Volume 137 No. 4 Pp. 381–520

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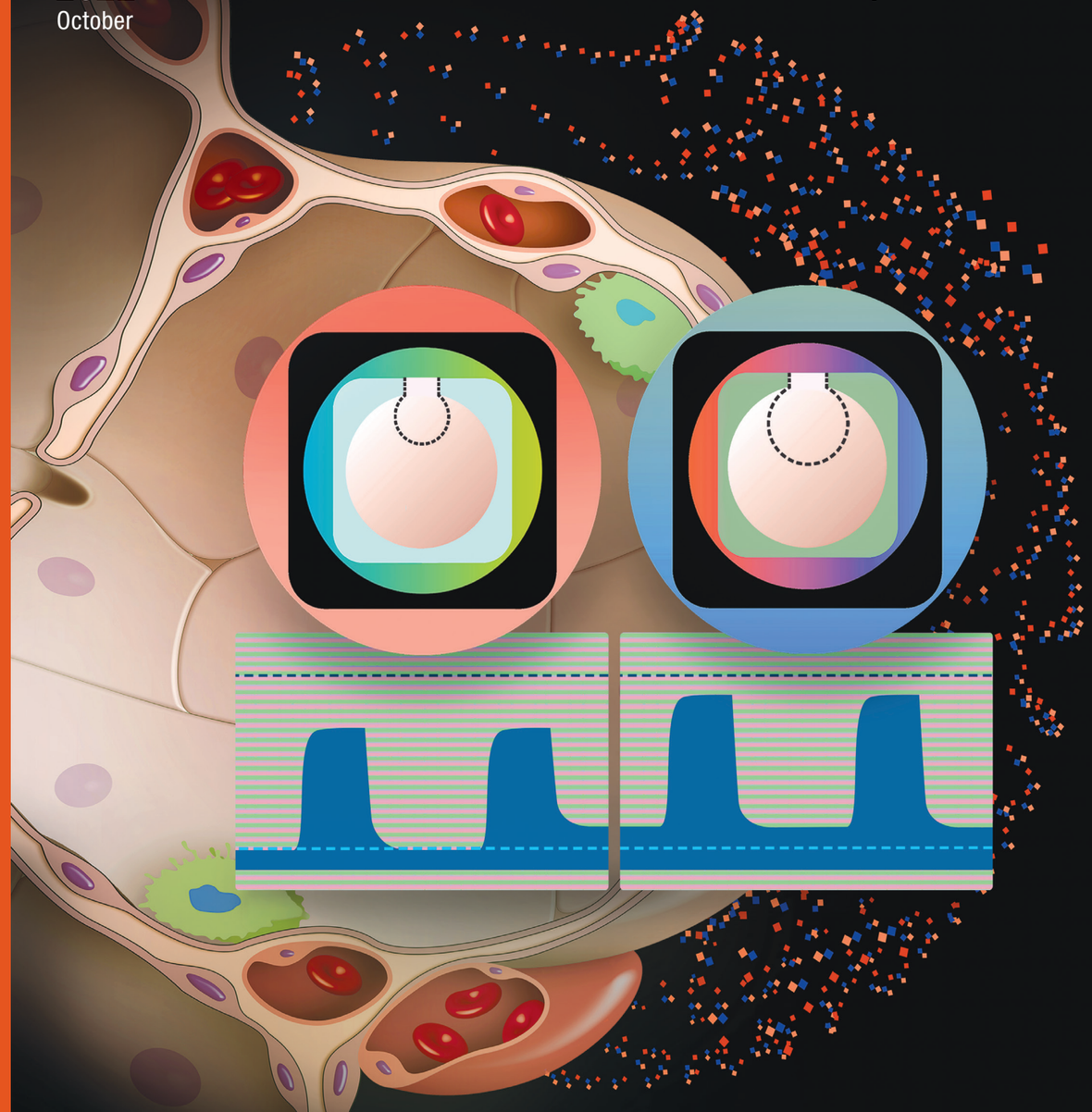

Tidal Volume, Positive End-expiratory Pressure, and Postoperative Hypoxemia

Volume 137
Number 4
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The Official Journal of the American Society of Anesthesiologists

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Reference:
1. U.S. Food and Drug Administration. 2021. K203224 510k Summary, Acumen Hypotension Prediction Index

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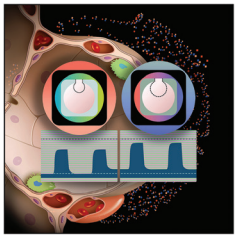
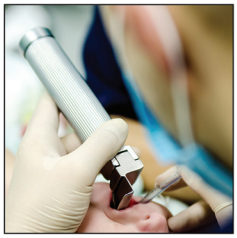


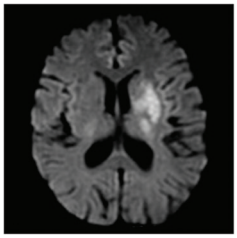
406 Tidal Volume and Positive End-expiratory Pressure and Postoperative Hypoxemia during General Anesthesia: A Single-center Multiple Crossover Factorial Cluster Trial

Intraoperative mechanical ventilation is a major component of general anesthesia. Two key ventilator settings are tidal volume and positive end-expiratory pressure (PEEP). The hypothesis that ventilation using different tidal volumes and PEEP levels affects oxygenation within the first hour in the postanesthesia care unit was tested in a robust 2-by-2 factorial crossover cluster trial of 2,860 adults having major orthopedic surgery with general anesthesia. Patients were assigned to factorial clusters with tidal volumes of 6 or 10 ml/kg of predicted body weight and to PEEP of 5 or 8 cm H_2O in 1-week clusters. Oxygenation was defined by the peripheral oxygen saturation divided by the fraction of inspired oxygen (Spo_2/Fio_2 ratio), a surrogate measure of oxygenation. Because the interaction between tidal volumes and PEEP was not significant, the effects of tidal volumes and PEEP on time weighted average Spo_2/Fio_2 ratios were assessed independently. The time-weighted average Spo_2/Fio_2 ratios were not different in patients assigned to high and low tidal volumes or in those assigned to high and low PEEP. *See the accompanying Editorial on* ***page 381****. (Summary: M. J. Avram. Image: A. Johnson, Vivo Visuals Studio.)*



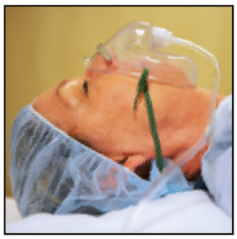
418 Sedation *versus* General Anesthesia for Tracheal Intubation in Children with Difficult Airways: A Cohort Study from the Pediatric Difficult Intubation Registry

The incidence of difficult tracheal intubation in the general pediatric population is nearly 1.5%. The hypothesis that in children with difficult airways tracheal intubation under sedation would be associated with lower first-attempt success and more complications than tracheal intubation under general anesthesia was tested using data from difficult airway encounters in 34 hospitals between 2017 and 2020. Propensity score matching to minimize selection bias and the effect of baseline characteristics on the outcome resulted in 58 sedated patients being matched to at least 1 general anesthesia patient, with 522 general anesthesia patients being matched. First-attempt tracheal intubation was successful in 48% (28 of 58) of sedated patients and 47.9% (250 of 522) of anesthetized patients (odds ratio, 1.02; 95% CI, 0.59 to 1.76). To complete tracheal intubation, 28% (16 of 58) of sedation cases were converted to general anesthesia. Complications were observed in 26% (15 of 58) of sedated patients and 17.3% (90 of 521) of anesthetized patients (odds ratio, 1.63; 95% CI, 0.87 to 3.08). *See the accompanying Editorial on* ***page 384****. (Summary: M. J. Avram. Image: Adobe Stock.)*



434 Carbon Dioxide, Blood Pressure, and Perioperative Stroke: A Retrospective Case–Control Study

The combination of reduced cerebral perfusion, *e.g.*, due to hypotension and compromised autoregulation, and impaired vasodilatory reserve, mediated by hypo- and hypercapnia, may create conditions for cerebral ischemia. The hypothesis that the combination of intraoperative hypo- or hypercarbia and intraoperative hypotension would be associated with postoperative stroke was tested in a multicenter, retrospective, observational case-control study. The primary outcome was perioperative ischemic stroke, defined as any new-onset cerebrovascular infarction that occurred within 30 days of surgery. One hundred twenty-two confirmed stroke cases were identified from the 1,244,881 noncardiac, nonintracranial neurologic, and nonmajor vascular surgical cases analyzed and matched 1:4 to controls for the primary analysis. The primary analysis included total area under the curve with mean arterial pressure less than 55 mmHg and $Etco_2$ less than or equal to 30 mmHg followed by $Etco_2$ less than or equal to 35 mmHg and $Etco_2$ greater than or equal to 45 mmHg as a separate, secondary analysis. Intraoperative hypotension and both hypo- and hypercarbia were independently associated with postoperative ischemic stroke in an additive, nonsynergistic manner. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*



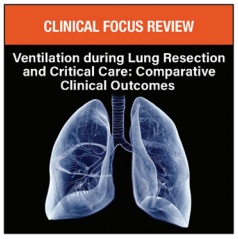
446 Respiratory Effects of the Atypical Tricyclic Antidepressant Tianeptine in Human Models of Opioid-induced Respiratory Depression

Tianeptine is an atypical antidepressant and cognitive enhancer that can be administered orally or intravenously. It may cause respiratory stimulation during opioid-induced respiratory depression by enhancing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated transmission and reducing glutamatergic transmission at *N*-methyl-d-aspartate (NMDA) receptors. However, tianeptine also acts as a μ-opioid receptor agonist, which may reduce its respiratory stimulatory capabilities. The hypothesis that tianeptine can effectively reverse opioid-induced respiratory depression was tested in 15 male and female subjects in a double-blind, randomized, placebo-controlled crossover study by determining the effect of four increasing target plasma tianeptine concentrations on remifentanil-induced respiratory depression at isohypercapnia. Over the plasma tianeptine concentration range tested (500 to 2,000 ng/ml), it did not produce respiratory stimulation during remifentanil-induced respiratory depression, but instead worsened respiratory depression with a further decline in ventilation at an extrapolated end-tidal carbon dioxide concentration of 55 mmHg (V_E55) by 5 l/min. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*

 DOI: 10.1097/ALN.0000000000004371

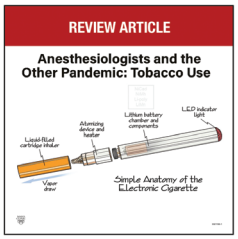
459 No Benefits of Adding Dexmedetomidine, Ketamine, Dexamethasone, and Nerve Blocks to an Established Multimodal Analgesic Regimen after Total Knee Arthroplasty

The hypothesis that adding five novel analgesic interventions to a standard multimodal analgesic regimen would decrease postoperative opioid requirements was tested in a randomized, double-blind, controlled trial of 78 patients undergoing total knee arthroplasty. All patients received a single-injection adductor canal block, spinal anesthesia with low-dose intrathecal morphine, intraoperative IV dexamethasone, periarticular local anesthetic infiltration, and round-the-clock oral acetaminophen and celecoxib, with immediate-release oxycodone or hydromorphone as needed. The treatment group also received a preoperative local anesthetic infiltration between the popliteal artery and posterior compartment of the knee, intraoperative IV infusions of low-dose dexmedetomidine and ketamine, a second dose of IV dexamethasone on postoperative day 1, and additional adductor canal block bolus injections on postoperative days 0 and 1. The additional interventions resulted in neither less opioid consumption or lower pain scores in the first 24 to 48 h after the operation nor better postoperative functional outcomes, quality of recovery, patient satisfaction, or longer-term pain and analgesic outcomes up to 6 weeks after surgery. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*



473 Ventilation during Lung Resection and Critical Care: Comparative Clinical Outcomes (Clinical Focus Review)

Positive-pressure ventilation has been reported to contribute to lung inflammation and might predispose general surgery and intensive care unit patients to a higher risk of ventilator-associated lung injury at high tidal volume (V_T) ventilation. This review highlights recent evidence from prospective studies of the use of low V_T ventilation and varying levels of positive end-expiratory pressure (PEEP) in patients with acute respiratory distress syndrome (ARDS), intensive care unit patients without ARDS, and patients receiving one-lung ventilation during lung resection. A randomized controlled trial that compared traditional ventilation with ventilation with a lower V_T in patients with ARDS reported decreased mortality, more ventilator-free days, and fewer organ failure days in the low V_T group. In contrast, in randomized controlled trials clinically important outcomes did not differ between intensive care unit patients without ARDS ventilated with a low or higher V_T or with low or higher PEEP. There is limited evidence to support use of protective lung ventilation, including manipulation of V_T, PEEP, and driving pressure, during one-lung ventilation to reduce postoperative pulmonary complications. *(Summary: M. J. Avram. Image: Adobe Stock.)*



484 Anesthesiologists and the Other Pandemic: Tobacco Use (Review Article)

Tobacco use is the leading cause of preventable death in many countries. Because receiving surgery is a teachable moment event for smoking cessation, anesthesiologists can play a unique role in the fight against this pandemic, providing not only immediate benefits to their tobacco-using patients' health through reduction of perioperative risk but also long-term benefits through reduction in diseases related to tobacco use. This review begins with an overview of the origins and evolution of the tobacco use pandemic, the pathophysiology of tobacco use and the natural history of quitting, and effective options for treatment of the underlying disease. It then presents the rationale for addressing tobacco use in perianesthesia practices and concludes by reviewing practical strategies by which anesthesiologists can take advantage of their unique opportunities to help their patients, including what is referred to as multimodal perianesthesia tobacco treatment. This incorporates four core components of successful treatment programs: consistent ascertainment and documentation of tobacco use, advice to quit, access to nicotine replacement therapy or other pharmacotherapy, and referral to counseling resources. *(Summary: M. J. Avram. Image: From original article.)*

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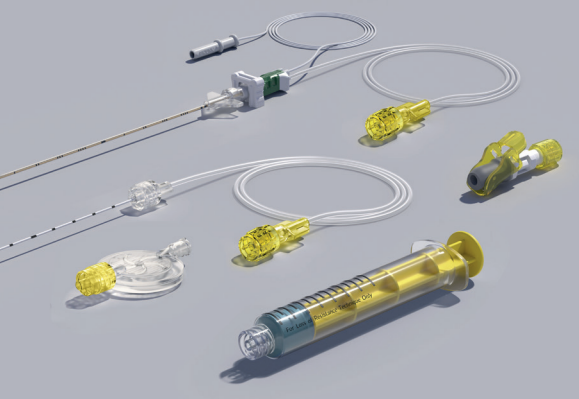

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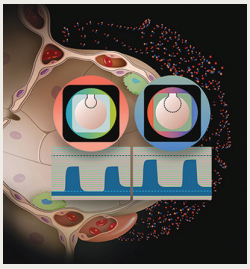

ON THE COVER: The effect of intraoperative positive end-expiratory pressure (PEEP) and tidal volume settings on postoperative oxygenation and respiratory complications is unclear. In this issue of ANESTHESIOLOGY, Turan et al. tested whether ventilation using different tidal volumes and PEEP levels affects postoperative oxygenation for adult patients undergoing orthopedic surgery. In an accompanying editorial, Musch and Vidal Melo examine the current challenges and potential applications of intraoperative protective mechanical ventilation. Cover illustration: A. Johnson, Vivo Visuals Studio

- Turan *et al.*: Tidal Volume and Positive End-expiratory Pressure and Postoperative Hypoxemia during General Anesthesia: A Single-center Multiple Crossover Factorial Cluster Trial, p. 406
- Musch and Vidal Melo: Intraoperative Protective Mechanical Ventilation: Fact or Fiction?, p. 381

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CME Editors: Leslie C. Jameson, M.D., and Dan J. Kopacz, M.D.

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Read the article by Sequera-Ramos *et al.* entitled "Sedation *versus* General Anesthesia for Tracheal Intubation in Children with Difficult Airways: A Cohort Study from the Pediatric Difficult Intubation Registry" on page 418. The CME exam can be accessed directly at: www.asahq.org/JCME2022OCT.

Learning Objectives

After successfully completing this activity, the learner will be able to identify the most successful method of intubating pediatric patients with an anticipated difficult airway, anticipate the proportion of pediatric patients that may require general anesthesia for tracheal intubation after intravenous sedation has failed, and cite the most common potential complication of tracheal intubation.

Disclosures

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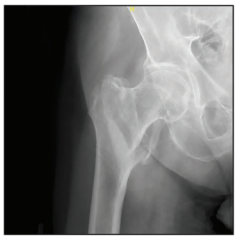
Key Papers from the Most Recent Literature Relevant to Anesthesiologists

Prothrombin complex concentrate vs plasma for post-cardiopulmonary bypass coagulopathy and bleeding: A randomized clinical trial. JAMA Surg 2022 Jun 29 [Epub ahead of print]. PMID: 35767271.

Prothrombin complex concentrate (PCC) is increasingly used to treat coagulopathy after cardiac surgery. In this single-institution, open-label randomized trial, adult patients preferentially undergoing complex cardiac surgical procedures developing excessive microvascular bleeding, a prothrombin time (PT) greater than 16.6 s, and an international normalized ratio (INR) greater than 1.6 after cardiopulmonary bypass received either PCC (15 IU/kg) or plasma (10 to 15 ml/kg). The primary outcome was chest tube output volume through midnight on day 1. Secondary outcomes were PT/INR, intraoperative and postoperative (day 1) transfusions, and adverse events. One hundred patients (mean age 67 yr, male 61%) met criteria for entry (49 received plasma, 51 received PCC). There was no significant difference in chest tube output (median [interquartile range], 1022 [799 to 1,575] ml for plasma *vs.* 937 [708 to 1443] ml for PCC), although allogenic transfusion was avoided in 14% of PCC subjects. After treatment, patients in the PCC arm had a greater improvement in PT (effect estimate, −1.37 s [95% CI, −1.91 to −0.84]; $P < 0.001$) and INR (effect estimate, −0.12 [95% CI, −0.16 to −0.07]; $P < 0.001$). Fewer patients in the PCC group required intraoperative red blood cell transfusion after treatment (14% *vs.* 31%; $P = 0.04$), although total intraoperative blood component transfusion rates were not different. There were no significant differences in postoperative bleeding, transfusions, or adverse events. *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

Take home message: In this randomized trial of high-risk adult cardiac surgical patients, intraoperative PCC administration *versus* plasma in response to bleeding and altered coagulation parameters did not alter early postoperative chest tube output but did result in fewer intraoperative red blood cell transfusions after treatment and greater improvement in coagulation parameters without more adverse events.



Pain, analgesic use, and patient satisfaction with spinal versus general anesthesia for hip fracture surgery: A randomized clinical trial. Ann Intern Med 2022; 175:952–60. PMID: 35696684.

While outcomes between general and spinal anesthesia for hip fracture have not been reported to differ for ambulation, survival, delirium, or hospital length of stay, less is known about pain- and opioid-related outcomes between these two techniques. This planned secondary analysis of a pragmatic randomized trial of these techniques across 46 U.S. and Canadian hospitals (Regional *versus* General Anesthesia for Promoting Independence after Hip Fracture [REGAIN] trial; n = 1,600) compared postoperative pain, analgesic use, and patient satisfaction between the groups. Using a 0 to 10 numeric rating scale for pain, pain over the first 24 h was greater with spinal anesthesia (mean difference, 0.4 [95% CI, 0.12 to 0.68]); however, this difference did not meet the threshold for a clinically meaningful difference. No other between-group differences for pain at later time points (postoperative days 2, 3, 60, 180, or 365) were noted. Prescription analgesic use at 60 days postoperatively was higher in the spinal anesthesia group (25%) compared with general anesthesia (19%; relative risk, 1.33 [CI, 1.06 to 1.65]). Notably, patient satisfaction, willingness to recommend the same approach to a family member, and exploratory cognitive status evaluations were not different between groups. *(Article Selection: Chad M. Brummett, M.D. Image: J. P. Rathmell.)*

Take home message: After surgery for hip fracture, patients receiving spinal anesthesia reported statistically higher, yet not clinically meaningful worse pain scores in the first 24 h and greater analgesic use 60 days after surgery when compared with those receiving general anesthesia.

Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults. Cell Rep Med 2022; 3:100633. PMID: 35584623.

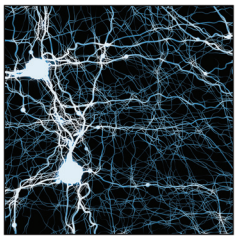
Age-associated decline in muscle mass may result from mitochondrial dysfunction. Mitophagy stimulating agents such as urolithin A, a gut-microbiome-derived metabolite of the polyphenolic compounds ellagitannins, might attenuate this decline. This randomized controlled trial evaluated 88 healthy, overweight, middle-aged subjects comparing 500 mg/day urolithin A orally (n = 29), 1,000 mg/day urolithin A (n = 30), and oral placebo (n = 29) for 4 months. The primary endpoint was peak muscle power output by lower- and upper-body muscle strength testing by dynamometry. Secondary endpoints included aerobic endurance (peak oxygen consumption [$\dot{V}O_2$]), physical performance (6-min walk test), and biomarkers of muscle/mitochondrial status and inflammation. Peak power output was comparable in the three groups, whereas muscle strength of the lower-body muscles was greater in both urolithin A groups compared to placebo (hamstring muscle strength: 12% greater in the 500 mg/day group [$P = 0.027$] and 10% greater in the 1,000 mg/day group [$P = 0.029$]; leg flexion: 11% greater in the 500 mg/day group [$P = 0.017$] and 11% greater in the 1,000 mg/day group [$P = 0.022$]). Peak $\dot{V}O_2$ and walking ability were similar in the urolithin A intervention and placebo groups. Acylcarnitines were lesser in the urolithin A 500 mg/day group, consistent with greater fatty acid oxidation. C-reactive protein plasma concentration was lower in the urolithin A 1,000 mg/day arm compared to placebo along with inflammatory mediators tumor necrosis factor-α and interferon-γ. Oral administration of urolithin A was well tolerated. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: Adobe Stock.)*

Take home message: In this randomized, placebo-controlled trial, overweight middle-aged subjects taking urolithin A (present in berries, walnuts, and pomegranates) for 4 months had significantly greater lower-extremity strength compared to placebo.

Cannabis-based products for chronic pain: A systematic review. Ann Intern Med 2022; 175:1143–53. PMID: 35667066.

The use of cannabis-based products has continued to surge in the United States and worldwide for medical indications, including chronic pain, despite persistent concerns regarding abuse and questions regarding effectiveness. This systematic review included 18 randomized, placebo-controlled trials (n = 1,740) and 7 cohort studies (n = 13,095) evaluating the effectiveness of the cannabinoids tetrahydrocannabinol (THC) or cannabidiol (CBD, which is devoid of psychoactive effects) for chronic pain. Studies were primarily short term (less than 8 weeks), with 56% enrolling patients with neuropathic pain. No study was at low risk for bias. Synthetic products with high THC:CBD ratios (more than 98% THC, n = 10) were associated with moderate improvement in pain severity and binary treatment response (greater than or equal to 30% improvement) but also a greater risk for dizziness. Within this class, the effect for nabilone was statistically significant (mean difference, 1.59 [95% CI, 2.49 to 0.82], while the effect for dronabinol was not. Medications with comparable THC:CBD ratios were associated with smaller improvements in pain (mean difference, 0.54 [95% CI, 0.95 to 0.19]) and function (mean difference, 0.42 [95% CI, 0.73, 0.16]). There was insufficient evidence to assess compounds containing only CBD and no data were provided on misuse. *(Article Selection: Steven Cohen, M.D. Image: Adobe Stock.)*

Take home message: Oral synthetic cannabinoids with high THC:CBD ratios and sublingual cannabis products with comparable THC:CBD ratios may be associated with short-term improvements in chronic pain but also greater risk for dizziness and sedation relative to placebo. Studies are needed to evaluate long-term outcomes.



A novel spinal neuron connection for heat sensation. Neuron 2022; 110:2315–33. PMID: 35561677.

Heat sensation is a fundamental perception necessary for the detection of potentially harmful stimuli. However, its spinal mechanisms, especially the identity of heat-processing neurons, is unknown. Using genetic manipulation and electrophysiologic and behavioral approaches, this study explored the responsible spinal network in mice, in particular a group of excitatory neurons that are ErbB4+ responding to noxious heat stimulation. ErB4 is a receptor tyrosine kinase of the epidermal growth factor receptor (EGFR) family, which is activated by the growth factor neuregulin 1 (NRG1). Specific ablation of spinal ErbB4 neurons reduced heat perception, whereas mechanical sensation was unchanged. The ErbB4 neurons receive inputs from heat nociceptor-containing C and A delta fibers, especially TRPV1 nociceptors and not by mechanosensory neurons. The expression in spinal ErbB4 neurons, of an engineered chemogenetic receptor, which solely responds to a synthetic ligand designed to activate or inhibit ErbB4 neurons, confirmed the role of ErbB4 in heat sensation. Spinal NRG1 and the phosphorylated active form of ErbB4 were increased after noxious heat stimulus, inflammation, and nerve injury. This demonstrates the involvement of NRG1-ErbB4 signaling in heat sensation in physiologic and pathologic conditions *via* regulation of the glutamatergic transmission. Blockade of either ErbB4 or NRG1 reduced thermal pain hypersensitivity produced by inflammatory or neuropathic pain. *(Article Selection: Cyril Rivat, Ph.D. Image: Adobe Stock.)*

Take home message: NRG1 activates spinal ErbB4 excitatory interneurons that are necessary for heat sensation and not involved in mechanosensitivity. NRG1-ErbB4 signaling is also responsible for thermal pain hypersensitivity produced by either inflammatory or neuropathic pain.

Effect of nitric oxide via cardiopulmonary bypass on ventilator-free days in young children undergoing congenital heart disease surgery: The NITRIC randomized clinical trial. JAMA 2022; 328:38–47. PMID: 35759691.

Preclinical and clinical studies suggest that nitric oxide added to the gas inflow of the cardiopulmonary bypass oxygenator may decrease the incidence of low cardiac output syndrome in young children. In this double-blind, multicenter, randomized clinical trial, a total of 1,371 children younger than 2 yr of age were randomized to receive either nitric oxide (20 ppm) delivered into the cardiopulmonary bypass oxygenator (n = 679) or standard care (n = 685). The primary endpoint was the number of ventilator-free days from bypass until day 28. Secondary endpoints include a composite of low cardiac output syndrome, extracorporeal life support, or death; intensive care and hospital length of stay; and postoperative troponin levels. The number of ventilator-free days did not differ between groups (median, 26.6 days with nitric oxide [interquartile range, 24.4 to 27.4] *vs.* 26.4 days without [24.0 to 27.2]; absolute difference of –0.01 days [95% CI, –0.25 to 0.22]). No statistical difference was noted for the composite secondary endpoint (adjusted odds ratio for age at randomization, surgical lesion type, and study site 1.12 [95% CI, 0.85 to 1.47]), intensive care or hospital length of stay (adjusted odds ratio, 1.00 [95% CI, 0.90 to 1.12]; 0.97 [95% CI, 0.87 to 1.09]), and postoperative troponin levels (adjusted odds ratio, –0.23 [95% CI, –0.88 to 0.42]). *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

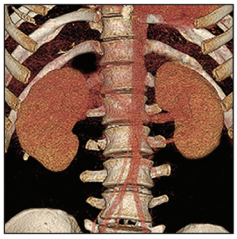
Take home message: In children younger than 2 yr undergoing congenital heart surgery, the use of nitric oxide *via* cardiopulmonary bypass did not significantly affect the number of ventilator-free days after surgery or composite secondary outcomes.

 DOI: 10.1097/ALN.0000000000004372

Association of changes in antithrombin activity over time with responsiveness to enoxaparin prophylaxis and risk of trauma-related venous thromboembolism. JAMA Surg 2022; 157:713–21. PMID: 35731524.

Venous thromboembolism after traumatic injury affects 2 to 20% of patients. Antithrombin, a crucial factor for effective anticoagulation with heparins, has been found to be deficient in 20% of trauma patients. This single-center, prospective cohort study was performed at a level 1 trauma center. The study objective was to assess time-dependent changes in antithrombin activity, responsiveness to enoxaparin (measured by anti–factor Xa levels), and the incidence of venous thromboembolism after severe trauma. In addition, this study examined the effect of *ex vivo* antithrombin supplementation on responsiveness to enoxaparin measured by anti-factor Xa levels 4 to 6 h after the first daily enoxaparin dose. Among 150 patients enrolled, 28 (19%) developed venous thromboembolism. Patients with venous thromboembolism had significantly lower antithrombin activity on admission compared with patients without (median [interquartile range], 91% [79 to 104%] *vs.* 100% [88 to 112%]; $P = 0.04$), as well as lower antithrombin activity on hospital days 5, 6, 7, and 8. Anti-factor Xa levels were significantly lower in patients with venous thromboembolism throughout the study. Multivariable analyses found that for every 10% decrease in antithrombin activity during the first 3 days, the risk of venous thromboembolism increased 1.5-fold. Addition of antithrombin *ex vivo* improved responsiveness to enoxaparin measured by anti-factor Xa. *(Article Selection: David Faraoni, M.D., Ph.D. Image: Adobe Stock.)*

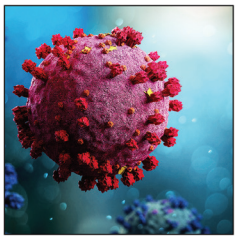
Take home message: After severe trauma in adults, antithrombin deficiency is common and contributes to enoxaparin resistance and venous thromboembolism.



Perioperative nonsteroidal anti-inflammatory drugs (NSAID) administration and acute kidney injury (AKI) in major gastrointestinal surgery: A prospective, multicenter, propensity matched cohort study. Ann Surg 2022; 275:904–10. PMID: 33074883.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used postoperatively to improve pain, decrease inflammation, and limit opioids. NSAIDs previously have been associated with increased risk of acute kidney injury (AKI) and anastomotic leaks. A multicenter, prospective cohort study evaluated patients having elective or emergency major gastrointestinal surgery from September to December 2015 across 173 hospitals in the United Kingdom and Ireland. A secondary analysis evaluated the 7-day postoperative AKI rate and anastomotic leaks in patients administered NSAIDs on postoperative days 0 to 3. Propensity score matching was used to balance treatment groups and estimate treatment effects. Within 3 days of surgery, 20% (1,039 of 5,240) of patients received NSAIDs. AKI occurred in 11% of the early-NSAID group and 15% of the no-NSAID group. After propensity score matching, early use of NSAIDs was not significantly associated with AKI (adjusted odds ratio, 0.80; 95% CI, 0.63 to 1.00; $P = 0.057$). The finding was consistent in subgroup analyses by NSAID dosage and timing. The anastomotic leak rate was 5% in the NSAID group and 6% in the no-NSAID group. NSAIDs were not associated with anastomotic leak (adjusted odds ratio, 0.85; 95% CI, 0.58 to 1.21; $P = 0.382$). *(Article Selection: BobbieJean Sweitzer, M.D. Image: J. P. Rathmell.)*

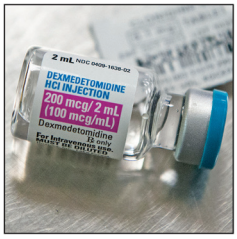
Take home message: In a large observational cohort, the use of NSAIDs in the early postoperative period after major gastrointestinal surgery was not associated with a greater risk of either acute kidney injury or anastomotic leak.



Use of pragmatic and explanatory trial designs in acute care research: Lessons from COVID-19. Lancet Respir Med 2022; 10:700–14. PMID: 35709825.

The COVID-19 pandemic led to an unprecedented increase in acute care clinical research. Optimal methodology has been questioned given the challenge of simultaneously treating and researching a novel illness, obtaining consent amid hospital visitor restrictions, and the widespread repurposing of common therapies. The 2020 Critical Care Clinical Trialists Workshop participants reviewed the ORCHID trial of hydroxychloroquine for COVID-19 and the RECOVERY trial of common therapies for COVID-19 to showcase the benefits and drawbacks of explanatory *versus* pragmatic trials during a public health crisis. Explanatory trials evaluate novel therapies while pragmatic trials assess known therapies in a real-world context. These different goals require different designs. For example, regulatory standards for explanatory trials are likely too restrictive for pragmatic trials. The need for informed consent is controversial for pragmatic trials given that participants receive the intervention as part of standard care and waiting for consent may hamper enrollment targets. Explanatory trials' stringent enrollment criteria maximize internal validity but compromise generalizability; pragmatic trials include a more representative population to facilitate early application of results. Explanatory trials require experienced research staff while pragmatic trials maximize efficiency by allowing nonresearch staff to enroll, administer interventions, and record data. *(Article Selection: Meghan Prin, M.D., M.S. Image: Adobe Stock.)*

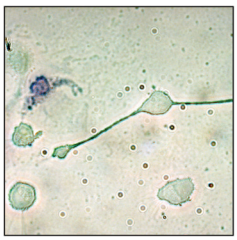
Take home message: Pragmatic clinical trials offer efficiency and generalizability, which may be more appropriate in the setting of a public health crisis relative to traditional explanatory trials. However, broad adoption of this design will require alignment of institutional stakeholders to match the intensity of regulatory oversight and human subjects' protection with potential impacts on trial enrollment.



Effect of perioperative dexmedetomidine on delayed graft function following a donation-after-cardiac-death kidney transplant: A randomized clinical trial. JAMA Netw Open 2022; 5:e2215217. PMID: 35657627.

Dexmedetomidine is postulated to have renal protective effects. However, its effects on renal allograft success after renal transplant have not been studied. This single-center, double-blind, placebo-controlled randomized controlled trial included 111 renal transplant patients. The treatment group (n = 56) received a 24-h IV infusion of dexmedetomidine: 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ intraoperatively and 0.1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ postoperatively. Controls (n = 55) received infusions of normal saline. The primary outcome was the need for dialysis in the first week posttransplant. The prespecified secondary outcomes were in-hospital repeated dialysis, in-hospital rejection, serum creatinine and cystatin, estimated glomerular filtration rate, and patient dialysis and survival at day 30. Patients receiving dexmedetomidine had a lower incidence of dialysis in the first week, 35% *versus* 18% (odds ratio, 0.41; 95% CI, 0.17 to 0.98; $P = 0.04$), and greater creatinine clearance on days 1 (9.9 [4.9 to 21.2] ml/min *vs.* 7.9 [2.0 to 10.4] ml/min) and 2 (29.6 [9.7 to 67.4] ml/min *vs.* 14.6 [3.8 to 45.1] ml/min). Dexmedetomidine had no beneficial effects on other secondary outcomes, and there was no difference in adverse events between the two groups. *(Article Selection: Jamie Sleigh, M.D. Image: J. P. Rathmell.)*

Take home message: In this single-center, randomized, double-blind, placebo-controlled study, patients receiving a 24-hr perioperative infusion of low-dose dexmedatomidine had a lower incidence of dialysis in the first week postoperatively.



Carbon dioxide sensing by immune cells occurs through carbonic anhydrase 2-dependent changes in intracellular pH. J Immunol 2022; 208:2363–75. PMID: 35477686.

Carbon dioxide, a major physiologic gas, is elevated in microenvironments of many inflammatory diseases that impair immune cell function, but little is known about its effects on downstream signaling pathways. This two-part human study (*in vitro* cell culture, *in vivo* analysis) demonstrates that higher levels of carbon dioxide (10% *vs.* 5%) inhibit autocrine inflammatory gene expression in macrophages by changing intracellular pH, which ultimately reduces macrophage activation and migratory functions. Mechanistically, inhibition of carbonic anhydrase 2 (a carbon dioxide–sensing enzyme) by pharmacologic or genetic (siRNA) means was found to prevent carbon dioxide–mediated intracellular pH alterations and attenuated the sensitivity of macrophages to carbon dioxide–mediated inhibition. Ten percent CO_2 decreased endotoxin-stimulated NFκB activation and its corresponding cytokine and chemokine response. Intestinal epithelial cells subjected to a scratch assay exhibited decreased simulated "wound closure" when media from 10%, as opposed to 5%, CO_2-treated M1 polarized macrophages was added. The significance of these *in vitro* findings was corroborated in patients undergoing colorectal surgery where macrophages from patients with elevated Pco_2 as measured by intraoperative blood gas analysis, exhibited reduced migration. Low intraoperative pH, but not Po_2 values, in these patients also correlated with reduced intestinal macrophage infiltration and a higher risk of anastomotic leakage secondary to wound healing problems. *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: Macrophage; the original uploader was Obli at English Wikipedia, CC BY-SA 2.0 <https://creativecommons.org/licenses/by-sa/2.0>,* via *Wikimedia Commons.)*

Take home message: High levels of carbon dioxide inhibit macrophage differentiation and activation *via* carbonic anhydrase in an intracellular pH-dependent manner. Hypercapnia and acidosis are associated with increased risk of anastomotic leakage in patients undergoing colorectal surgery.

Effect of intraoperative handovers of anesthesia care on mortality, readmission, or postoperative complications among adults: The HandiCAP randomized clinical trial. JAMA 2022; 327:2403–12. PMID: 35665794.

Intraoperative handovers between anesthesia providers are common. Observational data suggest associations between such handovers and adverse events. This parallel-group, randomized clinical trial (12 German centers without standardized handover protocols) enrolled 1,817 patients with American Society of Anesthesiologists (ASA) physical status III or IV undergoing inpatient surgery (duration greater than or equal to 2 h) to receive a complete (n = 908) or no handover of anesthesia care (n = 909). The primary outcome was a 30-day composite of all-cause mortality, hospital readmission, or serious postoperative complications. Nineteen secondary outcomes were collected. A total of 1,772 patients (mean ± SD age, 66 ± 12 yr; 56% male, 97% ASA physical status III, median duration of anesthesia, 267 min [interquartile range, 206 to 351 min], median time from start of anesthesia to first handover, 144 min in the handover group [interquartile range, 105 to 213 min]) completed the study. No difference in the primary outcome was noted (30% handover *vs.* 33% no handover group; absolute risk difference, –2.5%; 95% CI, –6.8% to 1.9%; odds ratio, 0.89; 95% CI, 0.72 to 1.10; $P = 0.27$)). There were no statistical differences in the composite components (30-day mortality, 2% *vs.* 3%; readmission, 13% *vs.* 16%; postoperative complications, 22% *vs.* 22%). None of the 19 prespecified secondary endpoints differed significantly. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: In this randomized trial of higher-risk patients undergoing major noncardiac surgery who received a structured intraoperative handover between anesthesia care providers *versus* no handover, no difference in mortality, readmission, or serious postoperative complications at 30 days after surgery were noted.

INFOGRAPHICS IN ANESTHESIOLOGY

Complex Information for Anesthesiologists Presented Quickly and Clearly

A Lung-Unanswered Question:

What is the effect of intraoperative positive end-expiratory pressure (PEEP) and tidal volume (V_T) on postoperative oxygenation and respiratory complications?

Do ICU data extrapolate to the OR?

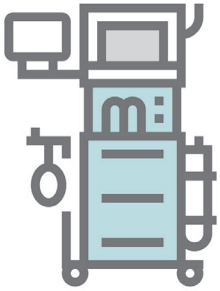
Low V_T combined with moderate PEEP improves morbidity and mortality in mechanically ventilated patients in the ICU.[1]

- Preexisting lung disease common
- Ventilated for ***days***

Data are conflicting regarding optimal combination of V_T and PEEP intraoperatively.

- Normal lung function common
- Ventilated for ***hours***

Prior Studies of V_T and PEEP in the Operating Room[2]



IMPROVE trial — Lower pulmonary complications

Compared V_T 6-8 ml/kg and PEEP 6-8 cm H_2O *vs.* V_T 10-12 ml/kg and no PEEP

PROVHILO trial — no difference in pulmonary complications

Compared PEEP 2 cm H_2O *vs.* 12 cm H_2O (V_T 8 ml/kg in all patients)

Karalapillai *et al.* — no difference in pulmonary complications

Compared V_T 6 ml/kg *vs.* 10 ml/kg (PEEP 5 cm H_2O in all patients)

In the current study, Turan *et al.* conducted a 2x2 factorial crossover cluster trial to assess V_T 6 or 10 ml/kg and PEEP 5 or 8 cm H_2O. They assessed oxygenation during the first hour in PACU using the time-weighted average (TWA) of SpO_2/FIO_2.[2]

	V_T 6 ml/kg	V_T 10 ml/kg	PEEP 5 cm H_2O	PEEP 8 cm H_2O
TWA SpO_2/FIO_2	355 ± 46	350 ± 47	353 ± 46	352 ± 47
	Mean difference 3.5% $P=0.042$		Mean difference −0.2% $P=0.906$	
Pulmonary complications	3.1%	3.2%	2.9%	3.4%
	OR 1.00, $P=0.992$		OR 0.87, $P=0.553$	

CONCLUSION **Oxygenation in the PACU is not different from V_T between 6 and 10 ml/kg and PEEP between 5 and 8 cm H_2O in patients having orthopedic surgery.**

FIO_2, fraction of inspired oxygen; ICU, intensive care unit; OR, operating room; PACU, postanesthesia care unit; SpO_2, oxygen saturation.

Infographic created by Holly B. Ende, Vanderbilt University Medical Center; James P. Rathmell, Brigham and Women's Health Care/Harvard Medical School; and Jonathan P. Wanderer, Vanderbilt University Medical Center. Illustration by Annemarie Johnson, Vivo Visuals Studio. Address correspondence to Dr. Ende: holly.ende@vumc.org.

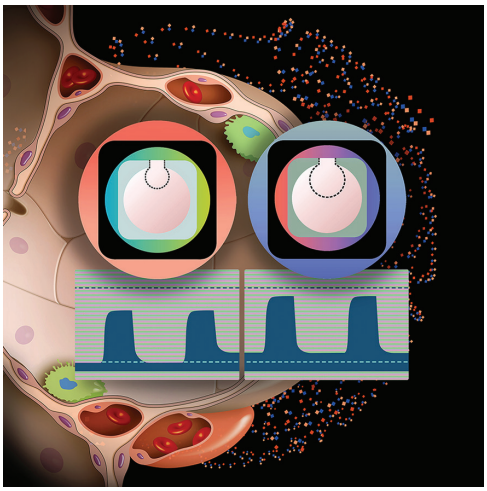
1. Acute Respiratory Distress Syndrome Network; Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301–8.

2. Turan A, Esa WAS, Rivas E, Wang J, Bakal O, Stamper S, Farag E, Maheswari K, Mao G, Ruetzler K, Sessler DI, for the Ventilation-PEEP Trial Group: Tidal volume and positive end-expiratory pressure and postoperative hypoxemia during general anesthesia: A single-center multiple crossover factorial cluster trial. ANESTHESIOLOGY 2022; 137:406–417.

Intraoperative Protective Mechanical Ventilation: Fact or Fiction?

Guido Musch, M.D., M.B.A., Marcos F. Vidal Melo, M.D., Ph.D.

Positive pressure ventilation gained widespread clinical acceptance during the Danish polio epidemic of 1952,[1] when it dramatically reduced the mortality of respiratory failure, and it has saved countless lives in ensuing years by enabling modern critical care and the safe practice of surgery under general anesthesia. Nonetheless, evidence emerged in the 1970s that positive pressure ventilation can itself cause lung injury.[2] Since then, two fundamental facts have been established. First, large tidal lung excursions are detrimental if they lead to end-inspiratory overdistension and/or cyclical alveolar or bronchiolar derecruitment–recruitment between breaths. Second, the lungs of patients during general anesthesia or with acute respiratory distress syndrome are functionally smaller: functional residual capacity is reduced because some of the airspaces become atelectatic, consolidated, or flooded with edema. A corollary of these facts has been the quest to restore the relationship between tidal volume and functional residual capacity either by decreasing the former or increasing the latter. This concept represents the physiologic underpinning of all "protective" ventilation strategies.



"When is protective intraoperative ventilation most beneficial?"

Such framework is helpful to analyze the study by Turan and colleagues[3] in this issue of Anesthesiology. In this large factorial crossover cluster trial, adults undergoing orthopedic surgery during general anesthesia (approximately 50% also with regional block and slightly more than 50% undergoing arthroplasty) were allocated to two levels of tidal volume (6 and 10 ml/kg of predicted body weight) and of positive end-expiratory pressure (PEEP, 5 and 8 cm H_2O). Presumably, ventilation with lower tidal volume and higher PEEP could lead to better postoperative oxygenation and lower incidence of respiratory complications, because such a strategy would limit both end-inspiratory overdistension and end-expiratory derecruitment, the two biophysical triggers of ventilator-induced lung injury. The results instead show no meaningful clinical or statistical difference among the four studied groups in oxygenation within the first postoperative hour, oxygenation later on the ward, frequency of postoperative pulmonary complications, or duration of hospitalization.

It is important to note that the authors did not use excessively high or low tidal volumes[4,5] and PEEP, but instead values considered acceptable in current clinical practice.[4–6] Accordingly, two main inferences can be drawn. First, in a cohort of patients with a low prevalence of lung disease and borderline obesity undergoing nonabdominal surgery of moderate duration (about 3.5 h) and without major physiologic impact (*e.g.*, blood loss), low tidal volumes as well as higher acceptable tidal volumes (10 ml/kg)[4,5] with higher PEEP were well tolerated. It is interesting that a tidal volume of 6 ml/kg did not result in lower oxygenation even at the lower PEEP, given that atelectasis is usually considered the main downside of low tidal volume. These results suggest that relatively healthy lungs in the studied conditions can withstand a few hours of low tidal volume ventilation during nonabdominal surgery without developing significant atelectasis even at low PEEP. Higher PEEP and tidal volume did not seem to compromise postoperative lung function either. Second, these results release the cognitive anchor to a single optimal PEEP or tidal volume, at least in this patient population, and instead portray a range of equally acceptable values, consistent with a range—not merely a point—of maximal compliance in the pressure–volume curve of a healthy lung. This message is important because it argues against the transposition without qualification of inferences and values derived from critical care studies to the operating room.

So, is intraoperative protective ventilation all fiction? Substantive observational evidence has identified tidal volume as a risk factor for postoperative pulmonary

Image: A. Johnson, Vivo Visuals Studio.

This editorial accompanies the article on p. 406. This article has a related Infographic on p. A19. This article has an audio podcast.

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complications after general anesthesia.[7,8] These studies indicated that "protective" ventilation (generally defined as lower tidal volume plus PEEP and/or recruitment maneuvers) may reduce such complications[4,8] that are associated with increased mortality, intensive care unit admission, and length of stay.[7] The Intraoperative Protective Ventilation (IMPROVE) trial confirmed a marked beneficial effect of protective ventilation on major abdominal surgery.[6]

Yet, as with Turan's trial, several trials on protective ventilation did not demonstrate a difference between groups.[5,9,10] What could explain these inconsistencies, and when is protective intraoperative ventilation most beneficial? It has been increasingly recognized that the ratio of tidal volume to end-expiratory lung volume, proportional to the driving pressure and a surrogate for lung strain, is the biophysical mediator of the effects of tidal volume and PEEP on ventilator-induced lung injury.[4] In fact, the potential of different tidal volumes to reduce postoperative pulmonary complications depends on the patient's respiratory compliance.[11] This physiologic individuality may be a reason for discrepancies. Patient population is another factor. The IMPROVE trial targeted a high-risk population for pulmonary complications[6] (major open abdominal surgery, pre-existent respiratory risk factors), whereas Turan and colleagues studied a population at lower risk[3] based on the Assess Respiratory Risk in Surgical Patients in Catalonia risk score.[12] There is evidence that pulmonary outcomes are less likely to depend on PEEP in nonabdominal/noncardiothoracic surgery, *e.g.*, neurologic *versus* abdominal surgery.[13] This also implies that Turan's results should not be extrapolated to abdominal or cardiothoracic surgery, when additional injury mechanisms are present and, consequently, the effects of different ventilatory settings could be more evident.[13] Time may also be an important variable. Normal lungs show only limited inflammation after 2 h of ventilation even at high driving pressures.[14] Sixteen to 24 h were necessary for a significant pulmonary inflammatory response and mechanical deterioration to develop in experiments applying clinical tidal volumes (6 to 8 ml/kg) in initially uninjured lungs.[15–17] Finally, the separation between ventilator settings is relevant. The IMPROVE trial acted on multiple variables (tidal volume, PEEP, recruitment maneuvers) setting them apart enough (tidal volumes of 6 to 8 ml/kg with PEEP = 6 to 8 cm H_2O *versus* 10 to 12 ml/kg with PEEP = 0 cm H_20) that, presumably, the effect could be detected in contrast to current practice used by Turan and colleagues.[3]

If there is a range of equally acceptable values for ventilatory settings, it may be hard to show an effect, especially when clinical practice has already converged toward such a range. Turan and colleagues studied a large population and observed a smaller SD for the primary outcome than that initially presumed, which ultimately yielded a high power to detect the predefined mean effect. The 97.5% CIs for the effect estimates were a time-weighted average Spo_2/Fio_2 of −0.4 to 7.3% for tidal volume and −4.0 to 3.6% for PEEP, numbers that convincingly demonstrate comparable postoperative oxygenation in the studied groups. These results also imply that, although previous clinical studies documented the presence of an effect, they did not necessarily provide the best or single setting of the variable of interest to achieve that effect.

The hemodynamic impact of mechanical ventilation is frequently a concern. A clinically meaningful finding by Turan and colleagues[3] in this regard was the similar intraoperative use of vasopressors and incidence of hypotension in all combinations of PEEP and tidal volume. This finding reinforces the concept that the mild-to-moderate range of ventilatory settings explored does not usually result in major hemodynamic effects.

The study opens several questions. Many patients were excluded by anesthesiologists, or due to comorbidities, instability, or other reasons. Such subset of potentially higher-risk patients could represent those patients who would most benefit from specific ventilatory interventions. Although the primary outcome of Spo_2/Fio_2 in the first hour is a sensitive marker of oxygenation impairment, it could be affected predominantly by factors other than ventilatory settings. The absence of differences in the ward reinforces that any influence of intraoperative settings on postoperative oxygenation was unlikely. Also, even if there was an intraoperative effect of the interventions, this could be lost at extubation, without subsequent benefit. Finally, the reported rate of pulmonary complications was quite low, implying a low-risk group and the potential risk for false negatives, given that the occurrence of those complications derived from registry and billing data not from prospective collection.

Such limitations will deserve future exploration to advance this relevant area. For now, Turan and colleagues provide evidence that mild-to-moderate differences in key ventilator settings—tidal volume and PEEP—within currently accepted ranges do not result in substantial differential effects on postoperative oxygenation and other pulmonary outcomes during orthopedic surgery. Mechanical ventilation in the operating room requires its own specific set of knowledge, with ranges different from those of patients with acute respiratory distress syndrome in intensive care units. Protective ventilation is not defined by single arbitrary numbers, but by ranges of ventilatory settings that likely differ in distinct conditions and in relation to patient-specific physiopathologic features.

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Competing Interests

The authors declare no competing interests.

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References

1. Ibsen B: The anaesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during

the epidemic in Copenhagen, 1952. Proc R Soc Med 1954; 47:72–4
2. Webb HH, Tierney DF: Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. Am Rev Respir Dis 1974; 110:556–65
3. Turan A, Esa WAS, Rivas E, Wang J, Bakal O, Stamper S, Farag E, Maheswari K, Mao G, Ruetzler K, Sessler DI; Ventilation-PEEP Trial Group: Tidal volume and positive end-expiratory pressure and postoperative hypoxemia during general anesthesia: A single-center multiple crossover factorial cluster trial. Anesthesiology 2022; 137:406–17
4. Ladha K, Vidal Melo MF, McLean DJ, Wanderer JP, Grabitz SD, Kurth T, Eikermann M: Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications: hospital based registry study. BMJ 2015; 351:h3646
5. Karalapillai D, Weinberg L, Peyton P, Ellard L, Hu R, Pearce B, Tan CO, Story D, O'Donnell M, Hamilton P, Oughton C, Galtieri J, Wilson A, Serpa Neto A, Eastwood G, Bellomo R, Jones DA: Effect of intraoperative low tidal volume vs conventional tidal volume on postoperative pulmonary complications in patients undergoing major surgery: A randomized clinical trial. JAMA 2020; 324:848–58
6. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B, Jaber S; IMPROVE Study Group: A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med 2013; 369:428–37
7. Fernandez-Bustamante A, Frendl G, Sprung J, Kor DJ, Subramaniam B, Martinez Ruiz R, Lee JW, Henderson WG, Moss A, Mehdiratta N, Colwell MM, Bartels K, Kolodzie K, Giquel J, Vidal Melo MF: Postoperative pulmonary complications, early mortality, and hospital stay following noncardiothoracic surgery: A multicenter study by the Perioperative Research Network Investigators. JAMA Surg 2017; 152:157–66
8. Serpa Neto A, Hemmes SN, Barbas CS, Beiderlinden M, Biehl M, Binnekade JM, Canet J, Fernandez-Bustamante A, Futier E, Gajic O, Hedenstierna G, Hollmann MW, Jaber S, Kozian A, Licker M, Lin WQ, Maslow AD, Memtsoudis SG, Reis Miranda D, Moine P, Ng T, Paparella D, Putensen C, Ranieri M, Scavonetto F, Schilling T, Schmid W, Selmo G, Severgnini P, Sprung J, Sundar S, Talmor D, Treschan T, Unzueta C, Weingarten TN, Wolthuis EK, Wrigge H, Gama de Abreu M, Pelosi P, Schultz MJ; PROVE Network Investigators: Protective *versus* conventional ventilation for surgery: A systematic review and individual patient data meta-analysis. Anesthesiology 2015; 123:66–78
9. PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology, Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ: High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet 2014; 384:495–503
10. Lagier D, Fischer F, Fornier W, Huynh TM, Cholley B, Guinard B, Heger B, Quintana G, Villacorta J, Gaillat F, Gomert R, Degirmenci S, Colson P, Lalande M, Benkouiten S, Minh TH, Pozzi M, Collart F, Latremouille C, Vidal Melo MF, Velly LJ, Jaber S, Fellahi JL, Baumstarck K, Guidon C; PROVECS Study Group: Effect of open-lung vs conventional perioperative ventilation strategies on postoperative pulmonary complications after on-pump cardiac surgery: the PROVECS randomized clinical trial. Intensive Care Med 2019; 45:1401–12
11. Suleiman A, Costa E, Santer P, Tartler TM, Wachtendorf LJ, Teja B, Chen G, Baedorf-Kassis E, Nagrebetsky A, Vidal Melo MF, Eikermann M, Schaefer MS: Association between intraoperative tidal volume and postoperative respiratory complications is dependent on respiratory elastance: A retrospective, multicentre cohort study. Br J Anaesth 2022; 129:263–72
12. Canet J, Gallart L, Gomar C, Paluzie G, Vallès J, Castillo J, Sabaté S, Mazo V, Briones Z, Sanchis J; ARISCAT Group: Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology 2010; 113:1338–50
13. de Jong MAC, Ladha KS, Vidal Melo MF, Staehr-Rye AK, Bittner EA, Kurth T, Eikermann M: Differential effects of intraoperative positive end-expiratory pressure (PEEP) on respiratory outcome in major abdominal surgery versus craniotomy. Ann Surg 2016; 264:362–9
14. Costa EL, Musch G, Winkler T, Schroeder T, Harris RS, Jones HA, Venegas JG, Vidal Melo MF: Mild endotoxemia during mechanical ventilation produces spatially heterogeneous pulmonary neutrophilic inflammation in sheep. Anesthesiology 2010; 112:658–69
15. Tucci MR, Costa EL, Wellman TJ, Musch G, Winkler T, Harris RS, Venegas JG, Amato MB, Melo MF: Regional lung derecruitment and inflammation during 16 hours of mechanical ventilation in supine healthy sheep. Anesthesiology 2013; 119:156–65
16. Szabari MV, Takahashi K, Feng Y, Locascio JJ, Chao W, Carter EA, Vidal Melo MF, Musch G: Relation between respiratory mechanics, inflammation, and survival in experimental mechanical ventilation. Am J Respir Cell Mol Biol 2019; 60:179–88
17. Motta-Ribeiro GC, Hashimoto S, Winkler T, Baron RM, Grogg K, Paula LFSC, Santos A, Zeng C, Hibbert K, Harris RS, Bajwa E, Melo MFV: Deterioration of regional lung strain and inflammation during early lung injury. Am J Respir Crit Care Med 2018; 198:891–902. 10.1164/rccm.201710-2038OC

Walk a Tightrope or Burn a Bridge?: Sedation *versus* General Anesthesia for Intubation of a Pediatric Difficult Airway

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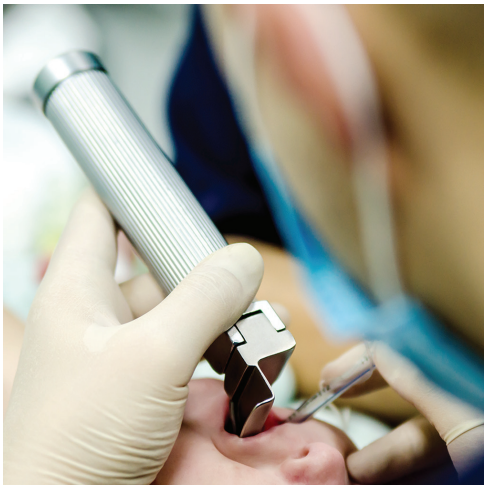
Children—and their airways—come in all shapes and sizes, and the most seasoned pediatric anesthesiologists can share harrowing stories of patients who were difficult to ventilate or intubate. In 2012, a special interest group in the Society for Pediatric Anesthesia created the Pediatric Difficult Intubation Registry, an international, multicenter, web-based registry of observational data on pediatric difficult airway management, with the goal of improving the care of these challenging patients. The Pediatric Difficult Intubation Collaborative has produced a panoply of clinically relevant findings, and their most recent research sought to answer how these patients fare when managed with sedation *versus* general anesthesia.[1–4] When confronted with a potentially or known difficult airway, most pediatric anesthesiologists induce general anesthesia, albeit with the goal of maintaining both adequate depth and spontaneous respiration.[1] In contrast, there are some who decry general anesthesia may "burn the bridge" of spontaneous ventilation and instead choose to walk the tightrope of sedation that is deep enough to diminish airway responses yet light enough to maintain spontaneous ventilation and reverse course if airway management is too treacherous.[5]



"[What are the] outcomes associated with sedation *versus* general anesthesia for tracheal intubation in children with difficult airways?"

In this issue of Anesthesiology, Sequera-Ramos *et al.*[6] drew on data from the Pediatric Difficult Intubation registry with the aim of comparing outcomes associated with sedation *versus* general anesthesia for tracheal intubation in children with difficult airways. Sequera-Ramos *et al.*[6] used propensity score matching to address selection bias and other confounders inherent in the analysis of retrospective observational, real-world clinical data. The primary study outcome was first-attempt success of tracheal intubation, which is a clinically important outcome because multiple attempts at intubation are associated with worse outcomes in pediatric airway management.[1,7] Sequera-Ramos *et al.*[6] observed similar rates of first-attempt success of tracheal intubation in the propensity score-matched sedation and general anesthesia groups (48.3 and 47.9%, respectively). Very few patients (4%, 75 of 1,839) underwent sedation rather than general anesthesia. Based on the similar rates of first intubation attempt success and complications in the two groups, the authors concluded their study did not support a preferred approach for tracheal intubation in children with difficult airways.

What can clinicians take from this study and its statement of equipoise? First, as the authors mention, clinicians should select an approach based on their skill and patient factors—keep calm and carry on. However, hold your horses! Nearly one-third of the 75 attempts in patients receiving sedation required conversion to general anesthesia for successful intubation. A failure rate of 30% in

Image: Adobe Stock.

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intubation attempts in the sedation group suggests that sedation may be inferior to general anesthesia, and this may be due to an inadequate depth of anesthesia. Indeed, the Pediatric Difficult Intubation Collaborative reported the use of neuromuscular blockade (presumably administered during a general anesthetic) was associated with improved success in some instances of difficult airway management.[4] Perhaps this failure rate reflected mild to moderate sedation that was inadequate for intubation, while deep sedation may have been the same as "light" general anesthesia. This is potentially a major limitation of this study, especially as there was no monitoring of the depth of either anesthesia or sedation.[8] It is possible that patients defined as receiving sedation received general anesthesia (and *vice versa*), resulting in crossover. A lack of data on administered medications and end-tidal volatile agent values precludes any conjecture on the subjects' depth of sedation. Second, as for many retrospective analyses of data sets, there may be known and, of course, unknown confounding. One plausible confounder was severity of any deformity. There was no measure of how difficult the airway was, *i.e.*, severe or mild retrognathia. A child with severe deformity may have been given sedation due to a clinician's fear of the patient obstructing under general anesthesia. The authors acknowledged both limitations, and these limitations certainly do not mean that the study is uninformative.

This study highlights limitations that are present in many retrospective analyses of data sets, particularly if the data set was created to answer a question that is a little different from the question being asked. The intervention or population of interest may not be as well defined as hoped, and important confounding factors may not have been collected.

How might a researcher address this challenge inherent to retrospective data analyses? One relatively novel approach to determining causal inference from large observational databases such as the Pediatric Difficult Intubation Registry is to perform the analysis in a way that emulates a randomized experiment. This is known as a target trial.[9] In a target trial, a researcher with a large observational data set "imagines" that they are performing a randomized controlled trial and defines the population, eligibility criteria, treatment strategies, outcomes, and timeframe as if it were a trial. An important aspect of the target trial is to aim for reducing all confounding, as if the treatment groups were randomized. A crucial step when trying to remove confounding is to ensure that all biologically plausibly principal factors are included in any adjustments. Ideally, a directed acyclic graph is created *a priori* and included in the publication.[10,11] It is good practice to generate the directed acyclic graph to include all key factors regardless of whether they are in the data set. This forces the researcher—and reader—to assess what factors could be missing and what their impact might be on any conclusions of causation.

A target trial of sedation *versus* general anesthesia based on Pediatric Difficult Intubation Registry data would need to provide details of the proposed interventions: sedation *versus* general anesthesia with standardized definitions and evidence of compliance. Similarly, if Sequera-Ramos *et al.*[6] had produced a directed acyclic graph before doing their analysis, then the degree of deformity (and other unmeasured but plausible confounding factors) may well have been elements in the directed acyclic graph, which would have forced them to consider the impact of not including them. Last, in a target trial, the conversion of 27.6% of sedation cases from sedation to general anesthesia would be accommodated in an intention-to-treat analysis, *i.e.,* if you start with the intention to use sedation, you may have to end up converting to a general anesthetic, but that is accommodated in the assessment of whether or not starting with sedation is equivalent to starting with a general anesthetic.

There are increasing amounts of clinical data available for analysis. Often the aim is to determine causal relationships, and most of these published analyses include phrases describing the limitations around confounding and missing data. They are inevitably, and appropriately, circumspect about what to conclude in terms of changing practice. In these retrospective studies, it is often tempting to dismiss any conclusion of causation, but this is likely an overly conservative approach. Target trials and directed acyclic graphs are methods to inch closer to understanding causation in these retrospective data sets, and hopefully readers will see a lot more of them.

For the reasons outlined above, the study by Sequera-Ramos *et al.*[6] does not provide definite evidence that sedation is equivalent to general anesthesia for managing difficult airways in children. Such evidence would require a prospective trial.[12] Organizers of pro–con debates on pediatric difficult airway management may seem to be the only group that will rejoice at this indeterminate conclusion. However, the study does provide some evidence that general anesthesia may not be a poor choice and may be a good rescue modality. Collaborative sharing and analysis of clinical data are the present and future of generalizable, clinically relevant, trusted evidence, and the Pediatric Difficult Intubation group is an excellent example of productive, meaningful collaboration.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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References

1. Fiadjoe JE, Nishisaki A, Jagannathan N, Hunyady AI, Greenberg RS, Reynolds PI, Matuszczak ME, Rehman

MA, Polaner DM, Szmuk P, Nadkarni VM, McGowan FX Jr, Litman RS, Kovatsis PG: Airway management complications in children with difficult tracheal intubation from the Pediatric Difficult Intubation (PeDI) registry: A prospective cohort analysis. Lancet Respir Med 2016; 4:37–48

2. Garcia-Marcinkiewicz AG, Kovatsis PG, Hunyady AI, Olomu PN, Zhang B, Sathyamoorthy M, Gonzalez A, Kanmanthreddy S, Gálvez JA, Franz AM, Peyton J, Park R, Kiss EE, Sommerfield D, Griffis H, Nishisaki A, von Ungern-Sternberg BS, Nadkarni VM, McGowan FX Jr, Fiadjoe JE; PeDI Collaborative Investigators: First-attempt success rate of video laryngoscopy in small infants (VISI): A multicentre, randomised controlled trial. Lancet 2020; 396:1905–13
3. Burjek NE, Nishisaki A, Fiadjoe JE, Adams HD, Peeples KN, Raman VT, Olomu PN, Kovatsis PG, Jagannathan N, Hunyady A, Bosenberg A, Tham S, Low D, Hopkins P, Glover C, Olutoye O, Szmuk P, McCloskey J, Dalesio N, Koka R, Greenberg R, Watkins S, Patel V, Reynolds P, Matuszczak M, Jain R, Khalil S, Polaner D, Zieg J, Szolnoki J, Sathyamoorthy K, Taicher B, Riveros Perez NR, Bhattacharya S, Bhalla T, Stricker P, Lockman J, Galvez J, Rehman M, Von Ungern-Sternberg B, Sommerfield D, Soneru C, Chiao F, Richtsfeld M, Belani K, Sarmiento L, Mireles S, Bilen Rosas G, Park R, Peyton J; PeDI Collaborative Investigators: Videolaryngoscopy *versus* fiber-optic intubation through a supraglottic airway in children with a difficult airway: An analysis from the multicenter Pediatric Difficult Intubation Registry. Anesthesiology 2017; 127:432–40
4. Garcia-Marcinkiewicz AG, Adams HD, Gurnaney H, Patel V, Jagannathan N, Burjek N, Mensinger JL, Zhang B, Peeples KN, Kovatsis PG, Fiadjoe JE; PeDI Collaborative: A retrospective analysis of neuromuscular blocking drug use and ventilation technique on complications in the Pediatric Difficult Intubation Registry using propensity score matching. Anesth Analg 2020; 131:469–79
5. Xue FS, Liao X, Xu YC, Yang QY: Sedation and anesthesia for fiberoptic intubation in management of pediatric difficult airways. Paediatr Anaesth 2008; 18:1239–41
6. Sequera-Ramos L, Laverriere EK, Garcia-Marcinkiewicz AG, Zhang B, Kovatsis PG, Fiadjoe JE; PeDI Collaborative: Sedation *versus* general anesthesia for tracheal intubation in children with difficult airways: A cohort study from the Pediatric Difficult Intubation Registry. Anesthesiology 2022; 137:418–433
7. Garcia-Marcinkiewicz AG, Matava CT: Safe in the first attempt: Teaching neonatal airway management. Curr Opin Anaesthesiol 2022; 35:329–36
8. American Society of Anesthesiologists: Continuum of depth of sedation: Definition of general anesthesia and levels of sedation/analgesia. Available at: https://www.asahq.org/standards-and-guidelines/continuum-of-depth-of-sedation-definition-of-general-anesthesia-and-levels-of-sedationanalgesia. Accessed July 27, 2022
9. Hernán MA, Robins JM: Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol 2016; 183:758–64
10. Gaskell AL, Sleigh JW: An introduction to causal diagrams for anesthesiology research. Anesthesiology 2020; 132:951–67
11. Sauer B, VanderWeele TJ: Use of directed acyclic graphs, Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide. Edited by Velentgas P, Dreyer NA, Nourjah P, Smith SR, Torchia MM. Rockville, MD, Agency for Healthcare Research and Quality, 2013; Suppl2:1–12
12. Hansen TG, Henneberg SW, Morton NS, Christensen K, Davidson AJ, Lee KJ, Hardy P, Wolf A: Pro–con debate: Cohort studies *vs.* the randomized clinical trial methodology in pediatric anesthesia. Paediatr Anaesth 2010; 20:880–94

Journal-related Activities and Other Special Activities at the 2022 American Society of Anesthesiologists Meeting

Michael J. Avram, Ph.D., Deborah J. Culley, M.D., Andrew Davidson, M.B.B.S., M.D., Evan D. Kharasch, M.D., Ph.D., Sachin Kheterpal, M.D., M.B.A., Martin J. London, M.D., Marcos F. Vidal Melo, M.D., Ph.D.

As in previous years, ANESTHESIOLOGY will sponsor several sessions at the annual meeting of the American Society of Anesthesiologists (ASA; Schaumburg, Illinois), Anesthesiology 2022. The meeting is being held in New Orleans, Louisiana. Details about the format and meeting attendance can be found on the website, asahq.org/annualmeeting.

Big Data Studies: How to Design, Conduct and Read Them

Saturday October 22, 2022, 1:15 PM to 3:15 PM
Room 243

Moderator

Sachin Kheterpal, M.D., M.B.A., Editor, ANESTHESIOLOGY, University of Michigan, Ann Arbor, Michigan.

Speakers

"Progress and Missteps in Perioperative Medicine Big Data Research" by Sachin Kheterpal, M.D., M.B.A., University of Michigan, Ann Arbor, Michigan.
"Choosing Wisely in Big Data Analysis: Risk Adjustment, Prediction, or Causation" by Elizabeth L. Whitlock, M.D., M.A., M.Sc., University of California, San Francisco, California.
"High-Stakes Epidemiology: Using Big Data to Estimate Causal Effects" by Brian T. Bateman, M.D., Stanford University School of Medicine, Stanford, California.
"Exciting Developments in Big Data Analysis Methods" by Timothy T. Houle, Ph.D., Massachusetts General Hospital, Boston, Massachusetts.

Description

Research, quality improvement, clinical guideline, and policy-making efforts based upon "big data" are increasingly common in perioperative medicine. All anesthesiologists must be facile in understanding and communicating the strengths and weaknesses of these databases and projects. This session will arm every anesthesiologist with the skills necessary to consume or create the in vogue and ubiquitous "big data" study with a discerning eye.

Initial Results: Major Clinical Trials

Saturday, October 22, 2022, 3:30 PM to 4:30 PM
Room 243

Moderators

Evan D. Kharasch, M.D., Ph.D., Editor-in-Chief, ANESTHESIOLOGY, Duke University Medical Center, Durham, North Carolina; Deborah J. Culley, M.D., Executive Editor, ANESTHESIOLOGY, University of Pennsylvania, Perelman School of Medicine, Philadelphia, Pennsylvania.

Description

ANESTHESIOLOGY is sponsoring its seventh Major Clinical Trials Session, a high-profile, large-audience forum for initial presentations of major randomized clinical trial results. It is designed for substantial trials, usually randomized and blinded, with a clinically important primary outcome.

31st Journal Symposium: Delirium

Sunday, October 23, 2022, 8:30 AM to 11:30 AM
Room 243

Moderators

Deborah J. Culley, M.D., Executive Editor, ANESTHESIOLOGY, University of Pennsylvania, Perelman School of Medicine, Philadelphia, Pennsylvania; Andrew Davidson, M.B.B.S.,

Michael J. Avram, Ph.D.: Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Deborah J. Culley, M.D.: University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania.

Andrew Davidson, M.B.B.S., M.D.: Royal Children's Hospital, Melbourne, Australia.

Evan D. Kharasch, M.D., Ph.D.: Duke University Medical Center, Durham, North Carolina.

Sachin Kheterpal, M.D., M.B.A.: University of Michigan, Ann Arbor, Michigan.

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M.D., Executive Editor, Anesthesiology, Royal Children's Hospital, Melbourne, Australia.

Description

Postoperative delirium affects a substantial portion of surgical patients and is associated with both short- and long-term complications and morbidity. The science behind delirium is rapidly evolving with better diagnostic tools, a greater understanding of the neurobiology, and greater understanding of the possible etiology. The symposium will feature both plenary lectures by experts in the field and presentations of eight featured top abstracts selected for their relevance to the mechanism and biology of postoperative delirium in both pediatric and geriatric patients. The full text for each abstract can be found at the ASA abstract website.

Speakers

"Removing the Confusion about Delirium" by Jamie W. Sleigh, M.D.
The University of Auckland, Hamilton, New Zealand.
"Pediatric Delirium: Do We Know What We Think We Know" by Andrew Davidson, M.B.B.S., M.D.
Royal Children's Hospital, Melbourne, Australia.

JS01

"Postoperative Changes in the Cerebrospinal Fluid Proteome Suggest a Role of the Complement Pathway in Postoperative Delirium" by Jake Thomas, B.S., Matt Foster, Ph.D., Joseph Lucas, Ph.D., Mary Wright, M.S., Joseph Mathew, M.D., M.B.A., Miles Berger, M.D., Ph.D., Michael Devinney, M.D., Ph.D.
Duke University School of Medicine, Durham, North Carolina (J.T.); Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina (M.F., M.W., J.M., M.B., M.D.); Vital Statistics, L.L.C., Chapel Hill, North Carolina (J.L.)

JS02

"Emergence Delirium and Behavior at 3 Months after General Anesthesia in Preschool Children" by Amira Joseph, M.D., David O. Warner, M.D., Yu Shi, M.D.
Mayo Clinic College of Medicine, Rochester, Minnesota

JS03

"Demographic Characteristics as Predictors of Clinical Outcomes in Very Elderly Adults" by Guillermo Madrid, M.D., M.Sc., Laura Cristina Moyano, M.D., Jairo Ricardo Moyano, M.D., Ph.D., Maria Jose Pelaez Jaramillo, M.D.
Anesthesiology, Fundacion Santa Fe de Bogota, Bogota, Colombia

JS04

"A Proteomic-derived Predictive Model for Postoperative Delirium in Cardiac Surgical Patients" by Tanvi Khera, M.D., Maria Carolina-Bittercourt Gonçalves, Ph.D., Shilpa Narayanan, B.A., Simon T. Dillon, Ph.D., Yoojin Jung, Ph.D., Hasan H. Otu, Ph.D., Long H. Ngo, Ph.D., Edward R. Marcantonio, M.D., Towia A. Libermann, Ph.D., Balachundhar Subramaniam, M.D.
Anesthesia Critical Care and Pain Medicine, and Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts (T.K., M.C-B.G., S.N., S.T.D., Y.J., L.H.N., E.R.M., T.A.L., B.S.); Electrical and Computer Engineering, University of Nebraska–Lincoln, Lincoln, Nebraska (H.H.O.)

JS05

"Anesthesia/Surgery Induces Delirium-like Behavior in Aged Mice Via Cells–Mediated Increase of TAU-PT217 in Blood" by Jing Lu, M.D., Ph.D., Feng Liang, Ph.D., Ping Bai, Ph.D., Zhengwang Sun, Ph.D., Wenjie Tian, M.D., Ph.D., Changning Wang, Ph.D., Edward R. Marcantonio, M.D., M.S., Guang Yang, Ph.D., Zhongcong Xie, M.D., Ph.D.
Anesthesiology, Critical Care and Pain Medicine, Cardiology, and Radiology, Massachusetts General Hospital, Boston, Massachusetts (J.L., F.L., Z.S., W.T., C.W.); Medicine, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, Massachusetts (E.R.M.); Columbia University, New York, New York (G.Y.); Massachusetts General Hospital–Harvard Medical School, Boston, Massachusetts (P.B., Z.X.)

JS06

"Postoperative Delirium and Altered Connectivity within the Default Mode Network and Hippocampus" by Heather Acuff, M.D., Ph.D., Laurel Zelnik, B.S., Joshua Siegel, M.D., Ph.D., Jacob Bolzenius, Ph.D., Mehdi Kafashan, Ph.D., Thomas Nguyen, B.S., Anhthi Luong, B.S., Michael S. Avidan, M.B., B.Ch., Tammie Benzinger, M.D., Ph.D., Ben Julian Palanca, M.D., Ph.D.
Anesthesiology, and Washington University School of Medicine, Washington University in St. Louis, St. Louis, Missouri (H.A., L.Z., J.B., M.K., T.N., A.L., M.S.A., T.B., B.J.P.); PeaceHealth Medical Group Anesthesiology, Longview, Washington (J.S.)

JS07

"Association of Malnutrition and Frailty with Postoperative Delirium in Older Patients after Hip Fracture Surgery" by Benayas Dereje Begashaw, B.Sc., Esteban Franco-Garcia, M.D., Marilyn Heng, M.D., M.P.H., Oluwaseun Johnson-Akeju, M.D., M.Sc., John A. Reich, M.D., Sadeq A. Quraishi, M.D.

Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts (B.D.B., J.A.R., S.A.Q.); Department of Medicine, Department of Orthopaedic Surgery, and Department of Anesthesiology, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts (E.F-G., M.H., O.J-A.)

JS08

"Postoperative Delirium and Blood Brain Barrier Breakdown in Older Noncardiac Surgical Patients" by Megan Wong, B.S., Mary Cooter Wright, M.S., Pallavi Avasarala, Ayesha Syed, B.A., Edward R. Marcantonio, M.D., Niccolo Terrando, Ph.D., Joseph P. Mathew, M.D., M.B.A., Miles Berger, M.D., Ph.D., Michael Devinney, M.D.

Duke University School of Medicine, Durham, North Carolina (M.W.); Duke University Medical Center, Durham, North Carolina (M.C.W., P.A., A.S., N.T., J.P.M., M.B., M.D.); Beth Israel Deaconess Medical Center, Boston, Massachusetts (E.R.M.)

Best Abstracts: Clinical Science and Basic Science

Anesthesiology is sponsoring two Best Abstract sessions: one in basic science and another in clinical science. The abstracts were chosen by a panel of editors who examined the highest scoring abstracts from the ASA subcommittees, choosing those with important scientific and clinical application and novelty. The following are summaries of the excellent abstracts that will be presented.

