neural Dynamics and Postoperative Delirium–like Behavior in Aged Mice

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative delirium is an important clinical entity, especially in at-risk populations
- The electroencephalographic features of postoperative delirium are incompletely characterized

What This Article Tells Us That Is New

- In aged mice, the combination of anesthesia/surgery decreased hippocampal interneuron activity and increased pyramidal neuron activity, as demonstrated by high-density silicon probe electrophysiologic recordings and *in vivo* calcium imaging
- Pretreatment of mice before anesthesia and surgery with indole-3-proprionic acid, a gut microbiome metabolite, mitigated the development of postoperative delirium–like behavior, and these protective behavioral effects were correlated with the absence of changes in excitation inhibition balance when compared to control animals

ABSTRACT

Background: Postoperative delirium (POD) is a common and serious clinical condition that occurs after anesthesia/surgery. While its clinical impact is well recognized, the underlying electrophysiologic mechanisms remain largely unknown, posing challenges for effective treatment. This study aims to investigate hippocampal neural dynamics before and after anesthesia/surgery in aged mice, which have a tendency to develop POD.

Methods: This study included adult and aged mice with a POD model. POD-like behavior was assessed in N = 10 mice at baseline (the day before surgery), as well as at 9 h and 24 h after anesthesia/surgery. A behavioral battery, including the open field test, Y maze, buried food test, and novel object recognition, was used for assessment. *In vivo* chronic brain recordings were performed on awake, restrained mice using a high-density silicon probe during the same time intervals. To further investigate hippocampal neural dynamics, *in vivo* two-photon calcium imaging was also conducted. Additionally, aged mice were pretreated with indole-3-propionic acid (IPA), and its effects on POD-like behavior and neural activity were evaluated using electrophysiology and calcium imaging.

Results: The first observation was that aged mice exhibited significant POD-like behavior, as measured by Z scores, compared to adult mice after anesthesia/surgery. Analysis revealed significant age-related differences in hippocampal neuronal activities. At 9 h after surgery, aged mice exhibited a marked increase in pyramidal cell activity and a reduction in interneuron activity compared to adult mice. These changes in neuronal dynamics were associated with the onset of POD-like symptoms in aged mice. By 24 h after surgery, both pyramidal cell and interneuron activity in aged mice had returned to presurgery levels, which coincided with an improvement in POD-like behavior. Additionally, IPA pretreatment modulated neuronal activity in aged mice, attenuating pyramidal cell hyperactivity and partially ameliorating interneuron dysfunction, changes associated with mitigated POD-like behavior.

Conclusions: Alterations in hippocampal neural activity may significantly contribute to brain dysfunction and POD-like behavior. IPA pretreatment may modulate neural circuit imbalances in aged mice, potentially mitigating POD incidence.

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Several serious cognitive syndromes can emerge after surgery and anesthesia. Postoperative delirium (POD) is a behavioral disorder that occurs during the perioperative period, marked

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Abbreviations: **EEG**, electroencephalogram; **HSP**, high-density silicon probe; **IPA**, indole-3-propionic acid; **NOR**, novel object recognition; **POD**, postoperative delirium

by impaired consciousness and cognitive dysfunction.[1,2] The incidence of POD is relatively low in the general surgical population (2 to 3%), but it rises significantly in high-risk patients, reaching as high as 50%.[3–5] Clinical studies have identified several risk factors for POD, including advanced age, preexisting dementia, being underweight, lower educational levels, smoking, and a history of delirium.[6,7] These risk factors contribute to a higher incidence of POD in certain populations. Among older adults, the incidence is particularly high, affecting 9 to 50% of cases. In this group, POD is associated with worse clinical outcomes, including increased postoperative complications, prolonged hospital stays, and higher mortality rates.[8–11] The healthcare costs attributable to postoperative delirium are estimated at $32.9 billion per year.[12]

Electroencephalogram (EEG) studies have provided insights into brain electrophysiologic activity in POD. While EEG features of delirium in the postoperative period remain incompletely characterized, a shift of EEG power into low frequencies is a typical finding shared among encephalopathies that manifest with delirium.[13–15] During loss of consciousness after the induction of general anesthesia, POD patients demonstrated decreased alpha and beta band power, as well as lower spectral edge frequencies, than patients without POD.[16] Preoperative awake, resting EEG alpha attenuation with eye opening was associated with the development of POD.[17] The predictive value of preoperative EEG was independently validated, particularly when combining resting state EEG and Montreal Cognitive Assessment scores (Ning M, Rodionov A, Ross JM, et al.: Prediction of post-operative delirium in older adults from preoperative cognition and alpha power from resting-state EEG. Preprint. Posted online November 1, 2024. doi:10.1101/2024.08.15.24312053). More recently, using high-density EEG, it was shown that delirium was associated with loss of feedback cortical activity.[18] However, in a recent study of older adults who underwent cardiac surgery, intraoperative EEG-guided anesthesia management to minimize burst suppression did not decrease the incidence of POD in these patients,[19] highlighting the complexity of POD pathogenesis.

Despite significant progress to link brain electrical activities and POD, the detailed electrophysiologic basis of POD is largely unknown. While seminal studies based on EEG identify important features with predictive power for POD, brain region– or neuron-specific information is not readily available due to the limited spatial resolution of EEG. The advent of high-density silicon probes (HSP), such as the Neuropixels 2.0 (IMEC, Belgium), offers a breakthrough in this regard. These miniaturized, high-density probes enable stable, long-term chronic brain recordings with single-unit resolution, while their high-density, multishank design facilitates precise localization of single-unit neural activity across different brain regions.[20] For example, the 5,120 recording sites across four shanks in these probes have been shown to track individual chronically recorded neurons in the primary visual cortex with a greater than 80% success rate for up to 2 months.[20] Despite the enthusiastic adoption of this technology within the neuroscience community,[21,22] *in vivo* high-density electrophysiologic studies with single-unit resolution have yet to be applied to understanding neuronal activity linked to POD.

In the current study, we first analyzed POD-like behavior in aged mice compared to adult mice. We then utilized high-density single-unit chronic electrophysiologic recording technology to capture single-unit electrophysiologic signals in the hippocampus of both adult and aged mice, while intravital two-photon calcium imaging was conducted in separate cohorts of animals, enabling direct visualization of neuronal activity. Building on our previous retrospective study, we demonstrated that indole-3-propionic acid (IPA), a gut microbiome metabolite,[23] effectively prevented POD in aged mice. This occurred through the promotion of PGC-1α expression in hippocampal interneurons, which protects against POD development linked to gut microbiota perturbation.[24] In this study, we aimed to further investigate the impact of IPA on hippocampal neural activity. Specifically, we hypothesized that dynamic changes in neural activity could be recorded in a model of POD-like behavior and that IPA modulates hippocampal neural activity to mitigate the disruptions associated with POD.

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Materials and Methods

Animals

All experiments conducted in this study adhered to the guidelines and regulations set by the National Institutes of Health (Bethesda, Maryland) and were approved by the Institutional Animal Care and Use Committee at Massachusetts General Hospital (Charlestown, Massachusetts). The study involved adult male and female C57BL/6 mice aged 12 to 16 weeks and aged male and female C57BL/6 mice aged 17 to 18 months at the start of the experiment. Every effort was made to minimize the number of animals used. The mice were obtained from the Jackson Laboratory (USA) and housed in a temperature-controlled environment with a 12-h light/12-h dark cycle (lights on at 7:00 AM and off at 7:00 PM), with behavioral testing carried out during the light phase. The mice had access to food and water *ad libitum*. The animal care and monitoring procedures adhered to the Animals in Research: Reporting In Vivo Experiments (ARRIVE) guidelines to ensure transparent reporting. Protocols were implemented to minimize pain, suffering, and distress, and all adverse events, whether anticipated or unexpected, were recorded. Humane endpoints were established, and specific signs, along with their frequency, were closely monitored throughout the study.

Anesthesia/Surgery Procedure of Postoperative Delirium Model

The procedure was performed as previously described.[24] Briefly, the mice were anesthetized using oxygenated isoflurane (3% for induction and 1.5% for maintenance) delivered in oxygen.[25,26] We used a mice model imitating femoral artery surgery,[24] as this surgery is widely used clinically. During the procedure, the mice were placed on a heating pad to ensure their body temperature was maintained, and eye ointment was applied to prevent corneal dryness. The mice were positioned in a supine posture, and the hair on both side of the hind limb was shaved. A small incision, approximately 0.5 cm in length, was made in the skin over the femoral artery, extending from the inguinal region down toward the knee. The subcutaneous tissue and fascia were carefully dissected to expose the bilateral femoral arteries, taking great care to avoid any damage to the surrounding tissues and nerves. Exposure of the artery was performed using a mini forceps, ensuring the artery remained intact to prevent bleeding. The skin incision was closed using 4-0 silk sutures. The total duration of anesthesia and surgery was 2 h for all mice. For sham procedures, animals underwent isoflurane anesthesia for similar duration, but no incision was made. For immediate postoperative pain management, the skin was infiltrated with 0.25% bupivacaine, and the wound was covered with EMLA cream (AstraZeneca, USA). For IPA intraperitoneal injection, IPA was dissolved in 0.9% NaCl:ethanol (v/v 10:1) and injected twice daily at 0.0625 mmol/kg.

Open Field Test

The mice were acclimated for approximately 30 min before testing began. The test was conducted in a 40-cm × 40-cm enclosure, which was divided into two sections: a center zone measuring 20 cm × 20 cm, and a surrounding area. The movements of the mice were recorded and analyzed using a video camera connected to the Any-Maze animal tracking system (Stoelting Co., USA). Each mouse was placed individually in the center of the enclosure, and various parameters were measured, including the time taken to enter the center zone, the duration spent in the center zone, and the amount of time spent freezing. The open field test lasted for 5 min.

Y Maze Test

The Y maze test was used to assess spontaneous alternation behavior and short-term spatial memory in mice. The Y maze apparatus featured three arms arranged at 120° angles, all connected at a central zone. Before testing, the mice were acclimated to the environment for 5 to 10 min. A video camera was positioned vertically above the Y maze to capture the movement of each mouse. The live tracking data were recorded and analyzed using the Any-Maze animal tracking system software (Stoelting Co.). Key metrics included the number of entries into the novel arm and the amount of time spent in the novel arm.

Buried Food Test

The buried food test was conducted to evaluate the alertness and consciousness of the mice, following a previously described protocol with slight modifications.[27,28] Two days before the test, the mice were introduced to sweetened cereal. On the day of the test, after acclimation, each mouse was placed in a clean cage where a sweetened cereal pellet had been buried under 3 to 5 cm of bedding. The time it took for the mouse to find and eat the buried food was recorded.

Novel Object Recognition

The novel object recognition (NOR) test was used to assess recognition memory in mice. Briefly, the mice were placed in a 40-cm × 40-cm enclosure, and their exploration of the objects was recorded using the Any-Maze animal tracking system (Stoelting Co.). The mice were placed in the center of the enclosure and allowed to explore two similar identical objects for 10 min, after which they were returned to their home cage to rest for 10 min. Subsequently, one of the two objects was replaced with a novel object, and the mice were placed back into the enclosure and tested for another 10 min. The exploration time for each object was recorded for statistical analysis.

Microelectrode Array Implantation

Microelectrode implantation was performed 3 weeks before electrophysiologic recording. The mice were anesthetized

with isoflurane (3% for induction and 1.2 to 1.5% for maintenance). Each mouse was placed in a stereotaxic frame, and the dorsal fur of the head was removed using microsurgical scissors. After drying the skull with a cotton tip, a craniotomy was performed, removing a 1-mm × 2-mm section of the skull above the hippocampus (coordinates: AP −2.0 mm, ML 2 mm). Care was taken to avoid bleeding and to ensure that the dura and cortex remained intact. An HSP (Neuropixels 2.0 probe, NP2013) was slowly implanted into the hippocampus (DV 2.5 mm) through the cranial window. A 0.8-mm-diameter micro screw (Asia Bolt, South Korea) was inserted into a drilled hole in the interparietal bone above the cerebellum to serve as a reference. Both the silicon probe connector and the reference wire were secured to the skull using dental cement (C&B-Metabond, catalog no. 171032, Parkell, USA). After the surgery, the mice were group-housed for a 3-week recovery period. On the recording day, the mice were habituated for 30 min before a 10-min recording session using a specific recording system (Neuropixels, Belgium).

In Vivo Chronic Brain Recording from Awake and Restrained Mice

The mice with implanted multishank HSP were recorded chronically before and 9 h after surgery. The electrophysiologic recordings were performed using Neuropixels PXIe acquisition system (PXIe1000) and PXI-chassis (PXIe1083, National Instrumentations, USA) with standard headstage (HS_2010). The mice were head-fixed and restrained on a homemade constrainer. Recordings started when the mice were assessed to be accommodated to the headplate and lasted for 5 min. Electrophysiologic recording was made with a 30-kHz sampling rate by Open Ephys GUI[29] and open-ephys-plugins Neuropixels PXI.

Virus Injection and Cranial Window

The procedures were performed as previously outlined.[25,27,30] In brief, the mice were anesthetized with oxygenated isoflurane (3% for induction and 1.5% for maintenance) delivered in oxygen while being carefully monitored. Eye lubricant was applied to prevent corneal dehydration. The dorsal fur between the outer canthus and concha was shaved, and the mouse was positioned in a stereotactic frame with ear bars, securing the front teeth onto the incisor bar. The mouse's snout was covered with an anesthetic mask delivering oxygenated gases. The skin was prepared with povidone–iodine solution (Aplicare, Inc., USA), followed by a 70% alcohol swab (BD, USA). After infiltrating the area with lidocaine (1%, 0.2 ml), the skin over the dorsal skull was removed. A curved scalpel blade (#12) was used to remove a 3-mm × 3-mm bone flap over the left hippocampus. Using a glass needle with a diameter of about 50 μm, 1 μl of AAV8-hDlx-GCaMP6f (Vigene) and AAV8-CaMKII-jRGECO1a (Canadian Neurophotonics Platform Viral Vector Core Facility, RRID: SCR_016477) was microinjected into the left hippocampus (Bregma −2 to −2.5 mm, lateral 1.5 to 3 mm, depth 1.5 to 2 mm) using a Nanoject (Drummond Scientific Company, USA). Immediately after the injection, the visual cortex over the dorsal hippocampus was removed, following established procedures for two-photon imaging of the hippocampus as previously detailed in studies[31,32] and a 3-mm round glass cylinder topped with a 5-mm round cover slip was placed in the cranial window. The assembly was secured with adhesive luting cement (C&B Metabond). Finally, a customized metal bar was attached for stabilization during intravital two-photon imaging.

Two-photon Imaging and Data Process

After 28 days of recovery and viral transfection, the mice were acclimated to the two-photon microscope setup, with their heads restrained for 30 min each day for 3 consecutive days. Baseline imaging was performed before surgery using a Discovery laser (Coherent, USA). The laser wavelength was set to 920 nm for GCaMP6f and 1,120 nm for jRGECO1a, with an average laser power output of approximately 25 mV during imaging. A 16×, 0.8 NA water immersion objective (Olympus, Japan) was used for image acquisition, and data were collected using Prairie View Software as previously described. Additional imaging was conducted 9 h after surgery. All images were captured at a frame rate of 6.2 Hz while the mice were awake and unanesthetized. To correct for motion between frames, the NoRMCorre software package was used.[26] Neurons were subsequently selected using custom scripts in MATLAB (MathWorks). Calcium fluorescence signals from each neuron were extracted from the corrected image series. Background fluorescence changes were accounted for by subtracting them from the signal of the immediate surrounding area. The activity time course for each neuron was quantified using the formula $\Delta F = (F - F0)/F0$, where F represents the fluorescence signal at a given frame, and F0 was calculated from a sliding window of ±30 s around the frame. Baseline correction was performed by fitting a linear function (MATLAB function robustfit) to the lowpass-filtered signal (cutoff: 0.3 Hz). A deconvolution algorithm (fast online deconvolution of calcium imaging data) was applied to detect transients, with the start and end of transients identified when the model exceeded 0.1, as previously described.[33] All analysis codes are available at https://github.com/harnett/Shiqian-analysis.

Data Analysis of Electrophysiologic Recording

Raw data went through filtering, thresholding (6σ) and automatic spike sorting using SpyKING CIRCUS (version 1.0.9, https://github.com/spyking-circus/spyking-circus). Unit analyses and postprocessing were performed using spikeinterface (0.101.0)[34] and custom codes with manual curation written in Python and are

available in our laboratory's GitHub repository (https://github.com/Shenlab-MGH/spike-sorting_neuropixels2), which uses the packages NumPy (version 1.26.4, https://numpy.org), SciPy (version 1.11.3, https://scipy.org), and pandas (version 0.5.3, https://pandas.pydata.org/) for data analysis and matplotlib (version 3.9.0, https://matplotlib.org) and spikewidgets (version 0.5.4, https://github.com/SpikeInterface/spikewidgets) for visualization. Units were sorted into putative pyramidal cells and interneurons on the basis of peak waveform shape, firing rate, and interspike interval.[35,36]

Statistics and Reproducibility

To minimize potential biases, all analyses were performed in a blinded manner. The data from behavioral, electrophysiology, and calcium imaging studies are presented as means ± SD. There were no missing data for any of the behavioral test variables. For the behavioral tests, all parameters at baseline, 9 h, and 24 h were expressed as percentages relative to the baseline values within the same group. Data normality was first assessed using the Shapiro–Wilk test. Because the data were not normally distributed, logarithmic transformation was applied to normalize the variables. One-way ANOVA followed by Tukey *post hoc* analysis was then used to determine differences between groups. A significance level of $P < 0.05$ was considered statistically significant, and all tests were two-tailed. Adjusted P values were calculated using the Bonferroni correction, dividing the real P values by the number of comparisons made, and the adjusted P values are reported. Degrees of freedom for the ANOVA were calculated using the Greenhouse–Geisser correction to adjust for violations of the sphericity assumption. When comparing Z scores from baseline to 9 and 24 h after surgery, we first calculated the difference score (*i.e.*, the change from baseline) for each time point. We then compared the difference scores between the two groups using one-way ANOVA. All data points, including outliers, were retained to ensure transparency. Statistical differences were evaluated using both parametric (ANOVA test) and nonparametric (Kruskal–Wallis test) methods, and the results were concordant across approaches, confirming the robustness of our findings. All statistical analyses were performed using Prism 6 software (GraphPad Software, Inc., USA). For two-group comparisons of the electrophysiologic data, a two-sided t test was used. Electrophysiologic statistical analysis was conducted using custom codes designed to assess single-unit changes before and after surgery. The code is written in Python and is available in our laboratory's GitHub repository (https://github.com/Shenlab-MGH/spike-sorting_neuropixels2). We used the packages NumPy (version 1.26.4, https://numpy.org), SciPy (version 1.11.3, https://scipy.org), and pandas (version 0.5.3, https://pandas.pydata.org/) for data analysis and matplotlib (version 3.9.0, https://matplotlib.org) for visualization.

The sample sizes were determined based on previous studies in the field, practical considerations, and the need to detect meaningful differences in the outcomes of interest. Specifically, for the behavioral tests, the power calculation was based on data from a preliminary study conducted under the same conditions. Using these data and assuming a two-sided t test, we determined that a sample size of 10 per group would provide 95% significance. Four groups, each with N = 10 (5 males and 5 females), were used for the behavioral studies. For *in vivo* calcium imaging, a sample size of N = 4 males was selected, consistent with previous studies and sufficient to demonstrate the observed differences.[27,37,38] Due to limitations in probe cost and implantation failure rates, electrophysiologic analysis was performed using three groups of male animals (N = 2).

Results

Anesthesia/Surgery Induces Postoperative Delirium–like Behavior in Aged but Not in Adult Mice

We assessed POD-like behavior in both natural and learned behaviors by evaluating a battery of tests, including the open field, Y maze, buried food, and NOR tests, in both adult and aged mice.[27,28,39] Baseline behavioral assessments were conducted before anesthesia/surgery, followed by repeat tests 9 and 24 h postoperatively (fig. 1A). At 9 h postoperatively, anesthesia/surgery in aged mice resulted in increased latency to enter the center (78.88% *vs.* 227.3%; 95% CI, −293 to −3.918; $P = 0.013$) during the open field test ($F [2.001, 18.01] = 5.526$; fig. 1B), indicating alterations in the mice's natural behavior, including increased anxiety and changes in their natural responses. In the Y maze test, aged mice displayed fewer entries (107.6% *vs.* 60.78%; 95% CI, 0.74 to 92.94; $P = 0.005$; $F [2.351, 21.16] = 6.277$) and spent less time (94.64% *vs.* 80.38%; 95% CI, −30.63 to 59.15; $P = 0.744$; $F [1.975, 17.78] = 0.2964$) in the novel arm (fig. 1C), indicating impairments in spatial memory, which may reflect deficits in attention, consciousness, and organized thinking. Furthermore, aged mice took significantly longer to locate and consume buried food (41.29% *vs.* 135.5%; 95% CI, −182.5 to −5.893; $P = 0.004$; $F [1.820, 16.38] = 8.153$) compared to young adults (fig. 1D), suggesting disruptions in natural behavior. In the NOR test, aged mice exhibited impaired recognition memory, demonstrated by a reduced exploration time (94.94% *vs.* 68.37%; 95% CI, 1.258 to 51.88; $P = 0.007$; $F [2.045, 18.40] = 6.424$) of the novel object relative to the familiar one (fig. 1E). These abnormalities were largely resolved at 24 h postoperatively. When the behavioral indices were computed into Z score, aged mice had significantly higher Z scores (0.35 *vs.* 9.36; 95% CI, −13.55 to −4.479; $P = 0.0001$; $F [2.155, 19.40[= 27.61$) than adult mice at 9 h after surgery. However, Z scores indicated no significant differences between male

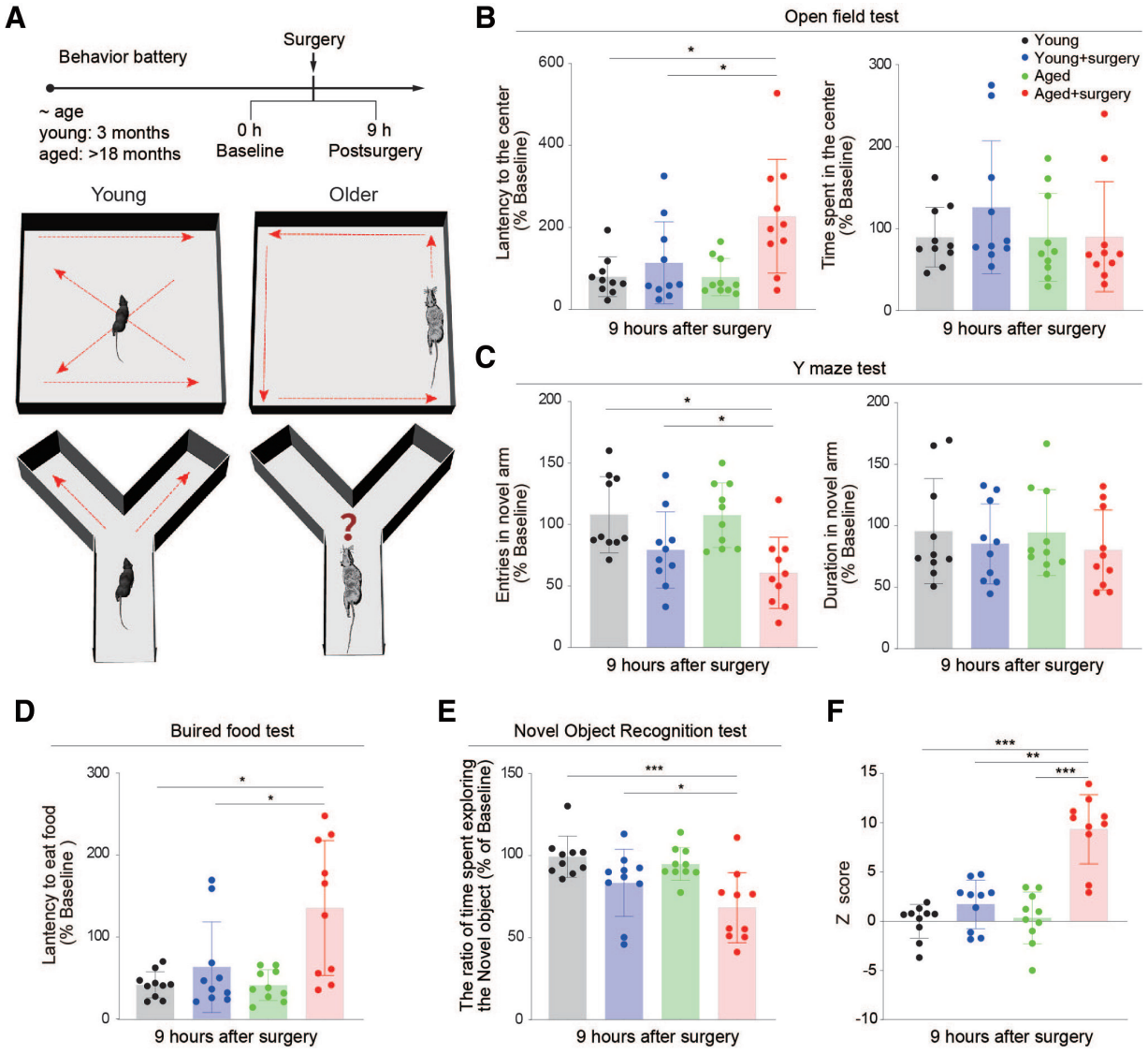


Fig. 1. Anesthesia/surgery induces postoperative delirium (POD)–like behavior in aged but not in young adult mice. (*A*) Diagram of procedures and behavioral tests (*top*) and graphic illustration of battery behavior test (*bottom*). (*B*) Comparison of young mice and aged mice on latency to the center (*left*) and the time spent in the center (*right*) of the open field test before and 9 h after the surgery. The *P* values indicate the difference in these changes between young and aged mice (n = 10, one-way ANOVA followed by Tukey *post hoc* analyses). (*C*) Comparison of young mice and aged mice on entries in the novel arm (*left*) and duration in the novel arm (*right*) of Y maze test before and 9 h after the surgery (n = 10, one-way ANOVA followed by Tukey *post hoc* analyses). (*D*) Comparison of young mice and aged mice on the latency to eat food before and 9 h after the surgery (n = 10, one-way ANOVA followed by Tukey *post hoc* analyses). (*E*) Comparison of young mice and aged mice on the ratio of time spent exploring the novel object before and 9 h after the surgery (n = 10, one-way ANOVA followed by Tukey *post hoc* analyses). (*F*) Comparison of young mice and aged mice on composite Z score in mice before and 9 h after the surgery (n = 10, one-way ANOVA followed by Tukey *post hoc* analyses). The data are means ± SD. **P* < 0.05; ***P* < 0.01; ****P* < 0.001.

and female mice (supplemental fig. S1, https://links.lww.com/ALN/D940). Z scores for both age groups at 24 h postoperatively were comparable to baseline levels, suggesting the improvement of POD-like behavior, which mirrors the fluctuating clinical course observed in human POD[40] (fig. 1F; supplemental fig. S2, https://links.lww.com/ALN/D940).

Electrophysiologic Recording from Large Neuronal Populations in the Hippocampus

We took advantage of the multishank HSP to record from the hippocampal regions. Specifically, the probes were implanted to capture neural activity across the hippocampal and cortical regions in awake, head-fixed mice (supplemental fig. S3, https://links.lww.com/ALN/D940).

Representative raw traces from the hippocampus are shown in figure 2B, illustrating local field potentials and spiking activity captured from multiple recording sites. To extract spike data, we employed a generic spike sorting toolbox, SpyKING CIRCUS,[42] which involves a generic five-step processing pipeline (fig. 2C): (1) recording extracellular potentials, (2) preprocessing raw traces with bandpass filtering (300 to 6000 Hz) and common reference subtraction, (3) spike detection using a thresholding method (6σ), (4) feature extraction and clustering, and (5) template matching to assign detected spikes to specific clusters. The representative sorted templates and auto-/cross-correlograms are plotted in supplemental figure S4 (https://links.lww.com/ALN/D940). After spike sorting, we identified distinct neuronal populations, including putative pyramidal neurons and interneurons, mapped to their respective locations along the probe (fig. 2, D and E). These sorted neurons were identified and mapped on the probe shanks, which were aligned with the Allen Brain Atlas to provide an accurate anatomical context for our recordings by measuring the distance between brain region layers and their respective angles. For the brain slice at bregma −2.06 mm, the lower boundary of the cortex and the upper boundary of the hippocampus form an 18-degree angle relative to the horizontal plane. This alignment showed that the distance between the cortex and the CA1 region was approximately 250 μm, with the 18-degree angle corresponding to the contour of the nonactive region between the cortex and CA1. This consistency with known anatomical features of the mouse brain[43] not only supports the accuracy of our probe placement but also confirms the anatomical precision of our recordings. Finally, spike rasters from the four shanks of the multishank probe

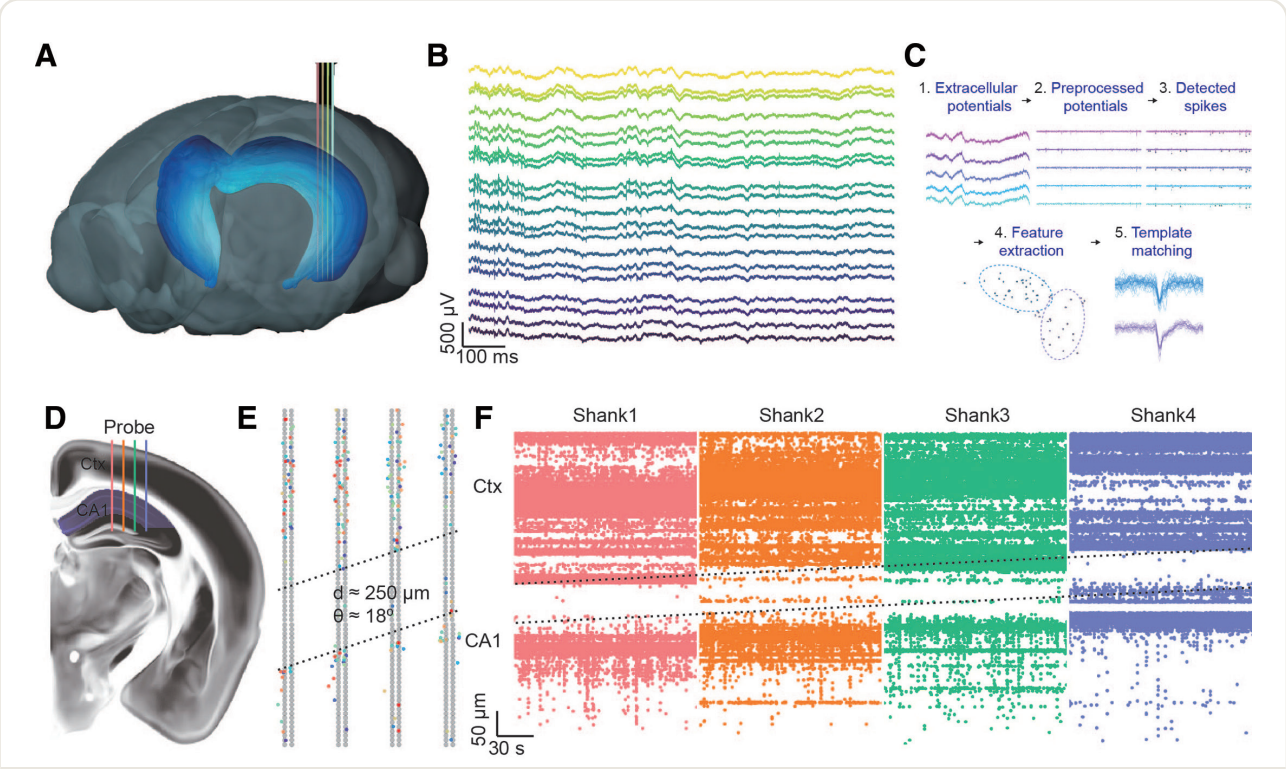


Fig. 2. Electrophysiology recording from large neuronal populations in hippocampus region in an awake head-fixed mouse. (*A*) Illustration of signals acquired from a four-shank high-density silicon probe inserted through hippocampus region. The approximate structure boundaries of four shanks are shown in four different colors. For the heat maps, each square represents a single site. (*B*) Example raw data traces show local field potentials and spiking signals recorded from 10 nearby recording sites in the hippocampus region in an awake, head-fixed mouse. (*C*) Spike sorting process of spiking signals: (1) record extracellular potentials by high-density neural probe with recording system, (2) preprocess raw traces by bandpass filter (300 to 6000 Hz) and common reference subtractions, (3) spikes are detected by thresholding (6σ) over traces, (4) assign each detected spike to a cluster by selecting and extracting features from spikes by principal component analysis, and (5) template matching process by computing similarity between any element and center of clusters. (*D*) The approximate probe implantation locations are shown overlaid on the Allen Mouse Brain Atlas (generated by BrainGlobe[41]). A total of 1,014 putative individual neurons in six animals were recorded simultaneously. (*E*) The probe map illustrates the physical locations of the recorded pyramidal neurons within the hippocampal region, with the *dotted line* indicating the boundary between the cortex (Ctx) and hippocampal CA1 regions. The distance between two regions is 250 μm with an 18-degree angle. (*F*) The example spiking raster plot presents data from a probe chronically implanted in a single mouse, capturing spike activity across 768 recording sites. Each colored block corresponds to spike times recorded from a shank with 192 channels, with the spikes plotted according to the depth along the probe where they were detected.

are presented in figure 2F. Each colored block represents spike times recorded from a shank consisting of 192 channels, plotted according to the depth along the probe where the spikes occurred. This comprehensive representation of neural activity across multiple hippocampal layers enables detailed examination of neural dynamics in both adult and aged mice, with single-neuron resolution. In summary, our results demonstrate that the high-density silicon probe can record neural activity across extensive brain regions, with the ability to specifically identify key areas such as the hippocampus from an electrophysiologic perspective.

Interneuron Hypoactivity and Pyramidal Neuron Hyperactivity Contribute to Neural Network Dysfunction in Postoperative Delirium–like Behavior

To investigate the role of neural activity implicated in POD, we first classified the spike-sorted units into three distinct neuronal types based on waveform peak-to-trough duration and the autocorrelogram τ_{rise}, following the criteria established by Petersen *et al.* (fig. 3A).[36] Each unit was plotted on a graph representing its peak-to-trough time against the autocorrelogram τ_{rise}, allowing for clear differentiation between pyramidal cells, narrow interneurons, and wide interneurons (fig. 3B). To validate the accuracy of this classification, we projected all units into a two-dimensional linear discriminant analysis space, demonstrating well-separated clusters corresponding to each neuron type (classification accuracy = 0.96). This projection confirmed the robustness of this classification method, with distinct groupings of pyramidal cells, narrow interneurons, and wide interneurons. In summary, we can cluster different neuron types, providing valuable insights for neuron-specific electrophysiologic analysis. This approach facilitates a comprehensive examination of neuronal dynamics, particularly in the context of POD within the hippocampus.

We then analyzed the spike count of these three neuron types before and after anesthesia/surgery in both adult and aged mice (fig. 3, D and E). The results indicated significant differences in neuronal activity between these two age groups. Specifically, aged mice showed an increase in hyperactive pyramidal cells (0.6 ± 2.46 Hz, $P = 0.0003$, t(225) = 2.665) and a decrease in total interneuron activity (−0.75 ± 1.99, $P = 0.0001$, t[112] = 4.009) at 9 h postoperatively, compared to adults. Notably, at 24 h postoperatively, these differences were largely diminished (supplemental fig. S5, https://links.lww.com/ALN/D940), concordant with the alleviation of POD-like behavior.

Finally, we present the statistical analysis highlighting the significant increase of hyperactive pyramidal neurons and the hypoactivity of integrated interneurons (both wide and narrow) in aged mice after anesthesia (fig. 3, F and G). The average firing rate of classified interneurons was also analyzed separately for narrow and wide interneurons (supplemental fig. S6, https://links.lww.com/ALN/D940). We also plotted a histogram of the difference between postanesthesia/surgery and preanesthesia/surgery spike counts, highlighting hypoactivity in aged mice, defined by the distance between the fitted curves of aged and adult mice (fig. 3H). These findings suggest a disrupted excitation–inhibition balance in the hippocampal network of aged mice in the early postoperative period, which may contribute to the development of POD-like behavior.

IPA Pretreatment Attenuates Postoperative Delirium–like Behavior in Aged Mice after Anesthesia/Surgery

Mitochondrial dysfunction is a key factor contributing to POD.[44,45] Repression of PGC-1α has been linked to neurodegeneration, while enhancing its expression has been shown to reverse mitochondrial dysfunction.[46,47] Building on our previous findings,[24] which highlighted the potential of IPA to enhance PGC-1α expression and protect against POD, we administered IPA to aged mice and evaluated their POD-like behavior.

Aged mice received daily IPA injections (12 mg/kg) for 14 days before anesthesia/surgery (fig. 4A). Behavioral assessments were conducted before and after the surgery, including open field, Y maze, buried food, and NOR tests. As shown in figure 4 (B through E), IPA pretreatment significantly reduced the latency in finding and eating buried food, which was markedly prolonged in control mice after surgery. This improvement suggests that IPA pretreatment alleviated some of the disruptions in natural behavior typically seen in aged mice after anesthesia/surgery.

Furthermore, IPA-pretreated mice exhibited improved performance in the Y maze, open field, and NOR tests compared to the control group, suggesting that IPA has the potential to improve cognitive function in aged mice after anesthesia/surgery. Specifically, IPA-pretreated mice showed better spatial memory, exploration, and anxiety-related behaviors, as evidenced by their increased entries into the novel arm of the Y maze (63.88% *vs.* 96.40%; 95% CI, 1.109 to 63.94; $P = 0.003$; F [1.949, 17.54] = 8.528), longer time spent in the center of the open field (128% *vs.* 115.1%; 95% CI, −88.74 to 114.5; $P = 0.662$; F [1.157, 10.41] = 0.2494), and increased exploration of the novel object in the NOR test (76.34% *vs.* 88.73%; 95% CI, 0.4713 to 24.30; $P = 0.0009$; F [1.982, 17.84[= 10.65). The significant increase in the composite Z score (1.484 *vs.* 7.214; 95% CI, −9.865 to −1.595; $P = 0.0004$; F [1.281, 11.53] = 21.00) indicates that POD-like behavior is more significant in aged mice without IPA compared to those pretreated with IPA (fig. 4F). Together, these results suggest that IPA may offer a promising preventive approach for mitigating cognitive dysfunction and POD in aging populations.

IPA Pretreatment Alleviates Electrophysiologic Alterations in Aged Mice after Anesthesia/Surgery

To assess the impact of IPA injection on neural activity changes, we recorded and analyzed electrophysiologic

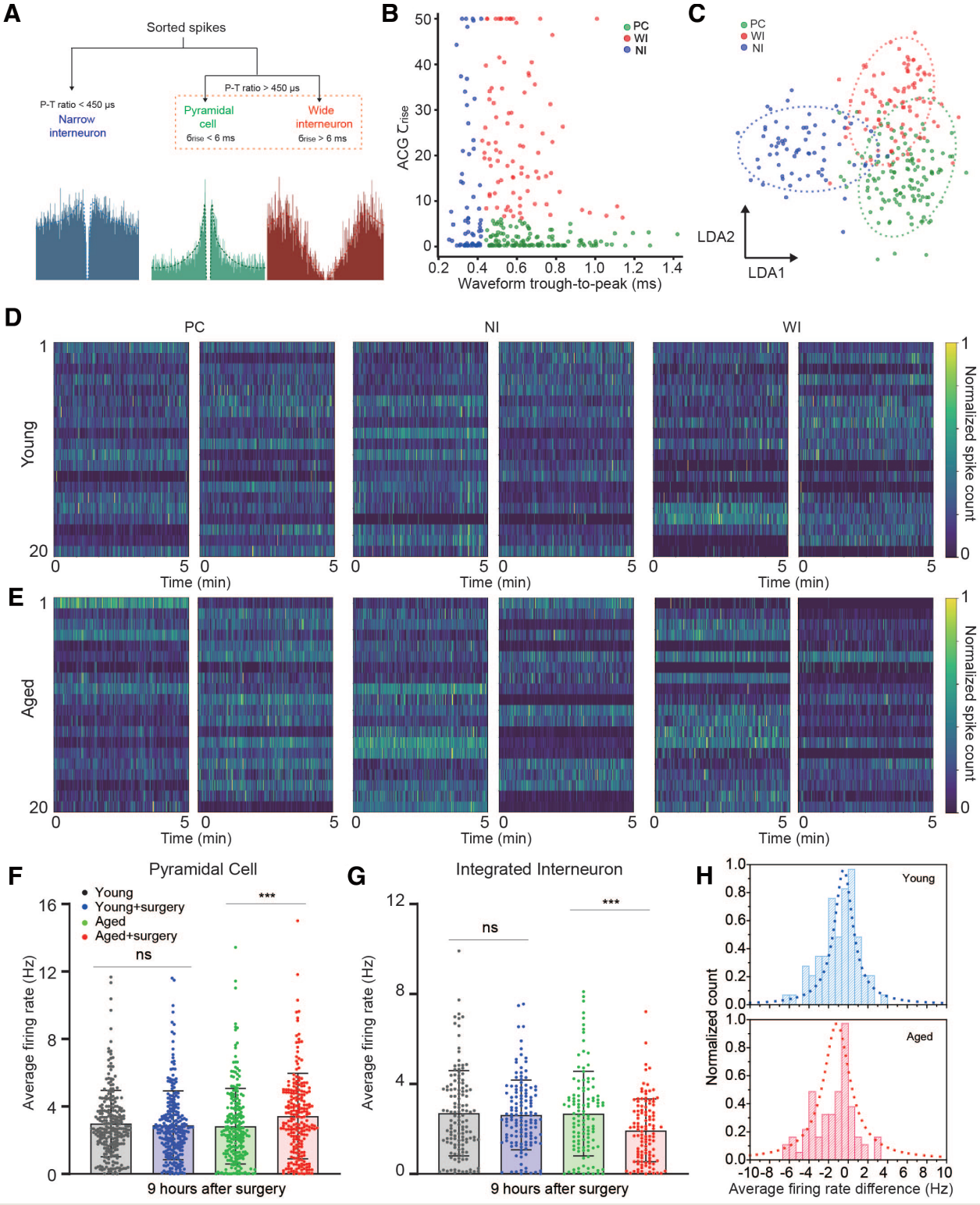


Fig. 3. Interneuron hypoactivity and pyramidal neuron hyperactivity contribute to neural network dysfunction and remote memory impairment after anesthesia/surgery. (*A*) Postprocessing step indicates the classification of pyramidal cells (PC), narrow interneurons (NI), and wide interneurons (WI) characterized by spike-waveform characterization.[36] Representative autocorrelograms show the difference of three types of neurons, with a *dotted line* representing the fitted curve to determine τ_{rise}. (*B*) Neuron-type classification based on spike-waveform width (trough-to-peak) and the temporal scale of the rising phase of the autocorrelogram (ACG; τ_{rise}).[36] (*C*) Clusters of different neuron *(Continued)*

signals in aged mice pretreated with IPA and compared them to untreated controls. We first analyzed the spike count of the three neuron types before and after anesthesia/surgery in aged mice with IPA pretreatment (figure 5A), suggesting that IPA pretreatment helps counteract the effects of anesthesia/surgery by reducing pyramidal cell hyperactivity and improving interneuron hypoactivity. Further statistical analysis indicated that, in IPA-pretreated mice, there were no significant changes in the activity of either pyramidal cells (0.029 ± 1.672, $P = 0.804$, $t(202) = 0.25$) or interneurons (0.407 ± 2.219, $P = 0.091$, $t(86) = 1.71$) when comparing pre- and postsurgery states (figure 5B and C). This suggests that IPA may help stabilize neuronal firing patterns, preventing the exaggerated activity often seen in untreated aged mice after surgery.

Additionally, we plotted a histogram showing the difference in spike count before and after anesthesia/surgery in aged mice with and without IPA pretreatment. The results revealed a notable attenuation of hypoactivity in IPA-pretreated mice, as evidenced by a smaller gap between the fitted curves for the two groups (figure 5D and E). These findings suggest that IPA pretreatment helps restore the excitation–inhibition balance in the hippocampal network of aged mice, potentially mitigating the development of POD-like behavior.

Overall, these findings are consistent with the hypothesis that IPA pretreatment prevents the excitation–inhibition imbalance within the hippocampal network of aged mice. By correcting disruptions in neural activity, IPA pretreatment may offer a potential strategy for mitigating POD-like behavior and cognitive impairments in aging populations (fig. 5).

Altered Hippocampal Neural Dynamics in Aging-associated Postoperative Delirium and Improvement with IPA Pretreatment

Our microelectrode recording data showed a decrease in interneuronal activity along with an increase in excitatory activity in the hippocampus of aged mice compared to adult mice. To further validate these findings, we used two-channel intravital two-photon calcium imaging to simultaneously examine excitatory neurons and interneurons in the hippocampus of mice undergoing anesthesia/surgery and developing POD. The neurons were labeled with green and red calcium indicators, respectively, using a well established viral strategy based on *CaMKII* and *dlx* promoters,[24,33,48] which efficiently target excitatory neurons and interneurons, respectively (fig. 6A). Specifically, AAV8-Dlx-GCaMP6f (green) and AAV8-CaMKII-jRGECO1a (red) viruses were injected into the hippocampus of mice to label the interneurons and excitatory neurons. Imaging was conducted before (0 h) and 9 h after surgery (n = 4; fig. 6B). The results showed that aged mice exhibited heightened calcium dynamics in excitatory neurons and attenuated calcium dynamics in interneurons 9 h after surgery, consistent with pyramidal neuron hyperactivity and interneuron hypoactivity captured using a high-density neural probe.

Notably, IPA pretreatment significantly improved these abnormal hippocampal neural dynamics by reducing excitatory neuron hyperactivity and enhancing interneuron activity in aged mice postoperatively (fig. 6, C through H). These findings from both calcium imaging and electrophysiologic recording implicate imbalanced neural dynamics in POD and suggest that IPA helps restore this balance to mitigate POD development.

Discussion

In this study, we investigated the impact of anesthesia and surgery on neural activity in the hippocampal region of aged mice and its association with POD-like behavior. Our results suggest a working hypothesis that delirium-like behavior in aged mice is accompanied by decreased interneuron activity and increased pyramidal neuron activity in the hippocampus. These results also revealed that IPA pretreatment could attenuate these abnormal neural activities and alleviate delirium-like behavior.

Our data indicated that anesthesia/surgery induced significant neural alterations in aged mice characterized by interneuron hypoactivity and pyramidal neuron hyperactivity. These changes in neural activity disrupted the excitation–inhibition balance within the hippocampal circuitry, the integrity of which is critical for maintaining cognitive function and memory consolidation.[49,50] The observed reductions in interneuron activity likely impaired the inhibitory control over pyramidal neurons, leading to a hyperactive state in excitatory neurons. This neural imbalance was closely associated with cognitive impairments observed in aged mice after surgery, as evidenced by their poor performance in behavioral tests such as the open field, Y maze, buried food, and NOR tests. This imbalance is consistent

Fig. 3. *(Continued)* types on low dimensional linear discriminant analysis (LDA) space span on the first two dimensions: LDA1 and LDA2. (*D*) Binned spike count of different neuron types before and after anesthesia/surgery in young mice (bin size, 1 s). (*E*) Binned spike count of different neuron types before and after anesthesia/surgery in aged mice (bin size, 1 s). (*F*) Comparison of young mice and aged mice on the average firing rate of pyramidal neurons before and 9 h after the surgery (n = 253/226 for young/aged mice, unpaired *t* test, double sided). (*G*) Comparison of young mice and aged mice on the average firing rate of integrated interneurons before and 9 h after the surgery (n = 132/113 for young/aged mice, unpaired *t* test, double sided). *$P < 0.05$; **$P < 0.01$; ns, not significant. (*H*) Histogram showing the difference in total spike count of integrated interneurons before and after anesthesia/surgery in young and aged mice. The *dotted line* represents a Lorentzian fit to the histogram data.

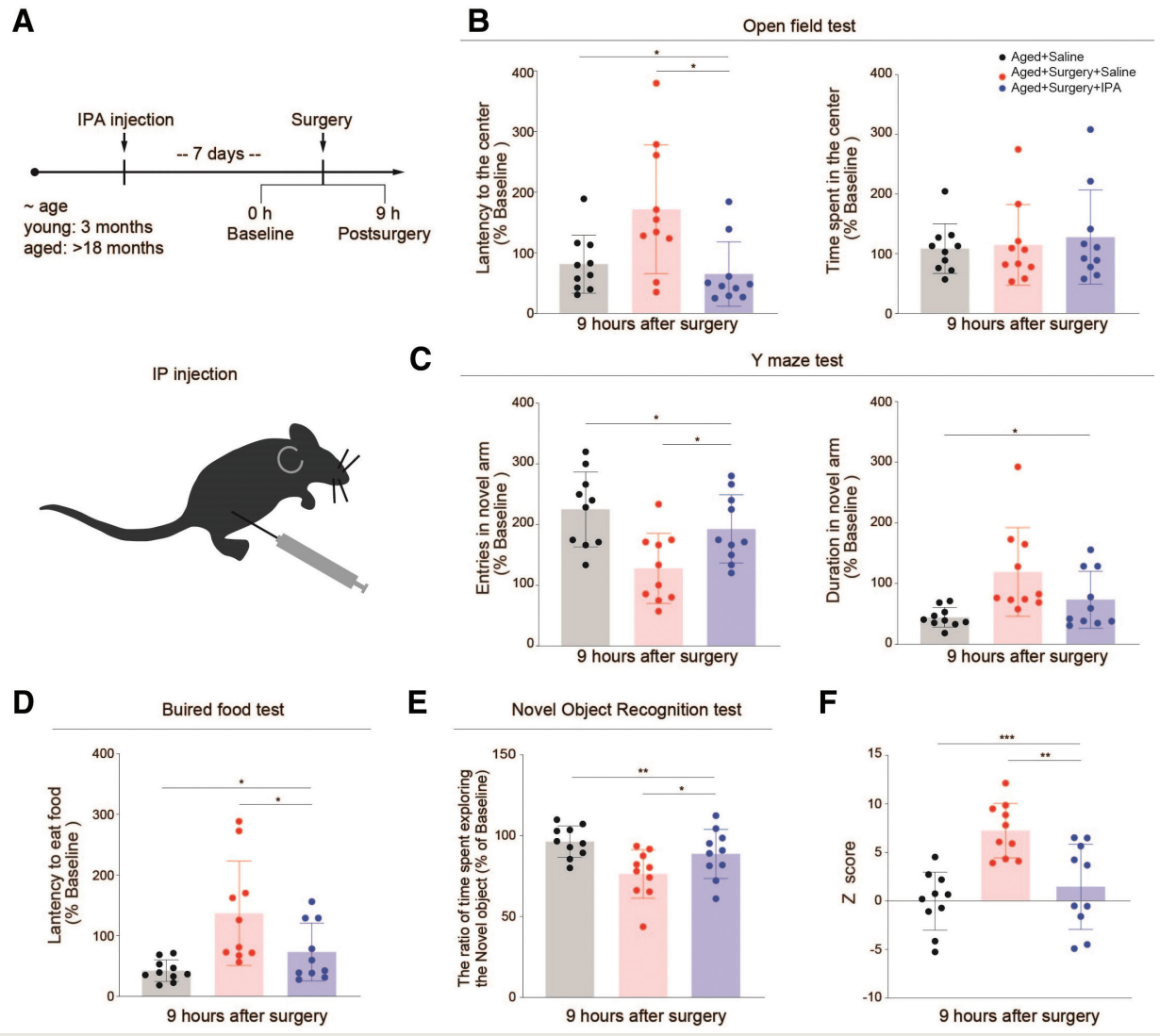


Fig. 4. IPA pretreatment ameliorates postoperative delirium (POD)–like behavior in aged mice after anesthesia/surgery. (*A*) Diagram of procedures of battery behavior test with and without indole-3-propionic acid (IPA) injection. (*B*) Comparison of aged mice with and without IPA injection, assessing the latency to enter the center (*left*) and the time spent in the center (*right*) in the open field test, both before and 9 h after the surgery. The *P* values indicate the differences in these changes between the groups of aged mice pretreated with IPA and those without the injection (n = 10, one-way ANOVA followed by Tukey *post hoc* analyses). (*C*) Comparison of aged mice with and without IPA injection, assessing the entries in the novel arm (*left*) and duration in the novel arm (*right*) of Y maze test before and 9 h after the surgery (n = 10, one-way ANOVA followed by Tukey *post hoc* analyses). (*D*) Comparison of aged mice with and without IPA injection, assessing the latency to eat food before and 9 h after the surgery (n = 10, one-way ANOVA followed by Bonferroni *post hoc* analyses). (*E*) Comparison of aged mice with and without IPA injection, assessing the ratio of time spent exploring the novel object before and 9 h after the surgery (n = 10, one-way ANOVA followed by Tukey *post hoc* analyses). (*F*) Comparison of aged mice with and without IPA injection with composite Z score before and 9 h after the surgery (n = 10, one-way ANOVA followed by Tukey *post hoc* analyses). The data are means ± SD. **P* < 0.05; ***P* < 0.01; ****P* < 0.001.

with previous studies that have shown similar dysfunctions in other brain regions during POD.[51,52] Our group has previously reported that chronic pain pushed cortical neural network into a hypersynchronous state, underpinned by interneuron hypoactivity.[37] Maintaining an intricate balance between excitation and inhibition, therefore, is of critical importance for normal neural function. A disruption of this balance is linked to the pathogenesis of many pathologic conditions, including POD.

IPA, which is known for its neuroprotective properties, has previously been shown to play a role in restoring neuronal function in various neurologic conditions.[53] In this study, IPA pretreatment was shown to reduce interneuron hypoactivity and ameliorate pyramidal neuron

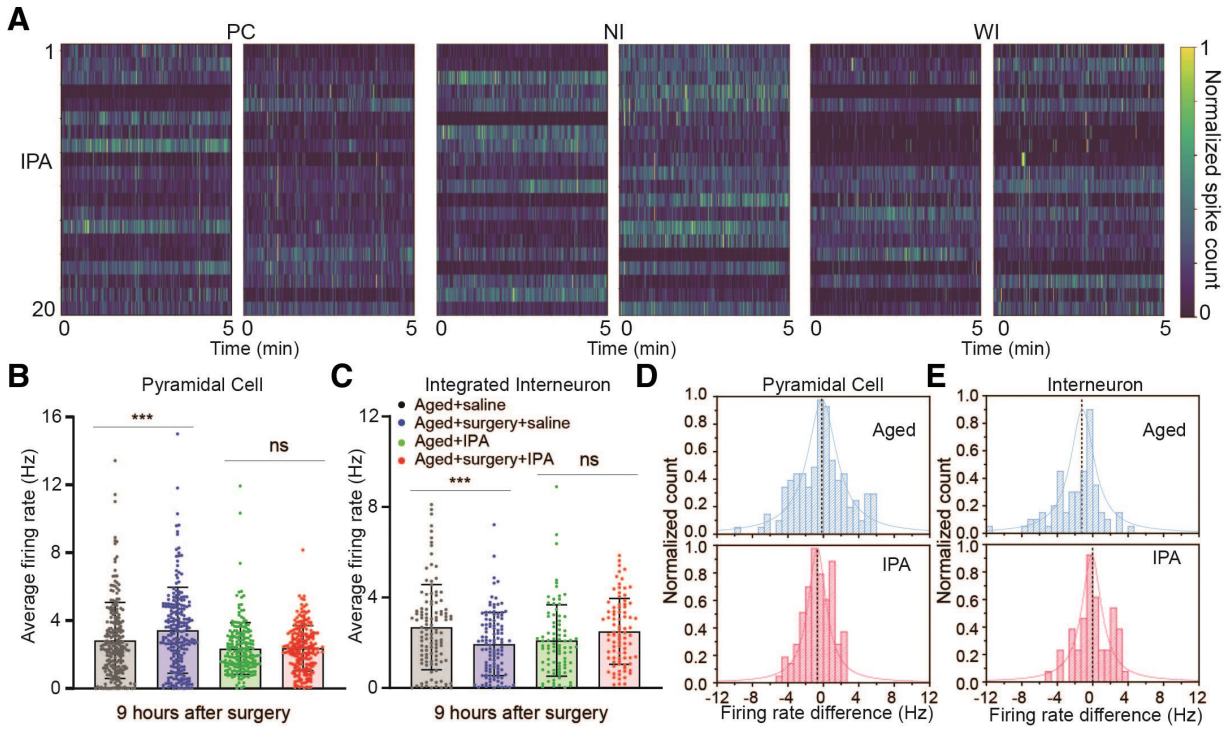


Fig. 5. Indole-3-propionic acid (IPA) pretreatment alleviates electrophysiologic alterations in aged mice after anesthesia/surgery. (*A*) Binned spike count of different neuron types (pyramidal cells [PC], narrow interneurons [NI], and wide interneurons [WI]) before and after anesthesia/surgery in IPA-injected aged mice (bin size, 1 s). (*B*) Comparison of aged mice with and without IPA injection on the average firing rate of pyramidal neurons before and 9 h after the surgery (n = 226/203 for saline/IPA-pretreated mice, unpaired *t* test, double sided). (*C*) Comparison of aged mice with and without IPA injection on the average firing rate of integrated interneurons before and 9 h after the surgery (n = 113/87 for saline/IPA-pretreated mice, unpaired *t* test, double sided). **P* < 0.05; ***P* < 0.01; ns, not significant. (*D*) Histogram showing the difference in total spike count of pyramidal neurons before and after anesthesia/surgery in aged mice with and without IPA injection. The *dotted line* represents a Lorentzian fit to the histogram data. (*E*) Histogram showing the difference in total spike count of integrated interneurons before and after anesthesia/surgery in aged mice with and without IPA injection. The *dotted line* represents a Lorentzian fit to the histogram data.

hyperactivity in aged mice after anesthesia and surgery. This aligns with previous findings demonstrating IPA's potential to enhance expression of PGC-1α, a regulator of neuronal integrity, particularly in interneurons.[24,54] Our results suggest that IPA's ability to restore the excitation–inhibition balance in the hippocampus could be a promising approach for mitigating POD-like behavior in aging animals.

To further understand the neural dynamics involved in POD, we used intravital two-photon calcium imaging to assess hippocampal neurons implicated in POD. Using previously validated methods to target excitatory neurons and interneurons, we were able to visualize neural dynamics in the hippocampus, particularly in the CA1 region, at single-neuron resolution in awake and resting mice before and after anesthesia/surgery. Our calcium imaging data corroborated the electrophysiologic findings, showing that aged mice exhibited heightened calcium activity in excitatory neurons and diminished activity in interneurons after surgery. Importantly, IPA pretreatment attenuated these neural alterations, further confirming its potential as a preventive strategy to mitigate POD-like behavior.

While our study focused on the hippocampus, a region crucial for cognitive functions such as memory, human studies investigating EEG biomarkers of POD have identified global brain network disruptions, including changes in slow-wave oscillations and cortical coherence. These EEG abnormalities suggest that similar disturbances in the excitation–inhibition balance may occur across multiple brain regions in POD patients. Although our approach, utilizing single-unit electrophysiologic recordings, differs from EEG studies in spatial resolution and scale, both methodologies emphasize the importance of disrupted neural activity in the development of POD. Our findings suggest that the hippocampal imbalance observed in aged mice may reflect similar disturbances in human POD, providing valuable insights into the neural mechanisms underlying this condition. Although our findings align with previous studies using high-density electrophysiologic recordings, the small sample size of animals might restrict the generalizability of our results. Future

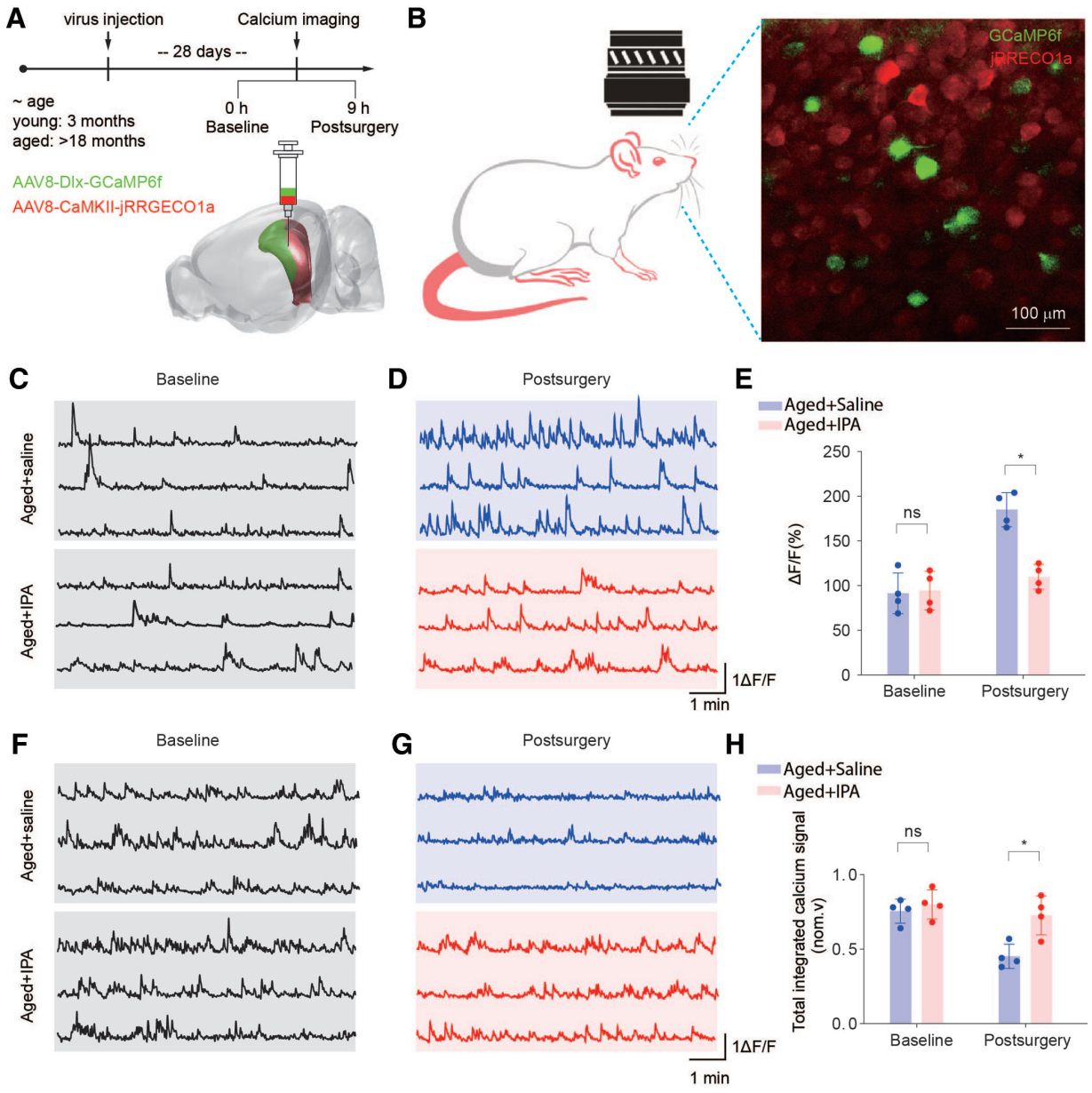


Fig. 6. Altered hippocampal neural dynamics in aging-associated postoperative delirium (POD) and improvement with indole-3-propionic acid (IPA) injection. (*A*) Flowchart and sketch depict the experimental design. AAV8-CaMKII-jRGECO1a and AAV8-Dlx-GCaMP6f were injected into the hippocampus 4 weeks ahead of the baseline imaging followed by anesthesia/surgery. (*B*) Diagram demonstrates intraviral imaging (*left*) and a representative image of GCamP6f (*green*) and jRGECO1a (*red*) expression. *Scale bar*, 100 μm. (*C* to *E*) Excitatory activity in response to anesthesia/surgery. (*C*, *D*) representative traces of excitatory neurons of hippocampus across groups. (*E*) Statistics of ΔF/F. N = 4 mice, two-way ANOVA followed by Bonferroni *post hoc* test to determine the difference among the groups. (*F* to *H*) Inhibitory activity in response to anesthesia/surgery. (*F*, *G*) representative traces of inhibitory neurons of hippocampus across groups. (*H*) Integrated calcium signal of inhibitory neurons across groups. N = 4 mice, two-way ANOVA followed by Bonferroni *post hoc* test to determine the difference among the groups. $^{*}P < 0.05$; $^{**}P < 0.01$; ns, not significant.

studies with larger cohorts are needed to strengthen these findings.

In conclusion, our study demonstrates that anesthesia/surgery induces an imbalance in hippocampal neural activity in aged mice, which might be associated with POD-like behavior. Moreover, our results indicate that IPA pretreatment attenuates the excitation–inhibition imbalance in the hippocampus, suggesting its potential as a therapeutic strategy for preventing or treating POD in aging populations. This study highlights the importance

of understanding the neural dynamics involved in POD and provides a promising avenue for future research and therapeutic interventions.

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Competing Interests

The authors declare no competing interests.

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Supplemental Digital Content

Supplemental figures, https://links.lww.com/ALN/D940

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ANESTHESIOLOGY®

Effects of the Quinone Analog Ubiquinone-5 on Murine Mitochondria and Hypnosis

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Disruption of mitochondrial bioenergetic capacity is believed to play a role in the anesthetic response
- The mechanisms through which changes in mitochondrial activity may result in the anesthetic response remain incompletely understood

What This Article Tells Us That Is New

- In mice, intravenous injection of ubiquinone-5, a coenzyme Q analog, rapidly induced loss of the righting reflex and electroencephalogram changes consistent with a deep state of anesthesia
- Ubiquinone-5 inhibited the mitochondrial electron transport chain and induced an uncompensated proton leak *via* targeting the aspartate–glutamate carrier protein Aralar located in the inner mitochondrial membrane

ABSTRACT

Background: A functional anesthetic target has long been suspected to reside within mitochondria, and disruption of bioenergetic capacity is believed to play a role in the anesthetic response. Unfortunately, the exact mechanism by which changes in mitochondrial target activity result in clinically relevant anesthetic endpoints remains unknown. Here, the authors leveraged knowledge of propofol toxicity to guide drug discovery and uncover a previously unknown pharmacologic target within mitochondria. They hypothesized that, like propofol, quinone analogs would interfere with electron transfer, cause excessive proton leak within mitochondria, and induce hypnosis. The authors tested their hypothesis using the short-chain coenzyme Q analog ubiquinone-5 (Ub5) and aimed to characterize its anesthetic phenotype in the mouse and elucidate the source of Ub5-induced mitochondrial leak.

Methods: Anesthetic phenotype was assessed *in vivo* in the mouse using behavioral and neurophysiological approaches. The authors measured biologic activity in isolated mitochondria using polarography and spectrophotometry and identified source of proton leak using pharmacologic inhibitors, mutant mouse strains, and transport activity assays in proteoliposomes. Finally, they assessed cardiotoxic effects in the isolated-perfused mouse heart *ex vivo*.

Results: Coenzyme Q analogs caused uncompensated proton leak in developing cardiomyocyte mitochondria and reversible cardiotoxicity in a manner reminiscent of propofol. Tail vein injection of Ub5 induced short-lived loss of righting, electroencephalogram changes consistent with a deep state of anesthesia, and reversible decreases in neuronal calcium transients and mitochondrial membrane potential *in vivo*. Precipitous decline in mitochondrial membrane potential played a role in Ub5-induced unconsciousness, and the authors identified the aspartate-glutamate carrier Aralar as a functional target and source of Ub5-mediated proton leak.

Conclusions: The data indicate that uncompensated mitochondrial proton leak is an important mechanistic contributor to the anesthetic response in addition to electron transport inhibition. These findings advance the authors' understanding of how anesthetics induce hypnosis and lay the foundation for next-generation drug discovery.

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Abbreviations: **ΔΨm**, mitochondrial membrane potential; **ACSF**, artificial cerebral spinal fluid; **AGC**, aspartate-glutamate carrier; **ATP**, adenosine triphosphate; **BSA**, bovine serum albumin; **CoQ**, coenzyme Q; **DB**, decylubiquinone; **DEPC**, diethylpyrocarbonate; **EEG**, electroencephalogram; **ETC**, electron transport chain; **GABA**, γ-aminobutyric acid; **KO**, knockout; **LORR**, loss of righting reflex; **ROI**, region of interest; **TMRE**, tetramethylrhodamine ethyl ester; **Ub5**, ubiquinone-5

General anesthetics are a unique class of drugs that affect a wide range of species with low variability across evolutionary biology, from single-celled organisms to humans.[1] They render vertebrates and higher mammals unconscious and insensitive to noxious stimuli, and their advent has made modern-day surgery and invasive therapy possible.[1,2] Despite advancements in understanding of how anesthetics induce unconsciousness, amnesia, and immobilization, the exact mechanisms remain incompletely understood.[1,2] Although anesthetics are known to modulate voltage-gated ion channels, leak channels, ligand-gated neurotransmitter receptors, cytoskeleton elements, and intracellular signaling proteins, the search for a phylogenetically conserved molecular target continues given that all living organisms across the evolutionary tree can be anesthetized.[1]

A functional anesthetic target has long been suspected to reside within mitochondria.[3–5] To date, complex I of the electron transport chain (ETC) serves as the most compelling example of such a target.[6–12] For example, anesthetic-mediated inhibition of complex I has been shown to interfere with the inability to synthesize adenosine triphosphate (ATP) at the synapse and blocks endocytosis and synaptic neurotransmitter recycling in presynaptic neurons.[9] This effect is thought to result in synaptic silencing.[9] Bypassing complex I inhibition to regenerate nicotinamide adenine dinucleotide improves neuron function, restores ATP levels, rescues endocytosis failure, and confers resistance to isoflurane in mice.[9] Thus, complex I inhibition may functionally contribute to the mechanism(s) of anesthesia.[9] However, it is unknown how changes in mitochondrial target activity result in clinically relevant anesthetic endpoints, and it is unclear whether other functional anesthetic targets exist within mitochondria.

Organisms and hosts that harbor genetic mutations in complex I demonstrate hypersensitivity to volatile anesthetics and propofol (2,6-diisopropylphenol).[6–8,10] Complex I-deficient *Ndufs4* knockout mice are also prone to isoflurane-induced metabolic disturbances, weight loss, and death, suggesting an association between anesthetic sensitivity and anesthetic toxicity.[13] In contrast, *Drosophila* carrying mutations in the ND23 subunit of complex I are hypersensitive to both sevoflurane and isoflurane but only prone to isoflurane-induced toxicity, indicating a dissociation between anesthetic mechanisms of action and drug toxicity.[14] Therefore, it is unclear whether there is a link between the behavioral response to anesthetics and the mitochondrial mechanism(s) of anesthetic-induced toxicity. A clinical scenario where mitochondria are widely accepted to be the effector organelle in mediating toxicity is propofol-related infusion syndrome.[15–19] Toxicity occurs when propofol inhibits various components of the ETC while simultaneously inducing excessive proton leak across the inner mitochondrial membrane to compromise mitochondrial membrane potential ($\Delta\Psi m$).[16–19] Since pharmacologic targets can be elucidated in the setting of toxicity when drug–protein interactions are on target and mechanism-based, we leveraged our knowledge of propofol toxicity to guide drug discovery and uncover a previously unknown mitochondrial target.[20,21] The findings presented here advance our understanding of how mitochondria mediate the anesthetic response and of how anesthetics induce reversible unconsciousness.

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Materials and Methods

Animals

The care of the animals in this work was in accordance with National Institutes of Health (Bethesda, Maryland) and Columbia University Irving Medical Center Institutional Animal Care and Use Committee and Animal Research Reporting of In Vivo Experiments (ARRIVE) guidelines and conformed to the provisions of the Animal Welfare Act (National Institutes of Health/Department of Health and Human Services, Washington D.C.) and the Association for Assessment and Accreditation of Laboratory Animal Care (Frederick, Maryland). C57Bl/6N breeding pairs were acquired (Charles River, USA) to yield male pups. Postnatal day 10 (P10) male pups were utilized for cardiac studies. Male mice 6 to 8 weeks old were used for all other experiments. This age range was chosen to model for a timepoint in late adolescence or young adulthood in the human when mice are sexually mature and demonstrate mature locomotion.[22] A subset of 6- to 8-week-old female mice was tested for loss of righting after tail vein injection of ubiquinone-5 (Ub5).