Best Abstracts: Basic Science

Sunday, October 23, 2022, 1:00 PM to 2:55 PM
Room 243

Moderators

Michael J. Avram, Ph.D., Assistant Editor-in-Chief, Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois; Deborah J. Culley, M.D., Executive Editor, Anesthesiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; Martin J. London, M.D., Editor, Anesthesiology, University of California, San Francisco School of Medicine and the Veterans Affairs Medical Center, San Francisco, California.

6935

"Discovery of a Quinone Analog as a Novel Anesthetic Agent" by Richard Levy, M.D., Abhishek Srivastava, B.S., Keren Griffiths, M.D., Ph.D., Yash Somnay, M.D., Ph.D.

Columbia University, New York, New York

Propofol interferes with electron transfer at the level of coenzyme Q and induces excessive proton leak within mitochondria. Synthetic coenzyme Q analogs have similar biologic activity *in vitro*. The hypothesis that quinone analogs would induce propofol-like sedation and hypnosis was tested in mice using the short-chain coenzyme Q analog ubiquinone-5. Ubiquinone-5 immediately induced loss of righting reflex with an ED50 of 81 mg/kg, and latency to return of righting reflex was correlated with dose. Ubiquinone-5 induced excessive proton leak in isolated forebrain mitochondria, inhibited electron transport chain enzyme complex activities, and compromised mitochondrial membrane potential.

6834

"A Genetically Engineered Mouse that Improves TRPV1-mediated Insulin Release and Glucose Handling Is Protected from Cardiac Injury" by Eric Gross, M.D., Ph.D., Yang Bian, Ph.D., Shufang He, Ph.D.

Anesthesiology, Perioperative and Pain Medicine, Stanford University, Stanford, California (E.G., Y.B.); Anesthesiology, Perioperative and Pain Medicine, Stanford University, Stanford, California, and Second Hospital of Anhui Medical University, Hefei City, Anhui Province, China (S.H.)

Transient receptor potential vanilloid 1 (TRPV1) regulates myocardial reperfusion injury, but the region of TRPV1 important for limiting organ injury is unclear. Because TRPV1 activation antagonizes insulin release from pancreatic β cells, mice with a missense mutation in TRPV1 (K710N) were studied to determine whether a specific amino acid within the C terminus of TRPV1 causes resistance to cardiac injury by modifying insulin release and glucose handling. A discrete amino acid of TPRV1, K710, was found to regulate the response to a glucose challenge and insulin release, changes in which led to improved glycolytic handling and protection of cardiomyocytes from cellular stress.

7088

"β-Arrestin Recruitment Does Not Explain Respiratory Depression from Opioids of the Nitazene Family" by Barbara Palkovic, M.D., Daniel J. Sprague, M.D., Ph.D., John D. McCorvy, Ph.D., Maggie M. Calkins, B.S., Thomas M. Langer III, M.D., Ph.D., Jennifer J. Callison, B.S., Eckehard A. Stuth, M.D., Astrid G. Stucke, M.D.

Faculty of Medicine Osijek, Osijek, Croatia (B.P.); Cell Biology, Neurobiology and Anatomy, and Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin (D.J.S., J.D.M., M.M.C., T.M.L., J.J.C., E.A.S., A.G.S)

Opioid-induced respiratory depression has been attributed to recruitment of the β-arrestin scaffold rather than G protein activation, both of which result from binding of the agonist to the mu-opioid receptor. The hypothesis that respiratory depression strongly correlates with β-arrestin recruitment

was tested by studying *in vitro* and *in vivo* effects of opioids of the nitazene family that are biased toward either mechanism. Although activation of G protein *versus* β-arrestin pathway by nitazene mu-opioid receptor agonists varied with their molecular structure, the degree of β-arrestin recruitment did not correlate with the magnitude of respiratory depression.

6819

"Effects of Low *versus* High Positive End-expiratory Pressure on Mechanical Power and Pulmonary Neutrophilic Inflammation in Experimental Acute Respiratory Distress Syndrome" by Nikola Anusic, M.D., Martin Scharffenberg, M.D., Robert Huhle, M.D., Jakob Wittenstein, M.D., Marcelo Gama De Abreu, M.D.

Outcomes Research, Cleveland Clinic, Cleveland, Ohio (N.A.); Universitätsklinikum Carl Gustav Carus Dresden, Dresden, Germany (M.S., R.H., J.W.); Outcomes Research Department, Anesthesiology Institute, Cleveland Clinic Foundation, Cleveland, Ohio (M.G.D.A.)

Mechanical ventilation may cause ventilator-induced lung injury. Mechanical power, which describes the energy transferred to the respiratory system per unit time, has been associated with surrogates of ventilator-induced lung injury. The hypothesis that protective mechanical ventilation strategies using different levels of positive end-expiratory pressure differ in their mechanical power and pulmonary neutrophilic inflammation was tested in a randomized study of 24 anesthetized pigs in which lung injury had been induced by saline lavage. Protective mechanical ventilation with low compared to high positive end-expiratory pressure increased mechanical power and worsened lung inflammation.

6589

"Altered Astrocytic Bioenergetics and Delayed Emergence from Propofol in a Rodent Model of Alcohol Intolerance" by Candida Goodnough, M.D., Ph.D., Ryan Ozawa, B.S., Rafaela Rodrigues Hell, Ph.D., Katie Chang, Eric R. Gross, M.D., Ph.D.

Stanford University, Stanford, California

Alcohol intolerance is due to a genetic variant in the mitochondrial enzyme aldehyde dehydrogenase 2 (ALDH2*2), which limits the metabolism of acetaldehyde, a metabolite of ethanol. The hypothesis that the inactivating genetic variant ALDH2*2 will delay recovery from anesthesia due to an altered mitochondrial redox state was tested in wild-type ALDH2 and ALDH2*2 knock-in mice. There was no difference between groups in time to loss of righting reflex or duration of propofol-induced general anesthesia, but ALDH2*2 mice had delayed recovery from anesthesia as defined by behavioral tests. Bioenergetics were altered in mitochondria of ALDH2*2 astrocytes at baseline and in the presence of propofol.

7059

"Mitigation of Burn-induced Motor Neuron Apoptosis, Synaptic Denervation, and Muscle Wasting by Decreasing Spinal Microglia Inflammatory Responses" by Jingyuan Chen, M.D., Ph.D., Yoshinori Kitagawa, M.D., Ph.D., Yang Ren, M.D., Shingo Yasuhara, M.D., Ph.D., J.A. Jeevendra Martyn, M.D., F.R.C.A.

Department of Anesthesiology, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China (J.C.); Tottori University Hospital, Yonago, Japan (Y.K.); Shriners Hospital for Children and Harvard Medical School, Boston, Massachusetts (Y.R., S.Y., J.A.J.M.)

The hypothesis that microglia-mediated cytokine release plays a pivotal role in motor neuron loss, distant synaptic disintegration, and muscle wasting after burn injury and that mitigation of microglia activation by α7AChR stimulation would attenuate these was tested in wild-type and α7AChR knock-out mice randomly divided into sham-burn or third degree 30% total body surface area burn injury groups. The selective α7AChR agonist GTS-21 or saline was administered after burn injury. GTS-21 ameliorated burn injury–induced microglia activation, as evidenced by decreased inflammatory cytokine release, and alleviated motor neuron loss, synaptic disintegration, and muscle wasting in wild-type but not knock-out mice.

6762

"**Dysfunction of the Endogenous Opioid System in Descending Pain-modulating Circuits Is Involved in the Augmented Pain Response after Traumatic Brain Injury" by Qiliang Chen, M.D., Ph.D., David J. Clark, M.D., Ph.D.**

Department of Anesthesiology, Perioperative and Pain Medicine, Stanford–Anesthesia School of Medicine, Stanford, California (Q.C.); Stanford–Anesthesia School of Medicine, Palo Alto, California (D.J.C.)

The hypothesis that traumatic brain injury exacerbates pain in response to a subsequent soft tissue injury by virtue of dysfunctional descending pain modulation was tested in a mouse model of mild traumatic brain injury. Animals with traumatic brain injury experienced a prolonged period of allodynia after a distal periphery injury. Their eventual recovery from allodynia was dependent on endogenous opioid tone on the pronociceptive neurons in the descending pain-modulation system. Loss of these pronociceptive neurons prevented the development of allodynia after traumatic brain injury.

6462

"Electroacupuncture Relieves Incision Pain by Regulating Inflammation and Immune System in Rats" by Lulin Ma, M.D., Ph.D., Daling Deng, M.D., Tianhao Zhang, M.D., Yuanyuan Ding, M.D., Wenjing Zhao, M.D., Xiangdong Chen, Ph.D.

Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Transcriptomic (messenger RNA [mRNA]) methods were used to detect the gene changes of dorsal root ganglia of male Sprague-Dawley rats randomly assigned to control, incision, and incision plus electroacupuncture groups. Pain behaviors were measured in the three groups the day before and 2, 4, and 24 h after surgery. Dorsal root ganglia were collected for mRNA sequencing 24 h after surgery. In the incision plus electroacupuncture group, the mechanical withdrawal threshold and thermal withdrawal latency increased, the cumulative pain score decreased, and there were 4 upregulated genes and 12 downregulated genes identified compared to the incision group.

6486

"The Biphasic Effects of Sevoflurane of Different Concentration on Airway Inflammation in Developing Asthmatic Rats" by Guangting Zhang, M.S., Fenglin Wang, M.S., Yin Ran, M.S., Yannan Zhou, M.S., Xiaoxi Zhang, M.S., Dexing Liu, M.D.

Anesthesiology Department, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China

The effects of different concentrations of sevoflurane on airway inflammation were studied in a developing female Sprague-Dawley rat ovalbumin-induced allergic asthma model. Sevoflurane concentrations of 0.4%, 0.8%, 1.6%, or 3.2% were inhaled for 30 min. Sevoflurane had opposite, concentration-dependent effects on airway inflammation. At 0.4%, sevoflurane aggravated alveolar septal thickening and inflammatory infiltration and upregulated IL-4 and IgE but downregulated IFN-γ concentrations. In contrast, 3.2% sevoflurane alleviated alveolar septal thickening and inflammatory infiltration, and downregulated IL-4 and IgE but upregulated IFN-γ concentrations.

7012

"Volatile Anesthetic Loading of the Sonoparticles: A Preparation for Future Clinical Applications" by Siavash Sedghi, M.D., Amir Teimouri Dereshgi, M.D., Eric Young, B.S., Bruce A. Davidson, Ph.D., Hilliard Kutscher, Ph.D., Paul R. Knight, M.D., Ph.D., Nader D. Nader, M.D., Ph.D.

Anesthesiology, Jacobs School of Medicine and Biomedical Sciences, Buffalo, New York

Although use of volatile anesthetics for ischemic preconditioning is well established, airway compromise is a major drawback when they are given at high enough concentrations to have systemic effects. The objective of these *in vitro* experiments was to load sevoflurane in Food and Drug Administration–approved (for use as a contrast material during ultrasonic examination) lipid microsphere sonoparticles as a vehicle and evaluate its release in response to externally delivered sound shock waves compared to its release from intralipid 20% and from 0.9% normal saline. The sonoparticle preparation released sevoflurane most rapidly and at the highest concentration (3.5%) during the 30-min sonication period.

7036

"Intergenerational Effects of Surgery and Sevoflurane Anesthesia in Young Adult Rats with Traumatic Brain Injury" by Anatoly Martynyuk, D.Phil., Lingsha Ju, M.D., Jiepei Zhu, D.Phil., Nikolaus Gravenstein, M.D., Christoph N. Seubert, M.D., Terrie Vasilopoulos, D.Phil.

Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida

The effects of general anesthesia/surgery, traumatic brain injury, and subsequent repeated exposure to sevoflurane on neurobehavioral and neuroendocrine abnormalities in exposed young adult males (F0 generation) and their future offspring (generation F1) was tested in male Sprague-Dawley rats. Surgery, traumatic brain injury, and subsequent exposure to sevoflurane in young adult male rats led to proinflammatory, neuroendocrine, and neurobehavioral abnormalities in the exposed rats and in their future, primarily male, offspring.

6677

"MicroRNAs Involved in Dexmedetomidine Preconditioning-induced Neuroprotection" by Hyunyoung Seong, M.D., Daun Jeong, M.Sc., Jang Eun Cho, M.D., Ph.D.

Anesthesiology and Pain Medicine, Anam Hospital, Korea University College of Medicine, Seoul, Korea (H.S., J.E.C.); Institute for Healthcare Service Innovation, Korea University, Seoul, Korea (D.J.)

Dexmedetomidine has been reported to protect the brain from cerebral ischemia. MicroRNAs play important roles in ischemic tolerance induced by preconditioning. The association of microRNAs with the preconditioning effects of dexmedetomidine in neural ischemia was studied in mice administered dexmedetomidine before transient infarcts were induced by middle cerebral artery occlusion for 1 h. The infarct volume was reduced, expression of five microRNAs was increased, and expression of three microRNAs was decreased in mice preconditioned with dexmedetomidine. *In vitro*, microRNA-323 inhibition reduced cell apoptosis in an oxygen-glucose–deprived environment and had a neuroprotective effect.

Best Abstracts: Clinical Science

Sunday, October 23, 2022, 3:05 PM to 5:00 PM
Room 243

Moderators

Michael J. Avram, Ph.D., Assistant Editor-in-Chief, Anesthesiology, Northwestern University Feinberg

School of Medicine, Chicago, Illinois; Deborah J. Culley, M.D., Executive Editor, Anesthesiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; Martin J. London, M.D., Editor, Anesthesiology, University of California, San Francisco School of Medicine and the Veterans Affairs Medical Center, San Francisco, California.

7146

"Artificial Intelligence-based Phenotyping of Thoracic Surgery to Anticipate Clinical Trajectory" by Pascal Laferriere-Langlois, M.D., Fergus Imrie, Ph.D., Maxime Cannesson, M.D.

Anesthesiology, and Department of Electrical and Computer Engineering, University of California in Los Angeles, Los Angeles, California

Classifying a patient's risk is important for clinical treatment, decision sharing, optimal resource distribution, and billing. Records of 1,933 surgical procedures performed by the thoracic surgery department since 2013 were extracted from the electronic medical record, 105 readily extractable features were extracted from each, and artificial intelligence, with clustering, was applied to identify phenotypes among these patients. Three phenotypes with distinct care trajectories and outcomes were identified among the records extracted. Patients with phenotype 3 (N = 424) experienced 66.7% of the deaths, 67.3% of prolonged intensive care unit stays, and 73.0% of prolonged hospital stays.

6467

"Preoperative Ultrasound-guided Percutaneous Cryoneurolysis for Treating Pain Following Mastectomy" by Adam Schaar, M.D., Brian M. Ilfeld, M.D., John J. Finneran IV, M.D., Matthew W. Swisher, M.D., Engy Tadros Said, M.D., Rodney A. Gabriel, M.D., Jacklynn F. Sztain, M.D., Bahareh Khatibi, M.D., Andrea Trescot, M.D., Anne M. Wallace, M.D.

Department of Anesthesiology, and Department of Surgery, University of California San Diego, San Diego, California (A.S., B.M.I., J.J.F., M.W.S., E.T.S., R.A.G., J.F.S, B.K., A.M.W.); Florida Pain Relief Group, Tampa, Florida (A.T.)

This randomized, observer- and participant-masked, sham-controlled pilot study evaluated preoperative ultrasound-guided percutaneous cryoneurolysis for the treatment of pain after mastectomy. On postoperative day 2, participants who had received active cryoneurolysis (n = 31) had a median [interquartile range] pain score, measured on a 0 to 10 numerical rating scale, of 0 [0 to 1.4] *versus* 3.0 [2.0 to 5.0] in patients given sham (n = 29). Cryoneurolysis decreased cumulative opioid use during the first 3 weeks by 98%. Chronic pain had developed after 1 yr in one (3%) active and five (17%) sham participants.

6433

"Perioperative Mortality of the COVID-19 Patient" by Michael Aziz, M.D., Katie J. Schenning, M.D., M.P.H., Vikas N. O'Reilly-Shah, M.D., Michael R. Mathis, M.D. Anesthesiology & Perioperative Medicine, Oregon Health & Science University, Portland, Oregon (M.A., K.J.S.); University of Washington, Seattle, Washington (V.N.O-S.); University of Michigan, Ann Arbor, Michigan (M.R.M.)

The 30-day mortality of 3,721 elective surgical patients who had recovered from previous COVID-19 infection was compared to that of a propensity-matched cohort of 3,721 elective surgical patients without previous COVID-19 infection in a multicenter retrospective observational study of cases performed between April 2020 and April 2021. Among COVID-19–exposed patients, 160 (4.3%) expired within 30 days of surgery, whereas 63 (1.7%) of the propensity-matched control patients expired within 30 days of surgery.

6517

"Automated End-tidal Control Device Achieves and Maintains Concentration of Exhaled Agent and Oxygen Effectively" by Guy Dear, F.R.C.A., Matthew A. Klopman, M.D., Melissa D. McCabe, M.D., Melinda S. Seering, M.D.

Anesthesiology, Duke University, Durham, North Carolina (G.D.); Emory University, Sandy Springs, Georgia (M.A.K.); Loma Linda University Medical Center, Loma Linda, California (M.D.M.); Anesthesia, University of Iowa, Iowa City, Iowa (M.S.S.)

Automated gas control alters fresh gas flow and controls end-tidal anesthetic and oxygen concentrations using an end-tidal control device. A multicenter randomized controlled trial compared end-tidal control with standard anesthesia practice in 220 patients. End-tidal control achieved the desired end-tidal anesthetic and oxygen concentrations quickly and maintained the end-tidal concentration within a closer tolerance with minimal overshoot than standard anesthesia practice. End-tidal control reduced mean inhaled agent usage by 26% for desflurane, 30% for isoflurane, and 5% for sevoflurane.

6642

"Persistent Brain Connectivity Changes in Healthy Volunteers following Nitrous Oxide Inhalation" by Ben Palanca, M.D., Ph.D., Thomas A. Zeffiro, Ph.D., Britt M. Gott, M.S., Thomas Nguyen, B.S., Charles F. Zorumski, M.D., Charles R. Conway, M.D., Peter Nagele, M.D., M.S. Anesthesiology, and Psychiatry, Washington University School of Medicine in St. Louis, St. Louis, Missouri (B.P., B.M.G., T.N., C.F.Z., C.R.C.); Diagnostic Radiology and Nuclear Medicine, University of

Maryland School of Medicine, Baltimore, Maryland (T.A.Z.); University of Chicago Medicine, Chicago, Illinois (P.N.)

Nitrous oxide alleviates treatment-resistant depression. The effects of nitrous oxide on brain connectivity after inhalation were determined in a single-blinded crossover study of 16 healthy volunteers who underwent inhalation sessions of a 50% nitrous oxide/oxygen mixture for 1 h or an oxygen/air mixture for 1 h, in a randomized order. Functional magnetic resonance imaging identified increases in global connectivity to primary visual regions at 2 and 24 h after nitrous oxide inhalation that are consistent with reported changes in visual perception of the external world.

6276

"A Liberal Transfusion Strategy Leads to Higher Infection Rates, Orthopaedic Trauma and Anemia: Conservative *versus* Liberal Transfusion Strategy (ORACL), A Prospective Randomized Study 30 Day Inpatient Complications" by Leilani Mullis, M.D., Brian Mullis, M.D., Walt Virkus, M.D., Laurence Kempton, M.D.

Indiana University School of Medicine, Indianapolis, Indiana

There is ongoing debate about what level of anemia should be used as a transfusion trigger for asymptomatic trauma patients no longer in a resuscitative phase. To determine if a more conservative strategy is safe and decreases the risk of infection, 99 asymptomatic young orthopedic trauma patients no longer being resuscitated were randomly assigned to a conservative transfusion strategy of 5.5 g/dl or a liberal strategy of 7.0 g/dl in this multicenter pilot study. A conservative transfusion strategy of 5.5 g/dl led to a lower deep infection rate without an increase in adverse outcomes.

6461

"Signaling Cascades of Circulating Glycosaminoglycans Reflect Pulmonary Injury in COVID-19" by Melanie Borrmann, M.D., Florian Brandes, M.D., Benedikt Kirchner, M.Sc., Matthias Klein, M.D., Marlene Reithmair, M.Sc., Michael Pfaffl, M.Sc., Gustav Schelling, M.D., Markus Rehm, M.D., Agnes Meidert, M.D.

Department of Anesthesiology, Ludwig Maximilian University of Munich, Munich, Germany (M.B., F.B., M.R., A.M.); Division of Animal Physiology and Immunology, Technical University of Munich, Weihenstephan, Germany (B.K., M.P.); Department of Neurology, Ludwig Maximilian University of Munich, Munich, Germany (M.K.); Institute of Human Genetics, Munich, Germany (M.R.); Ludwig Maximilian University of Munich, Munich, Germany (G.S.)

The circulating glycosaminoglycans hyaluronan and heparan sulfate were measured in 20 patients with COVID-19 pneumonia, 20 patients with COVID-19 acute respiratory distress syndrome (ARDS), and 20 healthy controls, and molecular signaling networks targeted by these glycocalyx components were identified. Plasma hyaluronan and heparan sulfate concentrations increased with disease severity and were higher in COVID-19 ARDS than in COVID-19 pneumonia and in healthy volunteers. Plasma hyaluronan concentrations were also higher in pneumonia than in healthy controls. Hyaluronan, heparan sulfate, and their upregulated degradative enzymes HYAL1 and HPSE activated cytokine signaling in immune cells and aggravated vascular barrier dysfunction in COVID-19 ARDS.

7277

"2019 Multicenter Hypotension Prediction Index Clinical Study" by Xiaodong Bao, M.D., Ph.D., Kamal Maheshwari, M.D., Donald H. Penning, M.D., Sydney E. Rose, M.D., Gaurav Malhotra, M.D., David R. Drover, M.D., Nirav J. Shah, M.D., Karen B. Domino, M.D., Claudia F. Clavijo, M.D.

Massachusetts General Hospital, Boston, Massachusetts (X.B.); Cleveland Clinic, Solon, Ohio (K.M.); Henry Ford Hospital–Residents, Detroit, Michigan (D.H.P.); Oregon Health and Science University, Portland, Oregon (S.E.R.); University of Pennsylvania Medical–Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania (G.M.); Stanford–Anesthesia School of Medicine, Stanford, California (D.R.D.); University of Michigan Medical School, Ann Arbor, Michigan (N.J.S.); Anesthesiology Department–Active, University of Washington, Seattle, Washington (K.B.D.); University of Colorado, Aurora, Colorado (C.F.C.)

The Hypotension Prediction Index software (Edwards Lifesciences, USA) provides insight into the likelihood of a patient experiencing a future hypotensive event, defined as mean arterial pressure less than 65 mmHg for at least 1 min. In a propensity matching model, 445 (3%) cases received advanced hemodynamic monitoring with the software, and 15,639 (97%) control cases did not. The patients underwent a surgical procedure for a median (IQR) duration of 291 (227 to 394) min. Patients treated using advanced hemodynamic monitoring guidance experienced hypotension for 9 (2 to 20) min, while the historical control group experienced it for 15 (5 to 39) min.

6919

"Effects of Pectoralis and Serratus Blocks for Minimally Invasive Cardiac Procedures on Opioid Consumption and Pulmonary Mechanics" by Omer Bakal, M.D., Donn Marciniak, M.D., Esra Kutlu Yalcin, M.D., Xuan Pu, M.S., Hassan Hamadnalla, M.D., Hani A. Essber, M.D., Tyler Karras, D.O., Stephanie Ezeoke, M.S., Alparslan Turan, M.D., Andrej Alfirevic, M.D.

Department of Outcomes Research, Department of Cardiothoracic Anesthesiology, and Department of Quantitative Health Services, Cleveland Clinic, Cleveland, Ohio (O.B., D.M., E.K.Y., X.P., H.A.E., T.K., S.E., A.T., A.A.); Henry Ford Health System, Detroit, Michigan (H.H.)
The hypothesis that use of ultrasound guided pectoral fascial plane and serratus anterior plane blocks using a mixture of bupivacaine and liposomal bupivacaine would decrease postoperative opioid consumption and improve respiratory function during the first 3 postoperative days was tested in a randomized controlled trial of 194 patients undergoing minimally invasive cardiac surgery for mitral valve repair or replacement. There was no difference in the cumulative opioid consumption and pulmonary mechanics during the first 3 postoperative days between patients who received blocks and those who had standard parenteral analgesia intraoperatively.

6630

"A Randomized, Double-blind Trial Comparing Oliceridine and Morphine on Ventilation in an Elderly Population" by P. Simons, M.D., Albert Dahan, M.D., Ph.D., Mark Demitrack, M.D., Michael Fossler, Pharm.D, Ph.D., Erik Olofsen, Ph.D., Maarten van Lemmen, B.Sc., Simone Jansen, M.D., Rutger van der Schrier, M.D.

Department of Anesthesiology, Leiden University Medical Center, Leiden, Netherlands (P.S., A.D., E.O., M.vL., S.J., R.vdS.); Trevena, Chesterbrook, Pennsylvania (M.D., M.F.)
Oliceridine differs from classical opioids in that it is biased toward activation of the G-protein intracellular pathway that is predominantly associated with analgesia, with limited recruitment of the β-arrestin pathway that is associated with opioid-related adverse events. The hypothesis that IV oliceridine would produce less respiratory depression than IV morphine at equianalgesic doses was tested in a randomized crossover trial of 18 volunteers 55 yr and older. In contrast to 2 mg morphine, 0.5 mg oliceridine was nearly devoid of respiratory depressant effects. Similarly, in contrast to 8 mg morphine, the respiratory depressant effect of 2 mg oliceridine waned within 3 h.

7269

"Improvement of Forced Vital Capacity after Saline Washout in the Setting of Post Interscalene Catheter Phrenic Nerve Palsy" by Mariam Sarwary, M.D., Jean Louis E. Horn, M.D., Jan Boublik, M.D., Ph.D., Ban Tsui, M.D.

Stanford University, Fremont, California; Stanford University, Stanford, California
A randomized, double-blinded study of 21 patients undergoing elective primary total shoulder arthroplasty with an ultrasound-guided interscalene nerve block was conducted to determine whether a large volume normal saline washout bolus through the interscalene catheter can reverse phrenic nerve paralysis resulting from the block. Patients were administered 10 ml 0.5% ropivacaine before surgery and an additional 10 ml 0.5% ropivacaine upon arrival to the recovery room. Thirty minutes later, they received either a 30 ml normal saline washout or no intervention. Clinical improvement of forced vital capacity was observed 30 min after the saline washout.

6256

"EEG-guided Anesthesia in Children Shortens Recovery Time with No Difference Thus Far in Emergence Delirium" by Kiyoyuki Miyasaka, M.D., Yasuyuki Suzuki, M.D., Ph.D., Yasuko Nagasaka, M.D., Ph.D.

Department of Anesthesia, National Center for Child Heath and Development, Tokyo, Japan (K.M., Y.S.); Tokyo Women's Medical University, Tokyo, Japan (Y.N.)
The hypothesis that pediatric anesthesia emergence delirium may be reduced by an electroencephalogram (EEG)-guided anesthesia management strategy designed to minimize exposure to anesthetics was tested in randomized controlled trial comparing the incidence of pediatric anesthesia emergence delirium after sevoflurane anesthesia maintained at 1.0 minimum alveolar concentration and EEG-guided sevoflurane anesthesia. Sixty children at least 1 and less than 6 yr old scheduled for surgical procedures involving minimal postoperative pain were studied. There was no difference between the groups in the proportion of patients with a pediatric anesthesia emergence delirium score of 10 or more despite reduced exposure to sevoflurane in the EEG group. Recruitment is ongoing.

22nd Annual Celebration of Research

Monday, October 24, 2022, 9:30 AM to 11:30 AM
LaNouvelle Ballroom B

Moderator

Evan D. Kharasch, M.D., Ph.D., Editor-in-Chief, Anesthesiology, Duke University Medical Center, Durham, North Carolina.

Description

Sponsored by Anesthesiology, join us for the 22nd Annual Celebration of Research, when the recipients of the 2022 ASA Excellence in Research Award and the James E. Cottrell, M.D., Presidential Scholar Award will be awarded. Each recipient will present brief lectures on their research accomplishments. The Foundation for Anesthesia Education and Research (Schaumburg, Illinois) Excellence in Mentoring Award recipient and the winner of the Resident Research Essay contest will be announced. There will be a brief update on Foundation for Anesthesia Education and Research activities.

Clinical Trials in Anesthesiology: New Findings, New Understanding

Monday, October 24, 2022, 1:15 PM to 3:15 PM
Room 243

Moderator

Marcos F. Vidal Melo, M.D., Ph.D., Associate Editor, ANESTHESIOLOGY, Columbia University Irving Medical Center, New York, New York.

Description

Discussion of four recently published clinical trial studies, presented by one of the authors and counterpointed by a friendly critique by another speaker. Speakers will comment on the methods and their implementation, providing education on those methods and relevant aspects of their implementation and results interpretation in the process. This will be followed by a response from the author.

Speaker

"First-Attempt Success Rate of Video Laryngoscopy in Small Infants (VISI): A Multicenter, Randomized Controlled Trial" by Annery G. Garcia-Marcinkiewicz, M.D.
Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Debater

Michael Aziz, M.D., Department of Anesthesiology and Perioperative Medicine, Oregon Health & Science University, Portland, Oregon.

Speaker

"Spinal Anesthesia with Targeted Sedation Based on Bispectral Index Values Compared with General Anesthesia with Masked Bispectral Index Values to Reduce Delirium: The SHARP Randomized Controlled Trial" by Charles H. Brown IV, M.D., M.H.S.
Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

Debater

Christopher G. Hughes, M.D., Department of Anesthesiology Critical Care Medicine, Vanderbilt University Medical Center, Nashville, Tennessee.

Speaker

"Aggressive Intraoperative Warming *versus* Routine Thermal Management during Noncardiac Surgery (PROTECT): A Multicenter, Parallel Group, Superiority Trial" by Eva Rivas Ferreira, M.D.
Department of Anesthesia, Hospital Clinic of Barcelona, August Pi i Sunyer Biomedical Research Institute, Universidad de Barcelona, Barcelona, Spain

Debater

Harriet W. Hopf, M.D., University of Utah, Salt Lake City, Utah.

Speaker

"Tranexamic Acid in Patients Undergoing Noncardiac Surgery" by Maura Marcucci, M.D., M.Sc.
Department of Health Research Methods, Evidence, and Impact, and Department of Medicine, McMaster University, Hamilton, Canada

Debater

Jerrold H. Levy, M.D., F.C.C.M., Executive Editor, ANESTHESIOLOGY, Duke University, Durham, North Carolina.

David O. Warner, M.D., Recipient of the 2022 Excellence in Research Award

Mark A. Warner, M.D.

It is my sincere pleasure to congratulate Dr. David O. Warner on his recognition with the 2022 Excellence in Research Award received from the American Society of Anesthesiologists (ASA). Dr. Warner has worked in multiple domains to make a difference in our patients' lives. He is highly deserving of this recognition because of the breadth and depth of his research activities and his ability to adapt a variety of research methodologies to pursue important questions.

Dr. Warner received both his undergraduate and medical school education at Ohio State University (Columbus, Ohio). After completing medical school, he spent time as a medical officer at Nigerian Christian Hospital before beginning his residency training at the Mayo Clinic (Rochester, Minnesota). His residency training incorporated a 2-yr research fellowship in pulmonary physiology. His record of National Institutes of Health funding, which continues to the current time, began immediately after joining the Mayo Clinic staff in 1988. He rose quickly through the institution's academic ranks and has been a professor of anesthesiology since 1999.

It is unusual to find a clinician investigator who has such as prolonged record of academic success in multiple domains of study. Dr. Warner's remarkable ability to transition from one important issue to another using diverse and sophisticated research methodologies make him unique. As a practicing anesthesiologist, he closely observes clinical practice, formulates important, clinically relevant questions, and seeks answers. Highlights of Dr. Warner's research and other contributions include the following.

Respiratory Physiology

Dr. Warner's initial research training was in respiratory physiology, benefitting from the combined mentorship of Dr. Robert Hyatt (the father of the pulmonary flow-volume curve) and Dr. Kai Rehder (himself a past recipient of the ASA Excellence in Research Award). Over two decades, Dr. Warner published more than 90 highly cited articles in pulmonary physiology with an initial focus on pulmonary mechanics and respiratory muscle physiology. His findings provided basic insights into normal chest wall function and how anesthesia affects this function. For example, he discovered that anesthesia-induced respiratory depression is caused not by universal depression of respiratory muscle activity but rather by impaired coordination among these muscles. His insights have been of fundamental importance to the daily practice of anesthesia, as respiratory depression continues to be a major source of anesthetic morbidity and mortality.

In addition to studying the effects of anesthetics on chest wall function, he examined the bronchodilatory effects of anesthetics on airway smooth muscle in a laboratory-based program that enjoyed R01 support for over 15 yr. With his Mayo Clinic colleagues Drs. Keith Jones and William Perkins, Dr. Warner discovered that volatile anesthetics relax

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smooth muscle both by impairing neural reflexes and by direct effects on airway smooth muscle. Regarding the latter, they demonstrated that volatile anesthetics relax airway smooth muscle by reducing intracellular calcium concentration, as well as myofibrillar calcium sensitivity. Their discovery that volatile anesthetics have the unique ability to relax even maximally stimulated airway smooth muscle (an ability not shared by other bronchodilators such as β-adrenergic agonists) provided a foundation for drug discovery efforts seeking novel bronchodilators.

Perioperative Tobacco Control

While Dr. Warner was pursuing his productive lab-based program, he was also developing additional interests and capabilities in clinical research, founding the Mayo Clinic Anesthesia Clinical Research Unit in 1999. His first major new focus was on perioperative tobacco control, based on his long-standing interest in improving perioperative lung health. With typical enthusiasm, he initiated a comprehensive multidisciplinary tobacco control research program to develop novel practice-based interventions that could help surgical patients quit smoking. He also initiated a line of research to explore the interactions between tobacco use and pain. His work in perioperative tobacco control, which has produced over 70 peer-reviewed publications, has shown that surgery/anesthesia is a "teachable moment" to promote smoking cessation, demonstrated the medical and economic benefits of helping patients stop smoking, and resulted in practical means for anesthesiologists to help their patients quit.

Based on his efforts, anesthesiology and surgical specialties have incorporated tobacco use interventions into clinical practice nationally and internationally, with great benefit to surgical and pain patients. He is recognized as the leading advocate and investigator in perioperative tobacco control, as recognized by his recent election as a Fellow of the Society for Research in Nicotine and Tobacco. He led the Cancer Center Cessation Initiative of the National Cancer Institute at Mayo Clinic to incorporate tobacco treatment into the routine care of cancer patients, successfully implementing a novel "opt out" automatic referral system. Dr. Warner founded the ASA Smoking Cessation Initiative Task Force, dedicated to helping anesthesiologists incorporate tobacco control measures into their practices, so that the evidence generated by his research and others can be widely disseminated and make a real impact in practice. This was a major impetus for his change in scientific direction away from lab-based studies.

Neurodevelopment after Anesthesia and Surgery in Children

Dr. Warner's clinical practice in pediatric anesthesiology raised his awareness of preclinical studies suggesting that the exposure of young animals to anesthetic drugs produced neurotoxicity. He published with his Mayo Clinic colleagues one of the first studies providing evidence that similar effects may occur in children, showing that anesthetic exposure within the first 3 yr of life is associated with a doubling of the risk for the later development of learning disabilities. This initial research has led to a series of 20 publications from his group, including the ongoing National Institutes of Health–funded Mayo Anesthesia Safety and Kids (MASK) study, which provided the first detailed neuropsychological and behavioral phenotype associated with exposure of young children to anesthesia. It is now apparent from the work of Dr. Warner and others that exposure to anesthesia/surgery may be associated with behavioral changes and diminished fine motor skills later in life, especially in those children with multiple exposures. Clearly, this work could have profound implications for children who require anesthesia at a young age and the anesthesiologists who care for them.

Cognition after Anesthesia and Surgery in the Elderly

His interests in how anesthesia and surgery may affect neurodevelopment and concerns raised by animal experiments led Dr. Warner to initiate an integrated series of studies with his collaborator Dr. Juraj Sprung to evaluate the potential impact of anesthesia on the cognitive function of patients at the opposite end of the age spectrum. These studies revealed that although surgery with anesthesia is not associated with an increased risk of clinical diagnoses of long-term cognitive impairment, it is associated with a modest acceleration of cognitive decline. However, similar changes were seen after hospitalization for medical care, intensive care, and after regional anesthesia, making it unlikely that exposure to general anesthesia was causative. Mechanistically, this decline was associated with accelerated cortical thinning in some brain regions but not increased amyloid deposition. These results are reassuring from the standpoint of anesthesia exposure but highlight the continued need to address perioperative brain health, as they confirmed the link between postoperative delirium and long-term cognitive decline.

Innovations in Postgraduate Medical Education and Assessment

Dr. Warner served for 12 yr as a Director of the American Board of Anesthesiology (Raleigh, North Carolina). In that role, he chaired the American Board of Anesthesiology's Research Committee for many years, which produced a series of 20 papers examining the value of both initial and continuing board certification and other related topics. He also led the development and validation of a novel objective structured clinical examination that was incorporated into the initial certification process for anesthesiologists, the first such examination among member boards of the American Board of Medical Specialties (Chicago, Illinois). Finally, he published seminal work examining substance

use disorder among anesthesiologists, showing that despite ongoing educational and support efforts, this problem continues to grow.

Research Education and Mentorship

Dr. Warner also inspires others to pursue research careers. He has mentored more than 40 graduate students and research fellows, as well as numerous junior faculty, with several subsequently establishing their own independent National Institutes of Health–funded research programs. His understanding of study design and research methods is extraordinary, as is his ability to teach this material to novice researchers. As a scientist, he has the rare gift of making complex, difficult concepts clear and easy to understand. His gentle and unassuming manner makes him easily approachable, and thus, when combined with his research expertise, he is the very model of a professor.

He is also an active educator in all five schools of the Mayo Clinic College of Medicine and Science and has received numerous awards for excellence in teaching. He founded and leads the College's Office for Applied Scholarship and Education Science, which brings the expertise of professional educators to Mayo Clinic educational programs, and is currently an Associate Dean for Faculty Affairs in the Mayo Clinic Alix College of Medicine.

Leadership and Services Roles in Research

Dr. Warner's commitment to promoting research is also apparent in his numerous leadership roles in institutional research administration in addition to his past role as Vice-Chair for Research in our Department of Anesthesiology and Perioperative Medicine. Research at Mayo Clinic is managed by a central institutional research committee. Dr. Warner has served in many different capacities on this committee and its subcommittees, including as Associate Dean for Clinical and Translational Research, Co-Director of the Office for Diversity in Clinical Research, Co-Principal Investigator and Associate Director of the Mayo Clinic Center for Clinical and Translational Sciences (CTSA award), and Principal Investigator of its associated KL2 Mentored Career Development award. Remarkably for an anesthesiologist, he also led for many years the institution's efforts to support community-engaged research. Thus, while maintaining his own active research program, he also has been and remains a major leader in clinical research throughout the institution, amplifying his influence.

Dr. Warner has also made other significant contributions to our specialty. For example, he served full terms as both Associate and Full Editor for the journal Anesthesiology. He has served as an *ad hoc* member for numerous National Institutes of Health study sections and chaired the ASA Subcommittee on Respiration for several years. He was recognized for his research excellence by being selected to give the Helrich Memorial Lecture by the Foundation for Anesthesia Education and Research.

Clinical Activities

It is remarkable that Dr. Warner has been able to accomplish all this while maintaining an active clinical practice. He was a founding member of our department's Pediatric Anesthesia Division, introduced nitric oxide into clinical practice at Mayo Clinic, and is recognized by his peers as a skilled and compassionate clinician. He has also been active in medical missions to underserved countries.

Summary

The breadth and quality of Dr. Warner's scientific accomplishments are remarkable. The methods used in his research range from saturation transfer difference nuclear magnetic resonance spectroscopy examining anesthetic binding to isolated proteins to cutaneous blood flow measurements in humans to randomized clinical trials of tobacco interventions to education science assessments to the tools of dissemination and implementation research in clinical anesthesiology practices, showing that sound scientific principles can be applied to any area of inquiry with success—if the investigator has curiosity and drive. He is the very model of the physician–scientist yet has not followed a "safe," traditional career path. Many scientists maintain their funding stream by developing an ever-more specialized expertise in a relatively narrow area that is recognized and rewarded by peer reviewers. In contrast, Dr. Warner has, when appropriate, completely changed scientific direction to pursue his passions while still maintaining scientific excellence and productivity. Along the way, he continues to recruit and train the best and brightest in scholarly anesthesiology careers. Dr. Warner has made extraordinary contributions to our specialty in multiple domains that will benefit our patients and is truly deserving of recognition for these efforts. Despite these scientific accomplishments, if you ask him, his greatest joys are Julie, his high school sweetheart and wife of 43 yr, his three grown-up children and five (so far) cute grandchildren.

Competing Interests

Dr. M. A. Warner is a first cousin of Dr. D. O. Warner, and both are members of the Mayo Clinic (Rochester, Minnesota) Department of Anesthesiology and Perioperative Medicine.

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Kristin Schreiber, M.D., Ph.D., a Recipient of the 2022 James E. Cottrell, M.D., Presidential Scholar Award

James P. Rathmell, M.D., M.B.A.

Kristin Schreiber, M.D., Ph.D., Vice Chair for Faculty Development at Brigham and Women's Hospital (Boston, Massachusetts) and Associate Professor of Anaesthesia at Harvard Medical School (Cambridge, Massachusetts), was awarded this year's James E. Cottrell, M.D. Presidential Scholar Award. This is a well-deserved honor for such a superb clinician–scientist. Dr. Schreiber's work has helped us to understand which patients are at highest risk for developing persistent postsurgical pain, while also probing personalized interventions to prevent this often debilitating outcome. I have followed her work, which overlaps with my own areas of research interest, watching her career develop over time, and so it gives me great pleasure to honor Dr. Schreiber with a few words about her career.

Kristin received a Bachelor of Science degree with honors, from the University of Wisconsin-Madison (Madison, Wisconsin), majoring in Psychology and German. She then received an M.D./Ph.D. in Neuroscience from the University of Minnesota in Minneapolis, Minnesota. Work for her doctoral thesis investigated the bidirectional cross talk between the nervous and immune systems in pain and infection. She demonstrated this bidirectional communication in two diverse settings: activation of spinal microglia in the development of persistent and widespread pain,[1] and modulation of pathogen adherence and invasion in the gut by the enteric nervous system.[2,3] She went on to complete an Residency in Anesthesiology at the University of Pittsburgh (Pittsburgh, Pennsylvania), where she focused her passion for understanding the development of chronic pain into clinical applications in regional anesthesia[4] and the development of persistent postsurgical pain,[5] contributing to the peer-reviewed literature during a busy clinical residency. Dr. Schreiber joined us at Brigham and Women's Hospital for Regional Anesthesia and Research Fellowships in July 2012, simultaneously joining our faculty, where she is now Associate Professor of Anesthesia at Harvard Medical School and a Staff Anesthesiologist at Brigham and Women's Hospital specializing in Regional Anesthesia. During her 10 yr with our department, she has excelled both clinically as an exceptional Regional Anesthesiologist and a prolific translational Pain Neuroscientist.

Working with a diverse team of mentors and collaborators in Pain Psychology, Neurophysiology, Psychophysics, Regional Anesthesia, Oncology, Neuroimaging, Preoperative Evaluation, and Placebo Research (Drs. Rob Edwards, Gary Strichartz, Kamen Vlassakov, Angela Bader, Vitaly Napadow, Marco Loggia, and Ted Katpchuk), Kristin has built an impressive collaborative clinical research program. She set out to identify factors predicting the transition to persistent postsurgical pain, earning her the support of a K23 grant in 2015. In 2018, her early success led to her being among the first Anesthesiologists nationally to be awarded a highly competitive National Institutes of Health Maximizing Investigators' Research Award (R35), equivalent to an R01, from the National Institute of General Medical Sciences. She has gained further independent funding, serving as the site Principal Investigator at Brigham and Women's Hospital for the Early Phase Pain Investigation Clinical Network (EPPIC-Net), part of the large National Institutes of Health Helping to End Addiction Long-term

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initiative, and as coinvestigator on grants from the National Cancer Institute and the National Science Foundation.

A notable hallmark of Kristin's research is the collaborative nature of everything she does. She has a tremendous track record of sparking interest in research among her colleagues and successfully engaging them in research projects. She has thoughtfully mentored premedical and medical students, residents, and clinical and postdoctoral fellows in conducting clinical studies. Her collaborative spirit and enthusiasm for research has fostered strong cross-departmental bonds, not only with the Department of Surgery, but also with the Departments of Oncology, Emergency Medicine, Neurology, and Pharmacy. She has served as a key consultant to oncologists and surgeons on a large Patient-Centered Outcomes Research Institute grant, bringing high quality and thoughtful assessment and treatment of pain to these projects.

Dr. Schreiber's active fostering of these observational, laboratory-based, randomized, or pragmatic trials have resulted in more than 60 peer-reviewed publications, most of which are as first or senior author. Her primary research focus is on the prediction and prevention of postsurgical pain and opioid use, with publications in *Annals of Surgical Oncology*, *Journal of Pain*, *Pain Medicine*, and *Anesthesia & Analgesia*. In addition, she has pursued mechanistic testing of pain processing among individuals, including studies in neuroimaging and the quantitative sensory testing laboratory, published in *Anesthesiology* and *Journal of Pain*. Her insights into the impact of regional anesthetic techniques have been published in *Regional Anesthesia and Pain Medicine*, *British Journal of Anesthesia*, and *Pain Medicine*, including contributions to understanding and reducing postsurgical pain after mastectomy,[6–11] liver resection,[4] cesarean delivery,[12] thoracotomy, total knee arthroplasty,[13–16] and spinal fusion.[17,18] For much of this research, she has adapted simple, validated psychometric measures, including objective quantitative sensory testing in the preoperative clinic, to "phenotype" patients preoperatively, and predict patients at risk for acute and chronic postsurgical pain and opioid use, including the development of bedside adaptations of these tests.[19] She has also examined the impact of alternative therapies on pain modulation, including the impact of yoga-based exercise on pain in fibromyalgia patients,[20–22] distraction in chronic pain patients,[23] music in emergency medicine patients,[24] and a randomized controlled trial of open-label placebo in spine surgery patients,[17] which was featured in press releases after its publication in *PAIN*. During the pandemic, she aptly pivoted to investigate the impact of social isolation on chronic pain and reported differential impact among individuals, with certain chronic pain patients being more impacted (minority and female).[25] This longitudinal study of the impact of COVID-induced isolation allowed insights into a rarely studied aspect of the biopsychosocial model: how social forces influence pain, and how they impact a patient's psychology and their processing of pain.[25–28] Her work is changing the way we think about personalizing perioperative care in an era of multiple enhanced recovery after surgery protocols that often dictate a one-size fits all approach.[29]

Dr. Schreiber has a tremendous record of local, national, and international academic service, ranging from local institutional review board expert review and leadership in research infrastructure, to involvement in the Early-Stage Anesthesia Scholars program as part of International Anesthesia Research Society and serving as an Editor of Anesthesiology. In our own department, she has demonstrated exceptional leadership as the Associate Vice Chair for Research working together with our Vice Chair for Research, Dr. Danny Muehlschlegel. Together Drs. Muehlschlegel and Schreiber developed a strong research core that serves to support basic, translational, and clinical research. She has served on scientific committees of major national organizations and on grant study sections, including as the Chair of the International Anesthesia Research Society Mentored Research Award review committee. She has also chaired a working group of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks-American Pain Society Pain Taxonomy Group, defining taxonomy and measurement guidelines for postsurgical pain.[30] She has been an sought-after speaker, addressing National Institutes of Health research workshops, as well as a diverse set of Anesthesiology and Pain–related societies' annual meetings.

Kristin and her husband Paul Wacnik, Ph.D., a pharmacology and neuroscience–trained engineer working at Pfizer in Cambridge, Massachusetts, enjoy spending time with their 15- and 17-yr-old boys Leo and Fredrik. Having the chance to mentor (a little) and to learn (a lot) from Kristin here at Brigham and Women's and Harvard Medical School has been a great pleasure. It reminds me why I enjoy academic medicine so enormously, watching extraordinary people like Kristin grow to their full potential. We are privileged to have this talented clinician–scientist who brings a holistic, personalized approach to perioperative pain prevention as our colleague and friend, and as a member of our specialty.

Competing Interests

The author declares no competing interests.

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References

1. Schreiber KL, Beitz AJ, Wilcox GL: Activation of spinal microglia in a murine model of peripheral

inflammation-induced, long-lasting contralateral allodynia. Neurosci Lett 2008; 440:63–7
2. Schreiber KL, Brown DR: Adrenocorticotrophic hormone modulates Escherichia coli O157:H7 adherence to porcine colonic mucosa. Stress 2005; 8:185–90
3. Schreiber KL, Price LD, Brown DR: Evidence for neuromodulation of enteropathogen invasion in the intestinal mucosa. J Neuroimmune Pharmacol 2007; 2:329–37
4. Schreiber KL, Chelly JE, Lang RS, Abuelkasem E, Geller DA, Marsh JW, Tsung A, Sakai T: Epidural versus paravertebral nerve block for postoperative analgesia in patients undergoing open liver resection: A randomized clinical trial. Reg Anesth Pain Med 2016; 41:460–8
5. Schreiber KL, Martel MO, Shnol H, Shaffer JR, Greco C, Viray N, Taylor LN, McLaughlin M, Brufsky A, Ahrendt G, Bovbjerg D, Edwards RR, Belfer I: Persistent pain in postmastectomy patients: comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain. Pain 2013; 154:660–8
6. Belfer I, Schreiber KL, Shaffer JR, Shnol H, Blaney K, Morando A, Englert D, Greco C, Brufsky A, Ahrendt G, Kehlet H, Edwards RR, Bovbjerg DH: Persistent postmastectomy pain in breast cancer survivors: analysis of clinical, demographic, and psychosocial factors. J Pain 2013; 14:1185–95
7. Schreiber KL, Kehlet H, Belfer I, Edwards RR: Predicting, preventing and managing persistent pain after breast cancer surgery: The importance of psychosocial factors. Pain Manag 2014; 4:445–59
8. Schreiber KL, Zinboonyahgoon N, Xu X, Spivey T, King T, Dominici L, Partridge A, Golshan M, Strichartz G, Edwards RR: Preoperative psychosocial and psychophysical phenotypes as predictors of acute pain outcomes after breast surgery. J Pain 2019; 20:540–56
9. Schreiber KL, Zinboonyahgoon N, Flowers KM, Hruschak V, Fields KG, Patton ME, Schwartz E, Azizoddin D, Soens M, King T, Partridge A, Pusic A, Golshan M, Edwards RR: Prediction of persistent pain severity and impact 12 months after breast surgery using comprehensive preoperative assessment of biopsychosocial pain modulators. Ann Surg Oncol 2021; 28:5015–38
10. Zinboonyahgoon N, Patton ME, Chen YK, Edwards RR, Schreiber KL: Persistent post-mastectomy pain: The impact of regional anesthesia among patients with high vs low baseline catastrophizing. Pain Med 2021; 22:1767–75
11. Flowers KM, Beck M, Chen Y-YK, Zinboonyahgoon N, Edwards R, Schreiber K. Longitudinal assessment of postmastectomy sensory disturbances: Distinguishing between painful neuropathic features and numbness alone. Pain Reports 2021;6:595.
12. Ende HB, Soens MA, Nandi M, Strichartz GR, Schreiber KL: Association of interindividual variation in plasma oxytocin with postcesarean incisional pain. Anesth Analg 2019; 129:e118–21
13. Nandi M, Schreiber KL, Martel MO, Cornelius M, Campbell CM, Haythornthwaite JA, Smith MT Jr, Wright J, Aglio LS, Strichartz G, Edwards RR: Sex differences in negative affect and postoperative pain in patients undergoing total knee arthroplasty. Biol Sex Differ 2019; 10:23
14. Edwards RR, Campbell C, Schreiber KL, Meints S, Lazaridou A, Martel MO, Cornelius M, Xu X, Jamison RN, Katz JN, Carriere J, Khanuja HP, Sterling RS, Smith MT, Haythornthwaite JA: Multimodal prediction of pain and functional outcomes 6 months following total knee replacement: A prospective cohort study. BMC Musculoskelet Disord 2022; 23:302
15. Abrecht CR, Cornelius M, Wu A, Jamison RN, Janfaza D, Urman RD, Campbell C, Smith M, Haythornthwaite J, Edwards RR, Schreiber KL: Prediction of pain and opioid utilization in the perioperative period in patients undergoing primary knee arthroplasty: Psychophysical and psychosocial factors. Pain Med 2019; 20:161–71
16. Meints SM, Wang V, Edwards RR: Sex and race differences in pain sensitization among patients with chronic low back pain. J Pain 2018; 19:1461–70
17. Flowers KM, Patton ME, Hruschak VJ, Fields KG, Schwartz E, Zeballos J, Kang JD, Edwards RR, Kaptchuk TJ, Schreiber KL: Conditioned open-label placebo for opioid reduction after spine surgery: a randomized controlled trial. Pain 2021; 162:1828–39
18. Hruschak V, Flowers KM, Patton ME, et al. A qualitative analysis of the experience of patients taking conditioned open-label placebos for reduction of postoperative pain and opioid exposure after spine surgery. Int J Behav Med 2022; (in press)
19. Koulouris AE, Edwards RR, Dorado K, Schreiber KL, Lazaridou A, Rajan S, White J, Garcia J, Gibbons C, Freeman R: Reliability and validity of the boston bedside quantitative sensory testing battery for neuropathic pain. Pain Med 2020; 21:2336–47
20. Lazaridou A, Koulouris A, Devine JK, Haack M, Jamison RN, Edwards RR, Schreiber KL: Impact of daily yoga-based exercise on pain, catastrophizing, and sleep amongst individuals with fibromyalgia. J Pain Res 2019; 12:2915–23
21. Lazaridou A, Koulouris A, Dorado K, Chai P, Edwards RR, Schreiber KL: The impact of a daily yoga program for women with fibromyalgia. Int J Yoga 2019; 12:206–17
22. Weerasekera A, Morrissey E, Kim M, Saha A, Lin Y, Alshelh Z, Torrado-Carvajal A, Albrecht D, Akeju O, Kwon YM, Bedair H, Chen AF, Napadow V, Schreiber K, Ratai EM, Edwards RR, Loggia ML: Thalamic neurometabolite alterations in patients with knee

osteoarthritis before and after total knee replacement. Pain 2021; 162:2014–23
23. Schreiber KL, Campbell C, Martel MO, Greenbaum S, Wasan AD, Borsook D, Jamison RN, Edwards RR: Distraction analgesia in chronic pain patients: The impact of catastrophizing. Anesthesiology 2014; 121:1292–301
24. Chai PR, Schwartz E, Hasdianda MA, Azizoddin DR, Kikut A, Jambaulikar GD, Edwards RR, Boyer EW, Schreiber KL: A brief music app to address pain in the emergency department: prospective study. J Med Internet Res 2020; 22:e18537
25. Hruschak V, Flowers KM, Azizoddin DR, Jamison RN, Edwards RR, Schreiber KL: Cross-sectional study of psychosocial and pain-related variables among patients with chronic pain during a time of social distancing imposed by the coronavirus disease 2019 pandemic. Pain 2021; 162:619–29
26. Flowers KM, Colebaugh C, Hruschak V, et al. Introversion, extraversion, and worsening of chronic pain impact during social isolation: A mediation analysis. J Clin Psychol Med Settings 2022; (in press)
27. Wilson JM, Colebaugh CA, Flowers KM, Meints SM, Edwards RR, Schreiber KL: Social support and psychological distress among chronic pain patients: The mediating role of mindfulness. Pers Individ Dif 2022; 190:111551
28. Wilson JM, Colebaugh CA, Flowers KM, Edwards RR, Schreiber KL. Profiles of risk and resilience in chronic pain: Loneliness, social support, mindfulness, and optimism coming out of the first pandemic year. Pain Med 2022 May 19 [Epub ahead of print]
29. Schreiber KL, Muehlschlegel JD: Personalization over protocolization. Anesthesiology 2021; 134:363–5
30. Schreiber KL, Belfer I, Miaskowski C, Schumacher M, Stacey BR, Van De ven T: AAAPT diagnostic criteria for acute pain following breast surgery. J Pain 2020; 21:294–305

Vivianne Tawfik, M.D., Ph.D., a Recipient of the 2022 James E. Cottrell, M.D., Presidential Scholar Award

Brian T. Bateman, M.D., M.Sc., Ronald G. Pearl, M.D., Ph.D.

It is extraordinarily fitting that Vivianne Tawfik, M.D., Ph.D., is a 2022 recipient of the James E. Cottrell, M.D., Presidential Scholar Award. Dr. Tawfik is a consummate physician–scientist, being an outstanding clinician, a rigorous researcher, and a dedicated mentor. She is passionate about our specialty and is committed to leading by example the next generation of academic anesthesiologists. She has already made major contributions to our fundamental understanding of pain mechanisms and has emerged as a national leader who promotes clinician–scientists in our specialty. As the current (B.T.B.) and former (R.G.P.) chairs of the Department of Anesthesiology, Perioperative and Pain Medicine at Stanford University (Stanford, California), we have observed and take great pride in Dr. Tawfik's extraordinary accomplishments and contributions.

Dr. Tawfik received her B.Sc. with First Class Honors from McGill University (Montréal, Canada) in 2002, where she first became interested in neuroscience and the potential to combine a career in research and medicine. As part of the M.D./Ph.D. program at Dartmouth Medical School (Hanover, New Hampshire), she sought to answer questions related to basic pain mechanisms and joined the laboratory of Dr. Joyce DeLeo. She graduated in just 7 yr with five first-authored publications and several awards recognizing her research, clinical, and community service achievements. After medical school, Dr. Tawfik completed her internship in general surgery at Dartmouth-Hitchcock Medical Center (Lebanon, New Hampshire). She was recruited and mentored by Dr. Rona Giffard for residency training in anesthesiology at Stanford University in the Fellowship in Anesthesia Research and Medicine residency research track, of which she now serves as the director. To fully integrate her research and clinical interests, after residency she completed her subspecialty clinical fellowship in pain medicine under the supervision of Dr. Sean Mackey. After being chosen as the top candidate in a competitive national search, in July 2017 she joined the faculty at Stanford in the physician–scientist faculty line (University Medical Line).

Dr. Tawfik's work to understand how peripheral and central immune cells contribute to persistent pain has spanned almost two decades. During her Ph.D. studies, she

discovered that two types of glial cells in the spinal cord (microglia and astrocytes) were important for postinjury pain responses and opioid tolerance.[1–4] These findings laid the groundwork for subsequent investigations during her postdoctoral fellowships investigating the identity of sensory and spinal neurons involved in pain perception and analgesia.[5,6] She previously demonstrated that spinal cord microglial cells were activated after chronic morphine administration; however, whether this occurred through glial mu opioid receptors remained a matter of debate. Using novel techniques during her postdoctoral training with Dr. Gregory Scherrer, she and her colleagues demonstrated that mu opioid receptors are not expressed by microglia *in vivo*,[7]

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a finding with widespread implications for the study of opioid tolerance that has already been cited in the literature more than 200 times.

Since starting her own independent research group in 2017, Dr. Tawfik has taken advantage of her years of training in cutting-edge techniques in neuroscience to focus on the contribution of peripheral immune cells and spinal cord glia to chronic pain conditions, including complex regional pain syndrome and peripheral nerve injury.

Recovery from surgery relies on a multicellular interplay between pro- and anti-inflammatory processes. Whether these processes exhibit sexual dimorphism has been largely underexplored but obviously would influence treatment paradigms. In a recent publication,[8] Dr. Tawfik utilized high-dimensional mass cytometry to perform a comprehensive analysis of phenotypic and functional immune system differences between male and female mice after orthopedic injury. Multivariate modeling of innate and adaptive immune cell responses after injury revealed sex-specific divergence after injury with a stronger immune response to injury in females. Using the tibial fracture model of complex regional pain syndrome, which she learned during her postdoctoral training with Dr. David Clark, she further explored the myeloid cell contribution to the acute-to-chronic pain transition common to most pain conditions. She and her team performed positron emission tomography using a myeloid lineage activation marker to identify the unique spatiotemporal dynamics of the innate immune response in complex regional pain syndrome.[9] She found early and persistent involvement of peripheral myeloid cells at the site of injury, and early and transient activation of central nervous system microglia distant from the injury site.

More recently, Dr. Tawfik published an exciting article detailing how activation of microglia through the pattern recognition receptor TLR4 promotes chronic pain specifically in males.[10] In contrast to published dogma, she found that microglia themselves contribute to female chronic pain, but not *via* TLR4 activation. Related translational work from her group reported clinical use of the antimalarial drug hydroxychloroquine in the treatment of refractory complex regional pain syndrome and a potential microglial modulatory mechanism for this effect in an accompanying mouse model study.[11]

Dr. Tawfik is leading several additional initiatives with collaborators at Stanford including projects to understand how targeted immune modulation to improve bone healing can decrease pain and improve recovery, to distinguish the contributions of astrocytes to persistent pain, and the use of targeted ultrasound to direct pain therapeutics to peripheral sites of action.

Dr. Tawfik has had impressive success with competing for independent funding, obtaining a 5-yr National Institute of General Medical Sciences R35 Maximizing Investigators' Research Award grant that funds investigators to "go where the science takes them," and a collaborative 3-yr Defense Advanced Research Projects Agency grant with Stanford Nobel Laureate Dr. Brian Kobilka. She was also recently awarded an National Institute of Neurological Disorders and Stroke R21 focused on the highly innovative concept of peripheral neuronal senescence as a target for the treatment of pain. Her work has been recognized with several prestigious awards. She is one of few practicing physician–scientists to have received the basic science–targeted Rita Allen Foundation Award in Pain since 2009. She received the McCormick and Gabilan Faculty Award in 2019 from Stanford University, a grant focused on supporting women researchers and leaders.

Dr. Tawfik is a highly effective mentor. She is the primary thesis advisor to two graduate students, both women from underrepresented backgrounds in the Stanford Ph.D. Neurosciences program, as well as three postdoctoral scholars and many undergraduate students. In 2018, Dr. Tawfik was appointed as Director of the Fellowship in Anesthesia Research and Medicine program, the residency physician–scientist training program. In this role, she recruits medical students to the Fellowship in Anesthesia Research and Medicine track, serves on the residency admissions committee, and mentors residents and fellows in the program, providing career development advice. She also directs the research track for the Stanford Anesthesia Summer Institute, a program that provides the opportunity for high school and college students interested in science, technology, engineering, and mathematics (STEM), especially those from underrepresented minorities, to gain exposure to the field of anesthesiology.

During the past 5 yr, Dr. Tawfik has continued to expand her involvement in the academic future of anesthesiology at the local, national, and international levels. She has served on multiple review panels at the National Institutes of Health (Bethesda, Maryland), is an Associate Editor for the *British Journal of Anesthesia*, and recently began in a new leadership role leading basic science efforts in our department as an Associate Vice-Chair. In 2016, she became the first Co-President of Early-stage Anesthesiology Scholars, an organization formed to represent and foster early career anesthesiologist–scientists. She is also a member of the first working group of the Anesthesia Research Council, a group formed with support from the American Society of Anesthesiologists (Schaumburg, Illinois), the Foundation for Anesthesia Education and Research (Schaumburg, Illinois), and the International Anesthesia Research Society (San Francisco, California), to address critical questions and challenges in research relevant to advancing science and patient care in anesthesiology. In recognition of her contributions to academic anesthesiology, she was recently appointed to the Board of Trustees of the International Anesthesia Research Society. Finally, Dr. Tawfik was also recently asked to take on the role of Vice-Chair of the American Society

of Anesthesiologists Scientific Advisory Committee, a role she will begin in fall 2022.

She brings the same level of thoughtful attention to the care of her patients in the Pain Management Clinic at Stanford as she does to her research program. She leads an active outpatient clinical practice focused on persistent pain after limb injury, complex regional pain syndrome, and chronic postsurgical pain. The clear alignment between her research and clinical duties provides added value to both domains of her work. To best care for patients with complex nerve pathology, she is involved in the development and implementation of an interdisciplinary "Nerve Team" consisting of pain physicians, radiologists, and three peripheral nerve surgeons.[12]

Dr. Tawfik is focused on making an impact on anesthesiology research and practice. She is scholarly, collaborative, skillful, and committed. She is also generous in giving her time to mentor others and takes great pride in fostering their success. Our specialty is fortunate to have someone with her talent and drive leading us into the future.

Competing Interests

The authors declare no competing interests.

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References

1. Tawfik VL, LaCroix-Fralish ML, Nutile-McMenemy N, DeLeo JA: Transcriptional and translational regulation of glial activation by morphine in a rodent model of neuropathic pain. J Pharmacol Exp Ther 2005; 313:1239–47
2. Tawfik VL, Lacroix-Fralish ML, Bercury KK, Nutile-McMenemy N, Harris BT, Deleo JA: Induction of astrocyte differentiation by propentofylline increases glutamate transporter expression *in vitro*: Heterogeneity of the quiescent phenotype. Glia 2006; 54:193–203
3. Tawfik VL, Nutile-McMenemy N, Lacroix-Fralish ML, Deleo JA: Efficacy of propentofylline, a glial modulating agent, on existing mechanical allodynia following peripheral nerve injury. Brain Behav Immun 2007; 21:238–46
4. Tawfik VL, Regan MR, Haenggeli C, Lacroix-Fralish ML, Nutile-McMenemy N, Perez N, Rothstein JD, DeLeo JA: Propentofylline-induced astrocyte modulation leads to alterations in glial glutamate promoter activation following spinal nerve transection. Neuroscience 2008; 152:1086–92
5. Bardoni R, Tawfik VL, Wang D, Francois A, Solorzano C, Shuster SA, Choudhury P, Betelli C, Cassidy C, Smith K, de Nooij JC, Mennicken F, O'Donnell D, Kieffer BL, Woodbury CJ, Basbaum AI, MacDermott AB, Scherrer G: Delta opioid receptors presynaptically regulate cutaneous mechanosensory neuron input to the spinal cord dorsal horn. Neuron 2014; 81:1312–27
6. Wang D, Tawfik VL, Corder G, Low SA, Francois A, Basbaum AI, Scherrer G: Functional divergence of delta and mu opioid receptor organization in CNS pain circuits. Neuron 2018; 98:90–108.e5
7. Corder G, Tawfik VL, Wang D, Sypek EI, Low SA, Dickinson JR, Sotoudeh C, Clark JD, Barres BA, Bohlen CJ, Scherrer G: Loss of μ opioid receptor signaling in nociceptors, but not microglia, abrogates morphine tolerance without disrupting analgesia. Nat Med 2017; 23:164–73
8. Tawfik VL, Huck NA, Baca QJ, Ganio EA, Haight ES, Culos A, Ghaemi S, Phongpreecha T, Angst MS, Clark JD, Aghaeepour N, Gaudilliere B: Systematic immunophenotyping reveals sex-specific responses after painful injury in mice. Front Immunol 2020; 11:1652
9. Cropper HC, Johnson EM, Haight ES, Cordonnier SA, Chaney AM, Forman TE, Biswal A, Stevens MY, James ML, Tawfik VL: Longitudinal translocator protein-18 kDa-positron emission tomography imaging of peripheral and central myeloid cells in a mouse model of complex regional pain syndrome. Pain 2019; 160:2136–48
10. Huck NA, Siliezar-Doyle J, Haight ES, Ishida R, Forman TE, Wu S, Shen H, Takemura Y, Clark JD, Tawfik VL: Temporal contribution of myeloid-lineage TLR4 to the transition to chronic pain: A focus on sex differences. J Neurosci 2021; 41:4349–65
11. Haight ES, Johnson EM, Carroll IR, Tawfik VL: Of mice, microglia, and (wo)men: A case series and mechanistic investigation of hydroxychloroquine for complex regional pain syndrome. Pain Rep 2020; 5:e841
12. Johnson EM, Yoon D, Biswal S, Curtin C, Fox P, Wilson TJ, Carroll I, Lutz A, Tawfik VL: Characteristics of patients with complex limb pain evaluated through an interdisciplinary approach utilizing magnetic resonance neurography. Front Pain Res (Lausanne) 2021; 2:689402

ANESTHESIOLOGY

Tidal Volume and Positive End-expiratory Pressure and Postoperative Hypoxemia during General Anesthesia: A Single-center Multiple Crossover Factorial Cluster Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Low tidal volume and high positive end-expiratory pressures (PEEP) are preferable in critical care patients, but it remains unclear whether they are beneficial in surgical patients.

What This Article Tells Us That Is New

- A total of 2,860 orthopedic surgical patients having general anesthesia were assigned in a 2 x 2 factorial cluster trial to 6 *versus* 10 ml/kg tidal volume *and* to 5 *versus* 8 cm H_2O PEEP.
- There was no interaction between V_T and PEEP. The primary outcome, the Spo_2/Fio_2 ratio, was similar in each tidal volume and PEEP group. Secondary outcomes including postoperative oxygenation, duration of hospitalization, and composite pulmonary complications also did not differ significantly.
- Tidal volumes between 6 and 10 ml/kg and PEEP between 5 and 8 cm H_2O are similar with respect to pulmonary outcomes.

ABSTRACT

Background: Intraoperative mechanical ventilation is a major component of general anesthesia. The extent to which various intraoperative tidal volumes and positive end-expiratory pressures (PEEP) effect on postoperative hypoxia and lung injury remains unclear. We hypothesized that adults having orthopedic surgery, ventilation using different tidal volumes and PEEP levels affect the oxygenation within first hour in the postoperative care unit.

Methods: We conducted a two-by-two factorial crossover cluster trial at the Cleveland Clinic Main Campus. We enrolled patients having orthopedic surgery with general anesthesia who were assigned to factorial clusters with tidal volumes of 6 or 10 ml/kg of predicted body weight and to PEEP of 5 or 8 cm H_2O in 1-week clusters. The primary outcome was the effect of tidal volume or PEEP on time-weighted average peripheral oxygen saturation measured by pulse oximetry divided by the fraction of inspired oxygen (Spo_2/Fio_2 ratio) during the initial postoperative hour.

Results: We enrolled 2,860 patients who had general anesthesia for orthopedic surgery from September 2018 through October 2020. The interaction between tidal volume and PEEP was not significant ($P = 0.565$). The mean ± SD time-weighted average of Spo_2/Fio_2 ratio was 353 ± 47 and not different in patients assigned to high and low tidal volume (estimated effect, 3.5%; 97.5% CI, –0.4% to 7.3%; $P = 0.042$), for those assigned to high and low PEEP (estimated effect, –0.2%; 97.5% CI, –4.0% to 3.6%; $P = 0.906$). We did not find significant difference in ward Spo_2/Fio_2 ratio, pulmonary complications, and duration of hospitalization among patients assigned to various tidal volumes and PEEP levels.

Conclusions: Among adults having major orthopedic surgery, postoperative oxygenation is similar, with tidal volumes between 6 and 10 ml/kg and PEEP between 5 and 8 cm H_2O. Our results suggest that any combination of tidal volumes between 6 and 10 ml/kg and PEEP between 5 *versus* 8 ml cm H_2O can be used safely for orthopedic surgery.

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Annually, 313 million surgical procedures are performed worldwide,[1] and many experience potentially preventable postoperative complications.[2] Among the most common are postoperative hypoxemia and pulmonary complications.[3,4] Sun *et al.*,[5] in a retrospective analysis, reported that hypoxemia was common and prolonged in patients recovering from major noncardiac surgery, with a fifth having at least 10 min/h with oxygen saturation measured by pulse oximetry (Spo_2) less than 90%. Postoperative hypoxemia can be caused by atelectasis,[6] ventilator-induced lung injury, ventilation/perfusion mismatch,[6] and

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pulmonary edema.[4] Hypoxemia, even without other respiratory complications, is associated with prolonged hospitalization, intensive care unit admissions, mortality, and increased cost of care.

Intraoperative mechanical ventilation is a major component of general anesthesia. Two key ventilator settings are tidal volume and positive end-expiratory pressure (PEEP). Traditionally, high tidal volumes (10 ml/kg or greater) were used because they reduce atelectasis and improve oxygenation. However, high tidal volumes increase concentrations of proinflammatory mediators, promote pulmonary edema, and over-distend alveoli—thus promoting lung injury and hypoxia.[7] In contrast, restricted tidal volumes reduce inflammation, improve breathing mechanics, and limit over-distention injury. However, low tidal volumes also promote atelectasis, which is an important cause of postoperative lung injury, and promotes pneumonia and hypoxia. It remains unclear which of these many competing effects dominates. Consequently, low tidal volume has only inconsistently been adopted for operating room use.[3]

There is similar ongoing debate about the optimal level of intraoperative PEEP. High PEEP reduces atelectasis and improves arterial oxygenation and respiratory system compliance, but also promotes alveolar over-distention hypotension.[8] Low PEEP decreases barotrauma but may not prevent atelectasis. Low tidal volumes combined with PEEP help maintain oxygenation in patients with acute respiratory distress syndrome and acute lung injury who are ventilated for days in critical care units. However, it remains unclear whether comparable benefit results when restricted tidal volumes and high PEEP are applied for just a few intraoperative hours.[9] Also unknown is how intraoperative tidal volume and PEEP interact—that is, which combination of high and low tidal volume and high and low PEEP is preferable.

The extent to which various intraoperative tidal volumes and PEEP levels effect on postoperative hypoxia and lung injury therefore remains unclear. We thus conducted a robust 2 by 2 factorial crossover cluster trial to determine the effects of tidal volumes of 6 *versus* 10 ml/kg of predicted body weight and PEEP of 5 *versus* 8 cm H_2O. Our primary outcome was oxygenation within the first hour in the postoperative care unit, defined by the peripheral Spo_2 divided by the fraction of inspired oxygen (Fio_2) ratio, a surrogate measure of oxygenation. Our secondary outcomes were (1) time-weighted average Spo_2/Fio_2 ratio on surgical wards, (2) postoperative duration of hospitalization, and (3) a composite of postoperative pulmonary complications.

Materials and Methods

This is a single-center, single-blinded, multiple crossover factorial alternating cluster trial. The protocol was approved by the Cleveland Clinic (Cleveland, Ohio) Institutional Review Board, and written informed consent was waived; however, all patients were given written information about the study well before surgery and had the opportunity to opt out of the trial. There were no substantive changes to the protocol after initiation of patient enrollment. The full protocol and statistical analysis plan are available in Supplemental Digital Content 1 (http://links.lww.com/ALN/C883). The trial was exclusively funded by departmental resources, and none of the authors has a personal financial interest in this research.

Subject Selection

Patients were enrolled at the Cleveland Clinic Main Campus between September 3, 2018, and October 24, 2020. The study was restricted to a physically distinct suite of five operating rooms that are primarily used by for orthopedic surgery and normally staffed by a small group of anesthesiologists.

All patients in the designated operating rooms were nominally included in the trial. However, the protocol specified that good clinical judgment should always prevail. Clinicians thus modified tidal volume and PEEP when they deemed it necessary. Similarly, they were able to *a priori* exclude particular patients whom they deemed clinically unsuitable for the trial.

Randomization and Blinding

Patients having general anesthesia in the designated operating rooms were assigned to factorial clusters with tidal volumes of 6 or 10 ml/kg of predicted body weight *and* to PEEP of 5 or 8 cm H_2O in 1-week clusters. Thus, in a given 4-week period, all four combinations of tidal volume and

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PEEP were each used for 1 week. Assignments sequentially alternated among the four combinations throughout enrollment. Anesthesiologists were not blinded to treatments, but patients and outcome assessors were blinded.

Study Procedures

Inspired oxygen concentration was normally 50% during surgery, but the concentration was increased as necessary to maintain oxygen saturation 95% or greater as determined by pulse oximetry. The respiratory rate was adjusted to maintain an end-tidal carbon dioxide partial pressure 35 to 45 mmHg, with a default inspired to expired ratio of 1:2. Clinicians were asked to perform a recruitment maneuver after induction of anesthesia at a F_{IO_2} of 50% and shortly before extubation. Typically, the recruitment maneuver consisted of maintaining an airway pressure of 40 to 45 cm H_2O for 40 s.[10] During the postoperative period, supplemental oxygen was increased as necessary to maintain oxygen saturation 92% or greater. We use the phase 1 discharge scoring tool to assess patients for postanesthesia care unit (PACU) discharge. It includes 10 items scored from 0 to 2 about the level of consciousness, physical activity, blood pressure, heart rate, respirations, oxygen saturation status, pain, postoperative nauseas and vomits, temperature, and bleeding. The maximum score is 20, and patients need to score 18 or more to be discharged from the PACU. Specifically, the oxygen saturation status scores 2 if the patient has an oxygen saturation more than 92% on room air or on supplemental oxygen with IV patient-controlled analgesia (PCA); 1 if saturation is greater than 92% on supplemental oxygen not involving IV PCA; and 0 if saturation less than 92% on supplemental oxygen, but in this case, if there is not a treatable cause, the patient is transfered to intensive care unit.

There was no other restriction on anesthetic management. Clinicians were thus free to use any combination of drugs they wished for general anesthesia and patients, although patients who had neuraxial anesthesia were excluded from analysis. There was no restriction on peripheral nerve blocks or postoperative analgesic management.

Monitoring, Measurements, and Data Collection

All data were obtained from the Cleveland Clinic Perioperative Health Documentation System and the Cleveland Clinic Electronic Medical Records. Demographic and morphometric characteristics were recorded, including age, sex, race, weight, height, and body mass index. We also recorded factors that might increase risk of pulmonary complications including American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status, preoperative comorbidities, and smoking history.

Types of surgery were characterized from International Classification of Diseases, Ninth Revision, codes using Clinical Classifications Software (Agency for Healthcare Research Quality, USA).