Aralar Mutant Mice

Mice harboring a heterozygotic mutation of the *Aralar* (*Slc25a12*) gene on a SVJ129 × C57BL/6 background were acquired from Taconic Biosciences (USA) and mated to yield *Aralar* knockout (KO; *Aralar*$^{-/-}$) mice, *Aralar* heterozygotes (*Aralar*$^{\pm}$), and wild-type (*Aralar*$^{+/+}$) littermate controls. Genotype was determined by standard polymerase chain reaction. P10 male pups were utilized for studies of *Aralar* KO mice (along with age-matched wild-type littermate controls) given the progressive neurologic impairment and markedly shortened lifespan seen in mutants.[23] Male *Aralar* heterozygotes and wild-type littermate mice 6 to 8 weeks old were used for all other experiments.

Thy1-GCaMP6 Transgenic Mice

Transgenic mice expressing GCaMP6 slow (*Thy1*-GCaMP6s) in L5 pyramidal neurons have been previously described.[24] These mice were bred in house to permit *in vivo* calcium imaging.

Compounds

Propofol (2,6-diisopropylphenol) was acquired from Fresenius Kabi (USA). Coenzyme Q0 was acquired from Sigma-Aldrich (USA; D9150), decylubiquinone was acquired from Sigma-Aldrich (D7911), coenzyme Q1 was acquired from Sigma-Aldrich (C7596) and Santa Cruz (USA; 727-81-1), intralipid was acquired from Sigma-Aldrich (I141), tetramethylrhodamine ethyl ester was acquired from Sigma-Aldrich (87917), tetraphenylphosphonium was acquired from Sigma-Aldrich (218790), glutamate was acquired from Sigma-Aldrich (G0355000), succinate was acquired from Sigma-Aldrich (398055), rotenone was acquiredd from Sigma-Aldrich (557368), oligomycin was acquired fromSigma-Aldrich (495455), dinitrophenol was acquired from Sigma-Aldrich (D198501), picrotoxin was acquired from Sigma-Aldrich (P1675), cyclosporine was acquired from Sigma-Aldrich (1158504), carboxyatractyloside was acquired from Sigma-Aldrich (PHL84196), diethylpyrocarbonate (was acquired from Sigma-Aldrich (159220), bathophenanthroline was acquired from Sigma-Aldrich (133159), pyridoxal 5'-phosphate was acquired from Sigma-Aldrich (P9255), γ-aminobutyric acid was acquired from Sigma-Aldrich (A2129), aspartate was acquired from Sigma-Aldrich (1043819), *Slc25A12* plasmid was acquired from Genecopoeia (USA; EX-Z2580-B31), ^{3}H-glutamate was acquired from American Radiolabeled Chemicals (USA; ART 08750), ^{3}H-γ-aminobutyric acid was acquired from American Radiolabeled Chemicals (ART 0207).

Experimental Design

Ub5 and Propofol Injection. Awake mice were randomly injected *via* tail vein with a single dose of Ub5 (20 mg/ml in intralipid), propofol (Fresenius Kabi), or equal volume vehicle (intralipid alone).

Righting Reflex Assessment. Righting reflex was tested immediately after tail vein injection for each animal.[25] Mice were considered to have an intact righting reflex if they successfully returned to the prone position twice in a row.[25] Otherwise, righting reflex was considered lost. Latency to return of righting was recorded.

Open Field Video Tracking. Mice were placed in a circular open field (radius, 76 cm), and spontaneous movement was recorded for 30 min before injection using a camera mounted above.[25] After tail vein injection and return of righting, mice were placed in a novel circular open field, and ambulation was recorded for a subsequent 30 min.[25] Movement before and after injection was tracked offline using MATLAB software (The Mathworks, Inc. USA) as previously described.[25]Total distance traveled was quantified.

Body Temperature. Rectal thermometry (Thermalert TH-5, Physitemp Instruments, USA) was used. Measurements were performed between 9:00 AM and 11:00 AM in a room maintained at approximately 20°C. All measurements were obtained hand-restrained mice.

Electroencephalogram Acquisition. Electroencephalogram (EEG) was acquired as previously described.[25,26] Six epidural EEG leads were surgically implanted over visual, somatosensory, and motor cortices bilaterally. Two electromyography leads were implanted in the dorsal neck muscles. All mice recovered for a minimum of 2 weeks before study. To minimize stress, mice were habituated to tethering in their home cages for 3 days before study. EEG biopotential waveforms were recorded and digitized at 1,000 Hz using 32 channel headstages (Intan Technologies, USA) and open-source software.[25,26] EEG was acquired before and after injection. EEG signals were filtered between 1 and 100 Hz using a fifth-order zero-phase Butterworth filter and re-referenced mean.

Intravital Microscopy. *In vivo* calcium and tetramethylrhodamine ethyl ester (TMRE) imaging was performed in *Thy1*-GCaMP6 mice.[24,27,28] Under surgical anesthesia (100 mg/kg ketamine intraperitoneally and 15 mg/kg xylazine intraperitoneally), the skull was exposed *via* scalp incision and somatosensory cortex identified based on stereotaxic coordinates (1 mm lateral from midline, 1.7 mm posterior to bregma). The head was immobilized and a circular cranial window created (approximately 200 μm in diameter). Animals recovered for at least 2 weeks before study. Awake mice were then placed under a two-photon system (Scientifica Hyperscope, United Kingdom) and temperature maintained with a heating pad (approximately 37°C). The two-photon laser was tuned to 940 nm. Neurons within layer II/III of the somatosensory neocortex (90 to 100 μm depth)

were imaged with a 1.05–numerical aperture 25× objective lens immersed in artificial cerebral spinal fluid (ACSF; NaCl 129 mM, KCl 3 mM, NaH_2PO_4 1.25 mM, $MgSO_4$ 1.8 mM, $CaCl_2$ 1.6 mM, $NaHCO_3$ 26 mM, and glucose 10 mM [pH 7.4]) to obtain 100× magnification (104 μm × 104 μm; 512 × 512 pixels) images. TMRE (20 μM freshly diluted in ACSF) was applied directly to the cortical surface and then washed with ACSF after 1 h incubation. Time lapse images were obtained using ScanImage software (Vidrio Technologies, USA) before and after tail vein injection in one focal plane with a 7-Hz frame rate and analyzed with National Institutes of Health ImageJ. Regions of interest (ROIs) were drawn around visually identifiable somata for quantification. Fluorescence of each soma was determined by averaging all pixels within the ROI. Baseline calcium fluorescence (F_0) was estimated using inactive portions of the time course using an iterative procedure, and calcium activity ($\Delta F/F_0$) was calculated as $(F - F_0)/F_0 \times 100\%$.[27] Arbitrary TMRE fluorescence was quantified (ImageJ; range, 0 to 255, 8-bit) within each ROI.[28] TMRE fluorescence was expressed in arbitrary units relative to vehicle preinjected control values and expressed as a ratio relative to baseline fluorescence.

Isolated–Perfused Mouse Heart Preparation. Newborn mouse pups were anesthetized (pentobarbital, 70 mg/kg intraperitoneally) and heparinized (10 kU/kg intraperitoneally). The heart was excised and aorta cannulated as described.[29] Constant flow retrograde perfusion was initiated (2.5 ml · min^{-1}) with modified Krebs–Henseleit buffer containing (mmol/l) NaCl 120, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.2, $CaCl_2$ 1.25, $NaHCO_3$ 25, and glucose 11. Nonrecirculating buffer equilibrated with 95% O_2 and 5% CO_2 was maintained at pH 7.4 and 37°C. After stabilization, surface electrocardiogram was captured using electrodes. Heart rate and rhythm were continuously recorded using an analog-to-digital converter system (Power Lab 4SP, ADInstruments, Australia). Hearts were then exposed to propofol (5.9 g · kg^{-1} · min^{-1}), decylubiquinone (1.1 g · kg^{-1} · min^{-1}), Ub5 (0.8 to 3.2 g · kg^{-1} · min^{-1}), or equal volume intralipid.

Open Field Test for Exploratory and Anxiety Behavior. Exploration was monitored during a 30-min session 1-week after injection of Ub5 (100 mg/kg) or vehicle with Activity Monitor Version 7 tracking software (Med Associates Inc., USA). Briefly, each mouse was placed in the center of a clear Plexiglas arena (27.31 × 27.31 × 20.32 cm; Med Associates Inc.; ENV-510) lit with dim light (approximately 5 lux) and allowed to ambulate freely. Infrared beams embedded along the *x*, *y*, *z* axes of the arena automatically tracked distance moved, horizontal movement, vertical movement, and time spent in center zone (14.29 × 14.29 cm). Data were blindly analyzed (D.L. and M.Y.) in six 5-min time bins.

Y Maze Spontaneous Alternation. The test was conducted in a Y maze apparatus (three arms of equal length [35 cm], width [5 cm], and height [10 cm]; Maze Engineer, USA) 1 week after injection of Ub5 (100 mg/kg) or vehicle. Each mouse was placed in the center of Y maze and allowed to explore freely for 8 min. Percentage of alternation was calculated as a measure of spatial working memory in a blinded manner (D.L. and M.Y.).

Morris Water Maze. Spatial learning and memory were assessed 2 weeks after injection of Ub5 (100 mg/kg) or vehicle in a 122-cm circular pool filled 45 cm deep with tap water and rendered opaque with the addition of nontoxic white paint (Crayola). Water temperature was maintained at 24° ± 1°C. The proximal cue was a sticker taped on the inner surface of the pool, approximately 20 cm above the water surface. Trials were videotaped and scored in a blinded manner (D.L. and M.Y.) with Ethovision XT 17 (Noldus, USA). Acquisition training consisted of four trials per day for 5 consecutive days. Each training trial began by lowering the mouse into the water close to the pool edge, in a quadrant that was either right of, left of, or opposite the target quadrant containing the platform (12 cm diameter). The start location for each trial was alternated in a semirandom order for each mouse. The hidden platform remained in the same quadrant for all trials during acquisition training for a given mouse but varied across subject mice. Mice were allowed a maximum of 60 s to reach the platform. A mouse that failed to reach the platform in 60 s was guided to the platform by the experimenter, and distance swum was determined based on visual tracking data collected within the 60 s. Mice were left on the platform for approximately 15 s before being removed. After each trial, the subject was placed in a cage lined with absorbent paper towels and allowed to rest under an infrared heating lamp for 1 min. An hour after the completion of the last training trial, the platform was removed and mice were tested in a 60 s probe trial. Latency to reach the platform, total distance traveled, and swim speed were recorded blindly (D.L. and M.Y). Time spent in each quadrant were used to analyze probe trial performance.

Liquid Chromatography–Mass Spectrometry Analysis of Ub5. Brain tissue was homogenized in a prechilled (4°C) hexane/2-propanol mixture (7:3, v/v). Samples were incubated on ice for 2 h and centrifuged at 18,000*g* for 20 min at 4°C. Organic phase lipids were collected, dried under a gentle stream of nitrogen gas, and then reconstituted in 2-propanol/acetonitrile/water solution (4:3:1, v/v/v; 200 μl). Samples were analyzed on an Acquity UPLC-H class system (Waters Corporation, USA) coupled to a high-resolution quadrupole time-of-flight mass spectrometer (XEVO G2 XS MS; Waters Corporation, United Kingdom). Chromatographic separation was carried out using high strength silica C18 analytical column (2.1 × 100 mm, 1.8 μm). Mobile phase A consisted of acetonitrile/water (60:40, v/v), and mobile phase B was 2-propanol/acetonitrile/water (85:10:5, v/v/v), both containing 10 mM ammonium acetate and 0.1% acetic acid. The gradient was held at 50% mobile phase B for

1 min and increased to 100% B in 6 min. The eluent composition returned to the initial condition by 10 min, and the column was re-equilibrated for an additional 1 min. Spectra were acquired in positive electrospray ionization mode. A capillary voltage and sampling cone voltage of 1.6 kV and 30 V were used. The data were collected in duplicates over the mass range m/z 50 to 1,000 Da. The structural assignment of Ub5 in the samples was confirmed by matching the retention time and the fragmentation patterns with the standard. Data were acquired with MassLynx (version 4.1) software and processed with QuanLynx (version 4.1) software (Waters Corporation, USA).

Isolation of Mitochondria. Cardiac ventricles and forebrain were harvested and homogenized in ice-cold isolation buffer (225 mM mannitol, 75 mM sucrose, 1 mM EGTA, 5 mM HEPES-KOH [pH 7.2], and 1 mg/ml fatty acid–free bovine serum albumin [BSA]). Homogenate was spun at 1,100*g* for 5 min at 4°C. For the heart, supernatant was centrifuged (18,500*g*) for 10 min at 4°C using a 15 vol% Percoll gradient. For brain, supernatant was mixed with 80 vol% Percoll solution and layered on 10% Percoll solution, then centrifuged. The pellet was resuspended in washing buffer (250 mM sucrose, 5 mM HEPES-KOH [pH 7.2], 0.1 mM EGTA, and 1 mg/ml BSA) and centrifuged at 10,000*g* for 5 min at 4°C. The mitochondrial pellet was resuspended and protein concentrations determined using the method of Lowry.

Mitochondrial Oxygen Consumption. Forebrain mitochondria (0.1 mg) or cardiomyocyte mitochondria (0.05 mg) were added to 0.5 ml respiration buffer (200 mM sucrose, 25 mM KCl, 2 mM K_2HPO_4, 5 mM HEPES-KOH [pH 7.2], 5 mM $MgCl_2$, 0.2 mg/ml BSA). Respiration was measured using a Clark-type electrode (Oxytherm, Hansatech, United Kingdom) with complex I–dependent substrates (10 mM glutamate and 5 mM malate) and complex II–dependent substrate (10 mM succinate in the presence of 5 μM rotenone) separately at 32°C. ADP (200 μM) was added to initiate state 3 respiration. Oligomycin (2.5 μg/ml) was added to induce state 4 respiration, and maximal rate of uncoupled state 3 respiration was induced with dinitrophenol (70 μM).

For leak respiration, oxygen consumption and $\Delta\Psi m$ were measured simultaneously with 5 mM succinate using cardiac (0.1 mg) or forebrain mitochondria (0.2 mg) in 1 ml respiration buffer (200 mM sucrose, 25 mM KCl, 2 mM K_2HPO_4, 5 mM HEPES-KOH [pH 7.2], 5 mM $MgCl_2$, 0.2 mg/ml BSA) containing 80 ng/ml nigericin (to collapse ΔpH), 5 μM rotenone, and oligomycin (2.5 μg/ml) at 37°C. $\Delta\Psi m$ was quantified using an ion-sensitive electrode selective for tetraphenylphosphonium ion (World Precision Instruments, USA) and calculated using the Nernst equation.[30]

In separate experiments, cyclosporine A (1 μM), carboxyatractyloside (1 μM), diethylpyrocarbonate (5 μM), and pyridoxal 5′-phosphate (1 mM) were added to inhibit the mitochondrial permeability transition pore, the adenine nucleotide translocase, and Aralar, respectively, to determine source of leak.[31–35] Picrotoxin (5 μM), a γ-aminobutyric acid (GABA) type A receptor antagonist, served as a control inhibitor.

Modular Kinetics. Proton leak, substrate oxidation, and ATP turnover were measured independently as previously described.[36] Oxygen consumption and $\Delta\Psi m$ were measured simultaneously using forebrain mitochondria (0.2 mg) in 1 ml respiration buffer (200 mM sucrose, 25 mM KCl, 2 mM K_2HPO_4, 5 mM HEPES-KOH [pH 7.2], 5 mM $MgCl_2$, 0.2 mg/ml BSA) containing 5 mM succinate, 80 ng/ml nigericin, and 5 μM rotenone at 37°C. $\Delta\Psi m$ was determined using tetraphenylphosphonium ion. For proton leak kinetics, state 4 was induced with oligomycin (2.5 μg/ml), and respiration was titrated with malonate (up to 2 mM). For substrate oxidation kinetics, state 4 was induced with oligomycin (2.5 μg/ml), and respiration titrated with dinitrophenol (up to 100 μM). For ATP turnover, state 3 was induced (100 μM ATP, 20 mM glucose, and 10 U/ml hexokinase [baker's yeast, Sigma-Aldrich]) and titrated with malonate (up to 200 μM).

Steady-state ETC Enzyme Complex Activities. Inhibitor sensitive ETC complex activities were measured in 1 ml volume spectrophotometrically in isolated mitochondria.[16,28] Rotenone-sensitive complex I–specific activity was measured in mitochondria (40 μg) using 4.8 mM^{-1} cm^{-1} as the extinction coefficient of NADH at 340 nm with a reference wavelength of 380 nm. Decylubiquinone (10 μM) served as the electron acceptor. 2-Thenoyltrifluoroacetone-sensitive complex II activity was measured in mitochondria (40 μg) using 19.1 mM^{-1} cm^{-1} as the extinction coefficient of 2,6-dichlorophenolindophenol at 600 nm. Decylubiquinone (50 μM) served as the electron acceptor. For complexes III and IV, inhibitor-sensitive first-order rate constants were calculated (4 μg and 2 μg mitochondria, respectively) using 18.5 mM^{-1} cm^{-1} as the extinction coefficient of cytochrome c at 550 nm. For complex III, decylubiquinol (100 μM) served as the electron donor. Oligomycin-sensitive complex V–specific activity was measured in mitochondria (40 μg) with 6.2 mM^{-1} cm^{-1} as the extinction coefficient of NADH at 340 nm. Rotenone-sensitive complex I plus III linked activity and antimycin A–sensitive complex II plus III linked activity were measured separately in mitochondria (40 μg) with 18.5 mM^{-1} cm^{-1} as the extinction coefficient of cytochrome c at 550 nm.

Aralar Purification. The plasmid-encoded *Slc25A12* gene (coding for Aralar; Genecopoeia, Inc., USA) was expressed in *Escherichia coli* C0214(DE3) by incubating the cells in the presence of 100 μg ampicillin/ml under aerobic conditions at 37°C.[37] Expression was induced by the addition of 1 mM isopropyl β-D-1-thiogalactopyranoside, and the cells were incubated under aerobic conditions at 30°C for an additional 16 h. Cells were harvested and homogenized (Emulsiflex

C-3, Avestin Inc.), and the Aralar-containing membrane fraction was collected by ultracentrifugation at 272,000*g* for 1 h at 4°C. Membranes were solubilized with 1.67% *N*-sodium lauroylsarcosine (sarcosine) in 10 mM Tris-Cl, pH 6.5, 150 mM NaCl, 0.1 mM EDTA, 0.5 mM tris(2-carboxyethylphosphine hydrochloride, 1 mM phenylmethylsulfonyl fluoride, and 10 mM imidazole for 1 h at 4°C. Insoluble material was removed by ultracentrifugation, and His-tagged Aralar was purified using TALON ion metal affinity chromatography (Takara, Inc.). Protein was assayed before reconstitution in preformed liposomes composed of total *E. coli* lipids (Avanti, Inc.).[38] Purified Aralar was mixed with Triton X-100–destabilized liposomes at a 100:1 (w/w) lipid-to-protein ratio following established protocols.[39] Uptake studies were performed with Aralar-containing proteoliposomes that were composed of 130 mM tris(hydroxymethyl) aminomethane/Mes (2-(N-morpholino)ethanesulfonic acid, pH 6.5, 20 mM L-aspartate for the transport of 500 μM ^{3}H-Glu (0.01 Ci/mmol) or 150 mM Tris/Mes, pH 6.5 for import of 500 μM ^{3}H-GABA (0.002 Ci/mmol); both radiochemicals were acquired from American Radiolabeled Chemicals, Inc. Reactions were carried out for 1 min in assay buffer composed of 150 mM Tris/MES pH 7.5, 10 mM $CaCl_2$ in the presence or absence of Ub5 (200 μM) and propofol (10 or 400 μM) with or without inhibitors (10 mM pyridoxal 5′-phosphate and 10 mM bathophenanthroline). Samples were quenched by the addition of ice-cold assay buffer and then filtered (0.45 μm). Filters were then subjected to scintillation counting (Hidex 300-SL scintillation counter).

Statistical Analysis. Statistical analysis was performed using GraphPad Prism 10 software (GraphPad Software, USA). Data were assessed for normality and are presented in the figures as mean ± SD (unless otherwise specified in the figure legends). The sample number of mice or biologic replicates (n) studied for each experiment is indicated for each figure. Sample size for each outcome measure was chosen *a priori* to provide 80% power to detect an effect size of 15% between groups at a significance level of 0.05. Statistical tests utilized are delineated in each figure legend. The Student's *t* test (two-tailed) was used to assess for significance between two groups. One-way ANOVA with Tukey *post hoc* test was used to calculate significance between more than two groups, and two-way ANOVA (with repeated measures when appropriate) with Tukey *post hoc* test assessed for significance between groups with two independent variables. Regression analysis was utilized to determine dose-dependent effect. Significance was set at $P < 0.05$.

Results

CoQ Analogs Induce Excessive Proton Leak and Are Cardiotoxic

Propofol, the most commonly used intravenous sedative-hypnotic, causes a dose-dependent cardiotoxicity, especially in children.[15,40,41] Toxicity in the developing heart manifests with bradyarrhythmias, conduction abnormalities, and myocardial failure and is believed to occur when ΔΨm becomes compromised by ETC inhibition combined with excessive proton leak across the inner mitochondrial membrane (fig. 1A).[16–19,41,42] The predominant source of propofol-induced leak has yet to be elucidated; however, it can be blocked by the coenzyme Q (CoQ) analog ubiquinone-0 (CoQ0 or 2,3-dimethoxy-5-methyl-*p*-benzoquinone).[16]

In an effort to identify a quinone-sensitive leak source within newborn cardiomyocyte mitochondria, we first assessed the *in vitro* effects of three different CoQ analogs on leak respiration (fig. 1B). Each analog was biologically active and caused a precipitous decline in ΔΨm (fig. 1C). However, in the absence of propofol, CoQ0 failed to block leak, inhibiting electron transport instead (fig. 1, C to H). On the other hand, both decylubiquinone (DB) and ubiquinone-5 (Ub5; CoQ1 or 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)-1,4-benzoquinone, Chemical Abstracts Service (CAS) Registry No. 727-81-1) induced uncompensated proton leak (fig. 1, C to H). Concentrations tested were chosen based on our previous work assessing *in vitro* mitochondrial biologic activity of DB and Ub5.[28] The effects of DB and Ub5 on leak respiration and ΔΨm were strikingly similar to that of propofol (fig. 1, C to H). Therefore, next we tested DB and Ub5 for cardiotoxicity. High concentrations of DB and Ub5 immediately induced bradyarrhythmias with or without heart block in the isolated-perfused newborn mouse heart (fig. 2). The onset and offset of dysrhythmias were rapid, completely reversible, and highly reminiscent of propofol-mediated cardiotoxicity (fig. 2).[17] Thus, DB and Ub5 demonstrated properties that were characteristic of propofol, compromising ΔΨm in developing cardiomyocyte mitochondria, inducing excessive proton leak, and causing reversible cardiotoxicity in the newborn mouse heart.

Ub5 Exhibits Anesthetic Properties

These findings led us to question whether the quinone-mediated effects on proton leak and ΔΨm were on-target and mechanism-based. In other words, did they result from an interaction with a therapeutic target in an organ outside the central nervous system? If so, then such CoQ analogs should be capable of inducing sedation and hypnosis, and uncompensated proton leak must contribute to the mechanism of anesthesia by compromising ΔΨm. To test these hypotheses, we injected young adult male mice with various doses of Ub5 *via* tail vein. We opted to test Ub5 given that it is the quinone analog with the shortest side chain (one isoprenoid unit), permitting rapid diffusion across membranes (fig. 1B).[43] In support of our hypothesis, Ub5 immediately induced unconsciousness over a range of doses, causing loss of the righting reflex (LORR; fig. 3A; Supplemental Digital Content video S1, https://links.lww.com/ALN/D987). The Hill slope of the dose–response curve was steep, consistent with that of known anesthetic

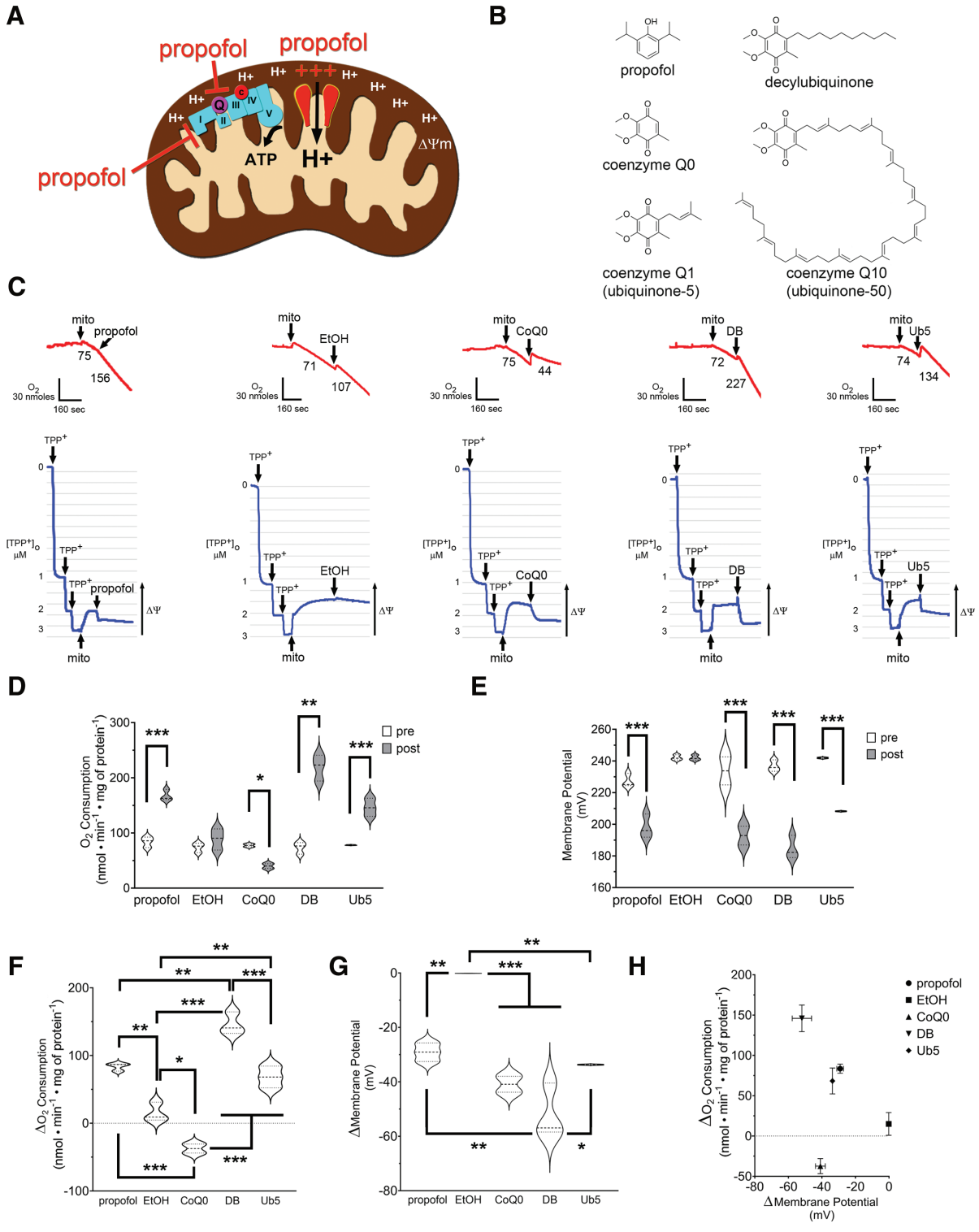


Fig. 1. Propofol and quinone analogs induce excessive proton leak in developing cardiomyocyte mitochondria. (*A*) Mechanism of propofol toxicity in cardiac mitochondria. (*B*) Structure of propofol, coenzyme Q10, and coenzyme Q (CoQ) analogs. (*C–H*) Simultaneous measurement of oxygen consumption and mitochondrial membrane potential (ΔΨm) during leak respiration in isolated newborn mouse cardiomyocyte mitochondria (mito) exposed to propofol (400 μM), the vehicle control, ethanol (EtOH), coenzyme Q0 (CoQ0; 100 μM), decylubiquinone (DB; 100 μM), or coenzyme Q1 (ubiquinone-5 [Ub5]; 100 μM). A decline in oxygen consumption with a concomitant fall in *(Continued)*

drugs.[44] Ub5-mediated hypnosis was short-lived, and mice regained their righting reflex within 4 min (fig. 3B). Latency to return of righting reflex demonstrated a positive and significant correlation with Ub5 dose ($P < 0.005$; fig. 3B). We subsequently tested Ub5-induced LORR in a subset of female mice to assess for sex-specific differences. The dose–response curves were similar between sexes, and there were no significant differences in ED_{50} or Hill slope (Supplemental Digital Content fig. S1, https://links.lww.com/ALN/D986). No mortality was observed in any mouse after injection.

Because anesthetics are known to cause immobilization and inactivity, we next utilized video tracking to assess the effect of Ub5 on spontaneous movement.[2,25] There was no difference between mice in distance traveled before injection (Supplemental Digital Content fig. S2, https://links.lww.com/ALN/D986). However, Ub5 significantly decreased total distance traveled after return of righting in a dose-dependent manner ($P < 0.001$; fig. 3C; Supplemental Digital Content fig. S2, https://links.lww.com/ALN/D986). Importantly, the effects of Ub5 on LORR and movement occurred in the absence of significant changes in body temperature (Supplemental Digital Content fig. S3, https://links.lww.com/ALN/D986).

Next, we assessed for changes in murine EEG to confirm that Ub5-induced loss of righting resulted from hypnosis rather than simply impaired movement. EEG signals were recorded continuously before, during, and after injection. Ub5 immediately induced low-amplitude electrical activity that evolved into delta waves, K-complexes, spindles, and burst suppression within 1 to 3 min after injection (fig. 3D). Delta activity and higher frequencies were seen 10 min after Ub5 injection, and high-frequency activity returned by 20 min (fig. 3D). The slow-wave EEG activity seen after injection confirmed Ub5-induced hypnosis, while burst suppression provided evidence of a deep state of anesthesia.[1] Thus, Ub5 exhibited anesthetic properties, indicating that it is, in fact, a novel intravenous sedative-hypnotic. Given the association between burst suppression and postoperative brain dysfunction, we next tested learning, memory, and behavior in mice 1 to 2 weeks after injection (Supplemental Digital Content fig. S4, https://links.lww.com/ALN/D986). The only significant difference seen between cohorts was with the water maze probe trial, suggesting a Ub5-mediated effect on reference memory ($P < 0.01$; Supplemental Digital Content fig. S4, https://links.lww.com/ALN/D986).

Ub5 Decreases Neuronal Activity and ΔΨm

Intraneuronal calcium transients are proxies for single action potentials within individual neurons.[24] Tetramethylrhodamine ethyl ester (TMRE) is a cell-permeable cationic fluorescent dye that permits quantification of ΔΨm.[28] We next performed real-time *in vivo* multiphoton laser imaging in *Thy1*-GCaMP6 transgenic mice after Ub5 injection to dynamically quantify changes in neuronal calcium transients and mitochondrial TMRE fluorescence over time in the living murine cortex. Calcium activity and TMRE fluorescence decreased significantly and profoundly in neurons within layer II/III of the somatosensory cortex immediately after Ub5 tail vein injection ($P < 0.001$; fig. 3, E to H; Supplemental Digital Content video S2, https://links.lww.com/ALN/D988, video S3, https://links.lww.com/ALN/D989, video S4, https://links.lww.com/ALN/D990, video S5, https://links.lww.com/ALN/D991, video S6, https://links.lww.com/ALN/D992, and video S7, https://links.lww.com/ALN/D993). By 20 min after Ub5 injection, neuronal calcium activity began to increase but remained significantly lower than time-matched vehicle-injected controls ($P < 0.001$; fig. 3, E to H; Supplemental Digital Content video S2, https://links.lww.com/ALN/D988, video S3, https://links.lww.com/ALN/D989, video S4, https://links.lww.com/ALN/D990, video S5, https://links.lww.com/ALN/D991, video S6, https://links.lww.com/ALN/D992, and video S7, https://links.lww.com/ALN/D993). In fact, calcium activity did not return to baseline until approximately 120 min after Ub5 injection (Supplemental Digital Content fig. S5, https://links.lww.com/ALN/D986). At 20 min after Ub5 injection, TMRE fluorescence differed only from vehicle-injected values at the 0- to 3-min timepoint (fig. 3, E and H; Supplemental Digital Content video S2, https://links.lww.com/ALN/D988, video S3, https://links.lww.com/ALN/D989, video S4, https://links.lww.com/ALN/D990, video S5, https://links.lww.com/ALN/D991, video S6, https://links.lww.com/ALN/D992, and video S7, https://links.lww.com/ALN/D993). Thus, Ub5 reversibly decreased neuronal activity and ΔΨm *in vivo*. Notably, perturbations in ΔΨm and neuronal calcium transients persisted after the time required for return of righting, suggesting that consciousness returned before complete normalization of neuronal activity and ΔΨm.

Fig. 1. *(Continued)* ΔΨm indicated electron transport chain inhibition, while an increase in respiration with a simultaneous decrease in ΔΨm indicated an uncompensated increase in proton leak. (*C*) Representative traces of oxygen consumption (*red*) above with ΔΨm (*blue*) below. Numbers are oxygen consumption rates (nmol · min^{-1} · mg mitochondrial $protein^{-1}$). ΔΨm was measured after tetraphenylphosphonium ion (TPP^+) calibration. Violin plots of (*D*) oxygen consumption rates, (*E*) membrane potential before and after exposure, (*F*) ΔO_2 consumption, and (*G*) Δmembrane potential after the addition of propofol, EtOH, CoQ0, DB, or Ub5 are depicted. (*H*) ΔO_2 consumption graphed as a function of Δmembrane potential. Data are mean ± SD. n = 3 biologic replicates from 3 different mice. For *D* and *E*, *P* values were calculated by two-way ANOVA with repeated measures. For *F* and *G*, *P* values were calculated by one-way ANOVA. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

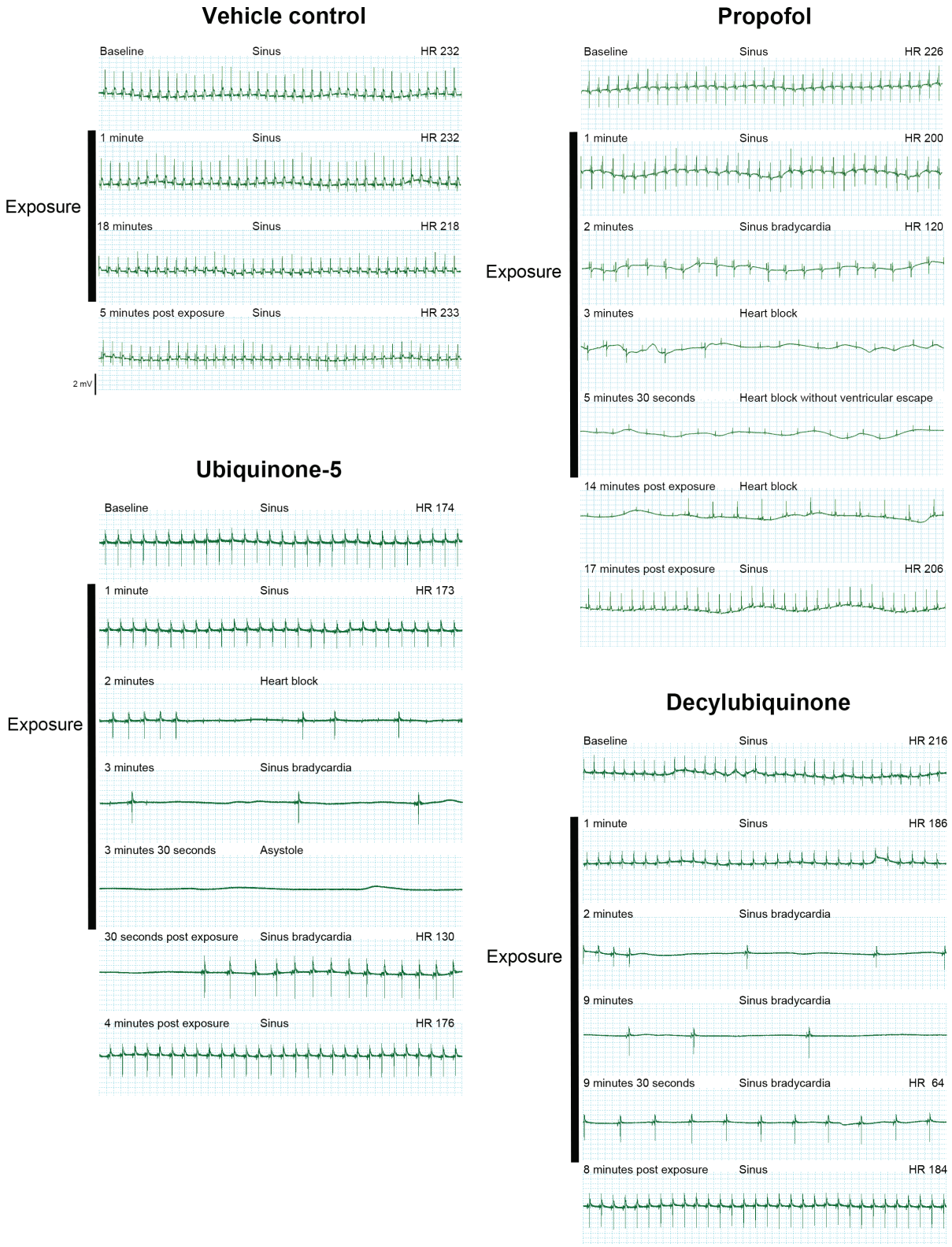


Fig. 2. Coenzyme Q analogs exhibit cardiotoxicity. Representative electrocardiogram tracings in the isolated-perfused newborn mouse heart before, during, and after exposure to propofol (5.9 g · kg^{-1} · min^{-1}), decylubiquinone (1.1 g · kg^{-1} · min^{-1}), or ubiquinone-5 (3.2 g · kg^{-1} · min^{-1}). Equal volume intralipid served as a vehicle control. n ≥ 3 biologic replicates.

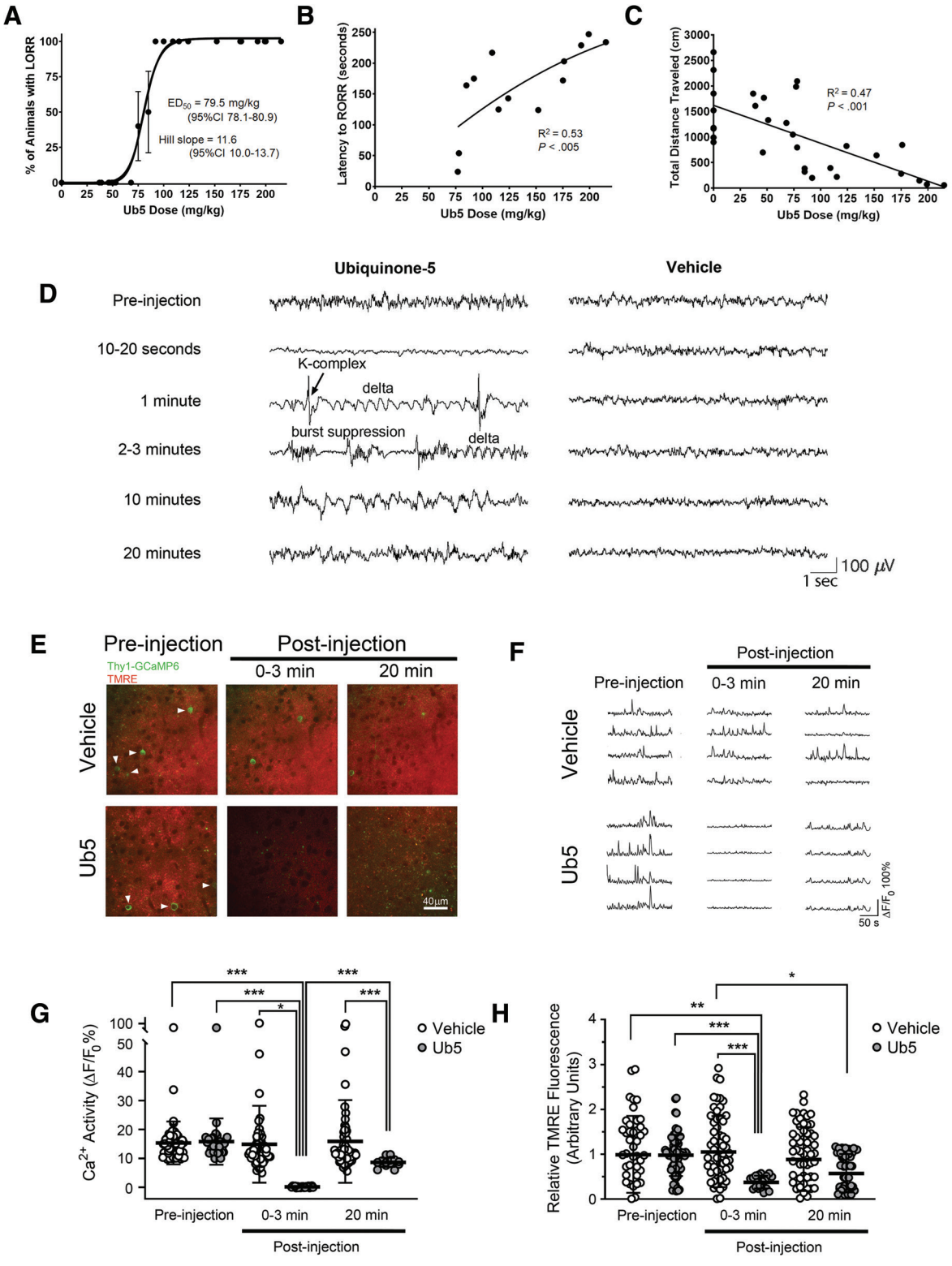


Fig. 3. Ubiquinone-5 (Ub5) is an anesthetic. (*A*) Loss of righting reflex (LORR) dose–response curve. (*B*) Latency to return of righting reflex (RORR) curve. (*C*) Spontaneous locomotion for 30 min after RORR. (*D*) Representative electroencephalogram (EEG) traces in mice injected with Ub5 (200 mg/kg) or vehicle. (*E–H*) *In vivo* two-photon imaging of calcium (Ca^{2+}) transients in GCaMP6-expressing neurons and tetramethylrhodamine ethyl ester (TMRE) fluorescence in layer II/III of the somatosensory neocortex. (*E*) Representative images before *(Continued)*

Ub5 Induces Uncompensated Proton Leak and Inhibits the ETC in Forebrain Mitochondria

To determine whether proton leak contributes to the mechanism of anesthesia by compromising $\Delta\Psi m$, we next assessed the *in vitro* effects of Ub5 in mouse forebrain mitochondria. We first quantified tissue concentration of Ub5 in murine brain extracts harvested immediately after intravenous injection (upon loss of righting; Supplemental Digital Content fig. S6, https://links.lww.com/ALN/D986). Using these concentrations to guide *in vitro* experimentation, we then assessed the effects of propofol and Ub5 on leak. Consistent with their biologic activities in cardiomyocyte mitochondria, both propofol and Ub5 induced excessive proton leak and compromised $\Delta\Psi m$ in forebrain mitochondria during leak respiration (fig. 4, A to E). The control vehicle, ethanol, caused an increase in leak without significantly affecting $\Delta\Psi m$ (fig. 4, A to E).

We next measured oxygen consumption during the various states of respiration using a Clark-type electrode. Ub5 caused concentration-dependent increases in complex I–dependent basal and uncoupled state 3 respiration in isolated forebrain mitochondria and stimulated complex II–dependent respiration across all states (fig. 4, F and G). To define these effects more precisely, we next quantified dynamic changes in oxygen consumption over a range of membrane potentials to independently assess proton leak conductance, substrate oxidation, and ATP turnover as they relate to the proton motive force.[43] Ub5 significantly increased proton leak and ATP turnover as evidenced by a left-shifted curve and increased oxygen consumption rates at the highest common $\Delta\Psi m$ ($P < 0.001$; fig. 4, H and J).[43] However, substrate oxidation was not significantly different between Ub5-exposed mitochondria and controls (fig. 4I). The lack of an increase in substrate oxidation in the presence of Ub5 indicated a defect in the ability of forebrain mitochondria to generate an adequate $\Delta\Psi m$ and compensate for the excessive proton leak. To determine how Ub5 interferes with substrate oxidation, we next quantified the steady state kinetic activity of each individual ETC enzyme complex in exposed forebrain mitochondria. Although complexes II and V were stimulated, Ub5 significantly inhibited complex I and complex IV in a dose-dependent manner ($P < 0.001$; fig. 4K). Therefore, Ub5 compromises $\Delta\Psi m$ in forebrain mitochondria by inducing excessive proton leak and inhibiting the ETC at complex I and complex IV (fig. 4L).

Aralar Is the Major Source of Ub5-mediated Proton Leak

We next aimed to determine the source(s) of Ub5-induced proton leak. To do so, we tested several specific and nonspecific inhibitors in isolated forebrain mitochondria during leak respiration, assessing for a decline in oxygen consumption with a concomitant rise in $\Delta\Psi m$. Only one inhibitor, diethylpyrocarbonate (DEPC), showed a significant effect in Ub5-exposed mitochondria, simultaneously decreasing oxygen consumption while increasing $\Delta\Psi m$ ($P < 0.01$; fig. 5A). The combination and magnitude of these effects indicated that DEPC blocked a major source of Ub5-induced leak.

DEPC is a nonspecific inhibitor of the aspartate–glutamate carrier Aralar.[33,34] Although best known for its role in the heteroexchange of glutamate for aspartate coupled with transport of a proton across the inner mitochondrial membrane, Aralar was recently identified as the mitochondrial transporter responsible for sequestering GABA within the mitochondrial matrix (fig. 5B).[34,45] Therefore, we next assessed the effect of DEPC on GABA-induced proton leak. As with Ub5, DEPC blocked GABA-induced leak, significantly increasing $\Delta\Psi m$ and stabilizing it ($P < 0.05$; fig. 5, C to E). Importantly, the effects of DEPC on GABA-mediated leak were not significantly different from the effects seen with Ub5 (fig. 5, C to E). Thus, DEPC inhibited Aralar to interfere with both GABA- and Ub5-induced leak. These inhibitory effects were also seen with the Aralar inhibitor, pyridoxal 5′-phosphate (Supplemental Digital Content fig. S7, https://links.lww.com/ALN/D986).

In order for Aralar to be the source of excessive leak, it must be activated. Therefore, we next tested the hypothesis that Ub5 could increase Aralar activity. We first overexpressed Aralar in *E. coli* and purified it (Supplemental Digital Content fig. S8, https://links.lww.com/ALN/D986).[46] We then reconstituted Aralar in liposomes and performed transport activity assays.[34,46] Ub5 significantly increased ^{3}H-glutamate uptake in antiport heteroexchange assays and significantly increased ^{3}H-GABA import ($P < 0.05$; fig. 5, F and G). Thus, Ub5 did, in fact, activate Aralar directly. Taken together, the data indicate that Aralar is a functional target of Ub5 and is the major source of Ub5-induced leak.

Aralar Mutants Are Relatively Resistant to Ub5

Given the role of Aralar in Ub5-mediated leak, we next bred *Aralar* (*Slc25a12*) mutant mice to yield *Aralar* KO (*Aralar*$^{-/-}$) mice, *Aralar* heterozygotes (*Aralar*$^{\pm}$), and wild-type (*Aralar*$^{+/+}$) littermate controls. We first assessed isolated *Aralar*$^{-/-}$ forebrain mitochondria for Ub5-induced

Fig. 3. *(Continued)* and after injection of Ub5 (200 mg/kg) or vehicle. *Arrowheads* indicate activated neuronal soma. (*F*) Representative Ca^{2+} fluorescence traces in pyramidal somata before and after injection. (*G*) Average activity of somatic Ca^{2+} transients. (*H*) Relative TMRE fluorescence. Preinjection vehicle control values were arbitrarily set to equal 1. Regression analysis was applied to *A* through *C*. n = 52 for *A* and *B*, and n = 31 for *C*. For *A*, data are mean ± SD. For *G* and *H*, data are mean ± SD with n = 88 cells from 3 vehicle-injected animals and n = 82 cells from three Ub5-injected mice. *P* values were calculated by two-way ANOVA with repeated measures. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

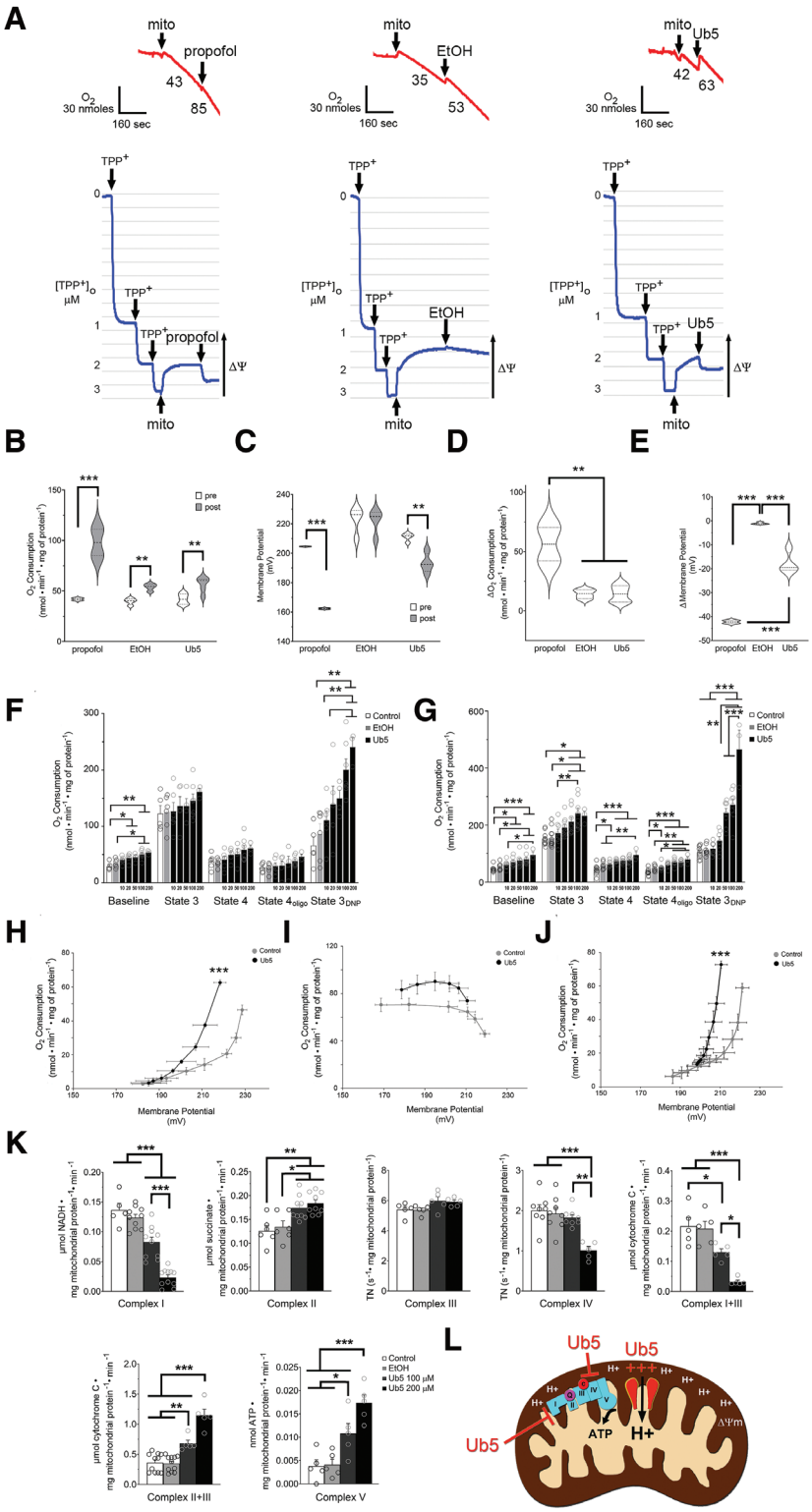


Fig. 4. Ubiquinone-5 (Ub5) induces excessive and uncompensated proton leak. (*A–E*) Simultaneous measurement of oxygen onsumption and mitochondrial membrane potential (ΔΨm) during leak respiration in isolated forebrain mitochondria (mito) exposed to propofol (400 μM), the vehicle control, ethanol (EtOH), or Ub5 (200 μM). (*A*) Representative traces of oxygen consumption (*red*) above with ΔΨm (*blue*) below. Numbers are oxygen consumption rates (nmol · min^{-1} · mg mitochondrial protein^{-1}). ΔΨm was measured after *(Continued)*

proton leak. Ub5 caused a significant decline in the leak rate of respiration ($P < 0.01$) and a concomitant decrease in $\Delta\Psi m$ (fig. 6). The profound decrease in oxygen consumption confirmed a lack of Ub5-induced leak in *Aralar* KO mitochondria while the combined changes in respiration and $\Delta\Psi m$ indicated Ub5-mediated inhibition of the ETC (fig. 6). The findings confirmed that Aralar is the source of Ub5-induced leak and unmasked the Ub5 effect on electron transport that persisted in the absence of excessive leak.

Unfortunately, the majority of *Aralar*$^{-/-}$ mice develop defects in motor coordination and impaired myelination, and do not survive beyond 3 to 4 weeks of life.[23] Therefore, we next evaluated *Aralar* heterozygotes and wild-type littermate controls. Similar to C57Bl/6 mitochondria, isolated *Aralar*$^{+/+}$ forebrain mitochondria demonstrated uncompensated proton leak with a significant decline in $\Delta\Psi m$ when exposed to Ub5 ($P < 0.05$; fig. 7, A to G). On the other hand, the effects of Ub5 on leak were modulated in *Aralar*$^{\pm}$ forebrain mitochondria as evidenced by lower rates of leak respiration, a limited decline in $\Delta\Psi m$, and less of a shift to the left in the proton conductance curve compared with wild-type littermate controls (fig. 7, A to G). Thus, *Aralar* heterozygote mitochondria demonstrated less Ub5-mediated leak.

Finally, we tested the hypothesis that Aralar is a mitochondrial target that mechanistically contributes to the anesthetic response. To do so, we injected *Aralar*$^{\pm}$ mice and wild-type littermate controls with various doses of Ub5 *via* tail vein. *Aralar* heterozygotes demonstrated a significantly right-shifted dose–response curve with regard to LORR such that the ED_{50} was significantly higher than controls ($P < 0.05$; fig. 7H). Therefore, *Aralar* mutants were relatively resistant to Ub5. There was no significant difference in latency to return of righting reflex between strains, suggesting that proton leak plays a role in the induction of anesthesia and not emergence (Supplemental Digital Content fig. S9, https://links.lww.com/ALN/D986). Importantly, Aralar appeared to be a specific pharmacologic target of Ub5, given the lack of an effect of propofol on Aralar transport activity, the persistence of propofol-induced leak in *Aralar*$^{-/-}$ forebrain and cardiac mitochondria, the ability of propofol to induce cardiotoxicity in isolated *Aralar*$^{-/-}$ hearts, and the lack of a shift in the propofol dose–response curve in *Aralar* mutants (fig. 8).

Discussion

Anesthetics are promiscuous drugs, binding to many intracellular proteins and structures.[1] Although several different channels, receptors, and signaling proteins are thought to contribute to the anesthetic response, interest in mitochondria has accelerated during the last few decades. Complex I is evolutionarily conserved and serves as the best example of a functional anesthetic target within mitochondria.[6–12,47] Numerous sedative-hypnotic agents bind to complex I, and anesthetic hypersensitivity manifests in *Caenorhabditis elegans*, *Drosophila melanogaster*, mice, and humans harboring mutations of specific complex I subunits.[6–8,10] Anesthetics inhibit complex I similarly across species, and recent data indicate that volatile anesthetic-mediated inhibition of complex I interferes with presynaptic ATP production and disrupts endocytosis and synaptic neurotransmitter recycling.[9]

Propofol inhibits complex I in cardiomyocyte mitochondria at therapeutic and toxic concentrations.[16,48] In addition, high concentrations induce uncompensated proton leak, compromising $\Delta\Psi m$ to cause cardiotoxicity.[16] Here, our attempts to identify a quinone-sensitive leak source within newborn mouse cardiomyocyte mitochondria resulted in the discovery of the novel anesthetic Ub5. As with propofol, Ub5 inhibits complex I and induces excessive leak in cardiac and forebrain mitochondria. These effects, combined with complex IV inhibition, compromise $\Delta\Psi m$. Importantly, limiting the effects on proton leak rendered mice relatively resistant to Ub5. Thus, uncompensated leak is an important mechanistic contributor to the anesthetic response in addition to ETC inhibition.

The search for phylogenetically conserved molecular targets endures given that anesthetics exert biologic activity across evolution.[1] Our discovery of Ub5 led us to uncover a previously unknown pharmacologic target within mitochondria: the aspartate–glutamate carrier, Aralar. Like complex I, aspartate–glutamate carriers are expressed over a wide evolutionary range of eukaryotes.[34] Aspartate–glutamate carriers exist as a single protein in protozoans, fungi, nematodes, and insects, and arise from two paralog genes in vertebrates.[34] Thus, they are intriguing to consider as potential anesthetic targets. Aralar is highly expressed in neurons, heart, and skeletal muscle and was previously found to be a binding target of

Fig. 4. *(Continued)* tetraphenylphosphonium ion (TPP^+) calibration. Violin plots of (*B*) oxygen consumption rates, (*C*) membrane potential before and after exposure, (*D*) ΔO_2 consumption, and (*E*) Δmembrane potential after the addition of propofol, EtOH, or Ub5 are depicted. (*F*) Complex I–dependent and (*G*) complex II–dependent oxygen consumption in isolated forebrain mitochondria exposed to various concentrations of Ub5 (μM). EtOH served as a vehicle control. Oligo, oligomycin; DNP, dinitrophenol. (*H*) Proton leak kinetics, (*I*) substrate oxidation, and (*J*) ATP turnover were quantified in forebrain mitochondria exposed to Ub5 (200 μM) or control conditions over a range of membrane potentials. (*K*) Steady state kinetic activities of the ETC complexes. First-order rate constants expressed as turnover number (TN) were determined for complexes III and IV. (*L*) Mechanism by which Ub5 compromises $\Delta\Psi m$ in mitochondria. Data for *F* through *K* are mean ± SD. For *A* through *E*, n = 3 to 5 biologic replicates from 3 to 5 different mice. For *B* and *C*, *P* values were calculated by two-way ANOVA with repeated measures. For *F* through *K*, n = 4 to 11 biologic replicates from 4 to 11 different mice. For *D* through *G* and *K*, *P* values were calculated by one-way ANOVA. For *H* through *J*, significance was determined for oxygen consumption rate at the highest common $\Delta\Psi m$ using Student's *t* test. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

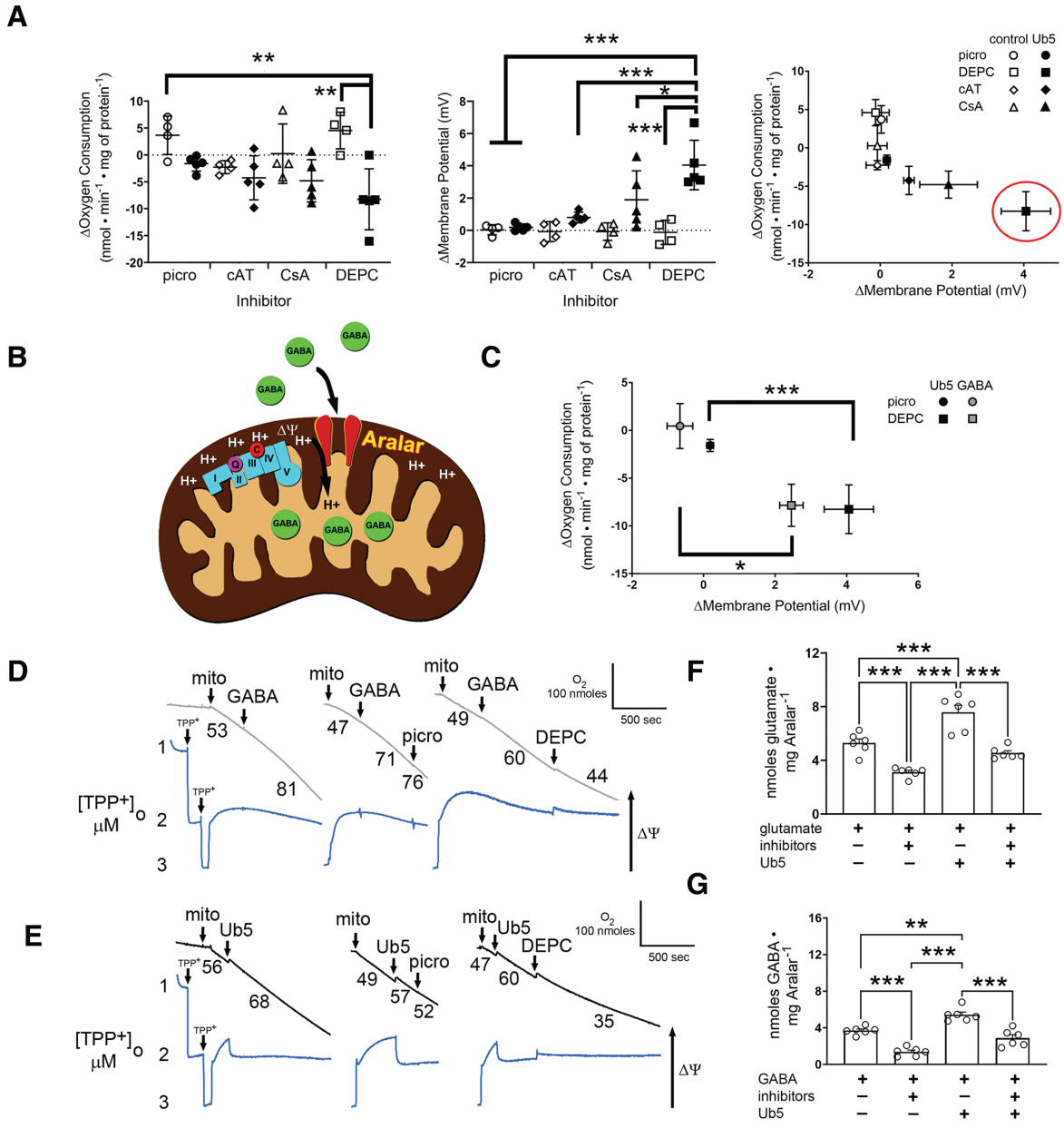


Fig. 5. Aralar is the source of ubiquinone-5 (Ub5)–mediated proton leak. Various inhibitors were used to determine source of leak. (*A, C–E*) Oxygen consumption and mitochondrial membrane potential (ΔΨm) were simultaneously measured during leak respiration in isolated forebrain mitochondria exposed to Ub5 (200 μM), γ-aminobutyric acid (GABA; 10 mM), or control conditions. ΔO_2 consumption and Δmembrane potential were quantified after addition of each inhibitor. Inhibition of leak was identified by a decrease in oxygen consumption with a concomitant increase in ΔΨm. Picrotoxin (picro), a GABA type A ($GABA_A$) receptor antagonist, served as a control inhibitor. cAT, carboxyatractyloside; CsA, cyclosporine; DEPC, diethylpyrocarbonate. *Red circle* highlights DEPC as the inhibitor with greatest effect on ΔO_2 consumption and Δmembrane potential. (*B*) Schematic of Aralar-mediated transport of GABA into the mitochondrial matrix. Representative traces of oxygen consumption above with ΔΨm (*blue*) below in the presence of (*D*) GABA (10 mM) or (*E*) Ub5 (200 μM) are depicted. Numbers are oxygen consumption rates (nmol · min^{-1} · mg mitochondrial $protein^{-1}$). ΔΨm was measured after tetraphenylphosphonium ion (TPP^+) calibration. (*F* and *G*) Aralar transport activity assays. Uptake of radioactive (*F*) glutamate or (*G*) GABA was determined in the presence or absence of Ub5 (200 μM). Pyridoxal 5'-phosphate and bathophenanthroline were used to inhibit the reaction. Data are mean ± SD. For *A* and *C*, n = 3 to 5 biologic replicates from 3 to 5 different mice. For *F* and *G*, n = 6 biologic replicates. *P* values were calculated by one-way ANOVA. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

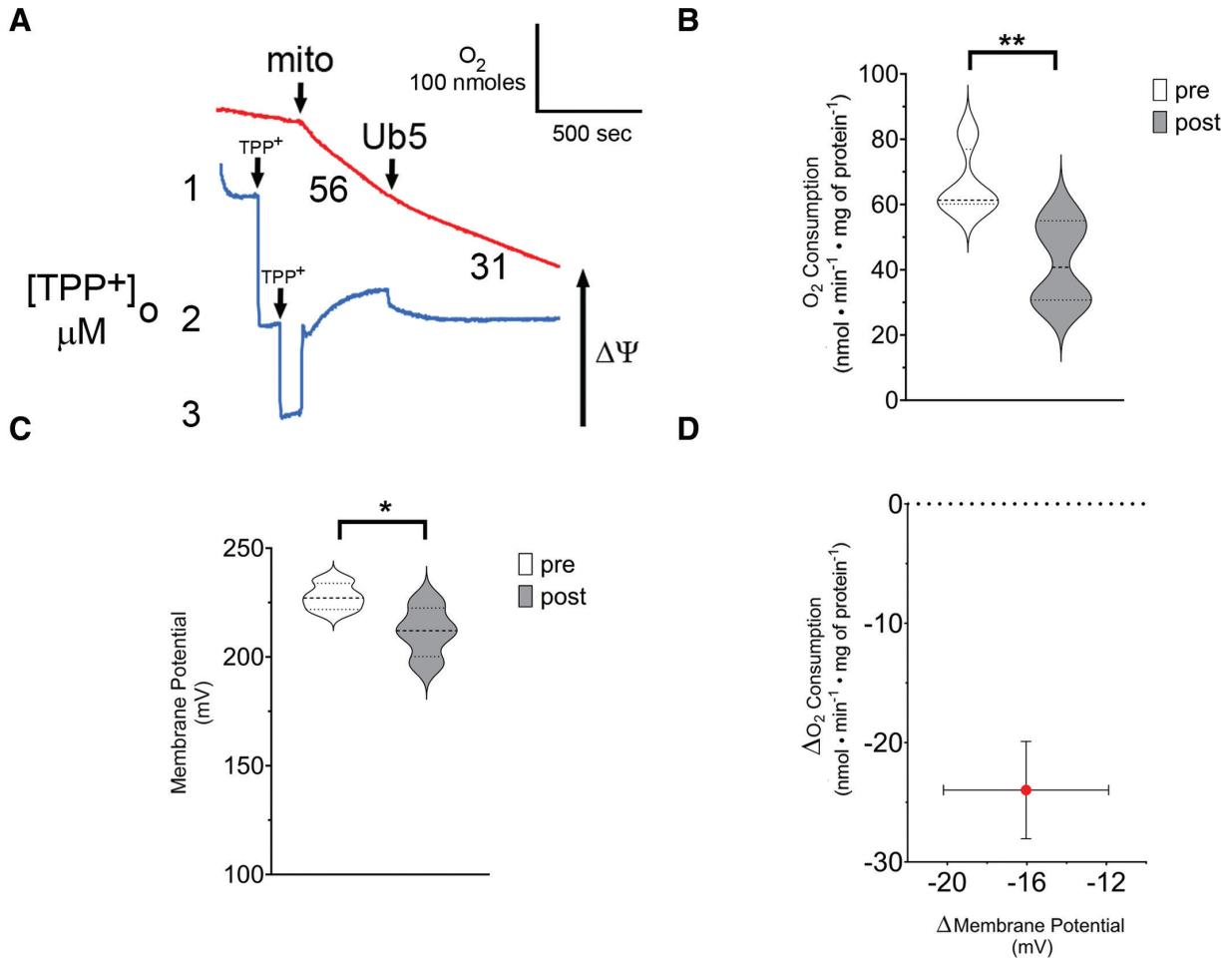


Fig. 6. Lack of ubiquinone-5 (Ub5)–induced leak in *Aralar* KO mitochondria. (*A–D*) Simultaneous measurement of oxygen consumption and mitochondrial membrane potential (ΔΨm) during leak respiration in isolated newborn *Aralar*$^{-/-}$ mouse forebrain mitochondria (mito) exposed to ubiquinone-5 (200 μM). (*A*) Representative traces of oxygen consumption (*red*) above with ΔΨm (*blue*) below. Numbers are oxygen consumption rates (nmol · min^{-1} · mg mitochondrial protein^{-1}). ΔΨm was measured after tetraphenylphosphonium ion (TPP^+) calibration. Violin plots of (*B*) oxygen consumption rates and (*C*) membrane potential before and after exposure are depicted. (*D*) ΔO_2 consumption graphed as a function of Δmembrane potential. Data are mean ± SD. n = 4 biologic replicates. For *B* and *C*, *P* values were calculated by paired Student's *t* test. *$P < 0.05$, **$P < 0.01$.

the photoactive propofol analog AziP*m-click* in mouse synaptosomes.[34,49] However, our findings indicate that Aralar is not a functional target of propofol. Thus, future work will need to explore whether Aralar is a pharmacologic target of other anesthetic agents in addition to Ub5.