Intraoperative data and routine anesthetic variables recorded in electronic medical records include use of regional anesthesia, patient position, blood pressure, heart rate, Spo_2, expired carbon dioxide partial pressure, anesthetic agent, tidal volume, PEEP, ventilation frequency, minute volume, airway pressures, inspired oxygen fraction, transfused blood products, IV fluid types and volumes given during surgery, vasoactive medication needs, and duration of surgery.

Spo_2 was monitored continuously in the PACU by pulse oximetry. F_{IO_2} was estimated from the type of device and the oxygen flow rate as described in Supplemental Digital table 1 (http://links.lww.com/ALN/C884). Both were electronically recorded at approximately every 15 min. Unreasonable values such as Spo_2 less than 10%, F_{IO_2} less than 21, and F_{IO_2} greater than 100% were excluded.

Outcomes

Primary Outcome. The primary outcome was the time-weighted average Spo_2/F_{IO_2} ratio during the initial postoperative hour. We first calculated the Spo_2/F_{IO_2} ratio at each measurement time point during the initial postoperative hour, and then averaged all Spo_2/F_{IO_2} ratios weighted by measurement interval. Diagnosis of acute lung injury has traditionally been based on clinical findings and the Pao_2/F_{IO_2} ratio.[11,12] For example, a Pao_2/F_{IO_2} ratio 300 mmHg or less characterizes acute lung injury, and a ratio 200 or less is consistent with acute respiratory distress syndrome.[13] Few patients having orthopedic surgery require arterial cannulation. We thus substituted arterial oxygen saturation/F_{IO_2}, which provides good sensitivity and specificity for diagnosing lung injury. For example, Rice *et al.*[14] found that Spo_2/F_{IO_2} ratio correlates well with a simultaneously obtained Pao_2/F_{IO_2} ratio in patients with acute lung injury and acute respiratory distress syndrome. Furthermore, the Spo_2/F_{IO_2} ratio correlates well with the Pao_2/F_{IO_2} ratio and predicts respiratory failure in critical care patients,[14] pediatric patients,[15,16] and emergency department patients.[17]

Secondary Outcomes. We defined three *a priori* secondary outcomes: (1) time-weighted average Spo_2/F_{IO_2} ratio on surgical wards, normally recorded at 4-h intervals until discharge; (2) postoperative duration of hospitalization; and (3) a composite of postoperative pulmonary complications defined as the presence of at least one of the International Classification of Diseases, Tenth Revision, codes listed in Supplemental Digital table 2 (http://links.lww.com/ALN/C885) that were not present at admission. Pulmonary complications included respiratory complications, respiratory failure and distress, reintubations, pulmonary edema, and atelectasis.

Statistical Methods

Analysis was restricted to nonexcluded adults 18 yr or older who had an ASA Physical Status score I to III, were

scheduled for elective orthopedic surgery lasting at least 2 h, and had general anesthesia with endotracheal intubation and mechanical ventilation.

Baseline Variables Balancing. Exposures were controlled but not randomly assigned. We therefore controlled for observed potential confounding variables (table 1) using the inverse probability treatment weighting method for multiple groups. Missing values for confounding variables were imputed using the chained equation, and the single imputation dataset was used in all analysis. We first fitted a multinomial logistic regression model with four group settings as the outcome variable, and all observed confounding variables in table 1 as the independent variables without interactions. We then estimated propensity scores, which are the probability of receiving treatment, for each patient from the model. After weighting each patient by the inverse of the corresponding propensity score, the success of the confounding control was assessed by pairwise comparison on potentially confounding baseline characteristics using the absolute standardized difference, defined as the absolute difference in means or proportions divided by the pooled SD. Observations in all primary and secondary analyses were weighted by the inverse of the relevant propensity score. Any confounding variables with an absolute standardized difference greater than 0.1 would be adjusted for in all analyses.

Primary Analysis. The effect of tidal volume, PEEP, and their interaction on the time-weighted average Spo_2/Fio_2 ratio in PACU was assessed in a linear mixed model with surgeries from the same patients as repeated measures, weighted using the inverse probability of propensity score and adjusting for unbalanced confounders as appropriate. If the interaction effect was not significant ($P > 0.10$), treatment effect estimates would be summarized using the mean difference comparing tidal volume of 10 *versus* 6 ml/kg and PEEP of 8 *versus* 5 cm H_2O. If the interaction was significant, the effects of each intervention would be assessed within levels of the other intervention. With an overall alpha of 0.05 for the primary analysis, the significance criterion is 0.025 for each treatment effect without significant interaction (*i.e.*, 0.05/2, Bonferroni correction). As a sensitivity analysis for the primary outcome, we included patients who were excluded based on decisions from surgeons or anesthesiologists, and then assessed the treatment effect using the same statistical method.

Post Hoc *Analysis.* We did *post hoc* analysis to explore whether the treatment effects of tidal volume and PEEP were modified by age, body mass index, smoking status, obstructive sleep apnea, or type of anesthesia.

Secondary Analysis. Secondary outcomes were restricted to inpatients and again included propensity score weighting to balance all baseline and surgery variables in table 1. Time-weighted average Spo_2/Fio_2 ratio while patients were on surgical wards was assessed using the same method as for the time-weighted average Spo_2/Fio_2 ratio in the PACU. We assumed that the Fio_2 remain until updated in the medical record.

Length of hospital stay was log-transformed to meet the assumption of normality and then assessed in a linear mixed model. The ratio of geometric means with CI was reported as treatment effect. The odds ratio for pulmonary complications comparing different treatment groups was estimated from a logistic regression model after weighting by propensity score. With an overall alpha of 0.05 for all secondary analyses, the significance criterion is 0.0083 for each treatment effect without significant interaction (*i.e.*, 0.05/6, Bonferroni correction).

Exploratory Analysis. Exploratory outcomes are presented descriptively without statistical analyses.

Sample Size and Power Estimation. Based on literature[14,17,18] and a retrospective data analysis of Spo_2/Fio_2 levels, we assumed that the mean time-weighted average Spo_2/Fio_2 would be 330% with a SD of 100%. After accounting for three interim analyses and one final analysis, a maximum of 2,500 total patients (*i.e.*, 625 for each of the four groups for assessing each main effect) were needed to provide 90% power at the 0.025 significance level for detecting main effects of 15% or more in Spo_2/Fio_2 ratio for the two tidal volumes and two PEEP levels. We used gamma error spending function for both type I and type II errosr. The parameter was −4 for alpha spending function to control the overall type I error at 0.025 and was −1 for beta spending function to preserve the overall power at 0.9 for multiple looks at the data for interim analyses. The significance level for the first, second, third, and final look was 0.0008, 0.003, 0.008, and 0.025, respectively.

Power Re-estimation. The observed SD of Spo_2/Fio_2 ratio was 49%, with our current sample size of 2,860, we have a power of more than 0.9 to detect the predefined mean difference of 15% at the significance level of 0.025 for the two tidal volumes and two PEEP levels.

All the tests were two-tailed hypotheses testing. All the analyses are conducted in SAS 9.4 (SAS Institute Inc., USA) and R 4.0 (R foundation for statistical computing, Austria).

Results

A total of 3,481 orthopedic surgeries with general anesthesia received assigned treatments from September 3, 2018, through October 24, 2020, and met the inclusion and exclusion criteria (fig. 1). Enrollment ceased when the target sample size was obtained. The number of patients enrolled well exceeded our sample size estimate because it was unknown how many would be excluded for various reasons. A total of 621 surgeries were excluded by surgeons and anesthesiologists, leaving 2,860 treated patients. Specific reasons for exclusion are summarized in Supplemental Digital table 3 (http://links.lww.com/ALN/C886) by treatment group. Patient characteristics, surgery information, and treatment compliance by group are summarized

Table 1. Patient Characteristics and Surgery Information by Treatment

	Total (N = 2,860)	V_T = 6 PEEP = 5 (N = 727)	V_T = 6 PEEP = 8 (N = 635)	V_T = 10 PEEP = 5 (N = 799)	V_T = 10 PEEP = 8 (N = 699)	Absolute Standardized Difference before Inverse Probability Treatment Weighting*	Absolute Standardized Difference after Inverse Probability Treatment Weighting*
Compliance							
Mean tidal volume (ml/kg)	8.1 ± 1.8	6.5 ± 1.0	6.5 ± 1.0	9.6 ± 1.0	9.6 ± 0.9		
Mean PEEP (cm H_2O)	6.2 ± 1.5	5.1 ± 0.4	7.5 ± 1.1	5.0 ± 0.5	7.6 ± 1.1		
Baseline information							
Age (yr)	63 ± 14	64 ± 15	64 ± 14	62 ± 15	63 ± 14	0.092	0.015
Female (%)	1,504 (53)	360 (50)	326 (51)	442 (55)	376 (54)	0.116	0.006
Race (%)†						0.138	0.030
White	2,344 (83)	603 (84)	511 (81)	655 (83)	575 (84)		
Black	409 (15)	97 (14)	108 (17)	115 (15)	89 (13)		
Other	65 (2)	16 (2)	12 (2)	15 (2)	22 (3)		
Body mass index (kg/m²)‡	31 ± 7	30 ± 7	30 ± 7	31 ± 8	32 ± 7	0.223	0.032
ASA Physical Status (%)#						0.089	0.035
I	56 (2)	23 (3)	9 (1)	10 (1)	14 (2)		
II	505 (18)	122 (17)	106 (17)	157 (20)	120 (17)		
III	2071 (72)	519 (71)	460 (72)	572 (72)	520 (74)		
IV or V	22 8 (8)	63 (9)	60 (9)	60 (8)	45 (6)		
Charlson score	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	0.056	0.012
Smoking (%)§	1,460 (51)	369 (52)	346 (55)	404 (51)	341 (49)	0.123	0.010
COPD (%)	377 (13.2)	87 (12)	85 (13)	103 (13)	102 (15)	0.077	0.011
Obstructive sleep apnea (%)	694 (24)	161 (22)	144 (23)	202 (25)	187 (27)	0.107	0.013
Asthma (%)	483 (17)	119 (16)	105 (17)	157 (20)	102 (15)	0.135	0.009
Surgery information							
Surgery duration (min)	215 ± 82	214 ± 81	214 ± 85	218 ± 81	215 ± 84	0.052	0.022
Intraoperative use of rocuronium (mg)‖	70 [50, 90]	70 [50, 90]	70 [50, 90]	70 [50, 90]	65 [50, 90]	0.062	0.009
Crystalloids (l)	1.7 ± 0.8	1.7 ± 0.8	1.7 ± 0.8	1.8 ± 0.8	1.7 ± 0.8	0.075	0.010
Estimated blood loss (ml)	150 [50, 300]	150 [50, 300]	150 [50, 250]	200 [50, 300]	150 [50, 300]	0.067	0.014
Anesthesia type (%)#						0.172	0.017
General	1,450 (51)	340 (47)	319 (50)	442 (55)	349 (50)		
General + regional	1,410 (49)	387 (53)	316 (50)	357 (45)	350 (50)		
Transfusion (%)	223 (7.8)	48 (7)	50 (8)	75 (9)	50 (7)	0.103	0.023
Surgery type						0.048	0.019
Arthroplasty	1,522 (53)	391 (54)	331 (52)	419 (52)	381 (55)		
–Others	1,338 (47)	336 (46)	304 (48)	380 (48)	318 (45)		

Summary statistics are presented as N (%) for categorical variables, and mean ± SD or median [quartile 1, quartile 3] for continuous variables.

*Absolute standard difference is the maximum absolute standard difference of pairwise comparisons. Variables with absolute standardized difference greater than 0.1 are considered to be imbalanced. †42 missing data points; ‡8 missing data points; §40 missing data points; ‖56 missing data points. #Totals not equal to 100% due to rounding error.

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; PEEP, positive end-expiratory pressure; V_T, tidal volume.

in table 1 and Supplemental Digital table 4 (http://links.lww.com/ALN/C887). Additional intraoperative factors and type of surgery are summarized in Supplemental Digital table 5 (http://links.lww.com/ALN/C888) and Supplemental Digital table 6 (http://links.lww.com/ALN/C889), respectively. After applying propensity score weighting, all baseline and surgery factors in table 1 were well balanced. The maximum pairwise absolute standardized difference among four groups was less than 0.10, decreased substantially from before matching.

Primary Analysis Results. The interaction between tidal volume and PEEP was not significant (P = 0.565). We therefore assessed the weighted treatment effects of tidal volume and PEEP on time-weighted average Spo_2/Fio_2 ratio

independently. The time-weighted average of Spo_2/Fio_2 ratio was not different in patients assigned to high and low tidal volume, and for those assigned to high and low PEEP, as shown in tables 2 and 3 and in figure 2. We also summarized he minimum, maximum, and range of Spo_2/Fio_2 ratio per group (Supplemental Digital table 7, http://links.lww.com/ALN/C890). Neither tidal volume nor PEEP significantly altered the time-weighted average Spo_2/Fio_2 ratio in PACU. The estimated difference of time-weighted average Spo_2/Fio_2 ratio between tidal volume groups (6 *vs.* 10 ml/kg) was just 3.5% (97.5% CI, –0.4 to 7.3; $P = 0.042$, with <0.025 required for significance), and the estimated difference of time-weighted average Spo_2/Fio_2 ratio between PEEP groups (5 *vs.* 8 cm H_2O) was only –0.2% (97.5% CI, –4.0 to 3.6; $P = 0.906$; tables 2 and 3). In the sensitivity analysis, we included the 621 surgeries that were excluded based on decisions from a surgeon or anesthesiologist. The results were consistent with the primary analysis, with the estimated difference of time-weighted average Spo_2/Fio_2 ratio being 2.5% (97.5% CI, –1.0 to 6.0; $P = 0.117$) for tidal volume (6 *vs.* 10 ml/kg) and –1.2% (97.5% CI, –4.7 to 2.3; $P = 0.430$) for PEEP (5 *vs.* 8 cm H_2O). Of note, the percentage of patients who required supplemental oxygen on the ward and the duration was not different between groups. Neither was the length of PACU stay (Supplemental Digital table 8, http://links.lww.com/ALN/C891).

Post Hoc *Analysis Results.* Additionally, we performed heterogeneity tests to evaluate whether the treatment effects of tidal volume and PEEP were modified by age, body mass index, smoking status, obstructive sleep apnea, or type of anesthesia. As shown in figure 3, A and B, we did not find significant evidence of heterogeneity for any factors. Age was considered as a continuous factor, and also had no significant impact on modifying the treatment effect of tidal volume and PEEP (interaction $P = 0.838$ for tidal volume, and $P = 0.914$ for PEEP).

Secondary Analyses Results. Among 2,340 inpatient surgeries, we compared the secondary outcomes among patients assigned to various tidal volumes and PEEP levels. We did not find significant differences in any of these outcomes, either by tidal volume or PEEP. The estimated difference in ward Spo_2/Fio_2 ratio for patients assigned to tidal volumes of 6 and 10 ml/kg was just –2.3% (99.2% CI, –6.8 to 2.2; $P = 0.172$).

The difference for patients assigned to PEEP of 5 *versus* 8 cm H_2O was only 1.1% (99.2% CI, –3.4 to 5.6; $P = 0.522$). The median length of hospital stay was 3 days (quartile 1 = 2, quartile 3 = 5) in each treatment group. The overall incidence of pulmonary complications was 3.1%. The odds ratio was 1.00 (99.2% CI, 0.53 to 1.87; $P = 0.992$) comparing low to high tidal volume, and was 0.87 (99.2% CI, 0.46 to 1.63; $P = 0.553$) comparing low to high PEEP.

Exploratory Analysis. Exploratory outcomes are summarized in Supplemental Digital table 8 (http://links.lww.com/ALN/C891) by treatment. Based on a limited number of events, there were fewer deaths in patients assigned to tidal volume of 10 ml/kg and PEEP of 8 cm H_2O, presumably a spurious signal.

Discussion

In this factorial multiple crossover cluster trial of 2,860 adults having orthopedic surgery, intraoperative mechanical ventilation with tidal volumes of 6 *versus* 10 ml/kg of predicted body weight and PEEP of 5 *versus* 8 cm H_2O did not have any clinical meaningful or statistically significant effect on the Spo_2/Fio_2 ratio in the PACU. There was also no interaction between tidal volume and PEEP. Secondary outcomes also did not differ significantly, including the Spo_2/Fio_2 ratio on surgical wards, a composite of respiratory events, and duration of hospitalization.

Our primary outcome was the Spo_2/Fio_2 ratio, a validated measure of oxygenation that presumably detects more subtle lung injury than overt complications. In previous studies, for example, the ratio was shown to be a reliable marker of impaired oxygenation, lung injury, and predictor for early development of acute respiratory distress syndrome and hospital mortality.[14,17,18] As expected, the need for oxygen decreased over time after surgery. However, there were no statistically significant or clinically meaningful differences in the Spo_2/Fio_2 ratio either just after surgery or subsequently on surgical wards. Lack of difference is consistent with a previous study reporting that intraoperative tidal volumes of 6 and 10 ml/kg of predicted body weight do not cause atelectasis as assessed by computerized tomography.[19]

Even small amounts of PEEP undoubtedly improve oxygenation during mechanical ventilation,[20] but our results indicate that there is no persistent benefit (or harm), at least over the range of 5 *versus* 8 cm H_2O. Our findings are consistent with those of Yakaitis *et al.*,[21] who reported with only 15 patients that intraoperative Pao_2 improved with PEEP, but that improvement was not sustained in the PACU.[21]

The initial major trials of mechanical ventilation were conducted in critical care patients, and protective lung ventilation with low tidal volumes, a moderate level of PEEP, and recruitment maneuvers decreased lung injury and reduced morbidity and mortality. However, most ventilated critical care patients have serious pre-existing or acquired lung disease, requiring high levels of ventilatory support that often continues for days. Surgical patients differ in usually having good lung function and requiring mechanical ventilation for a matter of hours. It therefore seems unlikely that results of studies of mechanically ventilated intensive care patients will extrapolate to surgical patients.

The initial studies on intraoperative optimization of mechanical ventilation were inconclusive and inconsistent. For example, the Intraoperative Protective Ventilation trial

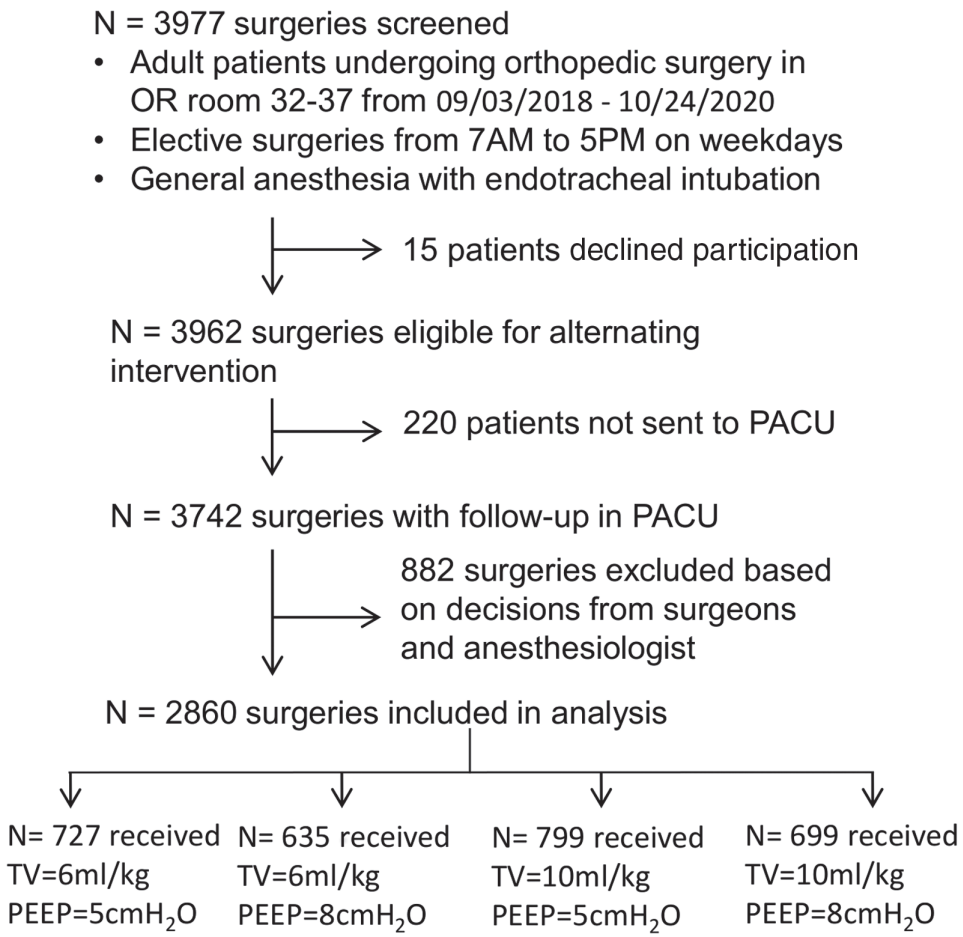

Fig. 1. Flow chart. PACU, postanesthesia care unit; PEEP, positive end-expiratory pressure.

(IMPROVE; N = 400 patients) compared protective ventilation with tidal volume of 6 to 8 ml/kg predicted body weight and PEEP of 6 to 8 cm H_2O, *versus* tidal volume of 10 to 12 ml/kg without PEEP.[22] In contrast to our findings, the researchers reported that protective lung ventilation decreased a composite of pulmonary complications (17% *vs.* 36%).[22] The results were somewhat fragile because sample size was limited. More importantly, the reference treatment was a tidal volume 10 ml/kg or greater without PEEP, which possibly caused overdistension and volume-related trauma. Better outcomes in the protective ventilation groups may therefore have partially resulted from deleterious nonstandard ventilation in the reference group.

Two recent randomized trials support our findings, each demonstrating similar outcomes with various intraoperative ventilation strategies. For example, the PROVHILO trial (N = 900) used a tidal volume of 8 ml of predicted body weight in all patients, and compared 2 cm H_2O PEEP without recruitment maneuvers to 12 cm H_2O PEEP with recruitment maneuvers.[23] Despite the high PEEP level, there were no differences in pulmonary complications—as in our patients. A recent trial by Karalapillai *et al.* (N = 1,236) compared 6 *versus* 10 ml predicted body weight of tidal volume. All patients had PEEP set at 5 cm H_2O without recruitment maneuvers. The incidence of pulmonary complications was similar in each group, which is consistent with our findings, although we tested different tidal volumes and PEEP levels, and allowed recruitment maneuvers.[24]

The incidence of complications in our patients was generally lower than reported previously, presumably because our patients all had orthopedic rather than abdominal surgery. Since oxygenation was comparable with each combination of tidal volume and PEEP, as was the incidence of complications, it is unsurprising that the duration of hospitalization was also similar across our groups.

Limitations

Our trial was not randomized, with allocation instead based on sequential weeks. It seems highly unlikely that surgical

Table 2. Treatment Effect of Tidal Volume on Primary and Secondary Outcomes

	V_T = 6 ml/kg	V_T = 10 ml/kg	Effect Estimate	*P* Value*
Primary outcome	(N = 1,362)	(N = 1,498)	Mean difference (97.5% CI)	
Time-weighted average Spo_2/Fio_2 in PACU†	355 ± 46	350 ± 47	3.5 (–0.4 to 7.3)	0.042
Secondary outcomes	(N = 1,112)	(N = 1,228)	Mean difference (99.2% CI)	
Time-weighted average Spo_2/Fio_2 in ward†	428 ± 42[36]	430 ± 41[60]	–2.3 (–6.8 to 2.2)	0.172
			Odds ratio (99.2% CI)	
Pulmonary complications‡	34 (3.1%)	39 (3.2%)	1.00 (0.53 to 1.87)	0.992
			Mean ratio (99.2%)	
Length of hospital stay§	3 [2, 5]	3 [2, 5]	1.03 (0.97 to 1.10)	0.154

Superscripts of summary statistics represent the number of missing.

*Significant if $P < 0.025$ for the primary outcome and $P < 0.0083$ for all secondary outcomes. †The mean difference was estimated from a linear mixed regression model with surgeries from the same patient as repeated measures, after propensity score weighting. ‡The odds ratio was estimated from a logistic regression model after propensity score weighting. §The ratio of geometric means was estimated from a linear mixed model for log-transformed length of hospital stay, with surgeries from same patient as repeated measures, after propensity score weighting.

Fio_2, fraction of inspired oxygen; PACU, postanesthesia care unit; PEEP, positive end-expiratory pressure; Spo_2, oxygen saturation measured by pulse oximetry; V_T, tidal volume.

Table 3. Treatment Effect of Positive End-expiratory Pressure on Primary and Secondary Outcomes

	PEEP = 5 cm H_2O	PEEP = 8 cm H_2O	Effect estimate	*P* Value*
Primary outcome	(N = 1,526)	(N = 1,334)	Mean difference (97.5% CI)	
Time-weighted average Spo_2/FiO_2 in PACU†	353 ± 46	352 ± 47	–0.2 (–4.0 to 3.6)	0.906
Secondary outcomes	(N = 1,250)	(N = 1,090)	Mean difference (99.2% CI)	
Time-weighted average Spo_2/Fio_2 in ward†	429 ± 41[49]	429 ± 41[47]	1.1 (–3.4 to 5.6)	0.522
			Odds ratio (99.2% CI)	
Pulmonary complications‡	36 (2.9%)	37 (3.4%)	0.87 (0.46 to 1.63)	0.553
			Mean ratio (99.2%)	
Length of hospital stay§	3 [2, 5]	3 [2, 5]	0.99 (0.94 to 1.05)	0.794

Superscripts of summary statistics represent the number of missing.

*Significant if $P < 0.025$ for the primary outcome and $P < 0.0083$ for all secondary outcomes. †The mean difference was estimated from a linear mixed regression model with surgeries from the same patient as repeated measures, after propensity score weighting. ‡The odds ratio was estimated from a logistic regression model after propensity score weighting. §The ratio of geometric means was estimated from a linear mixed model for log-transformed length of hospital stay, with surgeries from same patient as repeated measures, after propensity score weighting.

Fio_2, fraction of inspired oxygen; PACU, postanesthesia care unit; PEEP, positive end-expiratory pressure; Spo_2, oxygen saturation measured by pulse oximetry.

scheduling over a period of years was based on tidal volume and PEEP allocations. However, previous awareness of the ventilation allocation could have led to biased exclusion of otherwise eligible patients. In fact, though, the characteristics of patients across groups were well balanced after propensity score and inverse probability treatment weighting. Inverse probability treatment weighting helps to create a synthetic sample in which the distribution of measured baseline characteristics would be independent of treatment assignment. Furthermore, we performed a sensitivity analysis that included all patients, whether or not allocated to assigned treatments; the results were consistent with the primary analysis, suggesting no substantive selection bias or confounding.

Because of our cluster design, there were slight imbalances in the number of patients in each group because fewer patients had surgery during holiday weeks. However, differences in allocation were presumably unrelated to exposures and unlikely to influence the results. Pulmonary complications were abstracted from the Cleveland Clinic registry and billing system rather than individual evaluation of patients. It is therefore likely misclassification of outcome/exposures/covariates due to International Classification of Diseases, Tenth Revision, coding, or we missed some, presumably less serious, complications. Again, there is no reason to expect detection bias.

As usual for cluster trials, the current study was not blinded, which could have contributed to measurement bias. However, our outcomes were abstracted from electronic records and seem unlikely to have been influenced by treatment allocation. There are, of course, many other factors that can cause hypoxemia after surgery, including opioids, residual muscle relaxants, fluids, and pain—factors we did not adjust for. However, there is no reason to believe that the contribution of any of these factors differed by group.

Conclusions

Among adults having orthopedic surgery, intraoperative ventilation with 6 *versus* 10 ml/kg tidal volume and PEEP of 5 *versus* 8 ml cm H_2O did not significantly affect the $Spo_2/$

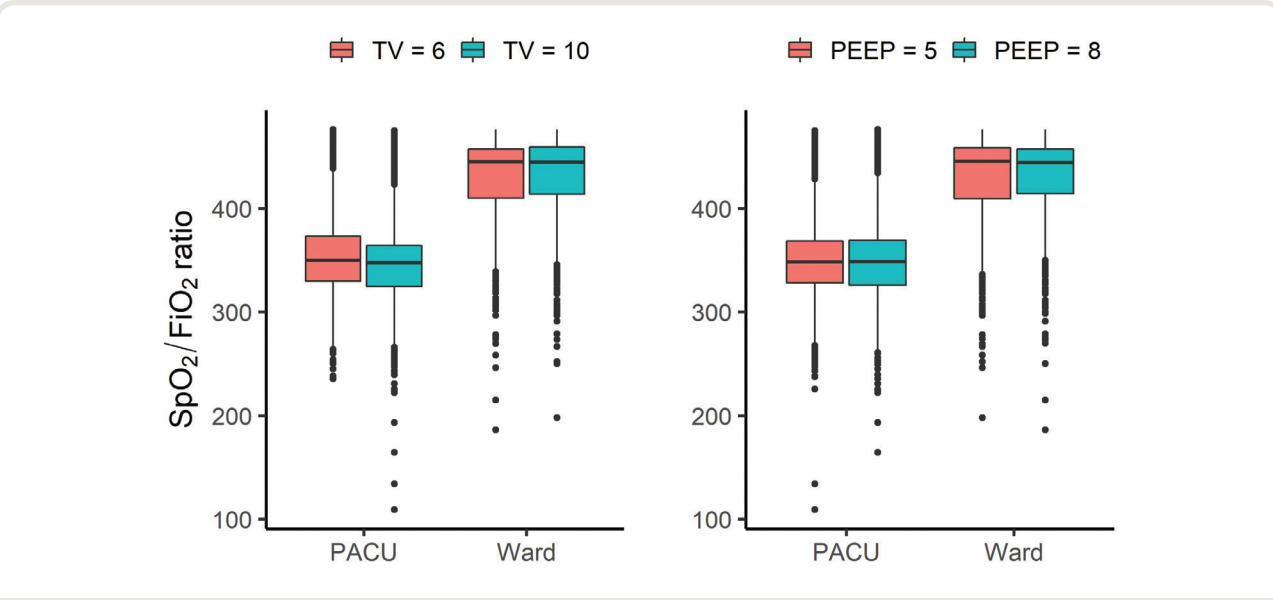

Fig. 2. *Box plot* of time-weighted average of oxygen saturation measured by pulse oximetry (Spo_2)/fractional inspired oxygen tension (Fio_2) ratio in postanesthesia care unit (PACU) and ward by tidal volume and positive end-expiratory pressure (PEEP).

Fio_2 ratio during the initial hour of recovery. Furthermore, the Spo_2/Fio_2 ratio on surgical wards was similar, as was the incidence of pulmonary complications and the duration of hospitalization. Our results suggest that combination of tidal volumes between 6 and 10 ml/kg and PEEP between 5 *versus* 8 ml cm H_2O can be used safely for orthopedic surgery.

Research Support

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

Competing Interests

The authors declare no competing interests.

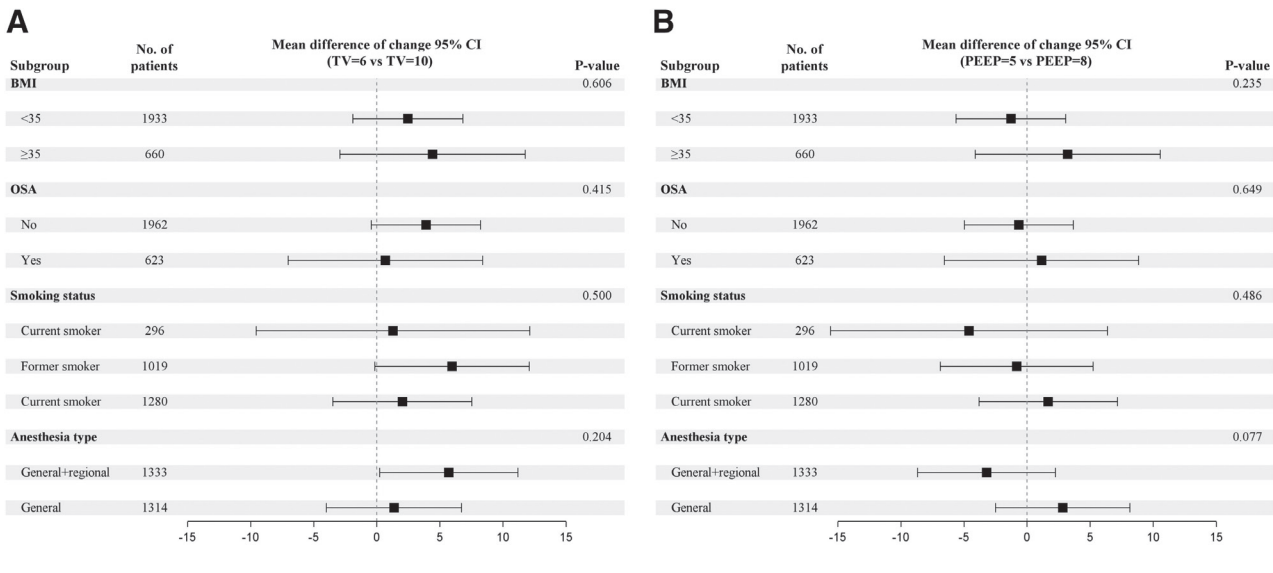

Fig. 3. *A*, Subgroup analysis on tidal volume. *B*, Subgroup analysis on positive end-expiratory pressure (PEEP). OSA, obstructive sleep apnea.

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Supplemental Digital Content

Supplemental Digital Content 1, Study protocol, http://links.lww.com/ALN/C883
Supplemental Digital Table 1, Estimation of FIO2, the type of device and the oxygen flow rate, http://links.lww.com/ALN/C884
Supplemental Digital Table 2, Composite of Pulmonary complications, http://links.lww.com/ALN/C885
Supplemental Digital Table 3, Reasons of surgeries excluded based on decisions from surgeons and anesthesiologist, http://links.lww.com/ALN/C886
Supplemental Digital Table 4, Compliance of treatment, http://links.lww.com/ALN/C887
Supplemental Digital Table 5, Summary of additional intraoperative factors, http://links.lww.com/ALN/C888
Supplemental Digital Table 6, Detailed surgery type, http://links.lww.com/ALN/C889
Supplemental Digital Table 7, Quantification of SpO2/FiO2 in PACU by treatment, http://links.lww.com/ALN/C890
Supplemental Digital Table 8, Summary of exploratory outcomes, http://links.lww.com/ALN/C891

References

1. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, Fu R, Azad T, Chao TE, Berry WR, Gawande AA: Estimate of the global volume of surgery in 2012: An assessment supporting improved health outcomes. Lancet 2015; 385(suppl 2):S11
2. Cai H, Gong H, Zhang L, Wang Y, Tian Y: Effect of low tidal volume ventilation on atelectasis in patients during general anesthesia: A computed tomographic scan. J Clin Anesth 2007; 19:125–9
3. LAS VEGAS Investigators: Epidemiology, practice of ventilation and outcome for patients at increased risk of postoperative pulmonary complications: LAS VEGAS - An observational study in 29 countries. Eur J Anaesthesiol 2017; 34:492–507
4. Canet J, Sabaté S, Mazo V, Gallart L, de Abreu MG, Belda J, Langeron O, Hoeft A, Pelosi P; PERISCOPE Group: Development and validation of a score to predict postoperative respiratory failure in a multicentre European cohort: A prospective, observational study. Eur J Anaesthesiol 2015; 32:458–70
5. Sun Z, Sessler DI, Dalton JE, Devereaux PJ, Shahinyan A, Naylor AJ, Hutcherson MT, Finnegan PS, Tandon V, Darvish-Kazem S, Chugh S, Alzayer H, Kurz A: Postoperative hypoxemia is common and persistent: A prospective blinded observational study. Anesth Analg 2015; 121:709–15
6. Rothen HU, Sporre B, Engberg G, Wegenius G, Hedenstierna G: Re-expansion of atelectasis during general anaesthesia: A computed tomography study. Br J Anaesth 1993; 71:788–95
7. Serpa Neto A, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, Pasqualucci Mde O, Damasceno MC, Schultz MJ: Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: A meta-analysis. JAMA 2012; 308:1651–9
8. Luecke T, Pelosi P: Clinical review: Positive end-expiratory pressure and cardiac output. Crit Care 2005; 9:607–21
9. Bluth T, Teichmann R, Kiss T, Bobek I, Canet J, Cinnella G, De Baerdemaeker L, Gregoretti C, Hedenstierna G, Hemmes SN, Hiesmayr M, Hollmann MW, Jaber S, Laffey JG, Licker MJ, Markstaller K, Matot I, Müller G, Mills GH, Mulier JP, Putensen C, Rossaint R, Schmitt J, Senturk M, Serpa Neto A, Severgnini P, Sprung J, Vidal Melo MF, Wrigge H, Schultz MJ, Pelosi P, Gama de Abreu M; PROBESE Investigators; PROtective VEntilation Network (PROVEnet); Clinical Trial Network of the European Society of Anaesthesiology (ESA): Protective intraoperative ventilation with higher *versus* lower levels of positive end-expiratory pressure in obese patients (PROBESE): Study protocol for a randomized controlled trial. Trials 2017; 18:202
10. Valente Barbas CS: Lung recruitment maneuvers in acute respiratory distress syndrome and facilitating resolution. Crit Care Med 2003; 31(4 suppl):S265–71
11. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149(3 pt 1):818–24
12. Douville NJ, Jewell ES, Duggal N, Blank R, Kheterpal S, Engoren MC, Mathis MR: Association of intraoperative ventilator management with postoperative oxygenation, pulmonary complications, and mortality. Anesth Analg 2020; 130:165–75
13. Villar J, Blanco J, del Campo R, Andaluz-Ojeda D, Díaz-Domínguez FJ, Muriel A, Córcoles V, Suárez-Sipmann F, Tarancón C, González-Higueras E, López J, Blanch L, Pérez-Méndez L, Fernández RL, Kacmarek RM; Spanish Initiative for Epidemiology, Stratification & Therapies for ARDS (SIESTA) Network: Assessment

of PaO_2/FiO_2 for stratification of patients with moderate and severe acute respiratory distress syndrome. BMJ Open 2015; 5:e006812
14. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB; National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Network: Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest 2007; 132:410–7
15. Ray S, Rogers L, Pagel C, Raman S, Peters MJ, Ramnarayan P: PaO2/FIO2 ratio derived from the SpO2/FIO2 ratio to improve mortality prediction using the Pediatric Index of Mortality-3 score in transported intensive care admissions. Pediatr Crit Care Med 2017; 18:e131–6
16. Khemani RG, Patel NR, Bart RD 3rd, Newth CJL: Comparison of the pulse oximetric saturation/fraction of inspired oxygen ratio and the PaO2/fraction of inspired oxygen ratio in children. Chest 2009; 135:662–8
17. Festic E, Bansal V, Kor DJ, Gajic O; US Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators (USCIITG–LIPS): SpO2/FiO2 ratio on hospital admission is an indicator of early acute respiratory distress syndrome development among patients at risk. J Intensive Care Med 2015; 30:209–16
18. Pandharipande PP, Shintani AK, Hagerman HE, St Jacques PJ, Rice TW, Sanders NW, Ware LB, Bernard GR, Ely EW: Derivation and validation of Spo2/Fio2 ratio to impute for Pao2/Fio2 ratio in the respiratory component of the Sequential Organ Failure Assessment score. Crit Care Med 2009; 37:1317–21
19. Cai H, Gong H, Zhang L, Wang Y, Tian Y: Effect of low tidal volume ventilation on atelectasis in patients during general anesthesia: A computed tomographic scan. J Clin Anesth 2007; 19:125–9
20. Kim JY, Shin CS, Kim HS, Jung WS, Kwak HJ: Positive end-expiratory pressure in pressure-controlled ventilation improves ventilatory and oxygenation parameters during laparoscopic cholecystectomy. Surg Endosc 2010; 24:1099–103
21. Yakaitis RW, Thomas JD, Mahaffey JE: Effects of intraoperative PEEP on postoperative arterial oxygenation. Anesth Analg 1975; 54:427–32
22. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B, Jaber S; IMPROVE Study Group: A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med 2013; 369:428–37
23. PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology; Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ: High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): A multicentre randomised controlled trial. Lancet 2014; 384:495–503
24. Karalapillai D, Weinberg L, Peyton P, Ellard L, Hu R, Pearce B, Tan CO, Story D, O'Donnell M, Hamilton P, Oughton C, Galtieri J, Wilson A, Serpa Neto A, Eastwood G, Bellomo R, Jones DA: Effect of intraoperative low tidal volume vs conventional tidal volume on postoperative pulmonary complications in patients undergoing major surgery: A randomized clinical trial. JAMA 2020; 324:848–58

Appendix

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ANESTHESIOLOGY

Sedation *versus* General Anesthesia for Tracheal Intubation in Children with Difficult Airways: A Cohort Study from the Pediatric Difficult Intubation Registry

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Scan for CME exam

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The incidence of difficult intubation is about 1.5% in children
- In most cases of anticipated difficult intubation, general anesthesia is used rather than sedation

What This Article Tells Us That Is New

- In a retrospective study using the Pediatric Difficult Airway Registry, intubation under sedation had a similar rate of first-attempt success compared to intubation with general anesthesia
- Nevertheless, 28% of the sedation cases needed to be converted to general anesthesia to complete tracheal intubation, and 1% in the general anesthesia group had failed intubations
- Complications overall were similar between the groups, and the rate of severe complications was low

ABSTRACT

Background: Sedated and awake tracheal intubation approaches are considered safest in adults with difficult airways, but little is known about the outcomes of sedated intubations in children. The primary aim of this study was to compare the first-attempt success rate of tracheal intubation during sedated tracheal intubation *versus* tracheal intubation under general anesthesia. The hypothesis was that sedated intubation would be associated with a lower first-attempt success rate and more complications than general anesthesia.

Methods: This study used data from an international observational registry, the Pediatric Difficult Intubation Registry, which prospectively collects data about tracheal intubation in children with difficult airways. The use of sedation *versus* general anesthesia for tracheal intubation were compared. The primary outcome was the first-attempt success of tracheal intubation. Secondary outcomes included the number of intubation attempts and nonsevere and severe complications. Propensity score matching was used with a matching ratio up to 1:15 to reduce bias due to measured confounders.

Results: Between 2017 and 2020, 34 hospitals submitted 1,839 anticipated difficult airway cases that met inclusion criteria for the study. Of these, 75 patients received sedation, and 1,764 patients received general anesthesia. Propensity score matching resulted in 58 patients in the sedation group and 522 patients in the general anesthesia group. The rate of first-attempt success of tracheal intubation was 28 of 58 (48.3%) in the sedation group and 250 of 522 (47.9%) in the general anesthesia group (odds ratio, 1.06; 95% CI, 0.60 to 1.87; $P = 0.846$). The median number of intubations attempts was 2 (interquartile range, 1 to 3) in the sedation group and 2 (interquartile range, 1, 2) in the general anesthesia group. The general anesthesia group had 6 of 522 (1.1%) intubation failures *versus* 0 of 58 in the sedation group. However, 16 of 58 (27.6%) sedation cases had to be converted to general anesthesia for successful tracheal intubation. Complications were similar between the groups, and the rate of severe complications was low.

Conclusions: Sedation and general anesthesia had a similar rate of first-attempt success of tracheal intubation in children with difficult airways; however, 27.6% of the sedation cases needed to be converted to general anesthesia to complete tracheal intubation. Complications overall were similar between the groups, and the rate of severe complications was low.

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This article has been selected for the Anesthesiology CME Program (www.asahq.org/JCME2022OCT). Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue. This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 384. This article has an audio podcast. This article has a visual abstract available in the online version. An abstract with initial analysis titled "Sedation *versus* General Anesthesia in Children with Difficult Airway" was presented at the International Anesthesia Research Society annual meeting (virtual), March 17 to 20, 2022.

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The incidence of difficult mask ventilation is approximately 6.6%, and the incidence of difficult tracheal intubation is close to 1.5% in the general pediatric population.[1] Difficult tracheal intubation has been estimated to be three times higher in neonates in a recent European multicenter international study.[2] Difficult intubation can be associated with significant complications including hypoxemia, airway trauma, cardiac arrhythmias, and cardiac arrest.[2,3] Anesthetic strategies to perform tracheal intubation in children with an anticipated difficult airway may differ depending on patient factors, institutional resources, and clinician experience. General anesthesia with volatile or intravenous agents remains the most common approach to perform tracheal intubation in children with difficult airways. However, some anesthesia clinicians prefer intravenous sedation for tracheal intubation.[3] Proponents of sedated intubation tout the maintenance of spontaneous ventilation and the ability to emerge the patient if intubation is impossible as advantages over intubation under general anesthesia. Previous data suggest that controlled ventilation with or without neuromuscular blockade is associated with fewer complications than spontaneous ventilation. A sensitivity analysis in that study suggested that the increased complications were related to airway reactivity during tracheal intubation, suggesting that the anesthetic depth may play a role in complications.[4]

Because sedation for airway management is not a common practice, there remains a knowledge gap about its efficacy and related complications in patients with difficult airways. It is unlikely that any single center would have enough sedated cases to perform a comparative analysis. The Pediatric Difficult Airway (PeDI) Registry is an international registry that prospectively collects data from pediatric patients with difficult airways.[3,5,6] Our study aimed to use data in the Pediatric Difficult Airway Registry to determine whether sedation for tracheal intubation in children with difficult tracheal intubation is associated with a lower first-attempt success rate and more complications than general anesthesia. We hypothesized that sedated intubation would be associated with lower first-attempt success and more complications than general anesthesia. Our study primary outcome was the first-attempt success rate of tracheal intubation.

Materials and Methods

The Pediatric Difficult Airway Registry

This observational study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[7] The Pediatric Difficult Intubation Registry is an international, multicenter, web-based registry created in 2012 by a special interest group of the Society for Pediatric Anesthesia. The Pediatric Difficult Airway Registry collaborative aims to improve the quality of airway management in children with difficult intubation.[3] The registry collects observational data prospectively from 34 international hospitals. The registry collects patient demographics, physical assessment, airway management techniques including devices, pharmacologic and ventilation strategies, and relevant outcomes from children under 18 yr old cared for by anesthesiologists in different hospital locations such as the operating room, the intensive care unit, and the emergency department. Each center was granted institutional review board approval for standardized data collection with the requirement for written informed consent waived. Each participant hospital enters data *via* a secure, password-protected web-based data entry portal using a centralized Research Electronic Data Capture. Data compliance is ensured by a pediatric anesthesiology attending physician identified as project coordinator at each center, and compliance and data accuracy are audited monthly at the central level, by the data-coordinating center, The Children's Hospital of Philadelphia. Pediatric Difficult Airway Registry data from a similar time period has been previously reported in a study analyzing standard *versus* nonstandard videolaryngoscopy blades. That study only examined patients in whom videolaryngoscopy was used, while this current study examines all patients enrolled in the registry.[6]

Selection of Patients and Variables

Patients included in the study were children under 18 yr old in whom tracheal intubation is difficult as defined by at least one of the following criteria:

1. Children with difficult laryngeal exposure as directly assessed by the attending anesthesiologist with direct laryngoscopy (Cormak and Lehane Classification of 3 or higher).[8]
2. Children in whom direct laryngoscopy was physically impossible because of anatomical reasons (*e.g.*, severely limited mouth opening).
3. Children who failed direct laryngoscopy within the preceding 6 months.
4. Children in whom the attending anesthesiologist deferred direct laryngoscopy because of a low chance of success or a perceived increased risk of harm.

Intubation encounters from consecutive patients in the registry that occurred from September 2017 to December 2020 were included in the study. Patients with missing demographic data, type of planned anesthesia technique, or reporting awake or no anesthesia

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technique planned and patients with unanticipated difficult airway were excluded.

Definitions

Planned anesthesia technique was defined as the technique that the anesthesia provider initially attempted to establish successful tracheal intubation. Final anesthesia technique was the anesthesia modality used to achieve successful tracheal intubation. Anesthesia technique refers to the approach used by the anesthesia provider to obtain appropriate conditions for tracheal intubation, including sedation, general anesthesia, and awake or no anesthesia. The technique was determined by the anesthesia attending physician. Failed intubation was defined as the inability to intubate the trachea despite multiple intubation attempts. All decisions on how to manage the airway were made by the attending anesthesiologist and were not dictated by the study design. The groups were categorized based on the planned anesthesia technique between sedation and general anesthesia.

We defined complications as nonsevere and severe using modified operational definitions from the National Emergency Airway Registry for Children (NEAR4KIDS).[9,10] Nonsevere complications were hypoxemia (defined as an oxygen saturation of less than 90% for more than 60 s or a 10% decrease in baseline saturation for more than 60 s), minor airway trauma (lips or dental), esophageal intubation with immediate recognition, laryngospasm, bronchospasm, pharyngeal bleed, epistaxis, arrhythmia, and emesis without aspiration. Severe complications included cardiac arrest, severe airway trauma (glottis, subglottis, palatoglossal arch, intraoral), esophageal intubation with delayed recognition, death, aspiration, and pneumothorax.

Propensity Score Matching

We used the nearest-neighbor matching method with the logit of propensity scores as the distance measure to balance baseline characteristics and avoid selection bias between patients who received general anesthesia and those who were sedated. Propensity scores estimated from the logistic regression model represent individual probabilities for being in the sedation group. Twenty-one baseline variables including patients' demographics (*i.e.*, age, weight, sex, history of prematurity) and medical characteristics data (*i.e.*, American Society of Anesthesiologists [ASA] status, entry criteria, physical exam findings, diagnosed syndrome, first-attempt provider's role, anticipated difficulties, intubating location), together with the site variable, were assessed for matching. Correlations between matching variables were assessed using variance inflation factor and Spearman correlation coefficient matrix: weight, entry criteria 4 (deferred direct laryngoscopy because of a low chance of success and a perceived increased risk of harm), and physical exam finding (yes/no) were not included for matching because they were highly correlated with age, other entry criteria, types of physical exam findings, respectively (but were included for pre- and postmatching balance assessment). To assess whether the association between age and use of sedation was linear, we divided age into 10 equal-length intervals and plotted log odds of use of sedation over the intervals. The association was found to be nonlinear, and we therefore grouped the patients into five age groups according to developmental classification (*i.e.*, neonates, less than 1 month old; infants, 1 month to 1 yr old; toddlers, 1 to 5 yr old; school-aged, 5 to 13 yr old; and teenagers, 13 to 18 yr old). All variables were included as categorical variables for matching. Type of ventilation was considered a posttreatment variable related to the anesthetic technique and was not included for matching. We used R package MatchIt[11] to implement the matching. Before matching, the ratio of the number of patients managed with sedation to general anesthesia was 75:1,764 (~1:23), so we allowed 15 matching iterations to reach the matching ratios from 1 to 1 to 1 to 15 (*i.e.*, up to 15 general anesthesia patients can be matched to each sedated patient). The matching algorithm allowed sedated patients with highest propensity score (*i.e.*, presumably the hardest to find a match for in the general anesthesia group) to be matched first for each iteration. Each iteration paired the general anesthesia patients with the highest digit match to the sedated patient. Once the general anesthesia patient was matched, it was not reconsidered. We also set the caliper width to be 0.1 of the SD of the logit of the propensity score to only allow patients within this distance to be paired. If no general anesthesia patient was found to be within the caliper width of a sedated patient, that sedated patient was left unmatched. On the other hand, if a general anesthesia patient could not be matched to a sedated patient within the specified caliper width within 15 iterations, that general anesthesia patient was left unmatched. To assess the effectiveness of matching, the balance in baseline characteristics between the treatment groups was assessed using absolute standardized mean difference (Cobalt: Covariate Balance Tables and Plots, R package version 4.3.0; https://CRAN.R-project.org/package=cobalt) before and after matching, with the absolute value greater than 0.1 considered imbalanced.

Study Endpoints

The primary outcome was first-attempt success of tracheal intubation. A tracheal intubation attempt was defined as the act of inserting an airway device into the pharynx or naris with the intent to perform tracheal intubation.

Secondary outcomes included number of intubation attempts, severe and nonsevere complications throughout all attempts, and complications during the first attempt of tracheal intubation. We also assessed devices used during first attempt to intubate the trachea and technical

difficulties encountered between the sedation and the general anesthesia groups.

Statistical Analysis

Descriptive analyses were conducted by treatment groups (sedation *vs*. general anesthesia). The frequencies and percentages were presented for categorical variables, while median and interquartile ranges were used for numeric variables. To account for the clustering within site and within matching pairs, we used marginal models (*i.e.*, generalized estimating equation) with exchangeable working correlation structure to establish the association between treatment (sedation *vs*. general anesthesia) and outcomes. Interaction of site and matching pair was included as the cluster variable. Binomial distribution and logit link function were specified for binary outcomes (*i.e.*, first-attempt success, failed intubation, and complications), and odds ratios and 95% CIs were computed where the model converged. For rare outcomes, defined as incidence being less than 5% in total, Gaussian distribution and identity link function were also specified, and absolute risk difference and 95% CIs were computed as a *post hoc* sensitivity analysis.[12] Incidence rate ratios with 95% CI (instead of odds ratios) were used to establish relations between treatment and count outcomes (*i.e.*, number of attempts) when a Poisson distribution and a log-link function were specified in the generalized estimating equation model. Generalized estimating equation models incorporating matching weights were conducted for matched data, and baseline characteristics found to be imbalanced after matching were included as covariates in postmatching models (except site since it was included as cluster variable). To assess difference in devices used between treatment groups, use of supplemental oxygenation, and use of nasal devices, a chi-square test or Fisher's exact test was used, as appropriate. Since these variables were decided after the anesthesia technique was chosen (posttreatment variable), the analysis was conducted for prematched data only. No *a priori* power calculations were conducted. The analysis was conducted using Statistical Analysis Software version 9.4 (SAS Institute Inc, USA) and R software version 3.5.1 (R Core Team, Vienna, Austria), and propensity score matching was performed with the MatchIt package.[11] A two-tailed test was conducted for all hypothesis testing, and a *P* value less than 0.05 was considered statistically significant.

Results

We collected data from difficult airway encounters in 34 hospitals between January 2017 and December 2020. We assessed 2,649 patients, of which 1,839 patients with anticipated difficult airway met the inclusion criteria for the study (fig. 1). Of those 1,839 patients, 75 received sedation, and 1,764 patients received general anesthesia for tracheal intubation. Compared to the general anesthesia group, patients receiving sedation included a higher percentage of teenagers, ASA status E, anticipated difficult mask ventilation, and difficult intubation, and a higher percentage of them were intubated in the intensive care unit (table 1). The matching resulted in 58 sedated patients matched to at least one general anesthesia patient, with a total number of 522 general anesthesia patients being matched. Each sedated patient was matched to a median number of 10 (interquartile range, 2 to 15) general anesthesia patients. Among 58 sedated patients, 21 (36.2%) were matched to 1 to 5 general anesthesia patients, 13 (22.4%) were matched to 6 to 14 general anesthesia patients, and 24 (41.4%) were matched to 15 general anesthesia patients. Matched sedation patients were more likely to be older (toddlers, school-aged, and teenagers), heavier, ASA classification I or II, less likely to have a diagnosed syndrome or airway-related diagnosis, and more frequently intubated in the operating room than the intensive care unit compared to unmatched sedation patients. Additionally, there were 34 sites in the prematched data set and 16 sites left after matching. Postmatching absolute standardized mean differences were greater than 0.1 for type of provider (*i.e.*, trainee, attending) during the first intubation attempt (absolute standardized mean difference = 0.104), and this variable was added as a covariate in postmatching generalized estimating equation models (fig. 2). The patient characteristics and case data are presented in table 1.

The rate of first-attempt success of tracheal intubation after applying propensity score matching was 28 of 58 (48.3%) in patients who had sedation and 250 of 522 (47.9%) in patients with general anesthesia (odds ratio, 1.06; 95% CI, 0.60 to 1.87; $P = 0.846$). The number of attempts was not significantly different between the groups with a calculated incidence rate ratio of 0.86 (95% CI, 0.58 to 1.28; $P = 0.460$; table 2). No intubation failures were reported in the sedation group, while 6 of 522 (1.1%) patients in the general anesthesia group had intubation failure. In 2 patients, the planned procedure was performed with a supraglottic airway, while 4 patients were awakened and their planned procedures were canceled. The rate of conversion from sedation to general anesthesia was 16 of 58 (27.6%; 18 of 75 [24.0%] in prematched data); all of these patients were eventually intubated using general anesthesia with no failed intubations reported.

The complications encountered and comparisons between the sedation and general anesthesia groups before and after propensity score matching are presented in table 2. The complications overall were similar between the sedation group and the general anesthesia group: 15 of 58 (25.9%) *versus* 90 of 521 (17.3%; odds ratio, 1.41; 95% CI, 0.72 to 2.76; $P = 0.323$). Nonsevere complications altogether in the sedation group and the general anesthesia group were not significantly different: 14 of 58 (24.1%) *versus* 90 of 521 (17.3%; odds ratio, 1.28; 95% CI, 0.65 to 2.55; $P = 0.478$). The most common nonsevere complication

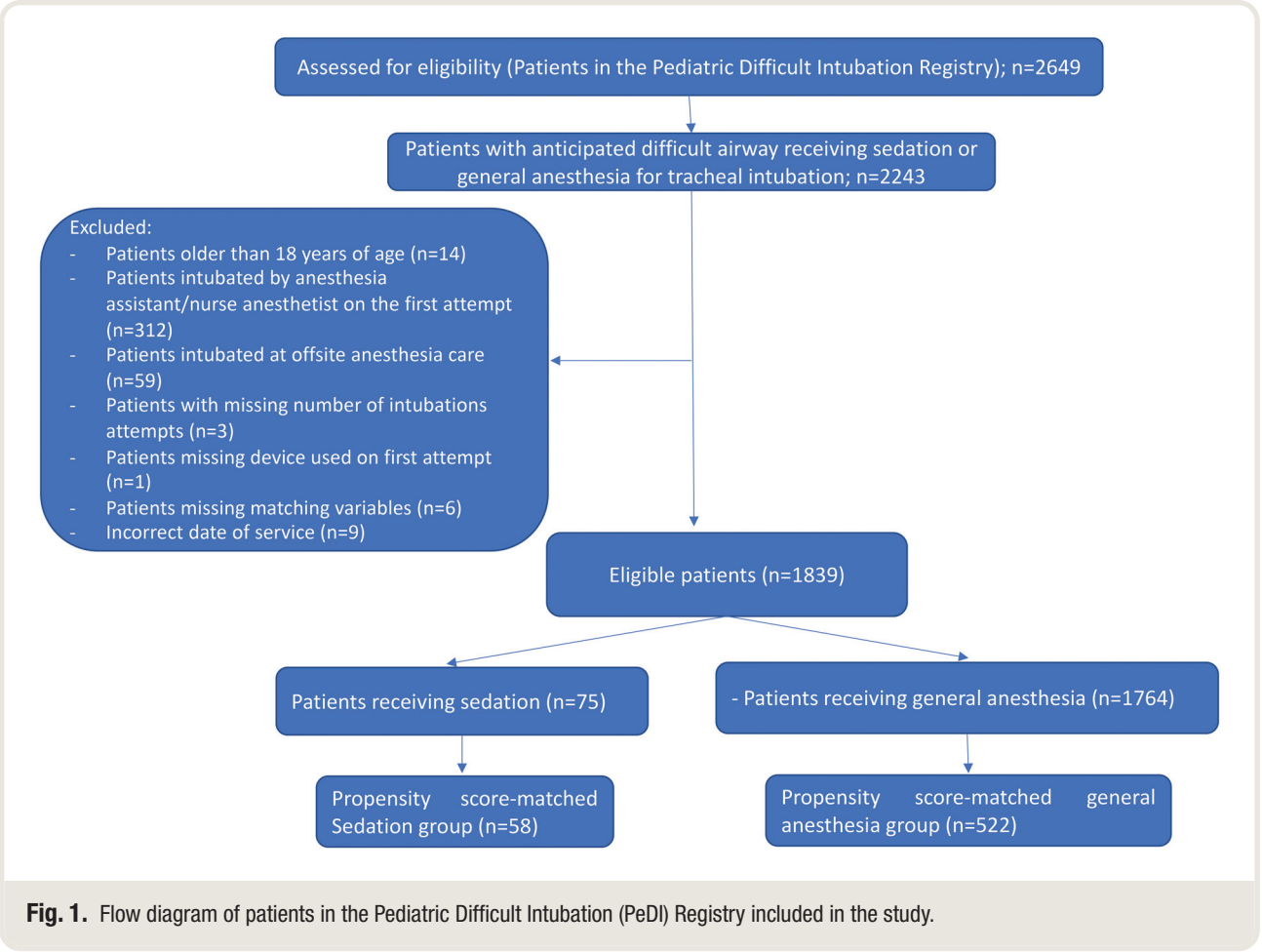

Fig. 1. Flow diagram of patients in the Pediatric Difficult Intubation (PeDI) Registry included in the study.

was hypoxemia, but it did not significantly differ between the groups (fig. 3). Severe complications were not different between the groups (table 2). When analyzing complications only during the first attempt, no significant differences were encountered between the sedation group and the general anesthesia group.

Post hoc sensitivity analysis for rare events showed that patients in the sedation group had lower risk of epistaxis (0 of 58 [0%] *vs.* 13 of 521 [2.5%]; risk difference, -2.2%; 95% CI, - 3.9% to -0.5%; $P = 0.012$) than the general anesthesia group. When analyzing complications only during the first attempt, patients in the sedation group had a lower risk of minor airway trauma (0 of 58 [0%] *vs.* 14 of 521 [2.7%]; risk difference, −3.5%; 95% CI, −5.8% to −1.2%; $P = 0.002$), esophageal intubation with immediate recognition (0 of 58 [0%] *vs.* 5 of 521 [1.0%]; risk difference, −0.6%; 95% CI, −1.1% to −0.1%; $P = 0.026$), and epistaxis (0 of 58 [0%] *vs.* 9 of 521 [1.7%]; risk difference, −1.1%; 95% CI, −1.8% to −0.3%; $P = 0.003$) than the general anesthesia group.

Table 3 presents descriptive data about airway devices, anesthetic technique, and technical difficulties between the groups using prematched data. Additionally, *post hoc* comparison of techniques for supplemental oxygenation, nasal endotracheal intubation, and use of nasopharyngeal airway during the first attempt are presented in table 3. A variety of drugs were used for sedation, the most common being midazolam, ketamine, dexmedetomidine, fentanyl, and propofol; common combinations of drugs used included opioids and propofol ± midazolam, dexmedetomidine and ketamine ± midazolam, and fentanyl and ketamine ± midazolam. Sevoflurane was the most common agent used for general anesthesia. Glycopyrrolate was used in 23 (30.7%) patients in the sedation group and 192 (10.9%) patients in the general anesthesia group. Topical lidocaine was used in 28 (37.3%) of the sedated patients and 121 (6.9%) of the general anesthesia patients. In the general anesthesia group, 48.0% (847 of 1,764) of the patients received neuromuscular blockade, and 5 of 18 of the patients in the sedation group that were converted to general anesthesia also received a neuromuscular blocking drug.

Discussion

In this propensity score–matched cohort of pediatric patients receiving sedation *versus* general anesthesia to

Table 1. Demographic Data and Standardized Mean Difference of the Cohort by Anesthesia Technique (Sedation *vs.* General Anesthesia) for Tracheal Intubation

		Before Propensity Score Matching (n = 1,839)			After Propensity Score Matching (n = 580)		
Characteristics	**Total (n = 1,839)**	**Sedation (n = 75)**	**General Anesthesia (n = 1,764)**	**Absolute Standardized Mean Difference**	**Sedation (n = 58)**	**General Anesthesia (n = 522)**	**Absolute Standardized Mean Difference**
Age group*							
Neonates	80 (4.4)	5 (6.7)	75 (4.3)	0.1	3 (5.2)	22 (4.2)	0.01
Infants	356 (19.4)	14 (18.7)	342 (19.4)	0.02	7 (12.1)	70 (13.4)	0.03
Toddlers	382 (20.8)	9 (12.0)	373 (21.1)	0.28†	8 (13.8)	74 (14.2)	0.02
School-aged	572 (31.1)	17 (22.7)	555 (31.5)	0.21†	17 (29.3)	179 (34.3)	0.03
Teenagers	449 (24.4)	30 (40.0)	419 (23.8)	0.33†	23 (39.7)	177 (33.9)	0.01
Weight, median [interquartile range], kg‡	18.8 [8.2, 36.2]	26.0 [6.1, 42.4]	18.5 [8.3, 36.0]	0.16†	29.0 [11.7, 47.2]	25.0 [11.5, 41.2]	0
Sex (male), n (%)	1,002 (54.5)	41 (54.7)	961 (54.5)	0	30 (51.7)	279 (53.4)	0.06
Prematurity, n (%)§							
Yes	377 (20.5)	9 (12.0)	368 (20.9)	0.27†	9 (15.5)	82 (15.7)	0.05
No	1,264 (68.7)	57 (76.0)	1,207 (68.4)	0.18†	44 (75.1)	392 (75.1)	0.01
Unknown	198 (10.8)	9 (12.0)	189 (10.7)	0.04	5 (8.6)	48 (9.2)	0.07
ASA physical status							
I to II	425 (23.1)	17 (22.7)	408 (23.1)	0.01	17 (29.3)	147 (28.2)	0.03
III to V	1,262 (68.9)	43 (57.3)	1,219 (69.1)	0.24†	31 (53.4)	322 (61.7)	0.06
E	152 (8.3)	15 (20.0)	137 (7.8)	0.31†	10 (17.2)	53 (10.2)	0.04
Criteria for entry‖#							
1	321 (17.5)	10 (13.3)	311 (17.6)	0.13†	8 (13.8)	74 (14.2)	0.04
2	233 (12.7)	26 (34.7)	207 (11.7)	0.48†	20 (34.5)	111 (21.3)	0.04
3	181 (9.8)	4 (5.3)	177 (10.0)	0.21†	2 (3.4)	34 (6.5)	0.06
4	1,189 (64.7)	42 (56.0)	1,147 (65.0)	0.18†	32 (55.2)	325 (62.3)	0.08
Normal physical exam, n (%)	276 (15.0)	2 (2.7)	274 (15.5)	0.8†	2 (3.4)	20 (3.8))	0.01
Physical exam findings, n (%)‖							
Limited neck mobility	630 (34.3)	31 (41.3)	599 (34.0)	0.15†	25 (43.1)	224 (42.9)	0.01
Facial asymmetry or dysmorphism	672 (36.5)	33 (44.0)	639 (36.2)	0.16†	25 (43.1)	214 (41.0)	0
Micrognathia or limited mouth opening	1,260 (68.5)	63 (84.0)	1,197 (67.9)	0.44†	48 (82.8)	417 (79.9)	0.05
Other findings	319 (17.3)	21 (28.0)	298 (16.9)	0.25†	14 (24.1)	117 (22.4)	0.01
Syndromic diagnosis, n (%)							
Yes	1,296 (70.5)	53 (70.7)	1,243 (70.5)	0	37 (63.8)	371 (71.1)	0.03
No	436 (23.7)	19 (25.3)	417 (23.6)	0.04	18 (31.0)	117 (22.4)	0.05
Unidentified	107 (5.8)	3 (4.0)	104 (5.9)	0.1	3 (5.2)	34 (6.5)	0.03
Specific syndrome, n (%)							
Pierre Robin sequence	222 (12.1)	12 (16.0)	210 (11.9)	0.11†	6 (10.3)	68 (13.0)	0
Goldenhar	147 (8.0)	3 (4.0)	144 (8.2)	0.21†	3 (5.2)	30 (5.7)	0.08
Type of provider, n (%)							
Attending	543 (29.5)	19 (25.3)	524 (29.7)	0.1†	15 (25.9)	122 (23.4)	0.1†
Trainee	1,296 (70.5)	56 (74.7)	1,240 (70.3)	0.1†	43 (74.1)	400 (76.6)	0.1†
Anticipated difficulty							
With face mask ventilation	23 (1.3)	1 (1.3)	22 (1.2)	0.01	1 (1.7)	8 (1.5)	0.02

(*Continued*)

Table 1. (Continued)

Characteristics	Total (n = 1,839)	Before Propensity Score Matching (n = 1,839)			After Propensity Score Matching (n = 580)		
		Sedation (n = 75)	General Anesthesia (n = 1,764)	Absolute Standardized Mean Difference	Sedation (n = 58)	General Anesthesia (n = 522)	Absolute Standardized Mean Difference
With direct laryngoscopy	1,469 (79.9)	38 (50.7)	1,431 (81.1)	0.61†	33 (56.9)	355 (68.0)	0.04
With mask ventilation and direct laryngoscopy	347 (18.9)	36 (48.0)	311 (17.6)	0.61†	24 (41.1)	159 (30.5)	0.03
Location							
Operating room	1,786 (97.1)	57 (76.0)	1,729 (98.0)	0.52†	53 (91.4)	507 (97.1)	0.06
ICU	38 (2.1)	14 (18.7)	24 (1.4)	0.44†	4 (6.9)	11 (2.1)	0.08
Other	15 (0.8)	4 (5.3)	11 (0.6)	0.21†	1 (1.7)	4 (0.8)	0.02

*The reported ages are chronological age not gestationally corrected age: neonates are less than 1 month old, infants are 1 month to 1 yr old, toddlers are 1 to 5 yr old, school-aged children are 5 to 12 yr old, and teenagers are 13 to 18 yr old. †Absolute standardized mean difference > 0.1. ‡Weight measured, not corrected for gestational age. §Less than or equal to 37 weeks of gestational age at birth. ||One patient can have more than one entry criteria. #Criteria for entry 1, difficult laryngeal exposure with direct laryngoscopy (Cormak and Lehane Classification of 3 or higher); criteria for entry 2, impossible direct laryngoscopy; criteria for entry 3, failed direct laryngoscopy within 6 months; and criteria for entry 4, deferred direct laryngoscopy because of a low chance of success and a perceived increased risk of harm.

ASA, American Society of Anesthesiologists; ICU, intensive care unit.

facilitate tracheal intubation, there was no difference in first-attempt tracheal intubation success between the two groups. The complications overall were low and similar between the groups. *Post hoc* sensitivity analysis showed that patients in the general anesthesia group had an increased risk of minor airway trauma, epistaxis, and esophageal intubation with immediate recognition.

Previous reports from the Pediatric Difficult Airway collaborative have shown a higher proportion of complications as the number of intubation attempts increases, leading to guidance to limit the number of intubation attempts.[3] A previous study from the Pediatric Difficult Airway collaborative analyzing ventilation techniques found that spontaneous ventilation was associated with more complications in children with difficult airway, but sensitivity analysis suggested that the relationship was mediated by airway reactivity rather than the ventilation technique itself.[4] This finding implied a possible relationship between lighter anesthetic depth and complications. The definitive effect of neuromuscular blockade and ventilation technique on complications is challenging to evaluate due to the overlap between the two techniques and the retrospective nature of our study; certainly, the general anesthesia group includes patients paralyzed during the first attempt, while none of the sedation group patients were paralyzed. The type of ventilation was dependent on the anesthetic technique, and our study specifically compares the outcomes of the two different anesthetic techniques (sedation *vs.* general anesthesia) using propensity score matching to account for such confounding variables. It is possible that complications in the sedated patients were related to airway reactivity, which is more likely in spontaneously ventilating patients. In this propensity score–matched cohort, there was no difference in the median number of tracheal intubation attempts between the sedation and general anesthesia groups. Although the rate of complications in our study was low, there were some interesting findings. There were no reported intubation failures (0 of 58) in the sedation group *versus* 6 of 522 in the general anesthesia group. The patients with failed intubation either were rescued and successfully oxygenated and ventilated with a supraglottic airway or emerged from anesthesia and the surgical case was canceled (table 2), but no emergent front-of-neck access was performed in this cohort. In the sedation group, 16 of 58 (27.5%) of patients had to be converted to general anesthesia before they were successfully intubated. Factors that could explain this need to convert to general anesthesia include the inability of some pediatric patients to follow commands during sedation and the quality of airway topicalization with local anesthetics; as mentioned before, previous work from our group identified airway reactivity as a contributor to complications in this population. In our study, the number of sedated patients that received topical local anesthetic was rather low (37.3%), and that may have influenced our results. Interestingly, the general anesthesia group had an increased risk of esophageal intubation with immediate recognition, minor airway trauma, and epistaxis, which seems remarkable since the sedation group had a higher rate of nasotracheal intubations and use of a nasopharyngeal airway as an adjunct. The causes for these associations are likely multifactorial; unfortunately, we can only hypothesize about possible contributing factors. There is limited data regarding sedation for tracheal intubation in children with difficult airways. Péan *et al.*[13] studied the use of sevoflurane *versus* propofol in adults with difficult airway and found similar success rates during intubation attempts

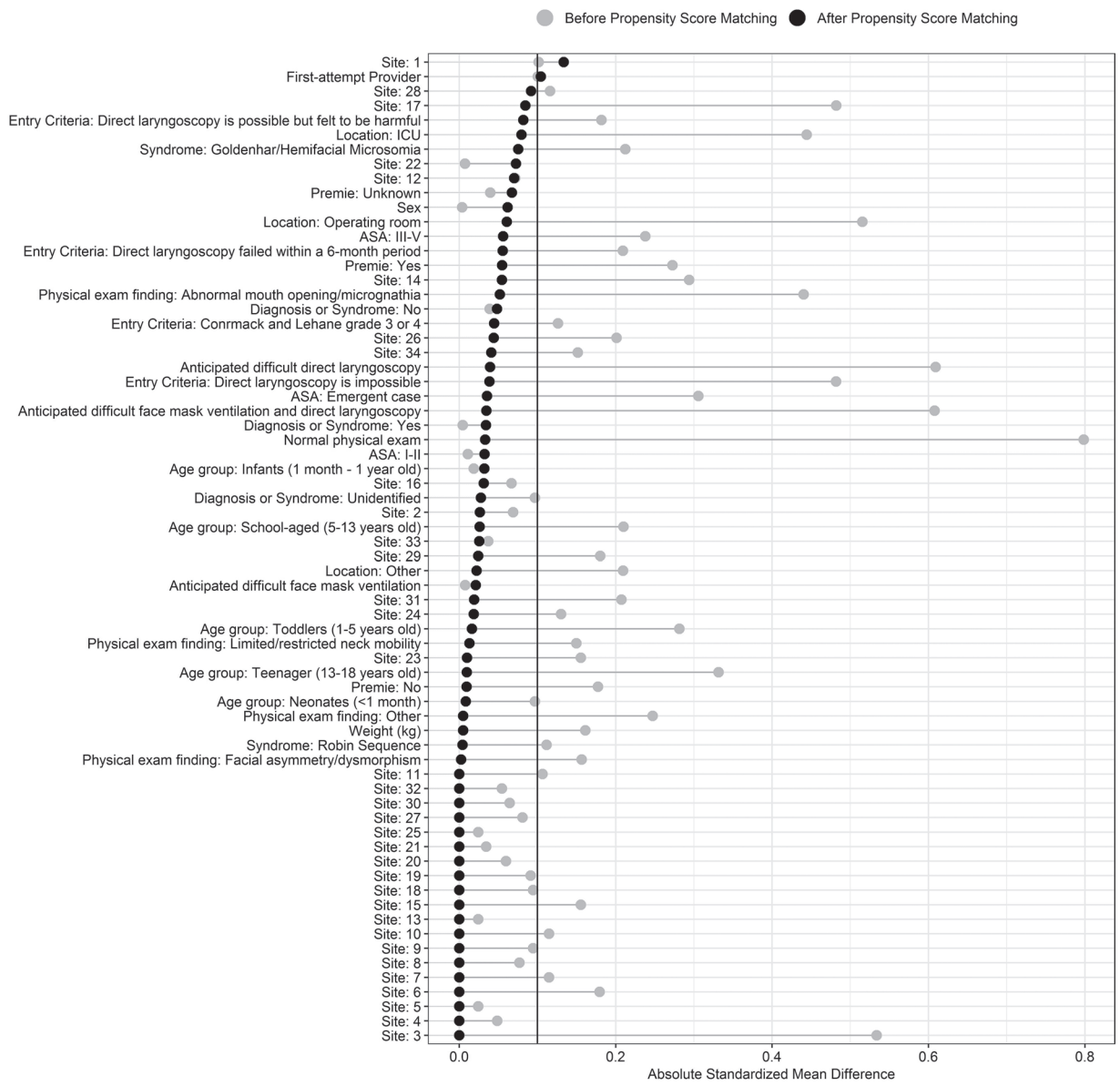

Fig. 2. Absolute standardized mean difference for patients of variables between patients receiving sedation *versus* general anesthesia before and after propensity score matching. Nearest neighbor matching with caliper width equal to 0.1 of the standard deviation of the logit of the propensity score was performed. To account for the clustering within site and within matching pairs, we used marginal models with exchangeable working correlation structure to establish the association between treatment (sedation *vs.* general anesthesia) and outcomes. Interaction of site and matching pair was included as the cluster variable. ASA, American Society of Anesthesiologists; ICU, intensive care unit.

and similar technical difficulties but higher incidence of tachycardia and hypertension in the sevoflurane group. Our study does not support a preferred approach for tracheal intubation in children with difficult airway based on the first-attempt success rate and the rate of complications. Clinicians should select an approach based on their skill and patient factors.