Neurons rely predominantly on oxidative metabolism for neurotransmission, and changes in ΔΨm affect synaptic activity.[50,51] An inability to generate ΔΨm in presynaptic neuronal mitochondria compromises energy production and impairs the processes necessary to restore ion gradients, maintain calcium transients, and traffic synaptic cargo.[51] Here, we found that the precipitous decline in ΔΨm played a role in inducing Ub5-mediated unconsciousness. The profound fall in ΔΨm after Ub5 injection resulted in a deep state of anesthesia as evidenced by the onset of burst suppression. Thus, Ub5 likely depressed global brain metabolism as described by the neurophysiologic–metabolic model for burst suppression.[52]

Burst suppression EEG patterns are known to be produced when high doses of anesthetic agents compromise neurometabolism.[53,54] However, burst suppression can also result from hypoxia and inadequate brain oxygen delivery.[54] As a limitation of our study, we did not assess for the cardiotoxic effects of Ub5 *in vivo* and did not quantify the effects on respiration. None of the animals died after Ub5 injection, arguing against profound life-threatening cardiotoxicity or hypoxia. However, it is possible that Ub5 could have induced transient hypotension and hypoxemia, especially at the highest doses. Such effects, if they occurred, would certainly have contributed to the observed behavioral outcomes after injection. Therefore, future investigation will need to assess for Ub5-induced

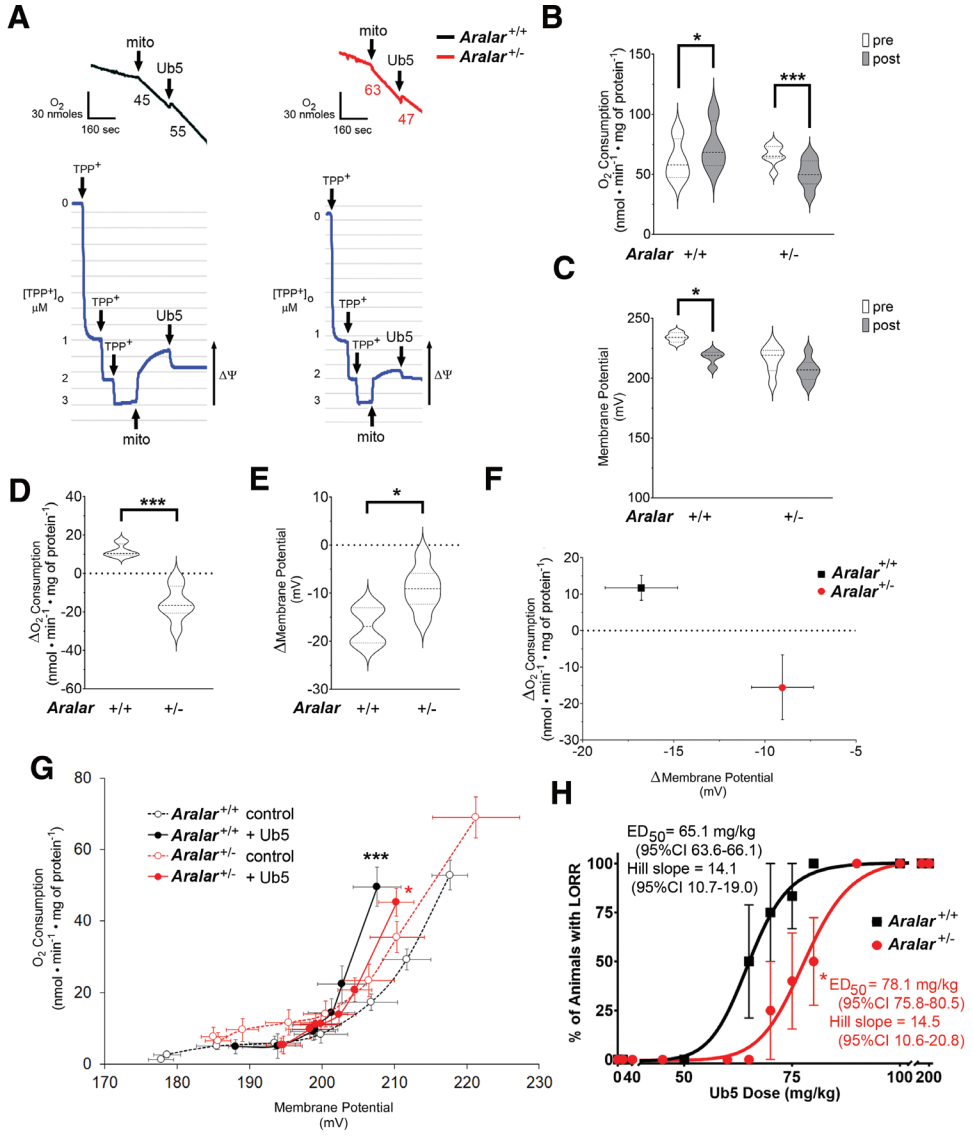


Fig. 7. *Aralar* mutants are resistant to ubiquinone-5 (Ub5). (*A–F*) Simultaneous measurement of oxygen consumption and mitochondrial membrane potential (ΔΨm) during leak respiration in isolated *Aralar*$^{\pm}$ or *Aralar*$^{+/+}$ (wild-type littermate controls) forebrain mitochondria (mito) exposed to Ub5 (200 µM). (*A*) Representative traces of oxygen consumption above with ΔΨm (*blue*) below. Numbers are oxygen consumption rates (nmol · min^{-1} · mg mitochondrial protein^{-1}). ΔΨm was measured after tetaphenylphosphonium ion (TPP^+) calibration. Violin plots of (*B*) oxygen consumption rates, (*C*) membrane potential before and after exposure, (*D*) ΔO_2 consumption, and (*E*) Δmembrane potential after the addition of Ub5 are depicted. (*F*) ΔO_2 consumption graphed as a function of Δmembrane potential after the addition of Ub5. (*G*) Proton leak kinetics were quantified in forebrain mitochondria exposed to Ub5 (200 µM) or control conditions over a range of membrane potentials. (*H*) Loss of righting reflex (LORR) dose–response curve. For *B* through *G*, data are mean ± SD. For *B* through *F*, n = 4 to 7 biologic replicates from 4 to 7 different mice. For *B* and *C*, *P* values were calculated by two-way ANOVA with repeated measures. For *D*, *E*, and *H*, *P* values were calculated by Student's *t* test. For *G*, n = 4 to 14 biologic replicates from 4 to 14 different mice, and significance was determined for oxygen consumption rate at the highest common ΔΨm using Student's *t* test. Regression analysis was applied to *H*, and n = 26 to 29 mice for each strain (*Aralar*$^{\pm}$ or *Aralar*$^{+/+}$ [wild-type littermate controls]). Data are mean ± SD. **P* < 0.05, ****P* < 0.001.

cardiotoxicity and hypoxia. As another limitation of our work, we did not assess for an interaction between Ub5 and the GABA type A receptor or other common anesthetic molecular targets, such as the *N*-methyl-D-aspartate receptor or the cyclic nucleotide–regulated channel, HCN1. Thus we cannot rule out other extramitochondrial mechanisms that may have contributed to loss of consciousness. Subsequent work will certainly need to investigate for these interactions.

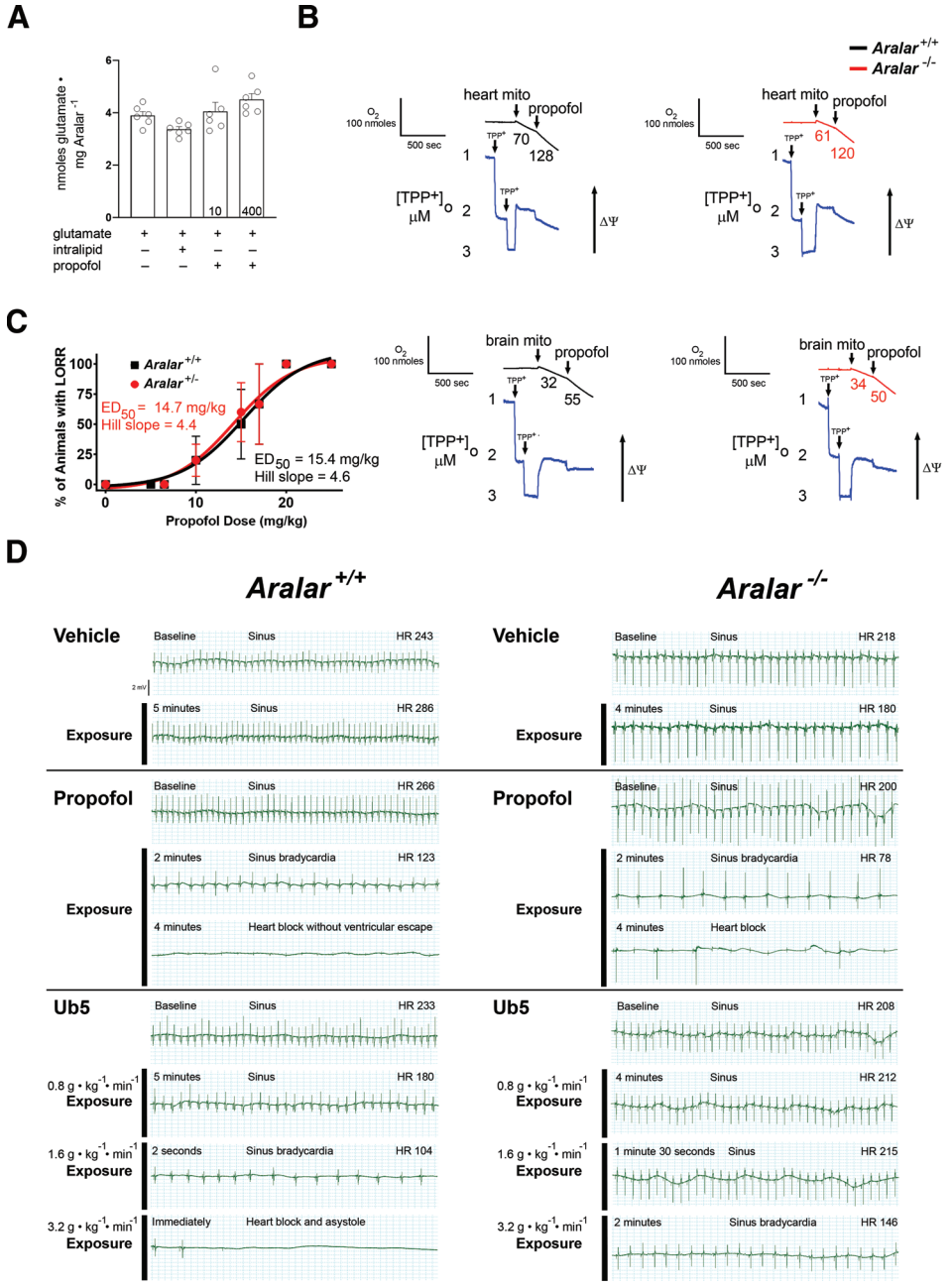


Fig. 8. Aralar is not a pharmacologic target of propofol. (*A*) Aralar transport activity assays. Uptake of radioactive glutamate was determined in the presence or absence of propofol (10 or 400 μM) or intralipid. (*B*) Simultaneous measurement of oxygen (consumption and mitochondrial membrane potential ($\Delta\Psi m$) during leak respiration in isolated newborn *Aralar*$^{-/-}$ or *Aralar*$^{+/+}$ (wild-type littermate controls) cardiac or forebrain mitochondria (mito) exposed to propofol (400 μM). Representative traces of oxygen consumption above with $\Delta\Psi m$ (*blue*) below. Numbers are oxygen consumption rates (nmol · min^{-1} · mg mitochondrial protein^{-1}). $\Delta\Psi m$ was measured after tetraphenylphosphonium ion (TPP^+) calibration. (*C*) Loss of righting reflex (LORR) propofol dose–response curve in *Aralar*$^{+/-}$ or *Aralar*$^{+/+}$ (wild-type littermate controls). (*D*) Representative electrocardiogram tracings in the isolated-perfused newborn mouse heart from *Aralar*$^{-/-}$ or *Aralar*$^{+/+}$ (wild-type littermate controls) mice before and during exposure to intralipid vehicle, propofol (5.9 g · kg^{-1} · min^{-1}), or ubiquinone-5 (Ub5; 0.8-3.2 g · kg^{-1} · min^{-1}). Propofol rapidly induced sinus bradycardia and heart block in both strains. *Aralar*$^{-/-}$ hearts were relatively resistant to Ub5. Sinus bradycardia with highest dose of Ub5 in *Aralar* KOs was likely due to Ub5-induced ETC inhibition. Data are mean ± SD for *A* and *C*. Statistical significance for *A* was determined using one-way ANOVA. n = 3 to 6 biologic replicates for *A*, *B*, and *D*. Regression analysis was applied to *C*, and n = 16 to 21 mice per strain.

Despite the limitations, the findings presented here advance our understanding of how anesthetics induce reversible unconsciousness, implicating uncompensated proton leak with a decline in $\Delta\Psi m$ as a mechanism of anesthesia. Along with previous knowledge, this work lays the foundation for further exploring the role of mitochondria in mediating the anesthetic response. Future work should focus on identifying agents that inhibit complex I and activate Aralar or other leak channels to induce proton leak. However, investigators should proceed with caution with drug development when using toxicity as a roadmap. Even if toxicity is on-target and mechanism-based, the risks of adverse effects could outweigh the benefits. It is quite possible that drug development efforts using this approach could yield agents with too narrow a therapeutic index. Thus, to maximize safety and efficacy, new anesthetic agents should be developed with the goals of limiting biologic activity to the central nervous system and preventing effects in other organ systems, such as the heart. Success could reduce the side effect profile of sedative-hypnotics and lead to the development of new designer drugs that will be more precise, more effective, and safer than existing agents.

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Competing Interests

Dr. Kelz serves on the board of trustees of the International Anesthesia Research Society (San Francisco, California) and serves as the president and chief scientific officer of the Foundation for Anesthesia Education and Research (Schaumburg, Illinois). The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental figures, https://links.lww.com/ALN/D986
Figure S1. Sex-dependent loss of righting
Figure S2. Spontaneous locomotion in injected mice
Figure S3. Ub5 does not affect temperature
Figure S4. Reference memory
Figure S5. Neuronal calcium activity
Figure S6. Brain tissue Ub5 concentrations
Figure S7. Inhibited Aralar-mediated leak
Figure S8. Aralar purification
Figure S9. Latency to righting in Aralar mutants
Video S1. Loss of righting after Ub5, https://links.lww.com/ALN/D987
Video S2. Prevehicle injection two-photon imaging, https://links.lww.com/ALN/D988
Video S3. 0- to 3-min postvehicle two-photon imaging, https://links.lww.com/ALN/D989
Video S4. 20-min postvehicle two-photon imaging, https://links.lww.com/ALN/D990
Video S5. Pre-Ub5 injection two-photon imaging, https://links.lww.com/ALN/D991
Video S6. 0- to 3-min post-Ub5 two-photon imaging, https://links.lww.com/ALN/D992
Video S7. 20-min post-Ub5 two-photon imaging, https://links.lww.com/ALN/D993

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ANESTHESIOLOGY®

Intergenerational Postoperative Neurocognitive Disorder in a Rat Model: Initiating Mechanisms and Pharmacological Prevention

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ABSTRACT

Background: Vulnerability to perioperative neurocognitive disorder (PND) and the mechanisms initiating PND, which may serve as targets for prevention, are incompletely understood. This study hypothesized that sevoflurane can induce persistent upregulation of the hypothalamic–pituitary–adrenal axis, inflammation, and behavioral deficits in young adult male rats by stimulating hypothalamic arginine vasopressin (AVP) production *via* Na^+-K^+-Cl^- (NKCC1) Cl^- importer/γ-aminobutyric acid type A receptor signaling. These changes may also result in neurocognitive deficits in the offspring of exposed rats (*i.e.*, intergenerational PND).

Methods: Sprague Dawley male rats (generation F0) were exposed to 2.1% sevoflurane for 3 h on postnatal days 56, 58, and 60. Before each sevoflurane exposure. they received vehicle (F0M_S group), the NKCC1 inhibitor bumetanide (F0M_BS group), or the glucocorticoid receptor inhibitor RU486 (F0M_RS group). They were mated on postnatal day 90 with treatment-naïve females to generate offspring (generation F1).

Results: Consistent with our hypothesis, short-term and sustained changes in F0M_S rats, but not F0M_BS and F0M_RS rats, included increased hypothalamic c-FOS and AVP (but not oxytocin) expression, increased hypothalamic–pituitary–adrenal axis activity, increased levels of systemic and central inflammatory markers, and increased *Nkcc1*/ K^+-$2Cl^-$ (*Kcc2*) Cl^- exporter mRNA ratios in the brain. F0M_S males, but not F0M_BS and F0M_RS males, exhibited anxiety-like behavior and deficits in sensorimotor gating and spatial memory. Male offspring of F0M_S sires, but not F0M_BS or F0M_RS sires, exhibited behavioral abnormalities similar to those in F0M_S, as well as alterations in social behavior. The only deficit in F1 females was impaired spatial memory in the offspring of F0M_S.

Conclusions: These findings suggest a role for hypothalamic NKCC1/γ-aminobutyric acid type A receptor/AVP signaling in sevoflurane-triggered PND in adult male rats, which also affects their future sevoflurane-unexposed offspring. NKCC1 and glucocorticoid receptors could serve as therapeutic targets for prevention of sevoflurane-induced PND in exposed rats and in their future offspring.

(ANESTHESIOLOGY 2025; 143:661–79)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- In rodents, general anesthetics have been shown to induce dysregulation of the stress axis and cognitive deficits not only in the exposed animals but also in their offspring
- The molecular mechanisms through which general anesthetics induce persistent dysregulation of the stress axis, potentially contributing to intergenerational cognitive deficits after anesthetic exposure, remain incompletely understood

What This Article Tells Us That Is New

- Sevoflurane administration in young-adult male rats increases the activity of arginine-vasopressin–producing hypothalamic neurons, leading to a persistent increase in stress and inflammatory signaling, as well as neurocognitive deficits in exposed sires and their future offspring
- Pre-exposure inhibition of the cation-chloride cotransporter NKCC1 or glucocorticoid receptors prevents sevoflurane-induced increases in stress and inflammatory signaling in exposed sires, as well as neurocognitive deficits across both generations

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Abbreviations: **ANOVA**, analysis of variance; **AVP**, arginine vasopressin; **CRH**, corticotropin-releasing hormone; **EPM**, elevated plus maze; **$GABA_AR$**, γ-aminobutyric acid type A receptor; **GFAP**, glial fibrillary acid protein; **GR**, glucocorticoid receptor; **HPA**, hypothalamic–pituitary–adrenal; **Iba1**, ionized calcium-binding adaptor molecule 1; **KCC2**, K^+-$2Cl^-$; **MR**, mineralocorticoid receptor; **mRNA**, messenger RNA; **MWM**, Morris water maze; **NKCC1**, Na^+-K^+-Cl^-; **OXT**, oxytocin; **P*n***, postnatal day *n*; **PND**, perioperative neurocognitive disorder; **PPI**, prepulse inhibition; **PVN**, paraventricular nucleus

Neurocognitive impairments attributed to general anesthesia/surgery may persist in neonates or endure for weeks to years in older patients.[1–3] The latter is historically referred to as perioperative neurocognitive disorder (PND) and is an important public health problem potentially affecting millions of patients. The mechanisms whereby anesthesia or surgery initiates PND, which may represent therapeutic targets for prevention, are poorly understood.[1–3] The current consensus is that patients of advanced age are most vulnerable to PND, likely due to aging-related heightened stress and inflammation.[1–4] Other studies, however, suggest that patients within a wider range of ages, including the prime reproductive period, may be susceptible to PND,[2,5] but also see the work of Sahoo *et al.*[6] Heightened stress and inflammation are recognized as potential drivers of the pathogenesis of PND.[1–4] Clinical and laboratory findings indicate that parental stress and inflammation can negatively affect neurocognitive function in future offspring.[7–13] Therefore, offspring of parents with a history of anesthesia or surgery might also experience neurocognitive impairments due to stress and inflammation induced by parental anesthesia and surgery, a phenomenon referred to as intergenerational PND. In direct support of this possibility, findings in mice as early as the 1980s showed that offspring of sires exposed to the halogenated general anesthetics enflurane or halothane developed learning deficits.[14,15] More recently, we found that neurocognitive deficits induced by the widely used halogenated general anesthetic sevoflurane in young adult male rats and their male offspring included short- and long-term dysregulated stress-like hypothalamic–pituitary–adrenal (HPA) axis activity in sires and neurobehavioral abnormalities in both generations (a rat model of intergenerational PND).[16,17] Furthermore, the same patterns of DNA hypermethylation were found in the K^+-2Cl^- (*Kcc2*) Cl^- exporter gene in the spermatozoa of sevoflurane-exposed sires and in the hypothalamus and hippocampus of their male offspring. The reduced expression of this gene in the male offspring hypothalamus and hippocampus points to the involvement of epigenomic, germ cell–mediated transmission of paternal sevoflurane-induced intergenerational PND in rats.[16]

The large number of young adults who undergo repeated or prolonged anesthesia or surgery, the even larger number of their offspring whose health may be affected by parental anesthesia or surgery, and a growing number of neurodevelopmental disorders of unknown etiology in which parental exposure to anesthesia or surgery may potentially play a role[18–20] form the impetus for investigating therapeutic approaches to mitigate neurocognitive consequences of PND in exposed parents and their future offspring. Because of the complexity of mechanisms underlying neurocognitive deficits in exposed subjects, and even more so in offspring, the most feasible approach to alleviate neurocognitive consequences of PND is to identify and target neurocognitive effects of anesthesia or surgery at their initiation. In contrast to the polyvalent, incompletely characterized molecular pathways activated by surgical procedures that may contribute to PND development, molecular targets involved in initiation of functional effects of general anesthetics are relatively well studied.[21] The latter may facilitate investigation of initial mechanisms of neurocognitive effects of general anesthetics and the development of therapeutic approaches to mitigate them and therefore may help to manage PND in more complex clinical settings that involve anesthesia, surgery, and accompanying pathophysiological conditions.

A primary molecular mechanism mediating the initial anesthetic effects of halogenated general anesthetics, including sevoflurane, is enhancement of γ-aminobutyric acid type A receptor ($GABA_AR$)–mediated inhibition of neuronal activity.[21] Whether $GABA_AR$ signaling is inhibitory or shifts toward excitatory is largely determined by the Na^+-K^+-Cl^- (NKCC1) Cl^- importer/ KCC2 Cl^- exporter ratio–dependent transmembrane gradient of Cl^-.[22] $GABA_AR$-mediated inhibitory control of the HPA axis plays a key role in the homeostatic responses to stress.[23,24] An increase in the NKCC1/KCC2 ratio and consequent shift in $GABA_AR$ signaling from inhibitory to excitatory may lead to dysregulated responses to stress and upregulated inflammatory processes.[23–28] The central questions are how general anesthetics such as sevoflurane induce persistent upregulation of the HPA axis and inflammation in young adult rats and whether disrupting the mechanisms underlying sevoflurane's initial effects can mitigate PND-related consequences across generations. To address these questions, we tested the hypothesis outlined below. Briefly, the main initial events in the HPA axis response to stress include stressor-stimulated secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) by parvocellular neurons into the pituitary portal circulation, which, in turn, stimulates release of pituitary adrenocorticotropin hormone.[24,25,29–31] At rest, $GABA_AR$ signaling is inhibitory in mature CRH- and AVP-producing parvocellular neurons.[23,24,32] In AVP (but not oxytocin [OXT])–secreting hypothalamic magnocellular neurons, however, NKCC1/KCC2 ratios are high enough to support $GABA_AR$-mediated excitatory Cl^- currents.[32] Notably, AVP stimulates and OXT inhibits HPA axis activity.[33] Hence, we hypothesize that sevoflurane, by acting as a $GABA_AR$ enhancer, stimulates hypothalamic magnocellular AVP-producing neurons, but not OXT-producing neurons, and, in turn, the HPA axis. We further hypothesize that this stimulation initiates sustained upregulation of the HPA axis and inflammation throughout the brain *via* a positive

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feedback loop between HPA axis activity, inflammation, and NKCC1/KCC2-$GABA_AR$ signaling.[24,26–28,34,35] Persistently upregulated parental HPA axis and inflammation induce neurocognitive deficits in sevoflurane-exposed sires and their future offspring. To test these hypotheses regarding the mechanisms initiating sevoflurane-induced intergenerational PND and pharmacotherapeutic approaches to prevent the development of intergenerational PND, we studied the effects of the NKCC1 inhibitor bumetanide[22,36,37] and the glucocorticoid receptor (GR) antagonist RU486 (mifepristone),[38] administered to sires before exposure to sevoflurane. According to this hypothesis, pretreatment with bumetanide may exert therapeutic effects by inhibiting the NKCC1 transporter, thereby shifting $GABA_AR$ signaling to an inhibitory state in AVP-producing neurons (as well as possibly other neurons involved in HPA axis regulation). The therapeutic effects of RU486 may involve disrupting sustained HPA axis upregulation by inhibiting corticosterone-induced increases in the NKCC1/KCC2 ratio and inflammation, as well as countering the GR-mediated genomic and epigenomic effects of corticosterone (although genomic and epigenomic effects of corticosterone mediated by GR were not investigated in this study).

Materials and Methods

Animals

All procedures were approved by the University of Florida Institutional Animal Care and Use Committee. The study was conducted and data are reported in accordance with ARRIVE guidelines.[39] Sprague–Dawley rats (112 males, 36 females [generation F0]) were purchased from Charles River. F0 females were used only to generate offspring (generation F1). The rats were housed under controlled illumination (12-h light/12-h dark, lights on at 7:00 AM) and temperature (23 to 24°C) with free access to food and water. Within 24 h of delivery, F1 litters were culled to 12 pups. At 21 days, the pups were weaned and housed two to a cage for the rest of the study. Experimental data are from 184 males and 72 females. Two F0 males died during exposure to sevoflurane and were excluded from all analyses.

Treatment Groups

Figure 1 shows the study design. F0 males were randomized into four treatment groups (n = 28 per group). Investigators were blinded to group assignments. F0 males were exposed to sevoflurane on postnatal day 56 (P56), P58, and P60 (F0M_S group). Sevoflurane was administered in a temperature-controlled chamber to maintain body temperature at ~37°C with a continuous supply of 30% oxygen in air (1.5 l/min) during anesthesia (6% sevoflurane for 3 min for anesthesia induction and 2.1% sevoflurane for 177 min for maintenance).[16,17] F0 males in the F0M_BS group received bumetanide (1.84 mg/kg, intraperitoneally) 30 min before each sevoflurane exposure, while F0 rats in the F0M_RS group received RU486 (10 mg/kg, intraperitoneally) 30 min before each sevoflurane exposure. The efficacy of these drugs and doses was verified in previous studies.[40,41] F0 males in the F0M_C group were placed in a novel cage and housed singly for an equivalent time on P56, P58, and P60. To control for nonspecific effects of bumetanide and RU486 injections, rats in the F0M_C and F0M_S groups were injected with a similar volume of saline.

A subset of F0 males (n = 10 per group) was sacrificed 1 h after the last sevoflurane exposure or at an equivalent timepoint in the F0M_C group to evaluate the initial effects of the respective treatments. Of the remaining 72 F0 rats, 36 (n = 9 per group) were mated on P90 by placing a male/female pair in the same cage for 72 h to produce offspring (generation F1). Thereafter, F0 females were housed individually for the remaining gestation and postpartum rearing periods. Nine breeding pairs per experimental group were used to produce F1 male and female offspring (18 F1 rats/sex/group), sired by: (1) F0M_C (the F1M_C and F1F_C groups, respectively); (2) F0M_S (the F1M_S and F1F_S groups, respectively); (3) F0M_BS (the F1M_BS and F1F_BS

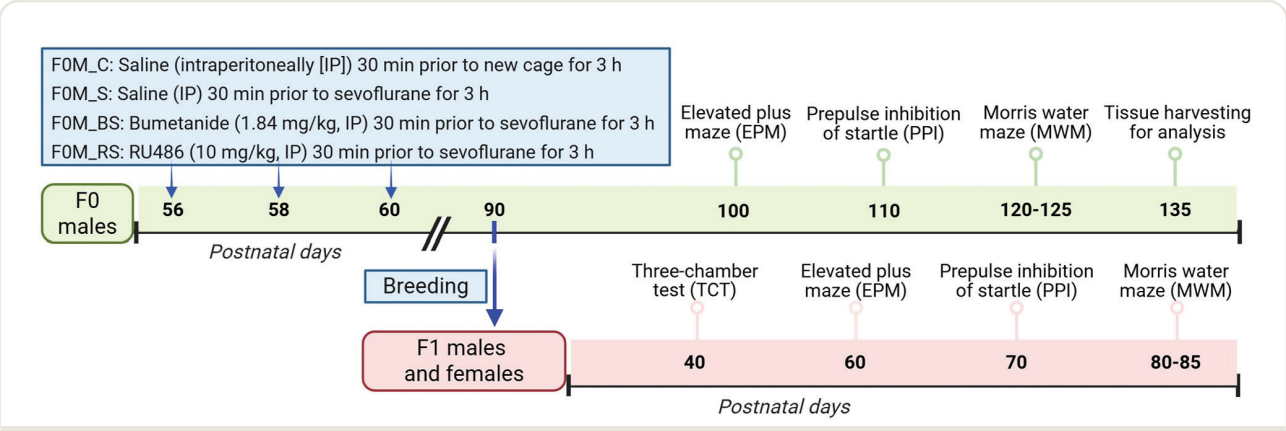


Fig. 1. Study design. Created in BioRender (https://BioRender.com/462brme). EPM, elevated plus maze; IP, intraperitoneally; MWM, Morris water maze; PPI, prepulse inhibition; TCT, three-chamber test.

groups, respectively); and (4) F0M_RS (the F1M_RS and F1F_RS groups, respectively). A given F1 offspring experimental group included two to four rats per sex from a given F1 litter. At P21, F1 pups were weaned and housed in sex-matched pairs for the rest of the study. F1 offspring were not exposed to any treatment aside from neurobehavioral

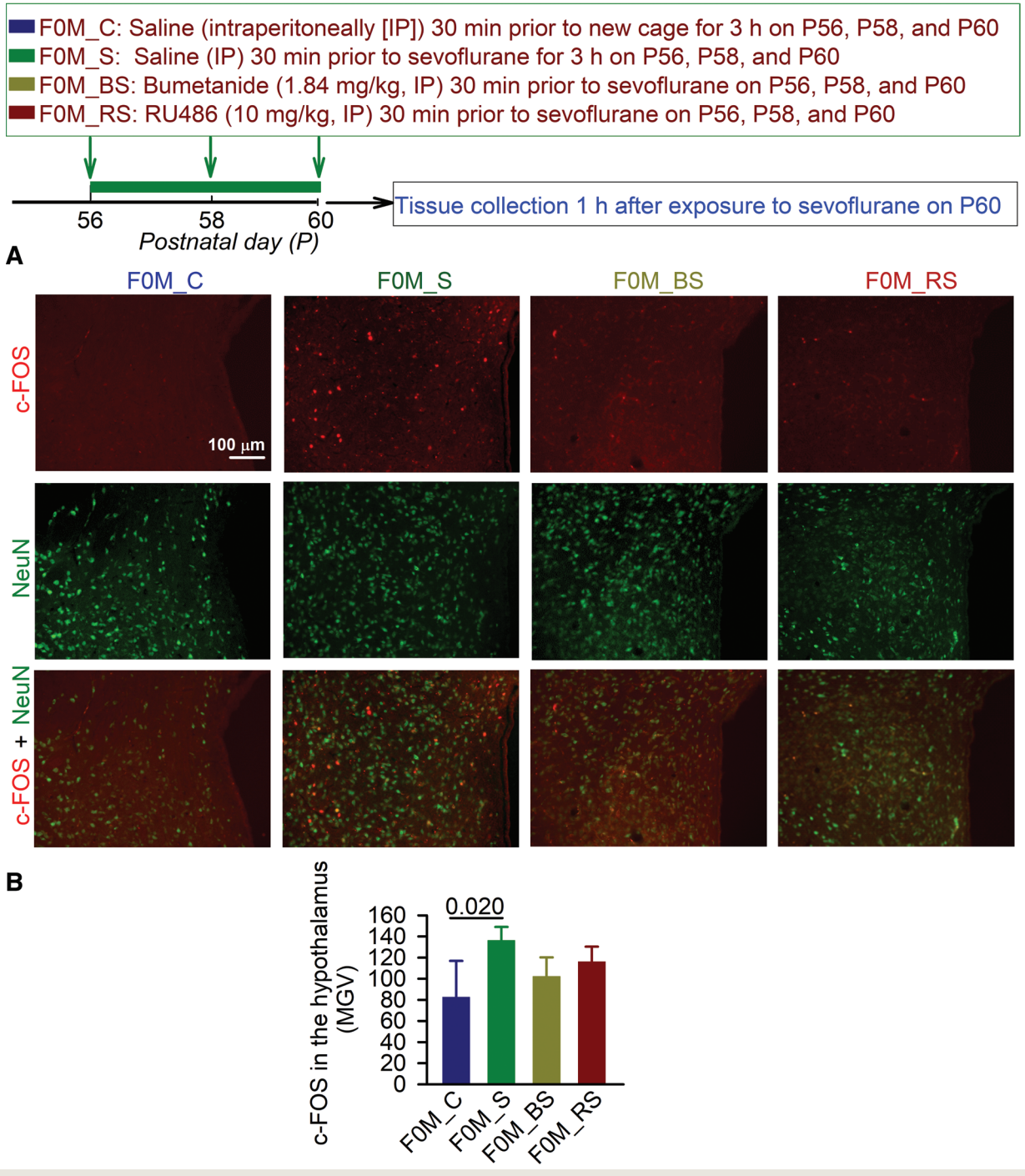


Fig. 2. Acute effects of exposure of F0 male rats to sevoflurane and respective treatments on F0 male paraventricular nucleus (PVN) of the hypothalamus c-FOS expression. (*Top*) Experimental design. (*A*, *B*) Representative images and results of quantification analysis of c-FOS mean gray value (MGV; fluorescence intensity) in the PVN of the hypothalamus. The data are means ± SD from four rats per group. The *P* value of the multiple pairwise comparison is shown in the plot above the *horizontal line*. The beginning and end of the *horizontal line* correspond to the compared experimental groups. A one-way ANOVA was performed, followed by Tukey's *post hoc* test to determine significant pairwise differences, with $P \leq 0.05$ considered statistically significant. IP, intraperitoneally; P*n*, postnatal day *n*.

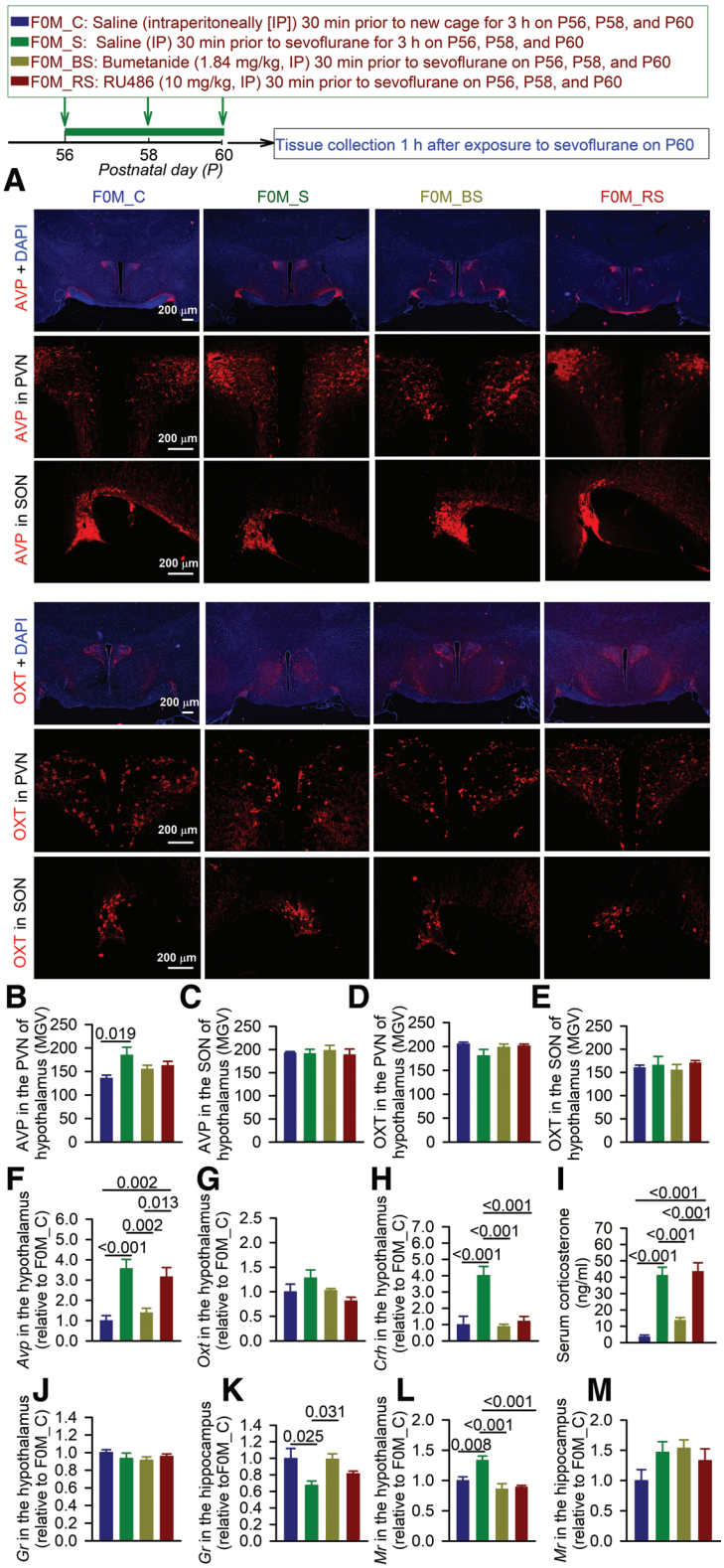


Fig. 3. Initial effects of exposure of F0 male rats to sevoflurane and respective treatments on F0 male gene transcription in the brain and systemic corticosterone levels. (*Top*) Experimental design. (*A* to *E*) Representative images and results of quantification analyses of arginine vasopressin (AVP), oxytocin (OXT) mean gray value (MGV; fluorescence intensity) in the paraventricular nucleus (PVN), and supraoptic nucleus (SON) of the hypothalamus. The data are means ± SD from three to four rats per group. (*F* to *H*) mRNA levels of AVP, OXT, *(Continued)*

evaluations. Analysis of breeding data did not indicate differences in fertility of sires from different experimental groups. Of nine breeding pairs per experimental group, one F0M_S pair and two F0M_RS pairs failed to produce offspring. There was also no statistical difference in the number of offspring sired by rats from the different groups.

After mating, F0 sires were evaluated sequentially in the elevated plus maze (EPM) on P100,[16,17] for prepulse inhibition (PPI) of the acoustic startle response on P110,[16,17] and in the Morris water maze (MWM) between P120 and P125.[16,17] To measure corticosterone responses to stress, blood samples were collected 30 min after the PPI test by using the "tail clip" method as previously described.[16,17] Ten days after the *in vivo* studies, these F0 rats were anesthetized and decapitated to collect trunk blood and brain tissue for further analyses (fig. 1). The F1 offspring were sequentially evaluated in the EPM on P60, PPI on P70, and MWM between P80 and P85. In addition, F1 offspring were tested in the three-chamber test on P40 to evaluate social behavior.[42] All methods have been described in the referenced studies[16,17] (see supplemental text 1, https://links.lww.com/ALN/E16, for detailed descriptions).

Statistical Analysis

The values are reported as means ± SD. Statistical analyses were carried out on raw data using SigmaPlot 15.0 software (Systat Software, Inc., USA) and SPSS version 27 (IBM Corp., USA). Boxplots were used to identify outliers. No outliers were detected that were not in the plausible range of values for each measure; therefore, all data were maintained in analyses. One- and two-factor ANOVAs and linear mixed models were used to analyze data (see supplemental text 1 for details, https://links.lww.com/ALN/E16). The models also included paternal treatment and offspring sex as main effects, as well as interaction terms. Multiple pairwise comparisons were done with the Tukey method. $P \leq 0.05$ was considered significant. Summary descriptive statistics and effect size with a CI are provided in supplemental table 4 (https://links.lww.com/ALN/E21) and supplemental table 5 (https://links.lww.com/ALN/E22), respectively.

Results

Initial and Sustained Effects of Repeated Exposure to Sevoflurane and Pretreatments with Bumetanide and RU486 in F0 Male Rats

Initial effects were assessed in tissue samples isolated 1 h after exposure of F0 male rats to sevoflurane on P60, or at equivalent time in F0M_C rats. First, by using c-FOS immunofluorescence as a biomarker of neuronal activity, we found that only F0M_S rats exhibited increased c-FOS immunofluorescence in the paraventricular nucleus (PVN) of the hypothalamus (fig. 2; supplemental table 1, https://links.lww.com/ALN/E18). Likewise, only F0M_S rats had increased AVP immunofluorescence in the PVN, but not supraoptic nucleus (SON), of the hypothalamus (fig. 3, A to E; supplemental table 1, https://links.lww.com/ALN/E18). In addition, only F0M_S rats had increased hypothalamic mRNA transcripts of *Avp*, but not *Oxt* (fig. 3, F and G; supplemental table 1, https://links.lww.com/ALN/E18), as well as increased mRNA transcripts for *Crh* (fig. 3H; supplemental table 1, https://links.lww.com/ALN/E18). Consistently, F0M_S rats had a multifold increase in corticosterone when compared to F0M_C and F0M_BS rats, but similar to that in F0M_RS rats (fig. 3I; supplemental table 1, https://links.lww.com/ALN/E18). Even though F0M_S rats had normal hypothalamic *Gr* mRNA levels, hippocampal mRNA levels *of Gr*[23,24] were decreased compared to the F0M_C and F0M_BS groups (fig. 3, J and K; supplemental table 1, https://links.lww.com/ALN/E18). Conversely, mineralocorticoid receptor (*Mr*) mRNA transcripts were increased in the hypothalamus of F0M_S rats only, whereas the increase in hippocampal *Mr* mRNA transcripts in this group did not achieve statistical significance (fig. 3, L and M; supplemental table 1, https://links.lww.com/ALN/E18). All these measures in F0M_BS and F0M_RS rats were no different from those in the F0M_C group (fig. 3, B to E, G, H, and J to M; supplemental table 1, https://links.lww.com/ALN/E18).

The F0M_S rats had elevated hippocampal levels of glial fibrillary acidic protein (GFAP; an astrocyte-specific marker) and ionized calcium-binding adaptor 1 (Iba1; a microglia/macrophage-specific calcium-binding protein; fig. 4, A to C; supplemental table 1, https://links.lww.com/ALN/E18), as well as serum levels of interleukin-1β and interleukin-6 (fig. 4, D and E; supplemental table 1, https://links.lww.com/ALN/E18). Brain and serum levels of these factors in F0M_BS and F0M_RS rats were no different from those in F0M_C rats (fig. 4, A to E; supplemental table 1, https://links.lww.com/ALN/E18). The F0M_S group was the only F0 group that had significantly increased hypothalamic and hippocampal *Nkcc1/Kcc2* mRNA ratios (fig. 4, F to K; supplemental table 1, https://links.lww.com/ALN/E18). Both hypothalamic (compared to F0M_RS rats) and hippocampal (compared to all other groups) *Nkcc1* mRNA transcripts were increased in F0M_S rats (fig. 4, F and I). Expression of *Kcc2* was significantly reduced only in the hypothalamus of F0M_S

Fig. 3. *(Continued)* and corticotropin-releasing hormone (*Crh*) genes in the hypothalamus. The data are means ± SD from six rats per group (n = 5 for hypothalamic *Crh* transcripts in F0M_C group). (*I*) The serum levels of corticosterone. The data are means ± SD from six rats per group. (*J* to *M*) The hypothalamic and hippocampal mRNA levels of glucocorticoid (*Gr*) and mineralocorticoid (*Mr*) receptors. The data are means ± SD from six rats per group. The *P* values of the multiple pairwise comparisons are shown in the respective plots above the *horizontal lines*. The beginnings and ends of the *horizontal lines* correspond to the compared experimental groups. The color coding of the experimental groups is shown in the *insets*. A one-way ANOVA was performed, followed by Tukey's *post hoc* test to determine significant pairwise differences, with $P \leq 0.05$ considered statistically significant. DAPI, 4′,6-diamidino-2-phenylindole; *Gr*, glucocorticoid receptor; IP, intraperitoneally; *Mr*, mineralocorticoid receptor; P*n*, postnatal day *n*.

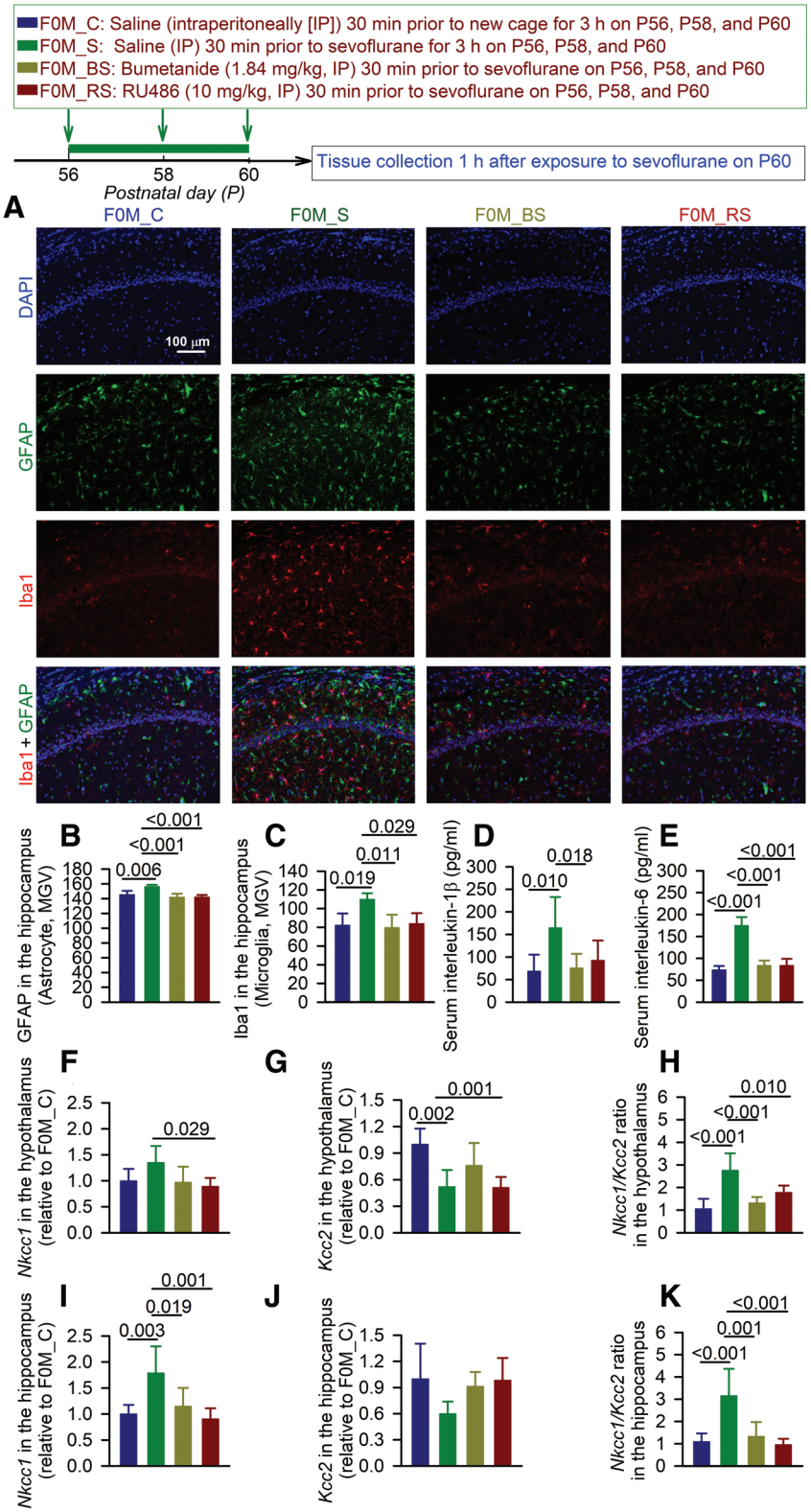


Fig. 4. Initial effects of exposure of F0 male rats to sevoflurane and respective treatments on F0 male inflammation responses and respective levels of Na^+-K^+-Cl^- (*Nkcc1*) Cl^- importer and K^+-$2Cl^-$ (*Kcc2*) Cl^- exporter. (*Top*) Experimental design. (*A* to *C*) Representative images and results of quantification analyses of glial fibrillary acidic protein (GFAP; an astrocyte-specific protein marker) and ionized calcium-binding adaptor 1 (Iba1; a microglia/macrophage-specific protein marker) mean gray value (MGV; fluorescence intensity) *(Continued)*

Fig. 4. *(Continued)* in the hippocampus. The data are means ± SD from four rats per group. (*D*, *E*) Serum levels of interleukin-1β and interleukin-6. The data are means ± SD from eight rats per group. (*F* to *K*) Respective levels of *Nkcc1* mRNA, *Kcc2* mRNA, and *Nkcc1/Kcc2* ratio in the hippocampus and hypothalamus of F0 male rats. The data normalized against F0M_C are means ± SD from six rats per group. The *P* values of the multiple pairwise comparisons are shown in the respective plots above the *horizontal lines*. The beginnings and ends of the *horizontal lines* correspond to the compared experimental groups. A one-way ANOVA was performed, followed by Tukey's *post hoc* test to determine significant pairwise differences, with $P \leq 0.05$ considered statistically significant. DAPI, 4′,6-diamidino-2-phenylindole; IP, intraperitoneally; P*n*, postnatal day *n*.

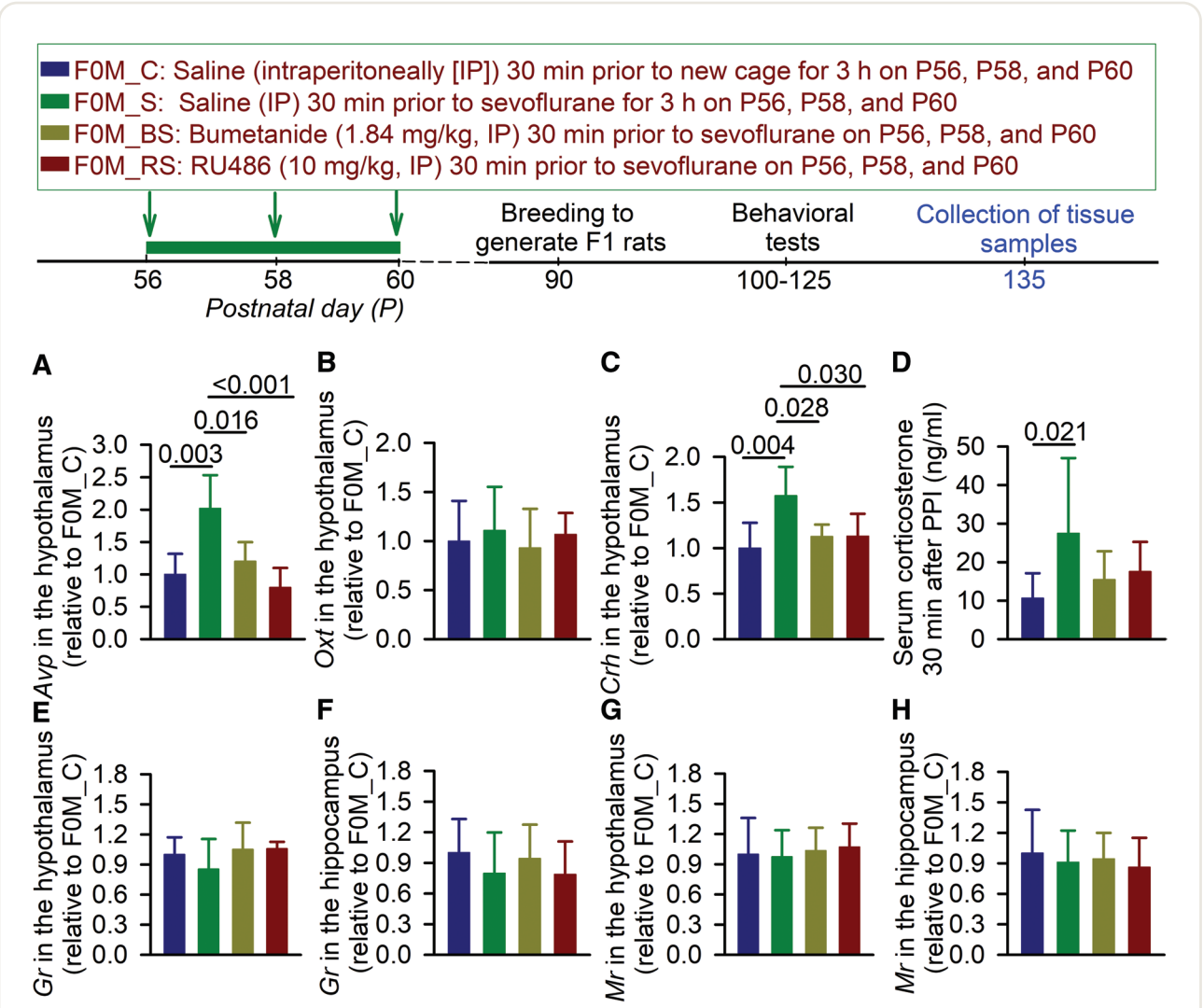


Fig. 5. Long-term effects of exposure of F0 male rats to sevoflurane and respective treatments on F0 male gene transcription in the brain and systemic corticosterone. (*Top*) Experimental design. (*A* to *C*) mRNA levels of arginine vasopressin (*Avp*), oxytocin (*Oxt*), and corticotropin-releasing hormone (*Crh*) in the hypothalamus. The data are means ± SD from six rats per group. (*D*) Serum levels of corticosterone 30 min after completion of the prepulse inhibition (PPI) of startle test. The data are means ± SD from nine rats per group. (*E* to *H*) Hypothalamic and hippocampal mRNA levels of glucocorticoid (*Gr*) and mineralocorticoid (*Mr*) receptors. The data are means ± SD from four to six rats per group. The *P* values of the multiple pairwise comparisons are shown in the respective plots above the *horizontal lines*. The beginning and end of the *horizontal lines* correspond to the compared experimental groups. The color coding of the experimental groups is shown in the *insets*. A one-way ANOVA was performed, followed by Tukey's *post hoc* test to determine significant pairwise differences, with $P \leq 0.05$ considered statistically significant. IP, intraperitoneally; P*n*, postnatal day *n*.

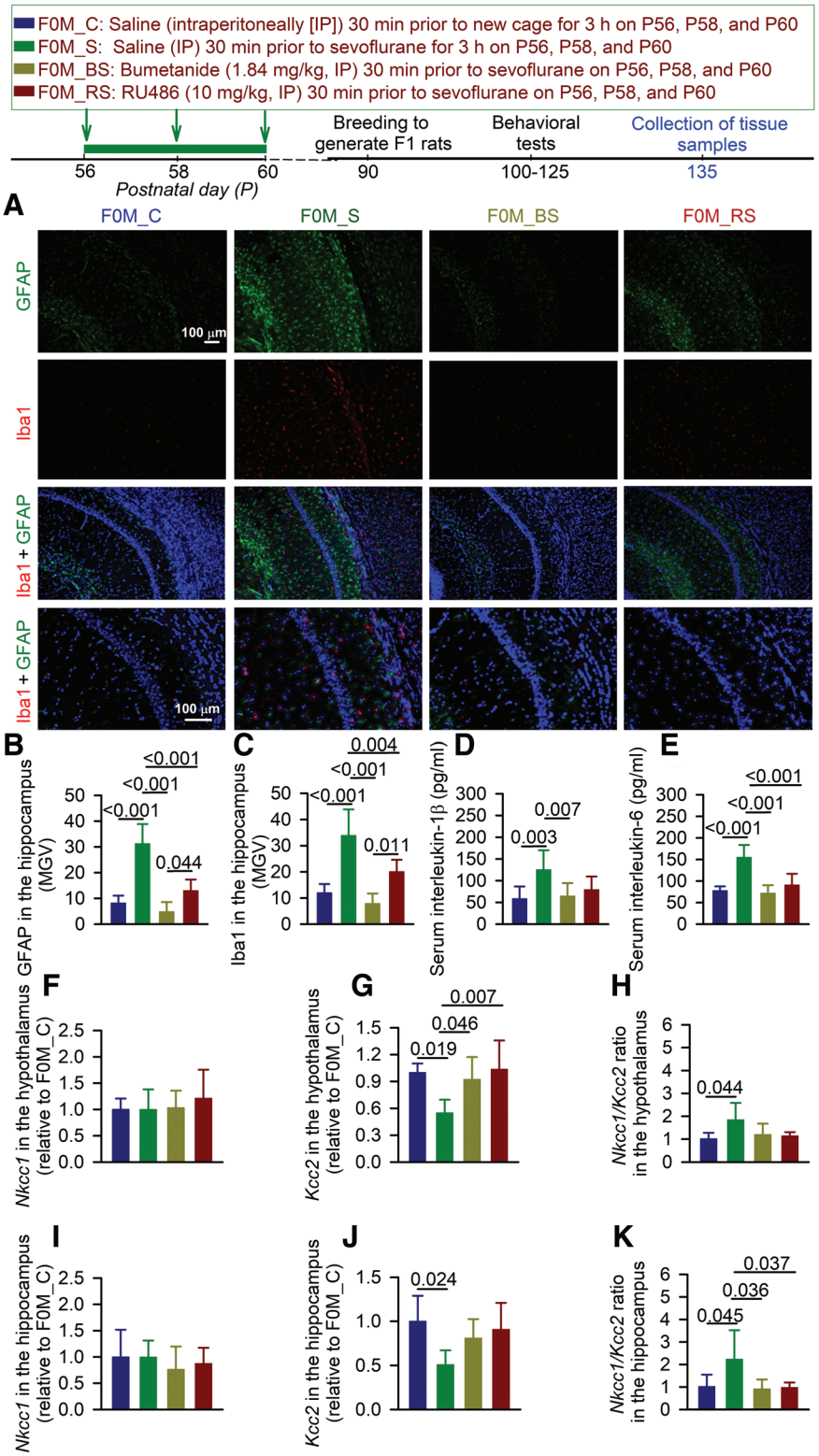


Fig. 6. Long-term effects of exposure of F0 male rats to sevoflurane and respective treatments on F0 male inflammation responses and respective levels of Na^+-K^+-Cl^- *(Nkcc1)* Cl^- importer and K^+-$2Cl^-$ (*Kcc2*) Cl^- exporter. (*Top*) Experimental design. (*A* to *C*) Representative images and results of quantification analyses of glial fibrillary acidic protein (GFAP; and astrocyte-specific protein marker) and *(Continued)*

rats (fig. 4G; supplemental table 1, https://links.lww.com/ALN/E18), although there was a trend toward decreased expression of *Kcc2* in hippocampus in F0M_S rats (fig. 4J; supplemental table 1, https://links.lww.com/ALN/E18).

Consistent with sustained upregulation of HPA axis activity and inflammation in F0M_S rats, almost all abnormalities detected 1 h after the last exposure to sevoflurane at P60 were evident after completion of behavioral testing at P135. Specifically, F0M_S rats, when compared to F0 rats from all other experimental groups, had increased hypothalamic *Avp* and *Crh* but not *Oxt* mRNA levels (fig. 5, A to C; supplemental table 2, https://links.lww.com/ALN/E19). The F0M_S group was the only group that showed exacerbated corticosterone responses to stress after the PPI test when compared to F0M_C rats (fig. 5D; supplemental table 2, https://links.lww.com/ALN/E19). Interestingly, even though RU486 before sevoflurane exposure did not affect sevoflurane-induced corticosterone secretion acutely (fig. 3I), the F0M_BS and F0M_RS rats were no different from F0M_C rats in their corticosterone responses to stress on P110 (fig. 5D; supplemental table 2, https://links.lww.com/ALN/E19). There were no group differences in hypothalamic and hippocampal *Gr* and *Mr* mRNA (fig. 5, E to H; supplemental table 2, https://links.lww.com/ALN/E19).

Similar to initial changes in central and systemic inflammatory markers (fig. 4, A to E; supplemental table 1, https://links.lww.com/ALN/E18), F0M_S at P135 had higher hippocampal GFAP and Iba1, as well as serum interleukin-1β and interleukin-6 levels compared to F0 males from the other groups (fig. 6, A to E; supplemental table 2, https://links.lww.com/ALN/E19). The levels of all these factors in F0M_BS and F0M_RS rats were no different from those in F0M_C rats (fig. 6, A to E; supplemental table 2, https://links.lww.com/ALN/E19). Interestingly, levels of hippocampal GFAP and Iba1 in F0M_BS rats tended to be even lower than those in F0M_C rats and were significantly lower than in F0M_RS rats (fig. 6, A to C; supplemental table 2, https://links.lww.com/ALN/E19).

Similar to the initial increases in hypothalamic and hippocampal *Nkcc1/Kcc2* mRNA ratios (fig. 4, F to K; supplemental table 1, https://links.lww.com/ALN/E18), only F0M_S rats had significantly increased *Nkcc1/Kcc2* mRNA ratios in the hypothalamus (compared to F0M_C rats) and hippocampus (compared to all other groups) at P135 (fig. 6, F to K; supplemental table 2, https://links.lww.com/ALN/E19). Notably, F0M_S rats had normal hypothalamic and hippocampal *Nkcc1* mRNA levels (fig. 6, F and I; supplemental table 2, https://links.lww.com/ALN/E19) but decreased *Kcc2* mRNA levels in the hypothalamus (compared to all other groups) and hippocampus (compared to F0M_C rats; fig. 6, G and J; supplemental table 2, https://links.lww.com/ALN/E19).

Long-term Behavioral Effects of Sevoflurane and Pretreatments with Bumetanide and RU486 in F0 Male Rats

In the EPM, F0M_S and F0M_BS groups exhibited anxiety-like behavior as manifested by less time spent in open arms (the F0M_S group *vs.* the F0M_C and F0M_RS groups and the F0M_BS group *vs.* the F0M_C group; fig. 7A; supplemental table 2, https://links.lww.com/ALN/E19). The F0 groups did not differ in number of open arm entries (fig. 7B; supplemental table 2, https://links.lww.com/ALN/E19).

The F0M_S group exhibited impaired sensorimotor gating as evidenced by reduced PPI of acoustic startle at a 3 dB prepulse when compared to all other F0 groups (fig. 7C; supplemental table 2, https://links.lww.com/ALN/E19). The F0M_BS and F0M_RS groups did not differ from the F0M_C group based on the PPI of startle values (fig. 7C; supplemental table 2, https://links.lww.com/ALN/E19).

No F0 rats exhibited impaired spatial learning across the 5-day training period in the MWM (fig. 7D; supplemental table 2, https://links.lww.com/ALN/E19). Evaluation of F0 rats in the probe test revealed impaired spatial memory in F0M_S rats. Thus, although F0 rats from all experimental groups did not differ in swim distance or speed, F0M_S rats made fewer crossings over the escape platform location than F0M_C and F0M_BS rats (fig. 7, E to G; supplemental table 2, https://links.lww.com/ALN/E19). In addition, F0M_S rats spent less time in the target quadrant compared to F0_C and F0M_BS rats (fig. 7H; supplemental table 2, https://links.lww.com/ALN/E19). Analysis of time spent in each quadrant showed that only F0M_S rats failed to discriminate between the target and other quadrants (fig. 7I; supplemental table 2, https://links.lww.com/ALN/E19).

Neurobehavioral Consequences of Paternal Exposure to Sevoflurane and Pretreatments with Bumetanide and RU486 on F1 Offspring

The social preference test showed that F1M_S, in contrast to F1M_C, did not discriminate between a social stimulus rat and an object (fig. 8A; supplemental table 3, https://links.

Fig. 6. *(Continued)* ionized calcium-binding adaptor 1 (Iba1; a microglia/macrophage-specific protein marker) mean gray value (MGV; fluorescence intensity) in the hippocampus. The data are means ± SD from six rats per group. (*D* to *E*) Serum levels of interleukin-1β and interleukin-6. The data are means ± SD from eight rats per group. (*F* to *K*) Respective levels of *Nkcc1* mRNA, *Kcc2* mRNA, and *Nkcc1/Kcc2* ratio in the hippocampus and hypothalamus of F0 male rats. The data normalized against F0M_C are means ± SD from five to six rats per group. The *P* values of the multiple pairwise comparisons are shown in the respective plots above the *horizontal lines*. The beginnings and ends of the *horizontal lines* correspond to the compared experimental groups. A one-way ANOVA was performed, followed by Tukey's *post hoc* test to determine significant pairwise differences, with $P \leq 0.05$ considered statistically significant. IP, intraperitoneally; P*n*, postnatal day *n*.

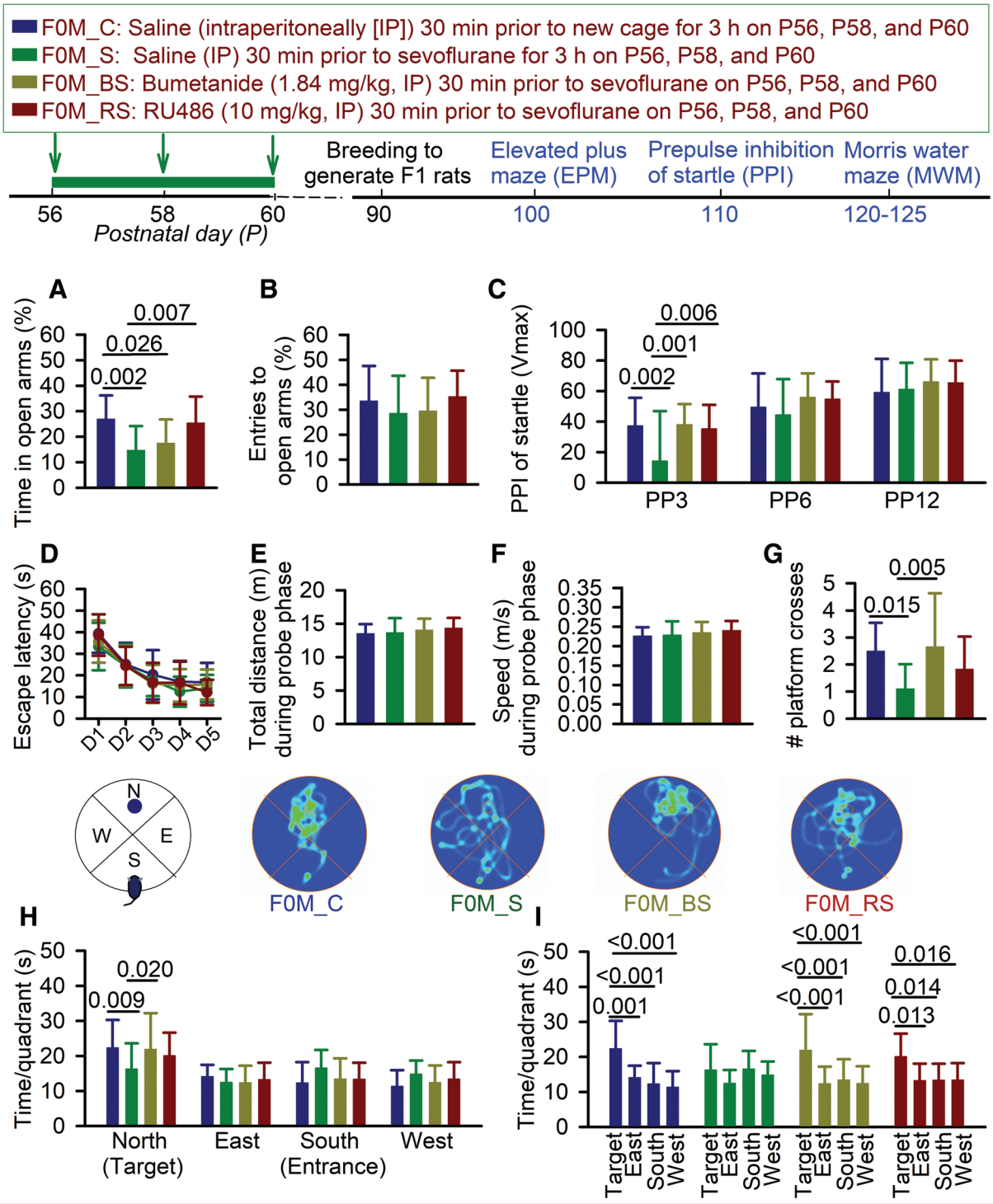


Fig. 7. Long-term effects of exposure of F0 male rats to sevoflurane and respective treatments on F0 male behavior. (*Top*) Experimental design. (*A*, *B*) The percentage of time spent in open arms and the percentage of entries to open arms during the elevated plus maze (EPM) test. The data are means ± SD from 18 rats per group (n = 17 in the F0M_C group). One rat in the F0M_C group was removed from the study because of a fall. (*C*) The percentage of prepulse inhibition (PPI) of acoustic startle response at prepulse intensities of 3, 6, and 12 dB above the background noise of 70 dB. The data are means ± SD from 18 rats per group. (*D*) Plots showing the values of escape latencies during the 5-day training period of the Morris water maze (MWM) test. (*E* to *I*) Histograms showing the total distance the rats traveled (*E*), the swimming speeds of rats during the probe test (*F*), the number of times that rats from different treatment groups crossed the previous location of the escape platform (*G*), the time that rats from different treatment groups spent in each quadrant (*H*), *(Continued)*

lww.com/ALN/E20). Conversely, preference for a social stimulus rat over an object was preserved in F1M_BS and F1M_RS rats (fig. 8A; supplemental table 3, https://links.lww.com/ALN/E20). Social behavior in F1 female offspring from all experimental groups was unaffected (fig. 8B; supplemental table 3, https://links.lww.com/ALN/E20). The social novelty test showed that only F1M_C and F1M_RS, but not F1M_S or F1M_BS, spent more time in the chamber with a nonfamiliar rat *versus* the chamber with a familiar rat (fig. 8C; supplemental table 3, https://links.lww.com/ALN/E20). Surprisingly, F1 female offspring of F0 sires from all four experimental groups, including F1F_C, did not discriminate between a nonfamiliar female rat and a familiar female rat (fig. 8D; supplemental table 3, https://links.lww.com/ALN/E20).

The results of the EPM test showed that only F1M_S exhibited signs of anxiety-like behavior, spending less time in open arms and making fewer open arm entries (fig. 8, E and F; supplemental table 3, https://links.lww.com/ALN/E20). Interestingly, bumetanide had similar weak effects on the time spent in open arms of the EPM in F0M_S (fig. 7A) and their F1 male offspring (fig. 8E; supplemental table 3, https://links.lww.com/ALN/E20). The behavior of F1 females was unaffected by paternal exposure condition (fig. 8, G and H; supplemental table 3, https://links.lww.com/ALN/E20).

Analysis of sensorimotor gating showed that F1M_S had impaired PPI of startle at PP 3 dB when compared to F1M_C, and at PP 6 dB and 12 dB when compared to F1 offspring of F0 sires from all other groups (fig. 9A; supplemental table 3, https://links.lww.com/ALN/E20). F1 female offspring of F0 sires from all treatment groups did not exhibit impaired PPI of startle, but F1F_BS had facilitated PPI of startle, resulting in PPI of startle responses greater than those in F1F_S and F1F_RS (PP 6 dB) and F1F_S (PP 12 dB; fig. 9B; supplemental table 3, https://links.lww.com/ALN/E20). Paternal treatment did not affect startle amplitudes in the absence of the prepulse in F1 male or F1 female rats.

Similar to F0 sires, the MWM showed no effect of paternal treatment on spatial learning in F1 male and female offspring (fig. 9, C and E; supplemental table 3, https://links.lww.com/ALN/E20). During the probe test, F1M_S, but not F1F_S, made fewer crossings over the escape platform location, indicating a spatial memory deficit (fig. 9, D and F ; supplemental table 3, https://links.lww.com/ALN/E20). Both F1M_S and F1F_S exhibited signs of impaired spatial memory, however, spending less time in the target quadrant during the probe test when compared to the respective F1 offspring of F0M_C sires (fig. 9, G and H; supplemental table 3, https://links.lww.com/ALN/E20). Neither F1 male or female offspring of F0M_BS or F0M_RS sires differed from F1 offspring of F0M_C sires in time spent in the target quadrant (fig. 9, G and H; supplemental table 3, https://links.lww.com/ALN/E20). A heritable deficit in spatial memory based on paternal sevoflurane exposure was also evident in the time that F1 male and female offspring from each experimental group spent in each quadrant. Only F1 male and female offspring of F0M_S sires failed to discriminate between the target and other quadrants (fig. 9, I and J; supplemental table 3, https://links.lww.com/ALN/E20).

Discussion

We identified molecular mechanisms that may initiate sevoflurane-induced PND in young adult male rats and their offspring and that may serve as targets for pharmacologic prevention of PND in both generations. More specifically, the findings of this study demonstrate that the commonly used general anesthetic sevoflurane, administered at clinically relevant doses and durations, initiates in otherwise healthy young adult male rats persistent stress-like changes in the HPA axis, systemic and central inflammation, and neurocognitive deficits that are also evident in their unexposed offspring, with males more affected than females. The NKCC1 inhibitor bumetanide and GR antagonist RU486, administered before sires' exposure to sevoflurane, disrupt the development of sevoflurane-induced abnormalities in the HPA axis and inflammation in F0 sires, as well as most neurobehavioral deficits in both generations. These findings suggest that NKCC1 Cl^- importer/KCC2 Cl^- exporter ratio-dependent and GR-dependent processes in F0 sires play important roles in initiation of paternal sevoflurane-induced PND in both generations. The NKCC1 Cl^- importer and GR may serve as promising molecular targets for effective and safe therapeutic prevention of sevoflurane-initiated intergenerational PND in exposed sires and their future offspring.

The findings of this study are in agreement with literature showing that parental preconception stress and

Fig. 7. *(Continued)* and the time that rats from a specific treatment group spent in each quadrant (*I*). The quadrant locations (S, south [rat entrance]; W, west; N, north [target]; E, east) and representative illustrations of the moves made by rats from different treatment groups during the probe trial are shown in the *insets*. The data are means ± SD from 18 rats per group. The *P* values of the multiple pairwise comparisons are shown in the respective plots above the *horizontal lines*. The beginnings and ends of the *horizontal lines* correspond to the compared experimental groups. The color coding of the experimental groups is shown in the *insets*. A one-way ANOVA was used to analyze the EPM data, as well as data on total distance, speed, and the number of crossings over the former platform location during the MWM probe test. A two-way repeated measures ANOVA was employed to analyze the PPI data, along with data on latencies to reach the escape platform during MWM training and time spent in each quadrant during the MWM probe test. Multiple pairwise comparisons were conducted using the Tukey method, with $P \leq 0.05$ considered significant. IP, intraperitoneally; P*n*, postnatal day *n*.

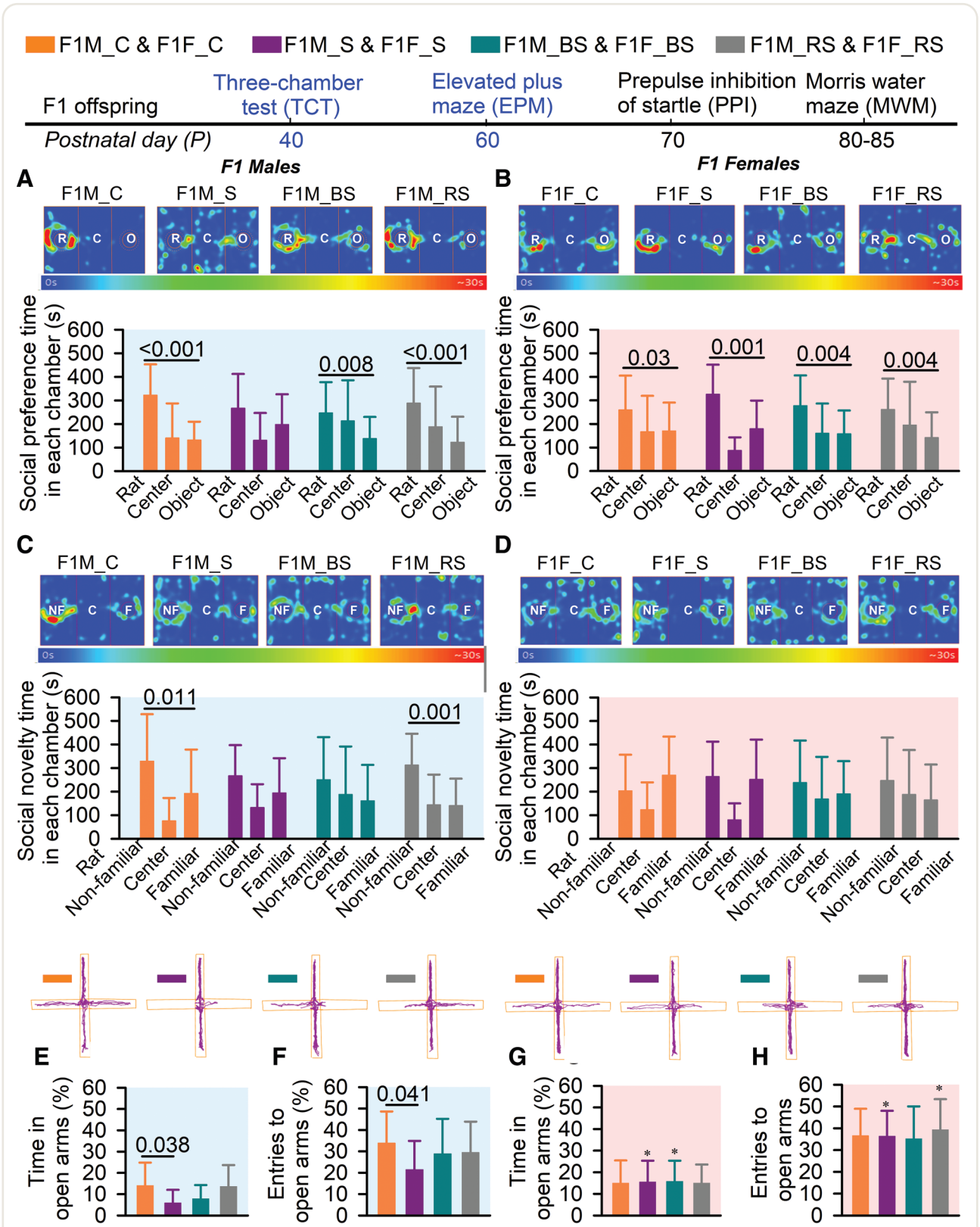


Fig. 8. Behavioral effects of paternal exposure to sevoflurane and respective treatments in F1 male and female offspring. (*Top*) Experimental design. (*A* through *D*) The results the three-chamber test (TCT) to assess cognition in the form of general sociability and interest in social novelty. (*A* to *D*, *upper*) Representative *heat maps* illustrating the topographical time distribution in social preference (*A*, *B*) and social novelty (*C*, *D*) tests of individual rats from different experimental groups. Respective *bar plots* show the results of quantitative *(Continued)*

inflammation cause heritable neurobehavioral abnormalities.[7–13] Furthermore, similar to the therapeutic effects of pretreatment with RU486 on intergenerational PND in this study, other groups demonstrated that treatment with RU486 during paternal preconception stress exposure ameliorates heritable detrimental effects of that stress in offspring.[12]

Although the magnocellular neurons secrete AVP and OXT through the posterior pituitary into systemic circulation, a number of studies indicate that these neuropeptides are also involved in HPA axis regulation.[29,30] In support of $GABA_AR$-mediated effects of sevoflurane on AVP-secreting neurons, sevoflurane increased c-FOS and AVP, but not OXT, expression in the hypothalamus. Additionally, sevoflurane-induced increases in hypothalamic c-FOS and AVP expression, as well as HPA axis activity, were prevented by pretreatment with the NKCC1 inhibitor bumetanide, while bumetanide did not affect hypothalamic OXT expression. The latter is in agreement with literature indicating that only AVP-producing, but not OXT-producing, magnocellular neurons have excitatory $GABA_AR$ signaling.[32] Most of these effects of sevoflurane were also prevented by pretreatment with the GR antagonist RU486. The lack of normalizing effects of RU486 on the sevoflurane-induced initial increase in hypothalamic *Avp* mRNA levels and corticosterone secretion is in line with the role of GRs in the negative feedback of corticosterone on the HPA axis.[23,24] Glucocorticoids suppress the activity of CRH-producing neurons in the PVN of the hypothalamus, as well as hypothalamic AVP- and OXT-producing magnocellular neurons, with more profound effects on the magnocellular neurons.[43,44]

The sevoflurane-initiated AVP-mediated stress-like responses and the resulting increase in the NKCC1/KCC2 ratio may play a key role in the sustained upregulation of the HPA axis and inflammation observed in this study. Supplemental figure 1 (https://links.lww.com/ALN/E17) illustrates potential pathways mediating these effects. Thus, $GABA_AR$-mediated inhibitory control of the HPA axis can be weakened or shifted toward excitatory by acute stress-induced increases in the NKCC1/KCC2 ratio.[23–25] Similarly, sevoflurane-elevated corticosterone *via* the $GABA_AR$–AVP–HPA axis pathway may cause an increase in the *Nkcc1/Kcc2* ratio, leading to a shift in $GABA_AR$ signaling toward excitatory in various brain regions or neurons (as supported by the elevated hypothalamic levels of *Crh* mRNA and increased *Nkcc1/Kcc2* mRNA ratios in both hypothalamus and hippocampus). Proinflammatory effects of paternal sevoflurane were alleviated by pretreatments with bumetanide and RU486, supporting the involvement of the same mechanisms in both the upregulation of the HPA axis and inflammation. Although the HPA axis and immune systems may interact through a negative feedback loop, both chronic and transient stress can induce proinflammatory signaling,[26–28] suggesting that in F0 sires, sevoflurane-initiated corticosterone release caused the upregulation of proinflammatory processes. In turn, proinflammatory cytokines can stimulate CRH and AVP production and HPA axis activity,[45] which would exacerbate the upregulation of the HPA axis. Considering that both acute and chronic stress and systemic and central inflammatory processes are known to increase the NKCC1/KCC2 ratio and neuronal excitability,[34,35] our findings are consistent with the possibility that sevoflurane-initiated increases in HPA axis functioning, NKCC1/KCC2-dependent neuronal activity, and inflammation interact through positive feedback loops, leading to the sustained upregulation of the HPA axis and inflammation in sevoflurane-exposed sires.

Bumetanide and RU486 (both U.S. Food and Drug Administration–approved agents) exhibited promising therapeutic effects in both generations when administered to F0 sires before sevoflurane exposure. According to the model presented in supplemental figure 1 (https://links.lww.com/ALN/E17), pretreatment with bumetanide may exert therapeutic effects by inhibiting the NKCC1 transporter, thereby shifting $GABA_AR$ signaling to an inhibitory state in AVP-producing neurons (as well as other neurons involved in HPA axis upregulation). This is supported by the normalization of c-FOS, AVP, and inflammatory marker immunofluorescence, as well as *Avp* and *Crh* transcripts and systemic corticosterone levels observed in the F0M_BS group. The therapeutic effects of RU486 may involve disrupting sustained HPA axis upregulation by inhibiting corticosterone-induced increases in the NKCC1/KCC2 ratio and inflammation while also counteracting the GR-mediated genomic and epigenomic effects of corticosterone that may

Fig. 8. *(Continued)* analyses of time spent by the test rats in one of the three chambers: in a chamber with a rat or an object in a case of the sociability test (*A*, *B*), or in a chamber with a nonfamiliar rat or familiar rat in a case of the social novelty test (*C*, *D*). The time spent in the middle empty chamber is labeled as *Center*. (*E* to *H*) Percentage of time spent in open arms and the percentage of number of entries to the open arms made by F1 male and female offspring during the elevated plus maze (EPM) test. (*Upper*) Representative illustrations of the tracks made by rats from different treatment groups during the EPM test. The data are means ± SD from 18 rats per sex per group for all experiments shown in this Figure. *$P \leq 0.05$ *versus* respective F1 male groups. The *P* values of the multiple pairwise comparisons are shown in the respective plots above the *horizontal lines*. The beginnings and ends of the *horizontal lines* correspond to the compared experimental groups. The color coding of the experimental groups is shown in the *insets*. For the TCT data, linear mixed models for repeated measures were applied, whereas a two-way ANOVA was utilized to analyze the EPM test data. Multiple pairwise comparisons were conducted using the Tukey method, with $P \leq 0.05$ considered statistically significant. C, center; F, familiar rat; MWM, Morris water maze; NF, nonfamiliar rat; O, object; P*n*, postnatal day *n*; PPI, prepulse inhibition; R, rat.

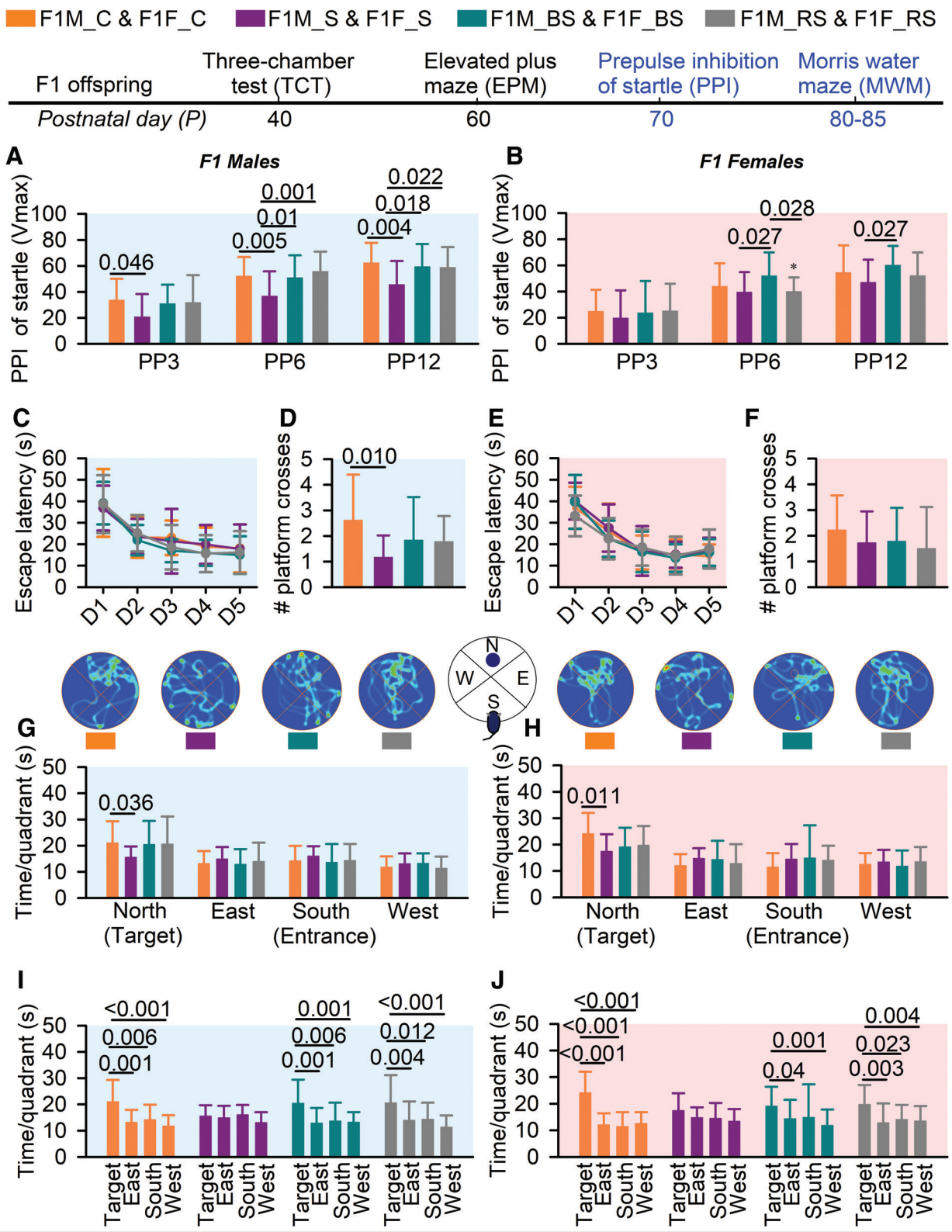


Fig. 9. Behavioral effects of paternal exposure to sevoflurane and respective treatments in F1 male and female offspring. (*Top*) Experimental design. (*A*, *B*) Percentage of prepulse inhibition (PP or PPI) of acoustic startle response at prepulse intensities of 3, 6, and 12 dB above the background noise of 70 dB. (*C*, *E*) Plots showing the values of escape latencies during the 5-day training period of the Morris water maze (MWM) test. (*D*, *F*) Histograms showing the number of times the rat crossed the previous location of the escape platform *(Continued)*

contribute to intergenerational neurobehavioral effects of paternal sevoflurane exposure. Note that the genomic and epigenomic effects of corticosterone were not analyzed in this study. According to this model, both agents may disrupt the sustained upregulation of the HPA axis and inflammation and, hence, protect against intergenerational neurobehavioral effects of sevoflurane, regardless of whether they are administered before, during, or after sevoflurane exposure. Such effects of bumetanide would align with the results of animal studies showing promising therapeutic effects in models of autism spectrum disorders, brain trauma, chronic pain, certain types of epilepsies, Parkinson's disease, and Down syndrome,[22] and in clinical studies of autism spectrum disorders.[36] Of broader relevance to accelerated cognitive decline, which is frequently associated with PND, patients treated with bumetanide may be less prone to developing Alzheimer's disease.[37]

In this proof-of-concept rat study, we demonstrate that repeated paternal exposure to sevoflurane triggers persistent stress and inflammation signaling in exposed young adult male rats and induces neurobehavioral abnormalities in both the sires and their future unexposed offspring. These findings align with numerous animal and human studies on the intergenerational effects of parental stress and inflammation.[7–13] While PND is a well established phenomenon in exposed human subjects, evidence of neurocognitive abnormalities in the offspring of former patients exposed to anesthesia or surgery remains lacking. Establishing a link between offspring abnormalities and past parental experiences, particularly anesthesia or surgery, is challenging in humans due to social and environmental confounding factors as well as ethical constraints. Consequently, a parent's past exposure to anesthesia or surgery is not even currently considered as a potential cause of abnormalities in children. Furthermore, our findings suggest that a parent with a history of sevoflurane exposure may act as a silent carrier of abnormalities to offspring. For instance, in F0M_S sires, PPI of startle was impaired only at the lowest prepulse intensity, whereas F1 male offspring of F0M_S sires exhibited impaired PPI of startle across all three prepulse intensities. Therefore, rodent studies like ours, which allow for strict control of experimental conditions, may provide experimental evidence supporting the importance of considering the neurocognitive consequences of parental anesthesia or surgery in offspring and serve as a foundation for similar studies in humans. To gain a more comprehensive understanding of the mechanisms mediating paternal sevoflurane exposure–induced intergenerational abnormalities, future studies should explore transcriptomic and proteomic changes in specific brain nuclei and neurons. Future study designs will also need to more closely model various clinical settings, such as the number, duration, and depth of maternal and paternal sevoflurane exposures, and the interaction of anesthesia with surgery to evaluate a broader range of cognitive, affective, and neurobiological outcomes. It will be important to determine whether parental conditions that are risk factors for heritable abnormalities, such as previous neurodegenerative abnormalities, substance misuse, or advanced parental age, exacerbate the heritable effects of exposure to sevoflurane and other general anesthetics with similar mechanisms of action.

In summary, the findings of this study show that the commonly used general anesthetic sevoflurane, administered to young adult male rats at clinically relevant concentrations and durations, initiates intergenerational neurobehavioral abnormalities through sustained upregulation of the stress response system and inflammation (a rat model of sevoflurane-induced intergenerational PND). Male offspring are more susceptible to paternal sevoflurane-induced neurobehavioral abnormalities than their female counterparts. The therapeutic effects of paternal pretreatment with bumetanide and RU486, both clinically approved agents, suggest potential molecular targets for the pharmacologic prevention of PND in exposed sires and their future offspring.

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Competing Interests

Dr. Gravenstein serves as a medical advisor for Teleflex Medical (Morrisville, North Carolina). The other authors declare no competing interests.

Fig. 9. *(Continued)* during the probe trial. (*G* to *J*) Histograms showing the time that rats from different treatment groups spent in each quadrant (*G*, *H*), and the time that rats from a specific treatment group spent in each quadrant (*I*, *J*). The quadrant locations (S – south [rat entrance]; W, west; N, north [target]; E, east) and representative illustrations of the swimming tracks made by rats from different treatment groups during the probe trial are shown in the *insets*. The data are means ± SD from 18 rats per group for all experiments shown in this figure. The *P* values of the multiple pairwise comparisons are shown in the respective plots above the *horizontal lines*. The beginning and end of the *horizontal lines* correspond to the compared experimental groups. The color coding of the experimental groups is shown in the *insets*. A two-way ANOVA was applied to analyze the number of crossings over the former platform location during the MWM probe test, while linear mixed models for repeated measures was used to evaluate the PPI test data, latency to reach the escape platform during the MWM training phase, and time spent in each quadrant during the MWM probe test. Multiple pairwise comparisons were conducted using the Tukey method, with $P \leq 0.05$ considered statistically significant. EPM, elevated plus maze; P*n*, postnatal day *n*; TCT, three-chamber test.

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Supplemental Digital Content

Supplemental Text 1. Methods, https://links.lww.com/ALN/E16
Supplemental Fig. 1. Hypothetical mechanism of sevoflurane-induced PND, https://links.lww.com/ALN/E17
Supplemental Table 1. Statistical analysis of initial F0 effects, https://links.lww.com/ALN/E18
Supplemental Table 2. Statistical analysis of long-term F0 effects, https://links.lww.com/ALN/E19
Supplemental Table 3. Statistical analysis of the F1 data set, https://links.lww.com/ALN/E20
Supplemental Table 4. Descriptive statistics data, https://links.lww.com/ALN/E21
Supplemental Table 5. Effect sizes with CI, https://links.lww.com/ALN/E22

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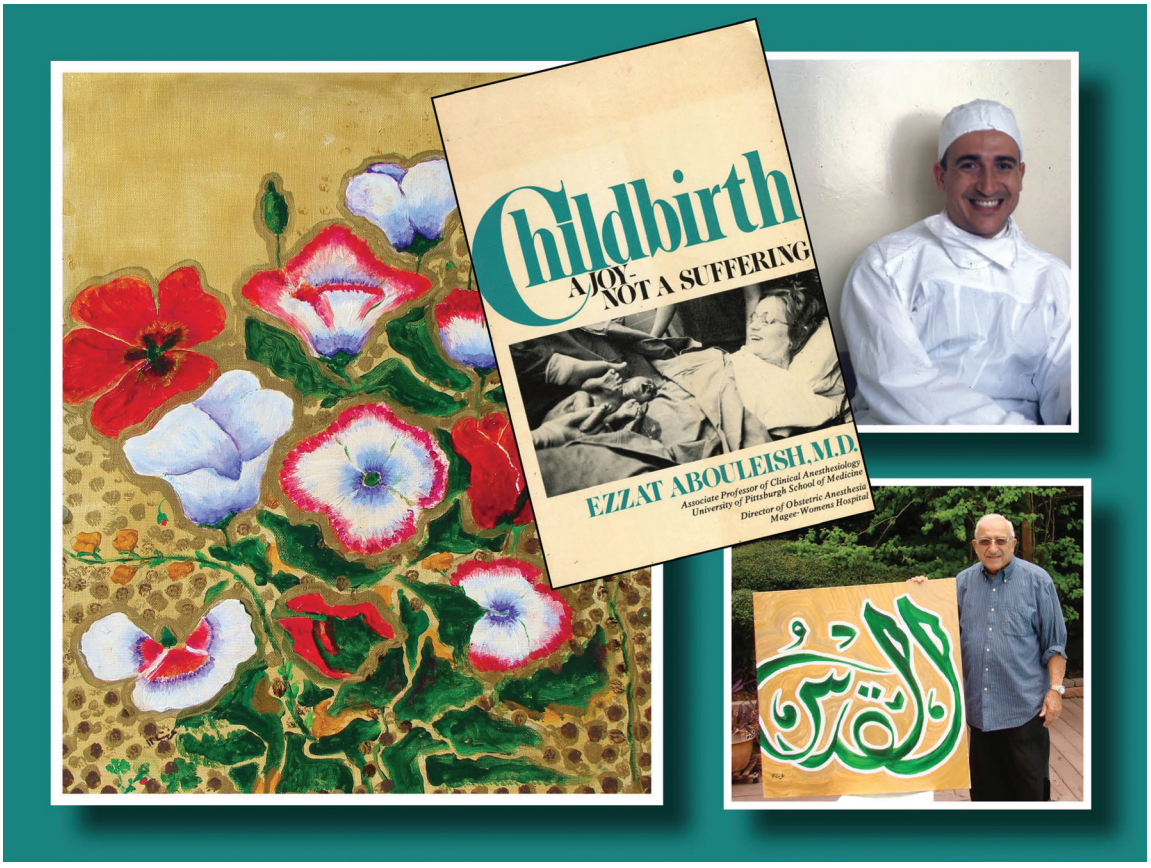
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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Joyful in Life and Labor: Dr. Ezzat Abouleish



Decades before you could ask a search engine "what to expect during labor and delivery," Ezzat Abouleish, M.D. (1931 to 2014, *upper, lower right*), published *Childbirth: A Joy, Not A Suffering* in 1975 (*center*). The maternal experience of childbirth was undergoing a significant transformation from the Twilight Sleep and "Natural" Childbirth eras. Dr. Abouleish's book was an unprecedented resource for women to better understand their options for labor and delivery analgesia. The book is composed of 20 easy-to-read chapters with illustrations that cover not only epidural block and general anesthesia but other labor and delivery analgesia techniques used at the time, including double catheter technique (epidural + caudal), pudendal nerve block, paracervical block, acupuncture, and hypnosis. His hope was that "every mother-to-be will better understand labor and be better prepared to make childbirth a truly joyous event." For those who knew him, the title of Dr. Abouleish's book was a fitting reflection of his demeanor and philosophy. He is remembered as a wise mentor who always provided a new perspective with humility and humor. Creative beyond the clinical realm, Dr. Abouleish was the long-time chair of the ASA Committee on Art and became a full-time artist (*left*) and Arabic calligrapher (*lower right*) in retirement. He found joy and beauty not only in anesthesia but in life itself. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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ANESTHESIOLOGY®

A Pharmacist-partnered Opioid-tapering Service before Total Hip or Knee Arthroplasty: Qualitative Analysis of Patient Counseling Sessions

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ABSTRACT

Background: Currently, no literature on patients' experiences with opioid tapering before elective surgery has been published. Recent evidence indicates that tapering opioids before total hip or knee arthroplasty improves postsurgical outcomes. This study qualitatively analyzed consultation sessions of patients receiving a pharmacist-partnered opioid-tapering service before total hip or knee replacement surgery to understand their experiences and attitudes.

Methods: A qualitative analysis of pharmacist counseling sessions within a randomized controlled trial was conducted. Participants were those recruited from seven hospitals between December 2021 and September 2022 who were assigned to the pharmacist-partnered opioid-tapering intervention arm of a randomized controlled trial. Consultations of participants with the pharmacist were audio-recorded and transcribed verbatim. Consultation data underwent inductive thematic analysis.

Results: Consultations were available for 20 participants, with a total of 48 audio-recorded consultations. Among these participants, four major themes including motivations to taper, knowledge and beliefs, psychosocial context, and attitudes toward tapering opioids were identified. Of the 20 participants, 70% tapered their opioids 50% or greater, with awareness of the surgery date appearing to be a key external motivating factor to taper opioids, regardless of the dose of opioids. Another notable theme was the motivation to improve fitness for participation in social activities, allowing participants to interact more with their kids and grandkids. Additionally, participant's psychosocial context revealed that factors such as stress affected their ability to taper. Pharmacists played a foundational role in shaping patients' attitudes and optimization of pain management strategies. Attitudes were identified as "optimistic," "hesitant," and "resistant," with patients displaying an optimistic attitude being more likely to taper.

Conclusions: Exploring the experiences of patients with osteoarthritis in a pharmacist-led opioid-tapering service before elective surgery revealed that external motivations, such as knowledge of a surgery date, play a crucial role in successful opioid tapering. Patients were more likely to taper if they knew their surgery date. Attitudes toward opioid tapering were identified as a modifiable factor. Tailoring tapering plans and patient education to individual patient contexts may enhance tapering outcomes.

(ANESTHESIOLOGY 2025; 143:680–90)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- There is growing recognition of the need for preoperative opioid tapering, with the potential for worse postoperative outcomes, opioid-induced hyperalgesia, and the burden of the opioid crisis as backdrop
- Understanding the diverse motivations for and relevant logistical barriers to successful support of preoperative opioid tapering would allow rational allocation of resources to this endeavor in various perioperative settings

What This Article Tells Us That Is New

- This secondary qualitative study analyzed 20 pharmacist-partnered, motivational interviewing–guided opioid-tapering consultations, which occurred *via* telehealth 3 months preoperatively in the course of a multisite randomized controlled trial
- Qualitative themes included knowledge of upcoming surgery and desire to be fit for functional and social activities as motivating factors and recognition of psychosocial stressors as important barriers to overcome for successful tapering
- A variety of initial attitudes were encountered (optimism, hesitancy, and resistance) among patients who ultimately successfully tapered (opioid dose reduced to 50% of the baseline daily opioid dose)

This article is featured in "This Month in ANESTHESIOLOGY," page A1. S.L. and J.P. are co–senior authors.

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Abbreviations: **oMEDD**, oral morphine equivalent daily dose; **OpioidHALT**, Responsible Opioid Use for Hip and knee ArthropLasTy; **THA**, total hip arthroplasty; **TKA**, total knee arthroplasty

Use of opioids outside of guidelines and prolonged use of opioids can lead to opioid dependence and various health problems, including respiratory depression and hyperalgesia.[1–4] Over the past decade, the availability of prescription analgesic opioids has increased significantly in countries such as the United States, the United Kingdom, and Australia.[5] Opioids remain a leading cause of drug overdose deaths in the United States,[6] with Australia[7] and the United Kingdom[8] witnessing a similar rising trend in opioid-related deaths over the last decade. In response to escalating opioid use, opioid-tapering guidelines in Australia[9] and the United States[10] have been developed to inform healthcare providers on how to safely and effectively taper opioids in patients with chronic noncancer pain.

Opioids are not recommended for pain related to osteoarthritis as opioids have a limited effect on chronic pain and a high rate of adverse effects.[11,12] Despite this, up to 54% of patients with severe osteoarthritis awaiting total knee arthroplasty (TKA) and total hip arthroplasty (THA) are on opioids.[13–15] This preoperative use of opioids is associated with worse postoperative pain, physical function, longer lengths of hospital stays,[16] and further harm after surgery.[13,16] Tapering opioids before TKA/THA may be beneficial as a retrospective study showed that reducing preoperative opioid doses of patients 50% or more improves postsurgical outcomes similar to opioid-naive patients.[17] Hence, addressing preoperative opioid use through tapering may have the potential to improve surgical outcomes and patient well-being.

Tapering opioids before surgery is complex, with limited literature available on the subject.[18] Known risk factors for incomplete tapering or relapse, such as depressive symptoms and pain intensity,[19–21] underscore the importance of understanding patient experiences to better inform tapering strategies. Although opioid-tapering guidelines exist, there is limited evidence identifying which patient populations benefit most from tapering before surgery.[22] Current guidelines emphasize the need for individualized approaches to tapering,[9] especially given the increased pain, medical complexities, and diverse patient experiences involved.

Qualitative research with chronic pain patients emphasizes the importance of tailored approaches to tapering,[23–28] and social and emotional factors of patients need to be identified for this purpose.[24,27] Patients have shared concerns over limited access to nonopioid alternatives for pain management during tapering,[29] and many value the presence of a trusted healthcare provider to assist with

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navigating the process.[23] None of these studies focus on surgical candidates, and the unique experiences of patients awaiting surgery need to be understood to tailor pain management strategies and navigate surgery-related stress. These insights reveal that centering the patient experience is essential to develop tapering strategies that are sensitive to individual needs and that can mitigate surgery-related stress. To address the gaps in knowledge of patients' tapering experiences before surgery, this study aims to explore the attitudes and experiences of patients with osteoarthritis in a pharmacist-partnered opioid-tapering service before total hip or knee replacement surgery.

Materials and Methods

Ethics approval was obtained from the South Western Local Health District Human Research Ethics Committee (approval No. 2021/ETH00343). Written informed consent was obtained from all participants before randomization in a broader trial assessing pharmacist-partnered opioid tapering.[30]

Design

The study employed a qualitative approach grounded in the epistemologic framework of constructivism. This choice stems from the assumption that an individual's meaning is subjective and constructed through interactions within their unique social and cultural circumstances.[31] Adopting this approach facilitated a comprehensive understanding of participants' attitudes and experiences with opioid tapering within the context of a pharmacist-partnered service. A qualitative analysis of pharmacist counseling sessions occurred within the Responsible Opioid Use for Hip and knee ArthropLasTy (OpioidHALT) randomized clinical pilot trial.[30] The OpioidHALT Trial was a pilot multicenter, parallel two-armed randomized controlled trial with an embedded observational arm, with full details of the trial published elsewhere.[30]

Participants and Setting

Participants were recruited from seven hospitals (four metropolitan and three regional hospitals) between December 2021 and September 2022 in New South Wales, Australia. Eligibility for this study included participants enrolled in the OpioidHALT trial[30] receiving the pharmacist-partnered opioid-tapering service and excluded control participants. Eligibility for participants in the OpioidHALT trial[30] included those undergoing THA or TKA for osteoarthritis who used opioid analgesics and had internet or telephone access. Participants were excluded if they were younger than 18 yr, were undergoing repeat surgeries (for example, the same procedure within 6 months), were already undergoing or had previously participated in an opioid-tapering study, or were currently attending a pain clinic or under the care of a pain specialist. Participants were also excluded if they were using opioids for oncology, palliative care, or substance use disorder; had other major psychiatric conditions (such as comorbid cognitive impairment or intellectual disability); had insufficient English; or had insufficient capacity to provide informed consent.

The intervention group of the OpioidHALT trial[30] involved one-on-one consultations with a pharmacist before surgery over telehealth to taper opioid doses to address known risks and improve postsurgical outcomes. The telehealth intervention commenced 3 months before planned surgeries and involved motivational interviewing with a focus on nonpharmacologic pain management strategies and opioid tapering. The participants' general practitioners were contacted before the opioid-tapering service to outline the intervention and address any concerns. Opioid tapering was done in partnership with the patient and pharmacist. No patient was forced to taper, and patients only tapered as much as they were willing. The target opioid dose reduction was 50% of the baseline daily opioid dose before the day of surgery. If patients wished to taper their opioid dose beyond the 50% reduction target, the pharmacist-partnered intervention continued, but this was voluntary. For the purpose of the trial, an opioid dose reduction of 50% or more was considered a successful opioid taper but only occurred in partnership with patients.[30] All opioid-tapering plans were reviewed and approved by a pain medicine specialist.

Data Collection Methods

Participants were contacted before tapering *via* telephone by a researcher (S.L.) to set up an initial consultation with C.T. and to collect baseline data including, but not limited to, current medications, opioid dose in oral morphine equivalent daily dose (oMEDD),[33] pain, and function. One-on-one consultations were conducted over the telephone or telehealth. Questions during consultations included participants' attitudes toward opioid medications and tapering their opioids, recovery goals after surgery, and nonopioid pain management strategies (see the appendix for the consultation topics and questions). The general structure of these sessions included exploring the patient's pain management expectations; eliciting the patient's motivations to taper their opioid dose; considering the patient's baseline opioid dependency and pain catastrophizing tendencies; agreeing on a target opioid dose and opioid-tapering rate; discussing ways to improve pain management with a focus on nonpharmacologic strategies and nonopioid analgesia as part of a multimodal approach; and scheduling a follow-up appointment.[30] Participants received follow-up appointments with the pharmacist to review their tapering progress, address any problems, and adjust their tapering plan if required. The frequency of follow-up appointments was

decided based on the participants' needs and availability but was aimed at a weekly basis.

Field notes were written during and after consultations, and tapering plans were completed and sent to the participant and their general practitioner. Consultations were recorded, transcribed verbatim by the research team, and entered into NVivo 14 (QSR International, USA) for coding and analysis.

Data Analysis

For thematic analysis, transcripts of participants were examined using inductive thematic analysis following the methodology proposed by Bernard and Ryan[32] to identify notable attributes of participants' tapering experiences, and attitudes toward tapering opioids. To understand participants' tapering experiences, two researchers (S.A.Y. and C.E.A.-J.) developed a codebook by independently coding five transcripts, comparing codes, and agreeing upon an initial code list. The process was then repeated for another three transcripts, applying agreed-upon codes and proposing new codes where necessary. This occurred iteratively until the coders no longer found information requiring a new code. To ensure methodical rigor, all transcripts were initially analyzed independently by two researchers (S.A.Y. and C.E.A.-J.). The pharmacist kept field notes throughout the recruitment and data collection process. A comprehensive record of decision-making and codebook development was done in NVivo 14 (QSR International) using time-stamped memos. Narrative participant case summaries were created that included information on psychosocial context, attitudes and motivations toward tapering and opioid use, and final taper outcomes. Any disagreement between the two researchers was communicated to the research team to reach a consensus.

Results

Summary of Parent Trial

The findings of the pilot study, in which this current study is nested, supported the feasibility of a pharmacist-partnered opioid-tapering service. Among patients in the intervention group, 27 of 30 successfully reduced their baseline daily opioid dose by 50% or more before surgery, compared with 5 of 30 in the usual care group ($P < 0.001$). The findings of this qualitative study will further explore patients' past experiences and biases related to opioid tapering, helping to tailor tapering approaches to individual patient circumstances.

Participant Characteristics

A total of 28 participants were recruited for consultations, with consultations of 21 participants recorded, because 7 participants elected to not have their consultations recorded (see fig. 1 for participant flow chart). One participant was lost to follow-up as they had already received their surgery, leading to an analysis of consultations of 20 participants. A total of 48 consultations occurred with follow-up consultations of nine participants. Consultations lasted an average (± SD) of 33 ± 16 min. Participants had an average age of 66 ± 8 yr.

Median (interquartile range [range]) opioid dose in oMEDD per day was 15 (8 to 43 mg [2 to 90 mg]) in patients allocated to the intervention group (more quantitative data can be found in the broader trial).[30] Of the 20 participants, 14 tapered their opioids 50% or greater, and three participants did not taper. The final doses for three participants were not included as they did not receive surgery before the study close-out. The consultation data for these three participants was still included in this study as it was still considered relevant to the study objectives and fit the eligibility criteria. Further details regarding participant sex, age, relationship status, employment status, geographic location, and duration of opioid therapy are outlined in table 1.

Thematic Analysis

The thematic analysis revealed four major themes that influenced participants' abilities to taper their opioid medications: (1) motivations to taper opioids, (2) knowledge and beliefs, (3) psychosocial context, and (4) attitudes toward tapering opioids. All quotes from the thematic analysis are available in table 2.

Motivations to Taper. Participants had varying motivations, but for many, a key driving factor to reduce their opioid dosage was receiving a surgery date. Other participants were motivated by the desire for a better quality of life, free from the undesirable side effects of opioids, enabling them to spend time with grandchildren and pursue their hobbies.

Participants were more motivated to taper if they had an exact date for their surgery: "*I just wanna get off that 10 mg [of opioid]. I've got 2 weeks before I go into the hospital*" (participant [P] 08, tapered 81%). This allowed for a taper plan to be more specific with a clear goal in mind. Other participants' surgeries were delayed due to COVID-19, which added more unease to the already difficult journey of tapering. Many participants expressed their desire to return to "normal" after their surgeries. These desires served as motivations to taper their opioids to reduce their recovery time and prevent postsurgical complications.

A majority of the participants had children and grandchildren and were motivated to be in a better physical and mental state for them. On the other hand, participants who lived alone or were distanced from family tended to rely more on returning to their hobbies. Adding to the desire for an improved quality of life, one participant expressed the effects that opioids had on her cognitive state: "*They used to call me Miss Thesaurus. . . . I'm not finding words so well*

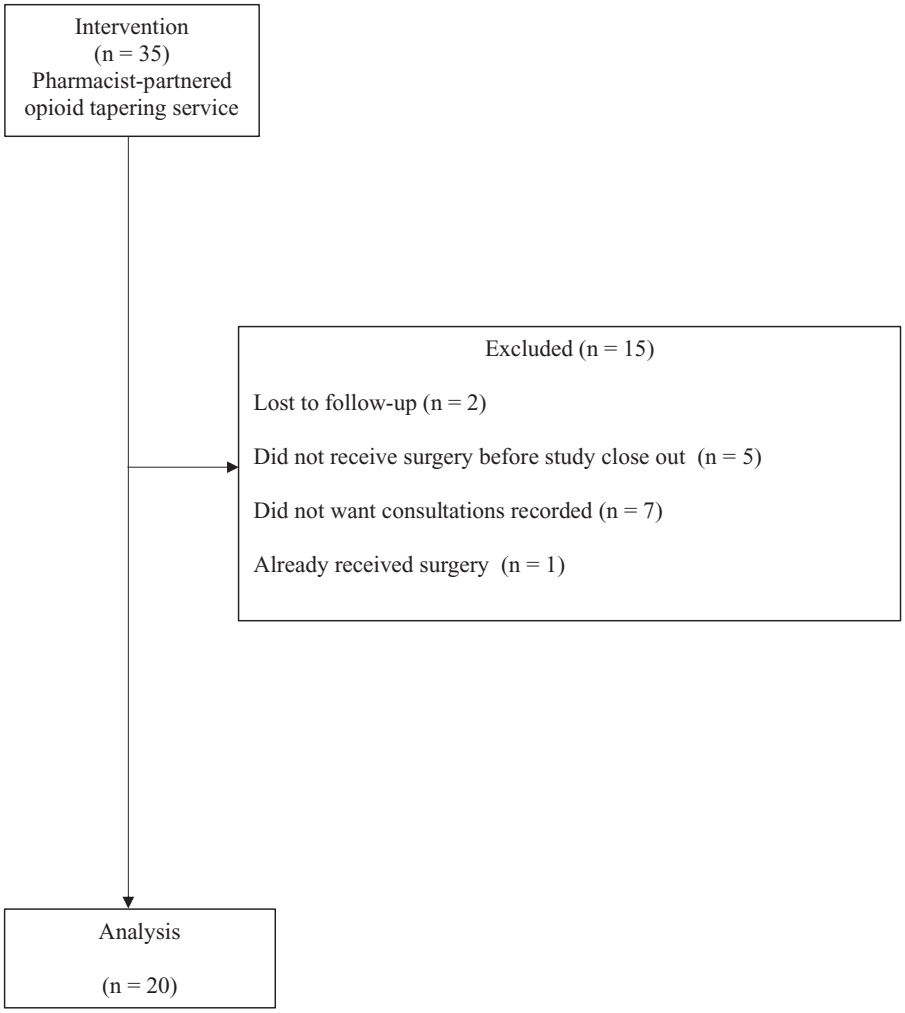


Fig. 1. Flow chart of included participants.

with the [opioids]" (P11, did not receive surgery before study completion).

Knowledge and Beliefs. In the context of pain management, knowledge included participants' understanding of opioid risks, benefits of tapering, nonopioid alternatives, and pain management optimization. Participants also came to consultations with their perspectives of pain and opioid use, as well as unique experiences. Their knowledge, or lack thereof, and beliefs influenced their ability to taper their opioids.

All participants were unaware of how to best approach the tapering process, meaning that the consultations with the pharmacist allowed for amendable tapering plans tailored to the participant to be constructed. Optimization of pain management was a priority for many participants during opioid tapering due to a lack of awareness of nonopioid pain management options, *"One of the reasons I haven't been really taking the [paracetamol] is because I'm not sure how much I'm allowed to have"* (P14, tapered 100%). Pharmacists were able to recognize these gaps in knowledge and work with the participants to optimize their nonopioid medication. One participant who required optimization of their pain medications had their own strategy for managing their pain: "*I take all those tablets [opioids and gabapentinoids] and then I have two glasses of wine because the medication says that alcohol will increase the effects and I think that's a very good idea*" (P18, did not receive surgery before study completion).

Participants' beliefs about opioids were primarily based on their general practitioner's advice: "*I just take what the doctor recommends*" (P12, did not taper), with one participant initially hesitant about receiving guidance from a pharmacist: "*You're [the pharmacist] not an actual medical doctor*" (P13, tapered 100%). Participants who had multiple consultations with the pharmacist were able to trial different strategies for pain management and keep a calendar documenting their activities and frequency of opioid medication.

Table 1. Participant Characteristics

Characteristics	Outcome (n = 20)
Sex, female	15 (75%)
Age, yr	66 ± 8
Employment status	
Working	4 (20%)
Not working	16 (80%)
Geographic location	
Metropolitan	14 (70%)
Regional	6 (30%)
Planned surgery	
Total hip arthroplasty	9 (45%)
Total knee arthroplasty	11 (55%)
Baseline opioid dosage, oMEDD	27 ± 25
Final opioid dosage before surgery, oMEDD	6 ± 12
Number of consultations	2 ± 1

The values are expressed as the number of patients (%) or mean ± SD.
oMEDD, oral morphine milligram equivalent.

Psychosocial Context. All participants identified psychosocial factors that had an impact on their ability to taper their opioids, including social support, life events, stress levels, and coping strategies. Some participants had the support of family members who could help them with physical goals during the tapering process as they experienced heightened pain and, in turn, increased stress. This included weight loss goals and increased mobility for a majority of the participants: "*My daughter is a personal trainer. She motivates me [to exercise] and tries to make me prepare my meals*" (P16, tapered 100%). Other participants had more challenging relationships with family members, with one participant who had to hide her opioids from her husband as he was previously addicted to them: "*All of the medications have been put away in my room so I can keep an eye on him*" (P10, tapered 100%). Both positive and negative experiences with family members influenced the participants to want to taper their opioids.

Some participants' taper outcomes were affected by their life circumstances, whereas other participants adopted a more positive mindset because of these circumstances: *"I tried to commit suicide a few years ago, I took a whole packet of Endone. . . . I've been to a lot of counseling, psychologists. So I can only have 20 [opioid tablets] in my house at one time"* (P07, tapered 100%).

Attitudes. Three distinct attitudes toward tapering opioids were identified in this sample of participants: optimistic, hesitant, and resistant. These attitudes were identified based on their initial consultations, but for some participants, these attitudes changed over time under the guidance of the pharmacist.

Optimistic

"I want to get off [my opioids]. If I can live without them, I'll just go straight off" (P03, tapered 89%).

Twelve participants were identified to have an "optimistic" attitude toward opioid tapering in their initial consultations. Eleven of the twelve participants kept this attitude and tapered their opioids, with only one participant who changed to a "resistant" attitude and finished on the same dose they started on (oMEDD). Eight participants tapered their opioids completely before their surgeries. The average initial dose (oMEDD) of optimistic participants was 29 ± 27 mg. The average final dose presurgery (oMEDD) was 7 ± 14 mg.

Participants in this category emphasized discomfort toward taking opioid medications but were also intent on tapering their opioid medications. The eight participants who tapered their opioids completely before surgery in this category shared similar support networks and motivations for tapering. Participants who knew their surgery dates utilized a diary to document opioid doses and other pain-management strategies up to the date of their surgery, as suggested by the pharmacist leading the opioid-tapering service. The three participants who tapered their opioids, but not 100%, had varying life circumstances that influenced their ability to taper. These circumstances included full-time work, caring for family members, long-term opioid use, and surgery date delays.

The one participant who changed from an optimistic to a resistant attitude initially reduced their dose; however, in the third consultation, returned to their original dose due to unbearable pain. This participant expressed that they would not be willing to try tapering again until they knew their surgery date. This participant went into surgery on the same dose that they had measured at baseline in this study.

Hesitant

"I don't want to be on [opioids], but if you take it away, I'm scared" (P07, tapered 100%).

Five participants were identified to have a "hesitant" attitude toward opioid tapering in their initial consultations. Two of these participants shifted to an optimistic attitude and tapered their opioids, with one tapering completely before surgery. Three participants remained hesitant throughout consultations. Two of these participants did not receive surgery before the study finished, and one participant was referred to their general practitioner to manage their medications and situation. The average initial opioid dose (oMEDD) was 33 ± 25 mg. The average final opioid dose (oMEDD) of the two remaining participants was 3 ± 3 mg.

Participants in this category expressed concerns about both using their opioids and reducing them. The transition from a hesitant attitude to an optimistic attitude for two participants was facilitated by education from the pharmacist on pain management and opioids, coupled with motivational interviewing. Significant changes for these participants included meticulous documenting of their

Table 2. Quotes from Thematic Analysis

Theme	Quotes
Motivations to taper	"*I just wanna get off that 10 mg [of opioid]. I've got 2 weeks before I go into the hospital.*" (P08, tapered 81%)
	"*They used to call me Miss Thesaurus. . . . I'm not finding words so well with the [opioids].*" (P11, did not receive surgery before study completion)
	"I've still been concerned. Obviously that's why I've been reducing [my opioids] as much as I can." (P11, did not receive surgery before study completion)
	"Well, my doctor's already decreased the dose [of my opioids]. It was on a stronger dose, so he's already decreased that." (P15, tapered 100%)
	"Before I go into surgery, it's six weeks, so. . . . I'd like to be off [my opioids] as low as I can by the time the surgery comes." (P10, tapered 100%)
Knowledge and beliefs	*"One of the reasons I haven't been really taking the [paracetamol] is because I'm not sure how much I'm allowed to have."* (P14, tapered 100%)
	"*I take all those tablets [opioids and gabapentinoids] and then I have two glasses of wine because the medication says that alcohol will increase the effects and I think that's a very good idea.*" (P18, did not receive surgery before study completion)
	"*I just take what the doctor recommends.*" (P12, did not taper)
	"*You're [the pharmacist] not an actual medical doctor.*" (P13, tapered 100%)
	"I'm not worried about the long-term effects [of opioids] because how long have I got?" (P12, did not taper)
	"[My pain] is going to get worse, and it doesn't matter what I do. I eat healthy, I don't drink, I don't smoke. What am I supposed to do [to manage my pain]?" (P09, did not receive surgery before study completion)
Psychosocial context	"*My daughter is a personal trainer. She motivates me [to exercise] and tries to make me prepare my meals.*" (P16, tapered 100%)
	"*I'm trying really hard to not have [my opioids], like distract myself, anything to not have it.*" (P07, tapered 100%)
	"*All of the medications have been put away in my room so I can keep an eye on him.*" (P10, tapered 100%)
	"I just had a bad weekend. . . . but because I've had the depression for so long, I know I've got to dig myself out of it. I use all my techniques that I know." (P10, tapered 100%)
	"I've got my daughter's support as well. she will help me a lot [with movement]." (P16, tapered 100%)
	"I tried to commit suicide a few years ago, I took a whole packet of Endone. . . . I've been to a lot of counseling, psychologists. So I can only have 20 [opioid tablets] in my house at one time." (P07, tapered 100%)
Attitudes toward tapering opioids	*"I want to get off [my opioids]. If I can live without them, I'll just go straight off."* (P03, tapered 89%)
	"I don't want to be on [opioids], but if you take it away, I'm scared." (P07, tapered 100%)
	"*I don't want to reduce [my opioids].*" (P05, did not taper)

P, participant.

tapering journeys and optimized pain management strategies, such as using paracetamol alongside reduced opioid doses.

Participants who remained hesitant throughout the opioid-tapering service experienced barriers to tapering such as financial difficulties, managing multiple medical conditions, and insufficient pain relief. Although the pharmacist could provide some guidance with nonopioid alternatives for pain management, all these participants required further guidance from their general practitioners, as well as financial aid, in the context of their life circumstances, which delayed the start of their tapering journey. This led to two of the participants not receiving surgery before the study finished.

Resistant

"I don't want to reduce [my opioids]" (P05, did not taper).

Three participants were identified to have a resistant attitude toward opioid tapering in their initial consultations. Two of these participants did not taper their opioids and remained resistant, whereas one participant shifted to an optimistic attitude and completely tapered their opioids before their surgery. The average initial opioid dose (oMEDD) was 10 ± 7 mg. The average final opioid dose (oMEDD) was 3.67 ± 3.3 mg.

Participants with a resistant attitude displayed a clear lack of intent to decrease their opioid dosage. Among these resistant participants, two participants faced the formidable challenge of dealing with multiple health conditions, including bursitis and kidney and liver issues, which rendered tapering their opioid intake unfeasible due to their high levels of pain. One participant staunchly resisted tapering, attributing it to their "old age" and expressing a desire to lead a pain-free life without concerns about opioid usage.

One participant with a resistant attitude embodied an optimistic attitude after their initial consultation. Toward the end of the initial consultation, the pharmacist was able to identify the upcoming surgery as a motivating factor, and the participant responded positively. After this consultation, the participant reduced their opioids by 100%.

Discussion

Thematic analysis revealed four central themes that emerged from the patients' narratives including motivations to taper, knowledge and beliefs, psychosocial context, and attitudes toward tapering opioids before hip and knee replacement surgery. Through this analysis, valuable insights into patients' pain journeys and their attitudes toward opioid tapering were gained, which were categorized into three distinct attitudes (optimistic, hesitant, and resistant).

This study showed that there was an interplay between attitudes and motivations to opioid tapering that was heavily facilitated by patients having a surgery date. The study's findings revealed a dynamic relationship, as patients with

an optimistic attitude demonstrated strong motivations to taper opioids, leading to successful reductions before planned surgeries. The key motivating factor was awareness of the surgery date, irrespective of the initial opioid dose. A systematic review of 10 opioid reduction studies revealed that three studies showed significant differences in opioid reductions.[34] The three studies that had a statistically significant difference identified unique motivating factors to taper opioids, such as mindfulness-oriented recovery and consultations from an integrated pain team. These findings highlight the impact that behavioral changes have on opioid tapering. A separate investigation in a study exploring attitudes toward tapering, conducted through a survey on hypothetical tapering scenarios, emphasized the importance of having a plan for tapering as a key motivator for dose reduction.[35] Together, these findings underscore the role that surgery awareness plays in influencing patients' attitudes and motivations toward opioid tapering.

This study also showed that involving a pharmacist in the opioid-tapering process optimized patients' pain management plans. Patients with a hesitant attitude required clearly defined pain management strategies before considering tapering, among the stress of their life circumstances. To address their varying experiences and tapering challenges that arose, the pharmacist offered psychosocial support. Patients' attitudes were positively influenced by this support, which included motivational interviewing, responding to concerns about tapering opioids, and providing nonopioid pain management options tailored to their needs. This support led to increased patient confidence, optimism, and tapering effectiveness. Such support was especially relevant in the optimistic and hesitant groups, in which the starting opioid doses were the highest and the patients were identified to be the most open to change. In the resistant group, the starting opioid doses were low, giving patients little reason or motivation to taper their doses. These findings align with current research emphasizing that tapering outcomes are influenced by patients' personal feelings about experiences during a taper, such as how engaged they are by the healthcare provider to willingly make a change to their dose.[25] The one-on-one consultations in the current study allowed for transparency about experiences with the tapering process to be shared and were responded to with personalized strategies. Similar success was shown in an existing pharmacist-partnered opioid-tapering service for patients with chronic pain[36] and a further qualitative study[28] from the service discussed patients' appreciation of an individualized approach to care with access to pharmacist expertise. Incorporating a pharmacist into the opioid-tapering process allows for the personalization of patients' experiences, ultimately enhancing the success of opioid-tapering outcomes.

Implications for Future Research and Clinical Practice

The findings of this study highlight that upcoming surgeries serve as a significant external motivator for the successful tapering of patients' opioid medications. Strategies for tapering and optimizing medication management should be directed toward understanding and leveraging this connection between patients' motivations and opioid-tapering outcomes. Future research should prioritize determining whether pharmacist-partnered opioid tapering before surgery leads to improved surgical outcomes. Furthermore, longitudinal qualitative studies are imperative to capture the fluctuations in the opioid-tapering process. Such research can provide a more accurate and nuanced depiction of patients' experiences and attitudes throughout their journey to improve long-term outcomes. This understanding gains heightened importance as the global scope of community pharmacist roles expands.[37–39] Future research should also consider vulnerable cohorts, including patients with serious pain and opioid use disorders, to better understand effective tapering strategies within a broader range of clinical scenarios. Recognizing the evolving nature of opioid tapering enables healthcare providers to better tailor their support, meeting the changing needs of patients over time and enhancing the overall quality of care and pain management outcomes.

Limitations

The findings of this study should be interpreted in the context of several limitations. The unprecedented changes and stress during the COVID-19 restrictions during the trial led to delayed surgeries, and these changes may not persist to the same level in the future. The broader trial within which this study was conducted excluded patients with substance use disorder, pain related to oncology and palliative care, patients under the care of a pain specialist, and patients who did not speak English. Tapering opioids in patients with substance use disorder has been associated with high rates of suicidal ideation.[40] Patients with substance use disorder or under specialist pain care often face unique risks that may require even more tailored opioid tapering approaches, and thus, the study's findings may not extend to these populations or extended groups. Participation in this study was voluntary, which may have led to participation bias. There is also the consideration of social desirability bias, as participants may have withheld information regarding their experience with the use of opioids due to the fear of judgment.

Conclusions

Qualitative analysis of consultations of patients with osteoarthritis in a pharmacist-partnered opioid-tapering service before elective surgery revealed that external motivations, such as knowledge of a surgery date, play a crucial role in successful opioid tapering. Attitudes toward opioid tapering were a modifiable factor, and patients with an optimistic attitude were more likely to taper. There remains a need to consider patients' unique psychosocial contexts and life circumstances to tailor effective opioid-tapering plans.

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Competing Interests

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Appendix: Semistructured Consultation Guide

Semistructured consultation guide:

Medication use:

- How do you feel about using opioid medications long-term?
- What are your current medications? How long have you been using them?
- Brief about benefits of tapering before surgery: Emphasis on shared decision-making, general practitioner is aware of this plan
- Other pain management; *e.g.*, nonpharmacologic, exercises (physio)

Goals:

- What are your goals after surgery?

Lifestyle:

- What is your diet like?
- How often do you exercise or walk?
- Mental health: Do they meditate? Assess coping strategies

ANESTHESIOLOGY®

The History of Ultrasound-guided Regional Anesthesia

Peter Marhofer, M.D., Stephan Kapral, M.D.

ANESTHESIOLOGY 2025; 143:691–7

Ultrasound-guided Supraclavicular Approach for Regional Anesthesia of the Brachial Plexus. By Kapral S, Krafft P, Eibenberger K, Fitzgerald R, Gosch M, and Weinstabl C. Anesth Analg 1994; 78:507–13.

Abstract: As science keeps evolving, there is a time for revolutionary change. The Classic Paper here revisited, published in *Anesthesia & Analgesia* in 1994, was the first report to describe an ultrasound-guided technique for regional anesthesia. Its publication met with a response of skepticism, given the inherent claim that here was a novel approach capable of supporting, or indeed replacing, other techniques that had been used for well more than a century. This article recounts both the early history of ultrasound guidance and how this Classic Paper started a paradigm shift in regional anesthesia. Today, ultrasound-guided techniques are being used around the world as the result of 3 decades of devoted research and education. Numerous collaborations have been part of this journey, and the authors look back on years replete with personal memories and some of the more relevant moments.

(ANESTHESIOLOGY 2025; 143:691–7)

We feel privileged by this opportunity to recount the scientific and clinical evolution of ultrasound-guided regional anesthesia from its beginnings. The initial idea came from the Classic Paper at the core of this article, published back in 1994, on the use of two-dimensional ultrasound for supraclavicular brachial plexus blockade.[1]



Fig. 1. Peter Marhofer, M.D., is Professor of Anesthesiology and Intensive Care Medicine at the Medical University of Vienna, Vienna, Austria. He heads the pediatric anesthesia unit of his department and leads a research team in regional and pediatric anesthesia. Peter is an honorary member of the Austrian Society of Anesthesiology, Reanimation and Intensive Care Medicine (Vienna, Austria), as well as the European Society of Regional Anaesthesia (Geneva, Switzerland). In 2010, he was awarded the Bruce Scott Medal by the United Kingdom Regional Anaesthesia Society (London, United Kingdom). In 2025, he received the Austrian Cross of Honor for Science and Art.

Nobody could have foreseen the developments that would follow.

The first attempts at regional blocks under direct ultrasound guidance continued a long tradition of regional anesthesia in Vienna, Austria. Karl Koller is widely credited with pioneering regional anesthesia; his 1884 reports on cocaine use for local anesthesia resulted in five nominations for the Nobel Prize in Medicine.[2–6]

Fast-forward to the summer of 1996, when a young resident, Peter Marhofer, M.D. (fig. 1), and a young consultant in anesthesia and intensive care, Stephan Kapral, M.D. (fig. 2), met up during a night call. By that time, Stephan had published two studies on the use of ultrasound to visualize nerve structures during regional anesthetic blocks, one being the Classic Paper revisited here.[1,7] Only two preexisting studies, spread over the previous 2 decades, were then available on ultrasound imaging in regional anesthesia: the first by la Grange *et al.*[8] for perineural blood flow during supraclavicular brachial plexus blockade, and the second by Ting and Sivagnanaratnam[9] for visualizing deposits of local anesthetic after brachial plexus blockade.

Stephan envisioned the possibility of harnessing ultrasound for regional anesthesia beyond visualizing local anesthetics and vessels. From the very beginning of his career, he had harbored a deep interest in ultrasound. Luckily, this interest coincided with a research focus within our department on the use of transesophageal echocardiography

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Fig. 2. Stephan Kapral, M.D., is Professor of Anesthesiology and Intensive Care Medicine. He worked at the Medical University of Vienna (Vienna, Austria), mostly in the Department of Trauma Surgery, from 1989 to 2009. From 2009 until his retirement in 2024, he headed the Institute of Anesthesia and Intensive Care Medicine at Trauma Hospital Linz (Linz, Austria). From 2007 to 2009, he was Chairman of the Austrian Society of Anesthesiology, Reanimation and Intensive Care Medicine. Stephan received the B. Braun Award and the Karl Koller Award from the European Society of Regional Anaesthesia (Geneva, Switzerland) in 2007 and 2013, respectively.

(TEE) for hemodynamic monitoring during liver transplantation at a time when clinicians' understanding of TEE was rudimentary. Against this background, Stephan had, in 1992, attended a specialized ultrasonography course at the Austrian Conference Center of Bad Gastein.

The Classic Paper

One evening, relaxing by the pool of the congress hotel with his child asleep, Stephan was lost in thought revisiting the content of the course. Just a few weeks before, the interim chairman of our department had suggested placing a stronger focus on regional anesthesia. A clinical and a research strand were to be pursued. As Stephan was connecting these pieces in his mind, the topics of ultrasound and regional anesthesia converged.

Upon returning to Vienna, he lost no time exploring the possibility of visualizing nerves using the linear probe of a large ultrasound machine (HP Sonos 1500, Hewlett Packard, USA). He discovered that structures were indeed traceable as he maneuvered the ultrasound probe. He also realized that this visibility was discontinuous; it was necessary to adjust the angle of the ultrasound beam in relation to the peripheral nerves on a case-by-case basis. What today is referred to as "anisotropy" in ultrasound imaging was an unknown concept at the time.

The Classic Paper highlighted here[1] was Stephan's first report on ultrasonography for regional anesthesia. The study, which compared supraclavicular and axillary approaches to the brachial plexus under ultrasound guidance, was remarkable because there had been no previous ultrasound-based description of the anatomy of the brachial plexus. Before starting the study, fundamental anatomical principles needed to be clarified. This was accomplished using ultrasonography as "dry practice" on family members and colleagues.

Practitioners of regional anesthesia tended to oversimplify the anatomy. A primary misunderstanding was the assumption that nerve plexuses are enveloped by fascial sheaths. The Classic Paper described the needle penetration of "axillary and supraclavicular plexus sheaths." Today, we know that the brachial plexus in the supraclavicular region is covered by the prevertebral fascia,[10] and the description by Winnie *et al.* of a "brachial plexus sheath"[11] was never confirmed. Similarly, for the axillary approach, the neurovascular structures are located below the deep axillary fascia, which separates the deep axillary space from the subfascial axillary space.[10] Although Stephan could identify the major anatomical structures *via* ultrasound, a precise classification of all anatomic details was not possible at the time.

Failure to block the musculocutaneous nerve in 25% of patients may serve as one example of the difficulties in connecting earlier descriptions of anatomy with what was being described with ultrasound imaging. Lying between the short head of the biceps and the coracobrachial muscles, the musculocutaneous nerve is separated from other nerve structures in the axillary region, and separate needle tip insertion was felt to be necessary for successful blockade. Nonetheless, successful blockade was observed in most cases, made possible with the ultrasound resolution available at the time and the visualization of both the cannula tip and the spread of local anesthetic. At the same time, ultrasound allowed adjacent anatomical structures (*i.e.*, vessels, cervical pleura) to be detected, minimizing the risk of complications.

Dynamic observation of the effect of upper-arm abduction on the relationship between vessels and bones could also be detected. The neurovascular bundle in the axillary region was compressed when the arm was abducted more than 90°. Subsequently, blocks were performed only with an upper arm abduction less than 90° to avoid this compression. To perform the axillary and supraclavicular blocks, Stephan placed the cannula with the short axis facing the ultrasound probe. In this way, the needle tip could be seen,

and subepineural puncture (carrying a risk of nerve injury) could be avoided. This needle guidance technique came to be known as the "out-of-plane" technique. Contrary to the study of Ting and Sivagnanaratnam,[9] he observed the spread of local anesthetic in a dynamic manner, allowing the needle to be replaced in cases of maldistribution.

The 30-ml volume of local anesthetic that was used for both approaches might be considered large from today's perspective. During that time, axillary plexus blocks were described with volumes of 60 ml,[12] and this Classic Paper initiated a movement to reduce the volumes of local anesthetic injected. All the fundamentals of ultrasound-guided regional anesthesia were described in this Classic Paper[1]—notably, direct visualization of anatomical structures, dynamic anatomical relations, visualization of the needle tip, and the spread of local anesthetic. However, since no comparison with a nerve stimulator-guided technique was performed, no conclusions could be drawn regarding differences in onset and duration of block times, and no definitive conclusions could be drawn regarding the risk of pneumothorax *via* the ultrasonographic approach to the supraclavicular brachial plexus. All these questions would be challenges for the ensuing decades.

The Beginnings of Ultrasound-guided Regional Anesthesia

During that night call when Stephan and Peter first met in the summer of 1996, Stephan shared several ideas for subsequent clinical studies with his residents. One suggestion was for Peter to investigate the use of ultrasound for three-in-one blocks[13] of the femoral, lateral cutaneous, and obturator (this has since been challenged[14]) nerves by injecting local anesthetic lateral to the femoral artery.

Peter was still early in his career as a clinician and researcher in 1996. He was fascinated by the idea of imaging a nerve and watching the spread of local anesthetic in real time or the movement of a needle from the skin to a target structure. After a year of hard work, preliminary results could first be analyzed, revealing better onset times and block durations than with the traditional accepted standard of identifying nerves by electrical stimulation. This was his first collaboration with Stephan.[15] This success encouraged an immediate follow-up study, demonstrating reduced amounts of local anesthetic with ultrasound guidance.[16]

Medical ultrasound, too, has a history of pioneering work in Vienna, Austria.[17–19] The first and foremost challenge lay in the development of usable equipment. Early units that lived up to clinical standards notably came from a small Austrian manufacturer that had introduced the first ophthalmologic scanner in 1954 (Kretztechnik AG). Forty years of technological evolution later, our first attempts to visualize nerves involved Hewlett Packard's Sonos 1000 and Sonos 1500, as well as Toshiba's (Tokyo, Japan) SAL 38B—ultrasound units with linear probes offering maximum frequencies of 5 to 7.5 MHz. This state of technology was adequate to visualize major (*e.g.*, femoral, sciatic, or forearm) nerves and vessels, and adjacent bone and pleural structures. Yet the images were low-resolution and had to be printed to paper. These printouts then had to be optically scanned for journal publications. Each of these steps detracted from a quality that was mediocre to begin with. In addition, these ultrasound systems were bulky, slow to start up, and very expensive.

Since that time, image quality has improved by leaps and bounds (fig. 3). Medical ultrasound images today are stored digitally using the Digital Imaging and Communications in Medicine (DICOM) format, which offers a depth of at least 16 bits with more than 30,000 shades per pixel. By contrast, the analog images at our disposal until the turn of the millennium offered 4 bits with 16 shades per pixel.

Despite these limitations, we began to teach ultrasound guidance for selected applications of regional anesthesia. In 1994, one of the first workshops in regional anesthesia

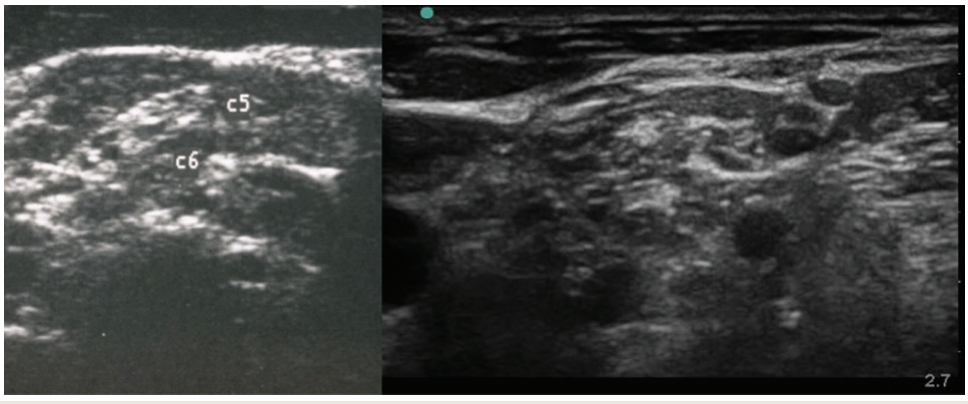


Fig. 3. Ultrasound images of the infraclavicular region. The example on the *left* illustrates what was state of the art in 1994. Native resolution was low, and the process of printing an analog image to paper, requiring an optical scan of the printout for publication, was also suboptimal. The image on the *right* was obtained by digital ultrasound 15 yr later.

worldwide was initiated in Innsbruck, Austria. Centering on hands-on cadaver dissections, these workshops were grounded in anatomy and, by around the year 2000, were well attended. Most of the talking and teaching was done by opinion leaders from German-speaking areas.

It was therefore a great honor for two young anesthesiologists (*i.e.*, Stephan and Peter) to be invited as tutors. To convey the state of the art in ultrasound-guided techniques, we formed an effective "ultrasound team" together with a young anatomy demonstrator who also collaborated with Stephan on studies of ultrasound guidance for lumbar plexus[20–22] and lumbar facet nerve[23,24] blockade. The latter paper is noteworthy as the first clinical report on needle guidance using the long axis of the ultrasound beam, which, more recently, came to be known as the "in-plane"—as opposed to the "out-of-plane"—technique.[24]

In 2002, we were invited to speak at a dedicated workshop on ultrasound-guided regional anesthesia in Schwetzingen, Germany. Yutaka Sato, M.D. (Junjindo Yuza Hospital, Yuza, Japan), was introduced to Stephan during dinner at the congress. Professor Sato bowed deeply, expressing his delight at meeting "the founder of ultrasound-guided regional anesthesia." This scene demonstrated what the new approach really meant to the evolution of anesthesia worldwide.

Around the same time, Michele Curatalo, M.D. (University Hospital of Bern, Bern, Switzerland), reached out to us for a research collaboration that gave rise to volunteer studies on ultrasound-guided blockade of the third occipital nerve[25] and on volume reduction.[26] We were able to pursue this avenue of volunteer studies further by initiating a fruitful collaboration with the Department of Clinical Pharmacology at our own center in Vienna.

In 2002, having begun to focus on pediatric anesthesia, Peter made a trip to present an abstract at the Pediatric Anesthesia Conference in Cape Town, South Africa. During a visit to a national park north of the city, he started pondering possibilities for a longer stay in this country. The organizer of the congress was anesthesiologist Adrian Bosenberg, M.D. (Red Cross Children's Hospital, Cape Town, South Africa). Adrian was both an impressive personality and an acknowledged pioneer of neuraxial pediatric regional anesthesia, and he expressed a keen interest in ultrasound guidance.

A plan emerged: Vienna would provide an ultrasound unit for clinical studies to be performed in Cape Town. Given the footprint of the machines we were using, this was easier said than done. Destiny again intervened. During a Vienna night call for trauma surgery, Stephan performed an ultrasound-guided paravertebral block to treat severe pain in a patient with fractured ribs. The grateful patient, a prominent executive, took an interest in our work and agreed to lease one of the latest-generation ultrasound machines that had recently become commercially available (SonoSite 180; SonoSite, Bothell, USA). This machine featured a linear probe capable of relatively high resolution and was the first portable unit of its kind.

With suitable technical equipment in hand, we were able to proceed with the scientific and administrative organization of the collaboration. In 2004, a young fellow moved from Vienna to Cape Town for a 9-month stay, and the stage was set for us to redefine most regional anesthetic techniques in children.[27–31]

Funding for this South African project was made available from the registration fees of ultrasound workshops in Austria. These events became popular, with one of the venues being the Austrian ski resort of Zuers. This is where, in 2017, all relevant contributors convened for the Zuers Ultrasound Experts Regional Anesthesia Statement (ZUERS) conference to reach consensus on important topics such as a nomenclature for needle-guidance techniques, cannula positions relative to nerve structures, and other technical considerations.[32] Details are provided in Supplemental Digital Content 1 (https://links.lww.com/ALN/D994).

The greatest challenge to improving the practice of ultrasound-guided regional anesthesia has been to disseminate the requisite knowledge as effectively as possible. Even the greatest science can be futile if appropriate teaching and training strategies are absent! Thankfully, major societies such as the American Society of Regional Anesthesia and Pain Medicine (Pittsburgh, Pennsylvania, US), European Society of Regional Anaesthesia (Geneva, Switzerland), New York Society of Regional Anesthesia (New York, New York), New York State Society of Anesthesiologists (New York, New York), and European Society of Anaesthesiology and Intensive Care (Brussels, Belgium) responded, organizing specialized workshops during their annual meetings by the mid-2000s.

A special milestone was our encounter with Per-Arne Lönnqvist, M.D., D.E.A.A., F.R.C.A., Ph.D., from the Karolinska Institute (Stockholm, Sweden). In 2004, this figurehead of pediatric regional anesthesia suggested a review article on current knowledge in ultrasound-guided regional anesthesia for the *British Journal of Anaesthesia*, where he served as an editor. The editor-in-chief at the time was Jennifer Hunter, M.B.E., M.B.Ch.B., Ph.D., F.R.C.A., F.C.A.R.C.S.I. (Hon.) (University of Liverpool, Liverpool, United Kingdom), who agreed to this proposal, leading to our first review article on the subject.[33] An editorial accompanying the publication pointed out three keys to successful regional anesthesia (*i.e.*, location, location, location) and, equally to the point, that regional anesthesia always works—"provided you put the right dose of the right drug in the right place."[34] Our 2005 review article remains one of the *British Journal of Anaesthesia*'s most cited articles (more than 550 citations currently).