We did not include the use of neuromuscular blockade as a matching variable since only the patients in the general anesthesia and failed sedation groups received it. Previous work from the Pediatric Difficult Airway Registry has reported on the effect of neuromuscular blockade,[4] but no significant differences in outcomes have been related to neuromuscular blockade. Sedation is a continuum that can be difficult to clearly establish, even by experienced clinicians.[14] Unlike in adults, infants and children may be unable to follow directions during stressful situations such as an awake or sedated tracheal intubation, making the use

Table 2. Outcomes before and after Propensity Score Matching: Tracheal Intubation First-attempt Success, Complications, and Number of Attempts

		Before Propensity Score Matching (n = 1,839)		After Propensity Score Matching (n = 580)			
						Generalized Estimating Equation Model*	
Outcomes	Total (n = 1,839)	Sedation (n = 75)	General Anesthesia (n = 1,764)	Sedation (n = 58)	General Anesthesia (n = 522)	Odds Ratio (95% CI)	*P* Value
First-attempt success, n (%)†	889 (48.3)	34 (45.3)	855 (48.3)	28 (48.3)	250 (47.9)	1.06 (0.60, 1.87)	0.846
No. of attempts, median [interquartile range]‡	2 [1, 2]	2 [1, 3]	2 [1, 2]	2 [1, 3]	2 [1, 2]	0.86 (0.58, 1.28)‡	0.460
Failed intubation	15 (0.8)§	0 (0.0)	15 (0.8)	0 (0.0)	6 (1.2)	NA	NA
Complications							
Overall‖	302 (16.5)	22 (29.3)	280 (16.0)	15 (25.9)	90 (17.3)	1.41 (0.72, 2.76)	0.323
Nonsevere	295 (16.1)	20 (26.7)	275 (15.7)	14 (24.1)	90 (17.3)	1.28 (0.65, 2.55)	0.478
Minor airway trauma	40 (2.2)	2 (2.7)	38 (2.2)	1 (1.7)	20 (3.8)	0.40 (0.062, 2.61)	0.340
ES intubation#	32 (1.7)	3 (4.0)	29 (1.7)	0 (0.0)	7 (1.3)	NA	NA
Epistaxis	28 (1.5)	0 (0.0)	28 (1.6)	0 (0.0)	13 (2.5)	NA	NA
Pharyngeal bleeding	56 (3.1)	8 (10.7)	48 (2.7)	8 (13.8)	21 (4.0)	2.03 (0.78, 5.3)	0.146
Hypoxemia	166 (9.1)	11 (14.7)	155 (8.8)	6 (10.3)	36 (6.9)	0.99 (0.36, 2.71)	0.977
Bronchospasm	19 (1)	4 (5.3)	15 (0.9)	3 (5.2)	3 (0.6)	5.0 (0.81, 31.5)	0.083
Laryngospasm	29 (1.6)	3 (4.0)	26 (1.5)	2 (3.4)	12 (2.3)	2.29 (0.50, 10.5)	0.283
Vomiting	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.4)	NA	NA
Arrhythmia	5 (0.3)	1 (1.3)	4 (0.2)	1 (1.7)	1 (0.2)	NA	NA
Severe	24 (1.3)	4 (5.3)	20 (1.1)	2 (3.4)	4 (0.8)	2.48 (0.33, 18.9)	0.381
Major airway trauma	8 (0.4)	1 (1.3)	7 (0.4)	1 (1.7)	2 (0.4)	NA	NA
ES intubation**	3 (0.2)	1 (1.3)	2 (0.1)	0 (0.0)	0 (0.0)	NA	NA
Aspiration	3 (0.2)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	NA	NA
Pneumothorax	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	NA	NA
Cardiac arrest	9 (0.5)	2 (2.7)	7 (0.4)	1 (1.7)	2 (0.4)	NA	NA
Death	2 (0.1)	1 (1.3)	1 (0.1)	0 (0.0)	0 (0.0)	NA	NA

*To account for within-site and within-matching-pairs clustering, the generalized estimating equation method was used to establish the association between planned anesthesia technique and outcomes. The generalized estimating equation model was not fitted for outcomes with less than five cases total or with no cases in one of the groups. †Attempt to intubate the trachea. ‡The incidence rate ratio is reported for the model of number of attempts. §Fifteen patients were reported as "failed intubation." Of these, seven patients were successfully ventilated and oxygenated using a supraglottic airway and the planned surgical or diagnostic procedure was performed, and eight patients were emerged from anesthesia and the planned surgical procedure was abandoned. No emergent front-of-neck access was performed in this group. ‖Any complication during all attempts (n = 12 missing). #Immediately recognized. **Delayed recognition.

NA, generalized estimating equation model did not converge, or total number of patients was less than five.

of sedation challenging. Several sedation scales have been developed to assess the level of the sedation by clinicians such as the Observer's Assessment of Alertness/Sedation,[15] the Pediatric Sedation State Scale,[16] the Vancouver Sedative Recovery Scale,[17] and the University of Michigan Sedation Scale.[18] Nonetheless, some of these scales may present limited ability to differentiate deeper states of sedation, and interprovider variability remains a problem. In this study, there was significant variability in the frequency of the use of sedation to facilitate tracheal intubation by center. It is possible that providers who do not use sedation often may have more complications than those providers with more familiarity with the technique. Additionally, this cohort had a significant number of trainees as the first-attempt clinician, and this variable remained imbalanced after matching, which may have affected our results. We added the type of clinician as a covariate to the final analysis to best control for this issue. Patients in the sedation group were

Outcomes n (%)	Sedation (n=58)	General Anesthesia (n=522)	Odds Ratio (95% Confidence Interval)	p value
First-attempt success	28 (48.3)	250 (47.9)	1.06 (0.60, 1.87)	0.846
Failed intubation	0 (0.0)	6 (1.1)	NA	NA
Complications overall (missing=1)	15 (25.9)	90 (17.3)	1.41 (0.72, 2.76)	0.323
Nonsevere complications	14 (24.1)	90 (17.3)	1.28 (0.65, 2.55)	0.478
Minor airway trauma	1 (1.7)	20 (3.8)	0.4 (0.062, 2.61)	0.34
Esophageal intubation with immediate recognition	0 (0.0)	7 (1.3)	NA	NA
Epistaxis	0 (0.0)	13 (2.5)	NA	NA
Pharyngeal bleeding	8 (13.8)	21 (4.0)	2.03 (0.78, 5.3)	0.146
Hypoxemia	6 (10.3)	36 (6.9)	0.99 (0.36, 2.71)	0.977
Bronchospasm	3 (5.2)	3 (0.6)	5.0 (0.81, 31.5)	0.083
Laryngospasm	2 (3.4)	12 (2.3)	2.29 (0.50, 10.5)	0.283
Vomiting	0 (0.0)	1 (0.2)	NA	NA
Arrhythmia	1 (1.7)	1 (0.2)	NA	NA
Severe complications	2 (3.4)	4 (0.8)	2.48 (0.33, 18.9)	0.381
Major airway trauma	1 (1.7)	2 (0.4)	NA	NA
Esophageal intubation with delayed recognition	0 (0.0)	0 (0.0)	NA	NA
Aspiration	0 (0.0)	0 (0.0)	NA	NA
Pneumothorax	0 (0.0)	0 (0.0)	NA	NA
Cardiac arrest	1 (1.7)	2 (0.4)	NA	NA
Death	0 (0.0)	0 (0.0)	NA	NA

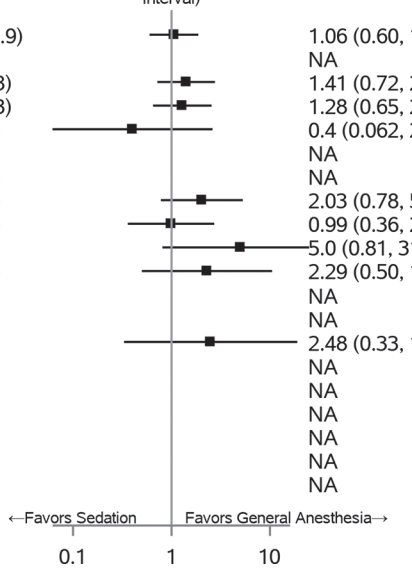

Fig. 3. Forest plot showing the primary and secondary outcomes after propensity score matching and generalized estimating equation analysis. NA, generalized estimating equation model did not converge or less than five patients had the outcome; the upper limit of the confidence interval was cut by 25. The *x* axis is on the log scale. *Odds ratios in the forest plot are generated from matched data using marginal model (*i.e.*, generalized estimating equation) with binomial distribution and logit link function.

more likely to receive supplemental oxygenation during intubation than those under general anesthesia, yet there was no significant difference in the incidence of hypoxemia between the groups.

Our study has to be considered in the context of its limitations. First, although sedation is one of the options for induction of anesthesia and airway management, the registry does not capture the level of sedation used by the anesthesia provider, which precludes our ability to classify according to the level of sedation. Additionally, sedation was not a commonly used technique in this cohort, leading to only a small number of sedation cases. Because our study is retrospective, we lose some granularity about why clinicians chose general anesthesia *versus* sedation. Although we matched physical exam findings, it is impossible to know all the factors that may have influenced the decision to choose one technique over another. It is possible that the patients who were sedated had more concerning physical exam findings and were anticipated to be more challenging to intubate. We also lack details about the timing and dosages of the various drugs used for sedation. The degree and duration of hypoxemia is not captured in detail by the registry, nor is the duration of supplemental oxygenation. We did not include this as part of the analysis of the complications that may have underscored the effect of supplemental oxygenation on hypoxemia in this cohort. Additionally, we cannot account for the different degrees of anticipated difficulty that were perceived by clinicians in these patients; it is possible that those patients with more severe syndromic features/anatomical abnormalities were planned for sedation, and we are unable to adjust for this. Despite these limitations, this study provides further insight to a small but challenging population that is difficult to study. Propensity score matching was used to minimize selection bias and the effect of baseline characteristics in the selected outcome but only accounts for measured variables. It is possible that unmeasured variables still may have influenced the studied outcomes.

In conclusion, the rate of first-attempt success of tracheal intubation was similar in children with difficult airways intubated under general anesthesia *versus* sedation. However, 27.6% of sedation cases needed to be converted to general anesthesia to complete tracheal intubation. The rate of nonsevere and severe complications were low and similar in both groups. *Post hoc* sensitivity analysis demonstrated that sedation was associated with a lower risk of minor airway trauma, esophageal intubation with immediate recognition, and epistaxis.

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Table 3. Devices Used during First Attempt, Technical Difficulties, and Use of Supplemental Oxygenation Reported (Data before Propensity Score Matching)

Outcome	Total (n = 1,839)	Sedation (n = 75)	General Anesthesia (n = 1,764)	*P* Value
Device used for first attempt, n (%)				
Direct laryngoscopy	348 (18.8)	10 (13.3)	338 (19.3)	< 0.001
Videolaryngoscopy	927 (50.4)	22 (29.3)	905 (51.3)	< 0.001
Flexible fiberoptic bronchoscope*	514 (28.1)	43 (57.3)	471 (26.8)	< 0.001
Other	50 (2.7)	—	50 (2.8)	< 0.001
Technical difficulties†				
Airway activation	54 (3.0)	10 (13.5)	44 (2.5)	< 0.001
Difficulty directing the endotracheal tube‡	218 (12.0)	4 (5.4)	214 (12.2)	0.112
Difficulty navigating flexible fiberoptic bronchoscope	88 (4.8)	8 (10.8)	80 (4.6)	0.023
Fogging	42 (2.3)	6 (8.1)	36 (2.1)	0.006
Heavy secretions	140 (7.7)	10 (13.5)	130 (7.4)	0.089
Other	235 (12.9)	13 (17.6)	222 (12.7)	0.293
Supplemental oxygenation during first attempt§				
Insufflation *via* oral Ring, Adair, and Elwyn endotracheal tube	54 (3.2)	2 (2.9)	52 (3.2)	< 0.001
High-flow nasal cannula	55 (3.2)	5 (7.2)	50 (3.1)	< 0.001
Low-flow nasal cannula	66 (3.9)	10 (14.5)	56 (3.4)	< 0.001
Modified nasal airway	96 (5.7)	5 (7.2)	91 (5.6)	< 0.001
Other	95 (5.6)	7 (10.1)	88 (5.4)	< 0.001
None	1,329 (78.4)	40 (58.0)	1,289 (79.3)	< 0.001
Nasal endotracheal tube placement‖	396 (21.7)	29 (38.7)	367 (21.0)	< 0.001
Use of nasopharyngeal airway during first attempt#	109 (6.1)	9 (12.3)	100 (5.8)	0.042

*Includes free-hand and supraglottic airway device-guided flexible fiberoptic bronchoscope. †A patient can have more than one (n = 15 missing). ‡Despite adequate view. §Data missing in 144 cases. ‖Data missing in 16 cases, of which 15 were failed intubation attempts. #Data missing in 44 cases.
NA, not assessed.

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Competing Interests

Dr. Kovatsis is a medical advisor to Verathon, Inc. (Bothell, Washington). Dr. Fiadjoe is a Board member for the American Board of Anesthesiology (Raleigh, North Carolina) and received past grant funding from the Anesthesia Patient Safety Foundation (Rochester, Minnesota). The other authors declare no competing interests.

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References

1. Valois-Gómez T, Oofuvong M, Auer G, Coffin D, Loetwiriyakul W, Correa JA: Incidence of difficult bag-mask ventilation in children: A prospective observational study. Paediatr Anaesth 2013; 23:920–6
2. Disma N, Virag K, Riva T, Kaufmann J, Engelhardt T, Habre W; NECTARINE Group of the European Society of Anaesthesiology Clinical Trial Network: Difficult tracheal intubation in neonates and infants. NEonate and Children audiT of Anaesthesia pRactice IN Europe (NECTARINE): A prospective European multicentre observational study. Br J Anaesth 2021; 126:1173–81
3. Fiadjoe JE, Nishisaki A, Jagannathan N, Hunyady AI, Greenberg RS, Reynolds PI, Matuszczak ME, Rehman MA, Polaner DM, Szmuk P, Nadkarni VM, McGowan FX Jr, Litman RS, Kovatsis PG: Airway management complications in children with difficult tracheal intubation from the Pediatric Difficult Intubation (PeDI) registry: A prospective cohort analysis. Lancet Respir Med 2016; 4:37–48
4. Garcia-Marcinkiewicz AG, Adams HD, Gurnaney H, Patel V, Jagannathan N, Burjek N, Mensinger JL, Zhang B, Peeples KN, Kovatsis PG, Fiadjoe JE; PeDI Collaborative: A retrospective analysis of neuromuscular

blocking drug use and ventilation technique on complications in the Pediatric Difficult Intubation Registry using propensity score matching. Anesth Analg 2020; 131:469–79
5. Burjek NE, Nishisaki A, Fiadjoe JE, Adams HD, Peeples KN, Raman VT, Olomu PN, Kovatsis PG, Jagannathan N, Hunyady A, Bosenberg A, Tham S, Low D, Hopkins P, Glover C, Olutoye O, Szmuk P, McCloskey J, Dalesio N, Koka R, Greenberg R, Watkins S, Patel V, Reynolds P, Matuszczak M, Jain R, Khalil S, Polaner D, Zieg J, Szolnoki J, Sathyamoorthy K, Taicher B, Riveros Perez NR, Bhattacharya S, Bhalla T, Stricker P, Lockman J, Galvez J, Rehman M, Von Ungern-Sternberg B, Sommerfield D, Soneru C, Chiao F, Richtsfeld M, Belani K, Sarmiento L, Mireles S, Bilen Rosas G, Park R, Peyton J; PeDI Collaborative Investigators: Videolaryngoscopy *versus* fiber-optic intubation through a supraglottic airway in children with a difficult airway: An analysis from the multicenter Pediatric Difficult Intubation Registry. Anesthesiology 2017; 127:432–40
6. Peyton J, Park R, Staffa SJ, Sabato S, Templeton TW, Stein ML, Garcia-Marcinkiewicz AG, Kiss E, Fiadjoe JE, von Ungern-Sternberg B, Chiao F, Olomu P, Zurakowski D, Kovatsis PG; PeDI Collaborative Investigators: A comparison of videolaryngoscopy using standard blades or non-standard blades in children in the Paediatric Difficult Intubation Registry. Br J Anaesth 2021; 126:331–9
7. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Lancet 2007; 370:1453–7
8. Cook TM: A new practical classification of laryngeal view. Anaesthesia 2000; 55:274–9
9. Graciano AL, Tamburro R, Thompson AE, Fiadjoe J, Nadkarni VM, Nishisaki A: Incidence and associated factors of difficult tracheal intubations in pediatric ICUs: A report from National Emergency Airway Registry for Children: NEAR4KIDS. Intensive Care Med 2014; 40:1659–69
10. Nishisaki A, Turner DA, Brown CA 3rd, Walls RM, Nadkarni VM; National Emergency Airway Registry for Children (NEAR4KIDS); Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: A national emergency airway registry for children: Landscape of tracheal intubation in 15 PICUs. Crit Care Med 2013; 41:874–85
11. Ho D, Imai K, King G, Stuart EA. MatchIt: Nonparametric preprocessing for parametric causal inference. J Stat Softw 2011; 42:28.
12. Pedroza C, Truong VT: Performance of models for estimating absolute risk difference in multicenter trials with binary outcome. BMC Med Res Methodol 2016; 16:113
13. Péan D, Floch H, Beliard C, Piot B, Testa S, Bazin V, Lejus C, Asehnoune K: Propofol *versus* sevoflurane for fiberoptic intubation under spontaneous breathing anesthesia in patients difficult to intubate. Minerva Anestesiol 2010; 76:780–6
14. Tobias JD: Sedation of infants and children outside of the operating room. Curr Opin Anaesthesiol 2015; 28:478–85
15. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL: Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990; 10:244–51
16. Cravero JP, Askins N, Sriswasdi P, Tsze DS, Zurakowski D, Sinnott S: Validation of the Pediatric Sedation State Scale. Pediatrics 2017; 139:e20162897
17. Macnab AJ, Levine M, Glick N, Susak L, Baker-Brown G: A research tool for measurement of recovery from sedation: The Vancouver Sedative Recovery Scale. J Pediatr Surg 1991; 26:1263–7
18. Malviya S, Voepel-Lewis T, Tait AR, Merkel S, Tremper K, Naughton N: Depth of sedation in children undergoing computed tomography: Validity and reliability of the University of Michigan Sedation Scale (UMSS). Br J Anaesth 2002; 88:241–5

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ANESTHESIOLOGY

Carbon Dioxide, Blood Pressure, and Perioperative Stroke: A Retrospective Case–Control Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- There is a high incidence of perioperative stroke in some patients
- Hypotension may lead to cerebral ischemia, and the impact on cerebral perfusion may be greater in the setting of hypercapnia or hypocapnia

What This Article Tells Us That Is New

- In a case–control study using the Multicenter Perioperative Outcomes Group data, hypocarbia, hypercarbia, and hypotension were each independently associated with postoperative stroke

ABSTRACT

Background: The relationship between intraoperative physiology and postoperative stroke is incompletely understood. Preliminary data suggest that either hypo- or hypercapnia coupled with reduced cerebrovascular inflow (*e.g.*, due to hypotension) can lead to ischemia. This study tested the hypothesis that the combination of intraoperative hypotension and either hypo- or hypercarbia is associated with postoperative ischemic stroke.

Methods: We conducted a retrospective, case–control study *via* the Multicenter Perioperative Outcomes Group. Noncardiac, nonintracranial, and nonmajor vascular surgical cases (18 yr or older) were extracted from five major academic centers between January 2004 and December 2015. Ischemic stroke cases were identified *via* manual chart review and matched to controls (1:4). Time and reduction below key mean arterial blood pressure thresholds (less than 55 mmHg, less than 60 mmHg, less than 65 mmHg) and outside of specific end-tidal carbon dioxide thresholds (30 mmHg or less, 35 mmHg or less, 45 mmHg or greater) were calculated based on total area under the curve. The association between stroke and total area under the curve values was then tested while adjusting for relevant confounders.

Results: In total, 1,244,881 cases were analyzed. Among the cases that screened positive for stroke (n = 1,702), 126 were confirmed and successfully matched with 500 corresponding controls. Total area under the curve was significantly associated with stroke for all thresholds tested, with the strongest combination observed with mean arterial pressure less than 55 mmHg (adjusted odds ratio per 10 mmHg-min, 1.17 [95% CI, 1.10 to 1.23], $P < 0.0001$) and end-tidal carbon dioxide 45 mmHg or greater (adjusted odds ratio per 10 mmHg-min, 1.11 [95% CI, 1.10 to 1.11], $P < 0.0001$). There was no interaction effect observed between blood pressure and carbon dioxide.

Conclusions: Intraoperative hypotension and carbon dioxide dysregulation may each independently increase postoperative stroke risk.

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Stroke is a potentially devastating surgical complication, with an incidence of up to 3% in high-risk noncardiac surgery populations.[1,2] Recent observational data also indicate that the risk of perioperative stroke, as detected by magnetic resonance imaging rather than clinical criteria, may be as high as 7% for older patients after noncardiac surgery.[3] Furthermore, postoperative stroke recognition is often delayed, and thrombolytic interventions are less commonly performed for surgical patients compared with stroke patients in the community setting.[4,5] Given the increased mortality, major disability, delayed diagnosis and treatment, and prolonged hospitalization,[1,4,5] identification of modifiable risk factors for perioperative stroke is of paramount importance.

Although several comorbidity-based preoperative risk factors have been identified,[1,6] there is a paucity of known intraoperative risk factors that may be modifiable. One such candidate risk factor is cerebral malperfusion. Emerging data suggest that intraoperative mean arterial pressure (MAP) may commonly fall below autoregulatory thresholds that maintain cerebral blood flow.[7,8] The combination of reduced cerebral perfusion (*e.g.*, due to hypotension and compromised autoregulation) and impaired vasodilatory reserve (*e.g.*, mediated by hypo- and hypercapnia) creates conditions for cerebral ischemia.[9] Indeed, functional magnetic resonance imaging data demonstrate that such vascular malperfusion can occur in watershed regions during periods of carbon dioxide dysregulation.[10] However, these data have been derived primarily from human volunteers, and it remains unclear whether the combination of hypotension and either hypo- or hypercarbia contributes to stroke risk in a surgical setting.

The primary objective of this study was therefore to determine the relationship between major perturbations in end-tidal carbon dioxide ($ETCO_2$), intraoperative hypotension, and postoperative ischemic stroke. Specifically, this study tested the hypothesis that the combination of intraoperative hypo- or hypercarbia and intraoperative hypotension—defined by specified total area under the curve thresholds—is associated with postoperative stroke. A multicenter electronic health record registry—with detailed intraoperative physiologic data—was used for retrospective data extraction.[11] A secondary objective was to identify stroke characteristics such as etiology, vascular territory affected, severity, management strategy, and outcomes.

Materials and Methods

Study Design and Overview

This was a multicenter, retrospective, observational case–control study. Institutional review board exemption approval (HUM00176953) was obtained from the University of Michigan Medical School (Ann Arbor, Michigan), which served as the coordinating study site. The institutional review board of each member organization also approved aggregation of this limited data set into the Multicenter Perioperative Outcomes Group centralized data repository. Written informed consent by the human participants was waived. The study protocol, which included a data and statistical analysis plan, was approved by the Multicenter Perioperative Outcomes Group Perioperative Clinical Research Committee and posted on a publicly accessible server before any data analysis.[12] The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[13] and Reporting of studies Conducted using Observational Routinely-collected health data statement extension (Supplemental Digital Content 1, http://links.lww.com/ALN/C908).[14]

Study Population

Inclusion Criteria. This study included adult (18 yr or older) patients presenting for noncardiac, nonintracranial, and nonmajor vascular surgeries at five large academic medical centers from January 1, 2004, through December 31, 2015. Cases from one institution were included only after June 31, 2009, because of a published study that included postoperative stroke data before this date.[15] Procedures requiring an

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inpatient stay were included, as were emergency and outpatient cases.

Exclusion Criteria. All intracranial neurosurgical cases were excluded, as were major cardiac and vascular procedures (*e.g.*, proximal aortic), based on intrinsic procedural risk of stroke. Oral–maxillofacial cases involving penetrating trauma and gunshot wounds to the face and skull were also excluded. All trauma cases involving multiple organ injury, traumatic brain injury, closed head injuries, and penetrating trauma to the neck were also excluded. Last, patients with an American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status classification of VI were excluded. Specific procedural exclusions were performed upon the basis of anesthesia Current Procedural Terminology codes (Supplemental Digital Content 2, http://links.lww.com/ALN/C909).

Primary Outcome

The primary outcome of this study was perioperative ischemic stroke, defined as any new-onset cerebrovascular infarction that occurred within 30 days after surgery. Stroke outcomes were screened using billing code data for the following International Classification of Diseases, Ninth Revision codes: 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, and 997.02 (without a diagnostic code indicative of hemorrhage, 430 to 432; see Supplemental Digital Content 2 for code definitions, http://links.lww.com/ALN/C909). Cases that screened positively for stroke then underwent manual chart review to confirm stroke diagnosis based on clinical notes and neuroimaging. For performing the chart review, a physician representative from each site reviewed the medical record. Neurology consultation notes and neuroradiologic reports were reviewed first, and then primary service and other consultation notes were reviewed. Stroke cases were recorded based on a stroke diagnosis reported in these records within 30 days after surgery. A subset of controls (25% from each institution) also underwent manual chart review to confirm the absence of perioperative stroke.

Data Source

Surgical case data were extracted from the Multicenter Perioperative Outcomes Group Database (an electronic health record–derived registry with detailed physiologic and billing code data[11]) and from electronic medical record systems at each respective institution. Data from each Multicenter Perioperative Outcomes Group site are routinely uploaded to a secure, centralized database. Standardized methods used for data input, storage, quality assurance, and extraction have been described previously.[11] Of note, the initial count of 1,244,881 cases (fig. 1) represents all cases available at the final stages of study analysis. The total number of cases available from all study sites was lower in the earlier stages of the study when stroke cases were initially screened and identified (see fig. 1 legend for additional detail). For intraoperative data extraction, the intraoperative time period was defined from anesthesia start to anesthesia end. Last, stroke characteristics were identified by manual extraction from the electronic medical record from each site. These data include etiology (when available), vascular territory, management, and outcomes as available.

Exposure Variables

The primary exposure variables of interest were the total area under the curve of intraoperative $ETCO_2$ and MAP thresholds. The total area under the curve is a continuous measure of the area between the empirical cumulative "curve" of a physiologic measure and the specified threshold.[16]

Specific thresholds were chosen and calculated using a previously described methodology.[16] The lower $ETCO_2$ limit was 30 mmHg or less because cerebrovascular resistance is maximally increased (and thus, cerebral blood flow is impaired) with $ETCO_2$ values of approximately 30 mmHg.[17,18] Conversely, high $ETCO_2$ may lead to steal phenomenon, particularly in patients with cerebral arteriosclerosis.[9] Thus, associations with high $ETCO_2$ were also tested for stroke risk. $ETCO_2$ values in the mid-40s (mmHg) and greater are associated with maximally reduced cerebrovascular resistance and increased blood flow.[18] Duration of time that intraoperative MAP is less than 55 mmHg is associated with end-organ injury[19] and was thus chosen as the threshold for the primary blood pressure analysis. Overall, total area under the curve was chosen to determine both the time and degree to which $ETCO_2$ and MAP values were below (or outside of) these thresholds. Details for calculating total area under the curve, along with artifact reductions strategies, are available in Supplemental Digital Content 3 (http://links.lww.com/ALN/C910).

Case–Control Matching

A case–control matching approach was taken for the current study because of the following advantages. First, case–control studies permit efficient resource allocation to refining exposure assessment and obtaining data on potential confounding factors, particularly for low-incidence outcomes.[20] Second, matching can be used to increase effect-size precision with measures of interest.[21] Last, matching provides marginal estimation, which is often the same technique used for reporting clinical trial treatment effects and is appropriate for population-level estimates.[22]

Stroke cases were matched 1:4 to controls using an optimal matching approach. First, the Mahalanobis distance was assessed between stroke cases and controls, considering each stroke case as a reference point. Mahalanobis distance pairs cases based on a scale-free Euclidean distance, whereby the distance between cases is reduced with increasing covariate similarity. This represents an optimized approach

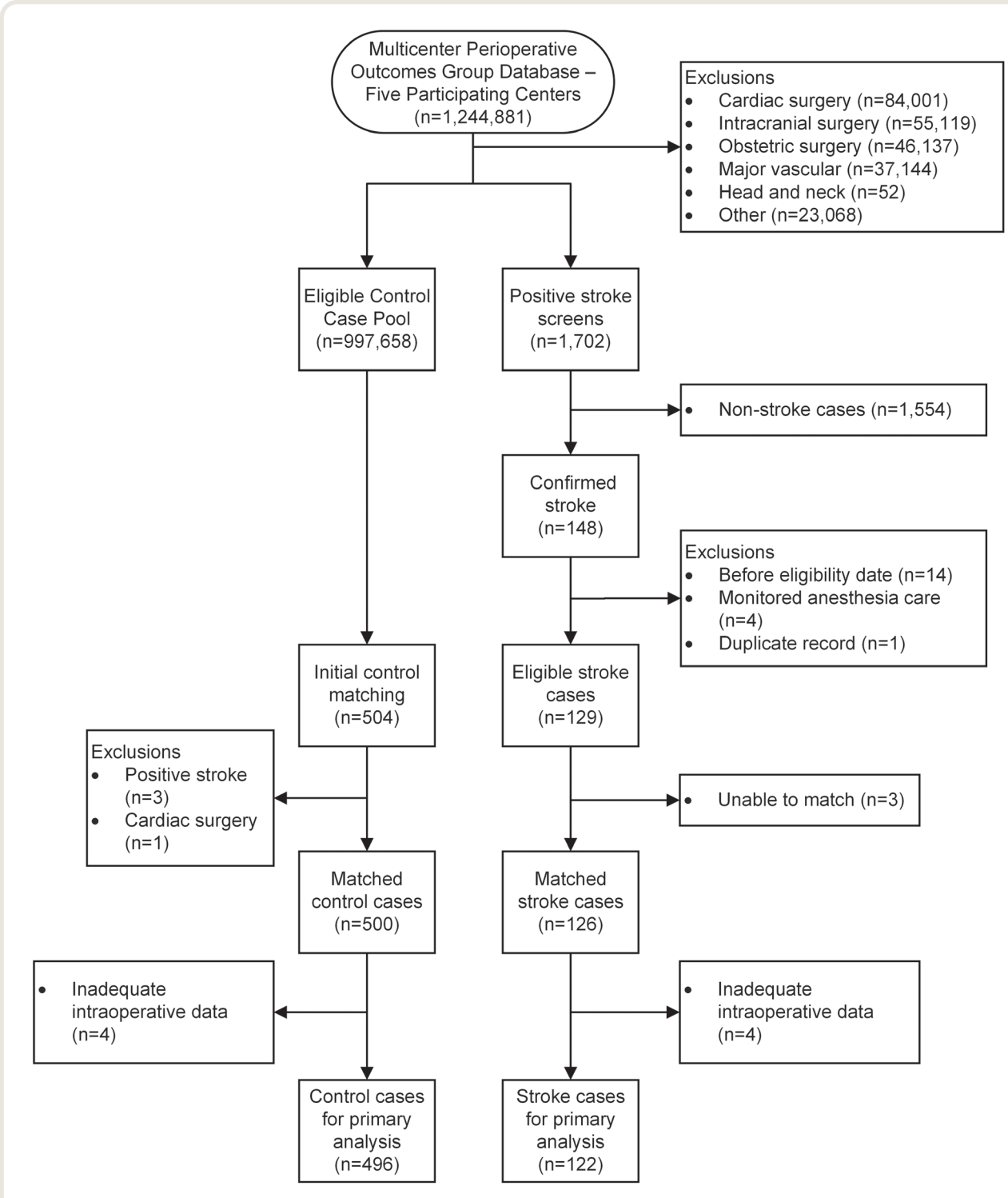

Fig. 1. Study flow diagram presented. Of note, this flow diagram is not meant to accurately depict stroke incidence, as stroke cases were initially screened and identified before control cases, when there were fewer cases overall in the Multicenter Perioperative Outcomes Group Database. Additional cases were then added to the database when control cases were later identified and matched.

for continuous exposure variables (*e.g.*, MAP, $ETCO_2$).[23] Principal component scores for each point (stroke and controls) were calculated using original scoring coefficients. Then Euclidean distance from each transformed control to the reference point (stroke case) was estimated. Once the distance measure was selected, the k-means nearest neighbor

matching algorithm was used without replacement to identify the closest control to each case. All matched controls were then removed from the available matching pool, and the nearest neighbor matching algorithm was conducted again using the controls remaining. Matching continued in this manner until up to four controls were matched. The matching process was performed within each institution based on joint distribution of age, height, weight, sex, and blood loss (given the effect of hemorrhage and hemodilution on cerebrovascular ischemia risk[24]). The following comorbidities were also incorporated into the matching process based on associations with stroke and determined using Elixhauser coding algorithms: atrial fibrillation, coronary artery disease, chronic heart failure, chronic kidney disease, chronic pulmonary disease, diabetes, hypertension, and neurologic disorders.[1,6,25,26] Neurologic disorders incorporated within these coding algorithms (*e.g.*, neurodegenerative disorders, multiple sclerosis, epilepsy) have been previously associated with stroke.[27–29] Last, the matched sample was compared on variable distributions using absolute standardized differences.

Statistical Analysis

Exploratory data analysis techniques were first used to assess the distribution of dependent and independent measures. Descriptive statistics were used for comparing stroke cases and controls in the matched cohort. Means ± SDs, medians (interquartile ranges), and frequencies with percentages were reported as appropriate.

Next, a technique termed seemingly unrelated regression modeling[30] was used to test the relationship between stroke and physiologic variables of interest (*e.g.*, MAP, $ETCO_2$). These models are designed specifically for analysis of variables that may be related, such as MAP and $ETCO_2$ (*i.e.*, in the setting of reduced cardiac output), through contemporaneous cross-equation error correlation, whereby the error terms in the regression equations are correlated. This approach allows the modeling of both exposures in two separate simultaneous equations while avoiding estimation problems relating to multicollinearity. These models can also detect associations too weak to detect with standard logistic models, which are highly sensitive to multicollinearity.[30–32] Seemingly unrelated models were thus constructed with stroke as the dependent variable, and the primary variables of interest—MAP and $ETCO_2$ total area under the curve—as continuous independent variables. The primary analysis included total area under the curve with MAP less than 55 mmHg and $ETCO_2$ 30 mmHg or less followed by $ETCO_2$ 35 mmHg or less and $ETCO_2$ 45 mmHg or greater as a separate, secondary analysis. An additional secondary analysis included the following: total area under the curve of MAP less than 60 mmHg and MAP less than 65 mmHg, both with the same $ETCO_2$ thresholds. These variables were assessed for nonlinearity using splines, as appropriate. Last, models were adjusted for the same variables mentioned in the matching process and time (year). MAP and $ETCO_2$ thresholds were then tested for interaction effects by including the exposure combination in one model and comparing the results to a second model without the combination.[33] Marginal estimates were then assessed using the Wald test with cross-model covariance structure.

Model measures of effect were reported as adjusted odds ratios and 95% Wald CIs. Quasi-likelihood under the independence model criterion was the statistic of choice for goodness-of-fit.[34,35] *P* values less than 0.05 and 95% CI that excluded 1 denoted statistical significance. Analyses were conducted with SAS version 9.4 (SAS Institute, USA).

Results

The study flow is presented in figure 1. In total, 126 eligible stroke cases were identified and successfully matched to controls. Four cases were then removed because they did not have adequate intraoperative data for analysis. This left 122 final stroke cases for the final primary analysis. Baseline characteristics are presented in table 1. Cohort imbalances were observed for race and American Society of Anesthesiologists Physical Status.

Carbon Dioxide, Blood Pressure, and Stroke

Descriptive statistics are presented for each $ETCO_2$ and MAP threshold in table 2. After adjusting for pertinent demographic and comorbidity confounders, there were significant associations between stroke and all MAP and $ETCO_2$ thresholds tested (table 3). The strongest associations were observed with total area under the curve thresholds less than MAP 55 mmHg, which conferred an approximately 10 to 17% increased relative risk of stroke per 10 units (mmHg-min) (table 3). Similar associations were present for $ETCO_2$ 30 or less and 45 mmHg or greater, which conferred an approximately 7% and 10% increased relative risk of stroke per 10 units (mmHg-min), respectively. There was no interaction effect observed between MAP and $ETCO_2$ in relation to stroke (Supplemental Digital Content 4, http://links.lww.com/ALN/C911).

Stroke Characteristics

Descriptive characteristics are presented for all 133 stroke cases that were identified through manually review (table 4), including 3 that could not be matched and 4 that did not involve general anesthesia (fig. 1). The majority of strokes (n = 77, 58%) occurred within the first 3 postoperative days. All patients received neuroimaging, and most received a neurology consultation during admission. Suspected etiologies varied, with embolism, large-vessel occlusion, and small-vessel occlusion all implicated, although cause was either not reported or documented as cryptogenic for 31 (23%) cases. Stroke was most common in the middle cerebral artery territory, and intravenous and endovascular interventions were uncommon. Documentation was poor at discharge, with no modified Rankin Scale documentation for 118 (89%) patients. Overall, 20 of 133 (15%) stroke

Table 1. Baseline Characteristics

	All (n = 626)	Stroke (n = 126)	Controls (n = 500)	Absolute Standardized Difference
Age, yr, mean ± SD n = 626	69 ± 10	69 ± 11	69 ± 10	0.10
Height, cm, mean ± SD n = 451	167 ± 12	165 ± 15	167 ± 11	0.16
Weight, kg, mean ± SD n = 533	83 ± 22	83 ± 20	83 ± 22	0.01
Body mass index, kg/m^2, mean ± SD n = 445	29 ± 7	30 ± 7	29 ± 7	0.08
Sex, male, n (%) n = 626	276 (44)	54 (43)	222 (44)	0.03
Race, n (%) n = 625				1.03
White	497 (79)	67 (53)	430 (86)	
Black	72 (12)	18 (14)	54 (11)	
Asian or Pacific Islander	8 (1.3)	1 (0.8)	7 (1.4)	
Native American	8 (1.3)	0 (0)	8 (1.6)	
Unknown	40 (6.4)	40 (32)	0 (0)	
ASA Physical Status, n (%) n = 626				0.27
Class I	15 (2)	4 (3)	11 (2)	
Class II	142 (23)	19 (15)	123 (25)	
Class III	348 (56)	76 (60)	272 (54)	
Class IV	118 (19)	27 (21)	91 (18)	
Class V	3 (0.5)	0 (0)	3 (0.6)	
Comorbidities, n (%)				
Cardiac arrhythmias	185 (30)	37 (29)	148 (30)	0.01
Cardiac valvular disease	92 (15)	19 (15)	73 (15)	0.01
Chronic pulmonary disease	187 (30)	39 (31)	148 (30)	0.03
Coronary artery disease	126 (22)	31 (26)	95 (21)	0.12
Congestive heart failure	146 (23)	30 (24)	116 (23)	0.02
Diabetes	155 (25)	32 (25)	123 (25)	0.02
Hypertension	492 (79)	100 (79)	392 (78)	0.02
Neurologic disease	232 (37)	47 (37)	185 (37)	0.01
Surgical subtype, n (%)				0.09
Dentistry	2 (0.3)	1 (0.8)	1 (0.2)	
General	123 (20)	29 (23)	94 (19)	
Gastrointestinal radiology	21 (3)	4 (3)	17 (3)	
Gynecologic	29 (5)	5 (4)	24 (5)	
Interventional radiology	11 (2)	0 (0)	11 (2)	
Nonintracranial neurosurgery	66 (11)	11 (9)	55 (11)	
Ophthalmologic	9 (1)	0 (0)	9 (2)	
Oral/maxillofacial	4 (0.6)	0 (0)	4 (0.8)	
Orthopedics	162 (26)	27 (21)	135 (27)	
Otolaryngological	31 (5)	5 (4)	26 (5)	
Plastics	13 (2)	1 (0.8)	12 (2)	
Thoracic	44 (7)	14 (11)	30 (6)	
Transplant	19 (3)	1 (0.8)	18 (4)	
Trauma	12 (2)	2 (1.6)	10 (2)	
Urology	56 (9)	13 (10)	43 (9)	
Vascular	24 (4)	13 (10)	11 (2)	

Surgical subtype is based on the surgical service that cared for the patient, as indicated in the Multicenter Perioperative Outcomes Group database.
ASA, American Society of Anesthesiologists.

patients died, and less than 30% of patients (39 of 133) were discharged home after the index hospitalization.

Discussion

In this multicenter, retrospective case–control study, intraoperative hypotension and both hypo- and hypercarbia were associated with postoperative ischemic stroke. While there did not appear to be a synergistic interaction between hypotension and either hypo- or hypercarbia, they were each associated with stroke risk in an additive manner. Upon manual review of stroke cases, embolic etiologies were commonly reported, although there was no documented etiology for many cases encountered. The location of most strokes appeared to be in the middle cerebral artery territory. Therapeutic interventions (*e.g.*, endovascular thrombectomy) were uncommon, and less than 30% of stroke patients were ultimately discharged home.

It is biologically plausible that the combination of intraoperative hypotension and dyscarbia (*i.e.*, either hypocarbia or hypercarbia) could lead to ischemic stroke. Reduced cerebral blood flow, *via* hypotension and carbon dioxide dysregulation, can cause watershed infarction directly by hypoperfusion and indirectly through impaired clearance of microemboli.[36] Indeed, functional magnetic resonance

Table 2. Bivariable Associations

Threshold	All n = 618	Stroke n = 122	Controls n = 496	*P* Value
AUC MAP < 55 mmHg, mean ± SD	5 ± 9	6 ± 11	5 ± 9	0.537
AUC MAP < 60 mmHg, mean ± SD	15 ± 21	15 ± 21	14 ± 21	0.811
AUC MAP < 65 mmHg, mean ± SD	33 ± 41	35 ± 38	33 ± 42	0.669
AUC $ETCO_2$ ≤ 30 mmHg, mean ± SD	6 ± 12	8 ± 13	6 ± 12	0.147
AUC $ETCO_2$ ≤ 35 mmHg, mean ± SD	44 ± 48	51 ± 51	42 ± 47	0.094
AUC $ETCO_2$ ≥ 45 mmHg, mean ± SD	9 ± 17	11 ± 21	8 ± 16	0.184

AUC, area under curve; $ETCO_2$, end-tidal carbon dioxide; MAP, mean arterial pressure.

Table 3. Adjusted Analysis—Seemingly Unrelated Regression Models

Model	Equation	Threshold	Adjusted Odds Ratio	95% CI	*P* Value
1*	1	AUC MAP < 55 mmHg	1.10	1.07–1.14	< 0.0001
	2	AUC $ETCO_2$ ≤ 30 mmHg	1.07	1.04–1.10	< 0.0001
2	1	AUC MAP < 60 mmHg	1.04	1.02–1.06	< 0.0001
	2	AUC $ETCO_2$ ≤ 30 mmHg	1.07	1.04–1.10	< 0.0001
3	1	AUC MAP < 65 mmHg	1.02	1.01–1.03	0.001
	2	AUC $ETCO_2$ ≤ 30 mmHg	1.07	1.03–1.12	0.0007
4	1	AUC MAP < 55 mmHg	1.17	1.10–1.23	< 0.0001
	2	AUC $ETCO_2$ ≤ 35 mmHg	1.02	1.01–1.03	< 0.0001
5	1	AUC MAP < 60 mmHg	1.07	1.04–1.10	< 0.0001
	2	AUC $ETCO_2$ ≤ 35 mmHg	1.02	1.01–1.03	< 0.0001
6	1	AUC MAP < 65 mmHg	1.04	1.03–1.05	< 0.0001
	2	AUC $ETCO_2$ ≤ 35 mmHg	1.03	1.02–1.04	< 0.0001
7	1	AUC MAP < 55 mmHg	1.15	1.13–1.17	< 0.0001
	2	AUC $ETCO_2$ ≥ 45 mmHg	1.10	1.08–1.11	< 0.0001
8	1	AUC MAP < 60 mmHg	1.06	1.05–1.07	< 0.0001
	2	AUC $ETCO_2$ ≥ 45 mmHg	1.10	1.09–1.11	< 0.0001
9	1	AUC MAP < 65 mmHg	1.03	1.03–1.03	< 0.0001
	2	AUC $ETCO_2$ ≥ 45 mmHg	1.11	1.10–1.11	< 0.0001

*Primary pre-specified analysis. The adjusted odds ratios are per unit (mmHg-min) scaled to 10 units below (or outside of) each threshold. Seemingly unrelated regression models adjusted for age, sex, race (white *vs.* nonwhite), year, estimated blood loss, cardiac arrhythmia history, chronic pulmonary disease, coronary artery disease, congestive heart failure, diabetes, hypertension, neurologic disorders, and valvular heart disease.

AUC, area under the curve; $ETCO_2$, end-tidal carbon dioxide; MAP, mean arterial pressure.

imaging data in human volunteers demonstrate that the combination of reduced cerebrovascular inflow and increased cerebrovascular resistance, induced by hypocapnia, can create conditions for cerebral ischemia, particularly in those with pre-existing cerebrovascular disease.[9,18] Hyperventilation is also associated with reduced cerebral oxygenation across different surgical populations,[37–39] and low $ETCO_2$ during endovascular thrombectomy is associated with poor functional outcomes.[40] Conversely, hypoventilation and hypercapnia can also increase ischemia risk *via* the so-called "steal phenomenon," whereby cerebral blood flow is shifted away from vulnerable cerebrovascular territories where compensatory vasodilation is already maximized (*i.e.*, in the setting of atherosclerotic disease).[9] In this unselected, noncardiac surgery population, pre-pecified MAP and $ETCO_2$ thresholds demonstrated an association with postoperative ischemic stroke after adjustments for key confounders. These associations could conceivably be even stronger for patients with pre-existing cerebrovascular disease, and for the more insidious outcome of clinically silent, radiographically detected stroke,[3] but this requires testing with a prospective trial design.

Alternative explanations are also possible for the associations identified. Patients inherently at high risk for stroke may be more likely to experience intraoperative hypotension and carbon dioxide derangements. In fact, a large-scale, retrospective observational study revealed that patients with high baseline risk for stroke were more likely to experience prolonged intraoperative hypotension.[41] In this same study, there was no association between any intraoperative blood pressure threshold tested and postoperative stroke, although depth below thresholds was not tested. These findings align with a retrospective single-center study demonstrating no association between time and depth below a MAP of 70 mmHg and risk of stroke, although the median time and depth below a MAP of 70 in stroke cases could be considered mild (19 mmHg-min).[42] Conversely, a single-center retrospective study

Table 4. Stroke Characteristics

	Stroke Cases (n = 133)
Age, yr, median (interquartile range)	70 (63–77)
Sex, male, n (%)	57 (43)
Race, n, (%)	
White	71 (53)
Black	19 (14)
Asian or Pacific Islander	1 (0.8)
Unknown	42 (32)
Weight, kg, mean ± SD*	83 ± 20
Body mass index, kg/m^2, mean (standard deviation)*	30 (7)
Neuroimaging, n (%)	
Computed tomography only	33 (25)
Magnetic resonance imaging only	9 (7)
Both computed tomography and magnetic resonance imaging	91 (68)
Neurology consultation, n (%)	129 (97)
Postoperative day, n (%)	
Day of surgery	11 (8)
1	32 (24)
2	17 (13)
3	17 (13)
4	12 (9)
5–10	19 (14)
11–15	12 (9)
16–20	4 (3)
21–30	5 (4)
Not reported	4 (3)
Initial National Institutes of Health Stroke Scale, n (%)	
1–4	24 (18)
5–15	23 (17)
16–20	5 (4)
≥ 21	11 (8)
Not documented	70 (53)
Etiology, n (%)	
Large-artery atherosclerosis	9 (7)
Cardioembolic	44 (33)
Embolic (noncardiac)	28 (21)
Small-vessel occlusion (lacune)	9 (7)
Watershed infarct	9 (7)
Cryptogenic	3 (2)
Other	3 (2)
Not documented	28 (21)
Vascular territory, n (%)†	
Middle cerebral artery	64 (48)
Posterior cerebral artery	32 (24)
Anterior cerebral artery	13 (10)
Internal carotid artery	8 (6)
Deep/small vessel (*e.g.*, thalamic, pontine)	17 (13)
Basilar	9 (7)
Vertebral	8 (6)
Not specified in medical record	22 (17)
Interventions, n (%)	
Intravenous alteplase	8 (6)
Endovascular thrombectomy	6 (5)
Modified Rankin Scale at discharge, n (%)	
0–2	3 (2)
3–6	12 (9)
Not documented	118 (89)
Disposition, n (%)	
Home	39 (29)
Inpatient rehabilitation facility	32 (24)
Skilled nursing facility	41 (31)
Hospice	1 (0.8)
Death	20 (15)

*Weight data are available from only 103 cases, and body mass index data are available for 80 cases. Of note, the 133 cases in this table include 3 stroke cases that were unable to be matched, and 4 cases where the surgical patients underwent monitored anesthesia care (see fig. 1). †All territories affected by a given stroke are reported.

that focused on relative hypotension from preoperative baseline revealed an association between stroke and duration of time more than 30% below preoperative baseline.[43] Of note, this association was not statistically significant with duration of time more than 40% below baseline. The authors acknowledged that intraoperative hypotension could contribute to stroke risk, although other factors may play a larger role. Intraoperative derangements in blood pressure and carbon dioxide may, at the least, serve as warning signs for increased stroke risk and suggest the possible need for close postoperative monitoring.

The embolic etiologies reported in this study might further weigh against the likelihood of intraoperative malperfusion as a primary driver of stroke. Forty of the stroke cases in this series also occurred on postoperative day 5 or later. As such, thromboembolic events and hemodynamic perturbations in the postoperative period may also cause postoperative stroke. Prospective trials will be required to determine the causal relevance and effect size of these intraoperative physiologic associations with stroke, because retrospective studies are not designed to detect clinically silent stroke.[3] To provide a quantitative example of effect size from this study, 10 min with a MAP of 50 mmHg and $ETco_2$ of 28 mmHg would confer an approximate adjusted 2.02 (202%) increased relative risk of stroke based on these results (see Supplemental Digital Content 3 for calculations, http://links.lww.com/ALN/C910). These associations may be much higher for covert stroke.

Stroke characteristics and outcomes in this study are consistent with previously reported findings. The majority of strokes tend to occur within the first few days after surgery,[15,44] which may reflect hemodynamic perturbations and thromboembolic events in the early postoperative setting. Indeed, anticoagulants and antiplatelet agents are often held perioperatively, and surgical interventions induce proinflammatory and thrombotic cascades.[45] In fact, discontinuing aspirin therapy can lead to increased stroke risk for up to 4 weeks.[46] It remains unclear which patients may have high risk for such cerebrovascular thromboembolic events, although inflammatory genetic predisposition may play a role.[47] Stroke interventions were also uncommon in this study, with less than 10% of patients receiving intravenous or endovascular therapy. A previous large-scale registry study similarly demonstrated that less than 5% of identified surgical stroke patients received thrombolytic therapy.[5] Reasons for infrequent therapy are unclear but may relate to delayed stroke identification and/or guideline recommendations. In terms of the latter, it is often unrecognized that many surgeries do not represent an absolute contraindication to the use of intravenous alteplase after major surgery.[48] Thus, interventional therapy is likely underutilized, and outcomes associated with postoperative stroke tend to be quite poor. Discharges to skilled care facilities were common in our study and previous investigations.[4,5] Mortality ranges between 15 and 30%.[4,5]

This study has important limitations. As this was a retrospective analysis, causality cannot be determined from

statistical inferences generated. Many patients did not have arterial lines, precluding analysis of arterial partial pressure of carbon dioxide and $ETCO_2$ gradients. Data for certain risk factors, such as β-blockade, were not available from most sites and were not included in the analysis. Since β-blockade can reduce cerebral perfusion and oxygen delivery,[49] β-blockade may further increase stroke risk in the setting of hypotension and/or carbon dioxide dysregulation. Additionally, the confounding effects of blood pressure and $ETCO_2$ from the pre- and postoperative periods could not be determined. For example, postoperative hypotension and hypo- or hyperventilation may also lead to cerebrovascular ischemia and stroke after surgery. Additionally, biologic systems are complex, and intraoperative physiologic perturbations can synergistically interact with other factors, such as hemorrhage and cerebrovascular disease, to increase stroke risk. Thus, adjusting for these covariates may not have been appropriate given the possibility of an interaction effect. While multilevel interactions can be challenging to interpret statistically, the relationships among blood pressure, carbon dioxide, blood loss, and pre-existing cerebrovascular disease can be tested prospectively through interaction analyses and with prespecified subgroups (*i.e.*, those with and without cerebrovascular disease history). As this study was reliant on billing code data for stroke case inclusion, we were unable to test the relationship between intraoperative physiologic variables and clinically undetected stroke. Additional overt stroke cases may have been missed due to billing code error. Likewise, the sole reliance on cerebrovascular-based International Classification of Diseases billing codes may have limited the ability to detect stroke cases. In addition, these data should not be interpreted to establish an incidence of stroke given the limitations of discharge diagnosis codes for this purpose. Stroke data are also from 2015 and earlier. Temporal patterns in stroke care have since changed.[50] Last, postdischarge data were not collected for control cases. As such, the impact of hypotension, hypocarbia, or hypercarbia was not tested in relation to postdischarge outcomes.

Overall, this study demonstrated that intraoperative hypocarbia, hypercarbia, and hypotension are each independently associated with postoperative stroke. These physiologic perturbations may serve as risk factors that can be modified to reduce the incidence of postoperative stroke.

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Competing Interests

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Supplemental Digital Content

Supplemental Digital Content 1: STROBE and RECORD Statements, http://links.lww.com/ALN/C908
Supplemental Digital Content 2: Case Exclusions, http://links.lww.com/ALN/C909
Supplemental Digital Content 3: Total Area Under the Curve Calculations, http://links.lww.com/ALN/C910
Supplemental Digital Content 4: Interaction Testing, http://links.lww.com/ALN/C911

References

1. Mashour GA, Shanks AM, Kheterpal S: Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. Anesthesiology 2011; 114:1289–96
2. Kamel H, Johnston SC, Kirkham JC, Turner CG, Kizer JR, Devereux RB, Iadecola C: Association between major perioperative hemorrhage and stroke or Q-wave myocardial infarction. Circulation 2012; 126:207–12
3. Perioperative covert stroke in patients undergoing non-cardiac surgery (NeuroVISION): A prospective cohort study. Lancet 2019; 394:1022–9
4. Vlisides PE, Mashour GA, Didier TJ, Shanks AM, Weightman A, Gelb AW, Moore LE: Recognition and management of perioperative stroke in hospitalized patients. A A Case Rep 2016; 7:55–6
5. Saltman AP, Silver FL, Fang J, Stamplecoski M, Kapral MK: Care and outcomes of patients with in-hospital stroke. JAMA Neurol 2015; 72:749–55
6. Vasivej T, Sathirapanya P, Kongkamol C: Incidence and risk factors of perioperative stroke in noncardiac, and nonaortic and its major branches surgery. J Stroke Cerebrovasc Dis 2016; 25:1172–6
7. Joshi B, Ono M, Brown C, Brady K, Easley RB, Yenokyan G, Gottesman RF, Hogue CW: Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. Anesth Analg 2012; 114:503–10
8. Ono M, Brady K, Easley RB, Brown C, Kraut M, Gottesman RF, Hogue CW Jr: Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. J Thorac Cardiovasc Surg 2014; 147:483–9
9. Fisher JA, Venkatraghavan L, Mikulis DJ: Magnetic resonance imaging-based cerebrovascular reactivity and hemodynamic reserve. Stroke 2018; 49:2011–8
10. McKetton L, Sobczyk O, Duffin J, Poublanc J, Sam K, Crawley AP, Venkatraghavan L, Fisher JA, Mikulis DJ: The aging brain and cerebrovascular reactivity. Neuroimage 2018; 181:132–41
11. Colquhoun DA, Shanks AM, Kapeles SR, Shah N, Saager L, Vaughn MT, Buehler K, Burns ML, Tremper KK, Freundlich RE, Aziz M, Kheterpal S, Mathis MR: Considerations for integration of perioperative electronic health records across institutions for research and quality improvement: The approach taken by the Multicenter Perioperative Outcomes Group. Anesth Analg 2020; 130:1133–46
12. Vlisides PE: Associations between intraoperative blood pressure, end-tidal carbon dioxide, and stroke risk: A retrospective case-control study from the Multicenter Perioperative Outcomes Group. Available at: https://doi.org/10.17605/OSF.IO/B83V9. Accessed May 4, 2021.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Lancet 2007; 370:1453–7
14. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM; RECORD Working Committee: The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med 2015; 12:e1001885
15. Mashour GA, Sharifpour M, Freundlich RE, Tremper KK, Shanks A, Nallamothu BK, Vlisides PE, Weightman A, Matlen L, Merte J, Kheterpal S: Perioperative metoprolol and risk of stroke after noncardiac surgery. Anesthesiology 2013; 119:1340–6
16. Akkermans A, van Waes JAR, Thompson A, Shanks A, Peelen LM, Aziz MF, Biggs DA, Paganelli WC, Wanderer JP, Helsten DL, Kheterpal S, van Klei WA, Saager L: An observational study of end-tidal carbon dioxide trends in general anesthesia. Can J Anaesth 2019; 66:149–60
17. Willie CK, Tzeng YC, Fisher JA, Ainslie PN: Integrative regulation of human brain blood flow. J Physiol 2014; 592:841–59
18. McKetton L, Cohn M, Tang-Wai DF, Sobczyk O, Duffin J, Holmes KR, Poublanc J, Sam K, Crawley AP, Venkatraghavan L, Fisher JA, Mikulis DJ: Cerebrovascular resistance in healthy aging and mild cognitive impairment. Front Aging Neurosci 2019; 11:79
19. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: Toward an empirical definition of hypotension. Anesthesiology 2013; 119:507–15
20. Checkoway H, Pearce N, Kriebel D: Selecting appropriate study designs to address specific research questions in occupational epidemiology. Occup Environ Med 2007; 64:633–8
21. Kleinbaum DG, Sullivan KM, Barker ND: Matching - Seems easy, but not that easy, A Pocket Guide to Epidemiology, 1st edition. Edited by Kleinbaum DG, Sullivan KM, Barker ND. New York, Springer Publishing, 2007; 257–75
22. Austin PC: The use of propensity score methods with survival or time-to-event outcomes: Reporting measures of effect similar to those used in randomized experiments. Stat Med 2014; 33:1242–58
23. Stuart EA: Matching methods for causal inference: A review and a look forward. Stat Sci 2010; 25:1–21
24. Ashes C, Judelman S, Wijeysundera DN, Tait G, Mazer CD, Hare GM, Beattie WS: Selective β1-antagonism

with bisoprolol is associated with fewer postoperative strokes than atenolol or metoprolol: A single-center cohort study of 44,092 consecutive patients. Anesthesiology 2013; 119:777–87
25. Lin MH, Kamel H, Singer DE, Wu YL, Lee M, Ovbiagele B: Perioperative/postoperative atrial fibrillation and risk of subsequent stroke and/or mortality. Stroke 2019; 50:1364–71
26. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA: Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; 43:1130–9
27. Chang CS, Liao CH, Lin CC, Lane HY, Sung FC, Kao CH: Patients with epilepsy are at an increased risk of subsequent stroke: A population-based cohort study. Seizure 2014; 23:377–81
28. Hong Y, Tang HR, Ma M, Chen N, Xie X, He L: Multiple sclerosis and stroke: A systematic review and meta-analysis. BMC Neurol 2019; 19:139
29. Kummer BR, Diaz I, Wu X, Aaroe AE, Chen ML, Iadecola C, Kamel H, Navi BB: Associations between cerebrovascular risk factors and Parkinson disease. Ann Neurol 2019; 86:572–81
30. Zellner A: An efficient method of estimating seemingly unrelated regressions and tests for aggregation bias. J Am Stat Assoc 1962; 57:348–68
31. Keshavarzi S, Ayatollahi SM, Zare N, Pakfetrat M: Application of seemingly unrelated regression in medical data with intermittently observed time-dependent covariates. Comput Math Methods Med 2012; 2012:821643
32. Beasley TM: Seemingly unrelated regression (SUR) models as a solution to path analytic models with correlated errors. Multiple Linear Regression Viewpoints 2008; 34:1–7
33. Mize TD, Doan L, Long JS: A general framework for comparing predictions and marginal effects across models. Soc Methodol 2019; 49:152–89
34. Pan W: Akaike's information criterion in generalized estimating equations. Biometrics 2001; 57:120–5
35. Hardin JW, Hilbe JM: Generalized Estimating Equations, 2nd edition. Boca Raton, Florida, CRC Press, 2013
36. Caplan LR, Hennerici M: Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. Arch Neurol 1998; 55:1475–82
37. Picton P, Dering A, Alexander A, Neff M, Miller BS, Shanks A, Housey M, Mashour GA: Influence of ventilation strategies and anesthetic techniques on regional cerebral oximetry in the beach chair position: A prospective interventional study with a randomized comparison of two anesthetics. Anesthesiology 2015; 123:765–74
38. Picton P, Shanks A, Dorje P, Mashour GA: The influence of basic ventilation strategies on cerebral oxygenation in anesthetized patients without vascular disease. J Clin Monit Comput 2010; 24:421–5
39. Picton P, Chambers J, Shanks A, Dorje P: The influence of inspired oxygen fraction and end-tidal carbon dioxide on post-cross-clamp cerebral oxygenation during carotid endarterectomy under general anesthesia. Anesth Analg 2010; 110:581–7
40. Takahashi CE, Brambrink AM, Aziz MF, Macri E, Raines J, Multani-Kohol A, Hinson HE, Lutsep HL, Clark WM, Fields JD: Association of intraprocedural blood pressure and end tidal carbon dioxide with outcome after acute stroke intervention. Neurocrit Care 2014; 20:202–8
41. Wongtangman K, Wachtendorf LJ, Blank M, Grabitz SD, Linhardt FC, Azimaraghi O, Raub D, Pham S, Kendale SM, Low YH, Houle TT, Eikermann M, Pollard RJ: Effect of intraoperative arterial hypotension on the risk of perioperative stroke after noncardiac surgery: A retrospective multicenter cohort study. Anesth Analg 2021; 133:1000–8
42. Hsieh JK, Dalton JE, Yang D, Farag ES, Sessler DI, Kurz AM: The association between mild intraoperative hypotension and stroke in general surgery patients. Anesth Analg 2016; 123:933–9
43. Bijker JB, Persoon S, Peelen LM, Moons KG, Kalkman CJ, Kappelle LJ, van Klei WA: Intraoperative hypotension and perioperative ischemic stroke after general surgery: A nested case-control study. Anesthesiology 2012; 116:658–64
44. Grau AJ, Eicke M, Burmeister C, Hardt R, Schmitt E, Dienlin S: Risk of ischemic stroke and transient ischemic attack is increased up to 90 days after non-carotid and non-cardiac surgery. Cerebrovasc Dis 2017; 43:242–9
45. Schietroma M, Carlei F, Mownah A, Franchi L, Mazzotta C, Sozio A, Amicucci G: Changes in the blood coagulation, fibrinolysis, and cytokine profile during laparoscopic and open cholecystectomy. Surg Endosc 2004; 18:1090–6
46. Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J: Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. Arch Neurol 2005; 62:1217–20
47. Grocott HP, White WD, Morris RW, Podgoreanu MV, Mathew JP, Nielsen DM, Schwinn DA, Newman MF; Perioperative Genetics and Safety Outcomes Study (PEGASUS) Investigative Team: Genetic polymorphisms and the risk of stroke after cardiac surgery. Stroke 2005; 36:1854–8
48. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL: Guidelines for the early management of patients

with acute ischemic stroke: 2019 update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019; 50:e344–418

49. Ragoonanan TE, Beattie WS, Mazer CD, Tsui AK, Leong-Poi H, Wilson DF, Tait G, Yu J, Liu E, Noronha M, Dattani ND, Mitsakakis N, Hare GM: Metoprolol reduces cerebral tissue oxygen tension after acute hemodilution in rats. Anesthesiology 2009; 111:988–1000
50. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, Sila CA, Hassan AE, Millan M, Levy EI, Mitchell P, Chen M, English JD, Shah QA, Silver FL, Pereira VM, Mehta BP, Baxter BW, Abraham MG, Cardona P, Veznedaroglu E, Hellinger FR, Feng L, Kirmani JF, Lopes DK, Jankowitz BT, Frankel MR, Costalat V, Vora NA, Yoo AJ, Malik AM, Furlan AJ, Rubiera M, Aghaebrahim A, Olivot JM, Tekle WG, Shields R, Graves T, Lewis RJ, Smith WS, Liebeskind DS, Saver JL, Jovin TG; DAWN Trial Investigators: Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 2018; 378:11–21

ANESTHESIOLOGY

Respiratory Effects of the Atypical Tricyclic Antidepressant Tianeptine in Human Models of Opioid-induced Respiratory Depression

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Tianeptine is an atypical antidepressant and cognitive enhancer that can be administered orally or intravenously

ABSTRACT

Background: Animal data suggest that the antidepressant and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor modulator tianeptine is able to prevent opioid-induced respiratory depression. The hypothesis was that oral or intravenous tianeptine can effectively prevent or counteract opioid-induced respiratory depression in humans.

Methods: Healthy male and female volunteers participated in two studies that had a randomized, double blind, placebo-controlled, crossover design. First, oral tianeptine (37.5-, 50-, and 100-mg doses with 8 subjects) pretreatment followed by induction of alfentanil-induced respiratory depression (alfentanil target concentration, 100 ng/ml) was tested. Primary endpoint was ventilation at an extrapolated end-tidal carbon dioxide concentration of 55 mmHg ($\dot{V}_E55$). Next, the ability of four subsequent and increasing infusions of intravenous tianeptine (target tianeptine plasma concentrations 400, 1,000, 1,500, and 2,000 ng/ml, each given over 15 min) to counteract remifentanil-induced respiratory depression was determined in 15 volunteers. Ventilation was measured at isohypercpania (baseline ventilation 20 ± 2 l/min). The primary endpoint was minute ventilation during the 60 min of tianeptine *versus* placebo infusion.

Results: Alfentanil reduced $\dot{V}_E55$ to 13.7 (95% CI, 8.6 to 18.8) l/min after placebo pretreatment and to 17.9 (10.2 to 25.7) l/min after 50-mg tianeptine pretreatment (mean difference between treatments 4.2 (–11.5 to 3.0) l/min, $P = 0.070$). Intravenous tianeptine in the measured concentration range of 500 to 2,000 ng/ml did not stimulate ventilation but instead worsened remifentanil-induced respiratory depression: tianeptine, 9.6 ± 0.8 l/min *versus* placebo 15.0 ± 0.9 l/min; mean difference, 5.3 l/min; 95% CI, 2.5 to 8.2 l/min; $P = 0.001$, after 1 h of treatment.

Conclusions: Neither oral nor intravenous tianeptine were respiratory stimulants. Intravenous tianeptine over the concentration range of 500 to 2000 ng/ml worsened respiratory depression induced by remifentanil.

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This article is featured in "This Month in Anesthesiology," page A1. This article has a video abstract. This article has a visual abstract available in the online version. H.A. and R.v.d.S. contributed equally to this article.

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- Tianeptine may cause respiratory stimulation during opioid-induced respiratory depression by enhancing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-mediated transmission and reducing glutamatergic transmission at *N*-methyl-D-aspartate receptors
- However, tianeptine also acts as a μ-opioid receptor agonist, which may reduce its respiratory stimulatory capabilities

What This Article Tells Us That Is New

- The hypothesis that tianeptine is able to cause effective reversal of opioid-induced respiratory depression was tested in 15 male and female subjects in a double-blind, randomized, placebo-controlled crossover study by determining the effect of tianeptine at four increasing target plasma concentrations on remifentanil-induced respiratory depression at isohypercapnia
- Over the plasma tianeptine concentration range tested (500 to 2,000 ng/ml), it did not produce respiratory stimulation during remifentanil-induced respiratory depression but instead worsened respiratory depression with a further decline in ventilation at an extrapolated end-tidal carbon dioxide concentration of 55 mmHg by 5 l/min

Modern medicine relies heavily on opioids for suppression of moderate to severe pain. Strong opioids are used during anesthesia to suppress autonomic responses and are given for treatment of acute (postoperative) pain, chronic cancer pain and noncancer pain.[1] However, the use of opioids comes with adverse effects, of which opioid-induced respiratory depression is most problematic, as it is potentially lethal.[2] Opioid-induced respiratory depression is related to depression or inactivation of respiratory rhythm generation within the brainstem due to activation of μ-opioid receptors predominantly in the pre-Bötzinger complex and Kölliker–Fuse nucleus.[3–5] One way of treating or preventing opioid-induced respiratory depression without compromising analgesia is by administration of respiratory stimulants that do not interfere with the opioid receptor system.[6] Many such stimulants are currently being developed; however, none seem adequate for therapeutic use, and all need further study of efficacy and toxicity.[6]

A possible novel option for respiratory stimulation could be the administration of tianeptine.[7] Tianeptine is an atypical antidepressant and cognitive enhancer that can be administered orally or intravenously. It induces neuroplastic changes and modulates noradrenergic, dopaminergic, and glutamatergic pathways.[8–10] For example, tianeptine facilitates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated glutamatergic transmission and reduces AMPA receptor surface diffusion. AMPA receptors are present in key brainstem centers involved in respiratory drive, such as the pre-Bötzinger complex, where they play an important role in the maintenance of respiratory rhythmogenesis and inspiratory drive, as well as sites outside the pre-Bötzinger complex.[2–6] One animal study that investigated the respiratory effects of tianeptine on morphine-induced respiratory depression showed that tianeptine pretreatment prevented opioid-induced respiratory depression without affecting antinociception.[7] Tianeptine is marketed currently in a number of countries, primarily as an antidepressant,[11] and consequently is a practical target for study as a reversal agent of opioid-induced respiratory depression. Moreover, the ampakines are among the most effective respiratory stimulants.[6] An important additional observation is that tianeptine is an agonist at the μ-opioid receptor,[12] making it an even more attractive candidate as a respiratory stimulant drug, because it may enhance pain relief while stimulating respiration.

The current study explored a possible therapeutic role for tianeptine in mitigating opioid-induced respiratory depression. In a first proof-of-concept study (study 1), we tested oral tianeptine on alfentanil-induced respiratory depression by measuring the hypercapnic ventilatory response. Next, we chose to further study intravenous tianeptine, as the intravenous route was deemed more clinically relevant when aiming at reversal of opioid-induced respiratory depression in the perioperative setting (study 2). In study 2, we first studied the pharmacokinetics of intravenous tianeptine in six healthy volunteers (study 2a). Using data from this initial population pharmacokinetic modeling study, we designed a tianeptine dose-escalating study to determine the effect of tianeptine on top of remifentanil-induced respiratory depression (study 2b). Both studies 1 and 2b had double-blind, randomized, placebo-controlled crossover designs. Our hypothesis was that in study 1, we would detect a signal that tianeptine is able to counteract opioid-induced respiratory depression and that study 2 would show that tianeptine is able to cause effective reversal of opioid-induced respiratory depression.

Materials and Methods

Ethics, Registration, and Changes in Study Protocol

The study protocols were approved by the institutional review board (METC [Medisch Ethische Toetsingscommissie] Leiden-Den Haag-Delft) in Leiden and the Central Committee on Research Involving Human Subjects (CCMO [Centrale Commissie Mensgebonden Onderzoek], competent authority) in The Hague, both in The Netherlands. All study procedures were conducted according to good clinical practice guidelines and adhered to the tenets of the Declaration of Helsinki. Before enrollment, all subjects gave written informed consent, after which their medical history was taken and a physical examination was performed. Study 1 was performed from January to July 2014, and the pharmacokinetic studies 2a and 2b started in June 2019 and were completed in January 2021. All studies were registered in the trial register of the Dutch Cochrane Center (www.trialregister.nl) under identifiers NL3849

(study 1) and NL7907 (study 2) with principle investigator Albert Dahan, M.D., Ph.D., and registration dates August 21, 2013 and July 26, 2019 for studies 1 and 2, respectively. Study 1 was exploratory and served to detect a clinically relevant reduction in alfentanil-induced respiratory depression (tianeptine effect is greater than the placebo effect; no *a priori* significance level was defined). Once an increase in minute ventilation was detected with 50 mg of tianeptine, we proceeded with a second study that determined the pharmacokinetics of intravenous tianeptine and the effect of escalating tianeptine doses on remifentanil-induced respiratory depression.

Study 1 initially had four dosing groups: 37.5, 50, and 100 mg of oral tianeptine to counteract alfentanil-induced respiratory depression at a target plasma concentration of 100 ng/ml and 100 mg of oral tianeptine to counter alfentanil respiratory effect at an alfentanil target plasma concentration of 50 ng/ml. After completion of three doses (37.5 mg of tianeptine + 100 ng/ml alfentanil, 50 mg of tianeptine + 100 ng/ml of alfentanil, and 100 mg of tianeptine + 50 ng/ml alfentanil), the study was prematurely ended. After the oral tianeptine study had demonstrated a clinically relevant effect, we developed an intravenous administration form of the drug as the intravenous route was considered more clinically relevant when aiming at reversal of opioid-induced respiratory depression in the perioperative setting. The second study had two parts: an initial population pharmacokinetic modeling study to obtain pharmacokinetic data to design an infusion scheme for study 2b, in which the effect of four sequential increases in tianeptine doses were given on top of remifentanil-induced respiratory depression and minute ventilation ($\dot{V}_E$) was measured at isohypercapnia.

Participants

Male and female participants were recruited by advertisements in the local newspaper and flyers posted on the campus of Leiden University. Inclusion criteria were: age 18 to 40 yr; body mass index of less than 30 $kg \cdot m^{-2}$; and the ability to communicate with the investigators. Exclusion criteria were: clinically relevant history or current physical or mental disease; systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 95 mmHg at screening; history of alcohol or substance abuse within 3 yr before screening; use of more than 20 units of alcohol per week; a positive alcohol breath test at screening or on the morning of the dosing days; use of any medication except oral contraceptives; not using contraceptives or not surgically sterilized when sexually active; positive pregnancy test at screening or on the morning of the study; history of allergic reaction to study medication; participation in an investigational drug trial in the 2 months before screening; or any other condition that in the opinion of the investigator would complicate or compromise the study or the well-being of the subject.

Study Design

To measure $\dot{V}_E$ and induce isohypercapnia in studies 1 and 2b, we used the dynamic end-tidal forcing technique.[13,14] This technique allows rapid changes in end-tidal carbon dioxide concentration while maintaining the end-tidal oxygen concentration constant. The technique has been described extensively before. In brief, subjects breathed through a facemask connected to a pneumotachograph (catalog no. 4813; Hans Rudolph Inc., USA) to measure respiratory flow and volume, which was connected to three mass flow controllers (Bronkhorst High Tech, The Netherlands) for the delivery of oxygen, carbon dioxide, and nitrogen. The mass flow controllers were controlled by a computer running the custom-made RESREG/ACQ software (Leiden University Medical Center, The Netherlands), allowing the manipulation of the end-tidal gas concentrations by varying the inspired concentration, breath-to-breath data acquisition and real-time visualization of the data. The inspired and expired oxygen and carbon dioxide partial pressures were measured at the mouth using a capnograph (Datex Capnomac, Finland). Heart rate, blood pressure, and arterial oxygen saturation were continuously measured from the arterial cannula (Datex Cardiocap, Finland), and by pulse oximetry (Masimo Corporation, USA), respectively.

Study 1. For study 1, a total of 24 subjects received alfentanil/tianeptine or alfentanil/placebo in a double-blind, randomized, crossover design with eight subjects receiving each tianeptine dose. The steady-state respiratory response to hypercapnia was measured using four 7-min steps in end-tidal carbon dioxide concentration were applied with step sizes of 4.5 mmHg (0.6 kPa), 9 mmHg (1.2 kPa), 13.5 mmHg (1.8 kPa), and 18.0 mmHg (2.4 kPa) above resting end-tidal carbon dioxide concentration.[14] Throughout the test, the end-tidal Po_2 was kept at normoxia (105 mmHg or 14 kPa). The hypercapnic ventilatory response was obtained before any drug administration and 15 min after ingestion of the tianeptine or placebo tablets; alfentanil target-controlled infusion (targets 100 or 50 ng/ml) started 45 min after tianeptine or placebo tablets, and subsequent hypercapnic ventilatory responses were obtained at 30, 90, and 150 min during alfentanil administration. A final hypercapnic ventilatory response was obtained 30 min after discontinuation of the alfentanil infusion. The design of the study considered the kinetics of oral tianeptine with rapid absorption (maximum concentration occurs after approximately 1 h), systemic availability of 99%, and an elimination half-life of 2.5 h.[15] The primary endpoint for analysis was the change from baseline of $\dot{V}_E$ at an extrapolated end-tidal carbon dioxide concentration of 7.3 kPa or 55 mmHg ($\dot{V}_E55$). Since bioavailability may vary due to alfentanil-induced delayed gastric emptying, a pragmatic approach was adopted for data analysis. In the analysis, we used the maximum change in $\dot{V}_E55$ value (relative to baseline) of the three measurements during alfentanil infusion

observed in the tianeptine group and compared this measurement to the corresponding measurement during the placebo experiment.

The Hypercapnic Ventilatory Response. The ventilatory response to hypercapnia (fig. 1) has a "dog leg" or hockey stick appearance with an initial flat part, where ventilation is independent of the carbon dioxide concentration, and, beginning at the so-called ventilatory recruitment threshold, a linear increasing part.[14,16] The linear increase is described by a slope (S) and an "apneic threshold" (B) or the extrapolated carbon dioxide concentration at which ventilation theoretically would be 0, defined by the following equation: ventilation = S × (end-tidal carbon dioxide concentration − B). Only during anesthesia does ventilation reach 0 at the apneic threshold; hence, the flat part is considered the wakefulness drive to breathe. Upon administration of an opioid, the linear part of the curve often shifts to the right, causing a prolongation of the flat part of the curve. This is apparent in figure 1A and B, which show that ventilation does not increase going from 5 to 6 kPa (fig. 1A) or from 6 to 7 kPa (fig. 1B).