Two years after this publication, one of the *British Journal of Anaesthesia*'s editors posed the question whether ultrasound guidance had already become a "gold standard" in regional anesthesia.[35] He predicted that growing public awareness would give rise to more patients asking

for ultrasound-guided blocks. He also put forward useful areas for research such as defining minimum doses of local anesthetic for effective blocks or applications of three-dimensional ultrasound. These topics have since been addressed by our study group.[36–38]

In 2007, collaboration with the University of Toronto (Toronto, Canada) gave rise to a review article in *Anesthesia & Analgesia*.[39] This follow-up publication to the successful *British Journal of Anaesthesia* review from 2005[33] came with an accompanying editorial by Terese Horlocker, M.D., and Denise Wedel, M.D. (Mayo Clinic College of Medicine, Rochester, Minnesota), opinion leaders in North America at the time.[40] They characterized the journey of ultrasound guidance as searching for the "holy grail" of regional anesthesia: to provide "neural blockade with rapid onset, long duration, certain success, and without complications."

Our successes would be inconceivable without the extensive anatomical studies that formed the backbone of all our reports on ultrasound guidance for specific regional blocks. This strong focus on anatomy led us to join forces with clinical anatomists in Austria who contributed significantly to knowledge in regional anesthesia and have supported our research activities.[10,41]

Ultrasound-guided regional anesthesia has been advanced by the progress we have seen in medical ultrasound technology over the years (fig. 3). The journey continues as new approaches to ultrasound-guided regional anesthesia appear on the horizon, including the recent introduction of "virtual" or "augmented" reality.[42]

Concluding Remarks

Writing this article has been guided by our desire to express appreciation for all of the undertakings that have advanced an important subspecialty of anesthesia to the next level. Today's state of the art is the sum of many contributions, and we extend our apologies to colleagues around the globe whose names we have failed to mention.

As science evolves, there is a time when all of the elements for revolutionary change come together. In regional anesthesia, a paradigm shift was ignited when Stephan and Peter chose to focus on ultrasound. In doing so, they took a radically different approach, and they have never ceased their research efforts, clinical work, and advocacy for ultrasound in the clinical practice of regional anesthesia.

What made ultrasound guidance novel was its departure from nerve stimulation, shifting the focus of attention from the position of the needle tip to the distribution of local anesthetic. Of course, the latter depends on the former, and visualizing the needle is still important to avoid complications. However, dwelling on these arguments would be missing the real point that regional anesthesia is not a function of the needle tip but of the local anesthetic!

Our journey in ultrasound-guided regional anesthesia, which began with the Classic Paper discussed in this article, has taken us to a point at which intra- and postoperative analgesia can be provided with excellent results across a wide range of surgical scenarios. There is still room for improvement in situations that require extended periods of postoperative analgesia. A broader perspective needs to be taken beyond the anatomical technicalities of nerve blockade by a new generation of clinicians and researchers.

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Supplemental Digital Content

Summary of the Zuers Ultrasound Experts Regional Anesthesia Statement (ZUERS), https://links.lww.com/ALN/D994

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Anesthesia Management of a Patient with a Giant Dilated Pulmonary Artery

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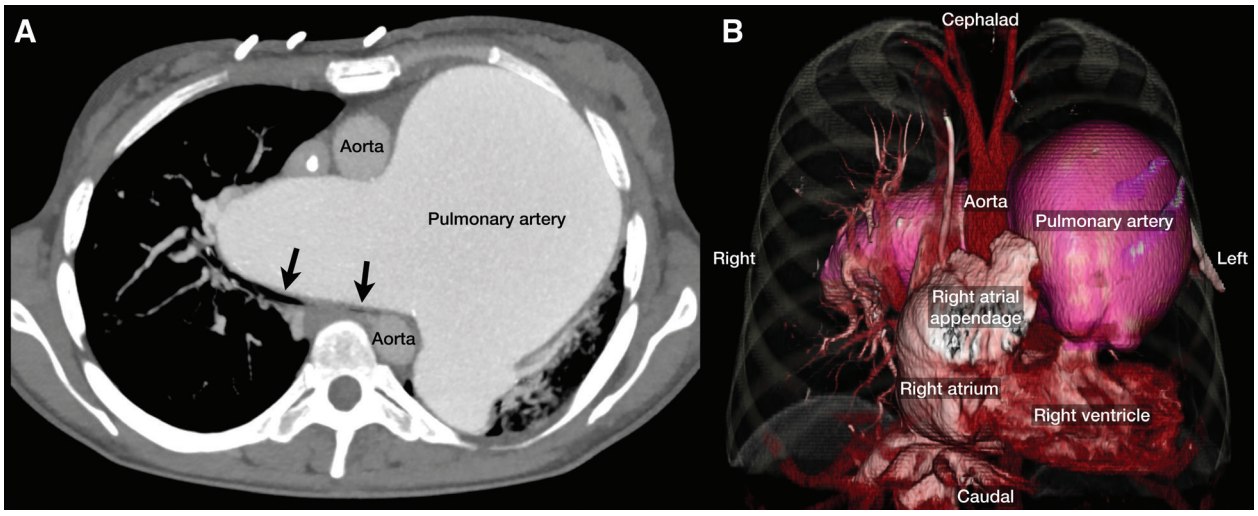


Fig. 1. Axial (*A*) and three-dimensional (*B*) chest computed tomography images showing a giant pulmonary artery compressing both main bronchi (*arrows*).

Figure 1 shows preoperative axial (A) and three-dimensional reconstructed (B) chest computed tomography images of a 41-yr-old female patient scheduled for bilateral lung transplantation due to idiopathic pulmonary arterial hypertension. A massively dilated pulmonary artery, measuring 144 × 184 mm, compresses both main bronchi (arrows), causing severe dyspnea. Preoperative transthoracic echocardiography (Supplemental Digital Content Video 1, https://links.lww.com/ALN/E54) demonstrated the enlarged pulmonary artery adjacent to the left main coronary artery without evidence of coronary compression or left ventricular wall motion abnormalities.

General anesthesia was induced after first establishing venoarterial extracorporeal membrane oxygenation (ECMO) support. Fiberoptic-guided intubation with a double-lumen tube was performed smoothly, owing to improved bronchial patency, possibly facilitated by pulmonary artery decompression with venoarterial ECMO. Dynamic changes in pulmonary artery morphology following a clamshell incision are shown in Supplemental Digital Content Video 2 (https://links.lww.com/ALN/E55). At the beginning of the video (section 1), the pulmonary artery remains only partially decompressed by venoarterial ECMO, progressively collapsing after conversion to cardiopulmonary bypass (CPB) with enhanced venous drainage (section 2) and further decompression after the initiation of pulmonary artery venting (section 3).

An enlarged pulmonary artery can impinge on adjacent anatomical structures, such as the tracheobronchial tree and the left main coronary artery.[1] Such compression may lead to life-threatening complications, including central airway obstruction and myocardial ischemia.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

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Furthermore, pulmonary artery dilation is associated with an increased risk of dissection or rupture.[2] These events may be precipitated not only by compromised airway patency and hemodynamic fluctuations under general anesthesia but also by positional changes or intrathoracic surgical manipulation.

In patients with massively dilated pulmonary arteries, compression of adjacent vital structures should be evaluated by computed tomography and echocardiography. When pulmonary artery dilation leads to symptomatic compression, early initiation of venoarterial ECMO or CPB may confer meaningful perioperative benefits.[3] Beyond providing cardiopulmonary support, venoarterial ECMO or CPB can reduce both the volume and pressure within the pulmonary artery through augmented venous drainage, thereby alleviating extrinsic compression and mitigating the risk of pulmonary artery dissection or rupture, ultimately enhancing perioperative safety.

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Competing Interests

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Supplemental Digital Content

Supplemental Digital Content Video 1: Preoperative transthoracic echocardiogram, https://links.lww.com/ALN/E54

Supplemental Digital Content Video 2: Surgical field after a clamshell incision, https://links.lww.com/ALN/E55

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Ephedrine and the Brain: Bridging Hemodynamics, Neuromodulation, and Potential Neuroprotection in Perioperative Medicine

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In 2024, two clinical studies provided initial evidence that ephedrine may reduce the incidence of postoperative delirium compared with phenylephrine, two vasopressors commonly used in perioperative care.[1,2] One study was a multicenter retrospective cohort involving 103,094 adults undergoing general anesthesia for noncardiac, nonneurosurgical procedures[2]; the other was a randomized controlled trial of 130 patients undergoing knee arthroplasty under general anesthesia.[1] These studies suggest that vasopressors routinely administered during anesthesia may differentially influence cerebral outcomes; specifically, ephedrine appears advantageous in reducing postoperative delirium. This raises important questions about underlying mechanisms and clinical implications for anesthetic practice.

Previous physiologic studies offer insights into these clinical observations (table 1). Compared with phenylephrine, ephedrine better preserves cardiac output and maintains cerebral oxygenation as measured by near-infrared spectroscopy.[3] Additionally, ephedrine increases cerebral blood flow and brain tissue oxygen tension more effectively.[5,8] Advanced imaging further indicates that ephedrine decreases capillary transit time heterogeneity—a marker of more uniform cerebral microcirculation and improved oxygen delivery—whereas phenylephrine exerts the opposite effect.[8] Collectively, these systemic and cerebral hemodynamic advantages may help explain the observed benefits of ephedrine on postoperative cerebral outcomes.[1,2]

Unlike other vasopressors such as phenylephrine and norepinephrine,[6,10] ephedrine crosses the intact blood–brain barrier, enabling direct modulation of central nervous system function.[11,12] This pharmacologic property may extend its clinical effects beyond improvements in cerebral hemodynamics to include direct neurocognitive, neurochemical, and neurovascular modulation.

Given ephedrine's widespread use for perioperative hypotension and the clinical importance of these findings, this review integrates fragmented physiologic and clinical evidence into a cohesive, practical framework (fig. 1). The aim is to provide anesthesiologists with a clear, evidence-based understanding of ephedrine's cerebral effects and its potential to improve outcomes.

Systemic Hemodynamics

Ephedrine is a widely used vasopressor in perioperative care, valued for its ability to increase blood pressure by stimulating norepinephrine and epinephrine release from sympathetic nerve terminals, activating α1-adrenergic receptors to induce vasoconstriction and β1-adrenergic receptors to enhance cardiac performance.[12] It also directly activates both receptor types.[12] Its β1-adrenergic stimulation increases myocardial contractility and heart rate; combined with increased preload from peripheral α1-mediated venoconstriction, this typically augments cardiac output.[3] This profile is similar to norepinephrine[4] but contrasts with phenylephrine, which reduces cardiac output by increasing afterload through selective α1-adrenergic–mediated peripheral arterial vasoconstriction.[3,10] This distinction makes ephedrine advantageous when both blood pressure stabilization and cardiac output preservation are essential. However, its utility may be limited by tachyphylaxis, a phenomenon characterized by diminished efficacy with repeated doses due to norepinephrine depletion.[13] Consequently, ephedrine is well-suited for treating transient hypotension but has limited effectiveness for sustained hemodynamic support, often requiring a transition to alternative vasopressors for prolonged or repeated use.

Cerebral Macrocirculation

Ephedrine increases cerebral blood flow. For comparable increases in arterial blood pressure, ephedrine produces a greater increase in cerebral blood flow than phenylephrine. In brain tumor patients during intravenous anesthesia, ephedrine increased cerebral blood flow in the contralateral healthy hemisphere by $5.5\,ml \cdot 100\,g^{-1} \cdot min^{-1}$.[5] In contrast, phenylephrine resulted in a smaller increase of $1.7\,ml \cdot 100\,g^{-1} \cdot min^{-1}$.[5] Norepinephrine increases cerebral blood

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Table 1. Comparison of Ephedrine, Phenylephrine, and Norepinephrine Effects in Humans*

Parameter	Ephedrine	Phenylephrine	Norepinephrine	Clinical Implications
Esophageal Doppler-measured cardiac output	Increase or maintained during anesthesia (0.5 l/min)[3]†	Decrease during anesthesia (–1.7 l/min)[3]†	Increase in severely hypotensive sepsis (transpulmonary thermodilution measurements)[4]	Ephedrine increase or maintains cardiac output
Cerebral perfusion pressure	Increase	Increase	Increase	Ephedrine's effects go beyond its augmentation of cerebral perfusion pressure
PET-measured cerebral blood flow	Significant increase in healthy brain during anesthesia (5.5 ml $100\,g^{-1}\,min^{-1}$)[5]‡	Small increase in healthy brain during anesthesia (1.7 ml $100\,g^{-1}\,min^{-1}$)[5]‡	Stable or decrease in healthy brain and increase in critical ill brain (TCD and non-TCD measurements)[6,7]	Ephedrine boosts brain perfusion and reduces the risk of cerebral ischemia
MRI-measured capillary transit time heterogeneity	Reduced heterogeneity in healthy brain during anesthesia (–0.4 s)[8]§	Increased heterogeneity in healthy brain during anesthesia (0.2 s)[8]§	No evidence	Ephedrine supports more uniform cerebral microcirculation
NIRS-measured cerebral tissue oxygen saturation	Increase in healthy brain during anesthesia (–0.4 to 4%)[3,5]‖	Decrease in healthy brain during anesthesia (–4.9% to –0.5%)[3,5]‖	Decrease in awake healthy human (NIRS measurements)[7]	Ephedrine maintains the balance between cerebral oxygen consumption and supply
MRI-measured brain tissue oxygen tension	Significant increase in healthy brain during anesthesia (brain tissue oxygenation ratio, 0.51)[8]#	Small increase in healthy brain during anesthesia (brain tissue oxygenation ratio, 0.17)[8]#	Significant increase in severe head injury (brain tissue oxygen tension measurements)[9]	Ephedrine boosts cerebral oxygen delivery and extraction
Blood–brain barrier	Crossing intact blood–brain barrier	Does not cross intact blood–brain barrier	Does not cross intact blood–brain barrier	Ephedrine exerts central stimulating effects
Central neuromodulation	Neurocognitive, neurochemical, and neurovascular modulation	No effect if no blood–brain barrier crossing	No effect if no blood–brain barrier crossing	Ephedrine may counter anesthesia-induced central suppression, promoting cognitive recovery
Risk of postoperative delirium	May reduce compared with phenylephrine	May increase compared with ephedrine	No direct evidence	Ephedrine may lower the risk of postoperative delirium

*The interpretation of the effects of intravenous vasopressor treatments on physiologic measurements in humans must account for demographic characteristics, physical status, comorbidities, consciousness (awake *vs.* anesthetized), anesthesia type, surgical procedures, controlled conditions during measurement (*e.g.*, arterial carbon dioxide levels during cerebral blood flow assessments), and measurement methodologies (*e.g.*, variations in near-infrared spectroscopy technology). Whenever possible, we utilized data from the same or identical studies to facilitate direct comparisons. †Change measured by esophageal Doppler, calculated as the mean posttreatment level minus the mean pretreatment level. ‡Change measured by positron emission tomography, calculated as the mean posttreatment level minus the mean pretreatment level in the nonlesion hemisphere. §Change measured by magnetic resonance imaging, calculated as the mean posttreatment level minus the mean pretreatment level in the nonlesion hemisphere. ‖Change measured by near-infrared spectroscopy, calculated as the mean posttreatment level minus the mean pretreatment level across two different studies. #Difference measured by magnetic resonance imaging, calculated as the posttreatment ratio minus the pretreatment ratio, with both ratios calculated by dividing the post- or pretreatment measurement by the pretreatment measurement in the nonlesion hemisphere.

MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; PET, positron emission tomography; TCD, transcranial Doppler.

flow in critically ill patients but does not significantly affect it in healthy individuals.[6,7]

The effect of ephedrine-induced increases in cerebral perfusion pressure on cerebral blood flow should be interpreted within the context of cerebral autoregulation, the physiologic mechanism that maintains stable cerebral blood flow despite fluctuations in perfusion pressure.[14–17] Evidence shows that autoregulatory mechanisms remain functional during intravenous anesthesia,[18] as used in the cited study,[5] ensuring that moderate increases in cerebral perfusion pressure within clinical ranges do not significantly alter cerebral blood flow. Indeed, similar elevations achieved with phenylephrine result in minimal changes.[5] Therefore, the greater increase in cerebral blood flow associated with ephedrine is likely mediated by mechanisms beyond perfusion pressure alone, notably cardiac output augmentation—a property not shared by phenylephrine.[3,5,14]

Another factor contributing to ephedrine's effect on cerebral blood flow may be its impact on arterial carbon dioxide levels. Koch *et al.* reported a 3.3-mmHg increase in arterial carbon dioxide after ephedrine administration, whereas phenylephrine had no effect.[5] This rise likely reflects increased metabolism driven by ephedrine's sympathomimetic effects.[19,20] Cerebral blood flow increases *via* cerebrovascular reactivity to elevated arterial carbon dioxide levels.[16,21]

Additionally, ephedrine may increase cerebral blood flow through neuronal activation or an elevated cerebral metabolic rate, involving mechanisms such as neurovascular coupling or cerebral metabolic rate–blood flow coupling.[21,22] These pathways are discussed further in the section "Neurovascular Modulation."

We note that many current theories on cerebral perfusion regulation, including cerebral autoregulation, remain conceptual and subject to debate. These uncertainties should be considered when interpreting the cerebral effects of vasopressors.

Cerebral Microcirculation

Ephedrine enhances cerebral microcirculation by promoting more uniform capillary flow,[8,23] reflected in reduced

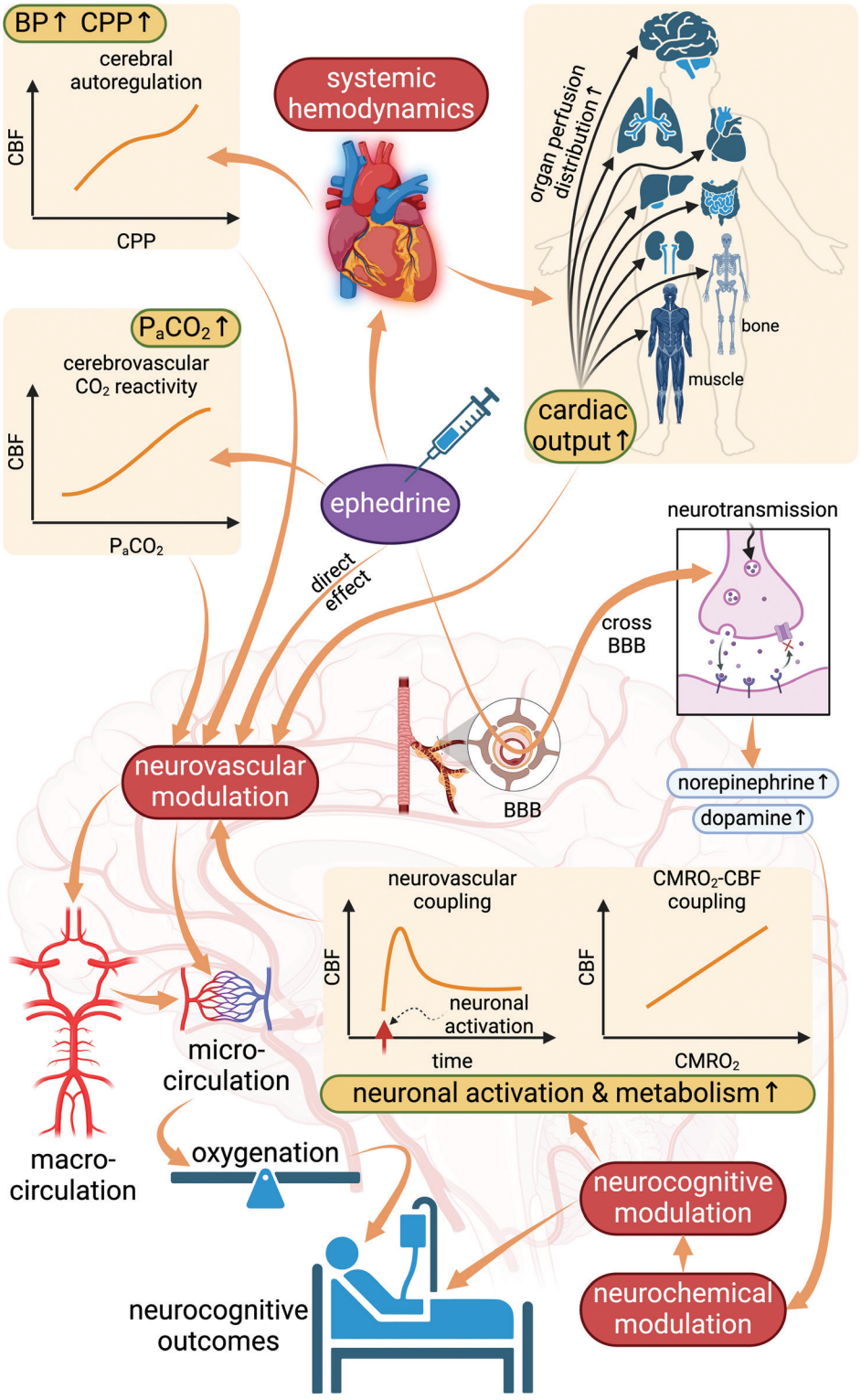


Fig. 1. Mechanisms underlying ephedrine's cerebral effects. Ephedrine enhances cerebral perfusion and oxygenation through systemic hemodynamic actions and neurovascular modulation. By stimulating α- and β-adrenergic receptors, it increases blood pressure and cardiac output, augmenting organ perfusion. Its effects on cerebral macrocirculation and microcirculation are mediated by multiple mechanisms, including cerebral autoregulation, redistribution of cardiac output, cerebrovascular carbon dioxide reactivity, direct vasomotor *(Continued)*

capillary transit time heterogeneity—a key determinant of efficient cerebral tissue perfusion and oxygen delivery.[24] Uneven capillary transit times can result in "functional shunting," where oxygenated blood traverses capillaries too rapidly to offload oxygen, increasing the risk of tissue hypoxia adequately.[25] This is particularly relevant in older individuals and those with neurodegenerative diseases, who are more vulnerable to microvascular dysfunction and hypoxic injury.[26] While mechanistically plausible and supported by imaging studies, this theory remains theoretical and has not been widely adopted as a clinical diagnostic or physiologic standard.[27,28] Nonetheless, ephedrine may enhance cerebral oxygenation by improving microcirculatory function and complementing its effects on macrocirculation, thereby supporting integrated perfusion across the cerebral vascular network.

Cerebral Oxygenation

Cerebral tissue oxygen saturation, measured by near-infrared spectroscopy, reflects the balance between oxygen supply and demand in brain tissue.[29–31] Studies suggest that ephedrine generally maintains or enhances cerebral oxygenation in anesthetized patients.[3,5] For instance, Koch *et al.* observed a 4% increase in near-infrared spectroscopy values with ephedrine, compared to a 0.5% decrease with phenylephrine.[5] Meng *et al.* reported minimal change (0.04%) with ephedrine and a decrease (–3.2%) with phenylephrine.[3] These discrepancies likely reflect differences in technologies, populations, and protocols. Despite this variability, evidence consistently suggests that ephedrine maintains or improves cerebral oxygenation, whereas phenylephrine typically reduces it.

Recognizing the methodologic limitations of near-infrared spectroscopy is important when interpreting these results. Signal contamination from extracranial tissues can reduce accuracy, particularly with phenylephrine, which induces extracranial vasoconstriction and decreases arterial blood volume captured by the device.[10] Although phenylephrine does not directly constrict intracranial vessels due to the intact blood–brain barrier, it induces intracranial vasoconstriction indirectly through cerebral autoregulation.[32,33] These effects lower near-infrared spectroscopy values by increasing the proportion of deoxygenated venous blood relative to oxygenated arterial blood, without necessarily indicating reduced cerebral blood flow or oxygen delivery.[5,10]

It is also important to distinguish spectroscopy-derived hemoglobin saturation from brain tissue oxygen tension, which reflects actual oxygen levels within brain tissue.[34] In patients undergoing craniotomy, brain tissue oxygen tension in the peripheral white matter remained stable after phenylephrine administration.[35] This observation aligns with the findings reported by Koch *et al.* but contrasts with decreased near-infrared spectroscopy values noted by Meng *et al.*, highlighting the complexity of interpreting near-infrared spectroscopy data in isolation.[3,5]

Penetration across the Blood–Brain Barrier

Ephedrine's ability to cross the blood–brain barrier distinguishes it from other vasopressors, including phenylephrine and norepinephrine, enabling direct access to central nervous system targets.[11,12] The blood–brain barrier, composed of endothelial cells, astrocytic end-feet, and pericytes, selectively restricts hydrophilic molecules while allowing lipophilic agents like ephedrine to diffuse into brain tissue.[36,37] This property reflects ephedrine's small molecular size, moderate lipophilicity, and structural similarity to amphetamines.[12] Radiolabeled studies confirm its presence in the brain,[11] and transient increases in Bispectral Index scores (Bispectral Index system, Medtronic, Ireland) during anesthesia provide indirect clinical evidence of central nervous system penetration.[5,38,39] In contrast, phenylephrine and norepinephrine generally do not cross an intact blood–brain barrier but may do so when barrier integrity is compromised, including advanced age, neurodegenerative diseases, or neurosurgical procedures.[23]

Central Neuromodulation

After its penetration across the blood–brain barrier, ephedrine exerts direct effects on the brain—a phenomenon referred to here as central neuromodulation. This concept encompasses diverse mechanisms by which ephedrine may influence the central nervous system, including modulation of neuronal activity, neurotransmitter signaling, and cerebral perfusion. To provide clinical and mechanistic clarity, we categorize these effects into three interrelated domains: neurocognitive, neurochemical, and neurovascular modulation. Each domain represents a distinct but overlapping set of physiologic responses, together forming a unified framework for understanding how ephedrine's central actions may lead to observable clinical outcomes. This structured

Fig. 1. *(Continued)* effects, neurovascular coupling, and cerebral metabolic rate of oxygen–blood flow coupling. These mechanisms converge on the cerebral vasculature and collectively constitute neurovascular modulation. Unlike other vasopressors, ephedrine crosses the blood–brain barrier, modulating central norepinephrine and dopamine transmission. These neurochemical effects may support arousal, cognition, and neuronal metabolism. Neurovascular, neurochemical, and neurocognitive modulation together comprise central neuromodulation. Through these integrated mechanisms, ephedrine may mitigate the risk of postoperative neurocognitive disorders in vulnerable patients. BBB, blood–brain barrier; BP, blood pressure; CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen; CPP, cerebral perfusion pressure; P_aca_2, arterial carbon dioxide partial pressure.

approach facilitates the interpretation of existing evidence and supports ongoing investigation into ephedrine's potential neuroprotective and therapeutic roles in perioperative care.

Neurocognitive Modulation

While extensive evidence exists on ephedrine's effects on physical and metabolic performance, fewer studies have systematically evaluated its influence on cognitive function and mood.[40] In stimulant-naive adults, a well-controlled randomized trial demonstrated that a single therapeutic dose of ephedrine (60 mg orally) significantly reduced fatigue during prolonged driving tasks.[41] Over a period of 4 h, ephedrine not only prevented performance deterioration observed with placebo but also improved response times to emergency signals.[41] These data suggest that ephedrine sustains cognitive performance, especially in prolonged tasks requiring continuous attention.

Ephedrine's cognitive-enhancing properties have also been observed when administered with agents known to impair cognitive function. For instance, ephedrine (15 mg orally) counteracted the sedative effects of chlorpheniramine maleate, significantly improving performance in tasks assessing auditory vigilance and sustained attention in healthy female volunteers.[42] Another placebo-controlled study found that ephedrine (25 mg orally) effectively reversed cognitive impairments induced by oral scopolamine in healthy males, including deficits in short-term memory and central nervous system integrative functions, as measured by flicker fusion tests.[43] These findings highlight ephedrine's role in mitigating drug-induced cognitive deficits.

Collectively, the evidence indicates that ephedrine, at doses comparable to those in over-the-counter preparations and nutritional supplements, consistently exhibits stimulant-like central nervous system effects—enhancing alertness, attention, mood, and cognitive vigilance while reducing subjective fatigue.[12,40–44] These beneficial cognitive effects correlate temporally with ephedrine's rapid absorption, typically completed within approximately 3 h after oral administration and characterized by first-order kinetics.[45] Thus, these oral doses provide clinically relevant insights into the potential cognitive effects of intravenous ephedrine administered perioperatively.

Neurochemical Modulation

Ephedrine influences central nervous system function, likely by enhancing the transmission of norepinephrine and dopamine. Laboratory studies using rodent brain tissue have demonstrated that ephedrine interacts with the transport systems responsible for reabsorbing these neurotransmitters—especially norepinephrine and, to a lesser extent, dopamine. By acting as a substrate for these transporters, ephedrine reverses transporter function, facilitating the release of norepinephrine and dopamine into the synaptic cleft—a mechanism recognized as fundamental to its stimulant effects.[46]

In rat studies, ephedrine has been shown to increase dopamine levels in brain regions involved in motivation and motor activity, such as the nucleus accumbens.[47] These changes increase movement and behavioral activation. Both effects are attenuated when dopamine receptors are pharmacologically blocked, indicating that dopamine signaling is essential for these responses.[48] Electrophysiologic recordings in rat substantia nigra slices have shown that ephedrine induces membrane hyperpolarization and reduces γ-aminobutyric acid–mediated inhibition in dopamine-producing neurons. These effects are reversed by dopamine receptor blockade or dopamine depletion and reinstated by exogenous dopamine, further supporting that ephedrine promotes endogenous dopamine release.[49]

Ephedrine may stabilize brain function during stress by increasing norepinephrine and dopamine. Norepinephrine supports memory, attention, and the reorganization of brain networks in response to new demands.[50,51] Dopamine modulates prefrontal cortical cognition and enhances executive function and motor learning by promoting communication between neurons, often through interactions with glutamate signaling pathways.[52–54] These neurochemical effects align with clinical and experimental findings that suggest a role for ephedrine in promoting arousal and supporting cognitive performance.

Neurovascular Modulation

As previously discussed, the brain's vascular system is regulated by multiple mechanisms—particularly in the arterial and arteriolar segments—that modulate vasomotor tone and influence cerebral blood flow.[14–16] These mechanisms include cerebral autoregulation, cerebrovascular carbon dioxide reactivity, cardiac output, neurovascular coupling, cerebral metabolic rate of oxygen–blood flow coupling, direct drug effects, and sympathetic nervous activity.[14–16,21] The term "neurovascular modulation" unifies these processes, emphasizing their integration in determining net cerebral blood flow while acknowledging their distinct roles.[14]

Ephedrine engages multiple mechanisms of cerebral blood flow regulation. It acts through cerebral autoregulation by affecting arterial pressure and cerebral perfusion pressure.[14–17] It alters cerebral blood flow by changing arterial carbon dioxide tension[5] and improves brain perfusion by increasing cardiac output.[3] Ephedrine crosses the blood–brain barrier and may directly affect cerebral vasculature, as suggested by its impact on microcirculation.[8] However, its direct adrenergic influence on vasomotor tone appears limited, as it primarily acts *via* norepinephrine release. Although ephedrine elevates central norepinephrine and dopamine levels, these changes do not directly modulate cerebral vasomotor tone. This is supported by findings that

norepinephrine infusion in resting dogs did not constrict denervated brain or hindlimb vascular beds; even under stress, elevated norepinephrine had minimal effect on hindlimb vessels and none on denervated cerebral vessels.[55]

Nonetheless, ephedrine's neurochemical and neurocognitive effects occur in the context of cerebral metabolic rate–blood flow coupling, ensuring alignment between oxygen use and delivery.[21] Neurovascular coupling refers to localized blood flow increases that may exceed immediate metabolic demands,[22] while cerebral metabolic rate–blood flow coupling ensures alignment between oxygen use and delivery.[21] Supporting evidence includes a study by Koch *et al.* in which ephedrine increased the cerebral metabolic rate of oxygen by 3.8 $\mu mol \cdot 100\,g^{-1} \cdot min^{-1}$, compared to a 4.4-$\mu mol \cdot 100\,g^{-1} \cdot min^{-1}$ decrease with phenylephrine in the healthy hemisphere of anesthetized patients.[5] Additional support comes from studies showing that ephedrine—but not phenylephrine—increased Bispectral Index scores in anesthetized patients, consistent with enhanced cortical activity.[5,38,39]

Taken together, ephedrine's neurovascular modulation reflects the coordinated action of multiple mechanisms converging on the cerebral vasculature. Understanding this integration offers a unified physiologic framework and may inform precision-targeted therapeutic strategies. However, these findings should be interpreted cautiously, as they are based on animal studies and small human cohorts,[3,5,8,32] and modeling-based methods limit their generalizability to broader clinical practice.

Emerging Evidence of Ephedrine's Neuroprotective Role

Postoperative delirium remains a challenge in perioperative medicine, disproportionately affecting elderly patients and those undergoing major surgeries.[56] This condition is associated with increased morbidity, prolonged hospital stays, and a heightened risk of long-term cognitive decline, placing a significant burden on patients, healthcare systems, and society.[57] Despite substantial efforts, prevention and management strategies remain inconsistent and often suboptimal.[56] Against this backdrop, ephedrine—a vasopressor with unique hemodynamic and central neuromodulation properties—has emerged as a promising candidate for reducing the incidence of postoperative delirium.

A randomized controlled trial involving 130 elderly patients undergoing knee arthroplasty reported a significantly lower incidence of postoperative delirium in the ephedrine group (7%) compared to the phenylephrine group (33%).[1] Findings from a multicenter retrospective cohort study found a 35% higher risk of postoperative delirium in patients receiving phenylephrine compared to those treated with ephedrine.[2] Together, these studies suggest that ephedrine may confer neuroprotective benefits, particularly in high-risk populations such as older adults or those with preexisting cognitive or cerebrovascular vulnerabilities.

However, these findings are not without limitations. While compelling, the randomized controlled trial had a small sample size and single-center design, limiting generalizability.[1] Additionally, its reliance on once-daily assessments could have missed transient episodes of delirium. The retrospective cohort study, based on administrative coding, may have underestimated delirium incidence and was susceptible to confounding by indication.[2] These limitations underscore the need for adequately powered, multicenter, high-quality randomized trials to validate and expand these findings.

Currently, the impact of ephedrine on other neurocognitive outcomes, such as stroke or long-term postoperative cognitive function, remains unreported. It would also be relevant to examine the impact of norepinephrine, another commonly used vasopressor, on postoperative neurocognitive outcomes. A randomized clinical trial showed that processed electroencephalographic monitoring–guided care reduced norepinephrine use in cardiac surgery patients; however, this approach did not reduce postoperative delirium incidence.[58] Notably, no studies have directly compared the neurocognitive effects of ephedrine and norepinephrine.

Potential Risks of Ephedrine

Ephedrine carries risks of both neurotoxicity and misuse liability.[12,59,60] Excessive dosing or nontherapeutic use has been associated with adverse neurocognitive effects, including jitteriness, restlessness, anxiety, insomnia, irritability, impaired working memory, confusion, psychosis, seizures, and stroke, as well as cardiovascular events such as hypertension, palpitations, tachycardia, arrhythmias, and myocardial infarction.[61–63] Its ability to enhance dopamine transmission raises concerns about abuse potential, given its structural similarity to amphetamines and activation of mesolimbic reward pathways.[64] However, ephedrine has a distinct subjective profile and is a less potent behavioral reinforcer than amphetamine, suggesting lower misuse potential.[65]

Clinical Implications and Future Research

Ephedrine has been used in anesthesia for more than a century and remains a primary agent for managing intraoperative hypotension.[66] Vasopressor selection is often guided by the presumed etiology of hypotension, cardiac function, and risk of myocardial ischemia or arrhythmia,[67,68] yet no evidence-based framework links vasopressor choice to neurocognitive outcomes. Given its combined hemodynamic and central neuromodulatory effects, ephedrine may be a reasonable option for patients at elevated risk of postoperative delirium, particularly older adults or those with preexisting cognitive impairment undergoing high-risk surgery.

Its clinical use requires balancing potential neuroprotective benefits against cardiovascular risks, especially in patients with underlying heart disease. Although concerns

about arrhythmias and myocardial ischemia persist, such adverse effects are uncommon when ephedrine is used appropriately in perioperative care. The commonly taught heuristic—ephedrine for bradycardia and phenylephrine for tachycardia—is overly simplistic. Heart rate variability is well tolerated in most patients, and ephedrine does not invariably increase heart rate.[3,69]

Future studies should include randomized trials in high-risk surgical populations, with outcomes focused on delirium, cognitive recovery, and long-term neurocognitive function. Comparative studies with other vasopressors are also needed to define ephedrine's relative benefits, optimal dosing strategies, and safety in anesthetic and critical care practice.

Conclusions

Ephedrine is a vasopressor with distinct hemodynamic and neuromodulatory properties that extend beyond blood pressure support. By preserving cardiac output, enhancing cerebral macro- and microcirculation, and modulating neurotransmission and neurocognitive function through its ability to cross the blood–brain barrier, it may reduce postoperative delirium and promote cognitive recovery in vulnerable patients (fig. 1). Preliminary findings and mechanistic insights support its potential role as a neuroprotective agent. However, its central mechanisms remain incompletely defined and require further investigation. Large randomized trials and comparative studies are needed to confirm these effects, establish optimal dosing, and inform protocols that integrate hemodynamic management with neurocognitive outcomes.

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Competing Interests

The authors declare no competing interests.

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A Comprehensive Update on Intraoperative Methadone Use

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Use of intraoperative methadone has increasingly been recognized as an effective approach to improve postoperative pain management and reduce consumption of other opioids. In a previous Clinical Focus Review (CFR), Murphy and Szokol[1] reviewed the available literature on the intraoperative use of methadone in surgical patients. They summarized the multiple reasons that make intravenous methadone an attractive option, including: (1) its potent activity as a μ-receptor agonist and *N*-methyl-D-aspartate (NMDA) receptor antagonist; (2) its rapid onset time with a $t_{1/2}k_{e0}$ of 4 min; (3) its long elimination half-life (24 to 36 h), such that stable blood concentrations are achieved after a single dose, reducing the need for frequent dosing and minimizing fluctuations in analgesia; and (4) its opioid-sparing effect, whereby administration of methadone *versus* other opioids reduces the need for additional other postoperative opioids as well as the total amount of opioids after surgery. Despite this, barriers to adoption remain given that: (1) optimal dosing regimens for different patient populations have not been thoroughly studied; (2) the effective serum concentration needed may vary depending on both the surgical procedure and individual patient characteristics, although the majority of studies at clinically relevant doses have not found major differences; and (3) not all centers have ready access to intravenous formulations of methadone.

Additional highlights from the CFR by Murphy and Szokol[1] are (1) clinical studies from 1982 to 2019 were included; (2) these studies consistently showed that methadone reduces pain scores and opioid consumption compared to other opioids in surgeries ranging from spine surgery, cardiac surgery, gynecologic and obstetric surgery, ambulatory surgery, and various pediatric surgeries; (3) targeting a blood concentration of methadone exceeding the minimal analgesic concentration is important such that the duration of action of lower doses of methadone mimics the duration of action in other short-acting opioids (approximately 3 to 4 h) as opposed to the longer clinical effect observed when higher doses of methadone are used (*e.g.*, 20 mg for an adult patient); (4) respiratory and cardiac risks in methadone randomized trials cited in the CFR (up to 2019) were not significantly different relative to their comparator group, although rare side effects such as serotonin syndrome have been reported when methadone was coadministered with serotonergic medications; and (5) a common limitation of many randomized trials was low sample size (less than 100 subjects).

Kharasch[2] also summarizes methadone's analgesic duration as follows (reprinted in the Murphy and Szokol[1] CFR): methadone doses of 5 and 10 mg result in an estimated analgesic duration of less than 0.5 h, while methadone doses of 20 and 30 mg resulted in an estimated analgesic duration of approximately 24 and 36 h, respectively. To maintain the steady-state plasma levels above 58 ng/ml (a concentration believed to provide adequate analgesia) for 24 h after painful procedures, Stemland *et al.*[3] suggest the following options based on simulation modeling: an initial bolus of 0.25 mg/kg before incision plus a second bolus of 0.35 mg/kg of methadone at 4 h or providing supplemental boluses based on pain severity (0.03 mg/kg used for mild pain and 0.05 mg/kg used for severe pain every 4 h). Notably, the time of greatest risk of respiratory depression after a single bolus dose of methadone is less than 30 to 45 min due to its rapid redistribution.[4]

Since the 2019 CFR, additional investigations have yielded incremental but, again, almost wholly positive data on the safety and efficacy of methadone, especially for special populations (*e.g.*, children, patients with obesity) and

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Abbreviations: **CFR**, Clinical Focus Review; **IQR**, interquartile range; **IV**, intravenous; **MME**, milligram morphine equivalents; **NMDA**, *N*-methyl-D-aspartate; **PACU**, postanesthesia care unit; **PONV**, postoperative nausea and vomiting; **QoR-40**, Quality of Recovery questionnaire; **RCT**, randomized controlled trial

various surgery types such as spine surgery, cardiac surgery, and certain ambulatory surgeries. Our motivation in presenting a comprehensive update is to provide clinicians with the latest data to make informed decisions about when and how to use methadone intraoperatively. Several journals have dedicated pro/con debates on the topic including D'Souza's "Pro–Con Debate: Role of Methadone in Enhanced Recovery After Surgery Protocols—Superior Analgesic or Harmful Drug?,"[5] Garcia's "Pro: Methadone Should Be Used as a Part of Enhanced Recovery After Cardiac Surgery Protocol,"[6] and Ibekwe's "Methadone Should Not Be Used in Cardiac Surgery as Part of Enhanced Recovery After Cardiac Surgery Protocol."[7] A number of editorials and commentaries have also discussed the merits, hesitations, and barriers to wider adoption of methadone as an analgesic.[8–12]

In this CFR, we systematically reviewed the literature indexed in PubMed from January 1, 2019 (because the Murphy and Szokol[1] 2019 review covers literature through 2018) to July 10, 2024, with a search strategy using the keywords: "intraoperative methadone," "methadone safety," "pediatric methadone," "methadone cardiac," "methadone anesthesia," and "methadone adverse events." Of the 926 articles found, the field was manually narrowed down to 98 relevant articles, of which 41 are clinical studies. Of these 41 studies, there were 4 meta-analyses of randomized clinical trials, 14 prospective randomized clinical trials, 19 retrospective cohort/observational studies, 2 prospective observational studies, and 2 pharmacokinetic studies. Of the 41 studies, 13 focused on pediatric patients. Our goal in this CFR is to provide a summary and synthesis of the studies that have been published since the previous CFR in 2019, given the breadth of surgery types and patient populations.

We carefully considered the inclusion of observational and retrospective studies in addition to randomized controlled trials (RCTs). Individual RCTs published since 2019 typically had small sample sizes, limiting their ability to effectively address rare outcomes such as adverse events. In fact, the four meta-analyses of existing trials before 2019 included fewer than a thousand patients in each of their studies. By comparison, we included two large retrospective studies on naloxone use in patients who had received methadone (each involving approximately 29,300 and approximately 14,500 patients, respectively).[13,14] These retrospective studies offer valuable insights that would be challenging to obtain solely from RCTs. Other retrospective studies provide intriguing groundwork for future prospective studies in special populations such as pediatrics.

Most studies that compare methadone to other analgesics evaluate either postoperative pain scores, opioid consumption, or both as a primary outcome. Wherever possible, doses for the methadone group and comparator group are described in the text and corresponding table. When doses in the comparator group are not reported, only the medication used in the comparator group is listed. For additional reference, quantitative results on opioid consumption are included in supplemental table 1 (https://links.lww.com/ALN/D996).

Systematic Meta-analyses

The four systematic meta-analyses published by Machado *et al.*,[15] Kendall *et al.*,[16] D'Souza *et al.*,[17] and Cheriyan *et al.*[18] are consistent in their finding that methadone is an effective analgesic, with studies favoring the methadone group compared to other intraoperative opioids when assessing postoperative pain scores (table 1). Although Cheriyan *et al.*[18] and Kendall *et al.*[16] did not find any differences in postoperative opioid consumption, Machado *et al.*[15] and D'Souza *et al.*[17] showed that methadone decreased postoperative opioid consumption compared to other opioids. Given the wide range of dosing strategies in these studies, it is possible that the use of smaller doses of methadone did not lead to a blood concentration exceeding the minimal analgesic concentration beyond the initial analgesic duration and therefore did not result in a reduction in postoperative opioid consumption. All four meta-analyses acknowledged a large degree of study heterogeneity due to the inclusion of different surgical procedures and lack of standardization in postoperative analgesic management. Cheriyan *et al.*[18] also discussed the importance of excluding trials in which interventions were continued postoperatively, reiterating the importance of consistent protocols. Importantly, none of the studies showed a difference in complications including postoperative nausea and vomiting, respiratory depression, excessive sedation, QT prolongation, or cardiac arrhythmia.

These meta-analyses serve as a good starting point for the subsequent studies discussed below, as all include studies were published in 2019 or earlier. A meta-analysis was not included in this CFR due to the heterogeneity of the more recent studies since 2019 including different surgery types, comparator groups, patient age, surgery disposition, and methadone dosing, timing, and routes.

Methadone in Adult Inpatient Surgery

Nine studies[19–27] investigated methadone for adult inpatient surgeries (table 2). Most of these studies consistently showed reduced opioid consumption or postoperative pain with methadone use as its primary outcome.

For example, Moro *et al.*[22] evaluated the quality of recovery as a primary outcome after the administration of 0.1 mg/kg methadone *versus* 0.1 mg/kg morphine in laparoscopic cholecystectomy patients in a prospective, randomized, double-blinded, controlled trial. No differences were observed in total or individual Quality of Recovery Questionnaire (QoR-40) dimension scores (median total QoR-40 score of 193 [interquartile range, 187 to 196] in the methadone group *vs.* 194 [186 to 196] in the morphine group; $P = 0.73$). However, postanesthesia care unit (PACU) opioid rescue (median, 1.0 ml [interquartile range,

Table 1. Methadone Meta-analyses 2019 to 2022

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Total Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Machado *et al.*[15]	2019	1986–2018	Systematic review and meta-analysis of double-blinded, controlled trials	929 patients (13 RCTs)	Varied: cardiac, spine, laparoscopic, abdominal, and pediatric surgeries	Range of 0.1–0.3 mg/kg or 20 mg as a fixed dose	Varied by trial and on patient weight	Morphine, fentanyl, sufentanil, or remifentanil	Morphine, fentanyl, or hydromorphone	Methadone group showed lower postoperative opioid consumption in morphine equivalent dosage at 24–72 h postoperatively	Pain at rest and at movement favored methadone until 48 h postoperatively	Patient satisfaction favored methadone in three trials	No significant differences were found in opioid-related side effects including respiratory depression or cardiovascular complications	Heterogeneity among the included studies, cumulative doses of opioids showed wide variations, small sample sizes across trials, variability in methadone dosing, control regimens, and multimodal analgesia
D'Souza *et al.*[17]	2020	1986–2018	Systematic review and meta-analysis of double-blinded, controlled trials	617 patients (10 RCTs)	Varied: cardiac, orthopedic, spine, laparoscopic, and abdominal surgeries	Range of 0.1–0.3 mg/kg or 20 mg as a fixed dose	Varied by trial and on patient weight	Morphine, fentanyl, sufentanil, or hydromorphone	Morphine, hydromorphone, or fentanyl	Methadone reduced 24-h postoperative opioid consumption by 15.22 mg oral morphine equivalents compared to other opioids; no significant differences were observed in opioid consumption after 48 and 72 h	Lower pain scores were observed in seven of the ten included studies within the first 48 h after surgery; significant reductions in pain scores were reported in most trials at rest and with movement		No significant differences in nausea, pruritus, sedation, respiratory depression, or hypoxemia between the methadone and control groups; QT interval prolongation and arrhythmias were not consistently reported; data were insufficient to draw conclusions	Heterogeneity among the included studies, cumulative doses of opioids showed wide variations, small sample sizes across trials, variability in methadone dosing, control regimens, and multimodal analgesia

(Continued)

Table 1. (Continued)

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Total Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Kendall *et al.*[16]	2020	1986–2018	Meta-analysis of randomized controlled trials comparing intraoperative methadone with morphine for postoperative pain management	337 patients (7 RCTs)	Varied: cardiac, abdominal, orthopedic, and laparoscopic	Range of 0.1–0.3 mg/kg	Varied by trial and on patient weight	Morphine, administered at equivalent doses to methadone	Morphine	No significant reduction in overall opioid consumption within the first 24 h postoperatively between methadone and morphine groups	Pain scores were significantly lower in the methadone group immediately postoperatively in the PACU (weighted mean difference −1.11 on a 0–10 scale)	Pain scores at 24 h were also significantly reduced in the methadone group (weighted mean difference −1.35 on a 0–10 scale)	No significant difference in complications such as respiratory depression, nausea, or vomiting between methadone and morphine groups; the meta-analysis did not report any notable cardiac disturbances related to methadone	Heterogeneity among the included studies (although comparator group was morphine only), cumulative doses of opioids showed wide variations, small sample sizes across trials, variability in methadone dosing, control regimens, and multimodal analgesia
Cheriyan *et al.*[18]	2022	1991–2019	Meta-analysis of randomized controlled trials	632 patients (9 RCTs)	Varied: cardiac, orthopedic, bariatric, laparoscopic, and spine surgeries	Range of 0.1–0.3 mg/kg	Varied by trial and on patient weight	Morphine, fentanyl, sufentanil, and hydromorphone	Morphine, fentanyl, and hydromorphone	No statistically significant reduction in postoperative opioid exposure (binary variable) between the methadone group and other opioid control groups (did not assess total opioid consumption difference)	Pain scores within 24 h were significantly lower in the methadone group (mean difference −0.49), but no significant difference was observed between 24 and 72 h		No significant differences were observed in adverse events such as nausea, vomiting, or respiratory depression between the methadone and control groups	Heterogeneity among the included studies, cumulative doses of opioids showed wide variations, small sample sizes across trials, variability in methadone dosing, control regimens, and multimodal analgesia

IV, intravenous; PACU, postanesthesia care unit; RCT, randomized controlled trial; VAS, visual analogue scale.

Table 2. Methadone in Adult Inpatient Surgery

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Bastian *et al.*[19]	2019	Not reported	Randomized double-blind controlled single-center study	130	Varied: thoracic, abdominal, breast, orthopedic, and vascular surgeries	0.2 mg/kg	Fentanyl (3 μg/kg)	Morphine	Methadone group showed lower median cumulative morphine consumption in the PACU and in the first 72 h after surgery	No significant differences in pain scores at rest and in motion	No significant difference in intraoperative fentanyl administration, length of PACU stay, and length of hospital stay	No significant difference in postoperative QTc times	Small sample size to detect adverse events, patients followed for only 72 h after surgery, severely ill patients were excluded
Moro *et al.*[22]	2019	2016–2019	Prospective, randomized, double-blinded, controlled clinical trial	62	Laparoscopic cholecystectomy	0.1 mg/kg	Morphine (0.1 mg/kg)	Tramadol	Similar opioid consumption between the methadone group and morphine group, but the methadone group required less rescue opioid in the PACU	No significant difference in pain scores		No significant differences in nausea, vomiting, or hypoxemia	Small sample size, patients followed for only 24 h after surgery
Mercadante *et al.*[21]	2020	2017–2019	Randomized controlled clinical trial	60	Open hysterosalpingectomy for gynecological cancer	0.15 mg/kg preoperatively, followed by a continuous infusion of 12 mg/day postoperatively	Morphine (0.15 mg/kg)	Morphine	Methadone group required significantly less postoperative opioid consumption compared to the morphine group	Methadone group had significantly lower pain intensity on the second postoperative day		No significant differences in adverse effects like respiratory depression, nausea, vomiting, or drowsiness	Small sample size, limited generalizability due to inclusion of specific type of gynecological surgery
Arriaza *et al.*[20]	2021	March 2013 to September 2013	Randomized clinical trial	86	Elective laparoscopic cholecystectomy	0.08 mg/kg	Morphine (0.08 mg/kg)	Morphine	Methadone group required significantly less rescue morphine in the PACU compared to the morphine group	Methadone group reported lower pain scores at 5 and 15 min, and 12 and 24 h postoperatively compared to the morphine group	Methadone group experienced fewer instances of nausea	No significant differences in complications such as vomiting, pruritus, and urinary retention	Use of intraoperative remifentanil could lead to hyperalgesia; possibly low nociceptive burden from surgery

(Continued)

Table 2. (Continued)

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Petrosan *et al.*[24]	2021	December 2019 to March 2020	Prospective single-center observational study with historical control group	240	Varied: cardiothoracic, neurosurgery, orthopedic, abdominal, oral and maxillofacial, and urologic surgery	Range of 0.08–0.60 mg/kg depending on the surgery	Not reported	Not reported	Mean postoperative MME was higher in the methadone group at 24, 48, and 72 h; however, when adjusted for opioid naive patients, there was a significant reduction in the methadone group at 48 h; mean total MME of discharge prescription was lower overall in the methadone group and when adjusted for opioid naivety	No significant difference in mean daily pain scores; opioid-naive patients showed lower mean daily pain scores in the methadone group	Mean length of hospital stay was shorter in the control group	Not reported	Unmatched groups, historical control group, postoperative analgesic treatment not described
Murphy *et al.*[27]	2021	2016–2021	Randomized, double-blind, placebo-controlled trial	130	Elective spinal fusion surgery	0.2 mg/kg ideal body weight	Remifentanil, fentanyl, hydromorphone	Hydromorphone	Methadone/ketamine group required significantly less hydromorphone on postoperative day 1 and lower overall opioid consumption over 3 days	Methadone/ketamine group had lower pain scores		No difference in incidence of adverse events, including respiratory depression, sedation, nausea, vomiting, neurologic changes, and surgical site infections	Small sample size to detect adverse events, patients followed for only 72 h after surgery

(Continued)

Table 2. (Continued)

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Esfahani *et al.*[25]	2023	July 2017 to July 2020	Retrospective, noninferiority analysis	1,010	Complex spine surgery involving more than three levels	IV group received 112.4 MME of methadone; oral group received 59.3 MME of methadone	NA	Hydromorphone	Oral methadone group demonstrated noninferiority in opioid consumption compared to the IV methadone group on postoperative day 3	Oral methadone group was noninferior to the IV methadone group for pain scores on postoperative days 0 to 3	Oral methadone group had a shorter time to first bowel movement	No significant differences in complications such as reintubation, myocardial infarction, arrhythmia, or QTc prolongation	Retrospective study design, perioperative analgesic treatment not standardized, lack of long-term follow-up
Vandse *et al.*[26]	2023	December 2020 to October 2022	Retrospective cohort study	60	Elective intracranial surgeries	5–20 mg	NA	Fentanyl, hydromorphone	Methadone group had lower postoperative opioid consumption compared to historical controls, particularly for supratentorial surgeries	Methadone group had lower pain scores		11.6% of patients experienced brief respiratory depression or hypoxia, but none required naloxone or airway interventions; 13.3% had hypotension, resolved with fluids	Small sample size, retrospective study design, perioperative analgesic treatment not standardized, methadone dosing not standardized, no control group
Boesl *et al.*[23]	2024	January 2018 to January 2022	Retrospective review, single institution	157	Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC)	Range of 15-20 mg	Four different groups: epidural analgesia *versus* CWIS with and without intraoperative methadone	Hydromorphone, oxycodone, tramadol	Median oral opioid use was significantly higher in the epidural group compared with the CWIS + methadone group; no significant difference in median IV opioid use between the epidural and CWIS + methadone groups; median total opioid was significantly higher in the epidural group	Not reported	Median hospital length of stay was significantly shorter in the CWIS + methadone group compared with the epidural group	One epidural abscess; no incidence of postoperative reintubation or inpatient naloxone use	Small sample size, retrospective study design, postoperative pain scores not assessed, postoperative analgesic treatment not standardized

CWIS, continuous wound irrigation system; IV, intravenous; MME, milligram morphine equivalents; NA, not applicable; PACU, postanesthesia care unit; VAS, visual analogue scale.

0 to 3] in the methadone group *vs.* 3.0 ml [1 to 4] in the morphine group; $P < 0.02$) and level of sedation (3 patients in the methadone group *vs.* 14 patients in the morphine group had Ramsay scores greater than or equal to 4; $P < 0.01$) were higher in the morphine control group. Note that the PACU rescue opioid is reported in milliliters as this study compared 0.1 mg/kg of methadone *versus* morphine diluted in a 10-ml syringe. Postoperative nausea and vomiting (PONV), PACU pain scores, and PACU length of stay were similar between groups, leading the authors to suggest that methadone may improve some recovery outcomes in laparoscopic cholecystectomy patients.

Although a prospective observational study by Petrosan *et al.*[24] reported an increase in milligram morphine equivalents (MME) at 24, 48, and 72 h in the methadone group compared to the nonmethadone control group (24 h [142.6 *vs.* 84.5; $P = 0.0026$], 48 h [119.7 *vs.* 64.3; $P = 0.0040$], and 72 h [116.1 *vs.* 55.2; $P = 0.0043$]), these results were confounded by the two nonmatched groups, which included more opioid-tolerant patients in the methadone group than the control group. In a subgroup analysis of opioid-naive patients, the methadone group had a significantly lower MME at 48 h (24 h [70.9 *vs.* 79.6; $P = 0.2278$], 48 h [42.4 *vs.* 59.7; $P = 0.0240$], and 72 h [38.5 *vs.* 50.9; $P = 0.1506$]) and daily pain scores at 24 h (4.5 *vs.* 5.1; $P = 0.0366$). The methadone group also had a lower discharge prescription MME (201.1 *vs.* 239.8, $P = 0.1257$).

Three additional studies highlight unique uses and considerations of methadone in the perioperative setting for patients undergoing surgeries with subsequent inpatient admission:

1. Mercadante *et al.*[21] conducted a randomized controlled trial in 60 patients undergoing open hysterosalpingectomy for gynecological cancer. Patients received either 0.15 mg/kg methadone preoperatively followed by a 12-mg/day methadone infusion postoperatively or 0.15 mg/kg morphine preoperatively followed by a similar morphine infusion (control group). The methadone group showed a 30% reduction in total opioid consumption without increased risk of adverse effects compared to the morphine group. Few studies have evaluated ongoing methadone use postoperatively for analgesia.
2. Esfahani *et al.*[25] compared 687 patients receiving oral methadone to 317 patients receiving intravenous (IV) methadone for multilevel spine surgery in a retrospective, noninferiority analysis. Oral methadone was noninferior to IV methadone in pain scores across all postoperative days and in postoperative opioid consumption on postoperative day 3. Substituting oral methadone for IV methadone could be a viable option where IV methadone is unavailable.
3. Murphy *et al.*[27] conducted a randomized, double-blind, placebo-controlled trial evaluating the combined effect of 0.2 mg/kg of methadone in addition to 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ of ketamine intraoperatively followed by 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ of ketamine postoperatively for the first 48 h *versus* methadone alone. They found a significant reduction in median (interquartile range) intravenous hydromorphone requirements in the methadone plus ketamine group on postoperative day 1 (2.0 [1.0 to 3.0] *vs.* 4.6 [3.2 to 6.6] mg in the methadone group; median difference [95% CI], 2.5 [1.8 to 3.3] mg; $P < 0.0001$) and lower overall consumption over 3 days compared to the methadone only group (11 [4.25 to 16] *vs.* 20 [12 to 30]; $P < 0.0001$). This study is of particular interest because it suggests that there is an additional opioid-sparing effect of ketamine to methadone. Moreover, there was no increase in adverse events by combining methadone with another opioid-sparing analgesic, even in the postoperative period. The specific contributions of methadone's NMDA antagonist effects *versus* its μ-agonist effects on postoperative analgesia remain unclear. The addition of ketamine, a known NMDA antagonist, appears to further enhance analgesia when used with methadone, which suggests that methadone's NMDA antagonist activity may be limited relative to ketamine.

Although these studies were small, none reported statistically significant differences in the incidence of severe respiratory depression, nausea/vomiting, or QT prolongation.

Methadone in Adult Same-day and Next-day Discharge Surgery

Four randomized controlled trials[28–31] investigated intraoperative methadone for adult same-day and next-day discharge surgery (table 3). Friesgaard *et al.*[28] and Green *et al.*[29] both demonstrated more effective pain control and reduced postoperative opioid consumption in patients receiving methadone (0.2 mg/kg ideal body weight methadone for laparoscopic hysterectomy *versus* 0.2 mg/kg morphine, and 0.15 mg/kg methadone with a maximum of 10 mg for gynecological laparoscopy *versus* as needed short-acting opioids, respectively). Patients who received methadone also reported lower pain scores and higher satisfaction toward their pain management.

Kharasch *et al.*[31] conducted a dose-finding RCT in 124 adults undergoing next-day discharge surgery (laparoscopic hysterectomy, laparoscopic hiatal hernia repair, or vaginal hysterectomy). Although they tested methadone doses of 0.1, 0.2, 0.25, and 0.3 mg/kg ideal body weight, all patients who received methadone demonstrated substantially decreased total in-hospital opioid use (25 [20 to 37], 20 [13 to 30], 27 [18 to 32], and 25 [20 to 36] mg, respectively, compared to 46 [33 to 59] mg in the control group) and lower home pain and opioid use compared to patients receiving shorter-duration opioids in the control group. Notably, the total opioid consumption for patients is inclusive of the methadone dose itself. The most effective and well tolerated single intraoperative induction dose

Table 3. Methadone in Adult Same-day and Next-day Discharge Surgery

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Komen *et al.*[30]	2019	March 2015 to May 2016	Randomized, double-blind, dose-finding pilot study	60 patients (with 2:1 randomization: 40 in the methadone group and 20 in the control group)	Adult laparoscopic cholecystectomy, tubal ligation, and salpingectomy/oophorectomy	0.1 mg/kg, 0.15 mg/kg on IBW (median dose was 6 mg for the 0.1 mg/kg group and 9 mg for the 0.15 mg/kg group)	Fentanyl, hydromorphone (at anesthesiologist's discretion)	Fentanyl, hydromorphone	0.15 mg/kg methadone group required significantly less postoperative opioids compared to the control group, while the 0.1 mg/kg group showed no significant difference	Pain scores were not significantly different between groups immediately postoperatively, but the 0.15 mg/kg methadone group had lower pain scores at rest at 30 days postdischarge		No significant differences in adverse effects such as nausea, vomiting, or respiratory depression were observed between the groups	Small sample size, lack of long-term follow-up
Friesgaard *et al.*[28]	2023	May 2019 to June 2022	Randomized double-blind controlled single-center study	127	Day-stay, elective, laparoscopic hysterectomy	0.2 mg/kg IV methadone given 60 min before extubation	0.2 mg/kg IV morphine given 60 min before extubation (anesthesia maintenance with propofol and remifentanil infusions)	IV morphine for moderate pain, oxycodone and fentanyl used for severe pain in PACU; oral morphine prescription for hospital discharge	Methadone compared with patients treated with morphine at 6 h (35.5 [0–61] mg *vs.* 48 [31–74.5] mg; *P* value = 0.01) and 24 h (42 [10–67] mg *vs.* 54.5 [31–83] mg; *P* value = 0.03); 18 of 64 patients treated with methadone required no opioids in the first 6 h as compared to 7 of 63 patients in the morphine group (*P* value = 0.01).	Pain at rest was significantly lower in methadone group on arrival to PACU (3 [2–5] *vs.* 5 [3–6]; *P* value = 0.01), whereas pain scores at rest and coughing were similar throughout the remaining observation period	No differences in patient satisfaction, time until hospital discharge, or rate of same-day discharge	No differences in PONV, sedation, respiratory depression (respiratory rate of less than 10 breaths/min, or hypoxia)	Small sample size (redefined due to COVID-19 pandemic), use of intraoperative remifentanil could lead to hyperalgesia, dose–response study was not performed before

(Continued)

Table 3. (Continued)

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Kharasch *et al.*[31]	2023	December 2014 to January 2018	Double-blind, randomized, dose-escalation feasibility and pilot study	124	Elective next-day discharge outpatient surgery (laparoscopic hysterectomy most common)	Single dose IV methadone (0.1 then 0.2, 0.25, and 0.3 mg/kg ideal body weight); average doses were 6, 11, 14, and 17 mg, respectively	As-needed short-duration opioid (fentanyl, hydromorphone, sufentanil, or morphine)	Fentanyl, hydromorphone	Lower PACU opioid consumption in the higher-dose methadone groups; lower in-hospital opioid use in the methadone groups compared to the short-duration opioid controls	Lower median pain scores were observed in patients receiving methadone, particularly in higher-dose groups (0.25 and 0.3 mg/kg)	Home pain and opioid use were numerically lower in patients receiving methadone	No significant differences in nausea, vomiting, or sedation between methadone and control groups; some minor instances of respiratory depression in PACU, which resolved without intervention	Small sample size, limited diversity of surgical population (majority females undergoing laparoscopic procedures), not all patients returned 30-day diaries
Green *et al.*[29]	2024	January 2021 to May 2022	Single-center, double-blind, randomized controlled trial	69	Same-day gynecological laparoscopy	10 mg at induction (0.15 mg/kg in smaller patients if less than 10 mg)	Short-acting opioid (fentanyl, morphine, or oxycodone)	Fentanyl, morphine, and oxycodone	Methadone group consumed 9.44 mg less OME than those receiving a short-acting opioid; hospital and discharge opioid consumption after 1 week did not differ	Pain scores were lower in the methadone group at all time points	Prescription of discharge opioids was relatively similar between groups	No differences in PACU respiratory depression, PONV, excess sedation, or clinically significant complications; no patients received naloxone for respiratory depression (though one methadone patient was given naloxone for PACU pruritus); one methadone patient had hypotension with bradycardia	Small sample size, anesthesiologists not blinded, no standard anesthetic management or discharge opioid prescribing practices

IBW, ideal body weight; IV, intravenous; OME, oral morphine equivalents; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting; VAS, visual analogue scale.

of methadone was 0.25 mg/kg ideal body weight (median, 14 mg) for next-day discharge surgery.

Komen *et al.*[30] conducted a similar dose-escalation study in 60 patients undergoing same-day ambulatory laparoscopic surgery (cholecystectomy, tubal ligation, salpingectomy with or without oophorectomy, or inguinal hernia repair). They started with single-dose intravenous methadone of 0.1 mg/kg ideal body weight with escalation to 0.15 mg/kg ideal body weight compared to conventional as-needed dosing of shorter duration opioids (*e.g.*, fentanyl, hydromorphone) in the control group. They only found a decrease in total opioid consumption in the PACU in subjects receiving 0.15 mg/kg methadone (0.1 mg [0.1 to 3.3]; $P < 0.001$) but not 0.1 mg/kg methadone (5.0 mg [3.3 to 8.1]; $P = 0.60$) as compared to the control group (9.3 mg [1.3 to 11.0]). However, total in-hospital opioid use was substantially lower in both methadone groups compared to control. Although in-hospital pain scores were not significantly different between groups, patients who received 0.15 mg/kg methadone had less pain at rest and fewer opioid pills used than controls at 30 days after discharge.

These studies provide dosing guidance for same-day and next-day surgeries. Taken in sum, this growing body of research suggests that methadone use for shorter-stay surgeries is both safe and effective.

Methadone in Adult Bariatric Surgery

Methadone's role in bariatric surgery is noteworthy due to the comorbidities in this patient population and the heightened risk of respiratory events associated with opioid use in patients with obesity.[32–34] However, if methadone can help reduce total opioid consumption and reduce pain without increasing adverse events, this may be an argument for using methadone in this population. Two key studies[35,36] provide insight into the use of methadone for bariatric patients (table 4).

da Silva *et al.*[35] conducted a retrospective study comparing three intraoperative analgesic strategies in 271 patients undergoing laparoscopic bariatric surgery. Methadone use was associated with a lower incidence of moderate-to-severe PACU pain scores (12.59% *vs.* 68.89% with sufentanil and remifentanil and 18.56% with sufentanil and dexmedetomidine) and reduced PONV (6.77% *vs.* 20.3% with sufentanil and remifentanil and 31.25% with sufentanil and dexmedetomidine; $P < 0.05$), although it also resulted in a higher incidence of intraoperative hypotension (39% *vs.* 17.46% with sufentanil and remifentanil and 20.31% with sufentanil and dexmedetomidine). The study's limitations include its retrospective before-and-after design, focus on PACU outcomes, lack of opioid consumption data, and the potential confounding effect of intraoperative remifentanil use, which may have influenced pain outcomes.

Pontes *et al.*[36] conducted a randomized controlled trial comparing intraoperative methadone (0.1 mg/kg lean body weight administered near the end of surgery) to morphine (0.1 mg/kg) in 137 patients undergoing laparoscopic gastroplasty. Methadone was associated with improved quality of recovery, as measured by the median total QoR-40 (194 [IQR, 190 to 197; range, 165 to 200] *vs.* 181 [IQR, 174 to 185.5; range, 121 to 200]); $P < 0.0001$), reduced opioid consumption, lower postoperative pain scores, decreased PONV, and shorter PACU stays. Additionally, after 3 months, they evaluated the same patients using the Short Form Health Survey, which showed similar findings except a greater "general health perception" in the methadone group.[37] Interestingly, they found a positive correlation between the pain subcomponent of QoR-40 score after surgery and global Short Form Health Survey score. However, the authors acknowledged that future trials are needed to evaluate the effect of methadone on long-term quality of life after surgery and likelihood of chronic postoperative pain. These findings support methadone as a viable option for enhancing the postoperative recovery in bariatric patients, who traditionally are thought of as high risk for respiratory depression and other adverse events.

Methadone in Adult Cardiac Surgery

Among the seven studies (five retrospective) on perioperative methadone use for adult cardiac surgery,[38–44] most focused on coronary artery bypass grafting surgery (table 5). Across these studies, methadone consistently improved postoperative analgesia, either by reducing postoperative opioid consumption (Wang *et al.*[39] and Bolton *et al.*[43]) or by decreasing both opioid use and pain scores (Murphy *et al.*,[38] Singh *et al.*,[40] Weinberg *et al.*,[41] Edwards *et al.*,[42] and Eisenbraun *et al.*[44]).

The impact of methadone on extubation times was mixed. Weinberg *et al.*[41] reported shorter extubation times with methadone, while Singh *et al.*[40] found slightly faster extubation times in patients not receiving methadone, likely influenced by variations in postoperative care. Wang *et al.*[39] and Edwards *et al.*[42] found no difference in extubation times.[39,42]

None of these studies reported differences in hospital or intensive care unit length of stay. Additionally, methadone use was not associated with higher rates of complications, such as naloxone use, QT prolongation, or PONV.

Two studies provided additional unique insights:

1. Murphy *et al.*[38] conducted a secondary analysis of two randomized, double-blind trials involving 135 complex spine patients and 156 cardiac surgery patients. Pain questionnaires assessed the weekly frequency and intensity of pain at 1, 3, 6, and 12 months after surgery. The methadone groups had reduced opioid requirements in the first 3 postoperative days, with a 60% decrease for spine surgery and a 43% decrease for cardiac surgery. Pain scores were also 30 to 40% reduced during the

Table 4. Methadone in Adult Bariatric Surgery

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Pontes *et al.*[36]	2021	Not reported	Prospective, parallel, randomized, double-blind controlled study	137	Laparoscopic bariatric surgery (Roux-en-Y or sleeve gastroplasty)	0.1 mg/kg methadone (lean body weight) at the end of surgery	Morphine (0.1 mg/kg)	Morphine	Methadone group required less rescue morphine in PACU and over the entire hospital stay	Methadone group had lower scores at rest and during movement	Methadone group had a shorter length of stay, lower incidence of nausea and vomiting, lower incidence of supplemental oxygen use, lower pain burden, lower dose of rescue morphine, and a lower sedation grade at admission and after 60 min; methadone group had a higher total QoR-40 score 24 h after surgery	No episodes of respiratory depression or cardiac arrhythmia in PACU	Use of intraoperative remifentanil could lead to hyperalgesia, patients followed for only 36 h after surgery
da Silva *et al.*[35]	2022	January 2014 to December 2019	Retrospective before-and-after study	271	Laparoscopic bariatric surgery (Roux-en-Y or sleeve gastroplasty)	0.2 mg/kg (actual body weight) up to 20 mg maximum + remifentanil infusion	The other two "control" groups either had: sufentanil–remifentanil–morphine or sufentanil–dexmedetomidine–morphine	Morphine	Not reported	Methadone group had a lower incidence of moderate/severe pain scores in PACU	Methadone group had a higher incidence of hypotension; nonmethadone groups had a higher incidence of PONV	One case of respiratory depression in the sufentanil–remifentanil–morphine group; no reintubations or other major complications were observed	Retrospective before-and-after study design, use of intraoperative remifentanil could lead to hyperalgesia, no follow-up beyond PACU, postoperative opioid consumption not assessed

IV, intravenous; PACU, postanesthesia care unit; QoR-40, Quality of Recovery Questionnaire; VAS, visual analogue scale.