Pharmacokinetic Study (Study 2a). The pharmacokinetics of intravenous tianeptine (AMO Pharma Ltd., United Kingdom) was measured in six subjects. *In silico* simulations were performed based on the pharmacokinetic data set of Salvadori *et al.*[15] to obtain four 15-min steps in tianeptine plasma concentration with escalation concentrations: 100, 200, 400, and 800 ng/ml. The simulations led to a specific dosing scheme in the pharmacokinetic study: a bolus dose given over 1 min followed by a 14-min continuous infusion. The first dose (t = 0) was 2 mg followed by an infusion of 0.7 mg given over 14 min (rate = 0.05 mg/min). After 15 min, a 2-mg bolus dose was followed by 1.4 mg over 14 min (0.10 mg/min). After 30 min, a 4-mg bolus was followed by 2.8 mg given over 14 min (0.2 mg/min). Finally, a bolus dose of 8 mg at t = 45 min was followed by an infusion of 5.6 mg over 14 min (0.4 mg/min). The total dose given was 26.5 mg. All doses were based on a 70-kg individual.

Study 2b. In study 2b, 15 subjects participated in a double-blind, randomized, crossover design receiving remifentanil/placebo or remifentanil/tianeptine. The effect of an intravenous tianeptine dose escalation on remifentanil-induced respiratory depression at isohypercapnia was measured. To that end, the end-expired end-tidal carbon dioxide concentration was increased such that $\dot{V}_E$ was 20 ± 2 l/min. Thereafter, remifentanil was infused by target-controlled infusion, such that isohypercapnic $\dot{V}_E$ decreased by approximately 40% of baseline. After steady-state $\dot{V}_E$ was reached, tianeptine or placebo was infused at four distinct target levels for 15 min each (total duration of infusion = 60 min) with target steady-state tianeptine plasma concentrations of 400, 1,000, 1,500, and 2,000 ng/ml. Breath-to-breath minute $\dot{V}_E$ was measured (in min) and analyzed.

Blinding, Dispensing, and Randomization. Both studies were fully blinded and randomized. Randomization was performed by the trial pharmacy using computer-generated randomization lists. After subject allocation, the Leiden University Medical Center trial pharmacy prepared the medication on the morning of the study. For study 1, all tablets were reencapsulated, with all capsules identical in

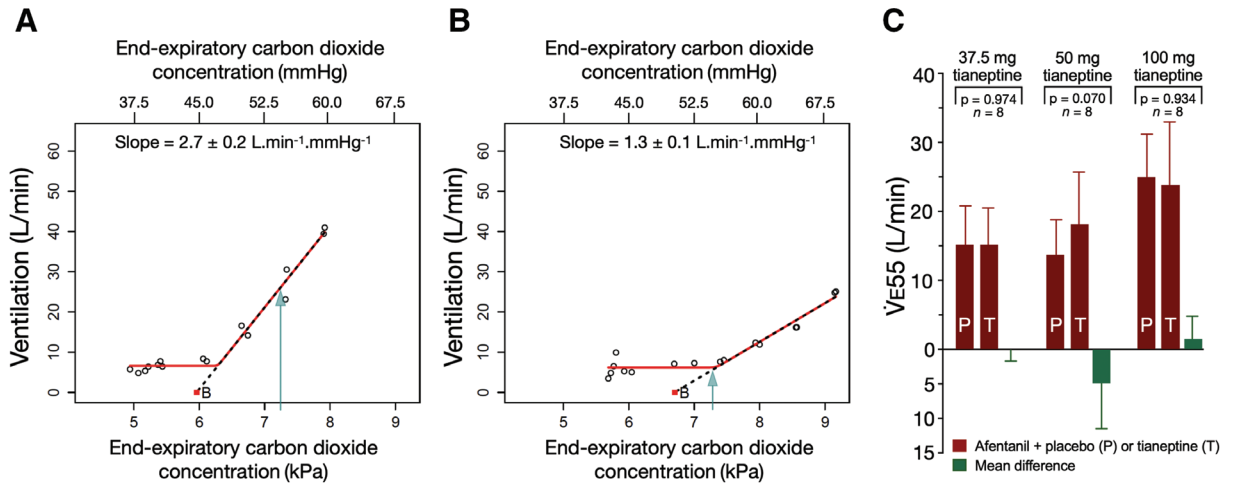

Fig. 1. Effect in study 1 of 50 mg of oral tianeptine (*A*) and placebo (*B*) on the steady-state ventilatory response to carbon dioxide in a single subject from a single run 90 min after the ingestion of tianeptine or placebo. The *arrow* indicates ventilation at an extrapolated end-expiratory concentration of 7.3 kPa or 55 mmHg ($\dot{V}_E$55). The *dots* represent 1-min averages of ventilation data obtained at rest (no added carbon dioxide; horizontal part of the *red curve*) or at elevated end-expiratory carbon dioxide concentration. The *black broken curve* is the fitted hypercapnic ventilatory response curve. The data at ventilation levels above resting ventilation are fitted to the following equation: Ventilation = slope × (end-tidal carbon dioxide concentration − B). (*C*) Pooled data of the primary endpoint of study 1: $\dot{V}_E$55. The *red bars* show the effects of either alfentanil plus placebo (P) or alfentanil plus tianeptine (T) for each of the three dosing groups. The mean differences are given in green. The data are means ± 95% CI.

size and color. For study 2b, the intravenous tianeptine or placebo were delivered in an opaque syringe for intravenous administration. The study drugs were packed in numbered (subject number) but otherwise unmarked containers or syringes and dispensed to the study team just before dosing. The study was independently monitored, and data analyses were performed after database lock.

Drug Development, Opioid, and Tianeptine Administration. In study 1, alfentanil (Jansen Cilag BV, The Netherlands; alfentanil HCl in 0.9% NaCl in water) was administered *via* an infusion cannula placed in the left or right cubital vein. The drug was administered by target-controlled infusion with a target plasma concentration of 50 or 100 ng/ml (on different occasions) using the pharmacokinetic data set from Maitre *et al*.[17] At 45 min after the ingestion of the tianeptine/placebo (37.5, 50, or 100 mg), the alfentanil infusion started and lasted for 2 h. Over this time range, we estimated that the plasma concentrations after the 37.5-mg oral tianeptine dose rapidly decrease from 500 to 180 ng/ml and after the 50-mg oral tianeptine dose decrease from 700 to 260 ng/ml.[15] Tianeptine was ingested with 100 ml of noncarbonated water. Tianeptine tablets (Stablon, 12.5 mg) were obtained from Laboratories Servier SA (France).

For studies 2a and 2b, a sterile tianeptine sodium intravenous formulation (sodium; 7-[(3-chloro-6-methyl-5,5-dioxo-11Hbenzo[c][2,1] benzothiazepin-11-yl)amino] heptanoate; 1 mg/ml) was developed by AMO Pharma Ltd. Tianeptine is a drug with two pKa values. Formulation approaches therefore sought to optimize the pH where ionization would afford physical stability at the target drug loading, without pH-mediated chemical instability. Drug loading optimization also addressed hydrophobic stacking instability concerns. The resulting formulation was manufactured under current Good Manufacturing Practice conditions by KABS Pharmaceuticals Inc. (Canada) with AMO Pharma Ltd. oversight. Sterility and bacterial endotoxin testing were performed by Nucro-Technics Inc. (Canada). Full current Good Manufacturing Practice release testing was performed by KABS Pharmaceuticals Inc. (Canada) using validated methods. Clinical labeling, packaging, and qualified person release were performed by the Leiden University Medical Center pharmacy, which is current Good Manufacturing Practice-certified.

In study 2b, remifentanil (Sandoz NV, Belgium) was infused by target-controlled infusion, using the pharmacokinetic set of Minto *et al*,[18] after $\dot{V}_E$ had stabilized at its isohypercapnic level of 20 ± 2 l/min. Remifentanil infusion was started at a target concentration of 1 ng/ml and was adjusted in steps of 0.1 ng/ml to reach a ventilatory depression level of 40% of baseline. Only when remifentanil-depressed $\dot{V}_E$ had reached its target steady-state level, did the tianeptine infusion start. Four consecutive dose escalations in tianeptine were performed at 15-min intervals to reach estimated steady-state tianeptine target concentrations of 400, 1,000, 1,500, and 2,000 ng/ml. This was done by administration of a bolus dose given over 1-min followed by a 14-min continuous infusion. The doses were determined based on the results of the pharmacokinetic study. The first dose was made up of a 4-mg bolus, given over 1 min, followed by 2.8 mg given over 14 min, with a subsequent dose increment of an 8-mg bolus, followed by 5.6 mg given over 14 min; the next incremental bolus dose was 9 mg, followed by 6.3 mg given over 15 min and finally a 10-mg bolus followed by 7 mg given over 14 min. Each bolus infusion lasted 1 min, and all doses are per 70 kg.

Blood Samples and Measurement of Tianeptine and MC5. In study 2a and 2b, blood samples were obtained from an arterial line, placed in the radial artery of the nondominant arm, to measure plasma concentrations of tianeptine and its metabolite MC5. Blood samples were obtained at t = 0 (pre-tianeptine baseline), and 1, 2, 9, 15, 16, 17, 24, 30, 31, 32, 39, 45, 46, 47, 54, 60, 61, 62, 70, 80, and 90 min after the start of tianeptine infusion. Plasma samples were shipped to Charles River Laboratories Montreal ULC (Canada), where the concentrations were measured by liquid chromatography-tandem mass spectrometry. The analytical range for both parent and metabolite was 1 to 1,000 ng/ml. The intraassay precision and bias were no greater than 6 and −11%, respectively, while the interassay precision and bias were no greater than 5 and − 6%, respectively, over the concentration range of 1 to 1,000 ng/ml for tianeptine and MC5.

Adverse Events. All adverse events were noted in the case report forms. Despite the fact that the literature indicates that tianeptine, even at high doses, is well tolerated, all subjects were closely monitored during tianeptine exposure and queried after finalizing the experiment with special focus on dry mouth, dizziness, drowsiness, and postural hypotension.

Sample Size and Data Analysis

Sample Size Determination. Because study 1 was a proof-of-concept study, the number of subjects was somewhat arbitrarily set at $n = 8$ per dose arm. The aim of this part of the project was to detect a clinically relevant reduction in alfentanil-induced respiratory depression after the ingestion of tianeptine with *a priori* definition of effects size or significance level. In study 2b, no data were available on the effect of intravenous tianeptine on remifentanil-induced respiratory depression. We therefore relied on earlier studies from our laboratory on the effect of the intravenous infusion of the experimental drug GAL021 (currently known as ENA001) and *S*-ketamine on reversal of opioid respiratory effects.[19,20] In those randomized controlled trials that used a crossover design, 12 subjects were sufficient to detect a significant reversal effect from the interventions. To consider the uncertainties in our assumptions, we performed the randomized controlled trial in 15 subjects using a crossover design (placebo *vs.* tianeptine; each subject underwent two experiments with at least 1 week between visits).

Data Analysis of Study 1. The slope of the hypercapnic ventilatory response was estimated in R (The R Foundation for Statistical Computing, www.r-project.org). Within R, data analysis was automated: (1) from the raw data, the medians of the 1-min breath-to-breath minute $\dot{V}_E$ were calculated; (2) all measurements obtained without carbon dioxide stimulation (baseline $\dot{V}_E$) and measurements during the final 2-min of each hypercapnic step of the hypercapnic ventilatory response, representing steady-state hypercapnic $\dot{V}_E$, were selected for further analysis; and (3) the linear increasing parts of the hypercapnic ventilatory response curves beyond the ventilatory recruitment threshold were fitted ($\dot{V}_E$ *vs.* end-tidal carbon dioxide concentration) to obtain the slope of the hypercapnic ventilatory response curve and the extrapolated $\dot{V}_E55$.[14]

A two-way repeated-measures analysis of variance (with factors treatment, time, and time × treatment) was run for each tianeptine dose to determine the effect of tianeptine *versus* placebo on $\dot{V}_E55$. Since this was a proof-of-concept trial aimed to detect an exploratory study, no *P* value was determined *a priori* for statistical significance. Statistical analysis was performed in R.

Data Analysis of the Pharmacokinetic Study (Study 2a). The pharmacokinetic data were analyzed with a two-compartment pharmacokinetic model using a population analysis in NONMEM version 7.5.0 (ICON Development Solutions, USA). The pharmacokinetic model estimates were used to design the dosing scheme used in study 2.

Data Analysis of Study 2b. Eight 1-min timepoints were defined: timepoint A = baseline, before hypercapnia and drug administration; timepoint B = isohypercapnia, before any drug administration); timepoint C = remifentanil at steady-state, before tianeptine administration; timepoint D = 15 min into tianeptine administration, *i.e.,* end of first tianeptine step with target concentration of 400 ng/ml; E = 30 min into tianeptine administration, *i.e.* end of second tianeptine step with target steady-state concentration 1,000 ng/ml; F= 45 min into tianeptine administration, *i.e.* end of third tianeptine step with target concentration 1,500 ng/ml; G = 60 min into tianeptine administration, *i.e.* end of last tianeptine step with target concentration 2,000 ng/ml; and H = 15 min after the end of tianeptine infusion. At each time point, 1-min averages were obtained of minute $\dot{V}_E$, tidal volume, and respiratory rate for data presentation. The minute $\dot{V}_E$ data (tianeptine *vs.* placebo over time) were analyzed by a two-way repeated-measures analysis of variance (with factors treatment, time, and time × treatment) in R with *P* values < 0.01 considered significant to correct for multiple comparisons (5). *Post hoc* tests were by two-tailed paired *t* tests. The data are means ± SD unless otherwise stated.

Results

All subjects completed the experimental sessions without serious adverse events. Apart from sedation, no adverse events were detected. Altogether, 45 healthy subjects (22 men and 23 women) participated with a mean age of 23 yr (range, 20 to 26 yr) and a mean body mass index of 23 kg/m^2 (range, 20 to 26 kg/m^2).

Study 1

An example of a placebo and tianeptine experiment after the oral ingestion of 50 mg of tianeptine or placebo in a single subject is shown in figure 1. It shows that alfentanil e 50-$\dot{V}_E55$ after thmg tianeptine pretreatment was greater than that after placebo pretreatment (26.4 l/min *vs.* 5.8 l/min) due to an increase in the slope of the hypercapnic ventilatory response curve and a leftward shift of the hypercapnic ventilatory response curve. The placebo curve is typical for an opioid effect, *i.e.* a rightward shift of the ventilatory response curve and a decrease of the slope (see fig. 1).[14]

Population analysis of the studentized residuals showed that there was normality, as assessed by the Shapiro–Wilk test of normality and no outliers, as assessed by nonstudentized residuals greater than 3 standard deviations. There was sphericity for the interaction term, as assessed by Mauchly's test of sphericity for each of the analyzed tianeptine doses. There was no statistically significant interaction between tianeptine or placebo and time on alfentanil-induced decrease in $\dot{V}_E55$ for 37.5 mg of tianeptine (n = 8; mean difference, –0.1 l/min; 95% CI, –1.7 to 1.5 l/min; P = 0.974). Tianeptine (50 mg) had a more pronounced effect on $\dot{V}_E55$: alfentanil reduced $\dot{V}_E55$ to 13.7 l/min (95% CI, 8.6 to 18.8 l/min) after placebo pretreatment and to 17.9 l/min (95% CI, 10.2 to 25.7 l/min) after 50-mg tianeptine pretreatment (n = 8; mean difference, 4.2 l/min; 95% CI, –11.5 to 3.0 l/min; P = 0.070; fig. 1C). We considered this ventilatory effect to be the signal that we were looking for. For the group treated with 100 mg of tianeptine and 50 ng/ml alfentanil, no effect on $\dot{V}_E55$ was observed; the interaction between tianeptine and alfentanil was not significant (n = 8; mean difference, 1.5 l/min; 95% CI, –1.8 to 4.8 l/min; P = 0.934).

Pharmacokinetic Study 2a

The mean plasma concentration of tianeptine and its metabolite TMC5 are given in figure 2A. On average, the measured steady-state tianeptine concentrations were within the target ranges as determined by the *in silico* simulation studies based on the pharmacokinetic data set of Salvadori *et al.*[15] The data fits are given in figure 3. They show the measured concentrations (closed circles) and data fit (continuous lines). Population parameter estimates derived from the NONMEM analysis were as follows: volume of compartment 1 (V_1) ± standard error of the estimate 1.5 ± 0.5 l, ω^2 (with between-subject variability in the log domain) = 0.17 ± 0.26; volume of compartment 2 (V_2) = 13.2 ± 1.2 l, with ω^2 = 0.02 ± 0.01; elimination clearance (CL_1) = 16.0 ± 1.0 l/h, with ω^2 = 0.002 ± 0.006; and intercompartmental clearance (CL_2) = 68.5 ± 25.3 l/h,

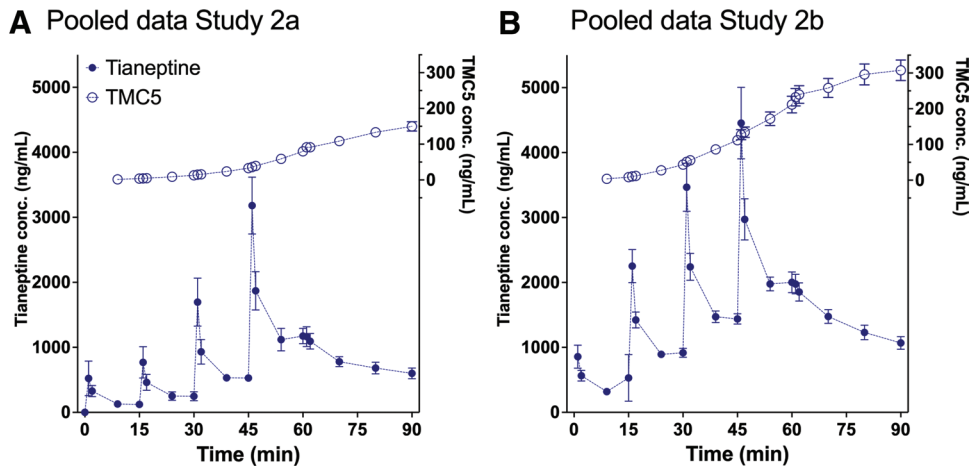

Fig. 2. Results of study 2a and 2b. (*A*) Study 2a. Plasma concentrations of tianeptine and its metabolite TMC5 in the pharmacokinetic study were obtained in six subjects with a dosing regimen based on the pharmacokinetic data from Salvadori *et al.*[15] (*B*) Study 2b. Plasma concentrations of tianeptine and its metabolite TMC5 observed during the randomized placebo-controlled trial in 15 subjects. The data are means ± 95% CI.

with $\omega^2 = 0.14 \pm 0.15$. Finally, σ^2 (with in-subject variability in the log domain) $= 0.014 \pm 0.003$. Using these data, a new infusion scheme was designed starting with an initial 15-min target steady-state tianeptine concentration of 400 ng/ml, followed by 1,000, 1,500, and 2,000 ng/ml.

Study 2b.

The mean plasma concentration of tianeptine and its metabolite TMC5 are given in figure 2B. Average measured steady-state tianeptine plasma concentrations were 530, 917, 1,440, and 2,000 ng/ml. Baseline end-tidal carbon dioxide concentration did not differ between treatment arms: placebo (mean ± SD), 5.2 ± 0.6 kPa (39 ± 4 mmHg) *versus* tianeptine, 5.2 ± 0.8 kPa (39 ± 6 mmHg). The end-tidal carbon dioxide concentration values at the initiation of the isohypercapnic clamp were: placebo, 6.7 ± 0.6 kPa (50 ± 5 mmHg) *versus* tianeptine, 6.6 ± 0.6 kPa (49 ± 5 mmHg); at the end of the experiment, the equivalent values were as follows: placebo, 6.7 ± 0.6 kPa (50 ± 5 mmHg) *versus* tianeptine, 6.7 ± 0.7 kPa (50 ± 5 mmHg). To get an indication of end-tidal carbon dioxide concentration control, we calculated the SD of end-tidal carbon dioxide concentration during a random 10-min period of the isohypercapnic clamp. These SD values were, on average, 0.06 and 0.08 kPa (0.45 and 0.60 mmHg) in the placebo and tianeptine arms of the study or 1 and 1.2% of the target end-tidal CO_2 concentrations, respectively. The remifentanil target concentrations did not differ between the placebo and tianeptine arms of the study and ranged from 0.7 to 2.0 ng/ml in the two arms.

Examples of placebo and tianeptine experiments in one subject (subject 001) are given in figure 4. The figure shows the breath-to-breath data (black dots). The difference between the two treatments is evident, with a slow tianeptine-induced further decline in $\dot{V}_E$ relative to placebo data. The mean ventilatory data are presented in figure 5. It shows that (1) isohypercapnia increased $\dot{V}_E$ to 23.2 ± 3.0 l/min (placebo) and 21.6 ± 2.6 l/min (tianeptine); (2) remifentanil decreased $\dot{V}_E$ by 40% in both groups; (3) placebo had no effect on $\dot{V}_E$ that remained constant at approximately 15 l/min throughout the last hour of the study (periods C through G: from 14.9 ± 0.5 to 15.0 ± 0.9 l/min); and (4) tianeptine infusion caused a further decrease in $\dot{V}_E$ from period C to G, from 14.2 ± 0.4 to 9.6 ± 0.8 l/min, a 35% decrease (fig. 5).

Analysis of the studentized residuals showed that there was normality as assessed by the Shapiro–Wilk test of normality and no outliers, as assessed by no studentized residuals greater than ± 3 SDs. There was sphericity for the interaction term, as assessed by Mauchly's test of sphericity. There was a statistically significant interaction between treatment and time on $\dot{V}_E$ ($P < 0.001$). Therefore, simple main effects were run. At the end of the 15-min remifentanil infusion, $\dot{V}_E$ was not statistically significantly different for the placebo condition (14.9 ± 0.5 l/min) compared to the tianeptine condition (14.2 ± 0.4 l/min) just before tianeptine or placebo infusion (mean difference, 0.6 l/min, 95% CI, –0.5 to 1.6 l/min; $P = 0.262$; fig. 5B, timepoint C). Next, $\dot{V}_E$ decreased after 15 min of tianeptine infusion (13.9 ± 0.4 l/min) compared to the placebo (15.4 ± 0.5 l/min; mean difference, 1.4 l/min; 95% CI, 0.1 to 2.8 l/min; $P = 0.040$; fig. 5B, timepoint D) and after 30 min of tianeptine infusion (12.1 ± 0.6 l/min) compared to placebo (14.5 ± 0.6 l/min; mean difference, 2.4 l/min; 95%

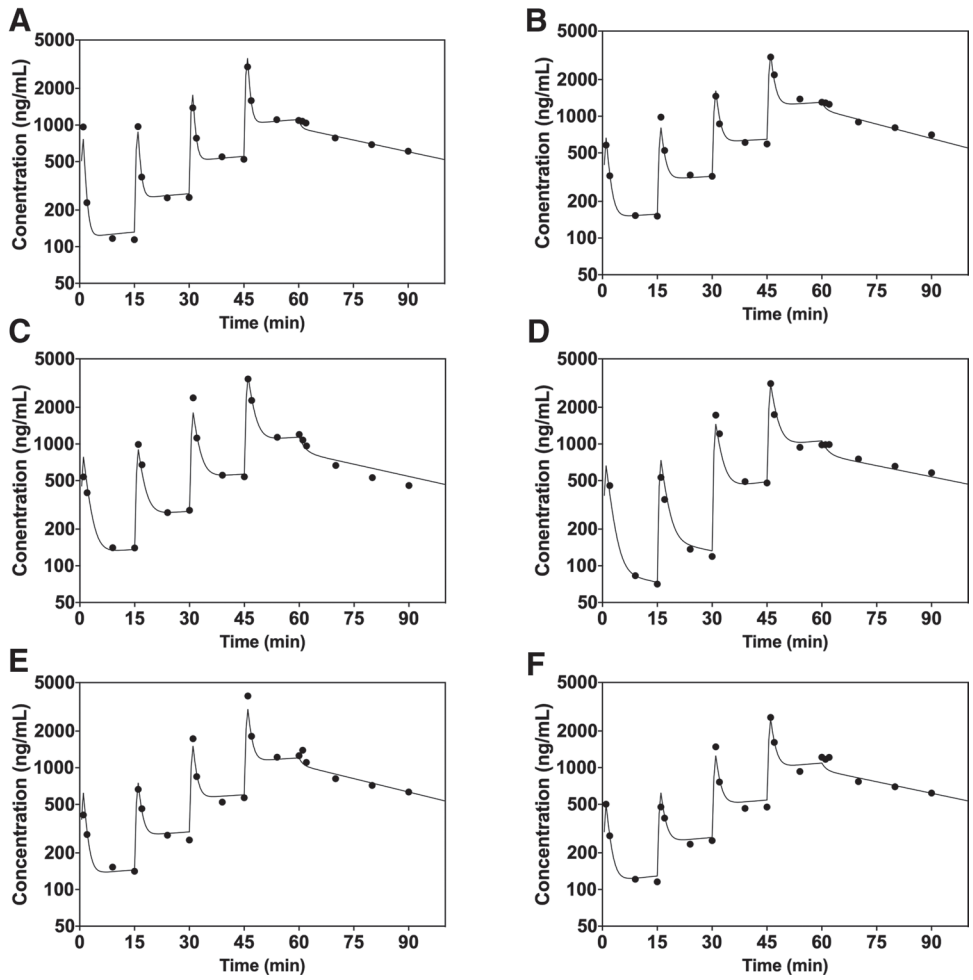

Fig. 3. NONMEM data fits of the pharmacokinetic study in six subjects (*A–F*) treated with a tianeptine infusion scheme based on the pharmacokinetic data set of Salvadori *et al.*[15] (study 2a). The estimated pharmacokinetic model parameters were used to design the infusion scheme of study 2b.

CI, 0.5 to 4.2 l/min; $P = 0.016$; fig. 5B, timepoint E). When correction for multiple comparisons was applied (P values $< 0.01 = 0.05/5$), $\dot{V}_E$ was significantly decreased after 45 min of tianeptine infusion (11.3 ± 0.5 l/min) compared to the placebo (14.4 ± 0.5 l/min; mean difference, 3.1 l/min; 95% CI, 1.8 to 4.4 l/min; $P < 0.001$; fig. 5B, timepoint F), 60 min of tianeptine infusion (9.6 ± 0.8 l/min) compared to the placebo (15.0 ± 0.9 l/min; mean difference, 5.3 l/min; 95% CI, 2.5 to 8.2 l/min; $P = 0.001$; fig. 5B, timepoint G) and remained decreased at 15 min after discontinuation of tianeptine infusion (10.3 ± 0.7 l/min) compared to the placebo (15.5 ± 0.7 l/min; mean difference, 5.2 l/min; 95% CI, 3.7 to 6.7 l/min; $P < 0.001$; fig. 5B, timepoint H). $\dot{V}_E$ did not change over time in the placebo condition ($P = 0.391$), whereas $\dot{V}_E$ did significantly decrease over time for the tianeptine condition from the start of infusion ($P < 0.001$).

Discussion

The main finding of our randomized controlled trial (study 2b) is that over the concentration range tested (500 to 2,000 ng/ml), tianeptine did not produce respiratory stimulation during remifentanil-induced respiratory depression but instead worsened respiratory depression with a further decline in $\dot{V}_E$ by 5 l/min (fig. 5). The rejection of our hypothesis deserves in-depth scrutiny of the drug, the animal data, and the various steps taken in our project.

Pharmacology of Tianeptine

Tianeptine has structural similarities to the tricyclic antidepressants but has no affinity for neurotransmitter receptors and does not interfere with monoaminergic modulators in the brain.[8,9,11] It has two metabolites: MC5, which is the main metabolite in plasma, and MC3, which is the main

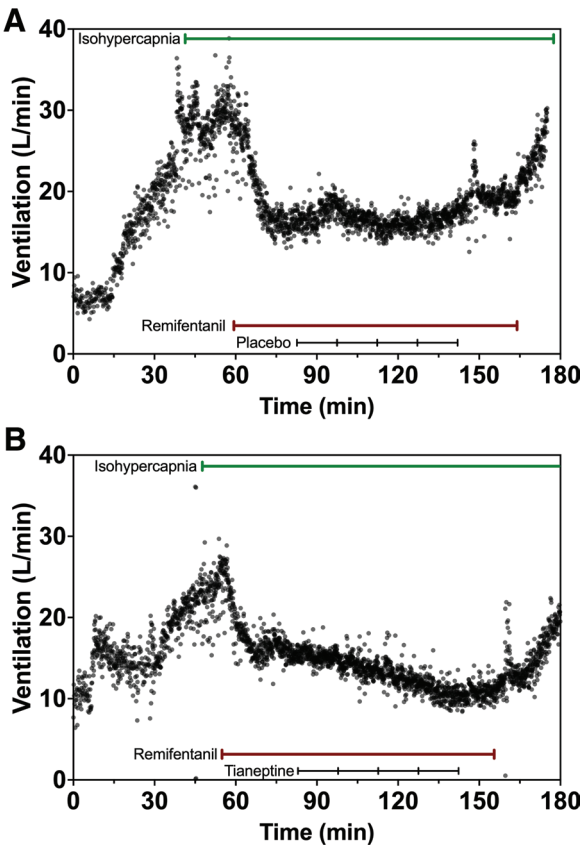

Fig. 4. Examples of the ventilatory effect of intravenous placebo (*A*) and tianeptine (*B*) on remifentanil-induced respiratory depression (study 2b). The *dots* show ventilation, with each dot representing one breath. The *red line* represents remifentanil infusion, the *black line* represents the four placebo or tianeptine steps, and the *green line* represents the isohypercapnic period. The data are from subject 001.

metabolite in urine.[11] Both tianeptine and MC5 possess antidepressant activity.[11] Tianeptine induces mood improvement and antianxiety effects by modification of synaptic plasticity and improving the performance of brain networks involved in mood and affective functioning.[8–10] Relevant to opioid-induced respiratory depression, tianeptine enhances AMPA receptor-mediated transmission by acting at allosteric sites; it increases AMPA receptor currents through kinase phosphorylation; and at the same time, glutamatergic transmission at *N*-methyl-D-aspartate receptors is reduced by tianeptine.[8–10] Both mechanisms may cause respiratory stimulation during opioid-induced respiratory depression. For example, the ampakines, that are able to counteract opioid-induced respiratory depression, do so by facilitating AMPA receptor-mediated glutamatergic transmission,[2,21] while ketamine, another drug, that is able to alleviate opioid-induced respiratory depression at subanesthetic doses, reduces *N*-methyl-D-aspartate–mediated

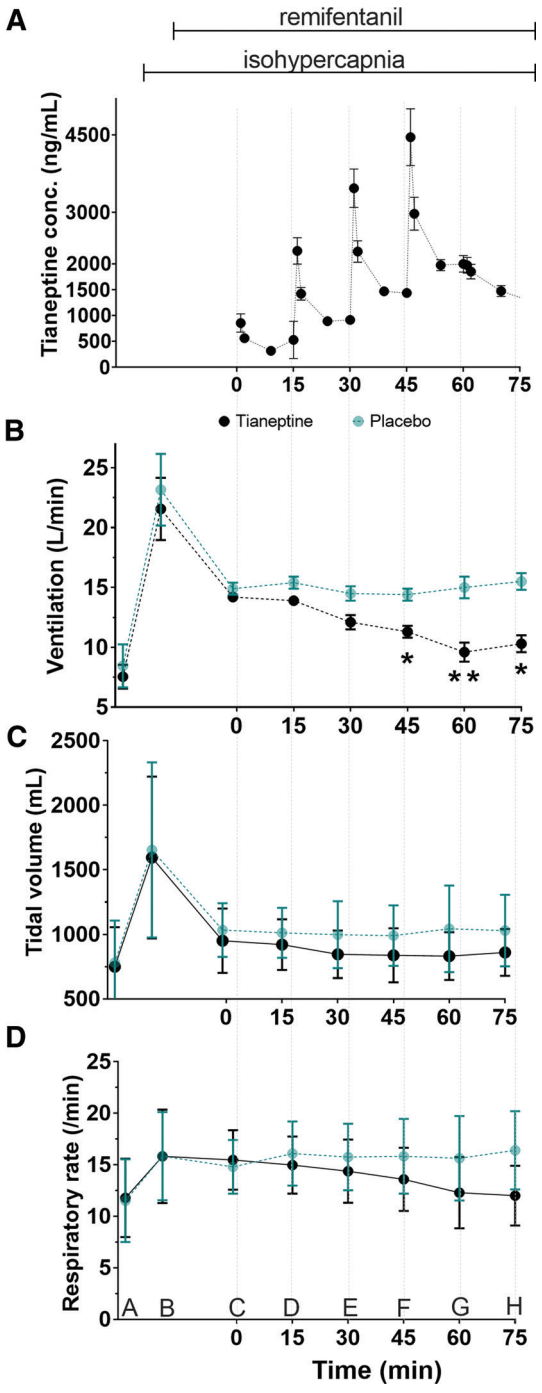

Fig. 5. Results of study 2b performed in 15 subjects. T = 0 min is the start of tianeptine (*green symbols*) or placebo (*black symbols*) infusion; T = 60 min is the end of tianeptine infusion. Timepoint *A* shows the baseline. Timepoint *B* shows isohypercapnia. Timepoints *C* to G show the 15-min intervals corresponding to tianeptine dose escalation. Timepoint *H* is 15 min following the end of tianeptine infusion. **P* < 0.001 *versus* placebo; ***P* = 0.001 *versus* placebo. The data are means ± SD. No statistical analysis was performed on tidal volume and respiratory rate. (*A*) Tianeptine concentration. (*B*) Ventilation. (*C*) Tidal volume. (*D*) Respiratory rate.

glutamatergic neurotransmission.[20] Hence, from a theoretical point of view, tianeptine is a valid candidate to counteract or prevent respiratory depression induced by opioids in ways similar to the ampakines and ketamine. Finally, tianeptine does act as an agonist on μ-opioid receptors, which may reduce its respiratory stimulatory capabilities.[12]

Animal Study

Cavalla *et al.*[7] studied the effect of tianeptine in conscious rats. The animals were pretreated with tianeptine 2 and 10 mg/kg, given intraperitoneally, 5 min before 10 mg/kg morphine, given intraperitoneally; $\dot{V}_E$ was measured by whole body plethysmography. Control arms consisted of pretreatment with placebo, the ampakine CX-546, and the tianeptine analog DP-201. Low-dose tianeptine, CX-546, and DP-201 but not high-dose tianeptine effectively increased respiratory activity before any morphine administration. In contrast to placebo, both tianeptine doses, CX-546, and DP-201 effectively prevented morphine-induced respiratory depression for at least 60 min after morphine injection. These results support the theoretical notion that tianeptine is a viable drug to be used in the treatment of opioid-induced respiratory depression.

Study 1

In the initial proof-of-concept trial, we tested the effect of pretreatment with oral tianeptine (37.5, 50, and 100 mg) and placebo on alfentanil-induced respiratory depression in healthy male and female volunteers. Our approach was similar to that of Oertel *et al.*,[21] who tested the effect of the ampakine CX717 on alfentanil-induced respiratory depression (alfentanil target concentration of 100 ng/ml) on the $\dot{V}_E55$ of the hypercapnic ventilatory response in 15 healthy volunteers and observed an increase in $\dot{V}_E55$ of 5.2 l/min from alfentanil/placebo to alfentanil/CX717 ($p = 0.02$). After the intake of 50 mg tianeptine, we observed that alfentanil $\dot{V}_E55$ was greater by 4.2 l/min compared to placebo ($P = 0.070$). We considered this the signal that we were searching for and subsequently initiated the development of an intravenous tianeptine formulation. Interestingly, no effect was observed when the tianeptine dose was increased to 100 mg and the alfentanil target concentration was lowered to 50 ng/ml. At the time, we related this to the small sample size ($n = 8$/group).

Study 2

After the development of intravenous tianeptine, we performed a pharmacokinetic study that allowed the design of the randomized controlled trial. The trial itself was modeled according to an earlier protocol that showed that intravenous *S*-ketamine partly restored remifentanil-induced respiratory depression.[20] The target remifentanil concentration, the magnitude of the remifentanil-induced respiratory depression, and the isohypercapnic levels were all comparable between the two studies. In contrast to expectation, we observed a slow decline in isohypercapnic $\dot{V}_E$ by approximately 5 l/min during the 1-h tianeptine infusion. These data are in sharp contrast to the animal study but also to study 1, which did not show a decrease in $\dot{V}_E55$ at any time period after tianeptine pretreatment. Several nonmutually exclusive mechanisms may be responsible for our findings. There are suggestions in the animal study, as well as in study 1, that tianeptine has a bell-shaped dose-response curve.[7] This then suggests that the excitatory effects of tianeptine on respiration wane at higher brain concentrations. This may well be related to the opioid receptor effects of tianeptine.[12,22,23] Gassaway *et al.*[12] showed that tianeptine is a full agonist at μ- and δ-opioid receptors, while Samuels *et al.*[23] showed opioid effects induced by tianeptine's metabolite MC5. It was speculated that these opioid effects could be responsible for triggering many of the effects attributed to tianeptine, including antidepression and anxiolysis.[12,22,23] Animal studies did find that tianeptine is an effective analgesic in acute and chronic inflammatory pain, related to μ-opioid receptor activation but also to activated adrenergic neurotransmission.[24,25] Finally, intoxication with tianeptine, often combined with other substances, is well treated with naloxone,[26,27] although there are case reports that describe acute and chronic high-dose tianeptine abuse (750 to 3,000 mg/day) without any cardiorespiratory side effects.[28,29] These latter observations suggest the absence of a clinically relevant opioid effect in humans. Given all of the above, we conclude that tianeptine over the concentration range of 500 to 2,000 ng/ml worsened the respiratory depression induced by remifentanil, possibly related to its μ-opioid agonistic effect, although we cannot exclude other causes. To determine the dose dependency of tianeptine's respiratory effects, it is necessary to study the effect of different doses on baseline ventilation and the hypercapnic ventilatory response without concomitant opioid infusion.

Another cause of the respiratory depression induced by tianeptine may be its sedative effects. In study 2b, when queried, all subjects indicated an increase in the level of sedation; however, we did not quantify this effect. Increase in sedation from any cause may worsen opioid-induced respiratory depression.[30] Our and other data indicate that sedatives such as alcohol, benzodiazepines, and also antidepressants worsen opioid-induced respiratory depression.[14,29] We considered some other issues that might have differed between the placebo and tianeptine arms of our randomized trial, such as differences in sensations that may have occurred during infusion of tianeptine *versus* placebo or unintentional differences in end-tidal CO_2 between study arms. Still, the study was fully blinded, and there were no differences in baseline $\dot{V}_E$, isohypercapnic level, and end-expired CO_2 control between study arms, and also no order effect was present in the data. In addition, none of the subjects complained of pain upon injection. Hence, there are

no methodologic issues or any imbalance between study arms that can explain the enhancement of remifentanil-induced respiratory depression in our study. Studies 1 and 2b, however, differed in the timing of treatment with tianeptine, pretreatment in study 1 (replicating the animal study of Cavalla et al.[7]), and tianeptine infusion after the establishment of respiratory depression in study 2. Still, it seems improbable that a fixed respiratory depressant effect precluded a clinical effect from tianeptine as a respiratory stimulant, since the animal data show that ampakines given before or after fentanyl both effectively reduce ventilatory depression.[31] Finally, we induced respiratory depression by two distinct phenylpiperidine derivatives with very different pharmacokinetics but similar pharmacodynamics. This was done to replicate earlier studies with these two opioids.[20,21] Whether the use of remifentanil contributed to the rejection of our hypothesis is questionable, as an earlier study showed that its respiratory effects are successfully counteracted by low-dose ketamine.[20]

Future Perspectives

We recently reviewed all current nonnaloxone reversal strategies currently applied or under development.[6] These included partial opioid agonists, cannabinoid 2 receptor agonists, ketamine, thyrotropin-releasing hormone, oxytocin, nicotinic acetylcholine receptor agonists, ampakines, serotonin receptor agonists, antioxidants, background potassium channel blockers, and opioid sequestration techniques. We argued that currently none of these often-still-experimental therapies are sufficiently examined with respect to effect and safety, and many of the compounds have little effect at deeper levels of respiratory depression or come with many side effects.[6] We therefore suggest development of reversal strategies that combine respiratory stimulants with, for example, naloxone. Possibly low-dose tianeptine combined with low-dose naloxone will attenuate any clinically relevant opioid effect, and consequently this combination will be able to effectively counteract opioid-induced respiratory depression.

Finally, we argue that our stepwise approach, *i.e.*, review of pharmacologic and animal data followed by a proof-of-concept study and finally a phase 1 randomized controlled trial (both studies were performed in established models of respiratory depression in human volunteers), exemplifies how we envision that nonopioid respiratory stimulants should be tested. Our project therefore serves as a model for studies that attempt to develop reversal strategies for potent opioid-related respiratory toxicity.

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Competing Interests

Drs. McMorn, Snape, Horrigan, Evans, and Kiernan are employees of AMO Pharma Ltd. (Leeds, United Kingdom) and are shareholders of the company. Dr. Cavalla is employee of Numedicus Ltd. (Cambridge, United Kingdom). Dr. Dahan received consultancy and/or speaker fees from Enalare Therapeutics Inc. (Naples, Florida), Grünenthal BV (Breukelen, The Netherlands), Medasense Biometrics Ltd. (Tel Aviv, Israel), Trevena Inc. (Chesterbrook, Pennsylvania), and MSD Nederland BV (Haarlem, The Netherlands). The Anesthesia and Pain Research Unit of the Department of Anesthesiology, Leiden University Medical Center (Leiden, The Netherlands) received/receives funding from AMO Pharma Ltd., Bedrocan BV (Emmeloord, The Netherlands), Grünenthal GmbH (Stolberg, Germany), Medasense Biometrics Ltd. (Tel Aviv, Israel), Medtronic (Washington, D.C.), MSD Nederland BV (Haarlem, The Netherlands), LTS Lohmann Therapie Systeme AG (Andernach, Germany), and Trevena Inc. (Chesterbrook, Pennsylvania). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: a.dahan@lumc.nl. Raw data available at: a.dahan@lumc.nl.

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References

1. Dahan A, Niesters M, Smith T, Overdyk F: Opioids. Clinical Anesthesia, 8th edition. Edited by Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, Ortega R, Sharar SR, Holt NF. New York, Wolters Kluwer, 2017, pp 505–26
2. Dahan A, Aarts L, Smith TW: Incidence, reversal, and prevention of opioid-induced respiratory depression. Anesthesiology 2010; 112:226–38
3. Palkovic B, Callison JJ, Marchenko V, Stuth EAE, Zuperku EJ, Stucke AG: Dose-dependent respiratory depression by remifentanil in the rabbit parabrachial

nucleus/Kölliker–Fuse complex and pre-Bötzinger complex. Anesthesiology 2021; 135:649–72
4. Baertsch NA, Bush NE, Burgraff NJ, Ramirez JM: Dual mechanisms of opioid-induced respiratory depression in the inspiratory rhythm-generating network. Elife 2021; 10:e67523
5. Varga AG, Reid BT, Kieffer BL, Levitt ES: Differential impact of two critical respiratory centres in opioid-induced respiratory depression in awake mice. J Physiol 2020; 598:189–205
6. van der Schrier R, Dahan JDC, Boon M, Sarton E, van Velzen M, Niesters M, Dahan A: Advances in reversal strategies of opioid-induced respiratory toxicity. Anesthesiology 2022; 136:618–32
7. Cavalla D, Chianelli F, Korsak A, Hosford PS, Gourine AV, Marina N: Tianeptine prevents respiratory depression without affecting analgesic effect of opiates in conscious rats. Eur J Pharmacol 2015; 761:268–72
8. McEwen BS, Chattarji S: Molecular mechanisms of neuroplasticity and pharmacological implications: The example of tianeptine. Eur Neuropsychopharmacol 2004; 14:S497–502
9. McEwen BS, Olié JP: Neurobiology of mood, anxiety, and emotions as revealed by studies of a unique antidepressant: Tianeptine. Mol Psychiatry 2005; 10:525–37
10. Zhang H, Etherington LA, Hafner AS, Belelli D, Coussen F, Delagrange P, Chaouloff F, Spedding M, Lambert JJ, Choquet D, Groc L: Regulation of AMPA receptor surface trafficking and synaptic plasticity by a cognitive enhancer and antidepressant molecule. Mol Psychiatry 2013; 18:471–84
11. Wilde MI, Benfield P: Tianeptine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. Drugs 1995; 49:411–39
12. Gassaway MM, Rives ML, Kruegel AC, Javitch JA, Sames D: The atypical antidepressant and neurorestorative agent tianeptine is a μ-opioid receptor agonist. Transl Psychiatry 2014; 4:e411
13. Dahan A, Nieuwenhuijs D, Teppema L: Plasticity of central chemoreceptors: Effect of bilateral carotid body resection on central CO_2 sensitivity. PLoS Med 2007; 4:e239
14. van der Schrier R, Roozekrans M, Olofsen E, Aarts L, van Velzen M, de Jong M, Dahan A, Niesters M: Influence of ethanol on oxycodone-induced respiratory depression: A dose-escalating study in young and elderly individuals. Anesthesiology 2017; 126:534–42
15. Salvadori C, Ward C, Defrance R, Hopkins R: The pharmacokinetics of the antidepressant tianeptine and its main metabolite in healthy humans–influence of alcohol co-administration. Fundam Clin Pharmacol 1990; 4:115–25
16. Nielsen M, Smith H: Studies on the regulation of respiration in acute hypoxia. Acta Physiol Scand 1951; 4:293–313
17. Maitre PO, Vozeh S, Heykants J, Thomson DA, Stanski DR: Population pharmacokinetics of alfentanil: The average dose-plasma concentration relationship and interindividual variability in patients. Anesthesiology 1987; 66:3–12
18. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 1997; 86:10–23
19. Roozekrans M, Olofsen E, van der Schrier R, van Gerven J, Peng S, McLeod J, Dahan A: Reversal of opioid-induced respiratory depression by BK-channel blocker GAL021: A pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. Clin Pharmacol Ther 2015; 97:641–9
20. Jonkman K, van Rijnsoever E, Olofsen E, Aarts L, Sarton E, van Velzen M, Niesters M, Dahan A: Esketamine counters opioid-induced respiratory depression. Br J Anaesth 2018; 120:1117–27
21. Oertel BG, Felden L, Tran PV, Bradshaw MH, Angst MS, Schmidt H, Johnson S, Greer JJ, Geisslinger G, Varney MA, Lötsch J: Selective antagonism of opioid-induced ventilatory depression by an ampakine molecule in humans without loss of opioid analgesia. Clin Pharmacol Ther 2010; 87:204–11
22. Han J, Andreu V, Langreck C, Pekarskaya EA, Grinnell SG, Allain F, Magalong V, Pintar J, Kieffer BL, Harris AZ, Javitch JA, Hen R, Nautiyal KM: Mu opioid receptors on hippocampal GABAergic interneurons are critical for the antidepressant effects of tianeptine. Neuropsychopharmacology 2022; 47:1387–97
23. Samuels BA, Nautiyal KM, Kruegel AC, Levinstein MR, Magalong VM, Gassaway MM, Grinnell SG, Han J, Ansonoff MA, Pintar JE, Javitch JA, Sames D, Hen R: The behavioral effects of the antidepressant tianeptine require the μ-opioid receptor. Neuropsychopharmacology 2017; 42:2052–63
24. Kim WM, Lee SH, Jeong HJ, Lee HG, Choi JI, Yoon MH: The analgesic activity of intrathecal tianeptine, an atypical antidepressant, in a rat model of inflammatory pain. Anesth Analg 2012; 114:683–9
25. Uzbay IT, Cinar MG, Aytemir M, Tuglular I: Analgesic effect of tianeptine in mice. Life Sci 1999; 64: 1313–9
26. Ari M, Oktar S, Duru M: Amitriptyline and tianeptine poisoning treated by naloxone. Hum Exp Toxicol 2010; 29:793–5
27. Dempsey SK, Poklis JL, Sweat K, Cumpston K, Wolf CE: Acute toxicity from intravenous use of

tricyclic antidepressant tianeptine. J Analyt Toxicol 2017; 41:547–50
28. Kisa C, Bulbul D, Aydemir C, Goka E: Is it possible to be dependent on tianeptine, an antidepressant? A case report. Progr Neuro-psychopharmacol Biol Psychiatry 2007; 31:776–8
29. Saatçioğlu Ő, Rahşan F Çakmak D: Abuse of tianeptine: A case report. Turk Psikiyatri Dergisi 2006; 17:1–4
30. Boon M, van Dorp E, Broens S, Overdyk F: Combining opioids and benzodiazepines: Effects on mortality and severe respiratory depression. Ann Pall Med 2020; 9:542–57
31. Ren J, Ding X, Funk GD, Greer JJ: Ampakine CX717 protects against fentanyl-induced respiratory depression and lethal apnea in rats. ANESTHESIOLOGY 2009; 110:1364–70

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

The Leech Airway: A Flute for Your "Champagne"?

In 1937, Canadian anesthesiologist Beverley Leech, M.D. (1898 to 1960), patented an early precursor to the laryngeal mask airway (LMA, *lower left*). His "pharyngeal bulb gasway," also called the Leech airway, featured a soft, detachable rubber bulb around a tough metal core (*upper left*). Leech's love for cyclopropane (*right*), dubbed the "champagne" of volatile anesthetics, inspired the airway's design. Although rapid and smooth in onset, cyclopropane was expensive and explosive, mandating closed-circuit delivery. However, leak-free ventilation was challenging to achieve, as endotracheal intubation had yet to become routine. Laryngoscopes and tubes were still being refined, and prolonged laryngospasm easily occurred pre-curare. To avoid the risk of intubation, Leech envisioned a supraglottic airway that would optimize cyclopropane delivery through a closed circuit. For more than a year, he painstakingly examined the wax casts of cadaver throats to design a malleable bulb that conformed to the average adult pharynx. Once manufactured, the Leech airway gained favor. Its bulb, lubricated with Vaseline, could be advanced gently into the oropharynx of a mask-induced patient. However, when succinylcholine arrived in 1952, wondrously facilitating tracheal intubation, the Leech airway became obsolete. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

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ANESTHESIOLOGY

No Benefits of Adding Dexmedetomidine, Ketamine, Dexamethasone, and Nerve Blocks to an Established Multimodal Analgesic Regimen after Total Knee Arthroplasty

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Multimodal analgesic strategies are effective in reducing postoperative pain
- It is unclear how many analgesic elements are required in a multimodal strategy to achieve optimal results

What This Article Tells Us That Is New

- A randomized trial design compared analgesic requirements after total knee replacement surgery for patients receiving a standard multimodal regime *versus* one with additional analgesics
- Compared to the combination of intrathecal morphine, periarticular anesthetic infiltration, dexamethasone, and adductor canal block, additional intravenous analgesics and nerve blocks provided no incremental benefit

ABSTRACT

Background: An optimal opioid-sparing multimodal analgesic regimen to treat severe pain can enhance recovery after total knee arthroplasty. The hypothesis was that adding five recently described intravenous and regional interventions to multimodal analgesic regimen can further reduce opioid consumption.

Methods: In a double-blinded fashion, 78 patients undergoing elective total knee arthroplasty were randomized to either (1) a control group (n = 39) that received spinal anesthesia with intrathecal morphine, periarticular local anesthesia infiltration, intravenous dexamethasone, and a single injection adductor canal block or (2) a study group (n = 39) that received the same set of analgesic treatments plus five additional interventions: local anesthetic infiltration between the popliteal artery and capsule of the posterior knee, intraoperative intravenous dexmedetomidine and ketamine, and postoperatively, one additional intravenous dexamethasone bolus and two additional adductor canal block injections. The primary outcome measure was 24-h cumulative opioid consumption after surgery and secondary outcomes were other analgesics, patient recovery, functional outcomes, and adverse events.

Results: Opioid consumption was not different between groups at 24 h (oral morphine equivalents, mean ± SD; study: 23.7 ± 18.0 mg *vs.* control: 29.3 ± 18.7 mg; mean difference [95% CI], –5.6 mg [–2.7 to 13.9]; P = 0.189) and all other time points after surgery. There were no major differences in pain scores, quality of recovery, or time to reach rehabilitation milestones. Hypotensive episodes occurred more frequently in the study group (25 of 39 [64.1%] *vs.* 13 of 39 [33.3%]; P = 0.010).

Conclusions: In the presence of periarticular local anesthesia infiltration, intrathecal morphine, single-shot adductor canal block and dexamethasone, the addition of five analgesic interventions—local anesthetic infiltration between the popliteal artery and capsule of the posterior knee, intravenous dexmedetomidine, intravenous ketamine, an additional intravenous dexamethasone dose, and repeated adductor canal block injections—failed to further reduce opioid consumption or pain scores or to improve functional outcomes after total knee arthroplasty.

(ANESTHESIOLOGY 2022; 137:459–70)

Severe pain after total knee arthroplasty can delay rehabilitation and hospital discharge, and patients commonly require opioid medication to obtain adequate postoperative analgesia. However excessive postoperative opioid use can increase adverse events and prolong hospital length of stay.[1] Furthermore, prolonged prescription use is the strongest predictor of long-term dependence and misuse, and studies show that approximately 8% of opioid-naive total knee

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arthroplasty patients are chronic opioid users at 6 months after surgery.[2] Designing an optimal perioperative analgesic strategy that minimizes postoperative opioid requirements is thus a critical part of an enhanced recovery total knee arthroplasty program.

Contemporary multimodal analgesic treatment for total knee arthroplasty consisting of oral nonopioid drugs (*e.g.*, acetaminophen, nonsteroidal anti-inflammatory agents, gabapentinoids) and surgical periarticular local anesthesia infiltration is only partially effective in regard to opioid sparing.[3] Several new options for multimodal analgesia have recently emerged. They include intraoperative administration of intravenous (IV) dexamethasone (steroid),[4] dexmedetomidine (α-2 agonist),[5] and ketamine (*N*-methyl-D-aspartate antagonist),[6] as well as peripheral nerve block procedures such as continuous adductor canal block[7] and iPACK block (infiltration between popliteal artery and posterior capsule of the knee).[8] While each of these individual interventions has demonstrable analgesic benefit after total knee arthroplasty when compared to placebo or no intervention, the impact of incorporating these treatments simultaneously into contemporary multimodal analgesic regimen for total knee arthroplasty remains unknown. In this randomized, double-blind, controlled trial, we hypothesized that adding five novel analgesic interventions to our institutional standard multimodal treatments would further decrease postoperative opioid requirements after total knee arthroplasty.

Materials and Methods

This prospective, randomized, double-blinded study was registered on www.clinicaltrials.gov (NCT03954379; principal investigator, Vincent Chan, M.D.; registration date April 16, 2019) and received approval from the University Health Network Research and Ethics Board (18-5920, approval date May 28, 2019). This study was conducted at Toronto Western Hospital between June 2019 and December 2020 in accordance with the Declaration of Helsinki principles and followed the Consolidated Standards of Reporting Trials guidelines.[9]

Participants

Patients aged 18 to 85 yr, with a body mass index of 38 kg/m^2 or lower, who were having elective primary, unilateral knee arthroplasty were included. Exclusion criteria were revision/bilateral arthroplasty procedures, contraindications to spinal anesthesia, allergy to any of the study medications, neuropathy in the operative extremity, inability or refusal to provide informed consent, uncontrolled cardiac, blood pressure and respiratory diseases, and history of chronic pain unrelated to knee pathology requiring more than 50 mg of oral morphine equivalents per day. All patients were informed about the study procedures and provided written informed consent before randomization.

Randomization and Blinding

Patients were randomized into either the control group or study group with a 1:1 allocation ratio using a computer-generated block randomization technique (www.randomization.com) and a block size of 6 patients per block. The investigator who generated the random allocation sequence was the one who enrolled and assigned study patients to the study group per the randomization list. Group allocation was concealed until the day of surgery using numbered sealed opaque envelopes. Each envelope was opened by an attending anesthesiologist, who then prepared the study medications accordingly; this anesthesiologist did not participate further in the study or care of the patient. The patient, surgeon, physiotherapists, acute pain nurses, and investigators performing patient assessment after surgery were blinded to treatment group allocation.

Preoperative Management

Preoperatively, all patients were administered 650 to 1,000 mg of acetaminophen and 100 to 200 mg of celecoxib orally. Regional anesthesia procedures were performed by attending anesthesiologists or fellows and residents under supervision before surgery in a dedicated block room where noninvasive blood pressure, electrocardiogram, pulse oximetry, supplemental oxygen *via* face mask, and IV access were established (table 1). Titrated doses of 1 to 2 mg of IV midazolam and 25 to 50 μg of IV fentanyl were administered as needed to provide anxiolysis and analgesia during block performance.

Continuous Adductor Canal Block

An adductor canal block catheter was inserted in all patients at the level of the midthigh. The adductor canal was identified using a linear 5 to 12 MHz ultrasound probe (Sonosite Edge, USA). The probe was rotated to obtain an oblique view of the superficial femoral artery and adductor canal to allow for a more proximal needle insertion site. After skin sterilization and infiltration with 1 to 2 ml of 2% lidocaine, an 80-mm, 17-gauge Tuohy needle (Arrow StimuCath kit, Teleflex Medical, USA) was advanced in plane in an anterolateral to posteromedial direction until the needle tip was positioned within the adductor canal deep to the vastoadductor membrane using

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Table 1. Summary of Analgesic Interventions

Intervention	Control Group (n = 39)	Study Group (n = 39)	Administration Time	Dose
IV Analgesic Interventions				
Dexmedetomidine		+	Intraoperative	1 μg/kg (single dose)
Ketamine		+	Intraoperative	0.5 mg/kg (single dose)
Dexamethasone	+	+	Intraoperative	8 mg (first dose)
		+	Postoperative day 1, AM	8 mg (second dose)
Regional analgesic interventions				
iPACK block		+	Preoperative	15 ml of 0.5% ropivacaine + 1:200,000 epinephrine
Spinal anesthesia	+	+	Preoperative	2-3 ml of 0.5% isobaric bupivacaine + 0.1 ml, 0.1% intrathecal morphine (100 μg)
Adductor canal block catheter bolus*	+	+	Preoperative	Bolus 1 = 15 ml of 0.5% ropivacaine + 1:200,000 epinephrine
		+	Postoperative day 0, PM	Bolus 2 = 10 ml of 0.5% ropivacaine + 1:200,000 epinephrine
		+	Postoperative day 1, AM	Bolus 3 = 10 ml of 0.5% ropivacaine + 1:200,000 epinephrine
Periarticular infiltration	+	+	Intraoperative	100 ml, 0.2% ropivacaine (200 mg) + epinephrine 0.6 mg + ketorolac 30 mg

*The control group received a 2-ml normal saline bolus for blinding purposes.
+, administration of a given intervention; iPACK, infiltration between the popliteal artery and capsule of the knee; IV, intravenous.

a hydrodissection technique with up to 10 ml of 5% dextrose solution. A 19-gauge catheter was advanced 2 to 3 cm into this fluid "pocket" within the adductor canal and then tunneled subcutaneously to exit the skin proximal to the site of the surgical thigh tourniquet and secured in place with adhesive dressings. After negative aspiration for blood, a bolus of 15 ml of 0.5% ropivacaine (75 mg) in 1:200,000 epinephrine was injected through the tunneled catheter for all patients preoperatively.

Spinal Anesthesia

After insertion of the adductor canal block catheter, spinal anesthesia was administered with patients in the sitting position. All patients received 2 to 3 ml of 0.5% preservative-free isobaric bupivacaine (total 10 to 15 mg) and 100 μg of intrathecal morphine injected through a 25-gauge Whitacre needle (CHS MED-RX, Canada) at an appropriate space between the L2 and L5 vertebrae. The patients were then placed in a lateral decubitus position with the operative side uppermost, and adequacy of motor and sensory blockade was confirmed before surgery.

Intraoperative Management

The surgical procedures were performed by a group of four experienced surgeons with patients in the supine position, using a standard medial parapatellar surgical approach and a thigh tourniquet. All patients received IV antibiotics and 1 g of tranexamic acid before surgical incision. The patients were sedated using IV propofol infusion (25 to 75 μg kg^{-1} min^{-1}) and supplemented with 1 to 2 mg of IV midazolam or 25 to 50 μg of fentanyl at the discretion of the anesthetic provider, in line with routine institutional practice. The surgeons, but not the anesthetic provider, were blinded to group allocation.

Periarticular local anesthetic infiltration was performed by the surgeon under direct vision using a mixture of 100 ml of 0.2% ropivacaine (total 200 mg) + 0.6 mg epinephrine + 30 mg ketorolac. The posterior capsule was infiltrated using half of the solution before placement of the prosthesis, and the periarticular and superficial soft tissues were infiltrated after the prosthesis was in place using the remaining volume. At wound closure, 3 g of topical tranexamic acid was applied to the surgical site, and all patients received 8 mg of IV dexamethasone and 4 mg of ondansetron for postoperative nausea and vomiting prophylaxis.

Postoperative Management

After surgery, the patients were managed in the postanesthetic care unit (PACU) by a nurse blinded to group allocation. Opioid analgesia was administered as required to treat pain scores of 4 or higher on an 11-point numerical rating scale (0 to 10 points) and 25 mg of IV dimenhydrinate and/or 4 mg of ondansetron for postoperative nausea and vomiting. The patients were discharged to the ward once they achieved an Aldrete score of 9. Multimodal analgesia on the ward comprised 650 to 1,000 mg of oral acetaminophen every 6 h and 100 to 200 mg of celecoxib every 12 h, supplemented by immediate-release oral oxycodone (5 to 10 mg) or hydromorphone (1 to 2 mg) every 2 h as needed. If oral analgesia was insufficient to control pain,

IV patient-controlled analgesia with hydromorphone or morphine was offered for rescue. Patients were followed-up twice daily by the acute pain service team, who titrated opioid dose ranges and transitioned opioids from IV to oral when needed.

Perioperative Management: Study Group Interventions

The study group received five additional analgesic interventions (table 1).

Preoperative iPACK Block. An ultrasound guided iPACK block in the lateral decubitus position was performed after spinal anesthesia. Thus, the sedated patient was unaware of the procedure. A bolus of 15 ml of 0.5% ropivacaine (75 mg) in 1/200,000 epinephrine was injected through an 80-mm 22-gauge block needle (SonoPlex, Pajunk, Germany) just proximal to the femoral intercondylar fossa.

Intraoperative IV Analgesic Adjuncts – Dexmedetomidine and Ketamine. Patients in the study group received an IV admixture containing 1 μg/kg dexmedetomidine (to a maximum dose of 100 μg) and 0.5 mg/kg ketamine (to a maximum dose of 50 mg) diluted with normal saline to a total volume of 20 ml. The solution was infused over 15 to 20 min without a loading bolus. Supplemental low-dose IV propofol infusion was given as necessary.

Postoperative Adductor Canal Block Injections. The study group received two additional 10-ml boluses of 0.5% ropivacaine in 1/200,000 epinephrine administered through the adductor canal block catheter by one of the study investigators. The first one was in the evening of the day of surgery (postoperative day 0) between 9 and 11 PM, and the second was in the morning of postoperative day 1 between 8 and 10 AM before the first physiotherapy session. Patients in the control group received placebo injections of 2 ml of saline at similar times. The catheter was removed after the second postoperative injection.

Postoperative IV Dexamethasone. The study group also received a second dose of 8 mg of IV dexamethasone at 8 AM on postoperative day 1, while the control group received 2 ml of IV saline.

Outcome Measures

All outcomes were collected by blinded researchers. The primary outcome was cumulative opioid consumption in oral morphine equivalents at 24 h after PACU arrival. Secondary analgesic outcomes were 11-point numerical rating scale pain scores in the operative knee, where 0 indicates "no pain," and 10 indicates "the worst pain imaginable." These were measured at rest and during movement or physical therapy at the following time points: before surgery, in the PACU, and three times a day on postoperative days 1 and 2 during the patient's hospital stay: (1) between 8 and 10 AM, 2) during physical therapy, and 3) between 8 and 10 PM. After hospital discharge, daily rest and dynamic pain scores were also obtained by phone on postoperative day 2 and at 1, 2, and 6 weeks after surgery. Opioid consumption on days 7, 14, and 42 after discharge was also documented. Other outcomes included the time to first opioid analgesic request, time to reach physiotherapy criteria for hospital discharge (*i.e.*, ability to ambulate independently from the bed to the bathroom, walk along a hallway unassisted with walker and climb stairs safely), and length of hospital stay (defined as the number of days from admission to discharge). Quality of recovery (QoR) was assessed using a validated QoR-15 tool[10] immediately before surgery and 24 h, 48 h, and 2 weeks after surgery.

Rehabilitation milestones were evaluated with the Timed Up and Go test (time it takes a subject to stand up from a standard-height armchair, walk 3 m, walk back to the chair, and sit down),[11,12] the distance walked during physiotherapy, and both active and passive joint range of motion, defined as knee flexion from neutral (0°) to maximum flexion. The Timed Up and Go test, distance walked, and range of motion were measured before surgery and on postoperative days 1 and 2 (unless the patient was discharged earlier). Patient satisfaction was assessed at the time of discharge, and adverse events (nausea, vomiting, sedation, hypotension, urinary retention, hyperglycemia, foot/ankle muscle weakness, and symptoms of local anesthetic systemic toxicity) were recorded. Motor function at the ankle was categorized as follows: 0 indicates no power, 1 indicates decreased power (any movement without resistance), and 2 indicates normal power (complete movement against resistance). Hypotension was defined as a decline of systolic blood pressure of 25% or greater from baseline or blood pressure lower than 90 mmHg requiring treatment.

Sample Size and Statistical Analysis

The primary outcome was cumulative postoperative opioid consumption in the first 24 h after surgery. Based on past institutional clinical data, we assumed that patients in the control group would require 80 ± 40 mg (mean ± SD; 95% CI, 67.1 to 92.9 mg) oral morphine equivalents in 24 h, and the new interventions would result in a 33% opioid reduction in the study group (*i.e.*, minimum clinically important difference of 26.7 mg; 95% CI, 22.3 to 31.1 mg); 37 patients would be needed per group based on a power analysis using a 5% type I error estimate and 80% power within a two-tailed *t* test. To allow for a 5% drop out, we enrolled 39 patients per group (78 in total).

The data were analyzed with SPSS 23.0 for Mac (IBM, USA). Normality of data distribution was tested using the Shapiro–Wilk test. The data with normal distribution were reported as means (SD), and data that were skewed are described as medians (interquartile range). For data that are normally distributed, the independent Student's *t* test was used to analyze for differences between groups, and the Mann–Whitney U test was used for analysis of differences between continuous variables with skewed

distribution. The differences of the medians and 95% CI were estimated using the Hodges–Lehman method. Categorical variables were described as numbers (percentages) or proportions and were compared using the chi-square or Fisher's exact test where appropriate. $P < 0.05$ was designated as statistically significant. All hypothesis testing was two-tailed.

Results

A total of 273 patients were screened, of which 138 met inclusion criteria. Of these, 50 refused to consent, 4 withdrew consent on the day of surgery, and 6 cases were postponed due to the COVID-19 pandemic. In the end, 78 patients were enrolled and randomized into 2 study groups (39 patients per group; fig. 1), and primary analysis was conducted on the data of 78 patients.

All subjects had similar baseline demographics (table 2). One patient in the study group required general anesthesia due to inadequate block height of the spinal anesthetic. Sixty-two patients (31 in each group) were discharged home on postoperative day 1. Two patients (1 in each group) were lost to follow-up at 6 weeks (fig. 1).

The primary outcome of cumulative 24-h postoperative opioid consumption was similar between the two groups (means ± SD; study: 23.7 ± 18.0 mg *vs.* control: 29.3 ± 18.7 mg oral morphine equivalents; mean difference [95% CI], –5.6 mg [–2.7 to 13.9]; $P = 0.189$; table 3). There was also no difference between groups in opioid consumption at any other assessment time points, up to

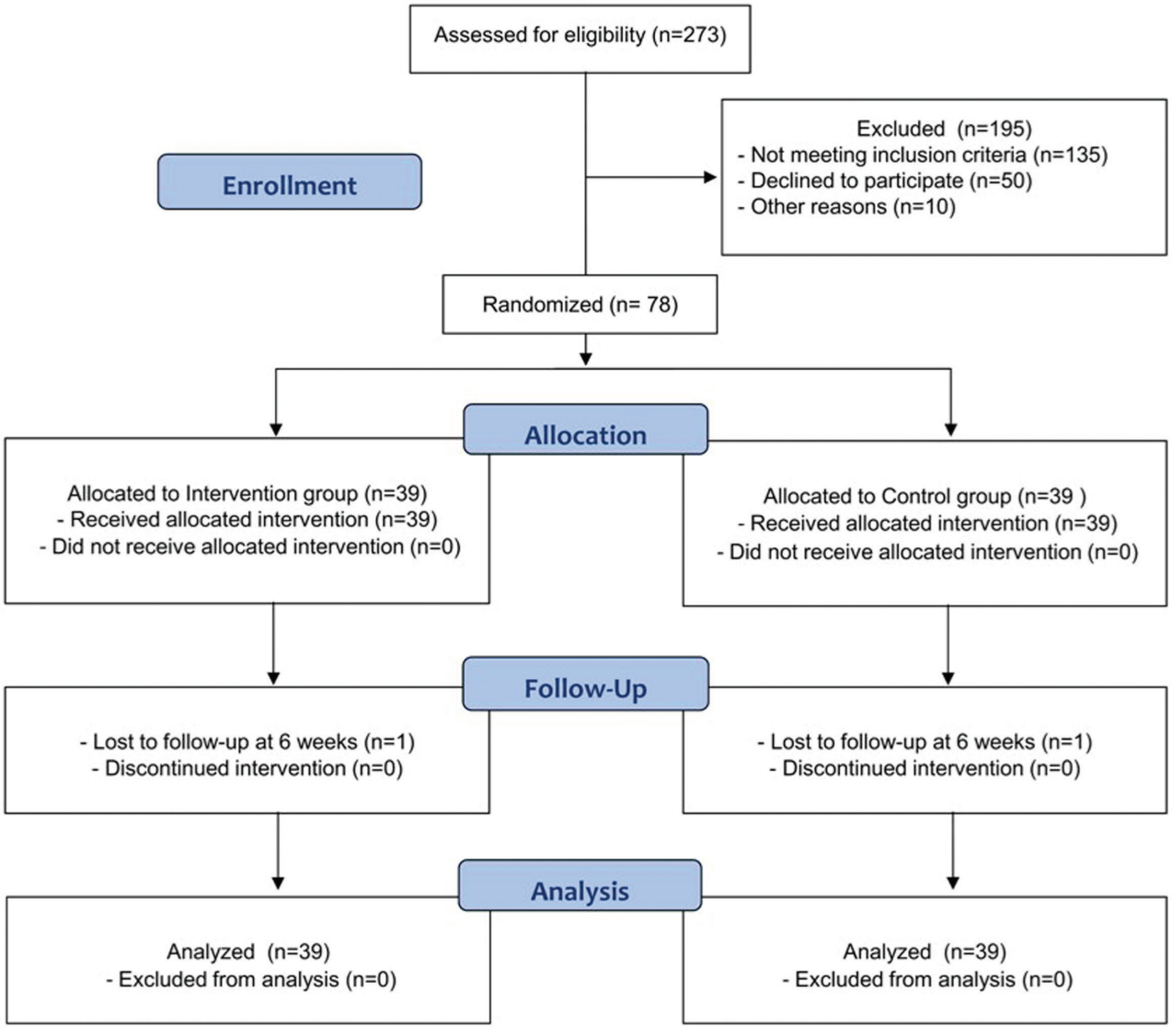

Fig. 1. Consolidated Standards of Reporting Trials diagram.

Table 2. Baseline Demographics of Study Subjects

Characteristic	Control Group (n = 39)	Study Group (n = 39)
Age, yr	68 ± 7	66 ± 8
Sex, male/female	22/17	23/16
Body mass index, kg/m²	29 ± 4	29 ± 4
ASA status, I/II/III	1/18/20	1/20/18
Operative side, left/right	18/21	18/21
Duration of surgery, min	59 ± 15	63 ± 11

The data are reported as means ± SD or the number of subjects.
ASA, American Society of Anesthesiologists.

6 weeks after surgery (fig. 2; table 3). No patient required rescue IV patient-controlled analgesia. Intraoperative fentanyl was given to 27 patients (69.2%) in the control group and 2 patients (5.1%) in the study group to complement sedation.

For secondary analgesic outcomes, there was no difference in the time to first opioid dose, (study: 635 ± 337 min *vs.* control: 574 ± 347 min; $P = 0.437$). In addition, there were no statistically significant differences in pain scores at rest at any time point up to 6 weeks after surgery (table 4). The lack of between-group differences in all primary and secondary analgesic outcomes persisted when adjusted for intraoperative fentanyl dose as a covariate. (A table showing the key analgesic outcomes analyzed by study group allocation and adjusted for intraoperative opioid dose can be found in the Supplemental Digital Content, http://links.lww.com/ALN/C880.)

Functional Outcomes, Quality of Recovery, and Adverse Events

After surgery, the range of movement, both active and passive, decreased from baseline similarly in both groups, but all patients managed to walk a mean distance of greater than 50 m on postoperative day 1 (table 5). No statistically significant differences were found between groups for Timed Up and Go test, range of movement, distance walked, or QoR-15 at baseline and on postoperative day 1. Neither was the time to reach discharge criteria/total in-hospital stay (table 5). Patient satisfaction was equally high in both groups.

The incidence of side effects was similar in both groups except for hypotension in the PACU (study: 64.1% *vs.* control: 33.3%, $P = 0.010$; table 6). Perioperative heart rate was comparable and remained within normal ranges (50 to 100 beats/min) for both groups. Plantar flexion was also more frequently impaired in the study group on postoperative day 0 (46.1% *vs.* 17.9%; table 6), although no falls were reported. Blood glucose level obtained in the morning of postoperative day 1 was not statistically different between groups and remained within the normal range (5 to 9 mM) at all time points despite a second IV dexamethasone dose (table 5). No patients experienced symptoms of local anesthetic systemic toxicity.

Table 3. Oral Morphine Equivalent Consumption at Different Time Points

Assessment Time	Oral Morphine Equivalent Consumption, mg: Control Group (n = 39)	Oral Morphine Equivalent Consumption, mg: Study Group (n = 39)	*P* Value	Estimate for Difference and 95% CI
Intraoperative	15.0 (0.0, 15.0)	0.0 (0.0, 0.0)	< 0.001*	15 (7.5, 15)
0 to 6 h	0.0 (0.0, 5.0)	0.0 (0.0, 0.0)	0.154	0 (0, 0)
6 to 12 h	5.0 (0.0, 10.0)	5.0 (0.0, 10.0)	0.157	0 (0, 5)
12 to 18 h	10.0 (5.0, 15.0)	5.0 (0.0, 10.0)	0.085	2.5 (0, 5)
18 to 24 h	8.0 (5.0, 15.0)	10.0 (5.0, 10.0)	0.968	0 (–4, 3.5)
24 to 36 h	15.0 (10.0, 30.0)	15.0 (10.0, 30.0)	0.293	5 (–2.5, 10)
36 to 48 h	20.0 (10.0, 30.0)	20.0 (10.0, 30.0)	0.724	0 (–5, 7.5)
0 to 12 h	10.0 (5.0, 10.0)	5.0 (0.0, 10.0)	0.081	2.5 (0, 5)
12 to 24 h	15.0 (10.0, 25.0)	15.0 (10.0, 20.0)	0.328	2.5 (–2.5, 7.5)
0 to 24 h	27.5 (15.0, 40.0)	20.0 (10.0, 30.0)	0.101	5 (0, 13)
24 to 48 h	35.0 (25.0, 60.0)	30.0 (15.0, 60.0)	0.609	5 (–10, 15)
0 to 48 h	65.0 (45.0, 93.0)	60.0 (35.0, 80.0)	0.303	10 (–8, 25)
Day 7 postdischarge	30.0 (10.0, 40.0)	20.0 (5.0, 40.0)	0.462	2.5 (–5, 15)
Day 14 postdischarge	10.0 (0.0, 20.0)	5.0 (0.0, 15.0)	0.463	0 (0, 7.5)
Day 42 postdischarge	0.0 (0.0, 5.0)	0.0 (0.0, 4.5)	0.887	0 (0, 0)

The data are reported as medians (25th, 75th) and were determined using the Mann–Whitney U test. The Hodges–Lehman method was used to estimate the differences of the medians and 95% CI.
*$P < 0.05$.

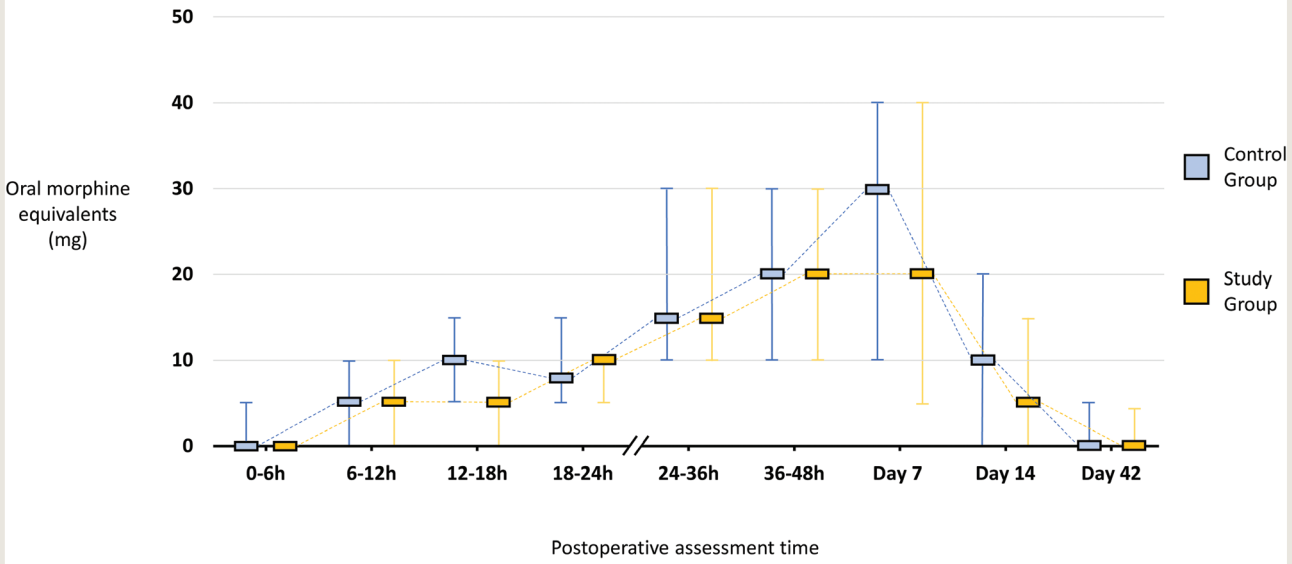

Fig. 2. Median oral morphine equivalent consumption in milligrams (*y* axis) for different postoperative assessment times (*x* axis). The values for the control and study groups are represented as *blue and yellow horizontal bars*, respectively, and the 25th and 75th percentiles are shown as *blue and yellow error bars* for the control and study groups, respectively. Opioid consumption was similar in both groups for all postoperative assessment times.

Table 4. Pain Scores Perioperatively and after Hospital Discharge

		Pain Score		
Assessment Time	**Status**	**Control Group (n = 39)**	**Study Group (n = 39)**	***P* Value**
Baseline	At rest	2 (0 to 4)	1 (0 to 5)	0.648
	With motion	6 (3 to 8)	6 (5 to 7)	> 0.999
PACU discharge	At rest	0 (0 to 0)	0 (0 to 0)	0.152
	With motion	0 (0 to 0)	0 (0 to 0)	0.152
4 to 6 h postoperatively	At rest	0 (0 to 0)	0 (0 to 0)	0.305
	With motion	0 (0 to 0)	0 (0 to 0)	0.135
Postoperative day 1 AM	At rest	1 (0 to 3)	1 (0 to 3)	0.482
	With motion	3 (0 to 5)	3 (1 to 5)	0.488
Postoperative day 1 postphysiotherapy	At rest	2 (1 to 4)	1 (1 to 2)	0.089
	With motion	4 (3 to 6)	3 (2 to 5)	0.173
Postoperative day 1 PM	At rest	2 (1 to 3)	1 (1 to 2)	0.165
	With motion	3 (2 to 5)	3 (2 to 3)	0.133
Postoperative day 2 AM	At rest	4 (3 to 4)	4 (3 to 4)	0.953
	With motion	6 (4 to 7)	5 (4 to 7)	0.564
Postoperative day 2 PM	At rest	4 (3 to 5)	4 (2.5 to 5)	0.927
	With motion	6 (4 to 7)	5 (4 to 6)	0.204
Day 7 postdischarge	Overall	5.5 (3.8 to 7)	5 (4 to 6.3)	0.646
Day 14 postdischarge	Overall	4 (3 to 5.3)	4 (2.8 to 5)	0.479
Day 42 postdischarge*	Overall	2 (2 to 3)	2 (1 to 4)	> 0.999

The data are reported as medians (interquartile range). The nonparametric median test was used.
*Data analysis on 76 patients (1 patient lost to follow up in each group).
PACU, postanesthesia care unit.

Table 5. In-hospital Functional/Recovery Parameters

Assessment	Time	Control Group (n = 39)	Study Group (n = 39)	Difference in Means, Control – Study (95% CI)	*P* Value
Timed Up and Go test, s	Baseline	16 ± 8	17 ± 7	1 (–4, 3)	0.634
	Postoperative day 1	48 ± 18	43 ± 16	5 (–3, 13)	0.182
Range of motion, °	Baseline (active)	112 ± 13	107 ± 19	5 (–2, 13)	0.144
	Baseline (passive)	117 ± 17	111 ± 17	6 (–2, 13)	0.150
	Postoperative day 1 (active)	85 ± 19	84 ± 19	1 (–8, 10)	0.801
	Postoperative day 1 (passive)	94 ± 18	94 ± 18	0 (–8, 8)	0.924
Distance walked, m	Postoperative day 1	60 ± 23	66 ± 31	6 (–18, 6)	0.296
Blood glucose, mmol/l*	Baseline	5.6 ± 1.4	6.1 ± 1.8	0.5 (–1.3, 0.2)	0.167
	Postoperative day 1	8.2 ± 2.0	8.3 ± 1.7	0.1 (–0.9, 0.8)	0.889
	Postoperative day 2*	6.6 ± 1.5	7.1 ± 1.9	0.5 (–2.2, 1.3)	0.595
QoR-15 assessment	Baseline	141.3 ± 10.3	140.5 ± 9.3	0.8 (–3.6, 5.2)	0.713
	Postoperative day 1	129.8 ± 14.0	130.4 ± 12.9	0.6 (–6.8, 5.4)	0.827
	Postoperative day 2	120.5 ± 19.3	121.2 ± 17.3	0.7 (–9.0, 7.6)	0.866
Time to reach hospital discharge criteria, h		25.2 ± 10.7	23.4 ± 7.6	1.8 (–2.3, 6.1)	0.369
Length of hospital stay, h		36.8 ± 26.5	35.8 ± 16.7	0.9 (–9.0, 11.0)	0.844
Patient satisfaction†		3 (3 to 3)	3 (3 to 3)	ND	0.209

No significant difference between the two groups was found for any of these parameters. The data are reported as means ± SD. The *t* test was used.

*Blood glucose results on postoperative day 2 were obtained from 8 patients in each group. †Patient satisfaction score at the time of discharge are given as 1 for unsatisfied, 2 fo somewhat satisfied, and 3 for satisfied. The data are reported as medians (interquartile ranges). The chi-square test was used.

ND, not determined; QoR, quality of recovery.

Discussion

In this study, we sought to examine the opioid-sparing effect of a comprehensive multimodal analgesic regimen combining multiple systemic and regional modalities that have been shown to provide analgesic benefit in total knee arthroplasty. Our current institutional perioperative analgesic regimen comprises a single injection adductor canal block, low-dose intrathecal morphine (100 μg), intraoperative IV dexamethasone (8 mg), periarticular local anesthetic infiltration, and round-the-clock oral acetaminophen and celecoxib, with immediate-release opioids as needed. We studied the addition of five recently described analgesic modalities to this regimen: a preoperative iPACK block,[13] an intraoperative IV infusion of low-dose dexmedetomidine[5,14–16] (1 μg/kg) and ketamine[17] (0.5 mg/kg), a second dose of IV dexamethasone[18] (8 mg) on postoperative day 1, and two additional adductor canal block[19] bolus injections on postoperative days 0 and 1.

Contrary to expectations and to reports of analgesic benefits of each novel intervention when compared to placebo or no intervention, this additional bundle of interventions did not further reduce opioid consumption or pain scores in the first 24 to 48 h after total knee arthroplasty. Neither did they improve postoperative functional outcomes, quality of recovery, patient satisfaction, or longer-term pain and analgesic outcomes up to 6 weeks after surgery. Our results suggest that the standard multimodal analgesic regimen currently prescribed for the control group is rather robust. Thus, the therapeutic value of adding more analgesic interventions is limited with diminishing return.

Compared with placebo, perioperative ketamine administration decreases pain scores[20] and opioid consumption after total knee arthroplasty.[6] The reported effective analgesic dose for IV ketamine varies widely—an initial 0.05 to 1 mg/kg bolus followed by an infusion of 1 to 16.7 μg/kg/min during and after surgery. Similarly, intraoperative sedation with low-dose IV dexmedetomidine (0.1 to 1 μg/kg bolus followed by 0.1 to 0.7 μg kg^{-1} h^{-1} infusion) has been shown to successfully reduce pain, postoperative nausea and vomiting, and delirium[5] compared with placebo after total knee arthroplasty.[15,16]

Dexamethasone is another drug that has analgesic properties in addition to its antiemetic effect for a myriad of surgical procedures including joint arthroplasties.[21] In the total knee arthroplasty population, a single perioperative IV dose (greater than 0.1 mg/kg) can be opioid-sparing and pain-relieving, and a second 10-mg dose after surgery may further improve postoperative nausea and vomiting, range of motion, and patient satisfaction.[22] Although the optimal dose and dosing interval remain unknown, perioperative IV dexamethasone (total of less than 20 mg) significantly reduces total opioid consumption and postoperative pain after total knee arthroplasty.[18] Furthermore, perioperative dexamethasone administration limited to one or two doses appears safe with no reported increase in surgical site infection or sustained hyperglycemia.

Table 6. In-hospital Side Effects

Side Effects	Time	Control Group (n = 39)	Study Group (n = 39)	*P* Value
Nausea/vomiting*	Postoperative day 0	13 (33.3%)	12 (30.8%)	0.808
	Postoperative day 1	7 (17.9%)	10 (25.6%)	0.411
Pruritus†	Postoperative day 0	8 (20.5%)	6 (15.4%)	0.555
	Postoperative day 1	3 (7.7%)	4 (10.3%)	0.692
Sedation‡	Postoperative day 0	1 (2.6%)	2 (5.1%)	0.555
	Postoperative day 1	0 (0%)	0 (0%)	
Urinary Retention§	Postoperative day 0	9 (23.1%)	11 (28.2%)	0.604
	Postoperative day 1	2 (5.1%)	1 (2.6%)	0.556
Hypotension‖	PACU	13 (33.3%)	25 (64.1%)	0.010#
	Postoperative day 1	7 (17.9%)	8 (20.5%)	0.774
Foot Plantarflexion = 0**	Postoperative day 0	7 (17.9%)	18 (46.1%)	0.028#
	Postoperative day 1	0 (0%)	0 (0%)	
Foot Dorsiflexion = 0**	Postoperative day 0	11 (28.2%)	18 (46.1%)	0.229
	Postoperative day 1	1 (2.6%)	0 (0%)	0.365

The data are reported as n (%). The chi-square test was used.

*Defined as nausea/vomiting that required treatment. †Defined as pruritus that required treatment. ‡Defined as a Ramsay scale score of higher than 2, where 1 indicates anxious, agitated, restless; 2 indicates cooperative, oriented; 3 indicates response to commands only; 4 indicates brisk response to glabellar tap/loud stimulus; 5 indicates sluggish response to glabellar tap/loud stimulus; and 6 indicates no response to stimulus. §Defined as the inability to urinate despite a full bladder requiring bladder catheter insertion. ‖Defined as a drop from baseline systolic blood pressure of 25% or more or blood pressure lower than 90 mmHg requiring treatment.

#$P < 0.05$. **Ankle motor block score, where 0 indicates no power, 1 indicates decreased power (any movement without resistance), and 2 indicates normal power (complete movement against resistance).

PACU, postanesthesia care unit.

Among regional analgesic modalities, adductor canal block has become a motor-sparing alternative to femoral nerve block to control anterior knee pain after total knee arthroplasty. Several randomized controlled trials reported that continuous adductor canal block could be superior to single-shot adductor canal block by further improving pain scores and time to rescue analgesia.[23] However, whether continuous adductor canal block can further improve postoperative rehabilitation and other functional outcomes is not clear.[24] Similarly, an iPACK block has been shown to reduce the incidence of posterior knee pain after total knee arthroplasty compared to a sham block.[13] However, its analgesic contribution in the presence of periarticular local anesthesia infiltration remains debatable because conceivably, local anesthesia infiltration into the posterior capsule of the knee likely overlaps with the analgesic coverage of the iPACK block (*i.e.*, terminal branches of the genicular nerves and popliteal plexus). Thus, the addition of an iPACK block to periarticular local anesthesia infiltration may be redundant, as suggested by recent randomized controlled trial data,[19] a meta-analysis,[25] and the results of our current study. Consistent with previous studies, we also failed to show that the addition of an iPACK block improves functional outcomes or quality of recovery after total knee arthroplasty, irrespective of pain score differences in the first 24 h.[13]

Both the study and control groups in the current study received a single IV dexamethasone dose, single-shot adductor canal block, intrathecal morphine (100 μg), and periarticular local anesthesia infiltration for postoperative analgesia (table 1). The synergistic analgesic effect of combining periarticular local anesthesia infiltration and single-dose adductor canal block can significantly delay rescue analgesia,[26] reduce cumulative opioid requirements,[27] and improve range of motion[28] and early discharge after total knee arthroplasty.[29] The addition of intrathecal morphine to adductor canal block and periarticular local anesthesia infiltration can further improve analgesia and reduce postoperative opioid requirements.[30] The intrathecal morphine dose selected for this study (100 μg) appears optimal for elderly patients undergoing total knee arthroplasty, balancing its analgesic effect with potential adverse effects[31] with no increase in the incidence of urinary retention, nausea, vomiting, or pruritus.[30] Furthermore, opioid-related respiratory complications are infrequent even in patients with obstructive sleep apnea.[32] Findings of the current study suggest that analgesia resulting from a combination of these interventions is rather robust, with little benefit derived from additional analgesic interventions.

Interestingly, we found that opioid requirement and pain scores were significantly lower in the control group of the current study as compared to an almost identical treatment group (single-shot adductor canal block plus 100 μg of intrathecal morphine and periarticular local anesthesia infiltration) in an earlier randomized controlled trial we conducted 4 years ago. For the past study,[30] the 24-h IV morphine equivalent requirement was 34 ± 21 mg (mean ± SD), which equates to 102 ± 63 mg oral morphine equivalents. For the current study, the 24 h oral morphine equivalent

consumption was 29.3 ± 18.7 mg (mean ± SD), representing a ~70% reduction, despite no significant change in the total knee arthroplasty perioperative care pathway, surgical/anesthetic technique, or medical staff. The median 24-h pain score at rest was likewise significantly lower, 1 (0 to 3) in the current study *versus* 5 (3 to 7) in the earlier study, corresponding to a five-fold reduction.

Significant improvement in pain scores and opioid consumption observed in the current study results possibly from two major changes in patient management made over the past 4 yr: intraoperative tranexamic acid and IV dexamethasone (8 mg). All patients received 1 g of IV tranexamic acid in the beginning and 3 g topical at the end of surgery. Conceivably, not only does tranexamic acid reduce major bleeding and transfusion requirements,[33] it can also potentially decrease pain and opioid consumption through a reduction in inflammatory surgical response,[34,35] articular swelling,[36] and hematoma within the wound. Blood conservation with tranexamic acid also prevents postoperative anemia and associated fatigue, resulting in expedited rehabilitation after total knee arthroplasty.[30,34,35,37] Some other contributing factors to pain relief and enhanced recovery were more consistent use of cryotherapy and early initiation of postoperative ambulation.

More patients in the study group developed hypotension (*i.e.,* systolic blood pressure of 90 mmHg or lower) in the PACU (table 6). This is likely the effect of IV dexmedetomidine through its central and peripheral presynaptic α-2 adrenoceptor–mediated sympatholysis and vasodilation.[14] Hypotension was, however, transient and quickly responded to IV fluid and phenylephrine rescue doses with no delay in PACU discharge. In addition, hypotension happened in the PACU and not during surgery. This is consistent with previous reports for timing of dexmedetomidine induced hypotension, which typically occurs 60 to 330 min after IV administration.[38,39]

Our study has several limitations. First, our control group received intrathecal morphine and periarticular local anesthesia infiltration. These interventions may not be possible in other institutions due to nursing monitoring policy and surgeon's preference, which limits the extrapolation of our results to these scenarios. Second, the optimal analgesic dose and duration of administration for IV dexmedetomidine[5] and ketamine[17] have not been established. Thus, the single doses administered during surgery in our study may be suboptimal. Similarly, our study was not powered to detect the impact of these multimodal analgesic components on the incidence of chronic postsurgical pain beyond 6 weeks. Third, we have only assessed muscle function qualitatively without using dynamometry. Currently, unintended local anesthetic spread toward the sciatic nerve or its branches with periarticular local anesthesia infiltration and/or iPACK cannot be ruled out. Fourth, we used repeated local anesthetic boluses for continuous adductor canal block rather than an infusion and have only extended adductor canal block to the morning of postoperative day 1 while many patients were discharged home.

Conclusions

In the presence of periarticular local anesthesia infiltration, intrathecal morphine, single-shot adductor canal block, and dexamethasone, the addition of iPACK block, IV dexmedetomidine, IV ketamine, an additional IV dexamethasone dose and repeated adductor canal block injections failed to further reduce opioid consumption or pain scores or to improve functional outcomes after total knee arthroplasty.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: vincent.chan@uhn.ca. Raw data available at: vincent.chan@uhn.ca.

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Supplemental Digital Content

Supplemental table, http://links.lww.com/ALN/C880

References

1. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F: Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. Anesthesiology 1999; 91:8–15
2. Hah JM, Bateman BT, Ratliff J, Curtin C, Sun E: Chronic opioid use after surgery: Implications for perioperative management in the face of the opioid epidemic. Anesth Analg 2017; 125:1733–40
3. McIsaac DI, McCartney CJ, Walraven CV: Peripheral nerve blockade for primary total knee arthroplasty: A population-based cohort study of outcomes and resource utilization. Anesthesiology 2017; 126: 312–20
4. Kopp SL, Børglum J, Buvanendran A, Horlocker TT, Ilfeld BM, Memtsoudis SG, Neal JM, Rawal N, Wegener JT: Anesthesia and analgesia practice pathway options for total knee arthroplasty: An evidence-based review by the American and European Societies of Regional Anesthesia and Pain Medicine. Reg Anesth Pain Med 2017; 42:683–97
5. Yang Q, Ren Y, Feng B, Weng X: Pain relieving effect of dexmedetomidine in patients undergoing total knee or hip arthroplasty: A meta-analysis. Medicine (Baltimore) 2020; 99:e18538
6. Wang P, Yang Z, Shan S, Cao Z, Wang Z: Analgesic effect of perioperative ketamine for total hip arthroplasties and total knee arthroplasties: A PRISMA-compliant meta-analysis. Medicine (Baltimore) 2020; 99:e22809
7. Schnabel A, Reichl SU, Weibel S, Zahn PK, Kranke P, Pogatzki-Zahn E, Meyer-Frießem CH: Adductor canal blocks for postoperative pain treatment in adults undergoing knee surgery. Cochrane Database Syst Rev 2019; 2019:CD012262
8. Kim DH, Beathe JC, Lin Y, YaDeau JT, Maalouf DB, Goytizolo E, Garnett C, Ranawat AS, Su EP, Mayman DJ, Memtsoudis SG: Addition of infiltration between the popliteal artery and the capsule of the posterior knee and adductor canal block to periarticular injection enhances postoperative pain control in total knee arthroplasty: A randomized controlled trial. Anesth Analg 2019; 129:526–35
9. Schulz KF, Altman DG, Moher D; CONSORT Group: CONSORT 2010 statement: Updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010; 152:726–32
10. Stark PA, Myles PS, Burke JA: Development and psychometric evaluation of a postoperative quality of recovery score: The QoR-15. Anesthesiology 2013; 118:1332–40
11. Kirkham KR, Grape S, Martin R, Albrecht E: Analgesic efficacy of local infiltration analgesia *vs.* femoral nerve block after anterior cruciate ligament reconstruction: A systematic review and meta-analysis. Anaesthesia 2017; 72:1542–53
12. Unnanuntana A, Mait JE, Shaffer AD, Lane JM, Mancuso CA: Performance-based tests and self-reported questionnaires provide distinct information for the preoperative evaluation of total hip arthroplasty patients. J Arthroplasty 2012; 27:770–5.e1
13. Ochroch J, Qi V, Badiola I, Grosh T, Cai L, Graff V, Nelson C, Israelite C, Elkassabany NM: Analgesic efficacy of adding the iPACK block to a multimodal analgesia protocol for primary total knee arthroplasty. Reg Anesth Pain Med 2020; 45:799–804
14. Farag E, Argalious M, Abd-Elsayed A, Ebrahim Z, Doyle DJ: The use of dexmedetomidine in anesthesia and intensive care: A review. Curr Pharm Des 2012; 18:6257–65
15. Chan IA, Maslany JG, Gorman KJ, O'Brien JM, McKay WP: Dexmedetomidine during total knee arthroplasty performed under spinal anesthesia decreases opioid use: A randomized-controlled trial. Can J Anaesth 2016; 63:569–76
16. Shin HJ, Do SH, Lee JS, Kim TK, Na HS: Comparison of intraoperative sedation with dexmedetomidine *versus* propofol on acute postoperative pain in total knee arthroplasty under spinal anesthesia: A randomized trial. Anesth Analg 2019; 129:1512–8
17. Xu B, Wang Y, Zeng C, Wei J, Li J, Wu Z, He H, Lei G, Xie D, Ding X: Analgesic efficacy and safety of ketamine after total knee or hip arthroplasty: A meta-analysis of randomised placebo-controlled studies. BMJ Open 2019; 9:e028337
18. Zhuo Y, Yu R, Wu C, Huang Y, Ye J, Zhang Y: The role of perioperative intravenous low-dose dexamethasone in rapid recovery after total knee arthroplasty: A meta-analysis. J Int Med Res 2021; 49:300060521998220
19. Kertkiatkachorn W, Kampitak W, Tanavalee A, Ngarmukos S: Adductor canal block combined with iPACK (interspace between the popliteal artery and the capsule of the posterior knee) block *vs.* periarticular injection for analgesia after total knee arthroplasty: A randomized noninferiority trial. J Arthroplasty 2021; 36:122–9.e1
20. Carstensen M, Møller AM: Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: A qualitative review of randomized trials. Br J Anaesth 2010; 104:401–6
21. De Oliveira GS Jr, Almeida MD, Benzon HT, McCarthy RJ: Perioperative single dose systemic dexamethasone for postoperative pain: A meta-analysis of randomized controlled trials. Anesthesiology 2011; 115:575–88
22. Wu Y, Lu X, Ma Y, Zeng Y, Bao X, Xiong H, Shen B: Perioperative multiple low-dose dexamethasones improves postoperative clinical outcomes after total knee arthroplasty. BMC Musculoskelet Disord 2018; 19:428

23. Yu R, Wang H, Zhuo Y, Liu D, Wu C, Zhang Y: Continuous adductor canal block provides better performance after total knee arthroplasty compared with the single-shot adductor canal block?: An updated meta-analysis of randomized controlled trials. Medicine (Baltimore) 2020; 99:e22762
24. Sun C, Zhang X, Song F, Zhao Z, Du R, Wu S, Ma Q, Cai X: Is continuous catheter adductor canal block better than single-shot canal adductor canal block in primary total knee arthroplasty?: A GRADE analysis of the evidence through a systematic review and meta-analysis. Medicine (Baltimore) 2020; 99:e20320
25. Hussain N, Brull R, Sheehy B, Dasu M, Weaver T, Abdallah FW: Does the addition of iPACK to adductor canal block in the presence or absence of periarticular local anesthetic infiltration improve analgesic and functional outcomes following total knee arthroplasty?: A systematic review and meta-analysis. Reg Anesth Pain Med 2021; 46:713–21
26. Kampitak W, Tanavalee A, Ngarmukos S, Amarase C, Apihansakorn R, Vorapalux P: Does adductor canal block have a synergistic effect with local infiltration analgesia for enhancing ambulation and improving analgesia after total knee arthroplasty? Knee Surg Relat Res 2018; 30:133–41
27. Lv J, Huang C, Wang Z, Ou S: Adductor canal block combined with local infiltration analgesia *versus* isolated adductor canal block in reducing pain and opioid consumption after total knee arthroplasty: A systematic review and meta-analysis. J Int Med Res 2020; 48:300060520926075
28. Zuo W, Guo W, Ma J, Cui W: Dose adductor canal block combined with local infiltration analgesia has a synergistic effect than adductor canal block alone in total knee arthroplasty: A meta-analysis and systematic review. J Orthop Surg Res 2019; 14:101
29. Perlas A, Kirkham KR, Billing R, Tse C, Brull R, Gandhi R, Chan VW: The impact of analgesic modality on early ambulation following total knee arthroplasty. Reg Anesth Pain Med 2013; 38:334–9
30. Biswas A, Perlas A, Ghosh M, Chin K, Niazi A, Pandher B, Chan V: Relative contributions of adductor canal block and intrathecal morphine to analgesia and functional recovery after total knee arthroplasty: A randomized controlled trial. Reg Anesth Pain Med 2018; 43:154–60
31. Murphy PM, Stack D, Kinirons B, Laffey JG: Optimizing the dose of intrathecal morphine in older patients undergoing hip arthroplasty. Anesth Analg 2003; 97:1709–15
32. Bai JW, Singh M, Short A, Bozak D, Chung F, Chan VWS, Bhatia A, Perlas A: Intrathecal morphine and pulmonary complications after arthroplasty in patients with obstructive sleep apnea: A retrospective cohort study. Anesthesiology 2020; 132:702–12
33. Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Bini SA, Clarke HD, Schemitsch E, Johnson RL, Memtsoudis SG, Sayeed SA, Sah AP, Della Valle CJ: Tranexamic acid in total joint arthroplasty: The endorsed clinical practice guides of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society. Reg Anesth Pain Med 2019; 44:7–11
34. Laoruengthana A, Rattanaprichavej P, Rasamimongkol S, Galassi M, Weerakul S, Pongpirul K: Intra-articular tranexamic acid mitigates blood loss and morphine use after total knee arthroplasty: A randomized controlled trial. J Arthroplasty 2019; 34:877–81
35. Lošťák J, Gallo J, Špička J, Langová K: Intra-articular application of tranexamic acid significantly reduces blood loss and transfusion requirement in primary total knee arthroplasty (Czech). Acta Chir Orthop Traumatol Cech 2016; 83:254–62
36. Ishida K, Tsumura N, Kitagawa A, Hamamura S, Fukuda K, Dogaki Y, Kubo S, Matsumoto T, Matsushita T, Chin T, Iguchi T, Kurosaka M, Kuroda R: Intra-articular injection of tranexamic acid reduces not only blood loss but also knee joint swelling after total knee arthroplasty. Int Orthop 2011; 35:1639–45
37. Grosso MJ, Trofa DP, Danoff JR, Hickernell TR, Murtaugh T, Lakra A, Geller JA: Tranexamic acid increases early perioperative functional outcomes after total knee arthroplasty. Arthroplast Today 2018; 4:74–7
38. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD: The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000; 93:382–94
39. Bloor BC, Ward DS, Belleville JP, Maze M: Effects of intravenous dexmedetomidine in humans: II. Hemodynamic changes. Anesthesiology 1992; 77:1134–42

Intraoperative Management of a Severely Kinked Endotracheal Tube and Difficult Airway

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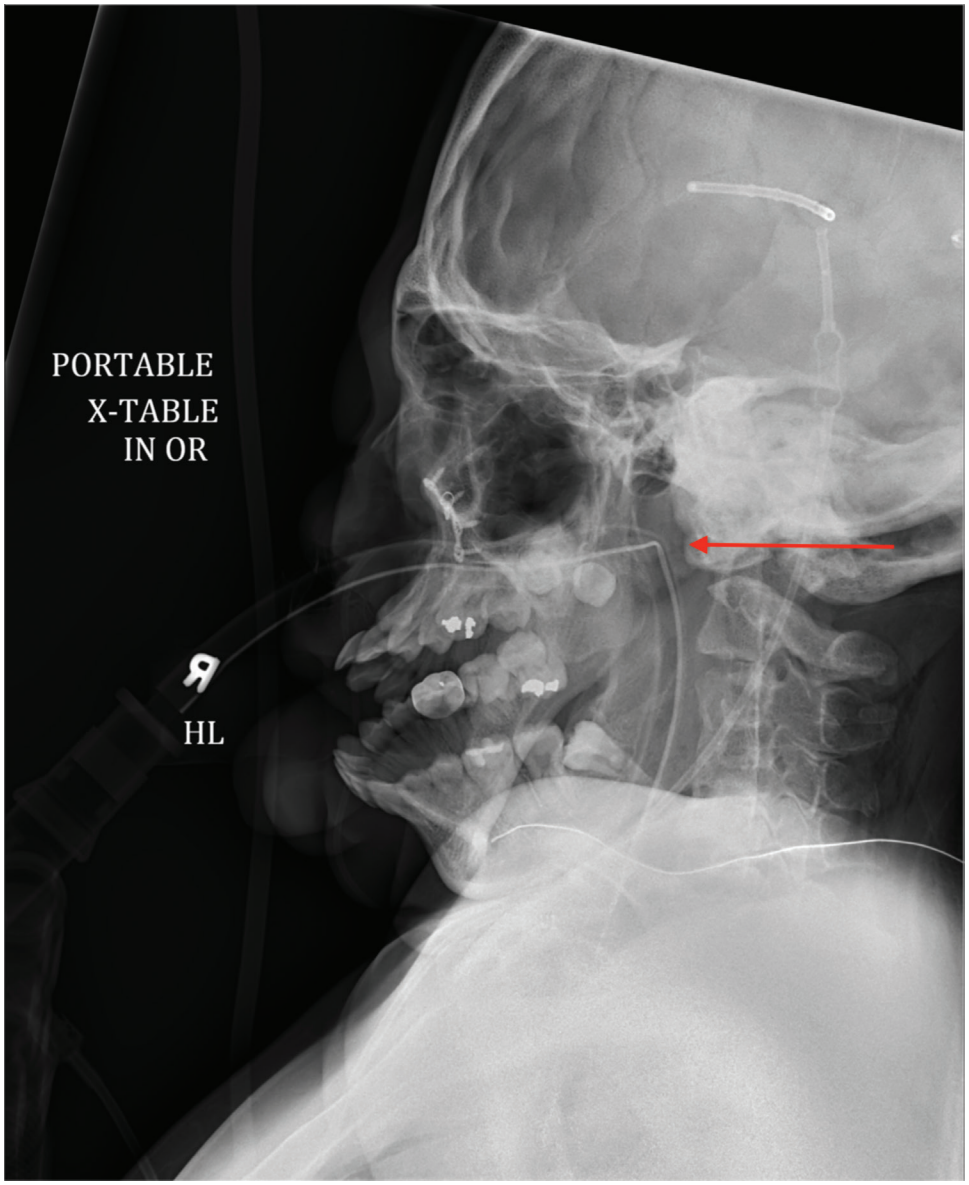

This figure is a lateral cervical radiograph of a nasally intubated 16-yr-old patient with Crouzon syndrome obtained after completion of cranial fossa surgery for Chiari malformation and returning to supine from a prone position. The standard endotracheal tube was severely kinked in the nasopharynx, as shown in the image, and the location

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of the kinking is indicated with a red arrow. This was likely caused by the warming of the endotracheal tube and the patient's unique pharyngeal anatomy. The tracheal intubation of the patient was difficult, requiring 11 attempts due to midface hypoplasia, obesity, macroglossia, and cervical spine instability. After the start of surgery, elevated airway pressures and the inability to pass a suction catheter suggested kinking of the endotracheal tube. Due to extremely difficult intubation, endotracheal tube replacement was not attempted. Because the severely kinked endotracheal tube limited inspiratory and expiratory airflow, adequate tidal volume was achieved by increasing peak inspiratory pressure.[1] Intermittent measurement of plateau pressure with an expiratory hold yielded additional information about the pressure at the alveoli. Because expiration was passive, increasing the expiratory time facilitated exhalation and reduced the risk of breath stacking.[2] A helium–oxygen mixture can also be used to improve ventilation by reducing gas density, increasing the likelihood of maintaining laminar flow across the point of obstruction, and improving bulk flow.[3] If the patient can tolerate permissive hypercapnia, a reduction in minute ventilation is also an option to minimize turbulent flow. The use of a wire-reinforced tube is often recommended to prevent endotracheal tube kinking in such a patient.

Competing Interests

The authors declare no competing interests.

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References

1. Manning HL: Peak airway pressure: Why the fuss? Chest 1994; 105:242–7
2. Gertler R: Respiratory mechanics. Anesthesiol Clin 2021; 39:415–40
3. Gupta VK, Cheifetz IM: Heliox administration in the pediatric intensive care unit: An evidence-based review. Pediatr Crit Care Med 2005; 6:204–11

Ventilation during Lung Resection and Critical Care: Comparative Clinical Outcomes

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After the landmark Acute Respiratory Distress Syndrome Network study in 2000, the idea of low tidal volume (V_T) ventilation spread through the critical care and anesthesiology communities.[1] Studies have shown that positive-pressure ventilation contributes to lung inflammation and might predispose general surgery and intensive care unit (ICU) patients to a higher risk of ventilator-associated lung injury at high V_T.[2] Whereas acceptance of low V_T has been nearly universal for management of patients with acute respiratory distress syndrome (ARDS), its application in the operating room has been varied.[3] The effects of V_T on pulmonary complications in general surgery patients undergoing two-lung ventilation were described in an extensive systematic review of studies published over a four-decade period and written by investigators with expertise in this field.[3] The authors did not find a temporal change in clinical outcomes despite decreases in V_T during this period. Although the use of low V_T in the operating room was adapted from the ICU literature to both two- and one-lung ventilation, we will focus on patients requiring one-lung ventilation here.

In large-animal experimental studies, one-lung ventilation was found to be injurious in and of itself, particularly with large tidal volumes and no positive end-expiratory pressure (PEEP).[4,5] The use of high fluid infusion rates in one of these studies may confound their observations.[4] Increased lung edema was noted, as well as evidence of cyclic recruitment injury, which may increase mechanical stress from repeated expansion and collapse.[4,5] Compared with the ICU, the duration of mechanical ventilation in the operating room is on the order of hours, rather than days. Specific to thoracic surgery and one-lung ventilation, the chest may be open and exposed to atmospheric pressure or subjected to varying amounts of insufflation pressure during minimally invasive surgery. Moreover, the patient may be in the lateral decubitus position, which can lead to nonhomogenous distribution of aeration and atelectasis in the dependent and ventilated lung.

The application of low V_T strategies to one-lung ventilation during thoracic surgery has also gained widespread acceptance. Low V_T ventilation may reduce the risk of ventilator-associated lung injury and clinically important postoperative pulmonary complications. Conversely, it might contribute to atelectasis and dead space ventilation with hypercarbia. The most salient strategies for protective lung ventilation are manipulation of V_T, PEEP, and driving pressure, but fraction of inspired oxygen (F_{IO_2}), fluid management, and choice of anesthetic agents must be considered. We presume that patients undergoing lung resection and one-lung ventilation are at risk of developing varying degrees of acute lung injury after surgery, similar to patients without ARDS (*i.e.*, with healthy lungs) who require mechanical ventilation. In this review, we highlight recent evidence from prospective studies on the use of low V_T ventilation and varying levels of PEEP in patients with ARDS and ICU patients without ARDS. We then compare this with evidence from studies of intraoperative one-lung ventilation during lung resection and clinical outcomes.

Randomized Controlled Trials of Patients with ARDS

The most influential ventilation management strategy for patients with ARDS comes from the Acute Respiratory Distress Syndrome Network trial.[1] In this study, the control group was treated at a V_T of 12 ml/kg predicted body weight, and the experimental group was treated at a V_T of 6 ml/kg predicted body weight. Mortality was 8.8% lower in the low V_T group. Low V_T ventilation was associated with more ventilator-free days and fewer organ-failure days. There was no difference in the incidence of barotrauma between groups. With the finding that low V_T is associated with lower mortality, enthusiasm mounted to optimize oxygenation and improve rates of atelectasis.

Three aspects of low V_T ventilation were postulated to have contributed to the lower mortality observed in the Acute Respiratory Distress Syndrome Network trial: coincident lower peak inspiratory airway pressure, plateau

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pressure, and driving pressure.[1] Limiting driving pressure to less than 15 cm H_2O (in addition to the use of low V_T) was analyzed in two meta-analyses that demonstrated a significant benefit on mortality.[6,7] Subsequent studies of higher PEEP or titration of PEEP to other physiologic parameters have not demonstrated a further benefit.

A strategy featuring higher PEEP, compared with that in the initial Acute Respiratory Distress Syndrome Network stepladder, while maintaining low V_T was associated with a higher initial partial pressure of oxygen to fraction of inspired oxygen ratio (Pao_2:FIO_2); however, survival and ventilator-free days were similar between groups.[8] The findings of a small study suggested that the use of a PEEP recruitment maneuver could improve rates of hypoxemia and reduce the need for respiratory rescue therapies.[9] Subsequently, a strategy to optimize PEEP—by performing recruitment maneuvers (PEEP of up to 45 cm H_2O) and then titrating PEEP to the optimal static compliance—was tested.[10] In this study, 1,013 patients were randomized to either standard PEEP or the recruitment maneuver plus titrated PEEP. Early oxygenation was better in patients managed with the recruitment maneuver. Unfortunately, rates of barotrauma and mortality were also higher in these patients, which instigated an early end to the trial.

It was hypothesized that titration of PEEP by optimizing pleural pressures could lead to better outcomes. To investigate this, PEEP was adjusted with esophageal manometry to achieve transpulmonary pressures of 0 to 6 cm H_2O. Pao_2:FIO_2 ratio and lung compliance within the first 3 days and 28-day survival were significantly better with this approach.[11] Unfortunately, advantages in 180-day survival, rates of kidney injury, and use of rescue ventilation procedures were not statistically significant. Further investigation revealed no benefits on mortality or ventilator-free days.[12]

Randomized Controlled Trials of ICU Patients without ARDS

With the substantially better outcomes among patients with ARDS managed with low V_T ventilation, the eagerness to examine lower V_T extended to ventilation of all ICU patients, particularly those at risk of developing ARDS. Although low V_T ventilation has been associated with a lower risk of ventilator-associated lung injury, it might contribute to ventilator dyssynchrony, delirium, atelectasis, and pulmonary dead space ventilation with hypercarbia. The findings of retrospective[13–19] and prospective[20–25] studies of ventilation of ICU patients without ARDS (*i.e.*, with healthy lungs) are summarized in table 1. Our discussion of ICU patients without ARDS is limited to contemporary prospective trials.

While the Acute Respiratory Distress Syndrome Network trial was underway, the results of a counterpart study of patients without ARDS emerged.[22] Patients who were at risk of developing ARDS were assigned a moderate *versus* high goal V_T. Patients were randomized, and V_T ranged from 6.8 to 7.2 ml/kg predicted body weight in the low V_T group and from 10.1 to 10.7 ml/kg predicted body weight in the high V_T group. In-hospital mortality was approximately 50% in both groups. The low V_T group had a higher partial pressure of carbon dioxide and more frequently required paralytics and hemodialysis than the high V_T group. One possible explanation for the lack of a benefit on mortality from this intervention might involve subsequent evolution in ICU practice. A relatively small trial of patients randomized to a V_T of either 6.4 ml/kg predicted body weight or 10 ml/kg predicted body weight was stopped at the interim analysis because of the finding of a higher incidence of "lung injury" in the high V_T group.[23] Lung injury in this study was identified as a change on chest radiography with a corresponding clinical decline in respiratory status. Neither barotrauma nor pneumothorax was identified. PEEP and FIO_2 were adjusted as in the Acute Respiratory Distress Syndrome Network trial.[1] Also correlated with lung injury were the number of blood transfusions, PEEP level, and interleukin-6 (IL-6) level. Mortality at 28 days and ventilator-free days were similar between the two groups.[23]

In the largest randomized trial of patients expected to require mechanical ventilation for more than 24 h, six institutions in the Netherlands managed intubated patients without ARDS with a low *versus* high V_T target.[24] The low V_T group was managed with 5.9 to 7.4 ml/kg predicted body weight, whereas the high V_T group was managed with 9.1 to 9.3 ml/kg predicted body weight. None of the studied outcomes—28-day ventilator-free days, ICU length of stay, and 28- or 90-day mortality—differed significantly between the groups. There was no obvious downside to either strategy, because the incidence of atelectasis, ARDS, delirium, pneumonia, and pneumothorax and the need for tracheostomy were similar between the groups.

Whereas low to moderate V_T is recommended by experts for patients without ARDS, the optimal PEEP is less clear. Current trends in mechanical ventilation practice suggest that many critical care physicians are targeting a PEEP of 8 cm H_2O, instead of the traditional 5 cm H_2O. The uncertainty regarding optimal PEEP was addressed in a recent large trial of intubated patients without ARDS who were randomized to a PEEP of either less than 5 cm H_2O or 8 cm H_2O. Although the study was not blinded, the study groups were well balanced, and the target PEEP levels were achieved. There were no significant differences in survival or freedom from mechanical ventilation.[25] With lower PEEP, there was a significantly lower Pao_2:FIO_2 ratio and higher driving pressure. Of note, the difference in PEEP level between groups (3 to 5 cm H_2O) might have been inadequate to determine the superiority of either approach.

Mechanical ventilation can be lifesaving; however, high V_T and high driving pressure can contribute to lung inflammation. Results from earlier retrospective studies demonstrating improved outcomes with lower V_T in patients with healthy lungs are inconsistent with results from more recent large prospective randomized trials (table 1). As this area

Table 1. Summary of Studies of Intensive Care Unit Patients without Acute Respiratory Distress Syndrome (Healthy Lungs)

Study Design	Total No.	Low V_T	Intermediate V_T	High V_T	Primary Study Endpoint	Results of Primary Study Endpoint	Other Events and Comments	Author (Year)
Retrospective or meta-analysis								
One-month snapshot of V_T practice among 361 international ICUs	5,183	< 6 ml/kg n = not available	6–10 ml/kg n = not available	> 10 ml/kg n = not available	ICU mortality within 30 d of initiating mechanical ventilation	ICU mortality for low V_T = 32%, intermediate V_T = 30%, and high V_T = 33%	ICU mortality was associated with peak pressure > 50 cm water (65%), plateau pressure > 35 cm water (78%), and PEEP > 10 cm water (50%)	Esteban[13] (2002)
Observed outcomes based on first day of mechanical ventilation	332		< 9 ml/kg n = 66	9–11 ml/kg predicted body weight n = 160 > 12 ml/kg n = 100	ARDS	Risk for ARDS with odds ratio of 1.3 per each ml increase in V_T > 6 ml/kg	ARDS by V_T group: 18% (< 9 ml/kg), 22% (9–11 ml/kg), and 34% (> 12 ml/kg)	Gajic[14] (2004)
Observation of risks contributing to outcomes on mechanical ventilation	3,261		< 700 ml n = not available	> 700 ml n = not available	ARDS	Odds ratio 2.67 for high V_T (> 700 ml) for development of ARDS	Peak pressure and high PEEP associated with ARDS (subset of patients from Esteban[11])	Gajic[15] (2005)
Mechanical ventilation in patients with spontaneous intracranial hemorrhage	697		< 8 ml/kg n = not available	> 8 ml/kg n = not available	Dual primary endpoints: ARDS and inpatient mortality	ARDS risk (hazard ratio 1.74, $P = 0.02$) for mechanical ventilation V_T > 8 ml/kg Inpatient mortality associated with high V_T (hazard ratio 2.52, $P < 0.001$)	Unique patient population with intracranial pathology	Elmer[16] (2013)
Individualized patient "meta-analysis" (data from original study were procured and analyzed for the study indices)	2,184	< 7 ml/kg n = 720	7–10 ml/kg n = 754	> 10 ml/kg n = 710	Development of ARDS and/or pneumonia	ARDS and/or pneumonia: low V_T = 23%, intermediate V_T = 28%, and high V_T = 31% (low *vs.* high $P = 0.042$)	V_T not associated with hospital mortality or ventilator-free days	Serpa Neto[17] (2015)
Mechanically ventilated patients in the emergency department	1,705		Protective lung ventilation n = 513	Traditional ventilation n = 1192	Hospital mortality in relation to driving pressure aspect of protective lung ventilation	Hospital mortality for intermediate V_T = 20% and high V_T = 28% ($P = 0.721$)	Higher driving pressure (15.9 *vs.* 15.1) associated with risk of death ($P = 0.005$) Higher peak pressure and higher plateau pressures also associated with higher hospital mortality ($P = 0.001$)	Fuller[18] (2018)
Analysis of V_T and driving pressure with 30-d mortality	1,239	V_T 6.3–7.8 ml/kg Driving pressure 8.1–12.2 cm H_2O			30-d mortality	Higher V_T was associated with greater 30-d mortality (odds ratio 1.22, $P = 0.01$)	Driving pressure not associated with 30-d mortality (odds ratio 1.02)	Lanspa[19] (2019)
Prospective observational								
Comparison of a pre- and postintervention plan to implement protective lung ventilation and restrict blood transfusions	375		7.7 ml/kg (median V_T 500 ml/kg) 34% transfused n = 163	10.6 ml/kg (median V_T 700 ml/kg) 58% transfused n = 212	Dual endpoints: ARDS and inpatient mortality	Simultaneous protective lung ventilation and restrictive blood transfusion were associated with lower ARDS (28% *vs.* 10%, $P < 0.001$) and inpatient mortality: ICU mortality (20% *vs.* 7%, $P < 0.001$) and hospital mortality (33% *vs.* 18%, $P < 0.001$)	Limiting V_T and blood transfusions was associated with more ventilator-free days and reduced ICU length of stay Improvement in ARDS was more pronounced in surgical patients	Yilmaz[20] (2007)
Outcomes related to V_T and/or maximal distention pressure*	116		< 8 ml/kg (mean V_T 6.9 ml/kg) n = 67	> 8 ml/kg (mean V_T 8.3 ml/kg) n = 49	Hospital mortality, 28-d mortality, and ICU mortality	28-d mortality for low V_T = 20.9% and high V_T = 42.9% ($P = 0.011$)	28-d mortality for low maximal distension pressure = 24.4% *vs.* 42.1% for high maximal distention pressure ($P = 0.051$) Multivariable regression for 28-d mortality related to V_T ($P = 0.113$) and for maximal distention pressure ($P = 0.036$)	Bastos-Netto[21] (2021)

(*Continued*)

Table 1. (Continued)

Study Design	Total No.	Low V_T	Intermediate V_T	High V_T	Primary Study Endpoint	Results of Primary Study Endpoint	Other Events and Comments	Author (Year)
Randomized Intermediate *vs.* high V_T	120		6.8–7.2 ml/kg n = 60	10.1–10.7 ml/kg n = 60	In-hospital mortality	Mortality for intermediate V_T = 50% and for high V_T = 47% (P = 0.72)		Stewart[22] (1998)
Low *vs.* high V_T target within 36 h of mechanical ventilation	150	6.4 ml/kg n = 76		10.0 ml/kg n = 74	Acute lung injury	Acute lung injury for high V_T = 13.5% and for low V_T = 2.6% (P = 0.01)	Equivalent sedation, mortality, and ventilator-free days in both groups Study stopped early because of frequency of acute lung injury	Determann[23] (2010)
Low *vs.* intermediate V_T assigned within 1 h of mechanical ventilation, also maintaining plateau pressure < 25 cm H_2O	961	5.9–7.4 ml/kg n = 477	9.1–9.3 ml/kg n = 484		Ventilator-free days	Ventilator-free days in both groups = 21 d (P = 0.71)	No difference in length of stay, ICU and 90-d mortality, and rates of pneumonia, atelectasis, or pneumothorax	PReVENT-Schultz[24] (2018)
Low *vs.* moderate PEEP strategies while maintaining V_T 7 ml/kg (noninferiority trial)	969	PEEP 3–5 cm H_2O n = 476	PEEP 8 cm H_2O n = 493		Ventilator-free days	Ventilator-free days for low PEEP = 18 d and for moderate PEEP = 17 d (difference was not significant)	No difference in oxygenation or ICU or 90-d mortality	RELAX[25] (2020)

Ventilator-free days is the number of days without ventilator support within 28 days.
*Maximal distention pressure is calculated as the difference between the peak airway pressure and the PEEP.
ARDS, acute respiratory distress syndrome; ICU, intensive care unit; PEEP, positive end-expiratory pressure; V_T, tidal volume.

of investigation evolves, current expert recommendations are that intubated patients without ARDS should be managed with a limited V_T of less than 10 ml/kg predicted body weight, and potentially 7 to 8 ml/kg predicted body weight, and a driving pressure of less than 15 cm H_2O. Management of hypoxemia and atelectasis can be further guided by use of the Acute Respiratory Distress Syndrome Network PEEP protocol.[26]

Retrospective Studies of One-Lung Ventilation

We identified 10 studies of varying sizes that retrospectively examined patients who underwent one-lung ventilation during lung resection (table 2). Licker *et al.*[27] published three studies, the first of which identified the following risk factors for development of acute lung injury: high intraoperative ventilatory pressure index (a product of peak inspiratory pressure and duration of one-lung ventilation), pneumonectomy, chronic alcohol use, and high volume of intravenously administrated fluids during the first 24 h after surgery. Large intraoperative fluid intake was also found to be a risk factor for postoperative pulmonary complications and/or death by three other studies.[28–30] In 2006, the authors expanded their original study to include patients treated from 1990 to 2004.[31] Preoperative forced expiratory volume in 1 s less than 60 (% of predicted) was identified as a strong predictor of respiratory complications and death at 30 days. The authors did not specifically comment on whether any ventilation variables were associated with outcomes.[31] In 2009, the same group compared an historical cohort with a retrospective cohort who had undergone protective lung ventilation and found that protective lung ventilation was associated with lower rates of postoperative respiratory complications, specifically acute lung injury, atelectasis, and shorter length of ICU stay.[32] In a large study of patients who underwent lung resection for cancer, preoperative chemotherapy and lower diffusion capacity of the lung for carbon monoxide were identified as independent predictors of postoperative pulmonary complications.[33] Pulmonary complications included atelectasis, pneumonia, pulmonary embolism, respiratory failure, and need for supplemental oxygen at hospital discharge. In this study, the inspiratory pressure was maintained at less than 35 cm H_2O, and V_T was 6 to 8 ml/kg actual body weight during one-lung ventilation. In two studies of patients undergoing pneumonectomy, low V_T was found to be a protective factor.[28,30] Conversely, in another study of patients undergoing pneumonectomy, ventilation variables were not associated with respiratory complications, although intraoperative administration of blood was.[34] Blank *et al.*[35] subsequently expanded their study to include all patients undergoing thoracic procedures that required one-lung ventilation. This is the only study identified to show higher rates of respiratory complications with low V_T during one-lung ventilation. Despite this finding, the authors did not conclude that the use of low V_T is injurious, but rather that it might not

Table 2. Summary of Observational Studies of Patients Undergoing Lung Resection with One-Lung Ventilation

Design/Population	Total No.	Primary Study Endpoint	Results of Primary Study Endpoint	Other Events and Comments	Author (Year)
Retrospective or meta-analysis					
Thoracotomy	879	Acute lung injury	Identified four risk factors: high intraoperative ventilatory pressure index (product of peak inspiratory pressure and duration of one-lung ventilation), pneumonectomy, chronic alcohol use, large fluid intake in first 24 h after surgery	Does not comment on other ventilation parameters	Licker[27] (2003)
Lung resection–all, during 15-yr period	1,239	Postoperative pulmonary complications and mortality	Preoperative FEV_1 < 60% is a main predictor of perioperative mortality and respiratory morbidity	Comparing periods 1990–1994 with 2000–2004, the authors observed significantly lower perioperative mortality (3.7% *vs.* 2.4%) and incidence of respiratory complications (18.7% *vs.* 15.2%) that were associated with lesser resection and greater use of thoracic epidural analgesia	Licker[31] (2006)
Pneumonectomy	170	Postoperative respiratory failure, defined as need for > 48 h of mechanical ventilation or reintubation	Identified larger intraoperative V_T associated with outcome, compared with those without outcome (median 8.3 *vs.* 6.7 ml/kg, $P < 0.001$)	Patients who developed respiratory failure also received larger intraoperative fluid volumes	Fernandez-Perez[28] (2006)
Lung resection–all	1,428	Postoperative lung injury, defined as hypoxemia accompanied by radiographic infiltrates	Postoperative lung injury associated with higher perioperative fluid administration and lower postoperative predicted lung function FEV_1 or diffusion capacity of the lung for carbon monoxide	Lung injury occurred in 5.3% of cases 3.1% met criteria for severe acute lung injury or ARDS	Alam[29] (2007)
Compared 533 patients from 1998–2003 with 558 patients after implementation of a protective lung ventilation strategy 2003–2008	1,091	Acute lung injury	Acute lung injury lower with protective lung ventilation use (0.9%) compared with historical cohort (3.7%)	Lower V_T associated with fewer ICU admissions (9.4% *vs.* 2.5%) and shorter length of stay (14.5 ± 3.3 d *vs.* 11.8 ± 4.1 d) Could be confounded by other practice changes (*e.g.,* fluid restriction)	Licker[32] (2009)
Pneumonectomy	129	Postoperative morbidity and mortality	Risk factors: ASA class > 2, liberal fluid administration Protective factors: preoperative hemoglobin > 10 and low V_T during surgery	Mortality = 10.8% and rate of complications = 42.6%	Marret[40] (2010)
Lung resection–all	956	Postoperative pulmonary complications	Preoperative chemotherapy (odds ratio 1.64) and lower diffusion capacity of the lung for carbon monoxide (odds ratio 1.13 per 5% decrement) were risk factors		Amar[33] (2010)
Pneumonectomy	129	Postoperative pulmonary complications	Identified blood product administration (odds ratio 1.47 [CI 1.06–2.05]) as risk factor	21% of patients received blood products	Blank[34] (2011)
Lung resection, transplant, esophageal, other	1,019	Postoperative pulmonary complications	V_T inversely related to postoperative pulmonary complications (odds ratio 0.837 [95% CI 0.729–0.958]) Driving pressure predicted development of postoperative pulmonary complications (odds ratio 1.034 [95% CI 1.001–1.068])	Concludes lower V_T *per se* (in absence of sufficient PEEP) is not unambiguously beneficial	Blank[35] (2016)
Lung resection from 5 centers Compared protective lung ventilation (V_T ≤5 ml/kg and PEEP ≥5 cm H_2O) with no protective lung ventilation	3,232	Postoperative pulmonary complications	Protective lung ventilation was not associated with significantly different 30-d postoperative pulmonary complications, compared with no protective lung ventilation Groups were propensity score matched (n = 762)	Higher modified airway driving pressures were not associated with composite 30-d postoperative pulmonary complications or V_T or PEEP analyzed in isolation as categorical ranges	Colquhoun[36] (2021)
Prospective observational					
Lung resection–all	1,080	Composite of pneumonia and/or ARDS	No difference when groups were propensity score matched for V_T < or > 8 ml/kg (n = 344) or by V_T < or > 6 ml/kg (n = 236)	Incidence of atelectasis did not differ between the groups Overall small number of observed complications	Amar[37] (2017)
Thoracotomy–lung resection (80%), no pneumonectomy	197	Postoperative pulmonary complications	Overall incidence 25.9%, atelectasis 17.8%, prolonged air leak 5.1%, pneumonia 1.5%, pleural effusion 1.5%, and respiratory failure 1%	Higher inspired oxygen in those with postoperative pulmonary complications	Okahara[38] (2018)
Not specified	690	Postoperative pulmonary complications	Overall incidence 11% with open lung approach (lower than the 15–32% in the literature) Open lung approach led to a mean PEEP of 8 ± 3 cm H_2O, lower driving pressure, and higher dynamic compliance	For open lung approach, recruitment maneuver was performed and then PEEP titrated to best compliance Plan for randomized controlled trial to test hypothesis that this results in lower postoperative pulmonary complications	iPROVE Belda[39] (2018)

ARDS, acute respiratory distress syndrome; ASA, American Society of Anesthesiologists; FEV_1, forced expiratory volume in 1 s; ICU, intensive care unit; PEEP, positive end-expiratory pressure; V_T, tidal volume.

be protective in the absence of sufficient PEEP, underscoring the difficulty of interpreting data from studies in which more than one parameter differs between the control and intervention groups. Colquhoun *et al.*[36] recently reported on the largest, five-center observational study of patients undergoing lung resection, comparing the use of a protective lung ventilation strategy (defined as V_T less than or equal to 5 ml/kg with PEEP greater than or equal to 5 cm H_2O during one-lung ventilation) with no protective lung ventilation. In the propensity score–matched analysis of 381 pairs, 30-day postoperative pulmonary complications were not significantly different between the groups. In addition, ventilation with higher modified airway driving or peak inspiratory pressures was not found to be associated with adverse pulmonary outcomes.

Prospective Observational Studies of One-Lung Ventilation

A small number of prospective observational studies of one-lung ventilation have been published (table 2). Amar *et al.*[37] prospectively collected data on a large cohort of patients, of whom 608 underwent pneumonectomy and lobectomy and 472 underwent wedge resection. In this study, the ventilation parameters during one-lung ventilation were left to the discretion of the anesthesiologist but, in general, consisted of limiting peak airway pressure to less than 30 cm H_2O coupled with intentional crystalloid restriction. Propensity score–matched analyses were performed for each surgical subgroup using a cutoff V_T of less than 8 ml/kg predicted body weight or less than 6 ml/kg predicted body weight. The primary outcome was incidence of acute lung injury, ARDS, and/or pneumonia; radiologically observed atelectasis was considered a secondary outcome. Overall, the total number of complications was small, and the primary and secondary outcomes were not significantly different by V_T cutoff. Okahara *et al.*[38] prospectively studied patients managed with one-lung ventilation, of whom most underwent lung resection for cancer. The primary outcome was the composite incidence of postoperative pulmonary complications within 7 days of thoracotomy, including pneumonia, pleural effusion, atelectasis, prolonged air leak, pulmonary embolism, and respiratory failure. The authors reported that higher oxygen concentration was associated with a higher rate of overall complications, which consisted mostly of atelectasis and prolonged air leak, and they did not observe a difference in ventilation parameters between patients who developed postoperative pulmonary complications and patients who did not. Finally, the Individualized Perioperative Open-lung Ventilatory Strategy trial (iPROVE Belda) investigators studied patients who underwent lung resection with PEEP titration as part of a protective lung ventilation protocol during one-lung ventilation that consisted of a V_T of 5 to 6 ml/kg predicted body weight, recruitment maneuvers, and plateau pressure of less than 25 cm H_2O.[39] The authors observed an overall low rate of postoperative pulmonary complications and an association between the use of this technique and increased lung compliance, which led them to conclude that future randomized controlled trials should examine whether this strategy is associated with better outcomes.

Randomized Controlled Trials of One-Lung Ventilation

We identified eight randomized controlled trials (one of which is ongoing) that examined aspects of protective lung ventilation in patients undergoing one-lung ventilation during lung resection (table 3). The studies by Schilling *et al.*[43] and Ahn *et al.*[44] included relatively small numbers of patients and focused on inflammatory markers. The largest of the randomized studies[40] included patients undergoing lobectomy or pneumonectomy. Rates of major postoperative complications were significantly lower in the protective lung ventilation group (22.2%) than in the control group (13.4%). Of note, this study had an important limitation in design, with substantial differences between the control group (V_T of 10 ml/kg predicted body weight without PEEP) and the intervention group (V_T of 5 ml/kg predicted body weight plus PEEP of 5 to 8 cm H_2O). This illustrates the difficulty determining which variable from the protective lung ventilation bundle was significant—namely, low V_T or use of PEEP and whether the PEEP used in the protective lung ventilation arm was optimal. Further criticism could be raised that the composite outcome used included nonpulmonary outcomes, such as shock secondary to sepsis, which could be unrelated to the patient's lung pathology and the ventilation strategy used. In a much smaller cohort, Yang *et al.*[41] compared a V_T of 10 ml/kg predicted body weight, no PEEP, and volume-controlled ventilation *versus* a V_T of 6 ml/kg predicted body weight, PEEP of 5 cm H_2O, and pressure-controlled ventilation. This study had the greatest divergence in approaches between the control and intervention groups, because the F_{IO_2} and ventilation modes used also differed between the cohorts. The authors reported a lower rate of postoperative pulmonary complications in the protective lung ventilation group (22% *vs.* 4%), which they defined as the presence of Pa_{O_2}:F_{IO_2} ratio less than 300 mmHg, lung infiltration, or atelectasis within 72 h. It can be argued that, although atelectasis or infiltrates on chest radiography might be associated with poor outcomes, they might also signify mild findings that do not meaningfully affect the patient's clinical course. In another small trial, Unzueta *et al.*[42] showed that the use of a recruitment maneuver, before and after one-lung ventilation, with a V_T of 6 ml/kg predicted body weight and PEEP of 8 cm H_2O was associated with lower rates of dead space and higher Pa_{O_2}. Nevertheless, recruitment maneuvers were not associated with clinically better outcomes and might simply be a useful strategy to treat transient hypoxemia intraoperatively.[43,44] The very small study by Maslow *et al.*[45] showed no differences in outcomes between high and low V_T groups, and neither trial arm had a single patient who developed

Table 3. Summary of Randomized Controlled Trials of Patients Undergoing Lung Resection with One-Lung Ventilation

Type of Surgery	Total No.	Control Group	Intervention Group	Primary Study Endpoint	Results of Primary Study Endpoint	Other Events and Comments	Author(Year)
Thoracotomy–major lung resection	32	V_T 10 ml/kg, zero end-expiratory pressure during one-lung ventilation (n = 16)	V_T 5 ml/kg, zero end-expiratory pressure during one-lung ventilation (n = 16)	Inflammatory markers in bronchoalveolar lavage fluid	Tumor necrosis factor-α and sICAM-1 concentrations significantly lower in intervention group	Small sample size Intraalveolar cells, protein, albumin, IL-8, elastase, IL-10 did not differ between groups	Schilling[43] (2005)
Thoracotomy and video-assisted thoracoscopic surgery lobectomy	100	V_T 10 ml/kg, zero end-expiratory pressure, volume control (n = 50) F_{IO_2} 1.0	V_T 6 ml/kg, PEEP 5 cm H_2O, pressure control (n = 50) F_{IO_2} 0.5	Pulmonary dysfunction defined as Pa_{O_2}:F_{IO_2} < 300 mmHg and/or lung infiltrates or atelectasis within 72 h of operation	Significantly lower in intervention group (4% *vs.* 22%, $P < 0.05$)	During one-lung ventilation, used volume control mode in control group and pressure control mode in intervention group During two-lung ventilation, both groups received volume control mode	Yang[41] (2011)
Video-assisted thoracoscopic surgery lobectomy	50	V_T 10 ml/kg, F_{IO_2} 1.0, zero end-expiratory pressure (n = 25)	V_T 6 ml/kg, F_{IO_2} 0.5, PEEP 5 cm H_2O (n = 25)	Powered to find a 50% difference in plasma IL-6 level	No difference between groups	Small sample size No differences in malondialdehyde, Pa_{O_2}:F_{IO_2} ratio, or chest radiograph findings	Ahn[44] (2012)
Thoracotomy–lobectomy and wedge	40	V_T 6 ml/kg PEEP 8 cm H_2O (n = 20)	Same ventilation settings plus recruitment maneuver for 10 breaths before and after one-lung ventilation (n = 20)	Alveolar dead space ratio	Lower in the intervention group	Small sample size Better arterial oxygenation and efficiency of ventilation	Unzueta[42] (2012)
Wedge to pneumonectomy	32	V_T 10 ml/kg, zero end-expiratory pressure (n = 16)	V_T 5 ml/kg, PEEP 5 cm H_2O (n = 16)	Postoperative morbidity and mortality	No difference between groups	Small sample size Control group had less hypercarbia, dead space, and atelectasis Better dynamic compliance Small study—for example, there were no deaths or ARDS or acute lung injury in either group	Maslow[45] (2013)
Lobectomy or Pneumonectomy	346	V_T 10 ml/kg, zero end-expiratory pressure (n = 172)	V_T 5 ml/kg plus PEEP 5–8 cm H_2O (n = 171)	Postoperative morbidity and mortality	Lower in the intervention group (13.4% *vs.* 22.2%, odds ratio 0.54 [0.31–0.95], $P = 0.03$)	Study was prematurely terminated because of slow accrual	Marret[40] (2018)
Open thoracic or video-assisted thoracoscopic surgery > 60 min, body mass index < 35	2,378	PEEP 5 cm H_2O, no recruitment maneuver, V_T 5 ml/kg (n = 1,186)	PEEP 10 cm H_2O plus recruitment maneuver, V_T 5 ml/kg (n = 1,189)	Postoperative pulmonary complications	Enrollment is ongoing with expected completion in 2022	Authors claim this is the first randomized controlled trial to look at high *vs.* low PEEP in thoracic patients	Kiss[50]–PROTHOR Study (2019)
Anatomic lung resection and esophagectomy	292	V_T 6 ml/kg, PEEP 5 cm H_2O plus recruitment maneuvers (n = 147)	V_T 6 ml/kg, individualized PEEP for lowest driving pressure plus recruitment maneuvers (n = 145)	Postoperative pulmonary complications	Lower in the intervention group (5.5% *vs.* 12.2%, odds ratio 0.42 [CI 0.18–0.99], $P = 0.047$)	Small number of outcome events Study combined outcomes of lung and esophageal resections Concerns over the frailty of outcome statistical results	Park[46] (2019)

ARDS, acute respiratory distress syndrome; F_{IO_2}, fraction of inspired oxygen; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; Pa_{O_2}, partial pressure of oxygen; PEEP, positive end-expiratory pressure; sICAM-1, soluble intercellular adhesion molecule-1; V_T, tidal volume..

the primary outcome of acute lung injury or ARDS. Park *et al.*[46] performed a randomized study comparing conventional protective ventilation with an approach that included individualized titration of PEEP to achieve the lowest driving pressure. They found lower rates of postoperative pulmonary complications with the limitation of driving pressure to 15 cm H_2O or less. Overall, the number of complications in this study was small, and patients underwent widely different surgeries—for example, wedge resections *versus* esophagectomies. Furthermore, the statistical methods used to analyze the primary outcome were criticized.[47]

Of interest, Peel *et al.*[48,49] conducted two meta-analyses combining retrospective and prospective studies. The first concluded that the use of PEEP and recruitment maneuvers during one-lung ventilation was not associated with significantly lower rates of postoperative pulmonary complications.[48] The second study concluded that lower V_T during one-lung ventilation was associated with lower rates of postoperative pulmonary complications.[49] The ongoing Protective Ventilation With High Versus Low PEEP During One-lung Ventilation for Thoracic Surgery study is more optimally designed to answer the question of whether high or low PEEP (10 *vs.* 5 cm H_2O) during one-lung ventilation is superior; the study aims to recruit a large group of patients undergoing pneumonectomy, lobectomy, or wedge resection.[50]

Conclusions

Recent and perhaps more relevant evidence derived from prospective randomized controlled trials on the ventilation of ICU patients without ARDS suggests that clinically important outcomes do not differ between patients who are ventilated with a low or higher V_T or with low *versus* higher PEEP. Although it can be hypothesized that protective lung ventilation during one-lung ventilation is a prudent strategy to reduce postoperative pulmonary complications, there is limited evidence to support this, and data from both observational and randomized studies are conflicting. Certainly, none of the trials showed that a strategy of high V_T ventilation was superior. Determination of the optimal V_T level during one-lung ventilation requires further study, because the identified V_T levels ranged from 4 to 8 ml/kg predicted body weight (which may not be low, *per se*, but reflect the physiologic level) and the effects of low *versus* higher PEEP are unclear. The importance of proven risk factors for postoperative pulmonary complications after lung resection, such as decrements in forced expiratory volume in 1 s or diffusion capacity of the lung for carbon monoxide and greater fluid administration during surgery, should also be emphasized and considered when interpreting observational data or in the design of future randomized controlled trials to examine the impact of protective lung ventilation during one-lung ventilation. Of these known risk factors, fluid restriction and ventilatory settings can be modified by anesthesiologists, as can less proven factors that may impact inflammatory responses, such as choice of inhalational or intravenous anesthetic agents, F_{IO_2}, and hypercapnia.[51]

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Competing Interests

The authors declare no competing interests.

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References

1. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301–8
2. Schilling T, Kozian A, Huth C, Bühling F, Kretzschmar M, Welte T, Hachenberg T: The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery. Anesth Analg 2005; 101:957–65
3. Schaefer MS, Serpa Neto A, Pelosi P, Gama de Abreu M, Kienbaum P, Schultz MJ, Meyer-Treschan TA: Temporal changes in ventilator settings in patients with uninjured lungs: a systematic review. Anesth Analg 2019; 129:129–40
4. Kuzkov VV, Suborov EV, Kirov MY, Kuklin VN, Sobhkhez M, Johnsen S, Waerhaug K, Bjertnaes LJ: Extravascular lung water after pneumonectomy and one-lung ventilation in sheep. Crit Care Med 2007; 35:1550–9
5. Kozian A, Schilling T, Schütze H, Senturk M, Hachenberg T, Hedenstierna G: Ventilatory protective strategies during thoracic surgery: Effects of alveolar recruitment maneuver and low-tidal volume ventilation on lung density distribution. ANESTHESIOLOGY 2011; 114:1025–35
6. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JC, Carvalho CR, Brower RG: Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015; 372:747–55
7. Guérin C, Papazian L, Reignier J, Ayzac L, Loundou A, Forel JM; investigators of the Acurasys and Proseva

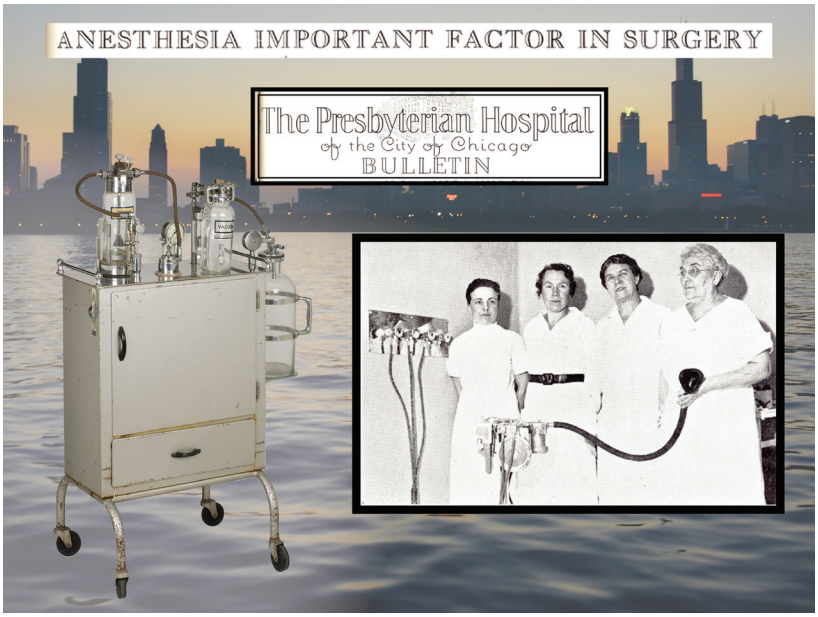
trials: Effect of driving pressure on mortality in ARDS patients during lung protective mechanical ventilation in two randomized controlled trials. Crit Care 2016; 20:384
8. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher *versus* lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004; 351:327–36
9. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE; Lung Open Ventilation Study Investigators: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. JAMA 2008; 299:637–45
10. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Cavalcanti AB, Suzumura ÉA, Laranjeira LN, Paisani DM, Damiani LP, Guimarães HP, Romano ER, Regenga MM, Taniguchi LNT, Teixeira C, Pinheiro de Oliveira R, Machado FR, Diaz-Quijano FA, Filho MSA, Maia IS, Caser EB, Filho WO, Borges MC, Martins PA, Matsui M, Ospina-Tascón GA, Giancursi TS, Giraldo-Ramirez ND, Vieira SRR, Assef MDGPL, Hasan MS, Szczeklik W, Rios F, Amato MBP, Berwanger O, Ribeiro de Carvalho CR: Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2017; 318:1335–45
11. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH: Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008; 359:2095–104
12. Beitler JR, Sarge T, Banner-Goodspeed VM, Gong MN, Cook D, Novack V, Loring SH, Talmor D; EPVent-2 Study Group: Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-Fio2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: A randomized clinical trial. JAMA 2019; 321:846–57
13. Esteban A, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguía C, Nightingale P, Arroliga AC, Tobin MJ; Mechanical Ventilation International Study Group: Characteristics and outcomes in adult patients receiving mechanical ventilation: A 28-day international study. JAMA 2002; 287:345–55
14. Gajic O, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, Rana R, St Sauver JL, Lymp JF, Afessa B, Hubmayr RD: Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. Crit Care Med 2004; 32:1817–24
15. Gajic O, Frutos-Vivar F, Esteban A, Hubmayr RD, Anzueto A: Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. Intensive Care Med 2005; 31:922–6
16. Elmer J, Hou P, Wilcox SR, Chang Y, Schreiber H, Okechukwu I, Pontes-Neto O, Bajwa E, Hess DR, Avery L, Duran-Mendicuti MA, Camargo CA Jr, Greenberg SM, Rosand J, Pallin DJ, Goldstein JN: Acute respiratory distress syndrome after spontaneous intracerebral hemorrhage. Crit Care Med 2013; 41:1992–2001
17. Neto AS, Simonis FD, Barbas CS, Biehl M, Determann RM, Elmer J, Friedman G, Gajic O, Goldstein JN, Linko R, Pinheiro de Oliveira R, Sundar S, Talmor D, Wolthuis EK, Gama de Abreu M, Pelosi P, Schultz MJ; PROtective Ventilation Network Investigators: Lung-protective ventilation with low tidal volumes and the occurrence of pulmonary complications in patients without acute respiratory distress syndrome: A systematic review and individual patient data analysis. Crit Care Med 2015; 43:2155–63
18. Fuller BM, Page D, Stephens RJ, Roberts BW, Drewry AM, Ablordeppey E, Mohr NM, Kollef MH: Pulmonary mechanics and mortality in mechanically ventilated patients without acute respiratory distress syndrome: A cohort study. Shock 2018; 49:311–6
19. Lanspa MJ, Peltan ID, Jacobs JR, Sorensen JS, Carpenter L, Ferraro JP, Brown SM, Berry JG, Srivastava R, Grissom CK: Driving pressure is not associated with mortality in mechanically ventilated patients without ARDS. Crit Care 2019; 23:424
20. Yilmaz M, Keegan MT, Iscimen R, Afessa B, Buck CF, Hubmayr RD, Gajic O: Toward the prevention of acute lung injury: Protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion. Crit Care Med 2007; 35:1660–6; quiz 1667
21. Bastos-Netto C, Reboredo MM, Vieira RS, Fonseca LMCD, Carvalho EV, Holanda MA, Pinheiro BV: Protective mechanical ventilation in patients with risk factors for ARDS: Prospective cohort study. J Bras Pneumol 2021; 47:e20200360
22. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD, Todd TR, Slutsky AS: Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. N Engl J Med 1998; 338:355–61
23. Determann RM, Royakkers A, Wolthuis EK, Vlaar AP, Choi G, Paulus F, Hofstra JJ, de Graaff MJ, Korevaar JC, Schultz MJ: Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: A preventive randomized controlled trial. Crit Care 2010; 14:R1
24. Writing Group for the PReVENT Investigators, Simonis FD, Serpa Neto A, Binnekade JM, Braber A, Bruin KCM, Determann RM, Goekoop GJ, Heidt J, Horn J, Innemee G, de Jonge E, Juffermans NP, Spronk PE, Steuten LM, Tuinman PR, de Wilde RBP, Vriends M,

Gama de Abreu M, Pelosi P, Schultz MJ: Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ARDS: A randomized clinical trial. JAMA 2018; 320:1872–80
25. Writing Committee and Steering Committee for the RELAx Collaborative Group, Algera AG, Pisani L, Serpa Neto A, den Boer SS, Bosch FFH, Bruin K, Klooster PM, Van der Meer NJM, Nowitzky RO, Purmer IM, Slabbekoorn M, Spronk PE, van Vliet J, Weenink JJ, Gama de Abreu M, Pelosi P, Schultz MJ, Paulus F: Effect of a lower vs higher positive end-expiratory pressure strategy on ventilator-free days in ICU patients without ARDS: A randomized clinical trial. JAMA 2020; 324:2509–20
26. Rackley CR, MacIntyre NR: Low tidal volumes for everyone? Chest 2019; 156:783–91
27. Licker M, de Perrot M, Spiliopoulos A, Robert J, Diaper J, Chevalley C, Tschopp JM: Risk factors for acute lung injury after thoracic surgery for lung cancer. Anesth Analg 2003; 97:1558–65
28. Fernández-Pérez ER, Keegan MT, Brown DR, Hubmayr RD, Gajic O: Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy. Anesthesiology 2006; 105:14–8
29. Alam N, Park BJ, Wilton A, Seshan VE, Bains MS, Downey RJ, Flores RM, Rizk N, Rusch VW, Amar D: Incidence and risk factors for lung injury after lung cancer resection. Ann Thorac Surg 2007; 84:1085–91; discussion 1091
30. Marret E, Miled F, Bazelly B, El Metaoua S, de Montblanc J, Quesnel C, Fulgencio JP, Bonnet F: Risk and protective factors for major complications after pneumonectomy for lung cancer. Interact Cardiovasc Thorac Surg 2010; 10:936–9
31. Licker MJ, Widikker I, Robert J, Frey JG, Spiliopoulos A, Ellenberger C, Schweizer A, Tschopp JM: Operative mortality and respiratory complications after lung resection for cancer: Impact of chronic obstructive pulmonary disease and time trends. Ann Thorac Surg 2006; 81:1830–7
32. Licker M, Diaper J, Villiger Y, Spiliopoulos A, Licker V, Robert J, Tschopp JM: Impact of intraoperative lung-protective interventions in patients undergoing lung cancer surgery. Crit Care 2009; 13:R41
33. Amar D, Munoz D, Shi W, Zhang H, Thaler HT: A clinical prediction rule for pulmonary complications after thoracic surgery for primary lung cancer. Anesth Analg 2010; 110:1343–8
34. Blank RS, Hucklenbruch C, Gurka KK, Scalzo DC, Wang XQ, Jones DR, Tanner SR, Jaeger JM: Intraoperative factors and the risk of respiratory complications after pneumonectomy. Ann Thorac Surg 2011; 92:1188–94
35. Blank RS, Colquhoun DA, Durieux ME, Kozower BD, McMurry TL, Bender SP, Naik BI: Management of one-lung ventilation: impact of tidal volume on complications after thoracic surgery. Anesthesiology 2016; 124:1286–95
36. Colquhoun DA, Leis AM, Shanks AM, Mathis MR, Naik BI, Durieux ME, Kheterpal S, Pace NL, Popescu WM, Schonberger RB, Kozower BD, Walters DM, Blasberg JD, Chang AC, Aziz MF, Harukuni I, Tieu BH, Blank RS: A lower tidal volume regimen during one-lung ventilation for lung resection surgery is not associated with reduced postoperative pulmonary complications. Anesthesiology 2021; 134:562–76
37. Amar D, Zhang H, Pedoto A, Desiderio DP, Shi W, Tan KS: Protective lung ventilation and morbidity after pulmonary resection: A propensity score-matched analysis. Anesth Analg 2017; 125:190–9
38. Okahara S, Shimizu K, Suzuki S, Ishii K, Morimatsu H: Associations between intraoperative ventilator settings during one-lung ventilation and postoperative pulmonary complications: A prospective observational study. BMC Anesthesiol 2018; 18:13
39. iPROVE Network investigators, Belda J, Ferrando C, Garutti I: The effects of an open-lung approach during one-lung ventilation on postoperative pulmonary complications and driving pressure: a descriptive, multicenter national study. J Cardiothorac Vasc Anesth 2018; 32:2665–72
40. Marret E, Cinotti R, Berard L, Piriou V, Jobard J, Barrucand B, Radu D, Jaber S, Bonnet F; and the PPV study group: Protective ventilation during anaesthesia reduces major postoperative complications after lung cancer surgery: A double-blind randomised controlled trial. Eur J Anaesthesiol 2018; 35:727–35
41. Yang M, Ahn HJ, Kim K, Kim JA, Yi CA, Kim MJ, Kim HJ: Does a protective ventilation strategy reduce the risk of pulmonary complications after lung cancer surgery?: A randomized controlled trial. Chest 2011; 139:530–7
42. Unzueta C, Tusman G, Suarez-Sipmann F, Böhm S, Moral V: Alveolar recruitment improves ventilation during thoracic surgery: A randomized controlled trial. Br J Anaesth 2012; 108:517–24
43. Schilling T, Kozian A, Huth C, Bühling F, Kretzschmar M, Welte T, Hachenberg T: The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery. Anesth Analg 2005; 101:957–65
44. Ahn HJ, Kim JA, Yang M, Shim WS, Park KJ, Lee JJ: Comparison between conventional and protective one-lung ventilation for ventilator-assisted thoracic surgery. Anaesth Intensive Care 2012; 40:780–8
45. Maslow AD, Stafford TS, Davignon KR, Ng T: A randomized comparison of different ventilator strategies during thoracotomy for pulmonary resection. J Thorac Cardiovasc Surg 2013; 146:38–44
46. Park M, Ahn HJ, Kim JA, Yang M, Heo BY, Choi JW, Kim YR, Lee SH, Jeong H, Choi SJ, Song IS: Driving pressure during thoracic surgery: A randomized clinical trial. Anesthesiology 2019; 130:385–93
47. Amar D: Driving pressure-guided ventilation: Comment. Anesthesiology 2019; 131:1193–4
48. Peel JK, Funk DJ, Slinger P, Srinathan S, Kidane B: Positive end-expiratory pressure and recruitment maneuvers during one-lung ventilation: A systematic review and meta-analysis. J Thorac Cardiovasc Surg 2020; 160:1112–22.e3
49. Peel JK, Funk DJ, Slinger P, Srinathan S, Kidane B: Tidal volume during 1-lung ventilation: A systematic review and meta-analysis. J Thorac Cardiovasc Surg 2020; S0022-5223(20)33408-5

50. Kiss T, Wittenstein J, Becker C, Birr K, Cinnella G, Cohen E, El Tahan MR, Falcão LF, Gregoretti C, Granell M, Hachenberg T, Hollmann MW, Jankovic R, Karzai W, Krassler J, Loop T, Licker MJ, Marczin N, Mills GH, Murrell MT, Neskovic V, Nisnevitch-Savarese Z, Pelosi P, Rossaint R, Schultz MJ, Serpa Neto A, Severgnini P, Szegedi L, Vegh T, Voyagis G, Zhong J, Gama de Abreu M, Senturk M; PROTHOR investigators; Research Workgroup PROtective VEntilation Network (PROVEnet) of the European Society of Anaesthesiology (ESA): Protective ventilation with high *versus* low positive end-expiratory pressure during one-lung ventilation for thoracic surgery (PROTHOR): Study protocol for a randomized controlled trial. Trials 2019; 20:213
51. Gao W, Liu DD, Li D, Cui GX: Effect of therapeutic hypercapnia on inflammatory responses to one-lung ventilation in lobectomy patients. Anesthesiology 2015; 122:1235–52

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Isabella C. Herb, M.D., a Seasoned Anesthesiologist and Advocate



In 1936, the *Chicago Presbyterian Hospital Bulletin* (*top, center*) boldly declared what modern society takes for granted: *anesthetics matter*. Isabella C. Herb, M.D. (1863 to 1943, *far right in photograph*), passionately advocated for anesthesiology's recognition as a medical specialty. She performed clinical research, made medicolegal arguments, and taught generations of physicians the art of anesthesia. An academic physician when few women had the opportunity, Herb was the first woman on medical staff at both the Mayo Clinic and Rush University School of Medicine. By the time she retired as a full professor emerita in 1941, Herb had forged many firsts, including the initial ethylene-oxygen anesthetic in 1923. Her legacy graces the Wood Library-Museum collection in the form of the Herb-Mueller Ether Vapor and Vacuum Apparatus (*left*). Though she still practiced the open-drop ether method on occasion, this machine delivered ether from a glass vaporizer seated in a heated bath. Housed in the metal cart beneath is the motor for the suction apparatus. Zesty but not overpowering, Herb carefully blended innovation with her well-seasoned career in anesthesiology. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

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ANESTHESIOLOGY

Anesthesiologists and the Other Pandemic: Tobacco Use

David O. Warner, M.D.