Table 5. Methadone in Adult Cardiac Surgery

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Total Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Bolton *et al.*[43]	2019	2016	Randomized, double-blind, placebo-controlled pilot study	24	CABG	0.3 mg/kg orally	average 24 mg oral methadone	Sufentanil	Morphine	Methadone group required significantly less morphine in the first 24 h postoperatively	No significant differences	Not reported	No significant differences in opioid-related side effects such as nausea, vomiting, pruritus, hypoventilation, and hypoxia	Small sample size, pilot study design, limited generalizability due to exclusion of high-risk and opioid-tolerant patients, lack of long-term follow-up
Murphy *et al.*[38]	2020	Not reported	Secondary analysis of two randomized, double-blind clinical trials	135	Complex spine surgery and cardiac surgery	0.2 mg/kg (spine surgery); 0.3 mg/kg (cardiac surgery)	Surgery dependent	2 mg hydromorphone (spine surgery); 12 μg/kg fentanyl (cardiac surgery)	Hydromorphone for spine surgery; morphine for cardiac surgery	Methadone groups had reduced opioid requirements in the first 3 days postoperatively, with a decrease of 60% in opioid use for spine surgery and 43% for cardiac surgery	Methadone groups had greater pain reduction during the first 72 h postoperatively	Not reported	No significant differences in complications such as PONV, respiratory depression, sedation levels, pruritus, and urinary retention	Small sample size to detect adverse events, postoperative analgesic treatment not standardized, loss to follow-up
Wang *et al.*[39]	2022	April 2017 to August 2018	Retrospective review, single institution	117	CABG, valvular surgery, or both	0.1–0.4 mg/kg	Mean 0.22 mg/kg	Fentanyl, hydromorphone, morphine	Fentanyl, hydromorphone, morphine	Methadone group had lower median cumulative intraoperative opioid consumption	No significant differences	No significant differences in time to extubation, use of CPAP or BiPAP, or ICU and hospital length of stay	Not reported	Small sample size, retrospective study design, anesthetic management not standardized, methadone dosing not standardized

(Continued)

Table 5. (Continued)

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Total Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Eisenbraun *et al.*[44]	2023	2015–2019	Retrospective cohort study	4,326	Various cardiac surgeries	0.3 mg/kg	230 mg MME of methadone	Fentanyl (1–7 μg/kg bolus followed by 2 μg · $kg^{-1} \cdot h^{-1}$ infusion in opioid-based regimen; 250–500 μg/kg maximum in multimodal regimen 1)	Morphine, hydromorphone	Methadone group had reduced opioid requirements	Methadone group had lower pain scores in the first 6 h postoperatively	Methadone group had significantly reduced time to first bowel movement	No significant difference in PONV and time to tracheal extubation	Retrospective study design, residual confounding
Singh *et al.*[40]	2024	January 2018 to March 2023	Retrospective cohort study	1,338	CABG	0.2 mg/kg	Average 18.1 mg	Sufentanil, fentanyl, hydromorphone	Fentanyl, hydromorphone	Methadone group had lower opioid consumption with a faster decline in opioid use over first 2 postoperative days	Methadone group had statistically significant lower pain scores	Not reported	Methadone group had slightly longer time to extubation in the methadone group; no significant differences in respiratory depression	Retrospective study design, residual confounding, lack of blinding, postoperative analgesic treatment not standardized
Weinberg *et al.*[41]	2024	February 2019 to February 2022	Retrospective, multicenter observational study	175	CABG	0.1–0.2 mg/kg	10–20 mg	Fentanyl	Fentanyl, morphine	Methadone group had lower IV morphine use	Methadone group had lower pain scores in the first 24 h postoperatively	Not reported	No significant differences in postoperative complications, including respiratory depression, bleeding, arrhythmias, or infection	Small sample size, retrospective study design, single geographical region, limited generalizability due to exclusion of higher-risk surgeries

(Continued)

Table 5. (Continued)

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Total Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Edwards *et al.*[42]	2024	2018–2023	Retrospective cohort study	11,967	Cardiac surgery with cardiopulmonary bypass	Not specified	Not specified	Fentanyl	Not reported	Methadone had lower total opioid requirements	Methadone group had statistically lower pain scores	Not reported	No significant differences in pruritus, urinary retention, PONV, time to tracheal extubation, incidence of reintubation, naloxone use, QTc prolongation, and length of stay in ICU or in the hospital	Retrospective study design, residual confounding, limitations in generalizability

BiPAP, bilevel positive airway pressure; CABG, coronary artery bypass grafting; CPAP, continuous positive airway pressure; ICU, intensive care unit; IV, intravenous; MME, milligram morphine equivalents; PONV, postoperative nausea and vomiting; VAS, visual analogue scale.

first 72 h postoperatively. Notably, the methadone group experienced less chronic pain in the first 3 months after spine surgery and in the first month after cardiac surgery, suggesting a possible longer-term benefit.

2. Bolton *et al.*[43] conducted a randomized double-blind pilot study evaluating preoperative oral methadone (0.3 mg/kg) for coronary artery bypass grafting patients. While oral methadone did not significantly reduce overall pain scores compared to placebo, it did reduce postoperative morphine requirements in the first 24 h (mean difference [99% CI], −23 [37 to 13] mg; $P < 0.005$). This suggests that preoperative oral methadone may be an effective preemptive analgesic in cardiac surgery, particularly when IV methadone is unavailable.

Methadone in Pediatric Inpatient Surgery

As with adult inpatient surgeries, there have been a number of studies[45–48] investigating methadone for pediatric inpatient surgeries (table 6). The majority of these studies focus on particularly painful settings such as multilevel spinal fusion, Nuss procedure for pectus excavatum,[49] and patients with burn injuries.[50] Although methadone consistently lowers postoperative opioid requirements, it is not always associated with a concurrent decrease in pain scores. Interestingly, multidose strategies have been trialed and were shown to be efficacious and without adverse events in their respective cohorts.[45,46,48,51] Moreover, Sadhasivam *et al.*[51] measured the pharmacokinetic profile of children undergoing multidose methadone (0.1 mg/kg every 12 h for three to five doses) that resulted in opioid-sparing analgesia without increasing the risk of respiratory depression or QT prolongation.

Methadone in Pediatric Cardiac Surgery

Three retrospective studies[52–54] evaluated the impact of intraoperative methadone for pediatric cardiac surgery with cardiopulmonary bypass (table 7). Iguidbashian *et al.*[52] studied 24 children with anticipated early extubation after cardiac surgery. All patients received a multimodal analgesic regimen that included methadone (mean dose, 0.26 mg/kg; range, 0.23 to 0.29 mg/kg). None required intraoperative supplemental opioids, and 95% were extubated in the operating room. One child required postoperative bilevel positive airway pressure support, but none required reintubation. Limitations included the lack of a control group and the small, heterogeneous sample size (consisting of a wide age and weight ranges, and different types of cardiac surgeries).

Robinson *et al.*[53] conducted a case-matched cohort study of 37 children undergoing congenital heart disease surgery who received intraoperative methadone (0.1 to 0.4 mg/kg, maximum 30 mg, actual body weight), compared to 37 matched controls who did not but received other opioids. The methadone cohort required less opioids

Table 6. Methadone in Pediatric Inpatient Surgery

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Total Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Ye *et al.*[46]	2020	2012–2019	Retrospective matched cohort study	122	Posterior spinal fusion surgery for AIS	0.1 mg/kg administered intraoperatively, with additional doses every 12 h postoperatively for a total of three additional doses	Approximately 0.4 mg/kg over the course of the perioperative period	Intrathecal morphine (5 μg/kg)	Morphine, hydromorphone, oxycodone	Methadone group had a 30% reduction in total opioid consumption	Methadone group had higher postoperative pain scores on day 0 but lower postoperative pain scores on days 2 and 3	Methadone group had significantly shorter time to first bowel movement	No significant opioid-related adverse effects, including respiratory depression	Retrospective study design, minor changes to the analgesic protocol during implementation, lack of prospective data collection on patient satisfaction and mobility
Sadhasivam *et al.*[51]	2021	Not reported	Prospective pharmacokinetic study (no control group)	38	Posterior spinal fusion for idiopathic scoliosis or pyectus excavatum	0.1 mg/kg IV methadone (maximum 5 mg) for one dose intraoperatively; 0.1 mg/kg PO methadone x1 dose POD 0 evening; 0.1 mg/kg PO methadone for two doses q12 h on POD 1; 0.1 mg/kg PO methadone for one dose on POD 2 (three to five doses PO q12 h total)	Not reported	Not reported	Morphine, hydromorphone, oxycodone	Median morphine equivalent dose 0–72 h (mg) was 120.2 (98.5–131.8).	Pain scores (median, IQR) for postoperative days 1–5 were 3.5 (2.3–5.1), 3.4 (2.9–4.6), 3.7 (2.0–5.2), 3.8 (2.7–5.0), and 3.7 (3.3–4.4), respectively	None of the children had blood methadone concentration greater than 100 ng/ml	No respiratory depression or clinically significant QT prolongation; PONV occurred in 12 (of 38) patients, correlated with morphine equivalent dose	Small sample size, lack of direct randomized comparison, no control group, lack of free methadone concentration measurements
Froehling *et al.*[49]	2023	2018–2020	Retrospective cohort study	40	Nuss procedure for pectus excavatum repair	0.1 mg/kg	Not reported	Fentanyl	Morphine, hydromorphone	Methadone group had significantly reduced postoperative opioid requirements	Not reported	Not reported	No significant differences in respiratory depression, nausea and vomiting, and fever	Small sample size, retrospective study design, postoperative pain scores not reported, type of opioid used in control cohort not reported, variability in the type of regional anesthesia used

(Continued)

Table 6. (Continued)

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Total Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Shaw *et al.*[47]	2021	May 2016 to August 2019	Retrospective cohort study	167	Posterior spinal fusion for AIS	0.1 mg/kg	Average 29.5 MME	Sufentanil, remifentanil	Hydrocodone, oxycodone	No significant differences in total opioid usage during the hospital stay	No differences in VAS pain scores were reported at discharge	Methadone group had a slightly shorter length of stay	No significant opioid-related complications reported in either group	Retrospective study design, methadone dosing was not standardized, lack of continuous pain assessment
Carlson *et al.*[50]	2022	January 2017 to November 2020	Retrospective cohort study	60	Tangential excision and grafting in pediatric burn wounds	Median dose of 0.16 mg/kg intraoperatively	Not reported	Fentanyl, morphine, hydromorphone	Morphine, fentanyl	Methadone group had decreased opioid consumption in the first 36 h	Not directly reported	Not reported	No significant differences in QTc, arrhythmia, respiratory depression	Small sample size, retrospective study design, inability to measure direct pain scores
Mok *et al.*[48]	2022	2015–2020	Retrospective case series	87	Posterior spinal fusion surgery for AIS	Group PCA + methadone: 0.2 mg/kg IV methadone; group methadone: 0.2 mg/kg IV methadone, 0.1 mg/kg IV methadone in PACU, and additional doses as needed	Not reported	Fentanyl, remifentanil	Hydromorphone	Methadone group (without PCA) used significantly less opioid compared to the PCA groups, with a 45% reduction in opioid usage	No significant differences in pain scores	Not reported	No significant opioid-related complications were reported; three patients in the methadone group had doses held due to sedation	Small sample size, retrospective study design, incomplete data, unequal group sizes, variable pain assessments
Fons *et al.*[45]	2024	February 2016 to October 2021	Double-blind, randomized controlled trial	47	Posterior spinal fusion involving at least 10 levels	Two doses of 0.1 mg/kg (maximum of 10 mg/dose)	Maximum 20 mg/patient	Morphine (0.1 mg/kg, maximum 10 mg before wound closure)	Morphine, hydromorphone	Methadone group consumed less total opioid postoperatively	No significant difference in pain scores	Not reported	No significant differences in side effects such as pruritus, vomiting, low pulse oximetry, or sedation; no patients required naloxone or intubation for respiratory depression	Small sample size, limited generalizability, lack of long-term follow-up, no measurement of blood methadone concentrations

AIS, adolescent idiopathic scoliosis; IQR, interquartile range; IV, intravenous; MME, milligram morphine equivalents; PCA, patient-controlled analgesia; POD, postoperative day; PONV, postoperative nausea and vomiting; VAS, visual analogue scale.

Table 7. Methadone in Pediatric Cardiac Surgery

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Dose of Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
Iguidbashian *et al.*[52]	2020	Not reported	Retrospective case series, single institution	24	0.23–0.29 mg/kg	No control group	Fentanyl, morphine, oxycodone	All children who received methadone did not require intraoperative supplemental opioids; median time to first supplemental opioid administration was 5.1 h	Not reported	96% were extubated in the OR	One child required postop BiPAP but none required reintubation	Small sample size, retrospective study design, no control group, heterogenous ages and weights, heterogenous cardiac surgeries, postoperative pain scores not assessed
Robinson *et al.*[53]	2020	November 1, 2017, to July 30, 2018	Single-center, retrospective, case-match cohort study	74	0.1–0.4 mg/kg (maximum 30 mg) based on actual body weight at the beginning of the case with repeat doses given in some cases	Not reported	Fentanyl, morphine oxycodone	Methadone group required less opioids intraoperatively and postoperatively	No significant difference in postoperative pain scores	Methadone group had fewer admissions to the CICU; no differences in time to extubation, duration of ICU stay, and PONV	Methadone group was not associated with a higher incidence of extubation failure, QTc prolongation, or in-hospital mortality	Small sample size, retrospective study design, no control group, intraoperative and postoperative analgesic treatments not standardized, potential for selection bias regarding higher doses of methadone
Barnett *et al.*[54]	2020	2017–2018	Retrospective chart review	198	Up to 0.4 mg/kg intraoperatively	Fentanyl (bolus and infusion, titrated to effect)	Morphine, hydromorphone	Methadone group had reduced analgesic requirements in the first 24 h postoperatively	No significant difference in pain scores	Not reported	No significant differences in extubation time or sedation scores; non-neonates in the methadone group had lower sedation	Retrospective study design, anesthetic management not standardized, postoperative analgesic treatment not standardized, postoperative extubation parameters not standardized, postoperative fentanyl infusions in neonates potentially negated methadone benefits

BiPAP, bilevel positive airway pressure; CICU, cardiac intensive care unit; ICU, intensive care unit; IV, intravenous; OR, operating room; PONV, postoperative nausea and vomiting; VAS, visual analogue scale.

intraoperatively and postoperatively, with no increase in extubation failure, QT prolongation, or in-hospital mortality. However, no dose-dependent reduction in opioid consumption was seen between high- and low-dose methadone groups, likely due to the small sample size. Other limitations included nonstandardized intraoperative analgesic regimens and the potential for selection bias for higher methadone doses in some patients.

Barnett *et al.*[54] implemented a practice change and compared cardiac patients before and after introducing intraoperative methadone. Among 44 neonates, the methadone group required significantly lower doses of intraoperative opioids (median [IQR], 1 [0.8 to 3] MME/kg in the methadone group *vs.* 3 [2 to 4] MME/kg in the control group; 95% CI, 0.4 to 2; $P = 0.01$), although postoperative opioid use did not differ significantly (3 [1 to 4] MME/kg in the methadone group *vs.* 3 [3 to 5] MME/kg in the control group; 95% CI, −0.4 to 2; $P = 0.11$). Non-neonates (more than 30 days old) demonstrated significantly reduced opioid use both intraoperatively (0.7 [0.6 to 0.9] MME/kg in the methadone group *vs.* 2 [1 to 2] MME/kg in the control group; 95% CI, 0.6 to 1; $P < 0.001$) and in the first 24 h postoperatively (0.4 [0.2 to 2] MME/kg in the methadone group *vs.* 0.8 [0.3 to 3] MME/kg in the control group; 95% CI, 0.03 to 0.5; $P = 0.02$). There were no significant differences in extubation times, extubation rates, or sedation scores, although non-neonates in the methadone group had lower rates of sedation.

These findings suggest that methadone may enhance recovery in pediatric cardiac surgery. Further prospective randomized controlled trials are needed to assess safety and optimal dosing.

Methadone in Pediatric Ambulatory Surgery

Methadone use in pediatric ambulatory surgeries poses a challenge, given the potential risks of respiratory depression with use of any intraoperative opioids, particularly in shorter surgeries with airway obstruction risk factors. Two studies[55,56] highlight the feasibility of using methadone (0.15 mg/kg) to enhance recovery (table 8).

Einhorn *et al.*[55] conducted a randomized double-blind trial evaluating the efficacy of single-dose intraoperative methadone (0.1 mg/kg and then 0.15 mg/kg age-ideal body weight, in a dose escalation paradigm) compared to fentanyl in pediatric total tonsillectomy with or without adenoidectomy. Methadone significantly reduced 7-day opioid use, with the 0.15-mg/kg group showing the lowest need for postoperative opioids (median oral morphine equivalents/kg [IQR]: 0.9 [0.1 to 1.4; $P = 0.045$] in the 0.1-mg/kg methadone group *vs.* 0.5 [0 to 1.4; $P = 0.023$] in the 0.15-mg/kg methadone group *vs.* 1.5 [1.2 to 2.1] in the control group). While postoperative pain scores were similar between groups, PACU opioid consumption was lower in the methadone groups (median oral morphine equivalents [IQR]: 0.04 [0 to 0.1]; $P = 0.061$) in the 0.1-mg/kg methadone group *vs.* 0.0 [0 to 0.1; $P = 0.021$] in the 0.15-mg/kg methadone group *vs.* 0.15 [0.1, 0.3] in the control group). Importantly, no serious opioid-related adverse events occurred despite the increased risk factors for airway obstruction in this patient population.

Dajani *et al.*[56] explored the use of methadone (0.15 mg/kg) for managing emergence delirium in pediatric ambulatory strabismus surgery in a prospective, controlled, before-and-after study. Compared to the control group, which received intraoperative fentanyl, the methadone group showed 42 and 85% reductions in peak and severe Pediatric Anesthesia Emergence Delirium scale scores, respectively, in the PACU and required less rescue analgesia. No significant postoperative complications were observed. This study is limited in that the study was not randomized so there may be unaddressed confounders between the two groups.

Both studies suggest that methadone may improve recovery outcomes in pediatric ambulatory surgeries. Moreover same-day discharge after methadone in these small cohorts did not surface any safety concerns. The study by Einhorn *et al.*[55] in particular addresses this, given the 7-day ongoing follow-up and tracking of postoperative pain and opioid use.

Methadone Safety

Clinicians considering the use of methadone often have three main concerns: (1) respiratory depression, (2) QT prolongation and arrhythmia, and (3) interpatient variability. Definitive studies to address these concerns are lacking and, although feasible, would likely require larger multicenter trials; however, some progress has been made in addressing these areas.

Respiratory Depression

Two recent studies[13,14] evaluated the safety of methadone with respect to respiratory depression (table 9). Although both are single-center retrospective studies, they adjust for potential confounders. Lumsden *et al.*[13] used propensity score matching and found that among 337 patients who had received methadone, the likelihood of receiving naloxone was not different compared to 674 matched patients who received other opioids (two patients [0.6%] in the methadone group *vs.* one patient [0.1%] in the control group; $P = 0.22$).

Carlé *et al.*[14] analyzed 14,522 patients, including 2,437 patients who received methadone and 12,085 who received morphine. Using inverse probability of treatment weighting to adjust for confounding, they found no significant difference in naloxone use for respiratory depression in the first 24 h postoperatively. In the methadone group, 15 of 2,437 (0.62%) patients received naloxone, compared to 68 of 12,085 (0.56%) patients in the morphine group. However, patients who received intraoperative methadone experienced a significantly shorter interval from extubation to

Table 8. Methadone in Pediatric Ambulatory Surgery

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Total Methadone	Intraoperative Opioid Used in the Control Group	IV Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Postoperative Complications	Limitations of the Study Design
Einhorn *et al.*[55]	2024	April 2022 to May 2023	Randomized, double-blind, parallel-group, dose-escalation trial	60	Pediatric total tonsillectomy with or without adenoidectomy	0.1 mg/kg, 0.15 mg/kg on IBW	Median doses were 1.7 mg (0.1 mg/kg) and 2.3 mg (0.15 mg/kg)	Fentanyl (as needed)	Oxycodone	Methadone groups required less total 7-day opioid use compared to the control group, with the 0.15 mg/kg group showing the lowest requirement	No significant difference in pain scores	No serious opioid-related adverse events occurred; minor complications like transient desaturations and vomiting were similar across groups	Small sample size, limited age-specific conclusions, no differentiation between PACU and post-PACU opioid consumption
Dajani *et al.*[56]	2024	Jan 2018 to Aug 2019	Prospective, controlled, before-and-after study	104	Pediatric strabismus surgery	0.15 mg/kg	Average 3 mg	Fentanyl	Not reported	Methadone group exhibited lower peak PAED scores	No pain scores recorded for non-methadone group	No significant differences in PONV and respiratory depression	Not randomized, not blinded, postoperative pain scores not assessed for control group limiting comparisons

IBW, ideal body weight; IV, intravenous; PACU, postanesthesia care unit; PAED, Pediatric Anesthesia Emergence Delirium; PONV, postoperative nausea and vomiting; VAS, visual analogue scale.

Table 9. Methadone and Respiratory Depression

Study	Date of Publication	Study Years	Trial Design	Enrolled, No.	Type of Surgery	Dose of Methadone	Intraoperative Opioid Used in the Control Group	IV opioid Used Postoperatively	Postoperative Complications	Limitations of the Study Design
Lumsden *et al.*[13]	2024	April 1, 2016, to July 1, 2022	Single-center, retrospective chart review	29,303	All surgeries with anticipated inpatient postoperative admission and surgical duration greater than 2 h	Mean dose was 9 mg (SD 4 mg)	Not reported	Not reported	No significant difference in naloxone administration	Retrospective study design, multivariable logistic regression model could not be fitted given the limited number of events, lack of standard to guide methadone use *versus* other opioids, lack of information characterizing severe cases of respiratory depression, potential for unmeasured confounding factors
Carlé *et al.*[14]	2024	March 2019 to March 2023	Retrospective cohort study	14,522	Various surgeries	0.16 mg/kg	Morphine	Morphine	No significant difference in the incidence of naloxone administration; methadone group spent more time in the PACU	Retrospective study design, incidence of primary outcome (naloxone administration) was rare leading to a wide CI, use of proxy variables (PACU length of stay) for sedation, potential for unmeasured confounding factors

IV, intravenous; PACU, postanesthesia care unit; VAS, visual analogue scale.

naloxone administration (98 min, SD 153) compared to the morphine group (247 min, SD 332). Taken together, when methadone is compared to other opioids, the risk of severe respiratory depression requiring naloxone is similar.

QT Prolongation

Many of the studies mentioned in this review assessed for QT prolongation and arrhythmia but did not find significant differences between patients who received methadone and those who did not. However, QT monitoring was inconsistently performed across studies. Therefore, we explored additional literature beyond the intraoperative and perioperative contexts, focusing on methadone's use in other contexts[57] including cancer pain,[58] infants,[59] and concomitant use with atypical antipsychotics in critically ill children.[60] In these scenarios, QT prolongation was not significantly increased with methadone use.

In contrast, the study of Schwinghammer *et al.*[61] found that half of the 89 pediatric inpatients studied over a 7.5-yr period had documentation of QT prolongation when methadone was used for opioid withdrawal. No patients developed torsades de pointes arrhythmia. Looking more closely, patients who had prolonged QT intervals had longer methadone courses (median [IQR], 29 [18 to 67] days) compared to patients who did not have prolonged corrected QT intervals (17 [9.8 to 25] days). Patients who had prolonged corrected QT intervals also had higher maximum doses (0.69 [0.40 to 1.13] mg · kg^{-1} · day^{-1}) compared to patients who did not have prolonged corrected QT intervals (0.44 [0.32 to 0.75] mg · kg^{-1} · day^{-1}).

By comparison, the perioperative dose of methadone used by most other studies ranges from 0.1 to 0.4 mg · kg^{-1} · day^{-1}. These findings suggest that a single intraoperative dose of methadone or a short course of methadone in the immediate perioperative period is unlikely to cause significant QT prolongation and subsequent cardiac arrhythmia. However, its chronic use is associated with QT prolongation, and electrocardiographic monitoring may help identify patients who are at risk for arrhythmia.

The combination of methadone and other routinely used perioperative medications that may prolong the QT interval, such as ondansetron, has not been specifically studied. Nonetheless, ondansetron is frequently given intraoperatively and postoperatively to prevent postoperative nausea and vomiting in many of the studies on intraoperative methadone. The studies cited in this review, as well as previous studies, do not suggest that routine use of ondansetron with methadone increases the risk of QT prolongation or arrhythmia.

An additional area of interest is use of the (*R*)-enantiomer of methadone, levomethadone, which has been used clinically in Europe. McCance-Katz[62] calls attention to the distinction that levomethadone may offer lower effective doses but acknowledges that Food and Drug Administration (Bethesda, Maryland) approval in the United States is

a major barrier. Santin *et al.*[63] found that in a cohort of patients using the racemic formulation of methadone, 14% of 165 subjects in their sample taking methadone for opioid use disorder had QT prolongation. Of the patients who were switched to levomethadone, 90% of these patients had normalization of their QT interval. This suggests that should levomethadone become available more widely, it would likely confer an additional safety margin over the racemic methadone formulation.

Methadone Pharmacokinetic and Pharmacogenomic Variability

Methadone is primarily cleared by P450 (CYP)–catalyzed *N*-demethylation. Differences in CYP2B6 allelic variants affect plasma metabolism and clearance such that patients with slower rates of elimination have higher methadone concentrations, whereas others have lower methadone concentrations in the setting of faster elimination rates. Numerous pharmacokinetic and pharmacogenomic studies in both adults and children have explored the impact of genetic variations in CYP2B6, characterizing variability at both the interindividual and intraindividual levels.[64–69] Additionally, CYP2B6 also metabolizes other opioids including codeine, tramadol, hydrocodone, and oxycodone.

Drug–drug interactions that induce or inhibit CYP2B6 can further influence plasma concentrations of methadone. In a pharmacoepidemiologic screening study, Miano *et al.*[70] demonstrated weak to moderate interactions between methadone and certain drugs (including gabapentinoids, baclofen, benzodiazepines, methocarbamol, quetiapine, and simvastatin) in a large claims database. However, given the correlational nature of this type of study, further confirmatory studies are needed to determine truly harmful drug–drug interactions.

Obesity can also have an impact on both drug metabolism and pharmacokinetics, which was explored by Gerhart *et al.*[71] in a modeling study that suggested that CYP2B6 variant in addition to obesity may only require half the predicted dose of methadone to match the exposure of wild-type children without obesity. However, since this was a modeling study, further clinical pharmacokinetic studies are needed to confirm these findings.

Conclusions

Despite methadone's long history of use in many clinical settings, such as for neonatal opioid withdrawal syndrome, medication-assisted treatment for opioid use disorder, and cancer pain management in adults and pediatrics, its intraoperative use is less common compared to other opioids. Intraoperative methadone is often administered alongside multimodal analgesics including other sedatives and opioids. Although this may lead to synergistic effects that raise the risk of sedation, respiratory depression, drug interactions, and other adverse outcomes, these considerations are no different for the use of any other opioids.[72–74] In fact, fentanyl, hydromorphone, and oxycodone are often combined with benzodiazepines, inhaled or intravenous anesthetic agents, and other sedatives to achieve a "balanced" anesthetic. While prospective randomized controlled trials are the gold standard in clinical research, this review also incorporates a range of retrospective studies to highlight the use of methadone in unique patient subpopulations. Similar to the findings of the 2019 CFR,[1] our review concludes that intraoperative methadone is associated with reduced total postoperative opioid requirements (which are inclusive of methadone as an opioid itself) without increasing opioid-related side effects.

Most studies conducted since 2019 remain retrospective in nature; however, six larger randomized, controlled studies (each with greater than 100 subjects) have further confirmed the efficacy of methadone in the perioperative period. Regarding safety, RCTs primarily evaluating efficacy may be underpowered to detect rare occurrences such as respiratory depression or respiratory failure requiring naloxone reversal. Similarly, QT prolongation and cardiac arrhythmias are also rare. Prospective RCTs addressing these outcomes would require a direct comparison to the risks associated with other opioids in a large multicenter trial, which would require overcoming logistical and funding barriers.

Although a definitive safety profile of intraoperative methadone use continues to be investigated, current retrospective cohorts and prospective randomized trials have not identified significant concerns, particularly regarding respiratory depression, QT prolongation, and its use within multimodal analgesic regimens. The available data suggest that clinically effective doses of methadone do not present any alarming safety signals. When used at clinically appropriate doses, methadone does not appear to have a different safety profile than other appropriately dosed opioids. However, large database studies could help further evaluate the relationship between the efficacy of different methadone doses and their incidence of adverse events.

Practically, available studies indicate that a dose as low as 0.1 mg/kg of intravenous methadone may provide analgesic benefits, although doses up to 0.3 mg/kg may be necessary depending on the expected pain severity of a procedure. For outpatient surgeries, including in pediatrics, a dose of 0.15 mg/kg of IV methadone may mitigate concerns regarding the synergistic effects of other postoperative opioids or sedatives such as dexmedetomidine. With respect to the timing of when to dose intraoperative methadone, there continues to be variability in dosing strategies. These range from dosing at the time of induction of anesthesia (to achieve peak plasma concentration by time of incision and to have the peak respiratory depression coincide with a time during which the patient is still under general anesthesia), to 1 h before extubation (to maximize the postoperative analgesic effects while also avoiding the respiratory

depressive peak), to giving methadone as the primary postoperative analgesic. As referenced in the 2019 CFR, lower doses of methadone may not confer long-lasting analgesia beyond 4 to 6 h. Thus, redosing methadone may be necessary to maintain a minimum effective concentration. The seminal 1984 study by Gourlay *et al.*[4] used a postoperative dosing regimen of 2.5, 5, or 10 mg IV methadone at intervals of more than 45 min as needed for pain as long as the patient's respiratory rate was greater than 10 breaths/min and there was no depression of level of consciousness. Since 2019, only a couple of studies have sought to readdress repeated doses of methadone in the perioperative period,[21,51] while the majority describe a single bolus dose of methadone intraoperatively.

Some research questions remain from the 2019 review by Murphy and Szokol.[1] There continues to be a need for clinical pharmacogenomic studies to better predict the variability in patients' response to methadone due to differences in enzyme expression and body habitus. A definitive answer on whether intraoperative methadone reduces the risk of chronic postsurgical pain is also unclear, but the 2020 long-term follow-up study by Murphy *et al.*[38] and the 3-month follow-up correspondence by Pontes *et al.*[37] suggest that there may be a positive effect. In addition, recommendations for intraoperative methadone use in opioid-tolerant patients (*e.g.*, patients with chronic pain on opioids or patients on medication-assisted treatment for opioid use disorder) are challenging, and few evidence-based guidance exists at present. Most pain management specialists would recommend continuing a patient's "basal" methadone or chronic opioid therapy and using additional analgesic modalities to treat acute postoperative pain.[75,76] Further study of this patient population is needed to ensure both their safety and comfort since opioid-tolerant patients are at higher risk of both inadequate analgesia and adverse events.

Overall, research on intraoperative methadone suggests that it provides multiple benefits over standard opioids for various surgeries, including reduced total perioperative opioid consumption and need for analgesic rescue, potentially lower postoperative pain scores, reduced postoperative emergence delirium and nausea and vomiting, improved quality of recovery, lower incidence of chronic pain, and faster extubation times, without any additional risks. The use of intraoperative methadone should be strongly considered in place of other opioids by anesthesiologists as part of routine multimodal analgesic strategies.

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Competing Interests

Dr. Xie is a consulting medical advisor for Develo, Inc. (Los Angeles, California), and Taiwan Liposome Co. (Taipei, Taiwan) and medical advisor and cofounder of AfaSci Therapeutics (Redwood City, California). The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental Table 1. Quantitative opioid consumption reported by study in morphine milligram equivalents (MME), https://links.lww.com/ALN/D996

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ANESTHESIOLOGY®

Potential Benefits of Medical Nutrition Therapy for Timely Ventilator Weaning in the Critically Ill

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ABSTRACT

Nutritional support and metabolic assessment are crucial in weaning from invasive mechanical ventilation. This review explores strategies for metabolic assessment and tailored nutritional interventions and their impact on weaning outcomes, highlighting individualized nutritional interventions. While indirect calorimetry provides direct metabolic data, diaphragm ultrasound can complement metabolic monitoring by assessing respiratory muscle function and detecting early signs of muscle wasting. Protein intake in critically ill patients remains controversial, as early high protein administration (greater than 1.2 g/kg each day) has not demonstrated clear benefits and may even be detrimental to successful ventilator weaning, supporting the adoption of a moderate, individualized nutritional strategy. Vitamin D deficiency is common in critically ill patients, and targeted supplementation may reduce mechanical ventilation duration. High-fat and ketogenic diets have shown limited benefit and are not currently recommended. Some nutritional supplements (*e.g.*, creatine, branched-chain amino acids, β-hydroxy-β-methylbutyrate) are under investigation, but current evidence does not support their routine use. A personalized approach integrating metabolic assessment, tailored protein intake, and vitamin D optimization may improve weaning success, functional recovery, and post–intensive care unit outcomes. Further research is needed to refine evidence-based guidelines.

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Nutritional support, guided by careful metabolic evaluation, plays a crucial role in the challenging process of weaning patients from invasive mechanical ventilation. During the transition off ventilatory support, adequate nutrition becomes essential to sustain respiratory function and promote recovery. However, the effectiveness of medical nutrition therapy can be significantly diminished by the presence of infection and inflammation.[1] When these conditions are not adequately controlled, the resulting catabolic state accelerates muscle protein loss, which in turn hampers weaning efforts.[2] Early and effective management of infection and inflammation is therefore key to minimizing muscle degradation and increasing the likelihood of successful weaning.[3]

It is important to recognize that while medical nutrition therapy is a critical component of supportive care, it remains an adjuvant therapy. It does not address the underlying causes of respiratory failure or the primary indications for mechanical ventilation. Despite the recognized importance of nutritional support in critical care, specific discussion and research on how to optimize nutritional strategies during the weaning phase remain limited in the current literature.[4,5] Undernutrition, particularly in underweight patients, may impair ventilatory drive and should be addressed as part of the weaning strategy.[6] However, nutrition in the intensive care setting is often inadequately personalized to meet the metabolic demands of critically ill patients—especially during the demanding phase of ventilator weaning. This process requires precise metabolic assessment and customized nutritional support, including tailored intake of calories, protein, and fat.

Just as proper nutritional support is essential to sustain physical exertion in any physically demanding context, patients undergoing weaning from invasive mechanical ventilation must receive targeted nutritional strategies to support this intense physiologic effort.[7] In this narrative review, we present an updated synthesis of current evidence on metabolic assessment and nutritional requirements during the weaning process. We also propose a six-step expert-guided approach aimed at optimizing nutritional support and improving weaning outcomes in critically ill patients.

This article is featured in "This Month in ANESTHESIOLOGY," page A1. This article is accompanied by an editorial on p. 501.

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Abbreviations: ICU, intensive care unit; **RCT**, randomized controlled trial

Nutritional Strategies during the Acute and Weaning Phases: Key Evidence and Principles

The nutritional approach in critically ill patients varies significantly between the acute and recovery phases.[8] During the early phase of critical illness, permissive underfeeding has been associated with better outcomes and fewer metabolic complications, as supported by large, randomized trials such as EPaNIC (Early *vs.* Late Parenteral Nutrition Completing Enteral Nutrition Study),[9] EDEN (Initial Trophic *vs.* Full Enteral Feeding in Patients with Acute Lung Injury Study),[10] and NUTRIREA-3 (Impact of Early Low-Calorie Low-Protein *vs.* Standard Feeding on Outcomes of Ventilated Adults with Shock).[11] These studies recommend cautious initiation of caloric intake (typically 12 to 25 kcal/kg each day) and avoidance of early high-protein administration.

In contrast, during the recovery and weaning phases, energy and protein needs progressively increase. Nevertheless, recent trials (EFFORT-Protein [Effect of Higher Protein Dosing in Critically Ill Patients],[12] and PRECISe [PRotEin Provision in Critical IllneSs],[13] EAT-ICU [Early Goal-Directed Nutrition in ICU Patients][14]) have challenged the routine use of high protein intake (greater than 2.0 g/kg each day), showing no clinical benefit and potential harm in certain patient subgroups. These findings support an individualized, moderate-protein approach (0.8 to 1.2 g/kg each day) tailored to metabolic tolerance and illness severity.

Understanding these principles is essential to guide nutritional therapy during ventilator weaning. The following sections outline key areas for consideration, each addressing a specific component of the nutritional strategy.

Key Consideration 1: Consider Serial Indirect Calorimetry for Measurement of Resting Energy Expenditure and Definition of Caloric Targets in Patients Requiring Invasive Mechanical Ventilation

Phases of the Metabolic Response and Nutritional Strategy

The metabolic response to critical illness evolves over time and can be divided into three main phases[15]: (1) the acute phase, characterized by systemic inflammation, catabolism, and metabolic instability; (2) the early recovery phase, during which inflammation decreases and metabolic demand increases; and (3) the late recovery or anabolic phase, in which the patient gradually restores lean body mass and functional capacity.[16] Nutritional strategies should be adapted accordingly. During the acute phase, evidence from large, randomized trials (EPaNIC,[9] EDEN,[10] and NUTRIREA-3[11]) supports the use of permissive underfeeding, with caloric intake below measured or estimated resting energy expenditure, typically between 12 and 25 kcal/kg each day, to avoid overfeeding-related complications and to promote better clinical outcomes, including earlier weaning. In the recovery phase, caloric intake should progressively increase to match resting energy expenditure and meet the patient's growing anabolic needs.[17]

Role and Limitations of Indirect Calorimetry in Critically Ill Patients

Resting energy expenditure reflects the energy required to sustain essential metabolic functions at rest.[18] In critically ill patients, resting energy expenditure is highly variable due to continuous nutritional delivery, sedation, inflammation, hemodynamic instability, and metabolic stress.[19,20] Predictive equations for estimating resting energy expenditure are unreliable in this setting. Indirect calorimetry is the reference method for measuring resting energy expenditure in critically ill patients, as it quantifies oxygen consumption and carbon dioxide production,[21] providing individualized metabolic data and insights into substrate utilization (table 1).[18] Additionally, indirect calorimetry allows calculation of the respiratory quotient, defined as the ratio of carbon dioxide production to oxygen consumption, which reflects the predominant substrate being metabolized (carbohydrates, fats, or proteins). Indirect calorimetry can be performed both during invasive mechanical ventilation and in spontaneously breathing patients. In ventilated patients, indirect calorimetry is integrated into the ventilator circuit to measure inspired and expired gas flows.[22] In spontaneously breathing patients, indirect calorimetry is typically performed using an open-circuit indirect calorimetry system, which employs either a canopy hood or a face mask connected to a metabolic cart to continuously measure oxygen consumption and carbon dioxide production.[22]

Although indirect calorimetry is the most accurate method for assessing resting energy expenditure, its clinical use is not without limitations. Several factors may affect the accuracy and interpretation of indirect calorimetry–derived data, including patient instability, ventilator settings, fractional inspired oxygen tension levels, temperature, sedation, inflammatory status, and device calibration. Moreover, indirect calorimetry provides an estimate of energy expenditure but does not directly dictate caloric targets, particularly during the acute phase.[22] Other variables that should be considered when defining nutritional needs include the phase of metabolic response to critical illness, degree of systemic inflammation, presence of infection or sepsis, organ dysfunction, nutritional status at baseline, and individual metabolic tolerance to nutrient administration.[22]

Current evidence does not support the routine use of indirect calorimetry–guided feeding strategies to improve clinical outcomes. Large trials and meta-analyses have shown that targeting full caloric intake based on measured resting energy expenditure in the early phase does not improve—and may even prolong—the duration of mechanical ventilation (table 2).[23]

One possible explanation for these negative findings is that previous trials may not have adequately accounted for

Table 1. Fundamentals of Indirect Calorimetry

Concept	Description
Definition	Noninvasive method to measure energy expenditure based on VO_2 and VCO_2
Principle	Uses respiratory gas exchange to estimate metabolic rate, assuming that oxygen consumption and CO_2 production correlate with energy metabolism
Measured parameters	VO_2: oxygen consumption VCO_2: carbon dioxide production RQ: VCO_2/VO_2 REE: Calculated from gas exchange data
Types of IC systems	Open-circuit systems: Measure exhaled gas composition Closed-circuit systems: Use a sealed environment where oxygen consumption is measured directly
Applications in clinical practice	Determining energy needs for critically ill patients Assessing substrate utilization (carbohydrates, fats, and proteins) Optimizing nutritional support to avoid underfeeding or overfeeding Monitoring metabolic adaptations in ICU patients
Limitations	Expensive and requires trained personnel Errors due to improper calibration or unstable patient conditions Affected by factors such as leaks in ventilator circuits, FIO_2 variability, and hemodynamic instability

FIO_2, fraction of inspired oxygen; IC, indirect calorimetry; ICU, intensive care unit; REE, resting energy expenditure; RQ, respiratory quotient; VCO_2, carbon dioxide production; VO_2, oxygen consumption.

Table 2. Checklist for Reliable Indirect Calorimetry Measurements

Item	Requirement for Accurate Measurement
Equipment calibration	Ensure the IC device is calibrated before each use; regular maintenance is required
Patient condition	Patient should be in a steady-state condition: no recent movement, no rapid changes in ventilator settings, and stable hemodynamics
Measurement environment	Minimize external disturbances (*e.g.*, avoid talking, handling, or interventions during the measurement)
Ventilator settings	Ensure a stable FIO_2 (preferably less than 60%) for accurate CO_2 measurement Verify that the ventilator circuit is leak-free to prevent measurement errors
Duration of measurement	Conduct the measurement for at least 5–10 min to obtain a stable REE value
Interpretation of data	Check for physiologic plausibility of the results Compare with clinical expectations and adjust MNT accordingly
Repeatability	If abnormal values are obtained, repeat the measurement to confirm accuracy
Staff training	Ensure that personnel using IC are trained to handle equipment, recognize errors, and interpret results properly

FIO_2, fraction of inspired oxygen; IC, indirect calorimetry; MNT, medical nutrition therapy; REE, resting energy expenditure.

individual differences in metabolic tolerance and substrate utilization when defining nutritional strategies. However, this remains a hypothesis and warrants further investigation.

Nonetheless, indirect calorimetry may remain a valuable tool in selected patients, particularly those with prolonged intensive care unit (ICU) stays, difficult weaning, or conditions associated with unpredictable energy needs.

Calorimetry measurements may help monitor metabolic changes over time and guide ongoing adjustments in nutritional support during recovery.[22] Recent technological advancements have made indirect calorimetry faster and more accessible, allowing accurate measurements even in patients requiring high oxygen support or renal replacement therapy.[24]

In summary, indirect calorimetry is an important tool for metabolic assessment in critically ill patients, but its use in clinical practice should be integrated into a broader strategy that accounts for the phases of the metabolic response, clinical condition, and nutritional tolerance. During the acute phase, energy intake should be cautiously limited below resting energy expenditure, while in the recovery phase, indirect calorimetry may assist in tailoring nutritional prescriptions to individual needs, supporting muscle preservation and timely weaning from mechanical ventilation.

Key Consideration 2: Consider the Use of Serial Ultrasound Examinations To Assess the Diaphragm

Achieving the optimal balance between the beneficial and detrimental effects of spontaneous breathing during weaning is challenging.[25] While spontaneous respiratory activity helps prevent diaphragm atrophy, excessive respiratory effort may increase respiratory load and impair weaning success.[26] Nutritional status is a crucial factor in this balance, as underfeeding and catabolic stress contribute to muscle wasting and diaphragm dysfunction.[26,27]

Diaphragm dysfunction is one of the leading causes of weaning failure and is associated with several risk factors, including malnutrition, sepsis, corticosteroid therapy, and prolonged mechanical ventilation.[28,29] Structural and functional alterations in the diaphragm can develop rapidly after ICU admission, underscoring the importance of early identification and monitoring. In this context, bedside diaphragm ultrasound has emerged as a practical, noninvasive tool for evaluating respiratory muscle function.[30,31]

Diaphragm ultrasound allows assessment of diaphragm thickness and inspiratory thickening fraction, reflecting muscle mass and contractile activity, respectively[30] (fig. 1). Reduced diaphragm thickening has been associated with impaired respiratory mechanics and worse weaning outcomes. While diaphragm ultrasound is only one of several clinical factors influencing weaning, it may serve as a valuable adjunct to evaluate the physiologic impact of nutritional interventions and overall muscle status.[30,32]

A systematic review and meta-analysis of 26 studies (1,204 patients) demonstrated an association between thickening fraction of the diaphragm and weaning success, with sensitivity and specificity around 80%.[33] A thickening-fraction-of-the-diaphragm threshold of 30 to 35% has been proposed as a predictor of successful weaning.[34–36] However, these findings are limited by significant heterogeneity in study populations and ultrasound methodologies.

Beyond the diaphragm, accessory respiratory muscles—particularly the parasternal intercostals—also contribute to inspiratory effort, especially when diaphragmatic function is impaired. Ultrasound assessment of these muscles, specifically the thickening fraction of the intercostals, has been proposed as a complementary tool to evaluate respiratory workload during weaning trials. Preliminary studies suggest that increased thickening-fraction-of-the-intercostals values, typically above 8 to 10%, may reflect heightened compensatory effort and are associated with diaphragm dysfunction and a higher risk of weaning failure.[37–39] Additionally, the thickening fraction of the intercostals/thickening fraction of the diaphragm ratio has been explored as a potential indicator of extra-diaphragmatic muscle recruitment and weaning difficulty. However, current evidence remains limited and heterogeneous, with no established reference values.[40] Therefore, while parasternal intercostal ultrasound may offer useful insights into respiratory muscle function, its application should be considered exploratory and complementary to clinical and metabolic assessments.[41]

While ultrasound evaluation of respiratory muscles cannot serve as a standalone predictor of weaning outcomes, serial measurements may help identify trends in muscle function deterioration or recovery. Progressive reductions in thickening fraction of the diaphragm or elevated thickening fraction of the intercostals may reflect ongoing muscle wasting, metabolic stress, or inadequate nutritional support.[42]

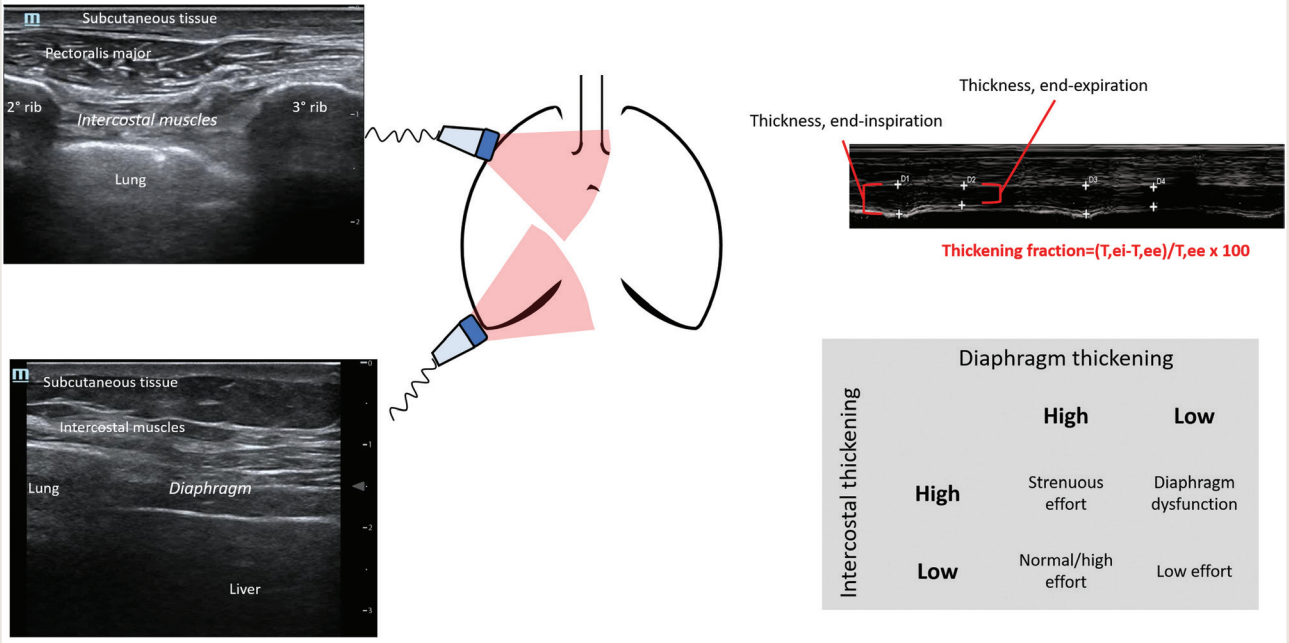


Fig. 1. Ultrasonographic assessment of diaphragm and intercostal muscles. The image depicts standardized ultrasound scans of the inspiratory muscles, including the diaphragm and parasternal intercostal muscles. In the *central area*, the linear probe is positioned on the anterior thorax, while the *upper left* focuses on the intercostal muscles with the probe placed laterally from the sternum. The *lower left* illustrates diaphragm assessment above the right tenth rib in the midaxillary line. The *upper right* shows M-mode images of diaphragm or intercostal thickening during inspiration, while the *lower right* offers an interpretation of combined diaphragm and intercostal thickening assessments.

In summary, the integration of diaphragm and intercostal ultrasound into a comprehensive nutritional and clinical management strategy may help personalize the weaning process in critically ill patients. Although further research is needed to define its prognostic value, this bedside tool may contribute to the early identification of patients at risk of weaning failure and guide tailored nutritional and ventilatory strategies.

Key Consideration 3: Monitor Individual Patient Tolerance to Exogenous Nutrients during Medical Nutrition Therapy

International guidelines and recent evidence suggest caution in providing full caloric and protein support early in critical illness. The European Society for Clinical Nutrition and Metabolism (Luxembourg, Grand Duchy of Luxembourg) practical guidelines (2023) recommend initiating early enteral nutrition within 48 h of ICU admission and progressively increasing intake to reach 70 to 100% of measured resting energy expenditure after the acute phase.

The guideline emphasizes avoiding full caloric feeding during the first 72 h to prevent overfeeding and recommends a protein target of approximately 1.3 g/kg each day.[43] Similarly, the American Society for Parenteral and Enteral Nutrition (Silver Spring, Maryland) guidelines (2022) advise providing 12 to 25 kcal/kg each day during the first 7 to 10 days of ICU stay, stressing the need for individualized nutrition strategies.[44]

Recent meta-analyses and large randomized trials have challenged the notion that achieving 100% of estimated caloric and protein targets improves clinical outcomes. Specifically, the EPaNIC, EDEN, and NUTRIREA-3 trials demonstrated that permissive underfeeding during the acute phase is associated with improved outcomes. More recently, the EFFORT-Protein trial, the PRECISe trial, and the EAT-ICU trial evaluated higher protein delivery compared with standard or lower protein intake. None of these trials demonstrated clinical benefit of higher protein intake, and some even indicated potential harm, particularly in patients with acute kidney injury or high disease severity. A recent systematic review and Bayesian meta-analysis by Heuts *et al.*[45] synthesized data from 22 randomized trials (n = 4,164 patients) and reported a 56% probability of increased mortality with higher protein delivery compared to lower doses. These findings reinforce the need to avoid aggressive early protein supplementation and to tailor nutritional strategies to individual patient tolerance and metabolic response.

A key determinant of appropriate energy delivery is the patient's metabolic tolerance to exogenous nutrients, which varies according to systemic inflammation and endogenous glucose production. During acute critical illness, endogenous glucose production is often incompletely suppressed by exogenous carbohydrate intake, contributing to hyperglycemia. In this context, insulin requirement can serve as a surrogate marker of metabolic tolerance. Elevated insulin needs may indicate poor tolerance to nutrient intake and suggest the need to reduce caloric administration to avoid metabolic complications.[46,47] Close metabolic monitoring, including glucose control and insulin requirements, can guide the dynamic adjustment of caloric delivery.

High-fat, low-carbohydrate diets have been explored as a potential strategy to reduce carbon dioxide production, particularly in hypercapnic patients. However, the available randomized trials, including those by Nourmohammadi *et al.*[48] and Abd El Sabour Faramawy *et al.*,[49] have shown only modest physiologic benefits without clear improvement in weaning outcomes. Therefore, these approaches remain experimental and are not currently recommended, despite available randomized trials. In addition, the potential role of omega-3 fatty acid supplementation, due to their anti-inflammatory and immunomodulatory properties, has been suggested in this setting, but clinical evidence remains limited. In summary, during the early phase of critical illness and weaning, caloric and protein intake should be carefully monitored and adjusted according to individual metabolic tolerance and clinical condition. Overfeeding, particularly in the form of early high protein intake, should be avoided. Further research is needed to clarify the potential role of specific dietary interventions, including ketogenic diets and omega-3 supplementation, in supporting weaning success.

Key Consideration 4: Maintain Adequate Protein Intake

Protein supplementation during medical nutrition therapy in critically ill patients remains a debated topic, with conflicting evidence regarding its optimal dose and timing.[50] During early hospitalization, rapid muscle protein loss occurs, and adequate protein intake is essential to mitigate depletion.[51] However, recent prospective randomized controlled trials have questioned the previously assumed benefits of early high protein delivery.

The EFFORT-Protein trial demonstrated that delivering greater than or equal to 2.2 g/kg of protein each day in nutritionally high-risk, mechanically ventilated patients did not improve hospital discharge outcomes and was associated with a potential increase in mortality, particularly in patients with acute kidney injury and higher disease severity. Similarly, the PRECISe trial reported that higher enteral protein provision (2.0 g/kg each day) compared to standard protein intake (1.3 g/kg each day) resulted in worse health-related quality of life and functional outcomes at 180 days. The EAT-ICU trial also failed to demonstrate benefits of early goal-directed nutrition, including high protein delivery, on long-term functional outcomes. These findings are further supported by the recent meta-analysis by Heuts *et al.*,[45] which highlighted a considerable probability of harm with early high protein intake compared to lower doses.

Collectively, this evidence suggests a U-shaped relationship between protein intake and clinical outcomes,

in which both inadequate and excessive protein provision may be harmful. The current data support a moderate and individualized approach, aiming for 0.8 to 1.2 g/kg of protein intake each day during the early phase of critical illness.[52]

Protein Needs in Long-staying ICU Patients and Weaning from Invasive Mechanical Ventilation

As critical illness progresses and anabolic resistance diminishes, protein requirements may increase.[53] A recent metabolic flux study in prolonged ICU patients revealed that while early skeletal muscle protein depletion is high, *de novo* protein synthesis increases over time, suggesting that a different protein strategy may be required in long-term ICU patients.[53]

Some observational studies have suggested that whey protein supplementation may improve nutritional status and weaning outcomes in these patients, although the quality of evidence remains low. For instance, a retrospective study of 280 patients indicated an association between higher protein intake during the weaning phase and successful extubation. However, this study was limited by significant risk of bias and confounding factors.[7]

Similarly, the randomized trial by Nakamura *et al.*[54] compared high-dose *versus* standard whey protein supplementation in 117 critically ill patients and found reduced femoral muscle loss in the high-protein group. Nonetheless, higher protein intake had no effect on the duration of mechanical ventilation, suggesting that muscle preservation alone does not necessarily facilitate faster weaning. Additionally, some studies have proposed that higher protein intake may contribute to faster diaphragm recovery; however, these findings are preliminary and require confirmation in well-designed randomized controlled trials.

Biologic Mechanisms of Whey Protein

Whey protein is of particular interest due to its high leucine content and potential anabolic effects. Skeletal muscle mass is regulated by a dynamic balance of anabolic and catabolic processes, with the mechanistic target of rapamycin pathway playing a central role in promoting muscle protein synthesis.[55] Whey protein, rich in leucine and essential amino acids, has a greater postprandial muscle protein synthetic response than casein or soy.[56] This effect is attributed to its ability to activate mechanistic target of rapamycin signaling and enhance muscle protein synthesis.[57,58] Nevertheless, current evidence does not support a specific clinical benefit of whey protein over other protein sources in critically ill patients. Available studies are small, observational, and prone to bias, limiting the strength of the conclusions. The potential synergistic effect of combining high-protein intake with physical activity or rehabilitation interventions during the recovery phase deserves further investigation, as recommended by recent expert consensus.

Key Consideration 5: Assess Vitamin D Status and Supplement Only in Case of Confirmed Deficiency

Vitamin D plays a crucial role in bone health, immune function, and inflammation regulation, particularly in critically ill patients.[59] Long-term invasive mechanical ventilation and immobilization contribute to bone and muscle loss, increasing the risk of falls and fractures[60] (fig. 2). Moreover, vitamin D deficiency is associated with impaired immune function, higher rates of ventilator-associated pneumonia, systemic inflammation, and multiple organ dysfunction syndrome, potentially leading to increased mortality and ICU length of stay.[61] Several randomized controlled trial(s) (RCTs) and meta-analyses have assessed the impact of vitamin D supplementation on invasive mechanical ventilation duration and patient outcomes. Menger *et al.*[62] analyzed 16 RCTs involving 2,449 critically ill patients and found that vitamin D supplementation was associated with a significantly shorter duration of invasive mechanical ventilation. The VITdAL-ICU (Correction of Vitamin D Deficiency in Critically Ill Patients) trial,[63] a large RCT involving 492 critically ill patients with vitamin D deficiency, did not demonstrate a reduction in hospital length of stay or mortality with high-dose vitamin D_3 administration. *Post hoc* analyses of this trial showed improvements in bone turnover markers at 6 months, suggesting possible long-term skeletal benefits.[64]

More importantly, the large, multicenter, phase 3VIOLET (Video-Assisted Thoracoscopic or Open Lobectomy) trial[65] evaluated the effect of early high-dose vitamin D_3 supplementation (a single enteral dose of 540,000 IU) in 1,078 critically ill, vitamin D–deficient patients. The trial found no significant difference in 90-day mortality between the vitamin D group (23.5%) and the placebo group (20.6%; difference, 2.9 percentage points; 95% CI, −2.1 to 7.9; $P = 0.26$). Secondary clinical and physiologic outcomes were also similar between groups, and no significant safety concerns were reported. Importantly, the trial was stopped early for futility, indicating a very low probability of benefit. While some meta-analyses and guidelines suggest that correcting vitamin D deficiency may have potential benefits in critically ill patients, current high-quality evidence does not support routine use of high-dose vitamin D supplementation for improving clinical outcomes in ICU patients. Additionally, potential risks associated with high-dose vitamin D administration, including hypercalcemia and related complications, must be acknowledged, although no excess adverse events were reported in the VIOLET trial.

The European Society for Clinical Nutrition and Metabolism guidelines[66] recommend assessment of vitamin D status and correction of deficiency in critically ill patients. However, the quality of evidence supporting these recommendations is low to moderate, primarily based on observational studies, small RCTs, and expert consensus. The VIOLET trial findings challenge the clinical relevance of such supplementation during acute critical illness. In

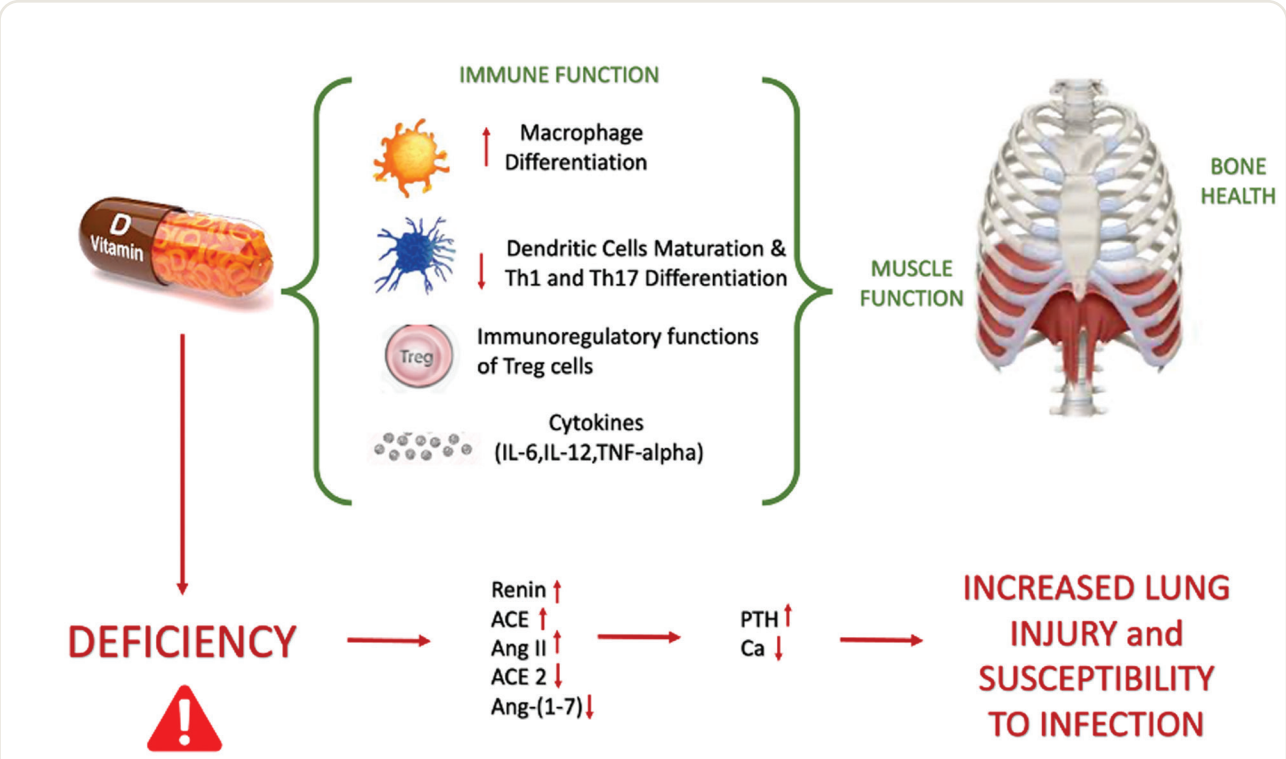


Fig. 2. Pathophysiological consequences of vitamin D deficiency in critical care. The image highlights the critical role of vitamin D in regulating immune function, muscle health, and bone integrity, while emphasizing the consequences of deficiency. Vitamin D supports immune processes by enhancing macrophage differentiation, regulating dendritic cell maturation, and modulating T-helper (Th1/Th17) and T-reg cell responses. It also influences cytokine activity (*e.g.*, interleukin [IL]-6, IL-12, tumor necrosis factor [TNF]-α), promoting a balanced immune response. In muscle and bone health, vitamin D maintains calcium homeostasis and reduces parathyroid hormone (PTH) levels, preserving skeletal integrity and muscle strength—key for respiratory function. Deficiency disrupts these pathways, leading to renin–angiotensin system (RAS) imbalance, increased susceptibility to lung injury, infections, and systemic inflammation. Vitamin D deficiency could exacerbate respiratory and systemic complications, highlighting the need for routine assessment and correction to improve clinical outcomes in critically ill patients.

summary, vitamin D supplementation should be targeted to correcting deficiency, with careful monitoring of serum levels to avoid potential complications. Routine use of high-dose vitamin D supplementation cannot currently be recommended to improve weaning outcomes or reduce mortality in critically ill patients. Further studies are needed to clarify its role in specific subgroups and in the post-ICU recovery phase.

Exploratory Use of Nutritional Supplements in the ICU: Current Evidence and Knowledge Gaps

Several nutritional supplements, including creatine, branched-chain amino acids, and β-hydroxy-β-methylbutyrate, have been investigated for their potential role in preserving muscle mass and supporting functional recovery in critically ill patients. These compounds are known to enhance muscle protein synthesis in healthy individuals or those with sarcopenia, but their effects in the context of critical illness and ventilator weaning remain uncertain.

Creatine

Creatine supplementation is known to improve muscle mass and energy production in healthy individuals undergoing resistance training. Its anabolic effects are mediated through the elevation of muscle creatine and phosphocreatine levels, along with increased insulin-like growth factor-1 activity and activation of anabolic signaling pathways.[67] Nevertheless, no clinical trials have evaluated the efficacy of creatine supplementation in critically ill patients. Preliminary hypotheses suggest that creatine could have beneficial effects when combined with physical rehabilitation[68], but this hypothesis remains untested in ICU settings. Therefore, the potential role of creatine supplementation in critically ill patients requires further investigation in adequately powered randomized trials.

Branched-chain Amino Acids

Leucine and other branched-chain amino acids play a key role in stimulating muscle protein synthesis and limiting

muscle breakdown. While branched-chain amino acid supplementation has shown some benefits in conditions such as sarcopenia, the available evidence in critically ill patients is weak.[69] A systematic review and meta-analysis of 17 trials in older adults failed to demonstrate a significant improvement in muscle mass or strength with leucine supplementation.[70] Furthermore, five randomized controlled trials comparing branched-chain amino acid–enriched parenteral nutrition with standard formulations in ICU patients reported no significant differences in mortality or infectious complications.[71–75]

Some studies have also suggested a U-shaped relationship between leucine levels and mortality, and excessive leucine intake has been associated with potential metabolic risks.[76,77] Therefore, further well designed studies are needed to clarify the safety and efficacy of branched-chain amino acid supplementation in critically ill patients.

β-Hydroxy-β-methylbutyrate

β-Hydroxy-β-methylbutyrate, a leucine metabolite with purported anti-catabolic effects, has shown promise in preserving muscle mass in athletes and older adults.[78] However, its effects on muscle strength and functional performance remain inconsistent. Recent studies have examined the role of β-hydroxy-β-methylbutyrate in ICU patients, but the results remain inconclusive.[79] A meta-analysis published in 2019 and three additional randomized trials have investigated the impact of β-hydroxy-β-methylbutyrate on muscle wasting and strength in critically ill, mechanically ventilated adults.[80] These studies did not demonstrate significant reductions in muscle wasting or improvements in strength with β-hydroxy-β-methylbutyrate supplementation. The potential anti-inflammatory and anabolic properties of β-hydroxy-β-methylbutyrate observed in preclinical models have yet to be confirmed in ICU settings.

At present, the evidence supporting the use of creatine, branched-chain amino acids, or β-hydroxy-β-methylbutyrate supplementation in critically ill patients is insufficient. Major limitations include the lack of high-quality randomized trials; uncertainty regarding optimal dosing, timing, and duration of supplementation; and the absence of studies evaluating these interventions in combination with structured rehabilitation programs. It is unlikely that a single nutritional supplement alone can effectively counteract muscle wasting in the complex metabolic environment of critical illness, particularly in the absence of resistance exercise.[81] Further well-designed clinical trials are needed to evaluate the potential role of these supplements as part of a comprehensive, multidisciplinary strategy for muscle preservation and functional recovery in critically ill patients, particularly in the postweaning and rehabilitation phases. A summary of the main randomized trials, meta-analyses, and clinical guidelines discussed in this review is provided in table 3.

Conclusions

This narrative review provides an updated analysis of metabolic assessments and nutritional strategies essential for successful weaning from invasive mechanical ventilation. Drawing parallels between the physical effort required for weaning and that of athletic preparation, we emphasize the need for tailored nutritional interventions to support this critical phase of recovery. Advances in metabolic monitoring, including indirect calorimetry and ultrasound assessment of respiratory muscles, have improved the understanding of medical nutrition therapy. Nevertheless, several uncertainties remain regarding: (1) the optimal protein intake during different phases of critical illness; (2) caloric targets and the risks associated with overfeeding or underfeeding; and (3) the role of specific nutritional strategies such as high-fat diets, micronutrient supplementation, and metabolic adaptations in prolonged ICU stay.

Despite the recognized importance of nutrition in critically ill patients, no clinical trials are currently registered with a primary focus on the effect of nutritional interventions specifically on weaning from mechanical ventilation. While some trials have evaluated the impact of protein intake, caloric targets, vitamin D supplementation (NCT03096314 and NCT01372118), and β-hydroxy-β-methylbutyrate (NCT02337847) in critically ill or surgical patients, none of these studies have explicitly included time-to-weaning as a primary functional outcome. This reflects a significant gap in the literature.

Therefore, we suggest that future research should prioritize the inclusion of time to weaning as a functional and clinically meaningful endpoint in studies investigating metabolic and nutritional strategies in ICU patients. High-quality, large-scale randomized controlled trials are needed to evaluate the impact of personalized nutritional interventions on weaning success, taking into account metabolic tolerance, disease severity, and individual patient needs. Furthermore, longitudinal studies should explore the integration of nutrition and rehabilitation interventions in post-ICU recovery, emphasizing the potential synergy between nutritional support and physical therapy.

By adopting a holistic, patient-centered, and evidence-based approach to metabolic and nutritional management, we can enhance the quality of care for critically ill patients, optimizing functional recovery, reducing complications, and improving long-term outcomes after invasive mechanical ventilation.

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Table 3. Summary of Key Randomized Trials, Meta-analyses, and Guidelines Addressing Nutritional Strategies and Supplementation in Critically Ill Patients

Source	Type	Intervention/ Recommendation	Population/Context	Main Outcomes	Main Results	Level of Evidence
EPaNIC Trial (2011)	RCT	Early *vs.* late parenteral nutrition	Critically ill adults	ICU length of stay, MV duration	Early PN associated with prolonged MV and ICU stay	High
EDEN Trial (2012)	RCT	Trophic *vs.* full enteral feeding	Patients with acute lung injury	Ventilator-free days	No difference between groups	High
NUTRIREA-3 Trial (2023)	RCT	Low *vs.* standard calorie and protein feeding	ICU patients with shock	90-day mortality, MV duration	No significant difference	High
EFFORT-Protein Trial (2023)	RCT	High (≥2.2 g/kg each day) *vs.* standard protein intake	Critically ill, high-risk patients	Hospital discharge, mortality	No benefit; potential harm in AKI patients	High
PRECISE Trial (2023)	RCT	High *vs.* standard protein intake	Mechanically ventilated ICU patients	QoL and functional outcomes	No benefit; worse long-term QoL	High
EAT-ICU Trial (2017)	RCT	Early goal-directed nutrition	ICU patients	Functional outcomes	No benefit of early high protein	High
Heuts *et al.* (2025)	Meta-analysis	High *vs.* low protein intake	Critically ill patients	Mortality	Possible increased mortality with higher protein intake	High
VITdAL-ICU Trial (2014)	RCT	High-dose vitamin D (540,000 IU)	Critically ill, vitamin D–deficient patients	Hospital LOS, mortality	No significant benefit	High
VIOLET Trial (2019)	RCT	High-dose vitamin D (540,000 IU)	Critically ill, vitamin D–deficient patients	90-day mortality	No benefit; stopped for futility	High
Menger *et al.* (2022)	Meta-analysis	Vitamin D supplementation	Critically ill patients	iMV duration	Shorter duration of iMV; heterogeneity present	Moderate
Nakamura *et al.* (2021)	RCT	High *vs.* standard whey protein	Critically ill patients	Muscle loss, MV duration	Reduced muscle loss; no difference in MV Duration	Moderate
HMB Supplementation Studies (2019–2022)	RCTs and meta-analyses	HMB supplementation	Critically ill, ventilated patients	Muscle wasting, strength	No clear benefit	Low
BCAA Supplementation Trials (1985–1997)	RCTs	BCAA-enriched TPN *vs.* standard	Critically ill, septic/ trauma patients	Mortality, infections	No significant difference	Low
ESPEN Guidelines (2023)	Guideline	Nutritional strategy, vitamin D assessment	Critically ill patients	Nutritional adequacy	Moderate protein intake, correct vitamin D deficiency	Low–moderate
ASPEN Guidelines (2022)	Guideline	Nutritional support strategy	Critically ill adults	Caloric/protein intake, timing	Early EN, individualized approach	Moderate

AKI, acute kidney injury; ASPEN, American Society for Parenteral and Enteral Nutrition; BCAA, branched-chain amino acid; EN, enteral nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; HMB, β-hydroxy-β-methylbutyrate; ICU, intensive care unit; iMV, invasive mechanical ventilation; LOS, length of stay; MV, mechanical ventilation; PN, parenteral nutrition; QoL, quality of life; RCT, randomized controlled trial; TPN, total parenteral nutrition.

Competing Interests

The authors declare no competing interests.

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ANESTHESIOLOGY®

Anesthetic Amnesia: The Forgotten Importance of Forgetting?

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ABSTRACT

There is increasing evidence that the impairment of consciousness by anesthetic drugs does not always lead to its complete absence and that the loss of subjective experience with anesthesia may at times be an illusion created by amnesia. However, the study of how anesthetic drugs cause amnesia, and importantly how they fail, has received less attention than the other cardinal properties of anesthesia. There is no reliable biomarker to determine the adequacy of pharmacologic amnesia in real time. Anesthetic drugs can influence all stages of memory formation and recall, and their amnestic effects are dissociable from their hypnotic effects; for example, propofol has potent specific amnestic potential, whereas dexmedetomidine is a pure hypnotic. Posttraumatic stress disorder cluster symptoms, which constitute a disorder of amygdala-centered memory systems, are commonly related to surgical memories under both general anesthesia and procedural sedation and need to be better understood and managed.