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ABSTRACT

Tobacco use will kill a projected 1 billion people in the 21st century in one of the deadliest pandemics in history. Tobacco use disorder is a disease with a natural history, pathophysiology, and effective treatment options. Anesthesiologists can play a unique role in fighting this pandemic, providing both immediate (reduction in perioperative risk) and long-term (reduction in tobacco-related diseases) benefits to their patients who are its victims. Receiving surgery is one of the most powerful stimuli to quit tobacco. Tobacco treatments that combine counseling and pharmacotherapy (*e.g.*, nicotine replacement therapy) can further increase quit rates and reduce risk of morbidity such as pulmonary and wound-related complications. The perioperative setting provides a great opportunity to implement multimodal perianesthesia tobacco treatment, which combines multiple evidence-based tactics to implement the four core components of consistent ascertainment and documentation of tobacco use, advice to quit, access to pharmacotherapy, and referral to counseling resources.

(ANESTHESIOLOGY 2022; 137:484–508)

During 2020 and 2021, the COVD-19 pandemic caused more than 845,000 deaths in the United States[1] and up to 18 million deaths worldwide,[2] accompanied by widespread social and economic disruption. However, another deadly pandemic has been ongoing for more than a century—the tobacco pandemic.[3–6] This pandemic originated in the United States in the early 20th century and then spread throughout the world. Globally, tobacco use kills more than 8 million people each year, including bystanders exposed to secondhand smoke.[7] It is the leading cause of preventable death in many countries, including the United States, where it accounts for approximately 1 in 5 deaths (480,000 annually).[8] If current trends continue, approximately 1 billion people will die of tobacco use in the 21st century.[4] The tobacco pandemic continues to evolve, as new products that spread the disease of tobacco use disorder, such as electronic cigarettes, are developed and marketed, perhaps analogous to coronavirus variants.

Pandemic control requires a mix of public policy and medical measures. The response to the COVID-19 pandemic was complex and multilayered, including a variety of government policies, such as lockdowns and masking, and medical innovations such as vaccines and monoclonal antibody treatment. Anesthesiologists played an important role in this response by providing outstanding surgical and intensive care to these patients, often at considerable personal risk. The response to the tobacco pandemic has been similarly multifaceted, including government policies such as increased tobacco taxation and bans on smoking in public places, and treatment innovations such as nicotine replacement therapy.[5,6] As with COVID-19, anesthesiologists can also play an important role in the response to tobacco pandemic—but many do not know how. In addition to improving public health, a collateral benefit of anesthesiologists' efforts is an immediate impact on perioperative risk and the long-term health of each individual tobacco user.

This narrative review is a primer for anesthesiologists who want to help their patients who are victims of the tobacco pandemic. An effective pandemic response requires first an understanding of the origins, natural history, pathophysiology, and treatment of the underlying disease. With this as a foundation, this review will then present the compelling rationale to address tobacco use in perianesthesia practices, putative barriers to anesthesiologist involvement, and practical strategies to take advantage of the unique opportunities available for anesthesiologists to help their patients. The focus will be on two popular tobacco products, conventional cigarettes that burn tobacco and electronic cigarettes, recognizing that there are numerous other forms of tobacco that can also cause harm.

Pandemic Origins and Evolution

Given the ubiquity of tobacco products in the modern world, it is easy to think that tobacco use has always been widespread in human societies. Indeed, tobacco has an important long-standing ceremonial role in some cultures.[9] However, until the beginning of the 20th century, only a small fraction of the world's population used tobacco, mostly in the form of chewing tobacco, snuff, and pipe tobacco.[4–6] Three factors combined to dramatically increase the prevalence of commercial tobacco use during the 20th century, first in the United States, then in the rest of the world: technological advances in tobacco product design and manufacture, sophisticated marketing campaigns by tobacco companies, and the high addiction potential

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of nicotine. Regarding technology, the invention in the United States of (1) flue-curing, a new method to process tobacco leaves that made tobacco smoke easier to inhale, (2) the safety match, and (3) machines that made cigarettes in large quantities enabled mass cigarette production and consumption.[5,6] Regarding marketing, the tobacco industry pioneered sophisticated marketing campaigns employing techniques that are still widely utilized today by many industries. Tobacco products remain one of the most heavily marketed products in the world.[4] Regarding addiction, cigarettes function primarily as devices to rapidly deliver to the brain high levels of nicotine, one of the most addictive substances known.[10] These factors combined to produce a dramatic increase in the prevalence of tobacco use; at the U.S. pandemic peak in the 1960s, more than 40% of the adult population smoked cigarettes (fig. 1).[3,8,11]

The health consequences of this pandemic became evident in the early 1950s, thanks to a series of classic observational studies linking smoking to lung cancer,[12,13] followed by other studies demonstrating similar links to cardiovascular and pulmonary disease.[14] In response, the tobacco industry launched a sustained disinformation campaign designed to refute these studies, cast doubt on any relationship between smoking and disease, and deny that cigarettes were addictive, with smoking presented rather as a personal choice.[4,5] It later became apparent from their own internal documents that the industry in fact had known for decades that smoking caused disease and was highly addictive; indeed, the industry continues to actively manipulate nicotine delivery by cigarettes to maximize addiction and sales.[5,15] In a landmark case, in 2006 the tobacco industry was found guilty under racketeering laws, demonstrating that criminal behavior contributed to the pandemic.[5,6,16]

The 1964 release of the U.S. Surgeon General's report *Smoking and Health*[14] summarized the conclusive evidence that smoking caused a host of serious diseases including chronic lung disease, cardiovascular disease, and cancer, and sparked the implementation of various policy measures that proved highly effective in reducing the prevalence of tobacco use.[4] For example, appreciation of the dangers of secondhand smoke (*i.e.*, breathing in smoke exhaled by others) led to policies banning smoking in public places,[17] and increased tobacco excise taxes significantly reduced sales.[18] These and other measures dramatically reduced smoking

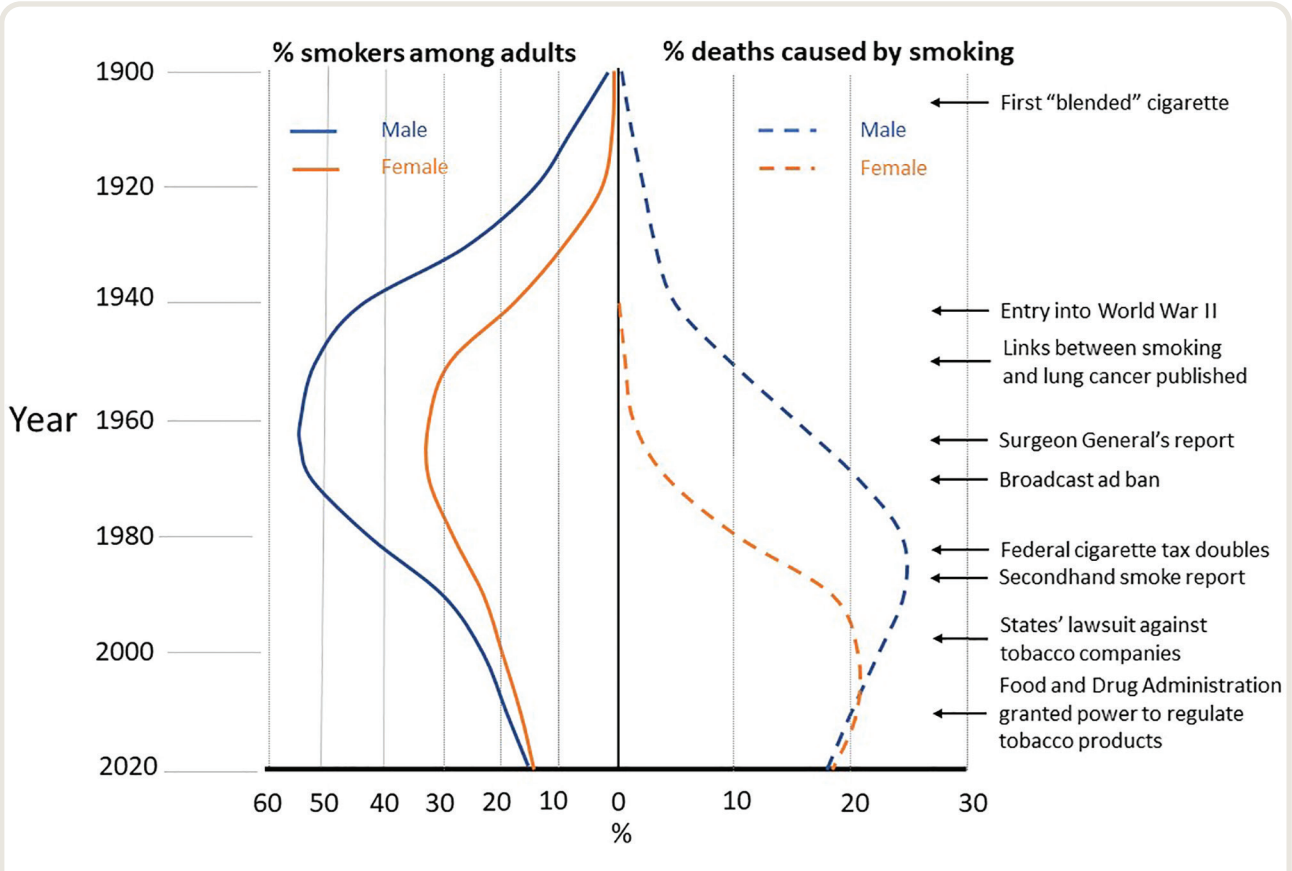

Fig. 1. Estimates of the proportion of adults who smoked cigarettes (*left*) and the proportion of adult deaths caused by smoking (*right*) in the United States from 1900 to 2020 for males and females. Also shown are the timing of major events related to tobacco control in the United States. "Blended" cigarettes include a mixture of flue-cured and other tobaccos that produce smoke that is sweeter and better tolerated. Data from Thun *et al.*[11]

prevalence in the United States and many other high-income countries (fig. 1). Nonetheless, nearly one in five U.S. adults still uses a tobacco product,[19] and smoking-related illnesses cost the United States more than $300B annually.[8] At this stage in the U.S. pandemic, compared with nonsmokers, smokers have lower educational attainment, have lower household income, and are more likely to have mental health conditions, including other substance use disorders.[19–21] Tobacco use thus contributes to widespread health disparities in the U.S. population.

In response to declines in tobacco sales in the United States, the tobacco industry took advantage of trade liberalization policies in the late 20th century and dramatically increased its international marketing efforts.[5,22] These efforts were highly successful—many low- and middle-income countries still have a high prevalence of tobacco use (*i.e.*, are in the earlier stages of the pandemic)—a disparity that mirrors (and contributes to) other disparities in health and health care among nations.[23]

Pathophysiology and Natural History of Tobacco Use

Most tobacco use can be conceptualized as a behavioral disorder, as recognized by the most recent *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition.[24] The majority of those who smoke cigarettes meet criteria for tobacco use disorder (table 1); however, not all people who use nicotine develop this disorder, for reasons that are unknown. Earlier editions of this manual employed the diagnostic term "nicotine dependence," which is still utilized. Most who suffer from tobacco use disorder begin using tobacco before age 18 yr. In 2021, 34% of U.S. high school students had tried a tobacco product, and 13% were current users.[25] Of these, almost a third already showed signs of nicotine dependence (*e.g.*, experienced cravings). The tobacco industry has recognized the importance of youth tobacco use in creating and sustaining a market for their products and has engaged in a variety of activities to promote such use.[6,26,27]

Pathophysiology

Although cigarette smoke contains literally thousands of pharmacologically active compounds, many of which cause disease, nicotine is the active ingredient responsible for reward and addiction.[10] Like other drugs of abuse, nicotine activates the mesolimbic dopamine system, a central mediator of drug reward and reinforcement,[28] such that smoking has pleasurable effects including stress reduction and enhanced mood (fig. 2). The rapid rise in brain nicotine levels produced by cigarette smoke contributes to this pleasure.[29] The pharmacology of the nicotinic acetylcholine receptor that mediates nicotine's actions is complex and beyond the scope of this review, but some characteristics explain the features of tobacco use disorder.[10,30,31] Although initial exposure to nicotine is usually unpleasant (*e.g.*, causes nausea), continued exposure to nicotine causes rapid desensitization of several nicotine subtypes, leading to the rapid development of tolerance, such that more tobacco is needed to achieve the desired effects.[32] Desensitization can also contribute to symptoms of craving and nicotine withdrawal, the latter characterized by irritability, anger, difficulty concentrating, increased appetite, restlessness, depressed mood, and insomnia, which can persist for at least several days after discontinuation of nicotine.[33,34] Daily smokers typically maintain saturation of nicotinic receptors, which prevents craving and withdrawal symptoms; *i.e.*, they self-medicate to prevent unpleasant withdrawal symptoms and regulate

Table 1. Criteria for Tobacco Use Disorder

A problematic pattern of tobacco use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period

1. Tobacco taken in larger amounts or over a longer period than intended
2. Persistent desire or unsuccessful efforts to cut down or control tobacco use
3. A great deal of time is spent in activities necessary to obtain or use tobacco
4. Craving, or a strong desire or urge to use tobacco
5. Recurrent tobacco use resulting in a failure to fulfill major role obligations at work, school, or home (*e.g.*, interference with work)
6. Continued tobacco use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of tobacco (*e.g.*, arguments with others about tobacco use)
7. Important social, occupational, or recreational activities given up or reduced because of tobacco use
8. Recurrent tobacco use in situations in which it is physically hazardous (*e.g.*, smoking in bed)
9. Tobacco use continued despite knowledge of having a persistent or recurrent physical or psychologic problem that is likely to have been caused or exacerbated by tobacco
10. Tolerance, as defined by either of the following:
    a. Need for markedly increased amounts of tobacco to achieve the desired effect
    b. Markedly diminished effect with continued use of the same amount of tobacco
11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for tobacco
    b. Tobacco (or a closely related substance, such as nicotine) taken to relieve or avoid withdrawal symptoms

Classified as mild (2 to 3), moderate (4 to 5), or severe (6 or more). Adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition.[24]

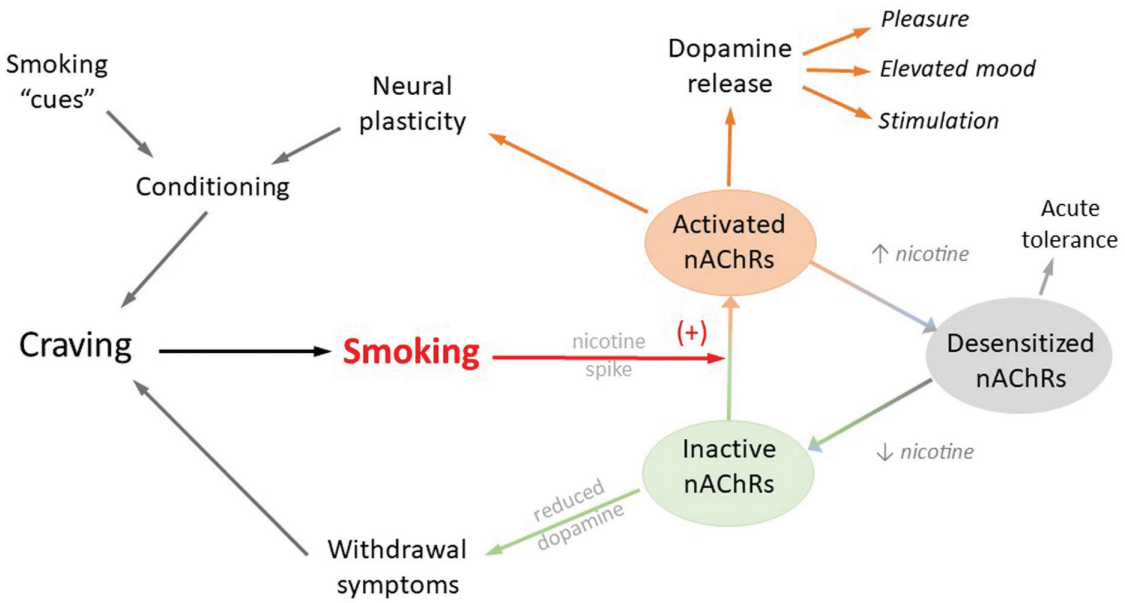

Fig. 2. Schematic of how smoking produces pleasure and how abstinence causes withdrawal symptoms. Smoking a cigarette produces a rapid increase in brain nicotine levels, activating brain nicotine acetylcholine receptors (nAChRs) that produce dopamine release in the "pleasure centers" of the brain. Nicotine acetylcholine receptors become desensitized soon after activation, which produces acute tolerance to nicotine. As nicotine levels fall, nicotine acetylcholine receptors become inactive (*i.e.,* not bound to nicotine), reducing brain dopamine levels and triggering nicotine withdrawal symptoms, which also increases cravings for cigarettes. Repeated activation also causes neural plasticity that, among other actions, results in a conditioned response to smoking "cues" (*i.e.,* smoking after meals), such that these cues trigger craving for cigarettes. Thus, smokers are rewarded for continued nicotine consumption to maintain nicotine acetylcholine receptors activation. Figure modified from Benowitz.[10]

their cigarette consumption to this end.[10] Exposure also causes long-term plastic changes in brain function, changes that are particularly pronounced in the adolescent brain.[35] For example, exposure of adolescents to nicotine causes increased rewarding effects of other abused drugs, and there is a strong association between tobacco use and later anxiety, depression, and other disorders of emotional regulation. Finally, conditioning, another consequence of neural plasticity caused by nicotine exposure, is an important component of addiction.[36,37] With conditioning, smokers associate particular moods or situations (*e.g.*, smoking after meals) with the pleasurable effects of nicotine, such that these smoking-related "cues" trigger the desire to smoke—even in those who have quit smoking for some period of time and no longer suffer from acute nicotine withdrawal symptoms.[10] Patients with tobacco use disorder thus continue to smoke for several reasons, including pleasurable effects, avoidance of the unpleasant effects of nicotine withdrawal, and conditioning—their brains are literally "rewired" in complex ways to seek nicotine.

Natural History of Quitting

The profound effects of sustained nicotine exposure on the brain can make it very difficult for patients with tobacco use disorder to quit using tobacco, even though the majority want to do so.[38,39] Each year, approximately half of smokers in the United States make at least one quit attempt, most without assistance.[40,41] Although the majority eventually succeed,[39] only about 1 in 20 unassisted attempts results in long-term abstinence, such that almost all smokers require multiple attempts—hence the frequent characterization of tobacco use disorder as a chronic relapsing disease.[42,43] Given the importance of quitting to health, surprisingly little is understood about the quitting process. Various theories of behavior have been proposed. For example, the transtheoretical model postulates that health behavior change such as quitting smoking involves progress through distinct stages including contemplation, preparation, action (*i.e.*, quitting), and maintenance.[44] However, this and other theories have proven largely unsatisfactory.[45] Most quit attempts appear to be in fact unplanned and spontaneous,[41,46–48] and those who make an unplanned attempt may indeed be more likely to succeed.[49] The only factors shown in the general populations to consistently predict quit attempts are the number of previous attempts and motivation to quit.[50] Thus, life events that increase such motivation can play an important role in the process—and as will be discussed in a subsequent section, surgery is one such event that has a powerful effect.

Electronic Cigarettes: A New Pandemic Vehicle

Since their introduction in 2003, a new vehicle for the widespread administration of the pathogen responsible for the addictive properties of tobacco has emerged—electronic cigarettes, also known by a variety of other names such as electronic nicotine delivery devices.[51] Although there are many different designs, all utilize a battery-powered atomizing device to heat and vaporize a liquid solution, which is then inhaled ("vaped"; fig. 3).[52] Solutions usually contain humectants such as propylene glycol and various flavors in addition to nicotine. It is also possible to vape other drugs such as opioids or cannabinoids. Although vapor does not contain the combustion products present in cigarette smoke, heat applied in the vaporization process creates a wide range of chemical compounds (such as formaldehyde) that can be pharmacologically active. As these devices have only recently come under regulation by the U.S. Food and Drug Administration (Silver Spring, Maryland) and regulatory authorities in other countries, the actual composition of solution is often unknown. In addition to electronic cigarettes, products have also been developed that heat, rather than burn, tobacco to produce a nicotine aerosol that can be inhaled (known as "heat-not-burn" products). Two of these products are currently available in the United States, but they have not yet achieved popularity, and nothing is known regarding their potential effects in the perioperative period.[53]

Electronic Cigarettes as a Vehicle for Nicotine

Electronic cigarettes now play a significant role in initiating and sustaining nicotine use. In 2019, approximately 5% of U.S. adults used these devices, especially young adults.[19] Alarmingly, in 2021, 11% of high school students and 3% of middle school students used electronic cigarettes.[25] This relatively high utilization has raised considerable concerns that these devices not only expose the developing brain to the deleterious effect of nicotine and promote addiction but also

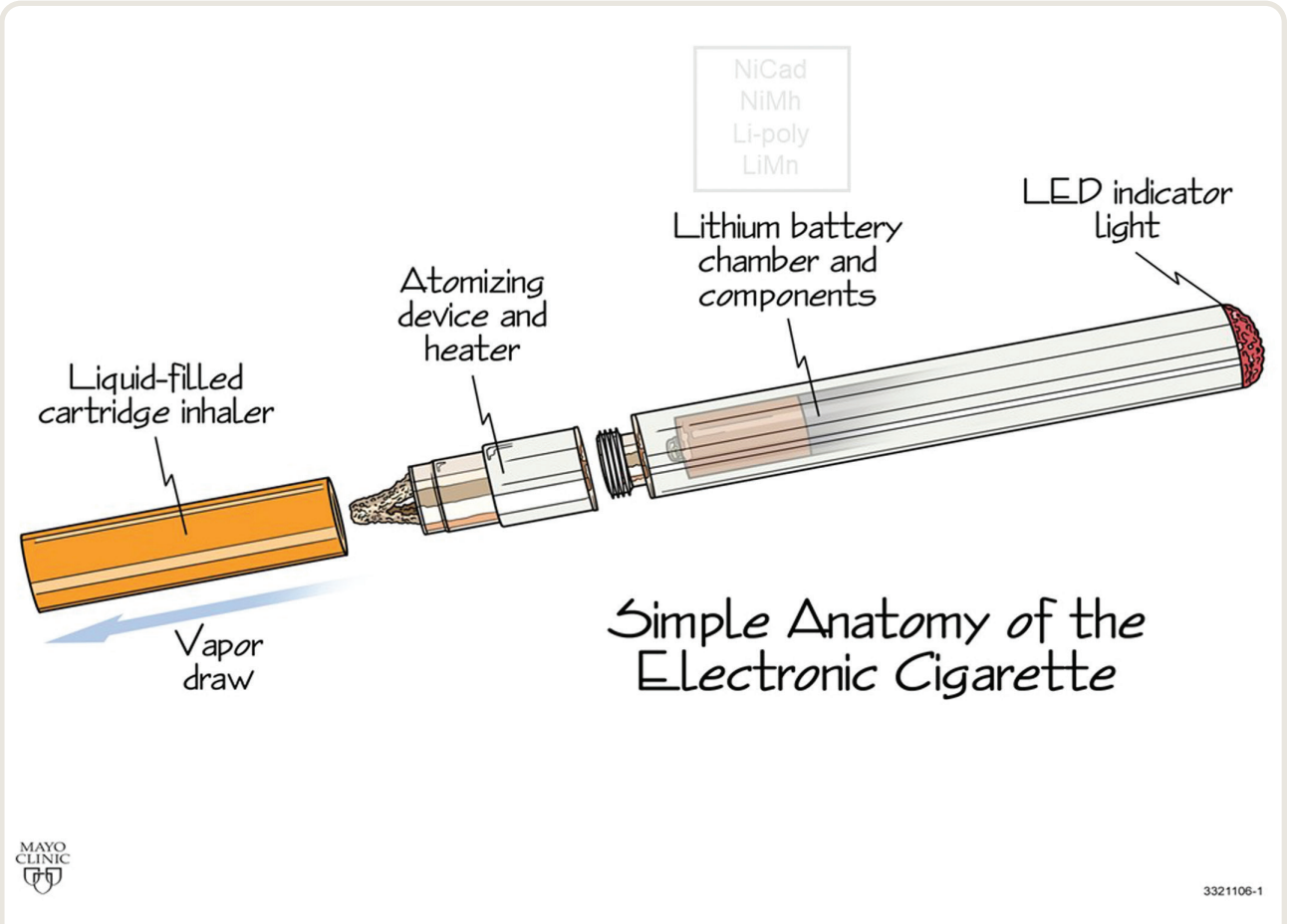

Fig. 3. Typical components of electronic cigarettes. All utilize a reservoir for liquid containing the substance to be vaporized (*e.g.*, nicotine), a device to atomize this liquid to produce a vapor that is inhaled, and a battery with electronic control components. These devices have multiple names and configurations. For example, in some devices, the liquid comes in prepackaged cartridges (as shown in this example), whereas others utilize reservoirs ("tanks") that can be filled with any solution the user desires ("juice"). Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.[52]

serve as a "gateway" facilitating a transition to smoking conventional cigarettes,[54] a pattern noted in recent observational studies.[55–57] Evidence suggests that despite protestations to the contrary, companies producing electronic cigarettes actively promote youth use through strategies such as flavors and the renormalization of nicotine use (*i.e.*, vaping as glamorous) to generate lifelong users of their products.[26,58] From this standpoint, these devices may threaten the progress made in fighting the tobacco pandemic.

Electronic Cigarettes as Nicotine Replacement

On the other hand, if cigarette smokers could switch to electronic cigarettes as their means to consume nicotine, it could reduce risk—to the extent that vapor may be less harmful than cigarette smoke.[59] In addition, these devices could function as a form of nicotine replacement therapy to facilitate attempts to quit tobacco use. When used as pharmacotherapy in randomized clinical trials of patients in tobacco treatment programs, electronic cigarettes promote quitting.[60] Feasibility studies, including surveys and distribution of electronic cigarettes in a preoperative clinic, have also explored the potential for using electronic cigarettes specifically to help surgical patients quit.[61,62] In contrast, observational studies that reflect use outside of randomized clinical trials generally do not support the hypothesis that cigarette smokers who use electronic cigarettes are more likely to quit smoking (with some exceptions); many continue to use both (dual use).[63–65] However, the quality of evidence is low, the analyses are complex, and controversy remains.[59,63,66–68] Thus, although some smokers have successfully used electronic cigarettes to quit, there is not yet good evidence that these devices are effective for this purpose across populations. In addition, similar to conventional cigarettes, most users of electronic cigarettes want to quit, but may find it difficult to do so as they experience symptoms of nicotine withdrawal and cravings.[25,69] Methods to treat electronic cigarette use are not yet well-established.[70]

"Safety" of Vapor

The potential benefits of trading one nicotine source (cigarette smoke) for another (vapor from electronic cigarettes) depend on whether vapor is "safer" than cigarette smoke. Unfortunately, evidence continues to accumulate that inhaled vapor can have adverse physiologic effects. Vapor exposure is cytotoxic to pulmonary cells *in vitro* and causes lung inflammation *in vivo*.[71,72] Use is associated with an increased incidence of respiratory diseases such as emphysema and asthma[73] and can cause severe acute lung injury (e-cigarette or vaping product use associated lung injury).[74,75] Vapor exposure causes acute increases in blood pressure and heart rate and chronic changes in measures of arterial stiffness consistent with increased cardiovascular risk, and detrimental changes in cardiovascular health in animal models.[76,77] Accordingly, use of electronic cigarettes may be a risk factor for myocardial infarction, independent of any concurrent cigarette use,[78] although such observational data have multiple limitations, and other studies have failed to find such associations.[79] Switching from conventional to electronic cigarettes may improve some measures of cardiovascular health such as flow-mediated vasodilation.[80] The risk of cancer is unknown, although switching to electronic cigarettes reduces exposure to carcinogens.[81] Vaping may affect surgical wound healing. Two animal studies found that both cigarette smoke and vapor decrease survival of surgical free flaps in animal models by a similar degree.[82,83] There are no data in patients save two case reports of problems with flaps in vapers that do not provide a convincing link.[84–86] Thus, even if vapor may prove "safer" than cigarette smoke in some respects, it is not "safe."[54]

Effect of Surgery on Tobacco Use

The term "teachable moment" refers to health events that motivate individuals to spontaneously (*i.e.*, without treatment) adopt risk-reducing health behaviors such as quitting tobacco use.[87–89] Teachable moment events for smoking cessation include disease diagnosis (especially those related to tobacco use such as lung cancer), office visits, abnormal test results, pregnancy—and surgery.[90–92] Numerous studies consistently show that receiving a surgical procedure increases long-term quit rates, even if patients are not treated for their tobacco use.[93–95] Quit rates are highest after major inpatient procedures necessitated by smoking-caused disease, such as lung resection for cancer and coronary artery bypass grafting. However, less invasive procedures can also motivate abstinence. An analysis of longitudinal data from a nationally representative survey of adults older than 50 yr found that smokers undergoing major inpatient surgery (heart, cancer, or joint replacement surgeries) were up to twice as likely to quit compared with those who did not have surgery, controlling for other factors including age, sex, and a new medical diagnosis.[96] Even those undergoing more minor outpatient surgery were approximately 30% more likely to quit. Approximately 1 in 12 quit events in older Americans could be attributed to their undergoing one of these four types of surgical procedures, representing a powerful effect on population health.

Despite the dramatic effect of surgery on this hard-to-change behavior, it is perhaps surprising that the mechanism is not understood. Factors associated with quitting include surgical acuity, perioperative intent to quit, and self-efficacy (*i.e.*, belief that quit attempts will succeed),[97,98] but none of these factors explain the underlying psychologic processes. A population-based analysis of longitudinal data examined the effect of children undergoing surgical procedures on their parents' smoking.[99] These parents were more than twice as likely to make a quit attempt compared with those whose children did not have surgery but were not more likely to succeed in actually quitting. Thus, whatever factors are operative, they are sufficient to

motivate a quit attempt in this situation, but insufficient to produce sustained quitting. It is not known whether treatment for tobacco use disorder may be more effective during "teachable moments" such a surgery, but the fact that these parents were motivated to make a quit attempt suggests that they may be receptive to treatment; clearly such treatment is necessary for success in this instance. Other work suggests that patients with some medical comorbidities are more likely to make quit attempts, but may not be more likely to succeed[100]—again suggesting that the "teachable moment" effect may be enhanced by effective treatment.

Treatment of Tobacco Use

Although most tobacco users quit without assistance, treatment can more than double the odds that a quit attempt will succeed.[101] Even so, only approximately one of four individual quit attempts by patients participating in good tobacco treatment programs succeed,[102,103] and most users require multiple attempts to maintain long-term abstinence, reinforcing the concept of tobacco use disorder as a chronic disease.[42,43] Like other chronic diseases such as hypertension or diabetes, tobacco use disorder may not be "cured" by a single treatment. However, the odds of success increase with the number of attempts and treatments—so it is important to make the most of every opportunity to motivate a quit attempt and provide treatment.[101] Even if treatment does not result in quitting immediately, the fact that smokers made an attempt increases the likelihood that a subsequent attempt will succeed.[50]

Treatment Components

Optimal treatment includes two components: counseling and pharmacotherapy.[104]

Counseling can range from brief discussions with physicians[105] to multiple sessions provided by trained tobacco treatment specialists.[103,106,107] These healthcare professionals are specifically trained to provide counseling services and to manage pharmacotherapy. A variety of counseling techniques are employed, with many grounded in principles of cognitive behavioral therapy. Techniques such as motivational interviewing are used for patients not yet ready to make a quit attempt, although it is not clear that these are effective.[108] As with other areas of healthcare, the COVID-19 pandemic prompted the expansion of telephone and video-based counseling services, which are effective.[109] For example, in the United States, the National Cancer Institute (Bethesda, Maryland) sponsors a single toll-free number (1-800-QUITNOW) that provides access to free state-sponsored "quitline" telephone counseling services. Other methods such as text messaging and web-based programs also show promise.[110–112] For all types of counseling, efficacy increases with intensity, although even just brief advice to quit by physicians increases quit rates by approximately 30%.[101,105] Effectiveness increases with the total patient contact time and the number of counseling sessions.[101]

Several medications increase quit rates.[113] Nicotine replacement therapy was the first approved class and remains a mainstay of therapy, as many forms are available in the United States and other countries without a prescription.[114,115] Nicotine replacement therapy can alleviate both nicotine withdrawal symptoms and cravings for cigarettes. Various formulations are available in different countries; in the United States, skin patches, chewing gum, and lozenges are available without prescription, and nasal spray and oral inhalers are available with a prescription. Formulations can be combined according to need. For example, patches provide extended release useful to prevent withdrawal, while gum is more rapid-acting and can be useful for cravings. Overall, nicotine replacement therapy increases quit rates by approximately 60%.[114,115] The overall safety profile of nicotine replacement therapy is excellent, even in patients with significant comorbidity such as cardiovascular disease.[116,117] Approved first-line non-nicotine medications include bupropion and varenicline.[115] Bupropion is an atypical antidepressant that blocks norepinephrine and dopamine reuptake in the mesolimbic system and may also act as an antagonist of nicotinic receptors. It also has an excellent safety profile and has efficacy similar to that of nicotine replacement therapy.[118] Varenicline is a partial agonist of the $\alpha_4\beta_2$ nicotinic receptor subtype that helps sustain mesolimbic dopamine concentration and alleviate nicotine withdrawal symptoms while blocking nicotine-induced dopaminergic activation and thus the rewarding effect of smoking. Varenicline is the most efficacious of available medications, more than doubling quit rates.[119] Nausea is the most common side effect. There were initial concerns regarding whether varenicline increased risk of depression and self-harm, but subsequent studies have not supported this link.[120] Both bupropion and varenicline should be started 1 week before a quit attempt to achieve therapeutic levels.

Approach to Treatment in Healthcare Settings

Evidence-based Guidelines

Given that tobacco use causes diseases, the relatively frequent contact that users have with the healthcare system provides opportunities to deliver tobacco treatment. A U.S. Public Health Service (North Bethesda, Maryland)–sponsored Clinical Practice Guideline provides recommendations for the implementation of tobacco treatment in healthcare settings, stating that "it is essential that clinician and health care delivery systems consistently identify and document tobacco use status and treat every tobacco user seen in a health care setting."[101] The guideline recommends the "5As" approach: *ask* every patient if they use tobacco, *advise* them to quit, *assess* willingness to make a quit attempt,

assist those willing to quit by offering medication and providing or referring for counseling, and *arrange* for follow-up contact to prevent relapse. Each of these steps is supported by compelling evidence for efficacy. Other countries have issued similar guidelines.[121,122] Unfortunately, these guidelines have proved challenging to implement into routine clinical practice. Although most healthcare systems in the United States attempt to ascertain tobacco use status (with varying degrees of effectiveness), a minority of patients receive even advice to quit on a consistent basis, much less assistance or follow-up.[123–130] Similar results have been found specifically in surgical patients. A national survey of anesthesiologists found that although most asked their patients about tobacco use, only 30% reported advising them to quit, and 5% provided any assistance.[131] Indeed, only 5% felt that it was part of their responsibility to provide assistance. Other surveys of anesthesiologists and surgeons have found similar results.[132–138]

Implementation of Recommendations in Clinical Practices

Many have attempted to increase the provision of tobacco treatment in clinical practices. In general, although such efforts can succeed in the context of clinical studies, it has proven much more difficult to embed them into routine clinical practice.[139,140] The most successful sustained efforts have targeted hospitalized patients. Intensive practice support efforts such as embedded outreach facilitators, decision-support tools within electronic medical records, extensive clinician training, and ongoing audits can increase the provision of tobacco treatment to hospitalized patients and produce measurable improvements in clinical outcomes.[141–144] However, these efforts are resource-intensive, and even so, many patients do not receive treatment. In the absence of this intensive approach, results are less favorable. A meta-analysis of studies examining efforts to increase clinician delivery of tobacco treatment to hospitalized patients found that such efforts increased the provision of assistance, but did not affect asking about tobacco use, advising to quit, or the provision of pharmacotherapy.[145] A consortium of nine research groups used a variety of locally tailored strategies and pragmatic approaches to provide tobacco treatment to hospitalized patients, but only two found that their strategies were effective in increasing postdischarge quit rates.[146] Attempts to increase the provision of tobacco treatment in outpatient settings have had mixed results in terms of how frequently treatment elements are provided.[147–156] There is little information regarding effects on actual quit rates and no information about whether efforts can be sustained in clinical practice.

Other Approaches

Given the very real challenges to implementing clinician-delivered tobacco treatment,[140] two other approaches have been proposed to consistently deliver tobacco treatment in clinical settings. The first is a modification of the "5As" approach, recognizing that most clinicians (and perhaps especially anesthesiologists) do not have the time or training to provide assistance (counseling and pharmacotherapy) or arrange for follow-up. Rather, clinicians should *ask* their patients about tobacco use, *advise* them to quit, and *refer* them to other resources that could provide assistance and follow-up—Ask-Advise-Refer.[149,157,158] Efforts to implement the Ask-Advise-Refer approach have focused on systems to facilitate referral and access to appropriate resources. Its feasibility in practice is now well-established, as well as its ability in study settings to increase referral to treatment resources.[149–151,159,160] However, its sustainability in routine practice and its ability to actually increase quit rates remain to be determined.[151]

The second approach challenges the utility of the third component of the "5As"—*assess* willingness to make a quit attempt. In the "5As" paradigm, the offer of treatment depends on the willingness of patients to make a quit attempt.[101] Thus, the default option for smoking cessation is "no treatment," as treatment is only offered if patients are willing to quit now. Richter and Ellerbeck[161] recently made a persuasive argument that this approach significantly limits the reach of tobacco treatment as only a minority of patients state a willingness to make a quit attempt. They proposed rather than the current "opt-in" approach to treatment, an "opt-out" approach to tobacco treatment should be adopted in clinical encounters. In this framework, analogous to the approach to other chronic conditions, the focus of the discussion would be on treatment options and mechanisms to access these options rather than first assessing readiness to quit. In other words, the default would be treatment; patients could choose not to accept treatment. In support of this concept, they note that changing defaults has changed choice and outcomes for numerous health behaviors, that most tobacco users want to quit, and that there is little evidence of the utility of "assessment" of readiness to quit. Contrary to some prevailing theories of behavior change, there is little evidence that tailoring interventions based on intent (as assessed by the stage of change) affects the efficacy of interventions.[45] Also, there is now evidence in healthcare settings that offering treatment to all, not just those motivated to quit immediately, is efficacious,[22,142] and that pharmacotherapy can be efficacious even when applied to those not ready to quit immediately.[162] This "opt-out" proposal has generated controversy but satisfies accepted principles of medical ethics.[163] Initial studies exploring this approach in cancer and hospitalized patients have produced encouraging results, but more work is needed to compare its effectiveness with the "opt-in" strategy.[164–166]

Benefits of Treating Surgical Patients

Risk of Tobacco Use

The perioperative period involves several clinical encounters that provide multiple opportunities to provide tobacco

treatment. We have already reviewed how surgery can serve as a powerful "teachable moment" to quit, with long-term benefit to health. In addition, treating perioperative tobacco use can improve perioperative outcomes, because tobacco use increases perioperative risk,[167] as has been recognized for more than 75 yr.[168] Mechanisms contributing to risk include tobacco-induced disease (*e.g.*, chronic obstructive pulmonary disease and coronary artery disease) and the acute effects of tobacco constituents (such as carbon monoxide in cigarette smoke).[30] A recent meta-analysis of 107 available studies found increased risk of pulmonary complications (relative risk, 1.73; 95% CI, 1.35 to 2.23), wound-related complications (relative risk, 2.15; 95% CI, 1.87 to 2.49), and neurologic complications (relative risk, 1.38; 95% CI, 1.01 to 1.88) for current smokers compared with nonsmokers.[169] Although smoking can increase the risk of intraoperative myocardial ischemia,[170] current smoking was not associated with major cardiovascular complications (relative risk, 1.07; 95% CI, 0.78 to 1.45). Smoking is also associated with delayed healing of bony fusions and fractures,[171–177] and adverse outcomes after joint and fracture surgeries.[174,178–186] Recent evidence suggests that smoking is also associated with an increased risk of surgical bleeding, perhaps reflecting vascular endothelial damage and inflammation caused by smoke constituents.[187–189] Some studies suggest that requirements for postoperative analgesics are higher in current smokers,[190–192] although as reviewed elsewhere,[193] it is difficult to control for other confounding variables in these observational studies. This same critique can be applied to the observational studies that support the link between smoking and the other complications, although the evidence from randomized trials of tobacco treatments reviewed in the next section supports the causal role of smoking.

Secondhand smoke from others' smoking also poses risks.[194] Approximately one in seven children undergoing surgery in the United States are chronically exposed to secondhand smoke,[99] which increases their risks of perianesthetic respiratory events such as laryngospasm and bronchospasm (relative risk, 2.52; 95% CI, 1.68 to 3.77 in a meta-analysis of 15 studies).[195] These risks of respiratory complications may extend also to adults.[196–198] Effects specifically on wound-related complications are unknown; one cohort study found an association between secondhand smoke exposure and a composite outcome of postoperative morbidity (which included wound-related complications).[199]

Benefits of Quitting

Quitting smoking reduces perioperative risk. A recent systematic review of 13 randomized trials concluded that both intensive (defined as multisession in-person counseling initiated at least 4 weeks before surgery) and brief interventions produced cessation at the time of surgery (pooled risk ratios of 10.8 [95% CI, 4.5 to 25.5] and 1.3 [95% CI, 1.2 to 1.5] for intensive and brief interventions, respectively).[200] Four trials examined whether smokers were abstinent 1 yr after surgery; only intensive (not brief) interventions were efficacious (risk ratio, 2.96; 95% CI, 1.57 to 5.55). More intensive interventions reduced the incidence of a composite outcome of any complication (wound-related, cardiovascular, or other complication requiring treatment; risk ratio, 0.42; 95% CI, 0.27 to 0.65) and the incidence of wound-related complications (risk ratio, 0.31; 95% CI, 0.16 to 0.62); brief interventions did not. Trials and meta-analyses subsequent to this systematic review are consistent with these findings.[201–204]

The duration of preoperative abstinence necessary for benefit has not been studied in randomized trials and likely depends on the complication. Most of the randomized trials showing benefit began treatment at least 4 weeks before surgery. Data from observational trials suggest that it may require several weeks of abstinence before the rate of pulmonary complications decreases.[205–211] Given the relatively short half-life of active cigarette smoke constituents such as nicotine (approximately 1 h) and carbon monoxide (approximately 4 h), even brief abstinence may be beneficial.[30] Randomized trials are not available, but one observational study found that among current smokers, smokers who smoked the morning of surgery were 75% more likely to develop a surgical site infection compared with smokers who did not.[212] Higher intraoperative exhaled carbon monoxide values, indicative of more recent preoperative smoking, are associated with an increased risk of myocardial ischemia.[170] These findings support the practice of advising smokers to at least not smoke on the morning of surgery—just like they "fast" from food, they should also "fast" from cigarettes. A randomized trial of tobacco treatment applied postoperatively in patients who had received acute surgical repair of fractures found that treatment reduced postoperative complications[213]; *i.e.*, even just postoperative abstinence was beneficial.

A reduction in complications with quitting may translate to a reduction in healthcare costs, although only observational studies comparing costs according to smoking status are available. Evidence that current smokers have higher costs for inpatient surgical care during admission compared with never-smokers is mixed,[214,215] but postoperative costs are increased.[215] Modeling studies suggest that, as in other settings, providing tobacco treatment to smokers undergoing surgery is cost-effective.[216–220]

Putative Barriers to Treating Surgical Patients

As noted, it has proved challenging to implement tobacco treatment in clinical practice. There are several additional potential barriers particular to the surgical setting which have been addressed in recent work.

Safety of Nicotine Replacement Therapy

Concerns have been raised regarding the safety of nicotine replacement therapy in surgical patients, primarily regarding the potential for nicotine to cause vasoconstriction that

could impair the healing of surgical wounds.[131] As outlined in recent reviews,[221–223] evidence supporting the safety of nicotine replacement therapy in the surgical setting includes the following: (1) most of the studies showing the efficacy of tobacco treatment to reduce perioperative complications (including wound-related complications) include nicotine replacement therapy in the treatment arm; (2) animal studies suggesting deleterious effects of nicotine on wound healing utilize nicotine doses that exceed those provided by nicotine replacement therapy; (3) randomized studies in an experimental human models show that nicotine replacement therapy does not affect the beneficial effects of abstinence from smoking on wound healing; and (4) a large observational study (including more than 25,000 patients undergoing major surgical procedures who received nicotine replacement therapy) showed no association between nicotine replacement therapy and adverse outcomes, including wound-related complications.[224] Thus, available evidence strongly supports the use of nicotine replacement therapy to treat tobacco use in surgical patients.[222,223]

Safety of Quitting Immediately before Surgery

Concerns have been raised regarding whether quitting smoking shortly before surgery increases the risk of pulmonary complications due to an increase in cough and sputum production. This concern arose from a misinterpretation of experimental data[225] and has persisted despite the facts that (1) smoking cessation is not associated with increased cough[226] and (2) multiple studies, summarized in two meta-analyses,[207,209] show that although several weeks of abstinence may be necessary to reduce risk, quitting shortly before surgery does not increase the risk of pulmonary complications. Thus, although prolonged preoperative abstinence likely has the greatest benefit, patients should not be discouraged from quitting at any time before (or after) surgery.

Increased Psychologic Stress and Nicotine Withdrawal Caused by Perioperative Abstinence

Smoking acutely reduces psychologic stress,[227] and abstinence could add to the already considerable stresses posed by surgery. However, studies show (1) no differences in changes in measures of psychologic stress over the perioperative period between smokers and nonsmokers[97]; (2) no effect of nicotine replacement therapy on perioperative stress or withdrawal symptoms in smokers[98]; and (3) surprisingly little reported craving for cigarettes.[97] Thus, perioperative abstinence can be urged without fear of adding to patient psychologic distress.

Patient Acceptance

Physicians may perceive that smokers already feel overwhelmed around the time of surgery and do not want physicians to address their smoking behavior.[131] Evidence shows that most patients have favorable attitudes toward attempting abstinence in the perioperative period,[97,98,228–230] but are not well-informed about the acute perioperative risks of smoking and the potential benefits of even temporary abstinence.[228,231–234] Most feel that their physicians are credible and should talk to them about how their smoking affects their risk.[135,228,235,236] Thus, anesthesiologists should not hesitate to do so.

Practical Methods to Treat Surgical Patients

Research studies find that treating surgical patients for their tobacco use can reduce both tobacco use and perioperative complications. As with so many other research findings, the challenge is to implement these results into routine clinical practice.[140] Fortunately, recent reports detail the results of implementing practical approaches into clinical practices and can provide guidance (table 2). Several themes are apparent.

Multimodal Treatment Maximizes Efficacy

Most successful programs incorporate four core components: consistent ascertainment and documentation of tobacco use (*i.e.*, "asking"), advice to quit, access to nicotine replacement therapy or other pharmacotherapy, and referral to counseling resources (fig. 4). This approach can be conceptualized as multimodal perianesthesia tobacco treatment, analogous to multimodal analgesia—the combination of multiple modalities that in isolation may be insufficient to provide adequate analgesia but are more effective when combined. In the same way, applying single components of tobacco treatment in isolation may not be effective. For example, telephone counseling services ("quitlines") are a primary referral resource in several studies. Treatments that incorporate quitlines are successful in many of these studies,[201,202,250] but it is not possible to determine how the quitlines may have contributed to this success. Observational studies show a positive association between quitline utilization and the odds of quitting postoperatively.[239,240,242] However, randomized trials in other settings show that quitline utilization may be simply a marker for those who would have quit in any event.[257] The only study isolating quitline use as an experimental factor (*i.e.*, included no other component of treatment) found only a nonsignificant trend toward greater quitting at 30 days after surgery.[254] Thus, quitline services alone may not be sufficient, and need to be combined with other treatment elements for efficacy. There are similar findings for applying nicotine replacement therapy alone in the perioperative setting without advice or counseling.[98]

Implementation of Multimodal Perianesthesia Tobacco Treatment into Clinical Practice Is Feasible and Effective

Initial implementation of multiple treatment components across practice sites is feasible and can be accomplished using existing clinical personnel.[233,239,242,244,258] Two reports provide

Table 2. Studies of Tobacco Treatment Delivered by Clinical Personnel in Surgical Settings

Study	Setting	Number of Smokers	Interventions*	Outcomes	Highlights of Findings
Implementation case series					
Akhavan *et al.*, 2017[237]	Total joint arthroplasty clinic	30	Brief advice, brochure with quitline number	Preoperative quitting, resource use	70% preoperative quitting, 5% used quitline, 24% used nicotine replacement therapy.
Hart *et al.*, 2019[238]	Total joint arthroplasty clinic	2,109	Brief advice, preoperative cotinine testing	Preoperative quitting	28% preoperative quitting with cotinine testing (n = 71), 16% without testing.
Howard *et al.*, 2022[239]	35 Michigan hospitals, vascular surgery	5,158	Brief advice, proactive quitline referral, nicotine replacement therapy prescription	Resource use, postoperative quitting at 30 days and 1 yr	44% received at least one intervention; 15% referred to quitline, 19% received nicotine replacement therapy. Overall, 35% quit at 30 days; quit associated with receiving multiple interventions (odds ratio, 1.29).
Mustoe *et al.*, 2020[240]	Thoracic surgery clinic	111; 58 received surgery	Brief advice, quitline referral	Preoperative quitting, postoperative quitting, quitline enrollment	50% used quitline. Having surgery increased preoperative quitting (odds ratio, 2.4). Using quitline associated with increased postoperative quitting at 6 months (odds ratio, 3.6) but not preoperative quitting.
Nolan *et al.*, 2016[61]	Preoperative anesthesia clinic	105	Brief advice, free supply of electronic cigarettes	Resource use, postoperative quitting	87% used electronic cigarettes in the perioperative period; reduction in conventional cigarette consumption at 30 days (statistically significant); 17% quit at 30 days.
Nolan *et al.*, 2019[241]	Preoperative anesthesia clinic	100	Text message cessation program	Resource use, postoperative quitting	80% of participants expressed satisfaction with the program; 31% quit at 30 days.
Saxony *et al.*, 2017[242]	Preoperative surgery clinic	2,867	Brief advice, referral to tobacco treatment specialist counseling with discounted nicotine replacement therapy	Resource use, postoperative quitting	18% of smokers referred to tobacco treatment specialist; 58% of those referred received treatment, and 56% of these (n = 123, 4% of all smokers) set a quit date. 49% of these quit at 12 months.
Warner *et al.*, 2009[230]	14 anesthesiology practices	—	Academic detailing (*i.e.*, clinician education) to promote ask-advise-refer	Clinician attitudes and practices	80% of those surveyed (74% response rate) agreed that it was part of their responsibility to help smokers quit, and 75% planned to incorporate ask-advise-refer into their practices.
Pre–post implementation studies					
Bottorff *et al.*, 2016[236]	2 Canadian practices	240	Patient promotional materials and encouragement of 5As	Rate of brief advice, preoperative quitting, patient knowledge	No effect on preoperative quitting (6% *vs.* 8%, not statistically significant). Increased rate of brief advice (55% *vs.* 70%, statistically significant). Correlation between brief advice and (1) preoperative quitting and (2) awareness of smoking-related complications.
Coffman *et al.*, 2019[243]	Preoperative clinic	133	Brief 5As, brochure, referral to unspecified resources	Preoperative quitting	Preoperative quitting went from 40 to 46% (not statistically significant); concluded feasibility
Stonesifer *et al.*, 2021[244]	Veterans Administration vascular and plastic surgery clinics	943	Electronic decision support tool for referral to tobacco treatment specialist	Tobacco treatment specialist treatment	No treatment before implementation; 20% of eligible patients treated after implementation (statistically significant).
Young-Wolff *et al.*, 2019[245]	Practices of 34 surgeons in integrated healthcare system	276	Brief counseling, decision aid, referral to tobacco treatment specialist, pharmacotherapy	Resource use, preoperative quitting, postoperative quitting	Referrals increased from 3 to 28% (statistically significant), no change in pharmacotherapy, counseling increased from 5 to 12% (statistically significant). Preoperative quitting changed from 21 to 29% (not statistically significant). 30-day continuous postoperative quitting increased from 18 to 39% (statistically significant).

(*Continued*)

Table 2. (Continued)

Study	Setting	Number of Smokers	Interventions*	Outcomes	Highlights of Findings
Webb *et al.*, 2014[246]	Preoperative anesthesia clinic	347	Mailed brochure and quitline referral form	Preoperative quitting	Increased preoperative quitting for > 4 weeks by 9% (statistically significant)
Webb *et al.*, 2017[247]	Preoperative anesthesia clinic	999	Standardized documentation of brief advice and referral	Documentation in medical record	Increased documentation of advice given (2 to 19%, statistically significant) and referral (1 to 6%, statistically significant)
Randomized trials					
Andrews *et al.*, 2006[248]	Preoperative clinic	102	Mailed advice letter from surgeon	Preoperative quitting	Letter increased preoperative quitting from 8 to 18% (statistically significant)
Goodney *et al.*, 2017[249]	8 vascular surgery practices, cluster randomized	156	Brief advice by surgeon, proactive quitline, nicotine replacement therapy	Resource use, postoperative quitting	75% of patients in intervention arm received all three elements (no information about actual quitline or nicotine replacement therapy utilization). Postoperative quitting at 3 months 40% *vs.* 31% active and control, respectively (not statistically significant). Brief counseling and nicotine replacement therapy, not quitline referral, associated with postoperative quitting.
Lee *et al.*, 2013, 2015[250,251]	Preoperative anesthesia clinic	168	Brief counseling by nurse (< 5 min), brochure, proactive quitline referral, nicotine replacement therapy	Resource use, preoperative quitting, postoperative quitting	52% intervention group contacted quitline. Preoperative quitting 4% *vs.* 14% (statistically significant), postoperative quitting 11% *vs.* 29% at 30 days (statistically significant), 8% *vs.* 25% at 1 yr (statistically significant).
Lee *et al.*, 2018[62]	Preoperative anesthesia clinic	30	Brief advice, proactive quitline referral, nicotine replacement therapy *via* patches *vs.* electronic cigarettes	Preoperative quitting, postoperative quitting	No differences in preoperative quitting or postoperative quitting (not statistically significant). Utilization of patches and electronic cigarettes similar.
Newhall *et al.*, 2017[233]	8 Vascular surgery practices, cluster randomized	156	Brief advice by surgeon, proactive quitline, nicotine replacement therapy	Survey of patient experiences and attitudes	Increased provision of brief advice by surgeons (77% *vs.* 99%, statistically significant), increased awareness of risks and interest in quitting.
Shi *et al.*, 2013[252]	Preoperative anesthesia clinic	183	Brief advice ± message that CO would be tested morning of surgery	Preoperative quitting assessed *via* CO on morning of surgery	No difference in CO levels the morning of surgery. CO levels significantly higher in patients receiving usual care who did not receive brief advice (indicating decreased preoperative quitting).
Sørensen *et al.*, 2007[253]	Preoperative anesthesia clinic	215	Brief advice ± reminder before surgery	Preoperative quitting, postoperative quitting	Brief advice increased preoperative quitting (2% *vs.* 19%, statistically significant), postoperative quitting at day 7 (2% *vs.* 18%, statistically significant), but not day 30. No effect of reminder.
Warner *et al.*, 2005[98]	Preoperative anesthesia clinic	121	Active *vs.* placebo nicotine replacement therapy patch; no advice to quit	Perceived stress scale, withdrawal, postoperative quitting	No effect on stress or withdrawal; delayed relapse to smoking in the first 30 days postoperatively only for outpatient surgery, not inpatient surgery. No effect on postoperative quitting at 30 days (30% *vs.* 39% placebo *vs.* active, not statistically significant).
Warner *et al.*, 2011[254]	Preoperative anesthesia clinic	300	Brief counseling by anesthesiologists to encourage quitline use, including faxed referral and free nicotine replacement therapy per quitline	Quitline utilization (completing ≥1 session), preoperative quitting, postoperative quitting	0% *vs.* 20% quitline utilization in controls and intervention (statistically significant), median of four sessions. No difference in preoperative quitting, postoperative quitting (37% *vs.* 45% abstinent at day 30 in control and intervention, not statistically significant).

Table 2. (Continued)

Study	Setting	Number of Smokers	Interventions*	Outcomes	Highlights of Findings
Warner *et al.*, 2015[255]	Preoperative anesthesia clinic	130	Decision aid for perioperative smoking	Decisional quality, patient involvement, postoperative quitting	Increased measures of decisional quality and patient involvement, no effect on postoperative quitting.
Webb *et al.*, 2020[256]	Preoperative anesthesia clinic	600	Brochure (all), offer of free mailed nicotine replacement therapy preoperatively.	Use of free nicotine replacement therapy, preoperative quitting	39% in intervention group accepted nicotine replacement therapy, 13% used for ≥ 4 weeks. 6% *vs.* 9% preoperative quitting for > 4 weeks (not statistically significant), 11% *vs.* 16% preoperative quitting for 24 h preoperatively (not statistically significant).
Webb *et al.*, 2022[202]	Preoperative anesthesia clinic	748	Brochure, offer of free mailed nicotine replacement therapy, proactive quitline referral	Resource use, preoperative quitting, postoperative quitting for those who quit preoperatively	Nicotine replacement therapy and quitline referral accepted by 32% of intervention group; 16% actually contacted quitline. Preoperative quitting greater for intervention (10% *vs.* 21%, statistically significant), postoperative quitting at 3 months for those who had preoperative quitting not different.
Wong *et al.*, 2017[201]	Preoperative anesthesia clinic	296	Brief counseling (10–15 min), varenicline, brochure, proactive quitline referral	Postoperative quitting	Treatment increased postoperative quitting (26% *vs.* 42% treatment *vs.* control, statistically significant). Postoperative quitting associated with quitline utilization,

Studies include those utilizing interventions provided by clinical personnel (including referral to quitlines). Studies that utilized trained study personnel to deliver interventions are not included.
*For randomized trials, active treatment arm is described, with usual care as control condition, unless otherwise specified.
CO, carbon monoxide.

successful examples of this approach. Lee *et al.* designed and evaluated a treatment program for their preoperative clinic that included a brief (less than 5 min) counseling session by a preadmission nurse who had received a 1-h training session, an informational brochure, a faxed referral to a quitline, and a 6-week supply of nicotine patches.[250,251] Quit rates at 1 yr after surgery were significantly higher in patients randomized to this program compared with a control condition of usual practice (25% *vs.* 8%, respectively; $P = 0.018$). Young-Wolff *et al.* established a screening system to consistently ascertain tobacco use, trained surgeons to provide brief counseling (facilitated by a decision aid), and referral to counseling services in the practice.[245] This intervention required less than 5 min. In a pilot study employing a pre–post implementation design, referral rates to counseling increased from 3 to 28% ($P < 0.001$), and the rate of counseling went from 5 to 12% ($P = 0.06$). Continuous abstinence at 30 days postoperatively increased from 18 to 39% ($P = 0.005$).

Advice to Quit Is Foundational

Multiple studies highlight the importance of even brief advice to quit before surgery. Although the number of patients included in some studies was insufficient for statistical significance, advice itself (delivered in person or with mailed materials) is associated with preoperative quitting.[236,237,243,246,248,252,253,256] The effect of advice on postoperative abstinence is not known, but it is included as a component of other interventions efficacious for this purpose. Advice may include the requirement for preoperative quitting for surgery to proceed,[93,238,259,260] which is cited as a powerful motivating factor by patients.[235] The ethics of this requirement have been questioned for nonelective procedures,[261] and it has not been reported outside of elective orthopedic and plastic surgery, where concerns for wound- or bone-related complications are especially acute. Biochemical verification of preoperative smoking status can be readily performed using exhaled carbon monoxide or urinary cotinine (a metabolite of nicotine)[262–264]; evidence is mixed as to whether verification itself increases the likelihood of quitting.[238,252]

Other Simple Tactics Can Facilitate Treatment

Several practical tactics can increase the provision of treatment to surgical patients. Decision support tools such as electronic reminders increase documentation and referrals.[244,247,258] Educational programs directed toward clinicians can increase the rate of brief advice and referrals.[230,233,234,236,239,249,254] Decision aids can effectively facilitate conversations between clinicians and their patients about smoking.[255] Mailed materials such as a letter from the surgeon or brochures can be efficacious.[246,248] Such tactics can be used to implement and optimize the core treatment components of asking, advising, and providing access

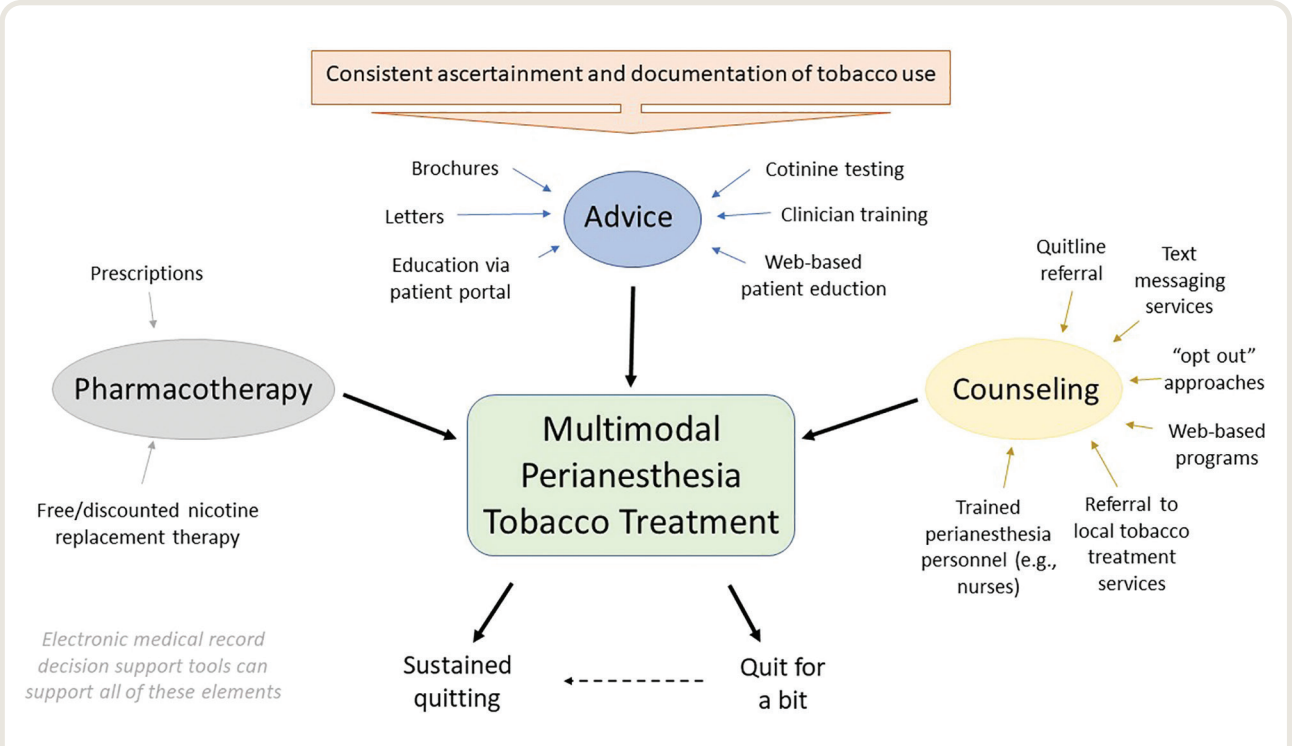

Fig. 4. Schematic of multimodal perianesthesia tobacco treatment, with four main components of consistent ascertainment and documentation of tobacco use, advice to quit by anesthesiologists and other clinicians, pharmacotherapy, and counseling. Goals of treatment can include both sustained quitting and "quit for a bit" (from at least the morning of surgery to at least 1 week after surgery), which may be attractive to some patients, and which may lead to sustained quitting. Also shown are representative evidence-based tactics that can be used to accomplish each element.

to pharmacotherapy and counseling, depending on the opportunities available in specific practice settings (fig. 4). Investigators are exploring other strategies to increase the feasibility of treatment, including additional methods of providing support such as text messaging services specifically designed for surgical patients,[241] and "opt-out" approaches that simplify and facilitate referral to treatment.[165,166,265]

Sustainability in Practice Is Key

Although recent progress is encouraging, considerable work remains to ensure that all surgical patients who smoke receive treatment, as there are not yet reports describing large-scale, sustained treatment efforts embedded into practices. We do not lack a menu of proven tactics that can be applied to perioperative patients (fig. 4), and many guidelines and recommendations for providing tobacco treatment to surgical patients are available.[121,157,266–274] Achieving the goal of incorporating these tactics into the routine care of surgical patients (*i.e.*, sustainability) requires an integrated systems approach adapted to the particular needs of individual practices—one size does not fit all. For example, some practices have ready access to in-person counseling services that can provide multiple sessions, whereas others may only have access to general quitline services. Fortunately, considerable recent progress has been made in understanding how changes in clinical practice occur through the new discipline of implementation science[275]; understanding these processes can guide efforts to make such changes. A recent review presents the principles of implementation science and how they can be applied to facilitate treatment of surgical patients who use tobacco.[140]

Getting Started

For those interested in how they can contribute to the fight against the pandemic by helping their patients who use tobacco, the task can seem daunting. However, there are simple evidence-based steps everyone can take.

Ask every patient if they use tobacco (*e.g.*, "Do you currently smoke or vape?"), even if you already know the answer. This communicates that you as an anesthesiologist view this as an important topic. For example, anesthesiologists routinely confirm *nil per os* status, even when others have already done so, because they think this is important. Once ascertained, ensure that tobacco use status is accurately documented in the medical record.

Advise all patients who use tobacco to quit for as long as they can before and after surgery. Many smokers who are not yet ready to quit for good are willing to "quit

for a bit" (*e.g.*, from at least the morning of surgery until at least 1 week after surgery) if informed that it will reduce perioperative risk.[255] Emphasize that it is especially important for them to not use tobacco the morning of surgery—just like they are not to eat the morning of surgery, they should also not use tobacco. Advice to those who use electronic cigarettes may need to be more nuanced if they are using these devices to quit conventional cigarettes, although there is not yet evidence that vaping is safer than smoking in the perioperative period. Given this state of knowledge, most patients should be advised to quit vaping as well.

These two actions alone are effective. To *go further*, explore what counseling services may be available in your healthcare system. These services are typically housed within departments of pulmonary or cardiovascular medicine but may also be found in cancer centers and departments of respiratory therapy or nursing. If your system does not have these services, everyone has access to telephone counseling services in through a single toll-free number, 1-800-QUITNOW. Similar resources are also available in many other countries. Consider mechanisms in your practice that can facilitate referral to these services. Such mechanisms can range from distributing cards and brochures with quitline information to electronic decision support tools that automatically refer all tobacco users to treatment (fig. 4).[166]

Ultimately, widespread implementation of consistent multimodal perianesthesia tobacco treatment in practices requires an implementation "champion."[276] The primary requirement of a champion is commitment; other elements of the role can be learned. My own experiences in tobacco research may be instructive. I was trained as a respiratory physiologist during my anesthesiology residency, and my interests in the tobacco pandemic originally came from a desire to improve perioperative lung health. However, I was a laboratory-based scientist at the time, with no training or experience in public health or tobacco control. Thanks to the supportive environment of the Mayo Clinic Nicotine Dependence Center and a passion to make a difference, I was able to change research direction and build a program to generate and disseminate evidence supporting perioperative tobacco treatment. Change is not always comfortable or smooth, but as is the case with patients who struggle yet succeed in changing their smoking behavior, ultimately can be rewarding.

Based on the research of many investigators, professional societies and others have issued several guidelines that are valuable sources of information.[121,157,266–274] Many online materials (which can be accessed at www.quitforsurgery.com) are freely available, including education for both clinicians and patients and useful implementation information such as how tobacco treatment can be reimbursed in the United States (separate from anesthesia services) and how outcomes of tobacco treatment can serve as anesthesiology-specific quality measures in the U.S. Merit-based Incentive Payment System.

Anesthesiologists Can Make a Difference

Of all the pandemics that have afflicted humanity, the tobacco pandemic is among the most tragic because it is sustained by human greed and could be largely eliminated—if societies can muster the political will to do so. As observed by Robert Proctor in his book *Golden Holocaust*,[6] "…the cigarette is the deadliest artifact in human history…and is still, apparently, the only consumer product that kills when used as directed. Half its users, in fact." Anesthesiologists can play a unique role in the fight against this pandemic, providing both immediate (reduction in perioperative risk) and long-term (reduction in tobacco-related diseases) benefits to their patients' health—if we choose to do so.

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Competing Interests

The author declares no competing interests.