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The significance and study of amnesia as a cardinal property of anesthetic drugs have been overshadowed by the attention paid to unconsciousness and immobility. This notion was well reflected in the first public demonstration of general anesthesia in 1846.[1] After being administered ether by dentist William Morton, the patient, Gilbert Abbott, did not move in response to the incision. Surgeon John Collins Warren reportedly proclaimed, "Gentlemen! This is no humbug," and the modern era of anesthesia was born. However, despite the transformational success of the exercise in facilitating the surgery, Abbott stated afterward that while he did not experience any pain, he was aware of the operation, "as though the skin had been scratched with a hoe."[2] While some aspects of the account may be apocryphal,[3] it is clear that from the start unresponsiveness to painful stimuli could create a powerful illusion of amnesia and unconsciousness. Although the dissociability of amnesia, unconsciousness, and immobility are now well understood,[4] and technological advances have greatly enhanced the ability to calibrate the dosing of anesthetic drugs against neurobiological feedback, the ability to directly assess their amnestic actions in real-time remains elusive. The inexactitude in clinically targeting amnesia makes a nuanced understanding of how anesthetic drugs affect memory processes highly valuable in guiding practice and presents ample opportunity for future research.

The state of general anesthesia has historically been viewed as a drug-induced reversible impairment of consciousness.[5] However, it is increasingly apparent that this *impairment* of consciousness does not necessarily imply the complete *absence* of consciousness; multiple human subject studies have created a compelling picture that some level of conscious processing may occur during what otherwise appears to be an adequately anesthetized state.[6–8] The fact that patients do not recall what happens to them during surgery may thus not just be the trivial result of there being no conscious substrate to begin with. Rather, albeit to an unknown degree, it may rely on the specific amnestic actions of the anesthetic drugs delivered. Indeed, evidence of some conscious processing is an everyday extubation criteria, yet rarely recalled.

The previous statement challenges one of the fundamental tenets of how both anesthesiologists and patients understand what general anesthesia is. It is mostly assumed that anesthesia is an absence of experience, but we may have to accept as truth that some experience is present and that the illusion of the absence of subjective experience is created through amnesia. The implications are quite profound and speak to the criticality of understanding how pharmacologic agents used by anesthesiologists affect memory. Added to this are the well described psychologic consequences of failure to achieve amnesia under general anesthesia.[9] However, despite the importance of

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Abbreviations: BIS, Bispectral Index; **EEG**, electroencephalography; **fMRI**, functional magnetic resonance imaging; **GABAA**, γ-aminobutyric acid type A; **GABAergic**, γ-aminobutyric acid–mediated; **PTSD**, posttraumatic stress disorder

understanding how anesthetic amnesia both succeeds and fails, the literature lacks any recent comprehensive, relevant review. We offer this systematic review to provide our colleagues with updated information, technologies, and opinions and discuss several clinically relevant applications of amnesia. Our discussion focuses on the adult population, as there are very few relevant studies in children and sound reasons to believe that the neuropharmacological and mechanistic underpinnings may differ from adults. Although the neuroscience of memory has advanced significantly over the past two decades, practitioners have struggled to successfully apply this knowledge in the clinical setting to improve patient experience. Part of the motivation for writing this article is to stimulate relevant translational research; accordingly, this review will not delve deeply into the technicalities of the intricate neurobiology of memory but will concentrate on clinical studies and their application.

The Physiology of Memory

Types of Amnesia and Related Terminology

Categorical descriptors of amnesia have remained remarkably preserved over centuries.[10] Multiple forms of memory exist, both conscious and nonconscious, but for the purposes of this review, the term *amnesia* references almost entirely the definition used by Cubelli and Della Sala[11]: an acquired impairment of explicit long-term memory. A frequent alternate term used is *declarative memory*. More specifically, amnesia as used in this context usually refers to the subcategory of *episodic* memory; this is memory for events that have a sense of time and place, in contrast to *semantic* memory, which is memory for facts and meaning that may have no spatiotemporal information. To facilitate discussion, we have summarized the neuroanatomic structures most relevant to anesthetic amnesia in figure 1. The etiology of amnesia is enormous. However, we mainly focus on perioperative amnesia in this review article.

Drug-induced amnesia is an acute self-limited episode of dense anterograde amnesia with no detectable neurologic deficits.[12] It shares phenomenological similarities with transient global amnesia[13,14] but differs importantly in that a period of retrograde amnesia—a consistent feature of transient global amnesia—is not a significant feature of drug-induced amnesia and its very existence is controversial. It

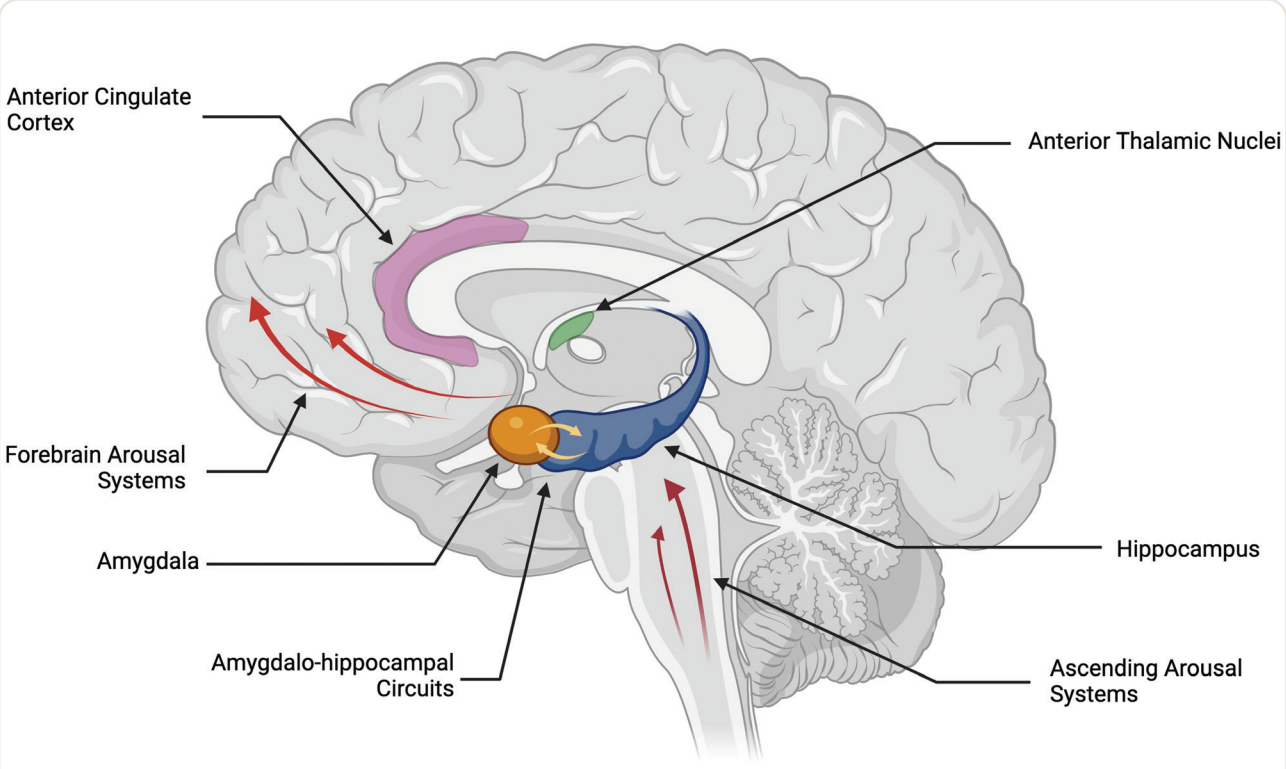


Fig. 1. Key neuroanatomic structures involved in episodic and emotional memory processes relevant to anesthetic amnesia. Episodic memory requires ascending arousal signals from brainstem and midbrain structures. A key subcortical network includes the anterior thalamic nuclei and the hippocampus (located in the medial temporal lobe), which are obligatory for the encoding and consolidation of episodic memory. Also critical is the anterior cingulate cortex, which is necessary for attentional processes. Just anterior to the hippocampus in the medial temporal lobe is the amygdala, which is the critical structure in fear systems and emotional memory; the hippocampus and amygdala richly interconnect to influence processes in each other. The subcortical and medial temporal lobe systems have long-range connections with forebrain structures, modulating downstream processes in multiple regions. Created in BioRender (https://BioRender.com/l43m552).

is important to recognize that drug administration is not the only potential source of amnesia in the perioperative period. Dynamics of emotion and attention are well known to modulate memory processes,[15] and so the psychologic responses of fear, anxiety, and divided attention surrounding surgery, anesthesia, and the perioperative setting have considerable potential to alter memory behavior but have not yet been comprehensively studied, as discussed by Chen *et al.*[16] Studies of drug-induced amnesia conducted in perioperative real-world settings are thus importantly different from those conducted in volunteers who are neither expecting nor actually undergoing surgery and anesthesia, and we urge cognizance of nonpharmacologic sources of memory effects in interpreting results.

What Are the Processes of Memory, and How Do Anesthetics Alter Them?

A primary feature of the brain is its functional ability to achieve both plasticity and stability, underlying the capacity to create, store, and process memory. Several conceptual models have been proposed to explain the mechanisms of memory, but the classical Atkinson and Shiffrin[17] models remain the most popular. Based on this model, figure 2 highlights the processes of memory formation, transformation, storage, retrieval, and decay and the effects of anesthetics on the processes.[18] Sensory input reaches the brain and is processed in specific cortical regions serving the sensory modality. *Sensory memory* refers to the transient initial registration of this input contained within the sensory cortical structures, which may last for only a few hundred milliseconds and no longer than a few seconds. The *primary engram*—an initial neural representation of integrated sensory, semantic, and other declarative information—may then form in working memory and short-term memory stores. These are connected but partially distinct concepts: *short-term memory* refers to a transient simple storage of information, while *working memory* additionally implies the capacity-limited manipulation of short-term information in what we experience as conscious thought.[19] Without rehearsal or organization, working memory stores decay over 15 to 30 s,[20] but information from short-term stores may survive through being encoded and transformed into a stable long-term memory *via* a process termed *consolidation*. This is a complex cascade of changes in synaptic structure and function that is vulnerable to interference at multiple points. Notably, consolidation is enhanced by sleep.[21] It is widely believed that consolidation is achieved by changes in synaptic strength driven by long-term potentiation,[22,23] a phenomenon repeatedly observed in cellular-level experiments in which strong or repetitive stimulations at critical frequencies trigger a cascade of processes that modulate

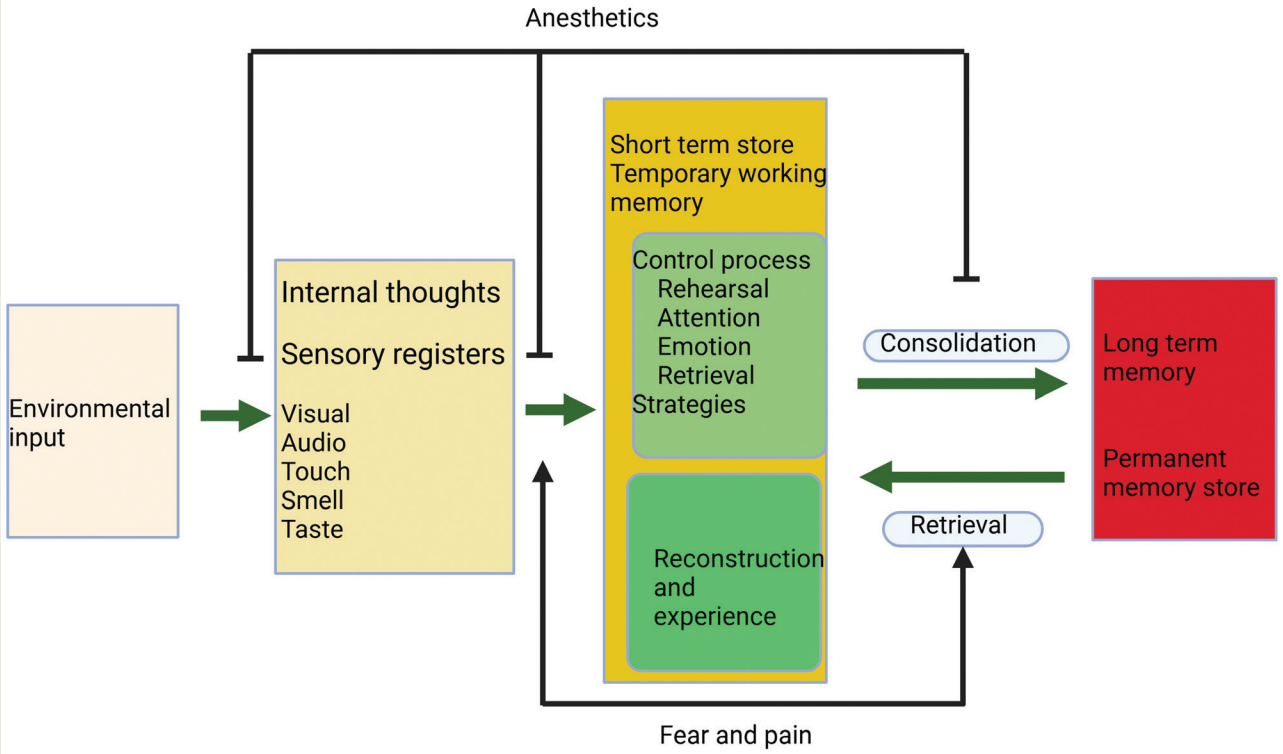


Fig. 2. Process of memory formation and effects of anesthetics on memory cascade. The *arrows* indicate facilitation, and the *T signs* indicate inhibition. This figure was modified from Atkinson and Shiffrin[18] and created with BioRender.

synaptic plasticity. The initial phase of potentiation (early long-term potentiation), lasting hours, depends on kinase activation and phosphorylation, while a second phase (late long-term potentiation), lasting weeks to months, results from changes in gene expression and permanent cytoskeletal modifications. Long-term potentiation is succinctly summarized by the Hebb's postulate: *neurons that fire together, wire together*. Rehearsal, attention, and emotion—including that associated with fear and pain—can positively reinforce consolidation efficacy and lead to longer lasting memory, while interference from competing memory tasks can negatively affect consolidation.[24] Even after consolidation, without reinforcement (*via* a process termed *reconsolidation* and described below), memory will decay as time passes, not in a linear fashion but rather following a negative logarithmic pattern as classically described by Ebbinghaus.[25,26] Other processes, including long-term depression, interplay with long-term potentiation[27]; theories of memory continue to evolve, and the reader is referred to recent reviews.[28–30]

The Anesthetic Pharmacology of Memory

Anesthetic Drugs and Mechanisms of Amnesia

Because most anesthetics tend to decrease neuronal excitability in various ways, it is perhaps unsurprising that most studies of their primary amnesic effects implicate the initial steps in synaptic transmission and plasticity that are induced by excitation.[31,32] However, other experiments suggest that anesthetic drugs may also act on downstream processes in the cascade of cellular events that lead to consolidation (fig. 2).[33,34] Table 1 describes several known molecular and neuroanatomic sites of action for commonly used anesthetic drugs. However, most anesthetic drugs impair multiple components of the memory pathway.

It is clear that anesthetics are able to cause amnesia by inhibiting the processes that lead to successful, sustained consolidation; in other words, anesthetics either prevent the formation of a memory or lead to a very weak memory that rapidly decays, but can anesthetics actually facilitate forgetting, accelerating the decay of what has already been established? As referenced earlier, since the seminal description by Ebbinghaus in 1885,[25] it has been generally accepted that the loss of memory over time is best described by a negative power function. This mathematical description largely preceded the nuanced multiphase mechanistic understanding of memory, and several attempts have been made to replicate and refine the mathematical description of forgetting in line with mechanistic principles,[53–55] including a recent proposal by Radvansky *et al*.[56] that attempts to parse changes in the decay curve across early, transitional, and long lasting phases of long-term memory. Nonetheless, while there are suggestions that individual memory traces may follow exponential or even linear decay and that contextual aspects may significantly alter the course of individual traces, the essential feature—that the average loss of memory follows a negative power function—remains. There is no clear evidence that anesthetic drugs actively

Table 1. Amnesic Mechanisms and Commonly Used Medications and Anesthetics

Drugs	Receptors and Action	Known Anatomic Locations of Amnestic Action	References
Benzodiazepines (representative agent: midazolam)	α-Subunit–containing $GABA_A$ receptors.	Hippocampus, amygdala	Hemmings *et al.*[35] Vogt *et al.*[36] Wang *et al.*[37] Weir, *et al.*[38]
Propofol	Activating $GABA_A$ receptors	Hippocampus, amygdala??	Veselis *et al.*[39] Pryor *et al.*[40]
Etomidate	Activating β2/3-$GABA_A$	Hippocampus, amygdala	Rudolph *et al.*[41]
Antimuscarinics, (representative agent: scopolamine)	Inhibiting muscarinic receptors	Hippocampus	Liem-Moolenaar *et al.*[42]
Dexmedetomidine	Highly selective α_2-adrenoceptor agonist	Locus coeruleus, hypothalamus	Hall *et al.*[43] Hayama *et al.*[44]
Ketamine	Inhibition of NMDA receptors	Hippocampus, prefrontal cortex	Hack *et al.*, 2023[45] Vogt *et al.*, 2021[36]
Volatiles (representative agent: sevoflurane)	Increasing GABAergic and glycine inhibition and decreasing glutamatergic NMDA activity	Hippocampus, amygdala	Krasowski and Harrison[46] Alkire *et al.*8[47] Ishizeki *et al.*[48]
Nitrous oxide	Both NMDA and non-NMDA receptor–mediated responses to exogenous agonists[49]	??	Mouquet *et al.*[50]
Xenon	Potent inhibition of the NMDA receptor channels[51]	Hippocampus??	Meloni *et al.*[52]
Opioids	Activating mu (μ), delta (δ), and kappa (κ) receptors; activating weak mu-opioid receptors is particularly relevant to the hypnotic and analgesic effects	Brain and spinal cord	Veselis *et al.*[39]

$GABA_A$, γ-aminobutyric acid type A; GABAergic, γ-aminobutyric acid–mediated; NMDA, *N*-methyl-D-aspartate.

accelerate decay once it has initiated. However, anesthetic drugs may interact with intrinsic processes that modulate decay. Memories are reinforced through a process of replay: during retrieval into consciousness, the memory becomes transiently plastic and able to undergo a process of *reconsolidation*, during which it can be both amplified and altered.[57] Reconsolidation shares mechanistic similarities with primary consolidation, and while less studied, there is some direct evidence that anesthetic drugs inhibit reconsolidation processes: in a notable recent study by Galarza Vallejo *et al.*,[58] propofol administered concurrently with the reactivation of a 1-week-old emotional memory impaired retention of that memory 24 h later relative to other memories that were not reactivated. Perhaps better appreciated are the potential effects of anesthetics on modulation of consolidation by pain, fear, and stress, which are frequently encountered perioperatively. Emotional modulation *via* amygdala-dependent systems enhances consolidation and shifts the decay curve toward endurance of negative memories over those that are neutral.[59] Negative emotional memories have the potential to induce "runaway" amplification processes and lead to memory-centered psychopathologies, with the most archetypal being classic posttraumatic stress disorder.[60] As recently discussed by Vogt and Pryor, prevention of fear and other modulators of memory and understanding how specific agents can be best used to prevent fear and its associated complications in clinical practice remain areas for further study.[61]

Which Drug Gives the Most Amnesia for the Least Sedation?

Most hypnotics, like propofol and midazolam, produce amnesia at much lower concentrations than those required to produce hypnosis or prevent movement in response to noxious stimuli.[62] Their amnestic effect at comparable levels of sedation and hypnosis is quite variable.[63] Figure 3 illustrates data from multiple studies examining various aspects of the relative hypnotic and specific amnestic effects of several anesthesia drugs.

To make sense of the results shown in figure 3, it is important to appreciate that there are two broad paths through which a drug might inhibit the establishment and preservation of a memory. The first path is through decreasing the initial strength of the memory that is encoded. Here, it is vital to understand that attention is necessary for memory encoding and that any form of sedation, be it pharmacologic or otherwise, diminishes attention and thus diminishes the strength of the initial engram. The second path is through inhibiting consolidation processes. Regardless of the initial encoded strength of a memory, it must undergo consolidation to be propagated as a long-term memory; inhibition of these consolidation processes will lead the engram to decay rapidly. While the term *amnesia* is colloquially used to describe a failure of memory from any combination of these processes, in the memory literature, the term *amnestic* is more precisely used to describe this latter ability of a drug to directly interfere with memory consolidation. Figure 3 presents data from studies that attempt to dissociate the relative contributions of each path to a drug's overall ability to inhibit memory. All anesthetic drugs possess the ability at sufficient doses to decrease arousal and attention, so dissociating direct amnestic effects from sedation effects is experimentally challenging. These dual effects may also underlie some of the heterogeneity seen between drugs that have similar targets. Even though midazolam, propofol, and barbiturates such as thiopental are all γ-aminobutyric acid type A ($GABA_A$) receptor agonists, the profile of their effects on sedation and amnesia have important differences, with thiopental notably less amnestic than either midazolam or propofol[65] and with propofol exhibiting a greater excitatory effect at low doses than midazolam[64]; this heterogeneity is likely attributable to the differing drug binding sites and the complexities of $GABA_A$ receptor pharmacology and brain distribution; for example, the hippocampus is notably rich in $GABA_A$ receptors expressing the α_1, α_2, α_5, β_3, and γ_2 subunits, with concentrated populations in different substructures.[66] Similarly, both atropine and scopolamine are antagonists of acetylcholine in the central nervous system, and their amnestic efficacies are also very different.[67] An illustrative example of attempts to dissociate sedative from amnestic effects is the early study by Glass *et al.*[63] in which healthy volunteers were presented with words or pictures, and amnesia was assessed at variable levels of sedation as estimated by the Bispectral Index (BIS). Propofol eliminated 95% of recall at a BIS of 77 (72 to 83), while for midazolam the BIS for the equivalent effect was 68 (50 to 78). However, for isoflurane, the same inhibition of recall occurred only at a much lower BIS of 42 (13 to 71), which, even allowing for an outlier subject, suggests that the amnesia caused by isoflurane was driven more by effects on arousal than by specific amnestic actions. Sedation is a challenging construct to assess with precision, and BIS certainly may not be a pure measure; subsequent studies have used other metrics such as subject ratings, observer ratings, and reaction times, although each of these has its own limitations. The preponderance of human studies support the notion that both propofol and midazolam produce profound amnestic effects that can be readily dissociated from their sedative effects.[39,62,64,68] One early study by Polster *et al.*[69] found midazolam to have a stronger amnestic effect than propofol, while a study by Pryor *et al.*[64] found that at very low doses, propofol may actually exert an excitatory, antisedating effect yet still causes amnesia because of a profound effect on consolidation; this profile was not seen with midazolam. Memory formation can be diminished entirely if the level of sedation is so deep as to remove any ability to consciously attend to a stimulus. Achieving amnesia through a purely sedative pathway is thus certainly possible but implies the need for a deep level of sedation that may have other clinical ramifications.

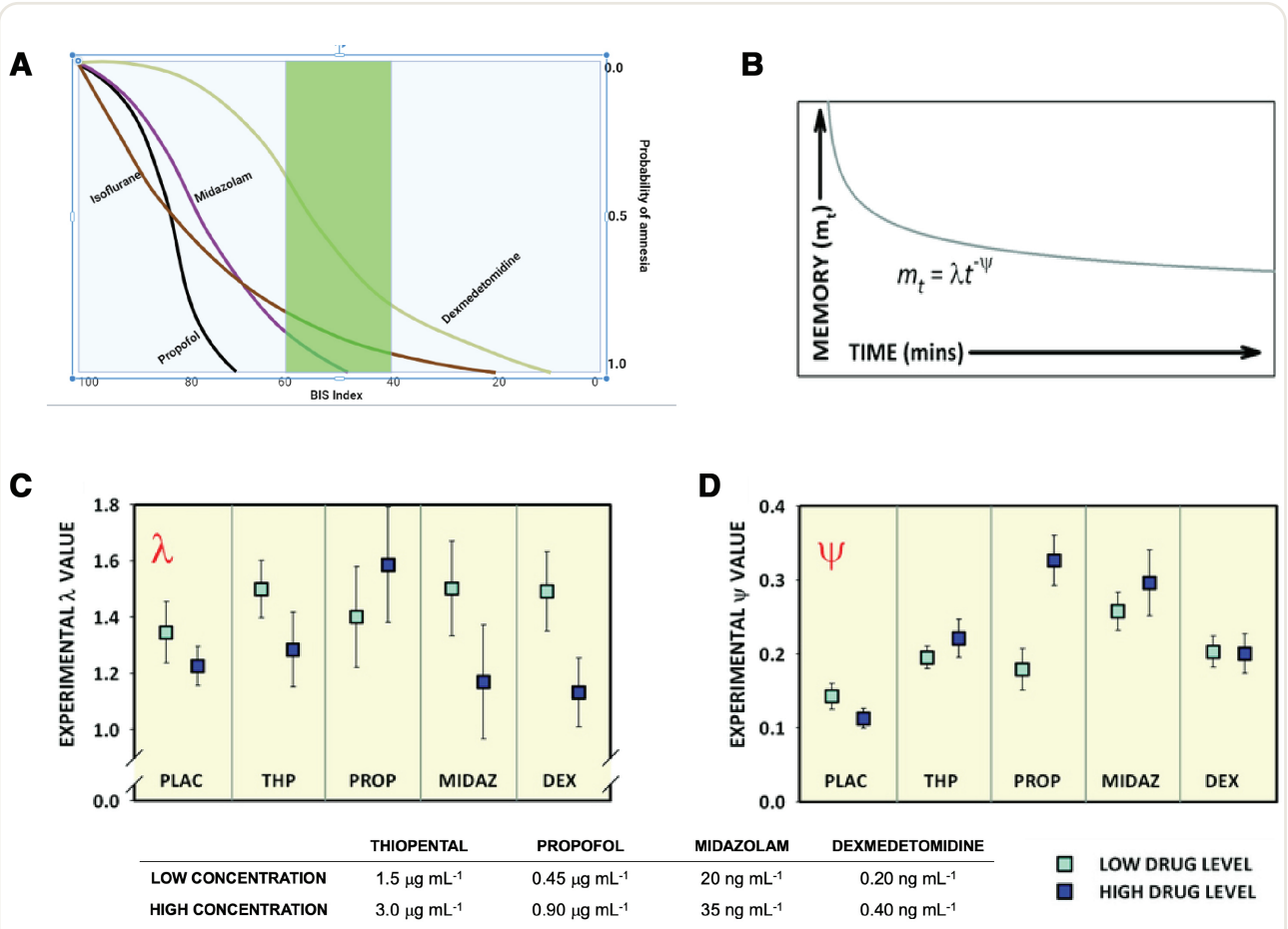


Fig. 3. Representations of how the memory effects of anesthetic drugs can be dissociated into effects due to sedation and effects due to a specific amnestic property. (*A*) Amnesia curves as a function of Bispectral Index (BIS) value, with data for propofol, isoflurane, and midazolam taken from Glass *et al.*[63] and data (N = 7, healthy adult volunteers) for dexmedetomidine taken from Hall et al.[43] The clinically recommend BIS values for general anesthesia are shown as a *green band*. If equal BIS values are taken to represent equisedative doses, then the probability of amnesia at equal levels of sedation is highest for propofol and lowest for dexmedetomidine, suggesting that propofol has specific amnestic properties dissociable from sedation. This is also illustrated in (*B*) through (*D*), taken from Pryor *et al.*[64] (*B*) Memory decay curve can be regressed to coefficient λ, which represents encoding strength and is inversely related to sedation; and ψ, a coefficient indexing the rate of memory decay, which is a specific memory effect. (*C*) and (*D*) Values of the coefficients λ and ψ at two sedative concentrations of multiple drugs. Increasing doses of propofol significantly increase the ψ coefficient but not the λ coefficient, suggesting that the loss of memory is highly driven by a specific memory effect and not by sedation. In contrast, increasing doses of dexmedetomidine decrease the λ coefficient but not the ψ coefficient, suggesting that the memory effects of dexmedetomidine are driven by sedation. DEX, dexmedetomidine; MIDAZ, midazolam; PLAC, placebo; PROP, propofol; THP, thiopental.

Whether ketamine has amnestic effects comparable to the γ-aminobutyric acid–mediated (GABAergic) drugs is less clear, in part because ketamine dissociation is qualitatively distinct from GABAergic sedation. Ketamine does not cause a comparable decrease in the BIS, so the dissociative "sedation" levels are challenging to quantify with processed electroencephalography (EEG). There are conflicting results. An early functional magnetic resonance imaging (fMRI) study demonstrated that low doses of ketamine altered the contributions of prefrontal and hippocampal regions to both encoding and retrieval memory processes but with minimal changes in memory performance.[70] A recent study emerging from the psychiatry literature using healthy volunteers demonstrated that a ketamine bolus of 0.23 mg/kg greater than 1 min followed by a constant infusion of 0.58 mg · kg^{-1} · h^{-1} over the course of 1 h reduced attention and working memory assessed 2 h after the ketamine administration.[71] A similar study demonstrated that ketamine-induced dissociative amnesia coexists with relief of negative emotional experiences.[54] Ketamine dampens the processing of affective stimuli, particularly unpleasant stimuli, in major depression disorder patients[72,73] and may also have a normalizing effect on brain function during attentional and emotional processing in this patient population.[74] Viewed alongside its well known benefits in the treatment of depression,[75] any signal that administration of ketamine

in perioperative settings can affect psychologic outcomes may represent a unique and useful feature of the drug. To this end, there is some supportive evidence in small efficacy studies. Low-dose ketamine has been found to elevate mood assessed postoperatively.[76,77] A recent study demonstrated that a low, single dose of ketamine given to patients after cesarean delivery reduces major depressive episodes in mothers with prenatal depression.[78] The mechanism behind this observation and whether it is mediated *via* an effect on emotional memory remains to be explored. It is plausible that ketamine may modulate the effect of painful stimuli on network activity influencing memory: painful stimulation during light sedation with ketamine is not accompanied by increased coherence in brain connectivity.[36] For all the promise seen in these small efficacy or translational studies, it is worthy to note that no large effectiveness trial has yet been completed. Further, a secondary analysis of an effectiveness trial evaluating ketamine's effects on postoperative depression did not find any benefit on depression-axis outcomes.[79]

Dexmedetomidine suppresses adrenergic brain activity and induces a state of sedation that converges on natural sleep processes,[80] but it appears to have no specific amnestic action and interferes with memory only through its sedative effect.[64] These sedative effects likely lead to weakened initial encoding of the memory trace.[44,64] At a dose with which patients are not spontaneously communicating with the external environment (BIS less than 60), they are easily arousable and have a high probability (nearly 50%) of recall.[43] Similarly, subjects receiving dexmedetomidine at doses causing loss of responsiveness are able to recognize as familiar some emotional stimuli (15% after correction for false positives) presented during loss of responsiveness, whereas those receiving the potent amnestic propofol can remember none.[8] While noting the limitations in comparing adult and pediatric memory studies, a similar observation has also been made in children (n = 30, age 6.1 ± 1.2 yr); during progressively increasing dosing of dexmedetomidine, memory function was present until shortly before verbal unresponsiveness occurred, and the curve mapping amnesia closely followed that mapping sedation.[81] In other words, the children's memory formation and/or retrieval are not profoundly affected by the drug until shortly before they lose response to verbal commands.

Scopolamine disrupts the transmission of cholinergic signals,[82] which is crucial for memory formation and cognitive processes. This disruption can lead to amnesia,[83] affecting both short-term and long-term memory. Historically, scopolamine was widely used as an amnestic agent during childbirth in the 1910s and 1920s, often in combination with morphine. The combination led the parturients to enter an altered state of consciousness where they were unable to recall the pain of childbirth afterward.[84,85] Its use as an amnestic has significantly declined in modern practice, mainly due to its broader cognitive effects, potential side effects, and unpredictable memory outcomes. However, it remains commonly used for antiemesis in transdermal patches of 1 to 1.5 mg. At such a dose, the incidence of severe amnesia is relatively rare. However, a study in healthy young volunteers demonstrated that 0.6 mg of scopolamine administered subcutaneously caused significant visual memory impairment when assessed at 2 h after the administration, and the effect lasted greater than 9 hours.[86] Scopolamine also appears highly effective at preventing dreaming, or the memory of dreaming, during general anesthesia in healthy female patients.[67] The memory effects of scopolamine are unlikely due to typical sedation as doses of 8.3 μg/kg do not alter the BIS significantly, while lower doses are associated with memory effects.[87]

Clinical Applications of Anesthetic Amnesia

Unintended Postoperative Recall during General Anesthesia: Failure of Intentional Amnesia. For a patient to recall events that occur during surgery, two complex brain functions must be intact: there must be some level of conscious substrate, and there must also be some level of intact memory encoding and consolidation. Consciousness is a required condition for memory. If consciousness is removed, then there is no substrate to be remembered, while if memory processes are selectively removed, then there will be no long-term memory formation *even if there was conscious perception*. Estimates of the incidence of awareness with recall depend very much on the method used to detect it. In studies that use voluntary patient report as the outcome, the incidence is in the vicinity of 1:15 to 20,000. The 5th National Audit Project reported by Pandit *et al.*[88] evaluated all anesthetics in the United Kingdom over a year and found the incidence of certain or probable and possible accidental awareness cases to be 1:19,600 anesthetics. This is similar to the incidence of 1:14,560 found by Pollard *et al.*[89] in a large quality study of a health system in which patients were not systematically asked focused questions about awareness. The incidence of recall in studies using this methodology is likely underestimated.[90] In contrast, in studies that use the Brice questionnaire,[91] which provides targeted questions on multiple days, the reported incidence is ~1:500 to 1,000. In a large prospective cohort of nearly 20,000 patients, Sebel *et al.*[92] reported an incidence of definite awareness of 0.13% and an additional 0.24% with possible awareness. Three randomized controlled trials evaluating the use of the BIS monitor in preventing awareness are particularly notable because of the rigor of their outcome evaluation, although in each study, the cohort was selected for a higher risk of awareness: the B-Aware Study reported an overall incidence of ~1:190,[93] the B-Unaware Study reported an overall incidence of 1:485,[94] and the BAG-RECALL Study reported an overall incidence of 1:410.[95] Recent Cochrane reviews are consistent with these estimates.[96,97] The American Society of Anesthesiologists (Schaumburg, Illinois) Closed

Claims database analysis in 1999 showed that recall counts for 1.9% of overall claims and ranked tenth of all causes of claims.[98]

It is worth noting that all the studies described above were conducted in developed countries, where the end-tidal gas analyzer is routinely used, and the use of processed EEG is also quite common. However, there is a substantial heterogeneity in anesthesia monitoring globally, and neither processed EEG nor end-tidal gas analyzer are routinely used in many developing nations. As such, the risk of awareness with recall in the populations of developing nations is subject to differences in both monitoring and drug availability and selection. The incidence of awareness with recall in such settings is poorly understood, but one recent study from Ethiopia found that 8.2% of patients undergoing abdominal surgeries—in which general anesthesia was mainly induced using ketamine with halothane as the maintenance agent)—had confirmed postoperative recall.[99] Estimating the global burden of awareness with recall is extremely challenging, but given a recent assessment of the total number of surgeries at 294 million per year worldwide,[100] even a conservative recall rate would suggest that at least 382,200 cases of confirmed intraoperative awareness with recall occur annually. Imputing the ratio of reports of stress, anxiety and pain from the study in 2004 by Sebel *et al.*,[92] about a quarter of these patients would suffer anxiety and pain associated with explicit recall of intraoperative events. This calculation is based only on the number of general anesthesia patients and omits adverse outcomes associated with neuraxial anesthesia or procedural sedation. There clearly is a need for improving the quality of anesthesia care as regards perioperative amnesia.

Not all items and experiences are equally memorable, and not all forms of memory are equally accessible. For example, visual material is generally more salient than is auditory material, and the "depth" of processing used in the evaluation of an item influences its memorability; subjects are more likely to remember a word when instructed to assess its meaning than some superficial characteristic such as whether it was spoken by a male or female voice. Further, there is an important distinction between *recollection*, which is clearly retrievable explicit memory for an item, and *familiarity*, which—although somewhat explicit—is a much vaguer sense that something was previously experienced (such as the common experience of feeling like you have seen a person before but are unable to recall any specifics). Recollection and familiarity are thought to represent two experimentally separable processes.[101] The hippocampus is an important node in the binding of a recalled item to its context. How anesthetic drugs modulate the influence of modality, recollection, and familiarity is only minimally understood, although it may be of real importance in determining what events under surgery might be remembered, what is required to trigger the memory, and whether the memory is retrieved as recollection or familiarity. One study by Veselis *et al.*[39] evaluated how item salience and form of recognition interacted with anesthetic amnesia. Subjects were presented both words and contextually rich images (photographs that told a story), and recognition was assessed through both a cued free recall (a slight hint) and recognition of the previously presented item (fig. 4). Visual items are significantly more resistant to the amnestic effects of propofol than are auditory items, and free recall is significantly more fragile than item recognition. A later study by Reder *et al.*[102] similarly found that the amnestic effect of midazolam is greater for words than it is for photographs and added the interesting finding that midazolam did not have a significant effect on memory for abstract images, which suggests an effect on the binding of a memory for a stimulus to the experimental context. Intramuscular scopolamine significantly reduced free recall but not cued recall.[103] It is plausible that these effects in part underlie the vast difference in the clinical incidence of intraoperative awareness seen between spontaneous report (which requires both unsolicited recall and behavioral motivation) and the Brice questionnaire (a form of cued recall).

Negative emotional experiences activate fear systems. Evolutionarily ancient components of these systems center around the amygdala, but cortical areas throughout the brain may also be involved.[104] These systems can modulate explicit memory processes but also mediate implicit, nonconsciousness memory processes. The experimental archetype is Pavlovian fear conditioning,[105] while the best known clinical manifestations relate to changes in anxiety and the posttraumatic stress disorder (PTSD) cluster of psychopathologies. While the impact of explicit recall of intraoperative awareness is well recognized, the effect of these implicit forms of memory on the patient's well-being are poorly understood. Implicit memory is not freely and consciously accessible, but manifests as altered behavior. It is challenging to accurately determine the association between the behavior change and the specific content of an implicit recall episode. There is evidence that suppression of implicit fear systems requires higher levels of anesthetic drugs than suppression of explicit memory formation; for example, concentrations of propofol that suppress explicit memory and hippocampal activation do not suppress the amygdala response to negative emotional images.[40]

More broadly, fear systems represent one subclass of implicit memory processes, mechanistically distinct from explicit memory[106] (see also fig. 1). The most common form assessed in studies of anesthetic amnesia is word stem completion, where subjects are prompted to complete words after being shown the first three letters; evidence of implicit memory is inferred if the subject is more likely to complete the stem with words that were presented while under anesthesia. This procedure is methodologically challenging because of contamination from conscious processes, cultural differences in natural frequencies of word completion, and nonstandardization of anesthetic

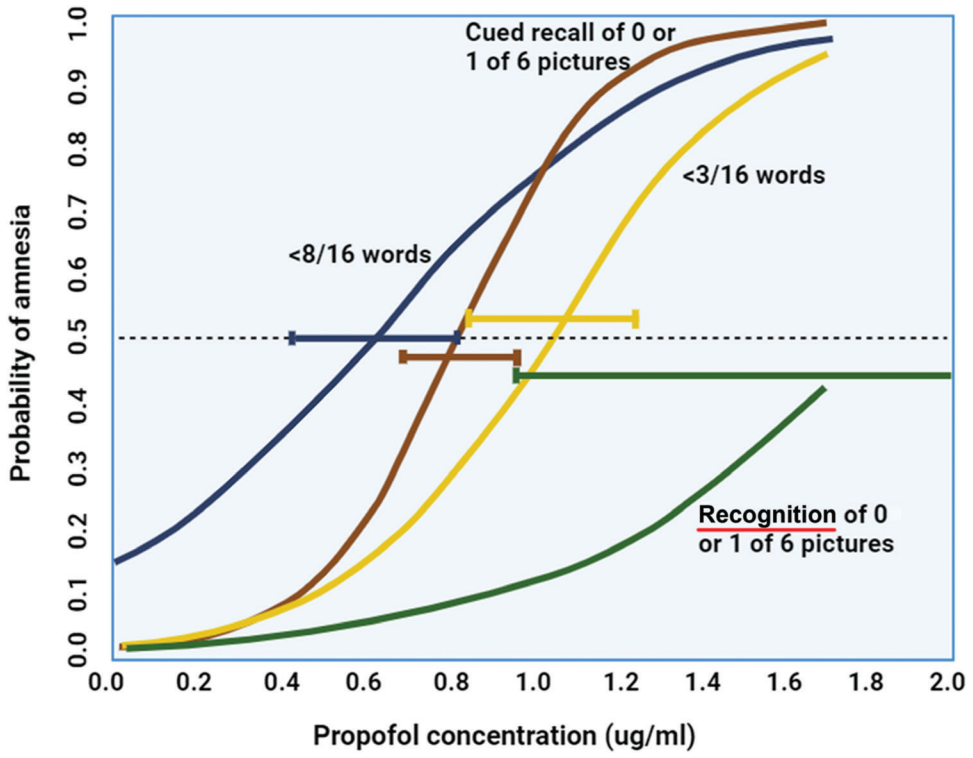


Fig. 4. Effect of propofol on various tests of memory using items of different salience and different forms of recognition. The data points represent the probability of amnesia being present as the serum concentration of propofol increases. CI for Cp50 amnesia are given as *horizontal bold lines*. Pictures are more salient than words, and significantly higher concentrations of propofol are required to cause amnesia when subjects are presented with the item and queried on recognition. However, free recall with only hints is more fragile and is as sensitive to drug effect as memory for words. A similar result is obtained for midazolam.[39]

protocols. Results have been highly varied, and the extent of implicit memory formation under anesthesia, the contexts in which it is more likely to occur, and any clinical significance remain undefined. To this end, a recent meta-analysis by Linassi *et al.*[107] found that only 36% of studies identified any form of implicit memory, and highlighted some counterintuitive characteristics, such as a lower likelihood of implicit memory formation in sedation cases than general anesthesia. It is unclear whether this represents a genuine finding challenging conventional explanation or a spurious outcome emerging from excessively methodologic heterogeneity.

Memory and Emotion during Monitored Anesthesia Care, Procedural Sedation, and Regional Anesthesia. Most research on anesthetic amnesia conducted in clinical settings has focused on intraoperative awareness under intended general anesthesia. However, patients receiving other forms of anesthesia are also concerned with unwanted awareness, memory, and negative emotional experiences. These patients represent a highly substantive proportion of the total population of patients who rely on effective anesthesia care: procedures or surgery under monitored anesthesia care and conscious sedation account for approximately one-third of ambulatory surgeries.[108] The 5th National Audit Project, which sampled all anesthetics across the United Kingdom over a year, found that intraoperative recall in patients receiving regional anesthesia and sedation is a very common cause of patient dissatisfaction,[88,109] with the overall incidence and negative sequelae (flashbacks, nightmares, anxiety and depression, and chronic fear) comparable to that seen with intended general anesthesia. The potential impact is illustrated in a study by Kent *et al.*,[110] reporting on a cohort of 27 patients from the Anesthesia Awareness Registry who had undergone regional anesthesia or sedation and subsequently reported awareness of their procedure accompanied by distress. Approximately 40% of the cohort had persistent psychologic sequelae similar to that observed in cases involving general anesthesia; this included long-term adverse impact on their job performance (15%), family relationships (11%), and friendships (11%), and 15% reported being diagnosed with PTSD.

A psychologic concept that may be of great relevance to these negative outcomes is that of *coherence*.[111] Coherence is a natural human trait that describes the psychologic

gravitation toward order, comprehension, structure, and predictability; loss of coherence has long been understood to lead to psychopathology. It follows that psychologic impact can be highly dependent on how events transpire *relative to expectations*, and this may be of importance in guiding how we approach patients undergoing sedation. A patient undergoing an awake craniotomy fully expects to have awareness of their surgery; a patient having a general anesthetic does not. Viewed in a coherence framework, it is the unexpectedness and potential incomprehensibility of such an awareness episode that so strongly predisposes it to cause psychologic morbidity, but what are the expectations of patients during sedation? Anesthesia providers may understand that awareness and postoperative recall are possibilities. However, this does not align with the expectation of patients: Bombardieri *et al.*[112] reported that 57% of patients who had recall from sedation had no previous expectation that awareness was possible. An important part of the remedy might be as simple as ensuring that in situations where awareness is possible, patients are appropriately informed of the possibility and guided to have expectations that will render it a comprehensible and nonthreatening event. However, another important principle is for clinicians' pharmacologic choices to be informed by an understanding of their effects on memory. To this end, current guidelines on sedation practices do not address the securing of amnesia.[113] The discussion in this review might suggest, for example, that a decision on whether to use propofol or dexmedetomidine as the basis for sedation should include consideration that propofol is a far more potent amnestic than dexmedetomidine. Practitioners frequently use the benzodiazepine midazolam in an empiric, unit dosing fashion to address amnesia, but a small study by Bulach *et al.*[114] demonstrated that a dose of 2 mg, often invariantly given to all patients, will not reliably achieve amnesia. There is no processed EEG marker specific to amnesia that can be used to guide a target-directed approach; hence, an appreciation of amnestic pharmacology and psychology fundamentals is potentially more important in guiding the clinical approach to sedation than it is to general anesthesia.

What Is the Role of Amnesia in Cesarean Delivery under Neuraxial Anesthesia?. Another challenging case example is the management of amnesia in cesarean delivery, which is commonly performed under neuraxial anesthesia.[115–117] These patients are young and healthy, and their open abdominal surgeries are performed awake with almost no sedation. There are thus compelling reasons to avoid the administration of any amnestic agent, but parturients frequently suffer stress and pain intraoperatively. A recent prospective observational study by Keltz *et al.*[118] revealed that 11.9% of parturients experienced pain intraoperatively, with a median pain score of 4.0, and further found that providers frequently failed to manage pain adequately. An even higher rate (22.7%) of intraoperative pain has been reported under neuraxial anesthesia.[119] Lopez *et al.*[120] reported that 9.2% of postcesarean patients had PTSD profile symptoms and 2.7% had full PTSD and that treatment with benzodiazepine after the precipitating distressing event did not reduce risk. Although there is a paucity of data, it is possible that these concerns may be magnified in certain cultural and healthcare settings: one study found that the overall prevalence of preoperative anxiety in patients undergoing elective cesarean delivery is 67.9%, and 65.9% of those patients with anxiety reported a fear of death.[121] Further evidence supporting the importance of these psychologic outcomes is reflected by the fact that intraoperative pain under neuraxial anesthesia has replaced accidental awareness under general anesthesia as the most common successful medicolegal claim against obstetric anesthetists in the United Kingdom.[122,123] The Statement on Pain during Cesarean Delivery by the American Society of Anesthesiologists acknowledged that pain under neuraxial anesthesia during cesarean delivery is considered failed anesthesia.[124] Clinicians are again referred to the importance of psychologic coherence and the need to define patient expectations so that events are comprehensible and expected. There has been considerable interest in the effects of ketamine and esketamine on psychologic outcomes after cesarean section, and meta-analyses suggest that administration perisection reduces the incidence of postpartum depression and depressive symptoms.[125,126] Esketamine also appears to have efficacy as a supplemental analgesic during cesarean section, although it has some transient side effects.[127] Ketamine's potential effects in fear memory systems pose interesting questions on whether it can be used to manage harmful affective associations of memories without causing amnesia,[128] but considerably more research is required before clinical recommendations are possible.

Does Preoperative Medication Sufficiently Reduce Anxiety or Produce Amnesia?. The reported incidence of preoperative anxiety widely ranges from 1 to 92%,[129,130] and its negative impact on surgical patients is well documented.[131–133] The full scope of how preoperative anxiety affects memory and affective associations of the perioperative period has not been systemically assessed. What is clear from the psychology literature is that negative emotions associated with the amygdala axis, including anxiety, usually enhance memory of events occurring concurrently, even if they are intrinsically nonemotional[36,134,135]; interestingly, these memories are frequently *perceived* as being more accurate but in actuality are not.[136] One caveat to this is that anxiety can also lead to fragmented attention, which can have the downstream effect of reducing memory for complex stimuli that require focused attention to assess. Extreme negative emotion such as extreme fear may even induce a retrograde amnesia,[137,138] and this is well described in critical illness.[139] Even with the relationship between

preoperative anxiety and postoperative psychologic morbidity being undefined, common sense would suggest that interventions to reduce preoperative anxiety have potential benefit. A common practice is to administer small doses (1 to 2 mg) of midazolam, although a recent small randomized study failed to verify its efficacy in reducing anxiety scores when compared to the day before surgery,[140] and a Cochrane review found only low-quality evidence to support its effectiveness.[141] In unselected adult populations, 2 mg of midazolam does not reliably produce amnesia in all patients,[114] and negative memories may be more resistant to the amnestic effect of GABAergic drugs.[40,142] As will be discussed further below, there is substantial evidence and concern that benzodiazepines given immediately after a traumatic event may worsen psychologic outcomes, although no study has been conducted to evaluate proactive use in the preoperative setting. We can offer no specific evidence-based guidance but alert clinicians to some of complex issues involved in making decisions regarding preoperative sedation and anxiolysis.[143]

Are There Harmful Cognitive Effects Associated with Drug-induced Amnesia?. An oft-cited concern is that the pharmacologic interventions used to achieve a short-term state of amnesia may have longer-lasting effects leading to postoperative delirium and cognitive dysfunction; the suggestion is usually that it is the parallel effect of the drug and not that amnesia *per se* is causative. There is a prevalent concern that benzodiazepines in general, and midazolam in particular, may cause postoperative delirium, especially in patients over age 70. What is frequently misunderstood is that the foundations for these concerns are heavily based on reports from the critical care setting.[144,145] Multiple recent studies and meta-analyses have provided reassurance that midazolam given preoperatively does not increase the risk of postoperative delirium.[146–148] Further, despite some earlier concerns derived from different clinical contexts,[149,150] there is no evidence that a single preoperative dose of midazolam increases the risk of longer-term postoperative dysfunction.[151–153]

Preoperative Fear and Amnesia. Fear systems are memory systems,[154] and the PTSD cluster of psychopathologies are, fundamentally, disorders of memory that involve connectivity paths in dysfunctional circuits mediating emotion regulation, threat detection, contextual processing, and fear learning (fig. 5).[60,155] Preoperative fear is relevant to any understanding of anesthetic amnesia for three reasons: (1) the amygdala-dependent fear systems are potent modulators of explicit memory and can amplify the strength of a memory, potentially making it more resistant to the amnestic effects of anesthetic drugs; (2) some fear memory processes are nonconscious, making it challenging to assess whether anesthetic drugs block those processes in the same way they do conscious memories; and (3) because conscious and nonconscious fear memory processes underpin psychopathologies, anesthetic drugs have a potential ability to modify risk for the development of these negative and sometimes long-arcing outcomes.[61]

Pooled analysis suggests that ~45 to 50% of all surgical patients experience preoperative anxiety,[156,157] which may increase to 80% in the case of higher-risk procedures.[158] A total of 70% of patients report some aspect of fear associated with upcoming surgery.[157] Postoperatively, 16% of patients meet the screening cutoff score for PTSD symptoms, and 8% will meet the criteria for a diagnosis of PTSD associated with their surgery.[159] This is significantly higher than the expected prevalence in the general population. Anxiety shares several neurobiological features with PTSD and has a strong comorbid association with PTSD.[160] However, the nature of the relationship between preoperative state or trait anxiety and the development of postoperative PTSD, and especially whether preoperative anxiety represents a modifiable risk factor, has not been systematically explored.

Many neurobiological processes and functions that are thought to be related to the development of PTSD have the potential to be profoundly affected by surgery and other aspects of perioperative care: autonomic reactivity, hypothalamic–pituitary–adrenal axis regulation, proinflammatory cytokines, neurosteroids, and sleep physiology are all domains of interest in PTSD.[160] The role of early central autonomic reactivity has driven some interest in the potential for dexmedetomidine to reduce some of the key promoters of PTSD, although most of this has been confined to animal or translational work[44,161]; clinically, Yu *et al.*[162] recently published a small randomized controlled trial of 310 patients undergoing emergency trauma surgery, showing that an infusion of dexmedetomidine delivered at 0.1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ during surgery and in the evenings of postoperative days 1 to 3 halved the incidence of PTSD at 30 days. In contrast, animal and translational fMRI studies suggesting that propofol may not block the processes underlying PTSD[40,161] have recently received some clinical reinforcement from a 300-patient randomized controlled trial by Zhong *et al.*[163] showing that, compared to sevoflurane, the use of propofol was associated with a twofold increase in the risk of PTSD after trauma surgery. The potential for ketamine to modify psychologic outcomes is of particular interest because of its known effectiveness in the treatment of refractory major depression.[164] However, depression and PTSD, although frequently comorbid, may have less neurobiological commonality, and the use of ketamine in the prevention and treatment of PTSD is controversial.[165] Clinical studies have provided little evidence that the use of ketamine perioperatively alters depression or other psychologic outcomes,[166] and there is no study specific to PTSD outcomes. While there is, at least theoretically, significant potential for pharmacologic choices made

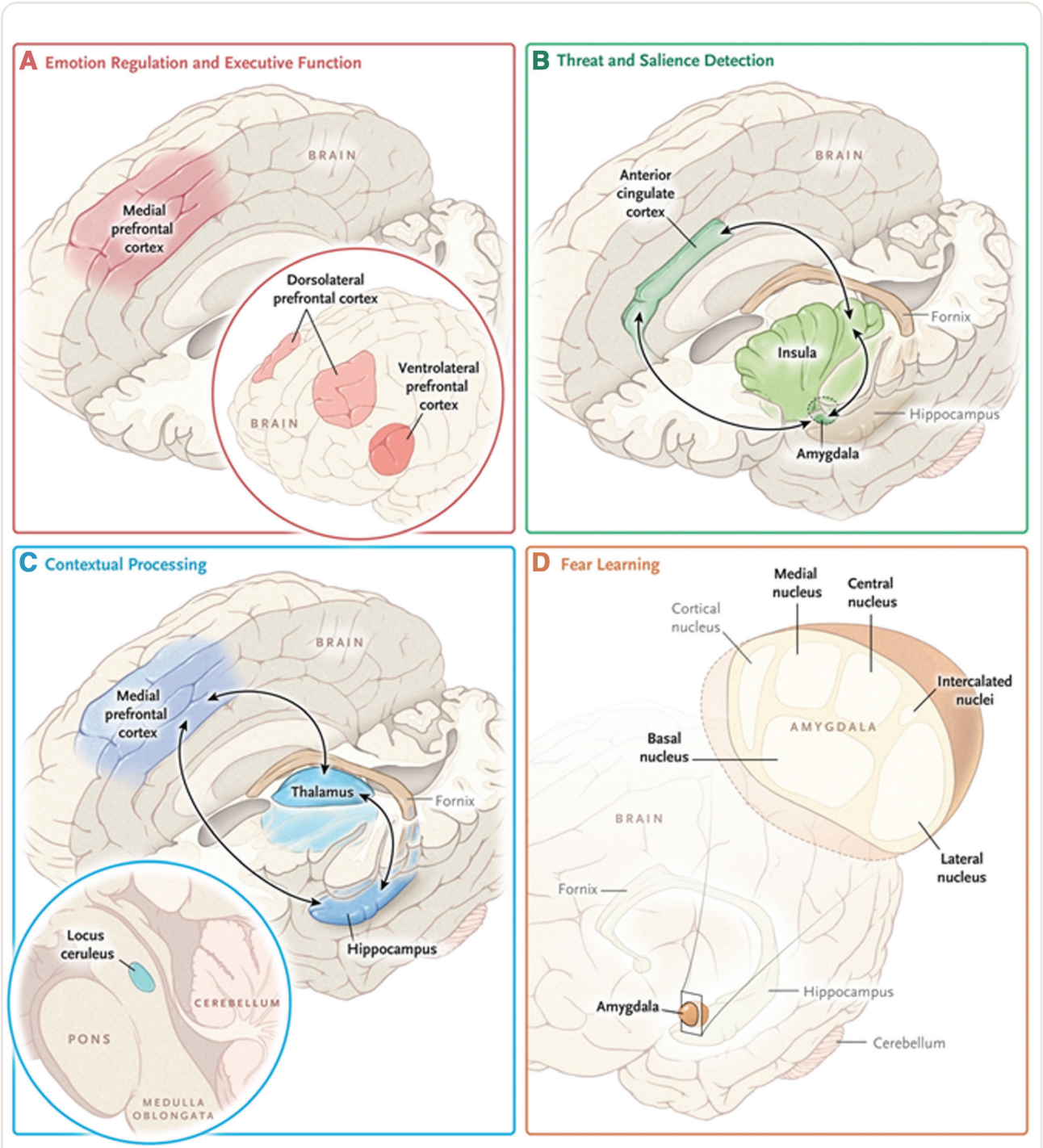


Fig. 5. Brain regions implicated in the pathophysiology of posttraumatic stress disorder. Shown are the known connectivity paths within four dysfunctional circuits that play a part in the psychopathology of posttraumatic stress disorder: (*A*) emotion regulation and executive function, (*B*) threat and salience detection, (*C*) contextual processing, and (*D*) fear learning. Many of the regions involved in these circuits are known targets of anesthetic drugs. Replicated from Shalev *et al.*[155]

by anesthesiologists to affect PTSD cluster outcomes after surgery, the current level of evidence falls short of enabling strong recommendations but provides a call for further research.

Management of Failed Amnesia. Anesthetic drugs do not cause clinically relevant retrograde amnesia in humans.[114] Thus, the use of rescue doses of midazolam *after* suspected awareness may reduce the likelihood of the memory of

the forward event but will not erase any memory already formed. In fact, the administration of an amnestic drug after the encoding of a memory may lead to the somewhat counterintuitive but well described phenomenon of *retrograde facilitation*, enhancing the consolidation of the memory formed immediately before drug administration.[167,168] Therefore, prevention is key in operative management. If recall is suspected or confirmed in either an early or delayed postoperative interview, there is a window within which decisions have the potential to either augment or reduce the probability that the experience will ultimately lead to PTSD. The most important principle for anesthesiologists to apply is a recognition of the limitations of their expertise in making decisions that will favorably influence this secondary prevention. Amplifying the 5th National Audit Project study recommendations,[88] we strongly advocate for early consultation of a psychiatrist or psychologist with experience in the prevention of PTSD after trauma, followed by a multidisciplinary approach. There are no studies to specifically guide the prevention of PTSD in the population of those experiencing intraoperative recall; however, there is extensive guidance that can be obtained from studies of early intervention in the prevention of PTSD after other forms of trauma.[169] Some treatment modalities commonly practiced in the prevention of PTSD that might feature in the approach to a traumatic episode of intraoperative awareness and postoperation recall are listed in Table 2.

Future Research. The premise of this review is that the intersection of anesthetic drugs and memory has multiple domains of clinical importance that are underinvestigated. We suggest the following as some of potential areas for research moving forward:

- *Elucidating biomarkers specific to amnesia.* Processed EEG algorithms that assess "depth of anesthesia" are undoubtedly useful but are not directly assessing a neurophysiologic signature specific to memory function. Given the evidence that anesthetic drugs do not reliably cause removal of all conscious processing, the development of an index that is specific to amnesia and robust across drugs from different receptor classes would be significant. Previous studies have suggested the alpha–beta ratio in the EEG as a possible indicator of amnesia,[170,171] but this needs to be further validated. It may be the case that EEG cannot access and measure deep brain regions that are crucial in memory formation, but it is worth investigating whether region-specific EEG indices, such as the posteriorization–anteriorization index, would be more accurate.[172]
- *Defining the trajectories of postoperative memory-based psychologic sequelae.* As discussed, PTSD cluster psychopathologies may represent one of the most common postoperative morbidities,[159] but there is minimal detail in understanding the epidemiology, risk factors, and clinical trajectories. The identification of candidate modifiable risk factors or treatments will require a far more thorough understanding of the problem than we have at present.
- *Understanding the effects of anesthetic drugs on fear memory systems.* If the occurrence of postoperative PTSD is modifiable through the clinical decisions of anesthesiologists, it will most likely come from understanding the actions of pharmacologic agents on the amygdala-centered fear memory systems that are the mechanistic basis for the pathologies. While some translational fMRI work has been conducted over the last 15 yr,[61] many questions remain.
- *Evaluating the role of novel, short-acting amnestic agents.* Because amnestic drugs also cause sedation, the ability to dose to a maximal, saturating amnestic effect may be limited by concerns for prolonged sedation. The metabolism and elimination kinetics of ultra-short acting drugs can facilitate the targeting of higher concentrations. Because of its metabolism by tissue esterases akin to remifentanil, the benzodiazepine remimazolam has promising properties worthy of further study.[173] Also intriguing are short-acting ketamine analogs.[174,175] The recovery time of short-acting ketamine is 10 to 15 times faster than ketamine in animals, but the pharmacokinetics must be validated in human subjects.
- *Explore novel and emerging approaches to the treatment of intraoperative recall PTSD.* Several novel approaches to the management of PTSD could be applied to patients who develop the disorder after intraoperative awareness with recall. The use of reconsolidation therapy, cannabidiol, ketamine, vagal nerve stimulation, and stellate ganglion block all have supportive studies[176]; of note, a small pilot study of PTSD patients receiving transcutaneous cervical vagal nerve stimulation found that the stimulation reduced the inflammatory response to stress triggers.[177] Repetitive transcranial magnetic stimulation uses targeted localized currents and can interfere with memory processes; translational studies have been shown to affect amnesia[178,179] and conversely to reactivate episodic memories into awareness[180] and have even be used to treat cognitive decline in early Alzheimer's disease.[181,182] There is some evidence of efficacy in the treatment of PTSD.[183]

Conclusions

With increasing evidence that the impairment of consciousness by anesthetic drugs does not always lead to its complete absence, we must accept that the apparent complete loss of subjective experience during anesthesia may at times be an illusion created by amnesia. However, the study of how anesthetic drugs cause amnesia, and importantly how they fail, has received less attention than the other cardinal properties of anesthesia. As there is no reliable biomarker to determine the adequacy of pharmacologic

Table 2. Strategy for Managing Postoperation PTSD

Category	Strategy	Details
Psychologic interventions	Cognitive behavioral therapy (CBT)	Focuses on changing unhelpful thoughts and behaviors and exposure therapy to reduce fear
	Eye movement desensitization and reprocessing (EMDR)	Involves processing traumatic memories through guided eye movement
	Trauma-focused therapy	Specifically designed to address trauma-related symptoms
	Mindfulness-based stress reduction (MBSR)	Utilizes mindfulness practices to reduce stress and enhance emotional regulation
Pharmacologic interventions	Selective serotonin reuptake inhibitors (SSRIs)	First-line medication treatment, such as sertraline or paroxetine
	Serotonin–norepinephrine reuptake inhibitors (SNRIs)	Alternatives to SSRIs, such as venlafaxine
	Prazosin	Used to reduce nightmares and sleep disturbances associated with PTSD
	Benzodiazepines	Used *with caution* for short-term anxiety relief
Supportive therapies	Peer support groups	Provides a supportive community for sharing experiences and coping strategies
	Family therapy	Involves family members to support the patient and improve communication
	Social support networks	Encourages building strong social connections for emotional support
Lifestyle and self-care	Regular exercise	Helps reduce anxiety and improve mood through physical activity
	Healthy diet	Promotes overall well-being and reduces stress through proper nutrition
	Adequate sleep	Ensures restorative sleep to enhance recovery and mental health
	Relaxation techniques	Techniques like deep breathing, yoga, and meditation to manage stress
Educational interventions	Patient education	Provides information about PTSD symptoms, treatment options, and coping strategies
	Pain management education	Educates patients on effective pain management to prevent PTSD-related pain anxiety
	Stress management workshops	Offers workshops to teach stress reduction techniques
Follow-up care	Regular follow-up appointments	Scheduled visits with healthcare providers to monitor progress and adjust treatment
	Telephone or online counseling	Provides continued support through remote counseling services
	Crisis intervention services	Access to emergency mental health services in case of severe distress
Alternative therapies	Acupuncture	May help reduce anxiety and improve overall well-being
	Animal-assisted therapy	Utilizes interactions with animals to reduce stress and improve emotional health
	Art or music therapy	Encourages expression of emotions and trauma through creative outlets
Long-term management	Chronic PTSD management plans	Involves ongoing therapy and medication for long-term symptoms
	Vocational rehabilitation	Helps reintegrate into work life by addressing PTSD-related challenges
	Community integration programs	Supports re-engagement with community activities and social roles

PTSD, posttraumatic stress disorder.

amnesia in real time, anesthesiologists will benefit from an understanding of how anesthetic drugs cause amnesia and the important differences between agents. One fundamental concept is that anesthetic drugs can possess amnestic effects; such effects are dissociable from their sedative effects, and there is marked heterogeneity in their amnestic:sedative profiles. For example, propofol has potent specific amnestic potential, whereas dexmedetomidine is a pure sedative—a consideration that might be used to guide sedative choice. Midazolam possesses a potent amnestic effect similar to that of propofol, but the practice of administering 2 mg invariantly may not secure complete amnesia in some patients, and common concerns regarding the effects of midazolam on postoperative delirium may be greater than a close reading of the literature suggests. Ketamine's well known effectiveness in patients with depression has not been replicated in the setting of perioperative use, but there are some promising findings at the intersection of emotion and memory that warrant further study. PTSD is a well documented sequelae of intraoperative awareness and recall, which are fortunately relatively rare events. Less well appreciated is that PTSD cluster symptoms are alarmingly common in postoperative patients in general. The mechanism of PTSD cluster psychopathologies, which are a disorder of memory systems, involves amygdala-centered neural circuits that include many known and potential targets—and perhaps nontargets—of anesthetic drugs. The heterogeneity in the way different anesthetic drugs interact with these systems is only nascently understood but provides plausible mechanisms that might make the occurrence of these negative sequelae modifiable by drug choice. There is considerable scope for further research in this domain, as there is in the elucidation of an EEG biomarker specific to memory function, defining the amnestic properties of novel drugs, and exploring emerging approaches to the treatment of the memory-based psychologic sequelae of surgery.

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Competing Interests

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MIND TO MIND

Creative writing that explores the abstract side of our profession and our lives

The Last Time

Sophia Zhao, B.S., B.A.

The last time I saw you, you didn't
look like this: skin grazing bone, dry & flaxen
like husks forgotten at an orchard.
For a while, I watch you lurch from room
to room. Past the old couch, the broken
tabletop radio. Where we once traded stories,
your laughter full, tender, crooning,
the day thick with our habits & then,
nothing. What more can I remember?
All I know now are your purpling vessels &
your shrunken coughs & too many hands
inspecting your organs for signs of collapse.
Each second seems to hide behind itself
as I look at you. The last time I saw you—
I want us to be like that again.

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MIND TO MIND

Creative writing that explores the abstract side of our profession and our lives

The Simple Luxury of Sleeping On My Stomach

Lealani Mae Y. Acosta, M.D.

Pregnancy was my first deprivation
first sleeping prone, then decubitus, ultimately supine,
    my contortions and comfort sacrificed to sustain the life
    growing inside me
140 days or so, plus-minus the months it took my
postpartum body to bounce back and curl up again
    diastasis recti stretched against the sheets
    cheek against pillow with the drool stains to prove it.
oh the privilege of leaving a pillow with the indentation of my head at 2 AM
    to nurse my crying infant
the simple miracle of surviving childbirth

1,487 days after the pandemic began, I
    finally
    catch COVID.
My month's worth of toddler preschool (and confirmed negative) back-to-back colds
    mutates to new nasal congestion
    so that's what a positive antigen test looks like

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Inflamed sinuses bar scent, taste, and a snort of O2 in my nasal passage
I toss from side to side to front to back
sleep and mucus evading my grasp
    as I gasp in my bed
yet here I am
    post vaccine
    post booster
    post pandemic

I have nightmares, flashbacks to 96 days into the throes of the first wave of COVID,
ICU beds yawned with patients from the first shift I was assigned,
    post intubation
    post ECMO
    patients who possessed no luxury of choice but to be placed
        prone

And now I repose
the sweet taste of that cotton-polyester blend pillowcase crusted with drool
I cherish the metallic trace of nirmatrelvir on my tongue,
the simple luxury of sleeping on my stomach

Impact of the U.S. Food and Drug Administration's Safety Communication on Gabapentinoid–Opioid Coprescription

To the Editor:

Pregabalin and gabapentin (gabapentinoids) have both been U.S. Food and Drug Administration (FDA; Bethesda, Maryland) approved for postherpetic neuralgia and partial-onset seizures, with pregabalin additionally indicated for treatment of diabetic peripheral neuropathy, post–spinal cord injury neuropathic pain, and fibromyalgia.[1] Off label, both have also been included in perioperative multimodal analgesia protocols.[2] In December 2019, the FDA issued a Drug Safety Communication concerning potential serious risk of respiratory depression when coprescribed with other central nervous system depressants or when prescribed in patients with impaired lung function. The Communication emphasized opioid–gabapentinoid coprescription while also cautioning about increased abuse risk of both agents when coprescribed.[1] This may have had impact on coprescription patterns as well as on pain management/opioid–sparing strategies farther downstream. Therefore, we compared gabapentinoid–opioid coprescriptions before and after the Communication.

This observational study included Merative MarketScan pharmaceutical claims data (February 2018 to December 2022) of adults (18 yr or older). This study was approved by the institutional review board at the Hospital for Special Surgery under protocol number IRB #2017-0169. Gabapentinoid–opioid coprescription fills (definition: any overlapping supply of opioids and gabapentin/pregabalin based on prescription date and days' supply of medication) were assessed with the patient as the analytic unit $\left(\frac{\text{patients with co-prescription fills}}{\text{total number of patients with opioid prescription fills for the same month}}\right)$, as the Communication expresses concern about overlapping prescriptions (at the unit of the patient).[1] Interrupted time-series analyses (using R Studio, v4.4.1, R Foundation for Statistical Computing, Austria) tested the Communication's effect on gabapentinoid–opioid coprescription fills (gabapentin and pregabalin analyzed separately), accounting for autocorrelation and the cyclic nature of the data. $P < 0.05$ was considered statistically significant.

Among 2,119,239 (fig. 1) and 583,344 (fig. 2) patients with gabapentin–opioid and pregabalin–opioid coprescription fills, respectively, we found significantly increasing monthly trends in gabapentin–opioid (trend coefficient [t] = 0.05; 95% CI, 0.02 to 0.08; $P < 0.001$) and pregabalin–opioid (t = 0.02; 95% CI, 0.01 to 0.03; $P < 0.001$) coprescription fills before the Communication. Post Communication, the rate of monthly trend change was significantly reduced only for gabapentin–opioid coprescription fills (interaction term = −0.04; 95% CI, [−0.07] to [−0.01]; $P = 0.023$), while an increasing trend remained. This was not observed for pregabalin–opioid coprescription fills (supplemental table 1, https://links.lww.com/ALN/E10). When evaluating pregabalin and gabapentin combined, we observed an increasing pre-communication trend with no reduction post communication (supplemental table 2, https://links.lww.com/ALN/E11). After excluding March 2020 to May 2020 (initial COVID-19 lockdown), a major medical and statistical outlier in the data, differences from our primary analysis were a statistically significant increase in the rate of month-to-month change in trends of pregabalin–opioid coprescription fills and a negation of the immediate increase after the warning for gabapentinoid–opioid coprescription fills (supplemental fig. 1, https://links.lww.com/ALN/E12).

In summary, while gabapentin–opioid coprescription fill trends were still increasing post Communication, the rate of increase was slower compared with pre Communication. No such impact was observed for pregabalin–opioid coprescription fills. Overall, gabapentinoid–opioid coprescription fills significantly increased immediately after the FDA Communication without the rate of change in trends being affected. In a sensitivity analysis, the immediate coprescription fill rate increase after the Communication—likely due to COVID-19[3]—did impact our main analysis, but our main conclusions remained.