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References

1. Ahmad RB, Cisewski JA, Anderson RN: Provisional mortality data — United States, 2021. Morb Mortal Wkly Rep 2022; 71:1–5
2. COVID Excess Mortality Collaborators: Estimating excess mortality due to the Covid-19 pandemic: A systematic analysis of Covid-19-related mortality, 2020-21. Lancet 2022; 399:1513–36
3. Warner KE, Mackay J: The global tobacco disease pandemic: Nature, causes, and cures. Glob Public Health 2006; 1:65–86
4. Wipfli H, Samet JM: One hundred years in the making: The global tobacco epidemic. Annu Rev Public Health 2016; 37:149–66
5. Brandt AM: The Cigarette Century. New York, Basic Books, 2007
6. Proctor RN: Golden Holocaust: Origins of the Cigarette Catastrophe and the Case for Abolition. Berkeley and Los Angeles, University of California Press, 2011

7. World Health Organization: Report on the global tobacco epidemic, 2011. Available at: https://www.who.int/teams/health-promotion/tobacco-control/global-tobacco-report-2021. Accessed May 3, 2022.
8. 2014 Surgeon General's Report: The health consequences of smoking—50 years of progress, US Department of Health and Human Services, Centers for Disease Control and Prevention Nation Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014
9. Struthers R, Hodge FS: Sacred tobacco use in Ojibwe communities. J Holist Nurs 2004; 22:209–25
10. Benowitz NL: Nicotine addiction. N Engl J Med 2010; 362:2295–303
11. Thun M, Peto R, Boreham J, Lopez AD: Stages of the cigarette epidemic on entering its second century. Tob Control 2012; 21:96–101
12. Doll R, Hill AB: Smoking and carcinoma of the lung; preliminary report. Br Med J 1950; 2:739–48
13. Wynder EL, Graham EA: Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma; a study of 684 proved cases. JAMA 1950; 143:329–36
14. Smoking and health: Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, D.C., U.S. Department of Health, Education, and Welfare, Public Health Service, 1964
15. Hurt RD, Robertson CR: Prying open the door to the tobacco industry's secrets about nicotine: The Minnesota Tobacco Trial. JAMA 1998; 280:1173–81
16. Kessler G. United States of America v. Phillip Morris Inc., *et al*. Civil Action No. 99-2496 (GK) amended final opinion, August 17, 2006. Available at: http://www.publichealthlawcenter.org/sites/default/files/resources/doj-finalopinion.pdf. Accessed July 7, 2022.
17. The health consequences of involuntary exposure to tobacco smoke. A report of the Surgeon General. Atlanta, U.S. Department of Health and Human Services, Center for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health, 2006
18. Sharbaugh MS, Althouse AD, Thoma FW, Lee JS, Figueredo VM, Mulukutla SR: Impact of cigarette taxes on smoking prevalence from 2001-2015: A report using the behavioral and risk factor surveillance survey (brfss). PLoS One 2018; 13:e0204416
19. Cornelius ME, Wang TW, Jamal A, Loretan CG, Neff LJ: Tobacco product use among adults - United States, 2019. MMWR Morb Mortal Wkly Rep 2020; 69:1736–42
20. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH: Smoking and mental illness: A population-based prevalence study. JAMA 2000; 284:2606–10
21. Han B, Volkow ND, Blanco C, Tipperman D, Einstein EB, Compton WM: Trends in prevalence of cigarette smoking among US adults with major depression or substance use disorders, 2006-2019. JAMA 2022; 327:1566–76
22. Aveyard P, Begh R, Parsons A, West R: Brief opportunistic smoking cessation interventions: A systematic review and meta-analysis to compare advice to quit and offer of assistance. Addiction 2012; 107:1066–73
23. World Health Organization report on the global tobacco epidemic, 2017: Monitoring tobacco use and prevention policies. Geneva: World Health Organization. Available at: https://www.who.int/publications/i/item/9789241512824. Accessed May 3, 2022.
24. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Arlington, VA, American Psychiatric Association, 2013
25. Gentzke AS, Wang TW, Cornelius M, Park-Lee E, Ren C, Sawdey MD, Cullen KA, Loretan C, Jamal A, Homa DM: Tobacco product use and associated factors among middle and high school students - National Youth Tobacco Survey, United States, 2021. MMWR Surveill Summ 2022; 71:1–29
26. Chen-Sankey JC, Unger JB, Bansal-Travers M, Niederdeppe J, Bernat E, Choi K: E-cigarette marketing exposure and subsequent experimentation among youth and young adults. Pediatrics 2019; 144:e20191119
27. Cummings KM, Morley CP, Horan JK, Steger C, Leavell NR: Marketing to America's youth: Evidence from corporate documents. Tob Control 2002; 11(suppl 1):15–7
28. Nestler EJ: Is there a common molecular pathway for addiction? Nat Neurosci 2005; 8:1445–9
29. Samaha AN, Yau WY, Yang P, Robinson TE: Rapid delivery of nicotine promotes behavioral sensitization and alters its neurobiological impact. Biol Psychiatry 2005; 57:351–60
30. Warner DO: Perioperative abstinence from cigarettes: Physiologic and clinical consequences. Anesthesiology 2006; 104:356–67
31. Picciotto MR, Kenny PJ: Mechanisms of nicotine addiction. Cold Spring Harb Perspect Med 2021; 11:a039610
32. Wang H, Sun X: Desensitized nicotinic receptors in brain. Brain Res Brain Res Rev 2005; 48:420–37
33. Hughes JR, Hatsukami D: Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry 1986; 43:289–94
34. Kenny PJ, Markou A: Neurobiology of the nicotine withdrawal syndrome. Pharmacol Biochem Behav 2001; 70:531–49
35. Leslie FM: Unique, long-term effects of nicotine on adolescent brain. Pharmacol Biochem Behav 2020; 197:173010

36. Kenny PJ, Markou A: Conditioned nicotine withdrawal profoundly decreases the activity of brain reward systems. J Neurosci 2005; 25:6208–12
37. Rose JE, Behm FM, Levin ED: Role of nicotine dose and sensory cues in the regulation of smoke intake. Pharmacol Biochem Behav 1993; 44:891–900
38. Chan ES, Yee CH, Hou SM, Ng CF: Current management practice for bladder cancer in Hong Kong: A hospital-based cross-sectional survey. Hong Kong Med J 2014; 20:229–33
39. Babb S, Malarcher A, Schauer G, Asman K, Jamal A: Quitting smoking among adults - United States, 2000-2015. MMWR Morb Mortal Wkly Rep 2017; 65:1457–64
40. Edwards SA, Bondy SJ, Callaghan RC, Mann RE: Prevalence of unassisted quit attempts in population-based studies: A systematic review of the literature. Addict Behav 2014; 39:512–9
41. Hughes JR, Solomon LJ, Naud S, Fingar JR, Helzer JE, Callas PW: Natural history of attempts to stop smoking. Nicotine Tob Res 2014; 16:1190–8
42. Steinberg MB, Schmelzer AC, Richardson DL, Foulds J: The case for treating tobacco dependence as a chronic disease. Ann Intern Med 2008; 148:554–6
43. Bernstein SL, Rosner J, Toll B: A multicomponent intervention including texting to promote tobacco abstinence in emergency department smokers: A pilot study. Acad Emerg Med 2016; 23:803–8
44. DiClemente CC, Prochaska JO, Fairhurst SK, Velicer WF, Velasquez MM, Rossi JS: The process of smoking cessation: An analysis of precontemplation, contemplation, and preparation stages of change. J Consult Clin Psychol 1991; 59:295–304
45. Cahill K, Lancaster T, Green N: Stage-based interventions for smoking cessation. Cochrane Database Syst Rev 2010; 11:CD004492
46. Larabie LC: To what extent do smokers plan quit attempts? Tob Control 2005; 14:425–8
47. Murray RL, Lewis SA, Coleman T, Britton J, McNeill A: Unplanned attempts to quit smoking: Missed opportunities for health promotion? Addiction 2009; 104:1901–9
48. West R, Sohal T: "Catastrophic" pathways to smoking cessation: Findings from national survey. BMJ 2006; 332:458–60
49. Ferguson SG, Shiffman S, Gitchell JG, Sembower MA, West R: Unplanned quit attempts–Results from a U.S. sample of smokers and ex-smokers. Nicotine Tob Res 2009; 11:827–32
50. Vangeli E, Stapleton J, Smit ES, Borland R, West R: Predictors of attempts to stop smoking and their success in adult general population samples: A systematic review. Addiction 2011; 106:2110–21
51. Hajek P, Etter JF, Benowitz N, Eissenberg T, McRobbie H: Electronic cigarettes: Review of use, content, safety, effects on smokers and potential for harm and benefit. Addiction 2014; 109:1801–10
52. Ebbert JO, Agunwamba AA, Rutten LJ: Counseling patients on the use of electronic cigarettes. Mayo Clin Proc 2015; 90:128–34
53. Ratajczak A, Jankowski P, Strus P, Feleszko W: Heat not burn tobacco product-A new global trend: Impact of heat-not-burn tobacco products on public health, a systematic review. Int J Environ Res Public Health 2020; 17:E409
54. Feeney S, Rossetti V, Terrien J: E-cigarettes-A review of the evidence-harm *versus* harm reduction. Tob Use Insights 2022; 15:1179173X221087524
55. Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, Yang J, Primack BA, Andrews JA, Miech RA, Spindle TR, Dick DM, Eissenberg T, Hornik RC, Dang R, Sargent JD: Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: A systematic review and meta-analysis. JAMA Pediatr 2017; 171:788–97
56. Romm KF, Childers MG, Douglas AE, Bray BC, Dino G, Blank MD: Transitions in tobacco use profiles among adolescents: Results from the Population Assessment of Tobacco and Health (PATH) study waves 3 and 4. Drug Alcohol Depend 2022; 232:109272
57. Loukas A, Marti CN, Harrell MB: Electronic nicotine delivery systems use predicts transitions in cigarette smoking among young adults. Drug Alcohol Depend 2022; 231:109251
58. Grana RA, Ling PM: "Smoking revolution": A content analysis of electronic cigarette retail websites. Am J Prev Med 2014; 46:395–403
59. Warner KE: How to think-not feel-about tobacco harm reduction. Nicotine Tob Res 2019; 21:1299–309
60. Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P: Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev 2021; 10:CD010216
61. Nolan M, Leischow S, Croghan I, Kadimpati S, Hanson A, Schroeder D, Warner DO: Feasibility of electronic nicotine delivery systems in surgical patients. Nicotine Tob Res 2016; 18:1757–62
62. Lee SM, Tenney R, Wallace AW, Arjomandi M: E-cigarettes *versus* nicotine patches for perioperative smoking cessation: A pilot randomized trial. PeerJ 2018; 6:e5609
63. Hedman L, Galanti MR, Ryk L, Gilljam H, Adermark L: Electronic cigarette use and smoking cessation in cohort studies and randomized trials: A systematic review and meta-analysis. Tob Prev Cessat 2021; 7:62
64. Osibogun O, Bursac Z, Maziak W: Longitudinal transition outcomes among adult dual users of e-cigarettes and cigarettes with the intention to quit in the United

States: PATH Study (2013-2018). Prev Med Rep 2022; 26:101750
65. Martinez U, Martinez-Loredo V, Simmons VN, Meltzer LR, Drobes DJ, Brandon KO, Palmer AM, Eissenberg T, Bullen CR, Harrell PT, Brandon TH: How does smoking and nicotine dependence change after onset of vaping? A retrospective analysis of dual users. Nicotine Tob Res 2020; 22:764–70
66. Wissmann R, Zhan C, D'Amica K, Prakash S, Xu Y: Modeling the population health impact of ENDS in the U.S. Am J Health Behav 2021; 45:588–610
67. Kasza KA, Edwards KC, Kimmel HL, Anesetti-Rothermel A, Cummings KM, Niaura RS, Sharma A, Ellis EM, Jackson R, Blanco C, Silveira ML, Hatsukami DK, Hyland A: Association of e-cigarette use with discontinuation of cigarette smoking among adult smokers who were initially never planning to quit. JAMA Netw Open 2021; 4:e2140880
68. Baker TB, Fiore MC: What we do not know about e-cigarettes is a lot. JAMA Netw Open 2020; 3:e204850
69. Alalwan MA, Singer JM, Roberts ME: Factors associated with quit interest and quit attempts among young adult JUUL users. Int J Environ Res Public Health 2022; 19:1403
70. Adams ZW, Kwon E, Aalsma MC, Zapolski TCB, Dir A, Hulvershorn LA: Treatment of adolescent e-cigarette use: Limitations of existing nicotine use disorder treatment and future directions for e-cigarette use cessation. J Am Acad Child Adolesc Psychiatry 2021; 60:14–6
71. Miyashita L, Foley G: E-cigarettes and respiratory health: The latest evidence. J Physiol 2020; 598:5027–38
72. Tsai M, Byun MK, Shin J, Crotty Alexander LE: Effects of e-cigarettes and vaping devices on cardiac and pulmonary physiology. J Physiol 2020; 598:5039–62
73. Xie W, Kathuria H, Galiatsatos P, Blaha MJ, Hamburg NM, Robertson RM, Bhatnagar A, Benjamin EJ, Stokes AC: Association of electronic cigarette use with incident respiratory conditions among US adults from 2013 to 2018. JAMA Netw Open 2020; 3:e2020816
74. Kalininskiy A, Bach CT, Nacca NE, Ginsberg G, Marraffa J, Navarette KA, McGraw MD, Croft DP: E-cigarette, or vaping, product use associated lung injury (EVALI): Case series and diagnostic approach. Lancet Respir Med 2019; 7:1017–26
75. Chatham-Stephens K, Roguski K, Jang Y, Cho P, Jatlaoui TC, Kabbani S, Glidden E, Ussery EN, Trivers KF, Evans ME, King BA, Rose DA, Jones CM, Baldwin G, Delaney LJ, Briss P, Ritchey MD; Lung Injury Response Epidemiology/Surveillance Task Force; Lung Injury Response Clinical Task Force: Characteristics of hospitalized and nonhospitalized patients in a nationwide outbreak of e-cigarette, or vaping, product use-associated lung injury - United States, November 2019. MMWR Morb Mortal Wkly Rep 2019; 68:1076–80
76. Kennedy CD, van Schalkwyk MCI, McKee M, Pisinger C: The cardiovascular effects of electronic cigarettes: A systematic review of experimental studies. Prev Med 2019; 127:105770
77. El-Mahdy MA, Ewees MG, Eid MS, Mahgoup EM, Khaleel SA, Zweier JL: Electronic cigarette exposure causes vascular endothelial dysfunction due to NADPH oxidase activation and eNOS uncoupling. Am J Physiol Heart Circ Physiol 2022; 322:H549–67
78. Alzahrani T, Pena I, Temesgen N, Glantz SA: Association between electronic cigarette use and myocardial infarction. Am J Prev Med 2018; 55:455–61
79. Berlowitz JB, Xie W, Harlow AF, Hamburg NM, Blaha MJ, Bhatnagar A, Benjamin EJ, Stokes AC: E-cigarette use and risk of cardiovascular disease: A longitudinal analysis of the PATH Study (2013-2019). Circulation 2022; 145:1557–9
80. George J, Hussain M, Vadiveloo T, Ireland S, Hopkinson P, Struthers AD, Donnan PT, Khan F, Lang CC: Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes. J Am Coll Cardiol 2019; 74:3112–20
81. Goniewicz ML, Gawron M, Smith DM, Peng M, Jacob P 3rd, Benowitz NL: Exposure to nicotine and selected toxicants in cigarette smokers who switched to electronic cigarettes: A longitudinal within-subjects observational study. Nicotine Tob Res 2017; 19:160–7
82. Rau AS, Reinikovaite V, Schmidt EP, Taraseviciene-Stewart L, Deleyiannis FW: Electronic cigarettes are as toxic to skin flap survival as tobacco cigarettes. Ann Plast Surg 2017; 79:86–91
83. Troiano C, Jaleel Z, Spiegel JH: Association of electronic cigarette vaping and cigarette smoking with decreased random flap viability in rats. JAMA Facial Plast Surg 2019; 21:5–10
84. Krishnan NM, Han KD, Nahabedian MY: Can e-cigarettes cause free flap failure? A case of arterial vasospasm induced by electronic cigarettes following microsurgical breast reconstruction. Plast Reconstr Surg Glob Open 2016; 4:e596
85. Fracol M, Dorfman R, Janes L, Kulkarni S, Bethke K, Hansen N, Kim J: The surgical impact of e-cigarettes: A case report and review of the current literature. Arch Plast Surg 2017; 44:477–81
86. Famiglietti A, Memoli JW, Khaitan PG: Are electronic cigarettes and vaping effective tools for smoking cessation? Limited evidence on surgical outcomes: A narrative review. J Thorac Dis 2021; 13:384–95
87. McBride CM, Emmons KM, Lipkus IM: Understanding the potential of teachable moments: The case of smoking cessation. Health Educ Res 2003; 18:156–70
88. Boudreaux ED, Bock B, O'Hea E: When an event sparks behavior change: An introduction to the sentinel event method of dynamic model building and its application to emergency medicine. Acad Emerg Med 2012; 19:329–35

89. Boudreaux ED, O'Hea E, Wang B, Quinn E, Bergman AL, Bock BC, Becker BM: Modeling health event impact on smoking cessation. J Smok Cessat 2022; 2022:2923656
90. Westmaas JL, Newton CC, Stevens VL, Flanders WD, Gapstur SM, Jacobs EJ: Does a recent cancer diagnosis predict smoking cessation? An analysis from a large prospective US cohort. J Clin Oncol 2015; 33:1647–52
91. Gummerson SP, Lowe JT, Taylor KL, Lobo T, Jensen RE: The characteristics of patients who quit smoking in the year following a cancer diagnosis. J Cancer Surviv 2022; 16:111–8
92. Lando H, Hennrikus D, McCarty M, Vessey J: Predictors of quitting in hospitalized smokers. Nicotine Tob Res 2003; 5:215–22
93. Van Slyke AC, Carr M, Knox ADC, Genoway K, Carr NJ: Perioperative and long-term smoking behaviors in cosmetic surgery patients. Plast Reconstr Surg 2017; 140:503–9
94. Jose T, Schroeder DR, Warner DO: Changes in cigarette smoking behavior in cancer survivors during diagnosis and treatment. Nicotine Tob Res 2022; Mar 21;ntac072
95. Warner DO: Surgery as a teachable moment: Lost opportunities to improve public health. Arch Surg 2009; 144:1106–7
96. Shi Y, Warner DO: Surgery as a teachable moment for smoking cessation. Anesthesiology 2010; 112:102–7
97. Warner DO, Patten CA, Ames SC, Offord K, Schroeder D: Smoking behavior and perceived stress in cigarette smokers undergoing elective surgery. Anesthesiology 2004; 100:1125–37
98. Warner DO, Patten CA, Ames SC, Offord KP, Schroeder DR: Effect of nicotine replacement therapy on stress and smoking behavior in surgical patients. Anesthesiology 2005; 102:1138–46
99. Shi Y, Warner DO: Pediatric surgery and parental smoking behavior. Anesthesiology 2011; 115:12–7
100. Kalkhoran S, Kruse GR, Chang Y, Rigotti NA: Smoking-cessation efforts by US adult smokers with medical comorbidities. Am J Med 2018; 131:318.e1–8
101. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A US Public Health Service report. Am J Prev Med 2008; 35:158–76
102. Burke MV, Ebbert JO, Hays JT: Treatment of tobacco dependence. Mayo Clin Proc 2008; 83:479–83; quiz 483–4
103. Burke MV, Ebbert JO, Schroeder DR, McFadden DD, Hays JT: Treatment outcomes from a specialist model for treating tobacco use disorder in a medical center. Medicine (Baltimore) 2015; 94:e1903
104. Stead LF, Koilpillai P, Fanshawe TR, Lancaster T: Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev 2016; 3:CD008286
105. Stead LF, Bergson G, Lancaster T: Physician advice for smoking cessation. Cochrane Database Syst Rev 2008; 2:CD000165
106. Pbert L, Ockene JK, Ewy BM, Leicher ES, Warner D: Development of a state wide tobacco treatment specialist training and certification programme for Massachusetts. Tob Control 2000; 9:372–81
107. Lancaster T, Stead LF: Individual behavioural counselling for smoking cessation. Cochrane Database Syst Rev 2017; 3:CD001292
108. Lindson N, Thompson TP, Ferrey A, Lambert JD, Aveyard P: Motivational interviewing for smoking cessation. Cochrane Database Syst Rev 2019; 7:CD006936
109. Stead LF, Perera R, Lancaster T: A systematic review of interventions for smokers who contact quitlines. Tob Control 2007; 16(suppl 1):i3–8
110. Scott-Sheldon LA, Lantini R, Jennings EG, Thind H, Rosen RK, Salmoirago-Blotcher E, Bock BC: Text messaging-based interventions for smoking cessation: A systematic review and meta-analysis. JMIR Mhealth Uhealth 2016; 4:e49
111. Hall AK, Cole-Lewis H, Bernhardt JM: Mobile text messaging for health: A systematic review of reviews. Annu Rev Public Health 2015; 36:393–415
112. Marcolino MS, Oliveira JAQ, D'Agostino M, Ribeiro AL, Alkmim MBM, Novillo-Ortiz D: The impact of mHealth interventions: Systematic review of systematic reviews. JMIR Mhealth Uhealth 2018; 6:e23
113. Cahill K, Stevens S, Perera R, Lancaster T: Pharmacological interventions for smoking cessation: An overview and network meta-analysis. Cochrane Database Syst Rev 2013; 5:CD009329
114. Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, Lancaster T: Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2012; 11:CD000146
115. Aubin HJ, Luquiens A, Berlin I: Pharmacotherapy for smoking cessation: Pharmacological principles and clinical practice. Br J Clin Pharmacol 2014; 77:324–36
116. Ford CL, Zlabek JA: Nicotine replacement therapy and cardiovascular disease. Mayo Clin Proc 2005; 80:652–6
117. Pack QR, Priya A, Lagu TC, Pekow PS, Atreya A, Rigotti NA, Lindenauer PK: Short-term safety of nicotine replacement in smokers hospitalized with coronary heart sisease. J Am Heart Assoc 2018; 7:e009424
118. Hughes JR, Stead LF, Lancaster T: Antidepressants for smoking cessation. Cochrane Database Syst Rev 2007; 1:CD000031
119. Cahill K, Stead LF, Lancaster T: Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev 2012; 5:CD006103
120. Tonstad S, Davies S, Flammer M, Russ C, Hughes J: Psychiatric adverse events in randomized, double-blind,

placebo-controlled clinical trials of varenicline: A pooled analysis. Drug Saf 2010; 33:289–301
121. CAN-ADAPTT. Canadian Smoking Cessation Clinical Practice Guideline. Toronto, Canada: Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment, Centre for Addiction and Mental Health, 2011. Available at www.nicotinedependenceclinic.com/en/canadaptt/PublishingImages/Pages/CAN-ADAPTT-Guidelines/CAN-ADAPTT%20Canadian%20Smoking%20Cessation%20Guideline_website.pdf. Accessed August 29, 2022.
122. National Institute for Health and Care Excellence. Public health guideline 48: Smoking: Acute, maternity and mental health services. 2021. Available at: https://www.nice.org.uk/guidance/ng209. Accessed May 3, 2022.
123. Jamal A, Dube SR, King BA: Tobacco use screening and counseling during hospital outpatient visits among US adults, 2005-2010. Prev Chronic Dis 2015; 12:E132
124. Jamal A, Dube SR, Malarcher AM, Shaw L, Engstrom MC; Centers for Disease Control and Prevention (CDC): Tobacco use screening and counseling during physician office visits among adults–National Ambulatory Medical Care Survey and National Health Interview Survey, United States, 2005-2009. MMWR Suppl 2012; 61:38–45
125. Ferketich AK, Khan Y, Wewers ME: Are physicians asking about tobacco use and assisting with cessation? Results from the 2001-2004 national ambulatory medical care survey (NAMCS). Prev Med 2006; 43:472–6
126. Ferketich AK, Pennell M, Seiber EE, Wang L, Farietta T, Jin Y, Wewers ME: Provider-delivered tobacco dependence treatment to Medicaid smokers. Nicotine Tob Res 2014; 16:786–93
127. Chase EC, McMenamin SB, Halpin HA: Medicaid provider delivery of the 5A's for smoking cessation counseling. Nicotine Tob Res 2007; 9:1095–101
128. Denny JT, Denny AM, Tse JT, Deangelis VJ, Chyu D, Pantin EJ, Yeh SS, Cohen S, Fratzola CH, Solina A: Hospital initiatives in promoting smoking cessation: A 12-year follow-up. Exp Ther Med 2016; 12:1599–603
129. Ramsay PP, Shortell SM, Casalino LP, Rodriguez HP, Rittenhouse DR: A longitudinal study of medical practices' treatment of patients who use tobacco. Am J Prev Med 2016; 50:328–35
130. Torjesen I: NHS hospitals must help patients quit smoking, says British Thoracic Society. BMJ 2016; 355:i6571
131. Warner DO, Sarr MG, Offord KP, Dale LC: Anesthesiologists, general surgeons, and tobacco interventions in the perioperative period. Anesth Analg 2004; 99:1766–73
132. Houghton CS, Marcukaitis AW, Shirk Marienau ME, Hooten M, Stevens SR, Warner DO: Tobacco intervention attitudes and practices among certified registered nurse anesthetists. Nurs Res 2008; 57:123–9
133. Kai T, Maki T, Takahashi S, Warner DO: Perioperative tobacco use interventions in Japan: A survey of thoracic surgeons and anaesthesiologists. Br J Anaesth 2008; 100:404–10
134. Shi Y, Yu C, Luo A, Huang Y, Warner DO: Perioperative tobacco interventions by Chinese anesthesiologists: Practices and attitudes. Anesthesiology 2010; 112:338–46
135. Hajjar WM, Al-Nassar SA, Alahmadi RM, Almohanna SM, Alhilali SM: Behavior, knowledge, and attitude of surgeons and patients toward preoperative smoking cessation. Ann Thorac Med 2016; 11:132–40
136. Zaballos M, Canal MI, Martínez R, Membrillo MJ, Gonzalez FJ, Orozco HD, Sanz FJ, Lopez-Gil M: Preoperative smoking cessation counseling activities of anesthesiologists: A cross-sectional study. BMC Anesthesiol 2015; 15:60
137. Oztürk O, Yılmazer I, Akkaya A: The attitudes of surgeons concerning preoperative smoking cessation: A questionnaire study★. Hippokratia 2012; 16:124–9
138. Vick CC, Graham LA, Henderson WG, Houston TK 2nd, Hawn MT: Translating preoperative smoking cessation interventions into routine clinical care of veterans: Provider beliefs. Transl Behav Med 2011; 1:604–8
139. France EK, Glasgow RE, Marcus AC: Smoking cessation interventions among hospitalized patients: What have we learned? Prev Med 2001; 32:376–88
140. Nolan MB, Warner DO: Perioperative tobacco use treatments: Putting them into practice. BMJ 2017; 358:j3340
141. Reid RD, Mullen KA, Slovinec D'Angelo ME, Aitken DA, Papadakis S, Haley PM, McLaughlin CA, Pipe AL: Smoking cessation for hospitalized smokers: An evaluation of the "Ottawa Model". Nicotine Tob Res 2010; 12:11–8
142. Mullen KA, Manuel DG, Hawken SJ, Pipe AL, Coyle D, Hobler LA, Younger J, Wells GA, Reid RD: Effectiveness of a hospital-initiated smoking cessation programme: 2-year health and healthcare outcomes. Tob Control 2017; 26:293–9
143. Slattery C, Freund M, Gillham K, Knight J, Wolfenden L, Bisquera A, Wiggers J: Increasing smoking cessation care across a network of hospitals: An implementation study. Implement Sci 2016; 11:28
144. Karn S, Fernandez A, Grossberg LA, Robertson T, Sharp B, Huang P, Loukas A: Systematically improving tobacco cessation patient services through electronic medical record integration. Health Promot Pract 2016; 17:482–9
145. Freund M, Campbell E, Paul C, Sakrouge R, McElduff P, Walsh RA, Wiggers J, Knight J, Girgis A:

Increasing smoking cessation care provision in hospitals: A meta-analysis of intervention effect. Nicotine Tob Res 2009; 11:650–62
146. Rigotti NA, Stoney CM: CHARTing the future course of tobacco-cessation interventions for hospitalized smokers. Am J Prev Med 2016; 51:549–50
147. Andrews JO, Tingen MS, Waller JL, Harper RJ: Provider feedback improves adherence with AHCPR Smoking Cessation Guideline. Prev Med 2001; 33:415–21
148. Katz DA, Muehlenbruch DR, Brown RL, Fiore MC, Baker TB; AHRQ Smoking Cessation Guideline Study Group: Effectiveness of implementing the agency for healthcare research and quality smoking cessation clinical practice guideline: A randomized, controlled trial. J Natl Cancer Inst 2004; 96:594–603
149. Vidrine JI, Shete S, Cao Y, Greisinger A, Harmonson P, Sharp B, Miles L, Zbikowski SM, Wetter DW: Ask-Advise-Connect: A new approach to smoking treatment delivery in health care settings. JAMA Intern Med 2013; 173:458–64
150. Bentz CJ, Bayley KB, Bonin KE, Fleming L, Hollis JF, Hunt JS, LeBlanc B, McAfee T, Payne N, Siemienczuk J: Provider feedback to improve 5A's tobacco cessation in primary care: A cluster randomized clinical trial. Nicotine Tob Res 2007; 9:341–9
151. Gordon JS, Andrews JA, Crews KM, Payne TJ, Severson HH: The 5A's vs 3A's plus proactive quitline referral in private practice dental offices: Preliminary results. Tob Control 2007; 16:285–8
152. Joseph AM, Arikian NJ, An LC, Nugent SM, Sloan RJ, Pieper CF; GIFT Research Group: Results of a randomized controlled trial of intervention to implement smoking guidelines in Veterans Affairs medical centers: Increased use of medications without cessation benefit. Med Care 2004; 42:1100–10
153. Taylor CB, Miller NH, Cameron RP, Fagans EW, Das S: Dissemination of an effective inpatient tobacco use cessation program. Nicotine Tob Res 2005; 7:129–37
154. Manfredi C, LeHew CW: Why implementation processes vary across the 5A's of the Smoking Cessation Guideline: Administrators' perspectives. Nicotine Tob Res 2008; 10:1597–607
155. DePue JD, Goldstein MG, Schilling A, Reiss P, Papandonatos G, Sciamanna C, Kazura A: Dissemination of the AHCPR clinical practice guideline in community health centres. Tob Control 2002; 11:329–35
156. Milne B, Towns S: Do paediatricians provide brief intervention for adolescents who smoke? J Paediatr Child Health 2007; 43:464–8
157. New Zealand Ministry of Health. The New Zealand guidelines for helping people to stop smoking. 2014. Available at: https://www.health.govt.nz/publication/new-zealand-guidelines-helping-people-stop-smoking-update#. Accessed May 3, 2022.
158. Schroeder SA: What to do with a patient who smokes. JAMA 2005; 294:482–7
159. Bentz CJ, Bayley KB, Bonin KE, Fleming L, Hollis JF, McAfee T: The feasibility of connecting physician offices to a state-level tobacco quit line. Am J Prev Med 2006; 30:31–7
160. Ebbert JO, Carr AB, Patten CA, Morris RA, Schroeder DR: Tobacco use quitline enrollment through dental practices: a pilot study. J Am Dent Assoc 2007; 138:595–601
161. Richter KP, Ellerbeck EF: It's time to change the default for tobacco treatment. Addiction 2015; 110:381–6
162. Ebbert JO, Hughes JR, West RJ, Rennard SI, Russ C, McRae TD, Treadow J, Yu CR, Dutro MP, Park PW: Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. JAMA 2015; 313:687–94
163. Ohde JW, Master Z, Tilburt JC, Warner DO: Presumed consent with opt-out: An ethical consent approach to automatically refer patients with cancer to tobacco treatment services. J Clin Oncol 2021; 39:876–80
164. Herbst N, Wiener RS, Helm ED, O'Donnell C, Fitzgerald C, Wong C, Bulekova K, Waite M, Mishuris RG, Kathuria H: Effectiveness of an opt-out electronic heath record-based tobacco treatment consult service at an urban safety net hospital. Chest 2020; 158:1734–41
165. Nahhas GJ, Wilson D, Talbot V, Cartmell KB, Warren GW, Toll BA, Carpenter MJ, Cummings KM: Feasibility of implementing a hospital-based "opt-out" tobacco-cessation service. Nicotine Tob Res 2017; 19:937–43
166. Jose T, Ohde JW, Hays JT, Burke MV, Warner DO: Design and pilot implementation of an electronic health record-based system to automatically refer cancer patients to tobacco use treatment. Int J Environ Res Public Health 2020; 17:4054
167. Hawn MT, Houston TK, Campagna EJ, Graham LA, Singh J, Bishop M, Henderson WG: The attributable risk of smoking on surgical complications. Ann Surg 2011; 254:914–20
168. Morton HJV: Tobacco smoking and pulmonary complications after operation. Lancet 1944; 1:368–70
169. Grønkjær M, Eliasen M, Skov-Ettrup LS, Tolstrup JS, Christiansen AH, Mikkelsen SS, Becker U, Flensborg-Madsen T: Preoperative smoking status and postoperative complications: A systematic review and meta-analysis. Ann Surg 2014; 259:52–71
170. Woehlck HJ, Connolly LA, Cinquegrani MP, Dunning MB 3rd, Hoffmann RG: Acute smoking increases ST depression in humans during general anesthesia. Anesth Analg 1999; 89:856–60
171. Kyrö A, Usenius JP, Aarnio M, Kunnamo I, Avikainen V: Are smokers a risk group for delayed healing of tibial shaft fractures? Ann Chir Gynaecol 1993; 82:254–62

172. Schmitz MA, Finnegan M, Natarajan R, Champine J: Effect of smoking on tibial shaft fracture healing. Clin Orthop 1999; 365:184–200
173. Scolaro JA, Schenker ML, Yannascoli S, Baldwin K, Mehta S, Ahn J: Cigarette smoking increases complications following fracture: A systematic review. J Bone Joint Surg Am 2014; 96:674–81
174. Hatta T, Werthel JD, Wagner ER, Itoi E, Steinmann SP, Cofield RH, Sperling JW: Effect of smoking on complications following primary shoulder arthroplasty. J Shoulder Elbow Surg 2017; 26:1–6
175. Glassman SD, Anagnost SC, Parker A, Burke D, Johnson JR, Dimar JR: The effect of cigarette smoking and smoking cessation on spinal fusion. Spine (Phila Pa 1976) 2000; 25:2608–15
176. Lau D, Chou D, Ziewacz JE, Mummaneni PV: The effects of smoking on perioperative outcomes and pseudarthrosis following anterior cervical corpectomy: Clinical article. J Neurosurg Spine 2014; 21:547–58
177. Jackson KL 2nd, Devine JG: The effects of smoking and smoking cessation on spine surgery: A systematic review of the literature. Global Spine J 2016; 6:695–701
178. Lavernia CJ, Sierra RJ, Gomez-Marin O: Smoking and joint replacement: Resource consumption and short-term outcome. Clin Orthopaedics Related Res 1999; 367:172–80
179. Singh JA: Smoking and outcomes after knee and hip arthroplasty: A systematic review. J Rheumatol 2011; 38:1824–34
180. Lombardi AV Jr, Berend KR, Adams JB, Jefferson RC, Sneller MA: Smoking may be a harbinger of early failure with ultraporous metal acetabular reconstruction. Clin Orthop Relat Res 2013; 471:486–97
181. Lampley A, Gross CE, Green CL, DeOrio JK, Easley M, Adams S, Nunley JA 2nd: Association of cigarette use and complication rates and outcomes following total ankle arthroplasty. Foot Ankle Int 2016; 37:1052–9
182. Wright E, Tzeng TH, Ginnetti M, El-Othmani MM, Saleh JK, Saleh J, Lane JM, Mihalko WM, Saleh KJ: Effect of smoking on joint replacement outcomes: Opportunities for improvement through preoperative smoking cessation. Instr Course Lect 2016; 65:509–20
183. Bedard NA, Dowdle SB, Wilkinson BG, Duchman KR, Gao Y, Callaghan JJ: What is the impact of smoking on revision total knee arthroplasty? J Arthroplasty 2018; 33(7S):172–6
184. Wells DB, Holt AM, Smith RA, Brolin TJ, Azar FM, Throckmorton TW: Tobacco use predicts a more difficult episode of care after anatomic total shoulder arthroplasty. J Shoulder Elbow Surg 2018; 27:23–8
185. Bedard NA, DeMik DE, Owens JM, Glass NA, DeBerg J, Callaghan JJ: Tobacco use and risk of wound complications and periprosthetic joint infection: A systematic review and meta-analysis of primary total joint arthroplasty procedures. J Arthroplasty 2019; 34:385–396.e4
186. Zhu Y, Liu S, Zhang X, Chen W, Zhang Y: Incidence and risks for surgical site infection after adult tibial plateau fractures treated by ORIF: A prospective multicentre study. Int Wound J 2017; 16: 16.
187. McCunniff PT, Young ES, Ahmadinia K, Ahn UM, Ahn NU: Smoking is associated with increased blood loss and transfusion use after lumbar spinal surgery. Clin Orthop Relat Res 2016; 474:1019–25
188. Langsted A, Nordestgaard BG: Smoking is associated with increased risk of major bleeding: A prospective cohort study. Thromb Haemost 2019; 119:39–47
189. Nordestgaard AT, Rasmussen LS, Sillesen M, Steinmetz J, King DR, Saillant N, Kaafarani HM, Velmahos GC: Smoking and risk of surgical bleeding: Nationwide analysis of 5,452,411 surgical cases. Transfusion 2020; 60:1689–99
190. Shen L, Wei K, Chen Q, Qiu H, Tao Y, Yao Q, Song J, Li C, Zhao L, Liu Y, Lu Z: Decreased pain tolerance before surgery and increased postoperative narcotic requirements in abstinent tobacco smokers. Addict Behav 2018; 78:9–14
191. Chiang HL, Chia YY, Lin HS, Chen CH: The implications of tobacco smoking on acute postoperative pain: A prospective observational dtudy. Pain Res Manag 2016; 2016:9432493
192. Woodside JR: Female smokers have increased postoperative narcotic requirements. J Addict Dis 2000; 19:1–10
193. Shi Y, Hooten WM, Warner DO: Effects of smoking cessation on pain in older adults. Nicotine Tob Res 2011; 13:919–25
194. Tsai J, Homa DM, Gentzke AS, Mahoney M, Sharapova SR, Sosnoff CS, Caron KT, Wang L, Melstrom PC, Trivers KF: Exposure to secondhand smoke among nonsmokers - United States, 1988-2014. MMWR Morb Mortal Wkly Rep 2018; 67:1342–6
195. Chiswell C, Akram Y: Impact of environmental tobacco smoke exposure on anaesthetic and surgical outcomes in children: A systematic review and meta-analysis. Arch Dis Child 2017; 102:123–30
196. Dennis A, Curran J, Sherriff J, Kinnear W: Effects of passive and active smoking on induction of anaesthesia. Br J Anaesth 1994; 73:450–2
197. Simsek E, Karaman Y, Gonullu M, Tekgul Z, Cakmak M: The effect of passive exposure to tobacco smoke on perioperative respiratory complications and the duration of recovery. Braz J Anesthesiol 2016; 66:492–8
198. Ozkan AS, Ucar M, Akbas S: The effects of secondhand smoke exposure on postoperative pain and ventilation values during one-lung ventilation: A prospective clinical trial. J Cardiothorac Vasc Anesth 2019; 33:710–6
199. Lee A, Chui PT, Chiu CH, Tan PE, Tam TP, Samy W, Tong PW, Critchley LA, Gin T: Risk of perioperative respiratory complications and postoperative morbidity in a cohort of adults exposed to passive smoking. Ann Surg 2015; 261:297–303

200. Thomsen T, Villebro N, Moller AM: Interventions for preoperative smoking cessation. Cochrane Database Syst Rev 2014; 3:CD002294
201. Wong J, Abrishami A, Riazi S, Siddiqui N, You-Ten E, Korman J, Islam S, Chen X, Andrawes MSM, Selby P, Wong DT, Chung F: A perioperative smoking cessation intervention with varenicline, counseling, and fax referral to a telephone quitline *versus* a brief intervention: A randomized controlled trial. Anesth Analg 2017; 125:571–9
202. Webb AR, Coward L, Meanger D, Leong S, White SL, Borland R: Offering mailed nicotine replacement therapy and Quitline support before elective surgery: A randomised controlled trial. Med J Aust 2022; 216:357–63
203. Berlin NL, Cutter C, Battaglia C: Will preoperative smoking cessation programs generate long-term cessation? A systematic review and meta-analysis. Am J Manag Care 2015; 21:e623–31
204. Min W, An R, Li S, Feng J, Yang J, Huang Z: The effects of preoperative smoking cessation on the healing of fractures and postoperative complications: A systematic review and meta-analysis. Biomed Res (India) 2017; 28:1883–9
205. Arinze N, Farber A, Levin SR, Cheng TW, Jones DW, Siracuse CG, Patel VI, Rybin D, Doros G, Siracuse JJ: The effect of the duration of preoperative smoking cessation timing on outcomes after elective open abdominal aortic aneurysm repair and lower extremity bypass. J Vasc Surg 2019; 70:1851–61
206. Rodriguez M, Gomez-Hernandez MT, Novoa N, Jimenez MF, Aranda JL, Varela G: Refraining from smoking shortly before lobectomy has no influence on the risk of pulmonary complications: A case-control study on a matched population+. Eur J Cardio-Thoracic Surg 2017; 51: 498–503
207. Myers K, Hajek P, Hinds C, McRobbie H: Stopping smoking shortly before surgery and postoperative complications: A systematic review and meta-analysis. Arch Intern Med 2011; 171:983–9
208. Mills E, Eyawo O, Lockhart I, Kelly S, Wu P, Ebbert JO: Smoking cessation reduces postoperative complications: A systematic review and meta-analysis. Am J Med 2011; 124:144–54.e8
209. Wong J, Lam DP, Abrishami A, Chan MT, Chung F: Short-term preoperative smoking cessation and postoperative complications: A systematic review and meta-analysis. Can J Anaesth 2012; 59:268–79
210. Lumb AB: Pre-operative respiratory optimisation: An expert review. Anaesthesia 2019; 74(suppl 1):43–8
211. Yoshida N, Baba Y, Hiyoshi Y, Shigaki H, Kurashige J, Sakamoto Y, Miyamoto Y, Iwatsuki M, Ishimoto T, Kosumi K, Sugihara H, Harada K, Tokunaga R, Izumi D, Watanabe M, Baba H: Duration of smoking cessation and postoperative morbidity after esophagectomy for esophageal cancer: How long should patients stop smoking before surgery? World J Surg 2016; 40:142–7
212. Nolan MB, Martin DP, Thompson R, Schroeder DR, Hanson AC, Warner DO: Association between smoking status, preoperative exhaled carbon monoxide levels, and postoperative surgical site infection in patients undergoing elective surgery. JAMA Surg 2017; 152:476–83
213. Nåsell H, Adami J, Samnegård E, Tønnesen H, Ponzer S: Effect of smoking cessation intervention on results of acute fracture surgery: A randomized controlled trial. J Bone Joint Surg Am 2010; 92:1335–42
214. Kamath AS, Vaughan Sarrazin M, Vander Weg MW, Cai X, Cullen J, Katz DA: Hospital costs associated with smoking in veterans undergoing general surgery. J Am Coll Surg 2012; 214:901–8.e1
215. Warner DO, Borah BJ, Moriarty J, Schroeder DR, Shi Y, Shah ND: Smoking status and health care costs in the perioperative period: A population-based study. JAMA Surg 2014; 149:259–66
216. Gaskill CE, Kling CE, Varghese TK Jr, Veenstra DL, Thirlby RC, Flum DR, Alfonso-Cristancho R: Financial benefit of a smoking cessation program prior to elective colorectal surgery. J Surg Res 2017; 215:183–9
217. Slatore CG, Au DH, Hollingworth W: Cost-effectiveness of a smoking cessation program implemented at the time of surgery for lung cancer. J Thorac Oncol 2009; 4:499–504
218. Boylan MR, Bosco JA 3rd, Slover JD: Cost-effectiveness of preoperative smoking cessation interventions in total joint arthroplasty. J Arthroplasty 2019; 34:215–20
219. Zhuang T, Ku S, Shapiro LM, Hu SS, Cabell A, Kamal RN: A cost-effectiveness analysis of smoking-cessation interventions prior to posterolateral lumbar fusion. J Bone Joint Surg Am 2020; 102:2032–42
220. Jiménez-Ruiz CA, Martín V, Alsina-Restoy X, de Granda-Orive JI, de Higes-Martínez E, García-Rueda M, Genovés-Crespo M, López-García C, Lorza-Blasco JJ, Márquez FL, Ramos-Pinedo Á, Riesco-Miranda JA, Signes-Costa J, Solano-Reina S, Vaquero-Lozano P, Rejas J: Cost-benefit analysis of funding smoking cessation before surgery. Br J Surg 2020; 107:978–94
221. Sørensen LT: Wound healing and infection in surgery: The pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: A systematic review. Ann Surg 2012; 255:1069–79
222. Nolan MB, Warner DO: Safety and efficacy of nicotine replacement therapy in the perioperative period: A narrative review. Mayo Clin Proc 2015; 90:1553–61
223. Kim Y, Chen TC: Smoking and nicotine effects on surgery: Is nicotine replacement therapy (NRT) a safe option? Ann Surg 2021; 273:e139–41

224. Stefan MS, Pack Q, Shieh MS, Pekow PS, Bernstein SL, Raghunathan K, Nason KS, Lindenauer PK: The association of nicotine replacement therapy with outcomes among smokers hospitalized for a major surgical procedure. Chest 2020; 157:1354–61
225. Shi Y, Warner DO: Brief preoperative smoking abstinence: Is there a dilemma? Anesth Analg 2011; 113:1348–51
226. Warner DO, Colligan RC, Hurt RD, Croghan IT, Schroeder DR: Cough following initiation of smoking abstinence. Nicotine Tob Res 2007; 9:1207–12
227. Parrott AC: Stress modulation over the day in cigarette smokers. Addiction 1995; 90:233–44
228. Warner DO, Klesges RC, Dale LC, Offord KP, Schroeder DR, Vickers KS, Hathaway JC: Telephone quitlines to help surgical patients quit smoking patient and provider attitudes. Am J Prev Med 2008; 35(6 suppl):S486–93
229. Thomas K, Bendtsen M, Linderoth C, Bendtsen P: Implementing facilitated access to a text messaging, smoking cessation intervention among Swedish patients having elective surgery: Qualitative study of patients' and health care professionals' perspectives. JMIR Mhealth Uhealth 2020; 8:e17563
230. Warner DO; American Society of Anesthesiologists Smoking Cessation Initiative Task Force: Feasibility of tobacco interventions in anesthesiology practices: A pilot study. Anesthesiology 2009; 110:1223–8
231. Wolvers PJD, Ayubi O, Bruin SC, Hutten BA, Brandjes DPM, Meesters EW, Gerdes VEA: Smoking behaviour and beliefs about smoking cessation after bariatric surgery. Obes Surg 2021; 31:239–49
232. Newhall K, Burnette M, Brooke BS, Schanzer A, Tan T, Flocke S, Farber A, Goodney P; VAPOR Investigators: Smoking cessation counseling in vascular surgical practice using the results of interviews and focus groups in the vascular surgeon offer and report smoking cessation pilot trial. J Vasc Surg 2016; 63:1011–7.e2
233. Newhall K, Suckow B, Spangler E, Brooke BS, Schanzer A, Tan TW, Burnette M, Edelen MO, Farber A, Goodney P; VAPOR Investigators: Impact and duration of brief surgeon-delivered smoking cessation advice on attitudes regarding nicotine dependence and tobacco harms for patients with peripheral arterial disease. Ann Vasc Surg 2017; 38:113–21
234. Bottorff JL, Seaton CL, Lamont S: Patients' awareness of the surgical risks of smoking: Implications for supporting smoking cessation. Can Fam Physician 2015; 61:e562–9
235. Nolan M, Ridgeway JL, Ghosh K, Martin D, Warner DO: Design, implementation, and evaluation of an intervention to improve referral to smoking cessation services in breast cancer patients. Support Care Cancer 2019; 27:2153–8
236. Bottorff JL, Seaton CL, Viney N, Stolp S, Krueckl S, Holm N: The Stop Smoking Before Surgery program: Impact on awareness of smoking-related perioperative complications and smoking behavior in Northern Canadian communities. J Prim Care Community Health 2016; 7:16–23
237. Akhavan S, Nguyen LC, Chan V, Saleh J, Bozic KJ: Impact of smoking cessation counseling prior to total joint arthroplasty. Orthopedics 2017; 40:e323–8
238. Hart A, Rainer WG, Taunton MJ, Mabry TM, Berry DJ, Abdel MP: Cotinine testing improves smoking cessation before total joint arthroplasty. J Arthroplasty 2019; 34(7S):148–51
239. Howard R, Albright J, Osborne N, Englesbe M, Goodney P, Henke P: Impact of a regional smoking cessation intervention for vascular surgery patients. J Vasc Surg 2022; 75:262–9
240. Mustoe MM, Clark JM, Huynh TT, Tong EK, Wolf TP, Brown LM, Cooke DT: Engagement and effectiveness of a smoking cessation quitline intervention in a thoracic surgery clinic. JAMA Surg 2020; 155:816–22
241. Nolan MB, Warner MA, Jacobs MA, Amato MS, Graham AL, Warner DO: Feasibility of a perioperative text messaging smoking cessation program for surgical patients. Anesth Analg 2019; 129:e73–6
242. Saxony J, Cowling L, Catchpole L, Walker N: Evaluation of a smoking cessation service in elective surgery. J Surg Res 2017; 212:33–41
243. Coffman CR, Howard SK, Mariano ER, Kou A, Pollard J, Boselli R, Kangas S, Leng J: A short, sustainable intervention to help reduce day of surgery smoking rates among patients undergoing elective surgery. J Clin Anesth 2019; 58:35–6
244. Stonesifer C, Crusco S, Rajupet S: Improving smoking cessation referrals among elective surgery clinics through electronic clinical decision support. Tob Prev Cessat 2021; 7:14
245. Young-Wolff KC, Adams SR, Fogelberg R, Goldstein AA, Preston PG: Evaluation of a pilot perioperative smoking cessation program: A pre-post study. J Surg Res 2019; 237:30–40
246. Webb AR, Robertson N, Sparrow M, Borland R, Leong S: Printed quit-pack sent to surgical patients at time of waiting list placement improved perioperative quitting. ANZ J Surg 2014; 84:660–4
247. Webb A, Wilson AC: The addition of tick-boxes related to tobacco cessation improves smoking-related documentation in the anaesthesia chart. Anaesth Intensive Care 2017; 45:52–7
248. Andrews K, Bale P, Chu J, Cramer A, Aveyard P: A randomized controlled trial to assess the effectiveness of a letter from a consultant surgeon in causing smokers to stop smoking pre-operatively. Public Health 2006; 120:356–8
249. Goodney PP, Spangler EL, Newhall K, Brooke BS, Schanzer A, Tan TW, Beck AW, Hallett JH,

MacKenzie TA, Edelen MO, Hoel AW, Rigotti NA, Farber A: Feasibility and pilot efficacy of a brief smoking cessation intervention delivered by vascular surgeons in the Vascular Physician Offer and Report (VAPOR) Trial. J Vasc Surg 2017; 65:1152–1160.e2
250. Lee SM, Landry J, Jones PM, Buhrmann O, Morley-Forster P: The effectiveness of a perioperative smoking cessation program: A randomized clinical trial. Anesth Analg 2013; 117:605–13
251. Lee SM, Landry J, Jones PM, Buhrmann O, Morley-Forster P: Long-term quit rates after a perioperative smoking cessation randomized controlled trial. Anesth Analg 2015; 120:582–7
252. Shi Y, Ehlers S, Hinds R, Baumgartner A, Warner DO: Monitoring of exhaled carbon monoxide to promote preoperative smoking abstinence. Health Psychol 2013; 32:714–7
253. Sørensen LT, Hemmingsen U, Jørgensen T: Strategies of smoking cessation intervention before hernia surgery–effect on perioperative smoking behavior. Hernia 2007; 11:327–33
254. Warner DO, Klesges RC, Dale LC, Offord KP, Schroeder DR, Shi Y, Vickers KS, Danielson DR: Clinician-delivered intervention to facilitate tobacco quitline use by surgical patients. Anesthesiology 2011; 114:847–55
255. Warner DO, LeBlanc A, Kadimpati S, Vickers KS, Shi Y, Montori VM: Decision aid for cigarette smokers scheduled for elective surgery. Anesthesiology 2015; 123:18–28
256. Webb AR, Coward L, Soh L, Waugh L, Parsons L, Lynch M, Stokan LA, Borland R: Smoking cessation in elective surgical patients offered free nicotine patches at listing: a pilot study. Anaesthesia 2020; 75:171–8
257. Warner DO, Nolan MB, Kadimpati S, Burke MV, Hanson AC, Schroeder DR: Quitline tobacco interventions in hospitalized patients: A randomized trial. Am J Prev Med 2016; 51:473–84
258. Young-Wolff KC, Klebaner D, Folck B, Carter-Harris L, Salloum RG, Prochaska JJ, Fogelberg R, Tan ASL: Do you vape? Leveraging electronic health records to assess clinician documentation of electronic nicotine delivery system use among adolescents and adults. Prev Med 2017; 105:32–6
259. Lilley M, Krosin M, Lynch TL, Leasure J: Orthopedic surgeons' management of elective surgery for patients who use nicotine. Orthopedics 2017; 40:e90–4
260. Carlson BB, Burton DC, Jackson RS, Robinson S: Recidivism rates after smoking cessation before spinal fusion. Orthopedics 2016; 39:e318–22
261. Pillutla V, Maslen H, Savulescu J: Rationing elective surgery for smokers and obese patients: responsibility or prognosis? BMC Med Ethics 2018; 19:28
262. Payne CE, Southern SJ: Urinary point-of-care test for smoking in the pre-operative assessment of patients undergoing elective plastic surgery. J Plast Reconstr Aesthet Surg 2006; 59:1156–61
263. Reinbold C, Rausky J, Binder JP, Revol M: Urinary cotinine testing as pre-operative assessment of patients undergoing free flap surgery. Ann Chir Plast Esthet 2015; 60:e51–7
264. Salandy A, Malhotra K, Goldberg AJ, Cullen N, Singh D: Can a urine dipstick test be used to assess smoking status in patients undergoing planned orthopaedic surgery? A prospective cohort study. Bone Joint J 2016; 98-B:1418–24
265. Richter KP, Ellerbeck EF: It's time to change the default for tobacco treatment. Addiction 2015; 110:381–6
266. Wong J, An D, Urman RD, Warner DO, Tønnesen H, Raveendran R, Abdullah HR, Pfeifer K, Maa J, Finegan B, Li E, Webb A, Edwards AF, Preston P, Bentov N, Richman DC, Chung F: Society for Perioperative Assessment and Quality Improvement (SPAQI) consensus statement on perioperative smoking cessation. Anesth Analg 2020; 131:955–68
267. WHO tobacco knowledge summaries: Tobacco and postsurgical outcomes. World Health Organization, 2020. Available at: https://www.who.int/publications/i/item/9789240000360. Accessed May 3, 2022.
268. Pierre S, Rivera C, Le Maître B, Ruppert AM, Bouaziz H, Wirth N, Saboye J, Sautet A, Masquelet AC, Tournier JJ, Martinet Y, Chaput B, Dureuil B: Guidelines on smoking management during the perioperative period. Anaesth Crit Care Pain Med 2017; 36:195–200
269. A guideline for perioperative smoking cessation. J Anesthesia 2017; 31:297–303
270. Yousefzadeh A, Chung F, Wong DT, Warner DO, Wong J: Smoking cessation: The role of the anesthesiologist. Anesth Analg 2016; 122:1311–20
271. Warner DO: Preoperative smoking cessation: the role of the primary care provider. Mayo Clin Proc 2005; 80:252–8
272. Warner DO: Helping surgical patients quit smoking: Why, when, and how. Anesth Analg 2005; 99:1766–73
273. Warner DO: Tobacco control for anesthesiologists. J Anesth 2007; 21:200–11
274. Yu C, Shi Y, Warner DO, Luo A: The role of anesthesiologists in tobacco control. Chinese J Anesth 2010; 30:129–31
275. Bauer MS, Damschroder L, Hagedorn H, Smith J, Kilbourne AM: An introduction to implementation science for the non-specialist. BMC Psychol 2015; 3:32
276. Shea CM: A conceptual model to guide research on the activities and effects of innovation champions. Implement Res Pract 2021; 2:1–13

Mind to Mind

Creative writing that explores the abstract side of our profession and our lives

Stephen T. Harvey, M.D., Editor

Hold Hope

Alexander Doyal, M.D., M.P.H., F.A.S.A.

Heavy-hearted, I awake before dawn and sit in the silence on the back porch. The low clouds roll quickly by, veiling and revealing the stars. Far off, bright burning beacons of light and joy and hope blazing in the firmament.

So clear one moment…obscured the next...

The moon's shining silver sliver paints the world in dim shades of blue-grey. Colors muted. Forms indistinct. Textures vague. Only the faint scent of spring's first blooming buds whisper the end of a long winter.

And a long winter we have endured. Full of fear, frustration, famine, pestilence, war. The world feels drab and colorless. Faceless masked forms pass expressionless in the streets. Another variant. Another tragedy.

Will this ever end?

Yet, as I sit in silence, a lonely bird voices a cry of joy in the darkness. Suddenly, the sky seems less dark. The stars fade. A change is coming! A second bird enters the aria. An enchanting duet of mirrored melodies fills the heavens. Hope builds in my heart with the coming dawn. So slowly, so very slowly, and almost imperceivable the sky lightens. More and more singers fill the trees with numerous instruments, a great

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triumphant symphony erupts in the stillness. The coming light exposes a world of shape and form, color and hue, texture and depth.

This long winter will not endure forever.

Take courage, my heart, and wait and see the coming of the dawn of spring.

Hold hope and wait and sing.

Stephen T. Harvey, M.D., Editor

Induction

Brian R. Smith, M.S.

Julio was a nervous boy, and his anesthesia started at 11:43.

Dr. M, the anesthesiologist I was shadowing, explained that this was not Julio's first time in the hospital. Far from it. He had been through a lot—unexplained seizures, a brain tumor diagnosis, excisional surgery, and chemo. In comparison, his visit today was minor: a restaging MRI. But Dr. M said Julio had been nervous the last time and would probably be today. He needed to be perfectly still for imaging, so he needed general anesthesia.

We walked into his room at 11:00. Sitting on the bed—no, crouching—was Spiderman. He looked up as we entered and flicked some imaginary webs at us. Dr. M's hands flailed in an exaggerated backstroke motion. With her hands up, she reintroduced herself and asked if she could approach the tiny superhero. He looked at the other person in the room, his sister Marietta, and nodded.

Dr. M explained the anesthesia procedure to Julio and Marietta. Julio's hands and feet never stopped moving and his eyes were constantly flicking around the room as if memorizing every detail. I went up to him and waved. He waved back and the first thing he said was, "I'm not nervous!" My mask hid my smile, and I gave him a high-five. He said it again, so forcefully I could hear the exclamation marks, as if saying it with enough force would make it true. Then he asked if I wanted to arm-wrestle.

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While I arm-wrestled with Spiderman… with Julio, I heard Dr. M ask Marietta about how Julio had been doing. "He misses Mom, but otherwise he's been a trooper. He's been watching a lot of basketball lately." I was later told that their grandparents had recently gotten custody because living at home was no longer safe.

After their sidebar, Dr. M and Marietta turned back toward us just in time to see me lose my seventh match in a row. Dr. M knelt so she was eye-level with Julio and asked if she could see his special mask.

He carefully unwrapped his blanket and pulled out a lovingly decorated anesthesia mask, cradling it like a baby rabbit he was afraid would hop away. I saw Marietta nod toward Dr. M and Julio extended the mask forward. The whole outside was decorated with stickers. It made me feel old, not recognizing the latest Disney characters. A disquieting feeling, for sure. Marietta piped up and said, "And he got to choose the flavor, too. Bubblegum."

Dr. M nodded and said, "Good choice!" Just before leaving, she asked Julio to pull his hospital mask down so she could check inside his mouth. He yanked it off and beamed at us, aiming his mouth at each of us deliberately in turn to make sure we saw the gaps of a few newly missing teeth. His smile widened a bit more with each of our claps and cheers.

With Marietta in tow, we entered the operating room and finalized preparations. Dr. M handed me some sheets of paper and told me to crumple them up into balls while she added the bubblegum flavor to Julio's anesthesia mask. She asked Julio to hold the mask himself for a minute and breathe, without any gas, to get used to the feeling and smell. Marietta squeezed his hand.

When we were ready to begin the induction, I handed the paper balls back to Dr. M. She gave them to Julio and had him shoot free throws into a trash bin. We all cheered every time he scored. I had not noticed, but the gas was on. He made one last shot with his eyes half-closed— another score—and Dr. M cradled his head, lowering him gently down to rest. Marietta squeezed his hand one more time, kissed his forehead, then headed to the waiting room. The MRI proceeded without any incident.

Since that day, I've thought a lot about Julio's visit—the elegance of it. The appointment had been seamless. Despite being warned that Julio was nervous, I had watched

his fear evaporate and be replaced by excitement. Dr. M had reinforced his confidence and courage by playing along with his Spiderman outfit. She had thoroughly involved Marietta, someone he trusted completely. She gave him autonomy in the process with his mask decorating and anesthetic gas flavoring. She validated and encouraged his emotions, especially when they were positive, like with his lost teeth. She had shown personalized care and comfort, having his last pre-anesthesia memories be about "basketball" and holding his sister's hand. When I contemplated all of the steps she had taken, it was nothing short of pure artistry. From the very start of his 11:00 appointment—from the moment we entered the room—she had been easing his pain and anxiety.

Julio had been a nervous boy, and his anesthesia start time was documented as 11:43. But in my head, I have it down as 11:00.

Author's note: Names and identifying details have been changed to protect patient privacy. Dialogue has been reconstructed to the best of my memory.

Practice Guidelines for Difficult Airway Management: Comment

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To the Editor:

We read with interest the 2022 America Society of Anesthesiologists Practice Guidelines for Management of the Difficult Airway by Apfelbaum *et al.*[1] We applaud the authors' efforts and, in particular, the inclusion of a pediatric-specific algorithm for the first time. We question the recommendation to "minimize the use of an airway exchange catheter with pediatric patients." The cited pediatric literature includes only a single case report of successful, uncomplicated use of an airway exchange catheter to facilitate extubation in a 30-kg patient with a difficult intubation.[2] The reported survey findings indicate strong consensus to consider airway exchange catheter use with only 2 of 163 survey respondents dissenting (refer to table 5).[1] So why make this strongly worded recommendation, which we fear will discourage, if not altogether eliminate, the use of airway exchange catheters in pediatric patients?

Airway exchange catheters are helpful in facilitating tracheal extubation and providing a pathway for rapid reintubation in patients in whom tracheal intubation was difficult, as well as patients in whom fluid shifts and/or surgical manipulation may lead to airway edema and upper airway obstruction after extubation. There is limited literature on the use of airway exchange catheters in pediatric patients, but what has been published supports their usefulness and safety, although the study populations are small.[3,4]

There are many reports of airway exchange catheter failure, trauma, barotrauma, and death in adult patients.[5–8] We are unable to find similar published reports in pediatric patients, although children are susceptible to similar serious adverse events. Most if not all such events appear to be associated with insufflation of oxygen through the airway exchange catheter.[5,6,8]

Airway exchange catheters have great value when used properly to facilitate extubation and tracheal tube exchange in both pediatric and adult patients. Rather than discouraging the use of airway exchange catheters in pediatric patients, we recommend that clinicians be aware of risks, including airway trauma and barotrauma in both pediatric and adult patients, and consider steps to mitigate these risks, including providing oxygen by other means such as a simple facemask.[6]

Competing Interests

The authors declare no competing interests.

References

1. Apfelbaum JL, Hagberg CA, Connis RT, Abdelmalak BB, Agarkar M, Dutton RP, Fiadjoe JE, Greif R, Klock PA, Mercier D, Myatra SN, O'Sullivan EP, Rosenblatt WH, Sorbello M, Tung A: 2022 American Society of Anesthesiologists Practice Guidelines for Management of the Difficult Airway. Anesthesiology 2022; 136:31–81
2. Yegian CC, Volz LM, Galgon RE: Use of an airway exchange catheter-assisted extubation with continuous end-tidal carbon dioxide monitoring in a pediatric patient with a known difficult airway: a case report. A A Pract 2018; 11:233–5
3. Wise-Faberowski L, Nargozian C: Utility of airway exchange catheters in pediatric patients with a known difficult airway. Pediatr Crit Care Med 2005; 6:454–6
4. Fayoux P, Marciniak B, Engelhardt T: Airway exchange catheters use in the airway management of neonates and infants undergoing surgical treatment of laryngeal stenosis. Pediatr Crit Care Med 2009; 10:558–61
5. Fetterman D, Dubovoy A, Reay M: Unforeseen esophageal misplacement of airway exchange catheter leading to gastric perforation. Anesthesiology 2006; 104:1111–2
6. Duggan LV, Law JA, Murphy MF: Brief review: Supplementing oxygen through an airway exchange catheter: efficacy, complications, and recommendations. Can J Anaesth 2011; 58:560–8
7. McLean S, Lanam CR, Benedict W, Kirkpatrick N, Kheterpal S, Ramachandran SK: Airway exchange failure and complications with the use of the Cook Airway Exchange Catheter®: A single center cohort study of 1177 patients. Anesth Analg 2013; 117:1325–7
8. Shehata IM, Hashim RM: Pneumomediastinum, pneumothorax, pneumoperitoneum, and subcutaneous emphysema complicating extubation of a difficult airway using an airway exchange catheter: Is oxygen insufflation innocent?: A case report. A A Pract 2020; 14:e01228

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Practice Guidelines for Difficult Airway Management: Comment

To the Editor:

The new American Society of Anesthesiologists (ASA) Difficult Airway Guidelines[1] shift a paradigm on mask ventilation: the definition of difficulty now emphasizes patient outcome. Previous literature[2-5] focused on the complexity of this procedure for the clinician—as the word "difficulty" implies.[6] The ASA update rightly redirects the focus onto objective results in the patient.

The outcome measure recommended is end-tidal carbon dioxide. The ASA definition of difficulty includes it, and the flowcharts specify mask ventilation adequate "as confirmed by end-tidal carbon dioxide."[1] This measure is both valid and accessible: capnography is objective, immediate, and highly visible to all, right there on our monitors.

The update does not define what end-tidal carbon dioxide reflects "adequate ventilation," however. There is a simple scale[7] that can be used to characterize and document ventilation based on end-tidal carbon dioxide: its grades C and D fit the ASA definition of difficulty (inadequate or absent end-tidal carbon dioxide).

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References

1. Apfelbaum JL, Hagberg CA, Connis RT, Abdelmalak BB, Agarkar M, Dutton RP, Fiadjoe JE, Greif R, Klock PA, Mercier D, Myatra SN, O'Sullivan EP, Rosenblatt WH, Sorbello M, Tung A: 2022 American Society of Anesthesiologists Practice Guidelines for Management of the Difficult Airway. Anesthesiology 2022; 136:31–81
2. Han R, Tremper KK, Kheterpal S, O'Reilly M: Grading scale for mask ventilation. Anesthesiology 2004; 101:267
3. Kheterpal S, Healy D, Aziz MF, Shanks AM, Freundlich RE, Linton F, Martin LD, Linton J, Epps JL, Fernandez-Bustamante A, Jameson LC, Tremper T, Tremper KK: Incidence, predictors, and outcome of difficult mask ventilation combined with difficult laryngoscopy. Anesthesiology 2013; 119:1–10
4. Nørskov AK, Rosenstock CV, Wetterslev J, Astrup G, Afshari A, Lundstrøm LH: Diagnostic accuracy of anaesthesiologists' prediction of difficult airway management in daily clinical practice: a cohort study of 188 064 patients registered in the Danish Anaesthesia Database. Anaesthesia 2015; 70:272–81
5. Lundstrøm LH, Rosenstock CV, Wetterslev J, Nørskov AK: The DIFFMASK score for predicting difficult facemask ventilation: a cohort study of 46,804 patients. Anaesthesia 2019; 74:1267–76
6. Nielsen JR, Lim KS: Increasing the scope on difficult airways: what about mask ventilation? Anesth Analg 2019; 129:e109
7. Lim KS, Nielsen JR: Objective description of mask ventilation. Br J Anaesth 2016; 117:828–9

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Practice Guidelines for Difficult Airway Management: Reply

In Reply:

We thank the authors[1,2] for their letters addressing the American Society of Anesthesiologists (ASA) Practice Guidelines on Management of the Difficult Airway published in January 2022.[3]

Regarding the letter from Drs. Nielsen and Lim addressing mask ventilation, we respectfully disagree with the letter's premise stating that "the new ASA Difficult Airway Guidelines shift a paradigm on mask ventilation: the definition of difficulty now emphasizes patient outcome."[2] The 2022 update has the same focus on patient outcomes as the original guidelines (1993)[4] and of previous updates (2003[5] and 2013[6]); each of the published ASA Difficult Airway evidence-based practice parameters have addressed patient outcome in both the evidentiary information collected and in the final recommendations.

We appreciate Drs. Nielsen and Lim's assessment of capnography as an objective, immediate, and visible measure for assessing adequate mask ventilation, and their reference to a scale for reporting ventilatory outcomes based on end-tidal carbon dioxide. Although our guideline development process did not evaluate such a scale, perhaps with additional evaluation and validation it could be considered in a future practice parameter.

The letter from Dr. Stein *et al.* on the use of airway exchange catheters in pediatric patients questioned the recommendation to "minimize the use of an airway exchange catheter with pediatric patients."[1] They accurately addressed the limited available literature addressing this topic for pediatric patients. They noted that survey responses from consultants and members of participating organizations (addressing all patients, both adult and pediatric) strongly agreed with the primary recommendation to "assess the relative clinical merits and feasibility of the short-term use of an airway exchange catheter and/or supraglottic airway that can serve as a guide for expedited reintubation."[3] This recommendation was followed by the subrecommendation to "minimize the use of an airway exchange catheter with pediatric patients."[3]

Dr. Stein *et al.* additionally noted, as we did, that literature reporting adverse events in adult difficult airway patients, such as airway exchange catheter failure, trauma, pneumothorax, and death, was extremely limited in the pediatric patient population. To minimize such potential harms to pediatric difficult airway patients, we placed the recommendation to minimize the use of airway exchange catheters in this population *after* the recommendation to address the "relative clinical merits and feasibility" of the short-term use of airway exchange catheters. These recommendations contain a footnote as follows: "These interventions are considered advanced techniques." The Task Force exercised caution for both this recommendation and the subrecommendation due to the paucity of evidence (particularly in the pediatric population) and the consideration that some advanced techniques such as airway exchange catheter may not be commonly used by a majority of adult or pediatric anesthesiologists. Although experienced anesthesiologists who have considerable clinical expertise with this technique may use airway exchange catheters successfully in their own practices, the lack of evidence of the safety of this practice in this population led to the subrecommendation to "minimize the use of an airway exchange catheter."

Dr. Stein *et al.* recommend preferentially providing oxygen by other means (*e.g.,* simple facemask) when possible, and "if rescue ventilation *via* an airway exchange catheter is needed, use the minimum pressure necessary to achieve chest wall rise and allow adequate time for exhalation" followed by "additional risk mitigation steps include advancing the catheter no further than the distal tip of the endotracheal tube, noting the depth marking, securing the catheter to prevent distal migration, and obtaining imaging, as indicated." Unfortunately, at the time of publication, we had no evidentiary information to address these interventions either.

We do agree that airway exchange catheter use needs to be re-addressed to assess whether airway exchange catheters have value for pediatric difficult airway patients and encourage those who have experience with this technique to publish their experience. We certainly intend to revisit this topic when the current guidelines are updated in the future. Thank you for your valuable feedback.

Competing Interests

Dr. Hagberg reports the following financial relationships: Ambu (Ballerup, Denmark), Karl Storz Endoscopy (El Segundo, California), Vyaire Medical (Mettawa, Illinois), UptoDate (Waltham, Massachusetts), Elsevier (Amsterdam, Netherlands), Teleflex (Wayne, Pennsylvania), Fisher & Paykel Healthcare Limited (Auckland, New Zealand), Lucid Lane (Los Altos, California). The other authors declare no competing interests.

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References

1. Stein ML, Bunten E, Butler CG, Egbuta C, Flynn S, Kovatsis PG, Nargozian CD, Park RS, Peyton JM: Practice guidelines for difficult airway management: Comment. Anesthesiology 2022; 137:514
2. Nielsen JR, Lim K-S: Practice guidelines for difficult airway management: Comment. Anesthesiology 2022; 137:515
3. Apfelbaum JL, Hagberg CA, Connis RT, Abdelmalak BB, Agarkar M, Dutton RP, Fiadjoe JE, Greif R, Klock PA, Mercier D, Myatra SN, O'Sullivan EP, Rosenblatt WH, Sorbello M, Tung A: 2022 American Society of Anesthesiologists practice guidelines for management of the difficult airway. Anesthesiology 2022; 136:31–81
4. Caplan RA; Benumof JL; Berry FA, Blitt CD; Bode RH, Cheney FW; Connis RT; Guidry OF; Ovassapian A: Practice guidelines for management of the difficult airway: A report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 1993; 78:597–602
5. Caplan RA; Benumof JL; Berry FA, Blitt CD; Bode RH, Cheney FW; Connis RT; Guidry OF; Nickinovich DG, Ovassapian A: Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on

Management of the Difficult Airway. Anesthesiology 2003; 98:1269–77

6. Apfelbaum JL, Hagberg CA, Caplan RA, Blitt CD, Connis RT, Nickinovich DG, Hagberg CA, Caplan RA, Benumof JL, Berry FA, Blitt CD, Bode RH, Cheney FW, Connis RT, Guidry OF, Nickinovich DG, Ovassapian A: American Society of Anesthesiologists Task Force on Management of the Difficult Airway: Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 2013; 118:251–70

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Admissions: Life as a Brain Surgeon

By Henry Marsh, C.B.E., F.R.C.S. New York, Thomas Dunne Books, St. Martin's Press, 2017. Pages: 261. Price: $26.99 (hardcover); $12.99 (ebook); $18.00 (paperback).

When the eminent British neurosurgeon Henry Marsh's celebrated first memoir titled *Do No Harm: Stories of Life, Death, and Brain Surgery* was published in 2014,[1] the English novelist and screenwriter Ian McEwan commented, "Neurosurgery has met its Boswell in Henry Marsh." I would argue that Marsh's second memoir, *Admissions: Life as a Brain Surgeon,* is even more insightful, introspective, and compelling than his first given its more expansive and probing reflections on the man rather than the surgeon. In this thoughtful, disarming, and elegantly written book, the author reveals poignant admissions (truths) about his admissions (patients).

Henry Marsh was the youngest of four children, born in 1950, to a German mother and an English father who was a storied academic lawyer at Oxford University. Young Henry read politics, philosophy, and economics at Oxford before studying medicine at the Royal Free Hospital in London, graduating with honors from both institutions. He became a Fellow of the Royal College of Surgeons in 1984. In 1987, he was appointed Consultant Neurosurgeon at Atkinson Morley's, St. George Hospital in London, where he worked until his abrupt retirement, triggered by a fit of anger and frustration related to administrative, bureaucratic, and regulatory miasma, in 2014. Marsh, who introduced and popularized awake craniotomy under local anesthesia in England, was made a Commander of the British Empire in 2010.

Henry's brilliance and enviable pedigree did not shelter him from life's vicissitudes. He briefly rebelled against his well-meaning and kindly father, temporarily abandoning his university studies to work as a hospital porter in a mining town north of Newcastle. Subsequently, he developed psychologic issues, was transiently suicidal, and was hospitalized for psychiatric care. It was, however, his experience as a theater porter, watching surgeons operate, that led him to become a surgeon. Newly motivated, Marsh reapplied himself to his studies with focus and enthusiasm. After becoming a surgeon, Marsh's personal challenges included dealing with his son's (successful) surgery for a brain tumor diagnosed at age 3 months, an acrimonious divorce with its attendant disorientation and recalibration, his own retinal detachments, his mother's terminal cancer, and his father's eventual dementia resulting in death at age 96 yr.

Admissions affords an intriguing glimpse into the life of a neurosurgeon, who is also a deeply thoughtful, searingly honest human being. What sort of person has the requisite fearlessness, boldness, and confidence to cut into and manipulate the physical substrate of consciousness? Marsh represents himself as an impatient, irascible, and sometimes arrogant neurosurgeon. With rigorous, unflinching candor, he reveals his own medical/surgical errors and miscalculations. He also exposes and sharply scrutinizes his failings as a human being.

The author underscores the difficulties of working in a profession that deals in probabilities, not certainties. Although he does not use the term "second victim," he revealingly writes, "As the French surgeon René Leriche observed, we all carry cemeteries within ourselves. They are filled with the headstones of all the patients who have come to harm at our hands. We all have guilty secrets, and silence them with self-deception and exaggerated self-belief."

Marsh tangentially suggests that the technical details of neurosurgery are less difficult to master than acquiring and exercising the judgment needed to know when *not* to operate. He worries that in some situations, the destructive consequences of surgery might be worse than death itself. He does not avoid these difficult conversations with his patients and their families, attempting to help them realize that palliative measures might be more humane than prolonging suffering. Marsh observes, "We are told we must not act like gods, but sometimes we must, if we believe that a doctor's role is to reduce suffering and not just to save life at any cost." (Parenthetically, Marsh is a vocal advocate of physician-assisted suicide in circumstances when a competent person has persistently expressed his or her wish for that intervention.)

Generally speaking, when anesthesiologists are asked to list personality traits of their neurosurgical colleagues, humility is not top of mind. Yet genuine humility is pervasive in this pitch-perfect memoir. Marsh is profoundly grateful for the contributions his colleagues make to safe and compassionate patient care. He is specifically appreciative of anesthesiologists, noting, "The relationship between anesthetist and surgeon is critical, especially if there is going to be trouble, and having colleagues who are friends is all-important." Marsh is appropriately generous in highlighting the vital role anesthesiologists have, particularly during an awake craniotomy when their kindness, sensitivity, and communication skills are invaluable. He writes, "I always relied on my anaesthetists, in particular Judith Dinsmore, whose highly skilled and reassuring manner never failed to keep the patients calm and cooperative."

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Marsh spent approximately 30 yr doing *pro bono* neurosurgical work in both Nepal and Ukraine, a service he continued into retirement. No doubt the reader will find his observations about the challenges of practicing medicine in regions with language barriers, limited resources, and suboptimal infrastructure, as well as in cultures where clinical practice is "eminence-based" rather than evidence-based, illuminating. The author firmly believes that health care systems reflect the societies they serve, and he shows no diffidence in criticizing both the British National Health Service and the American system.

Although Henry Marsh is a lifelong atheist who holds no belief in an afterlife, this memoir has a spiritual feel that is difficult to explain. Perhaps it is because the book is suffused with deep gratitude for all the opportunities and privileges afforded the author, as well as his genuine compassion for struggling people and his intense respect for human dignity.

Querulously likeable in spite of himself, the author is as gifted with the pen as the scalpel. This exquisitely quilted cache of memories, opinions, and trenchant observations seen through the eyes of an accomplished neurosurgeon is a gem. I enthusiastically recommend this captivating memoir to all but the terminally queasy. Nonetheless, *Admissions* will have particular resonance for medical students, trainees, clinician–educators, and retirees who are determined to retain their identity and sense of purpose in life. Sadly, Henry Marsh was diagnosed with advanced metastatic prostate cancer in 2021, but we can look forward to his next book, titled *And, Finally*, which is scheduled for release in early 2023.

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Reference

1. Marsh H: Do no harm: Stories of life, death, and brain surgery. London, Weidenfeld & Nicolson, 2014

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What If? Counterfactual Episodes in Anesthesiology History Part I

Moderator: Melissa L. Coleman, MD

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Moderator: Douglas R. Bacon, MD, MA, FASA

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