While evidence of the real-world impact of FDA warnings on pharmaceuticals is sparse, previous studies have evaluated drugs such as codeine (in pediatric tonsillectomy/adenoidectomy), varenicline, and febuxostat. Here, prescription rates generally declined before the FDA's first announcement, suggesting that physicians may already act on concerns from available literature before formal warnings.[4–6] Indeed, declines in codeine prescribing were steepest just before the first FDA communication and slowed following subsequent ones.[4] Conversely, febuxostat's and varenicline's decrease was steeper after each FDA escalation.[5,6] These different patterns may be attributed to the risk–benefit consideration of each drug in its prescribing setting. Arguably, the risk of sudden death in

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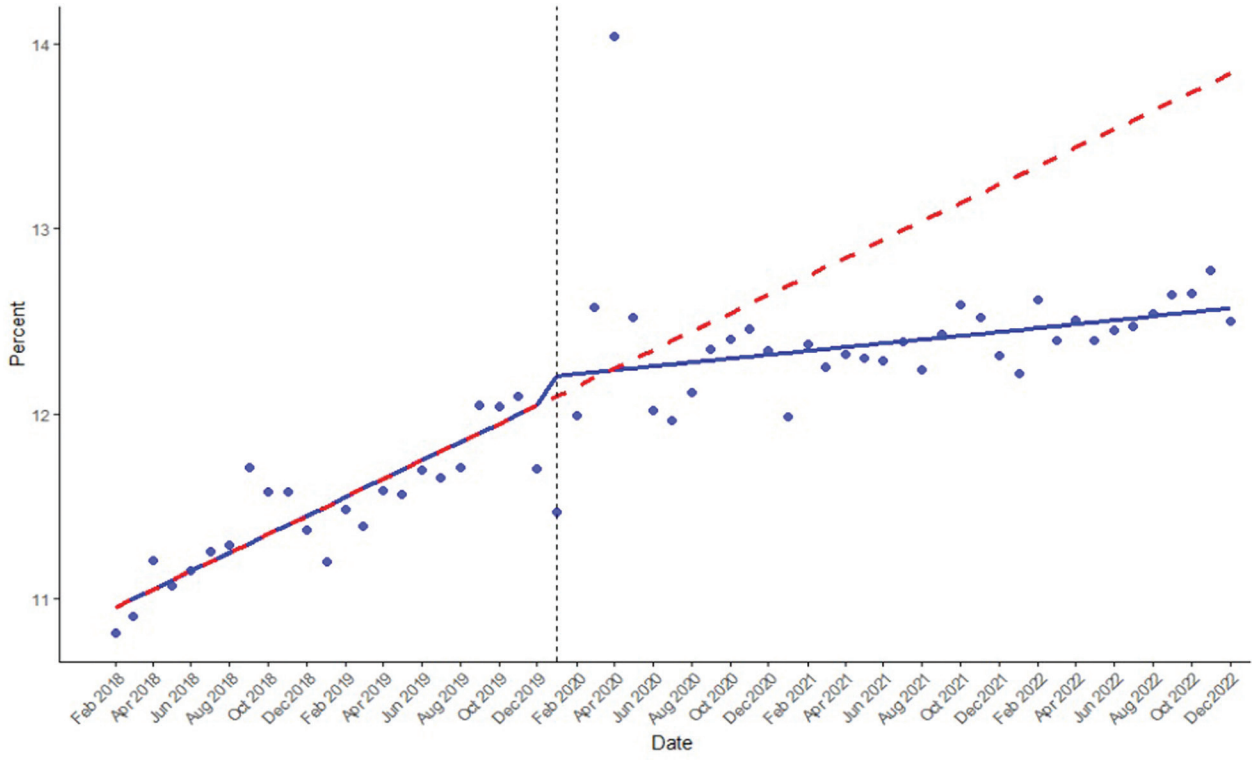


Fig. 1. Trends in gabapentin–opioid coprescriptions before and after the U.S. Food and Drug Administration warning in December 2019. *Blue dots* represent the monthly percentage of patients with coprescriptions. *Blue lines* represent the coprescription trend. The *red dotted line* represents the hypothetical trajectory of the trend existing before December 2019 if the U.S. Food and Drug Administration warning was never issued. The *black dotted line* marks the interruption point used for the interrupted-series analysis.

children undergoing tonsillectomy or adenoidectomy is very serious and unpredictable, leading physicians to perhaps not wait for the FDA to limit codeine prescription.[4] In contrast, risks of febuxostat and varenicline may be more manageable[5,6] allowing physicians more leeway to wait on FDA announcements and adjust prescriptions accordingly.

In our study, timing of the warning was crucial, as it came during a period representing high interest in gabapentinoids as opioid-sparing agents,[2] and physicians may have perceived reducing opioids as a higher priority than controlling the risk of respiratory depression due to coprescription. Perhaps prescribers operated from the belief that the risk–reward profile favors coprescription. While coprescription might increase the risk of respiratory depression due to gabapentinoids, it decreases overall opioid consumption,[5] which may lead to a net decrease of respiratory depression risk. Even if this hypothesis is not true, gabapentinoids remain an appealing choice for various neurologic and musculoskeletal pain conditions.[7,8] As gabapentinoid–opioid coprescriptions are likely for analgesia, this could explain the difference observed between the two agents, as pregabalin—the predominant analgesic—was not impacted, whereas gabapentin was somewhat affected. Additionally, some have demonstrated a favorable risk–benefit ratio of adding gabapentinoids to perioperative multimodal analgesia,[2] while others have questioned this.[9] The exact mechanisms behind variables influencing adoption or rejection of serious FDA warnings remain elusive. In April 2023, the FDA escalated the safety concern on gabapentinoid–opioid coprescription to a boxed warning, on the opioids' label.[10] Future studies should explore its impact on coprescriptions as well as the reasons behind the FDA's impact (or absence of) on coprescription patterns for different drugs and settings.

This study has limitations, including retrospective design and reliance on billing codes of pharmacy dispensing, which risks medication misclassification. The database does not provide data on the diagnosis associated with the prescriptions, which limits our ability to draw specific conclusions based on indication. Selection bias is also possible, as the database includes only patients with private insurance. Finally, gabapentinoids are subject to various regulations. While pregabalin has been federally flagged as a schedule V substance since 2004,[1] which could not have influenced our results, we acknowledge that state-specific regulations on gabapentin may impose limitations on interpreting our results. However, we argue that their impact is minor, as these states represent 10% of the U.S. population, and most regulations were implemented before December 2019.[1]

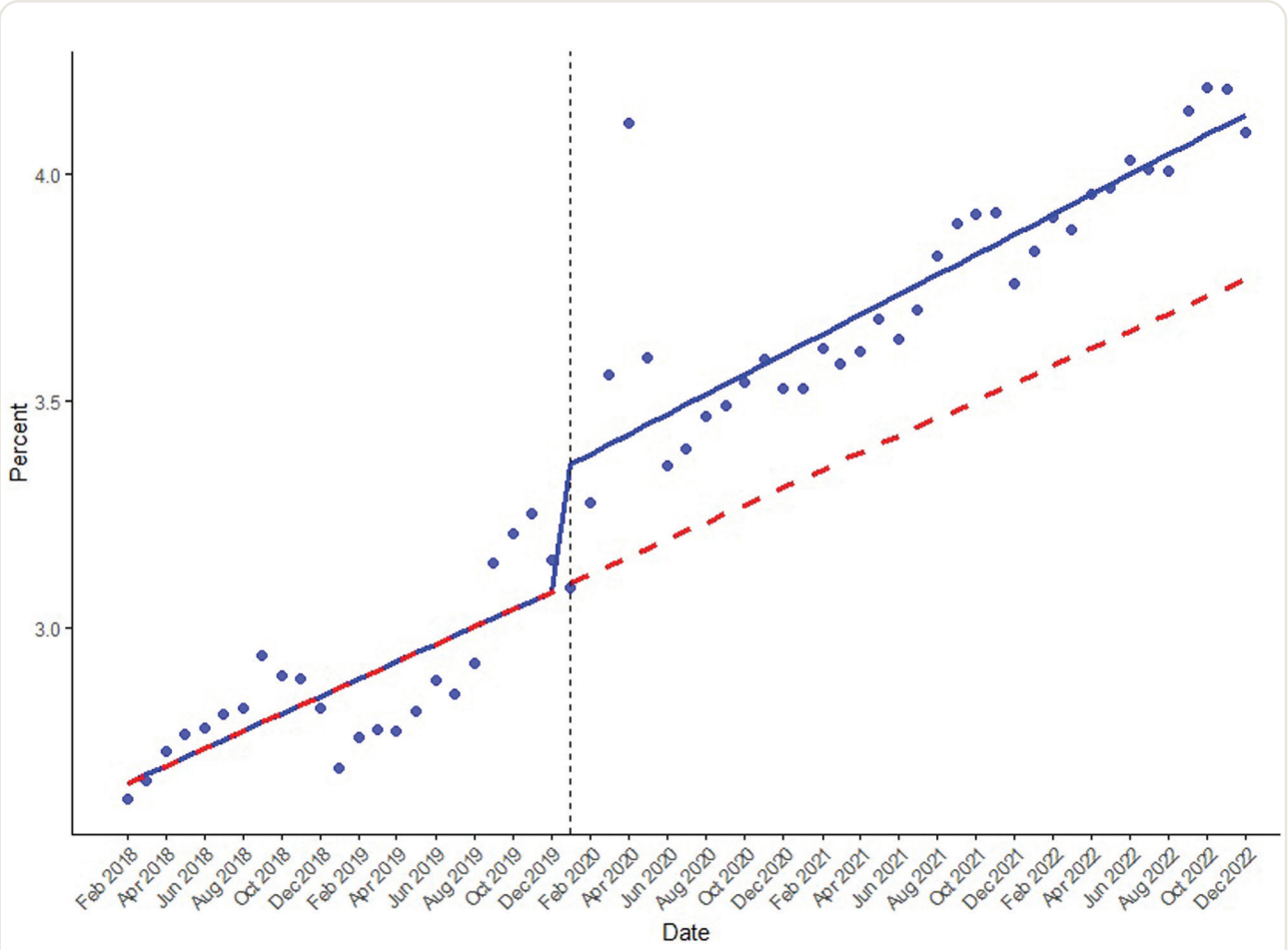


Fig. 2. Trends in pregabalin–opioid coprescriptions before and after the U.S. Food and Drug Administration warning in December 2019. *Blue dots* represent the monthly percentage of patients with coprescriptions. *Blue lines* represent the coprescription trend. The *red dotted line* represents the hypothetical trajectory of the trend existing before December 2019 if the U.S. Food and Drug Administration warning was never issued. The *black dotted line* marks the interruption point used for the interrupted-series analysis.

In conclusion, while gabapentin–opioid coprescription fills showed a deceleration in rate of change, pregabalin and overall gabapentinoid–opioid coprescription fill trends were not significantly affected by the FDA's December 2019 announcement. Future research should examine how different drug indications, prescription patterns, and associated physicians' perceptions affect the impact of FDA warnings.

Research Support

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Competing Interests

Dr. Memtsoudis has a U.S. patent application for a multicatheter infusion system (US-2017-0361063) and is the owner of SGM Consulting, LLC (Rumson, New Jersey). He is a partner in Parvizi Surgical Innovations, LLC (Philadelphia, Pennsylvania). None of the aforementioned relations influenced the conduct of the present study. The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental Table 1. Interrupted Time-series Analysis of Gabapentin–Opioid and Pregabalin–Opioid Coprescription Trends, https://links.lww.com/ALN/E10

Supplemental Table 2. Interrupted Time-series Analysis of Gabapentinoid–Opioid Coprescription Trends, https://links.lww.com/ALN/E11

Supplemental Figure 1. Trends in Coprescriptions before and after the FDA Warning in December 2019 without the Peak of COVID-19 First Lockdown (March to May 2020) and Interrupted Time-series Analysis, https://links.lww.com/ALN/E12

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Effect of Midazolam on Postoperative Delirium: Comment

To the Editor,

We read with great interest the article titled "Effect of Intraoperative Midazolam on Postoperative Delirium in Older Surgical Patients: A Prospective, Multicenter Cohort Study,"[1] in the February 2025 issue of Anesthesiology. The authors have provided an important contribution to the role of intraoperative midazolam on postoperative delirium in elderly patients. However, we would like to foster debate on some important issues related to this study.

Although the authors performed elaborate statistical analyses, we wondered why the use of dexmedetomidine in both studied groups was not discussed in more detail. Dexmedetomidine is associated with a reduced risk of delirium in surgical patients and exerts a modulatory effect on α5 subunit–containing γ-aminobutyric acid type A receptors, implicated in postoperative cognitive dysfunction, serving as a protective factor when used alongside midazolam by preserving normal inhibitory neurotransmission and cognitive function.[2] Multiple randomized controlled trials and meta-analyses have consistently demonstrated that dexmedetomidine is associated with a reduced risk of postoperative delirium, especially in noncardiac surgical settings. For instance, Duan *et al*. reported a significant reduction in postoperative delirium incidence with dexmedetomidine compared to benzodiazepines (odds ratio, 0.35; 95% CI, 0.24 to 0.51).[3] Similarly, a meta-analysis by Zeng *et al.*, focusing on elderly patients undergoing noncardiac surgery, highlighted a significant reduction in postoperative delirium risk with dexmedetomidine (relative risk, 0.61; 95% CI, 0.34 to 0.76).[4] Dexmedetomidine offers superior sedation with fewer complications than midazolam.[5] Silva-Jr *et al.*[5] highlighted dexmedetomidine's sympatholytic properties and minimal respiratory impact, with significantly lower rates of psychomotor agitation and respiratory depression compared to midazolam. These findings underscore the importance of safety profiles, particularly for elderly surgical patients. From the authors point of view, the administration of dexmedetomidine in this study should have been discussed in greater detail as a potential confounder despite statistical adjustments, given its significantly higher use in the midazolam group in the primary analysis.

In conclusion, the study by Li *et al.*[1] provided valuable new data on the role of intraoperative midazolam on postoperative delirium among elderly patients, supported by its robust statistical power and design. However, the potential for residual confounding due to dexmedetomidine use and the exclusion of patients at high risk for delirium underscores the challenges inherent in observational research. While the findings are strengthened by the large sample size and advanced statistical adjustments, the overlapping pharmacologic effects of midazolam and dexmedetomidine might complicate the attribution of outcomes. These limitations emphasize the need for caution when interpreting the results and highlight the importance of further research to disentangle the independent effects of these agents on postoperative delirium.

Competing Interests

The authors declare no competing interests.

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Effect of Midazolam on Postoperative Delirium: Reply

In Reply:

We appreciate the constructive comments from Esper Treml *et al.*[1] on our recent publication regarding intraoperative midazolam use and its association with delirium.[2] Their insightful comments are valued and prompt us to address the points they have raised.

The primary concern raised was the pharmacodynamic overlap between midazolam and dexmedetomidine, which could result in conflicting impacts on the occurrence of postoperative delirium, and we agree. Evidence from meta-analyses and randomized controlled trials has suggested neuroprotective effects of dexmedetomidine, suggesting this drug as a promising preventive agent against postoperative delirium.[3,4] We would like to emphasize that our analysis has taken this into account, since we have recognized its important role in cognition. The variable of dexmedetomidine use was collected and included in the multivariable adjustments and subgroup analysis to address potential confounding. Specifically, the subgroup analysis focused on patients who did not receive intraoperative dexmedetomidine (fig. 3 in the original article),[2] thereby eliminating potential confounding effects from drug interactions. Notably, the occurrence of postoperative delirium exhibited comparable rates between the midazolam and non-midazolam groups (264 of 1,975 [13.4%] *vs.* 302 of 2,380 [12.7%]; adjusted risk ratio, 1.03; 95% CI, 0.84 to 1.27; $P = 0.78$). The results established the independent impact of midazolam on delirium outcome, consistent with our main analyses. Following this analysis, we did not explore the impact of dexmedetomidine, as there was no indication of midazolam contributing to an increased risk of postoperative delirium in the subgroup not receiving dexmedetomidine.

As an observational study, we acknowledge the potential of unmeasured confounding factors despite adjusting for known confounders. Therefore, we cautiously suggest in our conclusion that the association between intraoperative midazolam use and postoperative delirium may not be definitive, needing to be confirmed by randomized controlled trials. We will conduct a multicenter prospective randomized controlled trial to further verify the relationship between midazolam administration and occurrence of postoperative delirium while restricting the use of dexmedetomidine to isolate the effect of midazolam. In the future, we expect to provide robust evidence that can guide future clinical guidelines regarding midazolam administration during the perioperative period.

Competing Interests

The authors declare no competing interests.

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Trends in Neuraxial Labor Analgesia Utilization: Comment

To the Editor:

We read with considerable interest the research letter titled, "Trends in Neuraxial Labor Analgesia Utilization by Race and Ethnicity among Nulliparous Individuals Undergoing Spontaneous Vaginal Delivery, United States 2007 to 2022" by Stockert *et al.*[1] The authors conducted a retrospective analysis using U.S. Revised Certificate of Live Birth data from 2007 to 2022 and examined neuraxial analgesia utilization among nulliparous individuals with singleton pregnancies resulting in inpatient spontaneous live birth vaginal delivery. The specific aim was to evaluate racial and ethnic trends in labor analgesia over 16 yr. The study demonstrated a 16-yr trend of increasing neuraxial analgesia utilization across all racial and ethnic groups, with variations in the magnitude of change. Hispanic individuals had the largest increase of 28.2% over the study period, and the smallest increase was among White individuals.

With a cohort size of 13,227,536 individuals, the study was sufficiently powered to detect meaningful associations. However, the study only included race and ethnicity variables, which may serve as proxies for broader determinants of health (*e.g.*, social, structural, political, and commercial factors). According to the authors' insightful work, access to neuraxial labor analgesia has improved significantly over the past few decades. However, racial and ethnic disparities in utilization persist, with limited research exploring the underlying influences, beyond race and ethnicity, contributing to these differences. Other variables available in the revised birth certificate, such as maternal and paternal education, place of birth, provider type (*e.g.*, physician, certified nurse–midwife, or other), maternal need for higher levels of care, number of prenatal visits, outcomes of previous pregnancies, source of payment, and pregnancy-related risk factors, may offer a more nuanced understanding of how social and structural factors influence neuraxial analgesia utilization. While adjusting for these factors in primary analysis may have masked underlying disparities, secondary analyses could provide key insights to identify the mechanisms behind disparities. Did the authors conduct any sensitivity analyses with these variables? If so, then what did these analyses reveal about the role of social factors in the observed disparities? Additionally, maternal age and parity may influence analgesia utilization. Secondary analyses could clarify how individual-level clinical risk profiles impact disparities.

The use of U.S. Revised Certificate of Live Birth data presents another methodologic consideration. The authors mention the adoption of revisions that were approved nationwide throughout the study period. These revisions included the addition of maternal reporting on Hispanic origin (item 21) and the ability to select multiple races or self-identify ethnicity (item 22).[2,3] Changes in racial and ethnic data collection standards impact epidemiologic analyses, as shifts in categorization methodologies introduce variability in trend analyses and influence effect estimates in health disparity research.[4] Inconsistent racial classification methods, such as hypodescent models or the use of the "other" category, can obscure health disparities and bias results.[5,6] While these updates were essential for improving the granularity of demographic data, reducing misclassification, and improving the precision of demographic analyses, their delayed implementation until 2016 likely introduced variability into the dataset. Federal revisions to race and ethnicity data collection standards pose challenges for longitudinal analyses, as shifts in racial classification can alter population subgroup sizes, complicating trend analyses and comparability over time.[7–9] Given these potential biases, how did the authors address coding for race and ethnicity over the study period? Addressing these methodologic challenges is crucial for further research that uses data from the U.S. Revised Certificate of Live Birth or similar evolving data sets to ensure that studies are consistent in reporting categorical variables while ensuring the accuracy and reliability of future research on disparities in analgesia utilization *vis-à-vis* race and ethnicity.

The authors have conducted an important analysis that establishes a strong foundation for understanding trends in neuraxial analgesia use. Their examination of large-scale birth certificate data provides key insights into both rising utilization rates and persistent disparities across racial and ethnic groups in the United States. By demonstrating narrowing yet enduring gaps, this study highlights the impact of evolving healthcare policies and patient education while underscoring the need for continued work to promote equitable pain management. Future research should examine the impact of social determinants of health, provider influences, and geographic disparities on analgesia

utilization to inform policies in education, cultural competency, and equitable resource allocation.

We commend the authors for their valuable contributions to the disparities in neuraxial labor analgesia utilization, and we appreciate the opportunity to engage in this meaningful discussion on the importance of equitable pain management for all individuals in labor.

Competing Interests

The authors declare no competing interests.

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Trends in Neuraxial Labor Analgesia Utilization: Reply

In Reply:

We appreciate the thoughtful comments from Carter *et al.*[1] on our research letter about temporal trends in neuraxial labor analgesia among racial and ethnic groups in the United States.[2]

We agree that studying the determinants of racial and ethnic differences in neuraxial labor analgesia utilization would be highly valuable. We comment in the letter that our findings "may reflect the influence of acculturation, language concordant care, structural racism, and access to anesthetic care on the differential utilization of neuraxial labor analgesia over time across these groups."[2] Carter *et al.* ask whether we examined the role of other factors that may affect the use of neuraxial labor analgesia, including socioeconomic factors, clinical care factors, and comorbidities. We agree that this is an important and needed area of research. We do, however, note that many of these factors are either not available in the public use U.S. birth files or have poor validity. Our team previously published how birth certificate data alone are inadequate for maternal health disparity research and can lead to incorrect conclusions and, thus, should be used with caution.[3]

How race and ethnicity are collected and classified by federal agencies has changed over time. Carter *et al.* ask how our study team handled temporal changes in race and ethnicity

variables in the U.S. live birth data files during the study period from 2007 to 2022.[4] To accurately account for these changes, we engaged in careful examination of data documentation, data quality checks, and correspondence with the National Center for Health Statistics Birth Data (Atlanta, Georgia) team. We would be very willing to share our detailed methodology and statistical programs with other researchers upon request. We further note that we restricted analyses to data collected using the 2003 Revision of the U.S. Certificate of Live Birth, which reduced the effect of changes in the collection and classification of race and ethnicity. In addition, the U.S. Office of Management and Budget's standards for maintaining, collecting, and presenting data on race and ethnicity—which are widely used by federal agencies—were updated in 2024 and will require attention to research on trends in future years that stratify by racial and ethnic groups.[5]

Our findings are a useful starting point for in-depth investigation of how patient, provider, hospital, policy, and structural factors influence neuraxial labor analgesia utilization across racial and ethnic groups in the United States.

Competing Interests

The authors declare no competing interests.

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Covert Strokes in Patients Having Surgery: Comment

To the Editor:

We read with great interest the article published by Cui *et al.* (PRECISION study) on covert perioperative stroke in the Journal.[1] We would like to comment on two issues regarding the association between the preoperative administration of steroids, blood pressure management, and perioperative covert stroke.

First, the study shows that the preoperative administration of steroids is associated with a lower incidence of perioperative covert stroke. Specifically, stroke was documented in 8 of 128 patients who received steroids preoperatively, compared to 92 of 486 patients who did not. This strong association, with an odds ratio of 0.28 (95% CI, 0.13 to 0.59; $P = 0.001$), suggests a protective role for preoperative steroids. Moreover, the calculated relative risk reduction is 0.67, and the number needed to treat is 8. However, does this association imply a causal relationship? Despite the strong association, there is no scientific evidence or coherence between preoperative steroids and perioperative covert stroke according to the current understanding of the pathophysiology of perioperative stroke.[2] Steroids interfere with the hypothalamic–pituitary–adrenal axis, stress response, and inflammation; modulate β-receptor synthesis; and maintain cardiac output and vascular tone through increased sensitivity to catecholamines.[3] If the authors provide additional data on perioperative steroid use (indications, dosage, and the number of patients with hypothalamic–pituitary–adrenal axis suppression due to chronic steroid use preoperatively), the nature of the association between preoperative steroid administration and perioperative covert stroke could be elucidated.

Second, although the authors report almost no intraoperative hypotension (defined as mean arterial pressure lower than 65 mmHg) and no significant association between hypotension and covert stroke, they present only data about intraoperative hypotension. However, most perioperative strokes usually develop in the postoperative period—a

period characterized by hypercoagulability and less intensive monitoring of blood pressure.[4,5] Furthermore, 65% of study patients received vasoactive drugs intraoperatively and postoperatively. More data on postoperative blood pressure management and vasoactive drug administration (drug, indication, timing of administration) would be valuable in interpreting the study results regarding the incidence of covert stroke, especially in the context of extensive steroid use.

The PRECISION study demonstrates that perioperative covert strokes are common, affecting 11.9% of older patients who underwent major noncardiac surgery and doubling the risk of postoperative delirium and long-term neurocognitive decline. The pathophysiology of this type of stroke is often obscure. Shedding light on key details of the perioperative period, such as steroid use and blood pressure management, could illuminate the mechanism of such strokes and improve our current perioperative practice.

Competing Interests

The authors declare no competing interests.

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Editor's Note: The corresponding author of the original article referenced above has read the letter and does not have anything to add in a published reply.

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Covert Strokes in Patients Having Surgery: Comment

To the Editor:

Cui *et al.* recently reported the results of a large, prospective cohort study demonstrating an alarming 11.9% incidence of perioperative covert stroke in noncardiac surgical patients.[1] Moreover, participants experiencing a stroke were more likely to experience early postoperative delirium and lower scores on telephone-based neurocognitive assessments 1 yr later. These results align with the international Neurological Impact of Cerebrovascular Events in Noncardiac Surgery Patients: a Cohort Evaluation (NeuroVISION) study,[2] and the reproducibility of these findings increases confidence in the results. This astonishingly high stroke incidence should serve as a call to arms for anesthesiologists to identify modifiable risk factors under our purview.

In this context, anesthesiologists may be interested in intraoperative physiologic contributions to cerebral hypoperfusion and stroke. The study team did perform a *post hoc* analysis to test the associations between hypotension, defined as mean arterial pressure (MAP) less than 65 mmHg, and subsequent stroke (odds ratio, 1.30; 95% CI, 0.65 to 2.59; $P = 0.464$). Additional clarity would be helpful with respect to the hypotension definition. It is not clear whether this definition meant any occurrence of MAP less than 65 mmHg, or if the mean MAP for the entirety of the case needed to be less than 65 mmHg. This is relevant because there is emerging evidence that stroke risk may increase with cumulative time and depth below a given hypotension threshold.[3] If possible, within the study dataset, it would thus be informative to test associations between stroke and both time and depth (*i.e.*, area under the curve) below a MAP of 65 mmHg. Indeed, while no significant association was found in the current analysis, it is worth noting that the upper bound of the CI has a greater than fourfold distance above 1 (1.59) compared to the lower bound distance less than 1 (0.35).[4] Likewise,

while mean arterial partial pressure carbon dioxide values were similar between patients with and without a stroke, area under the curve analyses may be more informative than descriptive, bivariable comparisons of means.

Perioperative covert stroke is a problem worthy of our attention, and the authors are to be commended for conducting and following through with this study, particularly given the coronavirus-related challenges. Hopefully studies like this will prompt clinical and scientific action to address this alarming yet insidious issue that has perhaps been hiding in plain sight.

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Competing Interests

Dr. Vlisides consults as an expert witness for perioperative stroke.

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Chewing Gum and Postoperative Nausea and Vomiting: Comment

To the Editor:

We read with great interest the study by Darvall *et al.* titled "Chewing Gum to Treat Postoperative Nausea and Vomiting in Female Patients: A Multicenter Randomized Trial."[1] We congratulate the authors on their well-designed multicenter noninferiority trial. We fully agree with the authors' conclusion that "Chewing gum cannot be recommended as an alternative to ondansetron for treatment of postoperative nausea and vomiting."

Nevertheless, we encourage the readers to carefully consider the research question by Darvall *et al.* when deciding on the role of chewing gum in their practice. For example, our team does not envision chewing gum primarily as a replacement for pharmacotherapy of postoperative nausea and vomiting (PONV). Chewing gum was associated with less nausea and/or vomiting[2,3] and may be used as a supplement to ondansetron. In addition, chewing gum can be used for other indications (not addressed in this study) due to its beneficial effects that were not measured by Darvall *et al.* Specifically, the presented trial did not address time to resumption of clear liquid and regular diet and patient satisfaction in both groups. We want to emphasize that postoperative chewing gum may still be beneficial for other outcomes and should not be completely excluded from anesthesiologists' arsenal based on its lower efficacy at reducing PONV compared to ondansetron. Indeed, Short *et al.* identified evidence supporting the benefits of postoperative chewing gum in improving gastrointestinal recovery in a Cochrane review published in 2015.[4]

Our team recently conducted a literature search focused on papers published after 2010 (prospectively registered systematic reviews in health and social care [PROSPERO] CRD42022370040). Multiple clinical trials have shown that chewing gum after recovery from anesthesia is generally well tolerated and is associated with improved postoperative recovery, including shorter time to bowel sounds,[5–9] earlier passing first flatus,[5–12] reduced incidence of postoperative ileus,[2,3] and decreased length of hospital stay.[7,8,10,13]

We thank Darvall *et al.* for clarifying that chewing gum cannot replace ondansetron for treatment of PONV. We also remind the reader of multiple other indications where chewing gum is likely to be effective: to enhance other postoperative gastrointestinal recovery and patient satisfaction, including mouth dryness. In addition, the fact of chewing and the aroma of gum can stimulate appetite and increase

patient comfort. Chewing gum is a straightforward intervention that can lead to improved recovery results beyond just managing nausea and vomiting. Therefore, one should continue to consider whether it be included in Enhanced Recovery After Surgery (ERAS) protocols.

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Chewing Gum and Postoperative Nausea and Vomiting: Reply

In Reply:

We thank Elmawieh *et al.*[1] for their interest in our recent study, "Chewing Gum to Treat Postoperative Nausea and Vomiting in Female Patients: A Multicenter Randomized Trial."[2] We particularly appreciate their comment, "[W]e fully agree with the authors' conclusion that 'Chewing gum cannot be recommended as an alternative to ondansetron for the treatment of postoperative nausea and vomiting.'"[1]

As Elmawieh *et al.* point out, our study was not designed to assess other well-known benefits of chewing gum after major surgery, namely resumption of diet, time to bowel function recovery, and reduced incidence of postoperative ileus,[3] which were mentioned in our study as proven effects of chewing gum. The authors are to be congratulated for their recent systematic review confirming these endpoints in multiple previous studies; however, the included studies did not compare the effect of chewing gum with other antiemetic rescue drug therapies. As such, the well-known and well-proven beneficial effect of chewing gum for other (non–nausea and vomiting) indications is a moot point as it relates to the purpose, findings, and interpretation of our trial.

Elmawieh *et al.* reference a study by Jernigan *et al.* in 110 gynecologic surgery patients randomized to chewing gum or routine care postoperatively to support a claim that "chewing gum was associated with less nausea and/or vomiting."[4] The methodology of this study was less robust than ours, relying on chart review 30 days after surgery, compared with our study design, which involved a blinded observer at the patient's bedside contemporaneously recording nausea and vomiting. We also note that the study by Jernigan *et al.*[4] reported no difference in the need for postoperative antiemetic rescue—somewhat at odds with the reported reduction in postoperative nausea with chewing gum—or any differences in postoperative vomiting. In summary, we consider that our large multicenter randomized trial is more reliable in assessing any antiemetic potential of chewing gum.

We also refer readers to the passage in our article that considers whether there is any potential effect of chewing gum *versus* placebo as, in common with many "rescue" postoperative nausea and vomiting trials, we did not include a placebo arm in our study. We referenced a study by Habib *et al.* that reported a complete response in 28.5% (95% CI, 22.7 to 34.3%) of their placebo group compared with 30.1% (95% CI, 21.5 to 39.9%) in our chewing gum group.[5] As we concluded, "Therefore, although our trial design cannot determine any potential antiemetic effect of chewing gum, it is unlikely to be clinically relevant."

We conclude by correcting one comment from Elmawieh *et al.*: "Specifically, the presented trial did not address … patient satisfaction in both groups." We presented results in our article confirming that no major differences were observed in the acceptability of randomized treatment to patients and postanesthesia care unit nurses, or willingness to pay to achieve the primary outcome. Appeals to patient acceptability (which we consider a reasonably equivalent metric to patient "satisfaction") thus cannot be used to justify chewing gum in preference to ondansetron based on our trial results.

In summary, chewing gum certainly has a role in modern perioperative practice, primarily in supporting recovery of bowel function after major abdominal surgery, but it cannot be recommended as a rescue antiemetic for postoperative nausea and vomiting.

Competing Interests

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Perioperative Management of Preeclampsia: Comment

To the Editor:

We read with great interest the review by Dennis *et al.*,[1] which provides a comprehensive summary of knowledge for general anesthesiologists in the perioperative management of patients with preeclampsia.

While the authors appropriately discuss the classification of preeclampsia as with and without signs of severity, we believe that this approach may not always be sufficient to guide intraoperative decision-making, particularly in patients experiencing hypertensive crises. In a case series of patients with severe preeclampsia or eclampsia and stroke, it was noted that 25 of 27 cases presented with subarachnoid hemorrhage, while 2 cases were diagnosed with ischemic stroke. Among these patients, 24 were under active medical care at the time of the episode, and all had documented systolic hypertension before the stroke, with systolic blood pressure exceeding 155 mmHg.[2] Therefore, while the authors recommend a systolic blood pressure target of less than 155 mmHg based on their observations, this reflects the complexity of the condition and the necessity of a personalized management. In this context, the identification of hemodynamic profiles could provide a more detailed pathophysiologic characterization,[3] offering an additional and practical perspective that facilitates the individualization of strategies in critical perioperative scenarios.

Thus we believe it is clinically useful for anesthesiologists to consider a recently proposed classification based on phenotypes, developed by various groups.[4,5] This classification highlights important differences in clinical presentation, pathophysiology, etiology, treatment, and outcomes, providing a more comprehensive characterization than the traditional distinction of cardiac failure with or without preserved ejection fraction.[1]

Preeclampsia with phenotype I, or "hypodynamic" preeclampsia, is characterized by incomplete remodeling of the spiral arteries, abnormal placentation, and an earlier onset of preeclampsia, typically associated with fetal growth restriction. This phenotype exhibits a significant imbalance between angiogenic and antiangiogenic factors, particularly involving the soluble fms-like tyrosine kinase-1 (sFLT1)/placental growth factor pathway. Studies by Admati *et al.*[4] indicate a notable alteration in gene expression during the early stages of preeclampsia, with upregulation of sFLT1 and downregulation of placental growth factor, findings that align with phenotype I. Clinically, this phenotype presents with low cardiac output and increased peripheral vascular resistance.

In contrast, phenotype II, or "hyperdynamic," is characterized by maternal cardiovascular maladaptation to the physiologic demands of pregnancy, typically in the later weeks of gestation and generally not associated with fetal growth restriction. As a compensatory mechanism, these patients present with reduced peripheral resistance and increased cardiac output; however, this response may be insufficient to meet metabolic demands.[5] From a pathophysiologic perspective, two primary mechanisms have been proposed to explain syncytiotrophoblast stress in term preeclampsia: compression of chorionic villi due to limited space for an enlarged placenta in late pregnancy stages and syncytiotrophoblast senescence associated with premature placental aging.[6]

For anesthesiologists, early identification of these phenotypes using tools such as intraoperative echocardiography, cardiac output measurement, or vascular resistance indices can guide critical decision-making. Real-time adjustment of hemodynamic management based on the patient's profile may help prevent complications such as treatment-resistant hypertension, pulmonary edema, or progression to heart failure. Evidence suggests that patients with a phenotype I

with hypodynamic profile experiencing hypertensive crises are at a higher risk of developing resistant hypertension, which has been linked to increased rates of both maternal and neonatal complications.[7]

This has significant implications for management, as treating patients with phenotype I preeclampsia with β blockers—thereby further decreasing cardiac output—would be counterproductive, if not harmful. In this group, calcium channel blockers such as nifedipine and nitric oxide donor drugs (including organic nitrates and S-nitrosothiols)[8] may play a beneficial role.

In patients with phenotype II with hyperdynamic profile, recent studies have demonstrated that selecting an appropriate first-line hemodynamic treatment—such as α and β blockers like labetalol—is associated with a lower incidence of severe hypertension before delivery. Conversely, inappropriate use of vasodilators in this group not only may be ineffective but also could contribute to suboptimal blood pressure control.[9]

The study by Stott *et al.* further elucidates this concept by identifying a subset of hypertensive patients who required additional vasodilator therapy after initiating labetalol treatment.[10] These findings align with previous observations regarding the hypodynamic profile, which is characterized by more severe blood pressure elevations, increased peripheral vascular resistance, lower heart rates at presentation, and an association with fetal growth restriction.

Although preeclampsia is operationally defined by the onset of elevated blood pressure and target organ involvement, it remains a heterogeneous disease in terms of clinical presentation, pathophysiology, and treatment. This heterogeneity may explain why certain pharmacologic therapies prove effective in some patients while appearing ineffective in others.

Classifying preeclampsia into distinct "phenotypes" and integrating this framework with pathophysiology, clinical presentation, and biomarker expression may help refine the anesthesiologist's clinical approach during the perioperative period. Moreover, this perspective could pave the way for future research on more targeted therapies and a more personalized approach to managing pregnant patients with preeclampsia.

Competing Interests

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Perioperative Management of Preeclampsia: Reply

In Reply:

Thank you for the opportunity to respond to Basso *et al.*[1]

Throughout our article, we have emphasized that preeclampsia is a hypertensive cardiovascular system problem.[2] We highlight the importance of individualized management of patients with preeclampsia. This includes determining the severity of hypertension and organ complications and hemodynamic monitoring with echocardiography. This is particularly important where severe complications are present such as hypertensive crises and eclampsia with stroke, and in the management of heart failure.

Like its use in nonpregnant adults with life-threatening cardiovascular problems, the use of transthoracic echocardiography to define an individual's hemodynamics is key to understanding cardiac function in patients with preeclampsia. It is also key to understanding the pathophysiology of preeclampsia, and the use of transthoracic echocardiography has been advocated in obstetric anesthesiology and obstetric critical care for more than 15 yr.[3] The current definition of heart failure,[4] which is divided into the two broad categories of preserved or reduced heart failure, is appropriate. It is underpinned by scientific research, is not problematic, and already guides correct and safe management in patients with preeclampsia. We disagree that an alternative classification that is not supported by the American Heart Association (Dallas, Texas) and the American College of Cardiology (Washington, D.C.) should be used.

Thank you for raising the issue of the proposed two-phenotype model of preeclampsia, of which we are aware. Our review specifically did not cover the pathophysiology of preeclampsia, but the correspondence has given us the opportunity to discuss this in the setting of pharmacologic agents for the management of hypertension.

It may appear appealing to make pharmacologic choices based on a proposed theory that categorizes patients into either a "hypodynamic" (phenotype 1) or a "hyperdynamic" (phenotype 2) clinical state, based on an arbitrary cardiac output threshold and/or peripheral vascular resistance from cohort data. It is, however, ill advised. This is because the two-phenotype model is a hypothetical construct. It fails to appreciate the heterogeneity of patient characteristics (such as gestation, age, body mass index, the presence of severe end-organ complications) and the wide range (variability) of cardiac output, at any gestation, found in patients with preeclampsia. This variability in cardiac output is one of the reasons it is not used in the definition of preeclampsia and individual patients cannot be classified as phenotype 1 or phenotype 2. For example, not all patients with preeclampsia presenting in the preterm period have lower cardiac output compared with healthy pregnant women. Nor do all of them have histologic abnormal placentas, or fetal growth restriction, or have the same clinical presentation with severe hypertension or organ system dysfunction. Conversely, patients presenting at term and after can present with fetal growth restriction and severe complications of hypertension. This means that one cannot accurately classify a person with preeclampsia as "hypodynamic" or "hyperdynamic" based on these variables. Therefore, treatment decisions based on an arbitrary number for cardiac output are likely to have no benefit over the usual randomized controlled trial–based clinical decision-making when choosing the appropriate antihypertensive agent.[5,6] Two key elements in the management of patients with preeclampsia that are highlighted in hemodynamic studies are rapid antihypertensive treatment that achieves timely target blood pressure control and the use of additional antihypertensive agents when hypertension is not controlled with a primary agent.[7]

Preeclampsia and its hemodynamics are better explained using the concept of a supply–demand mismatch described by a unified theory of preeclampsia first published in 2014.[8] It takes into account all the maternal, placental, and fetal variability (including cardiac output variability) of the condition and explains why pregnant women develop preeclampsia. The Constant Stimulus Adaptive Response model of preeclampsia is from the field of obstetric anesthesiology and leverages known interdisciplinary knowledge of hemodynamics and hypertension and applies it to obstetrics. Fundamentally the model proposes that preeclampsia is driven by the constant stimulus of the growing fetus (not the placenta) and a mismatch between maternal oxygen supply and fetal oxygen demand. Pregnant women who are able to match a changing oxygen supply to meet the varying oxygen demands of the fetus do not develop preeclampsia. In pregnant women whose oxygen supply does not match fetal oxygen demands (due to maternal, placental, or fetal conditions—or a combination), cardiac output increases as an adaptive response to address this mismatch to the fetus and restore balance (equation 1). The model predicts what we see in clinical practice, *i.e.*, patients may present at very early gestations when there are extreme placental abnormalities present, or at late gestations when the placenta undergoes apoptosis, or at any gestation in between. Patients may also present at very early gestations, in the presence of normal placentation, but when significant maternal comorbidities are present (fig. 1).

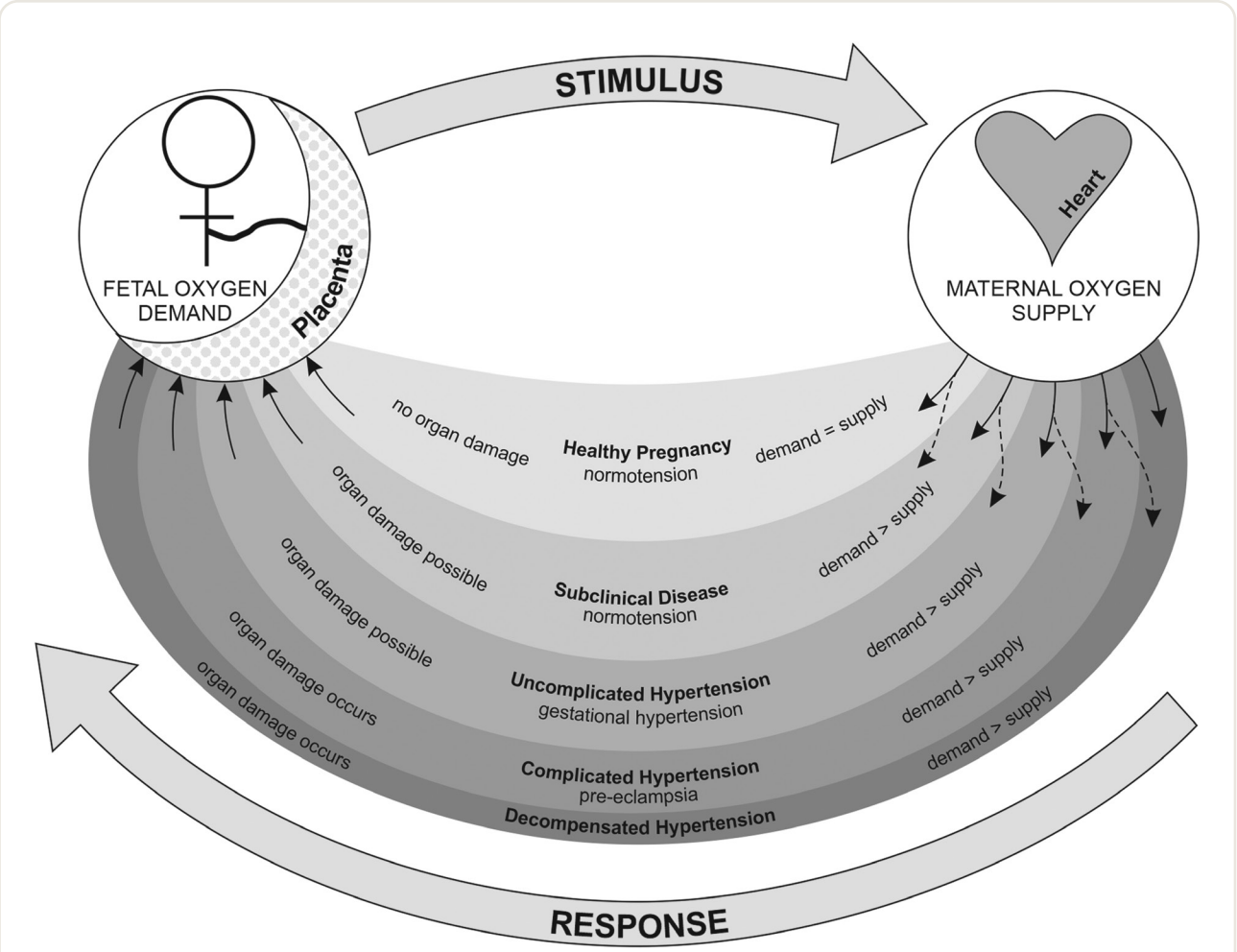


Fig. 1. The constant stimulus and adaptive response model for the development of hypertension in pregnancy. At any time during pregnancy, due to imbalance between maternal oxygen supply and fetal oxygen demand, the woman may progress from healthy to subclinical disease and beyond (*dashed arrows*). The rate at which this occurs and the extent to which it progresses down the clinical pathway to decompensated hypertension depend on the preplacental, placental, or postplacental conditions, as well as when correction of the supply/demand imbalance occurs, *i.e.*, cessation of pregnancy (delivery of the fetus). Reprinted with permission from Dennis AT, Castro JM: Anaesthesia 2014;69:1183–9.[8]

$$\textit{Supply of oxygen to fetus is proportional to maternal cardiac output} \times \textit{maternal blood content of oxygen}$$

$$\text{where content of oxygen} = (\text{hemoglobin concentration} \times \text{hemoglobin saturation} \times 1.34\ \text{ml} \cdot \text{g}^{-1}) + (\text{arterial oxygen partial pressure} \times 0.03\ \text{ml} \cdot \text{l}^{-1}) \quad \text{(eq. 1)}$$

By increasing maternal cardiac output, flow is increased not only to the fetus but also to other maternal vascular beds where vasocontraction limits the adverse effects of flow. This leads to hypertension and end-organ damage (preeclampsia). The rapidity, severity, and gestation at which this process occurs vary from woman to woman and from pregnancy to pregnancy in the same woman, explaining the heterogeneity of the condition. With this constant stimulus of fetal oxygen demand, ongoing vasoconstriction mechanisms in maternal vascular beds may be overwhelmed and fail after days, weeks, or months, leading to microvascular and endothelial damage. In the process, markers of ischemia (such as soluble fms-like tyrosine kinase [sFLT1]) are released, as well as markers of vascular damage from increased flow in the absence of ischemia. Overt clinical signs of life-threatening end-organ vascular dysfunction such as eclampsia and/or hemolysis, thrombocytopenia, liver damage (with enzyme elevation), or liver rupture may then occur.

The model fulfills many of the Bradford Hill Criteria for causality. It is supported by human experiments and refutes the idea that the placenta is the fundamental cause of preeclampsia and that biomarkers cause preeclampsia. It provides a framework that supports temporality, biologic gradient, specificity, consistency, plausibility, and coherence. It explains why the condition is so common and why treatments, including drugs, therapeutics, repurposed

Table 1. Constant Stimulus Adaptive Response (CSAR) Model Framework for Interventions to Prevent Preeclampsia*

Category of Problem		Proposed Preventative Interventions
Maternal oxygen supply to fetus	Optimizing oxygen delivery before and during pregnancy	1. Optimizing maternal fitness with exercise training 2. Attainment of ideal body mass index 3. Optimizing chronic health problems, especially cardiovascular, renal, and endocrine 4. Calcium supplementation in appropriate groups
	Optimizing blood oxygen content	1. Determining optimal hemoglobin levels in pregnant women and then treating anemia 2. Reducing periods of oxygen desaturation 3. Addressing sleep-disordered breathing that may occur in obesity and in later pregnancy through nocturnal continuous positive airway pressure delivery devices such a high-flow nasal oxygen using air 4. Reducing chronic exposure to low partial pressure oxygen environments
	Optimizing blood flow/rheology	1. Aspirin 2. Heparin in appropriate groups 3. Other medications that may improve blood flow and microaggregation
	Ensuring efficient materno-fetal transfer of oxygen	1. Anticipating, monitoring, and managing deterioration in placental function with advancing gestation by prevention of postterm birth
Fetal oxygen demand	Optimizing fetal oxygen demand	1. Discouraging multiple pregnancies such as in assisted reproductive technologies to reduce overall fetal oxygen demand

*The CSAR model predicts that the proposed interventions will reduce the incidence of preeclampsia and its maternal and fetal complications. Based on Dennis and Castro.[8]

medications, or plasmapheresis aimed at removing or reducing biomarkers in patients with preeclampsia, have failed and will continue to fail in their goal to benefit pregnant women and unborn babies, and may in fact worsen the condition. It provides the framework for interventions aimed at preventing and treating the condition by addressing oxygen supply to the fetus and fetal oxygen demand (table 1). The model has yet to be disproven.

Competing Interests

Dr. Farber receives financial research support from Flat Medical (Austin, Texas); is an UpToDate author for Wolters Kluwer (Waltham, Massachusetts); serves on advisory boards for Octapharma (Paramus, New Jersey) and HemoSonics (Durham, North Carolina); received travel and lodging reimbursement as an invited speaker from the SFOAI Swedish Obstetric Anesthesia Society (Malmö, Sweden); and received lodging reimbursement as an invited speaker from the Phu San Ha Noi Obstetric and Gynecology Hospital (Hanoi, Vietnam). The other authors declare no competing interests.

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Breath from Salt: A Story of Tenacity

By Bijal P. Trivedi. Dallas, BenBella Books, 2020. Pages: 576 pages. Price: $28.95 (Hardcover).

As practitioners who specialize in guiding human consciousness through perilous but therapeutic experiences, we find *Breath from Salt* to be a timely prescription for the ailments afflicting the modern enterprise of academic medicine. Bijal Trivedi's unparalleled access to the arc of therapeutic discovery for cystic fibrosis makes *Breath from Salt* an essential instruction manual for securing a sustainable future for American science.

The instructions laid out by Trivedi are simple. Step 1 is to identify your champions. At the core of the instruction manual is Joe O'Donell, a philanthropist whose son Joey was diagnosed with cystic fibrosis in an era when it was considered a death sentence. Excerpts of Joe's life are woven into the larger story, offering a refreshing perspective on the value that ultimately won the fight against cystic fibrosis: tenacity. "He had a sick child gasping for breath, a mortgage, no job, no health insurance, no backup plan." It was 1977, and "all doctors could do was treat his [son's] symptoms: antibiotics to kill the bacteria that caused infections, physical therapy to clear the muck from his lungs, and oral pancreatic enzymes to break down his [son's] food." This brings us to step 2: building around your champions. Joe went on to raise over $500 million for the Cystic Fibrosis Foundation (CFF; Bethesda, Maryland), the not-for-profit organization whose fingerprints covered the entire arc of therapeutic discovery for the disease. The Cystic Fibrosis Foundation advanced the search for a cure by funding critical research that led to the discovery of the *CFTR* gene, the driver mutation underlying cystic fibrosis. Through sustained investment and advocacy by way of a venture philanthropy model, the Cystic Fibrosis Foundation helped improve treatments and extend life expectancy for people living with the disease. This brings us to step 3: mobilizing around your champions. From disease characterization at Columbia University (New York, New York), to advocacy on Capitol Hill (Washington, D.C.), to gene discovery at the University of Michigan (Ann Arbor, Michigan) and University of Toronto (Toronto, Ontario, Canada), to drug development with Vertex Pharmaceuticals (Boston, Massachusetts), the Cystic Fibrosis Foundation, with Joe's contributions, was integral to the endgame of the academic mission: finding a cure for the disease through research and innovation.

While his son Joey ended up being a heartbreaking casualty of the fight at the age of 12 in 1986, Joe's tenacity never wavered. A tenacity palpable to other parents who lost their children to the disease, who together raised awareness and capital. A tenacity mirrored by the providers who channeled their frustrations of prescribing death sentences to these same parents into strengthening diagnostics and therapies. A tenacity that built foundation chapters and cystic fibrosis care centers across the country, erecting a backbone that could stand the test of public scrutiny, margin calls, budgetary constraints, and competing agendas. A tenacity inherited by the scientific community to do what it does best: question the status quo and deliver lifesaving clarity to otherwise nebulous disease processes. Be it fundraising for the Cystic Fibrosis Foundation, developing the sweat chloride test, introducing pancreatic enzyme supplementation, identifying the *CFTR* driver mutation, or the synthesis of ivacaftor (a gene-based therapy that targets the mutated *CFTR* protein),[1] this collective tenacity synthesizes the three-step instruction manual previously delineated into an accepted standard that the enterprise of academic medicine should strive to maintain. A standard that is patient oriented, provider driven, public facing, and product focused. Trivedi's *Breath from Salt* effectively captures this standard, recounting the various individual voices and entities that over time came together in harmony and with tenacity around a common purpose: finding a cure for the disease through research and innovation.

The standard set by *Breath from Salt* importantly forces the reader to consider the role they play on the larger world stage of academic medicine. As anesthesiologists, we recognize our own importance to patient care as vanguards of the operating room and intensive care unit, ensuring safe passage from a state of disease to a state of health. Our providers valiantly stood at the frontlines as COVID-19 terrorized our communities, taking care of patients "gasping for breath," facilitating dissemination of evidence for public consumption, and finding therapies to help flatten the curve. The contributions to the lives we touch at each individual bedside is however only the tip of the iceberg; scientific inquiry and research has allowed our field to reach many more bedsides than can ever be visited in a lifetime. Be it the Apgar score, Severinghaus electrodes, pulse oximetry, propofol, or MPOG (Multicenter Perioperative Outcomes Group), our field's history is rich with examples of discovery that are patient oriented, provider driven, public facing, and product focused. We are fortunate to have support from not-for-profit organizations like the Foundation

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for Anesthesia Education and Research (FAER; Schaumburg, Illinois) and the Anesthesia Patient Safety Foundation (APSF; Rochester, Minnesota) to galvanize progress through research and innovation in the way that Cystic Fibrosis Foundation did for cystic fibrosis. There is no specialty better positioned to guide humanity's consciousness through the perils that academic medicine faces at present. To do so, however, requires each of us to adhere to the value that consistently resurfaces in Trivedi's instruction manual: tenacity.

As the "Great Plague of 2020" continues to fall farther in the rearview mirror, and new challenges regarding prioritizing academic medicine stand before us, *Breath from Salt* is a reminder of what our community at large can accomplish if directed in the appropriate manner. Following the instructions laid out by Trivedi in this captivating read has great potential for ushering in a renaissance for American science if we chose to adopt its most salient value: tenacity. *Breath from Salt* is available in both digital and hard-copy formats and accessible through most widely known vendors.

Competing Interests

Anjan Saha is a co-founder and equity holder in Deoxylytics, LLC (Ann Arbor, Michigan).

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Hoping to Help: The Promises and Pitfalls of Global Health Volunteering

By Judith N. Lasker, Ph.D. New York, Cornell University Press, 2016. Pages: 272. Price: $25.95 (Paperback).

Although surgically treatable diseases account for 30% of the global disease burden, 5 million people worldwide do not have access to safe and timely surgical care.[1,2] While access to surgical care has improved recently in several developing nations, glaring deficiencies in quality of care are now the third-leading cause of death globally, behind only ischemic heart disease and stroke.[3] In many instances, cultural factors, including failure to honor patient autonomy and informed consent, enable deviation from the standard of care and blatant medical errors to escape both detection and correction. This is not surprising when one considers the typically patriarchal, underfunded, and fragmented healthcare systems in many developing countries where institutional and governmental reporting requirements are minimal, at best.

A recent publication reported a 54% incidence of anesthesia-related critical events, most often involving hypoxemia, during 6 surgical missions, spanning 5 days each, in Tanzania and the Democratic Republic of the Congo.[4] Pulse oximetry was consistently available during the procedures,[5] but access to an electrocardiogram was unusual owing to lack of electrodes. Moreover, suitably sized blood pressure cuffs were generally unavailable for children. Hence, the incidence of tachycardia, hypotension, and hypertension could not be documented. Equipment problems happened in 24% of cases and appeared to be preventable with more resources and better infrastructure.

Clearly, the need to improve health care in developing countries is undeniable, but the optimal approaches to achieving this goal are ambiguous. Judith Lasker, Ph.D., professor emerita of sociology and anthropology at Lehigh University (Bethlehem, Pennsylvania), has attempted to redress this deficiency in her rigorously researched and insightful book titled *Hoping to Help: The Promises and Pitfalls of Global Health Volunteering.* This searching, conscientious book focuses on short-term (defined as 2 weeks or fewer) volunteering and probes such relevant topics as how we can best allocate our finite human and economic resources and who actually benefits from global health volunteering. While acknowledging that "…in many cases, the health benefits contributed by short-term volunteers clearly improve and even save lives," Dr. Lasker adroitly questions the concept that volunteerism is universally beneficial and underscores that some well-intentioned projects not only fail to assist those whom we hope to help but may actually do harm and stifle self-sufficiency.

When medical students, for example, arrive in refugee camps and perform procedures they are not credentialed to perform in their home countries, or surgeons visit briefly and provide no aftercare to manage postoperative complications, the potential for harm is obvious. Projects with questionable sustainability devoid of accountability and with perfunctory linkages to local health services are distinctly undesirable. In other situations, volunteers may compete with, or even displace, local professionals, as happened after the 2010 earthquake in Haiti. Moreover, volunteers' logistical needs and expectations require considerable attention from local medical staff that may distract the latter from their professional responsibilities.

Sadly, volunteers often enter impoverished rural communities with little or no grasp of the locals' culture, priorities, and way of life. Their destination choices may be based on personal preference (*i.e.*, a form of "voluntourism") rather than on careful analysis of where needs are greatest. Although volunteer trips are typically perceived as a means to "give back" and "make a difference," some authorities contend that health volunteering is a new form of colonialism, devised to benefit the volunteers more than the host communities.

Short-term medical volunteering is a massive and growing enterprise. Dr. Lasker's concern is primarily with the ethical question of whether the investment of billions of dollars of resources in this enterprise can be justified by the results in terms of improvement in health outcomes, reduction in health disparities, or other measures of value to the host communities. To answer this question, the author collected quantitative data and qualitative findings from sponsoring organizations, volunteers, and host communities. This was accomplished *via* surveys, interviews, and participant observation by the author on two short-term trips. Among other findings, the author learned that most organizations do not even attempt to gather evidence of their impact.

In an effort to make volunteer programs more efficient and valuable for all concerned, but particularly for the host communities, Dr. Lasker offers nine principles that deserve careful consideration by the reader. Arguably, three of the most salient recommendations include enhancing the preparation of volunteers, extending the

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duration of volunteers' service in the host country, and evaluating processes and outcomes with input from the host country.

Reading *Hoping to Help* led me to reflect on my experience as a volunteer anesthesiologist. Although Dr. Lasker's book was published in 2016, more than 25 yr earlier, in 1990, the distinguished anesthesiologist Nicholas M. Greene, M.D. (1922 to 2004) founded the American Society of Anesthesiologists (Schaumburg, Illinois) Overseas Teaching Program (OTP) to address the urgent need for anesthesiologists from highly developed countries to educate anesthesia providers in Africa. Younger generations of anesthesiologists need to learn of his prescient and enduring contributions to our specialty.

Dr. Greene was profoundly disturbed by the fact that in Tanzania, for example, only 3 physician anesthesiologists were available to serve the country's population of 30 million. Merely 10 to 15% of the volume of surgery that should be done in East Africa could be performed because of the bottleneck created by lack of anesthesia care.[6] Most anesthesia care in East Africa was provided by laypersons who, after 2 yr of education as medical assistant trainees and another 2 yr as practicing medical assistants, became eligible for a 1- or 2-yr (depending on the country) course that made them anesthetic officers. And there were far too few anesthetic officers.

Initially, the OTP supported two programs, one in Moshi, Tanzania, and the other in Lusaka, Zambia. The Zambia program was terminated in its sixth year, with the Lusaka site replaced by an OTP program in Accra, Ghana. Today, two different programs remain active; the first is the Rwandan teaching program, established in 2006, and the younger program in Guyana, South America, began in 2016. Both programs are a collaboration between the American Society of Anesthesiologists and the Canadian Anesthesiologists Society International Education Foundation (Toronto, Canada).

Although Dr. Greene retired from his clinical duties at Yale University School of Medicine (New Haven, Connecticut) in 1987, he maintained a vital and venerable presence in the department of anesthesiology, serving as an exemplary role model, auctorial educator, and respected advisor until the new millennium. I had the extraordinary privilege to be mentored by Nick from 1987 until his death in 2004. To say he was special is an egregious understatement. Among other talents, Nick was a visionary with exceptional strategic and tactical skills. (I often thought that Nick's heritage shaped his disciplined and determined character and his no-nonsense personality. He was a descendant of the Revolutionary War hero Major General Nathanael [*sic*] Greene. Moreover, Nick's grandfather was an 1878 graduate of West Point and an Army officer, and his uncle, Douglass [*sic*] Taft Greene, was an eminent major general in World War II.)[6]

Nick took great pride in the uniqueness of the OTP.[6] His meticulous and methodical mind crafted programs that no doubt would receive Dr. Judith Lasker's seal of approval. Of supreme importance to Nick was the fact that the programs were designed by Africans, not Americans or Europeans, In addition, the OTP concentrated on teaching, both clinical and didactic, rather than providing clinical service. The programs were designed to respond to the Third World plea "Don't give me a fish, teach me how to fish." Importantly, the teaching emphasis was based upon what was germane to the practice of anesthesia in the context in which trainees function rather than more advanced circumstances in wealthier nations. Notably, the OTP recruited experienced anesthesiologists to teach, one at a time, providing continuous, year-round educational assistance rather than erratic, short-term services. Moreover, teaching was not restricted to trainees; Nick ensured that people at policy-making and decision-making levels, both locally and nationally, were educated as well.

Impressed by what Nick related to me about his experiences in East Africa, I volunteered to serve in the Tanzanian OTP for 5 weeks during the winter of 1993. Although more than 3 decades have passed, I remember as if it were yesterday the illuminating luncheon at Mory's (until 1974 a bastion of male chauvinism in New Haven, Connecticut) that Nick and I shared shortly before my departure for Moshi. Nick began the conversation by stating, "Now I will tell you what to REALLY expect in Tanzania." During what were probably the most educational 150 min of my life, Nick gave me explicit directives. He admonished me to be culturally sensitive and to restrict my remarks to teaching anesthesia and avoid gratuitous comments about poverty, politics, religion, and class distinctions. Further, he urged circumspection when taking photographs because impoverished people are disinclined to have their penury documented. After his sobering lecture on the many professional and logistical challenges I might encounter, I blithely informed Nick that I hoped to climb Mount Kilimanjaro after I completed my tour of duty. At that point, the preternaturally calm, if not stolid, Dr. Greene exploded in exasperation, "Kathy, there are damn better ways to die!" I was then given a fatherly lecture on Personal Safety 101 and exhorted to curb my enthusiasm for adventure and focus instead on narrowing the chasm between my aspirational goals and what was realistically possible. He gently, but firmly, reminded me that I was "not Dr. Alberta Schweitzer."

Not every potential volunteer has the opportunity for a personal preprogram tutorial with as perspicacious and wise a mentor as Dr. Nicholas Greene. However, reflecting on the information in *Hoping to Help: The Promises and Pitfalls of Global Health Volunteering* is a good place to begin.

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Careers & Events

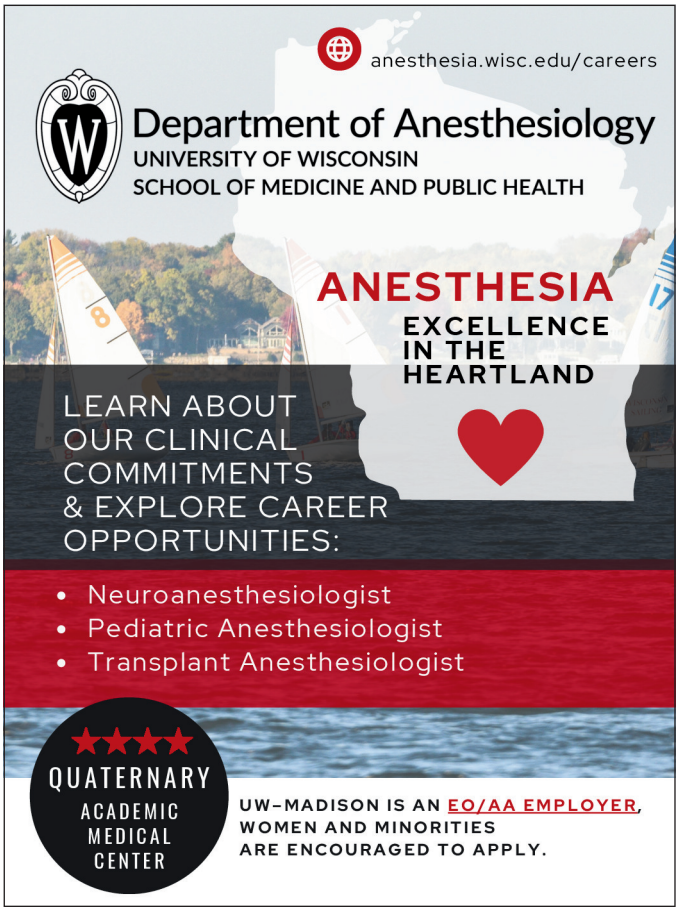
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Location: Chicago, IL
Open Date: Mar 26, 2025
Salary Range or Pay Grade
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Deadline: Mar 26, 2027 at 11:59 PM Eastern Time

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9:30 - 5:00 PM	Visit our Exhibit Booth
11:30 AM	WLM Woodchip Lecture
5:00 - 6:30 PM	WLM / Anesthesia History Association Reception

SUNDAY, OCTOBER 12

9:15 - 10:15 AM	Lewis H. Wright Lecture Crawford W. Long, MD, His Life and Times *Presented by William Hammonds, MD, FACA*
9:30 AM - 5:00 PM	Visit our Exhibit Booth
12:00 PM	WLM Woodchip Lecture
2:45 - 3:45 PM	History Panel I Old Tales Retold - Fresh Takes on Anesthesiology Pioneers ***Moderator:*** *Melissa Coleman, MD* ***Speakers:*** *Mary Dale Peterson, MD, MSHCA, FACHE, FASA, Bryant Murphy, MD, FASA*
4:00 - 5:00 PM	History Panel II Old Tales Retold - Fresh Takes on Anesthesiology Pioneers ***Moderator:*** *Douglas Bacon, MD, MA, FASA* ***Speakers:*** *Amy Woods, MD, FASA, N. Martin Giesecke, MD, Paloma Toledo, MD, MPH, FASA*

MONDAY, OCTOBER 13

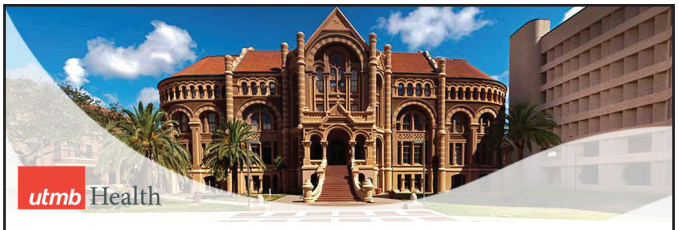
9:30 AM - 1:30 PM	Visit our Exhibit Booth
12:30 PM	WLM Woodchip Lecture
1:30 - 3:30 PM	Patrick P. Sim Forum Pushing the Envelope: Anesthesiology as a Daring Profession ***Moderator:*** *Jane S. Moon, MD* ***Speakers:*** *Anuj Aggarwal, MD, Todsaporn Rodbumrung, MD, Jordan Francke, MD, MPH, Hannah Wunsch, MD, MSc*
3:30 - 4:30 PM	Friends of the WLM Tea

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Seeking a board-certified anesthesiologist with fellowship training in Obstetric Anesthesia to serve as ***Division Chief of OB Anesthesiology across all UTMB campuses.*** This leadership role includes clinical care (90%), faculty mentorship, education, research, and administrative duties (10%) such as organizing clinical services, team deployment, evaluating residents and fellows, and participating in departmental and health system committees. The division works closely with the Department of Obstetrics & Gynecology, and their large training program, at our Level IV maternity care center nationally recognized for maternal critical care and placenta accreta management. **Competitive salary and benefits offered.**

APPLY TODAY!! Send Cover Letter and Curriculum Vitae (CV) to
Skott Harrington - saharrin@utmb.edu

UTMB Health strives to provide equal opportunity employment without regard to race, color, religion, age, national origin, sex, gender, sexual orientation, gender identity/expression, genetic information, disability, veteran status, or any other basis protected by institutional policy or by federal, state or local laws unless such distinction is required by law. As a Federal Contractor, UTMB Health takes affirmative action to hire and advance protected veterans and individuals with disabilities.

Department of Anesthesiology
Perioperative, Critical Care
and Pain Medicine

Cardiac, Pediatric, Neuro, Obstetric, General, and Critical Care Anesthesia

The Department of Anesthesiology, Perioperative, Critical Care, and Pain Medicine at the University of Kentucky seeks board-certified or board-eligible anesthesiologists in the areas of cardiac, pediatric, neuro, obstetric, general, and critical care anesthesia. These positions are open to all ranks.

UK HealthCare has undergone a sustained and remarkable growth trajectory for over a decade. Clinical volumes continue to increase and the acuity of patient care is high. UK HealthCare's Albert B. Chandler Hospital was named No. 1 in Kentucky in the U.S. News & World Report's Best Hospitals rankings. The Department of Anesthesiology is a collegial group that is well-respected in the medical center. The residency program is strong and nationally recognized. The enterprise financially supports the academic and the clinical mission of the Department of Anesthesiology.

Qualified applicants will possess an unrestricted Kentucky medical license, or eligibility for licensure, and will have completed an anesthesiology residency. Fellowship training and eligibility for ABA subspecialty certification is required within subspecialty positions.



Applications will be reviewed as received, and the positions will remain open until filled. Please include a CV along with application. Interested parties may reach out to **Christina Chessman** at **christina.chessman@uky.edu**.

HENRY FORD HEALTH

Section Head — Cardiovascular Anesthesiology

Henry Ford Health | Michigan
Department of Anesthesiology,
Pain Management & Perioperative Services

Henry Ford Health is seeking a dynamic, academically driven anesthesiologist to lead its Division of Cardiovascular Anesthesiology. The Section Head will provide clinical, academic, and administrative leadership across a multi-hospital system, overseeing high-complexity cardiovascular and thoracic anesthesia services, faculty development, education, and quality initiatives.

Responsibilities:

- Leadership role with oversight of cardiac anesthesia faculty and services
- Collaboration with cardiac surgery, cardiology, and ICU service lines
- Active involvement in academic mentorship and fellowship support
- Strategic planning, faculty recruitment, and quality improvement
- System-wide engagement in ERAS, TEE education, and research

Qualifications:

- MD or equivalent; ABA board certified
- ACGME fellowship in Cardiothoracic Anesthesiology
- Advanced Perioperative TEE certification (NBE)
- Eligible for Michigan licensure
- Academic rank of Assistant, Associate Professor, or Professor preferred

To apply:
Submit CV and letter of interest to **Nick Sullivan** at **nsulliv3@hfhs.org**.

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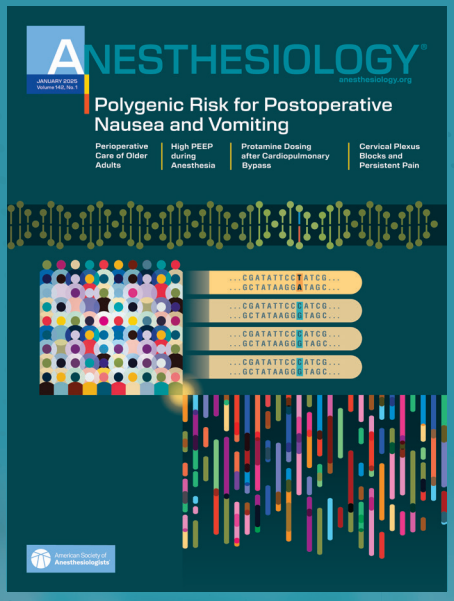
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ASA Practice Advisory for Perioperative Care of Older Adults Scheduled for Inpatient Surgery



This advisory provides evidence-based recommendations on the management of older adults undergoing inpatient surgery. The advisory focuses on aspects of preoperative, intraoperative, and postoperative care of specific relevance to older adults (i.e., 65 yr or older), and it addresses approaches to minimizing complications of anesthesia common among older patients.

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